Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Novartis**

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation

4. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Alastair Greystoke. Senior Lecturer, Clinical expert nominated by Novartis
   b. Roy Castle Lung Cancer Foundation patient organisation interview responses

8. **External Assessment Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dabrafenib and trametinib for advanced non-small cell lung cancer with a BRAF V600 mutation

Company evidence submission

Document B

August 2022

File name	Version	Contains confidential information	Date
[ID3851]_Novartis_DT in NSCLC_Document B_180822 [Fully redacted]	FINAL	No	18/08/22

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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In this template any information that should be provided in an appendix is listed in a box.

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Tables and figures

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ATP	Adenosine triphosphate
AUC	Area under the curve
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical laboratory improvement amendments
CR	Complete response
CT	Computerised tomography
D&T	Dabrafenib and trametinib
DCR	Disease control rate
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDM	Enhanced data mart
EGFR	Epidermal growth factor receptor
EHR	Electronic health records
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
ERK	Extracellular signal-regulated kinase
ESS	Effective sample size
GP	General Practitioner
HRG	Healthcare resource group
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Investigator assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
LYG	Life years gained
MAPK	Mitogen activated protein kinase
MEK	Mitogen-activated protein kinase kinase
MRI	Magnetic resonance imaging
NE	Not evaluable
NGS	Next-generation sequencing

NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life years
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation/stable disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TSD	Technical Support Document
UK	United Kingdom
VAS	Visual analogue scale
VBA	Visual Basic for Applications
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission demonstrates the cost-effectiveness of dabrafenib and trametinib as a treatment for patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

Patients and clinicians in England currently have access to dabrafenib and trametinib via National Health Service (NHS) England interim COVID-19 guidance, due to it being an oral treatment, removing the requirement for hospital visits, as well as reducing the risk of immunosuppression associated with standard of care treatments. This submission seeks to allow routine access to dabrafenib and trametinib at a cost-effective price, to ensure NHS England receive value for money for this clinically valued combination treatment.

The submission focusses on the full marketing authorisation for dabrafenib and trametinib in this indication which is: *dabrafenib and trametinib for the treatment of adult patients with advanced NSCLC with a BRAF V600 mutation*.[1]

This population is primarily those patients with previously untreated advanced NSCLC with a BRAF V600 mutation. This is based on data provided by NHS England, which suggests that [redacted]% of the initiations of dabrafenib and trametinib since August 2020 were in patients with previously untreated advanced NSCLC harbouring a BRAF V600 mutation, based on data from [redacted][2]

This is aligned with the typical treatment pathway for NSCLC in England[3], where actionable NSCLC mutations, such as BRAF V600, are routinely identified by Genomic Hubs,[4] and typically, patients identified with an actionable mutation will be offered a targeted treatment option.

Despite improvements being reported in turnaround times for routine testing of biomarkers in advanced NSCLC patients, insights from a market research survey conducted with pathology centres, as well as clinical opinion given to Novartis, noted that delays in receiving testing results remain in some parts of the country. Some centres noted an average turnaround time of [redacted] days for next generation sequencing (NGS) results to be returned (versus the recommended turnaround time of 10 working days).[4, 5]

As a result of these delays, the initial treatment for a small (but clinically important) minority of patients with previously untreated advanced NSCLC with a BRAF V600 mutation may continue to be pembrolizumab with chemotherapy. This would typically occur when a patient's mutation status is not yet known to the treating physician, but delaying treatment initiation would be detrimental to the patient.

As such, some patients with previously treated advanced NSCLC would be eligible for dabrafenib and trametinib. However, this population will likely diminish over time, as the turnaround times for testing continue to improve in line with the implementation of the Genomic Hubs strategy and a patient's mutation status is increasingly known at the time of the first treatment decision. This previously treated patient population of NSCLC exhibiting a BRAF V600 mutation presents a small (but clinically important) group within the total advanced NSCLC cohort. Based on the

availability of suitably robust evidence, cost-effectiveness analyses are presented only for the previously untreated population, although clinical data for previously treated patients are also provided in Appendix M.

In patients with previously untreated advanced NSCLC with a BRAF V600 mutation, pembrolizumab plus chemotherapy is considered to represent the standard of care, and so represents the principal comparator for this appraisal.

The National Institute for Health and Care Excellence (NICE) final scope lists all possible treatment options for advanced NSCLC, including treatments available by histology (non-squamous and squamous), programmed death-ligand 1 (PD-L1) expression, and line of treatment. Of these, pembrolizumab plus chemotherapy (specifically, pembrolizumab plus pemetrexed and platinum-based chemotherapy [carboplatin or cisplatin]), reflects the current standard of care for patients with previously untreated advanced NSCLC with a BRAF V600 mutation in the NICE treatment pathway and UK clinical practice.[3]

As discussed with the NICE and External Assessment Group (EAG) teams during the Decision Problem stage, this is aligned with recent NICE appraisals assessing treatments for an actionable mutation in patients with previously untreated advanced NSCLC, where the NICE Committee and Cancer Drugs Fund (CDF) clinical lead noted that immunotherapy with chemotherapy represents the standard of care in the UK for patients with previously untreated advanced NSCLC (NICE TA789 [tepotinib for treating advanced NSCLC with MET gene alterations], NICE TA781 [sotorasib for previously treated KRAS G12C mutation-positive advanced NSCLC]).[6, 7]

Novartis sought to verify the UK standard of care for patients with previously untreated advanced NSCLC with a BRAF V600 mutation via an advisory board with leading UK NSCLC clinical experts.[8] The clinicians explained that, in cases where dabrafenib and trametinib are not available, or in cases where BRAF status is unknown at the time of first treatment, the majority of patients would receive pembrolizumab plus chemotherapy.[3] Pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy irrespective of PD-L1 expression, given the aggressive nature of the disease and thus prognostic importance of the BRAF V600 mutation.

Patients with previously treated advanced NSCLC with a BRAF V600 mutation would typically receive pembrolizumab plus chemotherapy as their first treatment (if dabrafenib and trametinib was not available), for the reasons outlined above. As such, chemotherapy (consisting of either docetaxel monotherapy, or docetaxel plus nintedanib) would represent the most relevant treatment option for these patients, if dabrafenib and trametinib were not available.

Table 1 provides full details of the comparators suggested by NICE in the final scope for this appraisal, with an explanation for their inclusion or exclusion in the current submission. The decision problem for this submission in summarised in Table 2.

Table 1: Comparators suggested within the NICE final scope

Treatments listed in the NICE final scope	Inclusion as comparator	Justification
Treatments for previously untreated advanced NSCLC for a BRAF V600 mutation		
Pembrolizumab plus pemetrexed and	Yes	Clinical expert opinion sought by Novartis indicated that pembrolizumab plus chemotherapy represents the standard of care in the majority of patients with previously untreated advanced NSCLC irrespective of

platinum-based chemotherapy		PD-L1 status, as per the NICE treatment pathway and precedent in previous NICE appraisals.[3, 6-8] Clinical experts also noted that it is the most common treatment option for patients with previously untreated advanced NSCLC and a BRAF V600 mutation where dabrafenib and trametinib are not available or when BRAF status is unknown at the time of treatment decision.[8]
Pembrolizumab monotherapy	No	Clinical experts noted that pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy irrespective of PD-L1 expression, given the aggressive nature of the disease, and thus prognostic importance of the BRAF V600 mutation.[8]
Atezolizumab monotherapy	No	Clinical expert opinion noted the recent availability of atezolizumab, and referenced the years of clinical experience with pembrolizumab as a key driver for its lack of adoption.[8]
Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment	No	Clinical expert opinion indicated that chemotherapy is not widely used, as patients with previously untreated advanced NSCLC will be offered pembrolizumab plus chemotherapy whenever possible.[8] The clinicians noted that chemotherapy would only be considered for patients who had significant comorbidities or contraindications that would preclude them from being offered immunotherapy, which was estimated to be <5% of patients.[8]
Treatments for previously treated advanced NSCLC with a BRAF V600 mutation		
Pembrolizumab monotherapy	No	As the vast majority of patients will receive pembrolizumab plus chemotherapy as their first-line treatment option where dabrafenib and trametinib are not available or when BRAF status is unknown at the time of first treatment decision, the most common treatments for patients with previously treated advanced NSCLC with a BRAF V600 mutation are chemotherapy regimens, including docetaxel monotherapy, or docetaxel plus nintedanib. However, as detailed above, the previously treated patient population represents a small (but clinically important) minority of patients who would be eligible for dabrafenib and trametinib. This population is expected to diminish over time as the turnaround times for testing continue to improve, and a patient's mutation status is increasingly mutation at the time of the first treatment decision. Based on the small size of this patient population, and the limited availability of suitably robust comparative efficacy evidence, economic analyses are not presented for these patients within this submission (Section B.3.2.2, Table 22). Clinical results for this population are presented in Appendix M.
Nivolumab monotherapy	No	
Atezolizumab monotherapy	No	
Platinum-based doublet chemotherapy	No	
Docetaxel monotherapy, or docetaxel plus nintedanib	No	
Pemetrexed monotherapy	No	
Best supportive care	No	

Abbreviations: NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PD-L1: programmed death-ligand 1.
Source: Clinical Advisory Board Summary (14th July 2022).[8]

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.	Adult patients with advanced NSCLC with a BRAF V600 mutation.	This population is primarily patients with previously untreated advanced NSCLC with a BRAF V600 mutation; data from NHS England suggests that [redacted]% of the initiations of dabrafenib and trametinib since August 2020 were in patients with previously untreated advanced NSCLC.[2] Dabrafenib with trametinib will not routinely be used as a treatment option for patients with previously treated advanced NSCLC with a BRAF V600 mutation, as most patients with a BRAF V600 mutation would be identified at the time of their initial treatment, and offered a target treatment, as part of routine biomarker testing in UK NHS clinical practice.[4] Therefore, the previously treated patient population is expected to form a small (but clinically important) minority of patients eligible to receive dabrafenib and trametinib, and would constitute patients who have faced a delay in receiving routine biomarker testing. This population is expected to diminish over time as turnaround times continue to improve and knowledge of mutation status is known at the time of first treatment decision. These patients would instead be initiated on pembrolizumab plus chemotherapy. Based on this, and the lack of availability of suitably robust comparative efficacy evidence in

	Final scope issued by NICE		Decision problem addressed in the company submission	Rationale if different from the final NICE scope
				this patient population, economic analyses for patients with previously treated advanced NSCLC and a BRAF V600 mutation are not presented within this submission (Section B.3.2.2, Table 22). Clinical results for this population are presented in Appendix M.
Intervention	Dabrafenib and trametinib.		Dabrafenib and trametinib.	As per the NICE final scope.
Comparators	**First-line** *For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score:* • Pembrolizumab monotherapy • Atezolizumab monotherapy (Tumour PD-L1 expression of 50% or more or of 10% or more on tumour infiltrating immune cells) • Pembrolizumab combination with pemetrexed and platinum chemotherapy *For people with non-squamous NSCLC whose tumours express PD-L1*	**Second-line plus** *For people with non-squamous NSCLC PD-L1 ≥50%:* • Platinum doublet • Pemetrexed • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care *For people with non-squamous NSCLC PD-L1 <50%* • Atezolizumab monotherapy • Docetaxel, with (for adenocarcinoma histology) or without	The principal comparator considered relevant in this submission is pembrolizumab plus chemotherapy (specifically pembrolizumab, pemetrexed and carboplatin/cisplatin) in patients with previously untreated advanced NSCLC with a BRAF V600 mutation.	As outlined in Table 1 previously. Please see the 'Population' row for an explanation on the previously treated patient population. Please see the 'Subgroups to be considered' row for further discussion on squamous histology and PD-L1 status.

	Final scope issued by NICE		Decision problem addressed in the company submission	Rationale if different from the final NICE scope

	with a tumour proportion score below 50%
	• Pembrolizumab combination with pemetrexed and platinum chemotherapy
	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)
	  ○ With or without pemetrexed maintenance treatment
	For people with adenocarcinoma or large-cell carcinoma
	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin)
	  ○ With (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment
	For people with squamous NSCLC whose tumours express PD-L1 with at least
		nintedanib
		• Best supportive care
		
		For people with non-squamous NSCLC which is PD-L1 1% or more:
		• Pembrolizumab monotherapy
		• Nivolumab monotherapy
		
		For people with squamous NSCLC PD-L1 >50%
		• Gemcitabine with carboplatin or cisplatin
		• Vinorelbine with carboplatin or cisplatin
		• Docetaxel
		• Best supportive care
		
		For people with squamous NSCLC PD-L1 <50%
		• Atezolizumab monotherapy
		• Docetaxel
		• Best supportive care
		
		*For people with squamous NSCLC which is PD-L1 1% or more**
		• Pembrolizumab		

	Final scope issued by NICE		Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (only if urgent clinical intervention is needed) *For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%:* • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel	monotherapy • Nivolumab (no PD-L1 status requirement)		
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life		• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life	As per the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		(HRQoL)	
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • Previous therapy (treated or untreated) • Tumour histology (squamous or non-squamous) • Level of programmed death ligand 1 (PD-L1) expression (strong positive or weak positive)	No subgroup analyses have been conducted in this submission.	Please see the 'Population' row for further details on subgroups based on previous therapy. Subgroup analyses based on tumour histology or level of PD-L1 expression have not been conducted for the reasons detailed below. Dabrafenib and trametinib achieves clinical benefit via a mechanism of action that is independent of PD-L1 expression (see Section B.1.2). Furthermore, whilst BRAF V600 mutations occur predominantly in patients with adenocarcinoma histology (a type of non-squamous NSCLC), dabrafenib and trametinib are expected to show similar clinical benefit regardless of histology. Clinical experts commented that there is no particular phenotype for advanced NSCLC patients harbouring the BRAF V600 mutation (i.e., smokers versus non-smokers, younger adults versus older adults), and this patient population may also include patients with squamous histology.[8] As BRAF mutations occur most frequently in non-squamous histology, there is a lack of available evidence for studying interventions in this patient population. The pivotal trial for dabrafenib and trametinib recruited only one patient with squamous histology and did not collect data on PD-L1

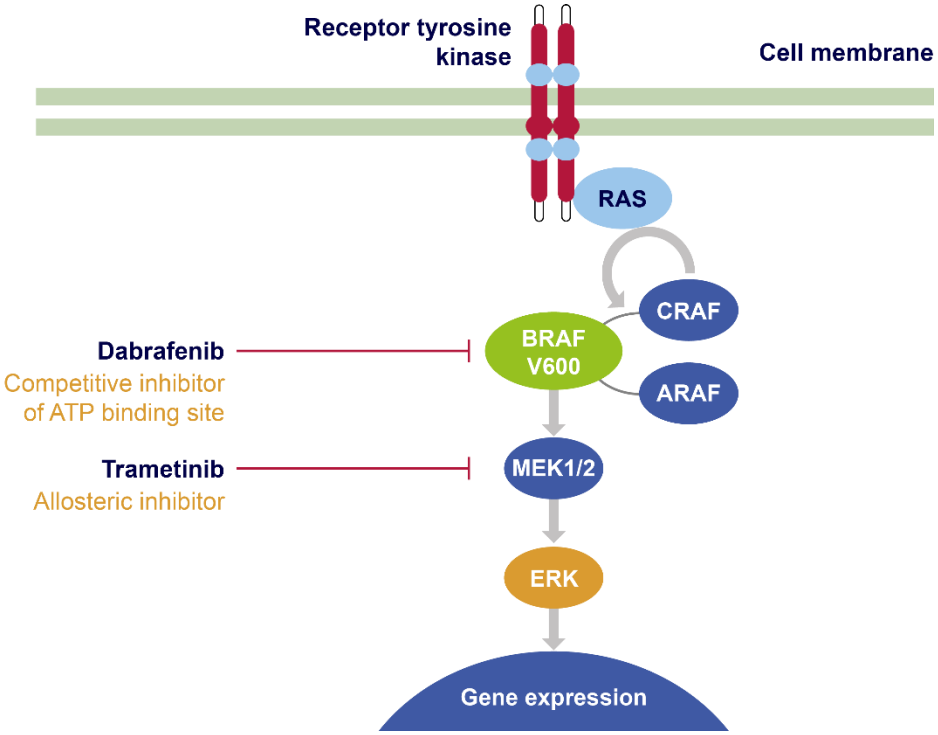
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			status, as the trial was conducted prior to the introduction of immunotherapy for NSCLC. Clinical experts agreed that targeting oncogenic driver mutations would be standard clinical practice if a relevant targeted treatment was available, as PD-L1 expression is not considered a treatment effect modifier in patients with a driver mutation.[8] Nevertheless, the rarity of the BRAF V600 mutation mean subgroup analyses by histology and PD-L1 expression are not feasible, as these would be informed by prohibitively small patient numbers. Therefore, no subgroup analyses have been presented as part of this submission, either as comparative clinical or cost-effectiveness analyses.

Abbreviations: HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; UK: United Kingdom.

B.1.2 Description of the technology being evaluated

A description of the technology being appraised is summarised in Table 3.

Table 3: Technology being appraised

UK approved name and brand name	Dabrafenib (Tafinlar®) and Trametinib (Mekinist®)
Mechanism of action	In NSCLC with a BRAF V600 mutation, the mutated form of BRAF plays a role in the development of the cancer by allowing uncontrolled division of tumour cells. The mutated BRAF protein also switches on another protein, called MEK, which is also involved in stimulating cell division, and consequently promotes the development of the cancer by allowing uncontrolled division of the tumour cells. Most cancer cells with a BRAF V600 mutation display a great reliance on MEK activity for growth and survival, and thus are very sensitive to both selective BRAF and MEK inhibitors.[9] Dabrafenib is an oral, selective inhibitor of BRAF; trametinib is an oral, selective inhibitor of MEK. By blocking the action of BRAF and MEK simultaneously, dabrafenib and trametinib help to slow down the growth and spread of the cancer (Figure 1). Pre-clinical studies have shown dabrafenib and trametinib to be highly efficacious BRAF and MEK inhibitors, respectively, validating their potential clinical benefits when used to treat patients with advanced NSCLC with a BRAF V600 mutation.[10] **Figure 1: Mechanism of action of dabrafenib and trametinib**  **Abbreviations:** ATP: adenosine triphosphate; ERK: extracellular signal-regulated kinase; MEK: mitogen-activated protein kinase kinase. **Source:** Dabrafenib SmPC and trametinib SmPC.[11, 12]
Marketing authorisation/	• A marketing authorisation for dabrafenib and trametinib was originally granted by the EMA for the indication of unresectable or metastatic melanoma with a BRAF V600 mutation on 25th August 2015.[13]

<table>
<tr><td>CE mark status</td><td>

Following a positive recommendation by the CHMP, EMA approval for dabrafenib and trametinib was extended to the indication of relevance for this submission, advanced NSCLC with a BRAF V600 mutation, on 27th March 2017.[1]
Following a further positive recommendation by the CHMP, the marketing authorisation of dabrafenib and trametinib was extended on the 26th August 2018, to the indication for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.[14]

</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>
NSCLC: Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.[11, 12]

Melanoma: Dabrafenib and trametinib are also indicated in melanoma, as detailed below:[11, 12]

Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.

</td></tr>
<tr><td>Method of administration and dosage</td><td>

Both dabrafenib and trametinib are oral therapies and the recommended doses as per their respective licences are as follows: dabrafenib 150 mg (two 75 mg capsules) twice daily, plus trametinib 2 mg (one 2 mg tablet) once daily.
The management of adverse reactions may require treatment interruption, dose reduction or treatment discontinuation, as detailed in the SmPCs.[11, 12]

</td></tr>
<tr><td>Additional tests or investigations</td><td>

In order to initiate treatment with dabrafenib and trametinib, patients must have confirmation of a BRAF V600 mutation using a validated test. In England, patients diagnosed with non-squamous NSCLC are routinely tested for common driver mutations, including BRAF V600 mutations, via NGS panel testing. BRAF V600 was added to the national testing directory as a result of the COVID-19 interim funding of dabrafenib and trametinib.[4]
As such, the need to identify patients with NSCLC with a BRAF V600 mutation would not result in any additional testing costs associated with the introduction of dabrafenib and trametinib.

</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>
The list prices for dabrafenib and trametinib are reported below.[15, 16]

<table>
<tr><th>Drug</th><th>Pack size</th><th>List price</th></tr>
<tr><td>Dabrafenib 75 mg</td><td>28 capsules</td><td>£1,400.00</td></tr>
<tr><td>Trametinib 2 mg</td><td>30 tablets</td><td>£4,800.00</td></tr>
</table>

The average cost of a course of treatment for dabrafenib and trametinib at list price is £[redacted] (reflecting a modelled mean of [redacted] weeks on treatment; Section B.3.3.2.4). Note this includes the relevant relative dose intensity reduction that patients might experience when receiving dabrafenib and trametinib based on the BRF113928 trial.[17]
</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>
Confidential simple PAS discounts on the list prices of dabrafenib and trametinib are currently available on the NHS whereby:

Dabrafenib is provided at a net price of £[redacted] per pack, a discount of [redacted]%
Trametinib is provided at a net price of £[redacted] per pack, a discount of [redacted]%

As part of the development of this appraisal, [redacted]
</td></tr>
</table>

	[redacted] As such, a confidential appendix to this submission (Appendix O) includes cost-effectiveness analyses at the following 'indicative prices' for dabrafenib and trametinib: • [redacted] • [redacted]

Abbreviations: ATP: adenosine triphosphate; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; ERK: extracellular signal-regulated kinase; MEK: mitogen-activated protein kinase kinase; NGS: next-generation sequencing; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; NSCLC: non-small cell lung cancer; PAS: Patient Access Scheme; SmPC: Summary of product characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

Advanced NSCLC with a BRAF V600 mutation

- Dabrafenib and trametinib, inhibitors of the BRAF V600 mutation pathway, are a treatment combination for patients with advanced NSCLC with a BRAF V600 mutation.[11, 12] The BRAF V600 mutation is rare, found in approximately 1–3% of NSCLC cases,[18] equating to a patient population of approximately 66 to 100 patients in England each year.
- Advanced NSCLC is an incurable and debilitating disease, and patients face an extremely poor prognosis. Stage III and IV NSCLC are associated with five-year survival rates of 12.6% and 2.9%, respectively.[19]

Current clinical pathway of care for patients with advanced NSCLC

- In the UK, patients diagnosed with advanced NSCLC with an oncogenic driver mutation receive treatments which are specifically designed to target their mutation.[3] Patients with a BRAF V600 mutation are only able to access a targeted treatment, dabrafenib and trametinib, on a temporary basis via interim COVID-19 guidance.[20]
- Clinical experts noted that, where dabrafenib and trametinib are not available, patients with previously untreated advanced NSCLC with a BRAF V600 mutation currently receive pembrolizumab plus chemotherapy.[21, 22] Pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy irrespective of PD-L1 expression, given the aggressive nature of the disease and thus prognostic importance of the BRAF V600 mutation. As such, pembrolizumab plus chemotherapy is the principal relevant comparator in this appraisal.

Dabrafenib and trametinib

- In response to the COVID-19 pandemic, dabrafenib and trametinib were made available to provide patients with an oral treatment option, to reduce the burden on the NHS due to patients attending hospital to receive IV treatment, as well as to reduce the risk of immunosuppression associated with standard of care treatments.[20]
- Dabrafenib and trametinib primarily represents a treatment for patients with previously untreated advanced NSCLC with a BRAF V600 mutation. Interim COVID-19 usage showed that [redacted]% of the patients who received dabrafenib and trametinib had previously untreated advanced NSCLC.[2] This is also aligned with the treatment pathway for other oncogenic driver mutations, where patients receive targeted treatment as early as possible.[3]
- Dabrafenib and trametinib will also represent an important treatment for patients with previously treated advanced NSCLC with a BRAF V600 mutation. However, this population represents a small (but clinically important) minority of patients eligible for dabrafenib and trametinib, and is expected to diminish over time, as turnaround times for testing continue to improve, and a patient's mutation status is increasingly known at the time of initial treatment.
- As oral treatments, dabrafenib and trametinib are associated with a reduced burden of administration versus pembrolizumab plus chemotherapy, which must be administered in hospital via intravenous (IV) infusion.[23] The availability of an oral treatment option has a positive impact on alleviating capacity issues within the NHS, while oral alternatives to IV therapies also represent an important preference for NSCLC patients.[24]
- Routine commissioning of dabrafenib and trametinib would establish a targeted treatment pathway for patients with advanced NSCLC with a BRAF V600 mutation, in line with the pathways for advanced NSCLC with other driver mutations.[3]

B.1.3.1 Overview of the disease

Lung cancer

According to the National Lung Cancer Audit annual report, 39,653 cases of lung cancer were reported in England and Wales in 2018.[25] There are two main categories of lung cancer: small-cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC accounts for the large majority of lung cancers in England and Wales (88%).[25]

Based on histology, NSCLC is typically divided into squamous cell carcinomas and non-squamous carcinomas (which can be subdivided into adenocarcinoma and large cell carcinoma, as well as other rare types).[26] The approximate distributions of each NSCLC subtype, based on data from the Royal College of Physicians (RCP), National Lung Cancer Audit 2020, indicate that non-squamous NSCLC represents the predominant histology.[27] Of these, adenocarcinomas represent the largest subtype (adenocarcinoma 66%; large cell 2%; squamous 23%; other 8%).[28] Whilst the BRAF V600 mutation occurs predominantly in adenocarcinomas, dabrafenib and trametinib represents a treatment option for all advanced NSCLC patients with a BRAF V600 mutation, irrespective of histologic subtype, as per the licensed indication.[11, 12]

The stage at which lung cancer is diagnosed plays an important role in patient survival outcomes.[29] Lung cancer is often diagnosed at an advanced stage, due to a low index of suspicion surrounding the symptoms of NSCLC, or the presence of symptoms only at an advanced stage of disease.[30] In England, 22% and 49% of all lung cancer patients are diagnosed at stage III and IV, respectively.[25] Dabrafenib and trametinib are licensed for all advanced NSCLC patients, and therefore represents a treatment option for patients with advanced NSCLC with a BRAF V600 mutation.[11, 12]

B.1.3.2 Epidemiology of BRAF V600 mutation in NSCLC

The BRAF protein, encoded by the BRAF gene, forms an important part of the MAPK signalling pathway, which plays a critical role in the proliferation and survival of normal cells (Figure 1).[31] Oncogenic mutations to the BRAF gene (most commonly V600) result in constitutive activation of the MAPK pathway, leading to disease progression.[9] Most cancer cells with a BRAF V600 mutation display a reliance on MEK activity for growth and survival and thus are sensitive to selective BRAF and MEK inhibitors.[9, 32] This represents an important actionable component of the MAPK pathway and a therapeutic target which underscores the rationale for combination therapy with a BRAF inhibitor and a MEK inhibitor. By inhibiting BRAF and MEK, respectively, dabrafenib and trametinib target this oncogenic growth and survival pathway.

BRAF V600 refers to BRAF mutations in which valine (V) is substituted at amino acid 600.[33] BRAF V600 mutations are rare and seen in approximately 1–3% of all cases of NSCLC, predominantly in adenocarcinomas.[18] This equates to a patient population of approximately 66 to 100 patients in England each year.

The most common activating BRAF mutation is V600E (valine [V] substituted by glutamic acid [E]), representing approximately 50% or more of the BRAF mutations detected in NSCLC.[34-36] Dabrafenib and trametinib are licensed for adult patients with advanced NSCLC with a BRAF V600 mutation. Non-V600 BRAF mutations can also be found in NSCLC, but this is outside the scope of the licence and thus not considered in this submission. It should be noted that, of relevance to this submission, BRAF mutations are generally considered to be mutually exclusive to other oncogenic driver mutations.[37]

Finally, it should also be noted that the treatment pathway for patients with previously untreated advanced NSCLC is stratified by PD-L1 expression in UK clinical practice, to determine eligibility and likely response to treatment with immunotherapy.[3] While patients with advanced NSCLC with a BRAF V600 mutation may display PD-L1 expression (previous studies have shown that PD-L1 positivity in BRAF patients can range between 40–80%),[38-40] several retrospective analyses did not find a clear correlation between PD-L1 and BRAF mutations.[41-45] Furthermore, dabrafenib and trametinib functions as a targeted therapy, where its mode of action is independent of the of the PD-L1/PD-1 immune checkpoint. As such, dabrafenib and trametinib will represent a treatment option for all patients with a BRAF V600 mutation, regardless of PD-L1 expression.

B.1.3.3 Diagnosis of NSCLC and molecular testing

NICE Guideline 122 (NG122) outlines the diagnosis and management of lung cancer.[3] The approach outlined in the guideline covers recommendations for diagnosis, staging, rapid assessment of suspected cases, appropriate diagnostic tools such as sputum cytology, bronchoscopy, computed tomography (CT) and magnetic resonance imaging (MRI) scans and X-rays.

As part of a broader programme to improve lung cancer management, the NHS England Lung Clinical Expert Group established the National Optimal Lung Cancer Pathway in August 2017 to streamline the pathway to improve outcomes in lung cancer by encouraging best practice and reducing variation or delays in diagnosis, staging and treatment.[46]

The pathway allows for a maximum of 49 days for a patient to be diagnosed and treated. In cases where a molecular diagnosis could influence treatment, biopsy results providing information on actionable mutations should be available within 10 working days from the point of referral. To facilitate access to molecular diagnostics, NHS England have established seven centrally funded Genomic Laboratory Hubs, with a central testing directory of molecular biomarkers that require routine testing.[4]

The BRAF gene, alongside other oncogenic driver mutations, such as EGFR, ALK and KRAS p.G12C, is tested through an NGS panel as recommended in the National Genomics Testing Directory 2022 for advanced or metastatic solid tumours.[4] While the panel is usually for non-squamous NSCLC, there may be scenarios where clinicians wish to test other subtypes (i.e., squamous) of NSCLC. UK clinical experts noted that while the Genomic Hubs are generally utilised, some parts of the country may rely on reflex or other forms of in-house testing to speed up the turnaround time for biomarker testing results.[8]

Given that BRAF V600 testing is confirmed and listed on the National Testing Directory, no additional tests, or associated costs, beyond those that are used in the routine diagnostic work up and management of patients with NSCLC, are anticipated to be required to determine eligibility for dabrafenib with trametinib.[4]

B.1.3.4 Burden of disease

Despite the recent UK initiatives to improve the diagnosis and management of lung cancer, the prognosis for patients diagnosed with lung cancer at an advanced stage remains poor.[29] According to data from Cancer Research UK from 2013 to 2017 (adapted from the Office for National Statistics), the one and five-year survival rates for patients diagnosed with Stage III lung cancer are 48.7% and 12.6%, respectively.[19] The prognosis for patients diagnosed with Stage IV

lung cancer is particularly poor: the one-year survival rate is 19.3%, whilst the five-year survival rate is 2.9%.[19] Considering nearly half of patients with lung cancer in England are diagnosed with Stage IV disease (49%, Section B.1.3.1), these extremely low survival rates underscore the need for better treatments for patients diagnosed with advanced lung cancer.

Furthermore, the impact of COVID-19 on lung cancer diagnosis and treatment has been the subject of several studies and reports.[47-50] The shifting of healthcare and hospital resources to treating COVID-19 patients led to delays in diagnosis of patients with lung cancer and changes in the treatment strategies of lung cancer patients.[49, 50] Delays in diagnosis attributed to COVID-19 may result in an additional 5% increase in the number of deaths of advanced NSCLC patients up to five years after diagnosis.[48]

The prognostic importance of the BRAF V600E mutation in NSCLC has not been widely studied, but some studies have found that patients harbouring the V600E mutation have shorter disease free survival and overall survival (OS) when compared to wildtype NSCLC.[36, 51] Marchetti *et al.* (2011) noted that the V600E mutation was associated with a more aggressive tumour histology, characterised by micropapillary features.[36] UK clinicians noted that patients harbouring the BRAF V600 mutation have a more aggressive disease compared to wild-type NSCLC.[8]

Patients with advanced NSCLC have a worse health-related quality of life (HRQoL) compared to both the general population and patients with other advanced cancers.[52] Various studies have shown that patients with advanced NSCLC experience diminished HRQoL compared to patients with less severe NSCLC.[53, 54] Advanced NSCLC is associated with severe symptoms, such as fatigue, loss of appetite, shortness of breath, as well as severe pain, depression and anxiety.[55-57]

NSCLC is also associated with a considerable burden of care. A descriptive, longitudinal study investigated the burden, skills preparedness, psychological distress, and quality of life for caregivers of patients with NSCLC.[58] The caregivers within the study experienced high self-perceived demands of caregiving responsibilities.[58] Over time, this burden increased significantly and in turn, caregiver preparedness to deal with the multiple domains of the care-giving role decreased.[58] Caregivers for patients with NSCLC also reported an increase in psychological distress and deterioration in psychological well-being and overall quality of life.[58]

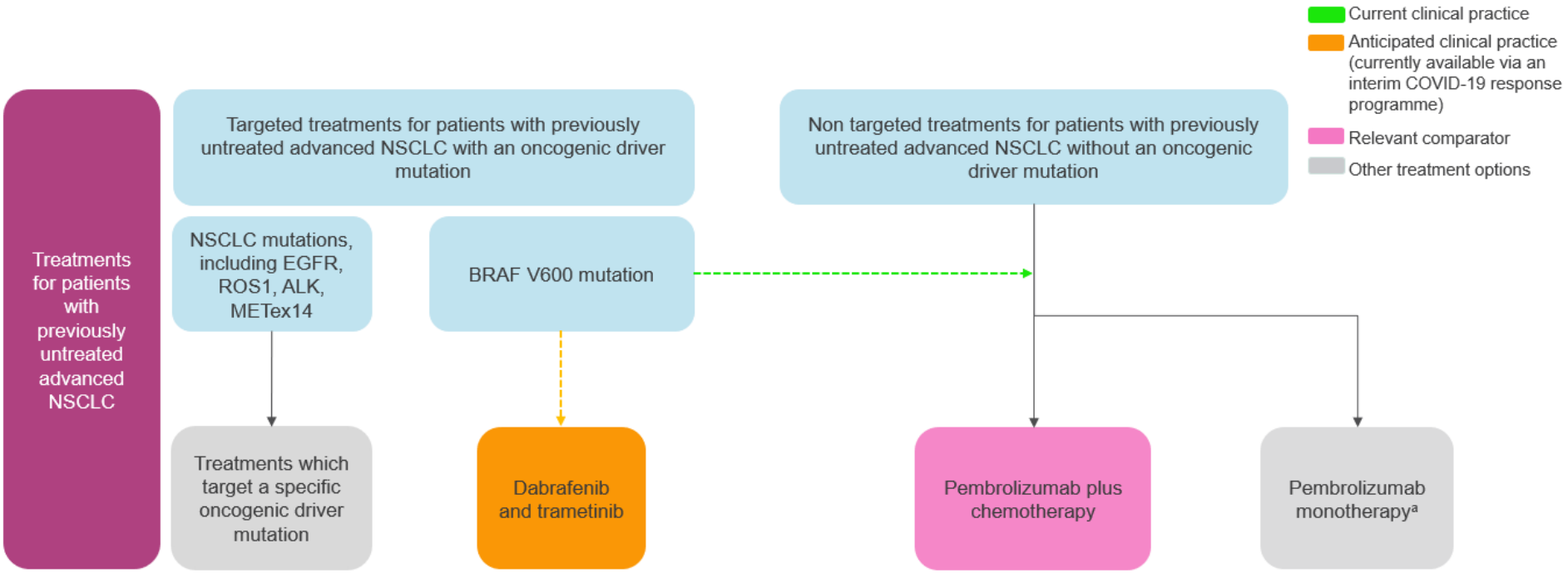
B.1.3.5 Clinical pathway of care

Overview of the treatment pathway

Testing for a BRAF mutation in NSCLC is now part of routine UK clinical practice as of August 2020 (Section B.1.3.3). NGS panels, typically performed at Genomic Hubs, are used to test for the BRAF mutation, alongside other actionable mutations (ALK, EGFR, EML4-ALK, KRAS, MET, MET 14 exon skipping, NTRK, RET and ROS1).[4] This has been confirmed in a Novartis market research survey, which reported that [redacted]% of surveyed pathology laboratories stated that BRAF testing has moved to the Genomic Hubs.[5]

The treatment pathway for patients with advanced NSCLC in England and Wales is separated by targeted and non-targeted treatment options as per the NICE clinical guideline for lung cancer (NG122, Figure 2).[3]

Figure 2: Current treatment pathway for previously untreated advanced NSCLC in UK clinical practice



Footnotes: [a] Clinical opinion noted that for patients with previously untreated advanced NSCLC with a BRAF V600 mutation, pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy, irrespective of PD-L1 expression, given the aggressive nature of the disease and thus prognostic importance of the BRAF V600 mutation (Section B.1.1).
Abbreviations: ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-L1: programmed death-ligand 1; TA: Technology Appraisal; UK: United Kingdom.
Source: Based on NICE NG122[3] and clinical expert opinion.[8]

As detailed in Section B.1.1, UK NSCLC experts confirmed to Novartis that, for patients with previously untreated advanced NSCLC without an oncogenic driver mutation, pembrolizumab plus chemotherapy is the most relevant treatment option. Clinical experts noted that pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy irrespective of PD-L1 expression, given the aggressive nature of the disease and thus prognostic importance of the BRAF V600 mutation.

As such, pembrolizumab plus chemotherapy represents the only relevant comparator to dabrafenib and trametinib in this appraisal (detailed in Table 1 of Section B.1.1).

Limitations with current treatment options for advanced NSCLC patients with BRAF mutation

Pembrolizumab-based treatment regimens have been extensively studied in the wider population of patients with advanced NSCLC.[21, 22, 59, 60] However, the available data for the effectiveness of pembrolizumab-based treatment regimens for patients with advanced NSCLC harbouring a BRAF V600 mutation is limited (clinical systematic literature review [SLR] results are detailed in Appendix D.2).

Treatment with pembrolizumab can be associated with adverse events (AEs) that can lead to complications, such as immunotoxicity, infusion-related reactions, or discomfort associated with administration. These AEs can have a detrimental and potentially long term impact to a patient's quality of life.[61, 62] Furthermore, pembrolizumab is administered via intravenous (IV) infusions and therefore requires nursing staff and in-patient hospital visits, which potentially represent an additional burden to patients and the healthcare system; an increased risk of IV cannulation-related infections also exists for patients treated in hospitals.[63]

The availability of an oral treatment option, such as dabrafenib and trametinib, would likely have a positive impact on alleviating capacity issues within the NHS. Receiving treatment with an oral therapy as an alternative to IV therapies is further highlighted as an important treatment preference for NSCLC patients; a recent patient preference survey reported that oral treatment was preferred over IV therapies by the majority (60%) of patients who were surveyed.[24]

Patient advocates have also reported a preference for receiving a targeted treatment option that targets a patient's specific gene mutation, potentially considering the improved survival outcomes observed for patients with other gene mutations. As part of the HTA for dabrafenib and trametinib in Canada, the registered clinicians and patient advocacy group providing input for the submission all emphasised the preference for patients with an identified driver mutation to be treated with targeted therapy upfront as first-line therapy, as opposed to non-targeted treatments.[64]

For these reasons, dabrafenib and trametinib was made available on an interim basis in response to the COVID-19 pandemic, to reduce the burden on the NHS due to patients attending hospital to receive IV treatment, as well as to reduce the risk of immunosuppression associated with standard of care treatments.[20] This highlights the enthusiasm of the clinical community to provide access to dabrafenib and trametinib for patients with advanced NSCLC with a BRAF V600 mutation.[20]

Data provided by NHS England via Blueteq forms suggest that [redacted] of the initiations of dabrafenib and trametinib since August 2020 were in previously untreated advanced NSCLC patients, with the majority of the remaining initiations being in previously treated patients (where most patients received immunotherapy with chemotherapy at the time of first treatment decision [[redacted]%]).[2]

Clinical experts indicated that patients with previously treated NSCLC who received dabrafenib and trametinib likely did so because their BRAF mutation status was not known at the time of first treatment decision, meaning they first received an alternative treatment.[8] Clinicians recognise the BRAF V600 mutation as an actionable driver mutation in NSCLC which is routinely identified in UK clinical practice, and are treating this cohort of patients in line with upfront usage of targeted treatments for previously untreated advanced NSCLC patients with EGFR, ALK or other oncogenic driver mutations.[3, 8]

Positioning of dabrafenib and trametinib within the current clinical pathway of care

A summary of the proposed positioning of dabrafenib plus trametinib in the treatment pathway for patients with advanced NSCLC with a BRAF V600 mutation is presented in Figure 2.

As detailed previously, dabrafenib and trametinib will primarily represent a treatment option for patients with previously untreated advanced NSCLC with a BRAF V600 mutation, in line with usage since August 2020, and the position taken in the treatment pathway for targeted treatments for other NSCLC driver mutations.[2, 65-69]

It is the view of Novartis that the population patients with previously treated advanced NSCLC with a BRAF V600 mutation eligible for dabrafenib and trametinib is likely to diminish in size over time. This decrease is expected as turnaround times for testing improve, and a patient's mutation status is increasingly known at the time of first treatment initiation. Therefore, the previously treated patient population is expected to form a small (but clinically important) minority of patients eligible to receive dabrafenib with trametinib, constituting patients that have faced a delay in receiving their routine biomarker testing (See Table 2).

B.1.4 Equality considerations

The inclusion of the BRAF V600 gene in the 2021/2022 National Genomic Testing Directory indicates BRAF V600 mutation testing is now routine in clinical practice.[4] However, Novartis understand that while the average testing turnaround time is between [redacted] days[5], the uptake and turnaround times for genetic testing are variable across regions of the UK, depending on individual Genomic Laboratory Hubs and testing pathways.[8] As such, equality considerations relating to BRAF V600 mutation testing may be relevant to this appraisal.

B.2 Clinical effectiveness

Clinical effectiveness summary

BRF113928 trial

- The pivotal trial for dabrafenib and trametinib is BRF113928 (NCT01336634), a phase II, multicentre, open-label, single-arm trial that enrolled 36 patients with previously untreated advanced NSCLC with a BRAF V600E mutation (Cohort C), and 57 patients with previously treated advanced NSCLC with a BRAF V600E mutation (Cohort B).[70-72]
- Patients in Cohort C showed a clinically meaningful response to dabrafenib and trametinib, with an overall response rate (ORR) of 63.9% (95% CI: 46.2%, 79.2%). Responses were durable, with a median duration of response (DOR) of 10.2 months (95% CI: 8.3, 15.2).
- At the time of the final data cut-off, once the trial was completed with a minimum of five years follow-up per patient, patients treated with dabrafenib and trametinib experienced a median PFS of 10.8 months (95% CI: 7.0, 14.5) and median OS of 17.3 months (95% CI: 12.3, 40.2), with estimated survival at Month 60 of [redacted]% (95% CI: [redacted]%, [redacted]%).
- Similar results were observed in Cohort B (presented in Appendix M).

Comparative efficacy evidence

- Robust data in the published literature for pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation is limited.
- Novartis have therefore conducted a series of real-world evidence (RWE) studies to provide evidence for pembrolizumab plus chemotherapy for patients with previously untreated advanced NSCLC with a BRAF V600 mutation, including Melosky *et al.* (2021)[73] and the FLATIRON RWE study (2022) (unpublished data).
- Melosky *et al.* (2021) was a RWE study that identified real-world patients with previously untreated advanced NSCLC with a BRAF V600 mutation, receiving either dabrafenib and trametinib, or pembrolizumab plus chemotherapy.[73] The weighted analysis did not report any statistically significant differences between the two treatments.
- As Melosky *et al.* (2021) used RWE for dabrafenib and trametinib rather than clinical trial data (which is considered more robust, with the BRF113928 trial having a minimum of five years' follow-up),[73] Novartis conducted a subsequent RWE study and associated weighted analysis: the FLATIRON RWE study (2022). The study (which is currently unpublished), aimed to compare the outcomes for dabrafenib and trametinib in the BRF113928 trial (Cohort C) to real-world treatment with pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600E mutation.
- The FLATIRON RWE study (2022) weighted analysis did not report any significant differences with respect to PFS or OS between the two treatments. The study was associated with limitations, such as small sample sizes and differences in follow-up.
- Given the results from both Melosky *et al.* (2021) and the FLATIRON RWE study (2022), an assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy was considered to be a reasonable conclusion. UK clinical experts also indicated that an assumption of clinical equivalence was the most reasonable conclusion that could be drawn from the data.[8]

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify clinical evidence of the efficacy and safety of dabrafenib and trametinib and pembrolizumab plus chemotherapy, as well as other treatments for patients with advanced NSCLC with a BRAF V600 mutation. The SLR was initially conducted to be broad in scope and included studies in patients with advanced NSCLC with any BRAF mutation, at any line of therapy, and receiving a range of treatments for NSCLC. All studies identified were subsequently reviewed for relevance: this section focusses on evidence for either dabrafenib and trametinib or pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation. For a full list of studies in the previously untreated and previously treated advanced NSCLC with a BRAF mutation patient populations, see Appendix D.

In total, 28 studies met the broad inclusion criteria of the SLR, of which 9 studies were conducted in patients with previously untreated advanced NSCLC and a BRAF mutation, receiving either dabrafenib and trametinib, or pembrolizumab plus chemotherapy. A summary of these 9 studies is provided in Table 4 below, alongside an assessment of their relevance to this submission.

Dabrafenib and trametinib

Of the 9 potentially relevant studies, 5 studies included data for dabrafenib and trametinib: the pivotal BRF113928 trial,[70-72, 74-76] and 4 observational studies.[77-82] Given the availability of clinical trial data with over 5 years' follow-up for dabrafenib and trametinib from the BRF113928 trial, the observational studies for dabrafenib and trametinib were not considered to represent robust sources of data and were not considered further. The one exception was Melosky *et al.* (2021),[73] which provided real-world evidence for patients with previously untreated advanced NSCLC with a BRAF V600 mutation receiving dabrafenib and trametinib and pembrolizumab plus chemotherapy (as well as other treatments). As such, Melosky *et al.* (2021) provides potentially relevant comparative efficacy evidence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in this submission, and is detailed in Section B.2.2.2 and Section B.2.9.2.

Pembrolizumab plus chemotherapy

To ascertain whether any of the 9 studies identified within the clinical SLR would be suitable for consideration as a source of comparative efficacy evidence for pembrolizumab plus chemotherapy, a feasibility assessment was conducted as follows. Each study was reviewed and only considered further if it met the following criteria:

- Studies with a sample size ≥10 patients, to avoid limitations from very small sample sizes
- Studies reporting PFS and OS Kaplan-Meier data, to allow inclusion in an economic model
- Studies reporting baseline characteristics within the relevant patient population (i.e., patients with a BRAF V600 or V600E mutation), so that the relevant patient populations can be analysed for comparability with the BRF113928 trial
- Studies reporting outcomes separately for patients in the previously untreated advanced NSCLC setting versus those in the previously treated setting

The results of this feasibility assessment are presented in Table 4. Only two studies were identified that provided potentially relevant comparative evidence for pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation: two RWE studies conducted by Novartis, Kanakamedala *et al.* (2020)[83] and Melosky *et al.* (2021).[73] These studies are discussed in more detail in Section B.2.2.2.

Table 4: Overview of studies included in the clinical SLR (for previously untreated patients)

Study ID	Study	Study design	Mutation type	Line of therapy	Treatments received	Sample size for outcomes	PFS KM data (Y/N)	OS KM data (Y/N)	Baseline characteristics for therapy and population of interest (i.e., V600 or V600E)	Reason for no further consideration as comparative efficacy evidence
1	BRF113928[70-72, 74-76]	Open-label, single-arm, multicentre trial	V600E	Previously untreated	Dabrafenib plus trametinib	36	Y	Y	Y	N/A – pivotal trial for dabrafenib and trametinib
2	Tan *et al.* (2019)[84]	Observational, retrospective, single-centre cohort study	BRAF (45% V600E)	Previously untreated	PD1/PD-L1 checkpoint inhibitors[a]	3	N	N	N	PFS and OS KM data not reported
					Chemotherapy and immunotherapy[a]	2	N	N	N	PFS and OS KM data not reported
3	Primary: Auliac *et al.* (2019)[77] Supplementary: Auliac *et al.* (2020)[78]	Observational, retrospective multicentre study	V600E	Previously untreated	Dabrafenib and trametinib	9	Y	Y	Y	Sample size ≤10
4	Primary: Mu *et al.* (2019)[79] Supplementary: Mu *et al.* (2020a)[80] and Mu et al. (2020b)[81]	Observational, retrospective cohort study	V600E	Previously untreated	Dabrafenib and trametinib	5	Y	N	Y	Dabrafenib and trametinib only
				Previously untreated and previously treated	Dabrafenib and trametinib	9	N	N	Y	Dabrafenib and trametinib only
5	Tamminga *et al.* (2019)[82]	Observational, prospective, single-centre cohort study	BRAF mutant	Previously untreated	Dabrafenib and trametinib	1	N	N	N	Sample size ≤10
6	Kanakamedala *et al.* (2020)[83]	Observational study	BRAF mutant	Previously untreated	Pembrolizumab plus platinum-based chemotherapy[a]	NR[b]	Y[b]	Y[b]	Y[b]	Taken forwards for consideration
7	Dawar *et al.* (2021)[85]	Observational retrospective,	V600	Previously untreated	Immuno-checkpoint	NR	N	N	N	Sample size not reported for

Study ID	Study	Study design	Mutation type	Line of therapy	Treatments received	Sample size for outcomes	PFS KM data (Y/N)	OS KM data (Y/N)	Baseline characteristics for therapy and population of interest (i.e., V600 or V600E)	Reason for no further consideration as comparative efficacy evidence
		multicentre study		and previously treated	inhibitors in combination with chemotherapy[a]					outcomes. PFS and OS KM data not reported
8	Melosky *et al.* (2021)[73]	Retrospective database study	V600	Previously untreated	Dabrafenib and trametinib	47.2	Y[b]	Y[b]	Y	Taken forwards for consideration
					Platinum-doublet chemotherapy and pembrolizumab	27.7	Y[b]	Y[b]	Y	Taken forwards for consideration
					Dabrafenib and trametinib	44.4	Y[b]	Y[b]	Y	Taken forwards for consideration
					Pembrolizumab	30.3	Y[b]	Y[b]	Y	Taken forwards for consideration
9	Wang *et al.* (2022)[86]	Retrospective database study	V600E	Previously untreated and previously treated	Chemotherapy plus immune-checkpoint inhibitors[a]	NR	N	N	N	Sample size not reported for outcomes. PFS and OS KM data not reported
					Immune-checkpoint inhibitors[a]	19	N	N	N	PFS and OS KM data not reported

Footnotes: [a]Specific regimens not reported. [b]PFS and OS KM data available to Novartis.
Abbreviations: KM: Kaplan-Meier; NR: not reported; OS: overall survival; PD1: programmed death 1; PD-L1; programmed death-ligand 1; PFS: progression-free survival; TKI: tyrosine kinase inhibitor.

B.2.2 List of relevant clinical effectiveness evidence (previously untreated patients)

B.2.2.1 Dabrafenib and trametinib

The primary clinical evidence for dabrafenib and trametinib is the BRF113928 trial, which was used in support of the marketing authorisation for dabrafenib and trametinib in this indication (Table 5). This was a single-arm trial including adult patients with advanced NSCLC and a BRAF V600E mutation. The BRF113928 trial was initiated in August 2011 and is now complete with a minimum of 5 years of follow-up per patient, with the last patient visit in January 2021.

It should be noted that the trial included patients with a BRAF V600E mutation, while the licence for dabrafenib with trametinib is for patients with a BRAF V600 mutation. BRAF V600E mutations comprise approximately 96% of all BRAF V600 mutations, meaning that the trial evidence can be considered generalisable to the wider licensed population for dabrafenib and trametinib.[32, 39, 87]

Table 5: Relevant clinical trial effectiveness evidence for dabrafenib and trametinib

Study	**BRF113928 (NCT01336634)**		
Study design	An open-label, multi-national, single-arm phase II study with three sequentially enrolled cohorts (Cohort A, Cohort B and Cohort C).		
Population	Adult patients (≥18 years of age) with confirmed stage IV NSCLC with a BRAF V600E mutation: • Disease relapsed or progressed after ≥ 1 prior line of platinum-based chemotherapy (Cohorts A and B) • No prior anti-cancer therapies for metastatic disease (Cohort C)		
Intervention(s)	• Dabrafenib 150 mg twice daily (Cohort A) • Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (Cohorts B and C)		
Comparator(s)	NA – single-arm trial		
Trial supports application for marketing authorisation?	Yes	**Trial used in the economic model?**	Yes
Rationale for use/non-use in the model	As the only clinical trial investigating dabrafenib and trametinib in previously untreated patients NSCLC patients with a BRAF V600 mutation, the trial represents the best source of clinical efficacy data for dabrafenib and trametinib, and therefore forms the base case source of efficacy for dabrafenib and trametinib in the submission and supporting cost-effectiveness analysis		
Reported outcomes specified in the decision problem	**Primary outcomes:** • **ORR** defined as the percentage of patients with PR or CR by IA according to RECIST v1.1[88] **Secondary outcomes:** • **DOR** • **PFS** • **OS**		

Abbreviations: CR: complete response; DOR: duration of response; IA: investigator assessment; NA: not applicable; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RCT: randomised controlled trial; RWE: real-world evidence
Source: BRF113928 Clinical Study Report.[17]

B.2.2.2 Pembrolizumab plus chemotherapy

As detailed above in Table 4, the clinical SLR identified two studies which provided evidence for pembrolizumab plus chemotherapy in previously untreated advanced NSCLC patients with a BRAF V600 mutation which were considered robust enough for further consideration as potential sources of comparative effectiveness evidence. Both studies were publications on distinct RWE studies conducted by Novartis. In addition, a more recent RWE study has been conducted by Novartis that is not yet published. These three studies are detailed below:

Melosky *et al.* (2021):[73] A publication of a RWE study conducted by Novartis, that compared real-world dabrafenib and trametinib versus real-world pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation.

Kanakamedala *et al.* (2020):[83] An earlier, distinct, external control analysis of the BRF113928 trial, which compared data for dabrafenib and trametinib from the BRF113928 trial with real-world pembrolizumab plus chemotherapy. However, in an effort to increase the sample size, this analysis focused on a BRAF-mutant population, including both BRAF V600 patients and other subtypes of the BRAF mutation.

FLATIRON RWE study (2022, unpublished): Since the publication of Kanakamedala *et al.* (2020), an updated data cut for the BRF113928 trial has been released. Novartis have therefore conducted an updated analysis, in line with the methodology used in Kanakamedala *et al.* (2020).[83] This study is termed the FLATIRON RWE study (2022), and is currently unpublished. The FLATIRON RWE study (2022) includes patients with advanced NSCLC and a BRAF V600E mutation. Kanakamedala *et al.* (2020) is therefore outdated, and not considered relevant to this submission.

Melosky *et al.* (2021) and the FLATIRON RWE study (2022) therefore represent the two relevant sources of comparative efficacy evidence for patients with previously untreated advanced NSCLC with a BRAF V600 mutation. These studies are discussed further in Section B.2.9.

Melosky *et al.* (2021) also compared real-world dabrafenib and trametinib to real-world pembrolizumab monotherapy, the results of which are presented in Appendix D.3.1. The FLATIRON RWE study (2022) additionally compared dabrafenib and trametinib to real-world pembrolizumab monotherapy, the results of which are presented in Appendix D.3.2.

As detailed in Section B.1.1, pembrolizumab monotherapy is not considered to represent a relevant comparator in this appraisal, but these results are presented for completeness.

B.2.3 List of relevant clinical effectiveness evidence (previously treated patients)

The BRF113928 trial included evidence for patients with previously treated advanced NSCLC with a BRAF V600E mutation receiving dabrafenib and trametinib (Cohort B), while the FLATIRON RWE study (2022) included a comparison between Cohort B of the BRF113928 trial versus patients with previously treated advanced NSCLC receiving chemotherapy in real-world US clinical practice.

As detailed previously in Section B.1, dabrafenib and trametinib primarily represents a treatment option for patients with previously untreated advanced NSCLC with a BRAF V600 mutation. The

previously treated advanced NSCLC population represents a small (but clinically important) patient population, which is expected to diminish over time as the turnaround times for testing continue to improve, and a patient's mutation status is increasingly known at the time of first treatment decision.

As a result, clinical effectiveness evidence for dabrafenib and trametinib for patients with previously treated advanced NSCLC with a BRAF V600 mutation from Cohort B of the BRF113928 trial is presented is presented in Appendix M, for completeness.

The sample sizes resulting from the comparative efficacy analysis in this population, with just [redacted] patients with previously treated advanced NSCLC with a BRAF V600E mutation receiving chemotherapy in the FLATIRON RWE study (2022) were also not considered large enough to constitute robust comparative efficacy evidence, and [redacted] of these patients received either docetaxel monotherapy or docetaxel plus nintedanib, the two most relevant chemotherapy regimens in UK clinical practice.

Therefore, economic analyses for patients with previously treated advanced NSCLC and a BRAF V600 mutation are not presented within this submission. However, alongside clinical results for Cohort B from the BRF113928 trial presented in Appendix M, comparative efficacy results from the FLATIRON RWE study (2022) between dabrafenib and trametinib and chemotherapy in patients with previously treated advanced NSCLC and a BRAF V600 mutation are presented in Appendix D.3.2.5 for completeness.

B.2.4 Summary of methodology of the relevant clinical effectiveness evidence

B.2.4.1 Dabrafenib and trametinib evidence: BRF113928 trial

The BRF113928 trial was conducted at 71 study sites in 11 countries across the Asia Pacific region, Europe and North America. There were five study sites in the UK, all of which were in England.

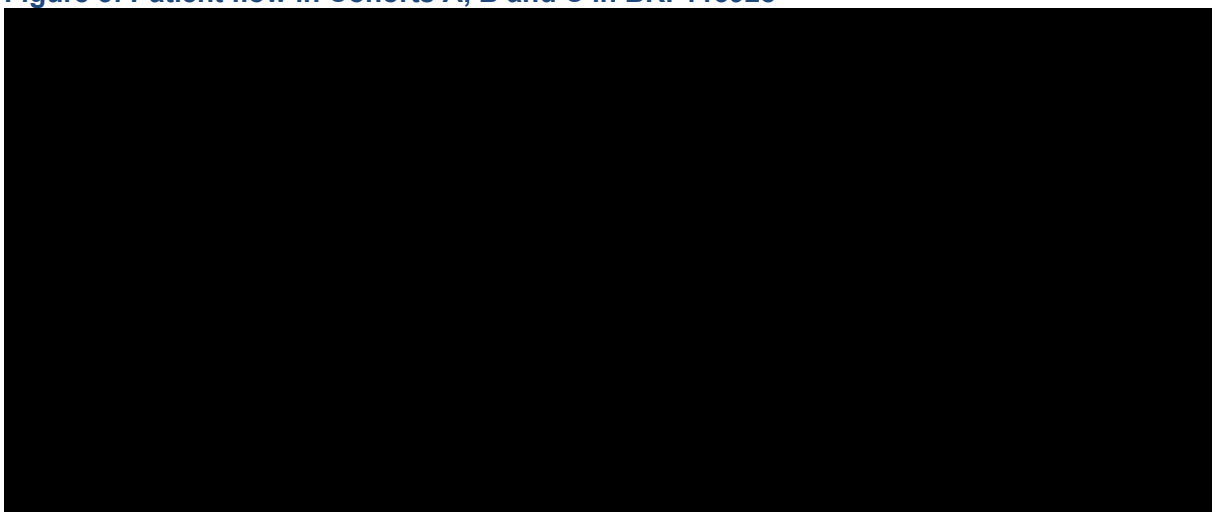
In total the trial enrolled 177 adult patients with confirmed Stage IV NSCLC with a BRAF V600E mutation and consisted of three sequentially enrolled patient cohorts A, B and C. The flow of the 177 enrolled patients through the three trial cohorts is depicted in Figure 3.

Patients in Cohort A received dabrafenib monotherapy 150 mg twice daily. Dabrafenib monotherapy is not licensed for the treatment of advanced NSCLC, and therefore Cohort A is not discussed further in this submission.

Patients in Cohort B had previously treated NSCLC and received dabrafenib and trametinib. As detailed previously, these results are presented for completeness in Appendix M. Patients in Cohort B are also included alongside patients in Cohort C in a combined population used for the analysis of safety outcomes, as safety outcomes for Cohort C alone are not available (Section B.2.10).

Patients in Cohort C had previously untreated NSCLC and received the combination of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily, with results presented in full below.

Figure 3: Patient flow in Cohorts A, B and C in BRF113928



Abbreviations: NSCLC: Non-small cell lung cancer
Source: BRF113928 Clinical Study Report;[89] BRF113928 Clinical Study Report – Updated Analysis.[17]

B.2.4.2 Study objectives

The outcomes measured in the BRF113928 trial are presented in Table 6. The primary objective was to assess overall response rate (ORR). Secondary objectives were to assess duration of response (DOR), progression-free survival (PFS), and OS, and to further characterise the safety, tolerability and pharmacokinetics (PK) of dabrafenib as a single agent (Cohort A) and in combination with trametinib (Cohorts B and C).

Table 6: Outcomes measured in BRF113928

	Outcome	Definition
Primary outcome	**Overall response rate (ORR)**	The percentage of patients with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST v1.1 criteria.[88]
Key secondary outcomes	**Duration of disease (DOR)**	The time from first documented evidence of CR or PR until time of first documented disease progression or death due to any cause.
	Progression-free survival (PFS)	The time between first dose and the earliest date of disease progression or death due to any cause.
	Overall survival (OS)	The time from first dose until death due to any cause.
Other secondary outcomes	**Safety**	Measurements used to evaluate safety included physical and dermatological examinations, ophthalmic examination, vital signs, 12-lead ECGs, echocardiogram, clinical laboratory tests, and AEs.

Abbreviations: AE: adverse event; CR: complete response; DOR: duration of response; ECG: electrocardiogram; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: BRF113928 Clinical Study Report.[17]

Eligibility criteria

Adult (18 years and older) male and female patients with stage IV NSCLC with a BRAF V600E mutation were enrolled into the study. A full list of inclusion and exclusion criteria is presented in Table 7.

Table 7: Eligibility criteria for BRF113928

Inclusion criteria
• Histologically or cytologically-confirmed diagnosis of Stage IV (according to AJCC Staging 7th Edition) NSCLC determined to be BRAF V600E mutation-positive in a CLIA-certified laboratory • Patients in Cohort C were required to have not received prior systemic anti-cancer therapies for metastatic disease (i.e., dabrafenib and trametinib was the first-line treatment for metastatic disease) • Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) V1.1[88] • Women of childbearing potential had to have a negative serum pregnancy test within 14 days before the first dose of study drug and must agree to use effective contraception during the study • Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2[90] • Previously tested for presence of EGFR and ALK mutations in lung cancer tissue confirmed in a CLIA-certified laboratory or equivalent. Patients with concomitant EGFR or ALK mutations were eligible if they had previously received EGFR or ALK inhibitor(s), respectively • Life expectancy of more than three months
Exclusion criteria
• Previous treatment with a BRAF inhibitor or a MEK inhibitor prior to the start of study treatment • Anti-cancer therapy including chemotherapy, radiation therapy, immunotherapy, biologic therapy or major surgery within 14 days prior to the start of study treatment • Use of any investigational anti-cancer drug within 14 days or 5-half-lives (minimum 14 days), prior to the start of study medication • Presence of active gastrointestinal disease or other condition that could interfere significantly with the absorption of drugs • Known Hepatitis B Virus or Hepatitis C Virus infection. Patients with laboratory evidence of the cleared virus infection could be enrolled • History of another malignancy < 3 years prior to starting study treatment or any malignancy with confirmed activating RAS mutation (although some exceptions were permitted) • Patients with brain metastases were excluded if their brain metastases were: ○ Symptomatic or treated (surgery, radiation therapy) but not clinically and radiographically stable three weeks after local therapy (as assessed by contrast enhanced MRI or CT) or were asymptomatic and untreated but > 1 cm in the longest dimension • A history or evidence of cardiovascular risk • Pregnant, or actively breastfeeding females

Abbreviations: AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; CLIA: clinical laboratory improvement amendments; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group performance status EGFR: epidermal growth factor receptor; MEK: mitogen-activated protein kinase kinase; MRI: magnetic resonance imaging; NSCLC: non-small cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: BRF113928 Clinical Study Report.[17]

B.2.4.3 Baseline characteristics

The baseline characteristics of the patients in Cohort C are outlined in Table 8. The median age of enrolled patients was 67 years (range: 44, 91). There were more female than male patients (61% versus 39%, respectively). Most patients (83%) were white. The median time since diagnosis reflects a first-line metastatic disease population (2.05 months). More than half (58%) of patients were former smokers, 14% were current smokers, and 28% never smoked. The median duration of smoking was 30 years. The generalisability of the BRF113928 trial to UK clinical practice is discussed in Section B.2.9.3.2.

Table 8: BRF113928 patient baseline characteristics for Cohort C

Characteristic	Cohort C (N=36)
Age, years	
Mean (SD)	[redacted] ([redacted])
Median (min, max)	67.0 (44, 91)

Characteristic	Cohort C (N=36)
<65 years, n (%)	14 (39)
≥65 years, n (%)	22 (61)
Sex, n (%)	
Female	22 (61)
Male	14 (39)
Race, n (%)	
White	30 (83)
Black or African American	1 (3)
Asian	3 (8)
Other	1 (3)
Missing	1 (3)
Smoking history, n (%)	
Never smoked	10 (28)
Current smoker	5 (14)
Former smoker	21 (58)
No. of years smoked	
n	[redacted]
Median (min, max)	[redacted]
ECOG PS, n (%)	
0	13 (36)
1	22 (61)
2	1 (3)
Histology, n (%)	
Adenocarcinoma	32 (89)
Adenosquamous carcinoma[a]	1 (3)
Adenosquamous carcinoma[b]	1 (3)
Large cell carcinoma	1 (3)
NSCLC not otherwise specified	1 (3)
Stage at screening, n (%)	
IIIA	[redacted]
IV	[redacted]
Time since diagnosis (months)	
n	[redacted]
Median (min, max)	[redacted]
Time since last progression (months)	
n	[redacted]
Median (min, max)	[redacted]

Footnotes: [a] Predominantly adenocarcinoma. [b] Predominantly squamous cell carcinoma.
Abbreviations: ECOG PS: European Cooperative Oncology Group Performance Status; NSCLC: non-small cell lung cancer; SD: standard deviation.
Source: BRF113928 Clinical Study Report;[91] Planchard *et al.* (2021).[72]

B.2.5 Statistical analysis and definitions of analysis sets

Details of the statistical methods and analysis sets used in BRF113928 are provided in Appendix M.1.1.

B.2.6 Quality assessment

Details of the quality assessment of the BRF113928 is provided in Appendix M.1.2.

B.2.7 Clinical effectiveness results

The BRF113928 trial was recently completed, with the last patient visit in 2021. Clinical effectiveness results are presented based on the most recent and complete data cut of the trial (24th February 2021), which includes a minimum of five years' worth of follow-up data for each patient. This extended follow-up, relative to many other trials for patients with advanced cancers, should be considered a key strength of the analyses. Patients had a median follow-up of 16.3 months, which ranged from 0.4 months to 80 months.

B.2.7.1 Overall response rate

As of the final 24th February 2021 data cut-off, a clinically meaningful response rate was observed following treatment with dabrafenib and trametinib, as shown in Table 9.

The proportion of patients with confirmed ORR by IA was 63.9% (95% CI: 46.2, 79.2), including two (6%) patients who had a CR and 21 (58%) patients who had a PR (Table 9). In addition, four (11%) patients had SD, resulting in a DCR of 75.0% (95% CI: 57.8, 87.9). No data for ORR by independent review committee (IRC) evaluation were available for this data cut-off.

Table 9: BRF113928 summary of ORR by IA for Cohort C

Endpoint	Cohort C (N=36)
Best confirmed response, n (%)	
Complete response (CR)	2 (6)
Partial response (PR)	21 (58)
Stable disease (SD)	4 (11)
Progressive disease	5 (14)
Not evaluable (NE)	4 (11)
ORR, n (%)	
CR + PR	23 (63.9)
95% CI	46.2, 79.2
DCR, n (%)	
CR + PR + SD	27 (75.0)
95% CI	57.8, 87.9

Abbreviations: CI: confidence interval; CR: complete response; DCR: disease control rate; IA: investigator assessment; NE: not evaluable; ORR: overall response rate; PR: partial response; SD: stable disease.
Source: BRF113928 Clinical Study Report - Table 11-1.[91]; Planchard *et al*. (2021).[72]

B.2.7.2 Duration of response

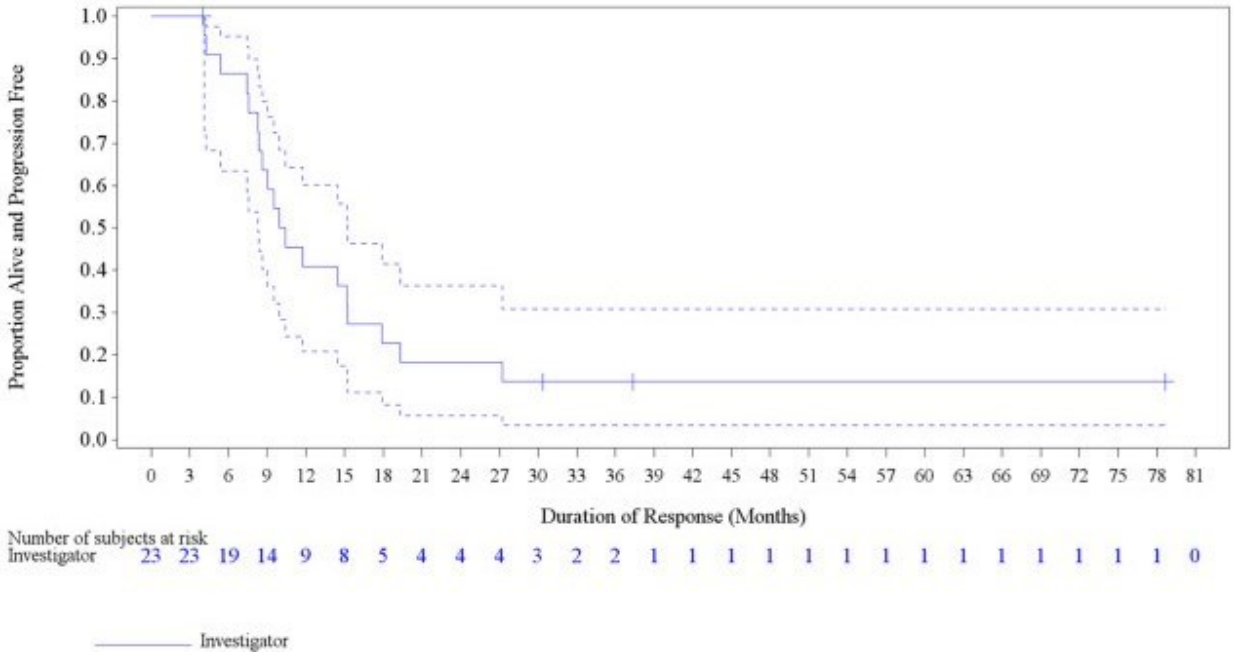
A durable response was observed by IA following treatment with dabrafenib and trametinib at the time of the 24th February 2021 data cut-off. In total, [redacted] ([redacted]%) patients with a confirmed response had subsequently experienced disease progression or death, with an estimated median DOR of 10.2 months (95% CI: 8.3, 15.2) (Table 10; Figure 4).

Table 10: BRF113928 summary of DOR by IA for Cohort C

Endpoint	Cohort C (N=36)
Number of patients with confirmed response, n (%)	
n	[redacted]
Progressed or died (event), %	[redacted]
Censored, follow-up ended	[redacted]
Censored, follow-up ongoing	[redacted]
Estimates for DOR (months)	
Median (95% CI)	10.2 (8.3, 15.2)

Abbreviations: CI: confidence interval; DOR: duration of response; IA: investigator assessment.
Source: BRF113928 Clinical Study Report - Table 11-7;[91] Planchard *et al*. (2021).[72]

Figure 4: BRF113928 KM curve for DOR by IA for Cohort C



Dotted lines indicate 95% CIs
Abbreviations: CI: confidence interval; DOR: duration of response; IA: investigator assessment; KM: Kaplan-Meier.
Source: Planchard *et al*. (2021).[72]

B.2.7.3 Progression-free survival

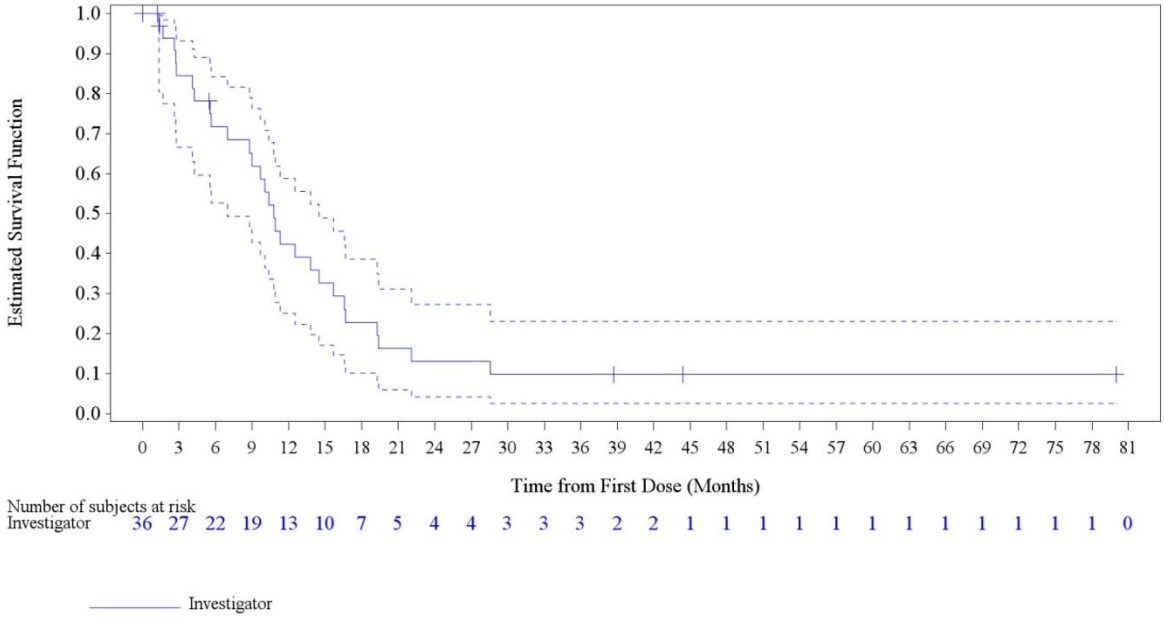
The IA-assessed PFS at the 24th February 2021 data cut-off are shown in Table 11 and Figure 5. Median PFS in patients receiving first-line dabrafenib and trametinib was 10.8 months (95% CI: 7.0, 14.5), with estimated PFS of [redacted]% after 12 months (95% CI: [redacted]%, [redacted]%).

Table 11: BRF113928 summary of PFS by IA for Cohort C

Endpoint	Cohort C (N=36)
Patient status, n (%)	
Progressed or died (event)	[redacted]
Censored, follow-up ended	[redacted]
Estimated PFS, months	
Median (95% CI)	10.8 (7.0, 14.5)
PFS distribution function (95% CI), %	
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

Abbreviations: CI: confidence interval; IA: investigator assessment; PFS: progression-free survival.
Source: Planchard *et al*. (2021);[72] BRF113928 Clinical Study Report: Table 11-4.[91]

Figure 5: BRF113928 KM curve for PFS by IA for Cohort C



Dotted lines indicate 95% CIs
Abbreviations: CI: confidence interval; IA: investigator assessment; KM: Kaplan-Meier; PFS: progression-free survival
Source: Planchard *et al*. (2021).[72]

B.2.7.4 Overall survival

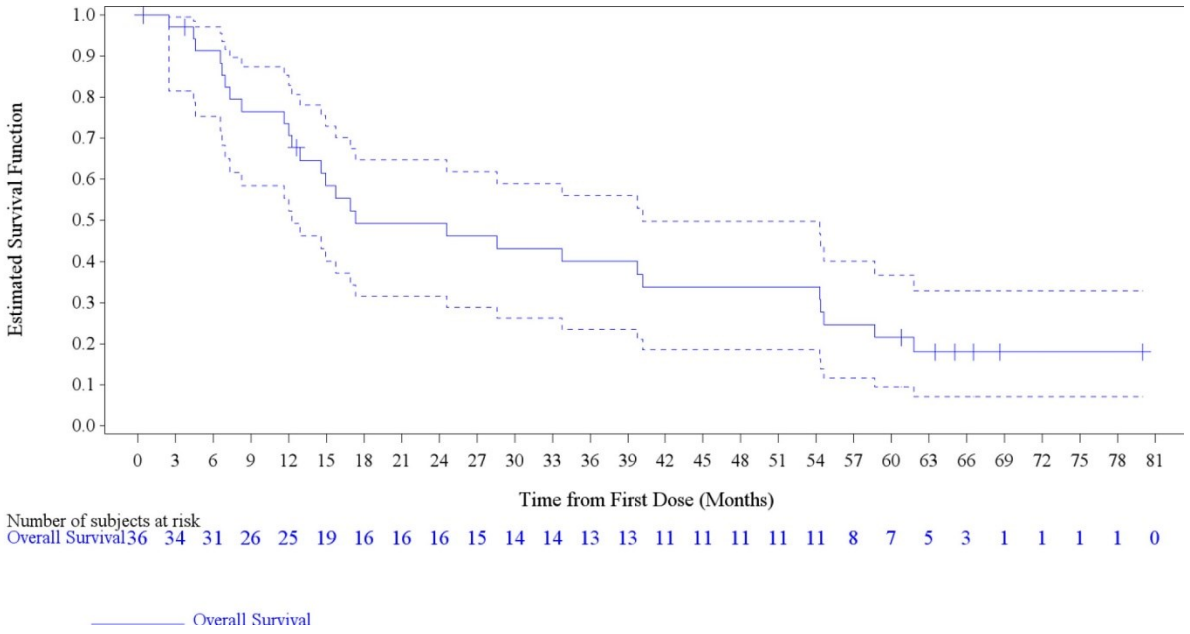
OS data from the 24th February 2021 data cut-off are presented in Figure 6. The estimated median OS of 17.3 months (95% CI; 12.3, 40.2) appears conservative, with an estimated survival at 60 months of [redacted]% (95% CI; [redacted], [redacted]), indicating that dabrafenib and trametinib may have potential long-term survival benefits not reflected by the median OS.

Table 12: BRF113928 summary of OS for Cohort C

Endpoint	Cohort C (N=36)
Patient status, n (%)	
Died (event)	[redacted]
Censored, follow-up ended	[redacted]
Estimated OS, months	
Median (95% CI)	17.3 (12.3, 40.2)
OS distribution function (95% CI), %	
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival.
Source: Planchard *et al*. (2021);[72] BRF113928 Clinical Study Report - Table 11-10.[91]

Figure 6: BRF113928 KM curve for OS in Cohort C



Dotted lines indicate 95% CIs
Abbreviations: CI: confidence interval; KM: Kaplan-Meier; OS: overall survival.
Source: Planchard *et al*. (2021).[72]

B.2.8 Subgroup analysis

No subgroup analyses of the BRF113928 trial were undertaken.

B.2.9 Indirect comparisons

B.2.9.1 Summary of relevant comparative effectiveness evidence

Given the single-arm nature of the BRF113928 trial, randomised comparative evidence between dabrafenib and trametinib and pembrolizumab plus chemotherapy is not available. Given the limited published data in the literature for pembrolizumab plus chemotherapy for patients with previously untreated advanced NSCLC and a BRAF V600 mutation (Section B.2.1), Novartis considered a series of RWE studies to represent the most robust source of evidence for comparative assessment (Section B.2.2.2).

Since routine testing for BRAF mutations in advanced NSCLC patients in the UK was only recently established (2021/2022), it would not be possible to identify patients with a BRAF V600 mutation receiving pembrolizumab plus chemotherapy from UK clinical data sets. Similarly, across Europe, testing for BRAF mutations in advanced NSCLC was only recently recommended by the European Society of Medical Oncology in 2018, following the European marketing authorisation of dabrafenib with trametinib in 2017.[92] However, testing rates and corresponding reimbursement of testing services remains variable across countries, so no further investigation was taken to assess registries in Europe, as identifying patients receiving pembrolizumab plus chemotherapy with a BRAF V600 mutation was considered unlikely.[93]

In contrast, dabrafenib and trametinib has been available in the United States since 2017, so it was assumed that BRAF testing would be available as part routine care. Furthermore, pembrolizumab plus chemotherapy has also been available in the United States since 2018. Novartis therefore conducted a series of RWE studies utilising the FLATIRON Health database to provide evidence for patients with advanced NSCLC with a BRAF mutation treated with current standard of care such as pembrolizumab plus chemotherapy.[73, 83] The FLATIRON Health enhanced data mart (EDM) constitutes a well-documented population of patients observed contemporaneously through electronic health records (EHR) ascertained in the FLATIRON Health network, which comprises over 280 community oncology practices and academic medical centres in the US.[94-97] The FLATIRON database has previously been used to inform comparative efficacy estimates for previous NICE appraisals in NSCLC.[98, 99]

As detailed in Section B.2.2, two RWE studies represent the comparative effectiveness evidence in this submission. Melosky *et al.* (2021)[73] compares real-world dabrafenib and trametinib with real-world pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC harbouring a BRAF V600 mutation. A weighted analysis has been conducted using these data and is presented in Section B.2.9.2

The FLATIRON RWE study (2022), which is an external control analysis of the BRF113928 trial compares data for dabrafenib and trametinib from the BRF113928 trial versus real-world pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600E mutation. The subsequent weighted analysis using these data is considered to represent the primary comparative effectiveness evidence in this submission, as this includes the more robust BRF113928 trial data for dabrafenib and trametinib (versus the real-world data for dabrafenib and trametinib used in Melosky *et al.* [2021]). Full details are provided in Sections B.2.9.3 to B.2.9.3.3 below.

B.2.9.2 Melosky *et al.* (2021)

Melosky *et al.* (2021)[73] was a non-interventional, retrospective observational study comparing real-world outcomes among patients diagnosed with previously untreated advanced NSCLC with a BRAF V600 mutation from the FLATIRON database.

A propensity score methodology was used to closely weight the two populations given differences in prognostic variables at baseline. A summary of the results of this weighted analysis are shown in Table 13.

After weighting, dabrafenib and trametinib resulted in numerically longer OS and similar PFS when compared with pembrolizumab plus chemotherapy (Table 13). However, no significant differences were detected with respect to OS or PFS between the two treatments. UK clinicians indicated that a reasonable conclusion was one of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy, citing the similar trajectory of the Kaplan-Meier curves for both treatments, and the low number of patients at risk after Month 12 (Figure 8 in Appendix D.3.1.4).

Full details of the Melosky *et al.* (2021) study[73] and associated weighted analysis are provided in Appendix D.3.1.

Table 13: Summary of results of Melosky *et al.* (2021)[73]

	Dabrafenib and trametinib	Pembrolizumab plus chemotherapy
Number of patients (unweighted)	48	31
Number of patients (weighted)	47.2	27.7
Results (weighted)		
Median OS, months (95% CI)	29.3 (16.4, NR)	17.7 (10.5, NR)
	p-value = 0.73	
HR (95% CI)	0.83 (0.32, 2.15), p-value = 0.71	
Median PFS, months (95% CI)	9.6 (6.5, 15.2)	10.5 (3.7, NR)
	p-value = 0.51	
HR (95% CI)	1.35 (0.63, 2.92), p-value = 0.44	

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; NR: not reached; OS: overall survival; PFS: progression-free survival.
Source: Melosky *et al.* (2021).[73]

B.2.9.3 FLATIRON RWE study (2022)

B.2.9.3.1. Methodology

In the FLATIRON RWE study (2022) Novartis compared dabrafenib and trametinib data from Cohort C of the BRF113918 trial, to an external control arm of real-world pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600E mutation. The FLATIRON RWE study (2022) and associated weighted analysis represent the pivotal source of comparative efficacy for this submission.

Overview

The FLATIRON RWE study (2022) included:

- Adult patients who received first-line treatment for advanced NSCLC
- Patients with a BRAF V600E mutation in lung cancer tissue
- Patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2
- Patients who had previously received treatment with a BRAF-inhibitor were excluded

Full details of the inclusion/exclusion criteria of the FLATIRON RWE study (2022), and the associated attrition table, are provided in Appendix D.3.2.1.

In total, [redacted] patients with previously untreated advanced NSCLC with a BRAF V600E mutation who received first-line treatment with pembrolizumab plus chemotherapy were identified.

In line with the Kanakamedala *et al.* (2020) study, a separate sensitivity analysis was also conducted as part of the FLATIRON RWE study (2022), where the BRAF V600E inclusion criterion was relaxed to include a wider population of patients with any BRAF mutation (termed the BRAF V600E+ population). While many of the patients in the BRAF V600E+ population are presumed to have a BRAF V600 mutation based on published epidemiology, the data captured in the FLATIRON database does not contain complete data on the subtype of BRAF mutation for all patients. The results for the BRAF V600E+ patient population are presented for completeness in D.3.2.3, but are not considered relevant for this submission.

Statistical methods

It was anticipated that differences in prognostic variables at baseline would exist between patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022) and patients in Cohort C of the BRF113928 trial. Weighting by odds and the inverse probability of treatment weighting (IPTW) was used to account for differences between the trial and real-world cohort. Propensity scoring is recommended by NICE Decision Support Unit guidance (Technical Support Document [TSD] 17) as an approach to minimise the risk of bias when making inferences on treatment effect using observational data.[100]

Propensity scoring was estimated using a logistic regression that modelled treatment assignment as a function of the following baseline characteristics:

- Age at index
- Sex
- ECOG PS
- History of smoking
- Race

Clinical experts consulted as part of this appraisal noted that all these covariates were appropriate.[8] Further details on the prognostic weighting methodology can be found in Appendix D.3.2.5, and assessment of proportional hazards can be found in Appendix N.1.

B.2.9.3.2. Results

Baseline characteristics

Baseline characteristics for the RWE patients who received pembrolizumab plus chemotherapy are shown in Table 14 (unweighted and weighted), and are compared to those in the BRF113928 trial, Cohort C. In the weighted analysis, the baseline characteristics for the adjusted pembrolizumab plus chemotherapy cohort were similar to those in BRF113928 Cohort C with the exception of the sex covariate where there was a slightly lower percentage of females in the real-world cohort.

Table 14: Baseline characteristics for patients in the FLATIRON RWE study (2022) (BRAF V600E mutation)

Characteristic	Dabrafenib plus trametinib (BRF113928 trial, Cohort C)	Pembrolizumab plus chemotherapy (unweighted)	Pembrolizumab plus chemotherapy (weighted)
Age at index date, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
<65 years, n (%)	[redacted]	[redacted]	[redacted]
≥65 years, n (%)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Other Race	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
0-1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Smoking status			
History of smoking	[redacted]	[redacted]	[redacted]
No history of smoking	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; IQR: interquartile range; SD: standard deviation

Generalisability to UK clinical practice

The baseline characteristics of patients in the BRF113928 trial and the FLATIRON RWE study (2022) appear broadly similar to those seen in UK clinical practice, based on the UK Lung Cancer Audit (2022) dataset,[27] which reports data for a cohort of 28,337 patients with NSCLC in the UK, including approximately 44% with advanced NSCLC. For patients with NSCLC, the UK Lung Cancer Audit (2022 data), reported a mean age of 72.8 years of age, 52% were male, and 46% had a history of smoking at time of diagnosis for a NSCLC patient (though it should be noted that a substantial further percentage of patients did not have their smoking status reported in the audit data).

It should be noted that given the rarity of the BRAF V600 mutation, no large UK studies reporting baseline characteristics of patients with advanced NSCLC with a BRAF V600 mutation are available to compare to those of patients in the BRF113928 trial. Whilst the association of certain characteristics with the BRAF V600 mutation has been suggested, there remains no clear

consensus as to the difference in characteristics in patients harbouring a BRAF V600 mutation, as compared to wild-type disease.

Clinicians consulted as part of an advisory board concluded that no clear phenotypes have been identified for the BRAF V600 mutation, and as such considered the baseline characteristics in the BRF113928 trial and the FLATIRON RWE study (2022) to be broadly aligned with the population of patients in UK clinical practice harbouring a BRAF V600 mutation.[8]

Progression-free survival

Table 15 presents a summary of the PFS comparison between dabrafenib and trametinib (BRF113928 trial, Cohort C) versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022]). Kaplan-Meier curves for PFS in the unweighted and weighted comparisons are presented in Figure 7.

The mean follow-up reported for dabrafenib with trametinib was [redacted] months versus [redacted] months for pembrolizumab plus chemotherapy. At the time of the respective data cut-offs, [redacted]% of patients receiving dabrafenib and trametinib had experienced a real-world progression event, versus [redacted] of patients receiving pembrolizumab plus chemotherapy (unweighted). This difference is driven by the limited follow-up in the FLATIRON RWE study (2022) and increased censoring compared to the BRF113928 trial. The HR point estimates between dabrafenib and trametinib and pembrolizumab plus chemotherapy were associated with wide 95% CIs, which included 1 in the weighted analyses.

Beyond the absence of significant differences, it is difficult to draw any robust conclusions from this comparison, as discussed further in Section B.2.9.3.3 to B.2.9.3.5 below.

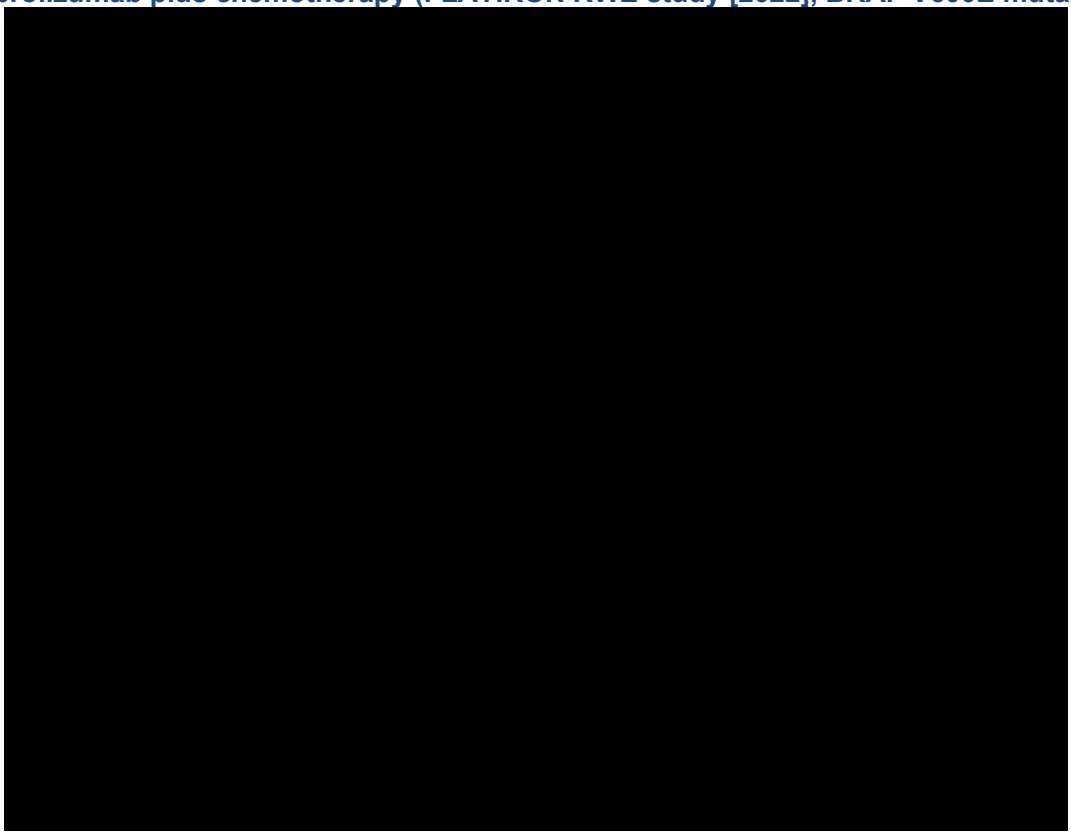
Table 15: PFS for patients receiving dabrafenib and trametinib (BRF113928 Cohort C) and patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022) (BRAF V600E mutation)

	Dabrafenib and trametinib (BRF113928 trial, Cohort C)	Pembrolizumab plus chemotherapy (unweighted)	Pembrolizumab plus chemotherapy (weighted)
Effective sample size			
ESS	36.0	[redacted]	[redacted]
Events			
Total number of patients	36	[redacted]	[redacted]
Total number of real-world progression events (%)	[redacted]	[redacted]	[redacted]
PFS distribution function			
Median PFS, months (95% CI)	10.2 (5.5, 13.8)	[redacted]	[redacted]
PFS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]
PFS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	[redacted]	[redacted]	[redacted]

PFS rate at 24 months (95% CI)	[redacted]	[redacted]	[redacted]
Comparative efficacy			
HR for PFS (95% CI) for dabrafenib and trametinib versus pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]
P-value for hazard ratio	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ESS: effective sample size; HR: hazard ratio; NA: not applicable; PFS: progression-free survival.

Figure 7: PFS KM curves – dabrafenib and trametinib (BRF113928 Cohort C) versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation)



Footnotes: "PD(L)1 + chemo" represents pembrolizumab plus chemotherapy.
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; PD-L1: programmed-death ligand 1

Overall survival

A summary of the OS comparison between dabrafenib and trametinib (Cohort C) versus pembrolizumab plus chemotherapy (FLATIRON RWE Study [2022]) is presented in Table 16, and Kaplan-Meier curves for OS in the unweighted and weighted comparisons are presented in Figure 8. Approximately [redacted]% of patients receiving dabrafenib and trametinib experienced an OS event, compared to [redacted]% in the real-world cohort (differences driven by varied follow-up durations and censoring between the two studies). The HRs between dabrafenib and trametinib and pembrolizumab plus chemotherapy were associated with wide 95% CIs, which included 1, across both the unweighted and weighted analyses.

Beyond the absence of significant differences, it is difficult to draw any robust conclusions from this comparison, as discussed further in Section B.2.9.3.3 to B.2.9.3.5 below.

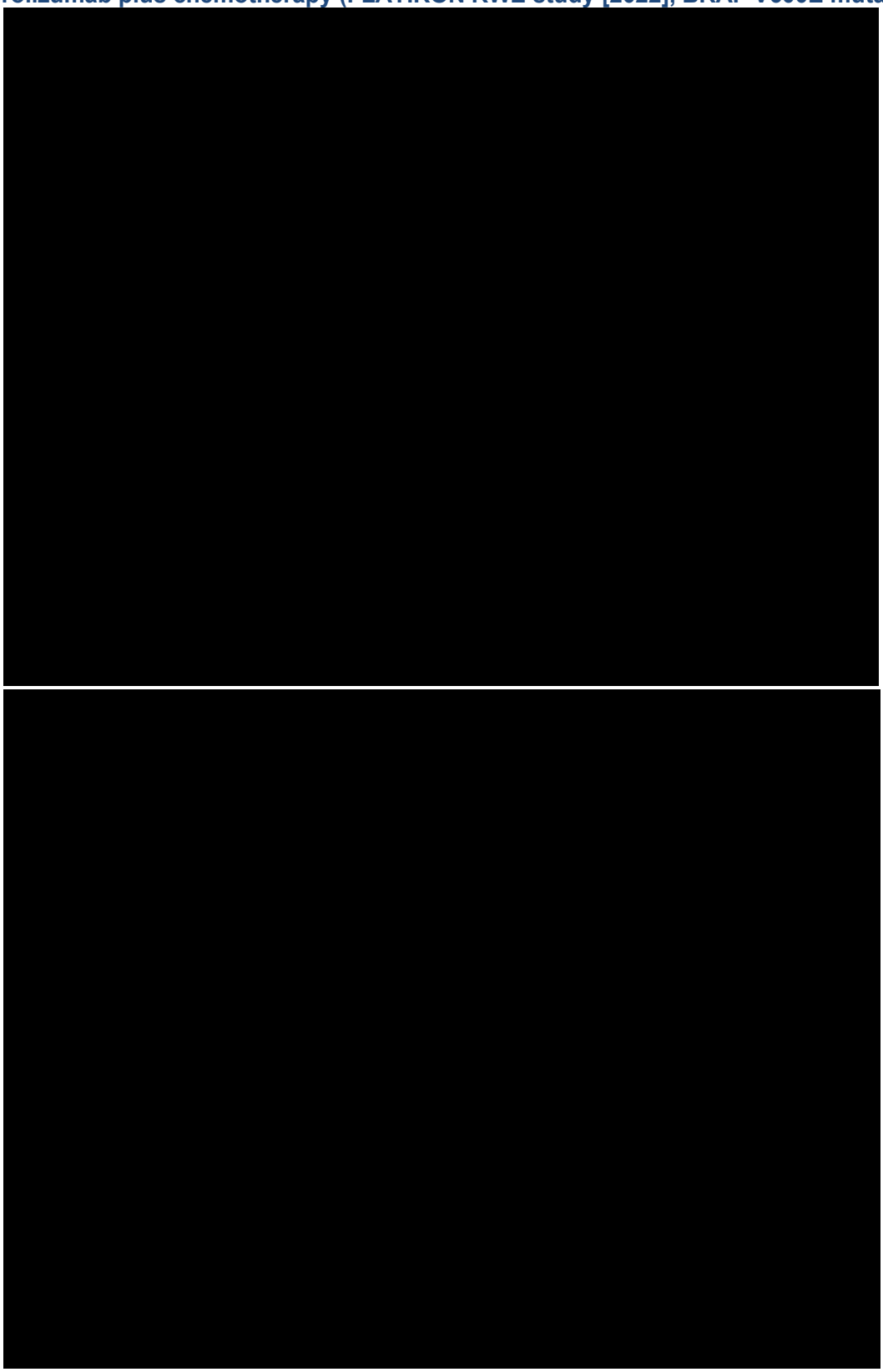
Table 16: OS for patients receiving dabrafenib and trametinib (BRF113928 Cohort C) and patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022) (BRAF V600E mutation)

	Dabrafenib and trametinib (BRF113928 Trial, Cohort C)	Pembrolizumab plus chemotherapy (unweighted)	Pembrolizumab plus chemotherapy (weighted)
Effective sample size			
ESS	36.0	[redacted]	[redacted]
OS events			
Total number of patients	36	[redacted]	[redacted]

Total number of OS events (%)	[redacted]	[redacted]	[redacted]
OS distribution function			
Median OS, months (95% CI)	17.3 (12.3, 40.2)	[redacted]	[redacted]
OS rate at 6 months (95% CI)	[redacted]	[redacted]	[redacted]
OS rate at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
OS rate at 18 months (95% CI)	[redacted]	[redacted]	[redacted]
OS rate at 24 months (95% CI)	[redacted]	[redacted]	[redacted]
Comparative efficacy			
Hazard ratio for OS (95% CI) for dabrafenib and trametinib versus pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]
P-value for hazard ratio	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ESS: effective sample size; NA: not applicable; OS: overall survival.

Figure 8: OS KM curves – dabrafenib and trametinib (BRF113928 Cohort C) versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation)



Footnotes: "PD(L)1 + chemo" represents pembrolizumab plus chemotherapy.
Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: Programmed-Death Ligand 1.

B.2.9.3.3. Clinical interpretation of the FLATIRON RWE study (2022)

UK clinical experts noted that drawing robust conclusions from the results of the updated external control analysis where real-world pembrolizumab plus chemotherapy (from the FLATIRON RWE study [2022]) was compared with dabrafenib and trametinib (Cohort C, BRF113928 trial) was not possible, given the important differences in follow-up between treatments, and the small patient numbers across both datasets.[8]

The results of the FLATIRON RWE (2022) study were presented to four UK clinical experts with experience of using dabrafenib and trametinib in UK clinical practice for patients with previously untreated advanced NSCLC harbouring a BRAF V600 mutation.[8] The clinicians were presented with unweighted and weighted PFS and OS results, and noted the small patient numbers in the weighted analysis.[8]

In the weighted analysis for PFS, the clinicians noted that until approximately Month 9, the Kaplan-Meier curves closely follow each other, suggesting similar outcomes.[8] This is broadly in line with time to discontinuation estimates for the two treatments ([redacted] months for dabrafenib and trametinib and [redacted] months for pembrolizumab plus chemotherapy, Section B.3.3.2.4). In the weighted analysis for OS, the clinicians noted that from Month 0 to Month 12, the results indicated that the Kaplan-Meier curves for both treatments were similar and overlap with one another, after which the estimates become more unstable.

The clinical experts noted that a true difference between the two treatments could not be assessed due to a lack of follow-up in the pembrolizumab plus chemotherapy cohort, and based on the early observations of the weighted analysis, clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy is a reasonable conclusion.[8]

This conclusion is supported by the clinical interpretation of the Melosky *et al.* (2021) results,[73] detailed in Section B.2.9.2, which provide further support that an assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy is reasonable.

B.2.9.3.4. Uncertainties in the FLATIRON RWE study (2022) weighted analysis

There are several uncertainties in the weighted analysis that are considered below:

- The BRF113928 is a complete and mature data set, with a minimum of five-years' worth of follow-up data available for all patients (mean follow-up is [redacted] months), reducing the uncertainty associated with the long-term PFS and OS outcomes for dabrafenib and trametinib. In contrast, the mean duration of follow-up in the FLATIRON RWE study (2022) for pembrolizumab plus chemotherapy was [redacted] months. The differences in follow-up time could also lead to the observed differences in event rates (% of real-world progression events) between the trial and real-world cohorts
- In total, [redacted]% of patients in the pembrolizumab plus chemotherapy cohort initiated treatment in 2021, and were only followed up for 12 months or less (with a data cut-off date of 31st January 2022). As a result of these patients in particular, the censoring rate was much higher in the real-world cohort during the first 12 months, compared to the BRF113928 trial. This limited follow-up, and the resulting censoring, could lead to overestimation of the HR point estimates in favour of pembrolizumab plus chemotherapy

- The overall effective sample size was [redacted] for pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022) after weighting, (compared to [redacted] in the unweighted analysis). The reduction in sample size means that greater weights are being placed on the outcomes for a select few patients, meaning that methods were used to minimise bias that led to lower effective sample size
- A small number of patients in the FLATIRON RWE study 2022 (N=[redacted]) had an unknown ECOG PS; it was therefore assumed that these patients had an ECOG PS equal to 1
- There were marked differences in how PFS was defined in the FLATIRON RWE study (2022) versus the BRF113928 trial. For instance, in the BRF113928 trial, PFS was evaluated based RECIST v1.1 criteria to determine disease progression, based on specific assessment timepoints prospectively outlined in the study protocol, and this adds to the uncertainty.[88]

B.2.9.3.5. Conclusions

An assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy was assumed based on the clinical interpretation of the FLATIRON RWE 2022 results.

B.2.10 Adverse reactions: BRF113928 trial

The assessment of safety for dabrafenib and trametinib was a secondary objective of the BRF113928 trial. No safety data were collected for the relevant comparators in the FLATIRON RWE (2022) study.

Safety data from the latest data cut-off of the BRF113928 trial are presented within this section. All patients who received dabrafenib and trametinib in the BRF113928 trial, in either the previously untreated (Cohort C) or previously treated (Cohort B), were combined for the analysis of safety outcomes; safety outcomes for Cohort C alone are not available.

B.2.10.1 Overview of adverse events

An overview of the AEs experienced by all patients in the combined safety population of the BRF113928 trial (N=93) at the 24th February 2021 data cut-off is presented in Table 17. Overall, the safety profile of dabrafenib and trametinib in patients with previously untreated advanced NSCLC with a BRAF V600 mutation can be considered manageable.

Table 17: BRF113928 summary of AEs (combined safety population)

Adverse event, n (%)	Combined safety population (N=93)
Any AE	92 (99)
AEs related to study treatment	[redacted]
AEs leading to permanent discontinuation of study treatment	[redacted]
AEs leading to dose reduction	[redacted]
AEs leading to dose interruption	[redacted]
AEs leading to dose escalation	[redacted]
Any SAE	[redacted]
SAEs related to study treatment	[redacted]

Adverse event, n (%)	Combined safety population (N=93)
Fatal SAEs	[redacted]
Fatal SAEs related to study treatment	[redacted]

Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: BRF113928 Clinical Study Report - Table 12-5;[91] Planchard *et al*. (2021).[72]

B.2.10.2 Adverse events leading to treatment discontinuation

An overview of AEs leading to treatment discontinuation for all patients in the combined safety population in the BRF113928 trial (N=93) at the 24th February 2021 data cut-off are presented in Table 18.

In total, [redacted] patients ([redacted]) had experienced at least one AE leading to permanent discontinuation of study treatment. Overall, [redacted] patients experienced a grade 3/4 AE that led to treatment discontinuation, and [redacted] patients ([redacted]) experienced a grade 5 AE that led to treatment discontinuation.

Table 18: BRF113928 summary of AEs (≥1% in total) leading to treatment discontinuation by maximum grade for all patients (combined safety population)

AE, n (%)	Combined safety population (N=93)						
	Maximum grade						
	1	2	3	4	3 & 4	5	Total
Any event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event.
Source: BRF113928 Clinical Study Report - Table 12-14.[91]

Dose reductions

Overall, in the combined safety population (N=93), [redacted] patients ([redacted]) experienced an AE resulting in dose reduction of treatment; of those, [redacted] patients ([redacted]) experienced a grade 3/4 AE resulting in dose reduction. The most frequently occurring AEs leading to dose reduction were [redacted] which occurred in [redacted] patients ([redacted]), followed by [redacted], [redacted] and [redacted] in [redacted] patients ([redacted]) each.[91]

Dose interruptions

Overall, in the combined safety population (N=93), [redacted] patients ([redacted]) experienced an AE resulting in dose interruption of treatment; of those, [redacted] patients ([redacted]) had a grade 3/4 AE, and [redacted] patients ([redacted]) had a grade 5 AE that led to dose interruption. The most frequently occurring AEs leading to dose interruption were [redacted] which occurred in [redacted] patients ([redacted]), followed by [redacted] in [redacted] patients ([redacted]), and [redacted] in [redacted] patients ([redacted]).[91]

B.2.10.3 Adverse events by preferred term for all patients

A breakdown of AEs by preferred term for all patients in the combined safety population BRF113928 trial (N=93) at the 24th February 2021 data cut-off are presented in Table 19.

Overall, 92 patients (99%) experienced at least one AE, the majority of events were classed as grade 3/4 (66%). Only eight patients in the total combined safety population experienced an AE of this maximum grade severity (grade 5).

The most frequently occurring AE was pyrexia, which was experienced in 52/93 (56%) of patients; most of these events were grade 2 (26%) and grade 1 (24%) in severity. Beyond pyrexia, the most frequently occurring AEs were nausea (47/93 [51%]), vomiting (38/93 [41%]) and dry skin (36/93 [39%]). Of these, the majority of events were either grade 1 or grade 2.

Table 19: BRF113928 summary of AEs by preferred term for all patients (combined safety population)

AE, n (%)	Combined safety population (N=93)							
	Maximum grade							
	1	2	3	4	3 & 4	5	Unknown	Total
Any event	6 (6)	17 (18)	52 (56)	9 (10)	61 (66)	8 (9)	0	92 (99)
Pyrexia	22 (24)	24 (26)	6 (6)	0	6 (6)	0	0	52 (56)
Nausea	25 (27)	22 (24)	0	0	0	0	0	47 (51)
Vomiting	25 (27)	9 (10)	3 (3)	0	3 (3)	0	1 (1)	38 (41)
Dry skin	32 (34)	3 (3)	1 (1)	0	1 (1)	0	0	36 (39)
Oedema peripheral	32 (34)	3 (3)	0	0	0	0	0	35 (38)
Diarrhoea	24 (26)	8 (9)	2 (2)	0	2 (2)	0	0	34 (37)
Decreased appetite	18 (19)	13 (14)	0	0	0	0	0	31 (33)
Cough	23 (25)	6 (6)	0	0	0	0	0	29 (31)
Asthenia	13 (14)	10 (11)	4 (4)	0	4 (4)	0	0	27 (29)
Fatigue	12 (13)	12 (13)	3 (3)	0	3 (3)	0	0	27 (29)
Rash	22 (24)	3 (3)	2 (2)	0	2 (2)	0	0	27 (29)
Dyspnoea	14 (15)	5 (5)	7 (8)	0	7 (8)	0	0	26 (28)
Arthralgia	20 (22)	4 (4)	1 (1)	0	1 (1)	0	0	25 (27)
Chills	17 (18)	8 (9)	0	0	0	0	0	25 (27)
Headache	16 (17)	2 (2)	1 (1)	0	1 (1)	0	0	19 (20)
Anaemia	6 (6)	7 (8)	4 (4)	1 (1)	5 (5)	0	0	18 (19)
Weight decreased	14 (15)	3 (3)	1 (1)	0	1 (1)	0	0	18 (19)
Back pain	10 (11)	4 (4)	2 (2)	1 (1)	3 (3)	0	0	17 (18)
Constipation	15 (16)	2 (2)	0	0	0	0	0	17 (18)
Dizziness	15 (16)	2 (2)	0	0	0	0	0	17 (18)
Pruritus	10 (11)	3 (3)	2 (2)	0	2 (2)	0	0	15 (16)
Hypotension	7 (8)	3 (3)	3 (3)	0	3 (3)	1 (1)	0	14 (15)
Nasopharyngitis	13 (14)	1 (1)	0	0	0	0	0	14 (15)
Abdominal pain	8 (9)	4 (4)	1 (1)	0	1 (1)	0	0	13 (14)
Blood alkaline phosphatase increased	4 (4)	8 (9)	1 (1)	0	1 (1)	0	0	13 (14)

AE, n (%)	Combined safety population (N=93)							
	Maximum grade							
	1	2	3	4	3 & 4	5	Unknown	Total
Hyponatraemia	4 (4)	0	8 (9)	1 (1)	9 (10)	0	0	13 (14)
Neutropenia	2 (2)	4 (4)	7 (8)	0	7 (8)	0	0	13 (14)
Pneumonia	6 (6)	6 (6)	0	0	0	1 (1)	0	13 (14)
Aspartate aminotransferase increased	7 (8)	2 (2)	3 (3)	0	3 (3)	0	0	12 (13)
Erythema	12 (13)	0	0	0	0	0	0	12 (13)
Muscle spasms	12 (13)	0	0	0	0	0	0	12 (13)
Urinary tract infection	5 (5)	7 (8)	0	0	0	0	0	12 (13)
Alanine aminotransferase increased	4 (4)	1 (1)	6 (6)	0	6 (6)	0	0	11 (12)
Myalgia	9 (10)	2 (2)	0	0	0	0	0	11 (12)
Weight increased	4 (4)	4 (4)	3 (3)	0	3 (3)	0	0	11 (12)
Hypertension	0	1 (1)	9 (10)	0	9 (10)	0	0	10 (11)
Pain in extremity	7 (8)	2 (2)	1 (1)	0	1 (1)	0	0	10 (11)
Rhinitis	10 (11)	0	0	0	0	0	0	10 (11)

Abbreviations: AE: adverse event.
Source: Planchard *et al*. (2021).[72]

B.2.10.4 Serious adverse events

The overview of SAEs occurring in all patients in the combined safety population of the BRF113928 trial (N=93) at the 24th February 2021 data cut-off are presented Table 20.

Overall, [redacted] patients ([redacted]) experienced at least one SAE, where the [redacted] of events were pyrexia ([redacted] patients; [redacted]). [redacted] patients ([redacted]) experienced a grade 5 SAE, including [redacted] patients who experienced respiratory stress.

Table 20: BRF113928 summary of SAEs for all patients (combined safety population)

SAE, n (%)	Combined safety population (N=93)						
	Maximum grade						
	1	2	3	4	3 & 4	5	Total
Any event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SAE, n (%)	Combined safety population (N=93)						
	Maximum grade						
	1	2	3	4	3 & 4	5	Total
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase Increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inflammation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung neoplasm malignant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tubulointerstitial nephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SAE: serious adverse event.
Source: BRF113928 Clinical Study Report - Table 12-13.[91]

B.2.10.5 Deaths

An overview of the deaths that occurred within the combined safety population in the BRF113928 trial (N=93) at the 24th February 2021 data cut-off are presented in Table 21.

A total of [redacted] ([redacted]) patients died whilst participating in the trial; however, [redacted] of these patients died due to an SAE that was likely to be related to study treatment. The [redacted] of deaths ([redacted]) were due to the study indication (i.e., advanced NSCLC) and [redacted] patients ([redacted]) died due to reasons other than the study indication (stroke, retroperitoneal bleed, pulmonary infection, respiratory and cardiac arrest, clozapine intoxication, myocardial infarction, euthanasia, subarachnoid

haemorrhage).

Table 21: BRF113928 summary of deaths for all patients (combined safety population)

Event, n (%)	Combined safety population (N=93)
Patient status	
Dead	[redacted]
Alive at last contact, follow-up ended	[redacted]
Alive at start of crossover	[redacted]
Primary cause of death	
Disease under study	[redacted]
SAE possibly related to study treatment	[redacted]
Other	[redacted]
Time to death from first dose	
≤30 days	[redacted]
>30 days	[redacted]
Time to death from last dose	
≤30 days	[redacted]
>30 days	[redacted]

Abbreviations: SAE: serious adverse event.
Source: BRF113928 Clinical Study Report - Table 12-11.[91]

B.2.10.6 Safety summary

In summary, the safety profile of dabrafenib and trametinib was consistent with that reported for patients treated with dabrafenib and trametinib in melanoma, with no new safety signals identified.[72]

In line with the safety profile for dabrafenib and trametinib in melanoma, the most frequently observed AE was pyrexia (56%), which led to a dose reduction in 11 patients (12%) and treatment withdrawal in two patients (2%).[72] Within the trial, antipyretics were given to control fever, with oral corticosteroids recommended in instances in which antipyretics were insufficient.

For pyrexia with a temperature greater than or equal to 38.5°C or a complication (any temperature with dehydration, hypotension, or renal insufficiency), dabrafenib was paused and trametinib continued until resolution of pyrexia, and then dabrafenib was restarted at a lower dose. For less severe pyrexia (temperature less than 38.5°C with no associated symptoms), dabrafenib was withheld until resolution of pyrexia and then resumed at the same dose.

It should be noted that an updated and simplified protocol (compared to the above) for the management of pyrexia following treatment with dabrafenib and trametinib has been developed since the BRF113928 trial. This new management protocol allows both dabrafenib and trametinib to be interrupted if a patient's temperature is ≥38.0°C. In case of recurrence, treatment can also be interrupted at the first symptom of pyrexia; both treatments can be restarted at the same dose level if patients are symptom free for ≥24 hours. This new algorithm appears to reduce the incidence of severe pyrexia outcomes, enabling patients to manage pyrexia at home, and helping an increased percentage of patients to remain on treatment compared to the BRF113928 trial. This protocol is now within the SmPCs for dabrafenib and trametinib, and represents guidance

for all pyrexia management, regardless of indication.[101, 102]

Finally, most grade 3/4 AEs were managed through dose modification, thereby mitigating the risk of unacceptable toxicity. The overall safety profile of dabrafenib and trametinib is therefore considered to be manageable with appropriate clinical protocols, supported by a wealth of experience amongst the melanoma clinical community.

B.2.11 Ongoing studies

No other studies of dabrafenib and trametinib in NSCLC are ongoing.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principle findings from the clinical evidence base

The comparison of the BRF113928 trial and the FLATIRON RWE study (2022) did not detect any significant differences with respect to PFS and OS between dabrafenib and trametinib and pembrolizumab plus chemotherapy. As such, and as detailed in Section B.2.9, UK clinical experts indicated that an assumption of clinical equivalence between the two treatments would be a reasonable conclusion, based on the early observations between the two treatments; longer-term estimates of pembrolizumab plus chemotherapy efficacy are associated with uncertainty, due to limited follow-up and high levels of censoring.

This conclusion was further supported by the clinical interpretation of the Melosky *et al.* (2021) data,[73] which compared real-world dabrafenib and trametinib with real-world pembrolizumab plus chemotherapy; again, a similar set of limitations were encountered with respect to limited follow-up and small patient numbers.

B.2.12.2 Strengths and limitations of the clinical evidence base

BRF113928 trial

Strengths

BRF113928 represents the only clinical trial investigating the efficacy and safety of dabrafenib and trametinib, and therefore the best clinical trial evidence for its efficacy and safety. The trial is completed, with a minimum of 5 years of follow-up per patient, and therefore represents a mature dataset. As such, this should be considered a key strength, and limits the uncertainty surrounding the long-term outcomes for dabrafenib and trametinib.

The trial assessed the survival outcomes of most relevance to the oncology setting, namely OS and PFS, with ORR and DOR providing additional key evidence for the anti-tumour activity of dabrafenib and trametinib. This response data benefited from being assessed by IA throughout the follow-up period, in addition to IRC in the 28th April 2017. IRC ORR data were in strong concordance with the IA assessment, providing greater confidence in the response data.

Limitations

Inclusion of a comparator or placebo arm was not considered for the BRF113928 trial as an RCT would require large sample sizes and an extended period of time to be adequately powered, something that is less feasible with a rare genetic mutation with a high unmet need, as is the

case for patients with advanced NSCLC with a BRAF V600 mutation.

FLATIRON RWE study (2022)

Strengths

There is very limited evidence for pembrolizumab plus chemotherapy in patients with advanced NSCLC with a BRAF V600 mutation in the published literature, and the quality of the evidence is hindered as there is a lack of follow-up for these patients.

The FLATIRON RWE study (2022) mitigates the limitations of the published literature, providing evidence for pembrolizumab plus chemotherapy in the patient population of relevance to this submission. The availability of individual patient data from the FLATIRON RWE study (2022) is a further advantage, facilitating the conduct of a more robust weighted analysis using propensity score weighting.

Limitations

The FLATIRON RWE study (2022) only identified [redacted] patients with previously untreated advanced NSCLC with a BRAF V600E mutation treated with pembrolizumab plus chemotherapy. One key factor in this is likely to be that patients have been able to access dabrafenib and trametinib in US clinical practice since 2017, and given the increasingly preferential use of targeted therapies for patients with oncogenic driver mutations, it is likely that only a minority of patients in the US with previously untreated advanced NSCLC would receive pembrolizumab plus chemotherapy.

Additionally, given the recent introduction of pembrolizumab plus chemotherapy, the majority of the patients in the FLATIRON RWE study (2022) receiving pembrolizumab plus chemotherapy were only recruited in 2019 or later, introducing further uncertainty in the long-term estimates of survival, given the limited follow-up for this study.

Summary

The clinical effectiveness evidence presented within this submission is associated with uncertainty, due to the small sample sizes and limited follow-up for the relevant comparator pembrolizumab plus chemotherapy that impact the ability to draw robust conclusions for the updated external control analysis.

The results presented in the sections above aim to mitigate these limitations, but uncertainty remains given the available data sets for patients with advanced NSCLC harbouring a BRAF V600 mutation. Nevertheless, the clinical interpretation of the results of the updated external control analysis (FLATIRON RWE study [2022]), support a reasonable assumption that dabrafenib and trametinib are likely to be clinically equivalent to pembrolizumab plus chemotherapy in terms of PFS and OS in patients with previously untreated advanced NSCLC with a BRAF V600 mutation.[8]

As such, and as detailed further in Section B.3, it was considered most appropriate to consider an assumption of equal efficacy between dabrafenib and trametinib versus pembrolizumab plus chemotherapy in the base case economic analysis, given the limitations associated with the FLATIRON RWE study (2022).

B.3 Cost effectiveness

Cost effectiveness summary

- A *de novo* cost-effectiveness model was developed in Microsoft Excel to estimate the cost-effectiveness of dabrafenib and trametinib versus pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation. The model was a partitioned survival model, with three health states of PFS, PD and death.
- Clinical efficacy data (PFS and OS) for dabrafenib and trametinib were based on the pivotal BRF113928 trial.
- As detailed in Section B.2.9.2 and Section B.2.9.3, comparisons between dabrafenib and trametinib and pembrolizumab plus chemotherapy in Melosky *et al*. (2021),[73] and between the BRF113928 trial and the FLATIRON RWE study (2022), did not detect any significant differences between the two treatments with respect to PFS or OS. Given this, and that using data from the FLATIRON RWE study (2022) led to clinically implausible estimates, PFS and OS for pembrolizumab plus chemotherapy were set to be equivalent to dabrafenib and trametinib in the base case economic analysis. This assumption of clinical equivalence was validated by UK clinical experts.[8]
- In the absence of utility data collected in the BRF113928 trial, health state utility values, AE disutility and duration estimates were sourced from relevant published literature. Costs included drug acquisition and drug administration costs, subsequent treatment costs, AE costs, monitoring and follow-up costs, and end-of-life costs.
- In the base case economic analysis, dabrafenib and trametinib (at current PAS price) was associated with cost savings of [redacted], and [redacted] more quality-adjusted life years (QALYs) versus pembrolizumab plus chemotherapy (at list price), meaning that dabrafenib and trametinib dominated pembrolizumab plus chemotherapy.
- [redacted], alongside assumed discounts for pembrolizumab and subsequent treatments. These analyses show dabrafenib and trametinib are associated [redacted] versus pembrolizumab plus chemotherapy.
- Deterministic and probabilistic sensitivity analyses (DSA/PSA) demonstrated the base case results were robust to uncertainty. With dabrafenib and trametinib at PAS price, versus pembrolizumab plus chemotherapy (at list price), the PSA showed that dabrafenib and trametinib had a [redacted]% probability of being cost-effective versus pembrolizumab plus chemotherapy at both the £20,000 and £30,000 willingness-to-pay (WTP) thresholds. The main drivers of the base case economic analysis were differences in quality of life between the two treatments.
- Scenario analyses were conducted to assess the appropriateness of the base case economic analysis assumptions, and across all scenarios, dabrafenib and trametinib was associated with a positive QALY gain and was dominant versus pembrolizumab plus chemotherapy.

- The NHS is under significant and increasing capacity constraints brought on by COVID-19 pandemic, and the administrative burden associated with the management of immunotherapy IV regimens. Dabrafenib and trametinib represents an appropriate use of NHS resources and provides patients with the opportunity to receive an orally available, targeted treatment early on within their treatment course, in line with other advanced NSCLC patients with oncogenic driver mutations.

B.3.1 Published cost-effectiveness studies

A series of economic SLRs were conducted on 10th May 2021 to identify relevant economic evidence in advanced NSCLC with a BRAF mutation by searching for published evidence on cost-effectiveness analyses, utility data and cost and resource use data as per NICE guidance.

The methodology of all three economic SLRs is presented in Appendix G.1 (with results of the economic evaluations SLR presented in Appendix G.3, the utility data SLR presented in Appendix H.3, and the cost and resource use data SLR presented in Appendix I.3). No relevant records relating to advanced NSCLC with a BRAF mutation were identified in the SLR.

B.3.2 Economic analysis

Since no prior published economic evaluations in patients with advanced NSCLC with a BRAF mutation were identified in the economic SLR, a *de novo* economic model was developed to assess the cost-effectiveness of dabrafenib with trametinib versus pembrolizumab plus chemotherapy for patients with previously untreated advanced NSCLC with a BRAF V600 mutation.

As discussed in Section B.2, an assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in terms of PFS and OS was assumed to be reasonable given the uncertainties associated with the updated external control analysis of the BRF113928 trial (FLATIRON RWE study [2022]). This assumption was therefore adopted within the base case economic analysis and was validated by UK clinical experts.[8] As described in Section B.3.3.1, alternative approaches using the FLATIRON RWE study (2022) data directly within the economic model were not plausible, when comparing the predicted survival outcomes for pembrolizumab plus chemotherapy with external sources.

Based on the assumption of equivalence for PFS and OS, the economic model does not calculate any differences in survival outcomes (life years [LYs]) between the two treatments. Any difference in QALYs is driven by the disutility associated with AEs and the administration of treatments via IV infusion. Time on treatment (ToT) and drug acquisition costs are still calculated separately for the two treatments, and cost differences are also calculated with respect to drug administration costs, subsequent treatment costs, and AE costs, as detailed in Section B.3.5.

The remaining sections below outline the approach for selecting the PFS and OS extrapolations for dabrafenib with trametinib based on data from the BRF113928 trial. Appendix N details the extrapolations for pembrolizumab plus chemotherapy (based on the weighted analysis of the FLATIRON RWE study [2022]) for completeness.

B.3.2.1 Model structure

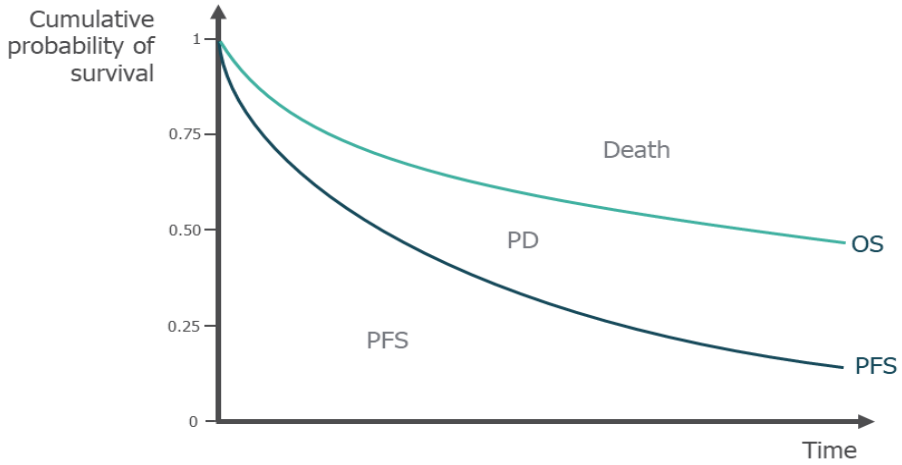
In line with the NICE reference case, the economic analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in the UK and included direct medical costs over a lifetime horizon.[103] The economic model constructed was a partitioned survival model (PSM) consisting of 3 health states (PFS, progressed disease [PD], and death).

A PSM was chosen primarily because of the maturity of the data available for dabrafenib with trametinib, where the BRF113928 trial provides a minimum of 5-years of follow-up data for each patient. At the time of trial completion, the data were mature; [redacted]% of patients within the BRF113928 trial experienced an event (progression or death) and the remaining patients ([redacted]%) were censored with follow-up ended, at the time of the final data cut-off (24th February 2021) (see Table 11).

Where mature data are available, extrapolations of PFS and OS KM curves are associated with less uncertainty and therefore render the PSM a more appropriate approach to consider. Secondly, advanced NSCLC is a progressive disease that, given patients are in the later stages of disease, typically follows a natural course of disease progression and ultimately death. As such it was not considered necessary for other additional health states (and therefore additional complexity) to be modelled, and so a PSM with three health states was considered appropriate. The use of a PSM model structure is consistent with all of the recent NICE appraisals in advanced NSCLC.[6, 7, 22, 98, 99, 104-108] As such, a PSM model was considered the most appropriate model structure for this submission.

Within the model, a cohort of patients on each treatment enter the model in the PFS health state and either remain in this health state, transition to the PD state and then die, or die without entering the PD state. KM OS and PFS data for dabrafenib and trametinib from the BRF113928 trial were used to determine the occupancy of the three health states within the economic model. These data were extrapolated beyond the recorded study period using statistical models, displayed with smooth curves, as displayed in diagrammatic form in Figure 9.

Figure 9: Partitioned-survival model with three health states



Abbreviations: OS: overall survival; PFS: progression-free survival.

B.3.2.2 Key features of the economic analysis

An overview of the key features of the base case economic analysis is provided below in Table 22, and described in more detail in the following sections.

Table 22: Key features of the economic analysis

Factor	Chosen values	Justification
Patient Population	Adult patients with previously untreated advanced NSCLC with a BRAF V600 mutation	Dabrafenib and trametinib will primarily represent a treatment for patients with previously untreated advanced NSCLC (Section B.1.1). Patients with previously treated advanced NSCLC with a BRAF V600 mutation represent a small (but clinically important) population that is expected to diminish over time. As such, clinical effectiveness data for dabrafenib and trametinib in this patient population is presented in Appendix M. However, generating a reliable economic analysis for this population was not considered to be feasible, due to a number of limitations: • Patients in Cohort B of the BRF113928 trial received chemotherapy prior to dabrafenib and trametinib. This does not reflect current UK clinical practice, where any patients who experienced testing delays would typically receive pembrolizumab plus chemotherapy prior to dabrafenib and trametinib • The sample size of patients with previously treated advanced NSCLC with a BRAF V600E mutation in the FLATIRON RWE study (2022) was extremely small (N=[redacted]) • Patients in the FLATIRON RWE study (2022) receiving chemotherapy did not receive regimens aligned with UK clinical practice – [redacted] of the patients received either docetaxel monotherapy, or docetaxel plus nintedanib, which are the two most commonly used chemotherapy regimens in UK clinical practice in this setting
Model structure	Partitioned-survival model (PSM)	A PSM was adopted due to the availability of a mature data set from the BRF113928 trial and past precedent across multiple previous NICE technology appraisals in advanced NSCLC.[6, 7, 22, 98, 99, 104-108]
Time horizon	Lifetime	The reference case stipulates that the time horizon should be sufficiently long to reflect any differences in costs and outcomes between the technologies being considered, thus a lifetime time horizon was adopted.[109]
Cycle length	7 days	A weekly cycle length was adopted to allow for the varied dosing schedules for the different NSCLC treatments used in UK clinical practice, and for any differences in efficacy and costs over time to be captured with granularity.
Discount rate	3.5% per annum for both costs and benefits	The appropriate discount rate was adopted in line with NICE reference case.[109]
Perspective	NHS/PSS in England	The appropriate perspective was adopted in line with NICE reference case.[109]

Source of utilities	Chouaid *et al.* (2013)[54]	The BRF113928 trial did not collect HRQoL data so utility values had to be sourced from the published literature.
Source of costs	NHS reference costs PSSRU BNF/eMIT	NHS Reference Costs, PSSRU, BNF and eMIT were used for cost data. Where costs were not reported in these sources, cost inputs were sourced from appropriate published literature.

Abbreviations: BNF: British National Formulary; eMIT: electronic Market Information Tool; HRQoL: health-related quality of life; NICE: National Institute of Health and Care Excellence NHS: National Health Service; NSCLC: non-small cell lung cancer; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; UK: United Kingdom.

B.3.2.3 Patient population

The patient population included in the base case economic analysis consisted of patients with previously untreated advanced NSCLC with a BRAF V600 mutation, based on cohort C of the BRF113928 trial.

As discussed in Section B.1.1, subgroup economic analyses by line of therapy, tumour histology or PD-L1 expression were not conducted. Further details on why an economic analysis within the previously treated patient population was not possible are presented in Table 22 above.

As detailed in Section B.1.1, Table 2, subgroup analyses by tumour histology or PD-L1 expression would not be feasible, as these would be informed by prohibitively small patient numbers. Furthermore, dabrafenib and trametinib achieves clinical benefit via a mechanism of action independent of PD-L1 expression, and is expected to show similar clinical benefit regardless of histology. This approach is aligned with previous NICE appraisals for targeted treatments in advanced NSCLC, including NICE TA789 (tepotinib for treating advanced NSCLC with MET gene alterations) and TA760 (selpercatinib for previously treated RET fusion-positive advanced NSCLC), where the NICE Committee did not make recommendations restricted by histology group, based on factors including the lack of data for patients with squamous NSCLC, and the fact that squamous NSCLC represents a generally small patient population.[6, 98]

The patient characteristics informing the model are presented in Table 23, based on Cohort C of the BRF113928 trial.

Table 23: Patient characteristics model inputs

Characteristic	Proportion
Percentage male	38.9%
Mean age	67.8
Mean BSA[a]	[redacted]

Footnotes: [a] Calculated using the Mosteller formula with data from BRF113928 trial (height and weight available only for combined Cohorts B and C; mean height: [redacted] cm, mean weight: [redacted] kg).
Abbreviations: BSA: body surface area.
Source: BRF113928 Clinical Study Report.[17]

B.3.2.4 Intervention technology and comparators

As discussed in Section B.1, the principal comparator to dabrafenib and trametinib in this submission is pembrolizumab plus chemotherapy. The base case economic analysis therefore compared dabrafenib and trametinib to pembrolizumab plus chemotherapy (specifically, pembrolizumab plus pemetrexed and platinum-based chemotherapy [carboplatin or cisplatin]).

Details of the dosing regimens modelled for both the intervention and comparator are presented below:

Dabrafenib and trametinib

- Dabrafenib 150 mg twice daily[11]
- Trametinib 2 mg once daily[12]

Pembrolizumab plus chemotherapy

A summary of the dosing regimen modelled for pembrolizumab plus chemotherapy is presented in Table 24.

Pembrolizumab plus chemotherapy was assumed to comprise pembrolizumab plus pemetrexed and either carboplatin or cisplatin and, in line with the licensed indication, was modelled for a total duration of two years (35 three-weekly treatment cycles) (see Table 24). The proportions of patients assumed to receive either carboplatin or cisplatin as part of this regimen were 84.4% and 15.6%, respectively, based on the assumed split between carboplatin and cisplatin adopted in NICE TA789.[6]

Of the patients still on treatment after four treatment cycles (12 model cycles), [redacted]% were modelled to receive maintenance treatment with pemetrexed alongside pembrolizumab, while the remaining [redacted]% were modelled to receive pembrolizumab alone. These proportions were based on the proportions of patients in the pembrolizumab plus chemotherapy arm of the FLATIRON RWE study (2022) who received maintenance treatment with pemetrexed or not following discontinuation of carboplatin or cisplatin.

The dosing of pembrolizumab was based on clinical expert feedback that confirmed that during the COVID-19 pandemic, the dosing of pembrolizumab when administered as a monotherapy, changed from 3-weekly dosing to 6-weekly dosing.[8] As such, after the first four treatment cycles (12 model cycles), pembrolizumab was assumed to be administered at a three-weekly dosing interval if patients were also receiving maintenance pemetrexed, but at a six-weekly dosing interval for patients who were not receiving maintenance pemetrexed.

Pembrolizumab and maintenance pemetrexed were assumed to be given for a maximum of 2 years to account for the stopping rule imposed within the recommendation for pembrolizumab in combination with platinum-based chemotherapy in NICE TA683 (pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC), which stipulates that all treatments should be stopped following two years of treatment, or earlier if the disease progresses.[21]

Table 24: Summary of the modelled pembrolizumab plus chemotherapy dosing regimen

Drug	Dose	Day of treatment cycle
For the first 4 three-weekly treatment cycles (12 model cycles)		
Cisplatin *(15.6% of patients)*	75 mg/m^2	1
Carboplatin *(84.4% of patients)*	AUC 5–7 (maximum dose 750 mg)	1
Pembrolizumab	200 mg	1
Pemetrexed	500 mg/m^2	1

Drug	Dose	Day of treatment cycle
For the next 31 three-weekly treatment cycles (up to 104 model cycles) (for the [redacted]% of patients receiving pemetrexed maintenance)		
Pembrolizumab	200 mg	1
Pemetrexed (*maintenance)*	500 mg/m^2	1
For the next 16 six-weekly treatment cycles (up to 104 model cycles) (for the [redacted]% of patients not receiving pemetrexed maintenance)		
Pembrolizumab	400 mg	1

Abbreviations: AUC: area under the curve.

B.3.3 Clinical parameters and variables

B.3.3.1 Summary of clinical data used in the model

In the base case economic analysis, PFS, OS and ToT data for dabrafenib and trametinib were derived from Cohort C of the BRF113928 trial.

In line with NICE DSU TSD 14, distributions were fitted independently to the KM curves for PFS and OS for dabrafenib and trametinib using data from Cohort C of the BRF1139128 trial (presented in Sections B.3.3.2.2 and B.3.3.2.3 below).

For completeness, the same was done for the real-world pembrolizumab plus chemotherapy cohort using the weighted data from the FLATIRON RWE study (2022) (presented in Appendix N). The predicted pembrolizumab plus chemotherapy PFS and OS outcomes were assessed for external validity by comparing them to the survival estimates in KEYNOTE-189, the pivotal RCT comparing pembrolizumab plus chemotherapy with platinum-based chemotherapy (see Table 25).[110] UK clinical experts noted that this trial did not select for patients harbouring the BRAF V600 mutation, but agreed it was an appropriate source to utilise for external validation.[8]

UK clinical experts noted that predicted PFS and OS for pembrolizumab plus chemotherapy from extrapolations of the FLATIRON RWE study (2022) weighted data were overestimated and clinically implausible compared to the published KEYNOTE-189 trial data (Table 25).[8, 110] KEYNOTE-189 reported a median OS of 22.0 months for pembrolizumab plus chemotherapy, with a 2-year OS rate of 45.7%. In contrast, the predicted 2-year OS rates for pembrolizumab plus chemotherapy were all higher than [redacted]%. The extrapolations predicted a median OS ranging from [redacted] months (for the exponential model) to [redacted] months (for the lognormal model)

Table 25: Comparison of pembrolizumab plus chemotherapy PFS and OS from extrapolations of the FLATIRON RWE study (2022) weighted data versus KEYNOTE-189

Endpoint	Pembrolizumab plus chemotherapy (extrapolations of weighted data from the FLATIRON RWE study [2022])	KEYNOTE-189[110]
PFS rate at Month 24	Range: [redacted]% to [redacted]%	22%
OS rate at Month 24	Range: [redacted]% to [redacted]%	45.7%
Median OS	Range: [redacted] to [redacted] months	22 months

Abbreviations: OS: overall survival; PFS: progression-free survival; RWE: real-world evidence.

Given these uncertainties, the clinical experts agreed that it would be reasonable to assume that the PFS and OS estimates for pembrolizumab plus chemotherapy would be equivalent to the predicted survival outcomes for dabrafenib and trametinib using data from the BRF113928 trial, in line with the conclusions made in Section B.2 of this submission.[8] An assumption of clinical equivalency between dabrafenib and trametinib and pembrolizumab plus chemotherapy was also assumed in the previously conducted Canadian Agency for Drugs and Technologies in Health (CADTH) appraisal for dabrafenib and trametinib in this indication in Canada.[64]

Therefore, in the base case economic analysis it was assumed that PFS and OS for pembrolizumab plus chemotherapy were equivalent to PFS and OS for dabrafenib and trametinib, based on Cohort C of the BRF113928 trial.

The weighted ToT data for pembrolizumab plus chemotherapy from the FLATIRON RWE study (2022), was used in the base case economic analysis, as the ToT data were consistent with ToT values for pembrolizumab plus chemotherapy reported in the published literature (as detailed in Section B.3.3.2.4 below).

B.3.3.2 Implementation of survival data

The proportion of patients in the PFS, PD and death health states at each cycle in the model were defined by PFS and OS curves (Section B.3.2.1). As the follow-up period of the BRF113928 trial and the FLATIRON RWE study (2022) were shorter than the model time horizon (~30 years), extrapolations of the observed PFS, OS and ToT data were required.

In accordance with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz and generalised gamma) were explored.[111] Alternative model choices such as spline models were not required, as the standard parametric extrapolations appeared to provide a good fit to the observed data in all cases.

The goodness-of-fit criteria (including the Akaike information criterion [AIC] and the Bayesian information criterion [BIC]) were then estimated for each parametric function.

In determining the choice of survival model for the base case for dabrafenib and trametinib, consideration was given to the following, according to the recommendations provided in NICE DSU TSD 14:[111]

- AIC and BIC goodness-of-fit statistics (i.e., statistical fit) in order to assess how well the statistical models fitted to the observed data
- Visual inspection of the extrapolated curves versus the observed Kaplan-Meier curves
- Clinical plausibility for both short-term and long-term estimates of survival based on discussion with UK clinical experts and published data

Additionally, in order to ensure that any OS extrapolations did not provide implausible estimates of mortality, all mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum (calculated using the 2018-2020 UK life tables).[112] Adjustments were made in the model traces to prevent logical inconsistencies:

- PFS could not exceed OS
- ToT could not exceed PFS

B.3.3.2.1. Summary

A summary of the base case clinical efficacy data for PFS, OS and ToT for the comparison of dabrafenib and trametinib versus pembrolizumab plus chemotherapy in patients with previously untreated advanced NSCLC with a BRAF V600 mutation is presented in Table 26. A range of scenario analyses, detailed in Section B.3.10.3, were conducted to explore alternative efficacy parameters for both dabrafenib and trametinib and pembrolizumab plus chemotherapy.

Table 26: Summary of the clinical parameters used in the economic model

Parameter	Base case input	Source	Reference in Submission
Baseline characteristics (dabrafenib and trametinib)	BRF113928 trial (Cohort C)		Section B.3.2.3
Baseline characteristics (pembrolizumab plus chemotherapy)			
PFS (dabrafenib and trametinib)	Log-logistic	BRF113928 trial (Cohort C)	Section B.3.3.2.2
PFS (pembrolizumab plus chemotherapy)	Equal to dabrafenib and trametinib	Assumption	Section B.3.3.1
OS (dabrafenib and trametinib)	Weibull	BRF113928 trial (Cohort C)	Section B.3.3.2.3
OS (pembrolizumab plus chemotherapy)	Equal to dabrafenib and trametinib	Assumption	Section B.3.3.1
ToT (dabrafenib and trametinib)	Exponential	BRF113928 trial (Cohort C)	Section B.3.3.2.4
ToT (pembrolizumab plus chemotherapy)	Exponential	FLATIRON RWE study (2022), weighted data	Section B.3.3.2.4
UK life tables	2018-2020 life tables	ONS	Section B.3.3.2
AE frequencies (dabrafenib and trametinib)	Grade ≥3 AEs occurring in greater than 1% of patients	BRF113928 trial (Cohort C)	Section B.3.3.3
AE frequencies (pembrolizumab plus chemotherapy)	Grade ≥3 AEs occurring in greater than 1% of patients	KEYNOTE-189	Section B.3.3.3

Abbreviations: AE: adverse events; OS: overall survival; PFS: progression-free survival; RWE: real-world evidence; ToT: time on treatment; UK: United Kingdom.

B.3.3.2.2. Progression-free survival

Dabrafenib and trametinib

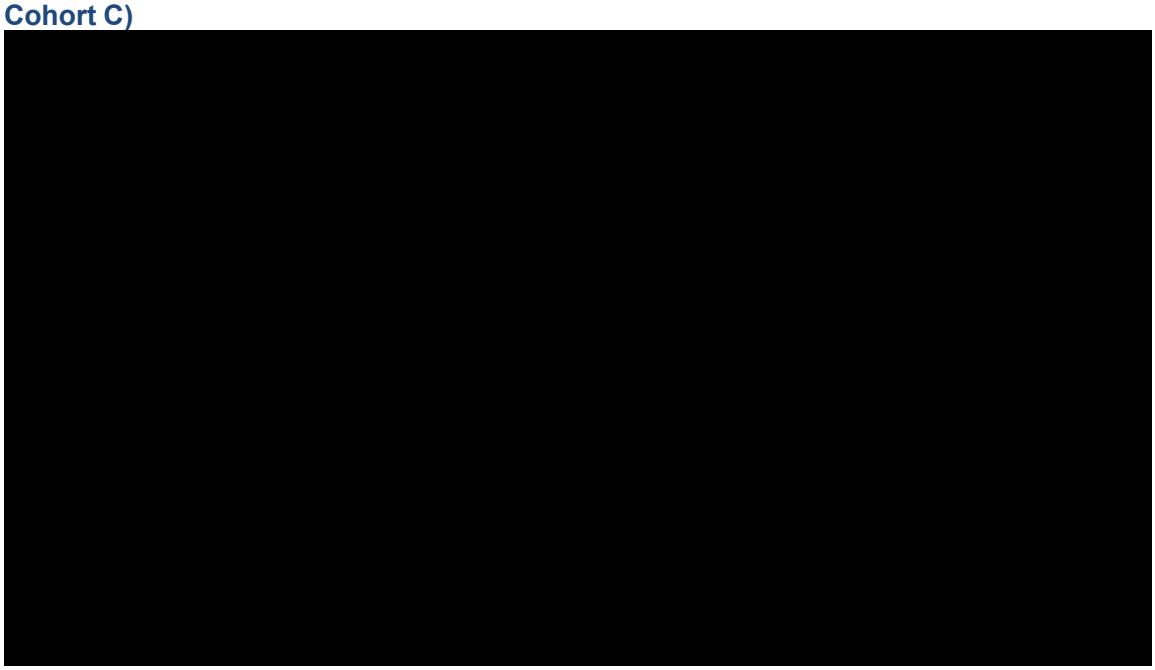
To model PFS, the standard parametric distributions were fitted to the PFS individual patient data (IPD) for patients receiving dabrafenib and trametinib in Cohort C of the BRF113928 trial. The AIC and BIC values for each of the extrapolations are summarised in Table 27. Extrapolations of PFS using each model up to ten years are presented for all functions in Figure 10, to aid investigation of the visual fit of the distributions to the observed study data, and to aid investigation of the clinical plausibility of the long-term extrapolations.

Table 27: Summary of goodness-of-fit data for dabrafenib and trametinib PFS (BRF113928 Cohort C); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression-free survival.

Figure 10: Dabrafenib and trametinib PFS extrapolations up to ten years (BRF113928 Cohort C)



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

NICE DSU TSD 14 indicates that, in cases where survival data are relatively complete, the use of AIC/BIC tests may be of most use in determining the most appropriate curve selection, as the extrapolated proportion of the curve contributes little to the overall mean area under the curve.[111]

As such, given the maturity of the data from the BRF113928 trial, the best statistically fitting log-logistic curve was considered to represent the most appropriate distribution to extrapolate the PFS KM curve in the base case analysis. UK clinical experts noted that approximately [redacted]% of patients remained on treatment for 2.5 years in the BRF113928 trial, and noted that it would be plausible for patients who experienced few AEs to be on treatment for an extended amount of time. Based on this, the log-logistic curve would be considered clinically plausible, citing that very few patients would not have progressed after 5 years, in line with the results observed in the BRF113928 trial (Section B.2.7.3). As clinical equivalence was assumed in the base case analysis, the same curve was adopted for pembrolizumab with chemotherapy.

Burnham and Anderson (2004) indicate that, for two parametric models with less than ≤2 AIC

points between them, there is substantial support for the fact that the two models have the same merits.[113] Similarly, Raftery *et al.* (1995) indicate that there is weak evidence of any differences between two parametric models with less than ≤2 BIC points between them.[114] Larger differences provide increasing evidence for significant differences between any two models. As such, the lognormal curve (within [redacted] AIC and BIC points of the log-logistic extrapolation) was explored within a scenario analysis (Section B.3.10.3). The next best fitting curve (the Generalised gamma, within [redacted] AIC points and [redacted] BIC points) was also explored for completeness. The remaining models were not considered in scenario analyses, as the AIC and BIC data indicate that they would be expected to provide a significantly worse fit to the observed PFS data, and, given the relative completeness of the PFS data from the BRF113928 trial, were not considered relevant.

B.3.3.2.3. Overall survival

Dabrafenib and trametinib

To model OS, the standard parametric distributions were fitted to the OS IPD for patients receiving dabrafenib plus trametinib in Cohort C of the BRF113928 trial. The AIC and BIC values for each of the extrapolations are summarised in Table 28. Extrapolations of OS using each model up to 15 years are presented for all functions in Figure 11, to aid the investigation of the visual fit of the distributions to the observed study data, and to aid investigation of the clinical plausibility of the long-term extrapolations.

Table 28: Summary of goodness-of-fit data for dabrafenib and trametinib OS (BRF113928 Cohort C); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival.

Figure 11: Dabrafenib and trametinib OS extrapolations up to ten years (BRF113928 Cohort C)

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

All of the OS extrapolations were seen to have a similar fit to the observed data, with only a [redacted] difference in AIC points, and a [redacted] difference in BIC points, between the best-fitting curve (the log-logistic) and the sixth-best fitting curve (the Weibull).

In the BRF113928 trial, the OS KM data estimated [redacted]% (95% CI: [redacted]) of patients were still alive after 4 years, and [redacted]% after 5 years (95% CI: [redacted]). Clinical experts were shown the above extrapolations of the KM data and asked to confirm which were clinically plausible.[8] The clinical experts noted the maturity of the BRF113928 trial data in this patient population as an advantage, but indicated that selection of the most appropriate curve was challenging, given the limited experience of dabrafenib and trametinib in this patient population in clinical practice.[8]

Clinicians also highlighted the aggressive nature of the BRAF mutation and expected survival to be less than [redacted]% at 10 years.[8] The clinicians ultimately agreed that the Weibull extrapolation was the most plausible, as it predicted the lowest 10-year OS rate ([redacted]%).[8] As such, the Weibull curve was selected to extrapolate OS in the base case analysis. As clinical equivalence is assumed in the base case analysis, the same curve was adopted for pembrolizumab with chemotherapy.

The exponential curve (10-year OS of 4.5%) was also considered potentially plausible, and explored in a scenario analysis (Section B.3.10.3). The other curves, which predicted a range of between [redacted]% to [redacted]% of patients would be alive at 10 years, were considered less clinically plausible and not explored further.

B.3.3.2.4. Time on treatment

Dabrafenib and trametinib

To model ToT, standard parametric distributions were fitted to the ToT IPD for patients receiving dabrafenib and trametinib in Cohort C of the BRF113928 trial. The ToT KM data from the BRF113928 trial were mature and provided a complete dataset.

Given this, it is possible to use the ToT KM curve directly. However, it was considered more appropriate to fit a parametric curve to the observed data, to smooth out the stepwise KM data and assume a more constant rate of discontinuation over time. The use of the KM data directly was explored in a scenario analysis.

The AIC and BIC values for each of the dabrafenib and trametinib ToT extrapolations are summarised in Table 29. Extrapolations of ToT using each model up to ten years are presented for all functions in Figure 12. No stopping rules were applied for dabrafenib and trametinib as per UK clinical practice; a relative dose intensity (RDI) was applied when calculating the costs, as detailed in Section B.3.5.1.

Table 29: Summary of goodness-of-fit data for dabrafenib and trametinib ToT (BRF113928 Cohort C); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; ToT: time on treatment.

Figure 12: Dabrafenib and trametinib ToT extrapolations up to ten years (BRF113928 Cohort C)

Abbreviations: KM: Kaplan-Meier; ToT: time on treatment.

In the BRF113928 trial, the median treatment duration was [redacted] months (range: [redacted] to [redacted] months). To evaluate the long-term plausibility of the chosen extrapolation, UK clinical experts noted that experience of dabrafenib and trametinib in current clinical experience is limited to the interim COVID-19 guidance period.[8] The experts referenced the median treatment durations from the BRF113928 trial as encouraging and noted that it is possible for some patients to have an extended treatment response if they did not experience any AEs. Therefore, the best statistically fitting exponential distribution was considered plausible, and used in the base case analysis.

The next two best statistically-fitting extrapolations, the Weibull and the Gompertz, had similar AIC and BIC estimates to the exponential distribution, and were explored in scenario analyses (Section B.3.10.3). As the dabrafenib and trametinib KM curve was complete, a scenario analysis also explored the use of the KM curve directly to model ToT.

Pembrolizumab plus chemotherapy

The standard parametric distributions were fitted to the weighted ToT IPD for patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022). In selecting the most appropriate curve for pembrolizumab plus chemotherapy, it is important to note that a 2-year stopping rule was applied, in line with UK clinical practice, as detailed below.[21]

As such, the parametric model is only required over the first two years of the model time horizon. This means that the use of the KM data directly could represent a plausible option. However, it was considered more appropriate to fit a parametric curve to the observed data, in order to smooth out the stepwise nature of the KM data and assume a more constant rate of discontinuation of treatment over time. A scenario analysis utilising the pembrolizumab plus chemotherapy ToT KM curve directly was also conducted (Section B.3.10.3).

The AIC and BIC values for each of the extrapolations for the pembrolizumab plus chemotherapy

BRAF V600E population are summarised in Table 30. Extrapolations of ToT using each model up to 3 years are presented in Figure 13.

Table 30: Summary of goodness-of-fit data for pembrolizumab plus chemotherapy ToT (BRAF V600E [weighted] population – FLATIRON RWE study [2022]); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; ToT time on treatment.

Figure 13: Pembrolizumab plus chemotherapy ToT extrapolations up to three years (BRAF V600E [weighted] population – FLATIRON RWE Study [2022])*

Footnotes: * Extrapolations are presented prior to the application of the stopping rules
Abbreviations: KM: Kaplan-Meier; ToT: time on treatment.

The median time to treatment discontinuation in the FLATIRON RWE study (2022) for patients with a V600E mutation receiving pembrolizumab plus chemotherapy was [redacted] months (95% CI: [redacted], [redacted]), versus a median duration of treatment of 7.2 months (range: 1 day, 35.4 months) in KEYNOTE-189.[110] As these estimates were closely aligned, the use of the pembrolizumab plus chemotherapy ToT data was considered appropriate.

However, despite the external validity when compared to KEYNOTE-189, the use of the pembrolizumab plus chemotherapy data from the FLATIRON RWE study (2022) was still considered to be associated with some uncertainty, due to the limited follow-up (mean [redacted] months), compared to a mean [redacted] months of follow-up for dabrafenib and trametinib in the

BRF113928 trial.

The exponential curve was selected in the base case analysis, as the curve providing the best fit to the observed data. The second and third best statistically fitting curves (lognormal and Gompertz) were explored in scenario analyses. Two further scenarios explored the use of the pembrolizumab plus chemotherapy ToT KM curve directly, and explored setting pembrolizumab plus chemotherapy ToT equal to ToT for dabrafenib and trametinib (but with the relevant stopping rules applied), to align with the assumptions for PFS and OS (Section B.3.10.3).

Stopping rules

Adjustments were made to the ToT extrapolation for pembrolizumab plus chemotherapy to account for the stopping rule imposed in NICE TA683, which stipulates that all treatments should be stopped following two years of treatment, or earlier if the disease progresses.[21] As such, after two years, the number of patients receiving pembrolizumab plus chemotherapy in the economic model was set to zero. Patients were assumed to discontinue carboplatin, cisplatin and pemetrexed earlier than this, based on the dosing regimens for each treatment, detailed in Section B.3.2.4 and B.3.5.1.

B.3.3.3 Adverse events

Given the base case economic analysis assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in terms of PFS and OS, the robust modelling of differences in the AE profiles of each therapy was considered important. In particular, clinical expert feedback indicated that it would be important for any modelled differences in AEs to reflect the risk of immune-mediated AEs experienced by patients receiving pembrolizumab plus chemotherapy.[8]

As such, in the base case economic analysis, costs and disutility estimates were included for any all-cause Grade ≥3 AEs experienced by ≥1% of patients receiving either dabrafenib and trametinib or pembrolizumab plus chemotherapy.

The proportions of patients modelled to experience these AEs for dabrafenib and trametinib and pembrolizumab plus chemotherapy are shown in Table 31, based on the safety cohort (Cohorts B and C) of the BRF113928 trial for dabrafenib and trametinib (Section B.2.10), and KEYNOTE-189 for pembrolizumab plus chemotherapy.[110] Where a Grade ≥3 AE was experienced by ≥1% of patients receiving one therapy, the proportion of patients experiencing that Grade ≥3 AE for the other therapy was included (for example, with pyrexia).

It should be noted that AEs were reported differently between the two treatments. The BRF113928 trial reported AEs reported the incidence of Grade ≥3 AEs in cases where that AE (any Grade) occurred in ≥10% of patients. In comparison, the KEYNOTE-189 trial publication only reports Grade ≥3 AEs where that AE (any Grade) occurred in ≥15% of patients in either treatment group, with the exception of immune-mediated AEs, which were reported in full. While there are likely some differences in AEs that are therefore not captured in the base case, this is unlikely to have any significant impact, since immune-mediated AEs are reported in full.

The disutility and costs associated with the AEs included within the model are detailed in Section B.3.4.4 and Section B.3.5.4, respectively.

Table 31: Summary of AEs included in the base case economic analysis

Adverse event	Dabrafenib plus trametinib[a] BRF113928; Planchard *et al.* (2021)[72]	Pembrolizumab plus chemotherapy KEYNOTE-189; Rodríguez-Abreu *et al.* (2021)[110]
Abdominal pain	1.08%	-
Alanine aminotransferase	6.45%	-
Anaemia	5.37%	18.50%
Arthralgia	1.08%	-
Aspartate aminotransferase increased	3.23%	-
Asthenia	4.30%	6.70%
Back pain	3.23%	1.50%
Blood alkaline phosphatase increase	1.08%	-
Colitis (immune-mediated)	-	1.70%
Constipation	-	1.00%
Decreased appetite	-	1.20%
Diarrhoea	2.15%	5.20%
Dry skin	1.08%	-
Dyspnoea	7.53%	4.00%
Fatigue	3.23%	7.70%
Headache	1.08%	-
Hepatitis (immune-mediated)	-	1.50%
Hypertension	9.68%	-
Hyponatremia	9.68%	-
Hypotension	4.30%	-
Nausea	-	3.50%
Nephritis (immune-mediated)	-	1.50%
Neutropenia	7.53%	16.30%
Pain in extremity	1.08%	-
Pneumonia	1.08%	-
Pneumonitis (immune-mediated)	-	3.00%
Pruritis	2.15%	-
Pyrexia	6.45%	0.20%
Rash	2.15%	2.00%
Severe skin reactions (immune-mediated)	-	2.50%
Thrombocytopenia	-	8.40%
Vomiting	3.23%	4.00%
Weight decreased	1.08%	-
Weight increased	3.23%	-

Footnotes: [a]Note AEs were not reported separately for Cohort C from the BRF113928 trial thus these data are derived from the combined safety cohort of Cohort B and Cohort C. It is not expected that the AE profile for dabrafenib and trametinib would differ depending on whether patients had previously untreated or previously treated disease.
Abbreviations: AEs: adverse events.

B.3.4 Measurement and valuation health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

This section is not applicable as HRQoL data were not collected within the BRF113928 trial.

B.3.4.2 Mapping

Not applicable.

B.3.4.3 Health-related quality-of-life studies

As detailed in Appendix H.3, no studies were identified in the economic SLRs that reported utility value estimates for patients with NSCLC with a BRAF mutation. As such, utility values for the economic model were derived from previous NICE appraisals in the wider NSCLC population, as detailed in Section B.3.4.7.

B.3.4.4 Adverse reactions

As discussed in Section B.3.3.3, the base case economic analysis included all-cause Grade ≥3 AEs experienced by ≥1% of patients in either the BRF113928 trial for dabrafenib and trametinib or KEYNOTE-189 for pembrolizumab plus chemotherapy. To accurately account for the disutility associated each of these Grade ≥3 AEs, disutility values were sourced from the published literature, alongside the duration that each AE was expected to be experienced for. This represents the most accurate approach to the modelling of AE disutility and ensures that each disutility is applied for the appropriate duration of time.

As one of the most recent appraisals conducted in advanced NSCLC for a targeted therapy, AE disutility estimates were sourced from NICE TA789.[6] The expected duration of each AE, and therefore the duration of the disutility application, was also sourced from NICE TA789, where the majority of AE durations were derived from the pivotal trial for tepotinib (the VISION trial).[6]

Where NICE TA789 did not report an appropriate disutility or duration for an AE of relevance, further NICE NSCLC appraisals or other sources in the published literature were reviewed (Table 32). Beyond that, data from the BRF113928 trial on the duration of AEs were utilised. The BRF113928 trial was not utilised for the duration of all AEs in the first instance as it did not report the duration of all AEs separately, and it did not report the duration for Grade ≥3 AEs only.[17]

In line with NICE TA812 (pralsetinib for treating RET fusion-positive advanced NSCLC), in cases where no disutility data or appropriate durations were able to be sourced from the literature, a disutility and AE duration of 0 was assumed.[7, 104] This was the case for “weight increased” and “weight decreased” and therefore in the base case economic analysis, these AEs were not associated with any disutility. As these AEs were only experienced by 1.08% and 3.23% of patients receiving dabrafenib and trametinib, respectively, it was not considered that this would have a large impact on the base case economic results.

Within the base case economic analysis, each AE disutility was applied as the associated QALY decrement, which was calculated by adjusting the AE disutility (which represents the total QALY loss over one year, if a patient were to experience the AE for one year) by the expected duration of each AE. A summary of the AE disutility estimates and AE durations including in the base case economic analysis is presented in Table 32.

Table 32: Summary of AE disutility estimates included in the base case economic analysis

Adverse event	AE disutility	Disutility source	AE duration (days)	AE duration source
Abdominal pain	-0.069	Derived from TA789 (Table 49) - assumed same as pain,[6] Source: Doyle et al. (2008)[115]	31	TA789 (assumed same as pain),[6] Source: VISION trial
Alanine aminotransferase	-0.05	Derived from TA789 (Table 49),[6] Source: Assumption based on TA347[116]	54.8	Duration: TA789,[6] Source: VISION trial
Anaemia	-0.073	Derived from TA789 (Table 49),[6] Source: Assumed same as fatigue as per TA181[117]	3	Duration: TA789,[6] Source: VISION trial
Arthralgia	-0.069	Assumed same as abdominal pain	31	Assumed same as abdominal pain
Aspartate aminotransferase increased	-0.051	Derived from NICE TA760 (Table 58),[98] Source: NICE TA621;[118] Disutility and Duration: Assumption (average of other disutilities) Duration: Assumed same as alanine aminotransferase increased	54.8	Duration: Assumed same as alanine aminotransferase increased
Asthenia	-0.073	Derived from NICE TA789 (Table 49),[6] Source: Assumed same as fatigue	52	Duration: NICE TA789,[6] Source: VISION trial
Back pain	-0.069	Assumed same as abdominal pain	31	Duration: Assumed same as pain
Blood alkaline phosphatase increase	-0.05	Assumed same as alanine aminotransferase increased	54.8	Assumed same as alanine aminotransferase increased
Colitis (immune-mediated)	-0.11	Assumed same as diarrhoea	3	Assumed same as diarrhoea
Constipation	-0.047	Assumed same as diarrhoea	3	Assumed same as diarrhoea
Decreased appetite	-0.085	Derived from NICE TA760 (Table 58),[98] Source: NICE TA428;[60] Disutility: KEYNOTE010 (NICE TA428)[60]	10.5	Duration: Assumed same as nausea
Diarrhoea	-0.047	Derived from NICE TA789 (Table 49),[6] Source: Nafees et al. (2008)[119]	3	Duration: NICE TA789,[6] Source: VISION trial
Dry skin	-0.032	Assumed same as rash	117.6	Assumed same as rash
Dyspnoea	-0.05	Derived from NICE TA789 (Table 49),[6] Source: Doyle et al. (2008)[115]	18.8	Duration: NICE TA789,[6] Source: VISION trial

Fatigue	-0.073	Derived from NICE TA789 (Table 49),[6] Source: Nafees et al. (2008)[119]	212	Duration: NICE TA789,[6] Source: VISION trial
Headache	-0.069	Assumed same as abdominal pain	31	Assumed same as abdominal pain
Hepatitis (immune-mediated)	-0.11	Derived from immune-related disorders, Table 41 (page 50) in the NICE committee papers for NICE TA684 (CDF review of NICE TA558) (nivolumab for melanoma),[120, 121] Source: https://www.nice.org.uk/guidance/ta684/history	7	Duration: Assumed same as nephritis
Hypertension	-0.03	Derived from NICE TA789 (Table 49),[6] Source: Paracha *et al.* (2018)[122] (Nafees et al. 2016)[119]	150	Duration: NICE TA789,[6] Source: VISION trial
Hyponatremia	-0.085	Derived from NICE TA760 (Table 58),[98] Source: NICE TA428;[60] Disutility: KEYNOTE010 (NICE TA428);[60] Duration: Assumption	7	Duration: NICE TA789 (assumed same as hypomagnesemia),[6] Source: VISION trial
Hypotension	-0.03	Assumed same as hypertension	183.4	Assumed same as hypertension
Nausea	-0.048	Derived from NICE TA789 (Table 49),[6] Source: Nafees et al. (2008)[119]	10.5	Duration: NICE TA789,[6] Source: VISION trial
Nephritis (immune-mediated)	-0.11	Derived from immune-related disorders, Table 41 (page 50) in the NICE committee papers for NICE TA684 (CDF review of NICE TA558) (nivolumab for melanoma),[120, 121] Source: https://www.nice.org.uk/guidance/ta684/history	7	Duration: NICE TA772[123]
Neutropenia	-0.09	Derived from NICE TA789 (Table 49),[6] Source: Nafees et al. (2008)[119]	158	Duration: NICE TA789 (assumed same as hypomagnesemia),[6] Source: VISION trial
Pain in extremity	-0.069	Derived from NICE TA789 (Table 49) (disutility for "pain"),[6] Source: Doyle et al. (2008)	31	Duration: Assumed same as abdominal pain
Pneumonia	-0.008	Derived from combined disutility for "pneumonitis/pneumonia" from NICE TA789 (Table 49),[6] Source: Marti et al. (2013)[124] as per NICE TA655[125] and NICE TA520[99]	19.6	Duration: NICE TA789,[6] Source: VISION trial
Pneumonitis (immune-mediated)	-0.11	Derived from combined disutility for "pneumonitis/pneumonia" from NICE TA789	19.6	Duration: Assumed same as pneumonia

		(Table 49),[6] Source: Marti et al. (2013)[124] as per NICE TA655[125] and NICE TA520[99]		
Pruritis	-0.032	Assumed same as rash	117.6	Assumed same as rash
Pyrexia	-0.11	Wehler *et al.* (2018)[126]	7.6	Duration: BRF113928 duration of pyrexia (AESI)
Rash	-0.032	Nafees *et al.* (2008)[119]	117.6	Duration: BRF113928 duration of skin toxicity (AESI)
Severe skin reactions (immune-mediated)	-0.11	Assumed same as rash	117.6	Assumed same as rash
Thrombocytopenia	-0.003	Derived from NICE TA789 (Table 49),[6] Source: Handorf *et al.* (2012)[127]	37.2	NICE TA789,[6] Source: VISION trial
Vomiting	-0.048	Derived from NICE TA789 (Table 49),[6] Nafees et al. (2008)[119]	2	NICE TA789,[6] Source: VISION trial
Weight decreased	0	Assumed 0	0	Assumed 0
Weight increased	0	Assumed 0	0	Assumed 0

Abbreviations: AEs: adverse event; AESI: adverse event of special interest; CDF: Cancer Drugs Fund; NICE: National Institute of Health and Care Excellence; TA: technology appraisal.

B.3.4.5 Treatment administration disutility

An important difference between dabrafenib and trametinib and pembrolizumab plus chemotherapy relates to the administration of both therapies. Dabrafenib and trametinib are oral therapies and can be taken at home, and therefore represent a more convenient, less painful, and less burdensome method of administration compared to pembrolizumab plus chemotherapy which must be administered via IV infusion and requires a patient to visit a hospital to receive treatment. Indeed, the ability for patients to receive treatment away from a hospital setting was one of the reasons behind dabrafenib and trametinib being provided through interim measures by NHS England during the COVID-19 pandemic.[20]

Pembrolizumab plus chemotherapy requires three separate IV infusions (pembrolizumab, carboplatin/cisplatin, and pemetrexed), which would be expected to last for at least 60 minutes in total (pembrolizumab: 30 minutes; carboplatin: 15–60 minutes or cisplatin: 120 minutes; pemetrexed: 10 minutes). Within the first 12 weeks, these therapies are administered every 3 weeks. As such, it is plausible that there may be a disutility associated with an IV regimen (versus an oral treatment) due to this burden of administration, and this should be captured in the model.

In the base case economic analysis, a disutility of -0.023 was applied to the PFS health state utility value for patients receiving pembrolizumab plus chemotherapy. This disutility was applied for the duration that patients remained on treatment, defined by the pembrolizumab plus chemotherapy ToT curve.

The disutility of -0.023 was based on the study by Matza *et al.* (2013),[128] which investigated the disutility associated with infusion-treatments for bone metastases. The disutility of -0.023 was reflective of patients receiving a treatment with a 30-minute IV infusion regimen every four weeks, and the question used to elicit the utility values focussed on the mode of administration of the treatment.

Matza *et al.* (2013) was previously used in NICE TA728 to support a disutility associated with IV infusions.[129] Another recent NICE appraisal in advanced NSCLC (NICE TA781) applied a similar disutility of -0.025 in all cycles that patients were on treatment receiving docetaxel monotherapy via IV infusion.[7] This disutility was derived from a cost-effectiveness study of erlotinib versus docetaxel, and reported utility values of 0.451 versus 0.426 for oral versus IV therapy, respectively, representing a difference of -0.025.[130] These utilities were determined by having a sample of the UK general population fill out a visual analogue scale (VAS) and not EQ-5D. However, despite the limitations of the data, the Committee agreed that a disutility may be plausible for IV infusion, and considered different scenarios in their decision making.[7]

In order to explore the uncertainty surrounding administration-related disutility, two alternative scenarios were considered.

First, as patients receiving cisplatin as part of their pembrolizumab plus chemotherapy regimen are likely to receive IV infusions that would last longer than 30 minutes, an increased disutility of -0.037 was applied for patients receiving pembrolizumab, pemetrexed and cisplatin (15.4% of the overall pembrolizumab plus chemotherapy cohort), for the first 4 treatment cycles (12 model cycles). This estimate was also taken from Matza *et al.* (2013), and represents a disutility associated with a 2-hour infusion.[128] As outlined in NICE TA181, cisplatin is associated with hydration requirements that require patients to be brought in the night before treatment, which is

likely to be associated with a further reduction in utility.[117] In this scenario, beyond 12 model cycles (and for all cycles for patients receiving pembrolizumab, carboplatin and pemetrexed), the original IV infusion disutility of -0.023 was applied for all patients remaining on treatment.

The second scenario used the disutility of -0.037 to reflect the complexity of the pembrolizumab plus chemotherapy regimen and, in the first 4 treatment cycles (12 model cycles), this was applied to all patients receiving pembrolizumab plus chemotherapy but during the model cycles that they would receive an infusion only. Beyond 12 model cycles, the original disutility of -0.023 was applied only in the cycles that patients would receive an infusion with pembrolizumab (with or without pemetrexed). While Matza *et al.* (2013) note that the value of -0.023 represents a "health state disutility" for patients receiving treatment with a 30-minute IV infusion regimen every 4 weeks, this assumption was relaxed in this scenario, to consider the impact of the frequency and intensity of IV infusions reducing over time as the number of IV administrations is decreased beyond the initial 4 treatment cycles.

B.3.4.6 Age-adjusted disutility values

In the base case economic analysis, health state utility values were also age-adjusted over the model time horizon using UK population norm values for EQ-5D as reported in the HSE 2014 dataset by the NICE DSU.[131]

B.3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utility values

In the absence of HRQoL data from the BRF113928 trial, it was necessary to derive health state utility value estimates from the published literature in order to inform the health state utility values for PFS and PD in the base case economic analysis. As the economic SLR for utility values did not identify any relevant utility data in patients with advanced NSCLC and a BRAF mutation, utility values were sourced from alternative advanced NSCLC population data utilised in previous NICE appraisals.

Given the base case assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in terms of PFS and OS, it is important to note that the choice of health state utility value has no impact on the incremental QALYs accrued for dabrafenib and trametinib versus pembrolizumab plus chemotherapy, because patients spend the same length of time in the PFS and PD health states in both treatment arms. As such, while the choice of health state utility value does impact the total QALYs accrued in the model, it has no impact on the base case ICER.

Nevertheless, to identify the most appropriate source of health state utility values, the three most recently published NICE appraisals for a targeted therapy in advanced NSCLC were reviewed: NICE TA789, TA781 and TA812.[6, 7, 104]

NICE TA781 utilised time-to-death utilities based on their pivotal trial which had collected EQ-5D data.[7] As this is a different approach to the use of health state utility values utilised in this economic analysis, the utility values from NICE TA781 were not considered further.

NICE TA789 utilised utility values derived from EQ-5D data collected in their pivotal trial in the

base case, with scenario analyses based on the published literature and a number of other prior appraisals.[6] NICE TA812 did not collect EQ-5D data in their pivotal trial and therefore utilised utility values from prior appraisals only: NICE TA654 in the base case, and NICE TA310 and NICE TA643 in scenario analysis.[104, 107, 132, 133]

Given the absence of any clear preferred source of utility estimates, the base case analysis used the utility values from Chouaid *et al. (*2013) as an assumption (Table 33).[54] These utilities were used in a scenario in NICE TA789, and are considered generalisable to UK clinical practice, as the study was a cross-sectional, multi-site study that prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK using EQ-5D and EQ-VAS.[54]

Table 33: Summary of utility values used in the base case economic analysis

	Mean	SD
PFS	0.71	0.24
PD	0.67	0.20

Abbreviations: PD: progressed disease; PFS: progression-free survival; SD: standard deviation.
Source: Chouaid *et al.* (2013)[54]

Scenario analyses exploring alternative utility estimates were not considered, given that health state utility values do not impact the incremental QALYs between dabrafenib and trametinib and pembrolizumab plus chemotherapy, given the assumption of clinical equivalence.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The base case economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Appropriate sources of unit costs, such as NHS reference costs 2019–20, the British National Formulary (BNF) online, and the electronic Marketing Information Tool (eMIT) (2021), were used for cost inputs in the model.

Specifically, the following costs components were considered in the base case economic analysis: drug acquisition and administration costs for dabrafenib and trametinib, pembrolizumab plus chemotherapy, drug acquisition and administration costs for subsequent therapies, follow-up and monitoring costs (based on health state), AE costs and terminal care costs.

B.3.5.1 Intervention and comparators' costs and resource use

Intervention

Dabrafenib and trametinib was modelled as dabrafenib 150 mg twice daily and trametinib 2 mg twice daily, in line with their respective SmPCs.[11, 12]

As described in Section B.3.3.2, treatment with dabrafenib and trametinib was modelled in line with the ToT data collected within the BRF113928 trial. As such, patients were assumed to discontinue treatment with dabrafenib and trametinib in line with the treatment discontinuation observed within the BRF113928 trial.

Comparators

Pembrolizumab plus chemotherapy was modelled as a weighted average, based on NICE TA789[6]:

- Pembrolizumab with pemetrexed and carboplatin (84.4%)
- Pembrolizumab with pemetrexed and cisplatin (15.6%)

Full details of the dosing regimens modelled for pembrolizumab plus chemotherapy are listed in Section B.3.2.4.

Based on these dosing regimens, a number of stopping rules were applied to carboplatin, cisplatin and pemetrexed, in addition to the two-year stopping rule applied to pembrolizumab plus chemotherapy.[21] Platinum-based chemotherapy (carboplatin and cisplatin) taken as part of this treatment combination is only given for a maximum number of four three-weekly treatment cycles (Section B.3.2.4). As such, patients in the pembrolizumab plus chemotherapy arm of the model were assumed to discontinue carboplatin or cisplatin in the model after four three-weekly treatment cycles (12 weekly model cycles).

It was also assumed that some patients discontinued pemetrexed after four three-weekly treatment cycles (12 model cycles). Of patients on treatment after 12 model cycles, [redacted]% of patients were assumed to receive maintenance treatment with pemetrexed after this point (Section B.3.2.4).

This is aligned with clinical expert opinion in NICE TA789, which indicated that between 50–60% of patients go onto receive pemetrexed maintenance therapy.[6] This approach was also aligned with the KEYNOTE-189 trial, where patients receive pemetrexed and platinum-based chemotherapy in combination with pembrolizumab every 3 weeks for four cycles, followed by pemetrexed maintenance plus pemetrexed for up to 35 three-weekly cycles.[110] A *post-hoc* analysis of the KEYNOTE-189 trial showed that the median number of three weekly treatment cycles of pemetrexed was 11, ranging from 5 to 30.[134] Given that all patients received at least one cycle of maintenance pemetrexed in KEYNOTE-189, the base case assumption that only [redacted]% of patients receive maintenance pemetrexed is likely to be conservative.[6]

Drug acquisition costs for all treatments were derived from the dosing regimens as detailed in Table 36, with the pack costs taken from the British National Formulary for branded medicines (BNF 2022) or electronic market information tool for generic medicines (eMIT 2021) as outlined in Table 34 and Table 35. Where treatment dosing was dependent on patient weight and/or BSA, drug acquisition costs were calculated based on average dose requirements for the population under evaluation in the model, using patient baseline characteristics from Cohort C of the BRF113928 trial (Section B.3.2.3).

No vial sharing was assumed in the base case economic analysis and where multiple vial/package sizes were available, the cheapest price per mg was applied. Once the drug acquisition costs for dabrafenib and trametinib and pembrolizumab plus chemotherapy were calculated from the respective ToT curves, treatment-specific relative dose intensities (RDIs) were subsequently applied to derive the final drug acquisition costs. RDIs were based on mean daily doses from the BRF113928 trial (detailed in Appendix F.1) and the KEYNOTE-189 trial, respectively.[72, 110]

Finally, it should be noted that a confidential patient access scheme exists for pembrolizumab (as well as atezolizumab, nivolumab and nintedanib that are considered within the model as subsequent therapies – see Section B.3.5.5) that is unknown to Novartis. As such, two sets of cost-effectiveness results have been presented within this submission.

The first set of results uses the currently approved PAS prices for dabrafenib ([redacted]) and trametinib ([redacted]), and the list prices for all comparator and subsequent treatments. These results are presented in the relevant sections of Section B.3 below.

A second set of results has been conducted, where Novartis have made assumptions regarding the PAS discount for pembrolizumab, as well as all subsequent treatments, in order to provide a more indicative set of results. Novartis have assumed that pembrolizumab is associated with a PAS discount of [redacted]%, and for completeness, have also assumed that atezolizumab and nivolumab are associated with PAS discounts of [redacted]%, and nintedanib is associated with a PAS discount of [redacted]. For these analyses, dabrafenib is provided at the [redacted]). These results are provided in a confidential appendix, Appendix O, alongside the main submission dossier.

The tables below provide details of the costs used in the first set of results, where dabrafenib is provided at a [redacted] PAS discount, and all comparators and subsequent treatments are provided at list price.

Table 34: Drug unit and pack costs (dabrafenib and trametinib)

Drug	Unit strength (in mg)	Pack size	Pack cost (list price)	Pack cost [redacted]	Source
Dabrafenib	75	28	£1,400.00	[redacted]	BNF 2022
Trametinib	2	30	£4,800.00	[redacted]	BNF 2022

Abbreviations: BNF: British National Formulary; eMIT: electronic Market Information Tool.

Table 35: Drug unit and pack/vial costs (pembrolizumab plus chemotherapy)

Drug (Intravenous therapies)	Vial/pack size (in mg)	Cost per vial/pack	Source
Pembrolizumab	100	£2,630.00	BNF 2022
Pemetrexed	500	£640.00	BNF 2022
Carboplatin	450	£13.51	eMIT National Database 2021
Cisplatin	100	£8.97	eMIT National Database 2021

Abbreviations: BNF: British National Formulary; eMIT: electronic Market Information Tool.

Table 36: Summary of drug acquisition costs for the treatments included in the base case economic analysis

Drug	Dosing regimen	Packs/ vials per dose	RDI	Cost per dose	Mean dose per cycle	Mean cost per cycle	Proportion of patients receiving each regimen	Source
Dabrafenib plus trametinib								
Dabrafenib	150 mg (two 75 mg capsules) twice daily, until patients no longer derive benefit or unacceptable toxicity	2	0.83	[redacted]	14.00	[redacted]	100%	Dabrafenib SmPC;[11] Appendix F.1 (BRF113928 Clinical Study Report)[91]
Trametinib	2 mg once daily, until patients no longer derive benefit or unacceptable toxicity	1	0.9	[redacted]	7.00	[redacted]		Trametinib SmPC;[12] Appendix F.1 (BRF113928 Clinical Study Report)[91]
Pembrolizumab plus chemotherapy								
Pembrolizumab with pemetrexed and carboplatin								
Pembrolizumab	200 mg every 3 weeks for the first 4 treatment cycles (12 weeks), followed by either:	4	0.956	£10,520.00	0.33 (three	£1,676.19	84.4%	Pembrolizumab SmPC;[23] NICE TA683

Drug	Dosing regimen	Packs/ vials per dose	RDI	Cost per dose	Mean dose per cycle	Mean cost per cycle	Proportion of patients receiving each regimen	Source
	• 200 mg every 3 weeks (for patients receiving pemetrexed maintenance therapy) • 400 mg every 6 weeks (for patients not receiving pemetrexed maintenance therapy). Pembrolizumab is given for a maximum treatment duration of two years in total				weekly dosing) or 0.17 (six-weekly dosing)[a]			for stopping rule;[21] KEYNOTE 189 for RDI[135]
Pemetrexed	500 mg/m^2 every 3 weeks for four treatment cycles (12 weeks), followed by 500 mg/m^2 for the [redacted]% of patients who continue to receive pemetrexed maintenance therapy, for a maximum total treatment duration of two years.	2	0.964	£1,280.00	0.33	£411.31		Pemetrexed SmPC;[136] NICE TA683 for stopping rule;[21] KEYNOTE 189 for RDI[135]
Carboplatin	AUC 5-7 every 3 weeks, for a maximum of 4 treatment cycles (12 model cycles)	1	0.964	£13.51	0.33	£4.34		Pemetrexed SmPC;[136] NICE TA531/TA600 for Carboplatin dose;[59, 137] NICE TA600/KEYNOTE 189 for stopping rule;[135, 137] KEYNOTE 189 for RDI[135]
Pembrolizumab with pemetrexed and cisplatin								

Drug	Dosing regimen	Packs/ vials per dose	RDI	Cost per dose	Mean dose per cycle	Mean cost per cycle	Proportion of patients receiving each regimen	Source
Pembrolizumab	200 mg every 3 weeks for the first 4 treatment cycles (12 weeks), followed by either: • 200 mg every 3 weeks (for patients receiving pemetrexed maintenance therapy) • 400 mg every 6 weeks (for patients not receiving pemetrexed maintenance therapy). Pembrolizumab is given for a maximum treatment duration of two years in total	4	0.956	£10,520.00	0.33 (three weekly dosing) or 0.17 (six-weekly dosing)[a]	£1,676.19	15.6%	Pembrolizumab SmPC;[23] stopping rule assumed same as for carboplatin regimen; RDI assumed the same as pembrolizumab, pemetrexed and carboplatin
Pemetrexed	500 mg/m^2 every 3 weeks for four treatment cycles (12 weeks), followed by 500 mg/m^2 for the [redacted]% of patients who continue to receive pemetrexed maintenance therapy, for a maximum total treatment duration of two years.	2	0.964	£1,280.00	0.33	£411.31		Pemetrexed SmPC;[136] stopping rule assumed same as for carboplatin regimen; RDI assumed the same as pembrolizumab, pemetrexed and carboplatin
Cisplatin	75 mg/m^2 every 3 weeks, for a maximum of 4 treatment cycles (12 model cycles)	2	0.964	£17.94	0.33	£5.76		Pemetrexed SmPC;[136] NICE TA600/KEYNOTE 189 for stopping rule;[137] RDI assumed the same as pembrolizumab,

Drug	Dosing regimen	Packs/ vials per dose	RDI	Cost per dose	Mean dose per cycle	Mean cost per cycle	Proportion of patients receiving each regimen	Source
								pemetrexed and carboplatin

Footnotes: [a] For the first 12 model cycles, all patients receive pembrolizumab once every three weeks. After 12 model cycles, [redacted]% of patients receive pembrolizumab (alongside pemetrexed), at a dose of 200 mg, once every three weeks. The remaining [redacted]% of patients receive pembrolizumab, at a dose of 400 mg, once every six weeks.
Abbreviations: AUC: area under the curve; RDI: relative dose intensity; SmPC: Summary of Product Characteristics; TA: technology appraisal.

B.3.5.2 Drug administration costs

Drug administration costs were considered within the model to reflect the fact that pembrolizumab plus chemotherapy is administered by IV infusion and therefore requires patients to attend hospital appointments to receive treatment. Dabrafenib and trametinib is administered orally and was not assumed to be associated with any administration costs. This assumption is aligned with a number of previous oncology NICE appraisals, where oral treatments have not been assumed to incur any administration costs, including NICE TA810 (abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence).[138]

The unit administration costs associated with pembrolizumab plus chemotherapy were derived from NHS reference costs (2019/2020) and are presented in Table 37.[139] The frequency of administration for the pembrolizumab plus chemotherapy regimens included in the model are outlined in Table 38.

In previous relevant NICE NSCLC submissions (such as NICE TA683[21]), to differentiate between the administration costs for regimens with carboplatin and cisplatin, the unit costs per cycle for regimens with carboplatin were considered 'complex chemotherapy, including prolonged infusional treatment – outpatient' while the costs for regimens with cisplatin were taken as 'complex chemotherapy, including prolonged infusional treatment – day case and regular day/night'.[21] The justification for this was that cisplatin has hydration requirements that requires patients to be brought in the night before treatment, as outlined in NICE TA181 (Pemetrexed for the first-line treatment of NSCLC).[117]

It should also be noted that one administration cost was applied per model cycle, regardless of the number of therapies being received via IV infusion in that cycle. As such in Table 38 below, some treatments administered via IV infusion as part of pembrolizumab plus chemotherapy are listed as having administration costs of £0.00 in particular cycles – for example, pembrolizumab has an administration cost of £0.00 in Cycles 0–2. This does not mean that pembrolizumab is not associated with an administration cost, but reflects the fact that the administration cost of pembrolizumab is assumed to be captured within the administration costs used for carboplatin/cisplatin within these cycles.

Table 37: Unit costs of drug administration used in the base case economic analysis

Admin. type	First admin	Subsequent admin	Source
Oral	£0.00	£0.00	Assumption
Simple IV, outpatient	£221.35	£170.92	NHS Reference Costs 2019/20,[139] Deliver simple parenteral chemotherapy at first attendance: SB12Z, outpatient (for first administration), Deliver subsequent elements of a chemotherapy cycle: SB15Z, outpatient (for subsequent admins)
Complex IV, outpatient	£352.24	£253.77	NHS Reference Costs 2019/20,[139] Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance: SB14Z, outpatient (for first admin), Deliver subsequent elements of a chemotherapy cycle: SB15Z, outpatient (for subsequent administrations)

Complex IV, day case	£431.72	£365.91	NHS Reference Costs 2019/20,[139] Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance: SB14Z, day case (for first admin), Deliver subsequent elements of a chemotherapy cycle: SB15Z, day case (for subsequent administrations)

Abbreviations: NHS: National Health Service; IV: intravenous.

Table 38. Summary of drug administration costs for pembrolizumab plus chemotherapy included in the base case economic analysis (comparators)

Drug	Dosing regimen	Admin type	Mean admins per cycle	Admin cost	Sources
Pembrolizumab plus chemotherapy					
Pembrolizumab with pemetrexed and cisplatin					
Pembrolizumab (Cycles 0–2)	200 mg every 3 weeks for the first 4 treatment cycles (12 weeks), followed by either: • 200 mg every 3 weeks (for patients receiving pemetrexed maintenance therapy) • 400 mg every 6 weeks (for patients not receiving pemetrexed maintenance therapy) for a maximum of 2 years	Simple IV, outpatient	0.33 (three weekly dosing) or 0.17 (six-weekly dosing)[a]	£0.00	Pembrolizumab SmPC,[23] stopping rule assumed same as for carboplatin regimen, RDI assumed the same as Pembrolizumab, Pemetrexed and Carboplatin
Pembrolizumab (Cycles 3–11)				£0.00	
Pembrolizumab (Cycles 12–103)				£9.00	
Pemetrexed (Cycles 0–2)	500 mg/m^2 every 3 weeks, for a maximum of 2 years	Complex IV, outpatient	0.33	£0.00	Pemetrexed SmPC,[136] stopping rule assumed same as for carboplatin regimen, RDI assumed the same as Pembrolizumab, Pemetrexed and Carboplatin
Pemetrexed (Cycles 3–11)				£0.00	
Pemetrexed (Cycles 12–103)				£57.86	
Cisplatin (Cycles 0–2)	75 mg/m^2 every 3 weeks, for a maximum of 4 treatment cycles (12 model cycles)	Complex IV, day case	0.33	£143.91	Pemetrexed SmPC,[136] NICE TA600/KEYNOTE 189 for stopping rule,[135, 137] RDI assumed the same as Pembrolizumab, Pemetrexed and Carboplatin
Cisplatin (Cycles 3–11)				£121.97	
Cisplatin (Cycles 12–103)				£0.00	
Pembrolizumab with pemetrexed and carboplatin					

Pembrolizumab (Cycles 0–2)	200 mg every 3 weeks for the first 4 treatment cycles (12 weeks), followed by either: • 200 mg every 3 weeks (for patients receiving pemetrexed maintenance therapy) • 400 mg every 6 weeks (for patients not receiving pemetrexed maintenance therapy) for a maximum of 2 years	Simple IV, outpatient	0.33 (three weekly dosing) or 0.17 (six-weekly dosing)[a]	£0.00	Pembrolizumab SmPC,[23] NICE TA683 for stopping rule,[21] KEYNOTE 189 for RDI[135]
Pembrolizumab (Cycles 3–11)				£0.00	
Pembrolizumab (Cycles 12–103)				£9.00	
Pemetrexed (Cycles 0–2)	500 mg/m^2 every 3 weeks, for a maximum of 2 years	Complex IV, outpatient	0.33	£0.00	Pemetrexed SmPC,[136] NICE TA683 for stopping rule, KEYNOTE 189 for RDI[135]
Pemetrexed (Cycles 3–11)				£0.00	
Pemetrexed (Cycles 12–103)				£57.86	
Carboplatin (Cycles 0–2)	AUC 5-7 every 3 weeks, for a maximum of 4 treatment cycles	Complex IV, outpatient	0.33	£117.41	Pemetrexed SmPC,[136] NICE TA531/TA600 for Carboplatin dose,[59, 137] NICE TA600/KEYNOTE 189 for stopping rule,[135, 137] KEYNOTE 189 for RDI[135]
Carboplatin (Cycles 3–11)				£84.59	
Carboplatin (Cycles 12–103)				£0.00	

Footnotes: [a] For the first 12 model cycles, all patients receive pembrolizumab once every three weeks. After 12 model cycles, [redacted]% of patients receive pembrolizumab (alongside pemetrexed), at a dose of 200 mg, once every three weeks. The remaining [redacted]% of patients receive pembrolizumab, at a dose of 400 mg, once every six weeks.
Abbreviations: AUC: area under the curve; IV: intravenous; NSCLC: non-small cell lung cancer; RDI: relative dose intensity; SmPC: summary of product characteristics; TA: technology appraisal.

B.3.5.3 Health state unit costs and resource use

Healthcare resource use costs (for example, the costs of follow-up and monitoring services and consultations) were modelled as per-cycle costs, with separate values for the PFS and PD health states. This aligns with prior NICE submissions in advanced NSCLC.[21, 59] The per-cycle costs (detailed in Table 39) were calculated by multiplying the unit costs of services (detailed in Table 40) by the mean frequency of resource use (detailed in Table 41). Unit costs were based on NHS reference costs (2019/20),[139] and the frequency of resource use was based on NICE TA789.[6]

Separate resource use frequencies, and resulting costs per cycle, were considered in the PFS and PD health states. However, given the base case assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in terms of PFS and OS, in the base case economic analysis, patients in both arms of the model are assumed to reside in the PFS and PD health states for the same duration of time. As a result, in the base case economic analysis, healthcare resource use costs were assumed to be the same for both dabrafenib and trametinib and pembrolizumab plus chemotherapy (i.e., they effectively cancel out). Nevertheless, it was still considered important to model the costs associated with follow-up and monitoring services and consultations accurately within the model.

Table 39: Summary of the resource use cost per cycle

Health state	Resource use cost per cycle
PFS	£78.30
PD	£106.17

Abbreviations: PD: progressed disease; PFS: progression-free survival.

Table 40. Resource use unit costs

Resource	Unit cost	Source
Outpatient visit	£150.62	NHS Reference Costs 19/20, Outpatient attendance, Consultant led, 800, Clinical Oncology[139]
Chest radiography	£34.27	NHS Reference Costs 19/20, Other Diagnostic Imaging, Consultant Led, DIM009[139]
CT scan (chest)	£119.01	NHS Reference Costs 19/20, TotalHRG, RD24Z[139]
CT scan (other)	£119.01	NHS Reference Costs 19/20, TotalHRG, RD24Z[139]
ECG	£107.77	NHS Reference Costs 19/20, TotalHRG, EY51Z[139]
Community nurse visit	£75.00	PSSRU 2021; p115; cost per hour Band 8a[140]
Clinical nurse specialist (hours of contact time)	£88.00	PSSRU 2021; p115; cost per hour Band 8b (assuming one hour of time)[140]
GP appointments	£39.00	PSSRU 2021; p118; cost per patient lasting 9.22 minutes[140]
GP home visit	£39.00	PSSRU 2021; p118; cost per patient lasting 9.22 minutes[140]
Therapist visit	£47.00	PSSRU 2021; p132; cost per hour for community occupational therapist (assuming one hour of time)[140]

Abbreviations: ECG: electrocardiogram; HRG: healthcare resource group; NHS: national health service; PSSRU: personal social services research unit.

Table 41. Resource use frequencies

Resource	Resource use per year (PFS)	Resource use per year (PD)	Source
Outpatient visit	9.61	7.91	NICE TA789[6]
Chest radiography	6.79	6.50	
CT scan (chest)	0.62	0.24	
CT scan (other)	0.36	0.42	
ECG	1.04	0.88	
Community nurse visit	8.70	8.70	
Clinical nurse specialist (hours of contact time)	12.00	12.00	
GP appointments	12.00	0.00	
GP home visit	0.00	26.09	
Therapist visit	0.00	26.09	

Abbreviations: ECG: electrocardiogram; GP: general practitioner; PD: progressed disease; PFS: progression-free survival; TA: technology appraisal.

B.3.5.4 Adverse reaction unit costs and resource use

As previously detailed, the base case economic analysis included all-cause Grade ≥3 AEs experienced by ≥1% of patients for dabrafenib and trametinib or pembrolizumab plus chemotherapy.

The unit costs associated with the management of the AEs included in the model are presented in Table 42. Cost estimates for the treatment of each AE were sourced from NHS reference costs (2019/2020) where possible, using the most appropriate HRG codes in line with each relevant AE, and calculating weighted averages where a range of codes were considered relevant. The use of NHS reference costs was aligned with NICE TA789,[6] and the NHS reference costs were reviewed directly to derive the most appropriate code for each AE. In some cases, the costs associated with certain AEs were assumed to be the same as other, similar AEs, as has been done in previous advanced NSCLC NICE appraisals. For example, the cost of an increase in aspartate aminotransferase was assumed to be the same as alanine aminotransferase, as detailed in Table 42, below.

The costs associated with each AE were applied as a lump sum in the first model cycle. Whilst this is a simplifying assumption, it is an approach that has been adopted in multiple previous NICE appraisals for advanced NSCLC, including NICE TA789,[6] and closely aligns with the assumption that the majority of AEs would be expected to be experienced soon after treatment initiation.

Table 42. Unit costs of the AEs included in the economic model

Adverse event	Unit cost	Source
Abdominal pain	£649.11	NHS Reference Costs: Weighted average of Total HRGs FD05A-B (Abdominal Pain Without Interventions)
Alanine aminotransferase	£1,755.79	NHS Reference Costs: Weighted average of Total HRGs GC17A-K (Non-Malignant, Hepatobiliary or Pancreatic Disorders)

Anaemia	£1,453.86	NHS Reference Costs: Weighted average of Total HRGs SA01G-K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia)
Arthralgia	£954.70	Assumed same as back pain
Aspartate aminotransferase increased	£1,755.79	Assumed same as alanine aminotransferase increased
Asthenia	£672.11	Assumed same as fatigue
Back pain	£954.70	NHS Reference Costs: Weighted average of Total HRGs HC32G-K (Low Back Pain)
Blood alkaline phosphatase increase	£1,755.79	Assumed same as alanine aminotransferase increased
Colitis (immune-mediated)	£1,366.10	Assumed same as diarrhoea
Constipation	£1,366.10	Assumed same as diarrhoea
Decreased appetite	£0.00	Assumed no cost
Diarrhoea	£1,366.10	NHS Reference Costs: Weighted average of Total HRGs FD01A-J (Gastrointestinal Infections)
Dry skin	£1,229.13	NHS Reference Costs: Weighted average of Total HRGs JD07E-K (Skin Disorders without Interventions)
Dyspnoea	£684.17	NHS Reference Costs: Weighted average of Total HRGs DZ19H (Other Respiratory Disorders)
Fatigue	£672.11	NHS Reference Costs: Weighted average of Total HRGs SA04G-L (Iron Deficiency Anaemia)
Headache	£643.29	NHS Reference Costs: Weighted average of Total HRGs AA31C-E (Headache, Migraine or Cerebrospinal Fluid Leak)
Hepatitis (immune-mediated)	£4,555.18	NHS Reference Costs: Weighted average of Total HRGs GC17A-F (Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions)
Hypertension	£638.81	NHS Reference Costs: Total HRG EB04Z (Hypertension)
Hyponatremia	£0.00	Assumed no cost
Hypotension	£638.81	EB04Z (Hypertension)
Nausea	£649.11	Assumed same as abdominal pain
Nephritis (immune-mediated)	£1,961.20	NHS Reference Costs: Weighted average of Total HRGs LA07H-P (Acute Kidney Injury)
Neutropenia	£1,694.30	NHS Reference Costs: Weighted average of Total HRGs SA35A-E (Agranulocytosis)
Pain in extremity	£1,000.07	NHS Reference Costs: Weighted average of Total HRGs WH08A-B (Unspecified Pain)
Pneumonia	£1,909.33	NHS Reference Costs: Weighted average of Total HRGs DZ11K-V (Lobar, Atypical or Viral Pneumonia, with Multiple Interventions)
Pneumonitis (immune-mediated)	£1,909.33	Assumed same as pneumonia
Pruritis	£1,479.28	Assumed same as rash
Pyrexia	£1,982.10	NHS Reference Costs: Weighted average of Total HRGs WH07A-D (Fever of Unknown Origin)

Rash	£1,479.28	NHS Reference Costs: Weighted average of Total HRGs JD07A-K (Skin disorders)
Severe skin reactions (immune-mediated)	£2,427.22	NHS Reference Costs: Weighted average of Total HRGs JD07A-C and E-H (Skin disorders)
Thrombocytopenia	£770.92	NHS Reference Costs: Weighted average of Total HRGs SA12G-K (Thrombocytopenia)
Vomiting	£649.11	Assumed same as abdominal pain
Weight decreased	£0.00	Assumed no cost
Weight increased	£0.00	Assumed no cost

Abbreviations: AE: adverse event; HRG: healthcare resource group; NHS: National Health Service; TA: technology appraisal.

B.3.5.5 Subsequent therapies cost and resource use

Proportions of patients receiving subsequent treatment

Subsequent therapy costs (comprising drug administration and drug acquisition costs) were included within the base case economic analysis and applied as a lump sum cost upon entry into the progressed disease (PD) state within the model. The subsequent treatments received by patients following treatment with dabrafenib and trametinib and pembrolizumab plus chemotherapy are shown in Table 43.

The proportions of patients receiving subsequent treatment was derived from Cohort C of the BRF113928 trial, where [redacted] out of [redacted] patients ([redacted]%) received a subsequent treatment after dabrafenib and trametinib. This proportion was used in the base case, and is aligned with previous NICE appraisals in advanced NSCLC. For example in NICE TA584 (atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer),[141] the Cancer Drugs Fund clinical lead estimated that no more than 50% of patients would receive subsequent treatment following atezolizumab and clinical experts assumed an upper limit of 60%.

Of the patients who received subsequent treatment in the BRF113928 trial, 55% received chemotherapy and 45% received immunotherapy. These proportions were applied to the dabrafenib and trametinib arm in the model. It was assumed that chemotherapy consistent of carboplatin plus pemetrexed, and immunotherapy was split equally between atezolizumab, nivolumab and pembrolizumab monotherapy.

For pembrolizumab plus chemotherapy, subsequent treatment data from the FLATIRON RWE study (2022) were based on very small patient numbers (N=5), and were not aligned with UK clinical practice, as some patients were re-challenged with immunotherapy regimens (Appendix D.3.2.2, Table 40).

Due to these limitations, the model assumed that [redacted]% of patients receive subsequent treatment following pembrolizumab plus chemotherapy, in line with the dabrafenib and trametinib arm. Of these, it was assumed that 50% of patients would receive docetaxel plus nintedanib, and 50% would receive docetaxel monotherapy, based on the assumptions accepted by the NICE committee in NICE TA789.[6] Similarly, Lester *et al.* (2021) indicated that similar proportions of patients receive docetaxel monotherapy or docetaxel plus nintedanib in the UK.[142]

The subsequent treatment proportions for dabrafenib and trametinib, and pembrolizumab plus chemotherapy are summarised in Table 43 below.

Table 43: Subsequent treatments modelled upon entry to the progressed disease state

Initial treatment / Subsequent treatment	Dabrafenib and trametinib	Pembrolizumab plus chemotherapy
Patients receiving subsequent treatment (%, out of patients receiving initial treatment)		
Proportion receiving subsequent treatment	[redacted]	[redacted]
Subsequent treatment distributions (%, out of patients receiving subsequent treatment)		
Pembrolizumab monotherapy	[redacted]	0%
Atezolizumab monotherapy	[redacted]	0%
Nivolumab monotherapy	[redacted]	0%
Pemetrexed plus carboplatin	[redacted]	0%
Docetaxel monotherapy	0%	50%
Docetaxel plus nintedanib	0%	50%

An additional scenario analysis was conducted where the proportion of patients receiving immunotherapy out of those receiving subsequent therapy after dabrafenib and trametinib was increased (60% of patients received immunotherapy, and 40% received chemotherapy). This was conducted to reflect the place of immunotherapy as standard of care in UK clinical practice in this setting, based on clinical expert feedback (Section B.3.10.3).[8]

However, it is important to note that clinicians believed that immunotherapy monotherapy may not be as effective in a patient population with an actionable mutation, but recognised that there is limited evidence available.[8]

Subsequent treatment duration

UK clinical experts indicated that the average duration of immunotherapy monotherapy in patients with previously treated advanced NSCLC would be approximately 12–15 weeks.[8] The clinicians considered that this would be an appropriate assumption for patients following treatment with dabrafenib and trametinib.

As such, in the base case economic analysis, it was assumed that treatment with subsequent immunotherapies would last for 13.5 weeks (the mid-way point). The same average treatment duration was applied to chemotherapy, for consistency.

However, given the uncertainty surrounding the durations of subsequent treatments, a scenario analysis was conducted, whereby the treatment durations for each treatment were aligned with the values used in NICE TA789 (or NICE TA347 [nintedanib for previously treated locally advanced, metastatic, or locally recurrent NSCLC] for docetaxel plus nintedanib), as detailed in Table 44 below.

The total costs and duration of each subsequent therapy regimen following entry into the PD state are shown in Table 44. A detailed breakdown of the dosing regimens and drug acquisition costs used for each subsequent treatment is presented in Appendix K.

Table 44: Calculated costs for each subsequent treatment

	Base case			Scenario analysis		
Subsequent treatment	**Total cost**	**Duration (weeks)**	**Source (for duration)**	**Total cost**	**Duration (weeks)**	**Source (for duration)**
Pembrolizumab monotherapy	£23,915.64	13.5	UK clinical expert opinion sought by Novartis[8]	£41,416.79	23.4	Derived from NICE TA789 (Table 58);[6] Sourced from NICE TA428[60]
Atezolizumab monotherapy	£18,781.65	13.5	UK clinical expert opinion sought by Novartis[8]	£19,229.38	14.8	Derived from NICE TA789 (Table 58);[6] Sourced from NICE TA520[99]
Nivolumab monotherapy	£18,834.71	13.5	UK clinical expert opinion sought by Novartis[8]	£35,253.56	25.3	Derived from NICE TA789 (Table 58);[6] Sourced from NICE TA483[143] and TA484[144]
Pemetrexed plus carboplatin	£6,807.60	13.5	Assumed equal to the duration of immunotherapy, based on clinical expert opinion[8]	£7,443.92	15.0	NICE TA789[6]
Docetaxel monotherapy	£872.63	13.5	Assumed equal to the duration of immunotherapy, based on clinical expert opinion[8]	£1,151.92	18.0	Derived from NICE TA789 (Table 58);[6] Sourced from NICE TA347[116]
Docetaxel plus nintedanib	£7,514.04	13.5	Assumed equal to the duration of immunotherapy, based on clinical expert opinion[8]	£10,173.35	18.3	NICE TA347[116]

Abbreviations: IPD: individual patient data; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PD-L1: programmed death-ligand 1; TA: technology appraisal.

B.3.5.6 End-of-life costs and resource use

In the base case economic analysis, a one-off cost was applied to all patients when they entered the death state of the economic model, to reflect the cost of terminal care. In line with recent NICE advanced NSCLC appraisals,[21, 59, 106] the terminal care costs from Brown *et al.* (2013)[145] were applied and inflated to 2020/2021 values as appropriate (Table 45). Costs were estimated as a weighted average over costs in various care settings (Table 45).

Table 45. Terminal care costs upon entering death state

Care setting	Unit cost	% of patients in care setting	Source
Terminal care in hospital	£4,290.68	56%	NICE TA531,[59] TA683[21] and TA705,[106] inflated to 2020/2021
Terminal care in hospice	£5,363.35	17%	NICE TA531,[59] TA683,[21] TA705:[106] assumed 25% price increase on hospital inpatient care
Other	£0.00	27%	Assumption
Total cost of terminal care, per patient	£3,314.55	NA	Weighted average of 'Terminal care in hospital' 'Terminal care in hospice' and 'Other'

Abbreviations: NA: not applicable; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

B.3.6 Severity

The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider *et al.* (2022).[146] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2018–2020.[147] The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava *et al.* (2022) through the NICE DSU.[131]

The total QALYs for the current UK population of patients with previously untreated advanced NSCLC with a BRAF V600 mutation was set equal to the QALYs associated with pembrolizumab plus chemotherapy in the base case economic analysis. Despite the fact that advanced NSCLC with a BRAF mutation is associated with a poor prognosis, the absolute QALY shortfall and proportional QALY shortfall were below the threshold of 12 and 0.85, respectively, therefore a severity modifier of 1 is applied in the base case results.

Table 46: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Percentage male	38.9%	Section B.3.2.3
Mean age	67.8	Section B.3.2.3

Abbreviations: QALY: quality-adjusted life year.

Table 47: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
PFS	0.710	[redacted]
PD	0.670	[redacted]

Abbreviations: PFS: progression-free survival; PD: progressed disease; QALY: quality-adjusted life year.

Table 48: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
9.871	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year.

B.3.7 Uncertainty

As highlighted in Section B.1.3 and throughout this submission, advanced NSCLC with a BRAF V600 mutation is a rare subtype of the overall NSCLC population. As a result, the patient population of the BRF113928 trial, and the patients identified in the FLATIRON RWE study (2022) receiving pembrolizumab plus chemotherapy were low (N=36 and N=[redacted], respectively), introducing unavoidable uncertainty into the economic analysis. Further limitations of the clinical evidence supporting this submission and therefore factors that may contribute to uncertainty within the base case analysis are detailed in Section B.2.12.2.

B.3.8 Summary of base case economic analysis inputs and assumptions

B.3.8.1 Summary of base case economic analysis inputs

A summary of the base case economic analysis inputs is provided in Table 49. A table detailing how the parameter uncertainty of each variable was sampled in the PSA is presented in Appendix P.

Table 49: Summary of base case economic analysis inputs

Input	Value	Reference to section in submission
Model settings		
Cycle length	7 days	Section B.3.2
Time horizon	Lifetime	Section B.3.2
Discount rate (costs and outcomes)	3.5%	Section B.3.2
Patient characteristics		
Percentage male	38.9%	Section B.3.2.3
Mean age	67.8	Section B.3.2.3
Mean BSA	1.82	Section B.3.2.3
Clinical efficacy: dabrafenib and trametinib		
PFS	Log-logistic	Section B.3.3.1
OS	Weibull	Section B.3.3.1
ToT	Exponential	Section B.3.3.1
Clinical efficacy: Pembrolizumab plus chemotherapy		

Input	Value	Reference to section in submission
PFS	Equal to dabrafenib and trametinib PFS	Section B.3.3.1
OS	Equal to dabrafenib and trametinib OS	Section B.3.3.1
ToT	Exponential	Section B.3.3.1
Pembrolizumab and pemetrexed stopping rule	2 years	Section B.3.5.1
Proportion of patients receiving pemetrexed maintenance therapy	[redacted]%	Section B.3.5.1
Carboplatin/cisplatin stopping rule	Four three-weekly cycles (12 model cycles)	Section B.3.5.1
AE frequency: dabrafenib and trametinib		
Abdominal pain	1.08%	Section B.3.3.3
Alanine aminotransferase	6.45%	Section B.3.3.3
Anaemia	5.37%	Section B.3.3.3
Arthralgia	1.08%	Section B.3.3.3
Aspartate aminotransferase increased	3.23%	Section B.3.3.3
Asthenia	4.30%	Section B.3.3.3
Back pain	3.23%	Section B.3.3.3
Blood alkaline phosphatase increase	1.08%	Section B.3.3.3
Diarrhoea	2.15%	Section B.3.3.3
Dry skin	1.08%	Section B.3.3.3
Dyspnoea	7.53%	Section B.3.3.3
Fatigue	3.23%	Section B.3.3.3
Headache	1.08%	Section B.3.3.3
Hypertension	9.68%	Section B.3.3.3
Hyponatremia	9.68%	Section B.3.3.3
Hypotension	4.30%	Section B.3.3.3
Neutropenia	7.53%	Section B.3.3.3
Pain in extremity	1.08%	Section B.3.3.3
Pneumonia	1.08%	Section B.3.3.3
Pruritis	2.15%	Section B.3.3.3
Pyrexia	6.45%	Section B.3.3.3
Rash	2.15%	Section B.3.3.3
Vomiting	3.23%	Section B.3.3.3
Weight decreased	1.08%	Section B.3.3.3
Weight increased	3.23%	Section B.3.3.3
AE frequency: pembrolizumab plus chemotherapy		
Anaemia	18.50%	Section B.3.3.3
Asthenia	6.70%	Section B.3.3.3
Back pain	1.50%	Section B.3.3.3
Colitis (immune-mediated)	1.70%	Section B.3.3.3

Input	Value	Reference to section in submission
Constipation	1.00%	Section B.3.3.3
Decreased appetite	1.20%	Section B.3.3.3
Diarrhoea	5.20%	Section B.3.3.3
Dyspnoea	4.00%	Section B.3.3.3
Fatigue	7.70%	Section B.3.3.3
Hepatitis (immune-mediated)	1.50%	Section B.3.3.3
Nausea	3.50%	Section B.3.3.3
Nephritis (immune-mediated)	1.50%	Section B.3.3.3
Neutropenia	16.30%	Section B.3.3.3
Pneumonitis (immune-mediated)	3.00%	Section B.3.3.3
Pyrexia	0.20%	Section B.3.3.3
Rash	2.00%	Section B.3.3.3
Severe skin reactions (immune-mediated)	2.50%	Section B.3.3.3
Thrombocytopenia	8.40%	Section B.3.3.3
Vomiting	4.00%	Section B.3.3.3
Health state utility values		
PFS	0.710	Section B.3.4.7
PD	0.670	Section B.3.4.7
AE disutilities		
Abdominal pain	-0.069	Section B.3.4.4
Alanine aminotransferase	-0.05	Section B.3.4.4
Anaemia	-0.073	Section B.3.4.4
Arthralgia	-0.069	Section B.3.4.4
Aspartate aminotransferase increased	-0.051	Section B.3.4.4
Asthenia	-0.073	Section B.3.4.4
Back pain	-0.069	Section B.3.4.4
Blood alkaline phosphatase increase	-0.05	Section B.3.4.4
Colitis (immune-mediated)	-0.11	Section B.3.4.4
Constipation	-0.047	Section B.3.4.4
Decreased appetite	-0.085	Section B.3.4.4
Diarrhoea	-0.047	Section B.3.4.4
Dry skin	-0.032	Section B.3.4.4
Dyspnoea	-0.05	Section B.3.4.4
Fatigue	-0.073	Section B.3.4.4
Headache	-0.069	Section B.3.4.4
Hepatitis (immune-mediated)	-0.11	Section B.3.4.4
Hypertension	-0.03	Section B.3.4.4
Hyponatremia	-0.085	Section B.3.4.4
Hypotension	-0.03	Section B.3.4.4
Nausea	-0.048	Section B.3.4.4

Input	Value	Reference to section in submission
Nephritis (immune-mediated)	-0.11	Section B.3.4.4
Neutropenia	-0.09	Section B.3.4.4
Pain in extremity	-0.069	Section B.3.4.4
Pneumonia	-0.008	Section B.3.4.4
Pneumonitis (immune-mediated)	-0.11	Section B.3.4.4
Pruritis	-0.032	Section B.3.4.4
Pyrexia	-0.11	Section B.3.4.4
Rash	-0.032	Section B.3.4.4
Severe skin reactions (immune-mediated)	-0.11	Section B.3.4.4
Thrombocytopenia	-0.003	Section B.3.4.4
Vomiting	-0.048	Section B.3.4.4
Weight decreased	0	Section B.3.4.4
Weight increased	0	Section B.3.4.4
AE durations (days)		
Abdominal pain	31	Section B.3.4.4
Alanine aminotransferase	54.8	Section B.3.4.4
Anaemia	3	Section B.3.4.4
Arthralgia	31	Section B.3.4.4
Aspartate aminotransferase increased	54.8	Section B.3.4.4
Asthenia	52	Section B.3.4.4
Back pain	31	Section B.3.4.4
Blood alkaline phosphatase increase	54.8	Section B.3.4.4
Colitis (immune-mediated)	3	Section B.3.4.4
Constipation	3	Section B.3.4.4
Decreased appetite	10.5	Section B.3.4.4
Diarrhoea	3	Section B.3.4.4
Dry skin	117.6	Section B.3.4.4
Dyspnoea	18.8	Section B.3.4.4
Fatigue	212	Section B.3.4.4
Headache	31	Section B.3.4.4
Hepatitis (immune-mediated)	7	Section B.3.4.4
Hypertension	150	Section B.3.4.4
Hyponatremia	7	Section B.3.4.4
Hypotension	183.4	Section B.3.4.4
Nausea	10.5	Section B.3.4.4
Nephritis (immune-mediated)	7	Section B.3.4.4
Neutropenia	158	Section B.3.4.4
Pain in extremity	31	Section B.3.4.4
Pneumonia	19.6	Section B.3.4.4
Pneumonitis (immune-mediated)	19.6	Section B.3.4.4

Input	Value	Reference to section in submission
Pruritis	117.6	Section B.3.4.4
Pyrexia	7.6	Section B.3.4.4
Rash	117.6	Section B.3.4.4
Severe skin reactions (immune-mediated)	117.6	Section B.3.4.4
Thrombocytopenia	37.2	Section B.3.4.4
Vomiting	2	Section B.3.4.4
Weight decreased	0	Section B.3.4.4
Weight increased	0	Section B.3.4.4
Treatment administration disutility		
Infusion administration (cycles 0-11)	-0.023	Section B.3.4.5
Infusion administration (cycles 12+)	-0.023	Section B.3.4.5
Drug acquisition costs (per cycle)		
Dabrafenib and trametinib	[redacted]	Section B.3.5.1
Pembrolizumab plus chemotherapy (Cycle 0–11)	£2,092.06	Section B.3.5.1
Pembrolizumab plus chemotherapy (Cycles 12–103)	£1,957.52	Section B.3.5.1
Drug administration costs (per cycle)		
Dabrafenib and trametinib	£0.00	Section B.3.5.2
Pembrolizumab plus chemotherapy (Cycle 0–2)	£121.55	Section B.3.5.2
Pembrolizumab plus chemotherapy (Cycle 3–11)	£90.42	Section B.3.5.2
Pembrolizumab plus chemotherapy (Cycle 12–103)	£66.86	Section B.3.5.2
Annual health state resource use: PFS		
Outpatient visit	9.61	Section B.3.5.3
Chest radiography	6.79	Section B.3.5.3
CT scan (chest)	0.62	Section B.3.5.3
CT scan (other)	0.36	Section B.3.5.3
ECG	1.04	Section B.3.5.3
Community nurse visit	8.70	Section B.3.5.3
Clinical nurse specialist (hours of contact time)	12.00	Section B.3.5.3
GP appointments	12.00	Section B.3.5.3
GP home visit	0.00	Section B.3.5.3
Therapist visit	0.00	Section B.3.5.3
Annual health state resource use: PD		
Outpatient visit	7.91	Section B.3.5.3
Chest radiography	6.50	Section B.3.5.3
CT scan (chest)	0.24	Section B.3.5.3
CT scan (other)	0.42	Section B.3.5.3
ECG	0.88	Section B.3.5.3
Community nurse visit	8.70	Section B.3.5.3

Input	Value	Reference to section in submission
Clinical nurse specialist (hours of contact time)	12.00	Section B.3.5.3
GP appointments	0.00	Section B.3.5.3
GP home visit	26.09	Section B.3.5.3
Therapist visit	26.09	Section B.3.5.3
Health state unit costs		
Outpatient visit	£150.62	Section B.3.5.3
Chest radiography	£34.27	Section B.3.5.3
CT scan (chest)	£119.01	Section B.3.5.3
CT scan (other)	£119.01	Section B.3.5.3
ECG	£107.77	Section B.3.5.3
Community nurse visit	£75.00	Section B.3.5.3
Clinical nurse specialist (hours of contact time)	£88.00	Section B.3.5.3
GP appointments	£39.00	Section B.3.5.3
GP home visit	£39.00	Section B.3.5.3
Therapist visit	£47.00	Section B.3.5.3
AE costs		
Abdominal pain	£649.11	Section B.3.5.4
Alanine aminotransferase	£1,755.79	Section B.3.5.4
Anaemia	£1,453.86	Section B.3.5.4
Arthralgia	£954.70	Section B.3.5.4
Aspartate aminotransferase increased	£1,755.79	Section B.3.5.4
Asthenia	£672.11	Section B.3.5.4
Back pain	£954.70	Section B.3.5.4
Blood alkaline phosphatase increase	£1,755.79	Section B.3.5.4
Colitis (immune-mediated)	£1,366.10	Section B.3.5.4
Constipation	£1,366.10	Section B.3.5.4
Decreased appetite	£0.00	Section B.3.5.4
Diarrhoea	£1,366.10	Section B.3.5.4
Dry skin	£1,229.13	Section B.3.5.4
Dyspnoea	£684.17	Section B.3.5.4
Fatigue	£672.11	Section B.3.5.4
Headache	£643.29	Section B.3.5.4
Hepatitis (immune-mediated)	£4,555.18	Section B.3.5.4
Hypertension	£638.81	Section B.3.5.4
Hyponatremia	£0.00	Section B.3.5.4
Hypotension	£638.81	Section B.3.5.4
Nausea	£649.11	Section B.3.5.4
Nephritis (immune-mediated)	£1,961.20	Section B.3.5.4
Neutropenia	£1,694.30	Section B.3.5.4
Pain in extremity	£1,000.07	Section B.3.5.4

Input	Value	Reference to section in submission
Pneumonia	£1,909.33	Section B.3.5.4
Pneumonitis (immune-mediated)	£1,909.33	Section B.3.5.4
Pruritis	£1,479.28	Section B.3.5.4
Pyrexia	£1,982.10	Section B.3.5.4
Rash	£1,479.28	Section B.3.5.4
Severe skin reactions (immune-mediated)	£2,427.22	Section B.3.5.4
Thrombocytopenia	£770.92	Section B.3.5.4
Vomiting	£649.11	Section B.3.5.4
Weight decreased	£0.00	Section B.3.5.4
Weight increased	£0.00	Section B.3.5.4
Subsequent therapy costs		
Dabrafenib and trametinib	£7,161.40	Section B.3.5.5
Pembrolizumab plus chemotherapy	£2,348.27	Section B.3.5.5
Terminal care costs		
Terminal care	£3,314.55	Section B.3.5.6

Abbreviations: AE: adverse event; BSA: body surface area; CI: confidence interval; CT: computerised tomography; ECG: electrocardiogram; GP: general practitioner; N/A: not applicable; OS: overall survival; PD: progressed disease; PFS: progression-free survival; ToT: time on treatment.

B.3.8.2 Assumptions

A summary of the assumptions adopted within the base case economic analysis is provided in Table 50.

Table 50: Summary of assumptions adopted within the base case economic analysis

Variable	Assumption	Justification	Scenarios conducted to explore uncertainty
PFS for dabrafenib and trametinib	The log-logistic extrapolation of the BRF113928 trial Cohort C PFS data was used in the base case.	NICE DSU TSD 14 states that, when the observed dataset is mature, AIC/BIC is particularly useful for curve selection.[111] As such, the best fitting log-logistic extrapolation was selected for the base case.	The two curves with the next best statistical fit (lognormal and Generalised gamma) were explored in scenario analyses (Section B.3.10.3)
OS for dabrafenib and trametinib	The Weibull extrapolation of the BRF113928 trial Cohort C OS data was used in the base case,	Clinical expert opinion indicated that the 10-year OS rate associated with dabrafenib and trametinib would likely be ~[redacted]%.[8] As such, the Weibull extrapolation, which provided the most pessimistic 10-year OS rate ([redacted]%), in line with the clinical expert estimates, was selected as the base case cost-effectiveness analysis.	The exponential curve, which predicted [redacted]% patients to be alive at 10 years, was explored in a scenario analysis, as the next most clinically plausible extrapolation (Section B.3.10.3).
ToT for dabrafenib and trametinib	The exponential extrapolation of BRF113928 trial Cohort C ToT data was used in the base case.	In line with PFS, given the maturity of the ToT data, the best-fitting exponential extrapolation was selected for the base case. While the ToT KM data were complete, fitting a parametric model to the KM data was considered more appropriate, to model a more continuous rate of discontinuation over time.	The next two best statistically fitting extrapolations after the exponential (Weibull and Gompertz) were explored in scenario analyses. A scenario was also conducted using the BRF113928 trial ToT KM data directly (Section B.3.10.3)
Source of PFS and OS data for pembrolizumab plus chemotherapy	PFS and OS for pembrolizumab plus chemotherapy were assumed to be clinically equivalent (equal) to PFS and OS for dabrafenib and trametinib in the base case economic analyses.	As previously detailed in Section B.2.9.2 and B.2.9.3 and Section B.3.2, an assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy in terms of PFS and OS was assumed to be reasonable given the uncertainties associated with the updated external control analysis of the BRF113928 trial (FLATIRON RWE study [2022]). This assumption was also supported by clinical expert feedback.[8]	No scenario analyses were conducted to explore alternative sources of PFS and OS data for pembrolizumab plus chemotherapy. Clinical experts consulted as part of this appraisal noted that the extrapolations for pembrolizumab plus chemotherapy based on the FLATIRON RWE study (2022) lacked clinical plausibility when compared to KEYNOTE-189.[8, 110] However, scenario analyses 1 to 3 explore alternative curve choices for PFS and OS for dabrafenib and trametinib (and therefore pembrolizumab plus chemotherapy)

Pembrolizumab plus chemotherapy ToT	ToT for pembrolizumab plus chemotherapy was assumed to be based on the ToT for pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022) weighted analysis.	It was deemed appropriate to utilise ToT for pembrolizumab plus chemotherapy from the FLATIRON RWE study (2022), given its similarity to external pembrolizumab plus chemotherapy data, rather than assuming equivalence to dabrafenib and trametinib ToT.	Scenario analyses 7 and 8 were conducted to explore alternative curve choices to extrapolate pembrolizumab plus chemotherapy ToT from the FLATIRON RWE study (2022). Scenario analysis 9 explored setting ToT for pembrolizumab plus chemotherapy equal to ToT for dabrafenib and trametinib (but with the relevant RDI and stopping rules applied for pembrolizumab plus chemotherapy) Scenario analysis 10 explored the use of the pembrolizumab plus chemotherapy KM data from the FLATIRON RWE study (2022) directly.
Composition of pembrolizumab plus chemotherapy	The following assumptions were made to model pembrolizumab plus chemotherapy in the base case economic analysis: • 84.4% of patients were assumed to receive carboplatin (alongside pembrolizumab and pemetrexed) and 15.6% of patients were assumed to receive cisplatin (alongside pembrolizumab and pemetrexed) • [redacted]% of patients were assumed to receive maintenance pemetrexed • After the first four treatment cycles (12 weeks), pembrolizumab was assumed to be provided as a three-weekly dosing interval if patients were also receiving maintenance pemetrexed,	• The 84.4%/15.6% split between carboplatin/cisplatin was used in NICE TA789,[6] which UK clinical experts found to be appropriate based on their experience • The proportion of patients receiving pemetrexed maintenance therapy ([redacted]%) was based on the proportion of patients in the pembrolizumab plus chemotherapy arm of the FLATIRON RWE study (2022) who received maintenance treatment with pemetrexed following discontinuation of carboplatin or cisplatin. • The dosing scheduling of pembrolizumab was based on feedback from UK clinical experts[8]	No scenario analyses were conducted to vary the proportion of patients receiving carboplatin versus cisplatin, or the proportion of patients receiving maintenance pemetrexed, as it was not considered that this would have a material impact on the base case ICER. The change in dosing schedule for pembrolizumab due to the COVID pandemic has no effect on the base case ICER.

	but at a six-weekly dosing interval for patients who were receiving it as monotherapy		
Pembrolizumab plus chemotherapy stopping rules	After four three-weekly treatment cycles (12 model cycles), patients were assumed to receive either pembrolizumab or pembrolizumab plus pemetrexed (based on the above) based on the ToT extrapolation until the end of Year 2, at which point, patients in the pembrolizumab plus chemotherapy arm were assumed to discontinue all treatment.	Adjustments were made to the ToT model trace for pembrolizumab plus chemotherapy to account for the stopping rule imposed in NICE TA683.[21] As such, after two years, the number of patients receiving pembrolizumab plus chemotherapy in the economic model was set to zero.	No scenario analyses were conducted to explore the impact of the application of the stopping rule for pembrolizumab and pemetrexed, given this rule is stipulated in the NICE guidance for these therapies (NICE TA683).[21]
Disutility associated with treatments administered via IV infusion	It was assumed that patients receiving pembrolizumab plus chemotherapy incur an infusion-related disutility of -0.023 in every cycle that they remain on treatment, based on a utility value derived from Matza *et al.* (2013).[128]	This assumption was adopted to reflect the fact that treatments administered via IV infusion, and requiring patients to visit hospital, are assumed to be less convenient, more painful and more burdensome, versus orally administered treatments.	Scenario analyses 13 and 14 were conducted to explore the use of increased and decreased infusion related disutility estimates, as previously detailed in Section B.3.4.5.
Sources of AE disutility and duration estimates	AE disutility and duration estimates were sourced from NICE TA789,[6] or from previous advanced NSCLC NICE appraisals.	There were no data identified in the published literature reporting the disutility associated with AEs for patients with previously untreated advanced NSCLC with a BRAF V600 mutation specifically, and no HRQoL data were collected in the BRF113928 trial. Therefore, NICE TA789 was considered to represent the most reliable source given its recent assessment by NICE.[6] Where required, other NICE	Whilst no specific scenario analyses were run to explore the assumptions adopted for AE disutilities and durations, the overall AE disutility estimates associated with AEs for dabrafenib and trametinib, and for pembrolizumab plus chemotherapy, which are calculated as a weighted average of the disutility, duration and frequency of each AE, have been included in the PSA and DSA, in order to explore the uncertainty associated with both of these inputs on the base case economic analysis.

		appraisals including patients with NSCLC, or publications in the literature. The BRF113928 trial reported only limited data on the durations of AEs. As such, it was necessary to use data from the published literature, and recent NICE NSCLC appraisals were considered to represent the most robust sources of data available.	
Health state utility values	Health state utility values for the PFS and PD health states in the base case economic analysis were assumed to be based on Chouaid *et al.* (2013).[54]	The BRF113928 trial did not collect HRQoL data so utility values had to be sourced from the published literature. Chouaid *et al.* (2013) was a cross-sectional, multi-site study that prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK using EQ-5D and EQ-VAS.[54] This was considered an appropriate source of health state utility values, in line with the NICE reference case. The resulting utility estimates were aligned with the range of estimates used in prior NICE appraisals in NSCLC.	The PFS and PD health state utility values were varied in the PSA and DSA to characterise the uncertainty surrounding these inputs. No scenario analyses using alternative utility values were conducted; given the assumption of clinical equivalence, the choice of health state utility values does not impact the incremental QALYs accrued between dabrafenib and trametinib and pembrolizumab plus chemotherapy.
Administration costs associated with oral treatments	It was assumed that dabrafenib and trametinib, as an oral treatment, was not associated with any administration costs.	This assumption is aligned with a number of previous appraisals in oncology where oral treatments have not been assumed to incur any administration costs, including NICE TA810.[138]	This assumption was not explored in sensitivity or scenario analyses.
Administration costs associated with pembrolizumab plus chemotherapy	It was assumed that, in treatment cycles where patients receive IV infusions for multiple components of pembrolizumab plus chemotherapy, then the	This represents a reasonable assumption, to reflect the potential efficiency gains and subsequently reduced costs, that may result from a patient who receive multiple IV infusions during one hospital visit – for example, when a patient receives	The overall administration costs associated with pembrolizumab plus chemotherapy were included within the DSA and PSA to explore the impact of any uncertainty in these estimates.

	administration costs are captured within the most expensive cost code associated with any one individual treatment component. For example, in a treatment cycle where a patient receives pembrolizumab, pemetrexed and carboplatin, it was conservatively assumed that only the administration cost associated with carboplatin is incurred.	carboplatin, pemetrexed and pembrolizumab during the same treatment cycle.	
Proportion of patients receiving subsequent therapy	It was assumed that, in UK clinical practice, [redacted]% of patients with previously untreated advanced NSCLC with a BRAF V600 mutation would receive subsequent therapy following treatment with dabrafenib and trametinib or pembrolizumab plus chemotherapy.	In the BRF113928 trial, [redacted]% of patients with previously untreated advanced NSCLC with a BRAF V600E mutation (Cohort C) received subsequent therapy following dabrafenib and trametinib. This was aligned with previous NICE appraisals including patients with previously untreated advanced NSCLC, where it was estimated that 50% to 60% of patients would receive subsequent treatment, and this was considered appropriate for both treatments.	The total costs associated with subsequent treatment following both dabrafenib and trametinib, and pembrolizumab plus chemotherapy, were explored in the PSA and DSA, which characterises any uncertainty relating to the proportion of patients receiving subsequent treatment. No additional scenario analyses were conducted.
Distribution of subsequent therapies after dabrafenib and trametinib	Out of the patients who were assumed to receive subsequent therapy after dabrafenib and trametinib, it was assumed that 55% of these received chemotherapy (consisting of carboplatin plus pemetrexed), and 45% of these received immunotherapy (equally distributed between atezolizumab, nivolumab and pembrolizumab monotherapy).	These assumptions were based on the proportions of patients receiving subsequent chemotherapy and immunotherapy in the BRF113928 trial, and were in line with feedback from UK clinical experts.	A scenario where patients received a higher proportion of immunotherapy (60%) was assumed, to reflect the place of immunotherapy as standard of care in UK clinical practice in this setting, based on clinical expert feedback.[8] However, it is important to note that clinicians believed that immunotherapy monotherapy may not be as effective in a patient population with an actionable mutation, but recognised that there is limited evidence available.[8]

Distribution of subsequent therapies after pembrolizumab plus chemotherapy	Out of the patients who received subsequent therapy after pembrolizumab plus chemotherapy, it was assumed that 50% would receive docetaxel monotherapy, and 50% would receive docetaxel plus nintedanib.	In the absence of published data, these assumptions were aligned with NICE TA789.[6]	No scenario analyses were conducted to explore adjustments to this assumption.
Healthcare resource use	It was assumed that healthcare resource use (monitoring, follow-up and consultant visits) would differ between the PFS and PD health states, but would not differ between patients receiving either dabrafenib and trametinib or pembrolizumab plus chemotherapy.	The healthcare resource use assumptions were aligned with NICE TA789, one of the most recently published NICE appraisals for a targeted therapy in previously untreated patients with advanced NSCLC.	No additional scenarios were explored to assess the uncertainty of this assumption as the healthcare resource use would be same for both treatments in the base case because patients were assumed to reside in the PFS and PD health states for the same duration of time.

Abbreviations: AE: adverse event; AIC: Akaike information criterion; BIC: Bayesian information criterion; DSA: deterministic sensitivity analysis; DSU: Decision Support Unit; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; IV: intravenous; KM: Kaplan-Meier; NICE: National Institute of Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressed disease; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; RDI: relative dose intensity; RWE: real world evidence; TSD: Technical Support Document; TA: Technology Appraisal; ToT: time on treatment; UK: United Kingdom.

B.3.9 Base case economic analysis results

The base case economic analysis results for dabrafenib and trametinib versus pembrolizumab plus chemotherapy for patients with previously untreated advanced NSCLC with a BRAF V600 mutation are presented in Table 51. These results use the currently approved PAS prices for dabrafenib [redacted] and trametinib [redacted], and the list prices for all comparator and subsequent treatments.

A second set of results has been conducted, where Novartis have made assumptions regarding the PAS discount for pembrolizumab, as well as all subsequent treatments, in order to provide a more indicative set of results. Novartis have assumed that pembrolizumab is associated with a PAS discount of [redacted]%, and for completeness, have also assumed that atezolizumab and nivolumab are associated with PAS discounts of [redacted]% and nintedanib is associated with a PAS discount of [redacted]%. For these analyses, [redacted] (trametinib is still provided at a [redacted] discount). These results are provided in a confidential appendix, Appendix O, alongside the main submission dossier.

Dabrafenib and trametinib (at current PAS prices) was associated with a cost saving of [redacted], and a [redacted] QALY gain versus pembrolizumab plus chemotherapy (at list price), meaning that dabrafenib and trametinib dominated pembrolizumab plus chemotherapy.

The lower costs and greater QALYs associated with dabrafenib and trametinib as compared to pembrolizumab plus chemotherapy resulted in a Net Health Benefit (NHB) of [redacted] and [redacted] at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY, respectively. NHB has been presented in line with the latest NICE guidance.[109]

Table 51: Base case deterministic cost-effectiveness results (comparator at list price)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incr. costs (£)	Incr. QALYs	Incr. LYG	ICER (£/QALY)	NHB (£20,000/QALY)	NHB (£30,000/QALY)
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dabrafenib and trametinib is dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the simultaneous effect of uncertainty in the different model parameters on the results of the cost-effectiveness analysis. The PSA was run for 2,000 iterations and in each iteration, model inputs were randomly sampled from the specified probability distributions, with 10% of the mean assumed as the standard error, except for survival parameters. Full details of the inputs used in the PSA are presented in Appendix P.

The results of the PSA with 2,000 iterations are presented in Table 52 and the cost-effectiveness plane and acceptability curves are presented in Figure 14 and Figure 15, respectively. These results use the currently approved PAS prices for dabrafenib [redacted] and trametinib [redacted], and the list prices for all comparator and subsequent treatments.

The results show that dabrafenib and trametinib was associated with a [redacted]% probability of being cost-effective at both a £20,000 and £30,000 willingness-to-pay (WTP) threshold. The PSA results were aligned with the deterministic base case results, indicating that the base case ICER is robust to parameter uncertainty.

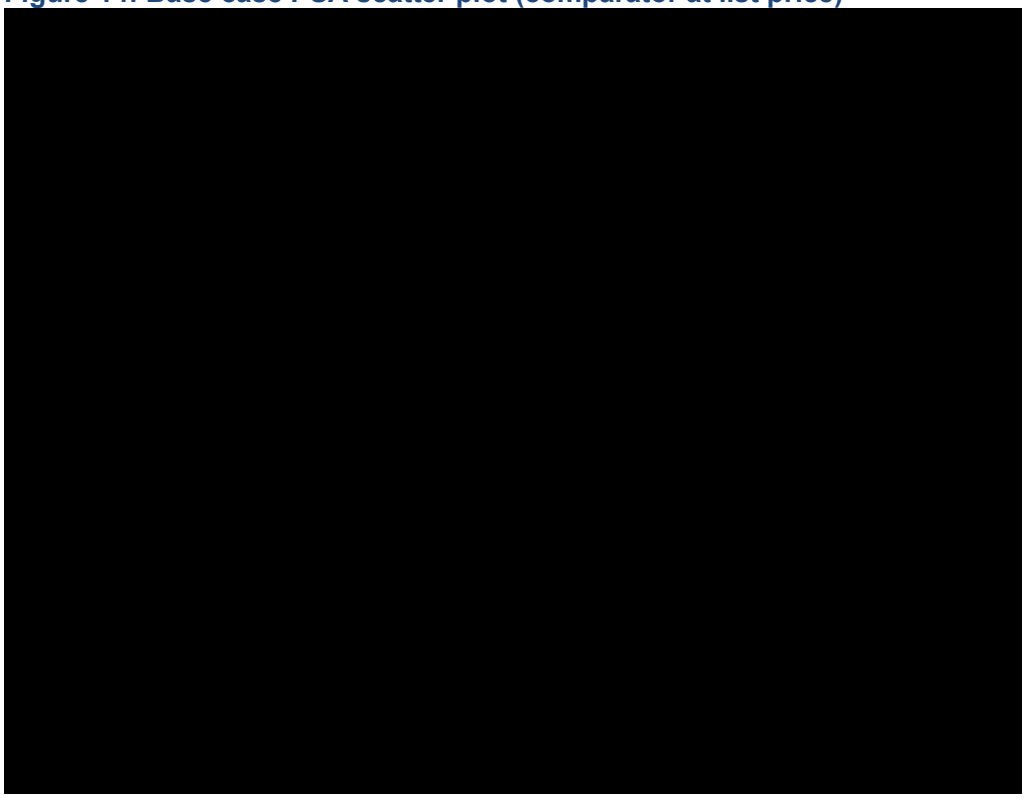
As shown in the stability plot presented in Figure 16 [redacted]. As such, this was considered a suitably high number of iterations for the probabilistic results to assess the uncertainty of simultaneously varying inputs in the model.

Table 52: Base case probabilistic cost-effectiveness results (comparator at list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	Dabrafenib and trametinib is dominant
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years.

Figure 14: Base case PSA scatter plot (comparator at list price)



Abbreviations: QALY: quality-adjusted life year; WTP: willingness-to-pay threshold (£20,000 per QALY)

Figure 15: Base case PSA cost-effectiveness acceptability curve (comparator at list price)

Abbreviations: D&T: dabrafenib and trametinib: PSA: probabilistic sensitivity analysis.

Figure 16: PSA stability plot (comparator at list price)

Abbreviations: ICER: incremental cost-effectiveness ratio.

B.3.10.2 Deterministic sensitivity analysis

In order to further assess the robustness of the base case model results, deterministic sensitivity analyses (DSA) were conducted by varying one model input at a time to assess which parameters had the most impact on the ICER. Parameters were varied within their 95% CI where available or by ±20%. The DSA does not include parameters which require assessment of joint uncertainty, these correlated parameters are assessed within the PSA.

The results of the DSA are presented in Figure 17. The infusion disutility for pembrolizumab plus chemotherapy applied in Cycles 12+ and the AE disutility estimates applied for both pembrolizumab plus chemotherapy and dabrafenib and trametinib were the largest drivers of the base case ICER, when pembrolizumab and subsequent treatments were included at list price.

Figure 17: Deterministic sensitivity analysis results (comparator at list price)

Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio.

B.3.10.3 Scenario analyses

A range of scenario analyses were conducted in order to test the key assumptions adopted within the base case economic analysis. A summary of the scenario analyses and the deterministic results of each is provided in Table 53. The results of the scenario analyses showed that, in all cases, dabrafenib and trametinib was associated with an incremental QALY gain versus pembrolizumab plus chemotherapy, supporting the results of the base case cost-effectiveness analysis.

Table 53: Summary of deterministic scenario analyses and results (comparator at list price)[a]

#	Scenario analysis description	Base case input	Scenario analysis input	Rationale	Results (for dabrafenib and trametinib)		
					Incr. costs	Incr. QALYs	ICER
1	Dabrafenib and trametinib PFS curve selection	Loglogistic.	Lognormal.	All of the curve choices for PFS had similar AIC/BIC, and predicted similar PFS rates (Section B.3.3.2.2). As such, the two curves with the next best statistical fit after the log-logistic extrapolation (the lognormal and the Generalised gamma), were considered in scenario analyses.	[redacted]	[redacted]	Dominant
2			Generalised gamma.		[redacted]	[redacted]	Dominant
3	Dabrafenib and trametinib OS curve selection	Weibull.	Exponential.	In addition to the base case Weibull curve, the exponential curve, (10-year OS estimate of [redacted]%), was also considered clinically plausible, and explored in a scenario analysis (Section B.3.3.2.3). The other curves, which predicted a range of [redacted]% to [redacted]% of patients alive at 10 years, were considered less clinically plausible and were therefore not explored.	[redacted]	[redacted]	Dominant
4	Dabrafenib and trametinib ToT curve selection	Exponential.	Weibull.	The two next best statistically fitting extrapolations after the exponential (Weibull and Gompertz) were explored in scenario	[redacted]	[redacted]	Dominant

5			Gompertz.	analyses (Section B.3.3.2.4). While fitting a parametric extrapolation to the ToT KM data was preferred in the base case, to assume a more constant rate of discontinuation, the use of the ToT KM data directly was also explored in a scenario analysis.	[redacted]	[redacted]	Dominant
6			KM data are used directly.		[redacted]	[redacted]	Dominant
7	Pembrolizumab plus chemotherapy ToT curve selection	Exponential (*based on the weighted FLATIRON V600E data)*	Lognormal.	The next two best fitting curves after the exponential (the lognormal and the log-logistic) were explored in scenario analyses (Section B.3.3.2.4). While fitting a parametric extrapolation to the ToT KM data was preferred in the base case, to assume a more constant rate of discontinuation, the use of the KM data directly was explored in a scenario analysis. Given the limitations of the FLATIRON RWE study (2022) data, an alternative scenario was explored where pembrolizumab plus chemotherapy ToT was assumed to be equal to dabrafenib and trametinib ToT, in line with the assumptions for PFS and OS. The treatment-specific stopping rules for pembrolizumab plus chemotherapy were still applied, in line with the base case.	[redacted]	[redacted]	Dominant
8			Log-logistic.		[redacted]	[redacted]	Dominant
9			Equal to dabrafenib plus trametinib ToT (with relevant RDI and stopping rules applied for pembrolizumab plus chemotherapy).		[redacted]	[redacted]	Dominant
10			KM data are used directly.		[redacted]	[redacted]	Dominant
11	Dabrafenib and trametinib subsequent treatment	Based on the BRF113928 trial, of the [redacted]% of patients who received	Based on clinical expert opinion, of the [redacted]% of patients who received subsequent	An increased proportion of immunotherapy reflects UK clinical expert feedback that immunotherapy represents the standard of care in UK clinical practice in this setting.[8]	[redacted]	[redacted]	Dominant

	distributions	subsequent treatment after dabrafenib and trametinib: • [redacted]% were assumed to receive immunotherapy (divided equally between pembrolizumab, atezolizumab and nivolumab) • [redacted]% were assumed to receive chemotherapy	treatment after dabrafenib and trametinib: • 60% were assumed to receive immunotherapy (divided equally between pembrolizumab, atezolizumab and nivolumab) • 40% were assumed to receive chemotherapy	However, it is important to note that clinicians believed that immunotherapy monotherapy may not be as effective in a patient population with an actionable mutation, but recognised that there is limited evidence.[8]			
12	Subsequent treatment durations	Subsequent treatment durations for second-line pembrolizumab, nivolumab, and atezolizumab were set to 13.5 weeks, based on clinical expert feedback.[8]	Subsequent treatment durations for second-line pembrolizumab, nivolumab, and atezolizumab were derived from NICE TA789.[6]	In the absence of robust subsequent treatment duration data from the BRF113928 trial or the FLATIRON RWE (study), alternative durations of subsequent treatments were adopted in this scenario analysis to explore the uncertainty surrounding the base case assumptions which were based on UK clinical expert feedback.	[redacted]	[redacted]	Dominant
13	Infusion administration disutility	An infusion-related disutility of -0.023 was applied (as a decrement to the PFS health state utility value) for patients receiving pembrolizumab plus chemotherapy, in all cycles that patients remained on	Patients receiving pembrolizumab, pemetrexed and cisplatin (15.4%) were assumed to incur an infusion-related disutility of -0.037 for the first 12 weeks of the model. The original disutility of	As detailed in Section B.3.4.5, cisplatin is associated with a much longer infusion duration (2 hours), and also requires patients to visit the hospital the night before treatment.[117] To reflect this and explore the impact on the base case ICER, an increased disutility was applied to patients receiving cisplatin, based on Matza *et al.* (2013).[128]	[redacted]	[redacted]	Dominant

		treatment.	-0.023 was then applied for the remaining cycles that these patients remained on treatment, as well as for all cycles for patients receiving pembrolizumab, pemetrexed and carboplatin.				
14			A disutility of -0.037 was applied in the first 12 model cycles to all patients receiving pembrolizumab plus chemotherapy, but only in the model cycles where they received an infusion. A disutility of -0.023 was then applied for the remaining model cycles that patients remained on treatment, but only in the model cycles where they received an infusion.	As detailed in Section B.3.4.5, a disutility of -0.037 is applied during the first 12 model cycles, to reflect the complexity of the pembrolizumab plus chemotherapy regimen. While Matza et al. (2013) note that the value of -0.023 represents a "health state disutility" for patients receiving treatment with a 30-minute IV infusion regimen every 4 weeks, this assumption was relaxed in this scenario, to consider the impact of the frequency and intensity of IV infusions reducing over time as the number of IV administrations is decreased beyond the initial 4 treatment cycles.	[redacted]	[redacted]	Dominant

Footnotes: Scenario analyses were run deterministically, given the run time of the model, although the economic model includes the functionality to run all the scenarios probabilistically.
Abbreviations: AE: adverse event; PFS: progression-free survival; OS: overall survival; RWE: real-world evidence; TA: technology appraisal; ToT: time on treatment; UK United Kingdom.

B.3.11 Subgroup analysis

No economic subgroup analyses have been conducted for this appraisal.

B.3.12 Benefits not captured in the QALY calculation

The economic analysis has attempted to capture all the potential benefits related to dabrafenib and trametinib within the QALY calculation. The model also captures the disutility for pembrolizumab plus chemotherapy (due to IV infusions) and the disutility associated with AEs for both treatments. There are, however, several potential benefits of treatment with dabrafenib and trametinib which are not captured within the assessment, specifically:

- The positive impact of an oral treatment which is administered outside the hospital setting during the continued COVID-19 pandemic
- The benefit on NHS capacity through the reduction in patients requiring IV infusions, amid the current backlogs faced by the NHS
- The positive impact on patient well-being associated with a treatment targeted to their individual mutation status
- The potential for earlier initiation of treatment
- The benefit through avoidance of the potential for longer-term complications associated with pembrolizumab plus chemotherapy

The health state utilities (and therefore QALY gains) for PFS and PD were equivalent for both treatments under the assumption of clinical equivalence. Whilst the disutility associated with IV infusions is incorporated into the analysis, the source of this disutility (Matza *et al.* [2013][128]) did not account for the anxiety that a patient may experience when attending hospital during the COVID-19 pandemic. Treatment with dabrafenib and trametinib was provided by NHS England as part of the interim COVID-19 measures due to it being an oral treatment option, removing the requirement for hospital visits.[20] It is therefore conceivable that there may be an additional benefit on quality of life for dabrafenib and trametinib that is not captured in the analysis.

Avoiding hospital visits also reduces the financial and administrative strain on NHS capacity. This is not captured in the calculation of the ICER. While direct (administration) costs are captured, keeping patients away from hospital and alleviating some burden on NHS staff and infrastructure (i.e. human and physical capital) are important elements to consider at a time when the NHS continues to face significant backlogs from the pandemic. This is particularly evident in settings such as oncology infusion clinics.

Targeted treatment options have been recognised as a valuable treatment option when considering an oncogenic driver mutation by patients with cancer. In the appraisal of alpelisib with fulvestrant for treating hormone receptor-positive, HER-negative, PIK3CA-mutated advanced breast cancer, patients noted that knowing a drug was targeted to their mutation was very important and had a positive emotional impact.[148] As part of the HTA for dabrafenib and trametinib in Canada, clinicians and the patient advocacy group emphasised that patients with an identified driver mutation preferred to be treated with targeted therapy upfront, as opposed to non-targeted treatments.[64]

Furthermore, clinical experts consulted on as part of this appraisal noted that patients are able to

initiate treatment with dabrafenib and trametinib immediately following a confirmed diagnosis of NSCLC harbouring a BRAF V600 mutation.[8] In comparison, initiation of pembrolizumab with chemotherapy can be subject to delays, due to capacity constraints associated with infusion clinics and NHS backlogs.

Neither of these potential benefits (i.e. a positive impact on patients due to knowledge of receiving a targeted treatment, and potential for earlier initiation of treatment) are captured within the QALY assessment.

While NHS reference costs were used to estimate a one-off cost for AEs, this may not reflect the longer-term complications of immune-mediated AEs that might be experienced by patients receiving pembrolizumab plus chemotherapy. Immune mediated AEs, such as hepatitis and colitis, can lead to complications that may require subsequent treatments which will have an impact on HRQoL. While the frequency of these events is low, the disutility (and potential cost) of longer-term complications from treatment with pembrolizumab plus chemotherapy is not captured in the economic analysis.

Given the above, it is plausible that additional potential benefits of dabrafenib and trametinib are not captured in the QALY (and ICER) calculation, and we would ask the Appraisal Committee to consider these factors when generating their recommendations.

B.3.13 Validation

B.3.13.1 Technical validation

In alignment with best practice, validation of the economic model structure was conducted by an independent expert health economist, not previously involved in the model conceptualisation or programming.[149] Once fully developed, the model underwent two independent quality control and technical validation processes which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks), based on the published TECH-VER checklist,[150] were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

B.3.13.2 Clinical validation

Clinical opinion was obtained to support the assumptions included within the base case economic analysis, as detailed throughout this section. Further details of the clinical validation process are provided in the reference pack alongside this submission.[8]

B.3.14 Interpretations and conclusions of economic evidence

In the base case economic analysis for patients with previously untreated advanced NSCLC with a BRAF V600 mutation, treatment with dabrafenib and trametinib resulted in a cost saving of -£[redacted] and an incremental gain of [redacted] QALYs per patient compared to pembrolizumab plus chemotherapy. This QALY gain was driven by the reduced AE and infusion-related disutilities for dabrafenib and trametinib versus pembrolizumab plus chemotherapy. With reduced costs and an incremental QALY gain, dabrafenib and trametinib were estimated to dominate pembrolizumab

plus chemotherapy, with a [redacted]% probability of being cost-effective at both a £20,000 and £30,000 WTP threshold.

The results support the improvements in HRQoL that are likely to be associated with dabrafenib and trametinib versus pembrolizumab plus chemotherapy, due to the more convenient mode of administration (oral versus IV infusion), and the reduced experience of AEs.

The results of the confidential cost-effectiveness analyses presented in Appendix O demonstrate that dabrafenib and trametinib is a cost-effective treatment option versus pembrolizumab plus chemotherapy, assuming a [redacted]% discount on the vial price for pembrolizumab, discounts for atezolizumab ([redacted]%), nivolumab ([redacted]%) and nintedanib ([redacted]%) (as subsequent treatments), [redacted], (Section B.1.2 and Section B.3.5). In the base case with these updated discounts, dabrafenib and trametinib was associated with a base case ICER of [redacted] versus pembrolizumab plus chemotherapy, with [redacted]% and [redacted]% probabilities of being cost-effective at £20,000 and £30,000 WTP thresholds, respectively. Dabrafenib and trametinib was cost-effective in [redacted] of the scenario analyses considered.

These results support that dabrafenib and trametinib represent a cost-effective treatment option and an appropriate use of NHS resources for patients with advanced NSCLC with a BRAF V600 mutation. Dabrafenib and trametinib are associated with similar efficacy to the current standard of care treatment, pembrolizumab plus chemotherapy, in line with the most reasonable conclusions that could be drawn from the comparative efficacy data based on UK clinical expert feedback.[8]

Finally, treatment with dabrafenib and trametinib allows patients to be managed away from a hospital setting, and so may help alleviate NHS capacity issues in terms of IV administrations and reduce the burden of AEs compared to pembrolizumab plus chemotherapy. The results, therefore, support the continued usage of dabrafenib and trametinib for patients with advanced NSCLC with a BRAF V600 mutation in clinical practice following the interim availability via COVID-19 funding.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Clarification questions

September 2022

File name	Version	Contains confidential information	Date
ID3851_Dabrafenib clarification questions to PM for company Fully redacted_26092022	Final	No	26/09/2022

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. Is dabrafenib and trametinib expected to have consistent efficacy in patients with BRAF V600 mutations other than the E type? If so, please justify why patients with other BRAF V600 mutations were excluded from the BRF113928 trial?

BRAF mutations can be divided into three classes based on mutation site. Class I mutations include V600E/K/D/R, which occurs in the valine residue at amino acid position 600 of exon 15. These mutations have high sensitivity to BRAF and MEK inhibitors, and efficacy is not expected to vary between Class I mutant subtypes.[1] The most common type of BRAF mutation is V600E (which represent approximately 90.1% of Class I mutations).[2]

BRAF mutations of mixed subtypes were also considered in the FLATIRON RWE study (2022). The results indicated that D&T (BRF113928) has the potential to extend OS compared pembrolizumab plus chemotherapy (unweighted OS HR: [redacted] and a weighted OS HR: [redacted], Document B, Appendix D.3.2.3).

At the time of the BRF113928 study, a companion diagnostic test (Oncomine™ Dx Target test) specific for the BRAF V600E mutation was only available so other Class I mutants could not be identified and enrolled in the study.

A2. For the flow diagram of study BRF113928 (Figure 3, Document B) please provide data for the following:

- Number of patients screened for eligibility
- Number ineligible/excluded – with a breakdown of reasons (including the number excluded for having confirmed activating RAS-mutations and the number excluded for having a history or evidence of cardiovascular risk)
- Number who declined participation

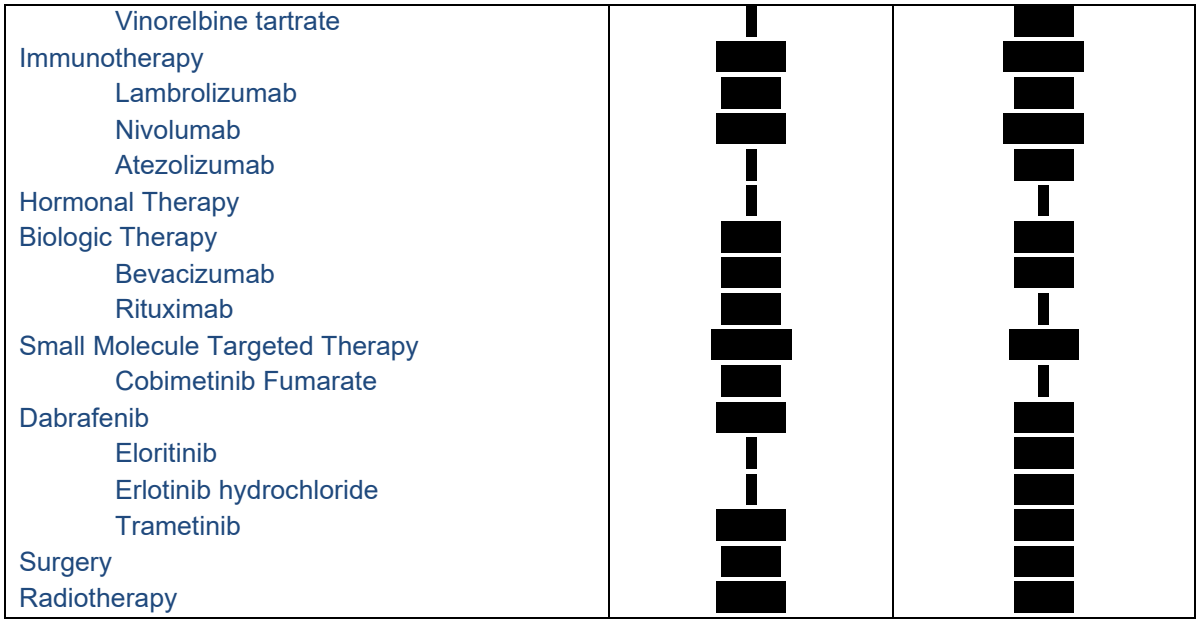
Information on patients screened for eligibility, ineligible or who have declined participation is either not available or collected for BRF113928.

A3. Priority. Please provide summary data (by cohort) on all the subsequent treatments received by patients in Study BRF113928 after they stopped taking dabrafenib and trametinib. Please also comment on the applicability of these treatments to NHS practice.

Subsequent treatments received by patients (by cohort) in study BRF113928 are presented in Table 1 below. It should be noted that patients could have received more than one subsequent treatment as part of follow-up, including combinations of chemotherapy regimen. For example, this means that the sum of patients receiving individual chemotherapy regimens will sum to greater than the total number of patients receiving a chemotherapy regimen.

Table 1: Summary of post-therapy anti-cancer therapy

	1st line Cohort C (N=36)	2nd line plus Cohort B (N=57)
Any anti-cancer therapy?		
Yes No	[redacted]	[redacted]
Type of anti-cancer therapy		
Chemotherapy Carboplatin Cisplatin Combinations of Antineoplastics Agents Docetaxel Epirubicin Gemcitabine Gemcitabine hydrocholoride Investigational Antineoplastic Drugs Nintedanib Paclitaxel Pemetrexed Pemetrexed Disodium Vinorelbine	[redacted]	[redacted]



Since the BRF113928 trial was a multinational study, it is expected that some variation in the treatment regimens following progression on dabrafenib and trametinib (D&T) would exist. Broadly, however, the use of follow-on treatments is reflective of UK clinical practice, where patients would receive either immunotherapy or chemotherapy following D&T.

As described in the Company Submission, the distribution of patients modelled as receiving immunotherapy and chemotherapy in the base case economic analysis were reweighted to reflect the [redacted]% of patients who received subsequent treatment with chemotherapy or immunotherapy in the BRF113928 trial ([redacted]% of these patients received chemotherapy and [redacted]% received immunotherapy) (Document B, Section B.3.5.5).

In the interpretation of all results, it is important to note that many of the patients included in the BRF113928 trial were recruited prior to the widespread use of immunotherapies in non-small cell lung cancer (NSCLC), and as such would not have had access to such treatments. As such, the number of patients receiving immunotherapy as a first subsequent treatment in the BRF113928 trial may be an underestimate, and may have resulted in lower over survival benefits for D&T than may be seen in clinical practice.

A4. References 77-82 (Table 4, document B) are reports of review-eligible studies on dabrafenib and trametinib, but few details are reported in the submission. Please provide a summary of their methods and results, including why they were "*not considered to represent robust sources of data*".

Auliac et al. (2019)

References 77 and 78 refer to a study by Auliac *et al*., published in a conference abstract in 2019,[3] and as a manuscript in 2020.[4] The study was a retrospective, multicentre study of patients with both previously treated and untreated patients in France receiving D&T. The study included patients with advanced NSCLC with a BRAF V600E mutation. The study reported overall survival (OS) and progression-free survival (PFS) for the cohort of patients as a whole, as well as for previously treated (n=31) and untreated (n=9) subgroups. Median OS and PFS for Auliac *et al.*

(2019) were provided in Table 19 of the Company Submission appendices.

Whilst this study represents a relevant additional source of efficacy data for D&T, a number of issues were identified which meant it was not considered to represent sufficiently robust evidence for use in the company's submission. Firstly, the study is a retrospective, observational study and therefore does not represent a more robust source of data than the BRF113928 clinical trial. Moreover, the patient numbers are substantially smaller than those reported in the untreated population of the BRF113928 trial (n=36). Any conclusions drawn from this study would have been associated with a much greater degree of uncertainty than those drawn from the BRF113928 trial, and was therefore not considered further for inclusion in the submission.

Mu *et al.* (2019)

References 79, 80 and 81 refer to a study by Mu *et al*., published across two conference abstracts, and a manuscript.[5-7] The study was a retrospective, multicentre study of patients with NSCLC harbouring a BRAF mutation, both V600E (n=54) and non-V600E (n=11), recruited through a patient community in China. The study focused on patients with a BRAF V600E mutation receiving first-line treatments, of whom just 5 received dabrafenib and trametinib, with four patients receiving D&T as a second-line treatment. Furthermore, several limitations were identified with the study as a source of evidence: PFS was not reported separately for first- and second-line treatment with D&T, and no Kaplan-Meier data was available for D&T, which was instead presented as a basket with other BRAF-targeting therapies (vemurafenib and dabrafenib). The lack of robust data from Mu *et al*. meant it was not considered appropriate to inform clinical or cost-effectiveness evidence of D&T in the submission, particularly given the availability of data from the BRF113928 trial.

Tamminga et al. (2019)

Reference 82 is a study by Tamminga *et al*., published as a manuscript in 2019.[8] The study was a prospective, observational, single-centre cohort study of patients with stage III or IV NSCLC, both previously treated and untreated. Eight of these patients had a BRAF V600E mutation, five of whom were previously untreated and three were previously treated. In the previously untreated cohort, one patient received vemurafenib, three patients received dabrafenib, and one patient received D&T. In the previously treated cohort, all three patients received D&T. These patient numbers are too low to inform clinical or cost-effectiveness evidence, and the study was therefore not considered for use in the submission.

A5. The Kanakamedala et al 2020 comparative study is reported only as a conference abstract. It states that "*data for the first-line pembrolizumab+ carboplatin+pemetrexed analysis were challenging to interpret due to high censoring".* Please provide full details of the methods of this study and the results for first-line pembrolizumab & chemotherapy vs dabrafenib and trametinib.

The full study report for the Kanakamedala *et al*. (2020) study has been provided as part of the reference pack submitted alongside these responses. Please refer to the file "Kanakamedala *et al.* (2020)_Study report" for full study details and results. Details of the study have also recently been published in a manuscript by Johnson *et al*. (2022), which is provided in the submission reference pack.[9]

A6. For the Melosky et al. 2021 comparative study, please provide details of the statistical methods used e.g. how were the propensity scores estimated? Please provide baseline characteristics tables both before and after propensity score matching. Please also compare the propensity scores before and after reweighting.

Melosky *et al.* (2021) was a non-interventional, retrospective observational study comparing real-world outcomes (OS and real-world PFS) among patients diagnosed with BRAF V600E NSCLC who received either D&T or standard of care as extracted from the Flatiron EDM. Propensity scores were estimated using a logistic regression modelling treatment assignment as a function of the following baseline characteristics: age, gender, race, stage at initial diagnosis, smoking status, Eastern Cooperative Oncology Group (ECOG) status, and histology. Stabilised inverse probability of treatment weighting (IPTW) based on propensity scores were used to estimate the average treatment effect.

The FLATIRON RWE 2022 study focused on examining the treatment effect on real-world patients had they been enrolled in the trial, therefore Average Treatment Effect on Treated (ATT) is the appropriate treatment effect. In contrast, Melosky et al. used Average Treatment Effect (ATE), which is relevant when the treatment is applicable to the entire population represented by the data. ATT maintains the composition of BRF113928 trial patients (in the weighted analysis, each patient is assigned a weight of 1), while real-world patients are assigned a weight between 0 and 1, based on their odds to reflect the trial population characteristics.

The baseline characteristics of patients in the Melosky *et al.* (2021), both before and after weighting, are shown in Table 2. Baseline characteristics before IPTW showed differences in age, gender, race, smoking status, and stage at initial diagnosis.

Table 2: Baseline characteristics for patients in the Melosky *et al.* (2021) study (real-world BRAF V600E) before and after weighting

Baseline Characteristic	Unweighted real-world cohort		Weighted real-world cohort	
	D&T	Pembrolizumab plus chemotherapy	D&T	Pembrolizumab plus chemotherapy
Sample size, n	**48**	**31**	**47.2**	**27.7**
Age at index date, years				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
<65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Other Race	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)				
0-1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]

Missing	[redacted]	[redacted]	[redacted]	[redacted]
Stage at initial diagnosis				
Stage I	[redacted]	[redacted]	[redacted]	[redacted]
Stage II	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status				
History of smoking	[redacted]	[redacted]	[redacted]	[redacted]
No history of smoking	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; ECOG OS: Eastern Cooperative Oncology Group perfomance status; IQR: interquartile range; SD: standard deviation.

The distributions of propensity scores for each cohort before and after weighting are shown in Figure 1 and Figure 2, respectively. Post-weighted distributions of propensity score show increased overlap between treatment groups.

Figure 1: Distribution of propensity scores – Before weighting

Taf_Mek = D&T
Abbreviations: PS: propensity scores.

Figure 2: Distribution of propensity scores – Post weighting

Taf_Mek = D&T
Abbreviations: PS: propensity scores.

A7. Tables 20-21 in the submission appendices document present risk of bias judgements. Please provide a risk of bias assessment for the unpublished Flatiron (2022) study. For the sake of both clarity and transparency please provide relevant text to justify the domain judgements made for the Kanakamedala 2020, Melosky et al. 2021 and unpublished Flatiron (2022) studies.

Risk of bias assessments for Kanakamedala *et al.* (2020),[10] Melosky *et al.* (2021)[11] and the FLATIRON real-world evidence (RWE) study (2022)[12] are presented in Table 3, based on the ROBINS-I tool for observational studies.[13] For completeness, these were carried out using the full study reports for each study, submitted as part of the reference pack submitted alongside these responses, and therefore the assessments differ from those reported in the submission, given the greater availability of evidence in these study reports.

In summary, all three studies can be considered to be at moderate risk of bias, which as RWE studies, is typically unavoidable versus a clinical trial.

Table 3: Risk of bias assessment (ROBINS-I tool) for Kanakamedala et al. (2020), Melosky et al. (2021) and the FLATIRON RWE study (2022)

Question	Description		
	Kanakamedala *et* al. (2020)[10]	**Melosky *et al.* (2021)[11]**	**FLATIRON RWE study (2022)[12]**
Bias due to confounding			
Is there potential for confounding of the effect of intervention in this study?	"PN", As propensity score weighing methodology was used to balance the comparison groups for potential confounders and standardised mean difference of <0.25 was achieved for all included variables, the risk of selection bias for measured confounders is low. However, residual bias due to cohort imbalances is inevitable.	"PN", As propensity score matching methodology was used to balance the comparison groups for potential confounders and standardised mean difference of <0.25 was achieved for all included variables, the risk of selection bias for measured confounders is low. However, residual bias due to cohort imbalances is inevitable.	"PN", As propensity score weighing methodology was used to balance the comparison groups for potential confounders and standardised mean difference of <0.25 was achieved for all included variables, the risk of selection bias for measured confounders is low. However, residual bias due to cohort imbalances is inevitable.
Risk of bias judgement	**"Moderate"**	**"Moderate"**	**"Moderate"**
Bias in selection of participants into the study			
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	"PN", Patients were selected by intervention received.	"PN", Patients were selected by intervention received.	"PN", Patients were selected by intervention received.
Do start of follow-up and start of intervention coincide for most participants?	"Y", The groups were comparable for treatment completion, and the definition of the timepoint of the start of follow-up and the start and intervention were aligned.	"Y", The groups were comparable for treatment completion, and the definition of the timepoint of the start of follow-up and the start and intervention were aligned.	"Y", The groups were comparable for treatment completion, and the definition of the timepoint of the start of follow-up and the start and intervention were aligned.
Risk of bias judgement	**"Moderate"**	**"Moderate"**	**"Moderate"**
Bias in classification of interventions			
Were intervention groups clearly defined?	"PY", Treatment regimens are reported but no dosing information.	"PY", Treatment regimens are reported but no dosing information.	"PY", Treatment regimens are reported but no dosing information.

Question	Description		
	Kanakamedala *et* al. (2020)[10]	**Melosky *et al.* (2021)[11]**	**FLATIRON RWE study (2022)[12]**
Was the information used to define intervention groups recorded at the start of the intervention?	"PY", Cohorts were divided by previous intervention.	"PY", Cohorts were divided by previous intervention.	"PY", Cohorts were divided by previous intervention.
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	"PN", Database study.	"PN", Database study.	"PN", Database study.
Risk of bias judgement	**"Low"**	**"Low"**	**"Low"**
Bias due to deviations from intended interventions			
Were important co-interventions balanced across intervention groups?	"NI", This is a retrospective study without reporting co-interventions for each line of therapy. Comparisons were between each intervention.	"NI", This is a retrospective study without reporting co-interventions for each line of therapy. Comparisons were between each intervention.	"NI", This is a retrospective study without reporting co-interventions for each line of therapy. Comparisons were between each intervention.
Was the intervention implemented successfully for most participants?	"Y", Treatment regimen was described.	"Y", Treatment regimen was described.	"Y", Treatment regimen was described.
Did study participants adhere to the assigned intervention regimen?	"N", Time to treatment discontinuation data provided.	"N", Time to treatment discontinuation data provided.	"N", Time to treatment discontinuation data provided.
Risk of bias judgement	**"Moderate"**	**"Moderate"**	**"Moderate"**
Bias due to missing data			

Question	Description		
	Kanakamedala *et* al. (2020)[10]	**Melosky *et al.* (2021)[11]**	**FLATIRON RWE study (2022)[12]**
Were outcome data available for all, or nearly all, participants?	"N", While the RWE data source attempts to capture all mortality and progression outcomes, some missing data exist. Published literature has shown that in non-small cell lung cancer the sensitivity for mortality outcome is 90.4% in the Flatiron database. It can be assumed that that the survival and progression assessments are more frequent and more complete in the clinical trial data. This may lead to a detection bias favouring the real-world cohort.	"N", While the RWE data source attempts to capture all mortality and progression outcomes, some missing data exist. Published literature has shown that in non-small cell lung cancer the sensitivity for mortality outcome is 90.4% in the Flatiron database. It can be assumed that that the survival and progression assessments are more frequent and more complete in the clinical trial data. This may lead to a detection bias favouring the real-world cohort.	"N", While the RWE data source attempts to capture all mortality and progression outcomes, some missing data exist. Published literature has shown that in non-small cell lung cancer the sensitivity for mortality outcome is 90.4% in the Flatiron database. It can be assumed that that the survival and progression assessments are more frequent and more complete in the clinical trial data. This may lead to a detection bias favouring the real-world cohort.
Were participants excluded due to missing data on intervention status?	"N", Intervention status was necessary for inclusion in the study.	"N", Intervention status was necessary for inclusion in the study.	"N", Intervention status was necessary for inclusion in the study.
Were participants excluded due to missing data on other variables needed for the analysis?	"NI", Not enough information in source to explicitly confirm.	"NI", Not enough information in source to explicitly confirm.	"NI", Not enough information in source to explicitly confirm.
Risk of bias judgement	**"Moderate"**	**"Moderate"**	**"Moderate"**
Bias in measurement of outcomes			
Could the outcome measure have been influenced by knowledge of the intervention received?	"PY", As a database study, the patients' physicians likely know what their patients are being treated with within the clinic which may influence any care decisions	"PY", As a database study, the patients' physicians likely know what their patients are being treated with within the clinic which may influence any care decisions	"PY", As a database study, the patients' physicians likely know what their patients are being treated with within the clinic which may influence any care decisions
Were outcome assessors aware of the intervention received by study participants?	"Y", This is a retrospective study	"Y", This is a retrospective study	"Y", This is a retrospective study

Question	Description		
	Kanakamedala *et* al. (2020)[10]	**Melosky *et al.* (2021)[11]**	**FLATIRON RWE study (2022)[12]**
Were the methods of outcome assessment comparable across intervention groups?	"PN", Progression was determined by treating physician assessment, which may vary	"PN", Progression was determined by treating physician assessment, which may vary	"PN", Progression was determined by treating physician assessment, which may vary
Were any systematic errors in measurement of the outcome related to intervention received?	"PN", It's unlikely that in the real world the measurement of progression or survival would depend on the intervention, it would more likely depend on the clinic the patient was attending.	"PN", It's unlikely that in the real world the measurement of progression or survival would depend on the intervention, it would more likely depend on the clinic the patient was attending.	"PN", It's unlikely that in the real world the measurement of progression or survival would depend on the intervention, it would more likely depend on the clinic the patient was attending.
Risk of bias judgement	**"Low"**	**"Low"**	**"Low"**
Bias in selection of the reported result			
Is the reported effect estimate likely to be selected, on the basis of the results, from... ... multiple outcome measurements within the outcome domain?	"N", Outcomes presented are the main ones of interest and no other outcomes were mentioned in the methods	"N", Outcomes presented are the main ones of interest and no other outcomes were mentioned in the methods	"N", Outcomes presented are the main ones of interest and no other outcomes were mentioned in the methods
... multiple analyses of the intervention-outcome relationship?	"N", Outcomes were assessed using time to event data from the FLATIRON data base, and analysed using propensity matching as a pre-specified analysis.	"N", Outcomes were assessed using time to event data from the FLATIRON data base, and analysed using propensity weighting as a pre-specified analysis.	"N", Outcomes were assessed using time to event data from the FLATIRON data base, and analysed using propensity weighting as a pre-specified analysis.
... different subgroups?	"NA", No subgroup analysis	"NA", No subgroup analysis	"PY", The study captures both a broad BRAF-mutated NSCLC population and a more specific BRAF V600E-mutated population, which may differ in outcomes.
Risk of bias judgement	**"Low"**	**"Low"**	**"Low"**
Overall bias			

Question	Description		
	Kanakamedala *et* al. (2020)[10]	Melosky *et al.* (2021)[11]	FLATIRON RWE study (2022)[12]
Risk of bias judgement	"Moderate"	"Moderate"	"Moderate"

Low: The study is comparable to a well performed randomised trial with regard to this domain; Moderate: The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well performed randomised trial.
Abbreviations: N: No; NA: Not applicable; NSCLC: non-small cell lung cancer; PN: Partial no; PY: Partial yes; RWE: real-world evidence; Y: Yes.
Source: ROBINS-I tool : Sterne *et al.* (2016).[13]

A8. For Table 38 in the submission appendices document please provide details of the incidence of ALK and EGFR mutations.

In the population of patients with a BRAF V600E mutation who received pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022), twenty-five patients had no ALK co-mutation, with one patient having no documented ALK mutation status. Twenty-three patients had no EGFR co-mutation, with three patients having no documented EGFR mutation status.

A9. To what extent do the pembrolizumab plus chemotherapy cohorts overlap in the Kanakamedala et al. (2020) study and the flatiron RWE 2022 study? (i.e. are all the patients from the earlier study also included in the later study?)

The Kanakamedala *et al.* (2020) study recruited BRAF positive patients and comprised of patients with a BRAF V600E mutation and patients with other BRAF subtypes classified in the FLATIRON database. FLATIRON RWE 2022 recruited only BRAF V600E patients, therefore, there is some overlap between the Kanakamedala *et al.* (2020) study where patients with documented BRAF V600E only were included.

A10. Please summarise the treatment non-compliance data for both Study BRF113928 and for dabrafenib and trametinib studies in melanoma patients. Please comment on the likely levels of non-compliance which might impact efficacy.

Within the BRF113928 CSR dose reductions and interruptions based on non-compliance of patients accounted for 20% of the dose reductions with dabrafenib, compared to 2% with trametinib. Exposure information in the CSR also states the median daily dose of dabrafenib and trametinib received by subjects in the study were comparable to the planned daily dose therefore we would envisage limited impact on efficacy.

Non-compliance information for melanoma patients is not available. Novartis consulted with one UK clinical expert as part of the clarification questions and noted no compliance concerns amongst melanoma patients.

However, it is important to note that since the study the management of drug related pyrexia has been updated and as this was the most common adverse event (56% of all AE's in the BRF113928 study) we anticipate improved compliance and re-escalation of patients back onto treatment following a dose interruption or reduction as seen in the pyrexia algorithm specific studies in melanoma previously provided further supporting the lack of impact on efficacy outcomes.

A11. Priority. The SmPCs for dabrafenib and trametinib list malignancies, haemorrhagic events and LVEF reduction/Left ventricular dysfunction as possible adverse events. Please summarise the trial data on these events across all indications to provide an estimate of their incidence.

As per the SmPC's, the safety of dabrafenib in combination with trametinib has been evaluated in the integrated safety population of 1076 patients with BRAF V600 mutant unresectable or

metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment) and advanced NSCLC treated with dabrafenib 150 mg twice daily and trametinib 2 mg once daily. The incidence of adverse events listed by the EAG across studies investigating dabrafenib and trametinib are summarised in Table 4.

Table 4: Summary of listed possible adverse events for dabrafenib and trametinib across indications

Adverse Event	Lung (BRF113928) listed in CSR (n=93)[14]	Melanoma (COMBI D+V 5 year publication) (n=559)[15]	All indications listed in Dabrafenib or Trametinib SmPC (n = 1076) [16, 17]
Malignancies	1% - Basal cell carcinoma 1% - Squamous cell carcinoma	NR	Cutaneous cell carcinoma (2 %) Non-cutaneous malignancy (<1%)
Haemorrhagic events	1% - Haemorrhage subcutaneous	NR	<1%
LVEF reduction/Left ventricular dysfunction	10% - Ejection fraction decreased 1% - Left ventricular dysfunction	8%	6 % - most cases being asymptomatic and reversible

Abbreviations: CSR: clinical study report; NR: not reported; SAE: serious adverse events; SmPC: summary of product characteristics.
Source: BRF113928 CSR Table 3.1280;[14] Robert *et al*. (2019) Supplementary Appendix Table S9;[15] Dabrafenib and trametinib SmPCs.[16, 17]

Section B: Clarification on cost-effectiveness data

Results

B1. Please provide results in the form of Net Health Benefit (NHB) for all analyses, including probabilistic analyses. Please also present credible intervals (CrI) around estimates of NHB derived from the PSA.

Results in the form of net health benefit (NHB) have been provided alongside all of the updated cost-effectiveness results presented throughout this document.

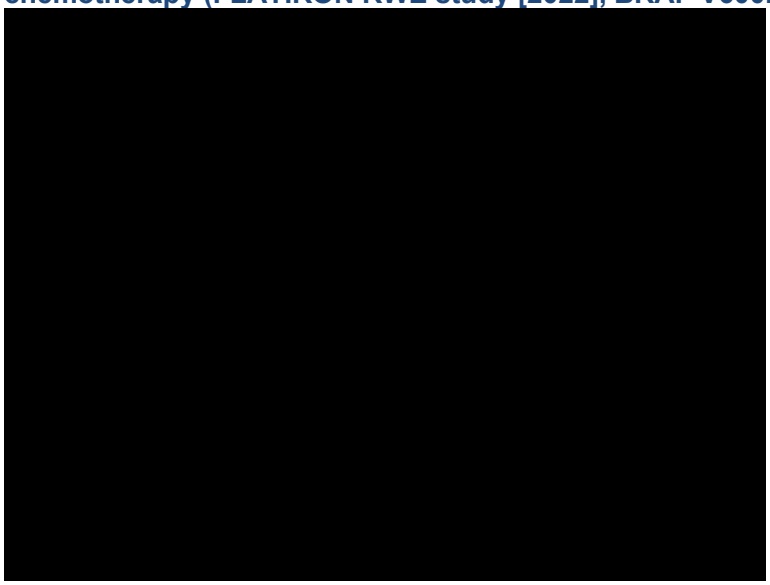
Treatment effectiveness

B2. Please provide diagnostic plots as recommended in NICE DSU TSD14 (section 3) for the assessments of proportional hazards described in Appendix N.1. Please also provide further details of the results of the statistical tests for proportional hazards undertaken.

As detailed previously, it was not considered feasible to use the pembrolizumab plus chemotherapy data from the FLATIRON RWE study (2022) directly in the base case economic analysis (Document B, Section B.3.3.1).

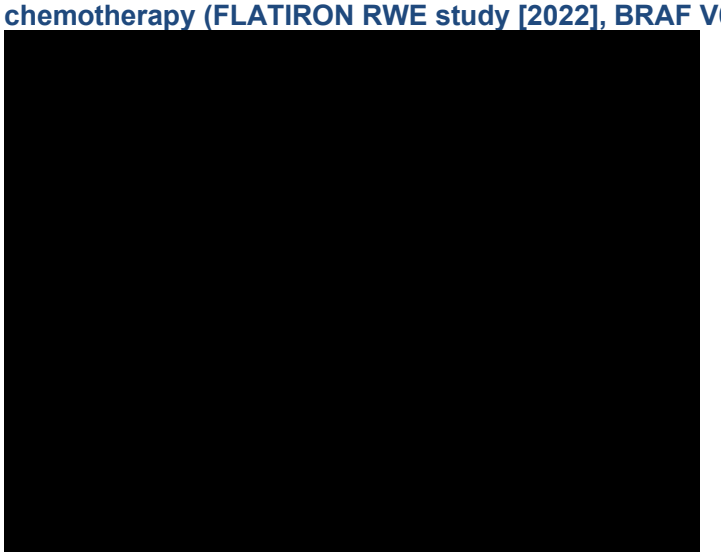
For completeness, log-cumulative hazard plots for the matched analysis between D&T from the BRF113928 trial and pembrolizumab plus chemotherapy from the FLATIRON RWE study (2022) for PFS, OS and TTD are provided in Figure 3, Figure 4 and Figure 5 below. A duration variable was added as an interaction term to test the PH assumption. Assessments were conducted using the cumulative sums of marginal residuals test, with the null hypothesis that the survival data satisfy the PH assumption, and a significant p-value (< 0.05) indicating violation of that assumption. There were no significant p-values for any of the time to events pre or post weighted. However, these results should be interpreted with caution given the small sample sizes and limited follow-up.

Figure 3: PFS log/log plot – D&T (BRF113928 Cohort C versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation, weighted analysis)



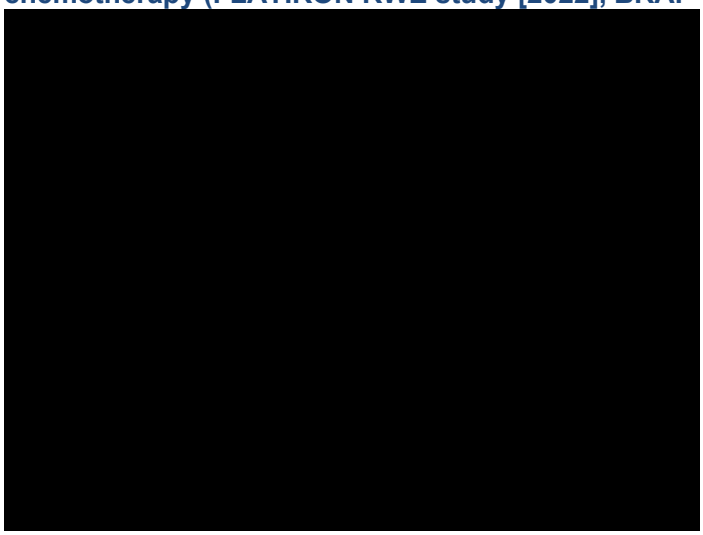
Footnotes: "PD(L)1 + chemo" represents pembrolizumab plus chemotherapy.
Abbreviations: PFS: progression-free survival; PD-L1: programmed-death ligand 1; RWE: real-world evidence.

Figure 4: OS log/log plot – D&T (BRF113928 Cohort C versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation, weighted analysis)



Footnotes: "PD(L)1 + chemo" represents pembrolizumab plus chemotherapy.
Abbreviations: OS: overall survival; PD-L1: programmed-death ligand 1; RWE: real-world evidence.

Figure 5: TTD log/log plot – D&T (BRF113928 Cohort C versus pembrolizumab plus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation, weighted analysis)



Footnotes: "PD(L)1 + chemo" represents pembrolizumab plus chemotherapy.
Abbreviations: PD-L1: programmed-death ligand 1; RWE: real-world evidence; TTD: time to treatment discontinuation.

B3. Please comment on the plausibility of equivalence in PFS and OS given the difference in modelled second line treatments.

a) Please add in model functionality to include OS and PFS benefits for those patients who receive immunotherapy or D&T as an additional line of therapy.

Considering the limitations of the external control arm analysis (the FLATIRON RWE [2022]), an assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy was used in the base case economic analysis of the Company submission (Document B, Section B.3.3.1).

This assumption is based on PFS results, which were broadly similar between D&T and pembrolizumab plus chemotherapy in the FLATIRON RWE 2022 analysis [based on observations up to ~ Month 6], and are not confounded by subsequent treatments. Likewise, OS is broadly similar to pembrolizumab plus chemotherapy up to ~ Month 10. Clinical experts noted that a true difference between the two treatments could not be assessed due to a lack of follow-up in the pembrolizumab plus chemotherapy cohort and based on the early observations of the weighted analysis, clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy was considered to be a reasonable conclusion (Document B, Section B.2.12).[18]

However, the assumption of clinical equivalence is likely to be conservative, given that more than 50% of patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE 2022 received subsequent treatment with immunotherapy. As this does not reflect UK clinical practice, the OS results for pembrolizumab plus chemotherapy from this source are likely overestimated. Furthermore, the OS results of the BRAF+ population in the FLATIRON RWE study (2022), report an unweighted OS HR: [redacted] and a weighted OS HR: [redacted] indicating that D&T has the potential to extend OS compared to pembrolizumab plus chemotherapy (Document B, Appendix D.3.2.3). The BRAF+ population consists of patients with BRAF V600E with other BRAF subtypes (see A1 for our commentary on the effect of D&T on the different BRAF subtypes).

As a further example of the conservative nature of the submitted base case economic analysis, the costs of subsequent immunotherapy for patients who progressed on D&T were included (Document B, Section B.3.5.5), but the potential clinical benefits associated with immunotherapy were not considered. Fundamentally, the conservative nature of the submitted analyses were based on the lack of robust data to present an analysis which would align more closely with expected outcomes in clinical practice.

As part of this response, an exploratory analysis was conducted whereby an additional OS benefit was modelled for patients who receive immunotherapy as a subsequent treatment (following D&T), compared to patients receiving chemotherapy (such as docetaxel monotherapy or docetaxel plus nintedanib) following pembrolizumab plus chemotherapy.

This functionality has been added on the Efficacy Dashboard tab of the cost-effectiveness model and can be amended in Cells I41–46, and takes the form of a reduced OS benefit for patients receiving pembrolizumab plus chemotherapy that is applied at the approximate timepoint that most patients would have progressed. Please refer to our response to QB3b for the rationale behind this approach (i.e. adjustment to the pembrolizumab plus chemotherapy arm, rather than the D&T arm), as well as further detail on this added functionality.

It is not expected that the receipt of different subsequent therapies would impact PFS between D&T and pembrolizumab plus chemotherapy, and so no additional benefit for PFS has been incorporated as part of this economic model update.

The benefit of D&T as an additional line of therapy for patients who have progressed on pembrolizumab and chemotherapy is not considered in these exploratory analyses. D&T primarily represents a first-line treatment option, and clinicians typically treat patients with advanced NSCLC with a BRAF V600 mutation upfront with targeted therapies, in line with the upfront usage of targeted treatments for previously untreated advanced NSCLC patients with EGFR, ALK or other oncogenic driver mutations (Document B, Section B.1.3.5).[18, 19] This is supported by BlueTeq data, which indicate [redacted]% of the initiations of D&T since August 2020 were in previously untreated advanced NSCLC patients.[20] Given this, it is not envisioned that D&T would be routinely used as a second-line treatment option in UK clinical practice. The relative efficacy of follow-on treatments routinely used after pembrolizumab plus chemotherapy in UK clinical practice, compared to those used after D&T, is implicitly captured by the approach taken and described in QB3b.

b Please explore options to include an incremental treatment benefit associated with an immunotherapy or D&T used as an additional line of therapy.

As noted in response to Question QB3a, an exploratory analysis has been conducted to include an incremental treatment benefit associated with an immunotherapy used as an additional line of therapy. For the reasons noted above, the benefits of D&T as an additional line of therapy have not been explored.

The incremental survival benefit for immunotherapy following D&T is based on the OAK, KEYNOTE-010 and CheckMate-057 trials, which demonstrated improvements in OS for atezolizumab, pembrolizumab and nivolumab monotherapy, respectively, when compared to chemotherapy, for patients with previously treated advanced NSCLC (i.e. second-line onwards) (see Table 5).[21-24]

- Pembrolizumab is recommended for patients with PD-L1 positive NSCLC (TA428).[25]

Therefore, results from the PD-L1 ≥1% group of the KEYNOTE-010 trial were utilised[21]

- Atezolizumab is recommended regardless of PD-L1 expression (TA520).[26] Therefore, results from the ITT population of the OAK trial were utilised[22]

- Nivolumab is recommended for patients with PD-L1 positive non-squamous NSCLC (TA713)[27], and is recommended for squamous NSCLC regardless of PD-L1 expression (TA655).[28] As the majority of patients with advanced NSCLC with a BRAF V600 mutation have non-squamous histology[29] (Document B, Section B.1.3.1), the results from the PD-L1 ≥1% group of a pooled analysis of the CheckMate-057 and CheckMate-017 trials were utilised[24]

Table 5: Efficacy data for immunotherapies for patients with previously treated advanced NSCLC

Trial	Intervention	Control	Population	OS HR for immunotherapy versus chemotherapy
KEYNOTE-010[21]	Pembrolizumab	Docetaxel	PD-L1 ≥1%	0.70 (0.61, 0.80)
OAK[22]	Atezolizumab	Docetaxel	ITT	0.73 (0.62, 0.87)
CheckMate-057 and CheckMate-017[24]	Nivolumab	Docetaxel	PD-L1 ≥1%	0.61 (0.49, 0.76)

Abbreviations: HR: hazard ratio; NSCLC: non-small-cell-lung cancer; OS: overall survival; PD-L1: programmed death ligand 1.

Five scenarios were considered. Three scenarios used the HRs from KEYNOTE-010 (#1), OAK (#2) and CheckMate-057/017 (#3) directly. A fourth scenario took a weighted average of these three HRs (#4). A fifth scenario also used a weighted average of these three HRs, and also assumed that an increased proportion of patients received immunotherapy ([redacted]%; reflecting [redacted]% of patients who received subsequent treatment received immunotherapy), compared to [redacted]% in the base case economic analysis (reflecting [redacted]% of patients who received subsequent treatment received immunotherapy), in line with Document B, Section B.3.10.3, Scenario 11 (#5).

In each scenario, the HR was applied as a reduction to the pembrolizumab plus chemotherapy OS extrapolation from Cycle 45 (10.32 months), as the time point where approximately 50% of patients had experienced disease progression, and therefore would be receiving subsequent treatment. The Weibull OS extrapolation used for D&T and pembrolizumab plus chemotherapy in the base case is based on the BRF113928 trial data, and therefore reflects the efficacy associated with D&T and subsequent treatments following D&T. This includes the [redacted]% of patients who receive immunotherapy as a follow-on treatment (in Scenarios 1–4, or 33.6% in Scenario 5). The hazard of death for the pembrolizumab plus chemotherapy arm was therefore increased from Cycle 45 (10.32 months) using the above HRs, to reflect the fact that the subsequent treatments following pembrolizumab plus chemotherapy are associated with reduced efficacy compared to subsequent treatments following D&T.

Whilst it would be more logical to apply the above HRs to only the [redacted]% of patients who receive immunotherapy following D&T, this was not possible due to the constraints of a partitioned survival model (PSM): such an approach would require significant modification to the model (or entirely new modelling approach), and a number of additional assumption in the absence of

supporting data.

Within a PSM, OS is mutually exclusive from PFS, and OS includes all patients, regardless of whether they have experienced disease progression or which subsequent treatment they have received. The PSM structure therefore does not allow for the application of an OS HR only to patients who have progressed and receive single-agent immunotherapy as a first subsequent treatment.

In order to track patients through the model with more granularity with respect to OS, disease progression and subsequent treatment received, the model structure would need to be fundamentally altered to a Markov model with a number of additional health states. This would result in substantially increased complexity and additional uncertainty, due to the paucity of data required to inform transitions to and from these additional health states. For this reason, and as previously detailed in Document B, Section B.3.2.1, a PSM was considered to represent the most appropriate model structure for this economic analysis, and exploration of alternative model structures was not considered feasible.

Despite these limitations, an exploratory analysis was conducted where an average HR was derived, assuming:

- [redacted]% of patients experience an incremental benefit from subsequent treatment, based on the chosen HR
- [redacted]% of patients do not experience an incremental benefit from subsequent treatment

For example, when the HR of [redacted] is used, then the weighted average HR applied is calculated as ((1/[redacted])*[redacted]) + (1*[redacted]), to derive a final weighted average HR of [redacted] which is then applied to the pembrolizumab plus chemotherapy OS extrapolation from Cycle 45 (10.32 months). In each scenario the HR is applied for 5 years, in line with the committee's preferred assumptions for the duration of treatment benefit for immunotherapy versus chemotherapy in TA520, TA655 and TA713.[26-28] Therefore, at Cycle 305 (70.32 months), the hazards of death was assumed to be equal across the D&T and pembrolizumab plus chemotherapy OS extrapolations.

The results of these scenarios are summarised in Table 6 below. The results presented throughout this clarification question response document use the currently approved PAS prices for dabrafenib ([redacted]) and trametinib ([redacted]), and the list prices for all comparator and subsequent treatments.

A second set of base case economic results have also been conducted (in confidential Appendix B), including assumptions regarding the PAS discount for pembrolizumab, as well as all subsequent treatments, in order to provide a more indicative set of results. These analyses assume a PAS discount of [redacted]% for pembrolizumab, atezolizumab and nivolumab and a [redacted]% discount for nintedanib. For these analyses, dabrafenib is provided at the [redacted]).

Table 6: Scenario analysis including an incremental benefit for immunotherapy (following D&T) versus docetaxel or docetaxel plus nintedanib (following pembrolizumab plus chemotherapy) (comparator at list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Scenario #1 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #2 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #3 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #4 (applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #5 (assuming [redacted]% of patients who receive subsequent treatment after D&T receive immunotherapy (in line with the Company submission, Document B, Section B.3.10.3, Scenario 11), and then applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86).	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Footnotes: [a] Calculated as 1/0.73. [b] Calculated as 1/0.70. [c] Calculated as 1/0.61. [d] Calculated as the average of 1.37, 1.43 and 1.64.
Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; OS: overall survival; QALY: quality-adjusted life year.

B4. Please integrate data from KEYNOTE-189 to model the efficacy of pembrolizumab with pemetrexed and platinum chemotherapy. Given the similarity in prognostic characteristics between the BRF113928 and KEYNOTE-189 trials, it may be useful to explore the impact of leveraging real trial data on pembrolizumab in the model.

As requested by the EAG, an exploratory analysis where (unweighted) data from KEYNOTE-189 are used to inform PFS and OS for pembrolizumab plus chemotherapy has been conducted below. This analysis should be interpreted with caution because the KEYNOTE-189 trial is an all-comer population (aside from the exclusion of patients with an ALK or EGFR mutation): results are, therefore, likely to overestimate the efficacy for pembrolizumab plus chemotherapy, given the aggressive nature of BRAF V600 NSCLC highlighted by UK clinical experts.[18, 30, 31]

In addition to the analysis requested by the EAG using the (unweighted) all-comer population from KEYNOTE-189, an additional exploratory analysis has been conducted using the treatment effect estimated from FLATIRON RWE study (2022) in patients with the BRAF+ mutation. The hazard ratio (HR) for D&T compared with pembrolizumab plus chemotherapy was applied to the D&T PFS and OS curves (based on the BR113928 trial, as per the Company base case) to represent the efficacy of pembrolizumab plus chemotherapy (results from the FLATIRON RWE study [2022] in the BRAF+ mutation previously presented in Document B, Appendix D.3.2.6).

As mentioned in response to QB3, the OS results of the BRAF+ population in the FLATIRON

RWE study (2022) report an unweighted OS HR of [redacted] and a weighted OS HR of [redacted] indicating that D&T has the potential to extend OS compared to pembrolizumab plus chemotherapy (Document B, Appendix D.3.2.3). The Company believe this would represent a more robust alternative source of efficacy for pembrolizumab plus chemotherapy than the KEYNOTE-189 trial, as the BRAF+ population consists of patients with BRAF V600E with other BRAF subtypes instead of the all-comer population in KEYNOTE-189. It would therefore represent a patient population much more closely aligned to the target patient population in this submission.

A summary of the methodology of the exploratory scenario analysis using KEYNOTE-189 is provided in the below sections, and uses the most recent KM data for PFS and OS from Rodriguez-Abreu *et al.* (2021).[32] The KM curves were digitised and the algorithm detailed in Guyot et al. (2012) was utilised to produce pseudo-individual patient data for PFS/OS from the aggregate trial data.[33] The standard parametric distributions were then fitted to the pseudo-individual patient data, as detailed below.

Progression-free survival

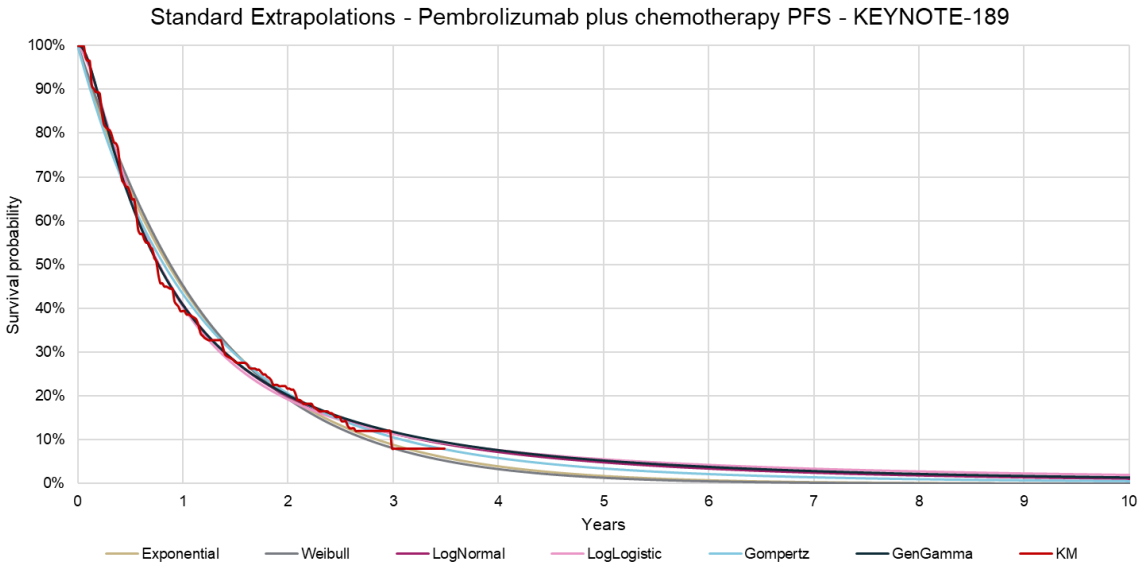
The AIC and BIC values for each of the extrapolations are summarised in Table 7, and extrapolations of PFS using each model up to ten years are presented for all functions in Figure 6.

Table 7: Summary of goodness-of-fit data for pembrolizumab plus chemotherapy PFS (KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	3517.8	5	3521.8	4
Weibull	3518.5	6	3526.5	6
Lognormal	3486.5	1	3494.5	1
Log-logistic	3492.9	3	3500.9	3
Gompertz	3517.7	4	3525.8	5
Generalised gamma	3488.4	2	3500.4	2

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; PFS: progression-free survival.

Figure 6: Pembrolizumab plus chemotherapy PFS extrapolations up to ten years (KEYNOTE-189)



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.
All of the PFS extrapolations appear to predict similar long-term estimates of PFS. As such, the log-logistic was selected since this distribution was used for D&T in our base case as per NICE TSD 14, which notes the same 'type of model' should be used so that the modelled survival for each treatment arm does not follow drastically different distributions.

Overall survival

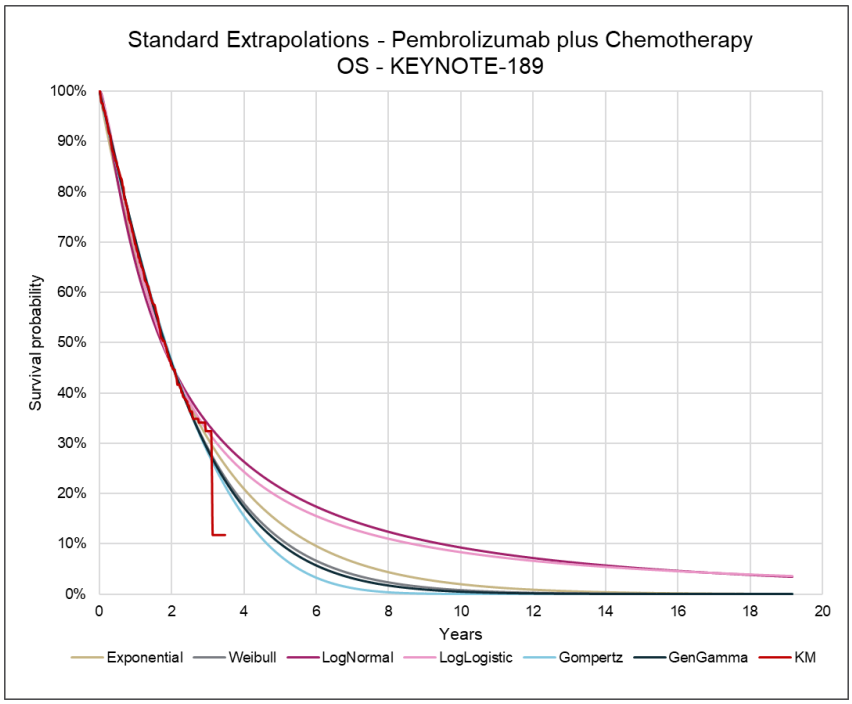
The AIC and BIC values for each of the extrapolations are summarised in Table 8, and extrapolations of OS using each model up to ten years are presented for all functions in Figure 7.

Table 8: Summary of goodness-of-fit data for pembrolizumab plus chemotherapy OS (KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	3102.9	4	3106.9	1
Weibull	3099.9	1	3107.9	2
Lognormal	3122.9	6	3131.0	6
Log-logistic	3107.8	5	3115.8	5
Gompertz	3100.1	2	3108.2	3
Generalised gamma	3101.8	3	3113.8	4

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival.

Figure 7: Pembrolizumab plus chemotherapy OS extrapolations up to twenty years (KEYNOTE-189)



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

All of the OS extrapolations provided a similar visual fit to the observed KM data, however, long-term predictions of OS varied widely between the extrapolations.

The Weibull curve was selected as this was the distribution selected for D&T in our base case, and it provided the best statistical fit to the KM data across AIC and BIC. Furthermore, the 10 year prediction of OS (1%) was aligned with clinical expert opinion, which highlighted the aggressive nature of the BRAF mutation and expected survival to be less than [redacted]% at 10 years (Document B, Section B.3.3.2.3).[18]

Summary of scenario analyses

Since time to treatment discontinuation was not available in KEYNOTE-189, two scenario analyses have been conducted. The first scenario analysis uses PFS and OS for pembrolizumab plus chemotherapy from KEYNOTE-189 as detailed above, and time-on-treatment (ToT) for pembrolizumab plus chemotherapy remains the same as the base case economic analysis (based on the FLATIRON RWE study [2022] BRAF V600E population). A second scenario analysis assumes that ToT for pembrolizumab plus chemotherapy is equal to PFS for pembrolizumab plus chemotherapy from KEYNOTE-189, as further detailed in QB12. A summary of the results from these scenario analyses are provided in Table 9.

Table 9: Scenario analysis using PFS and OS data for pembrolizumab plus chemotherapy from KEYNOTE-189 (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

clarification questions)					
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT based on the FLATIRON RWE study (2022)	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT assumed to be equal to PFS	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy OS derived using a HR of 0.714 from the BRAF+ dataset, applied for a duration of 5 years	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year.

In the original Company base case, clinical equivalence between D&T and pembrolizumab plus chemotherapy was regarded as a reasonable conclusion after reviewing the FLATIRON RWE study (2022) data in the BRAF V600E patient population. The analyses presented here, while exploratory, should be interpreted with caution and provide support that the Company base case is likely to be conservative. In addition, and as per QB3, the added benefit of second-line treatment with immunotherapy following progression on D&T may also be underestimated in these results, as the BRF113928 study was initiated and completed before the availability of immunotherapy as second-line standard of care. In an exploratory analysis in QB3, additional QALY gains can be shown when this was factored in the analysis.

B5. The median OS predicted for D&T in the model is 27.14 months (the most conservative scenario) while the Kaplan-Meier data from BRF113928 cohort C reports a median OS of 17.3 months. Please provide an overview of the predictions made by the extrapolations in the model compared to the observed KM data and/or external clinical data within the NHS, commenting specifically on any inconsistencies.

A comparison of OS estimates at yearly intervals based on the BRF113928 trial KM data, and the predicted estimates from the extrapolations in the base case economic analysis are provided in Table 10 below. These comparisons demonstrate that the predicted estimates of OS are broadly aligned with the results observed in the BRF113928 trial at each timepoint, and the CEM underestimates OS at later timepoints, compared to the trial. A comparison to external data was not possible as there is no other data source on D&T with substantial follow-up as reported in BRF113928.

Table 10: Comparison of OS in the BRF113928 trial versus the OS estimates predicted by the CEM

Timepoint	BRF113928 trial	Predicted estimates of OS in the CEM (Weibull)
Month 12, % (95% CI)	[redacted]	[redacted]
Month 24, % (95% CI)	[redacted]	[redacted]
Month 36, % (95% CI)	[redacted]	[redacted]
Month 48, % (95% CI)	[redacted]	[redacted]
Month 60, % (95% CI)	[redacted]	[redacted]

Abbreviations: CI: confidence interval; IA: investigator assessment; OS: overall survival.
Source: Planchard *et al*. (2021);[34] BRF113928 Clinical Study Report: Table 11-4.[14]

The similarity between the mean OS estimates in the BRF113928 trial and the cost-effectiveness model over 80 months of follow-up provides further confidence in the extrapolations used in the base case cost-effectiveness analysis (Table 11).

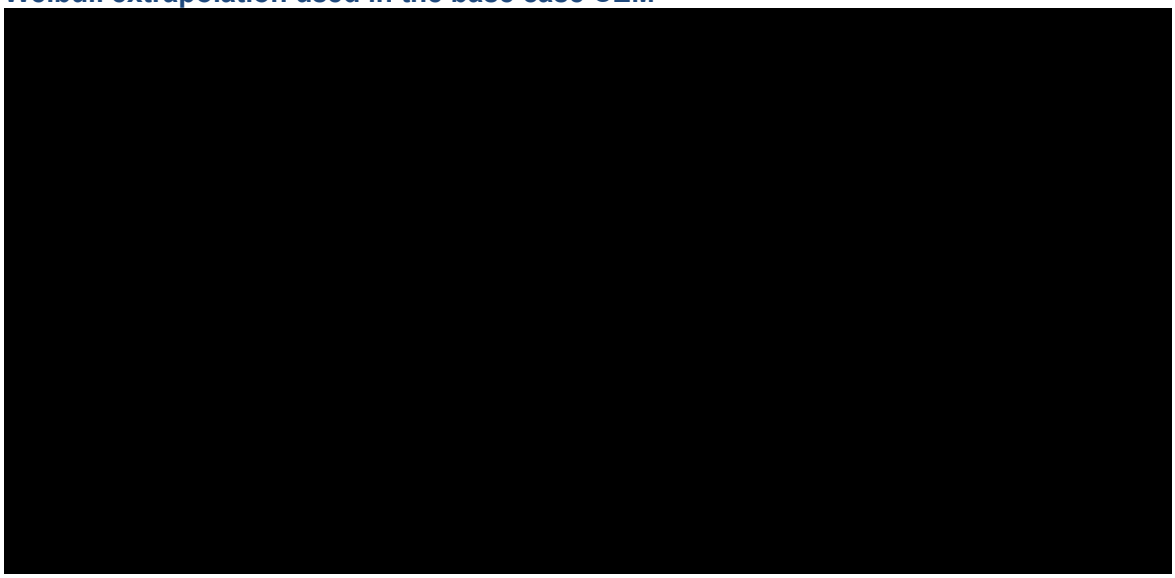
Table 11: Comparison of mean estimates of PFS and OS in the BRF113928 trial and the cost-effectiveness model

	BRF113928 trial	Cost-effectiveness model[a]
Mean OS, months (SE)	[redacted]	[redacted]

Footnotes: Calculated as the mean survival time after 80 months of follow-up.
Abbreviations: OS: overall survival; PFS: progression-free survival

It is worth noting that as shown in Figure 8 below, there are a number of small plateaus within the KM data for D&T from the BRF113928 trial. As such, when extrapolations are fitted to this KM data, there are a number of places where the extrapolation results in slightly different predicted estimates of survival, compared to the KM data. This is particularly pronounced for the median OS, due to the plateau observed in the BRF113928 trial immediately after the median OS is reached, between approximately 17.3 months and 24 months. However, as shown above, the predictions of OS in the model are broadly aligned with the trial data.

Figure 8: Comparison of the KM curve for D&T OS from the BRF113928 trial and the Weibull extrapolation used in the base case CEM



Abbreviations: CEM: cost-effectiveness model; D&T: dabrafenib and trametinib; KM: Kaplan-Meier; OS: overall survival;

Comparators and subgroups

B6. Priority. The EAG consider there to be several sub-populations within the non-squamous population based on PD-L1 expression, which may affect the choice of comparator. Clinical advice to the EAG suggests that in the absence of D&T, patients would be treated according to their level of PD-L1 expression. The following are relevant subgroups in the NICE scope, and are likely to differ in terms of comparator treatment costs and efficacy:

- **Patients with PD-L1 expression ≥50% are treated with pembrolizumab monotherapy;**
- **Patients with PD-L1 expression <50% would be given pembrolizumab plus chemotherapy.**
- **Patients with PD-L1 expression of <1% are unlikely to receive pembrolizumab**

a) Please explicitly model these subgroups with respect to treatment costs. Please present a scenario which weights treatment costs by sub-population prevalence.

During the clarification questions call, the Company highlighted a concern related to assumptions and feedback received by the EAG on the management of patients in clinical practice. Specifically, based on feedback received from UK thought leaders in the management of lung cancer, the Company believe that the approach outlined above would not be used in clinical practice for patients presenting with a BRAF mutation. The Company's rationale for this is provided below, along with responses to the queries for completeness. The Company look forward to hearing the views of clinical experts in the field of lung cancer management as part of this appraisal process on these points.

General comment on UK standard of care in patients with a BRAF-mutation

Clinical experts in the UK have confirmed that PD-L1 status is not relevant when deciding management strategies for a patient with a BRAF mutation as treatment would be with a targeted therapy due to the aggressive nature of the disease. The treatment landscape continues to evolve and adapt as further targetable mutations are identified, meaning that some areas of clinical practice in the UK may no longer be aligned with the prevailing NICE guidance.

As previously detailed, UK clinical expert opinion confirmed patients will be offered pembrolizumab plus chemotherapy whenever possible, in the absence of targeted therapies (CS Document B, Section B.1.1).[18] Clinicians noted that chemotherapy is not widely used and would only be considered for patients who had significant comorbidities or contraindications that would preclude them from being offered immunotherapy, which was estimated to be <5% of patients.[18]

Common approach to treatment in first-line NSCLC for patients with PD-L1 <1% and PD-L1 1%–49%

Whilst a response to the EAG's request is provided below, the Company would like to reiterate their view that it is not appropriate (or required) to consider patients with PD-L1 expression <1% and PD-L1 of 1%–49% as two separate subgroups, and particularly in a population with the BRAF-mutation (to the point above).

Furthermore, as part of TA770, the NICE committee concluded that considering patients with PD-L1 <1% and PD-L1 1%–49% as two separate subgroups was not generalisable to UK NHS clinical practice.[35]

Pembrolizumab plus chemotherapy is preferred to pembrolizumab monotherapy for patients with previously untreated NSCLC with a BRAF V600 mutation with a PD-L1 expression ≥50%

The Company considers that pembrolizumab plus chemotherapy represents the most relevant comparator in this appraisal, irrespective of PD-L1 expression. While in the wild-type population, pembrolizumab monotherapy is used in high PD-L1 expression, in patients with a BRAF V600 mutation, UK clinical experts indicated that pembrolizumab plus chemotherapy should be used given the aggressive nature of the disease in patients with the BRAF V600E mutation and the need for urgent intervention.[18]

Support for the view that clinical practice may not match prevailing NICE guidance is available through two recent appraisals:

- TA683 notes that pembrolizumab plus chemotherapy would be offered whether or not tumours are PD-L1 positive, and regardless of PD-L1 score.[36]
- As part of TA770, it was discussed some patients with a PD-L1 ≥50% require *urgent clinical intervention*, and in these patients, the aim of pembrolizumab plus chemotherapy is to use chemotherapy to shrink the tumour, which is compressing the airway, so the person can benefit from pembrolizumab later.[35]

Exploratory analyses to EAGs request

As requested by the EAG, exploratory scenario analyses to weight treatment costs by sub-population prevalence have been conducted, using an approach which combines PD-L1 <1% and PD-L1 1%–49%:

- **Patients with PD-L1 ≥50%: 33.5%**
    - UK clinical opinion sought during clarification questions noted that around one third of NSCLC patients are PD-L1>50%, so 33.5% was assumed as the proportion of patients that would represent patients PD-L1>50%. The Company assumed that 75% of patients receive pembrolizumab plus chemotherapy and 25% of patients receive pembrolizumab monotherapy based on our comments above
    - In the resulting scenario analysis, the costs of chemotherapy for patients receiving pembrolizumab monotherapy (~8% of the overall comparator patient population) are removed and equivalence is assumed to D&T
- **Patients with PD-L1 <50%: 66.5%**

- All of these patients are assumed to receive pembrolizumab plus chemotherapy, in line with the base case economic analysis

The results are provided in Table 12. However, this scenario analysis is highly conservative and must be interpreted with caution, as patients receiving pembrolizumab monotherapy incur reduced costs, but do not incur the any reduction in efficacy. This is discussed further in QB6b, below.

Table 12: Scenario analysis considering different costs for patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs to reflect this (as detailed in QB6a). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

b) Please identify data on these subgroups for pembrolizumab and include in model scenarios.

Clinical evidence on the relative effectiveness of D&T compared to pembrolizumab monotherapy in patients with PD-L1≥50% harbouring the BRAF V600E mutation is limited. There is evidence from FLATIRON RWE (2022) available in the BRAF V600E population, but there are limitations associated with sample size and length of follow-up.

While it was not possible to use data for the BRAF V600E population from FLATIRON RWE (2022) due to sample size ([redacted]), for completeness an exploratory analysis was conducted using data from the BRAF+ population (larger sample size, [redacted]) despite the differences in patient populations as described above (QB1) and PD-L1 status.

In this exploratory analysis, the assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy remains. The treatment effect between pembrolizumab plus chemotherapy compared with pembrolizumab monotherapy was based on the reported hazard ratios for the comparisons of D&T and pembrolizumab plus chemotherapy and pembrolizumab monotherapy, respectively (Table 13). For the purposes of this exploratory analysis, the hazard ratio for pembrolizumab plus chemotherapy was divided by pembrolizumab monotherapy to estimate the hazard ratio between these two treatments (Table 13). These resulting hazard ratios for pembrolizumab monotherapy versus pembrolizumab plus chemotherapy were therefore applied to the pembrolizumab plus chemotherapy PFS and OS curves to derive the efficacy of pembrolizumab monotherapy in the subgroup of patients with PD-L1 ≥50%. The treatment effect was applied for the first 4 years, after which the hazard of progression or death were assumed to be equal between both treatments. The extent to which pembrolizumab monotherapy is less effective than the pembrolizumab plus chemotherapy is uncertain, and this exploratory analysis may underestimate the true difference in efficacy between the two treatments.

Table 13: Summary of efficacy data from the FLATIRON RWE study (2022), BRAF+ population

Comparison	OS HR	PFS HR
D&T versus pembrolizumab monotherapy	[redacted]	[redacted]
D&T versus pembrolizumab plus chemotherapy	[redacted]	[redacted]
Pembrolizumab monotherapy versus pembrolizumab plus chemotherapy[a]	[redacted]	[redacted]

Footnote: These HRs were calculated as the HR for D&T versus pembrolizumab monotherapy, divided by the HR for D&T versus pembrolizumab plus chemotherapy.
Abbreviations: D&T: dabrafenib and trametinib; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

The results of this analysis are summarised in Table 14, below. These exploratory analyses are associated with several limitations and should be interpreted with caution.

Table 14: Scenario analysis considering different costs and efficacy for subgroups of patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs and efficacy to reflect this (as detailed in QB6b). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

c) Please present efficacy data on these subgroups from the BRF113928 trial and discuss the assumption of equal efficacy of dabrafenib and trametinib across these subgroups.

The BRF113928 trial did not collect data on PD-L1 status. Therefore, it is not possible to present subgroup data for D&T by PD-L1 status.

However, as previously detailed in the Company submission (Document B, Section B.1.3.2), and discussed with the EAG and NICE, D&T is a targeted therapy, which achieves clinical benefit via a mechanism of action that is independent of the PD-L1/PD-1 immune checkpoint. Therefore, the assumption of equal efficacy of D&T across PD-L1 subgroups should not be considered to represent a source of uncertainty in this appraisal.

B7. Please model the treatment sequence pembrolizumab -> D&T -> chemotherapy, compared to pembrolizumab -> chemotherapy. This scenario represents the cost-effectiveness of using D&T as an additional line of therapy in patients who were initiated on pembrolizumab in the absence of a timely NGS result.

As detailed in the Company Submission, patients with previously treated advanced NSCLC with a BRAF V600 mutation represent a small (but clinically important) population that is expected to diminish over time (Document B, Section B.1.1). Generating a reliable economic analysis for this population was also not considered to be feasible, due to a number of limitations (Document B, Section B.3.2.2):

- There are no robust data to inform the efficacy of D&T following pembrolizumab plus chemotherapy. All patients in Cohort B of the BRF113928 trial received chemotherapy prior to D&T. This does not reflect current UK clinical practice (as acknowledged by the EAG in Question B7), where any patients with previously untreated advanced NSCLC who experience testing delays would typically receive pembrolizumab plus chemotherapy prior to D&T. There are no data to inform an assessment of potential differences in outcomes for patients who received chemotherapy or pembrolizumab plus chemotherapy as prior therapy.
- There are no robust data to inform the efficacy of chemotherapy following pembrolizumab plus chemotherapy in patients with advanced NSCLC with a BRAF V600 mutation. The sample size of patients with previously treated advanced NSCLC with a BRAF V600E mutation in the FLATIRON RWE study (2022) was extremely small (N=[redacted]). Furthermore, patients in the FLATIRON RWE study (2022) receiving chemotherapy did not receive regimens aligned with UK clinical practice – [redacted] of the patients received either docetaxel monotherapy, or docetaxel plus nintedanib, which are the two most commonly used chemotherapy regimens in UK clinical practice in this setting

Given the extreme uncertainty associated with the data for both D&T and chemotherapy in this setting and the lack of available data, the requested scenario analysis was not considered feasible. Furthermore, based on the evolution of clinical practice in this patient population, the value of such an analysis is limited.

B8. As this appraisal covers the full marketing authorisation, the cost-effectiveness of D&T at a first- and second-line position should be assessed. Please model both treatment sequences, accounting for the proportion of patients who do not progress

onto second-line therapy. Please consider the inclusion of improved outcomes in patients who receive a second line of treatment (as in Question B3)

As described in B7, given the extreme uncertainty associated with the data for both D&T and chemotherapy in this setting and the lack of available data, the requested scenario analysis was not considered feasible.

Probabilistic analysis

B9. Priority. Please use source-derived SE values in the PSA where possible. For example, SE for baseline characteristics should be derived from trial data, rather than 10% of the mean. Please make clear where this is not possible and why.

The following inputs in the probabilistic sensitivity analysis (PSA) have been updated to use source-derived estimates of standard errors (SEs), as detailed in Table 15 below. In each case, these were calculated based on a source-derived standard deviation (SD), and the published number of patients in each source.

The SE for all other values in the PSA is still calculated as 10% of the mean, due to the absence of published SE values for these inputs.

Table 15: Summary of inputs which now use a source-derived SE in the PSA

Input	Value	Standard Error[a]	Source
Starting age	67.8	1.375	BRF113928 trial
Health state utility value (PFS)	0.710	0.017	Chouaid et al. (2013)[37]
Health state utility value (PD)	0.670	0.025	Chouaid *et al.* (2013)[37]
Treatment administration disutility (base case)	-0.023	0.008	Matza *et al.* (2013)[38]

Footnote: Calculated based on SD and N numbers from the relevant sources.
Abbreviations: CSR: clinical study report; PD: progressed disease; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; SD: standard deviation; SE: standard error.

A summary of the updated PSA results are provided in response to QB11. A summary of all of the inputs varied in the PSA can be found on the sensitivity analysis filter tab of the cost-effectiveness model.

B10. Priority. There are a number of parameters which are not varied in the probabilistic analysis. Please include the following parameters in the PSA, using appropriately derived standard errors and distributions: Relative dose intensity; treatment effect (if HRs added to model); proportion of patients receiving subsequent therapy; distribution of subsequent therapies; duration of subsequent therapy; adverse event rates. Please review other key model inputs and ensure they are included in the PSA.

The following additional parameters have now been included in the base case cost-effectiveness

analysis.

Treatment Costs

- The proportion of patients receiving carboplatin (versus cisplatin)
    - *The proportion of patients receiving cisplatin is also inherently varied, as this proportion is calculated as 100% minus the proportion of patients receiving carboplatin*
- Drug administration costs (first administration and subsequent administration costs are included separately)
- Relative dose intensities for D&T and pembrolizumab plus chemotherapy

Subsequent Therapies

- Relative dose intensities for all subsequent treatment regimens
- Subsequent therapy market shares
- Subsequent therapy treatment durations
- Proportion of patients progressing to 2L

Healthcare Resource Use

- Resource unit costs
- Resource use frequencies – (PFS and PD resource use frequencies are varied separately)
- Terminal care costs

Adverse Events

- Frequencies of all AEs - D&T and pembrolizumab plus chemotherapy
- Unit cost of all AEs
- AE QALY loss

A summary of the updated PSA results are provided in response to QB11. A summary of all of the inputs varied in the PSA can be found on the sensitivity analysis filter tab of the cost-effectiveness model.

B11. Priority. A number of PSA inputs are varied as aggregate values. Please update the model to vary cost and resource use inputs independently. This should include AE management costs, and monitoring and follow-up resource use per year and costs.

A summary of the PSA inputs which have now been disaggregated can be found in Table 16 below.

Table 16: Summary of inputs which have been disaggregated in the updated PSA

Aggregate values varied in the previous PSA	Disaggregated values varied in the updated PSA
• Total admin costs for D&T and pembrolizumab plus chemotherapy	• Costs for each type of administration (oral, IV, complex IV etc) for first administration and subsequent administrations • RDIs for each treatment • Proportion of carboplatin/cisplatin regimens for

	platinum chemotherapy therapies
• Total costs of each subsequent therapy	• Market shares of each subsequent therapy • Proportion of patients progressing to 2L • Subsequent treatment durations • Subsequent therapy RDIs
• Terminal care costs	• Terminal care unit costs (hospital, hospice etc.) • % of patients in each terminal care setting
• Healthcare resource use cost (PFS)	• Individual healthcare resource use unit costs (PFS) • Individual healthcare resource use frequencies (PFS)
• Healthcare resource use cost (PD)	• Individual healthcare resource use unit costs (PD) • Individual healthcare resource use frequencies (PD)
• AE disutilities (D&T and pembrolizumab plus chemotherapy)	• Individual AE frequencies for both D&T and pembrolizumab plus chemotherapy • Individual AE QALY loss
• AE costs (D&T and pembrolizumab plus chemotherapy)	• Individual AE frequencies for both D&T and pembrolizumab plus chemotherapy • Individual AE costs

Abbreviations: 2L: second-line; AE: adverse event; D&T: dabrafenib and trametinib; PD: progressed disease; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; RDI: relative dose intensity.

The results of the PSA with 2,000 iterations, incorporating the changes detailed in QB9, QB10 and QB11 are presented in Table 17 and the cost-effectiveness plane and acceptability curves are presented in Figure 9 and Figure 10, below. The results show that dabrafenib and trametinib was associated with a [redacted] probability of being cost-effective at a £20,000 WTP threshold, and a [redacted] probability of being cost-effective at a £30,000 WTP threshold.

As detailed in QB3b, [redacted] results of the updated PSA are provided in Appendix B.

Table 17: Probabilistic cost-effectiveness results (comparators at list price)

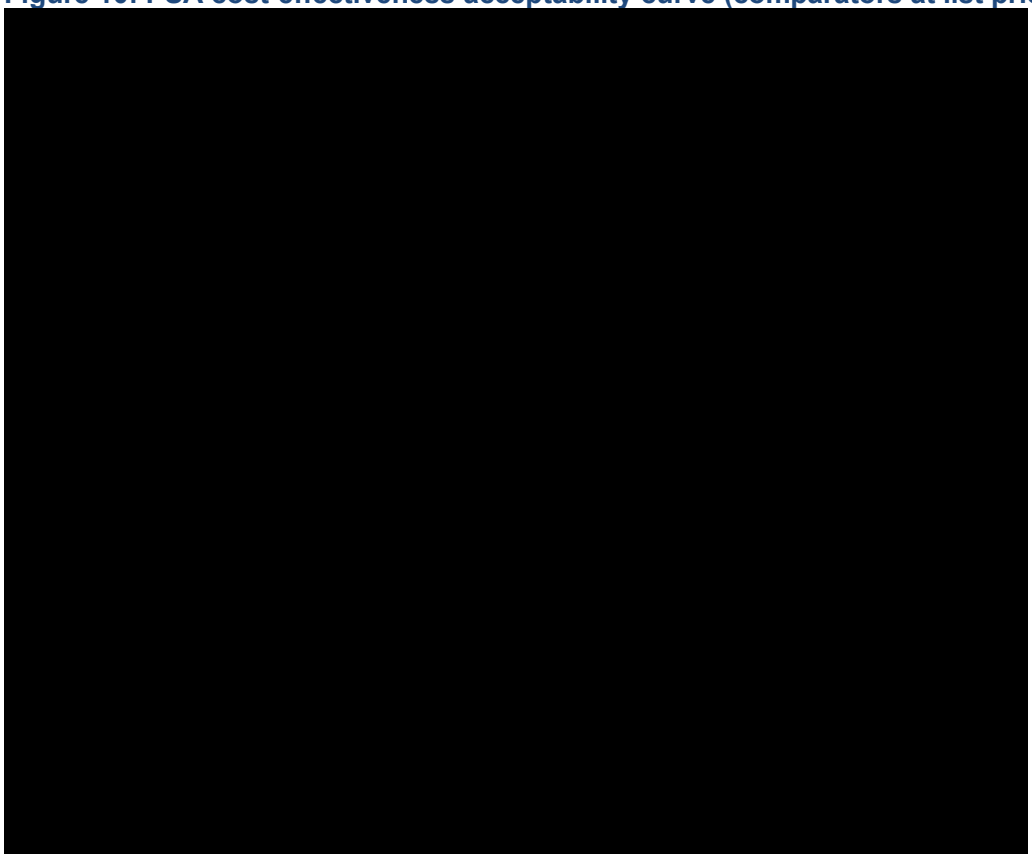
Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life years

Figure 9: PSA scatter plot (comparators at list price)

Abbreviations: QALY: quality-adjusted life year; WTP: willingness-to-pay threshold.

Figure 10: PSA cost-effectiveness acceptability curve (comparators at list price)



Footnotes: WTP threshold of £20,000 per QALY.
Abbreviations: D&T: dabrafenib and trametinib: PSA: probabilistic sensitivity analysis.

B12. Priority. Please model time on treatment for pembrolizumab based on data from the KEYNOTE-189 trial, rather than the small number of patients in FLATIRON.

Kaplan-Meier data for time on treatment from KEYNOTE-189 were not reported in the published literature. As such, a scenario analysis has been conducted whereby the time on treatment for pembrolizumab plus chemotherapy is assumed to be equal to PFS based on data from KEYNOTE-189, using the log-logistic extrapolation (as detailed in QB4),[32] and the relevant stopping rules are applied in line with the Company base case economic analysis.

The results of this scenario analysis are presented in Table 18 below. An additional analysis, where the below scenario is combined with the use of PFS and OS data from KEYNOTE-189 is presented in response to QB4 in Table 9 above.

Table 18: Scenario analysis with time on treatment for pembrolizumab plus chemotherapy based on KEYNOTE-189 (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Time on treatment for pembrolizumab plus chemotherapy is assumed to be equal to PFS from the KEYNOTE-189 trial, with relevant stopping rules applied as per the base case economic analysis	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Resource use and costs

B13. [redacted]

B14. Priority. The EAG understands that BRAF is included in NSCLC screening amongst other actionable mutations due to the interim availability of dabrafenib on the NHS in practice for BRAF V600 mutations. Please include the cost of testing for BRAF V600 mutations in the model. Modelled costs should be based on the costs of adding BRAF to multi-target NGS panels currently used in NHS practice. This approach has been previously accepted by NHS England and the Committee for targeted NSCLC treatments.

The cost of BRAF testing and reporting was not included in the base case economic analysis, based on feedback from UK clinical experts that it is already included in the 2021/2022 National Genomic Test Directory for cancer and is therefore routine clinical practice for previously untreated patients with advanced NSCLC in the majority of the UK.[39]

In this scenario analysis, the cost of reporting for the BRAF gene is included. Based on the opinion of a Genomic Lab Hub lead, the cost of adding the BRAF test to the panel would be zero and the only cost would be related to additional reporting of the BRAF gene results, which is estimated to be £50. The testing costs were calculated as follows (Table 19):

- The number of patients needed to be tested in order to identify one patient that has a BRAF V600 mutation was calculated as 1 divided by the incidence of the BRAF V600 mutation in advanced NSCLC
- This number was then be multiplied by the unit cost of a BRAF V600 mutation test

Table 19. BRAF V600 testing costs

Input	Value	Source
Incidence of the BRAF V600 mutation across the overall population of patients previously untreated advanced NSCLC	2.50%	Midpoint of range (1% to 4%): Barlesi *et al* (2016),[40] Carderella *et al.* (2013)
Patients tested per BRAF V600 patient identified	40	Calculation (1/2.5%)
Unit cost of BRAF V600 test	£50	UK clinical expert opinion
Proportion of patients tested in routine practice	0%	As a conservative scenario, it was assumed 0% of patients would not receive routine testing for a BRAF V600 mutation in UK clinical practice.

Abbreviations: NSCLC: non-small cell lung cancer; TA: technology appraisal.

The results of this scenario analysis are presented in Table 20. As detailed in QB3b, [redacted] results of the updated PSA are provided in Appendix B.

Table 20: Scenario analysis including the costs of BRAF V600 testing (comparator at PAS price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Testing costs applied to 100% of patients receiving dabrafenib and trametinib	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Section C: Textual clarification and additional points

Search strategies and methods

C1. Priority. For the clinical searches (Appendix D); the cost-effectiveness searches; health-related quality of life searches; and the cost and health resource identification measurement and valuation searches (Appendix G), databases are searched across multiple platforms. As an example, for the clinical searches MEDLINE is searched via three platforms; Embase via two platforms; and Cochrane CENTRAL and Cochrane CDSR via two platforms (as listed in the Data Sources section in Appendix D, page 12). However, the table descriptions throughout both Appendices (D and G) fail to make it clear which platform each of the strategies is for. Without this data the searches cannot be properly scrutinised in the context of the platform it is specifically designed for.

The platforms used for the main database searches of the clinical and economic SLRs are listed in the Company Submission appendices on Page 13 (clinical SLR) and Page 178 (economic SLRs). For clarity, the platforms used for each database search are listed in Table 21 below.

Table 21: Platforms used for the database searches of the clinical and economic SLRs

	Table in Company Appendices document	Databases searched	Date searched	Platform
Clinical SLR				
Original SLR	Table 2	MEDLINE, including MEDLINE In-Process, MEDLINE Daily, and MEDLINE Epub Ahead of Print	December 19th 2019	OvidSP
	Table 3	Embase	December 19th 2019	OvidSP
	Table 4	The Cochrane Library (CENTRAL, CDSR, DARE)	December 19th 2019	OvidSP
SLR update	Table 7	MEDLINE	28th May 2021	Embase.com
	Table 8	Medline In-Process	10th May 2021	Pubmed.com
	Table 7	Embase	28th May 2021	Embase.com

	Table 9	The Cochrane Library (CENTRAL)	27th May 2021	Wiley Platform
TLR update	Table 11	MEDLINE, including MEDLINE In-Process, MEDLINE Daily, and MEDLINE Epub Ahead of Print	22nd April 2022	OvidSP
	Table 12	Embase	22nd April 2022	OvidSP
	Table 13	The Cochrane Library (CENTRAL, CDSR)	22nd April 2022	Wiley Platform
Economic evaluations SLR				
Economic evaluations SLR	Table [ ][a]	MEDLINE In-Process	10th May 2021	Pubmed.com
	Table 78	Embase	10th May 2021	Embase.com
	Table 78	MEDLINE	10th May 2021	Embase.com
	Table 81	EconLit	10th May 2021	EBSCO.com
	Table 82	DARE, NHS EED, HTA	10th May 2021	CRD York
Utility values SLR				
Utility values SLR	Table [ ][a]	MEDLINE In-Process	10th May 2021	Pubmed.com
	Table 79	Embase	10th May 2021	Embase.com
	Table 79	MEDLINE	10th May 2021	Embase.com
	Table 81	EconLit	10th May 2021	EBSCO.com
	Table 82	DARE, NHS EED, HTA	10th May 2021	CRD York
Cost and resource use SLR				
Cost and resource use SLR	Table [ ][a]	MEDLINE In-Process	10th May 2021	Pubmed.com
	Table 80	Embase	10th May 2021	Embase.com
	Table 80	MEDLINE	10th May 2021	Embase.com
	Table 81	EconLit	10th May 2021	EBSCO.com
	Table 82	DARE, NHS EED, HTAD	10th May 2021	CRD York

[a]Note this table erroneously did not have a number in the Company Submission appendices
Abbreviations: CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; HTAD: Health Technology Assessment Database; NHS EED: National Health Service Economic Evaluation Database; SLR: systematic literature review.

C2. For the cost-effectiveness searches; health-related quality of life searches; and health resource identification measurement and valuation searches (Appendix G), the platform on which EconLit was accessed is not listed in the Data Sources section (Appendix G, page 178). This database is available on multiple platforms.

As listed above in Table 21, in all three economic SLRs (economic evaluations, utility values, cost and resource use), EconLit was searched via the EBSCO.com platform.

C3. For the clinical searches, The PRISMA flow diagram (listed in Appendix D, page 30) lists the use of the Northern Light database but this is not referred to in the Data

Sources section (listed in Appendix D, page 12). Nor it is clear which of the tables in Appendix D list the strategies for this database.

In the original clinical SLR, the following selected conferences were searched for relevant conference abstracts either via Northern Light Life Sciences Conference Abstracts (if the conference was indexed in this database) and via OncologyPro (https://oncologypro.esmo.org/Meeting-Resources):

- American Society of Clinical Oncology (ASCO) 2017-2019
- European Society for Medical Oncology (ESMO) 2017-2019
- European Lung Cancer Congress (ELCC) 2017-2019
- World Conference on Lung Cancer (WCLC) 2017-2019

Whilst these conferences are listed within the data sources section of the Company Submission appendices, the platforms used (OncologyPro/Northern Light Life Sciences) were not explicitly listed here.

The search strategy used for the conference abstract searches via the Northern Light Life Sciences database is presented in Table 5 (Page 16) of the Company Submission appendices. These searches searched all the conferences listed above.

The search strategy used for the conference abstract searches via OncologyPro is presented in Table 6 (Page 17) of the Company Submission appendices. These searches searched ELCC 2018 and 2019 and ESMO 2019 only.

C4. For the clinical searches, Table 4 (listed in Appendix D, page 16) lists that it contains search terms for Cochrane CENTRAL, Cochrane CDSR, and DARE. However, DARE is not referred to in the Data Sources section (listed in Appendix D, page 12) or the PRISMA diagram (Appendix D, page 30).

As listed above in Table 21, the original clinical SLR searched the Cochrane Library via the OvidSP platform which included the Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), and the Database of Abstracts of Reviews of Effects (DARE). Whilst the Cochrane Library is listed within the data sources section of the Company Submission appendices, the exact data sources were not explicitly listed.

The search strategy used to search these three elements of the Cochrane library is presented in Table 4 (Page 16) of the Company Submission appendices.

In the PRISMA diagram for the original clinical SLR in Figure 1, Page 30 of the Company Submission appendices, DARE is not explicitly listed, however it falls under the term “Cochrane” listed under the databases searched. “Cochrane” here refers to the Cochrane Library, which included CENTRAL, CDSR and DARE, and was searched in the original clinical SLR via the OvidSP platform.

C5. For the cost-effectiveness searches; health-related quality of life searches; and health resource identification measurement and valuation searches (Appendix G),

Table 82 (Appendix G, page 187) also searches DARE but this database isn't mentioned in the Data Sources section (Appendix G, page 178).

The searching of DARE was erroneously excluded from the list of databases searched via the York Centre for Reviews and Dissemination (CRD) platform for the three economic SLR streams.

For clarity, for all three economic SLR streams, the following databases were searched on 10th May 2021:

- MEDLINE® In-Process (via Pubmed.com)
- Embase® and MEDLINE (via Embase.com)
- EconLit® (via EBSCO.com)
- Centre for Reviews and Dissemination (CRD) York platform (archived records until 2015), for the following:
    - Health Technology Assessment Database (HTAD)
    - National Health Service (NHS) Economic Evaluation Database
    - Database of Abstracts of Reviews of Effects (DARE).

C6. For the clinical searches, Table 5 (listed in Appendix D, page 16) does not specify which source(s) was searched for these conference abstracts. The search cannot be scrutinised without further details of the source or platform.

As detailed above in the response to Question C3, in the original clinical SLR, the following selected conferences were searched for relevant conference abstracts via Northern Light Life Sciences Conference Abstracts (if the conference was indexed in this database) and via OncologyPro (https://oncologypro.esmo.org/Meeting-Resources):

- American Society of Clinical Oncology (ASCO) 2017-2019
- European Society for Medical Oncology (ESMO) 2017-2019
- European Lung Cancer Congress (ELCC) 2017-2019
- World Conference on Lung Cancer (WCLC) 2017-2019

Whilst these conferences are listed within the data sources section of the Company Submission appendices, the platforms used (OncologyPro/Northern Light Life Sciences) were not explicitly listed here.

The search terms used for the conference abstract searches in the original clinical SLR (via the Northern Light Life Sciences database) is presented in Table 5 (Page 16) of the Company Submission appendices. These searches searched all the conferences listed above.

The search strategy used for the conference abstract searches via OncologyPro is presented in Table 6 (Page 17) of the Company Submission appendices. These searches searched ELCC 2018 and 2019 and ESMO 2019 only.

C7. For the clinical searches, Table 6 (listed in Appendix D, page 17) lists that OncologyPro is searched but this source is not referred to in the Data Sources

section (listed in Appendix D, page 12) or the PRISMA diagram (Appendix D, page 30).

As stated above in response to Question C3, in the original clinical SLR, the following selected conferences were searched for relevant conference abstracts via OncologyPro (https://oncologypro.esmo.org/Meeting-Resources):

- European Society for Medical Oncology (ESMO) 2019
- European Lung Cancer Congress (ELCC) 2018-2019

The search strategy used for the conference abstract searches via OncologyPro is presented in Table 6 (Page 17) of the Company Submission appendices. In total 20 hits were identified via these searches, 1 from ELCC 2018, 4 from ELCC 2019 and 15 from ESMO 2019. These hits are listed on the PRISMA diagram for the original clinical SLR (Figure 1 in the Company Submission appendices) under "ELCC" and "ESMO" accordingly. The term "OncologyPro" is not explicitly stated on the PRISMA diagram.

C8. For the cost-effectiveness searches; health-related quality of life searches; and health resource identification measurement and valuation searches (Appendix G), the web addresses of the HTA bodies searched in table 84 (Appendix G, page 188) are not given. The HTA bodies are also erroneously listed under the column 'conference name' which is incorrect.

In the economic SLR, the following UK HTA websites were searched and their respective web-addresses are as follows:

- NICE, including the Cancer Drugs Fund (CDF) - https://www.nice.org.uk/
- The Scottish Medicines Consortium (SMC) - https://www.scottishmedicines.org.uk/
- All Wales Medicines Strategy Group (AWMSG) - https://awttc.nhs.wales/

The table heading should have read "HTA body" instead of "conference name".

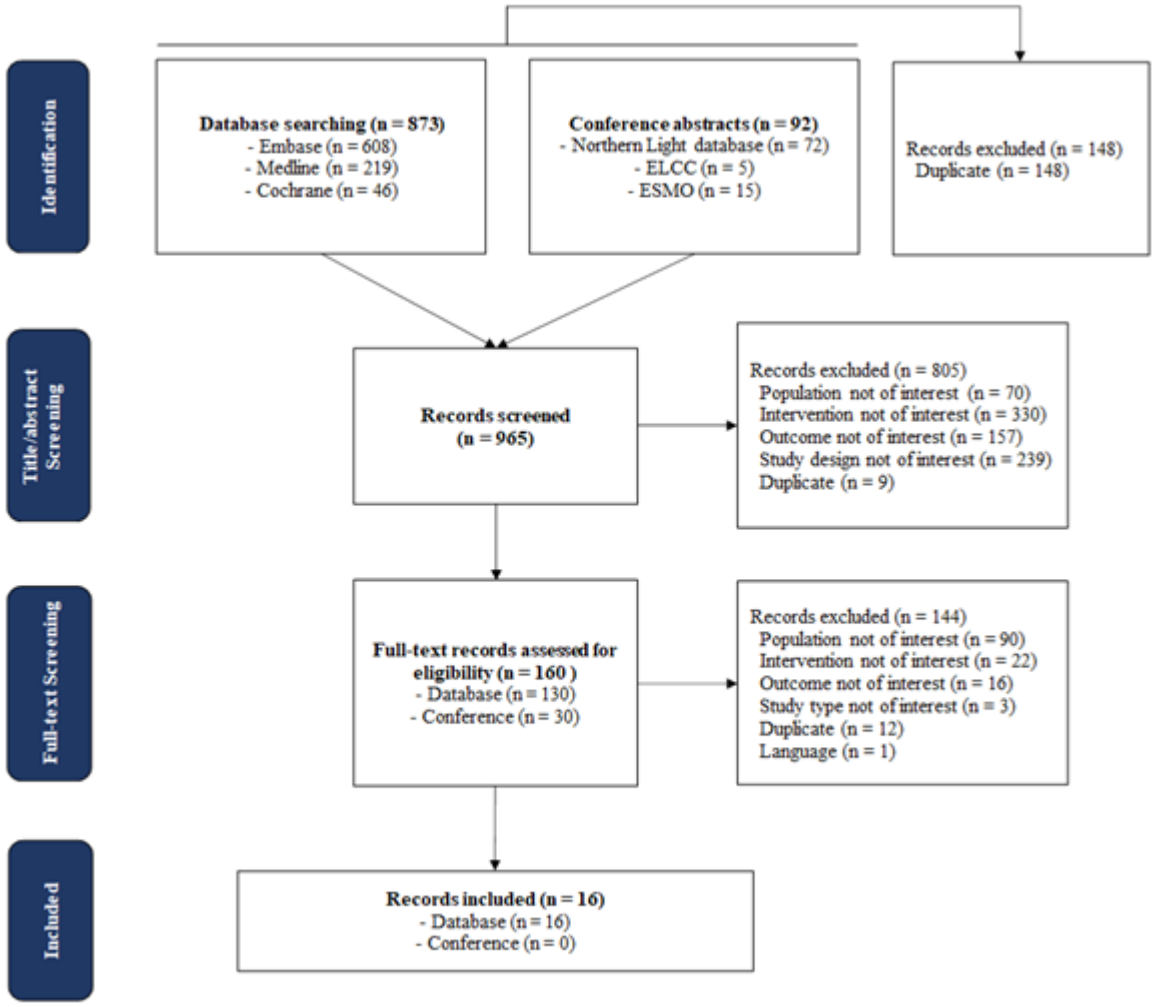
C9. Priority. For the clinical searches, in the original systematic literature review (SLR), Table 2 (MEDLINE) retrieves 222 hits, Table 3 (Embase) retrieves 721 hits, Table 4 (Cochrane CENTRAL and CDSR, and potentially DARE) retrieves 75 hits. This comes to 1,018 hits. The conference abstracts in Table 5 pick up 75 hits, Table 6 shows 20 hits from OncologyPro. This comes to 95 hits in total for conference abstracts. These are not the figures represented in the PRISMA diagram (Appendix D, p 30), so either duplicates have been removed (but the figure is not listed) or the PRISMA is wrong. Without the figure for the number of duplicates removed before screening the ERG cannot verify that the PRISMA figures are correct.

The discrepancy identified here is due to the 148 duplicate records that were removed prior to

screening. Please find a revised PRISMA diagram below to reflect this step.

A total of 1,113 records (MEDLINE: 222; Embase: 721; Cochrane: 75; conferences: 95) were identified across the database and conference abstract searches. Of these, 148 records were identified to be duplicates and removed prior to screening, leaving 965 records that were screened at the title/abstract stages (databases: 873; conferences: 92).

Figure 11: Updated PRISMA diagram for the original clinical SLR



Abbreviations: ELCC: European Lung Cancer Congress; ESMO: European Society for Medical Oncology; SLR systematic literature review.

C10. Priority. For the clinical searches, no trials registry databases were searched outside of Cochrane CENTRAL. Cochrane CENTRAL is not a sufficient replacement for searching clinical trials registries – the search functionality is different which means it will miss relevant content that could be found on ClinicalTrials.gov or WHO ICTRP, and it is not as up-to-date. Moreover, Cochrane CENTRAL only indexes some of the material on

ClinicalTrials.gov. Please can the company perform additional searches to investigate whether relevant studies were missed?

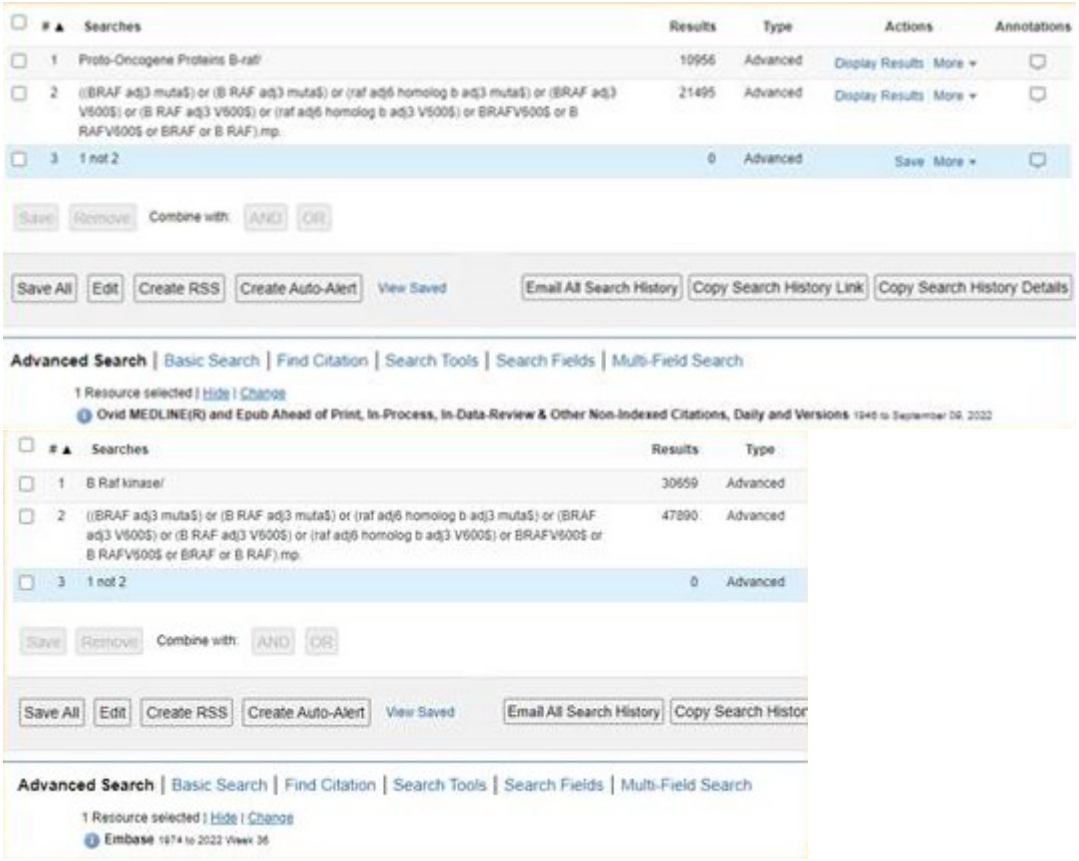
The clinical SLR focused on studies with published results on efficacy and safety in order to assess the feasibility of an indirect treatment comparison; therefore, the SLR was conducted over a comprehensive list of databases that index such studies, and registries do not usually report results. Whilst it is acknowledged that the searching of ClinicalTrials.gov or WHO ICTRP may have yielded additional records, it is not considered that any of these records would have ultimately been included in the SLR. It is expected that any relevant studies would have published their results beyond reporting their results solely in a trials registry. Moreover, given the need to identify robust data sources that would provide Kaplan-Meier data to inform the economic model, it is not considered that additional searches of Clinicaltrials.gov would yield any relevant studies that could have been leveraged within this submission. No further searches have been conducted.

C11. Priority. For the clinical searches, no health technology assessment (HTA) sources or databases were searched. Please can the company perform additional searches to investigate whether relevant studies were missed?

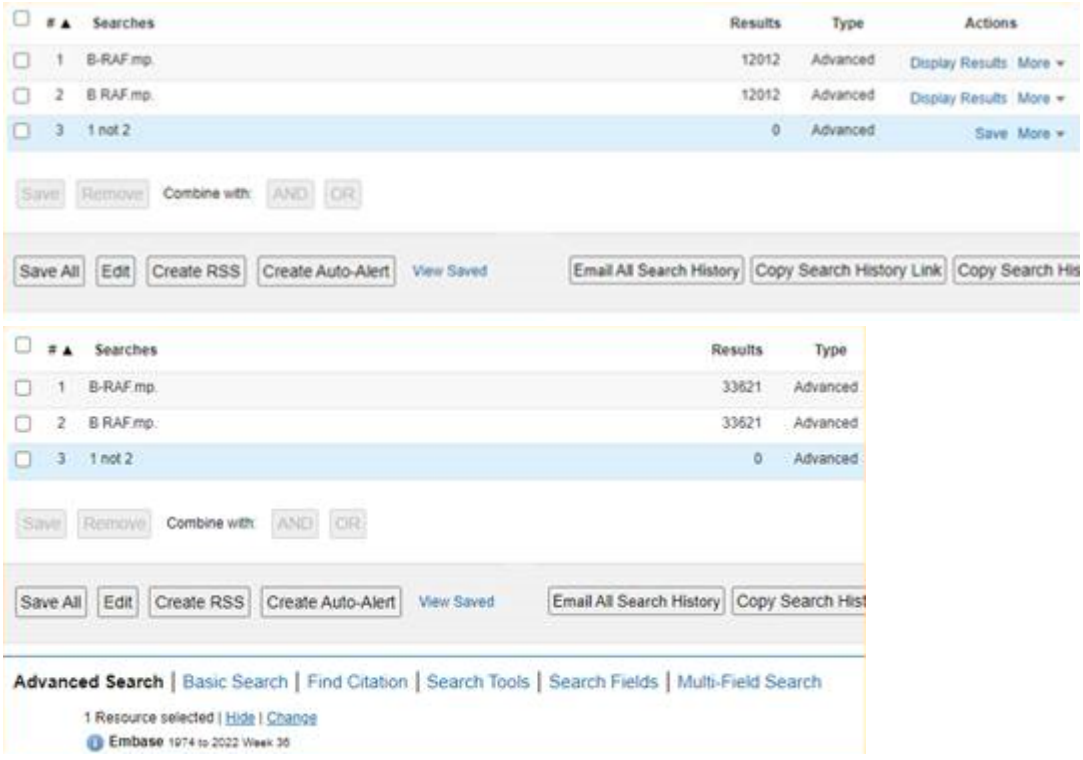
The clinical SLR(s) were conducted in line with guidance from Cochrane and the York Centre for Reviews and Dissemination (CRD). There is no specific recommendation in these guidelines to search HTA sources for clinical trials. It is also expected that any relevant clinical data available from a HTA source would also be published and would therefore have been identified via the comprehensive database searches. Given the paucity of available data in this indication, it is not expected that any studies aligned with the decision of the appraisal have been missed through not searching HTA sources. No further searches have been conducted.

C12. Priority. For the clinical searches, although there are no specific medical subject headings (MeSH) for BRAF V600 mutation available to use on MEDLINE, there are relevant MeSH terms which could have been applied in the original systematic literature review (SLR), e.g. Proto-Oncogene Proteins B-raf/. This would be missed by the field code .mp. on line 5 (Appendix D, page 13) as B-RAF is not searched for with hyphenation. In comparison, the update searches (Appendix D, pages 17-23) use an excellent range of subject headings to cover B-RAF on all databases (but these searches are limited to recent publication years only). Why weren't these terms applied in the original SLR? Please can the company perform additional searches to investigate whether relevant studies were missed?

In the original SLR MEDLINE and Embase searches, studies indexed with MeSH terms (Proto-Oncogene Proteins B-raf/ or B Raf kinase/) can be captured by the original search terms in line 5 (see screenshot below).



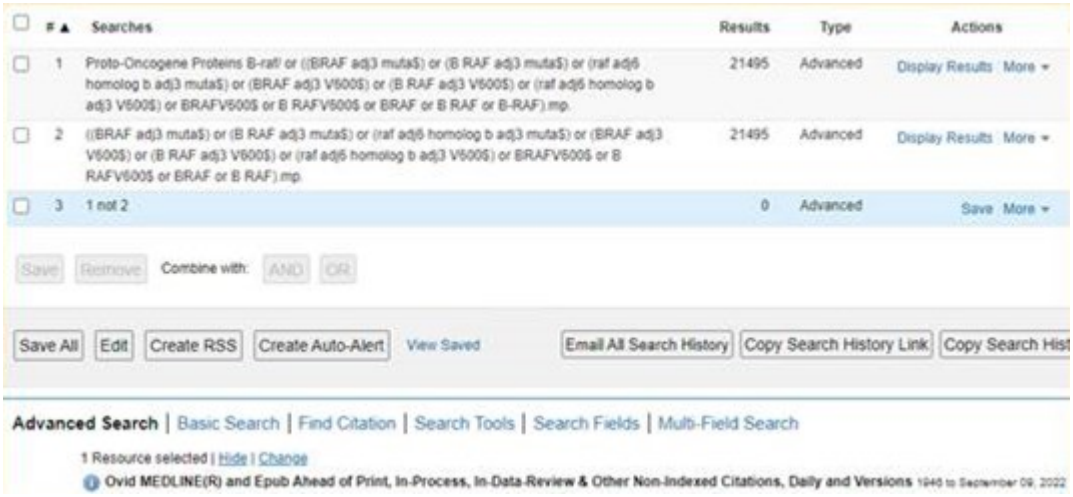
Similarly, ‘B-RAF’ with hyphenation would yield the same results as ‘B RAF’ with a space (see screenshot below). The latter was searched for by the field code .mp. on line 5.

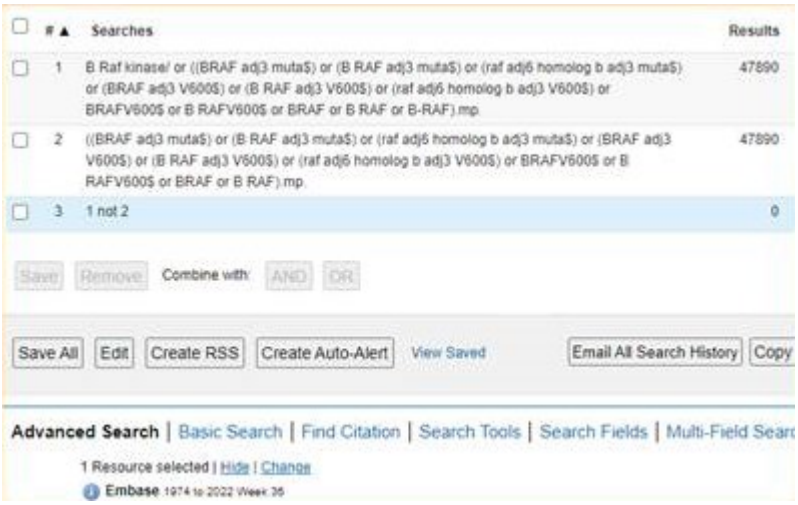


Therefore, the original search terms did not miss relevant studies, and line 5 can be updated to

below without any impact on search results.

- MEDLINE: Proto-Oncogene Proteins B-raf/ or ((BRAF adj3 muta$) or (B RAF adj3 muta$) or (raf adj6 homolog b adj3 muta$) or (BRAF adj3 V600$) or (B RAF adj3 V600$) or (raf adj6 homolog b adj3 V600$) or BRAFV600$ or B RAFV600$ or BRAF or B RAF or B-RAF).mp.
- Embase: B Raf kinase/ or ((BRAF adj3 muta$) or (B RAF adj3 muta$) or (raf adj6 homolog b adj3 muta$) or (BRAF adj3 V600$) or (B RAF adj3 V600$) or (raf adj6 homolog b adj3 V600$) or BRAFV600$ or B RAFV600$ or BRAF or B RAF or B-RAF).mp.





Appendix A: Scenario analyses results

For completeness, the below section includes results for all scenario analyses presented as part of the Company's responses to QB3, QB4, QB6, QB11, QB12 and QB14. These results match those presented throughout this document and have been conducted in line with the Company submission base case, based on the currently approved PAS prices for dabrafenib ([redacted]) and trametinib ([redacted]), and the list prices for all comparator and subsequent treatments.

QB3

Table 22: Scenario analysis including an incremental benefit for immunotherapy (following D&T) versus docetaxel or docetaxel plus nintedanib (following pembrolizumab plus chemotherapy) (comparator at list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #1 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #2 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #3 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #4 (applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Scenario #5 (assuming [redacted]% of patients who receive subsequent treatment after D&T receive immunotherapy (in line with the Company submission, Document B, Section B.3.10.3, Scenario 11), and then applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86).	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Footnotes: [a] Calculated as 1/0.73. [b] Calculated as 1/0.70. [c] Calculated as 1/0.61. [d] Calculated as the average of 1.37, 1.43 and 1.64.
Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; OS: overall survival; QALY: quality-adjusted life year.

QB4

Table 23: Scenario analysis using PFS and OS data for pembrolizumab plus chemotherapy from KEYNOTE-189 (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT based on the FLATIRON RWE study (2022)	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT assumed to be equal to PFS	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy OS derived using a HR of 0.714 from the BRAF+ dataset, applied for a duration of 5 years	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year.

QB6a

Table 24: Scenario analysis considering different costs for patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs to reflect this (as detailed in QB6a). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

QB6b

Table 25: Scenario analysis considering different costs and efficacy for subgroups of patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs and efficacy to reflect this (as detailed in QB6b). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

QB11

Table 26: Company base case probabilistic cost-effectiveness results (comparators at list price)

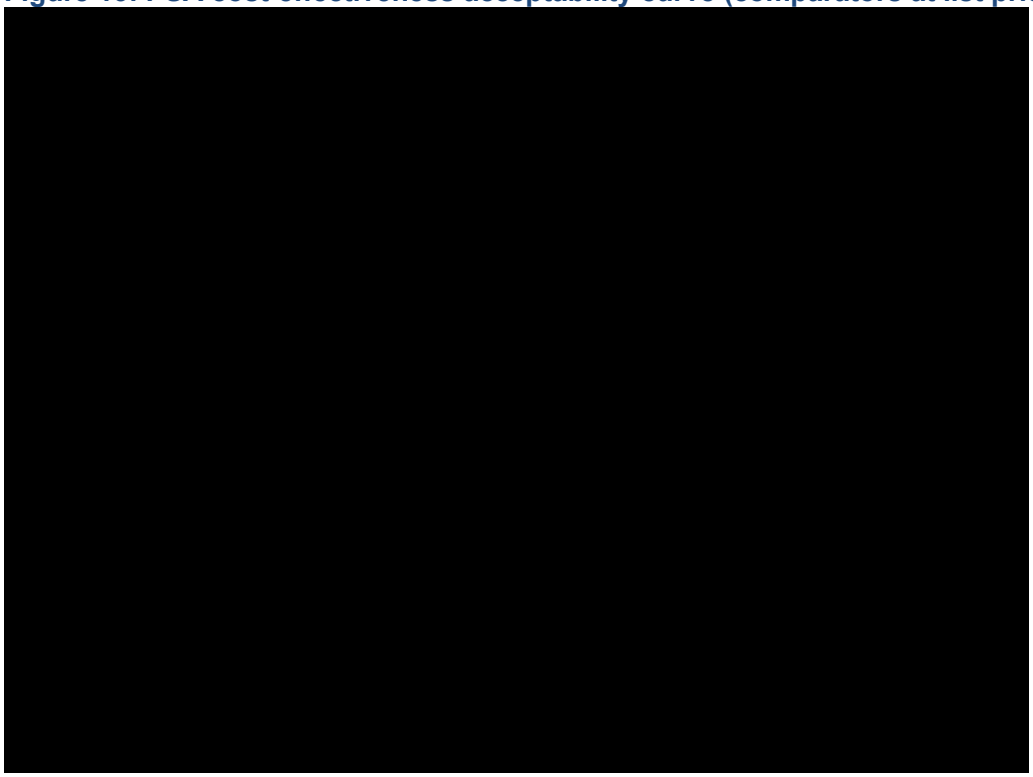
Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; QALYs: quality-adjusted life year

Figure 12: PSA scatter plot (comparators at list price)

Abbreviations: QALY: quality-adjusted life year; WTP: willingness-to-pay threshold.

Figure 13: PSA cost-effectiveness acceptability curve (comparators at list price)



Footnotes: WTP threshold of £20,000 per QALY.
Abbreviations: D&T: dabrafenib and trametinib: PSA: probabilistic sensitivity analysis.

QB12

Table 27: Scenario analysis with time on treatment for pembrolizumab plus chemotherapy based on KEYNOTE-189 (comparator list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Time on treatment for pembrolizumab plus chemotherapy is assumed to be equal to PFS from the KEYNOTE-189 trial, with relevant stopping rules applied as per the base case economic analysis	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

QB14

Table 28: Scenario analysis including the costs of BRAF V600 testing (comparator at list price)

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Testing costs applied to 100% of patients receiving dabrafenib and trametinib	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Appendix B: Scenario analyses results – [redacted]

The below section includes results for the scenario analyses presented as part of the Company's responses to QB3, QB4, QB6, QB11, QB12 and QB14. These results include assumptions regarding the PAS discount for pembrolizumab, as well as all subsequent treatments, in order to provide a more indicative set of results. A PAS discount of [redacted]% for pembrolizumab, atezolizumab and nivolumab and [redacted]% for nintedanib has been assumed. Dabrafenib is provided at the [redacted]).

QB3

Table 29: Scenario analysis including an incremental benefit for immunotherapy (following D&T) versus docetaxel or docetaxel plus nintedanib (following pembrolizumab plus chemotherapy) [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario #1 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario #2 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario #3 (applying an OS HR of [redacted] to [redacted]% of patients in receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario #4 (applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario #5 (assuming [redacted]% of patients who receive subsequent treatment after D&T receive immunotherapy (in line with the Company submission, Document B, Section B.3.10.3, Scenario 11), and then applying an OS HR of [redacted]) to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years from Year 0.86).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Calculated as 1/0.73. [b] Calculated as 1/0.70. [c] Calculated as 1/0.61. [d] Calculated as the average of 1.37, 1.43 and 1.64.

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; NHB: net health benefit; OS: overall survival; QALY: quality-adjusted life year.

QB4

Table 30: Scenario analysis using PFS and OS data for pembrolizumab plus chemotherapy from KEYNOTE-189 [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT based on the FLATIRON RWE study (2022)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT assumed to be equal to PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy OS derived using a HR of 0.714 from the BRAF+ dataset, applied for a duration of 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year.

QB6a

Table 31: Scenario analysis considering different costs for patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Company submission base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs to reflect this (as detailed in QB6a). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

QB6b

Table 32: Scenario analysis considering different costs and efficacy for subgroups of patients receiving pembrolizumab plus chemotherapy and pembrolizumab monotherapy [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs and efficacy to reflect this (as detailed in QB6b). The remaining patients are assumed to receive pembrolizumab plus chemotherapy, as per the base case economic analysis.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; PD-L1: programmed death ligand 1; QALY: quality-adjusted life year.

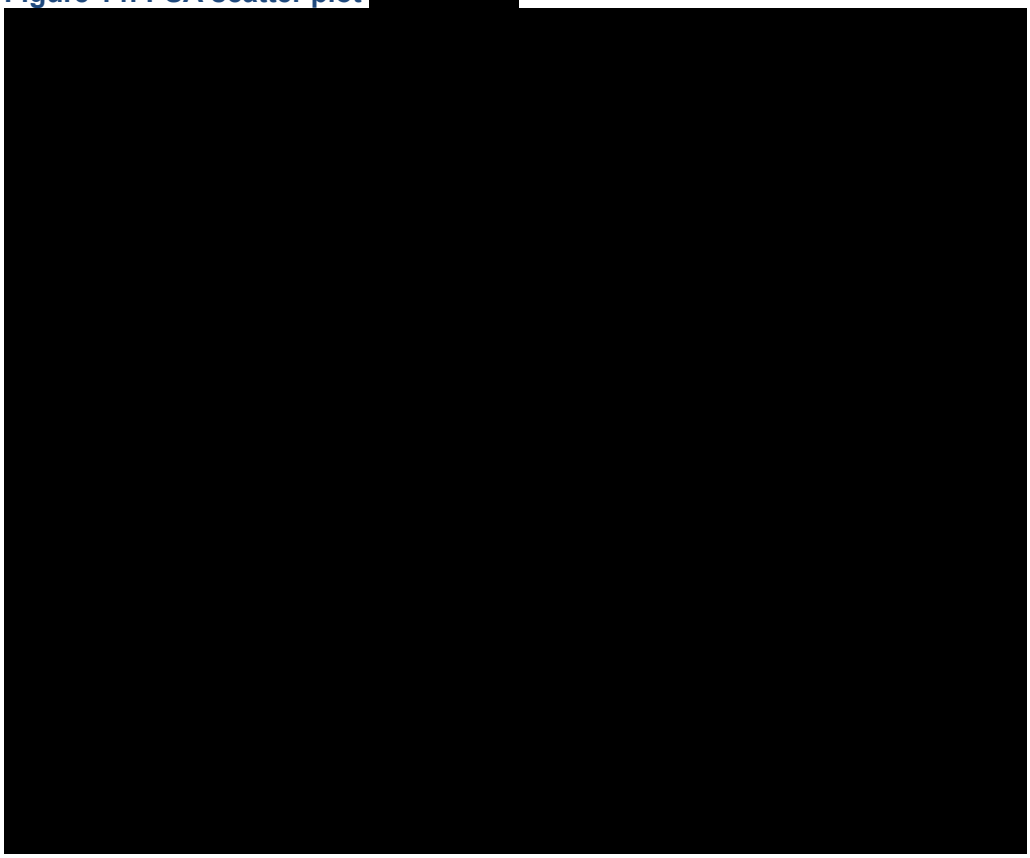
QB11

Table 33: Company base case probabilistic cost-effectiveness results [redacted]

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

Figure 14: PSA scatter plot



Abbreviations: PAS: patient access scheme**;** QALY: quality-adjusted life year; WTP: willingness-to-pay threshold.

Figure 15: PSA cost-effectiveness acceptability curve

Footnotes: WTP threshold of £20,000 per QALY.
Abbreviations: D&T: dabrafenib and trametinib; PAS: patient access scheme; PSA: probabilistic sensitivity analysis.

QB12

Table 34: Scenario analysis with time on treatment for pembrolizumab plus chemotherapy based on KEYNOTE-189 [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment for pembrolizumab plus chemotherapy is assumed to be equal to PFS from the KEYNOTE-189 trial, with relevant stopping rules applied as per the base case economic analysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year

QB14

Table 35: Scenario analysis including the costs of BRAF V600 testing [redacted]

Scenario Analysis Description	Inc. Costs	Inc. QALYs	ICER	NHB at £20,000	NHB at £30,000
Base case (prior to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Testing costs applied to 100% of patients receiving dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

2. Name of organisation	Roy Castle Lung Cancer Foundation
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	As a result of the COVID pandemic, our contact with patients and carers has become mainly virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is around 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. BRAF mutations have been reported in about 4% of non small cell lung cancer (nsclc). They are most common in adenocarcinoma nsclc. More specifically, about 1-2% of nsclc patients harbor the BRAF-V600 mutation.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some selected patients with nsclc – Target Therapies (EGFR, ALK, ROS1 etc…) and Immunotherapies. To date, there have been no NICE recommended therapies specifically for BRAF positive nsclc. There is, however, in melanoma, where there is considerable experience, over several years, with this two drug combination. Furthermore, this combination was approved for use in patients with nsclc, in 2017, by both the FDA and the EMA. Several studies have shown poorer outcomes with platinum based chemotherapy in patients with BRAF V600 mutant nsclc compared with those without BRAF mutations. There is an obvious unmet need.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As above, this would be the first NICE recommended therapy available specifically targeted for people with BRAF V600 mutations.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. We understand that this combination is relatively well tolerated. The most common adverse events are pyrexia, nausea, vomiting, dry skin, peripheral oedema, diarrhoea, decreased appetite and cough. We note the Phase 2 study of Dabrafenib plus Trametinib in patients with BRAF 600V mutant metastatic nsclc and the 5 year update (Planchard et al, JTO August 2021). In which, the 4 and 5 year survival rates were 26% and 19% in pre-treated patients and 34% and 22% in treatment naïve patients respectively. Dabrafenib plus Trametinib was found to have a substantial and durable clinical benefit, with a manageable safety profile in this highly selected patient group, regardless of previous treatment.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The first targeted therapy combination being assessed specifically for patients with BRAF V600 mutations in nsclc.
- Considerable knowledge with this combination and management of adverse events etc, as there are years of experience in melanoma patients.
- Studies show durable clinical benefit

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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External Assessment Group Report
Dabrafenib and trametinib for advanced non-small cell lung cancer with a BRAF V600 mutation

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Mark Corbett wrote the critique of the decision problem and contributed to the critique of the clinical effectiveness evidence. Sofia Dias supported the critical appraisal of the evidence and takes responsibility for the report as a whole. Kerry Dwan critiqued the comparative effectiveness evidence. Helen Fulbright wrote the search strategy sections. Robert Hodgson supported the critical appraisal of the economic evidence submitted by the company. Martin Njoroge co-authored the critique of the economic evidence submitted by the company. Matt Walton led the critique of the economic evidence submitted by the company. Eleanora Uphoff contributed to the critique of the clinical effectiveness evidence.

Note on the text
All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

AE	Adverse event
BID	Twice daily (*bis in die*)
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
D&T	Dabrafenib and trametinib
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
eMIT	Electronic Marketing Information Tool
EQ-5D	EuroQol - 5 Dimension
ERG	Evidence review group
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitors
IPD	Individual participant data
IPTW	Inverse probability of treatment weighting
IV	Intravenous
KM	Kaplan-Meier
LY	Life years
LYG	Life years gained
MEK	Mitogen-activated protein kinase kinase
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not Reported
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real-world evidence

SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TSD	Technical Support Document
TTO	Time trade off
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of the EAG's Key Issues

ID	Summary of issue	Report sections
1	The model does not adequately address the population described in the decision problem. The company anticipate a recommendation across two therapeutic lines but have not presented a case for the clinical or cost-effectiveness of dabrafenib and trametinib (D&T) in the significant proportion of patients who would be eligible for treatment after progression on pembrolizumab.	4.2.3, 4.2.4
2	The company claims that the availability of an oral treatment option has a positive impact on alleviating capacity issues within the NHS (because alternatives are delivered intravenously). However, non-compliance with D&T in a small but significant number of patients may have a negative impact on efficacy.	3.2.1.4
3	Several different datasets can be used for evaluating efficacy and only non-randomised comparisons are available. Clinical and methodological heterogeneity across these datasets means it is unclear which is the most appropriate.	3.2.2, 3.2.3
4	Uncertainty about the applicability of the results of trial BRF113928 to the NHS setting. [redacted] of patients who received the combination therapy (dabrafenib and trametinib) in BRF113928 had protocol deviations that meant they had not met the trial eligibility criteria. The clinical study report did not provide any detailed data to allay concerns about this, and the company could not provide basic data on the number of patients screened, the number excluded and why patients were excluded.	3.2.1.3
5	The assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy means demonstrating cost-effectiveness is challenging. Important differences in mode of action and availability of subsequent therapies mean it is plausible that outcomes on D&T may differ. Alternative approaches to modelling efficacy are presented, but it is unclear which is most appropriate.	4.2.6

ID	Summary of issue	Report sections
6	The EAG highlighted that BRAF V600 testing was only included in NSCLC screening due interim availability of dabrafenib under Covid-19 guidelines. As funding of BRAF mutation testing is integral and exclusive to implementation of D&T, it should thus be included for consistency with appraisals of other targeted therapies.	4.2.8.7
7	Alignment of resource use with previous appraisals – a number of previously accepted costings and resource use were omitted or were incompletely implemented. This may result in the model underestimating the costs associated with D&T.	4.2.8
8	A large and internally inconsistent disutility was applied to pembrolizumab plus chemotherapy in the company's base-case to reflect burden on health associated with monthly visits hospital to receive intravenous infusion. The EAG prefers to remove this disutility from the model.	4.2.7.4
9	In scenarios using KEYNOTE-189 to model pembrolizumab with the company's preferred utility value set, proportional QALY shortfall is very close to 0.85. The applicability of a severity modifier should be carefully considered.	7

Abbreviations: D&T, dabrafenib and trametinib; EAG, external assessment group; NSCLC non-small cell lung cancer; QALY, quality adjusted life year.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG considers scenarios including KEYNOTE-189 efficacy data to be potentially informative, the company prefer an assumption of clinical equivalence.
- The company prefers to apply a disutility to patients receiving intravenous infusions, the EAG prefers to omit this disutility.
- The EAG prefer health state utilities based on those used in TA812,[1] the company prefer an alternative value set.
- The EAG prefer wastage of dabrafenib and trametinib (D&T) to be estimated by halving the cost savings assumed to result from missed doses, the company does not include wastage for oral therapies.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Eliminating the need for intravenous (IV) infusions, which are modelled to impact HRQoL;
- A reduced adverse event burden.

Overall, the technology is modelled to affect costs by:

- Lower first-line treatment acquisition costs;
- Lower administration costs;
- Higher subsequent treatment costs.

The modelling assumptions that have the greatest effect on the ICER are:

- Assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy versus use of KEYNOTE-189;
- Inclusion of genetic testing costs;
- Assumed distribution of subsequent therapies;
- Consideration of drug wastage for D&T.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 No cost-effectiveness evidence presented for second-line use of dabrafenib with trametinib

Report section	4.2.3, 4.2.4
Description of issue and why the EAG has identified it as important	The submission and model do not adequately address the population described in the decision problem. A clinically significant proportion of eligible patients ([redacted]) are currently treated with pembrolizumab plus chemotherapy at first line due to delays in receipt of genetic testing results. These patients are likely to be treated with D&T following progression on pembrolizumab. Whilst second-line data for D&T from the BRF113928 study were presented in the submission, the company did not consider it feasible to conduct an economic analysis based on this population. The company argue that this population will shrink over time as NHS testing capacity improves, therefore it is not necessary to conduct this analysis. However, this group is likely to remain a clinically significant minority for some time. It is therefore important that the cost-effectiveness of D&T is considered in this second-line population if a recommendation is to cover the full population

What alternative approach has the EAG suggested?	The EAG requested in the points for clarification that a treatment sequence in which pembrolizumab plus chemotherapy followed by D&T followed by a docetaxel regimen be compared to pembrolizumab plus chemotherapy followed by a docetaxel regimen. Using data on D&T from the pre-treated Cohort B in BRF113928 may provide reassurance that treatment efficacy is maintained at second line, despite the populations not being strictly comparable.
What is the expected effect on the cost-effectiveness estimates?	The consequences of the omission of this group of patients are unclear.
What additional evidence or analyses might help to resolve this key issue?	The analysis described in the EAG's suggested approach may help provide reassurance that cost-effectiveness of D&T is maintained across different lines of therapy.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Risk-benefit considerations of using an oral therapy

Report section	3.2.1.4
Description of issue and why the EAG has identified it as important	The company stated that the availability of an oral treatment option has a positive impact on alleviating capacity issues within the NHS (because alternatives are delivered intravenously in hospital). The company also stated that oral alternatives to intravenous therapies represent an important preference for non-small cell lung cancer (NSCLC) patients. The EAG acknowledges that the addition of an oral therapy option has some benefits but notes that the company's submission did not consider possible drawbacks. In the pivotal D&T study, [redacted] of patients taking the combined therapy deviated from the study protocol due to treatment non-compliance. The EAG considers that non-compliance in a small but significant number of patients may have a negative impact on efficacy (when compared to comparators given intravenously). A relatively high disutility is also considered for IV drug administration which appears inconsistent with other modelled disutilities – see Issue 8.
What alternative approach has the EAG suggested?	The EAG has presented data from the clinical study report on this issue to enable a balanced assessment to be made of the risk-benefit considerations of using an oral therapy.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in cost-effectiveness of D&T.
What additional evidence or analyses might help to resolve this key issue?	The EAG asked for a summary of non-compliance data for the D&T trials in melanoma patients but was told this was not available.

Issue 3 Small, heterogenous non-randomised datasets for evaluating efficacy

Report section	3.2.2, 3.2.3
Description of issue and why the EAG has identified it as important	The submission (and responses to clarification) presented several non-randomised comparisons which could be used for evaluating the efficacy of dabrafenib and trametinib, using pembrolizumab plus chemotherapy as the comparator. There is clinical and methodological heterogeneity across these datasets, the sample sizes are small and results for all comparisons are at serious risk of bias. This means it is unclear which is the most appropriate dataset to inform the efficacy evaluation.
What alternative approach has the EAG suggested?	None. The EAG acknowledges the inherent difficulties in producing unbiased comparisons when few patients are available to be recruited into studies.
What is the expected effect on the cost-effectiveness estimates?	High level of uncertainty not captured in cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Larger datasets would help but this would probably be time-consuming to collect and would also likely be non-randomised comparisons.

Issue 4 Uncertainty about the applicability of the population recruited to trial BRF113928

Report section	3.2.1.3
Description of issue and why the EAG has identified it as important	[redacted] of patients who received the combination therapy (D&T) in study BRF113928 did not meet the trial eligibility criteria. In the version of the clinical study report (CSR) provided by the company, the EAG could not find specific reasons for why these included patients were ineligible. Additionally, the company were unable to provide basic data (requested by the EAG) on the number of patients screened and the number excluded from BRF113928. Collectively, these issues create some uncertainty about the applicability of the results of BRF113928 to the NHS setting. If these data were not collected this also raises concerns about the adequacy of the administration of the trial.
What alternative approach has the EAG suggested?	Transparent reporting of the data described. The company stated that information on patients screened for eligibility, ineligible or who have declined participation is either not available or collected (even though this has been part of the CONSORT guidelines for reporting trial results for many years).
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in the applicability of cost-effectiveness estimates to an NHS setting.
What additional evidence or analyses might help to resolve this key issue?	Presentation of progression free survival (PFS) and overall survival (OS) results with the ineligible patients removed from the analyses. Clear and transparent reporting of study conduct.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Clinical equivalence assumed between D&T and pembrolizumab plus chemotherapy

Report section	4.2.6
Description of issue and why the EAG has identified it as important	In the absence of comparative trial evidence, the company assumed that the efficacy of pembrolizumab plus chemotherapy would be equal to that observed for D&T in the BRF113928 trial. This is despite the existence of trial evidence for the comparator in an advanced NSCLC population. Important differences in availability of subsequent therapies mean it is plausible that the modelled sequence of D&T followed by an immunotherapy would generate superior outcomes compared to pembrolizumab plus chemotherapy followed by docetaxel-based regimens. The EAG also notes clinical advice suggesting that D&T is likely to be superior to pembrolizumab for patients in whom a driving BRAF V600 mutation has been identified. The EAG notes that this scenario is likely to be conservative, and may underestimate the benefits associated with D&T. Using this approach, a recommendation for D&T could only be made in a cost-saving scenario.
What alternative approach has the EAG suggested?	The EAG suggests two alternative approaches to produce potentially informative comparisons of the relative efficacy of D&T and pembrolizumab. Firstly, an analysis which adjusts the treatment effect for pembrolizumab plus chemotherapy, reducing the post-progression survival benefits derived from D&T under the assumption of clinical equivalence. Secondly, an analysis using KEYNOTE-189 trial data to directly model OS and PFS outcomes for the pembrolizumab plus chemotherapy arm. The EAG considers the predictions from KEYNOTE-189 data clinically plausible but highlights that this is an unanchored comparison of misaligned trial populations.
What is the expected effect on the cost-effectiveness estimates?	The use of literature-derived hazard ratios to adjust OS reduces total QALYs accrued on pembrolizumab plus chemotherapy by [redacted] Net health benefit (NHB) for D&T increases from [redacted] at a willingness to pay (WTP) threshold of £20,000. Using KEYNOTE-189 data instead of assuming clinical equivalence results in a reduction of total QALYs in the pembrolizumab plus chemotherapy arm by [redacted]. NHB for D&T increases from [redacted] to [redacted] at a WTP threshold of £20,000.
What additional evidence or analyses might help to resolve this key issue?	A formal indirect comparison of KEYNOTE-189 and BRF113928 may reduce uncertainty associated with misalignment of the study populations.

Issue 6 Inclusion of BRAF testing costs

Report section	4.2.8.7
Description of issue and why the EAG has identified it as important	The company base-case omitted the cost of BRAF V600 testing and reporting because it is already included in the Genomic Testing Directory. The EAG highlighted that BRAF testing was only included in NSCLC screening due to availability of D&T on the NHS under interim Covid-19 guidelines. As funding of BRAF mutation testing is integral and exclusive to the implementation of D&T, it should thus be included for consistency with appraisals of other targeted therapies.
What alternative approach has the EAG suggested?	The EAG has included a total testing cost of £1,360 per patient based on a 2.5% incidence, and a £34 standard cost of adding a mutation onto a next-generation screening (NGS) panel. This figure is based on NHS England advice in the recent appraisal of mobocertinib in NSCLC.[2]
What is the expected effect on the cost-effectiveness estimates?	The inclusion of BRAF testing costs leads to an increase in total cost of D&T from [redacted] in the company base-case to [redacted]. NHB at a WTP threshold of £20,000 is reduced from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Further input from NHS England on the relevance of testing costs in the particular circumstances of this appraisal.

Issue 7 Alignment of resource use with previous appraisals

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The EAG identified issues relating to omission or incomplete implementation to several resource use costs. Pharmacist time to dispense drugs, and some key components of end-of-life costs (the cost of home end-of-life care). Wastage of D&T was not accounted for in the company's base-case, assuming instead that all missed doses and unfinished packs would result in fewer packs being used. This could result in the model underestimating the acquisition cost of D&T.
What alternative approach has the EAG suggested?	The EAG has presented a number of scenarios which aim to align resource use with previous NSCLC appraisals. The EAG expects some wastage to be associated with dose adjustments and interruptions. Wastage for oral therapies was included using the assumption that only half of relative dose intensity (RDI) savings would be realised, around half a pack per patient.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of pharmacist dispensing time and terminal care costs have a minor impact on incremental costs under the company's base-case assumptions. The inclusion of wastage added [redacted] to the total cost of D&T. NHB on D&T is reduced from [redacted] to [redacted] at a WTP threshold of £20,000.
What additional evidence or analyses might help to resolve this key issue?	The EAG has included these amendments in the updated base-case analysis.

Issue 8 Inclusion of disutility associated with monthly IV infusion

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	The company applied an annualised disutility of -0.023 throughout each cycle patients remain on treatment with pembrolizumab plus chemotherapy, representing the ongoing impact on a patient's health-related quality of life of a 30-minute IV infusion once every four weeks. This disutility is more than double that applied in the model for pneumonia requiring hospitalisation, and lacks face validity. The time trade-off methodology used in the source study to generate this disutility is inconsistent with the NICE reference case and is not a reliable means of generating utilities.
What alternative approach has the EAG suggested?	The EAG prefers to remove this disutility from the model. Whilst a monthly IV infusion may be less convenient than an oral therapy, the health-related quality of life (QoL) impact is likely to be nominal and substantially smaller than modelled.
What is the expected effect on the cost-effectiveness estimates?	The removal of this disutility reduces incremental QALYs on D&T from [redacted] to [redacted]. This reduces NHB at £20,000 from [redacted].
What additional evidence or analyses might help to resolve this key issue?	Collection of EQ-5D data from UK patients on IV infusion. Patient comment on how receiving an IV infusion feels compared to other modelled disutilities.

1.6 Other key issues: summary of the EAG's view

Issue 9 Relevance of a severity modifier under particular assumptions

Report section	7
Description of issue and why the EAG has identified it as important	The modelling of pembrolizumab plus chemotherapy outcomes using the KEYNOTE-189 trial and company base-case assumptions results in a proportional QALY shortfall of [redacted] – very close to the threshold for a 1.2x QALY weighting. The EAG base-case is [redacted], although this increases to [redacted] using the company's preferred utility set. It is unclear how appropriate the application of a severity modifier would be in this appraisal. The selection of the source of health state utilities has an impact on the proximity of the QALY shortfall to the increased QALY weight threshold.
What alternative approach has the EAG suggested?	The EAG has presented the results without applying a severity modifier as the proportional QALY shortfall threshold of 0.85 is not reached. Scenarios using KEYNOTE-189 data combined with the company's preferred utility value set results in a QALY shortfall approaching 0.85. The health state utility set from TA812[1] is preferred by the EAG for consistency with previous appraisals, which reduces the proportional shortfall to 0.835. Depending on the combination of assumptions preferred by the committee the severity modifier may be applicable.
What is the expected effect on the cost-effectiveness estimates?	The application of a severity modifier would increase the apparent cost-effectiveness of D&T.

What additional evidence or analyses might help to resolve this key issue?	Guidance on the application of a severity modifier when plausible scenarios generate a QALY shortfall close to 0.85. Guidance on the relevance of severity modifier to the current appraisal.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Given the high level of uncertainty associated with the lack of comparative evidence for D&T, the EAG has presented two alternative base-case analyses. The first assumes pembrolizumab plus chemotherapy is clinically equivalent to D&T on the basis of the BRF113928 trial. The second is an unanchored comparison using data from the KEYNOTE-189 trial to directly model overall survival (OS) and progression free survival (PFS) outcomes for the pembrolizumab plus chemotherapy arm. For further details of the exploratory and sensitivity analyses done by the EAG, refer to Section 6. Please note that the impact of a number of scenarios differs according to efficacy assumptions adopted, and the inclusion of other commercial arrangements not accounted for in the main external assessment report. For cost-effectiveness estimates considering all available commercial pricing arrangements, please refer to the confidential appendix to this report.

The results of the EAG's alternative base-case analyses are presented in Table 2 and Table 3, with probabilistic results for these analyses presented in Table 4.

Table 2 Summary of EAG preferred assumptions (Clinical Equivalence)

Preferred assumption	Issue	Inc. cost	Inc. QALYs	Cumulative	
				ICER	NHB (30k)
Company base-case		[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Discounting applied continuously from model outset	*EAG Preference*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: All patients incur terminal care costs in line with TA705	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Cost of pharmacist dispensing time for oral therapies included	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Health state utilities based on TA812	*Issue 9*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: No disutility associated with IV infusion	*Issue 8*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Wastage of D&T accounted for (50% RDI discount method)	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Summary of EAG preferred assumptions (Pembrolizumab uses KEYNOTE-189)

Preferred assumption	Issue	Inc. cost	Inc. QALYs	Cumulative	
				ICER	NHB (30k)
Company base-case		[redacted]	[redacted]	[redacted]	[redacted]

Scenario 1: KEYNOTE-189 used to model pembro PFS/OS/ToT	*Issue 5*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Discounting applied continuously from model outset		[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: All patients incur terminal care costs in line with TA705	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Cost of pharmacist dispensing time for oral therapies included	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Health state utilities based on TA812	*Issue 9*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 8: No disutility associated with IV infusion	*Issue 8*	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Wastage of D&T accounted for (50% RDI discount method)	*Issue 7*	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 EAG's alternative base-case analysis results (probabilistic)

Technology	Total		Incremental			NHB (£20k) (95% CI)
	Costs	QALYs	Costs	QALYs	ICER	
EAG Scenario 1 (clinical equivalence)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
D&T	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
EAG Scenario 2 (pemb+chemo uses KEYNOTE-189)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
D&T	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the EAG has reviewed the clinical and cost-effectiveness evidence submitted by Novartis in support of dabrafenib and trametinib as a treatment combination for patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

Dabrafenib works as a blocker of BRAF and trametinib is a blocker of MEK (mitogen-activated protein kinase kinase). Different types of BRAF V600 mutations exist, the most common being BRAF V600E. BRAF V600 mutations are seen in approximately 1–3% of all cases of NSCLC. The company submission (CS) stated that there are approximately 66 to 100 patients diagnosed with advanced NSCLC with a BRAF V600 mutation in England each year, with patients being routinely tested for the mutation in England in Genomic Laboratory Hubs. The EAG's adviser noted that although in practice this type of testing is common, it is not yet available everywhere.

Prognostic value of BRAF mutations

In their submission, the company stated that some studies found that disease free survival and overall survival (OS) are less favourable for NSCLC patients with a V600E BRAF mutation, when compared to patients with wild type genes.[3, 4] The EAG scanned the literature on the prognostic value of the BRAF V600E mutation, both when compared to wild type and when compared to non-V600E BRAF mutations. Five further studies were identified (in addition to the aforementioned CS-cited studies).[5-9] Across these studies the results for PFS and OS were inconsistent, for both types of population comparison (i.e., BRAF V600E vs BRAF non-V600E and BRAF V600E vs wild type). Furthermore, the number of BRAF mutation patients included in these studies was small (the maximum was 37), making it difficult to draw any robust conclusions about the prognostic value of BRAF mutations.

The European Medicines Agency (EMA) also commented on this uncertainty in its 2017 assessment report on dabrafenib and trametinib, citing similar variation in results across studies.[10] The report also identified a large French study (which used the Intergroupe Francophone de Cancerologie Thoracique database) which found that patients with BRAF V600E mutations (n=189) were associated with slightly longer survival rates when compared with BRAF wild type patients.

In terms of the possibility of BRAF status having an impact on responses to currently used comparator therapies, the EAG's clinical adviser thought it was plausible that, in NSCLC patients taking immune checkpoint inhibitors (ICIs), those with a BRAF mutation may have worse outcomes than BRAF wild type patients. Further to this, the EAG notes the existence of some evidence that, in patients taking ICIs, OS may be significantly worse in patients with BRAF V600E mutations when compared with patients with BRAF non-V600E mutations (median OS: 5 months versus 14 months).[11] However, this evidence is also limited by sample size (22 patients had taken an ICI), again making it difficult to draw any firm conclusions on the issue.

2.2 Background

Dabrafenib and trametinib are currently available for treating advanced NSCLC with a BRAF V600 mutation via an interim Covid-19 response programme to reduce the burden on the NHS (i.e. patients receiving intravenous treatment in hospital). The company stated that dabrafenib and trametinib will primarily represent a treatment option for patients with previously untreated advanced NSCLC with a BRAF V600 mutation i.e. as a new first-line treatment. The EAG and their clinical adviser agree that if dabrafenib and trametinib were to be recommended for use in the NHS this would in effect be adding an extra line of therapy, either at first-line (for most patients), or at second-line (for those patients who did not get their genomic biomarker results before first-line treatment was commenced).

2.3 Critique of company's definition of decision problem

The EAG critique presented below does not reproduce the decision problem table (CS, pages 12-17), given that it covers 6 pages (due to the large number of comparator therapies), but we provide comments on each element of that table in the text below.

Population

The population in the CS matched the scope: adult patients with advanced NSCLC with a BRAF V600 mutation. At the clarification stage the company explained that the focus specifically on the V600E mutation (in pivotal trial BRF113928) was because around 90% of all V600 mutations are type E; also, when patients were recruited to the study, the diagnostic test available was specific to only the V600E mutation. Economic analyses for patients with previously treated advanced NSCLC and a BRAF V600 mutation were not presented, based on the limited data available and the expectation that this subgroup is expected to diminish over time.

Given the lack of RCT evidence in the CS – which is understandable, given that V600 mutations are uncommon in NSCLC – the EAG considered whether the population receiving comparator treatments could be broadened to include those without a BRAF mutation, such as the KEYNOTE-189 pembrolizumab trial.[12] In light of the uncertainty about the prognostic significance of V600E mutations on OS (see section 2.1), such an approach should be considered as being exploratory. Nevertheless, it would be worthwhile, considering that the CS reports (on page 66) that "*UK clinical experts noted that predicted PFS and OS for pembrolizumab plus chemotherapy from extrapolations of the FLATIRON [real-world evidence] RWE study (2022) weighted data were overestimated and clinically implausible compared to the published KEYNOTE-189 trial data*".

Intervention

The CS pointed out that since both dabrafenib and trametinib are oral therapies, this will present patients with a more convenient, less painful, and less burdensome method of administration compared to pembrolizumab plus chemotherapy, which is administered in hospital, intravenously. Dabrafenib is taken twice-daily and trametinib once-daily. While acknowledging these advantages, the EAG also notes that patients may sometimes forget to take oral therapies. The EAG therefore considers it is worthwhile evaluating the dabrafenib and trametinib trial data on non-compliance (see Section 3.2.1.4), as this was not mentioned in the CS.

The CS also stated that the availability of an oral treatment option has a positive impact on alleviating capacity issues within the NHS.

Comparators

Although the NICE scope listed numerous relevant comparators, subdivided by population groupings such as PD-L1 expression, histology, and line of treatment (previously untreated/treated), the company restricted the comparator treatments to just one: pembrolizumab plus chemotherapy in previously untreated patients (specifically pembrolizumab, pemetrexed and carboplatin/cisplatin). The EAG's clinical adviser reviewed the comparator treatments listed in the decision problem table (CS, Table 2) and stated that all are relevant NHS treatments, although they would be likely to vary in extent of use from centre to centre across the NHS. The EAG's adviser noted that a small proportion of the patients with PD-L1 expression >50% would receive immunotherapy alone (rather than with chemotherapy) and that atezolizumab is generally thought of as being equivalent to pembrolizumab, with decisions made on which particular therapy is used being based on frequency of administration issues and/or treatment preferences/experiences across NHS centres.

Nevertheless, these comparator omissions are unlikely to have had a significant impact on the evaluation of the clinical effectiveness of dabrafenib and trametinib, given that the evidence-base was very limited and sparse to the extent that it was difficult to make meaningful interpretations of the comparative results using the main comparator (pembrolizumab plus chemotherapy). This is likely to have been the case regardless of which comparator dataset was analysed. Consequently, the company assumed that dabrafenib and trametinib were clinically equivalent to pembrolizumab plus chemotherapy in terms of PFS and OS (see CS, page 67).

Despite the assumption of equivalent efficacy, the omission of other relevant first- and second-line comparator therapies will nevertheless have cost implications in the economic evaluation.

Outcomes

The outcomes reported in the clinical effectiveness evidence section (B2) of the CS matched those listed in the scope, apart from an absence of data on health-related quality of life. The EAG notes that a limitation of the pivotal study (BRF113928) was that health-related quality of life was not recorded as an outcome. The choice of health state utility values has no impact on incremental QALYs accrued in the company's base-case because of the assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab plus chemotherapy. However, the choice of utility values may be important in modelling scenarios that do not assume efficacy equivalence.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify all relevant evidence regarding the clinical efficacy and safety of treatments for patients with advanced NSCLC with a

BRAF V600 mutation. The SLR was first conducted in December 2019 and updated in May 2021. An additional targeted literature review update was conducted in April 2022. Details of the review are reported in Appendix D of the CS.

Searches

The original company submission included searches to identify clinical evidence for patients with advanced NSCLC with a BRAF V600 mutation. A description of the searches and the search strategies were included in Appendix D (pages 10-32). In response to the EAG's clarification questions, a further document was provided by the company, which included corrections to errors identified by the EAG. Please note that the EAG cannot appraise strategies on Embase.com as we do not have access. The EAG appraisal of the literature searching can be found in Table 5.

Inclusion criteria

The eligibility criteria used to select studies for inclusion in the SLR of treatment effectiveness were presented in Table 1 of Appendix D of the CS. The criteria used reflected those listed in the appraisal scope, although the company broadened the population criterion – based on the rarity of BRAF V600 mutations – to include patients with advanced NSCLC and an overall BRAF mutation (i.e. not specifically a V600 mutation). The EAG thinks this was a reasonable approach to take.

For the original and updated reviews titles and abstracts, and full-texts, were independently screened by two reviewers, with any disagreements resolved via a third reviewer. This will have minimised the possibility of errors or bias affecting the process. For the targeted update, a single reviewer assessed the titles and abstracts of all records and a second senior reviewer checked all included records and 10% of excluded records. Although the EAG sees this as a pragmatic approach (presumably due to time constraints) it is nevertheless possible that in using these methods some relevant studies may have been missed in the 2022 update.

Critique of data extraction

The data extraction process was performed by one reviewer and checked for errors by a second reviewer. Any inconsistencies were resolved via discussion. This will have minimised the possibility of errors or bias affecting the data extraction process.

Table 5 EAG appraisal of evidence identification

TOPIC	ERG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	**Ambiguities or Errors in Reporting:** In the original company submission, documentation of the database and platform used for each of the searches was unclear. This was raised as a clarification question so that the searches could be scrutinised within the context of the database and platform they were designed for. In response, the company provided a helpful table listing both the database and platform for each of the searches by table number. A similar question on the sources used for conference abstracts was also raised by the EAG. Although the company response made it clearer which tables corresponded to which database, no platform was listed for the Northern Light Life Sciences database. In the original company submission, it was also unclear which exact databases were searched, since Table 4 (Appendix D, page 16) listed that it contained search terms for Cochrane CENTRAL, Cochrane CDSR, and DARE. DARE was not referred to in the Data Sources section (Appendix D, page 12) or the PRISMA diagram (Appendix D, page 30). The company clarified that DARE was searched although argued that it shouldn't be explicitly listed since it comes under 'Cochrane'. The EAG disagrees with this – these individual databases should be listed for clarity. These databases can be searched on various platforms. Moreover, even by platform, what is included in database subscriptions can vary. For this reason, the Data Sources section (listed in Appendix D, pages 12-13) noting that the Cochrane Library is searched is also misleading. Moreover, Table 9 (listed Appendix D, page 22) is a search of Cochrane CENTRAL as it is limited to Trials, so it is misleading to for the table name to list 'Cochrane Library' where only one database was searched. In the original company submission, the number of duplicates found (prior to screening) was incorrect in the PRISMA diagram (Appendix D, p 30). This was corrected in the company response to clarification questions. It is unclear why the update searches (Appendix D, pages 17-23) didn't use the same terms as the original systematic literature review searches (Appendix D, pages 13-17).
Were appropriate sources searched?	PARTLY	A limited selection of relevant databases, conference proceedings and grey literature was searched. The EAG raised that no health technology assessment (HTA) sources or databases were searched. The company responded that relevant clinical data from HTA sources would have been obtained by database searches. However, assessments from HTA agencies tend to be published as reports rather than journal articles, so HTA databases are valuable sources of this grey literature, records of ongoing studies, and projects by HTA agencies. The EAG raised that no trials registry databases were searched outside of Cochrane CENTRAL. The company responded that although this would have yielded additional results, none of this data would have informed the economic model and that studies would have published their results beyond a trials registry. This is evidence of publication bias. Clinical trials records can still be valuable sources of data prior to the publication stage and are usually searched in single technology appraisals.

		However, in the context of this topic, the EAG agrees that it is unlikely that relevant useful studies would have been missed by excluding HTA databases or clinical trials registries as sources of evidence.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy. However, the update searches were restricted by year of publication from 2019-2021 for the update searches and 2021-current for the targeted literature review searches. This would have excluded new records added to the databases with a publication year before those date ranges. However, this is likely to have a minimal impact on the results.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study type.
Were appropriate search terms used?	PARTLY	However, in the original SLR (Appendix D, pages 13-17), there is no truncation applied to pick up plural variants of lung adenocarcinomas or lung squamous cell carcinomas. This could have missed relevant papers. The search terms used for conference abstracts on OncologyPro (Appendix D, Table 6, page 17) are all just acronyms which is rather limited. This could have missed relevant papers.
Were any search restrictions applied appropriate?	PARTLY	The original SLR limits its searches to English language. Although it is reasonable to limit to English language during the screening process, applying this limit in the search strategy risks losing any relevant material without metadata for English language. In the original SLR, the limit to human subjects in Table 2 (Appendix D, page 14) is incorrect. The limit uses Emtree headings for the Embase database. The correct Medical Subject Heading (MeSH) terms are Animals/, Human Experimentation/, and Humans/. There is no MeSH heading for nonhuman/ this is an Emtree term. However, this error will not affect the results.
Were any search filters used validated and referenced?	PARTLY	Search filters were not validated. In the original SLR, filters are clearly referenced where used. However, not all filters provided a reference – no filters are referenced for the subsequent update searches and targeted literature review searches.

Quality assessment

Risk of bias assessments were conducted using the ROBINS-I tool for non-randomised studies. No details were reported regarding how many reviewers were involved in this process. The results are critiqued in Section 3.2.2.1. No formal assessment was made of the applicability of the included studies to the NHS setting.

Evidence synthesis

Although evidence synthesis was not commented on in the CS, the EAG notes that the lack of an evidence synthesis is due to the rarity of NSCLC patients with BRAF V600 mutations and hence a paucity of studies which report results for patients with advanced NSCLC and a BRAF V600 mutation. This meant there was an absence of randomised trials and the few available non-randomised studies were heterogeneous, precluding evidence synthesis.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company's submission focussed on one single-arm study of dabrafenib and trametinib: the phase II BRF113928 study (NCT01336634) and two non-randomised comparative studies ('Flatiron'[13] and Melosky et al 2021[14]) which both compared dabrafenib and trametinib with pembrolizumab plus chemotherapy.

3.2.1 Study BRF113928

Study BRF113928 was a multicentre, open-label, single-arm trial that enrolled participants with advanced NSCLC with a BRAF V600E mutation: 36 previously untreated ('Cohort C') and 57 previously treated ('Cohort B'). The CS stated that the BRF113928 trial was recently completed, with the last patient visit in 2021; clinical effectiveness results were presented using the most recent and complete data cut (24th February 2021), which includes a minimum of five years' follow-up data for each patient.

Participants received the combination of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily. The study was conducted in 71 study sites in 11 countries. The primary outcome was overall response rate (ORR): the percentage of patients with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST v1.1 criteria. The submission focussed on results relating to Cohort C as this was the population deemed most likely to receive dabrafenib and trametinib (see Section 2).

3.2.1.1 Risk of bias

A quality assessment of study BRF113928 was reported in Appendix M.1.2. However, this was done using the ROBINS-I tool, which was designed to evaluate the risk of bias in the results of studies

which compare two or more interventions. The results are therefore limited, given that BRF113928 is a single-arm study. More meaningful risk of bias evaluations were reported for the non-randomised comparative studies identified in the company's SLR (see Section 3.2.1.1).

3.2.1.2 Applicability of Study BRF113928 trial results to the NHS setting

In study BRF113928, five of the 71 sites were based in the UK.

Population

Baseline characteristics were presented in Table 8 of the CS (Cohort C) and Table 97 of the CS appendices (Cohort B). For Cohort C (n=36) the mean age was [redacted] years, 61% were female, 83% were white and 58% were former smokers (the median number of years smoked was [redacted]).

Although participants with an ECOG PS score of 0-2 were eligible for inclusion, 97% of the recruited Cohort C patients had ECOG PS scores of 0 or 1, so there is very little data on efficacy in patients with an ECOG PS score of 2. The EAG's adviser stated that she would consider treating patients with ECOG PS of 2. Given the likely importance of the impact of ECOG PS score on PFS and OS, this raises questions about how less cost-effective dabrafenib and trametinib might be in this subgroup of patients.

Since only patients with V600E mutations were included in the study, the EAG asked the company why patients with other BRAF V600 mutations were not included (clarification question A1). The company clarified that at the time of the study only a companion diagnostic test specific for the BRAF V600E mutation was available, so other 'Class I' mutants could not be identified.

The EAG requested that the company provide more details in their CONSORT flow diagram of study BRF113928 (Figure 3, Document B), such as the number of patients screened for eligibility and the numbers ineligible/excluded, by reason (especially those excluded for having RAS-mutations or a history or evidence of cardiovascular risk). The company's response was vague, stating that such data "*is either not available or collected for BRF113928"*. Notwithstanding this lack of data, the EAG's adviser thought that the co-occurrence of a RAS mutation would be rare. The lack of data on exclusions for cardiovascular risk means there is some uncertainty about the applicability of study BRF113928's results to the population seen in the NHS. However, the EAG's adviser estimated that no more than 5% of patients would have a history or evidence of cardiovascular risk (as defined in BRF113928).

Subsequent therapies

At the clarification stage, the EAG asked the company to provide summary data (by cohort) on all the subsequent treatments received by patients in study BRF113928 after they stopped taking dabrafenib and trametinib (Table 6). The company added that many of the trial patients were recruited prior to

the widespread use of immunotherapies in NSCLC and would not have had access to such treatments; the number of patients receiving immunotherapy as a first subsequent treatment in BRF113928 may therefore be an underestimate of what happens in current practice.

Table 6 Summary of post-therapy anti-cancer therapies by cohort in study BRF113928

	1st line, Cohort C (N=36)	2nd line plus, Cohort B (N=57)
Any anti-cancer therapy?		
Yes	[redacted]	[redacted]
No		
Type of anti-cancer therapy		
Chemotherapy	[redacted]	[redacted]
Carboplatin		
Cisplatin		
Combinations of Antineoplastics Agents		
Docetaxel		
Epirubicin		
Gemcitabine		
Gemcitabine hydrocholoride		
Investigational Antineoplastic Drugs		
Nintedanib		
Paclitaxel		
Pemetrexed		
Pemetrexed Disodium		
Vinorelbine		
Vinorelbine tartrate		
Immunotherapy		
Lambrolizumab		
Nivolumab		
Atezolizumab		
Biologic Therapy		
Bevacizumab		
Rituximab		
Small Molecule Targeted Therapy		
Cobimetinib Fumarate		
Dabrafenib		
Eloritinib		
Erlotinib hydrochloride		
Trametinib		
Surgery		
Radiotherapy		

3.2.1.3 Protocol deviations

The CSR (page 135) indicated that [redacted] of participants experienced a protocol deviation. Of particular note, [redacted] of the included participants who took dabrafenib and trametinib had not met the eligibility criteria; a link to protocol deviations in the CSR appendices did not work, so no further data were available on the breakdown of reasons for ineligibility for patients included in study BRF113928, except that [redacted]. Also, [redacted] of

participants on combination therapy received either the wrong treatment ("study treatment administration or dispensing error") or the incorrect dose (study treatment non-compliance by subject) to the extent that they were classed as protocol deviations.

3.2.1.4 Summary of dose deviations in BRF113928

According to the CSR for study BRF113928, [redacted] deviated from the study protocol due to [redacted] Non-compliance was recorded for [redacted].

Level of compliance was not reported as an outcome but was reported as an explanation for outcomes relating to dose deviations (dose reductions, interruptions, and escalations). The CSR states that "compliance with study treatment dosing was assessed through pill counts and querying the subject during the site visits." No definitions are provided for 'dose reductions', 'dose interruptions', or 'dose escalations'.

The planned daily dose per participant was 300 mg for dabrafenib (150 mg twice daily [BID]) and 2 mg for trametinib. The actual daily dose per participant is shown in Table 7, based on CSR tables 3.0060 and 3.0061. On average patients took [redacted] of the daily combined therapy dabrafenib dose (Table 3.0060, CSR) due to a combination of adverse events and non-compliance.

Table 7 Actual daily dose received per participant in study BRF113928

	Monotherapy (N=84) Dabrafenib 150 mg BID = 300 mg	Combination therapy (N=93) Dabrafenib 150 mg BID = 300 mg Trametinib 2 mg QD	
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Table 8 provides an overview of dose deviations (reductions and interruptions) which were primarily due to non-compliance or adverse events. Deviations from the intended dose were [redacted].

Table 8 Dose deviations in study BRF113928

Outcome	Dabrafenib monotherapy 150 mg BID (N=84)		Dabrafenib 150 mg BID and trametinib 2 mg QD (N=93)	
	Events	Number of participants (proportion of total sample)	Events	Number of participants (proportion of total sample)
Dabrafenib dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Trametinib dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Trametinib dose interruption	[redacted]	[redacted]	[redacted]	[redacted]

Data from CSR tables 3.0160, 3.0260, 3.0161 & 3.0261

[redacted] **Table 9**

Number of dose reductions and interruptions (% of total sample)

Number of dose reductions	Dabrafenib monotherapy (N=84)		Dabrafenib combination therapy (N=93)		Trametinib combination therapy (N=93)	
	Dose reduction	Dose interruption	Dose reduction	Dose interruption	Dose reduction	Dose interruption
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 or more	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data from CRS tables 3.0160, 3.0161, 3.0260 &3.0261.

In conclusion, dose reductions and interruptions relating to non-compliance or adverse events were [redacted] It is possible that non-compliance leading to important deviations from the planned dose could have influenced the efficacy of the treatment for a subset of the study sample.

These data may underestimate non-compliance in clinical practice, because trial participants are often monitored and followed up more closely. Compared to patients receiving the same medications in practice, trial participants may be more likely to receive encouragement and reminders to adhere to the treatment protocol. Adverse events may also be resolved more quickly.

The company was not able to provide information requested by the EAG on non-compliance with dabrafenib and trametinib in trials of patients with melanoma.

3.2.1.5 Results of BRF113928

Efficacy

In Cohort C, 23 patients (64%) had a confirmed response (95% confidence interval [CI]: 46.2 to 79.2) with the result being based largely on the 21 patients who had a partial response. [redacted] of the patients with a confirmed response subsequently experienced disease progression or death; the median duration of response was 10.2 months (95% CI: 8.3, 15.2). Median PFS in Cohort C was 10.8 months (95% CI: 7.0 to 14.5) and median OS was 17.3 months (95% CI: 12.3 to 40.2). Further PFS and OS results for Cohorts B and C are summarised in Table 10.

Table 10 Summary of PFS and OS results in study BRF113928 by cohort

Endpoint	PFS		OS	
	Cohort C (N=36)	**Cohort B* (N=57)**	**Cohort C (N=36)**	**Cohort B* (N=57)**
Patient status, n (%)				
Progressed or died (event)	[redacted]	[redacted]	[redacted]	[redacted]
Died	[redacted]	[redacted]	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	10.8 (7.0 to 14.5)	10.2 (6.9 to 16.7)	17.3 (12.3, 40.2)	18.2 (14.3, 28.6)
Distribution function (95% CI), %				
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]

*Previously treated population

No subgroup analyses were undertaken in BRF113928 and patient-reported outcomes to measure the symptoms and quality of life of patients were not collected.

Safety

Data on adverse events (AE) (CS, section B2.10) were presented based on study BRF113928 cohorts B and C (total n=93). Safety data were not collected in the Flatiron comparative study. The most frequently observed AE was pyrexia (56%), which led to a dose reduction in [redacted] patients ([redacted]) and treatment withdrawal in [redacted] patients ([redacted]). The CS stated that there is a new management protocol (developed after the BRF113928 trial and now in the SmPCs) which allows both dabrafenib and trametinib to be interrupted if a patient's temperature is ≥38.0°C. In case of recurrence, treatment can also be interrupted at the first symptom of pyrexia; both treatments can be restarted at the same dose level if patients are symptom free for ≥24 hours. The CS added that this new algorithm appears to reduce the incidence of severe pyrexia outcomes, enabling patients to manage pyrexia at home.

In BRF113928, [redacted] of patients had a serious AE (SAE) judged to be related to the study treatment, [redacted] had an AE leading to permanent discontinuation of study treatment, [redacted] experienced a grade 3/4 AE that led to treatment discontinuation, and [redacted] had an AE leading to a dose reduction. The most frequently occurring AEs leading to dose reduction were pyrexia which occurred in [redacted].

The SmPCs for dabrafenib and trametinib list malignancies, haemorrhagic events and left ventricular dysfunction as possible adverse events. The EAG therefore asked the company to summarise the trial data on these events across all indications. However, very limited new data were provided for dabrafenib and trametinib as a combined treatment and the company indicated that malignancies and haemorrhagic events were not reported in a long-term follow up study of patients with melanoma (n=559).[15] The EAG notes that in the clinicaltrials.gov record for BRF113928 the rates of basal cell carcinoma (4.8%) and squamous cell carcinoma (8.3%) were quite high in the dabrafenib monotherapy arm (Cohort A, 11 events in total) but not in cohorts B and C (one event). The EMA commented that combination therapy reduces the incidence of newly detected squamous cancer of the skin.[16]

Other studies of dabrafenib and trametinib

Table 4 of the CS presented the other studies identified in the SLR of treatments for patients with advanced NSCLC with a BRAF V600 mutation. All the single-group studies of dabrafenib and trametinib had very small sample sizes (n<10), so the company did not present any further results for these studies. The largest of these (n=9 being treated at first-line) - a retrospective French study - reported a median PFS of 16.8 months (95% CI 6.1–23.2) and a median OS of 21.8 months (95% CI 1.0–not reached).[17]

Two comparative studies were also identified.[14, 18] These, together with the company's unpublished Flatiron study, are discussed in Section 3.2.2.

3.2.2 Comparator treatment studies

The company used the FLATIRON Health database[19] as the basis for forming a dataset of patients who received relevant comparator treatments. Section B.2.9.1 of the CS details that the FLATIRON Health database[19] includes a population of patients observed through electronic health records from the FLATIRON Health Network comprising over 280 community oncology practices and academic medical centres in the US. Data has been taken from this database as dabrafenib and trametinib has been available in the United States since 2017 and therefore BRAF testing has been available as part of routine care whereas routing testing for BRAF mutations in advanced NSCLC patients in the UK has only recently been established. The FLATIRON database[19] has previously been used for NICE

appraisals in NSCLC.[20, 21] It is not clear if other more suitable databases were available but not searched for, as recommended in the NICE RWE framework.[22]

Individual patient data were available from the FLATIRON database[19] which were used for comparative analyses with the BRF113928 dataset.[23] The EAG concurs with the CS statement that the availability of patient-level data to account for differences between patient characteristics and key prognostic factors is considered to be more rigorous and allows a more appropriate comparison.

The outcomes reported in the FLATIRON database[19] which were available for comparison with BRF113928[23] were PFS and OS.

Comparability of BRF113928 and FLATIRON cohorts

Three non-randomised studies were identified that provide evidence for dabrafenib plus trametinib versus pembrolizumab plus chemotherapy in previously untreated advanced NSCLC patients with a BRAF V600 mutation and are outlined in Table 11. The FLATIRON study[13] is an update of Kanakamedala et al. 2020[18] which considers BRAF V600E mutations and compares dabrafenib plus trametinib from the single arm trial BRF113928 to real world evidence of pembrolizumab plus chemotherapy from the FLATIRON database.[19]. Melosky et al. 2021[14] consider V600 mutations and compare real world evidence from the FLATIRON database[19] for both dabrafenib plus trametinib and pembrolizumab plus chemotherapy.

The baseline characteristics for the FLATIRON study[13] are shown in Table 14, Section B.2.9.3.2 of the CS. After data from the FLATIRON database[19] had been weighted, the baseline characteristics for pembrolizumab plus chemotherapy compared to dabrafenib plus trametinib were similar except for sex which had a lower percentage of females in the real world evidence cohort ([redacted] compared to [redacted]). This was similar to Kanakamedala et al. 2020[18] which had a lower percentage of females in the real world evidence cohort too (45% compared to 61%).

The baseline characteristics for Melosky et al. 2021[14] study were provided in Appendix D.3.1.2 of the CS and the weighted baseline characteristics were provided in the Company's response to clarification (A6, Table 2). After the data had been weighted, the baseline characteristics for pembrolizumab plus chemotherapy compared to dabrafenib plus trametinib were similar except for initial stage of diagnosis, where more patients where at Stage IV in the pembrolizumab plus chemotherapy arm ([redacted]) compared to the dabrafenib plus trametinib arm ([redacted]). There were no patients at Stage II-III in the pembrolizumab plus chemotherapy arm compared to [redacted] and [redacted] respectively in the dabrafenib plus trametinib arm. Few patients were at stage I in both arms ([redacted] dabrafenib plus trametinib arm compared to [redacted] pembrolizumab plus chemotherapy arm).

Table 11 Comparator treatment studies

Study	Data sources	BRAF Mutations	Unweighted sample size (weighted sample size)
Kanakamedala et al. 2020[18]	Dabrafenib and trametinib: BRF113928 Pembrolizumab plus chemotherapy: Flatiron database	V600E V600	36 34 (28)
Melosky et al. 2021[14]	Dabrafenib and trametinib: Flatiron database Pembrolizumab plus chemotherapy: Flatiron database	V600 V600	48 (47.2) 31 (27.7)
FLATIRON study[13] (unpublished)*	Dabrafenib and trametinib: BRF113928 Pembrolizumab plus chemotherapy: Flatiron database	V600E V600E Any BRAF mutation	[redacted] [redacted] [redacted]
Keynote (RCT) [12]	Pembrolizumab plus chemotherapy Platinum based chemotherapy	No BRAF mutation No BRAF mutation	410 206

*FLATIRON study[13] is an update of Kanakamedala et al. 2020[18]

3.2.2.1 Assessment of risk of bias

The studies were at an overall moderate risk of bias according to Table 3 in the Company's response to clarification (A7) although in the original submission Melosky et al 2021[14] was at an overall serious risk of bias. The company's response to the EAG clarification (Q A7) asking for text to justify the domain judgements for the three non-randomised studies, indicated that the risk of bias assessments in response to the clarification question differed from those reported in the submission as they used the full study reports which have more information.

The assessments have been undertaken by study rather than by outcome as the tool (ROBINS-I) was intended. It is concerning that the majority of the text for judgements are identical. The EAG do not agree with the risk of bias assessment for PFS, for the domain 'bias in measurement of the outcome' for the FLATIRON study[13] or Kanakamedala et al. 2020.[18] The EAG have assessed these two studies at serious risk of bias rather than 'low' as proposed by the company. This is due to methods of PFS assessment not being comparable across the intervention groups. In the BRF113928[24] single arm trial, PFS was measured prospectively at fixed timepoints based on RECIST v1.1 criteria, in an unblinded trial setting where the assessment might be influenced by knowledge of the intervention (dabrafenib plus trametinib) versus retrospective in a RWE study where the assessment is less likely to be influenced by the intervention. Melosky et al. 2021[14] avoids this issue as the FLATIRON database[19] is used for both treatment arms. In addition, 27% of patients in pembrolizumab plus chemotherapy cohort in the FLATIRON[13] study were only followed up for 12 months or less due to treatment initiation in 2021 also indicating a difference in measurement of the outcome between arms. In terms of PFS, Melosky et al.[14] has better validity than the FLATIRON study[13] due to the consistency in the

measurement of the outcome. Therefore, the EAG assessment is that the FLATIRON study[13] is at serious risk of overall bias for both PFS and OS.

3.2.2.2 Description and critique of the company's approach to creating and analysing a comparative clinical effectiveness dataset

Propensity scores were used to account for differences in prognostic variables between the two datasets at baseline, in both the FLATIRON study[13] and the Melosky et al 2021 study.[14] This approach is recommended by the NICE Decision Support Unit guidance (Technical Support Document [TSD] 17) to minimise the risk of bias when making inferences on treatment effect using observational data. This approach utilises the entire study population and adjusts for multiple confounders simultaneously. Stabilised inverse probability of treatment weighting (IPTW) was used to account for differences between the trial and real-world cohort and was estimated using logistic regression that modelled treatment assignment as a function of the baseline characteristics: age, gender, race, stage at initial diagnosis, smoking status, ECOG status and histology in Melosky et al. 2021[14] (Appendix D.3.1.3) and age, gender, ECOG status, smoking status and race in the FLATIRON study[13] (Appendix D.3.3.2.4).

Balancing of covariates appears to have been checked after propensity score methods using standardised mean differences for all three studies, and weighted distribution plots were provided in the clarification response for Melosky et al. 2021[14] showing increased overlap between the two treatment groups. It is unclear if the propensity score function was sufficiently flexible as no interactions or different functions were mentioned.

Results are presented in Section B.2.9.2 to B.2.9.3 of the CS and Table 12 below. In the FLATIRON study[13] there were more progression events in the dabrafenib and trametinib cohort compared to the pembrolizumab plus chemotherapy cohort which reflects that the follow up in the FLATIRON database[19] was much shorter at [redacted]months compared to [redacted]months for dabrafenib and trametinib in BRF113928[23]. In the weighted analysis, although the hazard ratio (HR) favoured pembrolizumab plus chemotherapy the CI for the HR for PFS contained one and was wide indicating no significant difference between the groups after weighting (HR [redacted] (95% CI[redacted]), Table 15 of the CS). In addition, [redacted] of patients in pembrolizumab plus chemotherapy cohort were only followed up for 12 months or less due to treatment initiation in 2021. The issue of follow up applies to OS as well and again the HR in the weighted analysis has wide CIs including one (HR [redacted] (95% CI: [redacted]), Table 16 of the CS).

The Melosky et al 2021[14] study provided longer follow up data for the pembrolizumab plus chemotherapy arm, according to the CS, compared to the FLATIRON study,[13] although the length of follow up was not stated. No significant differences were detected with respect to OS (weighted HR

0.83 (95% CI: 0.32, 2.15)) or PFS (weighted HR 1.35 (95% CI: 0.63, 2.92)) between the two treatments (Section B.2.9.2).

The assessment of the assumption of proportional hazards for the FLATIRON study[13] were presented in Appendix N.1 of the CS and in response to the EAG clarification letter (B2) by testing the significance of time dependent covariates, Kolmogorov-type supremum proportional test and log cumulative hazards plot. Although none of the p-values were statistically significant, the log cumulative hazards plot for OS cross and are not proportional and therefore the assumption of proportional hazards may be violated for OS. This is also suggested in Table 102 of the CS Appendix. However, the interpretation is difficult due to the small sample size and different follow up.

Table 12 Summary of Results

Study	**Median Overall survival and HR (95% CI)**		**Median Progression free survival and HR (95% CI)**	
	Dabrafenib and trametinib	**Pembrolizumab plus chemotherapy**	**Dabrafenib and trametinib**	**Pembrolizumab plus chemotherapy**
Kanakamedala et al. 2020[18]	17.3 (14.6, NR)	18.0 (5.1, NR)	10.2 (7.0, 14.5)	11.3 (3.7, NR)
	HR 0.57 (0.28–1.17), p-value = 0.13		HR 0.96 (0.51, 1.81)[1], p-value =0.90	
Melosky et al. 2021[14]	29.3 (16.4, NR)	17.7 (10.5, NR)	9.6 (6.5, 15.2)	10.5 (3.7, NR)
	HR 0.83 (0.32, 2.15), p-value = 0.71		HR 1.35 (0.63, 2.92), p-value = 0.44	
FLATIRON study V600E[13] (unpublished)*	17.3 (12.3, 40.2)	[redacted]	10.2 (5.5, 13.8)	[redacted]
	[redacted]		[redacted]	
FLATIRON study Any BRAF mutation[13] (unpublished)*	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
Keynote 189 trial[12]	Pembrolizumab plus chemotherapy	Placebo plus chemotherapy	Pembrolizumab plus chemotherapy	Placebo plus chemotherapy
	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
	HR 0.56 (0.46, 0.69)		HR 0.49 (0.41, 0.59)	

[1]Visual inspection of the Kaplan-Meier plot showed the curves cross. Interpret with caution. NR not reached. Medians in months with 95% CI

3.2.3 Keynote 189 trial

Due to the lack of evidence from randomised controlled trials and uncertainty in the treatment effect estimates from the non-randomised studies, the efficacy of dabrafenib and trametinib when compared to pembrolizumab plus chemotherapy remains unclear. Therefore, the company presented data for the randomized, double-blind, placebo-controlled KEYNOTE 189.[12] The median follow up was 31 months. The HR significantly favoured pembrolizumab plus pemetrexed platinum for both OS and PFS respectively (Table 12). In an exploratory analysis in the economic model, naïve use of the pembrolizumab plus pemetrexed platinum group was included. This is an unadjusted comparison with dabrafenib and trametinib using different (genomic) populations which compares a blinded assessment of PFS (pembrolizumab plus pemetrexed platinum[12]) with an unblinded assessment of dabrafenib and trametinib.[25]

ERG Summary of the company's analyses of comparative effectiveness

In all three studies (FLATIRON study[13], Melosky et al 2021[26], Kanakamedala et al 2020[18]) there was uncertainty in the estimates of OS and PFS when comparing dabrafenib and trametinib to pembrolizumab plus chemotherapy due to the wide confidence intervals encompassing one (i.e. no difference in effect) and the small sample sizes. Propensity scores (IPTW) were used to account for differences between the study arms and the EAG agrees this approach was appropriate although there may be residual confounding due to differences in baseline characteristics. The assumption of proportional hazards was likely violated for OS in the FLATIRON study.[13]

Section B.2.9.3.3 of the CS indicates that robust conclusions were not possible when comparing dabrafenib and trametinib versus pembrolizumab plus chemotherapy due to differences in follow up and small patient numbers for the FLATIRON study[13] and the EAG agrees with this statement. The EAG has also assessed both the FLATIRON study[13] and Kanakamedala et al. 2020[18] as being at serious risk of bias due to the inconsistency in how PFS was measured. Therefore, the EAG recommends that these results should be interpreted with caution.

3.3 Conclusions on clinical effectiveness and safety

The lack of randomised trial evidence on dabrafenib and trametinib means that important uncertainties arise from the clinical effectiveness evidence. The first key issue is the reliability of the equivalent efficacy assumption (used in the company's base case) i.e., how likely it is that the efficacy of dabrafenib and trametinib is equal to that of pembrolizumab plus chemotherapy (when compared head-to-head). This assumption was made using the opinions of UK clinicians' interpretation of the results from very small non-randomised studies, based largely on the similarity of results for observations up to around month 6 (PFS) - as results at this timepoint were judged not to be confounded by subsequent treatments - and month 10 (OS). The company's favoured comparative

study ('Flatiron') was judged by the EAG to have a serious risk of bias, especially for PFS; the EAG considers that none of the results from the other efficacy studies can be considered reliable due to risk of bias and small sample sizes.

The second issue is how to estimate what benefit is gained from having dabrafenib and trametinib as an additional line of therapy in the treatment pathway. Although some benefit would be expected, there is very little evidence to inform or quantify this.

In addition to these efficacy issues there are also concerns about the level of treatment adherence seen in some participants. Most participants taking dabrafenib and trametinib experienced at least one dose interruption or reduction relating to adverse events or non-compliance. Frequent dose interruptions (two or more) occurred more often for dabrafenib than trametinib. It is possible that non-compliance leading to important deviations from the planned dose could influence efficacy for a subset of patients.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company undertook three SLRs to identify relevant economic evaluations, literature relating to health-related quality of life, and on costs and healthcare resource use data for patients with advanced NSCLC with a BRAF mutation. These searches were conducted on 10th May 2021. The company also undertook a search of conference proceedings for the years 2020 and 2021 up to 10th May 2021. The company provided a detailed report of the methods and results of the SLRs in Appendix G, H, and I of the Company Submission.

4.1.1 Search strategy

The original company submission included searches to identify cost-effectiveness evidence, cost and healthcare resource use measurement and valuation, and health-related quality of life studies for adult patients with advanced NSCLC with a BRAF mutation in the first- or later-line (second-line or above) settings, or when outcomes are reported by line of therapy. A detailed description of the searches and most of the search strategies was included in CS Appendix G (pages 177 - 188).

The EAG requested that the company conduct additional searches in HTA sources or databases to investigate whether relevant studies were missed. The company stated in their response that they searched UK HTA websites. The EAG considered this sufficient. A number of errors identified by the EAG were also corrected in the company's clarification response.

4.1.2 Study eligibility criteria

Study eligibility criteria applied by the company were described in CS Appendix G for the review of economic evaluations (Table 77), CS Appendix H for the quality-of-life studies (Table 86) and CS Appendix I for the cost and healthcare resource studies (Table 88). There was no date or language limit applied. The population of interest in all cases was patients with advanced NSCLC with a BRAF mutation. Studies including other mutations such as ALK, EGFR, and ROS were excluded. While the inclusion criteria in terms of interventions was defined in the cost-effectiveness review, there were no specific inclusion criteria in terms of interventions and comparators received in the HRQoL and cost reviews. Two reviewers independently assessed studies based on title and abstract, with discrepancies resolved by a third reviewer. Full text screening for inclusion was again performed by two reviewers, with any discrepancies resolved by a third reviewer.

The EAG considered the eligibility criteria and the company's assessment of identified studies against them to be generally appropriate.

4.1.3 Identified studies (please identify the most important studies; where appropriate, provide a table of identified studies)

Based on titles and/or abstracts, the cost-effectiveness SLR identified 242 potentially relevant records, the health-related quality of life SLR identified 192 potentially relevant records, while the cost and healthcare resource use measurement and valuation SLR identified 396 potentially relevant records. However, among these, the company identified no relevant records relating to advanced NSCLC with a BRAF mutation. The company postulated that this could be due to the rarity and relative novelty of the BRAF mutation in NSCLC.

4.1.4 Interpretation of the review

The EAG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses, HRQoL, or costing studies conducted in a relevant population and setting. The EAG is therefore satisfied that the model presented by the company represents the most relevant analysis for decision making.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 13 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits for treated individuals were accounted for

Perspective on costs	NHS and PSS	An NHS and PSS perspective on costs was considered
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model adopted a 32-year (lifetime) time horizon. This duration adequately captured lifetime costs and benefits.
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review to identify relevant data sources.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were presented in QALYs using EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly from patients with NSCLC (wild type).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs based on UK sources including eMIT, BNF and NHS reference costs. Resource use based on previous appraisals and clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5% per annum.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

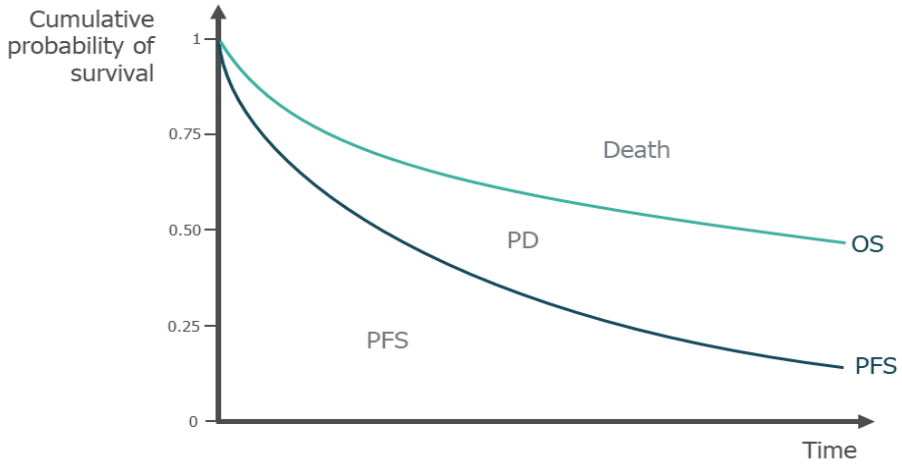
The company submitted a partitioned survival model (PSM) to estimate the lifetime cost-effectiveness of dabrafenib in combination with trametinib (D&T) in patients with previously untreated advanced NSCLC with a BRAF V600 mutation. The PSM comprised three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD), and death. Modelled patients were allocated to receive either D&T or pembrolizumab in combination with chemotherapy. The model uses a one-week cycle length, and applies a half-cycle correction.

The company justified the presented model structure on the basis of the maturity of data available on D&T from the BRF113928 trial, which provides at least 5 years of follow-up for each patient, during

which time [redacted] of patients had experienced an event (progression or death), with the remaining patients censored at the end of trial follow-up.

All patients enter the model in the PFS health state, with progression to either PD or death determined directly from survival curves derived from BRF113928 PFS and OS Kaplan-Meier (KM) data. These data were extrapolated beyond the trial period using parametric models (discussed in Section 4.2.6), with the resulting curves used to determine state occupancy. On entering the model patients can either transition to either the PD state, or move directly from the PFS health state to the death health. Upon transition to the PD health state patients can only transition to the death state. The proportion of patients in the PD state corresponds to the difference between the proportion of patients alive (given by the OS curve) and the proportion of patients in the PFS state (given by the PFS curve). This is depicted graphically in Figure 1.

Figure 1 Overview of company's economic model (Company Submission Figure 9, Page 62)



The BRF113928 trial was a single arm study, and therefore provided no comparator with which to anchor any indirect comparisons of effects. As discussed further in Section 4.2.6, extrapolation of data from the small number of patients in the FLATIRON RWE study who were positive for a BRAF V600 mutation, and treated with pembrolizumab plus chemotherapy, yielded clinically implausible long-term OS and PFS estimates compared to published data from the KEYNOTE-189 trial. The company therefore considered that the FLATIRON RWE an inappropriate source upon which to estimate relative efficacy and instead chose to assume equivalence in PFS and OS between D&T and pembrolizumab plus chemotherapy. Model outcomes for both D&T and pembrolizumab plus chemotherapy were therefore based on Cohort C of the BRF113928 trial.

4.2.2.1 Post-clarification exploration of treatment benefit

In recognition of the potential for a difference in treatment effects between D&T and pembrolizumab plus chemotherapy, particularly given the difference in availability of subsequent therapies between

the two treatment options, the EAG requested that the company explore the use of trial data to model pembrolizumab plus chemotherapy. In the company's clarification response, a number of alternative assumptions were explored, which allowed external sources of effectiveness data to be used in the model. These were designed to reflect the potential incremental benefits associated with D&T relative to pembrolizumab combination therapy. In response to clarification question B3, the company added a new structural element to the model, which allowed the application of a hazard ratio to OS for a variable proportion of pembrolizumab patients. The HR could not be selectively applied to a proportion of patients. Instead, a weighted average was calculated and applied to all patients, derived using the assumption that a HR of 1.0 applied to [redacted] of patients, and an incremental treatment benefit based on a selection of literature-derived HRs, applied to the remaining [redacted] A selection of hazard ratios for immunotherapies versus chemotherapy were sourced from trials in patients with previously treated NSCLC, and demonstrate improved efficacy on pembrolizumab (HR 0.70, 95% credible interval [CrI] 0.61 to 0.80), atezolizumab (HR 0.73, 0.62 to 0.87), and nivolumab (HR 0.61, 0.49 to 0.76) versus docetaxel alone.

The weighted inverse of the chosen hazard ratio is applied to the pembrolizumab plus chemotherapy arm from the point in the model at which approximately half of patients had already experienced disease progression, reflecting the reduced efficacy of subsequent treatments following pembrolizumab compared to the immunotherapies available following D&T.

The company also explored a second scenario in response to clarification question B4, where KM data on pembrolizumab plus chemotherapy from KEYNOTE-189 was directly implemented into the model for PFS and OS outcomes. This scenario had the effect of removing the assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy.

These scenarios are described in further detail in Section 4.2.6.

Points for critique

The EAG considers the three-state PSM structure adopted by the company to be appropriate for the current appraisal. However, the appropriateness of the assumption of clinical equivalence between D&T, and pembrolizumab plus chemotherapy is unclear. The model as presented can only capture the costs associated with treatment sequences. There is therefore potentially significant misalignment between the trial data used in the company's base-case analysis, and the decision problem the model attempts to address. The counterfactual pathway in this model is pembrolizumab plus chemotherapy, followed by docetaxel-based treatment regimens. However, the decision problem and trial evidence from BRF113928 is based on a treatment sequence of D&T, followed by an immunotherapy or pemetrexed plus carboplatin. As the model can only capture the costs associated with each line of targeted therapy (i.e. not the benefits), the assumption of clinical equivalence means that benefits from

D&T are projected onto pembrolizumab without the costs associated with the treatments used to generate these benefits. As discussed in Sections 3 and 4.2.6, the EAG considers the reliance on an assumption of clinical equivalence highly uncertain and given the availability of trial data on pembrolizumab from broadly similar populations, namely KEYNOTE-189, prefers not to assume equivalence. The preference of the EAG is therefore to use PFS and OS data directly from KEYNOTE-189 in the model, as opposed to setting these parameters as equal to D&T. However, the use of this data is subject to other uncertainties and weaknesses, as discussed at greater length in Section 4.2.6.

As the model cannot capture the effects of treatment sequences, it is also not possible to assess the cost-effectiveness of D&T at second-line in the estimated [redacted] of patients who are not in receipt of a BRAF test result at the point of treatment initiation, and are therefore treated with pembrolizumab. It is therefore unclear whether D&T is a cost-effective option in this significant minority of patients. The company declined to model this group in any form following a clarification request by the EAG, stating that this population was anticipated to disappear over time with improved reporting times, and that there was insufficient data available with which to model this group.

4.2.3 Population

The modelled population considered in the company's base-case analysis was adult patients with previously untreated advanced NSCLC with a BRAF V600 mutation. This population is narrower than that considered in the decision problem, which encompasses all advanced NSCLC patients with a BRAF V600 mutation, regardless of previous treatment. Patient baseline characteristics (See Table 14) and clinical effectiveness data were based on Cohort C of the BRF113928 trial, which aligned with the modelled population (i.e. previously untreated), comprising 36 patients.

Table 14 Baseline patient characteristics of modelled population

Characteristic	Value
Percentage male	38.9%
Mean age	67.8
Mean BSA	[redacted]

Due to small patient numbers and limited data availability in the BRF113928 trial, subgroup analysis by line of therapy, tumour histology, and PD-L1 expression was not conducted in the original submission. The EAG requested that the company consider subgroups based on PD-L1 expression for the comparator population, as the modelled population covers all levels of PD-L1 expression, may determine treatment selection and clinical effectiveness in current practice. In their clarification

response, the company stated that they had received clinician feedback suggesting that PD-L1 expression status would not factor into management decisions for patients with a BRAF mutation. The company also stated that the division of patients into PD-L1 <1% and PD-L1 1 to 49% subgroups was not appropriate or generalisable to NHS clinical practice. The company also reiterated their belief that pembrolizumab plus chemotherapy was the only relevant treatment option in patients with PD-L1 expression ≥50%, in spite of NICE guidelines which recommend otherwise. However, the company did present a scenario analysis in which treatment costs were weighted under the assumption that a proportion (25%) of PD-L1 ≥50% patients would receive pembrolizumab monotherapy.

The EAG also requested that the company consider explicitly modelling the second-line population, i.e. those patients who were not in receipt of a positive BRAF V600 mutation test result at the point of treatment initiation, who were subsequently treated with D&T. According to data presented in the company submission, this comprises around [redacted] of eligible patients. This population closely aligns with Cohort B of the BRF113928 trial, which comprised 57 patients who were previously treated with chemotherapy prior to initiating D&T. The company declined to consider this population further in their response, stating that Cohort B were not representative of a population previously treated with pembrolizumab. The company also stated that the value of this analysis was limited, anticipating that improvements in gene panel reporting standards would mean that this population is expected to diminish over time.

Points for critique

The extent to which NHS clinicians factor PD-L1 expression score into the use of chemotherapy alongside pembrolizumab remains unclear. The company states that treatment choice based on PD-L1 expression 'would not be used in clinical practice for patients presenting with a BRAF mutation'. This perspective does not represent the counterfactual scenario in which BRAF-targeted therapies are not approved, and thus BRAF mutation status goes unreported and is unactionable. The EAG does, however, acknowledge the company's position that pembrolizumab plus chemotherapy will tend to be offered regardless of PD-L1 score, and that this usage is noted in previous appraisals. The compromise presented in response to clarification question B6a appears a reasonable exploration of the impact of this issue, in which the company assumes that of the 33.5% of the population with PD-L1 ≥50%, 25% receive pembrolizumab monotherapy. This may reflect both the tendency towards urgency and thus use of faster-acting chemotherapy alongside pembrolizumab by many clinicians, but also the pervasiveness of NICE guidelines suggesting the use of monotherapy in patients with higher levels of PD-L1 expression, and clinical advice received by the EAG which supported this usage. The results of this scenario are presented in Sections 5 and 6.

The exclusion of the population pre-treated with pembrolizumab is an important omission from the company's submission. It is unclear how quickly the size of this population will shrink in the near

future, and may remain a clinically significant minority in NHS practice for some time. It is therefore important that the cost-effectiveness of D&T is considered in this second-line population. However, as discussed in Section 3, the EAG notes that D&T demonstrated similar efficacy in the pre-treated population (Cohort B) in the BRF113928 trial.

4.2.4 Interventions and comparators

As described in Section 2.2, dabrafenib is an oral selective inhibitor of B-Raf, which is used in combination with trametinib; an oral, selective inhibitor of MEK1 and MEK2. EMA marketing authorisation was extended to this indication, i.e. adult patients with advanced NSCLC with a BRAF V600 mutation, on 27th March 2017. The dosing regimen modelled for dabrafenib is 150 mg twice daily (two 75 mg capsules), and for trametinib is 2 mg (one 2 mg tablet) once daily. This aligned with the regimen used in Cohorts B and C of the BRF113928 trial. Treatment is to be continued until the patient no longer derives benefit, or until the development of unacceptable toxicity.

The NICE Scope identified a number of potentially relevant comparators in untreated NSCLC, which were grouped by level of PD-L1 expression, tumour histology, and line of therapy. For patients with non-squamous NSCLC expressing PD-L1 with at least 50% tumour proportion score, pembrolizumab monotherapy, atezolizumab monotherapy, and pembrolizumab plus pemetrexed and platinum chemotherapy are recommended. For non-squamous NSCLC with PD-L1 expression below 50%, pembrolizumab in combination with pemetrexed and platinum chemotherapy is recommended alongside chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin). Further comparators were listed in the scope for patients with squamous NSCLC at each level of PD-L1 expression, and across previously treated non-squamous and squamous disease at each level of PD-L1 expression and histology. See Section 3.2 for further discussion of the potential comparators. The company stated that they considered pembrolizumab plus chemotherapy to represent the standard of care in previously untreated advanced NSCLC on the basis of clinical opinion, and therefore this was selected as the only comparator for modelling purposes. The company noted the aggressive nature of the condition in ruling out pembrolizumab monotherapy as a relevant comparator, despite the wording of NICE guidance suggesting the use of monotherapy in patients with high levels of PD-L1 expression. The company also cited clinical opinion suggesting that atezolizumab has so far seen little uptake, given long-term clinical experience with pembrolizumab.

The modelled dosing regimen for pembrolizumab plus chemotherapy was assumed to comprise pembrolizumab plus pemetrexed and either carboplatin or cisplatin. Patients were modelled to receive pembrolizumab for a maximum of two years (35 three-weekly treatment cycles), in line with the stopping rule imposed in NICE TA683.[27] Of patients remaining on treatment after four treatment

cycles (i.e. the point of cis/carboplatin discontinuation), [redacted] were modelled to receive maintenance treatment with pemetrexed alongside pembrolizumab, whilst the remaining [redacted] were modelled to receive pembrolizumab alone. These proportions were derived from the FLATIRON study. On the basis of clinician feedback, the company modelled pembrolizumab monotherapy to be administered every 6 weeks after the first four treatment cycles, in light of changing practices during the COVID-19 pandemic. The modelled dosing of the comparator arm is summarised in Table 15.

Table 15 Summary of modelled pembrolizumab plus chemotherapy dosing (CS Table 24, Page 65)

Drug	Dose	Day of treatment cycle
For the first 4 three-weekly treatment cycles (12 model cycles)		
Cisplatin *(15.6% of patients)*	75 mg/m^2	1
Carboplatin *(84.4% of patients)*	AUC 5–7 (maximum dose 750 mg)	1
Pembrolizumab	200 mg	1
Pemetrexed	500 mg/m^2	1
For the next 31 three-weekly treatment cycles (up to 104 model cycles) (for the [redacted]% of patients receiving pemetrexed maintenance)		
Pembrolizumab	200 mg	1
Pemetrexed (*maintenance)*	500 mg/m^2	1
For the next 16 six-weekly treatment cycles (up to 104 model cycles) (for the [redacted]% of patients not receiving pemetrexed maintenance)		
Pembrolizumab	400 mg	1

Points for critique

As discussed in Section 2.3, the NICE scope listed numerous relevant comparators, which were subdivided by population groupings such as PD-L1 expression, histology, and line of treatment (previously untreated/treated). However, the company chose to include just pembrolizumab plus chemotherapy in their base-case–. The omission of other comparators is not aligned with the NICE scope, but may be reasonable given feedback received by the company and EAG regarding NHS practice. The EAG does not consider these omissions likely to have a significant impact on the modelling of cost-effectiveness, namely because the sparsity of data meant even a meaningful comparison with pembrolizumab was challenging. However, concerns remain regarding the failure of the company's submission to address the evaluation of D&T at two points in the treatment pathway.

As highlighted in Section 4.2.3, the EAG has two main concerns with the modelled comparator, from the perspective that the model incompletely represents the full population considered in this appraisal. Firstly, the extent to which NICE guidance relating to treatment choice by level of PD-L1 expression is followed in current practice. That is, it is uncertain how many patients in the comparator population

receive pembrolizumab monotherapy (see discussion in Section 4.2.3). Secondly, in the [redacted] of patients who currently receive pembrolizumab at first line due to delayed genetic testing results, the comparison should be between a sequence of pembrolizumab plus chemotherapy followed by dabrafenib plus trametinib, compared with pembrolizumab plus chemotherapy followed by the current standard of care at this line (i.e. docetaxel-based regimens). The cost-effectiveness of D&T in this clinically significant group of patients is uncertain (see Section 4.2.3 for further discussion). The EAG also notes that the company expect a recommendation to cover all sub-populations described in the NICE Scope, despite addressing only the first-line non-squamous population in the model. As evidence supportive of a constant treatment effect of D&T and pembrolizumab across all populations has not been presented, it is unclear how representative the modelled comparison is of the full population under consideration.

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE reference case,[28] the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. No other alternative discount rates for costs and QALYs were explored in scenario analysis.

A lifetime horizon of up to a maximum of 1681 weeks (approximately 32.2 years), was chosen to capture all relevant differences in costs and benefits between comparators in the executable model. This reflects the point at which the patient population would reach 100 years of age in the model. However, as the company's PFS and OS extrapolations were only calculated over 1500 weeks (approximately 28.8 years), this essentially represents the end of modelled period. Using the company's base-case parametric functions, this has no effect on the model outcomes, as [redacted] of the patient population is alive at the end of either time horizon.

Points for critique

Discounting was calculated discretely according to the number of whole years elapsed in the model, which means no discounting is applied until a full year has elapsed. This approach can overestimate the costs and benefits accrued over time compared to a continuous calculation of discounting from time zero, which is typically preferred in NICE appraisals. This has the effect of placing a greater weight on short-term costs and benefits. A scenario illustrating the effect of continuous discounting is presented in Section 6.2.

The use of a 1500-week (~28 years) lifetime horizon is considered appropriate by the EAG. Across all plausible OS extrapolations, no patients are expected to be alive at this time point. In the most optimistic extrapolation (generalised gamma), [redacted] of the population is alive at ~28 years. This is discussed further in Section 4.2.6.

4.2.6 Treatment effectiveness and extrapolation

As discussed in detail in Section 4.2.2, the company used a PSM consisting of three health states: PFS, PD, and death. Consistent with this model structure, OS and PFS survival curves were used to calculate the health state membership. In the original submission and the company's base-case analysis, the primary source of PFS and OS data for D&T was Cohort C of the BRF113928 trial, and in the absence of data considered appropriate by the company, an assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy was assumed. Other inputs for pembrolizumab plus chemotherapy including time on treatment (ToT) were based in the FLATIRON RWE study.

All model inputs from the BRF113928 trial were based on the most recent complete data cut-off, 24th February 2021. Inputs informed by the FLATIRON RWE study were derived from the FLATIRON NSCLC EDM database covering a period from the 1st of January 2011 to January 31st, 2022.

In recognition of the potential for a difference in treatment effects between D&T and pembrolizumab plus chemotherapy, particularly given the difference in availability of subsequent therapies between the two treatment options, the EAG requested that the company explore the use of trial data to model the efficacy of pembrolizumab plus chemotherapy. The company presented scenarios in which the modelled efficacy inputs for pembrolizumab plus chemotherapy were derived from the KEYNOTE-189 trial, with the aim of exploring the impact of leveraging available trial data on pembrolizumab. Data from the KEYNOTE-189[12] trial was based on the 20th May 2019 data cut-off. These alternative scenarios are unanchored comparisons and should therefore be interpreted with caution. Importantly, they also consider an all-comer (ALK and EGFR excepted), rather than BRAF V600E specific, population. Despite these limitations, the EAG considers the direct use of trial data the most relevant source of evidence to inform the effectiveness of pembrolizumab plus chemotherapy, and note that the base-case assumption of clinical equivalence is also subject to significant uncertainty due to the lack of supportive evidence. The comparability of the trial populations and conduct of each study is explored in greater detail in Section 3.3.

In addition to the use of KEYNOTE-189 trial data directly in the model, a further scenario was presented in the company's response to clarifications. This scenario sought to account for differences in subsequent therapies received in the D&T trial compared to those available to patients on pembrolizumab. Specifically, D&T patients in the BRF113928 trial and in NHS practice may receive either immunotherapy or pemetrexed combination therapy following progression, whereas patients treated with pembrolizumab are limited to a range of monotherapy chemotherapy agents. This scenario seeks to adjust for the potential difference in benefits of these subsequent treatments by down-weighting the OS curve in pembrolizumab plus chemotherapy arm. This is done by applying a hazard ratio derived from several trials (OAK,[29] KEYNOTE-010,[30] CheckMate-057 and CheckMate-

017[31]) comparing pembrolizumab, atezolizumab, and nivolumab) with docetaxel in previously treated NSCLC patients. The inverse of this hazard ratio was then applied to the pembrolizumab treatment arm over the approximate period patients on D&T would be experiencing the immunotherapy treatment effect. This was discussed further in Section 4.2.6.2. Table 16 summarises the alternative approaches to modelling the effectiveness of pembrolizumab plus chemotherapy, highlighting the effectiveness outcomes used, data sources, and key assumptions and limitations.

Table 16 Alternative PFS and OS outcome scenarios and data sources used

Scenario	Treatment arm	Data source	Strength and limitations
Scenario 1: Company base case - Clinical equivalence assumed	Dabrafenib with trametinib	Cohort C of the BRF113928 trial	*Strengths*: Simple and potentially conservative. *Limitations:* Clinical equivalence assumption has little supporting evidence; does not account for important differences in available subsequent treatments.
	Pembrolizumab plus chemotherapy		
Scenario 2: EAG requested treatment arms modelled from independent data sources and similar extrapolation distributions assumed.	Dabrafenib with trametinib	Cohort C of the BRF113928 trial	*Strengths:* Trial vs trial comparison allows potential differences in effectiveness to be explored in a similar setting; increased duration of follow up for pemb+chemo; larger sample size for pemb+chemo. *Limitations:* Unanchored comparison should be interpreted with caution; KEYNOTE-189 is an all-comer rather than BRAF V600E specific population; unblinded vs blinded assessors in D&T/pemb+chemo.
	Pembrolizumab plus chemotherapy	KEYNOTE-189 trial data	
Scenario 3: OS benefit modelled for patients who received a subsequent treatment following dabrafenib with trametinib. PFS assumed to be unchanged.	Dabrafenib with trametinib	Cohort C of the BRF113928 trial	*Strengths:* PFS assumed equal which is potentially conservative, avoids unanchored comparisons. *Limitations*: Requires strong assumptions about when to apply hazard ratio. Hazard ratios derived from all-comer population(s).
	Pembrolizumab plus chemotherapy	Hazard rate applied on the pembrolizumab plus chemotherapy calculated from OAK, KEYNOTE-010 and CheckMate-057 trials.	

Points for critique

The EAG considers the direct use of KEYNOTE-189 data in the model to provide a potentially appropriate scenario informing independently derived estimates of effect for both treatment arms. The EAG notes the historic committee preference for trial data over the direct use of observational data in

economic models (as in TA812 and TA724). In addition, advice from the EAG's clinical advisor suggests that D&T is likely to be superior to pembrolizumab for patients in whom the specific target oncogenic driver mutation has been identified. It is also likely to be the case that subsequent availability of immunotherapies in patients experiencing disease progression on D&T would generate improved OS outcomes versus docetaxel-based regimens, which are the only option available following progression on pembrolizumab plus chemotherapy. The EAG therefore considers it plausible that a sequence of D&T followed by an immunotherapy may generate different outcomes compared to pembrolizumab plus chemotherapy alone. While this may represent a pragmatic approach in the absence of comparative trial evidence, the assumption of clinical equivalence preferred by the company may not be an informative means of estimating the real-world cost-effectiveness of D&T.

The EAG notes that KEYNOTE-189 recruited an all-comer NSCLC population (with the exclusion of patients with an ALK or EGFR mutation), in whom it might be expected that outcomes on pembrolizumab may be more favourable – although there is limited evidence suggestive of a prognostic effect of BRAF V600 (See Section 2). Nevertheless, as pembrolizumab generates fewer QALYs using KEYNOTE-189, it is plausible that the company's base-case analysis may underestimate the relative effectiveness of D&T in an NHS setting.

4.2.6.1 Progression free survival and health state

Data on PFS were available over 5 years of follow-up from the BRF113928 trial, nonetheless, as not all patients had experienced an event, it was necessary to extrapolate the data through use of standard parametric models. The company's base-case analysis used a log-logistic curve on the basis that it had the best statistical fit in terms of AIC and BIC. Scenarios using the log-normal and generalised gamma curves were presented to explore the effect of curve selection, as these distributions had the second and third best fits in terms of AIC and BIC. Most extrapolations generated clinically plausible predictions, except for the Gompertz distribution. The EAG notes that the log-logistic curve represents the best of the extrapolations of available PFS data, though choice of curve has no impact on cost-effectiveness in the company's base case where equivalence is assumed. Table 17 presents a comparison of the predictions generated by each parametric model for PFS at key landmarks between 1 and 15 years, by which time most distributions estimate [redacted] of patients remain progression-free. Figure 2 compares these extrapolations graphically.

Table 17 Proportion of progression-free patients predicted by company's PFS extrapolation – dabrafenib with trametinib (based on company's base-case economic model)

Distribution	Modelled landmarks			
	1 year	5 years	10 years	15 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic (Preferred)	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2 Comparison of PFS extrapolations – dabrafenib with trametinib (based on company's economic model)

As previously stated, while clinical equivalence for pembrolizumab plus chemotherapy was assumed in the company's base case, the company also presented additional analysis at the clarification stage using PFS data from the KEYNOTE-189 trial. The company fitted standard parametric functions to published data from KEYNOTE-189. In selecting the appropriate parametric function, the company noted that NICE Decision Support Unit TSD14 recommends the use of a consistent statistical distribution between treatment arms in the absence of convincing evidence to demonstrate different shaped distributions.[32] Consequently, the company selected the log-logistic function to extrapolate data from both KEYNOTE-189 trial and validated this against the FLATIRON RWE study. As can be seen from Table 7 of the company's clarification response, the log-logistic distribution did not have the best statistical fit (log-normal for KEYNOTE-189, and generalised gamma for FLATIRON RWE). Due to the relative completeness of the available data, the standard distributions generate similar predictions of long-term PFS, and thus the statistical fit of the log-logistic curve generated

predictions that aligned with the statistically best fitting curve. Table 18 presents a comparison of each parametric model at key landmarks between 1 and 15 years, by which point all distributions result in less than [redacted] of patients remaining progression-free. Figure 3 compares these extrapolations graphically.

Table 18 Proportion of progression-free patients predicted by company's PFS extrapolations – pembrolizumab plus chemotherapy arm (based on KEYNOTE-189 data)

Distribution	Modelled landmarks			
	1 year	5 years	10 years	15 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic (Preferred)	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3 Comparison of PFS extrapolations – pembrolizumab plus chemotherapy arm (based on KEYNOTE-189 data)

Points for critique

The EAG considers the choice of a log-logistic function for the D&T arm appropriate as it has the best statistical fit and generates clinically plausible predictions. The EAG notes that all the other parametric extrapolations except for the Gompertz distribution also have a good fit to the data and generate similarly plausible predictions due to the relative completeness of PFS data in BRF113928. In the company's base case, the company adopted the same curve for the comparator arm, as the predicted PFS extrapolation for pembrolizumab plus chemotherapy from the FLATIRON RWE study were considered clinically implausible.

However, KEYNOTE-189 generated clinically plausible predictions and allows potential differences in effectiveness between the treatment arms to be explored. The EAG considers an analysis using KEYNOTE-189 data to model PFS for pembrolizumab plus chemotherapy a potentially informative alternative to clinical equivalence. However, the caveats described previously mean these results should be interpreted with caution. This scenario is presented in Section 6.2.

4.2.6.2 Overall survival, death health state and progressed disease state

Data for OS available from the BRF113928 trial was relatively mature, with [redacted]years of follow up. Available Kaplan-Meier data was, however, incomplete and so was extrapolated using standard parametric functions.

The company's base-case analysis adopted a Weibull curve to extrapolate OS, which was applied to D&T and thus also pembrolizumab plus chemotherapy, in line with the assumption of equivalence. The Weibull curve had the worst statistical fit in terms of AIC and BIC; however, the EAG notes that the Weibull curve represents one of the most pessimistic extrapolations of available OS data. In addition, the difference in AIC between the best fit curve (log-normal) and the worst fit (Weibull) is [redacted], a negligible difference in statistical fits. In addition, as the company notes, only the Weibull and exponential distributions result in clinically plausible predictions of 15-year OS, given the severity of the underlying condition. Table 19 presents a comparison of the predictions generated by each parametric model for OS at key landmarks between 1 and 15 years. While all result in reasonably similar predictions at 1 and 5 years compared to the KM data, which at 5 years was [redacted]beyond ~9 years the predictions begin to diverge, with the generalised gamma distribution resulting in the most optimistic OS of [redacted]at 10 years and Weibull distribution the most pessimistic at [redacted]at 10 years. Figure 4 compares these extrapolations graphically.

Table 19 Proportion of patients predicted by company's OS extrapolation – dabrafenib with trametinib (based on company's base-case economic model)

	Modelled landmarks			
Distribution	**1 year**	**5 years**	**10 years**	**15 years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (Preferred)	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4 Comparison of OS extrapolations – dabrafenib with trametinib (based on company's economic model)

[redacted]

In the scenario using KEYNOTE-189 to model the effectiveness of OS, the company similarly fitted parametric survival curves to extrapolate available data. In line with TSD14 and the approach taken to model PFS, the company selected the same parametric function as applied in the D&T arm and therefore used a Weibull curve. The Weibull curve had the best statistical fit in terms of AIC and the second best in terms of BIC, while the log-normal distribution had the worst AIC and BIC. Table 20

presents a comparison of the predictions generated by each parametric model for OS at key landmarks between 1- and 15-years using KEYNOTE-189 trial data. The log-normal and the loglogistic distributions result in clinically implausible outcomes at 15 years while all the other distributions result in less than [redacted] of patients alive at 15 years. Figure 5 compares these extrapolations graphically.

Table 20 Proportion of patients predicted by company's OS extrapolation – pembrolizumab plus chemotherapy (based on KEYNOTE-189 data)

	Modelled landmarks			
Distribution	**1 year**	**5 years**	**10 years**	**15 years**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (Preferred)	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]

Figure 5 Comparison of OS extrapolations – pembrolizumab plus chemotherapy (based on KEYNOTE-189 data)

Points for critique

The EAG is broadly in agreement with the OS extrapolation for the D&T arm in the model using the Weibull curve. While the distribution had the worst statistical fit in terms of AIC and BIC, the difference between the worst- and best-fitting curves was negligible. In addition, the Weibull distribution predicts the most conservative scenario, and thus is unlikely to risk inflating the estimated efficacy of D&T. The scenario using KEYNOTE-189 generated clinically plausible predictions and generated lower ICERs that the company's base-case analysis.

The EAG notes that the scenario incorporating KEYNOTE-189 data may be interpreted as representing a generally conservative approach to implementing a meaningful treatment effect for D&T. This scenario uses the most pessimistic extrapolation for D&T and a middling projection of pembrolizumab data. It is also plausible that in using the essentially all-comer KEYNOTE-189 population without adjustment, the model overestimates outcomes on pembrolizumab in a population with a BRAF V600 mutation. However, the usual caveats associated with an unanchored comparison between trials and an unblinded assessment of efficacy for D&T apply. The results are therefore subject to a great deal of uncertainty that cannot necessarily be captured in the scope of this model.

4.2.6.3 Time on treatment (ToT)

In the company's base case, ToT was estimated from the ToT individual data for patients in Cohort C of the BRF113928 study who received D&T. For the comparator arm, this was based on patients receiving pembrolizumab plus chemotherapy in the FLATIRON RWE study (2022). The ToT curve was used to estimate resource use for D&T and pembrolizumab plus chemotherapy. Discussion of extrapolations are presented in Section 4.2.8.

No stopping rules were applied for D&T as per UK clinical practice, while for pembrolizumab a two year (or 35 treatment cycles) stopping rule was applied based on TA683 and UK clinical practice. While the EAG considers the selected extrapolation of ToT to be appropriate, the sample size (N=26) from the FLATIRON RWE study (2022), from which pembrolizumab ToT was calculated, is very small, and introduces uncertainty into the company's results. It may be preferable to use data on the wider cohort of patients treated with pembrolizumab plus chemotherapy from FLATIRON in the clinical equivalence scenarios. Alternatively, data from KEYNOTE-189 should be used to estimate ToT in scenarios in which efficacy data are drawn from this study, as discussed further in Section 4.2.8.

4.2.6.4 Adverse events

Adverse events included in the economic model were all-cause Grade ≥3 events experienced by ≥ 1% of patients receiving either D&T in the BRF113928 trial, or pembrolizumab plus chemotherapy from KEYNOTE-189 trial. Adverse events were modelled to account for both the incidence and duration of events. To inform the disutilities and costs associated with each AE, event rates were estimated independently for each treatment arm of the model, and were imposed as a one-off cost and QALY decrement in cycle 1 of the executable model. Event rates were estimated as function of incidence. The incidence of each AE is summarised in Table 21.

Table 21 Incidence and rate of AE by treatment arm (adapted from company's executable model)

Adverse Event	Overall Incidence per patient	
	Dabrafenib and Trametinib	Pembrolizumab plus Chemotherapy
Alanine aminotransferase increased	6.45%	0.00%
Anaemia	5.37%	18.50%
Asthenia	4.30%	6.70%
Diarrhoea	2.15%	5.20%
Dyspnoea	7.53%	4.00%
Fatigue	3.23%	7.70%
Hypertension	9.68%	0.00%
Hyponatremia	9.68%	0.00%
Neutropenia	7.53%	16.30%

Pyrexia	6.45%	0.20%
Thrombocytopenia	0.00%	8.40%
Abdominal pain	1.08%	0.00%
Arthralgia	1.08%	0.00%
Aspartate aminotransferase increased	3.23%	0.00%
Back pain	3.23%	1.50%
Blood alkaline phosphatase increase	1.08%	0.00%
Colitis (immune-mediated)	0.00%	1.70%
Constipation	0.00%	1.00%
Decreased appetite	0.00%	1.20%
Dry skin	1.08%	0.00%
Headache	1.08%	0.00%
Hepatitis (immune-mediated)	0.00%	1.50%
Hypotension	4.30%	0.00%
Nausea	0.00%	3.50%
Nephritis (immune-mediated)	0.00%	1.50%
Pain in extremity	1.08%	0.00%
Pneumonia	1.08%	0.00%
Pneumonitis (immune-mediated)	0.00%	3.00%
Pruritis	2.15%	0.00%
Rash	2.15%	2.00%
Severe skin reactions (immune-mediated)	0.00%	2.50%
Vomiting	3.23%	4.00%
Weight decreased	1.08%	0.00%
Weight increased	3.23%	0.00%

Points for critique

The EAG considers the company's approach to modelling AEs to adequately represent the relative differences in the burden of AEs associated with each treatment regimen. As is discussed in reference to resource use and HRQoL modelling, while the company states that the burden of AEs is likely to be captured in the period immediately following treatment initiation, it may have been more appropriate to implement AE rates on a per cycle basis, using annualised AE rates from the trials. However, this issue would be complex to resolve and is likely to affect both arms equally, it has therefore not been explored further.

The EAG notes that previous appraisals (TA789 and TA812) included all-cause Grade ≥3 AEs experienced by between 5% and 2% respectively of the patients compared to the ≥ 1% incidence used

in appraisal. The impact of this omission of more AEs is likely to be modest however, it is unclear whether this would favour the D&T or pembrolizumab plus chemotherapy.

The EAG notes treatment-related AEs may manifest in patients on subsequent therapies; however, these events have not been explicitly considered within the company's model. The impact of these AEs is likely to be modest. It is similarly unclear whether this omission would favour D&T or pembrolizumab plus chemotherapy.

4.2.7 Health related quality of life

4.2.7.1 Health state utilities

The company assumed clinical equivalence between D&T and pembrolizumab plus chemotherapy, implying equivalent PFS and OS in their base-case analysis. Health state utilities therefore have no impact on the incremental QALYs, which are zero as patients spend the same length of time in the PFS and PD health states in both treatment arms. In scenarios which explore alternative assumptions regarding the source of efficacy data for pembrolizumab plus chemotherapy, the utility set adopted impacts incremental QALYs in the usual way.

No HRQoL data were collected in the BRF113928 trial. The company therefore reviewed recently published NICE appraisals for targeted therapies in advanced NSCLC (TA789,[33] TA781[34] and TA812[1]). The company considered none of the value sets used in these appraisals appropriate, as either time-to-death utilities or literature-derived sources were used. The company instead used utility values from Chouaid *et al*.[35] in the base-case analysis, which had previously been presented as a scenario in TA789. This study was based on an advanced NSCLC cohort which included UK centres and used EQ-5D to derive utilities. The PFS utility value of 0.710 (SD 0.240) was based on patients undergoing first-line treatment, and is similar to that used in TA789, while the PD utility value of 0.670 (SD 0.200) is similar to that used in TA654. The EAG notes that the utility of patients on second-line treatment in Chouaid *et al.* was 0.74 (SD 0.18) – higher than that of patients on first-line treatment. Because health state utilities had no impact on incremental QALYs due to the assumption of clinical equivalence, no further scenarios were considered in the company's submission.

Points for critique

The source of health state utility values used in model appears a reasonable option in the absence of appropriate trial data, but the rationale for choosing this utility set over others used in recent appraisals was unclear. It is also uncertain how appropriate this data source for first-line treatment is, given the potentially counterintuitive increase in utility reported at second-line. A comparison of the utility set used in the submission with utilities accepted in previous appraisals in NSCLC is presented in Table 22.

The EAG notes in particular that the applied PFS utility is the lowest of those accepted across recent appraisals. In the company's base-case analysis, the only effect of this low utility value is to potentially under-value QALY gain across both treatment arms. However, for scenarios in which time spent in the progression-free health state differs across treatment arms, benefits associated with preventing progression may be under-valued. Whilst this may appear conservative with regards to the valuation of treatment benefits on D&T in scenarios using KEYNOTE-189 data, it may serve to underestimate standard of care (SoC) QALYs in the calculation of QALY shortfall. The EAG therefore presents a scenario in Section 6 in which utilities are based on 'untreated' values accepted in the most recent TA812, which had amongst the highest PFS utility value, but a very similar PD utility to that derived from Chouaid *et al*.

Table 22 Comparison of health state utility values in NSCLC appraisals

NICE appraisal	PFS Utility value	PD Utility value
TA258	0.661 or 0.656	Calculated relative to PFS; Disutility of 0.1798 applied
TA310	0.784 (base-case), 0.710 or 0.663	0.725 (base-case), 0.62 (Third line)
TA416	0.815	0.678
TA643	0.780	0.660
TA654	0.794	0.704 (first line) or 0.678 (base-case)
TA789	0.732	0.694
TA812	0.794 (untreated base-case), 0.713 (pre-treated)	0.678 (untreated base-case), 0.628 (pre-treated)
Present submission	0.710	0.670

4.2.7.2 Effect of adverse events on HRQoL

To account for the impact of AEs on health-related quality of life, the company sourced event-specific utility decrements to be applied in the model. The base-case analysis included all-cause Grade ≥3 AEs experienced by ≥1% of patients in either the BRF113928 trial for D&T or KEYNOTE-189 for pembrolizumab plus chemotherapy. The AE-specific utility decrements and durations were based on several published literature sources, but primarily TA789,[33] see Table 23. The decrements and durations were used to estimate a treatment specific disutility that was applied as a one-off decrement in the first cycle of the model.

Table 23: Summary of AE disutilities included in the company's economic model (CS Table 32, Page 78)

Adverse event	Disutility	Duration (days)
Abdominal pain	-0.069	31
Alanine aminotransferase increased	-0.05	54.8
Anaemia	-0.073	3

Arthralgia	-0.069	31
Aspartate aminotransferase increased	-0.051	54.8
Asthenia	-0.073	52
Back pain	-0.069	31
Blood alkaline phosphatase increase	-0.05	54.8
Colitis (immune-mediated)	-0.11	3
Constipation	-0.047	3
Decreased appetite	-0.085	10.5
Diarrhoea	-0.047	3
Dry skin	-0.032	117.6
Dyspnoea	-0.05	18.8
Fatigue	-0.073	212
Headache	-0.069	31
Hepatitis (immune-mediated)	-0.11	7
Hypertension	-0.03	150
Hyponatremia	-0.085	7
Hypotension	-0.03	183.4
Nausea	-0.048	10.5
Nephritis (immune-mediated)	-0.11	7
Neutropenia	-0.09	158
Pain in extremity	-0.069	31
Pneumonia	-0.008	19.6
Pneumonitis (immune-mediated)	-0.11	19.6
Pruritis	-0.032	117.6
Pyrexia	-0.11	7.6
Rash	-0.032	117.6
Severe skin reactions (immune-mediated)	-0.11	117.6
Thrombocytopenia	-0.003	37.2
Vomiting	-0.048	2
Weight decreased	0	0
Weight increased	0	0

Abbreviations: AEs: adverse event; AESI: adverse event of special interest; CDF: Cancer Drugs Fund; NICE: National Institute of Health and Care Excellence; TA: technology appraisal.

Points for critique

The EAG notes that the utility decrements and durations are primarily sourced from TA789[33] rather than from EQ-5D data collected from the pivotal trial as recommended by the NICE reference case,[28] as EQ-5D data were not collected in the D&T trial. Nevertheless, the EAG considers the method used to capture the HRQoL impact of AEs reasonable, and are broadly comparable to previous appraisals of advanced NSCLC.

This appraisal included all-cause Grade ≥3 AEs experienced by ≥1% of patients unlike previous advanced NSCLC appraisal that included all-cause Grade ≥3 experienced by between 2% - 5% of patients. The likely impact is an increase in the proportion of patients experiencing AEs in both treatment arms. The EAG notes that the model results are not sensitive to this parameter, therefore, any uncertainty around this parameter is not explored further.

4.2.7.3 Age adjustment of utilities

Utilities were adjusted over time to reflect the effect of aging on health-related quality of life. Adjustment was made using UK population norm values for EQ-5D as reported in the HSE 2014 dataset by the NICE Decision Support Unit[36]. The EAG is satisfied with the approach taken in the company's economic model.

4.2.7.4 Utility disutility for infusion administration

In the original model, company applied an annualised disutility of -0.023 for infusion administration of pembrolizumab plus chemotherapy throughout each cycle that patients remain on treatment, including the three quarters of cycles in which patients do not receive an infusion. This disutility was applied to all patients on pembrolizumab plus chemotherapy arm treatment as determined by the ToT curve.

This disutility was based on the study by Matza *et al.* (2013)[37] which investigated the disutility associated with infusion-treatments for bone metastases. The utility was determined through sample a time trade-off (TTO) interviews with a sample of the UK general population and was not derived directly from patients.

Points for critique

While the EAG acknowledges that this disutility has been previously used in TA728, the EAG does not consider a disutility of this magnitude appropriate. The model implies that a disutility associated with a 30-minute IV infusion every four weeks is larger than that incurred for a number of severe adverse events in the model, including pneumonia requiring hospitalisation. This clearly lacks face validity and is likely a result of the TTO methodology which is not a reliable means of generating utility values. This is also inconsistent with preferred approach as outlined in the NICE reference case.

The EAG accepts that IV administration may be less convenient for patients than an oral therapy but considers that the *health-related* QoL impacts of IV administration are likely to be vanishingly small, and not persistent to the extent modelled by the company, and thus will have a minimal impact on total QALYs. As such, the EAG considers it appropriate to remove this disutility from the model in its entirety.

4.2.8 Resources and costs

The CS provided a description of resource use and costs applied in the model. This included drug acquisition and administration costs, costs associated with management of adverse events, monitoring costs, and the cost associated with subsequent treatments, and resource use associated with end-of-life care.

The analysis was conducted from an NHS and PSS perspective, and accordingly the company used NHS reference costs 2019-20,[38] the British National Formulary (BNF), and the electronic Marketing Information Tool (eMIT) to derive the cost values implemented in the model.

4.2.8.1 Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising the comparator regimen, and for drugs currently in use as subsequent treatment options. The treatment acquisition costs used in the analyses presented in the company submission (reproduced in Section 5.1 and the EA Report (Section 6), include only the confidential pricing agreement for D&T. Dabrafenib currently has a [redacted], and trametinib has a [redacted], [redacted], [redacted], [redacted] [redacted], Table 24 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG, and were used to replicate **all** analyses presented in the EA Report for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 6th September 2022.

Table 24 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Dabrafenib	Simple PAS
Trametinib	Simple PAS
Atezolizumab	Simple PAS
Nintedanib	Simple PAS
Nivolumab	Simple PAS
Pembrolizumab	Simple PAS
Pemetrexed	CMU

4.2.8.2 Drug acquisition costs

Acquisition costs for D&T were based on 150 mg dabrafenib taken twice daily, and trametinib 2 mg once daily, per their respective SmPCs. Time on treatment (ToT) was modelled using ToT data collected from Cohort C within the BRF113928 trial, for which complete KM data were available. Despite the availability of complete KM data, the company considered it more appropriate to fit a parametric curve to ToT data to smooth out KM data for a more stable rate of discontinuation. The extrapolations fitted by the company to D&T ToT are presented graphically for up to 10 years in Figure 6. The exponential function had the best statistical fit to these data, and was used in the company's base-case analysis. The model did not apply any stopping rules, per UK clinical practice. Observed median treatment duration was [redacted] months in the BRF113928 trial. The company also adjusted acquisition costs for observed relative dose intensity (see Table 25 below), but did not account for wastage.

Figure 6 Dabrafenib and trametinib ToT extrapolations (BRF113928 Cohort C) (CS Figure 12, Page 73)

Comparator acquisition costs were calculated using a weighted average, assuming that in line with TA789, 84.4% of patients would receive pembrolizumab in combination with pemetrexed and carboplatin, and 15.6% of patients would receive pembrolizumab in combination with pemetrexed and cisplatin. Each of these components was subject to separate stopping rules, which were reflected in the model:

- Pembrolizumab: Two years (or 35 treatment cycles)
- Platinum based-chemotherapy (carboplatin or cisplatin): Four treatment cycles (12 weeks)

- Pemetrexed: Four treatment cycles (12 weeks). Of those remaining on pembrolizumab at 12 weeks, [redacted] are assumed to receive maintenance treatment until cessation of pembrolizumab (as above).

Pembrolizumab ToT was based on the fitting of parametric distributions to the weighted ToT data for the [redacted] BRAF V600E mutation-positive patients receiving pembrolizumab plus chemotherapy in the FLATIRON study. Figure 7 shows the fit of the company's survival models to these data for up to 3 years. The exponential distribution had the best statistical fit, and was used in the base-case analysis, albeit with a stopping rule applied at 35 treatment cycles.

Figure 7 Pembrolizumab plus chemotherapy ToT extrapolations (FLATIRON BRAF V600E population)

Drug acquisition costs were derived from the dosing regimens presented in Table 25, using pricing data from the BNF for branded products, and from eMIT for generic medicines. Dosing based on BSA/weight used patient baseline characteristics from Cohort C of the BRF113928 trial. Treatment-specific relative dose intensity (RDI) taken from mean daily dose in BRF113928 and KEYNOTE-189 was applied to adjust final drug acquisition costs. No vial sharing was assumed for the comparator treatments, and no wastage was assumed for D&T.

A summary of drug acquisition costs for all first-line treatments included in the company's base-case analysis are reproduced in Table 25 below.

Table 25 Summary of first-line drug acquisition costs in company base-case analysis

Drug	Dosing regimen	Pack cost (size)	RDI	Cost per dose	Mean cost per cycle
Dabrafenib plus trametinib					
Dabrafenib	150 mg (two 75 mg capsules) BID	£1,400 (28 units)	0.83	[redacted]	[redacted]
Trametinib	2 mg QD	£4,800 (30 units)	0.9	[redacted]	[redacted]
Pembrolizumab plus chemotherapy					
Pembrolizumab	200 mg every 3 weeks for the first 4 treatment cycles (12 weeks), followed by either: • 200 mg every 3 weeks (for patients receiving pemetrexed maintenance therapy) • 400 mg every 6 weeks (for patients not receiving pemetrexed maintenance therapy). Maximum total treatment duration of two years	£2,630 (100mg)	0.956	£10,520.00	£1,676.19
Pemetrexed	500 mg/m^2 every 3 weeks for four treatment cycles (12 weeks), followed by 500 mg/m^2 for the [redacted]% of patients who continue to receive pemetrexed maintenance therapy, for a maximum total treatment duration of two years.	£640 (500mg)	0.964	£1,280.00	£411.31
Carboplatin	AUC 5-7 every 3 weeks, for a maximum of 4 treatment cycles (12 model cycles)	£13.51 (450mg)	0.964	£13.51	£4.34
Cisplatin	75 mg/m^2 every 3 weeks, for a maximum of 4 treatment cycles (12 model cycles)	£8.97 (100mg)	0.964	£17.94	£5.76

Points for critique

The EAG considers the calculation of acquisition costs in the economic model to be broadly appropriate, noting a few exceptions. Firstly, the assumption that [redacted] of patients on pembrolizumab plus chemotherapy would receive maintenance therapy with pemetrexed may be too high, given clinical advice to the company that 50 – 60% have maintenance therapy on the NHS. Due to the high acquisition cost of pemetrexed at list price, this assumption may overestimate the total costs associated with the comparator regimen in practice.

Secondly, whilst the company assumes that no vial sharing occurs on intravenously administered comparator and subsequent therapies, they assume that missed doses of D&T will result in fewer packs being used. The EAG considers that the stock-piling of pills avoiding wastage could be possible, but expects that some that some drug wastage would be associated with dose adjustments and interruptions. The company approach may therefore underestimate the acquisition cost associated with D&T. To explore this uncertainty a scenario is presented in Section 6 which assumes only half of the cost-savings associated with the RDI adjustment are realised due to wastage. This approach is consistent with several other appraisals of targeted therapies in NSCLC, such as TA670, TA571, and in cost terms equates roughly to patients wasting half a pack of D&T on average.

Finally, time on treatment for pembrolizumab was based on data from the FLATIRON study. This is inconsistent with assumption of equivalence imposed in the model and means that clinical outcomes in the model are inconsistent with the resource use data being implied. It is plausible that time spent on treatment with pembrolizumab may differ between a BRAF V600E mutation population and an all-comer population which could justify this assumption. The extent of any difference is however, unclear. At the clarification step the EAG requested a scenario in which ToT on pembrolizumab was based on data from KEYNOTE-189. As ToT data has not been published, the company presented an analysis in which ToT was assumed to be equal to PFS from the KEYNOTE-189 trial (with stopping rules applied). The results of this analysis are presented in Sections 5 and 6.

4.2.8.3 Treatment administration costs

Treatment administration costs were considered for all drugs administered by IV infusion in a hospital setting. D&T were assumed not to be associated with any administration costs. Administration costs were distinguished by first and subsequent visits, and for simple IV (single agent, e.g. pembrolizumab monotherapy), versus complex IV (multiple agent, e.g. pembrolizumab and chemotherapy). Administration costs are summarised in Table 26.

Table 26 Treatment administration costs in company base-case analysis (CS Table 37, Page 90)

Admin. type	First admin	Subsequent admin	Source
Oral	£0.00	£0.00	Assumption
Simple IV, outpatient	£221.35	£170.92	NHS Reference Costs 2019/20, [38] Deliver simple parenteral chemotherapy at first attendance: SB12Z, outpatient (for first administration), Deliver subsequent elements of a chemotherapy cycle: SB15Z, outpatient (for subsequent admins)
Complex IV, outpatient	£352.24	£253.77	NHS Reference Costs 2019/20, [38] Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance: SB14Z, outpatient (for first admin), Deliver subsequent elements of a chemotherapy cycle: SB15Z, outpatient (for subsequent administrations)
Complex IV, day case	£431.72	£365.91	NHS Reference Costs 2019/20, [38] Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance: SB14Z, day case (for first admin), Deliver subsequent elements of a chemotherapy cycle: SB15Z, day case (for subsequent administrations)

Points for critique

The EAG considers the company's approach to modelling administration costs associated with IV therapies using the simple and complex parenteral chemotherapy costs appropriate, and it is consistent with previous appraisals. However, other appraisals of oral therapies in NSCLC such as TA536, TA670, and TA628, have included the cost of a pharmacist's time to dispense each pack of oral medication. This typically amounts to approximately £10.80 per pack, based on the cost of 12 minutes of work for a Band 6 community-based scientific and professional staff member, sourced from Personal Social Services Research Unit (PSSRU) 2020 costs. The EAG presents a scenario in Section 6 in which this cost is applied once per month for patients treated with D&T.

4.2.8.4 Subsequent treatments

The company applied a one-off cost associated with subsequent treatment at the point of disease progression.

The proportion of patients modelled to receive a subsequent treatment was based on Cohort C of the BRF113928 trial, in which [redacted] patients ([redacted]) went on to receive a subsequent treatment after progression on D&T. The company noted that in TA584 of atezolizumab for advanced NSCLC, clinical advice to the Committee estimated that no more than 60% of patients would receive subsequent treatment following atezolizumab.

Of the patients receiving subsequent therapy in BRF113928, 55% received chemotherapy, and 45% immunotherapy. The company assumed that second-line chemotherapy following D&T comprised

carboplatin plus pemetrexed, while those receiving a subsequent immunotherapy were split equally between pembrolizumab, atezolizumab, and nivolumab – all as monotherapy.

In the absence of sufficient relevant data on subsequent treatments in FLATIRON for pembrolizumab plus chemotherapy, the company assumed the proportion of patients proceeding to subsequent line of therapy was equal to that observed for dabrafenib plus trametinib in BRF113928 (i.e. [redacted]). It was assumed that patients were split equally between docetaxel monotherapy, and docetaxel plus nintedanib, based on TA789.

The proportions of patients receiving each subsequent treatment in the company's base-case analysis is summarised in Table 27. The company also presented a scenario analysis in which the proportion of patients receiving immunotherapy following D&T was increased to 60% of those continuing to a subsequent treatment, to reflect the increasing place of immunotherapy as the standard of care in clinical practice.

Table 27 Subsequent therapies included in the company's model

Subsequent treatment	Dabrafenib and trametinib	Pembrolizumab plus chemotherapy
Patients receiving subsequent treatment (%, out of patients receiving initial treatment)		
Proportion receiving subsequent treatment	[redacted]	[redacted]
Subsequent treatment distributions (%, out of patients receiving subsequent treatment)		
Pembrolizumab monotherapy	[redacted]	0%
Atezolizumab monotherapy	[redacted]	0%
Nivolumab monotherapy	[redacted]	0%
Pemetrexed plus carboplatin	[redacted]	0%
Docetaxel monotherapy	0%	50%
Docetaxel plus nintedanib	0%	50%

It was assumed that immunotherapy monotherapy in previously treated patients would last for 13.5 weeks on the basis of clinical advice to the company. The company applied the same duration to subsequent chemotherapy for consistency. The company also explored scenarios in which subsequent treatment durations were aligned with the values used in TA789 and TA347.

Points for critique

The EAG considers the approach taken to modelling the costs of subsequent lines of therapy broadly appropriate. However, the EAG considers there to be uncertainty regarding the proportion of patients that will receive immunotherapy following progression on D&T. This reflects uncertainties in the effectiveness of immunotherapies in patients with an identified oncogenic driver mutation such as

BRAF V600E. It is plausible that the proportion of patients offered an immunotherapy following progression on D&T may be lower in this population due concerns about the effectiveness of immunotherapies. Equally, however, as clinical experience and the evidence base increases in such populations, it is similarly plausible that immunotherapy use will increase (reflecting evidence of the effectiveness of immunotherapy in this population). The EAG therefore presents two scenarios to explore this uncertainty. One in which all patients who progress to second-line therapy (56%) following progression on dabrafenib plus trametinib receive pemetrexed plus carboplatin and a second where all patients (56%) are assumed to receive immunotherapy (evenly split between pembrolizumab, atezolizumab, and nivolumab).

4.2.8.5 Health state unit costs and resource use

Resource use associated with state residence in the model was specific to the PFS and PD health states, and costs were modelled on a per-cycle basis. Progression into the death state was associated with a one-off cost which reflected end-of-life care (see Section 4.2.8.8). Resource use estimates were derived from TA789, and unit costs of services were based on NHS reference costs (2019/20).[38] Given the base-case assumption of clinical equivalence in terms of PFS and OS between the two treatment arms, health state residence and thus health state unit costs are the same for D&T, and pembrolizumab plus chemotherapy. The per-cycle cost associated with residing in the PFS health state was £78.30, and for PD was £106.17. Modelled health state costs are summarised in Table 28.

Table 28 Modelled health state resource use and unit costs (CS Tables 39 & 40, Page 94)

Resource	Unit cost	Resource use per year		Source
		PFS	PD	
Outpatient visit	£150.62	9.61	7.91	NHS Reference Costs 19/20, Outpatient attendance, Consultant led, 800, Clinical Oncology[38]
Chest radiography	£34.27	6.79	6.50	NHS Reference Costs 19/20, Other Diagnostic Imaging, Consultant Led, DIM009[38]
CT scan (chest)	£119.01	0.62	0.24	NHS Reference Costs 19/20, TotalHRG, RD24Z[38]
CT scan (other)	£119.01	0.36	0.42	NHS Reference Costs 19/20, TotalHRG, RD24Z[38]
ECG	£107.77	1.04	0.88	NHS Reference Costs 19/20, TotalHRG, EY51Z[38]
Community nurse visit	£75.00	8.70	8.70	PSSRU 2021; p115; cost per hour Band 8a[39]
Clinical nurse specialist (hours of contact time)	£88.00	12.00	12.00	PSSRU 2021; p115; cost per hour Band 8b (assuming one hour of time) [39]
GP appointments	£39.00	12.00	0.00	PSSRU 2021; p118; cost per patient lasting 9.22 minutes[39]
GP home visit	£39.00	0.00	26.09	PSSRU 2021; p118; cost per patient lasting 9.22 minutes[39, 40]

Therapist visit	£47.00	0.00	26.09	PSSRU 2021; p132; cost per hour for community occupational therapist (assuming one hour of time)[39]

Points for critique

The EAG is satisfied that the health state costs included in the model are appropriate and consistent with those used in previous submissions.

4.2.8.6 Adverse reaction management costs

The company's base-case analysis considered costs incurred for the management of any Grade ≥3 adverse event experienced by ≥1% of patients in either treatment arm. Modelled adverse event frequencies have been previously discussed in Section 4.2.6. Unit costs were derived from NHS reference costs 2019/20, and HRG codes were selected to align with those used in TA789. The costs associated with the total AE burden were applied as a one-off cost in the first model cycle, which the company considers to be consistent with previous appraisals, and with the assumption that most AEs would be experienced soon after treatment initiation. Modelled AE costs can be found in Table 42 of the Company Submission.

Points for critique

The EAG does not consider the implementation of AE rates to have been methodologically optimal (discussed in Section 4.2.6), as it is not clear that all AEs are experienced soon after initiation of treatment, and indeed many patients discontinue treatment throughout the BRF113928 trial due to adverse events. However, this issue is likely to affect both arms equally, therefore due to the complexity of implementation and nominal incremental impact on costs, this has not been explored further. The EAG considers the management costs included in the model to be appropriate and consistent with those accepted in previous appraisals.

4.2.8.7 Testing costs

In their original submission, the company included no consideration of the cost of BRAF testing and reporting, reasoning that because it is already included in the Genomic Test Directory and currently comprises routine clinical practice for this patient population, no additional costs would be incurred by the system if D&T entered routine commissioning. However, the EAG highlighted at the clarification stage that BRAF was only included in NSCLC screening due to the availability of dabrafenib on the NHS according to interim COVID-19 guidance. Therefore, the testing and reporting for BRAF V600 mutations is dependent on the ongoing availability of D&T, and testing costs should be considered in line with appraisals of other targeted therapies.

In their clarification response, the company described a scenario analysis which included the cost of reporting BRAF gene results, which based on expert consultation was estimated at £50 per patient. This was multiplied by the number of patients needed to be tested to identify a single patient with an actionable BRAF V600 mutation, i.e. the inverse of the incidence, estimated to be 2.5%, yielding a total testing cost of £2,000.

Points for critique

The EAG considers the testing costs included in the scenario presented in the company's clarification response to be largely appropriate. However, the incidence rate range (i.e. 1 – 4%) should be accounted for in the probabilistic cost calculations. In probabilistic analyses undertaken in the EAG version of the model which include this parameter, this range is accounted for. The EAG notes that the model uses a unit cost of £98.55 (cost per patient of £3,924, based on an uprated value from TA269). The EAG consider this to have been implemented incorrectly. However, in the recent appraisal of mobocertinib in NSCLC (ID3984),[2] the committee heard from NHS England that the standard cost of adding a mutation onto a next generation sequencing panel was £34, yielding a total testing cost of £1,360 per patient. This value was also confirmed to the EAG by NICE. The EAG presents a scenario in Section 6 in which this value is used.

4.2.8.8 End-of-life costs

The company applied a one-off cost of £3,314.55 per patient to account for terminal care when they entered the death state of the model. The end-of-life care cost was sourced from Brown *et al*. (2013)[41] and uprated to 2020/21 values. The company assumed that 27% of patients who died would not incur any terminal care costs.

Points for critique

The company's assumption that 27% of patients would incur no costs associated with terminal care appears to be partially derived from TA705 (atezolizumab in NSCLC), in which 27% of patients did not receive terminal care in hospital or a hospice, but instead at home. Terminal care at home in this appraisal was associated with community nursing, GP home visits, Macmillan nurses, and drugs and equipment, totalling £5,180.21 per patient. This omission significantly underestimates the costs of terminal care compared to previous appraisals in NSCLC, which in the case of TA812 were approximately double those in the present model.

The EAG therefore presents a scenario in Section 6 in which the terminal care costings from TA705 are implemented in full, with 27% of patients incurring a terminal care cost of £5,180.21, increasing the weighted cost of terminal care to £4,713.21 per patient.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

This section summarises the results of the company's updated base case as presented in the clarification response. The results presented in the following sections are inclusive of the PAS discounts for dabrafenib and trametinib unless otherwise stated. Results including commercial arrangements available for the pembrolizumab plus chemotherapy comparator treatment are provided in a confidential appendix to this report. The inclusion of the comparator PAS discounts has a material effect on the resulting ICERs and therefore the results presented below are purely illustrative.

5.1.1 Deterministic Results

The company presents in their submission a series of ICERs and NHBs for D&T versus pembrolizumab plus chemotherapy. The company presents the expected net health benefits (NHBs) at a willingness-to pay threshold of £20,000 and £30,000 per QALY gained.

The results of the company's cost-effectiveness analysis after application of the dabrafenib and trametinib PAS discount are summarised in Table 29. In the company's base-case, pembrolizumab plus chemotherapy was dominated. [redacted]. Given the assumed equivalence between D&T and pembrolizumab plus chemotherapy, incremental QALYs are driven entirely by AE disutilities, and the IV administration disutility applied to the pembrolizumab plus chemotherapy arm.

Table 29 Company base-case results: deterministic analysis (dabrafenib and trametinib PAS only)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	NHB (£20,000)
Pembrolizumab plus chemotherapy	[redacted]	[redacted]				
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.						

5.1.2 Probabilistic Results

The EAG requested several improvements to the model to more appropriately account for uncertainty in the probabilistic sensitivity analysis (PSA). In the amended model submitted in their clarification response, the company added the functionality to probabilistically vary a number of parameters comprising the modelling of treatment costs, subsequent therapies, healthcare resource use, and

adverse events. The company also disaggregated existing model parameters, including AE management costs, AE frequency and disutilities, and health state monitoring and follow-up resource use and costs, and varied them independently in the PSA. To more appropriately capture decision uncertainty the company were also asked to use source-derived standard error values where possible in the PSA, rather than simply varying all parameters by 10% of the mean.

The revised PSA was run with 2,000 iterations. The mean ICER and NHBs at threshold of £20,0000 and £30,000 for D&T compared to pembrolizumab plus chemotherapy is presented in Table 30, including relevant 95% confidence intervals. The results of the PSA show that D&T had a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY (Figure 8).

Table 30 Company base-case results: probabilistic analysis (dabrafenib and trametinib PAS only)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	NHB (£20,000) (95% CI)	NHB (£30,000) (95% CI)
Pembrolizumab plus chemotherapy	[redacted]	[redacted]					
Dabrafenib and trametinib	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; NHB, net health benefit.							

Figure 8 Cost-effectiveness acceptability curve for dabrafenib and trametinib versus pembrolizumab plus chemotherapy (generated from company's model)

Figure 9 shows that most model iterations produced results falling in the south-east quadrant, with a small number of simulation results falling in the north-east quadrant, meaning that the probability of D&T being the most cost-effective option never reaches 100% at thresholds up to £50,000.

Figure 9 Company base-case PSA scatter plot

5.2 Company's sensitivity analyses

The company presented a range of scenario analyses in the original submission. These scenarios had no material effect on costs or QALYs, with all scenarios ranging between incremental costs of [redacted], and incremental QALYs between [redacted]. These results are not replicated here, but can be found in Table 53 on Page 119 of the main company submission.

At the clarification stage, the EAG requested that the company present a number of scenarios which explored alternative assumptions and parameter inputs. The results of these analyses are presented in Table 31. The scenarios explored were as follows:

i. Integration of data from KEYNOTE-189 to model the efficacy of pembrolizumab with pemetrexed and platinum chemotherapy;
ii. Patients with PD-L1 expression ≥50% are treated with pembrolizumab monotherapy;
iii. OS and PFS benefits for those patients who receive immunotherapy or D&T as an additional line of therapy (implemented by adjusting the pembrolizumab plus chemotherapy arm, rather than the D&T arm);

iv. BRAF V600 testing costs were included, calculated as 1 divided by the incidence of the mutation in advanced NSCLC multiplied by the unit cost of adding a novel mutation to a NGS screening panel (£50).

Table 31 Company's additional scenario analysis (deterministic): dabrafenib and trametinib vs pembrolizumab plus chemotherapy (inclusive of dabrafenib and trametinib PAS)

Scenario description	Incremental costs	Incremental QALYs	ICER	NHB (£20,000)	NHB (£30,000)
Company submission base case	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Alternative efficacy assumptions: Clarification Questions B3, B4, and B5					
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT based on the FLATIRON RWE study (2022)	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Pembrolizumab plus chemotherapy PFS and OS data derived from KEYNOTE-189; ToT assumed to be equal to PFS	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Applying an OS HR of [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Assuming [redacted]% of patients who receive subsequent treatment after D&T receive immunotherapy and then applying an OS HR of [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Alternative comparator/subgroup assumptions: Clarification Question B6					
A subgroup of 33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy, and incur reduced costs to reflect this. The remaining patients are assumed to receive pembrolizumab plus chemotherapy.	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]
Inclusion of BRAF testing costs: Clarification Question B14					
Testing costs applied to 100% of patients receiving dabrafenib and trametinib	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; NHB, net health benefit

[a] Calculated as the average OS hazard rate from KEYNOTE-010,[30] OAK,[29] and CheckMate-057 and CheckMate-017[31] trials.

5.3 Model validation and face validity check

5.3.1 Validation undertaken by the company

The CS stated that the model structure was validated by an independent health economist, and underwent two further independent quality control and technical validation processes, including checking of model calculations and VBA macros. Checklists were completed based on TECH-VER to ensure results were consistent with inputs and were robust to extreme values. The outcomes of the model were also clinically validated to ensure the face validity of model predictions. The EAG notes

that these validation exercises are unlikely to have been replicated on the scenarios presented in the company's clarification response, in which alternative assumptions regarding the relative efficacy of D&T were adopted.

5.3.2 Internal validation undertaken by EAG

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Due to time constraints, only limited validation could be undertaken on the model scenarios presented by the company in their clarification response. No significant structural errors were identified in these checks, however, the EAG identified several issues with the parameterisation of the probabilistic analysis presented in the company submission. This comprised issues with both the omission of many parameters from the PSA, the aggregation of some parameters which were already included in the analysis (e.g., total costs were varied by 10%, rather than allowing component resource use and costs to vary independently), and the use of a 10% standard error for all parameters, rather than capturing the uncertainty observed in the source data. These issues were addressed by the company in the amended model submitted with the clarification response. However, this iteration of the model had further issues which resulted in errors being returned by the PSA macro. Whilst results could be generated, the model could not be used further without being restarted. This is an issue that must be resolved by the company at Technical Engagement.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the cost-effectiveness analysis presented by the company, which are discussed in detail in Section 4.

The following section presents a number of alternative scenarios in which s the EAG considers alternative approaches and assumptions. Given the high level of uncertainty associated with relative effectiveness of D&T, particular consideration has been given to this issue. These scenarios explore a range of alternative assumptions including the use of alternative data sources to model the effectiveness of pembrolizumab plus chemotherapy.

Descriptions of the EAG's exploratory analyses are provided in Section 6.1, and the degree of change on the ICERs and net health benefit compared to the company's base-case is explored in Section 6.2. As previously noted, there are a number of confidential commercial arrangements available for drugs comprising the comparator regimen, in addition to several subsequent therapies. These act in a number of different directions upon the cost-effectiveness outcomes presented at list price over the following sections, and thus the direction of change in costs between scenarios may not represent that

presented in the confidential appendix to this report. [redacted]

All results presented in Section 6.2 are replicated in the confidential appendix, inclusive of all confidential commercial arrangements available to NHS England.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The following scenarios include a number of those presented by the company in response to requests by the EAG. They are discussed in this section as they contribute the greatest uncertainty in the present appraisal, and are key areas for consideration by the committee. The three alternative approaches to modelling the efficacy of D&T are subject to a high degree of uncertainty.

1. KEYNOTE-189 used to model OS, PFS, and ToT for pembrolizumab plus chemotherapy

As discussed in Section 4.2.6, the EAG considered it plausible that a sequence of D&T followed by an IO (as occurred in BRF113928) will generate superior OS outcomes vs docetaxel-based regimens, which are the only option available following progression on pembrolizumab plus chemotherapy. Clinical advice to the EAG also suggested that there is reason to expect superiority of D&T over pembrolizumab plus chemotherapy in patients within the BRAF V600 population as D&T targets the oncogenic driver mutation. This scenario uses trial data from KEYNOTE-189 to inform the effectiveness of pembrolizumab plus chemotherapy using a Weibull curve for OS, and log-logistic for PFS and ToT, as in the analysis presented in the company's clarification response. This is implemented as an unanchored comparison. The EAG considers this to be a potentially informative way of modelling the relative efficacy of D&T and pembrolizumab plus chemotherapy given the absence of more directly appropriate data. The EAG notes that in previous appraisals without comparative trial data (e.g. TA812 and TA724), the committee has expressed a preference for comparator trial data over the use of observational cohorts.

2. Hazard ratios applied to OS to reflect reduced efficacy of post-pembrolizumab treatment options

This scenario applies an alternative approach to estimating the effectiveness of pembrolizumab plus chemotherapy and seeks to directly adjust available OS data to account for the availability of a second- line immunotherapy following D&T treatment. This scenario applies a pooled hazard ratio based on data from the OAK, KEYNOTE-010, and CheckMate-057/017 trials, which represent the treatment effect of pembrolizumab, atezolizumab, and nivolumab compared with docetaxel

respectively in previously treated patients. The inverse of this pooled hazard ratio is used to adjust OS on pembrolizumab plus chemotherapy (assumed to be clinically equivalent to D&T) following progression. This attempts to reflect poorer expected post-progression outcomes than were experienced in the BRF113928 trial and transposed onto pembrolizumab, as a proportion of patients in BRF113928 received immunotherapies following disease progression.

3. Discounting applied continuously from model outset

The company's base-case applied discounting only from the beginning of the second year of the model, and the discount coefficient was calculated using whole years elapsed, rather than being updated continuously. This approach can overestimate costs and benefits accrued over time, as the discount coefficient always lags behind time elapsed. This scenario applies a continuous approach in which the discount coefficient is updated every cycle.

4. All patients incur terminal care costs aligning with TA705

Terminal care costs in the company's base-case were based on TA705, which assumed 27% of patients received end-of-life care at home, which was costed accordingly. However, the company assumed no terminal care costs would be incurred for this proportion of patients, resulting in a significant under-estimate of per patient terminal care costs. This scenario brings the total terminal care costs applied in the model in line with TA705. The effect of this scenario is greater in combination with assumptions affecting relative OS effects between treatment arms.

5. Costs of testing for BRAF V600E mutations

The cost of adding BRAF V600 to next generation sequencing panels was confirmed by NHS England to be £34 per test. Accounting for a 2.5% incidence of the BRAF V600 mutation, this yields an additional per patient cost of £1,360. This is a commonly accepted practice in the appraisal of targeted therapies for which gene testing is not already in place for an established therapy. Whilst the EAG notes the provisional availability of D&T on the NHS means BRAF V600 testing is already in place, this represents a key component of the cost of treatment with this technology. As it would not be funded if D&T were not available, this cost incurred by the NHS is wholly attributable to D&T.

6. Cost of pharmacist dispensing time for oral therapies

The cost of dispensing each pack of oral medication was included for consistency with other appraisals of oral therapies in NSCLC. This was modelled as £10.80 per month, based on the cost of 12 minutes work for a Band 6 community-based scientific and professional staff member (PSSRU 2020). This assumed that D&T are always dispensed at the same time (unclear due to RDI

differences), and that this takes the same amount of pharmacist time as dispensing a single pack of medication.

7. Health state utilities based on TA812

As discussed in Section 4.2.7, the health state utilities adopted in the model have no impact on incremental QALY gain in the company's base-case analysis due to the assumption of clinical equivalence between treatment arms. However, the progression-free utility from Chouaid *et al*.[35] used in the model are markedly lower than that accepted across all recent appraisals in NSCLC. This scenario demonstrates the impact on total QALYs of the utilities adopted in TA812. This is particularly important when considering the relevance of the severity modifier in this population (see Section 7). This scenario also interacts with the scenarios 1 and 2, increasing the value of PFS gains on D&T modelled in these scenarios.

8. No disutility associated with IV infusion

As discussed in Section 4.2.7, the EAG does considers the disutility associated with IV administration to be implausibly large as it implies that the disutility associated with a 30-minute IV infusion every four weeks is larger than that applied for several adverse events requiring hospitalisation. This is likely a result of the TTO methodology which is not a reliable means of generating utility values comparable with EQ-5D weights. This approach is also inconsistent with the preferred approach described in the NICE reference case. This scenario removes this disutility from the model.

9. A proportion of PD-L1 ≥50% patients receive pembrolizumab monotherapy

Advice to the EAG suggested that a proportion of patients with high levels of PD-L1 expression may be treated with pembrolizumab monotherapy (as opposed to combination therapy). This scenario is as presented by the company at clarification and discussed in Section 4.2.3. The scenario assumes that 33.5% of eligible patients will have a PD-L1 expression score of ≥50%, and that 25% of this 33.5% will receive pembrolizumab monotherapy. Any differences in efficacy between pembrolizumab plus chemotherapy and pembrolizumab monotherapy are not captured in this analysis (due lack of appropriate data), which considers only the cost implications.

10. All subsequent therapies following D&T are an immunotherapy

As discussed in Section 4.2.8, the EAG considered there to be uncertainty regarding the distribution of subsequent therapies following progression on D&T in NHS practice. In the company's base-case analysis, 45% of the 56% of patients who proceed to a further line of therapy receive an immunotherapy, whilst the remainder receive chemotherapy. It is possible that all patients healthy

enough to continue treatment will first be offered an immunotherapy, as clinical experience and the evidence base expands in second-line populations with identified driver mutations.

The EAG explores the effect of a scenario in which all patients proceeding to a further line of treatment after D&T [redacted] receive an immunotherapy (evenly split between pembrolizumab, atezolizumab, and nivolumab).

11. All subsequent therapies following D&T are chemotherapy

As described in Scenario 10, the EAG also considers it plausible that uncertainties surrounding the effectiveness of immunotherapies in such patients will lead to fewer patients being offered second-line immunotherapies. This scenario explores the impact on cost-effectiveness of all patients continuing to a second-line therapy following progression receiving chemotherapy (pemetrexed plus carboplatin).

12. Wastage of D&T accounted for (50% RDI discount method)

The company base case assumes that missed doses of D&T will result in fewer packs being used, and doses unused at the point of progression will not go to waste. The EAG considers it likely that some drug wastage will be associated with dose adjustments, interruptions, and progression. This scenario assumes that only half of the cost-savings modelled for RDI adjustment are realised due to wastage. This approach is consistent with other appraisal of targeted therapies in NSCLC, and equates to the cost of wasting approximately half a pack of D&T.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the scenario analyses described in Section 6.1 are presented in Table #. These results include the agreed PAS discount for D&T only. [redacted] Net health benefit is presented at a willingness-to-pay threshold of £20,000, change in NHB from the company's base-case is also presented at £20,000. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 32 EAG Exploratory scenario analyses (deterministic)

Scenario	Technology	Total		Incremental			NHB (£20k)	NHB (£30k)	ΔNHB 30k
		Costs	QALYs	Costs	QALYs	ICER			
Company base-case	Pemb + chemo	[redacted]	[redacted]						
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. KEYNOTE-189 used to model pemb+chemo PFS/OS/ToT	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. HR applied to model effect of subsequent IO	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Discounting applied continuously from model outset	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. All patients incur terminal care costs (TA705)	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. BRAF testing costs included	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Pharmacist dispensing time for oral therapies	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Health state utilities based on TA812	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. No disutility associated with IV infusion	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Proportion of PD-L1 ≥50% patients on pembrolizumab monotherapy	Pemb + chemo/Pemb mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. All subsequent therapies on D&T are IO	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11. All subsequent therapies on D&T are chemo	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pemb + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12. D&T wastage (50% RDI discount method)	D&T	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 EAG's preferred assumptions

The EAG presents two combinations of the above scenarios in Table 33 and Table 34 below. These scenario analyses comprise the EAG's preferred assumptions with two approaches to modelling the relative efficacy of D&T and pembrolizumab plus chemotherapy. The EAG's preferred assumptions primarily comprise relatively minor changes to resource use and cost assumptions, in the interest of alignment with previous appraisals. In Table 33, the cumulative impact of the EAG's preferred assumptions under clinical equivalence is presented, per the company's base-case analysis. Table 34 presents an analysis in which KEYNOTE-189 trial data is used directly to model PFS, OS, and ToT for pembrolizumab plus chemotherapy, i.e. Scenario 1 in Table 32 above.

The EAG base-case adopts the following scenarios described in Section 6.1:

Scenario 3: Discounting applied continuously from model outset
Scenario 4: All patients incur terminal care costs in line with TA705
Scenario 6: Cost of pharmacist dispensing time for oral therapies included
Scenario 7: Health state utilities based on TA812
Scenario 8: No disutility associated with IV infusion
Scenario 12: Wastage of D&T accounted for (50% RDI discount method)

Table 33 EAG's preferred model assumptions (clinical equivalence) (deterministic)

Preferred assumption	Section in EA Report	Cumulative ICER £/QALY	Cumulative NHB (£20,000)	Cumulative NHB (£30,000)
Company base-case		D&T Dominant	[redacted]	[redacted]
Scenario 3: Discounting applied continuously from model outset	*4.2.5*	D&T Dominant	[redacted]	[redacted]
Scenario 4: All patients incur terminal care costs in line with TA705	*4.2.8*	D&T Dominant	[redacted]	[redacted]
Scenario 6: Cost of pharmacist dispensing time for oral therapies included	*4.2.8*	D&T Dominant	[redacted]	[redacted]
Scenario 7: Health state utilities based on TA812	*4.2.7*	D&T Dominant	[redacted]	[redacted]
Scenario 8: No disutility associated with IV infusion	*4.2.7*	D&T Dominant	[redacted]	[redacted]
Scenario 12: Wastage of D&T accounted for (50% RDI discount method)	*4.2.8*	D&T Dominant	[redacted]	[redacted]

Table 34 EAG's preferred model assumptions (KEYNOTE-189 pembrolizumab data) (deterministic)

Preferred assumption	Section in EA Report	Cumulative ICER £/QALY	Cumulative NHB (£20,000)	Cumulative NHB (£30,000)
Company base-case		D&T Dominant	[redacted]	[redacted]
Scenario 1: KEYNOTE-189 used to model pembro PFS/OS/ToT	*4.2.6*	D&T Dominant	[redacted]	[redacted]
Scenario 3: Discounting applied continuously from model outset	*4.2.5*	D&T Dominant	[redacted]	[redacted]
Scenario 4: All patients incur terminal care costs in line with TA705	*4.2.8*	D&T Dominant	[redacted]	[redacted]
Scenario 6: Cost of pharmacist dispensing time for oral therapies included	*4.2.8*	D&T Dominant	[redacted]	[redacted]
Scenario 7: Health state utilities based on TA812	*4.2.7*	D&T Dominant	[redacted]	[redacted]
Scenario 8: No disutility associated with IV infusion	*4.2.7*	D&T Dominant	[redacted]	[redacted]
Scenario 12: Wastage of D&T accounted for (50% RDI discount method)	*4.2.8*	D&T Dominant	[redacted]	[redacted]

Probabilistic results for the two EAG alternative base-case scenarios are presented in Table 35. In each case, the model was set to the EAG's preferred assumptions and run with 5,000 iterations. In both EAG base-case analyses, D&T remained dominant over pembrolizumab plus chemotherapy, generating more QALYs at a lower cost. In the first scenario in which clinical equivalence was assumed, D&T had a [redacted] probability of being cost-effective versus pembrolizumab plus chemotherapy at a WTP threshold of £30,000, and a [redacted] probability at £20,000.

In the second scenario in which KEYNOTE-189 data were used to model the efficacy of pembrolizumab plus chemotherapy, D&T had probabilities of [redacted] and [redacted] of being cost-effective at WTP thresholds of £30,000 and £20,000 respectively. NHB on D&T is higher at the lower WTP threshold because it is cost-saving versus pembrolizumab. The cost-effectiveness plane for this analysis is presented in Table 35.

The EAG notes that the inclusion of all commercial arrangements for the components of the comparator regimen, and other subsequent therapy options has a substantive effect on cost-effectiveness estimates for D&T. Equivalent results including all available commercial arrangements are provided in the confidential appendix to this report.

Table 35 EAG's alternative base-case analysis results (probabilistic)

Scenario	Technology	Total		Incremental			NHB (£20k) (95% CI)	Δ
		Costs	QALYs	Costs	QALYs	ICER		
Company base-case	Pemb + chemo	[redacted]	[redacted]					

	D&T	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
EAG base-case scenario 1: Clinical equivalence (Scenarios 3, 4, 6, 7, 8, 12)	Pemb + chemo	[redacted]	[redacted]	[redacted]				
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
EAG base-case scenario 2: Pemb + chemo uses KEYNOTE-189 (Scenarios 1, 3, 4, 6, 7, 8, 12)	Pemb + chemo	[redacted]	[redacted]	[redacted]				
	D&T	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Figure 10 EAG base-case scenario 1/2 cost-effectiveness plane

[redacted]

Figure 11 EAG base-case scenario 2/2 (KEYNOTE-189) cost-effectiveness plane

6.4 Conclusions of the cost effectiveness section

The company submitted a *de novo* economic analysis to assess the cost-effectiveness of D&T compared to pembrolizumab plus chemotherapy for the treatment of untreated advanced non-small-cell lung cancer with a BRAF V600 mutation. The company's model comprised three health states (progression free, progressed disease, and death) in the form of a partitioned survival model. The company's base-case analysis assumed clinical equivalence of the two treatment options, based on data from the single-arm BRF113928 trial of D&T. A small incremental QALY benefit was generated for D&T in the company's base-case analysis, mainly driven by the disutilities modelled to account for the burden of IV administration associated with pembrolizumab plus chemotherapy. Analyses were presented in the company's clarification response which explored the use of the pembrolizumab plus chemotherapy arm from the KEYNOTE-189 trial to model the effectiveness of pembrolizumab plus chemotherapy. A second analysis in which a hazard ratio derived from second-line trials of immunotherapies was used to 'remove' the post-progression OS benefits attributable to second-line immunotherapies following D&T, which were ascribed to pembrolizumab due to the assumption of clinical equivalence, despite these treatment options not being available to these patients on the NHS.

The company's base-case analysis suggested that D&T are a less costly and (marginally) more effective treatment option compared to pembrolizumab plus chemotherapy, with a probabilistic net health benefit of [redacted] at a willingness-to-pay threshold of £20,000 and £30,000 respectively. Dabrafenib and trametinib had a very high likelihood of being the most cost-effective treatment option at willingness-to-pay thresholds of

£20,000 and £30,000 per QALY. These results were based on the net price of dabrafenib and trametinib inclusive of patient access schemes for both components, but are exclusive of available confidential pricing arrangements for components of the comparator regimen, and a number of subsequent therapies.

6.4.1 Conclusions of the EAG's critique

The EAG's review of the company's evidence submission and executable model identified several areas of uncertainty, which the EAG has sought to highlight, and address where possible in the presented scenario analyses and revised base-case analyses.

The primary area of uncertainty relates to the company's assumption of clinical equivalence between the two treatment options considered in the base-case analysis. There are important differences in the treatment sequences implied in the model and underlying trial data, and clinical advice suggests a potential benefit of D&T over pembrolizumab plus chemotherapy. The EAG therefore consider it plausible that D&T followed by an immunotherapy could generate improved outcomes versus pembrolizumab plus chemotherapy followed by a docetaxel-based regimen, per NHS practice. The analysis presented by the company in which KEYNOTE-189 is used to model PFS, OS, and ToT outcomes for the pembrolizumab plus chemotherapy arm represents a plausible alternative approach. However, the usual caveats associated with an unanchored comparison between trials apply, along with the uncertainty generated by this comparison between BRAF mutation positive and wild-type populations, and unblinded and blinded outcome assessments. Importantly, the uncertainty associated with this comparison is fully not captured within the probabilistic sensitivity analysis and therefore such analysis is likely to underestimate the decision uncertainty.

The EAG is concerned that the model does not fully address the population described in the decision problem. Approximately [redacted] of patients are currently treated with pembrolizumab plus chemotherapy at first-line, despite the availability of D&T due to delays in the reporting of genetic testing results. The company stated a belief that improvements in NGS infrastructure in the UK would mean this population would disappear in the near future, and thus the cost-effectiveness of D&T following progression on pembrolizumab was not relevant to the decision problem. However, the EAG considers there to be a high likelihood that patients will continue to be treated with D&T following pembrolizumab for some time. It is therefore important that if the company expect a recommendation in the full population, the cost-effectiveness of D&T in a treatment sequence of which pembrolizumab plus chemotherapy followed by D&T followed by a docetaxel regimen is compared to pembrolizumab plus chemotherapy followed by a docetaxel regimen.

The EAG also noted several concerns regarding the modelling of health-related quality of life. Under the assumption of clinical equivalence, the health-state utility value set applied in the model had no

effect upon incremental outcomes, and thus the effects of alternative sources of HRQoL data were not explored by the company. However, the EAG noted in particular that the utility of patients in the progression-free health state was markedly lower than that accepted in previous appraisals in NSCLC. This serves firstly to under-value benefits associated with preventing disease progression, but also underestimates total standard of care QALYs in the calculation of QALY shortfall. The EAG was also concerned with the source and magnitude of the disutility applied by the company to the comparator arm to capture the effect of monthly IV infusions on HRQoL. The disutility was derived from time trade-off interviews with unaffected members of the general public. This methodology cannot generate utilities which are compatible with the NICE reference case, and can be thought of as measuring quality of life on a different scale to EQ-5D. This results in an internally inconsistent disutility, where the effect of a monthly 30-minute IV infusion is assumed to have twice the effect on health-related quality of life as being hospitalised for pneumonia. The EAG considers it appropriate to remove this disutility from the model in its entirety.

The company base-case omitted the cost of BRAF V600 testing and reporting, stating that it is already included in the Genomic Testing Directory. The EAG highlighted that BRAF testing is already included in NSCLC screening only due to availability of dabrafenib on the NHS via interim Covid-19 guidelines. As testing for BRAF mutations is funded on the basis of availability of D&T, testing costs are integral and exclusive to D&T, and thus should be included for consistency with appraisals of other targeted therapies.

The EAG considered the calculation of costs and resource use in the model to be broadly appropriate, but noted several inconsistencies with previous appraisals. The modelling of wastage was appropriate for the comparator and subsequent therapies, but the EAG preferred a scenario in which only half of the cost savings associated with RDI would be realised, equating to approximately half a pack of wastage per patient for each drug. The EAG also identified two other minor omissions from the company's resource calculations on the basis of consistency with previous appraisals.

The impact of these uncertainties was considered in a series of exploratory analyses. The assumptions with the largest impact upon the cost-effectiveness of D&T included use of KEYNOTE-189 to model PFS, OS, and ToT of pembrolizumab plus chemotherapy, the inclusion of genetic testing costs, the distribution of subsequent therapies, and the inclusion of wastage of D&T. The EAG produced two alternative base-case analyses, the first assumed clinical equivalence, and the second used KEYNOTE-189 data for the pembrolizumab arm. Using only the PAS discounts available for D&T, D&T was dominant over pembrolizumab plus chemotherapy in both alternative EAG base-case analyses. The EAG notes that the inclusion of available commercial arrangements for the other drugs used in the model has a substantial effect on estimates of the cost-effectiveness of D&T.

7 SEVERITY MODIFIER

The company undertook a QALY shortfall analysis by calculating the expected quality-adjusted life expectancy (QALE) for the general population, in line with methods described by Schneider *et al.* (2022).[42] Life expectancy for the modelled population was calculated using ONS population mortality data from 2018-2020 and did not account for specific patient characteristics associated with this population other than age and sex mix. Life expectancy was quality-adjusted using UK population norm values as reported by Hernández Alava *et al*. (2022).[36]

The company assumed that the total QALYs for the previously untreated advanced NSCLC population with a BRAF V600 mutation was equal to the total QALYs associated with pembrolizumab plus chemotherapy in the base-case analysis. The results of the company's QALY shortfall analysis are presented in Table 36, along with the values generated in the EAG base-case. The absolute and proportional QALY shortfall associated with the condition fell below the threshold of 12 and 0.85 respectively, for the use of a severity modifier of 1.2. Therefore, the company applied a severity modifier of 1 in the base-case results.

Table 36 Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs achieved on SoC in population with BRAF V600+ NSCLC	Absolute QALY shortfall	Proportional QALY Shortfall
Company base-case			
9.871	[redacted]	[redacted]	[redacted]
EAG base-case 2 (KEYNOTE-189 comparison)			
9.871	[redacted]	[redacted]	[redacted]

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Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 3 November 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Corrections

Issue 1 Clarification regarding the patients included the BRF113928 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 1 (Key Issue ID 4) – Page 9, the EAG states: "Uncertainty about the applicability of the results of trial BRF113928 to the NHS setting. [redacted] of patients who received the combination therapy (dabrafenib and trametinib) in BRF113928 had not met the trial eligibility criteria. The company did not provide any detailed data to allay concerns about this, nor could they provide basic data on the number of patients screened, the number excluded and why patients were excluded."	It is proposed that this sentence is amended as follows: "Uncertainty about the applicability of the results of trial BRF113928 to the NHS setting. [redacted] of patients who received the combination therapy (dabrafenib and trametinib) in BRF113928 **had protocol deviations that meant they** did not meet the trial eligibility criteria. The company **were unable to ~~did not~~** provide **~~any detailed data to allay concerns about this, nor could they provide basic~~** data on the **overall** number of patients screened, the number excluded and why patients were excluded.**"**	The Company was not explicitly asked at the Clarification Question stage to comment on the [redacted] of patients who received the combination therapy (dabrafenib and trametinib) in BRF113928 had not met the trial eligibility criteria. It is therefore inaccurate to report that the Company did not provide any detailed data to allay concerns about this, as this concern was not previously raised to the Company. With the greater clarity on the EAG's query provided as part of their report, further clarification regarding this [redacted] of patients will be provided as part of the Technical Engagement phase as	This is clarified in the more detailed section on Key Issue 4. However, for this summary section the text has been amended to: [redacted] of patients who received the combination therapy (dabrafenib and trametinib) in BRF113928 had protocol deviations that meant they had not met the trial eligibility criteria. The clinical study report did not provide any detailed data to allay concerns about this, and the company could not provide basic data on the number of patients screened, the number

		Novartis do have this information.	excluded and why patients were excluded.

Issue 2 Second-line evidence for dabrafenib with trametinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The heading for Issue 1 on Page 11 states: "No evidence presented for second-line use of dabrafenib with trametinib"	The heading for Issue 1 on Page 11 should be amended to "~~No evidence presented for~~ Second-line use of dabrafenib with trametinib", The wording related to this issue should include sufficient clarity that "**Whilst second-line data for D&T are available from the BRF113928 trial, it was not considered feasible to conduct an economic comparison for the second-line use of dabrafenib with trametinib for multiple reasons as detailed in the Company Submission.**"	It is important to accurately reflect that the Company did present second-line clinical evidence for D&T from the BRF113928 trial within the Company Submission, as well as potential comparative efficacy evidence between D&T and the relevant second-line comparators within the Company Submission appendices. However, after assessing the feasibility of including second-line data for both D&T and the relevant comparators within the economic model, it was not considered feasible for a number of reasons, as detailed within the Company Submission. It is important	The heading has been amended to reflect that this is issue relates to the cost-effectiveness evidence presented. The wording of the issue has been amended to acknowledge the presentation of second-line data in the submission.

		that the EAG report reflects this position. We regard this as being very different from not presenting any evidence or discussion relating to the second-line positioning of D&T.	

Issue 3 Classification of the NSCLC patient population in KEYNOTE-189 as "wild-type"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In several instances the NSCLC patient population from the KEYNOTE-189 trial are referred to as "wild-type": Section 4.2.6 – Page 47: *"Importantly, they also consider a wild type rather than BRAF V600E specific population."* Section 4.2.6 – Table 16 – Page 48:	Given the patient population included in the KEYNOTE-189 trial was one where BRAF genetic testing was not conducted, it is considered inaccurate to refer to this population as a fully "wild-type" patient population. In line with the terminology used in our response to Clarification Question B4, it is proposed that all references to the KEYNOTE-189 patient population are updated to "**an all-comer population (aside from the exclusion of patients with an ALK or EGFR mutation)**" and include reference to the fact that the population was one **"where BRAF genetic testing was not conducted; while it is likely that the vast majority of these patients would have wild-type**	The Company would like to clarify to the EAG that the patient population in KEYNOTE-189 was an all-comer population (aside from the exclusion of patients with an ALK or EGFR mutation) and where genetic testing for the BRAF mutation was not undertaken for each patient. It is proposed that the text relating to KEYNOTE-189 is updated accordingly for accuracy.	All references to the KEYNOTE-189 population have been amended to 'all-comer', with the caveat that this excluded ALK and EGFR mutations.

"KEYNOTE-189 is a wildtype rather than BRAF V600E specific population;" Section 4.2.6 – Page 49: *"The EAG notes that KEYNOTE-189 recruited a wild-type NSCLC population, in whom it might be expected that outcomes on pembrolizumab may be more favourable"* Section 4.2.6.2 – Page 55: *"It is also plausible that in using the wild-type KEYNOTE-189 population without adjustment"*	**NSCLC, the genetic status of each of these patients cannot be determined with certainty".**		

Issue 4 Appropriate labelling of results in Table 2 and Table 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2 and Table 3 – Page 17 It is unclear from the labelling of these tables whether the reported ICERs and NHB values	If the company's understanding is correct, the reported ICERs and NHB values are the cumulative values from Tables 33 and 34, **the labelling of the "ICER" and "NHB" columns**	The derivation of all reported ICERs and NHB values should be clearly stated.	Table labelling amended to reflect cumulative impact of scenarios included in base-case.

are results from each scenario analysis conducted separately or cumulatively.	**should be updated to include a mention of these being cumulative.**		

Issue 5 Clarification of curve choice changes for the EAG exploratory Scenario 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1 – Page 77 Under the EAG's first exploratory analysis titled, *"1. KEYNOTE-189 used to model OS, PFS, and ToT for pembrolizumab plus chemotherapy",* the EAG do not explicitly state the changes made to the curve selection choices for OS, PFS and ToT for pembrolizumab plus chemotherapy, compared with the same scenario analysis conducted by the Company as part of the Clarification Questions response.	For clarity, the following curve choices should be explicitly mentioned within the EAG report when describing this scenario analysis: • **OS: Weibull** • **PFS: LogLogistic** • **ToT: LogLogistic**	The Company acknowledges that the EAG have considered alternative curve choices to model KEYNOTE-189 that those used by the Company as part of Clarification Question B4. The Company will provide further comments on the most appropriate curve choices for this scenario analysis as part of the Technical Engagement phase, however, for clarity, the Company would request that the EAG's preferred curve choices be detailed within this section, to clearly distinguish between the Company and EAG's preferred KEYNOTE-189 scenarios.	The EAG did not make changes to curve selection. In the EA Report it was stated where appropriate that the curves selected by the company in their clarification response were appropriate. The EAG implemented the KEYNOTE-189 trial data in the same manner as the company in the exploratory analysis presented in the report, and in the updated base-case in which KEYNOTE-189 data were used to model pembrolizumab plus chemotherapy. The description of this scenario in Section 6.1 of the EAR has been updated to make it clear that the

			company's curve selections are preserved.

Issue 6 Description of utility decrements source

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.2 – Page 60 Under "Points for Critique" the report states: "The EAG notes that the utility decrements and durations are primarily sourced from TA789 rather than from EQ-5D data collected in the D&T trial as recommended by the NICE reference case."	This should be corrected along the lines of: "The EAG notes that the utility decrements and durations are primarily sourced from TA789 rather than from EQ-5D data **as recommended by the NICE reference case, as EQ-5D data were not collected in the D&T trial."**	The current wording in the EAG report suggests that EQ-5D data were collected as part of the D&T trial but were then not used to inform utility decrements and durations. It is therefore suggested that this sentence is updated for clarity.	Text amended to '…EQ-5D data collected from the pivotal trial as recommended by the NICE reference case, as EQ-5D data were not collected in the D&T trial'.

Issue 7 Errors in PFS extrapolation results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 17 in Section 4.2.6.1 – Page 49 Table 17 includes incorrect values. [redacted]	Table 17 should be corrected in line with the values presented below: [redacted]	Incorrect reporting of data.	Thank you for highlighting this error, the table has been amended.

Issue 8 Errors in PFS extrapolation results (based on KEYNOTE-189 data)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 18 in Section 4.2.6.1 – Page 51 Table 18 includes an error in the 10-year survival estimate when using the Generalised Gamma extrapolation. The value is reported as "[redacted]".	This should be corrected to: "[redacted]".	Incorrect reporting of data (rounding error).	Thank you for highlighting this error, the table has been amended.

Issue 9 Errors in OS extrapolation results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19 in Section 4.2.6.2 – Page 52 Table 19 includes incorrect values. [redacted]	Table 19 should be corrected in line with the values presented below: [redacted]	Incorrect reporting of data (rounding error).	Table amended.

Issue 10 Errors in OS extrapolation results (based on KEYNOTE-189 data)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 20 in Section 4.2.6.2 – Page 53 Table 20 includes an error in the 1-year survival estimate for pembrolizumab plus chemotherapy using the exponential extrapolation. The value is currently reported as "[redacted]".	This should be corrected to: "[redacted]" as presented in the company model.	Incorrect reporting of data (rounding error).	Table amended.

Issue 11 Application of HRs in Company scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2.1 – Page 40 With regards to the use of a weighted average HR in scenarios explored in response to clarification question 3b, the EAG report states: "The HR could not be selectively applied to patients, so instead a weighted average was used, with a HR of 1.0 applied to 74.8% of patients, an incremental treatment benefit applied to the remaining 25.2%."	This should be corrected to: "**As it is not possible to selectively apply a HR to certain patients within a partitioned-survival model, a weighted average HR was applied to all patients, which was derived by assuming that** a HR of 1.0 applied to 74.8% of patients and an incremental treatment benefit, based on a selection of HRs detailed below, was applied to the remaining 25.2%."	The wording presented in the EAG report could be interpreted to suggest that a HR of 1.0 was selectively applied to some patients. The Company suggests that the revised wording more clearly reflects that a weighted average HR is applied to all patients, clearly detailing how this has been derived.	Wording has been clarified in line with the company's suggestions.

Typographical errors

Issue 12 Missing "£" signs in Tables 2 and Table 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2 and Table 3 – Page 17 to 18 There are several instances of missing "£" and "-" signs (for negative incremental costs) across both tables.	For clarity, please could the EAG ensure that **all monetary values in these tables are labelled with a preceding "£" and "-"signs (for negative incremental costs).**	Typographical omissions.	Thank you for highlighting these typographical errors, amendments have been made accordingly.

Issue 13 Labelling of Figure 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Figure 5 in Section 4.2.6.2 – Page 54 Figure 5 has been labelled incorrectly as *"Comparison of OS extrapolations – dabrafenib with trametinib (based on company's economic model)" which is also the label for Figure 4 on Page 53.*	The label for Figure 5 should be corrected to: "Comparison of OS extrapolations – **pembrolizumab plus chemotherapy (based on KEYNOTE-189 data)**"	Incorrect reporting of data.	Thanks for highlighting this, the EA Report has been amended.

Issue 14 Minor typographical error in author name

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2 – Page 32–33 "update of Kanakmedala et al. 2020"	This should be corrected to: "update of **Kanakamedala** et al. 2020"	Typographical error.	Three instances of this error have been corrected in the EA Report.

Issue 15 Typographical errors in Table 31

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 31 – Section 5.2 – Page 75 Several scenario analyses are incorrectly classified under "Alternative efficacy assumptions: Clarification Questions B4 and B5"	• Scenario analysis in Row 6: *"33.5% of patients are assumed to have PD-L1 ≥50%, and of these, 25% are assumed to receive pembrolizumab monotherapy."* **is a duplicate of the scenario B6a included in Row 10 of the same table so should be removed.** • Scenario analysis in Row 7: *"Applying an OS HR of 1.48a) to 25.2% of patients receiving pembrolizumab plus chemotherapy for five years"* **should be labelled as relating to Clarification Question B3.**	Typographical errors.	Thank you, amendments made.

	• Scenario in Row 8: *"Assuming 33.6% of patients who receive subsequent treatment after D&T receive immunotherapy and then applying an OS HR of 1.48a) to 33.6% of patients receiving pembrolizumab plus chemotherapy for five years"* **should be labelled as relating to Clarification Question B3.**		

Confidentiality highlighting corrections

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG Report – Section 1.5 – Page 14	The following commercial-in-confidence (CiC) data is currently unmarked: *"The use of literature-derived hazard ratios to adjust OS reduces total QALYs accrued on pembrolizumab plus chemotherapy by [CiC data]."*	*"The use of literature-derived hazard ratios to adjust OS reduces total QALYs accrued on pembrolizumab plus chemotherapy by* [redacted]*."*	Amended.
EAG Report – Section 3.2.1.3 – 3.2.1.4 – Pages 27 to 29	In several instances in the sections mentioned, data from the clinical study report (CSR) is marked as CiC but should instead be highlighted as academic-in-confidence (AiC).	All data reported from the CSR that are not as of yet published should be marked as AiC not CiC.	Amended

EAG Report – Section 3.2.1.5 –Page 30	The following data are from the BRF113928 trial CSR and are as of yet unpublished. They should therefore be marked as AiC: *"The most frequently observed AE was pyrexia (56%), which led to a dose reduction in [AiC data]."*	*The most frequently observed AE was pyrexia (56%), which led to a dose reduction in [redacted] patients ([redacted]) and treatment withdrawal in [redacted] patients ([redacted]).*	Amended.
EAG Report – Section 3.2.2 – Page 32	The following data are from FLATIRON RWE study (2022) and are as of yet unpublished. They should therefore be marked as AiC: *"([AiC data] compared to [AiC data])"*	*"([redacted]% compared to [redacted]%)"*	Amended.
EAG Report – Section 3.2.2 – Page 32-33	The following data are from the FLATIRON RWE study (2021), forming the basis of the Melosky et al. 2021 study, but are as of yet unpublished. They should therefore be marked as AiC: *"After the data had been weighted, the baseline characteristics for pembrolizumab plus chemotherapy compared to dabrafenib plus trametinib were similar except for initial stage of diagnosis, where more patients where at Stage IV in the pembrolizumab plus chemotherapy*	*"After the data had been weighted, the baseline characteristics for pembrolizumab plus chemotherapy compared to dabrafenib plus trametinib were similar except for initial stage of diagnosis, where more patients where at Stage IV in the pembrolizumab plus chemotherapy arm ([redacted]%) compared to the dabrafenib plus trametinib arm ([redacted]%). There were no patients at Stage II-III in the pembrolizumab plus chemotherapy arm compared to [redacted]% and [redacted]% respectively in the dabrafenib plus trametinib arm. Few patients were at stage I in both arms ([redacted]%*	Amended.

	arm ([AiC data]) compared to the dabrafenib plus trametinib arm ([AiC data]) . There were no patients at Stage II-III in the pembrolizumab plus chemotherapy arm compared to ([AiC data]) and ([AiC data]) respectively in the dabrafenib plus trametinib arm. Few patients were at stage I in both arms ([AiC data] dabrafenib plus trametinib arm compared to [AiC data] pembrolizumab plus chemotherapy arm).”	*dabrafenib plus trametinib arm compared to [redacted]% pembrolizumab plus chemotherapy arm).”*	
EAG Report – Section 3.2.2.2 – Page 34	The following data are from the FLATIRON RWE study (2022) and are as of yet unpublished. They should therefore be marked as AiC: *“(HR [AiC data] (95% CI: [AiC data]), Table 15 of the CS). In addition, [AiC data] of patients in pembrolizumab plus chemotherapy cohort were only followed up for 12 months or less due to treatment initiation in 2021. The issue of follow up applies to OS as well and again the HR in the weighted analysis has wide CIs including one (HR [AiC data] (95% CI: [AiC data]), Table 16 of the CS).”*	*“(HR [redacted] (95% CI: [redacted], [redacted]), Table 15 of the CS). In addition, [redacted] of patients in pembrolizumab plus chemotherapy cohort were only followed up for 12 months or less due to treatment initiation in 2021. The issue of follow up applies to OS as well and again the HR in the weighted analysis has wide CIs including one (HR [redacted] (95% CI: [redacted], [redacted]), Table 16 of the CS).”*	Amended.

EAG Report – Section 4.2.6.2 – Page 52	The following data are from the Company's analysis of survival data and are as of yet unpublished. They should therefore be marked as AiC: *"In addition, the difference in AIC between the best fit curve (log-normal) and the worst fit (Weibull) is [AiC data], a negligible difference in statistical fits."*	*"In addition, the difference in AIC between the best fit curve (log-normal) and the worst fit (Weibull) is [redacted], a negligible difference in statistical fits."*	Amended.
EAG Report – Section 4.2.6.2 – Page 52	The following data are from the BRF113928 and are as of yet unpublished. They should therefore be marked as AiC: *"Data for OS available from the BRF113928 trial was relatively mature, with [AiC data] years of follow up"*	*"Data for OS available from the BRF113928 trial was relatively mature, with [redacted] years of follow up"*	Amended.
EAG Report – Section 4.2.7.4 – Page 60	The following data has been marked as AiC but as this value is in the public domain, the confidentiality highlighting can be removed: *"company applied an annualised disutility of [redacted] for infusion administration"*	*"…company applied an annualised disutility of -0.023 for infusion administration…"*	Amended in two instances.

EAG Report – Section 5.2 – Page 75 – Table 31	Hazard ratios and drug utilisation rates for certain scenarios in Table 31 are as of yet unpublished and should therefore be marked as AiC. *"Applying an OS HR of [AiC data] to [AiC data] of patients receiving pembrolizumab plus chemotherapy for five years"* AND *"Assuming [AiC data] of patients who receive subsequent treatment after D&T receive immunotherapy and then applying an OS HR of [AiC data] to [AiC data] of patients receiving pembrolizumab plus chemotherapy for five years."*	*"Applying an OS HR of [redacted] to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years"* *AND* *"Assuming [redacted]% of patients who receive subsequent treatment after D&T receive immunotherapy and then applying an OS HR of [redacted] to [redacted]% of patients receiving pembrolizumab plus chemotherapy for five years."*	Amended.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the Company involved in this appraisal, please complete the 'Summary of changes to the Company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **13th December 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: No evidence presented for second-line use of dabrafenib with trametinib *Is dabrafenib with trametinib also likely to be used second line after pembrolizumab with chemotherapy?*	Yes (new data; Appendix 6)	**The Company is of the view that dabrafenib and trametinib (D&T) will be used upfront as a first-line treatment for patients harbouring a BRAF mutation. Comparative effectiveness data in the second-line setting are only available from an observational data set of a very small sample size, and which included chemotherapy regimens not reflective of UK clinical practice. Cost-effectiveness modelling of D&T versus chemotherapy in the second-line is not feasible, given the limitations and uncertainty associated with the comparative data set.** The External Assessment Group (EAG) highlights in their report that the company submission (CS) and the associated cost-effectiveness model did not adequately address the population described in the decision problem due to absence of a cost-effectiveness comparison for the use of D&T as a second-line therapy following the receipt of pembrolizumab in combination with chemotherapy (pembro-chemo) as a first-line treatment option. As described in the CS, the second-line population is a small (but clinically important) minority of patients eligible for D&T and is expected to diminish over time. An updated analysis of BlueTeq prescribing data for D&T in NSCLC (additional six months of follow-up data vs. that presented in CS) shows the majority of patients received D&T as a first-line treatment option (Appendix 6). The Company therefore remains of the view that the use of second-line D&T is in patients who have experienced a delay in receiving their testing results, and this should improve as turnaround times for testing continue to improve in line with the implementation of the Genomic Hubs strategy and a patient's mutation status is increasingly known at time

of the first treatment decision. This view is also supported by feedback from clinical experts consulted by Novartis.

Robust evidence on the use of chemotherapy following pembro-chemo in NSCLC patients harbouring a BRAF mutation is limited. As described in Section B.2.1 of the CS, a systematic literature review (SLR) was performed to identify any studies relevant to the target treatment population: no suitably robust studies were identified, with many omitting key baseline characteristics and/or being carried out in very small patient populations. The only suitable efficacy data for the second-line use of chemotherapy in the target patient population were derived from real world evidence (RWE) data from the FLATIRON database (the FLATIRON RWE study [2022]). However, as presented in Appendix D.3.2.5 of the CS, the sample size for the second-line chemotherapy population in the FLATIRON study was extremely small ([redacted] for patients with a BRAF V600E mutation), was associated with limited follow up, and [redacted] of these patients received either docetaxel monotherapy or docetaxel plus nintedanib, the two most relevant chemotherapy regimens in UK clinical practice. These data are therefore associated with limitations too great to inform cost-effectiveness analyses.

In response to the EAG's request, a summary of the hazard ratios (HRs) resulting from the comparative clinical data between second-line D&T and chemotherapy for patients harbouring the BRAF V600E population are presented in Table 3. Full results are presented in Appendix 4 of this response (also in Appendix D.3.2.5 [Page 157] of the CS and Appendix 5).

Table 3: HR's for patients receiving D&T (BRF113928 Cohort B) versus patients receiving chemotherapy in the FLATIRON RWE study (2022)

	Chemotherapy (weighted) BRAF V600E population
HR for PFS (95% CI) for D&T versus chemotherapy	[redacted]
P-value for HR	[redacted]
HR for OS (95% CI) for D&T versus chemotherapy	[redacted]

		P-value for HR | [redacted] **Abbreviations:** CI: confidence interval; D&T: dabrafenib and trametinib; HR: hazard ratio; PFS: progression-free survival; OS: overall survival; RWE: real-world evidence.
Key issue 2: Risk-benefit considerations of using an oral therapy *Are there any drawbacks to an oral therapy? Could adherence to treatment be lower than for intravenous therapies (e.g forgetting to take a dose)?*	No	**The Company does not consider there to be to drawbacks to an oral therapy and it would not be appropriate to conduct the scenarios requested in this Key Issue.** The EAG notes that a proportion of patients receiving D&T deviated from the BRF113928 study protocol due to treatment non-compliance. D&T are administered orally and as such the EAG suggested that the Company present a scenario in which the disadvantages of oral therapies are explored, using oral therapy non-compliance as a proxy measure. The Company would like to note that non-compliance in the BRF113928 trial was mostly in the form of dose reductions, interruptions, or escalations. Adverse events (AEs) were the most common reason for a subject requiring a dose reduction, and most of the trial participants required only one dose reduction for both dabrafenib and trametinib. Dose interruptions were also common, with [redacted]% of trial participants experiencing a duration between [redacted] days. During the technical engagement process, the Company consulted with a clinician with experience treating lung and melanoma patients, who noted that 1 in 3 patients will need a dose reduction and/or interruption for the optimal management of AEs and this has not had an impact on efficacy. Following further review of two phase 3 studies of D&T in advanced melanoma (COMBI V and COMBI D), the median daily dose for both treatments were close to the planned dose (COMBI D: median daily dose of trametinib was between 1.98 and 2.0 mg and 294.41 to 299.62 mg for dabrafenib). The majority of dose interruptions for both treatments were for less than 7 days, and the studies have demonstrated long-term safety and efficacy outcomes. Furthermore, the Company would like to note that any non-compliance to D&T in the BRF113928 trial has already been accounted for in the modelled progression-free survival (PFS) and OS data. Dose reductions and/or dose interruptions are inherently included in the efficacy data from the BRF113928 trial. Similarly, the relative dose intensity (RDI) calculations for D&T inform the cost-effectiveness model, thereby also capturing the effect of non-compliance on costs. Therefore, the impact of non-compliance to D&T in the BRF113928

		trial is already captured with respect to both costs and efficacy. The Company does not consider that it would be appropriate to conduct any scenarios exploring this issue.
Key issue 3: Small, heterogenous non-randomised datasets for evaluating efficacy	No	**The use of KEYNOTE-189[1] to inform the evidence for pembro-chemo in the revised Company base case mitigates the uncertainty associated with the FLATIRON RWE study (2022) *[see Key issue 5]*** The Company acknowledges the inherent difficulties in producing robust comparative efficacy estimates, given the lack of randomised controlled trial (RCT) evidence for D&T and the small sample sizes underpinning the evidence base in the target patient population. In accordance with the EAG's preferences, the Company has presented a revised base case economic analysis, whereby KEYNOTE-189[1] is used to inform the evidence for pembro-chemo. The KEYNOTE-189 trial was an RCT with a large sample population (n=616) conducted in adherence to strict trial protocols.[2] Since the Company response to the EAG clarification questions, a more mature data cut of the KEYNOTE-189 trial has become available: this has been incorporated in the revised Company base case analysis.[1] All patients had a minimum follow up of five years in the revised data cut, with a median follow-up time of 64.6 months (range: 60.1–72.4 months).[1] Given, the availability of robust, mature trial data, the Company is supportive of using KEYNOTE-189[1] to provide evidence for pembro-chemo, which is in-line with recent NICE Appraisal Committee preferences for trial data over observational data in economic models (e.g. TA812 [pralsetinib] and TA724 [nivolumab with ipilimumab]).[3, 4] To minimise uncertainty arising from differences in the trial populations between the BRF113928 and KEYNOTE-189 trials[1], the Company has performed a matching adjusted indirect comparison (MAIC) between Cohort C of the BRF113928 trial, and the patient population in the KEYNOTE-189 trial.[1] This is detailed further in response to Key Issue #5 and in Appendix 3. It is important to note that adjusting for prognostic factors such as BRAF mutation and PD-L1 status was not feasible, as patients in KEYNOTE-189 are an all-comer population and patients in the BRF113928 trial were not tested for PD-L1.[1] Despite this limitation, the use of the larger, more robust dataset from KEYNOTE-189 to inform the evidence for pembro-chemo alleviates much of the uncertainty relating to Key Issue #3.

<table>
<tr>
<td>Key issue 4: Uncertainty about the applicability of the population recruited to trial BRF113928

Does inclusion of people who did not meet trial eligibility criteria affect applicability of the trial to clinical practice?</td>
<td>Yes
(new data)</td>
<td>
The Company has provided an explanation for the patients with protocol deviation and believe the BRF113928 trial results are applicable to UK clinical practice.

The EAG has noted that [redacted]% of patients enrolled across Cohorts B and C in the BRF113928 did not meet the trial eligibility criteria. The Company does not believe the protocol deviations will have an impact on the efficacy outcomes observed in the BRF113928 trial, so are of the view that the trial results are applicable to NHS clinical practice.

To allay the EAG's concerns with the applicability of the results for the overall Cohorts, the reasons for ineligibility of certain patients in each of trial Cohorts C and B are provided in Table 4 below.

Table 4: Explanations for protocol deviations in the BRF113928 trial
<table>
<tr><th></th><th>No. of patients affected</th><th>Explanation</th></tr>
<tr><td colspan="3">Cohort C ([redacted])</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Cohort B ([redacted])</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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</td>
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		[redacted] , [redacted] **Abbreviations:** CS: Company Submission.
Key issue 5: Assumed clinical equivalence assumed between D&T and pembrolizumab plus chemotherapy *Is dabrafenib with trametinib likely to be superior to pembrolizumab with chemotherapy in those whose non-small-cell lung cancer has a BRAF V600 mutation.*	Yes (new data and new analyses; Appendix 1–4)	**The Company acknowledges that the KEYNOTE-189 trial represents a more robust source of evidence for pembro-chemo.[1] In order to align the BRF113928 and KEYNOTE 189 trial population characteristics, a MAIC has been conducted and used to inform the revised Company base case analysis. This revised analysis uses the matched PFS and OS Kaplan-Meier (KM) data for D&T, and the PFS and OS KM data from KEYNOTE-189 for pembro-chemo.** For the reasons detailed in Key Issue #3, and in line with the EAG's preferences, the Company has used KEYNOTE-189 to provide efficacy evidence for pembro-chemo in the revised Company base case analysis.[1] The Company agrees that, given the large sample size and extended 5-year follow-up associated with this trial, KEYNOTE-189 represents an appropriate source of evidence for pembro-chemo.[1] The Company agrees with the EAG's clinical advisors' suggestion that D&T is likely to be superior to immunotherapy in whom the specific target oncogenic driver mutation has been identified. The Company also agrees with the EAG that an assumption of clinical equivalence between D&T and pembro-chemo is likely to be conservative and may underestimate the benefits associated with D&T, given the availability of subsequent immunotherapy in patients experiencing disease progression on D&T. A MAIC was conducted to adjust for differences in prognostic patient characteristics between the two studies. Individual patient data from Cohort C of the BRF113928 trial were weighted to match to aggregate baseline characteristics from the pembro-chemo arm of the KEYNOTE-189 trial.[1] Covariates identified as statistically significant prognostic variables, as well as those previously identified in previous NICE appraisals ((TA789 ([tepotinib],[5] TA653 [osimertinib],[6] TA628 [lorlatinib],[7] TA500 [ceritinib][8]), were adjusted for in the analysis, and are listed for both OS and PFS in Table 5 below.

A sensitivity analysis was conducted in which only statistically significant variables were adjusted for and the results of this analysis were broadly consistent with the base case analysis. Full details of the methodology and results of the MAIC are provided in Appendix 3.

Table 5: Covariates adjusted for in the MAIC between BRF113928 Cohort C and KEYNOTE-189[1]

Covariates adjusted for OS	Covariates adjusted for PFS
• Median age • Percentage male • ECOG PS 0 • Smoking status • Adenocarcinoma histology • Presence of liver metastases • Presence of M1a metastasis	• Median age • Percentage male • ECOG PS 0 • Smoking status • Adenocarcinoma histology • Presence of liver metastases • Presence of brain metastases • Presence of M1a metastasis

Abbreviations: ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; PS: performance status.

MAIC results

The weighted and naive KM survival plots for D&T, are shown for PFS and OS in Figure 1 and Figure 2, respectively, alongside the survival KM data for pembro-chemo. The PFS and OS HRs comparing D&T survival estimates (weighted and naïve) with pembro-chemo derived from the KM analyses are shown in Table 6.

The results of the MAIC indicate that D&T is likely to improve both PFS and OS compared to pembro-chemo. These results are aligned with clinician feedback provided to the EAG, suggesting that D&T is likely to be superior to immunotherapy in prolonging survival in patients with a BRAF V600E mutation.

		Figure 1: Naïve and weighted PFS KM curves for D&T and PFS KM for pembro-chemo, based on the MAIC between BRF113928 and KEYNOTE-189[1]  Taf-Mek = dabrafenib and trametinib **Abbreviations:** D&T: dabrafenib plus trametinib; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; PDC: platinum-doublet chemotherapy; PFS: progression-free survival.

Figure 2: Naïve and weighted OS KM curves for D&T and OS KM for pembro-chemo, based on the MAIC between BRF113928 and KEYNOTE-189[1]

Taf-Mek = dabrafenib plus trametinib
Abbreviations: D&T: dabrafenib plus trametinib; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival; PDC: platinum-doublet chemotherapy.

Table 6: Naïve and weighted OS and PFS hazard ratios for D&T versus pembro-chemo (based on the MAIC between BRF113928 and KEYNOTE-189[1])

	Naive		Weighted	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D&T versus pembro-chemo (PFS)	[redacted]	[redacted]	[redacted]	[redacted]
D&T versus pembro-chemo (OS)	[redacted]	[redacted]	[redacted]	[redacted]

		Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival. ***Revised Company base case analysis*** The Company has revised its base case to use KEYNOTE-189 to model pembro-chemo, via independent extrapolation of the PFS and OS KM data from the latest 5 year data cut-off .[1] The MAIC provides a more robust comparison of survival estimates for D&T relative to pembro-chemo than the naïve comparison, given the inter-trial heterogeneity in trial populations between BRF113928 Cohort C and KEYNOTE-189. Full details of the curve choices for the extrapolation of the pembro-chemo PFS and OS data from KEYNOTE-189 are provided in Appendix 4. It should be noted that time-on-treatment (ToT) for D&T is modelled in line with the original Company base case, using an exponential extrapolation of the ToT data from the BRF113928 trial Cohort C. As KEYNOTE-189 ToT data were not available,[1] ToT data for pembro-chemo could not be included in the MAIC and consequently ToT for pembro-chemo was assumed equal to PFS for pembro-chemo, with the relevant stopping rules applied in line with the original Company base case. Results for the Company's revised base case analysis are presented in Appendix 1 (current PAS price) [redacted]). The Company notes that the survival data presented in the revised base case analysis may still represent a conservative estimate of survival associated with pembro-chemo in the patient population of interest in this submission, for a number of reasons: • As noted by the clinical advisor to the EAG, patients with advanced NSCLC harbouring a BRAF V600 mutation are likely to experience worse outcomes when on treatment with immunotherapies: specifically, patients with the mutation may not experience outcomes with pembro-chemo in line with that suggested by results from KEYNOTE-189.[1] • The long-term survival benefits associated with pembro-chemo are associated with a high degree of uncertainty. The extent to which survival benefits continue past the two-year stopping rule in place for pembro-chemo remains unclear. Previous NICE appraisals relating to pembro-chemo in advanced

		NSCLC have incorporated treatment waning, in order to account for reduced treatment benefit of pembro-chemo not captured by immature trial data.[9] Whilst the 5-year data from KEYNOTE-189 represent the most mature data from the trial, it is unclear if treatment waning would still be appropriate to include.[1]
Key issue 6: Inclusion of BRAF testing costs *Is BRAF V600 mutation testing conducted routinely in practice?*	Yes (new analyses; Appendix 1)	**The Company maintains that BRAF testing costs should not be included in the base case, since testing for the BRAF mutation is part of current NHS clinical practice, and will remain so regardless of the outcome of the appraisal of D&T.** The EAG considers that the inclusion of BRAF V600 as a mutation in the national genomics testing panel is dependent on the ongoing interim availability of D&T under Covid-19 guidelines. The EAG therefore considers that costs of BRAF testing costs for patients receiving D&T should be included in the model. Clinical feedback received by the Company as part of the response to technical engagement suggests that it is unlikely that testing for the BRAF mutation would be removed from the next generation sequencing (NGS) testing panel, were D&T to not be recommended. The Company concludes that any cost of adding BRAF testing would be incurred by the NHS irrespective of the permanent availability of D&T following a positive recommendation. The Company therefore maintains that no such costs should be included in the cost-effectiveness analysis, and these are not included in its revised post-technical engagement base case analysis. However, in order to allay any concerns relating to the inclusion of BRAF testing costs in the Company's analysis, a scenario analysis has been presented in which patients receiving D&T are assumed to incur additional testing costs, based on the incidence of the BRAF V600 mutation. The calculations of BRAF testing costs are detailed in the Company's response to EAG clarification question B14. In line with the feedback received by the EAG, the cost of BRAF testing has been updated to a £34 unit cost per test. The results of this scenario analysis are presented in Appendix 1 (current PAS price) and [redacted]

Key issue 7: Omitted costs and resource use considerations	Y (new analyses; Appendix 1)	**Summary of Company responses:** • **The Company has accepted the EAG scenario on end-of-life (EoL) care (scenario 4) and has incorporated this into the revised Company base case analysis** • **In response to scenario 6, the Company has updated the base case to include a cost for a session of pharmacy time, once a month for three months, followed by once every three months thereafter** • **In response to scenario 12, the Company has updated the base case to account for some D&T wastage for orally administered therapies** ***Scenario 4: EoL care costs*** The Company has incorporated the EAG's approach to modelling EoL care costs, based on TA705 (atezolizumab), into the revised base case analysis presented in Appendix 1 (current PAS price) and [redacted] ***Scenario 6: Administration costs of oral therapies*** The EAG highlights the lack of any administration costs for oral therapies in the original Company base case analysis, which they state is not in line with previous NICE appraisals for oral therapies in NSCLC; the EAG points towards the inclusion of a cost for pharmacy time for oral therapies in TA536 (alectinib),[12] TA670 (brigatinib)[11] and TA628 (lorlatinib).[7] The Company has conducted a review of recent oral therapy NICE appraisals in NSCLC (TA536 [alectinib],[11] TA628 [lorlatinib],[7] TA670 [brigatinib],[12] TA781 [sotorasib],[13] TA789 [tepotinib],[5] TA812 [pralsetinib][3] and ID3984 [mobocertinib][14]) and within these, a range of approaches to modelling the administration costs for oral therapies were identified. These range from a one-off cost applied at treatment administration, to separate costs at first administration and subsequent administrations. UK clinical expert feedback during the technical engagement process indicated that patients with advanced NSCLC receiving treatment with D&T will move to less frequent dispensing of treatment once they are stable; this is typically after 3 months. Furthermore, the clinician noted that 1 in 3 patients will need a dose reduction or interruption and this is proactively discussed with the patient early on to avoid issues with

		toxicity; there is no impact on efficacy. Therefore, the Company proposes to include an administration cost for oral therapies incurred once a month for the first three months, followed by an administration cost once every three months (assuming that patients receive a three month supply of treatment at each administration). This has been included in the revised Company base case analysis presented in Appendix 1 (current PAS price) and [redacted] ***Scenario 12: Modelling wastage for oral therapies*** The EAG states in their report that the Company adjusted drug acquisition costs based on observed RDI but did not account for wastage of oral therapies, in this case D&T. A review of the most recent oral therapy NICE appraisals in NSCLC indicated that there was limited consensus on the preferred approaches to modelling wastage of oral therapies. From the appraisals reviewed (TA812 [pralsetinib],[3] TA789 [tepotinib],[13] TA781 [sotorasib],[5] ID3984 [mobocertinib][14]), no clear approach was adopted to account for wastage for oral therapies. In none of the appraisals was the approach to wastage commented on within the Appraisal Committee Document or Final Appraisal Document. However, in TA781 (sotorasib),[13] the ERG's preference was to model wastage based on the total number of packs opened rather than the number of treatments received. With the addition of the oral administration cost and considering that most dose interruptions and/or reductions are anticipated to be early on, there is no reason to assume that dose interruptions and/or dose reductions would result in any additional drug wastage, and the original Company base case analysis assumes that no additional treatment would be prescribed until the previous supply has been used. As a result, UK clinical expert feedback sought by the Company during the technical engagement process indicated that the proportion of RDI drug acquisition cost savings that would be wasted in clinical practice would be closer to 5%, not the 50% suggested by the EAG. But the Company acknowledges that there may be some potential for oral therapy wastage at the point of disease progression for patients who progress on D&T, or prior discontinuation of treatment due to AEs. The Company has updated the base case analysis to include the cost of half a pack D&T as wastage for any patients discontinuing treatment with D&T within the model, assuming that, on average, patients would discontinue halfway through a pack of treatment.

		The results of the revised Company base case analysis, incorporating all of the changes detailed above, are summarised in in Appendix 1 (current PAS price) and [redacted]. Scenario analyses based on the revised Company base case analysis have also been conducted whereby 5% of the RDI drug acquisition cost savings are wasted and whereby 50% of the RDI drug acquisition cost savings are wasted (based on the EAG's preferred assumptions) ([redacted]).
Key issue 8: Inclusion of disutility associated with monthly IV infusion *Is the disutility of -0.023 applied in the model for monthly intravenous infusions appropriate?*	Yes (new analyses; Appendix 1 and 2)	**The Company maintains that the inclusion of a disutility associated with IV administration is appropriate to capture the impact of receiving an IV infusion on patients, and an alternative approach to estimating this disutility has been incorporated into the Company revised base case analysis.** The EAG acknowledged that the receipt of monthly IV infusions may be less convenient for patients than taking an oral therapy, but considered the impact of this to be overestimated in the Company's original submission. The EAG considered that the impact of receiving IV infusions would be minimal, and therefore favoured the removal of any disutility associated with IV infusions from the model entirely, and the allowance of a qualitative assessment of impact. The Company maintains that a disutility associated with IV administration is appropriate to capture the impact of receiving an IV infusion on patients, compared with taking an oral therapy, and has therefore not completely removed the disutility associated with IV infusions from the revised Company base case analysis. However, rather than applying a weekly disutility to patients in each cycle of treatment, the same disutility of 0.023 is now applied only in cycles within which pembro-chemo is administered (resulting in a disutility of 0.008 applied every cycle for Cycles 0–11, and 0.006 in Cycles 12+). This disutility is assumed to be incurred every three weeks in cycles 1–12, and either every three or six weeks in subsequent cycles, in order to account for a proportion of patients receiving maintenance treatment with pemetrexed. The Company notes that this disutility was a key driver in the original Company base case, given the small differences in modelled QALYs between treatments resulting from the clinical equivalence assumption. However, this disutility now has a limited impact on the cost-effectiveness results in the revised Company base case analysis (due to amendments outlined in our response to Key issue #5). The results of the revised Company base case analysis, incorporating all of the changes detailed above, are summarised in in

		Appendix 1 (current PAS price) and [redacted]. A scenario analysis based on the revised Company base case analysis has also been conducted whereby the disutility associated with IV infusions has been entirely removed; the results of this scenario analysis have a very limited impact on the base case results. Finally, it should be noted that the potential advantages of oral therapies compared to IV therapies cannot be fully captured within the cost-effectiveness model, and there are likely to be further substantial benefits associated with D&T versus pembro-chemo that cannot be captured within the QALY calculation (see Section B.3.12 of CS). For example, in many cases, COVID-19 restrictions mean that patients are unable to attend IV appointments with family members or friends, leaving patients feeling isolated, and further accentuating the decreased HRQoL resulting from attendance of these appointments. Similarly, the potential benefit of reducing the number of IV appointments required due to pembro-chemo, particularly in light of the current capacity issues in the NHS, represents a key advantage with D&T that cannot be fully quantified in the cost-effectiveness model. The Company believes that it is important for all of the potential benefits associated with the increased usage of an oral therapy versus an IV therapy, both quantifiable and non-quantifiable, to be considered as far as possible as part of this appraisal.
Key issue 9: Relevance of a severity modifier under particular assumptions	Yes (new analyses)	**The revised Company base case analysis does not meet the criteria for a severity modifier.** In the Company's revised base case analysis, KEYNOTE-189 is used as the source of efficacy data for pembro-chemo.[1] Based on the use of KEYNOTE-189, revised severity modifier calculations are presented below, based on the methodology outlined in Section B.3.6 of the CS, except that the expected QALYs for patients with advanced NSCLC with a BRAF V600 mutation in current clinical practice are now based on KEYNOTE-189.[1] Based on these revised analyses, this submission is close to reaching but does not ultimately meet the criteria for a severity modifier, with an estimated absolute QALY shortfall of [redacted] years, and a proportional QALY shortfall of [redacted]. However, as previously detailed in response to Key Issues #3 and #5, it is important to reiterate that KEYNOTE-189 provides evidence for pembro-chemo in an all-comer population and is not specific to patients with the BRAF mutation.[1]

As highlighted by the EAG's clinical advisers, it is plausible that patients with a BRAF mutation receiving pembro-chemo may experience worse outcomes than BRAF wild-type patients. As such, while there is no robust evidence to inform the efficacy of pembro-chemo in a BRAF V600 patient population, it is plausible that these patients experience worsened outcomes than those observed in KEYNOTE-189[1], and that a severity modifier may be potentially relevant, although there are no robust data in the published literature to demonstrate this.

Table 7: Summary features of QALY shortfall analysis

Factor	Value
Percentage male	38.9%
Mean age	67.8

Abbreviations: QALY: quality-adjusted life year.

Table 8: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
PFS	0.794	[redacted]
PD	0.678	[redacted]

Abbreviations: PFS: progression-free survival; PD: progressed disease; QALY: quality-adjusted life year.

Table 9: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
9.871	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year.

Summary of changes to the Company's cost-effectiveness estimate(s)

A summary of the changes made to the Company's base case is provided below in Table 10 (PAS price) and Table 11 ([redacted]).

Table 10: Changes to the Company's cost-effectiveness estimate – current PAS price (comparators at list price)

Key issue(s) in the ERG report that the change relates to	Company base case before technical engagement	Change(s) made in response to technical engagement	Inc. costs	Inc. QALYs	ICER	Impact on the Company's base-case incremental cost-effectiveness ratio (ICER)
Company base case before technical engagement	N/A	N/A	[redacted]	[redacted]	D&T is Dominant	N/A
Key Issue 3/5 (PFS/OS for pembro-chemo)	Pembro-chemo PFS and OS were modelled based on assuming equivalence to D&T	Pembro-chemo PFS and OS are based on independent extrapolation of KM data from KEYNOTE-189[1]	[redacted]	[redacted]	D&T is Dominant	N/A
Key Issue 3/5 (pembro-chemo ToT	Pembro-chemo ToT was modelled using ToT data from the FLATIRON RWE study (2022)	Pembro-chemo ToT was modelled by assuming equivalence to PFS in the KEYNOTE-189 trial[1]	[redacted]	[redacted]	D&T is Dominant	N/A
Key Issue 3/5 (PFS and OS for D&T)	D&T PFS and OS were modelled using data from Cohort C of the BRF113928 trial	D&T PFS and OS were modelled using data from Cohort C of the BRF113928 trial, weighted based on the MAIC versus KEYNOTE-189[1]	[redacted]	[redacted]	D&T is Dominant	N/A
End of life costs	27% of patients who died would not incur any end-of-life costs, based	End-of-life costs have been revised in line with	[redacted]	[redacted]	D&T is Dominant	N/A

	on TA705 (atezolizumab)	the EAG's preferred approaches				
Administration costs for oral therapies	No administration costs were applied for oral therapies	Administration costs based on 12 minutes of pharmacist dispensing time was incurred once per month for the first three months of treatment with D&T, and once every three months thereafter	[redacted]	[redacted]	D&T is Dominant	N/A
IV infusion-related disutility applied in administration cycles	IV-infusion related disutility was applied in all cycles, based on Matza *et al.* (2013)	IV-infusion related disutility was assumed to apply only in cycles where pembro-chemo was administered[a]	[redacted]	[redacted]	D&T is Dominant	N/A
Health state utilities	Health state utilities were based on Chouaid et al. (2013)	Health state utilities were based on TA812 (pralsetinib)	[redacted]	[redacted]	D&T is Dominant	N/A
Pemetrexed cost	Pemetrexed was costed at £640 per pack, based on the latest BNF price	Pemetrexed was costed at £108.61, based on the latest eMIT (2022) cost.	[redacted]	[redacted]	D&T is Dominant	N/A
Costs for drug wastage	All of the cost-savings resulting from RDI were realised	The cost of drug wastage was applied by adding the cost of half a pack of D&T onto the total treatment acquisition costs at the point of discontinuation	[redacted]	[redacted]	D&T is Dominant	N/A
Company base case following technical engagement (PAS price)	N/A	N/A	[redacted]	[redacted]	D&T is Dominant	N/A

[a] Applied as a disutility of 0.008 (0.023/3) in every cycle for Cycles 1-12 and a disutility of 0.006 ([0.023/3*0.684] + [0.023/6*0.316]) from Cycles 13+, to account for pemetrexed maintenance

Abbreviations: D&T: dabrafenib and trametinib; eMIT: electronic market information tool; IV: intravenous; KM: Kaplan-Meier; MAIC: matching adjusted indirect comparison; N/A : not applicable; OS: overall survival; pembro-chemo: pembrolizumab plus chemotherapy; PFS: progression-free survival; RDI: relative dose intensity; ToT: time on treatment.

Table 11: Changes to the Company's cost-effectiveness estimate [redacted]

Key issue(s) in the ERG report that the change relates to	Company base case before technical engagement	Change(s) made in response to technical engagement	Inc. costs	Inc. QALYs	ICER	Impact on the Company's base-case incremental cost-effectiveness ratio (ICER)
Company base case before technical engagement	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Key Issue 3/5 (PFS/OS for pembro-chemo)	Pembro-chemo PFS and OS were modelled based on assuming equivalence to D&T	Pembro-chemo PFS and OS are based on independent extrapolation of KM data from KEYNOTE-189[1]	[redacted]	[redacted]	[redacted]	N/A
Key Issue 3/5 (pembro-chemo ToT	Pembro-chemo ToT was modelled using ToT data from the FLATIRON RWE study (2022)	Pembro-chemo ToT was modelled by assuming equivalence to PFS in the KEYNOTE-189 trial[1]	[redacted]	[redacted]	[redacted]	N/A
Key Issue 3/5 (PFS and OS for D&T)	D&T PFS and OS were modelled using data from Cohort C of the BRF113928 trial	D&T PFS and OS were modelled using data from Cohort C of the BRF113928 trial, weighted based on the MAIC versus KEYNOTE-189[1]	[redacted]	[redacted]	[redacted]	N/A
End of life costs	27% of patients who died would not incur any end-of-life costs, based on TA705 (atezolizumab)	End-of-life costs have been revised in line with the EAG's preferred approaches	[redacted]	[redacted]	[redacted]	[redacted]

Administration costs for oral therapies	No administration costs were applied for oral therapies	Administration costs based on 12 minutes of pharmacist dispensing time was incurred once per month for the first three months of treatment with D&T, and once every three months thereafter	[redacted]	[redacted]	[redacted]	[redacted]
IV infusion-related disutility applied in administration cycles	IV-infusion related disutility was applied in all cycles, based on Matza *et al.* (2013)	IV-infusion related disutility was assumed to apply only in cycles where pembro-chemo was administered[a]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utilities	Health state utilities were based on Chouaid et al. (2013)	Health state utilities were based on TA812 (pralsetinib)	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed cost	Pemetrexed was costed at £640 per pack, based on the latest BNF price	Pemetrexed was costed at £108.61, based on the latest eMIT (2022) cost.	[redacted]	[redacted]	[redacted]	[redacted]
Costs for drug wastage	All of the cost-savings resulting from RDI were realised	The cost of drug wastage was applied by adding the cost of half a pack of D&T onto the total treatment acquisition costs at the point of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case following technical engagement [redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]

[a] Applied as a disutility of 0.008 (0.023/3) in every cycle for Cycles 1-12 and a disutility of 0.006 ([0.023/3*0.684] + [0.023/6*0.316]) from Cycles 13+, to account for pemetrexed maintenance

Abbreviations: D&T: dabrafenib and trametinib; eMIT: electronic market information tool; IV: intravenous; KM: Kaplan-Meier; MAIC: matching adjusted indirect comparison; N/A : not applicable; OS: overall survival; pembro-chemo: pembrolizumab plus chemotherapy; PFS: progression-free survival; RDI: relative dose intensity; ToT: time on treatment.

Appendix 1: Revised Company base case following technical engagement – current PAS price

Results for the revised Company base case are presented below, whereby the existing PAS discounts for dabrafenib ([redacted]%) and trametinib ([redacted]%) are included. All comparator therapies and subsequent treatments have been included at their list prices. However, as noted above in the Summary of changes to the Company's cost-effectiveness estimate(s), pemetrexed is now included at a lower cost, in line with the latest eMIT 2022 cost.

The revised Company base case includes the following changes from the original Company base case:

- Efficacy data for D&T (PFS and OS) are based on the matched analysis versus the KEYNOTE-189 5-year analysis[1] (PFS curve choice: exponential; OS curve choice: Weibull)
- Efficacy data for pembro-chemo (PFS and OS) are based on the KEYNOTE-189 5-year analysis[1] (PFS curve choice: exponential; OS curve choice: Weibull), in line with the EAG's preferred assumptions
- End-of-life costs have been updated in line with the EAG's preferred assumptions
- Administration costs for D&T have been included, with the assumption of pharmacy time being required once per month for the first three months of treatment, followed by once every three months
- Wastage of D&T has been included, with the assumption that any patient discontinuing treatment with D&T will incur the wastage costs of half a pack (half a pack of dabrafenib and half a pack of trametinib)
- The health state utility values for PFS and PD are sourced from TA812 (pralsetinib) in line with the EAG's preferred assumptions
- The disutility associated with the IV administration of pembro-chemo has been updated to assume that disutility is only incurred in the cycles where pembro-chemo is administered
- Pemetrexed is now included at a lower cost, in line with the latest eMIT 2022 cost.

Revised Company base case – deterministic results – PAS price

Table 12: Revised deterministic Company base case and scenario analysis results – PAS price (comparators at list price)

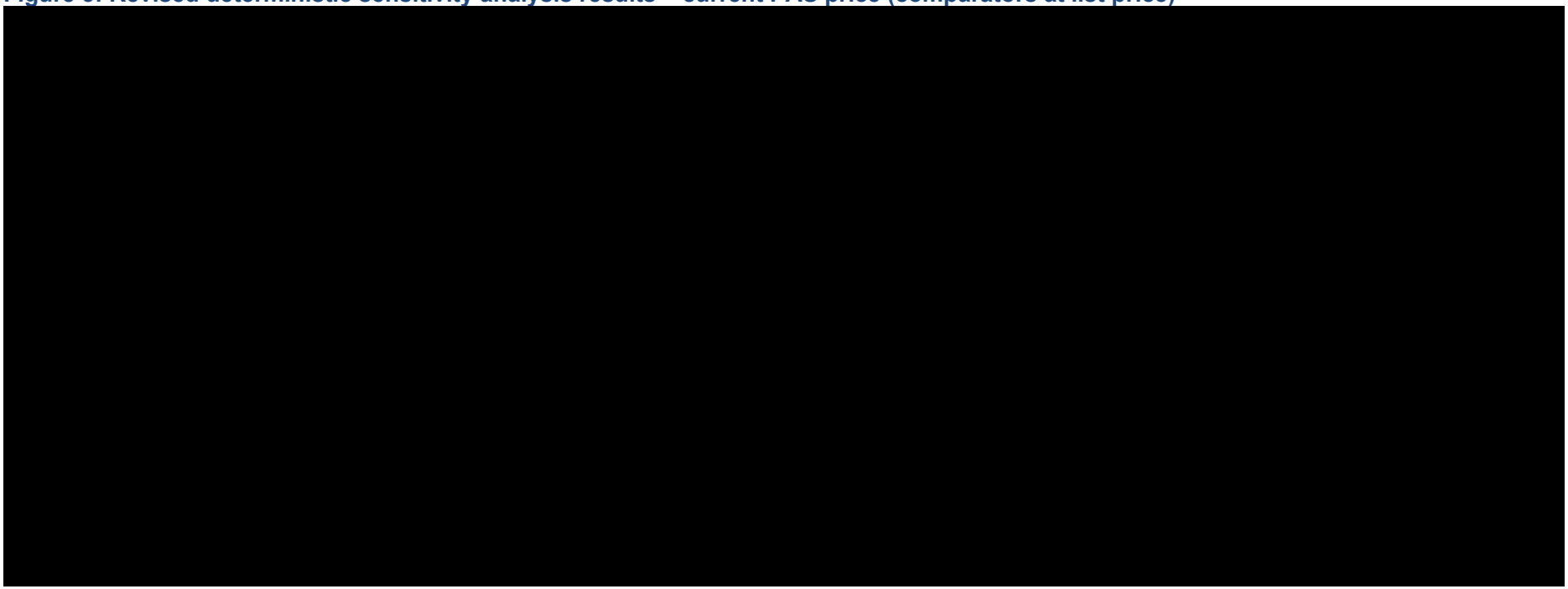
	Incr. costs (£)	Incr. QALYs	Incr. LYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: D&T OS curve choice (exponential)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: D&T OS and PFS: based on KEYNOTE-189 MAIC (Sensitivity analysis matched data)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Scenario: BRAF testing costs included (for all patients receiving D&T)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: IV disutility excluded (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: IV disutility excluded AND 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: 5% of RDI savings are wasted (based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB: net heath benefit; QALYs, quality-adjusted life years.

Revised Company base case – deterministic sensitivity analysis – current PAS price

Figure 3: Revised deterministic sensitivity analysis results – current PAS price (comparators at list price)



Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio.

Revised Company base case – probabilistic results – current PAS price

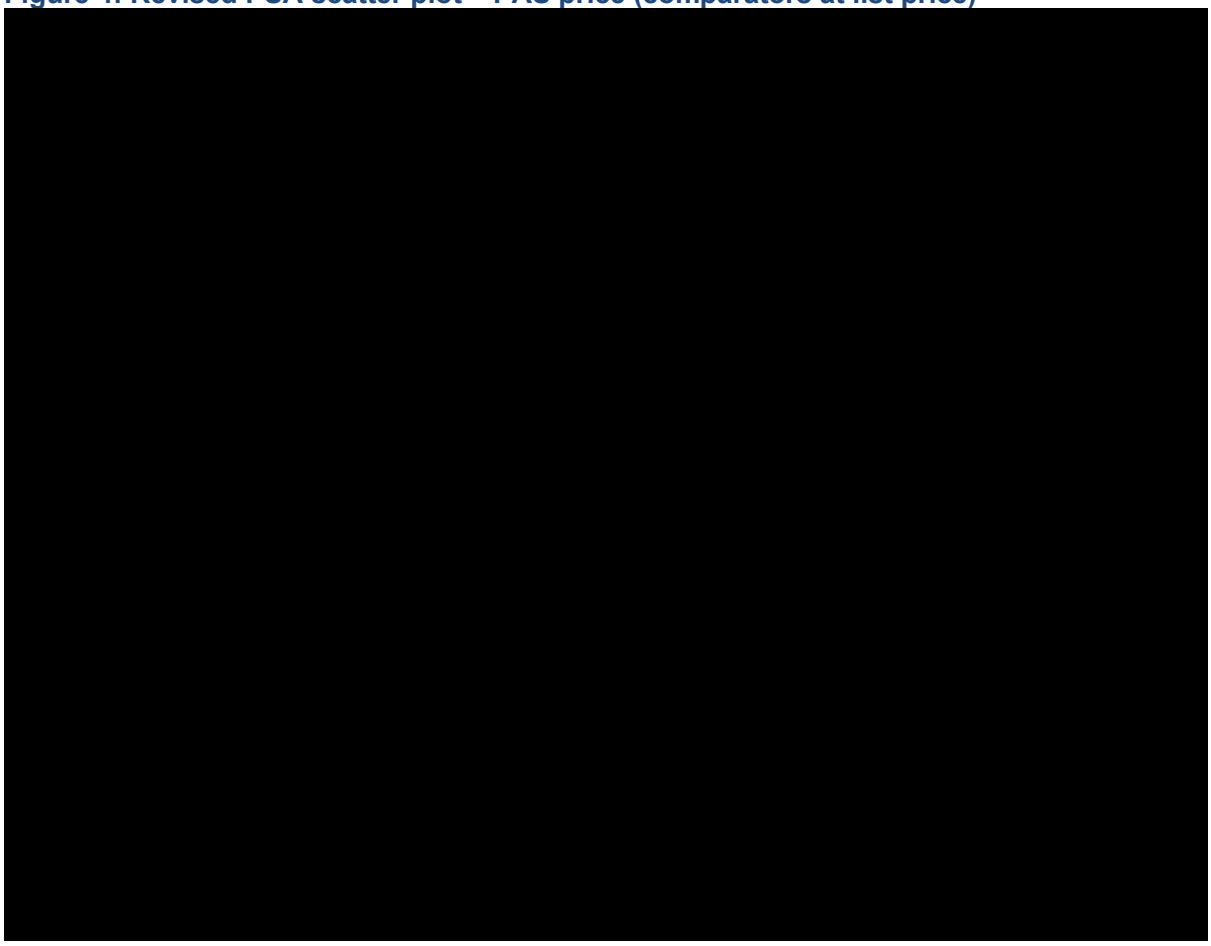
Table 13: Revised probabilistic Company base case results – current PAS price (comparators at list price)

	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB: net heath benefit; QALYs, quality-adjusted life years.

Revised Company base case – probabilistic sensitivity analysis – current PAS price

Figure 4: Revised PSA scatter plot – PAS price (comparators at list price)



Abbreviations: QALY: quality-adjusted life year; WTP: willingness-to-pay threshold (£20,000 per QALY)

Figure 5: Revised PSA cost-effectiveness acceptability curve – current PAS price (comparators at list price)

Abbreviations: D&T: dabrafenib and trametinib.

. It is assumed that pembrolizumab is associated with a PAS discount of %, PAS discounts of % for atezolizumab and nivolumab, and a % PAS discount for nintedanib. In line with the revised Company base case pemetrexed is included at a lower cost, in line with the latest eMIT 2022 cost.

For dabrafenib, a discount on the list price of % has been included, with trametinib .

Revised Company base case – deterministic results –

Table 14: Revised deterministic Company base case and scenario analysis results

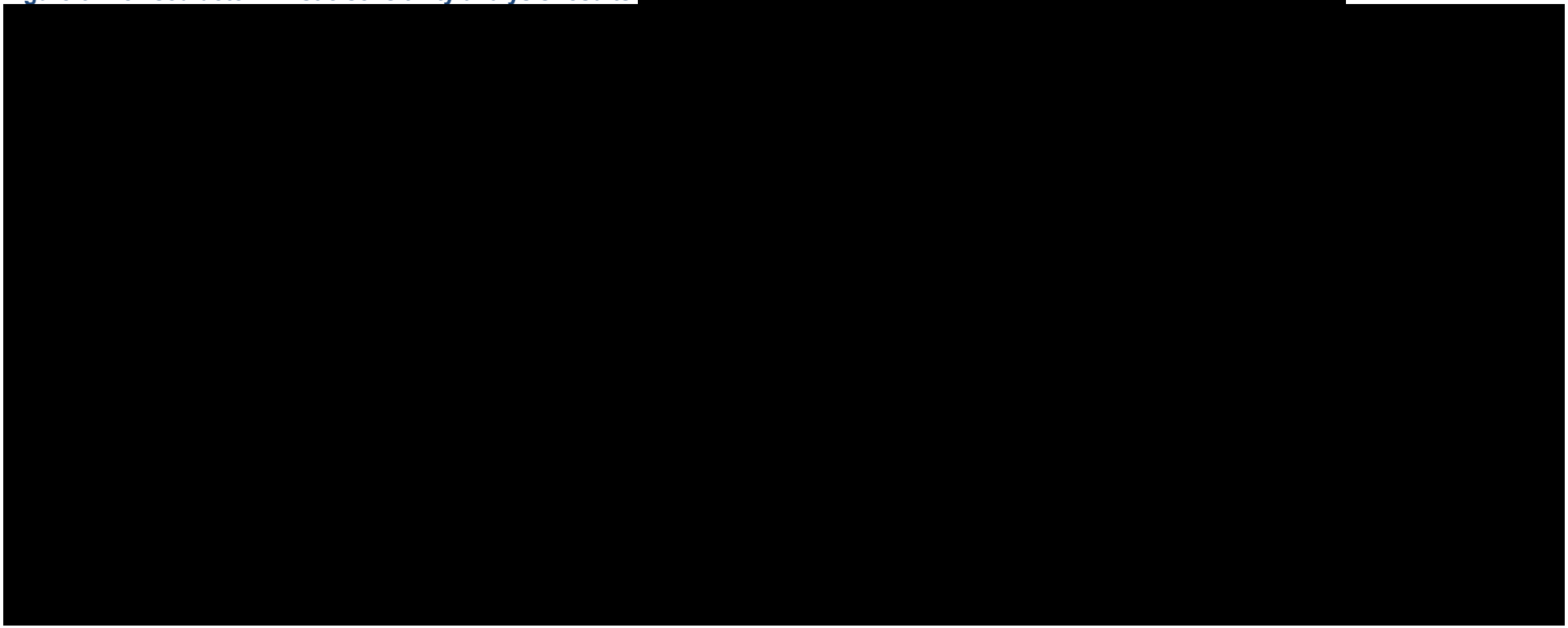
	Incr. costs (£)	Incr. QALYs	Incr. LYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case						

Scenario: D&T OS curve choice (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: D&T OS and PFS: based on KEYNOTE-189 MAIC (Sensitivity analysis matched data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: BRAF testing costs included (for all patients receiving D&T)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: IV disutility excluded (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: IV disutility excluded AND 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: 5% of RDI savings are wasted (based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; EAG: External Assessment Group; ICER: incremental cost-effectiveness ratio; IV: intravenous; LYs: life years; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; QALYs: quality-adjusted life years; RDI: relative dose intensity.

Revised Company base case – Deterministic sensitivity analysis – [redacted]

Figure 6: Revised deterministic sensitivity analysis results [redacted]



Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio.

Revised Company base case – Probabilistic results – [redacted]

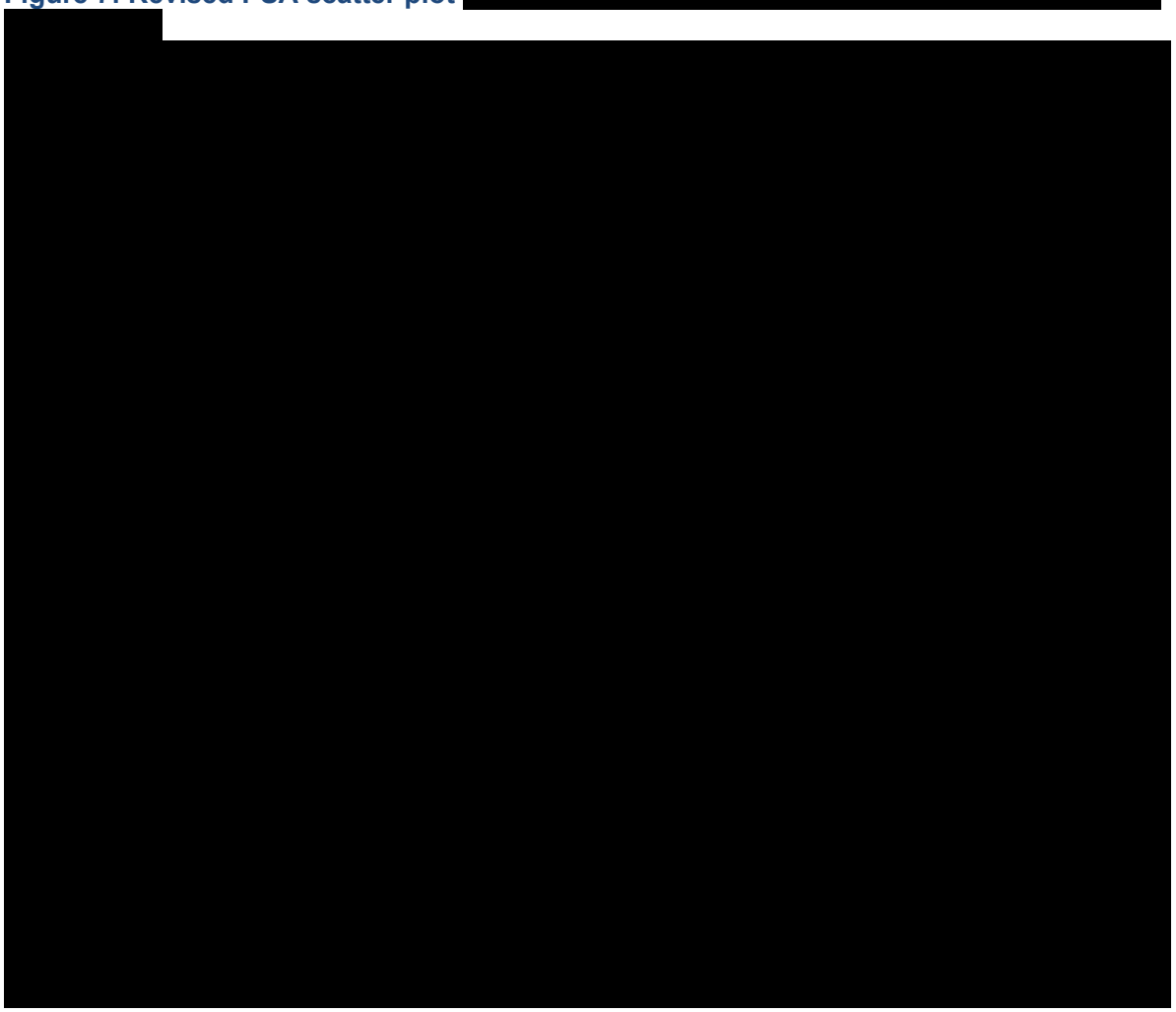
Table 15: Revised probabilistic Company base case results – [redacted]

	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB: net heath benefit; QALYs, quality-adjusted life years.

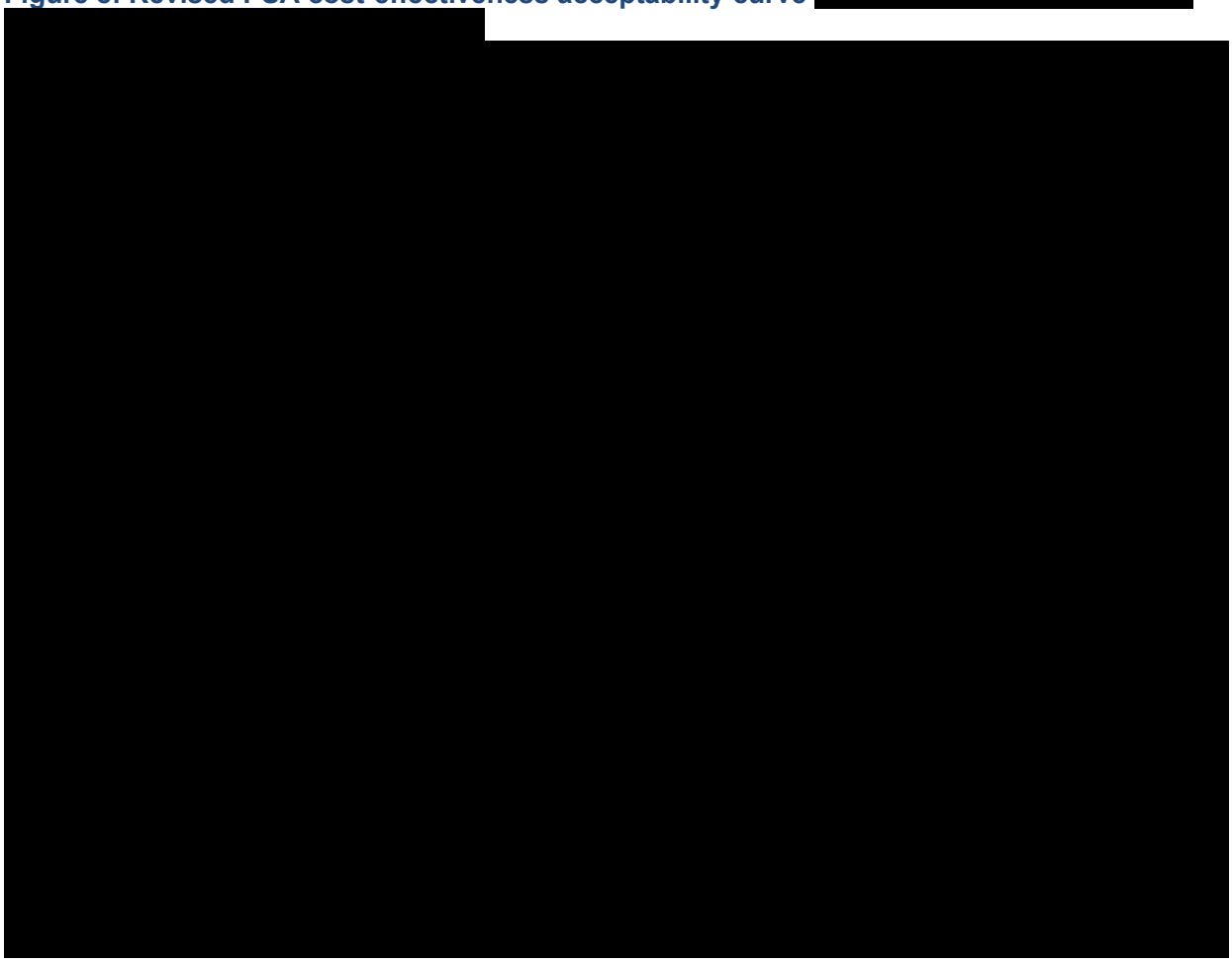
Revised Company base case – Probabilistic sensitivity analysis – [redacted]

Figure 7: Revised PSA scatter plot [redacted]



Abbreviations: QALY: quality-adjusted life year; WTP: willingness-to-pay threshold (£20,000 per QALY)

Figure 8: Revised PSA cost-effectiveness acceptability curve [redacted]



Abbreviations: D&T: dabrafenib and trametinib.

Appendix 3: MAIC methodology and results

The EAG has noted that a formal indirect comparison of the KEYNOTE-189[1] and BRF113928 trials may reduce uncertainty associated with the different patient characteristics in each study. In order to increase the robustness of the comparison between the two trials, the Company has conducted a MAIC in order to account for differences in patient characteristics between both trials. The methodology and results of the MAIC are presented in the sections below.

Methodology

MAICs are conducted based on assigning differential weights to individual patient data (IPD) available for the intervention, based on how well matched these data are to aggregate level data from a comparator study. When these weights are applied, the aggregate measures on the modelled prognostic and treatment effect variables equal (or are as close as possible to) the values in the matched aggregate studies. An important aspect of a MAIC is therefore selecting clinically important variables to be weighted for in the matching analysis.

In order to identify the most relevant prognostic variables to be adjusted for in the MAIC, a Cox regression analysis was conducted on different baseline characteristics reported in KEYNOTE-189. This regression analysis was conducted for both OS and PFS estimates reported in KEYNOTE-189. Variables having a Cox regression p-value <0.2 were deemed to be statistically significant prognostic variables eligible for inclusion in the matching analysis. The results of the Cox regression analyses, and variables identified as statistically significant prognostics variables, are presented in Table 16 below.

Table 16: Cox regression for prognostic value of covariates

Covariate	Reference	HR (*P*-value) for OS	HR (*P*-value) for PFS
Median age	< vs >= median age	[redacted]	[redacted]
Sex	Male vs female	[redacted]	[redacted]
Region	Europe vs other	[redacted]	[redacted]
	North America vs other	[redacted]	[redacted]
ECOG PS	0 vs other	[redacted]	[redacted]
Smoking history	Smoker vs never smoked	[redacted]	[redacted]
Histology	Adenocarcinoma vs other	[redacted]	[redacted]
Brain metastases	Present vs absent	[redacted]	[redacted]
Liver metastases	Present vs absent	[redacted]	[redacted]
Metastasis staging	M1a vs other	[redacted]	[redacted]

Shaded cells indicate variables identified as prognostic variables based on statistical significance.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PS: performance status.

Two matching analyses were conducted. The primary, base case analysis adjusted for the prognostic variables identified as statistically significant in Table 16, in addition to covariates commonly understood to be important prognostic variables in matching analyses identified in previous NICE submissions (TA789 ([tepotinib], TA653 [osimertinib], TA628 [lorlatinib], TA500 [ceritinib]). These included gender, race, Eastern Cooperative Oncology Group (ECOG) status, histology, sex, smoking history, and presence of brain metastases.

A secondary scenario analysis was additionally conducted in which only those covariates found to have statistical significance were adjusted for in the matching between cohorts, as detailed in Table 16 above.

Prior to matching, in order to assess the heterogeneity across both trial cohorts, a comparison of baseline characteristics reported in both trials was carried out, and the results are presented in below. Overall, key baseline characteristics were balanced across both arms, with the exceptions of sex and smoking status, with statistically significant differences in the percentages of males and smokers across both cohorts. These two variables were adjusted for in the base case analysis.

Table 17: Comparison of baseline characteristics between BRF113928 trial Cohort C and KEYNOTE-189 trial

Baseline characteristics	BRF113928 Cohort C	KEYNOTE-189	*P*-value
Sample size	36	410	
Median age, years	67	65	
Sex (% male)	38.9%	62.0%	[redacted]
Europe region	72.2%	59.3%	[redacted]
North America region	25.0%	27.1%	[redacted]
ECOG PS 0	36.1%	45.1%	[redacted]
Smokers	72.2%	88.3%	[redacted]
Adenocarcinoma histology	88.9%	96.1%	[redacted]
Brain metastases	5.6%	17.8%	[redacted]
Liver metastases	11.1%	16.1%	[redacted]
M1a metastasis	25.0%	30.0%	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Results – base case analysis

Overall survival

The patient characteristics of Cohort C patients both before and after weighting for OS prognostic variables are shown in Table 18. The weighting adjustment resulted in the loss of [redacted] patients from the effective sample size (ESS). Whilst this does represent a reasonably large number of patients in the context of the small sample size of Cohort C, this was necessary in order to ensure that all clinically important variables were adjusted for, allowing for a better comparison of treatment effect of D&T and pembro-chemo.

Table 18: Baseline characteristics of patients in BRF113928 Cohort C (pre- and post-weighting) and KEYNOTE-189 included in OS matching analysis

Characteristics	BRF1139289 Cohort C Before Weighting	BRF1139289 Cohort C After Weighting	KEYNOTE -189
ESS	36	[redacted]	410
Median age, years	67	[redacted]	65
Male	38.9%	[redacted]	62.0%
ECOG PS 0	36.1%	[redacted]	45.1%
Smokers	72.2%	[redacted]	88.3%
Adenocarcinoma histology	88.9%	[redacted]	96.1%
Liver metastases	11.1%	[redacted]	16.1%
M1a metastasis	25.0%	[redacted]	30.0%

Abbreviations: ESS: effective sample size; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; OS: overall survival; PS: performance status.

The naïve and matched OS KM plots for D&T in Cohort C are shown alongside the KEYNOTE-189 KM plot for pembro-chemo in Figure 9. The corresponding naïve and matched HRs are shown in Table 19. Both the naïve and adjusted OS estimates for D&T show [redacted] survival benefits compared to pembro-chemo, with naïve and adjusted HRs of [redacted] and [redacted], respectively. The KM curves show that the two treatments are initially associated with similar OS profiles, but then the curves begin to diverge after approximately two years.

Figure 9: OS KM curves – D&T in Cohort C (naïve and matched) versus pembro-chemo in KEYNOTE-189

Taf-Mek = D&T.
Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; OS: overall survival; PDC platinum doublet chemotherapy.

Table 19: Naïve and adjusted HRs for OS

	Unmatched		Matched	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D&T vs pembro-chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; HR: hazard ratio; OS: overall survival.

Progression-free survival

ECOG PS, presence of brain metastases, presence of liver metastases, and M1a metastasis (presence of tumours in both lungs) were identified as statistically important prognostic variables for PFS, and were therefore adjusted for in the matching analysis for PFS. Presence of adenocarcinoma histology, age, percentage of male patients and smoking status were additionally included in the base case matching analysis, based on covariates in previous MAICs conducted as part of NICE appraisals.

The patient characteristics of Cohort C patients both before and after weighting for PFS prognostic variables are shown in Table 20. The weighting adjustment resulted in the loss a greater number of patients from the ESS ([redacted]), as compared to the matching analysis for OS. This is due to the fact that there was a relatively large difference in the number of patients with brain metastases between the Cohort C and the KEYNOTE trial, which was adjusted for in the PFS matching analysis, but not for OS.

Table 20: Baseline characteristics of patients in BRF113928 Cohort C (pre- and post-weighting) and KEYNOTE-189 included in PFS matching analysis

Characteristics	BRF1139289 Cohort C before weighting	BRF1139289 Cohort C after weighting	KEYNOTE-189

ESS	36	[redacted]	410
Median age, years	67	[redacted]	65
Male	38.9%	[redacted]	62.0%
ECOG PS 0	36.1%	[redacted]	45.1%
Smokers	72.2%	[redacted]	88.3%
Adenocarcinoma histology	88.9%	[redacted]	96.1%
Brain metastases	5.6%	[redacted]	17.8%
Liver metastases	11.1%	[redacted]	16.1%

Abbreviations: ESS: effective sample size; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; PFS: progression-free survival; PS: performance status.

The naïve and matched PFS KM plots for D&T in Cohort C are shown alongside the KEYNOTE-189 KM plot for pembro-chemo in Figure 10. The corresponding naïve and matched HRs are shown in Table 21. Both the naïve and adjusted PFS estimates for D&T show [redacted] PFS benefits compared to pembro-chemo, with naïve and adjusted HRs of [redacted] and [redacted], respectively.

Figure 10: PFS KM curves – D&T in Cohort C (naïve and matched) versus pembro-chemo in KEYNOTE-189

Taf-Mek = D&T.
Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; PFS: progression-free survival; PDC platinum doublet chemotherapy.

Table 21: Naïve and adjusted HRs for PFS

	Unmatched	Matched

	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D&T vs pembro-chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; HR: hazard ratio; PFS: progression-free survival.

Results – scenario analysis

The adjustment for large numbers of covariates in the base case matching analysis resulted in the loss of a large number of patients in the ESS. In order to explore any uncertainty around the choice of matching variables, a scenario matching analysis was conducted.

In this analysis, only those covariates identified as statistically significant were adjusted in the MAIC between BRF113928 Cohort C and KEYNOTE-189. This resulted in the loss of fewer patients from the ESS, however, results in less well matched patient populations in the MAIC. The results of this scenario analysis, presented below, show consistent survival estimates with the base case analysis presented above, indicating results are robust with respect to the choice of adjusted covariates.

Overall survival

In the scenario matching analysis, the only covariate identified as statistically important prognostic variables for OS were adjusted for: patients' median age, ECOG PS, presence of liver metastases, and M1a metastasis (presence of tumours in both lungs).

The patient characteristics of Cohort C patients both before and after weighting for statistically significant prognostic variables for OS are shown in Table 22.

Table 22: Baseline characteristics of patients in BRF113928 Cohort C (pre- and post-weighting) and KEYNOTE-189 included in OS matching analysis

Characteristics	BRF1139289 Cohort C Before Weighting	BRF1139289 Cohort C After Weighting	KEYNOTE-189
ESS	36	[redacted]	410
Median age, years	67	[redacted]	65
ECOG PS 0	36.1%	[redacted]	45.1%
Liver metastases	11.1%	[redacted]	16.1%
M1a metastasis	25.0%	[redacted]	30.0%

Abbreviations: ESS: effective sample size; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PS: performance status.

The naïve and matched OS KM plots for D&T in Cohort C are shown alongside the KEYNOTE-189 KM plot for pembro-chemo in Figure 11. The corresponding naïve and matched HRs for the scenario matching analysis are shown in Table 23. Both the naïve and adjusted OS estimates for D&T show [redacted] survival benefits compared to pembro-chemo, with an adjusted HR of [redacted], which is in line with the matched OS results from the base case matching analysis (matched HR: [redacted]).

Figure 11: OS KM curves – D&T in Cohort C (naïve and matched) versus pembro-chemo in KEYNOTE-189

Taf-Mek = D&T.
Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; OS: overall survival; PDC platinum doublet chemotherapy.

Table 23: Naïve and adjusted hazard ratios for OS

	Unmatched		Matched	
	Hazard ratio	95% CI	Hazard ratio	95% CI
D&T vs pembro-chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; OS: overall survival.

Progression-free survival

ECOG PS, presence of brain metastases, presence of liver metastases, and M1a metastasis (presence of tumours in both lungs) we identified as statistically important prognostic variables for PFS, and were adjusted for in the scenario matching analysis for PFS.

The patient characteristics of Cohort C patients both before and after weighting for PFS prognostic variables are shown in Table 24. As with the base case analysis, the weighting adjustment resulted in the loss a greater number of patients from the ESS, as compared to the matching analysis for OS.

Table 24: Baseline characteristics of patients in BRF113928 Cohort C (pre- and post-weighting) and KEYNOTE-189 included in PFS matching analysis

Characteristics	BRF1139289 Cohort C Before Weighting	BRF1139289 Cohort C After Weighting	KEYNOTE-189
ESS	36	[redacted]	410
ECOG PS 0	36.1%	[redacted]	45.1%

Brain metastases	5.6%	[redacted]	17.8%
Liver metastases	11.1%	[redacted]	16.1%
M1a metastasis	25.0%	[redacted]	30.0%

Abbreviations: ESS: effective sample size; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; PFS: progression-free survival; PS: performance status.

The naïve and matched PFS KM plots for D&T in Cohort C are shown alongside the KEYNOTE-189 KM plot for pembro-chemo in Figure 12. The corresponding naïve and matched hazard ratios are shown in Table 25. Both the naïve and adjusted PFS estimates for D&T show [redacted] PFS benefits compared to pembro-chemo, with an adjusted HR of [redacted], which shows slightly improved PFS estimates for D&T as compared with the base case matching analysis (matched HR: [redacted]).

Figure 12: PFS KM curves – D&T in Cohort C (naïve and matched) versus pembro-chemo in KEYNOTE-189

[redacted]

Taf-Mek = D&T.
Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; OS: overall survival; PDC platinum doublet chemotherapy.

Table 25: Naïve and adjusted hazard ratios for PFS

	Unmatched		Matched	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D&T vs pembro-chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; PFS: progression-free survival.

Appendix 4: MAIC results survival analysis and curve selection

Curve selection for D&T

Progression-free survival

The AIC and BIC values for each of the matched D&T PFS extrapolations are summarised in Table 26, and extrapolations of PFS using each model up to 20 years are presented for all functions in Figure 13.

Table 26: Summary of goodness-of-fit data for D&T PFS (BRF113928 trial matched to KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	5	[redacted]	5
Weibull	[redacted]	4	[redacted]	4
Lognormal	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	3	[redacted]	3
Gompertz	[redacted]	1	[redacted]	1
Generalised gamma	[redacted]	5	[redacted]	5

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 13: D&T PFS extrapolations up to ten years (BRF113928 trial matched to KEYNOTE-189)

[redacted]

Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; PFS: progression-free survival.

As previously detailed in the CS (Section B.3.3.2.3), UK clinical experts noted that very few patients would not have progressed after 5 years, in line with the results observed in the BRF113928 trial.[15] Given this, only the exponential curve was considered to be clinically plausible to model PFS for D&T, and therefore was selected in the revised Company base case analysis.

Overall survival

The AIC and BIC values for each of the matched D&T OS extrapolations are summarised in Table 27, and extrapolations of OS using each model up to 20 years are presented for all functions in Figure 14.

Table 27: Summary of goodness-of-fit data for D&T OS (BRF113928 trial matched to KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	3	[redacted]	1
Weibull	[redacted]	6	[redacted]	6
Lognormal	[redacted]	1	[redacted]	2
Log-logistic	[redacted]	4	[redacted]	3
Gompertz	[redacted]	5	[redacted]	5
Generalised gamma	[redacted]	2	[redacted]	4

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 14: D&T OS extrapolations up to twenty years (BRF113928 trial matched to KEYNOTE-189)

Abbreviations: D&T: dabrafenib and trametinib; KM: Kaplan-Meier; OS: overall survival.

As previously detailed in the CS (Section B.3.3.2.3), UK clinical experts highlighted the aggressive nature of the BRAF mutation in patients with advanced NSCLC and expected survival to be less than [redacted]% at 10 years.[15] Based on this, the Weibull and the exponential distributions were the most clinically plausible curves, although both curves predicted survival to be slightly higher than 5% at 10 years. It is important to note that this is a likely consequence of matching the D&T trial data to the KEYNOTE-189 trial, an all-comer patient population who may be associated with more favourable outcomes compared to a BRAF mutated population (see Issue 5).

Given this, the Weibull curve was chosen as the most appropriate curve for D&T OS in the base case economic analysis; the use of the Weibull curve is aligned with the choice of Weibull curve for OS in the original Company submission. The exponential curve was considered in a scenario analysis.

Curve selection for pembro-chemo

Progression-free survival

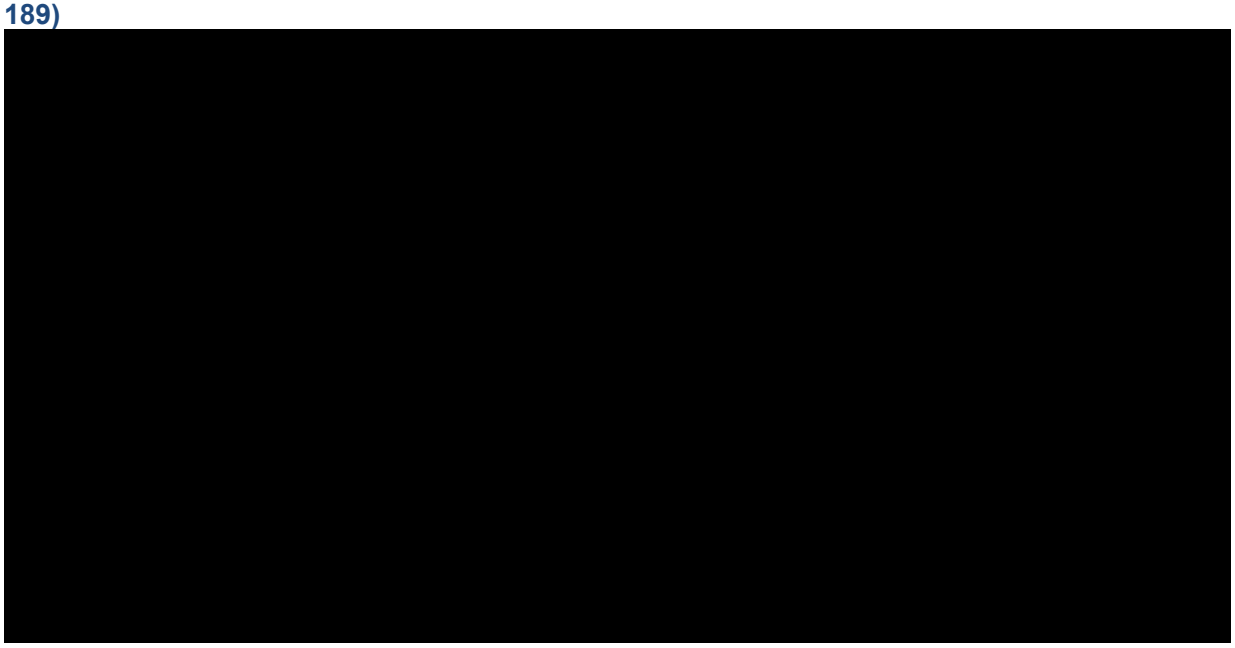
The AIC and BIC values for each of the pembro-chemo PFS extrapolations are summarised in Table 28, and extrapolations of PFS using each model up to 20 years are presented for all functions in Figure 15.

Table 28: Summary of goodness-of-fit data for pembrolizumab plus chemotherapy PFS (KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	6	[redacted]	6
Weibull	[redacted]	5	[redacted]	5
Lognormal	[redacted]	1	[redacted]	1
Log-logistic	[redacted]	2	[redacted]	2
Gompertz	[redacted]	4	[redacted]	4
Generalised gamma	[redacted]	3	[redacted]	3

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 15: Pembrolizumab plus chemotherapy PFS extrapolations up to ten years (KEYNOTE-189)



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

All of the PFS extrapolations appear to predict similar long-term estimates of PFS. As such, the log-normal was selected, as the distribution which provided the best statistical fit to the observed KM data from the KEYNOTE-189 trial.

Overall survival

The AIC and BIC values for each of the pembro-chemo OS extrapolations are summarised in Table 29, and extrapolations of OS using each model up to 20 years are presented for all functions in Figure 16.

Table 29: Summary of goodness-of-fit data for pembro-chemo OS (KEYNOTE-189); standard parametric models

Distribution	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	5	[redacted]	5
Weibull	[redacted]	6	[redacted]	6
Lognormal	[redacted]	3	[redacted]	2
Log-logistic	[redacted]	1	[redacted]	1
Gompertz	[redacted]	4	[redacted]	4
Generalised gamma	[redacted]	2	[redacted]	3

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival.

Figure 16: Pembro-chemo OS extrapolations up to twenty years (KEYNOTE-189)

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Based on the clinician estimates of survival to be less than [redacted]% at 10 years, the Weibull and exponential curves were the only extrapolations to be considered clinically plausible. As such, the Weibull distribution was chosen for the base case economic analysis in order to align with the extrapolation selected for D&T; the exponential was considered in a scenario analysis.

Appendix 5: Analysis of D&T (second-line) versus chemotherapy in the FLATIRON RWE study (2022)

Previously treated patients (V600E): D&T versus chemotherapy

Baseline characteristics

The baseline characteristics for patients with previously treated advanced NSCLC with a BRAF V600E mutation in the FLATIRON RWE study (2022) weighted analysis between D&T (BRF113928 trial, Cohort B) and chemotherapy (FLATIRON RWE Study [2022]) are provided below.

Table 30: Baseline characteristics of the previously treated patients with a BRAF V600E mutation in the FLATIRON RWE study (2022): D&T (BRF113928 trial, Cohort B) versus chemotherapy

Characteristic	Patients with previously treated advanced NSCLC with a BRAF V600E mutation		
	D&T (BRF113928 trial, Cohort B)	Chemotherapy (unweighted)	Chemotherapy (weighted)
Age at index date, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
<65 years, n (%)	[redacted]	[redacted]	[redacted]
≥65 years, n (%)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Other Race	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
0-1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Smoking Status			
History of smoking	[redacted]	[redacted]	[redacted]
No history of smoking	[redacted]	[redacted]	[redacted]
Time from initiation of the first line of treatment to index date, months			
N (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Systemic anti-cancer drugs received prior to index, n (%)			
Receipt of platinum in prior line	[redacted]	[redacted]	[redacted]

Abbreviations: D&T: dabrafenib and trametinib; ECOG PS: Eastern Cooperative Oncology Group Performance Score; IQR: interquartile range; NSCLC: non-small cell lung cancer; RWE: real world evidence; SD: standard deviation.

Progression-free survival

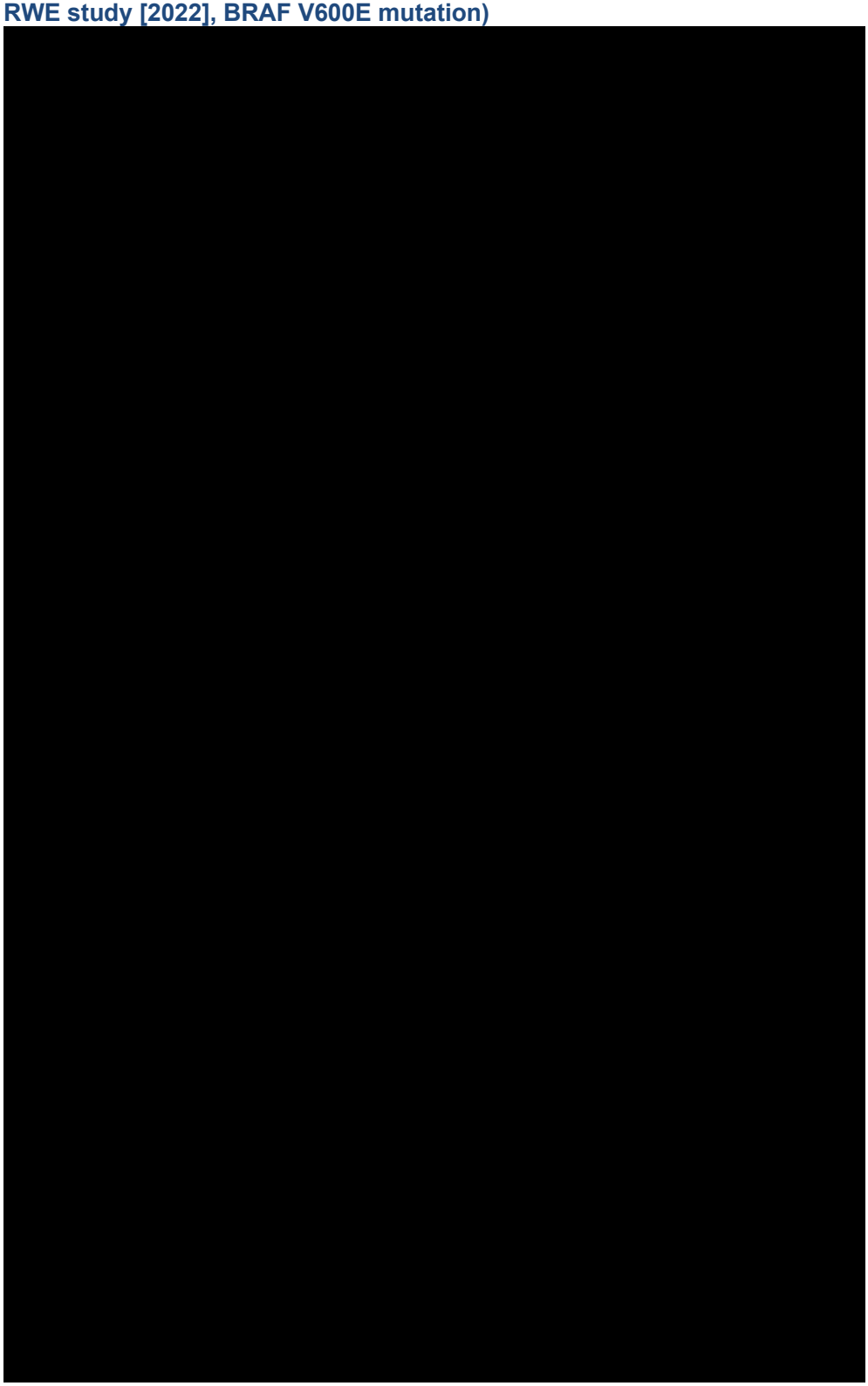
A summary of the PFS comparison for patients with previously treated advanced NSCLC with a BRAF V600E mutation receiving D&T (BRF113928 trial, Cohort B) versus chemotherapy (FLATIRON RWE Study [2022]) is presented in Table 31. Kaplan-Meier (KM) curves for PFS in the weighted comparison are presented in Figure 17.

Table 31: PFS for previously treated patients receiving D&T (BRF113928 trial, Cohort B) and patients receiving chemotherapy in the FLATIRON RWE study (2022) (BRAF V600E mutation)

	D&T (BRF113928 trial, Cohort B)	Chemotherapy (unweighted)	Chemotherapy (weighted)
ESS	57.0	[redacted]	[redacted]
Median PFS, months (95% CI)	9.7 (5.6, 13.6)	[redacted]	[redacted]
PFS rate at 6 months (95% CI)	61.4 (47.5, 72.6)	[redacted]	[redacted]
PFS rate at 12 months (95% CI)	40.4 (27.7, 52.7)	[redacted]	[redacted]
PFS rate at 18 months (95% CI)	29.8 (18.6, 41.9)	[redacted]	[redacted]
PFS rate at 24 months (95% CI)	21.1 (11.6, 32.4)	[redacted]	[redacted]
Hazard ratio for PFS (95% CI) for D&T versus Chemotherapy	[redacted]	[redacted]	[redacted]
P-value for hazard ratio	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; ESS: effective sample size; N/A: not applicable; PFS: progression-free survival.

Figure 17: PFS KM curves – D&T (BRF113928 trial, Cohort B) versus chemotherapy (FLATIRON RWE study [2022], BRAF V600E mutation)



Footnotes: "chemo" represents Chemotherapy.
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival; PD-L1: Programmed-Death Ligand 1

Overall survival

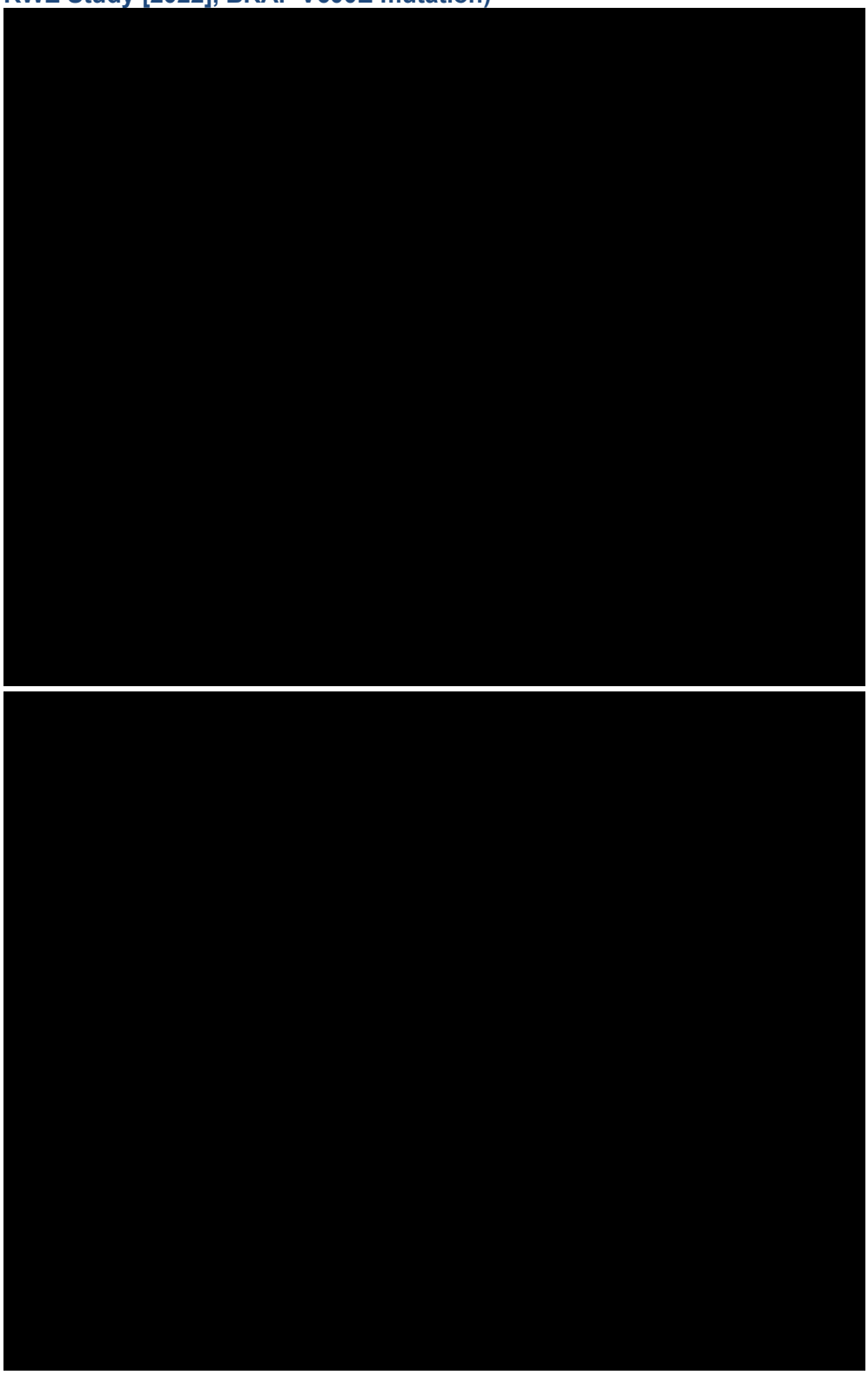
A summary of the OS comparison for patients with previously treated advanced NSCLC with a BRAF V600E mutation receiving D&T (BRF113928 trial, Cohort B) versus chemotherapy (patients with a BRAF V600E mutation in the FLATIRON RWE Study [2022]) is presented in Table 32. KM curves for OS in the unweighted and weighted comparisons are presented in Figure 18.

Table 32: OS for previously treated patients receiving D&T (BRF113928 trial, Cohort B) and patients receiving chemotherapy in the FLATIRON RWE Study (2022) (BRAF V600E mutation)

	D&T (BRF113928 trial, Cohort B)	Chemotherapy (unweighted)	Chemotherapy (weighted)
ESS	57.0	[redacted]	[redacted]
Median OS, months (95% CI)	18.2 (14.3, 28.6)	[redacted]	[redacted]
OS rate at 6 months (95% CI)	80.7 (67.9, 88.8)	[redacted]	[redacted]
OS rate at 12 months (95% CI)	66.4 (52.4, 77.1)	[redacted]	[redacted]
OS rate at 18 months (95% CI)	50.0 (36.4, 62.3)	[redacted]	[redacted]
OS rate at 24 months (95% CI)	40.8 (27.8, 53.3)	[redacted]	[redacted]
Hazard ratio for OS (95% CI) for D&T versus Chemotherapy	[redacted]	[redacted]	[redacted]
P-value for hazard ratio	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; D&T: dabrafenib and trametinib; ESS: effective sample size; N/A: not applicable; OS: overall survival; RWE: real-world evidence.

Figure 18: OS KM Curves – D&T (BRF113928 trial, Cohort B) versus chemotherapy (FLATIRON RWE Study [2022], BRAF V600E mutation)



Footnotes: "chemo" represents Chemotherapy.
Abbreviations: KM: Kaplan-Meier; OS: overall survival; PD-L1: Programmed-Death Ligand 1; RWE: real-world evidence.

Appendix 6: BlueTeq data

Table 33 and Table 34 show the total uptake of D&T via an interim COVID-19 commissioning policy to the months of November and May 2022, respectively.

Table 33: Interim D&T commissioning uptake data to November 2022

Previous treatment status	Count
No previous systemic therapy for metastatic NSCLC	[redacted]
The only prior line of systemic therapy for metastatic NSCLC has been cytotoxic chemotherapy	[redacted]
The only prior line of systemic therapy for metastatic NSCLC has been immunotherapy	[redacted]
The patient has EGFR mutation positive or ALK positive or ROS1 positive disease and has had all appropriate commissioned targeted therapies	[redacted]
Prior line(s) of systemic therapy for metastatic NSCLC have included both immunotherapy and cytotoxic chemotherapy	[redacted]
Total	[redacted]

Abbreviations: ALK: anaplastic lymphoma kinase; D&T: dabrafenib and trametinib; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer.

Table 34: Interim D&T commissioning uptake data to May 2022

Previous treatment status	Count
No previous systemic therapy for metastatic NSCLC	[redacted]
The only prior line of systemic therapy for metastatic NSCLC has been cytotoxic chemotherapy	[redacted]
The only prior line of systemic therapy for metastatic NSCLC has been immunotherapy	[redacted]
The patient has EGFR mutation positive or ALK positive or ROS1 positive disease and has had all appropriate commissioned targeted therapies	[redacted]
Prior line(s) of systemic therapy for metastatic NSCLC have included both immunotherapy and cytotoxic chemotherapy	[redacted]
Total	[redacted]

Abbreviations: ALK: anaplastic lymphoma kinase; D&T: dabrafenib and trametinib; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer.

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Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR, (sections 1.1 to 1.6). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 December 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Alastair Greystoke
2. Name of organisation	Newcastle upon Tyne Hospitals NHS Trust
3. Job title or position	Senior Lecturer and Honorary Consultant in Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	An improvement in survival by 2 months. A response rate of over 30% maintained for over 2 months. A significant improvement in health related quality of life maintained for over two months.
10. In your view, is there an unmet need for patients and healthcare professionals in non-small-cell lung cancer?	Yes once patients have been treated with chemotherapy and immunotherapy then further treatments. are limited and often poorly tolerated. In addition chemotherapy and immunotherapy combinations can be associated with significant side effects and difficult to deliver to a number of patients. Oral therapies that are easy to administer and have high efficacy and improved side effect profiles are needed. Lung Cancer remains the leading cause of cancer related death. Both the cancer and the treatments are associated with significant healthcare resource use. In the absence of a treatable oncogene or significant response to immunotherapy prognosis remains poor.
11. How is non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Pathways are outlined in https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.xml&content=view-index The Technology appraisal Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA683] provides guidance for treatment. The European Society of Medical Oncology guidelines are commonly used https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer Dabrafenib with trametinib is recommended in the ESMO guidelines for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer.

	Dabrafenib with trametinib is presently used in the NHS for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer through a COVID 19 interim funding measure
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	As above at present Dabrafenib with trametinib is being used routinely, through specialist oncology clinics. Compared to commissioned care it will enable oral therapy through out-patient clinics. This will be a major benefit at present times when chemotherapy units are struggling to administer IV therapies with long wait times to start treatment, and some units having to ration treatment. No extra resource or training would be required as already routinely used. B-RAF testing is already routinely included within the genomic laboratory hubs.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, although this may be difficult to formally quantify; the ability to receive an extra line of therapy should result in a longer life expectancy. In addition given the demographics of this population some may choose to decline chemotherapy but would accept an oral targeted therapy. In general the quality of life of patients with lung cancer is driven by lung cancer related symptoms potentially added to by the adverse effects of any therapy given. Given the efficacy of this agent, and it's reduced side effects compared to chemotherapy it will likely be associated with an improvement in quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**No**
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	This technology will be easier for doctors and patients to use given the oral nature. As described above this will have positive implications for the NH S in

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	reduction in use of chemotherapy day units which are under intense strain at present time. Monitoring will be as through many other oral tyrosine kinase inhibitors for lung cancer, with treatment delivered in the outpatient setting. Most practices now have dedicated clinics for patients on oral therapies for lung cancer where care can be split between oncologists, nurse specialists and trained pharmacists with improvements in care for patients, and reduction in burden on oncologists for overbooked clinic slots. Side effects are in general easy to manage with well defined and published algorithms based on the experience in Melanoma. The main problematic side-effect can be the early pyrexia as it can be difficult to distinguish from genuine infection.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required. Patients would be identified by B-RAF testing on the tumour which is already routinely included within the genomic laboratory hubs. Patients will be monitored clinically and with CT/MRI scans until symptomatic progression
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No It is difficult to determine if the instruments of quality of life fully capture the benefits of oral administration as this has not been well defined in this population.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes this will be the first oral targeted therapy available for this population within NHS care. This is likely to lead to improvement in outcomes including quality of life and survival, and boost treatment rates.

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This abnormality is commonly found in older patients with lung cancer who may not tolerate or accept treatment with chemotherapy with or without immunotherapy in combination, but who will accept an oral therapy
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Pyrexia is a common problem early in treatment. There are robust guidelines for the investigation and management of this and in general it does not remain a problem with persistent dosing. Arthralgia can also be a problem but again there are guidelines and it tends to be an early toxicity with improvement with persisted dosing. Other side effects are rash and diarrhoea which are managed according to standard oncology guidelines. Lastly patients need to be observed for the development of secondary skin growths and malignancies, although these are significantly less common with the combination treatment then single agent therapy. Dose adjustment is common in this population as outlined in the application. However in general few patients need to stop treatment due to side effects
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes the clinical trials reflect the UK population. However the primary study for efficacy (Planchard et al) was conducted before the routine availability of immunotherapy and particularly before the routine availability of chemotherapy and immunotherapy in combination. The most important outcomes are response rate, progression free survival and overall survival alongside health related quality of life. All these were measured apart from health related quality of life.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There was a real world French study presented at ASCO 2022. Efficacy of dabrafenib-trametinib combination in BRAF V600E-mutated metastatic non–small cell lung cancer: Results of the IFCT-2004 BLaDE cohort. Aurélie Swalduz, Michele Beau-Faller, David Planchard, Julien Mazieres, Sophie Bayle, Didier Debieuvre, Vincent Fallet, Margaux Geier, Alexis B Cortot, Sebastien Couraud, Catherine Daniel, Eric Pichon, Pascale Missy, Franck Morin, Virginie Westeel, Jean-Bernard Auliac, and Remi Veillon Journal of Clinical Oncology 2022 40:16_suppl, 9082-9082
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA770?	TA770 was in squamous NSCLC not adenocarcinoma which is the common histology in BRAF mutant NSCLC. There has been recent presentations of combined trial data in PDL1 high tumours by the FDA at ASCO 2022 (**Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis.** Oladimeji Akinboro, Jonathon Joseph Vallejo, Erica C. Nakajima, Yi Ren, Pallavi Shruti Mishra-Kalyani, Erin A. Larkins, Paz J. Vellanki, Nicole Lauren Drezner, Luckson Noe Mathieu, Martha Boeri Donoghue, Shenghui Tang, Richard Pazdur, Julia A. Beaver, and Harpreet Singh Journal of Clinical Oncology 2022 40:16_suppl, 9000-9000)and a real world publication in the same population (Pérol et al Ann Oncol. 2022 May;33(5):511-521)
23. How do data on real-world experience compare with the trial data?	Published real world data sets seem to be very comparable to the trial data assessed.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	No

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

No cost-effectiveness evidence presented for second-line use of dabrafenib with trametinib *Is dabrafenib with trametinib also likely to be used second line after pembrolizumab with chemotherapy?*	Yes it may be used although in 3 separate scenarios 1) Present nice guidance is that BRAF status does not need to be taken into account in assessment before either single agent immunotherapy or combination chemotherapy and immunotherapy as 1st line treatment. There may be clinicians who choose this strategy, although that would not be my recommendation. 2) Patients may start chemotherapy and immunotherapy with unknown or delayed BRAF status. on progression if this is known they may then be recommended to have treatment with dabrafenib and trametinib. This population will hopefully be going down over time. 3) There may be a small cohort of patients who have done well on single agent immunotherapy or combination chemotherapy and immunotherapy as 1st line setting, having initiated it before dabrafenib and trametinib was available. It would be recommended to have treatment with dabrafenib and trametinib at this point. This population will be small and going down over time.

Risk-benefit considerations of using an oral therapy *Are there any drawbacks to an oral therapy? Could adherence to treatment be lower than for intravenous therapies (e.g forgetting to take a dose)?*	There are minimal drawbacks to using an oral therapy. These can be difficult to administer in patients that have swallowing problems. Careful education is required to ensure that patients take the appropriate dose at the right time and have strategies if they miss a dose or vomit following a dose. These are well established. Whilst patients can occasionally forget to take a dose; in general in my experience compliance is high. Patients understand that this is an appropriate treatment for lung cancer and often feels significantly better on treatment because of the impact on their lung cancer related symptoms. The clinical efficacy data presented does take into account compliance.
Small non-randomised datasets used to inform efficacy	This is not a question. Unfortunately this is a common problem with molecularly targeted therapies in a small population and has been looked at in previous appraisals of similar agents.
Uncertainty about the applicability of the population in trial BRF113928 *Does inclusion of people who did not meet trial eligibility criteria affect applicability of the trial to clinical practice?*	Not really. In most clinical trials patients tend to be slightly younger and have less comorbidities than the real world population. Extrapolating to real world gives us less difficulties with these oral targeted therapies than with chemotherapy and immunotherapy. In addition NHS England will often restrict the available funding to patients who match more closely to the clinical trial criteria.

Assumed clinical equivalence between dabrafenib with trametinib and pembrolizumab plus chemotherapy *Is dabrafenib with trametinib likely to be superior to pembrolizumab with chemotherapy in those whose non-small-cell lung cancer has a BRAF V600 mutation.*	I do not think this is appropriate. Whilst median progression free survival and overall survivals may be similar these agents work in a very different manner on the cancer, have very different patterns of response and development of resistance. Targeted therapies may be associated with rapid and profound responses but slowly over time the cancer will develop resistance. This is usually through acquisition of secondary mutations either in the oncogenes being targeted, or in bypass mechanisms. This is probably invariable with long enough time on treatment. Similar resistance is seen to chemotherapy, but in a small proportion of patients receiving immunotherapy long term disease control can be seen, as the immune system keeps the cancer under control. The proportion of patients with BRAF V600 NSCLC who achieve this outcome is unknown and likely to be small, but would be different from patients receiving targeted therapies using dabrafenib with trametinib. Overall this means that the shape of the Kaplan Meier curves are likely to be different between the two treatments even if medians are similar.
Inclusion of BRAF testing costs *Is BRAF V600 mutation testing conducted routinely in practice?*	As described above B-RAF is routinely tested now within the genomic laboratory hub structure as part of a routine panel and has been for several years.
Omitted costs and resource use considerations	This is not a question. No additional input on the comments offered.

Inclusion of disutility associated with monthly intravenous infusion *Is the disutility of -0.023 applied in the model for monthly intravenous infusions appropriate?*	Intravenous administration is associated with significant impacts on quality of life. These include the discomfort associated with intravenous cannulation which can become significant with multiple treatments. There is significant time that can be spent on the unit particularly given the delays that are common in many oncology treatment units (this is the most common pieces of adverse patient feedback we receive in my centre from our lung cancer patients review) There is also the financial impact of attending for treatment both for patients and their carers, which can be significant. (Most units will require at least 2 visits for an IV treatment: one medical review with bloods and a separate treatment visit. These will normally be combined for an oral treatment visits). The exact disutility associated with this is uncertain but that estimate appears reasonable.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is the only available oral therapy for this sub-group of lung cancer patients
It will have significant positive impacts in terms of providing an extra line of therapy which is better tolerated than chemotherapy and immunotherapy
The exact benefits are difficult to determine as no randomised controlled trial and most trial data generated before chemotherapy and immunotherapy combinations routinely available.
The use of an oral therapy over IV has significant benefits to both the patient and NHS systems.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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Single Technology Appraisal

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

Informal patient expert feedback from patient organisation

As there was no patient expert on this appraisal at the technical engagement stage, a patient expert statement on two of the key issues in this appraisal was requested from the patient organisation (Roy Castle Lung Cancer Foundation)

The NICE request and RCLCF response are detailed below.

Response from Roy Castle Lung Cancer Foundation to NICE PIP team

Below is a summary of thoughts with 5 lung cancer patients. (conversational) We may well have more feedback and I will forward, although will have passed your deadline of today.

1. All found this question difficult to grasp. It was felt that the context of the 'monthly intravenous infusion', as being anti-cancer in nature needed to be factored in and majorly altered any negative impact of the procedure itself. For all, breathlessness, diarrhoea and back pain had greater impact on QOL. Hypertension, despite being largely asymptomatic from a patient perspective, but due to the medical impact, also felt to be of greater impact on QOL. With regards to dry skin and loss of appetite, it would depend on severity of symptoms. If only minor and not interrupting daily life, then on a par or of lesser impact.

2. If both oral and iv infusion had the same outcomes, all had a preference for oral, Fewer hospital visits, waiting around at hospitals, parking / transportation / relatives taking time to accompany etc... So much more convenient. Did not think that compliance would be an issue, as highly motivated to take it - one patient described viewing his oral medication as the thing he sees as 'keeping my cancer at bay and me alive'. On the side of intravenous, they could see that some patients may prefer that - all done on the one day. So, perhaps a question of patient choice. Of note, some patients have needle phobias and for some, the practical insertion of the infusion needle can be difficult, having undergone many previous venepunctures.

Hope the above is helpful

Email sent to Roy Castle Lung Cancer Foundation from NICE PIP team

We have recently had the technical engagement call for the above topic and the technical team raised some patient issues. As we currently have no patient experts, we wondered if you would be able to answer the below questions? We understand that you may not be able to due to capacity, but it would be great to have some patient input on the following questions if at all possible.

The two issues which the technical team have suggested need patient input on are listed below. For the first issue, ideally someone with experience of intravenous infusion and at least some of the adverse events listed would answer this. For the second question, it could be anyone who has used or considered using an oral treatment. It isn't important if their patient expert hasn't had all of the adverse events. So, if they haven't experienced dry skin it's not an issue. Those are just a random selection to give us an idea of IV infusion disutility so any comparisons you can give would be great!

1. A disutility of -0.023 has been applied to monthly intravenous infusions in the model. This means that quality of life is reduced by a certain amount each time someone in the model has an intravenous infusion. The Evidence Assessment Group consider that the amount by which utility is reduced could be too high and has suggested patient input could help resolve this. As utility values are not intuitive would it be possible to ask people to try and compare an intravenous infusion to having the following events for a month and state which they feel are equivalent (or have a higher or lower quality of life impact) than a monthly intravenous infusion in terms of the impact on quality of life:
   * Back pain
   * Decreased appetite
   * Dry skin

* Hypertension
* Diarrhoea
* Dyspnoea [shortness of breath]

If it makes the exercise easier then the person/s completing the status could try and rank the six events listed and a monthly intravenous injection in order of effect on quality of life (assuming they are all separate events)

1. We would like more information on how people would respond to an oral treatment for lung cancer, if the statement could answer any of the following questions we would be very grateful
   * Would people consider themselves more likely to forget to take a daily oral treatment than go for a monthly infusion
   * What are peoples opinions on an oral treatment, what benefits do they perceive?

If possible, would you be able to respond to this by Friday 20 January?

Please let me know if you have any questions.

Single Technology Appraisal (STA)

Dabrafenib with trametinib for treating advanced BRAF V600 mutation-positive non-small-cell lung cancer [ID3851]

EAG addendum: review of company's response to technical engagement

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the EAG in its report, which were discussed at technical engagement.

The technical engagement covered 9 key issues for consideration. The company's response to technical engagement included revised modelling approaches which resolved issues 7 and 9. A summary of the issues the EAG considers to be resolved, partly resolved or unresolved is provided in Table 1.

Table 1: Summary of the key issues

Issue		**Resolved?**
1	No cost-effectiveness evidence presented for second-line use of dabrafenib with trametinib	No
2	Risk-benefit considerations of using an oral therapy	No
3	Small, heterogenous non-randomised datasets for evaluating efficacy	No
4	Uncertainty about the applicability of the population recruited to trial BRF113928	Partly
5	Clinical equivalence assumed between D&T and pembrolizumab plus chemotherapy	Partly
6	Inclusion of BRAF testing costs	Partly
7	Alignment of resource use with previous appraisals	Yes
8	Inclusion of disutility associated with monthly IV infusion	No
9	Relevance of a severity modifier under particular assumptions	Yes

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: No cost-effectiveness evidence presented for second-line use of dabrafenib with trametinib

The company restates their view that D&T will be used as a first-line treatment for patients harbouring a BRAF mutation, and that cost-effectiveness modelling in a second-line population is not feasible. The company also maintain that the implementation of the Genomic Hubs strategy will mean the proportion of patients currently treated at second-line due to delayed identification of mutation status will decrease over time.

BlueTeq commissioning uptake data presented in Appendix 6 to the company's Technical Engagement response show that to November 2022, [redacted] patients initiating D&T had received previous systemic therapy. At the time of initiating D&T treatment, [redacted]

patients had received multiple prior lines of systemic therapy, including both immunotherapy and cytotoxic chemotherapy.

In response to the EAG's request for a comparison of the efficacy of D&T in systemic therapy-experienced patients with the first-line cohort used in the model, the company presented a comparison of Cohort B in the BRF113928 study (i.e. those treated with D&T at second-line), and patients receiving chemotherapy in the FLATIRON study. It was not clear what sub-population of the FLATIRON study this was, and dabrafenib appeared to show no statistically significant benefit versus chemotherapy in this group with large uncertainty [redacted]. If the FLATIRON population used was limited to those treated at second line with a BRAF V600E mutation, it would have comprised only [redacted] patients.

The EAG's response

The BlueTeq data provided by the company demonstrate the existence of a significant sub-population of patients eligible for D&T at second-line. The EAG maintains that it is currently unclear whether wait times for genomic test results will improve significantly in the near future.

The value of the analysis of Cohort B and FLATIRON is limited. While it appears to show there was [redacted], the very small numbers of previously treated patients with a BRAF V600E mutation in FLATIRON means no firm conclusions can be drawn from this analysis. The EAG notes that the comparator arm of studies in which pembrolizumab was compared to docetaxel in previously treated advanced NSCLC may have provided a more representative population against which to compare Cohort B outcomes. However, the EAG also notes that median PFS and OS results were similar on D&T across Cohorts B and C in study BRF113928. The assumption of similar effect is reasonable based on the limited data available, though nevertheless still uncertain.

The cost-effectiveness of D&T in this population remains a significant source of uncertainty. The EAG considers this issue unresolved.

2.2 Issue 2: Risk-benefit considerations of using an oral therapy

The company stated that it did not consider there to be drawbacks to using an oral therapy and that it would not be appropriate to conduct the scenarios requested in this key issue. The company provided data from two trials of D&T in advanced melanoma (COMBI V and COMBI D), stating that the median daily dose for both treatments were close to the planned doses.

The EAG's response

Contrary to the company's statement, the EAG did not request any scenarios to explore this issue. However, the company's statement that it does not consider there to be drawbacks to using an oral therapy does not appear to be well-supported by the available data. In BRF113928 data on 'dose reductions' and 'dose interruptions' were subdivided by reason, with most reductions/interruptions being due either to adverse events or subject non-compliance. Concerns remain about how well patients adhere to D&T, given that [redacted] who received D&T deviated from the study protocol due to [redacted]. It is unclear what the threshold was for patients to deviate from the protocol because of treatment non-compliance, although they were classed as having received an [redacted] (CSR Table 1.1322). It therefore seems that there are drawbacks to using an oral therapy for the small proportion of patients who do not adhere well to D&T; consideration should be made of the possibility that these patients may achieve better outcomes on pembrolizumab, given that is administered once every 3 or 6 weeks as an intravenous infusion.

The company's new data on daily dose in the melanoma trials is limited by the presentation of only medians. In study BRF113928, for dabrafenib, the means were notably lower than the medians, but means were not provided for the melanoma trials. The company did not provide data on protocol deviations specifically due to non-compliance.

2.3 Issue 3: Small, heterogenous non-randomised datasets for evaluating efficacy

The company presented a revised base case economic analysis, in which KEYNOTE-189 data are used to inform the evidence for pembrolizumab and chemotherapy. This trial provides a large, mature dataset of patients who took pembrolizumab and chemotherapy. The company performed a matching adjusted indirect comparison (MAIC) to match Cohort C of the BRF113928 trial (D&T) to the patient population in the KEYNOTE-189 trial.

Individual patient data from Cohort C of the BRF113928 trial for both OS and PFS were weighted to match aggregate baseline characteristics from the pembro-chemo arm of the KEYNOTE-189 trial. Covariates adjusted for were those identified as statistically significant prognostic variables and those previously identified in previous NICE appraisals (TA789 ([tepotinib], TA653 [osimertinib], TA628 [lorlatinib], TA500 [ceritinib]). See Table 16 of the company's TE response. These included race, Eastern Cooperative Oncology Group (ECOG) status, histology, sex, smoking history, and presence of brain metastases. However, the company did not adjust for prognostic factors such as BRAF mutation and PD-L1 status as this was not feasible. A secondary scenario analysis including only those covariates that were statistically significant was also conducted.

Prior to matching, baseline characteristics from Cohort C of the BRF113928 trial and the KEYNOTE-189 trial were compared (Table 17 of the company's TE response). They were generally balanced except for statistically significant differences in the percentage of males and smokers in both cohorts. These were adjusted for in the base case analysis.

For OS, the weighted adjustment resulted in a large loss of patients [redacted] from the effective sample size (from 36 to [redacted]). Both the naïve and MAIC-weighted HRs show slightly improved survival benefits with D&T, although results are not statistically significant (Table 2). For PFS, the weighted adjustment resulted in a greater loss of patients [redacted] from the effective sample size (from 36 to [redacted]) compared to OS. Both the naïve and MAIC-weighted HRs show improved survival benefits although results are not statistically significant (Table 2).

Table 2 Comparison of naive and weighted OS and PFS hazard ratios based on MAIC of BRF113928 and KEYNOTE-189 (Company TE response Table 6)

D&T versus pembro-chemo	Naive		Weighted	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
PFS	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]	[redacted]

The results for the scenario analysis were in line with the results from the base case matching analysis.

The EAG's response

The company's use of KEYNOTE-189 data provides a better source of comparator data (pembrolizumab and chemotherapy) as it has larger sample size and is based on trial data. However, this is still a non-randomised comparison, based on an external control and not based on a BRAF mutation population. Heterogeneity and uncertainty remain. Data for D&T are still scarce, which is exacerbated by the reduced effective sample size which results from using MAIC to compare the treatments (see also Key Issue 5).

The EAG considers this issue unresolvable with current data.

2.4 Issue 4: Uncertainty about the applicability of the population recruited to trial BRF113928

The company provided specific reasons why some of the patients enrolled in study BRF113928 did not meet the trial eligibility criteria.

The EAG's response

Having examined the reasons for ineligibility, the EAG is satisfied that the inclusion of these patients is unlikely to have had a noticeable effect on the results of study BRF113928. However, the company only partly addressed the EAG's concerns about the applicability of the BRF113928 population, as it was unable to provide even basic data on the number of patients screened and the number excluded prior to enrolment in BRF113928. The EAG further notes that the population used in the economic model is the MAIC-adjusted population, and so does not necessarily reflect outcomes in a BRAF mutation population (see also Issues 3 and 5).

2.5 Issue 5: Clinical equivalence assumed between D&T and pembrolizumab plus chemotherapy

The company incorporate the results of the MAIC described in their response to Key Issue 3 into their revised base-case analysis.

2.5.1 MAIC

The company consider this analysis to be a more robust and appropriate comparison than either the assumption of clinical equivalence between D&T and pembrolizumab plus chemotherapy, and the naïve comparison originally presented in the company's clarification response. The company generated weighted KM plots for PFS and OS using the MAIC (Figure 1 and Figure 2).

Figure 1 Naive and weighted PFS KM curves for D&T and pembro-chemo, based on MAIC of BRF113928 and KEYNOTE-189 (Company TE Response Figure 1)

Figure 2 Naive and weighted OS KM curves for D&T and pembro-chemo, based on MAIC of BRF113928 and KEYNOTE-189 (Company TE Response Figure 2)

The MAIC substantially reduced the effective sample for D&T (Taf-Mek weighted), the PFS outcomes of the matched-adjusted population appear to be worse than those of the unadjusted population in BRF113928, but the weighted group comprise a larger proportion of patients remaining progression-free in the long-term. The weighted analysis appears to reduce the relative effectiveness of D&T in terms of PFS (see hazard ratios presented in Table 2) and substantially widens the confidence intervals around the hazard ratios and survival probabilities. The loss of effective sample size is slightly smaller in the weighted OS analysis, and outcomes more closely resemble those in the naïve/unadjusted comparison, albeit with a small reduction in the risk of an event. The hazard ratio point estimate is improved for D&T versus pembro-chemo in this analysis.

Given the heterogeneity of the trial populations, the company considers the MAIC to be more robust, and chose to incorporate this analysis into their updated base-case whilst reiterating the view that even this analysis may be a conservative representation of the benefits of D&T relative to pembro-chemo.

The EAG's response

The relative effects generated from the MAIC apply to the KEYNOTE-189 trial population and not Cohort C of the BRF113928 trial. KEYNOTE-189 trial does not represent the target population as it does not include participants with a BRAF V600 mutation. An unanchored MAIC was performed which assumes all effect modifiers and prognostic factors have been adjusted for, which is a strong assumption. Failure of this assumption will lead to bias in the unanchored estimate. No evidence is

presented on the likely extent of error due to unaccounted for covariates, particularly BRAF mutation and PD-L1 status, in relation to the observed relative treatment effect.

The EAG did not have access to the data or analysis code so cannot fully critique the method.

Given the large uncertainty in the confidence intervals generated from the MAIC and in the relevance of the relative effects to the target population, it is unclear how meaningful the estimated benefit of D&T over pembro-chemo is, or indeed whether there is any benefit associated with D&T. The EAG emphasises a focus on the distribution of probabilistic results in Section 3, which illustrate the extent of decision uncertainty originating from the imprecision around the MAIC effect estimates.

The EAG considers this a key area of uncertainty.

2.5.2 Adjusted curve extrapolation

The company chose to apply a Weibull curve to the MAIC OS curves for D&T and pembro-chemo on the basis of clinical plausibility, and consistency with the curve selection in the original submission. The Weibull curve had the worst statistical fit to D&T OS data and the second-worst fit to pembro-chemo OS in terms of AIC and BIC. The statistical and visual fit of these curves are presented in Appendix 4 of the company's technical engagement response.

The company applied an exponential extrapolation to the adjusted PFS KM curve, as it generated the only clinically plausible long-term prediction of PFS on D&T. Again, the statistical fit was poor to D&T data, which ranked joint 5 out of 5 models, and 6 out of 6 for pembro-chemo, although the maturity of these data meant all extrapolations made very similar predictions.

The EAG's response

The EAG is satisfied that the company's chosen extrapolations of the adjusted D&T curves and updated pembro-chemo data from KEYNOTE-189 are appropriate. Whilst the statistical fits of the selected curves are generally poor, the Weibull and exponential curves are amongst the most pessimistic with regards to long-term predictions of OS and PFS.

Likewise, the significantly reduced numbers at risk in the survival analysis of adjusted PFS on D&T mean only the exponential produces a realistic prediction of long-term outcomes (i.e. all patients have progressed by 5 years). However, it has a poor visual and statistical fit to PFS data for D&T, notably appearing to significantly over-predict PFS over the first three years of the model. The MAIC analysis may therefore overestimate PFS outcomes on D&T.

Notably, pembro-chemo outcomes are significantly improved in the more mature 5-year data cut of the KEYNOTE-189 study. As a result, the naïve comparison of BRF113928 and KEYNOTE-189 as

presented in the EAR no longer generates a meaningful QALY benefit for D&T over pembro-chemo. This means that unless D&T is cost-saving, the cost-effectiveness of D&T depends upon the use of the adjusted analysis.

2.6 Issue 6: Inclusion of BRAF testing costs

The company provide a scenario analysis in which the cost of testing for BRAF V600 mutations is included, using a unit cost per test of £34 as provided by NHS England. The company maintains that this cost should not be included in the base case, as BRAF testing is already part of current NHS practice.

The EAG's response

The EAG considers the scenario in which testing costs are included to be informative. As discussed in the EAR, the funding of BRAF mutation testing is integral to the implementation of dabrafenib on the NHS, and it having been made available via Covid-19 guidelines should not preclude its inclusion in line with previous appraisals of targeted therapies. However, in recognition of input from NHS England, the EAG agrees this should remain an illustrative scenario for consideration by the committee.

2.7 Issue 7: Alignment of resource use with previous appraisals

The company accepted the EAG's approach to modelling end-of-life care costs and included this in their revised base-case analysis.

The company conducted a review of previous appraisals of oral therapies and consulted UK clinical experts to more accurately model administration costs for oral therapies. The company propose the inclusion of a monthly administration cost for the first three months of treatment, which reduces to once in every three months, with the assumption that a patient will then receive a three-month supply of treatment at each administration. This scenario has been included in the company's revised base-case analysis.

The company also reviewed recent approaches to modelling wastage of oral therapies in NICE appraisals. With reference to clinical advice, the company propose an approach in which half a pack of dabrafenib and trametinib are each wasted for all patients discontinuing treatment, assuming that on average patients would discontinue half way through a pack of treatment. This approach is incorporated into the company's updated model.

The company cited advice which suggested patients would not be prescribed additional treatment until the previous supply had been used, and therefore the RDI acquisition cost savings lost would be closer

to 5% than the 50% suggested by the EAG. They therefore present scenario analyses in which 5% of the RDI cost savings are wasted alongside an analysis in which 50% of RDI cost savings are wasted.

The EAG's response

The EAG considers the approaches proposed and incorporated by the company into their updated base-case analysis a reasonable compromise to the issues raised in the EAR. The EAG considers the approach taken to each of the three issues above to be appropriate as implemented in the company's revised base-case analysis, and has aligned the updated EAG base-case results presented in Section 3.2 with the approach used in the company's updated base-case analysis. The EAG considers this issue resolved.

2.8 Issue 8: Inclusion of disutility associated with monthly IV infusion

The company maintain that the application of a disutility is a preferable approach to capturing the impact of receiving IV infusions over the qualitative assessment suggested by the EAG. The company proposed an approach in which the same disutility of 0.023 was applied to patients on pembro-chemo only during those cycles in which administration takes place. This results in a per cycle disutility of 0.008 in Cycles 0-11, and 0.006 in Cycles 12+. The company notes that in the context of the revised base case in which a more substantial QALY gain is generated on D&T, the impact of this disutility on cost-effectiveness estimates is extremely small. The inclusion of this disutility increases total QALYs by [redacted] on D&T.

The EAG's response

The EAG maintains its preference for the removal of any quantitative consideration of a health-related quality of life impact of IV infusions from the model. It is noted that the approach proposed in the company's updated base-case has only a negligible impact upon incremental QALY gain. The EAG consider that a qualitative narrative around what is likely to be a fundamentally uncapturable benefit in HRQoL terms, to be more valuable for informing the committee's decision than to distil all the described benefits of an oral therapy into a minute QALY benefit.

It may therefore be preferable to omit any disutility from the model on the grounds that the advantages of an oral therapy over IV infusion cannot be adequately represented in a cost-effectiveness model, and that the key advantages to patients and the NHS described by the company should be weighed by the committee explicitly on their own merit. The EAG base case retains the assumption of not applying a disutility to reflect the impact of IV infusions, but again notes that the approach included in the company's updated analysis has very little impact on incremental QALY gain.

2.9 Issue 9: Relevance of a severity modifier under particular assumptions

In the company's revised base-case analysis in which a later data-cut of the KEYNOTE-189 study is used to inform the modelled efficacy of pembro-chemo, the company states that the criteria for a severity modifier are not met, as projected survival improves significantly with this more mature data. The estimated absolute QALY shortfall in their updated base-case analysis is [redacted] years, with a proportional shortfall of [redacted].

The EAG's response

The EAG is satisfied that this issue has been explored sufficiently using the company's updated and preferred source of comparator efficacy data. The EAG agrees that the criteria for a severity modifier have not been met in this appraisal and considers this issue resolved.

3 UPDATED MODELLING ASSUMPTIONS

In response to the issues noted in the EAR, and following the additional analyses undertaken by the company, an updated base-case cost-effectiveness model was presented.

The following EAG-preferred assumptions are incorporated within the company's revised model:

- Issue 3/5: Use of KEYNOTE-189 to model PFS and OS for pembrolizumab plus chemotherapy
- Issue 3/5: Pembrolizumab plus chemotherapy ToT modelled assuming equivalence to PFS in KEYNOTE-189
- Issue 3/5: Use of MAIC versus KEYNOTE-189 used to model D&T PFS and OS
- Issue 7: End of life costs aligned with EAG preferred approach
- Issue 7: Cost of pharmacist dispensing time included for D&T
- Health state utilities based on TA812

In addition, the following issues have been partially accommodated in the company's revised model:

- Issue 8: Disutility related to IV infusion is significantly reduced

The company maintain their original position on the following assumptions:

- Discounting calculated discretely according to whole years elapsed

3.1 Results

The results of the company's updated base case and a series of alternative scenarios are presented in

Table 3 below. Results of the company's revised probabilistic base-case are presented in Table 4. These results are inclusive of the approved PAS discounts for dabrafenib and trametinib, but are exclusive of confidential PAS discounts for comparator and subsequent treatments. Results with PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix separate to this document.

[redacted]

Table 3 Revised Company analysis results – deterministic (TE Response Table 12)

	Incr. costs (£)	Incr. QALYs	Incr. LYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: D&T OS curve choice (exponential)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: D&T OS and PFS: based on KEYNOTE-189 MAIC (Sensitivity analysis matched data)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: BRAF testing costs included (for all patients receiving D&T)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: IV disutility excluded (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: IV disutility excluded AND 50% of RDI savings are wasted (EAG preferred assumption)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
Scenario: 5% of RDI savings are wasted (based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Table 4 Revised Company base case results – probabilistic (TE Response Table 13)

	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Revised base case	[redacted]	[redacted]	D&T is dominant	[redacted]	[redacted]

3.2 Updated EAG base-case analysis

The EAG accept the majority of the amendments proposed by the company to address the Key Issues highlighted in the EAR. A small number of points remain contended between the two base-case analyses, the effect of these differences is therefore illustrated in the results below. The primary differences between the two analyses is that the EAG base-case excludes the disutility associated with IV infusions, and calculates discounting continuously from the model outset. For illustrative purposes, the EAG presents the updated naïve comparison between BRF113928 and KEYNOTE-189. The comparative efficacy of D&T in this analysis differs significantly from the naïve comparison presented in the EAR due to the later data cut for KEYNOTE-189 implemented by the company at Technical Engagement.

As discussed above, the potential reduction in bias in the matched adjusted D&T data was associated with a substantial loss of precision. The updated EAG base-case is presented both with and without the MAIC adjustment, this is of particular importance in the probabilistic analysis which illustrates the large degree of uncertainty around the ICER in the MAIC analysis.

The deterministic results of the updated EAG base-case analysis with and without the MAIC are presented in Table 5. The probabilistic equivalents of these results are presented in Table 6. Note that these results are inclusive only of the currently approved PAS discounts for D&T. Both sets of results inclusive of all cPAS discounts are presented in the confidential appendix to this report.

Table 5 Deterministic results of EAG updated base-case analyses

Option name	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	NHB (£20,000)	NHB (£30,000)
EAG updated base case 1 (naïve comparison of BRF113928 and KEYNOTE-189)							
Pembrolizumab plus chemotherapy	[redacted]	[redacted]					
D&T	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
EAG updated base case 2 (D&T OS and PFS: based on KEYNOTE-189 MAIC)							
Pembrolizumab plus chemotherapy	[redacted]	[redacted]					
D&T	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

In the first probabilistic analysis, D&T had a [redacted] probability of being the most cost-effective treatment option at a willingness-to-pay threshold of £20,000 per QALY gained, and [redacted] at £30,000. In the second analysis using the KEYNOTE-189 MAIC, D&T had a [redacted] probability of being the most cost-effective option at £20,000, which increased to [redacted] at £30,000. Scatterplots are presented for EAG base case 1 and 2 in Figure 3 and Figure 4 respectively.

Table 6 Probabilistic results of EAG updated base-case analyses (5000 iterations)

Option name	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER	NHB (£20,000)	NHB (£30,000)
EAG updated base case 1 (naïve comparison of BRF113928 and KEYNOTE-189)							
Pembrolizumab plus chemotherapy	[redacted]	[redacted]					
D&T	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]
EAG updated base case 2 (D&T OS and PFS: based on KEYNOTE-189 MAIC)							
Pembrolizumab plus chemotherapy	[redacted]	[redacted]					
D&T	[redacted]	[redacted]	[redacted]	[redacted]	D&T is Dominant	[redacted]	[redacted]

Figure 3 EAG updated base case 1 PSA scatter plot (£20k WTP)

[redacted]

Figure 4 EAG updated base case 2 PSA scatter plot (£30k WTP)