For public – confidential information redacted

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

Technology appraisal committee D 16th February 2023

Chair: Dr Megan John

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Company: Novartis

Background on non-small-cell lung cancer (NSCLC)

Epidemiology

- Non-small-cell lung cancer (NSCLC) makes up 80-85% of all lung cancers, and there were 28,300 cases diagnosed in England in 2020
- Mutations in the BRAF gene are one of several driver mutations in NSCLC, they are found in around 1-4% of NSCLCs and about half of all BRAF mutations are known as V600E mutations

Diagnosis and classification

- Most NSCLCs are diagnosed at advanced stage (the cancer has spread to lymph nodes or organs in the chest) or metastatic (the cancer has spread to other parts of the body)
- In 2020, 19% of all lung cancer cases were stage 3, and 40% were stage 4

Symptoms and prognosis

- Symptoms can include a persistent cough, recurrent chest infections, coughing up blood and persistent tiredness
- Survival rates are relatively low, in England between 2013 and 2017 five year survival for those diagnosed with stage 3 (advanced) and stage 4 (metastatic) lung cancer was 15% and 5% respectively

Equality considerations

- Neither the company, clinical experts or the patient organisation identified any equality considerations for this appraisal.

Patient perspectives

Roy Castle Lung Cancer Foundation (patient organisation)

Living with NSCLC

- 1 year survival is around 37% and the poor outlook impacts family and carers
- Symptoms are difficult to treat and can be distressing for people with NSCLC and family

Unmet need

- Important as the first targeted therapy for BRAF V600 positive disease in NSCLC. Various other mutations already have targeted therapies and dabrafenib with trametinib was approved by the EMA in 2017.

"Several studies have shown poorer outcomes with platinum based chemotherapy in patients with BRAF V600 mutations. There is an obvious unmet need"

The technology

- Combination relatively well tolerated, most likely adverse events are those generally common in cancer therapies
- Experience of this treatment in melanoma disease area means there is considerable knowledge around managing adverse events
- If an oral and intravenous treatment had the same outcomes. Patients would choose the oral treatment

 Abbreviations: NSCLC, non-small-cell lung cancer;

Clinical perspectives – Clinical expert submission

Unmet Need

- Lung cancer remains the leading cause of cancer related death
- Both the cancer and current treatments are associated with significant healthcare resource use
- There is an unmet need as once people have been treated with chemotherapy and immunotherapy further treatments are limited and often poorly tolerated

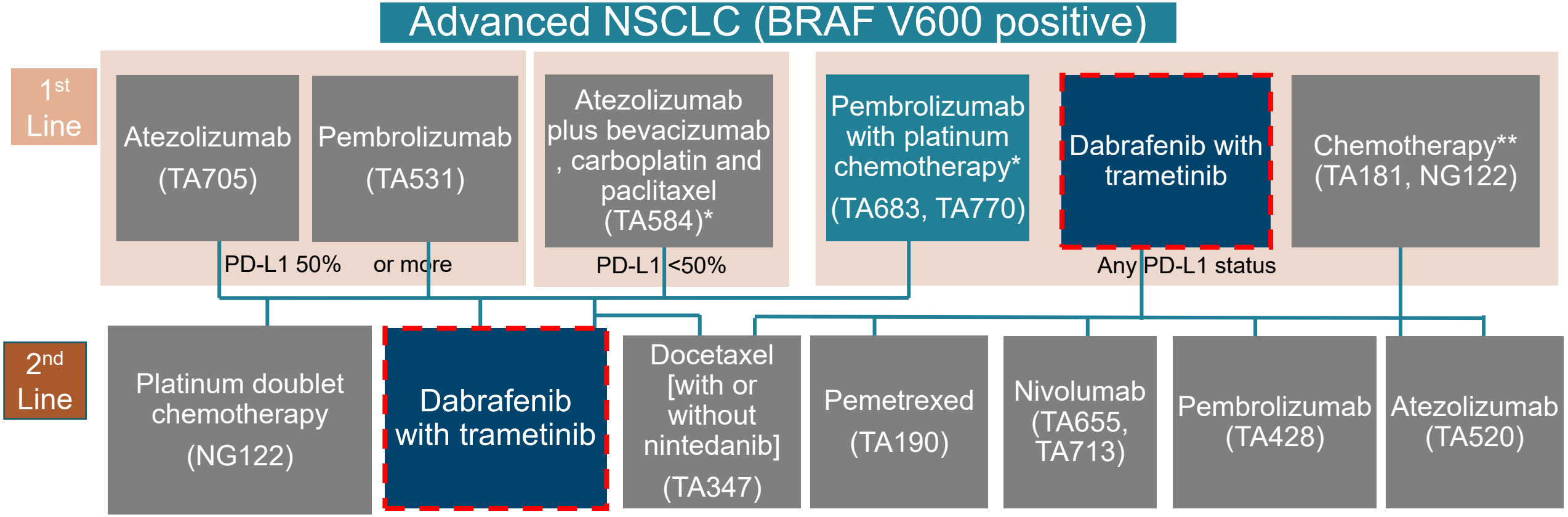
Benefits of the therapy

- Oral therapies will be a major benefit for the NHS as chemotherapy units are struggling to administer intravenous therapies and currently have long wait times
- Side effects are generally easy to manage with well defined and established practices from the disease are of melanoma.

"It [dabrafenib and trametinib] will have significant positive impacts in terms of providing an extra line of therapy which is better tolerated than chemotherapy and immunotherapy"

Treatment options (NSCLC)

For those with BRAF V600 mutation (mutually exclusive to other driver mutations)



Company: Pembrolizumab with platinum chemotherapy is the primary comparator. It is preferred to immunotherapy monotherapies due to the aggressive nature of the disease, and chemotherapy is rarely used alone.

Does the clinical expert consider pembrolizumab with chemotherapy to be the most frequently used first line treatment?

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*Pemetrexed with carboplatin or cisplatin; **Docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with a platinum drug

Key issues

Issue	Resolved?	ICER impact
Data informing clinical efficacy in the model / Use of small non-randomised datasets	Not fully resolvable	Large
No cost-effectiveness evidence presented for 2nd line use	No – to discuss	Unknown
Risk benefit considerations of using an oral therapy	No – to discuss	Small
Inclusion of disutility associated with monthly intravenous infusion	No – to discuss	Small
Applicability of the population in BRF113928	Partly resolved	N/A
Inclusion of BRAF testing costs	Partly resolved	Small
Omitted costs and resource use considerations	Resolved	Moderate

Abbreviations: ICER, incremental cost effectiveness ratio

Dabrafenib with trametinib (Tafinlar and Mekinist, Novartis)

Technology details

Marketing authorisation	• 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. • Marketing authorisation extension granted by the EMA on 27 March 2017
Mechanism of action	• Dabrafenib is a small molecule inhibitor specific to the ATP binding site of BRAF V600 mutant enzymes • Trametinib is a small molecule inhibitor specific to the allosteric site of the MEK1 + 2 enzymes • Together they function to disrupt a cellular growth pathway and reduce uncontrolled cell division
Administration	• Dabrafenib and trametinib are oral therapies • Recommended doses are: dabrafenib 150mg BID, and trametinib 2mg per day
Price	• Dabrafenib 75mg list price: £1,400 per 28 capsule pack (Monthly cost ~£5,600) • Trametinib 2mg: £4,800 per 30 tablet pack (Monthly cost ~£4,800) • There is a patient access scheme for dabrafenib with trametinib
Other	• Dabrafenib with trametinib has been available in this indication in the NHS since 2020 as a COVID-19 interim treatment, to reduce the need for travel to chemotherapy centres and the risk of immunosuppression associated with chemotherapy

NICE Abbreviations: EMA, European Medicines Agency; ATP, adenosine tri-phosphate; BID, twice daily;

Decision problem

Key differences from scope decision problem are around comparators

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adult patients with advanced NSCLC with a BRAF V600 mutation	Adult patients with untreated NSCLC with a BRAF V600 mutation	The company did not present economic analyses for those who would receive the intervention 2nd line
Intervention	Dabrafenib with trametinib	As per final scope	No comments
Comparators	Several immunotherapy, chemotherapy and combination regimens for both 1st and 2nd line. (*See company submission Table 2)*	Selected pembrolizumab with chemotherapy as the primary comparator at 1st line as this is the most used in practice	All comparators in NICE scope are relevant NHS treatments. Omission of other comparators unlikely to have significant impact on assessment of clinical effectiveness but will have cost implications in the economic evaluation
Outcomes	OS, PFS, response rate, adverse events, HRQoL	As per final scope	Outcomes in the submission match the scope, although note the absence of HRQoL data from the trial

Do the committee consider the choice of comparator is appropriate?

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Abbreviations: NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival; HRQoL, health related quality of life;

Clinical effectiveness

- BRF113928 trial (dabrafenib with trametinib)
- FLATIRON real world evidence study (pembrolizumab with chemotherapy, in BRAF V600E population)
- KEYNOTE-189 (pembrolizumab with chemotherapy, all comers population)

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Key clinical trial - BRF113928 (NCT01336634)

Clinical trial designs and outcomes

	BRF113928
Design	Open label, single arm phase 2 study (3 cohorts)
Population	Adult patients with confirmed stage 4 NSCLC with a BRAF V600E mutation Cohorts A + B: Disease relapsed or progressed after 1 or more prior lines of platinum based chemotherapy Cohort C: No prior anti cancer therapies for metastatic disease
Intervention	Dabrafenib 150mg BID (Cohort A); dabrafenib 150mg BID + trametinib 2mg QD (Cohorts B + C)
Comparator(s)	None
Duration	6 years of follow up
Primary outcome	Overall response rate (patients with confirmed complete or partial response)
Secondary outcomes	Duration of disease, progression free survival, overall survival
Locations	71 sites in 11 countries across Asia Pacific, European and North American regions. 5 sites in England.

NICE Abbreviations: NSCLC, non-small-cell lung cancer; BID, twice daily; QD, daily;

Key clinical trial - BRF113928 (NCT01336634)

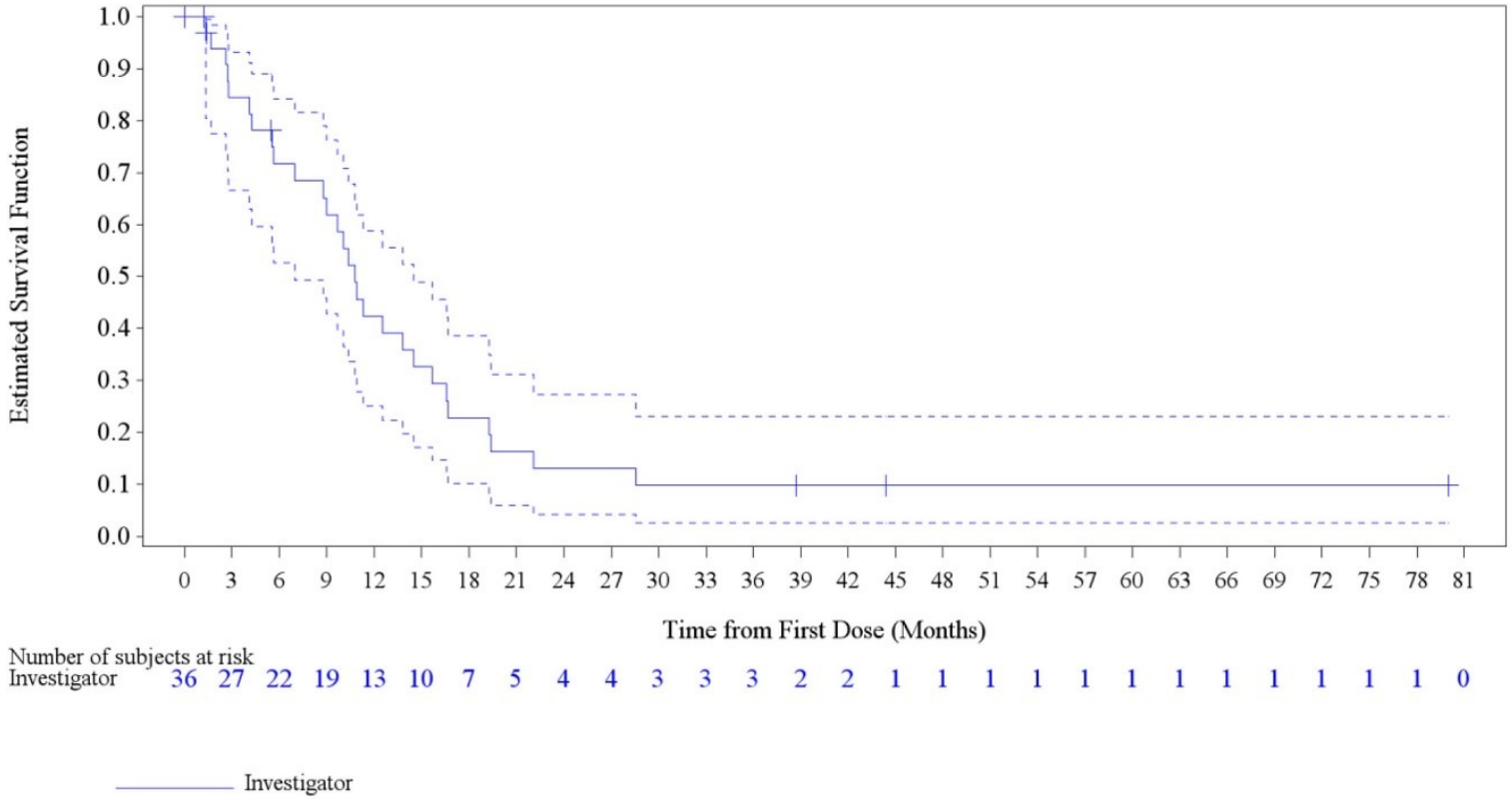
Clinical trial structure

- Cohort C was used to inform clinical efficacy in the model
- Cohort B was not used in the model, although data has been presented by the company to support the case for using dabrafenib and trametinib at second line.

Abbreviations: NSCLC, non-small-cell lung cancer

BRF113928 results - PFS

Progression free survival – Cohort C (untreated metastatic disease)

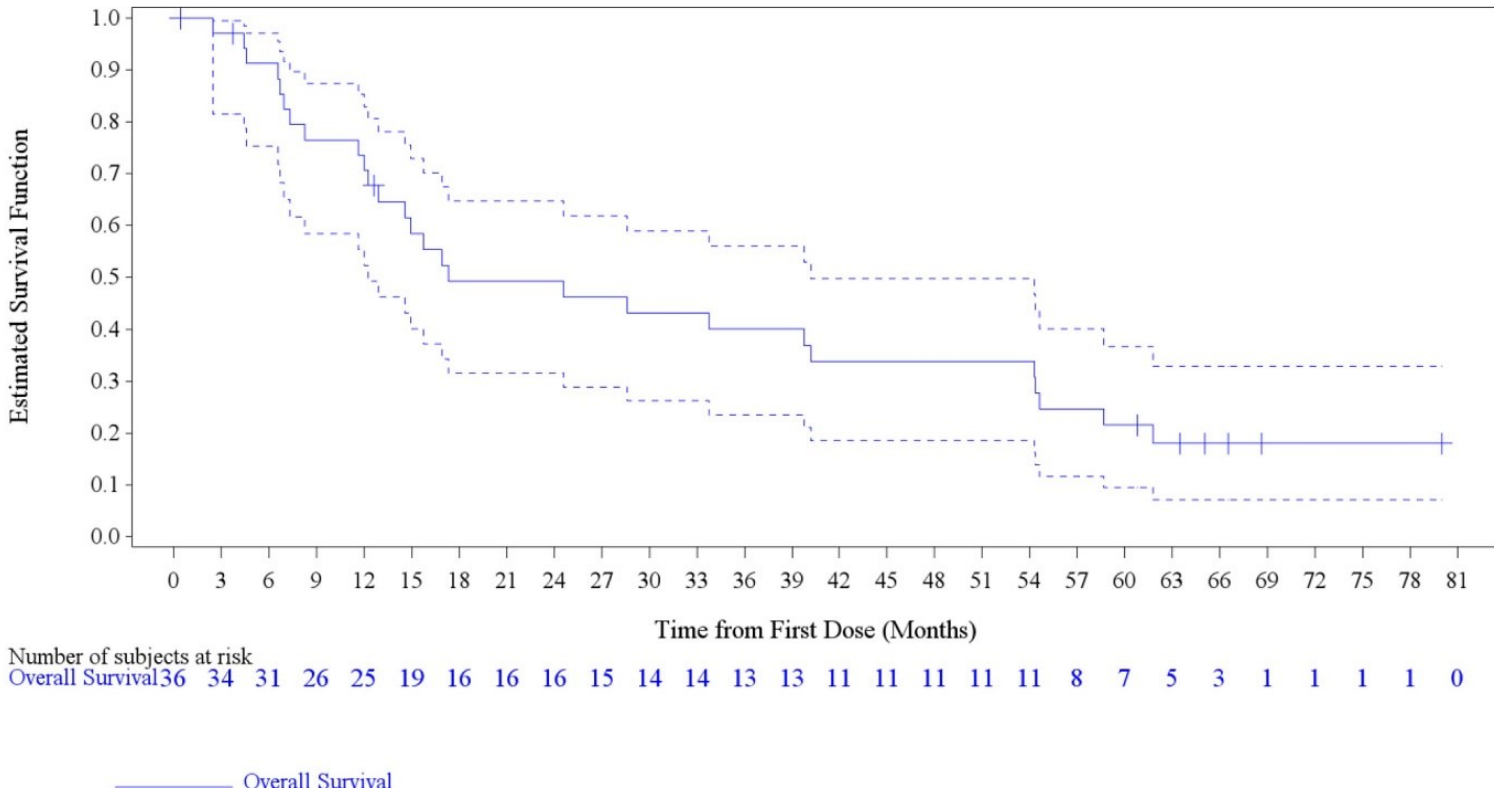


Estimated PFS, months	
Median (95% CI)	10.8 (7.0, 14.5)
PFS distribution function % (95% CI)	
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

NICE Abbreviations: DCO, data cut-off; CI, confidence intervals; PFS, progression free survival

BRF113928 results - OS

Overall survival – Cohort C (untreated metastatic disease)



Estimated OS, months	
Median (95% CI)	17.3 (12.3, 40.2)
PFS distribution function % (95% CI)	
Month 12	[redacted]
Month 24	[redacted]
Month 36	[redacted]
Month 48	[redacted]
Month 60	[redacted]

- Cohort C, overall response rate: 63.9% (95% CI 46.2 to 79.2)
  - Partial response rate: 58%
  - Complete response rate: 6%

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Abbreviations: DCO, data cut-off; CI, confidence intervals; OS, overall survival
Note: Overall response rate is define as anyone with either a partial or complete response

Key Issue: Data informing clinical efficacy in the model

Background

- Difficulty in modelling pembrolizumab and chemotherapy in a specific BRAF V600 population, various methods of informing efficacy of both intervention and comparator have been explored.

1. IPTW comparison between BRF113928 (Cohort C, [redacted] and FLATIRON V600E specific population [redacted]

EAG: Very wide CI, difficult to draw robust conclusions

2. Assumption of clinical equivalence between dabrafenib and trametinib and pembrolizumab and chemotherapy.

EAG: Not supported by evidence. Ignores effect of subsequent treatments

3. KEYNOTE-189 to inform comparator efficacy

Adjust BRF113928 Cohort C to match KEYNOTE-189 ([redacted]) using **MAIC**

3a. Base-case MAIC

3b. Sensitivity analysis MAIC

3c. Naïve comparison between BRF113928 and KEYNOTE-189

- A matching adjusted indirect comparison (**MAIC**) uses individual patient data from one trial and matches to summary statistics from another trial, aiming reduce the effect of cross trial differences.
- Essentially, participants in the adjusted trial (BRF113928) who are very different from the second trial (KEYNOTE-189) are excluded, and participants who are similar are given more weight in the analysis
- A MAIC can be anchored (when there is a common comparator between the two trials) or unanchored

Abbreviations: PFS, progression free survival; OS, overall survival; MAIC, matching adjusted indirect comparison; IPTW, inverse probability of treatment weighting; ECOG PS, Eastern cooperative oncology group performance score;

Key Issue: Data informing clinical efficacy in the model

Background – KEYNOTE-189

- KEYNOTE-189 was a randomised trial which compared chemotherapy with pembrolizumab and chemotherapy in an "all comers" NSCLC population
- Pembrolizumab plus chemotherapy arm of KEYNOTE-189 can be used to inform clinical efficacy in this appraisal
- Generalisability concern, KEYNOTE-189 all comers population could have better prognosis than the BRAF V600 population from BRF113928 (which could overestimate effectiveness of pembrolizumab and chemotherapy)
- EAG noted that whilst this is plausible, evidence is limited and did not suggest there would be differences in prognosis between "wild type" NSCLC and disease with a BRAF V600 mutation

Company – MAIC

- Adjusted BRF113928 population to better match KEYNOTE-189 based on various covariates
- Sensitivity analysis adjusted for only statistically significant covariates (helps maintain effective sample size)
  - PFS: ECOG PS, brain metastases, liver metastases, metastasis staging
  - OS: Age, ECOG PS, liver metastases, metastasis staging
  - PFS [redacted] OS [redacted]
- The base case adjusted for all of the above as well as covariates from previous similar appraisals (TA789, 653, 628, and 500) including
  - Gender, race, ECOG status, histology, sex, smoking history and brain metastases
  - PFS [redacted], OS [redacted]

Abbreviations: PFS, progression free survival; OS, overall survival; MAIC, matching adjusted indirect comparison; IPTW, inverse probability of treatment weighting; ECOG PS, Eastern cooperative oncology group performance score;

Key Issue: Informing clinical efficacy in the model

EAG comments

- The MAIC has strengths over naïve comparison between Cohort C and KEYNOTE-189 as it reduces the likelihood that differences in trial populations are responsible for any differences seen in the effect estimates
- However, the EAG notes several limitations

1. Relative effects generated from the MAIC apply to the KEYNOTE-189 population, which does not represent the target population (BRAF V600 mutations) – This could reduce the generalisability to NHS clinical practice of analyses based on the MAIC
2. MAIC is unanchored, makes strong assumption that all effect modifiers and prognostic factors identified, if this is untrue the effect estimate could be biased (and no evidence is presented on unaccounted for covariates)
3. The MAIC substantially reduces the effective sample size for dabrafenib and trametinib results in very wide confidence intervals.

- EAG therefore present base cases with efficacy informed by the MAIC and the naïve KEYNOTE-189 comparison
- Also emphasises a focus on the results of the probabilistic sensitivity analyses and probability of being cost-effective

If KEYNOTE-189 is an appropriate source for clinical efficacy, should the base case MAIC (including covariates from previous appraisals), sensitivity MAIC or naïve comparison be used?

Abbreviations: PFS, progression free survival; OS, overall survival; ALK, anaplastic lymphoma kinase; MAIC, matching adjusted indirect comparison; IPTW, inverse probability of treatment weighting; TE response, company technical engagement response

Comparative Evidence – PFS – From base case MAIC

No significant differences in PFS between treatments

[redacted]

PFS estimates		
Month	"D + T" *(MAIC)*	Pembro + chemo KEYNOTE-189
6	[redacted]	[redacted]
12	[redacted]	[redacted]
24	[redacted]	[redacted]
36	[redacted]	[redacted]
60	[redacted]	[redacted]

PFS	Naive		Weighted	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D+T versus pembro-chemo (base case)	[redacted]	[redacted]	[redacted]	[redacted]
D+T versus pembro-chemo (sensitivity analysis)			[redacted]	[redacted]

*Base case analysis adjusts for statistically significant covariates and key covariates from recent NICE appraisals. Sensitivity analysis adjusts for statistically significant covariates only (graph not shown here).

NICE Abbreviations; PFS, progression free survival; MAIC, matching adjusted indirect comparison; CI, confidence interval

Comparative Evidence – OS - From base case MAIC

No significant differences in OS between treatments

[redacted]

OS estimates		
Month	"D + T" (MAIC)	Pembro + chemo KEYNOTE-189
6	[redacted]	[redacted]
12	[redacted]	[redacted]
24	[redacted]	[redacted]
36	[redacted]	[redacted]
60	[redacted]	[redacted]

OS	Naive		Weighted	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
D+T versus pembro-chemo (base case)	[redacted]	[redacted]	[redacted]	[redacted]
D+T versus pembro-chemo (sensitivity analysis)			[redacted]	[redacted]

*Base case analysis adjusts for statistically significant covariates and key covariates from recent NICE appraisals. Sensitivity analysis adjusts for statistically significant covariates only (graph not shown here).

NICE Abbreviations; PFS, progression free survival; MAIC, matching adjusted indirect comparison; CI, confidence interval

Cost effectiveness

- Partitioned survival model

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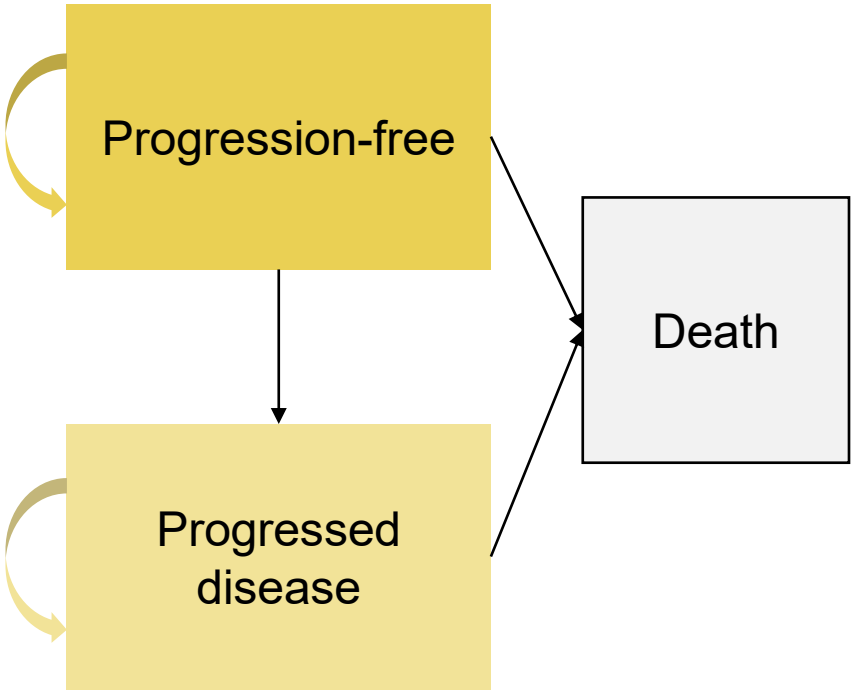
Company's model overview

Partitioned survival model

Model structure



- Technology affects costs by:
  - Accruing drug acquisition and administration costs
  - Modifying time in each health state and associated costs
  - Modifying adverse events and associated treatment costs
- Technology affects QALYs by:
  - Modifying time in each health state and associated utilities
  - Modifying adverse events and associated disutilities
  - Eliminating the need for intravenous infusions
- Assumptions with greatest ICER effect:
  - Whether or not to use MAIC or naïve comparison to inform efficacy
  - Assumed distribution of subsequent therapies
  - Inclusion of genetic testing costs

Abbreviations: QALY quality adjusted life year; ICER, incremental cost-effectiveness ratio

How company incorporated evidence into model

Input	Assumption and evidence source (company base case)
Baseline characteristics	Based on Cohort C (untreated advanced NSCLC) of the BRF113928 trial
Intervention efficacy	Informed by the MAIC of PFS and OS curves of Cohort C from BRF113928 (matching adjusted to KEYNOTE-189)
Comparator efficacy	Informed by the KEYNOTE-189 study
Utilities	Health state utility values for PFS and PD sourced from TA812. AE event utilities based primarily on TA789 (see Table 32 of company submission)
Costs	NHS reference costs 2019-2020, BNF, eMIT; PSSRU costs 2021
Resource use and treatment discontinuation	Drug costs informed by ToT data from BRF113928 and dosing regimens used in BRF113928 for dabrafenib and trametinib. For pembrolizumab with chemotherapy ToT was assumed to be equal to PFS
Adverse events	All-cause Grade 3 or more adverse events experienced by 1% or more of patients in either the BRF113928 or KEYNOTE-189 trials for the dabrafenib and trametinib and pembrolizumab plus chemotherapy arms respectively.
Subsequent treatments	Derived from Cohort C of BRF113928 and costs applied as a lump sum upon entering the PD health state. For pembrolizumab plus chemotherapy the breakdown of subsequent therapies was 50% docetaxel and 50% docetaxel with nintedanib

NICE Abbreviations: PSSRU, personal social services research unit

Extrapolations of intervention and comparator efficacy

Table – Distributions used to extrapolate from the base case MAIC – See figures 13 to 16 of company TE response

	Parameter	Distribution	EAG comment
PFS	Dabrafenib and trametinib	Exponential	Prefer exponential. It is the only curve with plausible predictions at 5 years
	Pembrolizumab and chemotherapy	Exponential	Prefer exponential. Although all curves are plausible.
OS	Dabrafenib and trametinib	Weibull (with exponential scenario)	Prefer Weibull. Note that Weibull and exponential have most pessimistic long term projections and both are appropriate.
	Pembrolizumab and chemotherapy	Weibull	Prefer Weibull

Note

- In the EAG alternative base case which uses the naïve comparison between BRF113928 and KEYNOTE-189 to inform clinical efficacy, the LogLogistic distribution is used to extrapolate PFS for both arms of the model.

Abbreviations; OS, overall survival; MAIC, matching adjusted indirect comparison; CI, confidence interval; TE response, company technical engagement response

Key issues partially resolved at tech engagement

Inclusion of BRAF mutation testing costs – (Partially resolved)

- EAG considered that BRAF V600 testing was only available as part of Covid-19 interim measures, and that its costs should be modelled to be in line with previous appraisals of targeted therapies
- The company considered that BRAF testing was part of NHS routine practice and should not be costed
- NHSE advised that BRAF mutation routine testing was now routinely carried out in clinical practice
- Clinical expert agreed that BRAF mutation testing was routine
- EAG acknowledge and removed from their base case, a scenario is included to illustrate these costs

Can NHSE confirm that BRAF mutation is now considered a routine test in practice?

Should BRAF mutation testing costs be included in the committee preferred base case?

Abbreviations: RDI, relative dose intensity

Key issue: Second line use of dabrafenib with trametinib

Background

- The MA allows use at 1st or 2nd line. In BlueTeq, [redacted] of people who were eligible for dabrafenib and trametinib, had other therapies* at 1st line, potentially due to delays in receipt of genetic testing result.
- No cost-effectiveness modelling was submitted for 2nd line use

Company – Did not model 2nd line treatment with dabrafenib and trametinib

- Dabrafenib with trametinib will not be used extensively in the previously treated cohort (second line) in practice as the small but significant minority of people with delayed genetic testing results likely to fall
- Cohort B (pre-treated) in BRF113928 not pre-treated with pembrolizumab, does not reflect UK clinical practice.
- Presented hazard ratios and KM graphs for dabrafenib with trametinib (Cohort B of BRF113928) compared with BRAFV600 mutation positive FLATIRON population. (Figures 17 + 18 of company TE response)

Other considerations (clinical expert)

- Under current guidance BRAF status does not need to be taken into account, some clinicians may choose pembrolizumab with chemotherapy at 1st line and in this case dabrafenib and trametinib would be used 2nd line

EAG comments

- Group may be clinically relevant for some time, unclear when genomic testing delays will improve
- “Cohort B versus Flatiron” analysis is limited due to small sample size
- Median PFS and OS similar in Cohorts B and C or trial, assumption of similar effect reasonable but uncertain

What is the committee’s position on recommending at 2nd line?

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Abbreviations: PFS, progression free survival; OS, overall survival; KM, Kaplan-Meier
*Note the [redacted] figure includes people who had ROS-1/ALK inhibitors. The figure for immunotherapy/chemotherapy is between [redacted] and [redacted]

Key issue: Risks and benefits of an oral therapy

Background

- Possible drawbacks of oral therapies not considered, [redacted] of people on dabrafenib and trametinib in BRF113928 had protocol deviations due to [redacted] This could have a negative, and unmodelled effect, on efficacy

Company

- Any non-compliance is already represented in the model efficacy through its effect on PFS and OS in the trial and in the model costs through relative dose intensity calculations
- Most non compliance was dose escalation or interruption or reduction in response to AEs
- In two key melanoma trials the median daily dose was close to the planned dose, suggesting good compliance

Clinical + Patient experts

- There are minimal drawbacks to oral therapy (difficulty administering in patients with swallowing problems)
- People can forget doses but compliance generally high. People feel better on treatment, unlikely to miss doses.
- Patients did not think that compliance would be an issue as they are highly motivated to take it "[dabrafenib and trametinib] is keeping my cancer at bay and me alive"
- Some people may prefer an IV infusion, "all done on one day". It is a question of patient choice

EAG comments

- There is likely a small proportion of people who do not adhere well to dabrafenib and trametinib treatment
- These patients may achieve better outcomes on pembrolizumab.

Have any risks and benefits of oral therapies been modelled appropriately?

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Abbreviations: AE, adverse event; IV, intravenous;

Key issue: Disutility associated with IV infusion

Background

- The company applied a per cycle disutility of 0.023 to those on pembrolizumab and chemotherapy
- The EAG considered this should was too high, (e.g. it is double that modelled for pneumonia requiring hospitalisation) and should either be reduced or removed

Company

- Maintains inclusion of IV infusion disutility is appropriate, however has modified how it is applied (IV disutility of 0.023 now only applied in cycles when pembrolizumab or chemotherapy is given)
- Every 3 weeks in cycles 1-12 and every 3 or 6 weeks afterwards (to account for pemetrexed maintenance). Inclusion of this disutility increases incremental QALYs for dabrafenib and trametinib by [redacted]

Clinical and Patient Expert responses

- Clinical expert: IV infusions significantly impact quality of life, significant time spent on chemotherapy unit, currently delays are common. The exact disutility is uncertain but the company estimates seems reasonable.
- Patient experts stated that the concept of the IV infusion as “anti-cancer” reduced any perceived QoL impact

EAG comments

- Maintains preference for not explicitly modelling an IV infusion disutility. Not included in EAG base case.
- However, notes that its inclusion has a negligible impact upon incremental QALY gain

Should IV infusion disutility be explicitly modelled and if so, at what level?

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Abbreviations: EAG, external assessment group; IV, intravenous;

Summary of company and EAG base case assumptions

Agreed upon assumptions

Parameter	Assumption
Costs and resource use	Terminal care costs as per TA705, pharmacist dispensing time modelled. Dabrafenib and trametinib wastage modelled by incurring half a pack cost at discontinuation.
Health state utilities	Based on TA812
BRAF testing costs	Not included in base case
Intervention efficacy	Base case MAIC of BRF113928 data to KEYNOTE-189 (EAG also present an alternate scenario with naïve comparison)
Extrapolation of efficacy	Weibull for OS in both arms. Exponential for PFS in both arms

Differing assumptions in company and EAG base case

Parameter	Company base case	EAG base case
Discounting	Applied discretely from beginning of second year of model	Applied continuously from the outset of the model
IV infusion disutility	-0.023 decrement modelled every cycle an infusion is due (-0.008 cycles 0-11, -0.006 cycles 12+)	No disutility associated with IV infusion

NICE Abbreviations: RDI, relative dose intensity; PFS, progression free survival; OS, overall survival;

Impact of EAG preferred assumptions on results

Table Impact of individual assumptions on NHB compared with company corrected base case

Scenario	What was done	Effect on results
IV disutility	EAG excluded disutility incurred for having IV infusion from their base case.	Results in a small increase in the ICER for dabrafenib and trametinib.
Discounting	EAG apply discounting continuously from model outset, as opposed to company applying it discretely according to whole years relapsed.	Results in a very small increase in the ICER for dabrafenib and trametinib.
Using naïve comparison instead of MAIC	EAG noted that the MAIC substantially reduced the effective population from BRF113928 which resulted in very wide confidence intervals for measures of relative effectiveness. It presented a cost-effectiveness scenario which used the naïve comparison between BRF113928 and KEYNOTE-189.	Using the MAIC to inform efficacy in the model results in a substantial reduction in the ICER however also results in increased uncertainty, demonstrated by wider confidence intervals around the measures of NHB.

Abbreviations: ICER, incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; IV, intra-venous

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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Thank you.