NICE National Institute for Health and Care Excellence

Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID1266]– STA

Lead team presentation: Background and Clinical Effectiveness

1st Appraisal Committee meeting
Committee A
Lead team: Jane Adam, Pam Rees, Steve Edwards
ERG: Liverpool Reviews and Implementation Group (LRiG)
NICE technical team: Emily Eaton Turner, Victoria Kelly
September 2018

Preview: Clinical effectiveness issues (1)

- Does pembrolizumab change the treatment pathway
  - Does it affect the subsequent use or effectiveness of immunotherapy in the metastatic setting?
- Is the committee satisfied with the definition of high risk of recurrence?
  - In KEYNOTE-054 patients had either Stage IIIA (>1mm metastasis), IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition
  - The company has suggested that 90% will develop metastatic disease within 5 years - is this correct? (lower figures have been quoted previously)
- Do the baseline characteristics of patients in KEYNOTE-054 match those in the NHS?
  - Practice not uniform in terms of resection within Stage III melanoma & the staging of melanoma has changed
  - Patients in KEYNOTE-054 had lower ECOG performance scores (all 0 or 1)

Preview: Clinical effectiveness issues (2)

- What conclusions can be drawn about recurrence-free survival (RFS)?
  - KEYNOTE-054 data is limited to 16 months follow up → median RFS for pembrolizumab not reached
  - Proportional hazards assumption may not hold → is it reasonable to assume RFS is an appropriate surrogate outcome for overall survival?
- Does pembrolizumab have a tolerable safety profile, both short and long term in patients with no known disseminated disease?

Advanced fully resected melanoma

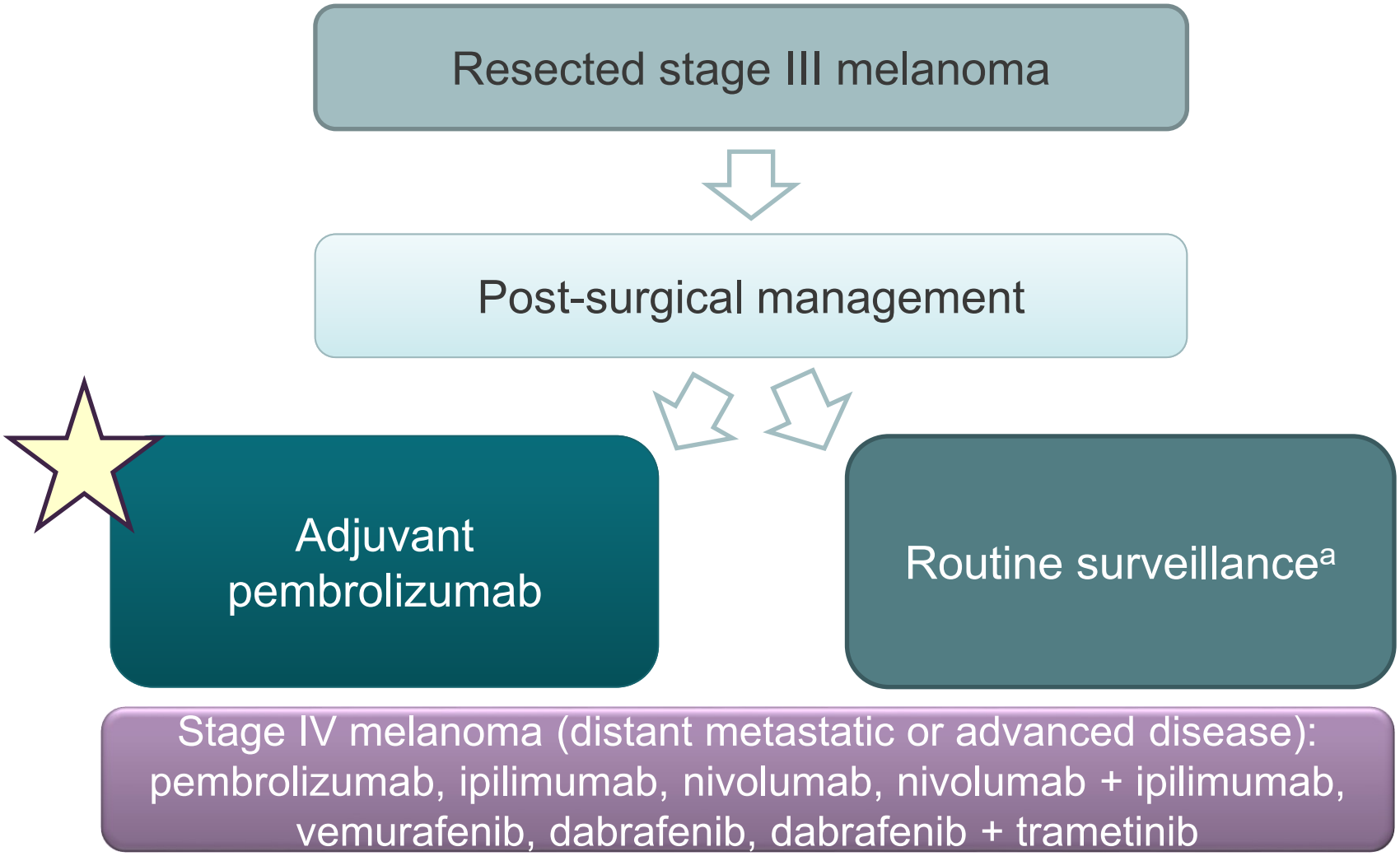
- Melanoma 5th most common cancer → incidence up by 50% in last decade
- Disease stage describes the extent of disease
  - Stages I and II: (most common) no evidence that melanoma has spread anywhere else in body
  - Stage III: melanoma is present in the skin, lymph vessels, or nearby lymph glands
  - Stage IV: melanoma has spread to other distant parts of the body

  ~ 8% (total N=1,000) patients diagnosed at Stage III or IV disease in 2014 in England but may progress from earlier stages
- Adjuvant therapy given after surgical clearance to remove any microscopic disease (locally or in the bloodstream) to reduce the rate of recurrence of melanoma & death from disseminated disease

Pembrolizumab

Mechanism of action	Monoclonal antibody of the IgG4/kappa isotype designed to exert a dual ligand blockade of the PD-1 pathway
Anticipated marketing authorisation	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXX
Administration, dosage & duration of treatment	Intravenous, 200 mg every 3 weeks for 1 year
Cost (list price)	£2,630 per 100 mg vial. Average cost of a course of treatment: XXXXXXX (list price). A commercial access agreement has been arranged with NHS England
Other NICE recommendations/ appraisals	Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]: publication date TBC

Treatment pathway in the UK



Adapted from NICE NG14 and expert clinician feedback

[a] No adjuvant systemic therapies included in NG14

Scope & company's decision problem

	Scope	Company
Population	People with completely resected melanoma at high risk of recurrence	Trial inclusion = ≥18 years → 'Adults'
Intervention	Pembrolizumab	✓
Comparators	Routine surveillance	✓
Outcomes	Overall survival (OS) Recurrence-free survival Distant metastases-free survival (DMFS) Adverse effects of treatment Health related quality of life	OS & DMFS data are immature Recurrence-free survival data used to assess the efficacy Other outcomes = ✓

Clinical expert & professional organisation perspective

- Main aim of treatment → prevent recurrences and cure population of people who would otherwise develop incurable advanced disease
  - Unmet need → risk reduction for high risk resected melanoma & no adjuvant treatment currently recommended by NICE
  - Clinical: Recurrence-free survival = an appropriate surrogate for overall survival
  - Absence of recurrence = clinically significant treatment response → no need for further systemic therapy for those who do not develop progressive disease
- Clinical: Indefinite treatment benefit after stopping treatment → permanent cure for some
- Clinical: Evidence that ipilimumab ↑ overall survival; nivolumab ↑ recurrence-free survival vs. ipilimumab → anti-PD1 treatments are superior to ipilimumab
- Clinical: Some uncertainty over the need to treat IIIa melanoma with metastatic deposits of <1mm in the sentinel lymph node → further data needed to confirm
- Generally well tolerated (some significant side effects reported). Auto-inflammatory side effects from anti-PD1 therapy may require medical intervention to manage → capacity in clinics and cancer day units
- Step-change in management → potential to bring forward benefit with anticipated significant improvement in overall survival

Patient perspective

- “People need to hear loud and clear that **melanoma is not just skin cancer**—it is an aggressive, unpredictable, and dangerous cancer”
- “The next weeks were filled with tears and trying to realise what was happening and how to accept this diagnosis. I could barely sleep as I would think about the worst possible scenario before I closed my eyes and breakout into tears the second I woke up”
- “I have had over 25 suspicious moles removed. My body is a mess”
- “You hope that you have another day, and hope is all you can have when you have melanoma, you don’t know what the future will hold”
- Currently, there is no adjuvant therapy available for earlier stage Melanoma
- Pembrolizumab is administered as a flat dose every 3 weeks → more convenient treatment option for patients?

NHS England perspective

- Stage III disease = sufficient marker of high risk (new AJCC staging system (8th Ed) in melanoma not an issue)
- Very clinically significant benefit of adjuvant pembrolizumab on recurrence rates → unusual for adjuvant therapies to show this degree of difference so early in follow-up
- Dataset is very immature with very short median trial follow-up duration → few patients at risk of recurrence after 16 months → long term difference for recurrence-free and overall survival uncertain but a long term survival benefit is likely (as shown by ipilimumab)
- No statistically significant difference between PD-L1+ve and PD-L1-ve subgroups and also substages of stage III disease → requires further follow-up
- Proportional hazards assumption → requires further follow-up to confirm
- Company's model produces optimistic differences in rates of RFS at 5 and 10 years, mainly due to the values for routine surveillance being pessimistic
- Subsequent treatments included in the company's model do not reflect use in clinical practice
- Administration costs for adjuvant therapies have been incorrectly excluded from the model
- Adjuvant therapies carry potentially significant and enduring toxicities → with an uncertain risk-benefit profile adjuvant pembrolizumab would be used in those with ECOG 0 or 1
- CDF candidate → clinical uncertainty, without a plausible range of ICERs

Company's clinical evidence: KEYNOTE-054

Design	Double-blind, routine surveillance-controlled phase 3 study
Population	Adults after complete resection of stage IIIA (>1mm lymph node metastasis), IIIB and IIIC melanoma (using the AJCC 7th edition)
Intervention	Pembrolizumab 200 mg, every 3 weeks for a total of 18 administrations
Comparator	Placebo
1◦ outcome	Recurrence-free survival. Subgroup with PD-L1 positive tumours (surrogate marker for overall survival) – October 2017 cut-off
2◦ outcomes	Adverse events, Distant metastasis free survival (DMFS) (XXXXXXXXXXXXXXXX), DMFS in patients with PD-L1 positive tumour expression (XXXXXXXXXXXXXXXX), OS XXXXXXXXXXXXXXXXXXX, OS in patients with PD-L1 positive tumour expression XXXXXXXXXXXXXXXXX

ERG comments:

- Unclear whether all patients can be considered 'high risk' of either death or disease recurrence → no definitive definition of 'high risk' identified
- Trial is well-designed & good quality

Recurrence-free survival

- Defined as time between randomisation and first recurrence (loco-regional, distant metastasis) or death, whichever first
- **Company**: recurrence-free survival (RFS) established as a reliable surrogate efficacy marker & appropriate endpoint to assess efficacy & safety in adjuvant setting
  - Meta-analysis (Suciu et al.) of 13 studies (n>5,000 patients) of adjuvant interferon recurrence-free survival shown to be a valid surrogate endpoint for overall survival
- In an ipilimumab study (EORTC 18071), a validated model predicted an overall survival benefit based on RFS → predicted that trials with a hazard ratio ≤0.77 for recurrence-free survival would also show a benefit to overall survival

ERG comments:

- Meta-analysis included trials with patients with Stage II or Stage III melanoma who were treated with interferon → questionable if this supports the company's claim
- Caution required because benefits shown with surrogate endpoints are not always realised when overall survival data become mature

KEYNOTE-054: baseline characteristics

		Pembrolizumab (n=514)	Placebo (n=505)
Locations		23 countries N= 677 from across Europe, N=52 from UK	
Melanoma stage at random-isation, n (%)	Stage IIIA	80 (15.6)	80 (15.8)
	Stage IIIB	237 (46.1)	230 (45.5)
	Stage IIIC 1-3 +ve nodes	95 (18.5)	93 (18.4)
	Stage IIIC ≥ 4 +ve nodes	102 (19.8)	102 (20.2)
ECOG score 0 or 1, n (%)		514 (100)	505 (100)
PD-L1 positive, n (%)		428 (83.3)	425 (84.2)

ERG comment:

- 20% of patients treated in the NHS are likely to be less fit (ECOG PS 2 or 3) than those in KEYNOTE-054 (100% ECOG PS 0 or 1)
- PD-L1 testing not routinely carried out → majority of trial participants had PD-L1+ disease
- **Satisfied that the trial population is representative of patients with resected Stage III melanoma who are treated in the NHS**

KEYNOTE-054 results (ITT population)

		Pembrolizumab (n=514)	Placebo (n=505)
Median follow-up (range)		16.0 months (2.5 to 25.3 months)	
Type of first event, n (%)			
Loco-regional recurrence		55 (10.7)	77 (15.2)
Distant metastasis		69 (13.4)	114 (22.6)
Death		2 (0.4)	1 (0.2)
Recurrence-free survival (95% CI)			
Median RFS in months		NR (NE to NE)	20.4 (16.2 to NE)
RFS rate, %	6 months	82.2 (78.6 to 85.3)	73.3 (69.2 to 77.0)
	12 months	75.4 (71.3 to 78.9)	61.0 (56.5 to 65.1)
	18 months	71.4 (66.8 to 75.4)	53.2 (47.9 to 58.2)
HR (98.4% CI); p-value		0.57 (0.43 to 0.74); p<0.0001**	

Abbreviations: NR: not reached; NE: not estimable; ITT: intention to treat

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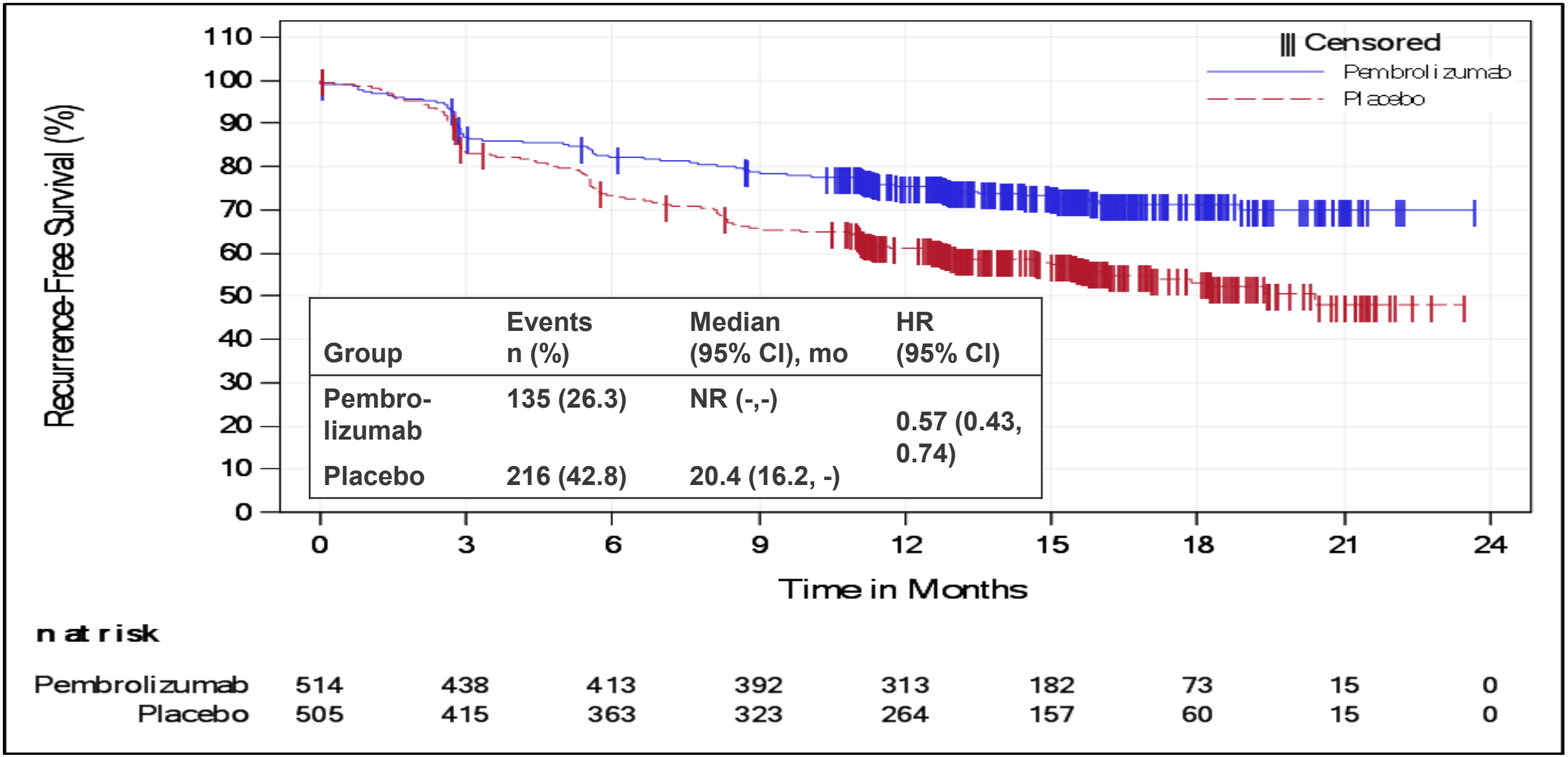
** Based on Cox regression model with treatment as a covariate stratified by stage (IIIA [>1 mm metastasis] vs. IIIB vs. IIIC 1-3 nodes vs. IIIC >=4 nodes) as indicated at randomisation.

Results: investigator assessed RFS (ITT population)



Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reached; RFS: recurrence-free survival.; mo: months

ERG comments: clinical effectiveness results

- No reliable evidence available to inform whether or not adjuvant treatment of stage III melanoma with immunotherapies delivers an overall survival benefit
- Concerned that:
  - median recurrence-free survival not reached in pembrolizumab arm
  - no data on overall survival (OS) & distant metastases-free survival (DMFS)
- Proportional hazards assumption is unlikely to hold → treat resulting estimates with caution
- Results of subgroup analyses by stage of disease suggest that patients with Stage IIIA melanoma have the best prognosis, while patients with Stage IIIC melanoma have the worst prognosis, irrespective of whether treated with pembrolizumab or placebo

Adverse events

Event, n (%)	Pembrolizumab (n=514)	Routine surveillance (n=505)
Any adverse event	396 (77.8)	332 (66.1)
Grade 3 to 5 adverse event	74 (14.5)	17 (3.4)
Adverse event leading to discontinuation	62 (12.2)	8 (1.6)
Any serious adverse event	66 (13.0)	6 (1.2)
Serious adverse event leading to discontinuation	22 (4.3)	2 (0.4)
Death	1 (0.2)	0 (0.0)

ERG comments:

- ERG's clinical experts: adverse events (≥ grade 2) arising from treatment can place a high burden on NHS staff
- Careful monitoring by a specialist clinical team is required → have experience to provide early recognition and management of immunotherapy related adverse events

Clinical effectiveness issues (1)

- Does pembrolizumab change the treatment pathway
  - Does it affect the subsequent use or effectiveness of immunotherapy in the metastatic setting?
- Is the committee satisfied with the definition of high risk of recurrence?
  - In KEYNOTE-054 patients had either Stage IIIA (>1mm metastasis), IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition
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Clinical effectiveness issues (2)

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Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence [ID1266]– STA

Lead team presentation: Cost effectiveness

Part 1

1st Appraisal Committee meeting
Committee A
Lead team: Jane Adam, Pam Rees, Steve Edwards
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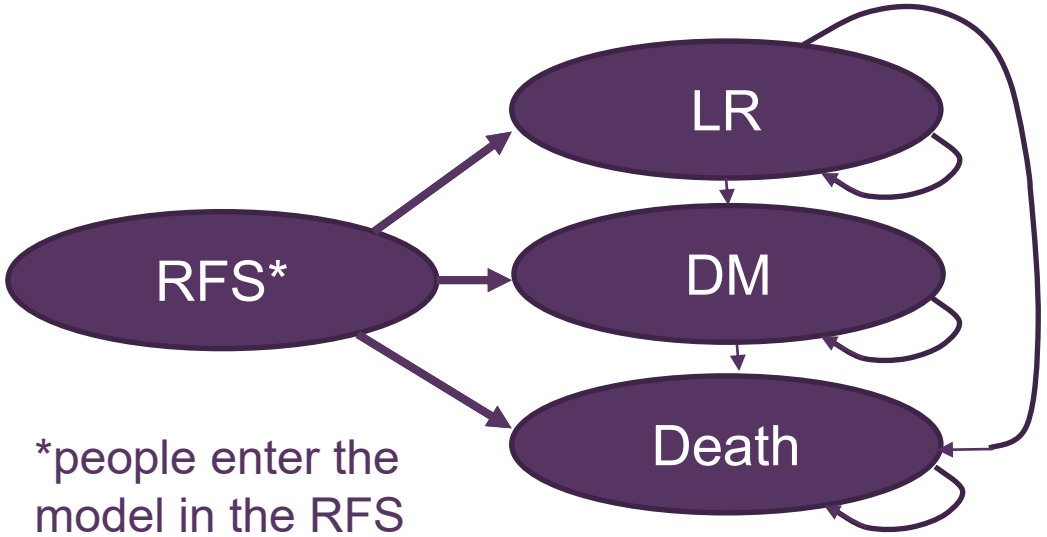
September 2018

Preview: cost effectiveness issues

- Is the use of a first recurrence event either loco-regional or distant metastases to inform model transitions appropriate considering they are not pre-specified outcomes in the KEYNOTE-054 trial?
- Are the company's DMFS and OS projections clinically plausible?
  - Would more robust OS and DMFS data reduce the uncertainty in the model predictions?
- Is it appropriate to assume a life time treatment effect with pembrolizumab?
- What is the most plausible ICER?

Company's state-transition model



*people enter the model in the RFS health state only

Model design	Markov model
Time horizon	46 years
Cycle length	7 days
Half cycle correction	Yes
Treatment waning effect	No
Discount rate	3.5% per year
Perspective	NHS and PSS

Summary of key drivers

- Model predicts **cost savings** → fewer people on pembrolizumab develop distant metastases or develop them later → this results in ↓ costs due to metastatic disease
- Model predicts **QALY gains** → the model predicts an overall survival benefit from pembrolizumab → fewer people develop distant metastases or they get them later → fewer people die from disseminated disease

ERG comment: Model structure is appropriate

Abbreviations: RFS: recurrence-free survival; LR: loco-regional recurrence; DM: distant metastases; PSS: personal social services

Company's modelling of transitions from RFS

- Kaplan-Meier curves generated for each event and for each KEYNOTE-054 trial arm : RF → LR, RF → DM and RF → death. Where another event occurred this was treated as a censoring event
- Parametric models were fitted to each of the K-M curves. Best fit was established by analysing how well the RFS fitted the European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial, mean square error & visual inspection
- Company's preferred models for the cause-specific hazards, shown below, generated 5-year RFS, DMFS and OS predictions that were most consistent with the values that were observed in the routine surveillance arm in the EORTC 18071 trial (ipilimumab vs placebo for adjuvant treatment in melanoma)

Treatment arm	RF → LR	RF → DM	RF → death
Pembrolizumab	Gompertz	Generalised gamma	Exponential
Routine surveillance	Gompertz	Generalised gamma	Exponential

Company's modelling of transitions from LR and DM

Transition	Data sources	Modelling transitions
LR → DM	• Flatiron database	• Developed a K-M curve using data for the LR population in Flatiron, with the event of interest being further progression to DM • Exponential parametric function fitted and the cause-specific hazard assumed to be the same across both treatment arms
LR → Death	• KEYNOTE-054	• No direct transitions from LR → death in the Flatiron sample • Cause-specific hazard estimated from the exponential model of RFS → death in the pembro arm of KEYNOTE-054
DM → Death	• KEYNOTE-006 • NMA comparing treatments for advanced melanoma	• For OS in the pembro arm an exponential curve was fitted to IPD from the pembro arm of KEYNOTE-006 (advanced setting) • For the other treatments for advanced melanoma, hazard ratios for OS and PFS vs. pembrolizumab were each obtained from a NMA conducted by the company • OS for each arm in model calculated as the sum of the expected mean OS with different first-line advanced treatments, weighted by their current market shares → given on next slide • The company assumed that no further treatment with a PD-1 inhibitor was permitted in the pembro arm

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Flatiron database = an electronic health records database used by cancer care providers in the US

KEYNOTE-006 = Phase III open-label RCT. Evaluated treatment with pembrolizumab vs ipilimumab in people with unresectable or advanced melanoma

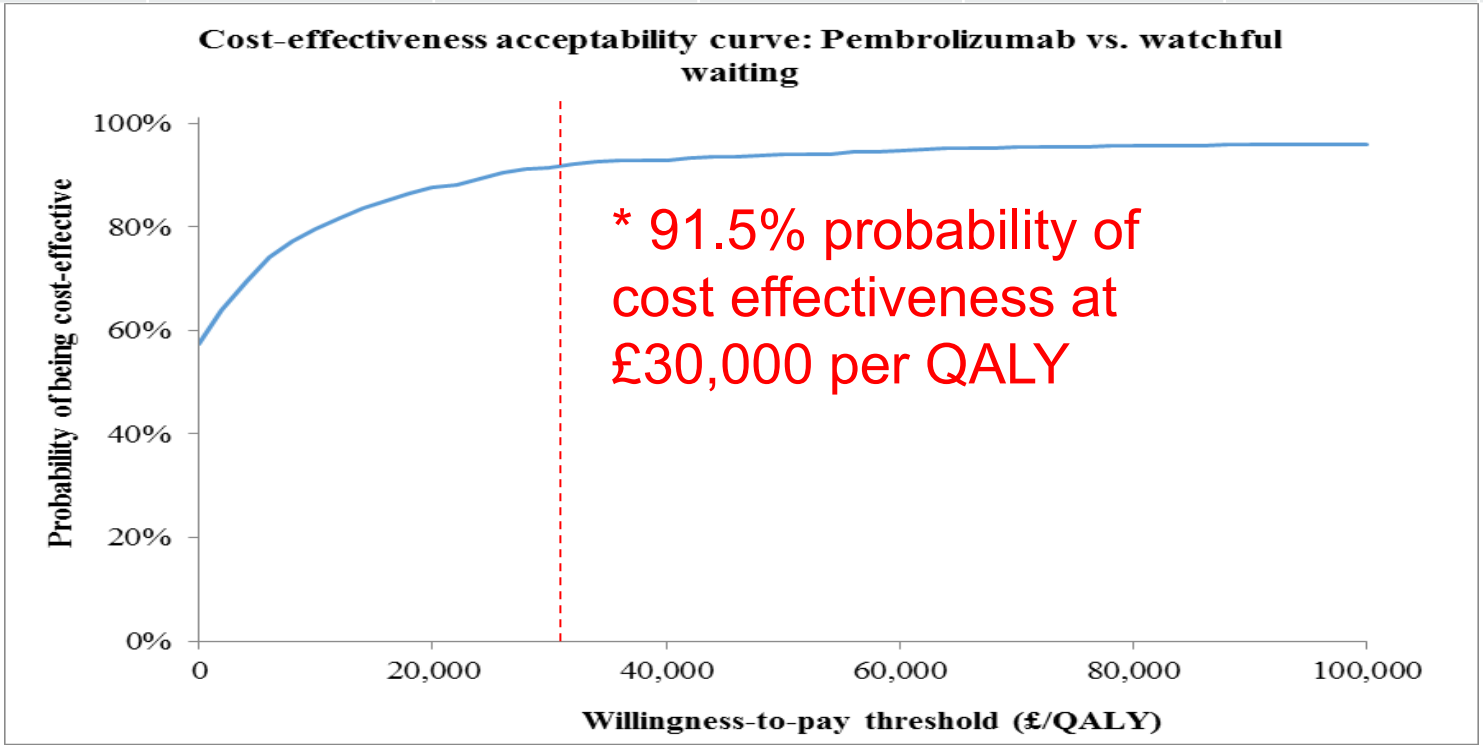
Distribution of 1st-line metastatic treatments for advanced melanoma (including company scenario of rechallenging with a PD-1 inhibitor)

Regimens in advanced setting	Market shares (%)				Reference
	Pembrolizumab (no re-challenge)	Routine surveillance	Pembrolizumab (re-challenge)	Routine surveillance	
Pembroliz-umab	0.0%	27.8%	27.8%	27.8%	Ipsos Oncology Monitor, 2018
Ipilimumab	50.2%	5.8%	5.8%	5.8%	
Nivolumab	0.0%	3.8%	3.8%	3.8%	
Nivolumab + ipilimumab	0.0%	18.7%	18.7%	18.7%	
Vemurafenib	16.3%	14.4%	14.4%	14.4%	
Dabrafenib	0.0%	0.0%	0.0%	0.0%	
Dabrafenib + trametinib	33.4%	29.5%	29.5%	29.5%	

ERG comment: treatments received for advanced melanoma do not have much impact on the model results

Company's probabilistic base case with commercial access agreement discount for pembrolizumab

	Total costs	Total QALYs	Life years (determin -istic)	Δ costs	Δ QALYs	ICER £/QALY
Pembrolizumab	£163,093	7.97	9.79	-	-	-
Routine surveillance	£167,063	5.36	6.61	-£3,970	2.62	Dominant



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Company's scenario analysis results with commercial access agreement discount for pembrolizumab

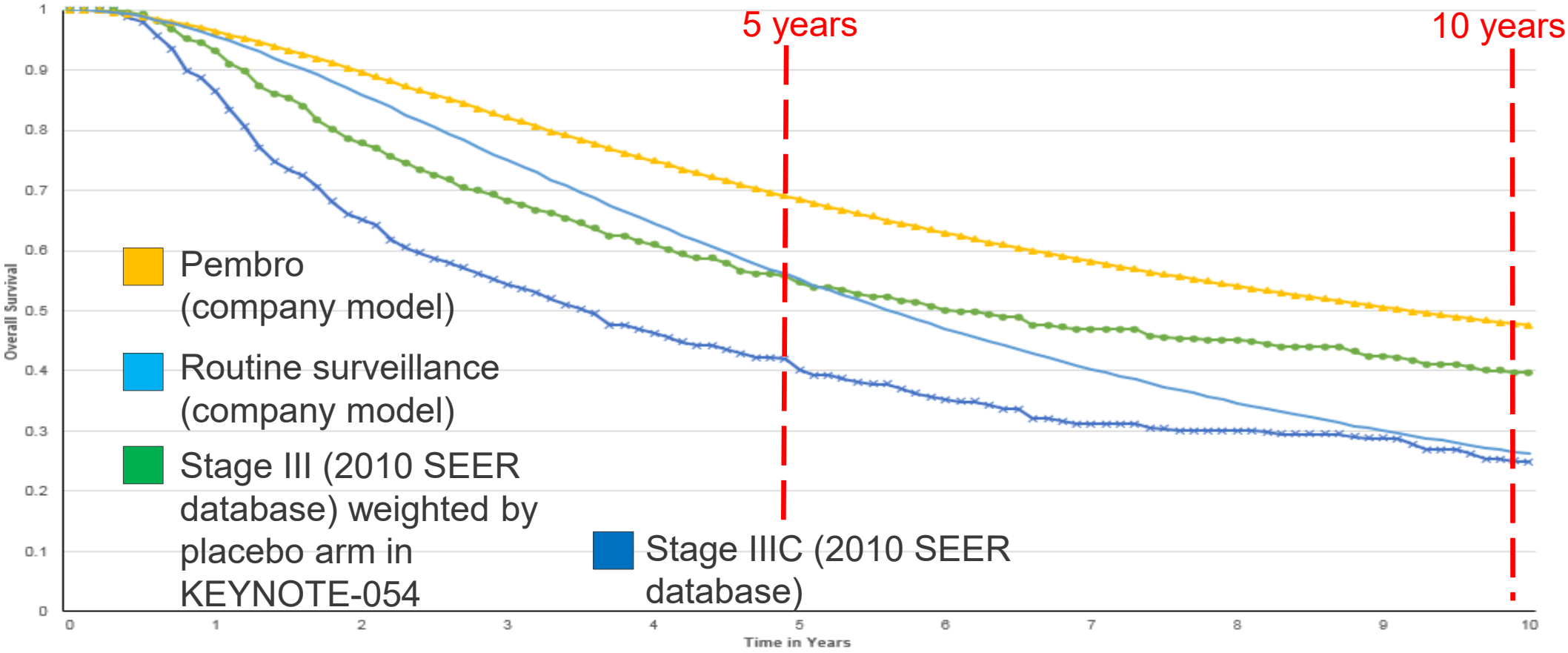
Scenario	Scenario detail	ICER £/QALY
Time horizon – 10 years		Pembrolizumab dominant
Distributions	RF → LR & RF → DM: both log-normal	Pembrolizumab dominant
	RF → LR: generalised gamma & RF → DM: log-normal	Pembrolizumab dominant
	RF→ LR: exponential & RF → DM: Gompertz	£6,992
PH model with a constant treatment effect	RF → LR: Weibull RF → DM: Gompertz RF → death: exponential	£6,073
PH model with a time-varying treatment effect	RF → LR: Weibull RF → DM: Gompertz RF → death: exponential	Pembrolizumab dominant
Rechallenge with pembrolizumab in advanced setting	People who transition from RF → DM >18 months from start of adjuvant treatment	Pembrolizumab dominant

ERG comments: affect of immature data on modelled overall survival (1)

Company validated model by comparing the estimated 5-year overall survival and distant metastases free survival for routine surveillance against those in the adjuvant ipilimumab trial (EORTC 18071 trial)

- Model estimates slightly higher 5-year OS & much lower 5-year DMFS for 'routine surveillance' than similar data from EORTC 18071
  - OS: 55.2% in company model vs 54.4% of EORTC 18071
  - DMFS: 30.2% in company model vs 38.9% of EORTC 18071
- ERG validated the company's OS projections by creating a composite stage III survival curve
  - Combined OS data from the 2010 SEER database for patients with Stage III melanoma by AJCC 7th edition, weighted by the proportions of patients in each of these stages in the KEYNOTE-054 trial
  - The composite OS curve approximated expected OS for routine surveillance arm of the KEYNOTE-054 trial, **next slide…**

ERG comments: affect of immature data on modelled overall survival (2)



ERG comments: Clinically implausible projections. **First 5-years**: projected OS in routine surveillance arm of company model is better than the ERG's composite expected OS curve **After 5-years**: company model projected OS curve for routine surveillance lies below the ERG's composite curve. **By year 10**: company model projected OS curve for routine surveillance is ≈ equal to the 2010 SEER OS curve for patients with stage IIIC disease

ERG comments: immature data on modelled distant metastases-free survival

- Analysis of distant metastases-free survival data from KEYNOTE-054 (from the trial published paper, Eggermont et al. 2018) shows a statistically significant difference for DMFS at 12 and 18 months between the pembrolizumab and placebo arms
  - Approach inappropriate to extrapolate hazards in both arms when the hazard rate changes over time
- Company's model estimates: at 5 years, 68.7% of patients on *routine surveillance* enter the DM state & of these 43.7% die
  - However, data from the 2017 IMDDP dataset mortality is estimated to be 28%
- Clinically implausible projections of distant metastases and death for people in the DM health state up to year 5 → increasingly more clinically implausible after 5 years
  - Company's model estimated that 91.6% of all people on routine surveillance have developed a DM over the model time horizon (46 years)

ERG comments: immature data on estimation of treatment effect

- Data too immature to assess whether there is a lifetime treatment effect associated with treatment with pembrolizumab (company's assumption)
- Duration of treatment effect & model time horizon impacts company ICER:
  - Scenario 1: Stop the treatment effect for pembrolizumab at 3 years from starting treatment → ICER approx. £19,330 per QALY
  - Scenario 2: Time horizon of the company model limited to 16 months (i.e. no extrapolation) → ICER aprox £750,000 per QALY

ERG comments: overall conclusions

- Company made best use of data from KEYNOTE-054 & other relevant trials
- Model not populated with RFS data from KEYNOTE-054 → first recurrence event used
- OS and DMFS data from KEYNOTE-054 have not reached maturity yet
  - Too immature to be analysed or included in the economic model → immature data can lead to spurious projections of overall survival (supported by previous research)
- None of the projections undertaken by the company produces clinically plausible OS or DM estimates for the routine surveillance arm due to the immaturity of the trial data
- Pembrolizumab treatment effect cannot be estimated from the data currently available given its immaturity
- Only 1% (0.03 QALYs) of the company's total discounted QALY gain estimate (2.73 QALYs) is accrued in first 16 months (the median period for available follow-up data from KEYNOTE-054)
- The company's estimated ICERs per QALY gained are unreliable
- No additional or exploratory analyses have been undertaken → ERG considers that KEYNOTE-054 is too immature to produce a reliable ICER

Equality and innovation

Equality

- No equality issues identified by the company or professional organisations (BAD & BASCSN)

Innovation

- Pembrolizumab has a novel mode of action → can be used as standard adjuvant treatment regardless of tumour BRAF mutation status, PD-L1 status and AJCC stage III classification

ERG comments: ERG's clinical expert advice & comments received during scoping highlighted that there is inequitable access to sentinel lymph node (SLN) mapping and biopsies across the UK → may limit access to adjuvant treatment

Committee decision-making: CDF recommendation criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

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Cost effectiveness issues

- Is the use of a first recurrence event either loco-regional or distant metastases to inform model transitions appropriate considering they are not pre-specified outcomes in the KEYNOTE-054 trial?
- Are the company's DMFS and OS projections clinically plausible?
  - Would more robust OS and DMFS data reduce the uncertainty in the model predictions?
- Is it appropriate to assume a life time treatment effect with pembrolizumab?
- What is the most plausible ICER?

Back up slides

Sources of clinical inputs to company model

Health states	Transition	Data sources
Recurrence-free	RF-to-LR	• KEYNOTE-054
	RF-to-DM	• KEYNOTE-054
	RF-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)
Loco-regional recurrence	LR-to-DM	• Flatiron database
	LR-to-death	• KEYNOTE-054 • Life tables for England & Wales (2014-2016)
Distant metastases	DM-to-death	• KEYNOTE-006 • NMA comparing treatments for advanced melanoma • Life tables for England & Wales (2014-16)

- Flatiron database = an electronic health records database used by cancer care providers in the United States. Company selected eligible individuals for inclusion in their analyses
- KEYNOTE-006 = Phase III open-label RCT that evaluated treatment with pembrolizumab vs ipilimumab in people with unresectable or advanced melanoma. Primary outcome = OS, defined as the time from randomisation to all-cause mortality

Utility values used in the company's model

Health state	Base case utilities		Source
	Value	Standard error	
Recurrence-free (without toxicity)	0.870	0.008	KEYNOTE-054
Loco-regional recurrence	0.830	0.016	
Distant metastases (pre-progression)	0.775	0.012	
Distant metastases (post-progression)	0.590	0.020	Beusterien (2009)
Adverse events (included diarrhea, hyperthyroidism, pneumonitis, fatigue, alainine aminotransferase increased, arthralgia, headache, dyspnoea)	-0.05457	0.0170	KEYNOTE-054

- Utilities were adjusted by UK general population utility where utility decreases with age based on Ara and Brazier study (2010)