NICE National Institute for Health and Care Excellence

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Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence (CDF Review of TA553) [ID3776]

Lead team presentation

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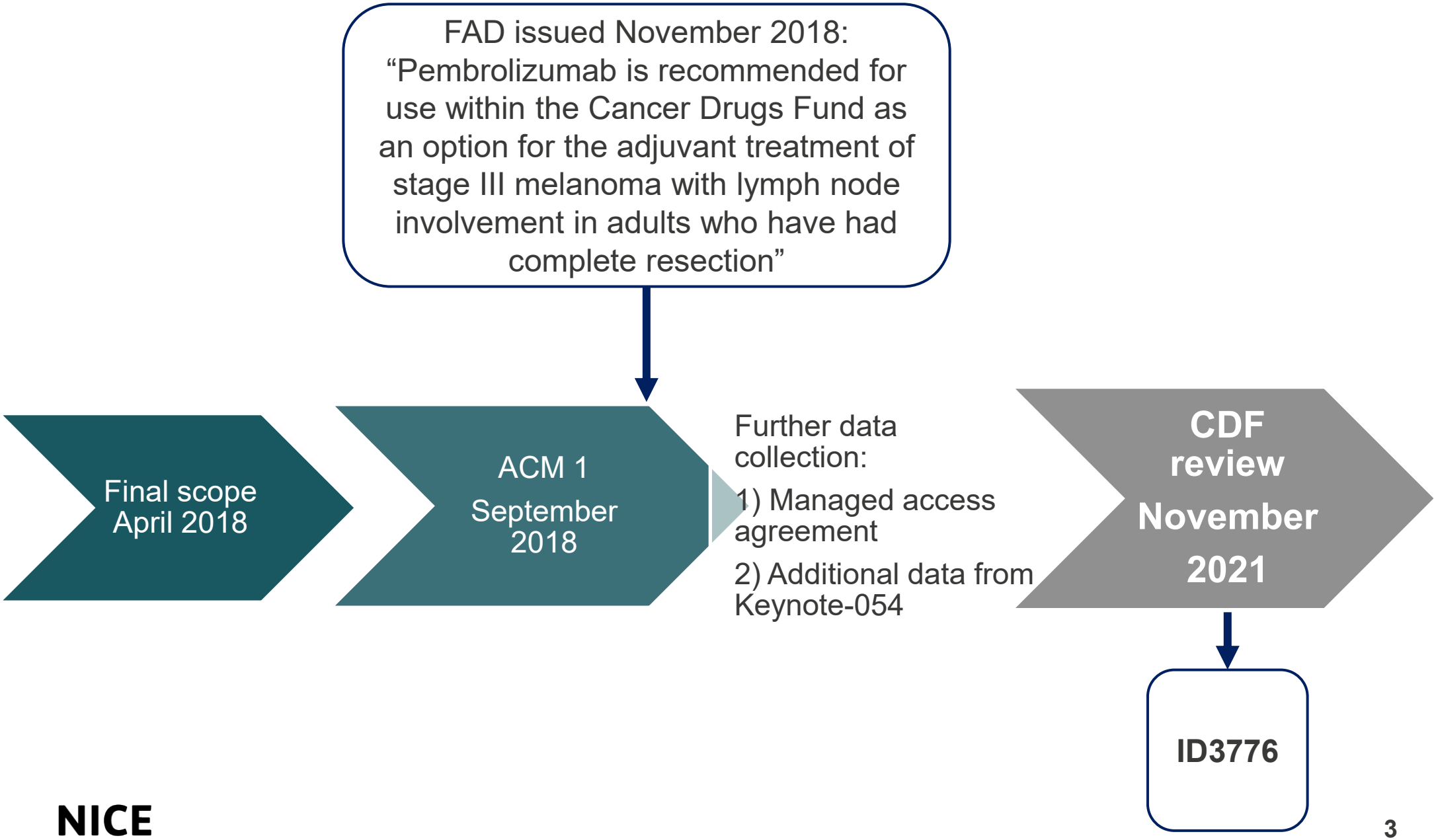
Company: MSD

1st Appraisal Committee meeting: November 2021

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
ACM	Appraisal consultation meeting	LR	Locoregional recurrence
AJCC	American Joint Committee on Cancer	LY	Life years
CDF	Cancer drugs fund	N	Number
CI	Confidence interval	NICE	National Institute for Health and Care Excellence
DM	Distant metastasis	NHS	National Health Service
DMFS	Distant metastasis free survival	NMA	Network meta-analysis
ECOG	Eastern Cooperative Oncology Group	OS	Overall survival
ERG	Evidence review group	PAS	Patient access scheme
FAD	Final appraisal determination	PS	Performance score
HR	Hazard ratio	QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio	RF	Recurrence-free
IA	Interim analysis	RFS	Recurrence-free survival
ITC	Indirect treatment comparison	SACT	Systemic anti-cancer therapy dataset
KM	Kaplan-Meier	TA	Technology appraisal

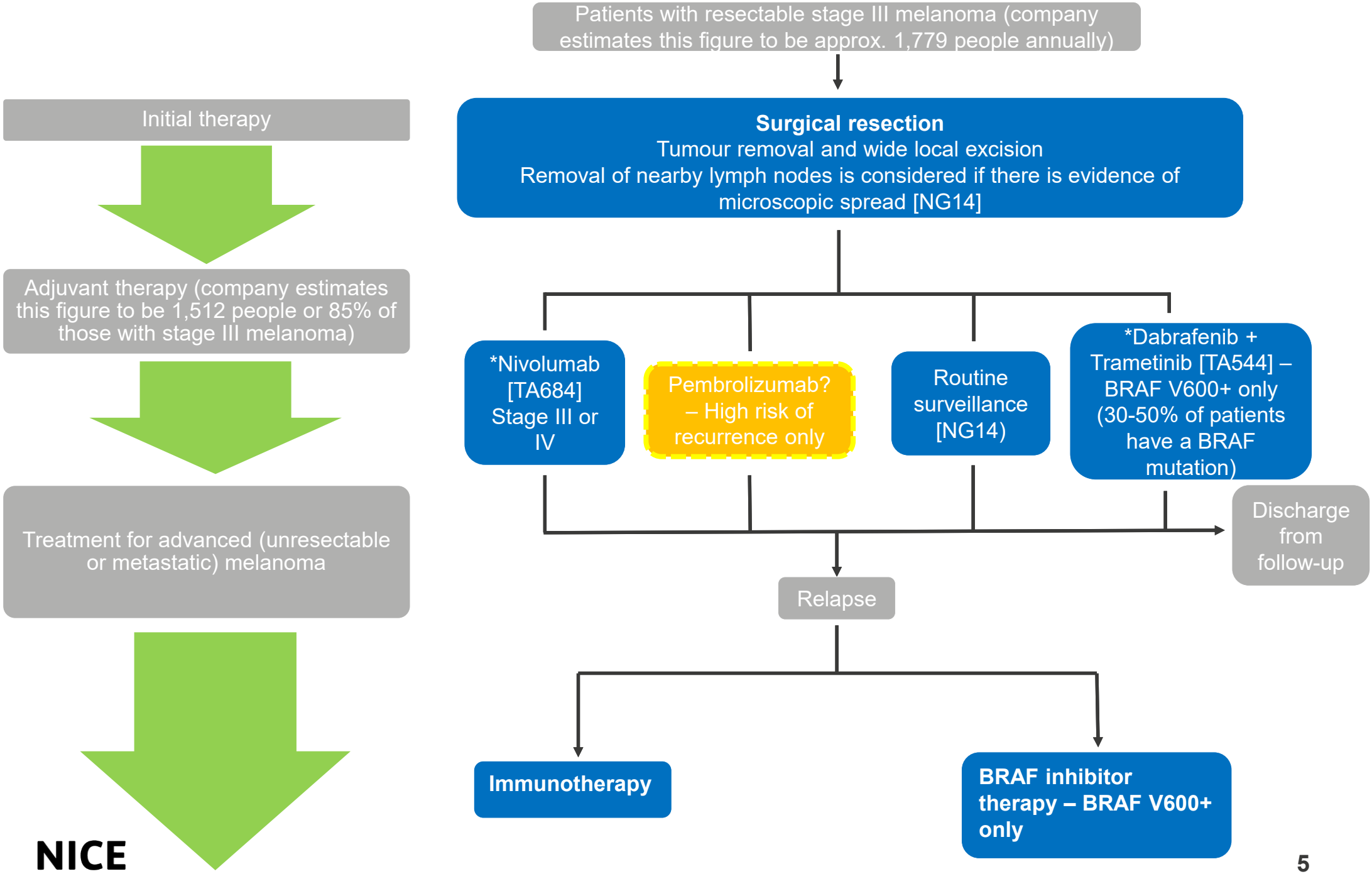
Summary of original appraisal TA553



Pembrolizumab

Marketing authorisation	As monotherapy for the adjuvant treatment of stage III melanoma with lymph node involvement who have undergone complete resection
Administration	• Intravenous infusion • Maximum treatment duration 12 months **Flat dose of 200mg every 3 weeks or 400mg every 6 weeks**
Cost (list price)	£2,630 per 100mg/4ml concentrate for solution for infusion vial
Patient access scheme	A patient access scheme (PAS) has been approved- simple discount

How is melanoma treated



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* TA684 and TA544 do not require a patient has to be high risk of recurrence

TA553 clinical effectiveness conclusions

- KEYNOTE-054 patients had lower ECOG performance scores (all 0 or 1) whereas in the initial appraisal it was believed that 20% of NHS population will have higher scores (2 or 3)
- KEYNOTE-54 patients were younger (54 years) whereas the NHS population is estimated to be older
  - KEYNOTE-054 population generalisable (section 3.3)
- View of recurrence-free survival (RFS)?
  - Based on “promising” effect on RFS, may improve overall survival vs routine surveillance. But “until overall survival data are reported from KEYNOTE-054, the survival benefit with pembrolizumab cannot be confirmed” (section 3.5)

Challenges of evaluation of adjuvant therapies

- Patients have no known disease at the time of treatment
- Some patients treated would never have develop advanced disease (already ‘cured’ by surgery)
- Early stages of cancer so even if they develop metastatic disease it may be many years and rounds of treatment before death, so very long follow up required for OS data
- Difficulty with knowing whether an adjuvant therapy regimen permanently cures, or just delays progression beyond when it would otherwise have occurred
- In the absence of OS data is recurrence-free survival (RFS) or distant metastasis free survival (DMFS) a surrogate if follow up is long enough?

Preview: clinical effectiveness issues

- **Survival data**
  - OS data are still immature 42 months follow-up. What does committee make of the updated RFS and DMFS data, and the uncertainty due to no OS data?
    - Updated RFS data and DMFS are available. Are these of value predicting OS benefit?
- **For how long is risk of recurrence reduced by having had pembrolizumab (i.e. when do risks become equal?)**
  - Does 1 year of adjuvant pembrolizumab prevent the development of further disease or just delay it? How long does the treatment effect of pembrolizumab last?
- **What does the SACT data from the NHS contribute? (Is it relevant for validation of the model?)**
  - 7.7 months follow up of people who received pembrolizumab, 8.8% deaths
- **Does the AJCC data provide a good indicator of survival on watch and wait? (relevant for validation of model)**

Patient perspectives

- Around 16,200 new melanoma cases in UK every year
- Melanoma becoming more common and affects people at younger age than some cancers. Substantial effect on patients, their carers and wider society
- “Patients have unanimously stated that the stress of living with melanoma can be seen physically, mentally, and emotionally. It’s not just the effects of the disease they are dealing with, it’s also stress, depression, and anxiety. It can be confusing with some patients (and carers) and depends on where they are in their diagnosis.” – Melanoma UK
- “The main unmet needs we hear from patients include uncertainty about their future, lack of information about risk of recurrence, outcomes if melanoma were to spread, fears of cancer returning, what next?” – Melanoma UK
- “Advantages: The HOPE that adjuvant therapy may reduce the risk of melanoma recurring following surgery.” – Melanoma UK
- “Disadvantages: Severity of side effects, difficulty in use (injection rather than tablet), downtime as the technology has to be used at hospital rather than home, might worsen their condition” – Melanoma UK

Patient perspectives – Melanoma UK

- *"I'm a stage 3 patient currently on adjuvant Pembro treatment (12 months). I have been so grateful to have this treatment to improve the chances of my cancer not coming back. Since diagnosis I have been acutely aware that just a few years ago this would not have been an option for me, I would have just had to watch and wait. Adjuvant treatment gives hope for a return to some normality and is such a recent improvement to the overall treatment options in melanoma."*
- *"It has given me hope for life."*
- *"Means I feel like I'm actually being treated rather than left to die."*
- *"Treatments available on the NHS for Melanoma have significantly improved but are still very limited - there are several effective and innovative treatments available in other countries that yield great results, but we don't have access to them here."*
- *"I think there should be more options available to patients who are unable to tolerate a treatment. My side effects have been few but even with them, I will tolerate them as they are saving my life."*
- *"The thought that this treatment may not be an option fills me with dread and it would devastate those with this awful disease, myself included. Please don't take away the hope we are clinging on to."*
- *"As far as I'm concerned 'Watch and wait' is not a medical option. It's the medical community saying go away and learn to live with the daily pressure of examining your own skin, whilst trying not to be paranoid and live a reasonably 'normal' life. Until you live in that situation I don't think you can comprehend that fear. Every twinge, headache, lump and bump could be cancer. Has it spread? Should I call my doctor? Before I had adjuvant Pembro I was preparing to die. Now I am just living my life."*

Clinical expert perspectives – technical engagement

- Adjuvant pembrolizumab for stage III resected melanoma is effective in significantly improving RFS
- 'Data from Keynote 054 are consistent with 5 other large pivotal studies (Checkmate 238, Combi AD, Keynote 716, Checkmate 915, and EORTC 18071)' [Studies are for drugs other than pembrolizumab but are all trials of immunotherapies or BRAF inhibitors in adjuvant setting]
  - '3 other pivotal trials in this scenario and none has yet presented definitive OS data. (CheckMate 238, Combi AD and CheckMate 915)'
  - 'EORTC 18071 ipilimumab vs placebo showed a clear survival benefit for ipilimumab over placebo'
  - 'Checkmate 238 ipilimumab vs nivolumab: early survival data shows no clear survival benefit for nivolumab but need to remember this was against ipilimumab, which shows a survival benefit vs placebo'
  - 'Combi AD dabrafenib + trametinib vs placebo: preliminary survival data show a survival benefit for adjuvant D+T'
  - 'Checkmate 915: nivolumab vs modified combo ipilimumab+ nivo showed no difference in RFS, again need to note that this was a comparison of 2 active treatments.'

What is the aim of this treatment? Has this trial achieved it? What is the significance of DMFS in the follow-up of patients? How many patients are receiving routine surveillance?

Clinical expert perspectives – technical engagement

- **'DMFS is considered a reliable surrogate for OS'**
- **'AJCC [American Joint Committee on Cancer – used for staging and by the ERG to validate the company's modelled results in the routine surveillance arm] V.8 may overestimate survival for patients on observation'**
  - 'a lot of debate about the whether the OS curves for AJCC V.8 are representative of this patient population or are overly optimistic... data for AJCC V.8 come from 10 large academic centres, they are not population based registry data… 3 major publications that report worse outcomes for Stage 3 patients than those reported by AJCC V.8… Isaksson et al. reports data from a population based registry. The others are clinical trial and/or hospital registry based data.'
  - ERG highlights company's model estimates of OS for routine surveillance arm are pessimistic vs AJCC data. But if AJCC overestimates survival, difference between company's modelled OS estimates and true survival of those with stage III melanoma would change.

What is the aim of this treatment? Has this trial achieved it? What is the significance of DMFS in the follow-up of patients? How many patients are receiving routine surveillance?

Decision problem

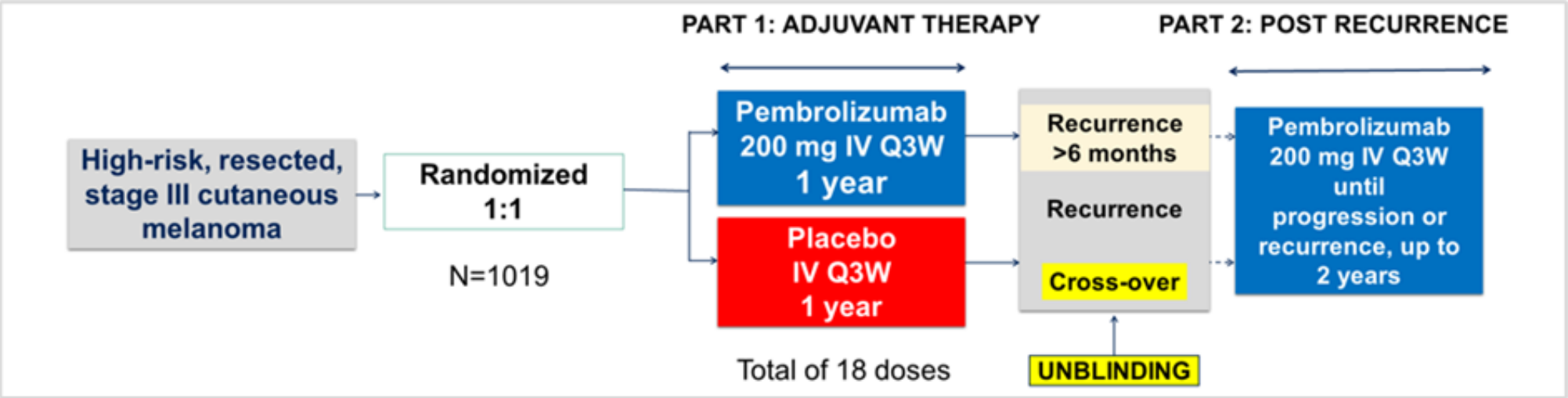
Population	People with completely resected stage III melanoma at high risk of recurrence (in the company model, all people with stage 3 disease who have undergone complete resection are eligible for pembrolizumab, though company assumes not all will receive adjuvant treatment)
Intervention	Pembrolizumab
Comparators	Routine surveillance
Outcomes	• overall survival – not incorporated in the model as OS data remain immature • recurrence-free survival • distant metastases free survival • adverse effects of treatment • health-related quality of life

What does the committee make of high risk of recurrence? Are all people with stage 3 disease at high risk of recurrence? Or does risk vary by stage (i.e. IIIA compared with IIID)?

TA553 - committee recommendations

Area	Assumptions
Recurrence-free survival (3.4)	Pembrolizumab showed statistically significant improvement vs placebo, but short follow up (16 months). **Company should use more mature data and fully explore most appropriate method to calculate the associated hazard ratio.**
Distant met-free survival (3.8)	Distant metastases-free survival data from KEYNOTE-054 were not available. **Company should use more mature distant metastases-free survival data from KEYNOTE-054 to inform the economic model.**
Overall survival (3.9)	KEYNOTE-054 overall survival data not available. ERG concerned that company's model produces clinically implausible overall survival estimates. **Company should use overall survival data from KEYNOTE-054 to inform the economic model.**
Duration of treatment effect (3.10)	Company assumed a lifetime treatment benefit after stopping pembrolizumab. **Company should use more mature data from KEYNOTE-054 to inform assumptions about the duration of treatment effect after stopping treatment**
Subsequent treatments (3.11)	Company used market share data to estimate proportion of people having subsequent treatment for metastatic disease. **Company should fully explore most appropriate assumptions about subsequent treatments using data collected through SACT. (Not major model driver)**
ICERs (3.12 and 3.13)	Committee noted that the company's ICERs were within the range usually considered a cost-effective use of NHS resources. **But, considering the very limited data for distant metastases-free and overall survival committee agreed that the ICERs for pembrolizumab vs routine surveillance were very uncertain.**

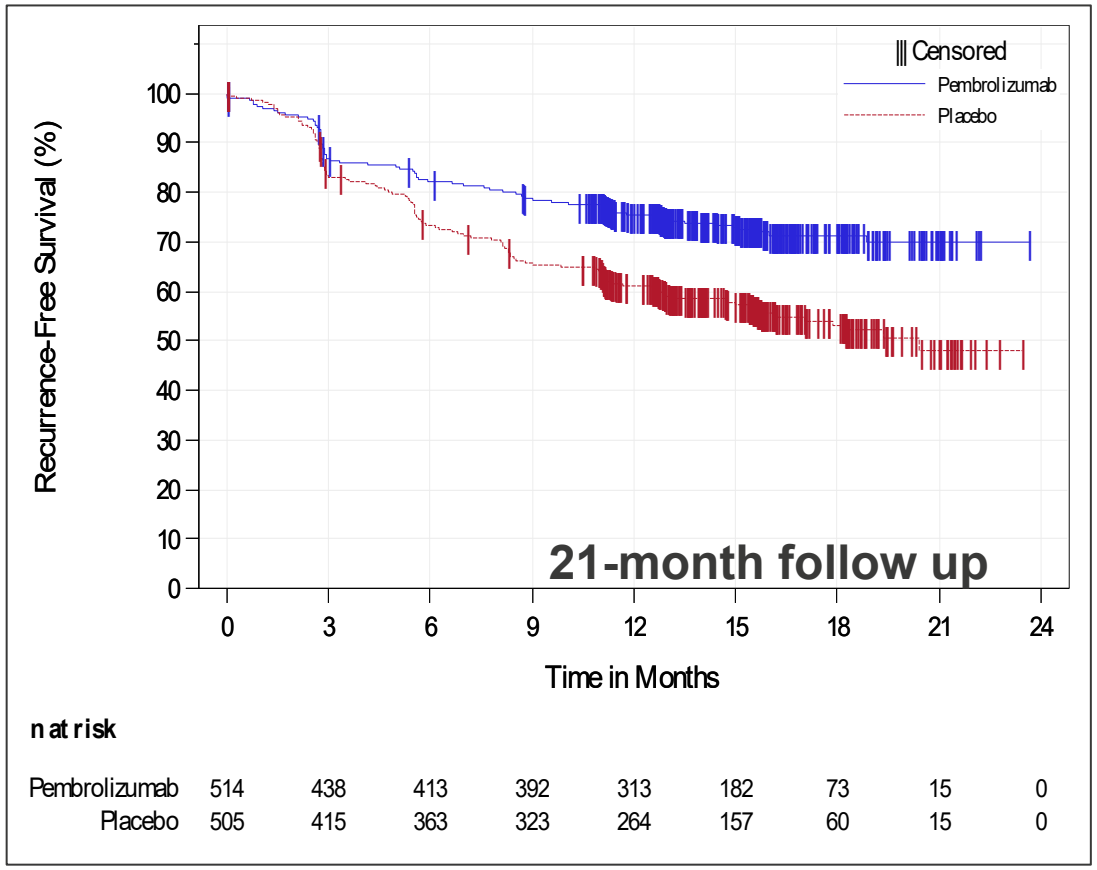
Clinical evidence

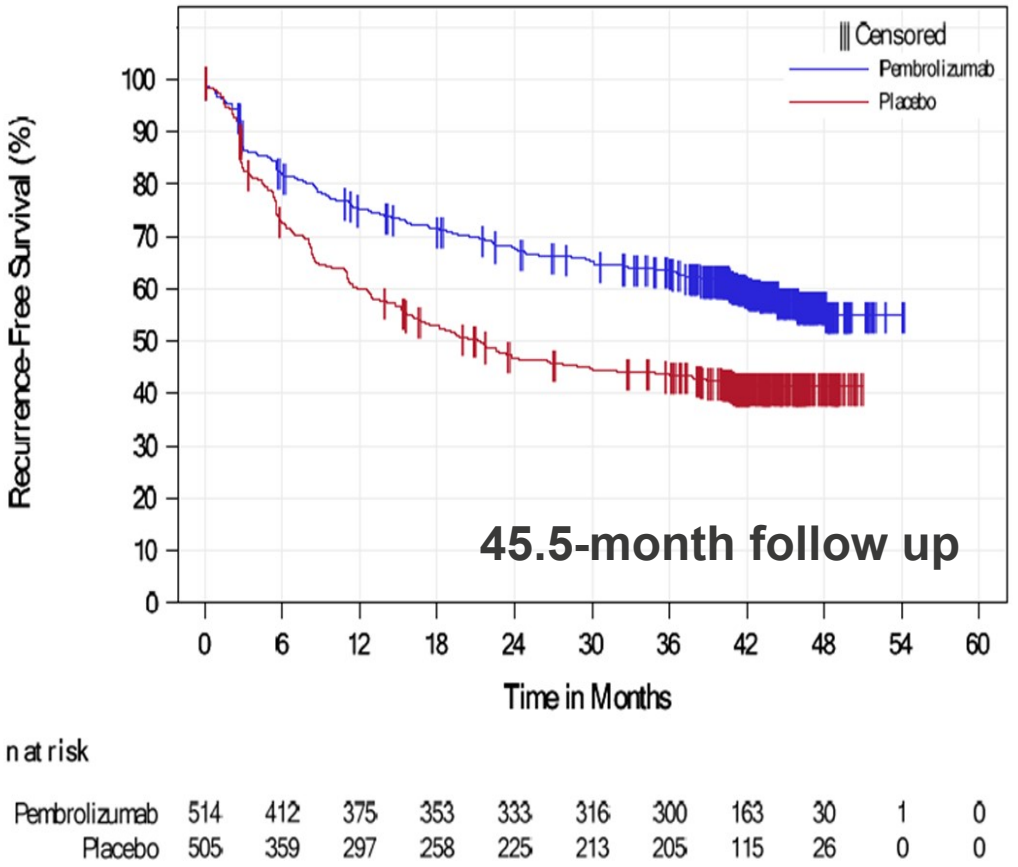


- **Keynote-054**:
  - N=1019 patients with **high-risk, resected, stage III cutaneous melanoma**
  - **Comparison: Pembrolizumab**: 200mg 3 weekly IV up to 1 year vs. **Placebo**: 3 weekly IV up to 1 year
- **Key outcomes**: recurrence free survival (RFS), distant metastases-free survival (DMFS), overall survival (OS)
- Patients who received placebo and had documented recurrence eligible to crossover to pembro
  - [redacted] patients in placebo arm with LR recurrence crossed-over
- Pembrolizumab arm patients with recurrence >6 months eligible for pembrolizumab rechallenge
  - [redacted] of patients in pembrolizumab arm with LR recurrence had rechallenge

If someone receive pembrolizumab as an adjuvant therapy and experiences a recurrence for which they receive treatment, will other immunotherapies work as effectively?

Updated clinical evidence RFS – Keynote-054

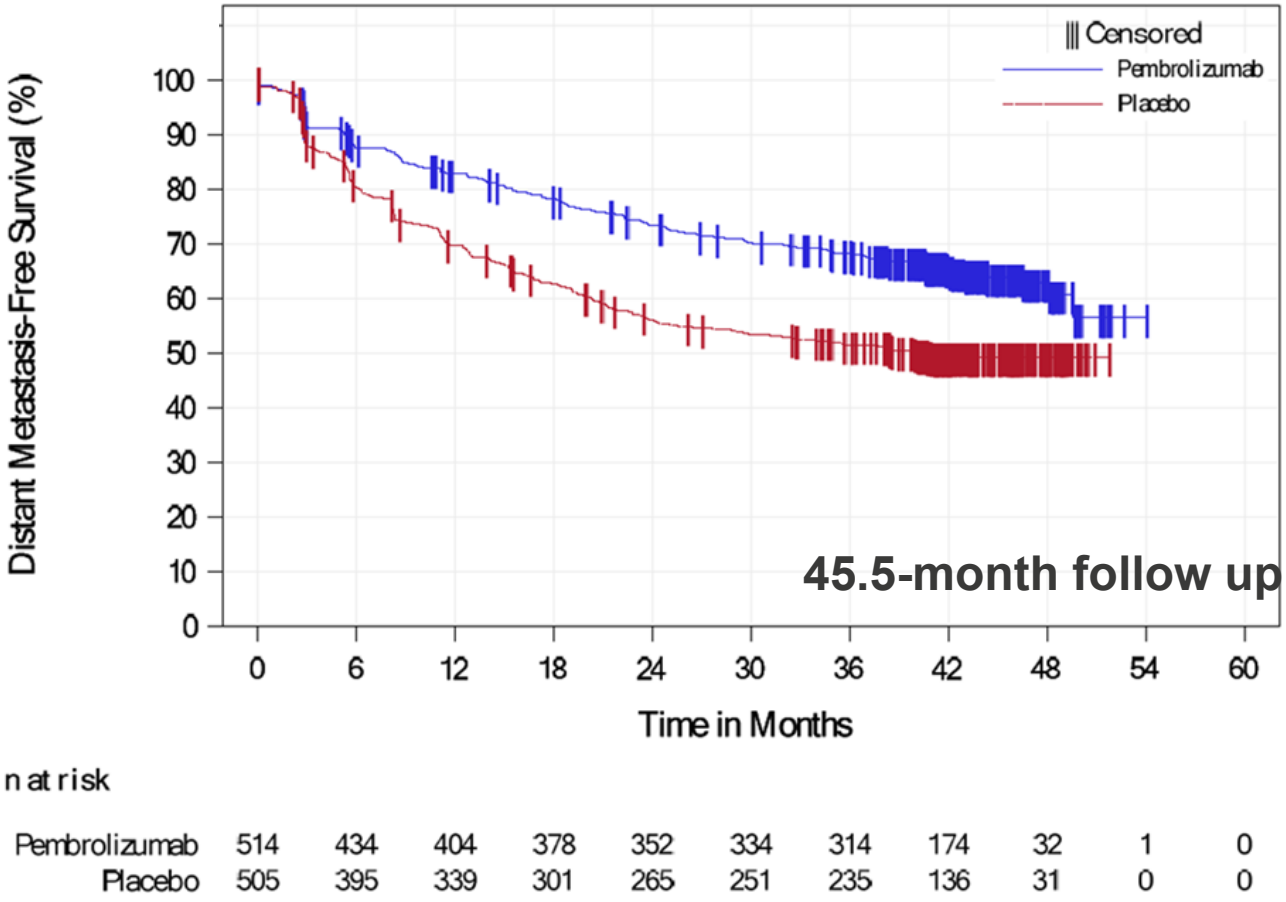




Treatment	Subjects	No. events (%)	Median (95% CI)	HR (95% CI)
21-month follow up				
Pembrolizumab	514	135 (26.3)	Not reached (–, –)	**0.57 (0.43, 0.74)**
Placebo	505	216 (42.8)	20.4 (16.2, –)	
45.5-month follow up				
Pembrolizumab	514	203 (39.5)	[redacted]	**0.59 (0.49, 0.70)**
Placebo	505	288 (57.0)	[redacted]	

Updated clinical evidence DMFS – Keynote-054

- **Within the original submission using interim analysis 1 data, DMFS was not analysed due to data immaturity**

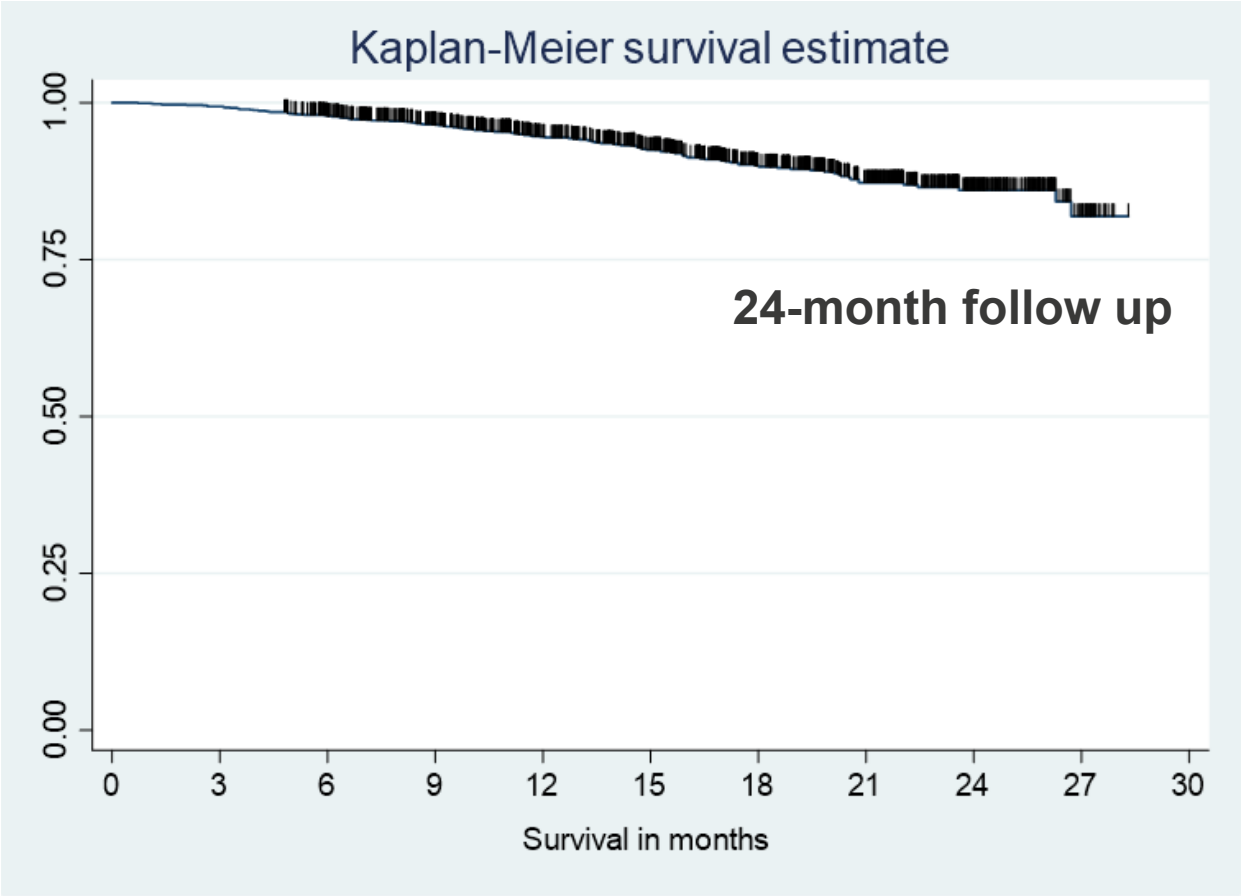


Treatment	Subjects	Events	Median (95% CI)	HR (95% CI)
45.5-month follow up				
Pembrolizumab	514	173 (33.7)	Not reached (49.6, –)	**0.60**
Placebo	505	245 (48.5)	40.0 (27.7, –)	**(0.49, 0.73)**

Committee: RFS promising' and may improve OS. Does the extra RFS and DMFS data help reduce the uncertainty in OS?

Updated clinical evidence OS – SACT dataset

- November 2018 to November 2020, n=[redacted]
- Company noted some differences between SACT and KEYNOTE-054 populations as follows:
- **Median age**
  - SACT older than KEYNOTE-054 (64 vs 54 years).
- **ECOG**:
  - SACT had fewer with ECOG 0 than KEYNOTE-54 (69% vs 94.4%).
- **BRAF V600+ mutation**:
  - SACT had fewer with mutation than KEYNOTE-054 (19% vs 47.5%)



Treatment	Subjects	Events	Median follow-up at censor date (minimum, maximum)
24-month follow up			
Pembrolizumab	[redacted]	[redacted]	[redacted] months ([redacted], [redacted])

What does the SACT data from the NHS contribute? What does committee make of the differences between the SACT and Keynote-054 populations?

Staging in KEYNOTE-054 and SACT cohort

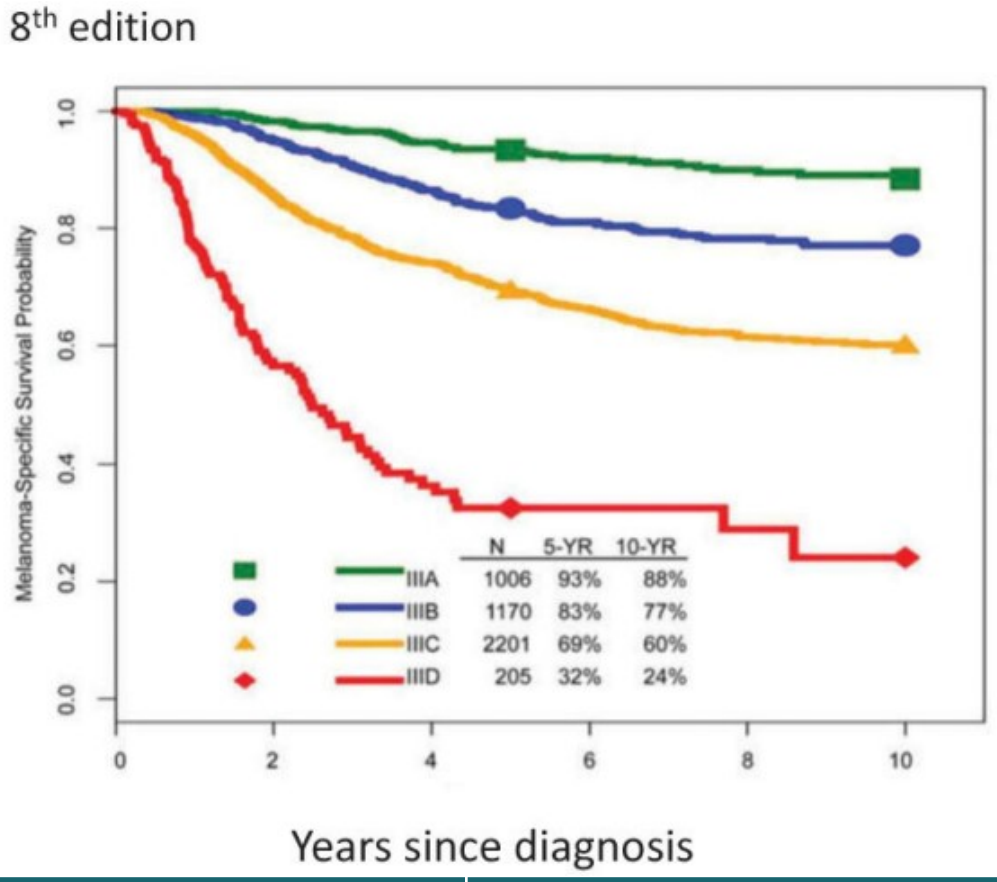
Stage	KEYNOTE-054		SACT Cohort
	Pembrolizumab N=514 (%)	Placebo N=505 (%)	Pembrolizumab N=[redacted] (%)
IIIA (> 1 mm)	80 (15.6%)	80 (15.8%)	[redacted]
IIIB	237 (46.1%)	230 (45.5%)	[redacted]
IIIC (1-3 LN+)	95 (18.5%)	93 (18.4%)	[redacted]
IIIC (≥ 4 LN +)	102 (19.8%)	102 (20.2%)	[redacted]
IIID	-	-	[redacted]

- KEYNOTE-054 uses AJCC 7th edition for staging (IIIA, IIIB, IIIC)
- SACT Cohort uses AJCC 8th edition for staging (IIIA, IIIB, IIIC, IIID)
- "When interpreting adjuvant therapy clinical trials, one must be cognizant that trial participants with stage IIIA/B/C (as defined by the seventh edition staging system) are at higher risk and have worse prognosis than patients with similar stage III subgroup as defined by the eighth edition staging system." – Keung and Gershenwald (2018)

What does committee make of the differences between the SACT and Keynote-054 populations?

Estimates of those eligible for pembrolizumab by AJCC stage

- American Joint Committee on Cancer (AJCC) reports incidence of stage III melanoma by level (A, B, C, D)
- Can estimate proportions from this, and apply to company estimate of number of people eligible for adjuvant therapy (1,512) to get estimates of number of people by stage (assumes NHS has similar incidence by stage as seen in AJCC)
- Despite not being UK evidence, relevant to our topic as it allows us to estimate the number of people eligible for pembrolizumab by stage



Stage	N	5-YR survival	10-YR survival	Predicted number of people for each stage based on AJCC (%) – NICE calculations	SACT cohort Pembrolizumab N=[redacted] (%)
IIIA	1006	93%	88%	332 (22%)	[redacted]
IIIB	1170	83%	77%	386 (25.5%)	[redacted]
IIIC	2201	69%	60%	726 (48%)	[redacted]
IIID	205	32%	24%	68 (4.5%)	[redacted]

Issue: Updated clinical data - OS

Background:

- Keynote-054 overall survival (OS) immature. As of April 2020 [redacted]% of the events required for analysis of OS had occurred . Final OS analysis is now estimated [redacted]

Stakeholder comments:

- Reasonable assumption that improved RFS will continue and the assumption that this means improvement in OS
- In adjuvant setting, if disease recurs, it tends to do so within the first few years. Late recurrences relatively rare, and effect likely small
- Other immunotherapy adjuvant studies continue to show an ongoing benefit. Reasonable assumption that this will continue to show benefit.

Company:

- Immaturity of Keynote-054 OS data is a good indication that adjuvant treatment with pembrolizumab is associated with positive long-term survival outcomes for patients.

ERG:

- SACT data are informative, but length of follow-up is short and the number of deaths is low. Uncertainty around OS cannot be resolved until after the final analysis of KEYNOTE-054 trial OS data and/or mature SACT data are available.

- **Survival data are still immature. Is updated RFS and DMFS informative?**

Subsequent treatments – SACT data

Pembrolizumab data	SACT dataset	
	Distribution of first treatment prescribed after a patient's last pembrolizumab cycle [redacted]	Distribution of further lines of therapy following a patient's last pembrolizumab cycle (interpreted as 2nd line metastatic) [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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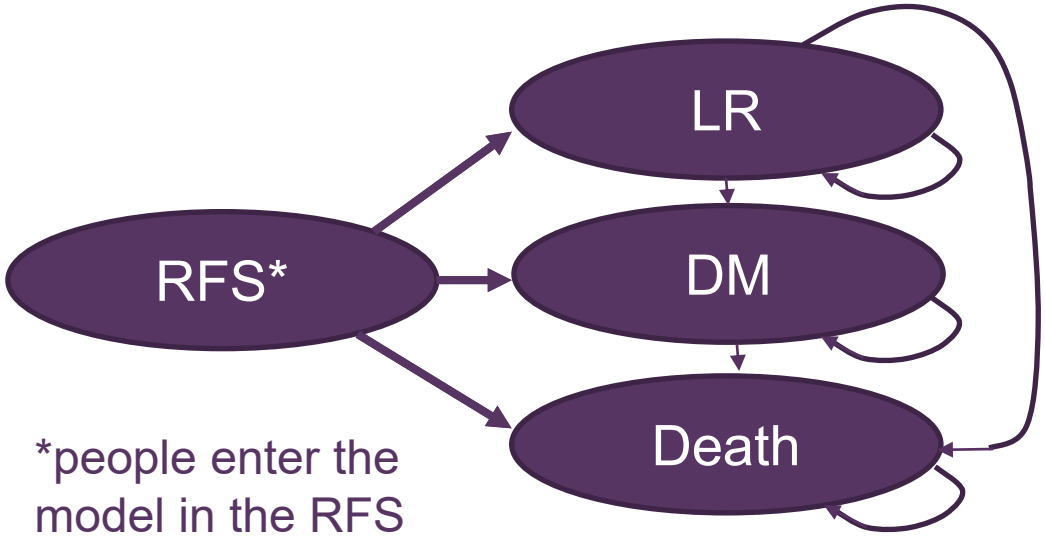
Clinical effectiveness issues

- **Survival data**
  - OS data are still immature 42 months follow-up. What does committee make of the updated RFS and DMFS data, and the uncertainty due to no OS data?
    - Updated RFS data and DMFS are available. Are these of value predicting OS benefit?
- **How long is risk of recurrence reduce by having had pembrolizumab (i.e. when do risks become equal?)**
  - Does 1 year of adjuvant pembrolizumab prevent the development of further disease or just delay it? How long does the treatment effect of pembrolizumab last?
- **What does the SACT data from the NHS contribute? (relevant for validation of model?)**
- - 7.7 months FU of people who received pembrolizumab, 8.8% deaths
- **Does the AJCC data provide a good indicator of survival on watch and wait? (relevant for validation of model)**

Key cost-effectiveness issues

- **Model structure:**
  - Given the absence of any OS data to populate the model, what does the committee make of the company's plausible ICERs and uncertainty surrounding them?
  - Are the company's modelled OS outputs for pembrolizumab reliable?
  - Are the company's modelled OS outputs for routine surveillance reliable?
  - Can the level of uncertainty be quantified?
  - What does the committee make of the risk of recurrence having had pembrolizumab? Does having had pembrolizumab permanently reduce the risk of recurrence? Or do the hazards equalize?

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

- Original model predicted **cost savings** and QALY gains including overall survival benefit (which is not a health state in the model, but is an output of the model), now updated to predict additional costs, and smaller modelled QALY gains

ERG comment: Model structure is appropriate

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

Company's results (Pembrolizumab PAS)

	Incremental			ICER £/QALY
	Costs, £	LYs	QALYs	
Initial appraisal (TA 553)				
• Deterministic base case	[redacted]	[redacted]	[redacted]	Dominant
• Probabilistic results	[redacted]		[redacted]	Dominant
Company's current submission				
• Deterministic base case	[redacted]	[redacted]	[redacted]	£9,357
• Probabilistic results	[redacted]	[redacted]	[redacted]	£10,378

Issue: Immaturity of OS data

Background:

- Model was considered appropriate and now includes updated RFS and DMFS data from Keynote-054.

Company:

- Acknowledges the limitations as a result of having no OS data to use in model
- But, immaturity of OS data is an indicator of positive long-term survival outcomes for patients

ERG:

- The model does not generate reliable OS results for patients on pembrolizumab or routine surveillance and therefore the company's estimated ICERs are unreliable
- In the absence of OS data, the ERG is unable to produce ICERs that are more reliable than those presented by the company

Survival data are still immature. What does the committee make of the updated RFS and DMFS data? Are these suitable surrogates for OS to make a decision?

ERG: Modelled OS outputs from the model for pembrolizumab are unreliable

Background:

- Company approach:
  - RF → LR: Generalized gamma
  - RF → DM: Gompertz
  - RF → Death; LR → DM; LR → Death: Exponential
  - DM → Death: Assumed to depend on expected mix of subsequent treatment for advance melanoma and their efficacy – comes from company's NMA

Company:

- OS outputs for active treatment arm matches very well with the OS data observed with nivolumab in Checkmate238 over approximately 5 years
  - Checkmate238: Adjuvant nivolumab or ipilimumab for patients aged 15 or older with resected stage IIIB-C or IV melanoma and an ECOG score of 0 or 1
- SACT dataset has slightly below OS observed in Checkmate238 – but this can be explained by the higher baseline age in the SACT cohort compared with the trials

ERG:

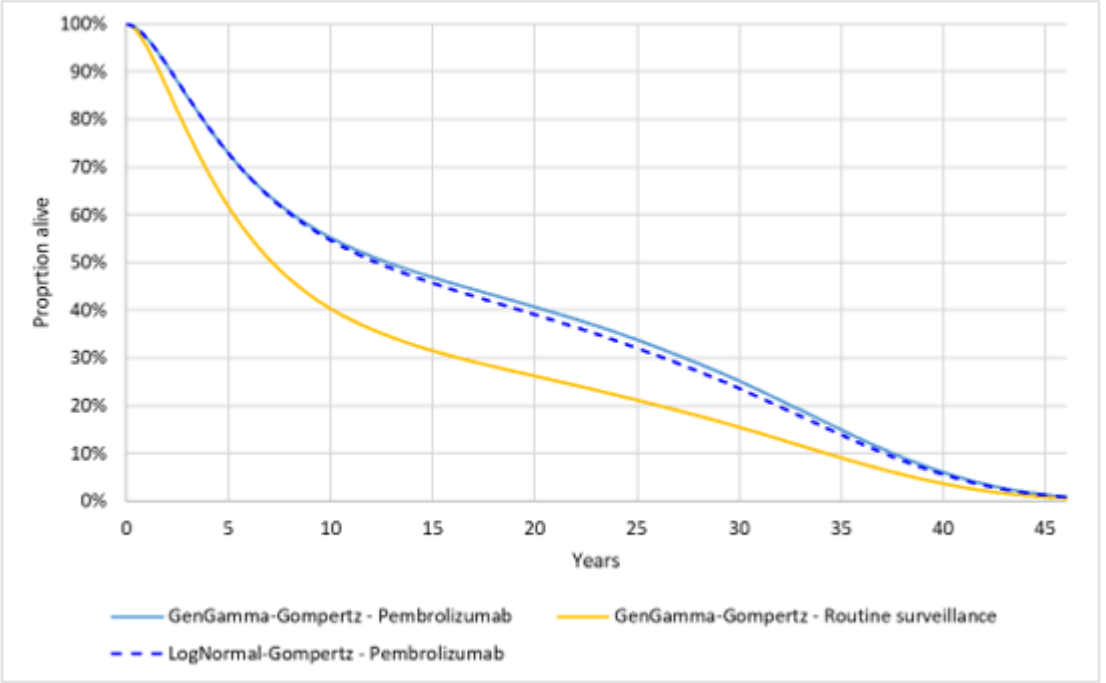
- At 18 months: SACT data showed [redacted] of patients treated with pembrolizumab had died, whereas company model mortality estimate was [redacted]% (i.e. [redacted]% lower than rate experienced by NHS patients)

Technical engagement: Modelled OS estimates for pembrolizumab are unreliable

Company:

- SACT: important differences which would lead to lower OS – limiting usefulness as validation tool
  - Fewer BRAF mutations than KEYNOTE-054 (19% versus 47.5%).
    - BRAF+ patients may receive additional targeted treatment, so may have better survival
  - Older than KEYNOTE-054 (64 vs. 54 years)
  - Less fit than KEYNOTE-054 (ECOG PS 0:69% vs 94.4%)
- Comparison of observed OS from KEYNOTE-053/SWOGS1404 with company modelled OS outputs reveal a close alignment in first 3.5 years
- Company stated ICER remained cost-effective (£12,231) even in a scenario using the more conservative lognormal curve (rather than gen gamma as in base case) for RF to LR transition

Figure 3: Scenario A, conservative pembrolizumab: Long term OS projections with alternative parametric function combinations



Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario.

Technical engagement: Modelled OS estimates for pembrolizumab are unreliable

ERG:

- Inconsistent to use trial data to validate model OS outputs for one arm and real-world for other
- KEYNOTE-053 potentially has superior RFS in pembrolizumab arm vs KEYNOTE-054. If RFS is predictive of OS, than not unreasonable to assume OS for pembrolizumab in KEYNOTE-054 will be worse than OS for those in KEYNOTE-053
- ERG does not consider scenario conservative – appears arbitrary selection of alternative curve for patients in the pembrolizumab arm and this curve makes little difference to OS output

ERG: Modelled OS estimates for routine surveillance are unreliable

Background:

- RF → LR: Generalized gamma
- RF → DM: Gompertz
- RF → Death; LR → DM; LR → Death: Exponential
- DM → Death: Assumed to depend on expected mix of subsequent treatment for advance melanoma and their efficacy – comes from company's NMA

Company:

- Clinical experts were consulted with who agreed the generalised gamma – gompertz provided reasonable, if slightly conservative predictions of OS output
- Early on, OS output is higher than seen in validation sources, but this is consistent with higher RFS and DMFS observed in KEYNOTE-054 vs EORTC-18071 (ipilimumab vs nivolumab)
- 3-year OS outputs for routine surveillance are aligned with OS outputs for placebo arm of the COMBI-AD trial (dabrafenib + trametinib vs placebo)
- From 7 years onwards, OS outputs for routine surveillance are closely aligned with the composite curve previously provided by the ERG in the initial appraisal

ERG:

- A comparison of the company model with Gershanwald/AJCC OS data shows that the company model OS outputs for routine surveillance arm are pessimistic compared with the Gershenwald/AJCC OS data and that the level of pessimism increases over time

Issue: Modelled OS estimates for routine surveillance are unreliable

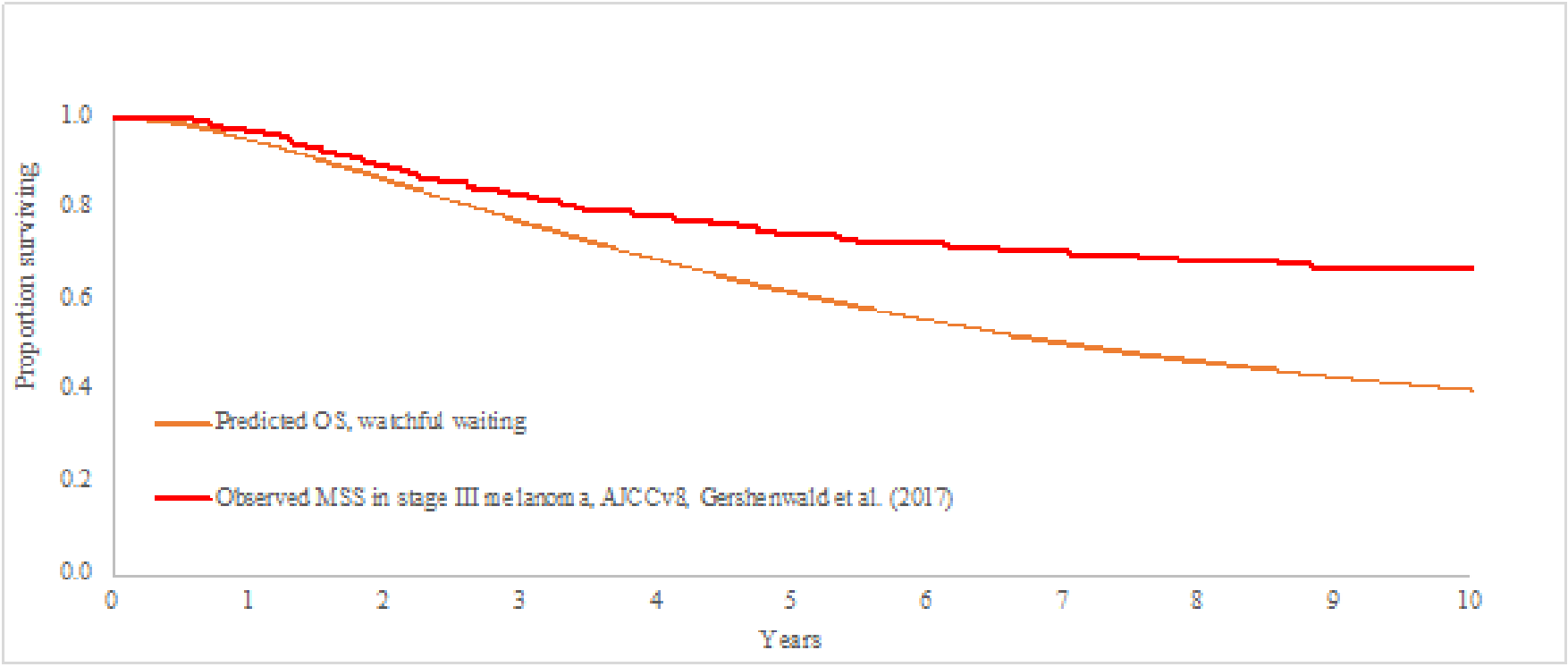


Figure 2 OS estimates for patients receiving routine surveillance (company model and Gershenwald/AJCC)

MSS=melanoma specifc survival; OS=overall survival
Source: Company model

Technical engagement: Modelled OS estimates for routine surveillance are unreliable

Company:

- Gershenwald/AJCC data is substantially higher than all other sources with available OS data and therefore should not be used to validate the modelled OS estimates for routine surveillance
- KEYNOTE-053/SWOG-S1404 should be the key source used to validate the OS projections for pembrolizumab
  - HR generated by ITC of KEYNOTE-053-SWOG-S1404 and EORTC-18071 ([redacted]) can be applied to the KM OS data for pembrolizumab from KEYNOTE-053/SWOG-S1404 to estimate the KM OS for routine surveillance – which is closely aligned with OS curve predicted by the model for routine surveillance.

ERG:

- ERG considers company ITC OS results should not be used to inform decision making as subsequent treatments available to patients in the included trials are very different across the trials

Company's OS output versus published data

Table 21: Validation of base case modelled projections vs. published data, for OS

Source	OS by year from baseline									
	1	2	3	4	5	6	7	8	9	10
Routine surveillance arm – OS										
COMBI-AD placebo [30, 31, 34]	94%	83%	77%	-	-	-	-	-	-	-
TA553 ERG report, composite [1]	95%	79%	69%	62%	56%	50%	47%	45%	43%	40%
EORTC-18071 placebo [18, 36]	89%	76%	66%	61%	54%	53%	51%	-	-	-
AJCCv8 [26]	97%	83%	79%	75%	72%	71%	69%	67%	67%	67%
SEER 2000-2017 [27]	94%	83%	75%	70%	66%	63%	61%	60%	58%	57%
TA553 projections [1]	95%	86%	75%	64%	55%	47%	40%	35%	30%	26%
Gompertz- Gompertz	*95%*	*86%*	*77%*	*69%*	*62%*	*56%*	*51%*	*48%*	*45%*	*43%*
Generalised gamma – Gompertz‡	***95%***	***87%***	***77%***	***69%***	***62%***	***56%***	***51%***	***47%***	***43%***	***40%‡***
Lognormal – Gompertz	*95%*	*87%*	*77%*	*69%*	*62%*	*55%*	*50%*	*46%*	*42%*	*39%*
Gompertz – Lognormal	*95%*	*87%*	*78%*	*69%*	*61%*	*55%*	*49%*	*44%*	*40%*	*36%*
Generalised gamma - Lognormal	*95%*	*87%*	*78%*	*70%*	*62%*	*54%*	*48%*	*43%*	*38%*	*34%*
Pembrolizumab – OS										
CheckMate238 nivolumab [30, 31, 34]	96%	88%	82%	78%	-	-	-	-	-	-
Pembrolizumab SACT [25]	95%	90%†	-	-	-	-	-	-	-	-
EORTC-18071 ipilimumab [18, 36]	93%	82%	73%	67%	65%	62%	60%	-	-	-
TA553 projections [1]	96%	89%	82%	75%	68%	63%	58%	54%	51%	48%
Gompertz- Gompertz	*97%*	*91%*	*85%*	*78%*	*73%*	*68%*	*64%*	*61%*	*59%*	*57%*
Generalised gamma - Gompertz	***97%***	***91%***	***85%***	***79%***	***73%***	***68%***	***64%***	***61%***	***58%***	***55%***
Lognormal – Gompertz	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*64%*	*60%*	*57%*	*55%*
Gompertz – Lognormal	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*63%*	*60%*	*56%*	*53%*
Generalised gamma - Lognormal	*97%*	*91%*	*85%*	*79%*	*73%*	*68%*	*63%*	*59%*	*55%*	*52%*

Issue: Risk of recurrence – is there a lifetime benefit of treatment? Or do hazards equalize at some point?

Background:

- In its initial submission, company assumed a lifetime treatment benefit after stopping pembrolizumab. The committee recognized the uncertainty in the assumption of lifetime treatment benefit with pembrolizumab as adjuvant treatment and concluded that more mature data on overall survival would help decision making.

Company:

- The extended follow up data for pembrolizumab demonstrated a statistically significant, sustained improvement in RFS and DMFS over time

ERG:

- In KEYNOTE-054, the risks of first recurrence and distant metastasis in the pembrolizumab arm were lower than the risks in the routine surveillance arm from 0 to 36 months
- This suggests that, for patients who are permitted a maximum of 12 months of treatment, RFS benefit endures for a maximum period of up to 3 years
- Over-estimating the RFS and DMFS benefit of patients receiving pembrolizumab results in the company model generating cost effectiveness results that are biased towards pembrolizumab

Issue: Risk of recurrence - TE

Company:

- Model employs assumption there is no ongoing benefit of pembrolizumab after recurrence, and therefore reduced risk of recurrence with pembrolizumab versus routine surveillance is only maintained while patients remain recurrence-free
  - This is a 'highly conservative assumption that biases in favour of routine surveillance'
- Longer follow-up data show sustained RFS and DMFS benefit
- Clinical evidence from KEYNOTE-054 is consistent with other clinical trials and indicates there is a durable separation of curves for RFS and DMFS also seen in CheckMate238, EORTC-18071 (CA184-029) and COMBI-AD

ERG:

- The ERG highlights the benefits of treatment with pembrolizumab compared with routine surveillance in KEYNOTE-054, in terms of a lower risk of first recurrence, appears to have disappeared by the end of 3 years

How long is risk of recurrence reduced by having had pembrolizumab?

ERG calculations showing risks of recurrence in company model over time

Table 8 Risk of experiencing a first recurrence: KEYNOTE-054 trial and company model data

	Pembrolizumab			Routine surveillance		
Months	Kaplan-Meier	Model	Difference (KM-Model)	Kaplan-Meier	Model	Difference (KM-Model)
0-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36-42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG calculations based upon the percentage of people having a first recurrence between different time periods divided by the percentage of people at risk of having a first recurrence at the start of the period

Table 9 Risk of experiencing a distant metastasis: KEYNOTE-054 trial and company model data

	Pembrolizumab			Routine surveillance		
Months	Kaplan-Meier	Model	Difference (KM-Model)	Kaplan-Meier	Model	Difference (KM-Model)
0-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36-42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG calculations based upon the percentage of people having a distant metastasis between different time periods divided by the percentage of people at risk of having a distant metastasis at the start of the period

What does the committee make of the risks of recurrence? Do they believe the risks of recurrence equalize? Or does pembrolizumab confer a lifetime benefit in terms of reduced risk of recurrence?

Company base case assumptions

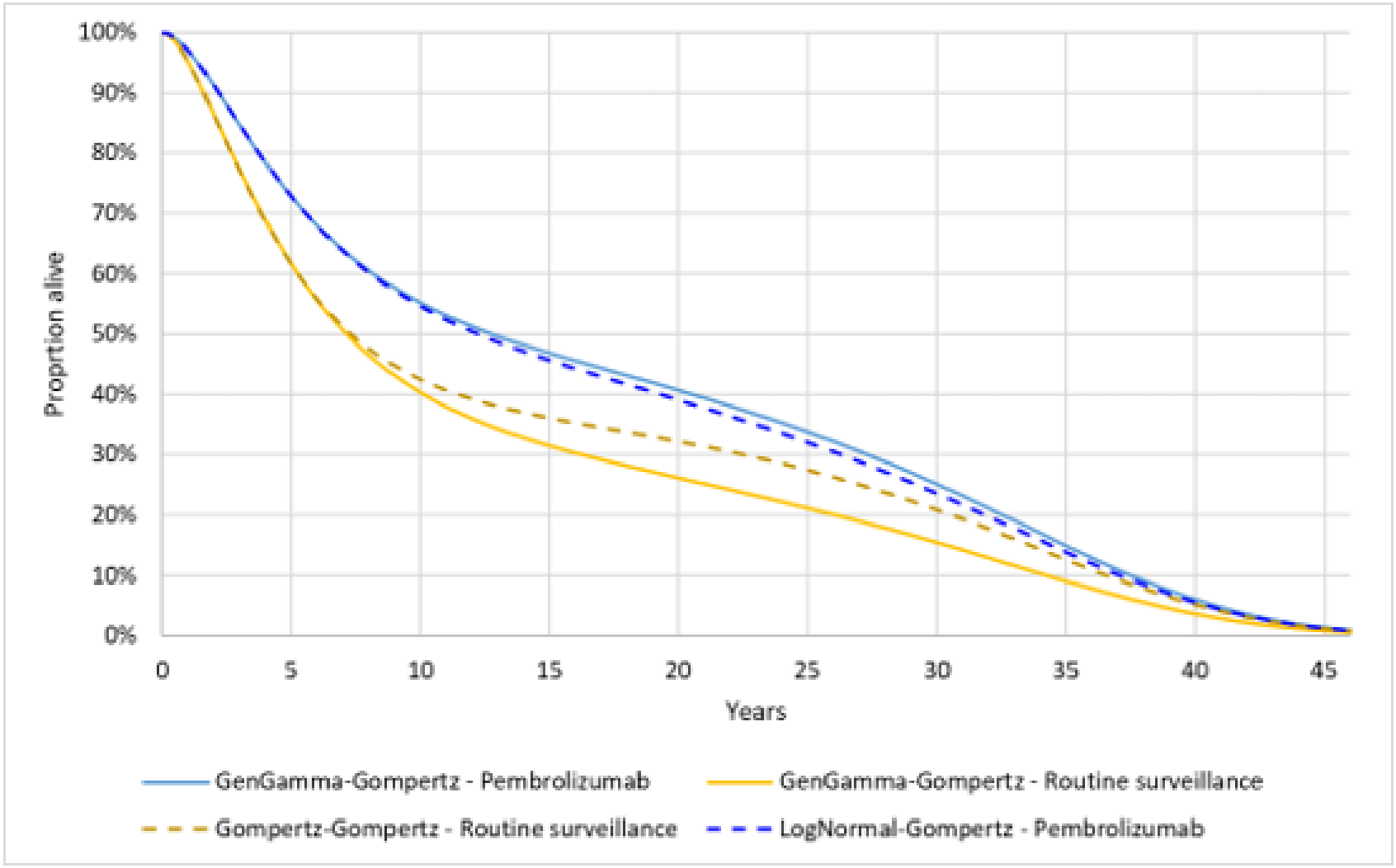
Input	TA553 parameter /assumption	Updated parameter/assumption
Clinical data from KEYNOTE-054		
RFS	KEYNOTE-054, IA1 data cut (October 2017)	KEYNOTE-054 IA2 data cut (April 2020)
DMFS data	No. DM events in KEYNOTE-054 (DMFS analysis not available at October 2017 data cut-off)	KEYNOTE-054, IA2 data cut-off April 2020
Model transition probabilities		
RF → LR	Gompertz fitted to KEYNOTE-054 IA1 treatment-specific RFS	Gen gamma fitted to KEYNOTE-054 IA2 treatment-specific RFS
RF → DM	Gen gamma fitted to treatment-specific KEYNOTE-054 DM events	Gompertz fitted to KEYNOTE-054 IA2 treatment-specific DMFS data
RF → Death	Exponential fitted to KEYNOTE-054 treatment-specific death events	Exponential model fitted to treatment-specific death events observed in KEYNOTE-054
LR → DM transition	Exponential model fitted to real-world patient-level data from the Flatiron database. Transition probabilities assumed equal between pembrolizumab and routine surveillance arms	Exponential models fitted to treatment-specific patient-level data of LR → DM, from DMFS analysis in KEYNOTE-054
LR → Death	Approximated based on exponential model for RF→ Death in pembrolizumab arm	Exponential model fitted to treatment-specific patient-level data from DMFS analysis in KEYNOTE-054
DM → Death	Transition probabilities depend on distributions of first-line treatments received in each arm. Exponential models fitted to patient-level OS data for all patients in the pembrolizumab arm of KEYNOTE-006 (trial in 1L advanced melanoma); HRs for alternative subsequent treatments sourced from NMA of advanced melanoma treatments.	
Other parameters		
Subsequent therapies	Ipsos market research 2018	Pembrolizumab arm: SACT report June 2021 Routine surveillance arm: SACT June 2021, adjusted to permit pembrolizumab use based on Ipsos Oncology Monitor, April 2021 Encorafenib + binimetinib added to reflect NICE TA562
Health state cost	Cost inputs based on 2017 reference year	Costs updated to latest available sources (2019-2020 reference year)

Company: Company base case and key sensitivity analyses

Parameter	Base case	Scenario	Incremental			ICER £/QALY
			Costs, £	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	£9,357
RF->LR and RF->DM conservative pembrolizumab	Gen Gamma-Gompertz	Lognormal-Gompertz				£12,231
RF->LR and RF->DM routine surveillance parametric functions more optimistic	Gen Gamma-Gompertz	Gompertz-Gompertz				£21,126
RF->LR and RF->DM for routine surveillance more optimistic and for pembrolizumab more pessimistic	Gen Gamma-Gompertz	Pembro: Log Normal-Gompertz Routine Surveillance: Gompertz-Gompertz				£26,493

Company: key sensitivity analyses

Figure 8: Scenario C, combined effect: Long term OS projections with alternative parametric function combinations



Notes: Solid lines represent the base case projections; Dashed lines represent the projections explored in the scenario.

ERG response to new company's TE sensitivity analyses

- ERG notes the scenarios produced by the company still assume a substantial survival benefit for pembrolizumab versus routine surveillance which has yet to be evidenced. These new company analyses are speculative and are not evidence based.

Key cost-effectiveness issues

- **Model structure:**
  - Given the absence of any OS data to populate the model, what does the committee make of the company's plausible ICERs and uncertainty surrounding them?
  - Are the company's modelled OS outputs for pembrolizumab reliable?
  - Are the company's modelled OS outputs for routine surveillance reliable?
  - Can the level of uncertainty be quantified?
  - What does the committee make of the risk of recurrence having had pembrolizumab? Does having had pembrolizumab permanently reduce the risk of recurrence? Or do the hazards equalize?

Back up slides

Company's modelled RFS versus published data

Table 19: Validation of base case modelled projections vs. published data, for RFS

Source	RFS by year from baseline					
	1	2	3	4	5	7
Routine surveillance arm - RFS						
KEYNOTE-054 observed [32, 33]	60%	47%	44%	41%	-	-
COMBI-AD placebo [30, 31, 34]	56%	44%	39%	38%	36%	-
EORTC-18071 placebo [18, 36]	56%	44%	35%	35%	30%	31%
TA533 projections [1]	62%	45%	37%	31%	27%	22%
Gompertz- Gompertz	*61%*	*48%*	*43%*	*41%*	*39%*	*38%*
Generalised gamma - Gompertz	***62%***	***49%***	***43%***	***40%***	***37%***	***35%***
Lognormal – Gompertz	*63%*	*49%*	*43%*	*39%*	*37%*	*33%*
Gompertz – Lognormal	*63%*	*50%*	*43%*	*39%*	*36%*	*31%*
Generalised gamma - Lognormal	*64%*	*51%*	*44%*	*38%*	*34%*	*28%*
Pembrolizumab arm - RFS						
KEYNOTE-054 observed [32, 33]	75%	68%	64%	57%	55%†	-
CheckMate238 nivolumab [22, 35]	70%	62%	58%	52%	-	-
TA533 projections [1]	76%	67%	61%	57%	54%	48%
EORTC-18071 ipilimumab [18, 36]	64%	52%	47%	46%	41%	39%
Gompertz- Gompertz	*77%*	*67%*	*61%*	*58%*	*56%*	*54%*
Generalised gamma - Gompertz	***77%***	***67%***	***62%***	***58%***	***55%***	***52%***
Lognormal – Gompertz	*78%*	*68%*	*62%*	*58%*	*55%*	*51%*
Gompertz – Lognormal	*77%*	*67%*	*62%*	*58%*	*56%*	*51%*
Generalised gamma - Lognormal	*77%*	*68%*	*62%*	*58%*	*55%*	*49%*

Abbreviations: RFS, recurrence-free survival.
Bold font indicates curve used for base case analysis; Underlined font indicates value was digitised from published figure.
† At 54 months follow-up.

Company's modelled DMFS versus published data

Table 20: Validation of base case modelled projections vs. published data, for DMFS

Source	DMFS by year from baseline					
	1	2	3	4	5	7
Routine surveillance arm - DMFS						
KEYNOTE-054 observed [32, 33]	70%	56%	52%	49%†	-	-
COMBI-AD placebo [30, 31, 34]	70%	60%	57%	56%	54%	
TA553 projections [1]	72%	55%	44%	36%	30%	23%
EORTC-18071 placebo [18, 36]	66%	53%	45%	42%	39%	37%
Gompertz- Gompertz	*72%*	*58%*	*50%*	*45%*	*42%*	*39%*
Generalised gamma - Gompertz	***72%***	***59%***	***51%***	***45%***	***42%***	***37%***
Lognormal – Gompertz	*73%*	*59%*	*51%*	*45%*	*42%*	*36%*
Gompertz – Lognormal	*74%*	*60%*	*51%*	*44%*	*39%*	*32%*
Generalised gamma - Lognormal	*74%*	*61%*	*51%*	*44%*	*39%*	*31%*
Pembrolizumab arm - DMFS						
KEYNOTE-054 observed [32, 33]	83%	74%	68%	65%†	-	-
CheckMate238 nivolumab [22, 35]	80%	70%	66%	59%	-	-
TA553 projections [1]	84%	73%	66%	60%	56%	49%
EORTC-18071 ipilimumab [18, 36]	75%	62%	55%	51%	48%	45%
Gompertz- Gompertz	*84%*	*73%*	*66%*	*61%*	*58%*	*55%*
Generalised gamma - Gompertz	***84%***	***73%***	***66%***	***61%***	***58%***	***54%***
Lognormal – Gompertz	*84%*	*73%*	*66%*	*61%*	*58%*	*53%*
Gompertz – Lognormal	*83%*	*73%*	*66%*	*61%*	*57%*	*52%*
Generalised gamma - Lognormal	*83%*	*74%*	*67%*	*61%*	*57%*	*51%*

Abbreviations: DMFS, distant metastasis-free survival
Bold font indicates curve used for base case analysis; Underlined font indicates value was digitised from published figure.
† At 42 months follow-up.

Company: Company base case and key sensitivity analyses

Parameter	Base case	Scenario	Incremental			ICER £/QALY
			Costs, £	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	£9,357
Threshold analysis on exponential rate parameter for OS in the DM health state required to result in average survival in line with finding in TA366	Exponential rate remains the same	Exponential rate uplifted so average survival in DM state aligned with Keynote006	[redacted]	[redacted]	[redacted]	£9,060
Threshold analysis on exponential rate parameter for OS in the DM health state required for the proportion of death necessary for OS analysis in KEYNOTE-054 ([redacted]%) to be reached at [redacted]	Exponential rate remains the same	Exponential rate uplifted so % dead at 10 years aligned with KEYNOTE-054	[redacted]	[redacted]	[redacted]	£8,613