Pembrolizumab for adjuvant treatment of stage 2 melanoma with high risk of recurrence

Part 1 - Technology appraisal committee A [9 August 2022]

For committee – contains ACIC information

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NICE

Key clinical issues

- A key driver of the economic model is what treatment people who have a local recurrence (stage 3 melanoma) will receive. Would a person who received adjuvant pembrolizumab for resected stage 2 melanoma receive subsequent adjuvant treatment at stage 3?
- What proportion of people in the UK have stage 2B vs 2C melanoma? Is the evidence from KEYNOTE-716 generalisable to people in the NHS?
- With very little data for adolescents from KEYNOTE-716, would any difference in outcomes be expected in adolescents in clinical practice?
- Currently there are limited overall survival data. Is RFS or DMFS a valid surrogate of overall survival? Can committee infer a survival benefit from these outcomes?
- Only data from the 200 mg 3 weekly pembrolizumab dose has been evaluated in KEYNOTE-716. Can the 400mg 6 weekly dose be considered as effective? What would be used in clinical practice?

Key issues

Table 1 Key issues

Issue	Resolved?	ICER impact
Trial population may not reflect UK population	No – for discussion	Unknown
Only 2 adolescents included in the trial	No – for discussion	Unknown
No data reported for OS	Partially – for discussion	Unknown
Uncertainty about the comparability of the two recommended doses of pembrolizumab (both 3 and 6 weekly recommended by the EMA, but only 3 weekly assessed in trial)	No – for discussion	Unknown

Abbreviations: EMA, European Medicines Agency; OS, overall survival; RF, recurrence free; QxW, every x weeks

Background

Causes

- Melanoma is malignancy arising from melanocytes in the skin
- Risk factors: family history of melanoma, fair skin and hair colour, multiple moles, intense or chronic exposure to UV light

Classification

- Stage 2 melanoma is defined as having no evidence of spread to lymph nodes or distant metastases
- Stage 2B and 2C are deeply penetrating tumours, with or without ulceration, and are at high risk of recurrence.

Epidemiology

- Melanoma accounts for 4% of all new cancers in UK
- 2019: 2,488 new cases of stage 2 melanoma diagnosed in England
    - Approximately half of people with stage 2 melanoma have stage 2B or 2C disease

Symptoms and prognosis

- Depth of primary tumour is leading prognostic factor in stage 2 melanoma
- Current treatment is surgical removal alone
- 5-year recurrence rates are 32% and 46% for resected stage 2B and 2C melanoma, respectively
- 5-year OS rates are 84% and 71% for resected stage 2B and 2C melanoma, respectively
- Risk of recurrence results in psychological burden for people with stage 2B and 2C melanoma

Abbreviations: OS, overall survival; UV, ultraviolet

Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Table 2 Technology details

Marketing authorisation	• Monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with stage 2B, stage 2C or stage 3 melanoma and who have undergone complete resection • Stage 3 melanoma (extension to adolescents) • **Pembrolizumab is already recommended by NICE in adjuvant stage 3 melanoma (TA766) – this appraisal is for stage 2B and 2C only**
Mechanism of action	• Monoclonal antibody that binds to PD-1 (a protein on the surface of T-cells) enabling the immune system to recognise and act against cancer cells
Administration	• IV infusion over 30 minutes • 200 mg every 3 weeks (Q3W)* or 400 mg every 6 weeks (Q6W) • Pembrolizumab should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

Price	• List price: £2,630 per 100 mg vial
	• Cost per administration (list price):
	  • 200 mg Q3W: £5,260
	  • 400 mg Q6W: £10,520
	• Confidential patient access scheme approved (simple discount)

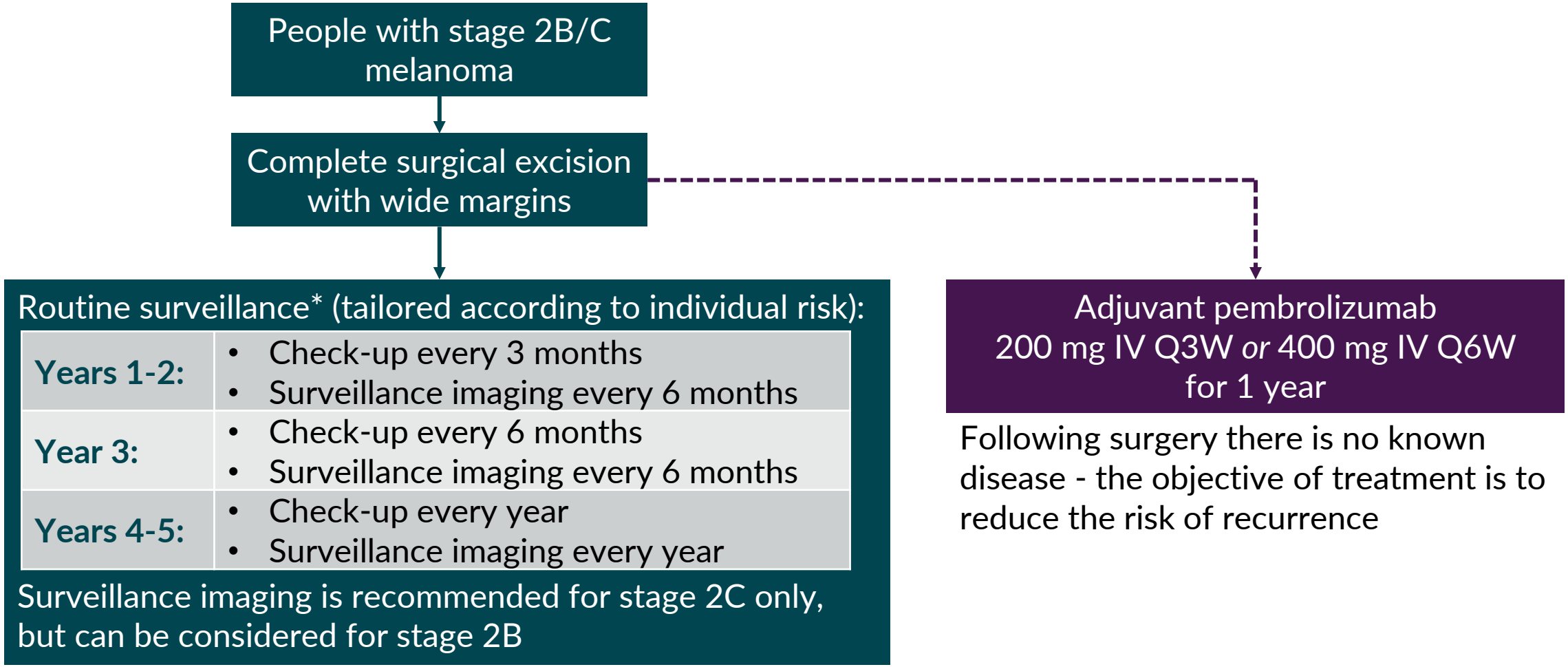
*** Only Q3W regimen was used in the trial**

NICE Abbreviations: IV, intravenous; QxW, every x weeks

Treatment pathway

No adjuvant treatment options beyond resection in stage 2 melanoma

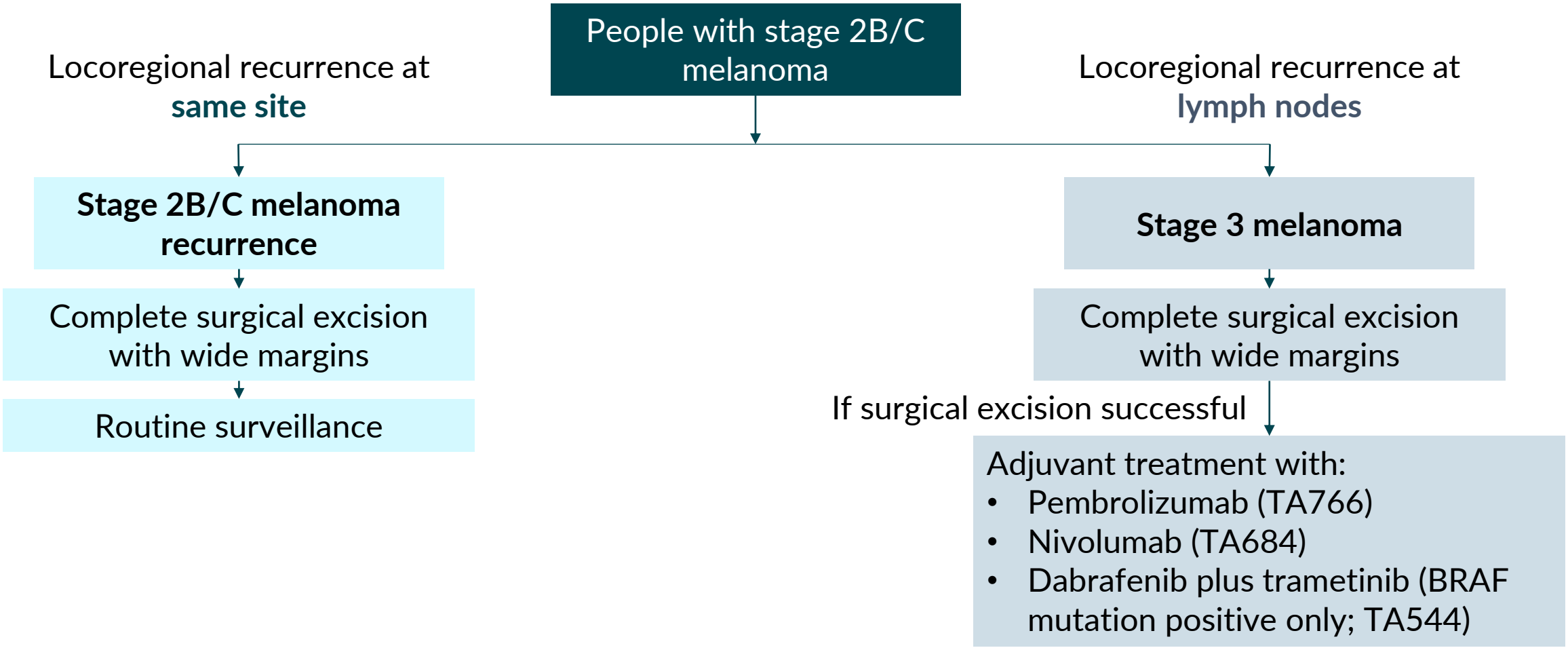
Figure 1 Treatment pathway for stage 2B/2C melanoma



NICE *NICE guideline [NG14]; Abbreviations: QxW, every x weeks

Locoregional recurrence

Figure 2 Treatment pathway for stage 2B/2C melanoma following locoregional recurrence



- How would locoregional recurrence be treated?
- If someone was reoperated for stage 3 disease, would they then have more adjuvant therapy after that?

Metastatic disease

Figure 3 Treatment pathway for stage 2B/2C melanoma following development of distant metastases

People with stage 2B/C melanoma

Development of **distant metastases**

First-line treatment for advanced disease:

- Pembrolizumab (TA366)
- Nivolumab (TA384)
- Ipilimumab (TA268)
- Nivolumab + ipilimumab (TA400)
- Dacarbazine (NG14)
- Vemurafenib* (TA269)
- Dabrafenib* (TA321)
- Dabrafenib + trametinib* (TA396, TA321)
- Encorafenib + binimetinib* (TA562)
- No systemic therapy

*BRAF mutation positive only

Second-line treatment for advanced disease:

- Pembrolizumab (TA366, TA357**)
- Nivolumab (TA384)
- Ipilimumab (TA268)
- Nivolumab + ipilimumab (TA400)
- Dacarbazine (NG14)
- Vemurafenib* (TA269)
- Dabrafenib* (TA321)
- Dabrafenib + trametinib* (TA396, TA321)
- Encorafenib + binimetinib* (TA562)
- No systemic therapy

*BRAF mutation positive only

**after disease progression with ipilimumab

- Is there reasonable consensus on the treatment of metastatic disease?
- Would a patient receive pembrolizumab or another immunotherapy for metastatic disease if they have already had adjuvant immunotherapy?

Patient perspectives

There is an unmet need for adjuvant treatment in stage 2 melanoma

Submissions from Melanoma Focus and Melanoma UK:

- Stress of living with melanoma can be seen physically, mentally and emotionally
- Unmet needs described by people with melanoma are uncertainty about their future, lack of information about risk of recurrence, outcomes if melanoma were to spread, fears of cancer returning, what next?
- Currently people with stage 2 melanoma receive clinical observation only
- Aim of treatment for stage 2 melanoma is to reduce the risk of cancer recurrence and death
    - A reduction in risk of death of 3-5% or more is clinically meaningful in this population
- Pembrolizumab may lead to side effects which can occasionally be severe and long lasting

An early-stage melanoma patient needs reassurance that they are not going to be forgotten and that if surgery doesn't work, that they have options available to them – this treatment gives them that

There are adverse side effects with pembrolizumab, however if the risk of recurrence is reduced it is worth doing

Clinical perspectives

Pembrolizumab is a step-change in management of stage 2 melanoma

Submissions from two clinical experts:

- The main aim of treatment for resected stage 2 melanoma is to reduce the risk of melanoma recurrence
- A clinically significant treatment response is:
  - Statistically significant hazard ratio of 0.75
  - 30% reduction in risk of relapse
- There is an unmet need for people with resected stage 2 melanoma:
  - Currently no systemic therapy for people with resected stage 2 melanoma
  - People with resected stage 2B and 2C melanoma have similar outcomes to people with stage 3A and 3B melanoma
  - Adjuvant therapy is available for resected stage 3 melanoma, but not stage 2 melanoma
- Pembrolizumab is widely prescribed in other indications and clinicians are familiar with the management of adverse events
  - About 2 in 10 patients treated may have a serious adverse event requiring medical intervention
  - About 1 in 10 will have a permanent life changing event
  - Risk of treatment-related death is extremely low

Decision problem

Table 3 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection (at high risk of recurrence)	People aged 12 years and older with stage 2B or 2C cutaneous melanoma who have undergone complete resection	Population aligned with scope. However, only one adolescent (12 to 17 years) was recruited to each arm
Intervention	Pembrolizumab	Pembrolizumab	No comments
Comparators	Routine surveillance	Routine surveillance	No comments
Outcomes	• Overall survival (OS) • Recurrence-free survival (RFS) • Distant metastasis-free survival (DMFS) • Adverse effects of treatment • Health-related quality of life (HRQoL)	• RFS • DMFS • Adverse effects of treatment • HRQoL Analyses of interim analysis 3 (data cut-off: January 2022), insufficient events had occurred to enable OS analysis to be conducted	OS data is not yet available from KEYNOTE-716

Abbreviations: DMFS, distant metastasis-free survival; HRQoL, health-related quality of life; OS, overall survival; RFS, relapse-free survival

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: KEYNOTE-716

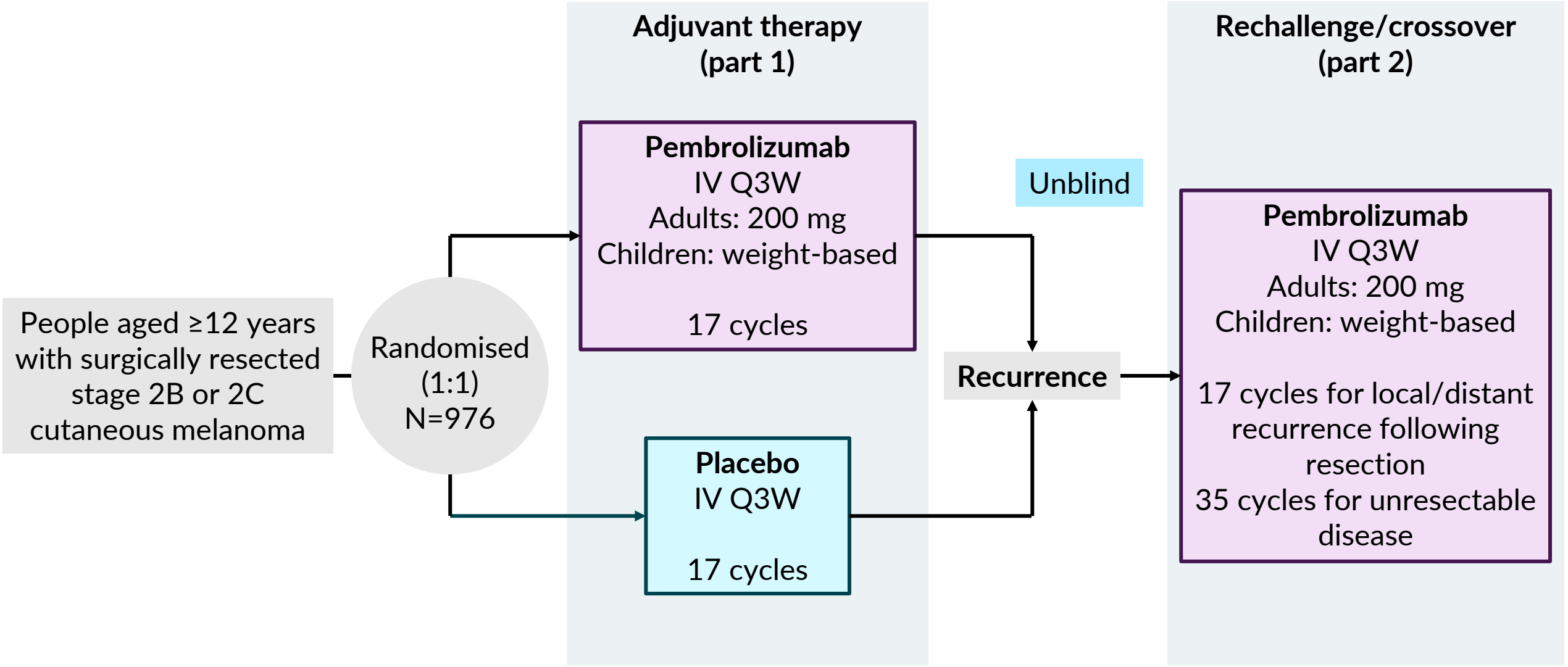
Table 4 Clinical trial designs and outcomes

	KEYNOTE-716
Design	2-part, phase 3, multi-centre, study. **Part 1:** randomised, double-blind, placebo-controlled study; **Part 2:** unblinded, rechallenge/crossover study
Population	People aged ≥12 years with surgically resected stage 2B or 2C cutaneous melanoma
Intervention	Pembrolizumab (**n=487**) iv 17 cycles at: • 200 mg Q3W for adults (≥18 years of age) • Weight related dose for children 12-18
Comparator(s)	Placebo (**n=489**) administered intravenously over 17 cycles
Duration	Ongoing – each patient followed-up for ~15 years
Primary outcome	Recurrence-free survival (RFS)
Key secondary outcomes	• Distant metastasis-free survival (DMFS) • Overall survival (OS) • Adverse events (AEs) • Discontinuation of treatment due to AEs • Health-related quality of life (HRQoL) • Time to subsequent therapy (TTST) • Progression/recurrence-free survival 2 (PRFS2) • Biomarkers
Locations	16 countries, including UK (4 sites; [redacted] participants)

NICE Abbreviations: QxW, every x weeks

KEYNOTE-716 study design

Figure 4 KEYNOTE-716 study design



Abbreviations: IV, intravenous; QxW, every x weeks

KEYNOTE-716 baseline characteristics

- Clinical experts confirmed baseline characteristics are representative of population in England
- Majority of participants are white, which is expected as fair skin is a risk factor for melanoma

Table 5 Baseline characteristics for pembrolizumab and placebo (ITT population)

Characteristic	Pembrolizumab (n=487)	Placebo (n=489)
Male, %	61.6	59.1
Age, %		
12-17	0.2	0.2
18-64	62.0	60.1
≥65	37.8	39.7
Median, years	60.0	61.0
Cancer stage, %		
2B	63.4	64.6
2C	35.1	34.6
Race, %		
White	89.3	89.8

NICE Abbreviations: ITT, intention to treat

Key issue: Trial population may not reflect UK population

Background

- There are differences in proportion of people with stage 2B and 2C disease in KEYNOTE 716 vs PHE published data

Stage, %	KEYNOTE-716	PHE Data
2B	64.0	57.0
2C	34.8	43.0

ERG comments

- Larger proportion of people in KEYNOTE-716 had less severe (2B) disease with a better prognosis compared with UK clinical practice
- Subgroup analyses appear to show a better outcome for stage 2B (HR for RFS for pembrolizumab vs placebo: stage 2B: [redacted] stage 2C: 0.82 [95% CI 0.54 to 1.26])

Company

- The differences between the KEYNOTE-716 population and PHE data are relatively small
- Clinical experts confirmed KEYNOTE-716 baseline characteristics are representative of UK population
- Subgroup analyses were not statistically powered to detect differences between stage 2B and 2C

Clinical expert comments

- Would not expect there to be differences in clinical outcomes between stage 2B and stage 2C

What proportion of people in the UK have stage 2B vs 2C melanoma? Is the evidence from KEYNOTE-716 generalisable to people in the NHS?

Abbreviations: CI, confidence interval; HR, hazard ratio; PHE, Public Health England; RFS, relapse-free survival

Key issue: Only 2 adolescents included in trial

Background
- KEYNOTE-716 study recruited one patient aged 12 to 17 to each treatment arm

ERG comments
- It is uncertain whether clinical effectiveness results in KEYNOTE-716 can be generalised to adolescents

Company response to technical engagement
- Melanoma incidence across all substages is low in the UK, therefore there is low adolescent recruitment in all melanoma trials
- The EMA have accepted extrapolation of adult results in adolescents because:
  - Similarity of melanoma disease biology in adults and adolescents and similar exposure-response for efficacy and safety in other disease areas
- High unmet need for adjuvant treatment options for adolescent population
- Budget impact in adolescents is minimal, due to small patient population

Clinical expert comments
- The results in adults are expected to be generalisable to adolescents

With very little data for adolescents from KEYNOTE-716, would any difference in outcomes be expected in adolescents in clinical practice?

KEYNOTE-716: Recurrence free survival (alive without local or distant recurrence)

Adjuvant pembrolizumab treatment statistically significant improved RFS vs placebo

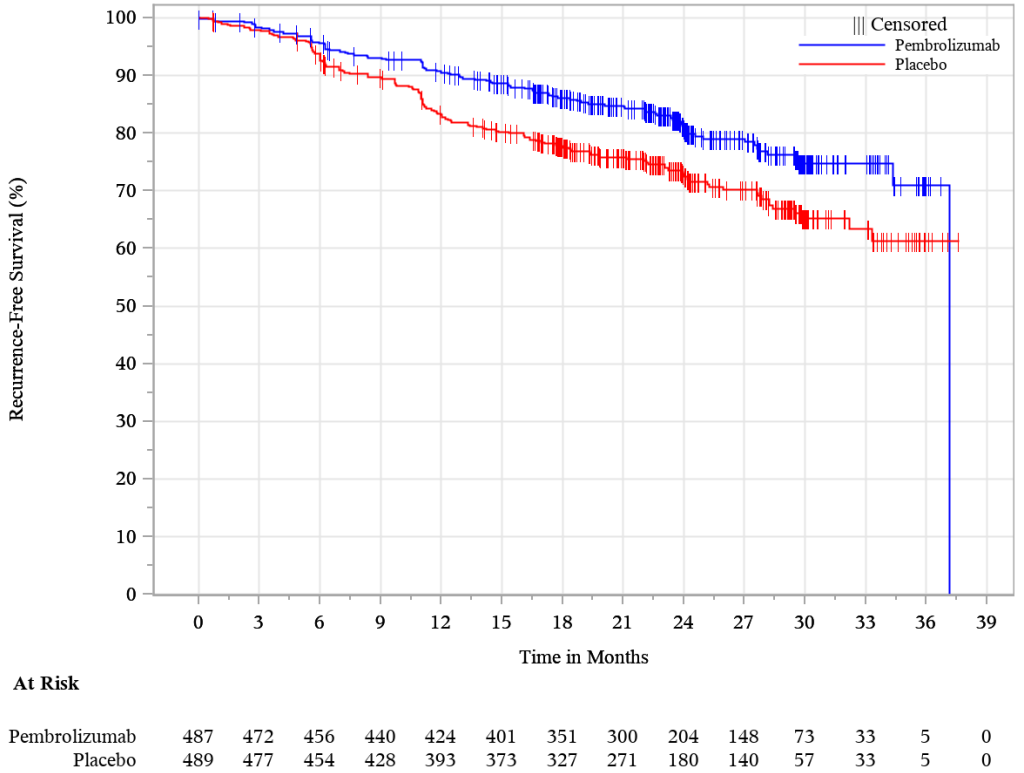
- KEYNOTE-716 met the primary RFS endpoint and hypothesis based on 1st interim analysis (IA1 HR: 0.65; 95% CI: 0.46 to 0.92; p=0.00658; December 2020)
- Data from further data cuts (IA2 [June 2021] and IA3 [January 2022]) supports the primary analysis with additional follow-up

Table 6 RFS analysis - IA3 data cut-off: January 2022

RFS (95% CI)	Pembrolizumab (n=487)	Placebo (n=489)
Median, months	37.2 (NR to NR)	NR (NR to NR)
24 months, %	81.2 ([redacted])	72.8 ([redacted])
HR	0.64 (0.50 to 0.84)	

Primary censoring rule; ITT population;

Figure 5 Kaplan-Meier estimates of RFS – IA3 data cut-off: January 2022



Primary censoring rule; ITT population

Abbreviations: CI, confidence interval; FU, follow-up; IA, interim analysis; ITT, intention to treat; HR, hazard ratio; NR, not reached; RFS, recurrence-free survival

KEYNOTE-716: Distant metastasis free survival (alive without distant recurrence, may have had local recurrence)

Adjuvant pembrolizumab treatment improved DMFS vs placebo

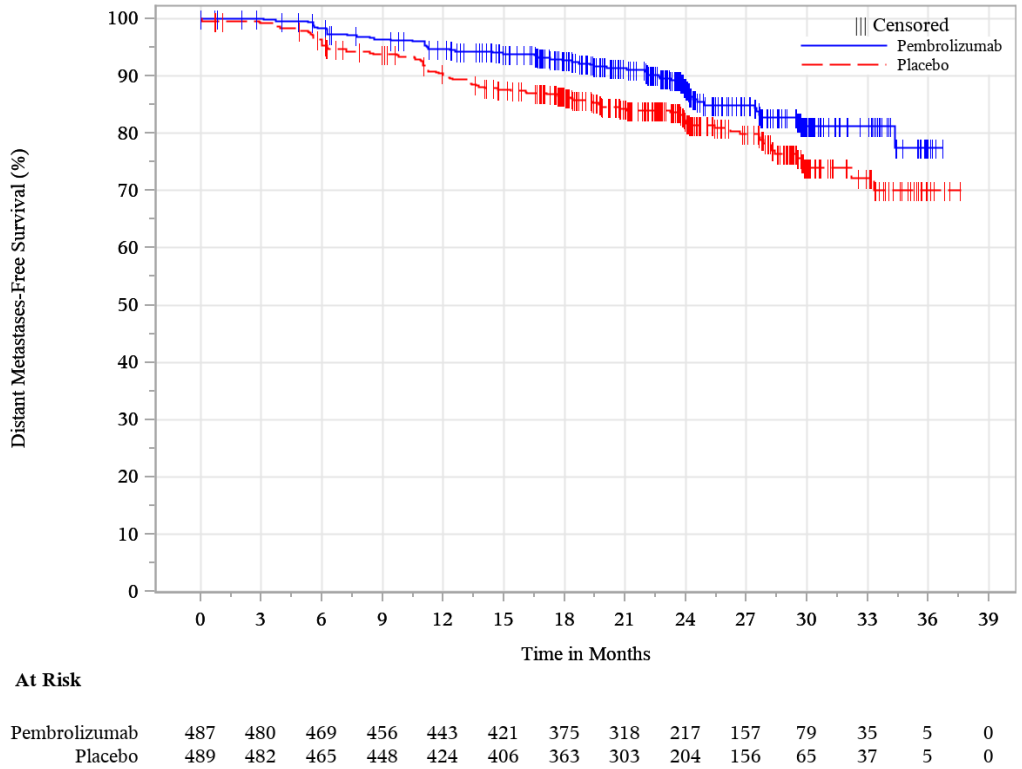
- Per protocol, IA3 was performed when approximately [redacted] DMFS events had been observed
- At IA3, insufficient events had occurred to enable analysis of OS
  - [redacted] OS events were reported, representing [redacted]% of final number of events needed for analysis

Table 7 DMFS analysis - IA3 data cut-off: January 2022

DMFS (95% CI)	Pembrolizumab (n=487)	Placebo (n=489)
Median, months	NR (NR to NR)	NR (NR to NR)
24 months, %	88.1 ([redacted])	82.2 ([redacted])
HR	0.64 (0.47–0.88); p=0.00292	

ITT population

Figure 6 Kaplan-Meier estimates of DMFS – IA3 data cut-off: January 2022



ITT population

Abbreviations: CI, confidence interval; DMFS, distant metastasis-free survival; FU, follow-up; IA, interim analysis; ITT, intention to treat; HR, hazard ratio; NR, not reached; OS, overall survival

Key issue: No data reported for OS

Background

- Company provided IA3 (data cut-off: January 2022) at technical engagement, including interim DMFS data
- At IA3, [redacted] OS events were reported, representing [redacted] of final number of events needed for analysis of OS

Company

- OS analyses are event driven and first interim analysis for OS (IA5; [redacted] events) is expected ~[redacted]
- 50% of recurrences in stage 2B/2C melanoma occur in first 2 years after resection
- Real-world evidence for positive correlation between RFS and OS in stage 2B/2C melanoma
- Retrospective US study found significant improvement in 3-year OS with adjuvant immunotherapy in resected stage 2B/2C melanoma vs those who did not receive immunotherapy (Wong *et al*. 2022)
- RFS is important outcome for people with stage 2B/2C melanoma due to fears of disease recurrence

ERG comments

- DMFS data are immature and OS data are not available
- Evidence for use of DMFS and RFS data as surrogate measures for OS is unconvincing

TA766 (adjuvant pembrolizumab for stage 3 melanoma) FAD:

- Challenging to collect OS data for adjuvant therapies (because they have no known disease at the time of treatment and some are already cured)
- If a treatment makes a clinically meaningful difference to DMFS, this will likely be reflected in OS

Is RFS or DMFS a valid surrogate of overall survival? Can committee infer a survival benefit from these outcomes?

Abbreviations: DMFS, distant metastasis-free survival; FAD, final appraisal document; IA, interim analysis; OS, overall survival; RFS, recurrence-free survival

Key issue: Comparability of two pembrolizumab doses

Background
- Recommended dose of pembrolizumab in adults is 200 mg Q3W or 400 mg Q6W
- KEYNOTE-716 only evaluated Q3W dose

ERG comments
- No efficacy or safety data available for 400 mg Q6W, therefore, relative clinical impact of the two dosing regimens is uncertain

Company
- Modelling of dose/exposure relationships found no significant differences in efficacy or safety between doses
- EMA has approved use of Q3W and Q6W doses
- Comparability of Q3W and Q6W demonstrated in any pembrolizumab monotherapy and in combination indications, including unresectable advanced melanoma
- Clinical experts and UK real-world evidence indicates preference for less frequent dosing
- Model base case used Q6W dosing, scenario analysis with Q3W dosing has limited impact on ICER

Clinical expert comments
- Do not expect any differences between Q3W and Q6W regimens. Published data suggests equivalent pharmacokinetic parameters and unpublished UK RWE shows no difference in efficacy or toxicity
- Q6W schedule is important to manage impact on clinics, oncology day units and pharmacies

Can the 400mg Q6W dose be considered as effective? What would be used in clinical practice?

Abbreviations: ICER, incremental cost-effectiveness ratio; QxW, every x weeks; RWE, real-world evidence

Key clinical issues

- A key driver of the economic model is what treatment people who have a local recurrence (stage 3 melanoma) will receive. Would a person who received adjuvant pembrolizumab for resected stage 2 melanoma receive subsequent adjuvant treatment at stage 3?
- What proportion of people in the UK have stage 2B vs 2C melanoma? Is the evidence from KEYNOTE-716 generalisable to people in the NHS?
- With very little data for adolescents from KEYNOTE-716, would any difference in outcomes be expected in adolescents in clinical practice?
- Currently there are limited overall survival data. Is RFS or DMFS a valid surrogate of overall survival? Can committee infer a survival benefit from these outcomes?
- Only data from the 200 mg 3 weekly pembrolizumab dose has been evaluated in KEYNOTE-716. Can the 400mg 6 weekly dose be considered as effective? What would be used in clinical practice?

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key cost-effectiveness issues

- Would people who received adjuvant pembrolizumab at stage 2 be eligible to receive adjuvant treatment at stage 3?
- Does the committee accept the uncertainty regarding the market shares of subsequent treatments in DM health state?
- Does the committee accept the uncertainty regarding the duration of subsequent treatments in DM state?

NICE

Key issues

Table 8 Key issues

Issue	Resolved?	ICER impact
Plausibility of assumptions regarding market shares of subsequent treatments in LRR state uncertain	No – for discussion	Large
Plausibility of assumptions regarding market shares of subsequent treatments in DM state uncertain	No – for discussion	Unknown
Plausibility of assumptions regarding duration of subsequent treatments in DM state is uncertain	No – for discussion	Unknown

Abbreviations: DM, distant metastases; EMA, European Medicines Agency; LRR, locoregional recurrence; OS, overall survival; RF, recurrence free; QxW, every x weeks

Company's model overview

- Pembrolizumab affects **costs** by:
  - **Increasing** adjuvant treatment costs in the RF state
  - **Reducing** subsequent treatment costs in the LRR and DM states
  - **Reducing** disease management costs in the DM state

- Pembrolizumab affects **QALYs** by:
  - **Reducing** incidence of recurrence (i.e. transition from recurrence free to locoregional recurrence or metastatic disease)

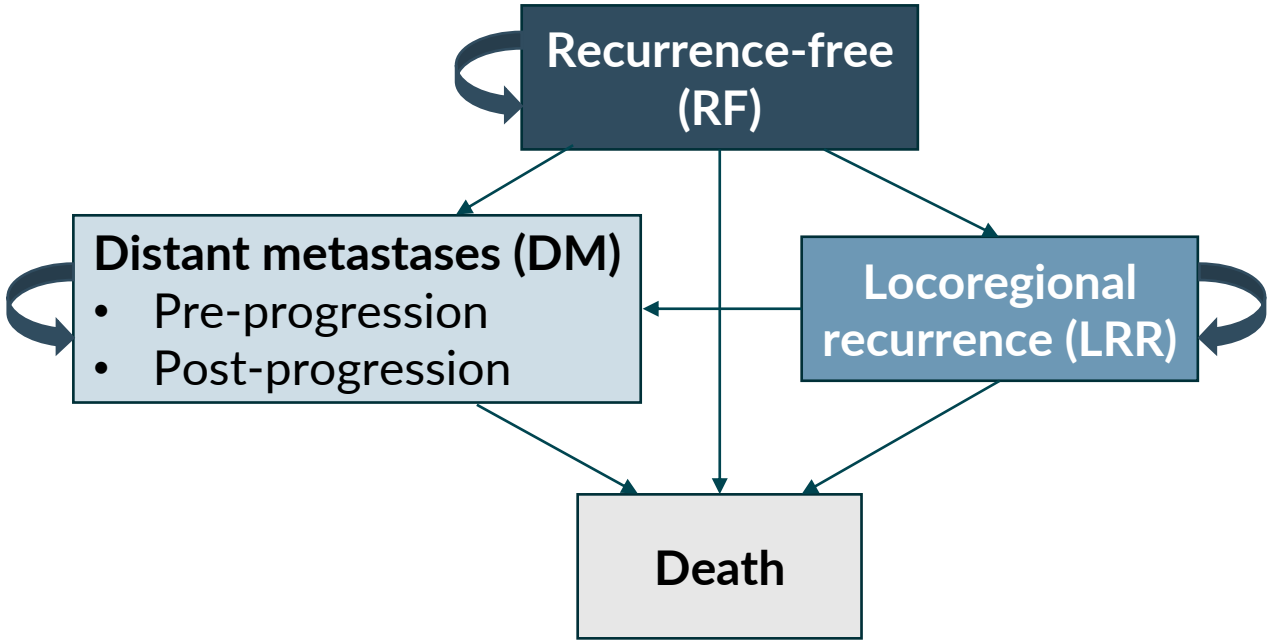
Company: Model structure aligns with TA766 (adjuvant pembrolizumab for stage 3 melanoma)

ERG: Model structure is reasonable

Table 9 Model characteristics

Design	Markov model
Time horizon	Lifetime
Cycle length	1 week
Half cycle correction	Yes
Treatment waning	No
Discount	3.5%
Perspective	NHS and PSS

Figure 7 Model structure



Abbreviations: DM, distant metastases; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; PSS, Personal Social Services; QALY, quality-adjusted life year; RF, recurrence free

How company incorporated evidence into model

Table 10 Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	KEYNOTE-716 (except % BRAF mutation-positive from KEYNOTE-054 trial)
Intervention and comparator efficacy	• **Transitions from RF and LRR states:** KEYNOTE-716 • **Transitions from DM state:** Dependent on treatment for advanced melanoma (based on market share data). OS/PFS from KEYNOTE-006 (pembro vs ipilimumab in 1L advanced melanoma), HRs adjusted for treatments other than pembro using NMA
Utilities	• Assumed same for both treatment arms • EQ-5D-5L from KEYNOTE-716, mapped to EQ-5D-3L • **RF, LRR and pre-progression DM states:** regression model with KEYNOTE-716 data • **Post-progression DM state:** Beusterien et al. 2009 (standard gamble in UK population) – insufficient data available from KEYNOTE-716
Costs and resource use	• Included intervention costs, health state costs, costs of managing AEs and terminal care costs • Unit prices based on NHS reference prices, BNF, PSSRU and MIMS • One-off terminal care cost for transitions from DM to death state • Resource use in routine surveillance arm in RF state from NG14 and Larkin et al (2014)

Abbreviations: 1L, first line; AE, adverse event; BNF, British National Formulary; DM, distant metastases; EQ-5D-XL, EuroQol Five Dimensions X Levels; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; MIMS, Medical Information Management System; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unity; QALY, quality-adjusted life year; RF, recurrence free

Areas of uncertainty for cost-effectiveness modelling (1/2)

Table 11 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case	Impact on ICER?
Subsequent treatments: LRR	Pembro arm: No subsequent treatment; Routine surveillance arm: Market share data	Equal proportions of subsequent treatment in both arms, using market share data	**Large impact on ICER (~£10,000/ QALY)**
Subsequent treatments: DM	**Market shares:** TA766 SACT and market share data, adjusted for pembrolizumab rechallenge **Treatment duration:** 1L DM: PFS for each regimen; 2L DM: mean time on treatment of 21 weeks for all regimens except ipilimumab (max 12 weeks duration)	Uncertain whether assumptions for market shares and durations of subsequent treatments are plausible **No changes to base case assumptions**	No difference in company and ERG base case Clinical experts note that this is an area of uncertainty
Transitions from RF state	• RF→LRR: lognormal (both arms) • RF→DM: lognormal (both arms) • RF→Death: exponential (both arms	Conducted scenario analysis with generalised gamma-lognormal (selected as it had the best statistical fit out of the 13 candidate combinations) **No changes to base case assumptions**	No difference in company and ERG base case Potential large impact on ICER

Abbreviations: 1L, first line; DM, distant metastases; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; PFS, progression-free survival; QALY, quality-adjusted life year; RF, recurrence free; SACT, Systemic Anti-Cancer Therapy dataset

Areas of uncertainty for cost-effectiveness modelling (2/2)

Table 11 (continued) Assumptions in company and ERG base case

Assumption	Company base case	ERG base case	Impact on ICER?
Costs	Terminal care cost for deaths from DM state only	Terminal care costs regardless of health state from which patients died	Small impact on ICER (<£500/QALY)
Utilities	**DM (post-progression):** 0.59 Source: Beusterien et al. 2009, uses standard gamble approach from UK general population	**DM (post-progression):** 0.7 Source: KEYNOTE-006, based on EQ-5D	Small impact on ICER (<£500/QALY)

- Assumptions above have minimal impact on the ICER
- Company assumptions align with TA766 (adjuvant pembrolizumab for resected stage 3 melanoma)
- Assumptions are unlikely to impact on decision making, therefore, proposed not to discuss in detail
- Further information is available in back-up slides

Company base case results

Please note: results do not include confidential commercial discounts for subsequent treatments

Table 12 Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	13,864
Routine surveillance	[redacted]	[redacted]			

Table 13 Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	16,147
Routine surveillance	[redacted]	[redacted]			

One ICER in the company scenario analyses was above £20,000/QALY (adjuvant pembrolizumab arm, BRAF+ patients [43.3%] who enter the LRR state are eligible for adjuvant treatment with dabrafenib + trametinib, adjusted for the [redacted]% of patients in the overall cohort who are expected to receive no systemic adjuvant therapy)

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

Differences between company and ERG base case

Please note: results do not include confidential commercial discounts for subsequent treatments

Table 14 Deterministic company and ERG base case

Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	**13,864**
Company base case + Alternative utility estimate for DM post progression	[redacted]	[redacted]	14,288
Company base case + Alternative subsequent treatment proportions/market share in LRR health state	[redacted]	[redacted]	23,582
Company base case + Alternative implementation of end-of-life costs	[redacted]	[redacted]	14,278
ERG base case	[redacted]	[redacted]	**24,731**

One ICER in the ERG scenario analyses was above £30,000/QALY (generalised gamma-lognormal distributions for transition probabilities from the RF health state)

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; QALY, quality-adjusted life year; RF, recurrence free

Key issue: Assumptions for market shares of subsequent treatments in LRR health state (1/2)

Background: Company base case assumes that people in the pembrolizumab arm receive no further adjuvant therapy at stage 3

Table 15 Company base case assumptions for subsequent treatments in LRR state (adjuvant stage 3 treatment)

Stage 3 adjuvant treatment	Pembrolizumab	Routine surveillance
Source:	No further adjuvant therapy	Ipsos Oncology Monitor, September 2021 & MSD market research, 2021
Pembrolizumab	0%	[redacted]
Nivolumab	0%	[redacted]
Dabrafenib + trametinib	0%	[redacted]
No systemic therapy	100%	[redacted]

Clinical expert comments

- Subsequent treatment after adjuvant pembrolizumab at stage 2 is uncertain and will be impacted by timing of recurrence and BRAF status

 Abbreviations: IA, interim analysis; IO, immuno-oncology; LRR, locoregional recurrence

Key issue: Assumptions for market shares of subsequent treatments in LRR health state (2/2)

Company

- Clinical experts say there is 'one shot' at adjuvant therapy, due to lack of data and uncertainty about reimbursement
- Fewer people in the pembrolizumab arm received any subsequent therapy compared with the placebo arm after LRR in KEYNOTE-716
- KEYNOTE-716 is a global trial and several recorded subsequent treatments after LRR in trial are not approved for use in UK, therefore the trial may not reflect UK clinical practice

Table 16 Subsequent treatments in KEYNOTE-716 (IA3)

First subsequent treatment after LRR (as first recurrence)	Pembro (N=487)	Placebo (N=489)
Received any subsequent treatment following LRR	[redacted]	[redacted]
% of subsequent treatments that were experimental or not approved for use in the UK	[redacted]	[redacted]

ERG comments

- Plausibility of assumptions regarding market shares at LRR are uncertain and have a large impact on the ICER
- ERG base case assumes equal proportions of people receiving subsequent treatment after LRR (e.g. adjuvant treatment at stage 3) in both arms – this increased the ICER by ~£10k/QALY

Would people who received adjuvant pembrolizumab at stage 2 be eligible to receive adjuvant treatment at stage 3?

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence

Key issue: Assumptions for market shares of subsequent treatments in DM health (no difference between company and ERG base cases)

Background: Company and ERG base cases use the same assumptions, however both note there is uncertainty

- Pembrolizumab rechallenge after 2 years: assumes 5% at 1L DM and [redacted]% at 2L DM

ERG comments

- Company assumptions not aligned with KEYNOTE-716
- Conducted scenario analysis assuming equal proportions of subsequent treatment after DM in both arms → reduced the ICER by ~£15,000/QALY

Company

- KEYNOTE-716 is a global trial and subsequent treatments may not reflect UK clinical practice. Part 2 of trial assessed rechallenge, therefore not reflective of clinical practice
- Clinical experts advised no rechallenge with IO monotherapy within 18 months, possibility of later rechallenges
- Aligns with TA684

Clinical expert comments

- Subsequent treatment after adjuvant pembrolizumab at stage 2 is uncertain and will be impacted by timing of recurrence and BRAF status

Does the committee accept the uncertainty regarding the market shares of subsequent treatments in DM health state?

Abbreviations: 1L, first line; DM, distant metastases; ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; LRR, locoregional recurrence

Key issue: Assumptions for duration of subsequent treatments in DM health state (no difference between company and ERG base cases)

Table 17 Assumptions for durations of subsequent treatments in DM health state

	1L DM	2L DM
Company base case	Duration of treatment based on modelled PFS for each regimen	Mean time on treatment of 21 weeks for all regimens except ipilimumab (max 12 weeks)
Clinical experts	Median treatment duration is ~12-18 months	Median treatment duration is ~6 months

ERG comments

- Unclear whether assumptions are clinically plausible
- Key driver of economic model. Conducted extreme scenario analysis excluding subsequent treatment acquisition costs in the DM state for both arms, which led to a substantial increase of the ICER (still below £30,000/QALY)

Company post-technical engagement

- Scenario excluding costs of subsequent therapies not appropriate, as excludes major benefit of adjuvant therapy

Does the committee accept the uncertainty regarding the duration of subsequent treatments in DM state?

Abbreviations: 1L, first line; DM, distant metastases; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival

Area of uncertainty: Transitions from RF state (potentially large impact on ICER)

Background

- In company base case, functions used to model transition probabilities from RF health state were:
  - RF→LRR: lognormal (both arms)
  - RF→DM: lognormal (both arms)
  - RF→Death: exponential (both arms)

Company

- RFS and DMFS from KEYNOTE-716 IA3 were used to model transition probabilities from RF health state
- Lognormal-lognormal combination selected for base case as:
  - High MSE ranking with respect to RFS (9th best-fitting) and DMFS (15th best-fitting) in observation arm
  - High ranking in statistical fit (3rd best-fitting)
    - Generalised gamma/log-normal and Gompertz/log-normal were best fitting in statistical fit but deviated further from external validation sources
  - Incremental RFS and DMFS benefit for pembrolizumab vs observation aligned with, or slightly below, average incremental benefit across 13 finalist combinations

ERG comments

- Used the same transitions as the company in their model base case
- Conducted scenario analysis with generalised gamma-lognormal (selected as it had the best statistical fit out of the 13 candidate combinations) – led to an increase in the ICER (>£30,000/QALY)

Does the committee accept the uncertainty regarding the modelling of the transition probabilities from the RF health state?

Abbreviations: DM, distant metastases; LRR, locoregional recurrence; MSE, mean squared error; RF, recurrence free;

Other considerations

Equality considerations

- There are not anticipated to be any equality considerations associated with the use of pembrolizumab in this indication

Innovation

- There are currently no adjuvant treatment options for people with stage 2 melanoma in the UK. Current standard of care is clinical observation
- Therefore, the introduction of pembrolizumab as adjuvant treatment for people with stage 2B and stage 2C melanoma would represent a step-change in clinical management

Key cost-effectiveness issues

- Would people who received adjuvant pembrolizumab at stage 2 be eligible to receive adjuvant treatment at stage 3?
- Does the committee accept the uncertainty regarding the market shares of subsequent treatments in DM health state?
- Does the committee accept the uncertainty regarding the duration of subsequent treatments in DM state?

NICE

Back-up slides

NICE National Institute for Health and Care Excellence

Key issue: Assumptions for terminal care costs (minimal impact on ICER)

Background
- In company base case, one-off terminal care costs applied to people who transitioned to death state from DM state only, assuming that deaths from RF or LRR states were not caused by melanoma

ERG comments
- People in any health state could die from causes involving terminal care
- Applied terminal care costs to all people who transition to death state, regardless of state they transition from – led to a small increase in the ICER (<£500/QALY)

Company
- Real-world evidence that cancer-related deaths are more costly than deaths from other causes

Clinical expert comments
- Terminal care costs with metastatic melanoma will likely be higher than deaths from most other causes
- However, terminal care for many chronic conditions requires intensive medical and care support

TA766: Terminal care costs applied to people who transitioned to death state from DM state only

Should terminal care costs apply to deaths from all states, or from DM state only?

NICE

Abbreviations: DM, distant metastases; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; RF, recurrence free

Key issue: Utilities in DM health state (minimal impact on ICER)

Background

- The company and ERG base cases use different utility values for DM (post-progression):
  - **Company:** 0.59 (Beusterien et al. 2009, uses standard gamble approach from UK general population)
  - **ERG:** 0.7 (KEYNOTE-006, based on EQ-5D)

ERG comments

- Use of a standard gamble approach to elicit utilities is not best practice
- Post-progression DM utility is low compared to pre-progression DM utility ([redacted])
- Used utility for progressed disease from KEYNOTE-006 (TA366) – small increase in the ICER (<£500/QALY)

Company

- Post-progression DM substate expected to be lower than the pre-progression DM substate as reflects entire period from progression to death
- Utility values in KEYNOTE-006 collected to drug discontinuation or 30-day-post-study follow-up visit only. Therefore, may not capture the decrease in HRQoL from toxicity of subsequent therapies or progression
- Aligned with TA384 and TA766

What is the most appropriate source of post-progression DM utility values?

Abbreviations: DM, distant metastases; EQ-5D, EuroQol- 5 Dimensions; ERG, evidence review group; HRQoL, health-related quality of life; LRR, locoregional recurrence; RF, recurrence free

Company deterministic scenario analysis

Table 18 Company scenario analyses (deterministic)

#	Scenario	Description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case		[redacted]	[redacted]	**13,864**
1	Alternative functions for transitions from RF	RF→LRR: Log-logistic; RF→DM: Lognormal	[redacted]	[redacted]	15,495
2		RF→LRR: Weibull; RF→DM: Lognormal	[redacted]	[redacted]	14,760
3		RF→LRR: Exponential; RF→DM: Exponential	[redacted]	[redacted]	6,509
4		RF→LRR: Log-logistic; RF→DM: Exponential	[redacted]	[redacted]	5,445
5	Alternative approaches for transitions from RF	Time-constant HR; RF→LRR: Log-logistic; RF→DM: Exponential	[redacted]	[redacted]	6,509
6		Time-varying HR; RF→LRR: Exponential; RF→DM: Exponential	[redacted]	[redacted]	11,200
7	Alternative risk reduction assumptions in RF state	80% risk reduction at 10 yrs, decreasing from 7 yrs	[redacted]	[redacted]	15,517
8		95% risk reduction at 10 yrs, decreasing from 5 yrs	[redacted]	[redacted]	13,014
9		95% risk reduction at 5 yrs, no gradual decrease	[redacted]	[redacted]	11,732
10		95% risk reduction at 10 yrs, no gradual decrease	[redacted]	[redacted]	15,293

Results do not include confidential commercial discounts for comparators

Abbreviations: DM, distant metastases; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; QALY, quality-adjusted life year; RF, recurrence free

Company deterministic scenario analysis

Table 19 Company scenario analyses (deterministic)

#	Scenario	Description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case		[redacted]	[redacted]	**13,864**
11	Reduced OS projections	Exponential rate of OS in DM state increased so routine surveillance aligns with external sources (exp [redacted])	[redacted]	[redacted]	13,818
12	Data source for transitions from LRR state	USON EHR database and stage 3 trials	[redacted]	[redacted]	14,008
13		USON EHR database for patient on or off adjuvant treatment	[redacted]	[redacted]	13,909
14	Alternative market shares in LRR state	In pembro arm, BRAF+ patients are eligible for stage 3 adjuvant treatment with dabrafenib + trametinib, adjusted for the [redacted]% of patients in overall cohort who receive no systemic adjuvant therapy	[redacted]	[redacted]	20,877
15	Alternative market shares in DM state	No rechallenge with pembro	[redacted]	[redacted]	16,378
16		In the pembro arm, people who entered DM state ≥2 years after adjuvant pembrolizumab initiation were assumed to be equal to those in the routine surveillance arm (1L and 2L)	[redacted]	[redacted]	3,262

Abbreviations: EHR, electronic health records; USON, US Oncology Network

Company deterministic scenario analysis

Table 20 Company scenario analyses (deterministic)

#	Scenario	Description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case		[redacted]	[redacted]	**13,864**
17	Shorter duration of first line therapies	Exponential rate of PFS increased by 10%, reducing ToT for 1L subsequent therapies in DM state	[redacted]	[redacted]	14,547
18	Only costs of first line systemic therapy in DM state included	Costs of second line therapies in the DM state excluded, as model does not consider the efficacy of 2L agents	[redacted]	[redacted]	10,401
19	Alternative sources of utility values	EQ-5D-5L utilities sourced from KEYNOTE-716	[redacted]	[redacted]	13,178
20		Utilities for LRR and pre-progression DM health states from KEYNOTE-054	[redacted]	[redacted]	13,762
21		Utilities for DM state from Middleton et al. 2017	[redacted]	[redacted]	13,643
22		Single regression model for utilities. AE status and health state assumed to be independent covariates. LRR and DM utilities include impact of any grade AEs	[redacted]	[redacted]	14,020

Abbreviations: 1L, first line; 2L, second line; AE, adverse events; DM, distant metastases; LRR, locoregional recurrence; PFS, progression-free survival; ToT, time on treatment

Company deterministic scenario analysis

Table 21 Company scenario analyses (deterministic)

#	Scenario	Description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case		[redacted]	[redacted]	**13,864**
23	Alternative dosing schedule for IO therapies	Shorter dosing schedules used for pembrolizumab (200 mg Q3W) and nivolumab (240 mg Q2W) in all settings	[redacted]	[redacted]	**14,823**
24		Shorter dosing schedules used for pembrolizumab (200 mg Q3W) in all settings	[redacted]	[redacted]	14,727
25	Vial sharing permitted	For agents where weight-based dosing is used, vial sharing is permitted	[redacted]	[redacted]	13,032
26	Discount rate	Discounting of costs and effects set to 1.5%	[redacted]	[redacted]	9,339
27		Discounting of costs at 3.5% and effects at 1.5%	[redacted]	[redacted]	10,310

Abbreviations: ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; QALY, quality-adjusted life year; QxW, every x weeks