Slides for public

Lead team presentation: Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer [ID1349] (rev TA447)

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee D

Lead team: Professor Femi Oyebode, Dr Malcolm Oswald

Evidence Review Group: Liverpool Reviews and Implementation Group

6 February 2018

Key issues

Clinical effectiveness

- KEYNOTE-024 allowed the SOC arm to switch to other PD-L1 treatments (such as pembrolizumab or nivolumab) which have now become standard of care after chemotherapy
  - Company suggest no adjustment for crossover may be more appropriate now that trial is more similar to UK practice

Cost-effectiveness

- Company base case estimated OS by appending exponential parametric distribution to KEYNOTE-024 trial OS K-M data at 33 weeks
  - Company chose 33 weeks on the basis of the changes to cumulative hazards, and patient numbers were sufficient to extrapolate from
  - ERG preferred 43 weeks based on visual fit
- Source for deriving the utility values
- Most plausible ICER for pembrolizumab
- End of life criteria
- Any health-related benefits not captured
- Any equality issues

TA447 recommendation

Pembrolizumab is currently available on the CDF as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:

- their tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations
- pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
- the conditions in the managed access agreement for pembrolizumab are followed

- The committee concluded that although there was sufficient evidence that pembrolizumab had an important extension-to-life benefit compared with standard care, the exact size of the overall survival gain was uncertain because of the immaturity of the data

DETAILS OF THE TECHNOLOGY

Technology	Pembrolizumab (KEYTRUDA)
Marketing authorisation: January 2017	First line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a TPS ≥50% with no EGFR or ALK positive tumour mutations
Mechanism of action	Humanised monoclonal antibody acts on the programmed cell death-1 (PD-1) receptor, part of the immune checkpoint pathway.
Administration	i.v. infusion in outpatient setting, 200 mg every 3 weeks until disease progression or unacceptable toxicity
Acquisition cost	100 mg vial: • List price: £2,630 per 100 mg vial • A discount through a Commercial Access Agreement has been agreed between MSD and NHS England
Cost of a course of treatment	Average time on treatment: XXXdays (equivalent to XXXcycles) based on KEYNOTE-024: • Average cost of a course of treatment at list price: £XXX

TA447: Rationale for CDF recommendation

The ICER range identified by the committee for its decision-making was **£46,083 to £61,577 per QALY gained**. This was based on:

1. All time points presented for extrapolation (22-, 14- and 30-weeks) being equally plausible because of the uncertainty around the extrapolation of OS data
2. The analyses which used an overall survival rate of 5% at 5 years for the SOC arm (based on NLCA 2006 to 2010 data)
3. The company's analysis setting the utility value for at least 360 days to death to that of the UK population norm
4. ERG's exploratory analyses with alternative (not time to death) utility values from the pemetrexed guidance (TA181), which increased the ICER by approximately £7,000 – leading to the upper estimate of the range being £61,577
   - company's ICER range (£46,083 to £54,577 per QALY gained) considered conservative as utilities were capped to population norm which did not seem in line with the physical symptoms and psychological distress reported by people with NSCLC

Patient and clinical expert submissions (new)

Roy Castle Lung Cancer Foundation

- Outcomes poor with chemotherapy; targeted treatment offers increased survival for high PD-L1 expressers

National Lung Cancer Forum for Nurses

- Pembrolizumab but offers targeted treatment with:
  - Less infusion time, fewer side effects (e.g. fewer neutropenia cases)
  - Improvement in quality of life

One other clinical expert comments

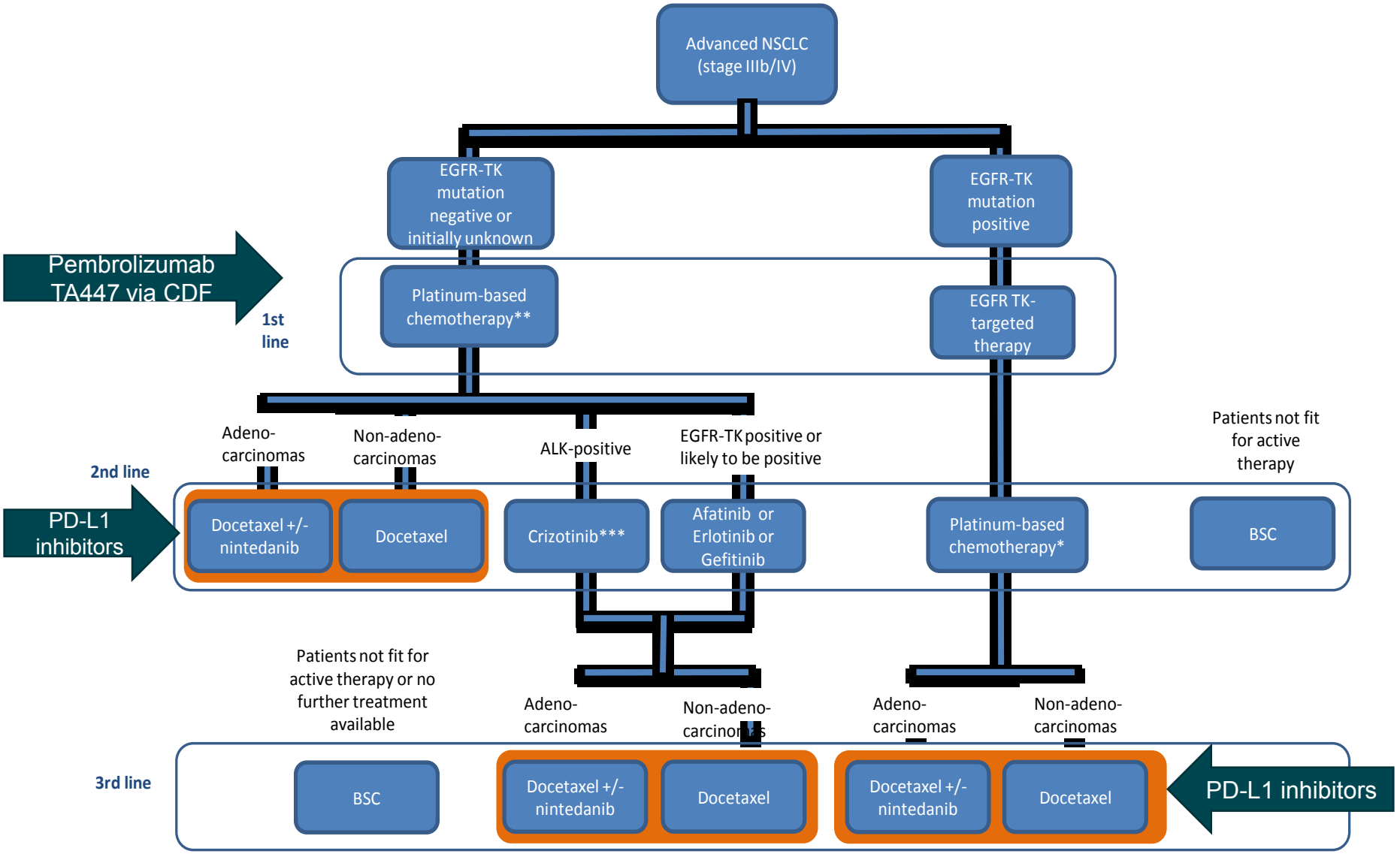
- Testing of tumours for PD-L1 is complex; limited access to testing may delay treatment
- Findings of Keynote 024 trial reflects UK practice
- Keynote 024 - median OS twice that achieved with standard care
- PD-L1 inhibition is a step change in NSCLC therapy for PD-L1 positive patients

NHS England comments

- CDF has funded 1st line pembrolizumab since the end of May 2017
- Confident that PD-L1 testing undertaken by all lung/cancer units
- NHSE note greater median follow up in trial (was 11 months, now 25 months)
  - Impact on median OS impressive – doubled from 14 to 30 months
- pembrolizumab is in baseline commissioning for 2nd line use in PD-L1 positive patients
  - Therefore no need to allow for crossover from chemotherapy to immunotherapy in this appraisal
- Some differences between KEYNOTE-024 and CDF:

Characteristic	CDF	KEYNOTE-024
Median age (years)	70	64.5
Ratio non-squamous:squamous	3:1	4:1
%male	53%	60%
Ratio of Performance status 0:1	1:4	1:2

Treatment pathway



Adapted from figure 3 of Company Submission (page 19)

TA447: Clinical effectiveness evidence

TA447 Clinical evidence: KEYNOTE-024

- Open-label, phase III RCT: Pembrolizumab (n=154) compared with standard of care (SOC; platinum based chemotherapy) (n=151)
- Inclusion criteria: untreated stage IV metastatic PD-L1-positive NSCLC (≥50% PD-L1 and no EGFR- or ALK-positive mutations) and an ECOG score of 0 or 1

Results were from an interim analysis: Pembrolizumab vs. SOC (ITT)

- Median OS (months): Not reached in either arm (35% of the total events had occurred):
    - OS HR: 0.60; 95% CI 0.41 to 0.89
    - OS HR (crossover adjusted): 0.50; 95% CI 0.34 to 0.76
- **A later 19 month follow up**: XXXXXXof total events occurred
    - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
- Median PFS: 10.3 months vs. 6 months (p<0.001)
- ORR: 44.8% vs. 27.8%

Updated clinical effectiveness evidence: Final analysis (FA) of KEYNOTE-024 (data cut-off date: 10 July 2017)

Company submission section B.2

Final Analysis of KEYNOTE-024: PFS, OS and ORR (ITT population) – 25.4 months median follow-up

	Number Patients (ITT)	Pembrolizumab 200 mg, N=154	SOC, N= 151
Primary endpoints	**PFS (BICR per RECIST 1.1)**		
	Median (95% CI), [months]	xxxxxxxxxx	xxxxxxxxxx
	Hazard Ratio; p-value	HR xxx (95% CI xxxxxx); *p*xxxxxx	
	PFS rate at 12 months	xxxxxxxxxx	xxxxxxxxxx
	PFS rate at 18 months	xxxxxxxxxx	xxxxxxxxxx
	PFS rate at 24 months	xxxxxxxxxx	xxxxxxxxxx
Secondary endpoints	**OS**		
	Median (95% CI), [months]	30.0 (xxxx)	14.2 (xxxx)
	Hazard Ratio; p-value	**HR 0.63 (95% CI 0.47, 0.86); *p=0.002***	
	OS rate at 12 months	xxxxxxxxxx	xxxxxxxxxx
	OS rate at 18 months	xxxxxxxxxx	xxxxxxxxxx
	OS rate at 24 months	xxxxxxxxxx	xxxxxxxxxx
	OS rate at 30 months	xxxxxxxxxx	xxxxxxxxxx
	ORR (BIRC per RECIST 1.1)		
	Confirmed ORR % (95% CI)	45.5% (37.4, 53.7)	29.8% (22.6, 37.8)
		Difference 14.9% (4.3, 25.4); *p=0.0031*	

Source: Company submission section B.2.6.1; table 6 (p25)

Progression-free survival: ITT population Kaplan-Meier

Based on BICR assessment per RECIST 1.1 (primary censoring rule)

From figure 10 (pg 36 of company submission)

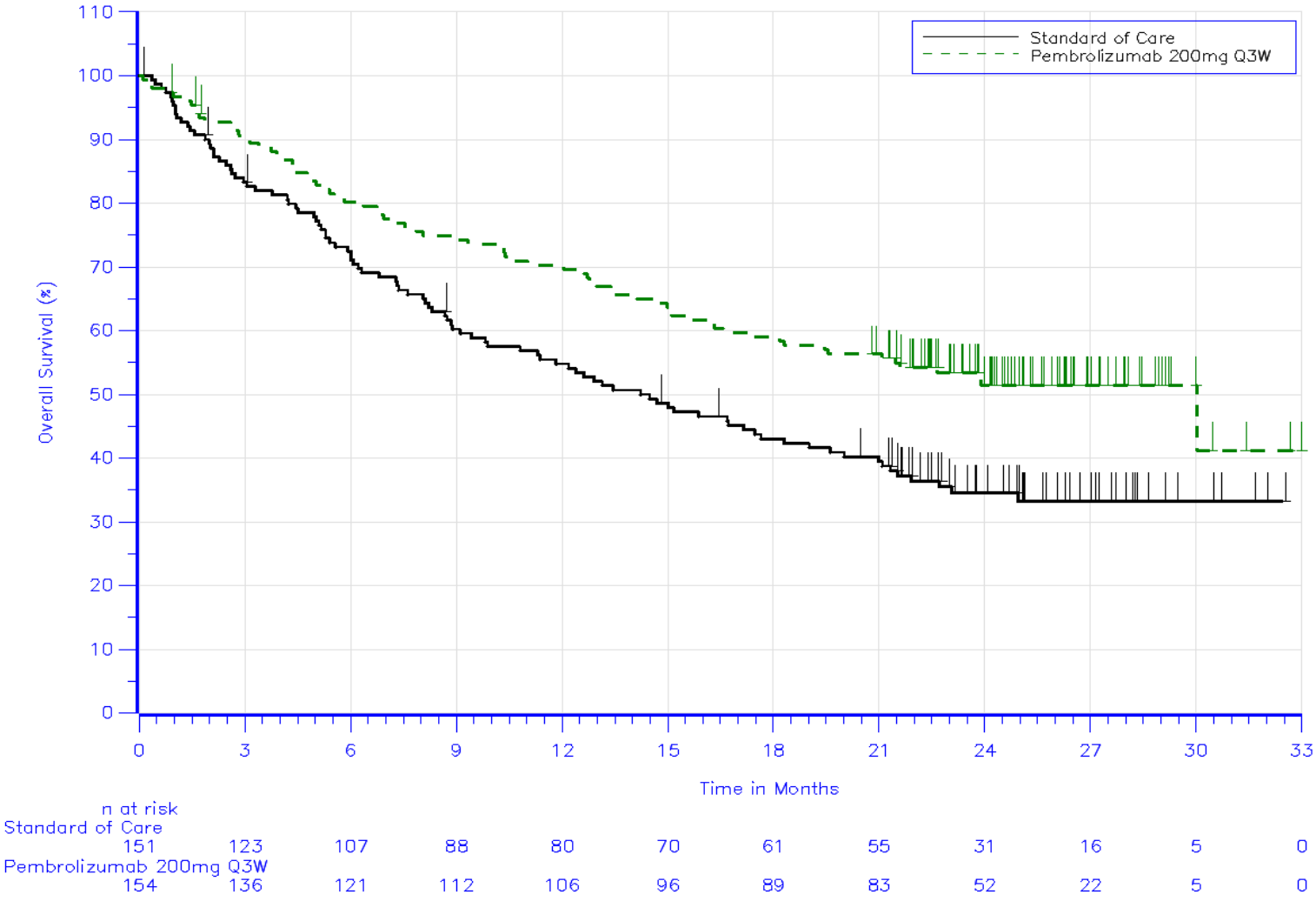
Summary and subgroups: Progression free survival (ITT)

- Pembrolizumab provides significant benefits in terms of PFS over SOC:
  - **Median PFS XXXX months versus XXX months**
  - **HR XXX; 95% CI XXXXXX; one-sided pXXXXXX**
- A consistent benefit of pembrolizumab over SOC was also shown for the subgroups considered in the company submission:

- Squamous disease XXXXXXXXXXXXXXXXXXXXXXX
- Non-squamous disease XXXXXXXXXXXXXXXXXXXXXXXXXX
- Platinum/pemetrexed XXXXXXXXXXXXXXXXXXXXXXXXXX
- Other platinum doublets (non-pemetrexed) XXXXXXXXXXXXXXXXXXXXXXXX

See Company submission document B figure 14, p47

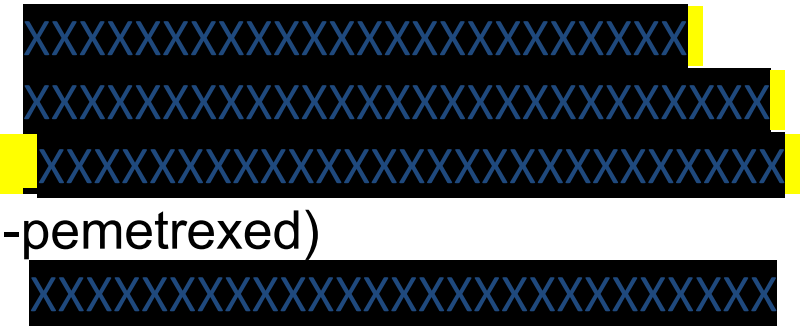
Overall survival: ITT population Kaplan-Meier



Summary and subgroups: Overall survival (ITT)

- Pembrolizumab provides significant benefits in terms of OS over SOC:
  - **Median OS 30 months versus 14.2 months**
  - **HR 0.63; 95% CI 0.47 to 0.86; one-sided p<0.002**
- A consistent benefit of pembrolizumab over SOC was also shown for the 2 subgroups considered in the company submission:

- Squamous disease
- Non-squamous disease
- Platinum/pemetrexed
- Other platinum doublets (non-pemetrexed)



Source: Company submission document B figure 13, p43

Summary: KEYNOTE -024 overall survival

- Statistically significant survival benefit for pembrolizumab compared with SOC. However, 54.3% of people randomised to the SOC arm of the KEYNOTE-024 trial crossed over to receive pembrolizumab:

Method of OS adjustment	HR (95%CI)
No adjustment (ITT)	0.63 (0.47; 0.86)
RPSFT	XXXXXXXX
IPCW	XXXXXXXX
2-stage	XXXXXXXX

- In TA447, OS data for the SOC arm were adjusted to account for crossover to pembrolizumab
  - 2-stage adjustment was considered the most appropriate
- Since TA447, PD-L1 targeting immune-oncology treatments have been recommended as options for second line therapy after progression on chemotherapy
  - pembrolizumab (TA428) and nivolumab (within CDF; TA483 and TA484)
- Company present analyses with and without cross-over adjustment to reflect change in UK clinical practice

KEYNOTE-024 Final analysis: adverse event summary (2)

- The most frequently reported AEs:
  - **Pembrolizumab**: diarrhoea (XXXX%), dyspnoea (XXXX%), fatigue (XXXX%), constipation (XXXX%), decreased appetite (XXXX%) and nausea (XXXX%)
  - **SOC**: anaemia (XXXX%), nausea (XXXX%), fatigue (XXXX%), decreased appetite (XXXX%), vomiting (XXXX%), neutropaenia (XXXX%), constipation (XXXX%), and diarrhoea (XXXX%)
- Incidence of pruritus, rash, viral upper respiratory tract infection, hypothyroidism and dry skin in pembrolizumab the arm were more than double that observed in the SOC arm
- Incidence of nausea, anemia, vomiting, neutropaenia, stomatitis, thrombocytopaenia, dysgeusia, neutrophil count decreased, dysgeusia, platelet count decreased, white blood cell count decreased and pneumonia in the SOC arm were more than double that observed in the pembrolizumab arm
- The safety profile of pembrolizumab remains consistent with previously reported findings and the safety profile for SOC was as expected

ERG comments

Treatment pathway

- ERG agree with company that PD-L1 therapies are becoming standard of care for people who have had prior chemotherapy

Crossover adjustments

- The ERG has concerns (also described in TA447) about the reliability of approaches to crossover adjustment - results should be viewed with caution
  - Although OS HR estimates similar, variation is bigger when accounting for direct and indirect switching

Indirect and mixed treatment comparisons

- Agree that updated ITC and MTC results would not be useful

Adverse events

- Discontinuations due to AEs and drug-related AEs have increased since the previous interim analysis

Key issues

Clinical effectiveness

- KEYNOTE-024 allowed the SOC arm to switch to other PD-L1 treatments (such as pembrolizumab or nivolumab) which have now become standard of care after chemotherapy
  - Company suggest no adjustment for crossover may be more appropriate now that trial is more similar to UK practice

Cost-effectiveness

- Company base case estimated OS by appending exponential parametric distribution to KEYNOTE-024 trial OS K-M data at 33 weeks
  - Company chose 33 weeks on the basis of the changes to cumulative hazards, and patient numbers were sufficient to extrapolate from
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1st Appraisal Committee meeting

Cost Effectiveness

Committee D

Lead team (cost effectiveness): Professor Rachel Elliott

Evidence Review Group: Liverpool Reviews and Implementation Group

6 February 2018

Key issues

Cost-effectiveness

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Updated cost-effectiveness model

Company submission, section B3

Summary of company's modelling approach

Assumption	Company approach in TA447	Current approach
Treatment continuation	2-year stopping rule (in line with KEYNOTE-024) **COMMITTEE: agree**	As before
Time on treatment	Max. 35 cycles (105 weeks) and 6 cycles (18 weeks) were assumed for those receiving pembrolizumab and SOC. Mean no. of cycles of pembrolizumab: **9.80 (6.76 mths)** SOC: **5.75 (3.97 mths)**	• As before KM data used to estimate ToT for pembrolizumab arm • Parametric fitting used to estimate ToT in the SOC arm) Mean no. of cycles of pembrolizumab: XXXXSOC: XXXX
OS extrapolation	KM data used then separate exponential models fitted at week 22, 14 and 30 (PH assumption violated) – **COMMITTEE: all equally plausible. 5% OS rate at 5yrs for SOC most plausible.**	2-phase piecewise method used. OS KM data for first 33 weeks then parametric curve fitted.
PFS extrapolation	Separate Weibull models fitted at week 9 (BICR) (PH assumption was violated)	KM data used for the first 27 weeks, followed by an exponential distribution. 9 and 37 week cut offs explored in sensitivity analyses

Abbreviations BICR, blinded independent central review; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards; SOC, standard of care; ToT, time on treatment

Summary of company's modelling approach (2)

Assumption	Company approach in TA447	Current approach
Long-term treatment effect	Assumed a sustained treatment benefit over the lifetime of the model **COMMITTEE: high uncertainty around this assumption**	Assuming the treatment effect stops 3 or 5 years after treatment initiation increases the ICERs Company state that no evidence that the treatment effect stops, suggested by the tail of the pembrolizumab KM OS in the latest data cut
Treatment switching	2-stage adjustment (43.7% switched from SOC to pembrolizumab on progression) **COMMITTEE: 2 stage adjustment most appropriate**	2-stage adjustment (54.3% switched from SOC to pembrolizumab) **Two base cases presented:** • With crossover adjustments (for transparency) • No crossover adjustments (pembrolizumab is now SOC 2nd line for PD-L1 TPS ≥ 1%)
Utilities (EQ-5D data from KEYNOTE-024)	QALYs from time-to-death utilities (<30 days to ≥360 days). Range: 0.48 to 0.808. **COMMITTEE: values from trial not in line with patient expert description of symptoms**	As before. Capped utility for >360 days category explored as sensitivity. Utilities from pemetrexed appraisal not explored*

Abbreviations: KM, Kaplan-Meier; SOC, standard of care; TPS, tumour progression score

Summary of company's modelling approach (3)

Assumption	Company approach in TA447	Current approach
AE (KEYNOTE-024)	Grade 3+ AEs in more than 5% of patients in either arm, plus diarrhoea (grade 2) and febrile neutropenia. Unit costs and disutility estimates are same for both arms.	As before
PD-L1 testing	11.6% with NSCLC stage IV eligible for treatment with pembrolizumab in England. 8.6 patients to be tested to identify 1 patient eligible for pembrolizumab • a total cost of £348.121 relative to each patient that eventually receives pembrolizumab	Similar. Total cost: £347.14
Costs	• Drug admin costs based on body surface area • Full vial sharing, no wastage for comparators • Model included a dose intensity adjustment for those where planned doses for both pembrolizumab and SOC not received • Subsequent therapy included as one-off cost in the post-progression state	The company only modelled one line of subsequent therapy. See slide 10

Abbreviations BICR, blinded independent central review; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards; SOC, standard of care; ToT, time on treatment

Modelling clinical outcomes

- Clinical evidence was derived from the final data of KEYNOTE-024

- The company presented **2 base-cases**:
  1. '*Base-case reflecting the original submission',* where SOC OS was adjusted using a 2-stage cross-over adjustment
  2. '*Updated base-case'*, where no cross-over adjustment was used to reflect current SOC

- PFS and OS for pembrolizumab and SOC were modelled using a 2-phase piecewise approach:
  - **For PFS**, Kaplan-Meier data was used during the first 27 weeks followed by extrapolation using a Weibull distribution
    - 2 additional cut-points: week 9 and 37
  - **For OS**, Kaplan-Meier data was used during the first 33 weeks (based on changes to cumulative hazard), and an exponential model was fitted afterwards following standard parametric approaches
    - 2 additional cut-points: week 23 and 43 explored in sensitivity analyses

- Quality-adjusted life years (QALYs) estimated using time-to-death utilities from EQ-5D data

OS with K-M exponential extrapolation at 33 weeks (company base case)

Adapted from fig 4 ERG report. For numbers at risk see Fig 5 of company submission

5 yr OS in SOC arm is 8%, 9%, and 11% for the 22-week, 33-week, and 43-week cut-off points respectively

In TA447, committee agreed 5 yr OS of 5% was appropriate, however the higher number in the updated analyses may reflect that some patients received immunotherapies in SOC arm.

Company model: Utility

- Mean EQ-5D utility scores were pooled from the pembrolizumab and SOC treatment arms of KEYNOTE-024 and UK preference-based scores were used for all patient data

State	Utility value: mean (SE)	95% CI
≥360*	XXXXXXXXXX	XXXXXXXXXX
[180, 360)	XXXXXXXXXX	XXXXXXXXXX
[30, 180)	XXXXXXXXXX	XXXXXXXXXX
<30	XXXXXXXXXX	XXXXXXXXXX
Disutility per patient experiencing grade 3-5 AEs	XXXXXXXXXXXXXXXXXXXX XXXXXXXXXX	

*** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days. Source: Company submission, document B, Table 45, p93. *grade 5 AEs refer to death only**

- An age-related utility decrement of 0.0045 was applied per year, from the age of 65 until 75, and thereafter 0.75 (males) and 0.71 (females) for people over 75 years to reflect the natural decrease in utility associated with increasing age (Kind et al., 1999)
- Utility decrements: Grade 3 to 5* AEs were associated with utility of XXX (95% CI XXX to XXX), compared those who did not experience any AEs XXX (95% CI XXX to XXX). Utility decrements were applied during the first cycle based on grade 3+ AE incidence rates and the corresponding mean duration across them.

Company model: Costs

The company only modelled one line of subsequent therapy:

- In the pembrolizumab arm: docetaxel was assumed as second line treatment
- In the SOC arm: 2 scenarios were presented:
    1. In the 'base case reflecting the original submission' (crossover adjustment for OS data), all people were assumed to receive docetaxel as the only second line treatment
    2. In the 'updated base case' (no crossover adjustments), people who progress are assumed to receive pembrolizumab based on the proportion of people who received a PD1 post-progression in KEYNOTE-024 (direct switching to pembrolizumab: XXX %; additional indirect switching to pembrolizumab or nivolumab: XXX %), with the rest assumed to receive docetaxel
        - Assumed duration of second line treatment for docetaxel and pembrolizumab are 3 cycles (9 weeks) or 9.7 cycles (29.1 weeks), respectively (based on KEYNOTE-024 FA)

Company base case model results*

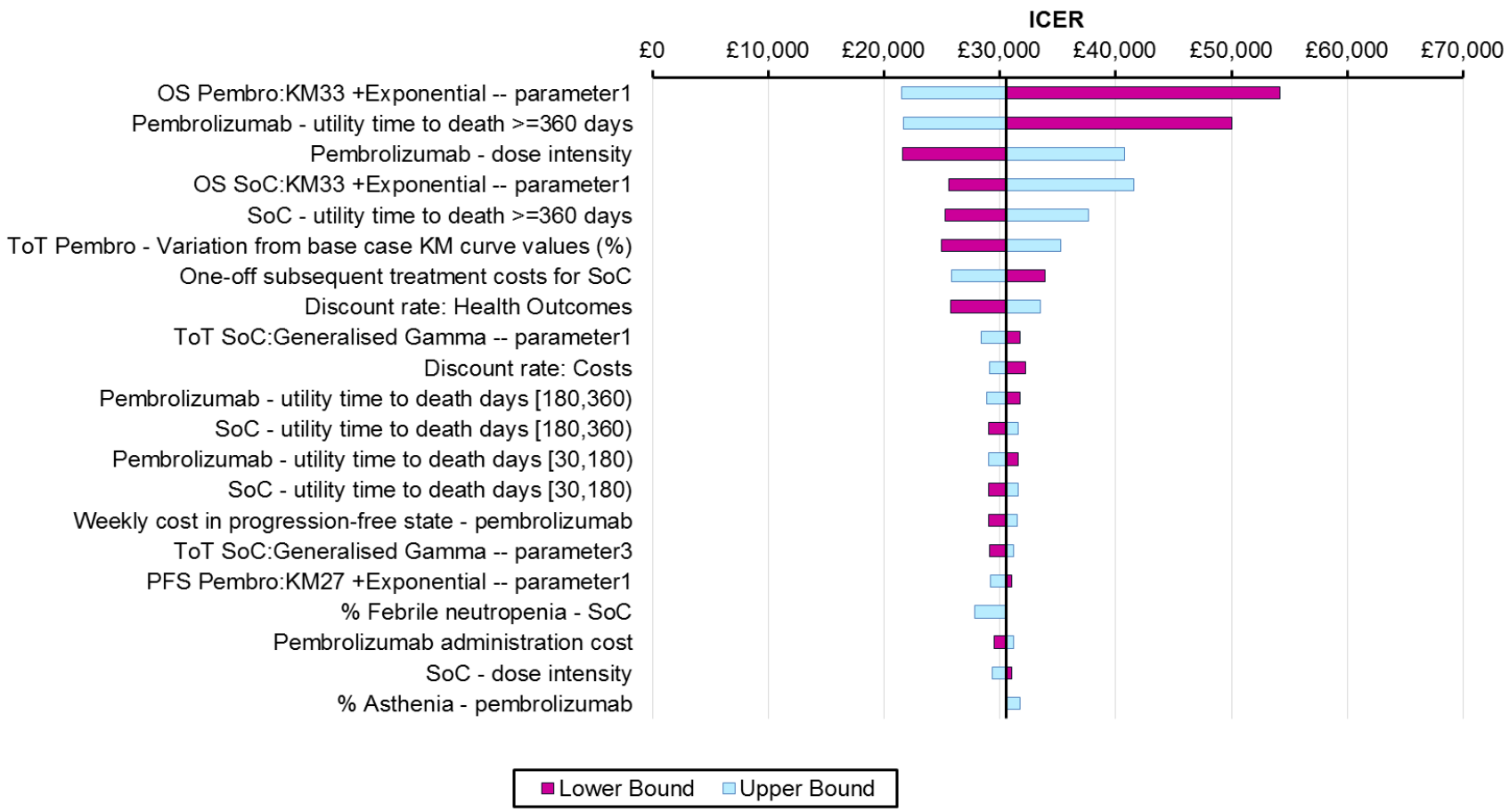
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incr. QALYs	ICER (£) versus baseline (QALYs)
Base case <u>unadjusted for crossover</u>						
SOC	£43,364	1.86	1.35	-	-	-
Pembrolizumab	£72,353	3.08	2.31	£28,989	0.96	**£30,244**

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Source: Table 60, pg113 of company submission

Probabilistic ICER for updated base case (based on 1,000 samples) = **£30,414** per QALY gained.

* Discounted, with proposed discount and an assumed discount for pemetrexed administered as maintenance therapy)

Company deterministic sensitivity analysis: Updated base case – no crossover



- 3 most influential parameters: (1) the extrapolation of OS, (2) utility values for long-term survivors, and (3) assumptions around dose intensity (all in the pembrolizumab arm)

Company scenario analysis: Updated base case (1) – no crossover adjustments

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
Company Base case	£28,989	0.96	**£30,244**
UK-specific BSA values (unadjusted by sex distribution)	£29,117	0.96	**£30,378**
UK-specific BSA values (adjusted by sex distribution)	£28,957	0.96	**£30,210**
Crossover- RPSFT adjustment	NA	NA	**NA**
Crossover- IPCW adjustment	NA	NA	**NA**
OS cut-off – 23 weeks	£28,637	0.91	**£31,321**
OS cut-off – 43 week	£27,946	0.83	**£33,829**
PFS cut-off – 9 weeks	£29,276	0.96	**£30,543**
PFS cut-off – 37 weeks	£28,697	0.96	**£29,940**
PFS extrapolation based on Weibull	£29,017	0.96	**£30,273**
PFS extrapolation based on GenGamma	£29,761	0.96	**£31,050**
No half cycle correction	£28,989	0.96	**£30,249**

Company scenario analysis: Updated base case (2) - no crossover adjustments

Scenario	Incremental costs	Incremental QALYs	ICER per QALY gained
SOC as for UK market shares	£29,354	0.96	**£30,624**
Utilities – Progression based (pooled)	£28,989	0.90	**£32,254**
Utilities – Time to death (per treatment arm)	£28,989	1.02	**£28,517**
Utilities – Progression-based (per treatment arm)	£28,989	1.03	**£28,266**
Utilities – Time to death by Chang et al (2017) [87]	£28,989	1.07	**£27,053**
Utilities for the time period ≥ 360 days to death equal to general population, same age	£28,989	0.94	**£30,874**
No age-related disutilities	£28,989	0.99	**£29,393**
Stop treatment effect at 3 years	£26,023	0.59	**£44,483**
Stop treatment effect at 5 years	£27,382	0.76	**£36,156**

ERG comments – cost effectiveness (1)

Treatment pathway

- Agree that SOC is chemotherapy followed by immunotherapy.
  - But, no data directly comparing efficacy of pembrolizumab in adv/met PD-L1 ≥50% NSCLC for those who have/had not had prior chemotherapy

Overall survival

- OS for the 54.3% of SOC arm who crossed over to pembrolizumab post-progression was much better than those who did not (or had not yet received) an immunotherapy
  - plausible some would have immunotherapy in the future and therefore potential OS gain could be underestimated

Treatment costs

- Model assumes fixed dose 200 mg Q3W for pembrolizumab post chemotherapy. EMA recommends 2mg/kg Q3W: **increases ICER**.

- Cost of pembrolizumab applied at progression, but, mean of 7 weeks before starting pembrolizumab after progression
  - could overestimate true discounted cost of treatment post progression

ERG comments – cost effectiveness (2)

Utility values

Utility values (from KEYNOTE-024 trial data) 360-day period before death higher than the UK population norms

- company literature review does not strongly support the use of this value (generalisability issues)
- ERG considers appropriate to cap utility values to age-related population norms

Overall survival extrapolation

- ERG state that closest fit to trial data occurs when distributions are appended at 43 weeks
  - But may still underestimate the survival of people receiving SOC (9.6% of patients alive at 5 years and 1.5% alive at 10 years*)
- KEYNOTE-010 trial (people with NSCLC who have had prior chemotherapy) suggests that the company's base survival projection for SOC may be pessimistic
  - casts doubt on the ICER for pembrolizumab versus SOC, and also whether pembrolizumab should be considered as an end of life treatment

OS with KM exponential extrapolation at 43 weeks – used for ERG exploratory analyses

ERG exploratory analyses*

ERG carried out the following analyses using the company's base case results:

R1) Cost of pembrolizumab in SOC in line with recommended dose (no vial sharing assumed)
R2) Utility value for >360 days to death set to population norm
R3) OS extrapolation at 43 weeks for pembrolizumab and SOC
B. Combined analyses of R1 to R3

All scenarios increase the company's ICER (details CIC because analyses contain confidential comparator discount)

*includes proposed discount for pembrolizumab and the CAA discount for pemetrexed which cannot be presented as both are confidential

End-of-life criteria

Life expectancy

- In KEYNOTE-024 trial, median OS was 14.2 months in the SOC arm
- OS in SOC arm is higher than previously seen
  - Other studies ranged from 9.9 to 13.9 months
- Mean life expectancy predicted by company model is **22.3 months**

- ERG analyses: estimates mean OS of **23.4 months**
  - ERG not certain that the mean life expectancy is <24 months

Extension to life

- Company state pembrolizumab offers an extension to life of at least 3 months compared to SoC
  - median OS for pembrolizumab-treated patients compared with SOC treatment patients was 15.8 months (30 months OS for pembroloizumab vs 14.2 months in SOC)
- ERG: no comments to add for this criteria

Key issues

Clinical effectiveness

- KEYNOTE-024 allowed the SOC arm to switch to other PD-L1 treatments (such as pembrolizumab or nivolumab) which have now become standard of care after chemotherapy
  - Company suggest no adjustment for crossover may be more appropriate now that trial is more similar to UK practice

Cost-effectiveness

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