Slides for public observers

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1536] *(review of TA519)*

Chair's presentation

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Evidence review group (ERG):	Warwick Evidence
Company:	Merck Sharp & Dohme
Technical team:	Lindsay Smith, Kirsty Pitt, Nicola Hay, Linda Landells
Second appraisal committee meeting:	6 February 2020

Topic history

TA519 – original appraisal (guidance published April 2018)

Pembrolizumab is currently available for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression

  and

- The conditions in the managed access agreement are followed

ID1536 – CDF review (ACM1 – October 2019)

Pembrolizumab is not recommended, within its marketing authorisation, for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy

Locally advanced or metastatic urothelial carcinoma pathway

First line

Platinum-based therapy:

- Cisplatin + gemcitabine
- Accelerated MVAC + G-CSF

When cisplatin is unsuitable:

- Carboplatin + gemcitabine

(Indication subject to a separate appraisal)

*Disease progression on/ after **platinum**-based therapy*

Second line

Taxanes (paclitaxel, docetaxel)

Best supportive care

Pembrolizumab

Access through CDF (TA519), subject of this review

Since original appraisal, atezolizumab recommended for routine commissioning (TA525), nivolumab not recommended (TA530)

This follows the original scope in TA519 (section 6.25 of process guide, no changes to scope allowed), and shows positioning of interventions which have been appraised since. Re-treatment with first line chemotherapy removed (as per TA519 FAD section 3.4).

FAD: final appraisal document; G-CSF: granulocyte-colony stimulating factor; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin

Additional 22 months of data collection in trial (cut-off Nov 2018) versus data seen by committee in TA519

KEYNOTE-045	Phase III RCT, n = 542
Population	People with metastatic or locally advanced/ unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy. ECOG performance status of 0, 1 or 2
Intervention	Pembrolizumab 200 mg IV every 3 weeks
Comparator	One of the following, IV every 3 weeks: • Paclitaxel 175 mg/m^2 • Docetaxel 75 mg/m^2 • Vinflunine 320 mg/m^2 (not in UK SoC)
Primary outcome	OS and PFS (per RECIST 1.1)
Key subgroups	PD-L1 positive tumours (CPS≥1%), strongly PD-L1 positive tumours (CPS≥10%)

Key abbreviations in appraisal	
SoC	Comparator arm of KEYNOTE-045 = paclitaxel, docetaxel or vinflunine
UK SoC	Committee preferred comparator in original appraisal = paclitaxel or docetaxel
ITT	Trial results that have not been adjusted for treatment switching (relevant to analyses with and without vinflunine included in comparator arm)

CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumours

Updated clinical evidence – overall survival (OS)

Pembrolizumab versus UK SoC – adjusted for treatment switch to anti-PD-L1 treatment in UK SoC arm using 2-stage analysis

		Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)			Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	**N**	**Median OS (months) (95% CI)**	**Treatment vs. Control**		**Median OS (months) (95% CI)**	**Treatment vs. Control**	
			Hazard ratio (95% CI)	**p-value**		**Hazard ratio (95% CI)**	**p-value**
Control (UK SoC)	182	7.0 (5.5, 8.7)	---	---	7.4 (6.1, 8.3)	---	---
Control (UK SoC), adjusted ¶	182	6.2 (5.2, 7.4)	---	---	6.9 (5.3, 8.1)	---	---
Pembrolizumab (200 mg Q3W)	188	10.1 (7.6, 12.9)	**0.64 (0.49, 0.81)**	0.0139	10.3 (8.0, 11.8)	[redacted]	Unknown

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

CI: confidence interval; Q3W: every 3 weeks

Updated clinical evidence – progression-free survival (PFS)

Pembrolizumab versus UK SoC – no adjustment for treatment switching

	Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)				Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	**N**	**Median PFS (months) (95% CI)**	**Treatment vs. Control**		**Median PFS (months) (95% CI)**	**Treatment vs. Control**	
			Hazard ratio (95% CI)	**p-value**		**Hazard ratio (95% CI)**	**p-value**
Control (UK SoC)	182	3.3 (2.3, 3.5)	---	---	3.3 (2.3, 3.4)	---	---
Pembrolizumab (200 mg Q3W)	188	2.1 (2.0, 2.2)	**0.95 (0.76, 1.19)**	0.6183	2.1 (2.0, 2.2)	[redacted]	0.956

Issues discussed at ACM1

Issue	Committee judgement in ACD
Is log-normal or Weibull the most appropriate extrapolation of PFS, for both pembrolizumab and UK SoC?	Weibull for both arms
How should treatment switching be factored into the decision making?	True OS benefit probably between with/without a 2-stage adjustment
What proportion of patients in pembrolizumab and UK SoC arms would be expected to be alive at 10 years?	No strong evidence for ≥5-year treatment effect; ≤5% of people treated with pembrolizumab alive after 10 years
Which OS extrapolation is most appropriate – Weibull, log-normal, log-logistic or generalised gamma?	Log-logistic, log-normal and generalised gamma are all plausible
Is a 2-year, 3-year or 5-year duration of treatment effect from start of pembrolizumab treatment appropriate?	3 years is appropriate based on the available evidence
Are cost-effectiveness results for PD-L1 subgroups appropriate for decision making?	No – not a clinically distinct subgroup

Cost effectiveness results – committee's preferred assumptions

Alteration	2-stage adjustment for treatment switching: Incr. QALYs	2-stage adjustment for treatment switching: ICER	2-stage adjustment for treatment switching: Change from company base case ICER	No adjustment for treatment switching (ITT): Incr. QALYS	No adjustment for treatment switching (ITT): ICER	No adjustment for treatment switching (ITT): Change from company base case ICER
Company base case (5-year treatment effect, log-normal PFS extrapolation)	0.74	£47,123	–	0.55	£56,422	+£9,299
Weibull distribution to extrapolate PFS after 21 weeks	0.72	£48,518	+£1,395	0.52	£58,850	+£11,727
3-year treatment effect duration	0.65	£51,970	+£4,847	0.49	£62,400	+£15,277
Cumulative impact	0.63	**£53,678**	+£6,555	0.46	**£65,469**	+£18,346
ICER range with plausible OS extrapolations (log-logistic, log-normal, generalised gamma)	£53,678 to £58,705 per QALY gained			£61,653 to £70,520 per QALY gained		

Consultation comments

General

- Clinicians would prefer to prescribe pembrolizumab than atezolizumab, docetaxel and paclitaxel, because the evidence is of higher quality
- It would be a backwards step to go back to using docetaxel and paclitaxel, which have low-level evidence, after having been using pembrolizumab
- Benefits of pembrolizumab have been seen in practice and this should be considered because there is insufficient follow-up from the trial
- Patients would prefer immune checkpoint inhibitors such as pembrolizumab because they are better tolerated and more effective than the cytotoxic comparators

Treatment switching [1]

Background

- In the trial, people in the UK standard of care (UK SoC) arm could have subsequent anti-PD-L1 or PD-1 treatment after progression, including pembrolizumab
- Company used 2-stage method to adjust for treatment switching using an acceleration factor (3.86) (ratio of survivor function for pembrolizumab and UK SoC arms)
- Committee conclusion: 2-stage method was appropriate in original appraisal
- With updated data, acceleration factor had higher magnitude (5.37) and applied to more people – greater influence on OS
- ERG suggested both adjusted and unadjusted results should be considered
  - Wide confidence interval around the acceleration factor
  - Method assumes all people switching had same OS benefit (unknown how many had pembrolizumab)
  - Potential for selection bias and unmeasured prognostic factors
- 40 people switched but acceleration factor calculated from 25 people who switched on documented progression

ACD: true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment

Treatment switching [2]

Company's consultation comments

- Issue was not area of concern in TA525 and method has been used in other appraisals including original TA519.
- ERG's critique is largely based on comparison with Bellmunt paper – heterogeneity between age, ECOG status and prior therapies. Also considers vinflunine treatment, which is not used in UK.
- New acceleration factor should be more reliable because calculated from larger sample size.
- Provided sensitivity analyses including the 15 patients who did not switch based on progression: HR for pembrolizumab vs UK SoC is 0.55 (CI 0.41, 0.69).
- 2-stage model assumed average adjustment for all eligible subjects not same OS benefits
- Other more complex modelling approaches would not be advisable or possible.

ERG comments

- Increased magnitude of acceleration factor increases influence of adjustment and importance of concerns.
- Relevance of additional analysis unclear as estimation of acceleration factor not adjusted in any way. Would expect reducing survival time of additional patients in UK SoC arm to improve HR for pembrolizumab.
- Adjustment applies same acceleration factor to all patients who switched at disease progression, regardless of whether they were thought to have received benefit from the switch. ERG considers immunotherapies typically only effective in some patients.

	Bellmunt 2013	KEYNOTE-045 UK SoC arm ITT	KEYNOTE-045 UK SoC arm 2-stage adjustment
Median OS	6.9 months	7.0 months	6.2 months
12 month OS	27%	32%	25.0%
24 month OS	11%	16%	10%
30 month OS	5.5%	12%	7.7%

Duration of treatment effect [1]

Background

- Company presented 5-year treatment effect duration from start of pembrolizumab treatment as base case, 3 and 10 years as scenarios
  - Supported by showing hazard ratio for pembrolizumab vs UK SoC arm had improved with additional follow-up data
- ERG considered improved HR could be explained by greater data completeness
  - Preferred to use 3-year duration because it considered there was reasonable evidence of an effect up to 2 years but limited evidence beyond 3 years

ACD: 3-year duration of treatment effect from start of pembrolizumab treatment is appropriate

Duration of treatment effect [2]

Company's consultation comments

- 5-year treatment duration accepted in TA525 (2 year stopping rule + 3 years' benefit after) with shorter trial follow-up
- 3-year treatment effect cap causes parametric curve to deviate below the observed survival data
- KEYNOTE-045 median follow up is over 3 years (40.9 months)
- No robust evidence of a loss of treatment effect
- Assuming 3-year effect is contradictory to rationale for selecting the log-logistic curve, which is stated to be that there is a sharply decreasing hazard over time, so a small number of patients will live for a long time
- With log-logistic, 10-year overall survival estimates would be 5.48% and 6.92% with a 5-year treatment effect cap and infinite treatment effect, respectively, in line with clinical opinion (stated 5-10%)
- Other pembrolizumab studies support sustained duration of treatment effect

ERG comments

- 5-year treatment duration in TA525 may not be the same as 3-year post-treatment effect duration because from 43 weeks in KEYNOTE-045, most patients alive in the pembrolizumab arm are no longer receiving pembrolizumab
- Due to small number of events in longer term follow-up, parametric model only provides clear evidence for treatment effect 2 years from start of treatment (beyond 3 years, only 1 death occurred in unadjusted UKSoC arm and none in the adjusted population)
- ERG disagrees that 3-year effect contradicts log-logistic curve because curve fitted to both arms so both would have decreasing HRs over time
- Studies referred to by company are either single arm studies, have different comparators, are from different cancers or have limited follow-up

Duration of treatment effect [3]

Company's additional evidence

	Pembrolizumab (n=270)	Control (n=272)
Median duration of response for responders	29.7 months	4.4 months
36 month OS rate	20.7%	11.0%
36-month duration of response rate	44%	-
Proportion of responses lasting 24 months or more	56.8%	28.3%
Median survival follow-up for responders	39.6 months	17.7 months
Overall response rate	21.1%	11.0%

- Updated analyses of KEYNOTE-045, Fradet et al: Patients who had complete or partial response with pembrolizumab had significantly longer OS (HR = 0.14) and PFS (HR = 0.27) compared with chemotherapy
- 38.5% in pembrolizumab arm achieved best overall response of disease control – these patients expected to receive a lifetime treatment effect
- Company presents scenario analyses with lifetime treatment effect for patients who achieve disease control and 3- or 5-year treatment effect for remainder

Duration of treatment effect [4]

ERG comments on company's additional evidence

- Unclear how response to UK SoC is modelled
- Company assumes same level of response to pembrolizumab for responders and non-responders for first 3 or 5 years of model – ERG considers that non-responders could have quite different survival outcomes to those whose disease responds
- Company appears to consider all patients in UK SoC arm not just those alive at 3 years

Does the committee still agree a 3-year treatment effect is appropriate or is it plausible there is a lifetime treatment effect when disease control is achieved?

Duration of treatment effect [5]

Comparison with other appraisals

Appraisal	Approach to treatment effect duration
TA525 – atezolizumab, urothelial carcinoma	Analyses with a treatment effect cap at 3 years after stopping were taken into account in decision making but there was not enough evidence to support a specific duration of benefit. Trial did not include a stopping rule.
TA428 – pembrolizumab, NSCLC	Size and duration of effect unknown for NSCLC. Lifetime effect implausible but no evidence presented on which to base single clinically plausible scenario.
TA519 – pembrolizumab, urothelial carcinoma	Lifetime effect implausible.
TA600 – pembrolizumab, squamous NSCLC	Lifetime effect implausible. FAD states ‘a treatment effect lasting between 3 years and 5 years had been considered more appropriate for those [appraisals] with a 2-year stopping rule’.
TA484 – nivolumab, non-squamous NSCLC	Plausible that after stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years.
TA483 – nivolumab, squamous NSCLC	Plausible that after stopping treatment at 2 years, nivolumab's treatment effect could last up to 3 years.
TA578 – durvalumab, NSCLC	Long-term treatment effect of durvalumab after stopping treatment is plausible but its duration is uncertain.
TA520 – atezolizumab, NSCLC	Treatment effect was unlikely to last more than 5 years after treatment had stopped.

Recap of previous evidence (ACM1)

ERG's response:

- Majority of information provided by company unrelated to estimation of a relative benefit of pembrolizumab to UK SoC beyond 3 years.
- Maximum follow-up from KEYNOTE-045 is 4 years, but only 1 death occurs in UK SoC beyond 3 years in the unadjusted (ITT) arm, with no events occurring after this in 2-stage adjusted analysis. Estimation of relative treatment effect of pembrolizumab compared to UK SoC not possible beyond this point. Maintain preference for a 3-year effect duration over a 5-year duration.

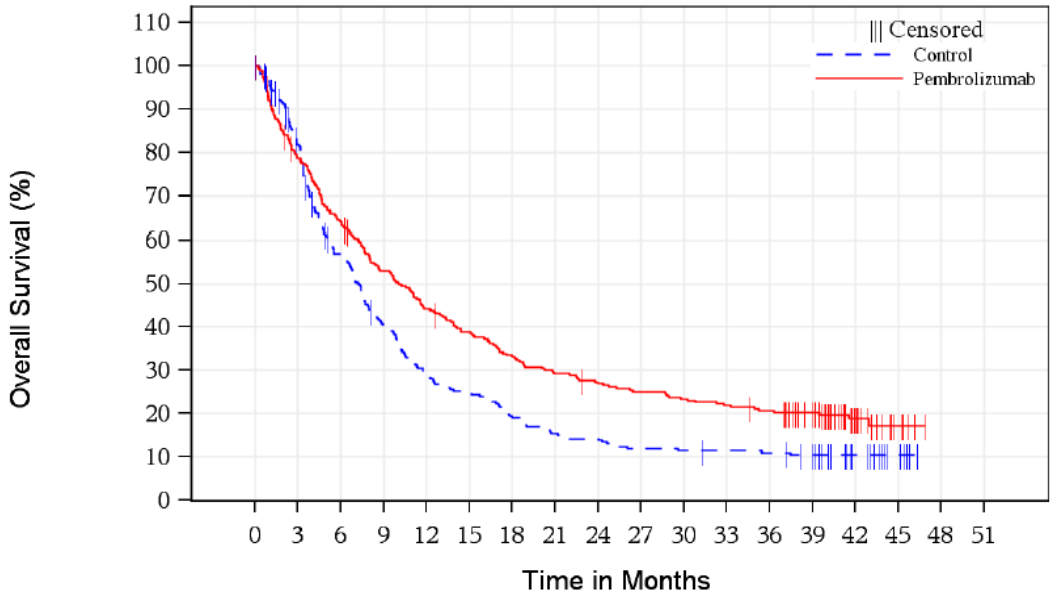

Figure 1, Appendix E, company submission

Company's scenario analyses

	Pembrolizumab vs UK SoC				
Alteration	**Incr. costs (£)**	**Incr. QALYs**	**ICER** (incl 2-stage adjustment)	**Change from company base case ICER**	**ICER** (without 2-stage adjustment)
Company base case from previous meeting (with 5-year treatment effect, log-normal PFS extrapolation)	**£35,035**	**0.74**	**£47,123**	**–**	**£56,422**
Lifetime treatment effect for disease control, 3-year for remainder	£34,833	0.72	£48,089	+£966	£57,566
Lifetime treatment effect for disease control, 5-year for remainder	£35,451	0.78	£45,540	-£1,583	£54,398
Lifetime treatment effect for disease control, 3-year for remainder, Weibull PFS extrapolation *(ctte preferred)*	£34,552	0.70	£49,573	+£2,450	£60,133
Lifetime treatment effect for disease control, 5-year for remainder, Weibull PFS extrapolation *(ctte preferred)*	£35,166	0.75	£46,839	-£284	£56,637

ERG's analyses

ERG preferred assumption	Scenario detail	Impact on base-case ICER
Company base-case		£47,123
1. PFS extrapolation Weibull	PFS extrapolation changed from log normal to Weibull	£48,518 (+£1,395)
2. 3-year duration of treatment effect	Duration of treatment effect reduced from 5 year cap to a maximum 3-year effect	£51,970 (+£4,847)
3. PFS extrapolation Weibull and 3-year duration of treatment effect (ERG base case)	PFS extrapolation and 3-year duration of treatment effect applied to company base-case	£53,678 (+£6,555)
ICER range with plausible OS extrapolations (log-logistic, log-normal, generalised gamma)		**£53,678 to £58,705**
ERG base case		£53,678
4.	ERG base case without 2-stage adjustment (ITT)	£65,469 (+£11,791)
ICER range with plausible OS extrapolations (log-logistic, log-normal, generalised gamma) without 2-stage adjustment (ITT)		**£61,653 to £70,520**

Additional company comments

- ACD should not state that atezolizumab was not established clinical practice in the NHS at the time of the original appraisal so is not included in scope
- ACD states that the model incorrectly changes outcomes for the pembrolizumab arm when survival for the UK SoC arm is adjusted. This is due to the implementation of the treatment effect cap resulting in a change in hazard rate and is not an error.
- ACD states company did not present clinical effectiveness data for PD-L1 positive subgroups with November 2018 cut-off data. Company did provide some results for PFS and OS for 2 PD-L1 positive subgroups.
- ACD states company did not present any new evidence comparing pembrolizumab with best supportive care. Company wishes to clarify it does not consider best supportive care to be a relevant comparator.
- ACD should not state that a 2-year stopping rule applied in the appraisal of nivolumab for urothelial cell cancer because nivolumab was not recommended.

Key issues for consideration

- Does the committee still agree that results both with and without the 2-stage adjustment should be considered?
- Does the committee still agree a 3-year treatment effect is appropriate or is it plausible there is a lifetime treatment effect when disease control is achieved?