Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer

Slides for public – confidential information redacted

Part 1 - Technology appraisal committee A [10 January 2023]

Chair: James Fotheringham

Lead team: Peter Baker, Richard Ballerand and Ana Duarte

Evidence assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Heather Stegenga, Joanna Richardson, Janet Robertson

Company: Merck Sharpe & Dohme

Process: STA 2018

NICE National Institute for Health and Care Excellence

© NICE 2023. All rights reserved. Subject to Notice of rights.

Abbreviations

AE	adverse event
BNF	British National Formulary
BSA	body surface area
CI	confidence interval
dMMR	deficient mismatch repair
DSU	Decision support unit
EC	endometrial cancer
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQol 5 dimensions 5 levels
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
IV	intravenous
KM	Kaplan-Meier
KN-146	KEYNOTE-146
KN-775	KEYNOTE-775
LY	life year
MIMS	monthly index of medical specialities
OS	overall survival
PD	progressed disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PEM+LEN	pembrolizumab with lenvatinib
PF	progression-free
PFS	progression-free survival
pMMR	proficient mismatch repair
PSS	personal support services
QALY	quality-adjusted life year
RTK	receptor tyrosine kinase
SD	standard deviation
TOT	time on treatment
TPC	treatment by physician’s choice
VEGF	vascular endothelial growth factor

Key issues

Table Key issues

Issue	Resolved?	ICER impact
Treatment switching	No – for discussion	Large
Maintenance or waning of treatment effect	No – for discussion	Large
Approach to determining utility / health-related quality of life	No – for discussion	Small to moderate
Overall and progression-free survival extrapolation	No – for discussion	Unclear
Modelling approach – using final data cut	Yes	N/A
Age of patients in model	Yes	N/A

Recap: Background, decision problem and clinical effectiveness

NICE National Institute for Health and Care Excellence

Background

Incidence and prognosis of endometrial cancer

- Endometrial cancer originates in endometrium or lining of uterus (womb)
- 8000 new cases 2019, increasing over time; 85% aged 55 or older.
- Mismatch repair status can be pMMR or dMMR (15-23%)
- dMMR/microsatellite instability-high: molecular biomarker for defective DNA repair process; immunogenic, so may respond better to immunotherapy
- 5-year survival rate with recurrent disease 20% (vs. 89% without recurrent disease)
- Recurrent or advanced endometrial cancer is reported to have a prognosis of 12 months or less

Predisposing factors

- Excessive oestrogen. Risk increases after menopause when oestrogen levels not counteracted by progesterone
- Increased risk with some conditions e.g. Lynch syndrome, polycystic ovary syndrome, type 2 diabetes

Pembrolizumab with lenvatinib

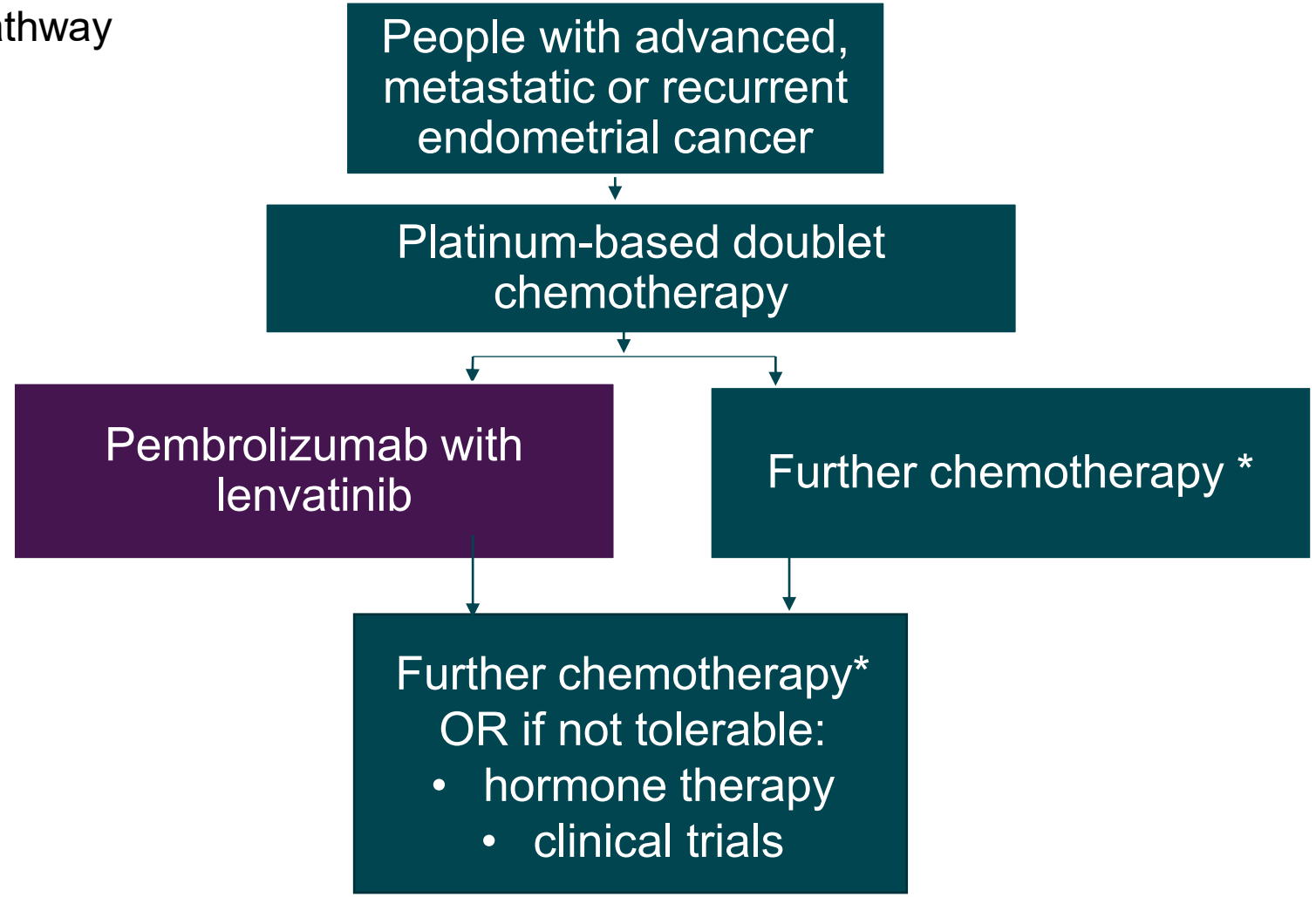
RECAP

Marketing authorisation – November '21	• Advanced or recurrent endometrial carcinoma with disease progression on or following treatment with platinum-containing therapy who are not candidates for curative surgery or radiation
Mechanism of action	• **Pembrolizumab**: antibody targets PD-1 receptor-blocks interaction with ligands PD-L1 and PD-L2; aim: enhance immune response to tumour cells • **Lenvatinib**: RTK inhibitor inhibits kinase activities of VEGF receptors and other RTKs, aiming to inhibit tumour growth
Administration	• **Pembrolizumab**: IV 200 mg 3 weekly or 400 mg 6 weekly • **Lenvatinib**: 20 mg per day (orally)
Price	• Pembrolizumab list price total cost per administration £5,260 • Lenvatinib list price total cost per administration is £239.50 for 4 mg x 30 pack/ £95.80 for 10 mg x 30 pack • Both drugs have a confidential patient access scheme approved (simple discounts)

Treatment pathway

No standard treatment options for second-line; MA specifies prior platinum which is the mainstay of current 1st line chemotherapy

Figure Treatment pathway



Dostarlimab (TA779) was recommended in the CDF for dMMR disease - not a comparator as not recommended in routine commissioning.

*Committee heard from experts at ACM1 that further chemotherapy may consist of paclitaxel monotherapy, doxorubicin monotherapy, or in some cases where neoadjuvant platinum was taken, carboplatin plus paclitaxel

Key clinical trial – KEYNOTE-775

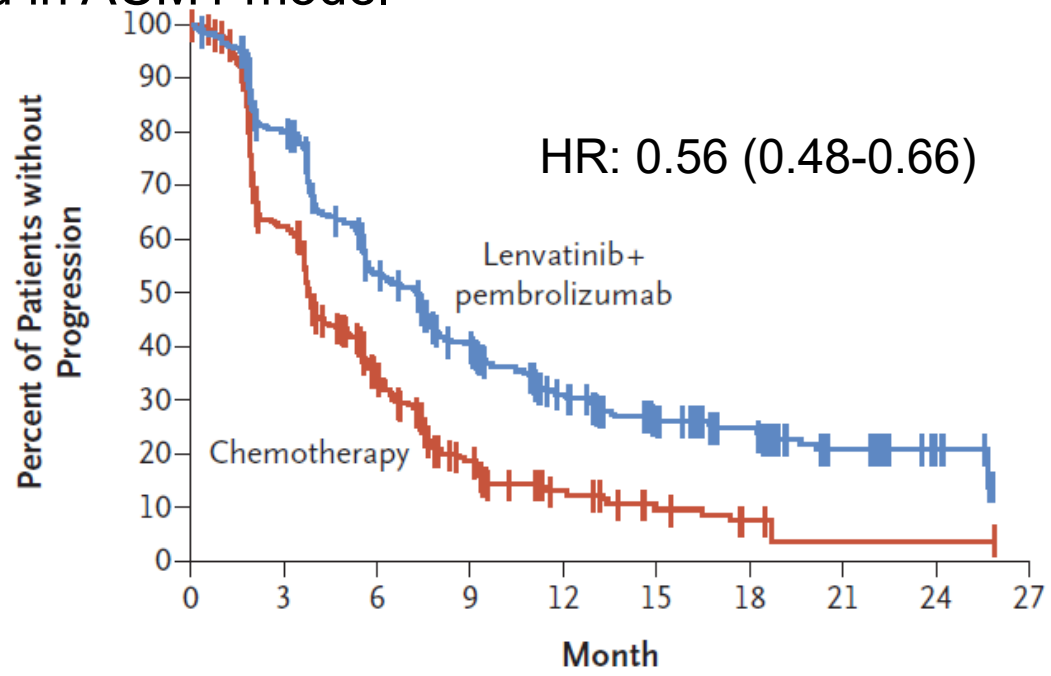
Design	Multi-centre, randomised, open-label, phase III study
Population	Advanced, metastatic or recurrent EC with disease progression after platinum chemotherapy; not candidates for curative surgery or radiation
Intervention	N= 411 Pembrolizumab 200 mg IV 3 weekly up to 35 cycles plus oral lenvatinib 20 mg / day
Comparator(s)	N=416 Treatment of physician's choice: IV doxorubicin 60 mg/m^2 3 weekly or IV paclitaxel 80 mg/m^2 weekly (3 weeks on, 1 week off)
Duration	~4 years (commenced June 2018; final data cut March 2022)
Primary outcome	Progression-free survival, overall survival
Secondary outcomes	Health-Related Quality of Life (HRQoL), adverse events
Locations	21 countries including UK (9 sites 39 participants)
Treatment stopping	35 cycles of pembrolizumab (approximately 24 months), or lifetime cumulative dose of 500 mg/m² of doxorubicin*

* Lenvatinib continued unless unacceptable toxicity or progression

KEYNOTE-775 results: progression-free survival

PEM+LEN treatment statistically significantly improved PFS compared with chemotherapy; final data cut not used in model at ACM1

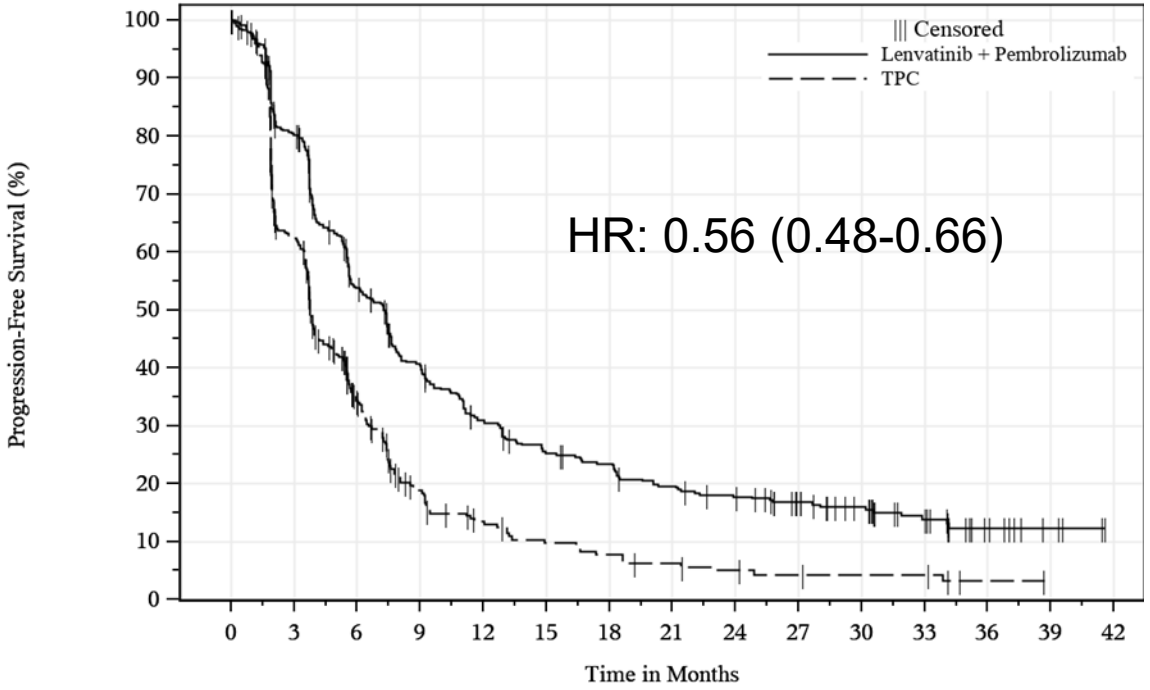
Figure 3 Interim data cut (26 October 2020) – used in ACM1 model



No. at Risk

Lenvatinib+pembrolizumab	411	316	202	144	86	56	43	17	6	0
Chemotherapy	416	214	95	42	18	10	4	1	1	0

Figure 4 Final data cut (1 March 2022) – **not included in ACM1 model**



n at risk

Lenvatinib + Pembrolizumab	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
TPC	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

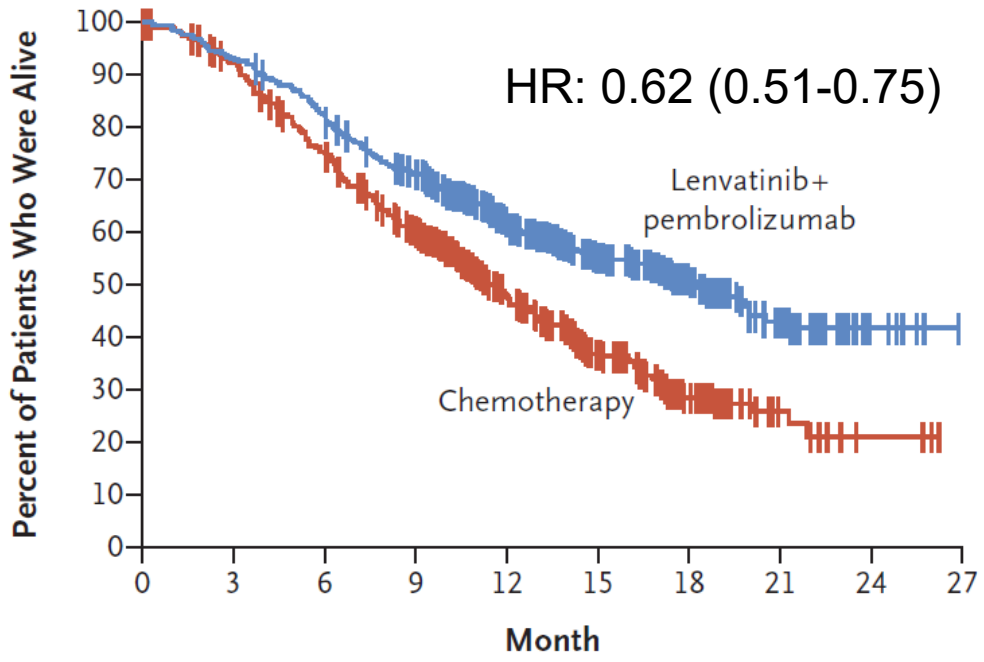
Progression-free survival	Interim Analysis		Final Analysis	
	PEM+LEN (n=411)	TPC (n=416)	PEM+LEN (n=411)	TPC (n=416)
Median months	7.2	3.8	7.3	3.8

NICE

KEYNOTE-775 results: overall survival

PEM+LEN treatment statistically significantly improved survival compared with chemotherapy; final data cut not used in model at ACM1

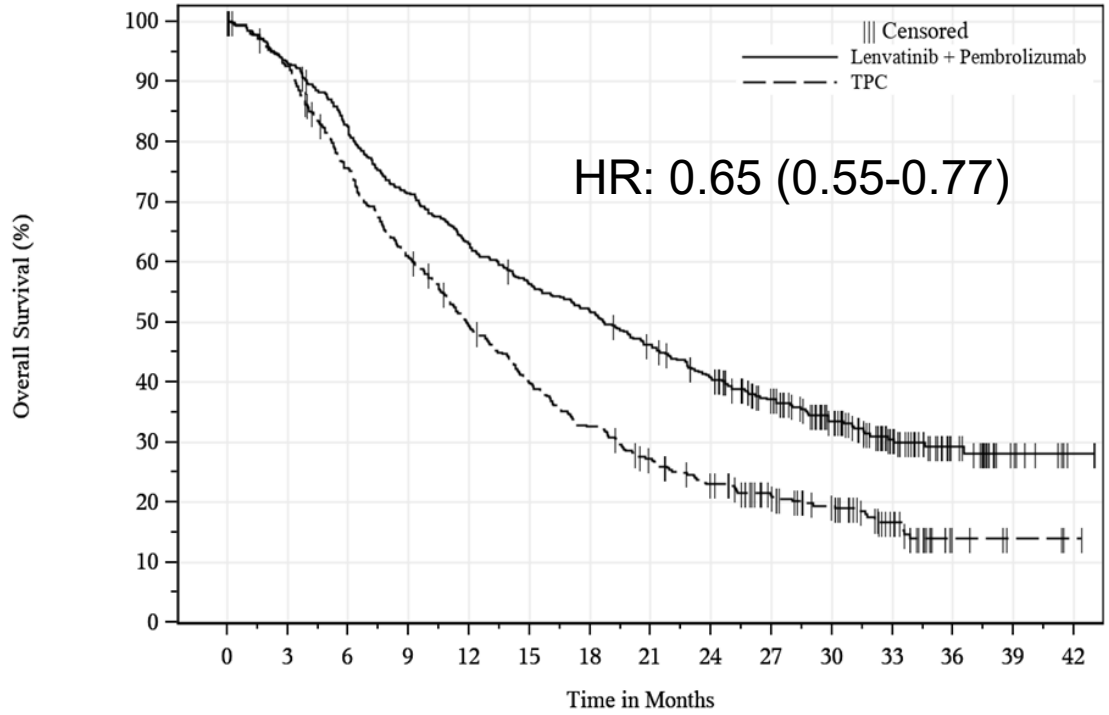
Figure Interim data cut (26 October 2020) – used in ACM1 model



No. at Risk

Lenvatinib+pembrolizumab	411	383	337	282	198	136	81	40	7	0
Chemotherapy	416	373	300	228	138	80	40	11	3	0

Figure Final data cut (1 March 2022) – **not included in ACM1 model**



n at risk

Lenvatinib + Pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
TPC	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

Overall survival	Interim Analysis		Final Analysis	
	PEM+LEN (n=411)	TPC (n=416)	PEM+LEN (n=411)	TPC (n=416)
Median months	18.3	11.4	18.7	11.9

Committee conclusions: clinical

Table Committee conclusions on unmet need and clinical effectiveness

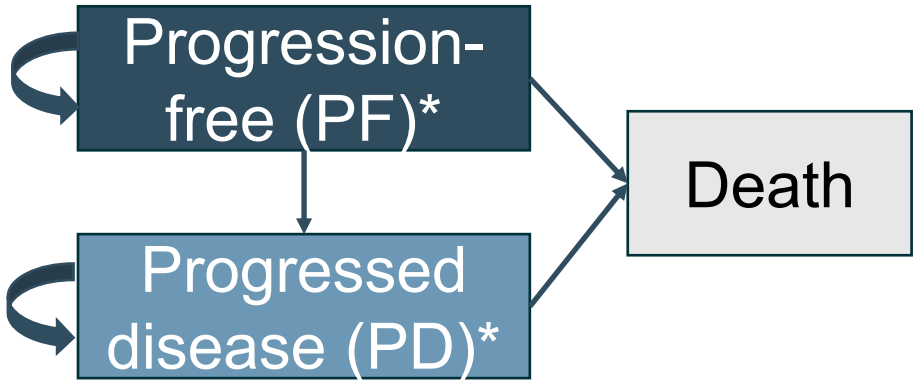
	Committee conclusion	ACD
Treatment option needed	People with advanced or recurrent endometrial cancer would welcome a new treatment option	3.1
Comparators	No standard second-line treatment but doxorubicin or paclitaxel monotherapy are appropriate comparators	3.2
Clinical evidence	KEYNOTE-775 trial is generalisable to NHS clinical practice	3.3
Clinical effectiveness	Pembrolizumab plus lenvatinib improves overall and progression-free survival compared with doxorubicin or paclitaxel monotherapy	3.4
Subgroups	Pembrolizumab plus lenvatinib may be better in dMMR than pMMR disease but there is not enough evidence to conclude this (study not powered for this)	3.5

Recap: Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Figure Model structure



* Utilities predicted using 6 time to death categories: < 30 days, 30–89 days, 90–179 days, 180–269 days, 270-359 days, ≥ 360 days

Table Model characteristics

Design	Partitioned survival cohort
Time horizon	40 years
Cycle length	1 week
Stopping rule	24 months for PEM (as per trial); treated to progression for LEN
Treatment waning	No
Discount	3.5%
Perspective	NHS and PSS

Modelled to affect costs

- ↑ drug acquisition costs
- ↓ adverse events, end of life costs and subsequent treatment costs (but incremental difference minor)

Modelled to affect QALYs

- ↑ time patients stay in PF and PD health states (accrue more QALYs and gain more LYs)
- ↑ time spent in PD and use of time-to-death to estimate utilities since most of incremental QALY gain ([redacted]%) is in this health state

How company incorporated evidence into ACM1 model

Table Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	KEYNOTE-775
Intervention efficacy	KEYNOTE-775 (interim data); validation of extrapolation from KEYNOTE-146
Comparator efficacy	KEYNOTE-775 (interim data); doxorubicin and paclitaxel have similar effectiveness validation of extrapolation from 2 UK real-world evidence studies (ECHO and Heffernan 2022)
Utilities	EQ-5D-5L from KEYNOTE-775 (interim data) mapped onto 3L
Costs and resource use	BNF, eMIT, MIMS, NHS reference costs, Unit Costs of Health and Social Care (Personal Social Services Research Unit), National Cost Collection data (Version 2; 2019/2020)*, NICE DSU report on the cost of febrile neutropenia 2007 (inflated to 2020 cost)
Subsequent therapy	Proportions as per KEYNOTE-775 (interim data), excluding those not reimbursed in the UK

* As used in TA620 (olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer) which includes assumptions taken from TA285 (bevacizumab with gemcitabine and carboplatin for first recurrence in platinum-sensitive advanced ovarian cancer) + clinical opinion

Committee conclusions: cost (1/2)

Table Committee conclusions on cost effectiveness

	Committee conclusion	ACD
Model	Model structure suitable for decision-making	3.6
Overall survival extrapolation	Kaplan–Meier plus log logistic curve preferred for extrapolating overall survival in both arms using interim data, but final data may change this conclusion	3.7
Model types explored for extrapolation	Exploring more flexible models may be needed	3.8
Treatment effect duration	It is appropriate to assume some treatment waning in the model Prefer to see alternative treatment waning scenarios in a model using final data cut	3.9
Utility derivation	The EAG's approach to deriving utilities using progression status is more appropriate than company's approach using time to death	3.10
Age in model	Prefer the clinical experts' estimation of average age in UK clinical practice (around 67 years) be used in the model	3.11
End of life	Treatment meets the end of life criteria	3.12

Committee conclusions: cost (2/2)

Table Committee conclusions on cost effectiveness

	Committee conclusion	ACD
Cost-effectiveness	The most plausible cost-effectiveness estimate is unknown, further analyses including data from the final data cut is needed	3.13
Innovation	It is uncertain if treatment meets NICE's criteria for an innovative treatment: is likely a step-change but no benefits uncaptured in the model identified	3.14
Equalities	There are no equalities issues impacted by the committee's draft recommendations	3.15

ACD - Pembrolizumab plus lenvatinib not recommended

Committee request to see:

- Results using final data cut in the model, ideally exploring more sophisticated flexible models to allow committee to see how this may affect choice of extrapolation for both arms
- Impact of alternative treatment effect waning scenarios on ICER
- Use mean age 67 in model
- EAG's approach to deriving utilities

ACD consultation responses

Received 3 consultation responses from:

- Peaches Womb Cancer Trust
- Submitting company (pembrolizumab)– Merck Sharpe & Dohme
- Companion company (lenvatinib) – EISAI

Plus:

- 2 web comments

NICE National Institute for Health and Care Excellence

Peaches Womb Cancer Trust response (1/3)

- Recommendation not in interest of 1200 diagnosed with advanced cancer in England each year or 1000 in whom it recurs
- Trust receives increasing numbers of enquiries about this treatment, which is seen as a source of hope for the future; people otherwise feel fearful of future with only standard treatments
- Slides at 1st committee did not adequately represent patient experts' submissions
- Survey from members of Peaches Womb Cancer Trust's patient and public involvement group (Peaches Patient Voices) or the private peer support group (Womb Cancer Support UK): 43/44 (97.7%) respondents agree with Trust's response
- Pembrolizumab and lenvatinib approval (vs a 'no' decision and continuing with current treatments) would support longer life with fewer side effects which affect people's day-to-day and overall quality of life (help maintaining independence) and provide hope for patients and their loved ones
- Staying well longer may enable people to have future treatments

Peaches Womb Cancer Trust response (2/3)

- Patients feel they are treated unfairly compared to people with other cancers
- Diagnosis of advanced or recurrent endometrial cancer is devastating already, but when patients discover lack of effective second line treatment options, it provokes feelings of anger, frustration, abandonment and hopelessness
- Inequality of access – geographically (since approved by Scottish Medicines Consortium), urgent unmet need for pMMR, chemotherapy not suitable for older patients with comorbidity, financial impact for both patients and carers

Peaches Womb Cancer Trust response (3/3)

Current treatment options are not effective and have significant impact on quality of life and hope for the future; Pembrolizumab with lenvatinib offers hope for future

You hear about all these different treatments out there, and people losing their lives when there are no other treatments available, and then you hear about treatments out there that could save or extend your life but they won't be used because they're too expensive. Nobody can fully understand this without having been in that position themselves

…my experience of womb cancer and my husband's of prostate cancer - same time period, different London hospitals - …provision for prostate cancer is 'better' and more joined up

…she had to choose in the end to suffer chemo and side effects or stop treatment and enjoy just a couple of quality months with her family

I feel …there is a shadow over me…[I] may appear healthy [but] I am haunted by the spectre of recurrence…I would have little faith in chemotherapy a second time and also because the thought of withdrawing from a job that I love and friends and family again, would be such a hard thing to do

Company consultation response – overview

Topic	Committee preference	Does company response addresses?
KEYNOTE-775 data cut	Final data cut (March 2022) needed in model	Yes – OS, PFS, TOT, HRQoL, AE & subsequent treatments
Patient age	Use clinical experts' estimation of average UK age in model (around 67 years)	Yes
Treatment switching	Noted impact of immunotherapies as subsequent therapy after TPC on effect estimate not explored	N/A – applied treatment switching methods in base case
OS extrapolation	Kaplan–Meier plus log logistic with interim data cut; more flexible models may be needed with final data cut	Yes – explored more flexible models and used in base case
Treatment effect duration	Some effect waning appropriate; prefer alternative scenarios	Partially – not in base case; alternative scenarios
Utility derivation	Based on progression status (EAG preferred)	Partially

Company response: treatment switching

Company adjust for switching from TPC to non-NHS treatments

Committee conclusion: '[committee] noted that the impact of having immunotherapies as subsequent therapy in the comparator arm on the effect estimate had not been explored.'

- [redacted] with progression after TPC in KEYNOTE-775 (final data cut) switched to PEM + LEN or PD1/PD-L1 or VEGF/VEGFR inhibitor therapies not available in this line in the UK ([redacted]*)
- Trial likely overestimates OS with TPC and underestimates benefit of PEM + LEN compared with TPC
- All methods improve benefit of PEM+LEN over TPC; TSE method least biased – used in updated base case

Treatment switching adjustment methods	HR (PEM + LEN vs TPC)	Median OS, TPC (months)
Unadjusted	0.65	11.9
Two-stage estimation (TSE) – without recensoring	[redacted]	[redacted]
Two-stage estimation (TSE) – with recensoring	[redacted]	[redacted]
Rank preserving structural failure time models (RPSFT) – without recensoring	[redacted]	[redacted]
Rank preserving structural failure time models (RPSFT) – with recensoring	[redacted]	[redacted]
Inverse probability of censoring weighting (IPCW)	[redacted]	[redacted]

Company base case

* Refers to records of a drug used in any line of treatment; patients may have used more than one drug in different lines

Treatment switching: EAG critique

EAG: TSE may be appropriate method but uncertainty remains; prefer not to use treatment switching methods in base case

- Committee did not request treatment switching in preferred base case, as company have done; just exploratory
- EAG have 2 base cases to characterise uncertainty: one with, and one without switching methods
- Unclear why company preferred results 'without re-censoring' which would be preferred but acknowledges differences in HR are small and that the lower treatment estimate was chosen (is 'conservative')
- Treatment switchers do not just have one treatment (PEM+LEN) after TPC, but a number of treatments (VEGR/VEGFR inhibitors or other PD-1/PD-L1 drugs); TSE assumes all treatments have the same treatment effect; creates uncertainty
- True effect likely between unadjusted and adjusted values

Should adjustment for treatment switching be included in base case? Which method is preferred?

Company response: flexible spline models fitted

Committee conclusion: 'The committee concluded that exploring different flexible models may be needed, because of the uncertainty and substantial impact on the ICER of the overall survival extrapolation curve and treatment waning assumption.'

Figure: final OS models in revised base case

Company select one-knot spline for OS for both arms based on low AIC/BIC values, statistical and visual fit to the observed Kaplan–Meier data as well as the smooth hazard functions

EAG critique

- agree company approach is defensible and has greater credibility
- note justification of placement of knot not provided – leads to uncertainty
- agree odds scale appropriate for PEM+LEN but all extrapolations predicted higher than observed hazards at end of observation period
- conduct additional scenario considering 2-knot spline for TPC arm (minimal impact on ICER)

Does committee consider one-knot spline model the most appropriate to extrapolate overall survival for both arms?

Company response: PFS extrapolation

Figure: final PFS models in revised base case

[redacted]

Company select one-knot spline for PFS for both arms based on low AIC/BIC values, statistical and visual fit to the observed Kaplan–Meier data as well as the smooth hazard functions

EAG critique

- Comparison via landmark survival not provided for PFS between models
- Different knots on odds scale (based on long-term visualisations) did not have meaningful differences
- Odds scale models better fit PEM+LEN, less clear for TPC
- Spline models fit TPC arm better than PEM+LEN, based on visual plots of spline-based hazard functions against smoothed spline functions
- Unable to test alternative types of models as company model only allows odds scale to be used

Does committee consider one-knot spline models the most appropriate to extrapolate progression-free survival for both arms?

Company response: duration of treatment effect (1)

Company maintain no waning in base case after pembrolizumab stops at 24 months; explore waning scenarios as requested by committee

'[Committee] preferred the EAG's scenario that included treatment waning over 3 years after stopping treatment with pembrolizumab, but the impact of alternative treatment waning assumptions would be helpful'

- No evidence of treatment effect waning in KEYNOTE-775: both data cuts show sustained longer-term benefit of PEM+LEN compared with TPC
- Biological reason: PEM+LEN work synergistically and then lenvatinib may continue benefit by helping to shift tumour environment to immune-stimulatory state by inhibiting VEGFR and FGFR
  - clinical experts consulted November 2022 confirm some will have durable response
  - [redacted]% still receiving lenvatinib at last recorded time point in KEYNOTE-775 (~3 years)
- Waning implausible and inappropriate:
  - cite multiple pembrolizumab RCTs in other disease areas (melanoma and NSCLC) with 5-year data – state all demonstrate a sustained treatment effect. [2 studies were 2nd-line]
    - Hazard plots show no structural difference in hazards between 2 melanoma trials, with and without 2 year stopping criteria
  - long-term data on durability of treatment effect for anti-CTLA4 agents in advanced melanoma (from year 3 up to year 10) which work similarly to anti PD-1 agents.
  - no evidence to suggest similar plateau would not be observed with PEM+LEN, also considering OS of 30% at 5 years among the patients with endometrial cancer in KEYNOTE-146 (note: this was the longest term data with PEM+LEN)

Company response: duration of treatment effect (2)

Company maintain no waning after pembrolizumab stops at 24 months; explore waning scenarios

- There is a higher survival probability over the long term – i.e. those who are farther away from diagnosis and are still alive have higher survival probability
  - KEYNOTE-775 final results show longer median PFS in PEM+LEN compared with TPC (7.3 vs 3.8 months), longer median duration of response (12.9 vs 5.7 months) and longer median OS (18.7 vs 11.9 months)
- Several waning scenarios conducted which considered the below factors:
  - Waning from years 5-7* (given no waning has been observed in pembrolizumab trials in other indications before 5 years, length of KEYNOTE-146 follow-up)
  - Application of waning of treatment effect to 60-80% of patients with PEM+LEN (reflecting small proportion with durable response and prolonged immunotherapeutic effect after stopping and continued lenvatinib monotherapy)
- Company considers scenarios with waning pessimistic for decision-making

EISAI (lenvatinib) comment: Inappropriate to assume treatment waning effect for lenvatinib plus pembrolizumab:

- lenvatinib continues after pembrolizumab stops, unless unacceptable toxicity or progression
- not appropriate to justify waning using precedence from dostarlimab [TA779], a monotherapy
- KEYNOTE-775 analysis up to 3.5 years: sustained separation of arms for overall survival and duration of response

* From treatment initiation, i.e. after stopping of treatment at 2 years, effect maintained for 3 years until year 5 when waning is applied up to year 7

Treatment effect waning: EAG critique

EAG apply waning in their base case

- Modelled 5-year OS for PEM +LEN in KEYNOTE-775 showed some evidence of a sustained response (OS: [redacted]), but this is lower than the sustained response in the only other PEM+LEN study, KEYNOTE-146 (OS: 30%)
- Some evidence to support some duration of effect after stopping pembrolizumab, but unable to conclude no waning over time:
    - Treatments, patient characteristics, disease severity differ in studies provided by company in different disease areas
    - KEYNOTE-146: uncertainty in survival rate at 5 years because few patients were at risk at 5 years
- EAG-preferred base case incorporates committee-preferred waning over 3 years, after stopping treatment with pembrolizumab at 2 year; this is consistent with other appraisals
- EAG conduct 2 alternative treatment waning scenarios show large impact on ICER (both significantly reduce ICER):
    - Waning from year 5 to year 7 (3 to 5 years after stopping treatment) to all patients in pembrolizumab arm

Does committee have sufficient evidence to change its preferred assumption of waning over 3 years after stopping pembrolizumab?

Company response: deriving utilities

Company used disease progression as a covariate in their time to death analyses to predict utility which they considered addressed committee preference

Committee conclusion: 'The committee noted that the company's approach in this appraisal limits the amount of information informing health states. So while the approach may provide **more granular information** than the progression status approach, the **increased uncertainty** in the utility estimates obscures differences between each of the time-to-death categories. The committee concluded that the EAG's approach to deriving utilities using progression status is more appropriate.'

Company approach:

- **Revised base case**: extended the initial utility regression models* within time to death utility analyses using disease progression as a covariate to predict utility (alongside 6 time to death categories: < 30 days, 30–89 days, 90–179 days, 180–269 days, 270-359 days, ≥ 360 days) for pre and post progression
- **Scenario**: following the approach in dostarlimab (TA779) which also used disease progression as a covariate within a time-to-death utility approach, but only two time to death categories (TTD <180 days and TTD ≥ 180 days) - small impact on ICER

* utility regression model included as explanatory variables clinical drivers of HRQoL, presence of AEs (Grade 3 and above), progression status (PF or PD) and patients' time to death

EAG critique of company changes to deriving utility

- Committee concerns about limited data used to inform each of the 6 time to death categories (per health state) and associated uncertainty still relevant
- Estimating utilities based on progression status alone aligns with model structure – EAG maintain in their base case
- Note that with updated KEYNOTE-775 data, the adverse event utility decrement in model decreased from [redacted] to [redacted]
- EAG conduct scenario based on model used for company's scenario (used in TA779) – small/moderate impact on ICER

Table. Utility values used in EAG's base case

Health state	Mean health state utility value	LB	UB
PF	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]

Key: LB, lower bound; UB, upper bound

Does committee consider the company's updated approach to determining utility (using progression as a covariate) appropriate to address their concerns?

Web comments (n=2)

- GSK (dostarlimab):
    - requested to remove a statement in guidance as dostarlimab is not a comparator given it is in the Cancer Drugs Fund

- Member of the public:
    - benefits of the technology not taken into account; no evidence provided it is not cost-effective (also noting that current treatments are not cost effective); committee appears to object based on cost and consider it not worth the money because the outcomes are not clear; people who cannot afford private healthcare are discriminated against

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator patient access scheme discounts

Innovation

Company disagrees with committee and consider treatment meets NICE's criteria for an innovative treatment

Committee conclusion: it is uncertain if treatment meets NICE's criteria for an innovative treatment; is likely a step-change but no benefits uncaptured in the model identified

- Company:
  - combination is innovative and "step-change" for patients with this type of cancer: combination of anti-programmed cell death-1 protein (PD-1) immune checkpoint inhibitor (pembrolizumab) and tyrosine kinase inhibitor (TKI) (lenvatinib) has synergistic effect
  - benefits associated with this technology exceed those directly modelled

Does committee have enough evidence to change its decision on innovation?

Summary of updated company and EAG base cases

Table Differences between company and EAG revised base cases updated after consultation and impact on ICER

Assumption	Company base case	EAG base case	EAG's preferred assumption -impact on ICER
Treatment switching	OS adjusted in TPC arm for switching to non-NHS treatments	2 preferred base cases: one adjusted, one unadjusted	↑ (unadjusted base case)
Waning of treatment effect	Model lifetime (scenarios with different %s of patients with waning from years 5 to 7)	Waning from year 3 to 5 in all patients (scenario with no waning and another with all patients with waning from years 5 to 7)	↑
Health state utilities	Based on time to death with progression as covariate	Based on progression status (progression-free and progressed disease)	↑
Extrapolation curves	1-knot spline for both arms for both OS and PFS	Same as company (but some concerns)	n/a

Biggest to smallest impact on ICER