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

Slides for public – does not contain confidential information

Part 1 - Technology appraisal committee A [11 October 2022]

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

Abbreviations

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
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
TPC	treatment by physician's choice
VEGF	vascular endothelial growth factor

Key issues

Table Key issues

Issue	Resolved?	ICER impact
Waning of treatment effect	No – for discussion	Large
Overall survival extrapolation	No – for discussion	Large
Age of patients in KEYNOTE-775 used in model and generalisability to UK clinical practice	No – for discussion	Moderate
Time to death approach to determining utility / health-related quality of life	No – for discussion	Moderate
Clinically distinct subgroups (dMMR and pMMR)	No – for discussion	Unknown

Key clinical issues

- How would these patients currently be treated in the NHS?
    - Is doxorubicin or paclitaxel monotherapy the most appropriate comparator for 2nd line treatment following platinum in the neoadjuvant or first line setting?
    - Should hormone therapy be considered a comparator?
- Is evidence from KEYNOTE-775 generalisable to the population in the NHS?
- Are committee satisfied that the outcomes for PFS and OS in the final data cut are similar enough to the interim data (October 2020) used in the model?
- Does KEYNOTE-775 provide enough evidence to allow subgroups of patients by mismatch repair status (pMMR and dMMR) to be considered separately?

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

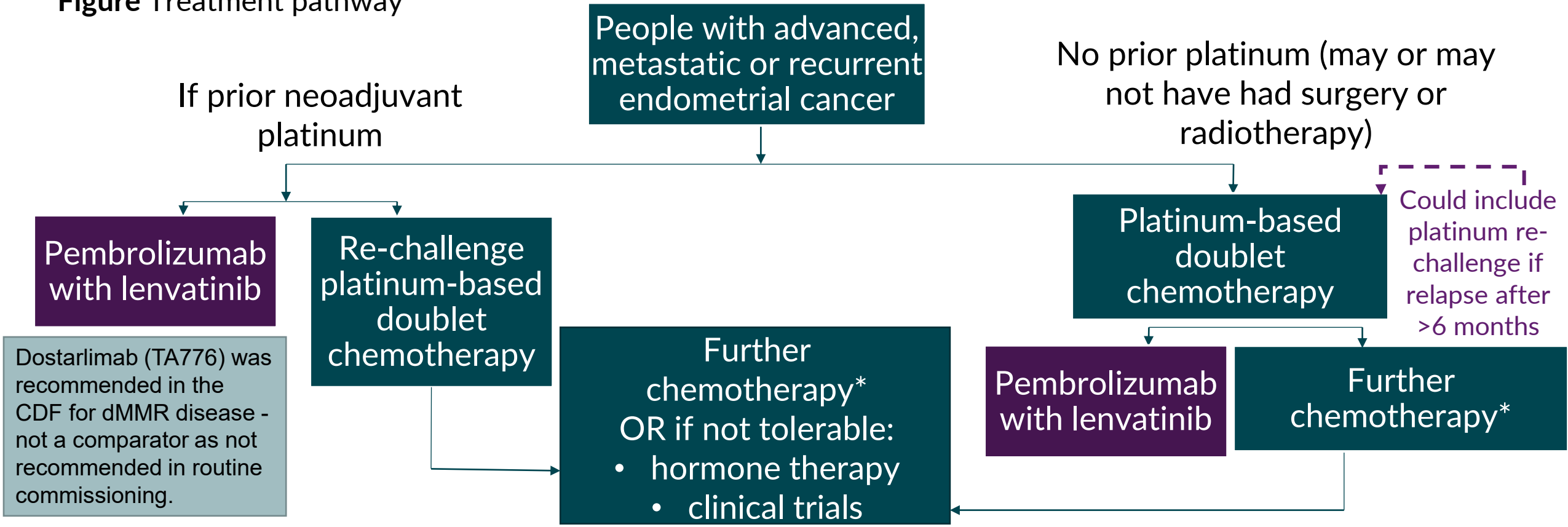
Pembrolizumab with Lenvatinib

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; company propose 2 settings for pembrolizumab with lenvatinib; MA specifies prior platinum which is the mainstay of current 1st line chemotherapy

Figure Treatment pathway



Which chemotherapy regimen is considered the most appropriate comparator for 2nd line treatment? When might further platinum be given? Should hormone therapy be considered a comparator? Is it reasonable to consider paclitaxel and doxorubicin as the main comparators?

*Further chemotherapy may consist of carboplatin plus paclitaxel, doxorubicin or gemcitabine, carboplatin monotherapy, paclitaxel monotherapy, doxorubicin monotherapy

Patient perspectives

Advanced or recurrent endometrial cancer has significant impact on every aspect of life; dissatisfaction and frustration with treatment options

Submissions from Peaches Womb Cancer Trust

- debilitating physical symptoms (bleeding, pain, discomfort, reduced appetite, nausea, fatigue); long term physical effects following treatment
- **psychological impact** of repeated intimate examinations on sexual function and intimacy, leading to distance in relationships
- reduced confidence going to social events because of tiredness, access to toilet and fear of accidents like urinary leakage
- limited mobility and pain: unable to leave home, unable to work or work less than full-time; financial impact with additional concerns and anxiety
- some **unable to live independently**, needing help for activities of daily living like cooking, cleaning, bathing
- carer impact financially due to time off work, worry, difficulty attending to own activities of daily living, disruption to family life
- frustration, disappointment, anger and feeling of being abandoned due to **limited effective treatment options** compared to other cancers; chemotherapy not an option for some women

I try to plan things like seeing friends [but] I have to cancel so often due to the pain, anxiety and constant tiredness

I had to get a cleaner in and have help from my 74-year-old mother as I can't cope with daily living tasks

Clinical perspectives

No current standard second-line treatment

Submissions from professional organisation and clinical expert

- Second-line chemotherapy used if patient fit enough
- European Society for Medical Oncology Guidelines: choice depends on time interval since previous chemo, previous response and toxicities, patient preference:
    - carboplatin and paclitaxel (re-treatment)
    - pegylated doxorubicin
    - weekly paclitaxel
    - high dose progesterone considered part of palliative care although may be given as 'holding measure' to patients more unwell or less fit to improve well-being
- Pembrolizumab with lenvatinib is 'game changer': far more effective, and well tolerated so can be used by more patients who previously would have had only palliative care. Also shorter treatment duration, less frequent administration, very little monitoring, no additional testing or unusual concomitant medication, better symptom control

10-15% response rate to … second line chemotherapy… no other realistic options aside from palliative care

We will be able to change our dialogue [in the clinic]…to be able to offer patients a meaningful treatment

Decision problem

Table Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	Advanced, metastatic or recurrent EC, previously treated with platinum-based therapy - not able to receive curative surgery or radiation	As MA	2 clinically distinct subgroups: people with dMMR and pMMR
Intervention	Pembrolizumab with lenvatinib		
Comparators	- Chemotherapy (including carboplatin and paclitaxel, paclitaxel /doxorubicin/carboplatin monotherapy - Hormone therapy (medroxyprogesterone acetate and megestrol) - Best supportive care	Chemotherapy (such as paclitaxel, carboplatin, doxorubicin) ***Paclitaxel or doxorubicin in base case*** Excludes best supportive care (reserved for patients not fit for active treatment) and hormone therapy (palliative).	Following neo-adjuvant, re-challenge with platinum-containing doublet chemotherapy may be first choice treatment if treatment at least 12 months prior
Outcomes	Progression-free survival, overall survival, response rates, duration of response, adverse effects of treatment, health-related quality of life		

NICE

* Company scenario adds in carboplatin, alone and with paclitaxel – minor impact

Clinical effectiveness

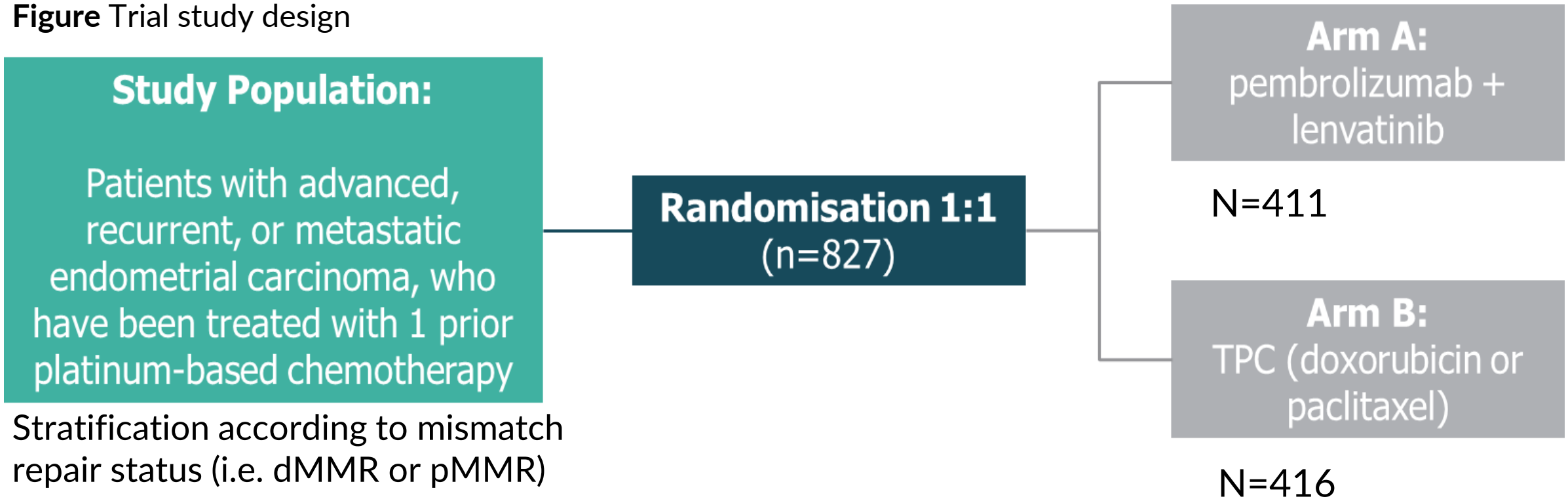
NICE National Institute for Health and Care Excellence

Key clinical trial – KEYNOTE-775: data used in model

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)

KEYNOTE-775 study design

Figure Trial study design



Study treatment stopped after disease progression, toxicity, withdrawal of consent, after 35 cycles of pembrolizumab (approximately 24 months), or lifetime cumulative dose of 500 mg/m² of doxorubicin
(Model assumes 2 year treatment of pembrolizumab)

KEYNOTE-775 generalisability: baseline characteristics

ERG: Patient age may not reflect UK clinical practice*

ERG: clinical input: UK patients older than in KN-775

- Used mean 75 years in base case - minimal impact on ICER

Company response: KN-775 values generalisable to UK patients

- UK patients in KN-775 older than ITT population: median [redacted] vs 63.5 years
- UK real-world evidence: mean [redacted] (ECHO), 65.5 (Heffernan 2022; second-line only/validated with clinicians)

Clinical experts:

- Trial patients bit younger than clinical practice but PEM+LEN suitable for poor performance and older patients - unlikely to affect treatment translatability

Table Baseline age from KN-775

Age at diagnosis		
	Intervention (n=411)	Comparator (n=416)
Mean age (SD)	[redacted]	[redacted]

Is evidence from KEYNOTE-775 generalisable to population in the NHS?

* ERG also note, based on clinical input, that average weight in trial (70kg) is less than in UK clinical practice; minimal impact on ICER

KEYNOTE-775 results

Company present final analyses but interim results used in model

- Final data cut available at technical engagement – insufficient time to include in model
- Additional 3.2 months median follow-up
- ERG: median survival and overall shape of KM curves sufficiently similar that failure to update the model is not key issue.

Table Interim and final results from KN-775

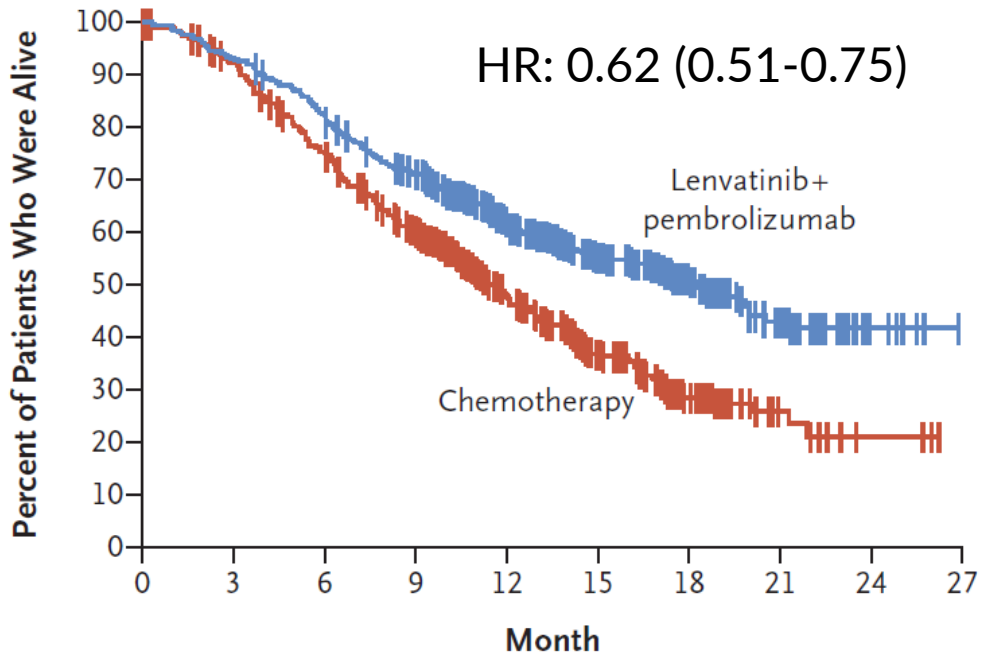
	Interim Analysis 1: October 2020		Final Analysis : 1st March 2022	
	PEM+LEN (n=411)	TPC (n=416)	PEM+LEN (n=411)	TPC (n=416)
Median months follow-up	11 .4		14.7	
Progression-free survival				
Median months	7.2	3.8	7.3	3.8
HR (p value)	0.56 (P <0.0001)		0.56 (P <0.0001)	
Overall survival				
Median months	18.3	11.4	18.7	11.9
HR (p value)	0.62 (P <0.0001)		0.65 (P <0.0001)	

Note: no significant difference between groups in health-related quality of life

KEYNOTE-775 results: overall survival

PEM+LEN treatment statistically significantly improved survival compared with chemotherapy

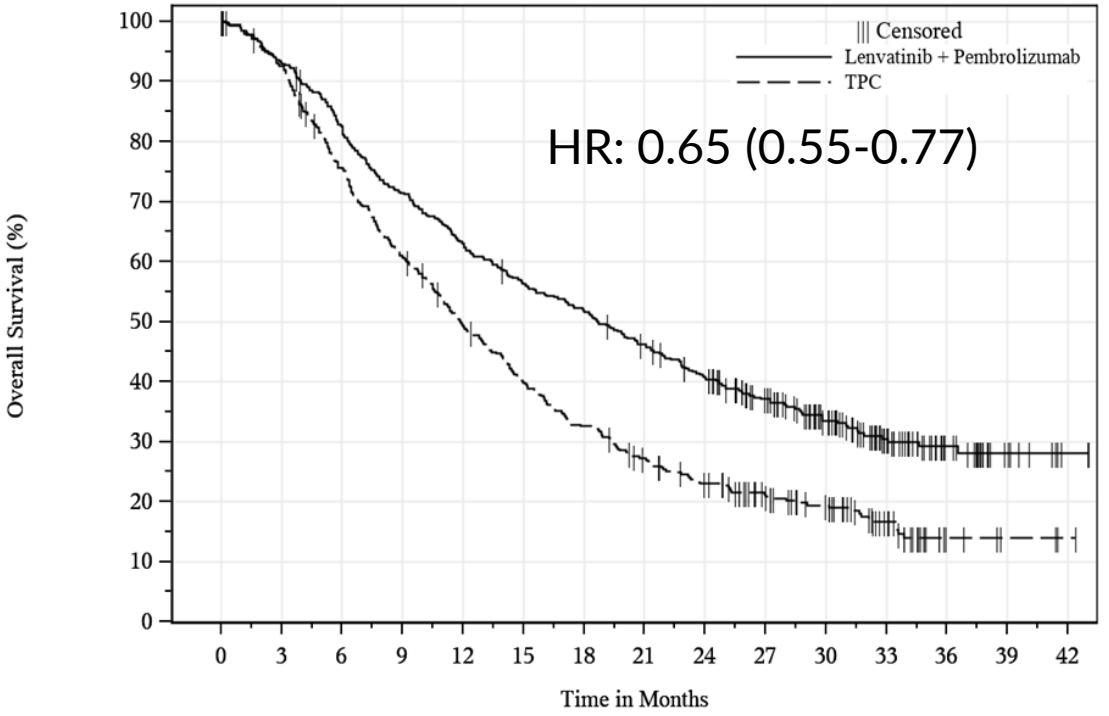
Figure Interim data cut (26 October 2020) – **used in model**



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 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

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.

Are committee satisfied OS from final data cut is similar enough to interim data to be used in model?

Key issue: Clinically distinct subgroups - dMMR and pMMR

Background: KN-775 improvement in PFS and OS for whole population. NICE must first consider **whole population in** marketing authorisation; if not cost-effective, can consider subgroups

ERG: differential results by mismatch repair status: dMMR (16% of population in KN-775) better

- Subgroup analyses exploratory: trial not powered to explore differences, limited follow-up
- Clinical expert: prognosis and treatment likely differ
- No separate cost-effectiveness analysis or model functionality to explore scenario
- Impact on ICER unclear; dMMR maybe lower as better OS

Table Results by mismatch repair status

HR (95% CI)	dMMR (n=130)	pMMR (n=697)
Progression-free survival	0.36 (0.23-0.57)	0.60 (0.50-0.72)
Overall survival	0.37 (0.22-0.62)	0.68 (0.56-0.84)

Company: unclear if subgroup results meaningful because trial not powered for subgroups

- Focus should be whole population as per scope and marketing authorisation
- Significant clinical effectiveness and unmet need in both subgroups
- Requiring mismatch repair status for treatment may limit access if biopsy / testing delayed

Clinical expert: same second-line treatment regardless of MMR status. If response differs cost-effectiveness will differ but no robust data to make this differentiation; not aware of differential prognosis

Does KEYNOTE-775 provide evidence to allow these subgroups to be considered separately?

Key clinical issues

- How would these patients currently be treated in the NHS?
    - Is doxorubicin or paclitaxel monotherapy the most appropriate comparator for 2nd line treatment following platinum in the neoadjuvant or first line setting?
    - Should hormone therapy be considered a comparator?
- Is evidence from KEYNOTE-775 generalisable to the population in the NHS?
- Are committee satisfied that the outcomes for PFS and OS in the final data cut are similar enough to the interim data (October 2020) used in the model?
- Does KEYNOTE-775 provide enough evidence to allow subgroups of patients by mismatch repair status (pMMR and dMMR) to be considered separately?

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key cost-effectiveness issues

Table Key cost-effectiveness issues

Biggest to lowest impact on ICER

Issue	ICER impact
Waning of treatment effect • Company assume no treatment effect waning after stopping PEM+LEN ? Is this appropriate or is assuming some treatment effect waning more appropriate?	Large
Overall survival extrapolation for TPC (comparator) • Choice of extrapolation curve is uncertain ? Which extrapolation curve is preferred?	Large
Age of patients used in model • Company use age of patients from KN-775 in model but ERG clinical experts consider this lower than in UK clinical practice. ? Is evidence from KEYNOTE-775 generalisable to NHS population?	Moderate
Approach to determining utility / health-related quality of life • Company use time to death approach to determine utility / health-related quality of life while ERG prefer progression status-based approach ? Which approach is preferred?	Moderate

Company's model overview

Figure Model structure

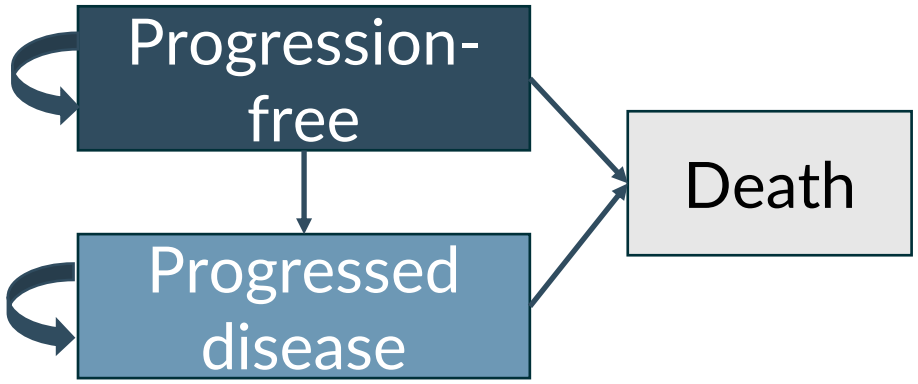


Table Model characteristics

Design	Partitioned survival cohort
Time horizon	40 years
Cycle length	1 week
Stopping rule	24 months for PEM (as per trial)
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 model

Table Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	KEYNOTE-775
Intervention efficacy	KEYNOTE-775; validation of extrapolation from KEYNOTE-146
Comparator efficacy	KEYNOTE-775; 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 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 (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

Summary of company and ERG base case

Table Assumptions in company and ERG base case

Assumption	Company base case	ERG base case	ERG's preferred assumption - impact on ICER
Waning of treatment effect	Model lifetime	As company, but scenario considering waning between 2 and 5 years	
Extrapolation curve for overall survival in TPC arm	Kaplan-Meier + Exponential	Kaplan-Meier + Log logistic	
Patient age	Based on KEYNOTE-775: median age: 63.5 years	Based on clinical input - mean age: 75 years	
Health state utilities	Based on time to death	Based on progression status (progression-free and progressed disease)	

Key issue: Overall survival extrapolation of TPC arm (1/2)

Company selected KM + exponential curve; ERG considers pessimistic, prefers KM + loglogistic

Background

- Company chose KM + log logistic for PEM+LEN extrapolations; ERG broadly agree
- Company selected KM + exponential curve for TPC arm; ERG did not accept and considered pessimistic, preferring KM + log logistic

Figure OS two-piece parametric survival curves for TPC

[redacted]

Key issue: Overall survival extrapolation of TPC arm (2/2)

Company provide ECHO and Heffernan studies to support extrapolation; ERG concerned with studies, prefer clinical expert input

Company trials used to support choice of KM + exponential curve

- ECHO: retrospective multicentre chart review of advanced or recurrent EC with disease progression after a prior systemic therapy 1 July 2016 – 30 June 2019; commissioned by company; UK cohort: n=[redacted], 24 month follow-up
- Heffernan (2022): retrospective review of National Cancer Registration and Analysis Service (England); only 2nd-line treatment; n=999, median 27.4 months follow-up

ERG comments

- ECHO: quality concerns (very little reported) and population different from KN-775: [redacted]
- Heffernan study: better quality and larger but median survival half compared to KN-775 (8.3 months carboplatin and 6.6 months paclitaxel vs 11.9); KN-775 may have overestimated survival in both arms (patient selection or extra monitoring)
- Unclear impact on ICER – difference between survival curves may increase or decrease if modelled independently

Table Trial and modelled survival estimates

Years	Source	1	2	5	10
TPC arm	KEYNOTE-775	[redacted]	[redacted]	-	-
	Company submission base case (exponential)			[redacted]	[redacted]
	ERG base case (log-logistic)				

Does committee prefer extrapolation for TPC chosen by company or ERG?

Key issue: Waning of treatment effect (1/3)

Background

- Company base case assumes no waning of treatment effect i.e. after patients discontinue PEM+LEN at 24 months (or earlier if adverse events) treatment effect maintained over model's 40-year time horizon.
- KN-146 used to validate long-term effectiveness: multi-centre, open-label arm Phase Ib/II basket trial of selected solid tumours, n=108 had pre-treated EC, median follow-up 34.7 months (95% CI: 30.9, 41.2); reported 30% survival at 5 years

Company

- Evidence to substantiate long-term effect (KN-775 and KN-146) but not to substantiate effect waning
- Waning not explored because long-term overall survival in KN-146 showed durable and sustained treatment effect beyond 2-year treatment with PEM+LEN
- Evidence shows sustained OS with a plateau
- Mechanism of immunotherapy supports maintenance of effect after stopping treatment ('immunotherapeutic effect)
- 2 pembrolizumab appraisals did not use waning assumption as longer-term immunotherapeutic effects after stopping treatment demonstrated: TA531 untreated PD-L1-positive metastatic non-small-cell lung and TA357 advanced melanoma after disease progression with ipilimumab

Key issue: Waning of treatment effect (2/3)

KEYNOTE-146 trial used for external validation of no treatment waning assumption: 30% survival at 5 years; same survival in KN-775 final data at 3 years

Figure KN-146 OS data on PEM+LEN

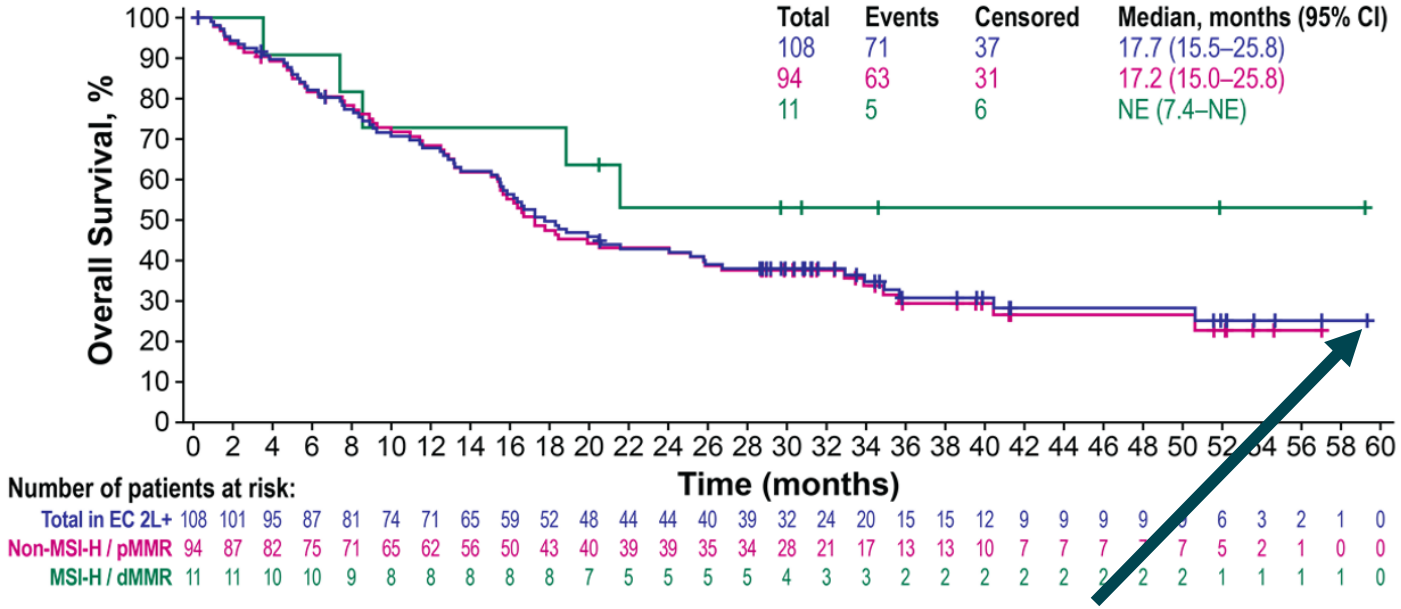
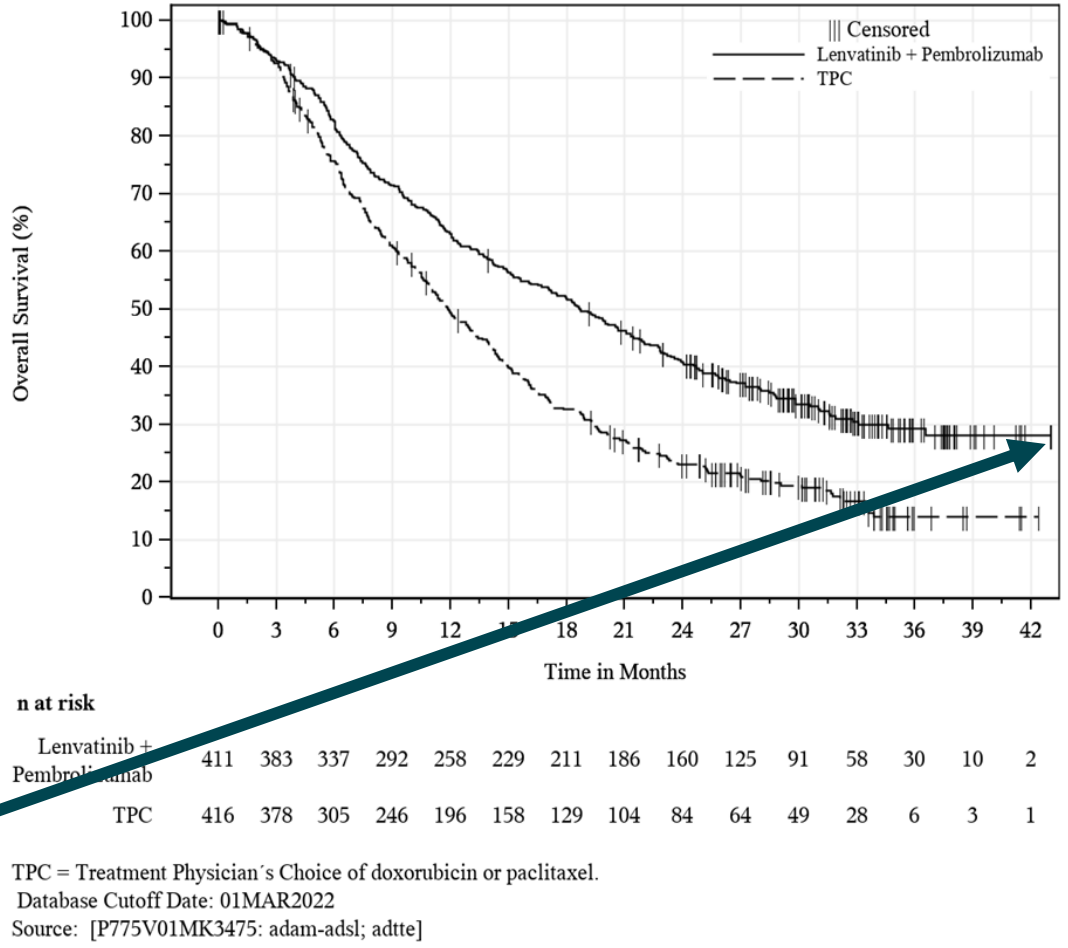


Figure KN-775 OS - final data cut (1 March 2022)



KN-146 PEM+LEN:
30% survival at 5 years

KN-775 PEM+LEN arm:
30% survival at 3 years

NICE

Key issue: Waning of treatment effect (3/3)

ERG comments

- Survival at 5 years likely lower in clinical practice vs KN-146: considerable censoring, few at risk by 28 months
- Clinical input: little data on effect of waning, reasonable to assume gradual waning after stopping treatment, some patients will relapse / have disease progression
- Not appropriate to justify with other appraisals in other disease areas as patient characteristics, drug mechanism, disease types and treatments received will differ
- Company base case and committee preference for dostarlimab appraisal (TA779) included treatment waning
- ERG scenario including waning between 2 and 5 years – results highly sensitive
- ERG did not include in their base case because of lack of data supporting assumption

Clinical expert comments

- No doubt treatment effect is durable, but must be assumed there would eventually be some waning effect

Does the committee accept continuous treatment effect after discontinuation of PEM+LEN?

Key issue: Derivation of utilities (health-related quality of life)

Company use time to death; ERG prefer using progression status

Background

- Company used time to death to derive utilities (used in TA531 and TA357) and captures decrease in utility as patients move closer to death, removing dependence on clinical assessment of progression status

Table Utility values used in ERG model

Health state	Mean utility
Progression-free	[redacted]
Progressed disease	[redacted]

ERG comments

- Company approach 'divorced health related quality of life from disease status in the model' - prefer using progression status (PD, PF) for utilities in line with model structure
- Company scenario varying PFS curve (with same OS) impacted costs but not QALYs – counter-intuitive
- Company scenario using utility values based on progression status increases ICER
- Dostarlimab (TA779) use time to death but included progression status as a covariate in regression

Company

- Time to death approach becoming more common for immunotherapy
- Allows for finer gradations in utility as distinguishes between 4 health states, not just 2 (PF and PD)
- Limited utility assessments in immunotherapy trials after disease progression – time to death approach captures patient utilities across full spectrum including close to death

Do committee prefer time to death or progression status-based approach to determining utility values?

End of life criteria

Company and ERG agree end of life criteria are probably met

Criterion 1 – treatment indicated for patients with a short life expectancy - normally <24 months	**Company:** • TPC arm of KEYNOTE-775 mean survival: interim data cut: 11.4 months • ECHO real-world evidence: median survival [redacted] • Heffernan 2022: real-world evidence: median survival: 10.3 • Model: mean undiscounted survival = [redacted] months • Clinical expectation: ≤ 12 months **ERG:** • ERG base case: mean survival in TPC arm [redacted] years • Clinical input: average life expectancy < 24 months for both sub-populations
Criterion 2 – sufficient evidence to indicate treatment offers an extension to life normally >= 3 months compared to current NHS treatment	**Company:** • KEYNOTE-775 median survival improvement: interim data cut: 6.9 months • Modelling: improvement in mean undiscounted survival = [redacted] months ([redacted] vs [redacted]) **ERG:** Clinical input supports survival gain at least 3 months

Is committee satisfied end of life criteria are met?

Equality

Patient expert:

Two groups disadvantaged by age and sex:

1. **Older people**: majority of women with endometrial cancer are postmenopausal, may have comorbidities/be are disabled (i.e. with obesity). PEM+LEN is effective and kinder treatment than chemotherapy (only 30 minutes and more tolerable than longer infusion)
2. **Younger people**: premenopausal women often diagnosed at advanced stage because healthcare professionals fail to recognise symptoms in younger people and no explicit guidance about referral under 55 years. These women let down by health services and deserve access to best available treatments

Innovation

Company and clinical expert consider PEM+LEN innovative for endometrial cancer; NICE's definition of innovation refers to benefits not captured in model

Company: Uncaptured value:

- no standard of care /very few treatment options
- no NICE Technology Appraisals in endometrial cancer until recently (dostarlimab, TA779)
- incidence of endometrial cancer increasing (by 15.4% since 2010), deaths also increased (by 33.8% since 2013)
- prevalence higher among older people, but many women still working age
- majority with advanced or recurrent disease have expected survival ~12 months
- Women's Health Strategy prioritised improved screening and increase survival rates for at least 5 years after diagnosis

Clinical expert:

- treatment is 'game changer', 'huge step change' – has real tenable meaningful difference in response – 40% compared with 10-15% with current second-line chemotherapy
- this immunotherapy innovative within this tumour type

Does the committee consider any benefits not captured in modelling?

Cost-effectiveness results

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

Summary

If it's accepted that End of Life criteria are met then:

- Company's base case could be **within the range** that would usually be considered a cost-effective use of NHS resources
- ERG's base case could be **within the range** that would usually be considered a cost-effective use of NHS resources.
- ERG's scenario **including treatment waning** is **higher** than what would usually be considered a cost-effective use of NHS resources

Key cost-effectiveness issues

Table Key cost-effectiveness issues

Biggest to lowest impact on ICER

Issue	ICER impact
Waning of treatment effect • Company assume no treatment effect waning after stopping PEM+LEN ? Is this appropriate or is assuming some treatment effect waning more appropriate?	Large
Overall survival extrapolation for TPC (comparator) • Choice of extrapolation curve is uncertain ? Which extrapolation curve is preferred?	Large
Age of patients used in model • Company use age of patients from KN-775 in model but ERG clinical experts consider this lower than in UK clinical practice. ? Is evidence from KEYNOTE-775 generalisable to NHS population?	Moderate
Approach to determining utility / health-related quality of life • Company use time to death approach to determine utility / health-related quality of life while ERG prefer progression status-based approach ? Which approach is preferred?	Moderate

NICE