PREDICTED EFFECTIVENESS OF FIRST- AND SECOND-LINE TREATMENT SEQUENCES IN ADVANCED OR RECURRENT ENDOMETRIAL CANCER

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BACKGROUND

For patients presenting with advanced stage or recurrent endometrial cancer (EC), primary treatment consists of surgery, hormone therapy, radiation and/or systemic therapy (ST).
- EC can be classified based on tumor DNA mismatch repair (MMR) status, classified as either MMR proficient (pMMR), or MMR deficient (dMMR).

Previously, the standard first ST was paclitaxel plus carboplatin (PAC+CARBO)[1], and the standard second ST was lenvatinib plus pembrolizumab (LEN+PEM, primarily for patients with pMMR disease).
- For recurrent pMMR tumors, LEN+PEM is also recommended as first ST where prior platinum-based therapy has been used as neoadjuvant or adjuvant therapy[2].

More recently, immunotherapies (IO) have been incorporated into the treatment paradigm as first ST.
- In 2023, the National Comprehensive Cancer Network treatment guidelines[3] were updated to include IO plus chemotherapy in the preferred systemic therapies for first line and recurrent EC.

Given the change in first ST treatment options, a sequencing model was developed to compare the effectiveness of potential first ST and second ST treatment sequences for the treatment of advanced/recurrent EC.

METHODS

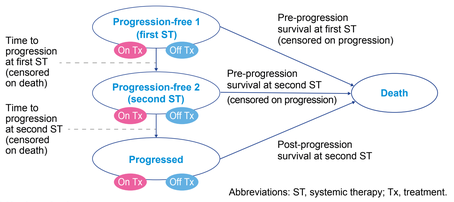
Decision problem

- The population considered was patients presenting with advanced stage or recurrent EC.
- Subgroup analysis was conducted for the pMMR and dMMR populations as some therapies are available for dMMR patients only.
- Modelled first STs included PAC+CARBO, dostarlimab+PAC+CARBO, and PEM+PAC+CARBO.
- Modelled second STs included LEN+PEM, non-platinum chemotherapy, platinum-based chemotherapy, and dostarlimab or PEM monotherapy (dMMR patients only).
- All combinations of first and second ST were considered, with the exception of dostarlimab+PAC+CARBO followed by dostarlimab monotherapy, as dostarlimab rechallenge is expected to be uncommon in practice.
- The outcomes evaluated were mean survival (life years [LY]) and quality-adjusted life years (QALY), and a lifetime time horizon was considered.

Model type and structure

- A multistate survival model was developed to estimate mean survival and QALYs for all considered treatment sequences.
- A cohort of patients is modelled to begin treatment with first ST and transition between health states at a time-dependent rate; in each model cycle, the cohort accrues LYs and QALYs, which are summed at the end of the model time horizon.
- The following health states were modelled to capture transitions between first ST and second ST, progression status and death:
  - Progression-free 1 (progression-free at first ST)
  - Progression-free 2 (progressed at first ST, progression-free at second ST)
  - Progressed (progressed at second ST)
  - Dead.
- Health states based on progression status and treatment line were chosen as progression is an important determinant of quality of life in EC, and treatment line affects the risk of mortality.
- It is assumed that patients transition to second ST immediately on progression from first ST.
- To inform the transitions between health states in the multistate model, five survival curves were generated:
  - Time to progression at first ST (censored on death)
  - Pre-progression survival at first ST (censored on progression)
  - Time to progression at second ST (censored on death)
  - Pre-progression survival at second ST (censored on progression)
  - Post-progression survival at second ST.
- These survival curves were used to estimate the time-dependent probability of transitioning between health states.
- To determine treatment status (on/off treatment) within each health state, two additional curves were used:
  - Time to discontinuation at first ST
  - Time to discontinuation at second ST.
- The relationships between the health states and the survival curves used to estimate the transitions between health states are illustrated in **Figure 1**.
- A cycle length of 28 days was used.

Figure 1: Model structure



Abbreviations: ST, systemic therapy; Tx, treatment.

Clinical data

- In the sequencing model, clinical data were used as inputs for progression and survival. Inputs were informed by patient-level data from LEAP-001 and Study 309/KEYNOTE-775, and reported data from RUBY, NRG-GY018, and other published literature (**Table 1**).
- Where patient-level data were available for a specific treatment, survival curves for each of the five transitions were derived directly; for all other treatments considered, hazard ratios were applied to the reference curves (PAC+CARBO for first ST, non-platinum chemotherapy for second ST).
- Reported overall survival (OS) hazard ratios (HR) were assumed to be applicable to the pre-progression survival and post-progression survival curves; reported progression-free survival (PFS) HRs were assumed to be applicable to the time-to-progression curves.
- In the absence of survival curves for platinum-based chemotherapy as second ST, HRs were calculated between paclitaxel monotherapy (representing non-platinum chemotherapy) and carboplatin monotherapy (representing platinum-based chemotherapy) from Heffernan 2022[10]. The resulting HRs (0.80 for OS; 0.94 for PFS) were applied to non-platinum chemotherapy as second ST (based on the TPC arm in Study 309/KEYNOTE-775) in the model to generate the curves for platinum-based chemotherapy as second ST. Hazard ratios were assumed to be the same for the dMMR and pMMR populations.
- Selected survival distributions were based on statistical fit only.
- As the efficacy of LEN+PEM following IO plus chemotherapy has not been evaluated in randomized clinical trials, efficacy data for LEN+PEM following IO plus chemotherapy was assumed to be the same as for LEN+PEM following chemotherapy alone. Threshold analysis was performed to test the sensitivity of the results to this assumption.
  - The threshold analysis evaluated how much worse the hypothetical efficacy of LEN+PEM after IO plus chemotherapy would need to be (compared with the observed data for LEN+PEM after chemotherapy alone) for the conclusions of the analysis to remain unchanged.

Utility data

- In the LEAP-001 and Study 309 trials, health-related quality of life was measured using EQ-5D questionnaires.
- EQ-5D responses were used to calculate utility values for each health state; in the model, the utility values were applied for the duration of time spent in each health state to calculate QALYs.
- In the progression-free 1 (first ST) state, mean utility values were derived from analysis of patient-level data from LEAP-001; utility values for the progression-free 2 (second ST) and progressed states were modelled using patient-level data from Study 309 (**Table 2**).

Table 1: Data sources used to inform efficacy

Therapy	Source of efficacy data	HR for pMMR population		HR for dMMR population	
First ST		**OS**	**PFS**	**OS**	**PFS**
PAC+CARBO	Patient-level data for PAC+CARBO arm in LEAP-001 trial[4]	Survival curves generated from patient-level data			
PEM+PAC+CARBO	Reported HR vs PAC+CARBO from NRG-GY018 trial[5]	0.79	0.54	0.55	0.30
Dostarlimab+PAC+CARBO	Reported HR vs PAC+CARBO from RUBY trial[6,7]	0.79	0.76	0.32	0.28
Second ST					
LEN+PEM	Patient-level data for LEN+PEM arm in Study 309/KEYNOTE-775[8]	Survival curves generated from patient-level data			
Platinum-based chemotherapy	Calculated adjustment factor vs TPC arm in Study 309/KEYNOTE-775[8]	0.80	0.94	0.80	0.94
Non-platinum chemotherapy	Patient-level data for TPC arm in Study 309/KEYNOTE-775[8]	Survival curves generated from patient-level data			
Dostarlimab monotherapy (dMMR population only)	HR vs LEN+PEM from MAIC of 2L treatments in advanced EC[9]	N/A	N/A	1.01	1.35
PEM monotherapy (dMMR population only)	HR vs LEN+PEM from MAIC of 2L treatments in advanced EC[9]	N/A	N/A	1.42	1.42

Abbreviations: 2L, second line; CARBO, dMMR, mismatch repair deficient; EC, endometrial cancer; HR, hazard ratio; LEN+PEM, lenvatinib plus pembrolizumab; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OS, overall survival; PAC+CARBO, paclitaxel plus carboplatin; PEM+PAC+CARBO, pembrolizumab plus paclitaxel and carboplatin; pMMR, mismatch repair proficient; ST, systemic therapy; TPC, treatment of physician's choice (doxorubicin or paclitaxel).

Table 2: Utility values

Therapy	pMMR population	dMMR population	Source
Progression-free 1 (first ST) utility	0.745	0.717	Mean utility calculated from LEAP-001 patient-level data
Progression-free 2 (second ST) utility, on-treatment	0.726	0.721	Regression model estimated from Study 309 patient-level data
Progression-free 2 (second ST) utility, off-treatment	0.635	0.625	
Progressed disease utility value	0.600	0.592	

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; ST, systemic therapy.

RESULTS

- In pMMR patients, PEM+PAC+CARBO followed by LEN+PEM was associated with the longest survival (2.51 LYs) and the highest number of QALYs (1.89) (**Table 3**).
- In dMMR patients, dostarlimab+CARBO+PAC followed by LEN+PEM had the most LYs (3.33) and QALYs (2.52) (**Table 4**).
- Threshold analysis showed that LEN+PEM remains the optimal second ST (as measured in LYs) even if the efficacy of LEN+PEM following IO therapy is 42% and 12% worse than the efficacy of LEN+PEM following non-IO therapy for dMMR and pMMR, respectively (i.e. HRs of 1.42 or 1.12 are applied to observed data for LEN+PEM).
- In both the pMMR and dMMR populations, PAC+CARBO followed by non-platinum chemotherapy was associated with the fewest LYs (2.08 and 2.27, respectively).

Table 3: Base-case results, pMMR population

Sequence (first ST - second ST)	QALYs	LYs
PEM+PAC+CARBO - LEN+PEM	1.89	2.51
PEM+PAC+CARBO - Platinum-based chemotherapy	1.85	2.45
PEM+PAC+CARBO - Non-platinum chemotherapy	1.79	2.35
Dostarlimab+PAC+CARBO - LEN+PEM	1.79	2.44
Dostarlimab+PAC+CARBO - Platinum-based chemotherapy	1.74	2.37
Dostarlimab+PAC+CARBO - Non-platinum chemotherapy	1.66	2.25
PAC+CARBO - LEN+PEM	1.64	2.29
PAC+CARBO - Platinum-based chemotherapy	1.59	2.21
PAC+CARBO - Non-platinum chemotherapy	1.50	2.08

Abbreviations: dostarlimab+PAC+CARBO, dostarlimab plus paclitaxel plus carboplatin; LEN+PEM, lenvatinib plus pembrolizumab; LY, life year; PAC+CARBO, paclitaxel plus carboplatin; PEM+PAC+CARBO, pembrolizumab plus paclitaxel and carboplatin; pMMR, mismatch repair proficient; QALY, quality-adjusted life year; ST, systemic therapy.

Table 4: Base-case results, dMMR population

Sequence (first ST - second ST)	QALYs	LYs
Dostarlimab+PAC+CARBO - LEN+PEM	2.52	3.33
Dostarlimab+PAC+CARBO - PEM monotherapy	2.46	3.23
Dostarlimab+PAC+CARBO - Platinum-based chemotherapy	2.44	3.20
PEM+PAC+CARBO - LEN+PEM	2.41	3.18
Dostarlimab+PAC+CARBO - Non-platinum chemotherapy	2.41	3.15
PEM+PAC+CARBO - Dostarlimab monotherapy	2.39	3.15
PEM+PAC+CARBO - PEM monotherapy	2.35	3.08
PEM+PAC+CARBO - Platinum-based chemotherapy	2.32	3.05
PEM+PAC+CARBO - Non-platinum chemotherapy	2.29	2.99
PAC+CARBO - LEN+PEM	1.90	2.73
PAC+CARBO - Dostarlimab monotherapy	1.85	2.66
PAC+CARBO - PEM monotherapy	1.75	2.49
PAC+CARBO - Platinum-based chemotherapy	1.70	2.41
PAC+CARBO - Non-platinum chemotherapy	1.61	2.27

Abbreviations: dMMR, mismatch repair deficient; dostarlimab+PAC+CARBO, dostarlimab plus paclitaxel plus carboplatin; LEN+PEM, lenvatinib plus pembrolizumab; LY, life year; PAC+CARBO, paclitaxel plus carboplatin; PEM, pembrolizumab; PEM+PAC+CARBO, pembrolizumab plus paclitaxel and carboplatin; QALY, quality-adjusted life year; ST, systemic therapy.

STRENGTHS AND LIMITATIONS

- A key strength of the analysis is that data have been incorporated across multiple lines of therapy, and the analysis includes newly available treatments.
- A limitation is that the current model relies on individual sources of HRs, which have not been combined into a formal network meta-analysis. In addition, for some treatments, assumptions have been made in the absence of data. In particular, no data is available on the use of LEN+PEM as second ST after prior IO, therefore threshold analysis was performed.

CONCLUSION

- Of the sequences tested, across both the pMMR and dMMR populations, IO plus chemotherapy followed by LEN+PEM is projected to result in the longest survival and the most QALYs.
- PAC+CARBO followed by non-platinum chemotherapy was the least effective of the sequences tested.
- Given the rapidly evolving treatment landscape, further studies are warranted to investigate the effectiveness of LEN+PEM after IO to inform treatment sequencing options in patients with advanced/recurrent EC.

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Disclosures

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