Health-related Quality of Life in Patients with Advanced or Recurrent Endometrial Cancer Who Have Disease Progression on or Following Prior Treatment with a Platinum-Containing Therapy: Analysis of EQ-5D Utility Scores

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Poster No. PCR283

Background

- Endometrial cancer (EC) is the fourth most commonly diagnosed cancer among British women [1] with the burden of EC expected to continue to grow in line with the ageing population [2].
- While prognosis is good in the early stages, the prognosis for advanced or recurrent EC is poor [3].
- Immunotherapies have previously been shown to maintain or improve patient reported outcomes compared to chemotherapy [4].
- Lenvatinib plus pembrolizumab (LEN+PEM) is a novel combination therapy for patients with advanced EC following prior platinum-based systemic therapy.
- In Study 309/KEYNOTE-775, LEN+PEM demonstrated significant improvements in progression-free and overall survival compared with treatment of physician's choice (TPC) of paclitaxel or doxorubicin [5].
- A total of 827 patients were randomly assigned to receive LEN+PEM (411 patients) or TPC (416 patients).
- At the planned interim analysis (database cut-off 26th October 2020), progression-free survival was longer with LEN+PEM than with TPC (hazard ratio for progression or death 0.56; 95% CI, 0.47 to 0.66; P<0.001). Overall survival was longer with LEN+PEM than with TPC (hazard ratio, 0.62; 95% CI, 0.51 to 0.75; P<0.001).
- However, quality of life (QoL) analyses for patients with EC are often under-reported [6], with studies mostly limited to cross-sectional designs [7].
- Here we present an analysis of patient-reported EQ-5D from Study 309/KN-775.

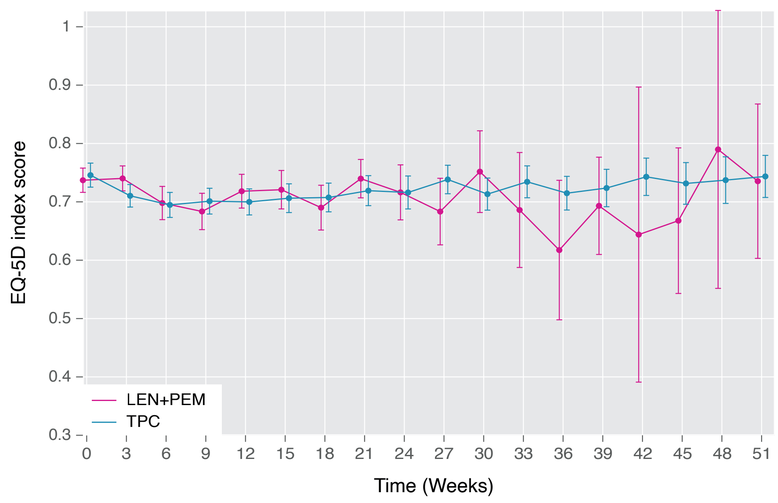
Methods

- Patients were randomized 1:1 to receive LEN 20 mg once daily + PEM 200 mg every 3 weeks (n=411) or TPC (doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly for 3 weeks then 1 week off; n=416).
- EQ-5D-5L was assessed at day 1 of each cycle, at time of discontinuation, and for 4 cycle lengths after discontinuation (either every 21 or 28 days depending on assigned treatment).
- EQ-5D-5L responses were converted to UK EQ-5D-3L utility index scores using the van Hout algorithm [8], hereafter referred to as the EQ-5D utility index score (values of 1 represent full health, values of 0 represent dead).
- Multivariable linear mixed models were used to estimate the association between EQ-5D and covariates considered to influence QoL in patients with advanced EC, including:
  - Proximity to death
  - Baseline EQ-5D
  - Presence of Grade 3–5 treatment-related adverse events (AEs)
  - On/off treatment status
  - Study arm (LEN+PEM or TPC)
  - Covariates defining subgroup membership (mismatch repair-proficient, mismatch repair-deficient).
- Models were compared using the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

Results

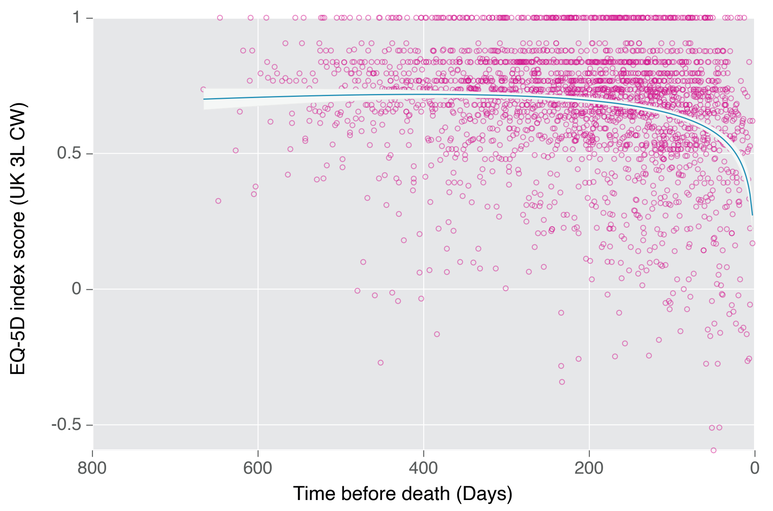
- A total of 7,481 complete EQ-5D observations were available at the database cut-off (26th October 2020).
- At baseline (n=731), the mean EQ-5D index score was 0.75 (standard deviation 0.20) and were similar in each arm (0.75 in both arms).
- There were no differences in EQ-5D index scores between LEN+PEM and TPC groups observed during the study (Figure 1).
- EQ-5D index scores declined as patients approached death (Figure 2).
- 13 alternative model specifications were considered. The lowest (best) AIC and BIC scores were found in three models, with similar AIC and BIC scores, that differed with respect to the inclusion/exclusion of interaction effects between LEN+PEM and on-treatment status, and age. The selected base-case model minimised the BIC and is presented in Table 1.
- In the selected model, post-progression status and experiencing AEs were independently associated with small decrements (–0.020; p<0.001 and –0.029; p<0.001, respectively).
- Increasing proximity to death was associated with worsening EQ-5D, with decline increasing as patients approached death (–0.216; p<0.001 for 0–28 days from death). Differences 183 days and beyond from death were not statistically significant.
- The direct effect for LEN+PEM vs TPC was not statistically significant, however being on treatment (independent of which treatment) was associated with higher EQ-5D than being off treatment (0.084; p<0.001).
- Models which included both time to death and progression status had lower (better) AIC scores than models which included only one of these factors (AIC of -7,245 and -7,103 for base-case model and the same model excluding proximity to death covariates, respectively).

Figure 1: Mean EQ-5D and 95% confidence intervals by study arm and visit



Abbreviations: LEN+PEM, lenvatinib and pembrolizumab; TPC, treatment of physician's choice.

Figure 2: EQ-5D index score vs time before death in patients who died during Study 309, with fractional polynomial line of best fit and corresponding 95% confidence interval (EQ-5D-3L UK tariff)



Abbreviations: UK, United Kingdom; 3L, three-level; CW, crosswalk.

Table 1: EQ-5D based on time-to-death

Parameter	Coefficient	s.e.	z	P>z	95% CI	
Baseline EQ-5D	0.614	0.022	27.61	0.000	0.57	0.66
Post-progression	–0.020	0.006	–3.6	0.000	–0.03	–0.01
Experiencing adverse events	–0.029	0.005	–5.36	0.000	–0.04	–0.02
On treatment (vs off treatment)	0.084	0.007	11.74	0.000	0.07	0.10
0–28 days away from death	–0.216	0.021	–10.39	0.000	–0.26	–0.18
29–91 days away from death	–0.090	0.011	–8.30	0.000	–0.11	–0.07
92–182 days away from death	–0.036	0.009	–3.82	0.000	–0.05	–0.02
183–364 days away from death	–0.006	0.008	–0.75	0.451	–0.02	0.01
Constant	0.192	0.019	9.81	0.000	0.15	0.23

Abbreviations: AE, adverse event; CI, confidence interval; s.e., standard error.

Conclusion

- EQ-5D utility index scores have previously not been reported for this patient population. Of the studies identified that present QoL analyses in EC, none are conducted directly on trial data.
- The design of Study 309/KN-775 included the collection of EQ-5D beyond disease progression, and therefore this permitted exploration of how EQ-5D utility index scores varied based on proximity to death.
- There were no differences in EQ-5D utility index scores between patients treated with LEN+PEM and TPC throughout the study.
- Models which incorporated both proximity to death and progression status performed better than models which only included one of these factors.
- AEs, disease progression, and time to death were associated with statistically significant decrements in utility in patients with advanced EC following prior platinum-based systemic therapy.
- These findings will support future economic evaluations of treatments in advanced EC and comparisons with HRQoL studies across different EC treatment strategies.

Disclosures

This research was funded by Eisai Inc., the manufacturer of lenvatinib. Qi Zhao are Carolyn Bodnar are employees of Eisai Inc. David Trueman and Oliver Burn are employees of Source Health Economics, who were commissioned by Eisai Inc. to perform this analysis.

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Presented at ISPOR EUROPE 2022, 6-9 November 2022, Vienna, Austria