Network Meta-Analysis to Assess Comparative Efficacy of Lenvatinib Plus Pembrolizumab Compared with Other First-Line Treatments for Management of Advanced Renal Cell Carcinoma

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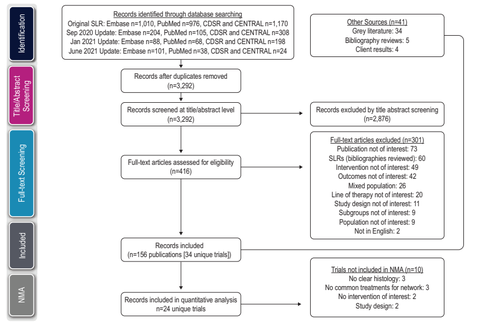
Background and Objectives

- Patients newly diagnosed with metastatic or advanced renal cell carcinoma (aRCC) have a poor prognosis. Despite the availability of approved products, patients receiving first-line (1L) treatment for aRCC have a historical average survival of about 13 months.[1]
- Lenvatinib (LEN) plus pembrolizumab (PEM) received approval in late 2021 from both the US Food and Drug Administration (FDA) and European Medicines Agency for treatment of 1L metastatic or aRCC.
- Given the unmet need for efficacious 1L treatment options, we conducted a systematic literature review (SLR) and network meta-analysis (NMA) to compare the clinical efficacy and safety of LEN + PEM with global 1L comparator treatments in aRCC.

Methods

- An SLR identified 34 randomized controlled trials (RCT), out of which 24 RCTs evaluating 22 interventions in 1L treatments of aRCC were included in the NMA. The flow of inclusion of studies in the SLR and NMA, including the reasons for exclusion of the 10 trials, is described in Figure 1.
- Efficacy outcomes included overall survival (OS), progression-free survival (PFS; as assessed by the FDA censoring criteria to align with the primary endpoint in the LEN + PEM pivotal trial [NCT02811861]), and overall response rate (ORR).
- Safety outcomes assessed were all-cause grade 3+ adverse events (AE), treatment-related grade 3+ AEs, and discontinuation due to AEs.
- Fixed-effects (FE) and random-effects (RE) Bayesian NMAs (where required due to the presence of multiple studies per comparison in case of substantial network heterogeneity) were conducted for each outcome.

Figure 1. PRISMA Diagram



Abbreviations: CDSR = Cochrane Database of Systematic Review; CENTRAL = Cochrane Central Register of Controlled Trial; NMA = network meta-analysis; SLR = systematic literature review

Methods (Cont'd)

- All analyses were carried out by performing Markov Chain Monte Carlo simulations in OpenBUGS (version 3.2.3) and followed the coding and examples described by the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 2.[2]
- Intermediate-/poor risk subgroup analyses were conducted based on the International Metastatic RCC Database Consortium (IMDC) criteria. IMDC and Memorial Sloan Kettering Cancer Center (MSKCC) risk score definitions were assumed equivalent. If both the IMDC and MSKCC definitions were available from a single trial, IMDC was prioritized.

Results

The results of best-fitting NMA models are presented in forest plots below comparing LEN + PEM vs. other treatments for each outcome and scenario of interest. Comparisons are presented via hazard ratio (HR) or odds ratio (OR) with corresponding 95% credible interval; the traditional term 'statistically significant' indicates 95% credible intervals that did not overlap 1.0. The probability that LEN + PEM was ranked higher than a comparator in Monte Carlo simulations is also presented.

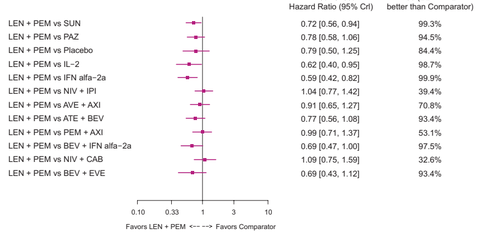
For each outcome, results are presented for intent-to-treat (ITT) population and intermediate-/poor risk subgroup.

OS

ITT Population

- For OS in the ITT population, based on monte carlo simulations LEN+PEM had a 32.6% - 99.9% probability of providing greater benefit than comparators; the OS benefit was statistically significant against three treatments [interferon alfa-2a (IFNα-2a), interleukin-2 (IL-2), and sunitinib].

Figure 2. OS Results – LEN + PEM vs. Other Treatments (ITT Population, FE)



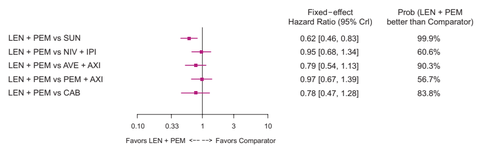
Abbreviations: ATE = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; CAB = cabozantinib; CrI = credible interval; EVE = everolimus; IFN = interferon; IL = interleukin; IPI = ipilimumab; LEN = lenvatinib; NIV = nivolumab; PAZ = pazopanib; PEM = pembrolizumab; SUN = sunitinib

Intermediate-/Poor Risk Subgroup

- For the intermediate-/poor-risk subgroup, LEN+PEM had a 56.7% - 99.9% probability of providing greater OS benefit than comparators; the benefit was statistically significant against sunitinib.

Results (Cont'd)

Figure 3. OS Results – LEN + PEM vs. Other Treatments (IMDC Intermediate/Poor Risk, FE)



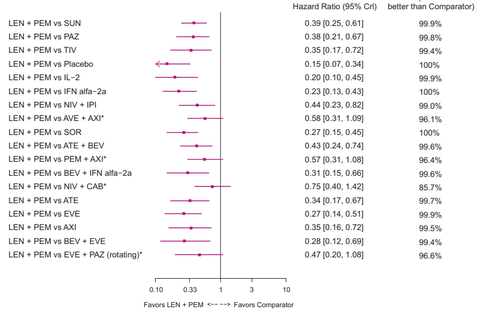
Abbreviations: AVE = avelumab; AXI = axitinib; CAB = cabozantinib; CrI = credible interval; IPI = ipilimumab; LEN = lenvatinib; NIV = nivolumab; PEM = pembrolizumab; SUN = sunitinib

PFS

ITT Population

- For PFS in the ITT population, LEN+PEM had a 85.7% - 100% probability of providing greater benefit than comparators; the PFS benefit was significant in 14 out of 18 comparators.
- Goodness of fit for RE and FE models was similar; an RE model is presented here as a conservative assumption.

Figure 4. PFS (FDA Censoring) Results – LEN + PEM vs. Other Treatments (ITT Population, RE)



*Comparisons of LEN + PEM against these treatments significantly favors LEN + PEM under an FE model.

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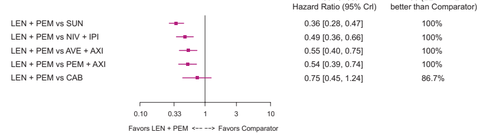
Intermediate-/Poor Risk Subgroup

- For the IMDC intermediate-/poor-risk network, LEN+PEM had a 86.7% - 100% probability of providing greater PFS benefit than comparators; the benefit was statistically significant against four of five comparators.

Figure 5. PFS (FDA censoring) Results – LEN + PEM vs. Other Treatments (IMDC Intermediate/Poor Risk, FE)



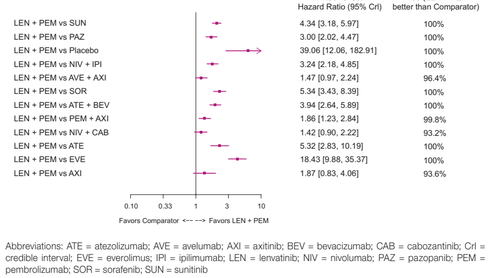
Abbreviations: AVE = avelumab; AXI = axitinib; CAB = cabozantinib; CrI = credible interval; IPI = ipilimumab; LEN = lenvatinib; NIV = nivolumab; PEM = pembrolizumab; SUN = sunitinib

ORR

ITT Population

- LEN+PEM had a 93.2% - 100% probability of providing greater benefit than comparators; the ORR benefit was statistically significant against nine of 12 comparators.

Figure 6. ORR Results – LEN + PEM vs. Other Treatments (ITT Population, FE)

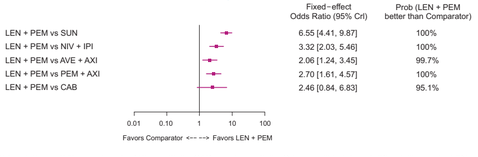


Abbreviations: ATE = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; CAB = cabozantinib; CrI = credible interval; EVE = everolimus; IPI = ipilimumab; LEN = lenvatinib; NIV = nivolumab; PAZ = pazopanib; PEM = pembrolizumab; SOR = sorafenib; SUN = sunitinib

Intermediate-/Poor Risk Subgroup

- LEN+PEM had a 95.1% - 100% probability of providing greater ORR benefit than comparators.

Figure 7. ORR Results – LEN + PEM vs. Other Treatments (IMDC Intermediate/Poor Risk, FE)



Abbreviations: AVE = avelumab; AXI = axitinib; CAB = cabozantinib; CrI = credible interval; IPI = ipilimumab; LEN = lenvatinib; NIV = nivolumab; PEM = pembrolizumab; SUN = sunitinib

Safety outcomes

- LEN + PEM did not significantly affect all-cause grade 3+ AEs compared to the majority of combination treatments reporting this outcome (NIV + CAB, PEM + AXI, BEV + EVE, and BEV + IFN-2a); for treatment-emergent AEs, LEN + PEM was comparable to two combination treatments (NIV + CAB, PEM + AXI).
- For treatment discontinuations due to AEs, LEN + PEM showed significant advantages over two combination treatments (BEV + IFNα-2a, and BEV + EVE) and was statistically non-inferior to all other monotherapies and combination strategies evaluated.
- No comparisons of safety outcomes were possible for the intermediate-/poor risk subgroup on either of the above endpoints (data not shown).

Conclusions

- The NMA results showed that combination therapy with LEN + PEM provided a substantial likelihood of clinically meaningful improvements in OS, PFS, and response outcomes compared with the majority of current global standard-of-care treatment options for patients with treatment-naïve aRCC.
- Comparison of the ITT population and intermediate-/poor subgroup results indicated that the benefit of LEN + PEM on PFS against comparators seen in the ITT population was generally maintained in the subgroup for those comparisons that were still feasible.

References

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2. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-analysis of Randomised Controlled Trials. http://nicedsu.org.uk/wp-content/uploads/2016/03/A-general-linear-modelling-framework-for-pair-wise-and-network-meta-analysis-of-randomised-controlled-trials..pdf.

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