Lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma: a systematic review and cost-effectiveness analysis

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Scientific summary

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Scientific summary

Background

Renal cell carcinoma (RCC) is the most common type of kidney cancer, comprising approximately 85% of all renal malignancies. Patients with advanced RCC (aRCC) have Stage 3 (locally advanced) or Stage 4 (metastatic) disease. A patient's risk of disease progression depends on a number of prognostic risk factors. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is used in NHS clinical practice to categorise patients into one of two groups, namely favourable risk or intermediate/poor risk.

This systematic review and cost-effectiveness analysis has been conducted to inform the following National Institute for Health and Care Excellence (NICE) multiple technology appraisal: lenvatinib with pembrolizumab for untreated aRCC (ID3760). In November 2021, the Medicines and Healthcare products Regulatory Agency approved the use of lenvatinib plus pembrolizumab as a treatment for all patients with untreated aRCC.

Objectives

The comparators listed in the final scope issued by NICE differ depending on the risk of disease progression. The objectives of this assessment were to appraise the clinical effectiveness and cost-effectiveness of lenvatinib plus pembrolizumab versus:

1. cabozantinib and nivolumab plus ipilimumab in the intermediate-/poor-risk subgroup
2. sunitinib, pazopanib and tivozanib in the favourable-risk subgroup
3. sunitinib, pazopanib and tivozanib in the all-risk population.

Clinical and economic systematic review methods

The assessment group (AG) carried out a systematic review of clinical effectiveness evidence following the general principles outlined by the Centre for Reviews and Dissemination (CRD). The review was reported using the criteria recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Searches were conducted between 11 October 2021 and 22 November 2021 in accordance with the general principles recommended by the European Network for Health Technology Assessment. The protocol is registered with PROSPERO (registration number: CRD42021285879). The AG reviewed only randomised controlled trials (RCTs) and full economic analyses identified by the searches. However, the group also considered evidence provided by the manufacturers of lenvatinib (Eisai Ltd) and pembrolizumab (Merck Sharp & Dohme, Whitehouse Station, NJ, USA) provided in submissions to NICE; company submission (CS) reference lists were searched for relevant RCTs.

In line with the final scope issued by NICE, the outcomes considered by the AG were overall survival (OS), progression-free survival (PFS), objective tumour response rate, adverse events (AEs), health-related quality of life (HRQoL), incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained.

Clinical effectiveness results

Direct clinical effectiveness evidence (CLEAR trial)

The AG systematic review included one RCT, the CLEAR trial. The CLEAR trial was a good-quality, phase III, multicentre, open-label RCT (with an ongoing extension phase) that provided evidence for the comparison of the efficacy of lenvatinib plus pembrolizumab versus sunitinib.

Results for all outcomes were assessed at the third interim analysis (August 2020, median OS follow-up of 26.6 months), that is the final data cut-off for PFS. The companies also presented OS results from an updated OS analysis (March 2021, median OS follow-up of approximately 33 months).

At the time of the third interim analysis, the CLEAR trial hazard ratio (HR) results showed statistically significant improvements in PFS and objective tumour response rate for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate-/poor-risk subgroup, the favourable-risk subgroup and the all-risk population. The HR results from the updated OS analysis showed a statistically significant improvement for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate-/poor-risk subgroup and the all-risk population; there were too few events in the favourable-risk subgroup for robust OS conclusions to be drawn. Eisai carried out a treatment-switching analysis to test whether adjusting for the effect of subsequent treatments affected OS results. Results were generated only for the all-risk population and were marked as academic-in-confidence.

Nearly all the patients in the CLEAR trial lenvatinib plus pembrolizumab and sunitinib arms experienced at least one all-grade AE, with more Grade ≥ 3 AEs reported in the lenvatinib plus pembrolizumab arm than in the sunitinib arm. The proportion of patients who discontinued treatment of either lenvatinib or pembrolizumab due to AEs was approximately twice as high as patients who discontinued treatment of sunitinib; the proportion of patients who withdrew treatment of both lenvatinib and pembrolizumab due to AEs was approximately the same as the proportion of patients who withdrew treatment with sunitinib.

Health-related quality of life was measured using three tools, including the EuroQol-5 Dimensions, three-level version questionnaire. When compared with treatment with sunitinib, treatment with lenvatinib plus pembrolizumab did not result in any clinically meaningful differences (as measured by predefined minimally important differences) in HRQoL measured using any of the three tools.

Indirect clinical effectiveness evidence

To compare the effectiveness of lenvatinib plus pembrolizumab versus relevant comparators other than sunitinib, the AG carried out Bayesian HR network meta-analyses. It was decided not to undertake a flexible modelling approach for network meta-analysis (NMA), which relaxes the proportional hazards (PH) assumption, such as fractional polynomial network meta-analyses because interpretation of the estimates provided by these complex modelling techniques can be difficult and results are often not intuitive. While deviance information criterion (DIC) statistics provide an approach to compare the fit of different models, they do not provide information about whether a model is a good fit to the data or whether the estimates generated by the model, including projections of results beyond the follow-up times of trials included in the NMA, are clinically plausible. Furthermore, flexible models, which appear similar according to model fit (i.e. according to DIC statistics), may generate very different long-term survival estimates.

The AG assessed the feasibility of conducting Bayesian HR NMAs for the three population risk groups (intermediate-/poor-risk subgroup, favourable-risk subgroup and all-risk population) for all outcomes listed in the final scope issued by NICE. However, due to limited data availability, it was not possible to carry out NMAs for all outcomes for all three patient risk groups. Further, as networks were sparse, it was only possible to generate results using fixed-effect NMAs.

The AG PFS NMA results for the intermediate-/poor-risk subgroup, the favourable-risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons because of within-trial PH violations or uncertainty regarding the validity of the PHs assumption.

The AG OS NMA results for the intermediate-/poor-risk subgroup suggested that there was a numerical, but not statistically significant, improvement in the OS for patients treated with lenvatinib plus pembrolizumab compared with patients treated with cabozantinib or nivolumab plus ipilimumab. Because of within-trial PH violations or uncertainty regarding the validity of the PH assumption, the AG OS NMA results for the favourable-risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons.

The AG objective tumour response rate NMA results for the intermediate-/poor-risk subgroup suggested that, although treatment with lenvatinib plus pembrolizumab led to a statistically significant improvement in objective tumour response rate compared to treatment nivolumab plus ipilimumab, it did not lead to a statistically significant improvement in objective tumour response rate for the comparison of lenvatinib plus pembrolizumab versus cabozantinib. It was not possible to generate results for the IMDC/MSKCC (Memorial Sloan-Kettering Cancer Center) favourable-risk subgroup due to data limitations. The AG objective tumour response rate NMA results for the all-risk population suggest that treatment with lenvatinib plus pembrolizumab led to a statistically significant improvement in objective tumour response rate versus treatment with sunitinib and versus treatment with pazopanib.

The AG Grade ≥ 3 AE NMA results for the intermediate-/poor-risk subgroup suggested that treatment with lenvatinib plus pembrolizumab led to statistically significantly more Grade ≥ 3 AEs versus treatment with cabozantinib. It was not possible to generate results for the IMDC/MSKCC favourable-risk subgroup. The AG Grade ≥ 3 AE NMA results for the all-risk population suggested that treatment with lenvatinib led to statistically significantly more Grade ≥ 3 AEs versus treatment with sunitinib and versus treatment with pazopanib.

Economic systematic review results

The AG systematic review identified one relevant cost-effectiveness study. This study compared the cost-effectiveness of lenvatinib plus pembrolizumab versus sunitinib (and vs. other treatments). However, the study was undertaken from the perspective of the US healthcare system and generated results only for the all-risk population and included comparators that are not recommended by NICE as treatment options for patients with aRCC. Therefore, the extent to which these results were generalisable to the NHS was unclear.

Cost-effectiveness analysis methods

The Eisai and Merck Sharp & Dohme CSs to NICE included partitioned survival models built in Microsoft Excel. The AG considered that results from both models could be used to inform decision-making but that, in some instances, the companies could have made more appropriate assumptions and parameter choices. The AG did not develop a de novo economic model; instead, it modified the model provided by Merck Sharp & Dohme [referred to as the Merck Sharp & Dohme/Assessment Group (MSD/AG) model]. Neither of the companies produced cost-effectiveness results for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab (intermediate-/poor-risk subgroup) despite both models having the functionality for this comparison. Furthermore, Eisai did not generate any cost-effectiveness results for the favourable-risk subgroup.

The MSD/AG model was populated with OS, PFS and time to treatment discontinuation (TTD) data from the CLEAR trial (lenvatinib plus pembrolizumab versus sunitinib for favourable-risk subgroup and the all-risk population). The AG PFS and OS NMA results were used to estimate effectiveness for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab for the intermediate-/poor-risk population. NICE appraisal committees have concluded that sunitinib and pazopanib are of equivalent effectiveness and that, at best, tivozanib may have a similar effect to sunitinib or pazopanib. These conclusions were based on all-risk population data; the AG has assumed that this assumption holds for the favourable-risk population.

The most important changes made by the AG to the Merck Sharp & Dohme model were different choices for estimating PFS, OS and TTD for the intervention and comparator treatments and for modelling two lines, rather than one line, of subsequent treatment.

Cost-effectiveness analysis results

The AG cost-effectiveness results presented in this report were estimated using list prices. Also, the AG cost-effectiveness results generated using confidential discounted prices were supplied to NICE in a confidential appendix, but cannot be presented here.

For the intermediate-/poor-risk subgroup, the AG base-case cost-effectiveness results suggested that treatment with lenvatinib plus pembrolizumab generated more QALYs versus treatment with cabozantinib and versus nivolumab plus ipilimumab, but at a greater overall cost than either of these two treatments. Using list prices, the incremental cost-effectiveness ratios per QALY gained for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab exceed £100,000.

For the favourable-risk subgroup, the AG base-case cost-effectiveness results suggested that treatment with sunitinib generated more QALYs than treatment with lenvatinib plus pembrolizumab at a lower overall cost, that is treatment with lenvatinib plus pembrolizumab was dominated by treatment with sunitinib (and, using the assumption of equivalent effectiveness, by pazopanib and tivozanib).

The AG carried out extensive one-way sensitivity analyses, scenario analyses and probabilistic sensitivity analyses. Results from these analyses demonstrate that the AG base-case cost-effectiveness results are robust.

Clinical and cost-effectiveness conclusions

Good-quality clinical effectiveness evidence for the comparison of lenvatinib plus pembrolizumab versus sunitinib was available from the CLEAR trial. For most of the AG Bayesian HR NMA comparisons, it was difficult to reach conclusions due to within-trial PH violations or uncertainty regarding the validity of the PHs assumption. However, the data (clinical effectiveness and cost-effectiveness) used to populate the MSD/AG model are relevant to NHS clinical practice and can be used to inform NICE decision-making. The all-risk population comprises patients with intermediate-/poor-risk and patients with favourable-risk disease. The AG cost-effectiveness analyses have focused on the two subgroups, and the AG cost-effectiveness results, generated using list prices for all drugs, show that lenvatinib plus pembrolizumab is less cost-effective than all other treatment options.

Study registration

This study is registered as PROSPERO CRD4202128587.

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