NICE National Institute for Health and Care Excellence

NICE guidance

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Lenvatinib with pembrolizumab is recommended as an option for untreated advanced renal cell carcinoma in adults, only if:

- their disease is intermediate or poor risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria and
- nivolumab with ipilimumab would otherwise be offered and
- the companies provide lenvatinib and pembrolizumab according to the commercial arrangements.

1.2 This recommendation is not intended to affect treatment with lenvatinib with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for untreated advanced renal cell carcinoma includes pazopanib, tivozanib or sunitinib. Cabozantinib, and nivolumab plus ipilimumab, are also recommended for intermediate- or poor-risk cancer as defined by the International Metastatic Renal Cell Carcinoma Database Consortium.

Clinical trial evidence suggests that people having lenvatinib plus pembrolizumab have longer before their disease gets worse than people having sunitinib. Pazopanib and tivozanib are thought to have similar clinical effectiveness to sunitinib, so lenvatinib plus pembrolizumab is also likely to be more effective than them. Results of indirect comparisons are uncertain, but suggest that lenvatinib plus pembrolizumab may increase the time people have before their disease gets worse compared with cabozantinib, and compared with nivolumab plus ipilimumab.

In favourable-risk cancer, all the cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources, so lenvatinib plus pembrolizumab is not recommended for this group. In intermediate- and poor-risk cancer, the cost-

effectiveness estimates are only within the range that NICE considers an acceptable use of NHS resources when nivolumab plus ipilimumab would otherwise be offered. So, lenvatinib plus pembrolizumab is recommended for this group.

2 Information about lenvatinib with pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD), in combination with lenvatinib (Kisplyx, Eisai), is indicated for 'the first-line treatment of advanced renal cell carcinoma in adults'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for pembrolizumab.

Price

2.3 The price of lenvatinib is £1,437 per 30 4-mg or 10-mg capsules (excluding VAT; BNF online accessed July 2022). The price of pembrolizumab is £2,630 per 100 mg per 4-ml vial (excluding VAT; BNF online accessed July 2022).

The companies have commercial arrangements. These make lenvatinib and pembrolizumab available to the NHS with discounts. The sizes of the discounts are commercial in confidence. It is the companies' responsibility to let relevant NHS organisations know details of the discounts.

3 Committee discussion

The appraisal committee considered evidence from a number of sources. See the committee papers for full details of the evidence.

New targeted treatment

People with untreated renal cell carcinoma would welcome a new treatment option

3.1 Advanced renal cell carcinoma has a devastating impact on people's life expectancy and quality of life. Symptoms can vary widely, and depend on the location of metastases, but can include blood in urine, persistent pain in the lower back or side, extreme tiredness, loss of appetite, persistent hypertension and night sweats. Advanced or metastatic renal cell carcinoma has a poor prognosis, with 5-year survival rates of approximately 12%. Patient experts described how the disease can have a devastating impact on a person's quality of life, and that it is not just limited to physical health, but also has a substantial impact on mental health and wellbeing. This is in part because of a lack of available treatment options, leading to people experiencing a lack of hope for the future. The clinical experts highlighted that an effective combined programmed death 1 (PD-1) inhibitor and anti-vascular endothelial growth factor (anti-VEGF) treatment would be welcomed by clinicians and patients to improve outcomes for people with untreated disease. The committee concluded that people with untreated renal cell carcinoma would welcome a new treatment option.

Comparators

Relevant comparators for advanced renal cell carcinoma depend on IMDC risk score

3.2 The companies explained that clinicians assess advanced renal cell

carcinoma on presentation using the International Metastatic Renal Cell Carcinoma (IMDC) risk score. This measure uses a range of criteria to determine whether a person has favourable, intermediate or poor risk of survival. Risk level is determined using 6 risk factors including Karnofsky performance status score, time from original diagnosis, and levels of haemoglobin, serum calcium, neutrophils and platelets. The likelihood of survival is considered intermediate ('intermediate risk') when there are 1 or 2 risk factors, and poor ('poor risk') when there are 3 or more risk factors. People without any risk factors are considered to have 'favourable risk'. This baseline score is used to determine treatment options. The clinical experts explained that people with poor risk scores are more likely to have more aggressive disease, which is more responsive to immunotherapy, and those with favourable risk scores are more likely to have less aggressive disease that is more sensitive to anti-VEGF tyrosine kinase inhibitors (TKIs). The clinical experts explained that the anti-VEGF TKI treatments sunitinib, pazopanib and tivozanib are options for treating advanced renal cell carcinoma irrespective of risk. But for people with intermediate- and poor-risk disease, cabozantinib, and nivolumab plus ipilimumab are treatment options, with nivolumab plus ipilimumab usually preferred for people who are medically fit enough to have it. For people who are not medically fit enough, cabozantinib is more likely to be offered. Nivolumab plus ipilimumab was available through the Cancer Drugs Fund for several years, and was recommended for routine commissioning in February 2022. The Cancer Drugs Fund clinical lead explained that the high number of people currently receiving nivolumab plus ipilimumab in the NHS suggests that it has become an established treatment option. The committee agreed that people will have different treatments according to their IMDC risk scores, and concluded that the most appropriate comparators for lenvatinib plus pembrolizumab differ according to the IMDC risk subgroups. It further concluded that nivolumab plus ipilimumab is a relevant comparator for people with an intermediate or poor IMDC risk score.

Clinical evidence

Key evidence for lenvatinib plus pembrolizumab comes from the CLEAR trial, which is generalisable to NHS clinical practice

3.3 The companies presented evidence from the CLEAR trial, a phase 3 randomised controlled trial of lenvatinib plus pembrolizumab (n=355) compared with sunitinib (n=357) in advanced renal cell carcinoma. The primary endpoint of the trial was progression-free survival, with overall survival, overall response rate, adverse events and health-related quality of life as secondary endpoints. Most of the participants in both groups had previously had a nephrectomy. The trial stratified people by risk score, with approximately two thirds in the intermediate- and poor-risk subgroup, and one third in the favourable-risk subgroup. The clinical experts explained that this represented the split seen in clinical practice, and was also typical of other clinical trials in advanced renal cell carcinoma. They further explained that the baseline characteristics were generally well balanced across the 2 treatment arms and were comparable to those of other clinical trials in the same indication. The committee concluded that the trial was generalisable to NHS clinical practice.

Lenvatinib plus pembrolizumab provides a survival benefit compared with sunitinib

3.4 The companies presented evidence from 2 data cuts: a final progression-free survival data cut from August 2020, and an updated overall survival data cut from March 2021 which had a median overall survival follow up of 33 months. The trial results demonstrated a progression-free survival benefit with lenvatinib plus pembrolizumab over sunitinib in the whole population and across all risk groups. It further demonstrated an overall survival gain for lenvatinib plus pembrolizumab in the all-risk population and in the intermediate- and poor-risk subgroup, but results in the favourable-risk subgroup were less certain. The companies explained that the CLEAR trial was not powered to provide robust analysis for the different risk subgroups, and that the results for the favourable-risk subgroup in particular could not be considered robust. But the committee

recalled that different treatments are available for the different risk groups. The committee concluded that lenvatinib plus pembrolizumab seemed to provide a survival benefit compared with sunitinib.

Subsequent therapy use is generalisable to treatment in the NHS

3.5 More people in the sunitinib arm of the CLEAR trial had subsequent treatment than those in the lenvatinib plus pembrolizumab arm. There were also differences in the types of treatments received between arms; specifically, people in the sunitinib arm were more likely to have a PD-1 inhibitor. The clinical experts commented that this was in line with expected use, because people who do not have a PD-1 inhibitor at first line and are medically fit enough are likely to have one in a later line of therapy. The committee concluded that subsequent therapy use was generalisable to treatment in the NHS.

Indirect treatment comparison

The EAG prefers a proportional hazards network meta-analysis despite uncertainty about whether the proportional hazards assumption holds

3.6 The CLEAR trial provided direct evidence for the comparison of lenvatinib plus pembrolizumab with sunitinib. The committee recalled that previous NICE technology appraisals (tivozanib for treating advanced renal cell carcinoma, cabozantinib for untreated advanced renal cell carcinoma, nivolumab with ipilimumab for untreated advanced renal cell carcinoma and avelumab with axitinib for untreated advanced renal cell carcinoma) had concluded that sunitinib and pazopanib are likely of equivalent clinical effectiveness, and that tivozanib may have a similar effect to sunitinib or pazopanib. The committee agreed with these conclusions. It recalled that for people with intermediate- or poor-risk disease, cabozantinib, and nivolumab plus ipilimumab, are the relevant treatment options. For these comparisons, network meta-analyses (NMAs) were needed. Both companies provided NMAs for the trial outcomes, and the external assessment group (EAG) provided its own NMAs. For time-to-event outcomes presented as hazard ratios (progression-free survival

and overall survival), the EAG assessed the validity of the within-trial progression-free survival and overall survival proportional hazards assumptions, for the intermediate- and poor-risk subgroup and the favourable-risk subgroup, and the all-risk population. It concluded that the proportional hazards assumption was violated for progression-free survival in the intermediate- and poor-risk subgroup. The committee recalled that when the proportional hazards assumption holds, the hazard ratio represents an average of the relative treatment effect during the trial follow-up period, and is proportional over time. When the proportional hazards assumption is violated, the hazard ratio is not applicable to all time points across the trial follow-up periods. This means that estimated hazard ratios may not produce accurate projections of relative survival across treatment arms beyond the observed trial follow-up period. In such cases, alternative flexible modelling approaches that relax the proportional hazards assumption, such as fractional polynomial NMAs, may be used. But the EAG cautioned that the results from these approaches can also be highly uncertain and difficult to interpret. On balance, the EAG preferred a proportional hazards NMA approach for the indirect treatment comparisons.

The companies provided results from fractional polynomial NMAs, but these are highly uncertain

3.7 The 2 companies submitted alternative approaches to the NMAs, including fractional polynomial NMAs, to estimate time-varying hazard ratios in which relative treatment effect changed over time. The companies considered that the proportional hazards assumption was violated for progression-free survival and overall survival in at least 1 of the trials. Their view was that the results from the fractional polynomial NMAs gave more plausible results than the proportional hazards approach preferred by the EAG (see section 3.6). The EAG cautioned that the estimates from these flexible modelling techniques can be unintuitive and difficult to interpret. For example, flexible models that appear similar according to model fit statistics for the observed period may generate very different long-term survival estimates. Because of these limitations, the EAG explained that it does not consider the results of the fractional polynomial NMAs to be appropriate for clinical decision making. Although the results of proportional hazards NMAs when the proportional hazards

assumption is violated are also uncertain, the EAG suggested that they are less uncertain than the results from more flexible models such as fractional polynomial NMAs. The committee considered the relative merits of each approach. It concluded that the proportional hazards assumption had not been shown to be violated and the fractional polynomial NMAs were highly uncertain.

Both approaches are associated with uncertainty, but the results of the EAG's proportional hazards NMAs could be used for decision making

3.8 The EAG's proportional hazards NMA approach demonstrated that there was a numerical advantage in terms of overall survival for lenvatinib plus pembrolizumab compared with cabozantinib and compared with nivolumab plus ipilimumab in the intermediate- and poor-risk subgroup. But neither of these numerical advantages was statistically significant. MSD noted that the EAG had applied a constant hazard ratio for the comparison of lenvatinib plus pembrolizumab against cabozantinib, and suggested that applying time-varying hazards was more appropriate. The committee agreed with the EAG that the proportional hazards assumption was violated for progression-free survival in the intermediate- and poor-risk subgroup, and that the results should be interpreted cautiously. It further noted the need for caution in interpreting the results of the treatment comparison in the favourable-risk subgroup and the all-risk population. The committee concluded that although the proportional hazards and more flexible fractional polynomial approaches to the NMAs were both associated with uncertainty, the EAG's approach was less uncertain and was appropriate for decision making. It noted that both approaches to the indirect treatment comparisons contained significant uncertainty that would need to be considered in its decision making. The committee further concluded that, without additional evidence, the proportional hazards approach preferred by the EAG could be used for decision making but the uncertainty would be taken into consideration.

Economic model

The model structure is suitable for decision making

3.9 The companies both used a partitioned-survival economic model that included 3 health states: pre-progression, post-progression and death. The EAG adapted MSD's model for its analysis, using different assumptions and parameter choices, because it included results for the favourable-risk subgroup. The committee concluded that the model structure was generally appropriate and consistent with models used in other appraisals for advanced renal cell carcinoma.

The EAG's extrapolation of progression-free survival is plausible but uncertain

3.10 To extrapolate progression-free survival in the model, the companies took broadly similar approaches by fitting a series of distributions to the data from the CLEAR trial. They assessed statistical fit using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), with the distribution producing the lowest AIC and BIC taken as being the best-fitting distribution. For the intermediate- and poor-risk subgroup, both companies selected the exponential distribution for lenvatinib plus pembrolizumab, as this had the best statistical fit with both the AIC and BIC and also had a good visual fit to the tail of the Kaplan–Meier curve. The EAG agreed with this selection. For cabozantinib, Eisai and the EAG used the hazard ratio from their respective NMAs applied to the extrapolation for lenvatinib plus pembrolizumab. MSD considered that the hazard ratio from the EAG's analysis was implausible because it overestimated median progression-free survival for cabozantinib when compared with median progression-free survival from the CABOSUN trial (which compared cabozantinib against sunitinib in people with advanced renal cell carcinoma and intermediate- or poor-risk disease). MSD believed that the hazard ratio from its fractional polynomial NMA was a more clinically plausible estimate, being slightly closer to the median progression-free survival for cabozantinib from CABOSUN. The EAG disagreed with the rationale of MSD's criticism, because it is not methodologically appropriate to make a naive treatment comparison

across different clinical trials. The EAG repeated its view that the uncertainty in extrapolating survival using fractional polynomial NMAs is greater than the uncertainty associated with using a proportional hazards approach that assumes a constant hazard ratio, even if the proportional hazards assumption may be violated. For the comparison of lenvatinib plus pembrolizumab against nivolumab plus ipilimumab, the EAG used the hazard ratio from its NMA. For the favourable-risk subgroup, the companies and the EAG selected survival curves using the same methodological approach, and agreed on the appropriateness of the selections. The committee noted MSD's view that the fractional polynomial NMA time-varying hazard ratio should be preferred over the EAG's fixed effects proportional hazards NMA. It concluded that the EAG's extrapolations for progression-free survival were clinically plausible, but that there was some uncertainty because of the limitations of the NMAs.

The EAG's extrapolation of overall survival in the intermediate- and poor-risk subgroup is suitable for decision making

3.11 For overall survival, the companies and EAG used the same approach for curve selection as described for progression-free survival (see section 3.10). For the intermediate- and poor-risk subgroup, the companies selected independent exponential distributions for lenvatinib plus pembrolizumab and sunitinib despite it not being the best fitting according to AIC statistics. They did this because these were the most conservative overall survival extrapolations, which also aligned better with long-term survival predictions from clinical experts. Other distributions in which the curves did not cross were the Weibull, log-normal, and log-logistic. The companies explained that the log-normal and log-logistic distributions produced overly optimistic extrapolations for the intermediate- and poor-risk subgroup, and so were discounted. The EAG was satisfied that the companies' approach was methodologically appropriate, but felt that the exponential distribution was not a good visual fit to the observed data from CLEAR. When the EAG examined the CLEAR trial's overall survival Kaplan–Meier data, it observed that the lenvatinib plus pembrolizumab overall survival hazard was constant beyond 50 weeks. So, it considered that the companies' choice of an exponential distribution was appropriate, but that

Kaplan–Meier data should be used up to the point that censoring and small numbers of events made the data too uncertain (120 weeks). The EAG then appended the exponential distribution (based on the hazard between 50 and 150 weeks) to the CLEAR trial overall survival Kaplan–Meier data from 120 weeks onwards. The companies felt that this approach was not methodologically robust, particularly because the cut-off point was not well justified or clinically validated, and so seemed arbitrary. They felt the extrapolation should use all the available data to be clinically plausible, not just extrapolating from the tail end of the data, which is the most uncertain data from which to extrapolate. For the extrapolation of overall survival for cabozantinib, the companies expressed the same criticism of the EAG approach as they had for progression-free survival (see section 3.10). Specifically, they said that the EAG's NMA overestimated overall survival for cabozantinib when contrasted with the median overall survival seen in the CABOSUN trial, and that the estimate from MSD's fractional polynomial NMA gave a more plausible result that should be considered for decision making. The committee noted again the EAG's view that the rationale of this critique was not methodologically robust. The committee concluded that the EAG's NMAs for overall survival in the intermediate- and poor-risk subgroup were appropriate for decision making.

The EAG's extrapolation of overall survival is not clinically plausible in the favourable-risk subgroup

3.12 For the favourable-risk subgroup, there was considerable uncertainty around the validity of the CLEAR trial overall survival estimates because of the low number of events experienced by these people. The companies explained their view, informed by clinical expert opinion, that long-term overall survival for lenvatinib plus pembrolizumab would not be expected to fall below that of sunitinib. So, they considered that any model in which this occurred during extrapolation was clinically implausible. MSD had selected the exponential distribution for extrapolating overall survival for lenvatinib plus pembrolizumab, based on clinical expert opinion. The EAG explained that the exponential distribution had the lowest AIC score, was a poor fit to the CLEAR trial overall survival Kaplan–Meier data, and was likely overoptimistic. The EAG considered that survival in the favourable-risk subgroup should be

no worse than survival in the intermediate- and poor-risk subgroup. Of the 7 distributions considered by MSD, 4 produced 10-year survival estimates that were above the EAG 10-year survival estimates for the intermediate- and poor-risk subgroup. Of these, the EAG selected the log-logistic distribution because it had the highest AIC and BIC scores. For estimating overall survival for sunitinib, the EAG explained that the 2 distributions (gamma and Weibull) selected by MSD were equally plausible; the EAG preferred the gamma distribution. The committee noted MSD's view that this distribution was optimistic for sunitinib relative to historical benchmarks, but that any other distribution would only increase this survival prediction even further. MSD agreed with the EAG that survival projections for the favourable-risk population should be higher than for the intermediate- and poor-risk subgroup, to preserve clinical plausibility. The committee noted that the Kaplan–Meier plots for the observed overall survival data for lenvatinib plus pembrolizumab in the favourable-risk subgroup were very close to that for sunitinib, with the curves almost overlaid. So, the overall survival extrapolation for sunitinib was not clinically plausible because the gamma distribution likely overestimated survival for sunitinib compared with lenvatinib plus pembrolizumab. The committee agreed that this discrepancy might be because of low patient numbers and the low number of events experienced by people in the favourable-risk subgroup, and concluded that the overall survival extrapolations in the favourable-risk subgroup were not clinically plausible.

Utility values in the economic model

A time-to-death approach for modelling health-related quality of life is appropriate for decision making

3.13 Both companies used EQ-5D-3L data from the CLEAR trial to estimate utility values. Eisai used the health state utility value approach, with treatment-specific utilities in the progression-free health state. MSD used a time-to-death approach in its base case, and explored the impact of using the health state utility approach in a scenario analysis. The EAG preferred the MSD time-to-death approach and incorporated it in its base case. It considered it to best reflect the health-related quality of life

of long-term survivors, in the context of limited EQ-5D-3L data to inform post-progression utility values. The committee noted that CLEAR had a lot of long-term survivors who had moved on from first-line treatment and were still doing well on a subsequent treatment. This was particularly true of the sunitinib arm, in which people would be offered an immunotherapy at second line, compared with people in the lenvatinib plus pembrolizumab arm who would not have another immunotherapy. In this context, a health state utility value approach may be biased because of the different treatments. The committee noted that MSD's and the EAG's scenario analyses showed that the choice of utility approach did not substantially affect the cost-effectiveness estimates. It concluded that because of the wide heterogeneity in people whose disease progressed in the CLEAR trial, particularly in relation to subsequent treatments, the time-to-death approach was acceptable for decision making.

Subsequent treatment costs after cabozantinib are likely to be underestimated in the model

3.14 After treatment with cabozantinib in the intermediate- and poor-risk subgroup, people are usually offered either nivolumab monotherapy or other standard oral second-line options. Clinical advice to the EAG was that 60% of patients treated with cabozantinib would have nivolumab and 40% of patients would have a TKI. MSD's clinical advisers considered that 80% would have nivolumab. The clinical experts stated that in the NHS, it may be that even more than 80% would be offered nivolumab. This is because immunotherapy treatments offer people the greatest chance of disease control when used as early as possible, and so only people who are unable to tolerate nivolumab would be offered an anti-VEGF TKI. The committee concluded that the treatment costs for the cabozantinib arm in the model are likely to be underestimated.

A 2-year stopping rule is in line with the evidence and appropriate for pembrolizumab

3.15 The economic model used Kaplan–Meier data from the CLEAR trial to determine when people stopped treatment with pembrolizumab. The trial protocol stated that a 24-month treatment duration with pembrolizumab

(no more than 35 3-weekly treatment cycles) should be used. People would sometimes miss a treatment cycle, for example because of feeling too fatigued, and this led to some people remaining on treatment beyond the 2-year time point. The committee noted that this assumption depended on what happens in clinical practice, and whether a 35-cycle or 2-year cut off is used. The Cancer Drugs Fund clinical lead explained that the NHS can implement the committee's preference as expressed in the economic model. The clinical experts agreed and suggested that 35 cycles is likely easier to monitor from a clinical perspective and allows a full course of treatment to be provided if a treatment cycle is missed, but that 2 years is the more commonly used cut-off point. The committee concluded that, in line with the trial evidence, it is appropriate for the economic model to limit the use of pembrolizumab to 2 years.

The waning of any treatment effect is uncertain

3.16 The committee was aware that the EAG base case did not include waning of treatment effect for pembrolizumab. The EAG had concluded that pembrolizumab treatment is limited to 2 years but lenvatinib treatment can continue after this time point. The EAG acknowledged that although there is uncertainty in the long-term treatment effect of pembrolizumab, it is not possible to plausibly separate out any potential waning of treatment effect. Comments received during draft guidance consultation noted potential inconsistencies with previous appraisals. The EAG noted a similar challenge with the long-term effect of nivolumab with ipilimumab, in which ipilimumab is restricted to 4 cycles of treatment but nivolumab treatment can continue. The EAG provided a number of scenarios around the assumption for treatment discontinuation and long-term benefits. The committee concluded that a treatment waning effect is plausible but uncertain.

Cost-effectiveness estimates

Because of the uncertainty, an acceptable ICER is around £20,000 per QALY gained

3.17 NICE's guide to the methods of technology appraisal notes that above a

most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the high levels of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.

Lenvatinib plus pembrolizumab is only cost effective when compared with nivolumab plus ipilimumab

3.18 The committee considered the cost-effectiveness results for the all-risk population, the intermediate- and poor-risk subgroup, and the favourable-risk subgroup. Because of the included confidential patient access schemes, the ICERs cannot be reported here. In the all-risk population and the favourable-risk subgroup, the cost-effectiveness estimates were above the range that NICE considers an acceptable use of NHS resources when lenvatinib plus pembrolizumab was compared with all relevant comparators. In the intermediate- and poor-risk subgroup, the cost-effectiveness estimates were above the range that NICE considers an acceptable use of NHS resources when lenvatinib plus pembrolizumab was compared with cabozantinib, but were within the range when it was compared with nivolumab plus ipilimumab. After consultation, the company that produces nivolumab and ipilimumab (BMS) provided additional analysis of 60-month follow-up data from the CheckMate 214 trial that compared nivolumab plus ipilimumab with sunitinib. The EAG incorporated this additional progression-free survival, overall survival and time-to-treatment-discontinuation data into its NMAs. The committee noted that this did not affect the cost-effectiveness results.

Equality

There are no equality issues

3.19 No equality issues were identified during the appraisal.

Conclusion

Lenvatinib plus pembrolizumab is recommended in intermediate- or poor-risk disease when nivolumab plus ipilimumab would otherwise be offered

3.20 The committee concluded that lenvatinib plus pembrolizumab was likely more effective than the treatments currently offered in the NHS for renal cell carcinoma, but that the most plausible cost-effectiveness estimates were above what NICE considers an acceptable use of NHS resources for most comparators. The exception was people with intermediate- or poor-risk disease who would otherwise be offered nivolumab plus ipilimumab. The committee recalled that further treatment options would be appreciated, and recalled earlier statements from the clinical experts that people with poor risk scores are more likely to have more aggressive disease, which is more responsive to immunotherapy. It further recalled that for people with intermediate- and poor-risk disease, treatment options are cabozantinib, and nivolumab plus ipilimumab, with nivolumab plus ipilimumab usually preferred for people who are medically fit enough to have it. So, lenvatinib plus pembrolizumab is recommended in intermediate- or poor-risk disease when nivolumab plus ipilimumab would otherwise be offered.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated advanced renal cell carcinoma and the doctor responsible for their care thinks that lenvatinib plus pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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