NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer

1 Recommendations

1.1 Pembrolizumab with pemetrexed and platinum chemotherapy is recommended as an option for untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive mutations. This is only if:

- it is stopped at 2 years of uninterrupted treatment, or earlier if the disease progresses and
- the company provides pembrolizumab according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for pembrolizumab with pemetrexed and platinum chemotherapy (pembrolizumab combination) for untreated, metastatic, non-squamous NSCLC (NICE technology appraisal guidance 557).

Standard care for tumours that have no EGFR-positive or ALK-positive mutations depends on PD-L1 status. If tumours are PD-L1 negative, or PD-L1 positive with a tumour proportion score below 50%, pemetrexed with carboplatin or cisplatin (pemetrexed platinum chemotherapy) may be offered. If tumours are PD-L1 positive with a score of at least 50%, pembrolizumab monotherapy is offered.

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Pembrolizumab combination would be offered whether or not tumours are PD-L1 positive, and regardless of tumour proportion score.

Clinical evidence collected while pembrolizumab combination was in the Cancer Drugs Fund shows that people having pembrolizumab combination for up to 2 years are likely to live longer than those who have pemetrexed platinum chemotherapy. There are no clinical trials directly comparing pembrolizumab combination with pembrolizumab monotherapy. But an indirect comparison suggests that for people with PD-L1 positive tumours with a tumour proportion score of at least 50%, there is no difference in how long people having pembrolizumab combination live compared with pembrolizumab monotherapy.

Pembrolizumab combination meets NICE's criteria to be considered a life-extending end of life treatment compared with pemetrexed platinum chemotherapy but does not meet the criteria when compared with pembrolizumab monotherapy.

The cost-effectiveness estimates for pembrolizumab combination are within what NICE considers to be an acceptable use of NHS resources, if it is stopped at 2 years. So, it is recommended.

2 Information about pembrolizumab with pemetrexed and platinum chemotherapy

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) with pemetrexed and platinum chemotherapy has a marketing authorisation for the first-line treatment of metastatic non-squamous non-small-cell lung carcinoma (NSCLC) in adults whose tumours have no epidermal growth factor (EGFR) receptor or anaplastic lymphoma kinase (ALK)-positive tumour mutations.

Dosage in the marketing authorisation

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

Price

2.3 Pembrolizumab solution for infusion costs £2,630.00 per 100-mg vial (excluding VAT; BNF online, accessed October 2020).

The company has a commercial arrangement (commercial access agreement). This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Merck Sharp & Dohme, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect updated efficacy data from the KEYNOTE-189 study for people with untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC).

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage. It agreed that the model time horizon for the cost effectiveness should increase to 25 years (issue 5, page 8 of technical report). Also, that a 2-year stopping rule for pembrolizumab was appropriate.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, page 8), and took these into account in its decision making. The committee discussed the following issues, which were outstanding after the technical engagement stage:

- The choice of parametric models to predict overall survival.

- The choice of parametric models to predict time on treatment.
- The continued duration of treatment benefit if pembrolizumab with pemetrexed and platinum chemotherapy (pembrolizumab combination) is stopped at 2 years.
- The choice of utility values.

Clinical management

Pemetrexed with carboplatin or cisplatin and pembrolizumab monotherapy are the most relevant comparators

3.1 In the original appraisal pemetrexed with carboplatin or cisplatin chemotherapy and pembrolizumab monotherapy were considered appropriate comparators. Chemotherapy using docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy is rarely used in NHS clinical practice for treating non-squamous metastatic NSCLC. NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic NSCLC recommends pembrolizumab monotherapy only for people whose tumours express at least a 50% PD-L1 tumour proportion score. Since the original appraisal was published, NICE has recommended atezolizumab combination for metastatic non-squamous NSCLC for people whose tumours express less than a 50% PD-L1 tumour proportion score. In line with NICE's methods guide for technology appraisals, the original scope was not changed for this Cancer Drugs Fund review. Therefore, atezolizumab was not considered as a comparator because it was recommended after the original guidance was published. The committee concluded that the appropriate comparators are:

- pemetrexed with carboplatin or cisplatin (referred to as pemetrexed platinum chemotherapy), with or without pemetrexed maintenance therapy
- pembrolizumab monotherapy for people whose tumours express at least a 50% PD-L1 tumour proportion score (referred to as the high PD-L1 subgroup).

Clinical effectiveness

For the intention-to-treat population pembrolizumab combination is more clinically effective than pemetrexed platinum chemotherapy

3.2 There were additional data from KEYNOTE-189, which was a randomised controlled phase 3 trial. The trial included 616 people with untreated advanced or metastatic non-squamous NSCLC regardless of PD-L1 tumour proportion score who were randomised to pembrolizumab combination or pemetrexed platinum chemotherapy. Two thirds of the trial population had tumours with a PD-L1 tumour proportion score of at least 50% while the rest had tumours with a PD-L1 tumour proportion score below 50%. The results showed that pembrolizumab combination was associated with a statistically significant improvement in overall survival compared with pemetrexed platinum chemotherapy (hazard ratio 0.56, 95% confidence interval 0.46 to 0.69). The committee concluded that for the intention-to-treat (ITT) population, that is, people with untreated advanced or metastatic non-squamous NSCLC regardless of PD-L1 tumour proportion score, pembrolizumab combination was clinically effective compared with pemetrexed platinum chemotherapy.

For the high PD-L1 subgroup overall survival is similar for pembrolizumab combination and pembrolizumab monotherapy

3.3 Pembrolizumab monotherapy is standard care in clinical practice in the NHS for people with untreated NSCLC and at least a 50% PD-L1 tumour proportion score (see section 3.1). The company presented updated results for this subgroup from an indirect treatment comparison based on data from:

- KEYNOTE-189 (see section 3.2)
- KEYNOTE-021 Cohort G, a trial including 267 people comparing pembrolizumab combination with platinum-based chemotherapy

- KEYNOTE-042, a trial including 1,274 people with PD-L1 positive tumours comparing pembrolizumab monotherapy with platinum-based chemotherapy
- KEYNOTE-024, a trial including 305 people with high PD-L1 tumour proportion score comparing pembrolizumab monotherapy with platinum-based chemotherapy.

Although the point estimate suggested better overall survival for pembrolizumab combination compared with pembrolizumab monotherapy, the 95% credible interval showed that this was not statistically significant. The exact results were academic in confidence so cannot be reported here. The committee concluded that overall survival was similar for people with at least a 50% PD-L1 tumour proportion score who had pembrolizumab combination compared with pembrolizumab monotherapy.

Overall survival and time on treatment

The 5-year survival rate for pembrolizumab combination is between that estimated by the company and the ERG

3.4 The company used a log-logistic distribution to extrapolate overall survival for both pemetrexed platinum chemotherapy and pembrolizumab combination in the model for the ITT population. This is because for the comparator arm this distribution gave the most clinically plausible estimates for overall survival at 5 years and had the best statistical fit. The ERG used a generalised gamma distribution for both arms because this distribution fitted the pembrolizumab combination arm better. Both the log-logistic and the generalised gamma distributions gave clinically plausible 5-year survival estimates for the comparator arm of between 5% and 11%. The clinical experts explained that people who have immunotherapy such as pembrolizumab second line have a 5-year survival rate of approximately 13%. They reasoned that people who have pembrolizumab combination earlier in the pathway will benefit from this treatment, so the

5-year survival rate is likely to be greater than 13%. They agreed that the overall survival in the pembrolizumab combination arm could be somewhere between what was predicted in the generalised gamma and log-logistic extrapolation (the estimates are confidential and cannot be reported here). The committee concluded that the ERG's overall survival estimates for the ITT population were pessimistic but the company's estimates were too optimistic.

Retreatment with pembrolizumab combination might affect the overall survival seen in the trial but is not NHS clinical practice

3.5 Some people in the pembrolizumab combination arm of KEYNOTE-189 were still having treatment after 2 years. It was not clear, however, how many people were still having combination therapy and how many were having pemetrexed platinum chemotherapy only. The Cancer Drugs Fund clinical lead explained that people could have pembrolizumab for up to 35 cycles, which could extend beyond 2 years. The company confirmed that some people did have further treatment with pembrolizumab alone or in combination with other therapies. From the data presented by the company it was unclear how many people this was. Retreatment with pembrolizumab is not NHS clinical practice. The committee noted that the overall survival curves for the pembrolizumab combination arm included the effect of retreatment. Therefore, the potential survival benefits in the trial might not be seen in NHS practice. The clinical experts explained that retreatment with pembrolizumab or similar drugs could improve survival prospects in this population, especially if they had a good response to initial treatment. The committee noted that retreatment with pembrolizumab could affect the overall survival outcome for the pembrolizumab combination arm. Also, it was aware that the costs of retreatment were not included in the model. The committee concluded that results from the trial might not be generalisable because retreatment with pembrolizumab is not NHS clinical practice.

Overall survival estimates for the high PD-L1 subgroup are uncertain

3.6 To estimate overall survival for the comparison with pembrolizumab monotherapy in the high PD-L1 subgroup the company used the same approach as for the ITT population (see section 3.4). Therefore, the committee could not establish whether the company's approach was the most appropriate approach, because no alternatives were provided by the company and ERG. The committee recalled that results from the indirect treatment comparison showed no statistically significant difference in the overall survival estimates for pembrolizumab combination compared with monotherapy (see section 3.3). It concluded that the overall survival estimates for the high PD-L1 subgroup were uncertain.

Generalised gamma distribution is appropriate for extrapolating time on treatment

3.7 The company extrapolated time on treatment in the model using the exponential distribution, which assumes a proportional hazard for both arms (that is, at every timepoint the difference between the time on treatment curves for the 2 treatment arms is the same). The company did not provide evidence to support this assumption. The ERG explained that the proportional hazards assumption might not hold because:

- the cumulative hazard plot showed a clear change in gradient of the pembrolizumab combination curve at just over 100 weeks
- pembrolizumab combination and pemetrexed platinum chemotherapy have different mechanisms of action.

The ERG preferred the generalised gamma distribution which does not require the proportional hazards assumption and had a better statistical fit. The ERG noted that the choice of distribution had a minimal effect on the cost-effectiveness estimates. The committee concluded that the generalised gamma distribution was the most appropriate for extrapolating time on treatment.

Gradually decreasing treatment effect from 3 years after treatment is started until 5 years is appropriate

3.8 In the company's base-case model the relative treatment effect of pembrolizumab combination remained constant for 5 years from the start of treatment. At 5 years the hazard in the pembrolizumab combination arm dropped to match the hazard in the comparator arm. The clinical experts explained that this was implausible and did not reflect their clinical experience with pembrolizumab and other similar drugs. The committee agreed that, although it was biologically plausible for the treatment effect to continue after stopping pembrolizumab, its course and duration was uncertain. The committee concluded that the ERG's approach of a gradually decreasing treatment effect from 3 years after treatment started until 5 years, at which point the treatment effect matches that of pemetrexed platinum chemotherapy, was appropriate for decision making.

Health-related quality of life

The approach taken in the original appraisal to estimate utility values is still preferred

3.9 The company did not present new data on health-related quality of life. In the original appraisal the committee preferred to combine the time-to-death approach with progression-based utility values. From the 2 approaches presented by the ERG the committee chose to calculate utilities using progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for people who are likely to live less than 360 days. This was included in the committee's preferred assumptions in the original appraisal. The committee concluded that its preference from the original appraisal had not changed.

End of life

Pembrolizumab combination meets NICE's end of life criteria when compared with pemetrexed platinum chemotherapy

3.10 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The updated KEYNOTE-189 data showed that life expectancy for the ITT population, that is, regardless of PD-L1 tumour proportion score, was less than 24 months and that pembrolizumab combination extended life by at least 3 months. Therefore, the committee concluded that pembrolizumab combination met the end of life criteria and could be considered a life-extending treatment at the end of life when compared to pemetrexed platinum chemotherapy.

Pembrolizumab combination does not meet NICE's end of life criteria when compared with pembrolizumab monotherapy

3.11 Standard care for people with at least a 50% PD-L1 tumour proportion score is pembrolizumab monotherapy (see section 3.1). The clinical expert explained that many people who have pembrolizumab monotherapy die within 2 years, but some people can live longer. Results from KEYNOTE-024 showed that median overall survival with pembrolizumab monotherapy was 30.0 months (95% confidence interval 18.3 months to not reached). The committee noted that the company's indirect treatment comparison showed no statistically significant difference in overall survival between pembrolizumab combination and pembrolizumab monotherapy in people with at least a 50% PD-L1 tumour proportion score (see section 3.33.3). Therefore, the additional 3-month survival gain for pembrolizumab combination therapy compared with pembrolizumab monotherapy was uncertain. The committee concluded that pembrolizumab combination did not meet the end of life criteria when compared with pembrolizumab monotherapy for people with a high PD-L1 tumour proportion score.

Cost effectiveness

Pembrolizumab combination is considered cost effective compared with pemetrexed platinum chemotherapy

3.12 For the ITT population the most plausible incremental cost-effectiveness ratios (ICERs) were within the range NICE considers a cost-effective use of NHS resources. The committee agreed that its preferred approach to modelling would:

- include an overall survival extrapolation for pembrolizumab combination between that of the log-logistic and generalised gamma distributions (see section 3.4)
- extrapolate time on treatment using the generalised gamma distribution (see section 3.7)
- include a gradual decrease of treatment effect from 3 years after the start of treatment until 5 years, when it matches pemetrexed platinum chemotherapy (see section 3.8)
- calculate utility values using progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for people who are likely to live less than 360 days (see section 3.9)
- include costs of retreatment with pembrolizumab combination (see section 3.5)
- include dose intensities and costs from the updated results
- include a 2-year stopping rule.

Using the committee's preferred assumptions the range of plausible ICERs for pembrolizumab combination compared with pemetrexed platinum chemotherapy was below £50,000 per quality-adjusted life year (QALY) gained. Because of confidential discounts for pembrolizumab, pemetrexed maintenance and subsequent therapies, the exact ICERs cannot be reported here. Because the end of life criteria are met for the ITT population, the committee concluded that

the cost-effectiveness estimates for pembrolizumab combination compared with pemetrexed platinum chemotherapy are within the range NICE normally considers a cost-effective use of NHS resources.

For the high PD-L1 subgroup the most plausible ICERs are within the range NICE considers cost effective

3.13 Using the committee's preferred assumptions for the ITT population (see section 3.12) the ICER for pembrolizumab combination compared with pembrolizumab monotherapy was between £20,000 and £30,000 per QALY gained. Because of confidential discounts for pembrolizumab and follow-on therapies, the exact ICERs cannot be reported here. The committee concluded that the cost-effectiveness estimates for pembrolizumab combination compared with pembrolizumab monotherapy for people with at least a 50% PD-L1 tumour proportion score are within the range NICE normally considers a cost-effective use of NHS resources.

Other factors

3.14 No equality or social value judgement issues were identified.

Conclusion

Pembrolizumab combination is recommended with a 2-year stopping rule

3.15 Pembrolizumab combination is more clinically effective than pemetrexed platinum chemotherapy. There is no statistically significant difference in the clinical effectiveness of pembrolizumab combination compared with monotherapy. The most plausible estimates of cost effectiveness for pembrolizumab combination compared with either comparator were within what NICE considers a cost-effective use of NHS resources. Therefore, pembrolizumab combination is recommended as an option for untreated, metastatic, non-squamous NSCLC with a 2-year stopping rule.

4 Implementation

4.1 Section 7(6) 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 person has untreated, metastatic, non-squamous non-

small-cell lung cancer and the doctor responsible for their care thinks that pembrolizumab with pemetrexed and platinum chemotherapy is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
January 2021

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

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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Technical lead

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