NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab–relatlimab for untreated unresectable or metastatic melanoma in people 12 years and over

Technology appraisal guidance
Published: 7 February 2024

www.nice.org.uk/guidance/ta950

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 Nivolumab–relatlimab is recommended as an option for untreated advanced (unresectable or metastatic) melanoma in people 12 years and over, only if:

- nivolumab–relatlimab is stopped after 2 years of treatment, or earlier if the cancer progresses, and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with nivolumab–relatlimab that was started in the NHS before this guidance was published. Anyone 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. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

People who have advanced melanoma usually have nivolumab plus ipilimumab. When this is not suitable, people can have nivolumab or pembrolizumab. In clinical practice, most people stop having these treatments after 2 years, and this is the assumption the company has made in its economic model. So nivolumab–relatlimab will also be stopped after 2 years.

Clinical trial evidence shows that people who have nivolumab–relatlimab have longer before their cancer gets worse than people having nivolumab. There is no direct evidence comparing nivolumab–relatlimab with pembrolizumab or with nivolumab plus ipilimumab. But, indirect comparisons suggest that people who have nivolumab–relatlimab also have longer before their cancer gets worse than people having pembrolizumab. Compared with nivolumab plus ipilimumab, the evidence suggests that nivolumab–relatlimab is as effective.

The indirect evidence also suggests that people who have nivolumab–relatlimab live longer than people who have the other treatments. But there's not enough data yet to be certain about this.

Because of the uncertainty in the clinical-effectiveness evidence, the cost-effectiveness estimates need to be towards the lower end of the range that NICE considers an acceptable use of NHS resources. The estimates for the comparison with pembrolizumab and with nivolumab plus ipilimumab, which are the treatments most commonly used in the NHS, are at or below this lower end. So nivolumab–relatlimab is recommended.

2 Information about nivolumab–relatlimab

Marketing authorisation indication

2.1 Nivolumab–relatlimab (Opdualag, Bristol Myers Squibb) is indicated for 'the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for nivolumab–relatlimab.

Price

2.3 Nivolumab–relatlimab costs £6,135 per 16 mg/ml vial (company submission).

2.4 The company has a commercial arrangement. This makes nivolumab–relatlimab 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 evaluation committee considered evidence submitted by Bristol Myers Squibb, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical management

Treatment pathway

3.1 Current standard care for untreated unresectable or metastatic melanoma is immunotherapy with nivolumab plus ipilimumab, if it's suitable for the person. Suitability is based on comorbidities, performance status, the risk of treatment toxicity, if the toxicity can be tolerated, the presence of symptomatic brain metastases, and tumour biology. If nivolumab plus ipilimumab is unsuitable or unacceptable, people are offered pembrolizumab or nivolumab monotherapy. The Cancer Drugs Fund lead said that pembrolizumab is used more often in the NHS because it is given only every 6 weeks, whereas nivolumab is given every 4 weeks.

Positioning of nivolumab–relatlimab

3.2 The company proposed that nivolumab–relatlimab is an alternative for when nivolumab plus ipilimumab is not suitable or acceptable. That is, for people who would normally be offered pembrolizumab or nivolumab monotherapy. The clinical experts agreed that people for whom the nivolumab plus ipilimumab combination treatment is unsuitable are the main population who would be offered nivolumab–relatlimab. This is because it is better tolerated than nivolumab plus ipilimumab. They also agreed a small proportion of people eligible for nivolumab plus ipilimumab, who did not want the toxicity of ipilimumab, may choose nivolumab–relatlimab. They emphasised that patient choice is an important factor in the treatment pathway for untreated unresectable or metastatic melanoma. A submission from a patient organisation said that, if

recommended, nivolumab–relatlimab would provide a valuable new option. This is because people who cannot have nivolumab plus ipilimumab could still benefit from a combination treatment, but without the toxicity associated with ipilimumab in the current combination. The committee concluded that nivolumab–relatlimab would mainly be an alternative for people who would normally have monotherapy in the NHS. But it also concluded that, given its marketing authorisation for people 12 years and over with advanced, unresectable metastatic melanoma, it could also be an alternative to nivolumab plus ipilimumab.

Clinical effectiveness

RELATIVITY-047

3.3 Direct comparative evidence was from the RELATIVITY-047 trial, which compared nivolumab–relatlimab (n=355) with nivolumab monotherapy (n=359). It was a phase 2/3 randomised, double-blind trial in people over 12 years with untreated metastatic or unresectable melanoma (stage 3 or 4). The primary outcome was progression-free survival (PFS), assessed by blinded independent central review (BICR). Secondary outcomes were overall survival, objective response rate, duration of response and adverse events. Investigator-assessed PFS was an exploratory outcome. Median BICR-assessed PFS was 10.2 months (95% confidence interval [CI] 6.5 to 14.8) in the nivolumab–relatlimab arm compared with 4.6 months (95% CI 3.48 to 6.44) in the nivolumab arm (hazard ratio [HR] 0.81; 95% CI 0.67 to 0.97). Investigator-assessed PFS was also longer in the nivolumab–relatlimab arm than in the nivolumab arm, although the difference was not statistically significant. The company marked exact figures and confidence intervals for investigator-assessed PFS confidential, so they cannot be reported here. For overall survival, at the October 2022 data cut, median overall survival was not reached in the nivolumab–relatlimab arm, and was 33.2 months in the nivolumab arm. The committee concluded that nivolumab–relatlimab was more effective than nivolumab.

Generalisability

3.4 The EAG considered that people in the RELATIVITY-047 trial did not represent everyone in the NHS who would be offered nivolumab–relatlimab. It said that the populations enrolled into RELATIVITY-047 and the CheckMate-067 trial (which assessed nivolumab plus ipilimumab) were very similar. It added that it had clinical advice that the RELATIVITY-047 population represented people having treatment in the NHS for whom combination immunotherapy was suitable and acceptable. So it suggested that the trial did not provide evidence for when combination immunotherapy is not suitable or acceptable. That is, for people who are currently offered monotherapy with pembrolizumab or nivolumab in the NHS. The clinical experts said that the population in the RELATIVITY-047 was similar to the population seen in clinical practice. That is, it contained a mixture of people who could have combination immunotherapy and people who could not. One clinical expert said that the main difference between the trial and clinical practice was that they saw people with brain metastases, but they were excluded from the trial. The company pointed out that the RELATIVITY-047 trial started in 2018, and NICE recommended nivolumab plus ipilimumab in 2016. Because of this, in practice people may have chosen to have combination immunotherapy if it was suitable for them, rather than enrolling in the trial. The clinical experts agreed that this was possible. The committee concluded that the available trial evidence could be generalised to people having monotherapy and people having combination therapy.

People 12 to 18 years old

3.5 The EAG questioned whether the trial data, which was only in adults, could be applied to 12 to 18 year olds, who are included in the marketing authorisation for nivolumab–relatlimab. Only 0.2% of new melanoma cases are in people under 20 and, according to a clinical expert, very few are enrolled in clinical trials. NICE's guideline on melanoma says that treatment should be the same for children and adults. The clinical expert said that melanoma tends to behave in a biologically similar way in people of different ages. They said that, although few 12 to 18 year olds are enrolled in clinical trials, clinical practice is to use currently available treatment, which has a comparable effect in adults. The clinical expert added that it would be unreasonable to exclude them from treatment. The Cancer Drugs

Fund lead said that in practice, if approved, nivolumab–relatlimab would be available to 12 to 18 year olds. The committee concluded that the available trial data could be generalised to this patient group.

Indirect treatment comparisons

3.6 After technical engagement, the company accepted the EAG's constant HR network meta-analyses (NMAs) for comparative evidence for nivolumab–relatlimab against nivolumab plus ipilimumab and against pembrolizumab. These used PFS and overall survival from RELATIVITY-047 plus data from:

- Checkmate-067, a phase 3 randomised, double-blind trial comparing ipilimumab with nivolumab plus ipilimumab, and with nivolumab
- CheckMate-069, a phase 2 randomised double-blind trial comparing ipilimumab with nivolumab plus ipilimumab
- KEYNOTE-006, a phase 3 randomised open-label trial comparing ipilimumab with pembrolizumab.

The EAG's constant HR NMAs used investigator-assessed PFS from RELATIVITY-047. This is because the other trials in the NMAs only reported investigator-assessed PFS so the EAG argued that using BICR-assessed data from RELATIVITY-047, as the company's original NMAs had, introduced inconsistency. The results of the EAG's constant HR NMAs favoured nivolumab–relatlimab for comparisons with pembrolizumab and nivolumab.

3.7 The EAG considered its own constant HR NMAs the best comparative data for nivolumab–relatlimab against pembrolizumab. But it was concerned that there was evidence that the proportional hazards assumption was violated (that is, the hazards were not proportional over time). There was also evidence that the proportional hazards assumption was violated for the comparisons of nivolumab-relatlimab against nivolumab and against nivolumab plus ipilimumab. So the EAG said the reliability of these NMAs was limited. The company also did adjusted indirect treatment comparisons (ITCs) for nivolumab–relatlimab compared with nivolumab plus ipilimumab and nivolumab using patient-level data from the

RELATIVITY-047 and CheckMate trials. The hazard ratio for progression or death for nivolumab–relatlimab was 1.07 (95% CI 0.87 to 1.31) compared with nivolumab plus ipilimumab. The EAG was satisfied that the company's adjusted ITCs were methodologically robust so it considered that they were the best source of data for the comparison with nivolumab plus ipilimumab. The committee concluded that these ITC results were suitable for decision making.

Pembrolizumab efficacy

3.8 The company was not able to include pembrolizumab in the ITCs because it did not have access to patient-level data from the KEYNOTE-006 trial. It accepted the value from the EAG's constant HR NMA for this comparison. The EAG preferred to assume, based on clinical advice, that pembrolizumab's efficacy and safety was similar to nivolumab's. A committee member questioned why the EAG had not accepted the company's fractional polynomial time-varying NMAs, which addressed the issue of the proportional hazards violation. The EAG said it did not consider that the time-varying NMAs were appropriate because it did not agree with how the company had chosen the fractional polynomial model. It added that, even if the proportional hazards assumption was not an issue, it did not believe that there was enough similarity between the trials to include pembrolizumab in the network. For example, the KEYNOTE-006 (pembrolizumab) trial did not exclude people with brain metastases, and 34% of participants had already had 1 line of systemic treatment for advanced disease. The clinical experts said that in clinical practice it's accepted that pembrolizumab and nivolumab are interchangeable in terms of efficacy and safety. The committee concluded that it preferred to use the EAG's assumption that pembrolizumab and nivolumab had the same efficacy for decision making.

Economic model

Company's modelling approach

3.9 The company submitted a partitioned survival model with a 40-year time horizon. It had 3 health states: progression-free, progressed disease and death. The EAG

considered that the model structure was reasonable given the relatively immature overall-survival data. The committee concluded that the model structure was generally appropriate.

Stopping rule

3.10 In its model, the company assumed that treatment with all first-line immunotherapies would stop at 2 years. This was in line with the economic model used for NICE's guideline on melanoma. But in RELATIVITY-047 (nivolumab–relatlimab compared with nivolumab) and CheckMate-067 (nivolumab plus ipilimumab compared with nivolumab), some people stayed on treatment after 2 years. So they continued to benefit from treatment, although the costs of this treatment were not captured in the model. The EAG considered that because of this, the stopping rule should not be applied in the model. The committee noted that the stopping rule had the biggest impact on the cost effectiveness results, and that the EAG's base case, which removed the stopping rule, resulted in a cost effectiveness estimate that could not be considered a cost-effective use of NHS resources. The clinical experts said that in clinical practice they routinely look at stopping treatment after 2 years. If the melanoma is well controlled, they stop treatment to reduce the risk of toxicity. They said that if someone is in good partial remission but they find active disease, they might continue treatment but this is a very small minority. One clinical expert added that the people who were still on treatment at 2 years in the trials would mostly be in remission and would want to stop treatment at that point. The Cancer Drugs Fund lead said that in practice healthcare professionals can treat until disease progression but often discuss stopping immunotherapies after 2 years. The committee heard that the 2-year stopping rule is part of commissioning practice. The Cancer Drugs Fund lead added that if nivolumab–relatlimab was recommended then the 2-year stopping rule would apply. The committee concluded that a stopping rule at 2 years was appropriate.

Proportion of people having second-line treatment

3.11 After first-line immunotherapy, people with a BRAF mutation can have second-line systemic treatment with BRAF and MEK inhibitors (dabrafenib plus trametinib,

or encorafenib plus binimetinib). Otherwise people can have ipilimumab, best supportive care, or they can enter a clinical trial. The company and EAG agreed that the proportion of people who have second-line treatment, and which treatment they have, is affected by the rates of treatment-related toxicity from their first-line treatment. But the EAG estimated that more people on first-line nivolumab–relatlimab would go on to have second-line treatment than the company did. The EAG considered that the company's figure was an underestimate and that, as a result, the cost-effectiveness results were optimistic and favoured treatment with nivolumab–relatlimab. The company pointed out that in the RELATIVITY-047 trial nivolumab–relatlimab had a higher rate of discontinuation because of grade 3 treatment-related adverse events than nivolumab. It said this was why it had modelled a smaller proportion of people on first-line nivolumab–relatlimab going on to second-line treatment than people who had first-line monotherapy. The clinical experts said that in their experience around 40% to 50% of people went on to second-line treatment. They pointed out that in practices with younger populations able to tolerate treatment better, the figure was likely to be at the upper end of the estimate. Practices with older populations with comorbidities were likely to be at the lower end. The committee agreed that the company's approach was reasonable but could be considered an optimistic scenario.

Distributions of second-line treatments: if monotherapy is the comparator

3.12 The EAG and company also differed on the systemic treatments that people would have after first-line nivolumab–relatlimab. They agreed on the distributions of dabrafenib plus trametinib and encorafenib plus binimetinib if people have a BRAF mutation. But they did not agree on the proportion of people having best supportive care or entering clinical trials, or the proportion of people without a BRAF mutation having ipilimumab. The clinical experts did not think that the EAG's estimates reflected clinical practice for people having monotherapy who would be offered nivolumab–relatlimab. In particular, they said that the proportion of second-line ipilimumab was too high and they preferred the company's estimates for second-line treatment for these people. Both clinical experts estimated that in clinical practice only around 20% of people who had nivolumab or pembrolizumab would have second-line ipilimumab, which was slightly lower

than the company's estimates. The committee noted that in the company's model more people had ipilimumab second line after first-line nivolumab or pembrolizumab than first-line nivolumab–relatlimab. Based on what it heard from the clinical experts, the committee agreed that it needed to see new analyses. So, it requested adjustments to the assumptions around second-line treatment distributions for the monotherapy comparisons using the company's second-line estimates and the clinical experts' estimates. The EAG did new cost-effectiveness analyses, which modelled the proportion on second-line ipilimumab in the monotherapy arms as the same as in the nivolumab–relatlimab arm. It provided scenarios in which the proportion was 24.59% (the company's original figure) and 20% (the clinical experts' estimate). The remaining people who did not have a BRAF mutation were modelled to have best supportive care or enter a clinical trial. The committee concluded that the EAG's new analyses were appropriate for decision making when monotherapy with nivolumab or pembrolizumab is the comparator.

Distributions of second-line treatments: if nivolumab plus ipilimumab is the comparator

3.13 The committee noted that people having nivolumab–relatlimab when nivolumab plus ipilimumab is also suitable, could have ipilimumab second line. It concluded that the EAG's original analyses were appropriate for decision making when combination therapy with nivolumab plus ipilimumab is the comparator.

Uncertainty over long-term overall survival

3.14 Median overall survival on nivolumab–relatlimab was not reached by the October 2022 data cut-off in the RELATIVITY-047 trial, so long-term survival estimates are uncertain. The company modelled long-term survival, which included the proportion of people reaching population background mortality – that is, their risk of dying was the same as the general population. But the way it was modelled meant people on nivolumab–relatlimab survived longer than people on the comparator drugs. The company's modelling approach also assumed that a proportion of people reached background mortality after their disease had progressed. This was at least twice as high in people who had

nivolumab–relatlimab first line than with the comparator drugs. The EAG pointed out that evidence from the CheckMate 067 trial suggests that background mortality was reached on nivolumab and nivolumab plus ipilimumab at around 5 years. So modelling a proportion of people as statistically 'cured' is plausible. But the EAG said that the figures modelled by the company implied that:

- people with worse disease could get a better response on second-line treatments after progression than on first-line treatments before progression
- the proportion statistically 'cured' after second-line treatment differs substantially depending on first-line treatment.

The EAG modelled alternative figures that assumed pembrolizumab's post-progression and overall survival was the same as nivolumab's. But it added that, within the constraints of a partitioned survival model, and without more mature overall data to inform a statistical cure model, it could not provide more reliable overall-survival estimates.

3.15 The clinical experts said that it was plausible for some people to reach background mortality after progression. They added that immunotherapies could affect overall survival in a way that does not correlate with progression-free survival. In particular, people who could have a second-line immunotherapy were likely to have better long-term survival. But, the committee noted that in RELATIVITY-047 fewer people who had first-line nivolumab–relatlimab in fact had second-line immunotherapy. The clinical experts also agreed that it was plausible for the choice of first-line immunotherapy to influence response after second-line treatment. The committee preferred the EAG's modelled figures because it had previously accepted the assumption that pembrolizumab's efficacy was the same as nivolumab's. But, it concluded that without any longer-term data there was still considerable uncertainty around the overall-survival estimates.

Cost-effectiveness estimates

The committee's preferred assumptions

3.16 Because of confidential discounts for nivolumab–relatlimab and the comparators,

the cost-effectiveness results are commercial in confidence and cannot be reported here. The committee preferred an analysis that included:

- the EAG's assumption that pembrolizumab's efficacy and safety was equivalent to nivolumab's (see section 3.8)
- the company's assumption of a 2-year stopping rule (see section 3.10)
- the company's assumptions for second-line treatments (24.59% of people have ipilimumab) when comparing nivolumab–relatlimab with monotherapies, with a scenario testing the clinical expert's estimate of 20% of people having second-line ipilimumab (see section 3.12)
- the EAG's assumptions for second-line treatments when comparing nivolumab–relatlimab with nivolumab plus ipilimumab (see section 3.12).

  Using the committee's preferred assumptions resulted in incremental cost-effectiveness ratios (ICERs) within the range NICE normally considers a cost-effective use of NHS resources. But the committee noted the substantial uncertainty around the overall-survival modelling. Above a most plausible ICER of £20,000 per quality-adjusted life year gained, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider the degree of certainty and uncertainty around the ICER. Because of the uncertainty around overall survival, the committee concluded that an acceptable ICER would be at the lower end of the range normally considered to be cost effective.

Other factors

Equality

3.17 The committee did not identify any equality issues.

Innovation

3.18 The committee considered if nivolumab–relatlimab was innovative. It did not identify additional benefits of nivolumab–relatlimab not captured in the economic modelling. So the committee concluded that all additional benefits of nivolumab–relatlimab had already been taken into account.

Conclusions

3.19 The committee concluded that the overall-survival modelling was very uncertain, which meant there was uncertainty in the cost-effectiveness estimates. Because of this, it also concluded that an acceptable ICER would be at the lower end of the £20,000 to £30,000 range normally considered a cost-effective use of NHS resources. When its preferred assumptions were incorporated, the cost-effectiveness estimates for nivolumab–relatlimab were at the lower end or under the acceptable range of ICERs for the comparisons with pembrolizumab and with nivolumab plus ipilimumab. For the comparison with nivolumab, the cost-effectiveness estimates were closer to the upper end of the range. But, pembrolizumab is the preferred choice for a monotherapy (see section 3.1), and nivolumab is less often used in the NHS. So, the committee concluded that nivolumab–relatlimab could be recommended for treating advanced (unresectable or metastatic) melanoma in people aged 12 years and older.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance 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 draft guidance.

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 unresectable or metastatic melanoma and the doctor responsible for their care thinks that nivolumab–relatlimab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

James Fotheringham
Vice chair, technology appraisal committee A

NICE project team

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

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Accreditation