NICE National Institute for Health and Care Excellence

NICE guidance

Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments

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

This guidance replaces TA869.

1 Recommendations

1.1 Teclistamab is recommended as an option for treating relapsed and refractory multiple myeloma in adults, only after 3 or more lines of treatment (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on the last treatment. It is only recommended if the company provides teclistamab according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with teclistamab 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

The main treatment that is used for relapsed (has come back) and refractory (has stopped responding to treatment) multiple myeloma after 3 or more lines of treatment is pomalidomide plus dexamethasone. If pomalidomide plus dexamethasone is not suitable, panobinostat plus bortezomib and dexamethasone can be used. If the myeloma is refractory to 5 or more treatments, selinexor plus dexamethasone can be used. For this evaluation, the company only compared teclistamab with treatments that are used after 3 or more lines of therapy. This does not include everyone who it is licensed for.

Teclistamab has not been directly compared in a clinical trial with pomalidomide plus dexamethasone, panobinostat plus bortezomib and dexamethasone, or selinexor plus dexamethasone. An indirect comparison suggests that teclistamab increases how long people have before their cancer gets worse and how long they live compared with these treatments.

When considering the condition's severity, and its effect on quality and length of life, the most likely estimates are within the range that NICE considers an acceptable use of NHS resources. So, teclistamab is recommended after 3 or more lines of treatment (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the

myeloma has progressed on the last treatment.

2 Information about teclistamab

Marketing authorisation indication

2.1 Teclistamab (Tecvayli, Johnson & Johnson Innovative Medicine) is indicated 'as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for teclistamab is £775.14 per 10-mg vial and £3,952.78 per 90-mg vial (excluding VAT, BNF online accessed June 2024).

2.4 The company has a commercial arrangement. This makes teclistamab available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson Innovative Medicine, 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.

The condition

Details of the condition

3.1 Multiple myeloma is an incurable and progressive condition that has a substantial impact on survival and quality of life. Complications of multiple myeloma can be significant, debilitating and painful. The relapsing-remitting nature of the condition has a huge psychological impact, because people are aware that treatment options and life expectancy reduce with each relapse. The patient organisation submission stated that there is a clear need for innovative treatments that deliver deep, durable responses for people with relapsed and refractory multiple myeloma. One patient expert explained how myeloma symptoms affected her physical health and made her feel very tired. She needs care from her husband and had to stop working as a nurse. The committee recognised the substantial impact multiple myeloma has on survival and quality of life. It acknowledged the unmet need for effective treatments for people with multiple myeloma who have already had several treatments.

Teclistamab

3.2 Teclistamab is a bispecific monoclonal antibody that binds to the B-cell maturation antigen on plasma cells, plasmablasts and multiple myeloma cells, as well as to the CD3 receptor on T-cells. The patient organisation submission highlighted that because teclistamab has a newer mechanism of action, it may overcome treatment resistance. The patient expert at the committee meeting explained that they had exhausted all treatment options offered on the NHS,

having had myeloma for almost 24 years. They stated that since starting teclistamab they have had a huge improvement in their physical health and quality of life compared with how they felt while having previous treatments. The patient and clinical experts highlighted that teclistamab does not have to be used in combination with corticosteroids, unlike other treatments for multiple myeloma, including pomalidomide. This is a distinct advantage of teclistamab because of the side effects associated with corticosteroids. The patient organisation submission also explained that prolonged corticosteroid treatment can be physically and mentally tough on people with multiple myeloma and their families, and has a huge impact on their quality of life. The committee concluded that teclistamab is an innovative medicine that could provide a novel treatment option for people with relapsed and refractory multiple myeloma.

Clinical management

Treatment pathway, positioning and comparators

3.3 According to the marketing authorisation, people having teclistamab must have had 3 or more treatments including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody. The condition must have also progressed on the last treatment. The company submission provided a comparison with pomalidomide plus dexamethasone, a fourth-line treatment. The EAG had clinical advice that pomalidomide plus dexamethasone was the most relevant comparator for this evaluation, given the company's positioning after 3 or more lines of treatment. The clinical experts at the committee meeting agreed that pomalidomide plus dexamethasone is the most frequently used fourth-line treatment option for relapsed and refractory multiple myeloma. At the second committee meeting, the clinical experts and NHS England explained that if pomalidomide plus dexamethasone is not suitable, or people have already had pomalidomide, panobinostat plus bortezomib and dexamethasone could be used. They also explained that if the myeloma is refractory to 5 or more treatments, selinexor plus dexamethasone has recently been recommended by NICE. The committee concluded that pomalidomide plus dexamethasone is the main comparator for this evaluation. It also concluded that panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone were

appropriate comparators when pomalidomide plus dexamethasone is not suitable.

Clinical effectiveness

Teclistamab clinical trial data

3.4 The key clinical-effectiveness evidence for teclistamab in this evaluation came from the MajesTEC-1 trial. This is a phase 1/2, single-arm, open-label, multicentre study in people with triple-class-exposed relapsed or refractory multiple myeloma that is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 monoclonal antibody. The company presented data from the phase 1 part 2 cohort and the phase 2 cohort A of the study (n=165), which were the groups with previous treatment that matched UK practice. It presented data from the August 2023 data cut, with a median follow up of 30.4 months. The overall response rate was 63%. Median overall survival was 22.2 months, median progression-free survival was 11.4 months and median time to next treatment was 12.6 months. The company also presented clinical evidence for teclistamab from 2 real-world retrospective studies (Dima et al. 2023 and Riedhammer et al. 2024), but it did not use these to inform the comparative effectiveness of teclistamab compared with pomalidomide plus dexamethasone. The committee noted that the median progression-free survival reported in these studies (5.4 months in Dima et al. and 8.7 months in Riedhammer et al.) was lower than in the MajesTEC-1 trial. It considered whether these studies may also have been appropriate to inform the comparative effectiveness of teclistamab. The clinical experts highlighted that the follow up in both Dima et al. and Riedhammer et al. was short but the overall response rate (66% in Dima et al. and 59.3% in Riedhammer et al.) was comparable to that in MajesTEC-1. The clinical experts also explained that 50% of the people in these studies would not have been eligible for MajesTEC-1 because they had more severe forms of myeloma, including plasma cell leukaemia and central nervous system involvement. So, the clinical experts considered that Dima et al. and Riedhammer et al. were less generalisable to UK clinical practice. The committee concluded the clinical-effectiveness evidence for teclistamab from MajesTEC-1 was appropriate.

Comparing teclistamab with pomalidomide plus dexamethasone

3.5 The clinical-effectiveness evidence for pomalidomide plus dexamethasone came from a UK real-world triple-class-exposed relapsed or refractory multiple myeloma registry study. In this study, people with an Eastern Cooperative Oncology Group performance status of 0 or 1 (n=645) had follow up from their first line of treatment after study registration until either death, relocation outside of England, or the data cut off. The company presented data from the March 2023 data cut. The study had a median follow up of 26 months. Median overall survival was 9.78 months and median time to next treatment was 7.03 months. Because MajesTEC-1 did not include a control arm, the company did adjusted indirect treatment comparisons to estimate the comparative effectiveness of teclistamab compared with pomalidomide plus dexamethasone for the relevant patient population. Because there was no progression-free survival data from the UK registry study, it used time to next treatment as a proxy for progression-free survival. This approach was validated by clinical expert advice to both the company and the EAG. There were 17 covariates identified, of which 5 were considered priority prognostic factors. Individual patient data from the UK registry study was available for only 6 of the variables, of which refractory status was the only priority prognostic factor. The company removed autologous stem cell transplant from the weighting process because there was no statistically significant difference in overall survival or time to next treatment found between people with or without previous autologous stem cell transplant. It adjusted for 5 covariates using the inverse probability of treatment weighting (IPTW) method. And it used the propensity score to derive weights for each person so that the baseline characteristics of people in the teclistamab arm and pomalidomide plus dexamethasone arm were balanced after adjustment. The results of the indirect treatment comparisons showed that teclistamab significantly improved both overall survival (hazard ratio 0.52, 95% confidence interval [CI] 0.36 to 0.74; p<0.0001) and time to next treatment (hazard ratio 0.56, 95% CI 0.40 to 0.79; p<0.0001), compared with pomalidomide plus dexamethasone. The EAG considered that the company's indirect treatment comparison methods had several limitations, including:

- The IPTW method to adjust the baseline characteristics may have been unstable, and the estimated treatment effects may have been biased.
- The company's base case did not use NICE Decision Support Unit guidance

to perform trimming of the sample, or matching, to improve overlap.

- There were 4 priority prognostic factors (cytogenetic profile, International Staging System [ISS] stage, time to progress on last regimen, and extramedullary plasmacytoma) that were not adjusted for. Clinical advice to the EAG was that cytogenetic profile was the most important factor.
- Violating the proportional hazards assumption introduced further uncertainty about the accuracy of reported treatment effects.

So, the EAG considered that the comparative effectiveness of teclistamab compared with pomalidomide plus dexamethasone was highly uncertain. The committee noted that the results of the indirect treatment comparisons looked promising for teclistamab compared with pomalidomide plus dexamethasone. But, because of the high level of uncertainty, particularly around the indirect treatment comparison methods, the committee questioned the reliability of these results. The people in MajesTEC-1 had different characteristics to the people in the UK registry study. So, the committee considered that the fact that the company's results were very similar before and after adjustment meant they lacked face validity.

There was also clinical-effectiveness evidence for pomalidomide plus dexamethasone available from another source, the ICARIA-MM trial. This was a phase 3 randomised controlled trial comparing isatuximab, pomalidomide, and dexamethasone with pomalidomide plus dexamethasone in people with refractory or relapsed and refractory multiple myeloma. The committee questioned whether clinical evidence for pomalidomide plus dexamethasone from ICARIA-MM could be used in an indirect treatment comparison. The company explained that it considered the UK registry study the best source of clinical evidence for pomalidomide plus dexamethasone, and had used this to inform the indirect treatment comparison. The committee considered there was a lot of uncertainty in the indirect treatment comparisons' methods. It concluded that these methods were unreliable and the resulting point estimates for teclistamab compared with pomalidomide plus dexamethasone were highly uncertain and should be interpreted with caution, although it agreed that the trend favoured teclistamab.

Comparison when pomalidomide plus dexamethasone is not suitable

3.6 In its response to consultation, the company did unanchored matching-adjusted indirect comparisons (MAICs) to compare teclistamab with panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone. The results indicated that compared with panobinostat plus bortezomib and dexamethasone, teclistamab reduced the risk of progression by 54% (hazard ratio: 0.46; 95% CI 0.26 to 0.84; p=0.0106) and risk of death by 59% (hazard ratio: 0.41; 95% CI 0.22 to 0.74; p=0.0030). Compared with selinexor plus dexamethasone, teclistamab reduced the risk of progression by 39% (hazard ratio: 0.61; 95% CI 0.33 to 1.13; p=0.116) and the risk of death by 45% (hazard ratio: 0.55; 95% CI 0.33 to 0.93; p=0.0265). The EAG considered that the company's MAIC methods were appropriate but noted the sample size was small after matching. The committee concluded that although the small sample size increased uncertainty, the unanchored MAIC provided a suitable comparison of the clinical effectiveness of teclistamab compared with panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone.

Economic model

Company's modelling approach

3.7 The company used a partitioned survival model with 3 health states:

- progression free
- progressed
- death.

The cycle length was 1 week and the time horizon was 40 years. Health-state occupancy of the cohort across model health states for the main comparison with pomalidomide plus dexamethasone was as follows:

- Teclistamab arm: parametric distributions were fitted to the IPTW-adjusted MajesTEC-1 trial data for overall survival and time to next treatment (proxy for

progression-free survival).

- Pomalidomide plus dexamethasone arm: parametric distributions were fitted to the UK registry study data for overall survival and time to next treatment.

  The EAG was broadly satisfied with the company's model structure but had reservations about several assumptions and the parameter selections used to determine health-state occupancy (section 3.5 and section 3.6). The committee noted that the company's model was similar to previous models used for multiple myeloma and concluded that the model structure was appropriate for decision making.

Overall survival and progression-free survival extrapolations

3.8 To estimate long-term overall survival and progression-free survival beyond the trial follow-up period, the company fitted parametric distributions to MajecTEC-1 Kaplan–Meier data for the teclistamab arm and to the UK registry study Kaplan–Meier data for the pomalidomide plus dexamethasone arm. Data on time to next treatment was used as a proxy for progression-free survival (see section 3.5). The company selected the best fitting curve based on statistical fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion scores and validated it with clinical advice. The company selected log-normal and Gompertz distributions for the teclistamab arm and the pomalidomide plus dexamethasone arm, respectively, to model both long-term overall survival and progression-free survival in the economic model. At an advisory board with 3 clinical experts, the company elicited a most likely range, most optimistic, and most pessimistic estimates of overall survival and progression-free survival at 5, 10, and 15 years for both the teclistamab arm and the pomalidomide plus dexamethasone arm. In its base case, for the teclistamab arm only, the company fixed the long-term overall survival and progression-free survival to the midpoint of the range of the company's clinical experts' most likely estimates at 10 and 15 years. For the pomalidomide plus dexamethasone arm, it used the selected curves to extrapolate overall survival and progression-free survival without fixing these to the midpoint of the range of the company's clinical experts' most likely estimates at 10 and 15 years.

The EAG considered that this approach was inconsistent between the treatment arms. Instead, the EAG applied the same approach to both the teclistamab and pomalidomide plus dexamethasone treatment arms. The EAG also questioned the credibility of using clinical expert estimates to fix the selected overall survival and progression-free survival distribution. This is because these estimates were based on the opinions of only 3 clinical experts and did not use the Delphi panel technique to elicit expert estimates. The EAG highlighted that these estimates did not provide exact values and the most optimistic and most pessimistic estimates were wider than the range for the clinical experts' most likely values. Because there was already a high level of uncertainty in the indirect treatment comparison results (see section 3.5), the committee explored a range of possible values provided by the company's clinical experts in its decision making. The committee agreed that it was appropriate to consider a more conservative approach to model long-term survival estimates to account for the uncertainty in the comparative effectiveness results. So, the committee concluded that it would consider:

- the long-term overall survival and progression-free survival modelled by fixing to the midpoint of the range of clinical experts' most likely values for both arms, and
- a scenario fixed to the highest of the range of clinical experts' most likely values for the pomalidomide plus dexamethasone arm.

Time to stopping treatment extrapolation

3.9 The company estimated the proportion of people remaining on teclistamab treatment by fitting parametric distributions to time to stopping treatment data from the MajesTEC-1 Kaplan–Meier data. For the pomalidomide plus dexamethasone arm, because there was no time to stopping treatment data from the UK registry study, the company used the ratio of teclistamab progression-free survival (using time to next treatment as a proxy) to teclistamab time to stopping treatment data. It then applied this to the Gompertz distribution selected to extrapolate the pomalidomide plus dexamethasone progression-free survival. In the absence of relevant data, the EAG considered this a reasonable approach. For teclistamab time to stopping treatment, the company selected the gamma distribution. The EAG considered that the curve selection for time to

stopping teclistamab was not consistent with curve selection for teclistamab overall survival and progression-free survival. It noted that based on the AIC scores, the log-normal distribution was the best fit to the MajesTEC-1 data. But, the company highlighted that this generated estimates of time to stopping treatment that were higher than the most likely values at 10 and 15 years estimated by the company's clinical experts. So, it selected the gamma distribution with poorer statistical fit because it generated time to stopping treatment estimates at 10 and 15 years that were close to the estimated most likely values. The company did not fix the selected curves to the midpoint of the most likely range of clinical values at 10 and 15 years for either the teclistamab arm or the pomalidomide plus dexamethasone arm. The EAG considered that this was inconsistent with the approach used for curve selection for teclistamab overall survival and progression-free survival (see section 3.8). So, the EAG selected the log-normal distribution to model teclistamab time to stopping treatment in its base case. It also fixed the time to stopping treatment curves to the midpoint of the range of the company's clinical experts' most likely values at 10 and 15 years. The committee recalled its preference for a more conservative approach to modelling long-term survival estimates, to account for the uncertainty in the comparative effectiveness results (see section 3.8). It preferred a similar approach to modelling long-term time to stopping treatment. The committee concluded that the log-normal distribution was more appropriate to model time to stopping teclistamab. It also concluded that the long-term time to stopping treatment should be modelled by fixing selected curves to the midpoint of the range of the clinical expert's most likely values for both arms. The committee considered a scenario fixing to the lowest of the range of the clinical expert's most likely values for the pomalidomide plus dexamethasone arm for its decision making.

Utility values

Source of utility values

3.10 For the teclistamab arm, the company used progression-free health state time-dependent utility values for people having treatment with teclistamab, based on EQ-5D data from MajesTEC 1 and validated by the company's clinical expert's

opinion. But the company did not implement time-dependent utilities for the teclistamab arm in the progressed disease health state, because of insufficient MajesTEC-1 data. The company considers the utility values to be confidential so they cannot be reported here. For the pomalidomide plus dexamethasone arm, the company did not implement progression-free and progressed disease health state time-dependent utility values using EQ-5D data from MajesTEC-1. Instead, it used pomalidomide plus dexamethasone utility values based on the MM-003 trial and accepted by the committee in NICE's technology appraisal guidance on daratumumab monotherapy for treating relapsed and refractory multiple myeloma (0.61 in the progression-free health state and 0.57 in the progressed disease health state).

The EAG considered the company's approach to using treatment-specific utility values for the teclistamab arm and the pomalidomide plus dexamethasone arm inconsistent. It noted that clinical advice to the company suggested that it was appropriate to use utility values derived from MajesTEC-1 data for the pomalidomide plus dexamethasone arm. So the EAG used utility values generated from MajesTEC-1 data for people having treatment with both teclistamab and pomalidomide plus dexamethasone. The EAG also highlighted that the utility values used in the company's base-case model resulted in lower baseline progression-free health-state utility values for the pomalidomide plus dexamethasone arm than the teclistamab arm. But the company did not provide any reasoning for this. The committee recalled the negative impact of corticosteroids on people with myeloma (see section 3.2). Because of the distinct advantage of teclistamab being a corticosteroid-free treatment, utility values for people with myeloma having teclistamab would be likely to differ from those of people having pomalidomide plus dexamethasone. The committee concluded that the treatment-specific utility values for the teclistamab arm and the pomalidomide plus dexamethasone arm were more appropriate than using the MajesTEC-1 utilities for both arms.

Costs

Switching teclistamab regimen

3.11 The summary of product characteristics (SmPC) for teclistamab states that people who have teclistamab and have a complete response or better for at least 6 months can be considered for a reduced dosing frequency (from once weekly to once every 2 weeks). The company assumed that people would switch to the reduced dose frequency at the same rate as in the MajesTEC-1 trial. It modelled this by fitting parametric distributions to the MajesTEC-1 data. The EAG considered this implausible because the company's approach resulted in people in the model switching to reduced dosing frequency much earlier than is allowed in the SmPC. The company considers the exact figure to be confidential so it cannot be reported here. Considering the mean time to complete response in MajesTEC-1, the EAG assumed that switching to a reduced dose frequency would start at 52 weeks. From that point onwards, the EAG modelled switching to reflect the proportion of people in MajesTEC-1 who switched to the reduced dose frequency at different time points. The committee considered the company's approach to model switching to the reduced teclistamab dose frequency was inconsistent with the SmPC and MajesTEC-1 data, and was highly implausible. It considered the EAG's approach more plausible. So, it concluded that it was more appropriate to switch to a reduced dose frequency of teclistamab starting from 52 weeks, followed by using MajesTEC-1 data to model switching to the reduced dose frequency at different time points from 52 weeks onwards.

Intravenous immunoglobulin use

3.12 People in MajesTEC-1 could have immunoglobulin to prevent or treat infections. In the company's base-case analysis, immunoglobulin use in people having teclistamab was modelled in line with the observed frequency and duration of intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin infusions in MajesTEC-1. The company considers the exact numbers to be confidential so they cannot be reported here. The company considered this a conservative approach, given that the eligibility criteria for having immunoglobulin in MajesTEC-1 were less stringent than the criteria currently used in UK clinical

practice. The NHS England submission noted that the overall response rate for teclistamab from MajecTEC-1 was high (63%) with a median duration of response of 24 months. It highlighted that clinical expert advice to NHS England is that most of the people whose myeloma responds to teclistamab will need secondary prophylaxis with immunoglobulin for substantial periods of time. So, it suggested that the committee should consider scenarios in which at least 50% of people have at least 6 and up to 10 doses of IVIG. The company and EAG agreed that without understanding the impact of IVIG on patient outcomes, the full impact of increased IVIG use on the cost effectiveness of teclistamab was unclear. The patient expert explained that they have had IVIG for a long time since starting teclistamab. One clinical expert highlighted that while current IVIG use is low in people with myeloma, recent real-world evidence suggests an increase in IVIG use. They stated that, in line with recent publications, 50% of people with myeloma having IVIG was a reasonable estimate. The committee concluded that the company's scenario, in which the proportion of people having 9 doses of IVIG was informed by MajesTEC-1, was appropriate.

Drug wastage

3.13 The company submission assumed that vial sharing, and 15% drug wastage for teclistamab, would occur in NHS practice. This was in line with NICE's evaluation of belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies. It considered that this was a conservative approach based on the shelf life of reconstituted teclistamab of 20 hours compared with 4 hours for belantamab mafodotin. The company also highlighted evidence from an early access programme for teclistamab. This supported the assumption of low drug wastage in the company's base case and had a plausible upper bound of about 25% wastage. The EAG advised that, given the evidence presented by the company, drug wastage is likely to be closer to 15% than 25%. The NHS England submission highlighted that drug wastage for teclistamab varies according to people's weight, and teclistamab vial sharing is unlikely in clinical practice. It calculated 28.8% wastage of teclistamab with no vial sharing, based on the overall weight distribution of people with having fourth-line treatment for myeloma. In the meeting, the company agreed that NHS England's estimate of 28.8% drug wastage was acceptable. The committee concluded that 28.8% drug wastage with teclistamab should be used in the economic model.

Teclistamab skipped doses

3.14 In the company submission, a proportion of maintenance doses of teclistamab skipped was included in the base-case model, based on MajesTEC-1 data. The company considers the proportion of skipped doses to be confidential, so it cannot be reported here. Dose skipping was applied from cycle 2 onwards in the model because none of the people in MajesTEC-1 missed a step-up dose. During clarification, the company updated its base-case model by applying a higher proportion of teclistamab skipped doses. The proportion of missed doses in the company's updated base case after clarification was based on:

- doses formally recorded as 'skipped' in MajesTEC-1
- dose delays between or within cycles in MajesTEC-1
- missed doses between last drug exposure and the decision to stop treatment in MajesTEC-1, and
- adjustment for monthly and bi-monthly regimens to align with the SmPC.

The EAG considered the company's updated approach acceptable, except for applying an adjustment for monthly and bi-monthly regimens to align with the SmPC. The EAG considered it inappropriate to model people moving to monthly and bi-monthly teclistamab treatment schedules, because this would be not permitted in NHS practice. So the EAG preferred the company's updated proportion of teclistamab skipped doses without adjustment for monthly and bi-monthly regimens, to align with the SmPC. The committee concluded that this approach was appropriate for decision making.

Cost-effectiveness modelling when pomalidomide plus dexamethasone is not suitable

3.15 In its response to consultation, the company did cost-effectiveness analyses to compare teclistamab with panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone. The inputs for the analyses were based on the results of the respective MAICs (see section 3.6) as well as utility values used in NICE's technology appraisal guidance on selinexor with dexamethasone for

treating relapsed or refractory multiple myeloma after 4 or more treatments. Assumptions in the models were aligned with the committee's preferences (see section 3.19). The committee concluded that these models were suitable for decision making.

Severity

3.16 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life-years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's manual on health technology evaluations. The company and the EAG agreed that it was appropriate to apply a severity weight of 1.2 to the teclistamab QALYs in the comparison with pomalidomide plus dexamethasone. The company and the EAG also agreed that it was appropriate to apply a severity weighting of 1.7 to the deterministic teclistamab QALYs in the comparisons with panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone. The appropriate severity weightings were applied to each run in the probabilistic model. The committee accepted these severity weightings.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 The cost-effectiveness estimates used by the committee for decision making took into account all of the available confidential discounts, including those for comparators and follow-up treatments. These estimates are confidential and cannot be reported here. The company's base-case results were within the range normally considered a cost-effective use of NHS resources. The EAG updated the company's model using its preferred assumptions. The EAG's base-case results for teclistamab compared with pomalidomide plus dexamethasone, panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone were

also within the range normally considered a cost-effective use of NHS resources.

Acceptable ICER

3.18 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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. But it will also take into account other aspects including uncaptured health benefits. The committee noted that there were benefits of teclistamab that may not have been captured in the economic modelling. Also, an advantage of teclistamab is that it does not have to be used in combination with corticosteroids, but this was indirectly accounted for by using treatment-specific utility values (see section 3.10). The committee noted the high level of uncertainty, specifically the:

- lack of a direct comparison between teclistamab and pomalidomide plus dexamethasone (see section 3.5)
- limitations in the indirect treatment comparison and uncertainty in its results (see section 3.5)
- long-term overall survival and progression-free survival estimates for teclistamab and pomalidomide plus dexamethasone (see section 3.8).

So, the committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.19 Because of confidential discounts for teclistamab and its comparators, all of the cost-effectiveness results are commercial in confidence and cannot be reported here. The committee's preferred assumptions were:

- scenario 1: overall survival, progression-free survival and time to stopping treatment extrapolations modelled by fixing selected curves to the midpoint of the range of the clinical experts' most likely values for both arms (see section 3.8 and section 3.9)
- scenario 2: as scenario 1 for teclistamab, but overall survival and progression-free survival extrapolations modelled by fixing selected curves to highest of the range of the clinical experts' most likely values, and time to stopping treatment modelled to the lowest of the range of the clinical experts' most likely values for the pomalidomide plus dexamethasone arm (see section 3.8 and section 3.9)
- using a log-normal distribution to extrapolate time to stopping treatment for the teclistamab arm (see section 3.9)
- treatment-specific utility values (see section 3.10)
- switching teclistamab from once weekly to once every other week starting at 52 weeks, then using the MajesTEC-1 data (see section 3.11)
- basing the number of people having IVIG on MajesTEC-1 data and 9 doses of IVIG (see section 3.12)
- using teclistamab drug wastage of 28.8%, as estimated by NHS England (see section 3.13)
- the company's updated approach to inform teclistamab skipped doses without adjustment for monthly and bi-monthly regimens to align with the SmPC (see section 3.14).

  Using the committee's preferred assumptions for the comparison with pomalidomide plus dexamethasone resulted in ICERs in both scenarios that were within the range considered a cost-effective use of NHS resources (see section 3.18). ICERs for the comparisons with panobinostat plus bortezomib and dexamethasone, and selinexor plus dexamethasone were also within the range considered a cost-effective use of NHS resources. So, the committee concluded that teclistamab could be recommended for routine commissioning for treating relapsed and refractory multiple myeloma in adults after 3 or more lines of treatment.

Other factors

Equality

3.20 The patient and carer organisation stated that teclistamab may need to be delivered at treatment centres with specialist equipment and specifically trained healthcare professionals. This may pose challenges for people who live further from these treatment centres and cannot afford, for financial or logistical reasons, to travel longer distances. The patient and carer organisation also highlighted that issues around capacity for day units and inpatient access may cause unequal access to teclistamab. The committee considered these equality issues, and agreed that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population. The committee considered that there were no equalities issues that could be addressed by its recommendations.

Conclusion

Recommendation

3.21 The comparative evidence for teclistamab compared with pomalidomide plus dexamethasone is highly uncertain because of the unreliable methods used in the indirect treatment comparisons. The real-world evidence for teclistamab is also uncertain because of short follow up. This means the long-term estimates of overall survival and progression-free survival with teclistamab compared with pomalidomide plus dexamethasone are also uncertain. Despite the uncertainty, the ICERs that incorporate the committee's preferred assumptions are within the range considered a cost-effective use of NHS resources. So, teclistamab is recommended for treating relapsed and refractory multiple myeloma in adults after 3 or more lines of treatment.

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 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 relapsed or refractory multiple myeloma and the healthcare professional responsible for their care thinks that teclistamab 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 C.

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

Stephen O'Brien
Chair, technology appraisal committee C

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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Project manager

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