NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Selinexor with bortezomib and dexamethasone for previously treated multiple myeloma

1 Recommendations

1.1 Selinexor with bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults, if:

- they have only had 1 previous line of treatment, and their condition is refractory to both daratumumab and lenalidomide, or
- they have only had 2 previous lines of treatment and their condition is refractory to lenalidomide.

Selinexor is only recommended if the company provides it according to the commercial arrangement (see section 2).

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

Why the committee made these recommendations

For this evaluation, the company asked for selinexor plus bortezomib and dexamethasone (selinexor combination) to be considered only:

- after 1 previous line of treatment (second line) for multiple myeloma that is refractory (stops responding) to both daratumumab and lenalidomide, and
- after 2 previous lines of treatment (third line).

This does not include everyone who selinexor combination is licensed for.

Carfilzomib plus dexamethasone is the relevant second-line comparator for selinexor combination for treating multiple myeloma that is refractory to daratumumab and lenalidomide. At third line, preferred treatments for multiple myeloma that is still sensitive to lenalidomide include ixazomib plus lenalidomide and dexamethasone (ixazomib combination). For multiple myeloma that is refractory to lenalidomide, the third-line treatment is panobinostat plus bortezomib and dexamethasone (panobinostat combination).

Selinexor combination has only been directly compared in a clinical trial with bortezomib plus dexamethasone, which is not considered a relevant treatment at second or third line. This clinical trial evidence shows that selinexor combination increases how long people have before their condition gets worse compared with bortezomib plus dexamethasone at second line, but not at third line. The trial evidence also shows that selinexor combination does not increase how long people live compared with bortezomib plus dexamethasone either at second or third line. There have only been indirect comparisons between selinexor combination and carfilzomib plus dexamethasone at second line, or ixazomib combination or panobinostat combination at third line. The results suggest that there are no differences between the treatments on how long people have before their condition gets worse or how long they survive. But these results are highly uncertain.

The cost-effectiveness estimates for selinexor combination compared with carfilzomib plus dexamethasone at second line and with panobinostat combination at third line are within the range that NICE considers an acceptable use of NHS resources. But the cost-effectiveness estimates for selinexor combination compared with ixazomib combination at third line are above what NICE normally considers an acceptable use of NHS resources. So, selinexor combination is only recommended as a second-line treatment for multiple myeloma that is refractory to both daratumumab and lenalidomide, or as a third-line treatment for multiple myeloma that is refractory to lenalidomide.

2 Information about selinexor

Marketing authorisation indication

2.1 Selinexor (Nexpovio, Menarini Stemline) is indicated 'in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for selinexor is £9,200 per 20-tablet pack of 20 mg tablets (excluding VAT; BNF online accessed March 2024). Other pack sizes are available.

2.4 The company has a commercial arrangement (simple patient access scheme). This makes selinexor 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 Menarini Stemline, 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.

Impact of the condition

3.1 Multiple myeloma is an incurable, relapsing and remitting cancer of plasma cells. Relapsed multiple myeloma refers to previously treated myeloma that has progressed. Refractory refers to multiple myeloma that shows no response to treatment or that has progressed within 60 days of the last treatment. The clinical experts emphasised that multiple myeloma

is a highly complex cancer with a wide range of symptoms and severity. The patient experts explained that the condition has a large psychological impact because of the constant possibility of relapse. They explained that the condition can have a large impact on quality of life, affecting all aspects of life for both the individual and their carers. The committee acknowledged that multiple myeloma is a chronic, incurable, highly individual condition that can have a negative impact on quality of life for people with the condition, and their families and carers.

Treatment pathway

3.2 At first line, treatment options for multiple myeloma depend on whether the person can have a stem cell transplant or not. For people who can have a stem cell transplant, NICE recommends the following treatments as options at first line:

- bortezomib plus dexamethasone, or bortezomib plus dexamethasone and thalidomide (NICE technology appraisal guidance TA311)
- daratumumab plus bortezomib, thalidomide and dexamethasone (NICE technology appraisal guidance TA763)
- lenalidomide maintenance treatment after stem cell transplant (NICE technology appraisal guidance TA680).

For people who cannot have a stem cell transplant, NICE recommends the following treatments as options at first line:

- thalidomide plus an alkylating agent and a corticosteroid (NICE technology appraisal guidance TA228)
- bortezomib plus an alkylating agent and a corticosteroid (TA228)
- lenalidomide plus dexamethasone, only if thalidomide is contraindicated or cannot be tolerated (NICE technology appraisal guidance TA587)
- daratumumab plus lenalidomide and dexamethasone (NICE technology appraisal guidance TA917).

At second line, NICE recommends the following treatments as options:

- bortezomib monotherapy (NICE technology appraisal guidance TA129), although clinical experts highlighted that this treatment is rarely used in NHS clinical practice and that bortezomib plus dexamethasone would be used instead
- lenalidomide plus dexamethasone, if the person has only had 1 previous line of treatment containing bortezomib (NICE technology appraisal guidance TA586)
- carfilzomib plus dexamethasone (NICE technology appraisal guidance TA657)
- carfilzomib plus lenalidomide and dexamethasone, if the person has only had 1 previous line of treatment containing bortezomib (NICE technology appraisal guidance TA695)
- daratumumab plus bortezomib and dexamethasone, if the person has only had 1 previous line of treatment that included lenalidomide or if lenalidomide is unsuitable at second line (NICE technology appraisal guidance TA897).

At third and fourth line, NICE recommends the following treatments as options:

- lenalidomide plus dexamethasone (NICE technology appraisal guidance TA171)
- panobinostat plus bortezomib and dexamethasone (NICE technology appraisal guidance TA380)
- ixazomib plus lenalidomide and dexamethasone (NICE technology appraisal guidance TA870).

At fourth line, NICE also recommends the following treatments as options:

- pomalidomide plus low-dose dexamethasone (NICE technology appraisal guidance TA427)
- daratumumab monotherapy (NICE technology appraisal guidance TA783).

At fifth line, NICE recommends the following treatments as options:

- panobinostat plus bortezomib and dexamethasone (TA380)
- pomalidomide plus low-dose dexamethasone (TA427).

The clinical experts agreed with the EAG's clinical advisers that:

- combination treatments with more agents are generally preferred
- for people who cannot have a stem cell transplant, daratumumab plus lenalidomide and dexamethasone will likely become the most used first-line treatment option in the NHS.

The clinical experts explained that choice of treatment depends on a range of factors including previous treatments. They highlighted that a large proportion of people with newly diagnosed multiple myeloma are 75 years and older. So, factors such as frailty and comorbidities are important considerations when offering treatment. They explained that, because of the highly individual nature of the condition and its response to treatment, a range of treatment options with different mechanisms of action are needed. The patient and clinical experts emphasised the high unmet need for effective and safe medicines that are easy to take, especially at later lines in the treatment pathway. The committee acknowledged the complex and evolving treatment pathway for multiple myeloma, and the high unmet need for effective and safe treatments, especially at later lines.

Positioning of selinexor combination

Second line

3.3 For this evaluation, the company positioned selinexor plus bortezomib and dexamethasone (selinexor combination) as a second-line treatment for people whose condition is refractory to previous treatment with both daratumumab and lenalidomide. The clinical experts agreed with the company's positioning of selinexor combination as a second-line treatment option. They highlighted that most people who cannot have a

stem cell transplant would be offered first-line treatment with daratumumab plus lenalidomide and dexamethasone. They said that the relevant comparator at second line is carfilzomib plus dexamethasone because this is the only option available to people whose condition is refractory to both daratumumab and lenalidomide. They explained that different factors would be considered when choosing between carfilzomib and selinexor such as comorbidities, individual preferences and ease of administration. Carfilzomib is associated with cardiac side effects and is administered by intravenous infusion in hospital. Selinexor, an oral tablet, is associated with gastrointestinal side effects and bortezomib is a subcutaneous medicine, so takes less time to administer in hospital.

Third line

3.4 The company also positioned selinexor combination at third line, for people who had 2 previous lines of any treatments. The clinical experts explained that, for people who can still have lenalidomide, ixazomib plus lenalidomide and dexamethasone (ixazomib combination) would be the preferred option. But they considered that, at third line, most people's condition would be refractory to lenalidomide. So, they explained that for these people, there are limited treatment options available. One treatment option is panobinostat plus bortezomib and dexamethasone (panobinostat combination). But they highlighted that, because of the toxicity associated with panobinostat, it is not often used. The clinical experts acknowledged the toxicity associated with selinexor. But they explained that emerging real-world data shows that a dose reduction of selinexor can help reduce gastrointestinal side effects and thrombocytopenia, with potentially the same level of clinical effectiveness. The company explained that Jagannath et al. (2023), a study analysing data from the main clinical trial (BOSTON, see section 3.6) showed that progression-free survival improved with dose reduction. It explained that a reason for this result could be that people continue to have selinexor for longer at the reduced dose. The clinical experts agreed that selinexor provides an option with a different mechanism of action. They also agreed that there are limited

treatments available at third line, particularly for people with multiple myeloma that is refractory to lenalidomide.

Conclusion on positioning

3.5 The committee acknowledged that the company's positioning of selinexor combination is narrower than its marketing authorisation. It agreed with the company's positioning of selinexor combination at second and third line, and concluded that the choice of comparators was appropriate.

Clinical evidence

Key clinical trial: BOSTON

3.6 The clinical-effectiveness evidence for selinexor combination came from BOSTON, a phase 3, randomised, open-label, multi-national trial. The trial was stratified by previous proteasome inhibitor treatments, number of previous lines of treatment and the Revised International Staging System stage at entry. It included people aged at least 18 years with relapsed or refractory multiple myeloma, or both, who had already had 1 to 3 previous lines of treatment. They were randomised to selinexor combination (n=195) or bortezomib plus dexamethasone (n=207). Seventy-seven people randomised to the bortezomib plus dexamethasone group changed treatment to selinexor combination or selinexor plus dexamethasone after their condition progressed during the trial. The company used data from subgroups that had treatment at second line (49%) and at third line (32%). The remaining subgroup, which had treatment at fourth line (19%), was not included in the analyses for this evaluation (see section 3.3 and section 3.4). The primary outcome was progression-free survival assessed by an independent review committee that was blind to treatment group allocation. The committee noted that the average age of people in the subgroups was 67 years at second line and 65 years at third line. This was younger than people seen in the NHS, whose condition is usually diagnosed around 75 years (see section 3.2). The committee also noted that BOSTON was not statistically powered to find differences in outcomes in the subgroups. Also, the trial comparator

was not relevant to the decision problem at second or third line. The committee noted that many people in the BOSTON subgroups had not had previous treatment with lenalidomide (68%). The committee was aware that most people having second- or third-line treatment in NHS clinical practice would have already had lenalidomide. So, it considered that there may be issues about how representative the population in BOSTON is to people likely to have selinexor combination in NHS clinical practice. These issues may lead to uncertainty in the generalisability of the results.

Indirect treatment comparisons

3.7 The company did Bayesian network meta-analyses using Markov chain Monte Carlo simulations to estimate the comparative effectiveness of selinexor combination to:

- carfilzomib plus dexamethasone at second line
- ixazomib combination at third line
- panobinostat combination at third line.

The company chose to use random effects models because of the significant heterogeneity in the studies in the network meta-analyses. The EAG considered that the network meta-analyses used for the second-line comparison and the third-line comparison with panobinostat combination were appropriate. But it considered that the third-line network meta-analysis with ixazomib combination was at high risk of bias because of:

- the unanchored matching-adjusted indirect comparison (MAIC) used between pomalidomide plus dexamethasone (ICARIA-MM study) and bortezomib plus dexamethasone (BOSTON)
- the double use of bortezomib plus dexamethasone BOSTON data to estimate hazard ratios
- using by-arm median progression-free survival data from the MM-009 and MM-010 trials

- potential violation of the proportional hazards' assumption for many comparisons in the networks for progression-free and overall survival
- including the MM-003 trial, which may not be representative of NHS clinical practice because people in this trial had an average of 5 previous lines of treatment
- substantial heterogeneity in some trials
- unadjusted crossover in some of the trials.

The EAG preferred to use an unanchored MAIC with the ixazomib combination. The company explained that it had adopted a pragmatic approach to deal with the heterogeneity between the trials. It considered that the unanchored MAIC did not solve all the underlying uncertainty. It emphasised that the network meta-analysis is still its preferred approach because of the very small numbers included in the unanchored MAIC. It confirmed that the unanchored MAIC was not adjusted for subsequent treatments because no data was available. The committee agreed with the EAG that the network meta-analyses for the second-line comparison, and the third-line comparison with panobinostat combination were appropriate. It acknowledged the limitations of the unanchored MAIC for ixazomib combination, in particular, that it had not been adjusted for subsequent treatments, which may have affected overall survival. But it concluded that the unanchored MAIC was preferred for this third-line comparison with ixazomib combination because of the substantial limitations of the network meta-analysis.

Clinical-effectiveness results

3.8 From BOSTON (see section 3.6), selinexor combination showed:

- in the second-line subgroup, a statistically significant improvement in progression-free survival (21 months compared with 11 months; hazard ratio (HR) 0.62, 95% confidence interval [CI] 0.41 to 0.95), but no statistically significant difference in overall survival (HR 0.91, 95% CI 0.57 to 1.45) compared with bortezomib plus dexamethasone.

- in the third-line subgroup, no statistically significant differences in progression-free survival (HR 0.75, 95% CI 0.46 to 1.22) or overall survival (HR 0.61, 95% CI 0.32 to 1.17) compared with bortezomib plus dexamethasone.

From the indirect treatment comparisons (see section 3.7):

- At second line, there were no statistically significant differences in progression-free survival (HR 0.73, 95% credible interval [CrI] 0.31 to 1.67]) or overall survival (HR 0.89, 95% CrI 0.32 to 2.45) when carfilzomib plus dexamethasone was compared with selinexor combination
- At third line, there were no statistically significant differences in progression-free survival (HR 0.66, 95% CI 0.34 to 1.28) or overall survival (HR 1.29, 95% CI 0.63 to 2.64) when ixazomib combination was compared with selinexor combination
- At third line, there were no statistically significant differences in progression-free survival (HR 0.80, 95% CrI 0.26 to 2.28) or overall survival (HR 1.24, 95% CrI 0.45 to 3.46) when panobinostat combination was compared with selinexor combination.

The clinical experts highlighted the heterogeneity of multiple myeloma and sequence of subsequent treatments across trials. They noted that BOSTON included mainly people whose condition was sensitive to a proteasome inhibitor, such as bortezomib. They considered that levels of previous lenalidomide use may be an important reason for the variation across trials because of the resulting differences in the underlying biology, such as enrichment of subclones. The company highlighted that, in its subgroup analysis of 106 people in BOSTON whose condition was refractory to lenalidomide, selinexor combination statistically significantly improved progression-free survival and overall survival (HR 0.53, 95% CI 0.30 to 0.95) compared with bortezomib plus dexamethasone. It explained that this data had not been included in the model because the other trials did not have lenalidomide-refractory data, and because the lenalidomide-

refractory analysis was not done by line of treatment. The committee noted that, in general, there was worse progression-free survival with selinexor combination than with its comparators at second- and third line, but that these findings were not statistically significant. It acknowledged that the BOSTON trial was not powered to detect differences in the subgroups. It also noted that the results of the indirect treatment comparisons had wide credible intervals, suggesting high levels of uncertainty.

Economic model

Company's modelling approach

3.9 The company presented a partitioned survival model with 3 health states: progression-free (including on and off treatment), progressed and death. The probability of being in each health state was calculated using extrapolated progression-free survival, overall survival and time-on-treatment curves. People started the model in the progression-free health state on second-line or third-line treatment. The model included a cycle length of 1 week with a half-cycle correction over a 35-year time horizon. The committee concluded that the company's model structure was acceptable for decision making.

Long-term extrapolations

Proportional hazards assumption

3.10 The company used BOSTON Kaplan–Meier data on progression-free survival, overall survival and time on treatment at second and third line to extrapolate longer-term outcomes in the model. The company considered whether the proportional hazards assumption was violated using standard tests. This determined whether the extrapolations used were independently or jointly fitted. The EAG considered that, because BOSTON patient-level data was available, independently fitted models would be more robust. The company selected the most appropriate extrapolated survival curves based on best statistical fit, visual inspection

and clinical plausibility. The company considered that the proportional hazards assumption was valid, except for progression-free survival at second line. It explained that, in addition to visual inspection of the log-log and Schoenfeld residual plots, statistical tests were used to assess the proportional hazards assumption. It explained that all the probability values from the tests were above 0.05 except for progression-free survival at second line. The company further explained that clinical expert advice it had received suggested that there was no reason why the hazards would vary over time. The EAG considered that the proportional hazards assumption was not valid, as evidenced by the variation over time in the log-log and Schoenfeld residual plots. The committee considered that the proportional hazards assumption was a strong assumption that needed clear evidence to support its application. It agreed with the EAG that the proportional hazards assumption was likely to not be valid. The committee concluded that the proportional hazards assumption was violated, and that independently fitted models should be used to extrapolate progression-free survival, overall survival and time on treatment.

Extrapolations for comparators

3.11 To model long-term progression-free and overall survival of the comparators, the company used the indirect treatment comparison results and applied them to the baseline curves for selinexor combination. For extrapolations of time on treatment, the company used the indirect treatment comparison progression-free survival hazard ratios and applied them to the same baseline time-on-treatment curve for selinexor combination. The EAG considered that it would have been more appropriate to use bortezomib plus dexamethasone baseline curves because the proportional hazards assumption did not hold for outcomes in BOSTON. In addition, the proportional hazards assumption was more robust for other trials comparing against bortezomib plus dexamethasone, which was a common network comparator. The company explained that it preferred its base case. This was because the proportional hazard assumption held for all other trials in the network meta-analyses, whereas

the log-log and Schoenfeld residual plots showed that it was violated in BOSTON. The committee agreed with the EAG that bortezomib plus dexamethasone was a more appropriate baseline for the comparator extrapolations. It also noted that, at third line for progression-free survival and time-on-treatment extrapolations, the EAG had used independently fitted accelerated failure time models because the proportional hazards models were not suitable. It also acknowledged the EAG's request that the company derive progression-free survival estimates from the indirect treatment comparisons for the third-line comparators suitable for use with accelerated failure time models. The committee concluded that it preferred to use the EAG's extrapolations for decision making.

Overall survival benefit

3.12 In its base case, the company modelled differences in overall survival between treatments based on data from BOSTON Kaplan–Meier curves and indirect treatment comparisons. The EAG's base case assumed no overall survival differences between treatments and used bortezomib plus dexamethasone as the baseline overall survival curve. The EAG considered that this was justified because the overall survival data from BOSTON was immature and uncertain. Also, there were no statistically significant overall survival differences for any of the comparisons. The EAG noted that an overall survival benefit likely includes varying effects of subsequent treatments on overall survival after disease progression. The company argued that an overall survival benefit was plausible. This was because selinexor combination provides a new mechanism of action, and a statistically significant improvement in overall survival was seen in the lenalidomide-refractory subgroup of BOSTON (see section 3.8). At the second committee meeting, the clinical experts agreed with the company that it is plausible for overall survival to improve, as shown with other treatments in this disease area. They added that this is because selinexor has a different mechanism of action, But they acknowledged that the clinical evidence did not show an overall survival benefit with selinexor combination compared with its comparators. The company considered

that the EAG had taken a pessimistic and inconsistent approach by adopting the indirect treatment comparison results for progression-free survival but assuming no benefit for overall survival. The EAG reiterated that there were no statistically significant differences in overall survival in any of the comparisons (see section 3.8). It also noted that, for the lenalidomide-refractory subgroup, the analysis included people at all treatment lines (second to fourth line) and not just third line. Also, there was no available comparative data from indirect treatment comparisons for the lenalidomide-refractory subgroup. The EAG explained that there was a difference in the degree of uncertainty for progression-free survival and overall survival because progression-free survival was the primary outcome of the key trials. BOSTON's progression-free survival data was more mature than its overall survival data. The EAG noted that overall survival was confounded by using different subsequent treatments in the key trials. It also noted that BOSTON's overall survival data was sensitive to adjustments for treatment cross over. The committee considered that it had not been presented with evidence of overall survival benefit for selinexor combination compared with the relevant treatment options at second and third line. So, it considered the EAG's assumption of no differences in overall survival between treatments to be appropriate for decision making.

Cost of subsequent treatments

3.13 The company included the cost of subsequent treatments by using a weighted average of these treatments in BOSTON, and adjusted for treatments available in the NHS. The EAG considered that the subsequent treatments modelled by the company do not reflect NHS practice. The EAG instead used market share data provided by the company, and assumptions based on the NHS treatment pathway and adjusted for the proportion of people from BOSTON having subsequent treatments (80%). At the first committee meeting, the clinical experts explained that there is significant attrition with each line of treatment. They noted that the average age of diagnosis is 75 to 80 years. They also noted

that some study results suggested that, at fourth and fifth line, only about 20% of people remain on treatment. The committee recalled the younger cohort included in BOSTON. It considered that, by using data from this study, the proportion of people continuing on subsequent treatments may have been overestimated. The clinical experts explained that, after third line, multiple myeloma is likely to be refractory to lenalidomide and people are more likely to have pomalidomide plus dexamethasone. They considered that there would be no significant differences in subsequent treatments after third line based on whether people had selinexor combination or panobinostat combination. The committee was aware that subsequent treatment assumptions were a key driver of costs and cost effectiveness in the model, particularly when assuming no overall survival benefits between treatments (see section 3.12). The committee acknowledged that the EAG's distributions of subsequent treatments excluded treatments that were not relevant to NHS clinical practice. But it considered that these distributions, particularly after third line, did not reflect the opinion of the clinical experts.

For the second committee meeting, the EAG provided 2 scenarios for modelling subsequent treatment costs. Scenario 1 was based on feedback from the clinical experts at the first committee meeting. It assumed that:

- 20% of people at third line would have subsequent treatments, and that there were no differences in subsequent treatments regardless of the third-line treatment
- 80% of people at fourth line would have pomalidomide plus dexamethasone and 20% would have chemotherapy
- 20% of people at fifth line would have pomalidomide plus dexamethasone and 80% would have chemotherapy.

For scenario 2, the EAG estimated a one-off cost for subsequent treatments for selinexor combination and its comparators. This approach

balanced the costs of subsequent treatments across all treatment arms so that the incremental cost was zero.

At the second committee meeting, the clinical experts clarified that they considered 20% of people continuing to have subsequent treatment at third line was too low. They considered 50% more plausible. They also explained that the composition of subsequent treatments at fourth line did not reflect clinical practice. The EAG explained that, because selinexor combination has a shorter progression-free survival than its comparators at third line, people having selinexor combination would accrue greater subsequent treatment costs. The committee recalled that it accepted the EAG's assumption that there was no overall survival benefit between treatment arms (see section 3.123.12). It was concerned that this assumption, combined with the shorter duration of progression-free survival for selinexor combination, was creating a difference in subsequent treatment costs. This was not supported by any evidence, and may not exist in clinical practice. The committee considered that scenario 2, which assumed that there were no differences in subsequent treatment costs between arms, would be a more consistent and appropriate assumption.

Modelling of adverse events

3.14 In the company's base case, grade 3+ treatment-emergent adverse events that occurred in at least 5% of people in BOSTON were modelled as weekly rates for the duration on therapy. The impacts of the adverse events on quality of life were also modelled as a weekly disutility. The company assumed that adverse events are managed in primary and secondary care. In its base case, the EAG modelled adverse events as a one-off event in cycle 1 in line with previous multiple myeloma technology appraisals. Also, it assumed that adverse events are managed in secondary care. The clinical experts explained that adverse events are generally managed in secondary care. If side effects are not manageable, treatment is stopped. They considered that adverse events are likely to become less frequent over time with improved management and dose

reduction, if appropriate. The committee considered that modelling a one-off event does not consider the distribution of adverse events over the duration on treatment. It also thought that it does not capture the long-term impact on quality of life. It acknowledged that the company's approach, using cumulative adverse event rates divided to provide weekly event rates ,assumed a constant incidence of adverse events over time. It did not think this was appropriate and led to benefits for treatments with shorter estimated progression-free survival such as selinexor. The committee concluded that the approach of modelling adverse events as a one-off event in cycle 1 was the best option.

Modelling of health-state utilities

3.15 In its base case, the company used EQ-5D-5L data from BOSTON for health-state utilities mapped to the EQ-5D-3L using the algorithm published in Hernandez Alava et al. (2020). It applied pooled utilities from trial arms and assumed that health-related quality of life did not depend on treatment, lines of treatment or differences in treatment-emergent adverse event profiles. The company also provided a scenario analysis using utility values from Hatswell et al. (2019), a source used in other multiple myeloma technology appraisals. In its base case, the EAG used EQ-5D-5L data from BOSTON and line of treatment as a covariate. The clinical experts noted the small difference in utilities between the progression-free survival and progressed health states in BOSTON, whereas a larger difference was shown using the data from Hatswell et al. (2019). The company explained that, often in trials, utilities for the progressed health state are based on an assessment at 1 timepoint shortly after disease progression. The clinical experts explained that disease-related and non-disease-related comorbidities increase over time. So, it is clinically plausible that over time and with later lines of treatment, the impact on health-related quality of life will be greater. The committee acknowledged the likely overestimation of the utility for the progressed health state but considered that it preferred to use the trial utility value data by line of treatment. It considered that the EAG's base-case

approach for health-state utilities was more appropriate for decision making.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 In response to the draft guidance consultation, the company accepted all the assumptions in the EAG's base case except for the assumption of no overall survival benefit. It still preferred to use indirect treatment comparison results for overall survival in its model (see section 3.12). The committee's preferred assumptions were largely in line with that of the EAG's base case, which were:

- using the results of the network meta-analyses for the second-line comparison with carfilzomib plus dexamethasone, and the third-line comparison with panobinostat combination (see section 3.7)
- using the results of the unanchored MAIC for the third-line comparison with ixazomib combination (see section 3.7)
- using independently fitted models for extrapolations of progression-free survival, overall survival and time on treatment (see section 3.10)
- using baseline curves of bortezomib plus dexamethasone for comparator extrapolations (see section 3.11)
- assuming no difference in overall survival between treatments and using bortezomib plus dexamethasone as baseline for overall survival for all treatments (see section 3.12)
- modelling of adverse events and associated disutility as a one-off event in cycle 1 (see section 3.14)
- modelling health-state utilities by line of treatment (see section 3.15).

Also, for subsequent treatment costs, the committee preferred to instead assume that there was no difference in costs between arms (see section 3.13). The committee considered that the EAG's base case with scenario 2 for subsequent treatment costs reflected its preferred assumptions.

Acceptable ICER

3.17 NICE's health technology evaluations manual notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. NICE's health technology evaluations manual also states that decisions about the acceptability of the technology will consider aspects that relate to uncaptured benefits and non-health factors. The committee recalled the statements from the clinical and patient experts on the significant unmet need for effective and safe treatments at later lines in the treatment pathway. It also noted that selinexor has a novel mechanism of action and, as an oral treatment, would be easily administered and fit into the existing care pathway. The committee acknowledged the high unmet need for novel treatments, especially at later lines in the treatment pathway. But it also noted the high levels of uncertainty, including:

- the representativeness of the population from BOSTON and the generalisability of the results to people with multiple myeloma likely to have selinexor combination in NHS clinical practice (see section 3.6)
- the wide credible intervals for outcomes in the indirect treatment comparisons (see section 3.8)
- the uncertainty in longer-term extrapolations of progression-free survival, overall survival and time on treatment (see sections 3.10 to 3.12).

The committee concluded that an acceptable ICER would be below £20,000 per quality-adjusted life year (QALY) gained.

Company and EAG cost-effectiveness estimates

Second line

3.18 The committee considered the cost effectiveness of selinexor combination compared with carfilzomib plus dexamethasone at second line. In the EAG's base case with scenario 2 for subsequent treatment costs (see section 3.16), the deterministic and probabilistic ICERs were substantially above £30,000 saved per QALY lost in the southwest quadrant of the cost-effectiveness plane. This suggested that selinexor combination is less effective and less expensive than carfilzomib plus dexamethasone. The estimated differences in QALYs between treatments were small. The exact ICERs cannot be reported here because some prices are commercial in confidence.

Third line

3.19 The committee noted that, at third line, there is an increasing unmet need for new treatment options for people whose condition is refractory to lenalidomide (see section 3.17). At third line, in the EAG's base case with scenario 2 for subsequent treatment costs (see section 3.16), the ICER was substantially above £30,000 per QALY lost in the southwest quadrant of the cost-effectiveness plane for selinexor combination compared with panobinostat combination. This suggested that selinexor combination is less effective and less expensive than panobinostat combination. The estimated differences in QALYs between the treatments were small. The exact ICERs cannot be reported here because some prices are commercial in confidence.

For the comparison with ixazomib combination, selinexor combination was dominated in both the deterministic and probabilistic analyses. This suggested that selinexor combination is less effective and more expensive than ixazomib combination. The estimated differences in QALYs between the treatments were small.

Other factors

Equality

3.20 The recommendations apply equally to all people with relapsed or refractory multiple myeloma. The clinical experts noted that multiple myeloma is common in men, elderly people, and people from African or Caribbean ethnic groups. The committee considered that its recommendations apply equally, regardless of sex, age and ethnicity. It concluded that the difference in prevalence did not represent an equality issue in this evaluation.

Innovation

3.21 The clinical experts considered that selinexor combination provides an alternative treatment option with a novel mechanism of action. The company highlighted some uncaptured benefits, including the impact on carer health-related quality of life. The committee considered that there may be benefits uncaptured in the economic modelling. For example, the value of an additional oral treatment option, particularly at second line, for which the ease of administration and adverse effect profile may make it more acceptable than existing options. The committee also acknowledged that there would be an increasing number of people whose condition is refractory to lenalidomide and daratumumab. It concluded that selinexor combination provides an alternative treatment option with a novel mechanism of action.

Severity

3.22 NICE's advice about conditions with a high degree of severity did not apply.

Conclusion

3.23 The ICERs using the committee's preferred assumptions were within the range that NICE considers a cost-effective use of NHS resources for:

- second-line use of selinexor combination for multiple myeloma that is refractory to both daratumumab and lenalidomide, or
- for third-line use of selinexor combination for multiple myeloma that is refractory to lenalidomide.

At third line, selinexor combination was not cost effective compared with ixazomib combination. So, selinexor combination is recommended for routine commissioning in the NHS for second-line treatment of multiple myeloma in adults that is refractory to both daratumumab and lenalidomide, or for third-line treatment of multiple myeloma in adults that is refractory to lenalidomide.

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 multiple myeloma and the doctor responsible for their care thinks that selinexor with bortezomib and dexamethasone 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

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. Because of this, some members of the technology appraisal committees were brought in to provide additional expertise to the committee. The highly specialised technologies evaluation committee and the 4 technology appraisal committees are standing advisory committees of NICE.

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

Paul Arundel

Chair, highly specialised technologies evaluation committee

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.

Sharlene Ting

Technical lead

Victoria Kelly and Alan Moore

Technical advisers

Leena Issa

Project manager

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