NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Tisotumab vedotin for treating recurrent or metastatic cervical cancer that has progressed on or after systemic treatment

1 Recommendation

1.1 Tisotumab vedotin can be used, within its marketing authorisation, to treat recurrent or metastatic cervical cancer that has progressed on or after systemic treatment in adults. Tisotumab vedotin can only be used if the company provides it according to the commercial arrangement (see section 2).

What this means in practice

Tisotumab vedotin must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Tisotumab vedotin must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that tisotumab vedotin provides benefits and value for money, so it can be used routinely across the NHS in this population

Why the committee made this recommendation

Usual treatment for metastatic or cervical cancer that has progressed on or after systemic treatment is single-agent chemotherapy.

Clinical trial evidence shows that tisotumab vedotin increases how long people have before their cancer gets worse, and how long they live, compared with the trial investigator's choice of single-agent chemotherapy.

When considering the condition's severity, and its effect on quality and length of life, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tisotumab vedotin can be used.

2 Information about tisotumab vedotin

Marketing authorisation indication

2.1 Tisotumab vedotin (Tivdak, Genmab) is indicated for 'the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after systemic therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for tisotumab vedotin is £1,995 per 40 mg powder vial (company submission addendum).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes tisotumab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Genmab will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Genmab, 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 Cervical cancer develops when abnormal cells in the lining of the cervix grow in an uncontrolled way and form a tumour. The human papillomavirus is detected in 99.7% of people with cervical cancer. The cancer is defined as recurrent when it has returned after treatment, and metastatic when it has spread beyond the cervix to other places in the body. The clinical experts noted that recurrent or metastatic cervical cancer often affects young people, and they may have young children. A patient expert said that cervical cancer leads to a substantial disruption to quality of life, and that living with the condition is physically and emotionally exhausting. They also highlighted that the side effects from chemotherapy, such as fatigue and nausea, further affect quality of life and make it more difficult to care for young children. For people whose cancer progresses after first-line systemic treatment, there are limited treatment options available for this type of cancer. The main aims of treatment are to relieve symptoms and improve quality of life, and to extend life. A patient expert noted that the fear of recurrence and uncertainty about the future can feel overwhelming. The committee noted that there is a high disease burden for people with recurrent or metastatic cervical cancer with disease progression on or after systemic treatment. It concluded that there is an unmet need for treatment options after disease progression on or after systemic treatment.

Clinical management

Treatment pathway and comparators

3.2 People with recurrent or metastatic cervical cancer, for whom chemotherapy is suitable, usually have platinum-based chemotherapy with paclitaxel, with or without bevacizumab. People whose cancer is PD-L1 positive usually also have pembrolizumab with chemotherapy (see NICE's technology appraisal guidance on pembrolizumab plus

chemotherapy for persistent, recurrent or metastatic cervical cancer). Although NICE's technology appraisal guidance on topotecan for the treatment of recurrent and stage 4B cervical cancer recommends topotecan, it is not frequently used in clinical practice. The clinical experts explained that, for second-line treatment of recurrent or metastatic cervical cancer, people usually have single-agent chemotherapy. These include, but are not limited to, topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed and paclitaxel. In line with its marketing authorisation, the company positioned tisotumab vedotin as a treatment for recurrent or metastatic cervical cancer with disease progression on or after systemic treatment in adults. Based on this positioning, the company included single-agent chemotherapy as the comparator.

The EAG's clinical experts advised that retreatment with platinum doublet chemotherapy is commonly used as a second-line treatment. So, the EAG questioned whether platinum doublet chemotherapy should also be included as a comparator. The company said that platinum doublet chemotherapy retreatment has not been specifically studied in cervical cancer. It also said that it had not been mentioned by healthcare professionals at its UK Cervical Cancer advisory board. But the company acknowledged that, in a subsequent survey in England, 5 of 8 healthcare professionals said they would consider platinum doublet chemotherapy retreatment for some people as a second-line treatment.

The clinical experts at the committee meeting explained that platinum doublet chemotherapy would usually be used in a different clinical scenario to tisotumab vedotin and single-agent chemotherapy. They explained that, because of the associated toxicities, retreatment with platinum doublet chemotherapy would be considered in people who are generally fit and have had a sufficiently long interval without chemotherapy. They added that they would consider tisotumab vedotin and single-agent chemotherapy after platinum doublet retreatment. One of

the clinical experts also said that, in about 90% of people with recurrent or metastatic cervical cancer, the condition progresses within a year of first-line treatment. So, very few people would be considered for retreatment with platinum doublet chemotherapy. The committee acknowledged the differing clinical scenarios. It concluded that the company's positioning of tisotumab vedotin was appropriate and that single-agent chemotherapy was the appropriate comparator.

Clinical effectiveness

InnovaTV 301

3.3 The primary clinical evidence for tisotumab vedotin came from the InnovaTV 301 trial. This is an ongoing phase 3 global randomised open-label trial comparing tisotumab vedotin (n=253) with investigator's choice single-agent chemotherapy (n=249). It has recruited people with recurrent or metastatic cervical cancer who have had 1 or 2 prior lines of systemic treatment. The primary efficacy endpoint is overall survival (OS), defined as the time from randomisation to the date of death from any cause. The key secondary efficacy endpoint is progression-free survival (PFS), defined as the time from randomisation to the first documentation by the investigator of disease progression, or to the date of death from any cause, whichever occurred first. At the time of the primary analysis, based on a data cutoff date of July 2023, median OS was 11.5 months in the tisotumab vedotin arm and 9.5 months in the chemotherapy arm in the intention-to-treat population (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.54 to 0.89). Median PFS was 4.2 months in the tisotumab vedotin arm and 2.9 months in the chemotherapy arm (HR 0.67, 95% CI 0.54 to 0.82). The company also did an ad-hoc follow-up analysis for OS and PFS in January 2024, which has been incorporated into the economic model. But the results are considered confidential by the company and cannot be reported here. The committee concluded that tisotumab vedotin improves OS and PFS compared with single-agent chemotherapy for

people with recurrent or metastatic cervical cancer who have had 1 or 2 prior lines of systemic treatment.

Eye-care management plan

3.4 The committee was aware that, in the US, tisotumab vedotin has a black box warning for ocular toxicity. In the safety analysis population in InnovaTV 301, 52.8% of people (132 out of 250) in the tisotumab vedotin arm had an ocular treatment-emergent adverse event compared with 6.3% (15 of 239) in the chemotherapy arm. Of people who had an ocular adverse event in the tisotumab vedotin arm, 69.7% had resolution of or improvement in all symptoms, with 24.2% having resolution or improvement in some symptoms. The company provided an eye-care management plan and said that this would form part of the UK management strategy for tisotumab vedotin. It noted that this was aligned with the recommendations in the summary of product characteristics for tisotumab vedotin. The eye-care management plan:

- states that an eye-care professional should carry out an ophthalmic examination before the first infusion, and then as clinically needed
- states that the treating healthcare professional should inspect the patient's eyes before each infusion, and identify whether they have any ocular signs and symptoms that need referral to an eye specialist
- provides a schedule for administration of 3 different eye drops during the treatment period
- states that cooling eye pads should be applied before starting the infusion, and used during and for 30 minutes after the infusion
- states that contact lenses should be avoided during treatment unless an eye-care professional advises otherwise.

The EAG noted that the approach for managing ocular adverse events in InnovaTV 301 seemed to align with the eye-care management plan provided by the company. But the EAG's clinical experts raised concerns about implementing the eye-care management plan in clinical

practice. They said that there are no facilities in oncology to carry out eye examinations and that this is not normally done before chemotherapy. The EAG's clinical experts also pointed out that the eye examinations, especially before treatment, would have to be done by an eye-care professional. Also, they said that oncologists may not be familiar enough with the signs and symptoms that should prompt referral for specialist assessment. The EAG's clinical experts thought that, if tisotumab vedotin were recommended, eye departments would not have available resources to manage referrals for eye assessments before and during treatment. Overall, the EAG's clinical experts advised that eye-care needs associated with tisotumab vedotin could present a barrier to introducing the treatment into a centre.

The committee was aware that eye-care management costs were included in the model. But it considered whether there may be implementation issues associated with introducing tisotumab vedotin into clinical practice. One of the clinical experts at the committee meeting said that they had recruited participants for InnovaTV 301. They explained that everyone had a baseline ophthalmic examination, and people who had tisotumab vedotin were referred to an eye specialist if new or worsening ocular symptoms developed. Overall, the clinical expert said that it was possible to manage ocular adverse events within the trial. They added that tisotumab vedotin is an antibody–drug conjugate and that other antibody–drug conjugates have similar ocular adverse events. So, the management pathway for these treatments is currently being developed in NHS clinical practice. The clinical experts also thought that people were likely to adhere to the eyedrops included in the eye-care management plan if they are appropriately counselled by healthcare professionals.

The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) explained that the need for ophthalmic monitoring

has been burdensome for ophthalmology departments in the NHS because of a lack of capacity. But they acknowledged that the population who will have tisotumab vedotin is smaller compared with other treatments that need similar monitoring. They added that some companies fund a scheme to manage eye care in the community rather than in secondary care. The company confirmed that it had not planned to provide such funding for tisotumab vedotin. But it also confirmed that the baseline eye examination can be done by an eye-care specialist, so could also be done outside of secondary care by a community optician. The committee noted that the company estimated an eligible patient population of 117 people in England. The committee concluded that, because the relevant patient population would be relatively small, it may be possible to implement the eye-care management plan within current clinical practice. But it acknowledged the impact that this would have on ophthalmology services.

Economic model

Company's modelling approach

3.5 The company presented a semi-Markov model with a time horizon of 30 years and a 1-week cycle length. The model comprised 3 mutually exclusive health states: progression free, progressed disease and death. Everyone was assumed to enter the model in the progression-free health state. From here, they could either remain in that health state, transition to the progressed-disease health state or transition to the death health state. From the progressed-disease health state, people could either remain in that health state or transition to the death health state. Transition probabilities between the 3 health states were estimated from InnovaTV 301 trial data, using a parametric multistate modelling approach. The company then combined transition probabilities to reconstruct estimates of PFS and OS, which were used to calculate health-state occupancy in the model. The company used InnovaTV 301 Kaplan–Meier (KM) data to

directly estimate OS during the first 12 months, followed by extrapolations based on the parametric multistate distributions (see section 3.10).

Model structure and post-progression survival

3.6 The company said that it chose a semi-Markov model, rather than a partitioned survival model (PSM). In state-transition models such as a semi-Markov model, health-state occupancy is estimated by applying a set of transition probabilities. These inform the movement of people between health states within each set time period. A PSM directly uses PFS and OS curves to estimate health-state occupancy. The company said it chose a semi-Markov model because it allowed the assumption that the risk of death after disease progression is constant and is the same in the tisotumab vedotin and chemotherapy treatment arms. Specifically, the company assumed an exponential hazard for post-progression survival, with the same hazard applied in both treatment arms. It estimated this rate using individual-level patient data on post-progression survival, pooled from the tisotumab vedotin and chemotherapy arms of InnovaTV 301. It explained that it had explored a PSM but this overestimated survival in the chemotherapy arm. For example, at 2 years, the PSM predicted survival of 16% to 20% for chemotherapy compared with 10% to 13% from clinical expert advice and evidence from McLachlan et al. (2017). The company noted that, in the PSM, there was an extended tail in the OS chemotherapy arm and overlap in the OS curves between arms. This meant that some people having chemotherapy remained alive for a long time after the data cutoff timepoint. It also meant that there was a higher proportion of people alive in the chemotherapy arm than in the tisotumab vedotin arm at certain timepoints. It said that this was likely caused by random variation rather than a genuine survival benefit for chemotherapy, because few people remained at risk.

The EAG had concerns about the company's use of a semi-Markov model because it did not think that the InnovaTV 301 data supported the

assumptions of a constant post-progression mortality rate. It noted that the hazard plot for post-progression survival pooled across treatment arms showed a time-varying hazard function (rather than a constant hazard). Also, the goodness-of-fit statistics (Akaike information criterion and Bayesian information criterion values) for the standard parametric distributions fitted to post-progression survival data from InnovaTV 301 showed that other distributions provided a better fit than the exponential distribution. The EAG noted that assuming the same post-progression survival hazard for tisotumab vedotin and chemotherapy may underestimate or overestimate OS if post-progression mortality risk differs between treatment arms. But the EAG could not override the assumption of a constant post-progression mortality risk in the company's model. This was because the model did not include 'tunnel states', which would retain information about the time of progression.

The committee agreed that the hazard plot did not support the assumption of a constant post-progression mortality. It also agreed that other distributions showed better statistical fit compared with the exponential distribution. It also noted that the semi-Markov model was restricted to using the exponential distribution to estimate post-progression survival because of the absence of tunnel states. It thought that this was a limitation in the company's model structure. But it acknowledged that adding tunnel states to the model would add complexity. It noted that this limitation could be overcome by using a PSM. It also noted that the extrapolations in the PSM were based on InnovaTV 301. So, if the chemotherapy arm in a PSM had higher OS than would be expected in clinical practice, the same might also apply to tisotumab vedotin. The company agreed that this may be the case. It said that, compared with the InnovaTV 301 data and estimates generated using a PSM, its modelling approach led to more conservative OS estimates for both chemotherapy and tisotumab vedotin. The committee acknowledged this but thought this limitation could be addressed by using appropriate parametric curves in a

PSM.

In response to the draft guidance consultation, the company stated that all PSM scenarios overestimated chemotherapy OS (see section 3.7). So, it retained the use of a semi-Markov model in its base case. The EAG reiterated that the available evidence did not support the assumptions needed for the company's semi-Markov modelling approach. Specifically, the assumption of the same, constant OS hazard after disease progression in both treatment arms was not supported. It thought that the fitted parametric curves showed an acceptable fit to the InnovaTV 301 trial data and preferred to use a PSM structure. The committee thought that there were some curve choices in the PSM that provided reasonable estimates of chemotherapy OS. But it acknowledged that all the parametric distributions for chemotherapy overestimated OS compared with clinical practice, so were associated with uncertainty. It also recalled that the semi-Markov model structure was associated with uncertainty. This was especially because of the assumption that the risk of death after disease progression was constant and the same in the tisotumab vedotin and chemotherapy treatment arms (see section 3.6). Overall, it thought that the PSM structure produced more reliable estimates of the relative treatment effect between tisotumab vedotin and chemotherapy, and acceptable estimates of the absolute treatment effect. The committee concluded that it preferred a PSM structure.

Extrapolation of chemotherapy OS in the PSM structure

3.7 At the first committee meeting, the committee said that further information from the company about the validity of different extrapolations in the PSM would be useful. It asked that the company explore the different standard parametric distributions in a PSM for PFS and OS. It also asked for information about validity of the distributions, including assessment of:

- visual fit to observed KM data from InnovaTV 301

- the underlying hazard functions over time and validation by clinical experts
- the clinical plausibility of extrapolations
- goodness-of-fit statistics.

In response to the draft guidance consultation, the company fitted 7 standard parametric curves to the InnovaTV 301 trial data using a PSM. The company stated that none of the parametric curves fitted the observed chemotherapy data well in the PSM structure. But it stated that the log-normal and log-logistic curves provided the closest visual fit and the best statistical fit (based on goodness-of-fit statistics). It added that there were notable differences between the observed and predicted OS estimates at the 1-year and 2-year landmarks. Also, it identified data from EMPOWER, a trial comparing cemiplimab with chemotherapy, in a similar population to InnovaTV 301. This showed a 1-year OS estimate of 34.26% and a 2-year OS estimate of 11.30% for chemotherapy. The company noted that all parametric extrapolations based on InnovaTV 301 predicted higher OS at these timepoints than in EMPOWER. The landmark survival rates predicted by the parametric extrapolations are considered confidential by the company and cannot be reported here. It also sought further clinical input from clinical experts, who stated that all parametric extrapolations overestimated OS for chemotherapy compared with what would be expected in clinical practice. They also stated that the benefit of chemotherapy is observed in the first year, and by 2 years, OS would not be higher than 10%. The company's clinical experts indicated that they would likely choose the gamma distribution.

At the second committee meeting, a clinical expert provided real-world evidence from the target population collected over a 5-year period. The clinical expert said that out of the 26 people who were followed up, survival at 1 year was 26.9% and survival at 2 years was 0%. Overall,

the company said that it preferred the gamma distribution to model chemotherapy OS for the PSM scenario. The EAG said that the log-logistic, log-normal and generalised gamma distributions all had a good visual fit to the data and provided OS estimates reasonably close to the KM data at 1 and 2 years. It also noted that the InnovaTV 301 KM estimates for chemotherapy were similar to those from EMPOWER at 1 year but considerably higher at 2 years. The EAG suggested that the better-than-expected survival at 2 years in InnovaTV 301 was likely because of low patient numbers and also possibly because people in the trial experienced better outcomes than in clinical practice. But it said that the InnovaTV 301 trial does not provide evidence of a persistent survival benefit with tisotumab vedotin beyond the point at which the KM curves converge. The EAG preferred to use log-logistic extrapolations for OS, independently fitted to each arm. It said that this provides the best fit to the available trial data, with a decreasing survival advantage for tisotumab vedotin compared with chemotherapy from the point where the KM curves cross. It also preferred to assume that the risk of mortality was the same in both treatment arms from the point where the extrapolated OS curves converged at about 45 months. But it acknowledged that depending on the choice of distribution for chemotherapy OS, the projected survival may be considered overly optimistic. So, it also provided scenario analyses using distributions with less favourable longer-term survival projections for chemotherapy that are still consistent with KM data from InnovaTV 301.

The committee agreed with the EAG that the parametric curves provided a reasonable fit to the InnovaTV 301 trial data. Based on visual fit, statistical fit and assessment of the underlying hazard functions, it thought that the log-logistic distribution provided the most reliable estimates of OS for chemotherapy. But it acknowledged that the chemotherapy OS in InnovaTV 301 appeared to be higher than would be expected in clinical practice. So, the longer-term OS

predictions from the extrapolated log-logistic OS curve were also higher than expected in clinical practice. The committee also noted the potential impact of this on the severity modifier calculation (see section 3.12). It acknowledged that this may have been caused by the low number of people at risk towards the end of follow up. But it noted that the same limitation also applied to the tisotumab vedotin arm. It questioned whether the company had considered a scenario using the OS chemotherapy arm data from EMPOWER with the treatment effect from InnovaTV 301 to generate OS estimates for tisotumab vedotin. It said that this approach could have been used to overcome the higher-than-expected chemotherapy OS in InnovaTV 301. The company confirmed that it had not done this scenario. The committee thought that, of all the parametric distributions, the gamma distribution provided the closest 2-year estimate of OS for chemotherapy compared with expected OS in clinical practice. It noted that the gamma distribution did not fit the InnovaTV 301 OS chemotherapy data as well as other distributions. But it thought that it provided an acceptable fit and concluded that it preferred to use a gamma distribution to model OS for chemotherapy.

Extrapolation of tisotumab vedotin OS in the PSM structure

3.8 For tisotumab vedotin OS, the company noted that the Weibull, log-logistic, gamma and generalised gamma distributions provided the closest visual fit to the observed KM data. It added that the Weibull and gamma distributions provided the best statistical fit. For external validation, the company compared the OS parametric estimates with data from InnovaTV 204, a phase 2 single-arm trial assessing tisotumab vedotin in a similar trial population to InnovaTV 301. The log-logistic and log-normal provided the closest predictions at 1 and 2 years. For its PSM scenario, the company selected the log-logistic and gamma distributions to model tisotumab vedotin OS. But it noted that the hazard ratio trend for the gamma distribution showed an implausible reversal of treatment effect from 18 months onwards (that is, a lower risk of death with chemotherapy

compared with tisotumab vedotin). So, it also provided a scenario using the gamma distribution for both chemotherapy and tisotumab vedotin OS in which the risk of death was the same in both arms (hazard ratio of 1) from 18 months onwards. The EAG noted that the Weibull, gamma and generalised gamma distributions were all very similar with good visual fit to the KM data. It added that the log-logistic distribution also provided a reasonable fit. It said that the predictions from these 4 distributions were close to the KM estimates from the phase 2 InnovaTV 204 trial at 1 year. But it said that the Weibull, gamma and generalised gamma curves were all lower than InnovaTV 204 KM data at 2 and 3 years. The EAG preferred to use the same distributions for both treatment arms and preferred to use the log-logistic distribution to model tisotumab vedotin OS. This was in line with its preferred distribution for chemotherapy OS (see section 3.7). The committee agreed that based on visual fit, statistical fit and assessment of the underlying hazard functions, the log-logistic distribution provided the most reliable estimates of OS for tisotumab vedotin. It also thought that it would be preferable to use the same distribution to model OS for both treatment arms. This is because it had not seen evidence that tisotumab vedotin and chemotherapy have fundamentally different underlying survival hazard shapes. It recalled that OS predictions from the extrapolated log-logistic OS curve for chemotherapy were higher than expected in clinical practice (see section 3.7). It noted that the gamma distribution provided a good visual and statistical fit to InnovaTV 301 data for tisotumab vedotin. But it agreed with the company that the hazard ratio trend for the gamma distribution, which showed a lower risk of death for chemotherapy compared with tisotumab vedotin, from 18 months onwards was implausible. So, on balance, the committee concluded that it preferred to use a gamma distribution to model OS for both treatment arms with a hazard ratio of 1 from 18 months onwards.

PFS extrapolation in the PSM structure

3.9 The incremental cost-effectiveness ratio (ICER) was not sensitive to the choice of distributions for PFS. The company and the EAG agreed that, in

the PSM structure, the log-logistic distribution provided the best estimate of PFS for both treatment arms. The committee concluded that it preferred a log-logistic distribution to model PFS for both treatment arms.

Direct use of KM data to model OS

3.10 The company estimated transition probabilities between the 3 health states in the semi-Markov model using a parametric multistate modelling approach (see section 3.5). But, for the first 12 months, it did not use modelled estimates based on transition probabilities to the death health state. Rather, it used KM data from InnovaTV 301 to override modelled OS predictions for the first 12 months. The company said that it chose this approach because empirical inspection and clinical validation showed that the fitted curves overestimated OS for chemotherapy and underestimated OS for tisotumab vedotin. It noted that the OS KM curves for the treatment arms overlapped, and attributed this to random variation because of diminishing sample size. The exact timepoint at which the OS KM curves converged is considered confidential by the company and cannot be reported here. The company said that, at 12 months, the number of people at risk was still meaningful. But, beyond this point, the number at risk changed substantially. So, it viewed the 12-month cutoff as appropriate because it maximised the use of robust empirical data before applying the fitted curves. The EAG agreed that the overlap of the KM OS curves was likely caused by the diminishing sample size. But it noted that the diminishing sample size applied in both arms. It said that an alternative interpretation of the OS results from the trial was that the survival advantage of tisotumab vedotin waned and did not persist beyond the point where the KM curves converged. Also, it thought that there was a risk of bias from:

- the company's post-hoc decision to use KM data to override the model predictions, and
- the choice of timepoint to switch from KM to the fitted curves.

So, the EAG preferred not to use KM data to override OS model predictions for the first 12 months in its base case. The committee noted the risk of bias associated with using direct KM curves, as highlighted by the EAG. It also noted that the direct use of observed KM data for the first 12 months treats survival as a fixed input. It noted that this prevents uncertainty in short-term outcomes from being reflected in the probabilistic results. It also thought that this approach implicitly treats a sample-based estimate as the true underlying survival function, rather than estimates that could vary because of chance (sampling variability). It thought that parametric approaches were more appropriate for representing both expected survival and associated uncertainty. Also, the committee recalled that it thought that the gamma distribution in a PSM structure provided an acceptable fit to InnovaTV 301 trial data (see section 3.7). So, the committee preferred to use extrapolated curves over directly using KM data in a PSM structure.

Administration cost for paclitaxel

3.11 Paclitaxel was not included in the chemotherapy arm of InnovaTV 301 but the company included it for costing single-agent chemotherapy in the economic model. This was because the company's clinical experts advised that paclitaxel, one of the single-agent chemotherapies, is commonly used as a second-line treatment in recurrent or metastatic cervical cancer. The company assumed that all treatments were administered in an outpatient setting, and used administration costs from NHS reference costs. In its submission, the company assumed a higher cost for administration of paclitaxel than for the other single-agent chemotherapies. For paclitaxel, it assumed an administration cost code (healthcare resource group) of SB14Z, based on delivery for 'complex' chemotherapy with a prolonged infusion. For the other single-agent chemotherapies, it assumed a lower administration cost based on a cost code for 'simple' chemotherapy (SB12Z). The company later provided additional data to support using a different administration cost code

(SB13Z). This was based on 2 NHS protocols for administration of single-agent paclitaxel: the NHS payments scheme for 2025 to 2026 and the National Tariff Chemotherapy Regimens workbook 2017 to 2018. The EAG's clinical experts advised the EAG that single-agent paclitaxel is typically administered as a relatively short infusion (around 1 hour). So, the costs should not differ from those for other chemotherapies. So, the EAG preferred to use the SB12Z cost code.

The Cancer Drugs Fund lead said that, for weekly paclitaxel, the SB13Z cost code would be used. This is because the SB13Z cost code would cover the time need to cannulate someone, administer the necessary premedication and the paclitaxel, flush the line and then remove the cannula. They added that more up-to-date costs for the relevant administration costs are now available compared with the costs used in the model. The committee concluded that it preferred to use the SB13Z cost code for the administration of weekly paclitaxel. It also requested the company to update the chemotherapy administration costs with the latest National Cost Collection data (formerly known as reference costs) that is available. In response to the draft guidance consultation the company provided a scenario using the latest National Cost Collection data (2024 to 2025) for chemotherapy administration costs. It also updated its base case using NHS payment scheme 2025 to 2026 tariff costs. The EAG preferred to use the National Cost Collection data in its base-case analysis because this source has conventionally been used for costing in NICE guidance. The Cancer Drugs Fund lead explained that the National Cost Collection data provides the average unit costs for a particular cost code. Whereas the payment scheme tariff costs represent the prices paid to NHS providers for a particular cost code. The committee noted that the use of National Cost Collection data was mentioned in the NICE technology appraisal and highly specialised technologies guidance manual as a source for determining the cost for services. It concluded that it preferred to use the National Cost Collection data in its base case for

chemotherapy administration costs because this reflects the average costs incurred by the NHS.

Severity

3.12 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 to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with the NICE technology appraisal and highly specialised technologies guidance manual. The committee noted that the QALY shortfall estimates were dependent on the total QALYs in the chemotherapy arm of the model and recalled that this was associated with uncertainty (see section 3.7). It noted that when using its preferred assumptions to estimate total QALYs for chemotherapy, a severity weight of 1.7 was applicable. The committee concluded that a severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.13 Because of the confidential commercial arrangements for the prices of tisotumab vedotin, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The deterministic and probabilistic ICERs for tisotumab vedotin in the company's base case were lower than the range normally considered an acceptable use of NHS resources. The deterministic and probabilistic ICERs for tisotumab vedotin in the EAG's base case were higher than the range normally considered an acceptable use of NHS resources.

Acceptable ICER

3.14 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 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 (see section 3.17). The committee noted the moderate level of uncertainty about the:

- impact that implementing the eye-care management plan for tisotumab vedotin would have on ophthalmology services (see section 3.4)
- tisotumab vedotin extrapolation (see section 3.8) and overestimation of chemotherapy OS for parametric distributions in the PSM structure (see section 3.7).

The committee noted that the uncertainty about the tisotumab and chemotherapy extrapolations increased uncertainty in the cost-effectiveness results. But it acknowledged this was mitigated to some extent because of low OS in the target population. The committee also noted the reduced frequency of administration for tisotumab vedotin compared with weekly paclitaxel. It thought that this may help reduce health inequalities (see section 3.16). It also noted the substantial unmet need in this population (see section 3.1) and the small population size (see section 3.4). The committee concluded that an acceptable ICER would be between the middle and upper end of the range NICE considers a cost-effective use of NHS resources.

The committee's preferences

3.15 For the cost-effectiveness analysis, the committee preferred using:

- a PSM structure (see section 3.6)

- a gamma distribution to model OS for both treatment arms with the same risk of death in both arms (hazard ratio of 1) from 18 months onwards (see section 3.8)
- a log-logistic distribution to model PFS for both treatment arms (see section 3.9)
- extrapolated curves rather than directly using KM data to model OS (see section 3.10)
- the SB13Z cost code for the administration of weekly paclitaxel (see section 3.11)
- National Cost Collection data to inform chemotherapy administration costs (see section 3.11).

Based on these assumptions and the committee's preferred cost-effectiveness threshold (see section 3.14), tisotumab vedotin represents a cost-effective use of NHS resources.

Other factors

Equality

3.16 The company noted that cervical cancer rates are 65% higher in the most deprived quintile compared with the least deprived quintile. It added that screening rates are lower among people from more deprived areas. It also noted that uptake for the human papillomavirus vaccine is lower in more deprived areas and in non-White ethnic groups. A patient expert also noted that access to new treatments can be unequal, with geographic, financial and cultural factors affecting access. Differences in prevalence and patient populations cannot usually be resolved in a technology appraisal. But the committee can consider whether a specific equality issue has a significant impact on access to treatments. The committee noted the disparities in care and unequal access to care based on specific demographics. It acknowledged that access to tisotumab vedotin may have a greater impact on people who have difficulty accessing transport (see section 3.17). It accepted that this could play a role in reducing

health inequalities and took this into account when determining its preferred ICER threshold.

Uncaptured benefits

3.17 The company noted that cervical cancer often affects young people with children and that even small improvements in survival would allow them to spend more time with their families. A clinical expert noted that paclitaxel, the most commonly used comparator treatment, is administered weekly and this may be limiting for people with difficulty accessing transport. In comparison, tisotumab vedotin is administered every 3 weeks, so may be beneficial for these people. A clinical expert also noted that tisotumab vedotin treatment may be associated with societal benefits. This is because, in their experience, people with recurrent or metastatic cervical cancer can return to work if they are well enough. The committee noted that the reduced administration frequency of tisotumab vedotin compared with weekly paclitaxel had been captured through the administration costs in the economic model. But it thought the reduced administration frequency could help to reduce health inequalities for people with difficulty accessing transport. It agreed that this may mean there are benefits not captured within the economic modelling. The committee concluded that it would take this into account when deciding its preferred threshold.

Conclusion

Recommendation

3.18 Clinical evidence shows that tisotumab vedotin improves OS and PFS compared with single-agent chemotherapy for people with recurrent or metastatic cervical cancer who have had 1 or 2 prior lines of systemic treatment. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, tisotumab vedotin can be used.

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 90 days 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 60 days 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 recurrent or metastatic cervical cancer and the

healthcare professional responsible for their care thinks that tisotumab vedotin 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

Radha Todd

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, a project manager and an associate director.

Dilan Savani

Technical lead

Caron Jones

Technical adviser

Jennifer Upton

Project manager

Lizzie Walker

Principal technical adviser

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