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RESEARCH LETTER

Challenges, considerations, and approaches for developing a cost-effectiveness model for the adjuvant treatment of muscle-invasive urothelial carcinoma: with a spotlight on nivolumab versus placebo

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ABSTRACT

Aims: To present alternative approaches related to both structural assumptions and data sources for the development of a decision analytic model for evaluating the cost-effectiveness of adjuvant nivolumab compared with surveillance in patients with high-risk muscle-invasive urothelial carcinoma (MIUC) after radical resection.

Methods and results: Alternative approaches related to both structural assumptions and data sources are presented to address challenges and data gaps, as well as discussion of strengths and limitations of each approach. Specifically, challenges and considerations related to the following are presented: (1) selection of a modeling approach (partitioned survival model or state transition model) given the available evidence, (2) choice of health state structure (three- or four-state) to model disease progression and subsequent therapy, (3) modeling of outcomes from subsequent therapy using tunnel states to account for time-dependent transition probabilities or absorbing health states with one-off costs and outcomes applied, and (4) methods for modeling health-state transitions in a setting where treatment has curative intent and available survival data are immature.

Conclusions: Multiple considerations must be taken into account when developing an economic model for new, emerging oncology treatments in early lines of therapy, all of which can affect the model's overall ability to estimate (quality-adjusted) survival benefits over a lifetime horizon. This paper identifies a series of key structural and analytic considerations regarding modeling of nivolumab treatment in the adjuvant MIUC setting. Several alternative approaches with regard to structure and data have been included in a flexible cost-effectiveness model so the impact of the alternative approaches on model results can be explored. The impact of these alternative approaches on cost-effectiveness results are presented in a companion article. Our findings may also help inform the development of future models for other treatments and settings in early-stage cancer.

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Introduction

Urothelial carcinoma (UC) consists of cancers in the urothelial cells lining the mucosal surfaces of the lower urinary tract (which includes the urethra and bladder) or the upper urinary tract (which includes the ureter and renal pelvis)[1,2], with a majority of cases (90%–95%) in the bladder[2,3]. Bladder cancer is the ninth most common cancer worldwide. Estimates from 2012 suggest that 430,000 new cases are diagnosed annually, resulting in approximately 165,000 deaths globally each year[4].

UC is considered to be muscle invasive when it invades the muscularis propria and beyond, and is classified as T2-T4a using the tumor-node-metastasis staging system[5,6]. For people with bladder cancer, it is estimated that up to 25% of cancers are muscle invasive at diagnosis, whereas for people with UC in the upper urinary tract, approximately 60% are muscle invasive at diagnosis[2].

Treatment of muscle-invasive UC (MIUC) depends on the location. Radical resection (RR) is the standard of care with the addition neoadjuvant cisplatin-based combination chemotherapy (e.g. gemcitabine plus cisplatin) being recommended[7,8]. However, neoadjuvant cisplatin-based combination chemotherapy is not always provided due to patient and provider preference (e.g. chemotherapy refusal, not wanting to delay surgery). Because of the lack of strong efficacy data supporting the use of adjuvant chemotherapy, clinical guidelines suggest that cisplatin-based adjuvant chemotherapy be considered for willing patients who do not

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receive neoadjuvant chemotherapy, have no contraindication to cisplatin, and are at high risk of recurrence[7,8].

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that in 2021 was the first immuno-oncology (IO) agent to receive US Food and Drug Administration approval as an adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing RR of UC[9]. The efficacy of adjuvant nivolumab for the treatment of MIUC was demonstrated in the placebo-controlled, phase 3 CheckMate 274 trial for adults (aged $\geq$ 18 years) who had undergone RR of MIUC and were at high risk of recurrence (NCT02632409)[10]. In CheckMate 274, adjuvant nivolumab, compared with placebo, significantly improved disease-free survival (DFS), with a hazard ratio of 0.70 (95% confidence interval [CI], 0.57–0.85)[11]. Median DFS (95% CI) with nivolumab (22.01 [17.68–36.93] months) was twice as long as the median DFS for patients who received placebo (10.87 [8.28–13.96] months). Data for overall survival (OS), a secondary outcome in CheckMate 274, were not available at the time of economic model development, as the prespecified boundary for declaring statistical significance had not yet been reached. Consequently, the timing of the specific type of DFS events (recurrences or deaths) had not been unblinded, so the events were not available for analysis.

The primary objective of this research was to develop a decision analytic model to evaluate the cost-effectiveness of adjuvant nivolumab compared with surveillance (wait-and-watch approach) which was approximated with placebo in CheckMate 274 in patients with high-risk MIUC after RR. More specifically, this article will present alternative approaches related to both structural assumptions and data sources during the model's development phase in light of key data gaps at the time of model development. Further, it will present alternative methods that were included in the model to address those challenges and data gaps to allow for exploring the impact of different methodologies and data considerations on cost-effectiveness, with discussion around strengths and limitations for potential alternative approaches. Some of these challenges and considerations are likely to be faced by other treatments and settings of early-stage cancer that may share similar data gaps from the pivotal clinical trial at the time of model development. The specific data used in the model, results from the analysis, and impact of the alternative modeling choices on the incremental cost-effectiveness ratio are presented in an accompanying article[12].

Challenges and considerations

As part of the initial conceptualization and specification stages informing the final model development, a number of approaches related to both structural assumptions and data sources were considered. The rest of the paper details the choice of model structure, number of health states, methodological approach to modeling outcomes of subsequent therapies, as well as data sources used to parameterize the model.

Model structure

The first major decision in the model development was whether to use a partitioned survival model (PSM) or instead adopt a state transition model (STM). Although the three-state PSM is the most common cost-effectiveness modeling approach in health technology assessment (HTA) submissions for oncology treatments in metastatic disease[13,14], the absence of OS data from CheckMate 274 presented challenges in generating a robust three-state PSM. Development of a PSM would rely on a surrogacy relationship between DFS or distant metastasis-free survival (DMFS) and OS, both regarding the individual patient level and between the treatment effects at the trial level. However, although a strong surrogacy has been established between DMFS and OS in the literature, there is only a moderate surrogacy relationship between DFS and OS for adjuvant treatment of MIUC[15,16]. In addition, studies of surrogacy in the MIUC literature primarily report adjuvant chemotherapy and active surveillance as the main treatment options and do not take into account patients with prior neoadjuvant therapy or cisplatin-ineligible patients[16]. Most of those studies were published in the 1990s and clinical practice has evolved significantly since then; thus, results from those studies may not be applicable for IO therapies given the different mechanisms of action they employ or to represent the modern and fast-evolving treatment landscape in subsequent lines of therapy after metastatic recurrence. Therefore, a PSM was deemed to have limitations for modeling of adjuvant nivolumab therapy in MIUC given currently available data.

In contrast, the use of STMs (e.g. Markov and semi-Markov models) allows for a more flexible modeling approach, providing a more explicit structural link accounting for dependency between intermediate (e.g. DFS) and final (OS) endpoints. STMs enable pivotal trial data for the investigational treatment to be more explicitly combined with external data sources (e.g. studies investigating the next line of treatment) to inform relevant transition probabilities—for example, the likelihood of transitioning from recurred disease to death. In this way, a lack of OS data from CheckMate 274 can be addressed explicitly by sourcing data from published sources to inform health-state transitions within the model.

In addition, when OS data are not available, STMs have greater flexibility than PSMs in situations where the availability and distribution of post-recurrence treatment options in the clinical trial are not reflective of a given local treatment practice. This is often the case, as clinical practice in later lines of therapy can differ across countries and thus affect their alignment with subsequent treatment provided in global clinical trials. Given the explicit structural links between health states and the possibility of incorporating external data into the model to inform health-state transitions in STMs, health outcomes and costs can be modeled for all relevant subsequent therapy (whether or not they are included in the clinical trial). Thus, STMs offer greater flexibility than PSMs to investigate the impact of alternative combinations of subsequent therapy on outcomes after recurrence, as well as allowing the model to align with treatment recommendations in different treatment jurisdictions. Because of

limitations regarding the availability of OS data, as well as the impact of subsequent therapy in the setting of adjuvant treatment of MIUC, an STM was chosen as the most amenable and appropriate model. Specifically, a semi-Markov model that relaxes the memoryless property of a standard Markov model was chosen to allow for incorporation of time-varying transition probabilities dependent on when patients are entering health states.

Number of health states

Another major decision in the model development was whether to construct it with three or four health states. As mentioned, a three-state model has been the most common structure applied in oncology HTA submissions to the National Institute for Health and Care Excellence (NICE). However, the prevalence of three-state models is mostly due to the majority of appraisals being in metastatic disease settings, where patients' prognoses are less favorable than those of patients with earlier-stage disease, such as MIUC. For metastatic cancers, particularly in previously treated settings, fewer health states differentiating patients' disease progression and mortality status can adequately reflect the natural evolution of the disease in a relatively shorter life span. Therefore, models with three health states are often found sufficient to convey the details in the evaluation of costs and health outcomes. In early-stage cancers, on the other hand, patients can experience different recurrence events (e.g. local recurrence [LR] and distant recurrence [DR]) that are often associated with significantly different cost and health outcomes as well as a potential for cure. Therefore, a model structure that captures different recurrence events in separate health states can better capture prognostic and cost differences between intermediate health states and their long-term implications beyond the trial follow-up. An STM can also enable different treatment effects to be applied not only prior to recurrence but also within each post-recurrence state. Indeed, in recent NICE appraisals of neoadjuvant and adjuvant cancer treatment, four or more health states have often been implemented[17–24].

In the development of the current model for the cost-effectiveness assessment of nivolumab as an adjuvant therapy for MIUC, the key factor influencing the number of health states was differentiation of LR and DR *via* a model with four health states, or the combination of LR and DR into a single recurrence health state for a more conventional model with three health states. Long-term follow-up data for patients with MIUC in real-world settings have shown that type of recurrence (LR or DR) can be a strong determinant for future prognosis and survival[25–27], and that treatment options may differ according to type of recurrence. Therefore, the use of a model with four health states could increase its clinical validity. However, as previously noted in the literature[13], there may be data limitations to inform transitions between different post-recurrence health states, and these limitations may require stringent assumptions. Given the absence of OS data in CheckMate 274 at the time of model development, information related to the timing of the specific type of each recurrence event was not available for analyses, which would be one source of uncertainty for the current model. As the specific type of recurrence events would not be known (data only available for the distribution of first-recurrence events over the whole trial follow-up period), a constant proportion of, for example, LR and DR for disease-free (DF) events was assumed.

In addition to prognostic differences between the types of recurrences, another important determinant for the number of health states in the model was whether subsequent treatments differ according to the treatment received in the adjuvant stage after RR (e.g. nivolumab or placebo). In such cases where subsequent treatments and their treatment effect differ by initial treatment arm[11], more granular modeling of recurrence events could be important to adequately capture the full impact of subsequent therapies for each treatment arm on overall costs and quality-adjusted life-years (QALYs). On the other hand, if the choice of adjuvant treatment did not impact either patient eligibility for or effectiveness of subsequent therapies, then multiple health states would be less important in the model structure. In the case of CheckMate 274, a higher proportion of immunotherapies was received by patients after recurrence by patients in the placebo arm of the trial[11], further supporting the separation of post-recurrence health states in the model.

Given the prognostic differences between the types of recurrences and potential subsequent therapies, a semi-Markov model consisting of four exclusive health states (DF, LR, DR, and death) was chosen as the base case.

Modeling of outcomes from subsequent therapies

Another critical decision in model development was the selection of an appropriate approach to model time dependence of transition probabilities, specifically to model post-DR survival using absorbing health states or tunnel health states. Given the absence of OS data from CheckMate 274 at the time of model development, it was necessary to estimate survival outcomes for the subsequent therapies based on data from the literature. This could be a benefit even in situations where OS data from the pivotal trial are available but immature so that external data for the relevant subsequent therapies can be included to better capture long-term outcomes and offer alternative and more mature data to estimate the impact on the model results. However, with more mature OS data from the pivotal trial and a better realization of the full sequence of initial and subsequent treatments, it would be possible to capture the survival outcomes of the full sequence of treatments (initial and subsequent) by basing the transition probabilities on the trial data. In such cases, external data can be used for validation. Regardless of the number of states in the model, transitions between health states are often time dependent and require monitoring of time spent in the corresponding health state. Therefore, a traditional Markov model is not an appropriate model option unless the survival outcomes from each possible health state can be characterized with an exponential distribution. However, survival from post-recurrence health

states can often be characterized with an exponential distribution, which assumes a constant hazard with time, because the risk of an event may decrease or increase with time from entering an intermediate health state[28,29].

In the case of treatment for first-line metastatic UC (1 L mUC) using cisplatin-based chemotherapy regimens, analyses of reconstructed survival data from published Kaplan–Meier curves showed a declining hazard for OS with time[30]. Therefore, two different approaches to account for such time-dependent behavior in hazards were considered (Table 1). One option was modeling the DR state as an absorbing health state, with one-off cost and QALYs applied to patients upon entering the DR state from either the DF or LR states. The one-off costs and QALYs represent the expected total costs and QALYs gained from DR to death estimated from analysis of 1 L mUC data. Another approach was to incorporate tunnel states into the model to enable time tracking of patients within the DR state and modeling of time-dependent transitions. Both methods would allow for survival distributions with a time-varying hazard structure to model post-DR survival. However, the two approaches handle the calculation of costs and QALYs and their subsequent incorporation into the model analysis differently, as summarized in Table 1.

The approach of using tunnel states was deemed to be most robust, given its ability to account for the discounting of costs and outcomes in each model cycle and to capture outcomes so that their occurrence can be presented in relation to the model time. Therefore, modeling subsequent therapies with tunnel states was selected as the base case. However, to investigate the impact of alternative options for calculating the costs and QALYs associated with subsequent therapies, the possibility of using an absorbing DR state, with one-off costs and outcomes applied, was also incorporated into the model.

Health-state transitions

Data were needed for the four–health-state model structure (Figure 1) to inform transitions after patients' starts in the DF health state, during which they receive adjuvant treatment with nivolumab up to 1 year, or surveillance. At each equally spaced cycle in time, patients who are in the DF state can either remain in DF, experience an LR, experience a DR, or die. Similarly, patients in the LR state can either remain as locally recurrent, experience a DR, or die. Lastly, patients in the DR state can remain distant recurrent or die. In addition, transitions to the dead state were permitted from all health states. The following sections present the potential approaches and data sources for estimating the transition probabilities in the STM.

Disease-free state

With median follow-ups in CheckMate 274 of 24.4 and 22.5 months for the nivolumab and placebo arms, respectively[11], extrapolations were needed to estimate long-term DFS within the model. Given the potential for long-term

Table 1. Advantages and limitations of absorbing health states and tunnel health states for modeling post-recurrence costs and outcomes.

Consideration	Tunnel health states	Absorbing health states
Accounting for time of transitioning into health state	Captures time of transition into health state and allows for adequate discounting of cost and outcomes with time	Does not account for effect of time of transitioning into health state on outcome of subsequent therapy. Thus, for example, discounting of cost and outcomes for subsequent therapies is not fully captured
Transparency	All data and modeling of (for example) extrapolations are included within the economic model, which aids transparency	Could be perceived as not fully transparent given that total one-off costs and outcomes specific to the DR health state are modeled external to the core model structure. However, could also be seen as more transparent if costs and outcomes are sourced from previous HTA assessments of treatment of interest (if available), where costs and outcomes have been validated by the relevant HTA
Model complexity	Commonly seen as requiring a complex matrix structure to adequately capture transitions. However, can be programmed in a more simplistic way than full transition matrix per treatment using a sum product function in Microsoft Excel (see example in supplementary material). This method captures survival from health state but has potential limitation for tracking time-dependent costs and QALYs. An individual Markov engine is required for each treatment, thus if multiple subsequent therapies are available, the model can become very large	Lump sum costs and outcomes are added when patients transition into a health state without further sub-modeling. This approach can be much less computationally complex than tunnel states if costs and outcomes are taken from, for example, previous HTA appraisals
Model validation	Outcomes are captured relative to model time, which allows for outcomes to be included in, for example, calculation of model OS, thus facilitating validation against external data	Given that costs and outcomes for remainder of time in health state are accounted for in the cycle the patients enter the health state, an OS curve (for example) cannot be calculated from the model. This limits the possibility to validate long-term projections of overall model outcomes in relation to external data

Abbreviations. DR distant recurrence; HTA health technology assessment; OS overall survival; QALY quality-adjusted life-year.

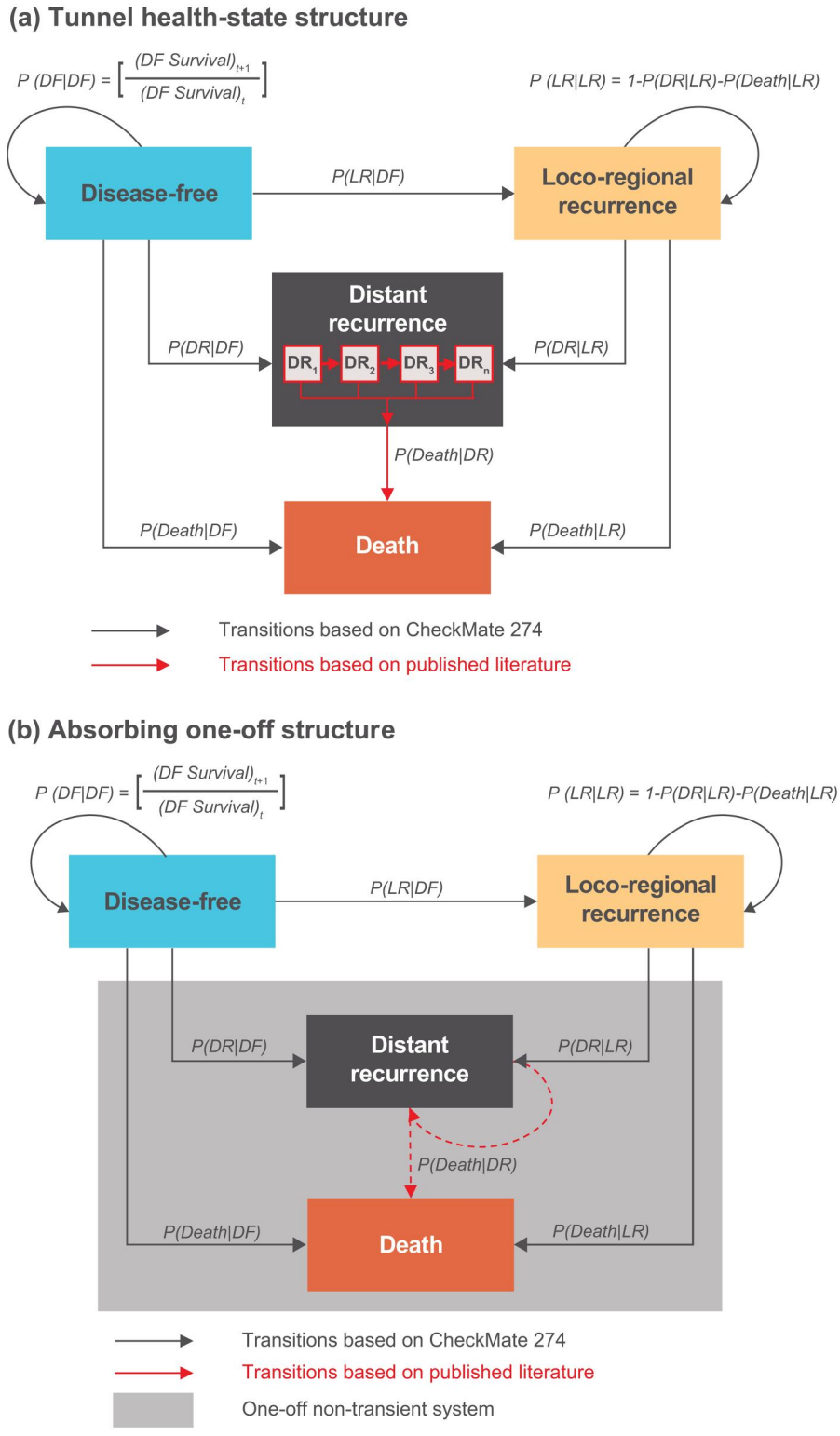

Figure 1. Four-state model structures: (A) tunnel health state structure adopted in the current model and (B) absorbing one-off structure. DF: disease-free; DR: distant recurrence; LR: local recurrence; P(Death|DF): probability of death from DF; P(Death|LR): probability of death from LR; P(DF|DF): probability of staying in DF; P(DR|DF): probability of moving from DF to DR; P(DR|LR): probability of moving from LR to DR; P(LR|DF): probability of moving from DF to LR; P(LR|LR): probability of staying in LR.

survival for patients with MIUC undergoing RR[27], methods for extrapolation must ensure a good fit both to trial data and long-term clinical validity[31,32].

In the model, an important assumption that can impact the long-term survival projections and the estimation of transition probabilities was the potential for cure. Treatment of early-stage cancer, including adjuvant treatment of patients with MIUC with RR, can have a curative intent and potential; thus, patients who remain DF beyond a certain timepoint could be considered cured[8,33,34]. Beyond this timepoint, patients would no longer be at risk of a recurrence event and disease-related death, and survival could be

characterized in the model by general population mortality. With the functional cure assumption, the DFS extrapolations would be needed for a considerably shorter horizon than a lifetime, and this can potentially reduce some of the uncertainty around the DFS and modeled OS predictions related to long-term extrapolations. This reduced uncertainty would pertain both to extrapolated survival and duration of treatment effect, which has often been a key area of uncertainty in appraisals of IO treatments[35]. However, by including the concept of cure in the model, a new uncertainty (the timepoint when patients are considered cured) is then introduced, and assumptions must be supported with clinical data.

Several options for extrapolation of DFS were considered during the development of the current economic model. First, extrapolations using standard parametric and spline-based survival models, as well as piecewise modeling approaches, were explored based on the CheckMate 274 data following NICE methods guidance[31,32]. In alignment with NICE guidelines, all fitted models were assessed for goodness of fit (statistical and visual fit) to observed trial data and to long-term survival predictions based on external data.

In addition to standard parametric and spline-based survival models for DFS extrapolations for a lifetime horizon, an alternative approach is to incorporate external evidence to predict long-term survival after trial follow-up[32,36]. In the setting of MIUC, where patients who remain DF beyond a certain timepoint could be considered cured, the survival from that timepoint could be assumed to be that of the general population. In addition, survival from the end of the trial until the time of cure can potentially be modeled based on external data for patients with MIUC who had longer follow-up than that in CheckMate 274. Addressing these data gaps with external data can minimize the need for extrapolation beyond the observed pivotal trial data and thus reduce uncertainty. Therefore, the current model incorporated external data to support extrapolation, in addition to the use of standard parametric and spline-based survival models.

A final consideration in modeling DFS concerned the lack of evidence on the timing of pre-recurrence deaths due to blinding and hence the inability to separate the specific DFS events (LR, DR, and death) in the core dataset. Early database locks as in CheckMate 274, with limited follow-up and unavailability of OS data, hampers the ability to employ a competing risk model where time from DF state to each subsequent state can be individually modeled. With OS data unavailable, DFS events cannot be split into subsequent LR, DR, and death events (with corresponding time of events) to model the distribution of DFS events over time. Therefore, in the model, a simplifying assumption of the constant proportion of events over time was used to estimate transition probabilities from DF to all other health states up to the cure timepoint, after which patients are only at risk of non–disease-related death. Under this assumption, transitions out of the DF state were split into three using weights calculated from the total number of LR, DR, and death events happening during the entire trial follow-up[11].

Local/regional recurrence state

In the model, patients entering the LR state were assumed to receive subsequent surgery and radiotherapy. In the LR state, patients can either maintain their status or experience a DR or death. The next challenge in the modeling process was to project transitions after LR. With the available follow-up time for CheckMate 274, the number of patients experiencing death or DR after an initial LR was limited. This limitation was also observed in the cost-effectiveness models for other adjuvant treatments in oncology[18,21]. With the limited number of events per treatment arm, extrapolating time to subsequent event after LR separately for each treatment arm would result in considerable uncertainty. In addition, limited evidence was available to support any assumption of carry-over of treatment effect from adjuvant treatment to improve survival after LR[15,16], and no external data on DR and death events after LR that could be used to inform the model were identified. Therefore, a simpler assumption was made that the CheckMate 274 study arms did not differ in outcomes after LR. Pooling data for both study arms to inform survival after LR increased the statistical power of the survival analysis.

As discussed previously, the model incorporated the possibility of a functional cure for patients in the DF health state. The clinical plausibility of cure after LR was also considered, but such a cure assumption could not be established based on the limited survival data available for patients experiencing LR. Therefore, the potential for cure after LR was not considered in the model. In clinical settings, where data or clinical judgment would be available to establish the potential for cure after LR, this could have implications for the structural modeling of LR. Incorporation of functional cure upon LR requires monitoring of time spent in this state, which would need additional tunnel states in the model structure, as described for the modeling of subsequent therapy in the DR health state. Similarly, if the exponential distribution does not provide an adequate fit to the time to subsequent event from LR, then additional tunnel states to track time spent in the LR health state would be required in the model.

Distant recurrence state

Patients entering DR are assumed to receive subsequent therapy with anticancer therapies for 1 L mUC. In the base-case analysis, health-state occupancy for DR was based on the estimation of survival after DR and applied through the tunnel state approach (described earlier) to track the time of entering the health state. Health-state occupancy, and hence QALYs and life-years, were estimated using sub-models for each individual 1 L mUC treatment and weighting the subsequent therapy distribution for each treatment arm. By specifying DR survival predictions (and hence, estimated OS) for the full selection of available subsequent therapy options and their distribution, the current model's OS predictions can be tailored to any 1 L mUC setting, making the model highly adaptable to local clinical practice in different jurisdictions. Further, DR outcomes can be tailored to align with 1 L mUC treatments for subgroups of patients (e.g. those who are

cisplatin eligible or ineligible), and potential new 1 L mUC therapies can be added. The model is thus flexible in reacting to rapidly changing subsequent therapy patterns.

Dead state

In the model, transitions to the dead state are state specific (i.e. separate transitions are applied to DF, LR, or DR). In the DF health state, deaths are modeled based on DFS extrapolation and the proportion of death events observed in CheckMate 274 up to the cure timepoint. After a functional cure, patients are only at risk of dying of non–disease-related causes, represented by general population mortality. Similarly, in the LR health state, deaths are modeled based on extrapolated survival after LR and the proportion of death events observed in CheckMate 274 for patients in LR. For the DR health state, mortality is based on OS data for each subsequent 1 L mUC treatment, weighted for each model arm according to the distribution of subsequent therapies.

Discussion

As demonstrated here, multiple considerations need to be taken into account when developing an economic model for new, emerging oncology treatments in early lines of therapy, all of which could have an impact on the model's ability to accurately estimate survival and QALY benefits. This paper highlights some of the challenges and considerations regarding modeling of nivolumab treatment in the adjuvant MIUC setting. Several options were included in a flexible cost-effectiveness model, where the impact of structural uncertainties on model results can be explored. The impact of these alternative approaches on cost-effectiveness results are presented in a companion article[12].

Specifically with regard to structural assumptions, we have explored how the absence of OS data affects the choice of STM compared with PSM. For the current model, STM was selected because a strong surrogacy relationship between DFS and OS could not be established from the literature for adjuvant treatment of MIUC[15,16]. Similarly, it was considered that even if strong surrogacy could have been established based on available evidence for the standard of care mainly consisting of chemotherapy or active surveillance, the surrogacy might not be fully applicable for IO therapies given the different mechanisms of action and the evolving treatment landscape in subsequent lines of therapy. However, in situations where a strong surrogacy relationship could be established or mature OS data were available from the pivotal trial, a PSM could be a viable modeling option that would require fewer external data sources to inform health-state transitions than STM.

The base-case model was developed with four health states because it could better represent the clinical progression of MIUC by explicitly capturing both LR and DR. The use of four health states, in combination with an STM, provides a flexible model to capture the different outcomes from each recurrence event (LR or DR), as well as the possibility to investigate the impact of different compositions of subsequent therapies. This flexibility was seen to be a strength, which allows the model to be adapted to multiple jurisdictions and capture the relevant composition of subsequent therapies for each jurisdiction.

However, although this allows for granular modeling of 1 L mUC treatment, it should be acknowledged that second and later line therapies are implicitly assumed to be accounted for within the 1 L mUC treatment data used. In the model, the impact of explicitly modeling further lines of therapies was assumed to have a limited impact on results given that survival with metastatic disease is limited and only a proportion of patients will proceed to further lines of therapy.

To model costs and outcomes of subsequent therapies, a structure allowing for time-dependent transition probabilities was chosen for the base case. This makes the model more flexible, because alternative survival distributions can be explored for each of the included 1 L mUC treatments, and avoids relying solely on exponential distributions, an approach criticized in previous models for adjuvant anticancer therapy[37]. However, given that approaches based on time-dependent transitions or absorbing states were included in the model, scenario analyses can be presented so the impact of these modeling assumptions can be investigated and potentially inform future model development in early-stage cancer.

The key source of data to inform the clinical parameters for the model was the CheckMate 274 trial. The need to extrapolate the trial data beyond the study follow-up time can present challenges for predicting the long-term outcomes of treatment with adjuvant nivolumab in patients with high-risk MIUC after RR. However, in modeling DFS, a balancing consideration is that treatment after RR has a curative intent, and a relatively short period of extrapolation was needed from the end of the trial to a timepoint of functional cure. To some degree, modeling cure may limit the uncertainty of long-term effects, compared with settings where much longer extrapolations (often to the full model time horizon) are needed.

A limitation of the data available from CheckMate 274 was that OS data were unavailable at the time of modeling. Because of this and the low number of events observed for some outcomes, the distribution of DF events was assumed to be constant with time and common between study arms. Similarly, because of the low number of LR events, survival after LR was based on pooled data across both treatment arms in CheckMate 274. Because of these limitations, treatment-specific proportions of events and LR survival were not explored in the base-case analysis. However, as presented in a companion paper, the impact of these assumptions has been explored using alternative data and assumptions[12].

In summary, the current STM provides a flexible framework that enables cost-effectiveness assessment of adjuvant treatment with nivolumab in patients with high-risk MIUC after RR over a lifetime horizon, when OS data are not available at the time of model development. The model is highly adaptable to reflect local market settings and treatment patterns and can be expanded to reflect rapidly changing

treatment landscapes in subsequent lines of therapy. For structural assumptions, such as the use of three or four health states and modeling of subsequent therapies based on absorbing health states versus tunnel health states, both options have been included so the impact of these structural assumptions can be explored. Assessment of the impact of these alternative structural assumptions and data choices on the model results are presented in an accompanying article[12].

Transparency

Declaration of funding

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Declaration of financial/other interests

ST, MK, and MYP are employees of Bristol Myers Squibb (BMS); TP was an employee of BMS at the time of the study. THB, CK, and FK are employees of RTI Health Solutions, which received payment from BMS for contracted analyses. SP received personal payment from BMS for attendance at an advisory board meeting.

Author contributions

All authors contributed to the study design. ST and THB developed the first draft of the manuscript. All authors reviewed and contributed critical revisions to the manuscript. All authors agree to be held accountable for the manuscript content and approve the final version for publication.

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Data availability statement

Data are available upon reasonable request. Bristol Myers Squibb's policy on data sharing may be found online at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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