Challenges in Economic Modelling of Adjuvant Cancer Therapy for Health Technology Assessments

SA6

Padgett K,[1] Brown T,[1] Krieger T,[1] Moseley O,[1] Gabb P,[1] Toron F,[2] Kassahun S,[3] Jones B[1]

[1]Health Economics Outcomes Research Ltd, Cardiff, UK; [2]Bristol Myers Squibb, London,UK;
[3]Bristol Myers Squibb, Uxbridge, UK

Introduction

- Urothelial and oesophageal cancers pose significant health burden in the UK, with approximately 10,292 and 9,272 newly diagnosed cases each year, respectively[1,2]
- Patients diagnosed with early-stage cancer may be able to receive potentially curative surgery
- Economic modelling of adjuvant cancer therapy is subject to several challenges that reduce the applicability of traditional oncology approaches, such as partitioned survival models
  - Immature or unavailable overall survival (OS) data and the requirement to model post-recurrence treatment options
  - Patients are often considered to be in remission by clinicians, with survival outcomes equivalent to the general population, and are discharged from care if no recurrence has occurred. An economic model evaluating the adjuvant cancer treatment setting should reflect this clinical pathway in order to retain face validity

Objectives

- This study aimed to identify the most appropriate modelling approach for adjuvant therapies in the UK setting, and subsequently implement these findings in the development of cost-effectiveness models for health technology assessments (HTAs) for the National Institute for Health and Care Excellence (NICE), specifically TA817 and TA746

Methods

- A targeted literature review conducted in February 2021 (in line with Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] guidelines), identified all NICE HTAs that assessed treatment for patients with resected cancers who received adjuvant therapy
- Relevant data was extracted that pertained to model approach, structure and assumption, including pre-relapse and post-relapse survival parameters, and relevant critiques provided by the Evidence Review Groups (ERGs) and NICE committees
- The output from this review was used to inform the strategy for two nivolumab HTAs, alongside clinical insights

Results

Review of previous HTAs of adjuvant cancer therapy

- Ten HTAs were identified, with summarised modelling approaches provided in **Table 1**
- Disease-free survival (DFS), invasive DFS, and recurrence-free survival were the most relevant clinical trial endpoints and were used for modelling pre-recurrence survival
- Markov modelling was the most common approach (8 HTAs)
  - In all models where the Markov approach was used, external data was used to inform post-recurrence modelling, including OS, as outlined in **Table 1**
- Two studies used partitioned survival models, and trial outcomes were supplemented by indirect treatment comparisons and a surrogate relationship between RFS and OS
- The methods for modelling pre-recurrence survival in Markov models were fairly diverse
  - Modelling of pre-recurrence survival could be split into one (n=3), two (n=2) or three (n=3) time periods, where the treatment effect would alter
  - Modelling of pre-recurrence survival was considered by ERGs and NICE committees to be a major source of uncertainty, requiring adequate justification for approach
- All identified economic models had to contend with immature or unavailable OS data
  - Four Markov models used a cure assumption, applying general population mortality for patients with no recurrence beyond a specific time point, with time applied ranging from 5 to 11 years (5 years: 1 model; 10 years: 2 models; 129 months: 1 model). Two of these models assumed a fixed proportion of patients would remain at risk of recurrence, while the other two models assumed background mortality rates
  - In Markov models, the most prevalent solution was to model an independent post-recurrence survival analysis
    - Published literature informed post-recurrence mortality (7 HTAs)
    - Post-recurrence survival analyses were most commonly driven by data sourced from trials with metastatic baseline populations, though the trials used were not always of sufficient maturity or comparability

Table 1. Identified technology appraisals

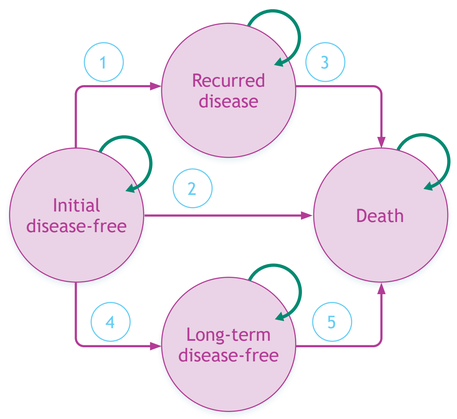
HTA # (year)	Indication	Treatment	Model approach	Pre-recurrence modelling	Post-recurrence modelling
TA100 (2006)[3]	Surgery of stage III (Dukes' stage C) colon cancer	Capecitabine + oxaliplatin	Markov	**DFS**: time dependent	Cure assumed; **OS**: external data
TA326 (2014)[4]	KIT (CD117)-positive gastrointestinal stromal tumours	Imatinib	Markov	**RFS**: treatment-dependent	**OS**: external data
TA501 (2018)[5]	Early breast cancer	INTRABEAM radiotherapy system	Markov	**RFS**: stratified by LR/ other recurrence	**Post-LR**: external data **Post-DM**: calculated from probability of other recurrence
TA544 (2018)[6]	Resected BRAF V600 mutation-positive melanoma	Dabrafenib + trametinib	Markov	**RFS**: time-dependent	**RFS**: trial data adjusted from external; **Death**: external data
TA553 (2018)[7]	Resected melanoma with high risk of recurrence	Pembrolizumab	Markov	**RFS**: stratified by LR, DM, and death	**Death, post-LR**: trial data; **risk of DM**: external data; **death, post-DM**: NMA
TA558 (2019)[8]	Completely resected melanoma with lymph node involvement/ metastatic disease	Nivolumab	Partitioned survival model	**RFS:** time dependent **OS:** hazard ratio applied to RFS relative to external data	
TA569 (2019)[9]	HER2-positive early stage breast cancer	Pertuzumab, trastuzumab and chemotherapy	Markov	**iDFS**: time dependent	Cure assumed; **risk of DM**: external data; **PFS/OS**: external data
TA612 (2019)[10]	HR-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab	Neratinib	Markov	**iDFS**: time dependent	Cure assumed; **risk of DM**: external data; **PFS/OS**: external data
TA619 (2020)[11]	HR-positive, HER2-negative locally advanced/metastatic breast cancer in adults who have had endocrine therapy	Palbociclib + fulvestrant	Partitioned survival model	PFS and OS	
TA632 (2020)[12]	HER2-positive early breast cancer	Trastuzumab emtansine	Markov	**iDFS**: time dependent	Cure assumed; **risk of DM**: external data; **PFS/OS**: external data

DFS: disease free survival; DM: distant metastasis; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease free survival; LR: local recurrence; NMA: network meta-analysis; OS: overall survival; PFS: progression free survival; RFS: recurrence free survival

Adjuvant cancer model implementation methodology

- Based on the findings of this review, de novo semi-Markov models were developed for nivolumab in the adjuvant treatment of oesophageal cancer and muscle-invasive urothelial carcinoma (**Figure 1**)
- For both models, pre-recurrence survival were derived from trial data
- Post-recurrence survival data for both economic models were derived from published literature describing relevant subsequent therapies as outlined in **Figure 1**
- Cure (long-term disease-free state) was assumed for those recurrence-free after 5 years in urothelial and oesophageal cancer models, respectively, based on smoothed hazard plots from trial data. The timing of cure was validated by clinical experts

Figure 1. Overview of adjuvant model approach



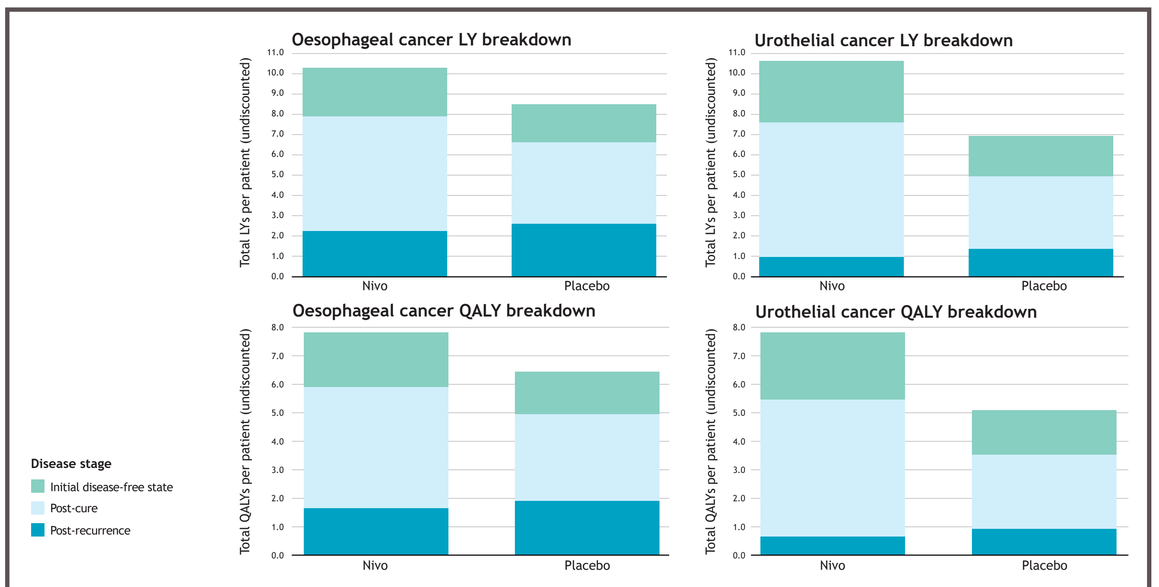
	Transition	Urothelial Cancer (TA817)	Oseophageal Cancer (TA746)
1	Disease-free to recurred disease	Trial data (CM274; DFS curve)[13]	Trial data (CM577; DFS curve)
2	Disease-free to death	Trial data (CM274; disease-specific deaths)[13] and background mortality[14]	Trial data (CM577; disease-specific deaths) and background mortality
3	Recurred disease to death	Bellmunt et al.[15] and De Santis et al.[16] (equal split)	Lou et al.[17]
4	Initial to long-term disease-free	All patients at 5-year timepoint, based on clinical feedback	All patients at 5-year-timepoint, based on clinical feedback
5	Long-term disease-free to death	Background mortality[14]	Background mortality[18]

CM274: CheckMate 274; CM577: CheckMate 577; DFS: disease-free survival.

Adjuvant cancer model results

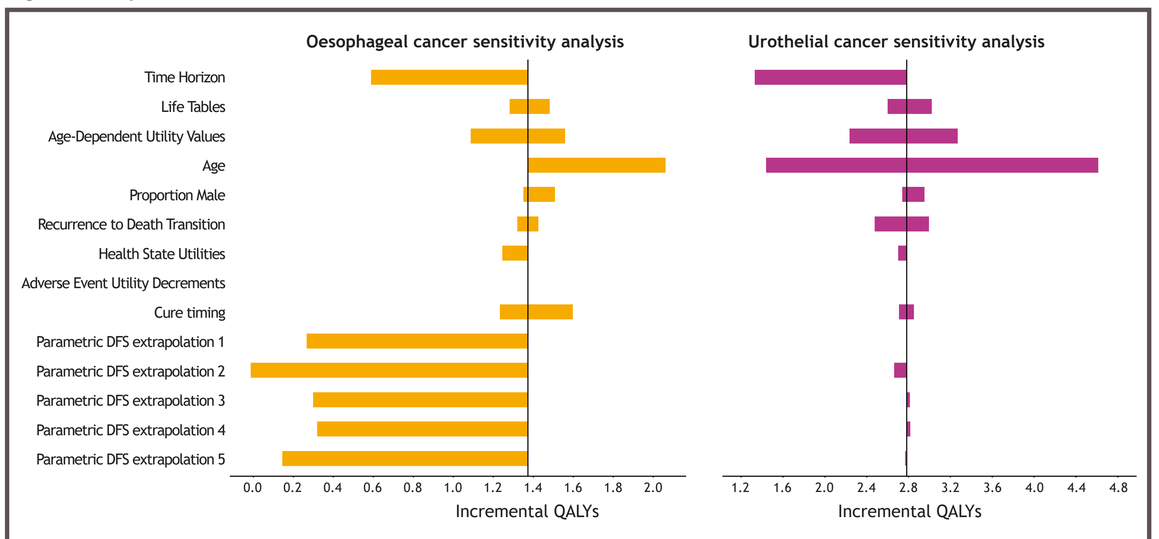
- Clinical benefits of nivolumab (life years and quality-adjusted life years) were predominantly accrued in the disease-free state (**Figure 2**)
- While outcomes varied by modelled population, the largest model drivers were DFS extrapolations, timing of the cure assumption, and baseline age (**Figure 3**)
- Outcomes were aligned with expectations from clinical experts

Figure 2. Breakdown of health benefits accrued in the economic models



LYs: life years; Nivo, nivolumab; QALYs, quality-adjusted life years.

Figure 3. Key economic model drivers



DFS: disease free survival; QALYs, quality-adjusted life years.

Conclusions

- It is important that adjuvant cancer modelling approaches are able to address relevant challenges such as immature OS data
- The Markov structure is most appropriate for the adjuvant setting, since it permits the application of published literature sources
- Markov models also provide greater flexibility for sensitivity analysis compared with the partitioned survival approach, which is very a important consideration for modelling of adjuvant therapies given immaturity and sometimes unavailability of OS trial data
- Validation from external experts and sources remains essential

References

1. Cancer Research UK. Bladder Cancer Statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence [Accessed 10 February 2021]
2. Cancer Research UK. Oesophageal Cancer Statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence [Accessed 14 September 2021]
3. National Institute for Health and Care Excellence. TA100: Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. 2006. Available at: https://www.nice.org.uk/guidance/ta100 [Accessed 10 February 2021]
4. National Institute for Health and Care Excellence. TA326: Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. 2014. Available at: https://www.nice.org.uk/guidance/ta326 [Accessed 10 February 2021]
5. National Institute for Health and Care Excellence. TA501: Intrabeam radiotherapy system for adjuvant treatment of early breast cancer. 2018. Available at: https://www.nice.org.uk/guidance/ta501 [Accessed 10 February 2021]
6. National Institute for Health and Care Excellence. TA544: Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma. 2018. Available at: https://www.nice.org.uk/guidance/ta544 [Accessed 10 February 2021].
7. National Institute for Health and Care Excellence. TA553: Pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence. 2018. Available at: https://www.nice.org.uk/guidance/ta553 [Accessed 10 February 2021
8. National Institute for Health and Care Excellence. TA558: Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease. 2019 Available at: https://www.nice.org.uk/guidance/ta558 [Accessed 10 February 2021]
9. National Institute for Health and Care Excellence. TA569: Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. 2019 Available at: https://www.nice.org.uk/guidance/ta569 [Accessed 10 February 2021]
10. National Institute for Health and Care Excellence. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. 2019 Available at: https://www.nice.org.uk/guidance/ta612 [Accessed 10 February 2021]
11. National Institute for Health and Care Excellence. TA619: Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. 2020 Available at: https://www.nice.org.uk/guidance/ta619 [Accessed 10 February 2021]
12. National Institute for Health and Care Excellence. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. 2020 Available at: https://www.nice.org.uk/guidance/ta632 [Accessed 10 February 2021]
13. Bristol Myers Squibb. Primary Clinical Study Report for Study CA209274. A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma. 2020
14. Office of National Statistics. National UK life tables: UK. 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Accessed 4 January 2021]
15. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13
16. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(33):5634-9
17. Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol. 2013;8(12):1558-62
18. Office for National Statistics. Cancer Registration Statistics, England, 2015. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2015 [Accessed August 2017]

Disclosures

- This analysis was supported by Bristol Myers Squibb

Presented at ISPOR Europe 2022; November 6-9, 2022; Vienna, Austria, and virtual

Email: tray.brown@heor.co.uk