MONASH University

Health economic modelling of oncology therapies

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Abbreviations

AE	Adverse Event
AIHW	Australian Institute for Health and Welfare
ALK	Anaplastic Lymphoma Kinase
AM	Advanced Melanoma
BRAF	B-RAF serine-threonine kinase
BTK	Bruton's Tyrosine Kinase
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CMA	Cost Minimisation Analysis
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CR	Complete Response
CTLA-4	Cytotoxic T-lymphocyte-Associated Protein 4
DPMA	Dispensed Price Maximum Amount
DUSC	Drug Utilisation Committee
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels
ESC	Economic Subcommittee
FACT	Functional Assessment of Cancer Therapy
GIST	GastroIntestinal Stromal Tumours
HER2	Human Epidermal growth factor Receptor 2
HCC	Hepatocellular carcinoma
HTA	Health Technology Assessment
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
ICI	Immune Checkpoint Inhibitor
IPD	Individual Patient Data

irAE	immune-related Adverse Event
JAK	Janus-Associated Kinase
MAUI	Multi-Attributed Utility Index
MEK	Mitogen-activated protein kinase
mTOR	mammalian Target Of Rapamycin
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PD-1	Programmed cell Death protein 1
PD-L1	Programmed cell Death protein Ligand 1
PFS	Progression Free Survival
Pi3K	Phosphatidylinositol-3-Kinase
PR	Partial Response
QALY	Quality Adjusted Life Year
QLQ-C30	Quality of Life Questionnaire for cancer patients
QLQL-H&N35	Quality of Life Questionnaire for Head and Neck cancer 35-items
QLU-C10D	Quality of Life Utility Measure-Core 10 dimensions
QoL	Quality of Life
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumours
SAMEP	South Australian Medicines Evaluation Panel
SD	Stable Disease
SF-36	36-item Short Form
SG	Standard Gamble
SoC	Standard of Care
TGA	Therapeutics and Goods Administration
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour, Node and Metastases
TTO	Time Trade Off
VAS	Visual Analogue rating Scale

VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization

Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name: Hansoo Kim

Date: 24 November 2021

Abstract

Background

The treatment of cancer has evolved from non-specific chemotherapy to targeted therapies and immune checkpoint inhibitors (ICIs). The costs of newer treatments are high and access is challenging for decision makers and payers. Health technology assessment (HTA) incorporating health economic modelling is pivotal for managing the financial risks of oncology treatments. However, there are many uncertainties relating to efficacy, safety and benefits to patients' quality of life (QoL). Better methods are needed to ensure timely access to appropriate new oncology therapies. The aim of this thesis was to examine key technical issues relating to the health economic evaluation of oncology therapies and identify potential solutions.

Methods

For context, a literature review was first performed to characterise current issues relating to health economic modelling of cancer therapies. Using a published Australian health economic model that evaluated the cost-effectiveness of ICIs for metastatic melanoma, a study compared the results from use of a new cancer-specific QoL instrument (the Quality-of-Life Utility Measure-Core 10 dimensions [QLU-C10D]) to results from use of a generic EuroQol 5-Dimensions-3-Levels (EQ-5D-3L) instrument. Another study reassessed a cost-effectiveness analysis (CEA) reviewed by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) in 2017 for nivolumab (an ICI) versus everolimus for renal cell carcinoma (RCC), with updates to the price of everolimus and efficacy data for nivolumab. A fourth study validated input variables used the aforementioned CEA reviewed by the PBAC of nivolumab versus everolimus for RCC against real-world prescription data from the Australian Pharmaceutical Benefits Scheme (PBS). Finally, Australian stakeholders with experience with HTA of oncology therapies were surveyed to provide insight into current and future challenges in this space.

Results

The literature review identified four areas of significance in the health economics of oncology therapies: i) finding ways of capturing the QoL impact of new treatments, including arising from adverse events; ii) transforming and translating clinical data; iii) modelling health outcomes and costs beyond the duration of clinical trials; and iv) financial impact and affordability. The QoL study noted key differences between the cancer-specific QLU-C10D instrument and the generic EQ-5D-3L instrument in terms of modelled benefits, but the choice of instrument did not affect overall estimation of the cost-effectiveness of ICIs for metastatic melanoma. In the third study, updating efficacy data for nivolumab as well as the (lower) price of everolimus did not alter the PBAC's 2017 conclusion that nivolumab was cost-effective for the treatment of RCC. Similarly, the PBAC's decision

was validated by the study that applied real-world PBS data to the CEA. The stakeholder survey identified a number of areas for improvement for HTA in oncology. In particular, access to individual patient data was deemed crucial, as this would increase transparency and hence confidence in the claims put forward by sponsors, as well as provide opportunities for continued training in CEA methods.

Conclusions

Currently, access to new oncology therapies is often delayed due to uncertainty associated with HTAs. This work highlights the key issues pertaining to health economic modelling and offers potential solutions. Its importance is underscored by the high, and rising, burden of cancer, as well as a rich pipeline of emerging therapies. Nevertheless, there remains a need for further research to help drug developers, sponsors, policy makers, payers, patients and clinicians make informed and collaborative decisions.

Publications during enrolment

Publications related to this thesis

Kim H, Goodall S, Liew D. Reassessing the Cost-effectiveness of Nivolumab for the Treatment of Renal Cell Carcinoma based on Mature Survival Data, Updated Safety and Lower Comparator Price. *Journal of Medical Economics*. Jan-Dec 2021; 24(1): 893-899.

Kim H, Cook G, Goodall S, Liew D. Comparison of EQ-5D-3L with QLU-C10D in Metastatic Melanoma Using Cost-Utility. *Pharmacoeconomics Open*. 2021; 5(3): 459-467.

Kim H, Liew D, Goodall S. Cost-effectiveness and financial risks associated with immune checkpoint inhibitor therapy. *British Journal of Clinical Pharmacology*. 2020; 86: 1703-1710.

Kim H, Goodall S, Liew D. The Potential for Early Health Economic Modelling in Health Technology Assessment and Reimbursement Decision-Making. *International Journal of Health Policy Management*. 2021; 10(2): 98-101.

Kim H, Goodall S, Liew D. Health Technology Assessment Challenges in Oncology: 20 Years of Value in Health. *Value in Health*. 2019; 22(5): 593-600.

Kim H, Liew D, Goodall S. Current issues in health technology assessment of cancer therapies: A survey of stakeholders and opinion leaders in Australia. Under review at the *International Journal of Technology Assessment in Health Care*. NB: Responses to (minor) reviewers' comments submitted 1 November 2021.

Kim H, Goodall S, Ilomaki J, Liew D. Validating the cost-effectiveness of cancer drugs in Australia using real world evidence from payer script data. Submitted for publication in *Value in Health.*

Conference abstracts

Kim H, Cook G, Goodall S, Liew D. Constructing Comparator Survival DATA: Simulated Versus Individual Patient Data. International Society Pharmacoeconomics and Outcomes Research Asia Pacific meeting 2020. *Value in Health Regional Issues*. 2020: 22, Suppl S22, PCN89.

Kim H, Cook C, Goodall S, Liew D. Comparison of Disease-Specific (QLU-C10D) and Generic (EQ-5D) Utilities in Cost-Effectiveness Analysis. *Value in Health Regional Issues*. 2020: 22, Suppl S23, PCN97.

NB: Participation in conferences was impacted by the global COVID-19 pandemic.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

At the time of writing, this thesis includes five original papers published in peer-reviewed journals, one under review and another submitted for publication. The core theme of the thesis is health economic modelling of oncology therapies. The ideas, development and writing of all the papers in this thesis were the principal responsibility of myself, the student, working within the School of Public Health and Preventive Medicine under the supervision of Professor Danny Liew (75%) and Professor Stephen Goodall from the Centre for Health Economics Research and Evaluation (CHERE) at the University of Technology Sydney (25%).

The inclusion of co-authors reflects the fact that the work arose from active collaboration among researchers and acknowledges input into team-based research.

In the case of Chapters 1, 2, 3, 4, 5, 6 and 7, my contribution and the work involved the following:

Thesis Chapter	Publication Title	Status: (*Published, In press, Accepted or Returned for revision, Submitted*)	Nature and % of student contribution	Co-author name(s) Nature and % of co-author's contribution	Co-author(s), Monash student Y/N*
1	Cost-effectiveness and financial risks associated with immune checkpoint inhibitor therapy	Published	85%. Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Danny Liew Involved in study design, reviewed study results and manuscript (5%) 2) Stephen Goodall Overseeing the conduct of the study, reviewed the results and the manuscript (10%)	No
2	Health Technology Assessment Challenges in Oncology: 20 Years of Value in Health	Published	85%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Stephen Goodall Involved in study design, reviewed study results and manuscript (5%) 2) Danny Liew Overseeing the conduct of the study, reviewed the results and the manuscript (10%)	No
3	Comparison of EQ-5D-3L with QLU-C10D in Metastatic Melanoma Using Cost-Utility.	Published	80%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Greg Cook Involved in data acquisition, reviewed study results and manuscripts (5%). 2) Stephen Goodall Involved in study design, reviewed study results and manuscript (5%). 3) Danny Liew	No

				Overseeing the conduct of the study, reviewed the results and the manuscript (10%).	
4	Reassessing the Cost-effectiveness of Nivolumab for the Treatment of Renal Cell Carcinoma based on Mature Survival Data, Updated Safety and Lower Comparator Price.	Published	85%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Stephen Goodall Involved in study design, reviewed study results and manuscript (5%). 2) Danny Liew Overseeing the conduct of the study, reviewed the results and the manuscript (10%).	No
5	Validating input for cost-effectiveness of oncology drugs. Explores the use of real-world prescription data.	Submitted	83%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Stephen Goodall reviewed study results and manuscript (5%). 2) Jenni Ilomaki, Involved in data acquisition, reviewed study results and manuscripts (2%) 3) Danny Liew Overseeing the conduct of the study, reviewed the results and the manuscript (10%).	No
6	Current issues in Health Technology Assessment of cancer therapies: a survey of stakeholders and opinion leaders in Australia.	Submitted	85%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Danny Liew Involved in study design, reviewed study results and manuscript (5%) 2) Stephen Goodall Overseeing the conduct of the study, reviewed the results and the manuscript (10%).	No
7	The Potential for Early Health Economic Modelling in Health Technology Assessment and Reimbursement Decision-Making.	Published	85%, Involved in study design, collecting data, analyses, critical interpretation of the data and manuscript writing.	1) Stephen Goodall Involved in study design, reviewed study results and manuscript (5%). 2) Danny Liew Overseeing the conduct of the study, reviewed the results and the manuscript (10%).	No

*If no co-authors, leave fields blank.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student's signature: Date: 24 November 2021

Main supervisor's signature: Date: 24 November 2021

Acknowledgement

I would like to thank my supervisors, Professor Danny Liew and Professor Stephen Goodall, who have been most supportive and to whom I owe a world of thanks.

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Chapter 1: Introduction

1.1 Overview

The number of cancer cases is growing steadily, and a plethora of new expensive medications are being brought to market. Developing innovative drugs are costly. A study led by Tufts University estimated that the costs per approved new compound were USD $1395 million in 2013. The main reasons are the lengthy process for establishing the efficacy and safety of the drug, and high rates of failure [1]. Almost 90% of investigated drugs fail during the development process [2]. Once in market, the costs of cancer therapies are also higher because fewer patients take them, and durations of therapy are shorter. Higher prices are needed on a per-patient basis for the sponsors to recoup investment. Lastly, cancer is a 'dreaded' disease, and therapies can command a price premium of up to 50%[3].

Funding of cancer drugs involves the careful balance between awarding innovation, providing timely access and ensuring affordability for not only the public purse but also for patients and families. Unfortunately, there is an increased reliance on earlier evidence (e.g. clinical trials that rely on surrogate endpoints or survival that has not matured) to support funding decisions and it is therefore vital to established new methodologies to cope with these issues.

This chapter will describe the background rationale for this thesis. It comprises several sections, providing an overview of:

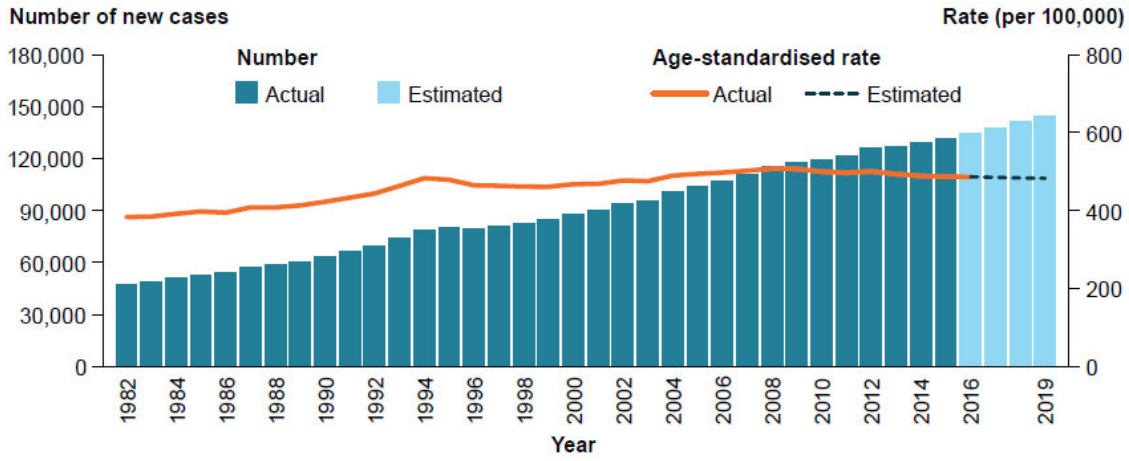
- the incidence, prevalence and burden of cancer
- oncology therapies
- access to oncology treatment in Australia

1.2 Incidence, prevalence and burden of cancer

The World Health Organization (WHO) estimated that 4.6 million people died due to cancer in 2016, and cancer is currently the leading cause of premature death in most developed countries in the world, including Australia [4].

The number of new cancer cases has grown steadily over the last four decades, with the Australian Institute for Health and Welfare (AIHW) reporting a three-fold increase between 1982 and 2019 [5]. The age-standardised incidence was approximately 500 cases per 100,000 in 2019 (Figure 1).

Figure 1 Trends in incidence of all cancers combined, persons, 1982 to 2019.



Notes

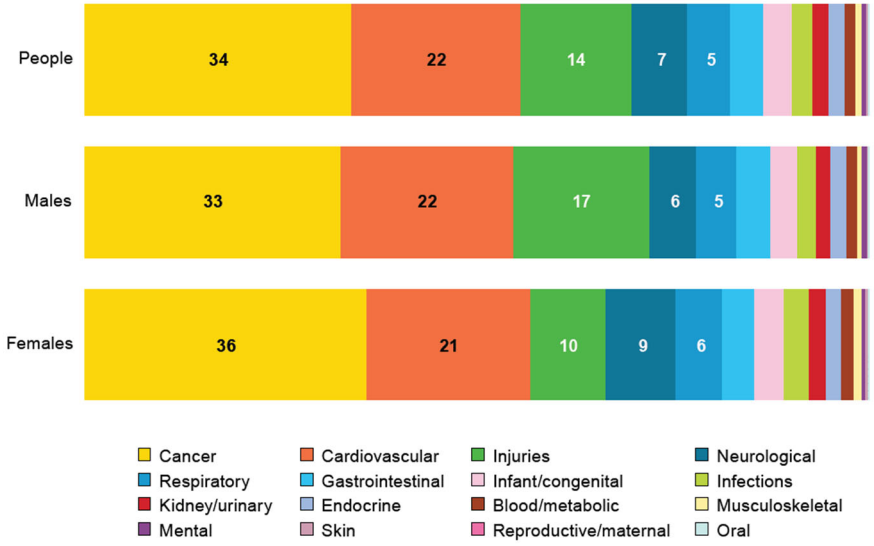
1. All cancers combined includes cancers coded in the ICD-10 as C00–C97, D45, D46, D47.1 and D47.3–D47.5, except those C44 codes that indicate a basal or squamous cell carcinoma.
2. The rates were age standardised to the 2001 Australian Standard Population and are expressed per 100,000 population.
3. The data for this figure are in online Table S5.2.

Source: Australian Institute of Health and Welfare 2019, Cancer in Australia, Cancer series no.119. Cat.no. CAN 123. Canberra: AIHW. [5]

Within the same time period, the increase in age-standardised incidence for some cancers have been especially notable. The incidence of renal cell carcinoma (RCC) increased by 108% from 6.2 to 12.9 per 100,000 person-years and the incidence of melanoma increased by 93% from 27 to 52 per 100,000 person-years. In 2021, it is estimated that 151,000 new cancer cases will be diagnosed and 49,000 people will die of cancer in Australia [6].

Cancer is the leading cause of mortality burden (premature death), as measured by years of life lost. According to the AIHW, cancer accounts for 34% of the total years of life lost in Australia, clearly exceeding the burden due to cardiovascular disease (22%) and injuries (14%) (Figure 2) [7].

Figure 2 Proportion (%) of fatal burden (year of life lost), by disease group and sex, 2015.



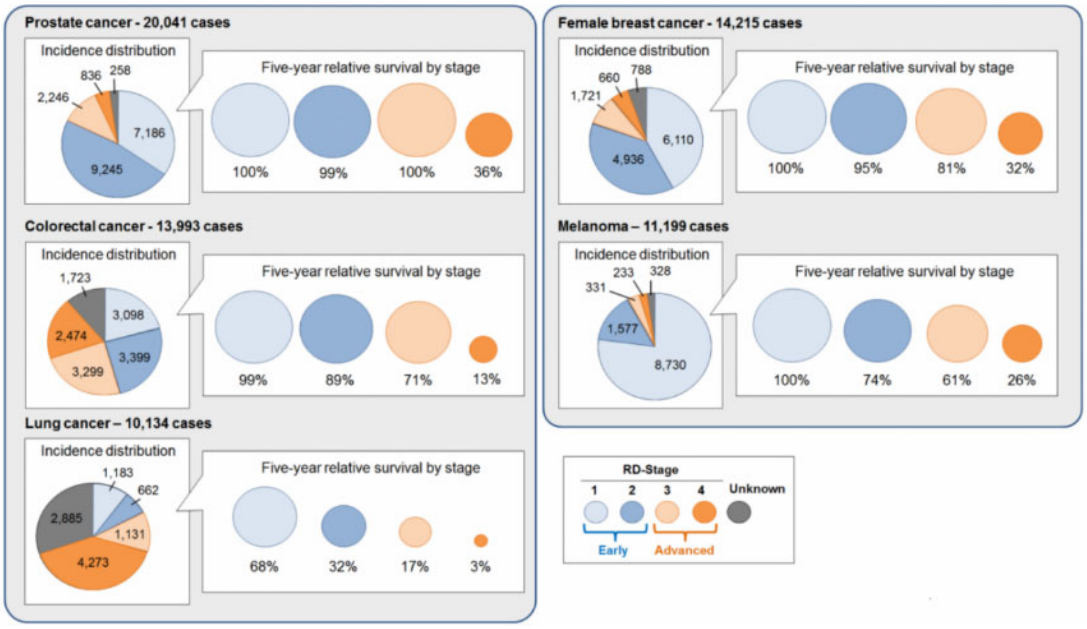
Note: Hearing & vision disorders are excluded as they did not cause any fatal burden.

Source: Australian Institute of Health and Welfare 2019. Australian Burden of Disease Study: impact and causes of illness and death in Australia 2015. Australian Burden of Disease series no. 19. Cat. no. BOD 22. Canberra: AIHW. [7]

The progression of cancer is often categorised into stages, with the generic stages being: I - localised to the organ of origin; II - regional spread but without involvement of lymph nodes; III - regional spread with involvement of lymph nodes; and IV - distant metastases [8]. Some cancers are further classified into sub-categories (for example, Stage IIa and IIb) to define more precise disease progression. There are other classification systems, such as the TNM (tumour, node and metastases) approach [8], but numbered staging is most commonly used to guide therapies. For example, Stage I and II RCC represents more localised disease that is generally amenable to surgical debulking, while Stage III and IV disease often indicates the need for (additional) systemic therapy [9].

Expectedly, cancer stage is a strong prognosticator regardless of type of cancer (which also guides cancer treatment). For example, 2011 data from Cancer Australia [10] demonstrated that the five-year survival in melanoma dropped from 100% for stage I disease to 26% for stage IV disease. In non-small cell lung cancer, five-year survival is 68% and 3% for stage I and stage IV patients, respectively (Figure 3).

Figure 3 Incidence distribution and 5-year survival by stage at diagnosis and cancer type, 2011.



Source: Cancer Australia, Relative survival by stage at diagnosis 2011–2016, a snapshot in time. Accessed 14-Aug=2021. https://ncci.canceraustralia.gov.au/features/relative-survival-stage-diagnosis-2011%E2%80%932016-snapshot-time. [10]

1.3 Evaluation of cancer therapies

The evaluation of cancer therapies focuses on four main groups of outcomes: (clinical) efficacy, safety, quality of life (QoL) and economic evaluation.

1.3.1 Efficacy

Progression free survival (PFS) and overall survival (OS) are the most commonly used efficacy endpoints in oncology clinical trials.

PFS is defined as the time between the date of randomisation and the first date of documented progression, based on radiology assessment of the cancer, or death due to any cause, whichever occurs first. Radiology assessment of progression is typically based on the response evaluation criteria in solid tumours (RECIST), with the outcomes being [11]:

- Complete response (CR): disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤ 10mm.
- Partial response (PR): ≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline.
- Progressive disease (PD): ≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded, or the

appearance of new lesions, including those detected by fluorodeoxyglucose positron emission tomography.

- Stable disease (SD): Neither PR nor PD.

Patients who die without a reported progression are considered to have progressed on the date of their death.

OS is defined as the time from randomisation to the date of death from any cause. For subjects who are alive, their survival time is censored at the date of last contact ("last known alive date").

1.3.2 Safety

The safety of oncology therapies is reflected by adverse events (AEs), which are defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient receiving an investigational treatment. An AE can therefore be any unfavorable and unintended clinical or laboratory finding, or a disease temporally associated with the use of the investigational treatment, whether or not these are considered related to the investigational product. AEs are graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [12]:

- Grade 1, Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2, Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3, Severe or medically significant but not immediately life-threatening: hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.
- Grade 4, Life-threatening consequences: urgent intervention indicated.
- Grade 5, Death related to AE.

1.3.3 Quality of life

Quality of life (QoL) reflects the trade-off between survival and several factors such as AEs of oncology treatments, treatment pathways, the cancer itself and the stage of disease progression. As such, it is an important tool for the assessment of oncology therapies.

There are two basic ways of quantifying QoL; via condition-specific instruments or generic instruments (Table 1). The former focuses on aspects specific to the disease under investigation.

Table 1 Taxonomy of measures of QoL

Approach	Strengths	Weaknesses
Generic instruments		
Health profile	Single instrument Detects differential effects on different aspects of health status Comparison across interventions; conditions possible	May not focus adequately on area of interest May not be responsive
Utility measurement	Single number representing net impact on quantity and quality of life Cost-utility analysis possible Incorporates death	Difficulty determining utility values Doesn't allow examination of effect on different aspects of quality of life May not be responsive
Specific instruments Disease specific Population specific Function specific Condition or problem specific	Clinically sensible May be more responsive	Doesn't allow cross-condition comparisons May be limited in terms of populations and interventions Restricted to domains of relevance to disease population, function, or problem; other domains that are important to overall HRQL not measured

Source: Cramer, J. and B. Spilker. Quality of Life and Pharmacoeconomics: An Introduction. 1998. [13]

The advantages of condition-specific QoL instruments include improved responsiveness to changes and the ability detect which dimensions are improved or worse. The advantage of generic instruments is that they are broad in scope and can be used in any patient population, thus allowing for comparisons across diseases and different health care programs [13]. This is particularly important when funding decisions need to be made across the entire health system.

An example of a condition-specific QoL instrument in cancer is the Quality of Life Questionnaire for Cancer patients (QLQ-C30) 30-item instrument [14]. The QLQ-C30 consists of five function scales (physical, roles, emotions, cognition and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea), a global QoL scale and a finance scale.

Population norms, (values for the general population) have recently been estimated by Mercieca-Bebber et al. [15] for Australia (Table 2). These population norms are informative comparator data that can be used as a benchmark as an individual cancer patient's QLQ-C30 score often fluctuates during the course of their disease. The data are also stratified by sex and age.

Table 2 QLQ-C30 Australian population norms.

	Total Australian sample
Number of respondents	1821
Global quality of life†	68.5 (21.5)
Physical functioning†	89.2 (19.0)
Role functioning†	88.8 (23.4)
Emotional functioning†	80.9 (24.1)
Cognitive functioning†	88.0 (21.9)
Social functioning†	90.7 (23.9)
Fatigue‡	23.9 (22.0)
Nausea/vomiting‡	4.6 (17.0)
Pain‡	21.8 (26.0)
Dyspnoea‡	11.7 (23.0)
Insomnia‡	24.4 (30.0)
Appetite loss‡	8.6 (21.9)
Constipation‡	9.4 (22.6)
Diarrhoea‡	5.9 (20.1)
Financial difficulties‡	6.2 (23.9)

Source: Mercieca-Bebber, R., et al., The EORTC Quality of Life Questionnaire for cancer patients (QLQ-C30): Australian general population reference values. Med J Aust, 2019. 210(11): p. 499-506.[15]

Generic instruments include health profiles and utility measurements. An example of a health profile is the 36-item short form survey (SF-36) [16]. SF-36 attempts to measure important aspects of health-related QoL by measuring different dimensions of health, such as physical functioning, social functioning, role limitations in terms of physical and emotional problems, mental health, vitality, pain and general health perception [17]. Utility is a concept used in health economics to estimate the preference of a patient with respect to different health states such as progressive disease or relapse of cancer. These measures arise from economic decision theory [13, 18]. Utility measures are summarised as a single score on a continuum from 0.00 (dead) to 1.00 (full health). Some instruments allow scores less than 0.00, which is interpreted as a state worse than death.

The actual utility values are obtained either through direct or indirect elicitation [19].

Direct elicitation is most commonly done through two techniques: time trade-off (TTO) or standard gamble (SG). In the SG approach a subject is offered a choice between two alternatives with different probabilities:

- Choice A: living in a health state with full health at a probability of *p* or death at a probability of *1-p*
- Choice B: taking a gamble on an intervention that leads to certain chronic health state

The probability *p* is varied until the subject is indifferent between choices A and B. Lower probability indicates that the subject is willing to consider risk of death meaning that the utility of the intervention is low. For respondents who have difficulty understanding probabilities, TTO is an alternative technique in which the subject is offered:

- Choice 1: living *x*/*t* years in perfect health
- Choice 2: living *t* years in alternative less desirable health state

The *x* is then varied in a systematic manner until the subject is indifferent between the shorter period in perfect health and the longer period in the less desirable state. The TTO preference score for the state then equals *x/t*.

A common weakness of these two approaches is that they do not impose a lower limit and in theory, utilities range from minus infinity to +1.0.

Indirect elicitation of utilities is done by using generic or condition-specific instruments. These tools are typically completed by patients and use 'off-the-shelf' preference-based scoring algorithms.

An example of a generic utility measurement is the EuroQol five-dimensional (EQ-5D) questionnaire [20]. The EQ-5D is a standardised instrument for use as a measure of self-reported health status. The EQ-5D comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety) (Figure 4) and a visual analogue rating scale (VAS).

Net changes in utility associated with treatment provide a single summary score of the QoL gains from treatment, which takes into consideration the QoL impact of AEs. Incremental changes in utility are usually calculated over a period of time that usually spans at least the duration of the clinical trial. Often these data are used to inform longer-term extrapolation over a defined period. This is useful for determining whether patients overall are better off with treatment, compared to no treatment or another treatment. As such, the utility data generated from the EQ-5D is recommended for, and commonly used, in health economics [21, 22]. However, it is important to note that EQ-5D is not the only source of utility data for economic evaluation of cancer therapies.

Figure 4 EQ-5D questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Source: Devlin, N., D. Parkin, and B. Janssen, An Introduction to EQ-5D Instruments and Their Applications, in Methods for Analysing and Reporting EQ-5D Data, N. Devlin, D. Parkin, and B. Janssen, Editors. 2020, Springer International Publishing: Cham. p. 1-22. [23]

1.3.4 Economic evaluation

High expense and the need to consider opportunity costs (benefits foregone by devoting resources away from other health interventions) [24] mean that new oncology treatments typically undergo formal economic evaluation of cost-effectiveness. Cost effectiveness analysis (CEA) is typically described in terms of improvements in health outcomes and costs associated with the intervention compared to current standard of care. The net cost per unit of health outcome benefit gained from the intervention is the incremental cost-effectiveness ratio (ICER), which is the main outcome of interest in CEAs. For example, assume that a new cancer drug procures two years of OS at a cost of $100,000, and standard of care yields a one year of OS at a cost of $25,000. The ICER can be calculated as ($100,000 - $25,000)/(2 years - 1 year) = $75,000 / year of life saved. A subgroup of CEA is cost-utility analysis (CUA), in which the health benefit is measured in terms of quality-adjusted life years (QALYs) saved.

Other types of economic evaluations are cost-minimisation analysis (CMA) and cost-benefit analysis (CBA). CMA is performed when improvements in health outcomes for a new intervention compared to standard of care are not expected. In this situation, the aim of the evaluation is to identify the least costly alternative. The use of CMA differs between jurisdictions. In Australia CMAs are used when there is a clinical claim of non-inferiority with respect to efficacy. In, the UK CMAs do not require strict non-inferiority.

CBAs consider all benefits of an intervention in monetary terms, with any health benefits considered only in terms of associated net costs [19]. Hence the key outcome of interest is net costs. For example, if a new intervention is $10,000 more costly than current standard of care, but the health benefits it procures leads to marginal savings of $20,000, then the net benefit is $10,000.

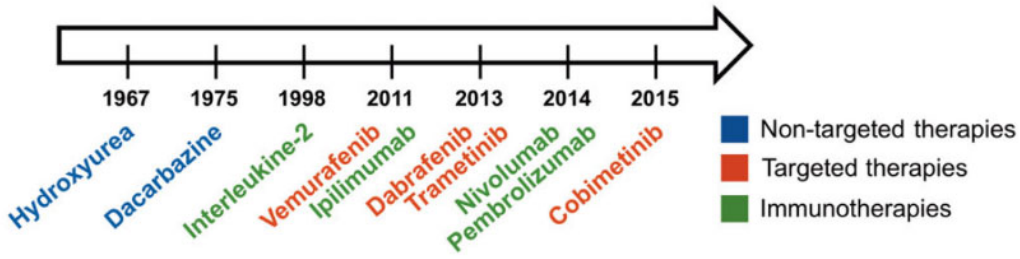
1.4 Overview of systemic oncology therapies

Oncology therapies can be categorised as non-systemic or systemic. Non-systemic (localised) therapies mostly comprise radiotherapy and surgical interventions and are performed to gain local control of disease. Systemic treatment aims to limit distant spread of cancer or treat cancer that has already metastasized and will be the focus of this sub-section.

Systemic oncology therapy has evolved from chemotherapy to targeted therapies to immune checkpoint inhibitors (ICI) over the past 20 years, with progressively improving efficacy. This is well-illustrated in systemic therapies for metastatic melanoma (Figure 5), which initially involved chemotherapies such as hydroxyurea and dacarbazine, before targeted therapies (vemurafenib,

dabrafenib, trametinib, cobimetinib) and ICIs (ipilimumab, nivolumab, pembrolizumab) entered the scene in 2011 [25]. Newer therapies have been pivotal in increasing survival among patients with advanced melanoma. Balch et al estimated the five-year survival for stage IV melanoma to be 10% in 2004 [26], while the AIHW estimated this figure to be 26% in 2019 [10].

Figure 5 Chronology of the therapies approved to treat metastatic melanoma.



Source: Millet, A., et al., *Metastatic Melanoma: Insights Into the Evolution of the Treatments and Future Challenges.* Medicinal Research Reviews, 2017. **37**(1): p. 98-148. [25]

1.4.1 Chemotherapies

The term 'chemotherapy' was coined by Paul Ehrlich in the early 20th century during his pioneering work on chemicals that bound to and specifically killed tumour cells [27]. In general, chemotherapies inhibit cell proliferation and tumour multiplication by affecting either macromolecular synthesis or the function of neoplastic cells. This is achieved by interfering with DNA, RNA or proteins synthesis of the cancer, thereby preventing further invasion and metastases [28].

Chemotherapies are widely used in Australia. They are listed as antineoplastic agents on the Australian Pharmaceutical Benefits Scheme (PBS) and classified according to their mechanism of action [29]. There are currently 42 different compounds listed as antineoplastic agents on the PBS (Appendix 1). They range in dispensed price for maximum amount (DPMA) from $39.50 for methotrexate to $14,288.65 for carmustine in public hospitals. The costs can be slightly higher in private hospitals as additional fees apply. For example, fotemustine costs $1847.78 DPMA in a public hospital, whereas the private hospital cost is $1913.47. The additional costs in a private setting includes a dispensing, a diluent fee and a distribution fee [30]. The majority of chemotherapies cost between $100 to $200 DPMA and only ten of the 42 drugs listed on the PBS cost more than $1000. Total costs of any chemotherapeutic agent to the PBS also depends on usage, which varies significantly. For example, docetaxel at $182.76 DPMA was dispensed 27,922 times from July 2020 to June 2021, whereas carmustine at $14,288.65 DPMA, was only prescribed 26 times in the same time period.

Chemotherapies are commonly associated with severe AEs as they also affect non-cancerous cells. Most chemotherapies target rapidly multiplying cells such as those in the gastrointestinal tract, skin, mucous membranes and bone marrow. Therefore, common AEs are constipation, nausea and vomiting, anorexia, mucositis and diarrhoea, [31-33] as well as alopecia, drowsiness, fatigue and myelosuppression [34, 35]. AEs can be managed with other therapies, but these are often ineffective and do not address potential long-term sequelae [31]. Chemotherapy therefore poses a significant challenge as treatment decisions need to carefully balance benefits against significant AEs that may ultimately worsen the QoL of patients.

Dacarbazine and fotemustine are archetypal examples of chemotherapies for advanced cancer. These agents have been used for the treatment of metastatic melanoma since their approval by the US Food and Drug Administration in 1975 [25]. In clinical trials, the OS of patients treated with dacarbazine and fotemustine were about 20% at 12 months and less than 10% at 24 months [36-39], which compares unfavourably with more modern therapeutic options. Furthermore, more than 25% of patients experienced grade 3 or 4 AEs, and measures of QoL were considerably worse than the Australian population norms (Table 1).

1.4.2 Targeted therapies

Chemotherapies kill normal cells in addition to cancer cells and are therefore toxic to many organs, as discussed in the previous section. Therapies that can discriminate between normal and cancer cells, thus leading to less AEs, are desirable. This was the main motivation for the development of new targeted therapies that inhibit cell growth of cancer cells. The idea of using cell growth inhibition in cancer treatments is far from new, with Ennis et al. publishing a review of the epidermal growth factor receptor (EGFR) system and tyrosine kinase inhibitors as antitumor therapy more than 30 years ago [40]. Targeted therapies inhibit kinases by stopping cell proliferation signaling [41]. There are many different kinase inhibitors affecting different kinases, as summarised in Figure 6. For example, vascular endothelial growth factor receptor (VEGFR) is considered the master regulator of angiogenesis during growth and development, as well as in disease states such as cancer, diabetes and macular degeneration [42]. Sorafenib and sunitinib are examples of drugs that inhibit VEGFR. Another tyrosine kinase that has been well studied is the EGFR, which is an enzyme that spans the cell membrane, with one end of the protein projecting from the cell surface. Gefitinib and lapatinib are examples of compounds that inhibit EGFR [43].

Figure 6 Mechanism of action of selected kinase inhibitors

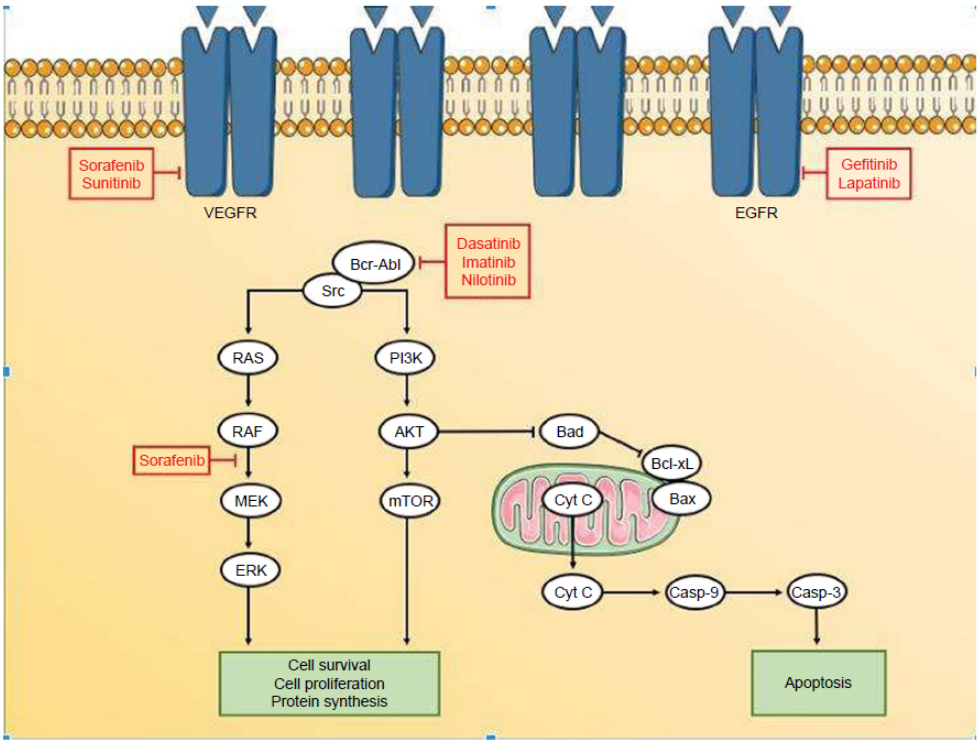


Figure 1 Mechanisms of action of FDA-approved tyrosine kinase inhibitors.
Abbreviations: AKT, protein kinase B; Bad, Bcl-2-associated death protein; Bax, Bcl-2-associated X protein; Bcl-xL, B-cell lymphoma extra large protein; Bcr-Abl, breakpoint cluster region-Abelson protein; Casp-3, caspase 3 protein; Casp-9, caspase 9 protein; Cyt C, cytochrome C protein; EGFR, epidermal growth factor receptor; ERK, extracellular signal regulated kinase; MEK, aka MAPK – mitogen activated protein kinase; mTOR, mammalian target of rapamycin protein; PI3K, phosphoinositide 3 kinase; RAF, rapidly accelerated fibrosarcoma protein; Src, sarcoma proto-oncogene; Ras, Ras protein superfamily; VEGFR, vascular endothelial growth factor receptor.

Source: Chaar, M., J. Kamta, and S. Ait-Oudhia, *Mechanisms, monitoring, and management of tyrosine kinase inhibitors-associated cardiovascular toxicities.* Onco Targets Ther, 2018. **11**: p. 6227-6237. [41]

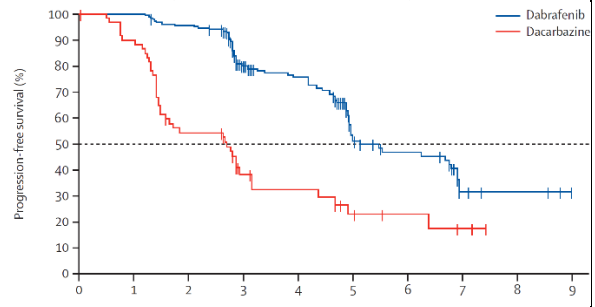
Targeted therapies have revolutionised cancer treatment in a number of ways. First, many of these drugs are small molecules that are administered orally, thereby saving patients time and costs of attending an infusion at a hospital or outpatient clinic. Secondly, these drugs slow progression of disease more effectively than chemotherapies. Erlotinib, one of the first targeted therapies developed to treat non-small cell lung cancer (NSCLC), was shown to significantly delay disease progression in patients with mutation of EGFR signaling pathway in clinical trials. A meta-analysis by Lee et al. [44] estimated the PFS hazard ratio for erlotinib versus chemotherapy to be 0.43 (95% CI: 0.38 to 0.49, p-value<0.001). Significant improvement in PFS is a common observation for targeted therapies. To illustrate, PFS for eight different targeted therapies for the treatment of advanced melanoma, gastrointestinal stromal tumours, hepatocellular carcinoma, NSCLC, RCC and soft tissue sarcoma are displayed in Figure 7. The observed hazard ratios for PFS vary from 0.30 (95% CI: 0.18 to 0.51) for dabrafenib versus dacarbazine for the treatment of advanced melanoma [45] to 0.44 (95% CI: 0.36 to 0.52) for cabozantinib versus placebo for the treatment of RCC [45]. Common to all these examples is

that the hazard ratio is statistically significantly lower than 1.0 for targeted therapies compared to standard of care of the time.

Figure 7 PFS of selected targeted therapies.

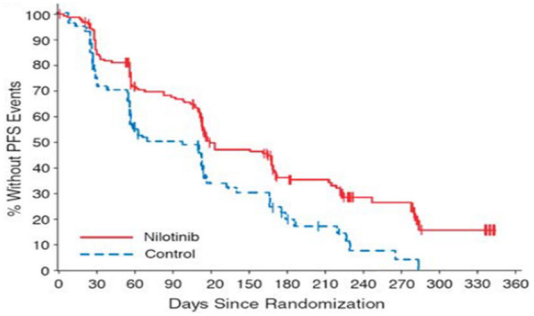
AM (BRAF+): dabrafenib vs dacarbazine

PFS: HR=0.30 (95% CI 0.18 to 0.51)[45]



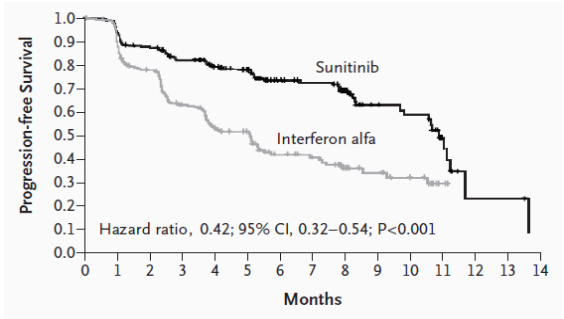
GIST: nilotinib vs best supportive care

PFS: HR=0.58 (95% CI: 0.42 to 0.80) [46]



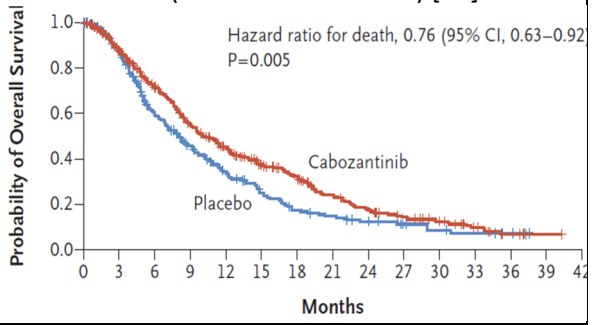
RCC: sunitinib vs interferon-alpha

PFS: HR=0.42 (95% CI: 0.32 to 0.54) [47]



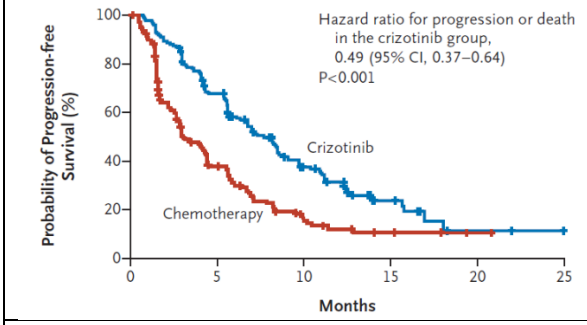
HCC: cabozantanib vs placebo

PFS: HR= 0.76 (95% CI: 0.36 to 0.52) [48]



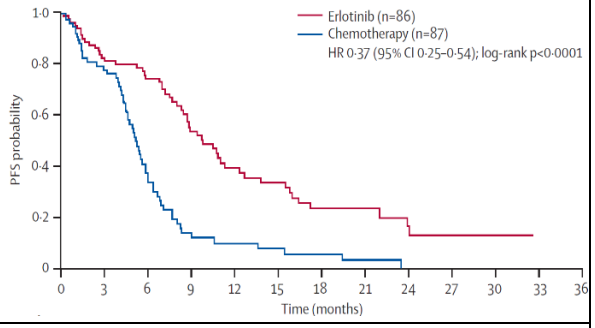
NSCLC (ALK+): crizotinib vs chemotherapy

PFS: HR=0.49 (95% CI: 0.37 to 0.64) [49]



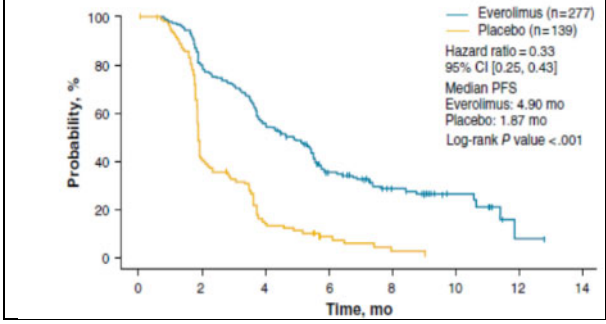
NSCLC (EGFR+): erlotinib vs chemotherapy

PFS: HR=0.37 (95% CI: 0.25 to 0.54) [50]



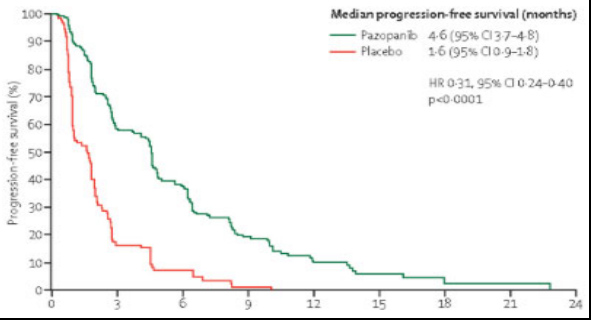
RCC: everolimus vs placebo

PFS: HR=0.33 (95% CI: 0.25 to 0.43) [51]



Soft tissue sarcoma: pazopanib vs placebo

PFS: HR=0.31 (95% CI: 0.24 to 0.40) [52]



ALK+: anaplastic lymphoma kinase positive, AM: advanced melanoma, BRAF+: B-Raf serine-threonine kinase, EGFR+: epidermal growth factor receptor positive, GIST: gastrointestinal stromal tumours, HCC: hepatocellular carcinoma, NSCLC: non-small cell carcinoma, RCC: renal cell carcinoma.

The third advantage of targeted therapy over chemotherapy is a better safety profile. Common AEs are gastrointestinal (similar to chemotherapy) and dermatological in nature, with cutaneous adverse reactions occurring especially with TKIs [53-56]. For EGFR inhibitors such as erlotinib and gefitinib, this is due to inhibition of EGFR activity, leading to a cascade of cellular events resulting in multiple cutaneous AEs, including rash, dry skin, pruritus and inflammation of the nail or periungual tissues [57]. A review by Livingstone et al. [56] found that AEs for BRAF and MEK inhibitors primarily affected the skin and the severity of the AEs were generally mild to moderate. Another review by Que et al. [54] found that VEGFR inhibitors such as pazopanib and sorafenib were associated with similar AEs. The most common (reported by more than 25% of patients) AEs (any grade) for EGFR inhibitors, BRAF/MEK inhibitors and VEGFR inhibitors are displayed in Table 3.

Table 3 Common AEs (any grade, >25%) for selected targeted therapies

EGFR inhibitors (e.g. erlotinib, gefitinib) [58, 59]	BRAF/MEK inhibitors (e.g. dabrafenib, vemurafenib) [56]	VEGFR inhibitors (e.g. pazopanib, sorafenib) [54]
Diarrhoea (19% - 96%) Elevated ALT (40% - 63%) Elevated AST (35% - 57%) Liver dysfunction (21% - 45%) Stomatitis (7% - 71%) Hypomagnesaemia (22% - 96%) Skin reactions (34% -90%) Paronychia (3% -57%)	• Rash (37% - 41%) • Photosensitivity (25% - 41%) • Alopecia (9% - 48%) • Pruritus (23% - 25%) • Arthralgia (35% - 56%) • Fatigue (20% - 46%) • Pyrexia (7% -28%) • Nausea (10% - 38%) • Headache (23% - 33%) • Skin papilloma (21% -28%)	• Nausea (7.6% - 47.2%) • Hypertension (9.3% - 40.9%) • Fatigue (30% - 54%) • Diarrhoea (24% - 43%) • Vomiting (5.4% - 27.4%) • Neutropaenia (0.0% -25%) • Leukopaenia (10.4% - 42.3%) • Anaemia (12.8% - 74.6%) • Rash (26.1%) • Hand-foot syndrome (33.4%) • Mucositis (38.5%)

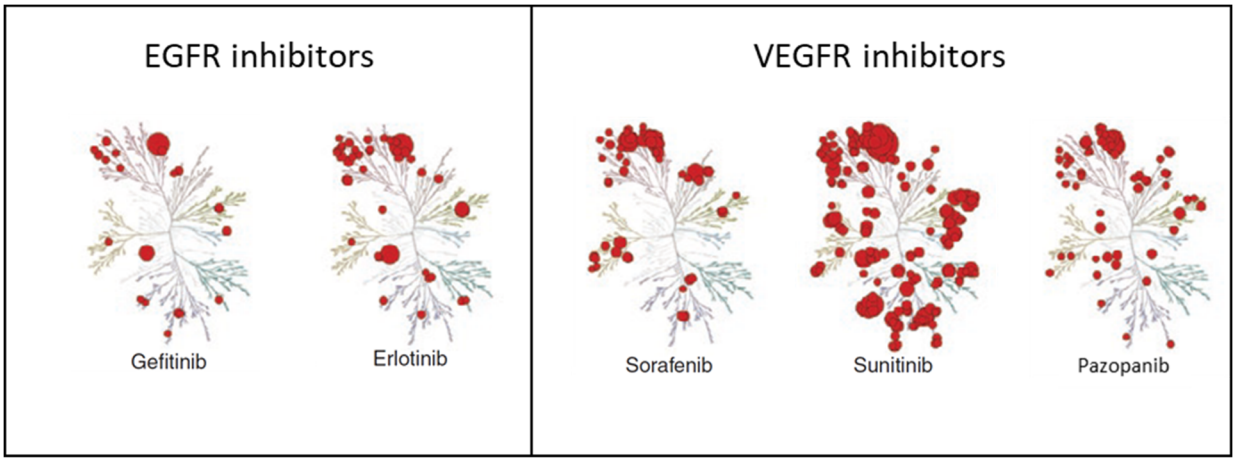
Sources:

- Shah, R.R. and D.R. Shah, Safety and Tolerability of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors in Oncology. Drug Saf, 2019. 42(2): p. 181-198.
- Huang, J., et al., Safety Profile of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: A Disproportionality Analysis of FDA Adverse Event Reporting System. Scientific Reports, 2020. 10(1): p. 4803.
- Livingstone, E. et al., BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management. Chin Clin Oncol,2014.3(3):p. 29.
- Que, Y., et al., Treatment-related adverse effects with pazopanib, sorafenib and sunitinib in patients with advanced soft tissue sarcoma: a pooled analysis. Cancer Manag Res, 2018. 10: p. 2141-2150.

The AE profile for each class of the targeted therapies is not uniform, which explains the wide range in proportions of patients experiencing a particular AE. For example, for VEGFR inhibitors, Que et al. reported that 47.2% of pazopanib treated patients had nausea, versus 7.6% for sorafenib. The reason

for differences, even within the same drug class, can be explained by the high variation in target sites and selectivity for these sites [60]. Figure 8 displays a quantitative evaluation of different kinase inhibitors against a panel of 287 distinct human protein kinases. Red dots represent inhibition of a kinase and the larger the dot, the more pronounced the inhibition is. The EGFR inhibitors gefitinib and erlotinib inhibit similar kinases as the two plots look the same. For VEGFR inhibitors, the pattern is quite different. Sunitinib clearly inhibits a larger number of kinases.

Figure 8 Small molecule–kinase interaction maps for 5 kinase inhibitors



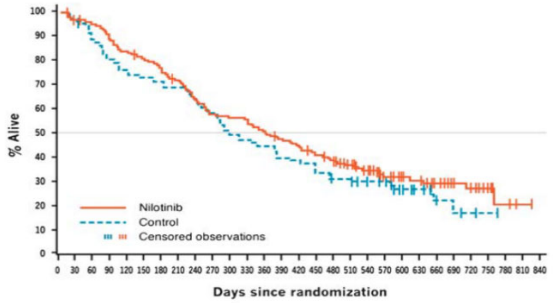
Source: Karaman, M.W., et al., A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol, 2008. 26(1): p. 127-32.

Although having a better safety profile than chemotherapy, QoL is still often impacted by targeted therapies [61]. Indeed, the number of QoL questionnaires developed has grown in line with the emergence of targeted therapies for specific cancers. For example, the functional assessment of cancer therapy (FACT) published a kidney version in 2007 [62] in line with sunitinib being developed. This was followed by a FACT instrument for melanoma in 2009 [63] as vemurafenib and dabrafenib were developed. Moreover, mapping of existing general cancer questionnaires such as QLQ-C30 are common [64-68].

Unfortunately, targeted therapies have not proven to be a long-term solution for cancer patients. While disease progression is hindered, very few patients experience complete response as per the RECIST criteria. For example, in the RCC trial presented above [47], no patients experienced a complete response (both sunitinib and interferon-alpha treatment arms) and in the advanced melanoma trial [45], 3% of dabrafenib-treated patients experienced a complete response versus 2% for dacarbazine-treated patients. In some instances, this has also translated into a lack of OS benefit. OS for the eight currently available targeted therapies is summarised in Figure 9.

Figure 9 OS for selected targeted therapies

<table>
<tr>
<td>
<u>AM (BRAF+): dabrafenib vs dacarbazine</u>
OS HR=0.61 (95% CI 0.25 to 1.48)
Cross-over upon progression allowed [45]

Overall survival curves not published.
</td>
<td>
<u>GIST: nilotinib vs best supportive care</u>
OS: HR=0.84 (95% CI: 0.62 to 1.15)
Cross-over upon progression not allowed [46]


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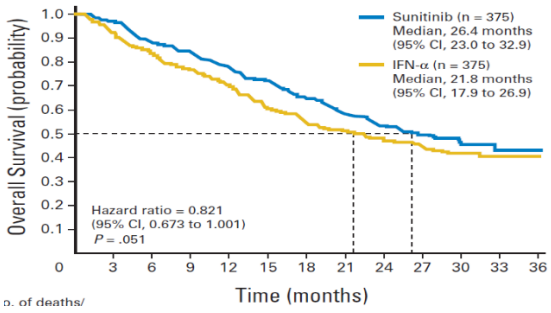
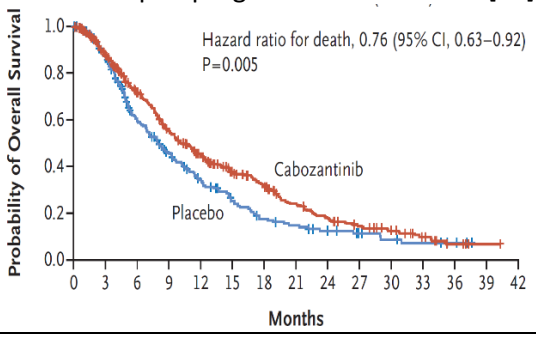
<tr>
<td>
<u>RCC: sunitinib vs interferon-alpha</u>
OS: HR=0.821 (95% CI: 0.673 to 1.001)
Cross-over upon progression allowed [69]


</td>
<td>
<u>HCC: cabozantanib vs placebo</u>
OS: HR= 0.76 (95% CI: 0.63 to 0.92)
Cross-over upon progression not allowed [48]


</td>
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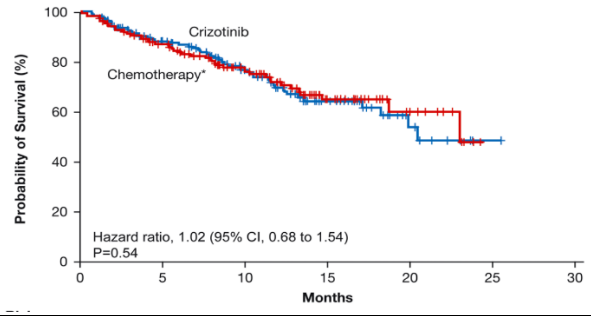
<tr>
<td>
<u>NSCLC (ALK+): crizotinib vs chemotherapy</u>
OS: HR=1.02 (95% CI: 0.68 to 1.54)
Cross-over upon progression allowed [49]


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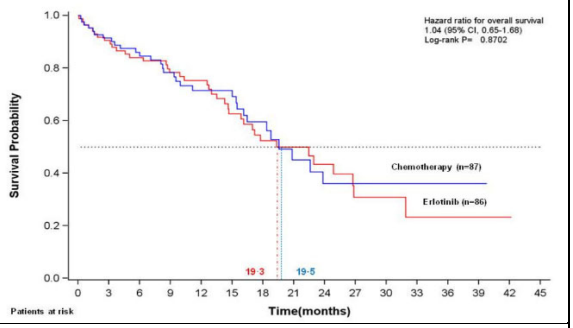
<td>
<u>NSCLC (EGFR+): erlotinib vs chemotherapy</u>
OS: HR=1.04 (95% CI: 0.65 to 1.68)
Cross-over upon progression allowed [50]


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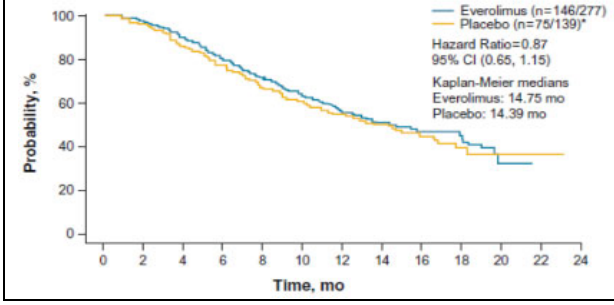
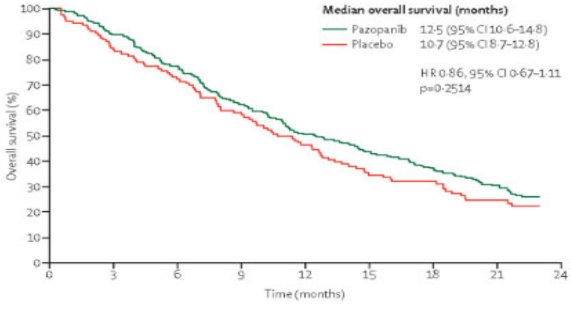
<tr>
<td>
<u>RCC: everolimus vs placebo</u>
OS: HR=0.87 (95% CI: 0.65 to 1.15)
Cross-over upon progression allowed [51]


</td>
<td>
<u>Soft tissue sarcoma: pazopanib vs placebo</u>
OS: HR=0.86 (95% CI: 0.67 to 1.11)
Cross-over upon progression not allowed [52]


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</table>

ALK+: Anaplastic lymphoma kinase positive, AM: advanced melanoma, BRAF+: B-Raf serine-threonine kinase, EGFR+: epidermal growth factor receptor positive, GIST: gastrointestinal stromal tumours, HCC: hepatocellular carcinoma, NSCLC: non-small cell carcinoma, RCC: renal cell carcinoma.

At present, there are 34 targeted therapies available on the PBS, divided into 13 different classes [29]:

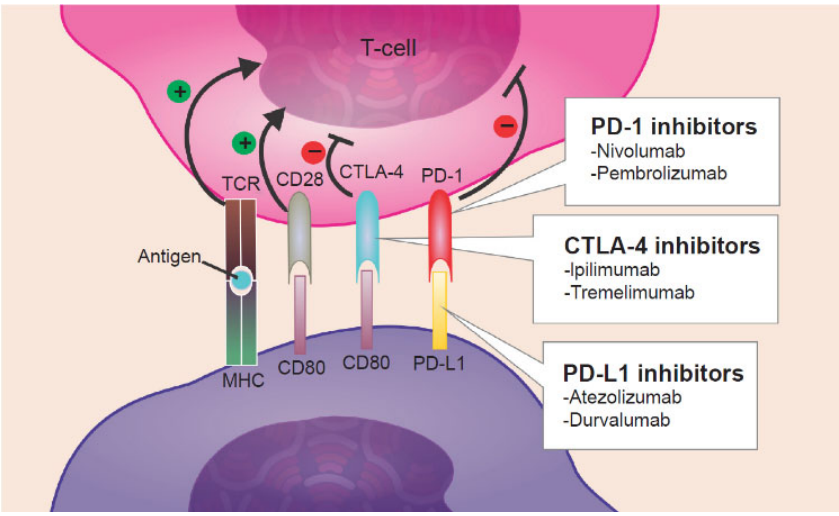
- L01EA - BCR-ABL tyrosine kinase inhibitors
- L01EB - EGFR tyrosine kinase inhibitors
- L01EC - BRAF (a gene that encodes the protein B-Raf) inhibitors
- L01ED - Anaplastic lymphoma kinase (ALK) inhibitors
- L01EE - Mitogen-activated protein kinase (MEK) inhibitors
- L01EF - Cyclin-dependent kinase (CDK) inhibitors
- L01EG - Mammalian target of rapamycin (mTOR) kinase inhibitors
- L01EH - Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors
- L01EJ - Janus-associated kinase (JAK) inhibitors
- L01EK - VEGFR tyrosine kinase inhibitors
- L01EL - Bruton's tyrosine kinase (BTK) inhibitors
- L01EM - Phosphatidylinositol-3-kinase (Pi3K) inhibitors
- L01EX - Other protein kinase inhibitors

The DPMA of targeted therapies range from $926.67 for gefitinib to $20,413 for midostaurin, with only three of 34 drugs costing less than $1000 (Appendix 2). Treatment costs are therefore often considerably higher than chemotherapy, with monthly drug costs of between $5000 to $10,000 [70]. It has been estimated that cancer treatment costs grew more than 40% from 2009 to 2012 for the government due to the introduction of targeted therapies, [71] which highlights the issue with funding and value for money as outlined previously.

1.4.3 Immune checkpoint inhibitors

The introduction of ICIs for the treatment of cancer marked a shift away from targeting cells to utilising the immune system to fight cancer. The concept is to disrupt the signaling pathways that allow cancer cells to evade T-cell-mediated death. This is achieved by preventing cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) from binding with specific ligands, thereby enhancing the immune system's ability to attack malignant cells [72]. There are currently three different types of ICIs used to treat cancer in Australia: CTLA-4, PD-1 and programmed cell death protein ligand 1 (PD-L1) inhibitors (Figure 10). CTLA-4 is normally expressed on the surface of naïve effector T-cells, which inhibit autoimmunity, and promotes tolerance to self-antigens. Similarly, PD-1 is an immune inhibitory receptor which negatively regulates T-cell functions through the engagement of programmed cell death protein ligand 1 PD-L1, which is found on varies malignant cells [73].

Figure 10 Mode of action of ICIs and different types.



Source: de Mello, R.A., et al., Potential role of immunotherapy in advanced non-small-cell lung cancer. OncoTargets and therapy, 2017. 10: p. 21-30. [74]

The first ICI approved by the Australian Therapeutics and Goods Administration (TGA) was ipilimumab for treatment of melanoma in 2012 (Table 4). This was followed by pembrolizumab and nivolumab in 2015, also for melanoma. Subsequently, atezolizumab (NSCLC), avelumab (Merkel cell carcinoma) and durvalumab (urothelial carcinoma) were approved in 2017, 2018 and 2019, respectively. Government subsidisation of each ICI via the PBS followed between nine and 38 months after registration. Currently, six ICIs are indicated for many different tumour types, including metastatic melanoma, colorectal cancer, NSCLC, metastatic urothelial cancer and RCC. Their DPMAs range from $7188.77 to $16,964.04.

The efficacy and safety profiles of the ICIs differ substantially from those of chemotherapies and targeted therapies. In general, they demonstrate superior PFS and OS over standard of care (SoC), whether that compromises chemotherapies, placebo, targeted therapies or any combination of these.

Table 4 ICIs TGA approvals, PBS listing dates and prices.

Drug	#TGA approval (1st indication)	*Listed on the PBS (1st submitted)	*Dispensed price maximum amount in public hospitals	Other indications
Atezolizumab	July 2017 (Non-small cell lung cancer)	April 2018 (July 2017)	$7,188.77	• Urothelial cancer • Small cell lung cancer • Liver cancer
Avelumab	January 2018 (Merkel cell carcinoma)	May 2019 (March 2018)	$8,230.44	
Durvalumab	October 2018 (Urothelial carcinoma)	March 2020 (July 2018)	$9,626.28	• Non-small cell lung cancer
Ipilimumab	June 2011 (Melanoma)	August 2013 (March 2011)	$16,964.04	• Non-small cell lung cancer • Renal cell carcinoma
Nivolumab	January 2016 (Melanoma)	May 2016 (March 2015)	$10,054.68	• Adjuvant melanoma • Non-small cell lung cancer • Renal cell carcinoma • Head and neck cancer • Relapsed/refractory Hodgkin's' lymphoma • Urothelial cancer
Pembrolizumab	April 2015 (Melanoma)	September 2015 (November 2014)	$7,733.78	• Adjuvant melanoma • Colorectal cancer • refractory primary • mediastinal large B-cell lymphoma • Relapsed/refractory Hodgkin's' lymphoma • Head and neck cancer • Non-small cell lung cancer

Sources: #www.tga.gov.au, * www.pbs.gov.au

Figure 11 and Figure 12 display the PFS and OS, respectively, for the six different ICIs currently available in Australia for different cancer types. ICIs need time to activate the immune system before they have an impact on the cancer. This is evident in a delay in separation of the PFS survival curves (Figure 11) compared to targeted therapies, for which the difference is apparent from the beginning of the clinical trial (Figure 7). As a result, no difference is occasionally reported for PFS despite a significant OS gain being observed which is especially the case when a targeted therapy is the comparator.

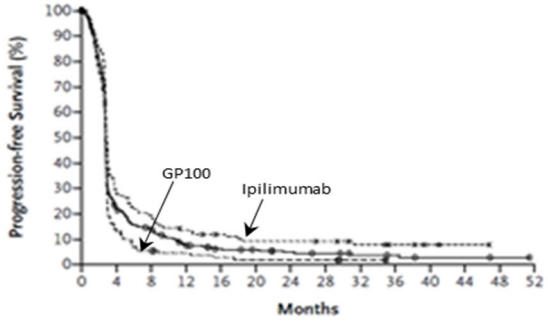
An example of this can be found in a randomised controlled trial of RCC patients treated with the PD-1 inhibitor nivolumab versus the targeted therapy everolimus [75]. The HR for PFS was observed to be not statistically significant, at 0.88 (95% CI: 0.75; 1.03), in contrast to the HR for OS, at 0.73 (98.5% CI: 0.57; 0.93). However, updated five-year data from the same study found PFS benefits to be statistically significant, with a HR of 0.84 (95% CI: 0.72; 0.99) [76].

Another example is nivolumab for the treatment of squamous cell carcinoma of the head and neck, the trial for which showed that PFS was not significantly better than a collection of comparators, with a HR of 0.89 (95% CI: 0.70−1.13), even though OS was superior (HR = 0.70, 97.73% CI: 0.51 to 0.96). The collection of comparators included cetuximab, a targeted therapy.

Figure 11 PFS for selected immune checkpoint inhibitors

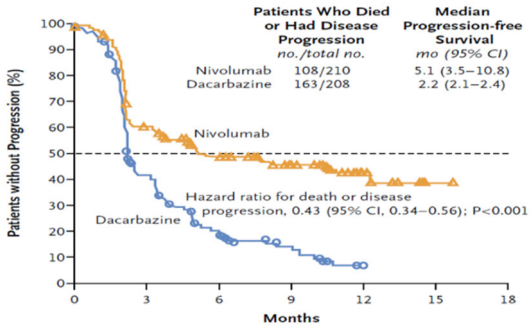
AM: ipilimumab vs GP100 [77]

PFS: HR=0.64 (p-value<0.001)



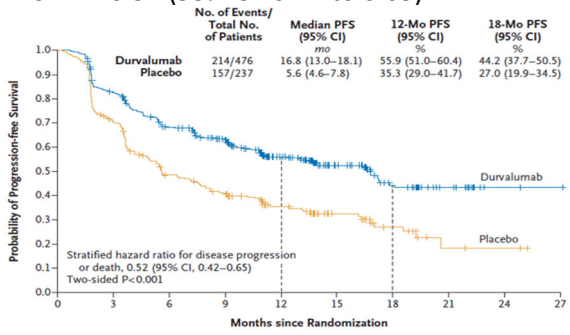
AM: nivolumab vs dacarbazine [78]

PFS: HR=0.43 (95% CI: 0.34 to 0.56)



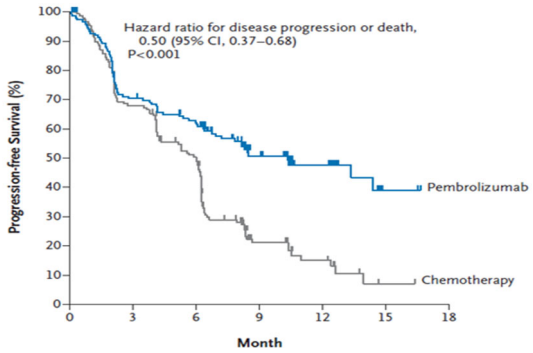
NSCLC (stage III): durvalumab vs placebo [79]

PFS: HR=0.52 (95% CI: 0.42 to 0.65)



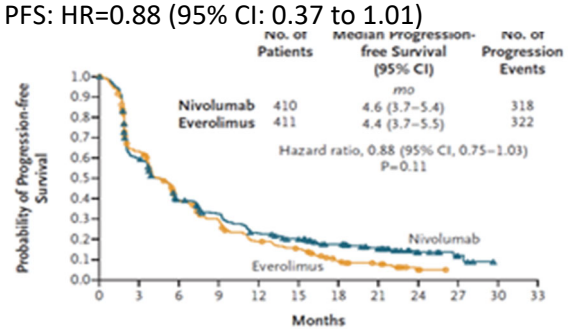
NSCLC (stage IV): pembrolizumab vs SoC [80]

PFS: HR= 0.50 (95% CI: 0.37 to 0.68)



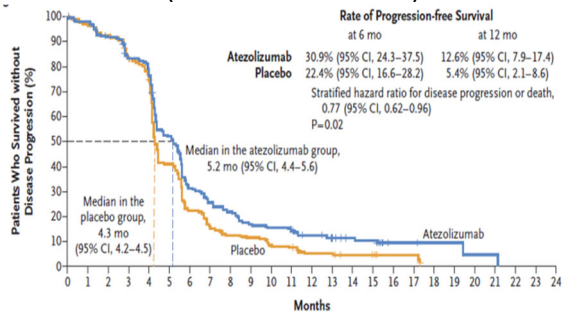
RCC: nivolumab vs everolimus [75]

PFS: HR=0.88 (95% CI: 0.37 to 1.01)



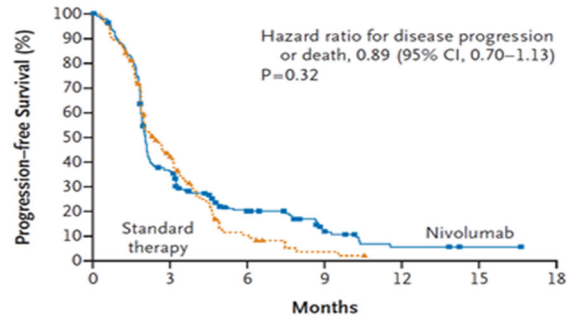
SCLC: Atezolizumab vs chemotherapy [81]

PFS: HR=0.77 (95% CI: 0.62 to 0.96)



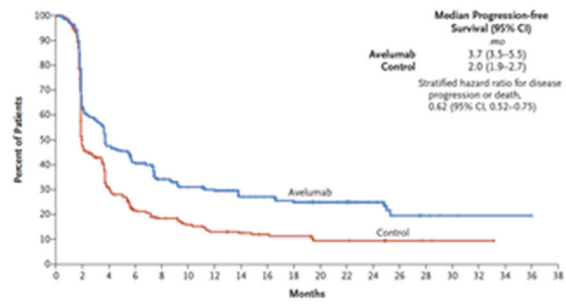
SCCHN: nivolumab vs SoC [82]

PFS: HR = 0.89 (95% CI: 0.70−1.13)



Urothelial cancer: Avelumab vs SoC [83]

PFS: HR=0.62 (95% CI: 0.52 to 0.75)

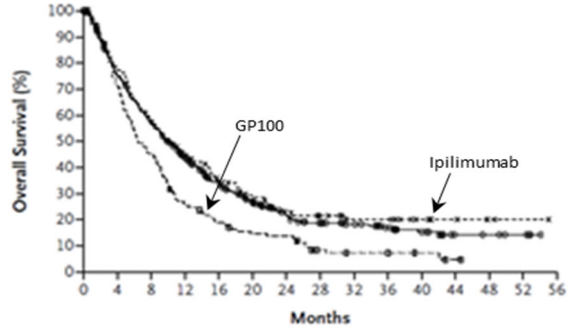


AM: advanced melanoma, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma, SCLC: small cell lung cancer, SCCHN: squamous cell carcinoma head and neck, SoC: standard of care – collection of different comparators.

Figure 12 OS for selected immune checkpoint inhibitors

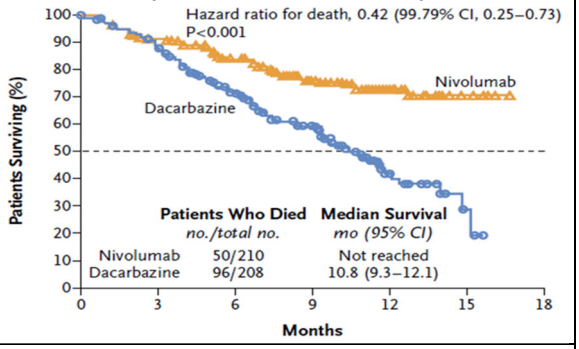
AM: ipilimumab vs GP100 [77]

OS: HR=0.66 (p-value=0.003)



AM: nivolumab vs dacarbazine [78]

OS: HR=0.42 (99.79% CI, 0.25 to 0.73)

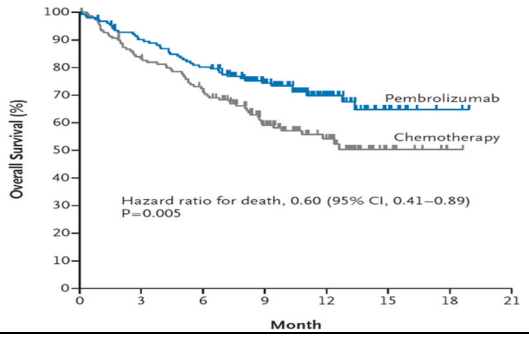


NSCLC (stage III): durvalumab vs placebo

Overall survival curves not published.

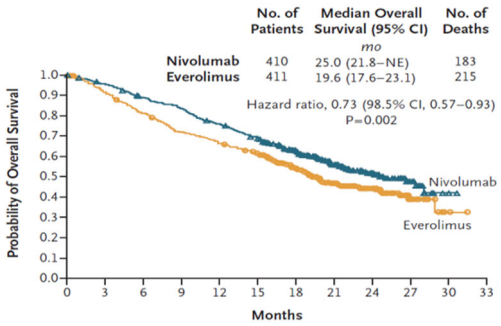
NSCLC (stage IV): pembrolizumab vs SoC [80]

OS: HR= 0.60 (95% CI: 0.41 to 0.89)



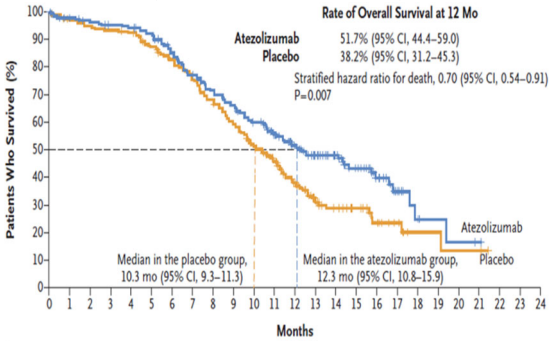
RCC: nivolumab vs everolimus [75]

OS: HR=0.73 (95% CI: 0.57 to 0.93)



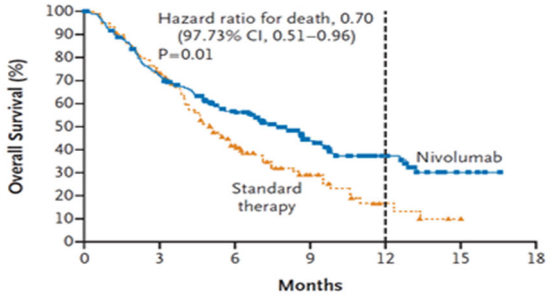
SCLC: Atezolizumab vs chemotherapy [81]

OS: HR=0.70 (95% CI: 0.54 to 0.91)



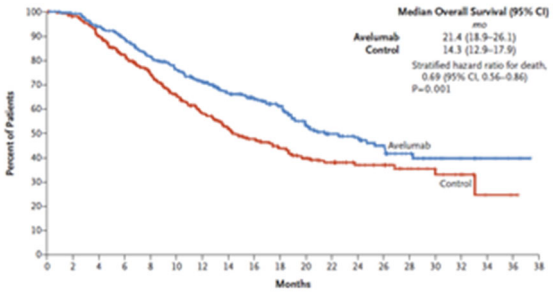
SCCHN: nivolumab vs SoC [82]

OS: HR=0.70 (97.73% CI: 0.51 to 0.96)



Urothelial cancer: Avelumab vs SoC [83]

OS: HR=0.69 (95% CI: 0.56 to 0.86)



AM: advanced melanoma, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma, SCLC: small cell lung cancer, SCCHN: squamous cell carcinoma head and neck, SoC: standard of care – collection of different comparators.

An interesting characteristic of the OS curves is that they often plateau, implying the potential for long term survival. For example, in the CheckMate066 trial [78] of nivolumab versus dacarbazine in patients with advanced melanoma, the OS curve for nivolumab only dropped 10% (from 80% to 70%) between seven and 17 months (Figure 12). In the same period, the OS for dacarbazine dropped 45% (from 65% to 20%). Only 7.6% of the nivolumab-treated patients had a complete response.

Safety profile also differs between ICIs and other systemic therapies. ICIs are associated with immune-related adverse events (irAE), which occur due to non-specific activation of the immune system [84].

Trial data for ipilimumab in advanced melanoma showed that almost all patients (98.4%) reported an AE (any grade) and 45% reported grade 3 or 4 AEs [77]. AEs specific to ipilimumab in the trial were life-threatening toxic epidermal necrolysis, colitis, hypophysitis, hepatitis, pancreatitis, iridocyclitis, lymphadenopathy, neuropathies, and nephritis. While the rate for AEs of any grade for other ICI treatments in advanced melanoma is also high (nivolumab=93.2% [78], pembrolizumab=79.5% [85]), the rate of grade 3 or 4 AEs is much lower (nivolumab=34.0% [78], pembrolizumab=13.3% [85]).

There is evidence that these rates are higher in a real-world setting. Indeed this was the concern of the South Australian Medicines Evaluation Panel (SAMEP), which submitted a letter to the PBAC [86]. The letter contained data on the incidence and the costs of treating AEs associated with ipilimumab. Specifically, eight ipilimumab-treated patients were admitted to hospital and received infliximab for severe, steroid-refractory colitis secondary to ipilimumab. Treatment of this particular irAE for these patients was estimated to cost between $395,976 and $483,840, thereby adding $50,000 - $60,000 to the total cost of ipilimumab per patient.

Treatment of irAEs has become increasingly important as ICI-treated patients are surviving longer with cancer. Treatment guidance and experience with irAEs is a major focus of ICI treatments [87-90]. NSW guidelines [91] outline in detail how to manage irAEs. As displayed in Table 5, various toxicities have been identified in connection with ipilimumab treatment for melanoma. These include cardiotoxicities, haematological toxicities, ocular toxicities and thyroid toxicities which were not widely reported for ipilimumab in clinical studies.

Table 5 Immune related adverse events for ipilimumab

Immune related adverse events	
Cardiotoxicity	Cardiotoxicity is a rare but serious side effect, which may manifest as asymptomatic reduction in left ventricular ejection fraction (LVEF), arrhythmia, cardiomyopathy, myocarditis, pericarditis, cardiac fibrosis, hypertension, cardiac ischaemia, congestive heart failure (CHF) and cardiac arrest. Read more about Management of immune related adverse events.
Gastrointestinal toxicity	Colitis, diarrhoea or more bowel movements than usual; blood or mucous in stools; dark, tarry, sticky stools; abdominal pain or tenderness. Read more about Management of immune related adverse events
Haematological toxicity	Autoimmune haemolytic anaemia (AIHA), acquired thrombotic thrombocytopenic purpura (TTP), aplastic anaemia (AA), immune thrombocytopenia (ITP), acquired haemophilia (AH), haemolytic uremic syndrome (HUS) and lymphopenia are rare but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events.
Hepatotoxicity	Transaminase and total bilirubin elevation, jaundice, severe nausea or vomiting, pain on the right side of the abdomen, drowsiness, dark urine, bleeding or bruising more easily than normal, anorexia. Read more about Management of immune related adverse events.
Musculoskeletal toxicity	Inflammatory arthritis, temporal arteritis, arthralgia, myalgia, synovitis, vasculitis, polymyalgia-like syndrome and myositis. Read more about Management of immune related adverse events.
Neurological toxicity	Aseptic meningitis, myasthenia gravis, Guillain-Barre syndrome, encephalitis, meningeal symptoms, neuropathy and acute inflammatory demyelinating polyneuropathy are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events.
Ocular toxicity	Eye pain, blurred vision, Uveitis/iritis, episcleritis, blepharitis, optic neuritis, tear duct stenosis, conjunctivitis, hyperlacrimation, watery or dry eyes and photophobia. Read more about Management of immune related adverse events.
Other endocrinopathies	Type 1 diabetes mellitus, hypophysitis, hypopituitarism and adrenal insufficiency are infrequent but potentially serious immune-related adverse events associated with immunotherapy treatment. Read more about Management of immune related adverse events
Pulmonary toxicity	Radiographic changes, dyspnoea, new or worsening cough, hypoxia, tachycardia, chest pain or fever. Read more about Management of immune related adverse events.
Renal toxicity	Increase in serum creatinine, oliguria, haematuria, peripheral oedema and anorexia. Read more about Management of immune related adverse events.
Skin toxicity	Rash including full thickness, pruritus, skin blisters, ulceration and necrosis. Radiation recall can occur at site of previous radiation therapy. Symptoms include vesiculation, desquamation and ulceration of the skin. Read more about Management of immune related adverse events
Thyroid toxicity	Thyroid toxicity is common with immune checkpoint inhibitors. Hypothyroidism is most frequent however hyperthyroidism can also occur. Read more about Management of immune related adverse events

Source: NSW, C.I. *Melanoma metastatic ipilimumab*. 2020; Available from: https://www.eviq.org.au/medical-oncology/melanoma/metastatic/1307-melanoma-metastatic-ipilimumab#side-effects

A systematic review by Abdel-Rahman et al. showed that the use of PD-L1 inhibitors was associated with an improvement in QoL across a variety of solid tumours using standard tools such as QLQ-C30 and FACT [92]. A systematic review by Hall et al. examined nivolumab, pembrolizumab, atezolizumab and ipilimumab across several cancer types and found that ICIs are well-tolerated with respect to QoL [93]. Similar to Abdel-Rahman et al., the instruments were QLQ-C30 and FACT, but this review also included evaluation of EQ-5D. A recent review by Faury et al. is highly critical of the review reported by Abdel-Rahman et al. and Hall et al., arguing that the QoL tools currently available have not been

validated in cancer patients treated with ICIs [94]. This is especially important when assessing the impact of irAEs. For example, in the clinical trial investigating nivolumab for squamous cell carcinoma of the head and neck, the Quality of Life Questionnaire for Head and Neck cancer 35-items (QLQL-H&N35) was used [82]. In the trial, 7.6% of nivolumab-treated patients reported rash and 7.2% reported pruritus, but the QLQ-H&N35 does not assess skin problems.

1.5 Reimbursement of oncology treatments in Australia

Funding of cancer medications is a challenge as mentioned in previous sections. This section will describe how cancer drugs are funded in Australia. The price of oncology drugs makes it impossible for most patients to pay out of their own pockets. Instead, patients rely on the PBS for access to these medicines. However, public funding of medications for cancer is a challenge when compared to other conditions. This is due to a combination of limited evidence available (e.g. immature survival, surrogate endpoints etc.) and the high price of the medications.

The PBS is a government-subsidised scheme that aims to provide affordable and equitable access to necessary medicines for Australians [95] with the current out-of-pocket co-payment of $42.50 [29]. From July 2019 to June 2020, 208 million prescriptions were dispensed through the PBS, from a list of more than 900 different medicines [96]. This accounted for $12.6 billion in government expenditure, which equated to 16.6% of the direct healthcare budget of $76.15 billion in that year [97]. Of the top three most costly drugs on the PBS, two were ICIs: nivolumab ($333,970,002) and pembrolizumab ($331,481,924).

The Australian health care budget is set to rise from $94.5 Billion to $103.2 Billion from 2020 to 2025 [98]. Pharmaceutical benefits and services (including cancer medications) are projected to account for $14.7 billion in 2020 and is expected to rise to $16.1 billion in 2025 (Table 6).

Table 6 Australian Health Care budget 2020-2025

$ million (estimates)	2020–21	2021–22	2022–23	2023–24	2024–25
Medical services and benefits	36,841	37,551	38,352	39,960	41,656
Assistance to the states for public hospitals	22,646	25,463	26,649	28,238	29,916
Pharmaceutical benefits and services	14,762	15,208	15,375	15,817	16,127
Health services	14,130	13,653	9,755	9,658	9,811
General administration	4,036	4,233	3,491	3,419	3,405
Hospital services	1,143	1,195	1,147	1,161	1,172
Aboriginal and Torres Strait Islander health	975	980	1,011	1,048	1,089
Total	**94,533**	**98,283**	**95,779**	**99,300**	**103,177**

Source: Parliament of Australia, P.L. Health Review. 2021; Available from: https://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/BudgetReview202122/HealthOverview

The cost of a prescription is made up of three main components: manufacturer's price, wholesale mark-up and pharmacy fees (for dispensing, administration, handling, and infrastructure overheads). Other fees that might apply are preparation fees, dangerous drug fees, and fees related to chemotherapies, targeted therapies and ICIs that are administered via infusions [99].

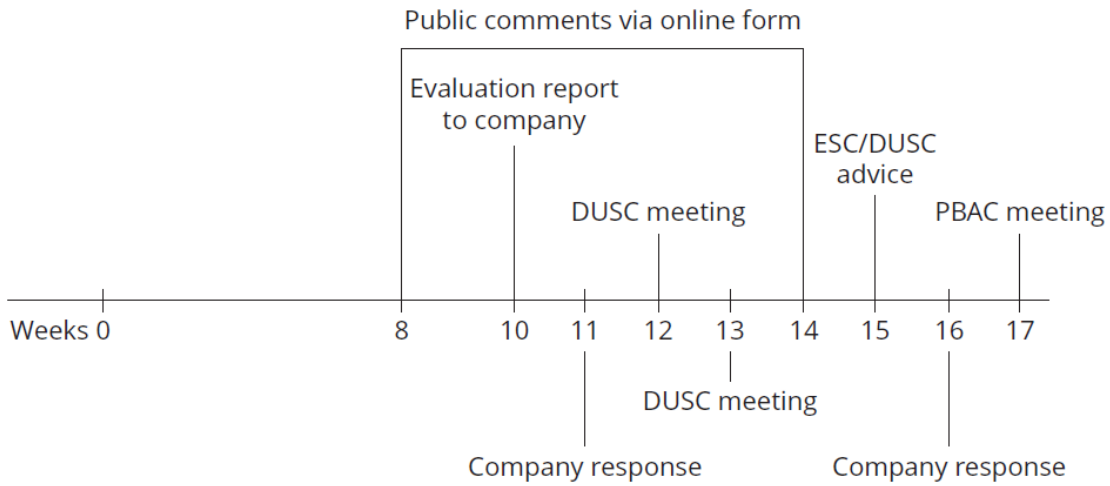
1.5.1 Pharmaceutical Benefits Advisory Committee

All medicines, including cancer drugs, undergo a comprehensive HTA process before being listed on the PBS. The process starts with a sponsor (usually a pharmaceutical company) submitting an application for the listing of the drug in question. The submission is assessed by the PBAC, which makes recommendations to the Commonwealth Department of Health and the Federal Minister of Health [100]. The PBAC comprises independent clinicians, other healthcare professionals, health economists, consumer representatives and an industry-nominated member. One-third of the members are nominated by the Health Minister and the others by professional organisations. Ultimately, the Health Minister determines which drugs are listed on the PBS, based on the advice of the PBAC.

1.5.2 Submission process

Submissions are categorised as either major or minor. Major submissions can either be for a new medicine or a new indication for a currently listed medicine. A minor submission generally relates to a change in an existing listing or similar. A resubmission subsequent to rejection of an initial submission can also be made [101]. Major applications follow a 17-week cycle, with submissions due three times a year in March, July and November [102]. The process is conceptualised in Figure 13.

Figure 13 Overview of the PBAC process.



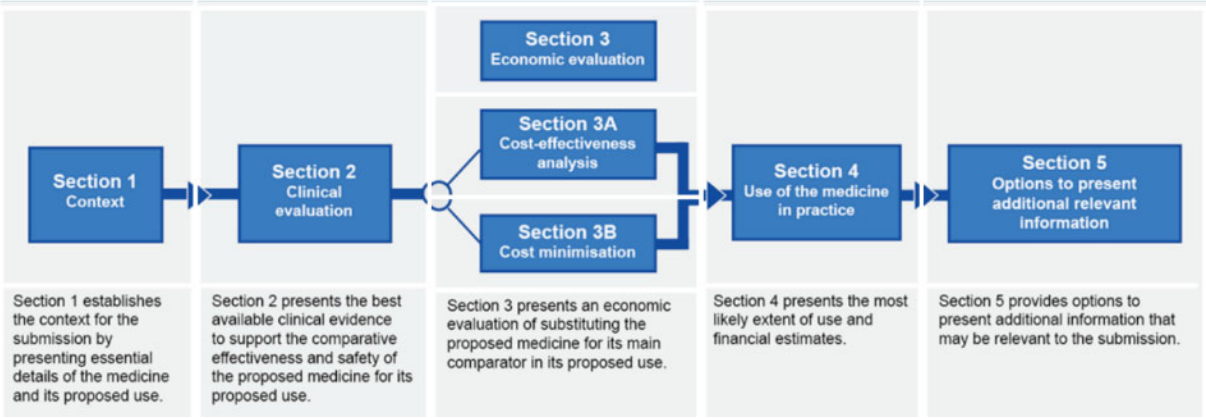
DUSC: Drug Utilisation SubCommittee; ESC: Economic SubCommittee; PBAC: Pharmaceutical Benefits Advisory Committee.

Source: Kim, H., J. Byrnes, and S. Goodall, Health Technology Assessment in Australia: The Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee. Value in Health Regional Issues, 2021. 24: p. 6-11.[103]

Major submissions are first evaluated by an external group (selected from a number of preapproved groups) during the first 10 weeks of the cycle, with an evaluation report sent to the sponsor. The sponsor has one week to respond. The submission, evaluation report, and the sponsor's responses are then reviewed by two technical subcommittees of the PBAC: the Economic Subcommittee (ESC) and the Drug Utilisation Subcommittee (DUSC). The ESC assesses the clinical and economic evidence and advises the PBAC on the technical aspects of the submission. The DUSC assesses the projected usage and financial costs of the medicine. However, this does not apply to all submissions. The advice provided by these subcommittees is provided to the sponsor 15 weeks into the submission process, and the sponsor has another week to respond. Feedback from the public, health professionals, professional organisations and other interested parties can be submitted via an online form up to three weeks before the PBAC meeting [104]. Finally, the PBAC meets approximately 17 weeks after the submission.

A major PBAC submission typically includes five sections (Figure 14), as described in the PBAC guidelines [22].

Figure 14 Overview of sections required for a PBAC submissions.



Source: Australian Government Department of Health, Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) Version 5.0. 2016; Available from: https://pbac.pbs.gov.au/.[22]

Section 1 is used to present the clinical algorithm, justify the comparator(s), and put forward the proposed reimbursement restriction. The clinical evidence is presented in Section 2. Systematic reviews are used to obtain the most relevant and up-to-date evidence. A thorough assessment of relevant clinical trials and other data to support claims of superiority or non-inferiority of the applicant drug versus its comparator is provided. The economic evaluation is presented in Section 3. A non-inferiority claim is typically accompanied by a CMA [105], in which total cost (drug acquisition, medical management, adverse events etc.) for the new drug is assumed to be the same as the comparator. A superiority claim is typically accompanied by a CEA or a CUA [105]. Both of these usually rely on health economic modelling and extrapolation of efficacy, safety, QoL and cost data beyond the duration of the relevant clinical trial(s). A budget impact model is presented in Section 4. These financial estimates can form the basis for any financial risk share agreements. Financial risk share agreements can either be based on agreed utilisation rates and a 50% rebate for expenditure beyond the agreed cap, as was the case for pembrolizumab in NSCLC [106] or even with a 100% rebate as was the case for nivolumab in RCC [107]. Finally, Section 5 is an optional section in which the sponsor presents any other relevant information, such as quality use of medicines.

The outcome of the PBAC meeting is communicated to the sponsor three to five weeks after the PBAC meeting [108]. A public summary document is published on the PBS website 16 to 18 weeks after the meeting on the PBS website [109]. After a positive recommendation, the sponsor and the Department

of Health will finalise a deed of agreement that includes the terms of the price (including any special pricing arrangements), restriction of use and financial risk share agreements [110]. Special pricing arrangements refer to an 'effective price' that is different from the published price. Usually this entails a commercial-in-confidence rebate to the government, such that the effective price is less than the published price. Confidentiality is maintained so that the price of the drug is not lowered via price referencing by jurisdictions outside of Australia [111]. Sponsors can choose to resubmit if the PBAC decision is not to recommend, and can in some circumstances request an independent review [112].

1.5.3 Immune checkpoint inhibitors and reimbursement

The reimbursement of ICIs is challenging. The costs of these drugs are high, and patients are living longer, thereby increasing the pressure on health care budgets.

Reimbursement assessments rely on evidence that often require translation and extrapolation. One important reason is that clinical trials typically do not provide data required for HTAs. (They satisfy regulatory requirements, for which short-term outcomes often are adequate to demonstrate a favourable risk/benefit profile.) This leads to uncertainty with respect to cost-effectiveness and value for money as outcomes in many instances need to be transformed or translated to suit a local patient population with different profile than the one examined in the clinical trial. This is usually the case with respect to QoL, as most clinical trials are reported using non-Australian weights. Another major problem is the extrapolation of premature survival data well beyond the trial duration. In some instances, cost-effectiveness is dependent on patients surviving more than 10-20 years into the future in order for the medications to be deemed cost-effective.

As part of this thesis, an analysis was published in the British Journal of Clinical Pharmacology [113] that focused on the financial challenges of ICIs in the UK and Australia, jurisdictions in which health economic modelling is commonly used for HTA.

Kim H, Liew D, Goodall S, Cost-effectiveness and financial risks associated with immune checkpoint inhibitor therapy. British Journal of Clinical Pharmacology, 2020. 86(9): p. 1703-1710.

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REVIEW-THEMED SECTION

Cost-effectiveness and financial risks associated with immune checkpoint inhibitor therapy

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The reimbursement of immune checkpoint inhibitors is challenging. Funding these technologies involves the careful balance between awarding innovation and ensuring affordability as increases in drug spending compete directly with other health care and social expenditure. This narrative review examines the recommendations of 2 health technology assessment agencies—the Australian Pharmaceutical Benefits Advisory Committee and the British National Institute of Clinical Excellence—to determine the factors that contribute to the approval and rejection of immune checkpoint inhibitors as well as the use of manage entry schemes and risk management strategies to control expenditure. Reimbursement decisions from 6 immune checkpoint inhibitor drugs (**ipilimumab**, **pembrolizumab**, **nivolumab**, **durvalumab**, **atezolizumab**, **avelumab**) covering 10 different cancers were examined. The extrapolation of survival beyond the clinical trial and lack of head-to-head evidence are some of the main issues relating to cost effectiveness. Payers managed financial risks using different mechanisms such as risk share agreements and financial caps. This review of the reimbursement decisions and subsequent financial impact in Australia and the UK suggests budgets for immune checkpoint inhibitor therapy have been well managed so far. Through risk agreements and managed entry programmes, the example of immune checkpoint inhibitor therapies illustrates that industry and payers can effectively collaborate to ensure that innovative, but expensive, drugs can be made readily available to patients.

KEYWORDS

cancer, health economics, immunotherapy, pharmacoeconomics

1 | INTRODUCTION

The reimbursement of new high-cost innovative medicines is particularly challenging. Costly to develop, funding these technologies involves the careful balance between awarding innovation and ensuring affordability as increases in drug spending compete directly with other health care and social expenditure.

The advent of immunotherapy drugs, such as immune checkpoint inhibitor (ICI) therapy, illustrates these issues. Marked as a paradigm shift in cancer treatment, ICI therapy offers the possibility of long-term survival among cancer patients.[1] Ipilimumab was the first ICI therapy to gain Food and Drug Administration and European Medicines Agency regulatory approval in 2011.[2] Australia[3] and the UK[4] undertook the first reimbursement evaluations the same year with approvals for funding granted the following year.[5,6] However, the initial costs of these drugs have caused anxiety among health care providers, patients, payers and researchers, as countries have to balance affordability and timely access to these drugs.[7,8]

To meet this challenge, reimbursement agencies have developed several approaches to ensure appropriate access whilst managing the financial risk to health care budgets. Health technology assessment (HTA) is now being used almost ubiquitously to assist health care providers and payers decide whether new therapies, such as ICI medicines represent good value for money.[8] HTA is the systematic

evaluation of direct and indirect effects of health technology,[9] and the subfield of health economic modelling is an integrated part of decision analysis when assessing the cost effectiveness of these drugs.[10] This principle was first implemented in Australia in 1992 as a mandatory part of evaluations of pharmaceutical products by Pharmaceutical Benefits Advisory Committee (PBAC). The use of HTA has been broadened to include medical devices with the issue of the National Institute for Health and Care Excellence (NICE) guidelines in 2001 in the UK.[11]

As part of the HTA process, a variety of managed entry schemes have been developed to improve affordability. Outcome-based schemes include schemes that require conditional treatment rules and coverage with evidence development. An example is avelumab for the treatment of Merkel cell carcinoma. The UK NICE approved avelumab for reimbursement under the condition that the sponsor report additional survival data as the initial data only consisted of a small number of patients with short follow-up.[12,13] Nonoutcome-based schemes refer to price volume agreements, dosing caps, discounts and hypothecated budgets. A discount in the form of a rebate is common.[14] These are sometimes referred as special price arrangements in Australia.[15]

This paper sought to examine the recommendations of 2 HTA agencies (PBAC and NICE) to determine the factors that contribute to the approval and rejection of ICIs. The paper also explores the use of managed entry schemes and risk management strategies to control expenditure.

2 | METHODS

A narrative review was undertaken of all published funding decisions by the Australian PBAC and the NICE in the UK regarding ICIs. These HTA agencies were chosen because they were among the first to appraise ICI therapies. A search was conducted among public summary documents issued by the PBAC and technology appraisal guidance reports issued by NICE that involved ICIs in https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd and https://www.nice.org.uk/guidance, respectively. Records from September 2009 (which was 12 months prior to the date of the first published phase III trial of an ICI agent) to 28 October 2019 were reviewed. Where available, listing and cost data were retrieved from government websites.

3 | RESULTS

Six ICI drugs (ipilimumab, pembrolizumab, nivolumab, durvalumab, atezolizumab, avelumab) were found to have been considered for reimbursement. In total, 29 guidance documents have been issued by NICE across 9 different tumour types. Only 1 of the guidance documents did not recommend reimbursement[16]; however, another ICI drug is available for that indication.[17] There were 46 public summary documents published by the PBAC covering 10 different cancers. Of the 46 PBAC reimbursement submissions 29 were rejections and the remaining 17 resulted in a recommendation to subsidise the drug on the Pharmaceutical Benefits Scheme (PBS: a programme of the Australian Government that provides subsidised prescription medicines; Table 1).

During this period, ICI drugs have also been considered in combination (such as nivolumab + ipilimumab), and in combination with other agents (such as pembrolizumab + chemotherapy and atezolizumab + bevacizumab). Most of the target tumours were stage IV metastatic disease, but more recent applications involved adjuvant therapy for stage III nonsmall cell lung cancer (NSCLC).

The first-time rejection rate is 76.2% (see Figure 1). Most of the rejections in Australia were followed up with subsequent resubmissions. However, for 2 tumour types, namely metastatic colorectal cancer and relapsed/refractory primary mediastinal large B-cell lymphoma, this has not occurred yet and as of Q1, 2020 no ICI drug is available for these indications in Australia.

Australian public summary documents report whether or not reimbursement listing was recommended by the PBAC, while NICE technical appraisal guidance reports 1 of the following outcomes:

- do not recommend
- recommend only when the company provides the therapy in line with the commercial access agreement with NHS England[21]
- recommend for use within the Cancer Drugs Fund only if the conditions in the managed access agreement for the therapy are followed[12]
- recommend when the company provides the therapy with the discount agreed on in the patient access scheme.[13]

It is important to note that all therapies were subject to special pricing arrangements in the form of either a rebate and/or a financial cap.

3.1 | Factors relating to cost-effectiveness

Ipilimumab was the first ICI to be considered for reimbursement by the PBAC (July 2011)[3] and NICE (December 2012)[6] for metastatic melanoma. The dosing regimen for ipilimumab is 4 infusions over a 9-week period[84] at a cost of approximate GBP 58 500. Both reimbursement agencies considered that the length of follow-up in the pivotal clinical trial did not provide robust evidence of the overall survival gain beyond the length of the trial, therefore extrapolation of the clinical benefit was necessary in order to demonstrate cost effectiveness. However, the way the 2 agencies addressed the gap in evidence differed. After 2 further submissions[5,19] the PBAC mandated an outcome-based risk share agreement to assess whether trial efficacy translated into real-world effectiveness.[5] As part of the agreement, the PBAC reassessed ipilimumab in 2016 using real-world data, which confirmed the initial estimate of cost-effective.[85] Similarly, NICE was unable to reliably quantify the long-term survival benefit even after real-world data in the form of register data from the USA was

TABLE 1 Immune checkpoint inhibitor drugs considered by British National Institute of Clinical Excellence (NICE) and Pharmaceutical Benefits Advisory Committee (PBAC)

Drug	NICE	PBAC
Ipilimumab	GBP 3750/50 mg[13]	AUD 16 962.82/120 mg[18]
• metastatic melanoma	• *Dec 2012,[6] *Jul 2014[14]	• ^July 2011,[3] ^Mar 2012,[19] *Nov 2012[5]
Pembrolizumab	GBP 1315/50 mg[20]	AUD 9005.06/200 mg[18]
• metastatic melanoma	• *Oct 2015[21,22]	• *Mar 2015[23]
• adjuvant melanoma	• *Dec 2018[24]	• ^Nov 2018,[25] ^Jul 2019[26]
• metastatic colorectal cancer	No assessment	• ^Mar 2019[27]
• relapsed/refractory primary mediastinal large B-cell lymphoma	No assessment	• ^Nov 2018[28]
• relapsed/refractory classical Hodgkin's lymphoma	• *Sep 2018[29]	• *Aug 2017[30]
• squamous cell carcinoma of the head or neck	• *Apr 2018[17], *Jun 2018[31]	• ^Jul 2018[32]
• metastatic urothelial cancer	No assessment	• ^Nov 2017,[33] *Jul 2018[34]
• nonsmall cell lung cancer	• *Jan 2017,[35] *Jun 2017,[36] *Jul 2018,[20] *Jan 2019[37]	• ^Nov 2016,[38] ^Mar 2017,[39] ^Nov 2017,[40] ^Mar 2018,[41] *Jul 2018[42]
Pembrolizumab + chemotherapy		
• nonsmall cell lung cancer	• *Sep 2019[43]	• ^Nov 2018,[44] ^Jul 2019[45]
Nivolumab	GBP 439/40 mg[13]	AUD 10 053.46/480 mg[18]
• metastatic melanoma	• *Feb 2016[46]	• ^Jul 2015,[47] *Nov 2015[48]
• nonsmall cell lung cancer	• *Nov 2017[49,50]	• ^Mar 2016,[51] ^Nov 2016,[52] *Mar 2017[53]
• renal cell carcinoma	• *Nov 2016[54]	• ^Jul 2016,[55] ^Nov 2016,[56] *Mar 2017[57]
• squamous cell carcinoma of the head or neck	• *Nov 2017[58]	• ^Nov 2017,[59] *Mar 2018[60]
• adjuvant melanoma	• *Jan 2019[61]	• ^Jul 2018,[62] ^Mar 2019,[63] *Nov 2019[64]
• relapsed/refractory classical Hodgkin's lymphoma	• *Jul 2017[65]	No assessment
• metastatic urothelial cancer	• ^Jul 2018[16]	No assessment
Durvalumab	GBP 592/120 mg[66]	Not reimbursed in Australia
• nonsmall cell lung cancer	• *May 2019[66]	• ^Nov 2018,[67] ^Jul 2019,[68] *Nov 2019[64]
• metastatic urothelial cancer	No assessment	• ^Jul 2019[69]
Nivolumab + ipilimumab		
• nonsmall cell lung cancer	• *Jul 2016[13]	• Nov 2015,[70] Mar 2017,[71] Jul 2018[72]
• renal cell carcinoma	• *May 2019[73]	• Jul 2018,[74] Nov 2018[75]
Atezolizumab	GBP 3807.69/1200 mg[76]	AUD 7561.36/1200 mg[18]
• nonsmall cell lung cancer	• *May 2018[76]	• *Nov 2017[77]
• metastatic urothelial cancer	• *Jun 2018,[78] *Jul 2018[79]	No assessment
• small cell lung cancer	No assessment	• ^Jul 2019,[80] *Nov 2019[64]
Atezolizumab + bevacizumab		
• nonsmall cell lung cancer	• *Jun 2019[81]	• *Mar 2019[82]
Avelumab	GBP 768/200 mg[12]	AUD 8229.22/1200 mg[18]
• metastatic Merkel cell carcinoma	• *Apr 2018[12]	• *Jul 2018[83]

^: not recommended,
*: recommended.

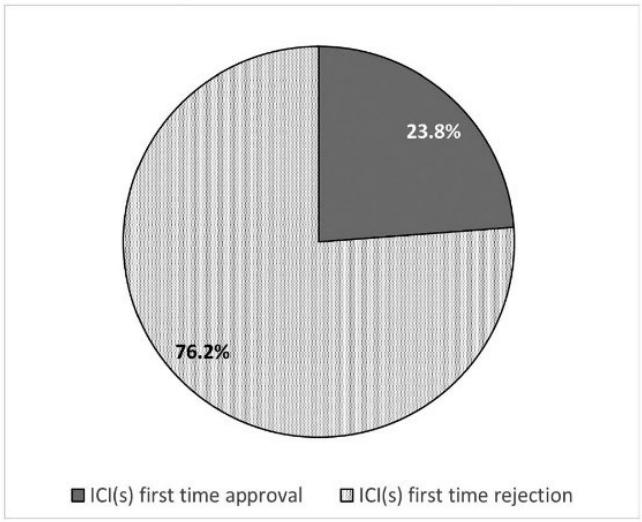

FIGURE 1 Proportion of first-time rejections in Australia. ICI, immune checkpoint inhibitor

presented by the sponsor during the consultation of the evaluation to fill the data gap. NICE decided that a simple discount was to be applied to the list price of ipilimumab to make it cost-effective, i.e. the price reduction mitigated the uncertainty in the estimated cost-effectiveness.

The funding of ipilimumab in Australia is a good example of industry and Government working together, via a risk-share agreement to allow early reimbursement as further evidence was collected. However, the sponsor may delay the reimbursement application and opt to wait for longer-term data to be available. This was the case for second-line treatment of renal cell carcinoma with nivolumab[56] and for the combination treatment of nivolumab and ipilimumab in metastatic melanoma.[72]

Choice of extrapolation of survival data is a common source of uncertainty in cost-effectiveness assessments of ICI drugs.[86] For example, in guidance document TA519 when considering pembrolizumab, NICE found that using the Gompertz curve for extrapolation assumed that no patient could reside in the post-progressive health state after year 6.[17] This meant that patients could only move from preprogression to death, which is not in accord with real-world observations.

Lack of head-to-head evidence is another common stumbling block for demonstrating cost-effectiveness for ICI therapies. Pembrolizumab sought reimbursement for NSCLC in 2016 in Australia, but the PBAC concluded that the magnitude of the gain in effectiveness over pemetrexed was unclear due to the need to conduct an indirect comparison.[37] Moreover, the PBAC did not find pembrolizumab cost-effective in squamous cell carcinoma of the head and neck due to uncertainty related to the indirect comparison (in addition to low unmet clinical need).[31] By contrast, high unmet need was the driver behind pembrolizumab getting first-time approval for metastatic melanoma despite the absence of head to head data.[23]

3.2 | Managing financial risks

The approach to funding ICI therapies differs between Australia and England/Wales. ICI therapies in Australia are funded through a scheme called *Efficient Funding of Chemotherapy (EFC)— Section 100 Arrangements* which is a part of the Australian PBS.[87] The total cost of the PBS is uncapped.[88] The total costs for ICI therapies across all tumour types was approximately AUD 578 million (approx. GBP 306.5 million or USD 394.9 million) for the financial year ending June 2019 (see Figure 2).

The total expenditure of the Australian PBS was AUD 11.8 billion for the financial year ending in June 2019.[94] Therefore, it appears that ICI drugs accounted for approximately 5% of the overall PBS expenditure. To put this into perspective, the combined costs of adalimumab (AUD 320.4 million[93]) and aflibercept (AUD 304.2 million[93]) amounted to AUD 46 million more than the whole class of ICI therapies, although as can been seen in Figure 2, expenditure on ICI drugs is increasing. It should be noted that these numbers are only indicative, as each therapy has its own special pricing arrangement and rebate, which are commercial in confidence.

England and Wales fund ICI therapies through the Cancer Drug Fund, which operates with a fixed budget.[95] A recent review found that they kept the spending for the Cancer Drug Fund within the GBP 340 million a year budget.[96]

Every ICI therapy had a special pricing arrangement on the Australian PBS or there was a requirement to provide the drug according to a commercial/patient/managed access agreement or scheme with NICE. One interpretation of this is that the companies had to offer a rebate of the public listed price of the ICI therapies, however, it is uncertain what the magnitude of the rebate is since the details are commercial in confidence. This lack of transparency is not necessarily negative as it enables companies to offer substantial discounts without being concerned about commercial risks due to reference pricing.[97] However, this also creates issues as there is a lack of visibility of the comparator price resulting in a possible

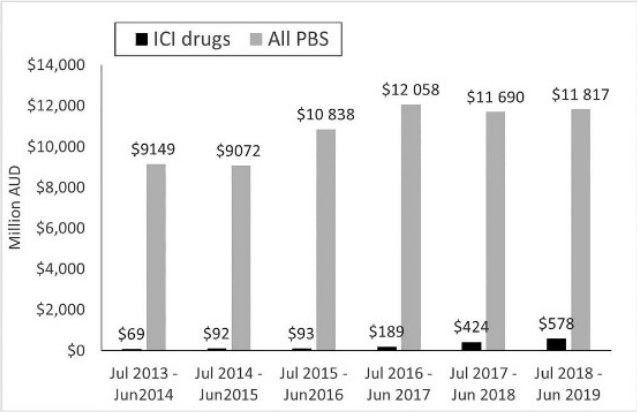

FIGURE 2 Cost of immune checkpoint inhibitor (ICI) therapies and total cost of the Pharmaceutical Benefits Scheme (PBS) in Australia[89–94]

underestimation of the cost-effectiveness because of high prices being used in cost-effectiveness analysis.[56]

Often a performance based financial risk share agreement is also needed in conjunction with these special pricing arrangements. As mentioned previously, payers can manage the treatment duration using stopping rules.[81] Another example of financial management is through expenditure caps. This can either be based on agreed utilisation rates and a 50% rebate for expenditure beyond the agreed cap (as was the case for pembrolizumab)[38] or even with a 100% rebate (nivolumab).[57]

Finally, the issue of ICI combination therapies needs to be mentioned. The financial implication of having to pay for 2 ICI therapies is potentially devastating. However, a classic HTA tool, namely cost minimisation analysis, has proven useful for indirectly managing the risk. Decision makers use cost minimisation analysis when it turns out that the clinical effectiveness is equivalent.[98] Briggs et al.[99] deemed this approach dead back in 2001, but it is still actively being used when a superiority claim of ICI combination therapies over monotherapy is not possible because of immature data.[72,82]

4 | CONCLUSION

This review of the reimbursement decisions and subsequent financial impact in Australia and the UK suggests that the costs of ICI therapies have been well managed so far. The cancer drug fund in England and Wales stayed within budget and in Australia ICI drugs only account for 5% of the total spend in 2019. Through risk agreements and managed entry programmes, the example of ICI therapies illustrates that industry and payers can effectively collaborate to ensure that innovative, but expensive, drugs can be made readily available to patients.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

All authors contributed to the conception, drafting and approval of the manuscript.

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The analysis examined reimbursement decisions for six ICIs (ipilimumab, pembrolizumab, nivolumab, avelumab, atezolizumab, durvalumab) by the PBAC and the British National Institute of Clinical Excellence (NICE).

Less than 25% of the submissions received first time approval, which indicated that the reimbursement agencies did not deem ICIs to be cost-effective at the initial price points. There was also significant uncertainty surrounding the CEAs. Extrapolation of survival data and lack of head-to-head evidence were common stumbling blocks. Payers were therefore forced to manage risk via risk share agreements, managed entry schemes, special pricing arrangements and financial caps. Further engagement between the industry and payers is encouraged in order to ensure that innovative, but expensive, drugs can be made readily available to patients.

1.6 Problem statement

HTA and health economic modelling are pivotal for controlling the financial risks of oncology treatments, especially in markets that have largely publicly funded healthcare. However, there are many uncertainties relating to efficacy, safety and QoL, as outlined in the previous sections. Furthermore, increasing costs and subsequent challenges of managing healthcare budgets, especially relating to ICIs, makes access to oncology treatments a challenge for decision makers like the PBAC. This leads to reduced or delayed access, which ultimately is not in anyone's interests. Payers, sponsors and most importantly, patients, are all adversely affected. Better methodology is needed to ensure that early and appropriate access to these medicines is achieved.

1.7 Aims of thesis

The aims of the body of work presented in this thesis were:

- To examine key technical issues relating to the health economic evaluation of oncology therapies, which ultimately lead to reduced or delayed access for patients. These issues are described fully in chapter two of this thesis.
- To identify potential solutions to the above issues.

1.8 Thesis outline

The thesis is divided into seven chapters. Chapter 1 (the current chapter) provides an introduction to oncology treatments and summarises the reimbursement process in Australia. It also provides insight into the challenges of funding oncology treatments as well as examining the recommendations of two HTA agencies (Australian PBAC and the UK NICE) to determine the factors that contribute to the approval and rejection of immunotherapies.

Chapter 2 presents findings from a literature review of HTA methods in oncology. Methodological issues relating to health economic modelling, such as extrapolating clinical trial data, limitations of QoL instruments, model structures and financial implications are characterised.

Chapter 3 comprises of an original study that examined the impact of using different QoL instruments on CEA. Using a published Australian health economic model that that evaluated the cost-effectiveness of ICIs for metastatic melanoma, the study compared CEA results from use of a new cancer-specific QoL instrument (QLU-C10D) to results from use of a generic EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) instrument.

Chapter 4 describes a study that reassessed a CEA reviewed by the Australian PBAC in 2017 for nivolumab versus everolimus for RCC, with updates to the price of everolimus and efficacy data for nivolumab.

Chapter 5 describes a study that validated input variables used the aforementioned CEA reviewed by the PBAC of nivolumab versus everolimus for RCC against real-world prescription data from the Australian PBS.

Chapter 6 comprises of a survey of Australian stakeholders with experience with HTA of oncology therapies, the aims of which was to provide insight into current and future challenges in this space.

Chapter 7 draws together the findings and conclusions from the research presented in the previous chapters and outlines recommendations for future research.

Chapter 2: State of play in HTA for oncology drugs

2.1 Introduction

The treatment of cancer has undergone significant change the past 20 years, with options originally being limited to non-specific chemotherapy, followed by the emergence of targeted therapies and more recently, ICIs. The field of HTA has witnessed many advances in line with the evolution in oncology. For example, assessing benefits and risks of chemotherapies stimulated research into treated-related QoL. Another example is prolonged OS for ICI-treated patients leading to a focus on extrapolation of survival beyond the durations of clinical trials.

HTA is mandated by the PBAC when considering oncology drugs for subsidisation via the PBS. The proliferation of new medicines for cancer and the growing prevalence of cancer have cast light on burgeoning costs. Payers have actively looked at different types of market access agreements to manage the financial risks while ensuring that patients get access to the latest medication. As such, HTA methodology has had to evolve in line with the change in the treatment landscape from chemotherapy to ICIs.

This chapter presents the findings of a literature review that assessed current HTA methods in oncology, and was published in Value in Health in 2019 [114].

2.2 Published paper

Kim H, Goodall S, Liew D. Health Technology Assessment Challenges in Oncology: 20 Years of Value in Health. Value Health, 2019. 22(5): p. 593-600.

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HEOR in the Broader Context of HTA/CER

Health Technology Assessment Challenges in Oncology: 20 Years of *Value in Health*

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ABSTRACT

Background: Oncology treatments have changed from chemotherapies to targeted therapies and more recently immuno-oncology. This has posed special challenges in the field of health technology assessment (HTA): capturing quality of life (QOL) associated with toxicity due to chemotherapy, crossover upon progression in targeted therapy trials, and survival extrapolation for immuno-oncology drugs.

Objectives: To showcase 20 years of *Value in Health* (*ViH*) publications in oncology.

Methods: A review was undertaken of oncology articles published in *ViH* from May 1998 to August 2018. Full-length articles published in *ViH* with the keywords "oncology," "cancer," "h(a)ematology," and "malignancy" were included for review. Conference abstracts were excluded.

Results: Four major themes were identified: (1) QOL and the development of multiple functional assessment of cancer therapy tools and mapping instruments; (2) analysis of clinical evidence using indirect comparisons, network analyses, and adjustment for crossovers; (3) modeling, Markov models, partitioned survival models, and extrapolation methods; and (4) financial implications and how to deal with uncertainty, introduction of conditional reimbursement, managed entry, and risk share agreements.

Discussion: This review article highlights the important role *ViH* has played in disseminating HTA research in oncology. A few key issues loom on the horizon: precision medicine, further development and practical application of new QOL measures, methods for translating clinical evidence, and exploration of modeling techniques. For a better understanding of the complex interplay between access and financial risk management, *ViH* will no doubt continue to promote pioneering research in HTA and oncology.

Keywords: cost-effectiveness, cost-utility, health technology assessment, oncology, quality of life

VALUE HEALTH. 2019; 22(5):593–600

Introduction

Value in Health (*ViH*) is the flagship publication for the International Society of Pharmacoeconomics and Outcomes Research (ISPOR). The first issue was published in May 1998, and the journal's aim is to publish best applications of pharmacoeconomics and outcomes research.[1] The fields of pharmacoeconomics and outcomes research have seen many advances over the past 2 decades and the readership of *ViH* has grown to more than 10 000.[2]

An important therapeutic area that likewise has undergone significant evolution in the same time period is oncology, in which treatment options have changed from nonspecific chemotherapy to targeted therapy and more recently immuno-oncology (Figure 1).

Chemotherapies such as carmustine, docetaxel, and paclitaxel constituted major treatments in oncology until the start of this century,[1] but their effects on healthy cells led to adverse toxic profiles.[2] The impact of toxicities when assessing benefits and risks of chemotherapies became important and this stimulated research into quality of life (QOL).

In the 2000s, new classes of targeted therapies such as imatinib, gefinitib, and bevacizumab emerged and gained regulatory approval.[1] These drugs selectively target the growth of cancer cells[3] as demonstrated through superior progression-free survival.[4–6] Nevertheless, some of these trials allowed patients to switch from placebo/control to active treatment upon progression,[7,8] thereby making it difficult to translate the clinical evidence as overall survival was confounded.

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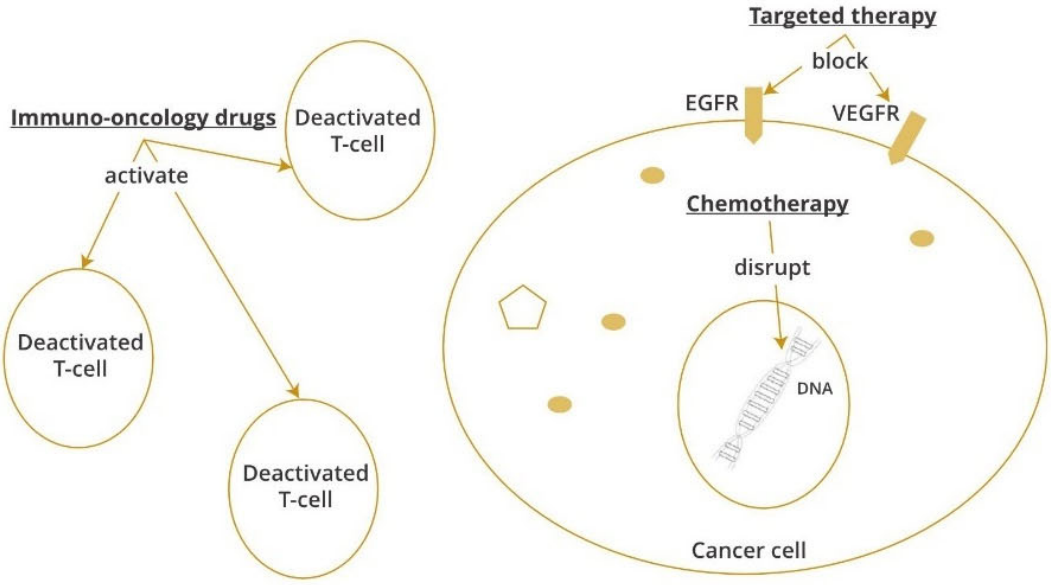
Figure 1. Modes of action: chemotherapy, targeted therapies, and immuno-oncology agents.



EGFR, epidermal growth factor receptor inhibitors; VEGFR, vascular endothelial growth factor receptor inhibitors.

More recently, immuno-oncology drugs have been developed (eg, ipilimumab, pembrolizumab, and nivolumab), which inhibit tumor-induced immunosuppression and enable the immune system to fight cancers.[9] These drugs often need time to work, which manifests in an efficacy profile in which there is seemingly no benefit in terms of progression-free survival despite a significant benefit in overall survival.[10,11] This has led to the focus on modeling techniques and especially on extrapolation of survival beyond the durations of clinical trials.

The proliferation of new medicines for cancer and the growing prevalence of cancer have meant that costs have threatened to spiral out of control.[12] As such, payers have actively looked at different types of market access agreements to manage the financial risks while ensuring that patients get access to the latest medication.

The aim of this article is to showcase the past 20 years of *ViH* publications in oncology over this period.

Methods

A search of every issue of *ViH* from May 1998 to August 2018 was performed using the *ViH* website. Full-length articles that were found using the keywords "oncology," "cancer(s)," "h(a)ematology," and "malignancy/malignant" were considered. Furthermore, ISPOR Task Force reports were reviewed. Conference abstracts were excluded. All articles were reviewed by a reviewer.

Results

A total of 147 issues of *ViH* were searched and 2628 publications were identified in the initial search. Of these, 2292 conference abstracts were excluded and the remaining 336 were full-length articles, review articles, correspondence, and editorials (Figure 2).

From these publications, 4 key themes were noted: (1) QOL and its measurement; (2) analysis of clinical evidence using indirect comparisons, network analyses, and adjustments for crossovers; (3) health economic modeling with respect to Markov models and partitioned survival models as well as extrapolation methods; and (4) financial implications and how to deal with uncertainty.

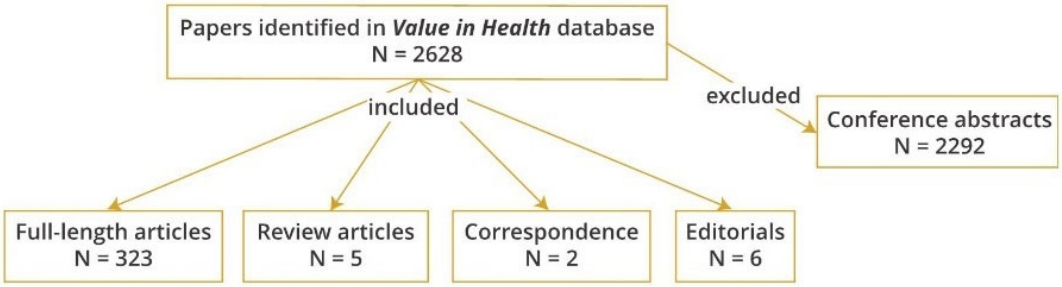
Quality of Life

The evolution of QOL in pharmacoeconomics and outcomes research in oncology is well documented in *ViH*. Twenty years ago, patients/physicians and payers were grappling with how to value chemotherapies despite severe toxicities. In this setting, QOL, which reflects the balance between benefits and harm to individuals, became an integral part of health technology assessments (HTAs) in oncology.

It was recommended in 1999 at the ISPOR Inaugural European Conference that quality-adjusted life-years (QALYs) be used instead of healthy-year equivalents when conducting health economic evaluations.[3] At the same conference, it was noted that current databases did not usually contain QOL data[4] and, as such, economic evaluations of cancer interventions did not necessarily focus on QALYs but rather on life-years gained.[5] Many challenges of QOL were identified by Leidy et al[6] who highlighted the need for rigorous study design and for more research into methodology, development of new instruments, and interpretation in the field of health-related quality of life (HRQOL). Later the same year, Wan et al[7] published an analysis on the demographic, social, and clinical factors that have an impact on the HRQOL of patients with 4 different types of cancer (breast, colon, head/neck, and lung) at different disease stages using the Functional Assessment of Cancer Therapy—General (FACT-G) instrument. This study not only showed that multiple factors influence patient assessments of HRQOL, but also showed that the management of cancer was diverse and that there were significant differences in functional well-being among people with different types of cancer. Several articles were published subsequently on FACT instruments specific to advanced kidney cancer,[8] metastatic hormone-refractory prostate cancer,[9] stage I-IV melanoma,[10] acute and chronic leukemia,[11] stage III/IV breast cancer,[12] and advanced brain cancer.[13]

Typically, utility values are not generated by authors of oncology economic evaluations and have been taken from separate published studies using standard gamble or time trade-off

Figure 2. Flowchart of the review.



(TTO).[14–17] Nevertheless, with increased use of the QALY as the key reported outcome, mapping tools were developed to allow the derivation of utilities from HRQOL instruments, such as the FACT-G mapping by Cheung et al[18] and the mapping of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) by Pickard et al,[19] both of which were used by patients at different stages of various cancers. Direct measurements were also undertaken. For example, a TTO study involving 50 oncology nurses was performed by Brown et al[20] as part of an economic evaluation in head and neck cancer, with the health state values being based on EQ-5D health states rather than on cancer-specific health states. The broader general EQ-5D instrument became more popular over time but was not without issues. In 2009, Norman et al[21] highlighted variation in EQ-5D utility values across the United Kingdom, the Netherlands, Denmark, and Germany. This variation meant that economic evaluations in Germany using UK weights would underestimate utility, because Germans generally valued each EQ-5D health state higher than did people in the United Kingdom. Viney et al[22] published Australia-specific EQ-5D TTO weights in 2011 and did a further comparison with Japanese and Spanish data. Around the same time, important contributions to the discussion surrounding important clinical differences of QOL were also published in *ViH*. Cella et al[9] reported estimates of meaningful difference in metastatic hormone-refractory prostate cancer, and Askew et al[10] published estimates of meaningful difference in stage I-IV melanoma. A review by Tosh et al[23] of economic models reviewed by the UK National Institute for Health and Care Excellence reported that the EQ-5D was the most common tool extracted from clinical trials for economic evaluation. Mapping, systematic reviews, and elicitation studies were and still are the basic techniques used when utility data are not measured alongside efficacy data in a clinical trial setting. A recent initiative to move toward an EORTC QLQ-C30–derived disease-specific utility in cancer called EORTC Quality of Life Utility Measure-Core 10 dimensions[24] has recently been revealed. The reliability of this tool was recently published in *ViH* by Gamper et al[25] who showed that it is more likely to measure health state preferences rather than mood-specific or condition-specific judgments. This is potentially a significant advance because it enables researchers not only to measure cancer-specific issues with respect to utilities, but also to apply it retrospectively to old studies in which EORTC QLQ-C30 was administered.

Table 1 lists key publications of QOL instruments in *ViH* published between 1998 and 2018.

Clinical Evidence

Direct head-to-head evidence provides an unbiased estimate of efficacy, safety, and QOL and is therefore considered the criterion standard criterion in HTA.[37] It is, however, not always possible to perform head-to-head trials. One reason is that interventions are developed in parallel, which makes it impossible to predict what the standard of care will be even in the short term. Another complicating factor may be the lack of an alternative effective treatment available. This means that patients are reluctant to join trials if they risk being randomized to placebo. These issues are well recognized in oncology by regulators[38] and researchers[39] and, as a consequence, single-arm trials are becoming common in the development of cancer drugs.

As the treatment landscape of cancer moved from chemotherapy to targeted therapies to immuno-oncology agents, several issues emerged that related to identifying, describing, and accounting for uncertainty as a result of lack of head-to-head evidence and economic evaluations based on evidence from single-arm trials.

Two ISPOR Task Force reports[37,40] have been published on indirect comparisons and network meta-analysis. The first report[37] provided guidance on the interpretation of indirect comparisons and network meta-analysis to assist policy makers and healthcare professionals in decision making. The second report[40] set out best practices for HTA practitioners who perform these types of analyses. A review of HTAs in endocrine early breast cancer[41] revealed that methods such as indirect comparisons are common. Nevertheless, Casciano et al[42] noted in an economic evaluation of metastatic renal cell carcinoma the inherent limitation of indirect comparisons arising from differences in baseline characteristics of groups being compared, which could confound the results. Exploring the use of propensity scoring to adjust baseline differences in a cohort of elderly patients with non-Hodgkin lymphoma was undertaken by Gruschkus et al.[43] An in-depth article extending this method to naive comparisons to perform matching-adjusted indirect comparisons for newly diagnosed patients with chronic myeloid leukemia was published by Signorovitch et al[44] (Figure 3).

Another significant issue with respect to patients switching treatment upon progression in a clinical trial was highlighted by Hoyle et al[45] for advanced renal cell carcinoma. This was typically done for ethical reasons, that is, to ensure that all patients have a chance of receiving potentially optimal treatment when participating in a clinical trial, regardless of whether they were randomized to control or intervention. Nevertheless, this meant that the impact of the intervention on overall survival would be confounded by treatment switching when progression occurred. Adjustment to postprogression survival using a calibration term so that the resulting median overall survival time was equal to that derived from advanced multiple myeloma trial data was presented by Ishak et al[46] and methods such as inverse of censoring weighting and rank preserved structural failure time became popular, as described by Jönsson et al[47] in a literature review. This

Table 1. Key publications of QOL instruments in *Value in Health* published between 1998 and 2018

Instrument	Cancer type	Reference
FACT—biological response modifiers	Not tumor-specific	Yost 2005[26]
Mapping of Functional Assessment of Cancer Therapy—Prostate and EORTC QLQ-C30 onto EQ-5D	Metastatic hormone-refractory prostate cancer	Wu 2007[27]
Functional Assessment of Cancer Therapy—Kidney Symptom Index	Kidney cancer	Cella 2007[8]
Functional Assessment of Cancer Therapy—General	Not tumor-specific	Dobrez 2007[28]
Cancer Therapy Satisfaction Questionnaire	Not tumor-specific	Trask 2008[29]
TTO and EQ-5D Australian weights	Not tumor-specific	Viney 2011[22]
Utility-Based Questionnaire—Cancer derived using TTO	Not tumor-specific	Grimison 2009[30]
Mapping of EORTC QLQ-C30 onto TTO utility scores	Not tumor-specific	Pickard 2009[19]
Mapping of EORTC QLQ-C30 onto EQ-5D, SF-6D, and 15D	Gastric cancer	Kontodimopoulos 2009[31]
Functional Assessment of Cancer Therapy—Melanoma	Melanoma	Askew 2009[10]
Mapping of Functional Assessment of Cancer Therapy—General onto EQ-5D	Not tumor-specific	Cheung 2009[18]
Mapping of EORTC QLQ-C30 onto EQ-5D	Esophageal cancer	McKenzie 2009[32]
Estimate utility scores and treatment preferences using VAS and TTO	Early-stage cervical cancer	Jewell 2011[33]
National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index	Breast cancer	Garcia 2012[12]
Functional Assessment of Cancer Therapy—Leukemia	Leukemia	Cella 2012[11]
Functional Assessment of Cancer Therapy—Cognitive Function	Not tumor-specific	Cheung 2013[34]
FACT in advanced kidney cancer	Advanced kidney cancer	Rothrock 2013[35]
Mapping of FACT onto EQ-5D	Metastatic castration-resistant prostate cancer	Skaltsa 2014[36]

EORTC QLQ-C30 indicates European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; FACT, Functional Assessment of Cancer Therapy; QOL, quality-adjusted life-year; SF-6D, 6-dimensional health state short form; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.

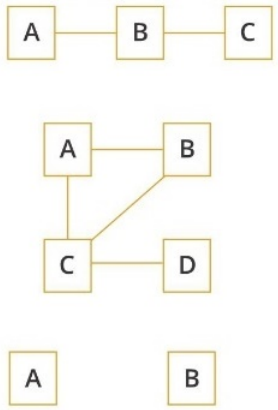
is still a hotly debated topic, with Bennett et al[48] publishing an article in 2018 highlighting issues with uncertainty of rank preserved structural failure time estimates when applied to parametric survival models. Isbary et al[49] reported that oncology medicines with switching received better additional benefit ratings, but were assigned lower evidence levels in Germany, reflecting the uncertainty associated with adjustment methods.

Modeling

The ISPOR Task Force Report on modeling good research[50] states that specifications of health states should generally reflect the disease condition modeled. This is well accepted in oncology, and Frederix et al[41] concluded in a review of breast cancer models that the underlying biological processes were taken into account to a large extent. Markov models with disease-/progression-free and progressive/recurrence health states are common across tumor types from adjuvant therapy to advanced stages of cancer.[14,17,51,52] Another popular method that was explored by Hoyle et al[53] in metastatic colorectal cancer was to estimate the proportion of patients in each health state (nonprogressive disease, progressive disease, and death) using the area under the survival curves. This type of modeling was later coined as "partitioned survival" modeling and several HTAs adopting the approach have been published in *ViH*, with recent examples in advanced ovarian cancer[54,55] and advanced melanoma.[55] Discrete event simulation (DES)[56] is also common in oncology because it enables models to take into account heterogeneity in baseline characteristics as well as to reflect the complexity of real-world treatment pathways. Other advantages of DES include tracking of health status, treatment history, and treatment switches over the course of the disease to improve accuracy and efficiency. Multiple examples have been published in *ViH* for testing of ovarian cancer,[57] chemotherapy-naive patients with prostate cancer,[58] follicular lymphoma,[59] and a surveillance program for melanoma.[60] Tappenden et al[61] even used DES to model the whole disease of colorectal cancer (Figure 4).

A hotly debated topic in oncology modeling is the extrapolation of survival curves. The issue is highlighted in the ISPOR Task Force Report on modeling good research[50] and relates to challenges with respect to transforming trial data, such as estimating survival curves on the basis of published summary data to extrapolate beyond trial durations. A practical implementation of these methods was outlined by Coyle et al,[62] who performed a cost-effectiveness analysis of systemic therapies in advanced pancreatic cancer. A lifetime horizon is frequently considered, and although for many cancer types the duration is short, a time horizon of 60 years was used by Johal et al[63] in a cost-effectiveness analysis of adjuvant treatments for osteosarcoma. Different time horizons are often applied, such as by Hsu et al,[64] who considered 3, 4, 5, and 10 years for their cost-effectiveness analysis of treatments for stage III colon cancer. Pure trial-based economic evaluations have also been published in *ViH*. For example, Goulart and Ramsey[16] showed that in stage III/IV non–small cell lung cancer, a trial-based evaluation for bevacizumab added on to chemotherapy would result in an incremental cost-effectiveness ratio of

Figure 3. Methods for dealing with lack of head-to-head data and practical examples published in *Value in Health*.



ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta analysis.

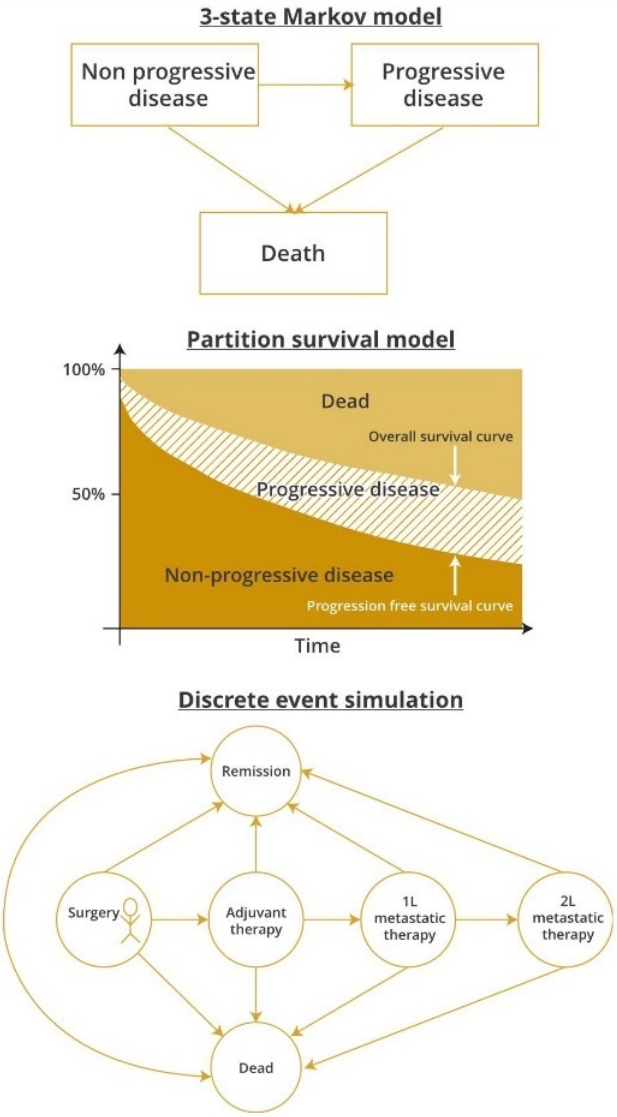
$500 000 per QALY gained. When extrapolating survival curves to longer time periods, the choice of distribution is most commonly justified using Akaike and Bayesian information criteria, as exemplified by models in chronic lymphocytic leukemia and ovarian cancer published by Woods et al[65] and Fisher and Gore,[66] respectively. Bohensky et al[52] used Akaike and Bayesian information criteria, as well as made sure that the selected function matched the underlying biological assumption with respect to the drug under investigation in stage IIIb/IV melanoma.

Financial Implications and How to Deal With Uncertainty

Cipriano et al[67] reported that the price of lung cancer treatment across all stages is approximately $10 000 per month for the first 6 months and up to $2000 thereafter. The high cost of cancer drugs and budget implications have been well highlighted in *ViH* over the years. A recent study by Leopold et al[68] looking at media coverage on high drug prices in the United States found that launch prices of cancer drugs have increased about 10% per year between 1995 and 2013. Nevertheless, drug prices are only a part of the equation. Tan et al[69] highlighted that inpatient hospital costs for patients with cancer are more than 50% higher than the average inpatient costs in the Netherlands. Félix et al[70] showed that the costs associated with common skeletal-related events for metastatic breast and prostate cancer were between €5700 and €6000 per patient in the Portuguese health system.

Different measures have been put in place around the globe to control the spending of cancer drugs, from setting up a special cancer fund independent of the drug reimbursement authority in the United Kingdom[71,72] to issuing government drug licenses to local manufacturers for patented drugs in Thailand.[73] Kircher et al[74] discussed whether legislation on parity can help reduce the cost burden of anticancer medications, but it remains unclear what an optimal plan would look like. Boersma et al[75] argue that a reduction in drug expenditure can be achieved with the introduction of a decision threshold using examples in non–small cell lung cancer and leukemia. In line with this, Wilson and Cohen[76] showed that in a comparison between Australia and the United States, implementing processes for cost-effectiveness assessments did indeed restrict budget and use of cancer medicines. Nevertheless, Franken et al[77] reported that economic evaluation has had limited impact in restricting access for controversial high-cost drugs such as cancer drugs in England, Germany, the Netherlands, and Sweden.

Figure 4. Common health economic models used in oncology.



A framework for coverage with evidence development to facilitate paying for use of new drugs in areas such as lung cancer and colorectal cancer despite uncertain evidence was put forward by Walker et al.[78] Wonder et al[79] described the Australian process in which the price of a drug was justified by the existing evidence, pending the availability of more conclusive evidence of cost effectiveness to support continued listing of, for example, anticancer medicine at a higher price.

New trial evidence for anticancer medicines is not always going to be available. Instead, real-world evidence (RWE) has been used to cover the evidence gaps, and *ViH* has published an ISPOR Task Force Report on the subject.[80] Several articles on the use of RWE in oncology have been published. Mohseninejad et al[81] showed how the use of registries could improve the follow-up for conditional approval of oxaliplatin in stage III colon cancer, and Lakdawalla et al[82] showed that real-world data generation can be used to predict overall survival and progression-free survival of chemotherapies using data from breast, colorectal, lung, ovarian, or pancreatic cancer. Nevertheless, RWE generally showed lower efficacy when compared with trial evidence. RWE can be used not only to prove that a drug works, but also to build pay-for-

performance schemes such as cost sharing and payment by results as reported by Navarria et al.[83] They reported on a so-called success fee scheme in Italy, where an anticancer drug is provided by the company at no initial cost and the payer provides payment only for those treatments that have shown effectiveness in a predefined period. Nevertheless, RWE is still considered lower level of evidence compared with randomized clinical trials by HTA agencies (Swedish TLV, UK National Institute for Health and Care Excellence, German IQWiG, French HAS, and Italian AIFA) around the world, as pointed out by Makady et al.[84]

Discussion

Over the last 20 years, as new treatments have emerged in oncology, they have brought new challenges to pharmacoeconomics and outcomes research. Regarding QOL, the inability of general instruments such as the EQ-5D to capture outcomes specific to chemotherapy led to the development of new instruments such as the EORTC QLQ-C30. Issues related to clinical data and lack of active comparators led to methods such as indirect comparisons, network analysis, and matching-adjusted indirect comparisons. Common to oncology, modeling beyond the trial horizon has generated numerous articles on extrapolation and non-Markov modeling techniques. The high costs of oncology medicines and the impact they have on budgets have stimulated research into risk share agreements, conditional reimbursement, and managed entry schemes.

It is not easy to predict what the future of pharmacoeconomics and outcomes research in oncology will look like. There seems to be room for further research into the practical application of disease-specific QOL instruments such as the newly created EORTC Quality of Life Utility Measure-Core 10 dimensions by King et al.[24] Translation of clinical evidence in the absence of head-to-head trial data is also becoming increasingly relevant as new biomarkers are discovered. Further exploration of extrapolation methods is also on the cards considering that trial evidence will need to be assessed well beyond the durations of clinical trials. Finally, it is predicted that the complex interplay between access and financials will be front and center of it all because payers will have to balance pressure from the public to get reimbursement with the ability to pay.

The limitation of an anniversary article such as this is obviously that contributions in other journals are not presented, but this article has outlined the rich heritage that *ViH* has in disseminating research in the areas of pharmacoeconomics, outcomes research, and oncology. Continued development of pharmacoeconomics and outcomes research methods in oncology is likely to continue well into the future, and *ViH* will hopefully continue to be an important platform for researchers to publish best applications in these fields. This was the explicit wish of the inaugural editor of *ViH*, James E. Smeeding, as outlined in the first editorial of the journal.

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2.3 Conclusion

There are still many challenges in HTA of oncology medications. Four specific areas are particularly important:

1. Finding ways of capturing QoL for new treatments and adverse events related to these.
2. Transforming and translating suboptimal clinical data.
3. Modelling health outcomes and costs beyond the trial horizon.
4. Financial impact and ensuring continued affordability.

It is predicted that the complex interplay between access and financial matters will be front and centre of future research as payers balance pressure to grant reimbursement with the ability to pay.

Chapter 3: Quality of life in health economic oncology models

3.1 Introduction

QALYs represent the preferred outcome by reimbursement authorities like the Australian PBAC and the UK NICE when undertaking economic evaluations of oncology treatments. The most widely used tool is the generic EQ-5D instrument. The EQ-5D is considered insensitive to changes in health status in cancer patients by some researchers, the rationale being that the use of condition-specific measures is more sensitive in capturing the disutility associated with treatment-related AEs for newer medications such as ICIs.

Recently, a cancer specific multi-attributed utility index (MAUI) based on the Quality-of-Life Questionnaire for cancer patients (QLQ-C30) was developed, called the Quality-of-Life Utility Measure-Core 10 dimensions (QLU-C10D).

The QLU-C10D was estimated using an Australian adult general population aged 18 years or older. Health states were operationalised as 12 attributes in a discrete choice experiment [115]. This is different from the standard valuation protocol recommended for EQ-5D, in which a composite time trade-off valuation is recommended, supplemented by a discrete choice experiment [116].

The QLU-C10D may be more sensitive than generic MAUIs such as the EQ-5D because it reflects symptoms and AEs commonly experienced by cancer patients. The first set of utility weights was published in 2018 for Australian cancer patients.

This chapter compares the QLU-C10D to EQ-5D and its impact on cost-effectiveness modelling in oncology, and was published in Pharmacoeconomics Open in 2021 [117].

3.2 Published paper

Kim H, Cook G, Goodall S, Liew D. Comparison of EQ-5D-3L with QLU-C10D in Metastatic Melanoma Using Cost-Utility Analysis. Pharmacoeconomics Open, 2021. 5(3): p. 459-467.

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ORIGINAL RESEARCH ARTICLE

Comparison of EQ-5D-3L with QLU-C10D in Metastatic Melanoma Using Cost-Utility Analysis

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Abstract

Background The National Institute for Health and Care Excellence (NICE) prefers the use of the generic EQ-5D instrument to estimate quality-adjusted life years (QALYs), and recommends that condition-specific instruments only be used when EQ-5D data are not available or not appropriate.

Objective This study aimed to compare the utility gain and cost-effectiveness results of using the generic EQ-5D-3L instrument to the condition-specific Quality-of-Life Utility Measure–Core 10 dimensions (QLU-C10D) by applying both sets of values in a published cost-utility analysis (CUA) of immunotherapy for metastatic melanoma.

Methods Quality-of-life data were drawn from a clinical study in which both QLQ-C30 and EQ-5D-3L tools were used. The potential influence of the two instruments on cost-effectiveness was assessed using a three-state Markov model. Descriptive statistics and standard health economic outputs were compared between analyses that applied the two different utility measures.

Results Mean baseline utility values as measured by the QLU-C10D (mean = 0.744, SD = 0.219) were not statistically different ($p > 0.05$) compared to values derived from EQ-5D-3L (mean = 0.735, SD = 0.239). The two instruments were correlated (Pearson's correlation = 0.74); however, concordance was low (Lin's concordance correlation coefficient < 0.90) at baseline. The model predicted slightly higher QALYs gained when using EQ-5D-3L over QLU-C10D-derived utilities (1.87 vs 1.74, respectively). This resulted in an incremental cost-effectiveness ratio of US$30.5K when using EQ-5D-3L utilities, compared to US$32.7K when using QLU-C10D utilities. Cost-effectiveness acceptability curves based on the two sets of utilities were almost indistinguishable.

Conclusion This study supports the use of the generic EQ-5D instrument in immunotherapy treated metastatic melanoma, and found no additional benefit for using the disease-specific QLU-C10D when using Australian weights.

Key Points for Decision Makers

Small differences are observed between the Quality-of-Life Utility Measure–Core 10 dimensions (QLU-C10D) and the EQ-5D-3L in metastatic melanoma.

The differences observed between instruments do not translate into difference in cost-effectiveness once the quality-of-life estimates are incorporated into a cost-utility analysis (CUA) model.

Utilities drawn from the EQ-5D-3L and QLU-C10D tools may be different, but the choice of one over the other may make little difference to CUAs.

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1 Introduction

A common area of discussion, particularly during the reimbursement of new technologies, relates to whether a condition-specific quality-of-life (QoL) instrument used to derive utilities delivers similar cost-effectiveness results compared to the use of a generic instrument, such as the EQ-5D [1]. The EQ-5D is considered insensitive to changes in health status in cancer patients by some researchers [2], who advocate the use of condition-specific measures instead because they capture the disutility associated with treatment-related adverse events. Brazier et al. [3] found lower ceiling effects for condition-specific preference based measures compared to the EQ-5D. However, other studies have found that condition-specific measures like the Functional Assessment of Cancer Therapy (FACT) underestimate benefit in terms of quality-adjusted life years (QALYs) gained compared to the EQ-5D in patients with advanced cancer [4], while some have found that the EQ-5D and condition-specific measure (EORTC-8D) are equally sensitive to disease characteristics among cancer patients [1].

The EQ-5D is a common tool for capturing QoL utilities in clinical trials [5] and is accepted by health technology assessment (HTA) agencies around the world, including the Australian Pharmaceutical Benefits Advisory Committee (PBAC) [6] and the National Institute for Health and Care Excellence (NICE) in the UK [7]. Proponents of the EQ-5D argue that non-generic instruments reduce the comparability between technology assessments across different indications and, therefore, as advocated by NICE, have a preference for using the EQ-5D to estimate QALYs [8]. According to the NICE technical support documents, condition-specific instruments should only be used when the EQ-5D is not available or not appropriate [9, 10]. Other agencies, such as the PBAC, have taken a less prescriptive approach to which utility instrument should be used [6].

As expected, based on this guidance, many HTAs are performed using the EQ-5D even if it has not been demonstrated to be appropriate for the specific condition of interest. This is the case for metastatic melanoma, which was the first condition for which the new generation of immunotherapies were granted reimbursement by the PBAC and NICE [11].

The QLQ-C30 is one of the most widely used condition-specific questionnaires used in cancer studies [12]. King et al. [13] developed a cancer specific multi-attributed utility index (MAUI) based on the QLQ-C30 called the Quality-of-Life Utility Measure–Core 10 dimensions (QLU-C10D). The QLU-C10D may be more sensitive than generic MAUIs such as the EQ-5D due to the fact that it contains symptoms and adverse events commonly experienced by cancer patients. The first set of utility weights was published in 2018 for Australian cancer patients [14].

Using QoL data from the CheckMate-066 trial, this study aimed to compare the generic EQ-5D-3L instrument to the condition-specific QLU-C10D by applying both sets of values in a published cost-utility analysis (CUA) evaluating immunotherapy for the treatment of metastatic melanoma.

2 Methods

2.1 Cost-Utility Analysis of Nivolumab Versus Ipilimumab

2.1.1 Treatments

The treatment of metastatic melanoma has undergone evolution over the last decade, from chemotherapies, such as dacarbazine and fotemustine, to immunotherapies such as ipilimumab and nivolumab. Ipilimumab was the first immunotherapy approved to treat melanoma in 2011 [15]. It is a monoclonal antibody that binds to cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and shifts the immune system balance towards T cell activation, thus increasing the number of activated T cells that can migrate to attack the tumour [16, 17]. Nivolumab is a human immunoglobulin G4 that acts as an immunomodulating agent by blocking the interaction between programmed cell death protein 1 (PD-1) and its ligands. This results in the activation of T cells and cell-mediated immune responses against tumour cells or pathogens [18].

2.1.2 Clinical Trial Data

The Food and Drug Administration (FDA) phase III clinical registration trial (CheckMate-066) randomly assigned 418 treatment-naïve patients with metastatic melanoma without a *BRAF* mutation to receive nivolumab or dacarbazine chemotherapy. Nivolumab improved 1-year overall survival (OS), with a hazard ratio of 0.42 (95% confidence interval [CI] 0.25–0.73) compared to chemotherapy. Median progression-free survival (PFS) was 5.1 months (95% CI 3.5–0.8) for nivolumab versus 2.2 months (95% CI 2.1–2.4) for chemotherapy [19]. QoL in CheckMate-066 was measured using the QLQ-C30 and EQ-5D-3L every 6 weeks on treatment and at two follow-up visits [20]. CheckMate-066 predated the EQ-5D-5L instrument, which is why the EQ-5D-3L was used. There were fewer adverse events for nivolumab than for chemotherapy.

2.1.3 Description of the Published Cost-Utility Analysis

A published CUA [21] comparing nivolumab to ipilimumab in an Australian setting was used for the basis of the present study. As no head-to-head evidence was

available at the time of the analysis, an indirect comparison of nivolumab versus ipilimumab using data from CheckMate-066 (CA209066—nivolumab vs dacarbazine) [19] and trial MDX010-020 (ipilimumab vs gp100) [22] was undertaken to estimate the efficacy of nivolumab compared to ipilimumab. Efficacy, toxicity, and QoL (i.e. the EQ-5D-3L) were modelled over a 10-year period using a three-state Markov model with progression-free disease, progressive disease, and death as health states. PFS and OS were extrapolated from CheckMate-066 using lognormal distributions. Utility was estimated using the whole trial population regardless of treatment, and a discount rate of 5% per annum was applied to utilities and costs. A probabilistic sensitivity analysis (PSA) was performed, assigning probability distributions to key model parameters using a Monte-Carlo simulation with 10,000 iterations. Compared to ipilimumab, nivolumab yielded an additional 1.30 QALYs at an approximate incremental cost of US$39,000. The incremental cost effectiveness ratio (ICER) was US$30,475 per QALY gained.

2.2 Comparison of EQ-5D-3L TTO and EQ-5D-3L DCE Versus QLU-C10D

QoL in CheckMate-066 was measured using the QLQ-C30 and EQ-5D-3L every 6 weeks on treatment and at two follow-up visits [20]. QLU-C10D utility data were calculated by applying Australian weights derived from a discrete choice experiment (DCE) published by King et al. [14] to relevant parts of the QLQ-C30 from the individual patient data of CheckMate066. Similarly, Australian weights were applied to the EQ-5D-3L using weights from two different types of valuation study: a time trade-off (TTO) study by Viney et al. [23] and a DCE study also by Viney et al. [24]. Both weights for TTO and DCE were included as these are routinely used in Australia.

Whether a patient was progression free or had progressive disease was calculated at baseline and at corresponding time points throughout the trial. Health state utilities were examined for the study sample (pooling treatment arms) as well as treatment-specific values.

The long-term QALY gain was modelled for dacarbazine and nivolumab using the state-transition Markov model published by Bohensky et al. [21], described in the previous section. The differences in EQ-5D-3L TTO, EQ-5D-3L DCE, and the QLU-C10D were examined by looking at the total QALYs accumulated for each health state (progression-free and progressive disease). Furthermore, both total and total discounted values are reported. Standard CUA outputs such as ICERs, plots of the cost-effectiveness plane, and the cost-effectiveness acceptability curves were produced to study differences/similarities.

2.3 Statistical Analysis

Descriptive statistics for each utility measure (i.e. EQ-5D-3L TTO, EQ-5D-3L DCE, and the QLU-C10D) such as means and standard deviations (SDs) were used to compare distributions at baseline. Differences between health states (i.e. progression-free and progressive disease) were examined using a paired *t* test for differences between two samples of continuous data. The intent of the *t* test was not to draw any firm conclusion with respect to differences, but rather it was an explorative exercise to give an indication of the direction of the difference. Analyses were performed in SAS v9.4 and R on a Windows platform.

2.3.1 Concordance

The association between the EQ-5D-3L and QLU-C10D was quantified by assessing the Pearson correlation coefficient and Lin's concordance correlation coefficient (CCC) between the two instruments [25].

The correlation was considered weak if the absolute value of the Pearson correlation coefficient was < 0.4, moderate if the absolute value of the Pearson correlation coefficient was 0.4–0.7, and strong if the absolute value of the Pearson correlation coefficient was > 0.7.

Assessment of Lin's CCC was based on the recommendations of McBride [26]. If the lowest one-sided 95% CI limit for Lin's CCC is:

- 0.99, then concordance is considered almost perfect
- Between 0.95 and 0.99, then there is substantial concordance
- Between 0.90 and 0.95, then the concordance is moderate
- < 0.90, then there is poor concordance.

Additionally, scatter plots and quantile-quantile (QQ) plots of the two instruments are used to analyse any potential differences.

3 Results

3.1 Clinical Trial CheckMate-066 Baseline Values

The mean baseline utility values as measured by the QLU-C10D ($\text{mean}_{\text{QLU-C10D}} = 0.744$, $\text{SD}_{\text{QLU-C10D}} = 0.219$) were not statistically different ($p > 0.05$) when compared to EQ-5D-3L TTO ($\text{mean}_{\text{EQ-5D-3L TTO}} = 0.735$, $\text{SD}_{\text{EQ-5D-3L TTO}} = 0.239$) and EQ-5D-3L DCE ($\text{mean}_{\text{EQ-5D-3L DCE}} = 0.742$, $\text{SD}_{\text{EQ-5D-3L DCE}} = 0.280$).

3.2 Concordance

The Pearson correlation was estimated to be 0.75 (p value < 0.0001, alternative hypothesis: true correlation is not equal to 0) and Lin's CCC was estimated to be 0.74 (95% CI 0.69–0.79) at baseline.

For change from baseline, a Pearson correlation of 0.43 was observed (p value < 0.0001, alternative hypothesis: true correlation is not equal to 0) and Lin's CCC was 0.40 (95% CI 0.30–0.48).

Scatter plots and QQ-plots are presented in Fig. 1.

3.3 Clinical Trial CheckMate-066 by Health State

The values of EQ-5D-3L TTO and DCE were higher for both the progression-free and progressive states, with differences between the EQ-5D-3L measures and the QLU-C10D ranging from 0.027 for dacarbazine in the progression-free state to 0.075 for the progressive state in the combined cohort (Table 1).

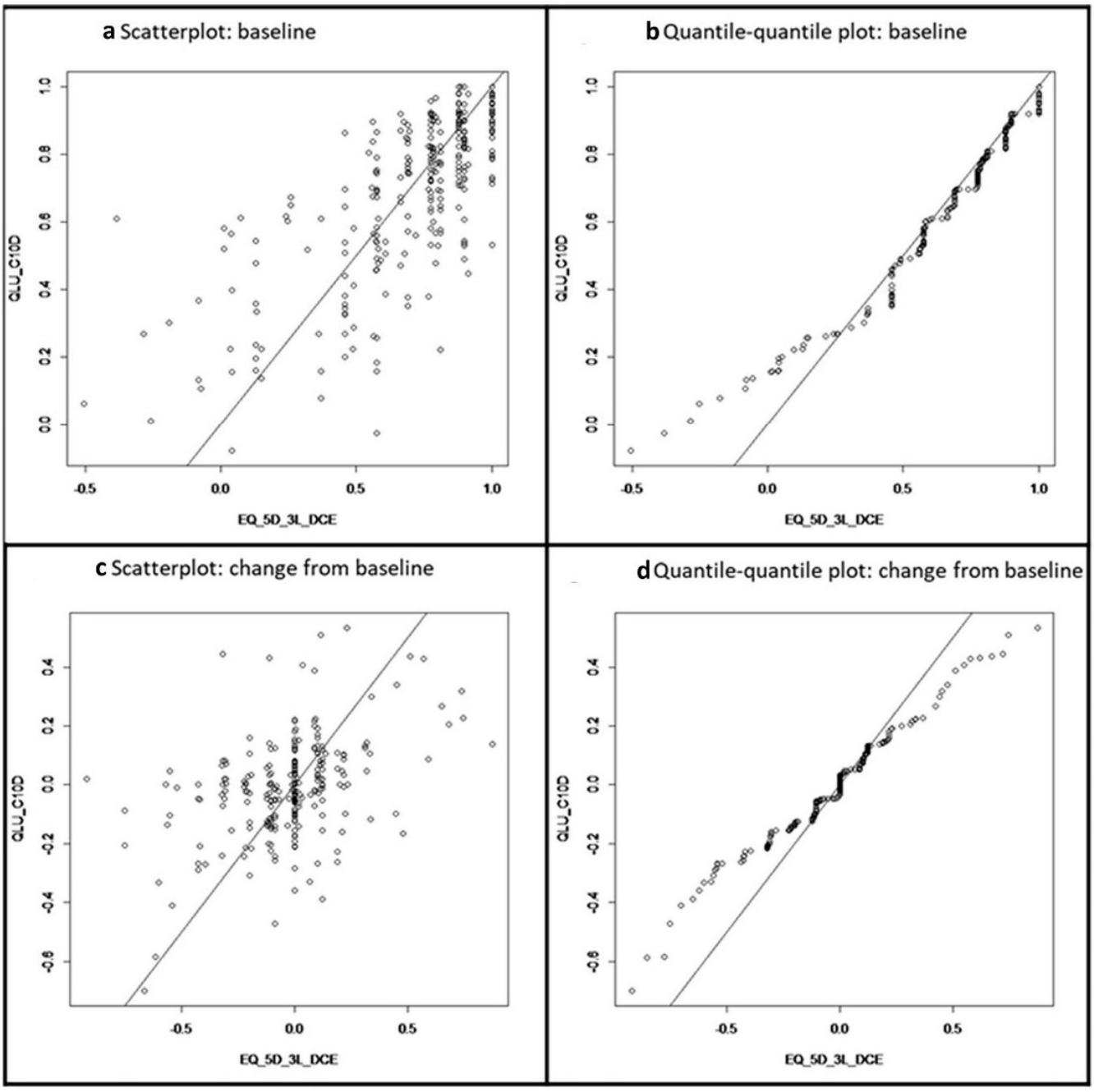

Figure 1 Scatter plots and quantile-quantile plots of EQ-5D-3L vs QLU-C10D at baseline and change from baseline. *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions

Table 1 EQ-5D-3L vs QLU-C10D by health state

	Utility based on all patients			Treatment specific utility for dacarbazine treated patients			Treatment specific utility for nivolumab treated patients		
	EQ-5D-3L TTO	EQ-5D-3L DCE	QLU-C10D	EQ-5D-3L TTO	EQ-5D-3L DCE	QLU-C10D	EQ-5D-3L TTO	EQ-5D-3L DCE	QLU-C10D
Progression free									
Mean	0.828	0.823	0.780	0.784	0.771	0.744	0.841	0.855	0.809
SD	0.174	0.231	0.207	0.235	0.278	0.225	0.174	0.190	0.187
Min–Max	−0.217 to 1	−0.507 to 1	−0.079 to 1	−0.217 to 1	−0.507 to 1	−0.026 to 1	−0.217 to 1	−0.507 to 1	−0.079 to 1
Diff. vs QLU-C10D	0.048*	0.043*	–	0.040*	0.027^{NS}	–	0.032*	0.046*	–
Progressive state									
Mean	0.798	0.788	0.723	0.703	0.711	0.662	0.829	0.846	0.780
SD	0.193	0.248	0.225	0.212	0.271	0.241	0.193	0.213	0.194
Min–Max	−0.158 to 1	−0.403 to 1	0.122 to 1	−0.158 to 1	−0.403 to 1	0.122 to 1	−0.073 to 1	−0.0366 to 1	0.137 to 1
Diff. vs QLU-C10D	0.075*	0.065*	–	0.041*	0.049*	–	0.049*	0.066*	–

DCE discrete choice experiment, *Diff.* difference, *NS* not significant, *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions, *TTO* time trade-off

NS: $p > 0.05$, *$p < 0.05$

The largest differences were observed for the progressive state when combining the two treatment arms. Furthermore, the minimum utilities measured for the EQ-5D-3L were below the preference of 'dead' (i.e. state considered worse than death), ranging from −0.507 to −0.073 compared to the QLU-C10D, where the minimum is above zero (0.122 to 0.137).

3.4 Modelling the QALY Gain Over 10 years: Dacarbazine Versus Nivolumab

QALY gains modelled over a 10-year time horizon are presented in Table 2. The EQ-5D-3L generated higher QALY gains for both the progression-free state (e.g. $\text{nivolumab}_{\text{EQ-5D-3L DCE}} = 1.571$ vs $\text{nivolumab}_{\text{QLU-C10D}} = 1.489$) as well as the progressive disease state (e.g. $\text{nivolumab}_{\text{EQ-5D-3L DCE}} = 1.361$ vs $\text{nivolumab}_{\text{QLU-C10D}} = 1.249$) for all measures compared to the QLU-C10D. This resulted in higher total (2.975 vs 2.738) and total discounted QALY gains (2.525 vs 2.324).

The model produced the largest differences between the EQ-5D-3L and QLU-C10D when applying the combined utility measure.

3.5 CUA Ipilimumab Versus Nivolumab

The QALY gain decreased from 1.30 when using the combined utility value for EQ-5D-3L TTO to 1.21 when applying the QLU-C10D (see Table 3). This resulted in a 7.5% [(US$32,748 − US$30,475)/US$30,475] increase in the ICER.

A smaller decrease of 4.3% [(US$27,638−US$26,491)/US$26,491] was observed for the ICER when treatment-specific estimates were used.

The scatter plots of the PSA (Fig. 2) showed more dispersion when using the QLU-C10D than for the simulation with the EQ-5D-3L. Moreover, higher QALY values for the EQ-5D-3L were observed.

The cost-effectiveness acceptability curves (Fig. 3) differed only marginally between the two measures.

4 Discussion

The aim of the present study was to compare the generic EQ-5D-3L utility measure with the QLU-C10D in metastatic melanoma using a practical, real-world CUA.

The EQ-5D has been criticised for being insensitive to changes in health status of cancer patients due to the limited number of dimensions and levels [2]. However, the responsiveness of the EQ-5D is dependent on condition [27], and to our knowledge, no assessment has been made in metastatic melanoma.

In the present study, the generic EQ-5D-3L valued mean progression-free and progressive health states 5–10% higher than the condition-specific QLU-C10D, with comparable SDs. Furthermore, the EQ-5D-3L was consistently

Table 2 Modelled quality-adjusted life years over 10 years

	Utility based on all patients			Treatment specific utilities		
	Dacarbazine	Nivolumab	Incremental	Dacarbazine	Nivolumab	Incremental
Alive total progression free						
EQ-5D-3L TTO	0.146	1.565	1.419	0.140	1.605	1.465
EQ-5D-3L DCE	0.147	1.571	1.424	0.137	1.632	1.495
QLU-C10D	0.139	1.489	1.350	0.133	1.544	1.411
Alive total progressive state						
EQ-5D-3L TTO	0.540	1.409	0.869	0.465	1.432	0.967
EQ-5D-3L DCE	0.521	1.361	0.840	0.470	1.461	0.991
QLU-C10D	0.478	1.249	0.771	0.438	1.347	0.909
Combined 1						
EQ-5D-3L TTO	0.680	2.975	2.295	0.605	3.037	2.432
EQ-5D-3L DCE	0.668	2.932	2.264	0.608	3.093	2.485
QLU-C10D	0.617	2.738	2.121	0.570	2.892	2.322
Combined discounted						
EQ-5D-3L TTO	0.651	2.525	1.874	0.575	2.578	2.003
EQ-5D-3L DCE	0.634	2.489	1.855	0.577	2.626	2.049
QLU-C10D	0.586	2.324	1.738	0.542	2.454	1.912

DCE discrete choice experiment, *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions, *TTO* time trade-off

Table 3 Results from cost-effectiveness analysis of ipilimumab vs nivolumab

	EQ-5D-3L TTO		EQ-5D-3L DCE		QLU-C10D	
	QALY	Costs	QALY	Costs	QALY	Costs
Utility based on all patients						
Ipilimumab	1.21	US$178,612	1.20	US$178,612	1.11	US$178,612
Nivolumab	2.51	US$138,987	2.49	US$138,987	2.32	US$138,987
Incremental	1.30	US$39,625	1.29	US$39,625	1.21	US$39,625
ICER	US$30,475		US$30,689		US$32,748	
Treatment specific utilities						
Ipilimumab	1.08	$178,612	1.09	US$178,612	1.02	US$178,612
Nivolumab	2.58	$138,987	2.63	US$138,987	2.45	US$138,987
Incremental	1.50	$39,625	1.54	US$39,625	1.43	US$39,625
ICER	US$26,491		US$25,779		US$27,638	

DCE discrete choice experiment, *ICER* incremental cost effectiveness ratio, *QALY* quality-adjusted life year, *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions, *TTO* time trade-off

associated with a wider range of utility values (−0.507 to 1) compared to the QLU-C10D (−0.079 to 1).

The lower values and shorter range for the QLU-C10D resulted in 4–8% higher ICERs, thereby indicating that the QLU-C10D might value survival less when compared to the EQ-5D-3L. However, this did not result in a change in the conclusion regarding cost-effectiveness, as there was little difference between the acceptability curves for the two scenarios.

The concordance analysis of the baseline values of the two instruments showed that they were highly correlated, with a Pearson correlation of 0.75. However, the lower 95% CI limit for Lin's CCC was 0.70, indicating that there was poor concordance between the EQ-5D-3L and QLU-C10D. The scatter plot and QQ plot reveal that there was seemingly concordance between the instruments for utilities from approximately 0.2 until 1 as quantiles of these values fell around the unity line. Quantiles for utilities below 0.2 were consistently lower for the EQ-5D-3L compared to the QLU-C10D. Change from baseline showed a moderate correlation of 0.42 between the two instruments. Concordance was poor with the lower 95% CI limit for Lin's CCC estimated to be 0.30. The scatter plot and QQ plot showed that there seem to be concordance between −0.2 to 0.2. For quantiles above 0.2, the EQ-5D-3L has higher values, and for quantiles below −0.2, the

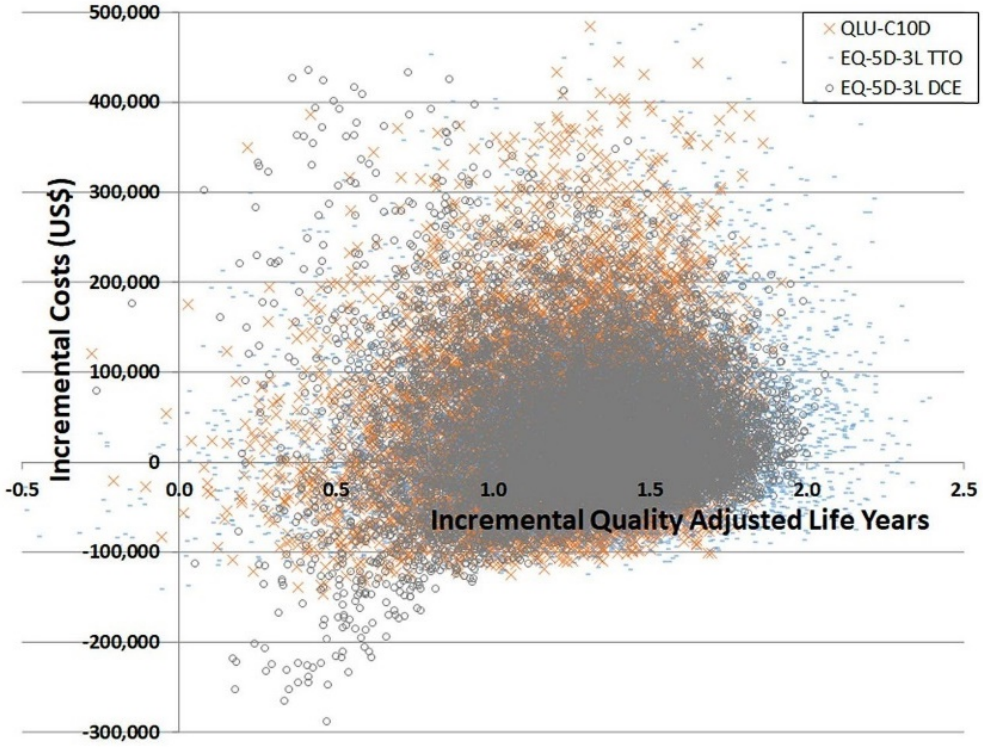

Figure 2 Cost-effectiveness plane. *DCE* discrete choice experiment, *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions, *TTO* time trade-off

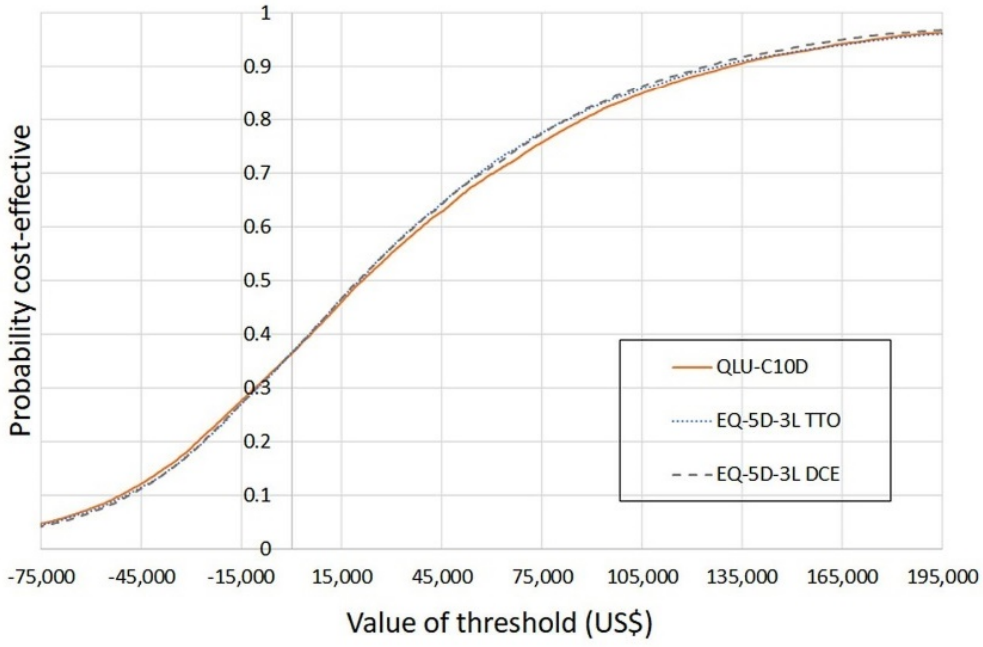

Figure 3 Cost-effectiveness acceptability curves. *DCE* discrete choice experiment, *QLU-C10D* Quality-of-Life Utility Measure–Core 10 dimensions, *TTO* time trade-off

EQ-5D-3L has lower values. Comparing QLQ-C30 data from the trial to the utility weights of the Australian QLU-C10D explores this issue further. The main QLQ-C30 data for this clinical trial were reported by Long et al. [20]. The QLQ-C30 single items with the largest influence on the QoL were fatigue and insomnia. These two items had the lowest disutility weights among the Australian QLU-C10D weights according to King et al. [14]. Moreover, the items that had the highest weights for the QLU-C10D were nausea and pain. These two items were not important for melanoma patients in the study. This suggests that the QLU-C10D weights are not suited to appropriately value the QoL for patients from the clinical trial of interest. A comparison with the Canadian [28] and UK [29] utility weights for the QLU-C10D was done to ascertain whether this is a general problem with the QLU-C10D. This did

not appear so as the Canadian and UK weights had more than 50% greater disutilities for sleep than the Australian weights. Fatigue, the other item with high influence on QoL in the trial, was also valued higher for the Canadian QLU-C10D. Thus, it appears that it is an issue with the Australian QLU-C10D weights and not in general for the QLU-C10D.

Another potential issue is that the QLQ-C30, upon which the QLU-C10D was developed, is not able to capture the impact of treatment-specific adverse reactions [30]. QLQ-C30 items are tailored to capture issues related to chemotherapies such as nausea/vomiting, constipation, appetite loss, and diarrhoea. Newer cancer treatments like immunotherapies have different adverse event profiles [31]. Common immune-related adverse events include colitis, pneumonitis, hypothyroidism, and inflammatory arthritis, [32] which are not explicitly captured by the QLQ-C30.

The QLU-C10D would seem to be a more sensitive instrument than the EQ-5D-3L. For example, the physical dimension in the QLU-C10D is represented by a four-level item for walking, whereas mobility for the EQ-5D-3L only has three levels. As discussed, the weights for the QLU-C10D do not seem to put emphasis on the items important for the patients in this study. The EQ-5D-3L on the other hand has broader questions that capture additional aspects compared to the QLU-C10D.

It has been argued that late-stage cancer patients may be particularly burdened by participating in clinical research and that it is the responsibility of the clinical researcher to ensure that they are not subjected to more tests than needed [33]. As such, it would be desirable to reduce the burden of filling out QoL questionnaires. However, our study suggests that the QLU-C10D or EQ-5D-3L cannot be considered substitutes for one another, with Lin's CCC showing low concordance between the two instruments. We therefore concur with recent recommendations by Faury et al. [12] that several QoL instruments might be needed to adequately cover the domains needed for immunotherapy.

There are several limitations to this study. Firstly, we did not have access to the full data set of the trial and were therefore not able to examine the two instruments in detail. For example, access to toxicity data would have enabled us to assess whether the QLU-C10D and the EQ-5D-3L capture disutilities connected with immune-related adverse events. Secondly, the conclusions from this study are limited to the Australian melanoma population as we only had access to an Australian decision model. Furthermore, the trial population comprised patients from other countries than Australia, and it is unclear whether the outcomes are directly translatable to the Australian melanoma population. Finally, the clinical data might not reflect current practice as it is from 2013, and future research is required for further validation.

5 Conclusion

To our knowledge, this is the first study to compare the EQ-5D-3L with the QLU-C10D using a CUA. This study demonstrates that there is no reason to consider the condition-specific QLU-C10D when using Australian weights for CUA in immunotherapy-treated metastatic melanoma as the existing generic EQ-5D-3L instrument adequately captures QoL impacts.

Declarations

Funding No funding was received for performing this study.

Conflicts of interest HK previously held employment at Bristol-Myers Squibb (until March 2018). DL has received grants, consultation fees, and travel support from Bristol-Myers Squibb for work unrelated to this article. SG has no conflict of interest in relation to the material reported in this article. GC is an employee of Bristol-Myers Squibb.

Ethics approval Sydney Local Health District Ethics Review Committee.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability All data generated or analysed during this study are included in this published article.

Code availability Not applicable.

Authors' contributions All authors contributed to the study conception and design. The analysis was performed by HK. All authors contributed to the interpretation and discussion of the results. The first draft of the manuscript was prepared by HK, and critically edited and reviewed by all other authors. All authors read and approved the final manuscript.

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3.3 Conclusion

Some differences were observed between the QLU-10D and EQ-5D-3L for patients treated with ipilimumab for metastatic melanoma. However, this study suggests that the condition-specific QLU-C10D offers an alternative to EQ-5D-3L when using Australian weights for CUA in immunotherapy-treated metastatic melanoma. A new five level version of the EQ-5D designed to be more sensitive by capturing a much larger number of health states could prove to be a better tool than the EQ-5D-3L and the QLU-C10D.

Chapter 4: Reassessment of the cost-effectiveness of oncology agents

4.1 Introduction

The evidence base for oncology is evolving at a rapid pace. Two of the main drivers in CEA are survival data and the price of the medications. In many instances, CEAs are based on immature survival data as clinical trials were terminated early due to overwhelming efficacy advantages.

This was the case in 2017, when nivolumab was deemed cost-effective versus everolimus by the Australian PBAC for the second-line treatment of RCC. The PBAC recommended PBS-listing despite that PFS was not statistically significant (p=0.11) between the two therapies. Mature survival data published later indicated that the PFS benefits of nivolumab was significant (p=0.0331), but additional AEs were also noted. Furthermore, the price of everolimus dropped significantly in the period from 2017 to 2020. This was a direct consequence of loss of exclusivity and the introduction of generic everolimus into the marketplace.

This chapters investigates the impact of updated mature survival data and change in comparator pricing due to patent expiry on CEAs, and was published in Journal of Medical Economics in 2021 [118].

4.2 Published paper

Kim H, Goodall S, Liew D. Reassessing the cost-effectiveness of nivolumab for the treatment of renal cell carcinoma based on mature survival data, updated safety and lower comparator price. J Med Econ, 2021. 24(1): p. 893-899.

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Reassessing the cost-effectiveness of nivolumab for the treatment of renal cell carcinoma based on mature survival data, updated safety and lower comparator price

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ABSTRACT

Aims: The aim of this study was to estimate the cost-effectiveness of nivolumab versus everolimus for second-line treatment of renal cell carcinoma (RCC) based on mature data, updated safety and decreased everolimus price.

Materials and methods: A 3-state (pre-progression/progression-free disease, progressive disease and death) Markov model was developed from the perspective of the Australian health care system. Two scenarios were tested. Scenario 1 used 30-months clinical data and scenario 2 used updated 80-months clinical data with updated everolimus price. Inputs for quality-of-life and costs were informed by the literature and government sources. Incremental cost-effectiveness ratio (ICER) per quality adjusted life years (QALY) gained was reported and an ICER threshold of AU$75,000 was assumed. Threshold analysis was performed, and uncertainty was explored using one-way and probabilistic sensitivity analyses.

Results: In scenario 1, the model estimated 1.73 QALYs at a cost of AU$105,000 for nivolumab and 1.48 QALYs at AU$38,000 for everolimus with an ICER = AU$266,871/QALY gained. A rebate of 54.4% was needed for nivolumab to reach the ICER threshold. For scenario 2, 1.93 QALYs at AU$111,418 was estimated for nivolumab and 1.60 QALYs at AU$31,942 for everolimus with an ICER of AU$213,320/QALY gained. The rebate needed to reach the ICER threshold was 54.9%. One-way sensitivity analyses for both scenarios showed that the cost of nivolumab, time horizon and utilities were main drivers. The cost-effectiveness acceptability curves highlighted the differences in cost-effectiveness of the two scenarios, as well as significant uncertainty in the results.

Conclusions: A 54% rebate of the published price is needed for nivolumab to be cost-effective in Australia for the treatment of RCC. At that rebate, nivolumab remains cost-effective despite severe price erosion of everolimus because of improved longer term follow-up data. We recommend that generic price erosion should be accounted for when performing cost-effectiveness analysis.

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Introduction

Kidney cancer is the ninth most common cancer diagnosed in Australia, with 3814 estimated cases and an age-standardized rate of 12.9 per 100,000 in 2019[1]. Renal cell carcinoma (RCC) accounts for approximately 90% of adult malignant kidney cancer cases in Australia. International five-year survival rates for metastatic (stage IV) kidney and renal pelvis cancer are estimated at between 12-20%[2,3], These data suggest a significant unmet clinical need.

Everolimus was the most commonly used second-line agent for patients with stage-IV clear cell variant RCC in Australia prior to 2017, with more than 90% market share[4]. Everolimus was accepted for listing on the government-subsidized Australian Pharmaceutical Benefit Scheme (PBS) with a special pricing arrangement in 2014[5,6]. A special pricing arrangement between the Australian government and a sponsor leads to a discounted "effective price" which includes arrangements whereby the government recovers a percentage of the expenditure through commercial-in-confidence rebates[7]. The special pricing arrangement for everolimus ended in June 2018 following patent expiry, at which time a second generic brand was launched in Australia[6]. As a result, everolimus was subjected to price disclosure, whereby the sponsor had to publicly disclose the volume and rebates given to the government. In price disclosures, if the effective price is 90% or less of the listed price on the PBS, the listed price of the drug is then lowered accordingly to reflect the actual price[8].

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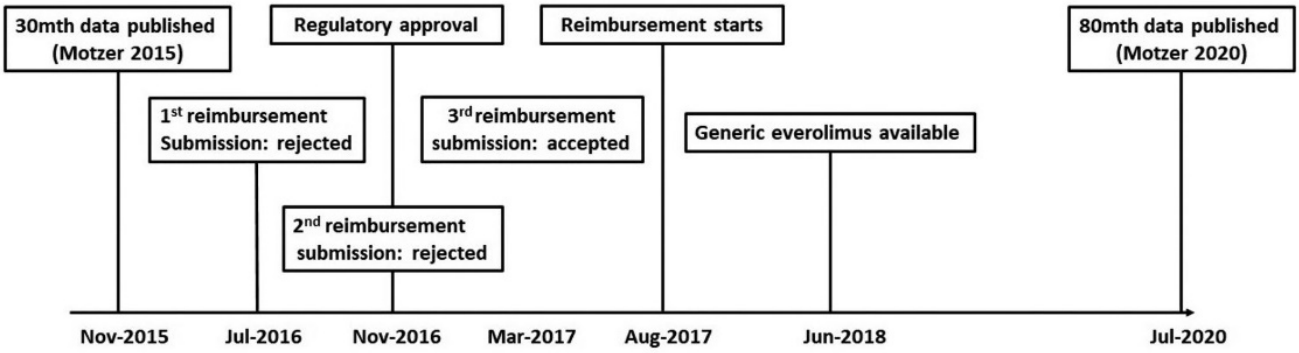

Figure 1. Timeline.

Nivolumab, a fully human immunoglobulin monoclonal antibody which binds to the programmed death-1 (PD-1) receptor on T-cells, was listed on the PBS in 2017 for the treatment of advanced RCC. Initial results from the pivotal phase-III clinical trial with 30 months of data were published in November 2015[9]. They showed that nivolumab reduces mortality as measured by overall survival (OS) (hazard ratio [HR] = 0.73, 98.5% confidence interval [CI] 0.57 to 0.93) compared with everolimus. The hazard ratio for progression-free survival (PFS) was 0.88, but the result was not statistically significant (95% CI: 0.75 to 1.03, $p = .11$).

Nivolumab was first considered by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) for treatment of RCC in July 2016, compared with everolimus[10]. The PBAC noted that there was no significant difference with respect to PFS between the two agents and mandated a 60-month time horizon for the modelled cost-effectiveness analysis (CEA). The PBAC approved nivolumab for listing on the PBS for the treatment of RCC in 2017 on the condition that the price of nivolumab be back calculated using the effective price of everolimus to ensure an acceptable incremental cost-effectiveness ratio (ICER) between AU$45,000 to AU$75,000[11].

Mature data from the pivotal efficacy study for nivolumab, based on up to 80 months of follow-up, were reported by Motzer *et al*[12] in July 2020. These showed that PFS was now significantly better for nivolumab compared to everolimus (HR = 0.84 [95% CI: 0.72–0.99]). OS was still better in the nivolumab group HR = 0.73 [95% CI: 0.62–0.85]. Furthermore, new adverse event (AE) data were presented.

An overview of the time line of events described above is depicted in Figure 1.

The aim of this study was to reassess the cost-effectiveness of nivolumab as per the decision by the Australian PBAC back in 2016. Everolimus was nominated and accepted as the comparator[10] with which nivolumab would replace due to the overwhelming market share back in 2016. The cost-effectiveness analysis was based on mature data, updated safety and new comparator price.

Methods

Model

A three-state (pre-progression/progression-free disease, progressive disease and death) Markov model was developed for the present analysis see Figure 2. This structure was consistent with most published economic evaluations of RCC therapies[13–16], as well as that considered by the PBAC in 2016 and 2017[10,11,17]. The cycle length was 14 days, and the time horizon was 60 months or 110 months depending on the scenario. The model population comprised an arbitrary 1000 subjects.

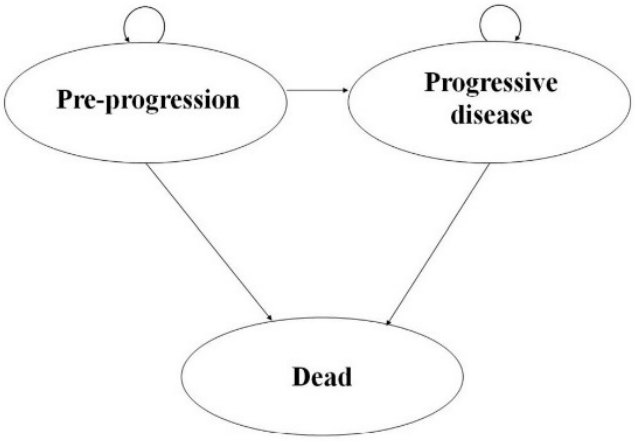

Figure 2. Three-state Markov model.

Scenario 1 was based on the early data used for the original submission presented by Motzer in 2015[9] and scenario 2 was based on the updated data from 2020[12] (see Table 1 for details on model inputs).

Transition probabilities

We assigned PFS and OS data from Motzer 2015 and Motzer 2020[9,12] over the trial-based period, followed by a further 30 months' of extrapolation. The time horizon was varied by ±25% to test whether it was a driver of the model. The authors chose 25% arbitrarily for this sensitivity analysis. Transition probabilities for PFS and death (1 minus OS) were calculated according to the relative percentage change observed in two-week cycles, with the remaining proportion being attributed to progressive disease.

Survival data from the pivotal trial was reconstructed using a published method by Hoyle et al. (2011)[18]. In brief, the published survival curves were first digitized to obtain proportions of patients at timepoints needed for the model.

Table 1. Model inputs.

	Scenario 1	Scenario 2	One-way sensitivity analysis	PSA distributions
Time horizon	60 months	110 months	−/+ 25%	–
Utilities				Beta
Pre-progression	0.78 (0.225)	0.78 (0.225)	±10%	
Progressive disease	0.72 (0.225)	0.72 (0.225)	±10%	
Price of treatment				
Everolimus	AU$3747.29/30 days	AU$1726.35/30 days	±20%*	
Nivolumab	AU$4984.20/infusion	AU$4984.20/infusion	±20%	
Costs				Gamma
Disease management costs				
1st year	AU$2388.40	AU$2388.40	±20%	
Subsequent years	AU$1489.40	AU$1489.40	±20%	
Adverse events costs				Gamma
nivolumab	AU$471.33	AU$1219.32	±20%	
everolimus	AU$1555.49	AU$1813.89	±20%	
Postprogression treatment costs				Gamma
nivolumab	AU$8636	AU$8636	±20%	
everolimus	AU$9255	AU$9255	±20%	

*Scenario 1: +/− 20%; Scenarios 2: pre-generic price = AU$3,747.29/30 days.

Individual patient data were then simulated by assigning a time interval during which outcomes (death or progression) or censoring occurred.

We then used the reconstructed survival data set to determine an appropriate survival distribution for the extrapolation. The choice of survival function was made by comparing goodness-of-fit statistics and on graphical assessments of the hazard and survival functions in the following way. The function with the lowest goodness-of-fit statistic: Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics were chosen in conjunction with graphical assessment as recommended by various guidelines[19,20]. Functions that were tested were exponential, Weibull, gamma, log-logistic and log-normal. The survival regression was fitted in one model with treatment as covariate.

Utility estimates

The pivotal trial assessed changes in reported global health outcomes in each treatment arm based on the EuroQoL five dimensions three level (EQ-5D-3L) utility index, but utilities were not reported by health state[21]. Furthermore, the public summary documents from the PBAC submissions did not report the utility values. A poster presented at the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) 2017 European meeting[22] reported utilities for the progression-free and progressive disease from the trial using UK tariffs. The average observed utilities were 0.78 and 0.72 for the progression-free and the progressive states, respectively. Overall, the differences between Australian tariffs and UK tariffs are relatively small for utility values between 0.7 and 0.9 as reported by Viney et al.[23], and therefore, the values from the ISPOR poster were used in the model.

Drug costs

The 2016 PBS drug costs for everolimus was AU$5,277.88 per 30 tablets of 10 mg[24]. The effective price of everolimus was unknown. The PBAC initially deemed everolimus not to be a cost-effective with an incremental cost-effectiveness ratio (ICER) between AU$75,000 to AU$105,000[25]. Subsequently, a price decrease was offered by the sponsor which resulted in an acceptable ICER between AU$45,000 to AU$75,000[5]. This equated to a rebate between 29.5% [=(AU$105,000-AU$75,000)/AU$105,000] and 40% (=[AU$75,000-AU$45,000]/AU$75,000). The upper boundary of the rebate interval was chosen for this study, and thus, the everolimus price in Scenario 1 was set to AU$5,277.88 x (1-40%) = AU$3747.29. For Scenario 2, the price of everolimus after patent expiry in 2018 was AU$1726.35. This information was obtained through publicly-available PBS archives[26].

The listed price for nivolumab was AU$2,076.75/100 mg vial and AU$830.70/40 mg vial at the time of the first reimbursement submission in 2016[24]. It was assumed that patients would receive 3 mg/kg per infusion every 2 weeks as per the clinical trial. The mean body weight of an Australian patient was assumed to be 80 kg, which meant that each patient would receive 80 kg × 3 mg/kg = 240 mg of nivolumab per infusion at a cost of: [2 × AU$2,076.75] + [1 × AU$830.70] = AU$4,984.20. It should be noted that wastage was not an issue in the model since each infusion could be given using 2 × 100 mg vials + 1 × 40 mg vial of nivolumab. The effective price of nivolumab was estimated by back calculating the minimum rebate required in order to obtain an ICER below AU$75,000 per QALY.

Disease management costs

Patients were assumed to see a specialist every fortnight for the first 12 weeks and subsequently every month. Blood test were performed every month, and CT scans every 3 months in the first year and every 6 months thereafter. Relevant costs from the Australian Medicare Benefit Schedule (MBS) were attached to the healthcare resource items (Supplementary Table 1).

Treatment-related grade 3–4 AEs reported by 1% or more patients were included in the model. For Scenario 1, these included fatigue, anemia, pneumonitis, hyperglycemia and stomatitis (Supplementary Table 2). Additional grade 3–4 gastrointestinal, hepatic and renal AEs were reported as part

of the update of the clinical data for scenario 2. The costs of these estimated to be AU$747.99 on average for nivolumab and AU$258.40 for everolimus (Supplementary Table 3). Costs were obtained from Australian refined diagnosis-related groups (AR-DRG) cost weights for 2016/2017[27] and were not inflated to present dollars for scenario 2 to ease the interpretation of the analysis.

Subsequent therapy costs

The proportion of patients using therapies postclinical progression was assumed to be consistent with that observed in the clinical trial using data from the initial cut of the data[9] (nivolumab arm = 55%; everolimus arm = 63%). In the nivolumab arm, 26% received everolimus and 24% received axitinib as subsequent therapy[9]. For everolimus-treated patients, 9% received sorafenib and 36% received axitinib. Treatment duration was assumed to be 6 months. Applying the respective published monthly cost for axitinib (AU$6,457.59), everolimus (AU$5,277.88) and sorafenib (AU$5,186.87) and utilization estimates from clinical trial resulted in a weighted drug cost of AU$8,636 (nivolumab arm) and AU$9,255 (everolimus arm) being attached to the first cycle of the economic model.

The study has been performed from an Australian payer perspective and as such in line with the PBAC reimbursement guidelines. The PBAC guidelines do not recognize for inclusion of indirect costs and we have therefore not included these.

Discounting

Costs, years of life lived and quality-adjusted life years (QALYs) lived were discounted at an annual rate of 5%, as per Australian guidelines[20].

Sensitivity analyses

A series of one-way sensitivity analysis for key variables were performed, with variations to key input parameters described in Table 1. Probabilistic sensitivity analyses (PSA) were also undertaken using standard distributions[28].

Software

Survival data were digitized using WebPlotDigitizer[29]. The reconstruction of survival data was performed using Excel 2019 and the statistical software R. SAS version 9.4 and R were used to assess the estimated survival functions. The model was developed in Microsoft Excel 2019 and @Risk version 8 was used for the PSA.

Input data and PSA distributions are summarized in Table 1.

Results

Extrapolation of survival data

AIC and BIC values for the extrapolation of PFS and OS data suggested that the log-normal and log-logistic functions, respectively, were the most appropriate, in both Scenario 1 and Scenario 2 (Supplementary Table 4).

Comparison of the predicted survival based on the extrapolation from the interim data cut to the actual observed survival is displayed in Supplementary Figures 1(a,b). The observed OS was generally well predicted for both nivolumab and everolimus, with only a slight underestimation of OS for nivolumab at 60 months (observed 26% vs predicted 24.2%). PFS at 36 months for nivolumab was underestimated (observed 9% vs predicted 3.5%). On the other hand, PFS for everolimus was overestimated (observed 1% vs 2.9% predicted).

Results of the cost-effectiveness analysis

The results of the CEA are reported in Table 2. In Scenario 1, using the lognormal distribution to extrapolate PFS and the loglogistic distribution to extrapolate OS, the model estimated 1.73 QALYs and 2.35 life years (LY) for nivolumab compared to 1.48 QALYs and 2.00 LYs for everolimus (discounted) over the 60-month time horizon. Total costs (discounted) were AU$105,000 for nivolumab and AU$38,000 for everolimus (taking into account the 40% rebate). This resulted in an ICER of AU$266,871 per QALY gained. A rebate of 54.4% (effective price = listed price×(1- rebate) = AU$4984.20 – (1 – 54.4%) = AU$2272.80) was needed for nivolumab to reach the ICER threshold AU$75,000 per QALY gained[11].

In Scenario 2, with updated safety and a new price of everolimus, the model estimated 1.93 QALYs and 2.86 LYs for nivolumab and 1.60 QALYs and 2.34 LYs for everolimus (discounted). Total costs (discounted) were AU$111,418 for nivolumab and AU$31,942 for everolimus. As a result, the ICER decreased to AU$213,320 per QALY gained. The rebate needed to reach the ICER threshold of AU$75,000 per QALY

Table 2. Cost-effectiveness analysis results.

	Scenario 1 (time horizon = 60 months)		Scenario 2 (time horizon = 110 months)	
	Nivolumab	Everolimus	Nivolumab	Everolimus
LY	2.35	2.00	2.86	2.34
QALY	1.73	1.48	1.93	1.60
Total costs	AU$104,798	AU$37,749	AU$111,418	AU$31,942
QALY difference	0.25		0.38	
Cost difference	AU$67,049		AU$80,796	
ICER (AU$ per QALY gained)	AU$266,871		AU$213,320	
% nivolumab rebate needed for ICER = 75,000	54.4%		54.9%	

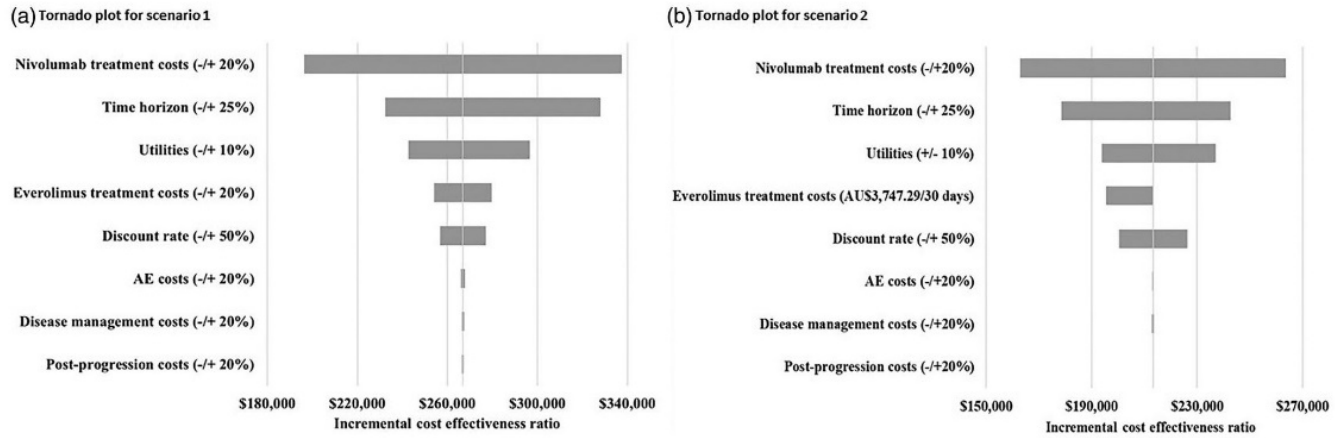

Figure 3. One-way sensitivity analyses.

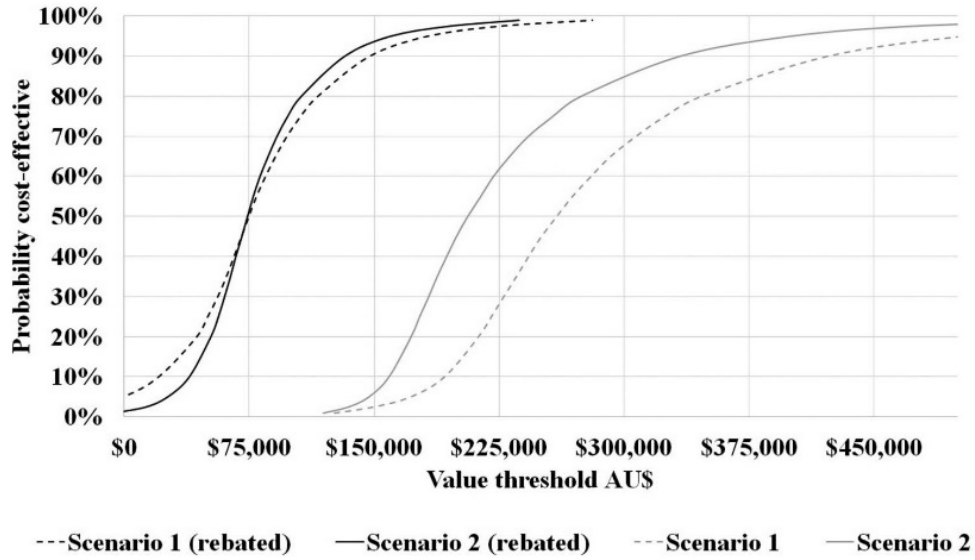

Figure 4. Cost-effectiveness acceptability curves.

gained was 54.9% (effective price = listed price×(1- rebate) = AU$4984.20 – (1 – 54.9%) = AU$2247.87).

Increasing the time horizon to 110 months increased the incremental QALYs gained by more than 40% (from 0.27 to 0.38) at a modest 20% increase in costs (from AU$67,049 to AU$80,796). This was most likely due to the fact that more than 95% of the patients have already progressed (Figure 2) by 60 months, and therefore, little extra treatment cost was accrued from then on. It is worth noting that the additional QALY gain from 60 months to 110 months largely arose from patients in the progression health state. The inclusion of the additional AEs only slightly increased the costs from AU$28,364 to AU$28.894.

The one-way sensitivity analysis for both scenarios showed that the cost of nivolumab, the time horizon and utilities are the main drivers of the model (Figure 3).

For the one-way sensitivity analysis of the everolimus price at pre-generic level (AU$3747.29/30 days), a rebate of 47.8% (effective price = listed price×(1- rebate) = AU$4,984.20×(1 – 47.8%) = AU$2,601.75) was required for nivolumab to be cost-effective at the AU$75,000 threshold.

The cost-effectiveness scatterplots (Supplementary Figure 2) and acceptability curves (Figure 4) highlighted the differences in cost-effectiveness of the 2 scenarios, as well as significant uncertainty in the results. With rebates to make the base-case ICER at AU$75,000 per QALY gained, uncertainty reduced considerably.

Discussion

Reassessing the cost-effectiveness of nivolumab for the treatment of RCC versus everolimus resulted in nivolumab being cost-effective at a threshold of $75,000 with a rebate level of approximately 54%. This CEA was sensitive to the price of nivolumab, the time horizon and quality of life utilities.

The updated clinical data[12] enable reassessment of the cost-effectiveness of nivolumab while clarifying some of the uncertainties surrounding PFS and OS as pointed out the PBAC in its original assessment[10]. While PFS was not significant at the initial data cut[9], the present study suggests that the PFS was a major source of uncertainty. Furthermore, the extrapolation of the OS predicted the observed mature OS

reasonably well, which provides confidence in the accuracy of the model. Another issue that the updated clinical data provided was an update on AEs. It is well known that AEs for immune-checkpoint inhibitors are different from other cancer drugs and that they can occur late in the treatment regimen[30]. However, the one-way sensitivity analysis show that AEs were not a source of major uncertainty.

A limitation of our study was that the extrapolations were restricted by the unavailability of individual patient data (IPD). Another published nivolumab CEA by Mahon et al.[22] did not provide details on the extrapolations, and therefore, the reconstructed survival data could not be validated. There are other methods for reconstructing survival data [31], but the one we adopted was developed using RCC data and therefore deemed more appropriate to use. A major challenge with the method that we used is the availability of statistical software to deal with interval censoring data, making it a challenge to asses extrapolations based on spline models and other nonstandard statistical distributions. Regardless of these shortcomings, the choice of log-logistic functions for both Scenario 1 and 2 was consistent with what was derived from the IPD in the PBS submission by the sponsor[11]. Another limitation is that subsequent therapy data were only included for the 30-months data. It is possible that inclusion of data from the longer 80-month data cut would yield another estimate. However, the sensitivity analysis did not have subsequent therapy as a main driver of the model and therefore this would most likely not have a big influence on the results. Finally, access to IPD would also have enabled further investigation with respect to gender, age and comorbidities.

The effective price of nivolumab is unknown as there is a special pricing arrangement. This current listed price of a 100 mg vial of nivolumab is AU$2077. We estimated that a rebate between 54.4% to 54.9% was required for nivolumab to be cost-effective at an ICER threshold of AU$75,000 per QALY gained. This would mean that the effective price per 100 mg vial would be around between AU$937 to AU$947. A public summary document of the deliberations of the PBAC for the reimbursement of nivolumab in adjuvant melanoma[32] reports updating the 100 mg vial price from AU$1200 to AU$955 during the health technology assessment. This would equate to a rebate on the list price of 42.2% to 54.0%, which provides confidence that the rebate level that we estimated for nivolumab is comparable to the true rebate.

Another limitation is the dosage of nivolumab and everolimus in the real world. We assumed that the for nivolumab the average body weight was 80 kg, but this is likely to be different in the real world which would also have an impact wastage. It is well known that AEs can be managed by lowering the dose of everolimus[33,34], which would reduce the cost of the comparator. Further research is needed to assess this.

Our study demonstrates that re-evaluation of drugs post-reimbursement is worthwhile. While our assessment did not result in a major difference in ICER or the proposed rebated price of nivolumab, it highlights the complex issue of assessing cost-effectiveness. The drop in list price of the comparator everolimus from AU$5277.88 to AU$1726.35 following patent expiry had the potential to dramatically impact the cost-effectiveness including any rebates of nivolumab. However, updated clinical trial data demonstrated better effectiveness and the improved survival data offset the additional incremental costs. Nonetheless, this study highlights potential issues of not taking generic prices into account when performing CEA. We therefore recommend that payers develop policies to ensure that in the long term they do not over pay for new drugs, especially when the comparator loses patent protection.

Conclusion

Nivolumab is a cost-effective option with a price reduction of 54% for the treatment of RCC in Australia despite severe price erosion of the comparator. The price rebate needed for nivolumab to be cost-effective at a AU$75,000 threshold for the treatment of RCC in Australia is estimated to be between around 54%. In general, taking generic price erosion into account when performing CEA is recommended.

Transparency

Declaration of funding

This study did not receive any funding.

Declaration of financial/other relationships

DL has received grants from: Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, CSL-Behring, Novartis, Pfizer, Sanofi and Shire.

DL has participated as an advisor at advisory boards for: Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi and Edwards Lifesciences.

HK has previously held employment at Novo Nordisk, Pfizer, GlaxoSmithKline and BMS.

SG has nothing to declare.

JME peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

Author contributions

HK, DL and SG made substantial contributions to the conception and design of the study. Data analysis was conducted by HK. All authors contributed to the interpretation of data, took part in the drafting and revising of the manuscript, and gave final approval of the manuscript to be published. All authors agree to be accountable for all aspects of this work.

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None reported.

Data availability statement

The data for this study all came from public available sources.

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Supplement S1

Supplement table 1 Disease management costs

Medical resource	Frequency	Units per patient	Unit Cost	Annual cost
Year 1				
Specialist visit: week 1-12	Every 2 weeks	6	AU$43.00	AU$258.00
Specialist visit: week 13-52	Every 4 weeks	9	AU$43.00	AU$387.00
Blood test	Every 4 weeks	12	AU$16.95	AU$203.40
CT scan	Every 12 weeks	4	AU$385.00	AU$1,540
		Total estimated cost per cycle		**AU$2,388.40**
Subsequent years				
Specialist visit	Every 4 weeks	12	AU$43.00	AU$516.00
Blood test	Every 4 weeks	12	AU$16.95	AU$203.40
CT scan	Every 26 weeks	2	AU$385.00	AU$770.00
		Total estimated cost per cycle		**AU$1,489.40**

Supplement table 2 Scenario 1: Adverse events costs

Adverse event	Unit cost	Nivolumab		Everolimus	
		Frequency	Weighted cost	Frequency	Weighted cost
Fatigue	AU$8,616	2%	AU$172.32	3%	AU$258.49
Anemia	AU$6,205	2%	AU$124.09	8%	AU$496.38
Pneumonitis	AU$9,535	1%	AU$95.35	3%	AU$286.04
Hyperglycemia	AU$7,957	1%	AU$79.57	4%	AU$318.26
Stomatitis	AU$4,908	0%	AU$172.32	4%	AU$258.49
Total costs		**AU$471.33**		**AU$1,555.49**	

Supplement table 3 Scenario 2: Additional adverse events costs

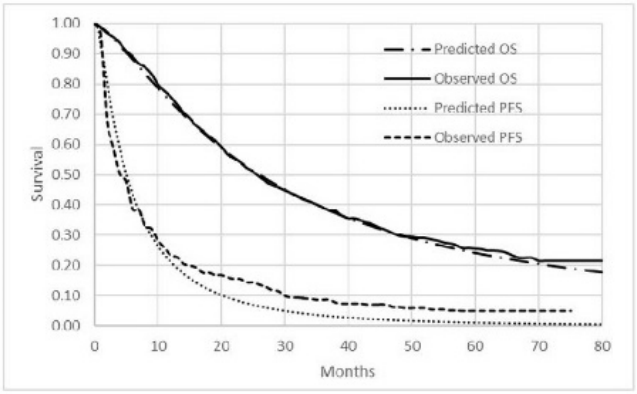
Adverse event	Unit cost	Nivolumab		Everolimus	
		Frequency	Weighted cost	Frequency	Weighted cost
Gastrointestinal	AU$8,616	2.2%	AU$162.69	1.5%	AU$110.93
Hepatic	AU$6,205	3.0%	AU$435.54	0.5%	AU$72.59
Renal	AU$9,535	1.0%	AU$149.76	0.5%	AU$74.88
Total costs		**AU$747.99**		**AU$258.40**	

Supplement Table 4 AIC/BIC for PFS and OS

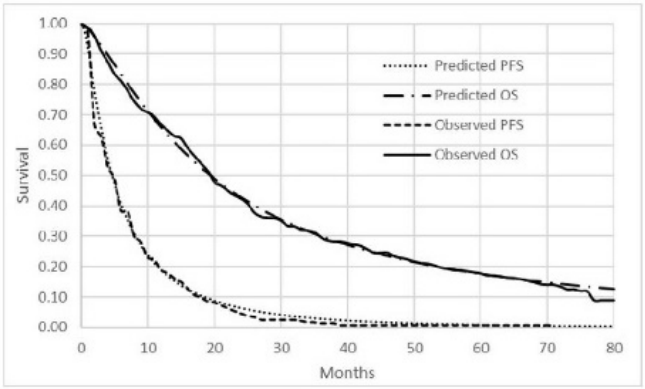
	Scenario 1				Scenario 2			
	OS		PFS		OS		PFS	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	3807.2	3816.6	4405.8	4415.2	5966.8	5976.2	4612.1	4621.5
Weibull	3799.0	3806.4	4407.8	4415.2	5967.6	5975.0	4575.2	4582.6
Gamma	3798.2	3805.6	4404.7	4412.1	5968.7	5976.1	4602.5	4609.9
Log-logistic	***3797.8***	***3805.2***	4299.2	4306.6	***5934.6***	***5942.0***	4433.2	4440.6
Log-normal	3802.6	3810.0	***4277.4***	***4284.8***	5942.4	5949.8	***4414.4***	***4421.8***

Figure 1 Predicted vs observed survival

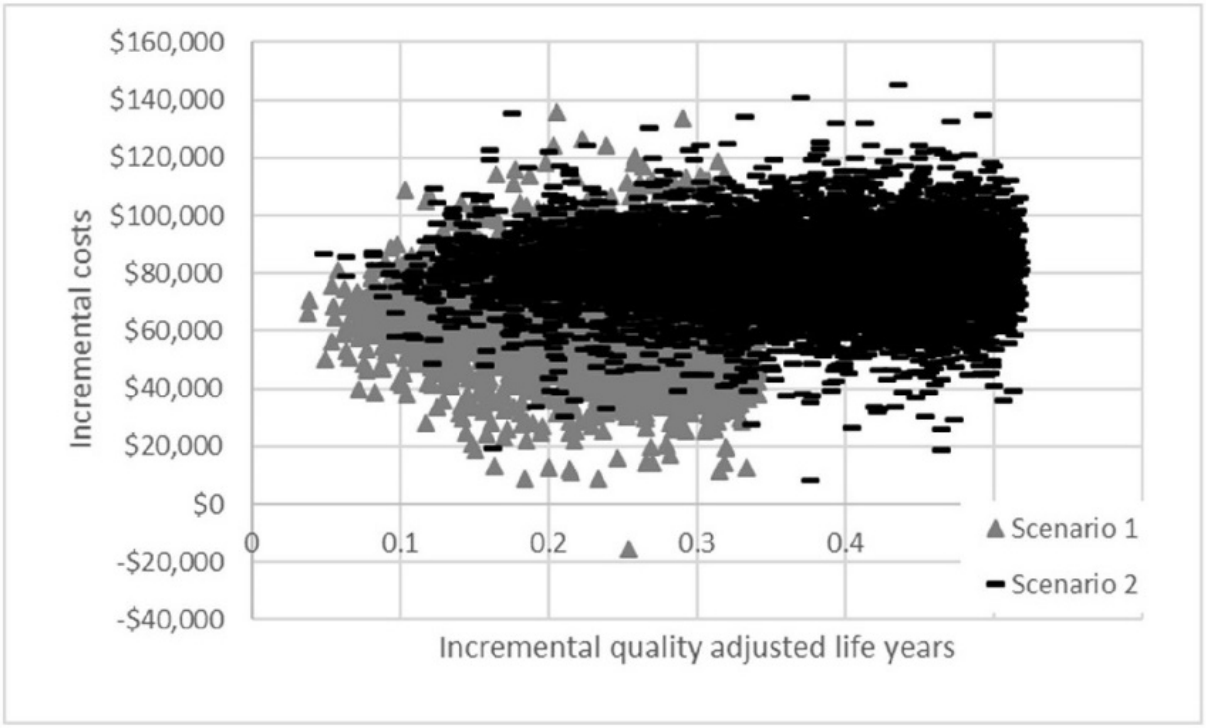
a) Predicted vs observed survival for nivolumab



b) Predicted vs observed survival for everolimus



Supplement figure 2 Scatter plot of PSA for scenario 1 and scenario 2



4.3 Conclusion

Nivolumab was observed to be a cost-effective alternative to everolimus for the second-line treatment of RCC in light of updated PFS data and substantial lower price of the comparator. This analysis demonstrates that reassessing the cost-effectiveness of oncology drugs is necessary when the initial assessment was performed using premature outcomes data. There are several examples of specific policies introduced by payers to ensure that over-payment for new drugs does not occur. In the UK there are cases of performance-based risk share agreements in which cost-effectiveness analysis of real-world data is performed after a set time period in order to assess whether a drug is value for money [119]. Another example is conditional agreements for innovative therapies in Italy where the Italian Medicines Agency AIFA uses monitoring registries to continuously evaluate drugs in clinical practice [120]. It is recommended that payers develop policies to ensure that in the long term, they do not overpay for new drugs, especially when the comparator loses patent protection.

Chapter 5: Validating input for cost-effectiveness of oncology drugs

5.1 Introduction

There is uncertainty surrounding the translation of clinical trial data regarding the use of new cancer medications into real-world settings. Factors such as the duration of treatment, dosing and wastage are all unknowns when CEAs are performed. This could potentially have a significant impact on the cost-effectiveness of new drugs.

Cancer drugs are most commonly accessed through the Australian PBS. The Australian Department of Health makes a 10% sample of the PBS data available to researchers as a longitudinal dataset.

The present chapter examines the validation of cost-effectiveness of nivolumab, an ICI, by using real-world prescription data from the PBS for duration of treatment, dosage and wastage of new cancer drugs.

A manuscript arising from this work has been submitted for publication.

5.2 Submitted paper

Kim H, Goodall S, Ilomaki J, Liew D. Validating the cost-effectiveness of cancer drugs in Australia using real world evidence from payer script data. Submitted for publication in *Value in Health.*

VALIDATING INPUT PARAMETERS FOR COST-EFFECTIVENESS ANALYSIS OF CANCER DRUGS IN AUSTRALIA USING REAL WORLD EVIDENCE

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Keywords: cost-effectiveness analysis, nivolumab, cancer, validation, real world evidence

Running head: Validating CEA in AU using RWE

Abstract (word limit: 250)

Objectives

Nivolumab was reimbursed in Australia for the treatment of renal cell carcinoma (RCC) in 2017 after demonstrating cost-effectiveness versus everolimus. The main driver of the cost effectiveness analysis (CEA) was cost of nivolumab, which is dependent on the duration of treatment (DoT) and dosage. The aim of this study was to examine the DoT for nivolumab and everolimus, as well as dosage of nivolumab using real world claims data in Australia.

Methods

The Australian Department of Health makes a 10% sample of the Pharmaceutical Benefits Scheme (PBS) data available to researchers as a longitudinal dataset. DoT and wastage were calculated for patients receiving everolimus or nivolumab for the treatment for RCC from 2017 to 2020. Standard summary statistics and Kaplan-Meier plots were used to describe the time to discontinuation of treatment, wastage and flat dosing. The potential impact on cost-effectiveness analysis (CEA) was estimated using a published model.

Results

Information on 231 patients who received nivolumab or everolimus was obtained with a total of 2665 scripts dispensed from January 2017 to December 2020. DoT was 294 days for nivolumab and 119 days for everolimus. There was 5.3% wastage, associated with a financial impact of AUD$684,000. An update of the published CEA with these values resulted in a six-fold increase in incremental quality adjusted life years, but at a 69% increase in incremental costs.

Conclusion

The PBS sample is a useful data set for providing insight into treatment patterns and more specially in validating CEA input variables.

Introduction

Immune checkpoint inhibitors (ICI) have demonstrated superior overall survival (OS) and progression free survival (PFS) for the treatment of many different types of advanced cancer, such as melanoma [1] and renal cell carcinoma (RCC) [2]. However, the high costs of ICIs, which can be more than US$100,000 per year, [3] has made it a challenge to fund these drugs, with fears of patients facing bankruptcy [4]. In Australia, the federal government provides subsidised access to most drugs via the Pharmaceutical Benefits Scheme (PBS), and in 2019, ICIs accounted for approximately 5% of PBS expenditure [5]. Health technology assessment (HTA) forms the basis for the Australian reimbursement system [6] and clinical trial evidence plays an essential role when assessing cost-effectiveness. Translating clinical trial evidence into real world practice is associated with uncertainty as assumptions have to be made in terms of extrapolation of data beyond the clinical trial, duration of treatment, dosing and wastage [7]. Validation of cost effectiveness analysis (CEA) is recommended by the World Health Organization (WHO) and various HTA societies such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society of Medical Decision Making (SMDM) [8]. However, assumptions pertaining to the CEA are rarely validated as it is challenging to obtain data from real world clinical settings.

In January 2017, everolimus and axitinib were available via the PBS for the treatment of RCC following disease progression with a tyrosine kinase inhibitor (TKI) (sunitinib or pazopanib) [9]. Another TKI, cabozantinib, [10] was approved in 2017, as was the ICI nivolumab [11].

The HTA assessment of nivolumab relied on an OS benefit (hazard ratio [HR] = 0.73, 95% confidence interval [CI]: 0.62-0.85) of nivolumab compared to everolimus [12]. PFS was non-significant (HR=0.88, 95% CI: 0.75-1.03) and this lack of superiority for PFS was noted by the Pharmaceutical Benefits Advisory Committee (PBAC, which makes recommendations for PBS listing) as a significant source of uncertainty [13]. Updated survival data was provided in 2020, which indicated that PFS benefit was statistically significant HR=0.84, 95% CI: 0.72 – 0.99 [14]. However, the results should be validated as

multiple post-hoc analyses were performed after the study formally was stopped, thereby having little statistical power to confirm the original hypothesis. A recent reconstruction of the CEA [15] showed that PFS is an important variable with respect to the accrual of quality adjusted life years (QALYs). Moreover, the cost of nivolumab was the main driver for the CEA and this depends on three factors: the list price per mg, duration of treatment (DoT) and dosage.

DoT is linked to PFS as the nivolumab is restricted to patients who have not developed disease progression while being treated with nivolumab for RCC [16]. Nivolumab was reimbursed using a dosage of 3mg/kg and was available in two forms 40mg/4ml and 100mg/10ml. A body weight of 80 kg was assumed in the reconstructed CEA which resulted in no wastage of nivolumab (i.e. 240mg per infusion = 2 x 100mg/10ml vials + 1 x 40mg/4ml vial). This assumption was likely to have underestimated the cost of nivolumab as some wastage is to be expected. Furthermore, the dosing of nivolumab was updated in 2019 with the acceptance of flat dosing of 240mg every two weeks or 480mg every four weeks on the PBS [17]. The PBAC noted in its deliberations that the current mean doses were below the proposed 240 mg flat dose, which could have an impact on wastage and overall costs of nivolumab. The PBAC also noted that there was limited clinical data to support the claim that flat dosing regimens are non-inferior in efficacy to the 3 mg/kg weight based dosing regimen [18].

The aim of this study was to examine the treatment patterns in RCC, the duration of treatment for nivolumab and everolimus, as well as the dosage of nivolumab using a random 10% sample of the Australian PBS claims data.

Methods

The Australian Department of Health makes a sample of the PBS data available to researchers as a longitudinal dataset containing all PBS medicine dispensed in a random 10% sample of Australians. This dataset can be matched with Fact of Death data compiled by the Australian Institute of Health

93 and Welfare using monthly data from state and territory registries of births, deaths and marriages [19].
94 These two datasets combined provide real world insight into the use of nivolumab and everolimus for
95 the treatment of RCC in Australia.

96 Patients for who a benefit has been claimed for axitinib, cabozantinib, everolimus or nivolumab for
97 treatment of RCC following disease progression with a TKI were identified using PBS item numbers
98 (Table 1) [16].

99

100 Table 1: PBS item numbers

Drug	Item numbers for treatment of renal cell carcinoma	Reference
Axitinib	10539Q, 10540R, 10556N, 10572K	https://www.pbs.gov.au/medicine/item/10539Q-10540R-10556N-10572K
Cabozantinib	11360X, 11367G, 11368H, 11369J, 11371L, 11374P	https://www.pbs.gov.au/medicine/item/11360X-11367G-11368H-11369J-11371L-11374P
Everolimus	10132G, 10133H, 11257L, 11262R	https://www.pbs.gov.au/medicine/item/10131F-10132G-10133H-10135K-11254H-11257L-11258M-11262R-11267B-11362B-11377T-11591C-11592D-11598K-11599L-11607X-11608Y-2818H-2819J-2985D-5737Y-5738B-5739C-5740D-6459Y-6460B-6461C-8840G-8841H-8842J-9352F-9582H
Nivolumab	11150W, 11157F, 11159H, 11160J	https://www.pbs.gov.au/medicine/item/10745M-10748Q-10764M-10775D-11143L-11150W-11152Y-11153B-11157F-11158G-11159H-11160J-11411N-11425H-11434T-11435W-11532Y-11543M-11626X-11627Y-11636K-11642R-11900H-11906P-12303M-12312B-12315E-12323N-12574T-12602G

101

102 DoT was obtained by observing the time to discontinuation of the scripts with the assumption that a
103 patient was treated up top 14 days after the last script was dispensed. Kaplan-Meier estimates, along
104 with median and corresponding 95% confidence intervals, were calculated for DoT.

105 Wastage was estimated by subtracting the prescribed dose from the dispensed dose. Costs were
106 derived using list price of $20.77/mg for nivolumab [15].

Kaplan-Meier plots for OS of weight-based patients and flat dosed patients were constructed and a hazard ratio was estimated.

The potential impact of DoT on QALYs and costs in a pre-progressive health state was estimated using a published CEA model [15].

As mentioned, the dataset consists of 10% of the total PBS population. The total number of scripts dispensed for nivolumab and everolimus was queried through the Australian Department of Health website [20] to confirm that the sample received was indeed a 10% sample.

Data access was approved by the External Request Evaluation Committee (application: RMS110) of the Australian Department of Health and Monash University Human Research Ethics Committee (project: 22877).

All analyses were performed in SAS 9.4 on a MS Window platform and in Excel 2019.

Results

The 10% PBS dataset contained prescription information from 251 patients who received nivolumab (n=179) and everolimus (n=52). A total of 2451 nivolumab scripts and 214 everolimus scripts were dispensed in the time period from January 2017 to December 2020. The PBS reported that 24,721 nivolumab scripts and 2069 scripts everolimus scripts were dispensed for the second line treatment of RCC [21]. This means that the sample data contained approximately 9.9% (=2451/24721) of all the nivolumab scripts and 10.3% (=214/2069) of all the everolimus scripts in the time period.

Treatment patterns

The treatment pathway in Australia for clear cell RCC is as follows: sunitinib or pazopanib for treatment naïve patients; axitinib, cabozantinib, everolimus or nivolumab upon progression following sunitinib

or pazopanib. Subsequent treatment with axitinib, cabozantinib, everolimus or nivolumab is possible if patients have not received and progressed on the same drug before. More than 80% of all RCC patients received nivolumab or everolimus as second line treatment (Table 2). Axitinib and cabozantinib were used before nivolumab and everolimus in some instances, but the use of axitinib decreased from 2017 (9%) to 2020 (<1%). A small proportion of patients (<1%) were prescribed a TKI after everolimus and some were prescribed everolimus after nivolumab.

Table 2 Treatment patterns post sunitinib/pazopanib in RCC patients over time

RCC treatment post sunitinib/pazopanib	2017 N=242	2018 N=151	2019 N=232	2020 N=58
nivolumab	69.40%	67.09%	62.71%	69.40%
everolimus	19.83%	20.09%	18.64%	21.12%
axitinib -> nivolumab	7.76%	5.98%	2.97%	1.72%
axitinib -> everolimus	2.16%	0.85%	0.00%	0.00%
cabozantinib -> nivolumab	0.00%	3.42%	10.17%	6.03%
cabozantinib -> everolimus	0.00%	0.43%	1.69%	0.43%
everolimus -> axitinib	0.43%	0.43%	0.42%	0.43%
everolimus -> cabozantinib	0.00%	0.43%	1.27%	0.43%
everolimus -> nivolumab	0.43%	0.43%	0.00%	0.43%
nivolumab -> everolimus	0.00%	0.85%	2.12%	0.00%

Duration of treatment

Median DoT of nivolumab was 294 days, with a 95% confidence interval (CI) of 194 days – 423 days, which exceeded the median PFS of 127 days observed in the relevant clinical trial [14]. For everolimus, the median DoT was 119 days, with a 95% CI of 79 days to 185 days, compared to the median PFS of 137 days observed in the pivotal clinical trial [14] (Table 3).

Table 3 Duration of treatment compared to PFS in the pivotal clinical trial.

	Nivolumab		Everolimus	
	PBS script data DoT	Motzer 2020 PFS	PBS script data DoT	Motzer 2020 PFS

Median (95% CI) min-max	294 (194; 423) 28 – 1232	127 129 – 164	19 (79; 185) 28 – 546	137 113 – 167

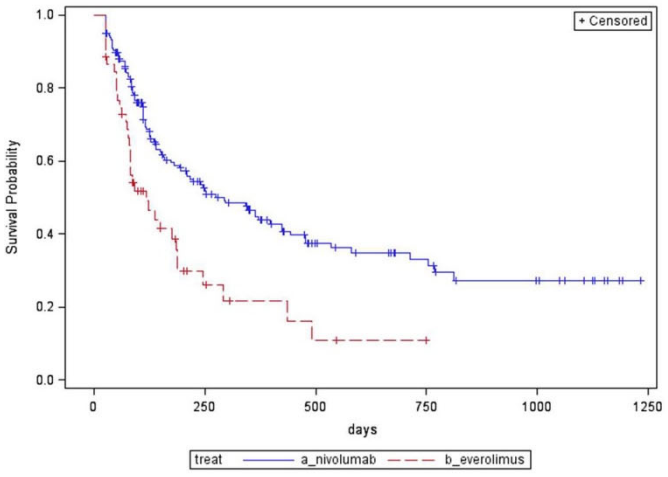
146

147 The Kaplan-Meier plot for the DoT clearly shows that patients are treated much longer with nivolumab

148 than everolimus (Figure 1).

149

150 Figure 1 Kaplan-Meier plot of duration of treatment



151

152

153 Nivolumab wastage

154 The mean prescribed dose of nivolumab was 240.5mg compared to 253.9mg dispensed. Over the

155 observational period, 32,915mg was wasted, at a total cost of $683,645 (Table 4).

156

157 Table 4 Wastage of nivolumab

	Mean dose	Total mg	Mean costs	Costs (listed price)
Prescribed	240.5mg (SD=39.0)	589,488	$4995 (SD=$810)	$12,243,666
Dispensed	253.9mg (SD=41.2)	622,403	$5274 (SD=$856)	$12,927,310
Wastage	13.3mg (SD=12.3)	32,915	$279 (SD=255)	$683,645

158

159 This equates to a 5.3% (32,915/622,403) wastage for nivolumab.

160

161 Flat dosing of nivolumab

162 Seventy-nine patients were prescribed flat dosing of nivolumab, with 34.2% receiving 240mg every
163 two weeks and 65.8% receiving 480mg every four weeks. Less dosage would have been required if flat
164 dosing was given to everyone (weight-based dose=622,403 vs flat dose=588,240mg) (Table 5). Flat
165 dosing would have saved $709,566 (5.4% of total nivolumab costs).

166

167 Table 5 Dispensed dose vs flat dosing of nivolumab

	Total mg	Costs (listed price)
Dispensed	622,403	$12,927,310
Flat dosing	588,240	$12,217,745
Difference	34,163	$709,566

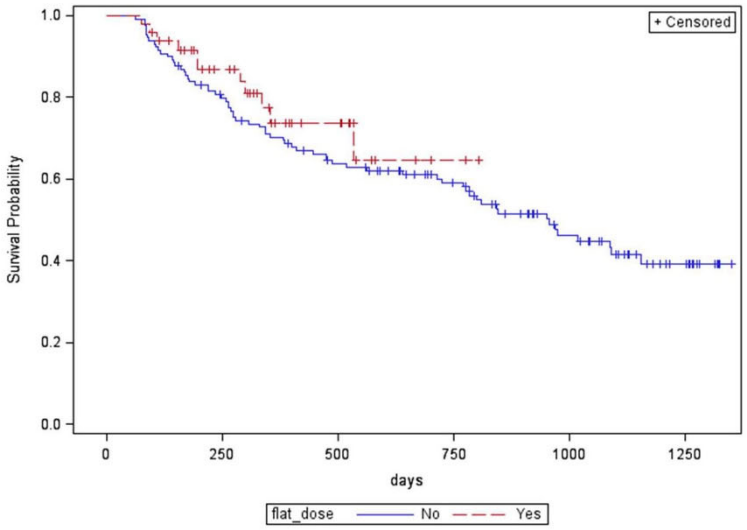
168

169 There was no difference in OS between patients receiving weight-based dosing compared to flat
170 dosing, with the HR estimated to be 1.34 (95% CI: 0.70 – 2.59).

171 Figure 2 below depicts the Kaplan-Meier plot for the overall survival by dosing.

172

173 Figure 2 Kaplan-Meier plot of overall survival.



174

175

176 Potential impact on cost-effectiveness

177 A six-fold increase (0.42 versus 0.07) in QALYs was observed when using DoT from the PBS script data
178 instead of PFS from clinical trial data in Motzer 2020 [14] to estimate the QALYs in the pre-progressive
179 state of the published model. However, drug costs increased 1.69 times ($145,116 versus $85,922) as
180 patients were treated with nivolumab for longer (Table 6).

181 Table 6 Projected QALYs and Costs of PBS script data

	PBS script data		Motzer 2020	
	Nivolumab	Everolimus	Nivolumab	Everolimus
QALY in pre-progressive state	0.96	0.54	0.62	0.55
QALY difference	0.42		0.07	
Drugs costs	$163,788	$18,672	$105,082	$19,161
Cost difference	$145,116		$85,922	

182

183

184 Discussion

In Australia from 2017 to 2020, more than 80% of patients received nivolumab and everolimus as second line treatment after a TKI. A small proportion (<10%) received the two drugs as third line treatment following axitinib or cabozantinib after sunitinib/pazopanib and a fraction (<1%) received nivolumab after everolimus. This is all within the PBS restriction, which do not specify which line of therapy the drugs can be used for [22]. This seems reasonable from a clinical perspective as advanced RCC is a serious disease and more treatment options increase the chance for patients to obtain a favourable outcome [23]. From a financial perspective, all the drugs in question have a financial risk share agreement in place (everolimus [24], axitinib [25], cabozantinib [10], nivolumab [11]). With respect to nivolumab, the PBAC even advised that any expenditure over the proposed risk share arrangement caps should be 100% rebated to the government, which indicates that there limited risk of the expenditure on nivolumab exceeding the financial cap to the government in terms of the use of nivolumab outside the PBS restriction.

The use of nivolumab after other TKIs than sunitinib and pazopanib or as third line treatment raises the question in terms of uncertainty of the effectiveness as the original trial population only included second line patients. The present study shows that DoT in real life is longer than observed in the clinical trial, with a difference between nivolumab and everolimus. The dataset did not contain patient characteristics and therefore these results have to be interpreted with caution as there was no randomisation or any correction for baseline characteristics and comorbidities. Another potential issue is that many patients remain on the treatment despite having progressive disease. This is outside of the PBS restriction, which specifically states : “Patient must not have developed disease progression while being treated with this drug for this condition” [26]. The pivotal clinical study [12] did allow for patients to be treated beyond progression of disease. Unfortunately, relevant publications do not report any details with respect to patients who were treated beyond progression and therefore it was not possible to assess if the results were biased. The extended DoT is estimated to increase the QALYs for nivolumab-treated patients as they are projected to stay significantly longer in a progression free state than was observed in the clinical trial, at an increased cost for the payer.

The original CEA used 240mg as base for the dose, which is in line with what was prescribed in this study. The estimated wastage of 5.3% for nivolumab is relatively small. This estimate could be considered as the upper boundary as there is anecdotal evidence that hospital pharmacies 'share' vials if several patients are coming on the same day for their infusions [27]. Moreover, that patients are now being moved over to a flat dosing means that wastage for nivolumab is less of an issue.

As mentioned, the PBAC was uncertain about the effectiveness of the flat dosing of nivolumab. This study shows that there is no difference in OS between patients who received the flat dose (either 240mg or 480mg) and those who received nivolumab using weight-based dosing. It is worth noting that although flat dose patients receive nivolumab for longer, the risk financial share agreement mentioned earlier means that this does not necessarily translate into higher government expenditure.

The major weakness of the present study is that the analyses comprise of simple naïve comparisons between two real observational cohorts and therefore no firm conclusions can be drawn. The dataset only constitutes 10% of the whole cohort and therefore do not give the whole picture. It would be useful if researchers could get access to a higher proportion of patients than the 10% especially in late-stage cancer as the patient numbers are small. Furthermore, linking PBS script data to medical services data via from the Australian Medicare Benefits Schedule [28] would enable researchers to investigate other health resource use (such as special visits and imaging) for these conditions. These are often overlooked as inputs in CEA and are rarely validated. Another limitation of this study is that OS could not be compared between nivolumab and everolimus even though there was access to death data. The problem was that quite a few of the patients had received different treatments before and/or after they received nivolumab treatment, which would confound the results. There are statistical techniques available to correct for crossover or switching of treatment [29], but they are not applicable in this instance due to the lack of information on baseline characteristics and comorbidities. Finally, this lack of baseline characteristics is a limitation which meant it was not possible to compare the current study population with that from the pivotal clinical trial.

Conclusion

In the period from 2017 to 2020, the DoT for nivolumab was longer than suggested in the pivotal clinical trial, wastage was minimal and flat dosing was not worse than weight base dosing in terms of impact on OS. The PBS sample is a useful data set for providing insight into treatment patterns and more specially in validating CEA input variables.

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5.3 Conclusion

The analysis validated the cost-effectiveness of nivolumab using real-world prescription data.

There are some limitations for using prescription data to validate CEAs. In particular, any comparison between different treatments is limited to naïve comparisons of two observational cohorts. Furthermore, the sample only consists of 10% of the whole population and the results are therefore not necessarily generalisable to the whole population.

Despite this, PBS sample data provide valuable insight into real-world treatment patterns and allow for validation of CEA input variables.

Chapter 6: Stakeholder opinions regarding health economic modelling in oncology

6.1 Introduction

The pharmaceutical industry and the Australian PBAC have occasional adversarial interactions. Industry claims that reimbursement guidelines increase complexity, leading to more uncertainty, while the PBAC often has reservations about the quality of data assembled by companies and their consultants. One in four major submissions for newer cancer drugs is rejected for reimbursement by the PBAC, which indicates a difference in opinion between industry and PBAC with respect to CEA methods and health economic modelling.

This chapter explores the opinion of major stakeholders from both the public (academia and government) and private sector (pharmaceutical industry and specialist consultants) in terms of the health economic modelling of oncology therapies. A copy of the survey can be found in Appendix 3.

A manuscript arising from this work has been submitted for publication and is currently under review.

6.2 Submitted paper

Kim H, Liew D, Goodall S. Current issues in Health Technology Assessment of cancer therapies: A survey of stakeholders and opinion leaders in Australia. Under review at the *International Journal of Technology Assessment in Health Care.* NB: Responses to (minor) reviewers' comments submitted 1 November 2021.

Title page

Title: CURRENT ISSUES IN HEALTH TECHNOLOGY ASSESSMENT OF CANCER THERAPIES: A SURVEY OF STAKEHOLDERS AND OPINION LEADERS IN AUSTRALIA.

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Running title: STAKEHOLDER SURVEY OF HTA OF CANCER THERAPIES IN AUSTRALIA

Abstract

Objective

The aim of this study was to find ways of bridging the gap in opinions concerning health technology assessment (HTA) in reimbursement submission between manufacturers and payers to avoid access delays for patients of vital medicines such as oncology drugs. This was done by investigating differences and similarities of opinion among key stakeholders in Australia.

Methods

The survey comprised of nine sections: background demographics, general statements on HTA, clinical claim, extrapolations, quality of life, costs and health resource utilisation, agreements, decision making and capability/capacity. Responses to each question were summarised using descriptive statistics and comparisons were made using chi-square statistics.

Results

There were 97 respondents in total, 37 from the public sector (academia/government) and 60 from the private sector (industry/consultancies). Private and public sector respondents had similar views on clinical claims. They were divided when it came to extrapolation of survival data and costs and health resource utilisation. However, they generally agreed that rebates are useful, outcomes-based agreements are difficult to implement, managed entry schemes are required when data is limited and willingness to pay is higher in cancer compared to other therapeutic areas. They also agreed that training mostly takes place through on the job training and that guideline updates were a least favoured opportunity for continued training.

Conclusions

Private sector respondents favour methods that reduce the incremental cost-effectiveness ratio when compared to the public sector respondents. There still exists a number of challenges for HTA in oncology and many research opportunities as a result of this study.

Keywords: Cancer, Oncology, Pharmacoeconomics, Health economics, Reimbursement, Health technology assessment

Funding: None

Introduction

The burden of cancer is steadily increasing in Australia, with almost 50,000 deaths from cancer in 2019, compared to 44,171 in 2014 (1). Chemotherapy has traditionally been used to treat most cancers (2), but the last 15 years has witnessed a paradigm shift to more targeted therapies (3) and novel agents that activate the immune system (4) to fight cancer. These new agents show great promise in terms of health benefits, with increased survival and delay of disease progression. Regulators such as the European Medicine Agency and the US Food and Drug Administration have created rapid assessment and approval processes (5), which has resulted in sponsors looking for every opportunity to accelerate the time to market authorisation. Acceleration of assessment is rarely the case when it comes to reimbursement. In Australia, it is estimated that only 23.8% of the reimbursement submissions for check point inhibitors receive first time approval (6). Moreover, check point inhibitors required an average of 2.23 submissions before getting approved, compared to 1.70 submission for pharmaceuticals in general (7).

All medicines, including cancer drugs, undergo a comprehensive health technology assessment (HTA) process before being approved for reimbursement. The process starts with a sponsor (usually a pharmaceutical company) submitting an application for the listing of the drug in question. The submission is assessed by the Australian Pharmaceutical Benefits Advisory Committee (PBAC), which makes recommendations to the Department of Health and the Minister of Health. The PBAC comprises independent clinicians, other healthcare professionals, health economists, consumer representatives and an industry-nominated member. Submission guidelines issued by the PBAC mandate HTAs, which often include cost-effectiveness analysis (CEA) and health economic modelling for the assessment of pharmaceuticals including oncology drugs (8). The evolution of oncology-specific issues is well illustrated by the PBAC submission guidelines. In its 2002 guidelines, (9) time-to-event

data, which is the primary way of reporting cancer survival data, were only mentioned four times, compared to 23 times in the 2006 guidelines (8). In the 2016 update of the guidelines, time-to-event data was mentioned 54 times (10).

Anecdotally, the pharmaceutical industry and the government occasionally have adversarial interactions. The pharmaceutical industry claims that PBAC guidelines updates increase complexity, leading to more uncertainty (11) and it has been suggested that early dialogue may be beneficial (12). Interaction between the government and pharmaceutical companies are possible through pre-submission meetings, (13) but they are most commonly behind closed doors and are commercial in confidence.

It is possible that misaligned incentives between manufacturer (private sector) and funder (public sector) may lead to differing views regarding the current issues facing HTA. For example, manufacturers want early access at the maximum price, therefore they are prepared to use early evidence. Whereas the funder, who needs to manage multiple competing requests for funding, must consider the opportunity cost of making the wrong decision and over financial implications. Consequently, manufacturers and funders have difference in opinions with respect to attributes of risk and uncertainty. This leads to delays in access to medicines for patients as multiple submissions are needed to resolve the differences. An example of this is dupilumab for the treatment of atopic dermatitis where three submissions were needed before the PBAC in March 2020 (14). However, the pharmaceutical company chose to make a further submission in November 2020 due to issues arising during the listing process pertaining to the cost-effective price (15). Public subsidised dupilumab was subsequently made available to patients in March 2021 (16) which was three years after the initial submission by the manufacturer.

A recent review of HTA in oncology (17) found the following major themes to be important: analysis of clinical evidence, quality of life, modelling, financial implications and how to deal with uncertainty. Uncertainty is a perpetual problem and stalls decision-making; sponsors and payers often fail to agree on a suitable price that reflects the level of uncertainty. This is reflected in the low first-time approval rate of immune checkpoint inhibitors in Australia.

The aim of this study was to find ways of bridging the gap in opinions concerning HTA in reimbursement submission between manufacturers and payers to avoid access delays for patients of vital medicines such as oncology drugs. This will be done by investigating differences and similarities of opinion with respect to HTA in oncology among key stakeholders from the private sector (pharmaceutical industry and specialist consultants), as well as public sector stakeholders (academia and government) in Australia.

Methods

A quantitative survey was conducted of stakeholders involved in CEA of oncology agents, representing academia, government and industry. An invitation was emailed to potential participants identified in the memberships of local professional societies. Initial invitees were encouraged to forward the survey to other relevant colleagues. Respondents were kept anonymous as required by the relevant Human Research Ethics Committee.

The survey was developed using the Qualtrics Survey platform and was completed between October 2020 and March 2021. Questions based on a review of the most common topics arising in the public summary documents describing PBAC deliberations for oncology products from 2006 to 2019 were developed and discussed with a group of experienced health economists. The survey comprised 22 questions arranged in nine sections (Supplement S1): background demographics, general statements on cost-effectiveness of oncology treatments, clinical effectiveness claim, extrapolations, quality of life, costs and health resource utilisation, agreements, decision making and capability and capacity. The survey took respondents approximately 10 minutes to complete. Most responses were categorised in a Likert scale (1=strongly disagree, 2=somewhat disagree, 3=neither disagree nor agree, 4=somewhat agree, 5=strongly agree, 6=don't know). For the analyses, the categories 'strongly agree' and 'somewhat agree' were collapsed into one group and also the categories 'strongly disagree' and 'somewhat disagree'. This was done to ensure that there were an adequate number (>5) of observations available in each category for the chi square tests. The category 'neither disagree nor agree' is henceforth referred to as 'neither' within the text. Some of the questions were ranking exercises, in which the respondents were asked to rank items from best to worst.

Responses to each question were summarised using descriptive statistics. Test for difference between responses from private and public sector participants were performed using chi-square

statistics as the outcome variable consisted of three categories. A standard 5% significance level was used.

All analysis were performed using SAS and Excel on a MS Windows platform.

The study was approved by the Monash University Human Research Ethics Committee (project ID: 25627).

Results

Characteristics of the respondents

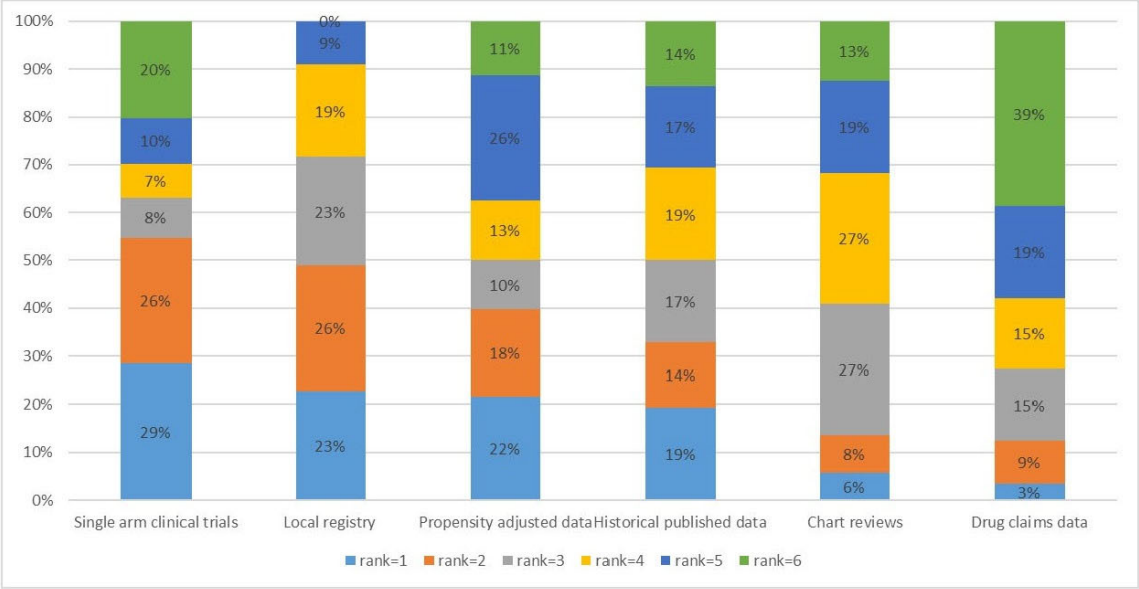
There were 97 respondents in total, with 37 from the public sector (academia and government) and 60 from the private sector (pharmaceutical companies and consultancies).

Mean (standard deviation, SD) years of working experience in health economic oncology modelling was 14.1 (7.6) years and there was good representation of leadership/managerial and non-managerial positions. The majority of respondents in both groups had a post graduate degree (master 48.4% and doctoral 34.7%) and the top three primary qualifications were in economics (28.4%), pharmacy (20.0%) and science (16.8%).

Data sources

The participants were asked to rank six different clinical data sources (not randomised clinical trials). Preferred data sources by order were single arm clinical trials, local registries, propensity adjusted data and historical published data (Figure 1). Chart reviews and drugs claims data were the least preferred. No difference between public sector and private sector respondents was observed.

Figure 1 Ranking of data sources



The clinical effectiveness claim

Use of surrogate endpoints were perceived to be major source of uncertainty with respect to clinical effectiveness claims by both sectors (all respondents: agree=57.9%, p=0.1164) however, there was no consensus that superiority should be demonstrated in a head-to-head trial(disagree: public=36.1%, private=11.9%, p-value=0.0120) and that statistically superiority was not considered sufficient for clinical effectiveness claims (agree: public=8.3%, private=25.4%, p-value=0.0350). This was consistent with the fact that 61.1% of all respondents disagreed with the statement that the minimal clinically important difference (MCID) was not relevant versus neither=24.2% and agree=14.7% (p-value=0.0704 for difference between sector).

	All (n=97)			Public sector (n=36)			Private sector (n=59)			Public vs private
	Disagree	Neither	Agree	Disagree	Neither	Agree	Disagree	Neither	Agree	p-value
Clinical claim										
Clinical superiority needs to be demonstrated in head-to-head trial	37.9%	21.0%	41.1%	36.1%	25.0%	35.9%	11.9%	45.8%	42.4%	0.0120
Minimal clinically important difference is not relevant for superiority claims	61.1%	24.2%	14.7%	61.1%	33.3%	5.6%	61.2%	18.6%	20.3%	0.0704
Superiority claim on surrogate endpoints leads to major uncertainty	12.6%	29.5%	57.9%	16.7%	38.9%	44.4%	10.2%	23.7%	66.1%	0.1164
Statistical superiority is sufficient in most instances	47.4%	33.6%	19.0%	44.4%	47.2%	8.3%	49.2%	25.4%	25.4%	0.0350
Extrapolations										
Extrapolation is a black box	43.2%	27.4%	29.5%	24.4%	38.9%	33.3%	52.5%	20.3%	27.1%	0.0433
Graphical check and Akaike/Bayesian information criterion are sufficient	43.2%	39.0%	17.9%	44.4%	44.4%	11.2%	35.6%	42.4%	22.0%	0.3748
Perfect fit like splines is preferred	23.2%	64.2%	12.6%	25.0%	63.9%	11.1%	22.0%	64.4%	13.6%	0.9085
Kaplan-Meier curve should be used for part of the modelling	5.3%	29.5%	65.3%	5.6%	50.0%	44.4%	5.1%	17.0%	78.0%	0.0023
Survival curves should converge	23.2%	42.1%	34.7%	5.5%	63.9%	30.6%	33.9%	28.8%	37.3%	0.0007
Reasonable to assume cure	31.6%	41.1%	27.4%	30.6%	63.9%	5.6%	32.2%	27.1%	40.7%	0.0002
Time horizon no longer than 10 years	50.5%	37.9%	11.6%	25.0%	61.1%	13.9%	66.1%	23.7%	10.2%	0.0003
External validation inadequate	12.6%	34.7%	52.6%	2.8%	33.3%	63.9%	18.6%	35.6%	45.8%	0.0528
Access to Individual patient data helpful	9.5%	21.1%	69.5%	0.0%	30.6%	69.4%	15.3%	15.3%	69.5%	0.0185
Enough guidance in guidelines	42.1%	31.6%	26.3%	38.9%	38.9%	22.2%	44.1%	27.1%	28.8%	0.4742
Quality of life										
Validation of quality of life not important	43.2%	27.4%	29.5%	24.4%	38.9%	33.3%	52.5%	20.3%	27.1%	0.6444
Surveys using proxies okay	43.2%	39.0%	17.9%	44.4%	44.4%	11.2%	35.6%	42.4%	22.0%	0.1185
Costs and Health resource utilisation										
Duration of treatment is major source of uncertainty	14.7%	28.4%	56.9%	2.8%	44.4%	52.8%	22.0%	18.6%	59.3%	0.0040
Post progressive treatments should always be accounted for	12.6%	34.7%	52.6%	0%	36.1%	63.9%	20.3%	33.9%	45.8%	0.0126
Adverse events are a major source of uncertainty	44.2%	35.8%	20.0%	11.1%	50.0%	38.9%	27.1%	64.4%	8.5%	<0.0001
Treatment beyond progression is a major concern	12.6%	40.0%	47.4%	5.6%	41.7%	52.8%	16.9%	39.0%	44.1%	0.2598
Palliative costs/best supportive care should be included	9.5%	30.5%	60.0%	2.8%	33.3%	63.9%	13.6%	28.8%	57.6%	0.2188
Different discount rates should be used for costs and outcomes	47.4%	38.9%	13.7%	44.4%	44.4%	11.2%	49.1%	35.6%	15.3%	0.6588
Agreements										
Financial agreements are necessary to ensure cost effectiveness	31.6%	33.7%	34.7%	13.9%	50.0%	36.1%	42.4%	23.7%	33.9%	0.0056
Rebates are a good tool to reach agreement between payer and pharma	5.3%	23.2%	71.5%	5.6%	38.9%	55.5%	5.1%	13.6%	81.3%	0.0159
Outcomes based risk share agreements difficult to implement	3.2%	23.1%	73.7%	2.8%	33.3%	63.9%	3.4%	17.0%	79.6%	0.1852
Managed entry scheme are good tools when data is limited	10.5%	33.7%	55.8%	8.3%	55.6%	36.1%	11.9%	20.3%	67.8%	0.0019
Review of cost-effectiveness is useful to assess value for money	10.5%	20.0%	69.5%	2.8%	30.6%	66.7%	15.2%	13.6%	71.2%	0.0369
Risk share agreements are not balanced – too much risk for either payer or pharma	12.6%	53.7%	33.7%	11.1%	72.2%	16.7%	13.6%	42.4%	44.1%	0.0123
Decision making										
Evidence requirements are higher for oncology than other therapeutic areas	61.0%	22.4%	11.6%	58.3%	30.6%	11.1%	62.7%	25.4%	11.9%	0.8623
Cost effectiveness analysis of oncology therapies are often black boxes	54.7%	34.7%	10.5%	36.1%	47.2%	16.7%	66.1%	27.1%	6.8%	0.0154
The opinions of patient advocates are import for informing cost effectiveness	35.8%	42.1%	22.1%	36.1%	55.6%	8.3%	35.6%	33.9%	30.5%	0.0239
More public transparency is needed surrounding reimbursement decisions of oncology therapies	13.7%	38.9%	47.4%	13.9%	58.3%	27.8%	13.6%	27.1%	58.3%	0.0058
The ICER threshold is higher in cancer compared to other therapeutic areas	14.7%	35.8%	49.5%	11.1%	47.2%	41.7%	17.0%	28.8%	54.2%	0.1875
HTA and CEA are good tools for reimbursement of oncology therapies	6.3%	24.2%	69.5%	0.0%	30.6%	69.4%	10.2%	20.3%	69.5%	0.0990
Alternative funding methods would be more appropriate than current reimbursement practice	36.8%	40.0%	23.2%	47.2%	47.2%	5.6%	30.5%	35.6%	33.9%	0.0061
The reimbursement process is too long	19.0%	30.5%	50.5%	27.8%	52.8%	19.4%	13.6%	16.9%	69.5%	<0.0001
Capacity and capability										
Comfortable with technical level in terms of cost effectiveness analysis	13.7%	16.8%	69.5%	5.5%	27.8%	66.7%	18.6%	10.2%	71.2%	0.0305
Organisation has plenty of capacity to deal with methodological issues	14.7%	21.1%	64.2%	8.3%	27.8%	63.9%	18.6%	17.0%	64.4%	0.2394
Continued training opportunities in cost effectiveness analysis are scarce	19.0%	24.2%	56.8%	25.0%	30.6%	44.4%	15.3%	20.3%	70.4%	0.1610
Prefer web-based training in own time	23.2%	32.6%	44.2%	27.8%	36.1%	36.1%	20.3%	30.5%	49.2%	0.4472

Extrapolation of survival data

Private sector respondents did not see extrapolation of survival data as a 'black box' (disagree: private=52.5%, public=24.4%, p-value=0.0433). Regarding the question on whether graphical checks and Akaike Information Criterion/Bayesian Information Criterion were sufficient justification for choice of extrapolation both groups predominantly responded disagree (all respondents: agree=17.9%, p=0.3748). Both groups were indifferent to methods like splines (all respondents: agree=12.6%, p=0.9085) however, majority of public respondents were indifferent to using the observed Kaplan Meier curve for part of the modelling (neither: public=50.0% versus private=17.0%, p=0.0023).

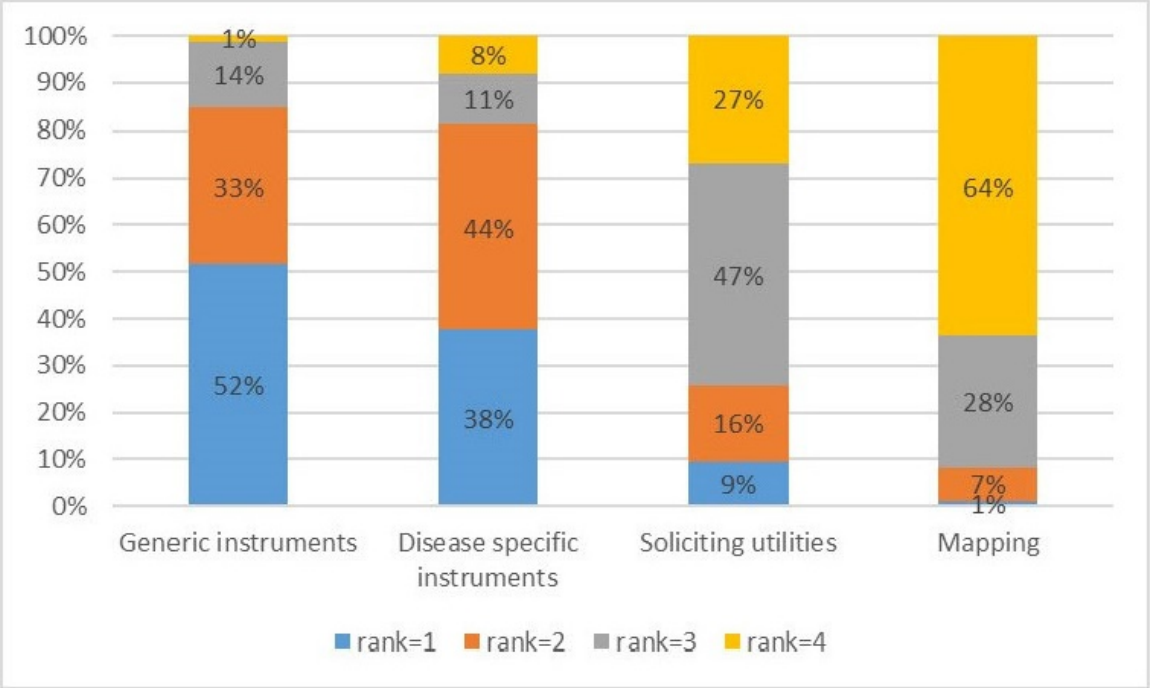
It is common in Australia for the PBAC to request extrapolated survival curves that converge over time (10), but a third of the respondents from the private sector disagreed that the survival curves should be forced to converge over time, compared to only 5.5% of public sector respondents (p=0.0007). Similarly, a large proportion of private sector respondents agreed that it was reasonable to assume cure (agree=40.7%), which was significantly different (p=0.0002) when compared to public sector respondents (agree=5.6%). Having a time horizon of no longer than 10 years was another point on which private (disagree=66.1%, neither=23.7%, agree=10.2%) and public responses (disagree=25.0%, neither=61.1%, agree=13.9%) were not aligned on (p=0.0003).

External validation was thought to be inadequate by both groups (all respondents: agree=52.6%, p=0.0528). While access to individual patient data (IPD) was seen as helpful by a majority in groups (agree: public=64.9%, private=69.5%) more private sector respondents disagreed (disagree: private=15.3% versus public=0.0%, p=0.0185). Finally, both groups disagreed (all respondents: agree=26.3%, p=0.4742) that there was enough guidance in the PBAC guidelines.

Quality of life (QoL)

A generic utility instrument such as EQ-5D was preferred (85% of respondents ranked it either 1 or 2), whereas mapping of a non-utility instrument to a utility instrument was the least preferred method (92% of respondents ranked it either 3 or 4) (Figure 2).

Figure 2 Ranking of quality-of-life instruments

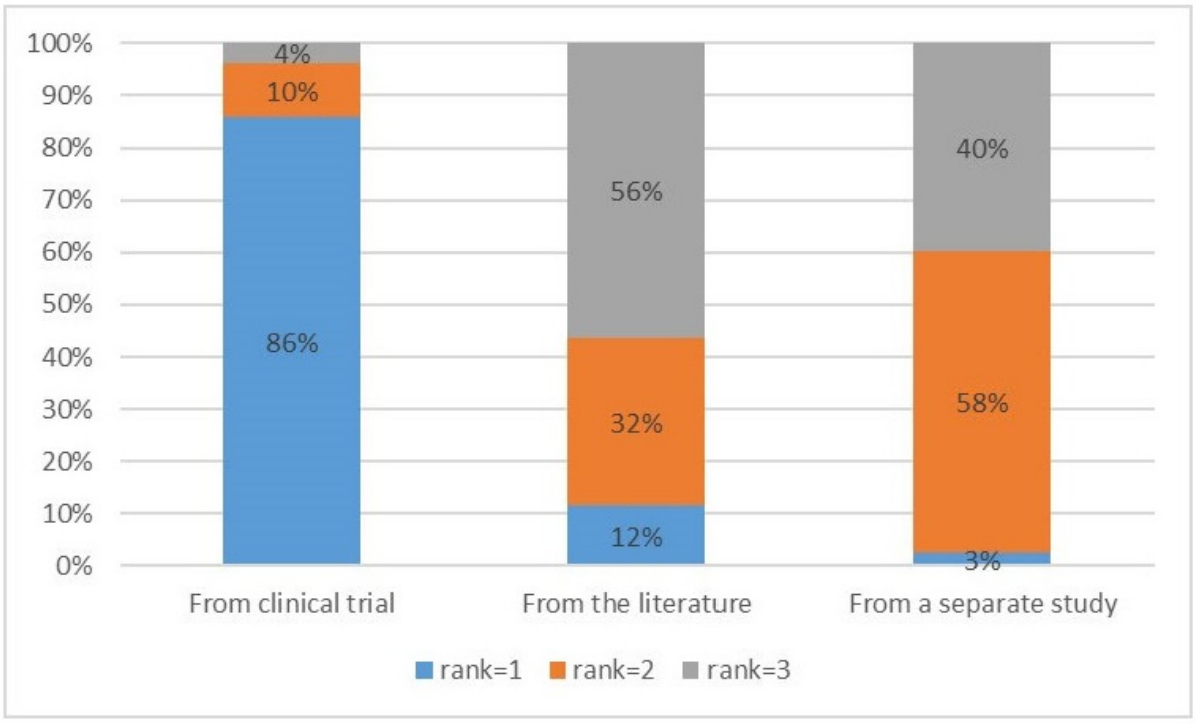


Both private and public respondents disagreed that validation of QoL instruments was not important (all respondents: agree=29.5%, p=0.6444). Only a minority of respondents agreed that using proxies instead of patients to generate QoL valuations were appropriate (all respondents: agree=17.9%, p=0.1185).

214 Overall, the respondents preferred utilities to be measured directly in the clinical trial
215 (preferred=86.3%) and the least preferred method was to source QoL information from the
216 literature (least preferred=57.5%) (Figure 3). There was no difference between private and
217 public respondents (p>0.05).

218

219 Figure 3 Ranking of quality-of-life data sources



220

221

222 *Costs and health resource utilisation*

223 Regarding the question on whether duration of treatment was a major source of uncertainty
224 only few of public sector respondents disagreed compared to private sector respondents
225 (disagree: public=2.8%, private=22.0%, p=0.0040). A similar trend was observed for other
226 costs and health resources: post progressive treatments should always be accounted for
227 (disagree: public=0.0%, private =20.3%, p=0.0126), adverse events (AE) are a major source of

uncertainty (disagree: public=5.6%, private=16.9%, p<0.0001). No difference was observed in terms of treatment beyond progression is a major concern (all respondents: agree=47.4%, p=0.2598), palliative/best supportive care costs (all respondents: agree=60.0%, p=0.2188) and whether different discount rates should be used for costs and outcomes (all respondents: disagree=47.4%, p=0.6588).

Risk share agreements

Both public and private sector respondents agreed that outcomes-based risk share agreements (RSAs) are difficult to implement (all respondents: agree=73.7%, p=0.1852). On the other hand, there was no consensus that that financial agreements are necessary to ensure cost effectiveness (disagree: private=42.2% vs public=13.9%, p=0.0056). Likewise, there was a difference in the response to the statement that managed entry schemes are good tools when clinical data is limited with the majority of private respondents agreeing with the statement (agree: private=67.8% versus public=36.1%, p=0.0019). Relative few public sector respondents agreed that RSAs are not balanced and that there is too much risk for either the payer or the sponsor compared to private sector respondents (agree: private =44.1% versus public=16.7%, p=0.0123).

The majority of respondents both public sector and private respondents agreed that rebates are a good tool to reach an agreement between payer and the sponsor (private agree=81.3%, public agree=55.5%) and that review of cost-effectiveness is useful to assess value for money (private agree=71.2%, public agree=66.7%).

Decision making

Private and public sector respondents agreed that the ICER threshold is higher for cancer compared to other therapeutic area (all respondents: agree=49.5%, p=0.1875), and that HTA and CEA are useful tools for assessing reimbursement of oncology therapies (all respondents: agree=69.5%, p=0.0990). They also both disagreed that the evidence requirements are higher for oncology when compared to other therapeutic areas (all respondents: disagree=61.0%, p=0.8623).

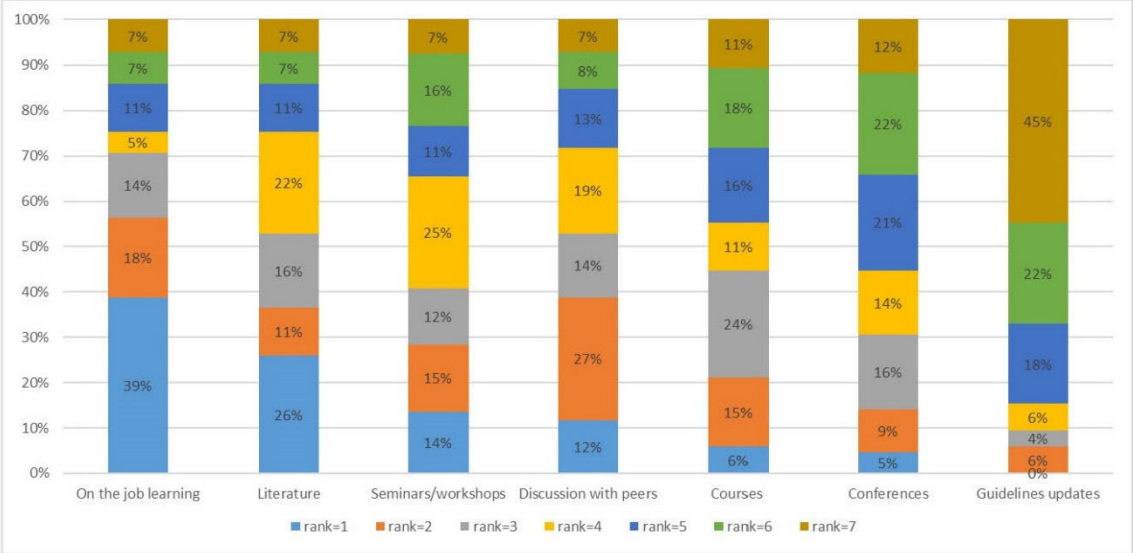
Very few public sector respondents thought that opinions of patient advocates are important for informing cost-effectiveness (agree: private=30.5% versus public=8.3%, p=0.0239) and that alternative funding methods are more appropriate than current practice (agree: private=33.9% versus public=5.6%, p=0.0061). The majority of private sector respondents agreed that the reimbursement process is too long (agree: private=69.5% versus public=19.4%, p<0.0001) and that more public transparency is needed surrounding reimbursement decisions of oncology therapies (agree: private=58.3% versus public=27.8%, p=0.0058).

Finally, very few private sector respondents agreed that CEA of oncology therapies are often black boxes (agree: private=6.8% versus public=16.7%, p=0.0154).

Capacity and capabilities

More private sector respondents compared to public sector respondents disagreed that they were comfortable with their technical level of CEA (disagree: private=18.6% versus public=5.5%, p=0.0305). The majority from both groups concurred that their organisation has plenty of capacity to deal with methodological issues (all respondents: agree=64.2, p=0.2394). However, a majority also felt that continued CEA training opportunities are scarce (all respondents: agree=56.8%, p=0.1610).

Figure 4 Sources of methodological advances



The sources for methodological advances seemed to come from a variety of sources such as on the job learning, the peer reviewed literature, seminars, discussion with peers and workshops by professional bodies. The least popular way was guideline updates (see Figure 4).

Discussion

To our knowledge this is the first study surveying both industry and payers with respect to opinions on cost-effectiveness and HTA at a national level in Australia.

Main findings of the study

Private sector and public sector respondents had similar views on clinical effectiveness claim as they agreed that clinical superiority needs to be demonstrated in a head-to-head clinical trial and that superiority claims made on surrogate endpoints lead to major uncertainty. However,

290 they were divided when it came to extrapolation of survival data. Costs and health resource
291 utilisation were also a contentious issue between private sector and public sector respondents.
292 With respect to risk share agreements and decision making, respondents generally agreed that
293 rebates are a useful tool, outcomes-based agreements are difficult to implement, managed entry
294 schemes are required when data is limited, review of CEA is useful to assess value for money,
295 evidence requirements are not higher for oncology than other areas and the ICER threshold is
296 higher in cancer compared to other therapeutic areas. In general, HTA training takes place
297 through on the job training, keeping abreast of the peer reviewed literature and through
298 discussions with peers. Guideline updates were a least favoured opportunity for continued
299 training in CEA.

300 The differences in responses were not surprising as the two sectors have different goals. For
301 example, private sector respondents downplay additional costs which makes a drug less cost-
302 effective option whereas public respondents err on the side of caution in the absence of robust
303 evidence. Unfortunately, the differences are likely the cause delay in access to medicines due
304 to multiple resubmissions and extended pricing negotiations.

305 Both private sector and public sector respondents were largely aligned with the PBAC
306 guidelines. For example, both disagreed that minimal clinically important difference is not
307 relevant for superiority claims. Interestingly, both groups agreed that the observed Kaplan-
308 Meier curves should be used for part of the modelling, which is specific to the PBAC
309 guidelines; for example, the UK National Institute for Health and Care Excellence (NICE)
310 guidelines do not require this (18).

311

312 *Comparison to previous literature*

313 Previously reported studies have primarily focused on the response of payers in a broader
314 perspective than what is presented here.

315 Stephens et al (19) performed an international survey of methods used in HTA in 2012. Thirty
316 respondents were recruited from HTA bodies worldwide, with three respondents from
317 Australia. Common attributes among the HTA bodies were evaluation of cost-effectiveness,
318 safety and quality of life. Issues that the HTA bodies faced were lack of evidence and data
319 availability for emerging technologies. The authors concluded that future efforts should address
320 additional aspect of research methods in HTA.

321 Moloney et al. (20) conducted a survey of payers in the US and Europe on comparative
322 effectiveness research. A total of 14 respondents provided feedback on study design,
323 methods/analytics, data capacity and burden of evidence generation and accountable care. The
324 responses were very broad and did not include any detail on specific issues with respect to
325 CEA. The authors concluded that more engagement with payers, manufacturers and regulatory
326 agencies was needed to discuss key methodological tradeoffs. It should be noted that this
327 research was sponsored by the pharmaceutical industry and so conclusions might have been
328 biased.

329 Another survey by Ciani et al (21) surveyed 36 HTA agencies across 20 non-European
330 countries with respect to HTA and medical devices. The survey compared processes and
331 methods between medical device agencies and non-medical device agencies. The conclusion
332 was that scientific methods for HTA of devices need further development to adapt to new
333 methods for medical devices. No feedback was sought from the private sector.

334

335 *Strengths and limitations*

As described above, previous surveys have primarily included payers and been small. The present study was based on 97 respondents from across industry, academia and government. One of the main strengths is that it comprises of in-depth questions with respect to specific methodology issues in HTA of oncology drugs. Furthermore, the respondents were in general very experienced, with more than an average of 14 years of experience. Hence, the findings are likely to be a reliable representation of opinions of health economists familiar with this subject in Australia.

A main limitation of the present study was the generalisation of questions. Issues differ between drugs, tumour types and lines of therapy, which makes it difficult to make general statements with respect to CEAs in oncology. Respondents were asked to fill out the survey with an average case in mind. It was possible to assess the response rate for the survey as the pool of potential respondents was not known. Specific affiliation (e.g. pharmaceutical company, university or government department) was not collected due to risk of identification of the respondents. This meant that generalisability could not be assessed. Another limitation was that the question of using proxies as source for health-related quality of life evidence was possibly confounded by combining clinicians with the general population.

Implications for research

Based on this survey, the ideal seems to be: head-to-head clinical trial versus a superiority claim on a final outcome measured directly in the clinical trial. However, this is unfortunately not always the case and therefore there are still many areas that need further research in terms of HTA and oncology. For example, there are still issues with respect to surrogate to final outcomes which is recognised by the majority of the respondents in this survey. Previous recommendations surrounding transparency and quantification of exploration of uncertainty

have been published both in general (22, 23) and for several tumours types like breast cancer (24) and colorectal cancer (25). While extensive guidance is available from different HTA organisations (26, 27) the issue of extrapolation is still perceived by public sector respondents as black boxes. Validation is seen as inadequate and further research is needed.

Opinions differed markedly with respect to costs and health resource utilisation between the two sectors and therefore offers and opportunity for further research. These include issues with respect to the duration of treatment, inclusion of post progression treatment in the CEA and costs and health resources in connection with adverse events.

Implications for improving capability/capacity

The PBAC guidelines have been updated three times the past 20 years, which explains why the majority of the respondents ranked guidelines updates as the least preferred source for methodological advances. The UK NICE is supported by a Decision Support Unit which publishes reports on methodological advances on an ongoing basis (28). There are examples of this approach in Australia. For example, Cancer Australia supports a health economic support program in which an academic institution is commissioned to support the clinical trials groups with health economic training and input into their trial protocols (29). The PBAC and its stakeholders could benefit from something similar.

Both groups of respondents agreed that continued training opportunities in cost-effectiveness analyses are scarce. Moreover, they ranked courses and conferences low in terms of sources of methodological advances. As such, universities and health economic societies should be encouraged to cover this gap by setting up short courses and host conferences in this field.

383 *Implications for policy*

384 Outcomes based risk share agreements are seen as difficult to execute and therefore specific
385 set of guidelines and policies on this particular topic could be helpful. Public transparency was
386 seen as important by the respondents. There are pros and cons of improved transparency. More
387 transparency could give the public more clarity as to why reimbursement decisions are made
388 and in particular offer guidance when a drug is rejected. On the other hand, confidentiality
389 mitigates the risk of reference pricing for pharmaceutical companies and enables them to offer
390 lower prices (30).

391 It appears that both private and public stakeholders are in favour of inclusion of IPD as part of
392 the reimbursement submission. Requirements for submission of IPD is a novel idea in the
393 regulatory space as the FDA have required this for some time as part of new drug applications
394 (31). There are of course some considerations if such a policy was to be implemented since it
395 may contain sensitive personal data. These include ethics approval by appropriate bodies,
396 development of processes to ensure that access to the data is limited to relevant staff and that
397 everything be kept commercial-in-confidence. Alternatively, pharmaceutical companies could
398 calculate both AIC/BIC values and quality of life estimates with country specific weights as
399 part of the CSR. This would of course mean that there would be more planning from the
400 company side, as all analyses would have to be prespecified in the statistical analysis plan
401 before the unblinding. However, this would give regulators and payers more confidence in the
402 estimates.

403 A convergence of understanding between the public and private sector is desirable as it would
404 result in faster access to medications for patients. A formal pre-submission process could
405 improve this. Currently, there is an opportunity for a manufacturer to meet with the Department
406 of Health before a submission. Any advice given at these meetings is non-binding and is

407 therefore of limited value in terms of reaching agreement on opinions. For medical devices and
408 medical procedures, the first step in the reimbursement process is to establish the framework
409 for the economic evaluation (32). This is done by clearly articulating the population,
410 intervention, comparator, outcomes (PICO) and confirming the relevant clinical algorithms. A
411 similar process for pharmaceuticals would be beneficial. This would ensure that the
412 manufacturer and the payer have agreed on key issues up front thereby avoiding multiple
413 submissions as well as minimize delays to access for patients.

414

415 **Conclusions**

416 The study presented here is the largest survey of both private sector and public health economic
417 practitioners in Australia. Not surprisingly the private sector respondents favour methods that
418 reduce the ICER when compared to the public sector respondents. While the field of health
419 economics is mature, this study has identified a number of challenges for HTA in oncology
420 that warrant further research.

421

422 **Conflict of interest**

423 HK and SG declares no conflict of interest. DL has participated in advisory boards and/or
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425 Edwards Lifesciences, Novartis, Pfizer, Sanofi and Shire.

426

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6.3 Conclusion

Not surprisingly, private sector respondents favoured methods that reduce incremental cost-effectiveness ratios compared to public sector respondents. While the field of health economics is mature, this study identified a number of improvements for HTA in oncology. In particular, access to individual patient data was deemed crucial by both types of respondents, as this would increase transparency and hence confidence in the claims put forward by sponsors, as well as provide opportunities for continued training in CEA methods.

Chapter 7: Discussion and conclusions

This body of research offers new insights into contemporary challenges in the health economic modelling of oncology therapies.

7.1 Principal findings

7.1.1 Literature review

The demand for newer and better oncology medications is driving pharmaceutical companies to look for opportunities to accelerate development of these treatments. This race to market has resulted in smaller clinical trials that often rely on small single arm trials. While this is adequate in order to gain market authorisation, HTA-based reimbursement decision-making is fraught with challenges pertaining to high costs and uncertainty.

The literature review aimed to define the 'state of play' of HTA in oncology. Specifically, the review highlighted the important role HTA has played in access to oncology drugs, with the development of methods such as indirect comparisons, network meta-analysis, and matching-adjusted indirect comparisons. Moreover, modelling beyond the duration of clinical trials has generated a lot of research with regards to extrapolation and non-Markov modelling techniques. Finally, the high costs of oncology medicines and the impact they have on financial budgets have stimulated research into risk share agreements, coverage with evidence development, conditional reimbursement and managed entry schemes.

A few key issues loom on the horizon: further development and practical application of new QoL measures, methods for translating clinical evidence, and exploration of modelling techniques. These are needed for better understanding of the complex interplay between affordable access and financial risk management.

7.1.2 Quality of life study

The aim of this study was to compare the generic EQ-5D utility measure with the cancer-specific QLU-C10D in metastatic melanoma using a practical, real-world CEA.

In the study, the generic EQ-5D valued mean progression-free and progressive health states 5–10% higher than the condition-specific QLU-C10D, with comparable standard deviations. Furthermore, the EQ-5D was consistently associated with a wider range of utility values compared to the QLU-C10D.

The lower values and shorter range for the QLU-C10D resulted in 4–8% higher ICERs, thereby indicating that the QLU-C10D might value survival less compared to the EQ-5D. However, this did not result in a change in the conclusion regarding cost-effectiveness, as there was little difference between the acceptability curves for the two scenarios.

A potential issue is that the QLQ-C30, upon which the QLU-C10D was developed, is not able to capture the impact of treatment-specific adverse reactions with respect to ICIs. QLQ-C30 items are tailored to capture issues related to chemotherapies such as nausea/vomiting, constipation, appetite loss and diarrhea. Newer cancer treatments like immunotherapies have different adverse event profiles. Common irAEs include colitis, pneumonitis, hypothyroidism and inflammatory arthritis, which are not explicitly captured by the QLQ-C30.

This study demonstrated that there is no reason to consider the condition-specific QLU-C10D when using Australian weights for CEA in immunotherapy-treated metastatic melanoma as the existing generic EQ-5D instrument adequately captures QoL impacts.

7.1.3 Reassessment of a cost-effectiveness analysis of nivolumab versus everolimus for renal cell carcinoma

The aim of this study was to reassess the cost-effectiveness of the ICI nivolumab based on updated mature survival and safety data, as well as the off-patent lower price of everolimus.

A price reduction of 54% for the treatment of the ICI was required for it to be cost-effective at a $75,000 per QALY saved threshold. Updated clinical trial data demonstrated better effectiveness and the improved survival data offset the additional incremental costs.

A major issue was that the extrapolations were restricted by the unavailability of individual patient data (IPD). Published CEAs for nivolumab did not provide details on the extrapolations and therefore the reconstructed survival data could not be validated. Furthermore, the availability of statistical software to deal with interval censoring data of simulated data is limited, making it a challenge to assess extrapolations based on spline models and other non-standard statistical distributions. Access to IPD would also have enabled further investigation with respect to gender, age and comorbidities.

This study demonstrates that re-evaluation of drugs post reimbursement is worthwhile. While the assessment did not result in a major difference in ICER or the proposed rebated price of nivolumab, it highlights the complex issue of assessing cost-effectiveness. The drop in list price of the comparator everolimus from AU$5,277.88 to AU$1,726.35 for 30 tablets following patent expiry had the potential to dramatically impact the cost-effectiveness including any rebates of nivolumab. However, updated

clinical trial data demonstrated better effectiveness and the improved survival data offset the additional incremental costs.

Nonetheless, this study highlights potential issues of not taking generic prices into account when performing CEA. It is therefore recommended that payers develop policies to ensure that in the long term they do not overpay for new drugs, especially when the comparator loses patent protection.

7.1.4 Validation of a cost-effectiveness analysis of nivolumab versus everolimus for renal cell carcinoma

The aim of this study was to validate the input variables used in a cost-effectiveness analysis of nivolumab versus everolimus for renal cell carcinoma against real world data from the Australian PBS.

More than 80% of patients received nivolumab and everolimus via the PBS as second line treatment. A small proportion (<10%) received the two drugs as third line treatment following axitinib or cabozantinib after sunitinib/pazopanib and a fraction (<1%) received nivolumab after everolimus. This is all within the reimbursement restriction, which do not specify which line of therapy the drugs can be used for. From a financial perspective, all the drugs in question have a financial risk share agreement in place and any expenditure over the proposed risk share arrangement caps is 100% rebated to the government, which indicates that there is limited risk of the expenditure on nivolumab exceeding the financial cap to the government in terms of the use of nivolumab outside the restriction.

The present study shows that duration of treatment in real life is longer than observed in the clinical trial, with a difference between nivolumab and everolimus and that wastage is minimal. An update of the published CEA with these values resulted in a six-fold increase in incremental QALYs, but at a 69% increase in incremental costs.

A major weakness of the present study is that the analyses comprise simple naïve comparisons of two observational cohorts and therefore no firm conclusions can be drawn. The dataset only constitutes 10% of the whole cohort and therefore do not give the whole picture. It would be useful if researchers could get access to a higher proportion of patients than the 10% especially in late-stage cancer as the patient numbers are small. Furthermore, linking PBS script data to medical services data via from the Australian Medicare Benefits Schedule (MBS) would enable researchers to investigate other health resource use (such as special visits and imaging) for these conditions.

PBS script data provide real world evidence of the prescription patterns of drugs in Australia. The duration of treatment for the ICI nivolumab was not observed to be worse compared to the clinical

trial evidence and wastage was minimal. Thus, claims data validated the clinical trial data used for the health economic modelling of nivolumab.

7.1.5 Stakeholder survey

The stakeholder survey sought to determine which factors in modelled CEA of oncology treatments are considered important from the perspective of key stakeholders from the private sector (pharmaceutical industry and specialist consultants), as well as public sector stakeholders (academia and government). The focus was on factors that contribute to uncertainty in CEA.

While the field of health economics is mature, this study identified a number of challenges for HTA in oncology that warrant further research with respect to surrogate to final outcomes, extrapolation and validation. Opinions differed markedly with respect to costs and health resource utilisation between the two sectors. These include issues with respect to the duration of treatment, inclusion of post progression treatment in the CEA and costs and health resources in connection with adverse events. Not surprisingly, private sector respondents favoured methods that reduce the ICER compared to public sector respondents.

Both private and public sector respondents agreed that continued training opportunities in CEAs are scarce. As such, universities and health economic societies should be encouraged to cover this gap by setting up short courses and host conferences in this field.

Outcomes-based risk share agreements are seen as difficult to execute and therefore specific set of guidelines and policies on this particular topic could be helpful. Public transparency was seen as important by the respondents. There are pros and cons of improved transparency. More transparency could give the public more clarity as to why reimbursement decisions are made and in particular offer guidance when a drug is rejected. On the other hand, confidentiality mitigates the risk of reference pricing for pharmaceutical companies and enables them to offer lower prices.

Lastly, it appears that both private and public stakeholders are in favour of inclusion of IPD as part of the reimbursement submission. There are of course some considerations if such a policy was to be implemented since it may contain sensitive personal data. These include ethics approval by appropriate bodies, development of processes to ensure that access to the data is limited to relevant staff and that everything be kept commercial-in-confidence. This would of course mean that there would be more planning from the company side, as all analyses would have to be prespecified in the statistical analysis plan before the unblinding. However, regulators and payers would have more confidence in the estimates.

7.2 Strengths and limitations of this research

The strengths and limitations of each specific study are discussed in the relevant chapters. Here, the broader merits and limitations of the research included in this thesis are summarised.

Care was taken in following current pharmacoeconomic guidelines with respect to HTA and economic modelling. Regardless, there were several limitations that warrant mention. First, the individual studies were restricted to specific tumour types. Common feedback received from the respondents in the stakeholder survey was that answers to many of the questions were dependent on the situation. This reflects the multi-faceted issues facing researchers in this field and that every case is unique. It is difficult to claim that the results presented in this thesis can be generalised to every cancer and every situation. However, the research was documented step by step and critical decisions were justified in an unbiased manner, making it possible for others to perform similar research for other tumour types. Furthermore, where possible, the findings were validated by external sources.

Secondly, selection bias would have arisen from non-representativeness of the subjects or data used in the individual studies, but the direction and extent of the bias could not be estimated. Similarly, some studies were limited by small sample sizes, which introduced uncertainty. However, it was unlikely that these limitations would have altered the overall conclusions of the body of research.

Finally, a major limitation specific to the modelled analyses was the lack of IPD. These were requested but ultimately not made available due to commercial interests. (Interestingly, in the stakeholder survey, respondents from the private sector agreed that access to IPD would be helpful.) IPD would have reduced uncertainty in the analyses. These were specified in the relevant chapters.

7.3 Future direction and conclusions

Oncology therapies are still evolving, with newer therapeutic approaches in development, along with the discovery of new immune checkpoints exploited by cancerous cells [121]. While some of these treatments, such as chimeric antigen receptor (CAR) T-cell therapy, show promising potential [122], funding will be a challenge. For example, it is estimated that CAR T-cell therapy will cost more than US$500,000 per patient [123]. Furthermore, it is not only newer therapies that will pose a challenge for payers. Combinations of targeted therapies and ICIs are actively being explored [124, 125] and ICIs are being used in earlier stage of cancer, such as in adjuvant and neoadjuvant settings [126-128], in which populations are larger and hence also the impact on healthcare budgets. A potential solution is to incorporate health economic modelling into the early stages of development of oncology therapies. This potential future use of health economic modelling for oncology therapies is discussed the paper

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Commentary

The Potential for Early Health Economic Modelling in Health Technology Assessment and Reimbursement Decision-Making

Comment on "Problems and Promises of Health Technologies: The Role of Early Health Economic Modeling"

Hansoo Kim[1*], Stephen Goodall[2], Danny Liew[1]

Abstract

Grutters et al recently investigated the role of early health economic modelling of health technologies by undertaking a secondary analysis of health economic modelling assessments performed by their group. Our commentary offers a broad perspective on the potential utility of early health economic modelling to inform health technology assessment (HTA) and decision-making around reimbursement of new health technologies. Further we provide several examples to compliment Grutters and colleagues' observations.

Keywords: Early Assessment, Health Economic Modelling, Reimbursement, Health Technology Assessment, Australia

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Introduction

Health technology assessment (HTA) is routinely used to support reimbursement decisions. The process typically involves health economic modelling of available efficacy and resource utilisation data on health technologies. However, the role is less clear for *early* health economic modelling to identify potentially cost-effective new technologies during their development phases; that is, prior to robust efficacy data being available. Grutters et al recently investigated this issue by undertaking a series of case studies of 32 health economic modelling assessments of 30 innovations performed by their group.[1] There were some limitations to the study, mainly stemming from the authors drawing a small sample of unpublished HTAs (n = 32) from a single group (their own), and considering only the perspective of the Dutch healthcare system. Nonetheless, their conclusion that early assessment provided insight into the potential cost-effectiveness and uncertainty associated with the technology highlights an important point: that any intelligence on the future market for a new health technology is valuable, not only for its sponsors, but also payers as well as providers and patients even though the these have different informational needs.

Early consideration of the cost-effectiveness of a new health technology is a logical step, given its prominence in reimbursement decisions. The present commentary offers a broad perspective on the potential utility of early health economic modelling to inform HTA and decision-making around reimbursement of new health technologies.

First, it is important to recognise that there is significant variation in HTA requirements from country to country,[2,3] and not all HTA agencies even require health economic modelling to inform decision-making. As such, it can be expected that the usefulness of early health economic modelling will depend on the market within which it is undertaken, as well as the rules for HTA in that market.

In HTA jurisdictions like Australia, Canada and the United Kingdom, there is formal requirement for health economic modelling, and although there are well established guidelines for undertaking this, there is generally also acceptance of novel approaches to accommodate innovative therapies. For example, the advent of immuno-oncology agents, which have unique biological mechanisms of action and clinical effects, has necessitated new approaches to economic evaluation, especially with regards to extrapolating and translating data beyond the pivotal clinical trials.[4]

In countries without mandatory health economic modelling, like South Korea and Taiwan, the utility of early modelling is less clear. However, this strategy can still be used to characterise both the clinical and economic environments within which the new health technology will be assessed for reimbursement. Insights could be gained into the unmet clinical need, the extent to which the health technology would

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address this, and the price at which this could be done in a cost-effective manner. Hence although formal early health economic modelling may not be mandated for stop/go decisions with respect to reimbursement, the exercise would still be very informative.

Regardless of the jurisdiction, there are three key areas in which early health economic modelling offers the most potential in HTA and reimbursement decision-making: identifying uncertainty, assist in the generation of real world evidence and informing risk-share agreements.

Minimising Uncertainty

Parameter uncertainty and structural uncertainty in economic evaluations is a major problem, and a common reason for failure of reimbursement applications.[5] Early health economic modelling provides a means to identify input that will contribute most to the parameter uncertainty of a cost-effectiveness analysis. For example, early modelling with deterministic or probabilistic sensitivity analyses may demonstrate that the relative efficacy (such as the hazard ratio associated with an outcome) of the new health technology will exert the greatest influence on the likelihood of its cost-effectiveness, even after taking into account other key input parameters. Alternatively, it could identify thresholds in the risk of the target disease at which an intervention is most likely to be effective, and hence cost-effective and aid in calibration of the model structure. This type of information could inform the ongoing clinical development of the new health technology, and/or recommend further research to minimise parameter uncertainty.

Another common source of uncertainty lies in the long-term benefits of health technologies. In most HTAs, it is necessary to extrapolate outcome data beyond the duration of clinical trials, which are typically short (and may be surrogate). The Australian Pharmaceutical Benefits Advisory Committee (PBAC)[6] and the National Institute for Health and Care Excellence[7] recommend using visual inspection of several possible distributions such as the Weibull, loglogistic, lognormal, Gompertz and exponential as well as comparisons of the Akaike information criteria (AIC) when choosing distributions for extrapolations. The guidelines stipulate that the distribution with lowest AIC score should be chosen.

The AIC is agnostic to the underlying behavior in the data and the mathematical properties of the distributions. Sometimes the AIC values can be almost identical as reported by Bohensky et al[8] where the AIC for the Weibull distribution was observed to be 243.204 and 243.451 for the loglogistic distribution in the post progression health state. This equates to a 0.1% difference but more importantly the two distributions are fundamentally different. The Weibull distribution is monotone and the hazard cannot change direction. This means that if an increasing hazard (eg, risk of death) is assumed then it will keep increasing over time. The loglogistic distribution on the other hand allows for the hazard to change direction over time.[9,10] For some of the immune-oncology drugs it is well-known[11] that after an initial steep drop in the survival curve there is a plateau like effect meaning that the hazard increases to begin with but then decreases after a while.

Early modelling would be able to assist in validating the behavior of the hazard and guide modelers in the choice of distribution instead of relying on measures like the AIC.

Another issue is time horizon of the extrapolation. For example, in Australia, trastuzumab for patients with HER2 positive early breast cancer following surgery in association with chemotherapy was considered for reimbursement by the PBAC in July 2006. The sponsor had extrapolated outcome data from the clinical trial over a 40-year time horizon, but not detailed the methods for extrapolation.[12] This was a major source of uncertainty. There were no explicit guidelines regarding the extrapolation of observed data but this was a major source of uncertainty. However, since then, the topic has been widely debated[13,14] and current guidelines now mandate rigorous examination of extrapolation methods.[6] Had early health economic modelling been undertaken as part of the HTA for trastuzumab, the multiple sources of uncertainty would have been identified, including timeframes over which efficacy measures could have been assumed, the various functions that could have been fit to extrapolate survival data, and the impact of decreasing adherence over time.

Underlying uncertainty relating to the structure of the model (structural uncertainty) such as how health states are linked in a Markov model or choice of underlying survival functions in a partitioned survival model can also be minimised through early health economic modelling. This can be done by ensuring that economic models are set up in flexible ways to allow for testing of different scenarios. These scenarios could relate to key structural assumptions that are not normally taken tested in models such as Markovian assumptions surrounding time dependent transition probabilities, or what time point to apply extrapolation to Kaplan Meier data in partitioned survival models. Key to this is the mapping of future treatment pathways for the particular diseases of interest. Predicting future treatment pathways is challenging, but achievable with available data and expertise. For example, a review of clinical trial registries like www.clinicaltrials.gov and the convening of expert advisory panels are both useful. It is important to note that future comparators may not be the same modality; for example, what is a drug comparator now may be a device in the future.

Generation of Real-World Data

The use of real-world data is an area of major increasing interest in HTA.[15] Early health economic modelling uses real-world data in conjunction with clinical trial data, and is potentially a useful tool that can used to aid and guide gathering of real world data. An example of real-world data and early modelling guiding decision-making can be found in the work by Tappenden et al in 2017.[16] Here, registry data, evidence drawn from the literature and expert opinion were used to populate an early model on an adherence intervention to improve outcomes for patients with cystic fibrosis. The analysis allowed for estimation of health gains and expected costs savings over a five-year period and the study is still ongoing.

Clinical trials are typically designed with the aim of

obtaining regulatory approval for the health technology, not reimbursement approval. Moreover, due to patient selection and strict protocols, clinical trials can often overestimate an interventions effect when implemented into clinical practice. Thus, a major issue in HTA is whether efficacy data from a clinical trial translates into real-world effectiveness.[17] Early modelling is a vehicle for translating and synthesizing efficacy data from early phase clinical trials into real-world effectiveness data and can therefore support future reimbursement decisions. A major advantage of modelling is that multiple and complex scenarios can be explored with currently available modelling techniques. For example, agent-based systems can take into consideration that many clinicians do not prescribe drugs exactly as per reimbursement criteria, and patients are often not compliant with the intended regimen.[18] Other examples include dynamic simulation of systems and discrete event simulations.[19]

Furthermore, early health economic modelling could aid the generation of real-world data when no other data are available. This would typically be the case when clinical trials have not yet been reported. Real-world data such as clinical registries, patient charts and script data can easily be synthesised using a health economic model. This would then enable additional research recommendations to be based on many different types of evidence particularly health resource utilisation data, which is often protocol driven in clinical trials.

Risk Share Agreements

There is currently increased focus on how to accelerate access to new health technologies. Initiatives include streamlining processes between regulatory and HTA authorities,[20] as well as through harmonisation initiatives like the European Network for Health Technology Assessment.[21] Moreover, there seems to be a tendency for payers to be to prepared to enter into 'coverage with evidence' development schemes or risk share agreements.[4,22] This is typically done in order to acquire further data to support the evidence for the incremental cost-effectiveness ratio. Unfortunately, while these schemes and agreements offer a solution to early funding as reimbursement is granted even though evidence such as mature survival data is not yet available, the risks are often not well-understood.[23,24] Early health economic modelling could bridge this gap by better conceptualising the risks and uncertainties for both payers and sponsors.

Early modelling would have been valuable in the high unmet need case of ipilimumab for advanced melanoma in Australia. After three failed initial applications by the sponsor for reimbursement, the Australian PBAC finally granted coverage of ipilimumab under a condition that the sponsor to provide future evidence of improved overall survival.[25] A post marketing follow-up program was established and the overall survival claim was verified.[26] Early health economic modelling with input from the payer could have identified the overall survival claim as a major issue up front, thereby avoiding multiple submissions.

Many risk share agreements are still financial in nature,[27] which is another area where early modelling can be valuable. For example, the Australian PBAC determined that a financial risk share agreement for pembrolizumab in first line treatment of non-small cell lung cancer was needed.[28] A 100% rebate beyond a subsidisation cap was proposed to mitigate the overall budgetary risk to the government if the number of actual patients exceeded that which was agreed upon. Early economic modelling could have been used to inform the budget modelling and subsequently offer alternatives to this arrangement, in which all the risk is carried by one party.

Conclusion

Early health economic modelling provides a mechanism for early assessment of new health technologies, as pointed out by Grutters et al. Its acceptance and utility will depend on the environment and context within which it is undertaken, but minimising uncertainty, generation of real-world evidence and informing risk share agreements stand out as areas of greatest potential. There is unfortunately a lack of literature demonstrating the power of early modelling and researchers from academia and industry are encouraged to publish more papers describing health economic modelling before/during/after development of health technologies.

It would be surprising if pharmaceutical and device industry did not already use early modelling in some form to inform development of their products.[29] However, through wider collaboration with stakeholders and payers, early health economic modelling could be instrumental in bridging the gap from laboratory to patient access in a more seamless way.

Ethical issues

Not applicable.

Competing interests

Authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the conception, drafting and approval of manuscript.

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Early health economic modelling could provide a mechanism for early assessment of new health technologies. Its acceptance and utility will depend on the environment and context within which it is undertaken, but minimising uncertainty, generation of real-world evidence and informing risk share agreements stand out as areas of greatest potential. Wider collaboration with stakeholders and payers, early health economic modelling could be instrumental in bridging the gap from laboratory to patient access in a more seamless way.

This thesis examined issues pertaining health economic modelling of oncology therapies. It found that the generic EQ-5D QoL instrument adequately captures QoL impacts of newer oncology therapies. However, there is a need for the development of drug-specific instruments that can capture QoL for relevant irAEs. It also revealed that reassessment of cost-effectiveness is feasible as clinical trial data often present premature survival data and the drug comparator prices can change. In that respect, it is recommended that payers develop policies to ensure that in the long term, they do not overpay for new drugs, especially when the comparator loses patent protection. To this end, companies are encouraged to make IPD available as this would strengthen the confidence in health economic modelling. Moreover, validation of clinical trial data can be undertaken using real world claims data, but further improvements can be made from the governments side by granting access to more than 10% of the PBS script data and enable linkage with MBS data and other outcomes datasets. Finally, this research found that a vast majority of all stakeholders agree that health economic modelling is useful for reimbursement of oncology therapies, but there are still many challenges, which points to areas of future research and continued training opportunities. As such, universities and health economic societies should be encouraged to cover this gap by setting up short courses and host conferences in this field and the government and academics would benefit from publishing reports on methodological advances on an ongoing basis, similar to what the UK NICE does.

The issue of providing patient access to new cancer therapies is complex.

There is a push towards earlier reimbursement by patients and clinicians with a promise of life-extending or even curative therapies motivated by a well-resourced pharmaceutical industry.

The issue of providing patient access to new cancer therapies is complex with more targeted therapies being investigated in smaller populations. This has the potential to lead to more uncertainty with respect to cost-effectiveness. Moreover, there is a shift away from the concept of single HTA resulting in a one-off funding decision towards reassessments and initial coverage under the expectation that companies provide updated clinical data.

Cooperation among all parties and generation of better data are needed to ensure that patients get timely access to improved cancer treatments. This includes agreeing on methods and data requirements that allow for early access, re-analysis of IPD, and price adjustments. The alternatives are delayed or bad decisions, both unfavourable to everyone. The aim is to get a right decision that optimises benefits to patients, sustainable funding for payers and return of investment for industry.

This work highlights the importance of health economic modelling when assessing of oncology therapies. There is a need for increased research in this area to aid drug developers, drug sponsors, policy makers and payers as the burden of cancer continues to increase. Currently, access to new therapies is delayed due to uncertainty surrounding cost-effectiveness. An important way forward is through early HTA that will help guide study design and identify potential issues up front. In addition, collaboration among key stakeholders, including with the private sector, is desirable to ensure timely access for patients.

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Appendix 1

	Drug	Dispensed price maximum amount in public hospitals
	L01AA - Nitrogen mustard analogues	
1	Bendamustine	$1700.92
2	Chlorambucil	$135.34
3	Cyclophosphamide	$155.71
4	Ifosfamide	$282.92
5	Melphalan	$64.03
	L01AB - Alkyl sulfonates	
6	Busulfan	$78.11
	L01AD - Nitrosoureas	
7	Carmustine	$14,288.65
8	Fotemustine	$1847,78
	L01AX - Other alkylating agents	
9	Temozolomide	$610.30
	L01BA - Folic acid analogues	
10	Methotrexate	$39.50
11	Pemetrexed	$187.44
12	Pralatrexate	$4,446.28
13	Raltitrexed	$1129.12
	L01BB - Purine analogues	
14	Cladribine	$1126.72
15	Fludarabine	$149.96
16	Mercaptopurine	$380.30
17	Tioguanine	$193.38
	L01BC - Pyrimidine analogues	
18	Azacitidine	$2192.54
19	Capecitabine	$79.27
20	Cytarabine	$884.28
21	Fluorouracil	$125.28
22	Gemcitabine	$149.33
23	Trifluridine+tipiracil	$3932.70
	L01CA - Vinca alkaloids and analogues	
24	Vinblastine	$159.62
25	Vincristine	$104.12
26	Vinorelbine	$157.18
	L01CB - Podophyllotoxin derivatives	
27	Etoposide	$279.78
	L01CD - Taxanes	
28	Cabazitaxel	$1032.44
29	Docetaxel	$182.76
30	Nanoparticle albumin-bound paclitaxel	$1116.09
31	Paclitaxel	$160.76
	L01CE - Topoisomerase 1 (TOP1) inhibitors	
32	Irinotecan	$151.28
33	Topotecan	$118.36
	L01DB - Anthracyclines and related substances	
34	Doxorubicin	$137.43
35	Doxorubicin hydrochloride (as pegylated liposomal)	$893.76
36	Epirubicin	$166.53
37	Idarubicin	$265.74
38	Mitozantrone	$178.88
	L01DC - Other cytotoxic antibiotics	
39	Bleomycin	$208.43

	L01XA - Platinum compounds	
40	Carboplatin	$157.26
41	Cisplatin	$176.25
42	Oxaliplatin	$145.50

Appendix 2

	Drug	Dispensed price maximum amount in public hospitals
	L01EA - BCR-ABL tyrosine kinase inhibitors	
1	Dasatinib	$4275.74
2	Imatinib	$937.89
3	Nilotinib	$5056.76
4	Ponatinib	$6172.87
	L01EB - Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors	
5	Afatinib	$2885.22
6	Erlotinib	$932.97
7	Gefitinib	$926.67
8	Osimertinib	$7971.22
	L01EC - B-Raf serine-threonine kinase (BRAF) inhibitors	
9	Dabrafenib	$7524.62
10	Encorafenib	$7033.72
11	Vemurafenib	$7033.78
	L01ED - Anaplastic lymphoma kinase (ALK) inhibitors	
12	Alectinib	$6814.30
13	Brigatinib	$6814.30
14	Ceritinib	$7289.52
15	Crizotinib	$6933.11
16	Lorlatinib	$7289.52
	L01EE - Mitogen-activated protein kinase (MEK) inhibitors	
17	Binimetinib	$7395.44
18	Cobimetinib	$7395.44
19	Trametinib	$7524.62
	L01EF - Cyclin-dependent kinase (CDK) inhibitors	
20	Abemaciclib	$4249.07
21	Palbociclib	$4249.07
22	Ribociclib	$5521.23
	L01EG - Mammalian target of rapamycin (mTOR) kinase inhibitors	
23	Everolimus	$1737.00
	L01EH - Human epidermal growth factor receptor 2 (HER2) tyrosine kinase inhibitors	
24	Lapatinib	$2932.36
	L01EJ - Janus-associated kinase (JAK) inhibitors	
25	Ruxolitinib	$4911.22
	L01EK - Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors	
26	Axitinib	$4949.22
	L01EL - Bruton's tyrosine kinase (BTK) inhibitors	
27	Acalabrutinib	$8218.96
28	Ibrutinib	$11672.27
	L01EM - Phosphatidylinositol-3-kinase (Pi3K) inhibitors	
29	Idelalisib	$5378.97
	L01EX - Other protein kinase inhibitors	
30	Cabozantinib	$9961.22
31	Entrectinib	$7289.52
32	Lenvatinib	$9626.23
33	Midostaurin	$20413.00
34	Nintedanib	$3398.82
35	Pazopanib	$4462.14

36	Sorafenib	$5556.88
37	Sunitinib	$5933.40

Appendix 3

Informed consent

The burden of cancer in Australia is large and growing. Recent years have witnessed a shift to more targeted therapies and novel agents that activate the immune system to fight cancer. These new agents show great promise in terms of clinical benefits, but are expensive.

This study seeks to gather feedback from stakeholders regarding the health economic evaluation of cancer treatments.

It will form part of a PhD project by Hansoo Kim under the supervision of Professor Stephen Goodall and Professor Danny Liew (main supervisor). The survey will take less than 10 minutes to complete. Thank you.

Please contact Hansoo Kim (hansoo.kim@monash.edu) or Danny Liew (danny.liew@monash.edu) if you have any questions.

Mandatory consent form:

I agree to take part in the Monash University project specified above. I have read the Explanatory Statement, which I keep for my records. I understand that my participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw at any stage of the project without being penalised or disadvantaged in any way. I understand that any data extracted for use in reports will not, under any circumstances, contain names or identifying characteristics. I understand that any information I provide is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project, or to any other party. I understand that reports will be kept in a secure storage and accessible to the researchers only.

- ○ Yes I consent
- ○ No I do not consent

Demographics

The survey will take less than 10 minutes and has 9 sections:

1. Background demographic questions
2. General statements on cost effectiveness of oncology treatments
3. Clinical claim
4. Extrapolation
5. Quality of life
6. Costs and health resource utilisation

7. Agreements
8. Decision making
9. Capacity/capabilities

1. Background demographic questions

Primary sector

- ○ Academia
- ○ Consultant
- ○ Government: Department or Ministry of Health
- ○ Pharmaceutical industry
- ○ Other

Years of experience

Current position

- ○ Leadership position (e.g. director, head of a department)
- ○ Managerial position (e.g. team lead: people reporting to you)
- ○ Non-managerial position (e.g. evaluator, health economist, statistician)
- ○ Other

Highest academic degree

- ○ Bachelor degree (e.g. BSc)
- ○ Master degree (e.g. MBA, MPH, MSc)
- ○ PhD degree
- ○ Other

Main qualification

- ○ Biology
- ○ Economics
- ○ Medical science
- ○ Medicine
- ○ Pharmacy
- ○ Psychology
- ○ Science (e.g mathematics, statistics)
- ○ Other

General questions on cost-effectiveness of oncology treatments

2. General questions on the cost effectiveness of oncology treatments.

Please indicate level of agreement for each statement:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Clinical claim is a major source of uncertainty	○	○	○	○	○	○
Extrapolation method is a major source of uncertainty	○	○	○	○	○	○
Quality of life is a major source of uncertainty	○	○	○	○	○	○
Costs and health resource utilization are major sources of uncertainty	○	○	○	○	○	○

Clinical claim

3. A clinical superiority claim often form the basis for cost effectiveness analysis. In oncology it is sometimes not possible to obtain perfect head to head evidence for various reasons and so other sources must be used for health technology assessment.

Please indicate level of agreement with the following statements:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Clinical superiority needs to be clearly demonstrated in a head-to-head trial	○	○	○	○	○	○
Minimal clinical important difference is not relevant for superiority claims	○	○	○	○	○	○
Clinical superiority claimed on surrogate endpoints leads to major uncertainty	○	○	○	○	○	○
Statistical superiority (as opposed to clinical superiority is sufficient in most instances	○	○	○	○	○	○

Rank the preferred data sources in absence of head-to-head clinical trial data (1=best,...,6=worst)

Local registry (e.g. established hospital registries)

Historical published data

Observational individual patient data on file (e.g. chart reviews)

Drug claims data (e.g. 10% PBS sample, HIRA claims data)

Propensity adjusted data (from any source)

Single arm clinical trials (e.g. phase I trials)

Extrapolation

4. Extrapolation of survival curves is often an integral part of the health economic modelling of oncology treatments.

Please indicate level of agreement with the following statements:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Extrapolation is a black box and easily manipulated in either direction	○	○	○	○	○	○
Graphical check of survival curves and Akaike or Bayesian Information Criteria are sufficient to justify extrapolation methods	○	○	○	○	○	○
Methods that give a perfect fit such as spline techniques are preferred over probability distributions.	○	○	○	○	○	○
The Kaplan-Meier curve should be used for parts of the modelling time period	○	○	○	○	○	○
Survival curves should converge after a period of time	○	○	○	○	○	○
It is reasonable to assume that patients who have not progressed after a long period of time are cured	○	○	○	○	○	○
The time horizon of the model should be no longer than 10 years	○	○	○	○	○	○
External validation of extrapolation methods are often inadequate	○	○	○	○	○	○
Access to individual patient data would be helpful for validation of the extrapolation	○	○	○	○	○	○

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
There is enough guidance in the local pharmaco-economics guidelines with respect to extrapolation	○	○	○	○	○	○

Quality of life

5. We would now like you to focus on quality of life.

Rank the following QoL instruments for use in cost effectiveness analysis (1=best,...,4=worst)

Disease specific instrument (e.g. QLU-C10D)

Soliciting utilities using standard gamble or time trade off methods

Generic instruments (e.g. EQ-5D)

Mapping of non-utility instruments to utility instruments

Rank source of QoL evidence (1=best,...,3=worst)

Measured directly in clinical trial

From literature

Obtained from separate study

Validation of utilities is not important in terms of cost effectiveness analysis

- ○ Strongly disagree
- ○ Somewhat disagree
- ○ Neither agree nor disagree

- ○ Somewhat agree
- ○ Strongly agree
- ○ Don't know

Surveys using proxies such as physicians and healthy people are appropriate for oncology modelling purposes

- ○ Strongly disagree
- ○ Somewhat disagree
- ○ Neither agree nor disagree
- ○ Somewhat agree
- ○ Strongly agree
- ○ Don't know

Estimation of costs and health resource utilisation

6. We would now like you to consider health care costs and resource utilisation

Please indicate level of agreement for each statement:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
The duration of treatment is a major source of uncertainty	○	○	○	○	○	○
Post-progression treatment or subsequent lines of therapy should always be taken into account in oncology cost effectiveness analysis	○	○	○	○	○	○
Treatment of adverse events and toxicity are major sources of uncertainty in cost effectiveness analysis of new oncology therapies	○	○	○	○	○	○

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Treatment beyond progression is a major concern with respect to cost effectiveness analysis of oncology treatments	○	○	○	○	○	○
Palliative costs and/or best supportive care costs should be included	○	○	○	○	○	○
Different discount rates should be used for costs and outcomes (e.g. higher discount rate for costs than for benefits)	○	○	○	○	○	○

Agreements and arrangements

7. Financial and risk share agreements are common in relation to reimbursement of oncology treatments.

Please indicate level of agreement for each statement:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Financial agreements (e.g. price/volume agreements) are necessary to ensure cost effectiveness of oncology treatments	○	○	○	○	○	○
Rebates (e.g. special pricing arrangements) are good tools for reaching agreement between a payer and a pharma company	○	○	○	○	○	○

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Outcomes based risk share agreements are good in theory but difficult to implement in practice	○	○	○	○	○	○
Managed entry schemes or coverage with future evidence schemes are good tools for granting access to therapies with limited data	○	○	○	○	○	○
Review of cost effectiveness is useful to assess value for money	○	○	○	○	○	○
Risk share agreements are not balanced and often result in too much risk for either the payer or pharma company	○	○	○	○	○	○

Decision making

8. There are many factors relating to decision making. This section seek to get a better understanding of your experiences with health technology assessments of oncology treatments.

Please indicate level of agreement for each statement:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
Evidence requirements for oncology therapies are higher than for other therapeutic areas	○	○	○	○	○	○
Cost effectiveness analysis of oncology therapies are often black boxes	○	○	○	○	○	○

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
The opinion of patient advocates play an important role in informing cost effectiveness	○	○	○	○	○	○
More public transparency is needed surrounding reimbursement decisions of oncology therapies	○	○	○	○	○	○
The ICER threshold for cost effectiveness of oncology therapies is on average higher than for other therapeutic areas	○	○	○	○	○	○
HTA and cost effectiveness analysis are good tools for determining reimbursement of oncology therapies	○	○	○	○	○	○
Alternative funding methods such as a cancer fund in the UK would be more appropriate than current reimbursement practice in my country	○	○	○	○	○	○
The reimbursement process is too long	○	○	○	○	○	○

Capability and capacity

9. This last section will focus on capability and capacity of assessing and performing cost effectiveness analysis of oncology treatments.

Please indicate level of agreement for each statement:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	Don't know
I am comfortable with my technical level in terms of cost effectiveness analysis	○	○	○	○	○	○
My organisation have plenty of capacity to deal with methodological issues	○	○	○	○	○	○
Continued training opportunities in cost effectiveness analysis are scarce	○	○	○	○	○	○
I prefer web-based training that I can do in my own time	○	○	○	○	○	○

My primary source of methodological advances are (1=best,..., 7=worst)

The peer reviewed literature

Courses (e.g. short course at universities)

Attending conferences

Discussion with peers

Guideline updates

On the job learning

Seminars/workshops by professional bodies (e.g. AHES, ISPOR)