

Tumour-agnostic immunotherapy for rare and uncommon cancers

The patient's dilemma

Robert Tindle

EIGHT Therapeutic Goods Administration (TGA)-approved immune checkpoint inhibitor (ICI) drugs are licensed for cancer immunotherapy, three of which, namely pembrolizumab (Keytruda, Merck), ipilimumab (Yervoy, Bristol-Meyers Squibb) and nivolumab (Opdivo, Bristol-Myers Squibb) are listed on the Pharmaceutical Benefits Scheme (PBS), predominantly for common cancers. Approximately 40% of all cancer deaths (25,000 patients per annum in Australia) are caused by the group of approximately 200 rare and less common cancers (RLCs).^{1,2}

PBS listing of ICI drugs for RLCs has been confounded by the Pharmaceutical Benefits Advisory Committee (PBAC) requirement of demonstration of efficacy of each new drug for each cancer type in Phase 3 trials, a criterion that cannot be met by the low frequency of individual RLC types.

Drug manufacturers ask high prices for the supply of ICI drugs, which the Federal Government is reluctant to pay. RLC sufferers for whom all conventional therapies have failed are caught in the stalemate between the PBAC and pharmaceutical companies over pricing and evidentiary requirements. These patients can expect to pay A\$135,000 for a single course of an ICI drug,³ approximately 1000-fold more than the PBS-subsidised price charged for the same drug to a patient with a common cancer.

Homes are remortgaged, businesses are sold, retirement savings are spent and superannuation is cashed in to pay for the ICI drug. The family might never recover.⁴⁻⁷

Although there is evidence that deaths can be prevented or suffering ameliorated with ICIs, the drug(s) might not work for a given patient because there is response variability not only between cancer types, but also between patients with the same cancer type.⁸

Those with an RLC struggle with guilt over the financial and emotional turmoil their disease brings to their families, with one RLC patient asking 'How much is my life really worth?' (Danielle Tindle, neuroendocrine carcinoma, pers. comm., 2015).

PBS listings are too specific in some cases. Thus, the PBS approves ICIs for clear cell renal cell carcinoma (RCC) but not non-clear cell RCC, even though the drug works for all subtypes.⁹ Initiatives to define tumour type not by site of origin or histology but by genetic profile further muddy the waters; even histologically identical tumours arising at the same anatomical site might not be genetically identical.^{10,11}

History

The cancer immunotherapy revolution took off in 2011 when the US Food and Drug Administration (FDA) licensed ipilimumab, improving the survival of patients with late-stage melanoma refractory to conventional therapies.¹² As later Phase 3 clinical trial data emerged, approval was

extended to other common cancer types. Nivolumab, for example, is now approved to treat approximately eight common tumour types alone or in conjunction with ipilimumab.¹³ In Australia, each of these drugs was initially approved by the TGA and PBAC for government subsidy via the PBS for a single common cancer type. Clinicians now use ICIs as single agents or combined with chemotherapies, surgery or tumour-specific vaccines as first- or second-line treatment.¹⁴

By 2021, seven other ICI drugs were licensed.^{15,16} These pan-tumour (tumour-agnostic) agents signal an important new paradigm in clinical management in which tumour genomic signature supersedes tumour location and histology in informing treatment decisions.¹⁶

Not all cancer types have responded as well as melanoma or, more recently, non-small cell lung cancer. There is considerable response variability among different tumour types and among patients with the same tumour type. Although transient partial regressions might be achieved, a cure will be realised only for a minority of patients.¹⁶

Knowledge of RLC patient outcomes is incomplete because of inconsistency in data collection.²

Some cancers have evolved mechanisms for avoiding attacks through ICI pathways; some respond less well to ICIs than to standard therapies.^{17,18} Only 10-20% of patients treated might obtain clinical benefit. Genome sequencing might identify genetic signatures that are

associated with tumour susceptibility to ICIs, allowing future prediction of those patients likely to respond.¹⁹ That, plus multiorgan autoimmune adverse events associated with non-specific immune activation caused by ICI drugs, might indicate high-quality palliative care as a better option in some cases.²⁰

The PBS currently spends A\$14.7 billion per annum subsidising drugs for various diseases.²¹ When considering a new immunotherapy drug for subsidy, the PBAC deliberates what it will cost the Federal Government to buy it from the pharmaceutical manufacturer and how effective the drug is compared with existing therapies. With many demands on a limited healthcare budget, cost-effectiveness to the overall population is best served by subsidising the most common cancers individually rather than individual RLCs. For RLCs, the PBAC has been found wanting.

The pharmaceutical companies defend the high purchase prices they propose, citing expenditure on drug development costs, expensive Phase 3 trials and costs incurred complying with TGA and PBAC submission requirements.²² The asking price is also influenced by what profit margin the companies can sustain internationally. Ultimately, registration for RLCs relies on the willingness of pharmaceutical companies to invest in new drugs; they hesitate to spend in the small markets, which individual RLCs provide. Furthermore, they criticise the PBAC for setting the bar too high by insisting that a company demonstrates the efficacy of a new drug for each individual cancer type, this stipulation being a hangover from the *National Health Act 1953*, in which legislation on drug subsidy is embedded.

In 1983, the US government passed the *Orphan Drug Act* to give drug companies certain financial benefits for developing orphan (ie rare disease) drugs. This law is meant to help bring more drugs to patients with rare diseases.

Clinical trials and costing

Enrolling in a clinical trial to access an immunotherapeutic for their cancer has not been an option for most patients

with an RLC. Although multicountry randomised trial data have secured PBS subsidy for the uncommon cancers, gastrointestinal stromal tumour, chronic myeloid leukaemia and gall bladder cancer,²³ no such trials have been conducted for most of the approximately 200 RLC types. In 2018 there were

roughly 10-fold fewer clinical trials for all RLCs than for common or advanced common cancers.²

There is a call for more innovative trials with more flexible inclusion criteria.²⁴

In collaboration with Big Pharma, Australia has proposed to 'bolt on' rare cancers to trials of common cancers

Box 1. Recommendations for drug agencies, pharmaceutical companies and governments to expedite affordable access to novel immunotherapies for sufferers of rare and less common cancers

- Allow flexible approaches within existing legislative frameworks to gain access to medicines for RLC.
- TGA and PBAC to simplify and streamline the listing of drugs for RLC cancer, where the RLC is already approved in jurisdictions overseas (FDA or European Medicines Agency).
- TGA and PBAC to accept multi-indication submissions for RLC therapy.
- PBAC to acknowledge the molecular perspective that ultimately ALL cancers are potential RLCs and to frame evidentiary requirements accordingly.^{10,11,16}
- PBAC to acknowledge more deeply the RLC patients' concerns regarding the affordability of new cancer immunotherapies (Danielle Tindle, neuroendocrine carcinoma, pers. comm., 2015).³⁻⁷
- PBAC to accommodate evidence from animal clinical sciences into its decision-making.
- PBAC to consider a provisional listing of drugs for RLCs pending definitive evidence-based formal listing in a process incorporating risk-share arrangements and managed-access schemes.
- PBAC to review the cost imposed on Big Pharma to make a submission for subsidy of a new drug.
- Big Pharma to use multi-indication submissions to proactively seek registration and PBAC-recommended subsidy for rare cancers. Data from patients who have used managed-access and risk-sharing schemes for drug access might be used.
- Big Pharma to price its medicines in Australia irrespective of what the company charges in the unregulated pricing environment of the USA, its primary market.
- Big Pharma to establish clarity in their compassionate access schemes.
- Encourage investigator-led local RLC clinical trials designed with flexible criteria to include several 'lumped' RLC cancer types and different drugs in different arms to provide data to support TGA listing and subsequent PBS listing.²⁶
- Dedicated Governmental and Big Pharma funding for local RLC clinical trials.²²
- Expand global clinical trials to include 'bolt-on' RLC cancer types in a TRICEPS (Treat Rare Collect data and share) rare solutions approach.²
- Design clinical trials to incorporate a 'work-around' to take into account the potential exclusion of patients because of previous treatments.
- Establish a national framework for RLC cancers, which includes physicians, researchers, patient groups, Pharma and government, to allow access by patients and their managing physicians and define standards and best-management practices.²
- Establish a centralised database of all RLC cancer incidence and outcomes (building on the REDcap Rare Cancer Database), which can be interrogated nationally and internationally.²
- Equity in research funding for RLCs.²⁷
- Equity for support services for RLC patients.
- Raise the profile of RLCs among the news media and high-profile celebrities whose social media pronouncements on common cancers bias the public's inclination regarding where to donate its cancer charity dollars.

Big Pharma, major pharmaceutical companies; FDA, US Food and Drug Administration; TGA, Therapeutic Goods Administration; PBAC, Pharmaceutical Benefits Advisory Committee; RLC, rare and less common cancers.

with similar genetic signatures or to 'lump' several RLC types displaying the same genetic signature together.² The Federal Government's Clinical Trials Activity initiative provides A\$750 million over 10 years between 2022–23 and 2031–32 to increase clinical trial activity, particularly addressing rare diseases, including RLCs.²⁵ The initiative includes bringing investigator-led international clinical trials to Australia.²² The International Rare Cancers Initiative functions as the main global platform for achieving new international clinical trials in rare tumours.²⁶

For use in the UK's National Health Service (NHS), ICI drugs are considered with less mature clinical trial data on their effectiveness than in the past. In addition, there is a recognition that clinical trials, although essential to proving a drug's safety and efficacy, might not always reflect a drug's benefit to patients in a clinical setting. Greater emphasis is now placed on real-world treatment outcomes data to agree on a price that better reflects the drug's true benefit to NHS patients. If a drug is deemed not cost-effective at the price initially proposed by the manufacturer, the Voluntary Pricing and Access Scheme, an agreement between the UK Government's Department of Health and the pharmaceutical industry, can negotiate

a different pricing arrangement with the manufacturer, often a simple percentage discount on the medicine's price.

Because Australia is responsible for only 2% of the global pharmaceutical spend, it has little negotiating clout with the international pharmaceutical industry over drug pricing.

An urgency to bring new drugs to patients as early as possible while evidentiary data are still incomplete, plus the uncertain costs of manufacturing complex new drugs foment uncertainty about what a government should pay. More flexible ways for price setting are necessary. Various outcome-based payment models link the price the NHS pays for a drug to the outcomes the drug achieves in practice. These models include manufacturer rebates or refunds if the medicine fails to meet pre-agreed outcome targets for individual patients. Conversely, if a drug is subsequently proven to have clinical value, the manufacturer can renegotiate a price increase. In effect, the patient with an RLC has a safety net; if the drug that costs them so much does not work for them, they get their money back, in whole or in part.

Today, in Australia, many RLC patients must pay approximately A\$8000 each time they visit the oncology clinic for their ICI injection. There is little

chance of recompense; pharmaceutical company 'compassionate access schemes' are notoriously unreliable and non-transparent, hospital and hospital foundation funds are overstretched, any financial help from charities is transient and crowd-funding soon dries up (Box 1).

RLC research

Common cancers get most of the research and new treatments because they drain the public purse. Government funding in Australia has increased for cancer research, but mainly for common cancers. Of the A\$400 million spent annually in Australia, only a negligible proportion goes to RLCs.²⁷ Cancer researchers follow the money and gravitate towards common cancers to survive in their careers. Accordingly, many influencers on research grant awarding committees have backgrounds in common cancers. A Medical Research Future Fund funding initiative started in 2021 with rare cancers as a priority will help redress these balances.²⁸ Cancer survival is directly related to research funding.²⁹ The lack of funding for RLCs extends beyond the clinic and research laboratories into policy and services for those diseases.

Over the past two decades, there has been improvement in treatment for all types of cancer, but improvement for RLCs is less than for common cancers, and the gap continues to widen.² Diagnosis is slower for RLCs, and misdiagnosis is common. RLC patients might encounter a lack of clinical expertise or receive 20-year-old treatments.

Call to action

Managing physicians must navigate all this if they are to broach ICI therapy to a family already shouldering the turmoil of the impending death of a loved one. The likelihood of a positive outcome given the current data, how the subsidising landscape might change during a putative extended survival and the impending results from ongoing clinical studies of combinations of ICIs and other interventions all need to be communicated (Box 2).

Box 2. Note to the patient: 12 questions for your GP/oncologist

1. Why are you recommending this immunotherapy drug for me? Why is it preferable to other drugs, including those we have already tried?
2. What does this treatment do, exactly? How well does it usually work for my type of cancer?
3. What is the evidence for its effect on my cancer type?
4. How many immunotherapy drugs are available for my cancer? Can we try several together?
5. Can the immunotherapy drugs be combined with other forms of treatment?
6. What are the risks and side effects of this treatment?
7. What is the cost of this immunotherapy drug? Is it available on the PBS?
8. How can I get help paying for the treatment if I cannot afford it?
9. Are there clinical trials of this drug in which I am eligible to enrol?
10. How long will I need this treatment?
11. What should I expect from the treatment itself? How long before I'll see a response?
12. Suppose it doesn't work, what then?

Note: An easy-to-read guide to immunotherapy for cancer can be found at www.cancercenter.com/treatment-options/precision-medicine/immunotherapy

GP, general practitioner; PBS, Pharmaceutical Benefits Scheme.

The future

Government health budgets will ultimately be overwhelmed by a plethora of new drugs vying for subsidy, the fruits of burgeoning new technologies and expertise. Thus, advocacy must be sustained to seek ways of making unsubsidised novel medicines affordable. Formalised arrangements with megaphilanthropy might help in the short term.³⁰

It is a sad commentary on society that the fruits of brilliant biomedical research, ultimately paid for by public money, are becoming unaffordable to most people who need them.

Author

Robert Tindle PhD, Emeritus Professor in Immunology, University of Queensland, Faculty of Science, Brisbane, Qld; Director (Retired), Sir Albert Sakzewski Virus Research Centre, Royal Children's Hospital, Brisbane, Qld; Director, Clinical Medical Virology Centre, University of Queensland, Brisbane, Qld

Competing interests: None.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Correspondence to: r.tindle@uq.edu.au

References

1. Australian Institute of Health and Welfare (AIHW). Cancer in Australia 2017. Cancer Series no. 101. AIHW, 2017. Available at www.aihw.gov.au/getmedia/3daf13c2-30f0-4475-8aed-1f19f8e16d48/20066-cancer-2017.pdf.aspx?inline=true [Accessed 1 August 2023].
2. Rare Cancers Australia. Rare solutions, a time to act. Rare Cancers Australia, 2023. Available at www.rarecancers.org.au/page/144/rare-solutions-a-time-to-act [Accessed 1 August 2023].
3. Pearce IP. Reimbursement for Keytruda® (pembrolizumab) expanded. Pearce IP, 2022. Available at www.pearceip.law/2022/09/26/reimbursement-for-keytruda-pembrolizumab-expanded/ [Accessed 1 August 2023].
4. Merck Sharp & Dohme Corp. Australians with a rare form of bowel cancer will have access to KEYTRUDA® (pembrolizumab) on the PBS from 1 August 2021. MSD, 2021. Available at www.msd-australia.com.au/news/keytruda-listed-for-patients-with-a-rare-form-of-bowel-cancer/ [Accessed 8 October 2023].
5. Rare Cancers Australia. Rare Cancers Australia welcomes life-saving investment in genomic testing and clinical trial development for cancer patients. Rare Cancers Australia, 2022. Available at www.rarecancers.org.au/news/429/rare-cancers-australia-welcomes-life-saving-investment-in-genomic-testing-and-clinical-trial-development-for-cancer-patients [Accessed 8 October 2023].
6. Ross C. A new cancer care dilemma: Patients want immunotherapy even when evidence is lacking. STAT, 2018. Available at www.statnews.com/2018/06/04/cancer-care-dilemma-immunotherapy/ [Accessed 8 October 2023].
7. Perillo S. Leukaemia and blood cancer patients sell houses, cars to pay for treatment. Herald Sun, 2023. Available at www.heraldsun.com.au/news/victoria/leukaemia-and-blood-cancer-patients-sell-houses-cars-to-pay-for-treatment/news-story/8fc968be67a718d178b2c5ff39f44457 [Accessed 8 October 2023].
8. Chitsike L, Duerksen-Hughes P. The potential of immune checkpoint blockade in cervical cancer: Can combinatorial regimens maximize response? A review of the literature. *Curr Treat Options Oncol* 2020;21(12):95. doi: 10.1007/s11864-020-00790-4.
9. Díaz-Montero CM, Rini BI, Finke JH. The immunology of renal cell carcinoma. *Nat Rev Nephrol* 2020;16(12):721-35. doi: 10.1038/s41581-020-0316-3.
10. Harris TJR, McCormick F. The molecular pathology of cancer. *Nat Rev Clin Oncol* 2010;7(5):251-65. doi: 10.1038/nrclinonc.2010.41.
11. Rare Cancer Genomics. Multidisciplinary and multi-omics characterisation of rare cancers. Rare Cancer Genomics, 2019. Available at <https://rarecancersgenomics.com/> [Accessed 1 August 2023].
12. Chapman PB, D'Angelo SP, Wolchok JD. Rapid eradication of a bulky melanoma mass with one dose of immunotherapy. *N Engl J Med* 2015;372(21):2073-74. doi: 10.1056/NEJMc1501894.
13. Drugs.com. Nivolumab (Monograph). Drugs.com, 2023. Available at www.drugs.com/monograph/nivolumab.html [Accessed 6 August 2023].
14. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, Phase 3 trial. *Lancet Oncol* 2021;22(2):198-211. doi: 10.1016/S1470-2045(20)30641-0.
15. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996;271(5256):1734-36. doi: 10.1126/science.271.5256.1734.
16. Looney AM, Nawaz K, Webster RM. Tumour-agnostic therapies. *Nat Rev Drug Discov* 2020;19(6):383-84. doi: 10.1038/d41573-020-00015-1.
17. Passaro A, Brahmer J, Antonia S, Mok T, Peters S. Managing resistance to immune checkpoint inhibitors in lung cancer: Treatment and novel strategies. *J Clin Oncol* 2022;40(6):598-610. doi: 10.1200/JCO.21.01845.
18. Chowell D, Yoo SK, Valero C, et al. Improved prediction of immune checkpoint blockade efficacy across multiple cancer types. *Nat Biotechnol* 2022;40(4):499-506. doi: 10.1038/s41587-021-01070-8.
19. Garvan Institute. MoST clinical trials. Garvan Institute, [date unknown]. Available at www.garvan.org.au/research/genomic-cancer-medicine-program/molecular-screening-clinical-trials [Accessed 1 August 2023].
20. Okiyama N, Tanaka R. Immune-related adverse events in various organs caused by immune checkpoint inhibitors. *Allergol Int* 2022;71(2):169-78. doi: 10.1016/j.alit.2022.01.001.
21. Australian Government, Department of Health and Aged Care. PBS expenditure and prescription report 1 July 2021 to 30 June 2022. Australian Government, 2022. Available at www.pbs.gov.au/statistics/expenditure-prescriptions/2021-2022/PBS-Expenditure-and-Prescriptions-Report-1-July-2021-to-30-June-2022.PDF [Accessed 8 October 2023].
22. Emanuel EJ. Big pharma's go-to defense of soaring drug prices doesn't add up. Just how expensive do prescription drugs need to be fund innovative research? *The Atlantic*. 23 March, 2019. Available at www.theatlantic.com/health/archive/2019/03/drug-prices-high-cost-research-and-development/585253/. [Accessed 8 October 2023].
23. Australian Government, Department of Health and Aged Care. Nivolumab for the treatment of renal cell carcinoma: 24 month predicted versus actual analysis. Drug utilisation sub-committee (DUSC). Pharmaceutical Benefits Scheme, 2020. Available at www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2020-06/nivolumab-for-the-treatment-of-renal-cell-carcinoma [Accessed 8 October 2023].
24. Panageas KS. Clinical trial design for rare cancers: Why a less conventional route may be required. *Expert Rev Clin Pharmacol* 2015;8(6):661-63. doi: 10.1586/17512433.2015.1088382.
25. Australian Government, Department of Health and Aged Care. Clinical trials activity initiative. Australian Government, 2023. Available at www.health.gov.au/our-work/clinical-trials-activity-initiative?language=und22. [Accessed 8 October 2023].
26. Cancer Research UK. International rare cancer initiatives. Cancer Research UK, 2023. Available at www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/our-research-partnerships/international-rare-cancers-initiative [Accessed 8 October 2023].
27. Australian Government. Department of Health and Aged Care. Rare cancers, rare diseases and unmet need clinical trials initiative. Australian Government, 2023. Available at www.health.gov.au/our-work/rare-cancers-rare-diseases-and-unmet-need-clinical-trials-initiative [Accessed 8 October 2023].
28. Australian Government, National Health and Medical Research Council. MRFF 2022 clinical trials activity grant opportunity; Rare Cancers, rare diseases and unmet need. Australian Government, [date unknown]. Available at www.nhmrc.gov.au/funding/find-funding/mrff-2022-clinical-trials-activity-grant-opportunity-go5887 [Accessed 8 October 2023].
29. Hall BR, Cannon A, Atri P, et al. A comparative analysis of survival and funding discrepancies in cancers with high mortality. *Ann Surg*. 2020;271(2):296-302. doi: 10.1097/SLA.0000000000003042.
30. Schmitz HP, McCollim EM. Billionaires in global philanthropy: A decade of the giving pledge. *Society* 2021;58(2):120-30. doi: 10.1007/s12115-021-00580-0.

correspondence ajgp@racgp.org.au