RADIO: Rational Dose ImmunOtheraphy

Project Impact

Imagine if immunotherapy was affordable enough to be available to everyone who might benefit…? The RAtional Dose ImmunOtherapy (RADIO) trial will prove that a much lower dose of nivolumab anti-PD1 immunotherapy is effective and helpful for people with rare kidney cancers.

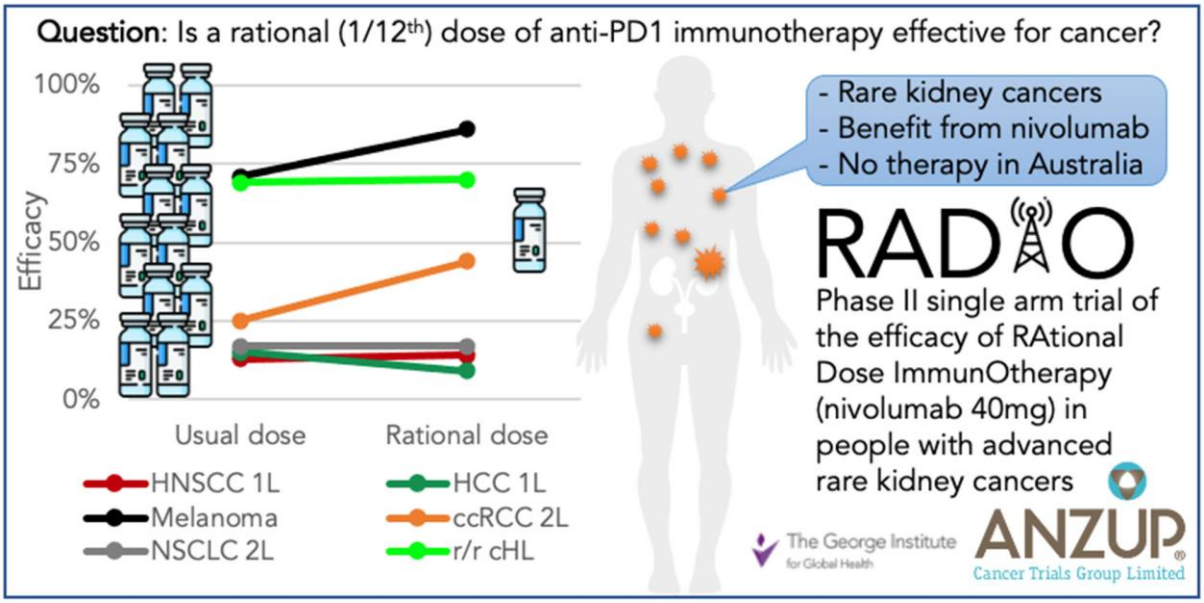

***Figure 1**. Overview of the RADIO clinical trial.*

Problem: Many people with rare or uncommon advanced cancers lack treatment options due to a lack of reimbursement for expensive novel cancer treatments.

Context: Antibodies targeting programmed-death-1 (anti-PD1 immunotherapy) such as nivolumab have revolutionised cancer therapy, potentially curing some people across diverse cancer types. ANZUP has previously shown that nivolumab helps some people with rare kidney cancers, metastatic non-clear cell renal cell carcinoma (nccRCC). Nivolumab and other anti-PD1 antibodies are prescribed at doses well in excess of the dose required for their therapeutic effect. Many reports suggest a "rational" lower dose of nivolumab may be just as effective. Proving this prospectively would make nivolumab immunotherapy much more affordable and allow us to help more people.

Hypothesis: Rational dose nivolumab (40mg, one vial, 1/12th 'usual' dose) has comparable efficacy to historical outcomes of usual dose nivolumab in nccRCC.

Aim: To conduct a phase II single arm clinical trial of RAtional Dose ImmunOtherapy (RADIO) with nivolumab 40mg 4-weekly in people with metastatic nccRCC, primary objective of efficacy

(endpoint: progression-free survival at 6 months [PFS6]), secondary objectives of safety (toxicity as per CTCAEv5), health-related quality-of-life, and cost-consequence economic analysis.

Impact: The RADIO study will inform and empower people with rare nccRCC (and by implication other unreimbursed cancers) to rationally consider access to more affordable immunotherapy. Future work may then re-examine 'over-dosed' reimbursed regimens, with the potential to deliver savings of hundreds of millions of dollars per annum for Australia.

Background: Kidney cancer, renal cell carcinoma (RCC) is a **rare cancer**, with approximately 4000 Australians diagnosed and 1000 dying each year of advanced or metastatic disease (incidences 16/100,000 and 4/100,000 per annum). Seventy-five percent of RCC are clear-cell renal cell carcinomas (ccRCC), where immunotherapy and anti-angiogenic targeted therapies improve patients' outcomes, but long-term survival remains rare, costs of treatment have risen sharply, and no predictive biomarker guides treatment choice. Treatment options for people with nccRCC (~1/100,000 per annum) are much more limited, as nccRCC encompasses a biologically and clinically heterogeneous group of neoplasms, and people with nccRCC are excluded from most commercial clinical trials in RCC. People with nccRCC suffer much shorter survival compared to people with ccRCC1, though there is a strong biological rationale for the use of immune checkpoint inhibition in nccRCC. There are no reimbursed treatments in Australia for people with advanced nccRCC, so clinicians must extrapolate from studies in ccRCC or rely on retrospective nccRCC data. Some prospective studies of anti-PD1 immunotherapy in nccRCC have been reported, but given the heterogeneous nature of nccRCC, it is difficult to compare between histologic subtypes of nccRCC, though they tend to show lower response rates when compared to ccRCC. The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) created and led the UNISoN clinical trial (NCT03177239), where we tested nivolumab (usual dose) for people with nccRCC. Nivolumab showed freedom from progression at 6 months (PFS6) in 45% of people, with a median duration of response of 20.7 months (95% CI 3.7-not reached).

Too much of a good thing?: Dosing schedules have been highly variable across many indications during the clinical development of nivolumab; 1mg/kg q3w, 240mg fixed dose q2w, 3mg/kg q3w, but now most often 480mg fixed dose q4w. However, the registration trial for nivolumab suggested clinical and pharmacodynamic equivalence at doses as low as 1/100th of the approved dose, while other studies suggest nivolumab has linear pharmacokinetics over a dose range of 0.1 to 10 mg/kg across multiple tumour types. For example, single dose of 20 mg nivolumab, PD-1 receptor occupancy is predicted to stay above the 90% threshold for a median of 23 days from a single 20mg dose of nivolumab. Multiple recent retrospective series suggest that much smaller doses may be just as effective as the 'usual dose' of nivolumab (Figure 2).

In particular, a recent randomised trial in people with metastatic head and neck squamous cancer (HNSCC) treated added nivolumab 20mg q3w to metronomic chemotherapy (methotrexate 15 mg/m2 PO weekly, celecoxib 200 mg PO daily and erlotinib 150 mg PO daily), improving overall survival at 12 months from 16.3% to 43.4% (HR for death 0.55; 95%CI 0.362-0.82; p=0.00358). Numerous other case reports and small series of "low-dose" nivolumab and pembrolizumab anti-PD1 immunotherapy have reported patient benefit (Figure 2), often specifically indicating that financial toxicity forced the modified dosing. **We hypothesise that rational dose nivolumab has comparable efficacy to 'usual' dose nivolumab in people with metastatic nccRCC.**

Disease	mg/wk	Endpoint	(%)	# pts	Author	Year	PMID
HNSCC 1L	6.66	ORR	14%	76	Patil	2022	36265101
HNSCC 1L	120	ORR	19%	123	*Vasiliadou*	*2021*	*33808781*
HNSCC 1L	120	ORR	13%	240	**Ferris**	**2016**	**27718784**
HCC 1L	10	ORR	9%	78	*Chen*	*2022*	*36348292*
HCC 1L	120	ORR	15%	371	**Yau**	**2022**	**34914889**
Adj melanoma	5	RFS12	86%	55	*Schwarze*	*2022*	*35158952*
Adj melanoma	120	RFS12	71%	453	**Weber**	**2017**	**28891423**
ccRCC 2L	50	ORR	44%	32	*Zhao*	*2021*	*33440374*
ccRCC 2L	120	ORR	25%	410	**Motzer**	**2015**	**26406148**
NSCLC 2L	10	ORR	17%	18	*Yoo*	*2018*	*30094065*
NSCLC 2L	200	ORR	17%	129	**Gettinger**	**2015**	**25897158**
r/r cHL	20	ORR	70%	30	*Lepik*	*2020*	*33062947*
r/r cHL	120	ORR	69%	243	**Armand**	**2018**	**29584546**

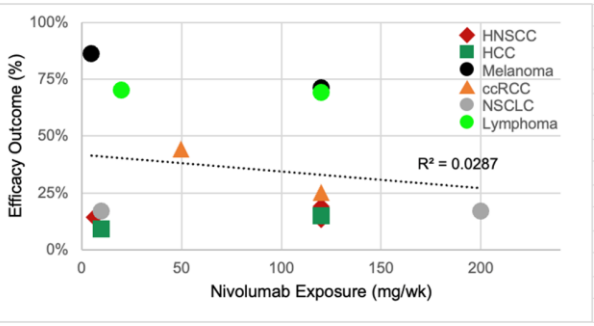

Figure 2. Nivolumab appears to deliver similar efficacy outcomes across diverse cancers with no relationship between outcome and drug exposure (mg per week). HNSCC = head and neck squamous carcinoma; HCC = hepatocellular carcinoma, ccRCC = clear cell renal cell carcinoma; NSCLC = non-small cell lung cancer; r/r cHL = relapsed/refractory Hodgkin's lymphoma; ORR = objective response rate; RFS12 = relapse-free survival at 12 months. *Retrospective case series*; **registrational phase II/III trials**.

People with rare kidney cancers, and those with other rare cancers will benefit from the results of the RADIO trial, as the study will provide prospective evidence for rationalizing the dose, and thus the cost of nivolumab anti-PD1 immunotherapy. The dose/cost will fall more than 90%, enabling individuals, families, communities, or health systems to consider funding treatment. Considerable **economic benefits** will also flow from the RADIO study. In 2021-22, the PBS recorded expenditure of Australian tax-payer funded nivolumab was $395,902,325 across all reimbursed indications incurring the third highest total cost to government of any drug treatment, with the competing anti-PD1 antibody pembrolizumab even higher, in second place at $427,247,534.Given the high cost of these therapies, the potential to reduce the dose per patient by 90% represents a significant opportunity benefit to the health care system, making those resources available for deployment elsewhere in the health care system.

RADIO draws on an existing **collaboration** of oncologists across Australia, including regional and rural locations, with demonstrated ability to recruit and care for patients in this rare cancer population, having worked together with ANZUP on the UNISON trial. RADIO also builds further collaboration between ANZUP and with The George Institute (TGI). Like ANZUP, TGI creates leading worldclass clinical trials to transform treatments for chronic and critical conditions;

working with partners, governments, and communities to address local priorities; and developing low-cost, innovative solutions that can be integrated in health systems globally; the RADIO trial will draw perfect synergy from ANZUP and TGI.

Australia's healthcare system suffers **health inequity,** and people from First Nations and culturally and linguistically diverse (CALD) communities remain less likely to be offered or recruited to clinical trials. ANZUP attempts to mitigate these fundamental social determinants of inequity by encouraging and enlisting research-engaged hospitals throughout Australia, including regional, rural and low socioeconomic status services. Deliberately diverse site selection attempts to bring ANZUP clinical trials to as broad a range of Australians as possible. Modernised **simple and comprehensible patient information materials** are now a core part of ANZUP clinical trials, further enabling inclusion.

ANZUP has established best-practice processes for **consumer engagement** through our Consumer Advisory Panel (CAP). The ANZUP CAP provides a mechanism for advice on specific studies, general research direction, and priorities from a consumer perspective. The CAP also provides a conduit for communication from ANZUP to the community to promote research and engage community support. CAP members attend and contribute to the ANZUP Board, Scientific Advisory Committee (SAC), subcommittees, and Trial Management Committees. The CAP has actively participated in the review of the RADIO trial, and development of the project plan and protocol with respect to its value, importance and impact. The proposal was discussed at the ANZUP RCC Ideas Generation Workshop in March 2023 and was well received by CAP Chair and other consumers. A statement from ANZUP CAP members:

"The RADIO study has the potential to be of great benefit to patients. A successful study would improve patients' quality of life by being able to achieve the same benefit Nivolumab offers using a lesser amount, and the lower cost could mean the difference between it being an affordable choice or financially out of reach for consumers who may already have limited or no other treatment options. I think this is a truly important study, and I am excited by the potential hope it offers to patients who may not have a lot of hope at that stage of disease and with current treatment options."

The RADIO clinical trial is **highly significant and potentially practice changing.** There are no reimbursed treatments for people with nccRCC in Australia. Most Australians are unable to self-fund the prohibitive costs of anti-PD1 immunotherapy. The RADIO trial extends upon our existing ANZUP clinical trials in nccRCC, potentially unleashing an opportunity for treatment that is affordable and effective to people with these rare cancers.