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ORIGINAL ARTICLE

Real-world experience of immune checkpoint inhibitors in patients with solid tumours in the Top End of the Northern Territory, Australia from 2016 to 2021: a retrospective observational cohort study

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Key words
immune checkpoint inhibitor, adverse drug event, Indigenous Australians, rural health, healthcare disparities.

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Abstract

Background: Use of immune checkpoint inhibitors is growing, but clinical trial data may not apply to Indigenous patients or patients living in remote areas.
Aims: To provide real-world incidence of immune-related adverse events (irAE) in the Top End of the Northern Territory and compare incidence between demographic subgroups.
Methods: This retrospective, observational, cohort study collected data from electronic records of patients living in the Top End with solid organ cancer treated with immunotherapy between January 2016 and December 2021. The primary outcome was cumulative incidence of any-grade and severe irAE. Secondary outcomes were overall survival, treatment duration and reason for treatment discontinuation.
Results: Two hundred and twenty-six patients received immunotherapy. Forty-eight (21%) lived in a remote or very remote area, and 36 (16%) were Indigenous. Cumulative incidence of any-grade irAE was 54% (122/226 patients); incidence of severe irAE was 26% (59/226 patients). Rates were similar between Indigenous and non-Indigenous patients of any-grade (42% vs 56%, $P = 0.11$) and severe (11% vs 18%, $P = 0.29$) irAE. However, Indigenous patients had shorter treatment duration, more frequently discontinued treatment due to patient preference and appeared to have shorter median overall survival than non-Indigenous patients (17.1 vs 30.4 months; hazard ratio (HR) = 1.5, 95% confidence interval (CI) = 0.92–2.66). There was no difference in mortality between remote and urban patients (median overall survival 27.5 vs 30.2 months; HR = 1.1, 95% CI = 0.7–1.7).
Conclusions: Rates of irAE in our cohort are comparable to those in the published literature. There was no significant difference in any-grade or severe irAE incidence observed between Indigenous and non-Indigenous patients.

Introduction

Immune checkpoint inhibitors (ICIs) have rapidly transformed the oncological landscape and are now used to treat patients with a wide range of malignancies. With the rising number of cancer cases in Australia[1] and expanding indications for ICI, their use will continue to grow. Because of this, the incidence of immune-related adverse events (irAE) is also expected to rise.[2]

irAE can affect any organ system and exist on a spectrum from mild clinical or laboratory observations to fatal drug reactions. While reported incidence of irAE varies greatly between different tumour types and drugs, typically around two-thirds of patients will be affected during their treatment course.[3] Early detection of irAE and initiation of

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treatment are vital to minimise drug-related morbidity and avoid premature cessation of anti-cancer treatment. Increased awareness and a collaborative approach across the healthcare system are therefore essential.

Underrepresentation of women, older adults, and ethnic minorities is a known issue in oncology clinical trials.[4] Patients who live outside major cities are also underrepresented in trials and have worse mortality outcomes than their metropolitan counterparts.[5,6] Patients living in very remote areas have the lowest 5-year observed survival of all Australian cancer patients.[1,7] This is compounded by a higher age-standardised incidence of cancer in Aboriginal and Torres Strait Islander persons, with the largest disparity seen in those living in very remote areas.[1] While ICI should be equally game-changing for Indigenous patients, there is a lack of data about the experience of ICI toxicity in this population.

This single-centre study aims to provide real-world incidence of irAE in all patients receiving ICI for solid tumours in the Top End of the Northern Territory, Australia, and to compare the frequency and severity of irAE between demographic groups by Remoteness Area and Indigenous status. We hypothesise that rates of irAE will be comparable within our population groups and in line with the published literature.

Methods

Design

This is a retrospective, observational, population-based cohort study conducted entirely through clinical health records. Therefore, it adheres to both Strengthening the Reporting of Observational Studies in Epidemiology and Reporting of Studies Conducted using Observational Routinely-collected Data statements (Supporting Information, Table 1).

Setting

The clinical records were reviewed for all patients with a solid organ cancer who received treatment with any immune checkpoint inhibitor (ICI) between 1 January 2016 and 31 December 2021 in the Top End of the Northern Territory, Australia. The Top End covers a large and sparsely inhabited area of northern Australia, comprising a population of around 175 000 people across nearly 500 000 km^2, with the majority living in urban Darwin (population 137 000 in 2016). The Top End has a larger proportion of Aboriginal and Torres Strait Islander residents compared to other jurisdictions in Australia (26.3% of the Northern Territory population, compared to 3.2% nationwide), most of whom live in remote or very remote areas.[8] Patients received anti-cancer treatment at either Royal Darwin Hospital or its satellite unit at Katherine Hospital (317 km from Darwin), with a small number of additional patients treated privately. The Human Research Ethics Committee of Northern Territory Health and Menzies School of Health Research approved this study (HREC 2022-4285).

Inclusion and exclusion criteria

Patients with a solid organ tumour who were prescribed any ICI were included, including anti-programmed cell death-1 (PD-1), anti-programmed cell death-ligand 1 (PD-L1), anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or combination anti-PD-1/anti-CTLA-4 drugs during the target period. Patients were excluded if they were primarily treated elsewhere (private setting or interstate travellers), never received the prescribed ICI or had incomplete or inaccessible medical records.

Selection procedures

Patients were identified through the health system's electronic oncology prescribing system, MOSAIQ. This was cross-referenced with pharmacy records to detect patients who received ICI from paper prescriptions during the phase-in period of MOSAIQ (January to March 2016).

Data extraction

Clinical data were extracted from MOSAIQ, paper hospital records and electronic medical records (Clinical Work Station) between April and October 2022. Extracted data items were demographic characteristics (age, sex, Indigenous status, Remoteness Area), cancer diagnosis, treatment intent and drugs received, and irAE. Indigenous status was self-reported by patients as documented in the medical record. Remoteness Area was based on postcode as per the Australian Statistical Geography Standard (ASGS); Darwin is classed as an outer regional area, so no participants live in Major cities or Inner regional areas. Patients living in remote or very remote areas are grouped in analyses as 'remote or very remote'. Grade of irAE was defined by the Common Terminology Criteria for Adverse Events Version 5.0. Data were collected from the date of tissue diagnosis until the date of last follow-up (defined as the last recorded encounter with a medical oncologist at the time of data collection) or the date of death. Where patients received sequential ICI therapy or suffered multiple irAE, data were recorded separately for each event.

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Analyses

Statistical comparisons were performed using GraphPad Prism version 8.1.2 for Windows, GraphPad Software, San Diego, CA, USA. Other graphs were prepared using Microsoft Excel 365 version 2603, Seattle, WA, USA. Descriptive statistics were used to summarise the cumulative incidence of irAE (any-grade and Grades 3–5) by tumour type. Differences among demographic subgroups were compared using chi-squared tests. Duration of follow-up was calculated as the date of first dose of ICI to the date of last follow-up or date of death. Overall survival is shown in Kaplan–Meier curves; we assessed between-group differences with log-rank tests and reported median overall survival (from date of diagnosis to date of death or last seen, mOS) and hazard ratios (HRs) with 95% confidence intervals (CIs). We did not adjust for age or sex, as these factors did not correlate with irAE in unadjusted analyses.

Results

Patient characteristics

Details of patient demographics are shown in Table 1. Two hundred and seventy-six patients were prescribed immunotherapy for a solid tumour, of whom 50 were excluded (33 private patients or interstate travellers were

Table 1 Demographics of 226 patients treated with immune checkpoint inhibitors in Top End of Northern Territory, 2016–2021

		All patients, $N = 226$		Lung, $N = 130$		Melanoma, $N = 61$		Other, $N = 35$	
		N	%	*N*	%	*N*	%	*N*	%
Age	Mean in years (range)	62.2 (28–84)		63.9 (40–84)		59.0 (28–82)		61.1 (32–82)	
Sex	Female	68	30	48	37	14	23	6	17
	Male	158	70	82	63	47	77	29	83
Cancer diagnosis	Lung	130	58	130	100	-	-	-	-
	Melanoma	61	27	-	-	61	100	-	-
	Head and neck	11	5	-	-	-	-	11	31
	Renal	10	4	-	-	-	-	10	29
	Bladder	3	1	-	-	-	-	3	9
	Unknown primary	3	1	-	-	-	-	3	9
	Liver	2	1	-	-	-	-	2	6
	Mesothelioma	2	1	-	-	-	-	2	6
	Cutaneous squamous cell carcinoma	2	1	-	-	-	-	2	6
	Colorectal	1	0	-	-	-	-	1	3
	Merkel cell	1	0	-	-	-	-	1	3
ECOG performance status	0	73	32	34	26	30	49	9	26
	1	126	56	76	58	26	43	24	69
	2	25	11	18	14	5	8	2	6
	3	1	0	1	1	0	0	0	0
	Not known	0	0	1	1	0	0	0	0
Smoking status	Non-smoker	42	19	9	7	24	39	9	26
	Ex-smoker	108	48	68	52	24	39	16	46
	Current smoker	73	32	53	41	11	18	9	26
	Not known	3	1	0	0	2	3	1	3
Indigenous status	Aboriginal but not Torres Strait Islander	34	15	24	18	4	7	6	17
	Torres Strait Islander but not Aboriginal	0	0	0	0	0	0	0	0
	Aboriginal and Torres Strait Islander	2	1	2	2	0	0	0	0
	Neither Aboriginal nor Torres Strait Islander	190	84	104	80	57	93	29	83
Geographical classification	Major city	0	0	0	0	0	0	0	0
	Inner regional	0	0	0	0	0	0	0	0
	Outer regional	177	78	99	76	51	84	27	77
	Remote	25	11	14	11	7	11	4	11
	Very remote	23	10	17	13	2	3	4	11
	Not known	1	0	0	0	1	2	0	0
Survival status	Died ($N = 1$ lung unknown date of death)	120	53	77	59	20	33	23	66
	Alive	106	47	53	41	41	67	12	34

ECOG, Eastern Cooperative Oncology Group.

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primarily treated elsewhere; 10 never received a dose of immunotherapy; and seven had inaccessible medical records). Among the 226 patients included in the analyses, the median age at first dose of ICI was 63 years (range 28–84), most were male (70%), and 36 (16%) were Indigenous. The majority of patients (78%) lived in an outer regional area. Eleven per cent lived in a remote area and 10% in a very remote area. Most patients were treated for lung cancer (58%), followed by melanoma (27%), head and neck (5%), renal cell carcinoma (4%) and others (6%). Patients were followed up for a median of 12.0 months (range 6 days to 77.8 months). Short follow-up periods represented loss to follow-up, death or cancer diagnosis occurring very late in the study window. One hundred and nineteen patients (52.7%) were deceased at the completion of data collection.

Treatment characteristics

Table 2 shows the treatment characteristics for patients included in this study. The vast majority (87%) of patients were treated in the palliative setting with immunotherapy as their first line of anti-cancer treatment (69%). Twelve per cent received combination therapy (for melanoma, renal cell carcinoma or mesothelioma) versus 88% single-agent ICI. The most prescribed ICI was pembrolizumab (n = 101), followed by nivolumab ($n = 54$), combination ipilimumab-nivolumab ($n = 27$) and atezolizumab ($n = 26$).

Frequency and severity of immune-related adverse events

Table 3 shows a summary of irAE encountered by patients in this study. Figure 1A shows irAE by category

Table 2 Treatment characteristics of 226 patients treated with immune checkpoint inhibitors in Top End of Northern Territory, 2016–2021

		All patients, $N = 226$		Lung, $N = 130$		Melanoma, $N = 61$		Other, $N = 35$	
		N	%	*N*	%	*N*	%	*N*	%
ICI treatment	Pembrolizumab	101	45	73	56	23	38	5	14
	Nivolumab	54	24	19	15	18	30	17	49
	Ipilimumab-nivolumab	27	12	0	0	20	33	7	20
	Atezolizumab	26	12	25	19	0	0	1	3
	Durvalumab	13	5.8	13	10	0	0	0	0
	Cemiplimab	4	1.8	0	0	0	0	4	11
	Avelumab	1	0.4	0	0	0	0	1	3
ICI target	PD-1	159	70	92	71	41	67	26	74
	PD-1/CTLA-4	27	12	0	0	20	33	7	20
	PD-L1	40	18	38	29	0	0	2	6
Treatment intent	Adjuvant	30	13	13	10	17	28	0	0
	Palliative	196	87	117	90	44	72	35	100
ICI line of treatment	1	157	69	98	75	15	25	14	40
	2 or more	69	31	32	25	46	75	21	60
Prior chemotherapy	No	135	60	76	58	46	75	12	34
	Yes	91	40	54	42	15	25	23	66
Concurrent chemotherapy	No	176	78	83	64	61	100	32	91
	Yes	50	22	47	36	0	0	3	9
Reason for discontinuation	Progressive disease	81	36	53	41	10	16	18	51
	Toxicity	45	20	20	15	20	33	5	14
	Completion of treatment	32	14	11	8	18	30	3	9
	Ongoing treatment	25	11	16	12	3	5	6	17
	Unfit for further treatment	19	8	12	9	6	10	1	3
	Death	12	5	8	6	4	7	0	0
	Patient choice	10	4	9	7	0	0	1	3
	No supply of drug	1	0.4	0	0	0	0	1	3
	Unknown	1	0.4	1	1	0	0	0	0
Treatment response	Yes	144	64	85	65	42	69	17	49
	Responder	96	42	59	45	25	41	12	34
	Stable disease	45	20	26	20	14	23	5	14
	No	76	34	43	33	15	25	18	51
	Unknown response	6	3	2	2	4	7	0	0

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1.

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and severity. Fifty-four per cent (122/226) experienced any-grade irAE and 26% (59/226) had a severe (Grades 3–5) irAE. As anticipated, there was a higher rate of irAE among patients treated with combination immunotherapy (ipilimumab-nivolumab) (81% (22/27) any-grade and 48% (13/27) severe) compared to single-agent immunotherapy (50% (100/199) any-grade and 13% (26/199) severe). The most common category irAE of any-grade was endocrine disorders (15%), including thyroid dysfunction and adrenal insufficiency, followed by gastrointestinal disorders (14%) and skin and subcutaneous disorders (14%). Non-severe (Grades 1 and 2) irAE were more likely to be skin, endocrine and musculoskeletal disorders. Severe irAE were more commonly gastrointestinal, respiratory, hepatobiliary or cardiac disorders. Age did not impact rates of irAE. Two (0.88%) patients died; both received pembrolizumab for non-small cell lung cancer and were diagnosed with immune-related pneumonitis.

IrAE were experienced throughout the treatment course, which is shown in Figure 1B. Those who experienced milder irAE (Grades 1 and 2) did so in later cycles (median cycle 8.2) than those who had severe (Grades 3–5) irAE (median cycle 4.5). Nine percent (11/122) of patients had onset of irAE with ICI treatment duration greater than 12 months. One patient (0.8%) had onset of irAE after 2 years of treatment.

Eighty per cent (97/122) of patients who experienced an irAE required treatment, but only 23% (28/122) were hospitalised. There was a strong association between the requirement for hospitalisation and discontinuation of immunotherapy. Drug toxicity accounted for cessation of immunotherapy in 28% (34/122) of patients. The reasons for discontinuation of ICI treatment are summarised in Figure 1C.

Kaplan–Meier survival curves to show mOS by grade of irAE are shown in Figure 1D. Patients who experienced an irAE at any time point lived significantly longer than those who had no irAE: mOS was 48.2 months with any irAE versus 12.2 months with no irAE (HR = 0.32, 95% CI = 0.22–0.47). This was driven by those who had non-severe irAE; patients with Grades 1 and 2 irAE (mOS = 58.2 months) lived longer than patients with no irAE (HR = 0.26, 95%

Table 3 Summary of immune-related adverse events in 226 patients treated with immune checkpoint inhibitors in Top End of Northern Territory, 2016–2021

		All patients *N* = 226		Lung *N* = 130		Melanoma *N* = 61		Other *N* = 35	
		N	%	*N*	%	*N*	%	*N*	%
Any irAE	No	104	46	62	48	25	41	17	49
	Yes	122	54	68	52	36	59	18	51
irAE	Any grade	122	100	68	100	36	100	18	100
	Severe (Grades 3–5)	39	32	22	32	12	33	5	28
Cycle where irAE occurred	1	32	23	14	21	15	42	3	17
	2	10	7	6	9	2	6	2	11
	3	27	19	4	6	2	6	3	17
	4	12	8	8	12	2	6	2	11
	5	9	6	5	7	3	8	0	0
	6–10	28	20	16	24	8	22	3	17
	11–20	15	11	10	15	2	6	3	17
	21–30	6	4	3	4	2	6	1	6
	31–83	3	2	2	3	0	0	1	6
irAE treatment	No	25	20	14	21	9	25	2	11
	Yes	97	80	54	79	27	75	16	89
	Supportive care only	20	21	11	20	4	15	5	31
	Oral steroids	54	56	31	57	15	56	8	50
	Intravenous steroids	10	10	5	9	5	19	0	0
	Topical steroids	13	13	7	13	3	11	3	19
	Second-line immunosuppression	11	11	5	9	5	19	1	6
irAE hospitalisation	No	93	76	51	75	26	72	16	89
	Yes	28	23	16	24	10	28	2	11
	Not known	1	1	1	1	0	0	0	0
irAE caused discontinuation	No	86	70	49	72	23	64	15	83
	Yes	34	28	18	26	13	36	3	17
	Not known	2	2	1	1	0	0	0	0

irAE, immune-related adverse event.

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CI = 0.18–0.39) or Grades 3–5 (mOS = 30.2 months, HR = 0.47, 95% CI = 0.23–0.93). This was similar across tumour streams and drugs, including in melanoma patients treated with single-agent versus combination immunotherapy.

Incidence of irAE by demographic groups

There was no significant difference in the rates of any irAE (42% vs 56%, $P = 0.11$) or Grades 3–5 irAE (11% vs 18%, $P = 0.29$) in Indigenous compared to non-

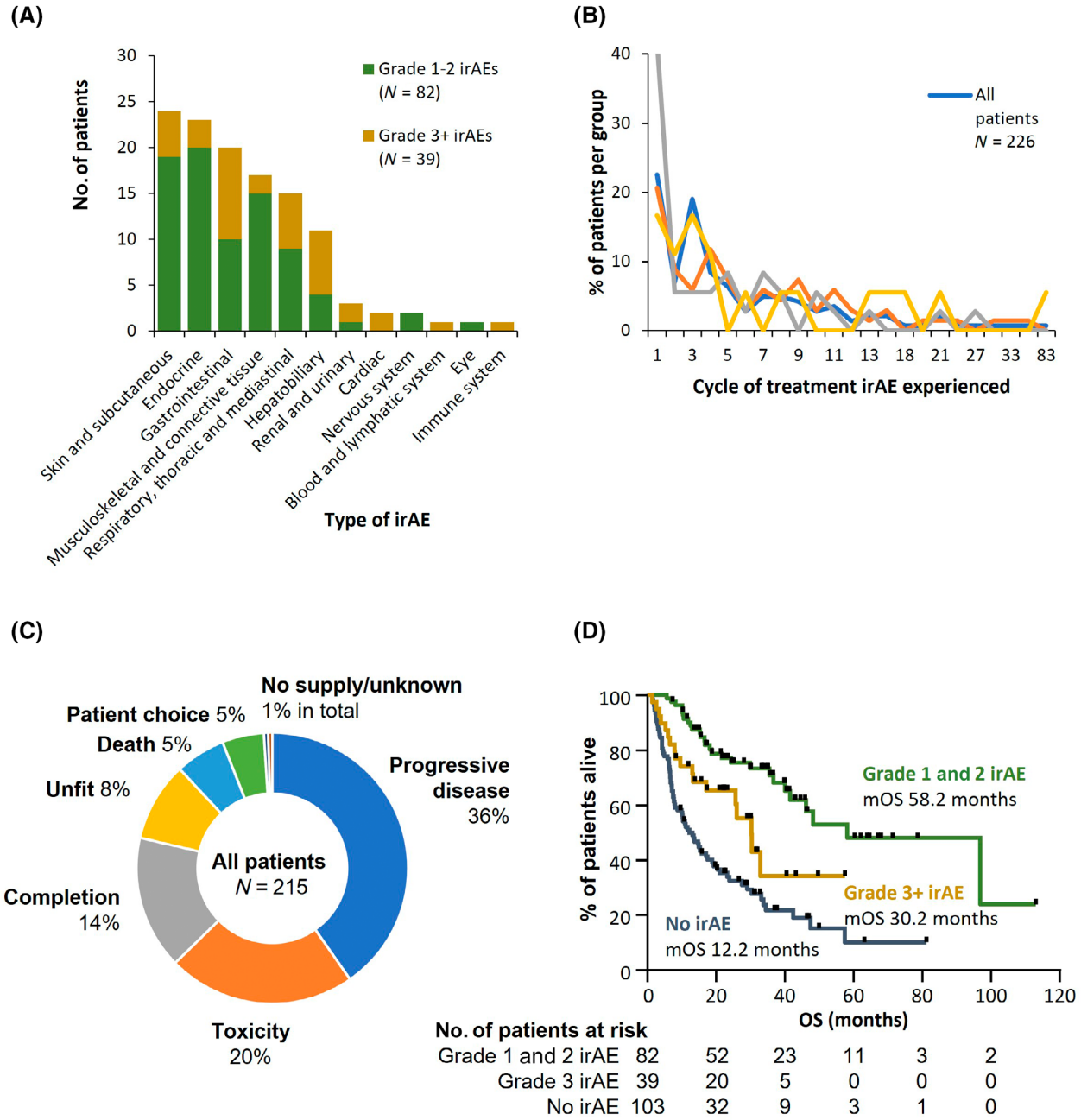

Figure 1 Immune-related adverse events (irAE) in 226 patients treated with immune checkpoint inhibitors in Top End of Northern Territory, 2016–2021. (A) No. patients who experienced irAE by category and severity. (B) Timing of irAE overall and by tumour type. (C) Reasons for discontinuation of ICI treatment; at the time of study completion $N = 11$ patients remained on treatment and are not included in this figure. (D) Kaplan–Meier survival curves to show median overall survival from date of diagnosis to date of death or last seen (mOS) by grade of irAE. ICI, immune checkpoint inhibitor; mOS, median overall survival.

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Table 4 Immune-related adverse events by Remoteness Area and Indigenous status in 226 patients treated with immune checkpoint inhibitors in Top End of Northern Territory, 2016–2021

		Geographical classification			Indigenous status	
		Major city or inner regional	Outer regional	Remote or very remote	Indigenous	Non-Indigenous
All patients	Total *N*	0	177	48	36	190
	Any irAE *N*	0	98	24	15	107
	Any irAE %	**0**	**55**	**50**	**42**	**56**
	Grades 3–5 irAE *N*	0	35	4	4	35
	Grades 3–5 irAE %	**0**	**20**	**8**	**11**	**18**
Lung	Total *N*	0	99	31	26	104
	Any irAE *N*	0	51	17	9	59
	Any irAE %	0	52	55	35	57
	Grades 3–5 irAE *N*	0	51	17	9	59
	Grades 3–5 irAE %	0	52	55	35	57
Melanoma	Total *N*	0	51	9	4	57
	Any irAE *N*	0	31	5	4	32
	Any irAE %	0	61	56	100	56
	Grades 3–5 irAE *N*	0	31	5	4	32
	Grades 3–5 irAE %	0	61	56	100	56
Other	Total *N*	0	37	8	6	29
	Any irAE *N*	0	16	2	2	16
	Any irAE %	0	43	25	33	55
	Grades 3–5 irAE *N*	0	16	2	2	16
	Grades 3–5 irAE %	0	43	25	33	55

irAE, immune-related adverse event.

Indigenous patients, but there was a trend towards lower rates of irAE among Indigenous patients (noting small patient numbers). mOS was 17.1 months in Indigenous patients versus 30.4 months in non-Indigenous patients (HR = 1.5, 95% CI = 0.92–2.66, $P = 0.049$).

Remoteness did not affect rates of irAE (Table 4, any-grade irAE $P = 0.51$; Grades 3–5 irAE $P = 0.06$). mOS was 30.2 months for those in outer regional areas and 27.5 months for remote or very remote patients (HR = 1.1, 95% CI = 0.7–1.7).

Median duration of treatment was shorter in Indigenous patients than non-Indigenous patients (6.5 months ± 7.0 SD vs 10.1 months ± 12.9 SD), and in remote or very remote patients (8.5 ± 8.2 SD) compared to outer regional (9.8 ± 13.1 SD). Indigenous patients were more likely to be treated in the palliative setting than non-Indigenous patients (94% vs 85%). Both Indigenous and remote patients had higher rates of discontinuation due to patient choice (17% and 13% respectively) than non-Indigenous (2%) and non-remote patients (2%).

Discussion

Principal findings

This study confirms the well-described varying rates of irAE between tumour types and ICI drugs in a diverse real-world cohort. It highlights the similarities and differences in patients who are under-represented in clinical trials, specifically those living in remote areas and Aboriginal and Torres Strait Islander peoples.

Although Indigenous patients had rates of irAE similar to those of non-Indigenous patients, overall survival was lower in Indigenous patients. This may be due to several factors, including heterogeneity of cancer (more Indigenous patients experienced lung and other category cancers), more advanced cancer stage at diagnosis and higher rates of treatment discontinuation due to patient choice.

Our finding that patients with Grades 1 and 2 irAE live longer than those with no irAE or Grades 3–5 irAE is consistent with published literature.[9]

Strengths and limitations

There are several strengths to this study. While barriers to accessing cancer treatment and clinical trials are well described in the published literature, there is a paucity of data inclusive of Indigenous Australians and patients living in remote areas. We are confident that the study included every patient residing in the Top End with an ICI-treated solid tumour with the exception of a small number of private patients. Sixteen percent of patients in our cohort were Indigenous; while data regarding

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clinical trial participation for Aboriginal and Torres Strait Islander peoples are lacking,[10] this is significantly higher than reported trial participation of minority groups internationally.[11]

The broad inclusion criteria across tumour streams and drugs allow for a holistic representation of immunotherapy treatment in our population. This also imposes a limitation, in that the demography of the Northern Territory is such that its capital (Darwin) is too small to be classified as a Major city or Inner regional area and so does not allow for comparison to the majority of Australian patients who live in Major cities or Inner regional areas.

There are several further limitations. The electronic medical record lacks data on patient ethnicity other than Indigenous Status, precluding comparisons by different ethnicities. Duration of follow-up is highly variable, as we included patients who commenced treatment at any time point within the study period and data collection was completed in October 2022. Finally, the descriptive data presented here rely solely on data recorded in the electronic medical record and are, therefore, subject to documentation by the treating medical team. Although this is likely to have captured all clinically serious irAE, minor adverse effects may be underestimated. Taken together, these limitations would act to underestimate the true incidence of irAE, but we believe it would have captured the vast majority of all but minor irAE.

Comparison with other studies

When compared to meta-analyses of irAE by tumour stream in clinical trials, this study reported lower rates of irAE. For example, a 2020 meta-analysis of irAE in the treatment of 23, 761 patients with non-small cell lung cancer reported an incidence of any-grade irAE as 84% (95% 0.81–0.86, $P < 0.1$).[12] In comparison, among our patients treated for lung cancer, incidence of any-grade irAE was 52%. However, our rates were higher than some analyses of real-world data, such as a 2022 study of 1905 patients in China that reported a rate of any-grade irAE of 26.9%.[13] The lower rates of irAE in real-world studies, including this study, are probably due to the lack of rigorous documentation that is mandated in clinical trials.

Real-world oncology data are increasingly reported in Australia. A 2018 study assessing real-world efficacy and toxicity of ipilimumab-nivolumab reported comparable toxicity (88% any-grade irAE; 54% Grades 3 and 4 irAE) to our patients on combination therapy.[14] Two Australian studies describe real-world toxicity of single-agent immunotherapy: 27% of patients treated with pembrolizumab for malignant mesothelioma experienced any-grade irAE (8% Grade 3 or higher); 30% of patients with advanced cutaneous squamous cell carcinoma who received pembrolizumab or cemiplimab reported any irAE (19% Grade 2 or higher).[15,16] We believe our study is the first to report irAE in under-represented population groups.

Wang *et al.*'s 2018 meta-analysis of fatal toxicity due to ICI was in line with our results; toxicity-related fatality ranged from 0.36% (anti-PD-1) to 1.23% (combination PD-1/CTLA-4).[17] Fujiwara *et al.*'s more recent study (Lancet Oncol, 2023) assessed treatment-related adverse events in patients who received neoadjuvant or adjuvant immune checkpoint blockade; 40 (0.4%) fatal treatment-related adverse events were observed in 9864 patients who received an ICI[18]. As in our cohort, pneumonitis was the most common fatal adverse event (six out of 40 patients) and the most common culprit ICI was pembrolizumab (13 out of 40 patients).

Implications of findings

To our knowledge, rates of irAE in remote and Indigenous patients have not yet been reported. While this study did not identify unexpected safety concerns in these populations, the numbers were small. The increased rates of discontinuation due to patient choice in Indigenous and remote patients are likely due to geographic and cultural barriers to seeking healthcare. Work is ongoing in Australia to better understand how Aboriginal and Torres Strait Islander peoples view and experience cancer and to improve cancer outcomes nationally.[19] Projects such as the Regional Trials Network Victoria and the Australian Teletrial Program aim to increase the accessibility of clinical trials in regional, rural and remote areas and thereby bridge the gap in health outcomes for all Australians.[5,20]

Conclusion

ICIs, which offer major survival benefits, appear to be no less safe in a real-world population with high numbers of remote or very remote and Indigenous patients than in clinical trials with optimal management in tertiary centres. These findings offer confidence in treating patients who reside in rural and remote areas, including Aboriginal and Torres Strait Islander persons. It also signals conviction in safely conducting clinical trials in these settings and eliminating a safety concern that may have been falsely presumed. It is vital that real-world studies like ours be conducted early, so that remote and minority groups have equal access to safety and benefits data assisting them in choosing their oncology treatments.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. STROBE and RECORD statements – checklist of items that should be included in reports of *cohort studies*.

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