Outcomes of patients with solid tumor malignancies treated with first-line (1L) Immuno-oncology (IO) agents who do not meet eligibility criteria for clinical trials

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Background

- IO-based therapies have been approved based on randomized controlled clinical trials, yet a significant proportion of real-world patients are not represented in these clinical trials.
- We sought to compare the clinical outcomes of trial-ineligible vs. eligible patients with advanced solid tumors treated with 1L IO therapy.

Methods

- Using the International mRCC Database Consortium (IMDC) database and the Alberta Immunotherapy Database, patients with advanced RCC, non-small cell lung cancer (NSCLC) and melanoma treated with 1L PD-(L)1 inhibition based therapy were retrospectively deemed ineligible for clinical trials (according to commonly used inclusion/exclusion criteria in IO trials, Table 3).
- Primary outcome was overall survival (OS).
- Secondary outcomes of interest were overall response rate (ORR), time to treatment failure (TTF), time to next treatment (TTNT)
- Multivariable Cox regression models were performed to adjust for imbalances in baseline prognostic factors.

Results

- 395/1241 (32%) of patients were deemed trial-ineligible (36%, 40%, and 24% were RCC, NSCLC and melanoma, respectively). Baseline characteristics are reported in Table 1 and 2.
- The reasons for ineligibility were: KPS < 70%/ECOG > 1 (40%), brain metastases (32%), Hb < 9 g/dL (16%), eGFR < 40 mL/min (15%), platelets < 100,000/mm^3 (2%), neutrophils < 1500/mm^3 (1%) and no clear-cell component (RCC only; 12%). These are listed in Table 3.
- The overall trial-ineligible cohort had inferior OS, ORR, TTF and TTNT compared to the trial-eligible cohort, as shown in Figure 1 and Table 4. In subgroup analyses, trial-ineligible patients had significantly worse OS, TTF and TTNT across all three tumor types (Table 4).

Table 1: Baseline characteristics of patients with RCC

Baseline characteristics	RCC Trial-ineligible (n=142)	RCC Trial-eligible (n=382)	P-Value
Median age (yrs)	63 (56-70)	62 (55-68)	0.16
Male	64% (91/142)	72% (275/382)	0.08
Sarcomatoid histology	27% (28/102)	21% (57/267)	0.21
Prior nephrectomy	64% (91/142)	74% (282/382)	0.03
LDH > ULN	34% (32/95)	10% (25/260)	< 0.01
First-line treatment			
NIVO IPI	68% (97/142)	65% (247/382)	< 0.01
PEM AXI	1% (2/142)	9% (34/382)	
AVEL AXI	5% (7/142)	13% (50/382)	
ATEZ BEV	25% (36/142)	13% (51/382)	
Patients who received second line therapy	39% (56/142)	42% (162/382)	0.54
IMDC risk groups			
Favorable	10% (12/123)	18% (61/333)	< 0.01
Intermediate	45% (56/123)	65% (217/333)	
Poor	45% (55/123)	17% (55/333)	
IMDC risk factors			
KPS < 80%	22% (30/139)	6% (21/369)	< 0.01
Diagnosis to therapy < 1 yr	74% (104/141)	66% (249/379)	0.08
Calcium > ULN	30% (35/116)	11% (34/322)	< 0.01
Hemoglobin < LLN	65% (89/136)	42% (149/359)	< 0.01
Neutrophils > ULN	19% (25/129)	10% (35/348)	< 0.01
Platelet > ULN	22% (29/135)	10% (37/358)	< 0.01

AVEL AXI = avelumab + axitinib; ATEZ BEV = atezolizumab + bevacizumab; KPS = Karnofsky performance status; LLN = lower limit of normal; LDH = lactate dehydrogenase; NIVO IPI = nivolumab + ipilimumab; PEM AXI = pembrolizumab + axitinib; ULN = upper limit of normal

Table 2: Baseline characteristics of patients with NSCLC and Melanoma

Baseline characteristics	Non-small cell lung cancer			Melanoma		
	Trial-ineligible (N=157)	Trial-eligible (N=242)	P-Value	Trial-ineligible (N=96)	Trial-eligible (N=222)	P-Value
Age	68 (63-74)	70 (63-75)	0.40	68 (58-79)	65 (56-76)	0.09
Male	49% (77/157)	50% (120/242)	0.92	61% (59/96)	71% (157/222)	0.10
Smoker	92% (136/148)	92% (216/235)	0.99	-	-	-
M1c or M1d status	-	-	-	75% (72/96)	41% (90/222)	< 0.01
Histologic features						
Adenocarcinoma	75% (117/156)	75% (180/241)	0.95	-	-	-
SCC	19% (29/156)	19% (47/241)		-	-	-
Other histology	6% (10/156)	6% (14/241)		-	-	-
EGFR mutation	2% (2/125)	1% (2/195)	0.65	-	-	-
ALK mutation	0% (0/125)	0% (0/201)	-	-	-	-
BRAF mutation	-	-	-	20% (18/88)	29% (52/182)	0.15
First-line treatment						
Pembrolizumab	89% (139/157)	85% (205/242)	0.28	57% (55/96)	47% (103/220)	0.18
Nivolumab	-	-		17% (16/96)	16% (35/220)	
Pembrolizumab + Chemo†	11% (18/157)	15% (37/242)		-	-	
Nivo + Ipi	-	-		26% (25/96)	37% (82/220)	
Patients who received second line therapy	13% (21/157)	16% (38/242)	0.52	13% (12/96)	22% (48/222)	0.06
Baseline dNLR > 3	78% (122/157)	61% (147/242)	< 0.01	66% (63/96)	43% (95/222)	< 0.01
Baseline LDH > ULN	38% (43/112)	24% (34/143)	0.01	47% (35/75)	25% (46/183)	< 0.01
PD-L1 IHC status						
< 1%	6% (10/156)	7% (17/240)	0.29	-	-	-
1-49%	8% (12/156)	13% (30/240)		-	-	-
≥ 50%	86% (134/156)	80% (193/240)		-	-	-

dNLR = derived neutrophil to lymphocyte ratio; IHC = immunohistochemistry IOIO = Immuno-oncology agent combinations; IOVE = IO + vascular endothelial growth factor receptor inhibitor; KPS = Karnofsky performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; Nivo + Ipi = Nivolumab and Ipilimumab combination; ULN = upper limit of normal; SCC = squamous cell carcinoma

†Chemotherapy includes cisplatin or carboplatin-based doublet chemotherapy

Table 3: Number of patients excluded due to each exclusion criteria

Exclusion parameter†	Number of patients excluded due to this parameter/patients with available data %*(n/n)			
	Overall cohort (n=395)	RCC (n=142)	NSCLC (n=157)	Melanoma (n=96)
ECOG > 1 or KPS < 70%	40 (158/395)	14 (20/142)	61 (96/157)	44 (42/96)
Brain metastases	32 (126/395)	18 (26/142)	36 (57/157)	45 (43/96)
Hemoglobin < 9.0 g/dL	16 (63/395)	30 (43/142)	9 (14/157)	6 (6/96)
eGFR < 40 mL/minute	15 (61/395)	18 (26/142)	11 (17/157)	19 (18/96)
Platelet < 100 x 10^3/µL	2 (6/395)	3 (4/142)	0 (0/157)	2 (2/96)
Neutrophil count < 1500/µL	1 (5/395)	0 (0/142)	1 (2/157)	3 (3/96)
Nonclear-cell histology	12 (48/395)	34 (48/142)	-	-

ECOG = eastern cooperative oncology group performance status; GFR = estimated glomerular filtration rate; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; RCC = renal-cell carcinoma

† 467 exclusion criteria met in 395 patients

*Total > 100% because patients may have had multiple exclusion parameters

Figure 1: Treatment outcomes of trial-ineligible vs. eligible patients

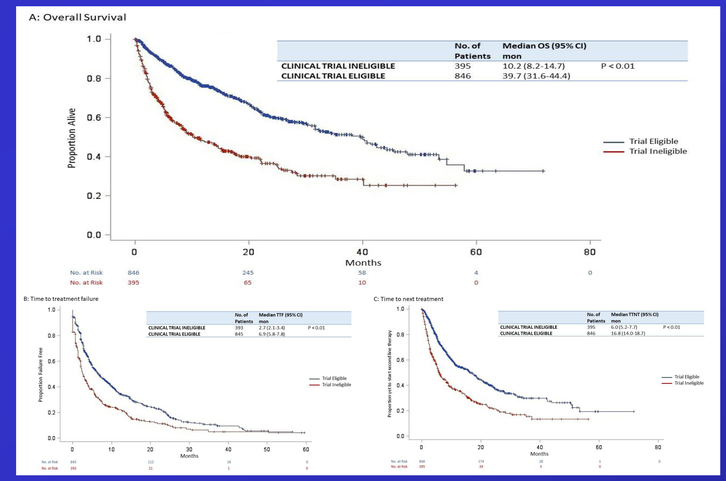

Table 4: Clinical outcomes of trial-ineligible vs. eligible patients

Clinical outcome	Trial-ineligible (n=395)	Trial-eligible (n=846)	p-value
Median OS (mon) (95% CI)			
RCC	25.1 (15.2-40.2)	44.4 (39.7-57.8)	< 0.01
NSCLC	5.3 (4.0-7.0)	20.4 (14.2-24.8)	< 0.01
Melanoma	9.3 (5.6-17.7)	40.1 (33.2-NR)	< 0.01
ORR			
Overall cohort	36% (99/276)	47% (329/706)	< 0.01
RCC	32% (36/113)	44% (138/315)	0.03
NSCLC	26% (26/99)	35% (71/205)	0.14
Melanoma	58% (37/64)	65% (120/186)	0.34
Median TTF (mon) (95% CI)			
RCC	3.7 (2.5-5.5)	7.8 (6.2-9.7)	< 0.01
NSCLC	2.1 (1.4-3.0)	5.9 (4.8-7.8)	< 0.01
Melanoma	2.6 (1.6-4.1)	5.6 (4.6-8.1)	< 0.01
Median TTNT (mon) (95% CI)			
RCC	8.2 (5.7-11.2)	15.9 (11.5-18.6)	< 0.01
NSCLC	4.7 (3.0-5.7)	10.3 (8.1-16.2)	< 0.01
Melanoma	8.3 (5.1-12.3)	21.9 (18.0-50.5)	< 0.01
Adjusted HR (95% CI) for death†			
RCC	1.84 (1.22-2.77), p < 0.01		
NSCLC	2.21 (1.58-3.11), p < 0.01		
Melanoma	1.82 (1.21-2.74), p < 0.01		

CI = confidence interval; HR = hazard ratio, RCC = renal cell carcinoma; NSCLC = non-small cell lung cancer; ORR = Objective response rate; OS = overall survival; TTF = time to treatment failure; TTNT = time to next treatment

†Adjusted for prognostic factors according to tumor sites: Renal (Calcium > upper limit of normal, Diagnosis to systemic therapy < 1 year, Neutrophils > upper limit of normal, Platelet > upper limit of normal, Hemoglobin < lower limit of normal), Lung (lactate dehydrogenase, derived neutrophil to lymphocyte ratio), Melanoma (lactate dehydrogenase and M1c/M1d status)

Conclusions

- 32% of real-world patients treated with contemporary 1L IO-based therapies would have been ineligible for clinical trials. The two most common reasons for ineligibility were the presence of brain metastases and poor performance status.
- These patients had inferior outcomes compared to trial-eligible patients.
- These data may guide patient counselling and inform real-world practice.

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