Immunotherapy Response Score (IRS) Predicts Pembrolizumab Clinical Benefit in Patients with NSCLC in TPS≥50%

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Introduction

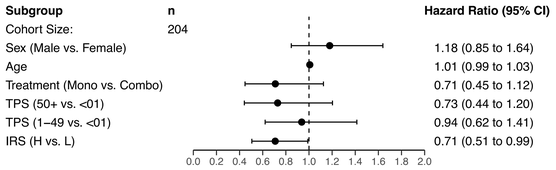
Immunotherapy Response Score (IRS) is a tissue-based multivariable algorithm previously validated to predict anti-PD-(L)1 benefit pan-tumor (PMID:36750617) from routine tissue samples. The IRS algorithm integrates tumor mutation burden (TMB) and quantitative gene expression of PD-L1, PD-1, ADAM12 and TOP2A from routine formalin fixed paraffin embedded samples.

We evaluated IRS in an independent cohort of Kaiser Permanente Northern California (KPNC) patients with advanced non-small cell lung cancer (NSCLC) following a pre-specified statistical analysis plan for the primary objective.

Table 1 | Study population characteristics

Variable	Statistic	Overall N = 204	IRS High N = 103	IRS Low N = 101	Post-Hoc N = 214
Age					
	mean (stddev)	68.9 (9.25)	70.3 (8.78)	67.4 (9.52)	68.8 (9.27)
	median	69	71	67	69
	min, max	36, 89	51, 88	36, 89	36, 89
Sex	n (%)				
Female		94 (46.1)	42 (40.8)	52 (51.5)	99 (46.3)
Male		110 (53.9)	61 (59.2)	49 (48.5)	115 (53.7)
Race	n (%)				
Asian/Pacific Islander		29 (14.2)	16 (15.5)	13 (12.9)	29 (13.6)
African-American		25 (12.3)	17 (16.5)	8 (7.9)	28 (13.1)
Hispanic		11 (5.4)	5 (4.9)	6 (5.9)	12 (5.6)
Multi-race		3 (1.5)	1 (1.0)	2 (2.0)	3 (1.4)
Unknown		8 (3.9)	1 (1.0)	7 (6.9)	9 (4.2)
Non-Hispanic White		128 (62.8)	63 (61.2)	65 (64.4)	133 (62.15)
Line	n (%)				
1st		204 (100)	103 (100)	101 (100)	204 (95.3)
2nd		0	0	0	7 (3.3)
3+		0	0	0	3 (1.4)
TPS			n (%)		
<01%		45 (22.1)	18 (17.5)	27 (26.7)	47 (22.0)
1-49%		73 (35.8)	30 (29.1)	43 (42.6)	75 (35.0)
50+%		86 (42.2)	55 (53.4)	31 (26.7)	92 (43.0)
Treatment Type	n (%)				
Single Agent		80 (39.2)	53 (51.5)	27 (26.7)	90 (42.1)
Combo		124 (60.8)	50 (48.5)	74 (73.3)	124 (57.9)

Figure 1 | Forest plot(s) of IRS association with 1L pembrolizumab TTNT



IRS is the only significant factor in the model indicating the addition of IRS provides information beyond sex, age, treatment, and PD-L1 IHC TPS score.

Conflict of Interest disclosure

BJB, NAK, LEL, DH, KK, DBJ, DRR, SAT are equity holders and/or employees for Strata Oncology. SAT and DRR are equity holders in Javelin Oncology. SAT previously served as a consultant to Strata Oncology and has consulted for Astellas/Medivation and Janssen. SAT has received research (to University of Michigan) funding from Astellas and has received travel support from the Prostate Cancer Foundation. JMS has received research funding from Astrazeneca. Remaining authors declare no conflict of interest. Funding: Strata Oncology

Methods

NSCLC patients treated with pembrolizumab with IRS were included (timeframe 2018-2022). Primary endpoint included time to next treatment (TTNT). The primary objective was to determine if IRS status (High or Low) is associated with >1st line pembrolizumab TTNT independent of single agent or combination therapy and PD-L1 Tumor Proportion Score (TPS) comparing full vs. reduced (excluding IRS) Cox proportional hazards models. Post-hoc analysis assessed IRS association with ≥1st line single- agent treated patients within PD-L1 TPS>50% to determine if IRS provided benefit beyond TPS.

Figure 2 | IRS is significantly associated with ≥ 1L pembrolizumab single-agent TTNT benefit in TPS ≥50%

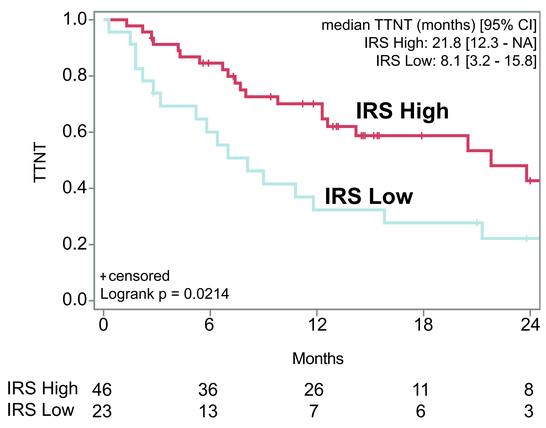
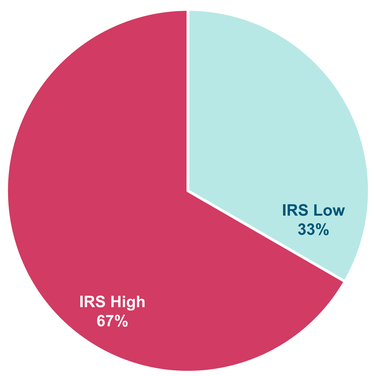


Figure 3 | IRS distribution in TPS ≥50%

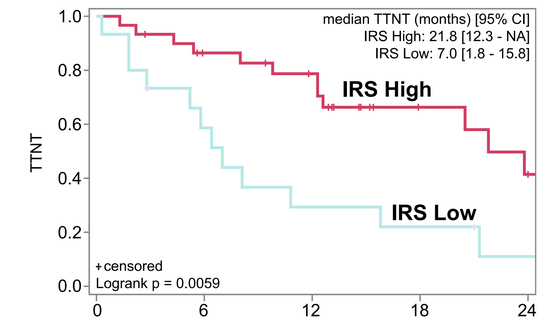


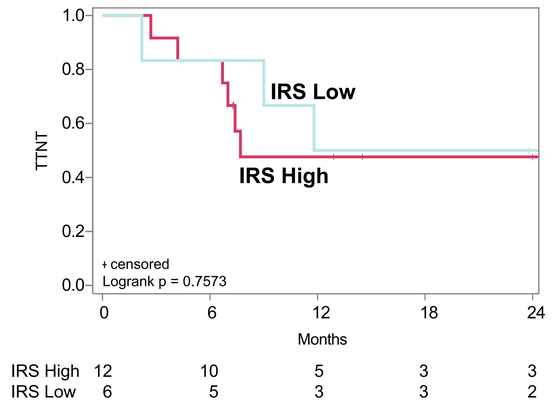
Results

204 1st line NSCLC patients were treated with pembrolizumab monotherapy or combination therapy, and IRS was significantly associated with pembrolizumab TTNT independent of therapy type and TPS (Fig. 1, HR=0.71; LRT p=0.043). Post-hoc analysis demonstrated that IRS provided benefit within TPS≥50% as IRS High patients had longer single-agent pembrolizumab TTNT than IRS Low patients (Fig. 2, n= 69 median TTNT 21.8 95%CI [12.3, NA] vs. 8.1 95%CI [3.2 - 15.8] months).

Figure 4 | IRS association of single-agent pembrolizumab stratified by TPS 50-90% and >90%

In 1L single-agent pembrolizumab patients treated with TPS 50-90%, IRS High had significantly longer pembrolizumab TTNT benefit compared to IRS Low, but not in TPS >90%, although sample size was limited. This suggests that the IRS effect is not driven by patients with TPS >90%.

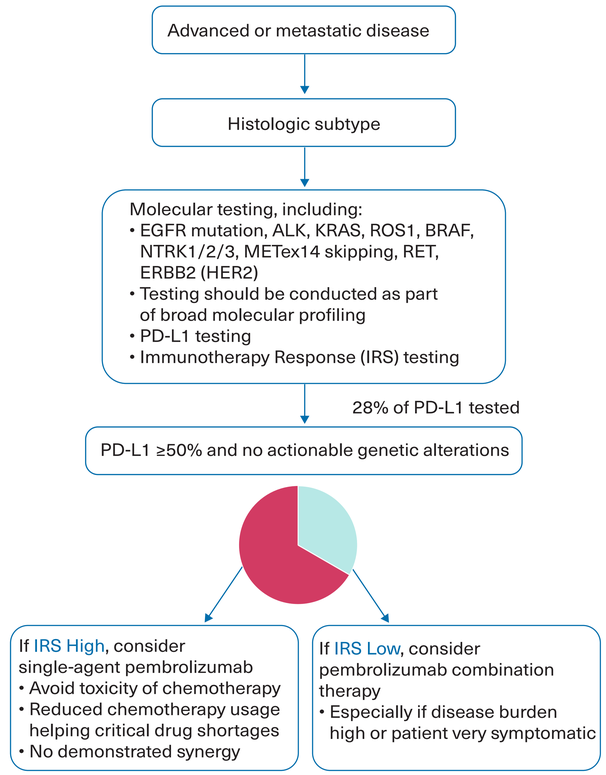




Conclusions

IRS supports informed clinical decisions beyond TPS for determining if a patient with NSCLC will benefit from single-agent pembrolizumab (IRS High) or could consider combination therapy (IRS Low). Importantly, IRS stratified single-agent benefit within PD-L1 TPS>50% which may support clinical decision making.

Clinical implications | Proposed treatment decision schema*



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*Within NCCN Guidelines