Development of a Novel Risk Stratification Model for Immune-Related Adverse Events for Patients with Advanced Melanoma and Non-Small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors

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Background

- Immune checkpoint inhibitors (ICI) have transformed the treatment paradigm across cancers.
- There remain few reliable, clinically accessible, predictors of ICI-related immune related adverse events (irAEs).
- In this study we derive a novel risk stratification model for irAEs using clinically accessible, baseline, patient, tumor, and treatment variables in a large cohort of patients with advanced melanoma (AM) or non-small cell lung cancer (NSCLC) treated with ICI.

Methods

Study Design

- Multi-centre retrospective observational cohort study

Study cohort

- Inclusion criteria:
  - Age equal to or over age 18
  - Confirmed diagnosis of advanced melanoma or NSCLC
  - Received at least 1 cycle of single-agent or combination ICI, in any line, from 2015 to 2023 in Alberta, Canada
- Data Collection
  - Baseline demographic, clinical, laboratory, and tumor characteristics
  - Treatment data
  - Survival outcomes
  - **Outcome of interest: clinically significant irAEs**
    - Defined as requiring either treatment delay or use of systemic steroids/steroid sparing agents

Statistical Analysis

- Cox Proportional Hazards regression adjusted for primary tumor location was used to assess the association between development of irAEs and overall survival (OS) and time to next treatment (TTNT).
- Stepwise logistic regression was utilized to select and weight baseline variables associated with development of irAEs to derive a predictive risk score.
- Model validation was carried out on 500 iterations of bootstrapped samples. Harrel's C-index was calculated and internally validated to ascertain the model's discriminatory performance.

Risk stratification model

Table 1. Risk stratification model. Out of the 1292 AM and NSCLC patients included in the total study cohort, 801 patients were identified to have a complete baseline profile of demographic, clinical, laboratory and tumor characteristics. Utilizing the subset of 801 patients, the below variables were identified and weighted for creation of the risk model with risk score assigned (left). Patients were stratified into 3 irAE risk groups based on their combined score (right).

Predictor (Risk containing strata)	**Score**
Malignancy (NSCLC)	1
Age (>60 years)	1
ECOG (≥ 1)	-1
BMI (≥25)	1
Line of Therapy (second or later line)	-1
Type of Therapy (combination ICI)	4
Number of ICI Cycles (>10)	2
Albumin level (Below LLN)	-1
Adrenal Metastasis (Present)	1
Multiple Metastasis (>1 Metastasis)	-1

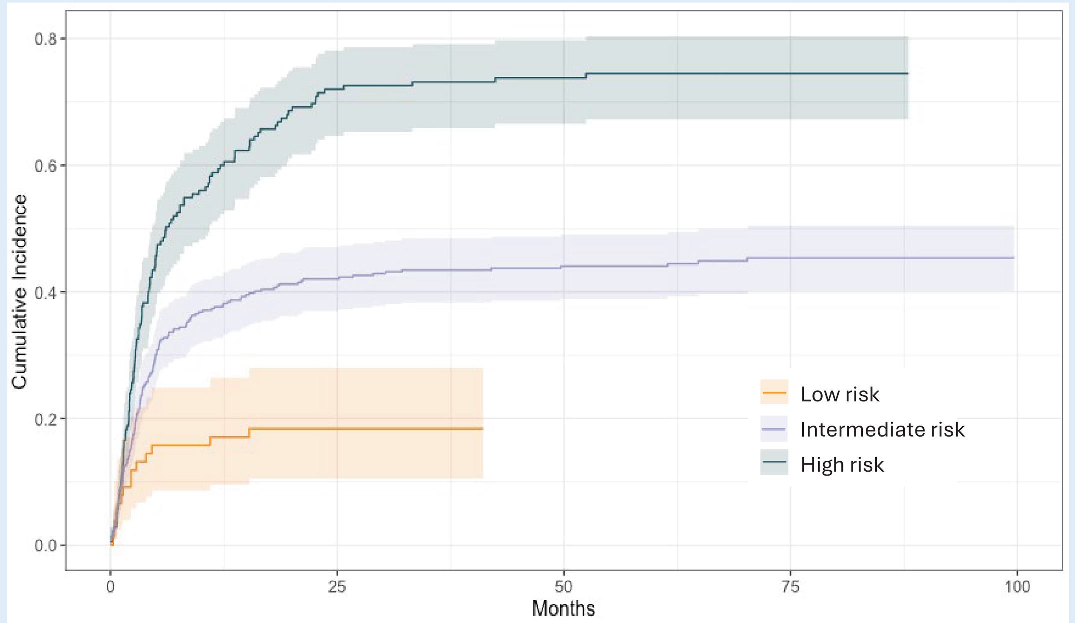
Risk Strata	**Score Range**
Low Risk	≤0
Medium Risk	1-2
High Risk	≥3

- The risk model performed well with an optimism-corrected c-index of 0.707 in internal validation.

Table 2. Rate of irAE by risk groups with associated OR. **Higher risk group is strongly associated with increasing odds of irAE development.**

Risk Strata	irAE Event Rate	OR (95% CI), p-value
Low Risk	43/230 (18.7%)	Ref
Intermediate Risk	233/412 (56.6%)	1.28 (1.19-1.38), p<0.001
High Risk	120/159 (75.5%)	1.76 (1.61-1.93), p<0.001

Figure 1. Cumulative incidence of irAE by risk strata adjusted for death by any cause.



Results

- A total of 1,292 patients were included in the study cohort: 519 (218/489 [44.6%] AM and 301/803 [37.5%] NSCLC) developed a clinically significant irAE.

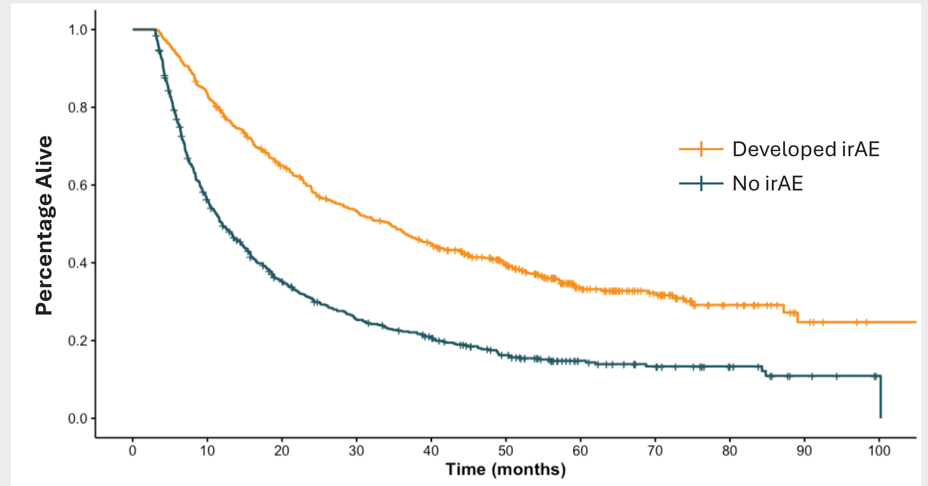


Figure 2A: Overall Survival by irAE status. The development of an irAE was associated with an improvement in OS (left) (HR 0.48, 95% CI 0.41-0.44, p<0.001), with a median OS of 34.3 (95% CI 28.8-39.6) months compared to 12.0 (95% CI 10.6-14.3) months for those who did not develop an irAE.

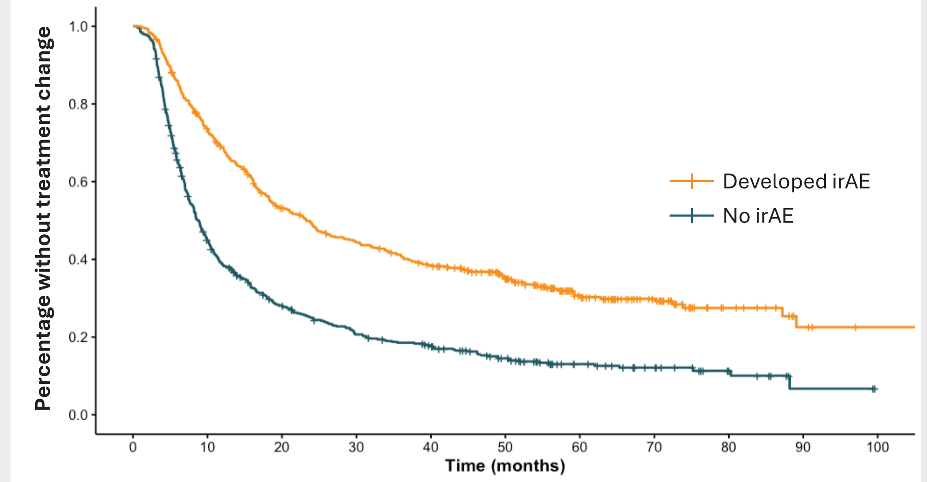


Figure 2B: TTNT by irAE status. The development of an irAE was associated with an improvement in TNTT (HR 0.50, 95% CI 0.43-0.57, p<0.001), with a median TNTT of 23.3 (95% CI 18.9-28.4) months compared to 8.7 (95% CI 7.9-9.9) months for those who did not develop an irAE.

- Higher risk group is strongly associated with an improvement in both OS (Figure 3A) and TNNT (Figure 3B), with HR and 95% CI listed in Table 3.

Figure 3. Overall Survival (A) and TTNT (B) by irAE Risk Groups

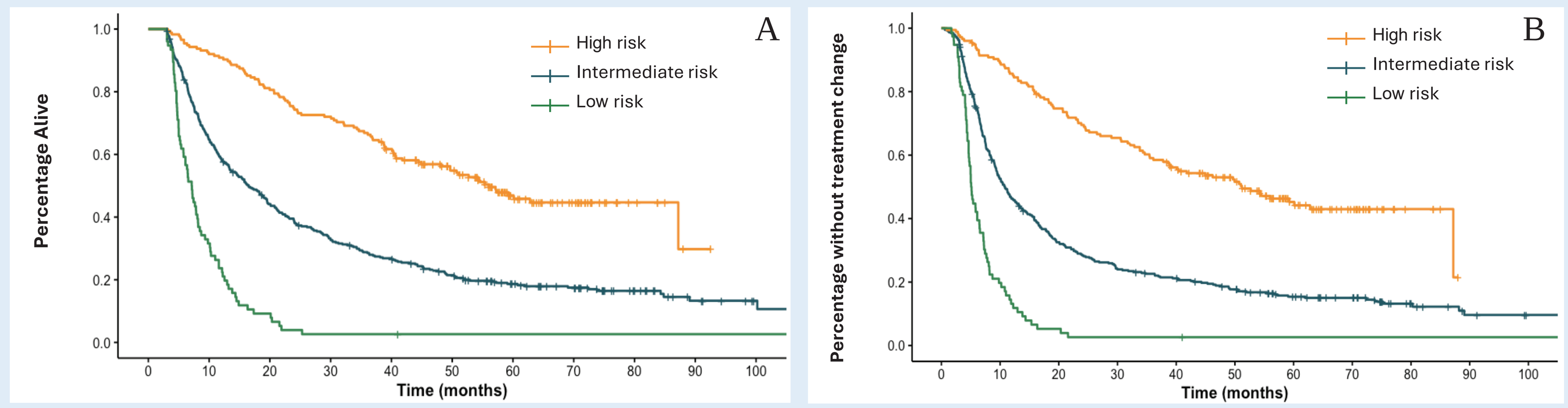


Table 3

Risk Strata	OS HR (95% CI), p-value	TNNT HR (95% CI), p-value
Low Risk	Ref	Ref
Medium Risk	0.37 (0.28-0.48), p<0.001	0.34 (0.26-0.44), p<0.001
High Risk	0.14 (0.10-0.19), p<0.001	0.13 (0.09-0.18), p<0.001

Conclusions

- Development of an irAE was associated with significant improvements in key survival outcomes. We present, and internally validate, a simple risk stratification tool that utilizes readily available baseline patient, tumor, and treatment characteristics to robustly stratify risk of irAE development.