A multi-omic immune profile score (IPS) stratifies real-world outcomes of microsatellite stable (MSS) advanced colorectal cancer patients treated with immune checkpoint inhibitors

Yan Liu[1], **Rossin Erbe[1]**, Ailin Jin[1], Alia D. Zander[1], Seung Won Hyun[1], Michelle M. Stein[1], Ben Terdich[1], Kyle A. Beauchamp[1], Dana F. DeSantis[1], Victoria L. Chiou[1], Charles Koyias[1], Kate Sasser[1], Chithra Sangli[1], Halla Nimeiri[1,2], Michelle Ting-Lin[1], Wade Iams[3], Aparna Kalyan[2]

[1]Tempus AI, Inc., Chicago, IL; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Greco-Hainsworth Centers for Research, Tennessee Oncology, Nashville, TN

Abstract # 134

INTRODUCTION

Immune checkpoint inhibitors (ICI) are approved in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) advanced colorectal cancer (CRC), a subgroup that represents a small fraction of the advanced CRC patient population. Thus, the lack of a predictive biomarker of ICI response for the majority of advanced CRC patients that are microsatellite stable (MSS) represents an urgent unmet clinical need. The Tempus immune profile score (IPS), a DNA and RNA-based molecular algorithm, was validated as a prognostic biomarker in >1,500 advanced solid pan-cancer patients treated with on-label ICI regimens. To attempt to address the clinical need in this population, we conducted an exploratory study evaluating IPS as a biomarker of ICI benefit in a real-world cohort of MSS CRC patients treated with ICI.

METHODS

We used the Tempus Database to identify advanced MSS CRC patients who received an ICI alone or ICI-containing regimen in the third line and beyond. Using tissue samples collected prior to ICI initiation, IPS was calculated using the Tempus xT (DNA) and xR (RNA) assays. Patients were stratified as IPS-High vs. IPS-Low. The prognostic value of IPS for real-world overall survival (rwOS) was assessed using Cox proportional hazards (Cox PH) models. To evaluate the relative stratification of IPS (high vs. low) for ICI regimens compared to non-ICI regimens, we compared IPS association with time-to-next-treatment (TTNT) on prior chemotherapy regimens to rwOS on ICI therapy, anchoring on prior regimen start.

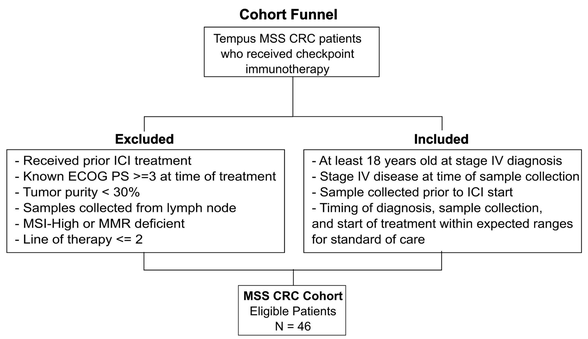

Figure 1. Study Inclusion/Exclusion criteria
List of criteria used to filter patients from the Tempus real-world database to identify advanced or metastatic MSS CRC patients treated with ICI in 3rd line or later.

SUMMARY

- The multi-omic IPS biomarker may stratify rwOS in advanced MSS CRC patients who received ICI therapy
- Comparison of IPS-High to IPS-Low on ICI versus prior non-ICI suggests possible predictive utility of IPS as an ICI specific biomarker beyond its established prognostic validity

RESULTS

Table 1. Cohort Characteristics

Characteristic	Overall N = 46	IPS-High n = 6	IPS-Low n = 40
Age			
Median (Min-Max)	54.0 (39.0-83.0)	49.0 (43.0-73.0)	54.5 (39.0-83.0)
Sex			
Male	24 (52.2%)	2 (33.3%)	22 (55.0%)
Female	22 (47.8%)	4 (66.7%)	18 (45.0%)
Race			
White	26 (56.5%)	2 (33.3%)	24 (60.0%)
Black or African American	4 (8.70%)	1 (16.7%)	3 (7.50%)
Asian	5 (10.9%)	1 (16.7%)	4 (10.0%)
Other Race	1 (2.17%)	0 (0%)	1 (2.50%)
Unknown	10 (21.7%)	2 (33.3%)	8 (20.0%)
ECOG Score			
0	10 (21.7%)	3 (50.0%)	7 (17.5%)
1	18 (39.1%)	3 (50.0%)	15 (37.5%)
2	4 (8.70%)	0 (0%)	4 (10.0%)
Unknown	14 (30.4%)	0 (0%)	14 (35.0%)
LOT			
3	16 (34.8%)	0 (0%)	16 (40.0%)
4	15 (32.6%)	2 (33.3%)	13 (32.5%)
4L+	15 (32.6%)	4 (66.7%)	11 (27.5%)
Liver Metastasis Documented			
Yes	38 (82.6%)	3 (50.0%)	35 (87.5%)
No	8 (17.4%)	3 (50.0%)	5 (12.5%)
Therapy Type			
ICI + Additional	22 (47.8%)	3 (50.0%)	19 (47.5%)
ICI Only	24 (52.2%)	3 (50.0%)	21 (52.5%)
TMB			
High	8 (17.4%)	2 (33.3%)	6 (15.0%)
Low	38 (82.6%)	4 (66.7%)	34 (85.0%)
***KRAS* Pathogenic Mutation**			
TRUE	24 (52.2%)	3 (50.0%)	21 (52.5%)
FALSE	22 (47.8%)	3 (50.0%)	19 (47.5%)
***NRAS* Pathogenic Mutation**			
TRUE	2 (4.35%)	0 (0%)	2 (5.00%)
FALSE	44 (95.7%)	6 (100.0%)	38 (95.0%)
***BRAF* V600E Mutation**			
TRUE	0 (0%)	0 (0%)	0 (0%)
FALSE	46 (100.0%)	6 (100.0%)	40 (100.0%)

Figure 2. IPS-High MSS CRC have longer OS after ICI

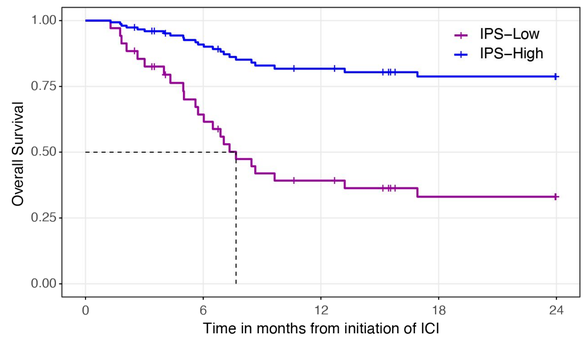

Figure 2. Cox Proportional Hazards model curves for real world overall survival stratification of IPS fit to advanced/metastatic MSS CRC patients treated with ICI (N = 46). The Hazard Ratio is 0.22, 90% Confidence Interval (CI) (0.04, 1.16). Median OS for IPS-Low is 7.67 (5.74, 13.2) months. Median OS for the IPS-High group was not reached in 24 months.

Table 2. Cox Model Hazard Ratios with Possible Confounding Variables

Cox PH Model Covariates	Hazard Ratio (90% CI)
IPS only	0.22 (0.04, 1.16)
IPS, stratified by therapy line	0.18 (0.03, 1.02)
IPS + therapy type, stratified by therapy line	0.20 (0.04, 1.09)
IPS + therapy type + liver metastasis + age, stratified by therapy line	0.24 (0.04, 1.47)

Table 2. Cox Proportional Hazards models were fit for real world overall survival stratification of IPS. The stability of the Hazard Ratio was assessed by incorporating potential confounding variables into a stratified Cox model to account for potential differing baseline hazards for patients in different lines of therapy. Therapy type is binarized between ICI-only regimens and ICI+other drug regimens. Liver metastasis is a binary variable based on documented liver metastases in a patient's records at the time of ICI start.

Figure 3. Stratification of OS by IPS-High vs IPS-Low on ICI compared to TTNT on prior non-ICI Treatment

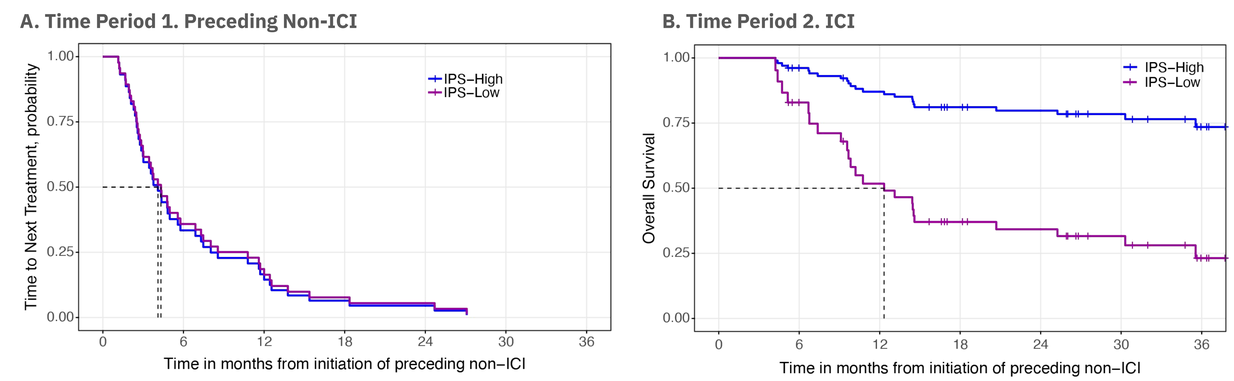

Figure 3. Cox Proportional Hazards model curves stratified by IPS fit to (**A.**) Real-world time to next treatment (TTNT) for MSS CRC patients on the treatment line prior to ICI therapy. The Hazard Ratio (90% CI) is 1.07 (0.60, 1.91). (**B.**) Real-world overall survival for ICI treated MSS CRC patients. The Hazard Ratio (90% CI) is 0.21 (0.04, 1.22)

ACKNOWLEDGMENTS

We thank Matthew Campbell, MD from the Tempus Clinical Development team for feedback and critical discussions.

Correspondence: rossin.erbe@tempus.com