Utilizing serum proteome to understand response and resistance to immune checkpoint inhibitors in advanced non-small cell lung cancer

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Disclosures

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Freenome	Research Grant
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AstraZeneca	Honoraria/Advisory Boards
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Commercial Interest	Relationship(s)
Boehringher Ingelheim	Honoraria/Advisory Boards
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Guardant Health	Honoraria/Advisory Boards

Introduction & Background

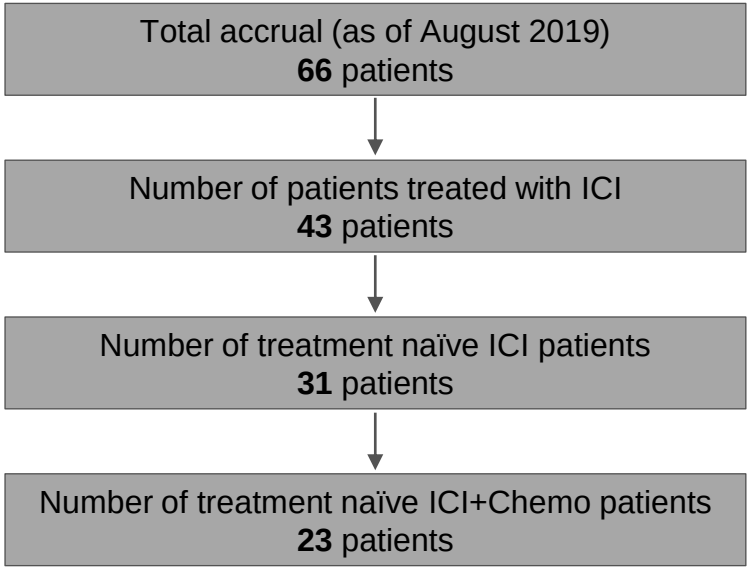
- Responses and resistance to immune checkpoint inhibition (ICI) treatment for non-small cell lung cancer (NSCLC) are poorly understood and better biomarkers are needed.
- A validated serum based proteomic test, Primary Immune Response (PIR) test classifying patients into PIR-resistant or PIR-not resistant, was used to predict patient outcome in NSCLC treated with ICI.[1]
- Protein Set Enrichment Analysis (PSEA) scores, continuous variables assessing the level of various biological processes, were used to elucidate mechanisms of early resistance to ICI in patients with advanced NSCLC. [2]

1. Muller et al. A Serum Protein Classifier Identifying Patients with Advanced Non-Small Cell Lung Cancer Who Derive Clinical Benefit from Treatment with Immune Checkpoint Inhibitors. Clin Cancer Res. 2020 26(19):5188-5197
2. Roder et al. A proposal for score assignment to characterize biological processes from mass spectral analysis of serum. Clin Mass Spec 2020 18:13-26

Methods

- Serum of 43 consented patients with NSCLC was collected prospectively prior to treatment.
- PIR classifications and PSEA scores for all samples were generated blinded to all clinical data.
- Outcomes, including progression-free survival (PFS) and overall survival (OS), were analyzed by PIR classifications as not resistant vs. resistant at baseline.
- Multivariate regression of OS was performed.
- PSEA scores indicating activity of 10 processes of interest were compared between PIR classification groups.

Subject Population Summary



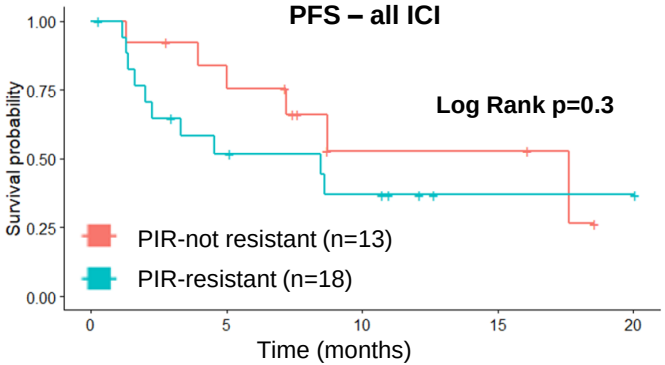
Patient characteristics in the ICI treated population (n=43)

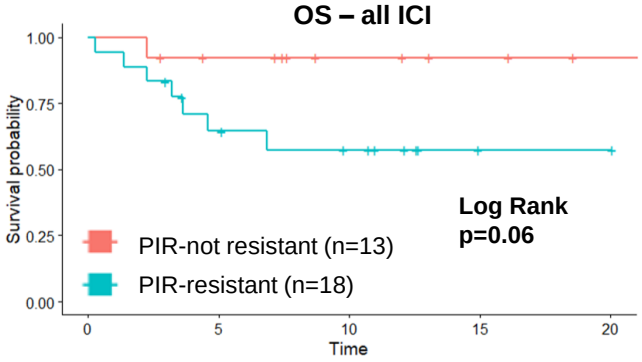
Variable	Condition	PIR-not resistant (n=19)	PIR-resistant (n=24)	P-value
Age	Mean Years ± SD Median Years [Q1-Q3]	69 ± 7 70 [66-74]	67 ± 12 66 [59-74]	0.403 0.460
Gender, n(%)	Female Male	13 (68) 6 (32)	9 (38) 15 (63)	0.067
Ethnicity, n(%)	White Non-White	12 (63) 7 (37)	12 (52) 11 (48)	0.542**
Performance status, n(%)	0-1 2-3	17 (89) 2 (11)	16 (67) 8 (33)	0.145
Histology, n(%)	non-squamous squamous NA	15 (79) 3 (16) 1 (5)	17 (71) 5 (21) 2 (8)	0.709**
Stage, n(%)	III IV	5 (26) 14 (74)	1 (4) 23 (96)	0.072
PD-L1, n(%)	<1% 1%-50% >50% NA	10 (52) 5 (26) 2 (11) 2 (11)	8 (33) 11 (46) 2 (8) 3 (13)	0.331**
Tissue TMB*	Median [Q1-Q3]	4.2 [1.7-6.8]	6.7 [2.5-8.3]	0.428**
Line of Tx, n(%)	1st line 2nd & higher line	13 (68) 6 (32)	18 (75) 6 (25)	0.738

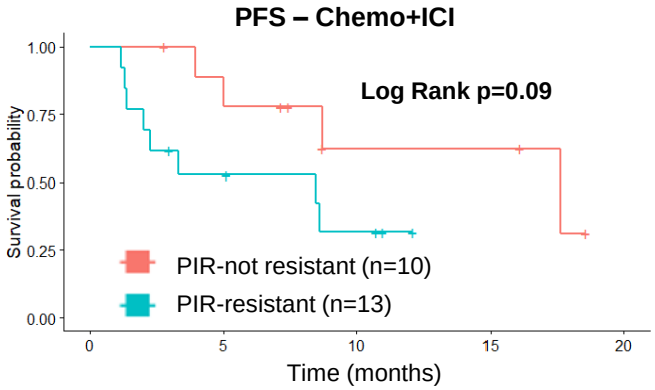
*Only available for 12/19 in the not resistant group and 13/24 in the resistant group ** not including NA

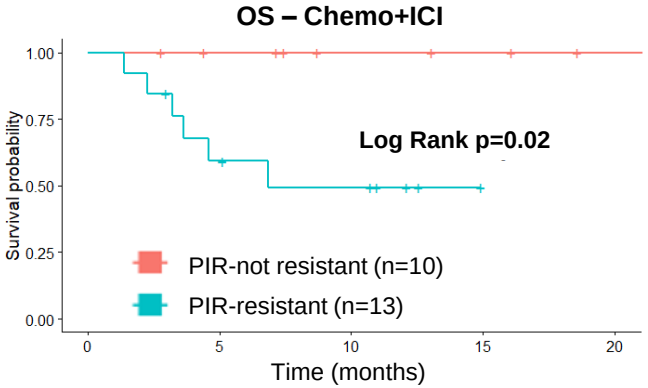
Performance status evaluated by Eastern Cooperative Oncology Group (ECOG) criteria

Survival by PIR classification – 1st line ICI pts









Multivariate analysis of overall survival

Variable	HR [95% C.I.]	*P*-value
PIR-resistant vs. not resistant	8.2 [1-67.4]	0.049
Performance status 2-3 vs. 0-1	3.9 [1-15.4]	0.053
PD-L1 expression (continuous)	0.6 [0.2-1.4]	0.24
Line of therapy, 2+ vs. 1	0.7 [0.2-3.1]	0.66

In multivariate analysis, PIR classification at baseline remained a significant prognostic factor in the all ICI patient population even when adjusted for performance status, line of therapy, and PD-L1 expression.

Association of PSEA score with PIR classification (all ICI)

PSEA Score	Non-Resistant	Resistant	P-value	Padj value*
Angiogenesis	0.66 [0.36;1.24]	0.50 [0.17;0.95]	0.7256	0.8941
Complement	0.08 [-0.16;0.25]	0.98 [0.73;1.33]	<.0001	<.0001
Extracellular Matrix	-0.14 [-0.36;0.85]	0.83 [-0.89;1.21]	0.4027	0.5753
Glycolysis	1.12 [0.71;1.62]	1.33 [0.66;1.74]	0.8941	0.8941
IFN-γ	0.02 [-0.34;0.18]	1.07 [0.76;1.31]	<.0001	<.0001
Type 1 Immune Response	0.39 [0.04;0.52]	1.31 [1.09;1.52]	<.0001	<.0001
Type 17 Immune Response	0.05 [-0.46;0.50]	0.12 [-0.77;0.65]	0.8371	0.8941
Type 2 Immune Response	-0.07 [-0.91;0.86]	-0.37 [-1.37;0.23]	0.2689	0.4482
Immune Tolerance	0.20 [-0.14;0.33]	1.17 [0.87;1.35]	<.0001	<.0001
Wound Healing	-0.60 [-0.94;-0.28]	-1.53 [-1.92;-1.11]	<.0001	<.0001

*False discovery rate adjusted *P* value, corrected using the Benjamini-Hochberg method
All data are represented as median [first quartile; third quartile].

Summary & Conclusions

1. Blood-based immune profiling with the PIR test identifies an aggressive disease state (PIR-resistant) associated with resistance to ICI therapy.
2. PIR result is an independent predictor of outcome for ICI treated patients when adjusted for clinical and pathologic characteristics including PD-L1 expression.
3. PIR-resistant identifies a disease state characterized by increased complement, IFNγ, Th1, immune tolerance, and decreased wound healing.

These data support the utility of the PIR test in predicting patient survival on ICI. Processes associated with PIR-resistant result elucidate mechanisms of primary resistance to ICI in a clinical cohort.