Real-World Performance of Blood-Based Host Immune Profiling in First-line Immunotherapy Treatment in Advanced Stage Non-Small Cell Lung Cancer

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Poster # 311

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Introduction

- Immune checkpoint inhibition (ICI) has improved outcomes for many patients with treatment-naïve advanced non-small cell lung cancer (NSCLC).
- However, better biomarkers are needed to predict patient response and guide treatment decisions considering added toxicity and higher cost of combination treatments.
- A prospectively designed, observational registry study (NCT03289780) assesses the ability of a clinically validated, blood-based, host immune classifier (HIC) to predict ICI therapy outcomes.
- The proteomic classifier was based on MALDI-TOF mass spectrometry and a machine learning algorithm for classification (K-Nearest Neighbor).

Methods

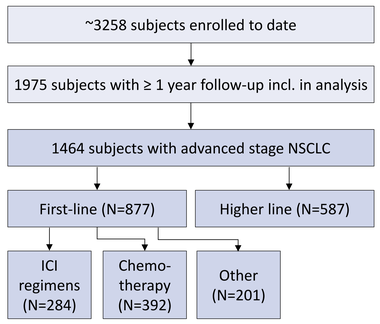
INSIGHT study overview:

- All enrolled subjects are tested and designated HIC-Hot (HIC-H) or HIC-Cold (HIC-C) prior to therapy initiation.
- Subject characteristics, therapeutic decisions, staging, disease monitoring metrics and available biomarker data have been collected.
- Subject follow-up occurs for up to 18 months.
- First subject first visit for was May 11, 2016
- Last subject first visit for the first 2000 subject cohort was January 15, 2019
- Database lock for interim analysis was March 2020

Statistical Methods:

A pre-specified interim analysis was performed on the first 2000 subjects enrolled in the study with at least 1 year follow up. Overall survival (OS) in months (mo) is summarized as median and 95% confidence interval (CI) and as Kaplan-Meier plots and compared between HIC-defined subgroups or between therapies by Cox Proportional hazard ratios and P values. Data from the subgroup (N=877) comprising subjects with advanced stage (IIIB and higher) NSCLC treated with first-line regimens are presented here.

Figure 1. Study subject population summary.



Results

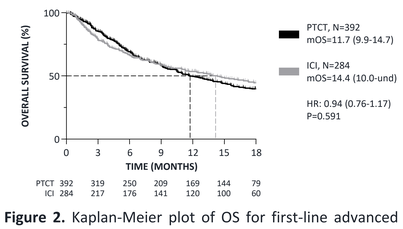


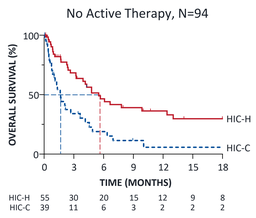
Figure 2. Kaplan-Meier plot of OS for first-line advanced stage NSCLC subjects receiving platinum-doublet chemo- (PTCT) or ICI-containing therapy (ICI). Und: Undefined.

Table 1. Subject demographics by HIC subgroup.

	HIC-Hot (N=622)	HIC-Cold (N=255)
Age (years)		P=0.075
Mean (SD)	68.4 (10.3)	67.0 (10.0)
Median (Range)	68 (35 – 92)	66 (36 – 95)
Gender, N (%)		P=0.004
Female	290 (46.6%)	92 (36.1%)
Male	332 (53.4%)	163 (63.9%)
Histology, N (%)		P=0.006
Adenocarcinoma	430 (69.1%)	143 (56.1%)
Squamous	116 (18.6%)	72 (28.2%)
NSCLC Other	76 (12.2%)	40 (15.7%)
Disease Stage at Study Entry, N (%)		P=0.749
Stage IIIB	78 (12.5%)	34 (13.3%)
Stage IV	544 (87.5%)	221 (86.7%)
ECOG Status At Study Entry, N (%)		P=0.075
0	184 (29.6%)	38 (14.9%)
1	299 (48.1%)	133 (52.2%)
2	117 (18.8%)	66 (25.9%)
3	22 (3.5%)	13 (5.1%)
4	0	5 (2.0%)
Smoking Status, N (%)		P=0.062
Current Smoker	230 (37.0%)	102 (40.0%)
Former Smoker	308 (49.5%)	133 (52.2%)
Never Smoker	84 (13.5%)	20 (7.8%)
PD-L1 Expression, N (%)		P=0.809
Negative (< 1%)	144 (41.9%)	51 (39.2%)
Low (≥ 1% and < 50%)	81 (23.5%)	30 (23.1%)
High (≥ 50%)	119 (34.6%)	49 (37.7%)
N/A	278	125
Treatment Regimen, N (%)		P=0.022
ICI Monotherapy	80 (12.9%)	37 (14.5%)
ICI Combination	116 (18.6%)	51 (20.0%)
Pt-based Chemotherapy	284 (45.7%)	108 (42.4%)
Other Chemotherapy	13 (2.1%)	6 (2.4%)
TKI	35 (5.6%)	5 (2.0%)
Radiation	25 (4.0%)	7 (2.7%)
Other Active Treatment	14 (2.3%)	2 (0.8%)
No Active Treatment	55 (8.8%)	39 (15.3%)

N/A: PD-L1 expression levels not reported in the study (excluded from percentage and Chi²), Pt: platinum, TKI: tyrosine kinase inhibitor

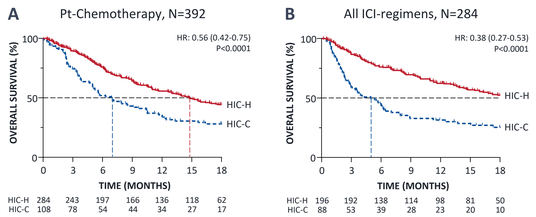
Results



	mOS (mo)
HIC-Hot, N=55	5.5 (3.2-12.4)
HIC-Cold, N=39	1.6 (0.8-3.6)

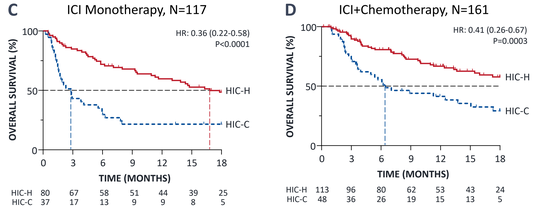
HR: 0.40 (0.24-0.68), P=0.0007

Figure 3. Kaplan-Meier plot of OS for subjects with advanced stage NSCLC without active treatment by HIC result. HR: Hazard ratio by Cox proportional hazards.



	mOS (mo)
HIC-Hot, N=284	14.8 (11.6-und)
HIC-Cold, N=108	7.0 (5.0-10.4)

	mOS (mo)
HIC-Hot, N=196	NR (15.4-und)
HIC-Cold, N=88	5.0 (2.9-6.4)



	mOS (mo)
HIC-Hot, N=80	16.8 (11.3-und)
HIC-Cold, N=37	2.8 (1.6-5.9)

	mOS (mo)
HIC-Hot, N=113	NR (15.4-und)
HIC-Cold, N=48	6.4 (3.6-13.7)

Figure 4. Kaplan-Meier plot of OS by HIC for subjects with advanced stage NSCLC receiving first-line (A) platinum (pt) chemotherapy, (B) any ICI-containing regimen, (C) ICI monotherapy or (D) ICI and chemotherapy combinations. NR: Not reached, Und: Undefined.

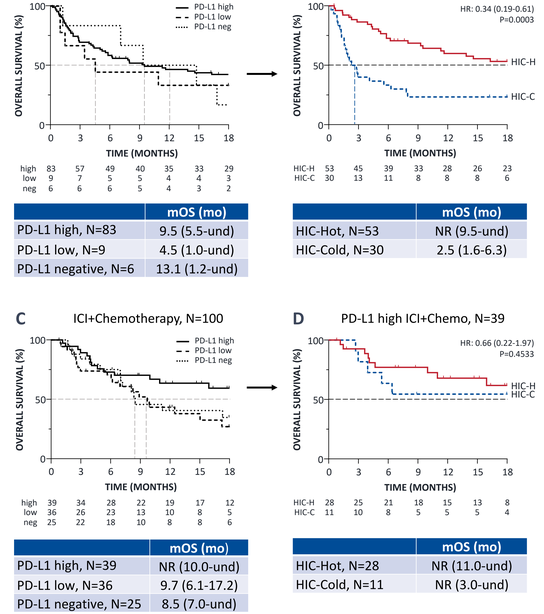
Table 2. PD-L1 expression of ICI-receiving subjects by HIC subgroup.

PD-L1 Expression, N (%)	HIC-Hot (N=126)	HIC-Cold (N=64)	P Value by Chi²
Negative (< 1%)	13 (10%)	9 (14%)	0.694
Low (≥ 1% and < 50%)	32 (25%)	14 (22%)	
High (≥ 50%)	81 (65%)	41 (64%)	

Results

Table 3. Multivariate analysis of OS of subjects receiving an ICI-containing regimen in first-line, including HIC classification and therapy type.

Covariate	vs.	HR (95% CI)	CPH p-value
HIC-Cold	HIC-Hot	0.37 (0.25-0.53)	**<0.0001**
ECOG PS 0	PS 1	1.48 (0.90-2.43)	0.125
	PS 2+	2.62 (1.52-4.50)	**0.0005**
Adenocarcinoma	Squamous Cell	1.42 (0.86-2.34)	0.168
	NSCLC Other	0.54 (0.30-1.00)	**0.047**
ICI+Chemotherapy	ICI Monotherapy	1.67 (1.11-2.51)	**0.013**
	With Other	1.94 (0.66-5.74)	0.232
PD-L1 high (≥ 50%)	PD-L1 low (≥ 1% and < 50%)	1.54 (0.91-2.60)	0.104
	PD-L1 negative (< 1%)	1.88 (1.07-3.32)	**0.028**
	N/A	0.99 (0.62-1.61)	0.987
Age < 65	Age ≥ 65	1.51 (1.07-2.15)	**0.020**
Never Smoker	Ever Smoker	1.81 (0.89-3.91)	0.112
Stage IIIB	Stage IV	1.50 (0.72-3.14)	0.283
Female	Male	1.02 (0.71-1.46)	0.933



	mOS (mo)
PD-L1 high, N=83	9.5 (5.5-und)
PD-L1 low, N=9	4.5 (1.0-und)
PD-L1 negative, N=6	13.1 (1.2-und)

	mOS (mo)
HIC-Hot, N=53	NR (9.5-und)
HIC-Cold, N=30	2.5 (1.6-6.3)

	mOS (mo)
PD-L1 high, N=39	NR (10.0-und)
PD-L1 low, N=36	9.7 (6.1-17.2)
PD-L1 negative, N=25	8.5 (7.0-und)

	mOS (mo)
HIC-Hot, N=28	NR (11.0-und)
HIC-Cold, N=11	NR (3.0-und)

Figure 5. Kaplan-Meier plot of OS for subjects with advanced stage NSCLC receiving first-line (A) ICI monotherapy or (C) ICI and chemotherapy combinations by PD-L1 expression and (B,D) PD-L1 high subgroup by HIC. Neg: Negative, NR: Not reached, Und: Undefined, Tx: Therapy.

Conclusions

1. In a real-world clinical setting, overall survival of patients with treatment-naïve advanced stage NSCLC receiving platinum-based chemotherapy did not differ significantly from patients receiving any type of ICI containing regimen.

2. Profiling the immune response to lung cancer using the proteomic host immune classifier identifies a chronic inflammatory disease state, HIC-Cold, in almost 30% of subjects which is associated with poor prognosis:
   - in the absence of treatment
   - independent of treatment type
   - independent of PD-L1 and other clinical factors

3. Subjects receiving ICI and chemotherapy in combination experienced longer overall survival than subjects receiving ICI alone, with and without adjusting for PD-L1 expression and other clinical factors.

4. In subjects with high PD-L1 expression:
   - HIC-Hot receiving ICI alone experienced similar overall survival to that of triplet combination.
   - HIC-Cold had shorter overall survival on ICI alone than on ICI combination indicating that HIC might identify a disease state less responsive to ICI alone.

Blood based HIC is independent of PD-L1 expression and may provide clinically meaningful information for selection of ICI treatment type or best supportive care in patients with advanced stage NSCLC.

We thank the INSIGHT investigators and all subjects participating in the study.

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