Prediction of primary resistance to anti-PD1 therapy in 2nd line NSCLC

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DISCLOSURE SLIDE

J. G. J. V. Aerts:
Advisory board - BMS, MSD, Boehringer Ingelheim, Eli-Lilly, Astra-Zeneca, Roche, Amphera, Takeda
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Ownership Interest - Amphera

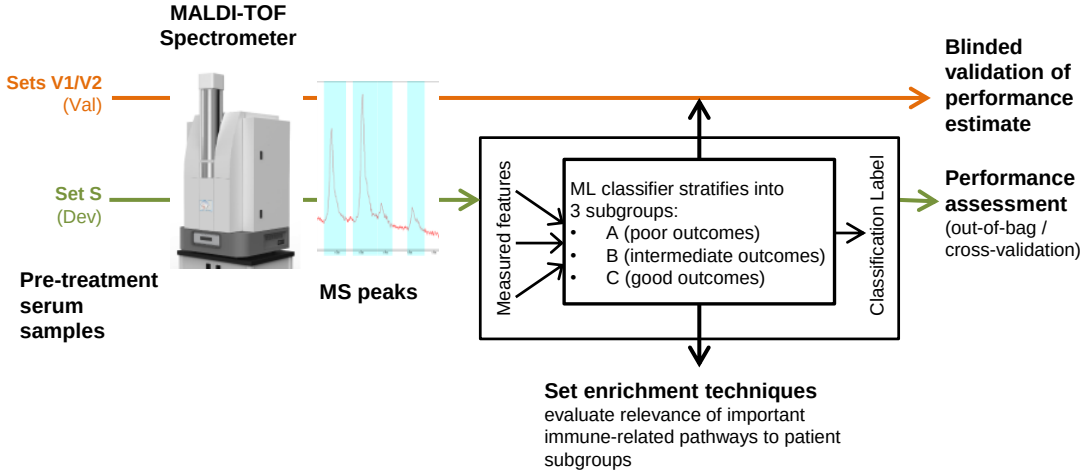
4 Patient Cohorts (all 2nd line advanced NSCLC):

- Development Set "S" (N=116) treated at NKI with nivolumab
- Validation Set 1 "V1" (N=58) treated at NKI with nivolumab
- Validation Set 2 "V2" (N=75) treated at Erasmus with nivolumab
- Chemotherapy Controls "D" (N=68) treated with docetaxel

Patient characteristics and outcomes

		S (N=116)	V1 (N=58)	V2 (N=75)	D (N=68)
Age	Median (Range)	65 (43-83)	63 (29-75)	65 (35-78)	64 (39-77)
* % of available data		n (%*)	n (%*)	n (%*)	n (%*)
Gender	Male	66 (57)	31 (53)	48 (64)	52 (76)
	Female	50 (43)	27 (47)	27 (36)	16 (24)
PS	0	36 (32)	15 (26)	18 (32)	35 (51)
	1	60 (54)	38 (66)	37 (66)	29 (43)
	2+	15 (14)	5 (9)	1 (2)	4 (6)
Smoking Status	Ever	104 (91)	55 (95)	61 (92)	64 (94)
	Never	10 (9)	3 (5)	5 (8)	4 (6)
Histology	Adenocarcinoma	77 (66)	27 (75)	49 (65)	47 (75)
	Squamous	26 (22)	6 (17)	17 (23)	12 (19)
	Other	13 (11)	3 (8)	9 (12)	4 (6)
Response	CR	1 (1)	0 (0)	0 (0)	0 (0)
	PR	16 (14)	16 (28)	15 (20)	7 (10)
	SD	19 (16)	19 (33)	25 (33)	23 (34)
	PD	65 (56)	19 (33)	31 (41)	22 (32)
	NA/NE	15 (13)	4 (7)	4 (5)	16 (24)
PFS (months)	Median	2.6	5.2	4.3	3.5
OS (months)	Median	8.5	11.3	12.0	8.0

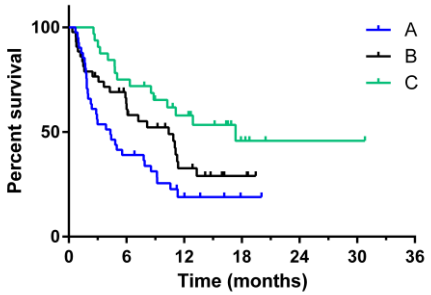
Multivariate Test Development using measurements of the circulating proteome



Similar methods used in recent work in melanoma (J Weber et al., Cancer Immunol Res. 2018 6(1):79-86)

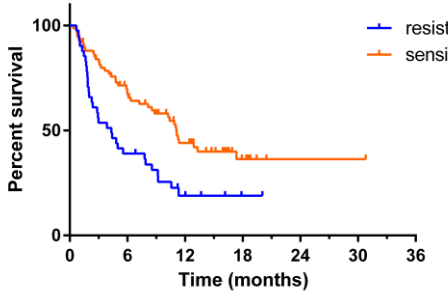
Results: Development Set "S"

PIR test stratifies patients as 41 (35%) A (poor outcomes), 43 (37%) B (intermediate outcomes), 32 (28%) C (good outcomes)

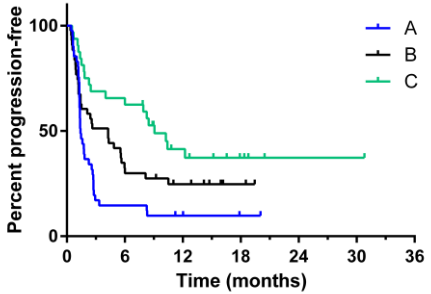


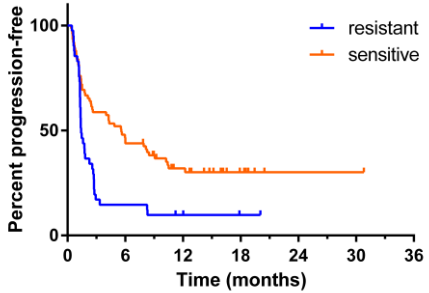
A (poor) → resistant

B+C → sensitive



HR (95% CI)	0.48 (0.30-0.77)
P value	0.002
OS Median (95% CI): resistant	4.3 (2.0-7.9) months
OS Median (95% CI): sensitive	11.1 (8.1-17.3) months





HR (95% CI)	0.46 (0.30-0.71)
P value	<0.001
PFS Median (95% CI): resistant	1.4 (1.3-2.3) months
PFS Median (95% CI): sensitive	5.6 (2.5-8.5) months

Results: Development Set "S" continued

Multivariate analysis

	OS		PFS	
	HR (95% CI)	p value	HR (95% CI)	p value
PIR Test (sensitive vs resistant)	0.60 (0.35-1.00)	0.050	0.52 (0.32-0.83)	0.006
ECOG PS (1 vs 0)	1.94 (1.06-3.56)	0.032	1.51 (0.91-2.52)	0.114
ECOG PS (≥2 vs 0)	4.01 (1.86 – 8.64)	<0.001	2.38 (1.19-4.78)	0.014
Never vs ever smoker	2.11 (0.99-4.50)	0.054	1.34 (0.64-2.80)	0.435
Squamous vs Non-squamous	0.87 (0.48-1.57)	0.648	1.05 (0.62-1.77)	0.865
PD-L1 <1% vs ≥1%	1.03 (0.11-9.62)	0.979	0.36 (0.04-2.93)	0.337
PD-L1 NA vs ≥1%	2.58 (0.91-7.33)	0.076	1.63 (0.76-3.46)	0.207

Test classification is an independent predictor of OS and PFS when adjusted for PS, histology, smoking history, and PD-L1 status (analysis ongoing, currently only available for 20 patients).

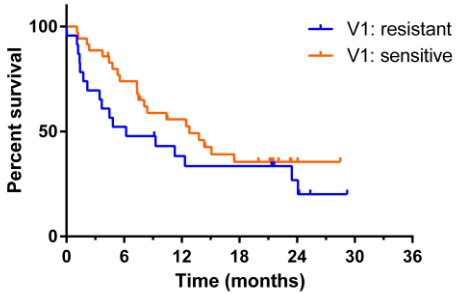
Biological Interpretation via Set Enrichment Methods

Biological Process	Enrichment p value	FDR
Complement	0.002	<0.05
Acute phase	0.002	<0.05
Extracellular matrix	0.009	<0.10
Wound healing	0.017	<0.15
Acute inflammation	0.051	<0.25
Immune response	0.056	<0.25
Immune Response Type 2	0.074	<0.30
Interleukin-10	0.079	<0.30
Angiogenesis	0.088	<0.30
Growth factor receptor signaling	0.139	<0.40
Acute response	0.224	<0.50
Cell adhesion	0.227	<0.50
Cytokine activity	0.326	<0.70
NK regulation	0.384	<0.70
Innate Immune Response	0.413	<0.70
Immune Response Type 1	0.422	<0.70
Mesenchymal transition	0.572	<0.90
Immune T-cells	0.631	<0.90
Cancer biomarkers	0.702	<0.90
Glycolytic Processes	0.734	<0.90
Immune B-cells	0.871	<1.0
Adaptive immune response	0.918	<1.0
Hypoxia	0.938	<1.0
Interferon	0.951	<1.0
Cell cycle	0.962	<1.0

Complement, acute phase, extra-cellular matrix and wound healing show increased activation in resistant compared with sensitive subgroups

Results: Validation Sets

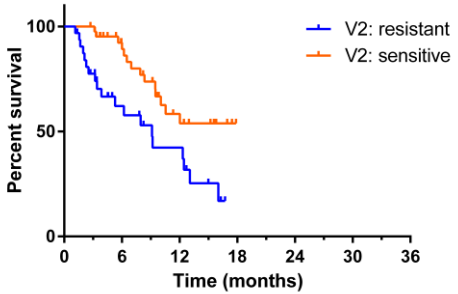
V1: N=58 (40% resistant)



resistant vs sensitive in V1

HR (95% CI) :	0.69 (0.36-1.33)
P value	0.267
OS Median (95% CI): resistant	6.2 (2.2-23.5) months
OS Median (95% CI): sensitive	12.8 (7.4-undefined) months

V2: N=75 (43% resistant)

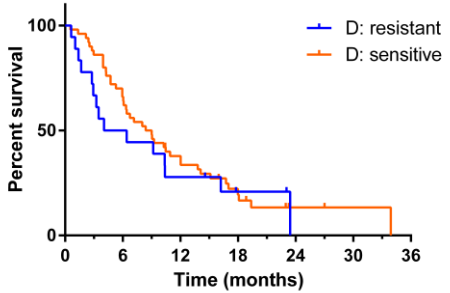


resistant vs sensitive in V2

HR (95% CI)	0.39 (0.19-0.77)
P value	0.007
OS Median (95% CI): resistant	9.1 (3.9-13.1) months
OS Median (95% CI): sensitive	not reached (9.5-undefined) months

Chemotherapy Control: Docetaxel

D: N=68 (26% resistant)



resistant vs sensitive in D

HR (95% CI)	0.80 (0.45-1.46)
P value	0.471
OS Median (95% CI): resistant	5.2 (2.8-10.4) months
OS Median (95% CI): sensitive	8.7 (6.0-12.0) months

- We developed and validated a pre-treatment serum test separating 2nd line NSCLC patients into groups with different degrees of benefit from nivolumab.
- While the good performance group contained ~40% of patients with durable benefit, the poor (resistant) performance group had very poor outcomes.
- The test was an independent predictor of outcome in multivariate analysis.
- The test showed no evidence that it could predict outcomes in docetaxel-treated patients, and so may have predictive potential between nivolumab and docetaxel.
- The resistant group was characterized by significant pre-treatment activation of complement, acute phase, wound healing, and processes related to the extracellular matrix.

- If validated in a prospective randomized study the test could be used to inform on anti-PD1 efficacy.
- Evaluation in front-line treatment with IO and IO combinations is in progress.