Plasma proteomics to predict clinical benefit and irAEs In NSCLC treated with anti-PD(L)1 ICIs

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BEAUMONT RCSI CANCER CENTRE

ONCOHOST GUIDED ONCOLOGY

Disclosure Information

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Commercial Interest	Relationship(s)
AstraZeneca	Research funding, Consulting/Advisory Board, Data Safety Monitoring Board, Honoraria
Bristol Myers Squibb	Research funding, Consulting/Advisory Board, Data Safety Monitoring Board, Honoraria
Roche/Genentech	Research funding, Consulting/Advisory Board, Honoraria
Amgen	Research funding, Consulting/Advisory Board
Arcus Biosciences	Research funding, Consulting/Advisory Board/Steering committee
NGM Pharmaceuticals	Consulting/Advisory Board
Bayer	Consulting/Advisory Board
Regeneron	Consulting/Advisory Board
Takeda	Consulting/Advisory Board
Pfizer	Consulting/Advisory Board
Elevation Oncology	Consulting/Advisory Board
Abbvie	Consulting/Advisory Board
Kaleido Biosciences	Consulting/Advisory Board
Mirati	Research funding
Daiichi Sankyo	Consulting/Advisory Board Data Safety Monitoring Board, Honoraria

Introduction:

Biomarkers for ICI therapy in NSCLC: Areas of Need

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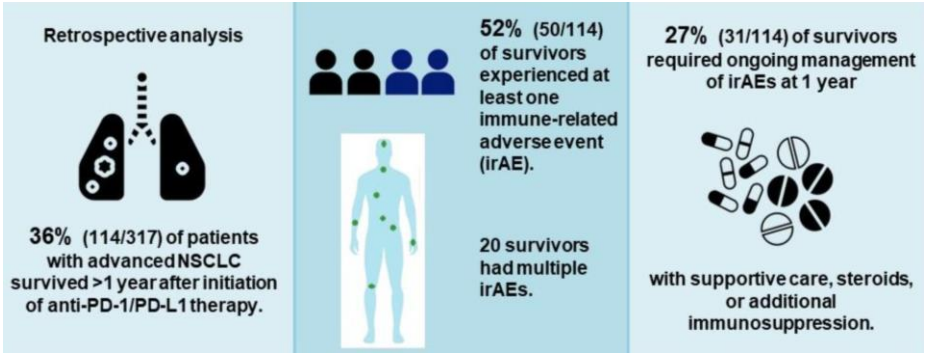
ICI Use for Advanced NSCLC*

PD-L1 ≥50%	PD-L1 1-49%	PD-L1 <1%
ICI + chemotherapy	ICI + chemotherapy	ICI + chemotherapy
ICI Monotherapy		

* Preferred treatment (NCCN)

PD-L1 is the only biomarker used to direct ICI therapy in NSCLC

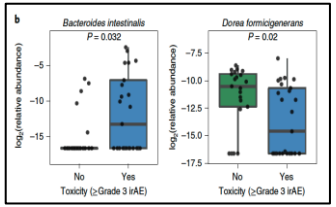
irAEs from ICI Therapy in Advanced NSCLC




nature medicine

Article https://doi.org/10.1038/s41591-022-02094-6

Germline variants associated with toxicity to immune checkpoint blockade



There are no validated biomarkers for irAEs from ICIs, an area of increasing clinical relevance

Hsu, Naidoo et al, Oncologist 2022

Methods:
Study Schema

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Prophetic Trial:

Prospective, Observational Trial

Predicting clinical benefit using plasma proteomics profiling (NCT04056247)

- Stage IV NSCLC
- No actionable genomic driver mutations
- 1L systemic therapy

Baseline blood sample proteomic profiling 

→ PD (L)1 based therapy

→ PD (L)1 based therapy + Platinum based chemotherapy

Endpoints (5yr follow-up)
- OS
- PFS
- Clinical Benefit
- Toxicity (AEs; irAEs)

Proteomics profiling

- SomaScan technology (Aptamer-based)
- Examines protein expression levels
- >7000 proteins/sample

Target binding → *UV cleavage* → *Array hybridization* → *Array scanning*

Study Endpoints:
PROphet (Clinical Benefit)

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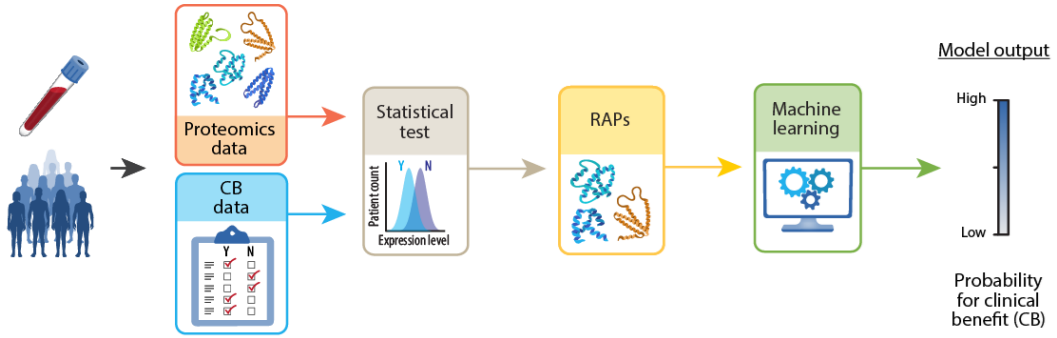
Definition:

- **Clinical benefit** was defined based on PFS at 12 months

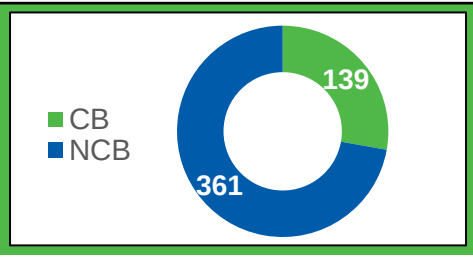
Proteomic Assessment:

- Identify proteomic signature associated with ICI resistance:
- RAP: 'Resistance Associated Proteins'
- Machine learning algorithm associates with clinical benefit



Prophet Trial:
Clinical Benefit Cohort (n=500)

Patient Features		Clinical Benefit
Sex	Male	302
	Female	198
ECOG-PS	0	191
	1	270
	2	37
	Unknown	2
PD-L1	High	199
	Low	141
	Negative	131
	Unknown	29
Histology	non-SqCC	370
	SqCC	101
	Unknown	29
Treatment type	ICI+Chemo	290
	ICI	210



Results:
PROphet (Clinical Benefit)

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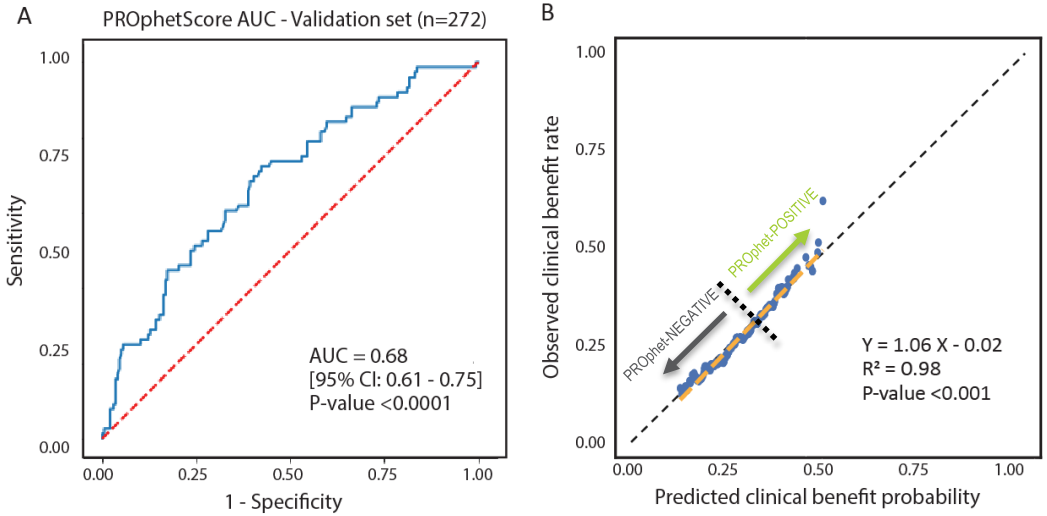
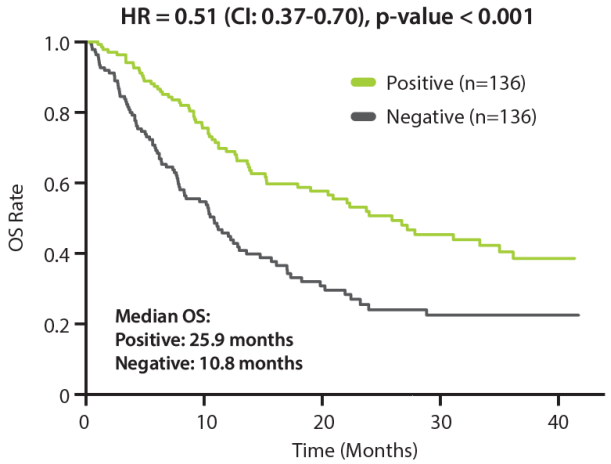


High correlation between predicted clinical benefit probability and the observed clinical benefit rate (R^2 = 0.98)



A positive PROphet result is associated with a significant survival benefit

Christopoulos et al., JCO PO 2024

Results:

Proteomic Signature + PD-L1: Associates with Clinical Benefit

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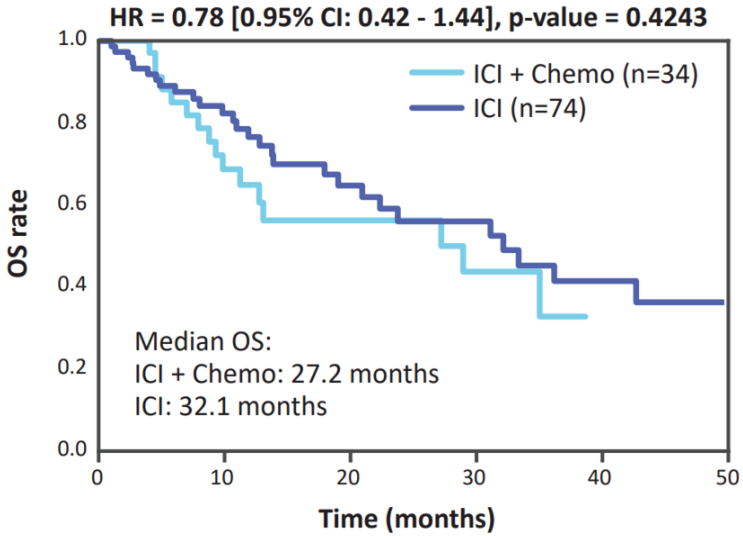
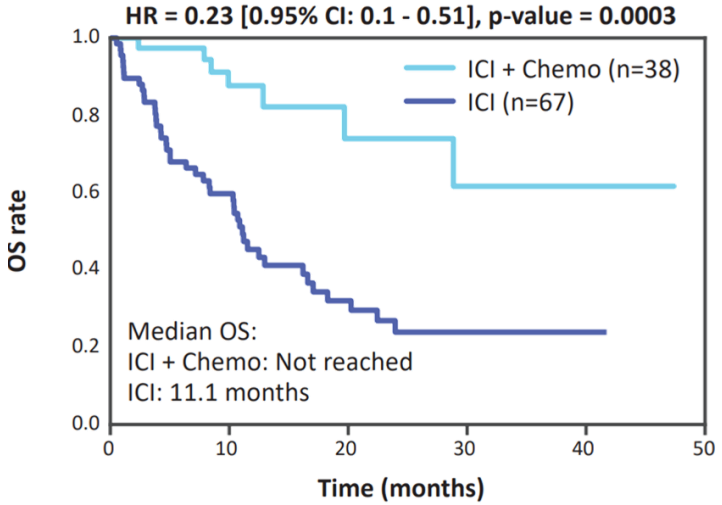
PD-L1 ≥50%

‘PROphet’ POSITIVE + PD-L1 ≥50%



‘PROphet’ NEGATIVE + PD-L1 ≥50%



PROphet result identify NSCLC patients with PD-L1 >50% who are more likely to benefit from chemo-ICI (compared to ICI)

Christopoulos et al., JCO PO 2024

Study Endpoints:
PROphet-irAE Prediction

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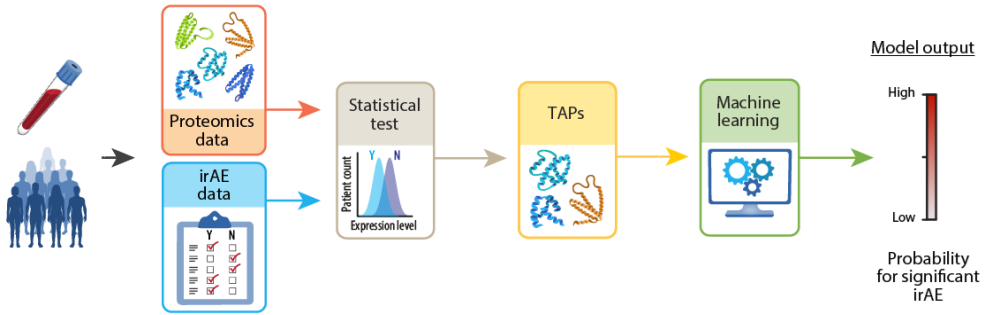
Definition:

- **Severe irAE:** grade ≥3 irAEs within the first 100 days that leading to treatment discontinuation

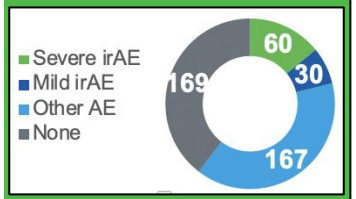
Proteomic Assessment:

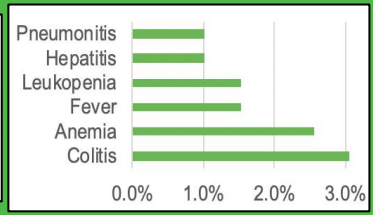
- Identify proteomic signature associated with irAEs:
- TAP: 'Toxicity Associated Proteins'
- Machine learning algorithm associates with irAE development
- irAE: AEs that required immunosuppressive therapy, annotated by treating physicians



Prophet Trial: irAE Cohort (n= 426)

Category	Parameter	irAE cohort
Sex	Male	249
	Female	177
ECOG	0	136
	1	240
	2	47
	Unknown	3
Histology	non-SqCC	312
	SqCC	97
	Unknown	17
Treatment type	ICI+Chemo	151
	ICI	275





Results:
PROphet-irAE Prediction

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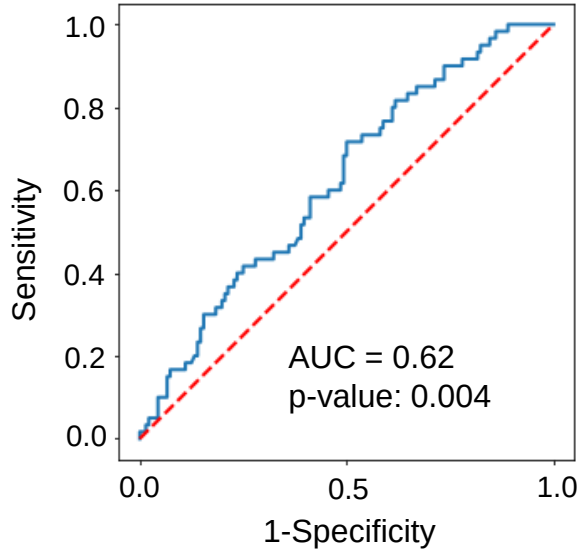

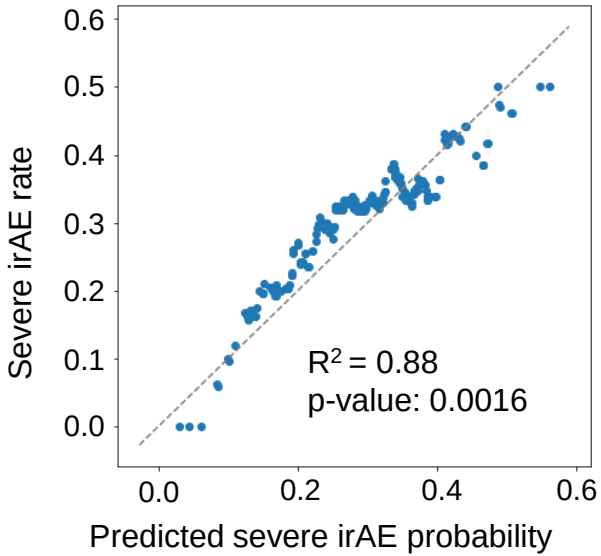

irAE model demonstrated statistically significant predictive capabilities

High correlation between predicted severe irAE probability and the observed severe irAE rate

Future Directions:

Mechanistic insights from RAPs and the TAPs

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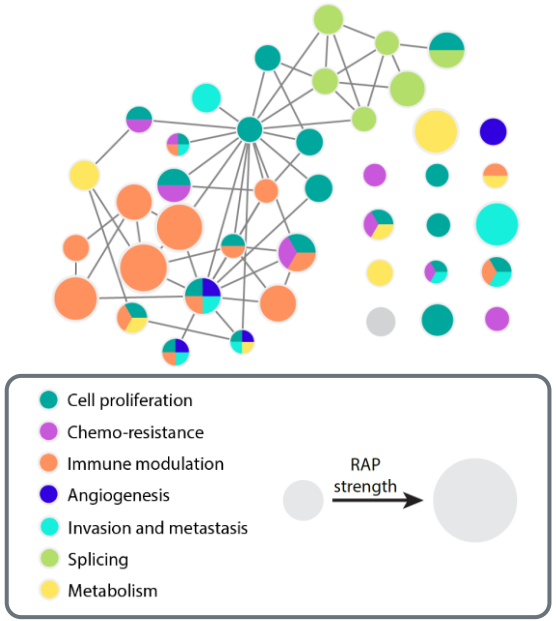
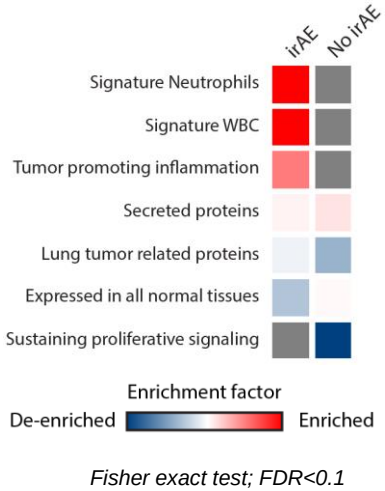
Resistance-Associated Proteins (RAPs)

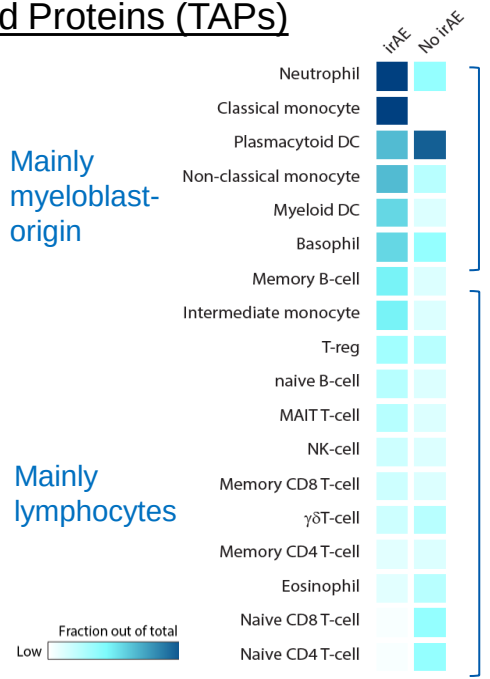


Proteins higher in no clinical benefit are involved in different resistance mechanisms

Toxicity-Associated Proteins (TAPs)



Fisher exact test; FDR<0.1



Neutrophil and monocyte related proteins

Future Directions:

Overlap Between PROphet (Clinical Benefit) and PROphet-irAE Predictions

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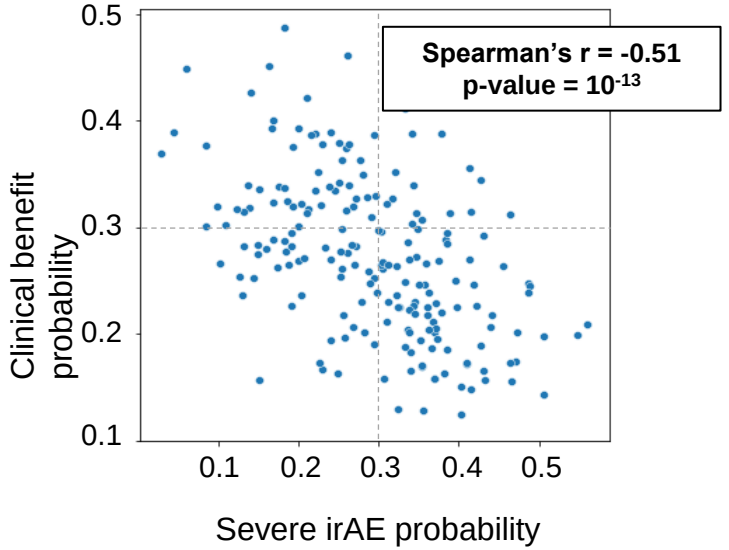
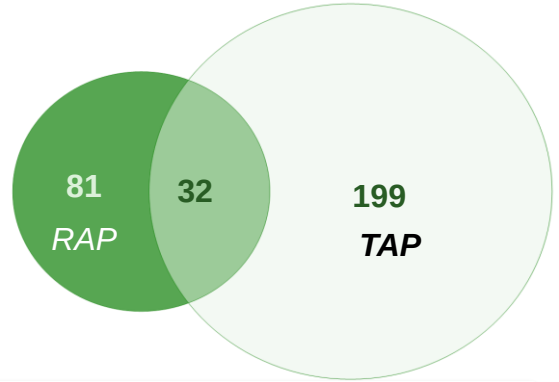


Negative correlation between irAE probability and clinical benefit



RAP = Resistance-Associated Protein
TAP = Toxicity-Associated Protein

Minimal overlap between proteins associated with clinical benefit (RAP) and irAEs (TAP)

Conclusions:

Proteomic signatures and ICI therapy in NSCLC

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- A proteomic signature from blood may enrich for prediction of clinical benefit in PD-L1>50% advanced stage NSCLC, based on presence/absence of resistance-associated proteins (RAPs)
- A different proteomic signature from baseline blood, may predict for development of severe irAEs in advanced NSCLC, based on presence of toxicity associated proteins (TAPs)
- There is little overlap between proteomic signatures for response and toxicity
- RAPs are associated with multiple potential resistance mechanisms for treatment
- TAPs are associated with inflammation and neutrophil- and monocyte-related signals, related to irAEs
- Integration of proteomic signatures for clinical benefit and irAEs may be the future of refining ICI-based treatment selection in NSCLC

Colleagues and Collaborators

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Beaumont RCSI Cancer Centre
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- Catriona Dowling, PhD

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- Ryan J. Sullivan, MD PhD

Northwestern University
- Young Kwang Chae, MD

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- David Gandara

Roswell Park Comprehensive Cancer Center
- Igor Puzanov

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- David Carbone

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- Petros Christopoulos

Shamir Medical Center
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- Michal Harel

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- Niels Reinmuth, **Asklepios Kliniken GmbH**
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- Ido Wolf, **Sourasky Medical Center**
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All the patients who participated in this study