Pre-existing Immunity and Treatment Outcome with Anti-PD1 in Melanoma

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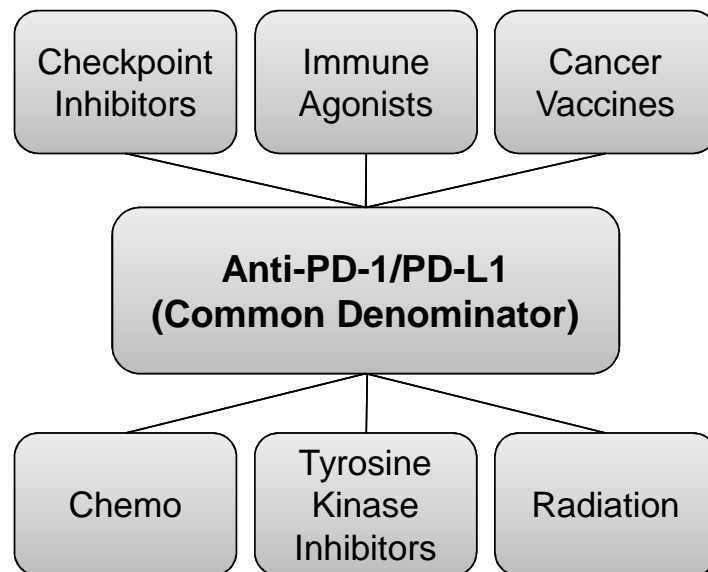Department of Medicine
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Disclosures

Acteris, consultant/co-founder, stockholder

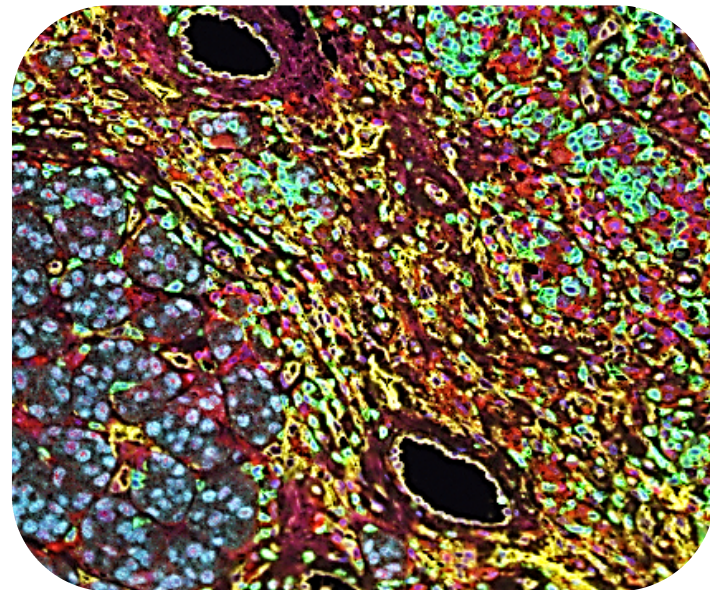# The Challenge: Most patients do not respond to anti-PD1

Immune Checkpoint Blockade:
A Common Denominator Approach to Cancer Therapy

CellPress

Combinations in Clinical Development

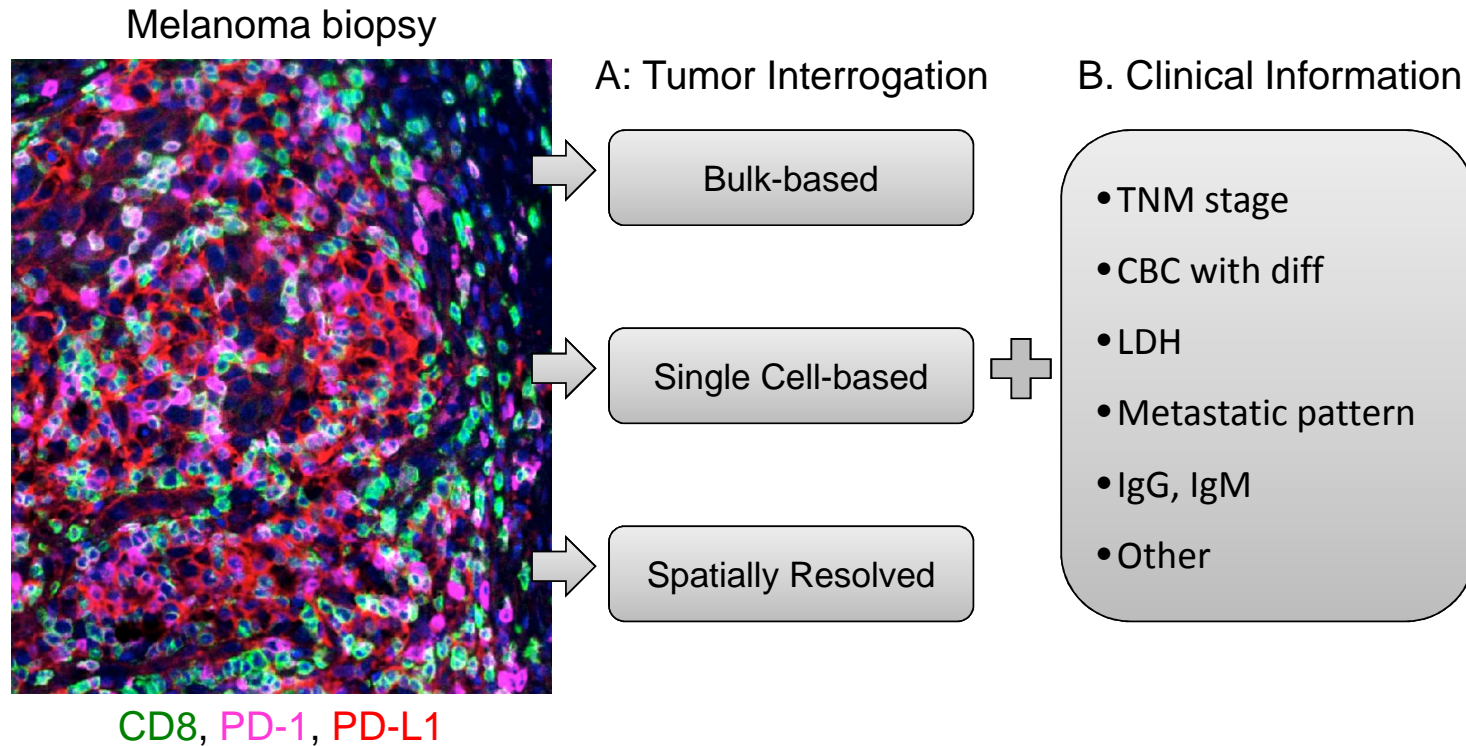Main site of anti-PD-1/PD-L1 activity

Checkpoint Inhibitors | Immune Agonists | Cancer Vaccines

Anti-PD-1/PD-L1 (Common Denominator)

Chemo | Tyrosine Kinase Inhibitors | Radiation

How do we identify the best treatment option for each individual patient?
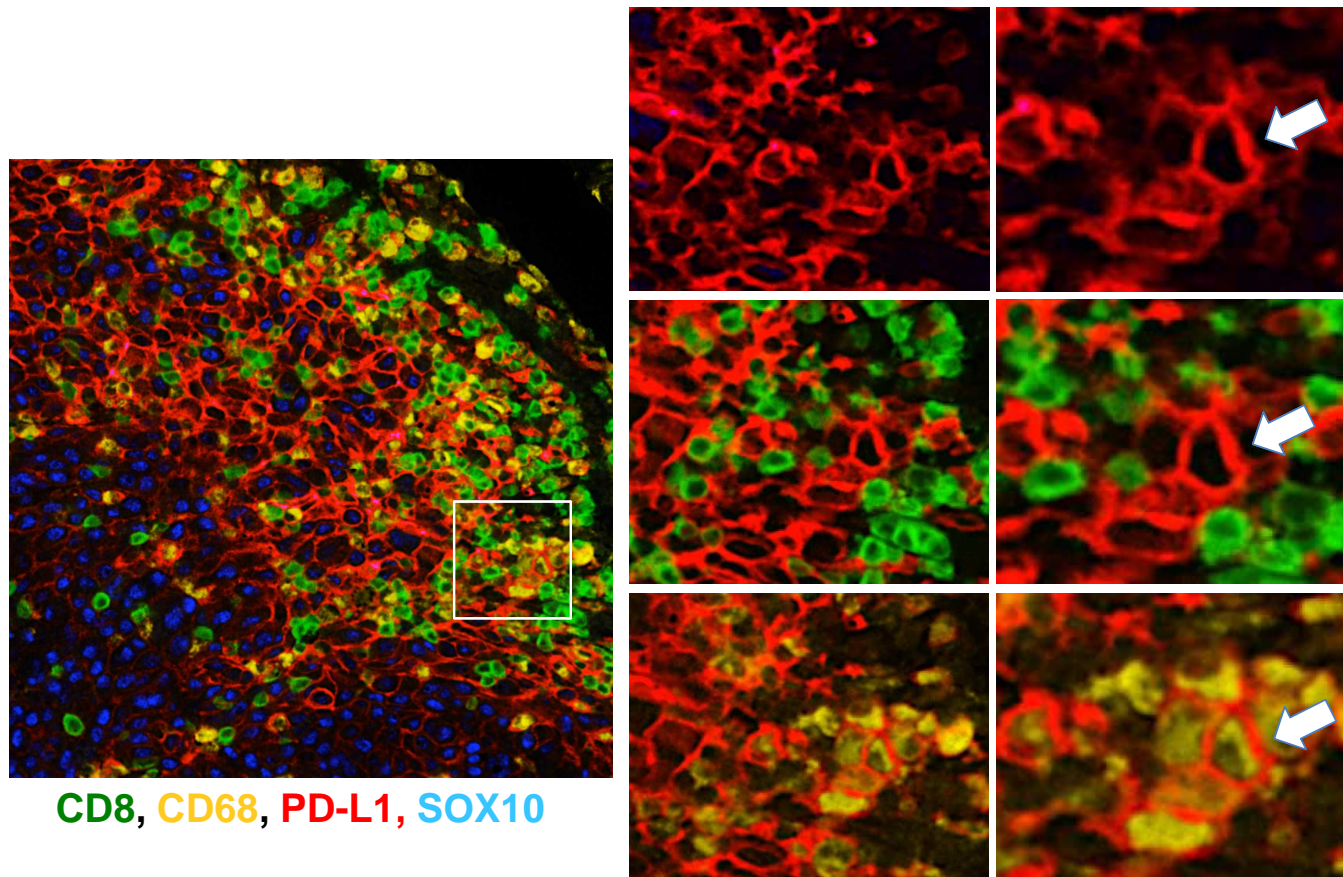
*Suzanne L. Topalian, Charles G. Drake, Drew M. Pardoll

Integrating tumor and clinical data sources

Melanoma biopsy

CD8, PD-1, PD-L1

A: Tumor Interrogation

- Bulk-based
- Single Cell-based
- Spatially Resolved

B. Clinical Information

- TNM stage
- CBC with diff
- LDH
- Metastatic pattern
- IgG, IgM
- Other

Capturing cell-cell interactions in native context

CD8, CD68, PD-L1, SOX10
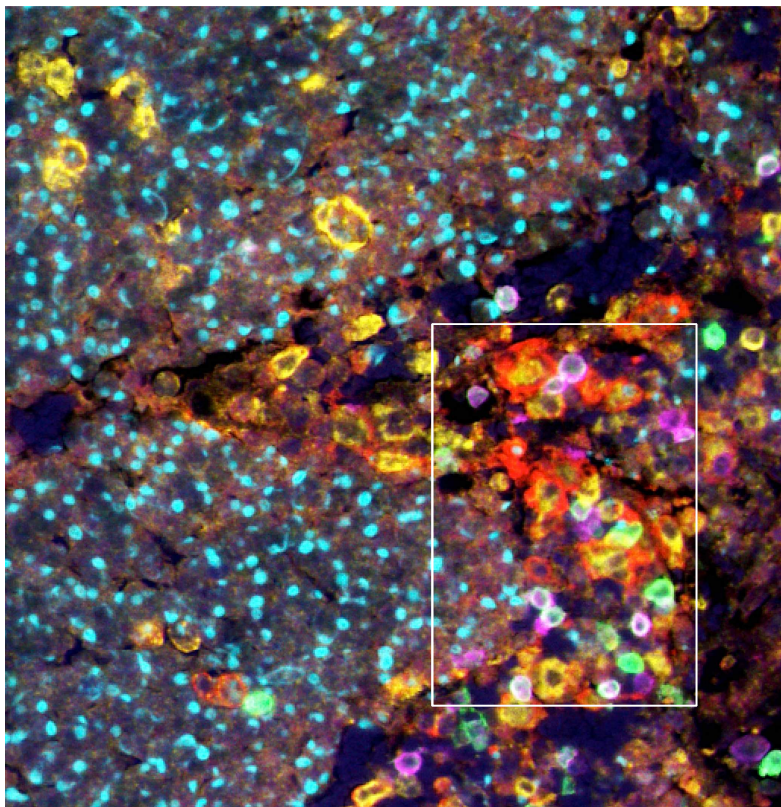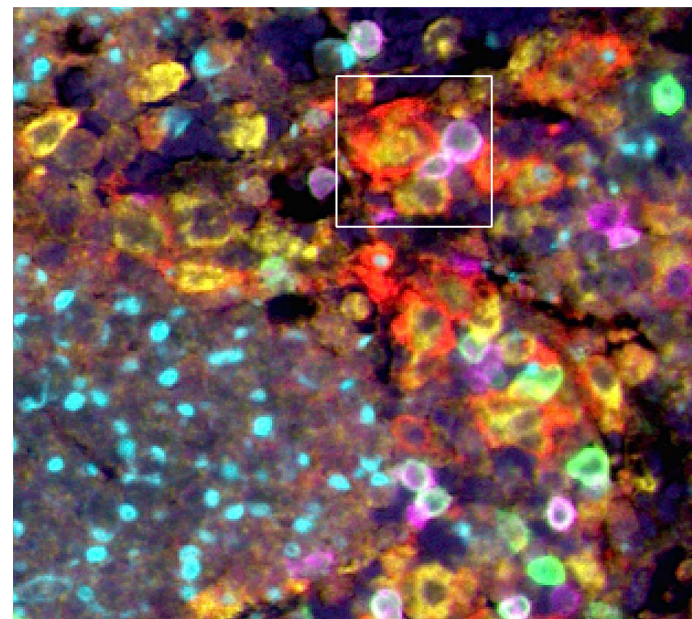
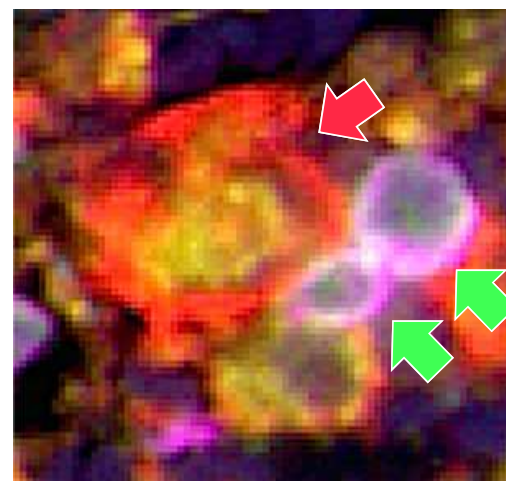What are the other surface receptors and ligands being expressed between distinct cell types?

A

B

C

CD8+PD-1+ T cells

CD68+PD-L1+ MDCs

Capturing multiparametric information according to response

PD-L1: Single parameter vs. multi-parameter

APS Score (PD-L1): 3

Responder

APS Score (PD-L1): 4

Non-Responder

PDL1= red (membraneous)
SOX10= blue (nuclear)
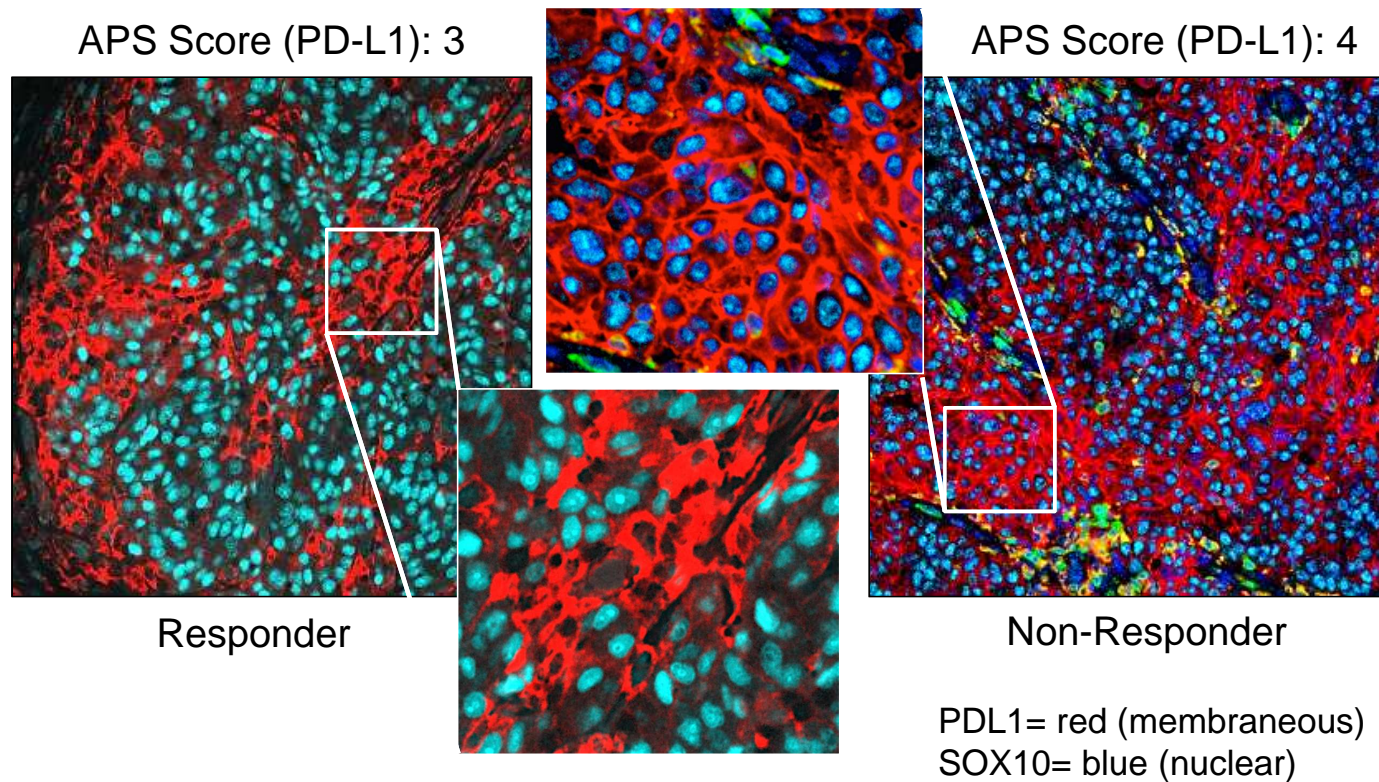
Both patients would be predicted to respond to anti-PD1

Capturing multiparametric information according to response

CD68, PD-L1   CD8, PD-L1   SOX10, PD-L1
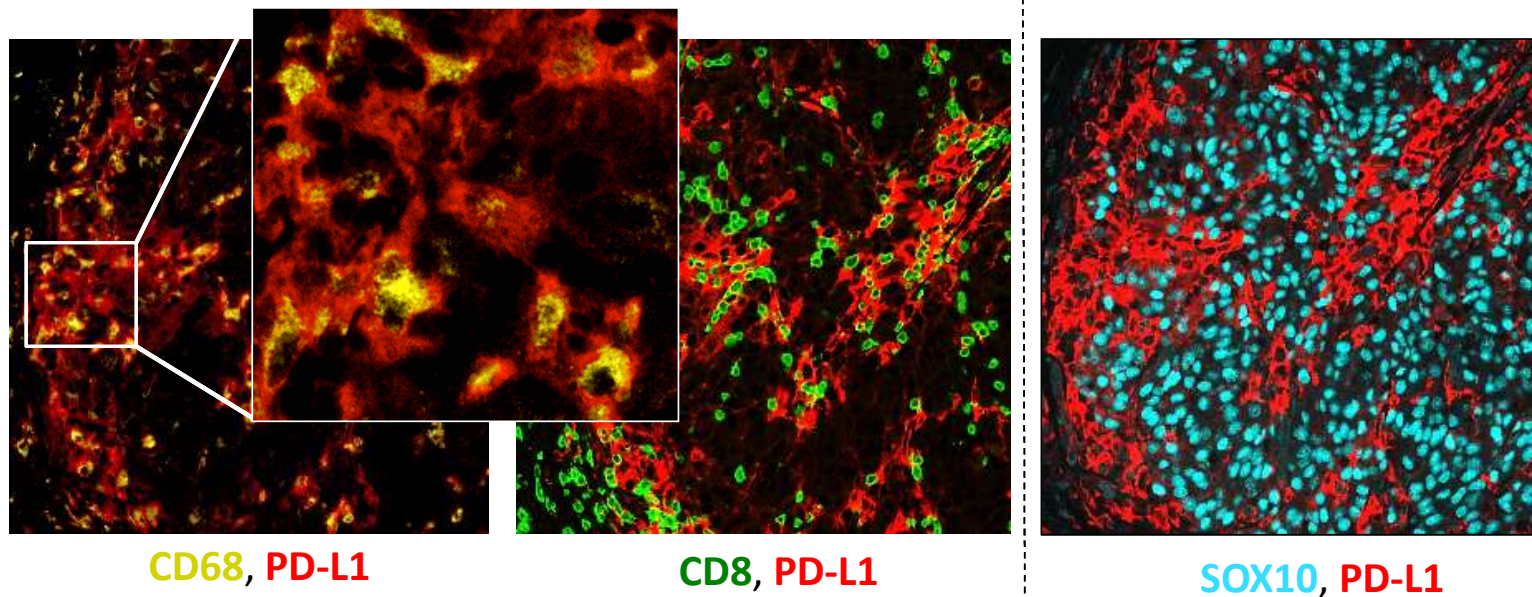
Primary source of PD-L1	Myeloid-derived cells	Cancer cells
T-cells, IFN-gamma	Dependent (Upregulated)	Independent (Constitutive)
Treatment Outcome	Response	Progression

There are niches that are commonly shared across cancer types
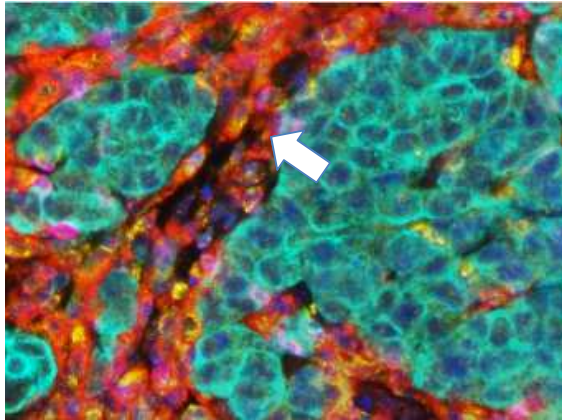
Triple Negative Breast Ca
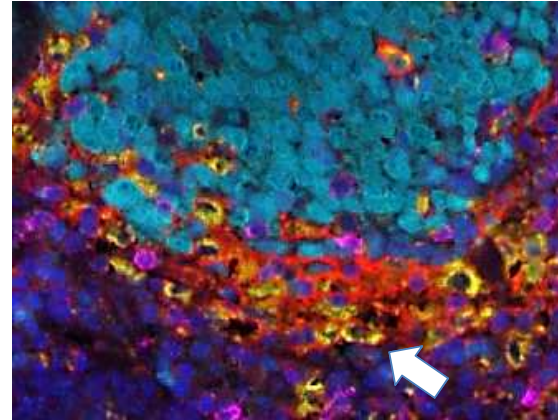
Head&Neck SCC
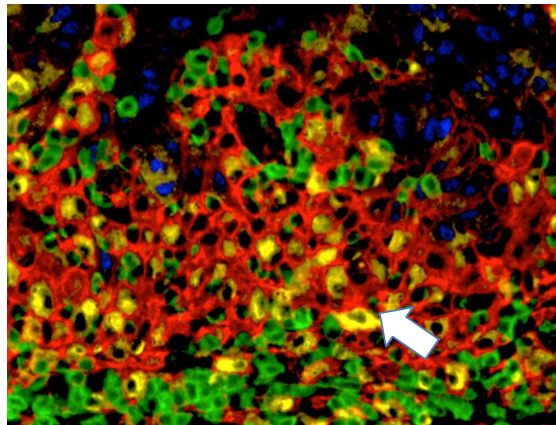
Melanoma
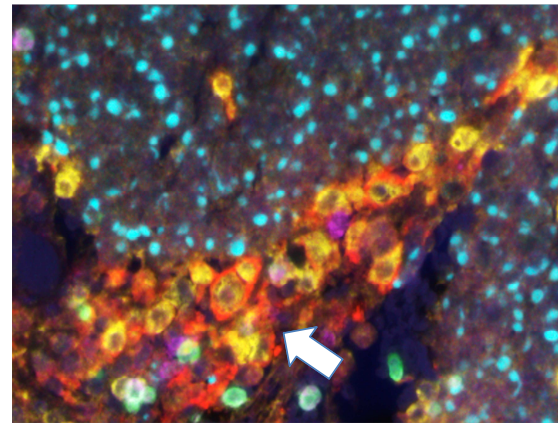
Merkel Cell Carcinoma

Integrated Omics: Bulk + Single cell + Spatially resolved

Spatial Organization	Multiparametric	Subcellular localization
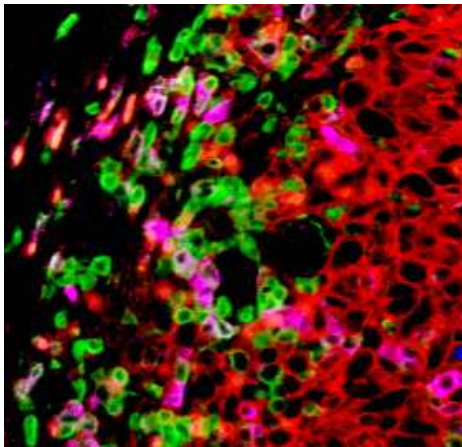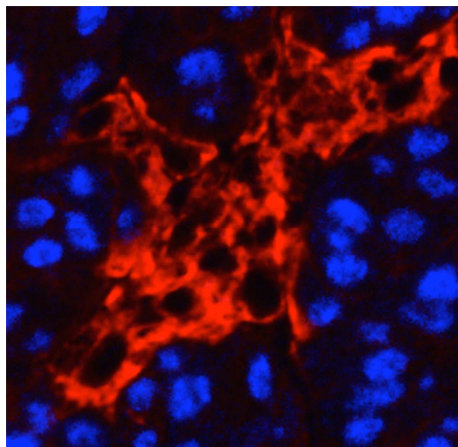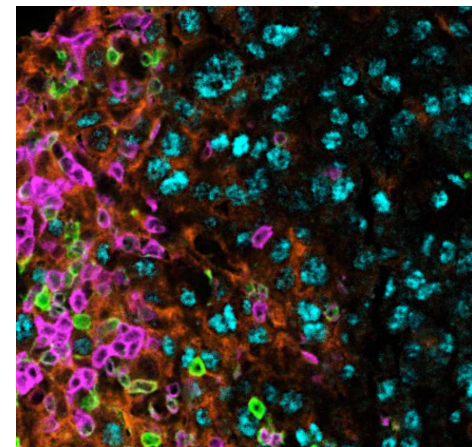
CD8, **PD-1**, **PD-L1**   **PD-L1**, **SOX10**   **CD8**, **PD-1**, **HLA Class I**

An integrated Omics approach: Bulk + Single cell + Spatially resolved
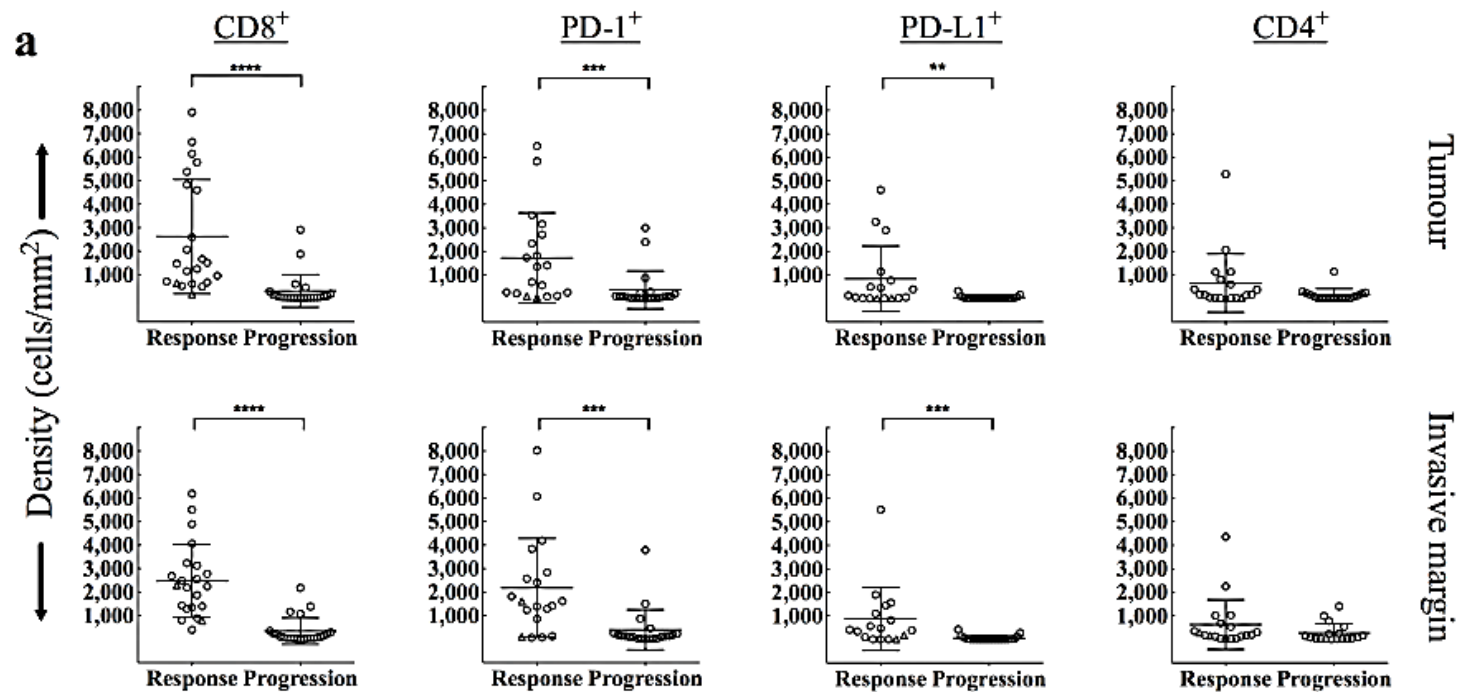
Can we develop a systematic multiplexed IHC approach that builds on this?

Integrating tumor and clinical data sources

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Spatially Resolved

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- TNM stage
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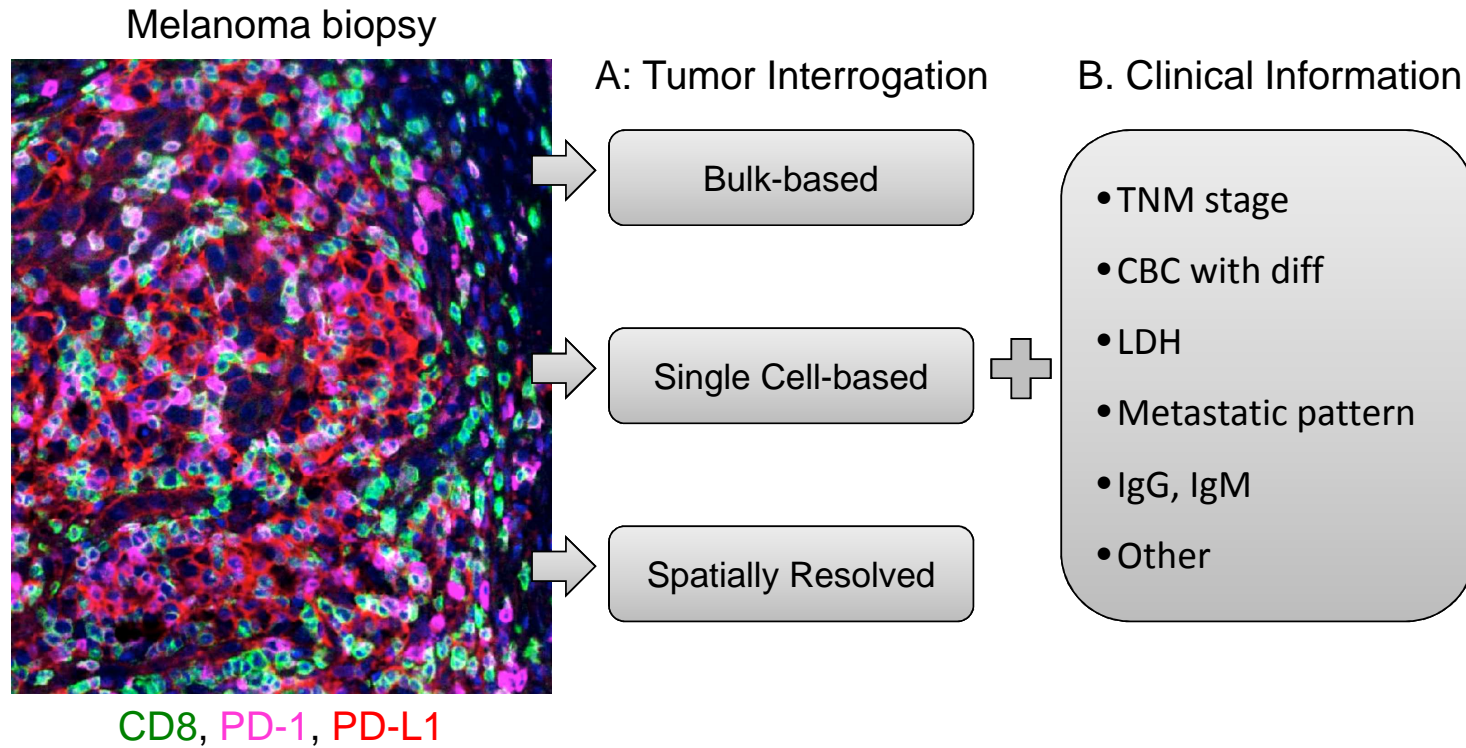
Clinical activity of anti-PD-1 according to metastatic pattern

A Progression-free Survival According to Metastatic Pattern

- Liver-/Lung+ (median, 19.36 mo)
- Liver-/Lung- (median, 16.21 mo)
- Liver+/Lung+ (median, 5.59 mo)
- Liver+/Lung- (median, 2.96 mo)

Progression-free Survival

Months
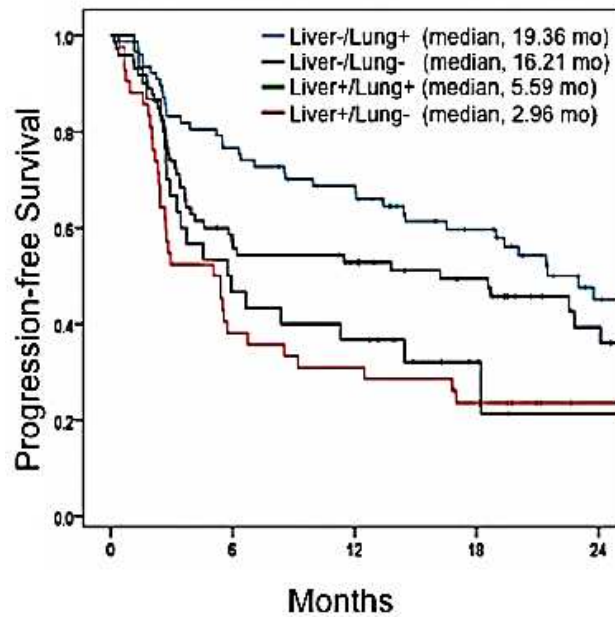
Full Analysis Set Population: N=199

B Objective Response Rates According to Liver Metastases in Patients with Primary Cutaneous Melanoma

54.4%

Liver Metastasis	Patients (n)	ORR (95% CI) P=0.015
Present	46	39.1% (24.5-53.8)
Absent	125	60% (51.3-68.7)

Lower response rate   Higher response rate
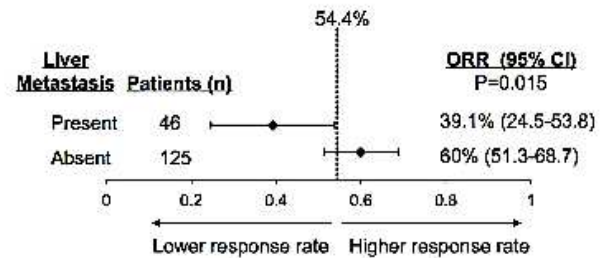
The Liver + groups: shorter PFS when compared to Liver – groups

Objective response rate according to metastatic pattern

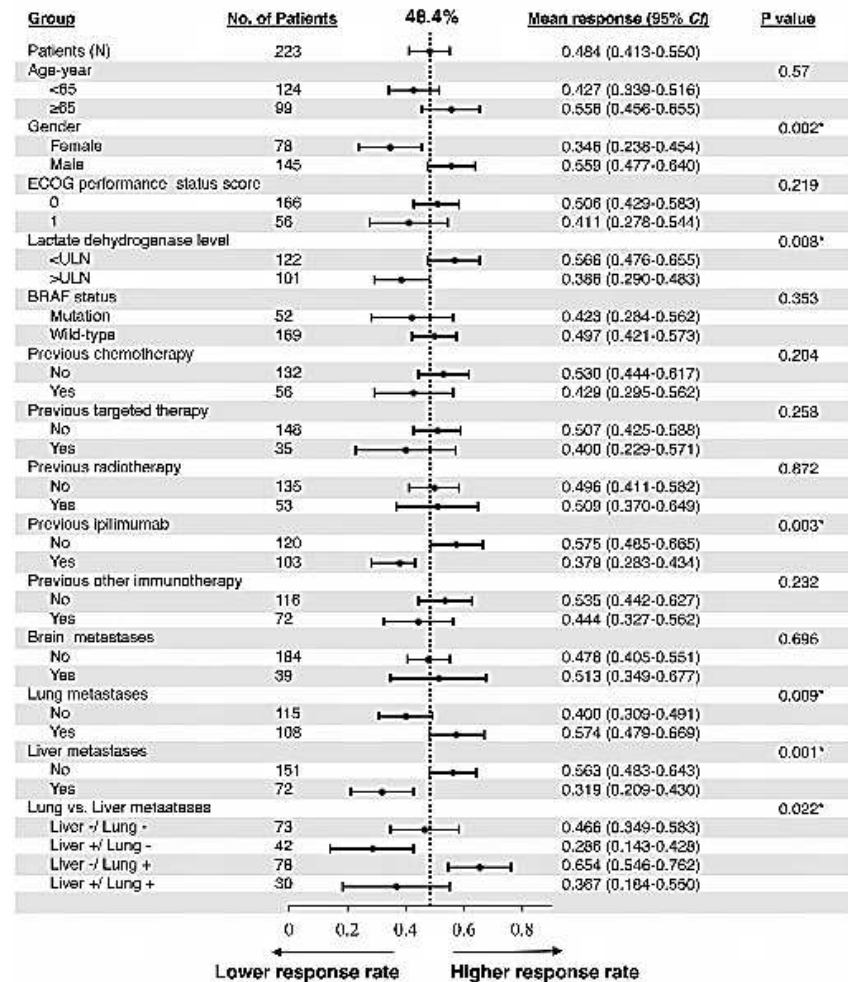| Group	No. of Patients	48.4%	Mean response (95% CI)	P value
Patients (N)	223		0.484 (0.413-0.550)	
Age-year				0.57
<65	124		0.427 (0.339-0.516)	
≥65	99		0.556 (0.456-0.655)	
Gender				0.002*
Female	78		0.346 (0.238-0.454)	
Male	145		0.559 (0.477-0.640)	
ECOG performance status score				0.219
0	166		0.506 (0.429-0.583)	
1	56		0.411 (0.278-0.544)	
Lactate dehydrogenase level				0.008*
<ULN	122		0.566 (0.476-0.655)	
>ULN	101		0.386 (0.290-0.483)	
BRAF status				0.353
Mutation	52		0.423 (0.284-0.562)	
Wild-type	169		0.497 (0.421-0.573)	
Previous chemotherapy				0.204
No	132		0.530 (0.444-0.617)	
Yes	56		0.429 (0.295-0.562)	
Previous targeted therapy				0.258
No	148		0.507 (0.425-0.588)	
Yes	35		0.400 (0.229-0.571)	
Previous radiotherapy				0.672
No	135		0.496 (0.411-0.582)	
Yes	53		0.509 (0.370-0.649)	
Previous ipilimumab				0.003*
No	120		0.575 (0.485-0.665)	
Yes	103		0.379 (0.283-0.434)	
Previous other immunotherapy				0.232
No	116		0.535 (0.442-0.627)	
Yes	72		0.444 (0.327-0.562)	
Brain metastases				0.696
No	184		0.478 (0.405-0.551)	
Yes	39		0.513 (0.349-0.677)	
Lung metastases				0.009*
No	115		0.400 (0.309-0.491)	
Yes	108		0.574 (0.479-0.669)	
Liver metastases				0.001*
No	151		0.563 (0.483-0.643)	
Yes	72		0.319 (0.209-0.430)	
Lung vs. Liver metastases				0.022*
Liver -/ Lung -	73		0.466 (0.349-0.583)	
Liver +/ Lung -	42		0.286 (0.143-0.428)	
Liver -/ Lung +	78		0.654 (0.546-0.762)	
Liver +/ Lung +	30		0.367 (0.184-0.550)	

0   0.2   0.4   0.6   0.8

← Lower response rate   Higher response rate →

Subgroup analyses: ORR and PFS

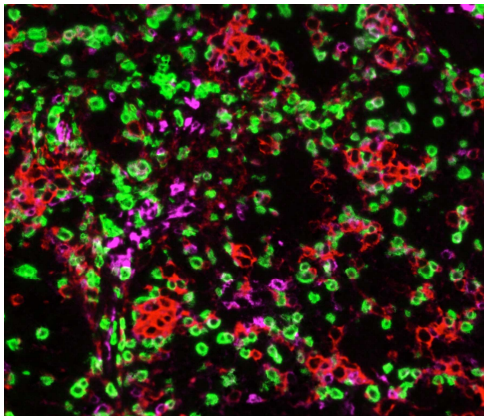| Variable	Best Overall Response		Progression-free survival	
	Odds Ratio (95% CI)	**P value**	**Hazard Ratio (95% CI)**	**P value**
LDH level > ULN	0.53 (0.30-0.97)	0.038*	1.58 (1.11-2.25)	0.011*
Metastatic Pattern		0.024*		0.174
Liver-/Lung+ vs Liver+/Lung+	0.38 (0.15-0.97)	0.043	1.59 (0.91-2.78)	0.101
Liver-/Lung+ vs Liver+/Lung-	0.30 (0.12-0.74)	0.009	1.73 (1.03-2.90)	0.039*
Liver-/Lung+ vs Liver-/Lung-	0.44 (0.22-0.89)	0.022	1.24 (0.79-1.95)	0.348
Primary Site of Melanoma		0.007*		0.020*
Cutaneous vs Mucosal	0.36 (0.13-1.03)	0.057	1.68 (0.92-3.07)	0.094
Cutaneous vs Unknown	0.29 (0.07-1.26)	0.098	1.38 (0.63-3.03)	0.425
Cutaneous vs Uveal	0.12 (0.03-0.60)	0.010	2.21 (1.25-3.88)	0.006
BRAF wild-type	1.17 (0.54-2.50)	0.695	0.88 (0.55-1.41)	0.598
Previous targeted therapy	0.82 (0.35-1.88)	0.634	1.44 (0.87-2.39)	0.152

Abbreviations: ULN, upper limit of normal

LDH and Tumor Burden (Pearson's correlation= 0.51, p<0.001)
R^2 = 26.3% (Percent of Variation in LDH explained by tumor burden)

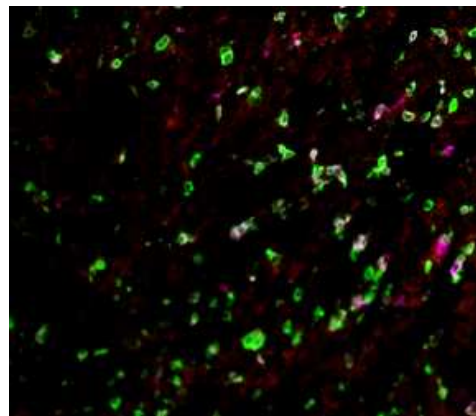# IHC analysis of CD8, PD1, PDL1 according to metastatic pattern
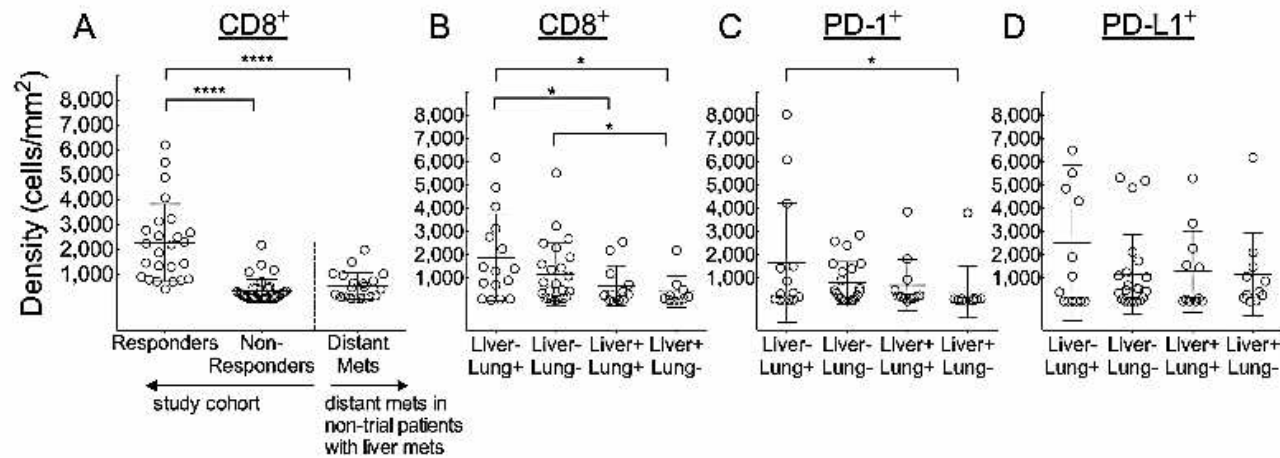
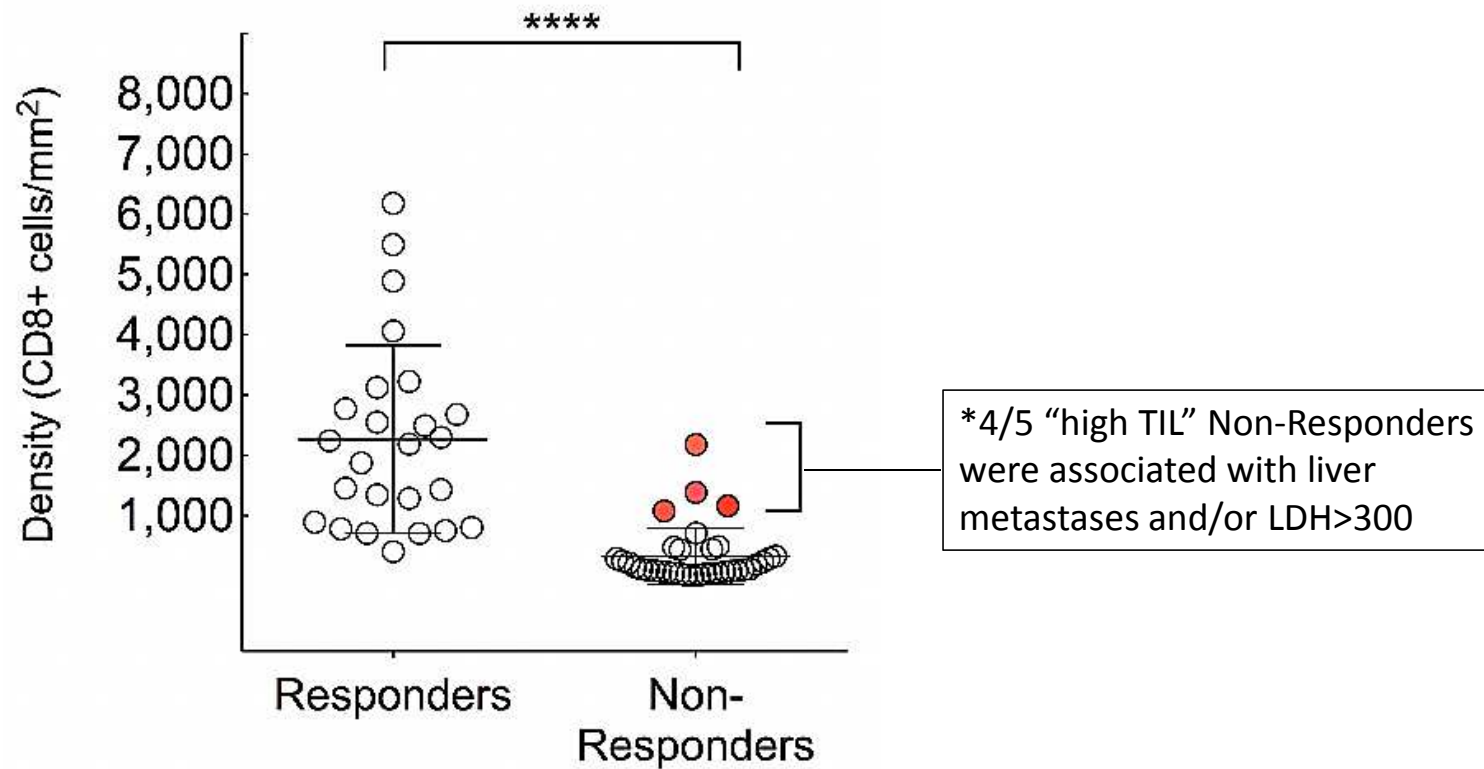Responder (No Liver Mets)   Non-Responder (+ Liver Mets)

CD8, PD-1, PD-L1

2nd Cohort
N=52 patients
N=28 responders
N=24 nonresponders
N=10/15 NR Liver+
N= 14/23 R Lung+

Integrating clinical information will aid in biomarker development

*4/5 "high TIL" Non-Responders were associated with liver metastases and/or LDH>300

Conclusions

- Spatially resolved approaches measures parameters that add value to bulk and single cell assays

- Current challenges include variability in pre-analytical variables

- The integration of clinical information may aid in biomarker development

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