Immune cell-tumor cell interactions

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Disclosure Information

AACR Tumor Immunology

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I have the following financial relationships to disclose:

Consultant for: Amgen, Astellas, Genentech, GSK, Merck, Novartis, Pierre-Favre

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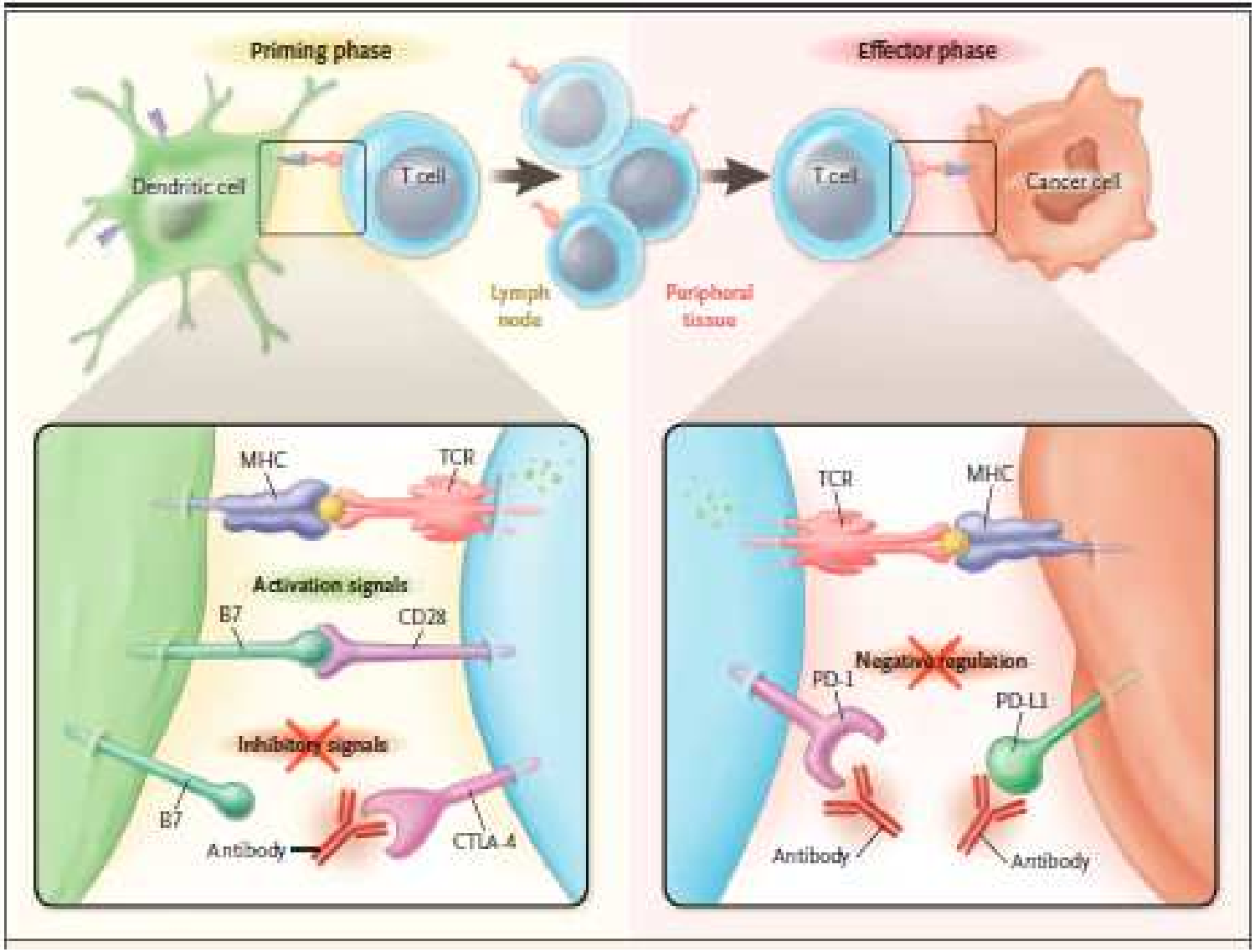

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RESEARCH ARTICLE

CANCER

Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape

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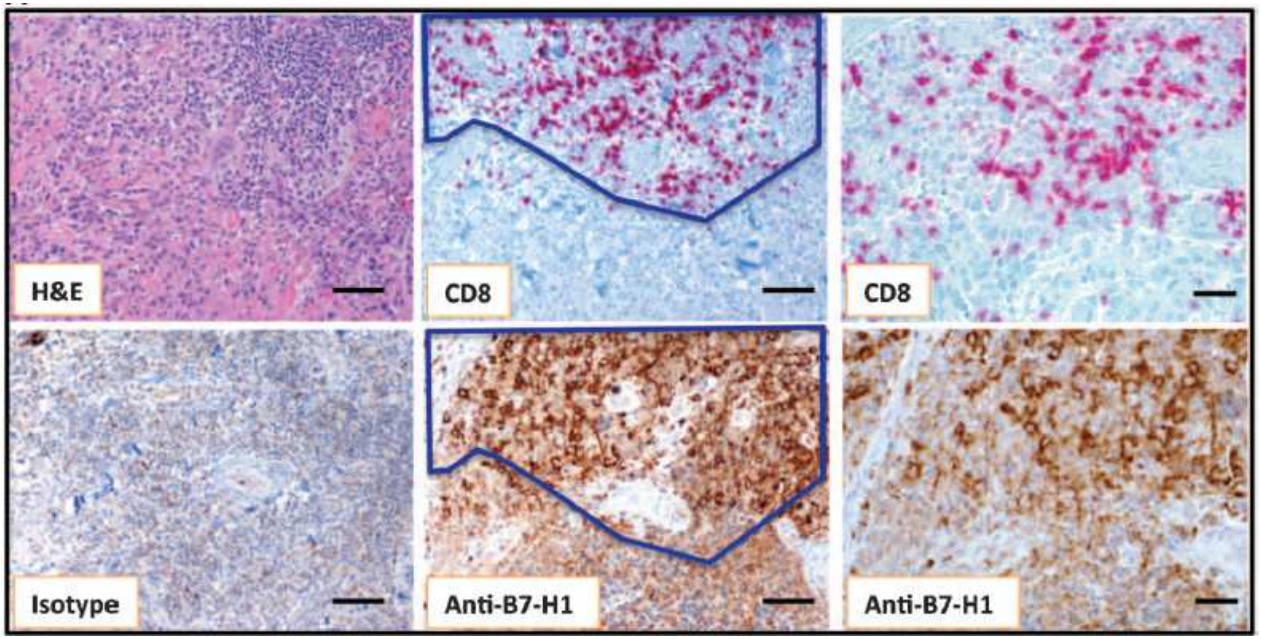


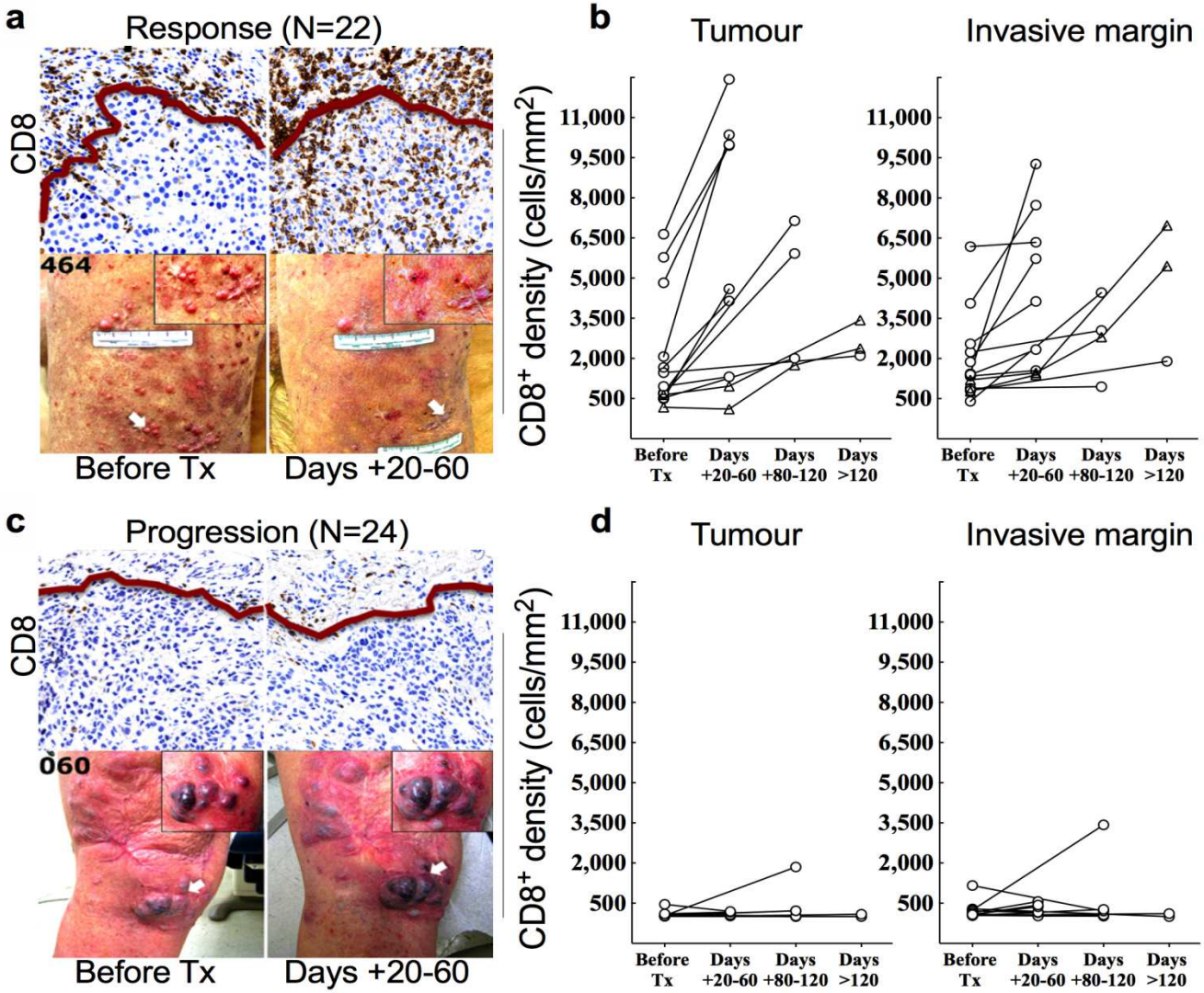
Melanoma responds to T cell infiltration by expressing PD-L1 (adaptive immune resistance)

Patient Characteristics of the UCLA Study Cohort

Variable	Response	Progression	p-value*
UCLA Patients (N = 46)	N = 22§	N = 24	
Male (%)	17 (74%)	19 (79%)	>0.99
Median Age (range)	65 (45-90)	64 (36-86)	0.86†
Median WBC Count (range)	6.9 (3.9-21.3)	7.1 (4.0-24.8)	0.52
Median Pre-TX Tumour Burden in cm (range)‡	8.7 (1.1-32.2)	7.9 (1.1-19.4)	0.9†
Metastatic Status			
M0	3 (13%)	2 (8%)	0.13†
M1a	4 (17%)	2 (8%)	
M1b	7 (30%)	6 (25%)	
M1c	8 (35%)	14 (58%)	
Dosing Regimen			
10Q2W	9 (39%)	5 (21%)	0.2
10Q3W	8 (35%)	8 (33%)	
2Q3W	5 (22%)	11 (46%)	
BRAF Mutation			
Mutant (# not WT)	7 (30%)	9 (38%)	0.76
Previous Treatment			
chemotherapy	3 (13%)	5 (21%)	0.7
BRAF or MEK inhibitor	3 (13%)	5 (21%)	0.7
immunotherapy			
ipilimumab	8 (35%)	13 (54%)	0.25
other	7 (30%)	9 (38%)	0.76
Pre TX Biopsy Location‖			
Subcutaneous	14 (61%)	11 (46%)	0.02†
Liver	0	8 (33%)	
Lung	5 (22%)	1 (4%)	
Other	3 (13%)	3 (13%)	

Paul C. Tumeh, Christina L. Harview, Lidia Robert, Bartosz Chmielowski, Manuel Carmona, Christine Kivork, Elizabeth Seja, Grace Cherry, Antonio Gutierrez, John A. Glaspy

Evolution of CD8+ T-cells, According to Treatment Outcome



IHC Analysis of CD8+ T-cells in samples obtained before and during anti-PD1 treatment

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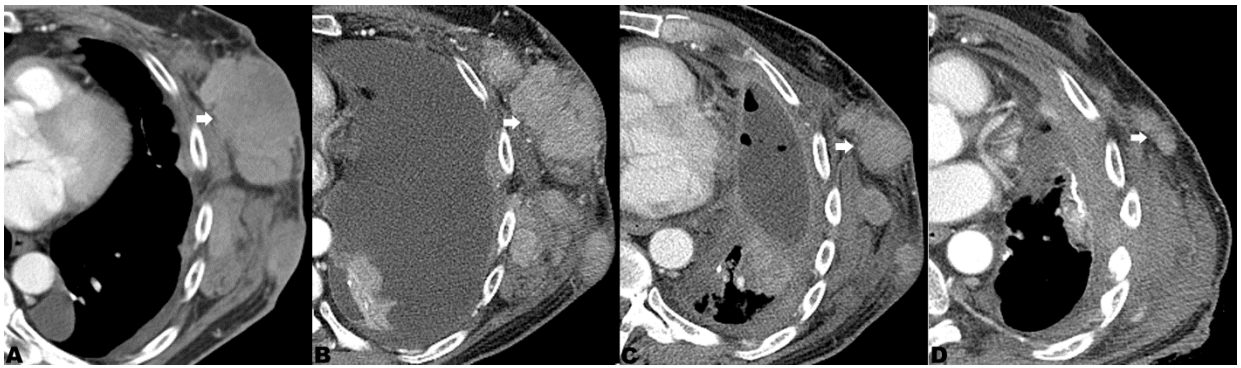
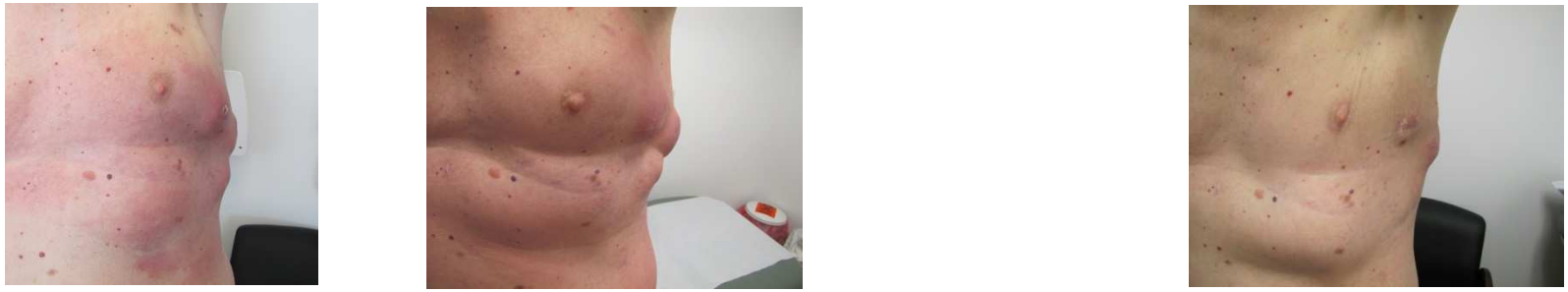
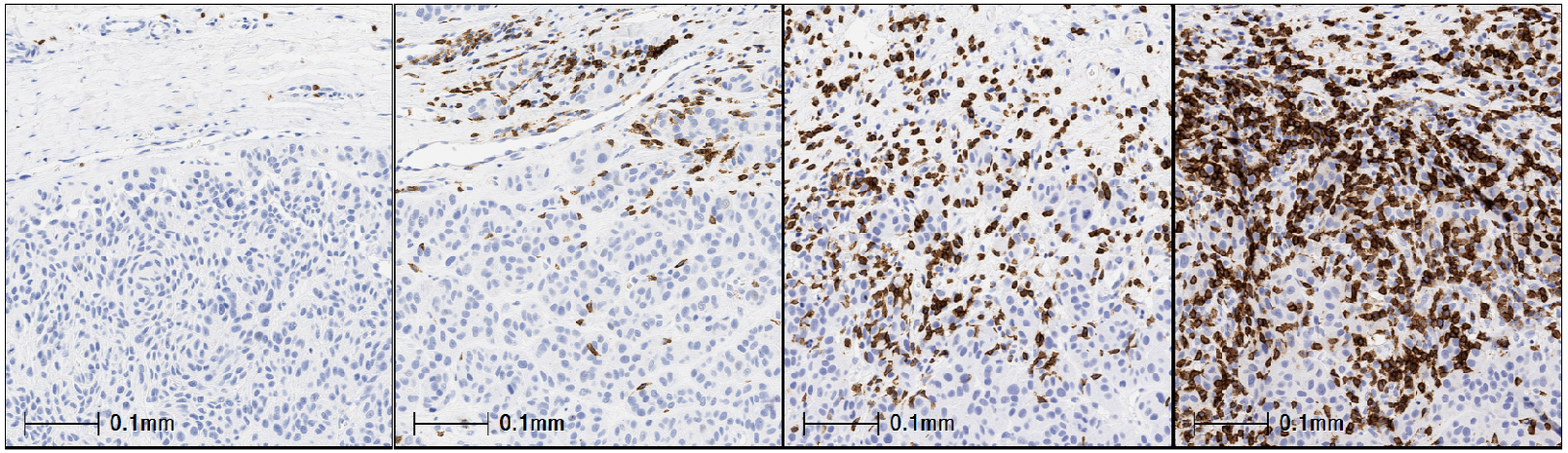
Response to PD-1 blockade after transient progression

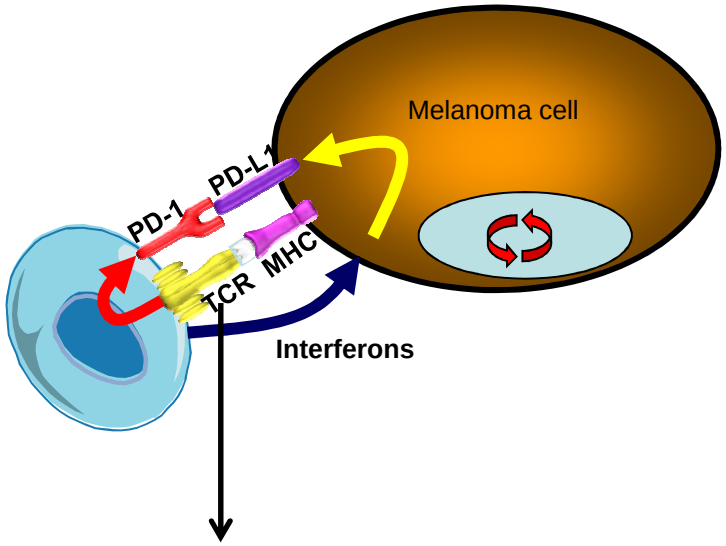




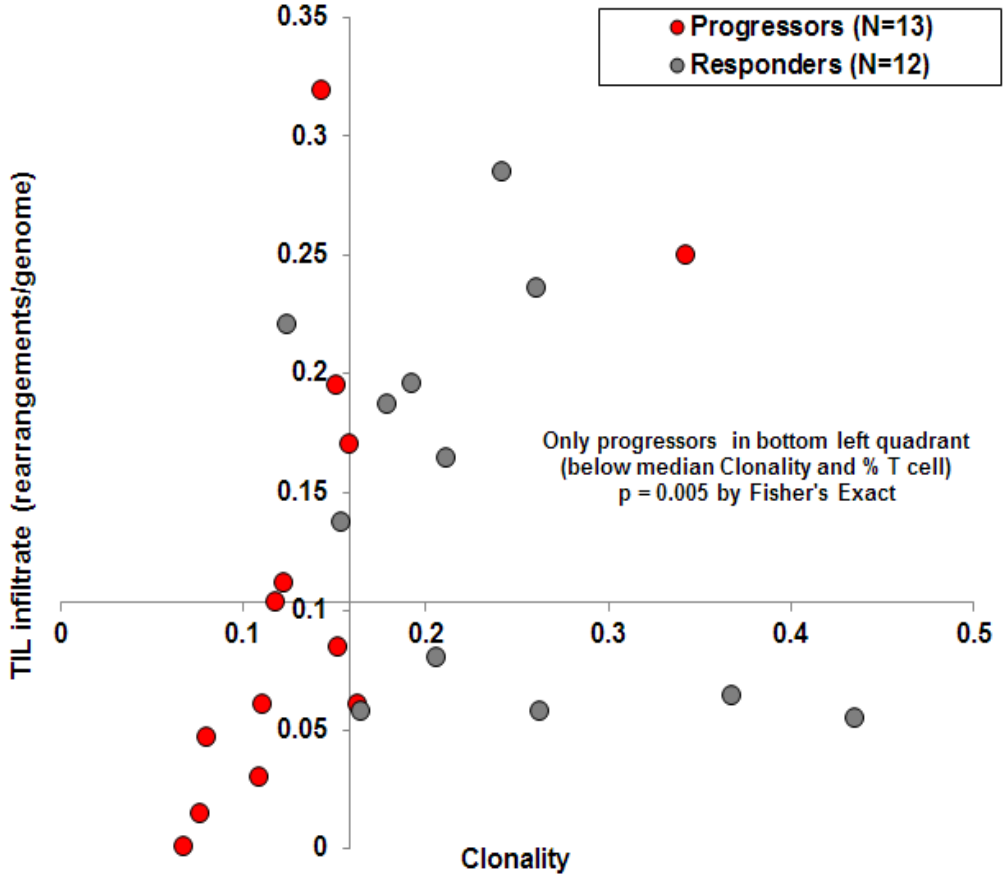


Baseline Day +27 Day +92 Day +130

Usage of TCR sequences to analyze T cell clonal distribution at baseline



Deep sequencing of
TCR Vb CDR3s
by ImmunoSeq



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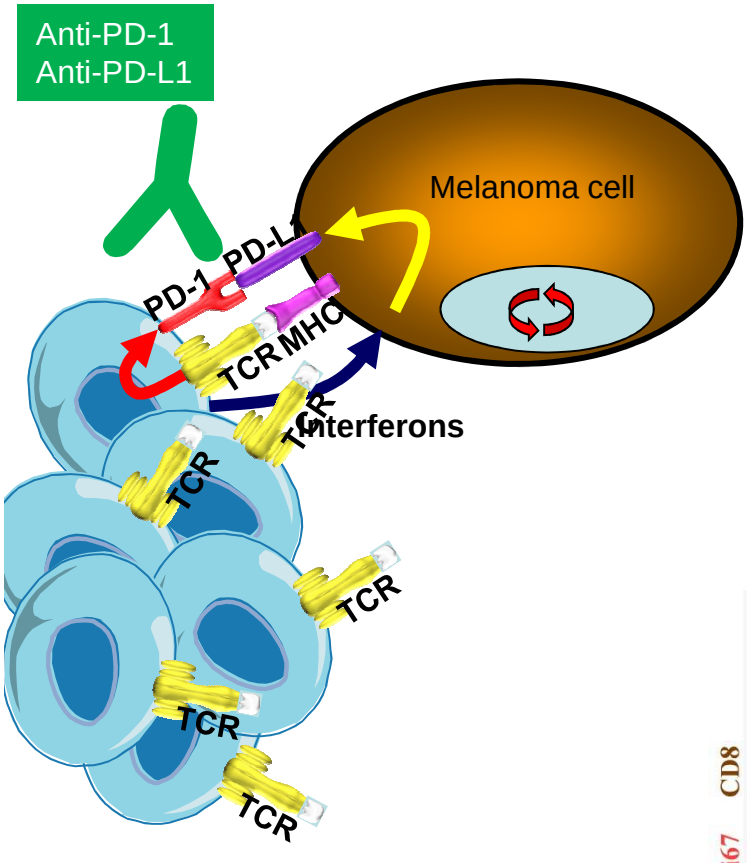
Intratumoral T cell replication upon PD-1 blockade



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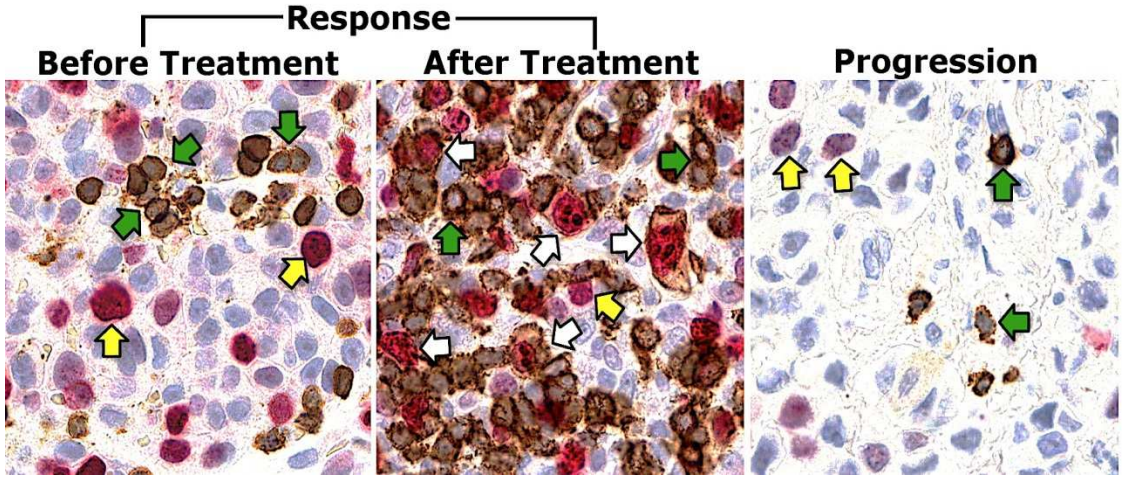
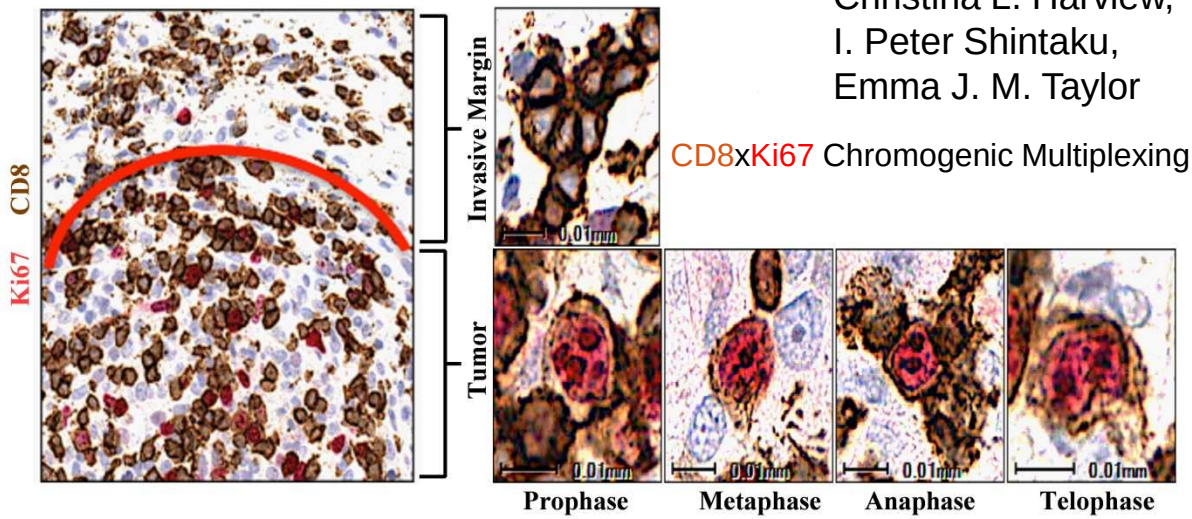


Yellow arrows: Ki67+ melanoma cells
Green arrows: CD8+ T-cells
White arrows: CD8+/Ki67+ T-cells



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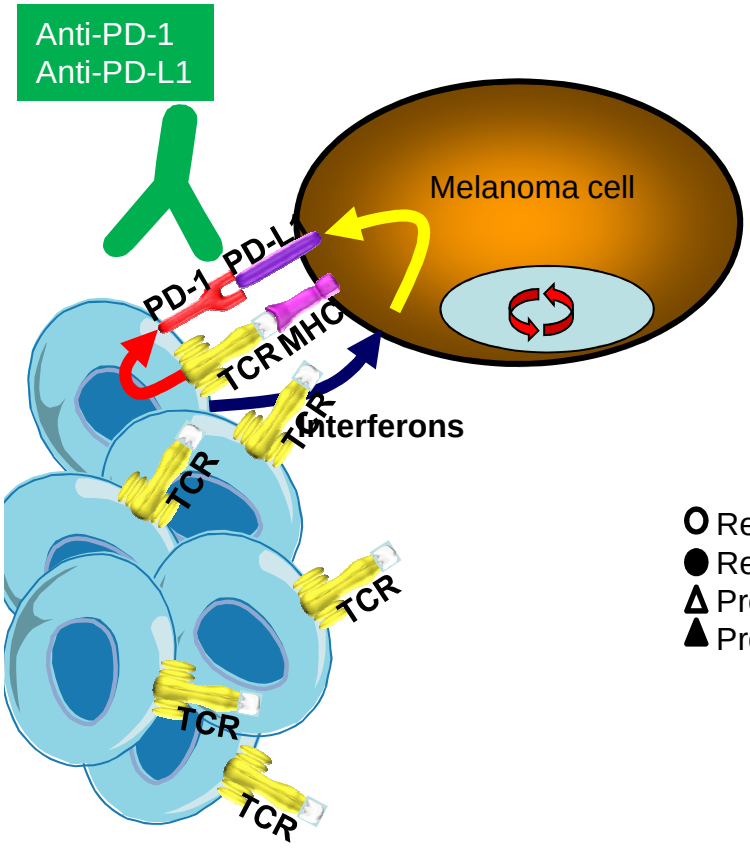
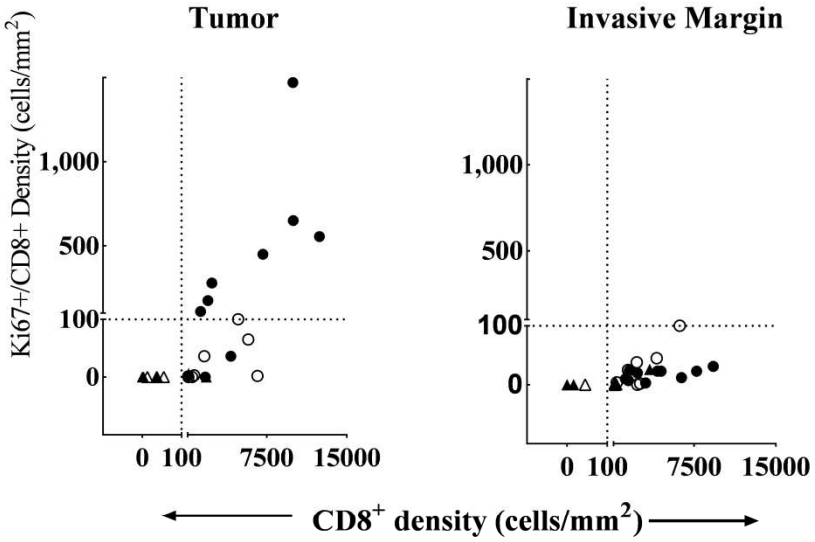
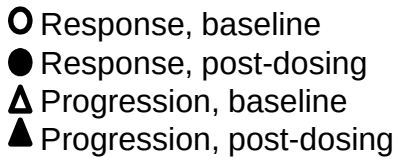
I. Peter Shintaku,
Emma J. M. Taylor

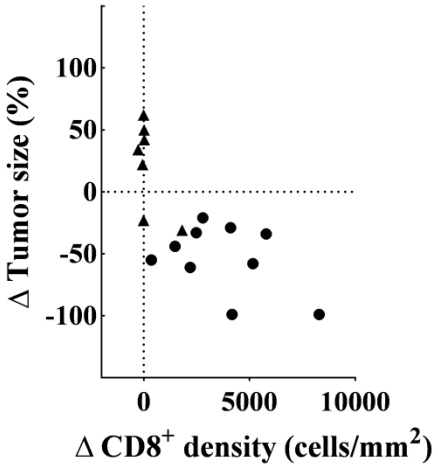
CD8xKi67 Chromogenic Multiplexing

Intratumoral T cell replication upon PD-1 blockade









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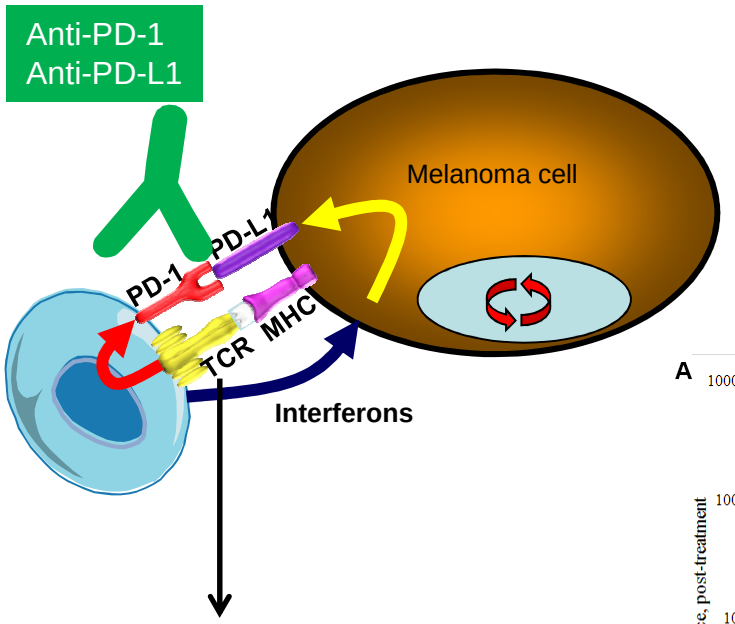
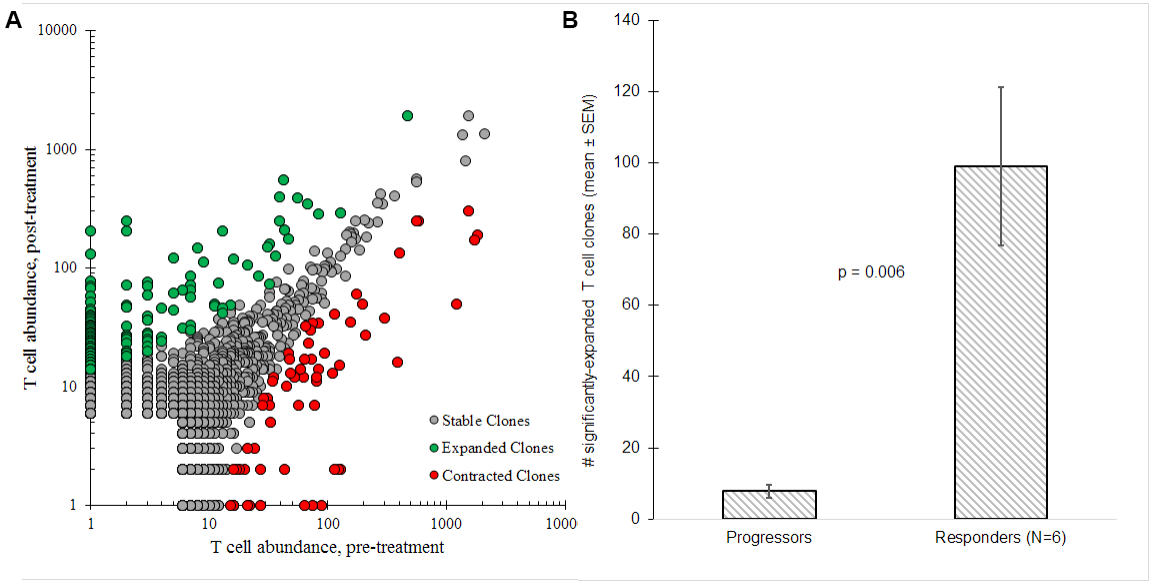
Usage of TCR sequences to analyze T cell clonal expansion after PD-1 blockade





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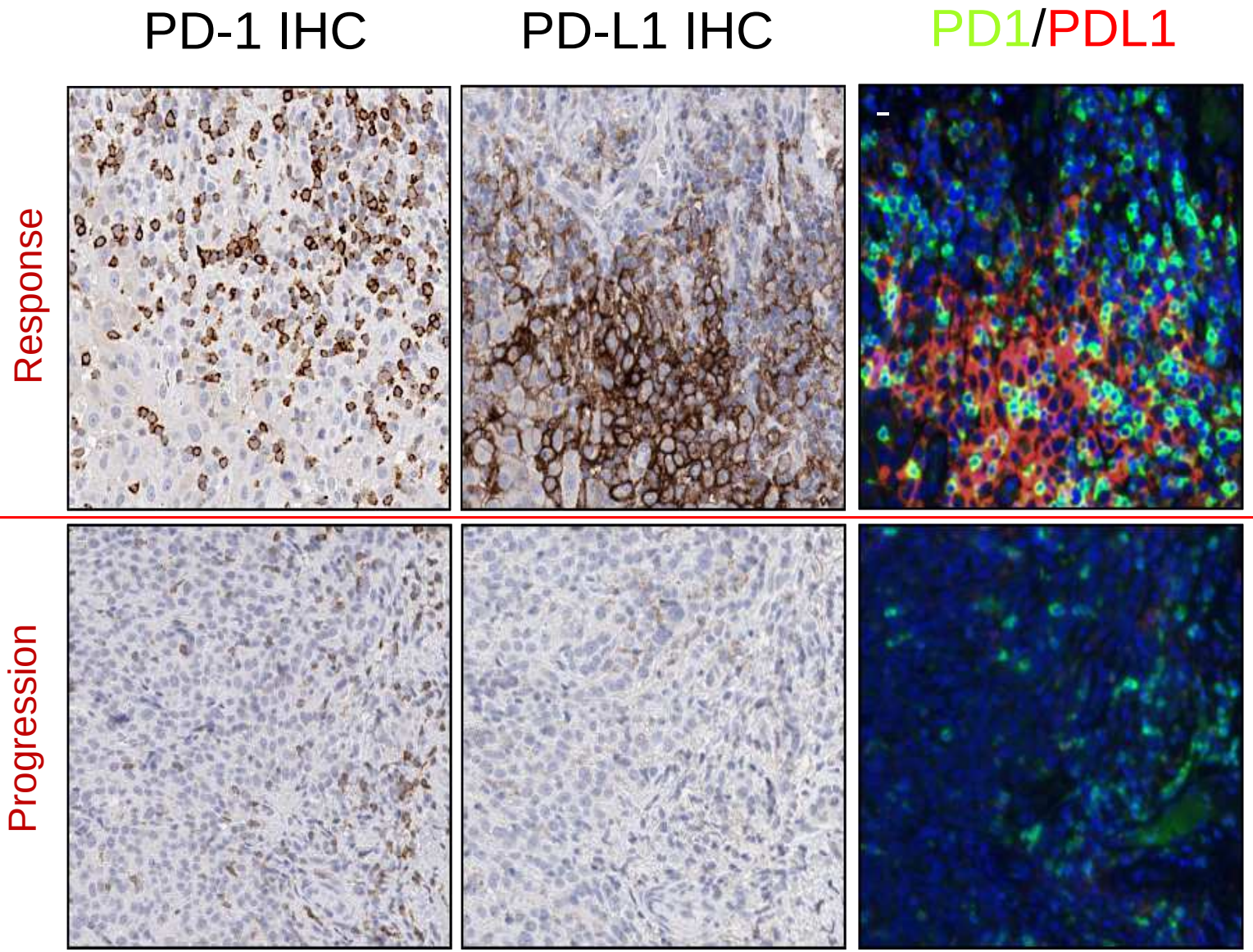
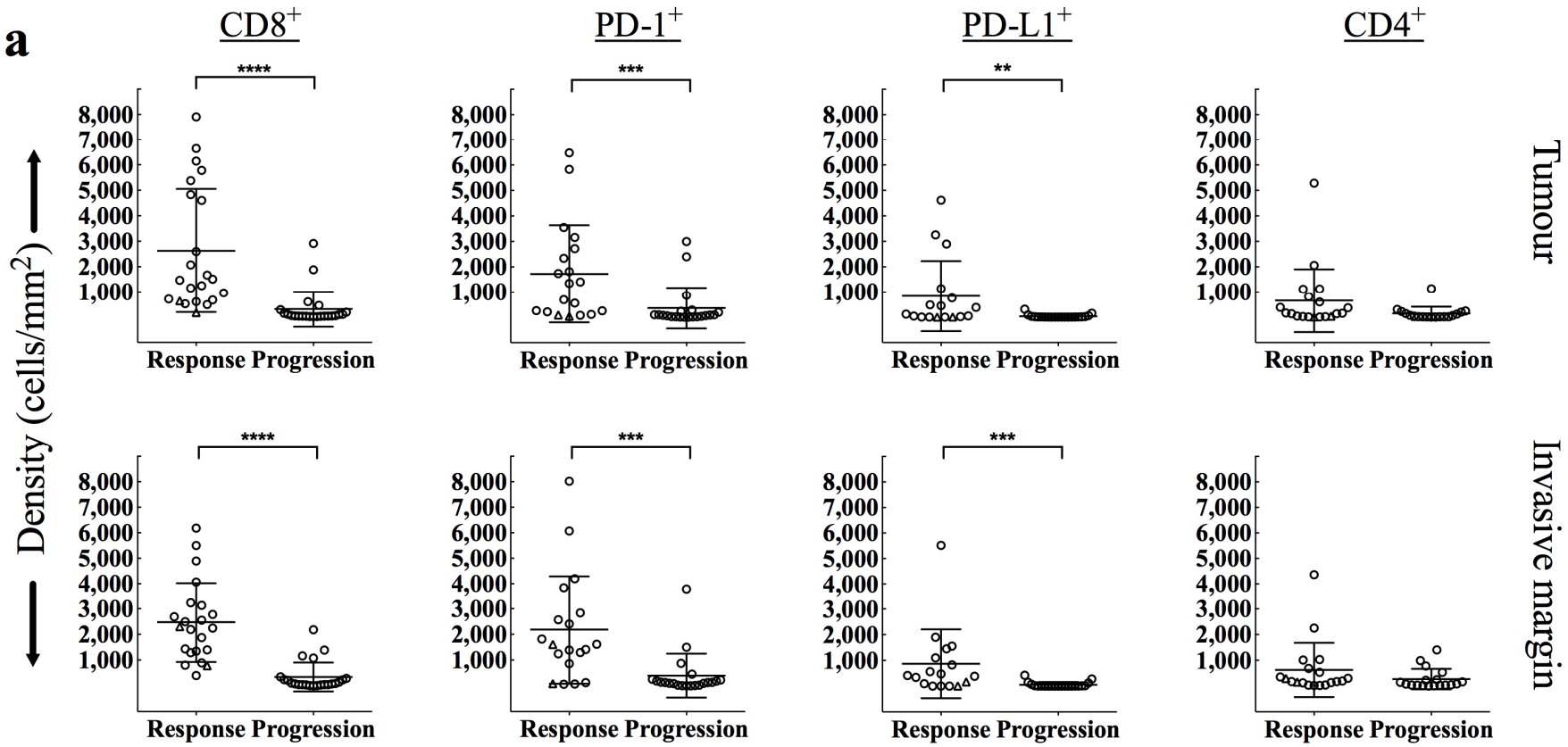
Immunophenotypic characterization of the T cell to tumor cell interaction (invasive margin)



Jennifer H. Yearley, Robert H. Pierce

Patients with response to PD-1 blockade have higher initial intratumoral and in the invasive margin CD8, PD-1 and PD-L1



Baseline density and location of $CD8^+$, $PD\text{-}1^+$, $PD\text{-}L1^+$, and $CD4^+$ cells by IHC, according to treatment outcome

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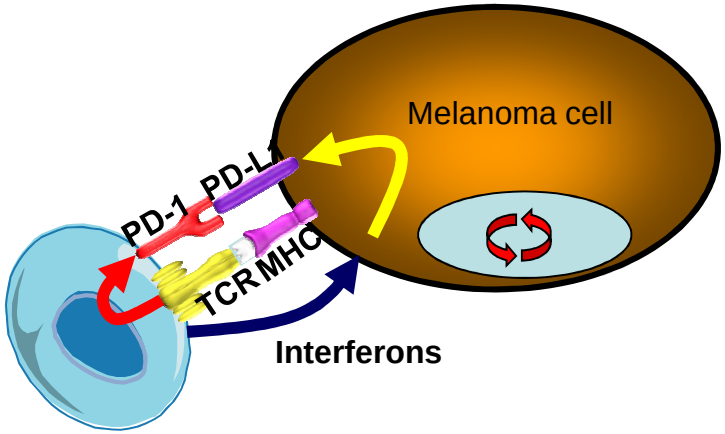
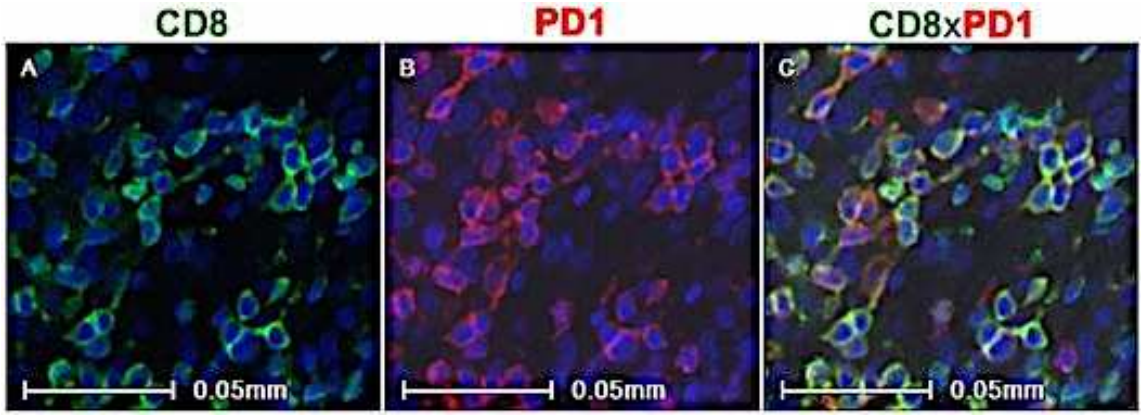
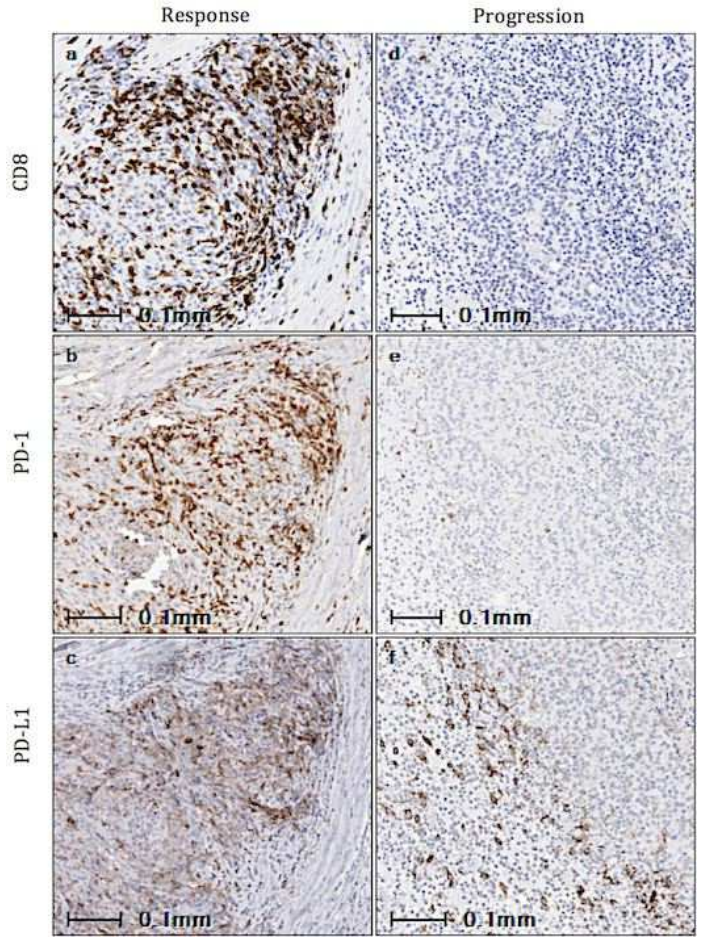
PD-1 and PD-L1 expression in response to CD8 infiltration and adaptive immune resistance







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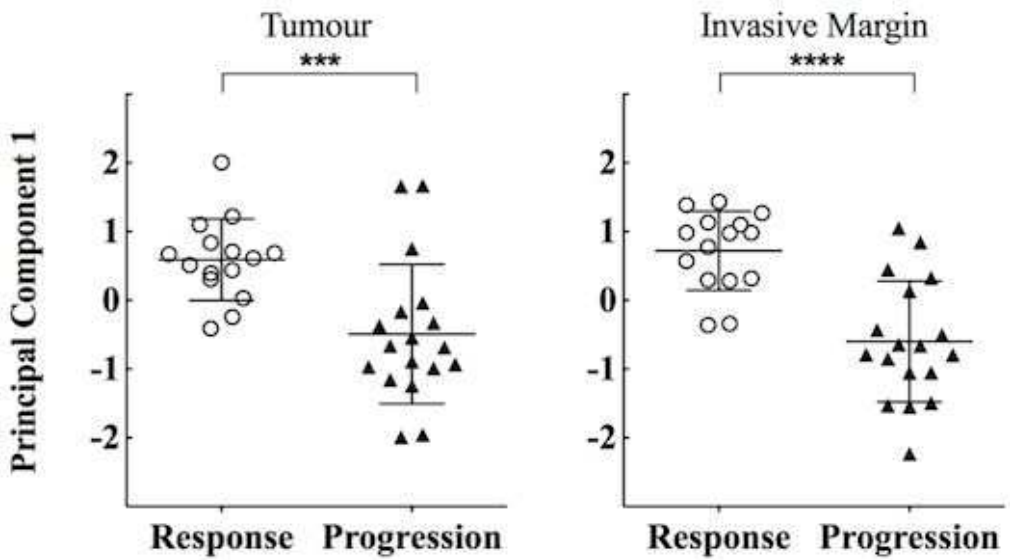
A Logistic Regression Model Analysis: Predicting Response

Variable	AUC (95% CI)*	P-value**
Tumour		
CD8+ Density	.91 (0.81, 1.00)	<0.001
PD-1+ Density	.80 (0.67, 0.94)	0.001
PD-L1+ Density	.71 (0.54, 0.88)	0.026
CD4+ Density	.66 (0.48, 0.84)	0.095
Invasive Margin		
CD8+ Density	.94 (0.88, 1.00)	<0.001
PD-1+ Density	.80 (0.66, 0.94)	0.001
PD-L1+ Density	.79 (0.64, 0.95)	0.002
CD4+ Density	.66 (0.48, 0.84)	0.095

*The area under the ROC curve (AUC) was used to measure response prediction performance for pre-treatment CD8+, PD-1+, PD-L1+, and CD4+ cell densities (cells/mm^2).

**P-values were computed on the basis of the Wilcoxon rank sum statistic.



David A. Elashoff

Predicting responses in a validation set from Gustave Roussy

Patient ID	Multi-Protein Score (Before Treatment)	Predicted Probability of Response (Logistic Model)	Blinded Prediction
IGR - A	58	0.35	Progression
IGR - B	159	0.37	Progression
IGR - C	329	0.40	Progression
IGR - D	341	0.41	Progression
IGR - E	366	0.41	Progression
IGR - F	2120	0.75	Response
IGR - G	5466	0.98	Response
IGR - H	6320	0.99	Response
IGR - I	2211	0.76	Response
IGR - J	3810	0.92	Response
IGR - K	4294	0.95	Response
IGR - L	4948	0.97	Response
IGR - M	5565	0.98	Response
IGR - N	6004	0.99	Response
IGR - O	5951	0.99	Response
IGR - P	7230	0.99	Response

Paul C. Tumeh, UCLA,
Christine Mateus, Gorana Tomasic, Caroline Robert, Gustave Roussy

Conclusions

- PD-1 blockade induces responses by inhibiting adaptive immune resistance
- PD-1+ expressing CD8+ T cells co-localize with PD-L1 expressing tumor cells at the invasive margin in responding patients
- PD-L1 alone cannot be used as a biomarker for response to PD-1 blockade, as it requires having information about CD8 T cell infiltration
- Patients with a tumor response to PD-1 blockade have a higher frequency of clonal TCRs at baseline
- Blockade of PD-1 results in CD8 T cell proliferation inside tumors, expansion of TCR clones and increased effector functions (granzyme B)
- The presence of CD8s in the tumor margin can be used to predict likelihood of response to PD-1 blockade

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