Anti-CTLA-4 Therapy in Prostate Cancer

NASPCC Symposium on Immuno-Oncology in Prostate Cancer: Current and Future Trends

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Sumit K. Subudhi, MD, PhD

Assistant Professor

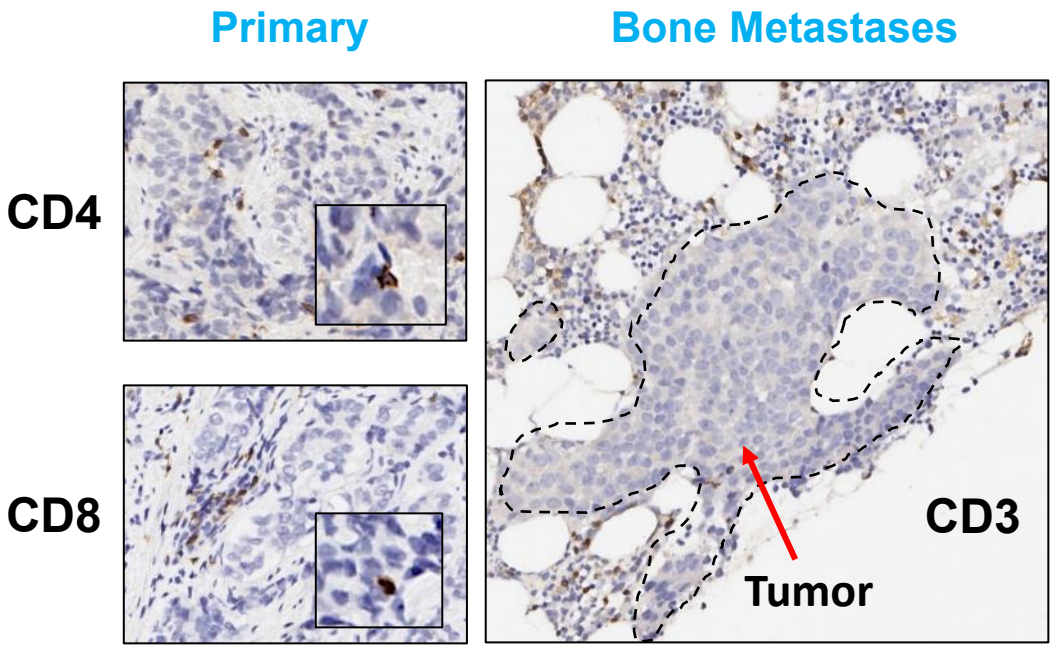
Genitourinary Medical Oncology

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

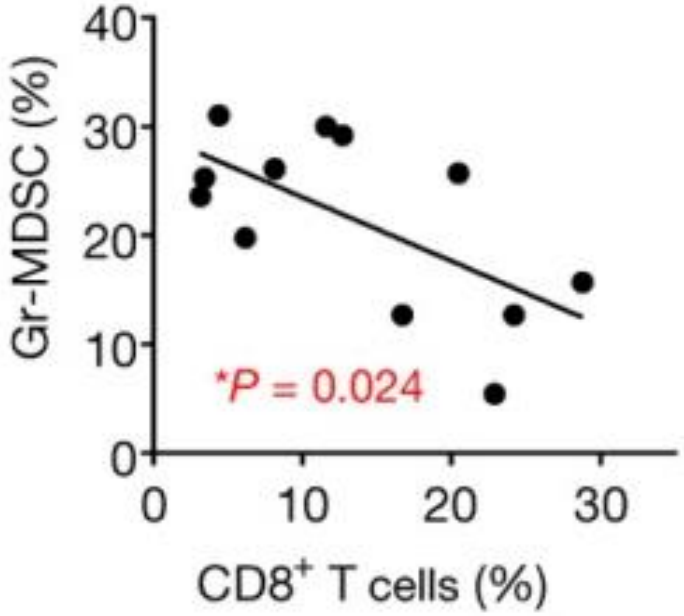
Disclosures

- **Consulting or Advisory Role:** Amgen, Apricity Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Cancer Expert Now, Dava Oncology, Dendreon, Exelixis, Janssen Oncology, Javelin Oncology, Kahr Bio, and MD Education Limited
- **Research Funding:** AstraZeneca, Bristol-Myers Squibb, and Janssen Oncology
- **Joint Scientific Committee:** Janssen Oncology, Polaris
- I **will** be discussing non-FDA approved indications during my presentation.

Immunosuppressive Cold Prostate Tumor Microenvironment



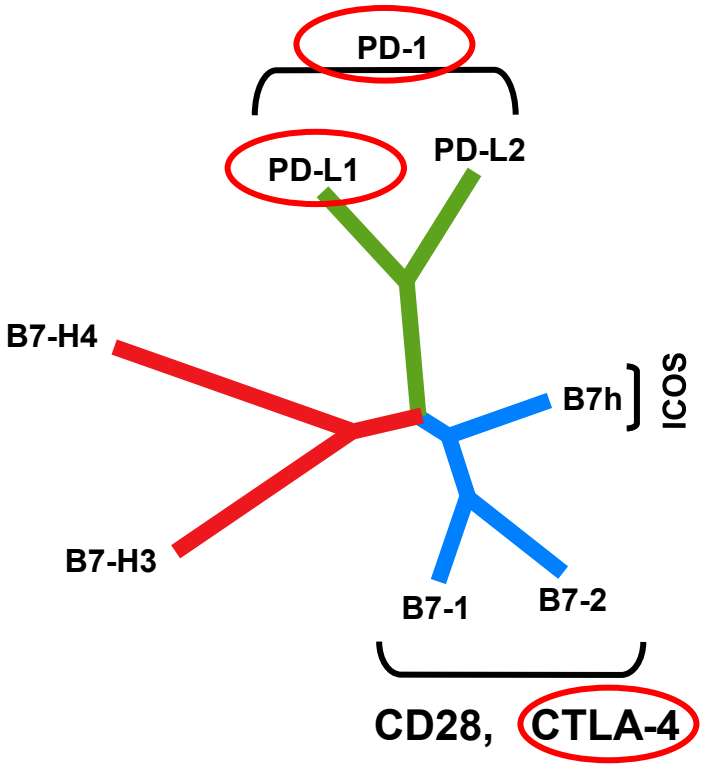
Allison JP, Sharma P and Subudhi SK
MD Anderson Cancer Center Immunotherapy Platform



Lu X et al., *Nature,* 2017.

Do immune checkpoint therapies work in prostate cancer?

FDA-Approved Immune Checkpoint Therapies



Zang X et al., *Proc Natl Acad Sci*, 2003.

Melanoma
- Ipilimumab (2011)
- Nivolumab (2014)
- Ipilimumab + Nivolumab (2015)
- Pembrolizumab (2019)
- Atezolizumab (2020)

Lung Carcinoma
- Nivolumab (2015)
- Pembrolizumab (2015)
- Atezolizumab (2016)
- Durvalumab (2018)
- Ipilimumab + Nivolumab (2020)

Urothelial Carcinoma
- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)
- Nivolumab (2017)
- Pembrolizumab (2017)

Renal Cell Carcinoma
- Nivolumab (2015)
- Ipilimumab + Nivolumab (2018)
- Avelumab (2019)

Colorectal Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2017)
- Ipilimumab + Nivolumab (2018)

Head and Neck Squamous Cell Carcinoma
- Nivolumab (2016)
- Pembrolizumab (2016)

Lymphoma
- Nivolumab (2016)
- Pembrolizumab (2017)

Hepatocellular Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2018)
- Ipilimumab + Nivolumab (2020)

Merkel Cell Carcinoma
- Avelumab (2017)
- Pembrolizumab (2018)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)
- Pembrolizumab (2020)

Esophageal Carcinoma
- Pembrolizumab (2019)
- Nivolumab (2020)

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab (2017)

Cervical Carcinoma
- Pembrolizumab (2018)

Breast Carcinoma
- Atezolizumab (2019)

Uterine Carcinoma
- Pembrolizumab (2019)

Mesothelioma
- Ipilimumab + Nivolumab (2020)

Basal Cell Carcinoma
- Cemiplimab (2020)

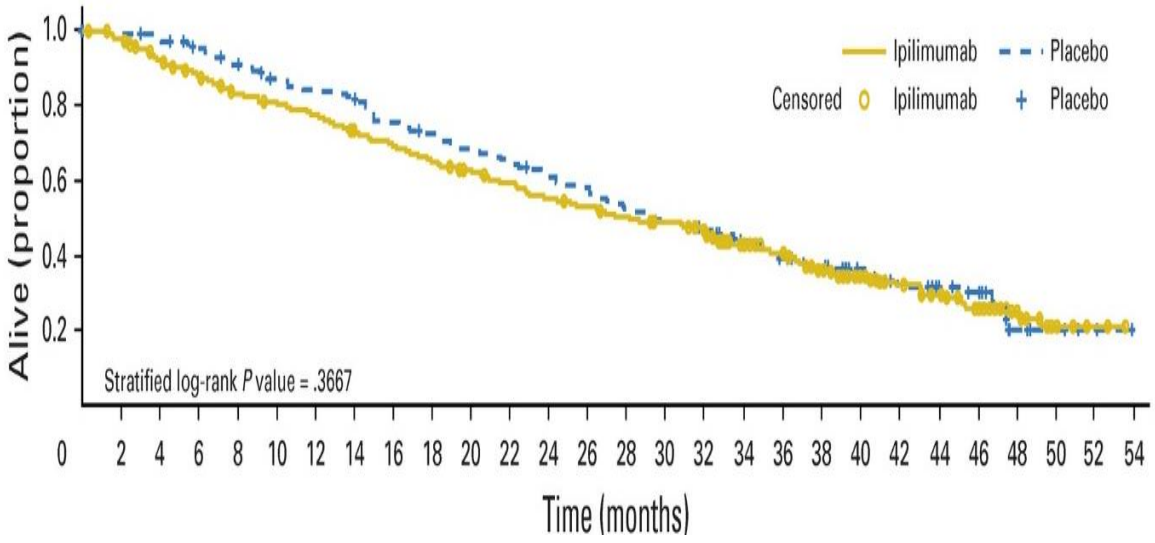
Pembrolizumab Induced Radiographic Responses in a Subset of Metastatic Prostate Cancer

Response	PD-L1 Positive n = 133	PD-L1 Negative n = 66
Complete Response (CR)	2 (2)	0
Partial Response (PR)	5 (4)	2 (3)
SD ≥ 6 months	10 (8)	10 (15)

Adapted from Antonarakis ES et al., *J Clin Oncol,* 2019.

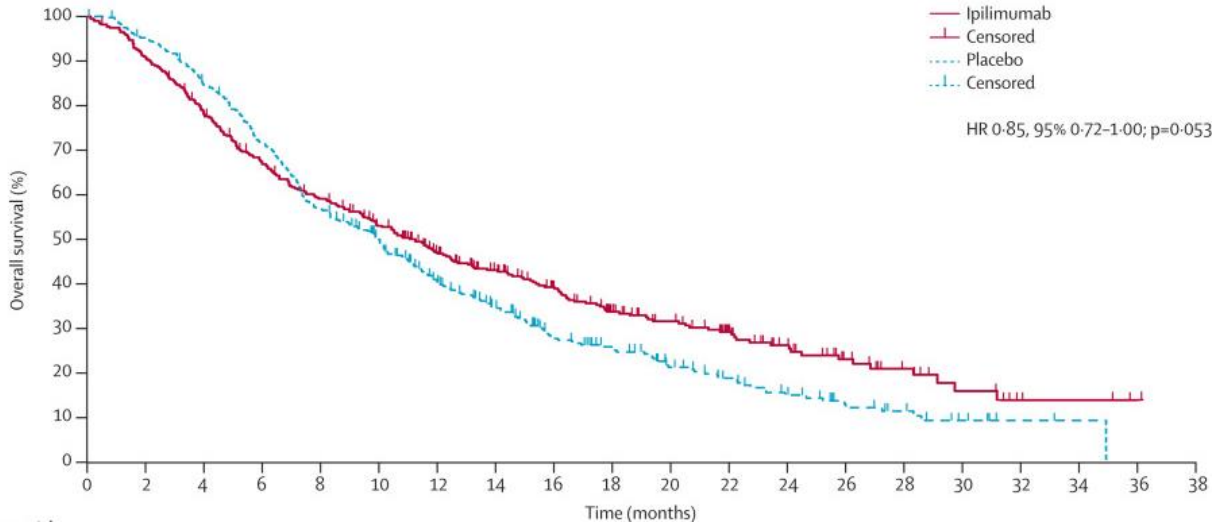
Ipilimumab Did *Not* Improve Overall Survival (OS) in Patients with Metastatic Prostate Cancer

Pre-Chemotherapy



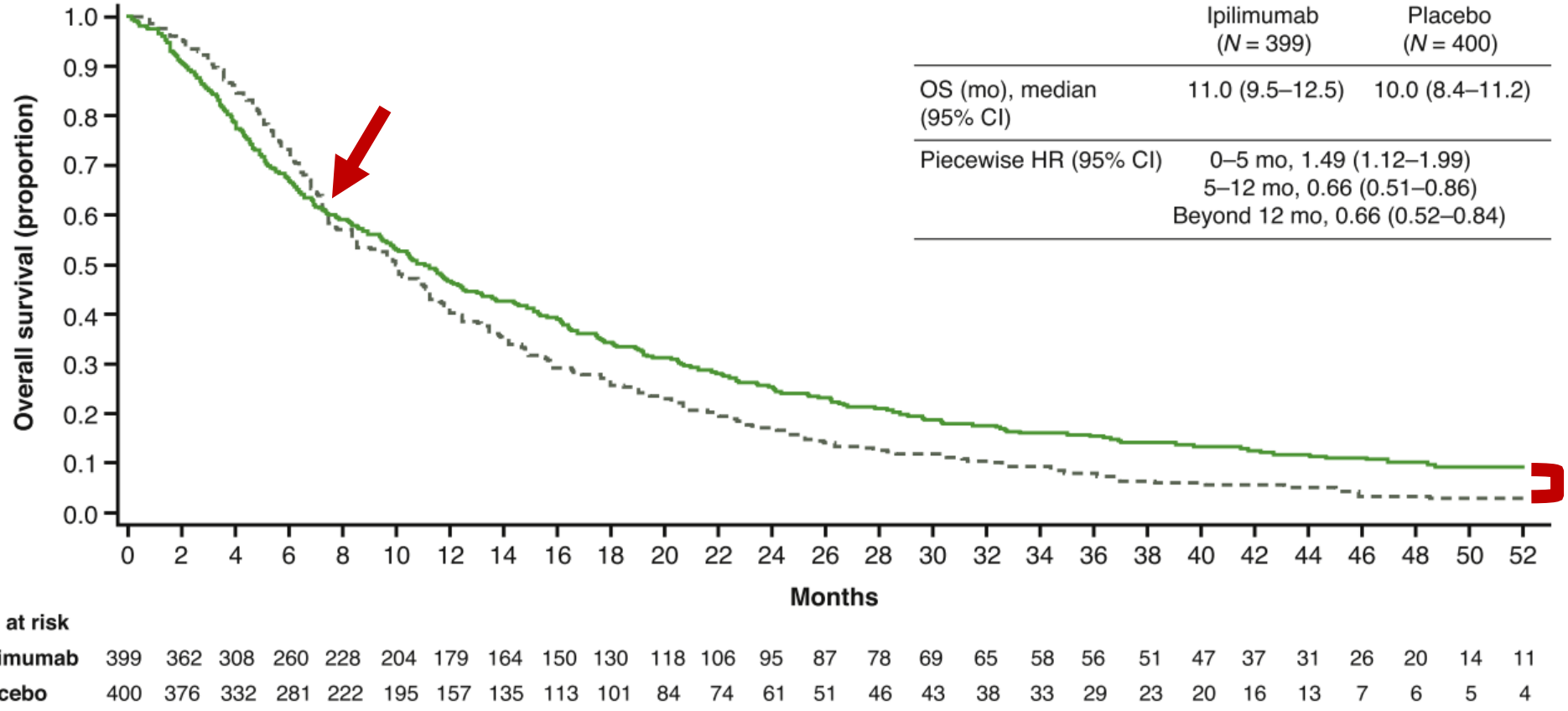
Beer TM et al., *J Clin Oncol,* 2016.

Post-Chemotherapy



Kwon ED et al., *Lancet Oncol,* 2014.

Subset of Patients Derive Durable Benefit from Ipilimumab



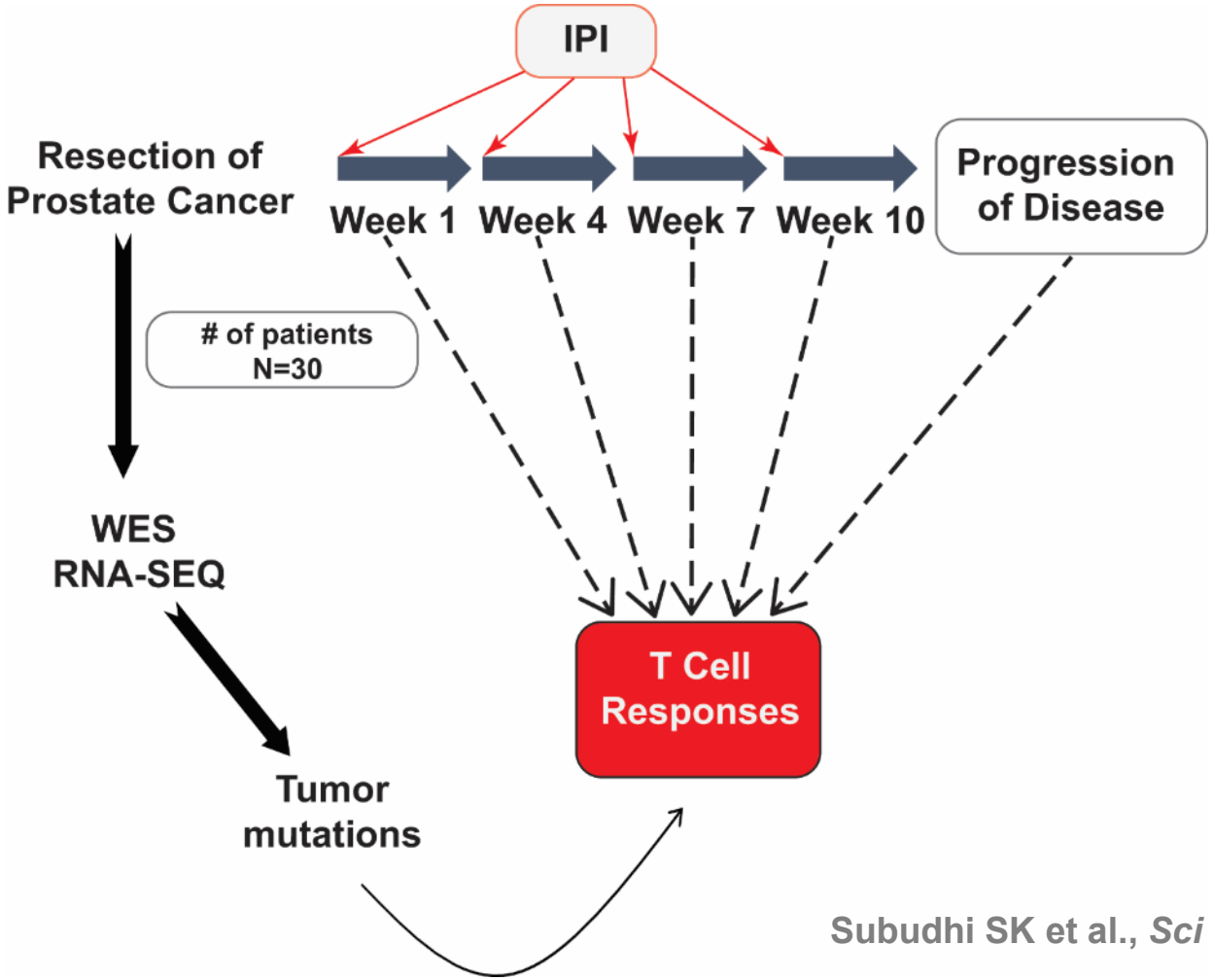
	Ipilimumab (*N* = 399)	Placebo (*N* = 400)
OS (mo), median (95% CI)	11.0 (9.5–12.5)	10.0 (8.4–11.2)
Piecewise HR (95% CI)	0–5 mo, 1.49 (1.12–1.99) 5–12 mo, 0.66 (0.51–0.86) Beyond 12 mo, 0.66 (0.52–0.84)	

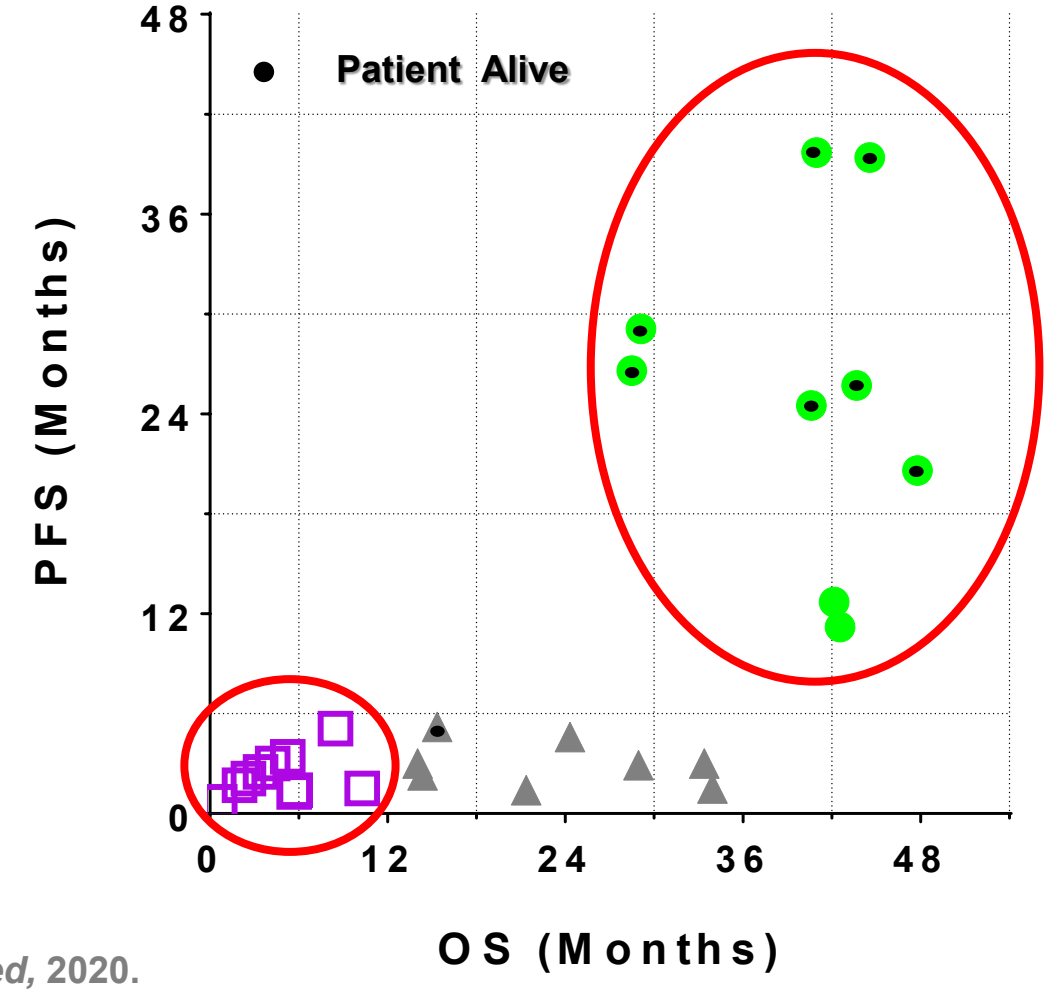
Fizazi K et al., *Eur Urol*, 2020.

Can we identify the subset of patients with metastatic prostate cancer who benefit from anti-CTLA-4?

Clinical Outcomes in Patients with Metastatic Prostate Cancer After Ipilimumab

Clinical Trial Schema (NCT02113657)



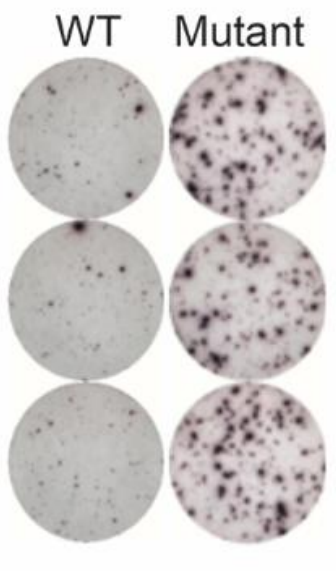


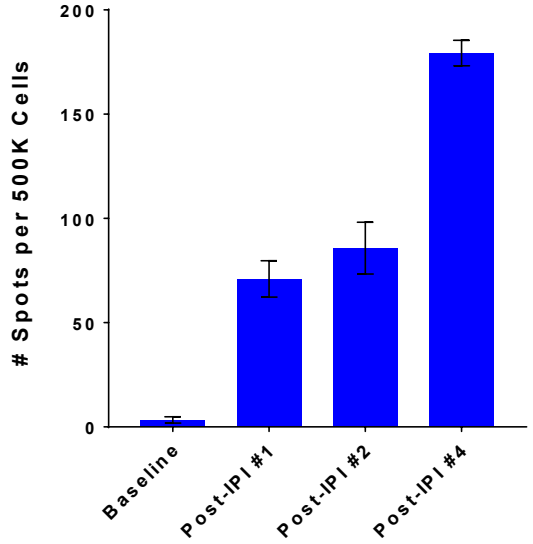
Subudhi SK et al., *Sci Transl Med*, 2020.

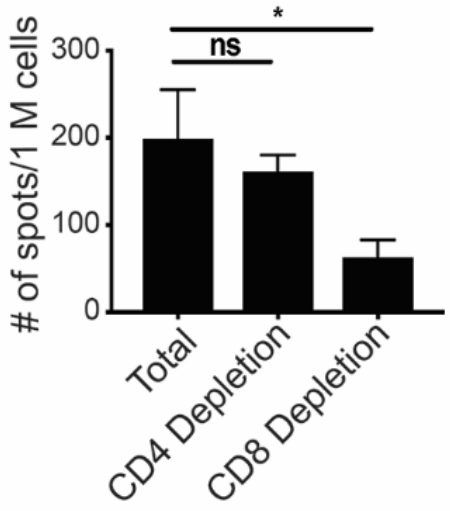
Ipilimumab Enhanced T Cell Responses Against Prostate Cancer Mutant Neoantigens for Patient #7

# Somatic Mutations	# Non-Synonymous Mutations	# Expressed Non-Synonymous Mutations	# Neoantigens Detected by ELISPOT
122	13	8	2

Peptide Name	Sequence
rho guanine nucleotide exchange factor 37 (WT)	H-GYVPSGFLARARSPVLWGWSLPS-OH
rho guanine nucleotide exchange factor 37 (MUT)	H-GYVPSGFLARAWSPVLWGWSLPS-OH

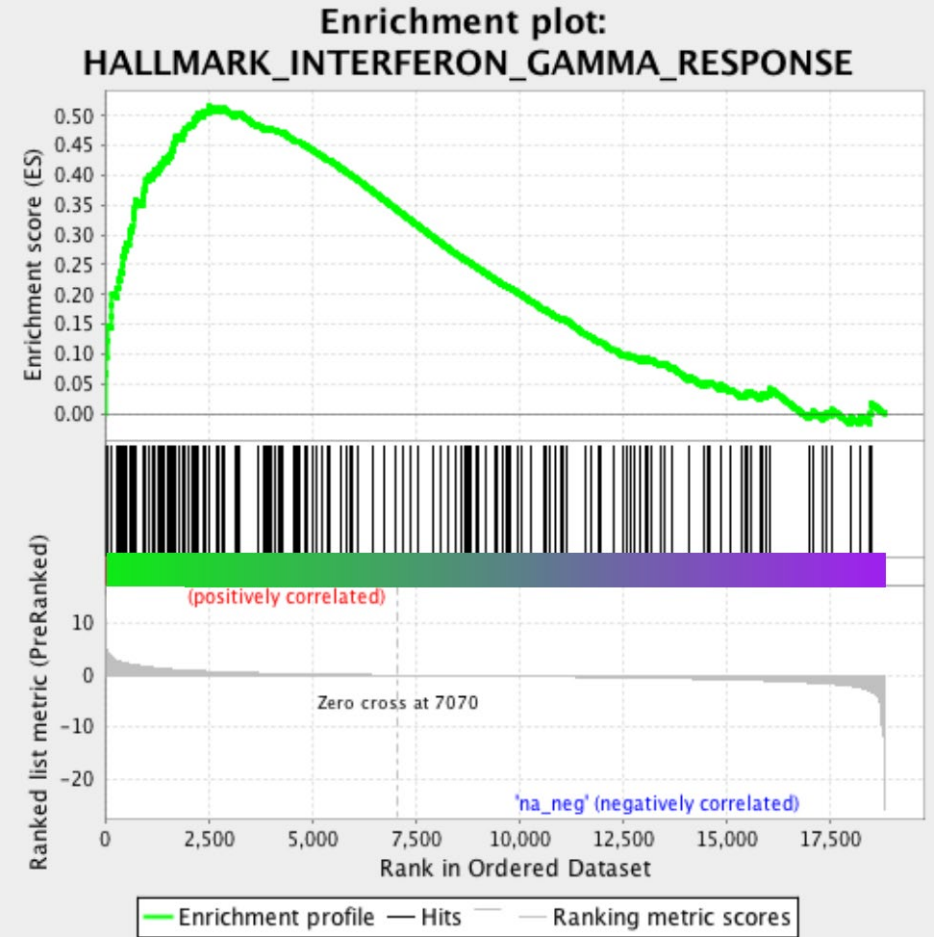


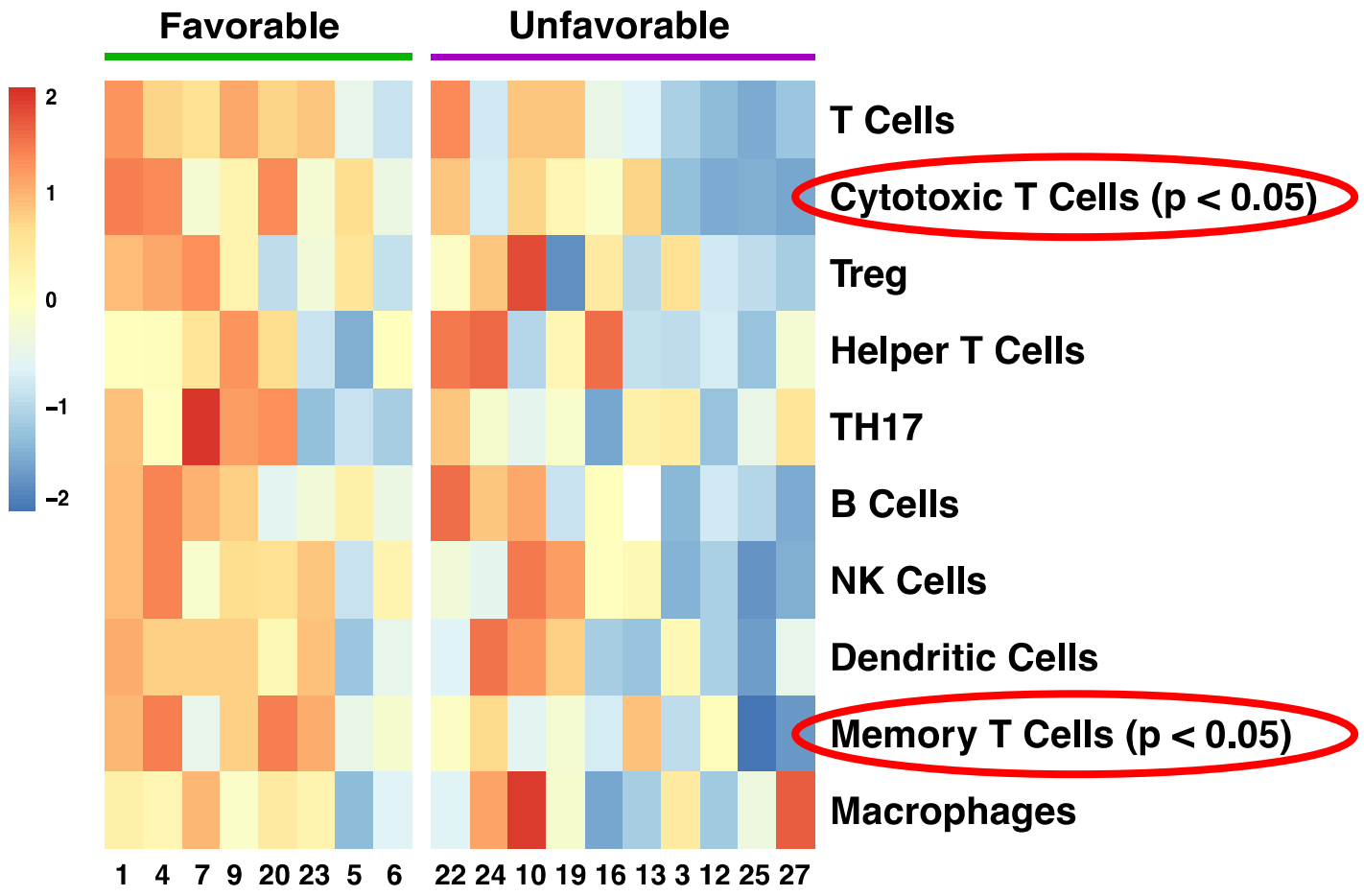




Subudhi SK et al., *Sci Transl Med,* 2020.

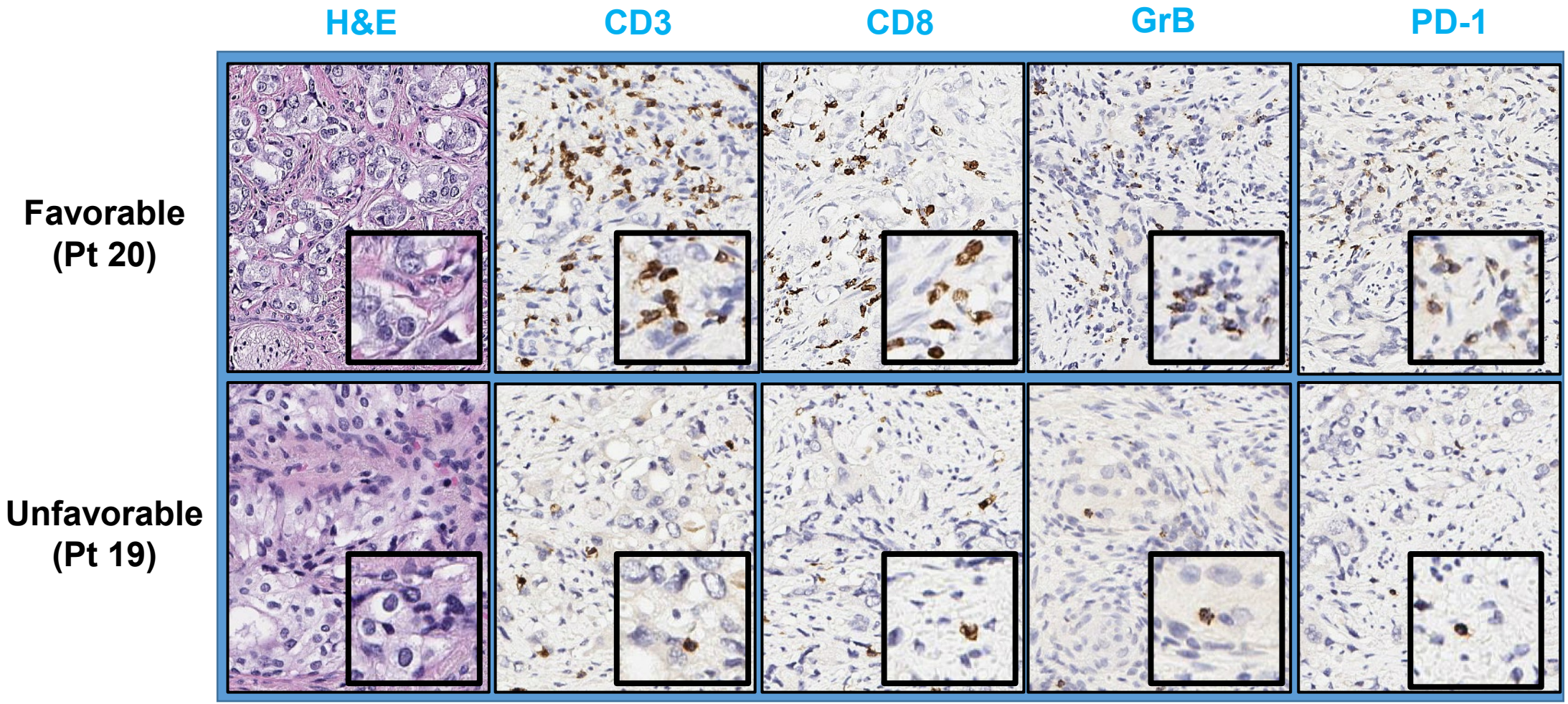
Transcriptional Signatures of T Cell Effector Cells/Functions were Associated with Favorable Outcomes





Subudhi SK et al., *Sci Transl Med*, 2020.

Increased Density of Effector T Cells was Associated with Favorable Outcomes



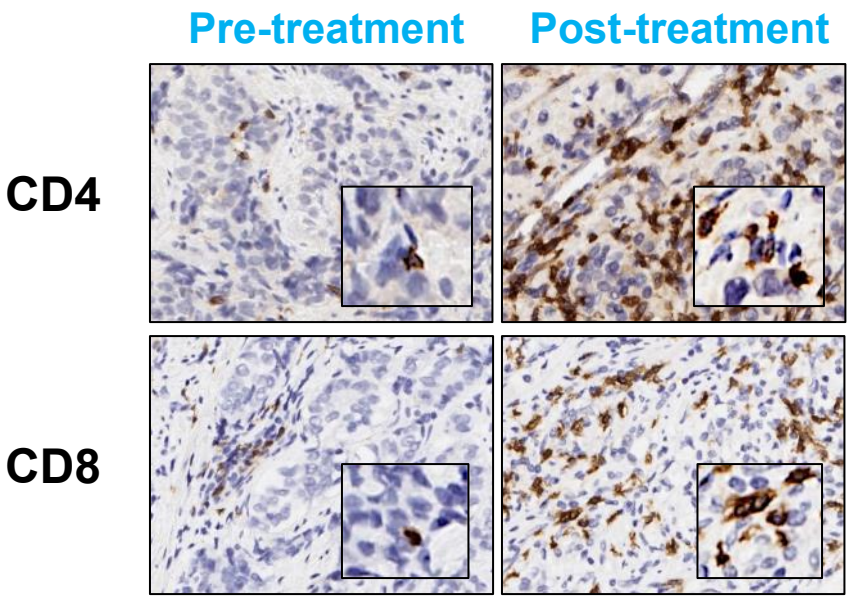
Subudhi SK et al., *Sci Transl Med,* 2020.

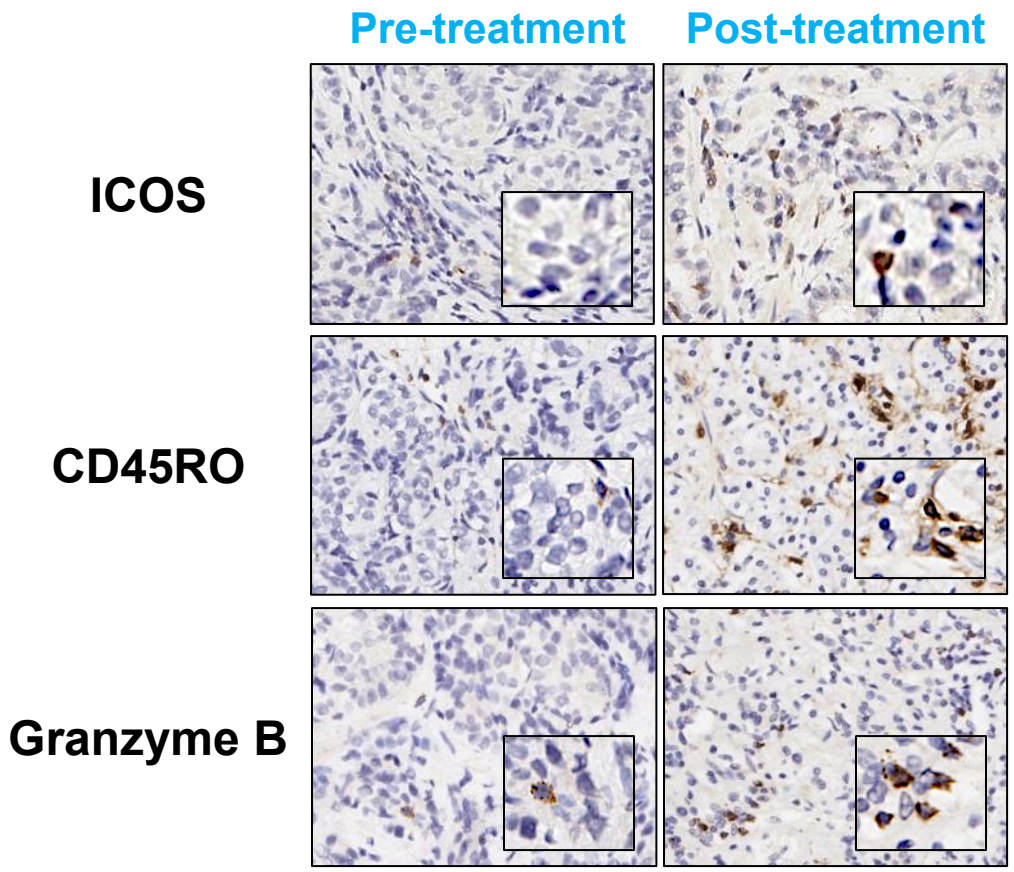
Conclusions

- **Low TMB prostate tumors can have high density of effector T cells and/or IFN-γ response signature**
- **These biomarkers *may* select for patients benefiting from ipilimumab**
- **Ipilimumab enhanced systemic antigen-specific T cell responses**

What prevents anti-CTLA-4 from being more effective in prostate cancer?

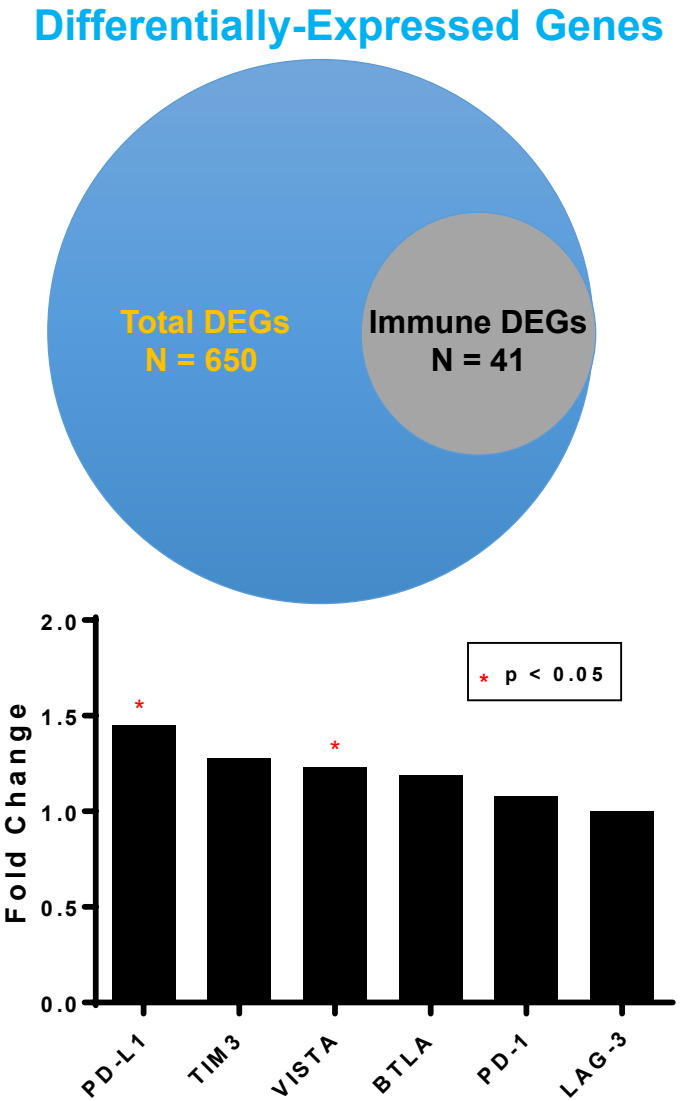
Anti-CTLA-4 Increased Immune Infiltration Within the Primary Prostate Tumor Microenvironment

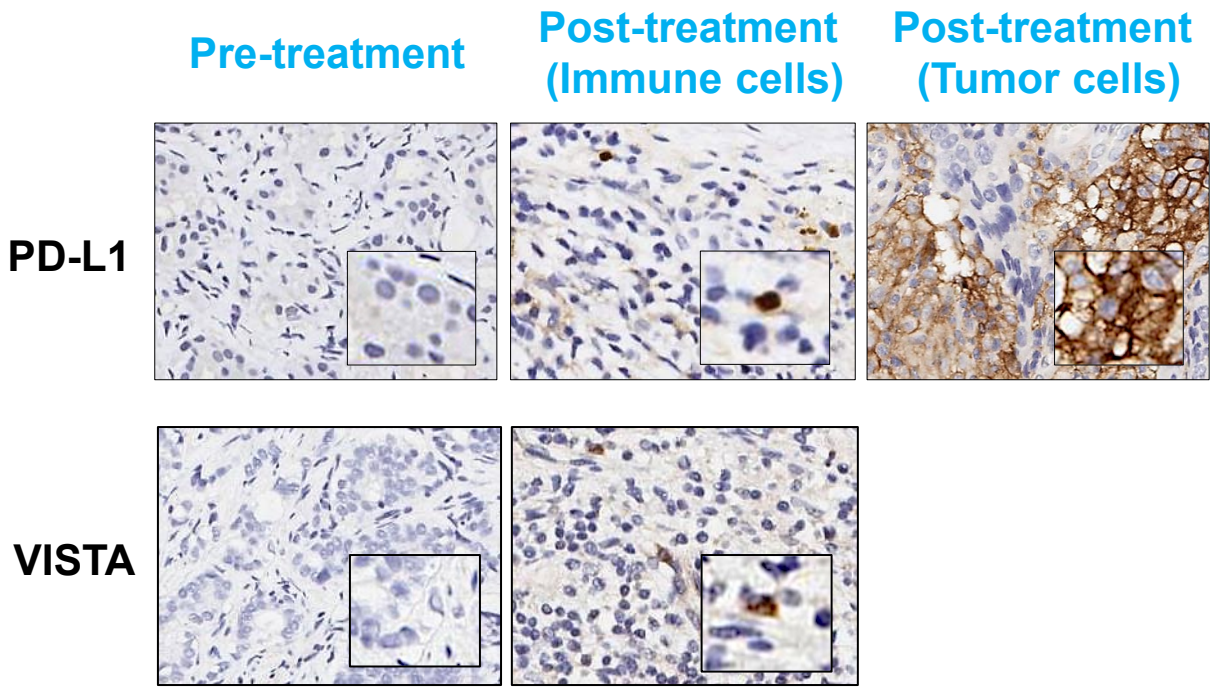




Gao JJ et al., *Nature Med,* 2017.

Increased Tumor-Infiltrating T Cells were Insufficient Due to Adaptive Resistance (Upregulation of PD-L1 and VISTA)

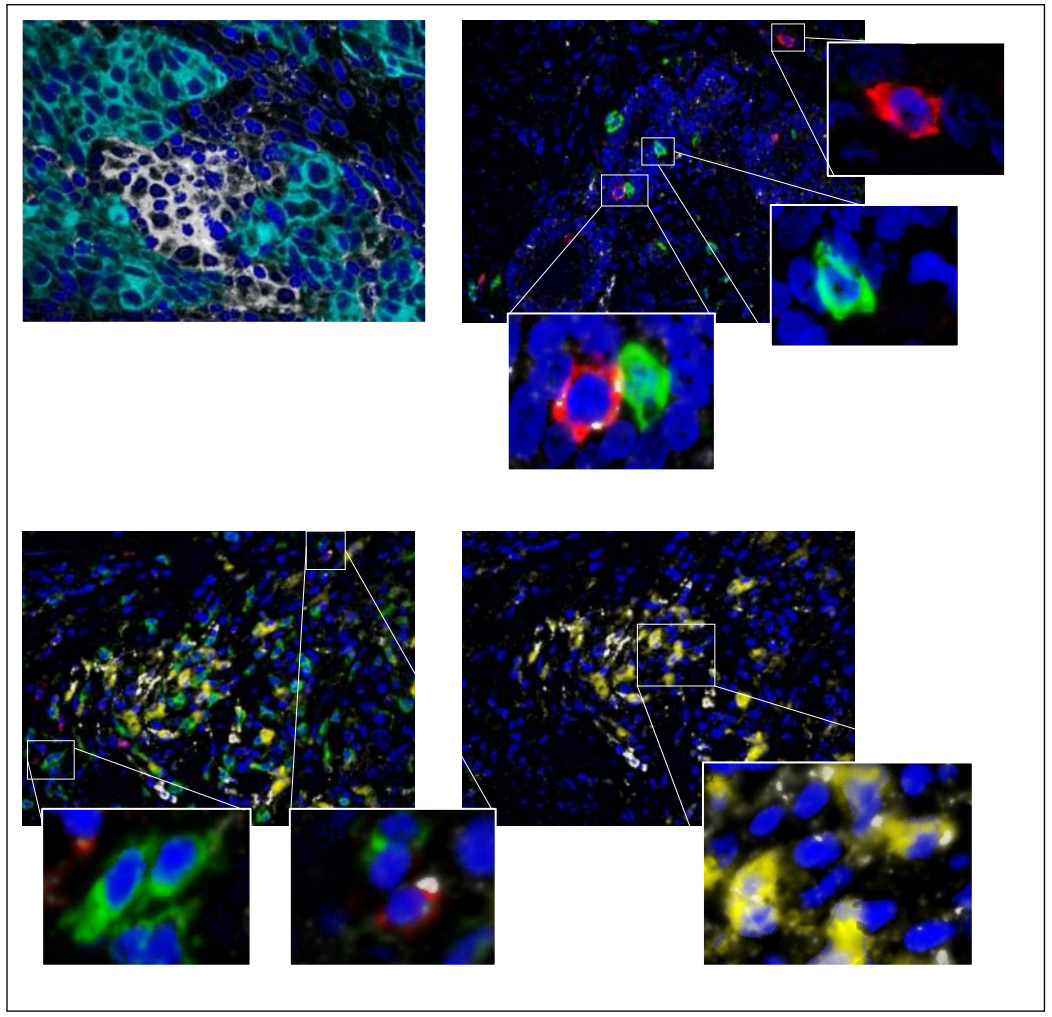


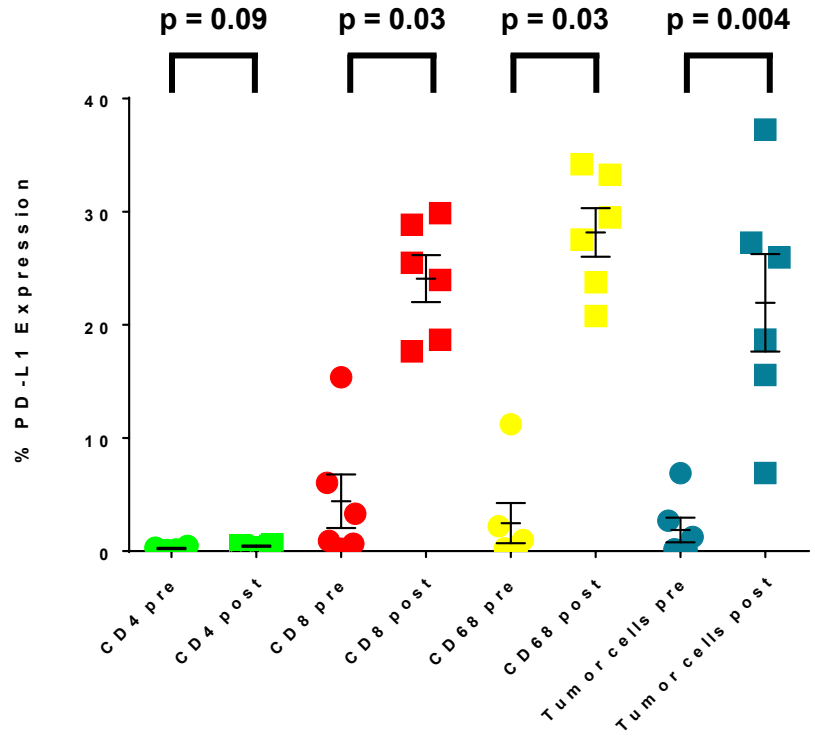


Gao JJ et al., *Nature Med,* 2017.

Ipilimumab Increased PD-L1 Expression on CD8, CD68, and Prostate Tumor Cells

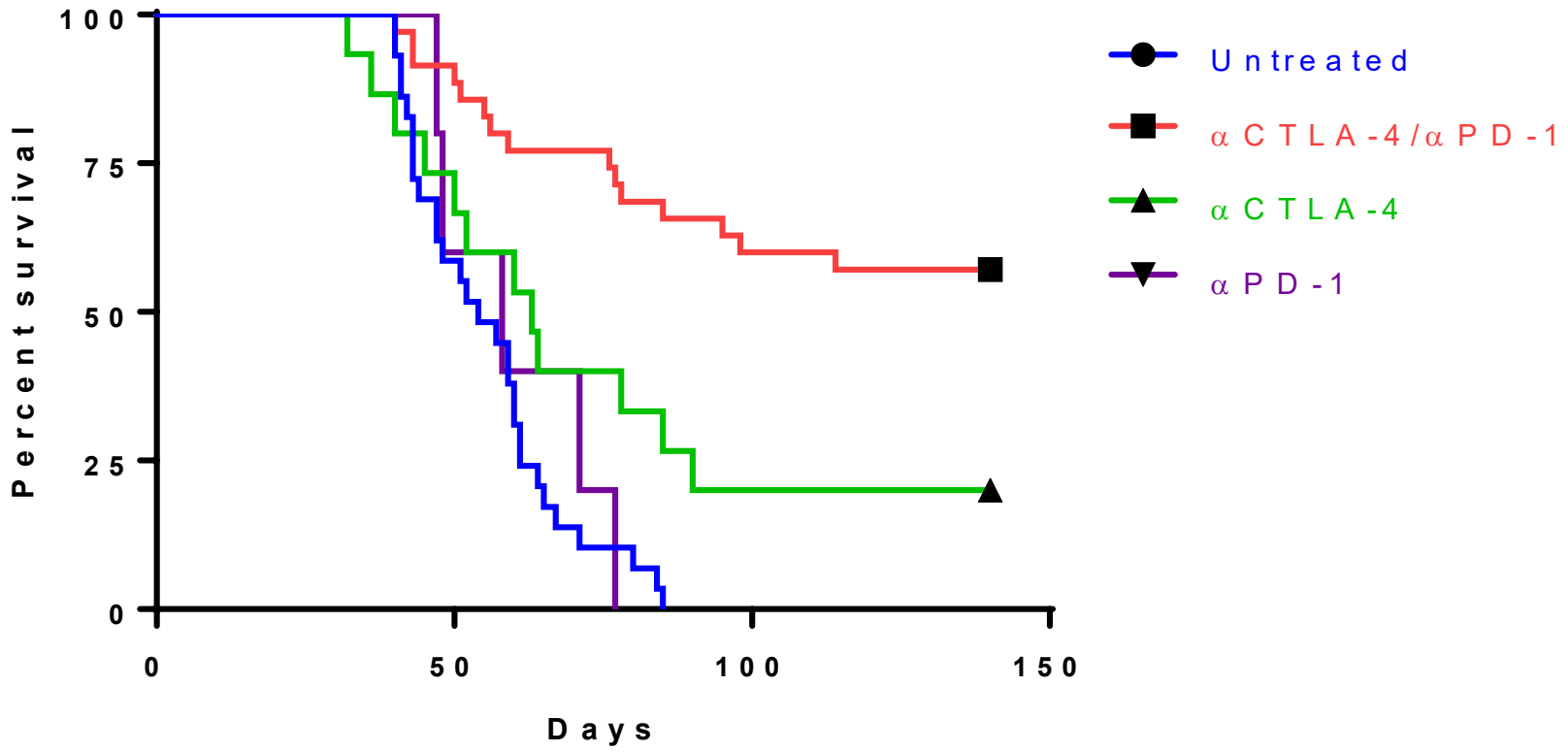
Nucleus
Tumor/Epithelial cells
PD-L1
CD4
CD8
CD68





Gao JJ et al., *Nature Med,* 2017.

Concurrent Targeting of the CTLA-4 and PD-(L)1 Pathways Improved Survival in a Murine Model of Prostate Cancer



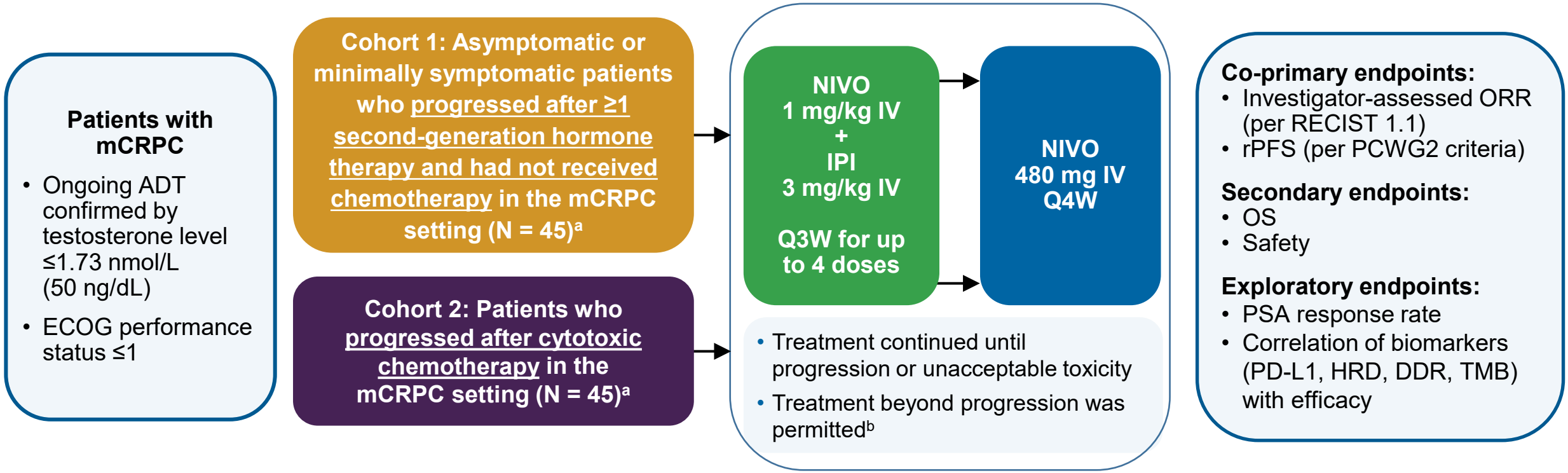
Conclusions

- Ipilimumab induced upregulation of PD-L1/VISTA within the TME
- PD-L1/VISTA have different mechanisms of inhibiting T cell functions
  - Myeloid cells expressing PD-L1 or VISTA suppress T cell functions
- Targeting both CTLA-4 and PD-1 improved outcomes in a preclinical model of prostate cancer

Can we improve clinical responses by co-targeting the CTLA-4 And PD-(L)1 pathways?

Study Design for CheckMate 650 in Prostate Cancer

Open-label, multicenter, phase 2 study (NCT02985957)



- Patients who had received ≥1 combination dose and who had toxicity that did not meet discontinuation criteria were permitted to begin NIVO maintenance before completion of all 4 combination doses

Sharma P et al., *Cancer Cell*, 2020.

Treatment Exposure and Patient Disposition

Characteristic	Cohort 1 (N = 45)	Cohort 2 (N = 45)
Median follow-up, months	11.9	13.5
Treatment exposure		
Median duration of therapy, months (range)	2.1 (0–13.6+)	1.4 (0–17.2+)
Combination doses received, median (range)		
NIVO	3.0 (1–4)	3.0 (1–4)
IPI	3.0 (1–4)	3.0 (1–4)
Patients receiving 4 combination doses, n (%)	15 (33.3)	11 (24.4)
NIVO maintenance doses received, median (range)	n = 14 2.0 (1–11)	n = 9 2.0 (1–15)
On study treatment, n (%)	2 (4.4)	1 (2.2)
Reasons for treatment discontinuation, n (%)		
Disease progression	15 (33.3)	20 (44.4)
Study drug toxicity	23 (51.1)	20 (44.4)
Adverse event unrelated to study drug	1 (2.2)	1 (2.2)
Patient withdrew consent	2 (4.4)	0 (0)
Other/not reported	2 (4.4)	3 (6.7)

+ Indicates a censored value.

Sharma P et al., *Cancer Cell*, 2020.

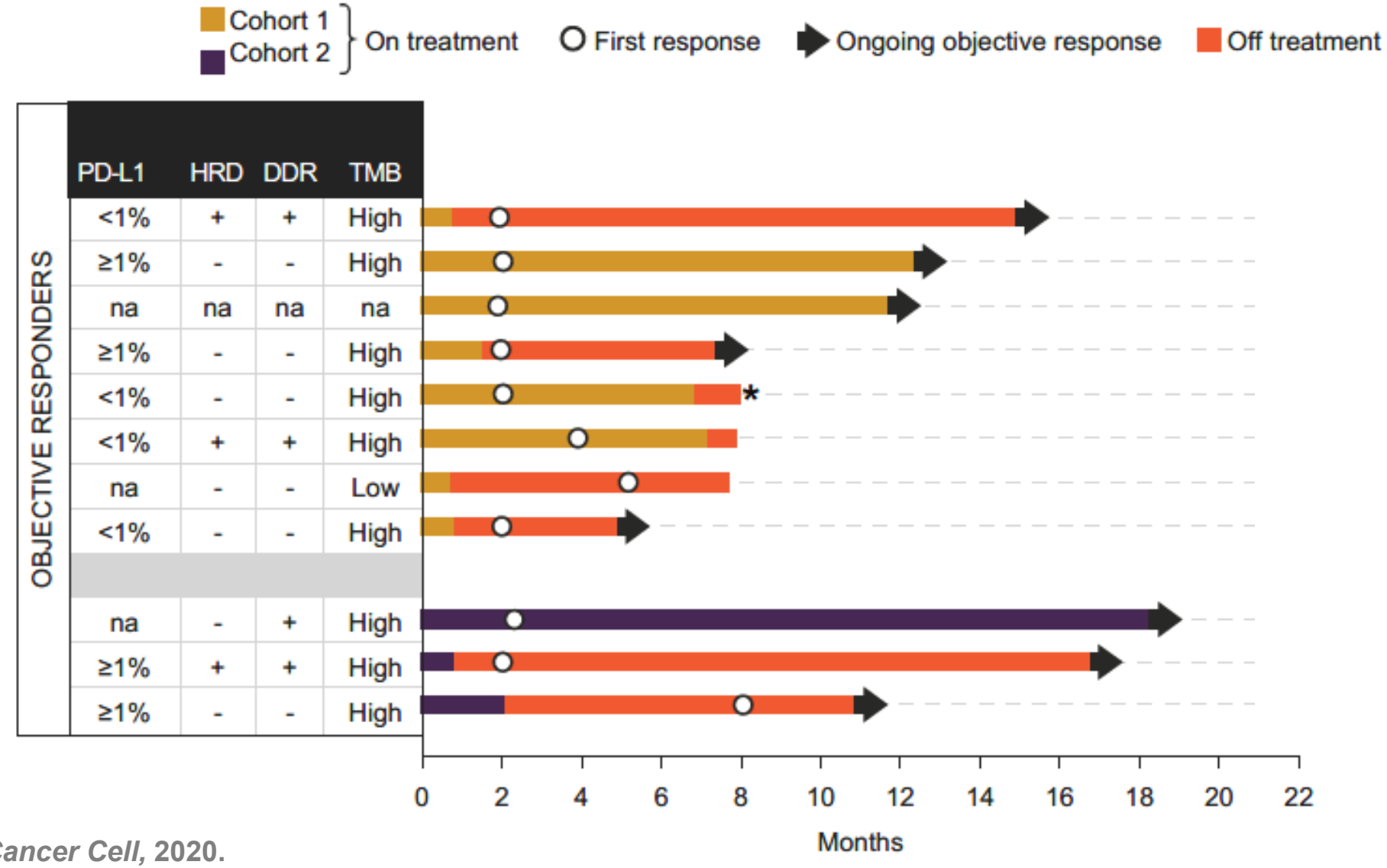
Clinical Response Outcomes for Nivolumab Plus Ipilimumab

Objective response (measurable disease only)[a]	Cohort 1 (N = 32)	Cohort 2 (N = 30)
Confirmed ORR, n (%)	8 (25.0)	3 (10.0)
95% CI	11.5–43.4	2.1–26.5
Best overall response, n (%)		
Complete response	2 (6.3)[b]	2 (6.7)
Partial response	6 (18.8)[c]	1 (3.3)
Stable disease	13 (40.6)	11 (36.7)
Progressive disease	9 (28.1)	13 (43.3)
Unable to determine	2 (6.3)	3 (10.0)
Disease control rate, n (%)	15 (46.9)	4 (13.3)
Median time to response, months (Q1–Q3)	1.9 (1.9–2.8)	2.1 (1.9–7.4)

- Objective response was ongoing in 5/8 responders in cohort 1 and all 3 responders in cohort 2

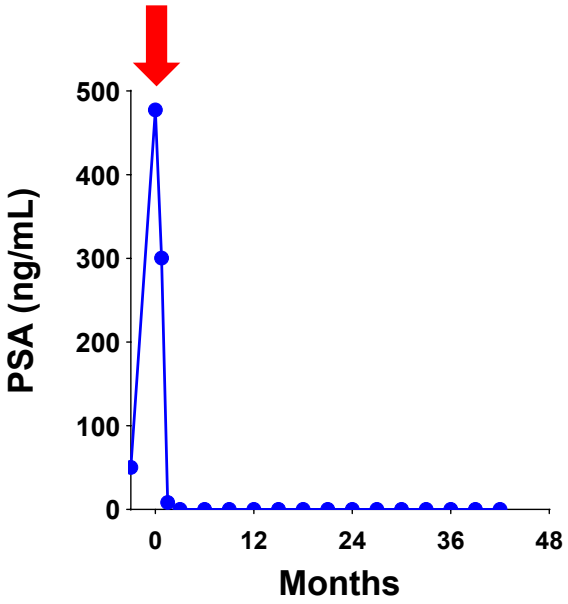
Sharma P et al., *Cancer Cell*, 2020.

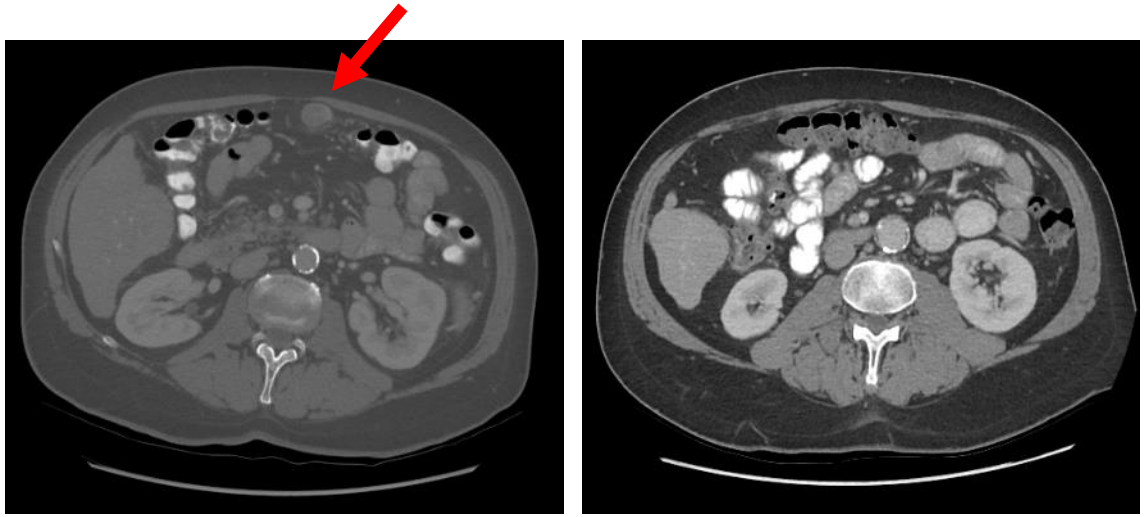
Duration of Responses for Patients with Objective Responses

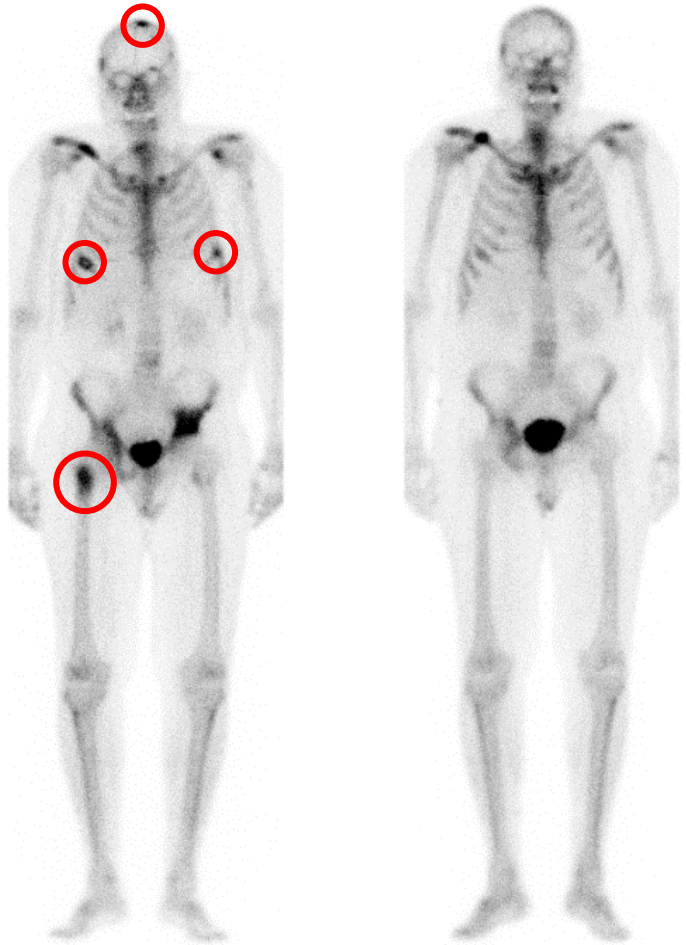


Sharma P et al., *Cancer Cell,* 2020.

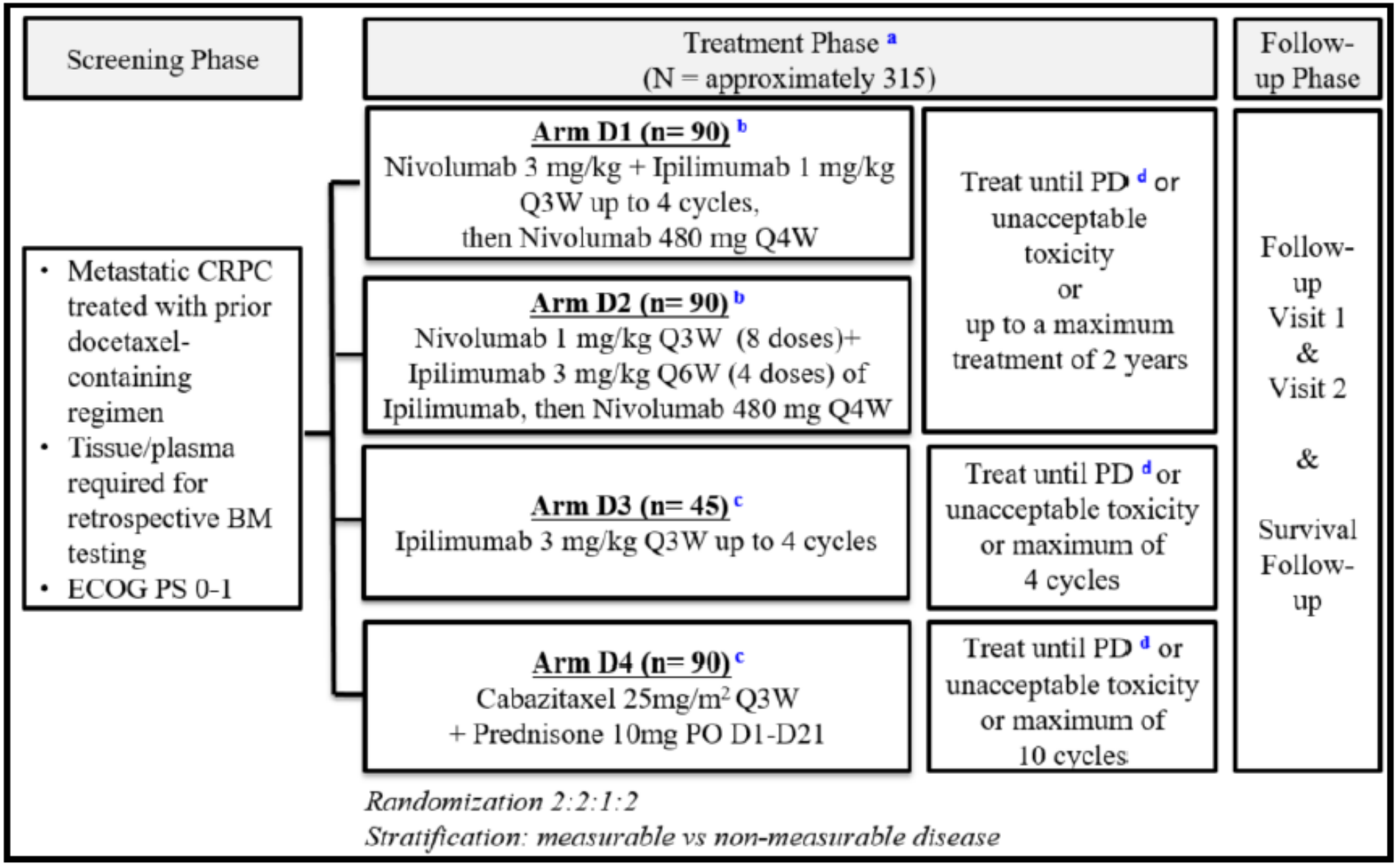
Responder at MD Anderson







Expanded Phase 2 Clinical Trial



Conclusions

- Combining anti-CTLA-4 and anti-PD-1 may improve clinical outcomes in a subset of patients
- Need to explore dose/schedule to potentially mitigate toxicities
- New rational combinations will be needed to provide clinical benefit for a greater number of patients

Prostate Cancer Bone Metastases were Associated with Poorer Survival

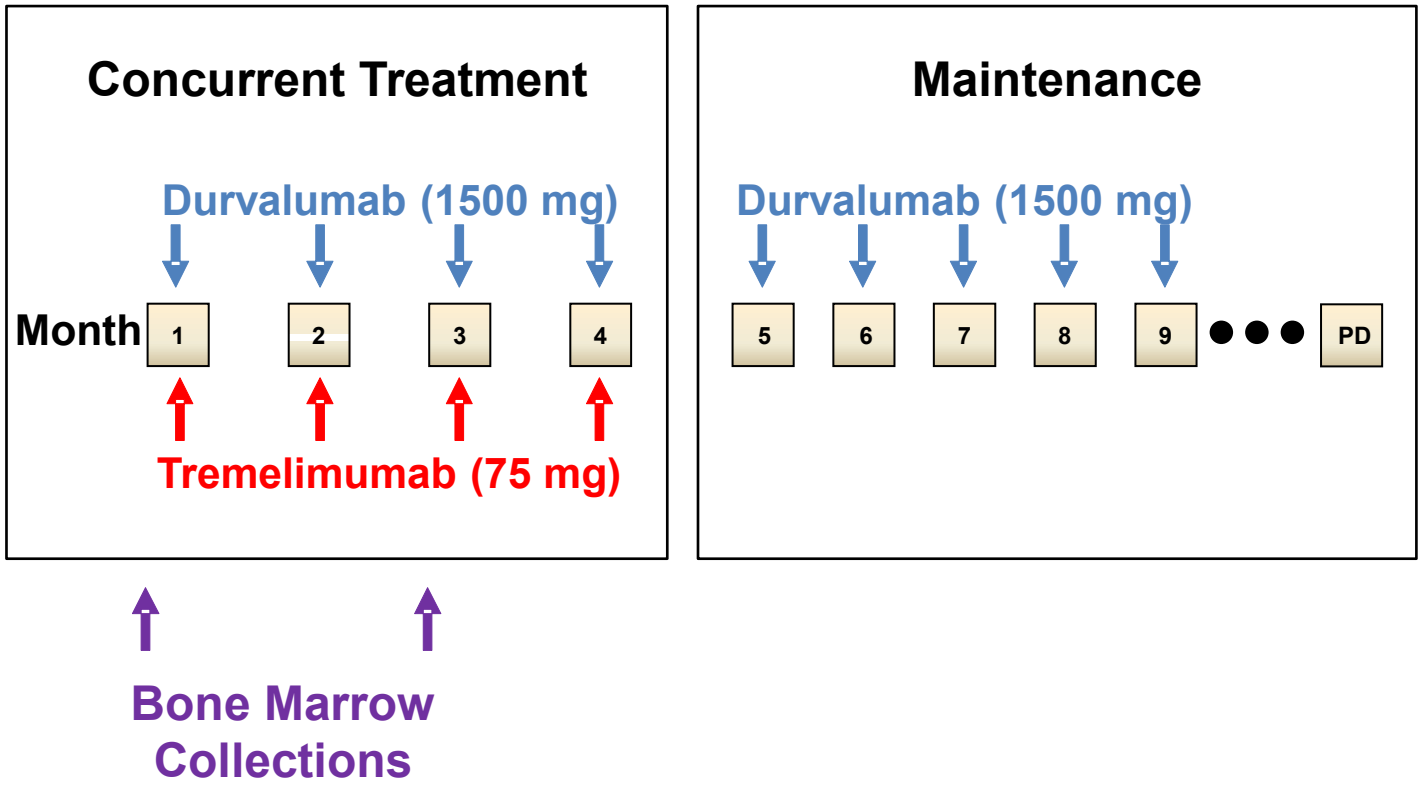
	Lymph Node Only	Bone Only	Bone + Lymph Node
% Men	6.4	42.9	29.8
Overall Survival (Months)	31.6	21.3	

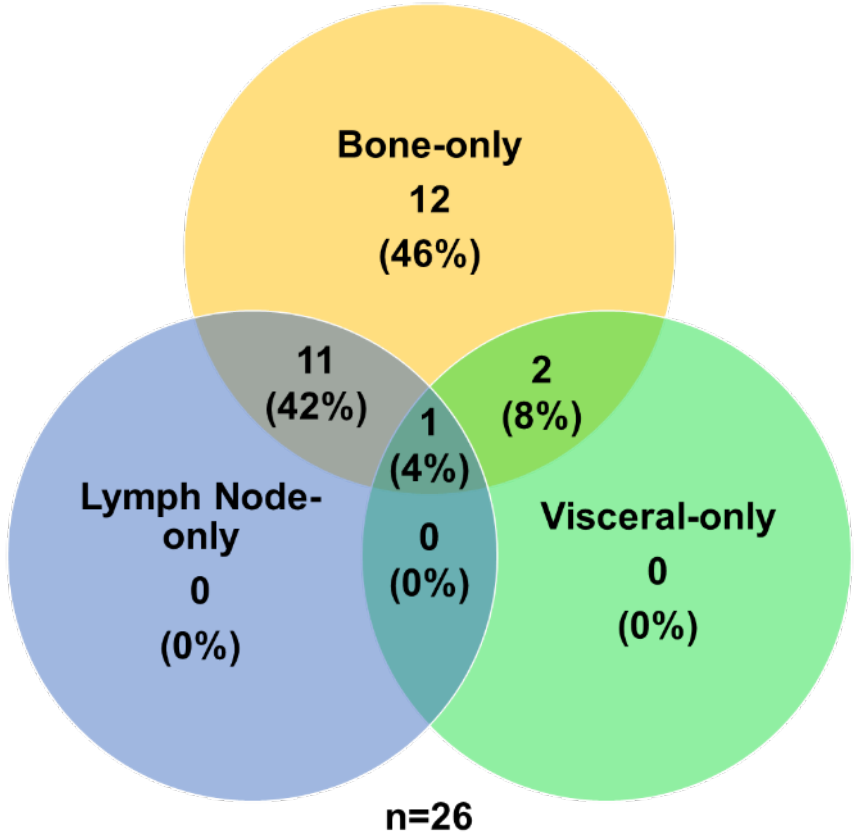
Adapted from Halabi, S et al., *J Clin Oncol,* 2016.

How effective is concurrently targeting the CTLA-4 and PD-(L)1 pathways in patients with mCRPC to the bones?

Durvalumab + Tremelimumab in mCRPC to the Bones

NCT03204812 (N=26)

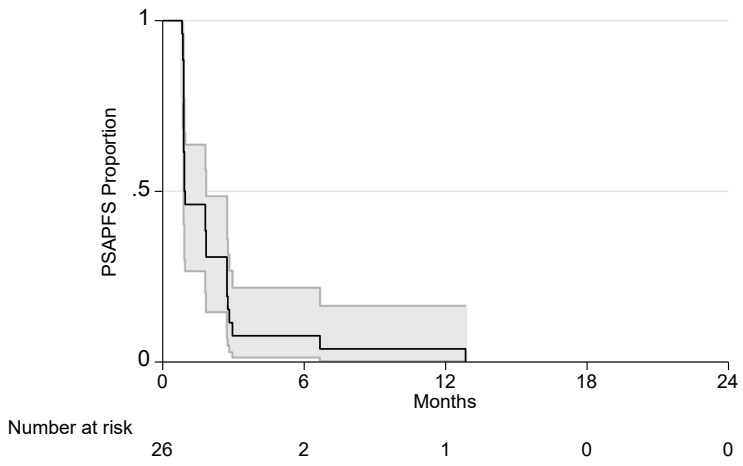




Subudhi SK, Siddiqui B et al., *manuscript in review*

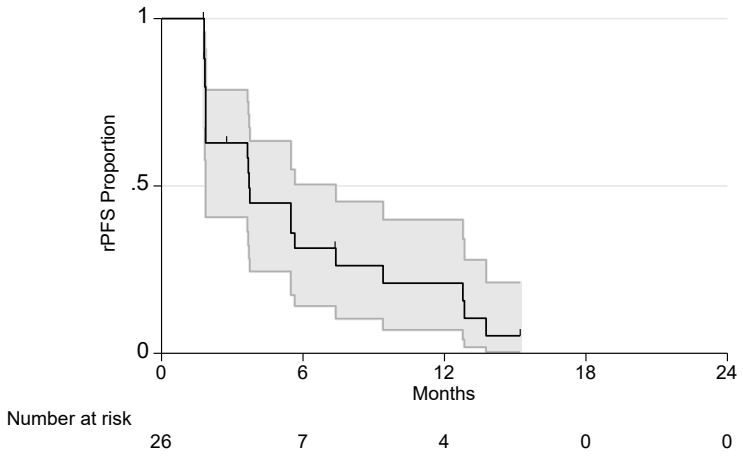
Efficacy Outcomes

PSA PFS



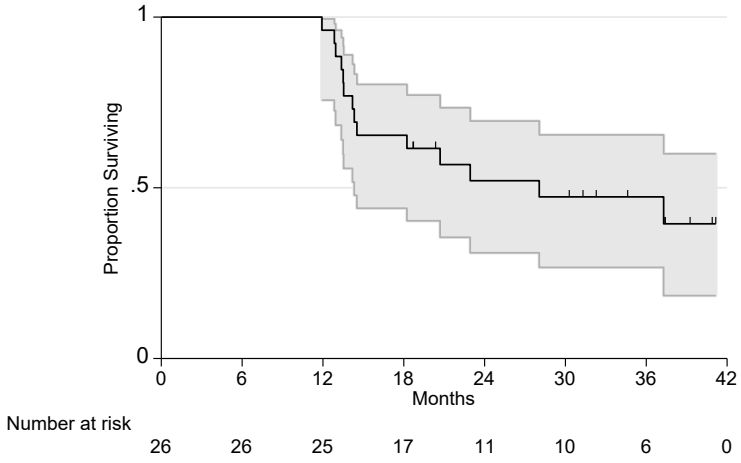
Median PSA PFS: **0.9 months**
(95% CI: 0.9-1.8)

Radiographic PFS



Median rPFS: **3.7 months**
(95% CI: 1.9-5.7)

Overall Survival



Median OS: **28.1 months**
(95% CI: 14.5 – NR)

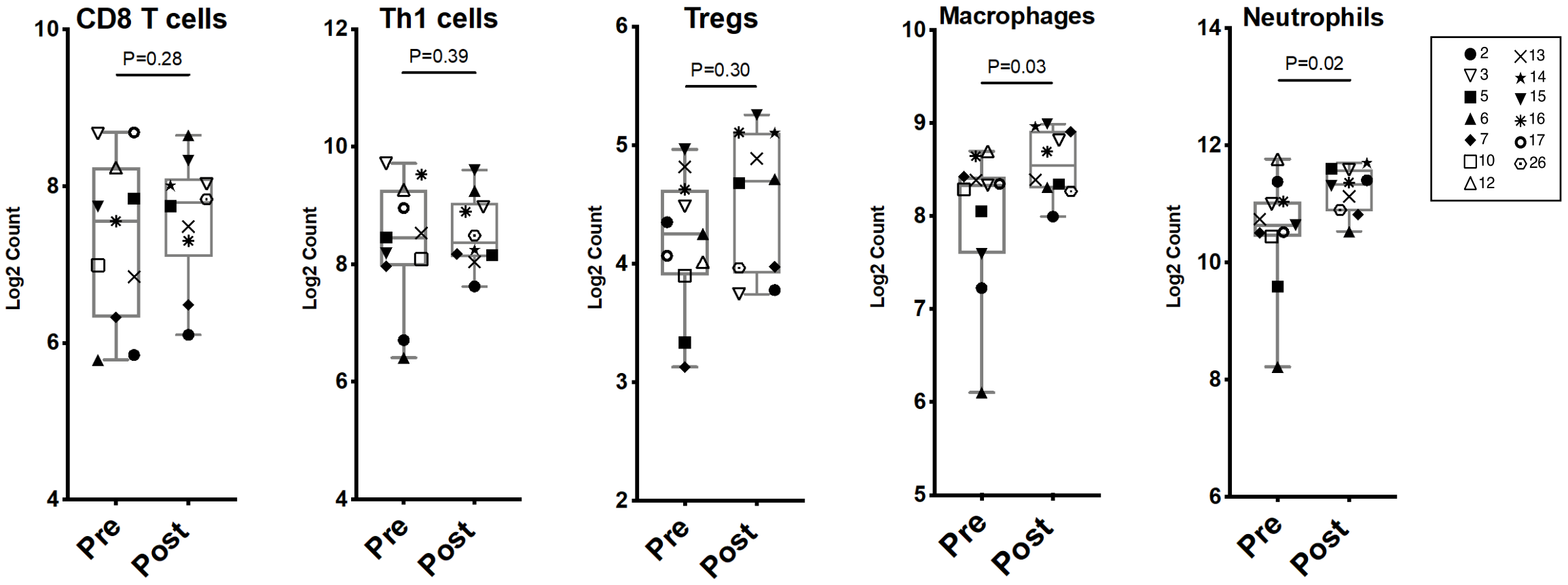
Subudhi SK, Siddiqui B et al., *manuscript in review*

Summary of Efficacy Outcomes

Outcome	N (%)
All Patients with Response Information	25 (100)
PSA Response*	3 (12)
ORR	0 (0)
DCR	6 (24)
CR	0 (0)
PR	0 (0)
SD	6 (24)
PSA PFS – Months, Median (CI)	0.9 (0.9 - 1.8)
rPFS – Months, Median (CI)	3.7 (1.9 - 5.7)
OS – Months, Median (CI)	28.1 (14.5 – NR)
12 month OS (Standard Error)	96% (4%)
24 month OS (Standard Error)	54% (10%)

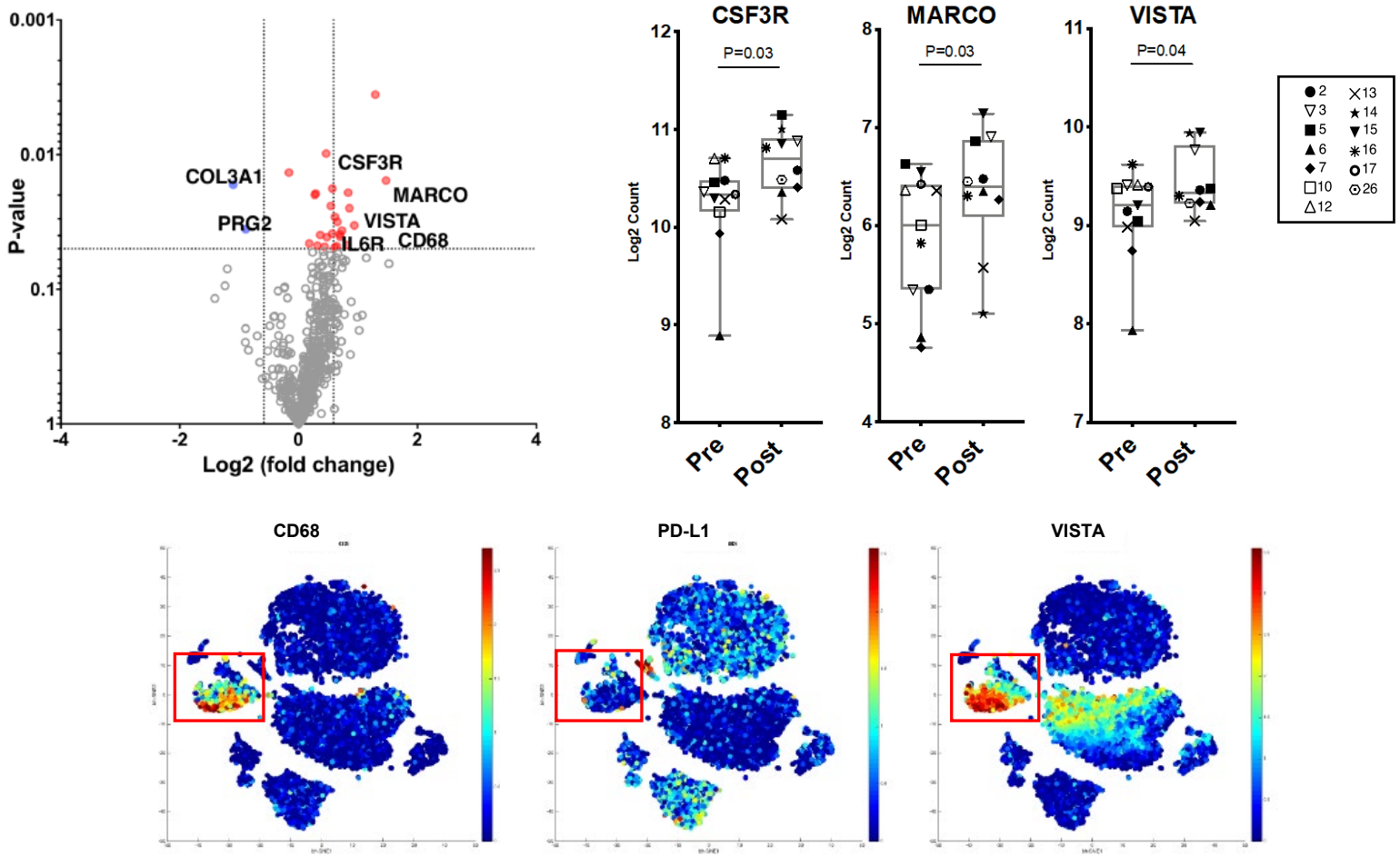
Subudhi SK, Siddiqui B et al., *manuscript in review*

Macrophage/Neutrophil Transcriptional Signatures Upregulated Within the Bone Tumor Microenvironment



Subudhi SK, Siddiqui B et al., *manuscript in review*

Targets of Immunosuppressive Myeloid Cells Within the Bone Tumor Microenvironment



Subudhi SK, Siddiqui B et al., *manuscript in review*

Conclusions

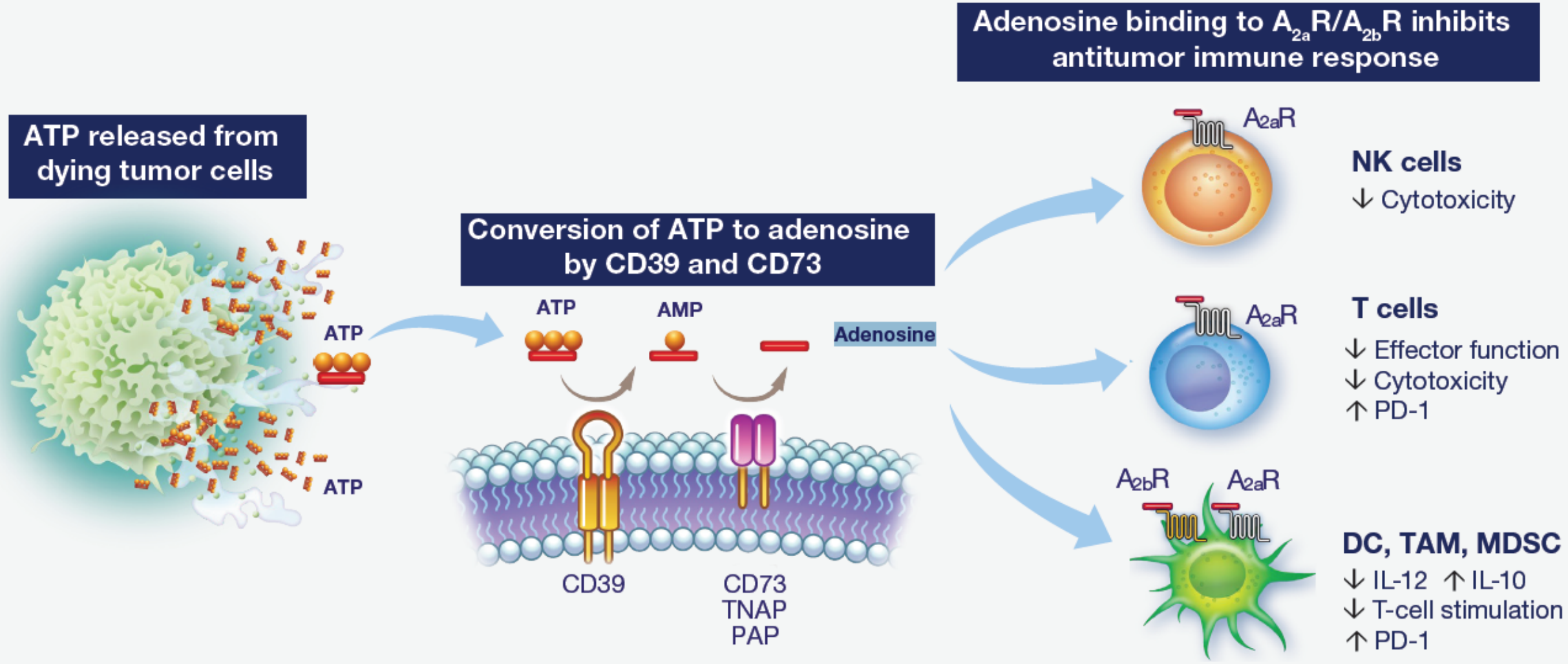
- **Combining anti-CTLA-4 and anti-PD-L1 was safe and tolerable**
- **Concurrently targeting immunosuppressive myeloid cells may improve clinical benefit for a greater number of patients**

Are there clinically effective ways to target immunosuppressive myeloid cells?

Therapeutic Approaches for Targeting Immunosuppressive Myeloid Cells

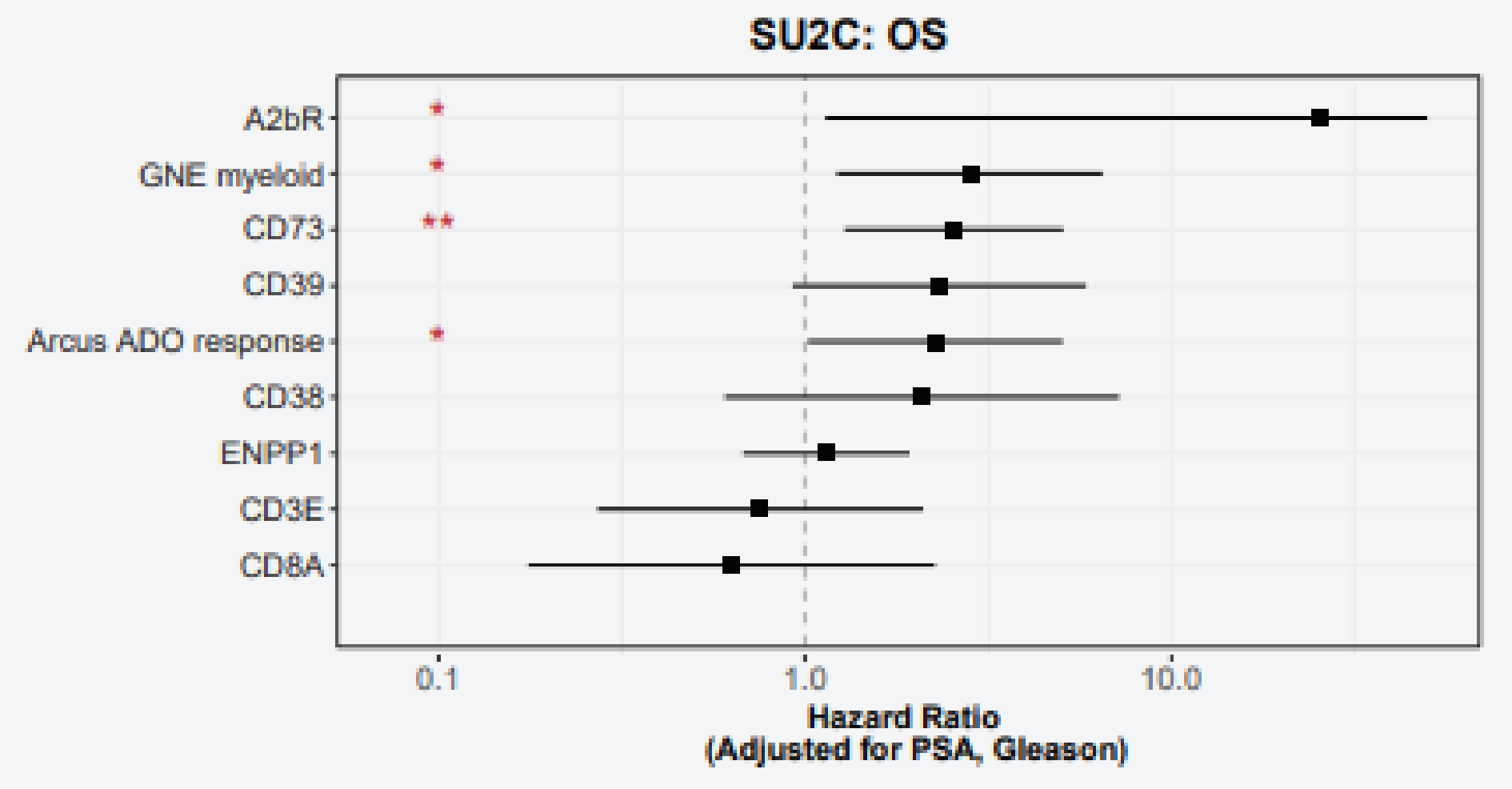
- Immune checkpoints (PD-L1, VISTA)
- Cytokines / Chemokines (IL-8, IL-23)
- Tyrosine kinase pathways (VEGFR2, AXL, PTEN/PI3K)
- Metabolic pathways (adenosine, arginine)

Adenosine Pathway



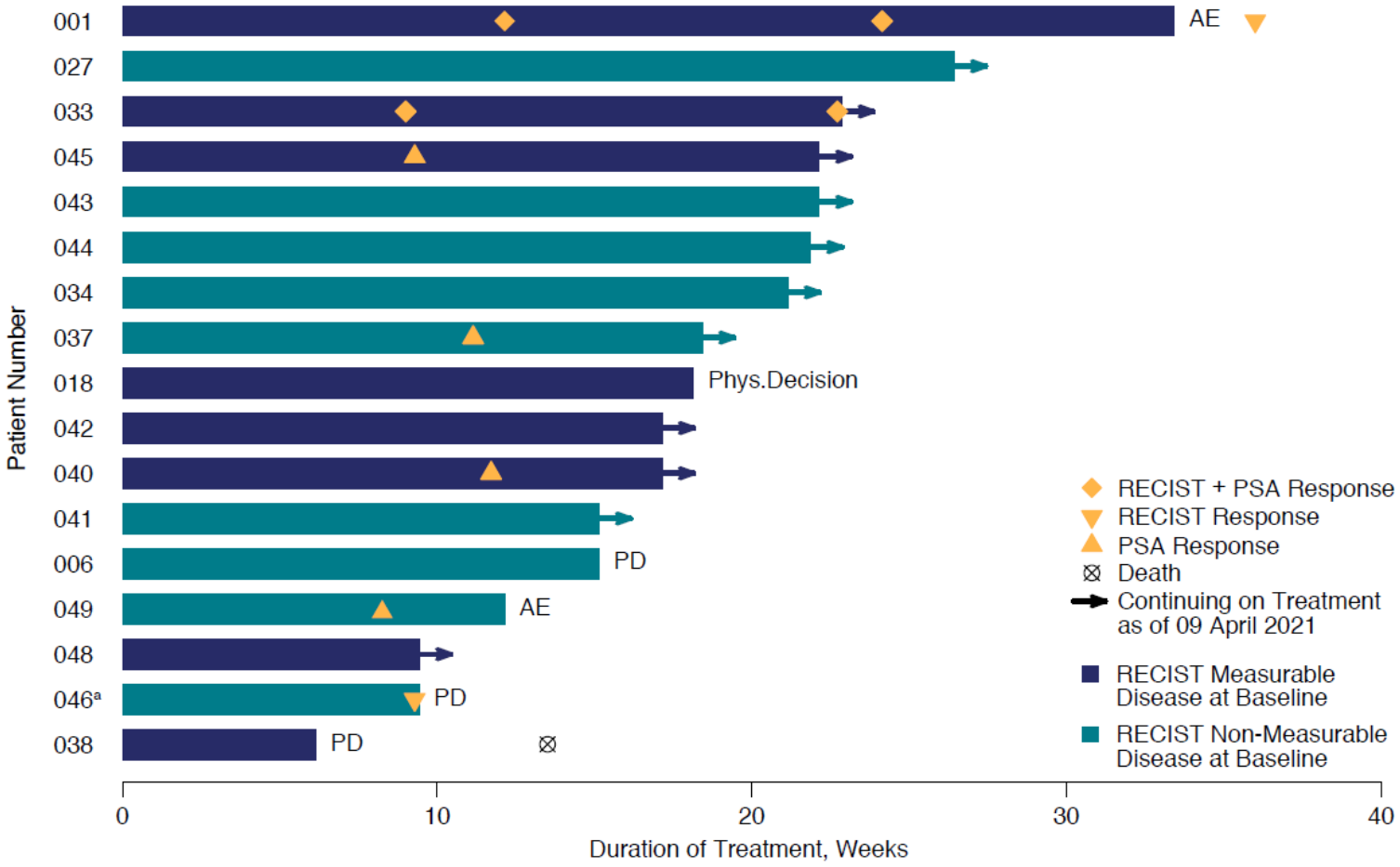
Subudhi SK et al., ESMO 2020.

Adenosine Pathway Expression Correlates with Unfavorable Survival in Prostate Cancer



Subudhi SK et al., ESMO 2020.

Radiographic PFS: Docetaxel + anti-PD-1 + Adenosine Receptor Antagonist



Subudhi SK et al., ASCO 2021.

Conclusions

- **Targeting the adenosine pathway may improve outcomes with immune checkpoint based-combinations**

Moving Forward

- **Rational sequential/combinatorial strategies:**
  - **Increase T cell infiltration**
  - **Target immune checkpoints**
  - **Modulating immunosuppressive cells**
  - **Influence of other factors (e.g., metabolism, hypoxia, microbiome, epigenetics, etc.)**
- **Improve patient selection**

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