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Why Aren't We Immune to Prostate Cancer

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Disclosure Information
Jedd Wolchok, MD, PhD, FASCO

Consultant for:
Apricity; Arsenal IO; Ascentage; AstraZeneca; Bicara Therapeutics; Boehringer Ingelheim; Bristol Myers Squibb; Daiichi Sankyo; Dragonfly; Georgiamune; Imvaq; Larkspur; Psioxus, Recepta; Tizona; Trieza; Sellas; Werewolf Therapeutics

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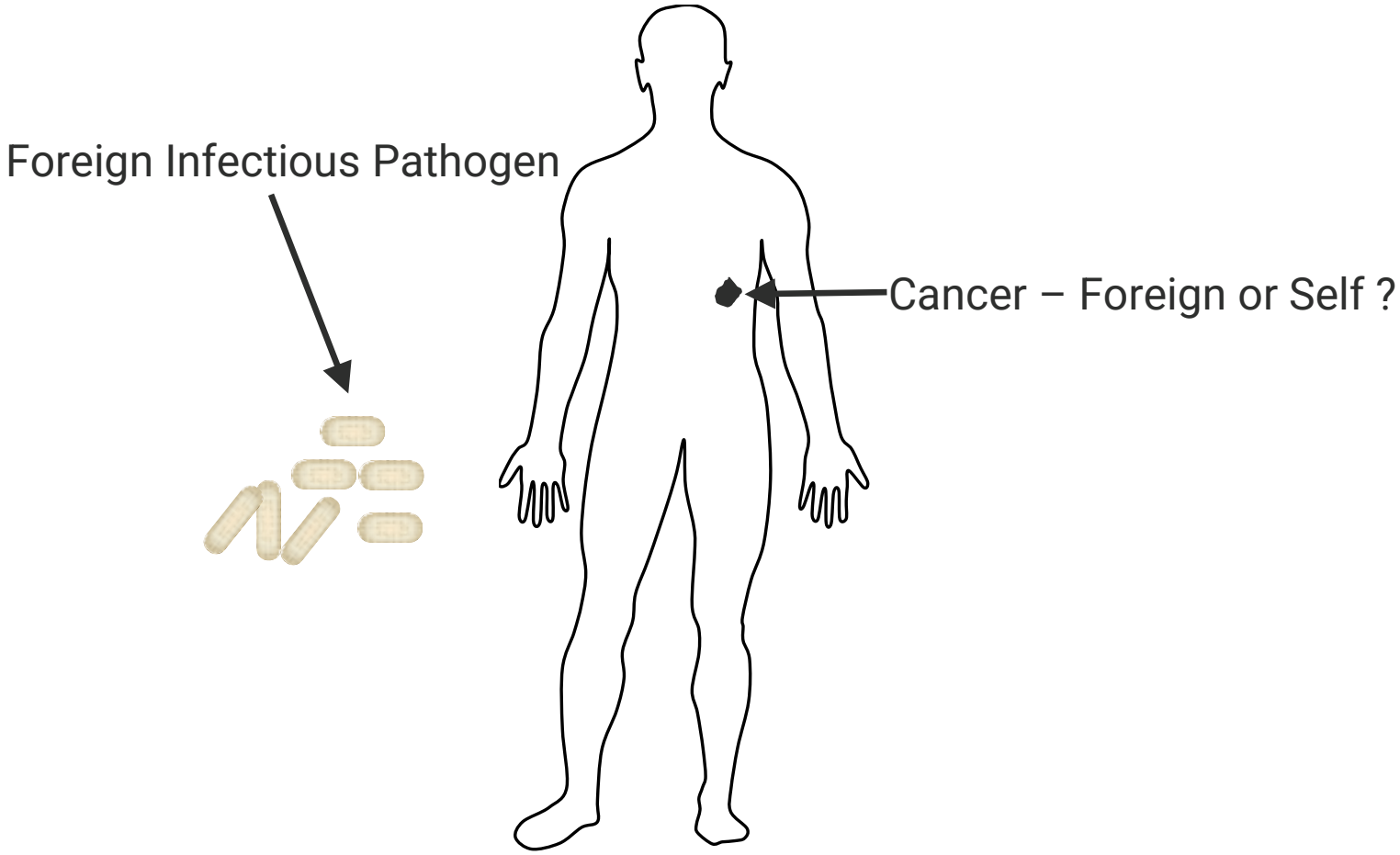
Equity in:
Tizona; Imvaq; Linneaus; Larkspur; Xenimmune; Apricity; Arsenal IO; Georgiamune; Trieza; Ascentage

Cancer: Is it self or non-self?



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‘Driving’ An Immune Response

T-cell receptor:
Antigen-MHC

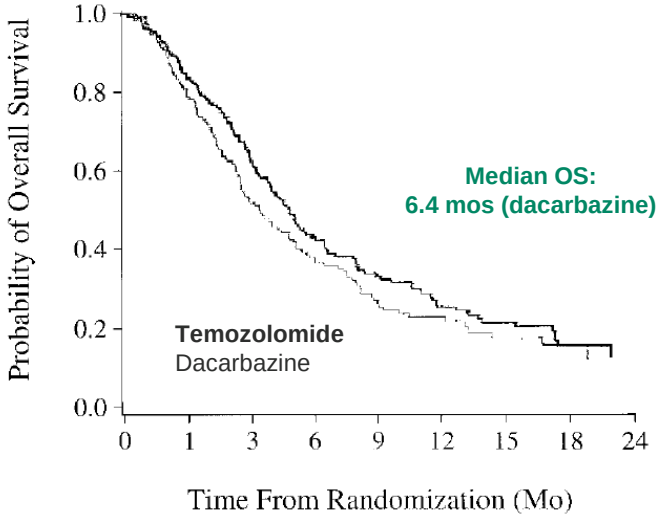
CD28:B7

CTLA-4: B7

Vaccine?

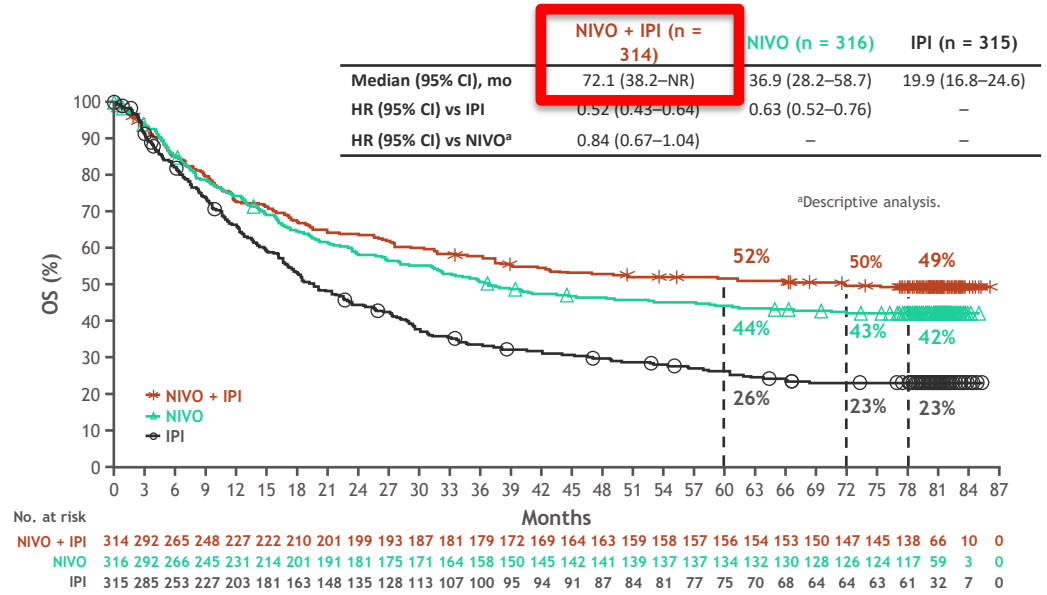
Change in expectations for overall survival in metastatic melanoma with use of immunotherapy: 2000-2021

Pre-Checkpoint Blockade/
BRAF-Targeted Therapy: Chemotherapy



(Middleton MR *et al. J Clin Oncol* 2000)

PD-1 +/- CTLA-4 Inhibition



(Wolchok *et al*. *ASCO* 2021)

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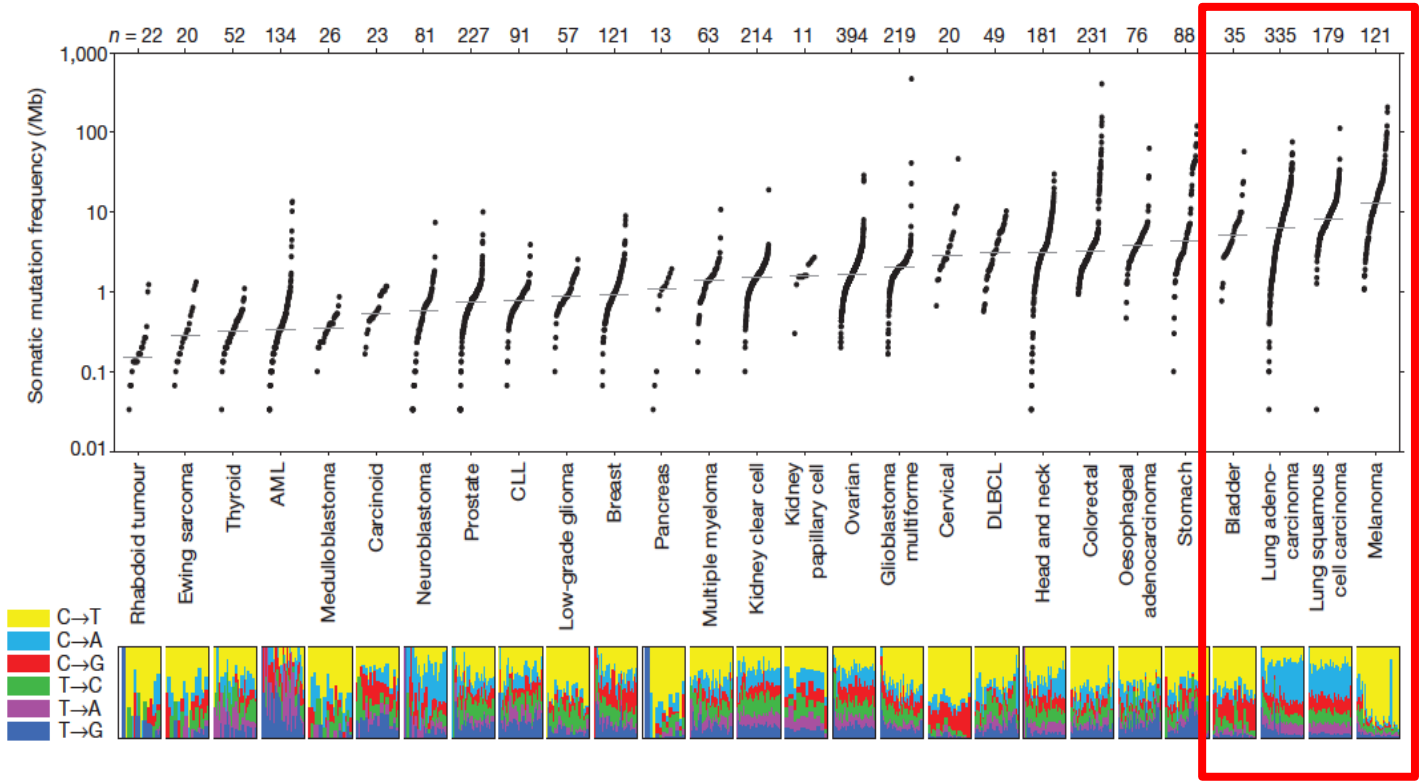
Genomics may explain why some cancers respond to immunotherapy



Lawrence *et al*, *Nature* 2013

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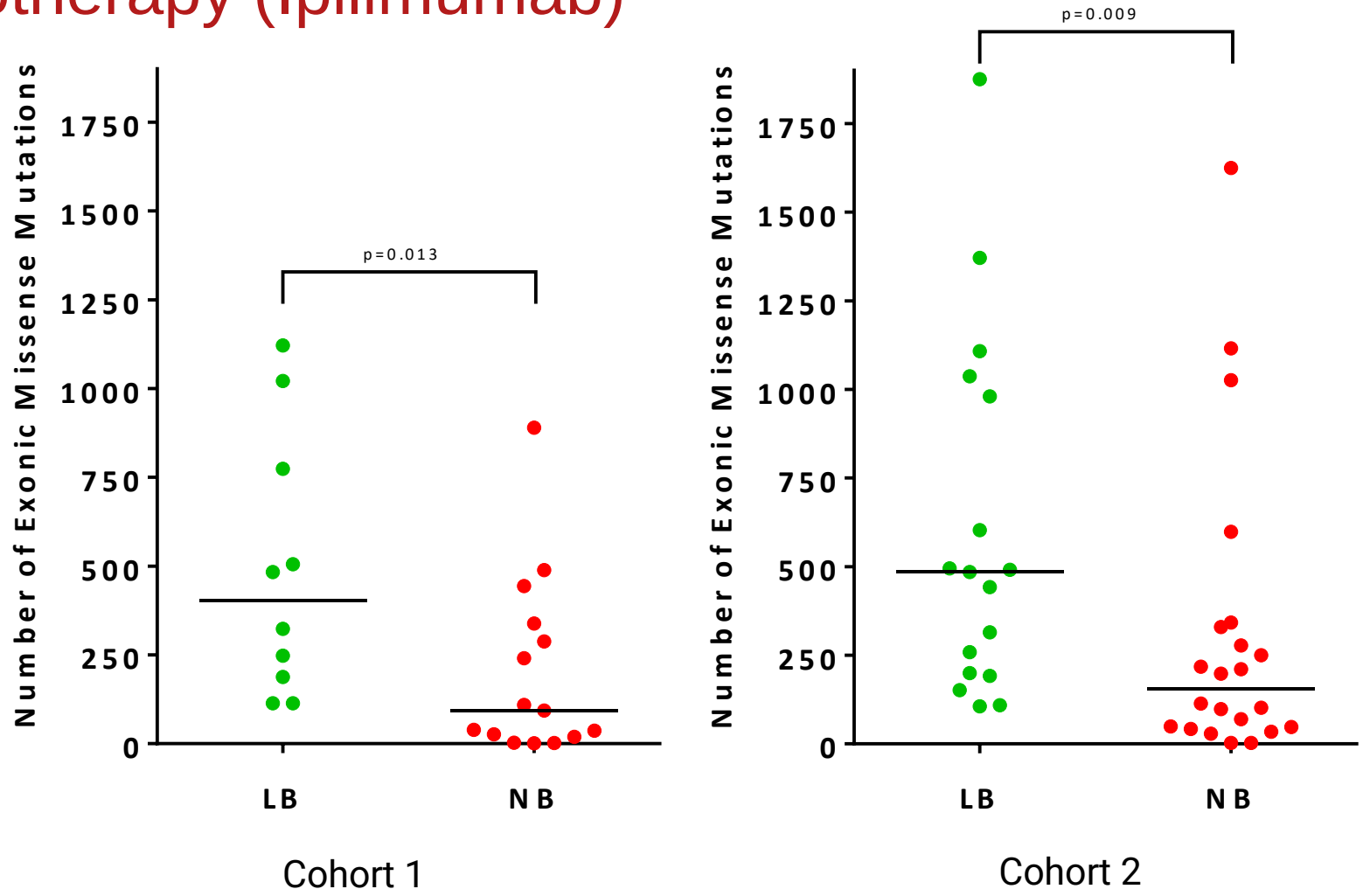
Number of mutations in melanoma tumors correlates with clinical outcome from immunotherapy (Ipilimumab)

Hypothesis: More mutations makes a tumor look less like ‘Self’ to the immune system, increasing immune interest in tumor



LB, long-term clinical benefit lasting ≥6 months
NB, no durable benefit

Snyder *et al.*, *New Engl J Med*, 2014

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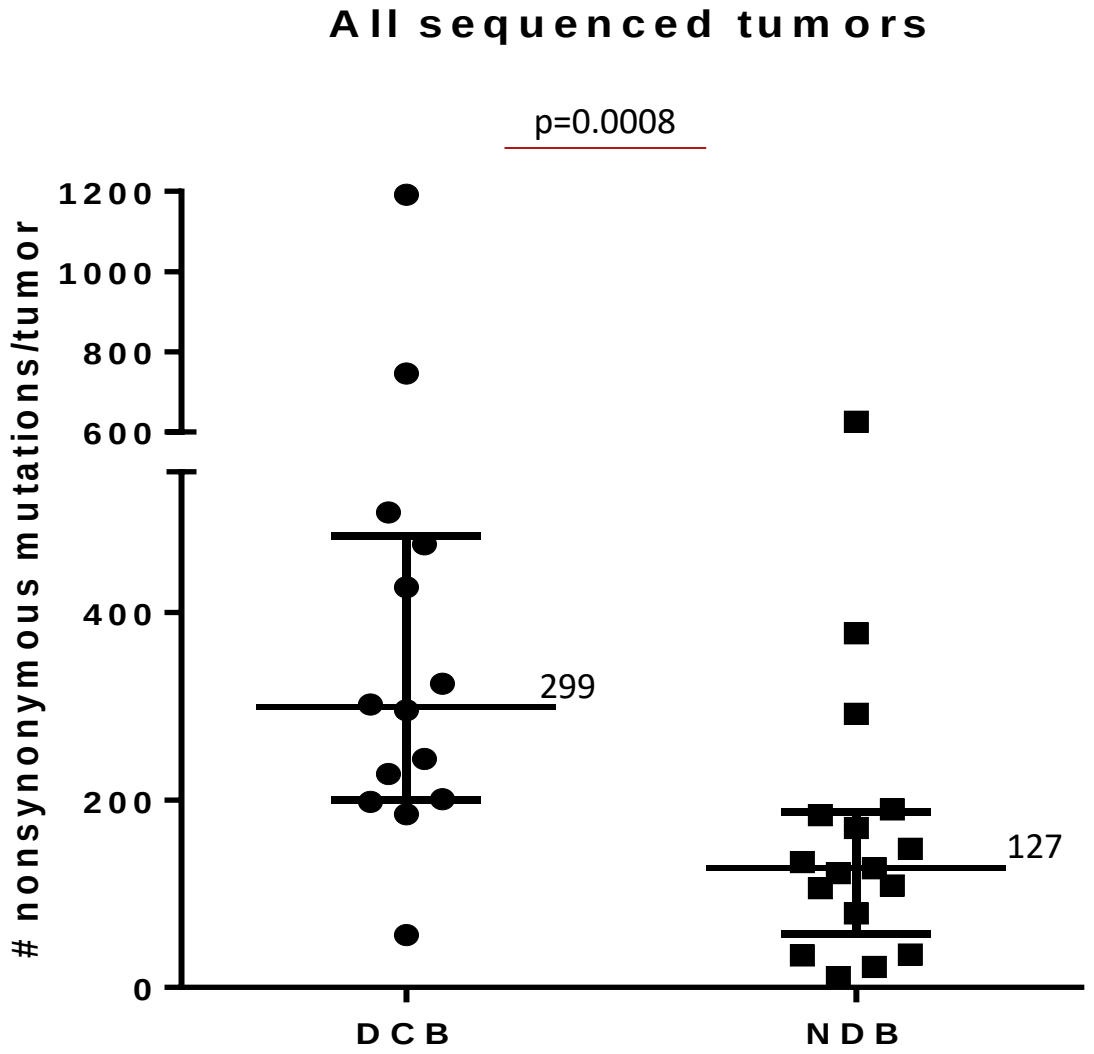
Number of mutations in lung cancer tumors correlates with clinical outcome from immunotherapy

Hypothesis: More mutations makes a tumor look less like 'Self' to the immune system, increasing immune interest in tumor



Rizvi, Hellmann, Snyder *et al*, *Science* 2015

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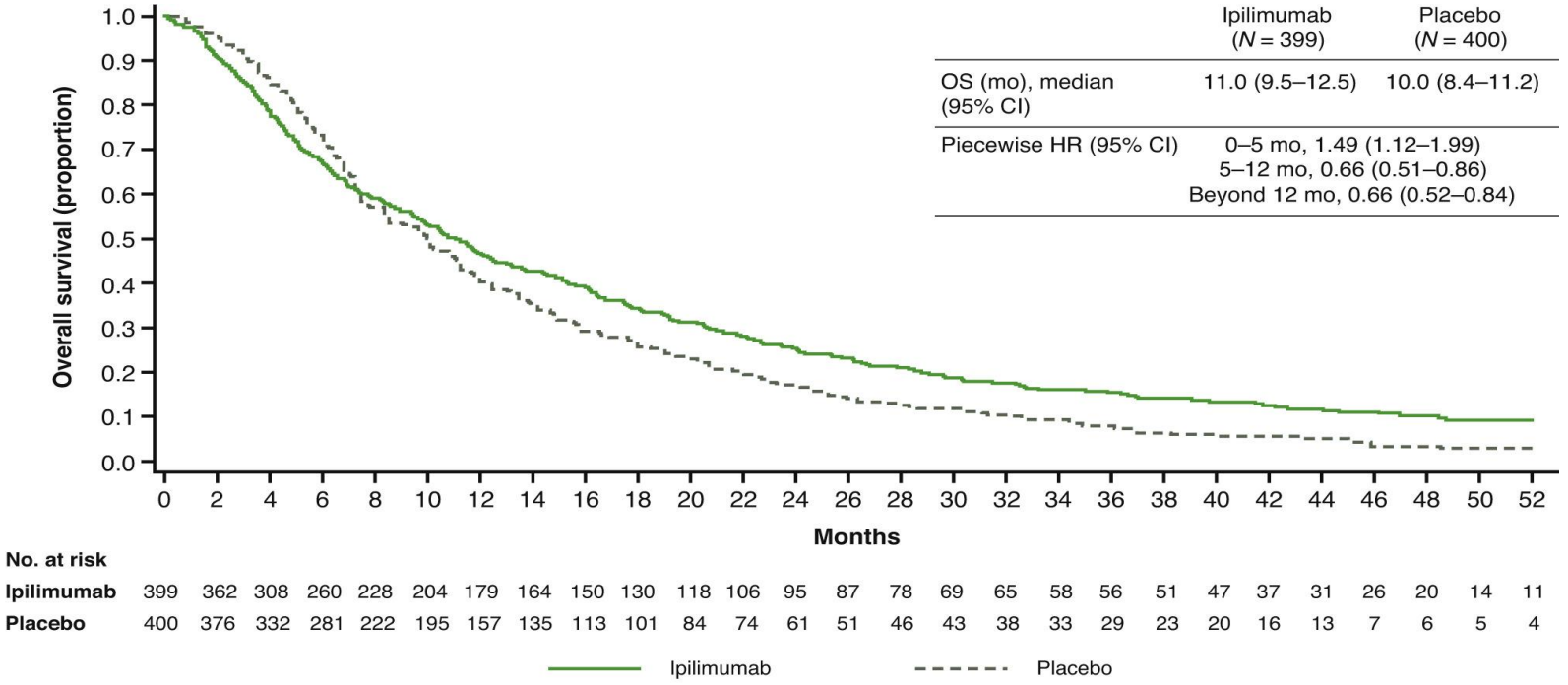
Final Analysis of the Ipilimumab Versus Placebo Following Radiotherapy: Phase III Trial in Postdocetaxel Metastatic Castration-resistant Prostate Cancer



	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)	

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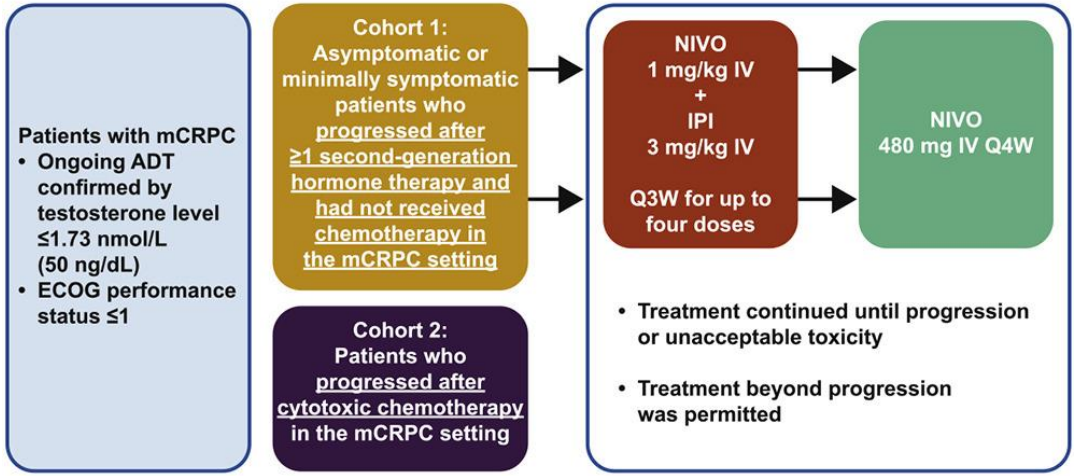
Fizazi et al, European Urology 2020 78822-830DOI: (10.1016/j.eururo.2020.07.032)

CheckMate 650 (NCT02985957)
Part I: Signal seeking study (N = 90)
Open-label, multicenter, phase II study



Endpoints	Cohort 1 (n = 45)	Cohort 2 (n = 45)
Co-primary		
Investigator assessed ORR	25.0%	10.0%
rPFS	Median 5.5 months (95% CI, 3.5–7.1)	Median 3.8 months (95% CI, 2.1–5.1)
Secondary		
OS	Median 19.0 months (95% CI, 11.5–not evaluable)	Median 15.2 months (95% CI, 8.4–not evaluable)
Safety	Grade 3–4 treatment-related AEs in 42.2% of patients	Grade 3–4 treatment-related AEs in 53.3% of patients
Exploratory		
PSA response rate	17.6%	10.0%
Correlation of biomarkers with efficacy	Preliminary evidence of potential biomarkers of response	

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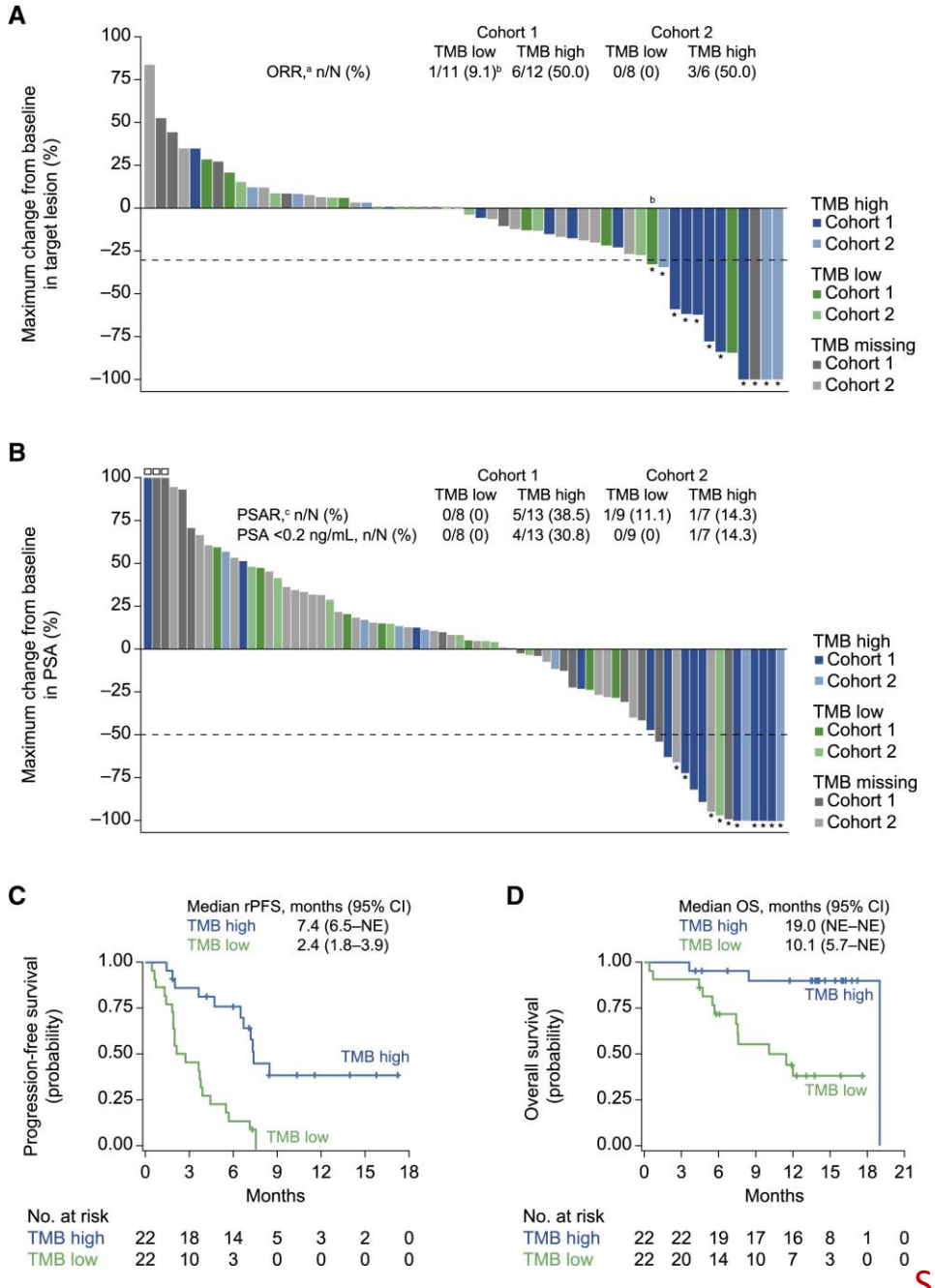
Sharma et al., *Cancer Cell*, 2022



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Sharma et al., *Cancer Cell*, 2022

So…what can we do to improve?

- **Identify patients with high mutation burden early**
- **Explore other novel combinations**
- **Consider antibody targeting (PSMA) with checkpoint blockade**
- **Further investigate the prostate cancer tumor microenvironment**

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