Dual translational biomarker strategies to stratify patients for personalized cancer immunotherapy

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Outline

- Broad clinical responses by PD-1 blockade pembrolizumab treatment and challenges in personalized cancer immunotherapy
- Translational biomarker strategies and the emerging potential biomarkers for pembrolizumab:
  - PD-L1 IHC
  - IFN-γ gene signature or Tumor Inflammation Signature (TIS)
  - Microsatellite instability (MSI)
  - Tumor Mutational Burden (TMB)
- Dual biomarker strategies with different biology for personalized combination cancer immunotherapy. (Maximize clinical efficacy)

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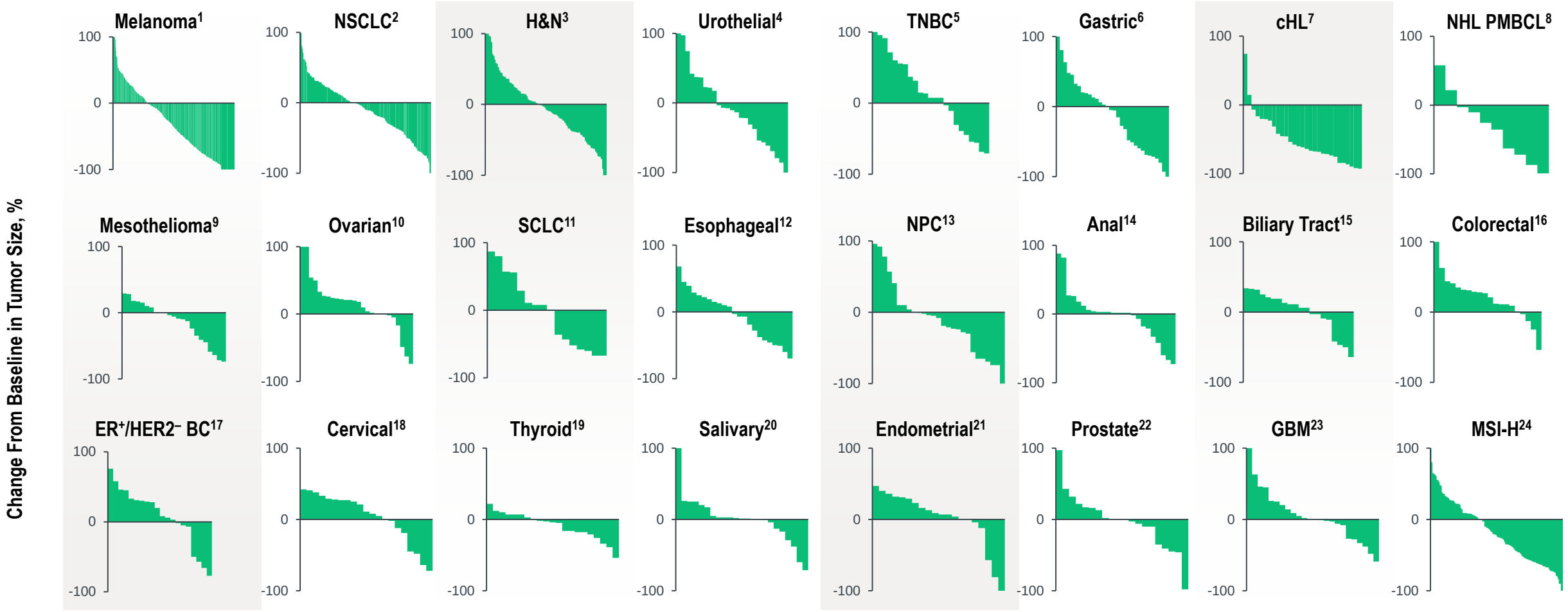
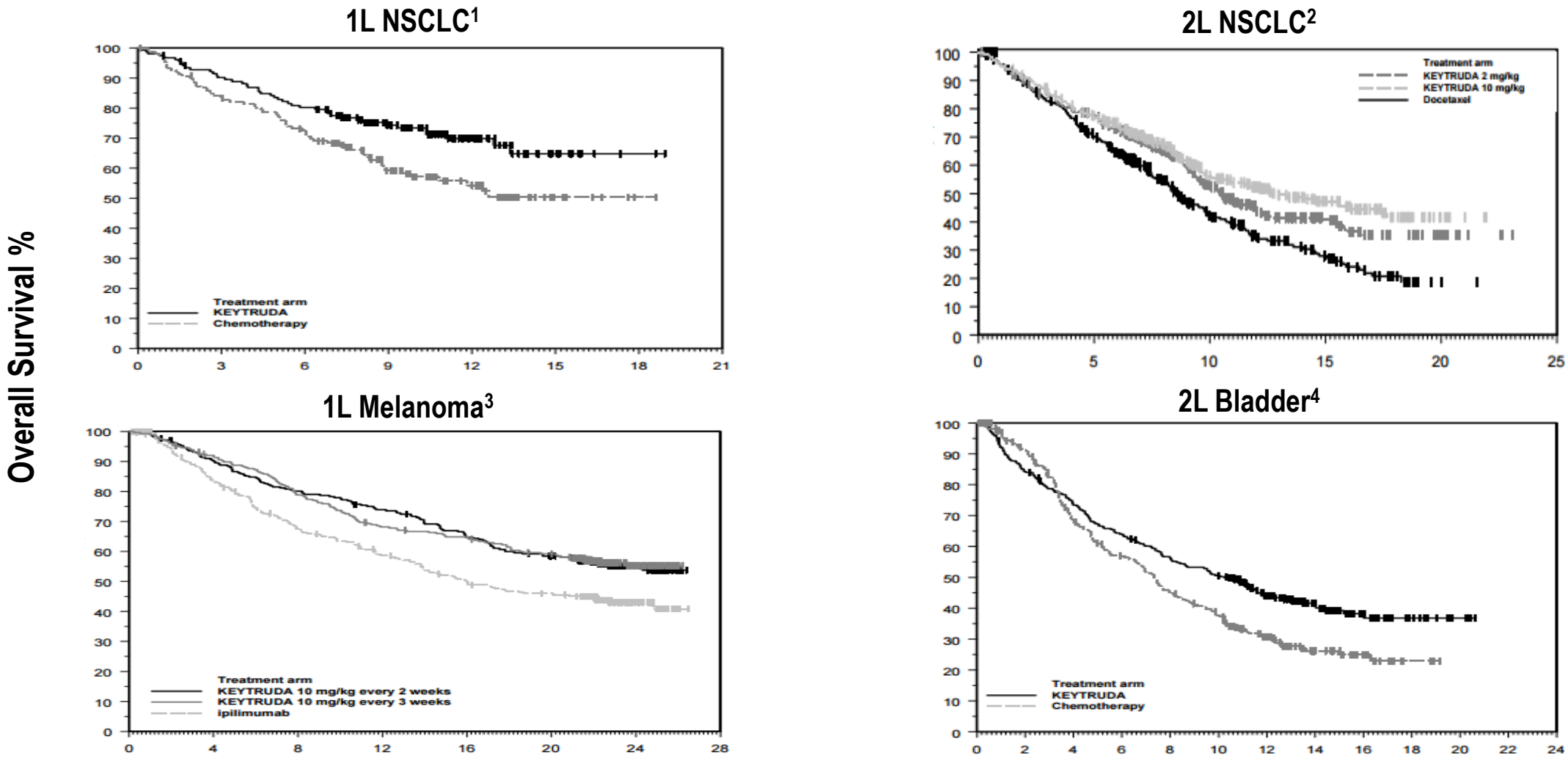
Keytruda Monotherapy Has Shown Activity in >20 Tumors



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016; 21. Ott PA et al. ASCO 2016; 22. Hansen AR et al. ESMO 2016; 23. Reardeon D et al. SNO 2016; 24. Diaz L et al. ASCO 2017.

KEYTRUDA: Improvements in Overall Survival



1. Section 14.2, Figure 3, KEYTRUDA prescribing information; 2. Section 14.2, Figure 4, KEYTRUDA prescribing information; 3. Section 14.1, Figure 1, KEYTRUDA prescribing information; 4. Section 14.5, Figure 5, KEYTRUDA prescribing information

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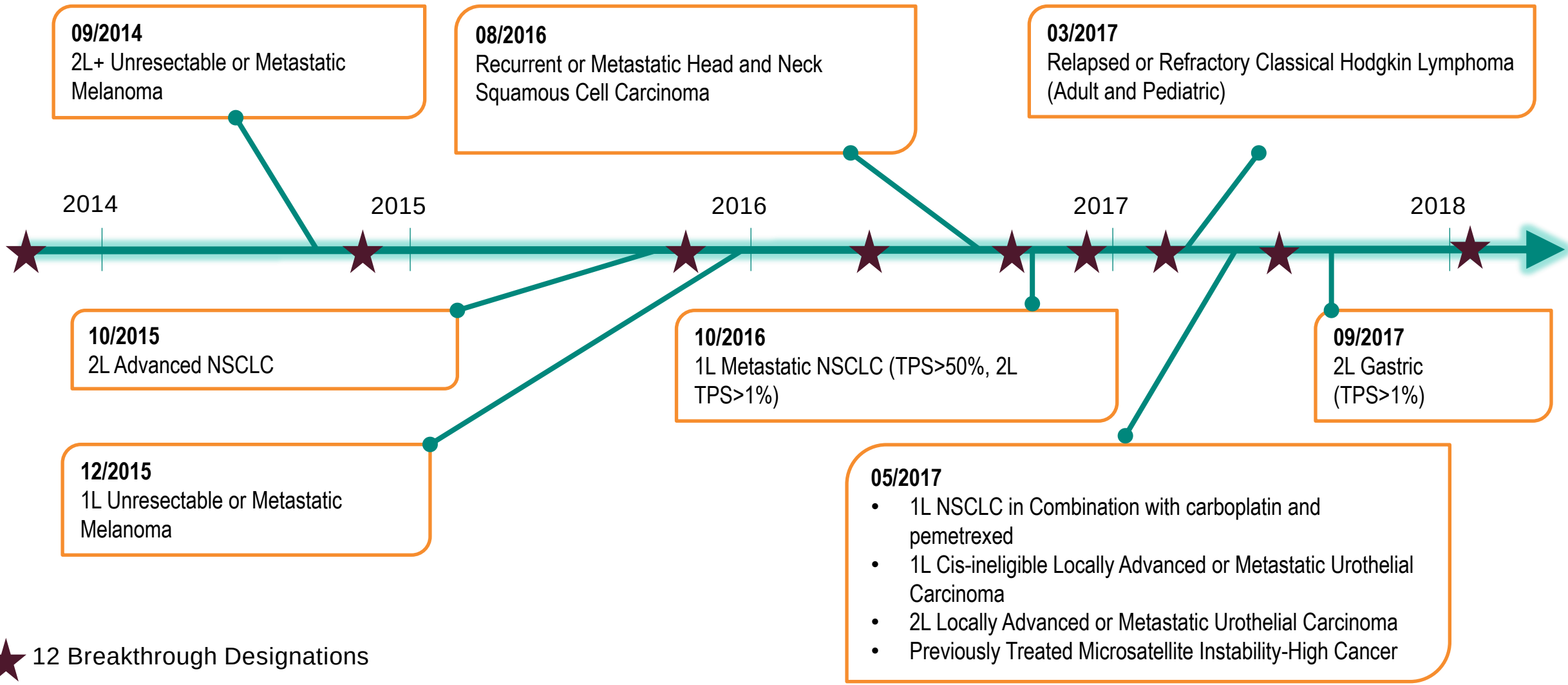
Keytruda FDA Approval Timeline



Multiple Strategies May Work to Overcome Primary Resistance to PD1 Blockade

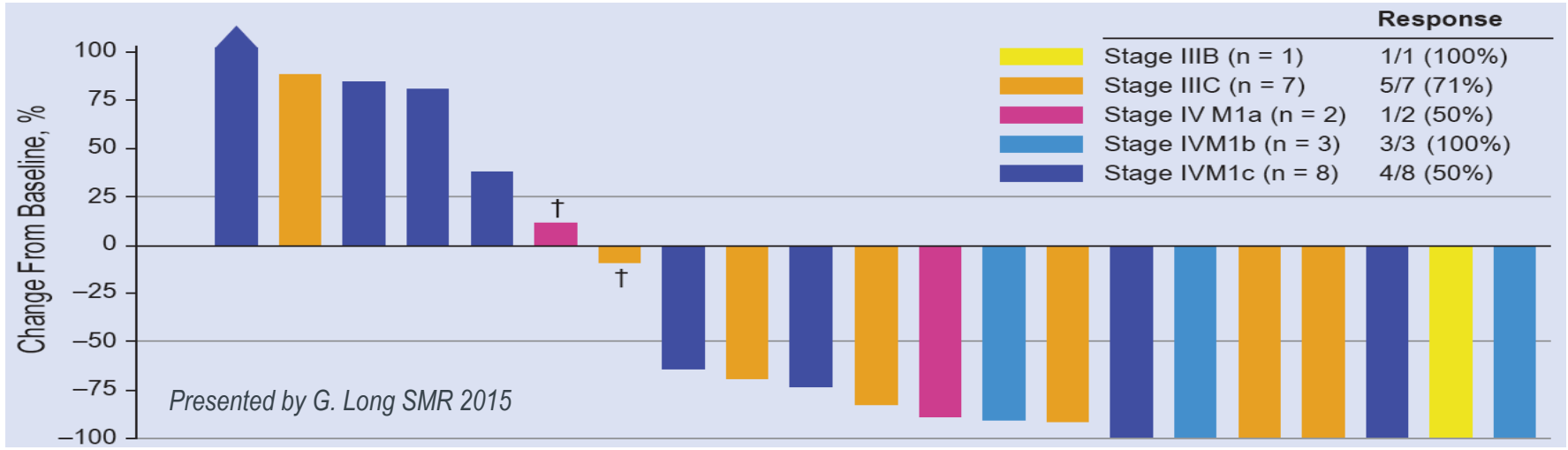
Presenter	Data Presented	Combination agent(s)	Indication	N	ORR	Notes
Ribas	SMR 2016	SD-101	Melanoma	5	80%	
Kaufman	SITC 2016	Cavatak	Melanoma	10	70%	
Taylor	ESMO 2016	Lenvatinib	All comers	13	69%	
Atkins	ESMO 2016	Axitinib	RCC	52	67%	
Ribas	ASCO 2016	Dabraf-tramet	melanoma	15	60%	
Bedros	ASH 2015	Pomalidomide-dex	RRMM	27	60%	
Gangadhar	ESMO 2016	Epacadostat	melanoma	19	58%	Treatment naive melanoma
Long	ASCO 2016	T vec	melanoma	21	57%	
Long (KN029 EC)	ASCO 2016	ipilimumab	melanoma	107	57%	
Langer	2016 Lanc Oncol	Pemetrexed-carbo	NSCLC	60	55%	Chemo alone 29%; pfs 8 mos vs 4.9 mos
Gadgeel	ASCO 2016	Paclitaxel-carbo	NSCLC	25	52%	
Mateos	ASCO 2016	Lenalidomide-dex	RRMM	40	50%	
Gadgeel	ASCO 2016	Paclitaxel-carbo-bev	NSCLC	25	48%	
Davar (Pitt OCSP)	ASCO 2016	PEG-IFN	melanoma	24	43%	
Algazi	SITC 2016	IT-pIL12 EP	Melanoma	15	40%	High risk biomarker group
McDermott	ESMO 2015	Pazopanib	RCC	20	40%	
Tolaney	SABCS 2016	Eribulin	TNBC	39	33%	
Atkins (KN-029)	ASCO 2016	ipilimumab	RCC	10	30%	
Herbst	ESMO 2016	Ramucirumab	NSCLC	27	30%	
Besse	World Lung 2016	Necitumumab	NSCLC	34	29%	
Stenehjem	ESMO 2016	FOLFOX	GI	7	29%	

Challenges in the Era of Combination Cancer Immunotherapy

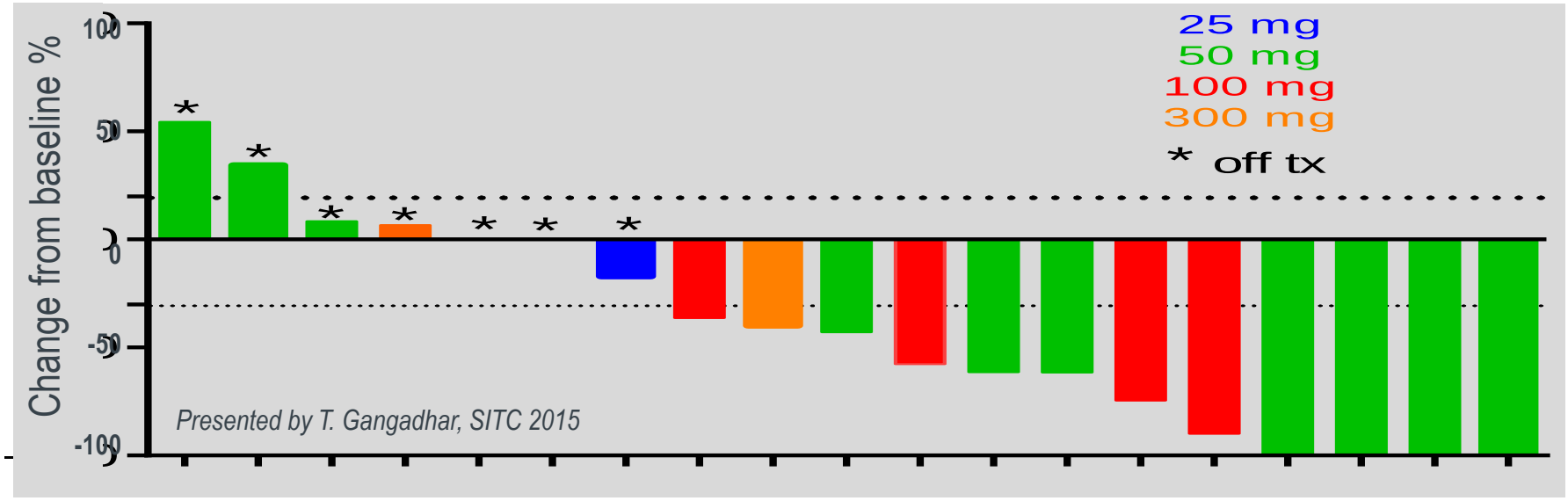
- Many anti PD-1/L1-based combos exhibit initial clinical signals (ORR) in small Ph1b/2a clinical studies and beyond:
  - What is additive vs. synergistic?
  - False discovery rate (enormous combinatorial diversity)
  - How do we prioritize and differentiate the promising combos?

- How do we identify the patients likely to benefit from specific combos?
  - Avoidance of unnecessary toxicity
  - Maximize efficacy/show unambiguous clinical benefit
  - Cost/value

An Melanoma Example: Radiographic Response to Two Pembrolizumab Combos



Pembrolizumab + TVEC in Melanoma



Pembrolizumab + epacadostat in Melanoma

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Dynamic Translational Immuno-oncology Biomarker Research Strategies

To elucidate target engagement, pharmaco-kinetics and pharmaco-dynamics changes	To understand the potential mechanisms of action	To find new correlates associated with clinical benefits and/or immune related adverse events	To identify new targets and patients potentially responding to therapy	To provide combination therapies upon understanding of mechanisms of action and resistance
↓	↓	↓	↓	↓
Right dose	**MOA**	**Right patient**	**New target**	**Right combo**

Merck is a Leader in Identifying Predictive Biomarkers for Cancer Immunotherapy

Ligand Expression on Tumor

- PD-L1 Expression
- First PDL-1 Companion Diagnostic Approved

Immunogenic Microenvironment

- Immune-Related Gene Expression Profile (GEP) or Tumor Inflammation Signature (TIS)
- First collaboration to explore RNA tumor microenvironment signature

Increased Antigenicity due to High DNA Mutation Burden

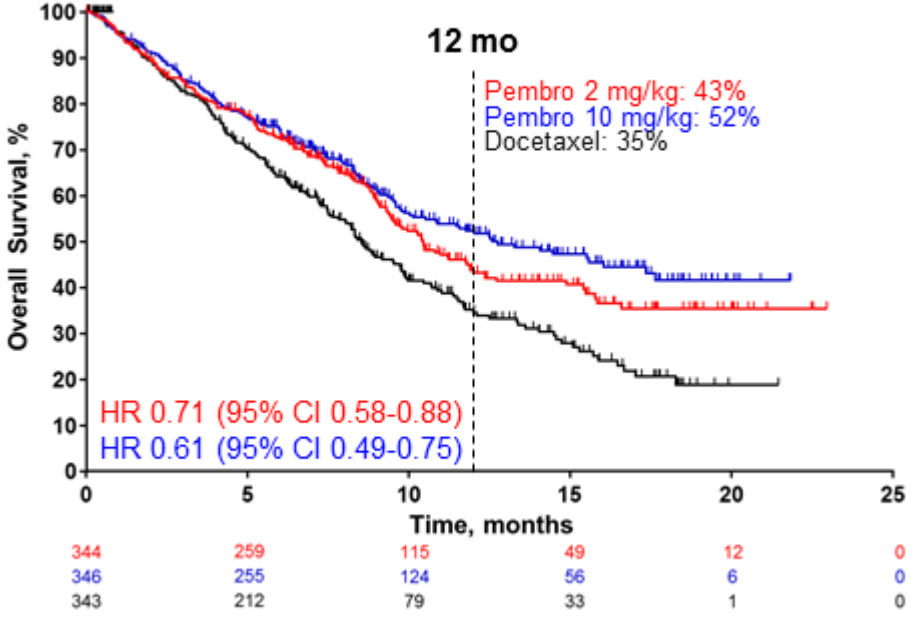
- DNA Mismatch Repair Deficiency, DNA Polymerase mutation
- First to identify MSI-High as a predictive biomarker (with Hopkins investigators)
- First FDA tumor agonistic approval 2017

Goal is to identify patients most likely to benefit from treatment

Our clinical trials and predictive biomarker approaches are based on strong biomarker hypotheses, with use of prospectively defined cutoffs, based on ROC analyses in independent training sets

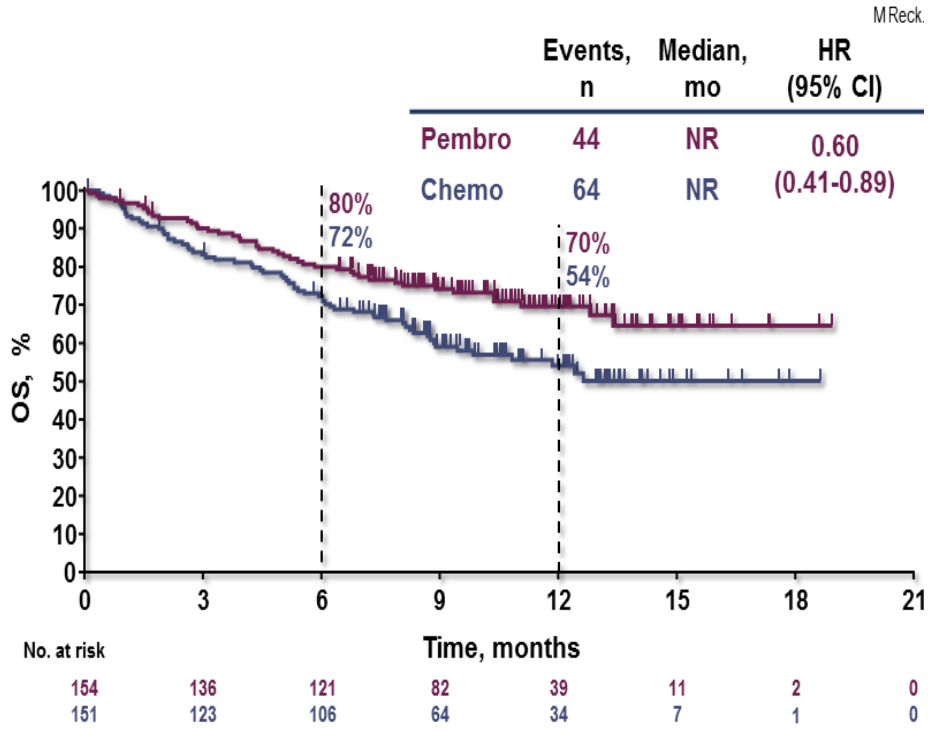
NSCLC: Superior Overall Survival vs. Chemotherapy in PD-L1-Defined Subgroups

KEYNOTE 010: Advanced NSCLC
PD-L1 ≥1% TPS



R Herbst et al. Lancet 2016

KEYNOTE 024: Previously Untreated NSCLC
PD-L1 ≥50% TPS



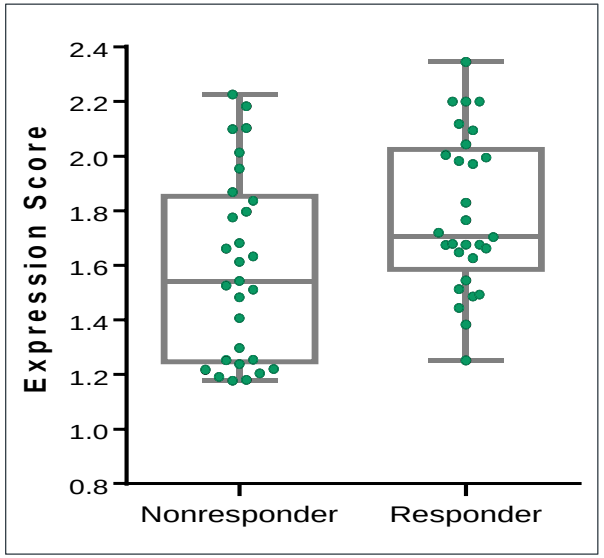
M Reck et al. NEJM 2016

Derivation of T-Cell Inflamed Gene Expression Profile (GEP)

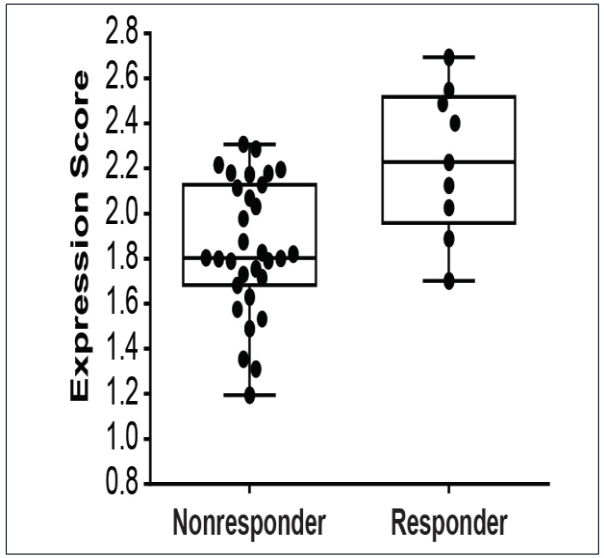
Signatures Defined and Validated in Melanoma

Signatures Validated and Refined in SCCHN and Gastric CA

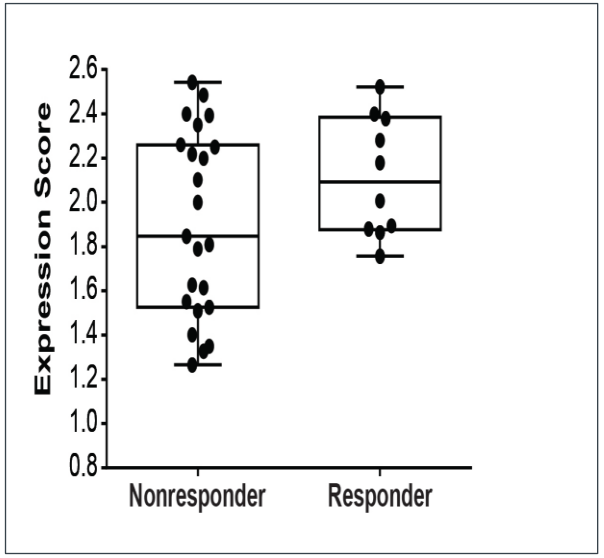
Final GEP Generated Using Penalized Regression Model in 9 Solid Tumors



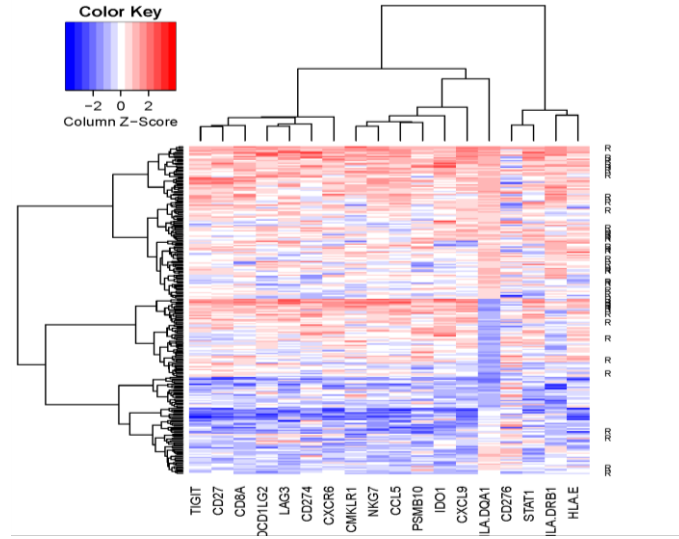
(N=19 training, N=62 validation)



SCCHN (N=43)

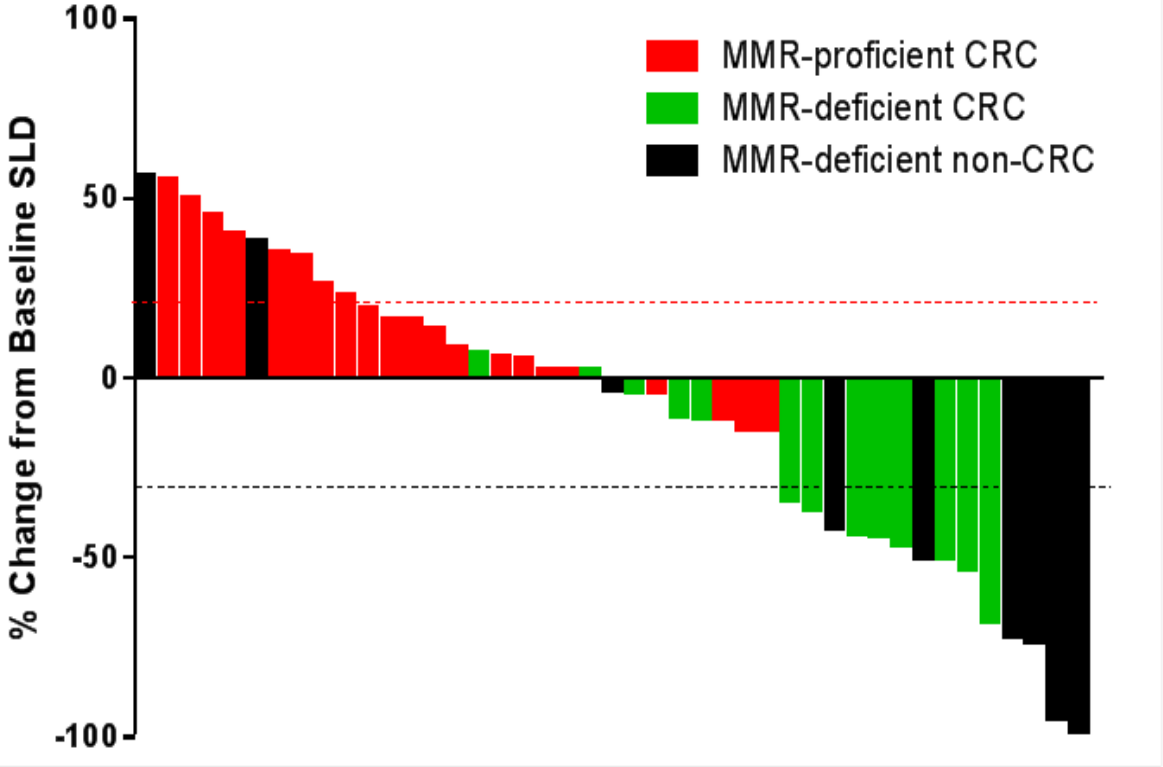


Gastric CA (N=33)

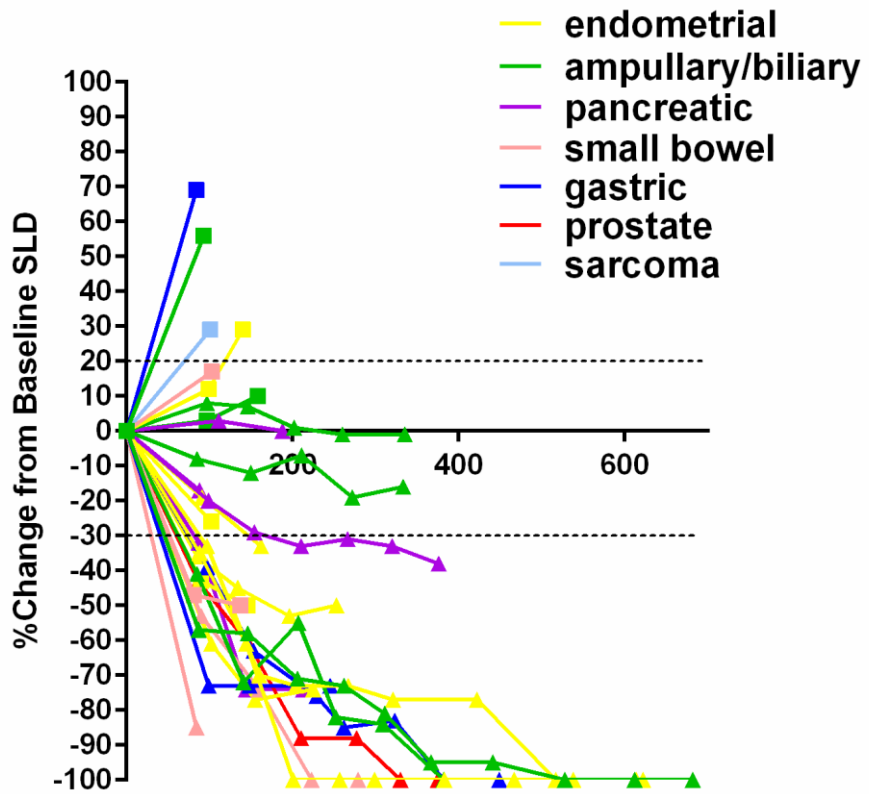


N=220 (gastric, TNBC, SCCHN, urothelial, anal, biliary, colorectal, esophageal and ovarian cancers)

Pembrolizumab in MSS Colorectal and MSI Colorectal and Non-Colorectal Tumors



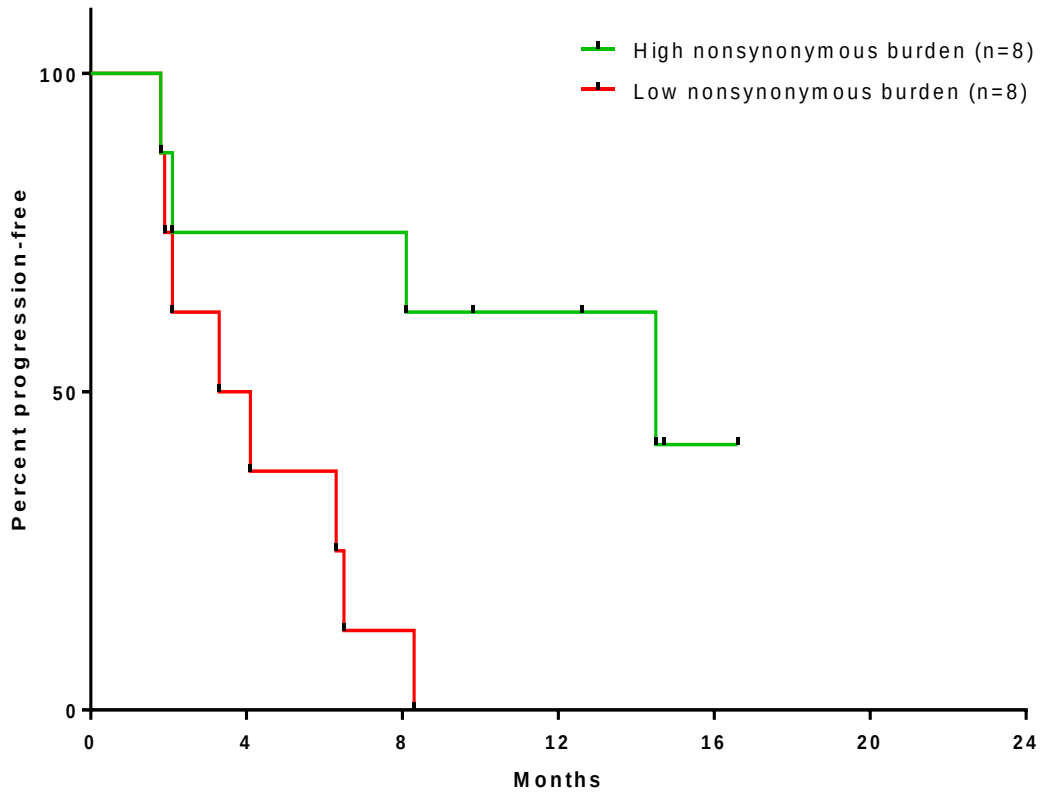
Presented by Dung Le, ASCO 2015



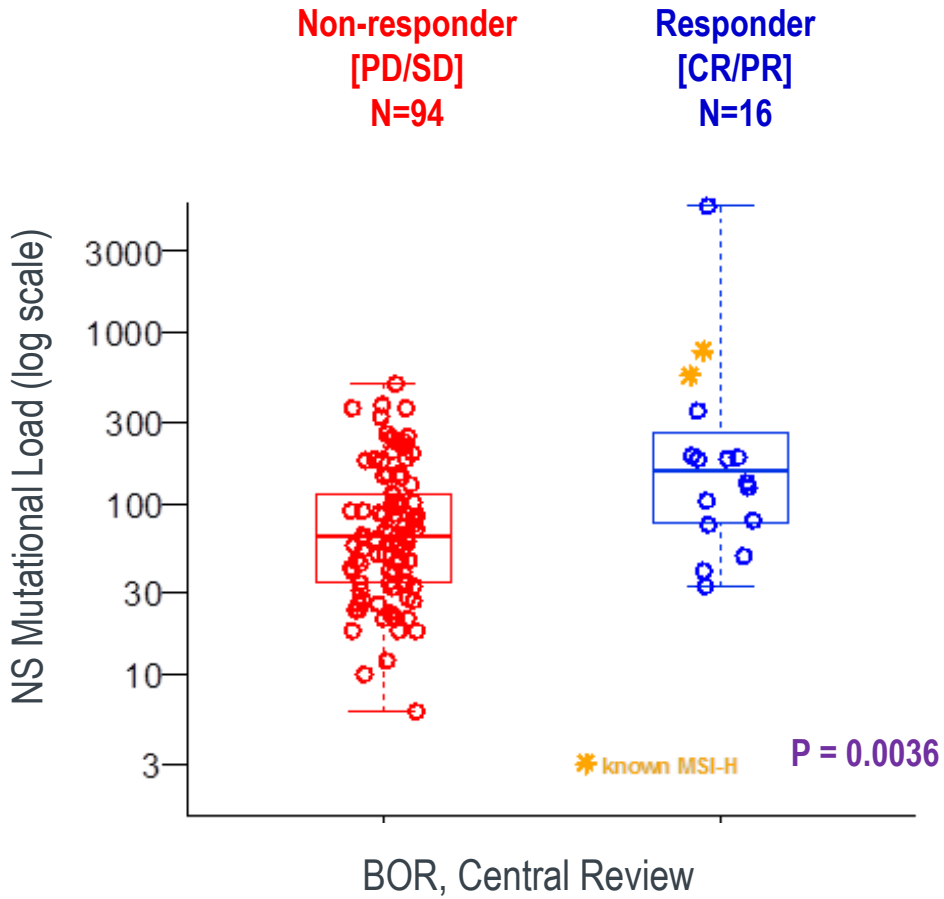
Presented by L. Diaz, ASCO 2016

FDA Approval MSI-H/dMMR on May 23rd, 2017

Tumor Mutational Burden Predicts Response to Pembrolizumab Across Tumor Types



Rizvi NA et al. Science 2015;348:124-128



Subgroup of patients from KEYNOTE N012 and KEYNOTE 028 (n=119, representing 20 tumor types)

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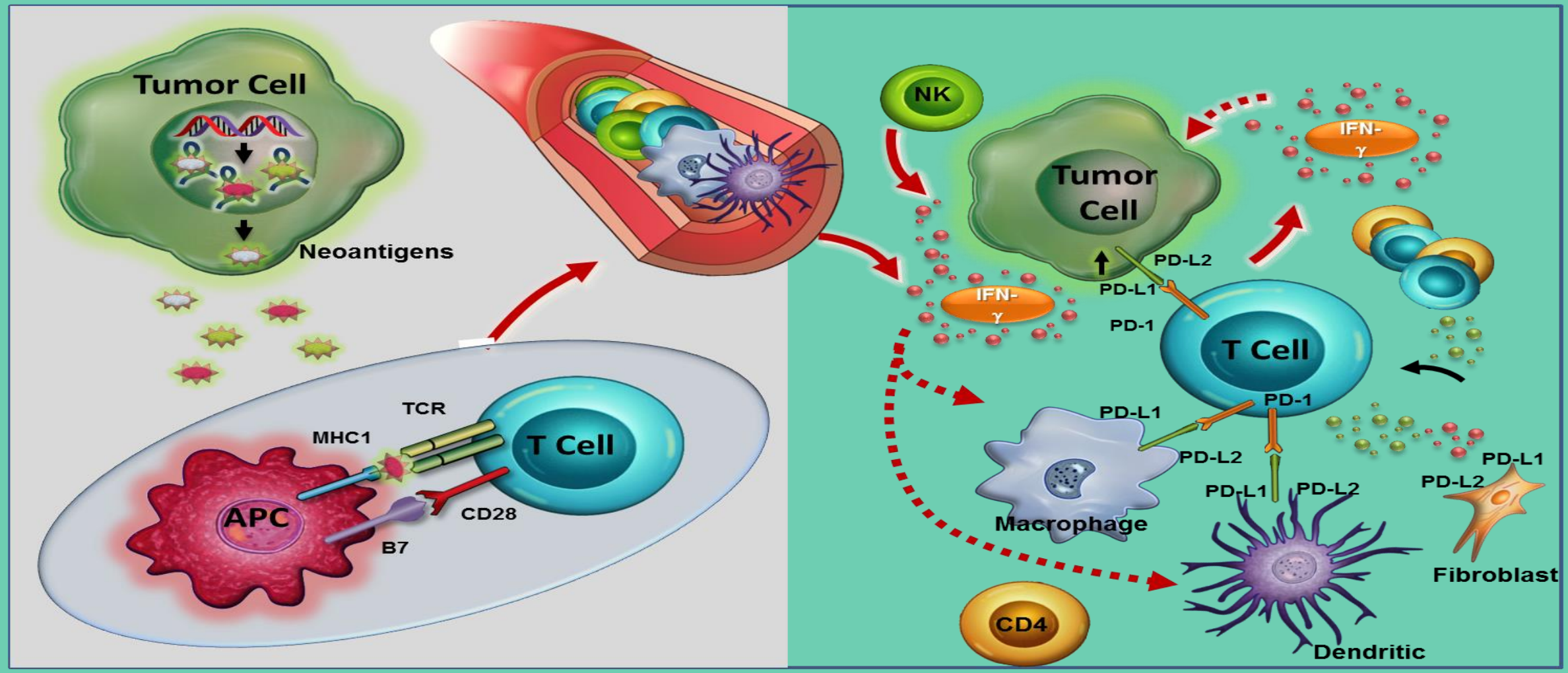
Keytruda Biomarkers: Different Biology Assessed by TMB vs. PD-L1/GEP

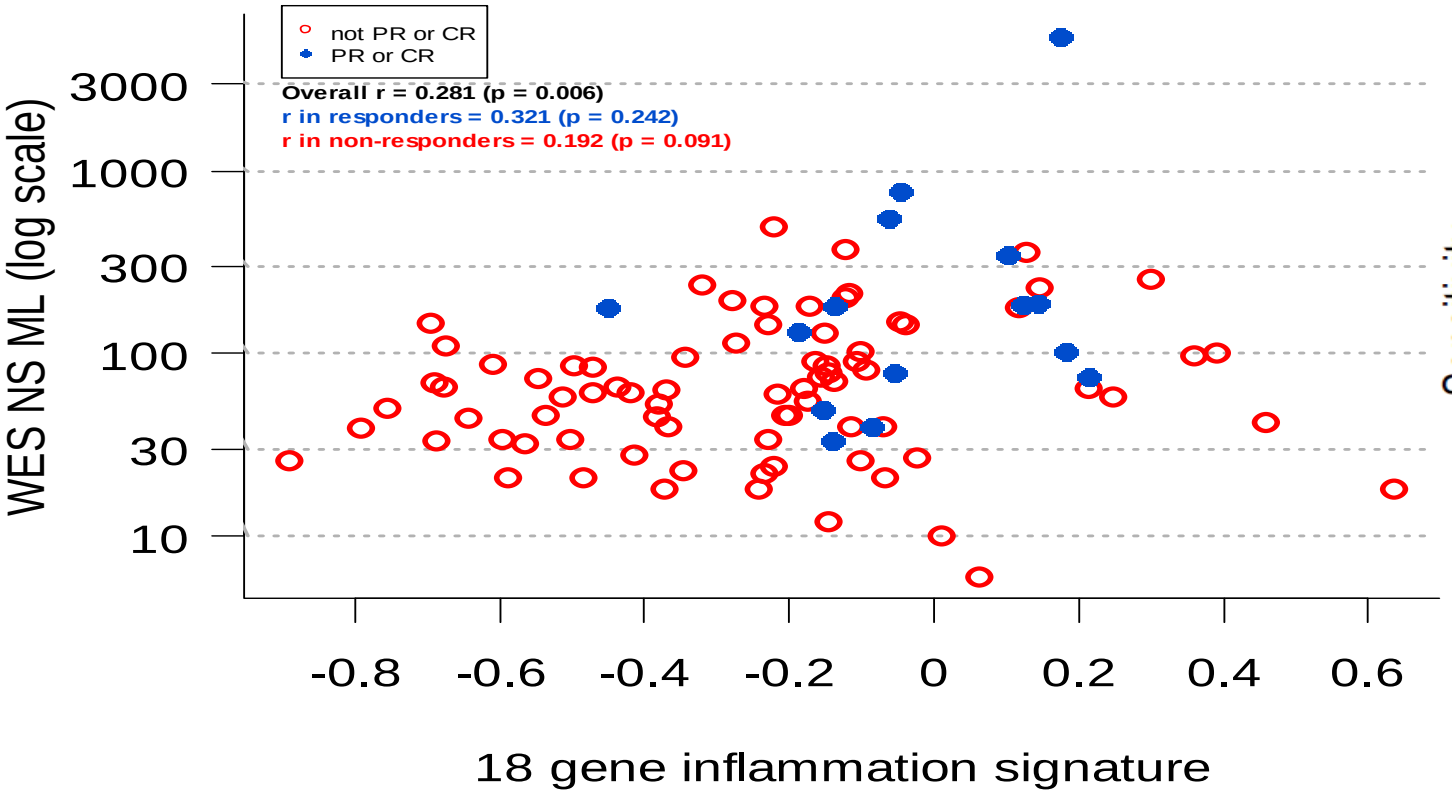
TMB measures tumor antigenicity

PD-L1/GEP measure activated T-cells in TME

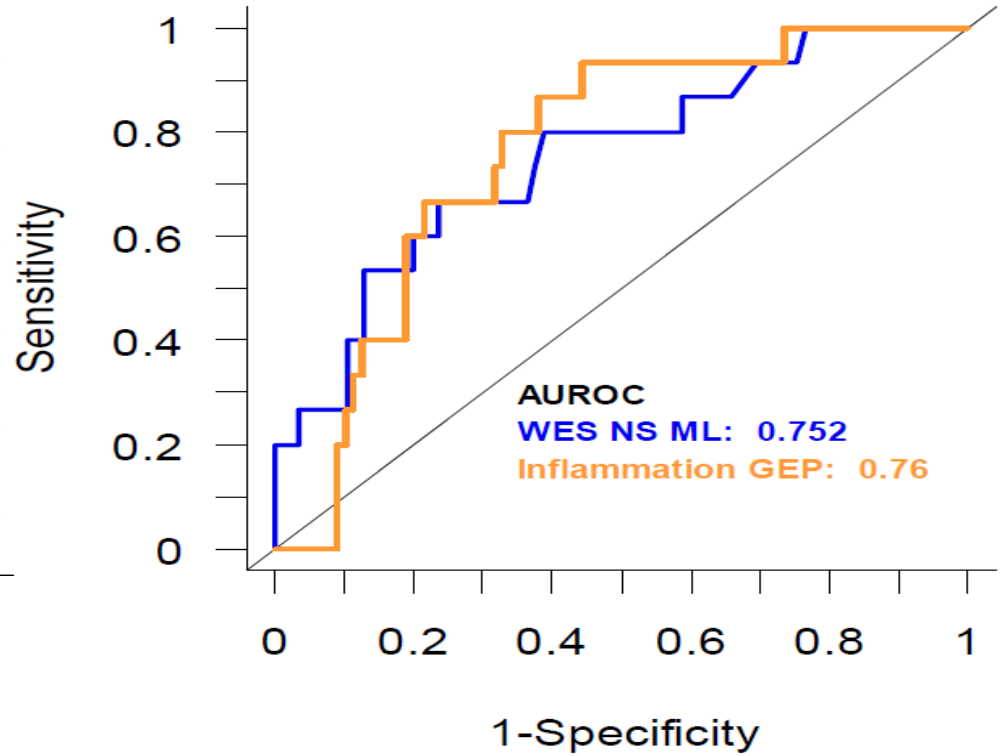


PD-L1/GEP and TMB: Independent Measures with Comparable Predictive Value (Low Correlation)

Low correlation between TMB and T-cell inflamed gene signature (NanoString)



High and comparable predictive value of gene signature and ML



- Pre-specified hypothesis testing using KN028/12 as validation set
- When jointly modeled, ML showed significant association with response (p=0.0078) after adjusting for GEP (also significant, p=0.0251).

Key Takeaways for Dual Biomarker Strategies for Combination Cancer Immunotherapy

- PD-(L)1 blockade cancer immunotherapies especially pembrolizumab have broad clinical activity, and represent the backbone of cancer immunotherapy.
- Biomarkers measuring either T cell activation in TME (PD-L1, GEP) or tumor antigenicity (MSI and TMB) independently predict patients response to PD-(L)1 blockade immunotherapies with low correlation.
- Dual biomarker strategies as part of precision immuno-oncology to triage patients to the appropriate combination cancer therapies.

THANK YOU!

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