SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

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Society for Immunotherapy of Cancer

Pan-Tumor Genomic Biomarkers for PD-1 Checkpoint Blockade-based Immunotherapy

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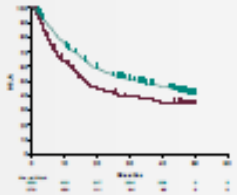
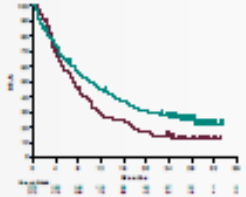
KEYTRUDA: REPEATED OVERALL SURVIVAL BENEFITS IN MONOTHERAPY AND IN COMBINATION

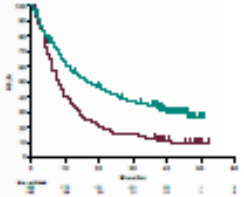
Ipi-Naive Melanoma, Any PD-L1
KEYNOTE-006
Pembro vs Ipi



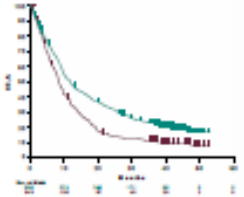
2L Bladder, Any PD-L1
KEYNOTE-045
Pembro vs Chemo



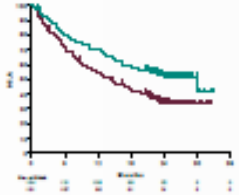
2L+ NSCLC, TPS ≥50%
KEYNOTE-010
Pembro vs Docetaxel



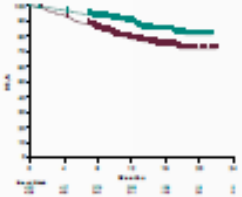
2L+ NSCLC, TPS ≥1%
KEYNOTE-010
Pembro vs Docetaxel



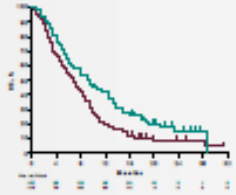
1L NSCLC, TPS ≥50%
KEYNOTE-024
Pembro vs Chemo



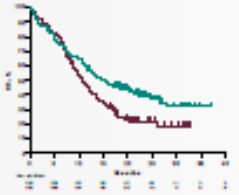
1L RCC, Any PD-L1
KEYNOTE-426
Pembro + Axitinib vs Sunitinib



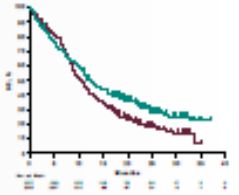
1L Esophageal, CPS ≥10
KEYNOTE-181
Pembro vs Chemo



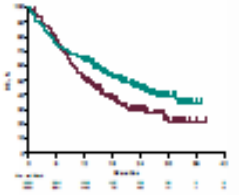
1L HNSCC, CPS ≥20
KEYNOTE-048
Pembro vs EXTREME



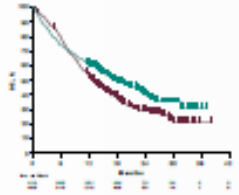
1L HNSCC, CPS ≥1
KEYNOTE-048
Pembro vs EXTREME



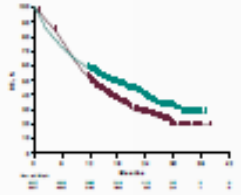
1L NSCLC, TPS ≥50%
KEYNOTE-042
Pembro vs Chemo



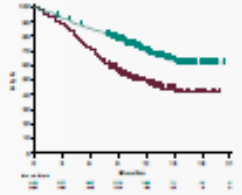
1L NSCLC, TPS ≥20%
KEYNOTE-042
Pembro vs Chemo



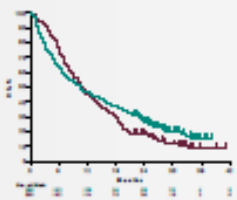
1L NSCLC, TPS ≥1%
KEYNOTE-042
Pembro vs Chemo



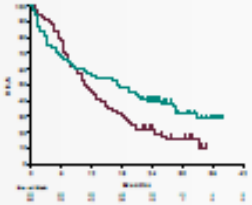
1L NSQ NSCLC, Any PD-L1
KEYNOTE-189
Pembro + Pem/Platinum vs Placebo + Pem/Platinum



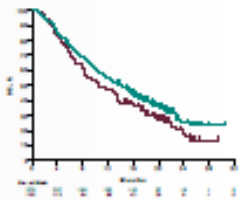
1L Gastric, CPS ≥1
KEYNOTE-062
Pembro vs Chemo



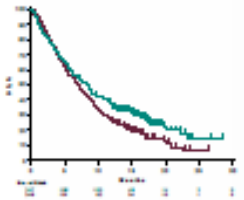
1L Gastric, CPS ≥10
KEYNOTE-062
Pembro vs Chemo



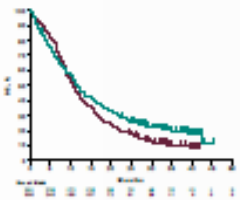
2L HCC, Any PD-L1
KEYNOTE-240
Pembro vs Placebo



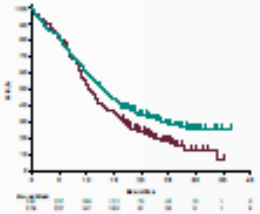
2L+ HNSCC, Any PD-L1
KEYNOTE-040
Pembro vs SOC



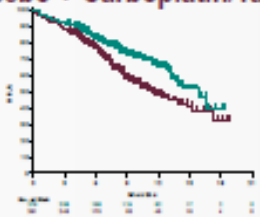
1L HNSCC, Any PD-L1
KEYNOTE-048
Pembro vs EXTREME



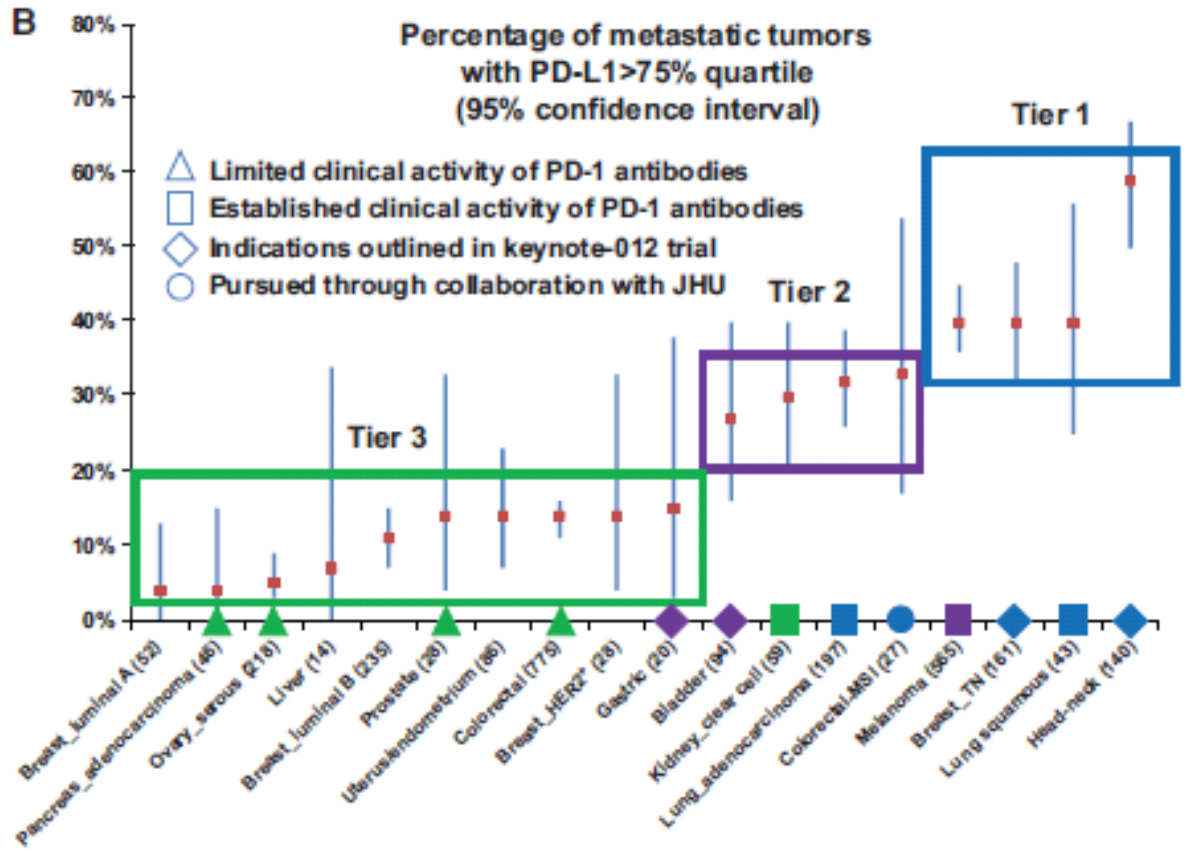
1L HNSCC, CPS ≥1
KEYNOTE-048
Pembro + Platinum vs EXTREME



1L SQ NSCLC, Any PD-L1
KEYNOTE-407
Pembro + Carboplatin/Taxane vs Placebo + Carboplatin/Taxane

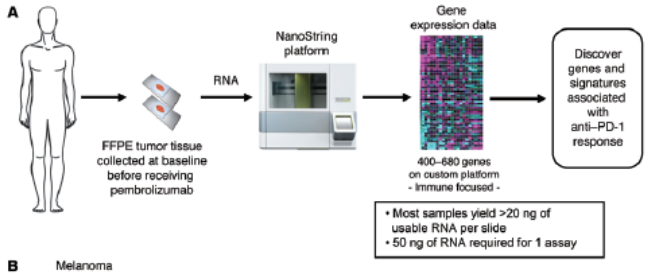


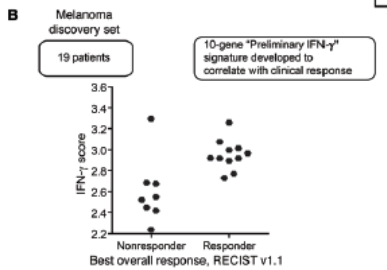
Initial value in large scale genomic profiling: molecular epidemiology of PD-L1 expression in Moffitt-Merck database and Pembrolizumab indication expansion



Ayers et al, CCR 2018

An IFN-γ-related gene expression profile predicts clinical response to PD-1 blockade





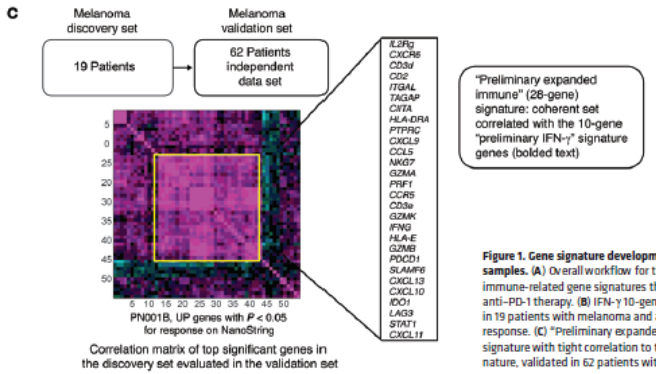
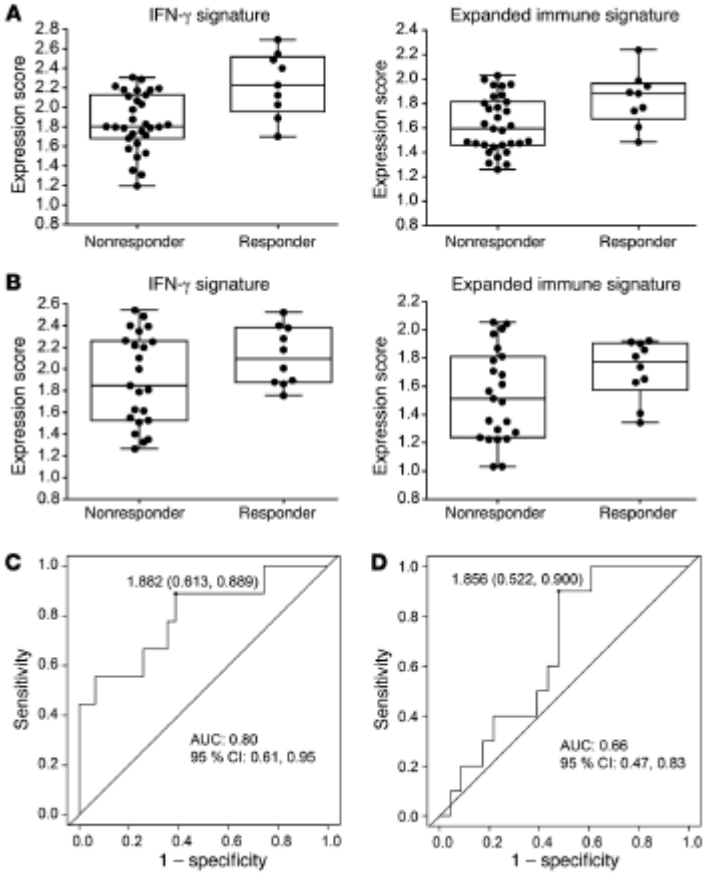


Figure 1. Gene signature developm samples. (**A**) Overall workflow for t immune-related gene signatures t anti–PD-1 therapy. (**B**) IFN-γ 10-gen in 19 patients with melanoma and response. (**C**) "Preliminary expande signature with tight correlation to nature, validated in 62 patients wit

Table 2. IFN-γ and expanded immune gene signatures

IFN-γ	Expanded immune gene signature	
IDO1	*CD30*	*IL2RG*
CXCL10	*IDO1*	*NKG7*
CXCL9	*CIITA*	*HLA-E*
HLA-DRA	*CD3E*	*CXCR6*
STAT1	*CCL5*	*LAG3*
IFNG	*GZMK*	*TAGAP*
	CD2	*CXCL10*
	HLA-DRA	*STAT1*
	CXCL13	*GZMB*



Ayers et al, JCI 2017

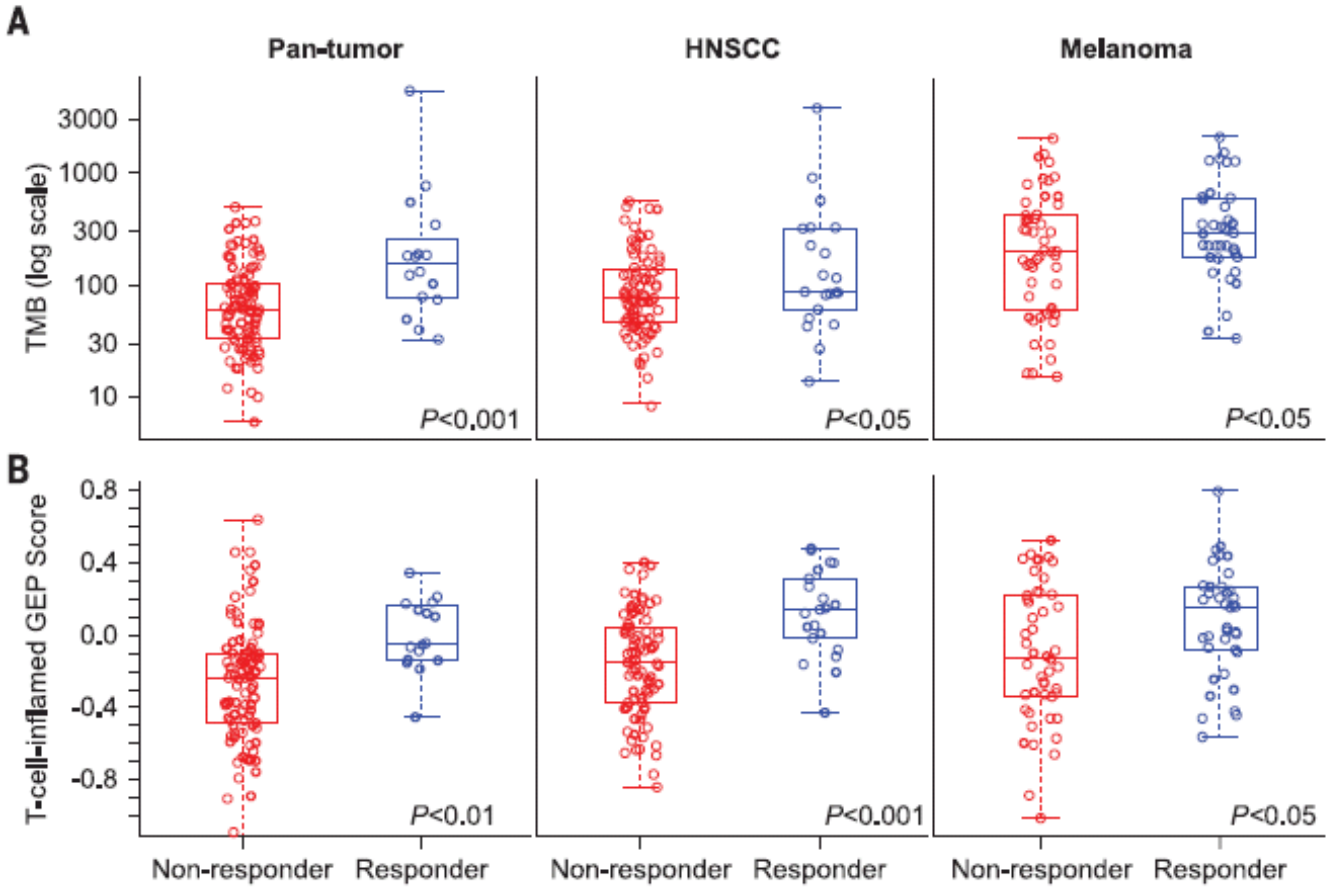
Pan-cancer Mutational Spectrum: many causes for high TMB beyond MSI-h

TMB association with antiPD-1/L1 response has been shown for major indications regardless of TMB etiology

Seiwert et al, ASCO-SITC 2017

Alexandrov LB, et al. *Nature*. 2013;500(7463):415-421.

TMB and GEP associate with Pembrolizumab BOR



RESEARCH

RESEARCH ARTICLE SUMMARY

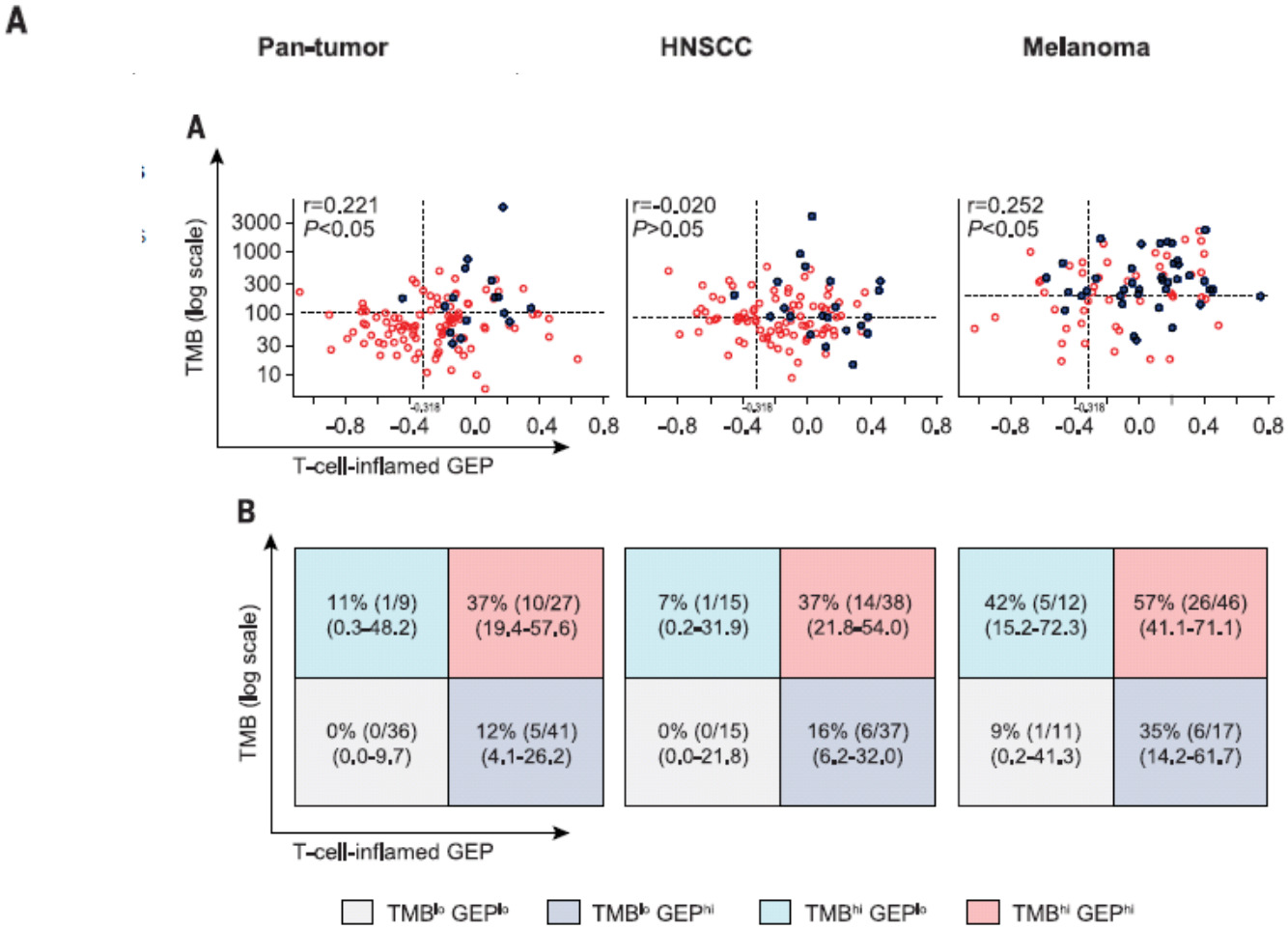
CANCER BIOMARKERS

Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy

Razvan Cristescu*, Robin Mogg, Mark Ayers, Andrew Albright, Erin Murphy, Jennifer Yearley, Xinwei Sher, Xiao Qiao Liu, Hongchao Lu, Michael Nebozhyn, Chunsheng Zhang, Jared Lunceford, Andrew Joe, Jonathan Cheng, Andrea L. Webber, Nageatte Ibrahim, Elizabeth R. Plimack, Patrick A. Ott, Tanguy Seiwert, Antoni Ribas, Terrill K. McClanahan, Joanne E. Tomassini, Andrey Loboda, David Kaufman

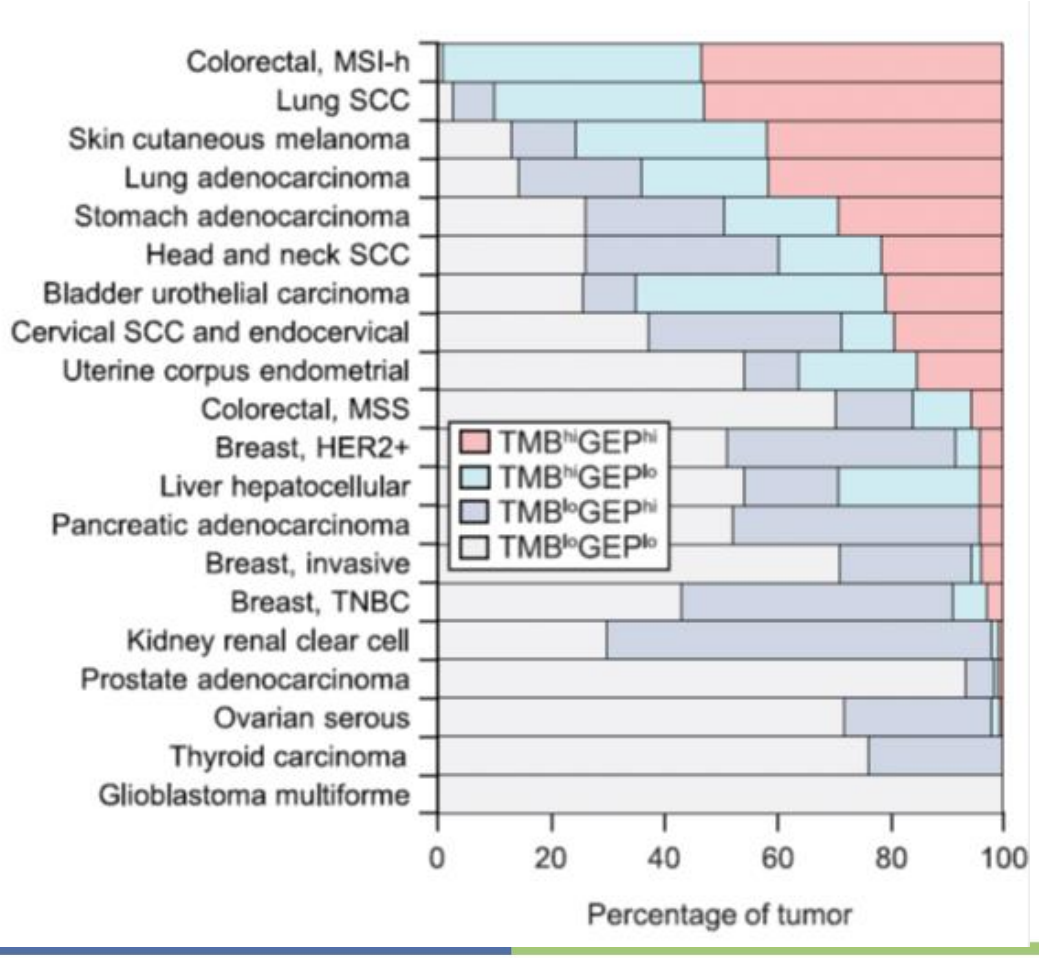
Cristescu et al, Science 2018

TMB and GEP independently associate with BOR across indications



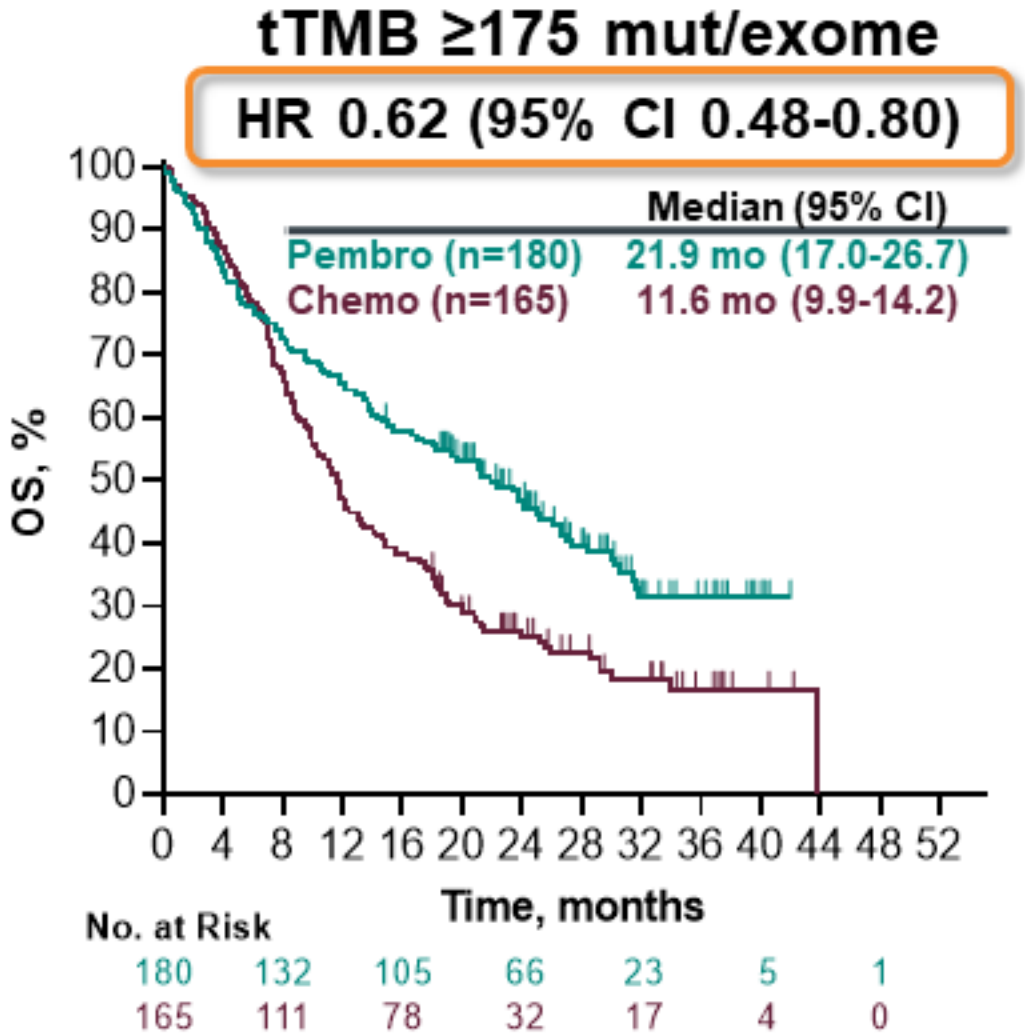
Cristescu et al, Science 2018

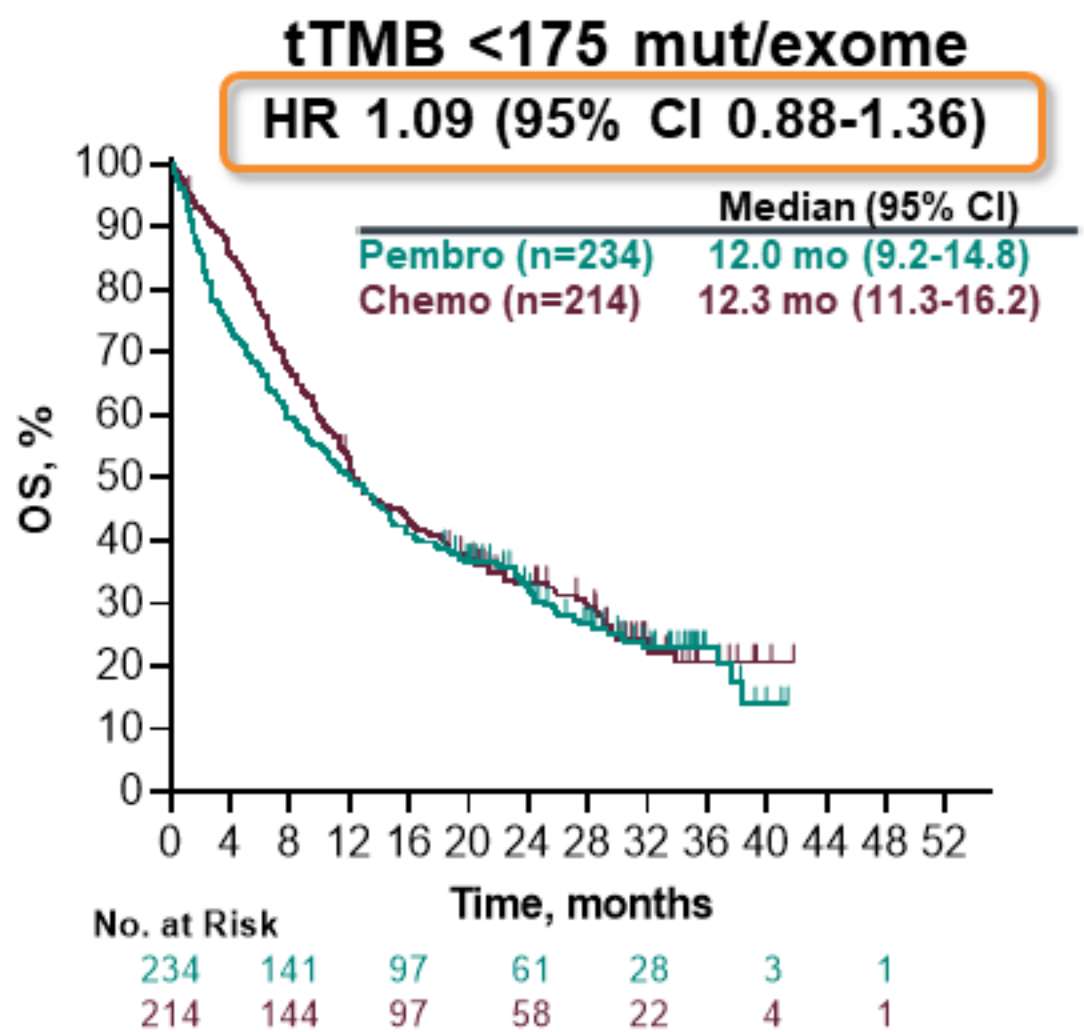
Fraction of TMB+/GEP+ tumors associate with aPD1/PDL1 monotherapy clinical response/success



Cristescu et al, Science 2018

Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175 mut/exome

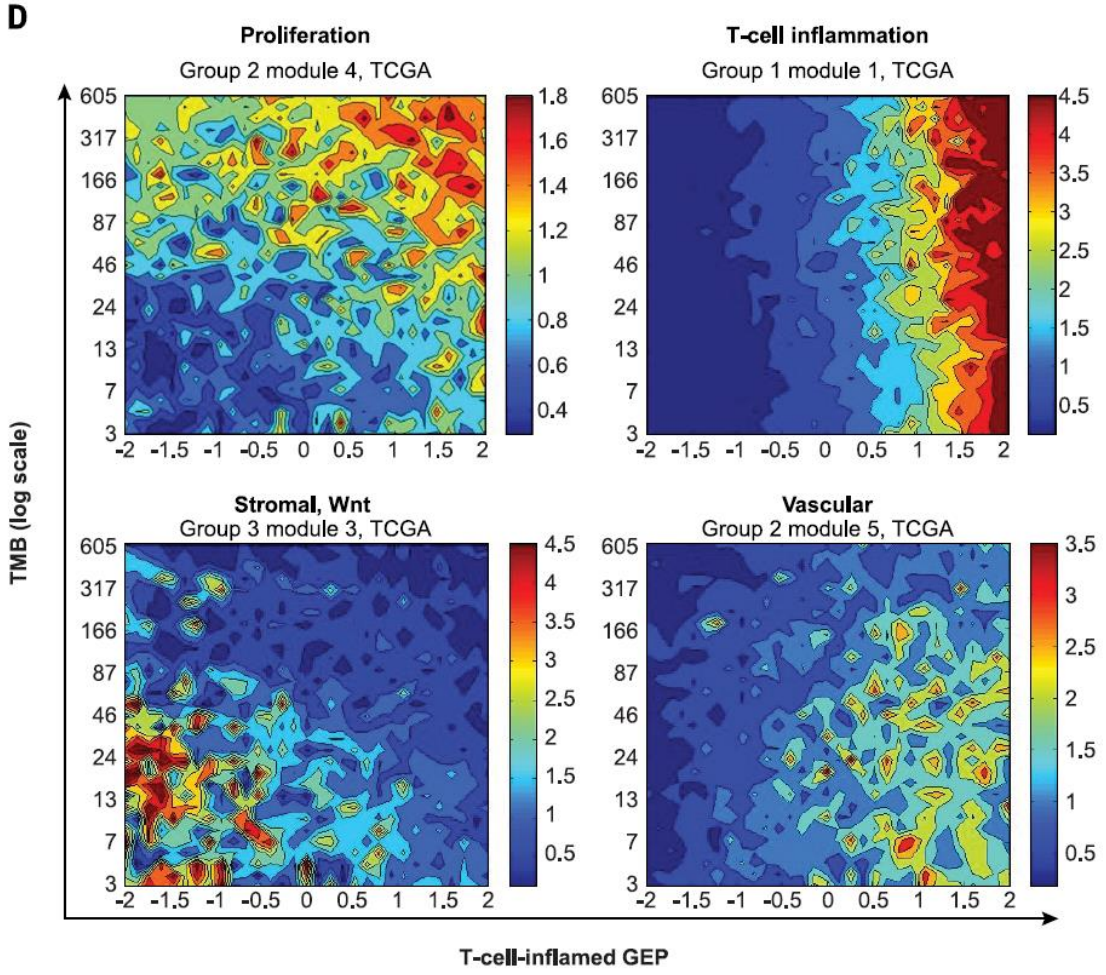




[a]All patients were PD-L1-positive (TPS ≥1%). Data cutoff date: Sep 4, 2018.

TMB and GEP combination may provide a rationale for prioritizing combination therapies

Moderate aPD1/PD-L1 activ
Immune evasion



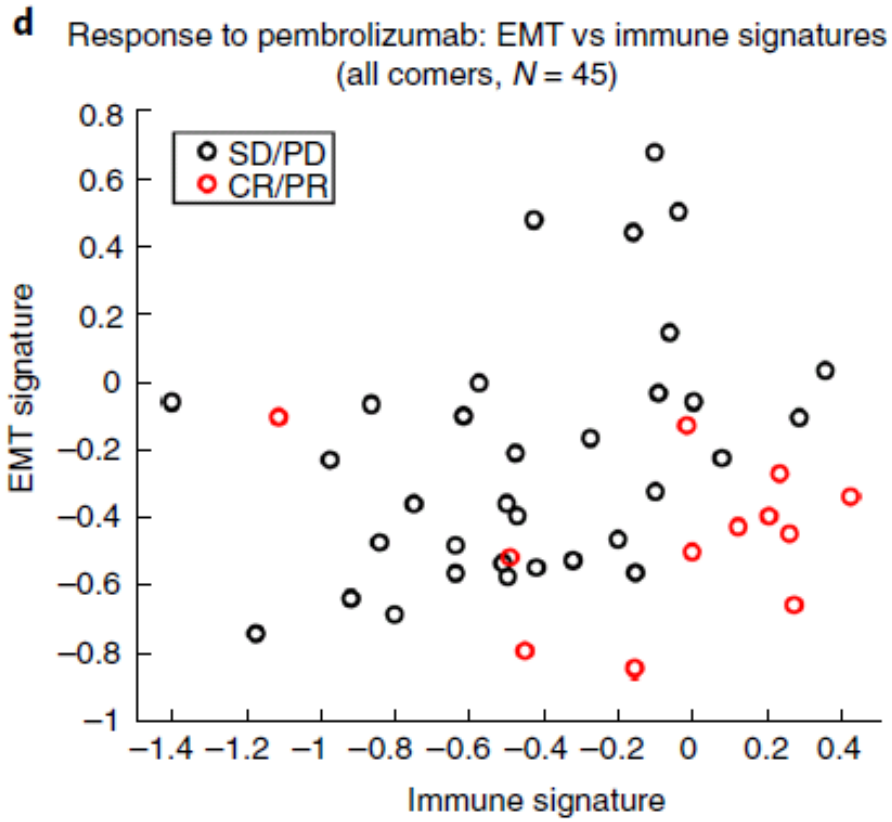
Major aPD1/PD-L1 activity:
Cytolytic-ready

Reduced aPD1/PD-L1 activi
Immune desert

Moderate aPD1/PD-L1 activity:
T-cell inflammation
with hostile TME

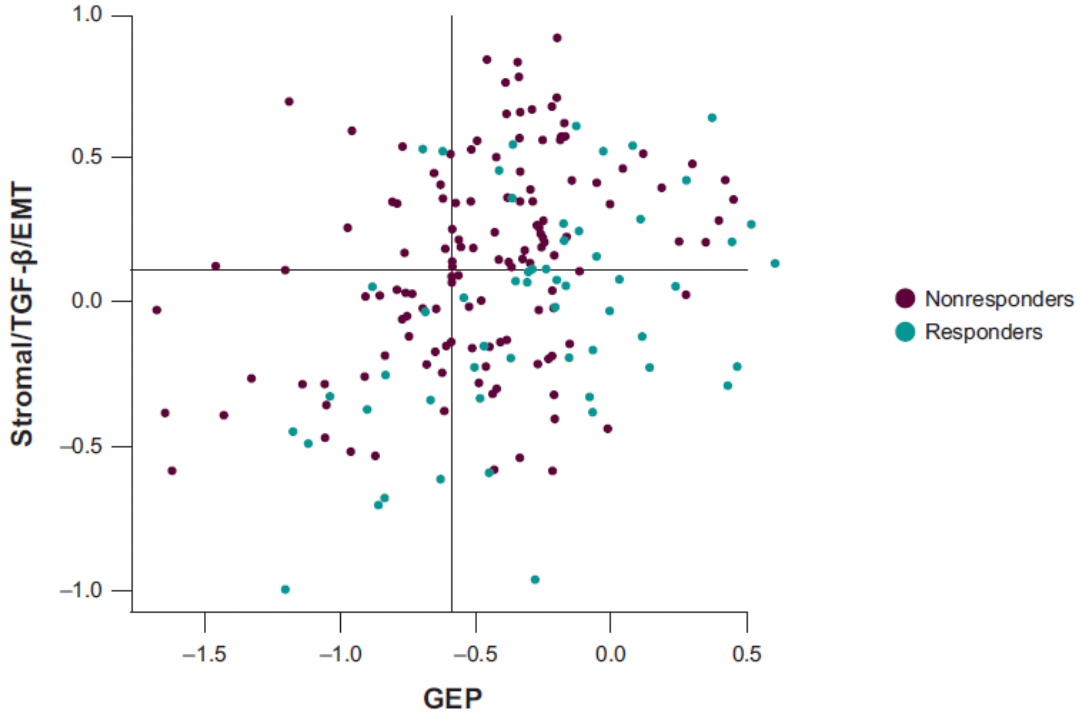
Cristescu et al, Science 2018

EMT/Stromal/TGFbeta signature associates with response to monotherapy Pembrolizumab in inflamed Gastric and mUC tumors



Kim et al, Nat Med 2018

Figure 4. Scatter Plot for Stromal/TGF-β/EMT Signature Score Versus RNA-Seq 18-Gene T Cell–Inflamed GEP Score With Response Status in the Total Population



Grivas et al, ASCO-GU 2019

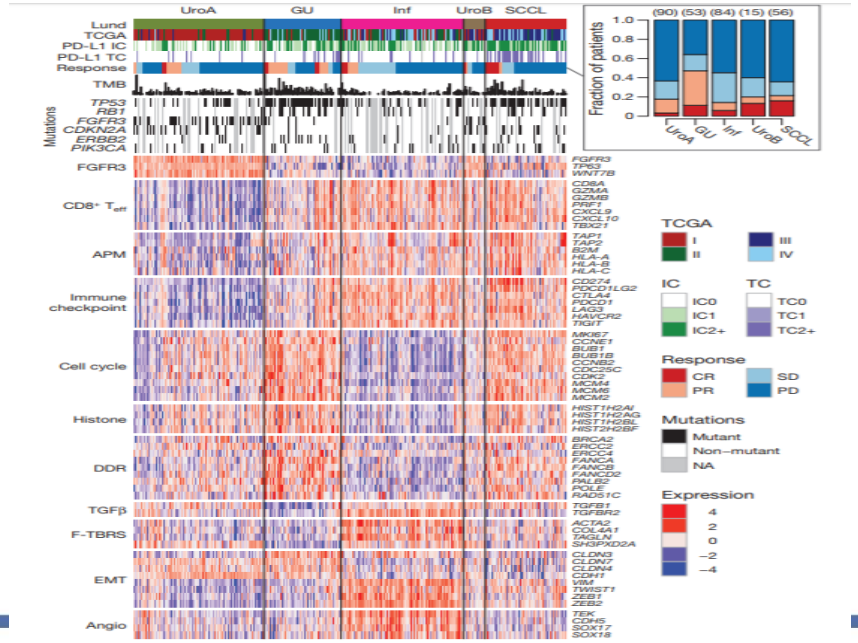
RNA-seq data demonstrate resistance signatures to Atezolizumab

LETTER

doi:10.1038/nature25501

TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

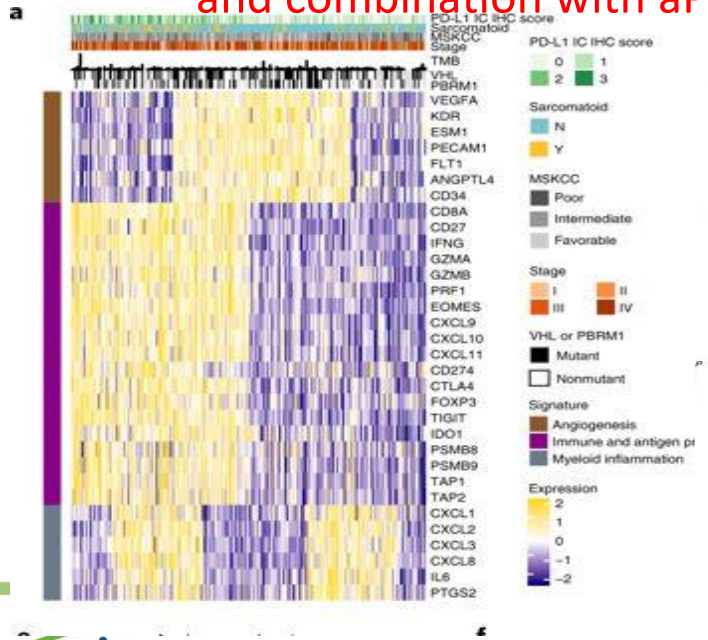
mUC: **TGFbeta/Stromal** signature determines response to aPD-L1 beyond Teff

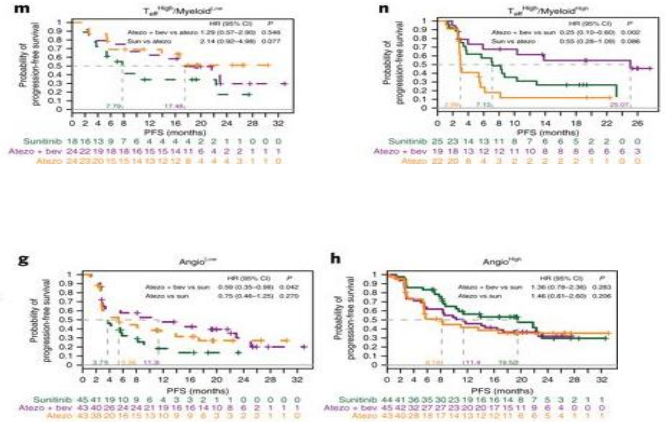


nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0053-3

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma

RCC: **Angiogenesis** and **gMDSC** signatures determine response to VEGF inhibitor and combination with aPD-L1 beyond Teff





Pan-tumor analysis of the association of cancer and immune biology-related gene expression signatures with response to Pembrolizumab monotherapy

Studies with RNASeq data **(N=1188):**

KN001/KN006-Melanoma (N=476),

KN052-urothelial (N=186),

KN012/KN055-HNSCC (N=147; HPV(-ve)),

KN086-TNBC (N=132),

KN059-Gastric (N=92),

KN427-RCC (N=78),

KN100-Ovarian (N=77).

Associations will need validation in randomized studies.

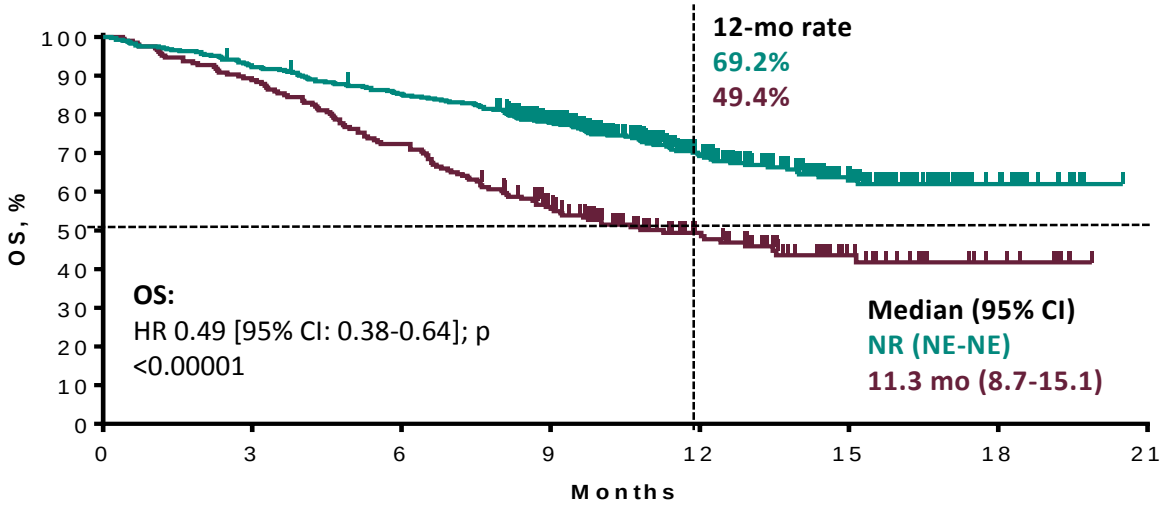
Table 1. Testing Results for Pan-cancer Regression Modeling of ORR

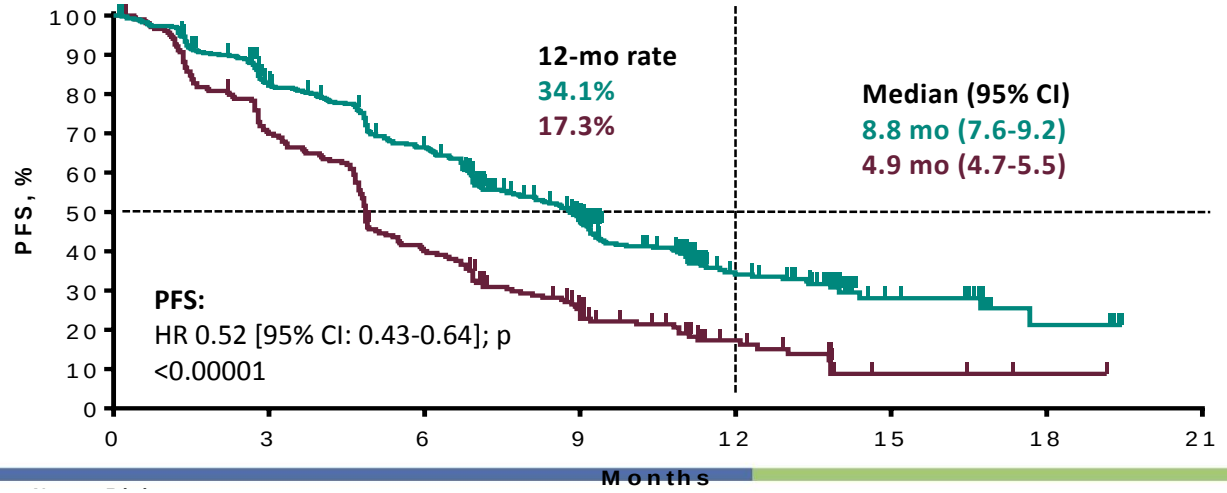
Signature	AUROC Curve[a] (95% CI)	Nominal One-sided P-value[b]	Multiplicity Adjusted P-value[c]
T-cell Inflamed GEP	0.63 (0.60-0.67)	<<0.0001*	N/A
Angiogenesis	0.58 (0.54-0.61)	0.0001	0.0009
mMDSC	0.56 (0.53-0.60)	0.0001	0.0009
Stroma/EMT/TGFβ	0.56 (0.52-0.60)	0.0003	0.0023
gMDSC	0.53 (0.50-0.57)	0.0318	0.2225
Proliferation	0.53 (0.49-0.56)	0.0882	0.4523
WNT	0.52 (0.48-0.56)	0.0951	0.4523
RAS	0.52 (0.48-0.56)	0.1131	0.4523
Hypoxia	0.51 (0.47-0.54)	0.3790	0.8193
MYC	0.51 (0.47-0.55)	0.4096	0.8193
Glycolysis	0.48 (0.44-0.52)	0.8274	0.8274

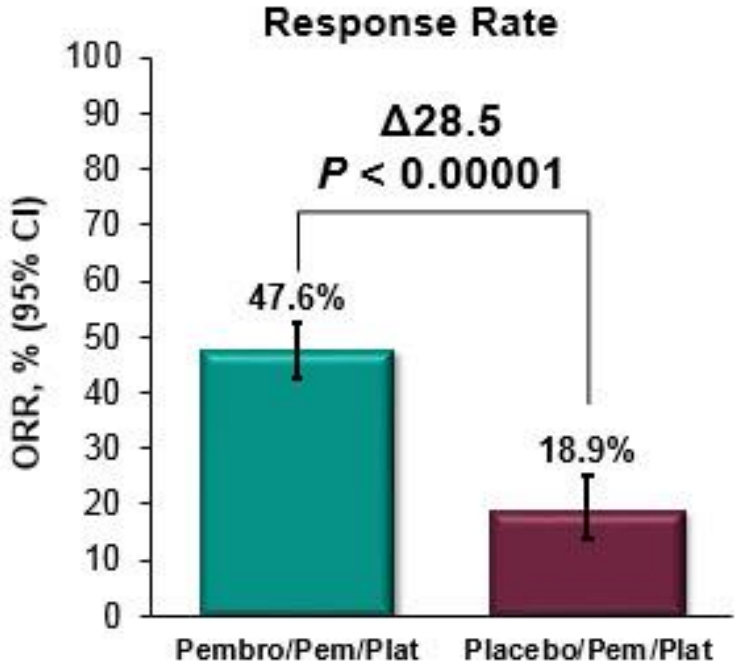
AUROC, Area Under the ROC Curve; EMT, epithelial to mesenchymal transition; GEP, gene expression profile; gMDSC and mMDSC, granulocytic and monocytic myeloid-derived suppressor cells, respectively; TGFβ, transforming growth factor beta. *P=3.6E-12. [a]For the GEP, predictor is residual score after adjusting for cancer type and for non-GEP residual score after adjustment for cancer type and GEP. For the GEP and for Proliferation, AUROC was estimated for positive association and for negative association in the remainder. [b]For the GEP and for Proliferation, testing was for positive association and for negative association in the remainder. [c]Consensus signature tests adjusted using Hochberg step-up procedure.

To be presented at SITC 2019: Sat Nov 5th, poster P324

KN-189 (Pembro+Chemo vs Chemo in 1L non-squamous NSCLC) met all primary endpoints (and regardless of PD-L1 status)

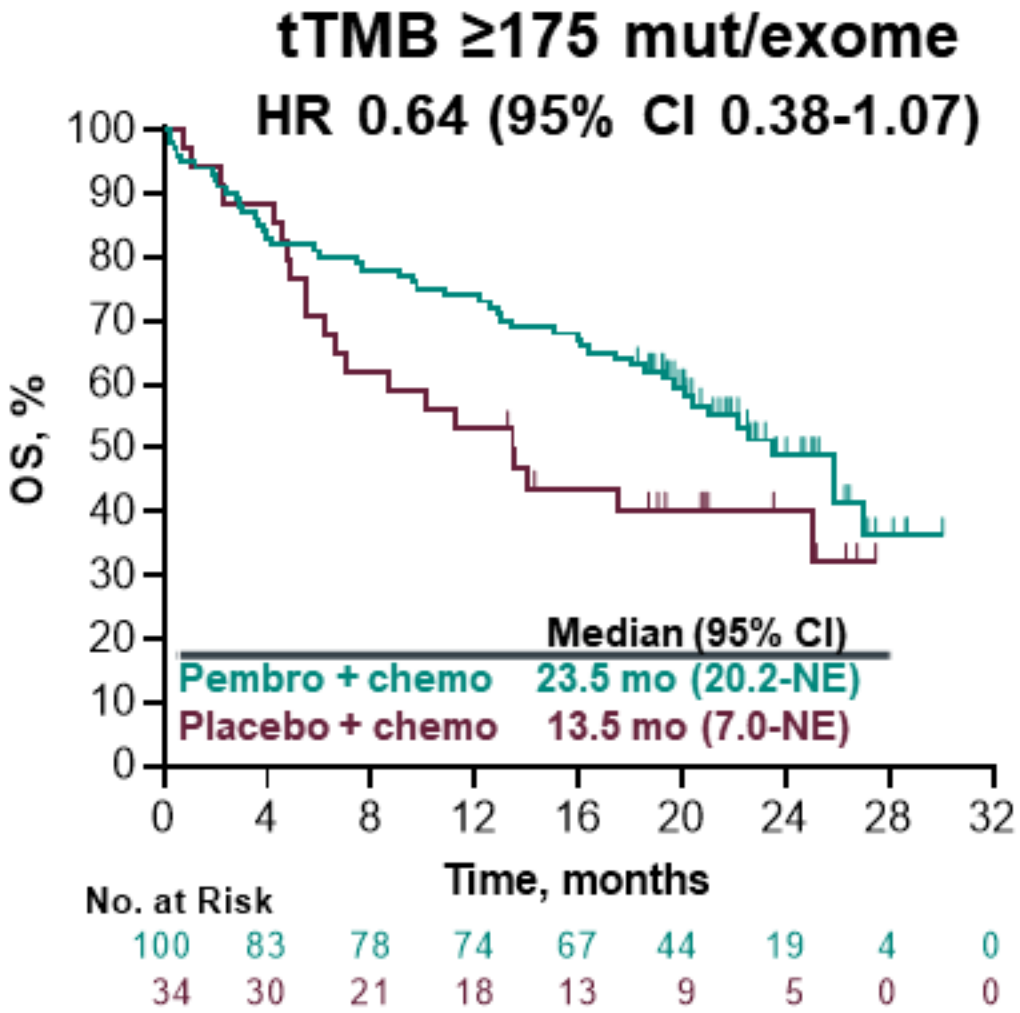


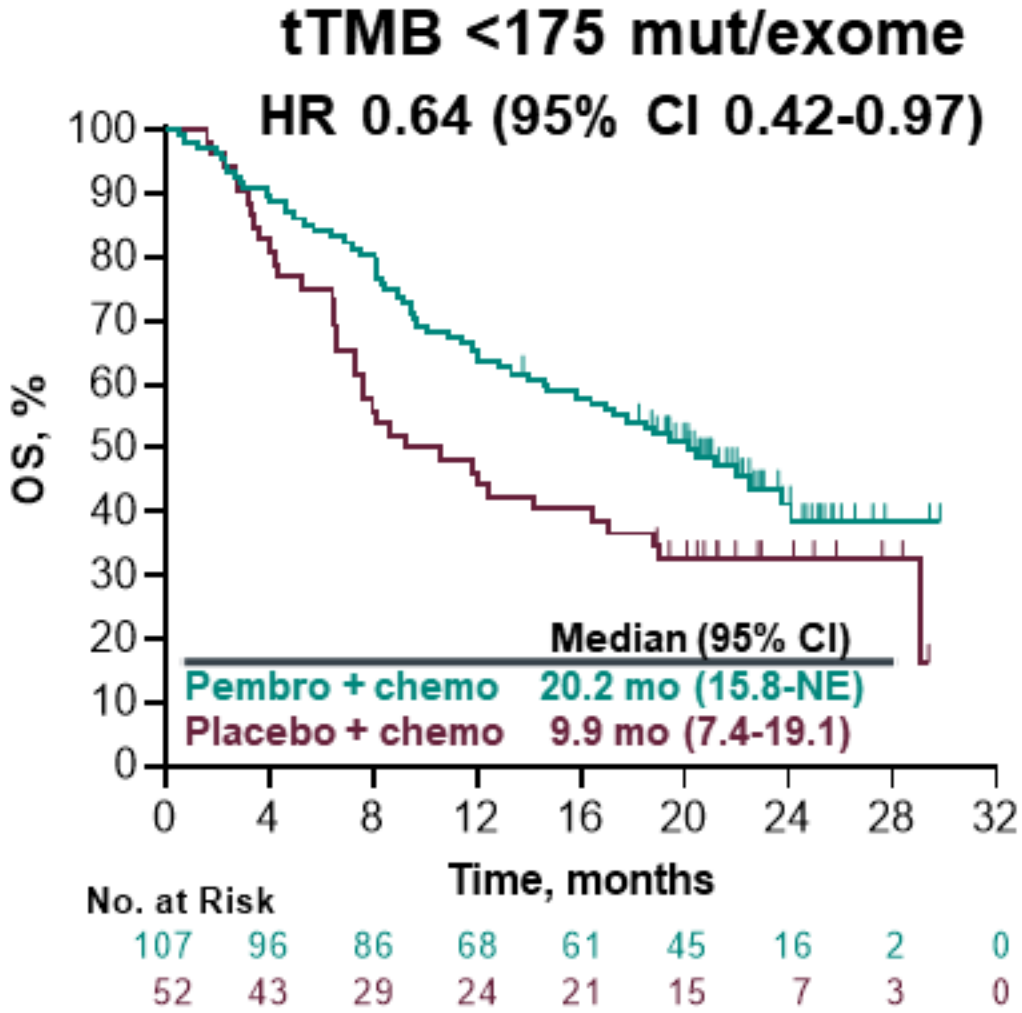




Gandhi et al, AACR 2018/NEJM 2018

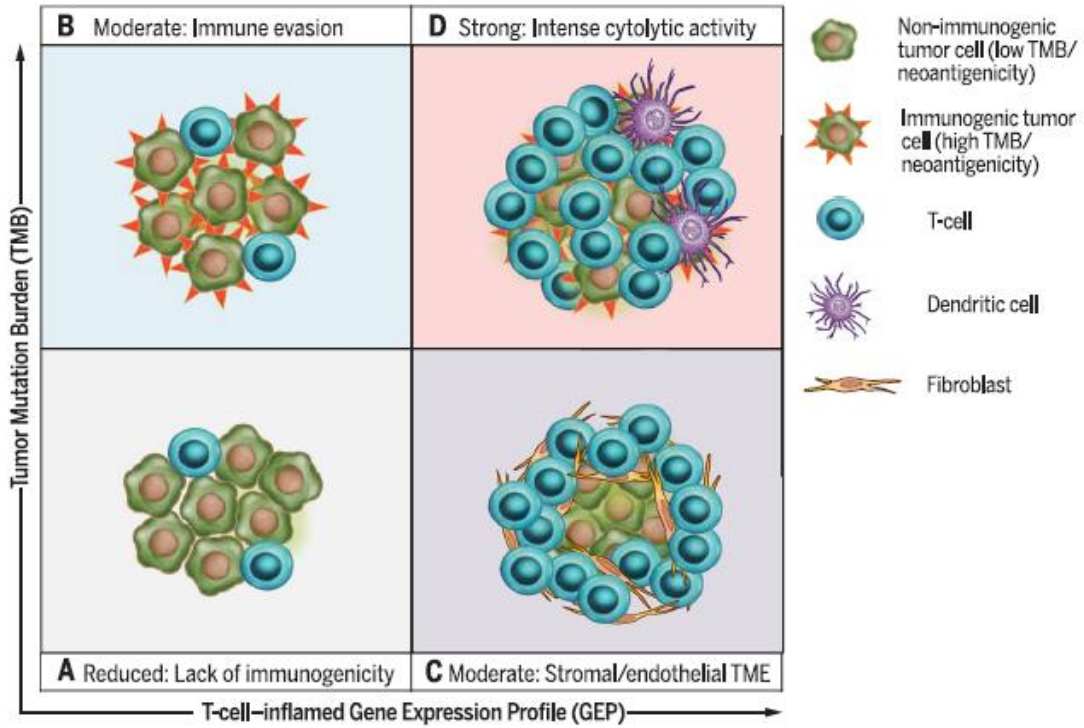
Clinical Utility for OS in KEYNOTE-189: tTMB Cutpoint of 175 mut/exome





Data cutoff date: Sep 21, 2018.

Summary: Inflammation and neoantigenicity biomarkers can define a framework useful for identifying rational combination therapies



Biomarker-defined responses to pembrolizumab monotherapy identify targetable-resistance biology. (**A**) Tumors have low TMB and low neoantigenicity and lack a T cell–inflamed TME. (**B**) Tumors can evade the immune response despite high TMB and high neoantigenicity. (**C**) Although T cells are present, stromal and/or endothelial factors in the TME, low TMB, and low neoantigenicity impede their activity. (**D**) Tumors have high TMB, high neoantigenicity, and a T cell–inflamed TME, typified by activated T cells and other immune cells with cytolytic roles.

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Please visit our poster: Sat Nov 5th, poster P324

Title: Pan-tumor analysis of the association of cancer and immune biology-related gene expression signatures with response to pembrolizumab monotherapy

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