16th ASEICA INTERNATIONAL CONGRESS
Valencia, 6th - 7th - 8th November 2018

MILESTONES IN TRANSLATIONAL RESEARCH IN ONCOLOGY 2018

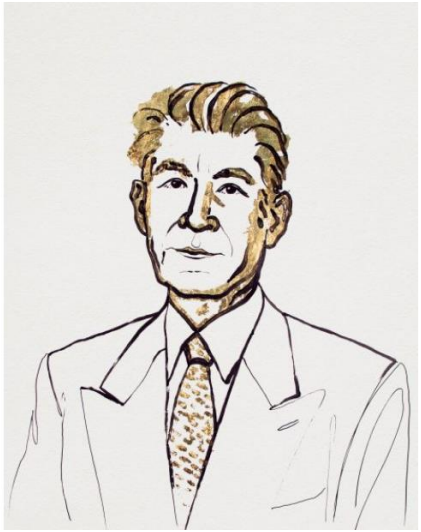
CLINICAL RESARCH POINT´S OF VIEW

JUAN MANUEL SEPÚLVEDA SÁNCHEZ
Hospital Universitario 12 de Octubre

aseica
Asociación Española de Investigación sobre el Cáncer

- Disclosures:
  - Advisor: Bayer, Pfizer, Astellas, Abbvie, Jansen
  - Research Grants: Pfizer

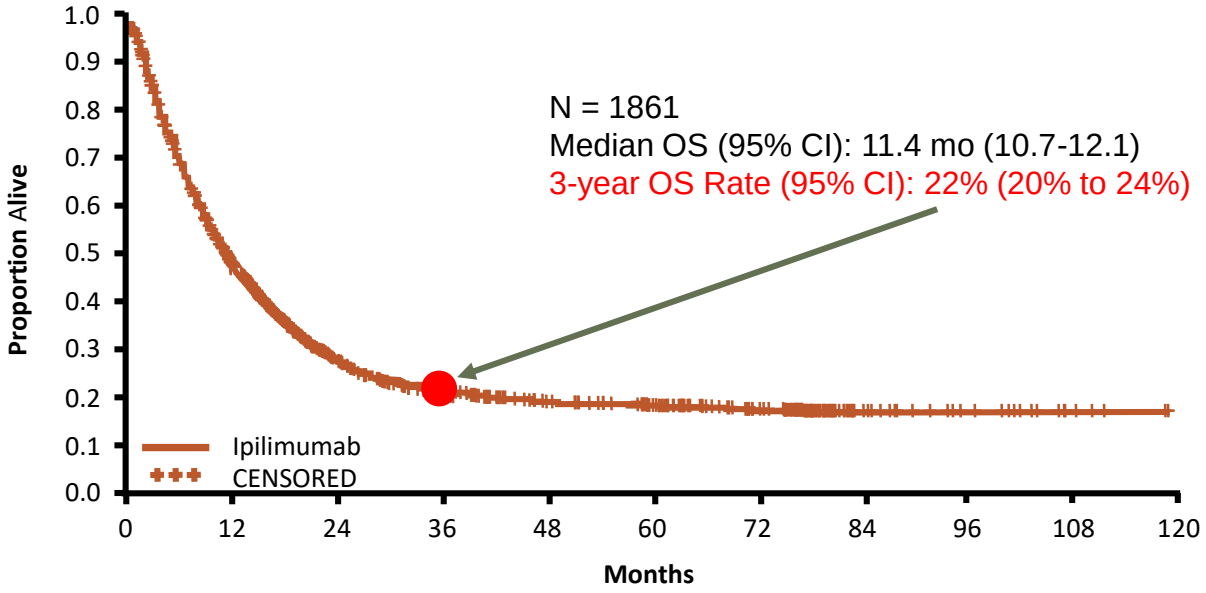
The Nobel Prize in Physiology or Medicine 2018



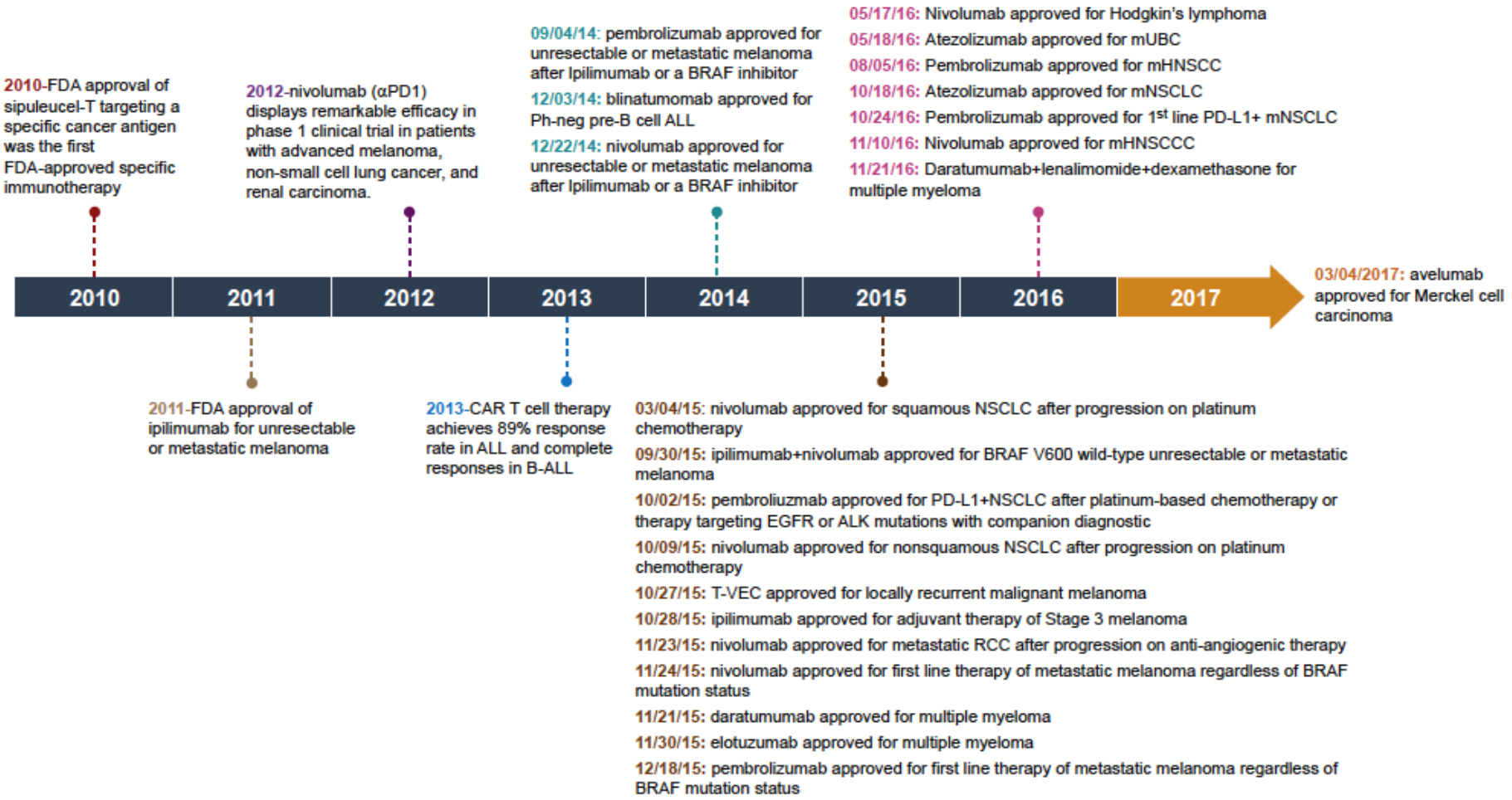
James P. Allison
Tasuku Honjo

aseica
Asociación Española de Investigación sobre el Cáncer

Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



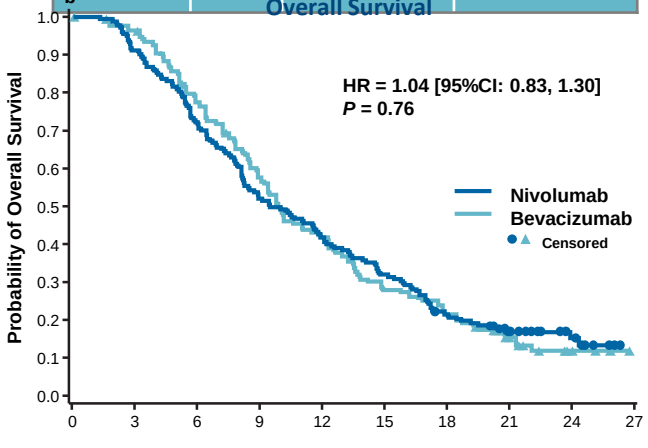
Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015;33:1889-94.


2010-FDA approval of sipuleucel-T targeting a specific cancer antigen was the first FDA-approved specific immunotherapy
2012-nivolumab (αPD1) displays remarkable efficacy in phase 1 clinical trial in patients with advanced melanoma, non-small cell lung cancer, and renal carcinoma.
09/04/14: pembrolizumab approved for unresectable or metastatic melanoma after Ipilimumab or a BRAF inhibitor
12/03/14: blinatumomab approved for Ph-neg pre-B cell ALL
12/22/14: nivolumab approved for unresectable or metastatic melanoma after Ipilimumab or a BRAF inhibitor
05/17/16: Nivolumab approved for Hodgkin's lymphoma
05/18/16: Atezolizumab approved for mUBC
08/05/16: Pembrolizumab approved for mHNSCC
10/18/16: Atezolizumab approved for mNSCLC
10/24/16: Pembrolizumab approved for 1st line PD-L1+ mNSCLC
11/10/16: Nivolumab approved for mHNSCCC
11/21/16: Daratumumab+lenalimomide+dexamethasone for multiple myeloma
2010
2011
2012
2013
2014
2015
2016
2017
03/04/2017: avelumab approved for Merckel cell carcinoma
2011-FDA approval of ipilimumab for unresectable or metastatic melanoma
2013-CAR T cell therapy achieves 89% response rate in ALL and complete responses in B-ALL
03/04/15: nivolumab approved for squamous NSCLC after progression on platinum chemotherapy
09/30/15: ipilimumab+nivolumab approved for BRAF V600 wild-type unresectable or metastatic melanoma
10/02/15: pembroliuzmab approved for PD-L1+NSCLC after platinum-based chemotherapy or therapy targeting EGFR or ALK mutations with companion diagnostic
10/09/15: nivolumab approved for nonsquamous NSCLC after progression on platinum chemotherapy
10/27/15: T-VEC approved for locally recurrent malignant melanoma
10/28/15: ipilimumab approved for adjuvant therapy of Stage 3 melanoma
11/23/15: nivolumab approved for metastatic RCC after progression on anti-angiogenic therapy
11/24/15: nivolumab approved for first line therapy of metastatic melanoma regardless of BRAF mutation status
11/21/15: daratumumab approved for multiple myeloma
11/30/15: elotuzumab approved for multiple myeloma
12/18/15: pembrolizumab approved for first line therapy of metastatic melanoma regardless of BRAF mutation status

Overall Survival and Progression-Free Survival

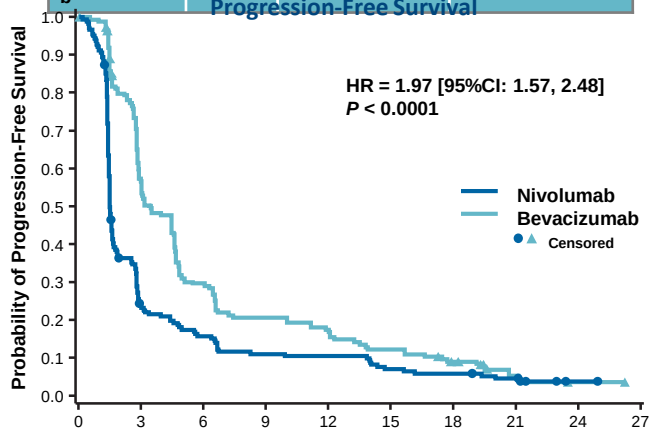
Nivolumab vs Bevacizumab in Recurrent Glioblastoma

	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], months
Nivolumab	154	9.8 [8.2, 11.8]	41.8 [34.7, 48.8]
Bevacizumab	147	10.0 [9.0, 11.8]	42.0 [34.6, 49.3]



No. at Risk										
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

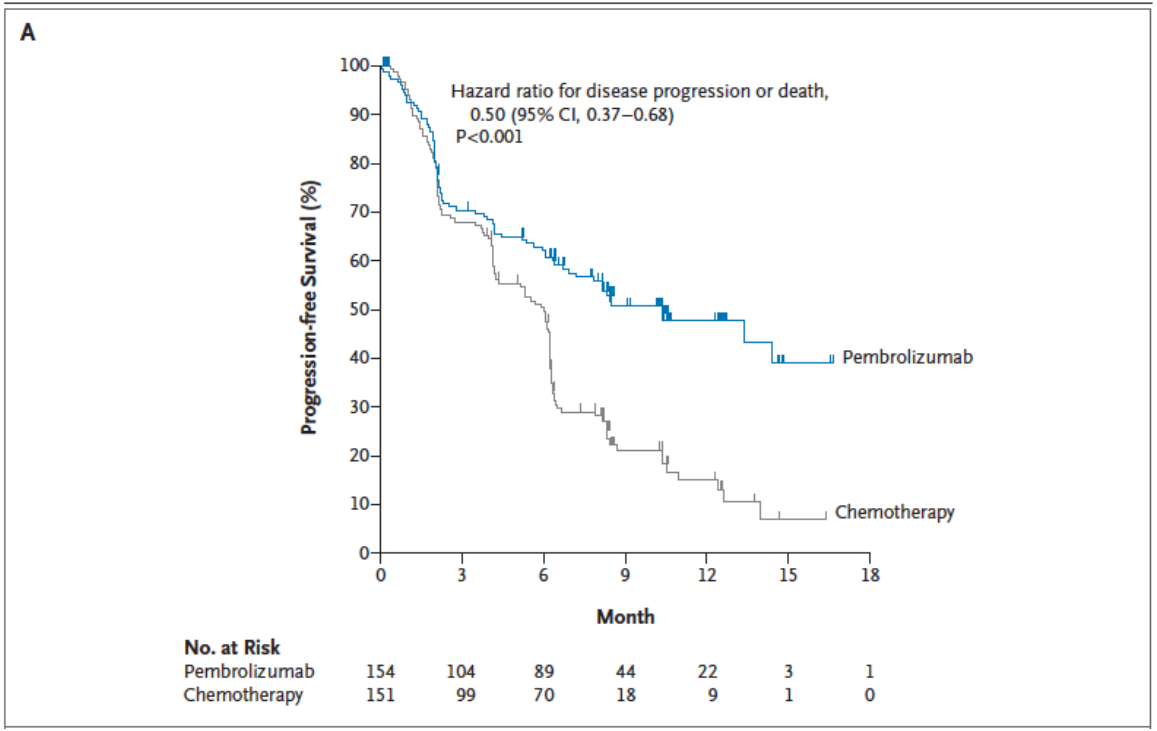
	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]



No. at Risk										
Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

HR, hazard ratio.

Pembrolizumab Vs Chemotherapy in PDL-1-Positive Non-Small-Cell Lung Cancer



-Even in tumors where immunotherapy is very active: 1/3 of patients had no benefit

Rerk M et al. NEJM 2016

BIOMARKERS IN IMMUNO-ONCOLOGY

- To improve the outcome of immunotherapy, accurate and trustworthy biomarkers are needed in order to:
  - Select patients with clear benefit
  - Find drug associations that could surpass resistances to checkpoint inhibitors

- Emerging biomarkers for checkpoint blockade immunotherapy are placed in two categories:
  - **Related to tumor neoepitope burden**: Microsatellite instability (MSI) and high tumor mutational burden
  - **Related to T cell-inflamed tumor:** PDL1 protein expression and gene expression related to T-Cell cytolitic activity

BIOMARKERS IN IMMUNO-ONCOLOGY

- However, these two types of biomarkers:
  - Related to neoepitope burden
  - Related to T-cell inflamation
- Show different faces of the same phenomenon
- And the relationship between them had not been clarified

RESEARCH ARTICLE

CANCER BIOMARKERS

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

Razvan Cristescu[1]*, Robin Mogg[1]†, Mark Ayers[1], Andrew Albright[1], Erin Murphy[1], Jennifer Yearley[1], Xinwei Sher[1], Xiao Qiao Liu[1], Hongchao Lu[1], Michael Nebozhyn[1], Chunsheng Zhang[1], Jared K. Lunceford[1], Andrew Joe[1], Jonathan Cheng[1], Andrea L. Webber[1], Nageatte Ibrahim[1], Elizabeth R. Plimack[2], Patrick A. Ott[3], Tanguy Y. Seiwert[4], Antoni Ribas[5], Terrill K. McClanahan[1], Joanne E. Tomassini[1], Andrey Loboda[1], David Kaufman[1]†

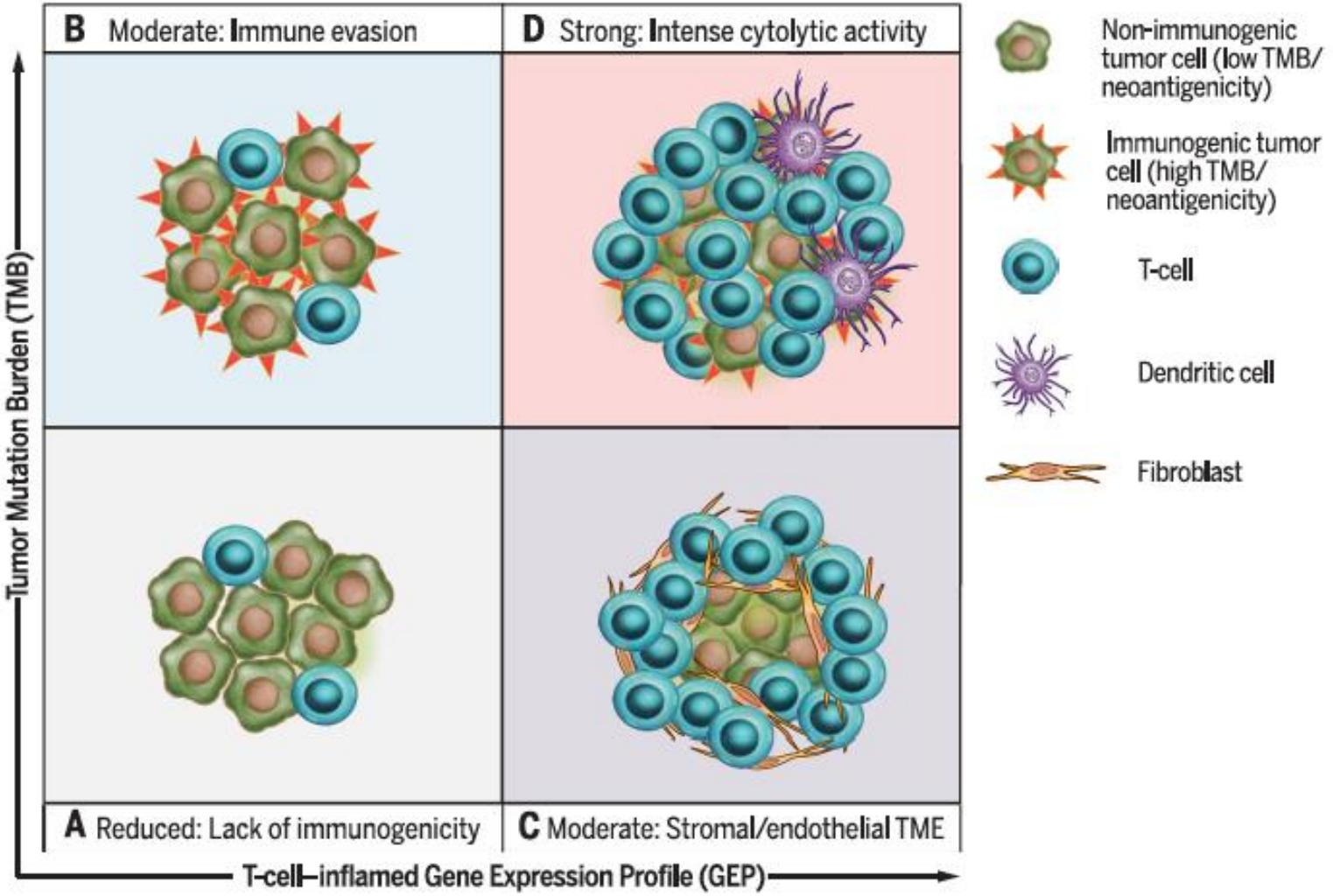
Science, 12 Oct 2018

OBJECTIVES

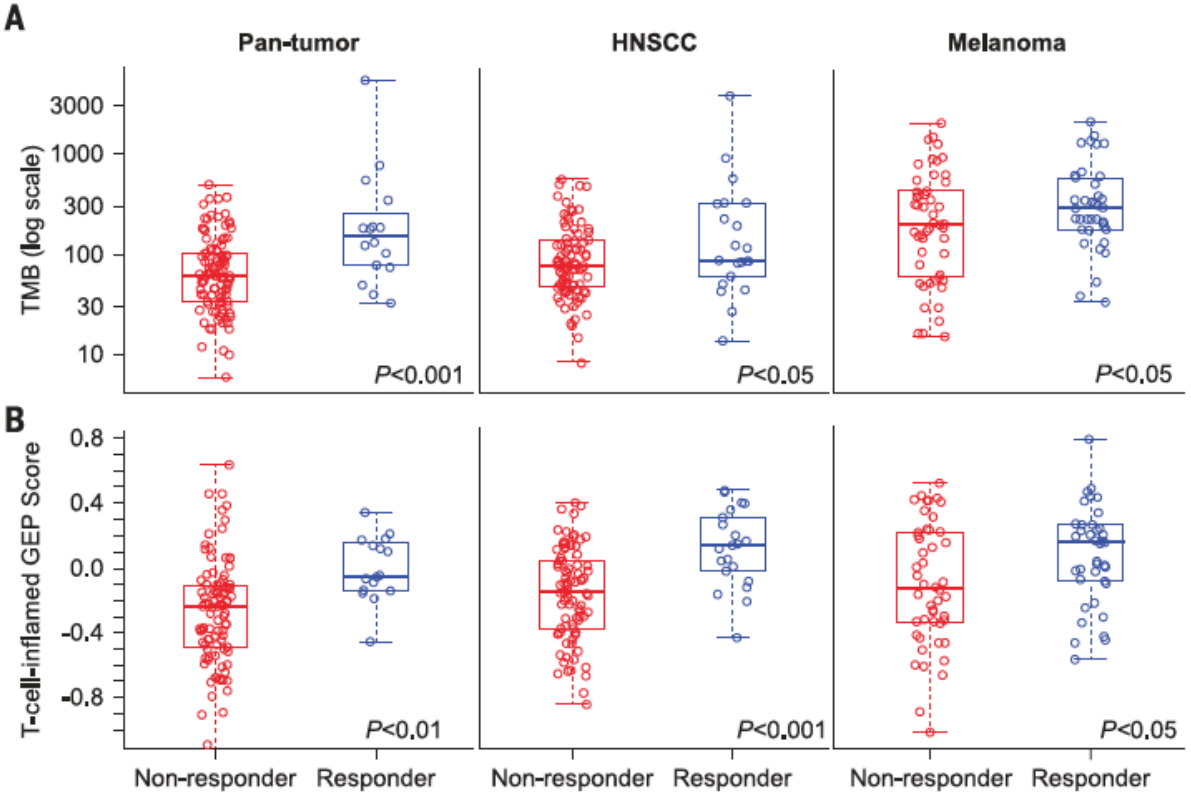
- To assess TMB and T-Inflamed Genome Expression Profile (GEP) to jointly predict response to Pembrolizumab, a PD1 antibody that has been approved for several tumors.

- >300 patients with 22 different tumor types participating in KEYNOTE clinical trials.

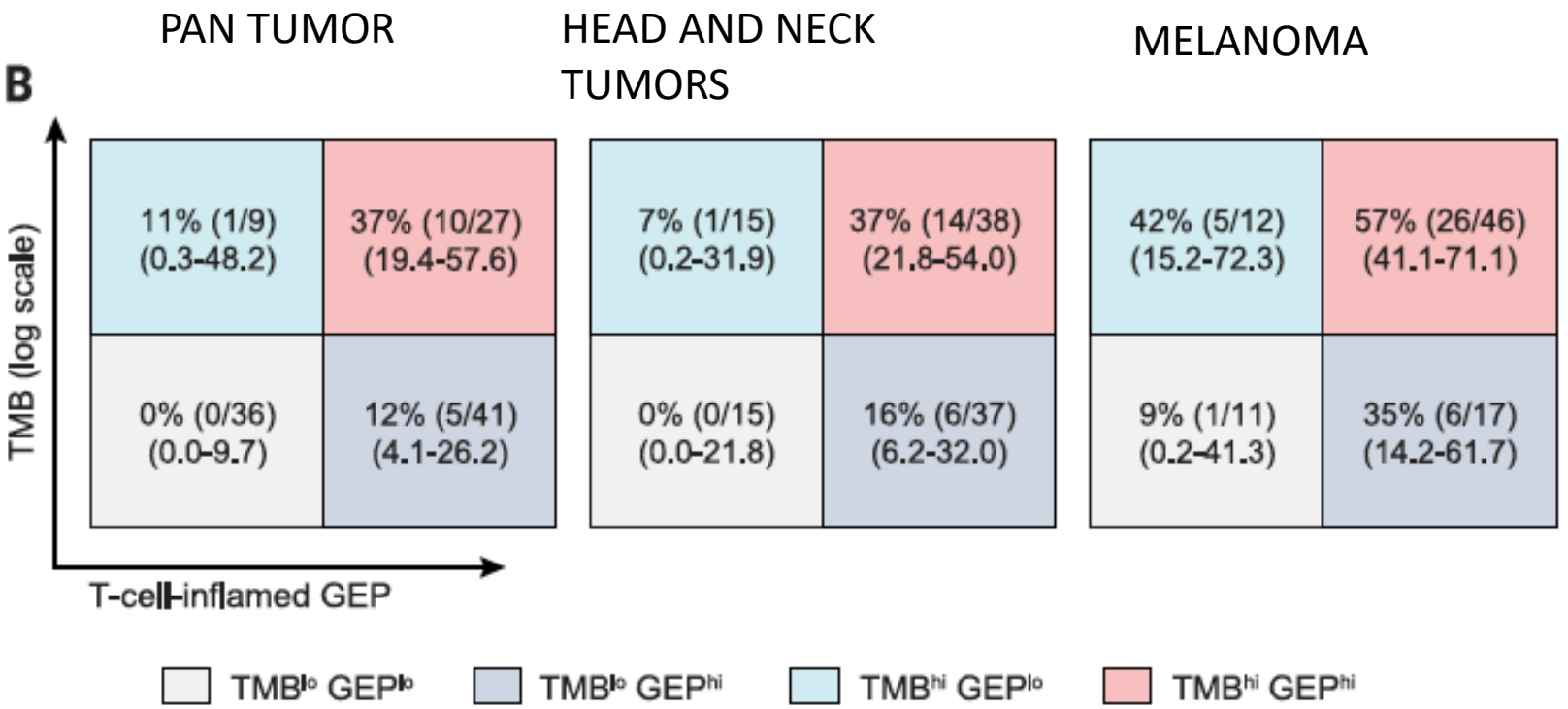
- Patients were classified into four biomarker-defined clinical response groups:
  - T cell-inflamed gene expression profile low and TMB low ($GEP^{low}TMB^{low}$)
  - T cell-inflamed gene expression profile low and TMB high ($GEP^{low}TMB^{high}$)
  - T cell-inflamed gene expression profile high and TMB low ($GEP^{high}TMB^{low}$)
  - T cell-inflamed gene expression profile high and TMB high ($GEP^{high}TMB^{high}$)


B Moderate: Immune evasion
D Strong: Intense cytolytic activity
A Reduced: Lack of immunogenicity
C Moderate: Stromal/endothelial TME
Tumor Mutation Burden (TMB)
T-cell–inflamed Gene Expression Profile (GEP)
Non-immunogenic tumor cell (low TMB/ neoantigenicity)
Immunogenic tumor cell (high TMB/ neoantigenicity)
T-cell
Dendritic cell
Fibroblast

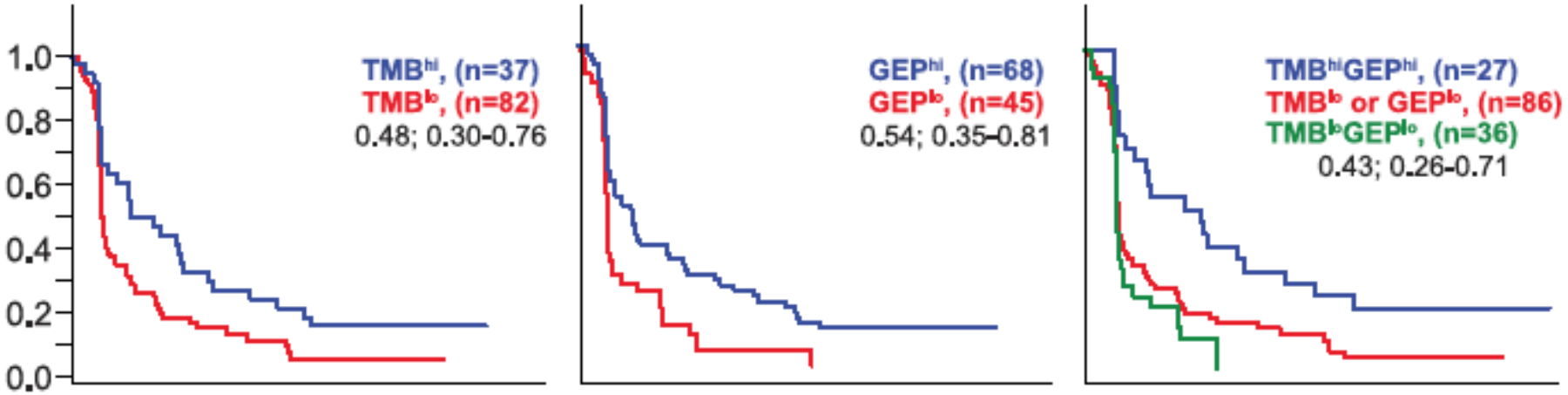
Both TMB high and T-Cell-inflamed Score high were most common in responders than in non-responders to Pembrolizumab



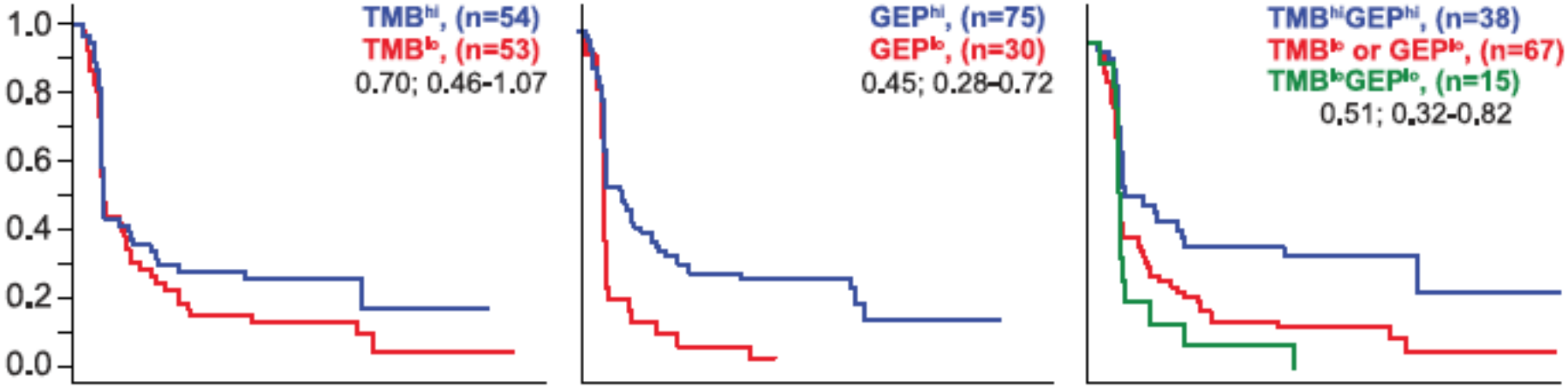
RESPONSE RATE ACCORDING TO TMB AND T-CELL INFLAMED PROFILE: JOINT ANALYSIS



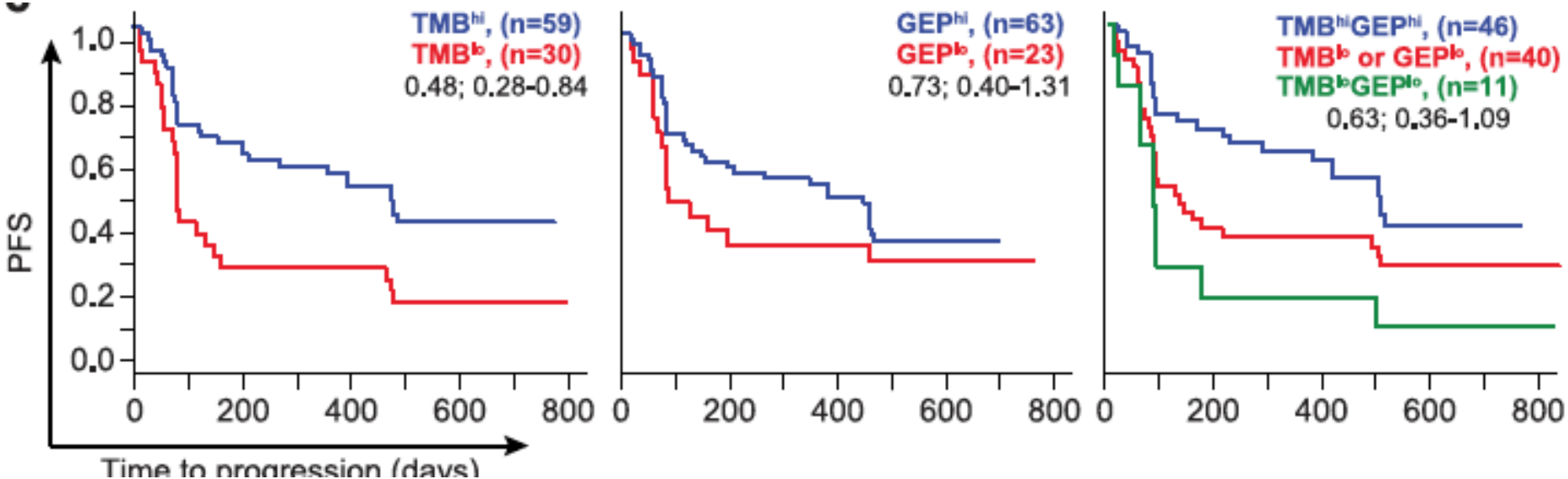
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Pan Tumor Cohort



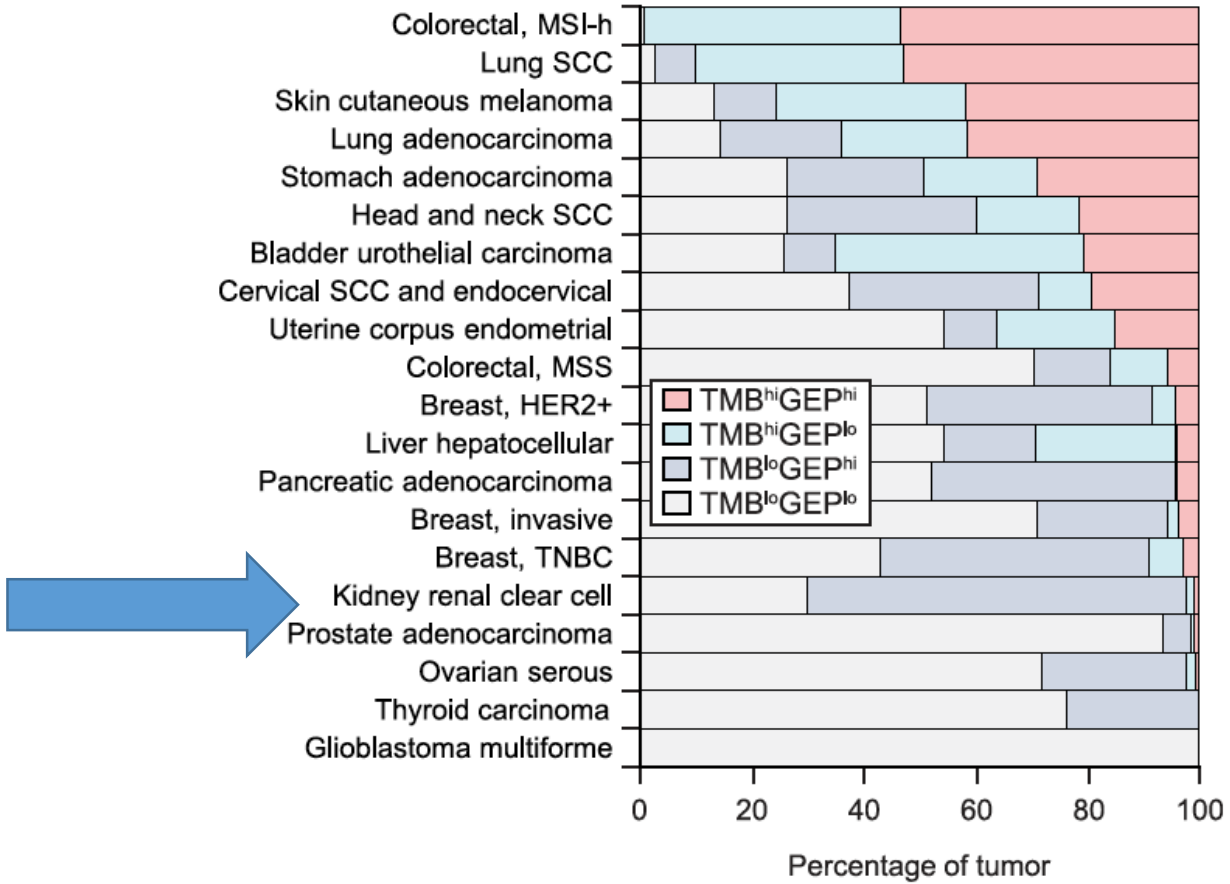
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Head and Neck



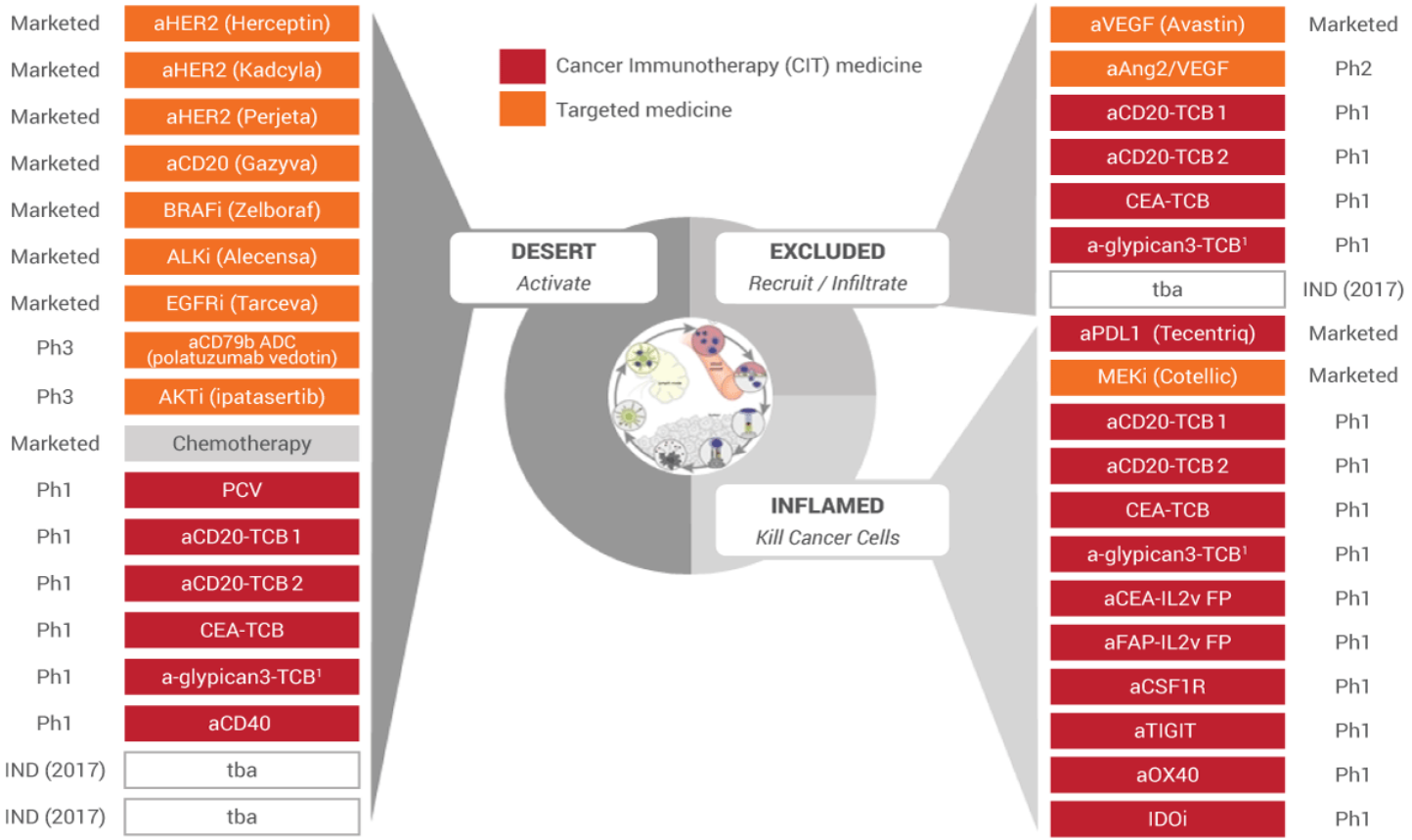
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Melanoma



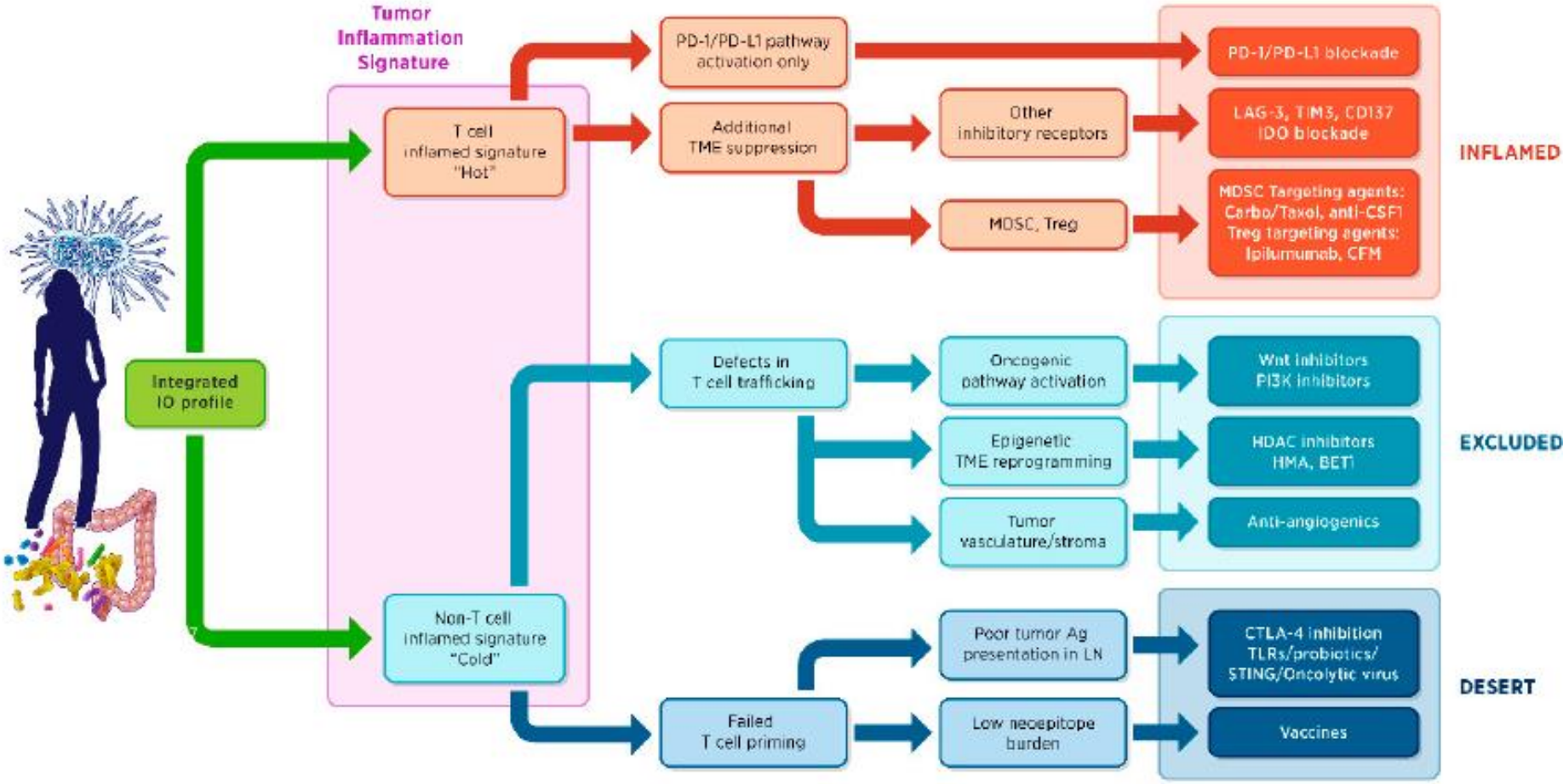
RELATIONSHIPS OF TMB, GEP WITH GENE EXPRESSION ACROSS TUMOR TYPES IN TCGA



Multiple approaches across three tumor phenotypes



PCV* = personalized cancer vaccine in collaboration with BioNTech; 1= in early development at Chugai; NME = new molecular entity; IND = new investigational drug application; TCB = T-cell bispecific; tba = to be announced


Tumor Inflammation Signature
Integrated IO profile
T cell inflamed signature "Hot"
Non-T cell inflamed signature "Cold"
PD-1/PD-L1 pathway activation only
Additional TME suppression
Other inhibitory receptors
MDSC, Treg
PD-1/PD-L1 blockade
LAG-3, TIM3, CD137 IDO blockade
MDSC Targeting agents: Carbo/Taxol, anti-CSF1 Treg targeting agents: Ipilumumab, CFM
INFLAMED
Defects in T cell trafficking
Oncogenic pathway activation
Epigenetic TME reprogramming
Tumor vasculature/stroma
Wnt inhibitors PI3K inhibitors
HDAC inhibitors HMA, BETi
Anti-angiogenics
EXCLUDED
Failed T cell priming
Poor tumor Ag presentation in LN
Low neoepitope burden
CTLA-4 inhibition TLRs/probiotics/ STING/Oncolytic virus
Vaccines
DESERT

- CONCLUSIONS
  - Real data from patients treated in controlled clinical trials with Pembrolizumab confirm the presence of four tumor phenotypes associated to clinical responses to immunotherapy.
  - TMB and T-Cell profiles are independent biomarkers of response.
  - Combining these two biomarkers, it is possible to improve the prediction of response in individual patients.

- Thank you very much for your attention