

16th ASEICA INTERNATIONAL CONGRESS

Valencia, 6th - 7th - 8th November 2018

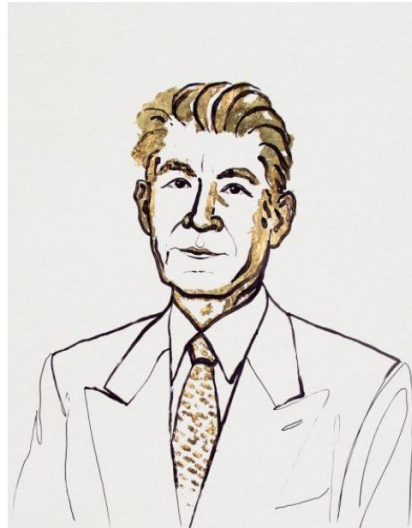
MILESTONES IN TRANSLATIONAL RESEARCH IN ONCOLOGY 2018

CLINICAL RESEARCH POINT'S OF VIEW

JUAN MANUEL SEPÚLVEDA SÁNCHEZ
Hospital Universitario 12 de Octubre

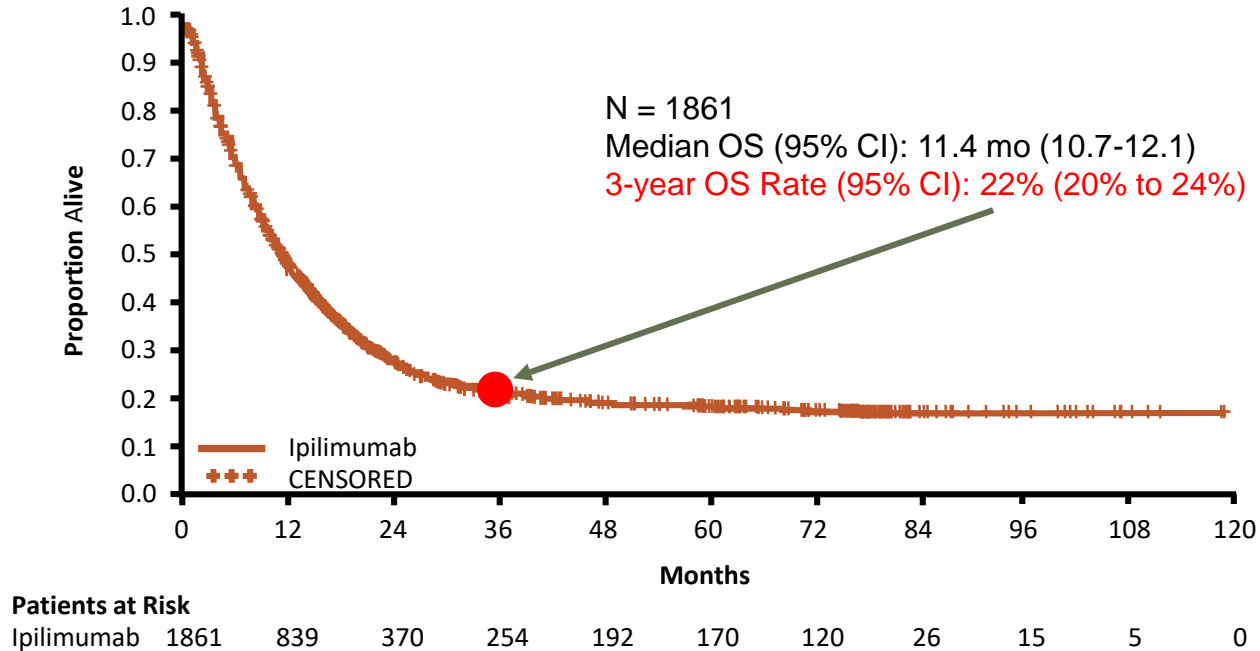
- Disclosures:
 - Advisor: Bayer, Pfizer, Astellas, Abbvie, Jansen
 - Research Grants: Pfizer

The Nobel Prize in Physiology or Medicine 2018



James P. Allison
Tasuku Honjo

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



2010-FDA approval of sipuleucel-T targeting a specific cancer antigen was the first FDA-approved specific immunotherapy

2012-nivolumab (α PD1) 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

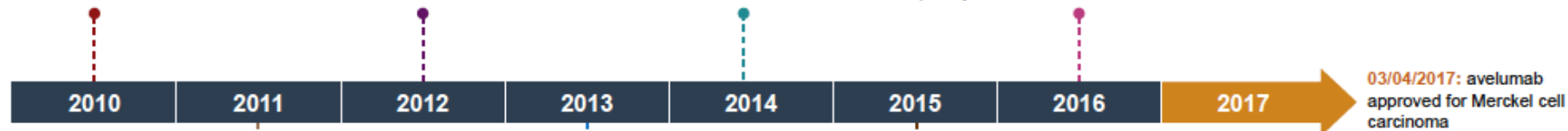
08/05/16: Pembrolizumab approved for mHNSCC

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

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: pembrolizumab 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

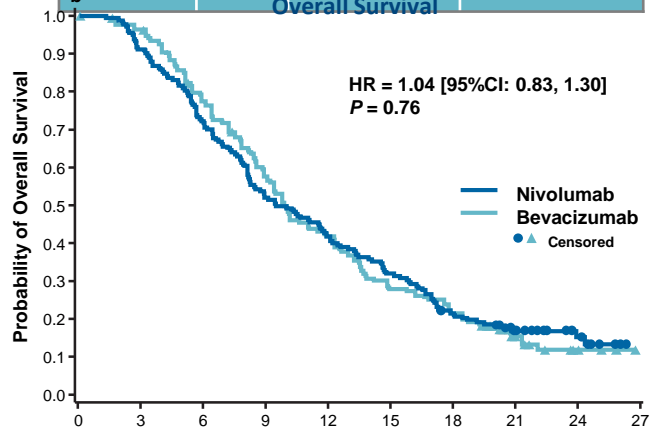
12/18/15: pembrolizumab approved for first line therapy of metastatic melanoma regardless of BRAF mutation status

03/04/2017: avelumab approved for Merkel cell carcinoma

Overall Survival and Progression-Free Survival

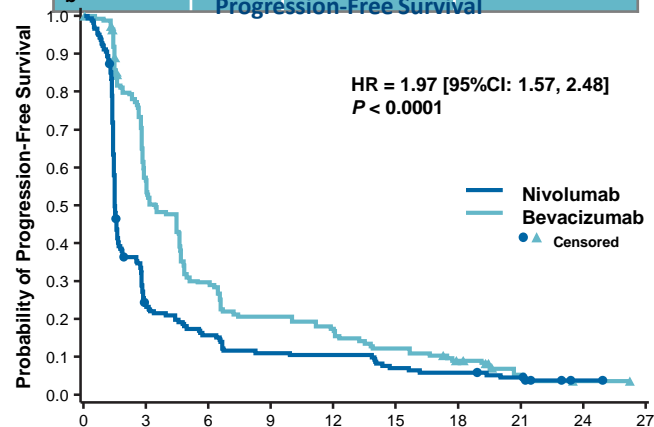
Nivolumab vs Bevacizumab in Recurrent Glioblastoma

	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]



	Months									
No. at Risk	0	3	6	9	12	15	18	21	24	27
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

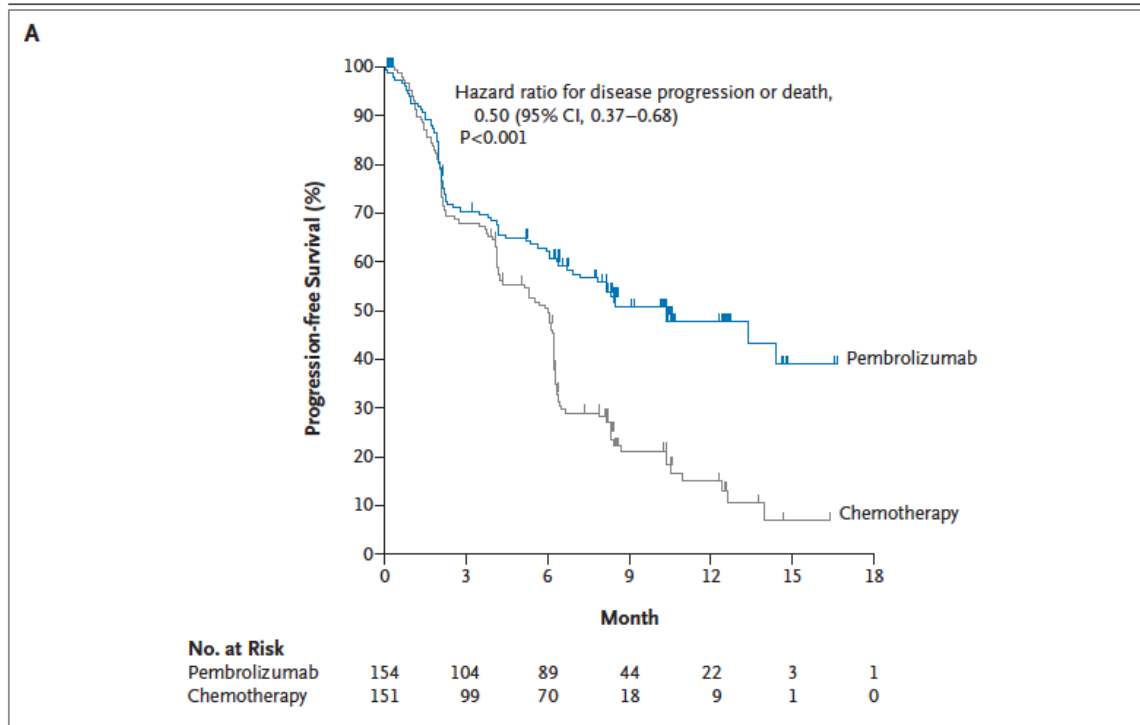
	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]



	Months									
No. at Risk	0	3	6	9	12	15	18	21	24	27
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 cytotoxic activity

BIOMARKERS IN IMMUNO-ONCOLOGY

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

RESEARCH ARTICLE

CANCER BIOMARKERS

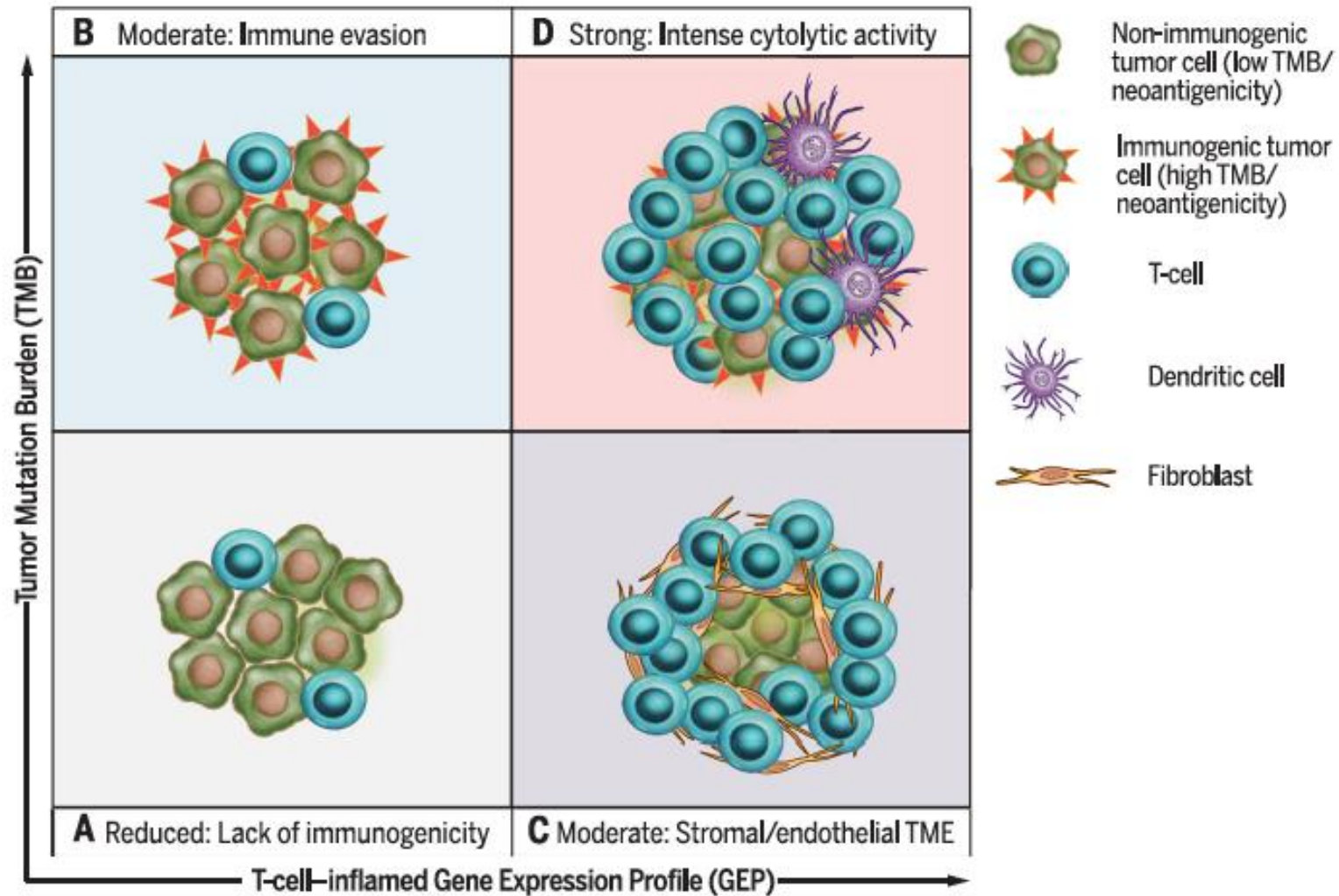
Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy

Razvan Cristescu^{1*}, Robin Mogg^{1†}, Mark Ayers¹, Andrew Albright¹, Erin Murphy¹, Jennifer Yearley¹, Xinwei Sher¹, Xiao Qiao Liu¹, Hongchao Lu¹, Michael Nebozhyn¹, Chunsheng Zhang¹, Jared K. Lunceford¹, Andrew Joe¹, Jonathan Cheng¹, Andrea L. Webber¹, Nageatte Ibrahim¹, Elizabeth R. Plimack², Patrick A. Ott³, Tanguy Y. Seiwert⁴, Antoni Ribas⁵, Terrill K. McClanahan¹, Joanne E. Tomassini¹, Andrey Loboda¹, David Kaufman^{1†}

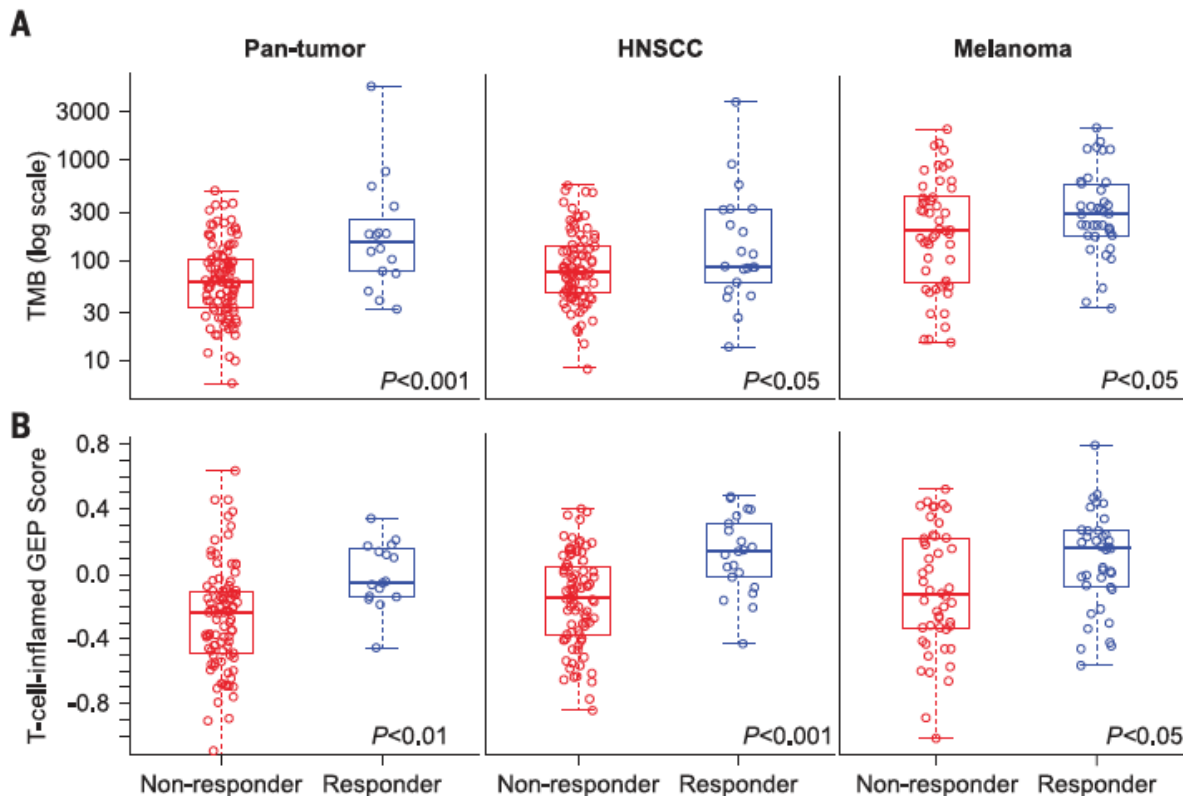
Science, 12 Oct 2018

OBJECTIVES

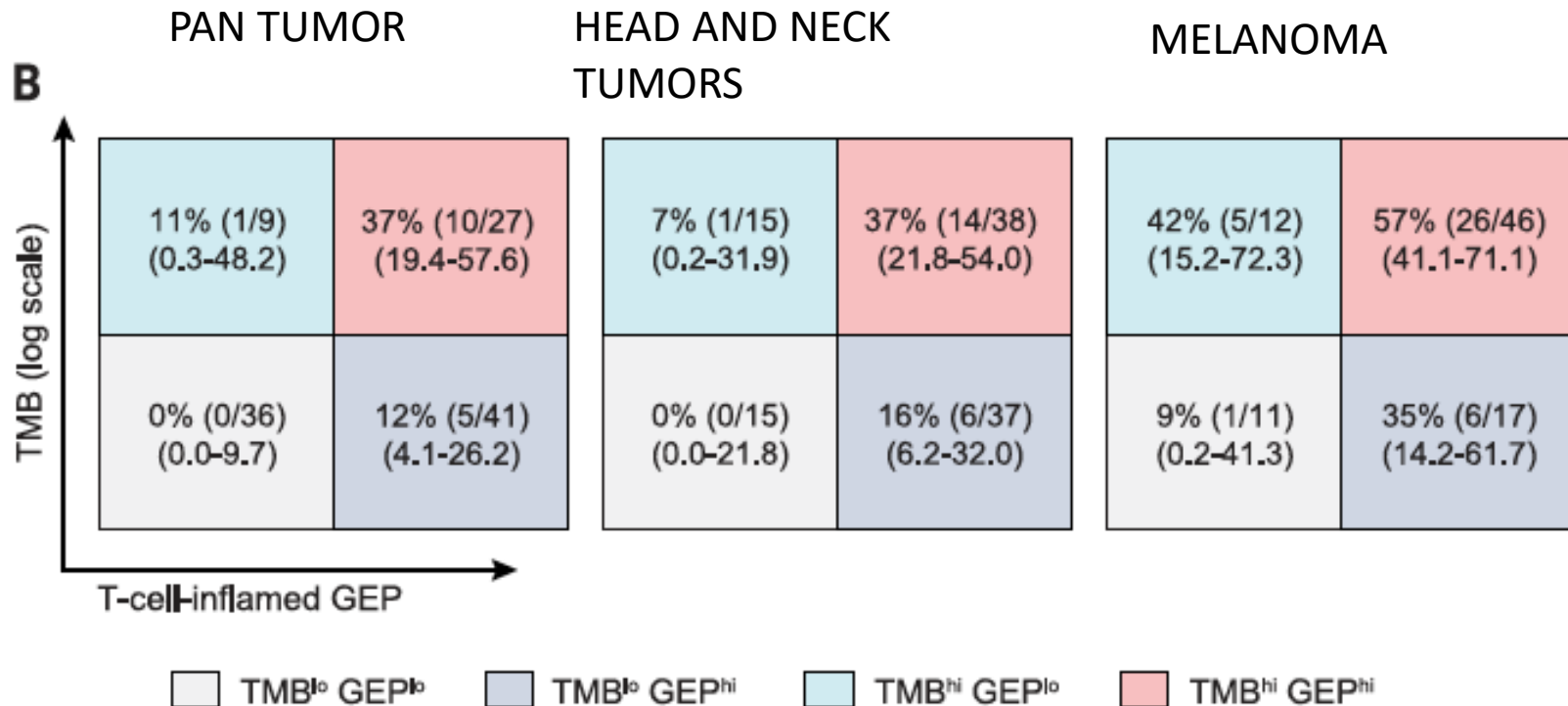
- To assess TMB and T-Inflamed Genome Expression Profile (GEP) to jointly predict response to Pembrolizumab, a PD1 antibody that has been approved for several tumors.
- >300 patients with 22 different tumor types participating in KEYNOTE clinical trials.
- Patients were classified into four biomarker-defined 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})



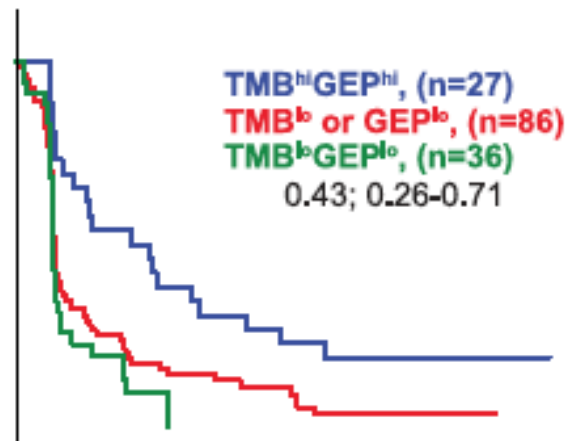
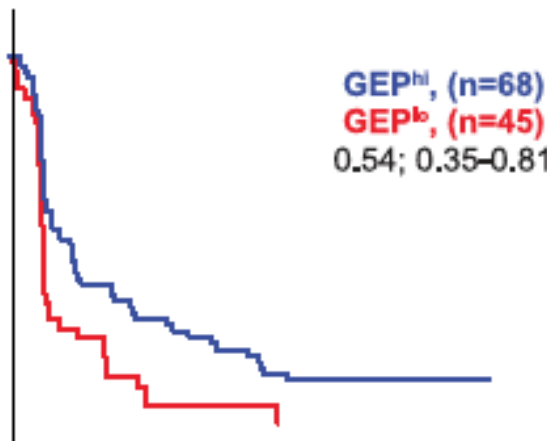
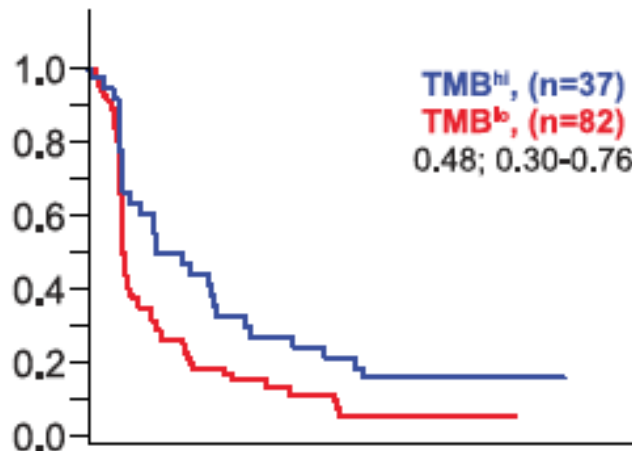
Both TMB high and T-Cell-inflamed Score high were most common in responders than in non-responders to Pembrolizumab



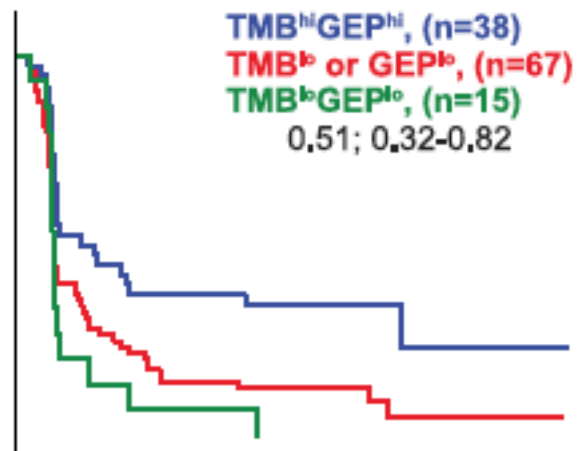
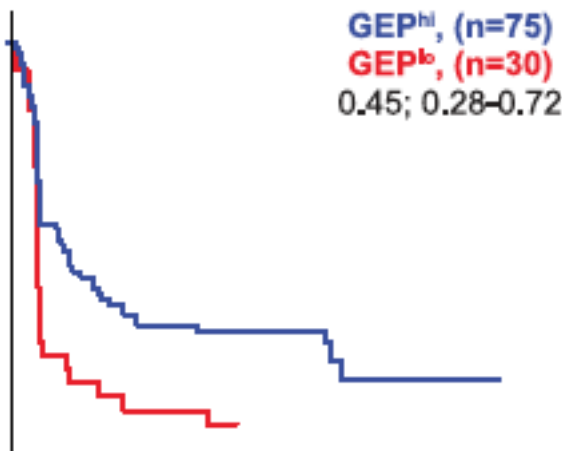
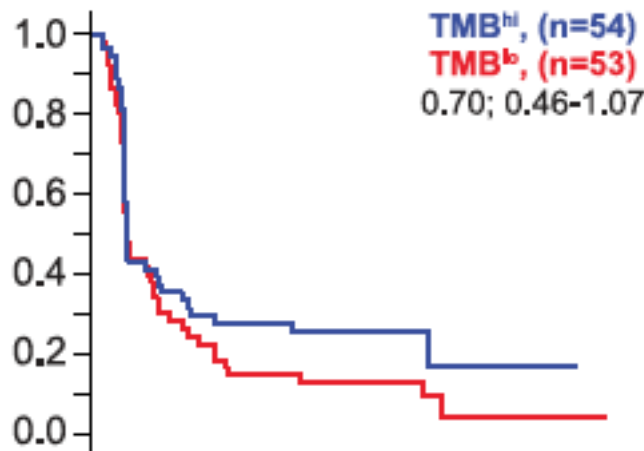
RESPONSE RATE ACCORDING TO TMB AND T-CELL INFLAMED PROFILE: JOINT ANALYSIS



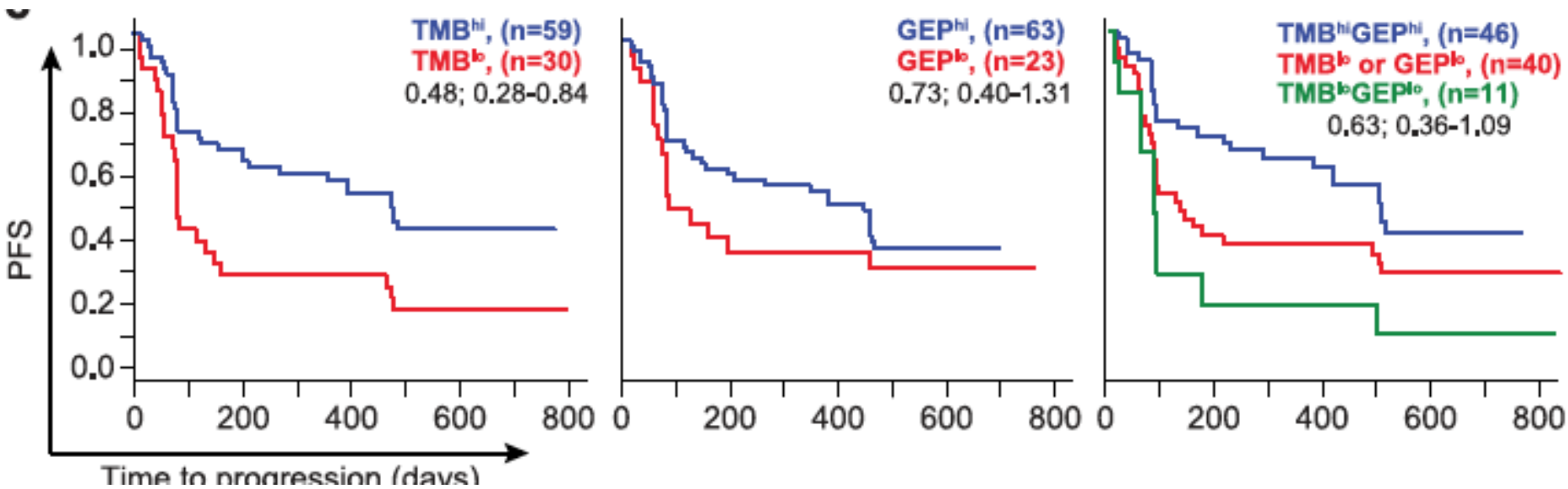
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Pan Tumor Cohort



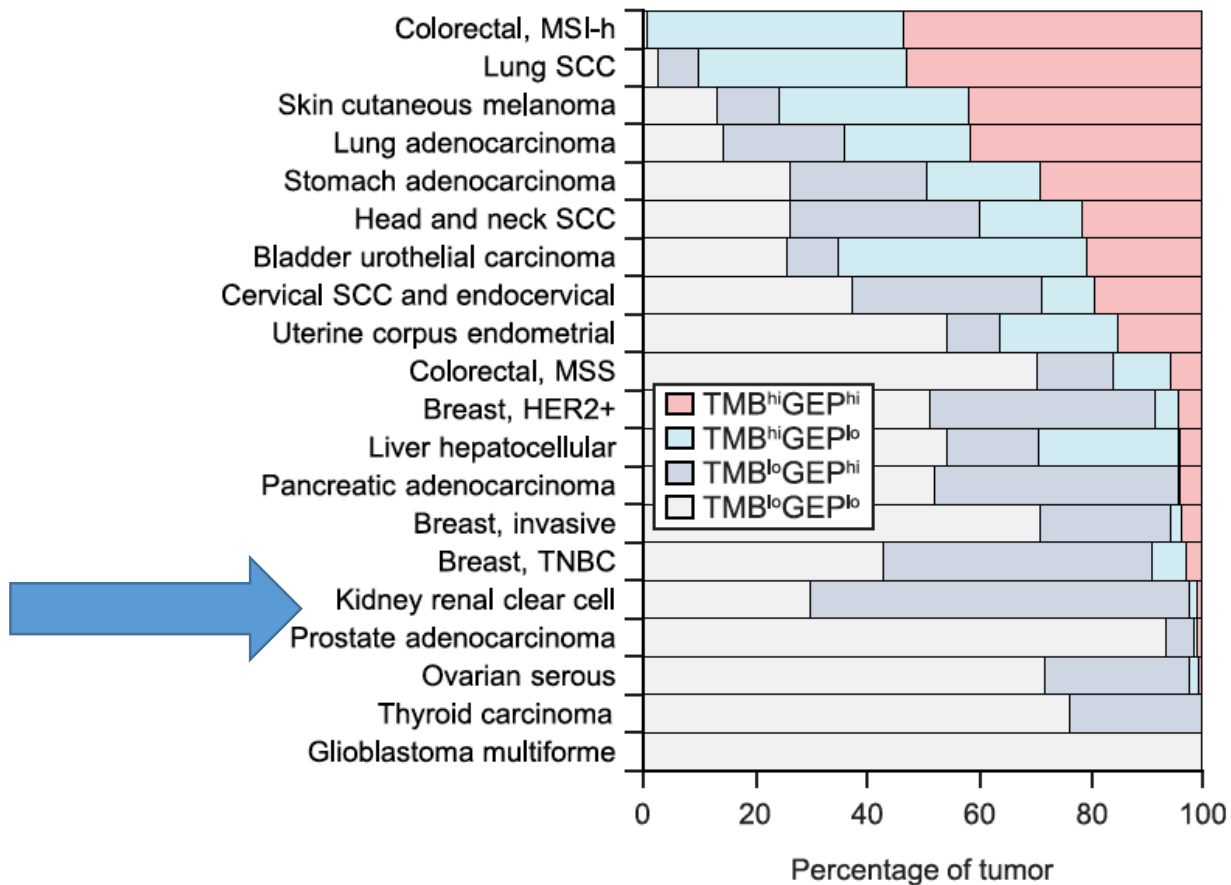
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Head and Neck



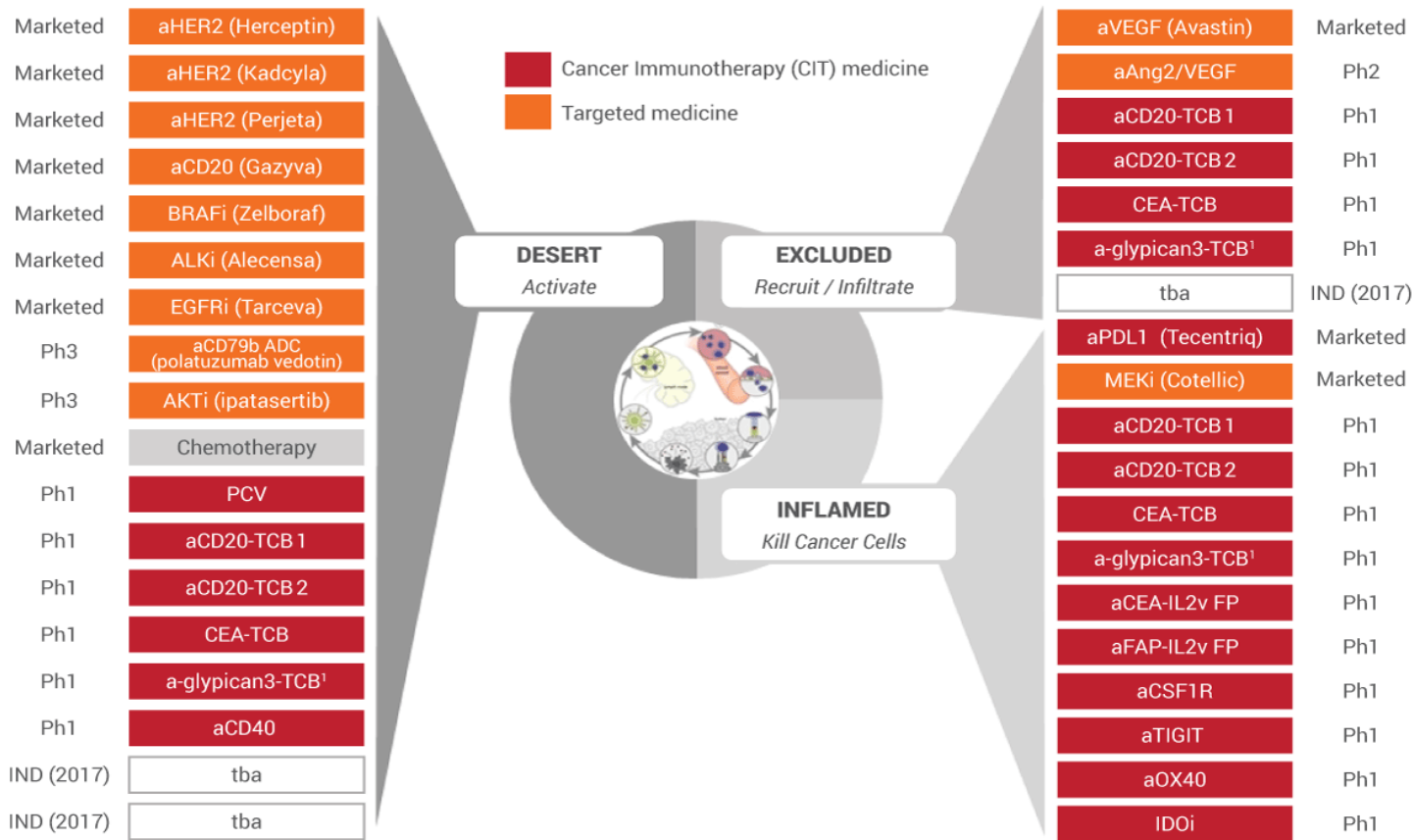
Significant Improved Progression-Free Survival in patients with TMB^{Hi} + GEP^{hi}. Melanoma



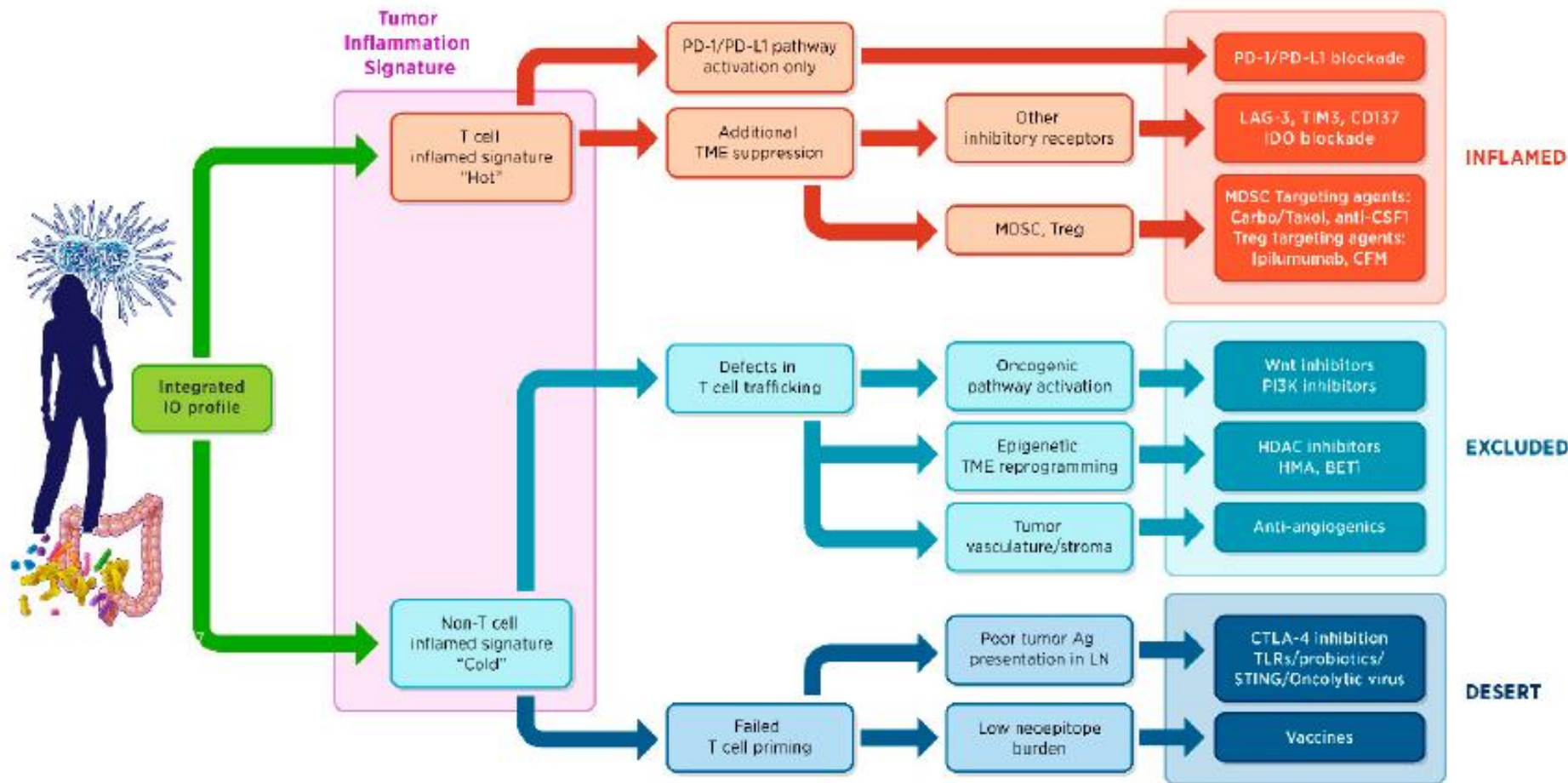
RELATIONSHIPS OF TMB, GEP WITH GENE EXPRESSION ACROSS TUMOR TYPES IN TCGA



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



- 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