Immuntherapien
– was ist im Alltag angekommen?

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Universitätsmedizin Berlin

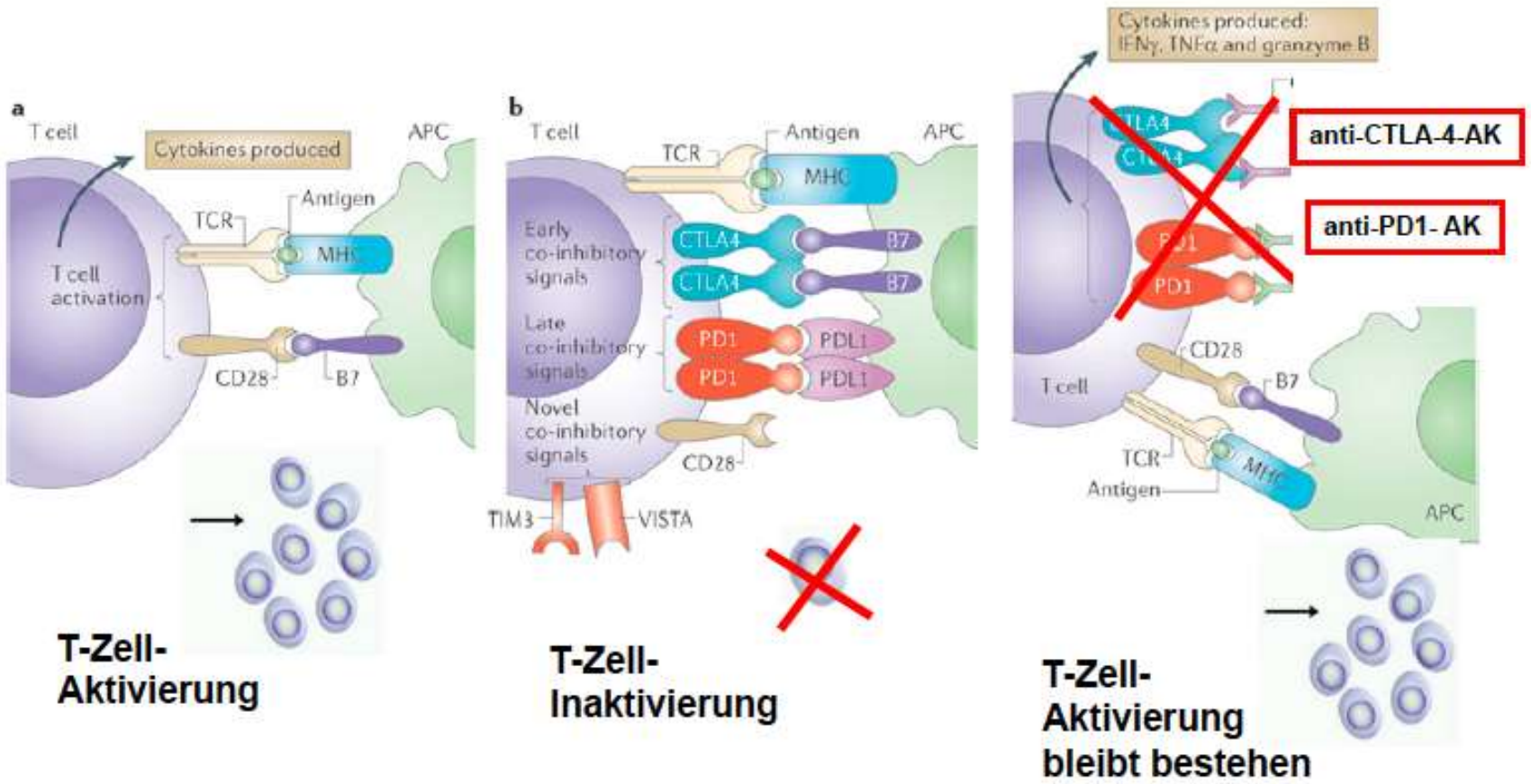

Science
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

2013

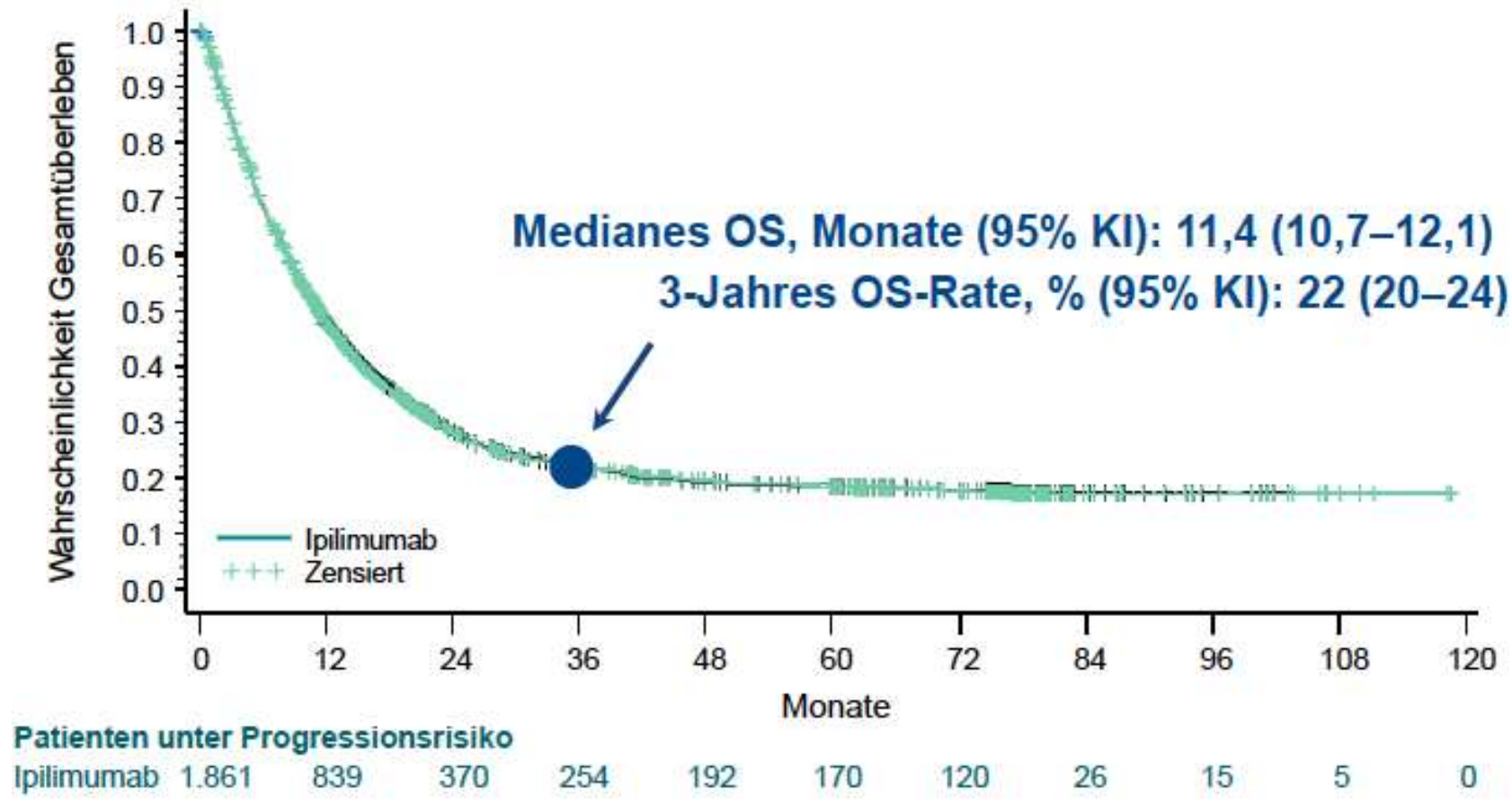
?

2018

Release the Break

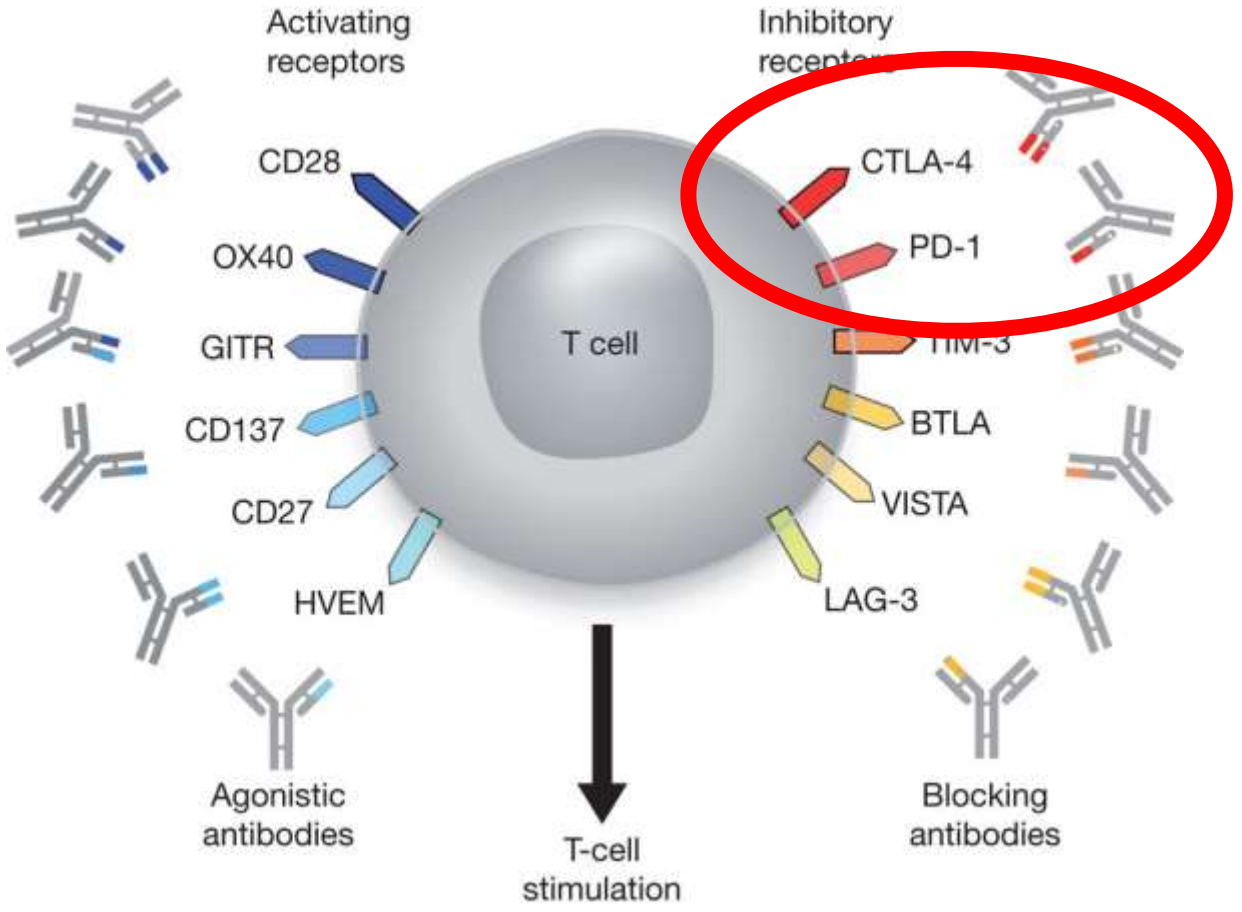


Proof of concept anti-CTLA4—Antibody Melanoma



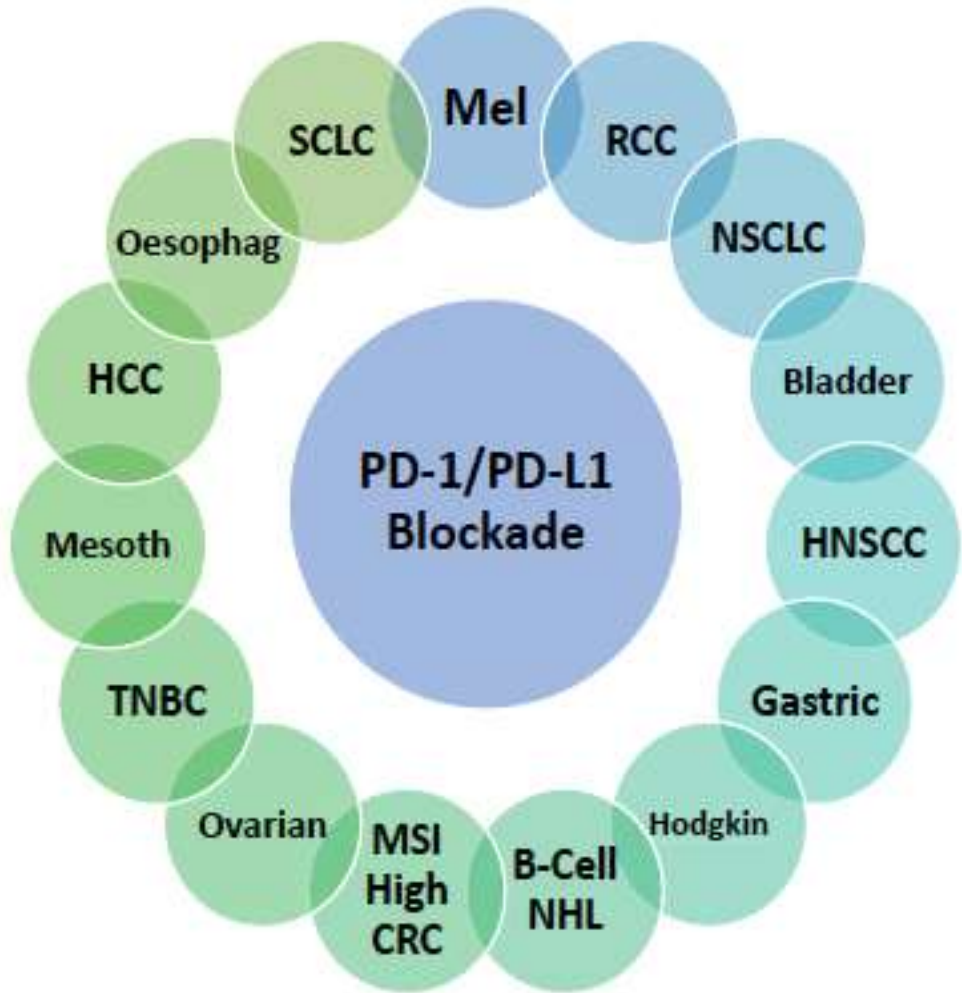
Schadendorf D, ECCO/ESMO 2013 #24LBA

T-cell-Targets
for immunoregulatory antibodies

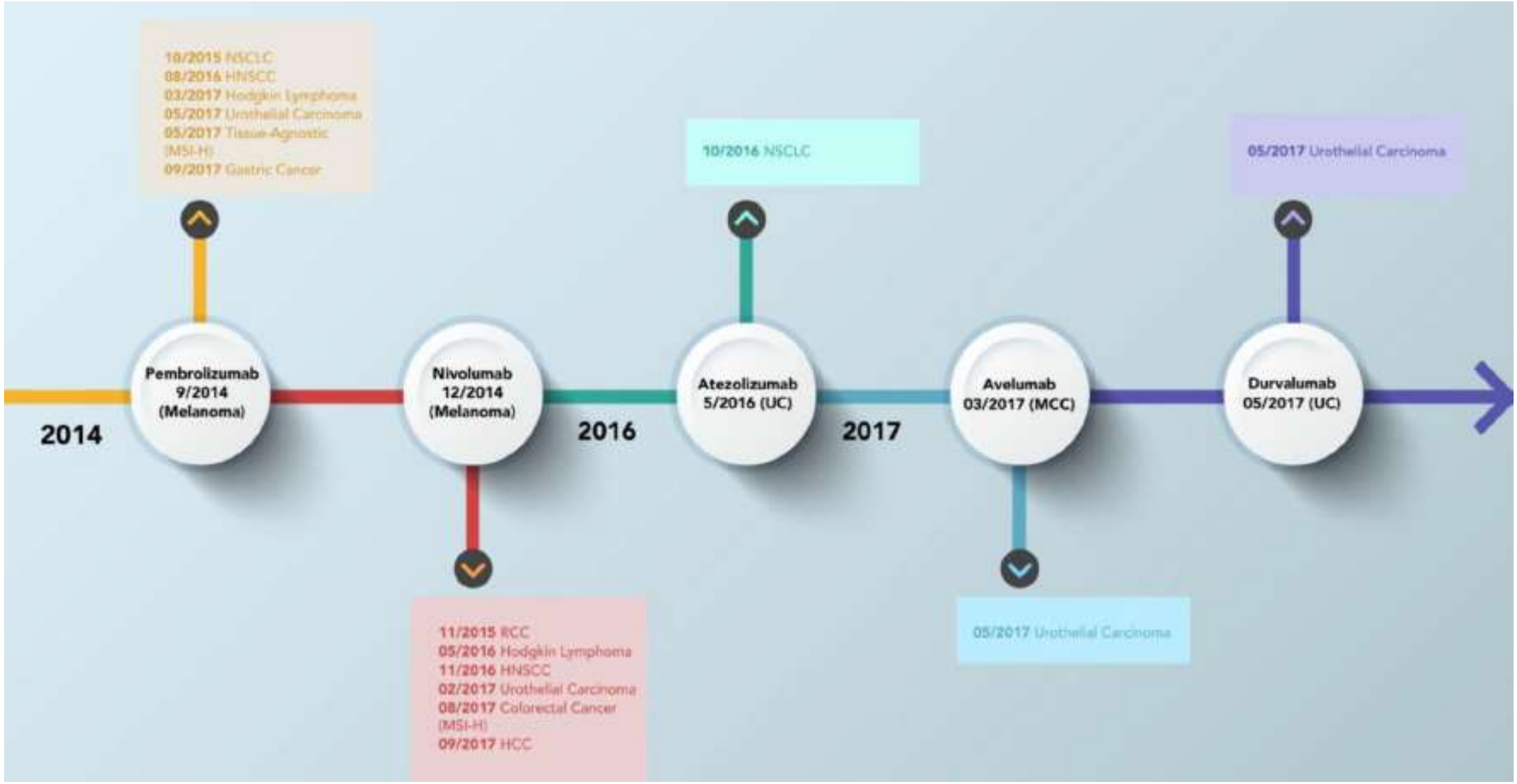


I Mellman *et al. Nature* 480, 480-489 (2011)

"PDLOMAS" ACTIVITY IN 2015



Zulassungsstatus Immuncheckpoint-Inhibitoren



Gastric cancer Pembrolizumab

- September 2017,
- Pembrolizumab 200 mg every 3 weeks
- approved for advanced gastroesophageal cancer, PD-L1 ≥ 1% (IHC 22C3 ab)
- refractory ≥2 lines of chemotherapy phase II KEYNOTE-059 trial
- Out of 259 patients, the ORR was 11.2% (95% CI 7.6-15.7) with a median duration of response of 8.1 months
- Grade 3-5 treatment-related AEs occurred in 43 patients (16.6%)
- leading to discontinuation in 2 patients
- death in 2 patients due to renal failure and pleural effusion.

Hepatocellular carcinoma Nivolumab

- September 2017,
- nivolumab 3 mg/kg every 2 weeks
- advanced hepatocellular carcinoma (HCC)
- refractory to sorafenib in the phase I/ II CheckMate 040 trial
- Of 262 eligible patients, ORR was 20% (95% CI 15-26%)
- Activity and tolerability did not appear to be affected by PD-L1 status or presence or absence of viral hepatitis
- Twelve of 48 patients (25%) grade 3-4 Aes,
- 3 patients (6%) having treatment-related serious AEs (pemphigoid, adrenal insufficiency, liver disorder).

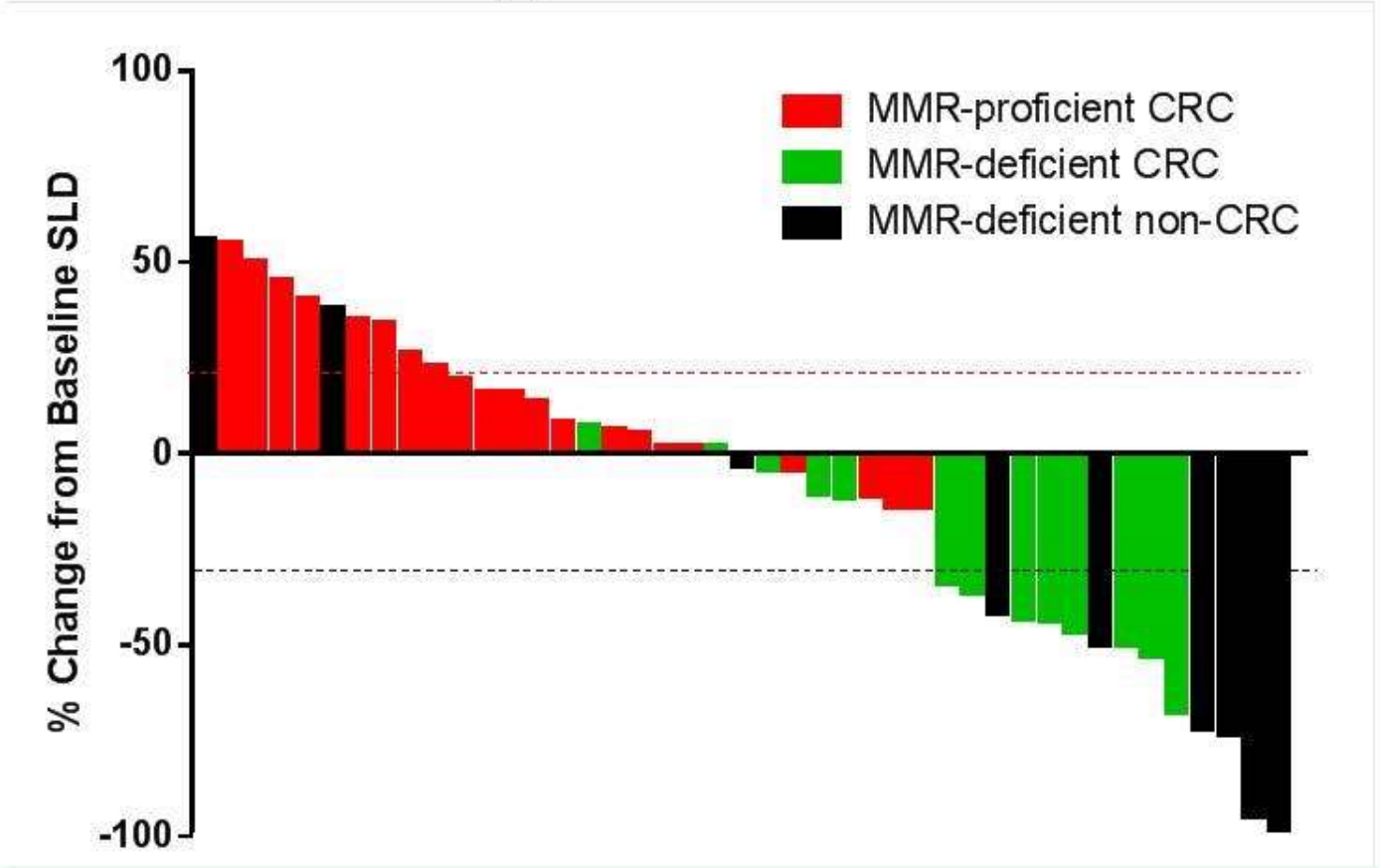
PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Dung Le, Jennifer Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Andrew Skora, Brandon Luber, Nilofer Azad, Daniel Laheru, Barbara Biedrzycki, Ross Donehower, Atif Zaheer, George Fisher, Todd Crocenzi, Steven Duffy, James Lee, Richard Goldberg, Albert de la Chapelle, Minori Koshiji, Feriyl Bhaijee, Thomas Huebner, Ralph Hruban, Laura Wood, Nathan Cuka, Drew Pardoll, Nickolas Papadopoulas, Kenneth Kinzler, Shibin Zhou, Toby Cornish, Janis Taube, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA
Ohio State University Comprehensive Cancer Center, Columbus, OH
Merck & Co., Inc., Kenilworth, NJ

PRESENTED AT: ASCO Annual '15 Meeting

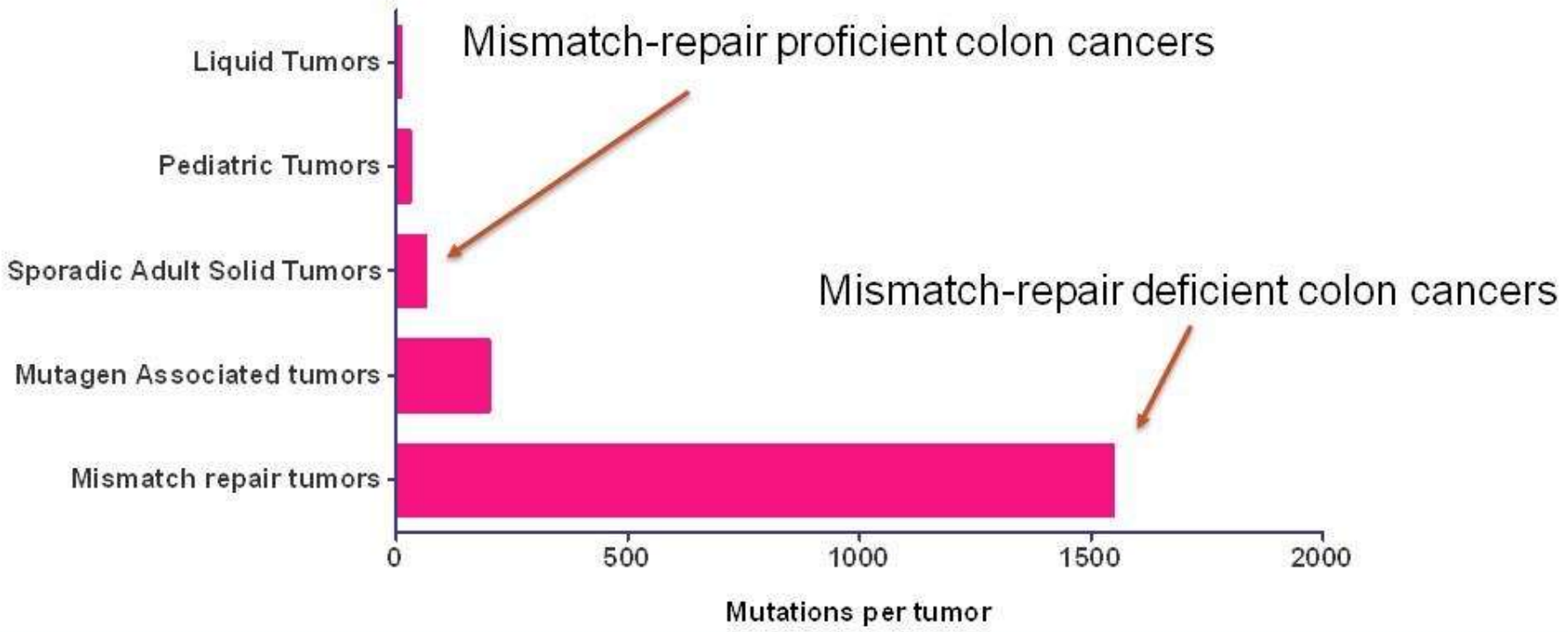
Target Lesions



Colorectal cancer - Nivolumab

- August 2017
- in dMMR/ MSI-H metastatic colorectal cancer (mCRC)
- Refractory to fluoropyrimidine, oxaliplatin, and irinotecan
- Check-Mate 142 trial, a phase II trial in which patients received nivolumab 3 mg/kg every 2 weeks and were stratified by PD-L1 < 1% and PD-L1 ≥ 1%.
- primary endpoint was ORR per RECIST 1.1.
- Of the 74 patients enrolled, 23 patients (31%) achieved ORR irrespective of PD-L1 levels
- Nivolumab-related grade ≥ 3 Aes occurred in 12% of patients, most commonly fatigue, diarrhea, and pruritus.

Mutations per tumor



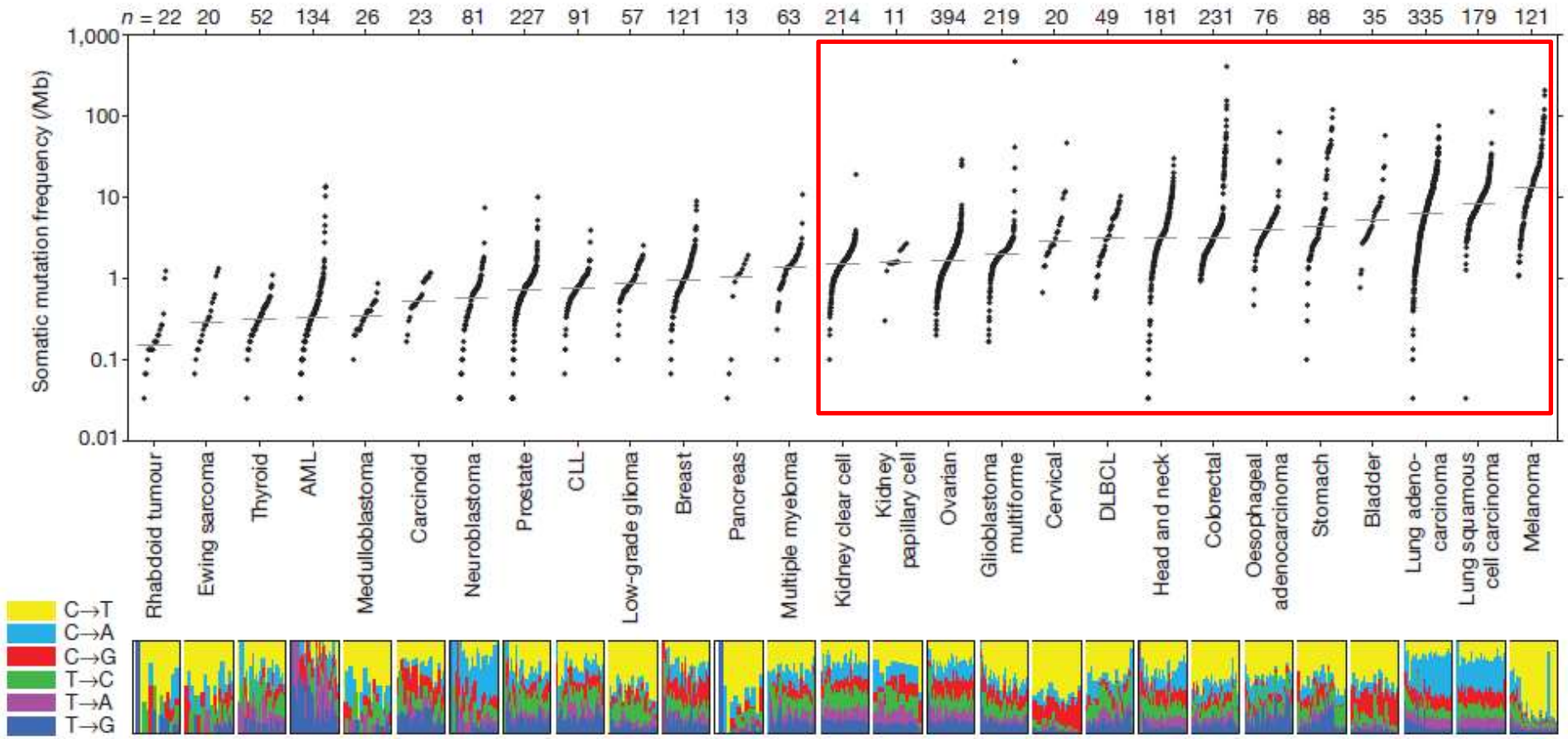


Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs. Each dot corresponds to a tumour–normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated. Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

“This is an important first for the cancer community,” said Richard Pazdur, M.D., acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research and director of the FDA’s Oncology Center of Excellence. “Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor’s biomarker without regard to the tumor’s original location.”

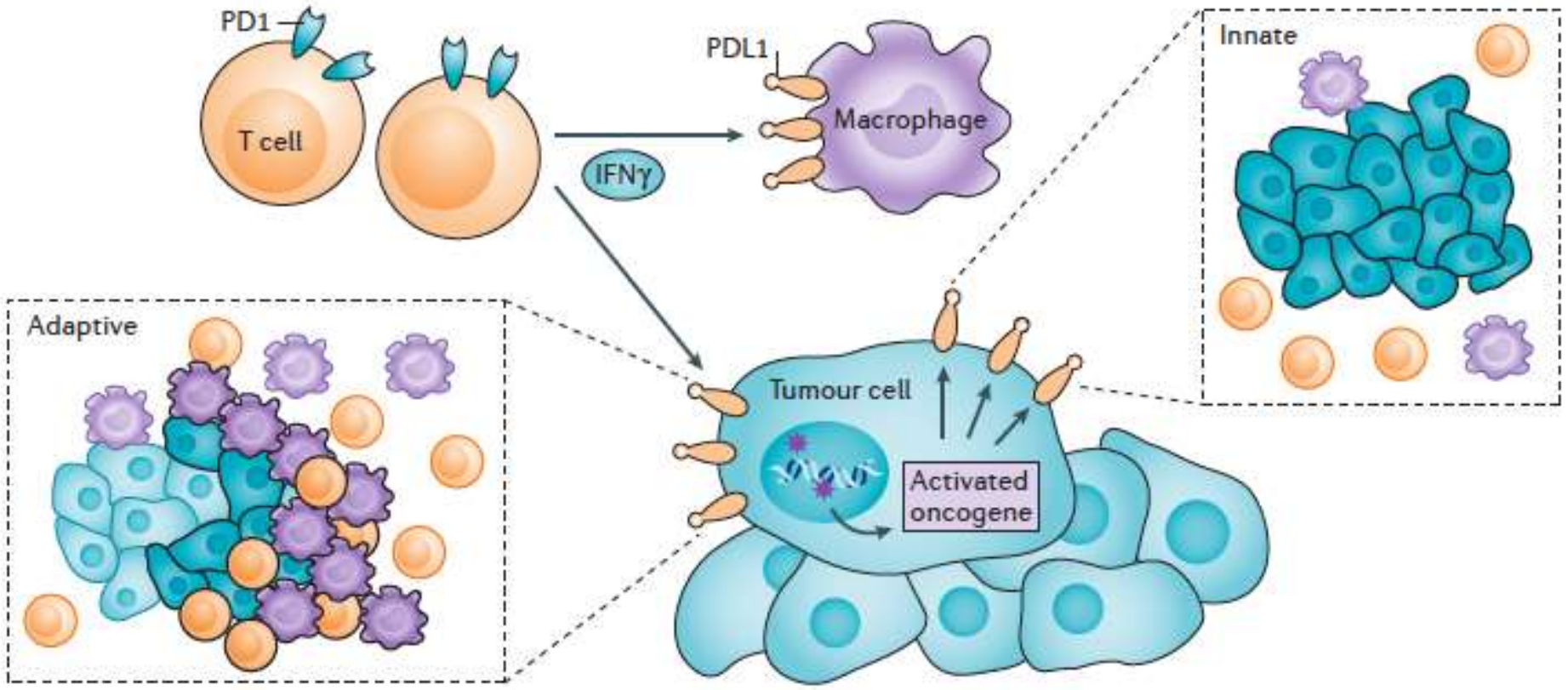
Table 3: The frequency of microsatellite instability (MSI-H) in each gastrointestinal cancer

Cancer	Frequency of MSI-H
Colorectal cancer	12-17 %
Gastric cancer	8-37 %
Hepatocellular carcinoma	0-18 %
Pancreatic cancer	0-13 %
Intrahepatic cholangiocarcinoma	10 %
Gallbladder cancer	0-42 %
Ampullary carcinoma	0-22 %

Yuza et al, Oncotarget 2017

Welche weiteren Marker sind relevant ?

PD-L1 expression in tumors



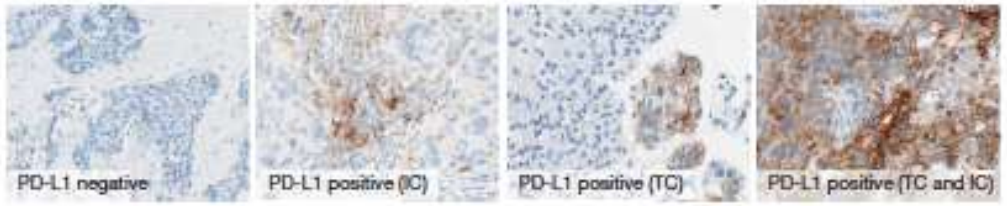
Topalian et al, Nat Rev Cancer 2016

not only PD-L1 on Tumor cells

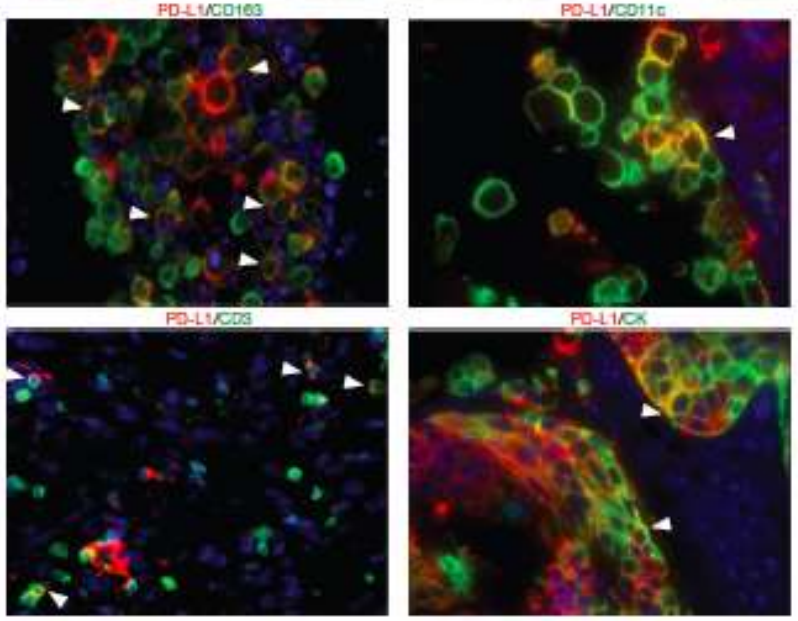
a PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

Indication	*n*	Percentage of PD-L1 positive (IC)	Percentage of PD-L1 positive (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric cancer	141	18	5
CRC	77	35	1
Pancreatic cancer	83	12	4

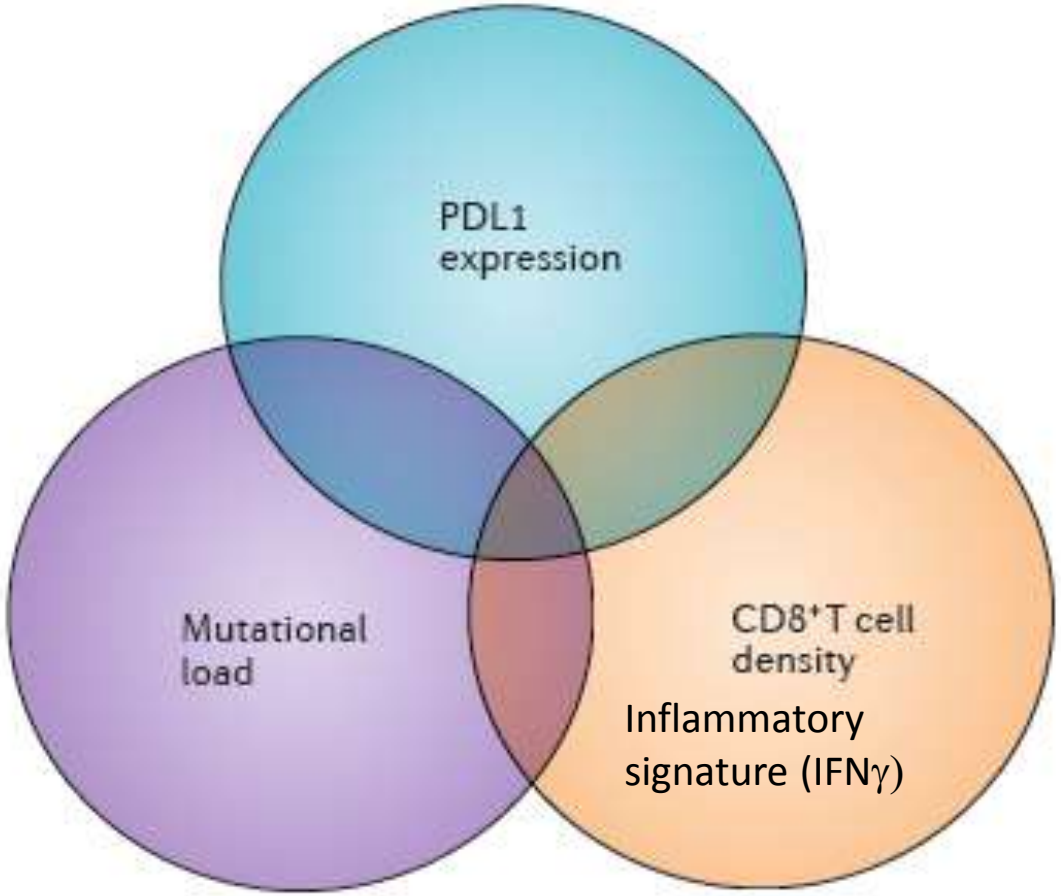
b



c

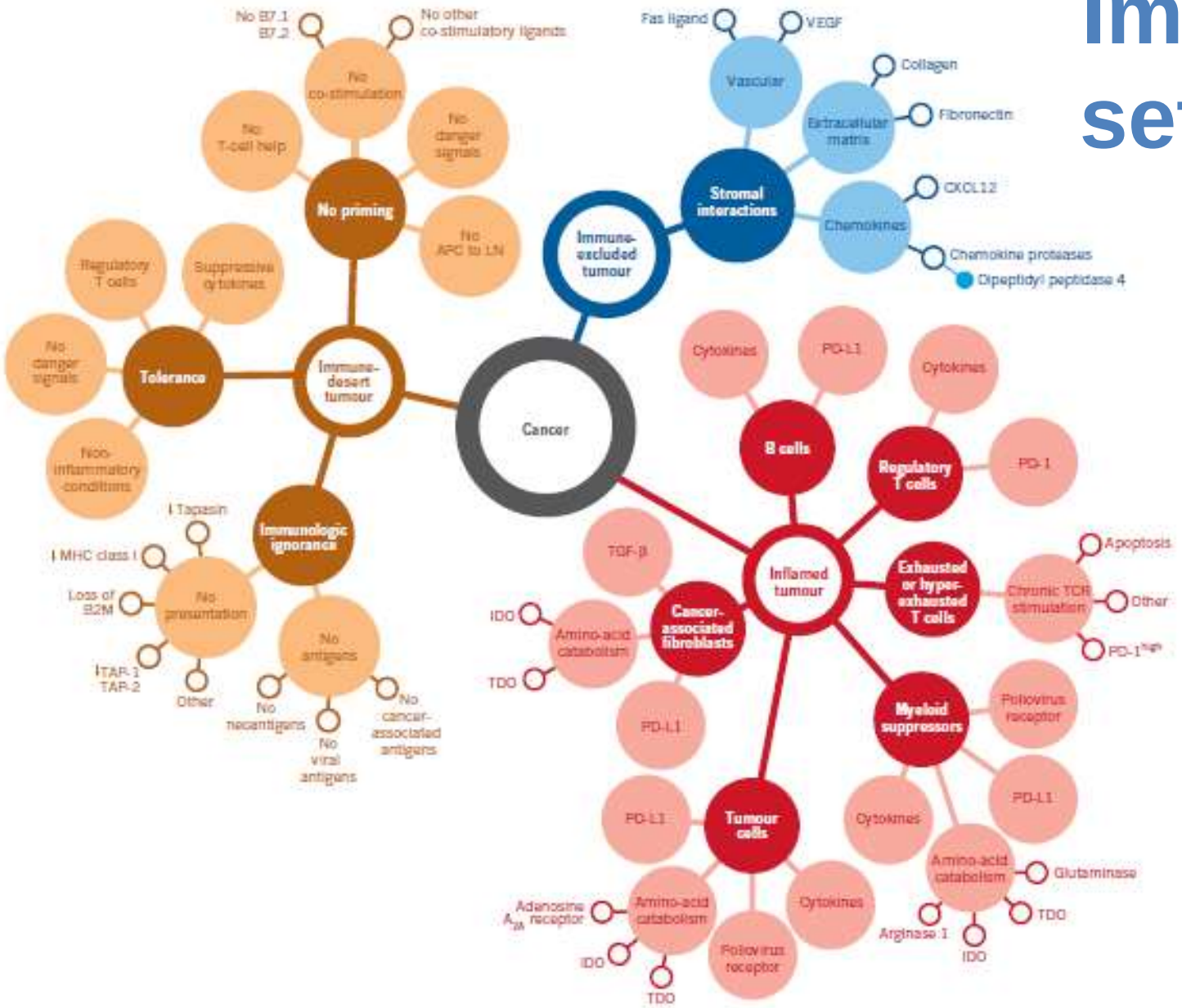


Predictive factors for efficacy of PD1 / PD-L1 blockade



modified Topalian et al, Nat Rev Cancer 2016

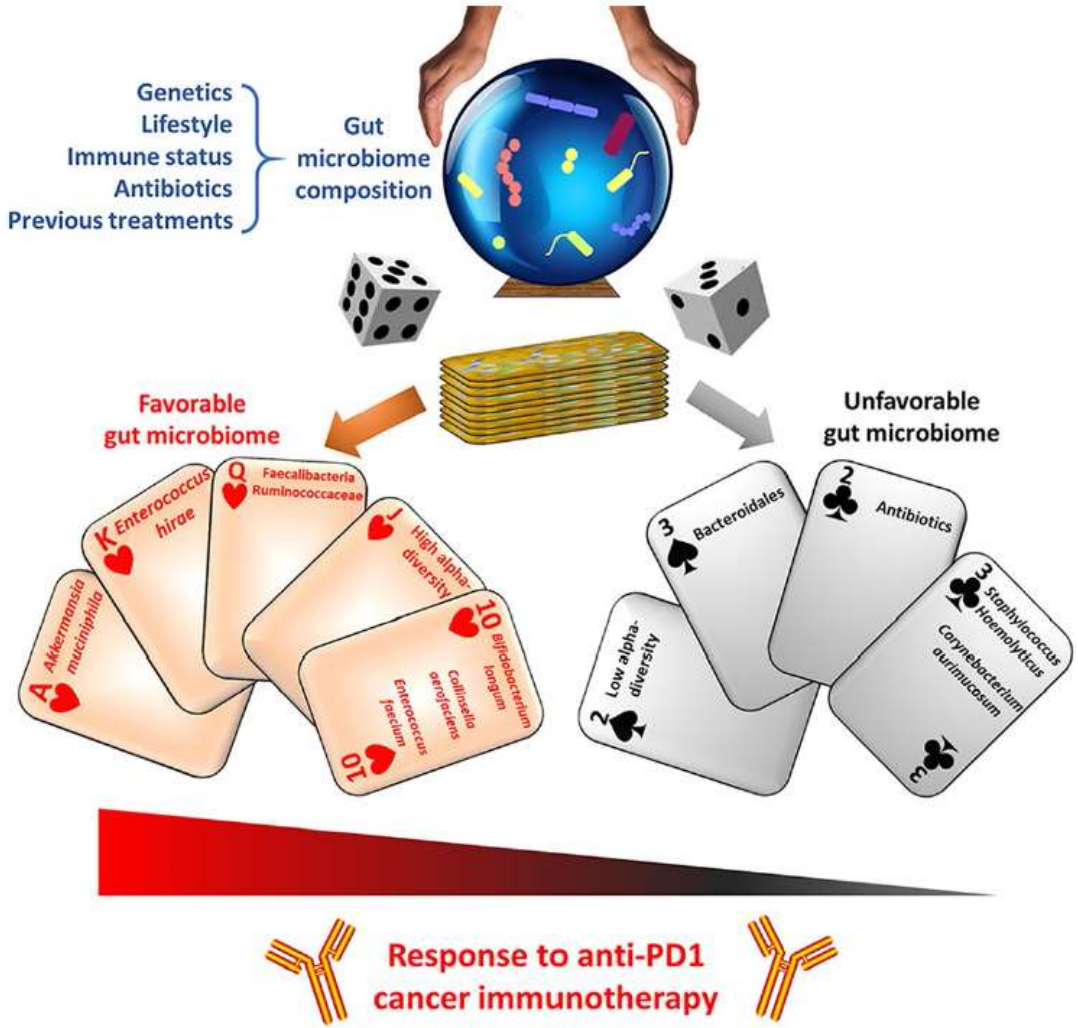
Immune set point



Chen and Mellman, Nature 2017

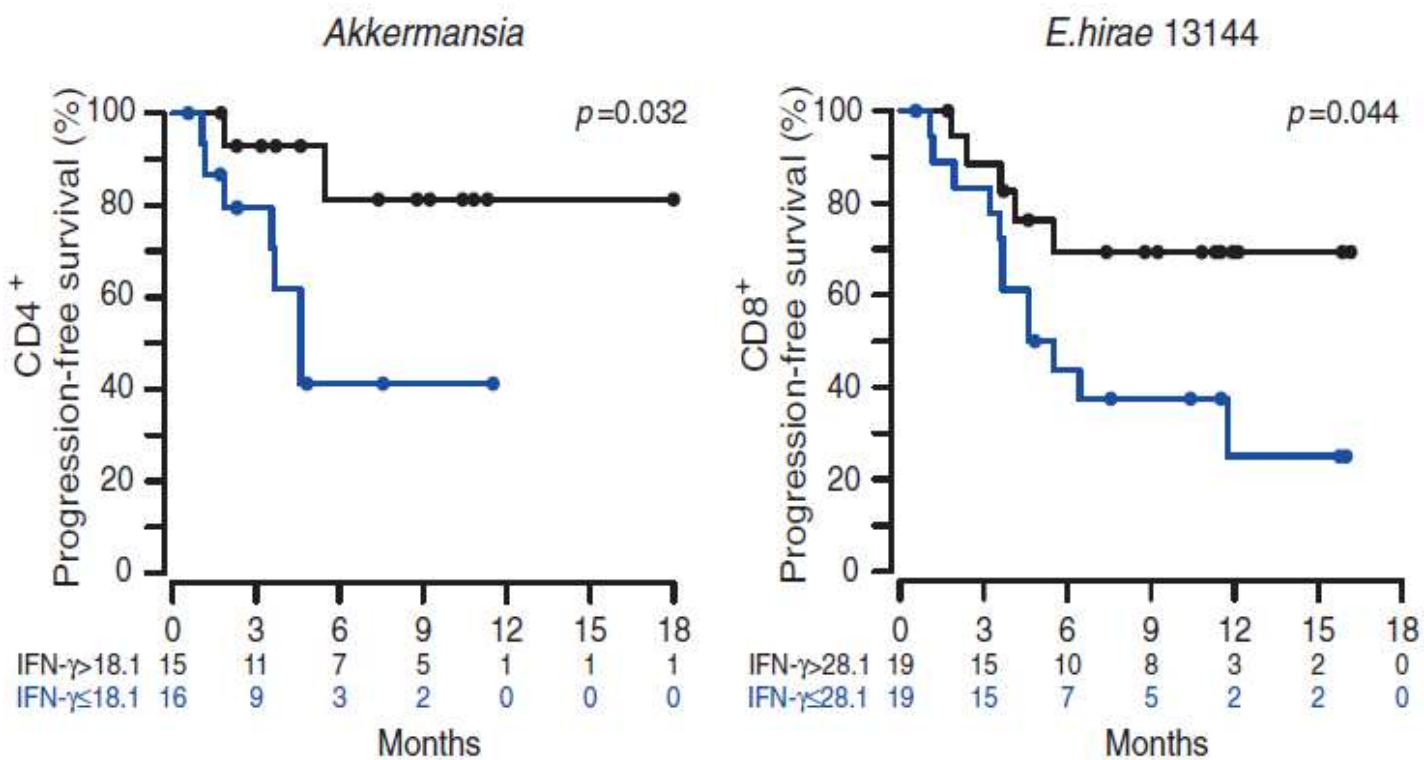
Science Jan 2018

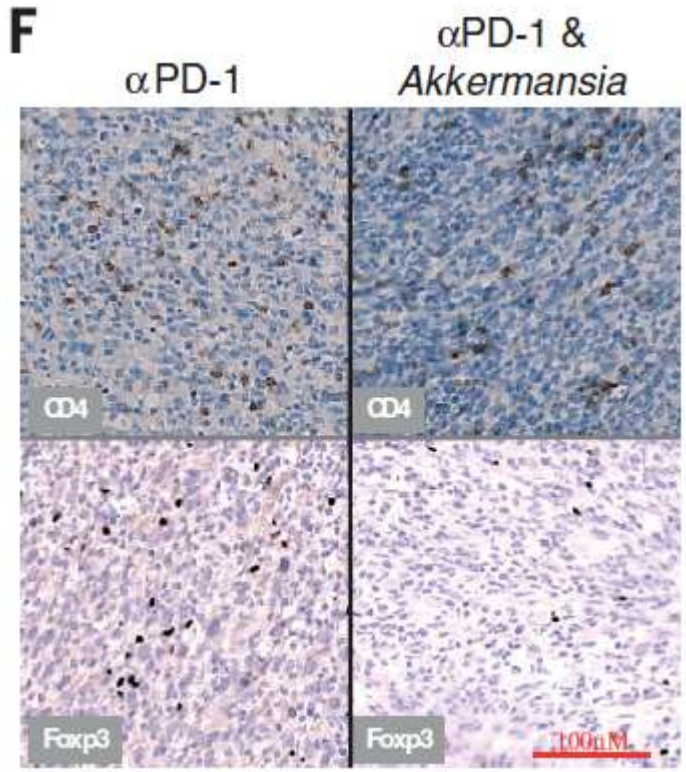
Anti-PD1 in the wonder-gut-land



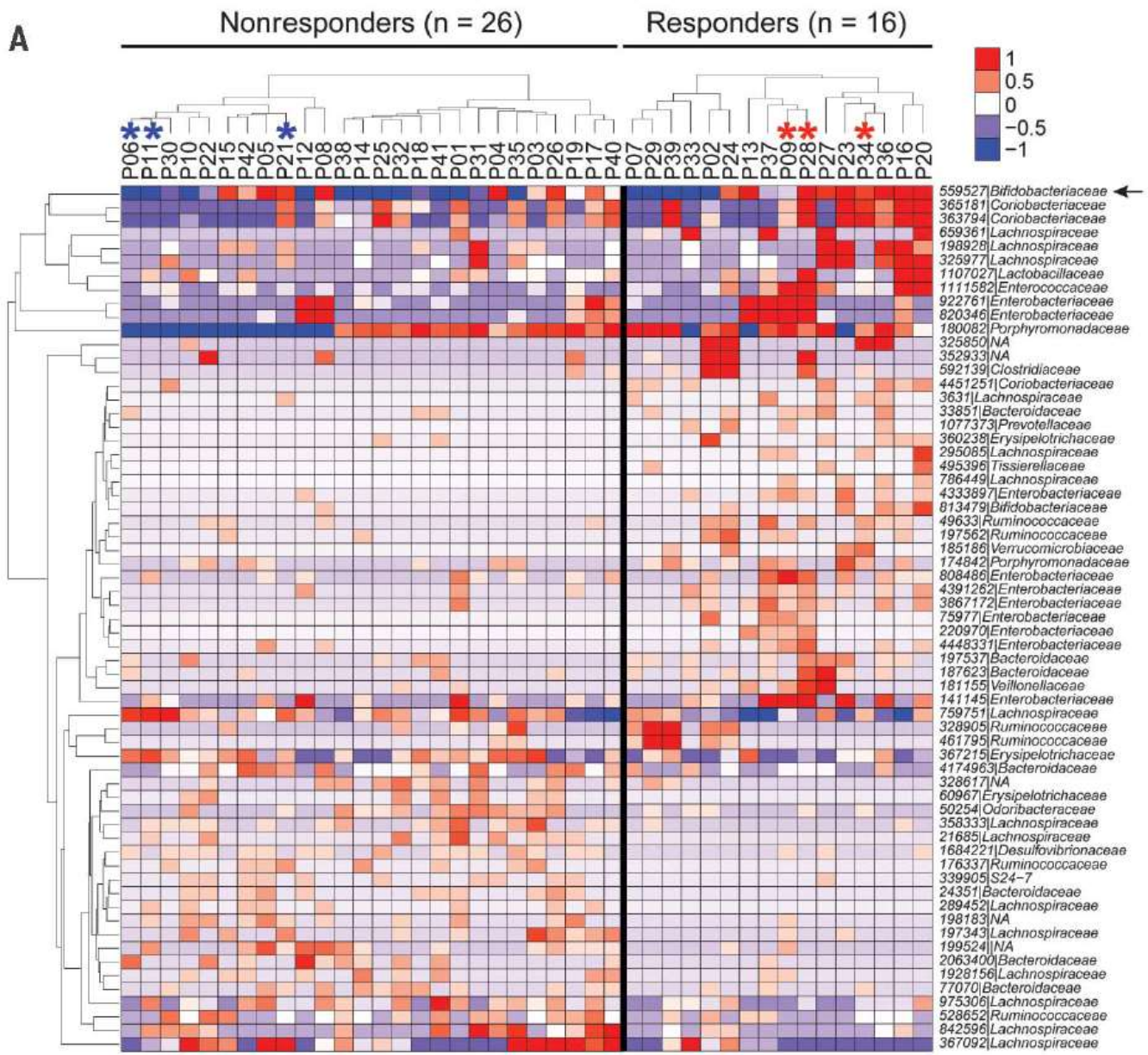
CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors





Bei Neurodermitis, Allergien vermindert



Gopalakrishnan *et al.*, *Science* **359**, 97–103 (2018)

CANCER IMMUNOTHERAPY

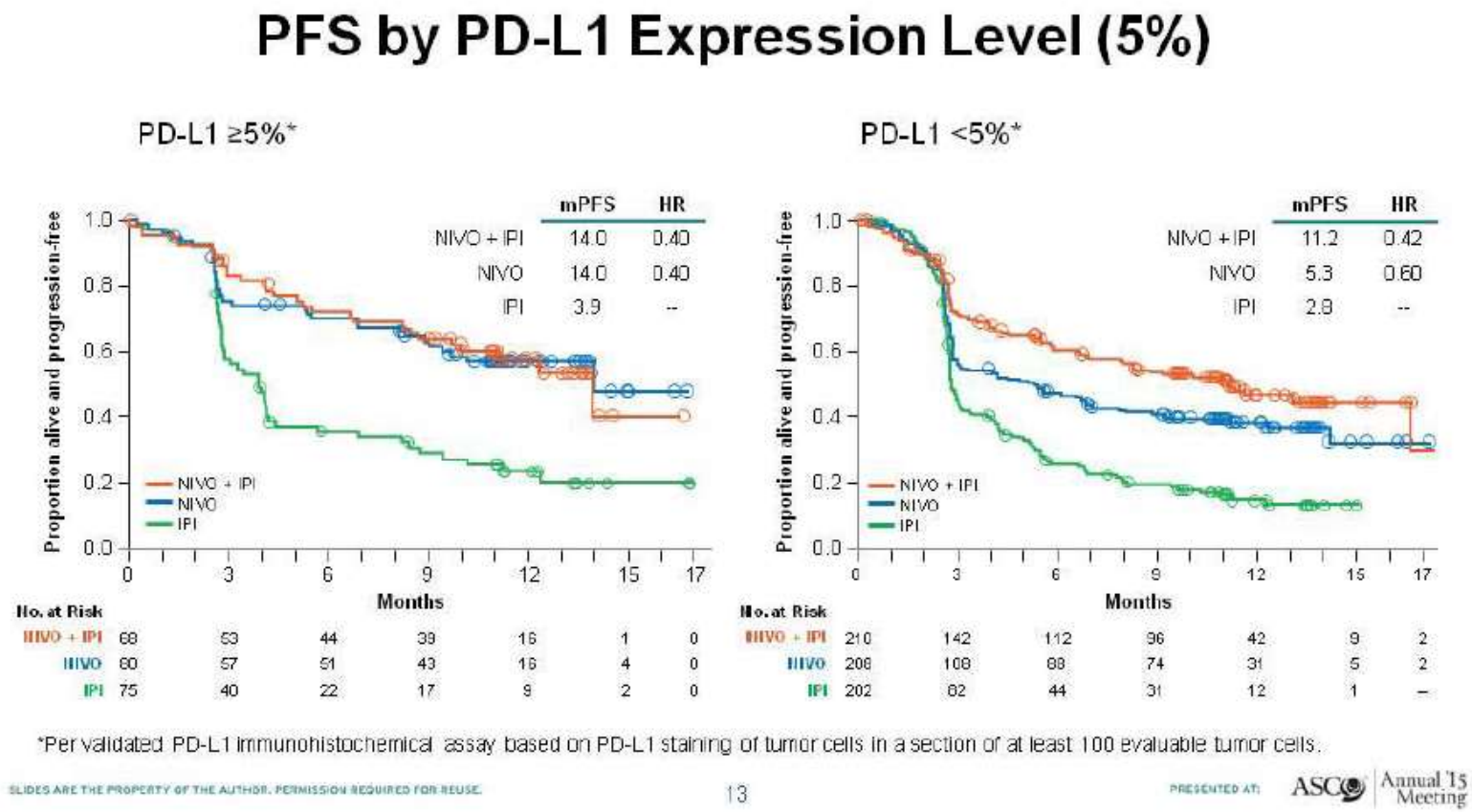
Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

Our results indicate that the gut microbiome may modulate responses to anti–PD-1 immunotherapy in melanoma patients. We propose that patients with a favorable gut microbiome (for example, high diversity and abundance of Ruminococcaceae and Faecalibacterium) have enhanced systemic and antitumor immune responses mediated by increased antigen presentation and improved effector T cell function in the periphery and the tumor microenvironment. By contrast, patients with an unfavorable gut microbiome (for example, low diversity and high relative abundance of Bacteroidales) have impaired systemic and antitumor immune responses mediated by limited intratumoral lymphoid and myeloid infiltration and weakened antigen presentation capacity. These findings highlight the therapeutic potential of modulating the gutmicrobiome in patients receiving checkpoint blockade immunotherapy andwarrant prompt evaluation in cancer patients through clinical trials.

Gopalakrishnan *et al.*, *Science* **359**, 97–103 (2018)

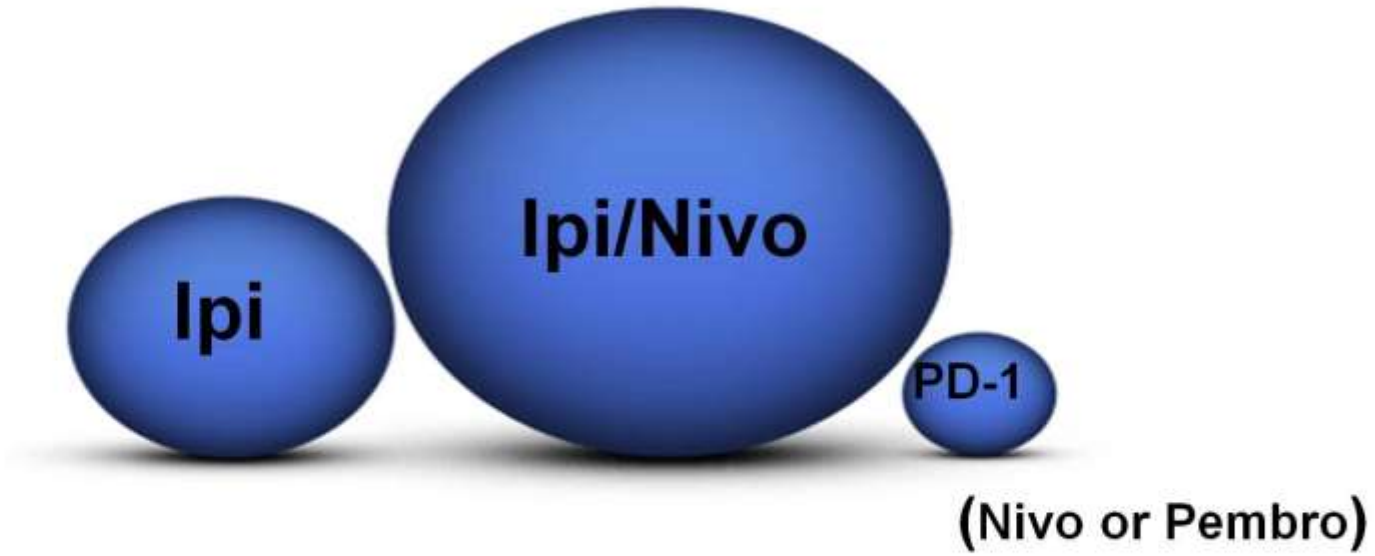
Toxicity

Melanoma Immuncheckpoint combination - PD-L1 expression -



Presented By Jedd Wolchok at 2015 ASCO Annual Meeting

Immune Adverse Events
Autoimmune Toxicities- On target



Immune Related Toxicity

- Mechanism Based
- May Be Severe and Life Threatening
- Time Limited and Reversible
- Highly Corticosteroid Responsive

Nebenwirkungen

GASTROINTESTINALE NEBENWIRKUNGEN, wie z. B.:
- Durchfall
- Bauchschmerzen
- Blut im Stuhl
- Darmperforation
- Peritoneale Zeichen
- Ileus

HEPATISCHE NEBENWIRKUNGEN / VERÄNDERUNGEN DER LABORWERTE, wie z. B.:
- Erhöhung der Leberwerte (z. B. AST, ALT oder Gesamtbilirubin)

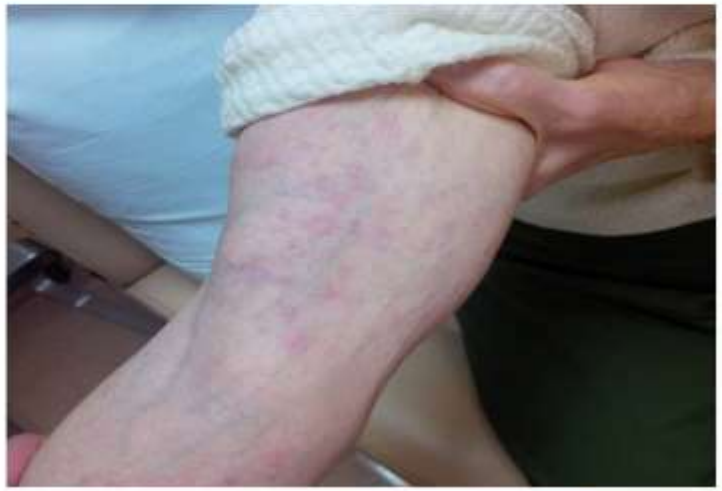
DERMATOLOGISCHE NEBENWIRKUNGEN, wie z. B.:
- Juckreiz
- Rash

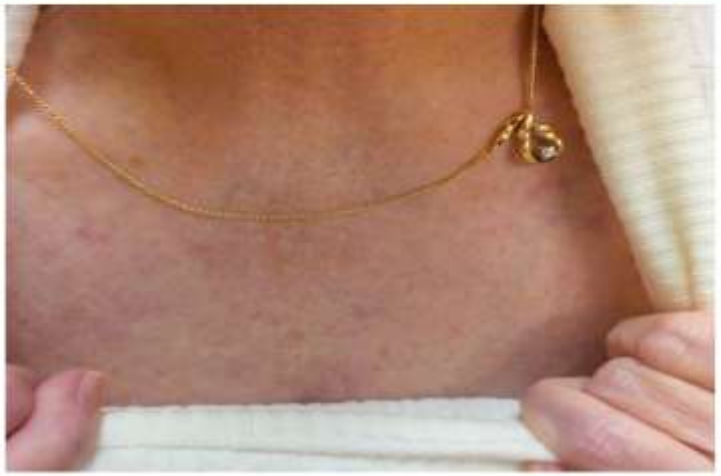
NEUROLOGISCHE NEBENWIRKUNGEN, wie z. B.:
- Unilaterale oder bilaterale Muskelschwäche
- Sensorische Veränderungen
- Parästhesie

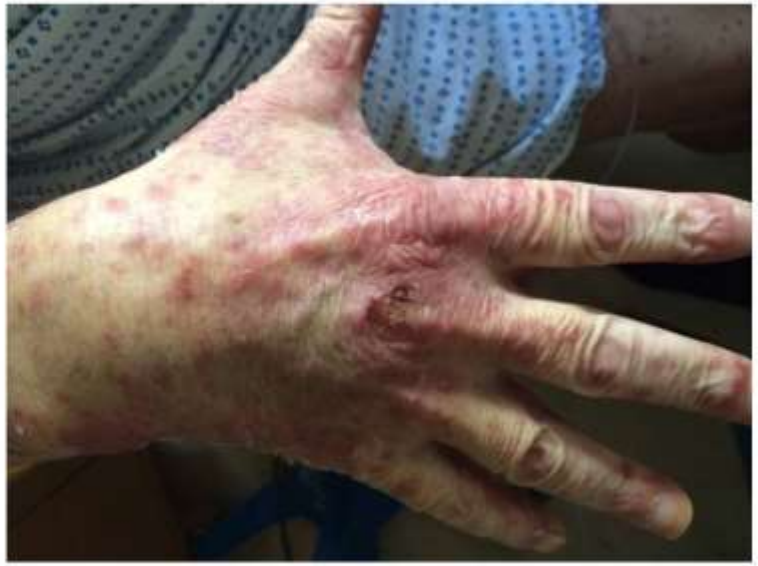
ENDOKRINE NEBENWIRKUNGEN, wie z. B.:
- Müdigkeit
- Kopfschmerzen
- Veränderungen der psychischen Verfassung
- Bauchschmerzen
- Ungewöhnliche Stuhlgewohnheiten
- Hypotonie
- Auffällige Ergebnisse bei Schilddrüsen-Funktionstests und/oder Serumchemie

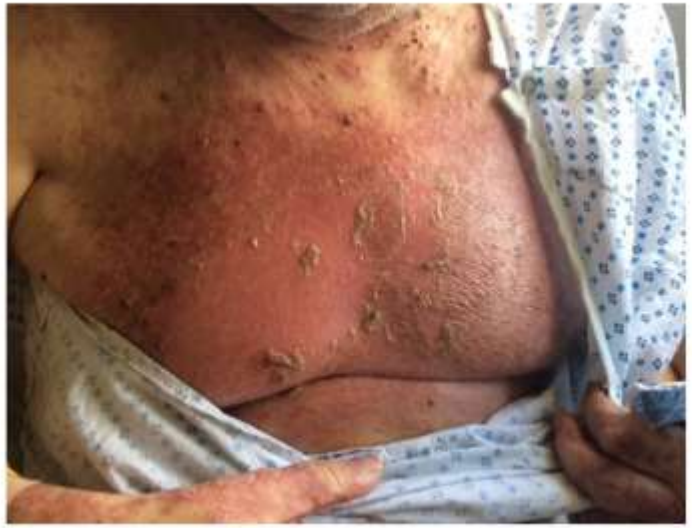
SONSTIGE IMMUNVERMITTELTE NEBENWIRKUNGEN
- Uveitis, Iritis oder Konjunktivitis
- Amylase- und/oder Lipaseerhöhung
- Eosinophilie, hämolytische Anämie
- Glomerulonephritis, Pneumonitis
- Multiorganversagen
- Thyreoiditis
- Sarkoidose
- Vitiligo

Rash



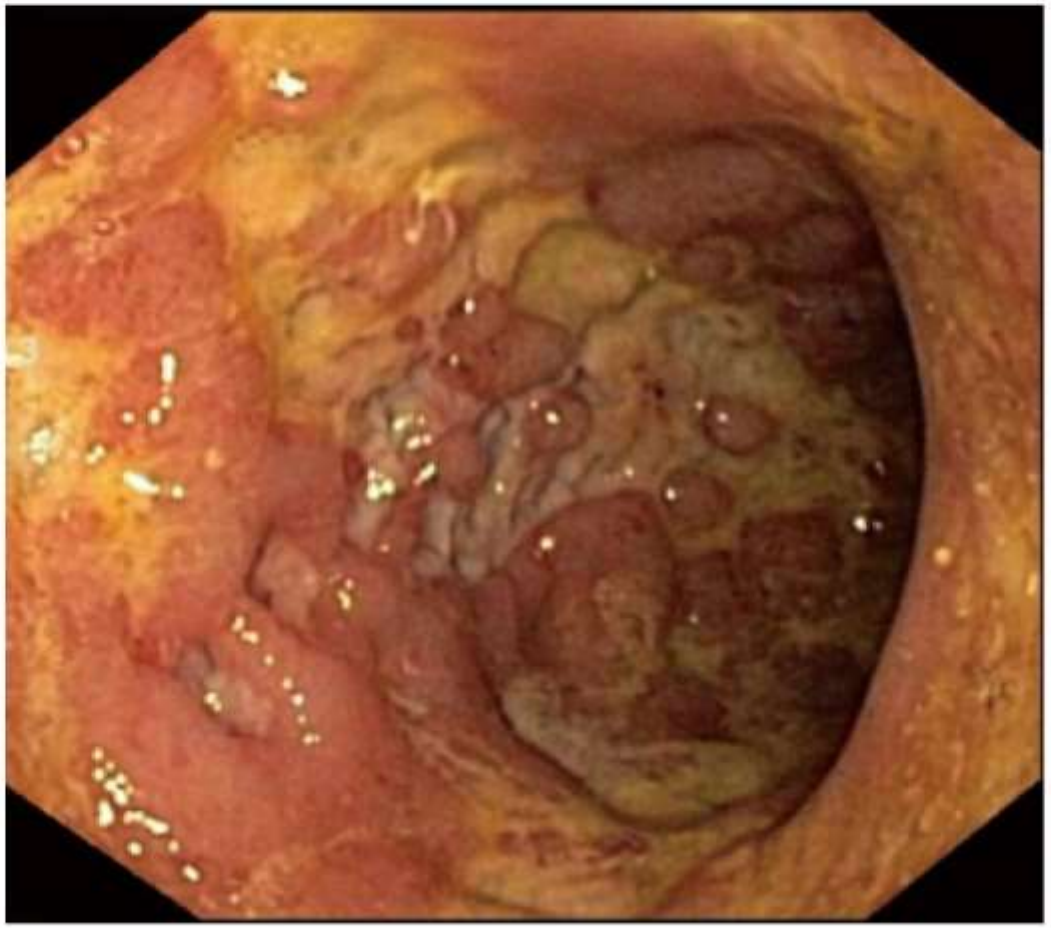






Postow

Diarrhea and Colitis



Postow

Slangen et al., *World J Gastrointest Pharmacol Ther,* 2013

Diarrhea/Colitis Management

1. Stools < 4X baseline: imodium, budesonide

2. Stools < 7X baseline: 1mg/kg of prednisone

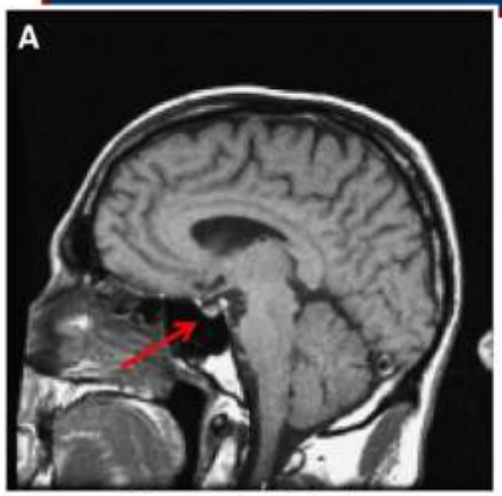
3. Stools > 7X baseline or refractory to oral steroids:
    1. Hospitalize for IV solumedrol 1-2mg/kg
    2. Consider colonoscopy and CT scan
    3. Consider infliximab 5mg/kg

Taper steroids slowly over at least several weeks and consider opportunistic infectious prophylaxis

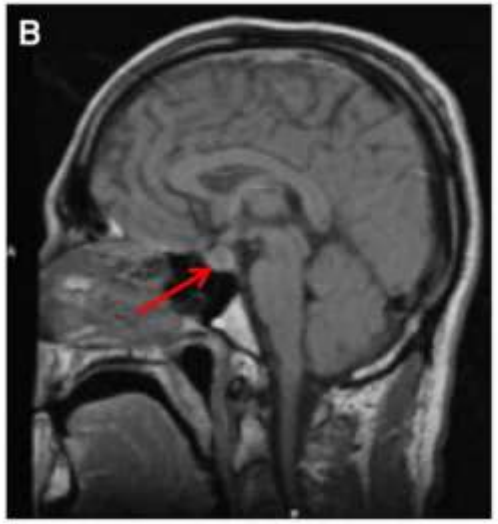
Liver toxicity

- Monitor liver function tests before each dose
- Rule out viral hepatitis, disease progression
- Treatment of mild elevation
  - Increase frequency of monitoring
- AST/ALT > 2.5-5x ULN or Bilirubin > 1.5-3x ULN
  - Hold treatment, increase monitoring
- ASLT/ALT > 5x ULN or Bilirubin > 3x ULN
  - Permanently discontinue, start steroids

Endocrinopathies and Hypophysitis



6/30/04 - Baseline (4.5 mm)



12/3/04 - Headache/fatigue (10.8 mm)

- Can present with severe HA
- Differential of HA includes CNS mets, bleed, Hypophysitis
- MRI with pituitary cuts
- Monitor TSH before each dose
- Treat with high dose steroids if HA, hormone replacement as indicated
- Consultation with endocrinology
- Pituitary dysfunction may be reversible or permanent

Weber JCO 2012

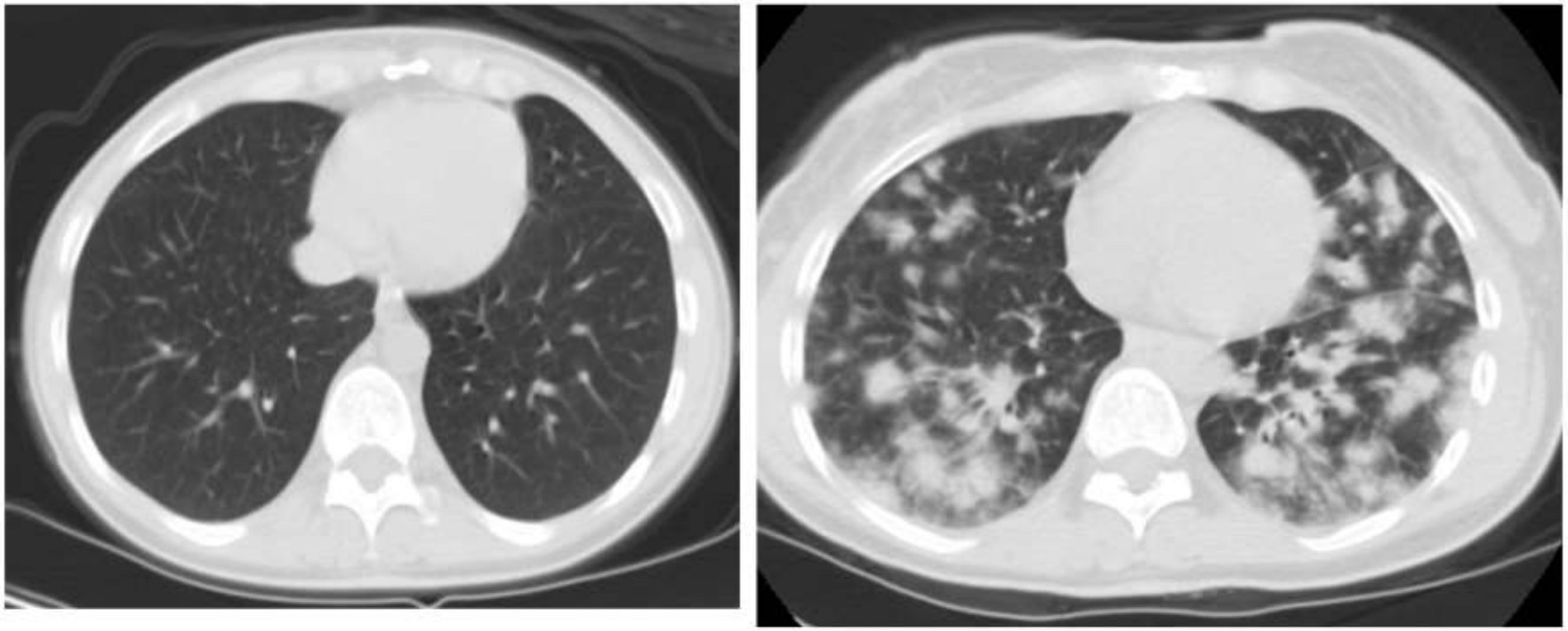
Endocrinopathy Management

1. Replace the missing hormones
    1. Levothyroxine
    2. Hydrocortisone

2. Controversial whether higher doses of steroids during acute hypophysitis can prevent long-term pituitary dysfunction

3. Be aware of adrenal crisis

Pneumonitis

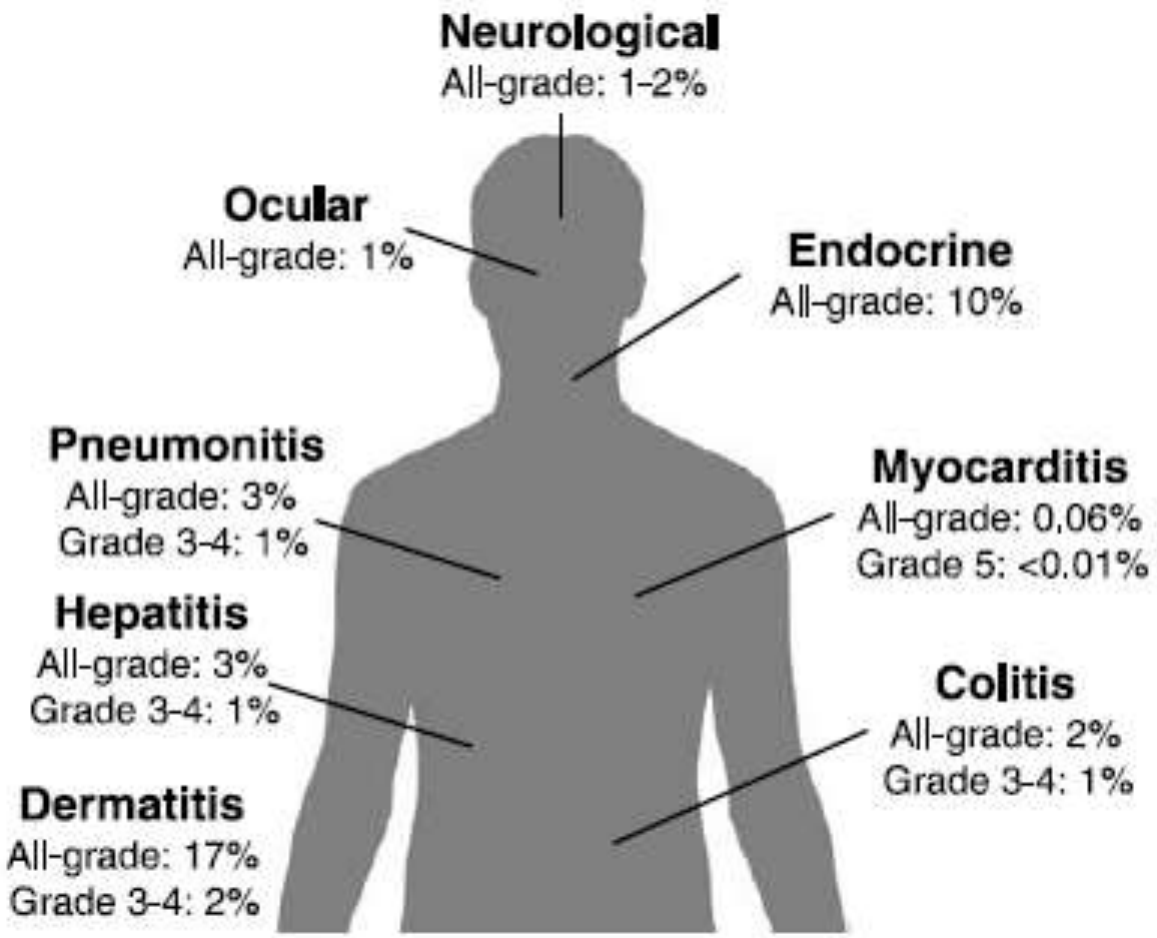


2/21/2011

3/30/2011

Two doses of ipilimumab and four of nivolumab

Immune related adverse events



ANNALS OF ONCOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Article Navigation

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up† FREE

J. B. A. G. Haanen, F. Carbonnel, C. Robert, K. M. Kerr, S. Peters, J. Larkin, K. Jordan, on behalf of the ESMO Guidelines Committee

Annals of Oncology, Volume 28, Issue suppl_4, 1 July 2017, Pa

Puzanov *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:95
DOI 10.1186/s40425-017-0300-z

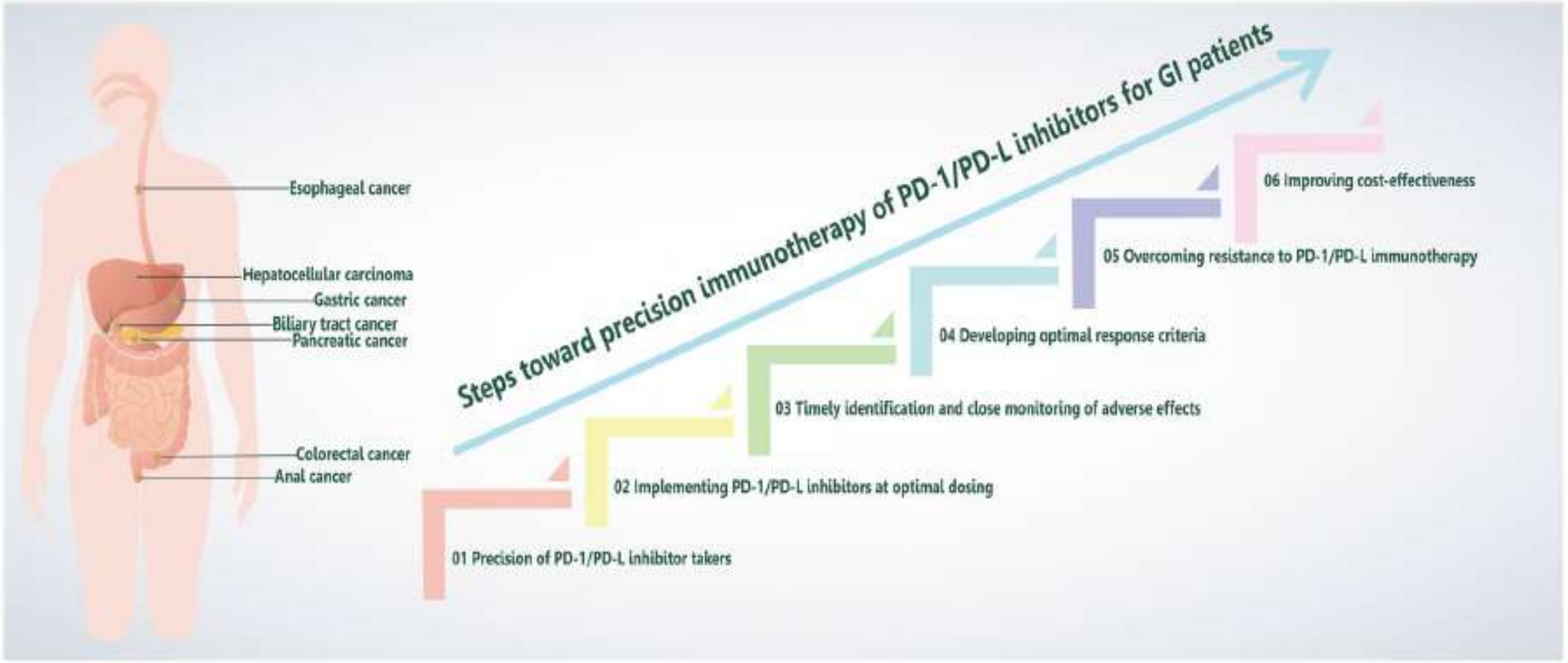
Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

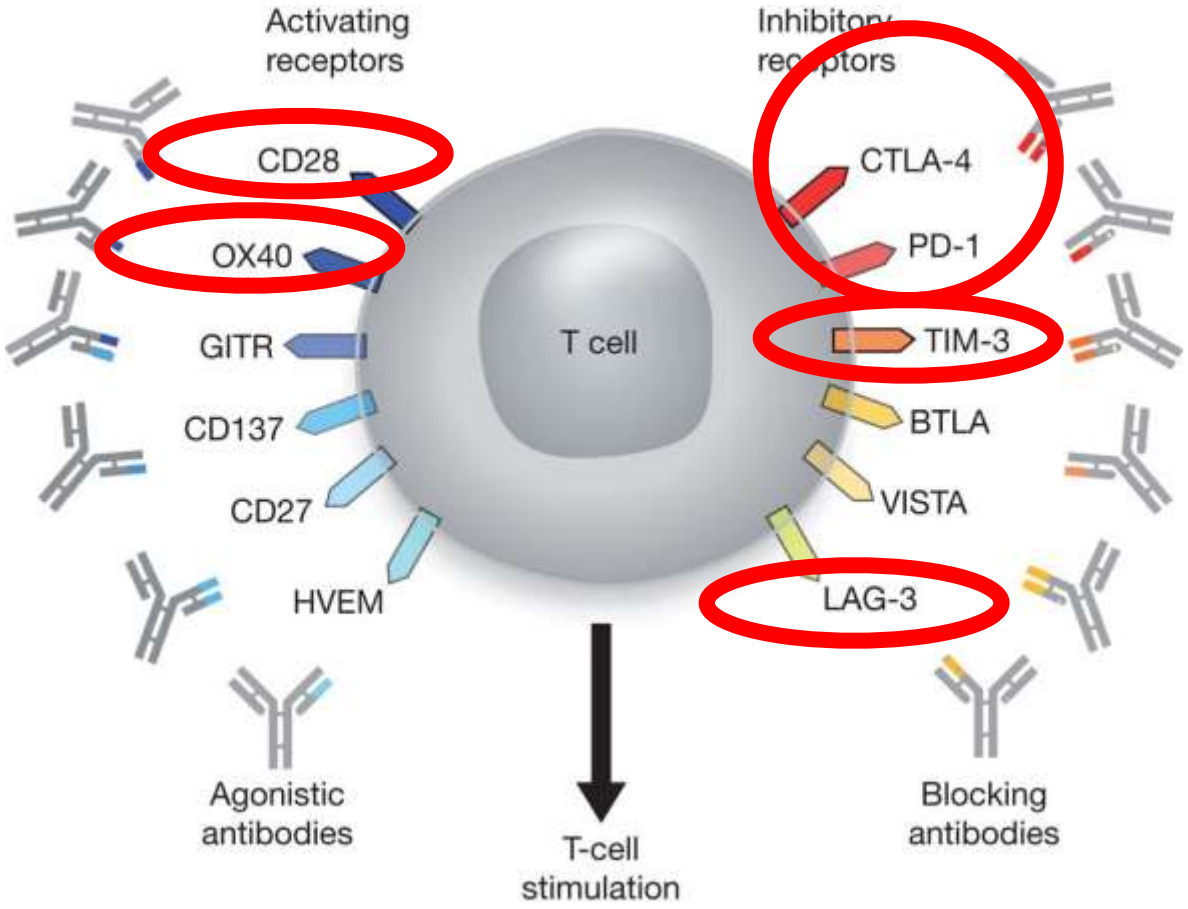
Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

What next ?

PERSPEKTIVE

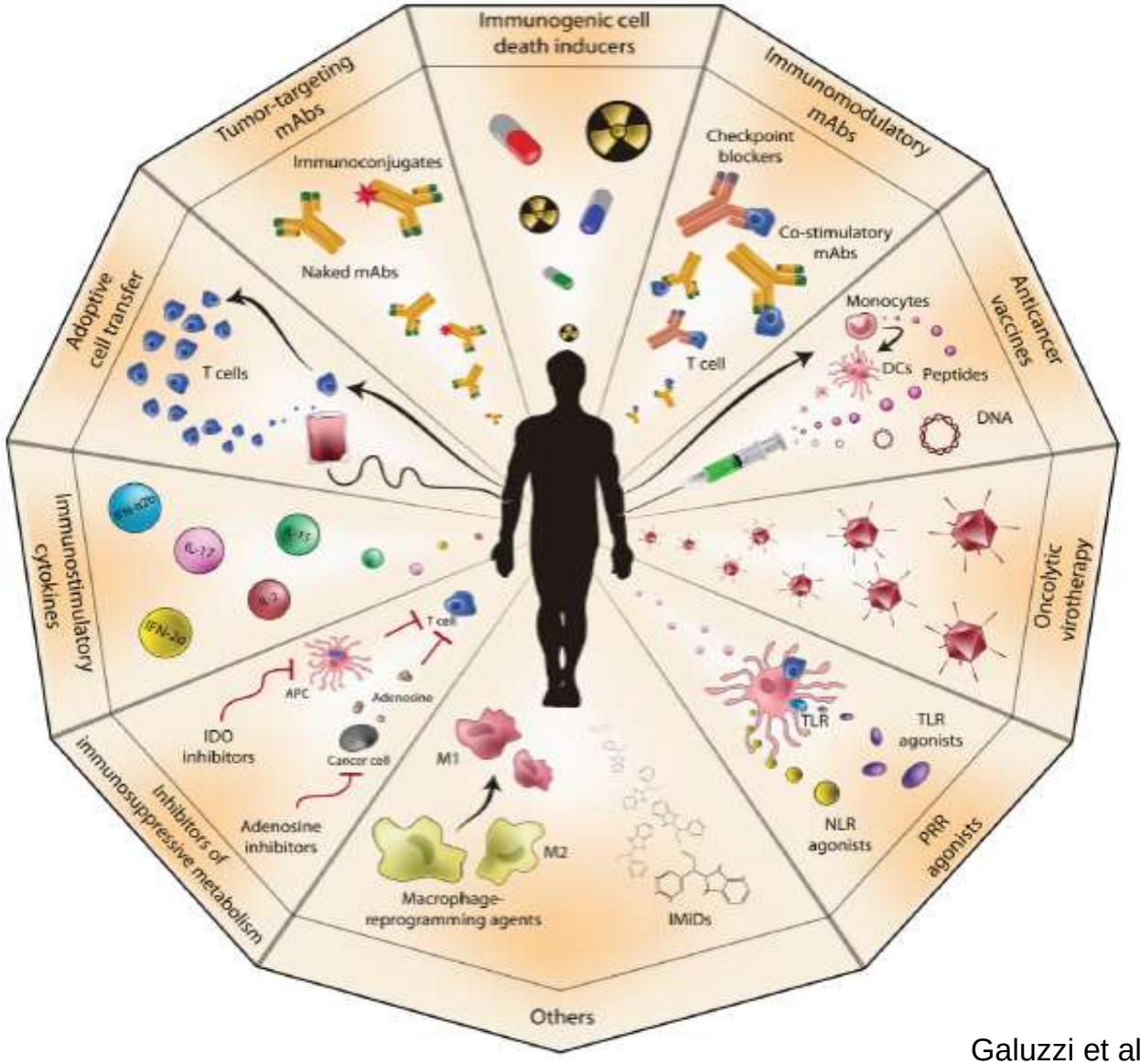


Immunoregulatory antibodies in early clinical testing



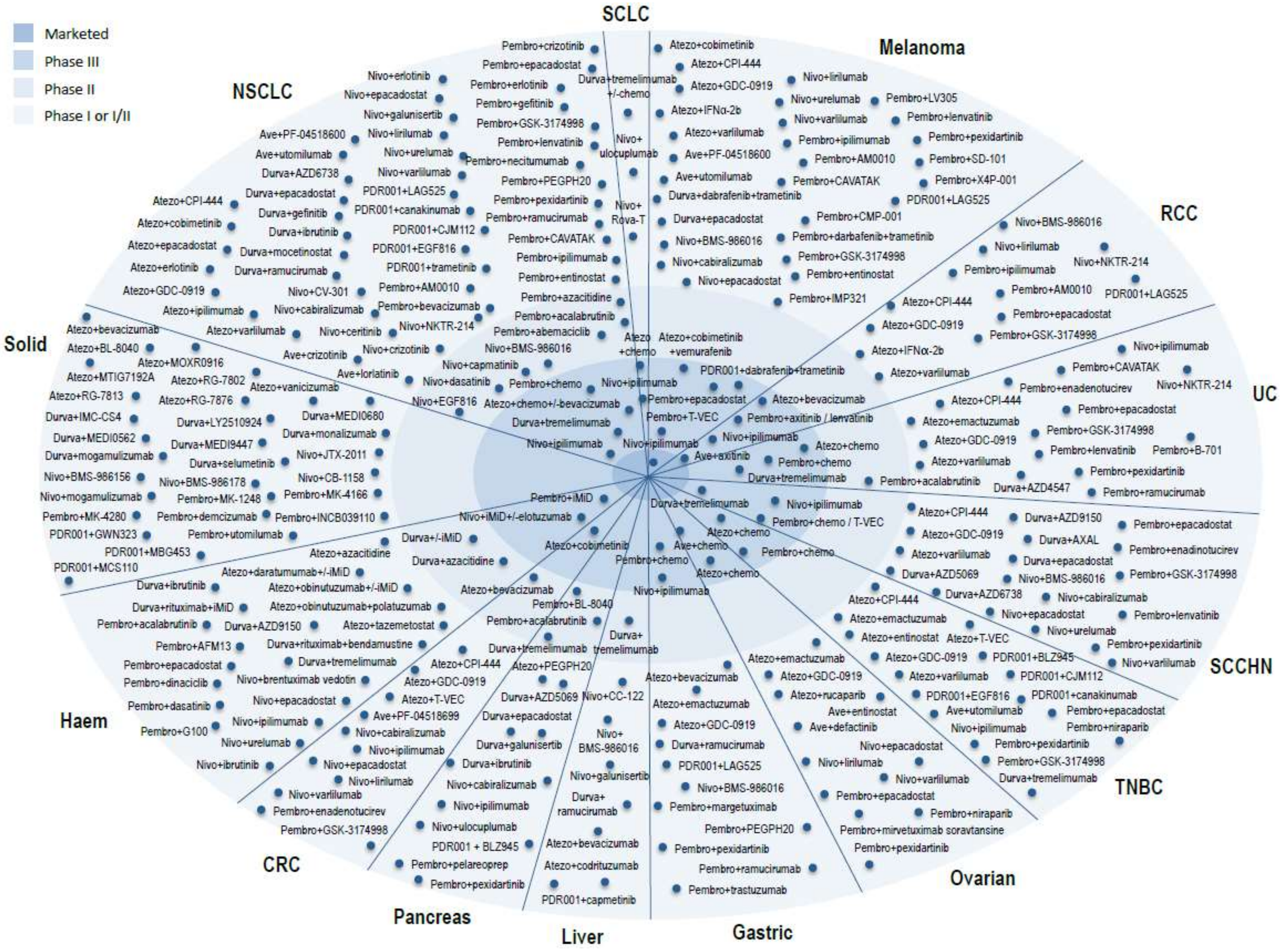
I Mellman *et al. Nature* 480, 480-489 (2011)

Anticancer Immunotherapy



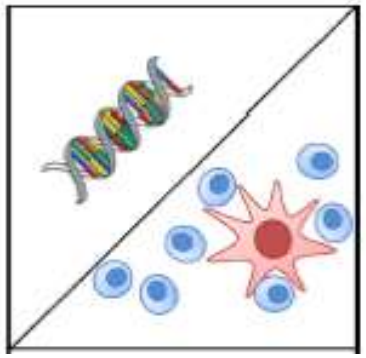
Galuzzi et al, Oncotarget 2014

Cancer immunotherapy-based combination studies underway in 2016.

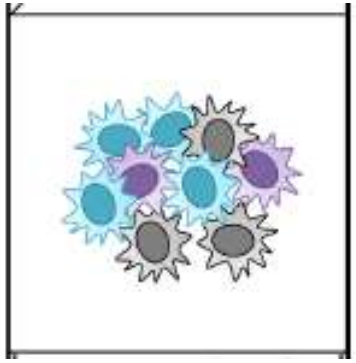


Chen and Mellman, Nature 2017

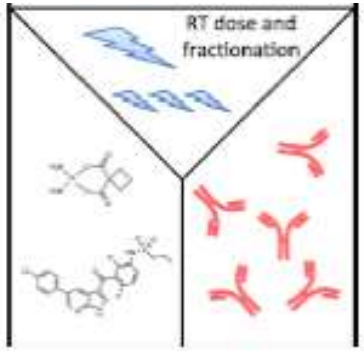
Biomarker identification



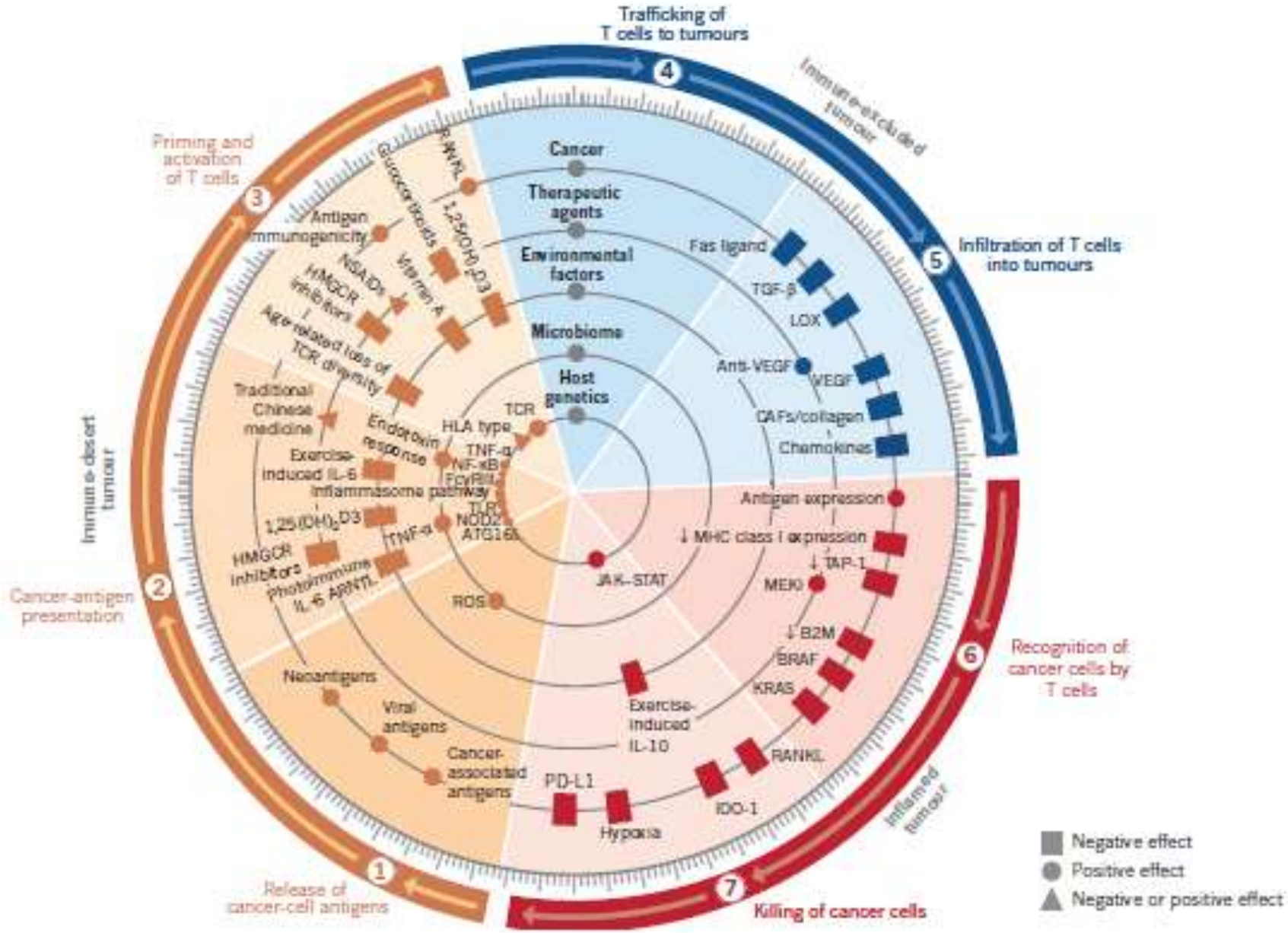
- Host



- Tumor



- Treatment characteristics



Chen and Mellman, Nature 2017

Immune related Adverse Events
- eine besondere interdisziplinäre Herausforderung-

Konsildienst und Register für IrAE

Med Klinik m.S. Hämatologie, Onkologie CBF
Comprehensive Cancer Center, Clinical Trials Unit

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Evaluation von irAE unter Checkpoint-Inhibition
mittels PRO-Fragebögen und Evaluation Biomarker

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