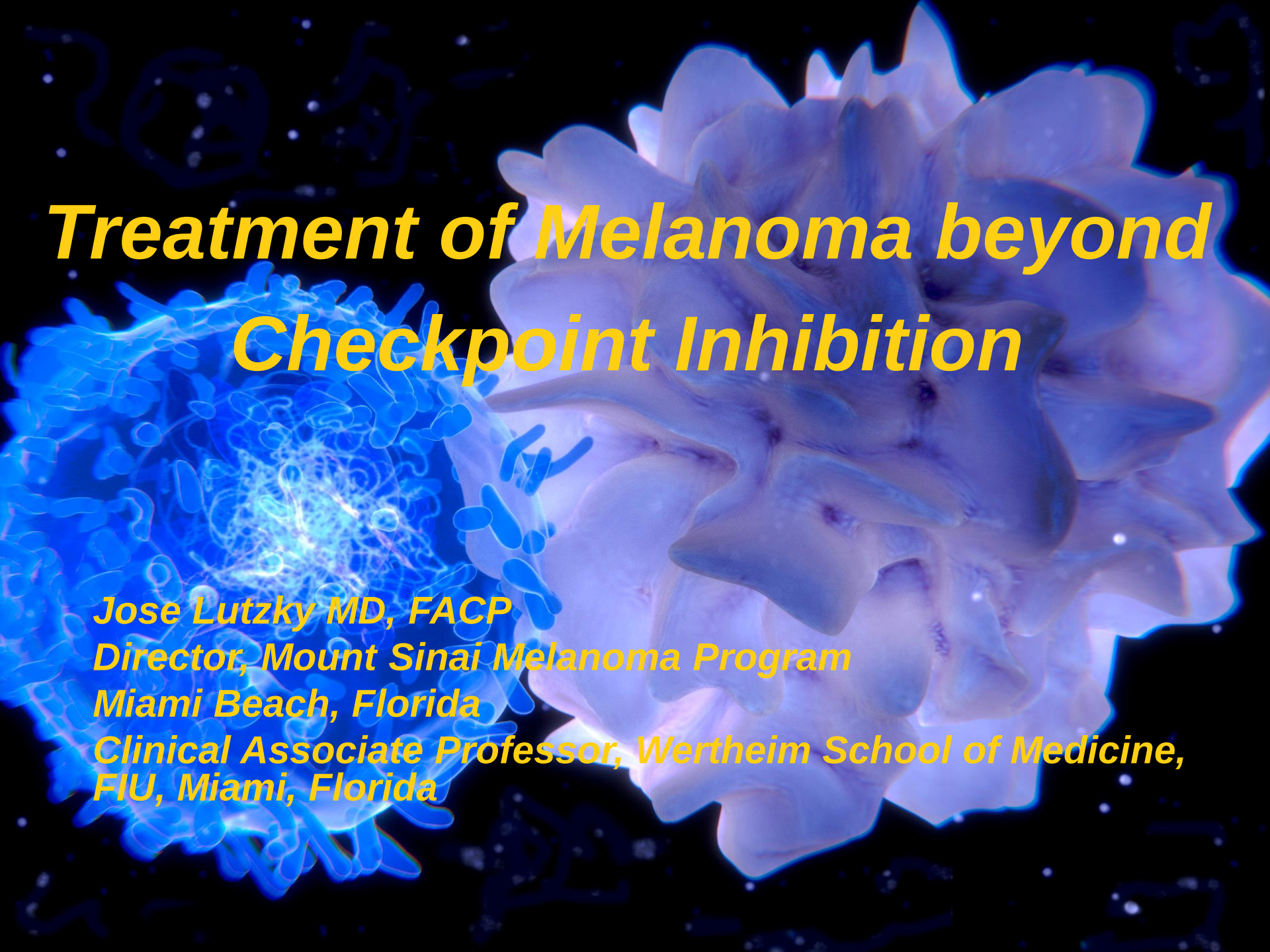

Treatment of Melanoma beyond Checkpoint Inhibition

Jose Lutzky MD, FACP
Director, Mount Sinai Melanoma Program
Miami Beach, Florida
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Jose Lutzky, MD

Treatment of Melanoma beyond Checkpoint Inhibition

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Array, Novartis, BMS
Speakers Bureau: Novartis, BMS

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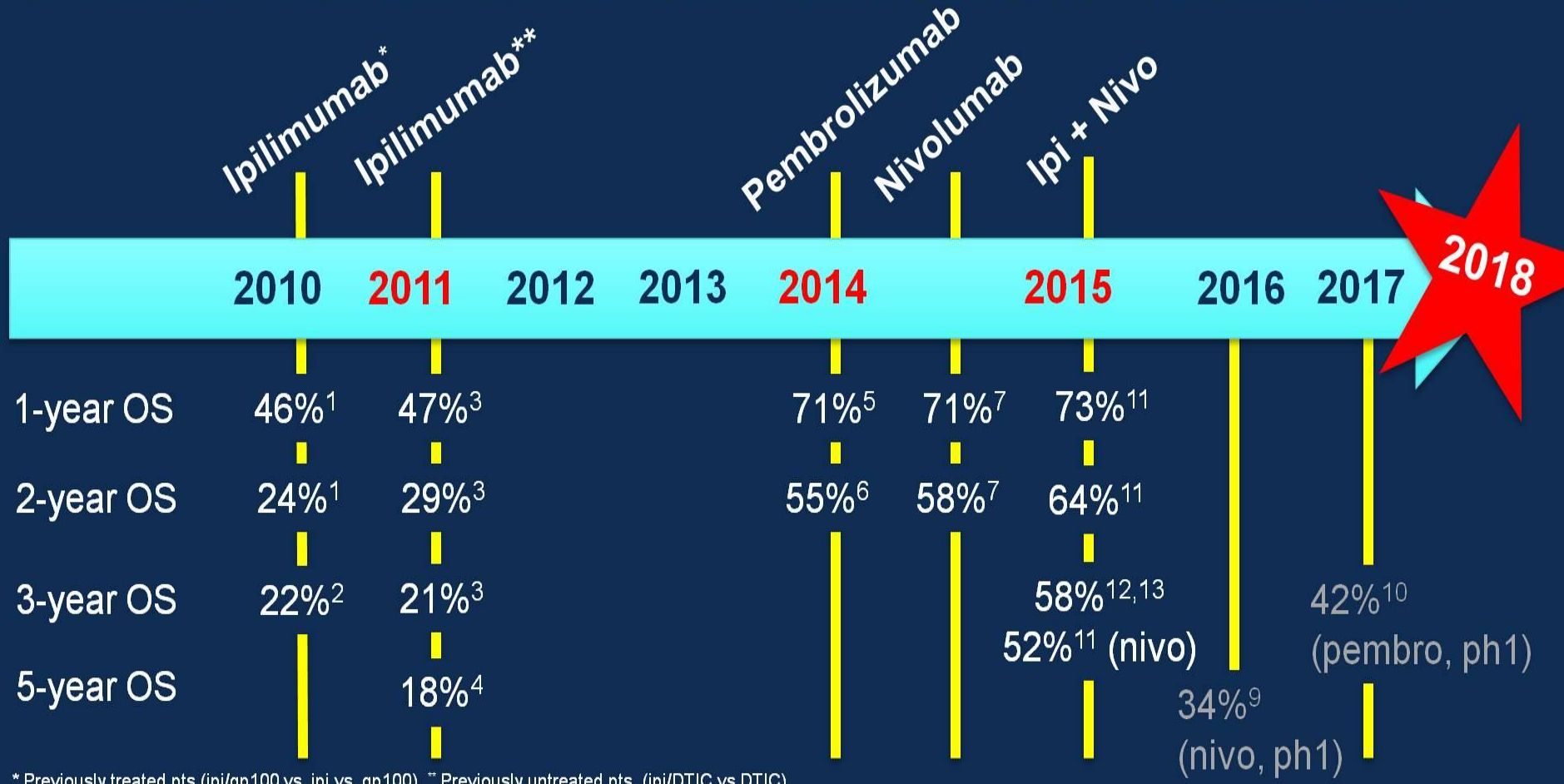
Melanoma therapy beyond ipi/nivo/pembro

- More CPIs
- Adjuvant and neoadjuvant therapy
- More targeted therapy
- Neoantigens, mutation burden, repair gene defects, PARP inhibition
- Tumor microenvironment modification: indoleamine 2,3-dioxygenase(IDO) inhibition
- Innate immune sensing: TLRs, STING, oncolytic virotherapy
- Adoptive cell/construct therapy
- Metabolic intervention
- Radiation therapy and the immune system
- Gut microbiome

Current FDA Approved Immunotherapy For Melanoma

- *High-dose IL-2*: advanced melanoma
- *Interferon alpha-2b*: HD, pegylated: adjuvant high risk resected
- *Ipilimumab*: advanced melanoma and adjuvant treatment of high risk resected
- *Pembrolizumab*: advanced melanoma
- *Nivolumab*: advanced melanoma, adjuvant therapy
- *Ipilimumab + nivolumab*: advanced melanoma
- *Talimogene Laherparepvec*: unresectable cutaneous, subcutaneous and nodal

Overall Survival: IO and Metastatic Melanoma



* Previously treated pts (ipi/gp100 vs. ipi vs. gp100). ** Previously untreated pts (ipi/DTIC vs DTIC).

1. Hodi et al, N Engl J Med 2010. 2. Schadendorf et al, J Clin Oncol 2015. 3. Robert et al, N Engl J Med 2011. 4. Maio et al, J Clin Oncol 2015. 5. Robert et al, N Engl J Med 2015. Pooled data from pembro 10Q2 and 10Q3. 6. Schacter et al, Lancet 2017. 7. Atkinson et al, SMR 2015. 8. Weber et al, SMR 2016. 9. Hodi et al, AACR 2016. 10. Robert et al, J Clin Oncol 2017. 10. Larkin et al, AACR 2017. 12. Wochok et al, N Engl J Med 2017. 13. Postow et al, SITC 2017 (pooled ph2/3).

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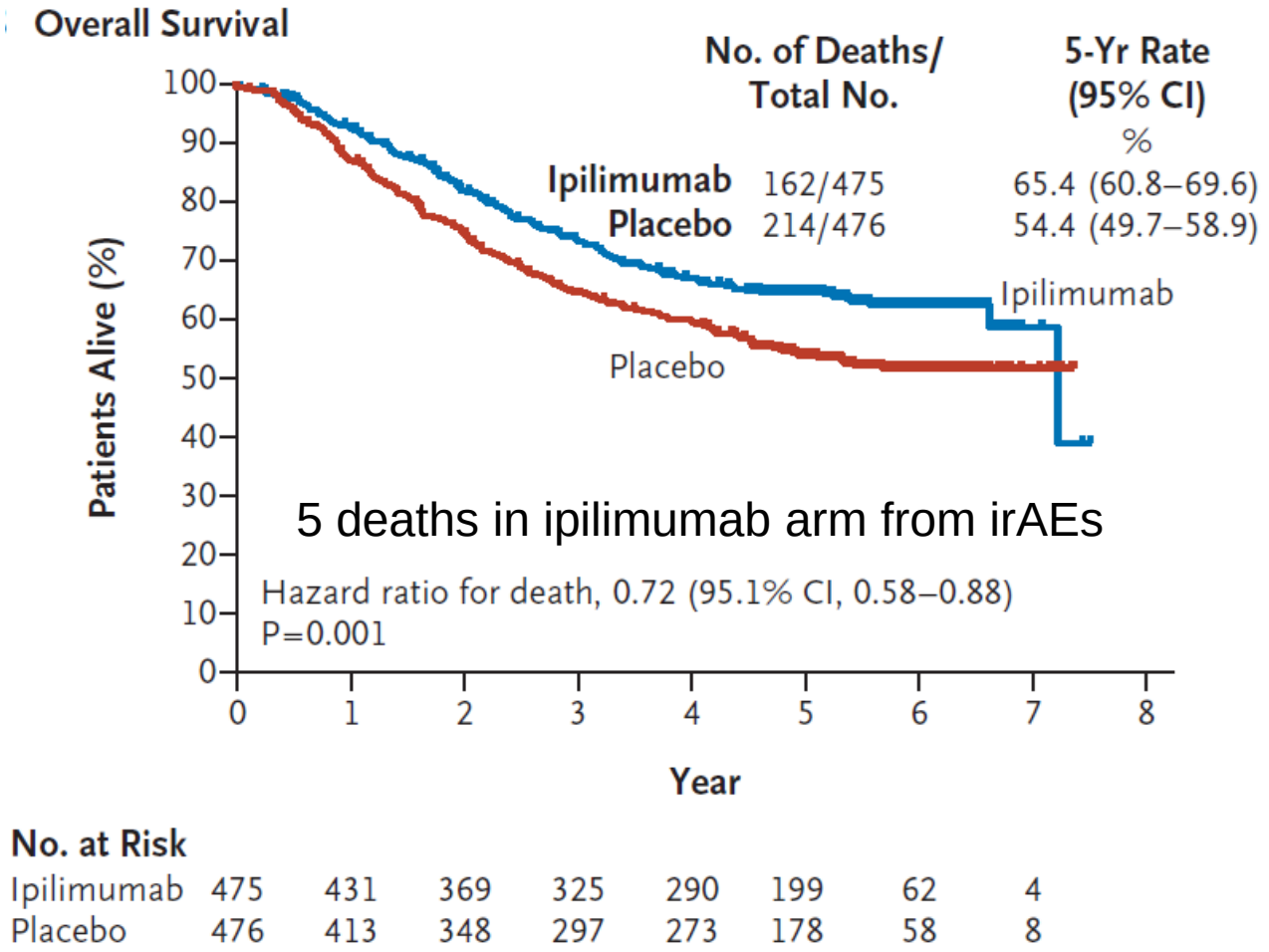
Presented by: Katy K. Tsai, MD

Presented By Katy Tsai at 2018 ASCO-SITC Clinical Immuno-Oncology Symposium

Adjuvant Ipilimumab in High-Risk Melanoma



Eggermont *et al*. NEJM 2016

Adjuvant nivolumab vs ipilimumab in High-Risk Melanoma
3 mg/kg IV q 2 weeks x 1 year

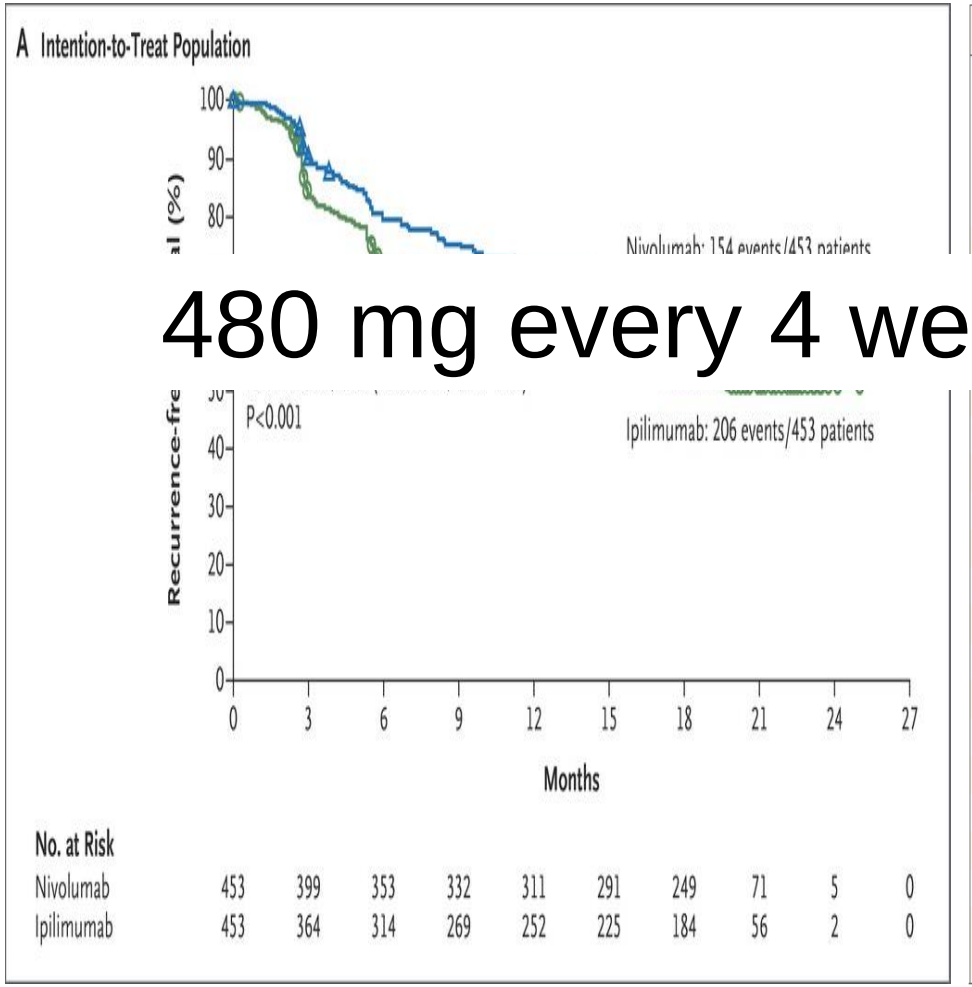


Table 2. Adverse Events*

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

480 mg every 4 weeks FDA approved

Weber *et al*. NEJM 2017

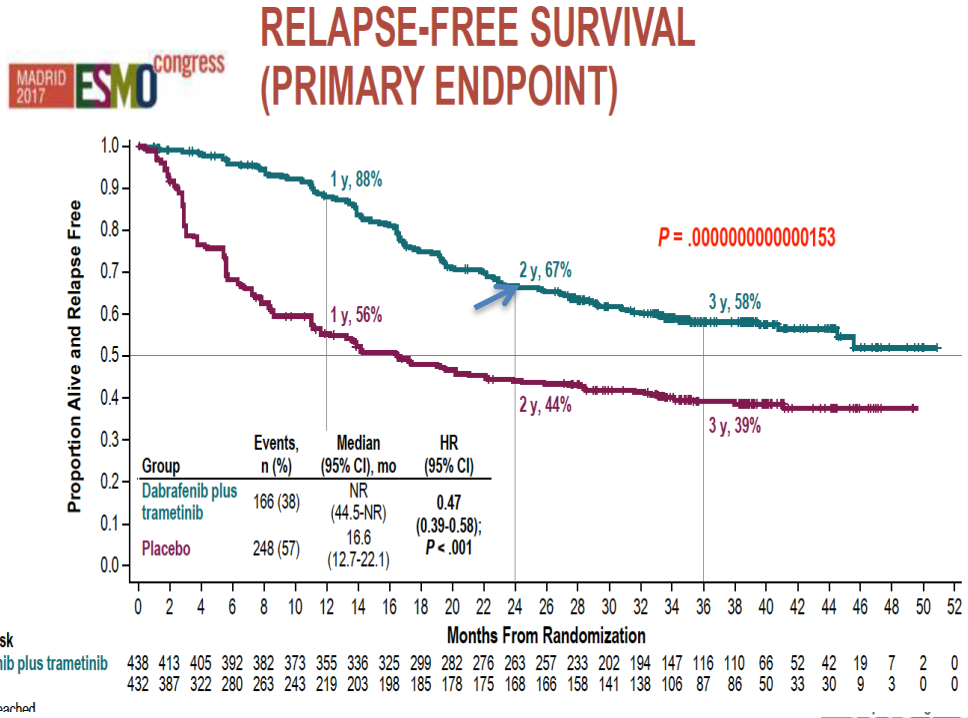
Other adjuvant trials with pending data

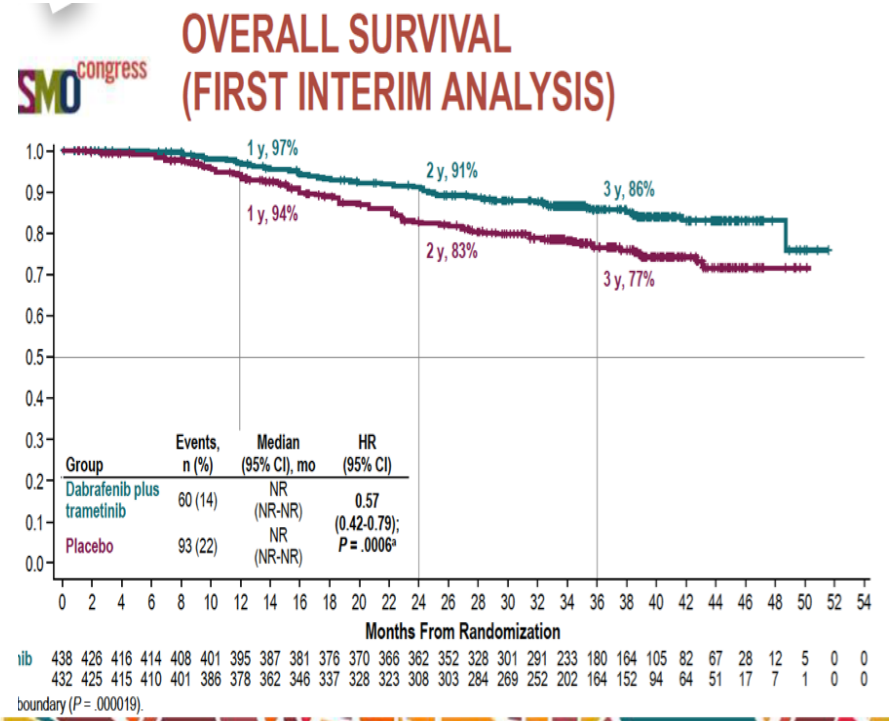
- S1404
  - IFN/ipilimumab vs. pembrolizumab
  - Accrued; results pending
  - Inclusion criteria: IIIA (N2a), IIIB, IIIC, IV

- EORTC-1325/KEYNOTE-054
  - pembrolizumab vs. placebo
  - RFS (primary endpoint) HR=0.57 favoring pembrolizumab
  - Inclusion criteria: IIIA (> 1mm nodal met), IIIB, IIIC

- CheckMate 915
  - nivolumab vs ipilimumab + nivolumab (attenuated)
  - Ongoing
  - Inclusion criteria: IIIB,IIIC,IIID, IV (AJCC 8th edition)

Adjuvant therapy of high risk BRAF V600 mutant melanoma





Long, GV et al. NEJM, 2017

SAFETY SUMMARY

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)		Placebo (n = 432)
Any AE	422 (97)	Nivo 238	380 (88)
AEs related to study treatment	398 (91)		272 (63)
Any grade 3/4 AE	180 (41)	25.4%	61 (14)
Any SAE	155 (36)		44 (10)
SAEs related to study treatment	117 (27)		17 (4)
Fatal AEs related to study drug	0		0
AEs leading to dose interruption	289 (66)		65 (15)
AEs leading to dose reduction	167 (38)		11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	9.7%	12 (3)

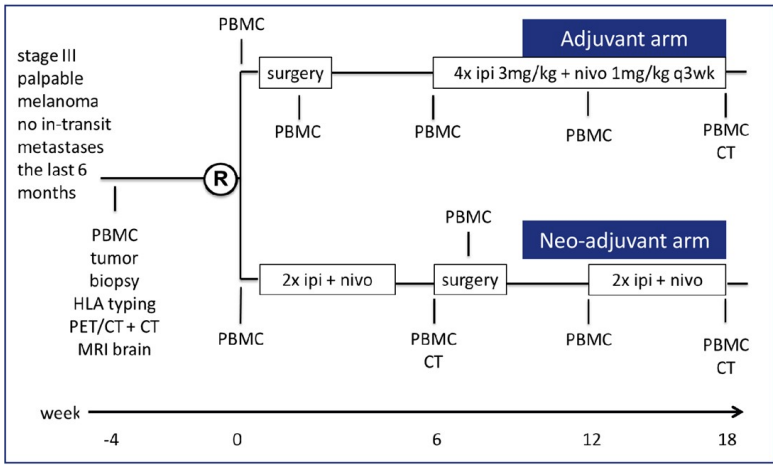
AE, adverse event; SAE, serious adverse event.

[a] Most common AEs leading to treatment discontinuation in the dabrafenib plus trametinib arm were pyrexia (9%) and chills (4%).

(Neo-)adjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage III melanoma: Updated data from the OpACIN trial and first immunological analyses

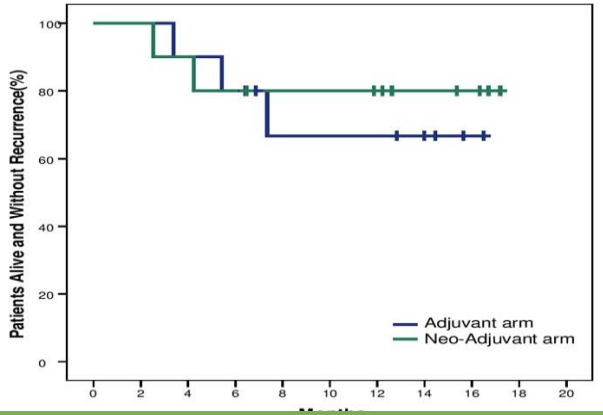
Key eligibility criteria

- Histologically confirmed stage 3b metastatic cutaneous melanoma, palpable disease (no in-transit only) of the axilla or groin
- No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1
- Normal LDH
- Adults at least 18 years of age
- World Health Organization (WHO) Performance Status 0 or 1
- Presence of at least two of the defined HLA alleles that allow MHC tetramer analysis



Efficacy

- Pathological response rate was 80% in the neo-adjuvant arm.
- 5 patients relapsed, all relapses were early after post-surgery (median of 4.2 months).
- 2/10 (20%) patients in the neo-adjuvant arm relapsed (SD, only 2 courses due to grade 3 colitis, PD only 1 course due to grade 3 dermatitis).
- 3/10 (30%) patients relapsed so far in the adjuvant arm (one had 3 courses and two had 2 courses, stopped due to colitis, hypophysitis, and colitis, respectively).



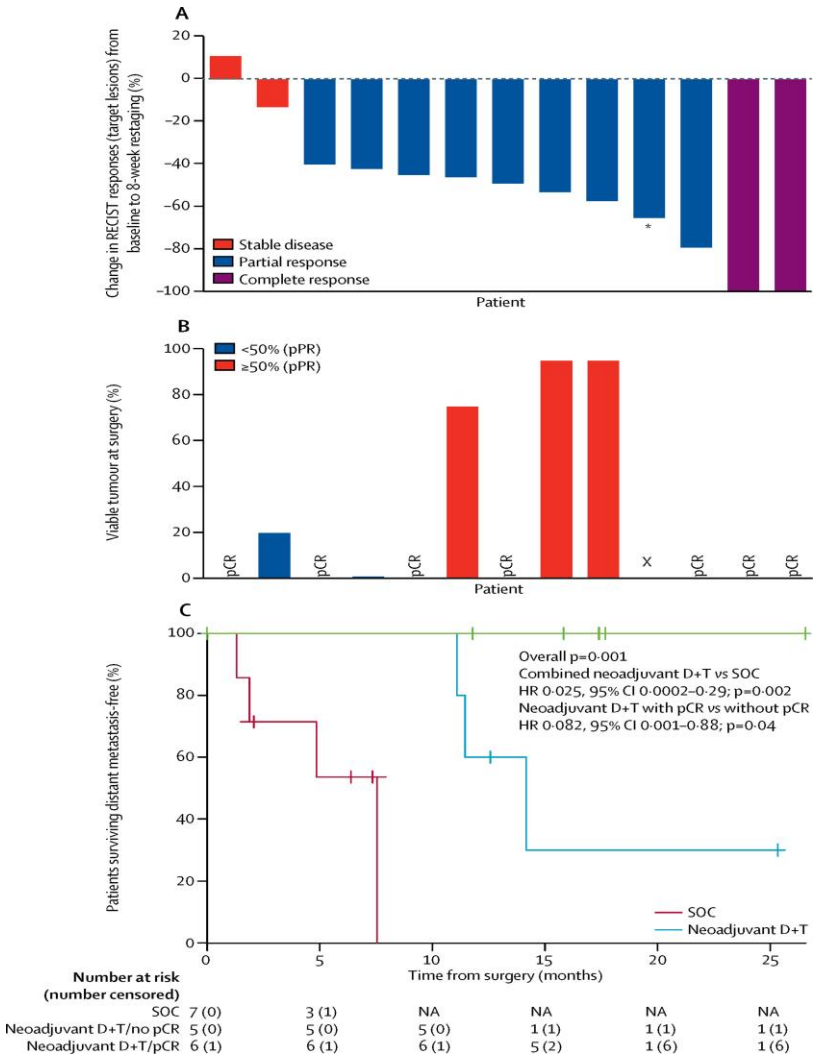
- So far 9/20 (33%) patients recovered fully from irAEs, 11 patients have ongoing AEs (8 need only hormonal substitution, 3 have other ongoing irAEs: low-grade diarrhea, PNP, and rash + elevated ALT/AST).
- All patients are still alive; however two are progressive upon last line standard therapy.

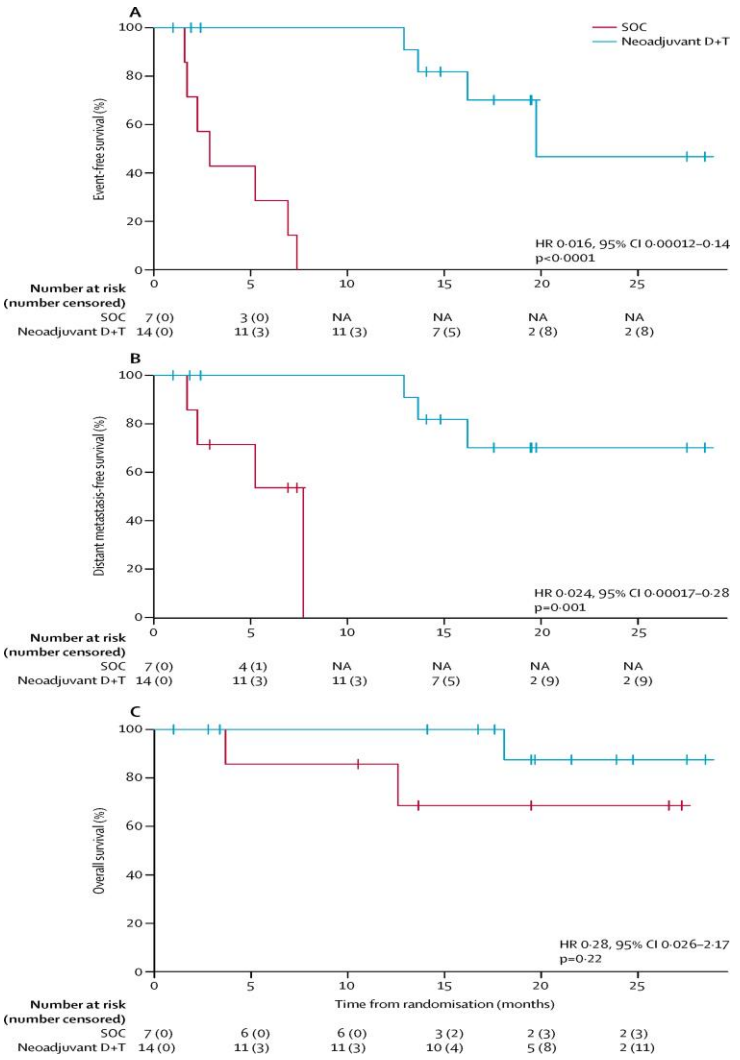
Conclusions

- Neo-adjuvant ipilimumab + nivolumab induces unexpected high frequency and depth of responses, but also a high percentage of grade 3 and 4 toxicities.
- At median follow up of 14 months none of the responders in the neo-adjuvant arm has relapsed.
- RNAseq based methods and mutational load do not seem to identify all patients with favorable outcome.
- Selective protein profiling (26 antibodies) of tumor (CD45lo) and margin areas (CD45hi) by the Nanostring™ microscope technique identified PD-L1 and B2M (absolute protein counts) as possible markers to identify patients benefitting from (neo)adjuvant ipilimumab + nivolumab; multi-parameter analysis might improve specificity.

Rozeman E et al. ASCO 2017

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-center, open-label, randomized, phase 2 trial

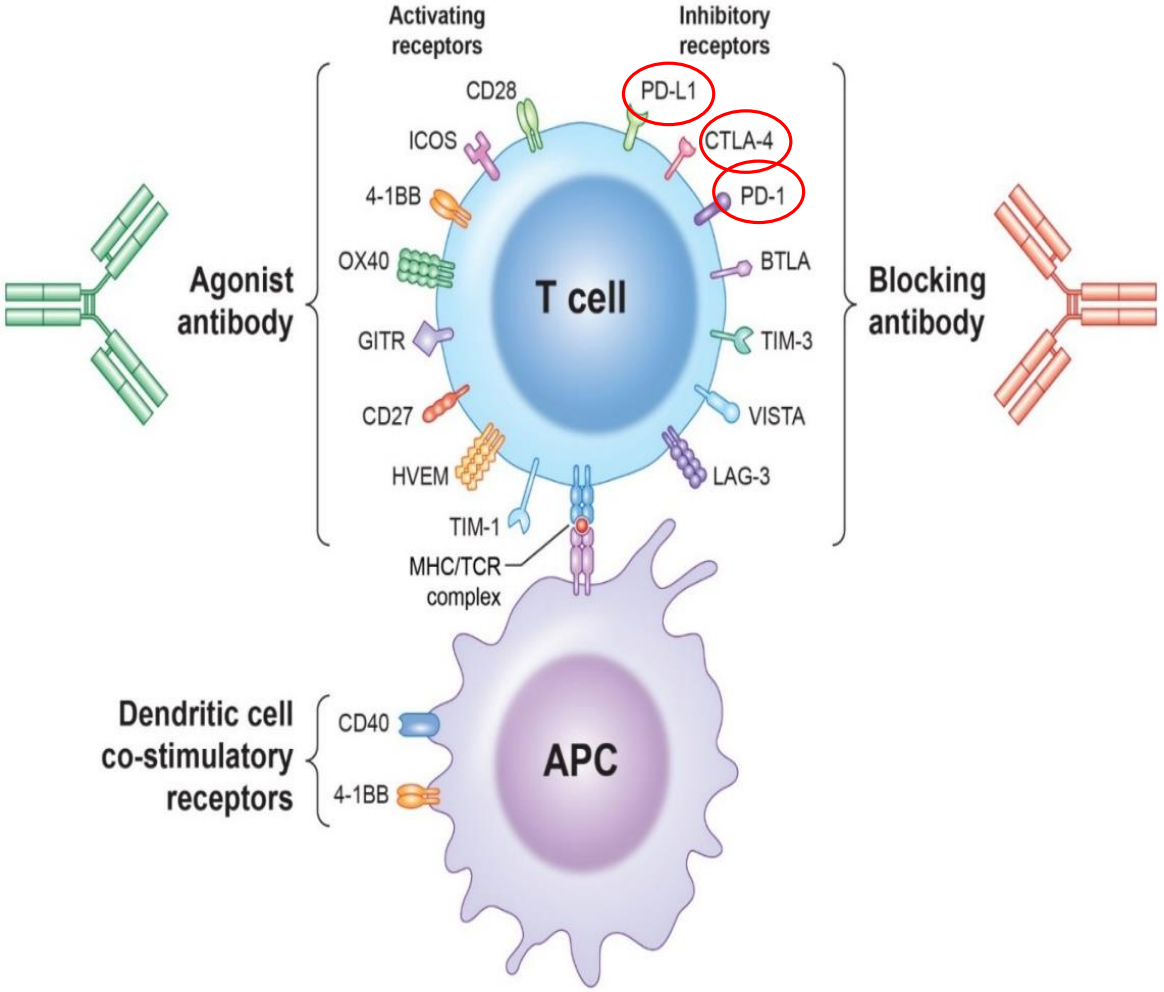




Amaria R et al. Lancet 2018

T cell checkpoint modulation

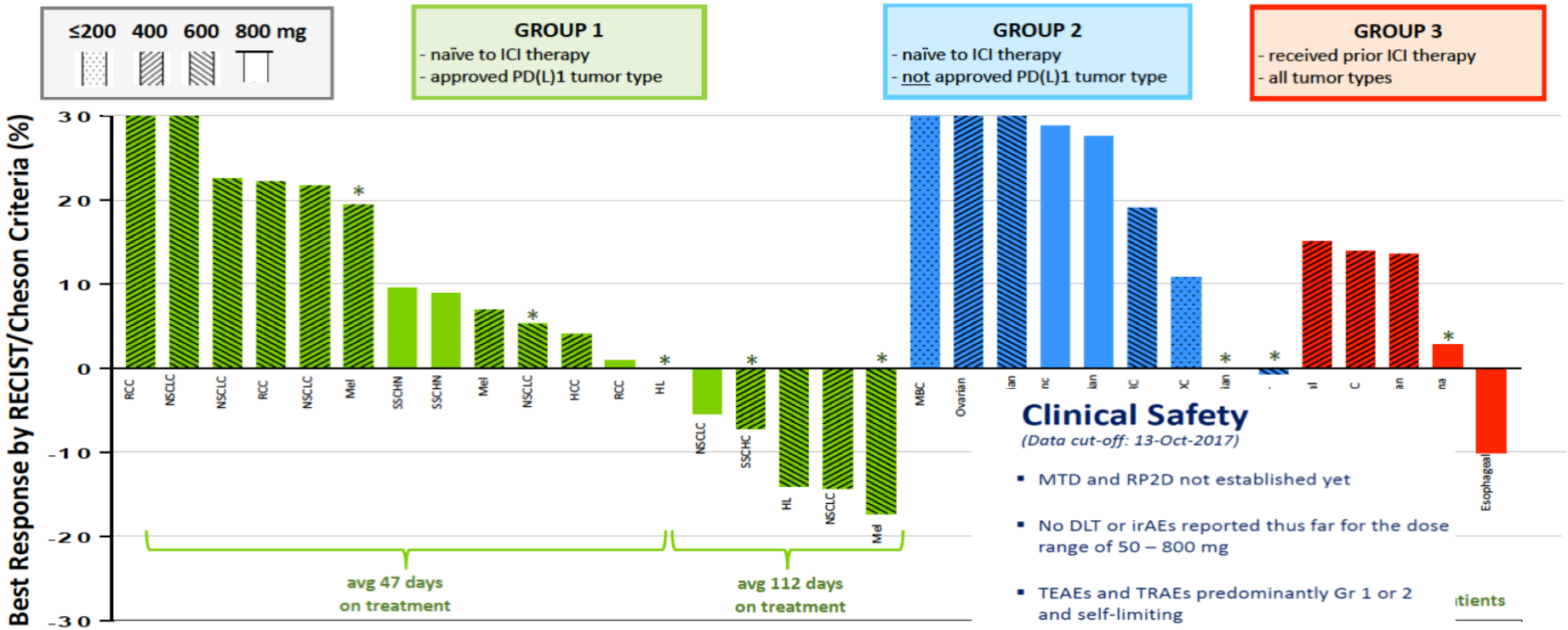
- ***Single Agents***
  - **Agonists**
    - **Anti-ICOS**
    - **Anti-GITR**
    - **Anti-OX40**
    - **Anti-41BB (CD 137)**
    - **Anti-CD27**
  - **Antagonists**
    - **Anti-LAG3**
    - **Anti-TIM3**
    - **Anti-VISTA**
- ***Combinations***
  - **IDO + ipi/pembro/durva**
  - **TVEC+ ipi/pembro**
  - **pembro/ipi + IFN**
  - **pembro + JAK/STAT inhibitors**
  - **nivo + CD 137/TRAIL-R2 Ab/LAG-3**
  - **ipi + nivo + HDAC inhibitors**



CA-170 Compound Overview

- Rationally designed, Oral small molecule
- Targets 2 separate and non-redundant immune checkpoint pathways:
  - **PD-L1** (Programmed Death Ligand 1)
  - **VISTA** (V-domain Ig-containing Suppressor of T-cell Activation)

Anti-Tumor Activity Correlated with Tumor Types



Clinical Safety

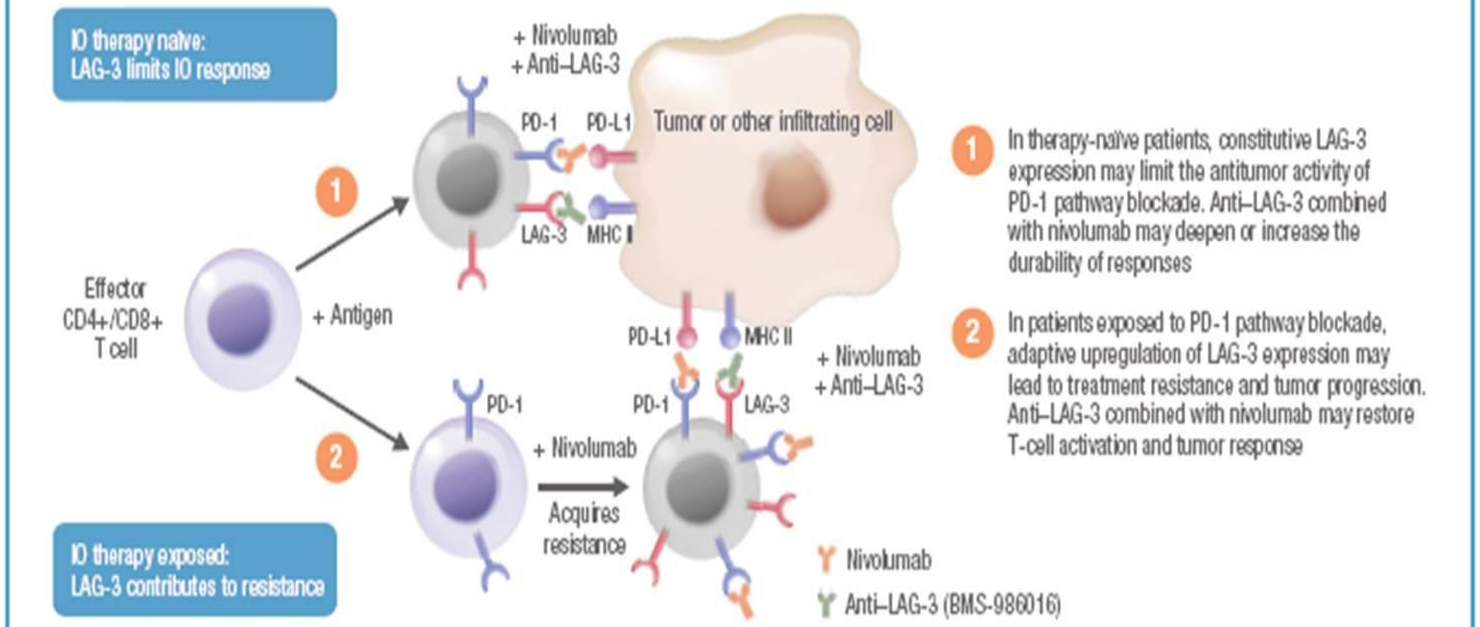
(Data cut-off: 13-Oct-2017)

- MTD and RP2D not established yet
- No DLT or irAEs reported thus far for the dose range of 50 – 800 mg
- TEAEs and TRAEs predominantly Gr 1 or 2 and self-limiting

Bang YJ et al. SITC 2017

LAG-3 Inhibition (BMS-986016)

Figure 1. Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance



Data presented by Paolo Ascierto, MD, ASCO 2017.

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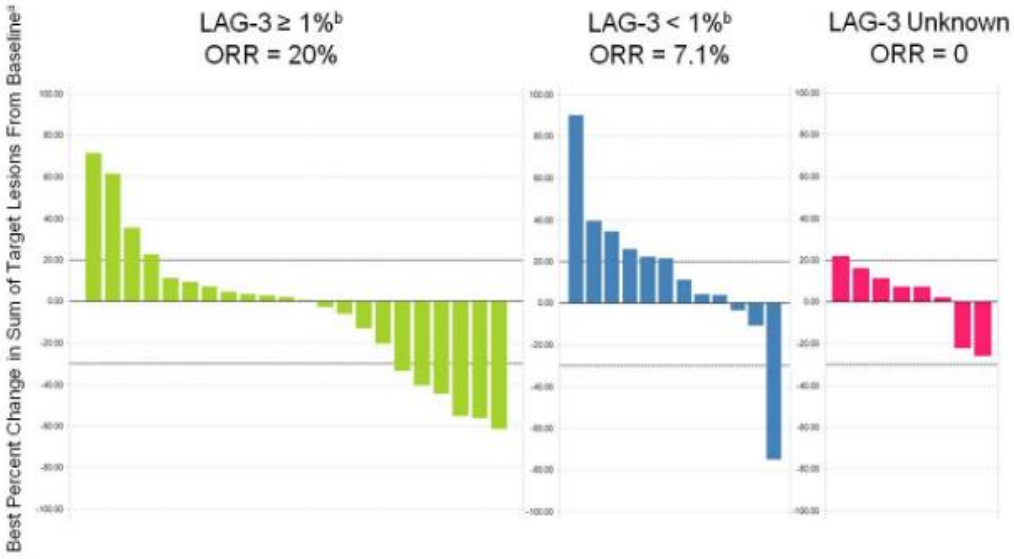
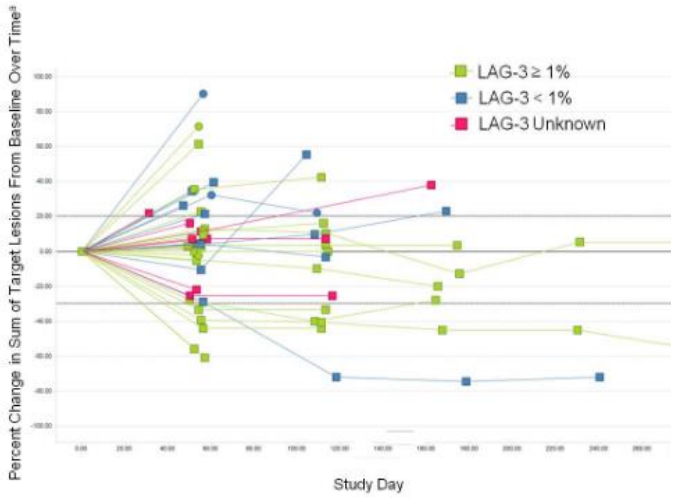
Presented by: Katy K. Tsai, MD

Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy.

Patients, n (%)	Mel Prior IO (n = 55)
Lactate dehydrogenase	
Normal	25 (45.5)
Normal to < 2X ULN	13 (23.6)
≥ 2X ULN	8 (14.5)
Prior radiotherapy	16 (29.1)
Prior systemic therapy	54 (98.2)
Immunotherapy	54 (98.2)
Anti–CTLA-4[a]	32 (58.2)
Anti–PD-1/PD-L1[b]	52 (94.5)
Best response to prior anti–PD-1/PD-L1[c]	
CR	1 (1.8)
PR	12 (21.8)
SD	16 (29.1)
PD	22 (40.0)
BRAF inhibitors	16 (29.1)
MEK inhibitors	11 (20.0)



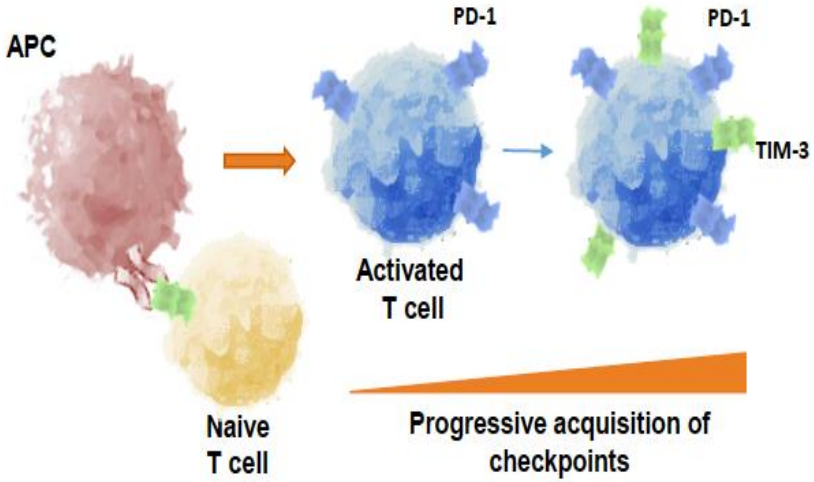


- Anti-LAG 3 (BMS-986016) in combination with nivolumab demonstrates encouraging initial efficacy, with a safety profile similar to nivolumab monotherapy
  - Treatment-related AEs of any grade occurred in 45% of patients (grade 3/4, 9%)
- These data provide first proof of principle that combining anti–LAG-3 and anti–PD-1 in IO-experienced patients overcomes tumor PD-L1 resistance and restores T-cell activity
- Greater and deeper response rate with LAG-3 expression ≥ 1% suggests that LAG-3 is a potential biomarker enriching for clinical benefit
- Evolving tumor biology provides confidence that this combination can overcome tumor immune escape mechanisms with the potential for broad applicability across lines of therapy and tumor types

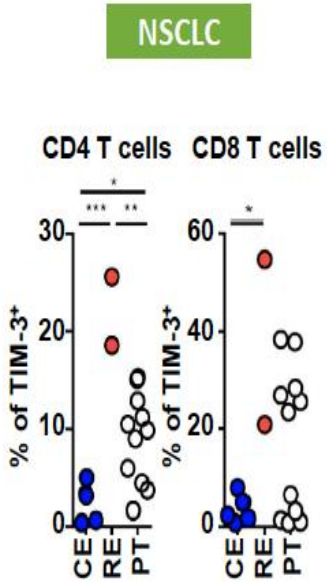
Ascierto P et al. ASCO 2017

TIM-3 is a key immune checkpoint and a next-generation cancer immunotherapy target

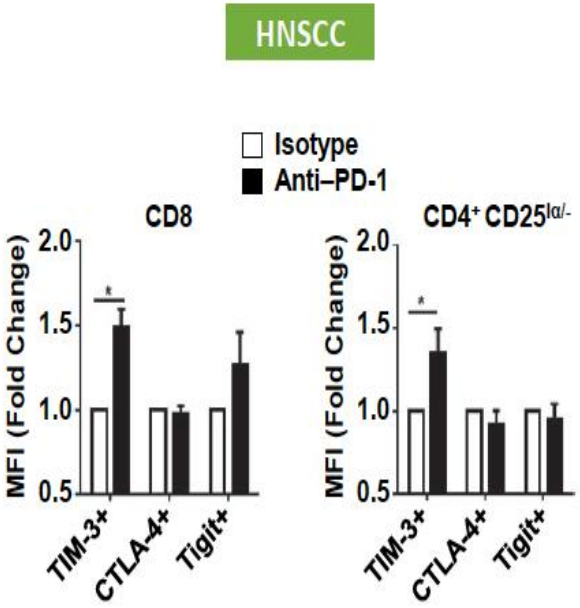
TIM-3 negatively regulates T-cell activation and is a marker of exhausted T cells



PD-1 resistance is associated with increased TIM-3 expression in patient TILs



Koyama et al. Nature Comm. 2016.

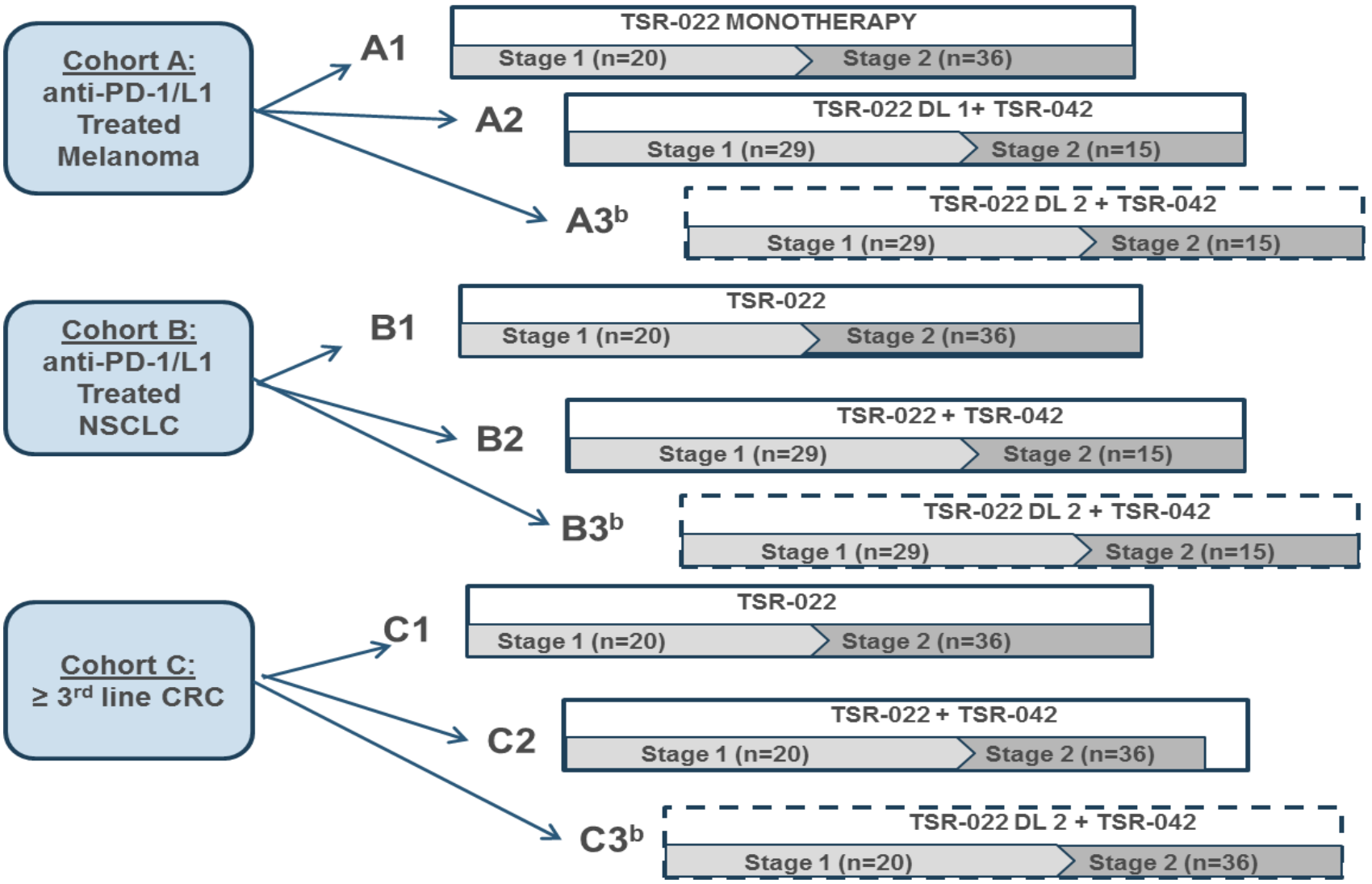


Shayan et al. OncoImmunology. 2016.

HNSCC=head and neck squamous cell carcinoma; NSCLC=non–small cell lung cancer; PD-1=programmed death 1; TIL=tumor-infiltrating lymphocyte; TIM-3=T-cell immunoglobulin and mucin-domain–containing-3; CE=control effusion; RE=resistant effusion; PT=primary tumor.

Weiss GJ et al. SITC 32017

Part 2 dose Expansion Cohorts



PEGylated IL-10 - Mechanism of Action

CD8+ T cells that recognize the tumor cell, become exhausted and undergo apoptosis, in the absence of a survival factor (IL-10)

AM0010

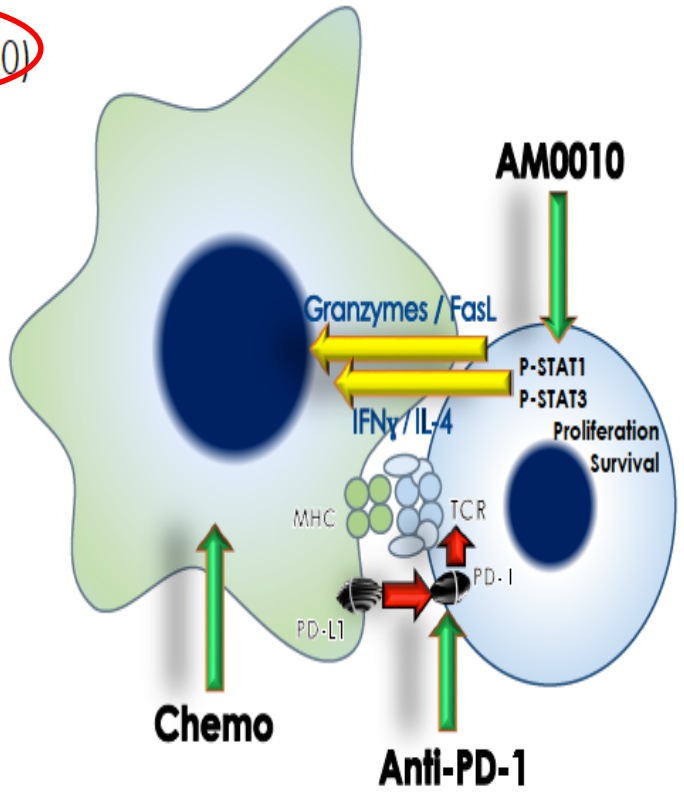
- Tumor recognizing CD8+ T cells are activated and proliferate
- AM0010 inhibits CD8+ T cell apoptosis and induces Granzymes and FasL
- Granzyme and FasL induces tumor cell death

⇨ Rationale for AM0010 + anti-PD-1

- Increased TCR signal
- Two complementary pathways activated

⇨ Rationale for AM0010 + Chemo

- Chemo induces immunogenic tumor cell death and AM0010 primes a sustained immune memory

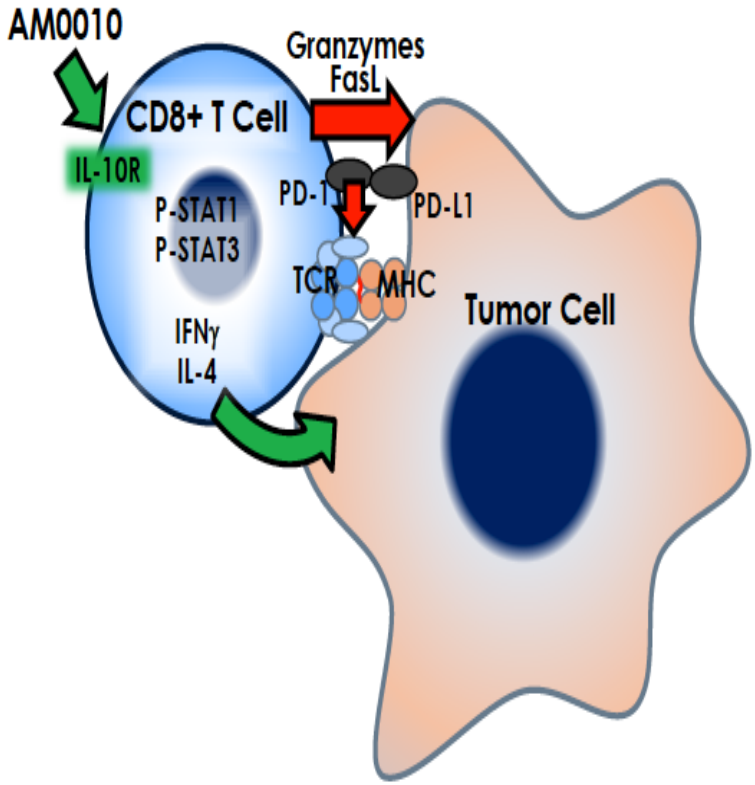


➡ Sequoia - Phase 3
PDAC 2nd Line (n=566)
FOLFOX + AM0010

Naing A. SITC Meeting 2017

AM0010 (Pegilodecakin) in IO Therapy

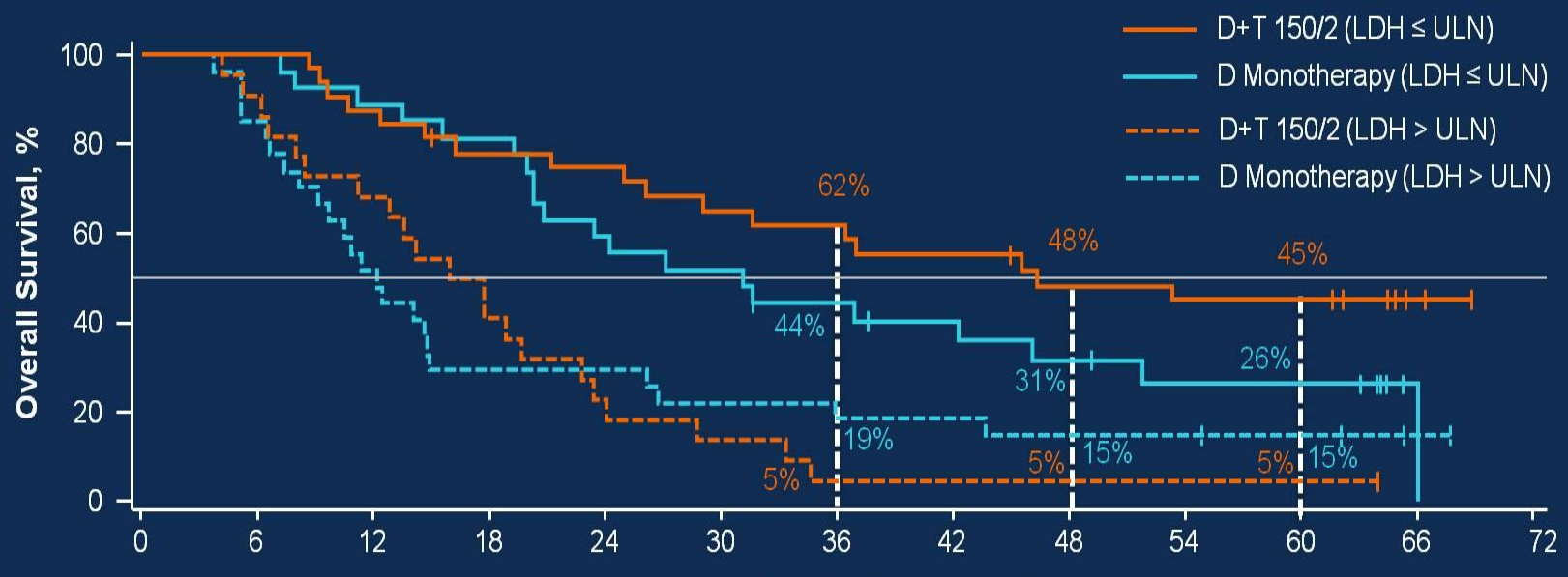
- Tumor antigen recognition by CD8+ T cells (TCR) induces IL-10R and PD-1 on CD8+ T cells
  - PD-1 is a negative feedback ("Immune Checkpoint")
  - IL-10 expands antigen activated CD8+ T cells (cytotoxic license)
- AM0010 (Pegilodecakin) induces
  - Phospho-STAT3 in intratumoral CD8+ T cells
  - Accumulation of immune checkpoint positive CD8+ T cells (PD-1+ / Lag-3+)
  - Expansion of several hundred previously not detectable T cell clones / patient



- AM0010 induces objective tumor responses in monotherapy
  - 25% ORR in RCC
  - Long lasting response in RCC, ocular melanoma and CTCL (CR)
- AM0010 synergizes with anti PD-1
  - Tolerated with no significant increase in AE profile over either agent in monotherapy
  - ORR in RCC 44% (15 of 34 pts (2 CRs), 2x expected RR)
  - ORR in NSCLC 41% (11 of 27 pts, 2x expected RR)

Naing A. SITC Meeting 2017

OS by Baseline LDH Level (ITT)



Patients at risk (LDH ≤ ULN), n

32	32	28	24	23	20	19	17	14	13	13	4	0
27	27	24	22	16	14	11	9	7	5	5	1	0

Patients at risk (LDH > ULN), n

22	20	15	9	4	3	1	1	1	1	1	0	0
27	23	14	8	8	6	5	5	4	4	3	1	0

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Background

- BRAF/ MEK inhibitor combination therapy is standard of care in *BRAF V600*-mutant locally advanced or metastatic melanoma,[1] based on improved survival with manageable tolerability.[2,3]
- **Binimetinib (BINI):** potent, selective allosteric, ATP-uncompetitive inhibitor of MEK1/2[4] with shorter half-life than other MEK1/2 inhibitors; may provide more rapid resolution of toxicity upon interruption[5]
  - MTD 45 mg BID
- **Encorafenib (ENCO):** ATP-competitive BRAFi with unique pharmacologic profile[6]
  - Single agent MTD 300 mg QD[7]
  - Dose able to be increased to 450 mg QD when combined with BINI[8]

IC_{50}=half-maximal inhibitory concentration; MTD=maximum tolerated dose.

1. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.
2. Robert C, et al. *N Engl J Med*. 2015;372(1):30-39.
3. Long GV, et al. *Lancet*. 2015;386(9992):444-451.
4. Ascierto PA. et al. *Lancet Oncol*. 2013:14(3):249-256.
5. Data on File. Array BioPharma Inc.
6. Stuart DD, et al. *Cancer Res*. 2012;72(8 suppl):3790.
7. Delord JP, et al. *Clin Cancer Res*. 2017:[Epub ahead of print]
8. Sullivan RJ. et al. *Journal of Clinical Oncology*. 2015:33(15)..

Dummer R. ESMO 2017

PFS: COMBO300 vs ENCO300 by Central Review

COMBO300 vs ENCO300 (Parts 1 + 2)

Median PFS in months (95% CI)

Confirmed Response	COMBO300 n=258		ENCO300 (Parts 1+2) n=280		ENCO300 (Part 2) n=86	
	Central Review	Local Review	**Central Review**	Local Review	**Central Review**	Local Review
ORR* (95% CI†), %	**66 (60–72)**	73 (67–78)	**50 (44–56)**	56 (50–62)	**50 (39–61)**	54 (42–64)
CR, %	8	11	5	8	3	3
PR, %	58	62	45	49	47	50
Median DOR (95% CI), mo	12.7 (9.3–15.1)	13.1 (10.8–16.6)	12.9 (8.9–15.5)	13.0 (9.5–15.0)	7.5 (5.6–14.0)	9.2 (7.4–14.8)
SD,‡ %	25	22	32	29	29	29
PD,¶ %	9	5	18	15	21	17
DCR§ (95% CI), %	91 (87–94)	95 (91–97)	83 (78–87)	85 (81–89)	79 (69–87)	83 (73–90)

HR (95% CI), 0.57 (0.41–0.79)

P<0.001†

Patients at risk

Time (months)

COMBO300	258	204	144	92	27	0
ENCO300 (Part 2)	86	52	30	17	9	0

*Median duration of potential follow-up approximately 5 months longer than with COMBO300 due to longer duration in study of ENCO300 Part 1 patients.

†Nominal *P*-value.

BINI=binimetinib; COMBO300=ENCO 300 mg QD + BINI 45 mg BID; ENCO=encorafenib; PFS=progression free survival

Dummer R. ESMO 2017

Selected AEs of Interest

	COMBO300 n=257		ENCO300 (Parts 1+2) n=276	
Median duration of exposure, weeks	**52.1**		**31.5**	
Event, %	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Pyrexia*	17	0	16	1
Rash†	15	1	43	5
Transaminases increased‡	14	5	5	1
Retinal pigment epithelial detachment¶	9	<1	1	0
Left ventricular dysfunction§	6	1	3	1
Secondary skin neoplasms‖	6	1	10	1
Skin papilloma	6	0	12	0
Dermatitis acneiform	2	0	4	0
Photosensitivity#	2	0	4	0
Blood bilirubin increased	1	<1	0	0

*Includes pyrexia, body temperature increased, and hyperthermia.
†Includes rash, rash generalized, rash erythematous, rash maculo-papular, dermatitis, rash follicular, rash macular, rash papular, rash pruritic, generalized erythema, rash vesicular, dermatitis psoriasiform, and rash pustular.
‡Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatic function abnormal, and hepatic enzyme increased.
¶Includes chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, and subretinal fluid.
§Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, left ventricular failure, cardiac output decreased, and ventricular hypokinesia.
‖Includes basal cell carcinoma, Bowen's disease, keratoacanthoma, lip squamous cell carcinoma, neoplasm skin, squamous cell carcinoma, and squamous cell carcinoma of skin.
#Includes photosensitivity reaction, solar dermatitis, and sunburn.

Dummer R. ESMO 2017

Target-Immuno Triplets: BRAF + MEK + PD1/L1

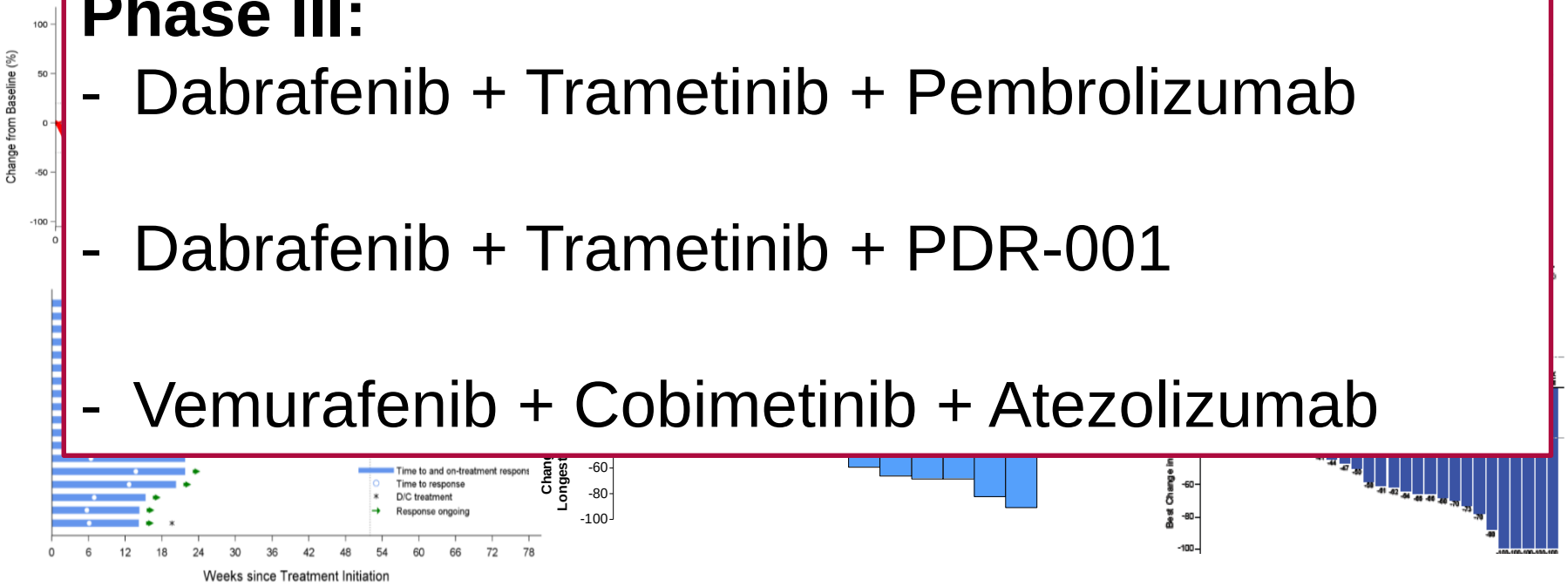
Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

Vemurafenib+Cobimetinib+ Atezolizumab

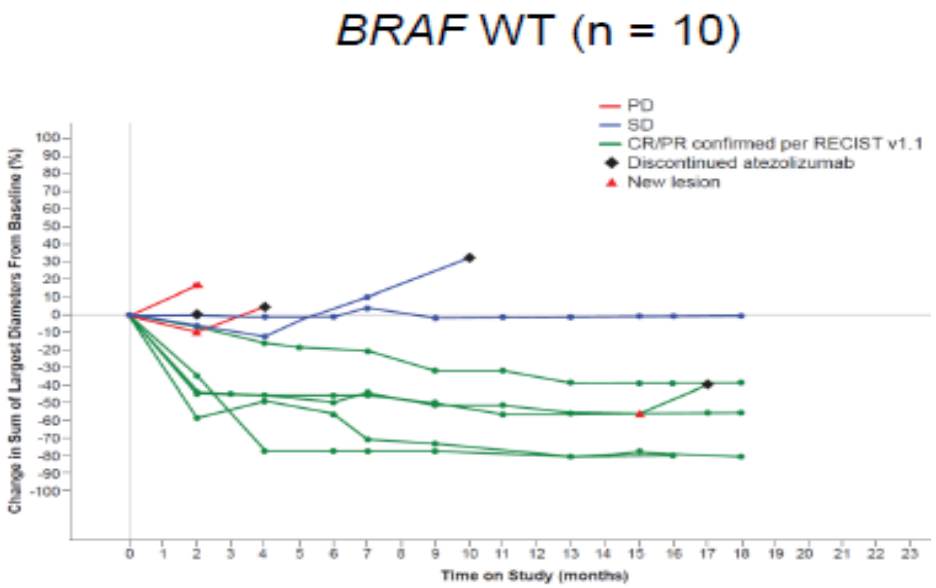
Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab



Ribas A. ASCO/SITC 2018

Cobimetinib (MEK inhibitor) + Atezolizumab (PDL-1 Ab)for BRAF WT Melanoma Phase I

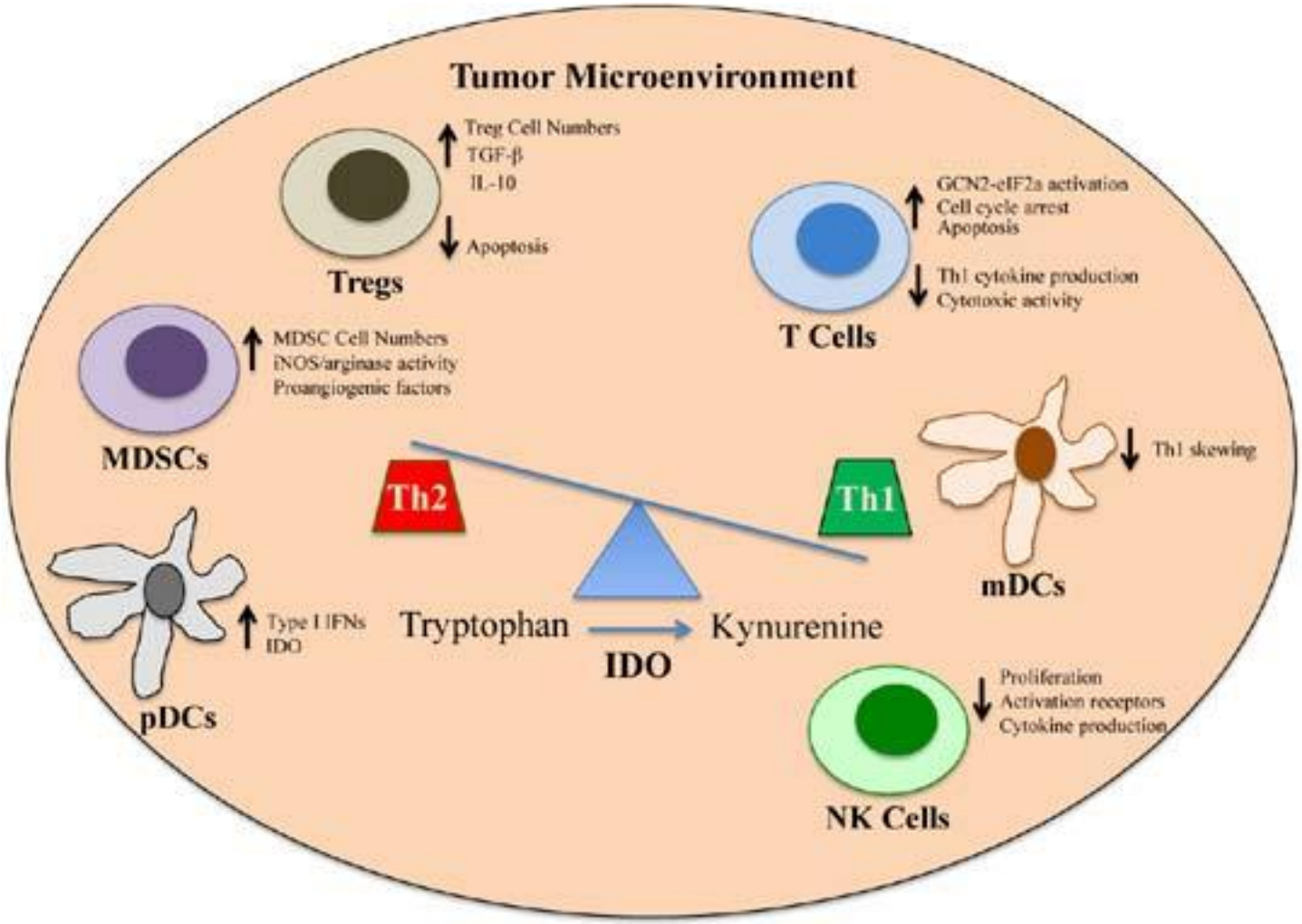


Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

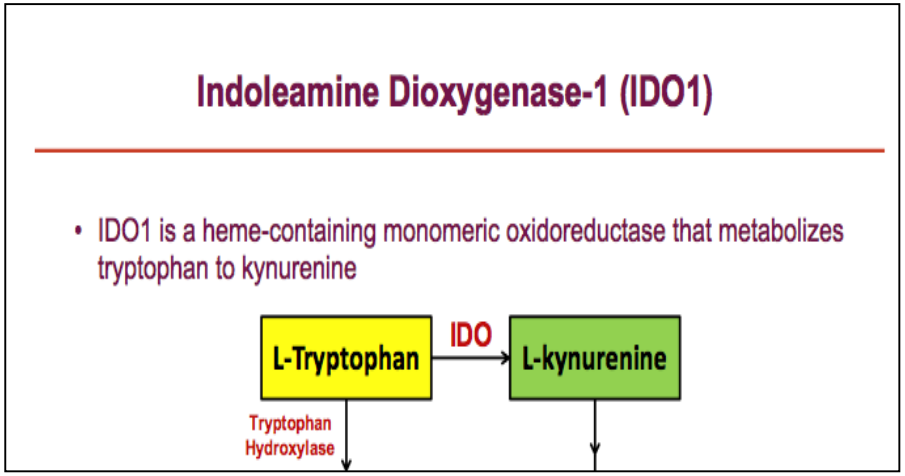
	N = 22, n (%)
Median safety follow-up, mo (range)	14.0 mo (2.4-20.2)
All grade treatment-related AEs	22 (100%)
Grade 3-4 treatment-related AEs	13 (59%)
Grade 3-4 atezolizumab-related AEs	8 (36%)
Grade 3-4 cobimetinib-related AEs	10 (45%)
AEs leading to treatment dose modification/interruption	14 (64%)
Treatment-related SAEs[a]	4 (18%)
Treatment discontinuation[b]	3 (14%)
Cobimetinib discontinuation	3 (14%)
All treatment discontinuation	1 (5%)

Ribas A. ASCO/SITC 2018



Selvan, SR. Current Cancer Drug Targets, 2016

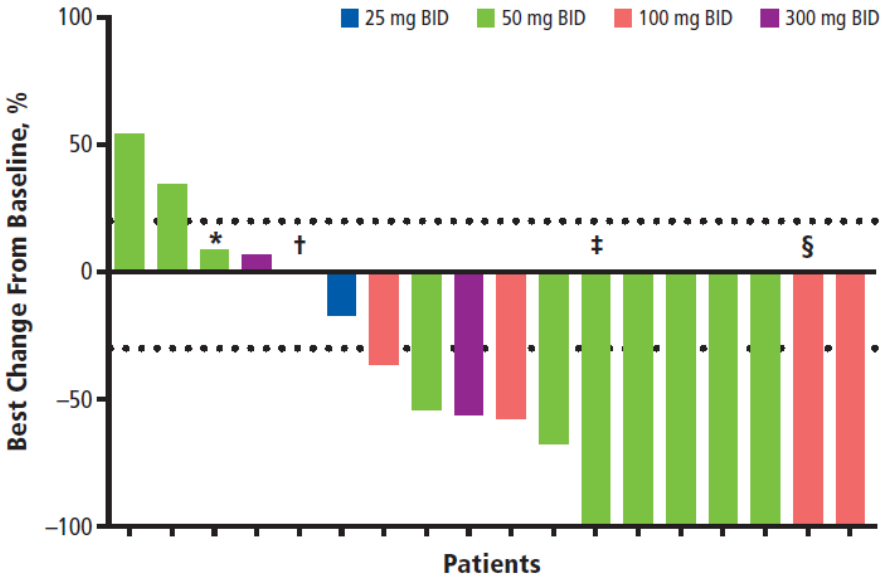
IDO inhibitor epacadostat + pembrolizumab



A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301) ClinicalTrials.gov Identifier: NCT02752074

RECIST response = 58%, no increase in toxicity from pembrolizumab alone

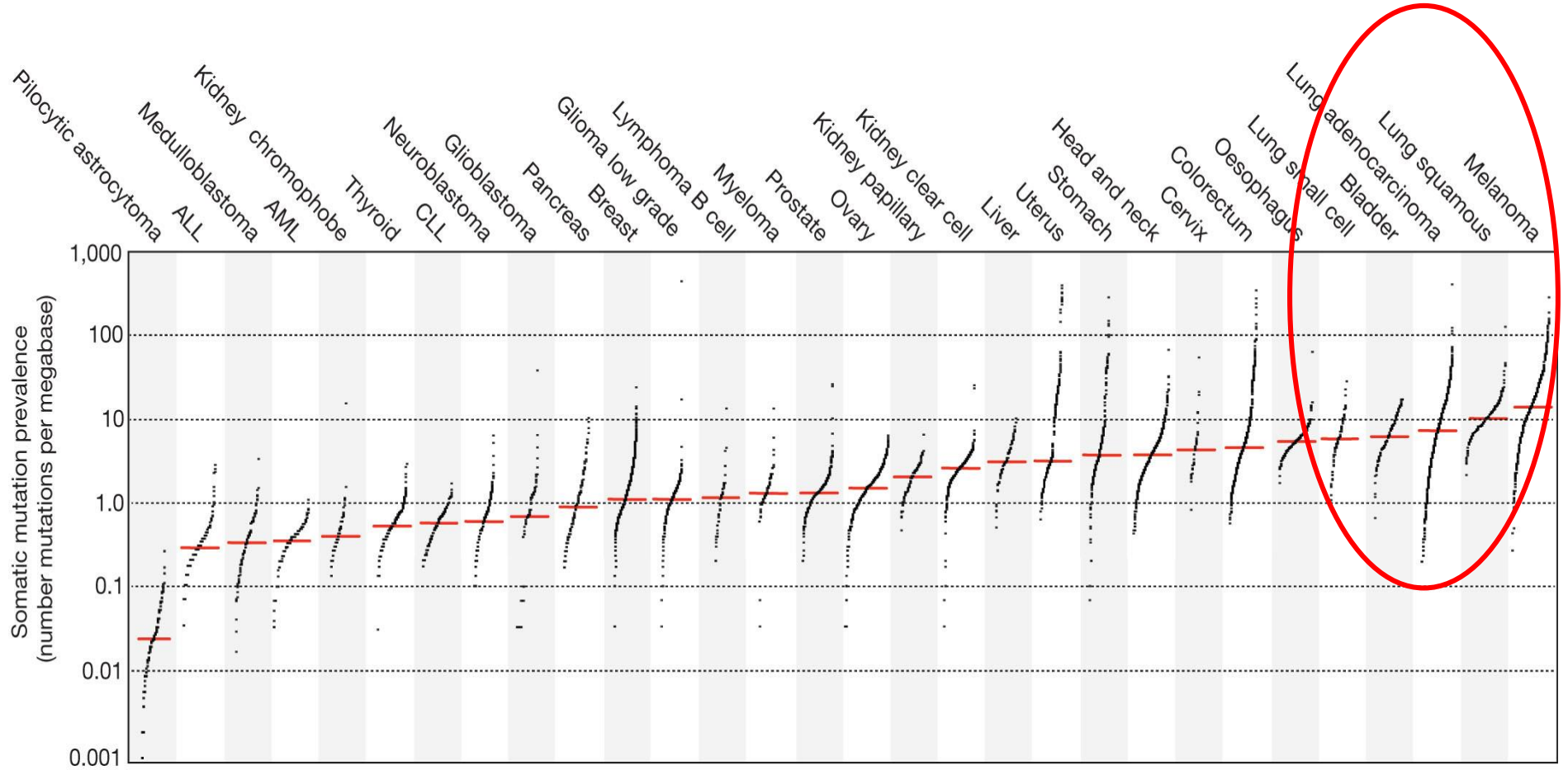
Phase 1/2 Study of **Epacadostat** (INCB024360) + **Pembrolizumab** in Patients With Melanoma



Beatty et al. ASCO 2012
Gangadhar et al. ESMO 2016

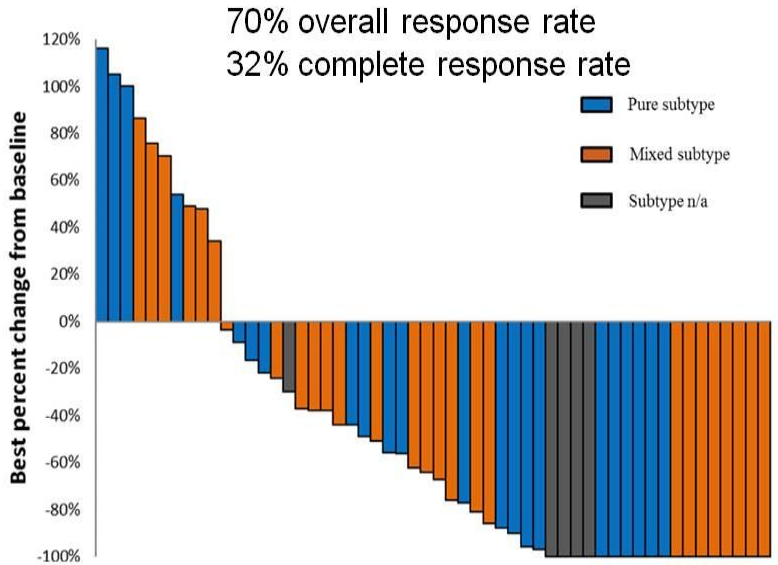
The prevalence of somatic mutations across human cancer types.

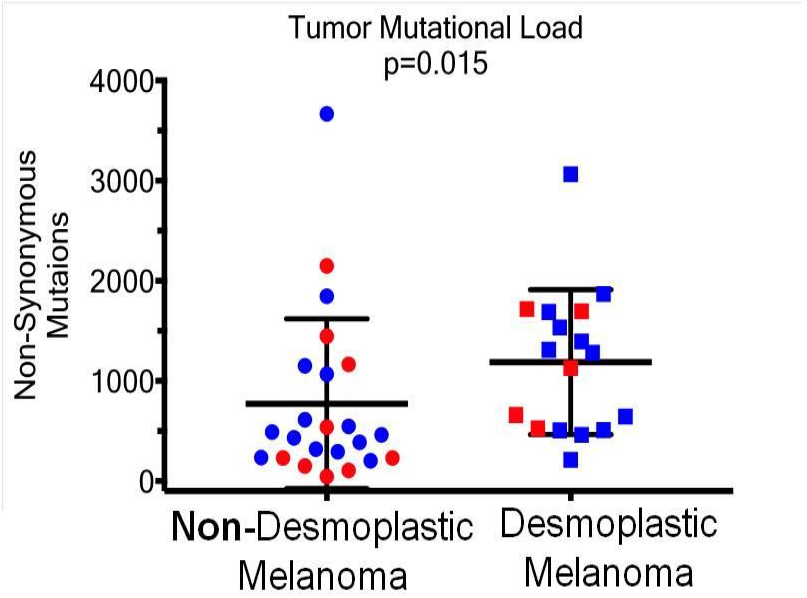
Mutation = Neoantigen



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

High response rate and high mutational load in Desmoplastic melanoma

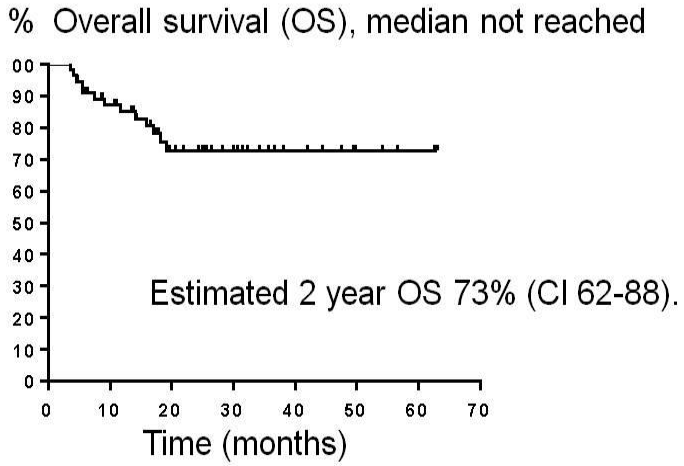




n=60 (out of 1058 cases Reviewed*)

2 sIIIc
3 M1a
20 M1b
35 M1c

*Retrospective Review



= Progressive Disease

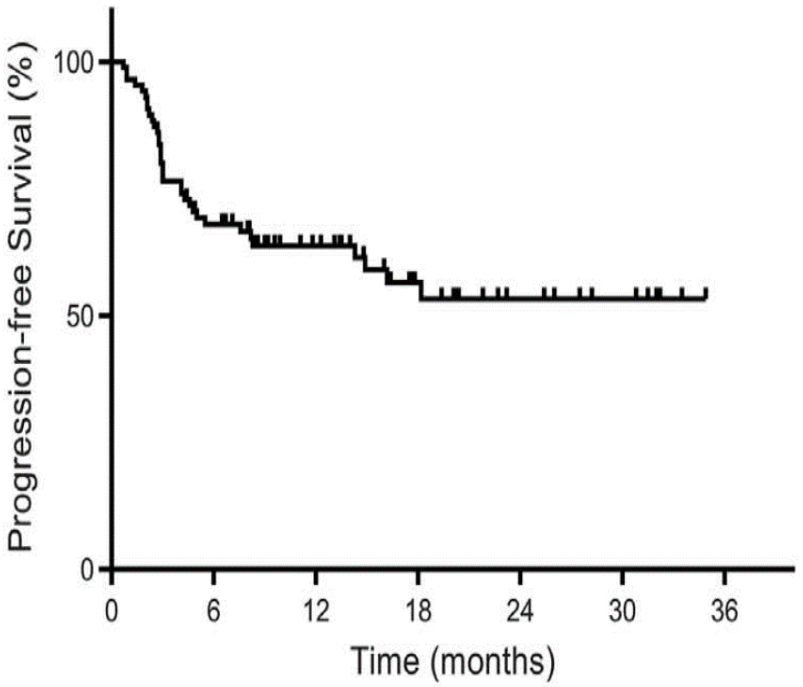
= Response (RECIST1.1)

Zeynep Eroglu, Zeynep Eroglu, Jesse M. Zaretsky, Siwen Hu-Lieskovan, Dae Won Kim, Alain Algazi, Douglas B. Johnson, Elizabeth Liniker, Ben Kong, Rodrigo Munhoz, Suthee Rapisuwon, Pier Federico Gherardin, Bartosz Chmielowski, Xiaoyan Wang, I. Peter Shintaku, Cody Wei, Jeffrey A. Sosman, Richard Joseph, Michael A. Postow, Matteo S Carlino, Wen-Jen Hwu, Richard A. Scolyer, Jane Messina, Alistair J. Cochran, Georgina V. Long, Antoni Ribas. High response rate to PD-1 blockade in desmoplastic melanomas. Nature 2018

Presented By Antoni Ribas at 2018 ASCO-SITC Clinical Immuno-Oncology Symposium

Mismatch-repair Deficiency Predicts Response of Solid Tumors to PD-1 Blockade

Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate 95% CI	53% 42% to 64%
Disease control rate 95% CI	77% 66% to 85%
Median progression-free survival time 95% CI	NR 14.8 months to NR
2-year progression-free survival rate 95% CI	53% 42% to 68%
Median overall survival time 95% CI	NR NR to NR
2-year overall survival rate 95% CI	64% 53% to 78%



Le DT, et al. *Science*. 2017.

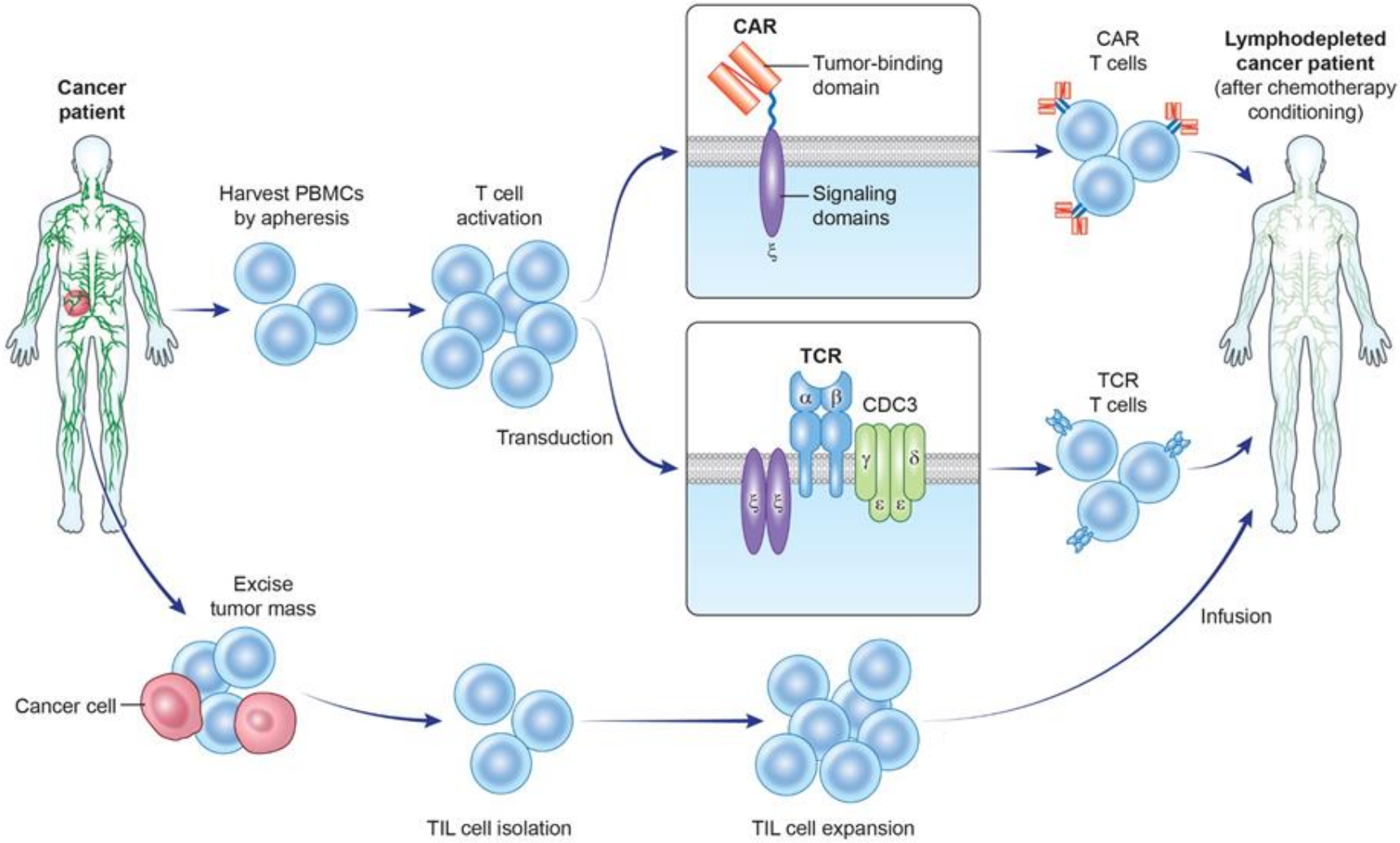
DNA Repair Defects: Surrogate for High Mutation Load and Therapeutic Targets

Table 2.1 Essential genes of the five major DNA repair mechanisms

Base excision repair (BER)	DNA glycosylase, APE1, XRCC1, PNKP, Tdp1, APTX, DNA polymerase β, FEN1, DNA polymerase δ or ε, PCNA-RFC, PARP
Mismatch repair (MMR)	MutSα (MSH2-MSH6), MutSβ (MSH2-MSH3), MutLα (MLH1-PMS2), MutLβ (MLH1-PMS2), MutLγ (MLH1-MLH3), Exo1, PCNA-RFC
Nucleotide excision repair (NER)	XPC-Rad23B-CEN2, UV-DDB (DDB1-XPE), CSA, CSB, TFIIH, XPB, XPD, XPA, RPA, XPG, ERCC1-XPF, DNA polymerase δ or ε
Homologous recombination (HR)	Mre11-Rad50-Nbs1, CtIP, RPA, Rad51, Rad52, BRCA1, BRCA2, Exo1, BLM-TopIIIα, GEN1-Yen1, Slx1-Slx4, Mus81/Eme1
Non-homologous end-joining (NHEJ)	Ku70-Ku80, DNA-PKc, XRCC4-DNA ligase IV, XLF

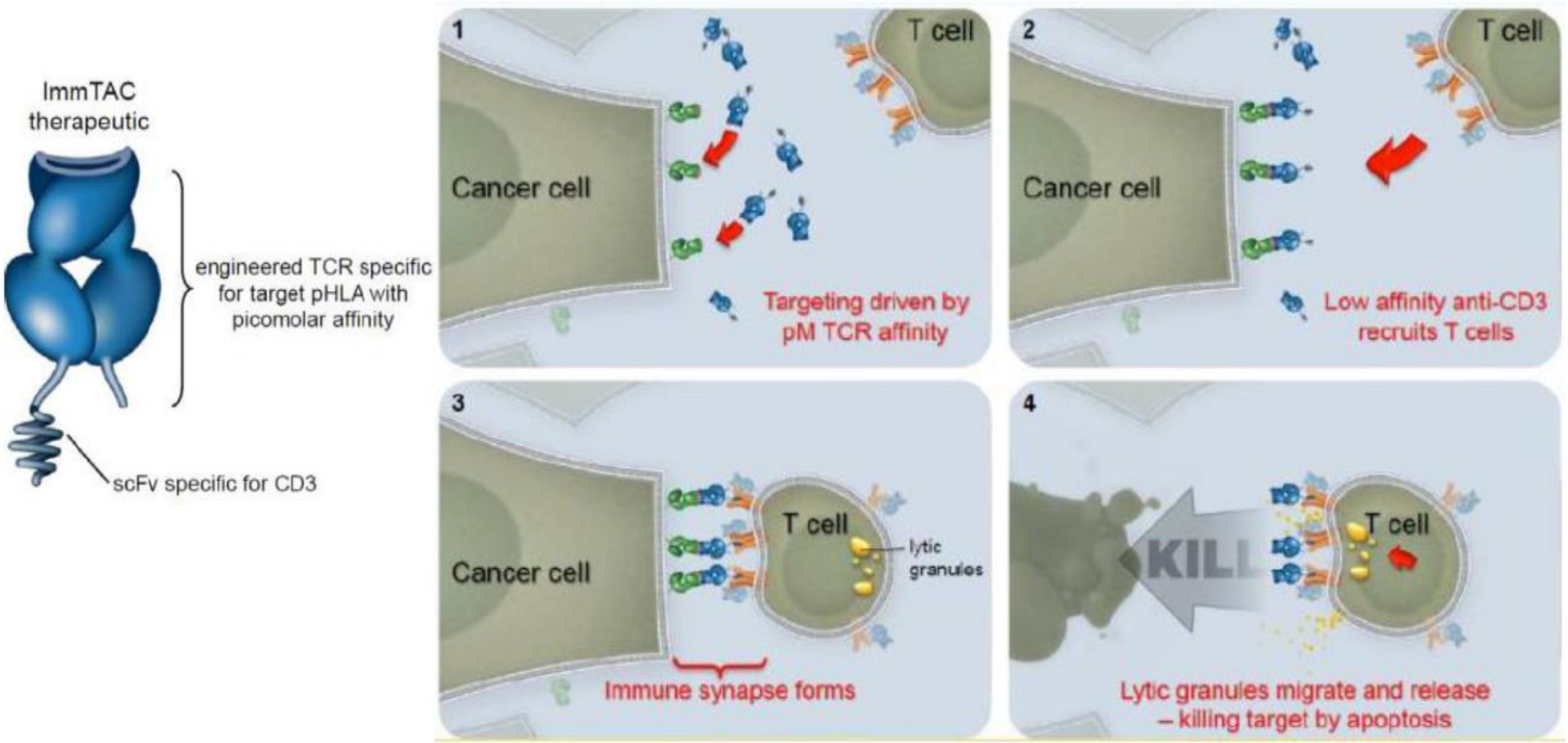
Dexheimer TS. DNA Repair of Cancer Stem Cells. 2013.

Adoptive T cell therapy can involve engineered (CAR, TCAR) or patient-derived (TIL, PBMC) T cells



Engineered T-cell redirector

IMCgp100 (ImmTAC gp100 & CD3)



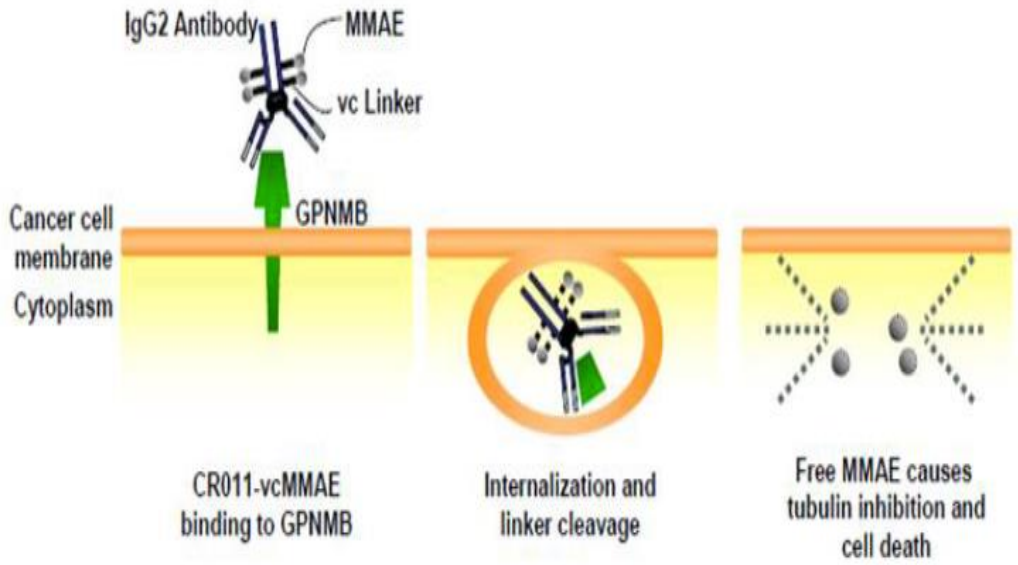
Middleton et al. ASCO 2016

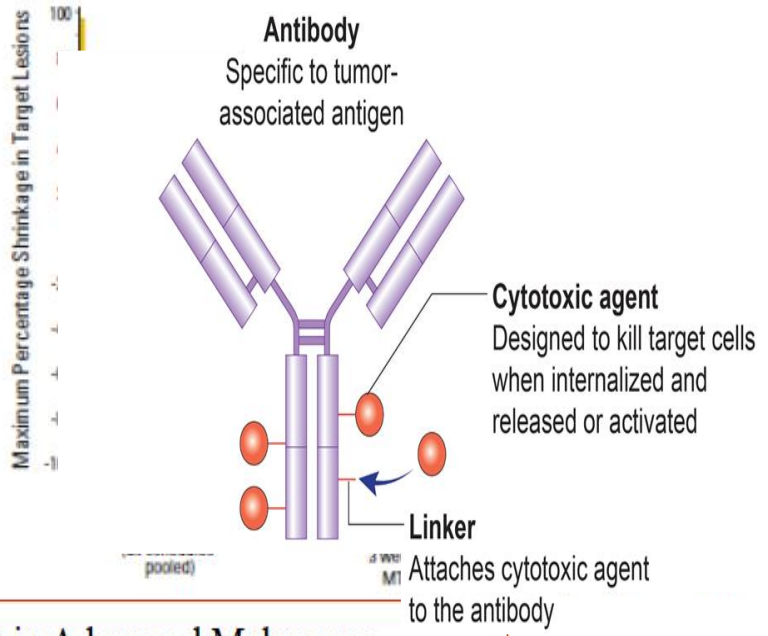
Antibody-drug conjugate

- Glembatumumab vendotin (CDX-011)
- Targets gpNMB
- Expressed on melanocytes, cutaneous and uveal melanoma

MTD (all schedules pooled; n = 32)

Event	All Grades	Grade 3 or Higher
Nonhematologic toxicity		
Rash	81	22
Fatigue	63	13
Pruritus	59	3
Alopecia	41	—
Diarrhea	38	6
Neuropathy	34	3
Nausea	41	—
Anorexia	28	3
Dysgeusia	16	—
Constipation	16	—
Vomiting	25	—
Myalgia	19	6
Dry skin	9	—
Pyrexia	13	—
Pain in extremity	6	—
Arthralgia	16	6
Mucosal inflammation	9	6





Phase 2 Study of Glembatumumab Vedotin +/- Varlilumab (CD27) in Advanced Melanoma

Phase 2 Study of Glembatumumab Vedotin for Metastatic Uveal Melanoma

Ott et al. J Clin Oncol 2014

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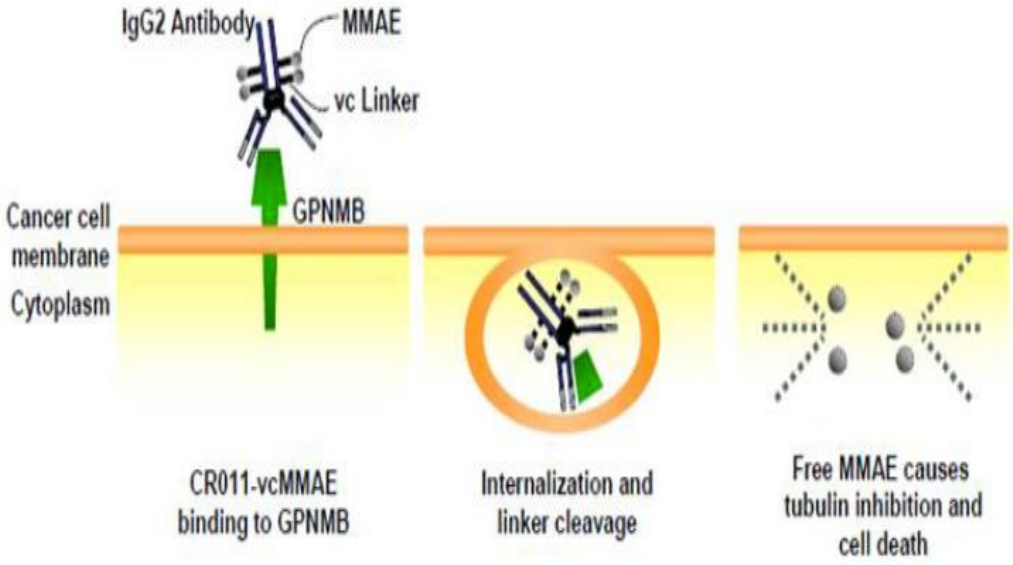
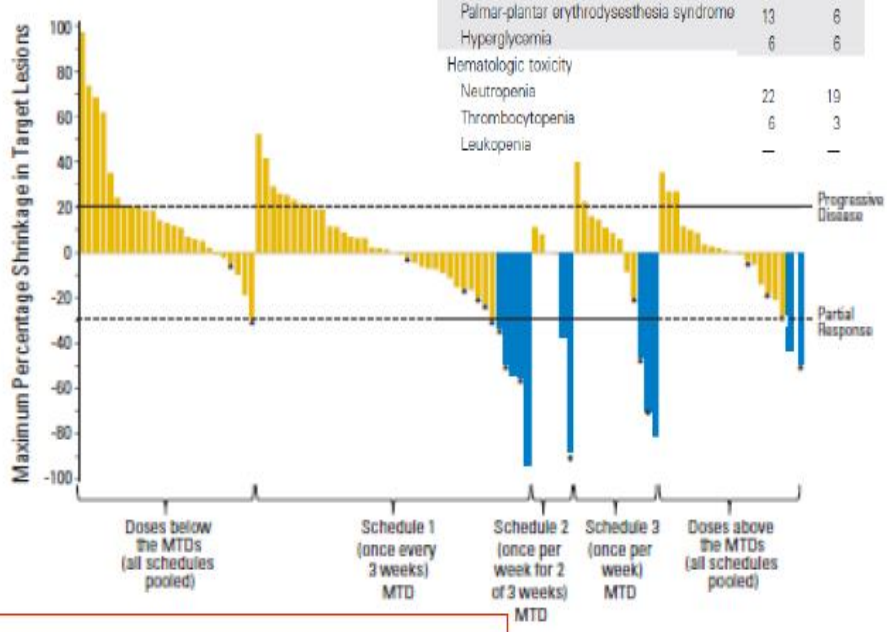
Vomiting	25	—
Myalgia	19	6
Dry skin	9	—
Pyrexia	13	—
Pain in extremity	6	—
Arthralgia	16	6
Mucosal inflammation	9	6
Palmar-plantar erythrodysesthesia syndrome	13	6
Hyperglycemia	6	6
Hematologic toxicity		
Neutropenia	22	19
Thrombocytopenia	6	3
Leukopenia	—	—





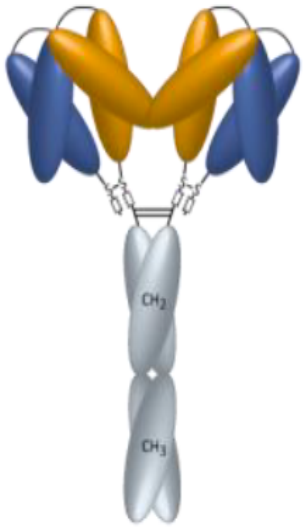
Phase 2 Study of Glembatumumab Vedotin +/- Varlilumab (CD27) in Advanced Melanoma

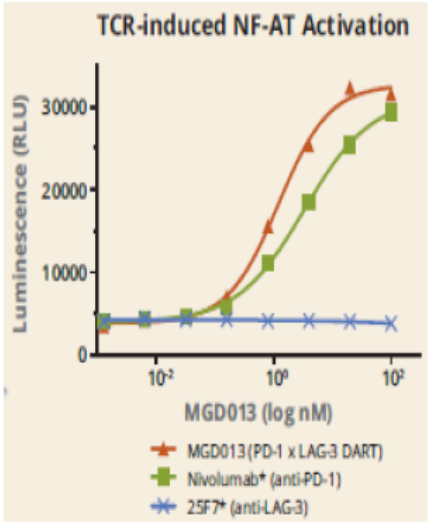
Phase 2 Study of Glembatumumab Vedotin for Metastatic Uveal Melanoma

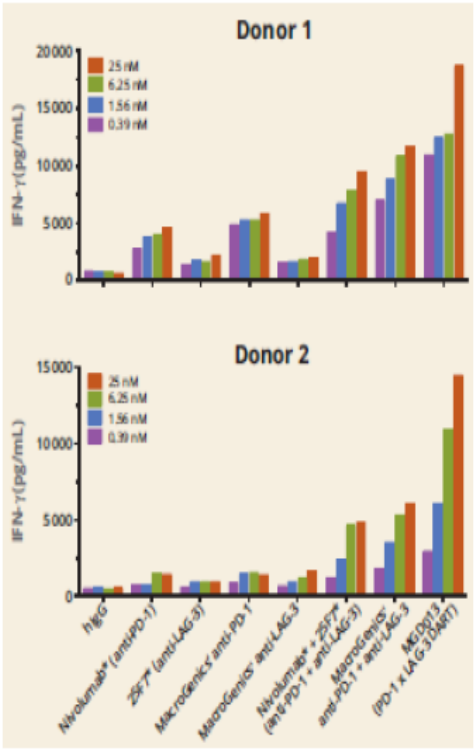
Ott et al. J Clin Oncol 2014

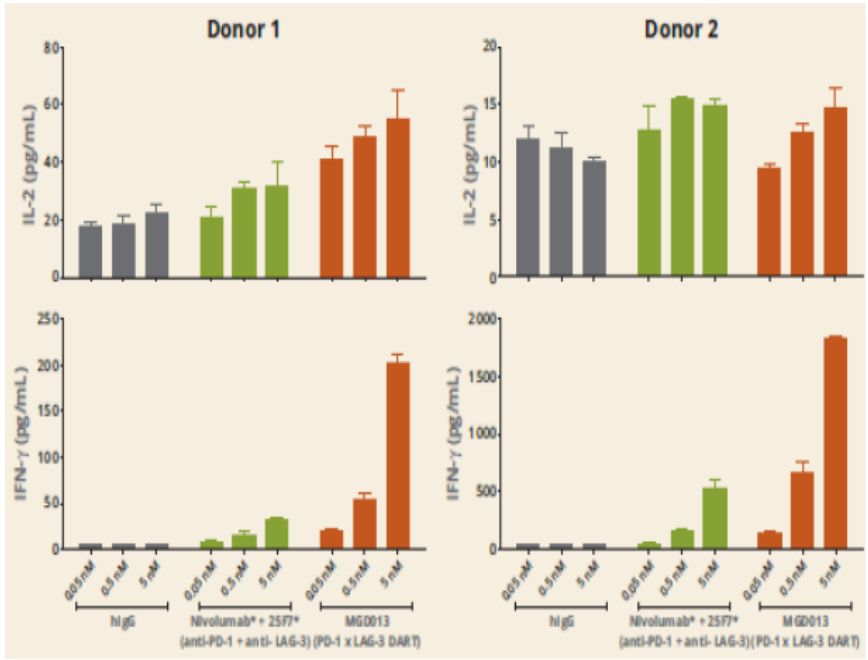
Bispecific PD-1 x LAG-3 DART Checkpoint Inhibitor Molecule

PD1 - LAG3







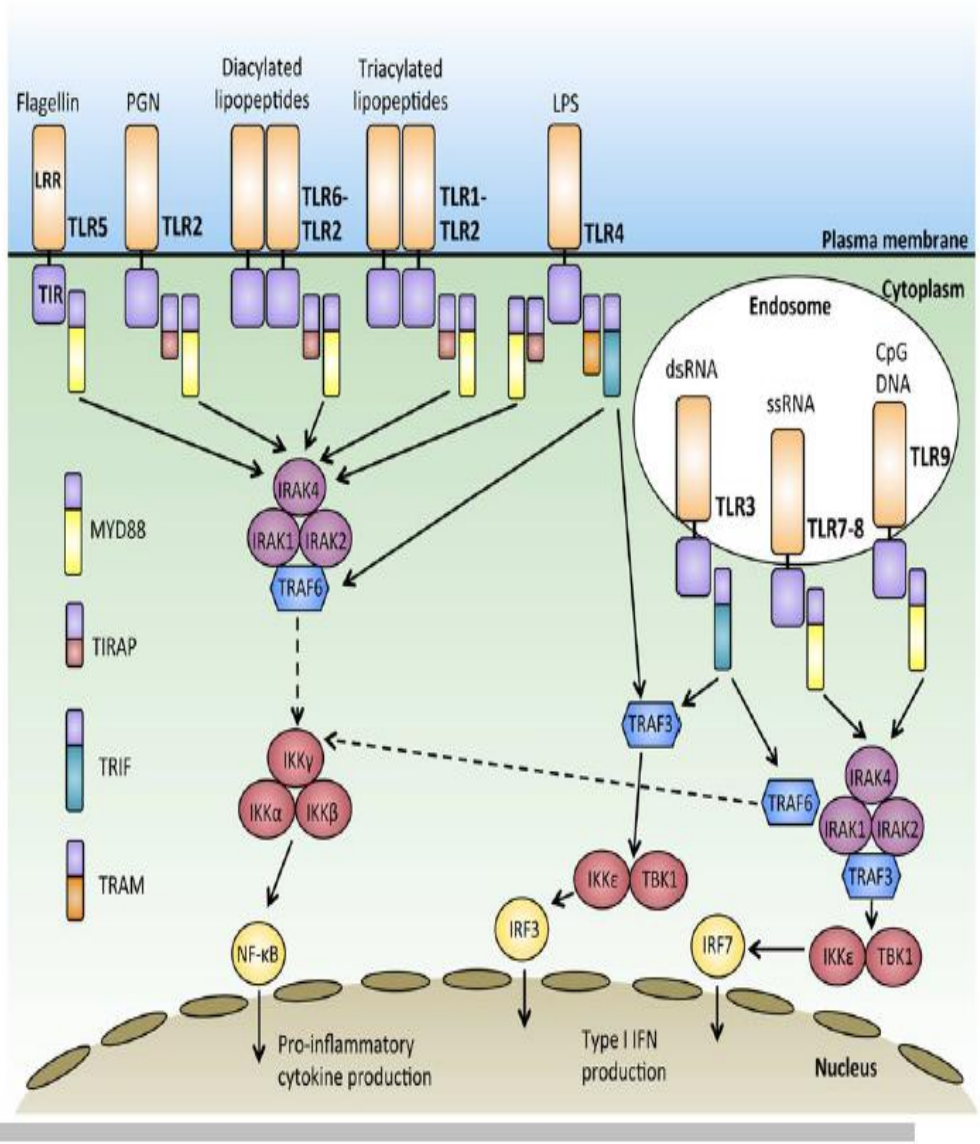


Motte-Mohs et al. AACR 2016

Innate Immune-Tumor Sensing

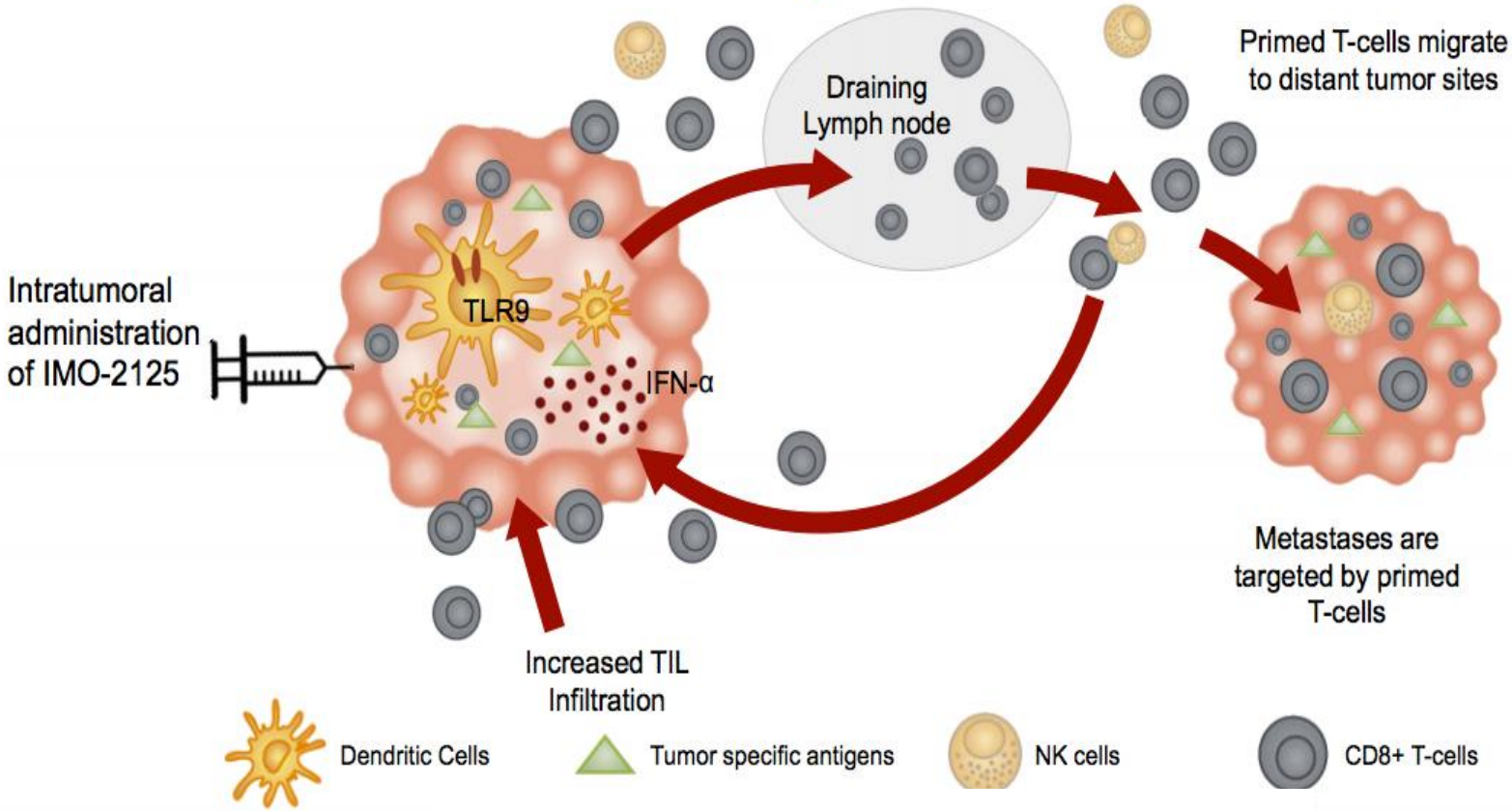
- TLR agonists
- STING agonists
  - Poly-ICLC (TLR3)
  - G100 (TLR4)
  - Imiquimod (TLR7)
  - SD-101 (TLR9)
  - CYT003 (TLR9)

Multiple TLR agonist clinical trials in combination with tumor vaccines and check-point blockade on-going



Wang et al. Front. Immunol 2014

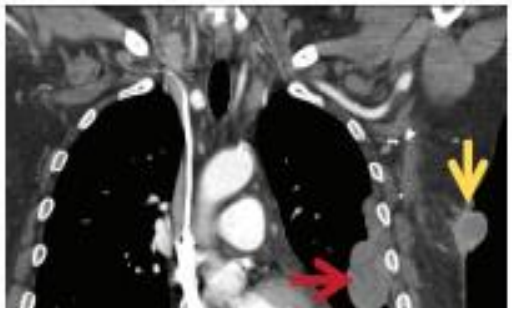
Modulation of the tumor microenvironment by intratumoral administration of IMO-2125

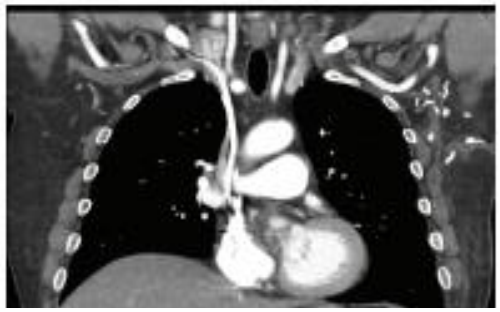


Cornfeld, MJ. SITC 2016

Tumor imaging of patient with a complete response

Pre-Therapy
03/2016

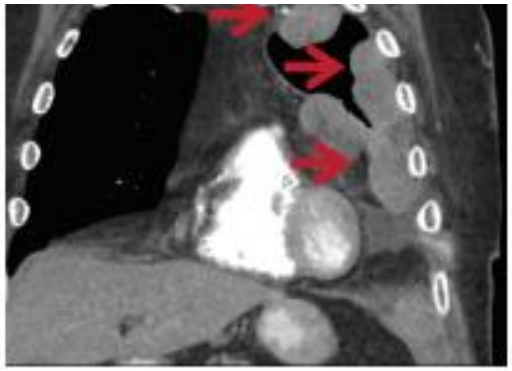


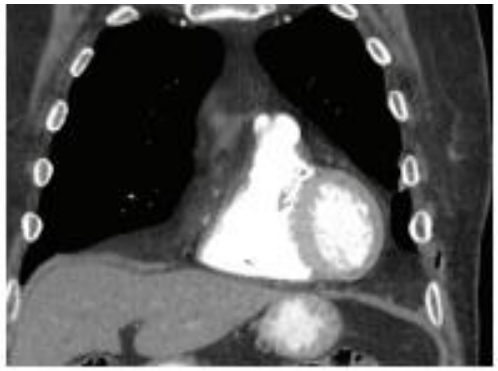


Post-Therapy
08/2016

A Randomized Phase 3 Comparison of IMO-2125 with Ipilimumab versus Ipilimumab Alone in Subjects with Anti-PD-1 Refractory Melanoma

Distant Lesions





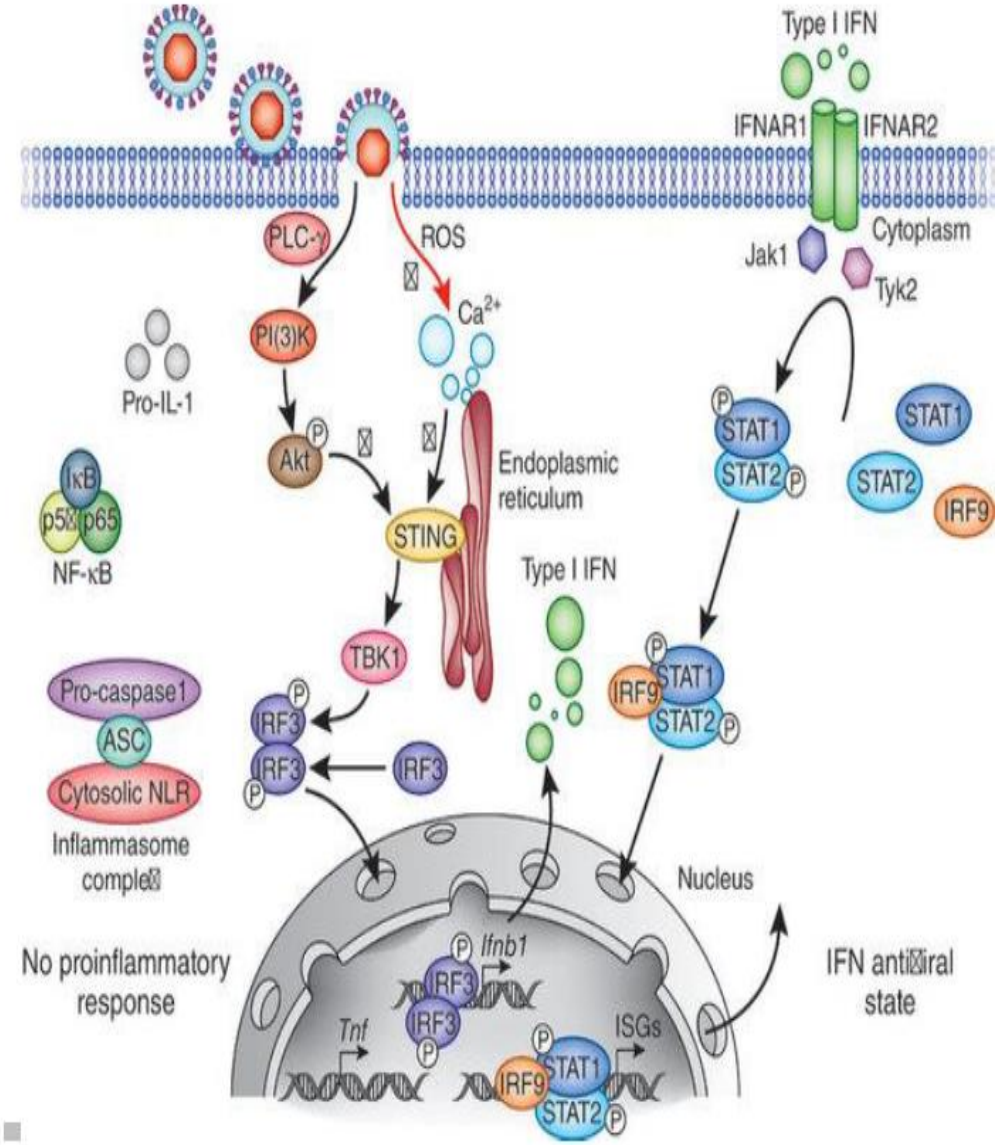
Diab A. ESMO 2016

Innate Immune-Tumor Sensing

- TLR agonists
- STING agonists

Virotherapy

- Talamogene laharparepvec (T-VEC)
- Coxsackievirus A21 (CVA21)
- JX-594
- ONCOS-102
- Pelareorep



Pol et al. OncoImmunology 2016

T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

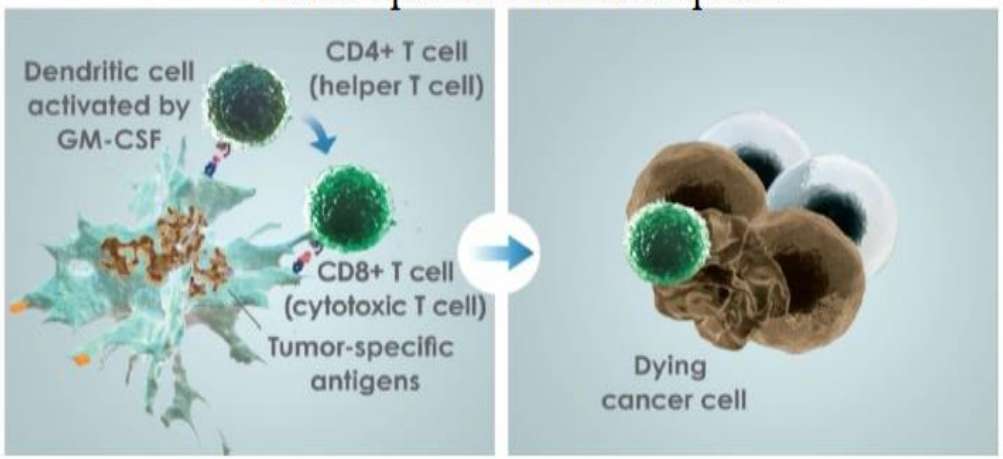
Local Effect:
Virally-Induced Tumor Cell Lysis

OPTiM: Ph 3 T-VEC vs GM-CSF[1]

- Improved Durable Response Rate (response for ≥6 months)
- 16% vs 2%, p<0.0001
- *led to FDA approval 2015*

Tumor-Specific Immune Response

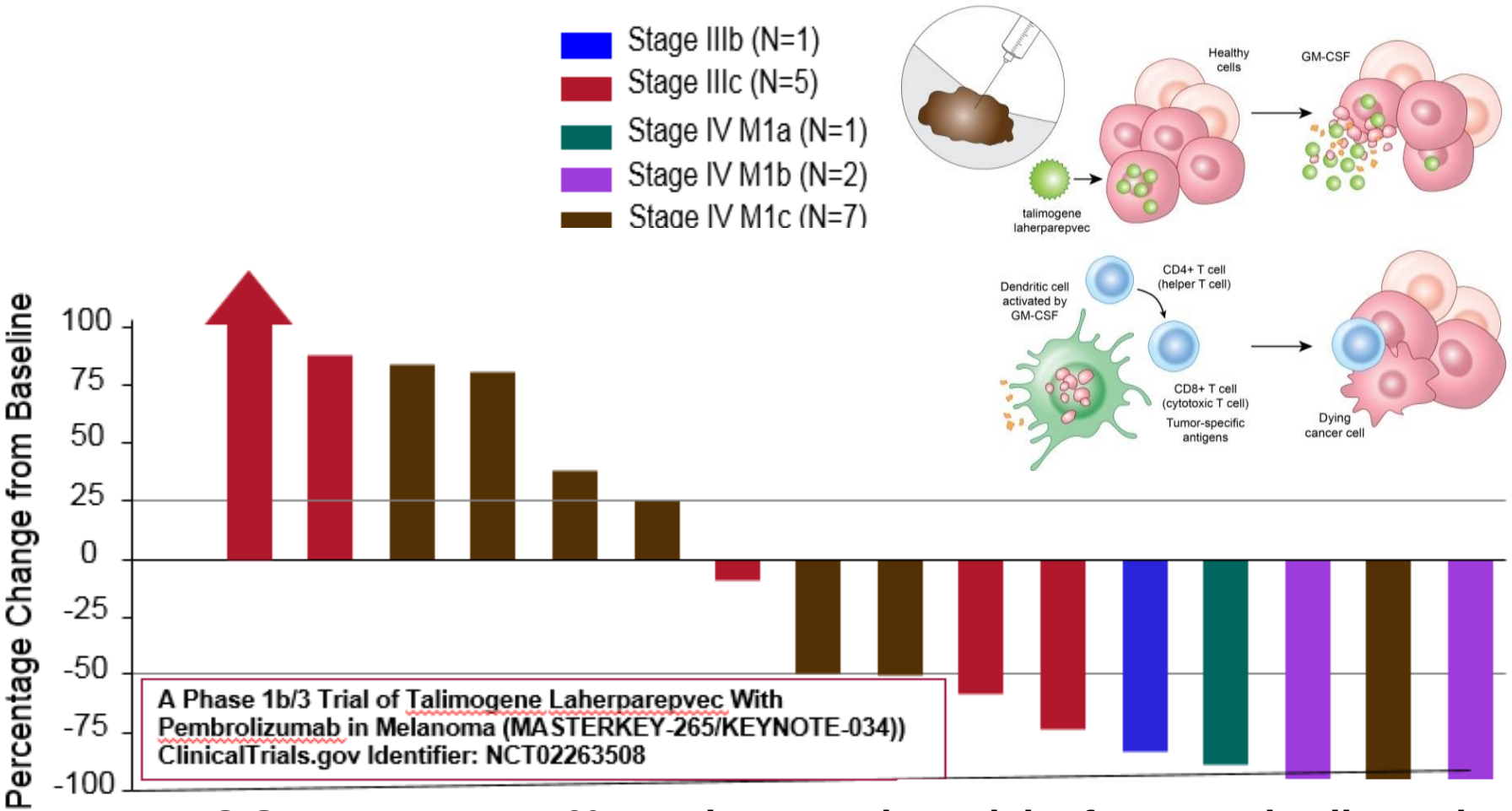
Systemic tumor-specific immune response



Death of distant cancer cells

Kaufman et al. ASCO (2014), abstr LBA9008

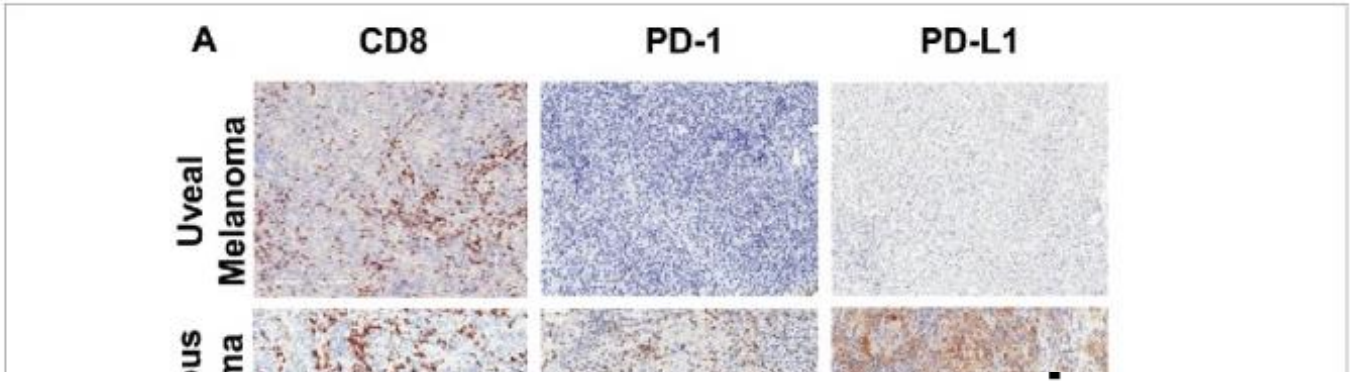
T-VEC + Pembrolizumab in Stage IIIB-IV Melanoma



RECIST response = 46%, no increase in toxicity from pembrolizumab alone

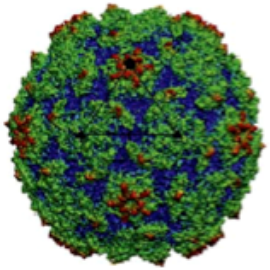
Long et al. SMR 2015

Uveal melanoma is a “cold” tumor that primarily metastasizes to the liver



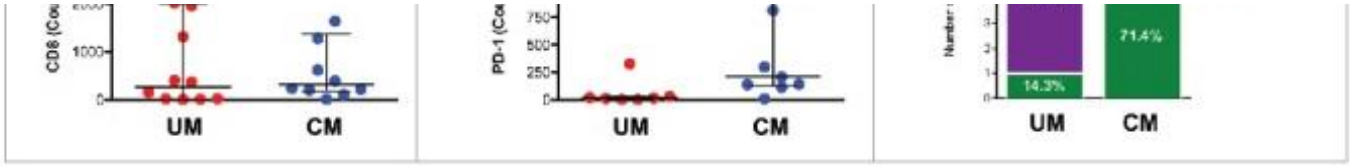
TREATMENT

- Chemotherapy
- Targeted Rx
- Checkpoint



Coxsackievirus A21 (CVA21)

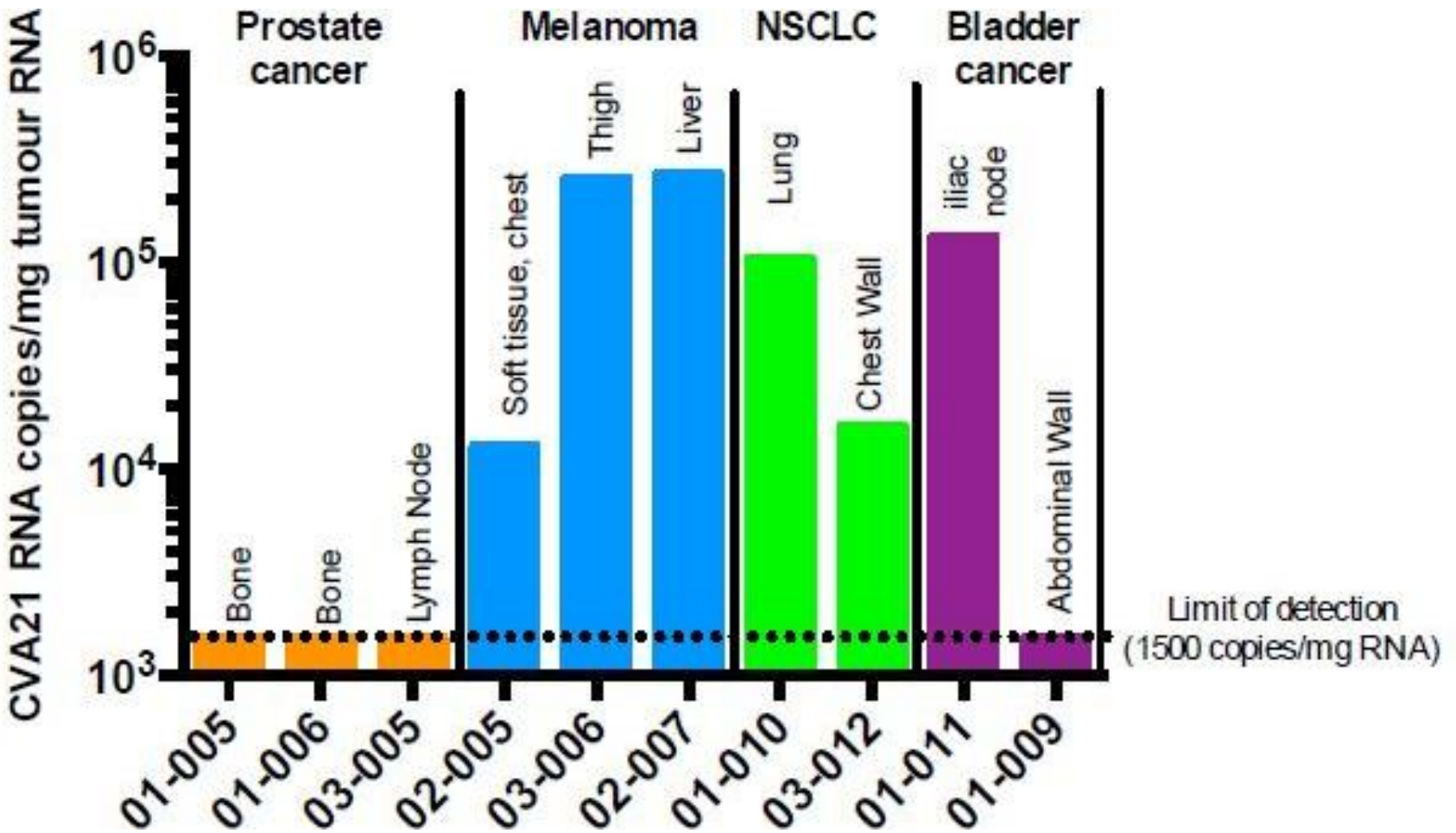
Non-enveloped, single –stranded RNA virus
In general, CVA21 natural infection causes mild upper respiratory illness “common cold”



Decreased PD-1 and PD-L1 expression in UM metastases. (A) Representative IHC for CD8, PD-1, and PD-L1 in UM and CM metastatic tissues. Quantification of CD8 (B), PD-1 (C), and PD-L1 (D) in UM and CM metastases as counts/mm2 (B-C) and % positivity (D). Each dot represents a sample. Green, PD-L1-positive; Purple, PD-L1-negative. Statistical comparison between UM and CM cohorts was performed using non-parametric Mann-Whitney test (B-C) and Chi-square test (D).

Qin Y, Petaccia de Macedo M, Reuben A, et al. Parallel profiling of immune infiltrate subsets in uveal melanoma versus cutaneous melanoma unveils similarities and differences: A pilot study. Oncoimmunology. 2017;6(6):e1321187. doi:10.1080/2162402X.2017.1321187.

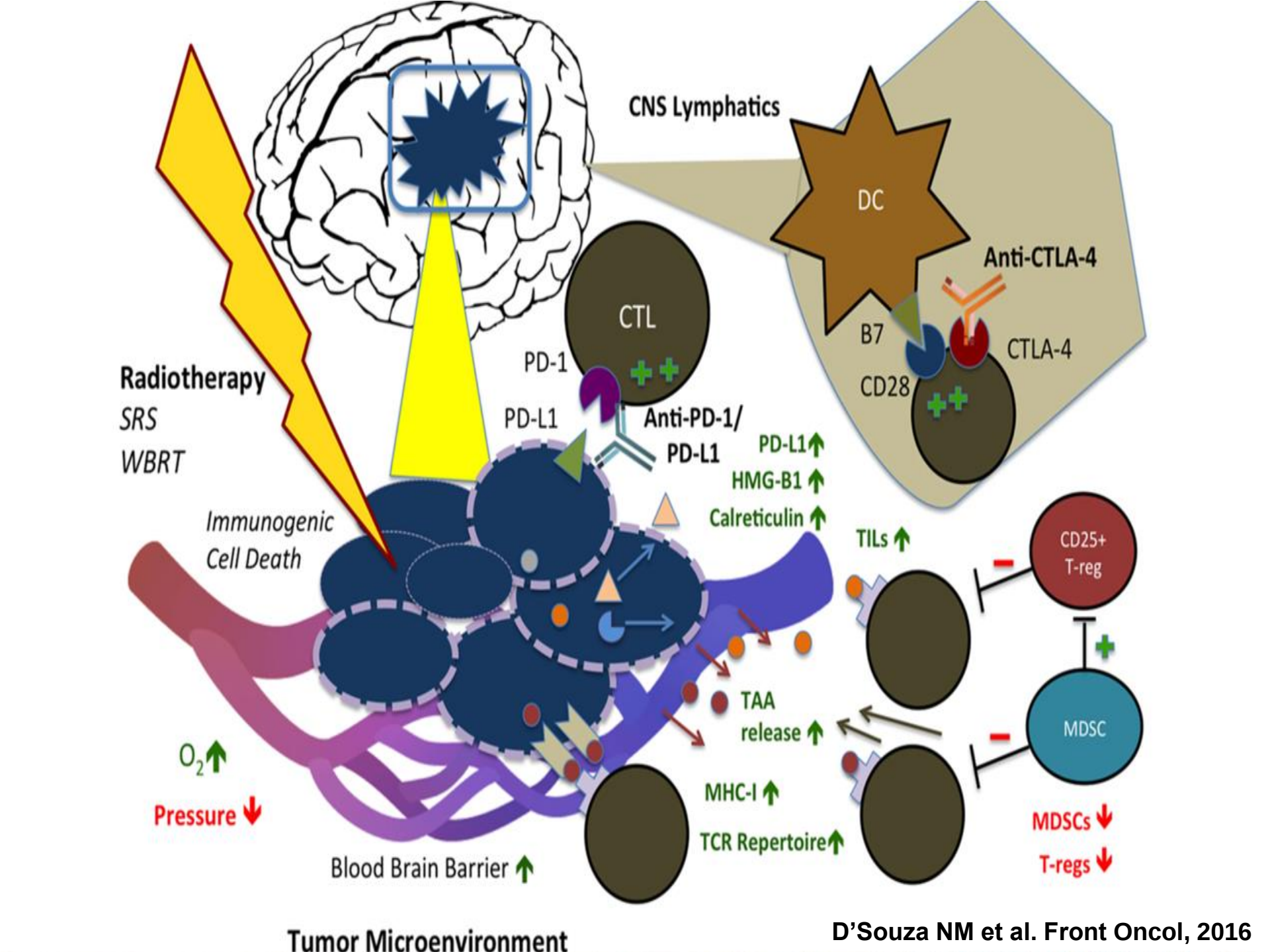
CVA21 levels in tumor cells after IV administration in stage IV cancer patients



Liauw WS, Chern B, Shafren DR. Phase I, Open-Label, Cohort Study of CAVATAK (Coxsackievirus A21), Given Intravenously to Stage IV Patients Bearing ICAM-1 Expressing Solid Tumours; Poster presented at: EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; 6–9 November 2012; Dublin, Ireland

VLA-24 Study Design

- Phase 1b, open label for patients with metastatic uveal melanoma
- CVA21 intravenous infusion – max of 8 cycles (11 infusions) per subject
- Ipilimumab co-administered AFTER first 4 doses of CVA21 on Days 8, 29, 50 and 71
- On days were ipilimumab is given with CVA21, CVA21 will be given first.
- 10 patients
- 2-3 study sites



D'Souza NM et al. Front Oncol, 2016

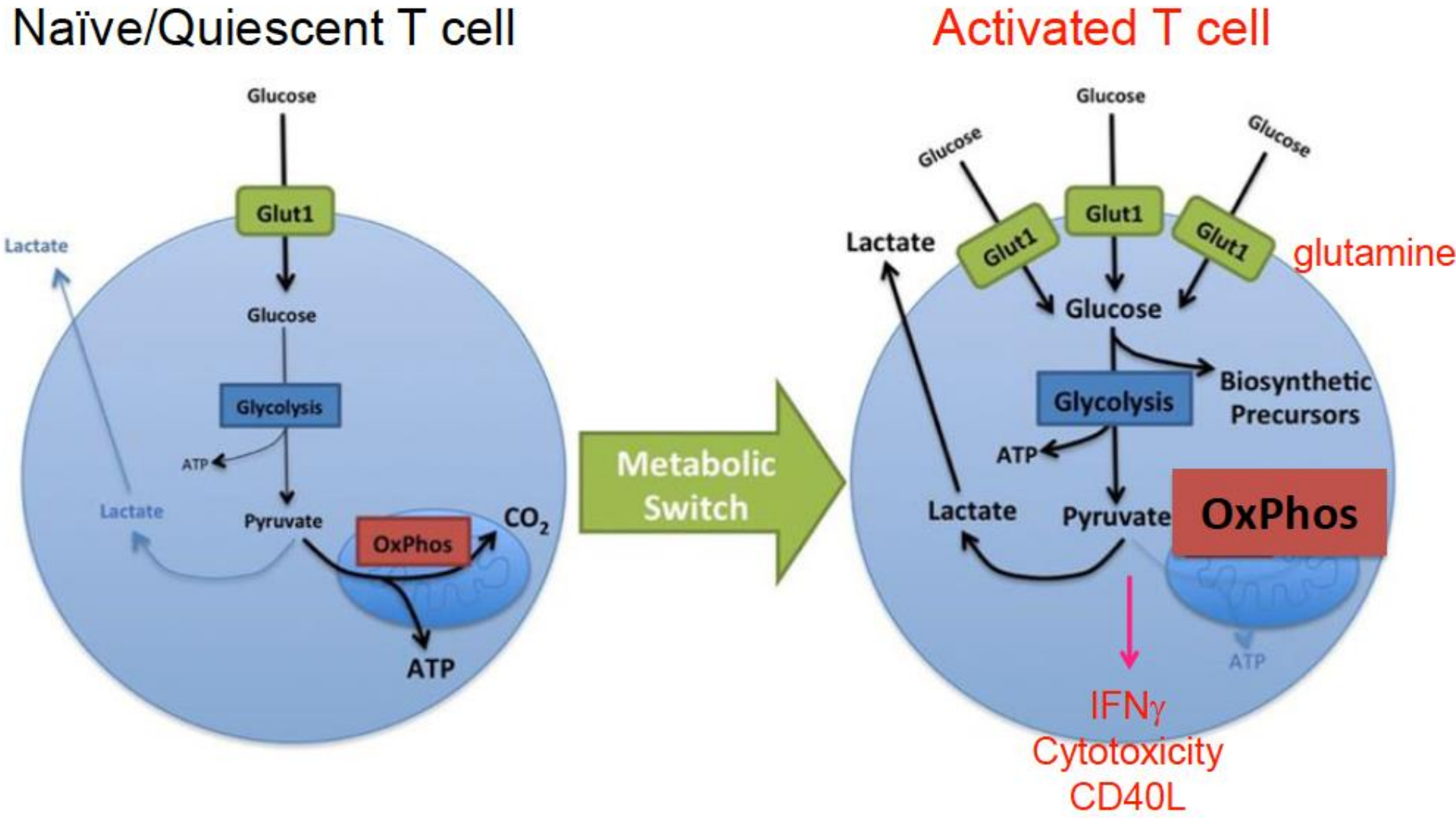
TABLE 1 | Current clinical trials of immunotherapy with radiation for primary and metastatic CNS malignancy.

Study phase	Institution/ group	ClinicalTrials. gov ID	Disease site	Cohorts	Planned accrual	IT mechanism	Est. completion date	Primary outcome measure
II	Multi-institutional (CheckMate548)	NCT02667587	Newly diagnosed glioblastoma	Nivolumab + temozolomide + RT vs. placebo + temozolomide + RT	$n = 320$	anti-PD-1	May 2017	OS
III	Multi-institutional (CheckMate498)	NCT02617589	Newly diagnosed glioblastoma	Nivolumab + RT vs. temozolomide + RT	$n = 550$	anti-PD-1	October 2019	OS
II	Ludwig Institute for Cancer Research	NCT02336165	Newly diagnosed, recurrent glioblastoma	MEDI4736 vs. MEDI4736 + standard RT vs. MEDI4736 + bevacizumab	$n = 108$	anti-PD-1	July 2017	OS, PFS
I/II	Northwestern University	NCT02530502	Newly diagnosed glioblastoma	RT + temozolomide + pembrolizumab → temozolomide + pembrolizumab	$n = 50$	anti-PD-1	March 2018	Dosage, PFS, OS
I	H. Lee Moffitt Cancer Center	NCT02313272	Recurrent glioma	HFSRT + pembrolizumab + bevacizumab	$n = 32$	anti-PD-1	June 2017	Dosage
I/II	MD Anderson Cancer Center	NCT02696993	NSCLC BM	Nivolumab + SRS; nivolumab + WBRT; nivolumab + ipilimumab + SRS; nivolumab + ipilimumab + WBRT	$n = 130$	anti-PD-1; anti-CTLA-4	April 2020	Dosage; PFS
II	Grupo Español Multidisciplinar de Melanoma (GEM)	NCT02115139	Melanoma BM	Ipilimumab + WBRT	$n = 66$	anti-CTLA-4	October 2016	1-year survival rate
II	University of Michigan Cancer Center	NCT02097732	Melanoma BM	Ipilimumab → SRS → ipilimumab vs. SRS → ipilimumab	$n = 40$	anti-CTLA-4	May 2017	Local control rate
I	Thomas Jefferson University	NCT01703507	Melanoma BM	Ipilimumab + WBRT vs. ipilimumab + SRS	$n = 24$	anti-CTLA-4	November 2017	Dosage
I	Sidney Kimmel Comprehensive Cancer Center	NCT01950195	Melanoma BM	Ipilimumab + SRS	$n = 30$	anti-CTLA-4	December 2016	Adverse events and safety
II	University Hospital, Lille	NCT02662725	Melanoma BM	Ipilimumab + SRS	$n = 73$	anti-CTLA-4	December 2015	OS

RT, radiation therapy; PD-1, programmed cell death protein 1; OS overall survival, PFS, progression-free survival; HFSRT, hypofractionated stereotactic radiotherapy; IMRT, intensity-modulated radiation therapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; irRC, immune-related response criteria; WBRT, whole brain radiation therapy; NSCLC, non-small cell lung cancer; BM, brain metastases; SRS, stereotactic radiosurgery; MM, metastatic melanoma; SBRT, stereotactic body radiation therapy.

D'Souza NM et al. Front Oncol, 2016

Metabolic switch to aerobic glycolysis is essential for effector T cell development and function



Kaech S. Presented at SITC annual Meeting, Nov 2017

Metabolic approaches in IO

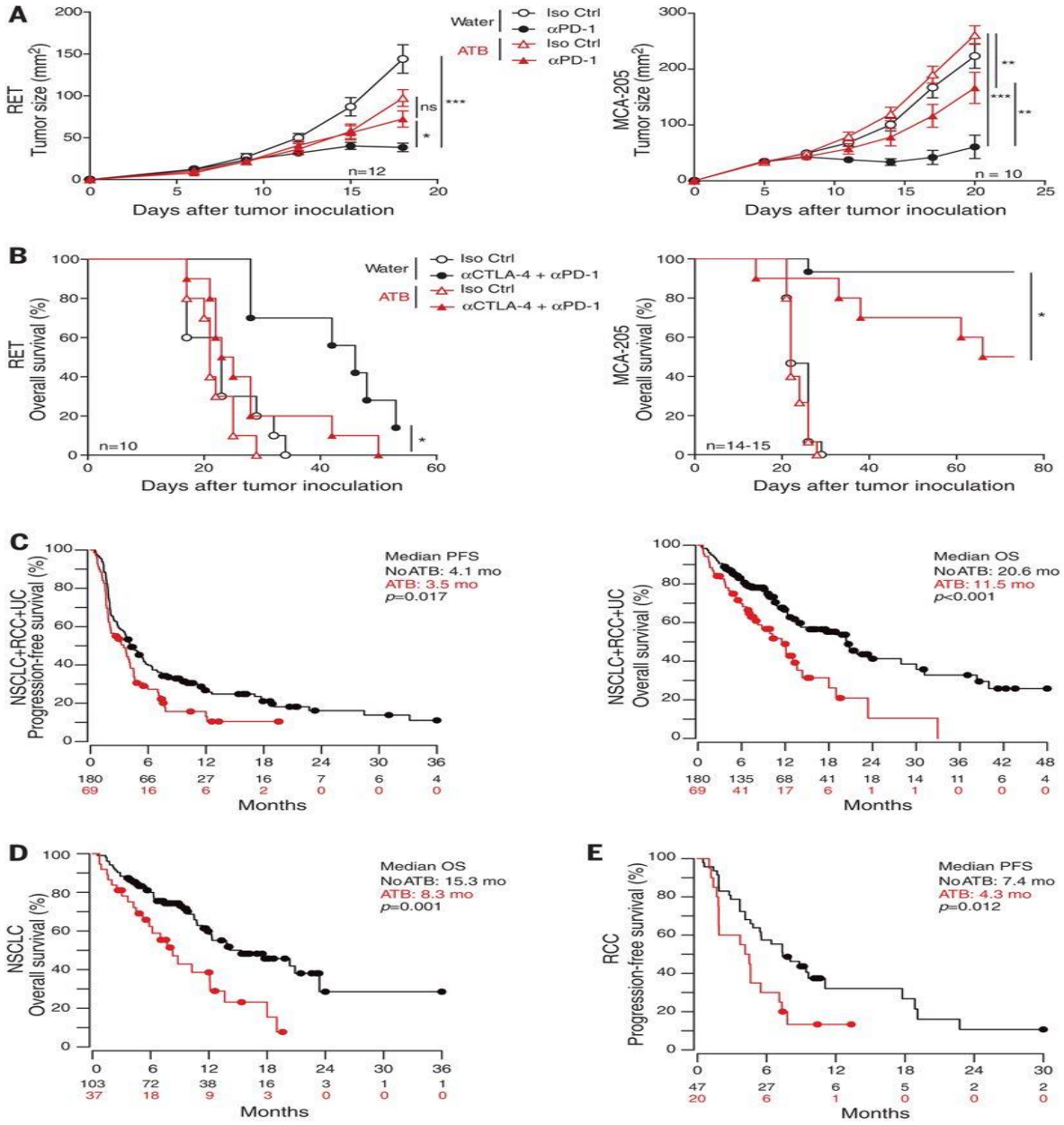
- Adenosine (A2A receptor block)
- Arginine depletion
- Glutamine depletion
- IDO (tryptophan) inhibition
- Hypoxia inducible factor-1 (HIF-1) inhibition
- Oxidative phosphorylation (OXPHOS): metformin
- other

- **Higher gut microbiome *diversity* is associated with improved response to anti–PD-1 immunotherapy in patients with metastatic melanoma**
- ***Compositional* differences in the gut microbiome are associated with responses to anti–PD-1 immunotherapy**
- ***Antibiotics* compromise the efficacy of PD-1 blockade in mouse tumor models and cancer patients**
- **Metagenomic analyses of fecal samples *predicts* response to PD-1 at 3 months in cancer patients**
- **Gut microbiome effects on response to immunotherapy are *transferable***

V. Gopalakrishnan et al. Science 2018;359:97-103;

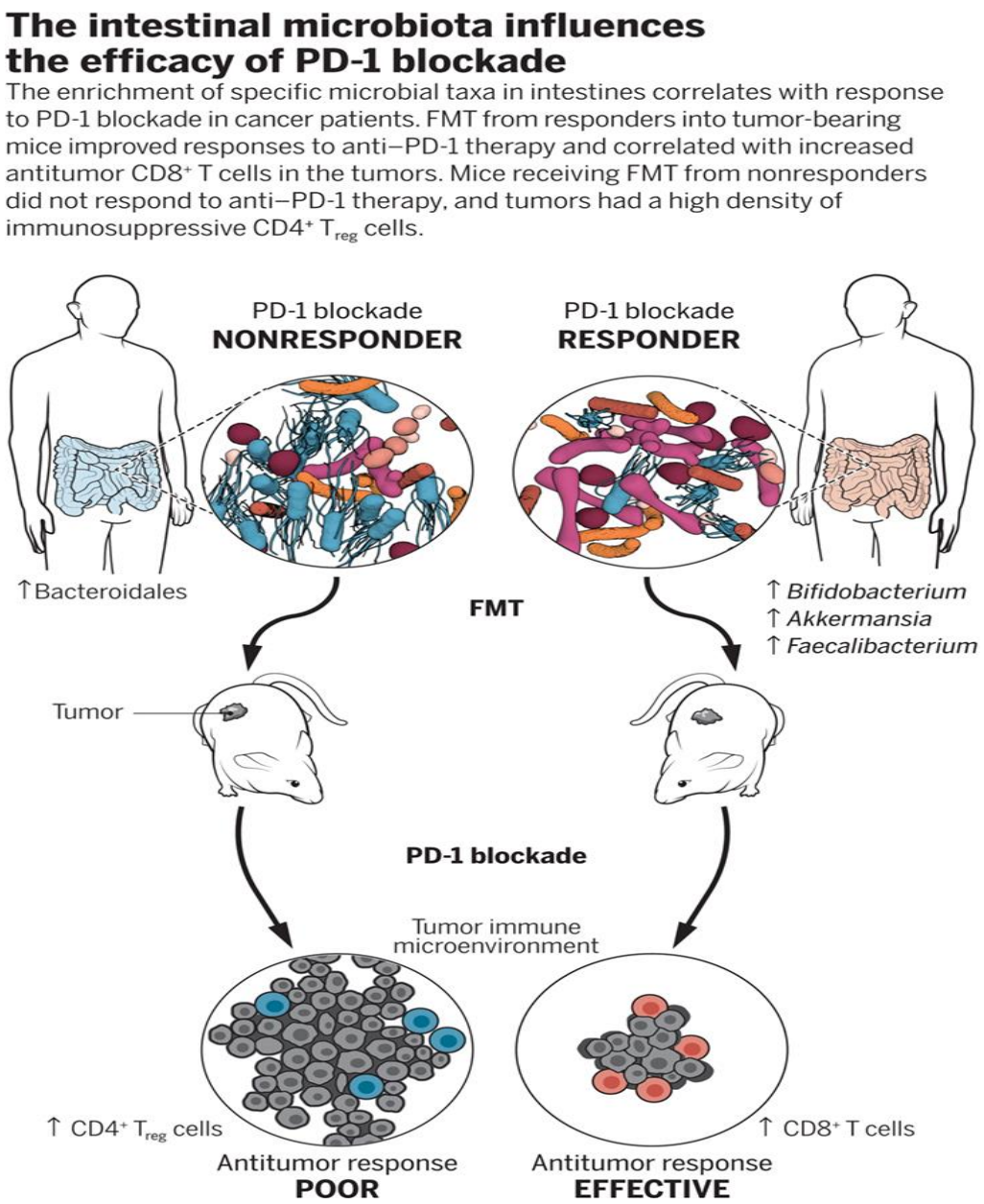
Bertrand Routy et al. Science 2018;359:91-97

Antibiotics compromise the efficacy of PD-1 blockade in mouse tumor models and cancer patients.



Bertrand Routy et al. Science 2018;359:91-97

The intestinal microbiota influences the efficacy of PD-1 blockade



Christian Jobin Science 2018;359:32-34


EVEN
THE FUTURE IS BRIGHTER