ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

Immunotherapy Advances in Melanoma

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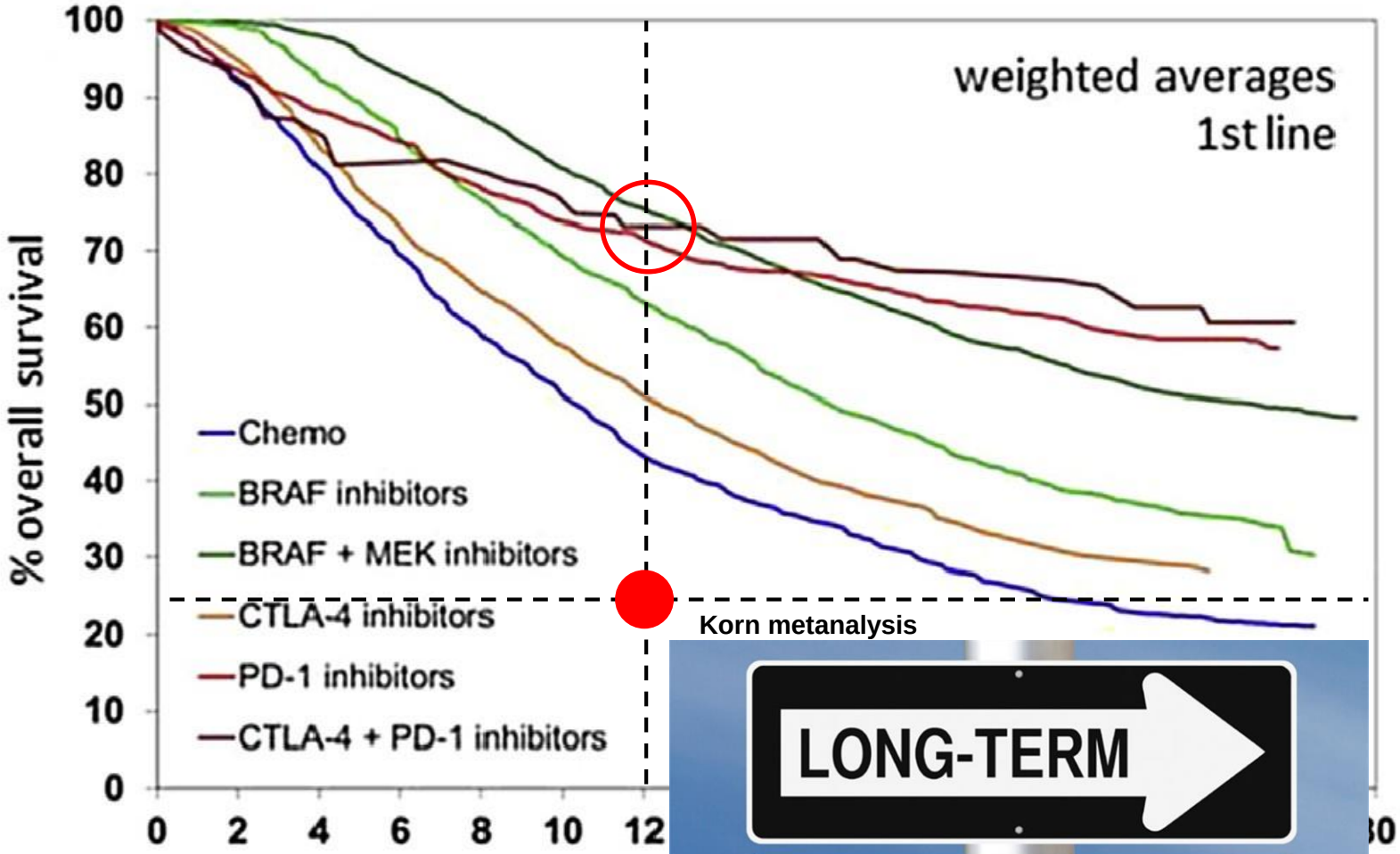
Disclosure

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre-Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes.
- **Stock Ownership:** Primevax
- **Research Funding:** Bristol-Meyers Squibb, Roche-Genentech, Array
- **Expert Testimony:** None
- **Other Remuneration:** Travel support from MSD

First-line therapy: Overall survival

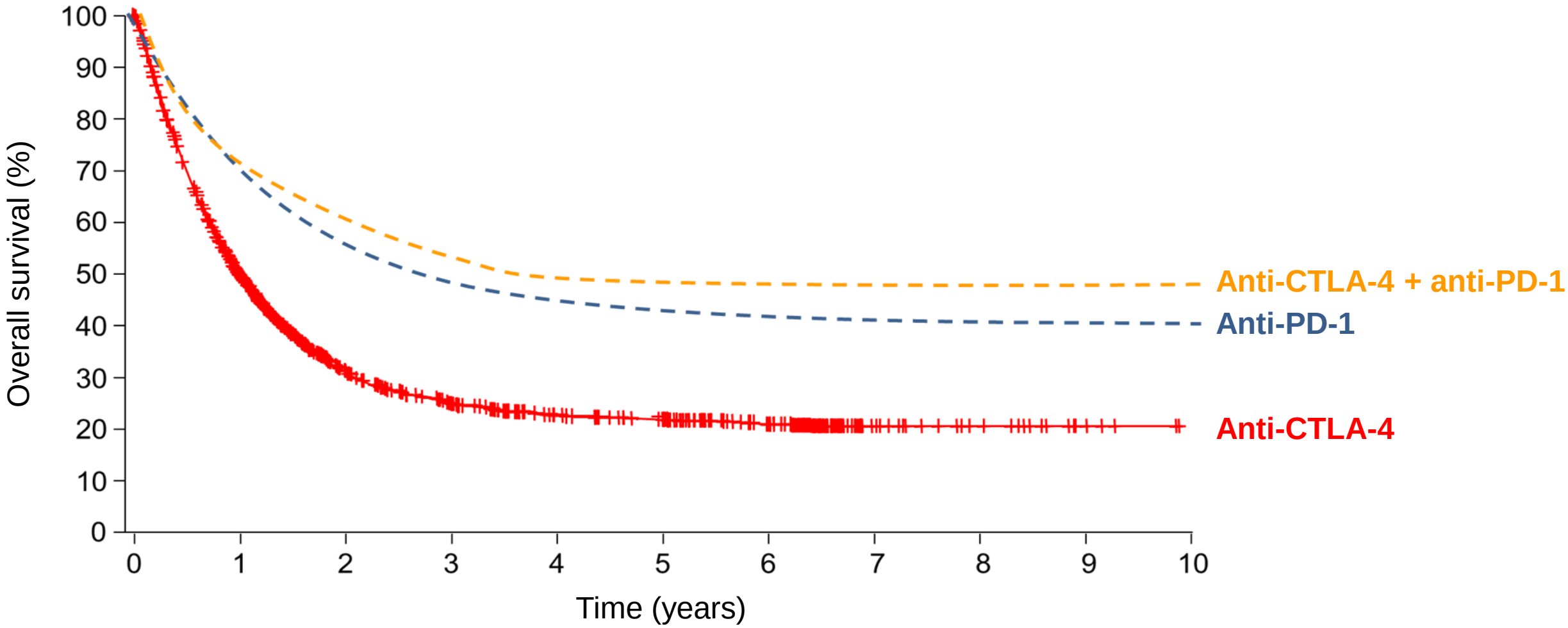


Korn metanalysis

Mean survival curves created by weighted averaging of
Ugurel S, Roehmel J, Ascierto PA, Flaherty KT, Grob JJ, Hau

na patients treated in selected clinical trials.
A, Robert C, Schadendorf D, and Garbe C:
Eur J Cancer 53: 125-134 (2016)

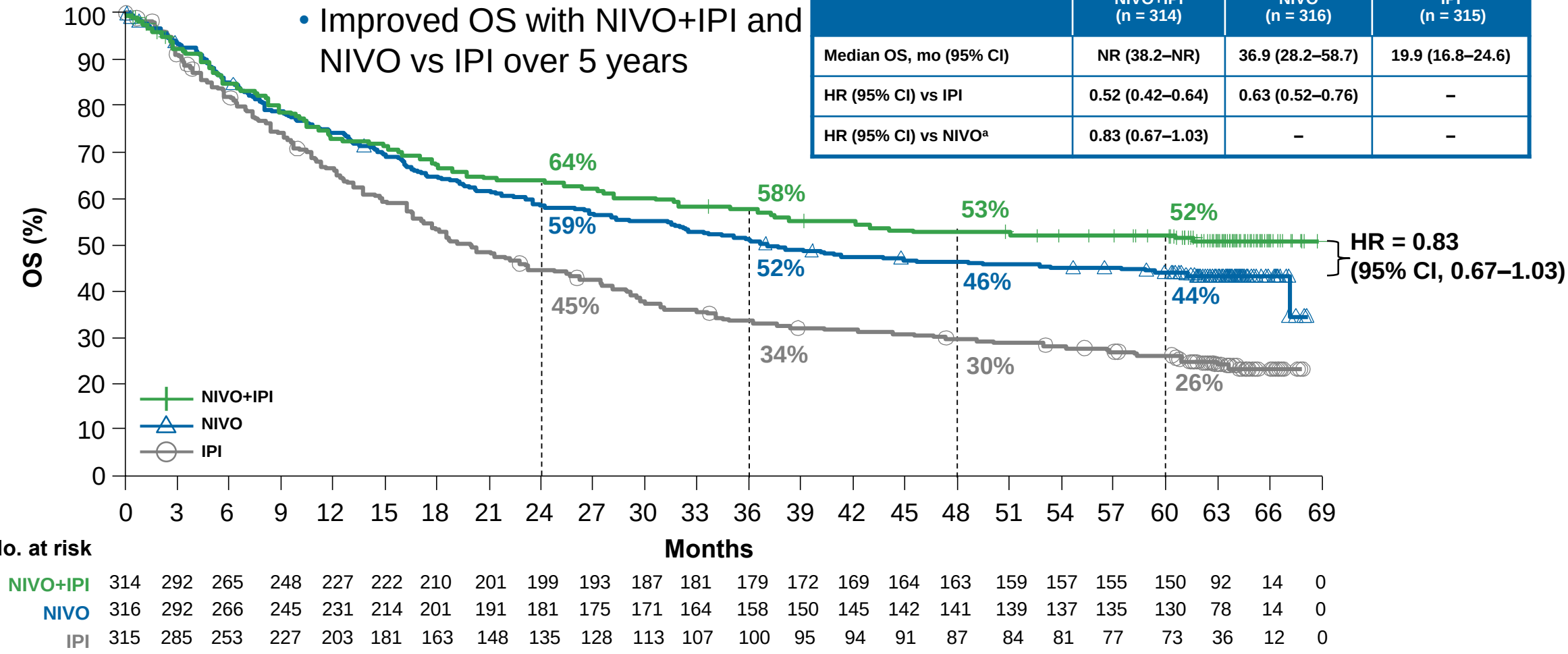
Long-term benefit in metastatic melanoma patients …



Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

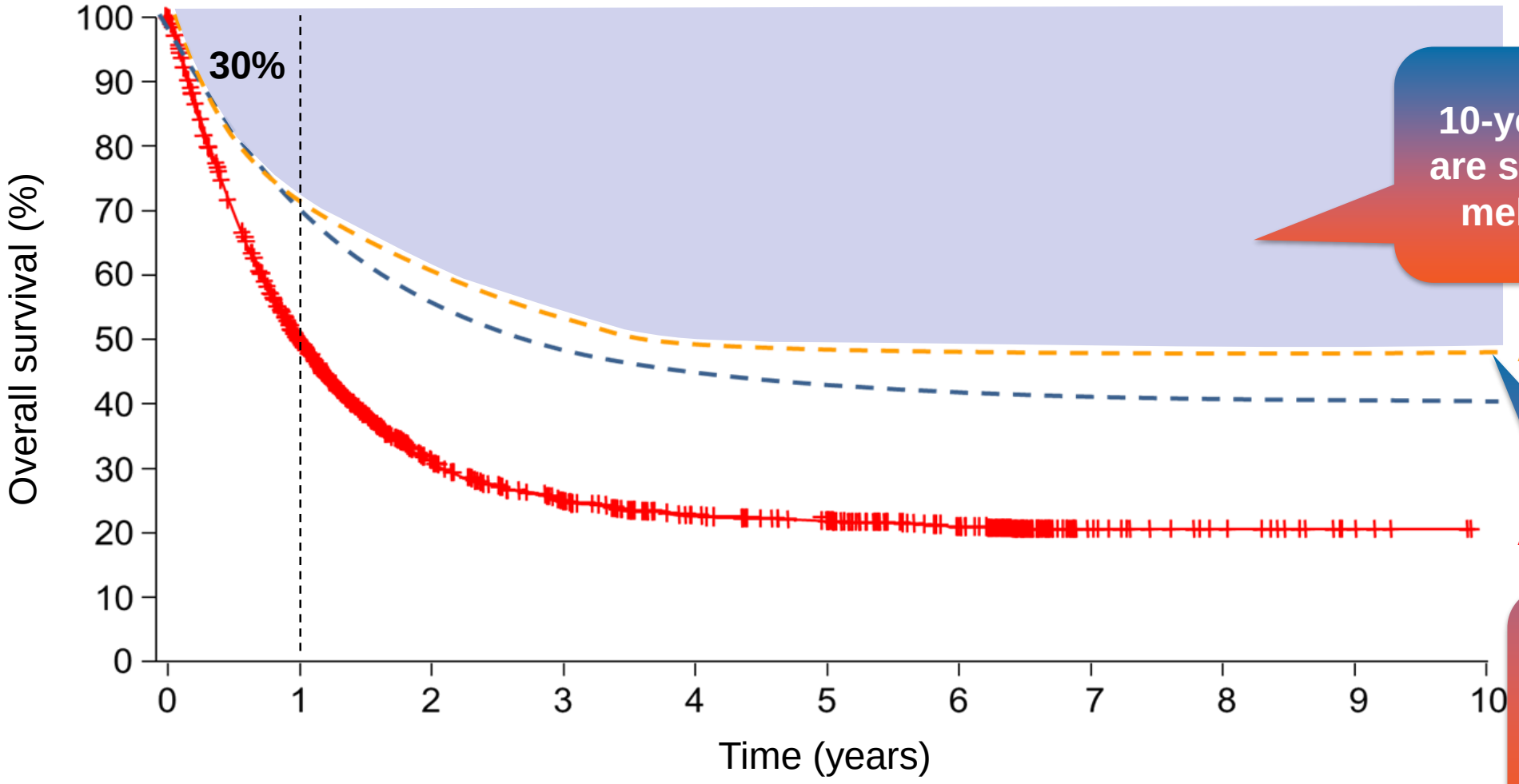
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Larkin et al. NEJM 2019

Despite the durable responses observed, many patients do not benefit from the treatment



10-year survival rates are still poor in 50% of melanoma patients

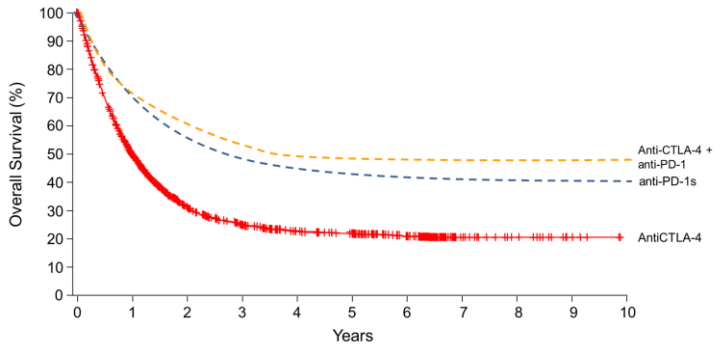
No biomarkers can predict long-term benefit

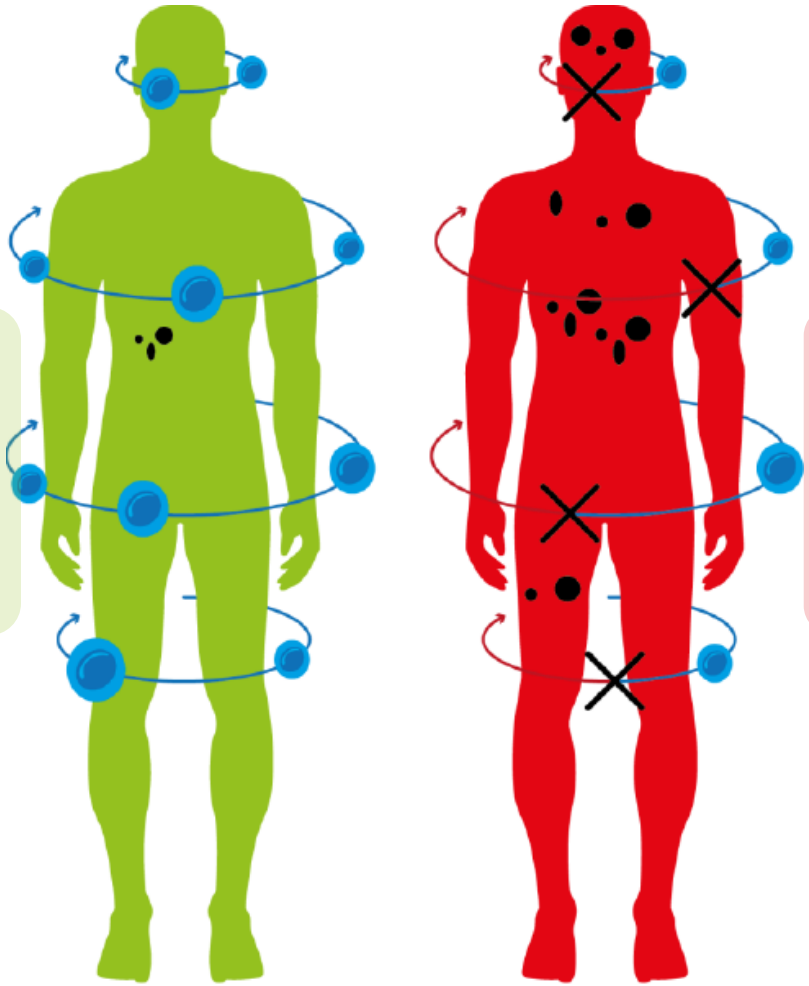
Patient characteristics affecting immune surveillance

Active immune surveillance

Long-term benefit patients

- ≤ 3 brain metastases (size < 2 cm)
- Low tumour burden (< 3 organ involved?)
- Normal LDH

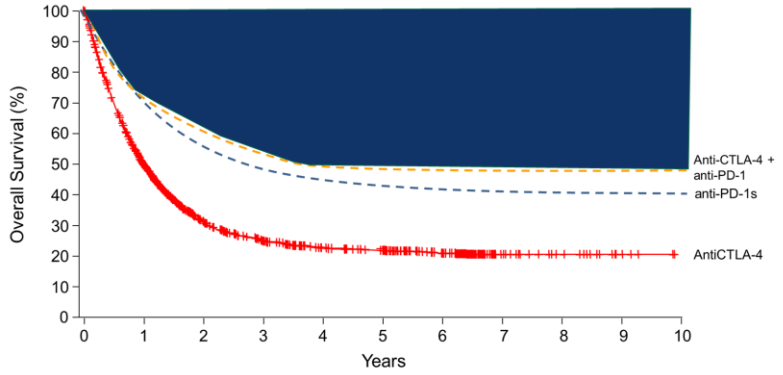




Inactive immune surveillance

No long-term benefit patients

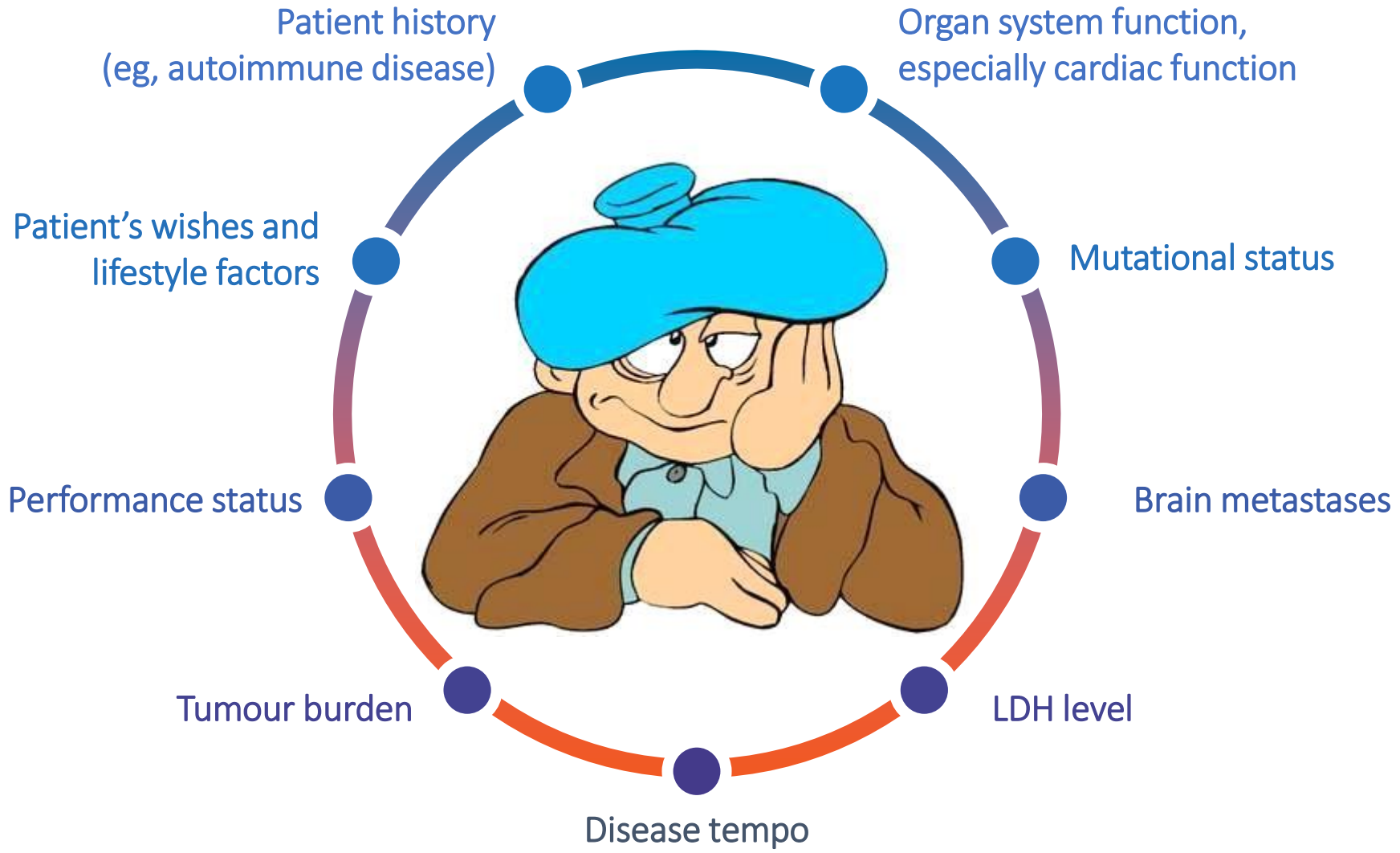
- Multiple (>3) brain metastases
- High tumour burden (>3 organ involved?)
- High LDH



LDH, lactate dehydrogenase

Ascierto P, Dummer R. Oncoimmunology. 2018; Ascierto P, Ed. Session ASCO. 2019

Is there a patient subgroup where combination therapy may have greater clinical benefit?



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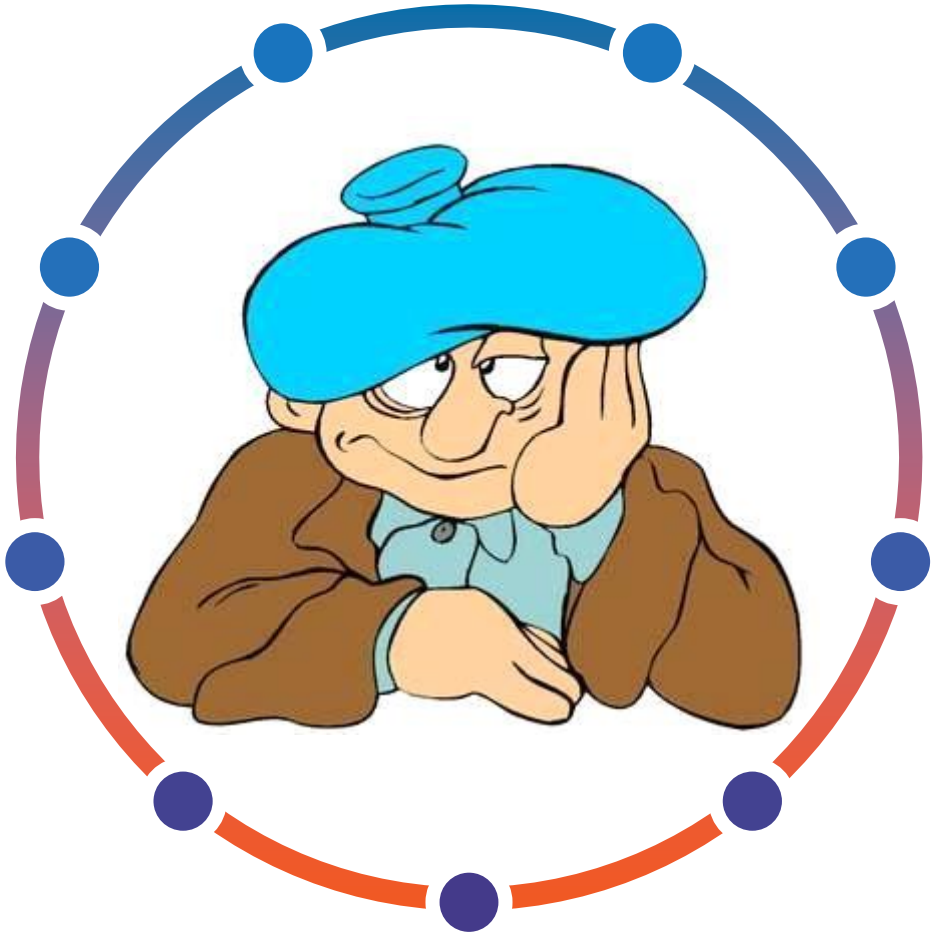
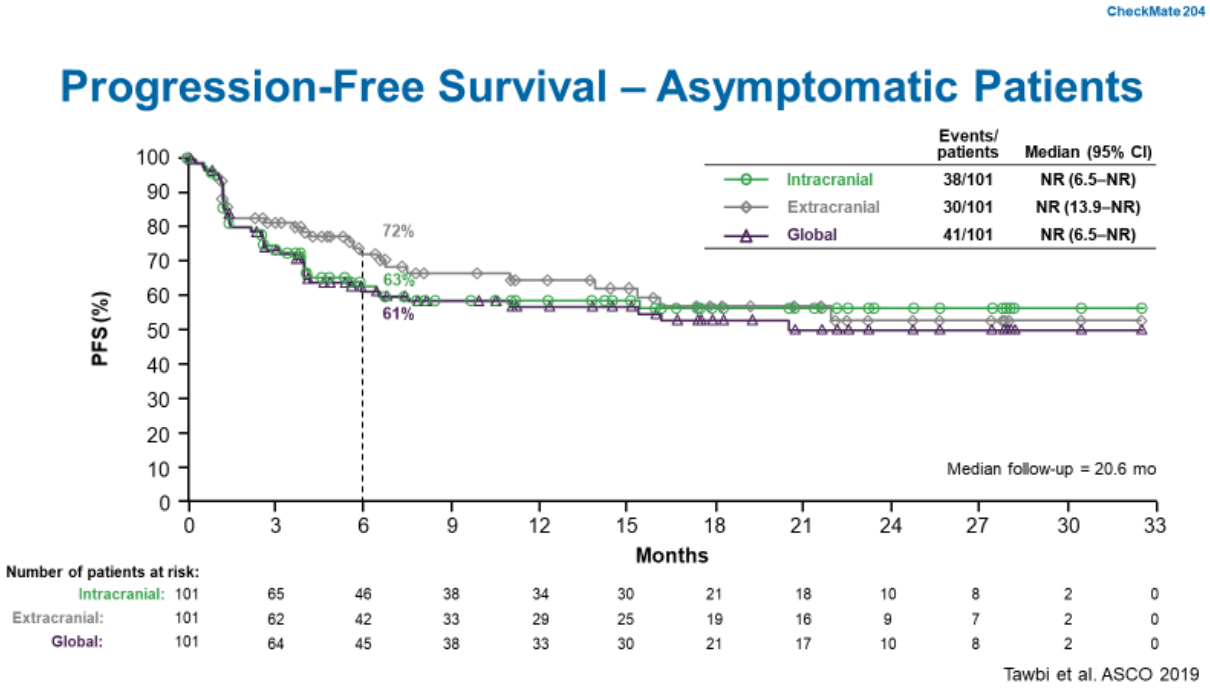
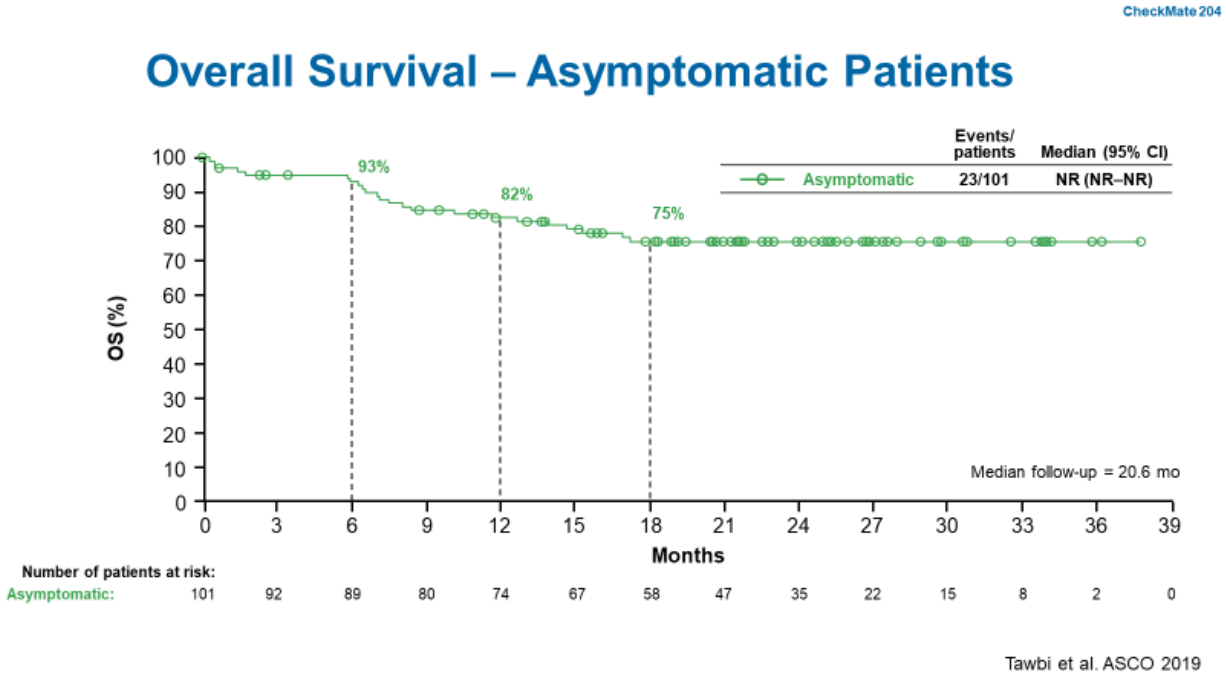


Brain metastases

Checkmate 204 PFS and OS (asymptomatic patients)



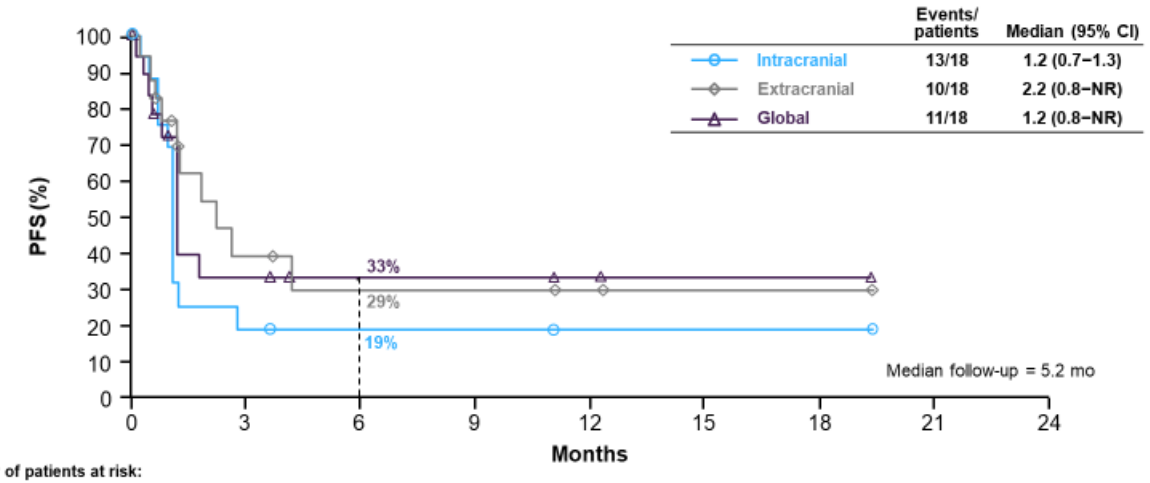


Tawbi et al. ASCO 2019

Checkmate 204 PFS and OS (symptomatic patients)

CheckMate 204

Progression-Free Survival – Symptomatic Patients



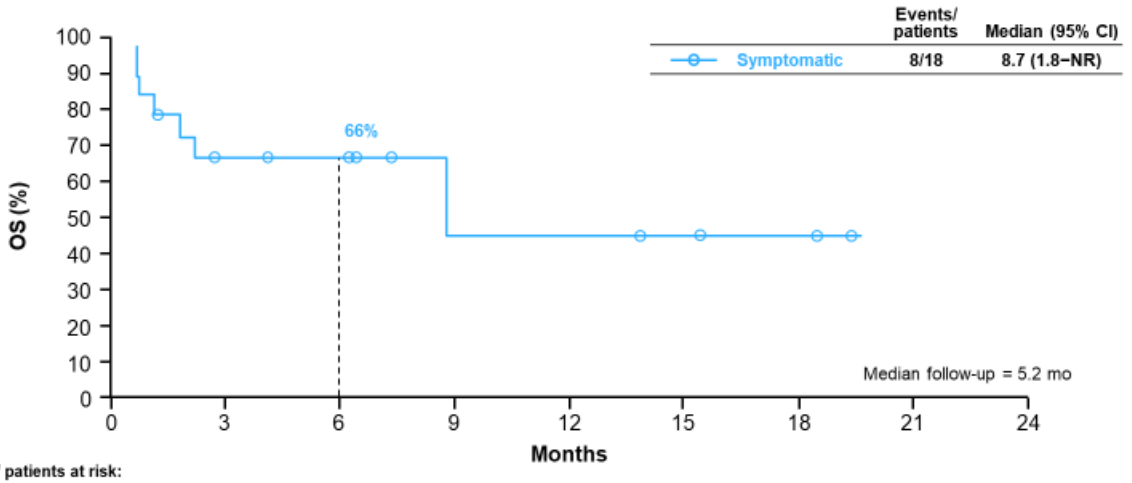
Number of patients at risk:

Intracranial:	18	3	2	2	1	1	1	0	0
Extracranial:	18	5	3	3	2	1	1	0	0
Global:	18	5	3	3	2	1	1	0	0

Tawbi et al. ASCO 2019

CheckMate 204

Overall Survival – Symptomatic Patients



Number of patients at risk:

Symptomatic:	18	10	9	4	4	3	2	0	0

Tawbi et al. ASCO 2019

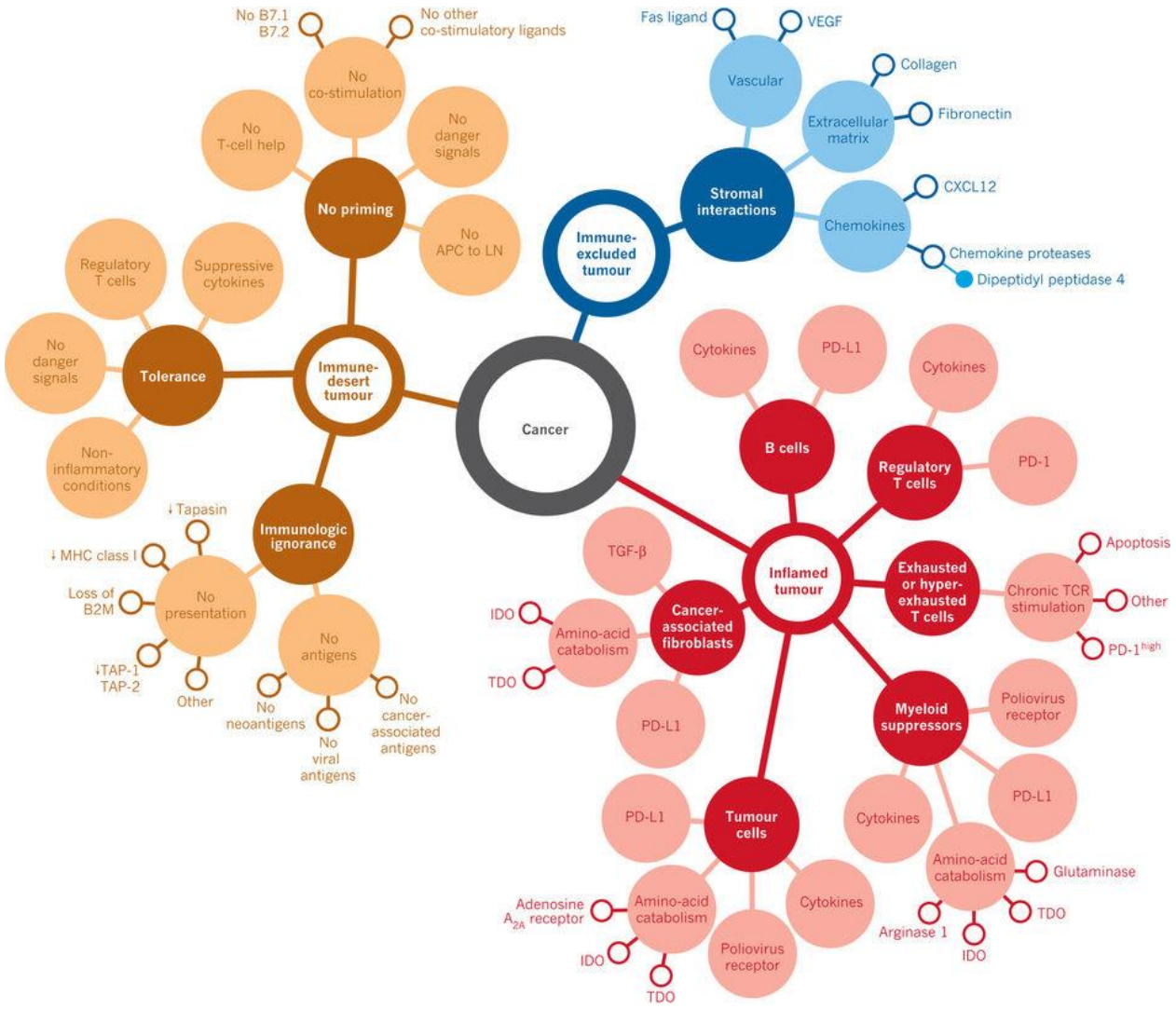
Tawbi et al. ASCO 2019

Open questions …

How can we make more responsive the tumor?
(*overcoming primary resistance*)

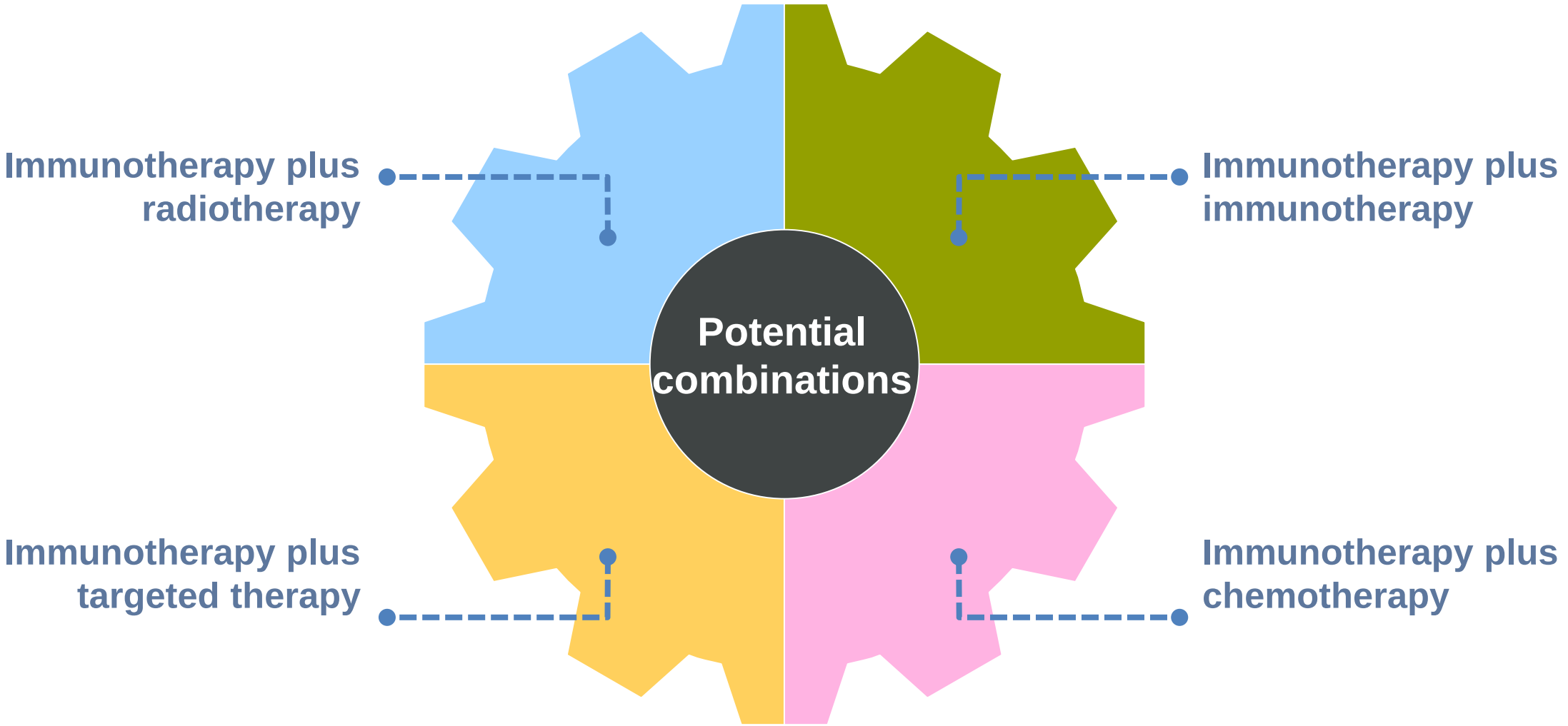
How can we reduce the risk of relapse?
(*overcoming acquired resistance*)

Cancer-immune phenotypes

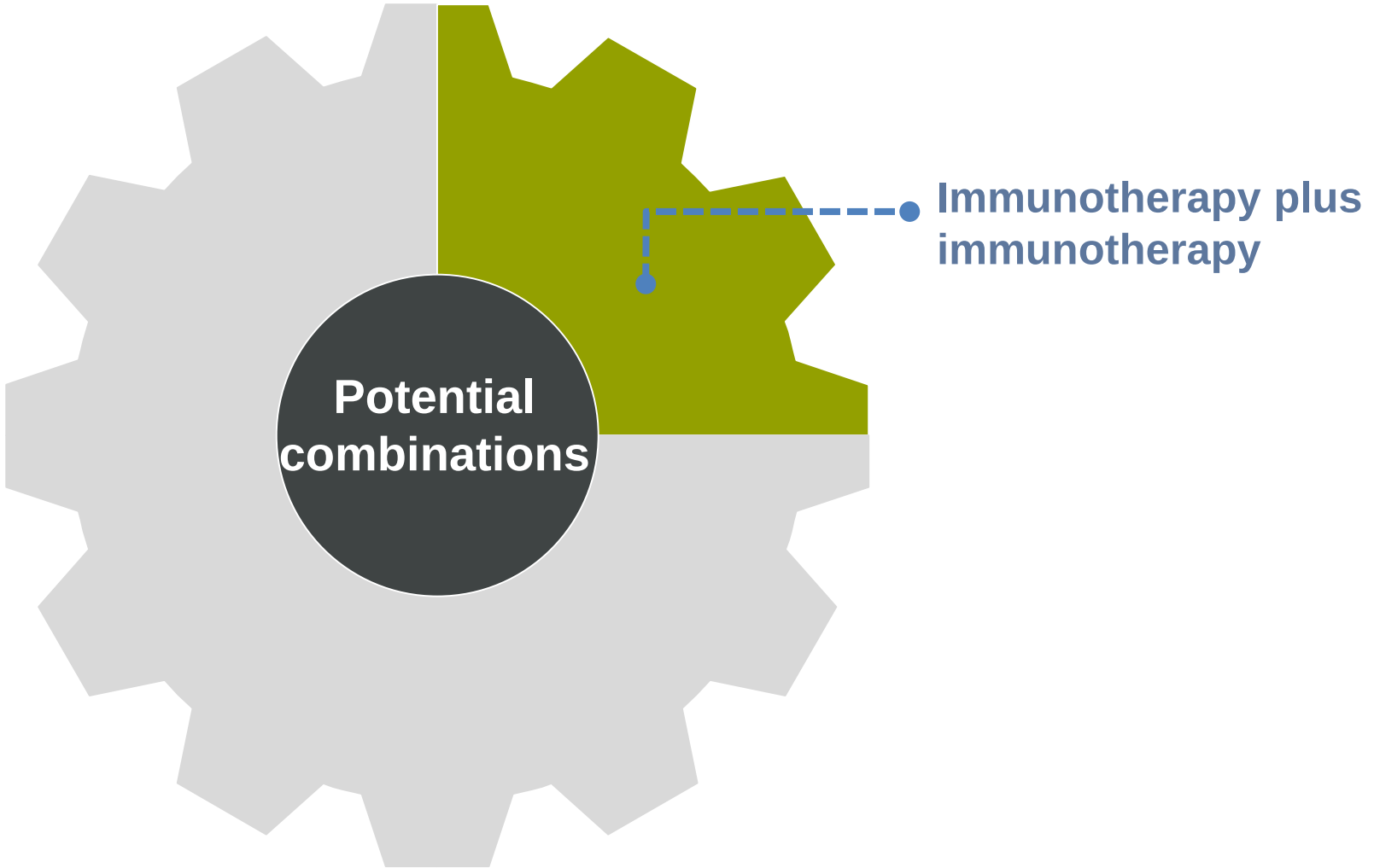


Chen DS, Mellman I Nature 2017; 541, 321–330.

Potential combination strategies for the treatment of cancer

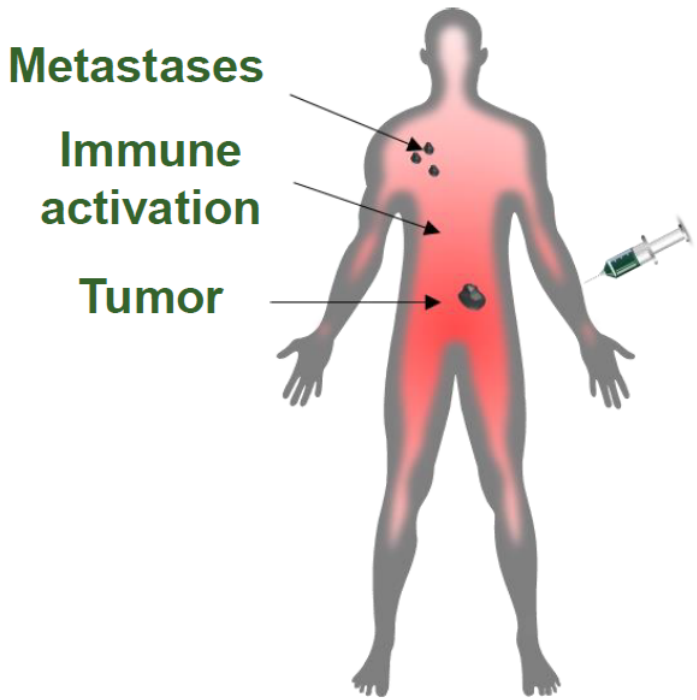


Potential combination strategies for the treatment of cancer

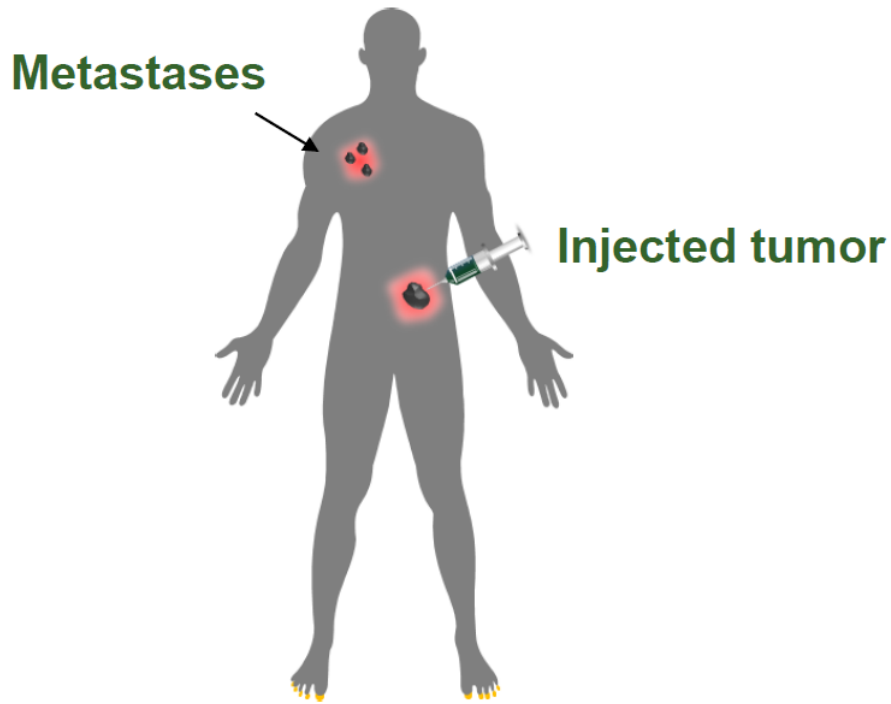


What about the role of loco-regional treatments ?

Tumor-directed immuno-oncology



GENERAL IMMUNE-ACTIVATION

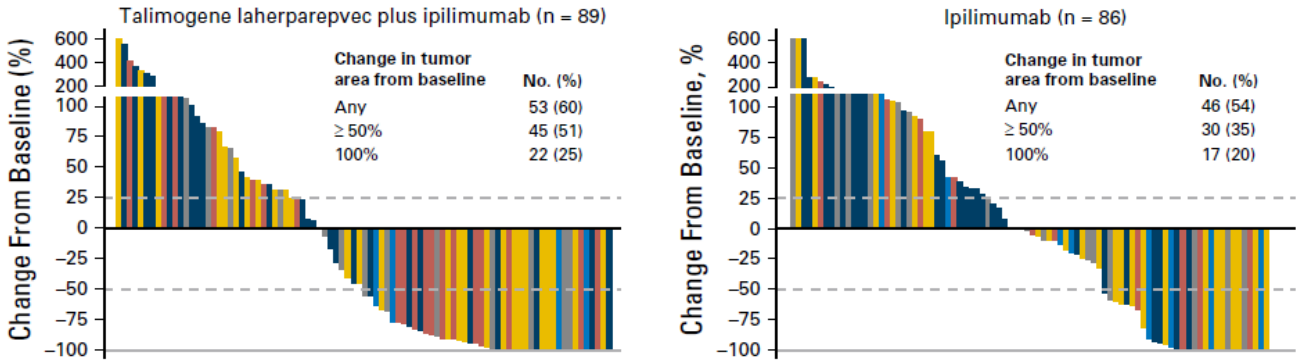


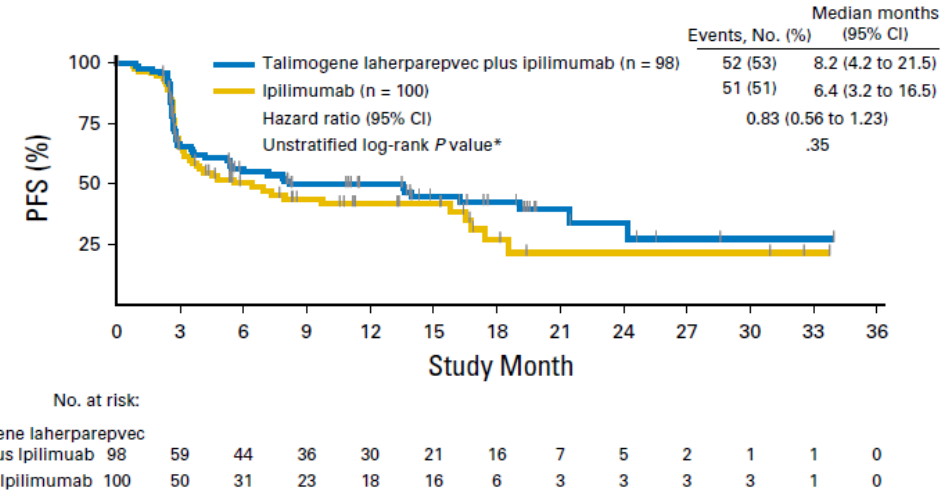
TUMOR-DIRECTED IMMUNE-ACTIVATION

Adapted from Ellmark *et al* 2016, CII

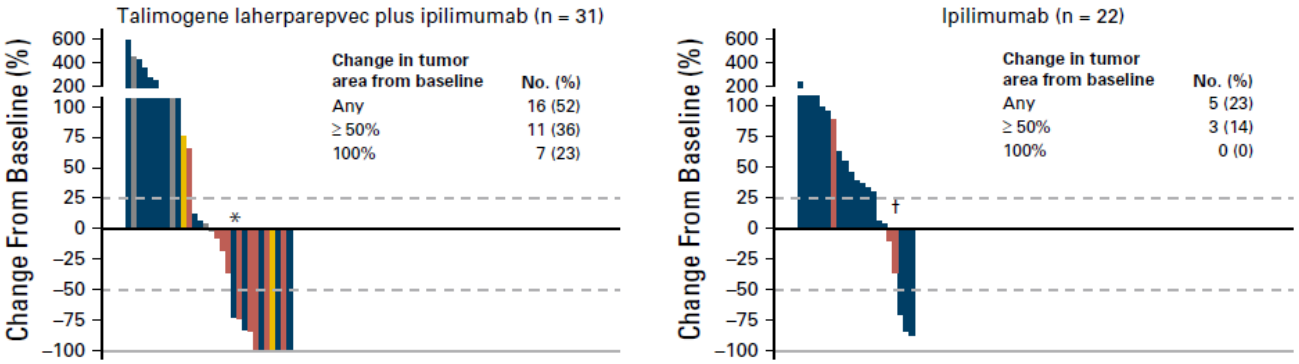
T-VEC + ipilimumab

All lesions





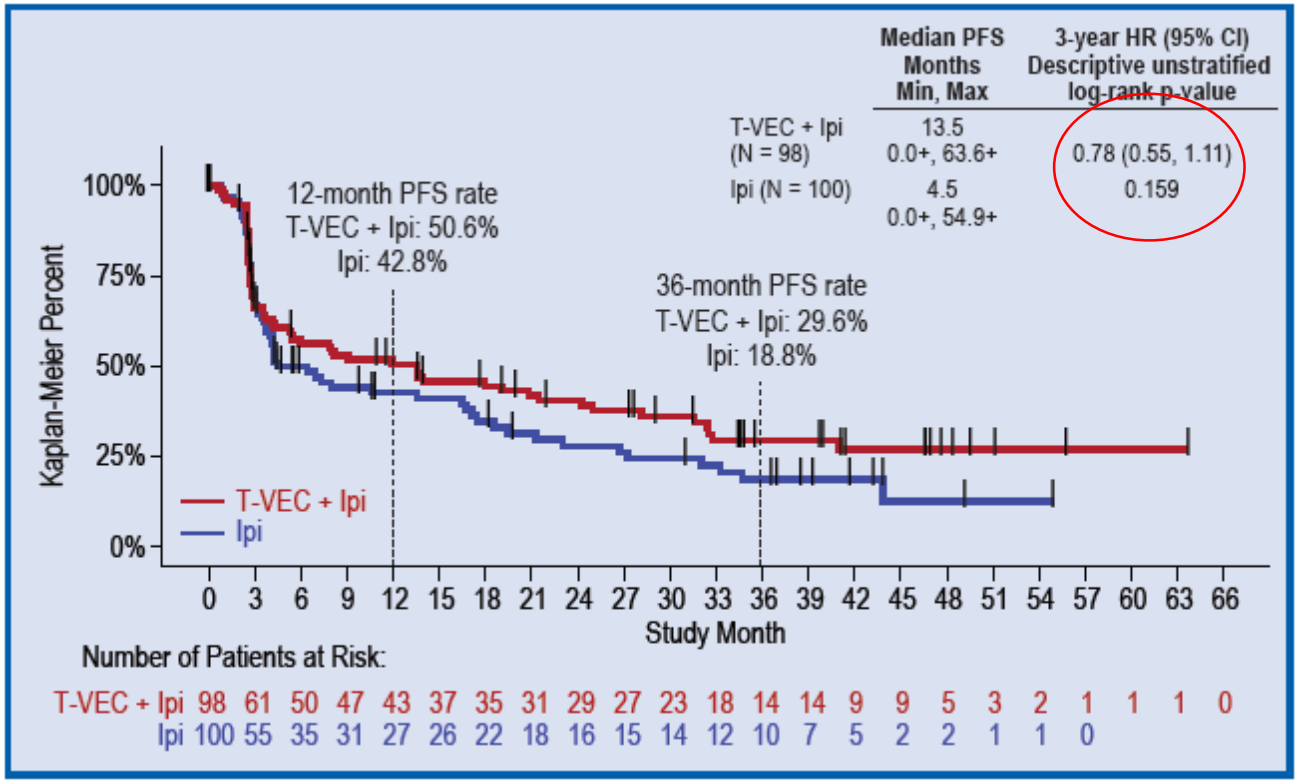
Non injected visceral lesions



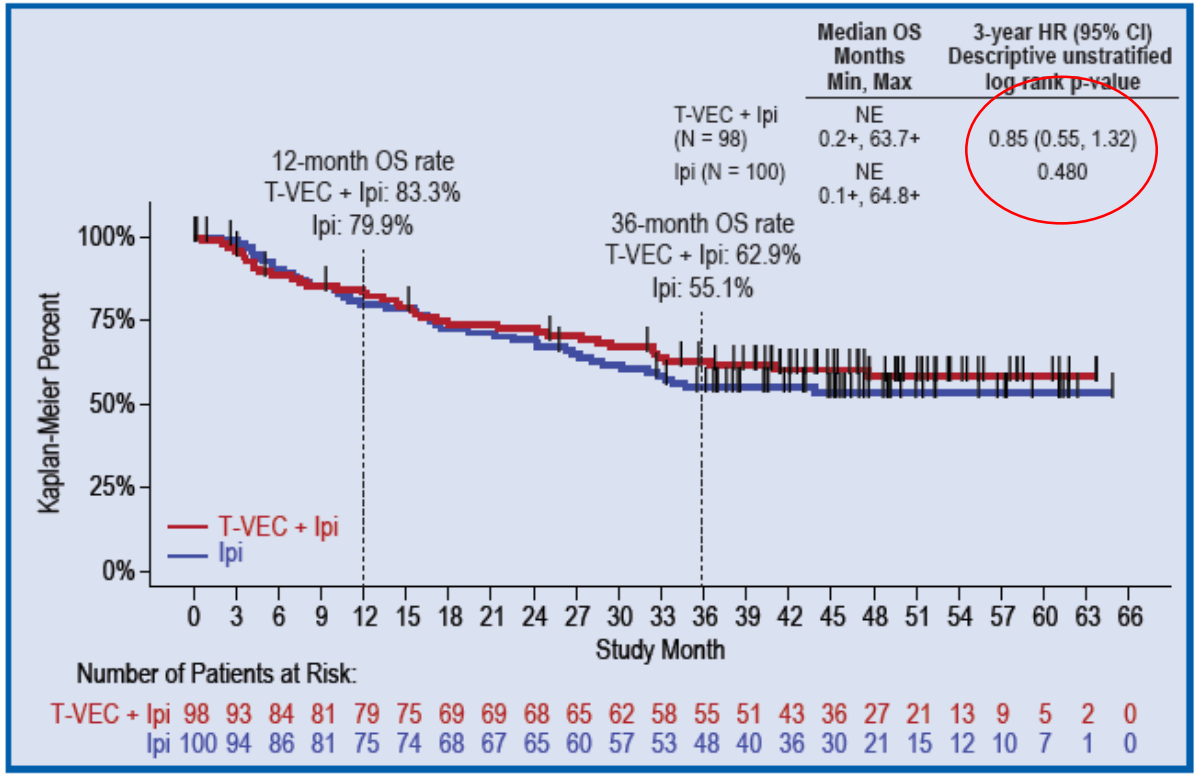
Chesney et al JCO 2017

PFS and OS

Progression-Free Survival (ITT Set)

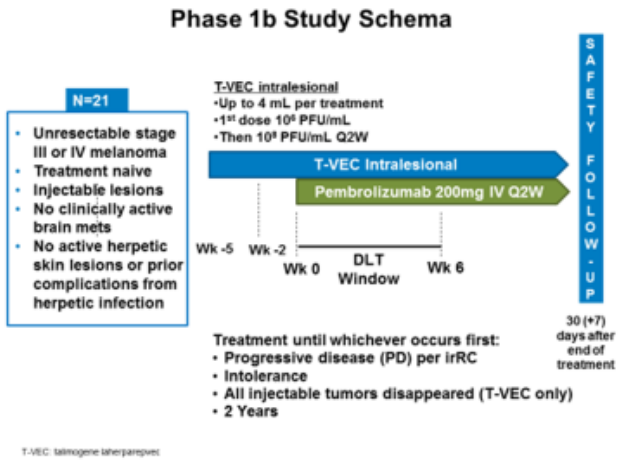


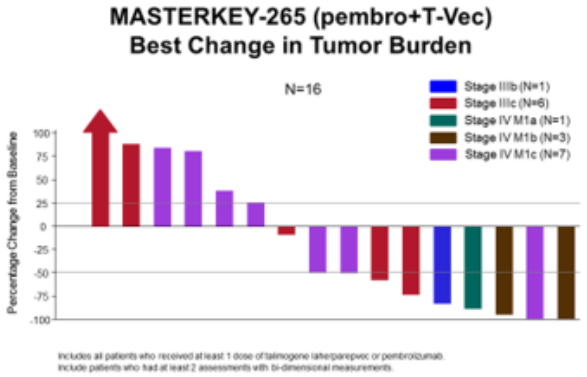
Overall Survival (ITT Set)



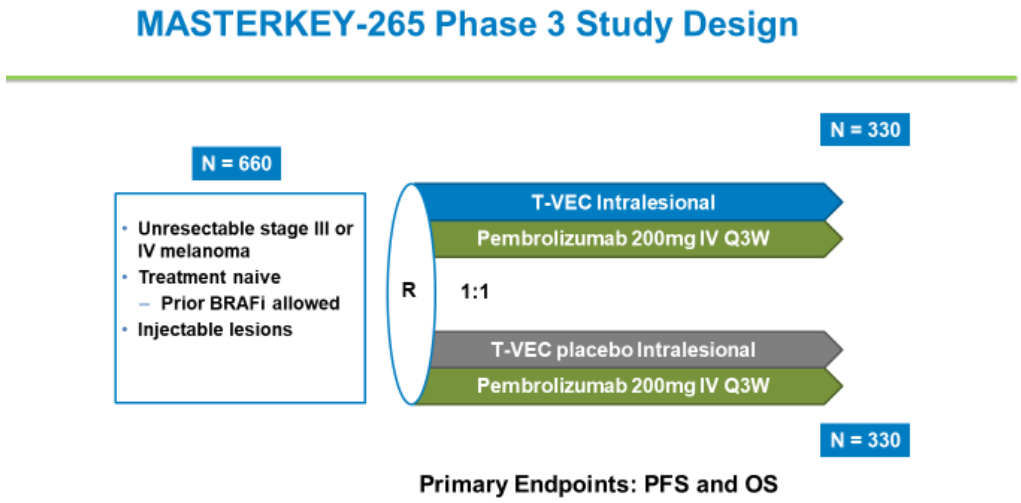
Chesney et al ESMO 2019

T-VEC + pembrolizumab





Long et al SMR 2015



NCT02263508

Long et al SMR 2015

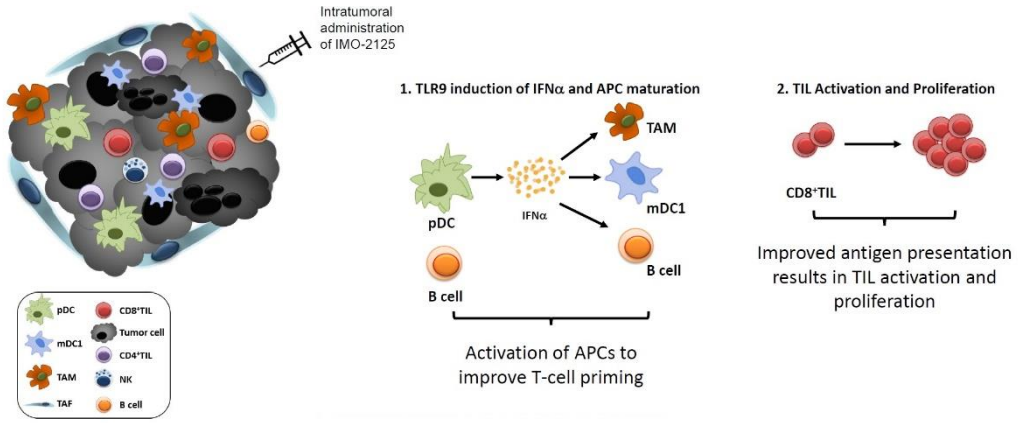
Long et al SMR 2015

Loco-regional drugs in clinical development …

- **T-VEC (Talimogene laherparepvec) (approved FDA/EMA)**
- **PV-10 (10% rose bengal disodium) (phase III)**
- **CVA21 (Coxsackie virus A21) (phase I-II)**
- **pIL-12 (Plasmid IL-12 and electroporation) (phase I-II)**
- **LTX-315 (peptide derived from lactoferricin) (phase I)**
- **Others (TLRs, STING agonist, etc.) (phase I and III)**

New emerging compounds for future combinations: TLR-9

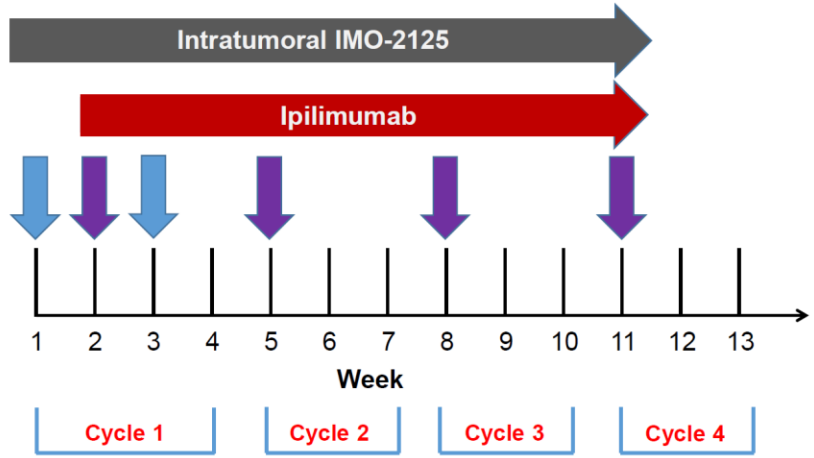
Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125



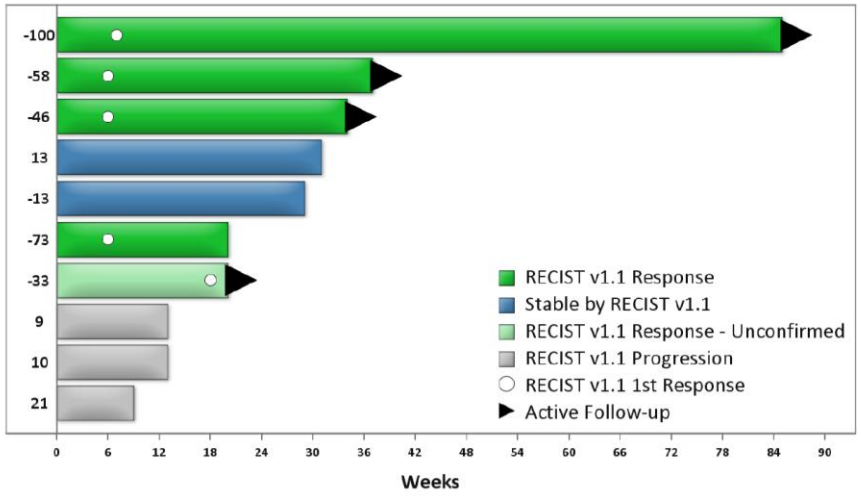
i.t. IMO-2125 alone

i.t. IMO-2125 + Ipilimumab

Trial Design (NCT02644967)

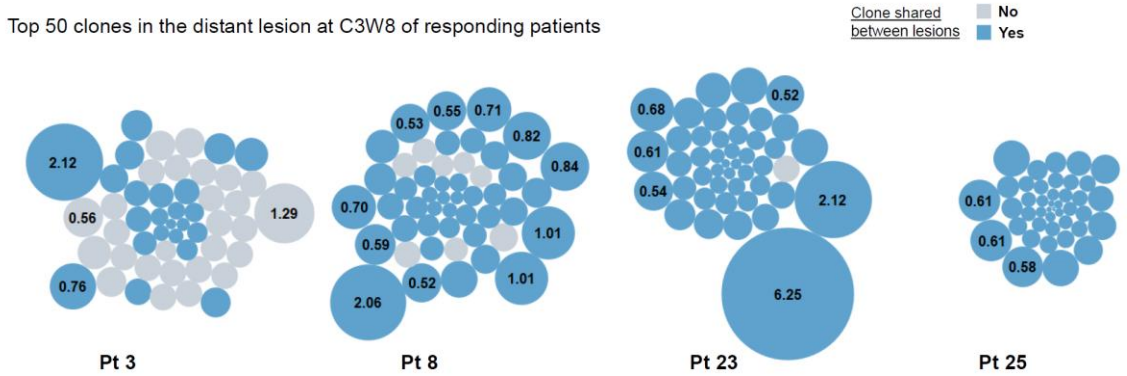


Early response data to IMO-2125 + Ipilimumab



Time on study ends at RECIST v1.1 PD (including death & start of new anti-cancer therapy) or study withdrawal for any reason.
Subjects treated with IMO-2125 8mg + Ipilimumab with at least 1 post-baseline disease evaluation.
Data cut-off date: 03NOV2017 Produced on 06NOV2017

Expanding clones in the distant lesion are shared with the injected lesion



Presented by Paolo A. Ascierto at ASCO 2018

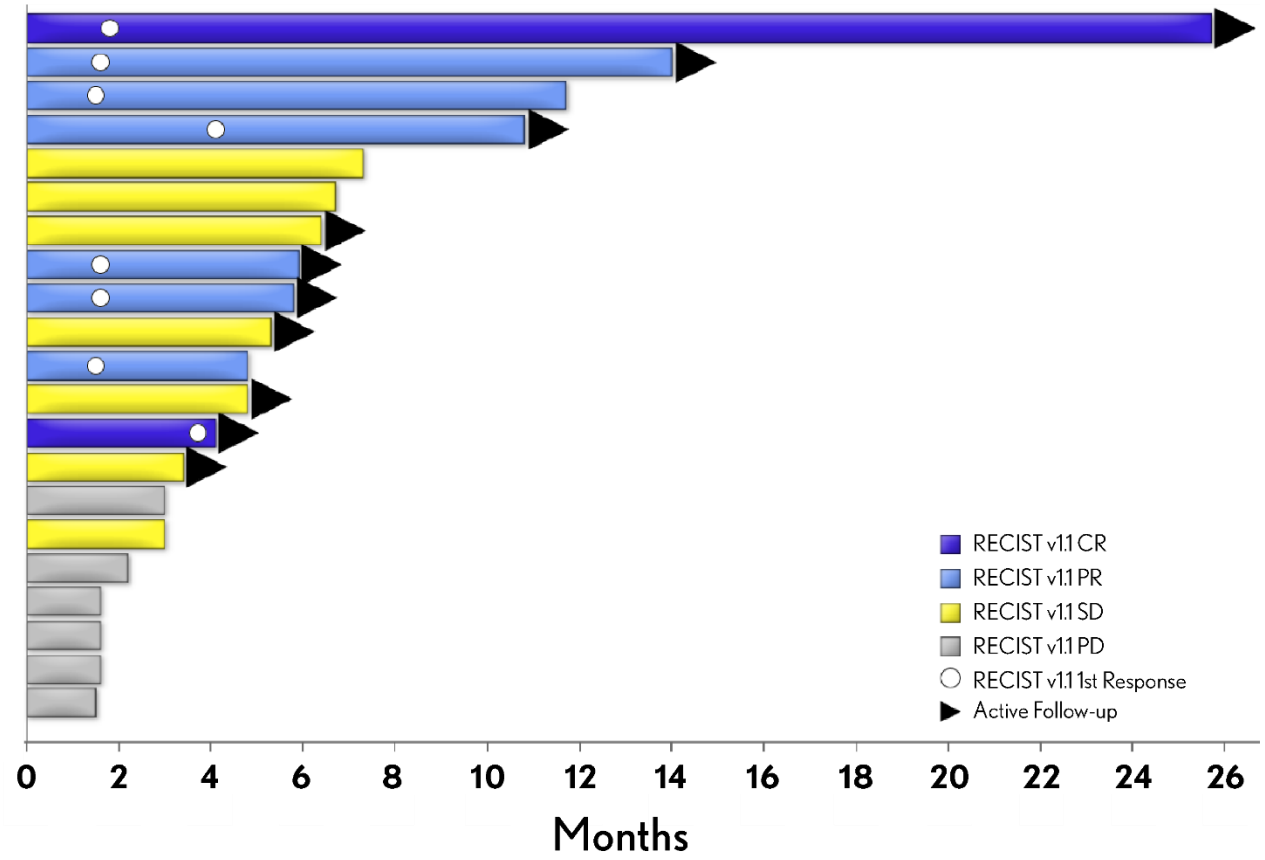
Haymaker et al SITC 2017

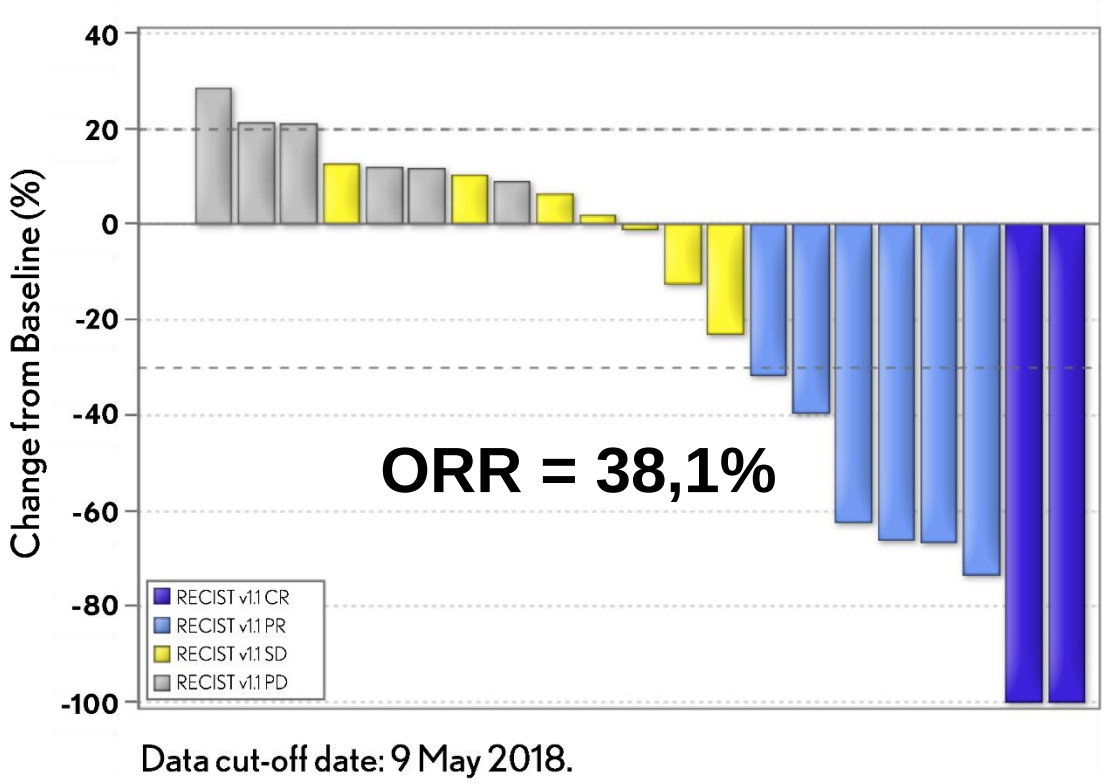
New emerging compounds for future combinations: tilsotolimod

Abstract: 9515

A phase 1/2 study to evaluate the safety and efficacy of intratumoral injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab in patients with PD-1 inhibitor refractory metastatic melanoma

Adi Diab[1], Cara Haymaker[2], Chantale Bernatchez[1], Robert Andtbacka[3], Marthella James[1], Douglas Johnson[3], Joseph Markowitz[4], Ravi Murthy[1], Igor Puzanov[5], Monte Shaheen[6], Shah Rahimian[7], James Gaib[7], Srinivas Chunduru[7], Suzanne Swann[7], and Patrick Hwu[1]
[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; [3]Vanderbilt University, Nashville, TN; [4]Moffitt Cancer Center, Tampa, FL; [5]Roswell Park Comprehensive Cancer Institute, Buffalo, NY; [6]University of Arizona Cancer Center, Tucson, AZ; [7] Idera Pharmaceuticals, Inc., Exton, PA
Corresponding author: Adi Diab, ADiab@mdanderson.org





Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Diab et al ASCO 2018

Phase 1b/2, open label, multicenter, study of the combination of SD-101 and pembrolizumab in patients with advanced melanoma who are naïve to anti-PD1 therapy

Antoni Ribas,1 Mohammed Milhem,2 Christopher Hoimes,3 Asim Amin,4 Inderjit Mehmi,5 Christopher Lao,6 Robert Conry,7 Montaser Shaheen,8 Sekwon Jang,9 April Salama,10 Sanjeev Deva,11 Theresa Medina,12 Shivaani Kummar,13 Joseph J Drabick,14 Minal Barve;15 Gregory A Daniels,16 Deborah L Wong,1 Emmett V. Schmidt,17 Abraham C.F. Leung,18 Albert Candia,18 Biao Xing,18 Robert Janssen,18 Georgina Long,19

[1]David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA; [2]University of Iowa Health Care, Iowa City, IA, USA; [3]University Hospitals Seidman Cancer Center, Cleveland, OH, USA; [4]Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA; [5]West Virginia University - Mary Babb Randolph Cancer Center, Morgantown, WV, USA; [6]The University of Michigan Health System, Ann Arbor, MI, USA; [7]University of Alabama, Birmingham, AL, USA; [8]University of Arizona Cancer Center, Tucson, AZ; [9]Inova Health System, Fairfax, VA, USA; [10]Duke University Medical Center, Durham, NC, USA; [11]Auckland City Hospital, Auckland, NZ; [12]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [13]Stanford University, Palo Alto, CA, USA; [14]Milton S. Hershey Medical Center, Penn State Cancer Institute, Hershey, PA, USA; [15]Mary Crowley Cancer Research Center, Dallas, TX, USA; [16]University of California, San Diego, San Diego, CA, USA; [17]Merck & Co., Kenilworth, NJ, USA; [18]Dynavax Technologies Corporation, Berkeley, CA, USA; [19]Melanoma Institute Australia, Wollstonecraft, NSW, Australia

ASCO Abstract 9513
Poster Board 340
Monday, June 4, 2018
Poster 1:15 PM - 4:45 PM CDT
Discussion 4:45 PM - 6:00 PM CDT

Study Design

Patients

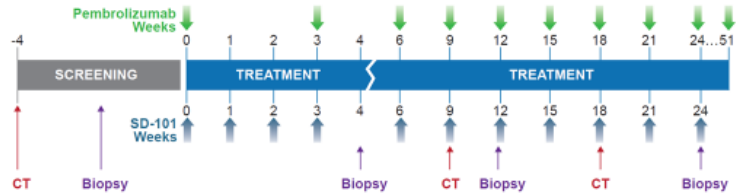
- Stage IIIc, Stage IV metastatic melanoma*
- ECOG performance status of 0 or 1
- At least one injectable site
- Response by RECIST v1.1
- Prior anti-PD-1 or anti-PD-1 naive

Phase 1b Dose Escalation**

- SD-101 **2 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **4 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **8 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **1 mg** i.t. + Pembrolizumab 200 mg i.v.

Phase 2 Expansion

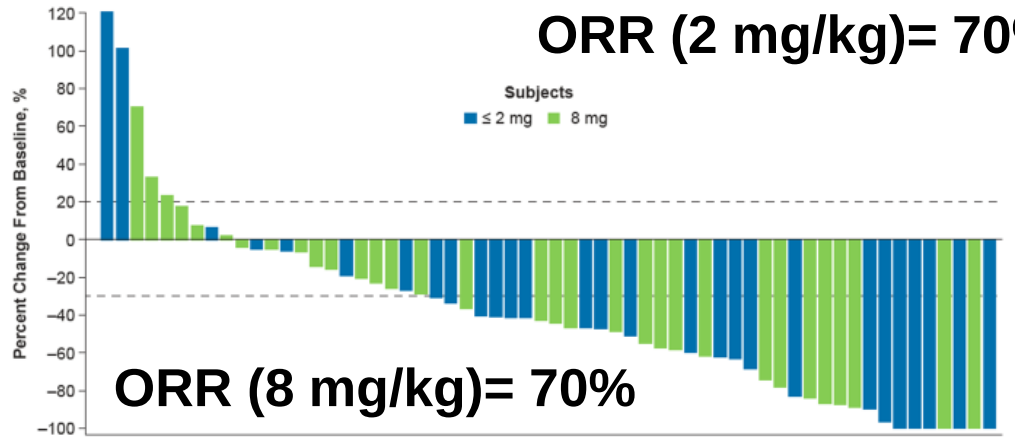
SD-101 **2 mg** i.t. in up to 4 lesions
+
Pembrolizumab **200 mg** i.v.
OR
SD-101 **8 mg** i.t. in one lesion
+
Pembrolizumab **200 mg** i.v.



*Histologically confirmed **DLT period 29 days, i.t. = intratumoral; i.v. = intravenous.

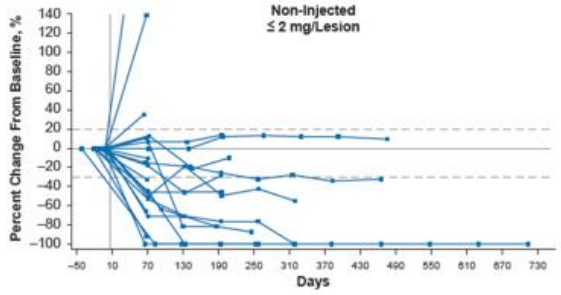
Best Percent Change from Baseline in All Target Lesions

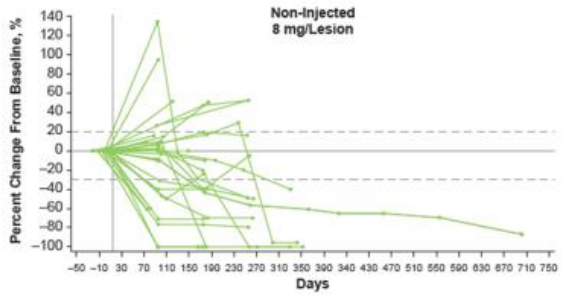
ORR (2 mg/kg)= 70%



ORR (8 mg/kg)= 70%

Percent Change from Baseline over Time in All Target Lesions for Patients Who Received ≤ 2 mg vs. 8 mg SD-101 Per Lesion (3)

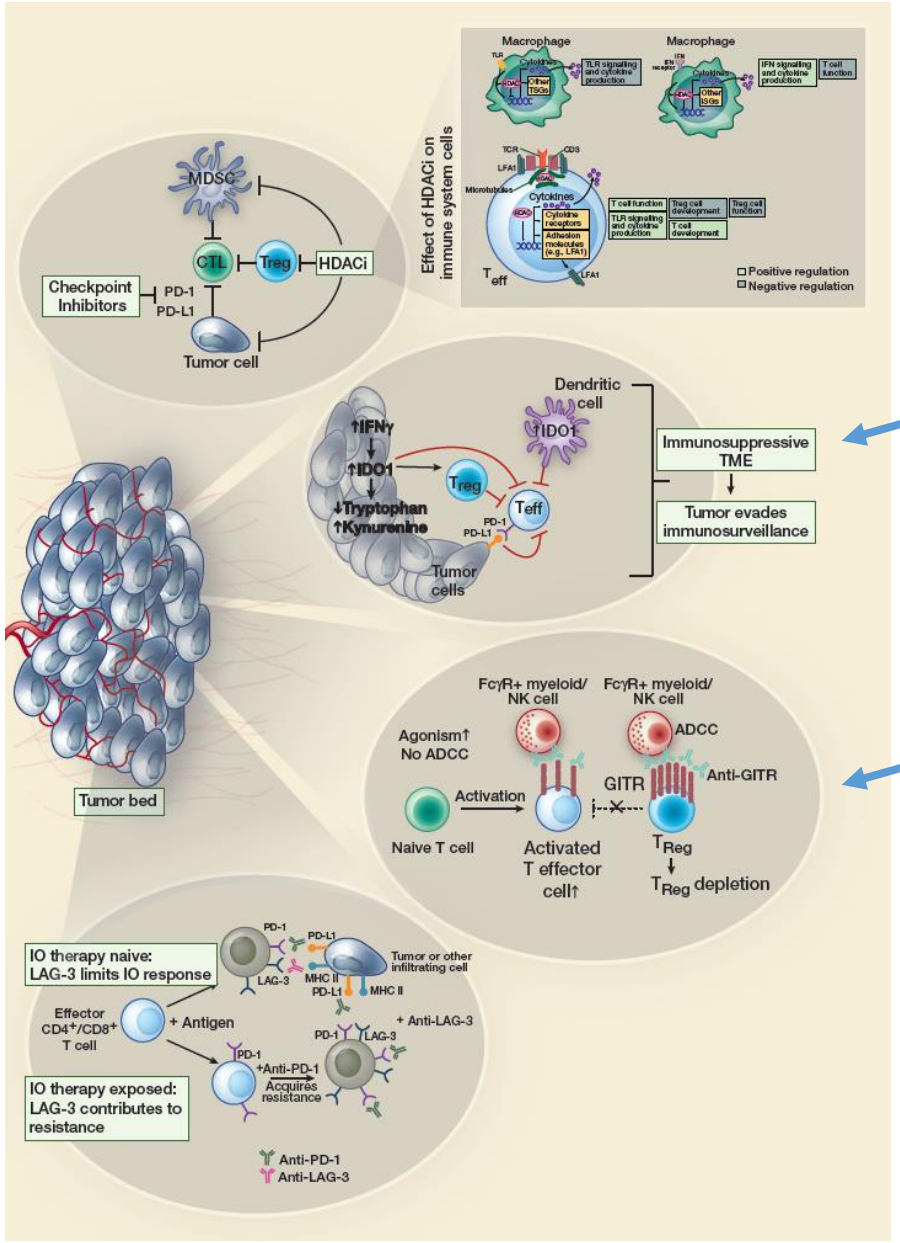




Ribas et al ASCO 2018

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

HDAC inhibitor
(eg., entinostat [Ph 2])



IDO1 inhibitor
(eg., epacadostat [Ph 3], etc.)

Anti-GITR
(eg., BMS-986156 (Ph 1/2])

Anti-LAG-3
(eg., relatlimab [Ph 1/2])

GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

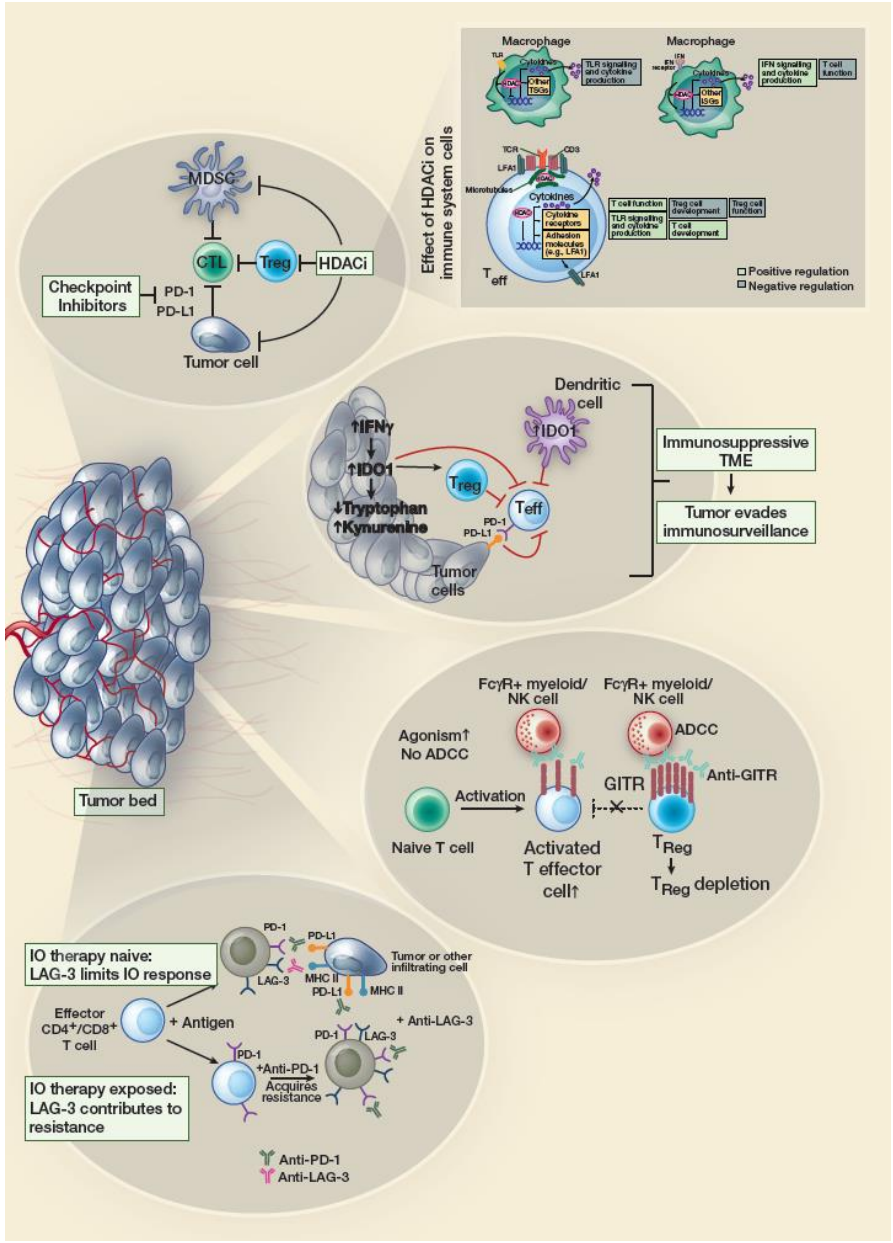
Presented by Paolo A. Ascierto at ASCO 2018

Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

HDAC inhibitor
(eg., entinostat [Ph 2])

Anti-LAG-3
(eg., relatlimab [Ph 1/2])



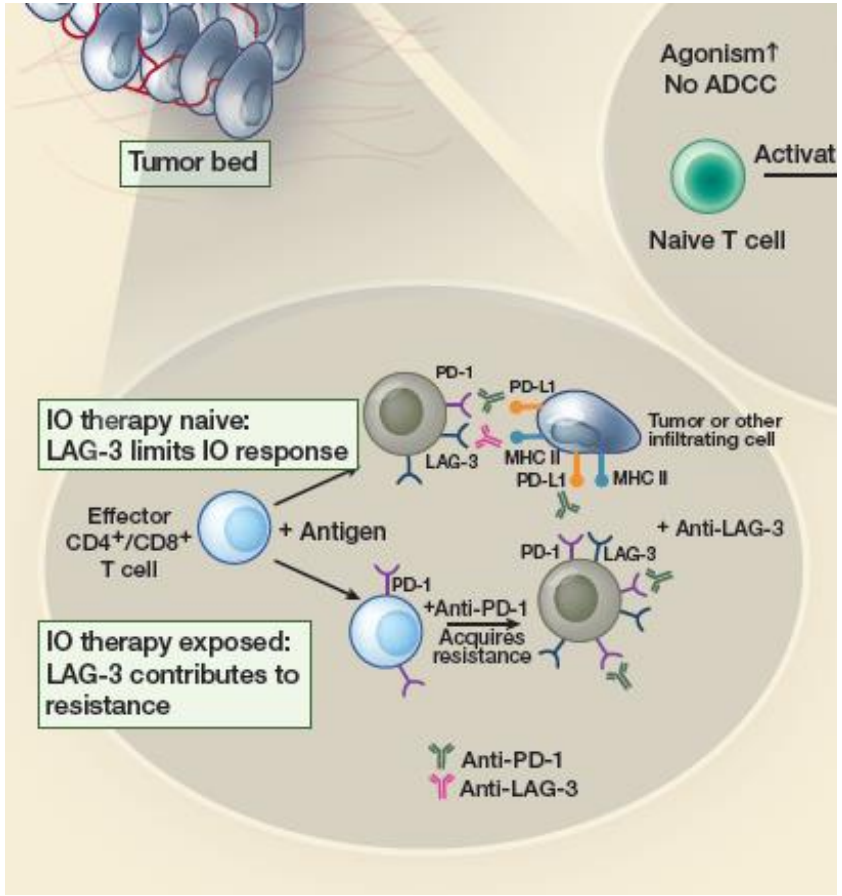
GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

Presented by Paolo A. Ascierto at ASCO 2018

Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds: *anti-LAG-3*

anti-LAG-3
(eg., relatlimab [ph. 1/2/3], etc.)



Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti–LAG-3; BMS-986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated With Anti–PD-1/PD-L1 Therapy

Dose Escalation N = 8 (advanced solid tumors)

→ **Relatlimab (80 mg) + Nivolumab (240 mg) IV Q2W**

Dose Expansion N = 262

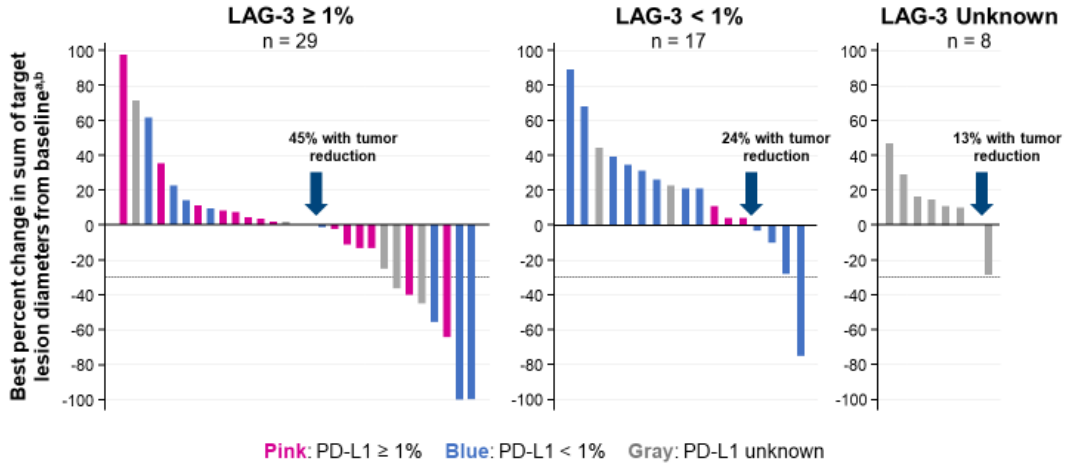
Efficacy: Melanoma (progressed during prior I-O) n = **68**[b]

Safety: All patients

Study Endpoints (dose expansion)

- **Co-Primary:** Preliminary efficacy and safety/tolerability
- **Other:** Immunogenicity, QTc, PK, PD, biomarkers

Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression



[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

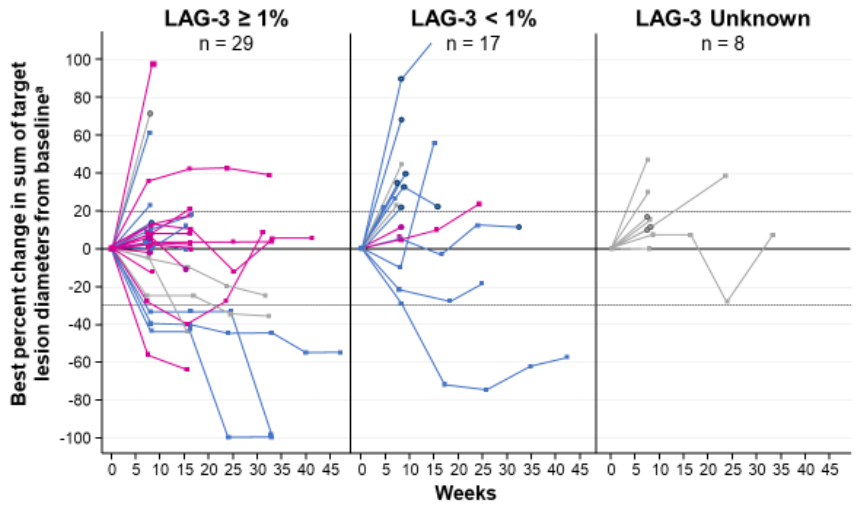
Safety of Relatlimab 80 mg + Nivolumab 240 mg Q2W

	All Patients[a] N = 270	
	Any Grade n (%)	Grade 3–4 n (%)
Any TRAE[b]	137 (51)	27 (10)
TRAEs in ≥ 5% of patients		
Fatigue	30 (11)	0
Pruritus	19 (7.0)	0
Diarrhea	18 (6.7)	3 (1.1)
Arthralgia	17 (6.3)	0
Infusion-related reaction	15 (5.6)	0
Any serious TRAE[b]	18 (6.7)	12 (4.4)
Serious TRAEs in > 1 patient		
Colitis	4 (1.5)	3 (1.1)
Pneumonitis	2 (0.7)	2 (0.7)
Myocarditis[c]	2 (0.7)	0
Pyrexia	2 (0.7)	0
Any TRAE leading to discontinuation[b]	11 (4.1)	8 (3.0)

- The safety profile of the melanoma prior PD-(L)1 cohort was similar to that of the overall population
- No treatment-related deaths were reported[d]

TRAE, treatment-related adverse event.
[a]Patients treated with relatlimab 80 mg + nivolumab 240 mg in the dose-escalation and -expansion phases as of the June 15, 2017, data cutoff.
[b]Safety evaluated per CTCAE v4.0 during treatment and up to 135 days after discontinuation. [c]There were a total of 4 myocarditis events (1.5%), all of which were grade 1, and 2 of which were serious AEs. [d]One TRAE of grade 5 myocarditis was observed with relatlimab 240 mg + nivolumab 240 mg Q2W.

Depth and Duration of Response by LAG-3 and PD-L1 Expression



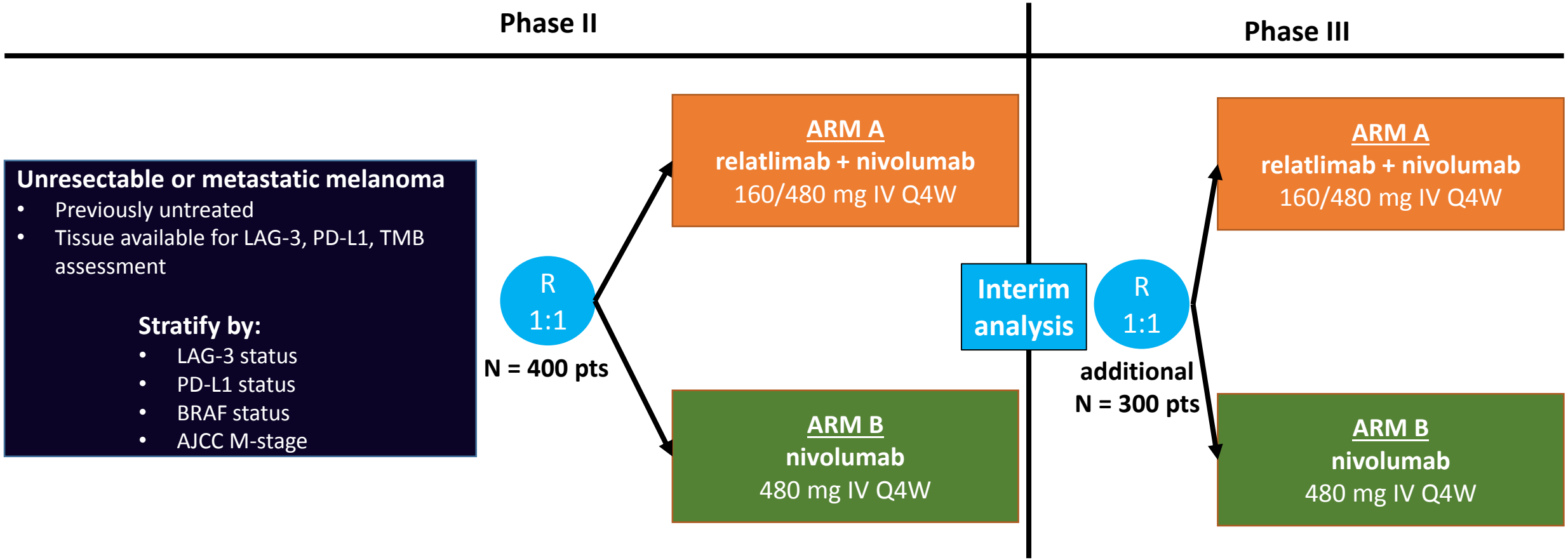
- Responses were more likely in patients with LAG-3 expression ≥ 1%
- PD-L1 expression did not appear to enrich for response

[a]Six patients with clinical progression prior to their first scan and 1 patient with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.

Presented by Paolo A. Ascierto at ASCO 2018

Ascierto PA, et al. *ESMO* 2017

CA224-047: Randomized, Double-blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma



Phase II primary endpoint: PFS assessed by a BICR
Phase II secondary endpoint: ORR, DOR, DCR, PFS rates, and 1- and 2-year OS rates according LAG-3 and PD-L1 status, safety and tolerability

Phase III primary endpoint: PFS
Phase III secondary endpoint: ORR, OS

Presented by Paolo A. Ascierto at ASCO 2018

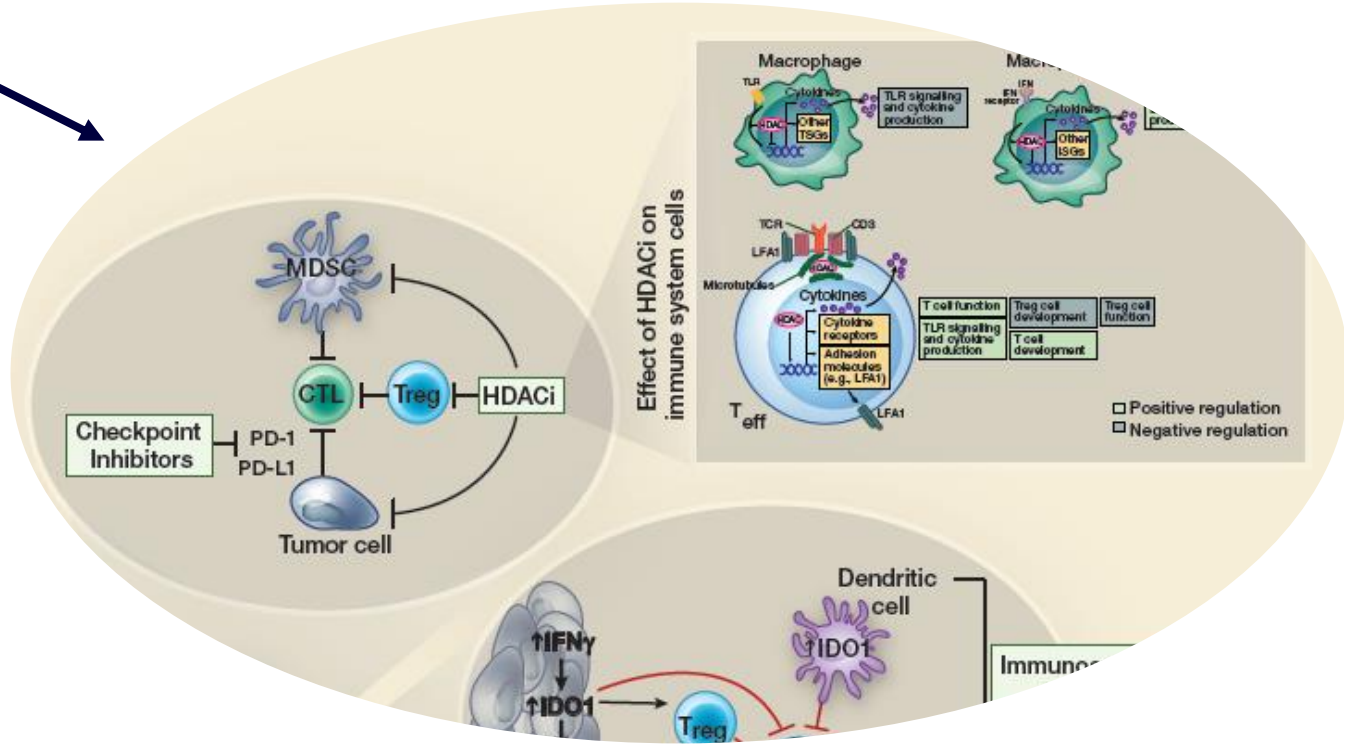
Clinicaltrial.gov identifier NCT03470922

Anti-LAG-3 development

Company	Drug	Study phase	Cancer type	Combination
BMS	relatlimab	Phase 1,2, and 3	Solid tumors Haematological malignancies	nivolumab
Novartis	LAG525	Phase 1, 2	Solid tumors Haematological malignancies	spartalizumab
MSD	MK4280	Phase 1	Solid tumors	pembrolizumab
Regeneron/Sanofi	REGN3767	Phase 1	Solid tumors	cemiplimab (anti-PD-1)
Macrogenics	MGD013	Phase 1	Solid tumors Haematological malignancies	-
Tesaro	TSR-033	Phase 1	Solid tumors	Anti-PD-1
Boehringer/ Ingelheim - Sarah Cannon Research Institute	BI754111	preclinical	-	BI754091 (anti-PD-1)
Agenus/Incyte	Not available	preclinical	-	-
PRIMA	IMP321	Phase 1,2	Solid tumors	pembrolizumab, chemotherapy

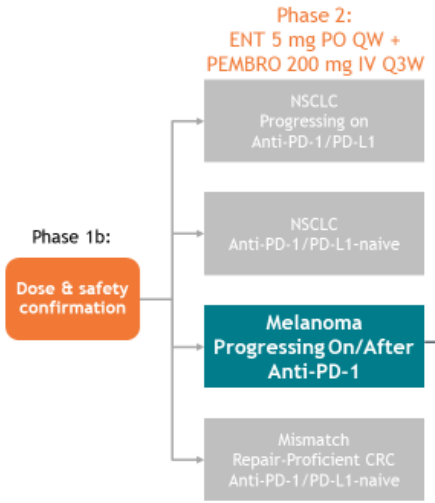
New emerging pathways for future combination with anti-PD-1/PD-L1 compounds: *HDAC inhibitors*

HDAC inhibitors
(eg., entinostat, etc.)



Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy



Inclusion Criteria:

- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint
- ORR (irRECIST)

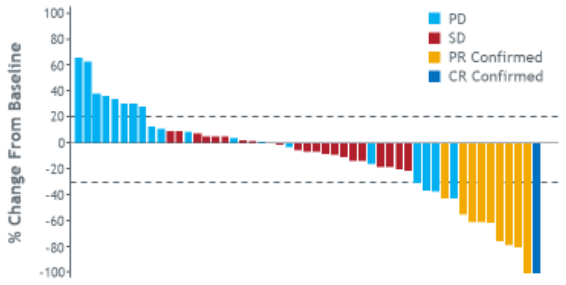
Secondary Endpoints
- CBR, PFS, OS, safety & tolerability

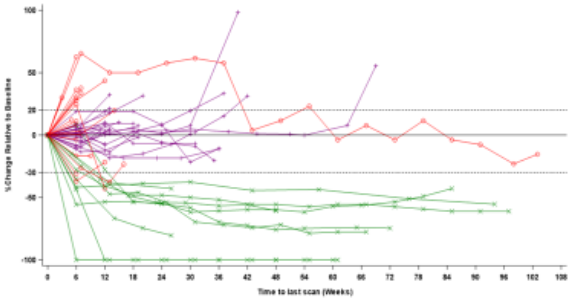
53 patients enrolled, last patient enrolled April 2018

CBR, clinical benefit rate; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; QW, once a week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Sullivan et al AACR 2019

Change in Tumor Volume and Change in Tumor Volume Over Time per irRECIST in ENCORE-601





- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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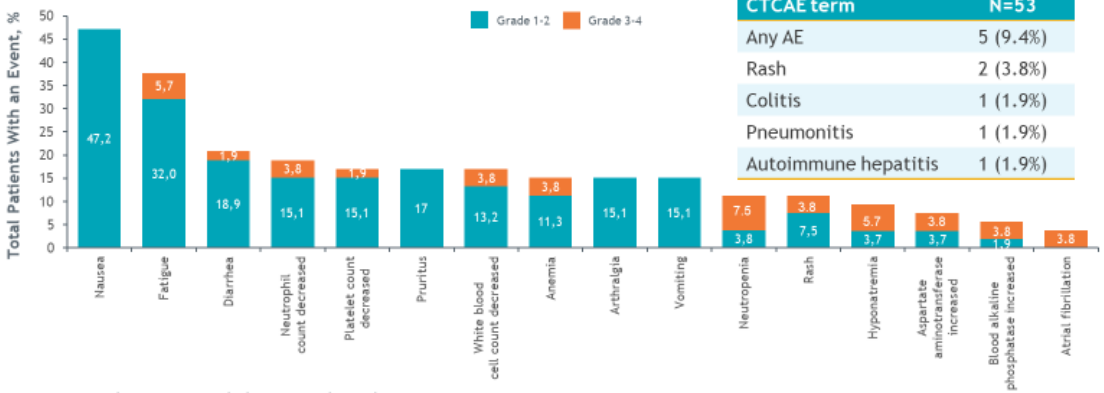
Safety: Treatment-Related Adverse Events Occurring in ≥15% of Patients for All Grade or ≥2 Patients for Grade 3/4



Grade 3/4 Immune-Related AEs

CTCAE term	N=53
Any AE	5 (9.4%)
Rash	2 (3.8%)
Colitis	1 (1.9%)
Pneumonitis	1 (1.9%)
Autoimmune hepatitis	1 (1.9%)

- 6 pts discontinued due to related AEs:
  increased bilirubin, mucosal inflammation, neutropenia, pneumonitis, constipation and autoimmune hepatitis

AE, adverse event; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

Sullivan et al AACR 2019

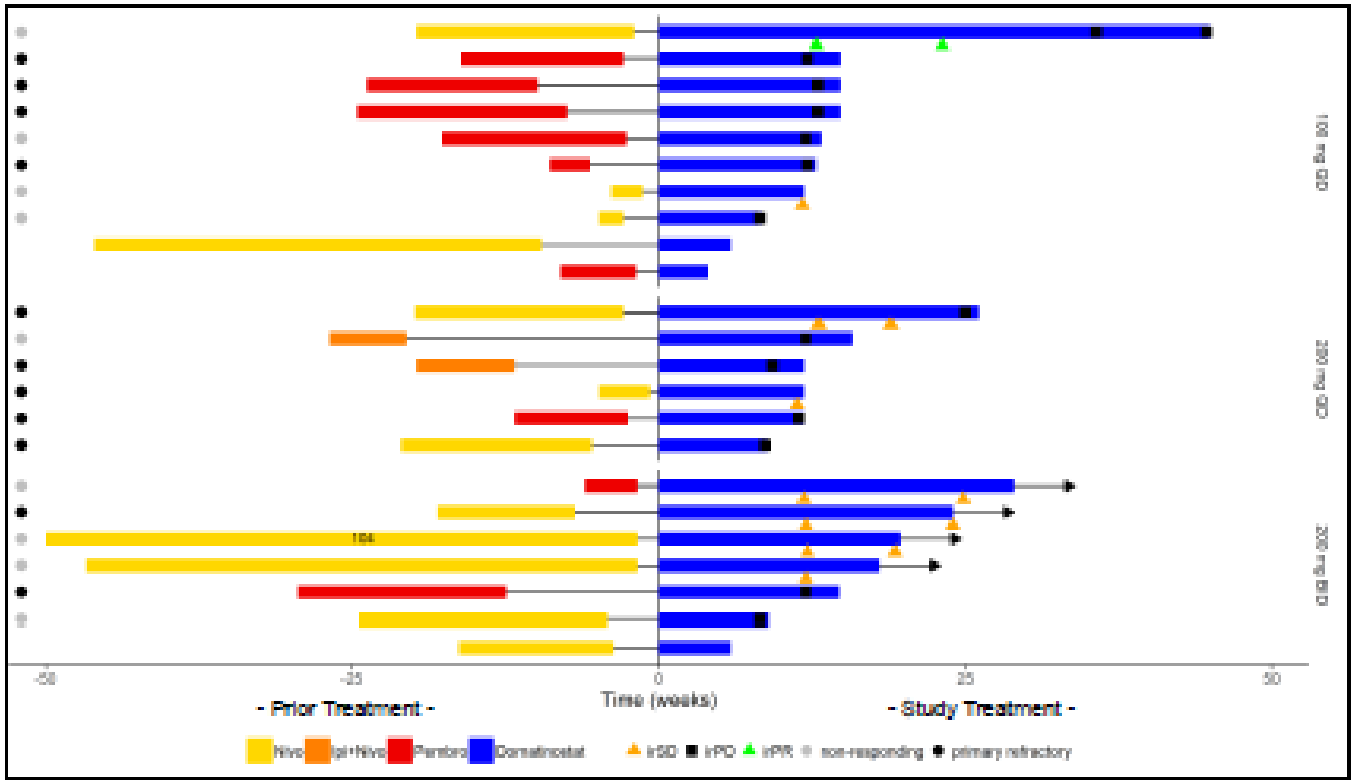
Sullivan R. et al. *AACR 2019*

#5545

Phase Ib/II Study (SENSITIZE) assessing safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcome of domatinostat in combination with pembrolizumab in patients with advanced melanoma refractory/non-responding to prior checkpoint inhibitor therapy

Jessica C. Hassel[1], Carola Berking[2], Thomas Eigentler[3], Ralf Gutzmer[4], Paolo A. Ascierto[5], Bastian Schilling[6], Frank Hermann[7], René Bartz[7] and Dirk Schadendorf[8]

1: University Hospital Heidelberg, Department of Dermatology and National Center for Tumor Diseases; Heidelberg, Germany; 2: University Hospital Munich (LMU), Department of Dermatology; Munich, Germany; 3 University Hospital Tuebingen, Center for Dermatooncology, Department of Dermatology; Tuebingen, Germany; 4: Medizinische Hochschule Hannover, Department of Dermatology and Allergy, Skin Cancer Center Hannover; Hannover, Germany; 5: Istituto Tumori Napoli IRCCS Fondazione Pascale, Melanoma Cancer Immunotherapy and Development Therapeutics Unit; Naples, Italy; 6: University Hospital Würzburg, Department of Dermatology, Venereology and Allergology; Würzburg, Germany; 7: 4SC AG, Planegg-Martinsried, Germany; 8: University Hospital Essen, Department of Dermatology; Essen, Germany



MedDRA System Organ Class / Preferred Term		Domatinostat, p.o. D1-14, q3w + pembrolizumab 2mg/kg, i.v., D1 q3w			
		100 mg OD (n=10)	200 mg OD (n=6)	200 mg BID (n=7)	Total
Gastrointestinal Disorders	Diarrhea	3	2	2	7
	Nausea	3	0	2	5
	Vomiting	1	1	1	3
General disorders and administration site conditions	Fatigue	1	1	2	4
	Fever	0	3	1	4
	Chills	0	2	1	3
Blood and lymphatic system disorders	Anemia	0	0	2	2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	2	0	3
	Cough	1	1	0	2
Skin and subcutaneous tissue disorders	Exanthema/Rash	1	2	0	2

Summarized safety data:*

- AEs were mainly mild to moderate
- The most frequent treatment emergent AEs were related to the gastrointestinal tract (e.g. diarrhea, nausea)
- Pattern of AEs were similar to the known safety profile of domatinostat and pembrolizumab
- No increase in frequency or intensity of immune-related AEs observed
- MTD not reached

*Data cut off: 15-July 2019

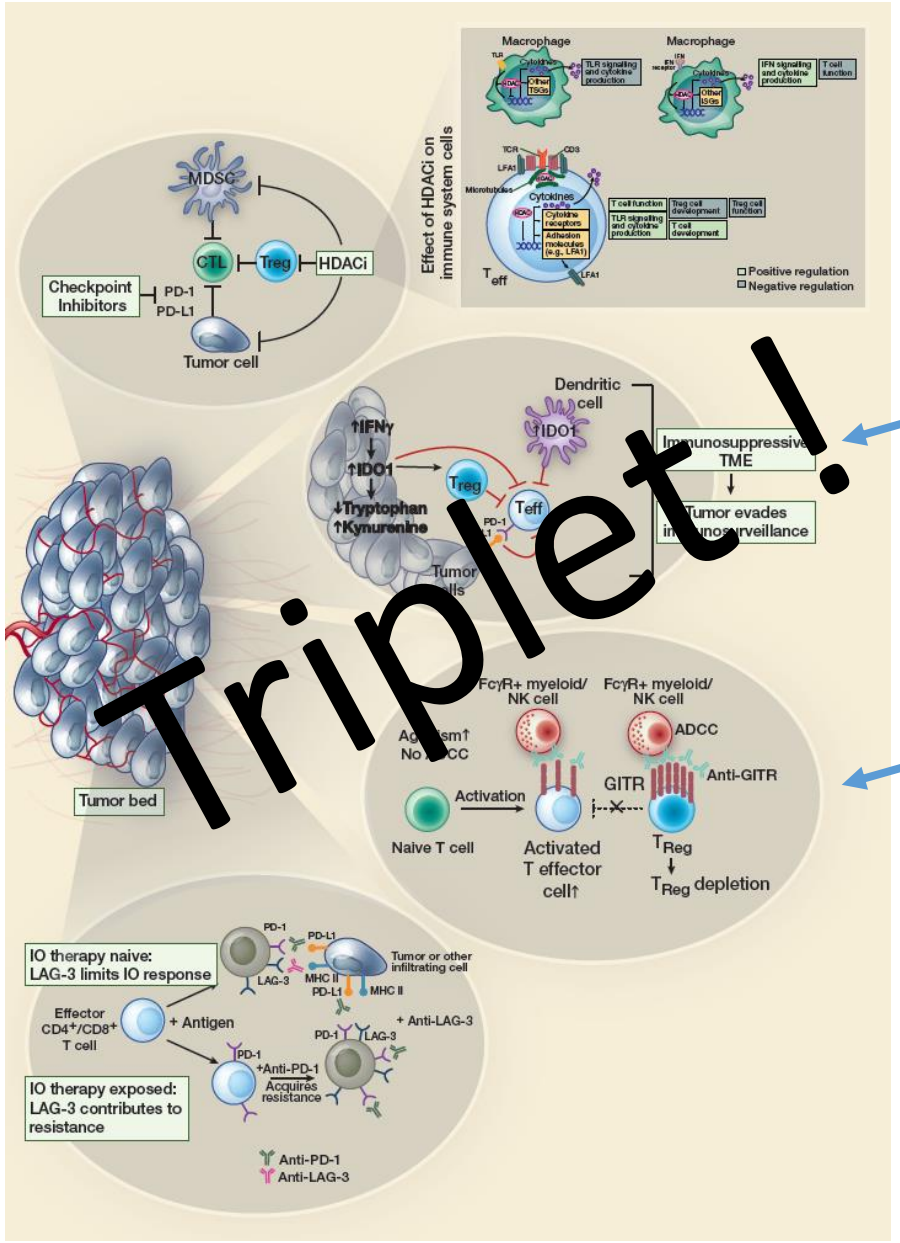
New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

HDAC inhibitors

IDO1 inhibitors

Anti-GITRs

Anti-LAG-3s



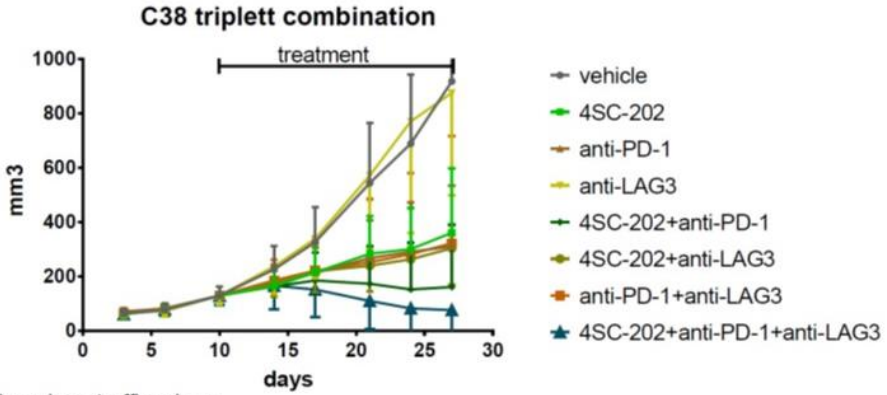
Triplet!

GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

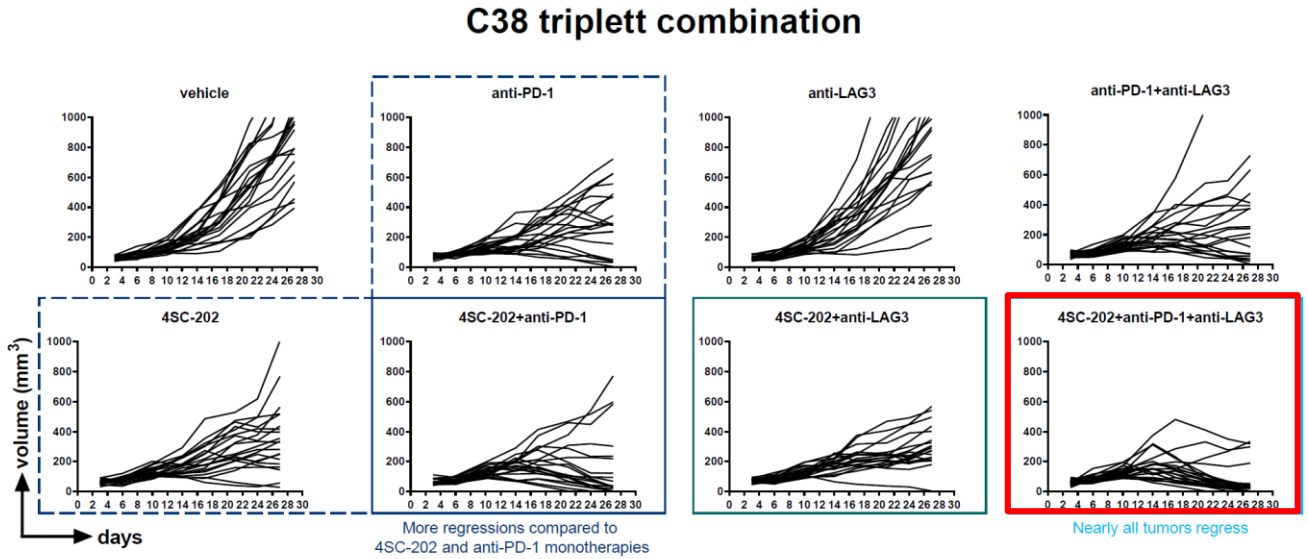
Presented by Paolo A. Ascierto at ASCO 2018

Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

Evaluation of the HDACi +anti-PD1+anti-LAG3 triple combination



- Anti-LAG3 alone is not efficacious
- 4SC-202 and anti-PD-1 alone reduce tumor growth
- 4SC-202+anti-LAG3 is similar to 4SC-202, anti-LAG3+anti-PD-1 is similar to anti-PD-1
- 4SC-202+anti-PD-1 is beneficial compared to mono-therapies
- But triple is superior to all incl. the double 4SC-202+anti-PD-1



Hamm et al AACR 2018 Abstract #4722

Poster no. P391

A Phase 1b/2 Trial of Lenvatinib in Combination With Pembrolizumab in Patients With Advanced Melanoma

Matthew H. Taylor[1], Nicholas J. Vogelzang[2], Allen L. Cohn[2], Daniel E. Stepan[3], Robert C. Shumaker[3], Corina E. Dutcus[3], Matthew Guo[3], Emmett Schmidt[4], Drew W. Rasco[5]

[1]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [2]The US Oncology Network, McKesson Specialty Health, Houston, TX, USA; [3]Eisai Inc., Woodcliff Lake, NJ, USA; [4]Merck & Co., Inc., Kenilworth, NJ, USA; [5]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA

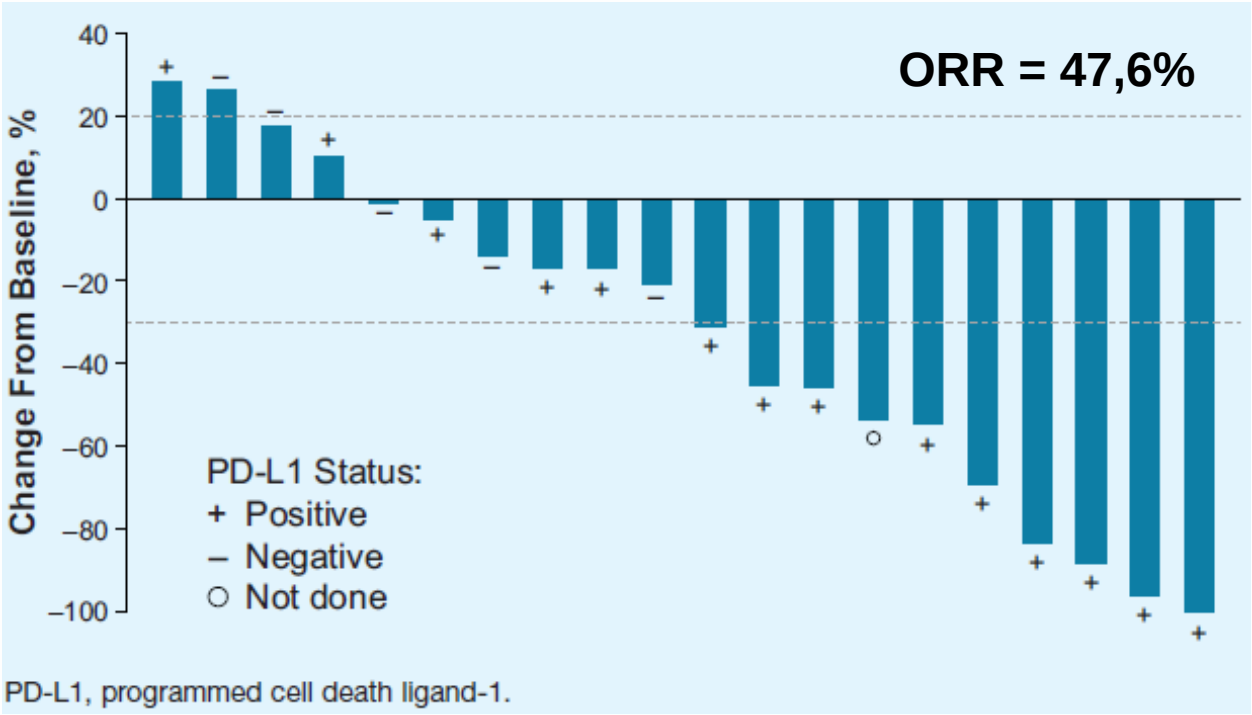
Key Eligibility Criteria
- Histologically confirmed metastatic melanoma
- Measurable disease per irRECIST
- ≤ 2 Prior systemic regimens
- ECOG PS of 0 or 1
- Life expectancy ≥ 12 weeks

Study Treatment

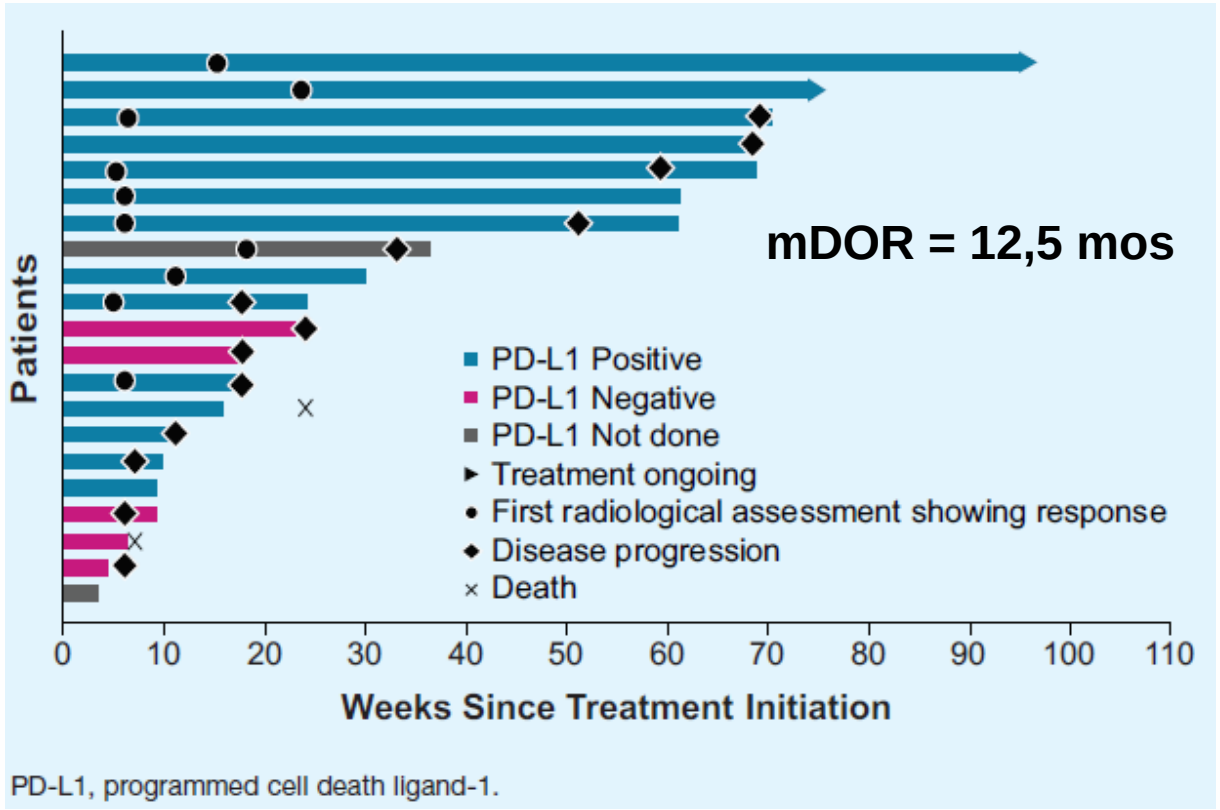
Lenvatinib
20 mg QD orally
+
Pembrolizumab
200 mg IV (Q3W)
(21-day cycles)

Primary End Point
- ORR_{Week24}

Key Secondary End Point
- ORR
- DOR
- PFS
- Safety



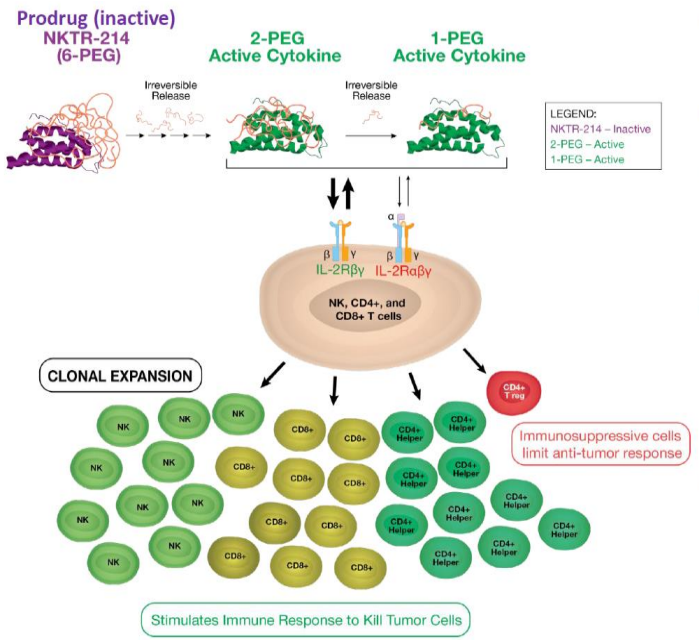
PD-L1, programmed cell death ligand-1.



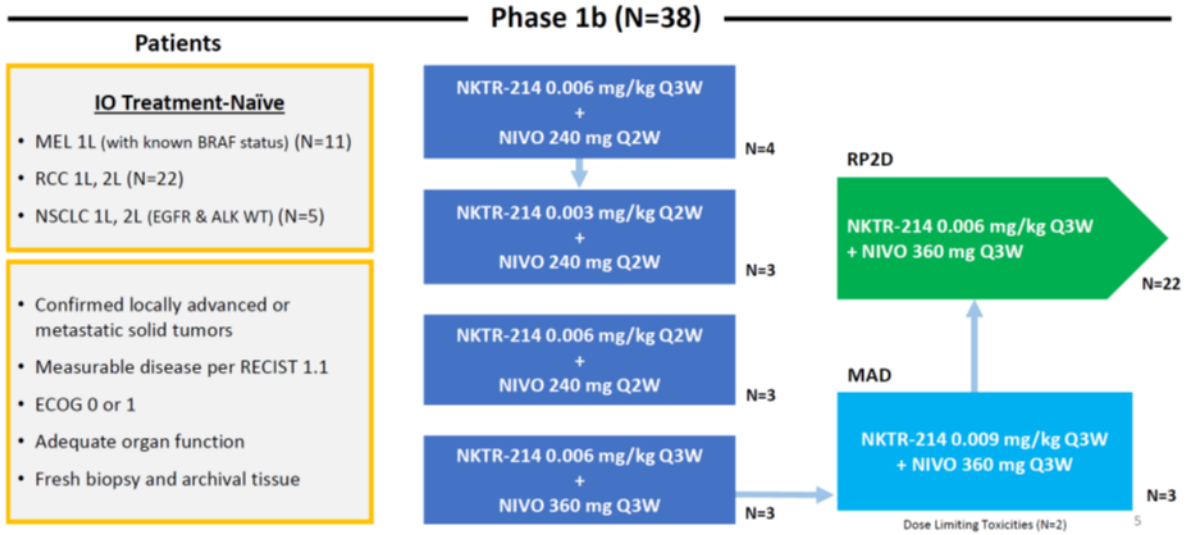
PD-L1, programmed cell death ligand-1.

Taylor et al. *SITC 2018*

Combination of CD122 agonist with anti-PD-1/PD-L1

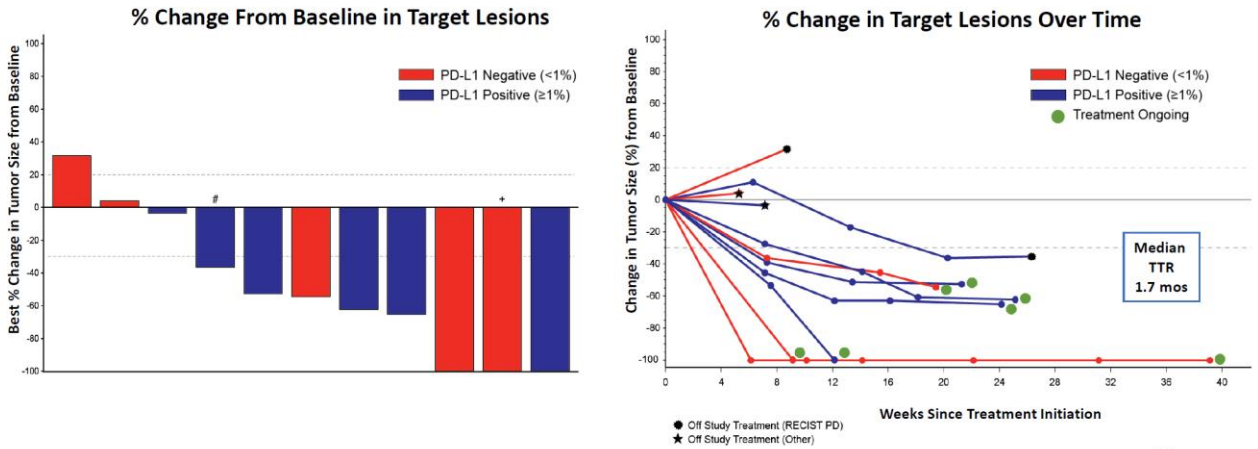


PIVOT-02 Dose Escalation



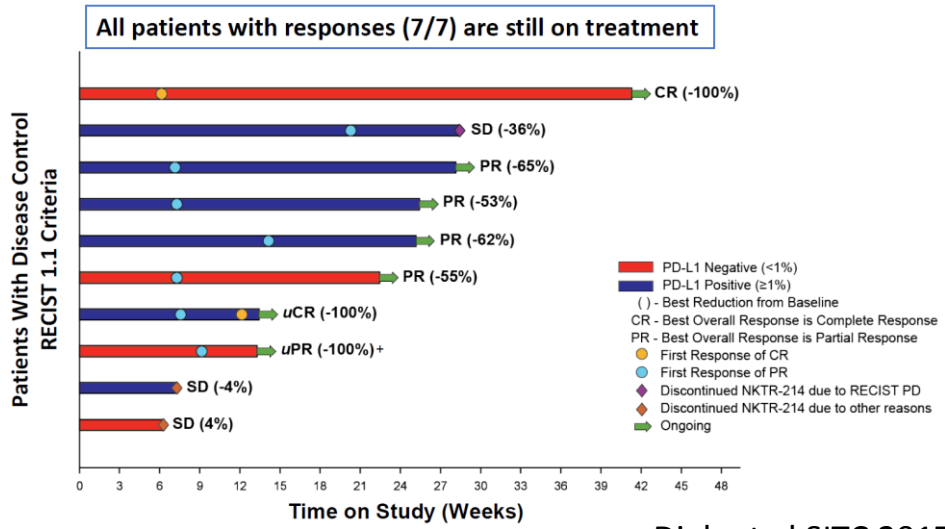
Stage IV Treatment-Naïve Melanoma Patients (N=11)

Best Overall Response by RECIST*: ORR=7/11 (64%); DCR=10/11 (91%)
Best Overall Response by irRECIST: ORR=8/11 (73%); DCR=10/11 (91%)



Time to and Duration of Response

Stage IV Treatment-Naïve Melanoma



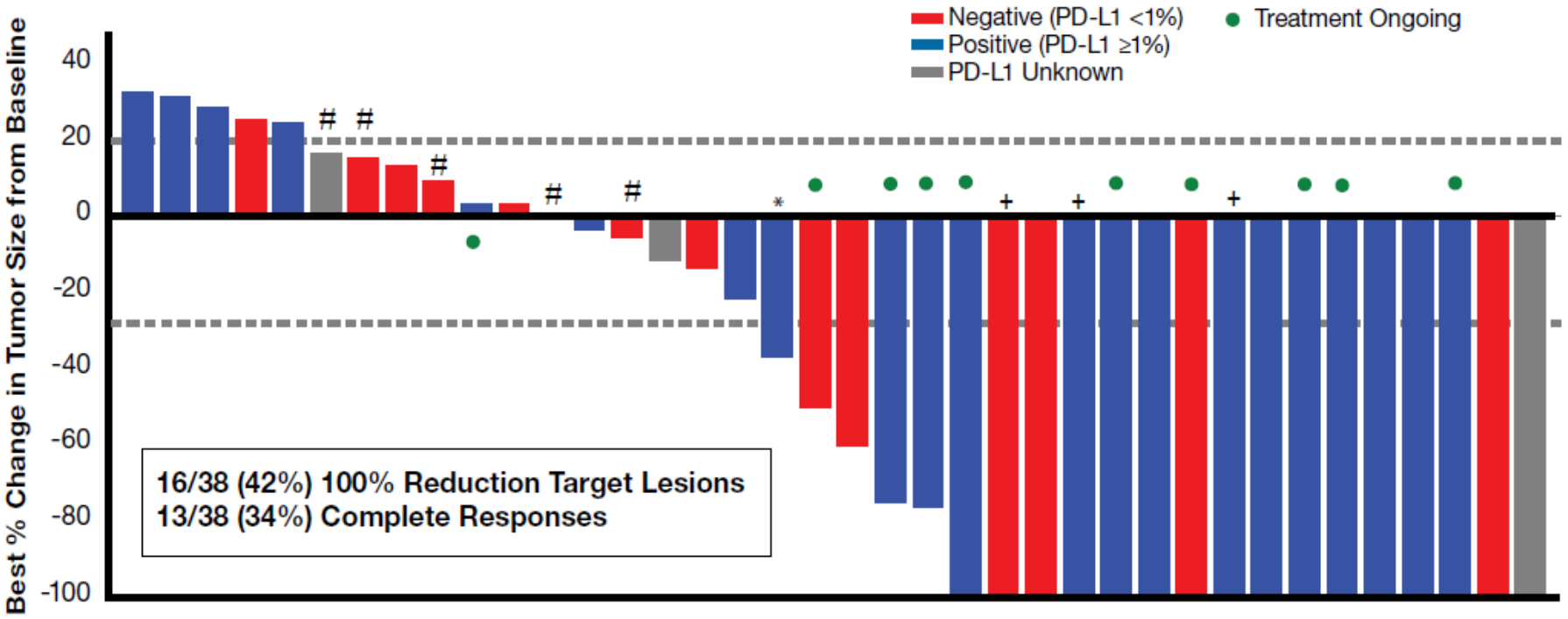
Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. # Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best Overall response is PR (CR for target lesions, non-target lesions still present)
*One patient in ORR calculation has unconfirmed PR.

+ Best Overall response is PR (CR for target lesions, non-target lesions still present)

Presented by Paolo A. Ascierto at ASCO 2018

Diab et al SITC 2017

Stage IV 1L Melanoma Cohort at RP2D: Best Overall Response by Independent Radiology



1L melanoma (n=38 efficacy evaluable**)	Overall response rate
Confirmed ORR (CR+PR)	20 (53%)
CR	13 (34%)
DCR (CR+PR+SD)	28 (74%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=21)	13 (62%)
PD-L1 unknown (n=3)	1 (33%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

#Best overall response is PD due to non-target lesion progression or presence of new lesion. *Best overall response is SD. +Best overall response is PR. CR for target lesion(s). Non-target lesion(s) still present.
**Efficacy-evaluable population includes patients who have measurable disease (per RECIST v1.1) at baseline and also have at least 1 post-baseline tumor assessment. ITT = 41: 3 patients are excluded because they are not response evaluable:1 patient discontinued treatment after 1 dose due to unrelated adverse event (MI); 1 patient discontinued treatment after 1 dose due to patient decision; 1 patient discontinued treatment after 3 doses due to patient decision.

Hurwitz et al ASCO 2018

Lifileucel (LN-144): Cryopreserved Autologous TILs

C-144-01: phase 2 trial for patients with stage IIIC/IV metastatic melanoma and ≥ 1 prior systemic therapy including an immune checkpoint inhibitor and a BRAF inhibitor (if *BRAF* mutation-positive)

Unresectable or metastatic melanoma treated with ≥ 1 systemic prior therapy including a PD-1 blocking antibody and if *BRAF* ^{V600} mutation positive, a BRAFi or BRAFi/MEKi

Cohort 1:
Non-cryopreserved TIL product,
n = 30 *Closed to enrollment*

Cohort 2:
Cryopreserved TIL product, n = 60
Closed to enrollment

Cohort 4:
Cryopreserved TIL product, n = 75
Now enrolling

Cohort 3:
TIL re-treatment
n = 10

Extracted from Sarnaik A et al. Presented at ASCO 2019; abstract 2518.

Lifileucel (LN-144): Data From Phase 2 Trial

- 3.3 mean prior therapies (range, 1–9)
- High tumor burden at baseline (106 mm sum of diameters for target lesions)
- 44% of patient with liver and/or brain mets

TRAEs (≥ 30%)

Preferred term	Cohort 2, n = 66		
	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Patients reporting ≥ 1 treatment-emergent AE	**65 (98.5)**	**63 (95.5)**	**2 (3.0)[a]**
Thrombocytopenia	59 (89.4)	53 (80.3)	0
Chills	52 (78.8)	4 (6.1)	0
Anemia	44 (66.7)	36 (54.5)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Febrile neutropenia	36 (54.5)	35 (53.0)	0
Neutropenia	36 (54.5)	25 (37.9)	0
Hypophosphatemia	29 (43.9)	22 (33.3)	0
Fatigue	27 (40.9)	1 (1.5)	0
Leukopenia	27 (40.9)	22 (33.3)	0
Hypotension	23 (34.8)	7 (10.6)	0
Tachycardia	22 (33.3)	1 (1.5)	0
Lymphopenia	21 (31.8)	19 (28.8)	0

[a]One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term. Treatment-emergent AEs refer to all AEs starting on or after the first dose date of TIL up to 30 days.

mets = metastases; NR = not reached; TRAE = treatment-related adverse event.

Extracted from from Sarnaik A et al. Presented at ASCO 2019; abstract 2518.

Efficacy

Response (RECIST v1.1)	n = 66 n (%)
ORR	**25 (38)**
CR	2 (3)
PR	23 (35)
SD	28 (42)
PD	9 (14)
Non-evaluable	4 (6)
DCR	53 (80)
DOR	
Median (min, max)	NR (1.4+, 19.8 +)
ORR by subgroup	**n = 66 n (%)**
Prior anti–CTLA-4	
Yes (n = 53)	20 (38)
No (n = 13)	5 (39)
***BRAF* mutation status**	
Mutated (V600E or V600K) (n = 17)	8 (47)
Non-mutated (n = 49)	17 (35)

8.8 months of follow-up

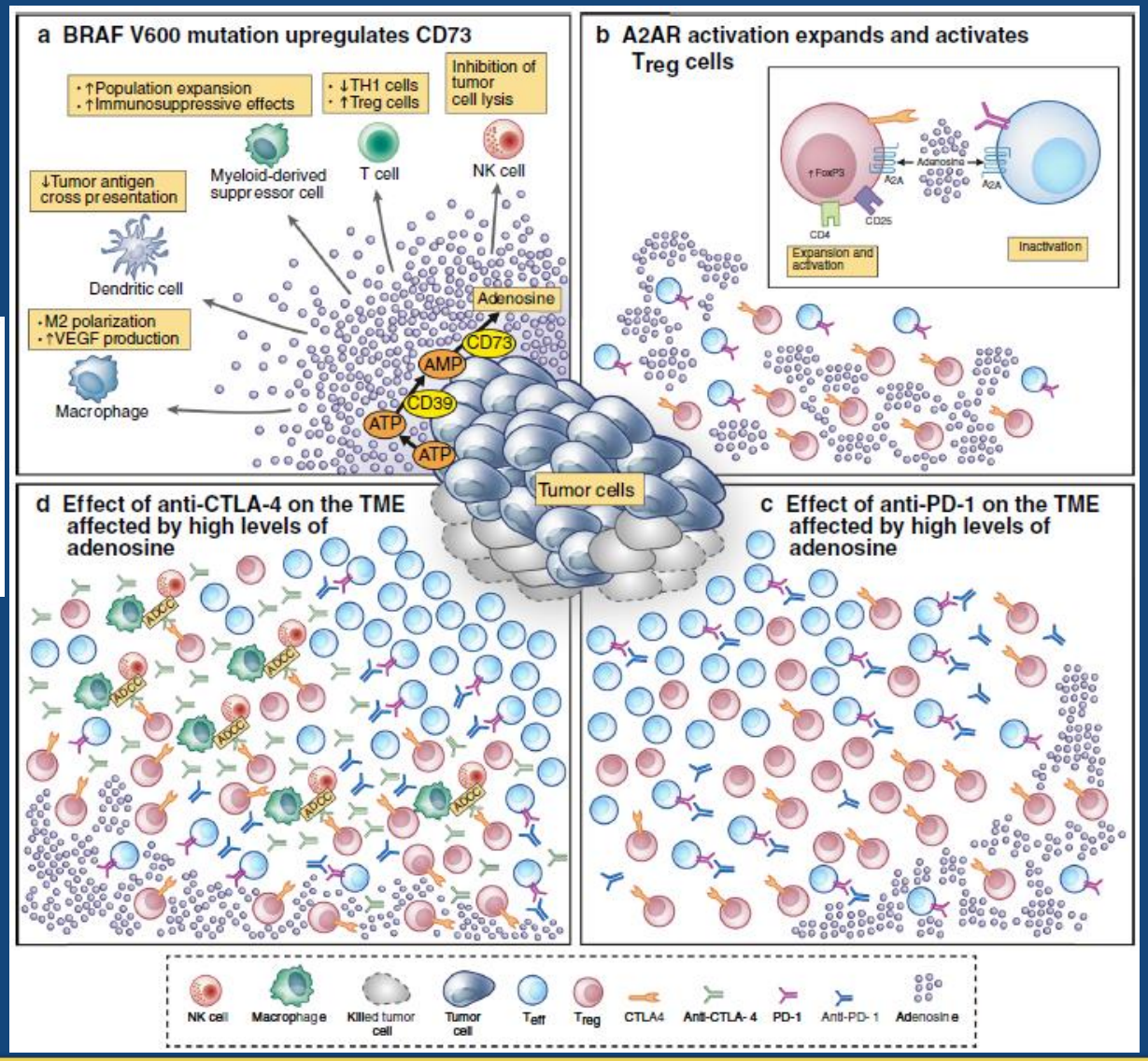
Hypothetical model about how BRAFV600 mutation in melanoma cells could affect the tumor microenvironment and response to ipilimumab and combination of ipilimumab and nivolumab.

Microenvironment and Immunology

Cancer Research

Targeting Adenosine in BRAF-Mutant Melanoma Reduces Tumor Growth and Metastasis

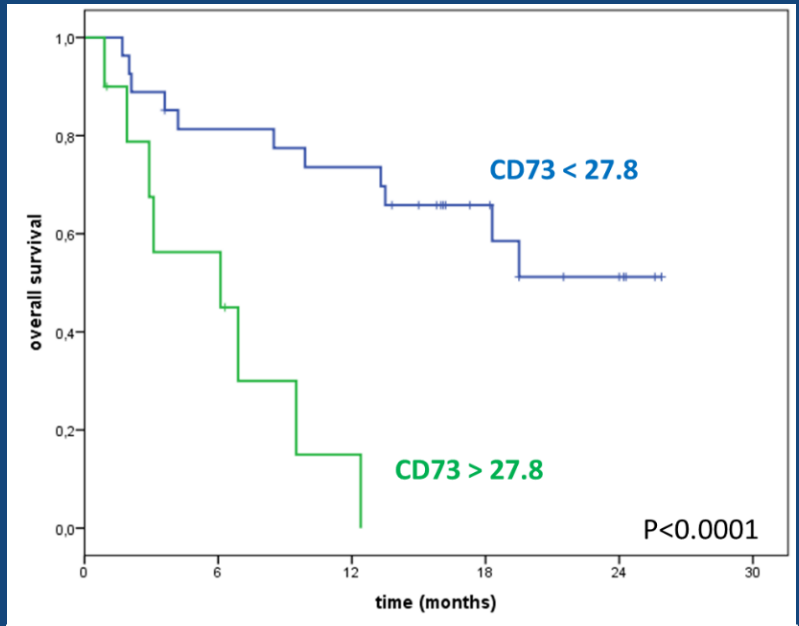
Arabella Young[1,2], Shin Foong Ngiow[1,2,3], Jason Madore[4,5], Julia Reinhardt[6], Jennifer Landsberg[7,8], Arash Chitsazan[9,10], Jai Rautela[11,12], Tobias Bald[1], Deborah S. Barkauskas[1], Elizabeth Ahern[1,2,13], Nicholas D. Huntington[11,12], Dirk Schadendorf[8], Georgina V. Long[4,5], Glen M. Boyle[14], Michael Hölzel[6], Richard A. Scolyer[4,5], and Mark J. Smyth[1,2]



Ascierto and McArthur
J Trans Med 2017

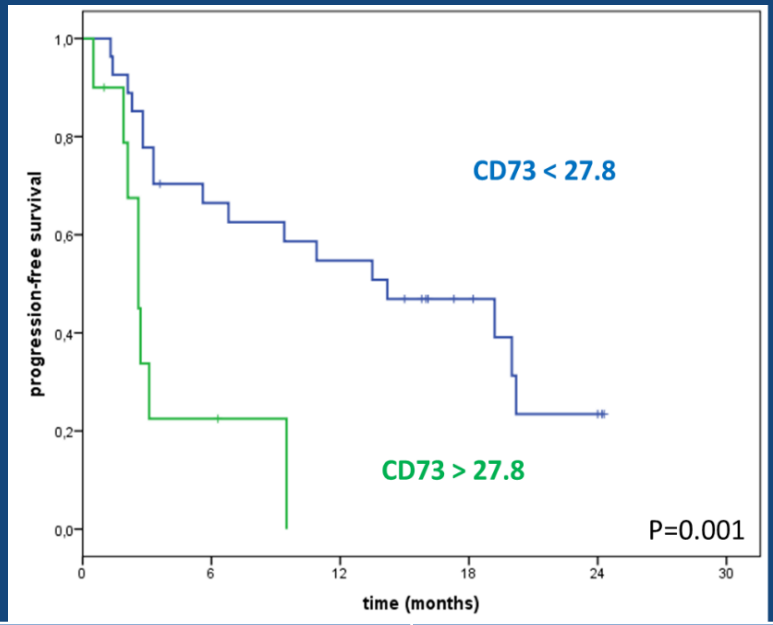
sCD73 baseline enzymatic activity and survival with anti-PD-1

Overall survival



CD73<27.82	CD73>27.82
Not reached	6,1 months (95% CI: 0-14.8)

Progression-free survival



CD73<27.82	CD73>27.82
14.2 months (95% CI: 4,6-23,8)	2.6 months (95% CI: 1,9-3,3)

The optimal cut-off* of sCD73 activity for both overall survival and progression-free survival was 27,82 pmol/min/mg protein

* Best cut-off values were located with an R routine implemented on the online software (Cut-off Finder) which maximize differences in survival between the two groups.

Morello S et al. J Transl Med 2017

Combination of anti-CD73 with anti-PD-1/PD-L1

AACR American Association for Cancer Research ANNUAL MEETING 2018 CHICAGO, IL

CT180

Preliminary Phase 1 Profile of BMS-986179, an Anti-CD73 Antibody, in Combination With Nivolumab in Patients With Advanced Solid Tumors

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CA013-004

BMS-986179 ± Nivolumab Safety Summary

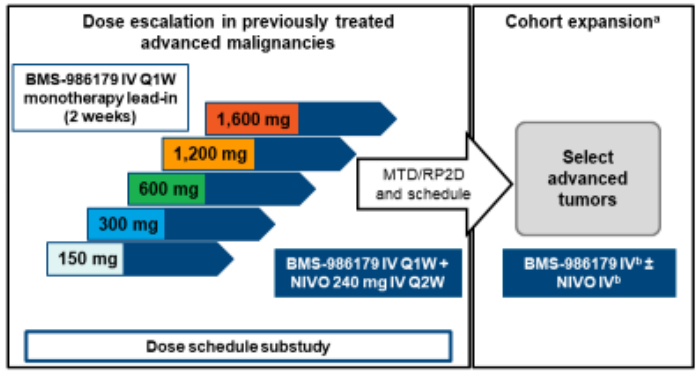
Treatment-related adverse events (TRAEs)	BMS-986179 Q1W		BMS-986179 Q1W + nivolumab 240 mg Q2W											
	Total (N = 89)		BMS-986179 150 mg (n = 12)		BMS-986179 300 mg (n = 11)		BMS-986179 600 mg (n = 12)		BMS-986179 1,200 mg (n = 7)		BMS-986179 1,600 mg (n = 10)		Total (N = 52)	
	Any, n (%)	Gr 3, n (%)	Any, n	Gr 3, n	Any, n	Gr 3, n	Any, n	Gr 3, n	Any, n	Gr 3, n	Any, n	Gr 3, n	Any, n (%)	Gr 3, n (%)
Any TRAE	23 (39)	1 (2)	7	2[a,b]	7	2	5	3[a,c]	5	0	6	1[a,d]	30 (58)	8 (15)[a–d]
TRAEs in ≥ 5% of patients*														
Headache	5 (8)	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	2 (3)	0	2	0	2	1	1	0	1	0	0	0	6 (12)	1 (2)
Increased lipase	0	0	0	0	1	1	2	2	0	0	1	0	4 (8)	3 (6)
Hypothyroidism	0	0	2	0	2	0	0	0	0	0	0	0	4 (8)	0
Increased ALT	1 (2)	1 (2)	1	0	0	0	1	1	1	0	0	0	3 (6)	1 (2)
Increased amylase	0	0	0	0	1	0	1	0	0	0	1	0	3 (6)	0
Diarrhea	2 (3)	0	1	0	0	0	0	0	1	0	1	0	3 (6)	0
Periorbital edema	1 (2)	0	1	0	1	0	1	0	0	0	0	0	3 (6)	0
Pruritus	2 (3)	0	0	0	3	0	0	0	0	0	0	0	3 (6)	0
Pyrexia	1 (2)	0	1	0	1	0	0	0	1	0	0	0	3 (6)	0
TRAEs leading to DC	0	0	2	1	0	0	1	1	0	0	0	0	3 (6)	2 (4)

*Other Grade 3 TRAEs included: [a]adrenal insufficiency and increased transaminases (150 mg, n = 1 each), [c]autoimmune hepatitis and hepatitis (600 mg, n = 1), and [d]pancreatitis (1,600 mg, n = 1); *Total patients treated with BMS-986179 ± nivolumab during dose escalation as of the February 20, 2018 data cutoff; mono = monotherapy; combo = combination therapy

- Two patients had Grade 3 myocardial infarctions (MIs; 150 mg mono; 600 mg combo), which were unrelated per investigator
  - Both patients had multiple cardiovascular risk factors prior to study entry, and both recovered
  - More stringent study entry criteria and cardiac risk factor monitoring were implemented in the study, and no additional MIs have occurred

CA013-004

First-in-Human Phase 1/2a Study of BMS-986179 ± Nivolumab in Advanced Solid Tumors



- Primary objective:
  - Safety and tolerability
- Key secondary/exploratory objectives:
  - Pharmacodynamics (PD)
  - Pharmacokinetics (PK)
  - Preliminary antitumor activity
  - Associations of PD activity with efficacy and safety outcomes
- Key inclusion criteria:
  - Prior treatment with immune checkpoint inhibitors is permitted

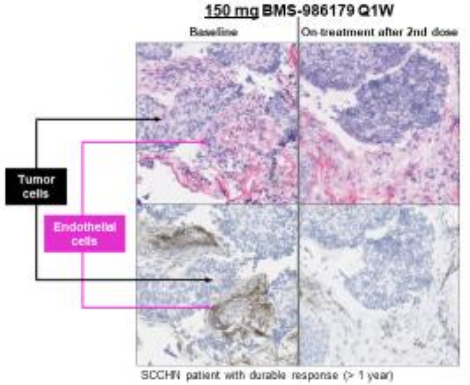
Data cutoff: February 20, 2018

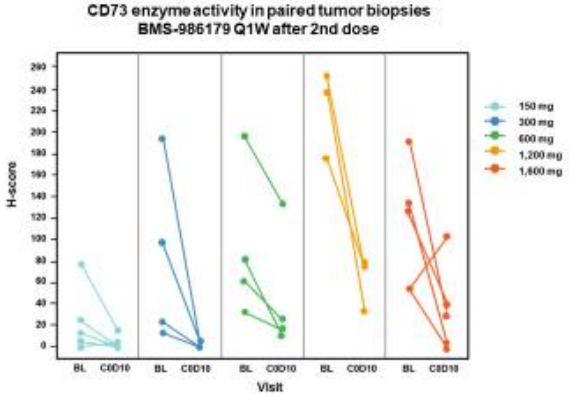
ClinicalTrials.gov identifier: NCT02754141
[a]Expansion cohorts are ongoing; [b]BMS-986179 and NIVO doses and schedules to be based on data from escalation phase and substudy
IV = intravenous; MTD = maximum tolerated dose; NIVO = nivolumab; Q1W = every week; Q2W = every 2 weeks; RP2D = recommended phase 2 dose

CA013-004

Changes in CD73 Enzymatic Activity* With BMS-986179 in Tumors at Q1W

- BMS-986179 efficiently inhibited CD73 enzyme activity in the tumor vasculature and tumor cells





*Assay measures enzymatic activity directly in the tumor.
BL = baseline.

Siu et al AACR 2018

Presented by Paolo A. Ascierto at ASCO 2018

Safety, efficacy, and pharmacodynamics of MEDI9447 (oleclumab) alone or in combination with durvalumab in advanced pancreatic cancer or colorectal cancer

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P4123

Introduction

- The adenosine pathway represents a major immunosuppressive mechanism that may exert local suppression through tumor intrinsic and host mediated mechanisms.
- CD73, an ecto-5'-nucleotidease, converts extracellular adenosine monophosphate (AMP) to adenosine, is highly expressed in many human solid tumors, and is associated with worse clinical prognosis.[1]
- MEDI9447 (oleclumab) is a human IgG1λ monoclonal antibody (mAb) that inhibits CD73-mediated enzymatic production of adenosine by 2 proposed mechanisms of action.[2]
  1. Inhibition of CD73 enzymatic activity
  2. Decreased expression of CD73 through internalization
- Oleclumab was shown to enhance antitumoral immune responses and inhibit tumor growth in animal models.[3]

Objective

This is a first-in-human study (NCT02503774) to investigate the safety, efficacy, and PD of oleclumab alone or in combination with durvalumab in patients with advanced solid tumors.

Study Design

NCT02503774 is an open-label, dose-escalation and dose-expansion study in treatment-experienced patients with advanced solid tumors. A standard 3+3 dose-escalation design was followed in 2 treatment study arms (**Figure 1**).

Arm 1 – Ascending doses of oleclumab alone administered IV Q2W

Arm 2 – Ascending doses of oleclumab in combination with a single dose level of durvalumab 10 mg/kg IV Q2W

Dose expansion in patients with advanced solid tumors (pancreatic cancer [Panc] and colorectal cancer [CRC] patient cohorts presented here) was done with doses of oleclumab and durvalumab identified from the dose escalation phase. In both dose expansion treatment arms, patients were initially treated for up to 52 weeks. Patients who achieved and maintained disease control (CR, PR, or SD) through end of the 52-week treatment period entered a period of follow-up. The protocol was subsequently amended to allow for treatment continuation until disease progression.

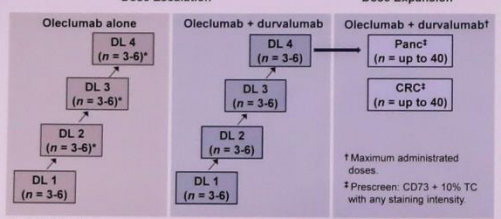
Primary endpoint

Safety was assessed by treatment-related and non-treatment-related adverse events (AEs) and serious AEs (SAEs) collected from time of signature of informed consent through 12 weeks after last dose of study drug.

Secondary endpoints

- Tumor response assessed according to RECIST v1.1 criteria
- Oleclumab serum pharmacokinetic characterization
- Assessment of PD according to tumoral CD73 expression by IHC

Figure 1: Study design



DL = dose level.

*DL 2-4 cohorts were able to enroll up to an additional 10 subjects for further PD exploration.

Results

Table 1: Patient demographics

	Oleclumab monotherapy				Oleclumab + durvalumab therapy					
	Dose escalation phase				Dose escalation phase				Dose expansion phase	
Patient Characteristic	DL 1 n = 3	DL 2 n = 11	DL 3 n = 12	DL 4 n = 16	DL 1 n = 7	DL 2 n = 3	DL 3 n = 4	DL 4 n = 10	Panc (DL 4) n = 42	CRC (DL 4) n = 21
Age (years), median (range)	67.0 (56–69)	62.0 (40–81)	56.0 (36–75)	57.5 (39–71)	55.0 (32–71)	57.0 (46–60)	57.0 (49–68)	52.5 (44–64)	63.5 (32–77)	53.0 (32–80)
Sex, n (%) Female	2 (66.7%)	7 (63.6%)	7 (58.3%)	6 (37.5%)	6 (85.7%)	1 (33.3%)	1 (25.0%)	7 (70.0%)	26 (61.9%)	9 (42.9%)
Prior therapies, n (%)										
0	0	0	0	0	0	0	0	0	2 (4.8%)	0
1	0	0	2 (16.7%)	0	2 (28.6%)	0	1 (25.0%)	1 (10.0%)	16 (38.1%)	2 (9.5%)
2	0	2 (18.2%)	3 (25.0%)	6 (37.5%)	2 (28.6%)	1 (33.3%)	1 (25.0%)	3 (30.0%)	23 (54.8%)	8 (38.1%)
3	3 (100%)	4 (36.4%)	5 (41.7%)	4 (25.0%)	1 (14.3%)	1 (33.3%)	1 (25.0%)	3 (30.0%)	1 (2.4%)	7 (33.3%)
≥4	0	5 (45.5%)	2 (16.7%)	6 (37.5%)	2 (28.6%)	1 (33.3%)	1 (25.0%)	3 (30.0%)	0	4 (19.0%)

DL = dose level.

Table 2: Treatment-related AEs occurring in >10% of patients in any arm of oleclumab monotherapy dose escalation

Preferred Term (MedDRA v20)	DL 1 n = 3	DL 2 n = 11	DL 3 n = 12	DL 4 n = 16	Total n = 42
Fatigue	1 (33.3%)	2 (18.2%)	4 (33.3%)	0	7 (16.7%)
Anemia	0	1 (9.1%)	2 (16.7%)	1 (6.3%)	4 (9.5%)
Nausea	0	0	2 (16.7%)	2 (12.5%)	4 (9.5%)
ALT increased	0	0	0	2 (12.5%)	2 (4.8%)
AST increased	0	0	0	2 (12.5%)	2 (4.8%)
Influenza-like illness	0	0	2 (16.7%)	0	2 (4.8%)
Myalgia	1 (33.3%)	0	0	0	1 (2.4%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

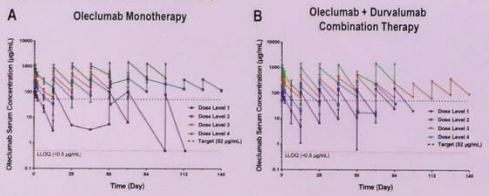
Table 3: Treatment-related AEs occurring in >5% of patients in any arm in dose expansion oleclumab + durvalumab

Patients with:	Panc n = 42	CRC n = 21	Total
Diarrhea	2 (4.8%)	3 (14.3%)	5 (7.0%)
Fatigue	2 (4.8%)	2 (9.5%)	5 (7.0%)
AST increased	1 (2.4%)	3 (14.3%)	4 (5.6%)
Pyrexia	3 (7.1%)	1 (4.8%)	4 (5.6%)
ALT increased	1 (2.4%)	2 (9.5%)	3 (4.2%)
ALP increased	1 (2.4%)	2 (9.5%)	3 (4.2%)
Anemia	0	2 (9.5%)	2 (2.8%)
Pneumonia	0	2 (9.5%)	2 (2.8%)
Rash, maculo-papular	0	2 (9.5%)	2 (2.8%)

- **No treatment-related deaths or dose-limiting toxicities were reported.**
- Treatment related SAEs
  - Monotherapy (*n* = 42) – None
  - Combination (*n* =95) – 5 Subjects: Gr 4 thrombocytopenia (DL4); Gr2 Abdominal pain (Panc); Gr4 pneumonia (CRC); Gr3 hepatitis (Panc and other tumor).
- Treatment-related AEs that led to discontinuation
  - Monotherapy (*n* = 42) – None
  - Combination (*n* = 95) – 4 Subjects: Gr2 Nausea and Vomiting (DL1); Gr3 Increased AST and Gr2 bilirubin (DL1); Gr3 hepatitis (Panc and other tumor).

Pharmacokinetics and Pharmacodynamics

Figure 2: Serum PK of oleclumab Q2W as monotherapy (A) or in combination with durvalumab (B)



LLOQ = lower limit of quantification.

Figure 3: Sustained decrease in free soluble CD73 with oleclumab monotherapy (A) or in combination with durvalumab (B)

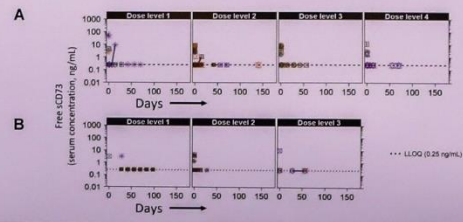
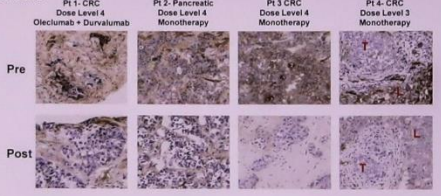
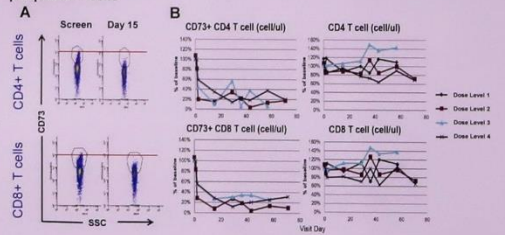


Figure 4: Oleclumab treatment decreases CD73 enzymatic activity in tumor cells



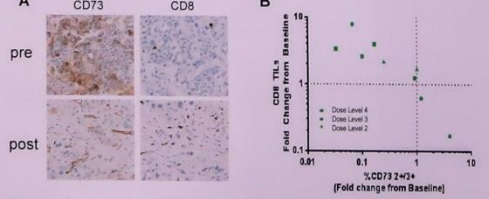
Decrease in CD73 enzymatic activity 20 days post treatment initiation in 3 of 4 patients as demonstrated by an in situ enzymatic assay (Wachstein and Meisel method). Pt 4 had no tumor cell CD73 expression or enzymatic activity at baseline but had CD73 enzymatic activity in adjacent liver pre-treatment that decreased on treatment. Representative images from OCT embedded tissue at 20X magnification. In this method, enzymatic activity leads to a brown coloring. T = tumor; L = liver.

Figure 5: Oleclumab treatment decreases surface expression of CD73 on peripheral T cells



Oleclumab decreased CD73 surface expression as measured by MFI (A) and percent CD73+ CD4 and CD8 cells (B) across all doses without a concomitant decrease in total CD4 and CD8 cells. SSC; side scatter

Figure 6: Oleclumab decreases CD73 expression and increases CD8 TILs in a subset of patients

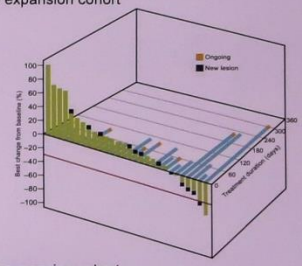


Representative images of CD73 and CD8 IHC staining (A) observed in a pancreatic cancer patient tumor at pre-treatment and post-treatment (20 days) after Dose Level 4 of oleclumab monotherapy. Treatment with oleclumab alone decreased tumoral CD73 expression in 5/9 patients who expressed >5% 2+/3+ CD73 at baseline while increasing CD8+ TILs in all 5 samples (B).

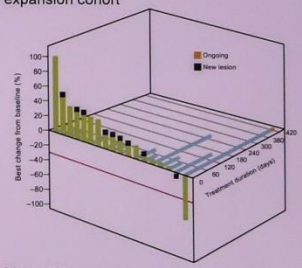
Clinical Activity

Figure 7: Best change in tumor size (y-axis) and duration of treatment (z-axis) of oleclumab in combination with durvalumab in the panc or CRC expansion cohort

A Panc dose expansion cohort



B CRC dose expansion cohort



As of 23 Apr 2018, PR was observed for 1/21 CRC and 2/34 panc patients; SD was observed in 2/21 CRC and 5/34 panc patients in the dose expansion phase.

Conclusions

- Treatment with oleclumab alone or with durvalumab demonstrated a manageable safety profile as measured by low incidence of treatment-related discontinuation and SAEs.
- Oleclumab both inhibits CD73 enzymatic activity and decreases protein expression in tumors consistent with its mechanism of action.
- Dose Level 4 of oleclumab has been selected for expansion into treatment of multiple solid tumors in combination with durvalumab.
- Preliminary results of oleclumab with durvalumab in the pancreatic and CRC cohorts has shown encouraging clinical activity to support further development.

Acknowledgments

We thank the patients and their families and the site investigators who participated in this study.

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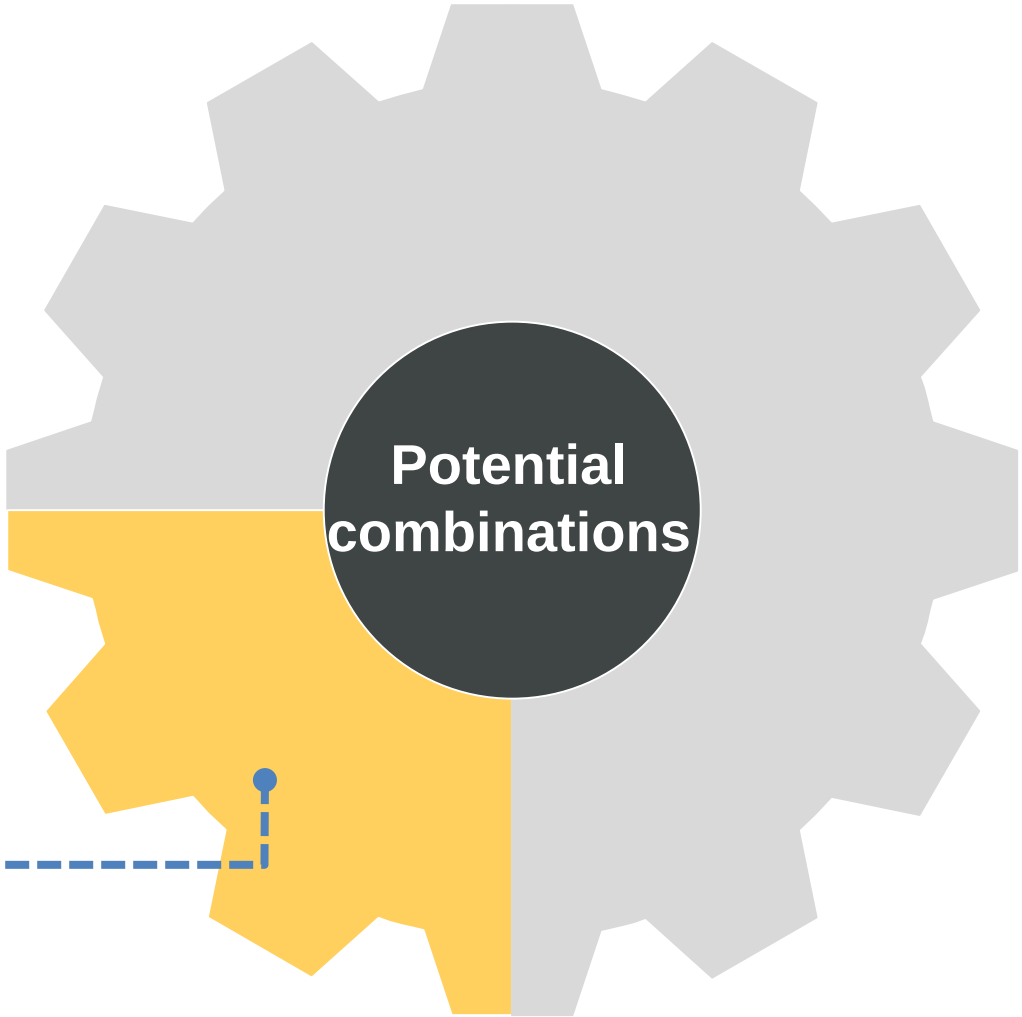
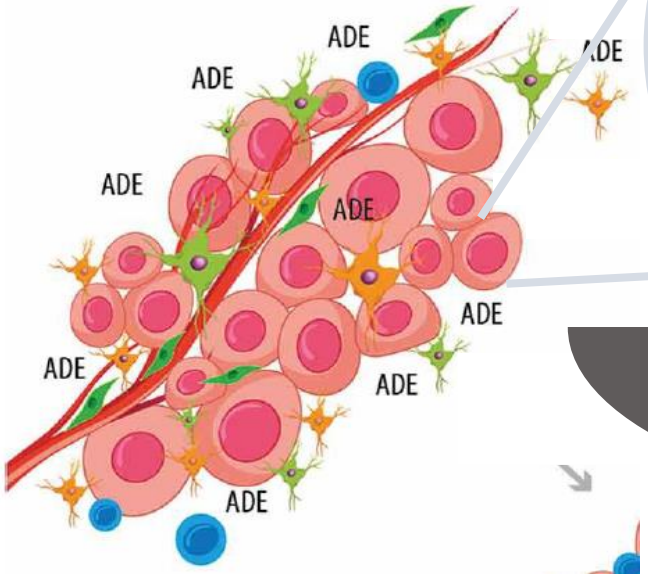
Presented at the 2018 ASCO Annual Meeting; Chicago, IL; June 1–5, 2018

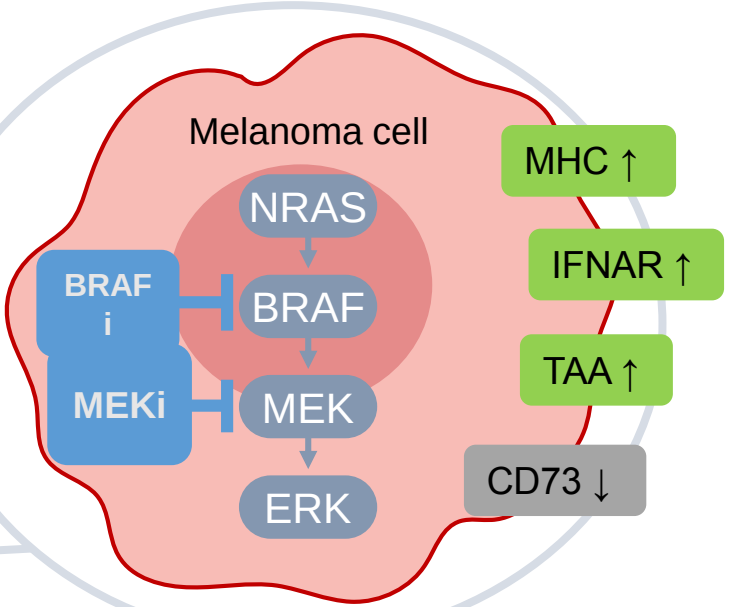
Potential combination strategies for the treatment of cancer

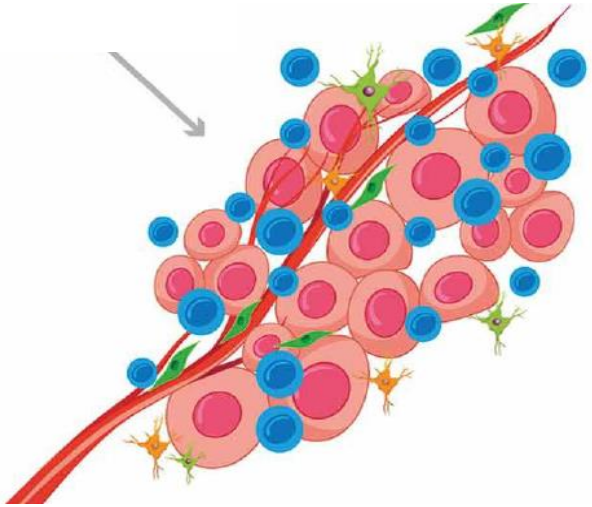


BRAF/MEK inhibitors as immunomodulating agents

T reg
CD4-CD8+ lymphocytes
Myeloid-derived suppressor cells







Tumour microenvironment before BRAFi and MEKi

BRAFi/MEKi induce profound changes in:
Antigen display ↑
Expression of MHC ↑
IFNAR ↑ and CD73 ↓

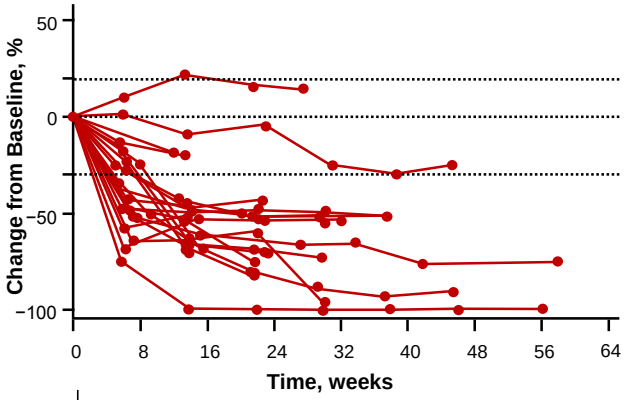
Tumour microenvironment after BRAFi and MEKi:
↓ Adenosine
↓ Treg and myeloid-derived suppressor cells
↑ Activity of CD4-CD8+ lymphocytes

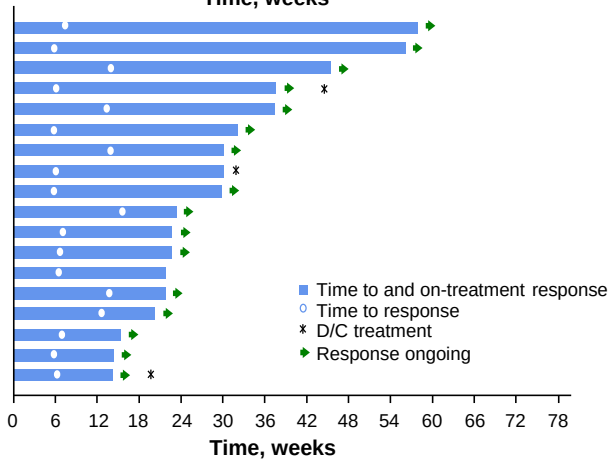
ADE, adensosine; IFNAR, interferon-α/β receptor; MHC, major histocompatibility complex; TAA, tumour-associated antigen; Treg, regulatory T cell

Image modified from Ascierto & Dummer, Oncoimmunology 2018

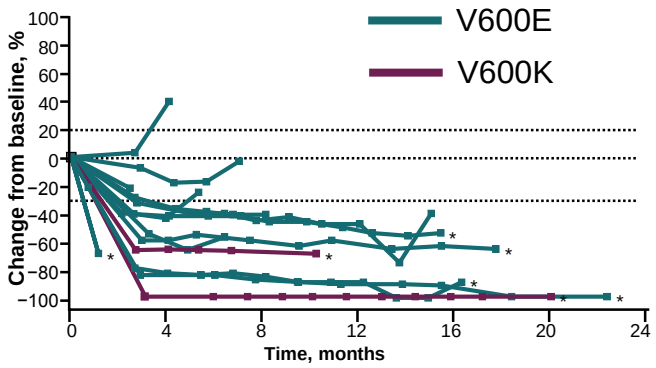
Clinical Trials Combining BRAFi + MEKi + anti–PD-1/L1

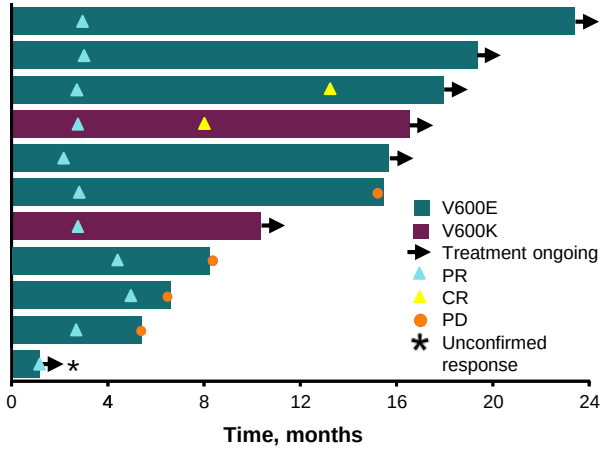
Dabrafenib + trametinib + durvalumab[1]



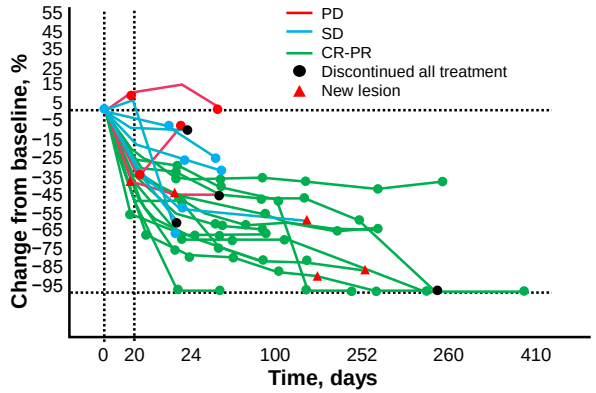


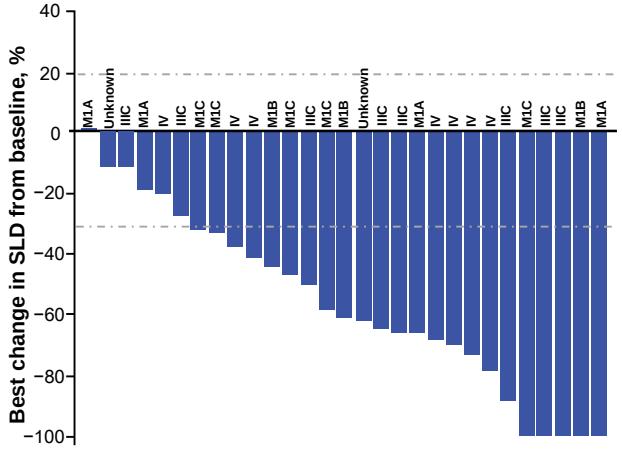
Dabrafenib + trametinib + pembrolizumab[2,3]



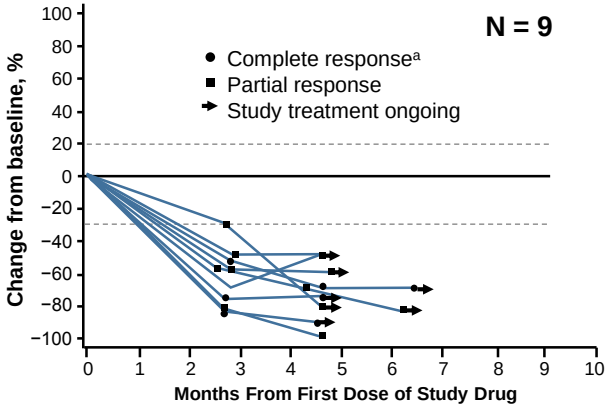


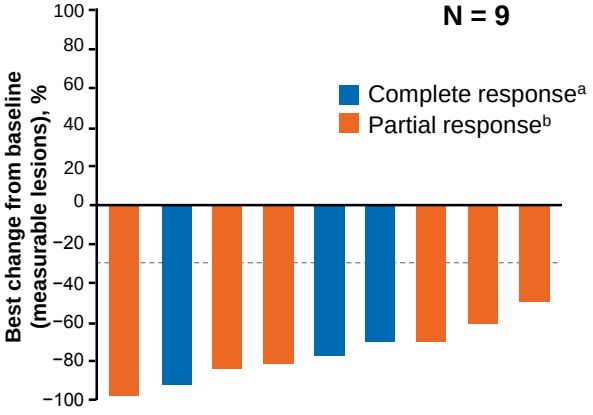
Vemurafenib + cobimetinib + atezolizumab[4]





Dabrafenib + trametinib + spartalizumab[5]





BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

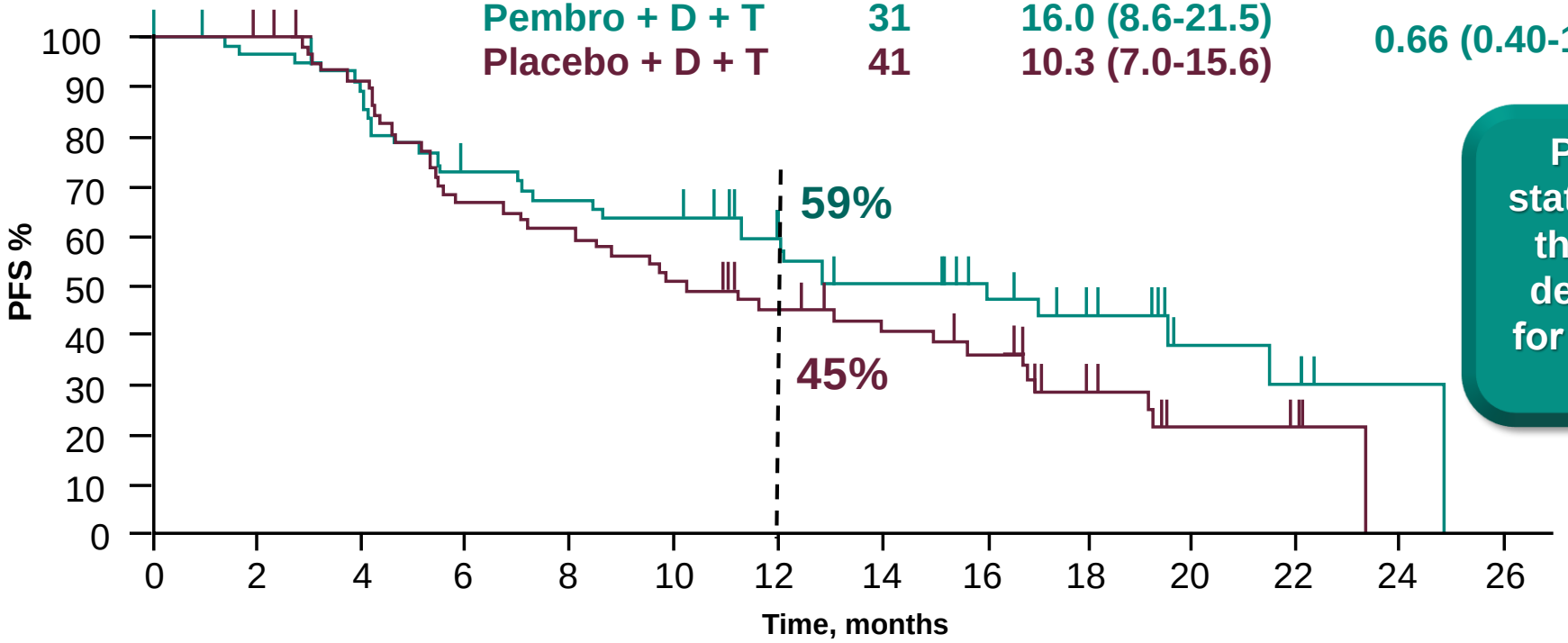
1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

PRESENTED BY R DUMMER AT AACR 2018

Courtesy of Dr Dummer

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, *P* ≤ 0.025)

No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Open questions …

We really need to combine ?

Is there a patients subgroup where combination might be more useful?

Any role in case of PD after/during adjuvant or metastatic treatment?

Is really toxicity a limiting factor for combining TKI to IO … ?

Can we use a different schedule for combination (intermittent or short course of TKI) ?

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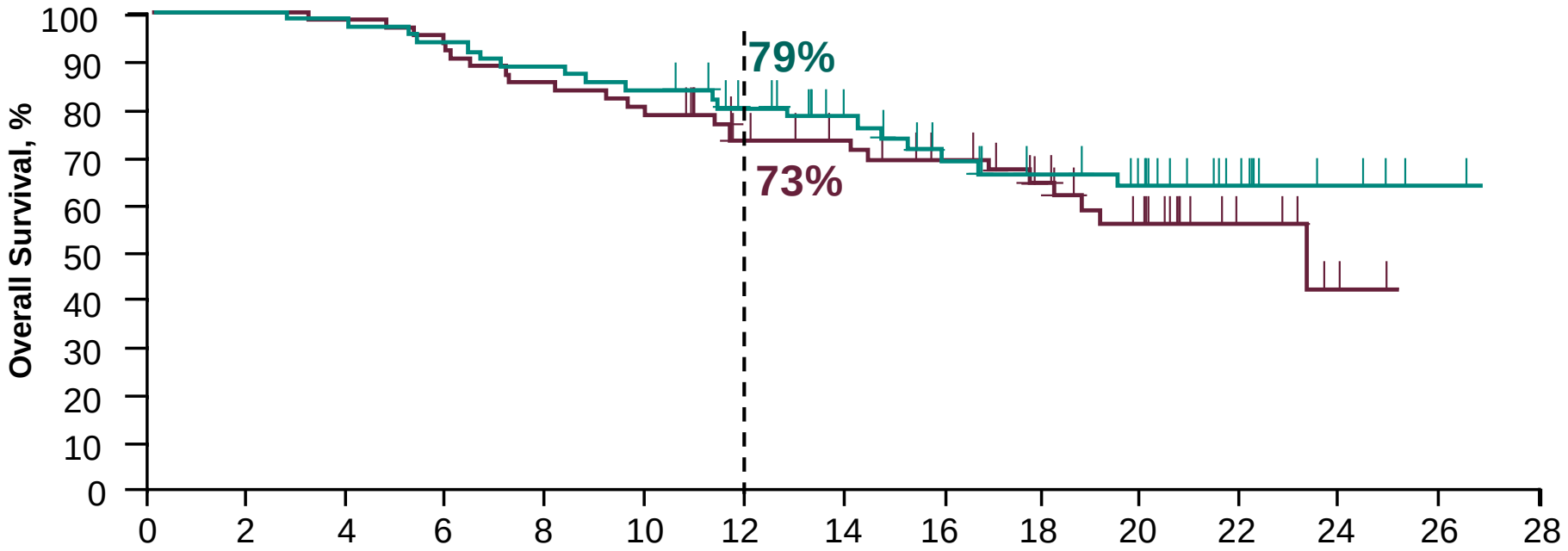
Overall Survival

	Events, n	Median[a] (95% CI), mo	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	19	NR (19.6-NR)	0.76 (0.41-1.39)	0.18467
Placebo + D + T	24	23.4 (17.8-NR)		



No. at risk

Pembro + D + T	60	60	59	56	53	50	43	35	29	23	18	9	4	1	0
Placebo + D + T	60	60	59	55	51	47	39	36	31	25	18	7	2	0	0

[a]Based on Kaplan-Meier estimate of overall survival.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Ascierto et al. ESMO 2018

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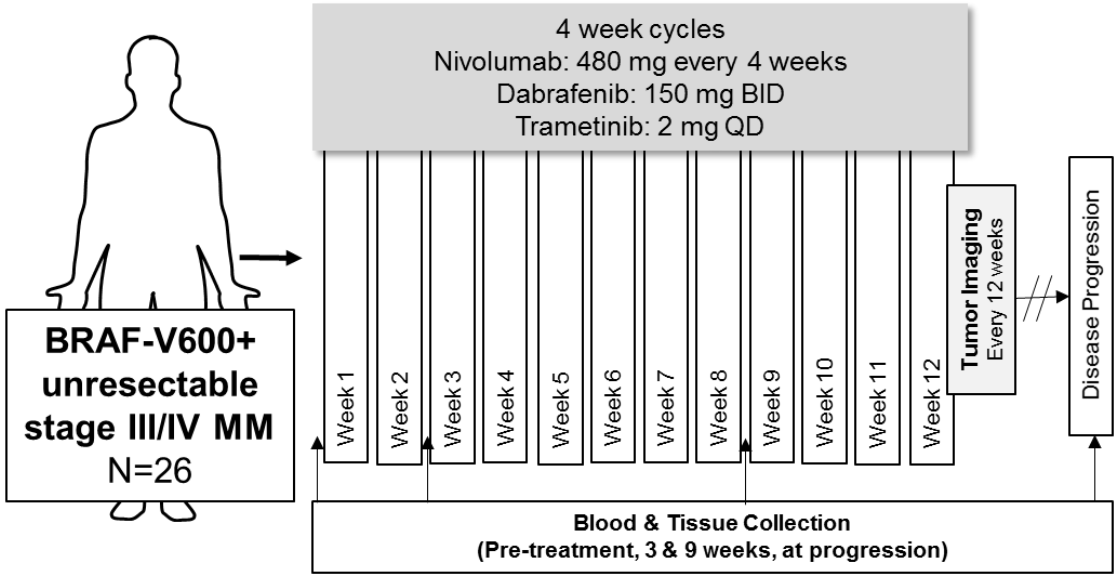
Study Design and Objectives



Hypothesis:

- Nivolumab in combination with dabrafenib and trametinib will demonstrate clinical activity in BRAF mutated pts, including those with checkpoint inhibitor refractory disease and those with brain metastases

Primary Objective:

- To determine the safety, tolerability, and efficacy (by objective response rate by RECIST 1.1) of nivolumab in combination with dabrafenib and trametinib in pts with BRAF-mutated metastatic melanoma

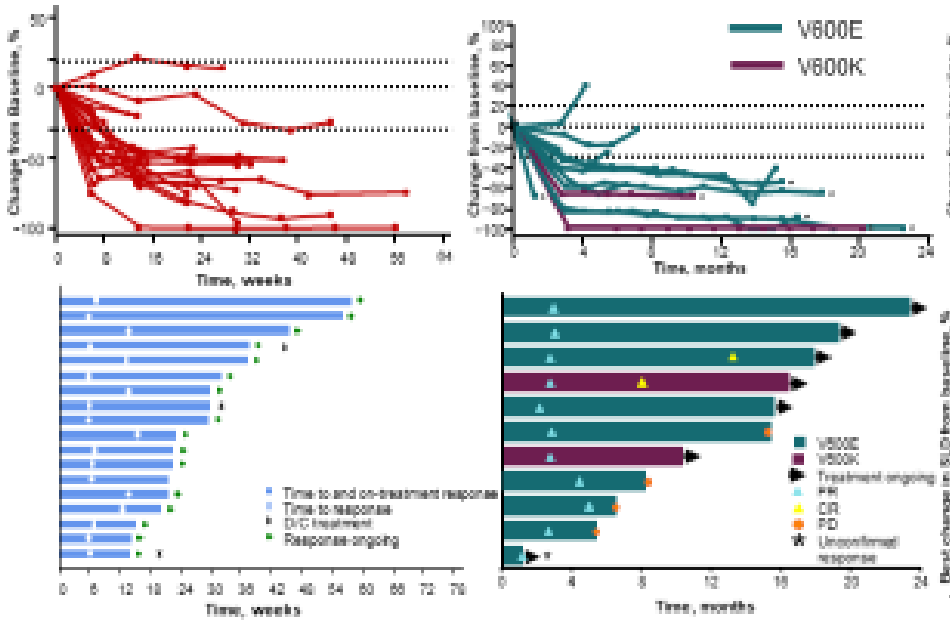
Secondary Objectives:

- Efficacy of the combination as measured by depth and duration of response
- Progression- free and overall survival for patients with and without prior anti-PD1 exposure
- Pharmacodynamic evaluation of the combination on circulating markers and tumor tissue

Burton E. et al. ESMO 2019

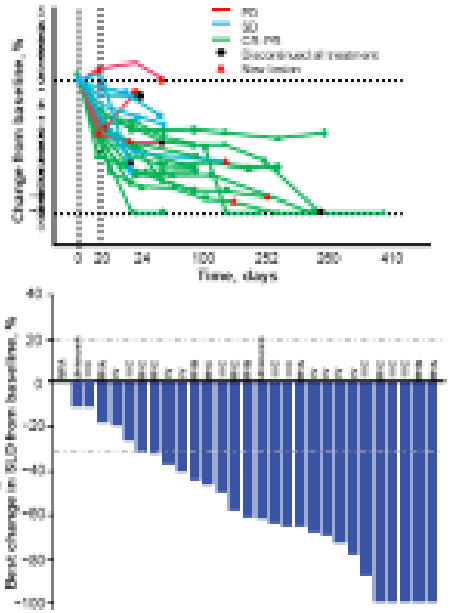
Different triple combination BRAF/MEK + anti-PD-1/PD-L1

Dabrafenib + trametinib + durvalumab

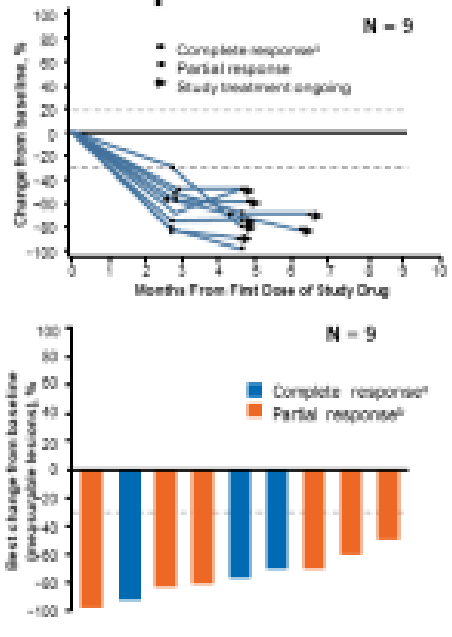


Dabrafenib + trametinib + pembrolizumab

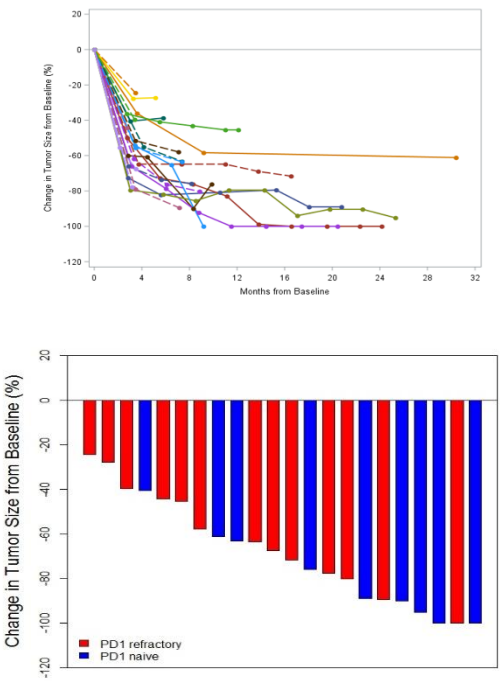
Vemurafenib + cobimetinib + atezolizumab



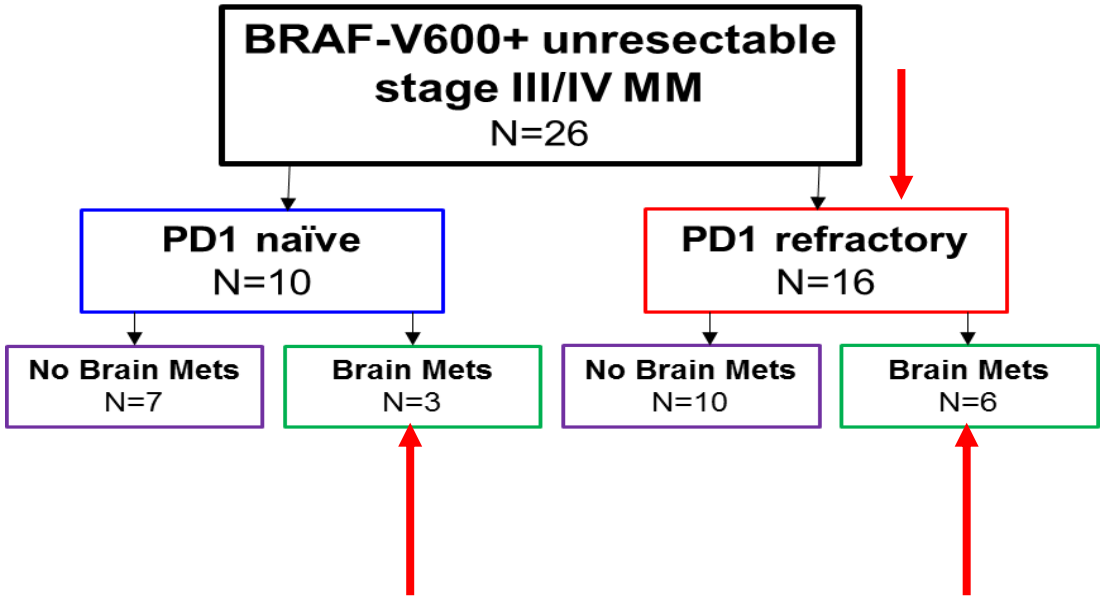
Dabrafenib + trametinib + spartalizumab



Dabrafenib + trametinib + nivolumab



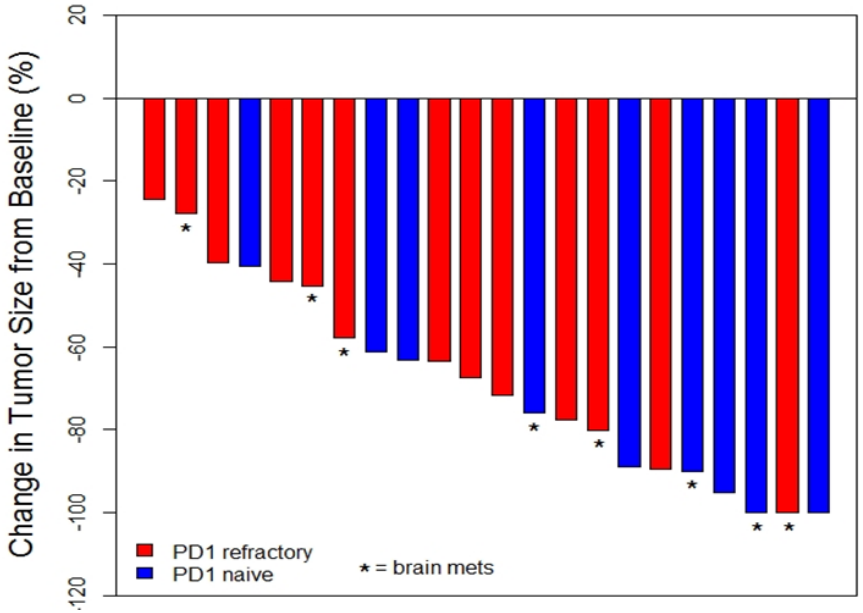
Patient Demographics



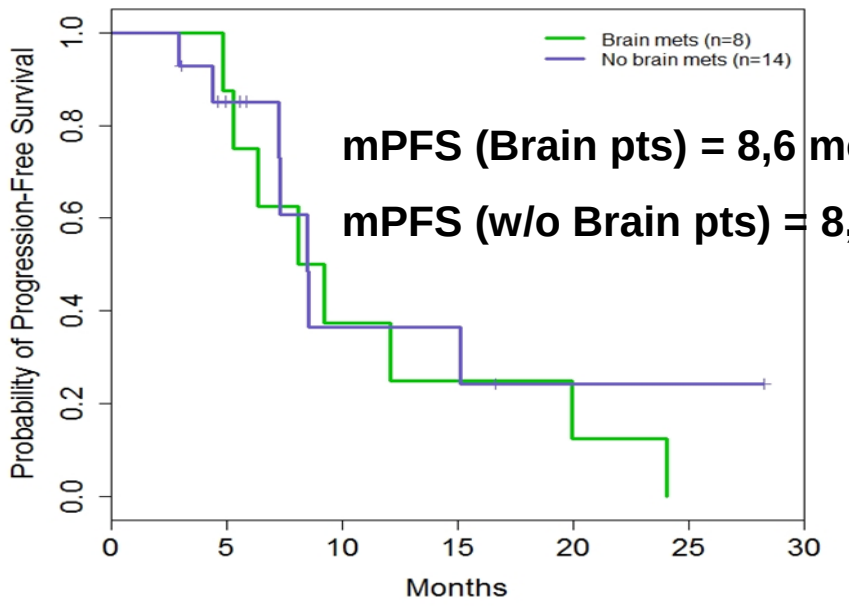
Measure	All Patients (N=26)
Age, n (%)	
< 65 years	19 (73)
≥ 65 years	7 (27)
Gender, n (%)	
Male	15 (58)
Female	11 (42)
ECOG status, n (%)	
0	17 (65)
1	9 (35)
LDH, n (%)	
≤ 1 x ULN	15 (58)
> 1 – ≤ 2 x ULN	6 (23)
> 2 x ULN	5 (19)
Sites of disease, n (%)	
≤ 3	9 (35)
> 3	17 (65)
Follow-up time in months (all patients) Median (range)	13.1 (0.3 – 30.6)

Burton E. et al. ESMO 2019

Responses and Outcomes (Pts with brain mtx)

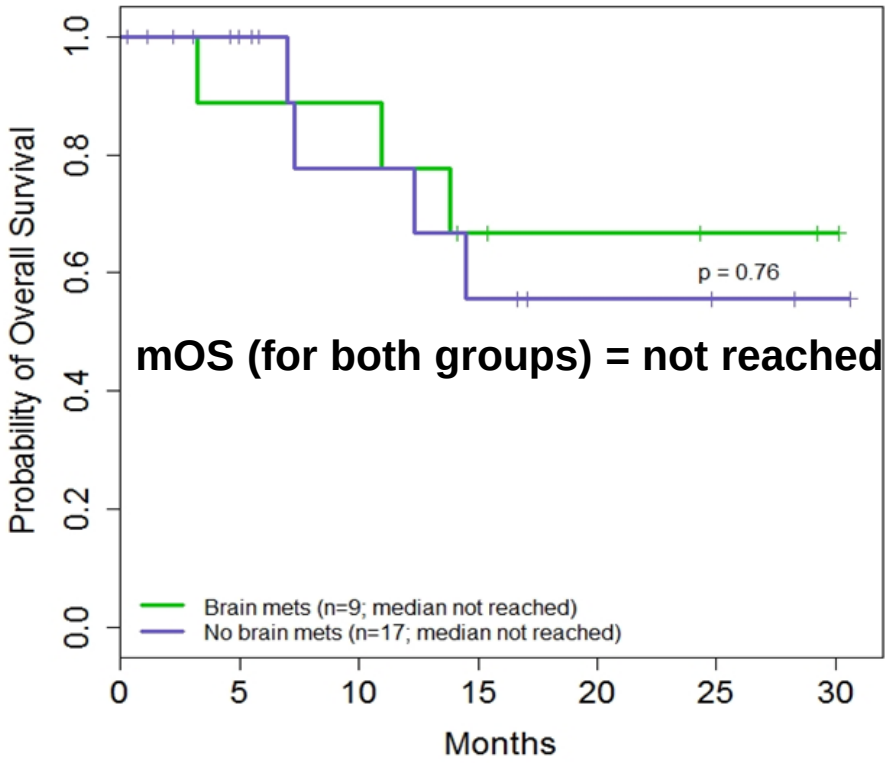


6/8 evaluable pts, 4 (**67%**) experienced an intracranial response, including 2 CRs.



mPFS (Brain pts) = 8,6 mos

mPFS (w/o Brain pts) = 8,4 mos



mOS (for both groups) = not reached

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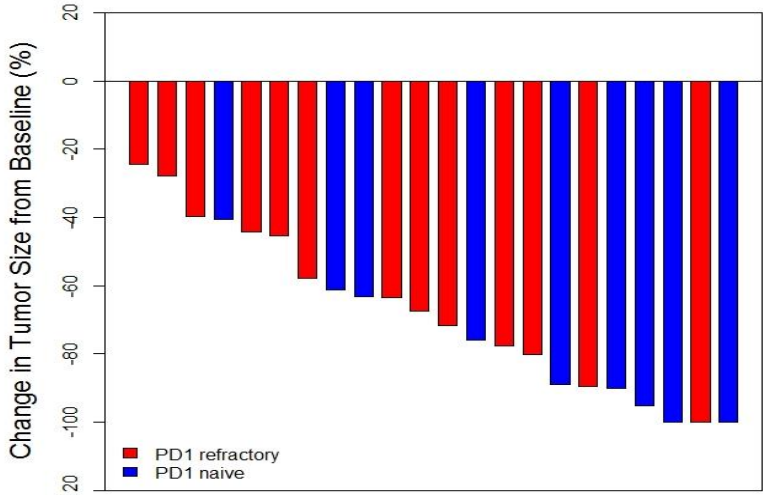
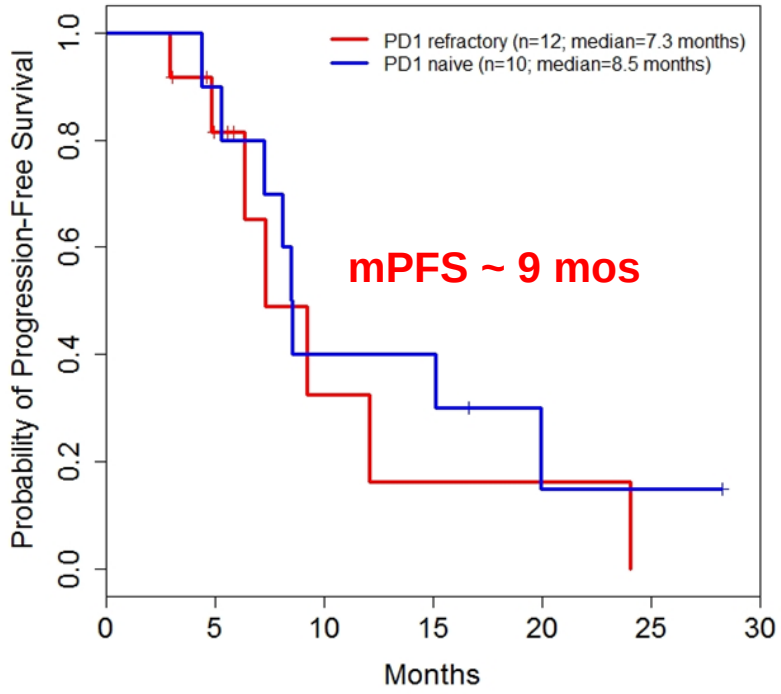
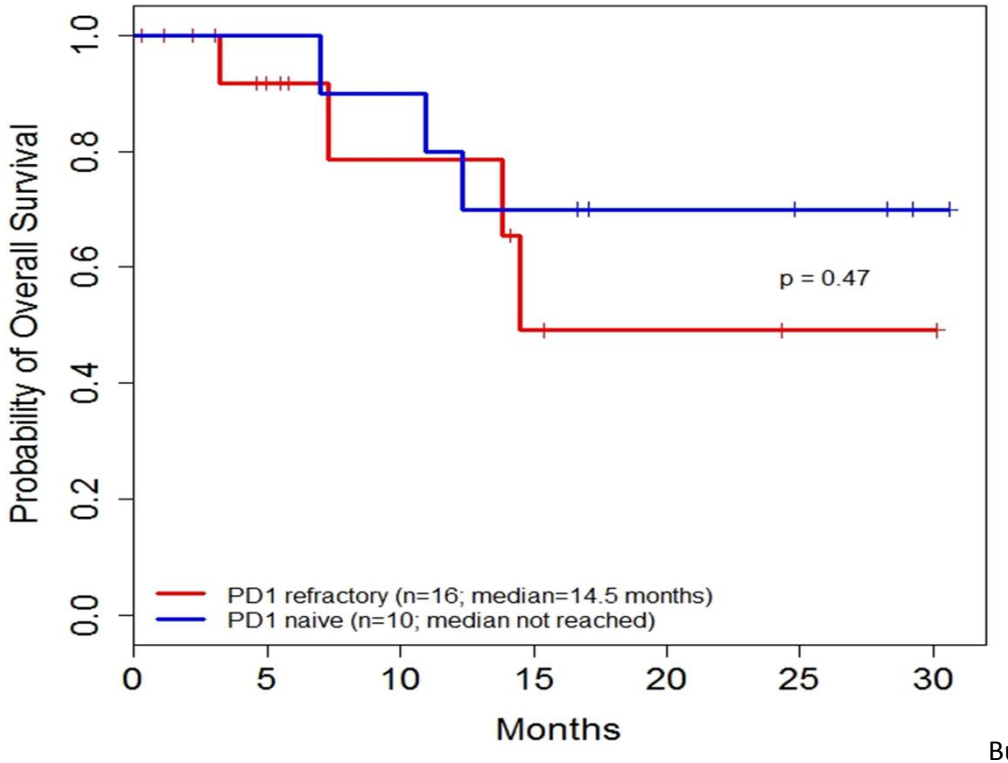
Responses and Outcomes (anti-PD-1 refractory pts)





The **objective response rate** was **83% in PD1 refractory pts** including 1 CR.



Burton E. et al. ESMO 2019

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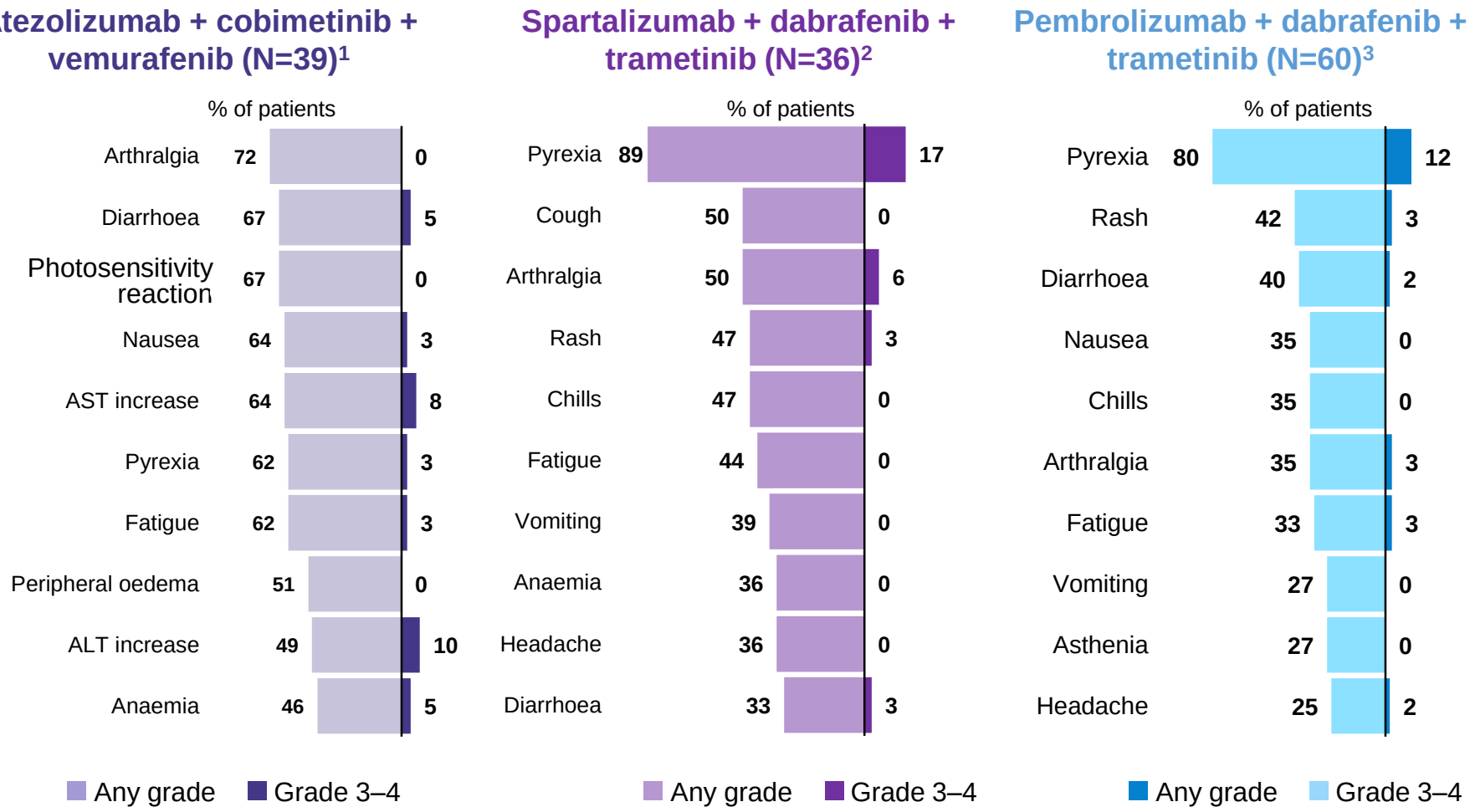
Most frequently reported AEs are aligned with the safety profile of the TT; no new safety signals observed with combination TT + CIT



Treatment-related AEs reported for atezolizumab + cobimetinib

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase

1. Sullivan RJ, et al. Nat Med. 2019; 2. Long G, et al. ASCO. 2019; 3. Ascierto P, et al. Nat Med. 2019

Modified by Ana Arance. Munich 20 June 2019. Melanoma Post-ASCO 2019

Summary of Adverse Events from TRIDeNT compared to P+D+T from Kn022

	Pembro + D + T n (%) N = 60	TRIDeNT N=26
Any-grade AE	59 (98)	NR
Grade 3-4	40 (67)	NR
Led to death[a]	2 (3)	NR
Led to discontinuation	25 (42)	NR
Led to discontinuation of all 3 study drugs	15 (25)	NR
Treatment-related AE	**57 (95)**	**25 (96)**
Grade 3-4	**34 (57)**	**17 (65)**
Led to death	**1 (2)**	**0**
Led to discontinuation of ≥1 study drug	**24 (40)**	**3 (12)**

early dose interruptions (6 pts, 23%)

Ascierto et al. ESMO 2018
Burton et al. ESMO 2019

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause. NR: not reported


The best
Is yet
To come

Thank you!

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