Reimagined SITC 2020 NOVEMBER 9–14

ISTITUTO NAZIONALE TUMORI IRCCS – Fondazione Pascale

Mechanisms of Resistance and Possible New Combinations for Overcoming Them

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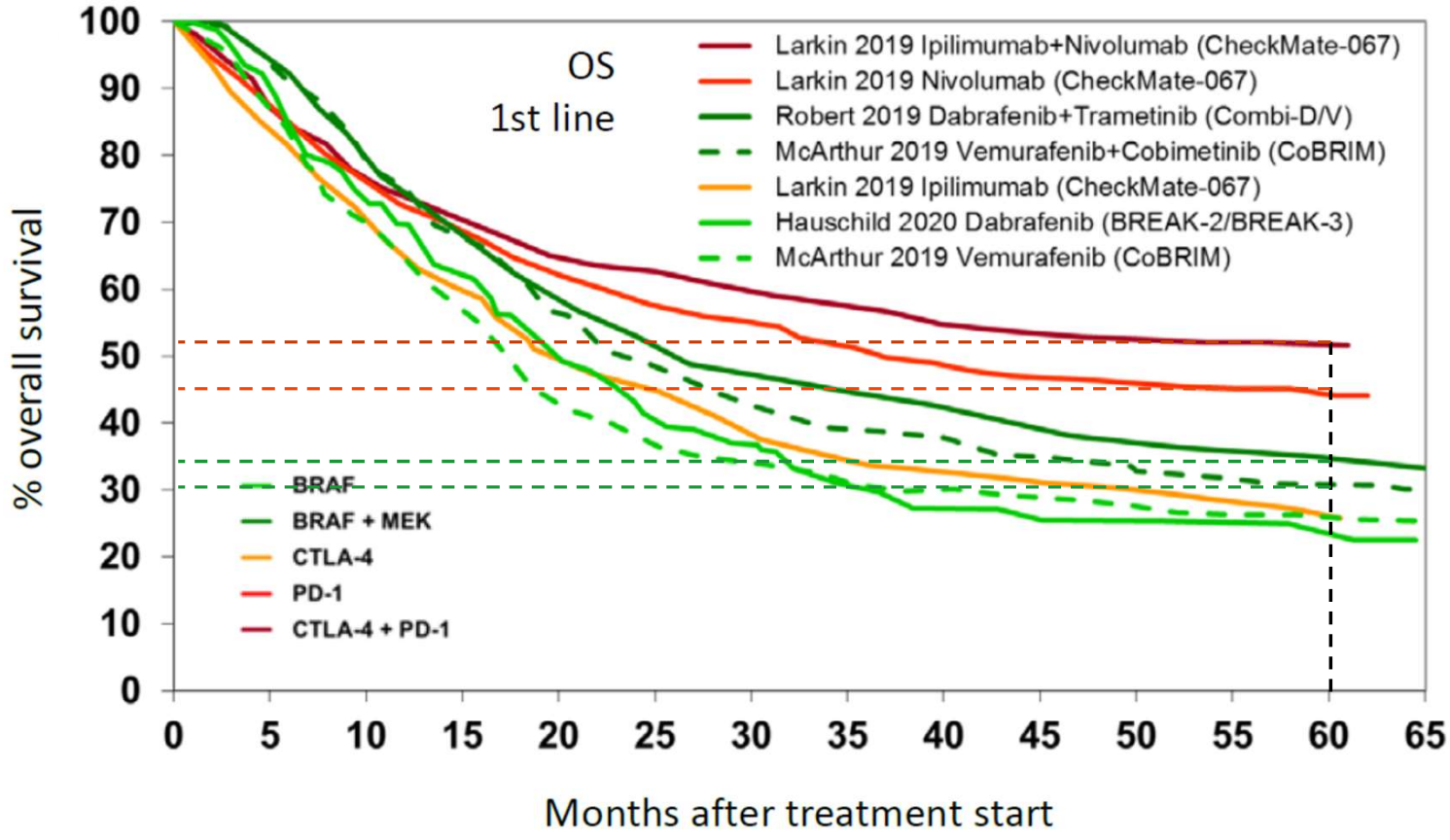
Disclosure

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

OS Kaplan-Meier survival curves of melanoma patients treated in selected clinical trials with published 5-year follow-up data.



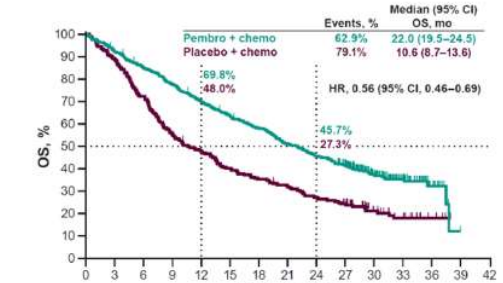
Ugurel et al. Eur J Cancer 2020; 130:126-138

Long-term benefit in Lung Cancers

Rodriguez-Abreu et al. ASCO 2020
Ramalingam et al. ASCO 2020
Baas et al. WLCL 2020
Liu et al. ESMO 2020

Rodriguez-Abreu KN189 ASCO 2020

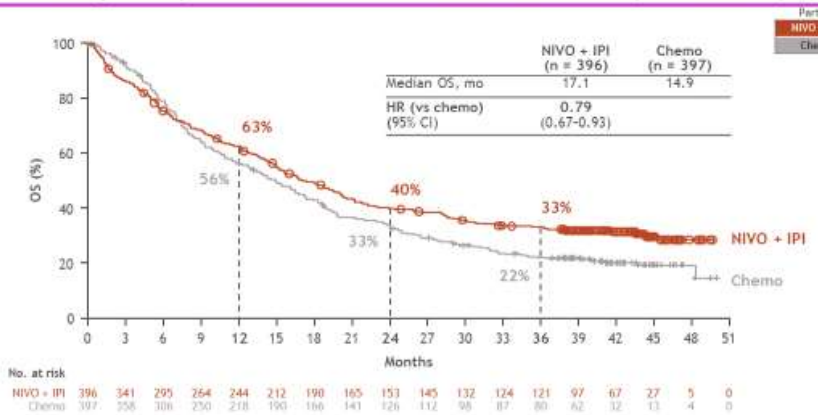
Kaplan-Meier Estimate of OS in the ITT Population



Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pembro, pembrolizumab.

NSCLC

CKM 227 3-year update: OS with NIVO + IPI vs chemo (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

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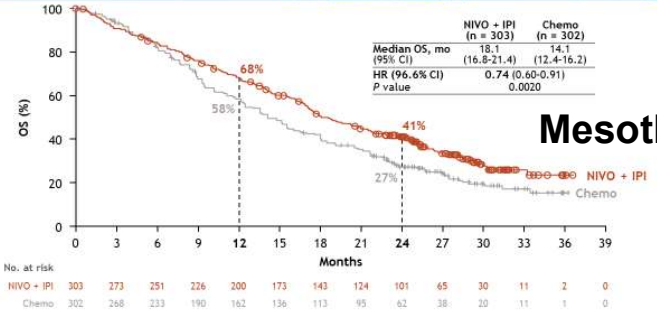
2020 Presidential Symposium
AUGUST 8, 2020 | WORLDWIDE

Primary endpoint: Overall survival

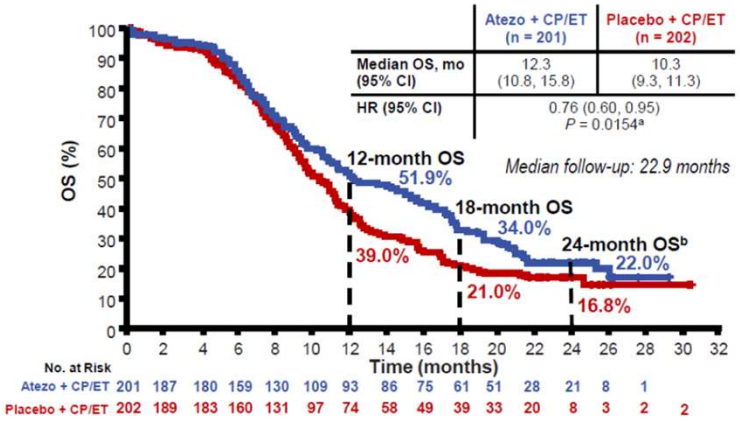


Mesothelioma

Minimum follow-up: 22.1 months; median follow-up: 29.7 months.
Subsequent systemic therapy was received by 44% of patients in the NIVO + IPI arm and 41% in the chemo arm; subsequent immunotherapy was received by 3% and 20%, and subsequent chemotherapy by 43% and 32%, respectively.

Paul Baas, Netherlands Cancer Institute and The University of Leiden, The Netherlands

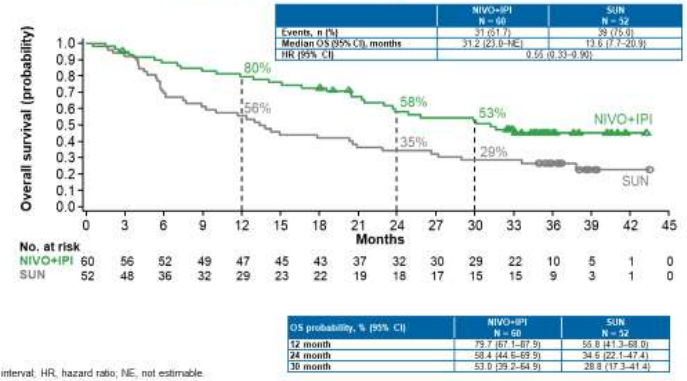
ES-SCLC Updated OS in ITT



Long-term benefit in RCC, Urothelial, TNBC, Gastric

McDermott et al. ASCO 2020
Sharma et al ESMO 2020
Emens LA et al ESMO 2020
Moehler et al. ESMO 2020

CheckMate 214: Overall survival in intermediate/poor-risk sarcomatoid patients



	NIVO+IPI N = 60	SUN N = 52
Events, n (%)	31 (51.7)	39 (75.0)
Median OS (95% CI), months	31.2 (23.0–NE)	13.6 (7.7–20.9)
HR (95% CI)	0.55 (0.33–0.90)	

OS probability, % (95% CI)	NIVO+IPI N = 60	SUN N = 52
12 month	79.7 (67.1–87.9)	55.8 (41.3–68.0)
24 month	58.4 (44.6–69.9)	34.6 (22.1–47.4)
30 month	53.0 (39.2–64.9)	28.8 (17.3–41.4)

CI, confidence interval; HR, hazard ratio; NE, not estimable.

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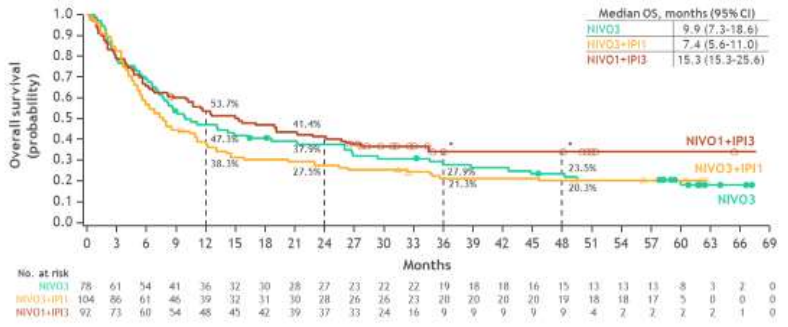
Checkmate 032 (urothelyal): OS



*Not calculated due to the minimum follow-up of 26.7 months in the NIVO1+IPI3 arm.

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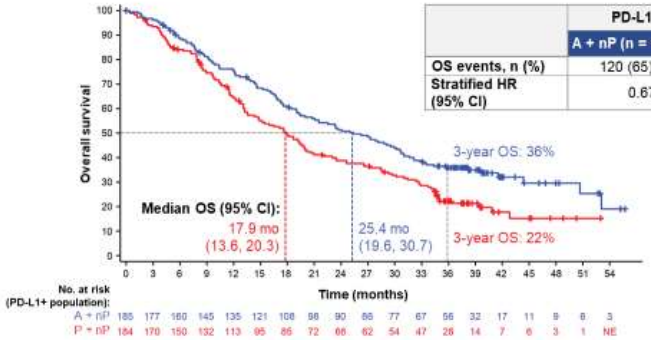
CheckMate 649

OS in the PD-L1 IC+ population

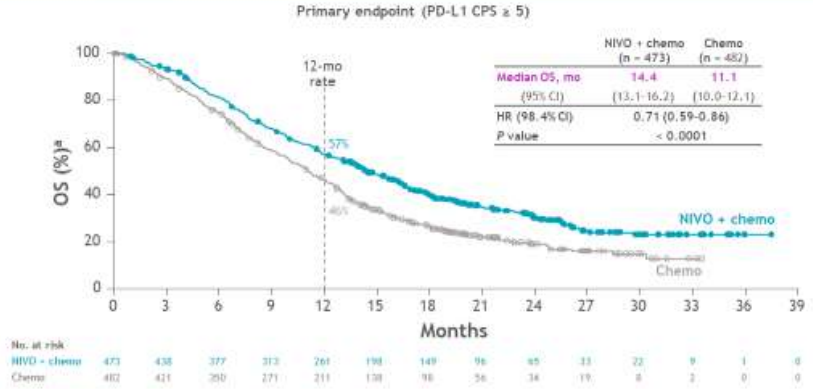


	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

Data cutoff, 14 April 2020. NE, not estimable.
*P value not displayed since OS in the PD-L1+ population was not formally tested due to the hierarchical study design.

8

CheckMate 649: Overall survival

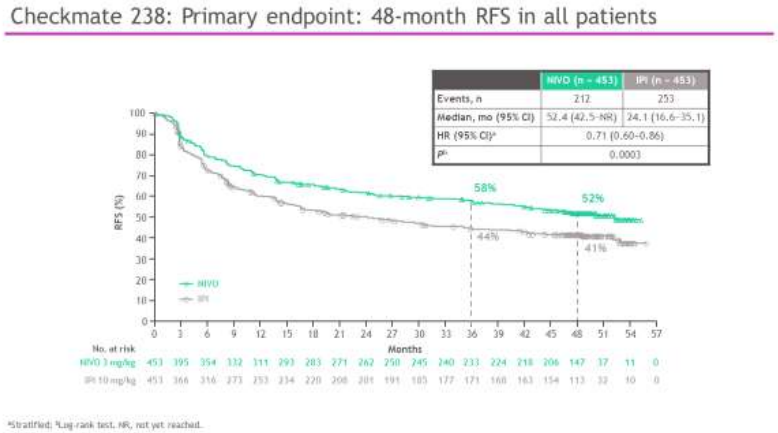


- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

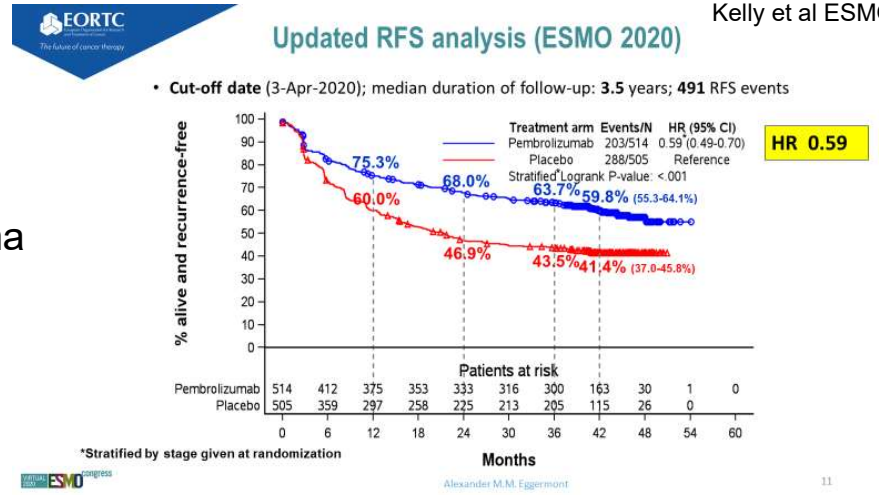
[a]Minimum follow-up 12.1 months.

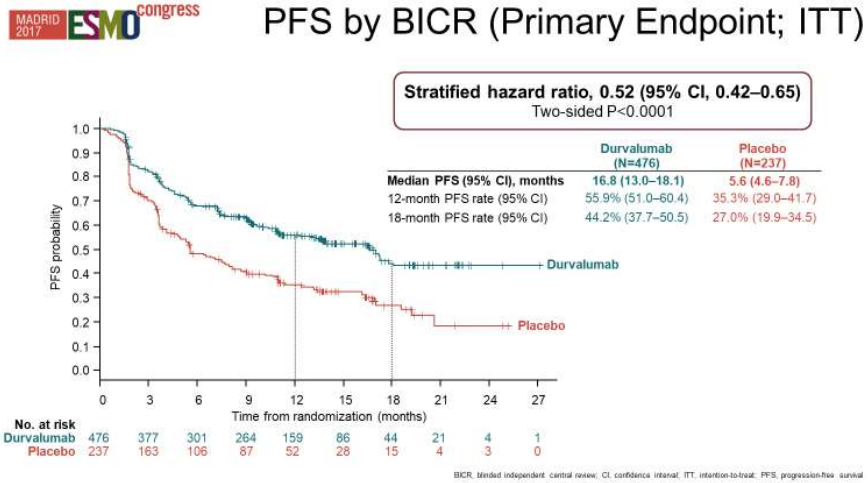
I-O in earlier stages

Weber et al. ESMO 2020
Eggermont et al. ESMO 2020
Paz Ares et al. ESMO 2017
Kelly et al ESMO 2020

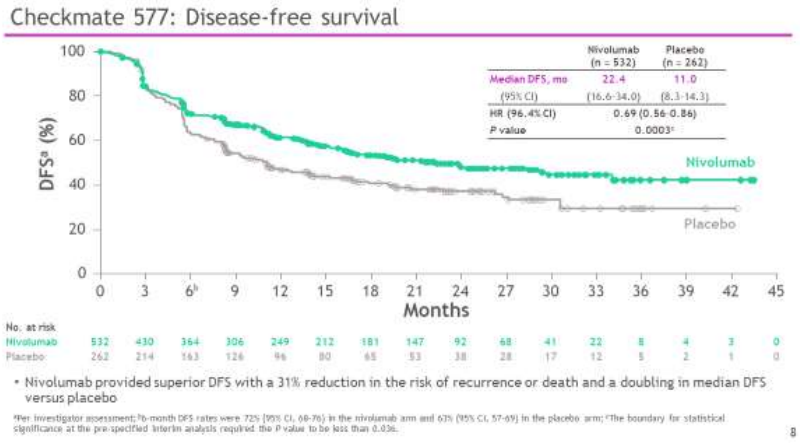


Melanoma



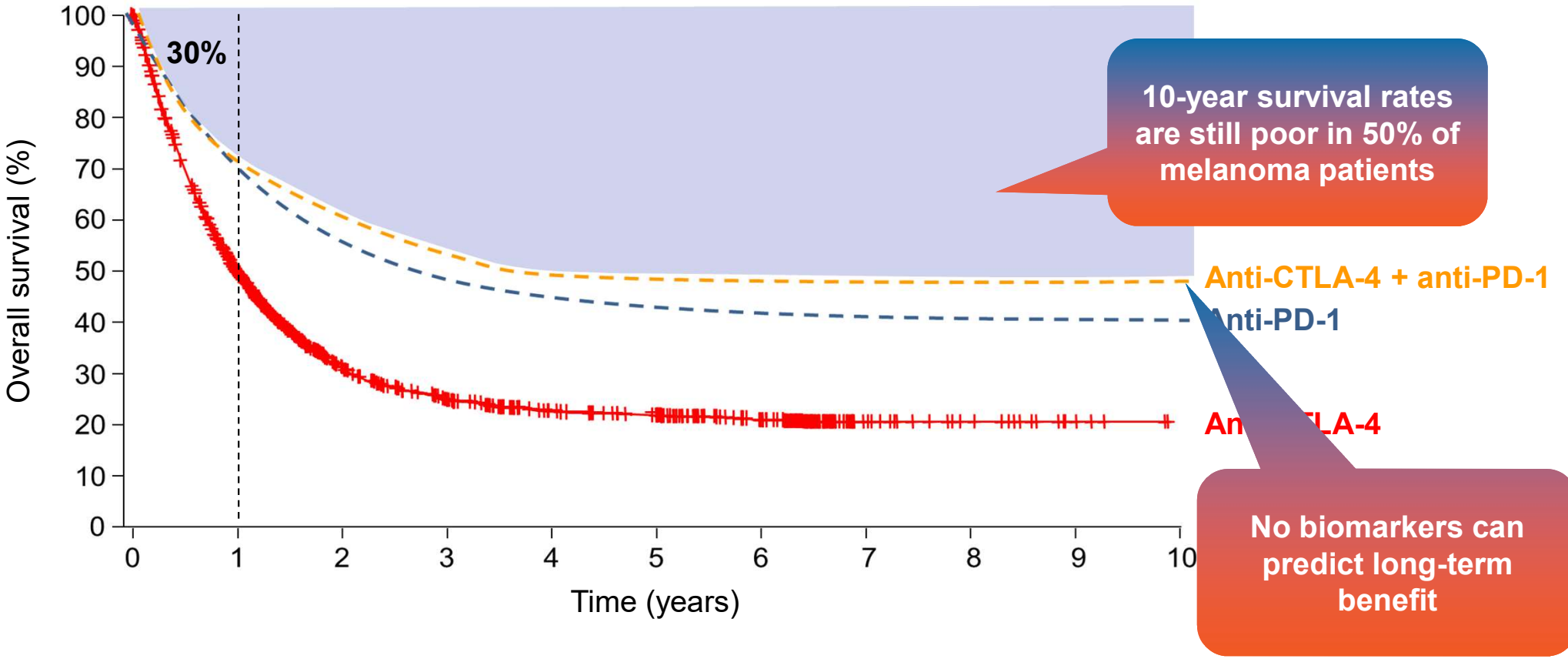


NSCLC

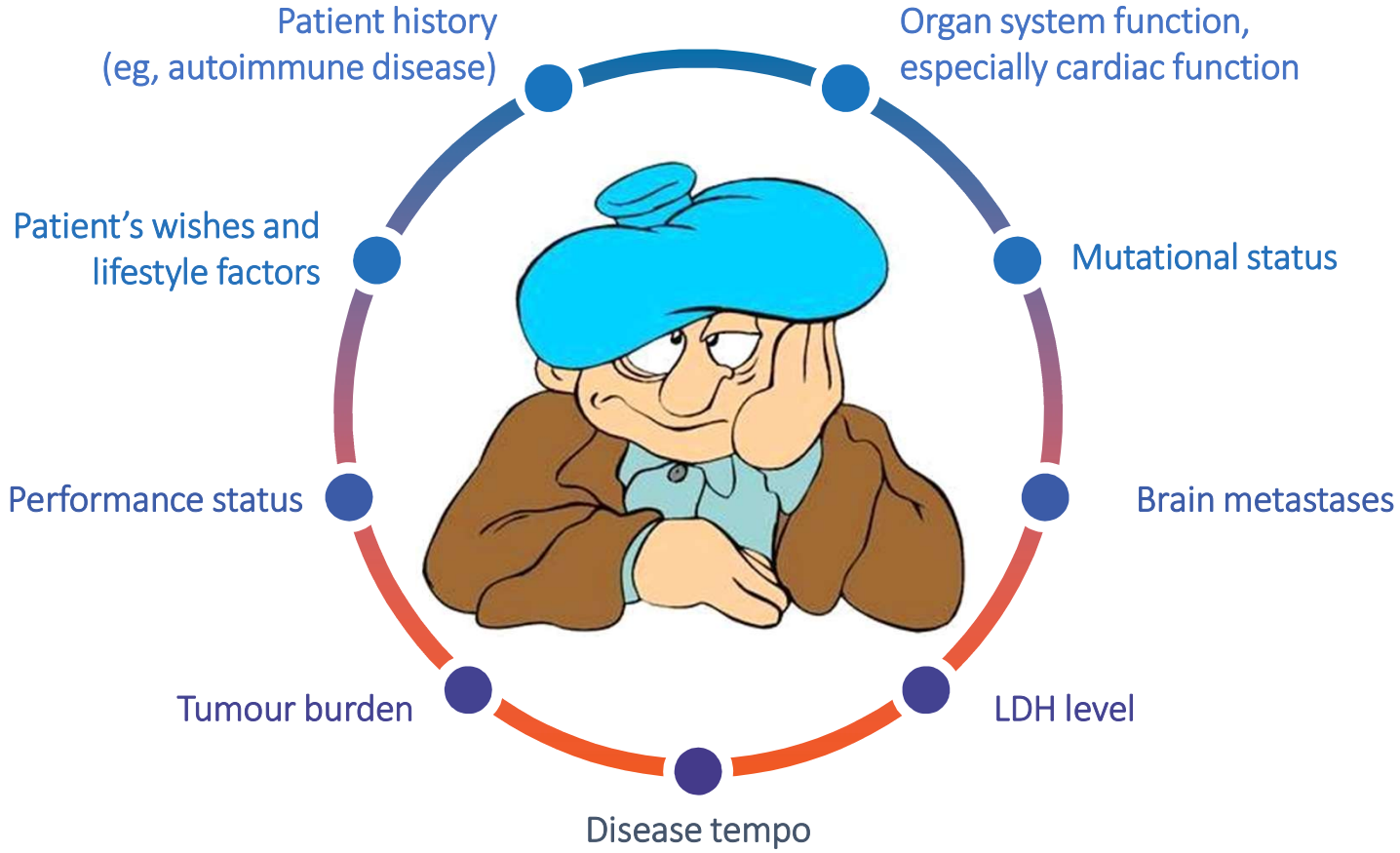


Esophageal

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

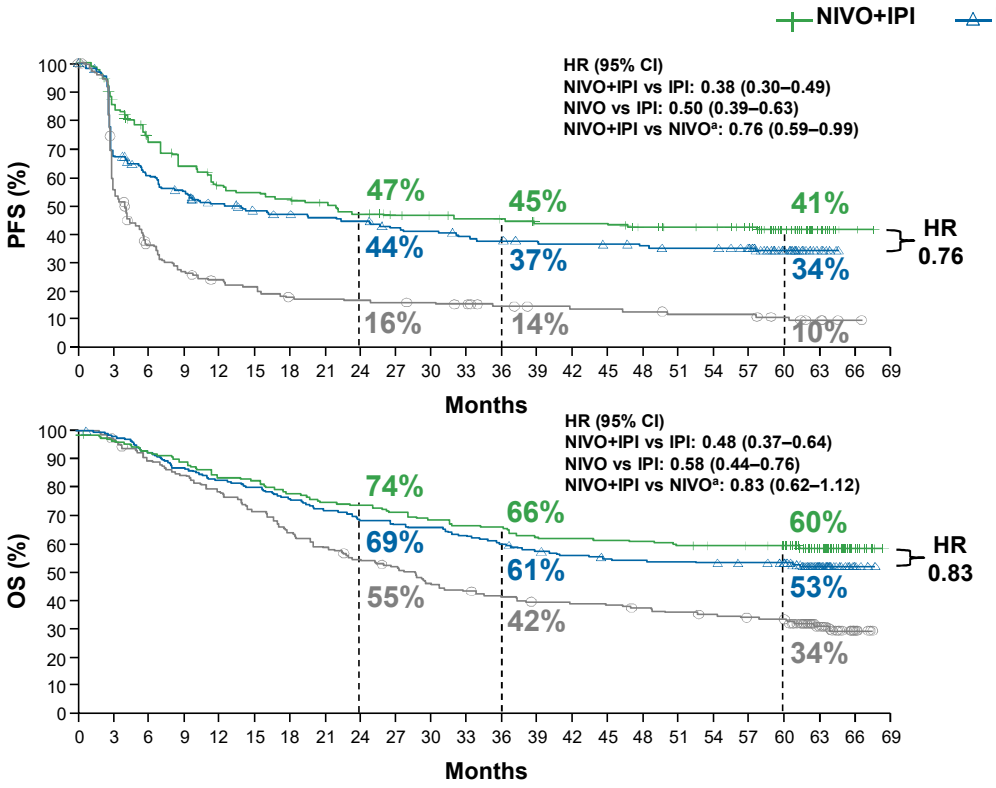


Is there a patient subgroup where combination therapy may have greater clinical benefit?

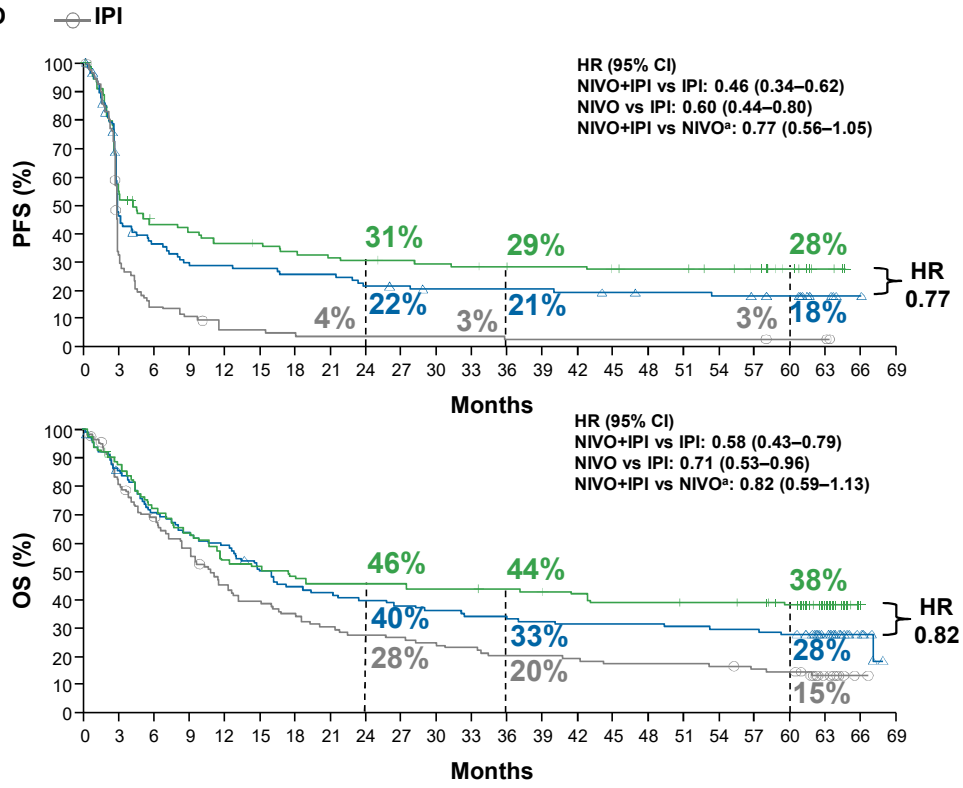


CKM 067: PFS and OS by LDH Level
Improved with NIVO+IPI and NIVO vs IPI regardless of LDH

LDH ≤ ULN (n = 590)



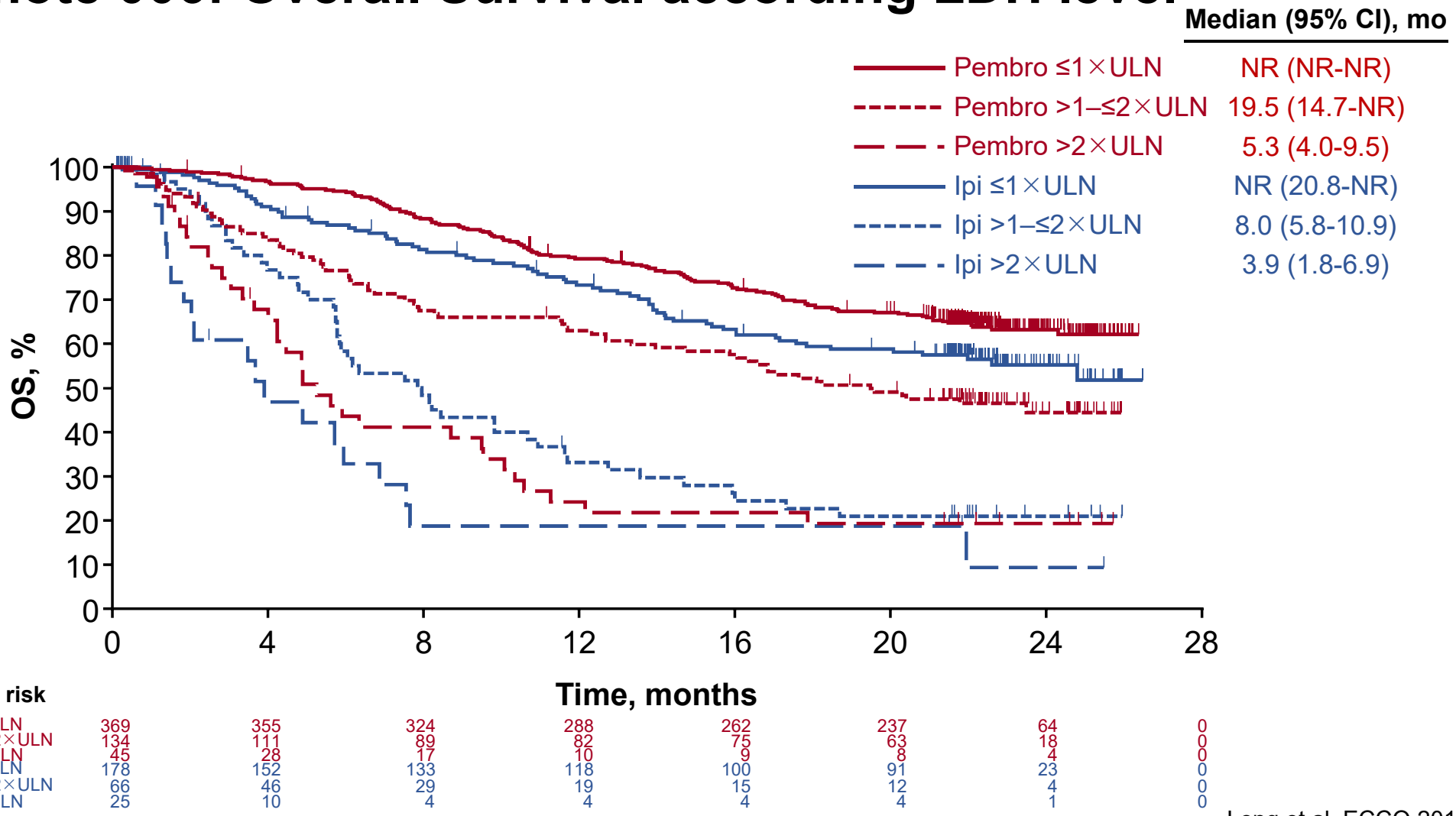
LDH > ULN (n = 341)



[a]Descriptive analysis. LDH, lactate dehydrogenase; ULN, upper limit of normal. Larkin J, et al. *N Engl J Med* 2019:381:1535–1546.

PRESENTED BY GV LONG AT SMR 2019

Keynote 006: Overall Survival according LDH level



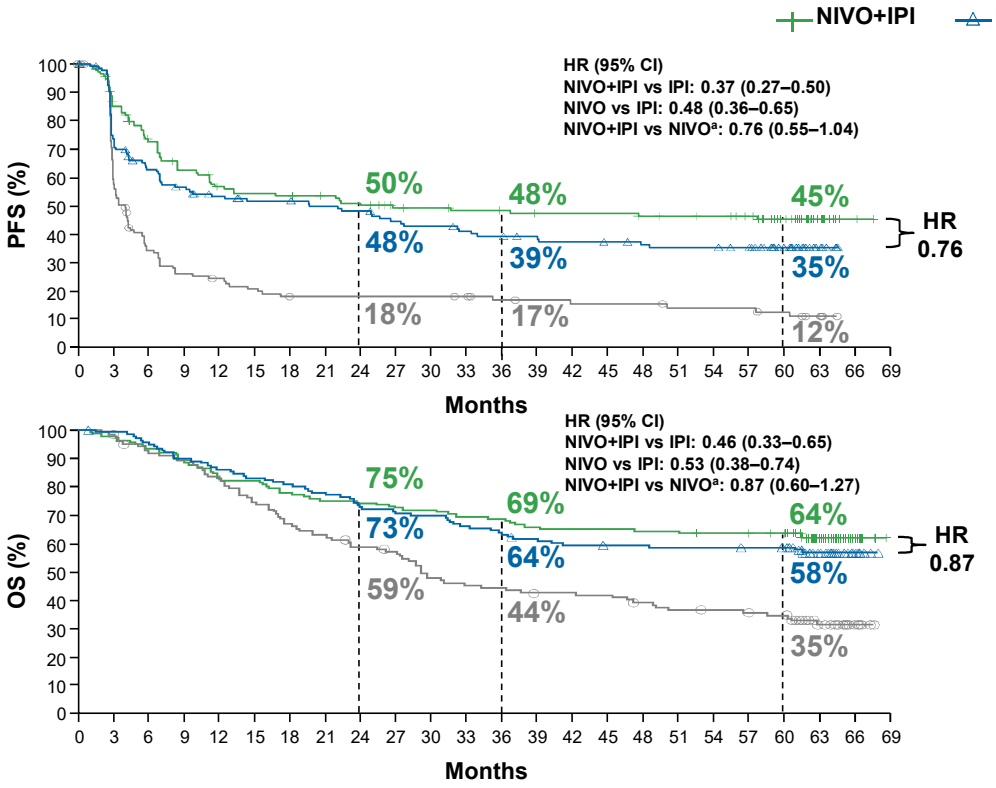
Data cutoff date: Dec 3, 2015.

Long et al. ECCO 2017

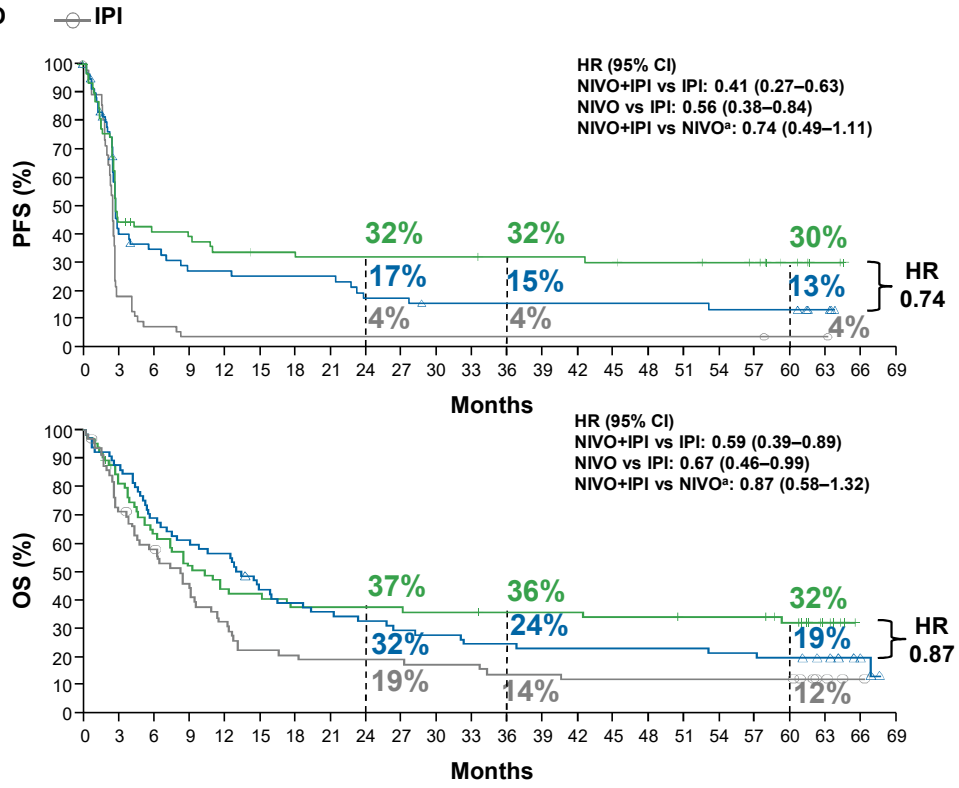
CKM 067: PFS and OS by LDH and 3 Sites With ≥ 1 Target or Non-Target Lesion

Improved with NIVO+IPI and NIVO vs IPI regardless of LDH

LDH ≤ ULN; < 3 sites (n = 399)



LDH > ULN; ≥ 3 sites (n = 191)



[a]Descriptive analysis. Larkin J, et al. *N Engl J Med* 2019:381:1535–1546.

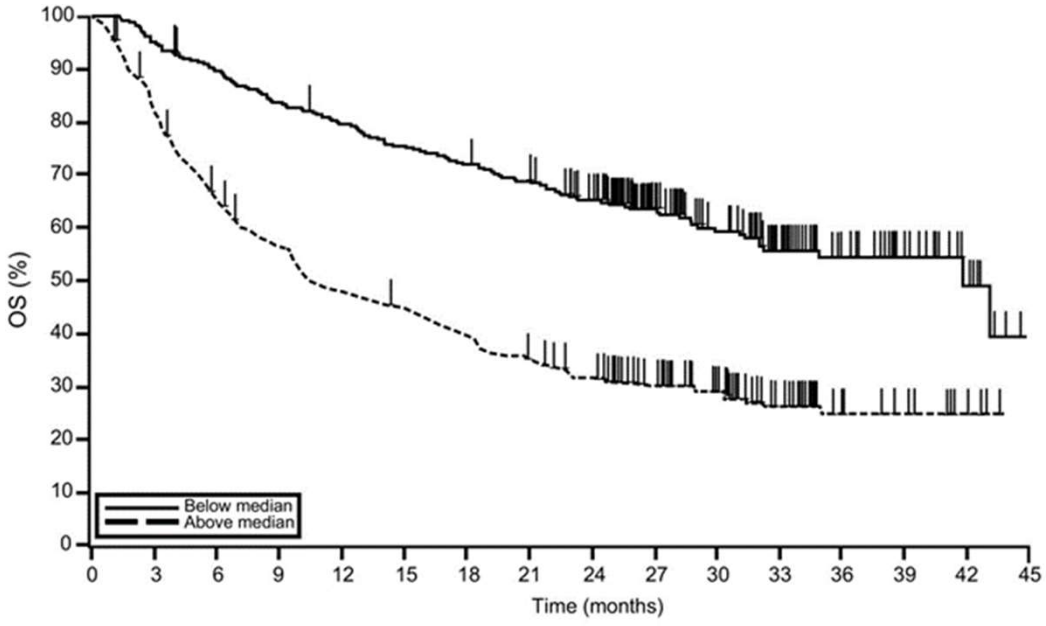
PRESENTED BY GV LONG AT SMR 2019

Precision Medicine and Imaging

Clinical Cancer Research

Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients with Melanoma Treated with Pembrolizumab

Richard W. Joseph[1], Jeroen Elassaiss-Schaap[2], Richard Kefford[3,4], Wen-Jen Hwu[5], Jedd D. Wolchok[6], Anthony M. Joshua[7,8], Antoni Ribas[9], F. Stephen Hodi[10], Omid Hamid[11], Caroline Robert[12], Adil Daud[13], Roxana Dronca[14], Peter Hersey[15], Jeffrey S. Weber[16], Amita Patnaik[17], Dinesh P. de Alwis[18], Andrea Perrone[18], Jin Zhang[19], S. Peter Kang[18], Scot Ebbinghaus[18], Keaven M. Anderson[19], and Tara C. Gangadhar[20]

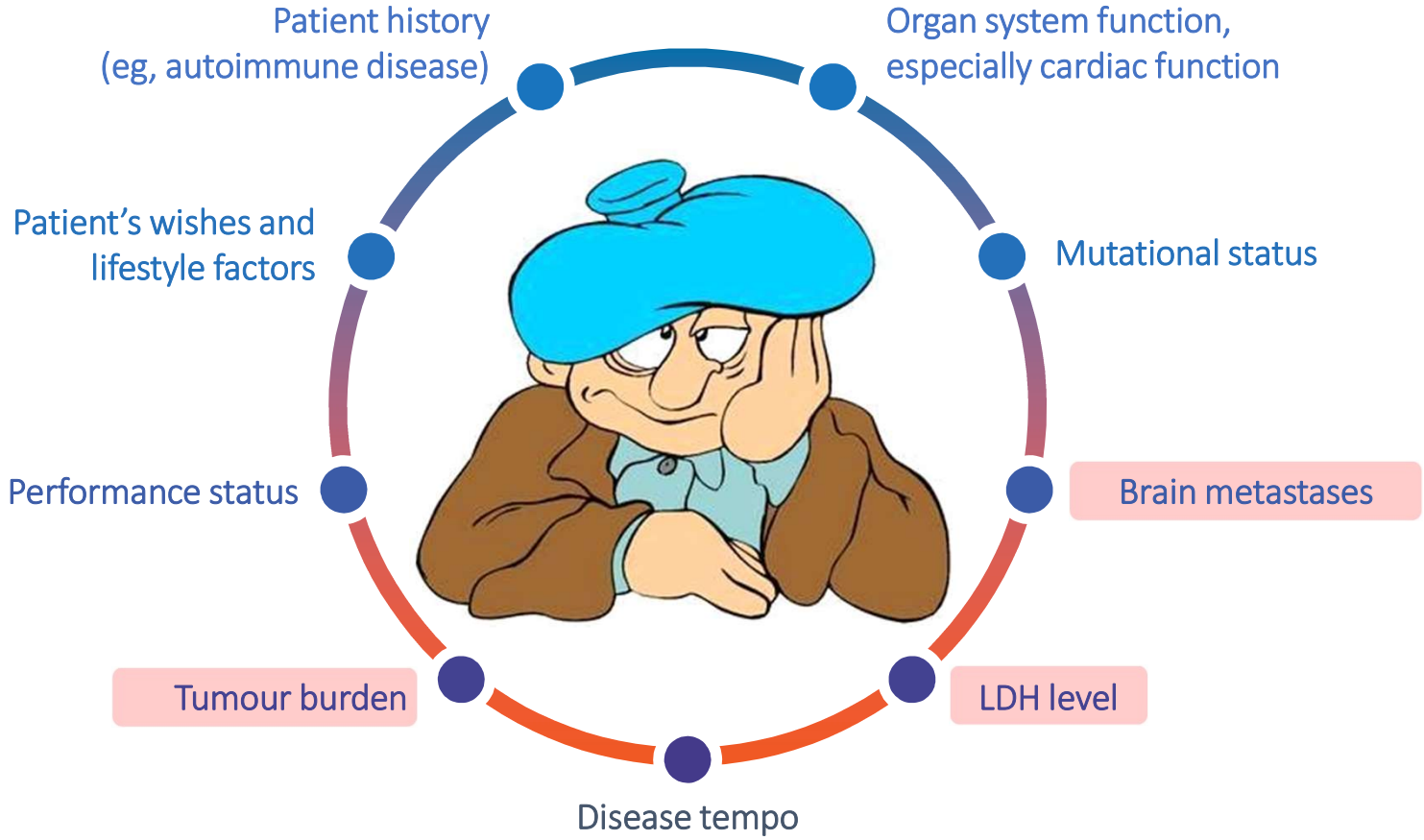


n at risk

Below median	292	278	260	243	230	218	208	197	178	119	91	63	38	24	9	0
Above median	291	237	187	159	135	126	110	97	84	65	49	32	12	10	3	0

Joseph RW et al. Clin Cancer Res 2018;24:4960-4967

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

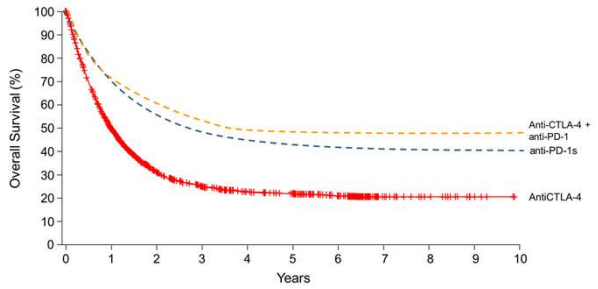


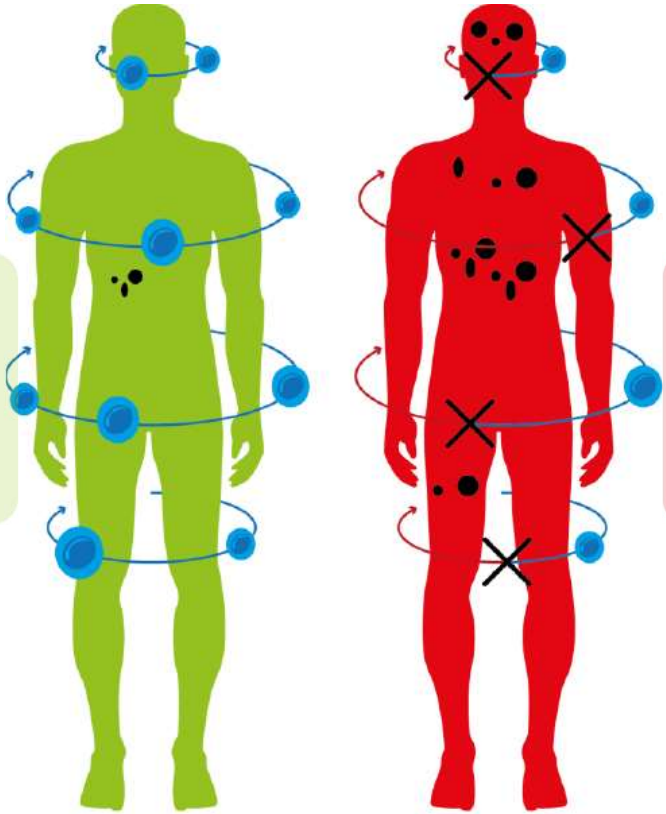
Patient characteristics affecting immune surveillance

Active immune surveillance

Long-term benefit patients

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

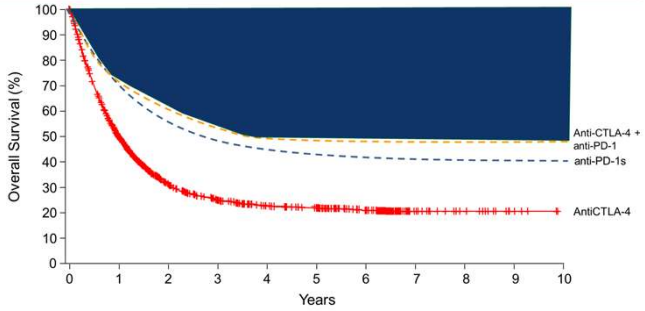




Inactive immune surveillance

No long-term benefit patients

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



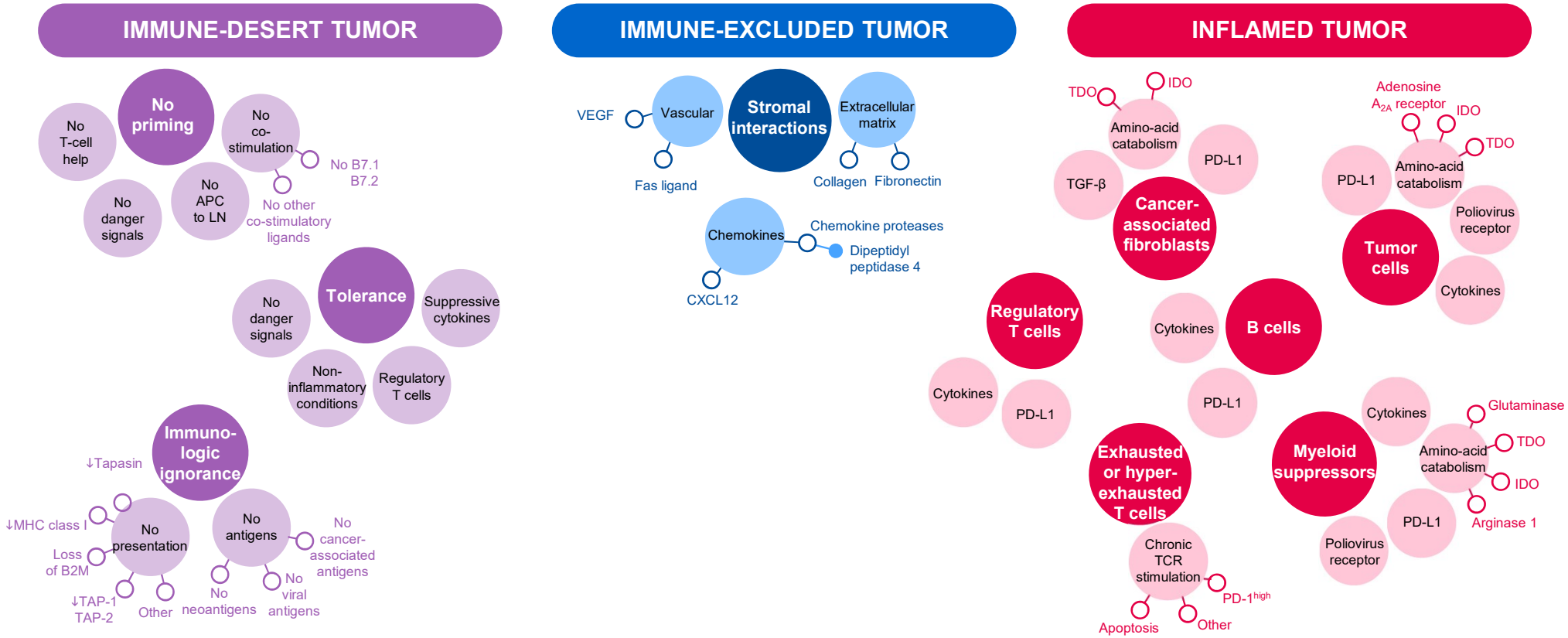
LDH, lactate dehydrogenase

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

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

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

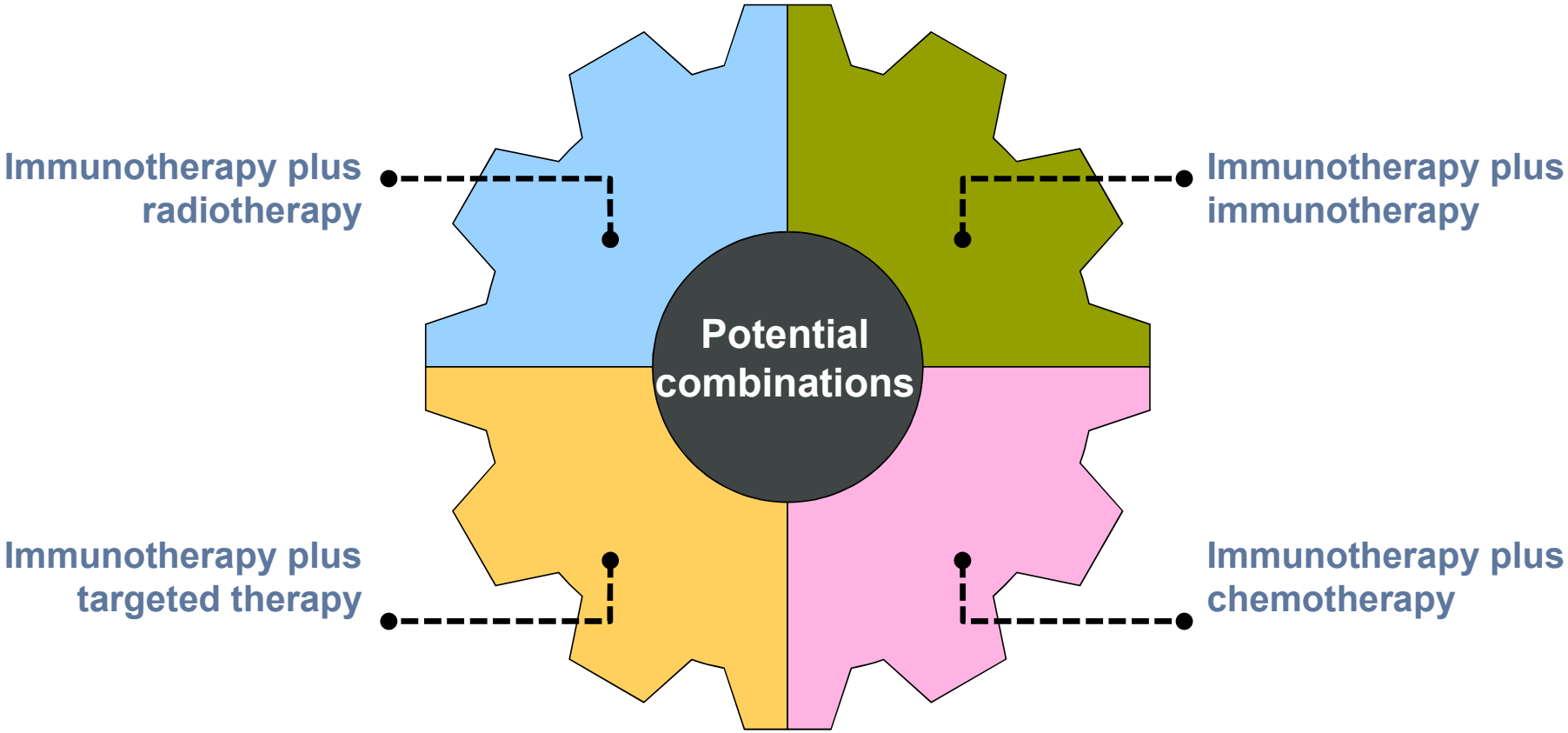
The Tumor Microenvironment Is a Key Driver of Response or Resistance to Treatment



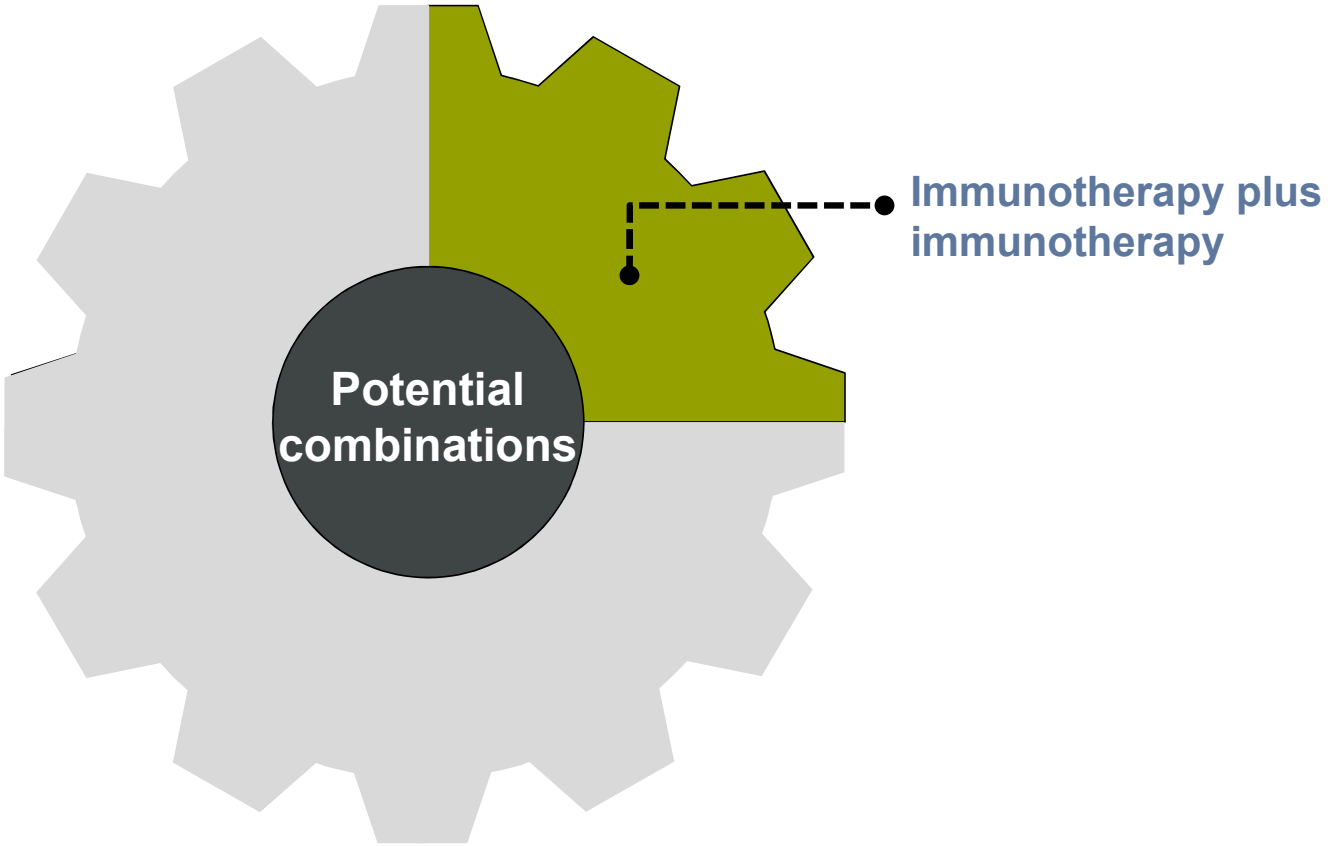
APC = antigen-presenting cell; IDO = indoleamine 2,3 dioxygenase; LN = lymph node; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing; TCR = T-cell receptor; TDO = tryptophan 2,3-dioxygenase; TGF = tumor growth factor; VEGF = vascular endothelial growth factor.

Extracted from Chen DS, Mellman I. *Nature*. 2017;541:321-330.

Potential combination strategies for the treatment of cancer



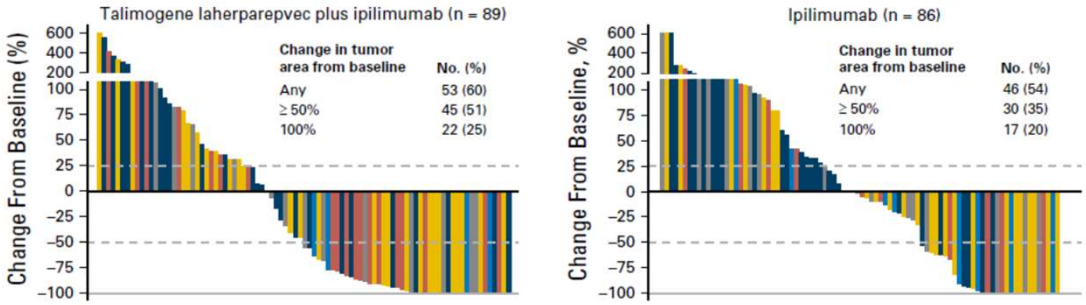
Potential combination strategies for the treatment of cancer



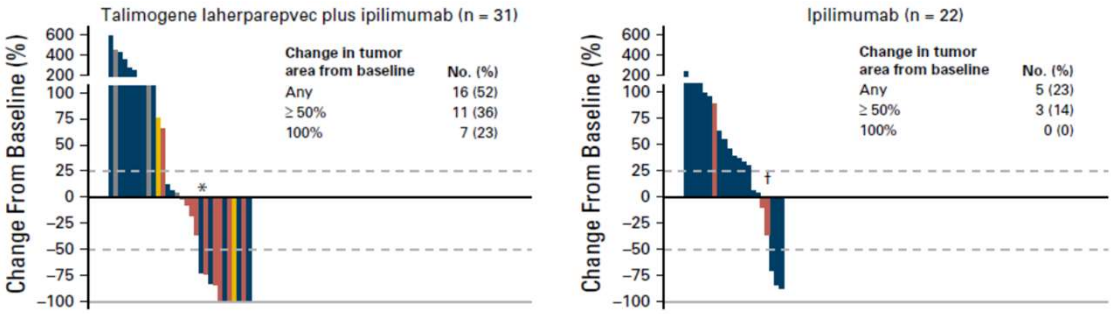
What about the role of loco-regional treatments ?

T-VEC + ipilimumab

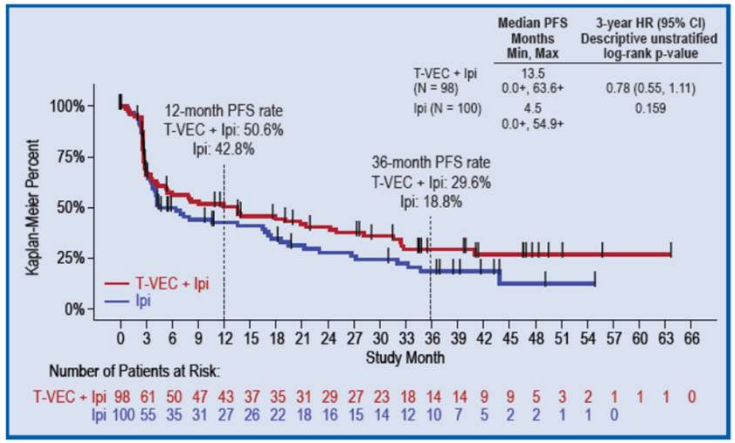
All lesions



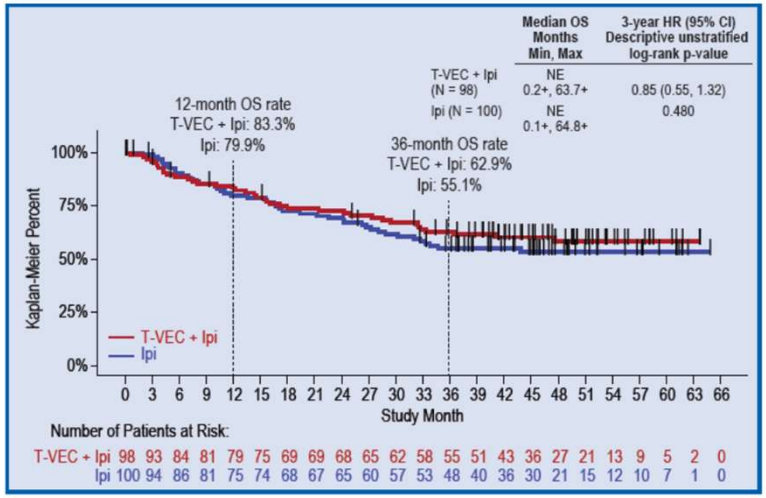
Non injected visceral lesions



Progression-Free Survival (ITT Set)

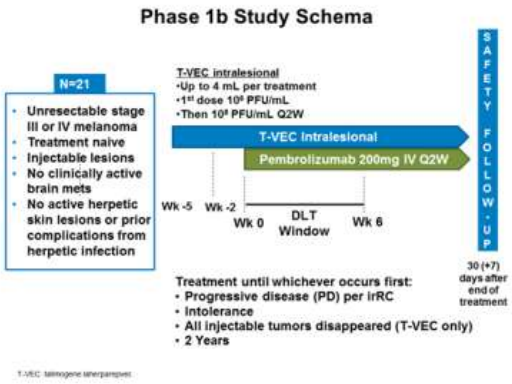


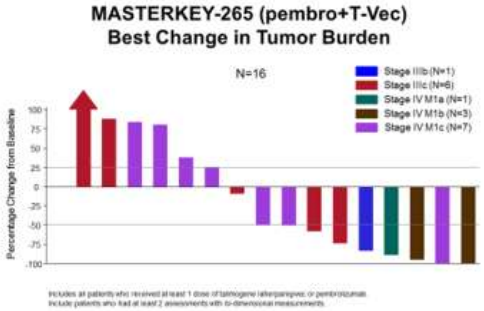
Overall Survival (ITT Set)



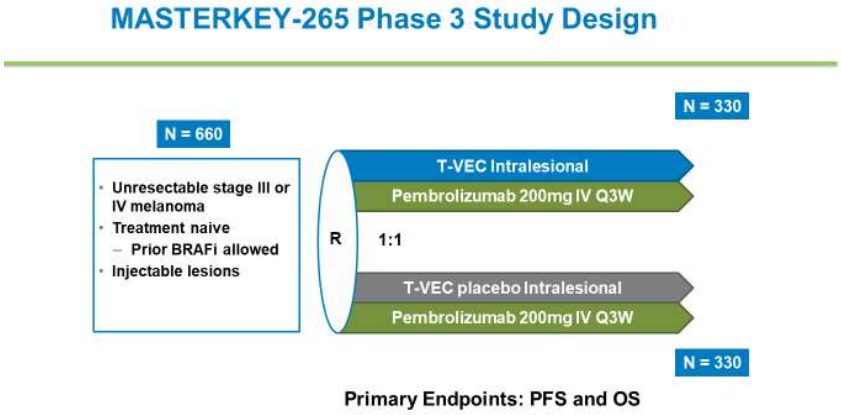
Chesney et al JCO 2017
Chesney et al ESMO 2019

T-VEC + pembrolizumab





Long et al SMR 2015

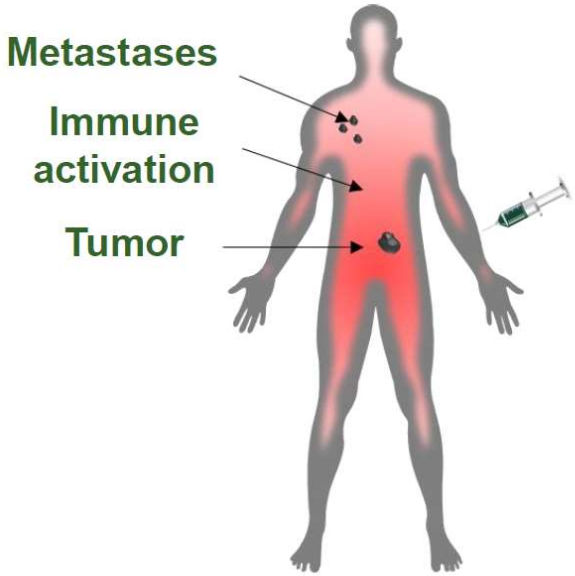


NCT02263508

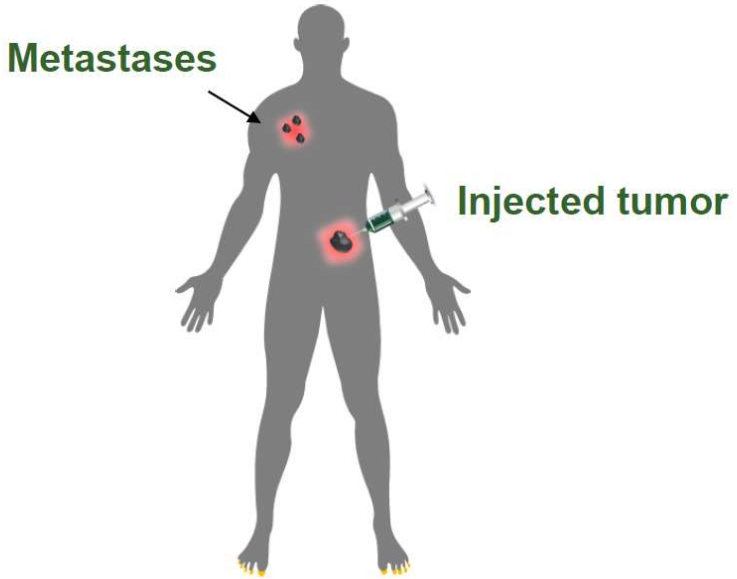
Long et al SMR 2015

Long et al SMR 2015

Tumor-directed immuno-oncology



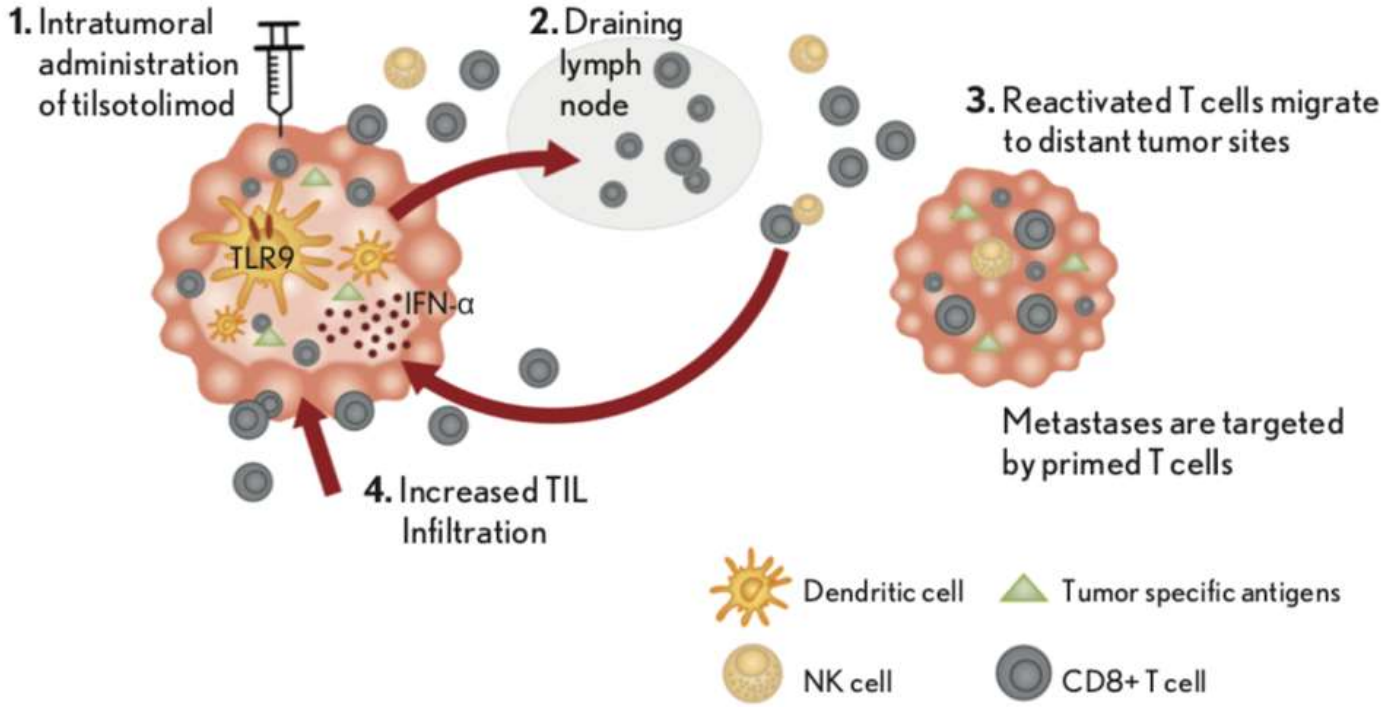
GENERAL IMMUNE-ACTIVATION



TUMOR-DIRECTED IMMUNE-ACTIVATION

Adapted from Ellmark *et al* 2016, CII

Toll-Like Receptor 9 (TLR9) Inhibition: Intratumoral Mechanism of Action of Tilsotolimod

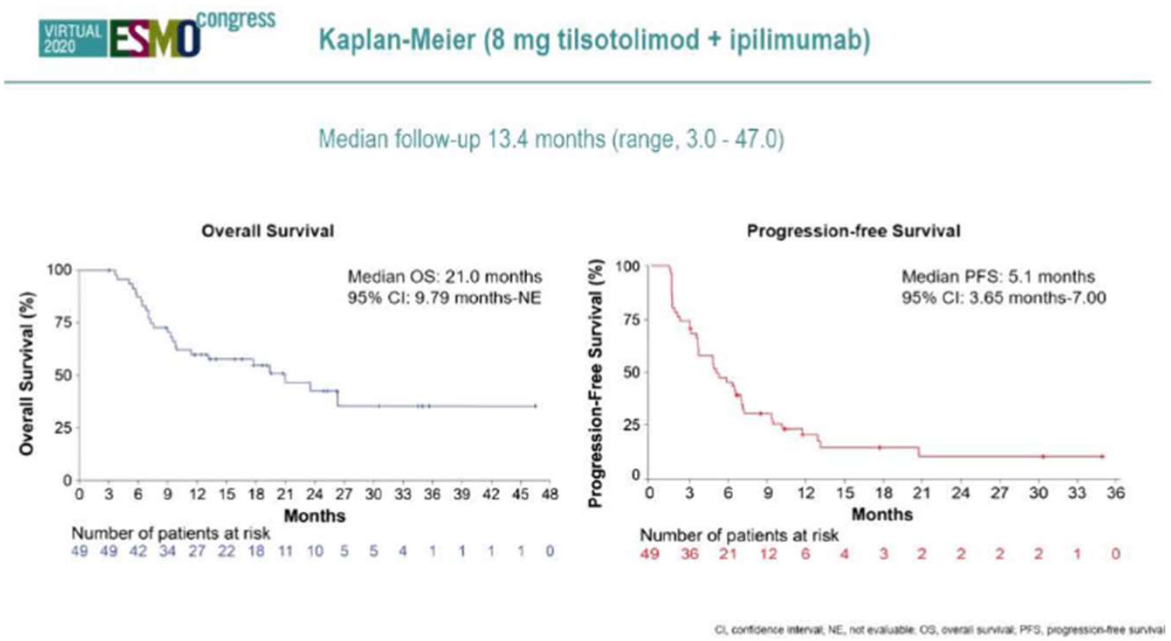


Extracted from Babiker HM et al. Presented at AACR 2019; abstract 4062.

Final Results from ILLUMINATE-204, a Phase I/II trial of Intratumoral Tilsotolimod in Combination with Ipilimumab in PD-1 Inhibitor Refractory Advanced Melanoma

Efficacy Endpoint	In 49 Patients
mOS, months (95% CI)	21.0 (9.8-NR)
mPFS, months (95% CI)	5.1 (3.65-7)
ORR, % (95% CI)	22.4 (11.8-36.6)
DCR, % (95% CI)	71.4 (56.7-83.4)
mDOR, months (95% CI)	11.4 (3.3-NR)

- Tumor reduction was observed in both injected and noninjected tumors



Clinical trial information: https://clinicaltrials.gov/ct2/show/NCT02644967

CI = confidence interval; DCR = disease control rate; IPI = ipilimumab; irAEs = immune-related adverse events; mDOR = median duration of response; mOS = median overall survival; NR = not reached; ORR = objective response rate; PD-1 = programmed cell death protein 1; RECIST = Response Evaluation Criteria in Solid Tumors; TEAE = treatment-emergent adverse event;

Haymaker C, et al. ESMO 2020

A randomized phase 3 comparison of IMO-2125 with ipilimumab versus ipilimumab alone in subjects with anti-PD-1 refractory melanoma

Paolo Ascierto,[1] Petr Arenberger,[2] Victoria Atkinson,[3] Johan Hansson,[4] Ellen Kapiteijn,[5] Carmen Loquai,[6] Sylvie Négrier,[7] Heather Shaw,[8] Ahmad Tarhini,[9] John Walker,[10] James Geib,[11] Shah Rahimian,[11] Adi Diab[12]

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Illuminate 301 Study Design (N=308)

308 adult subjects with unresectable or metastatic melanoma with confirmed radiologic progression during or after PD-1 inhibitor therapy who

- were ≥21 days from the most recent anti-PD-1 treatment and underwent no intervening systemic treatment
- underwent no prior ipilimumab treatment except adjuvant
- underwent no BRAF+ treatment or else declined it
- had no ocular melanoma

1:1 randomization stratification:

- Anti-PD-1 therapy for ≥12 or <12 wk
- Stage M1c or other metastasis
- BRAF mutation status and prior targeted therapy: wild type, mutation positive with targeted therapy, or mutation positive with no prior targeted therapy
- No crossover

Arm A

Ipilimumab 3 mg/kg (4 doses: wk 1, 4, 7, 10)

Disease assessments

- Baseline
- Week 12
- Every 8 wk during first year, then
- Every 12 wk

Arm B

Ipilimumab 3 mg/kg (4 doses: wk 2, 5, 8, 11)

plus

Intratumoral tilsotolimod 8 mg (9 doses: wk 1, 2, 3, 5, 8, 11, 16, 20, 24)

Active follow-up if there is no disease progression or new cancer treatment

Survival follow-up if there is disease progression or new cancer treatment

Active follow-up if there is no disease progression or new cancer treatment

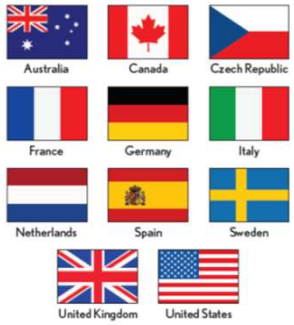
Survival follow-up if there is disease progression or new cancer treatment

Primary endpoints

- Overall survival (HR, 0.63)
- Overall response rate*

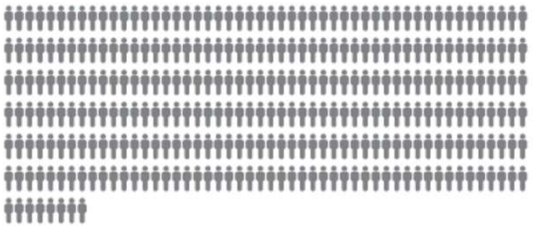
*Using Response Evaluation Criteria in Solid Tumors (RECIST), v1.1

11 countries



80 centers

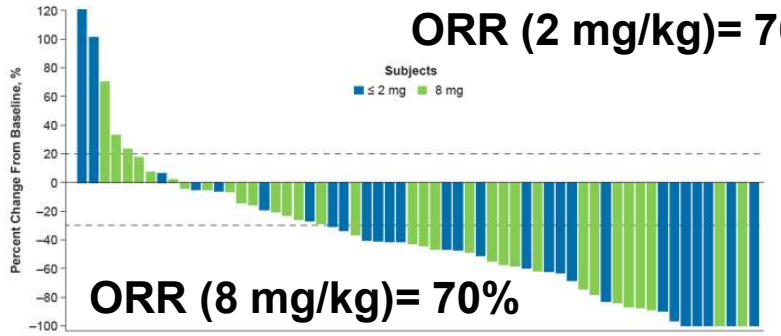
308 subjects



Ascierto et al ESMO 2018

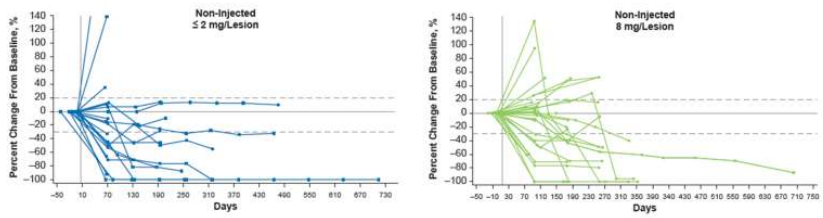
Other TLRs agonist on development: SD101 and CMP-001

Best Percent Change from Baseline in All Target Lesions



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: 9

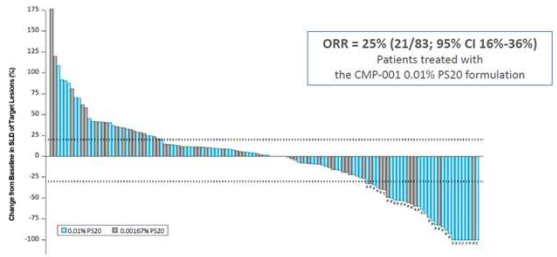
Percent Change from Baseline over Time in All Target Lesions for Patients Who Received ≤ 2 mg vs. 8 mg SD-101 Per Lesion (3)



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: 12

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Best Tumor Response (ITT, RECIST v1.1, All Patients [N=144])

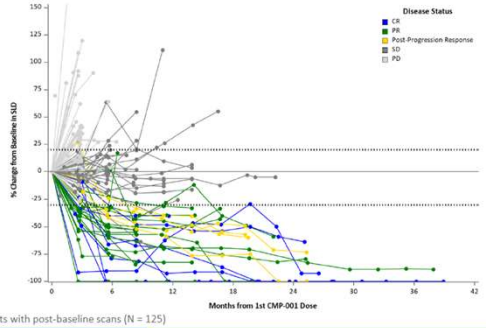


- Waterfall Plot includes all patients with post-baseline scans (N = 125)
- C=Complete response, P=Partial response. Patients with partial response after progression noted as 'X'

34th Annual Meeting & Pre-Conference Programs sitc 10 #SITC2019

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Percent Change from Baseline in Target Lesions Sum of Longest Diameters (All Patients (N=144)



- Spider Plot includes all patients with post-baseline scans (N = 125)

34th Annual Meeting & Pre-Conference Programs sitc 12 #SITC2019

Ribas et al ASCO 2018
Kirkwood et al. SITC 2019

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)

Presented by Paolo Ascierto at ASCO 2018

Loco-regional drugs in clinical development …

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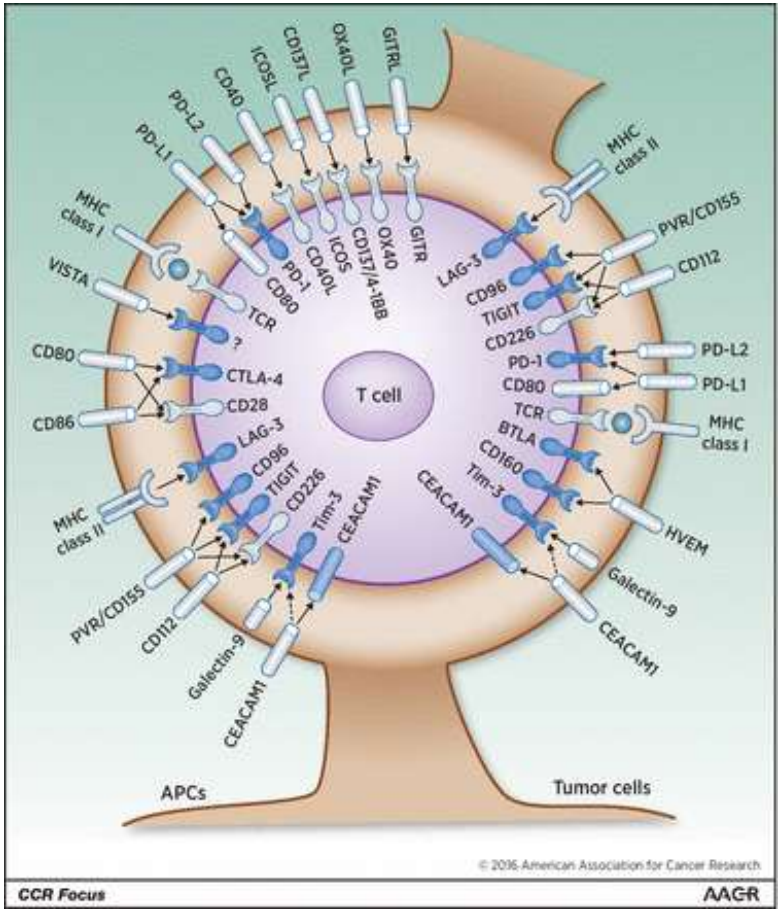
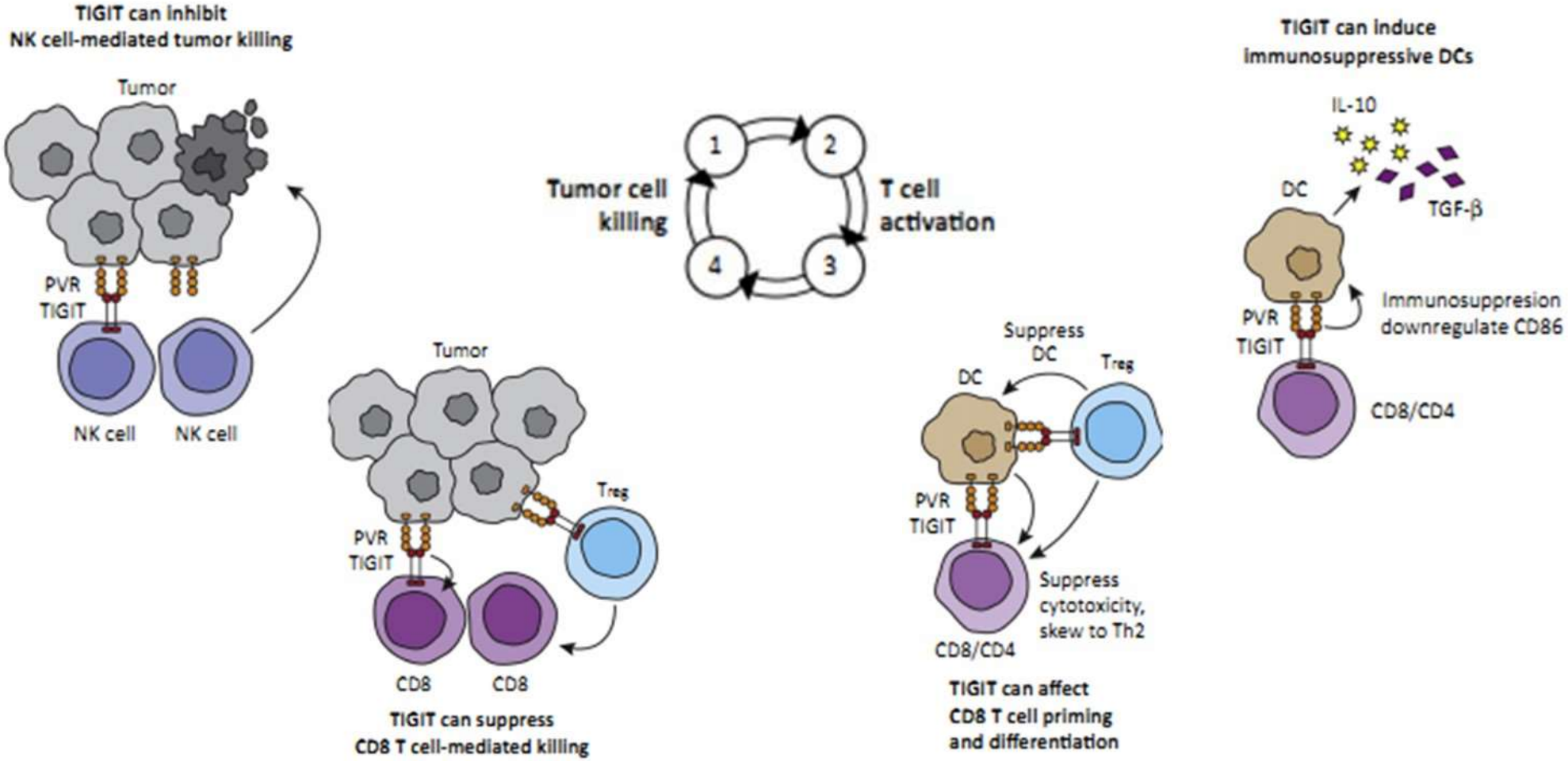
Presented by Paolo Ascierto at ASCO 2018

Coinhibitory and costimulatory receptors



Zaraour H. Clin Cancer Res; 2016; 22(8)

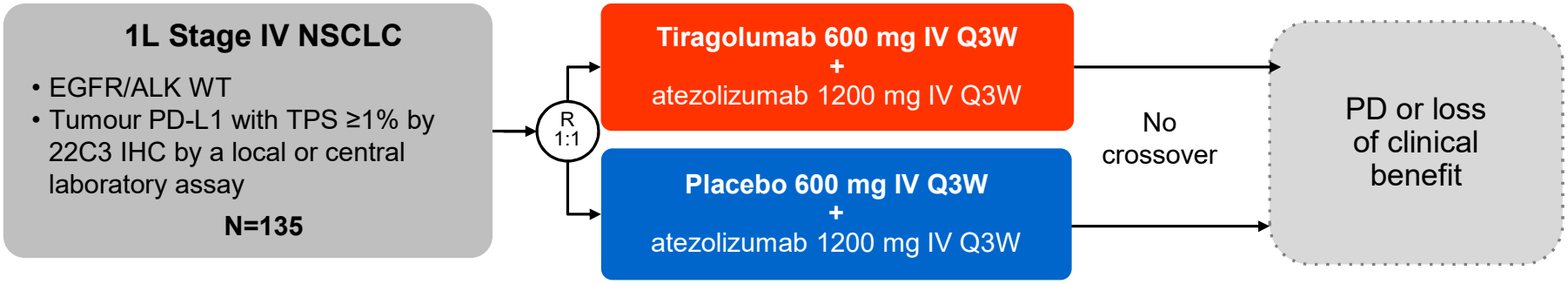
TIGIT: T-Cell Immunoreceptor with Ig and ITIM domains



Manieri et al., *Trends in Immunol* 2017

CITYSCAPE: randomised phase II study of tiragolumab + atezolizumab in PD-L1+ patients with NSCLC

Phase II, randomised, double-blind, placebo-controlled study (NCT03563716)



Stratification factors:

- PD-L1 22C3 TPS (1–49% versus ≥50%)
- Histology (NSQ versus SQ)
- Tobacco use (yes versus no)

Co-primary endpoints:

- ORR
- PFS

Key secondary endpoints:

- Safety
- DOR
- OS
- PROs

Exploratory endpoints:

- Efficacy analysis by PD-L1 status

1L, first-line; ALK WT, anaplastic lymphoma kinase wild-type; EGFR, estimated glomerular filtration rate; IHC, immunohistochemistry; IV, intravenously; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PRO, patient-reported outcomes; Q2W, every 2 weeks; Q3W, every 3 weeks; SQ, squamous; TPS, tumour proportion score

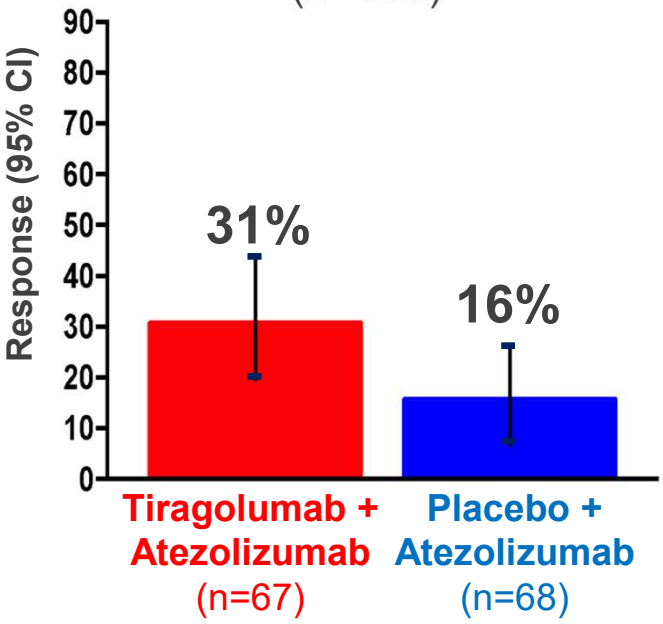
NCT03563716
Rodriguez-Abreu et al. ASCO 2020 (abstract 9503)

Primary analysis

Confirmed ORR and PFS

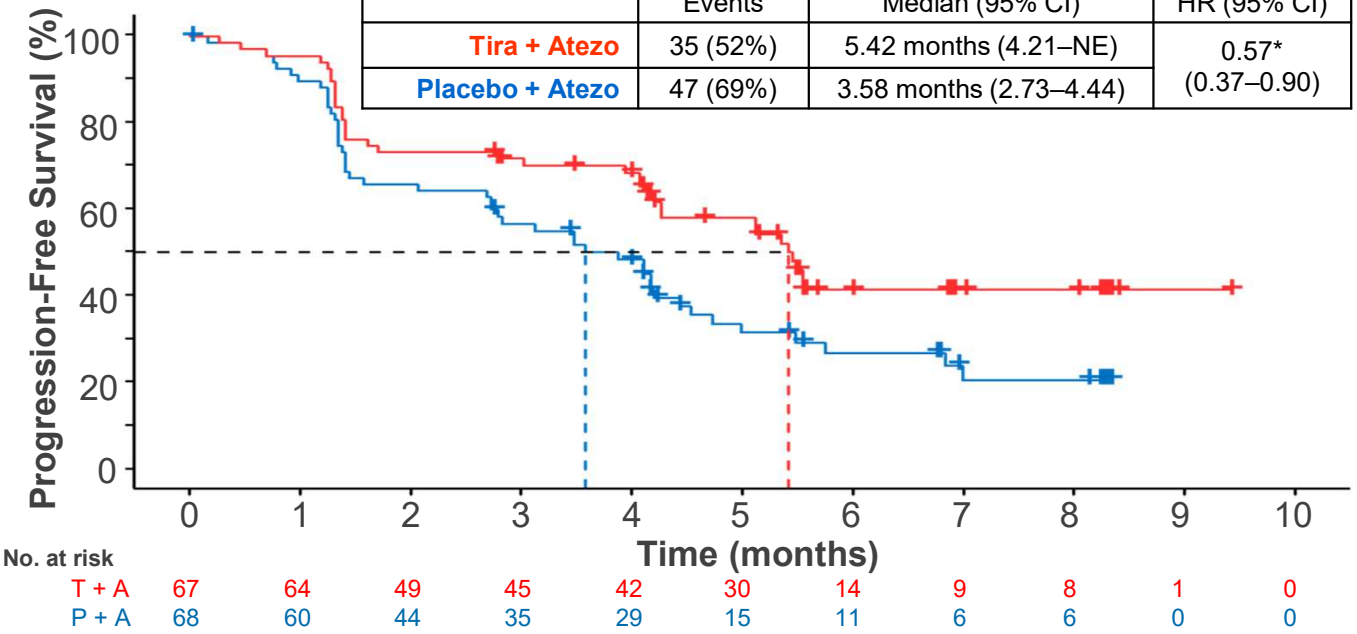
ITT: ORR

(n=135)



ITT: investigator-assessed PFS

	Events	Median (95% CI)	HR (95% CI)
Tira + Atezo	35 (52%)	5.42 months (4.21–NE)	0.57* (0.37–0.90)
Placebo + Atezo	47 (69%)	3.58 months (2.73–4.44)	



At the primary analysis, tiragolumab + atezolizumab improved ORR and median PFS compared with placebo + atezolizumab, with median follow-up of 5.9 months

Primary analysis data cutoff: 30 June 2019. Median follow-up: 5.9 months. *Stratified.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, non-evaluable, ORR, objective response rate; P+A = placebo + atezolizumab; PFS, progression-free survival; T+A, tiragolumab + atezolizumab

Rodriguez-Abreu et al. ASCO 2020 (abstract 9503)

Study Design: Part A

- Modified toxicity probability design
  - DLT evaluation period: cycle 1
  - Target DLT rate: ~30%
  - Patients per dose level: minimum of 3, maximum of 14
- Treatment: IV once every 3 weeks for up to 35 cycles or until PD, intolerable toxicity, physician decision, or consent withdrawal
- Crossover from MK-7684 monotherapy to combination therapy upon PD was permitted for eligible patients

Arm 1: MK-7684 Monotherapy

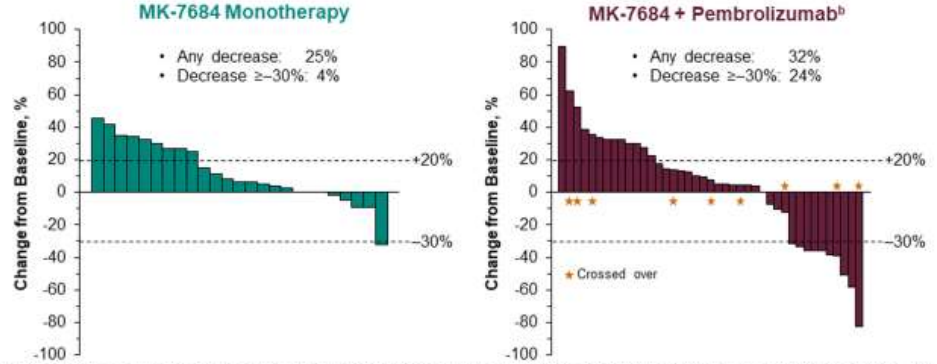
MK-7684 2.1 mg	MK-7684 7 mg	MK-7684 21 mg	MK-7684 70 mg	MK-7684 210 mg	MK-7684 700 mg

Arm 2: MK-7684 + Pembrolizumab

MK-7684 2.1 mg + Pembro 200 mg	MK-7684 7 mg + Pembro 200 mg	MK-7684 21 mg + Pembro 200 mg	MK-7684 70 mg + Pembro 200 mg	MK-7684 210 mg + Pembro 200 mg	MK-7684 700 mg + Pembro 200 mg

DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02964013.

Best Percentage Change from Baseline in Target Lesions[a] (RECIST v1.1, Investigator Review)



[a]Evaluated in patients with measurable disease at baseline and ≥1 evaluable post-baseline imaging assessment (n = 25 for MK-7684 monotherapy, n = 41 for MK-7684 + pembrolizumab).
[b]Includes 32 patients originally allocated to the combination and 9 who crossed over from MK-7684 monotherapy.
Data cutoff date: Aug 16, 2018.

Treatment-Related Adverse Events

MK-7684 Monotherapy

Occurred in ≥2 patients, n (%)	N = 34
Fatigue	5 (15%)
Pruritus	4 (12%)
Anemia	3 (9%)
Infusion-related reaction	3 (9%)
Arthralgia	2 (6%)
Decreased appetite	2 (6%)
Dermatitis acneiform	2 (6%)
Diarrhea	2 (6%)
Headache	2 (6%)
Nausea	2 (6%)
Rash	2 (6%)
Rash maculopapular	2 (6%)

- 2 grade 3: anemia and diarrhea (n = 1 each)
- 0 grade 4 or 5

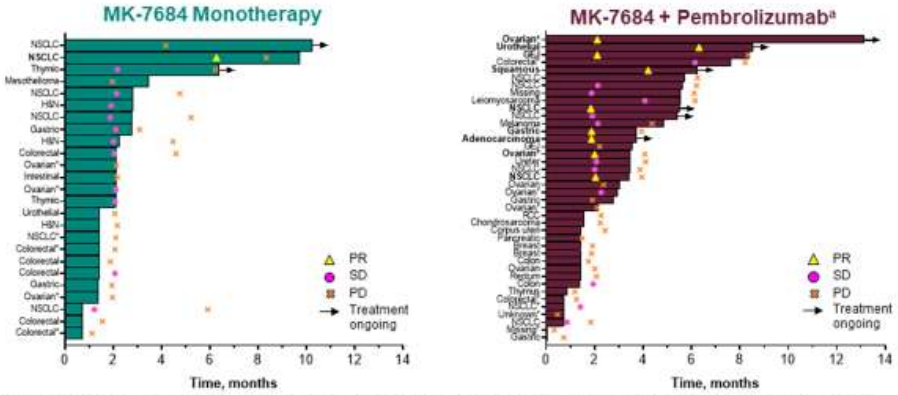
MK-7684 + Pembrolizumab

Occurred in ≥2 patients, n (%)	N = 47
Pruritus	10 (21%)
Fatigue	4 (9%)
Nausea	4 (9%)
Rash	4 (9%)
Decreased appetite	3 (6%)
Diarrhea	3 (6%)
ALT increased	2 (4%)
Dyspnea	2 (4%)
Hypophosphatemia	2 (4%)
Neuropathy peripheral	2 (4%)
Pyrexia	2 (4%)
Rash maculopapular	2 (4%)

- 5 grade 3: ALT increased, colitis, γGT increased, hypersensitivity, and rash maculopapular (n = 1 each)
- 0 grade 4 or 5

[a]Includes the 34 patients originally allocated to the combination and the 13 who crossed over from MK-7684 monotherapy.
Data cutoff date: Aug 16, 2018.

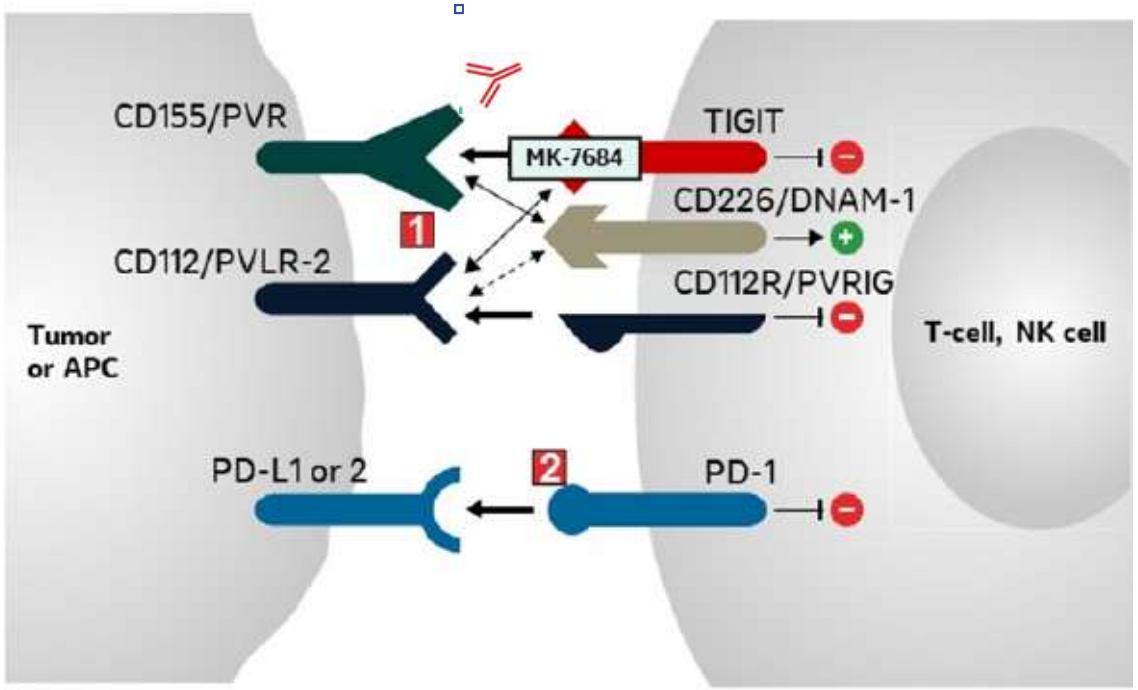
Treatment Duration and Response (RECIST v1.1, Investigator Review)



Line length represents the time to the last dose of study treatment. Time to best response and subsequent PD or death, whichever occurred first, are shown for each patient. Only those patients who had ≥1 post-baseline imaging assessment are included.
[a]Patients who crossed over.
[b]Includes 32 patients originally allocated to the combination and 9 who crossed over from MK-7684 monotherapy. Data cutoff date: Aug 16, 2018.

Mechanism of Action: Anti-TIGIT mAb (MK-7684, Vibostolimab)

- **MK-7684** (vibostolimab) is a humanized, IgG1 monoclonal antibody that binds TIGIT and blocks its interaction with its ligands, CD112 and CD155
- Blocking additional ligand-receptor interactions, such as PD-L1/PD-1, may enhance the antitumor response



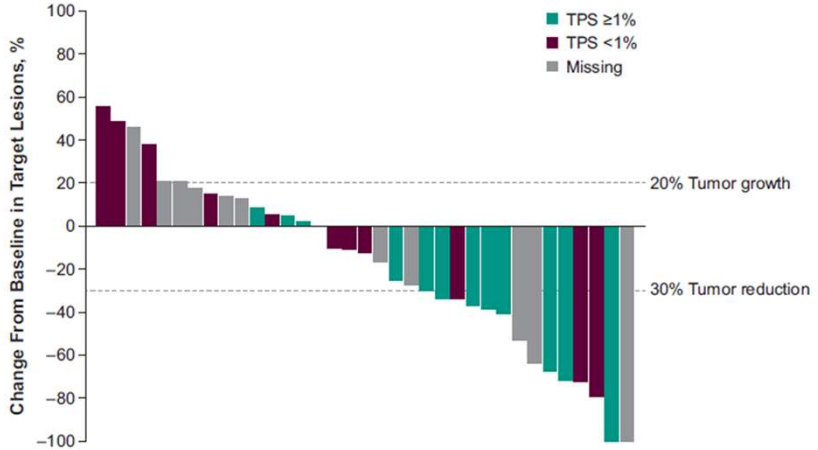
1. Golan T et al. Presented at SITC 2018. 2. Hung AL et al. Oncoimmu
Image adapted from Anderson AC et al. Immunity. 2016;44(5):989-1

Safety and Efficacy of Vibostolimab, an Anti–TIGIT Antibody, Plus Pembrolizumab in Patients With Anti–PD-1/PD-L1–Naive NSCLC

J. Niu[1]; A. Nagrial[2,3]; M. Voskoboynik[4]; H. C. Chung[5]; D. H. Lee[6]; M.-J. Ahn[7]; T. M. Bauer[8]; A. Jimeno[9]; V. Chung[10]; K. Mileham[11]; E. Chartash[12]; Q. Chen[12]; J. Healy[12]; M. Rajasagi[12]; C. Maurice-Dror[13]

[1]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [2]Blacktown Hospital, Blacktown, NSW, Australia; [3]University of Sydney, Sydney, NSW, Australia; [4]Alfred Health and Monash University, Melbourne, VIC, Australia; [5]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [6]Asan Medical Center, Seoul, South Korea; [7]Samsung Medical Center, Seoul, South Korea; [8]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [9]University of Colorado, Anschutz Cancer Pavilion, Aurora, CO, USA; [10]City of Hope National Medical Center, Duarte, CA, USA; [11]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]Rambam Health Care Campus, Haifa, Israel

Figure 1. Best Change From Baseline in Target Lesions Based on Investigator Assessment per RECIST v1.1 in Patients With Anti-PD-1/PD-L1-Naive NSCLC[a]



[a]Includes all patients with at least one postbaseline target lesion measurement (n = 35).

Figure 3. Kaplan-Meier Estimates of PFS in Patients With Anti-PD-1/PD-L1-Naive NSCLC

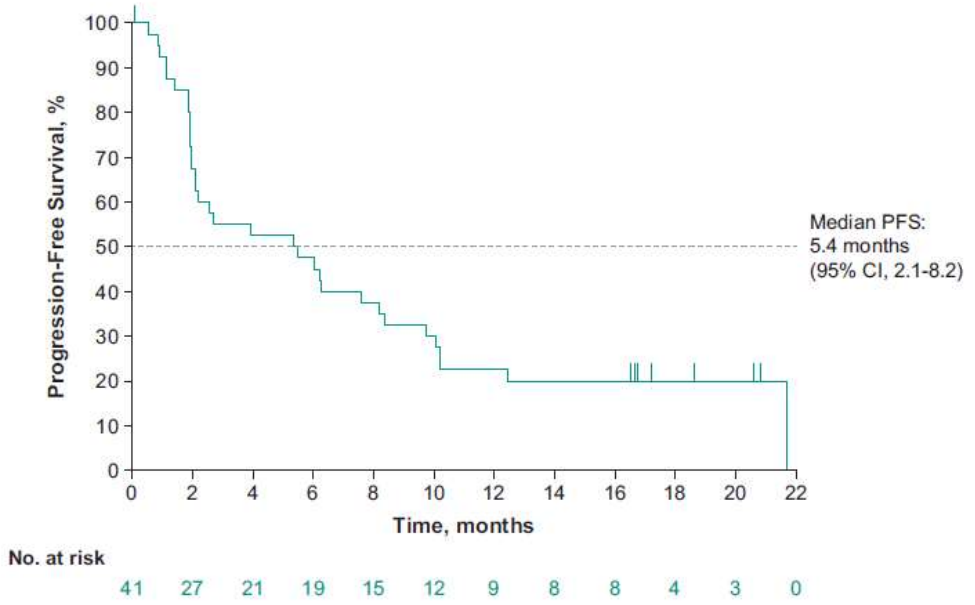


Table 3. PFS by TPS Status in Patients With Anti-PD-1/PD-L1-Naive NSCLC[a]

	TPS ≥1% n = 13	TPS <1% n = 12
Median (95% CI), months	8.4 (3.9-10.2)	4.1 (1.9-NR)

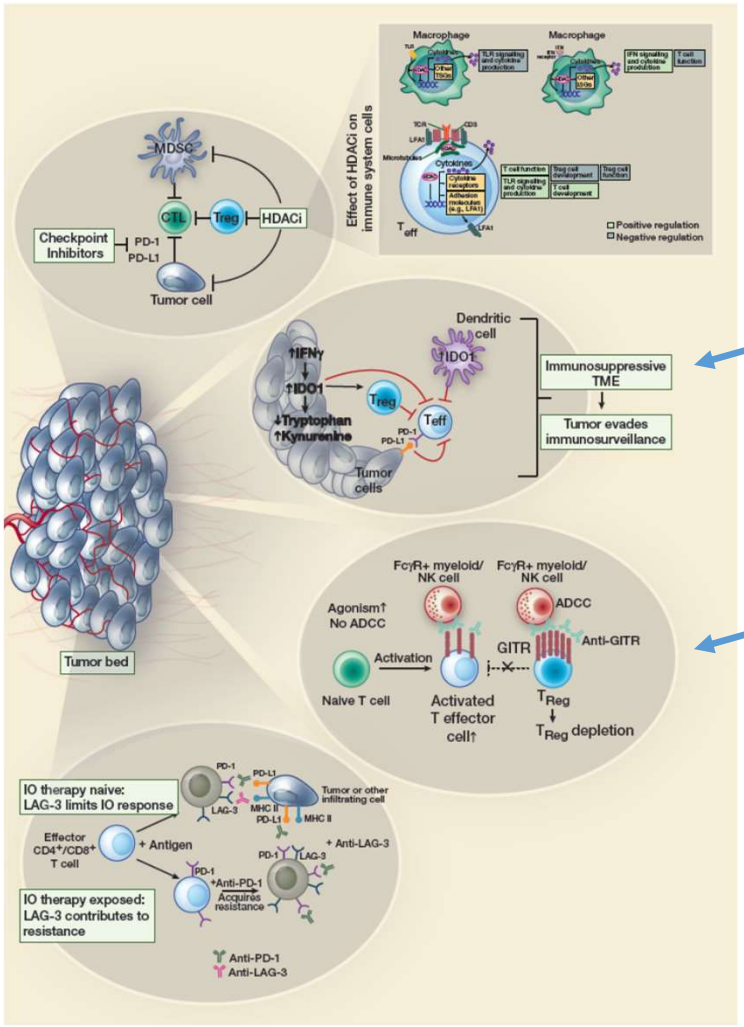
NR, not reached.

[a]Data shown for patients with available PD-L1 data.

Niu et al. ESMO 2020

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])

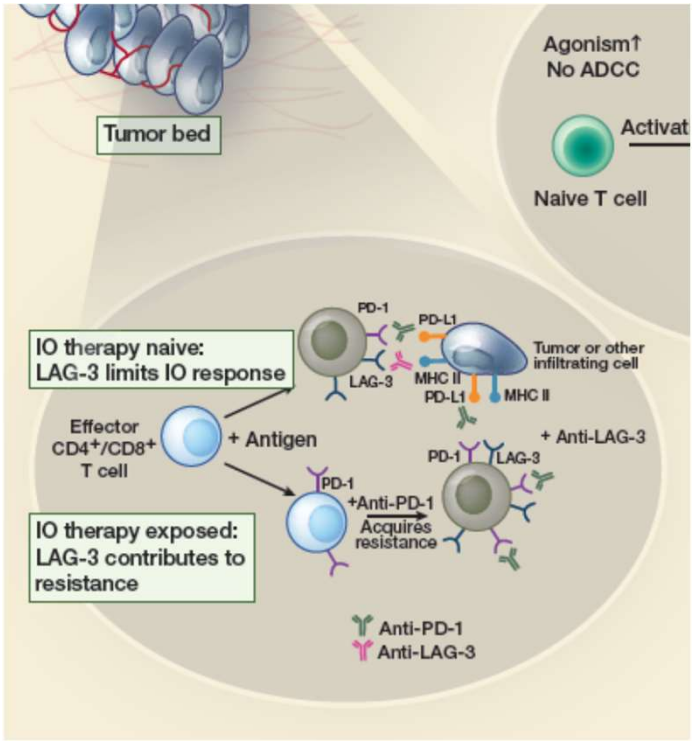
GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

Presented by Paolo A. Ascierto at ASCO 2018

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

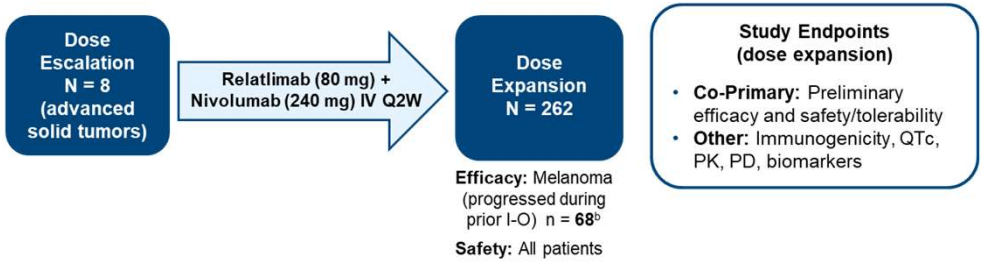
New emerging pathways for future combination with anti-PD-1/PD-L1 compounds: *anti-LAG-3*

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

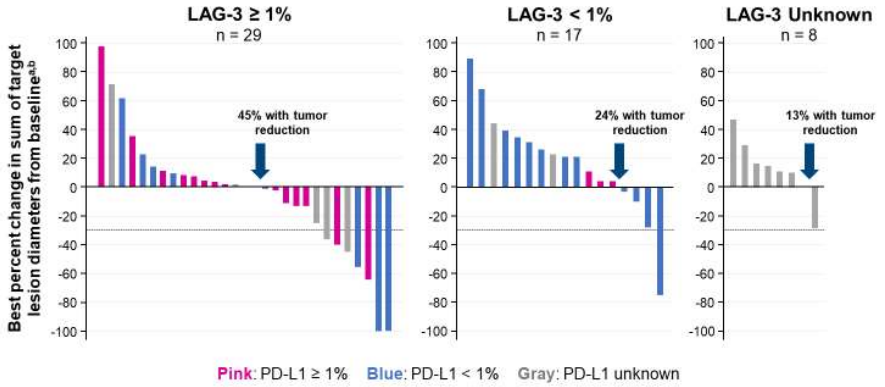


Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

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



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.

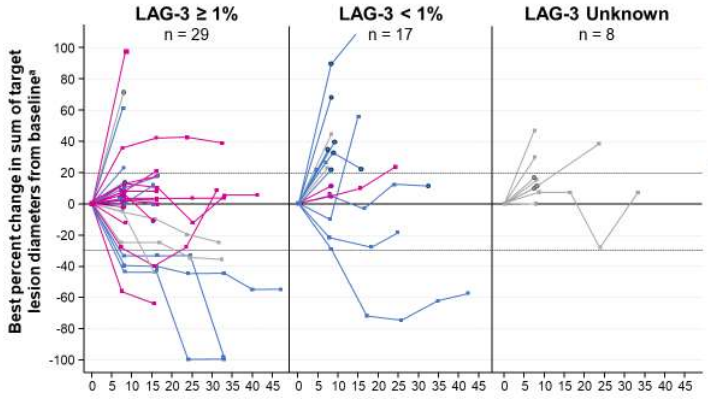
Safety of Relatlimab 80 mg + Nivolumab 240 mg Q2W

	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



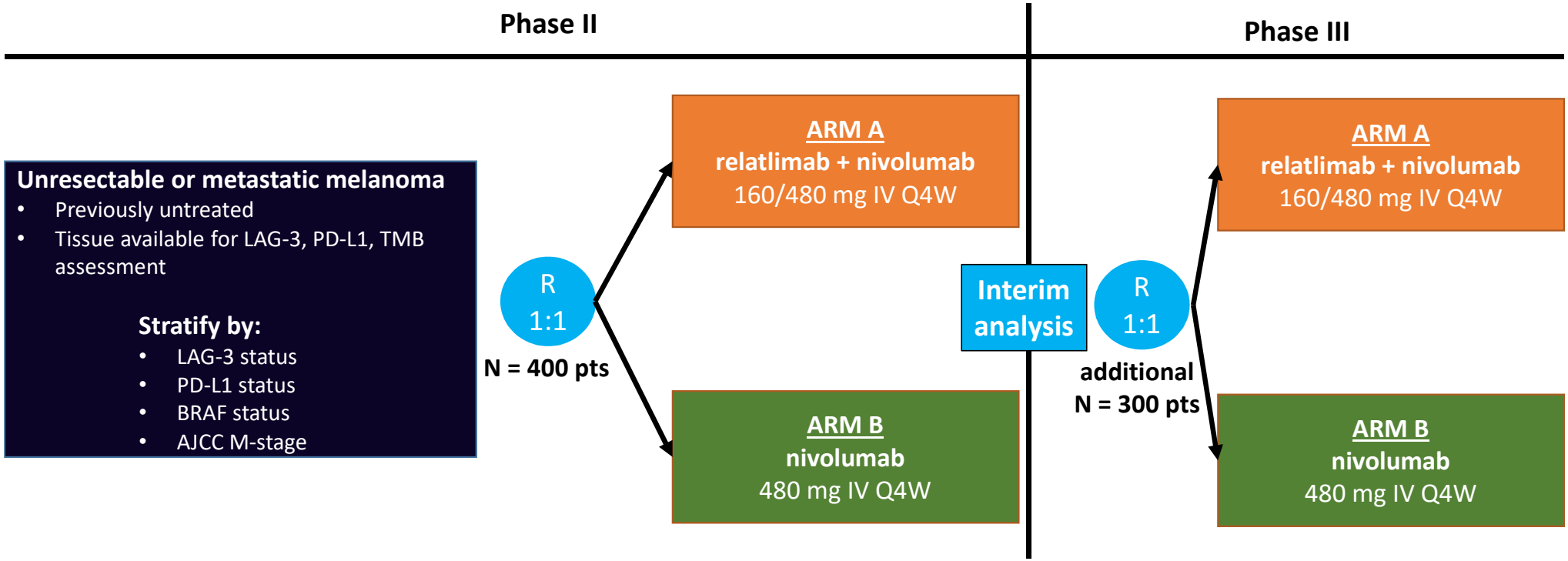
- Responses were more likely in patients with LAG-3 expression ≥ 1%
- PD-L1 expression did not appear to enrich for response

Pink: PD-L1 ≥ 1%
Blue: PD-L1 < 1%
Gray: PD-L1 unknown
o: Appearance of new lesions

[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.

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

Study Design: Part A

- Standard 3+3 dose escalation
  - DLT evaluation period: cycle 1
  - Patients per dose level: minimum of 3, maximum of 6
- Treatment: IV once every 3 weeks for up to 35 cycles or until PD, intolerable toxicity, physician decision, or consent withdrawal
- Intrapatient dose escalation and crossover from monotherapy to combination therapy were not permitted

Arm 1: MK-4280 Monotherapy

MK-4280 7 mg	MK-4280 21 mg	MK-4280 70 mg	MK-4280 210 mg	MK-4280 700 mg

Arm 2: MK-4280 + Pembrolizumab

MK-4280 7 mg + Pembro 200 mg	MK-4280 21 mg + Pembro 200 mg	MK-4280 70 mg + Pembro 200 mg	MK-4280 210 mg + Pembro 200 mg	MK-4280 700 mg + Pembro 200 mg

DLT, dose-limiting toxicity.
ClinicalTrials.gov, NCT02720068.

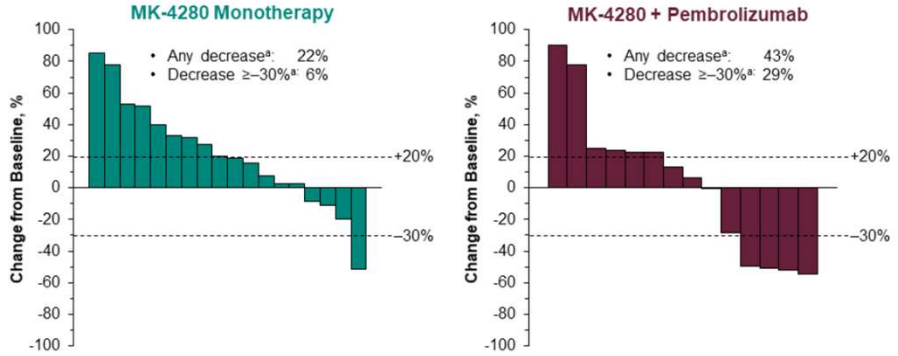
Baseline Characteristics

Characteristic, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembro N = 15
Age, median (range)	55.5 (36-82)	62.0 (40-79)
Male sex	7 (39%)	8 (53%)
ECOG PS		
0	4 (22%)	7 (47%)
1	14 (78%)	8 (53%)
Prior therapy		
Neoadjuvant	1 (6%)	0
Adjuvant	3 (17%)	4 (27%)
1	2 (11%)	0
2	5 (28%)	2 (13%)
3	3 (17%)	1 (7%)
4	0	3 (20%)
≥5	4 (22%)	5 (33%)

Primary Cancer, n (%)	MK-4280 Monotherapy N = 18	MK-4280 + Pembro N = 15
Sarcoma	4 (22%)	0
Appendiceal	2 (11%)	1 (7%)
Biliary	2 (11%)	0
Colorectal	2 (11%)	5 (33%)
Adrenocortical	1 (6%)	1 (7%)
Breast	1 (6%)	2 (13%)
Small intestinal	1 (6%)	1 (7%)
RCC	0	2 (13%)
Other	5 (28%)[a]	3 (20%)[b]

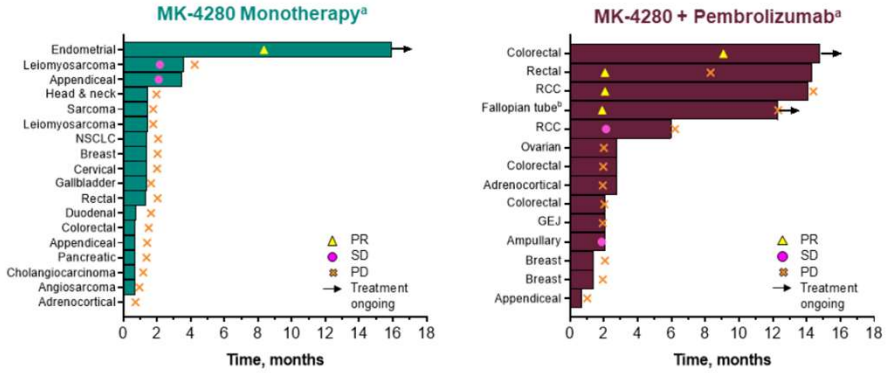
[a]Includes 1 patient each with cervical, endometrial, head & neck, NSCLC, and pancreatic cancer.
[b]Includes 1 patient each with fallopian tube, gastroesophageal junction, and ovarian cancer.
Data cutoff date: Jun 12, 2018.

Best Percentage Change from Baseline in Target Lesions[a] (RECIST v1.1, Investigator Review)



[a]Evaluated in patients with measurable disease at baseline and ≥1 evaluable post-baseline imaging assessment (n = 18 for MK-4280 monotherapy, n = 14 for MK-4280 + pembrolizumab).
Data cutoff date: Jun 12, 2018

Treatment Duration and Response (RECIST v1.1, Investigator Review)

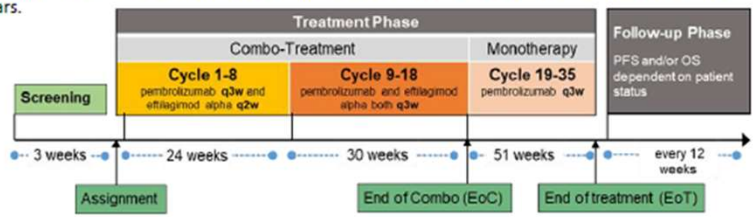


Line length represents the time to the last dose of study treatment. Time to best response and subsequent progression are shown for each patient.
[a]Only those patients who had ≥1 post-baseline imaging assessment are included (n = 18 for MK-4280 monotherapy, n = 14 for MK-4280 + pembrolizumab).
[b]Patient discontinued treatment on Jun 18, 2018 because of an adverse event (persistent grade 1 pneumonitis despite corticosteroids).
Data cutoff date: Jun 12, 2018

Lakhani N, et al. *SITC 2018*

Initial results from a Phase II study (TACTI-002) of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab as 2nd line treatment for PD-L1 unselected metastatic head and neck cancer patients

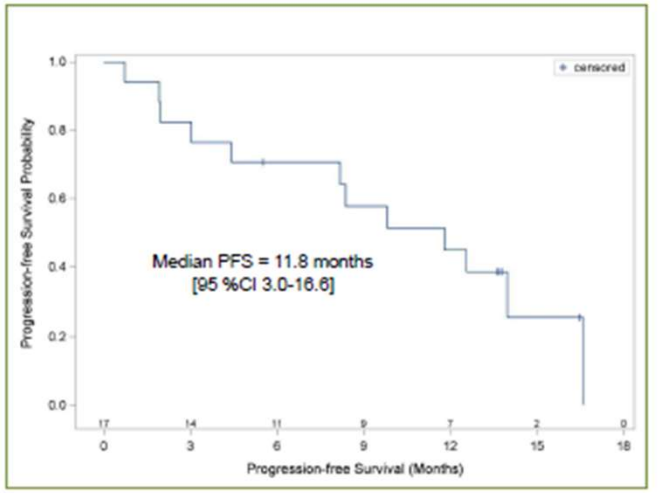
Efti is administered as 30 mg subcutaneous injection every 2 weeks for the first 8 cycles and every 3 weeks for the following 9 cycles. Pembrolizumab is administered at a standard dose of 200 mg intravenous infusion every 3 weeks for maximum 2 years.



Legend: 1 cycle = 3 weeks; q2w – every 2 weeks, q3w every 3 weeks

Enrolment to Part A + C stage 1 was completed in 2019, while Part B stage 1 and Part A stage 2 was completed in 2020. Recruitment in Part C stage 2 is ongoing.

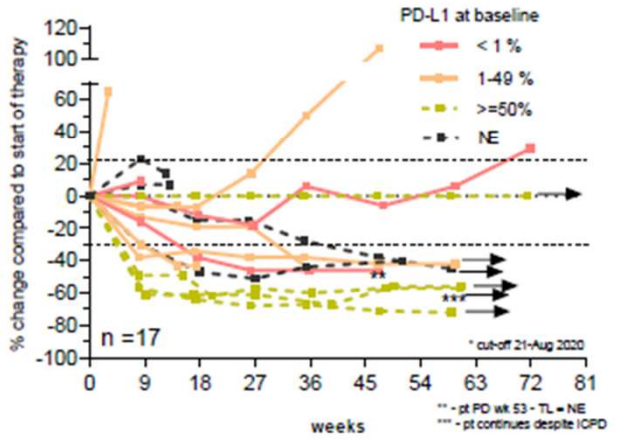
Kaplan-Meier Plot for PFS



Summary:

- iORR of 52.9 % [95 % CI 27.8-77.0]
- Confirmed responses for 8 out of 9 patients with irPR/irCR
- 1 pt with a complete response
- 12/17 (71 %) with target lesion decrease
- Responses in all PD-L1 subgroups
- **4 responses in patients with PD-L1 expression of < 50 %; 1 response in PD-L1 negative patients**
- Two late responders after 8 and 11 months
- Median PFS: 11.8 months [95 % CI 3.0;16.6]; PFS at 12 months: 45 %
- 12-months overall survival rate: 71 % → median OS not yet reached; minimum FU of 14 months
- At data cut-off 6 pts still under therapy → all 12+ months on therapy

Spider Plot



Felip et al. ESMO 2020

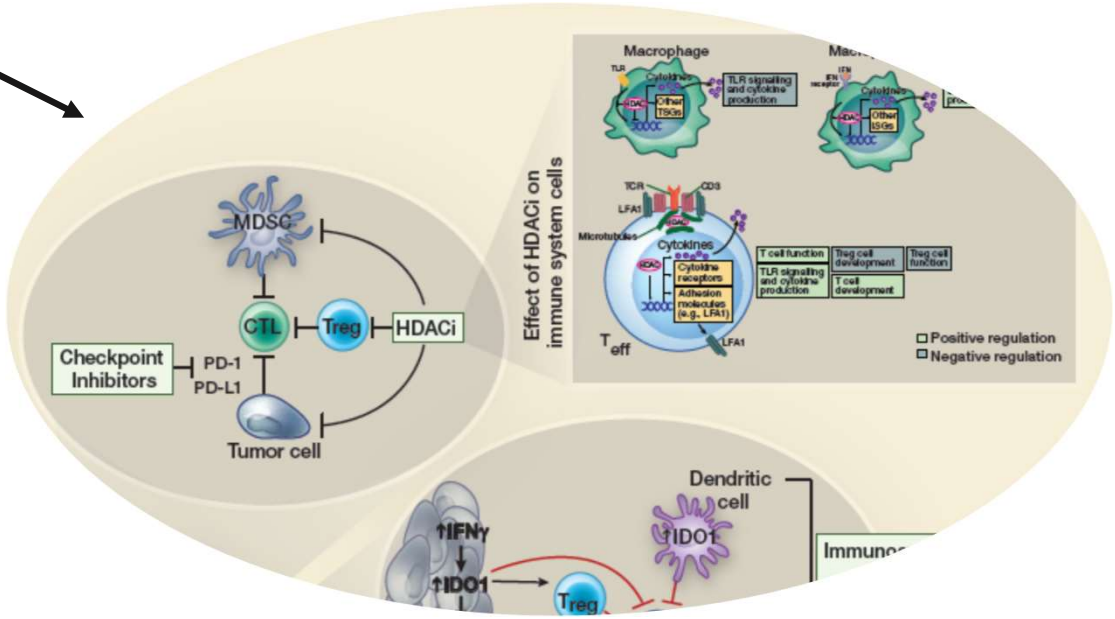
Anti-LAG-3 development

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

Presented by Paolo Ascierto at ASCO 2018

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

HDAC inhibitors
(eg., entinostat, etc.)

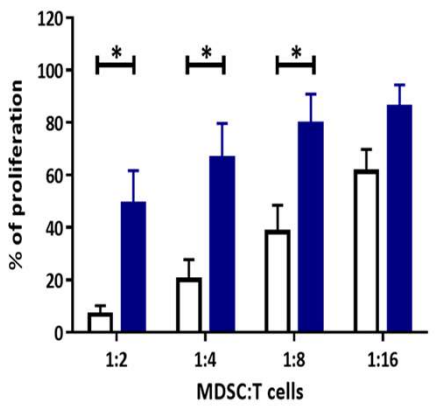


Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

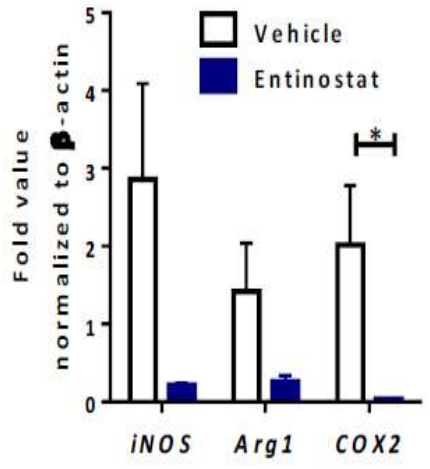
Rationale for Entinostat in Combination with anti-PD-(L)1 Therapy

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment
- Synergy with anti-PD-1 inhibition in preclinical models

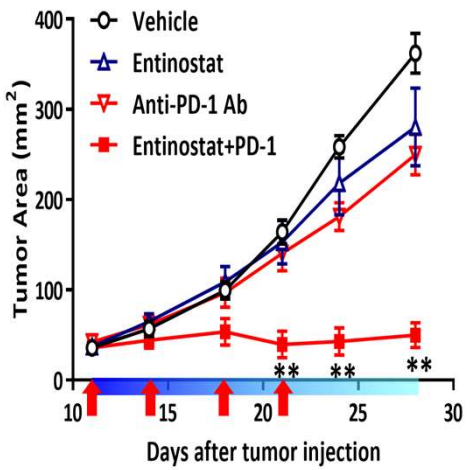
MDSC function[1†]



MDSC mRNA expression[1†]



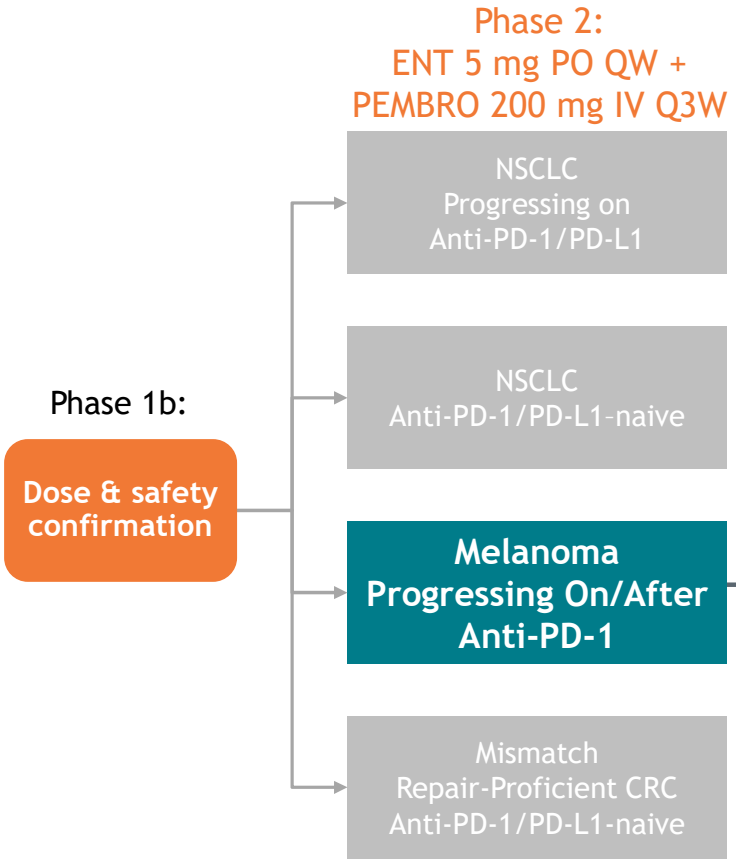
Tumor growth[1†]



† *In vivo* and *in vitro* studies were performed using Lewis Lung Carcinoma (LLC) cells. ***P*<0.001. **P*<0.05.
Ab, antibody; Arg1, arginase 1; COX2, cytochrome oxidase subunit 2; iNOS, inducible nitric oxide synthase; MDSC, myeloid-derived suppressor cells.
Orillion A, et al. *Clin Cancer Res*. 2017;23(17):5187-5201.

Sullivan et al AACR 2019

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

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 19th World Conference on Lung Cancer

September 23–26, 2018 Toronto, Canada

WCLC2018.IASLC.ORG #WCLC2018

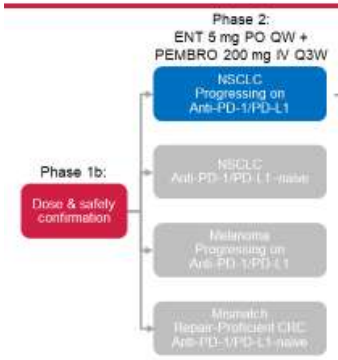
Efficacy/safety of entinostat (ENT) and pembrolizumab (PEMBRO) in NSCLC patients previously treated with anti-PD-(L)1 therapy

Matthew D. Hellmann[1], Pasi A. Jänne[2], Mateusz Opyrchal[3], Navid Hafez[4], Luis E. Raez[5], Dmitry Gabrilovich[6], Fang Wang[6], Peter Ordentlich[7], Susan Brouwer[7], Serap Sankoh[7], Emmett Schmidt[8], Michael L. Meyers[7], Suresh S. Ramalingam[9]

[1]Memorial Sloan Kettering Cancer Center, New York, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [4]Yale Cancer Center, New Haven, CT, USA, [5]Memorial Cancer Institute, Pembroke Pines, FL, USA, [6]The Wistar Institute, Philadelphia, PA, USA, [7]Syndax Pharmaceuticals, Inc., Waltham, MA, USA, [8]Merck & Co., Inc., Kenilworth, NJ, USA, [9]The Winship Cancer Institute of Emory University, Atlanta, GA, USA

WCLC 2018

ENCORE-601: Open-label study evaluating ENT + PEMBRO in patients with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy



Inclusion Criteria:

- Recurrent or metastatic NSCLC, measurable by RECIST 1.1
- Prior progression on anti-PD(L1) treatment
- Prior chemotherapy in the advanced/metastatic setting
- Prior ALK or EGFR treatment if indicated
- ECOG Performance Status < 2
- Willingness to baseline and on-Tx biopsy and blood samples

Phase 2 Primary Endpoint

- ORR (irRECIST)

Phase 2 Secondary Endpoints

- PFS, OS, safety & tolerability

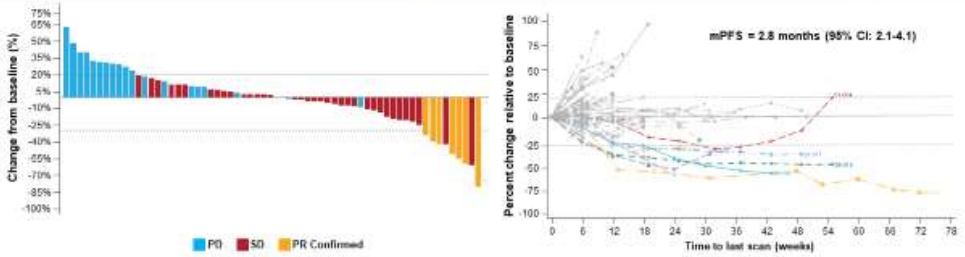
76 patients enrolled (72 efficacy evaluable[a]), last patient enrolled December 2017

- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

[a]4 patients were non-evaluable due to withdrawal of consent or discontinuations for administrative reasons prior to the first tumor assessment.

ALK, anaplastic lymphoma kinase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ENT, entinostat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; QW, once a week; Q3W, every 3 weeks

Durable responses were observed in patients who experienced progression on prior anti-PD(L)1 therapy



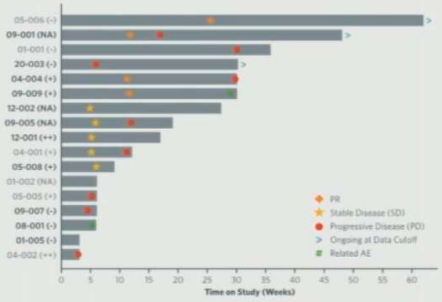
- Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)
  - Prespecified ORR target not reached; median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- Experience similar in PD1-pretreated melanoma (ORR = 18%)[1]

CI, confidence interval; ENT, entinostat; PEMBRO, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease

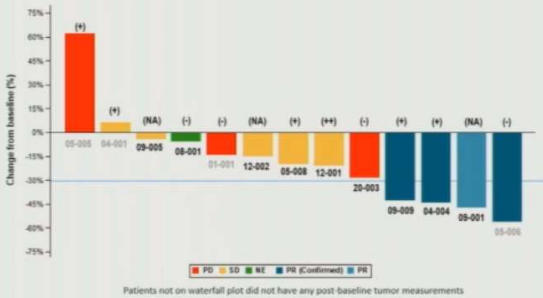
1. Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

Efficacy in Cohort 1: Anti-PD-(L)1–naive group

Time to Response and Time on Treatment



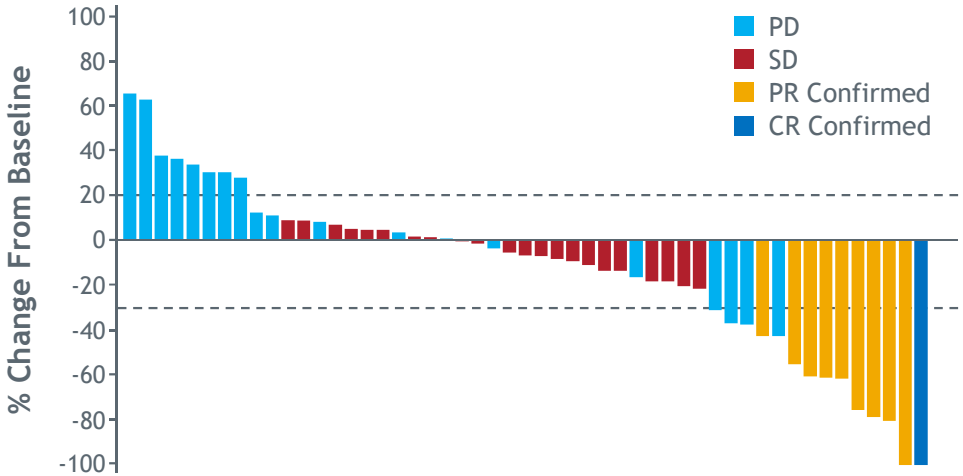
Change in Tumor Size From Baseline

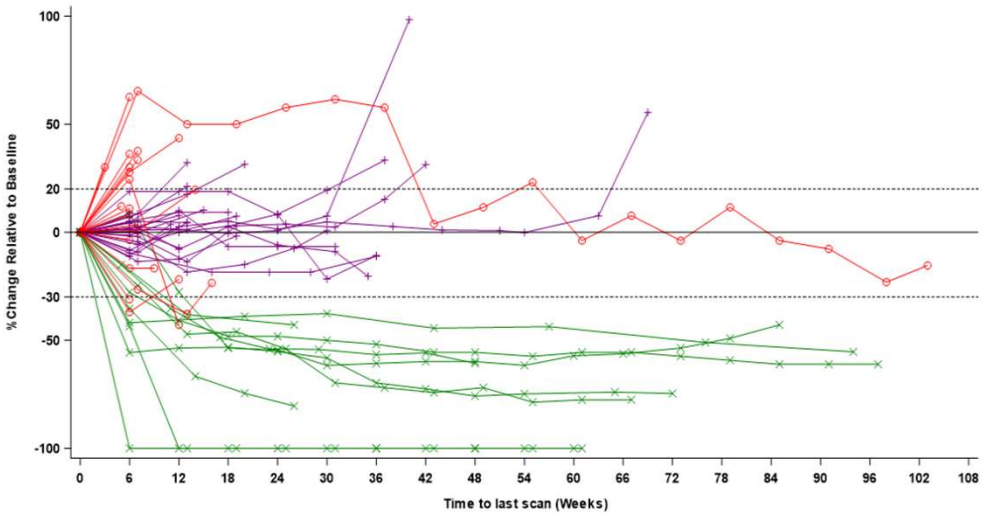


- 4 PRs out of 17 evaluable patients (24% ORR, 95% CI: 7–50)
  - 3 confirmed PRs, one unconfirmed PR due to new pericardial effusion with malignant cells
  - 3 with negative or low baseline PD-L1 expression, 1 with unknown PD-L1 expression

Gandhi et al. SITC 2017
Hellmann et al IASLC 2018

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.

Sullivan et al AACR 2019

A phase II, open label study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with advanced unresectable/metastatic Merkel Cell Carcinoma progressing on anti-PD-(L)1 antibody therapy – the MERKLIN 2 study

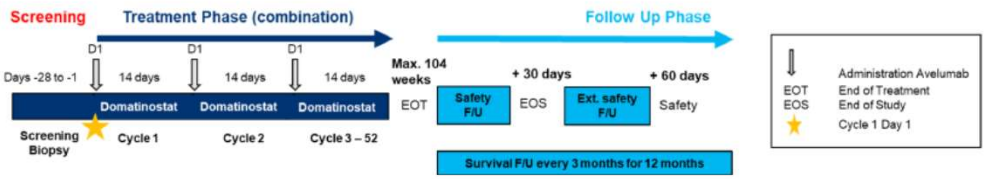
Alexander van Akkooi[1]; Paolo A. Ascierto[2], Jürgen C. Becker[3,4], Paul Nathan[5], Paul Nghiem[6], Ulrike Ostermeier[7], Philip Reimann[7], and Frank Hermann[7]

1: Department of Surgical Oncology, Netherlands Cancer Institute Antoni van Leeuwenhoek, Amsterdam; Netherlands; 2: Istituto Nazionale Tumori IRCCS Fondazione 'G. Pascale', Naples, Italy; 3: Translational Skin Cancer Research, Deutsches Konsortium für Translationale Krebsforschung (DKTK), Deutsches Konsortium für Translationale Krebsforschung (DKTK), Essen, Germany;4: Department of Dermatology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; 5: Department of Medical Oncology, Mount Vernon Cancer Centre, London, United Kingdom; 6: University of Washington, Seattle Cancer Care Alliance, Seattle, WA.; 7: 4SC AG, Planegg-Martinsried; Germany

Background and Rationale

- Merkel cell carcinoma (MCC) is a rare but highly aggressive human skin cancer; patients with this cancer are usually treated with checkpoint inhibitors (avelumab, PD-L1; pembrolizumab, PD-1) [1-3]
- Despite successes a significant proportion of MCC patients do not respond or relapse during anti-PD-(L)1 monotherapy, thus requiring additional treatment options[4,5]
- MCC resistance to checkpoint inhibitors include epigenetic downregulation of the antigen processing and presentation machinery
- Preclinical studies with the small molecule selective class I histone deacetylase inhibitor (HDACi) domatinostat have shown a beneficial modulation of the tumor environment and have demonstrated promising synergy with immune-oncology drugs[6,7]

Trial Design



MERKLIN 2 trial:

- Phase II, multicenter, single-arm clinical trial of the orally administered domatinostat in combination with avelumab
- Target indication: patients with advanced unresectable/metastatic MCC that are progressing on previous anti-PD-(L)1 therapy
- Primary Objective: Objective Response Rate (ORR) defined as the percentage of patients having a confirmed CR or PR according to RECIST v1.1
- Secondary objectives: additional efficacy assessments, safety, Health related quality of life (HRQoL) and pharmacokinetics of domatinostat in combination with avelumab
- Exploratory objectives: analysis of tumor biopsies and blood sampling for the evaluation of biomarkers and their association with clinical benefit

Email first author: a.v.akkooi@nki.nl

Patient Eligibility

Key Inclusion Criteria:

- Histologically confirmed Merkel Cell Carcinoma (MCC)
- ECOG performance status ≤ 1
- MCC in an advanced, unresectable stage III or metastatic stage IV (includes patients who refused surgical resection or are not eligible for such surgical resection)
- Progressing on previous anti-PD-(L)1 antibody monotherapy within the last 12 weeks before planned first administration of study medication

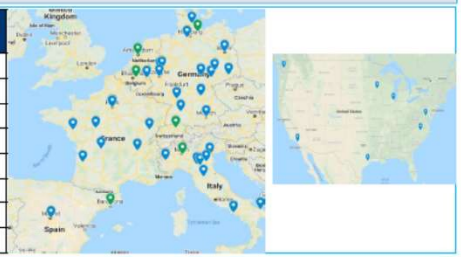
Key Exclusion Criteria:

- History of serious anti-PD-(L)1 therapy-related adverse reactions prohibiting further avelumab treatment
- More than one line of previous systemic anti-neoplastic therapy other than anti-PD-(L)1 antibody monotherapy.
- Excluded: Palliative radiation therapy of single lesions within 2 weeks before planned administration of study medication
- Significant active or chronic disease (infections, immunodeficiencies, cardiovascular, psychiatric disorders)

Current Status

- Enrollment of 40 patients planned in 18 - 24 months
- 39 trial centers in 7 European countries
- 6 centers in USA,
- Total 45 centers
- Global P.I.: Alexander van Akkooi (NKI, Amsterdam; The Netherlands)

Country	Number of sites (planned/open)
Belgium	1 / 0
France	9 / 0
Germany	14 / 3
Italy	9 / 1
Netherlands	2 / 0
Spain	3 / 1
Switzerland	1 / 0
United States	6 / 0



Funding and Disclosures

This trial is sponsored by 4SC AG, Martinsried, Germany. Avelumab is provided by Merck KGaA Darmstadt, Germany, and is part of an alliance between Merck KGaA, and Pfizer Inc, New York, NY, USA. UO, PR and FH are full time employees of 4SC.
COI declaration of Alexander van Akkooi: Advisory Board / Consultancy Honoraria (all paid to institute): Amgen, Bristol-Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Sanofi, 4SC Research grant (all paid to institute): Amgen, Novartis, Merck-Pfizer

References

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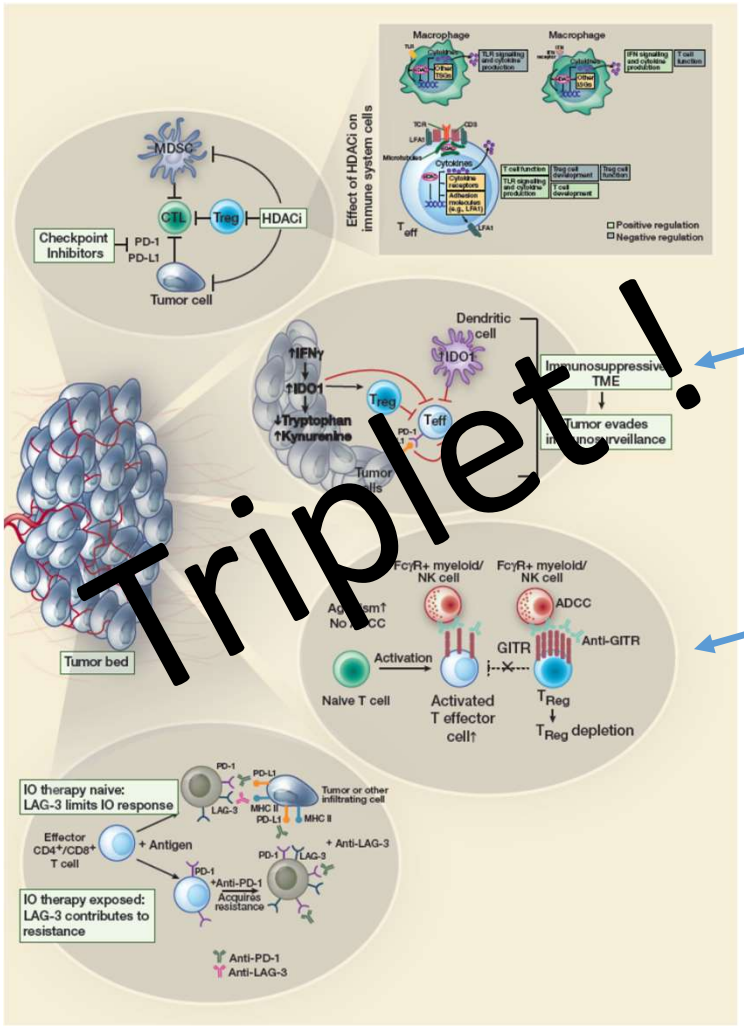
New emerging pathways for future combination with anti-PD-1/PD-L1 compounds

HDAC inhibitors

IDO1 inhibitors

Anti-GITRs

Anti-LAG-3s

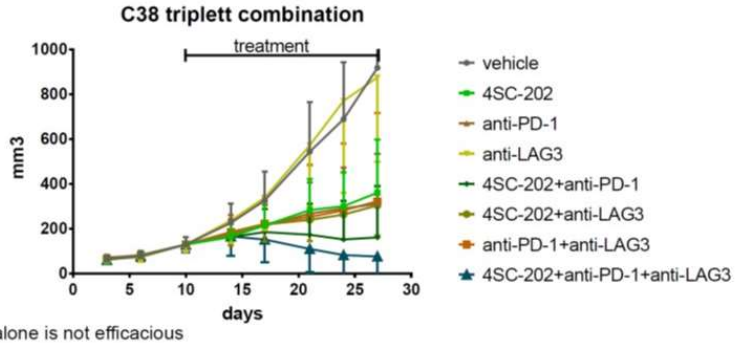


Triplet!

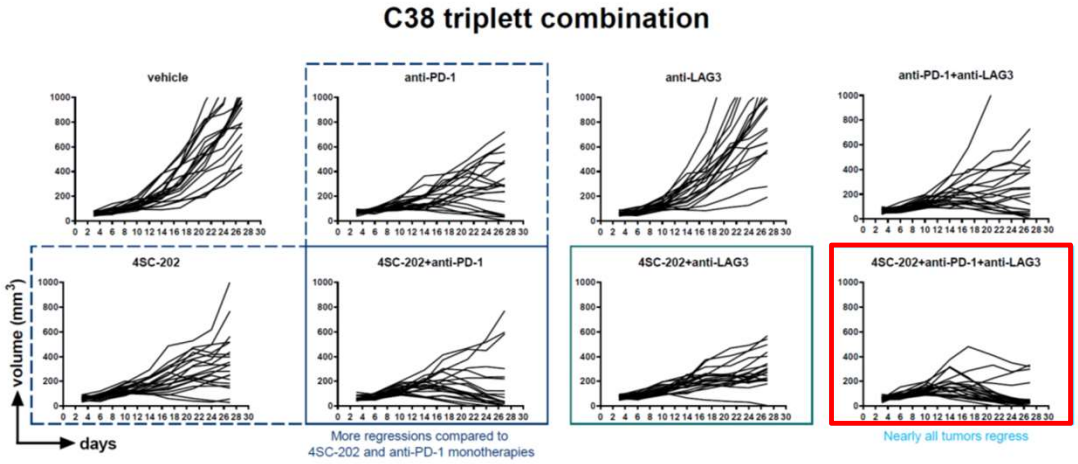
GITR, glucocorticoid-induced TNFR-related protein; HDAC, histone deacetylases; IDO1, indoleamine 2,3-dioxygenase 1; LAG-3, lymphocyte-activation gene 3

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

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



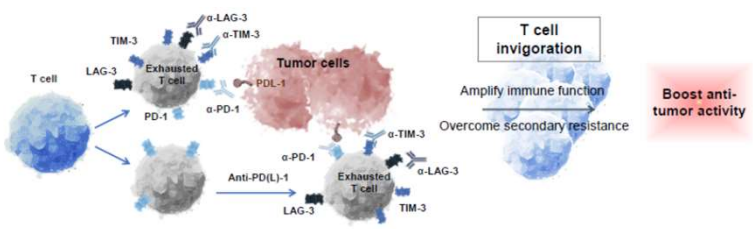
- Anti-LAG3 alone is not efficacious
- 4SC-202 and anti-PD-1 alone reduce tumor growth
- 4SC-202+anti-LAG3 is similar to 4SC-202, anti-LAG3+anti-PD-1 is similar to anti-PD-1
- 4SC-202+anti-PD-1 is beneficial compared to mono-therapies
- But triple is superior to all incl. the double 4SC-202+anti-PD-1

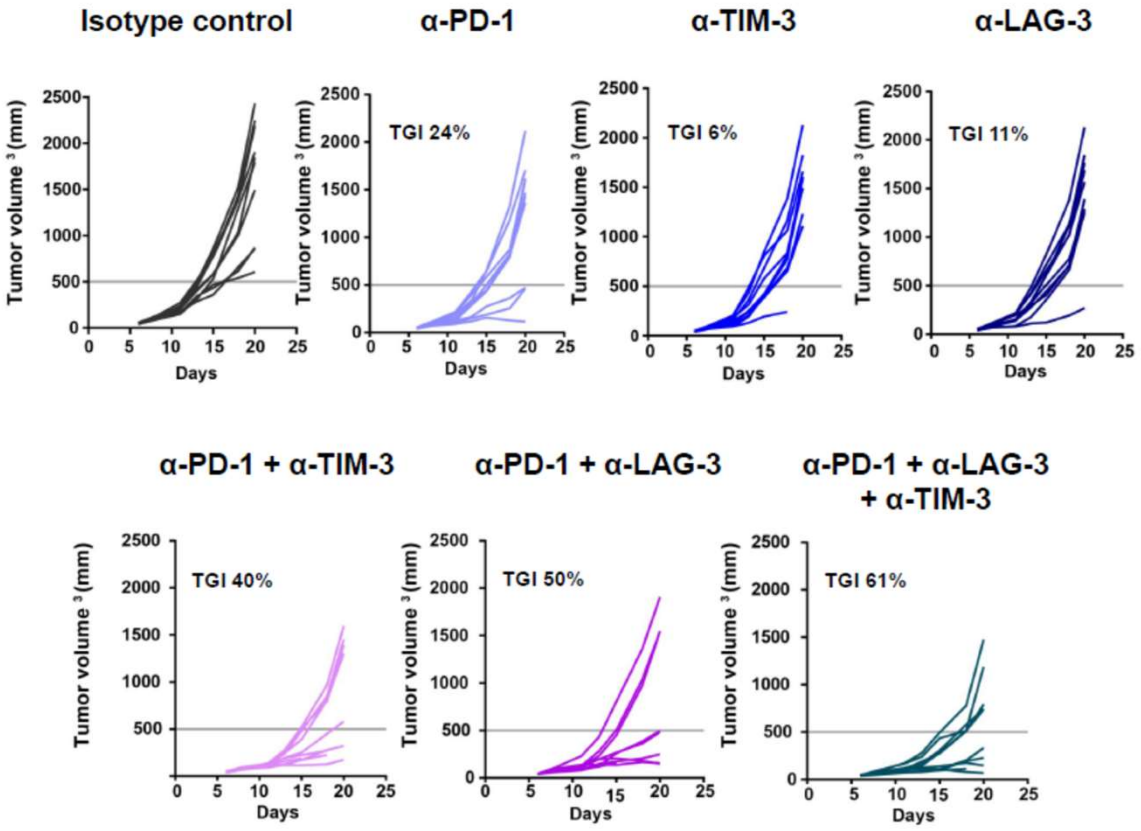


Hamm et al AACR 2018 Abstract #4722

Triple checkpoint blockade targeting PD-1, TIM-3, and LAG-3 improves T cell reinvigoration and antitumor efficacy over single and double combinations

Johanna K. Kaufmann, Geeta Sharma, Srimoyee Ghosh, Sujatha Kumar, Kevin G. Coleman, Sridhar Ramaswamy, David Jenkins
TESARO, Inc., Waltham, MA, USA

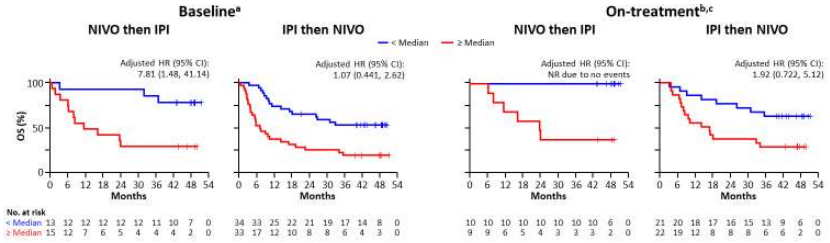




Kaufmann et al. *SITC* 2018

IL-6 and CRP as possible biomarkers

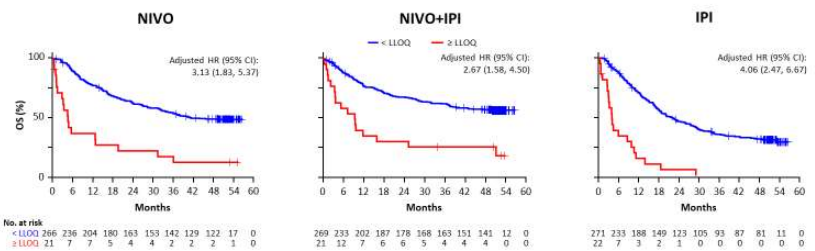
CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With OS Across Treatment Arms



High baseline and on-treatment IL-6 levels were associated with shorter OS

[a]Median IL-6 at week 0: 13.3 pg/mL; [b]Median IL-6 at week 13: 13.6 pg/mL; [c]On-treatment at week 13; switch in treatment occurred at week 13.
HR adjusted for The Eastern Cooperative Oncology Group performance status (ECOG), *BRAF* status, M stage, and baseline lactate dehydrogenase (LDH). NR, not relevant.

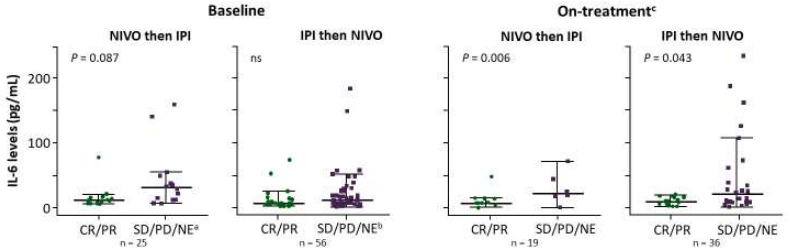
CheckMate 067: Association of Baseline IL-6 Levels With OS Across Treatment Arms



High IL-6 levels were associated with shorter OS

IL-6 LLOQ: 11 pg/mL.
HR adjusted for ECOG, *BRAF*, M stage, and baseline LDH.

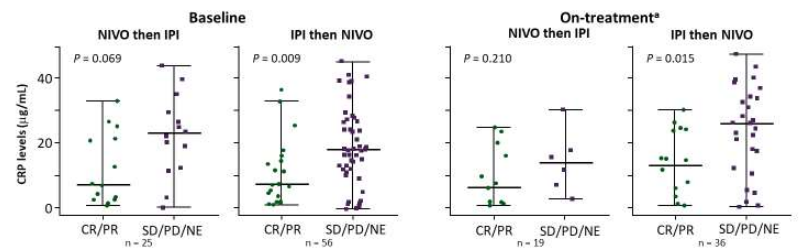
CheckMate 064: Association of Baseline and On-Treatment IL-6 Levels With BOR



Lower baseline and on-treatment IL-6 levels were observed in patients with CR/PR vs SD/PD/NE

Data include non-evaluable (NE) classified as non-responders if OS < 3 months. [a]n = 2, [b]n = 9. [c]On-treatment at week 13; switch in treatment occurred at week 13.
P values based on Wilcoxon rank sum test. CR, complete response; ns, not significant; PD, progressive disease; PR, partial response; SD, stable disease.

CheckMate 064: Association of Baseline and On-Treatment CRP Levels With BOR



Lower baseline and on-treatment CRP levels were observed in patients with CR/PR vs SD/PD/NE

Data include non-evaluable (NE) classified as non-responders if OS < 3 months. [a]On-treatment at week 13; switch in treatment occurred at week 13. *P* values based on Wilcoxon rank sum test.

Weber et al. ASCO 2019

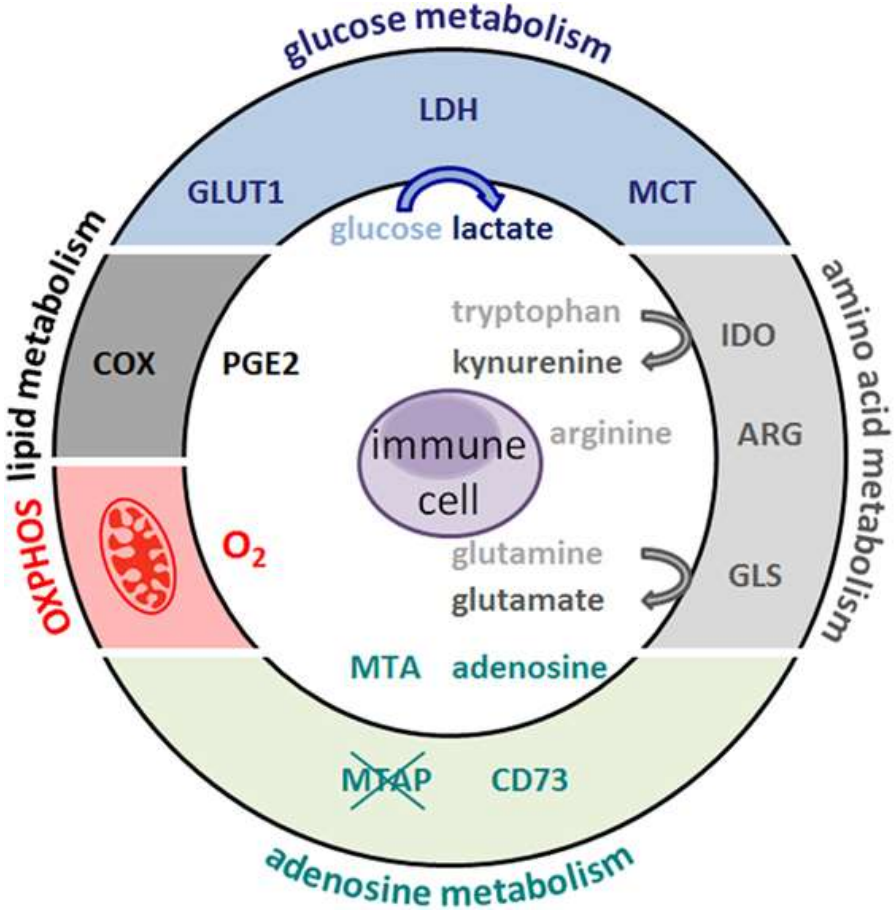
Phase II trial of IPI + NIVO + TOCILIZUMAB in melanoma

(ClinicalTrials.gov: NCT03999749)

- Simon design, two-stage study of "flipped dose" IPI + NIVO with IL-6R blocking antibody tocilizumab in first-line stage IV melanoma; 18 patients in stage I, 49 patients in stage II = 67 total patients
- IPI at 1 mg/kg and NIVO at 3 mg/kg X 4 doses then NIVO at 240 mg every 2 weeks X 12 weeks, then NIVO at 480 mg every 4 weeks up to 2 years; TOCI at 4 mg/kg every 6 weeks X 5 total up to week 24
- Primary endpoints: reduction in grades 3-4 irAEs to 25% or less, and/or increase ORR to 60% from 45% (seen in the Checkmate 511 trial)
- Secondary endpoints are PFS, duration of response, and correlative endpoints; so far 14 patients treated since February 2020; finish first stage by end of 2020, and finish second stage by end of 2021/early 2022

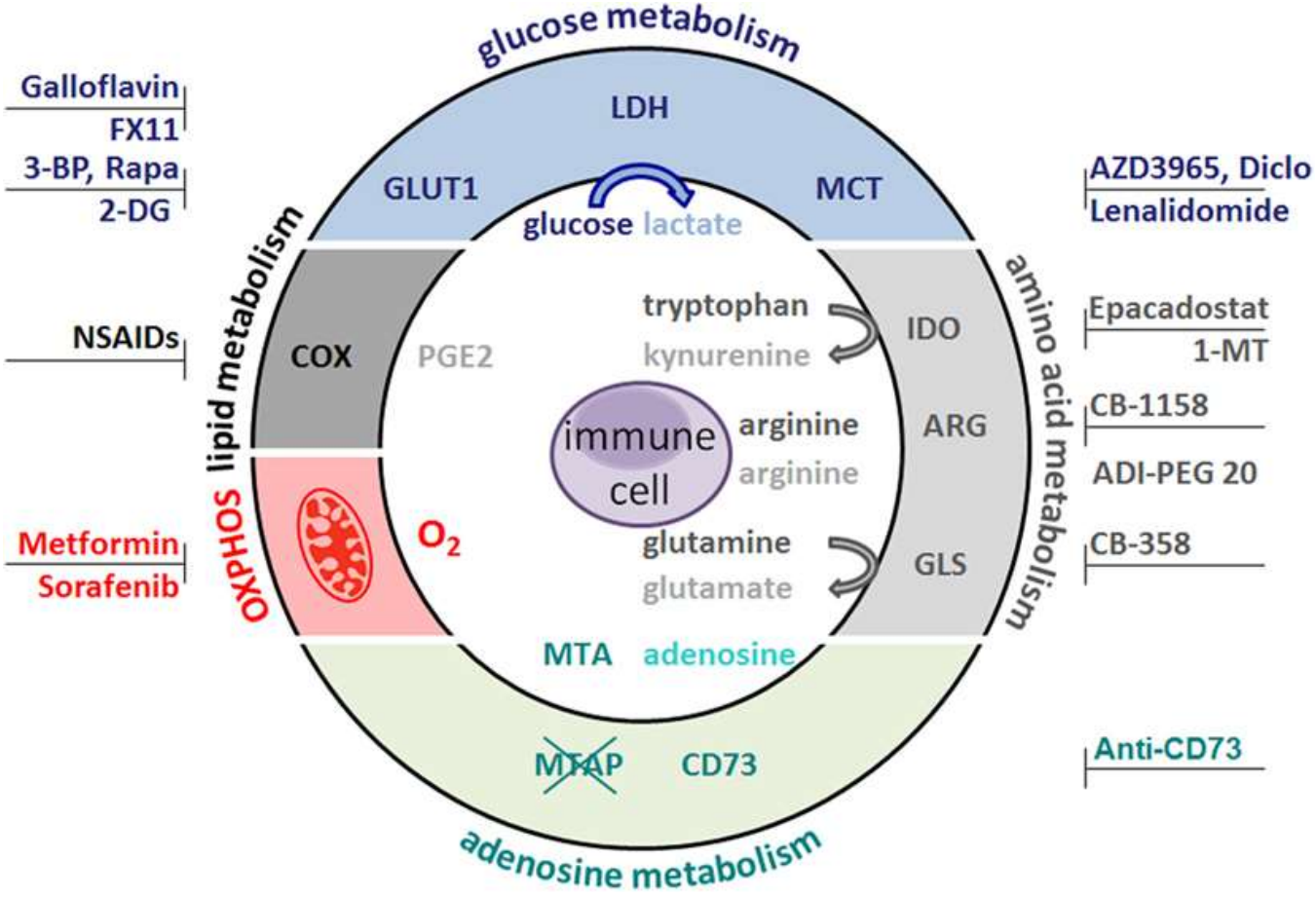
Courtesy of Jeff Weber

Metabolic Hallmarks of Tumor and Immune Cells in the Tumor Microenvironment



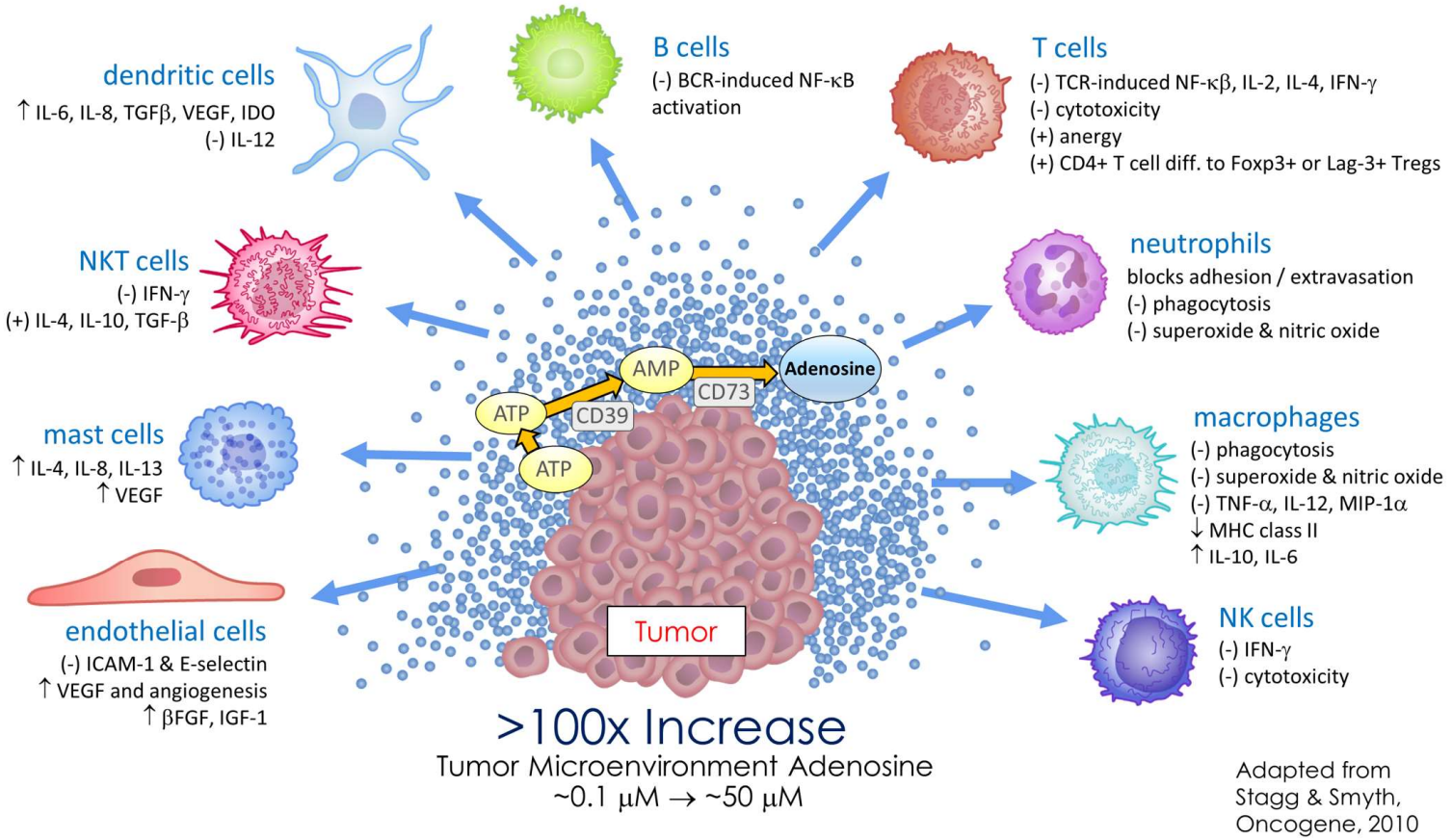
Renner K. et al. *Front. Immunol*. 2017

Metabolic Hallmarks of Tumor and Immune Cells in the Tumor Microenvironment



Renner K. et al. *Front. Immunol*. 2017

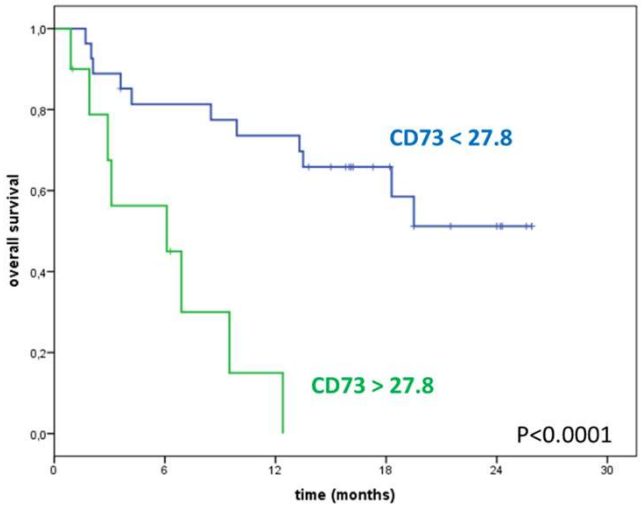
Adenosine: A Key Suppressor of Immune Cells in the Tumor Microenvironment



Extracted from Stagg J, Smyth MJ. *Oncogene*. 2010;29:5346-5358.

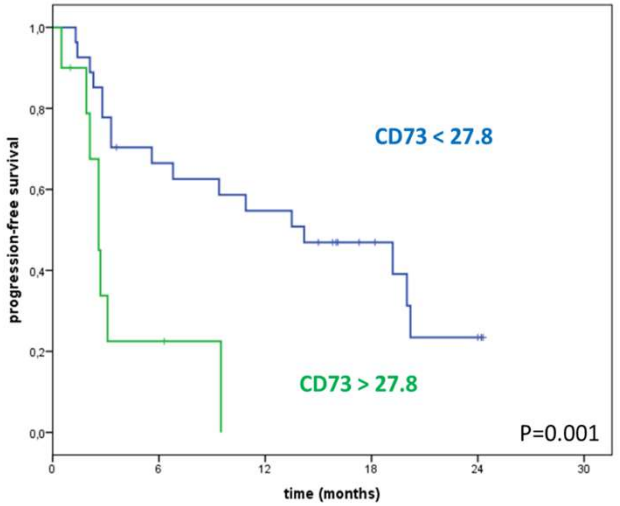
sCD73 baseline enzymatic activity and survival with anti-PD-1

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 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

Lillian L. Siu,[1] Howard Burris,[2] Dung T. Le,[3] Antoine Hollebecque,[4] Neeltje Steeghs,[5] Jean-Pierre Delord,[6] John Hilton,[7] Bryan Barnhart,[8] Emanuela Sega,[8] Kinjal Sanghavi,[8] Anke Klippel,[8] Cyrus Hedvat,[8] Ed Hilt,[8] Mark Donovan,[8] Adrianna Gipson,[8] Paul Basciano,[8] Jennifer Postelnek,[8] Yue Zhao,[8] Raymond P. Perez,[8] Richard D. Carvajal[9]

[1]Princess Margaret Cancer Centre, Toronto, ON, Canada; [2]Sarah Cannon, Nashville, TN; [3]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; [4]Institut de Cancérologie Gustave Roussy, Paris, France; [5]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [6]Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; [7]Ottawa Cancer Centre, Ottawa, ON, Canada; [8]Bristol-Myers Squibb, Princeton, NJ; [9]Columbia University Medical Center, New York, NY

CA013-004

BMS-986179 ± Nivolumab Safety Summary

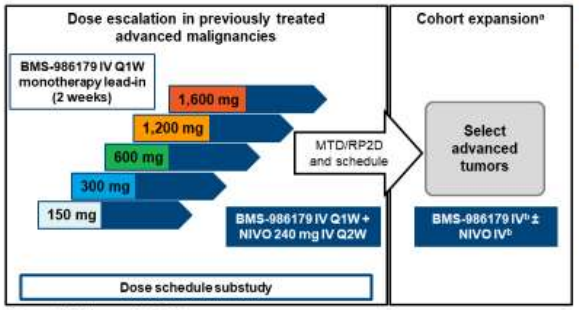
Treatment-related adverse events (TRAEs)	BMS-986179 Q1W		BMS-986179 Q1W + nivolumab 240 mg Q2W											
	Total (N = 89)		BMS-986179 150 mg (n = 12)		BMS-986179 300 mg (n = 11)		BMS-986179 600 mg (n = 12)		BMS-986179 1,200 mg (n = 7)		BMS-986179 1,600 mg (n = 10)		Total (N = 52)	
	Any, n (%)	Gr 3, n (%)	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[b,k]	7	2	5	3[b,k]	5	0	6	1[k,l]	30 (58)	8 (15)[k–n]
TRAEs in ≥ 5% of patients[a]														
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)

[a]Other Grade 3 TRAEs included: [b]adrenal insufficiency and increased transaminases (150 mg, n = 1 each), [k]autoimmune hepatitis and hepatitis (600 mg, n = 1), and [l]pancreatitis (1,600 mg, n = 1); [n]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

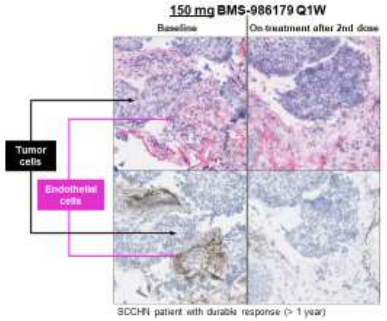
[a]Expansion cohorts are ongoing; [b]BMS-986179 and NIVO doses and schedules to be based on data from escalation phase and substudy

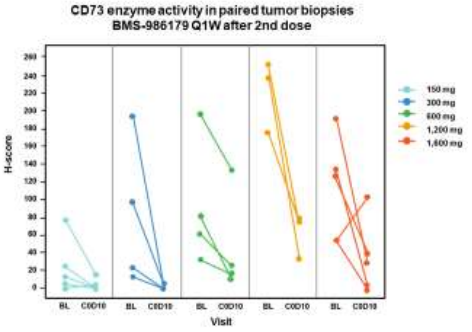
IV = intravenous; MTD = maximum tolerated dose; NIVO = nivolumab; Q1W = every week; Q2W = every 2 weeks; RP2D = recommended phase 2 dose

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

Michael Overman,[1] Patricia LoRusso,[2] John Strickler,[3] Sandip Patel,[4] Stephen Clarke,[5] Anne Noonan,[6] Thiru Prasanna,[7] Manik Amin,[8] John Nemunaitis,[9] Jayesh Desai,[10] Kenneth O'Byrne,[11] Thomas George,[12] Judson Englert,[13] Dewei She,[13] Zachary A. Cooper,[13] Yuling Wu,[13] Anis Khan,[13] Rakesh Kumar,[13] Johanna Bendell[14]

[1]MD Anderson Cancer Center, Houston, TX; [2]Yale University Cancer Center, New Haven, Connecticut; [3]Duke Comprehensive Cancer Center-Duke Cancer Institute Duke University Health System, Durham, NC; [4]Moores Cancer Center, University of California San Diego, La Jolla, CA; [5]Royal North Shore Hospital, St Leonards, NSW, Australia; [6]Arthur G. James Cancer Hospital and Solove Research Institute, Ohio State University Comprehensive Cancer Center, Columbus, OH; [7]Chris O'Brien Lifehouse, Camperdown NSW, Australia; [8]Washington University School of Medicine, St. Louis, MO; [9]University of Toledo College of Medicine; Toledo, Ohio; [10]Royal Melbourne Hospital, Parkville Victoria, Australia; [11]Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; [12]University of Florida, Health Cancer Center, Gainesville, FL; [13]MedImmune, Gaithersburg, MD; [14]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN

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'-nucleotidase, 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.

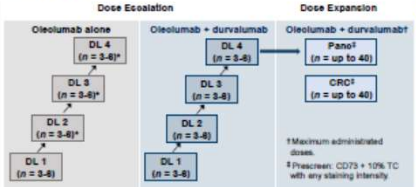
Primary endpoint

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

Patient Characteristic	Oleclumab monotherapy: Dose escalation phase DL 1 n = 3	DL 2 n = 11	DL 3 n = 12	DL 4 n = 16	Oleclumab + durvalumab therapy: Dose escalation phase DL 1 n = 7	DL 2 n = 3	DL 3 n = 4	DL 4 n = 18	Dose expansion phase 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)	56.0 (32–71)	57.0 (46–60)	57.0 (49–66)	52.5 (44–64)	63.5 (32–77)	53.0 (32–60)
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.

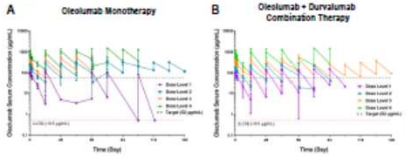
Table 3: Treatment-related AEs occurring in >5% of patients in any arm in dose expansion oleclumab + durvalumab

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)

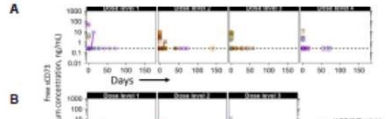
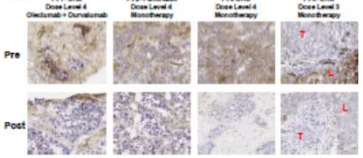
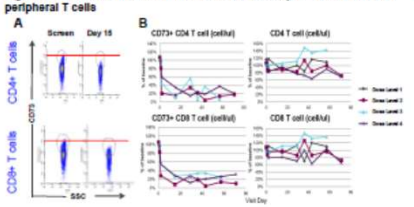


Figure 4: Oleclumab treatment decreases CD73 enzymatic activity in tumor cells



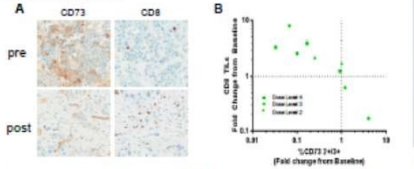
Decrease in CD73 enzymatic activity 20 days post treatment initiation in 3 of 4 patients as demonstrated by an in situ enzymatic assay (Wachstein and Meisel method). Pt 4 had no tumor cell CD73 expression or enzymatic activity at baseline but had CD73 enzymatic activity in adjacent liver pre-treatment 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

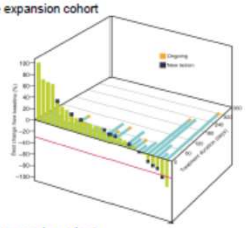


Representative images of CD73 and CD8 IHC staining (A) observed in a pancreatic cancer patient tumor at pre-treatment and post-treatment (20 days) after Dose Level 4 of oleclumab monotherapy. Treatment with oleclumab alone decreased tumoral CD73 expression in 5/9 patients who expressed >5% 2+/3+ CD73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

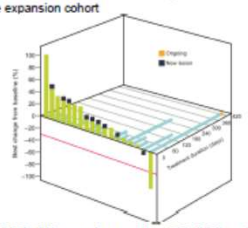
Clinical Activity

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.

References

1.Linden J, Cekic C. *Arterioscler Thromb Vasc Biol.* 2012; 32(9): 2097-103.
2.Geoghegan JC, et al. 2016. mAbs;8(3):464-67.
3.Hay CM, et al. Oncoimmunology. 2016. 5(8): e1208875.

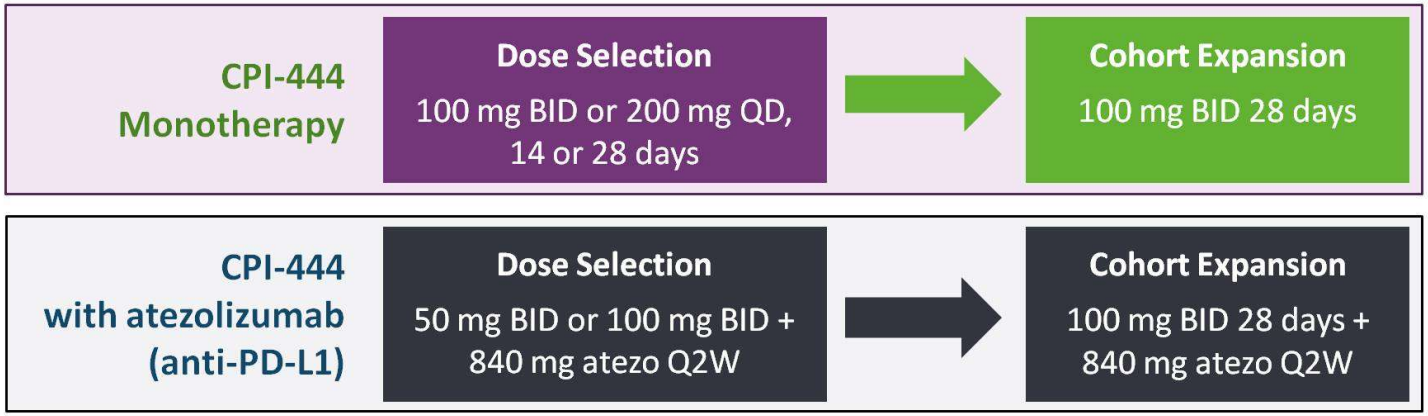
This study was supported by MedImmune, the global biologics R&D arm of AstraZeneca.

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

Overman et al ASCO 2018

Phase 1/1b Clinical Study with Oral Drug CPI-444

Expansion cohorts: renal cell and non-small cell lung cancer

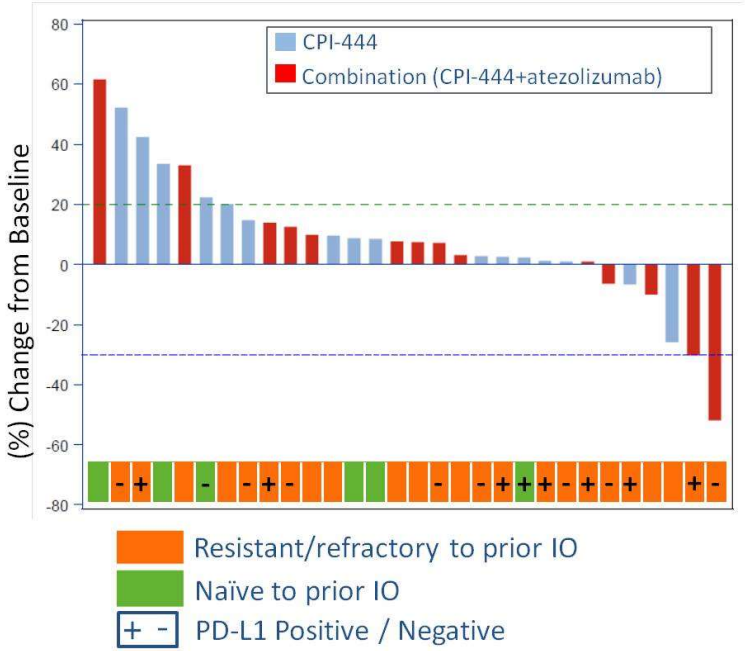


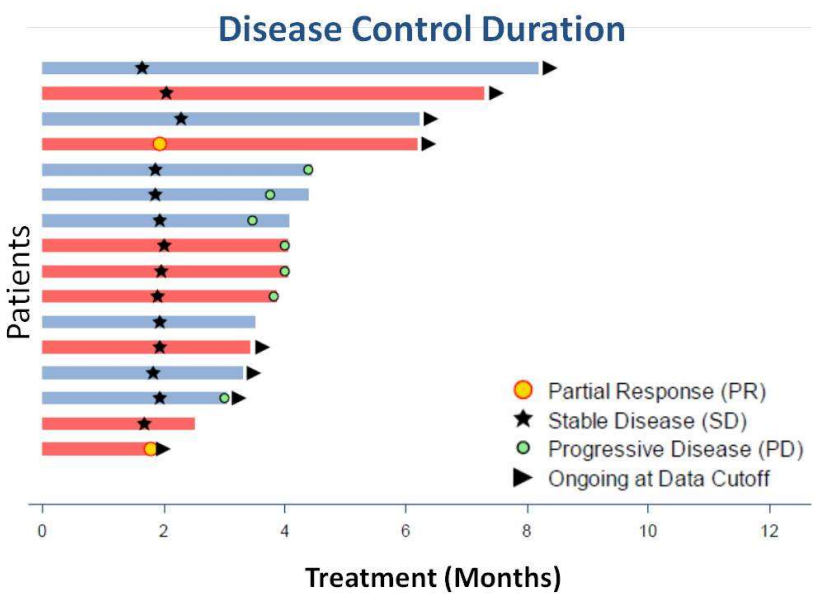
Eligibility

- Tumor types: RCC, NSCLC, Melanoma, TNBC, Others
- Prior anti PD-(L)1 allowed
  - Resistant: SD or better > 3 months of treatment
  - Refractory: progression within 3 months
- Must have progressive disease on prior therapy
- No selection for PD-L1 expression

Phase 1/1b Trial with CPI-444: Disease Control in NSCLC

Partial responses can be seen in anti-PD-1 progressors

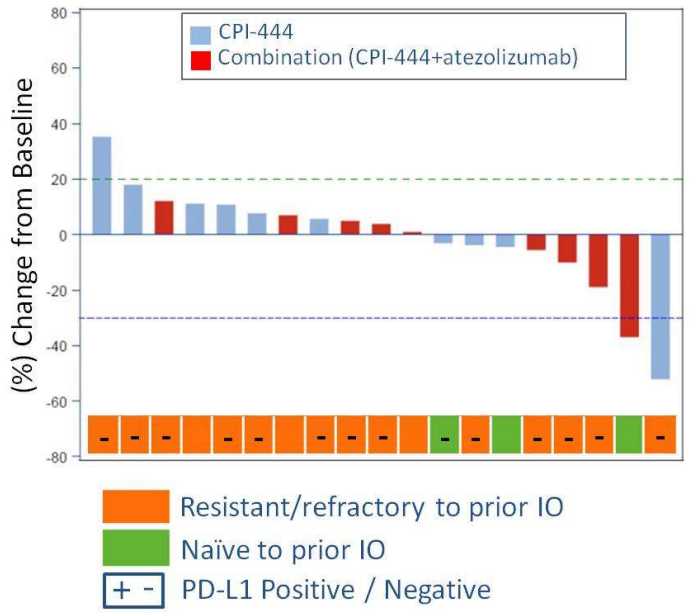


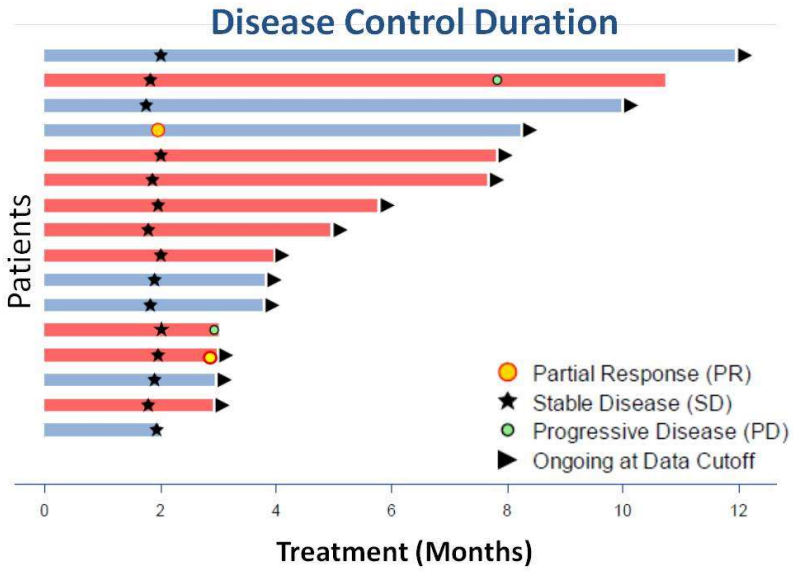


Presented By Lawrence Fong at 2017 ASCO Annual Meeting

Phase 1/1b Trial with CPI-444: Disease Control in Renal Cell Cancer

Partial responses can be seen in an anti-PD-1 progressing and naïve patients



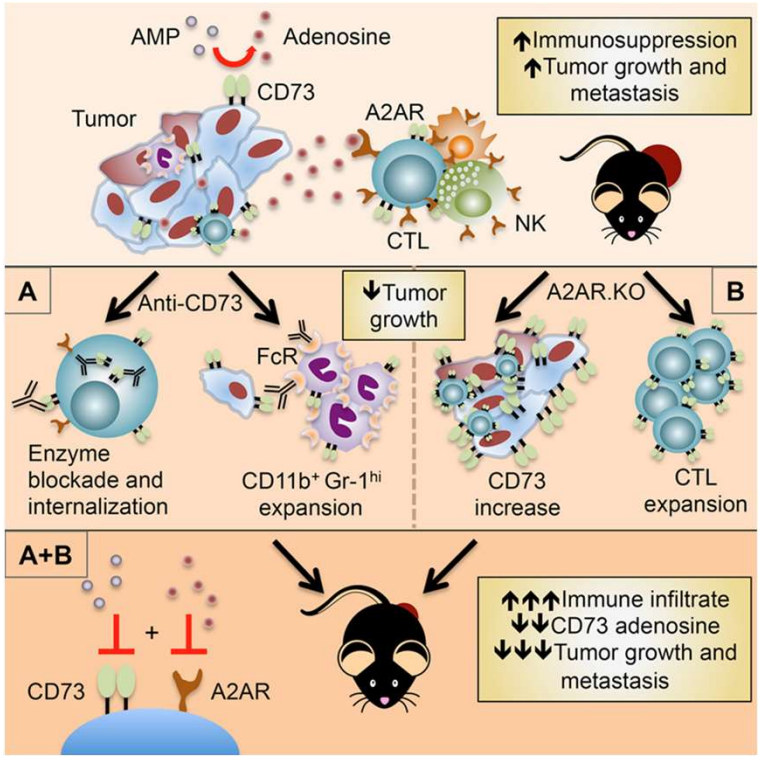


Presented By Lawrence Fong at 2017 ASCO Annual Meeting

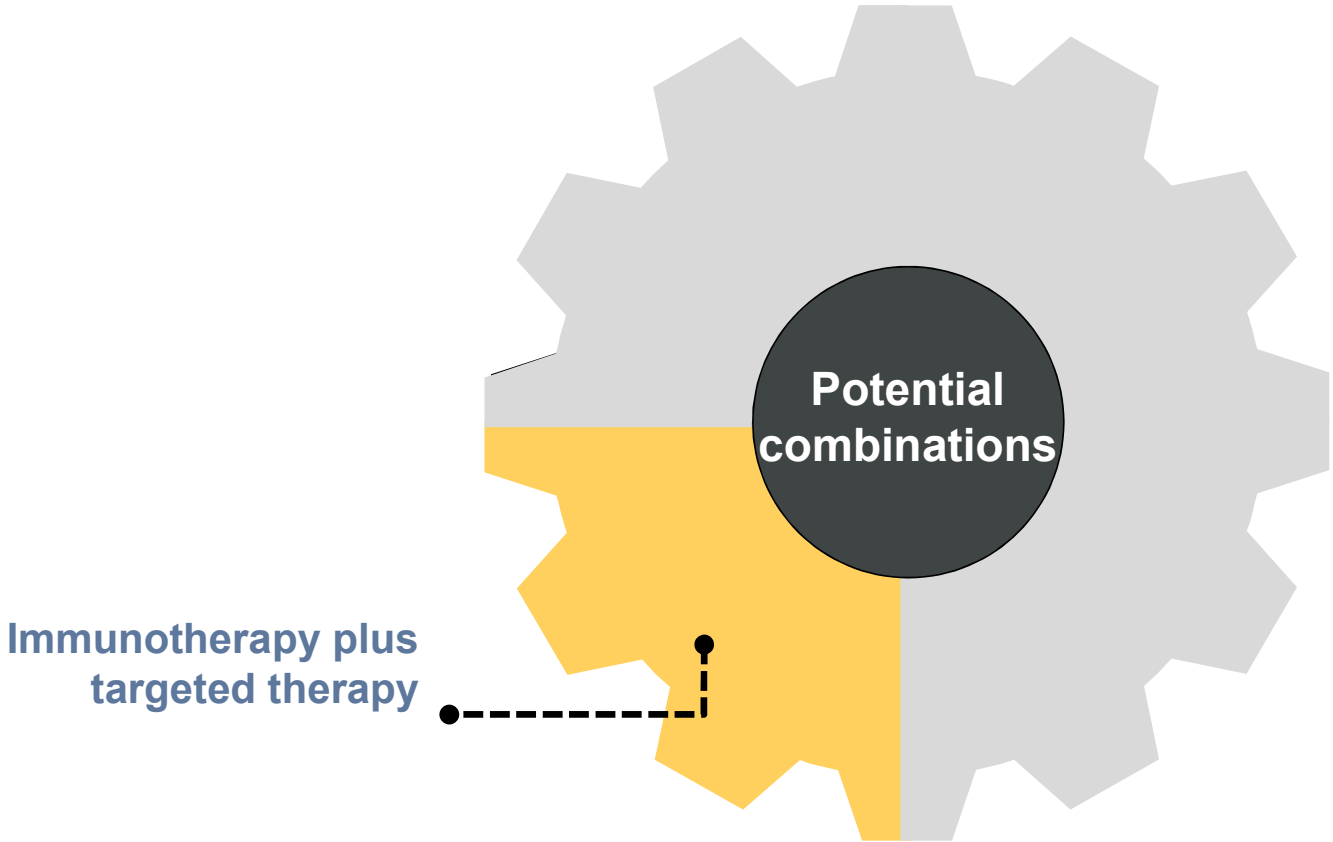
Cancer Cell
Article

Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses

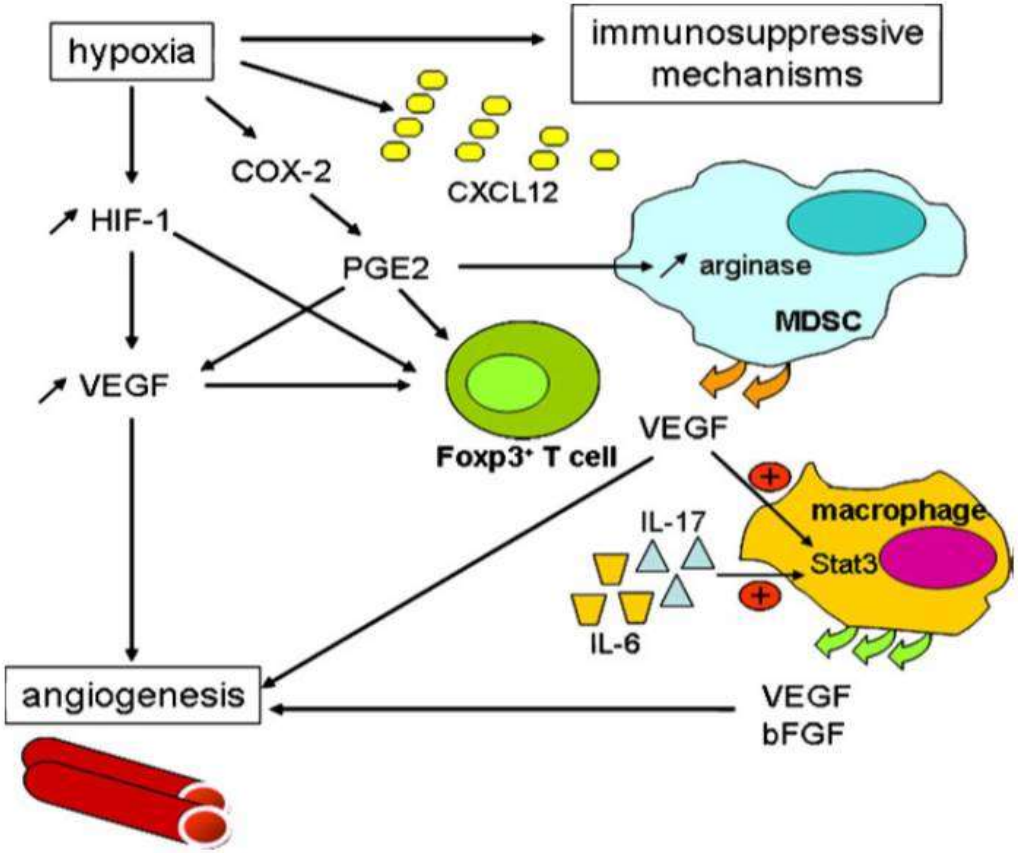
Arabella Young,[1,2] Shin Foong Ngiow,[1,2] Deborah S. Barkauskas,[1] Erin Sult,[3] Carl Hay,[3] Stephen J. Blake,[4] Qihui Huang,[3] Jing Liu,[1,2,4] Kazuyoshi Takeda,[5] Michele W.L. Teng,[2,4] Kris Sachsenmeier,[3] and Mark J. Smyth[1,2,6,*]



Potential combination strategies for the treatment of cancer



Immune Effects of VEGF



Tartour et al., *Cancer Metastasis Rev*, 2011

Research Article

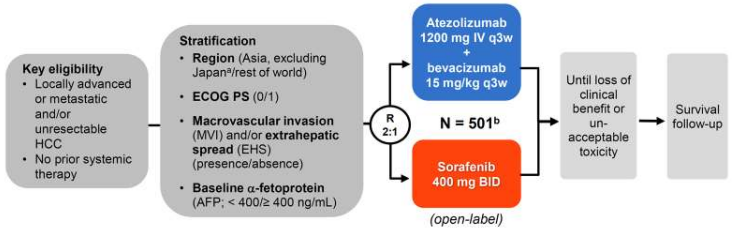
Cancer Immunology Research

Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi[1], Donald Lawrence[4], Cecilia Lezcano[10], Xinqi Wu[1], Jun Zhou[1], Tetsuro Sasada[1], Wanyong Zeng[1], Anita Giobbie-Hurder[2], Michael B. Atkins[11], Nageatte Ibrahim[1], Philip Friedlander[12], Keith T. Flaherty[4], George F. Murphy[5], Scott Rodig[5], Elsa F. Velazquez[7,9], Martin C. Mihm Jr[5], Sara Russell[6], Pamela J. DiPiro[3], Jeffrey T. Yap[3], Nikhil Ramaiya[3], Annick D. Van den Abbeele[3], Maria Gargano[1], and David McDermott[8]

Hodi et al. CIR 2014

IMbrave150 study design

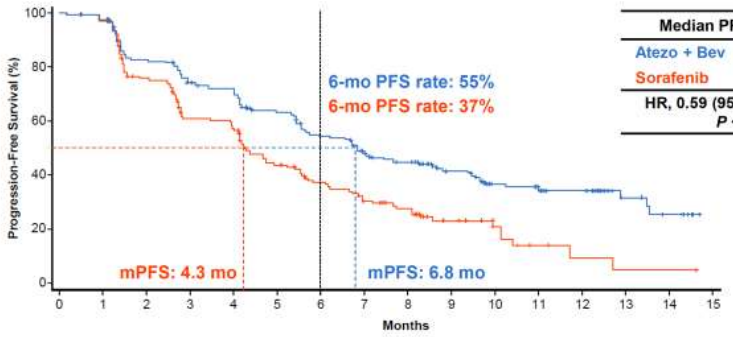


Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

Confirmed PFS[a]: co-primary endpoint

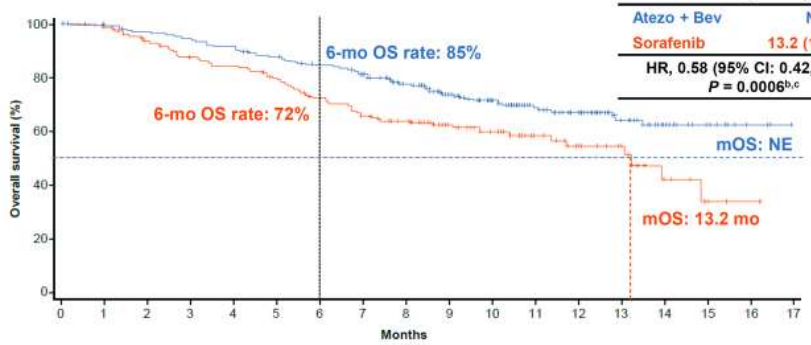


Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d]	
P < 0.0001[d]	

No. at risk																
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

OS: co-primary endpoint



Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	

No. at risk																
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

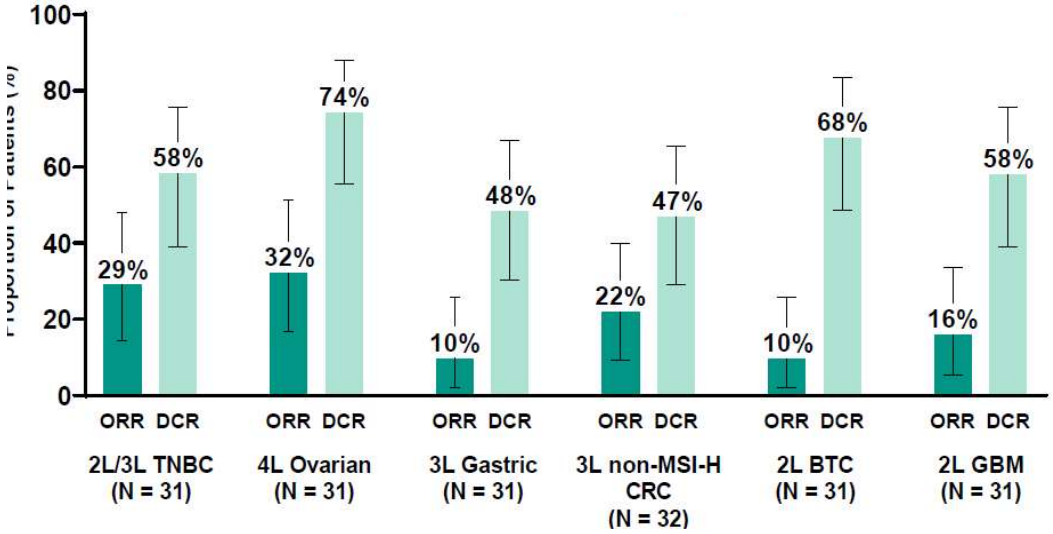
NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Ann-Lii et al. ESMO Asia 2019

LEAP-005: Phase 2 Study of Lenvatinib Plus Pembrolizumab in Patients With Previously Treated Advanced Solid Tumors

Zarnie Lwin,[1] Carlos Gomez-Roca,[2] Esma Saada-Bouzid,[3] Eduardo Yanez,[4] Federico Longo Muñoz,[5] Seock-Ah Im,[6] Eduardo Castanon,[7] Hélène Senellart,[8] Donna Graham,[9] Martin Voss,[10] Mark Doherty,[11] Juanita Lopez,[12] Razi Ghori,[13] Peter Kubiak,[14] Fan Jin,[13] Kevin Norwood,[13] Hyun Cheol Chung[15]

[1]Department of Medical Oncology, Royal Brisbane and Women's Hospital, University of Queensland, Australia; [2]Institut Claudius Regaud, Toulouse, France; [3]Department of Medical Oncology, Centre de Lutte Contre le Cancer Antoine Lacassagne, Nice, France; [4]Oncology-Hematology Unit, Department of Internal Medicine, School of Medicine, Universidad de la Frontera, Temuco, Chile; [5]Hospital Universitario Ramón y Cajal, IRYCIS, CIBERONC, Madrid, Spain; [6]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [7]Clínica Universidad de Navarra, Pamplona, Spain; [8]Institut de Cancérologie de l'Ouest, Centre René Gauducheau ICO, Saint-Herblain, France; [9]The Christie NHS Foundation Trust, Manchester, UK; [10]Universitaetsklinikum Frankfurt, Frankfurt, Germany; [11]Department of Medical Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [12]The Royal Marsden Foundation Trust and the Institute of Cancer Research, London, UK; [13]Merck & Co., Inc., Kenilworth, NJ, USA; [14]Eisai Inc., Woodcliff Lake, NJ, USA; [15]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea



Lwin et al. ESMO 2020

Lenvatinib Plus Pembrolizumab in Patients With Advanced Melanoma Previously Exposed to Anti–PD-1/Anti–PD-L1 Agents: Phase 2 LEAP-004 Study

A. Arance[1]; P. A. Ascierto[2]; M. S. Carlino[3]; A. Daud[4]; A. M. M. Eggermont[5]; A. Hauschild[6]; H. Kluger[7]; M. H. Taylor[8]; A. Smith[9]; K. Chen[10]; C. Krepler[10]; S. J. Diede[10]; S. O'Day[11]

[1]Hospital Clinic de Barcelona, Barcelona, Spain; [2]Istituto Nazionale Tumori IRCCS [3]Fondazione G. Pascale," Naples, Italy; [3]Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, NSW, Australia; [4]University of California, San Francisco, San Francisco, CA, USA; [5]Gustave Roussy, Cancer Campus, Grand Paris and Université Paris-Saclay, Villejuif, France; [6]University Hospital Schleswig-Holstein, Kiel, Germany; [7]Yale Cancer Center, Yale New Haven Hospital, New Haven, CT, USA; [8]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [9]Eisai Ltd., Hatfield, United Kingdom; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]John Wayne Cancer Institute, Santa Monica, CA, USA

Patients

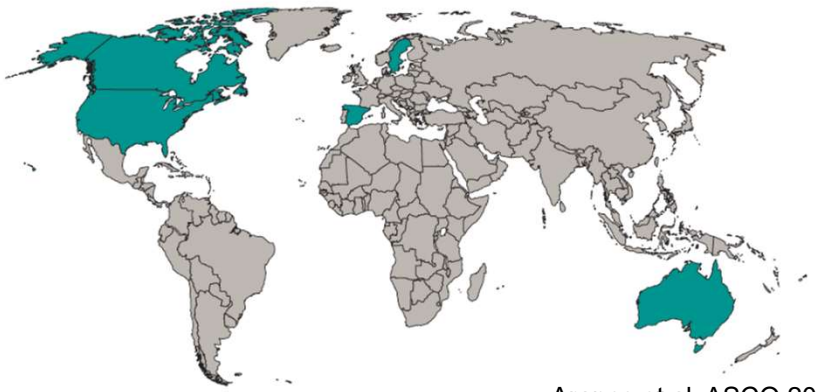
- Unresectable stage III or IV melanoma[a]
  - All comers with regard to PD-L1 and *BRAF* status
- Confirmed progression[b] with ≥2 doses of anti–PD-1/anti–PD-L1 monotherapy or combination therapy
- ECOG PS 0 or 1

→ **Pembrolizumab 200 mg IV Q3W + Lenvatinib 20 mg PO QD Up to 35 cycles**

→ **Lenvatinib 20 mg PO QD**

→ **Treatment to continue until**
- Disease progression or unacceptable toxicity

→ **Posttreatment follow-up to assess**
- Safety
- Disease
- Survival status



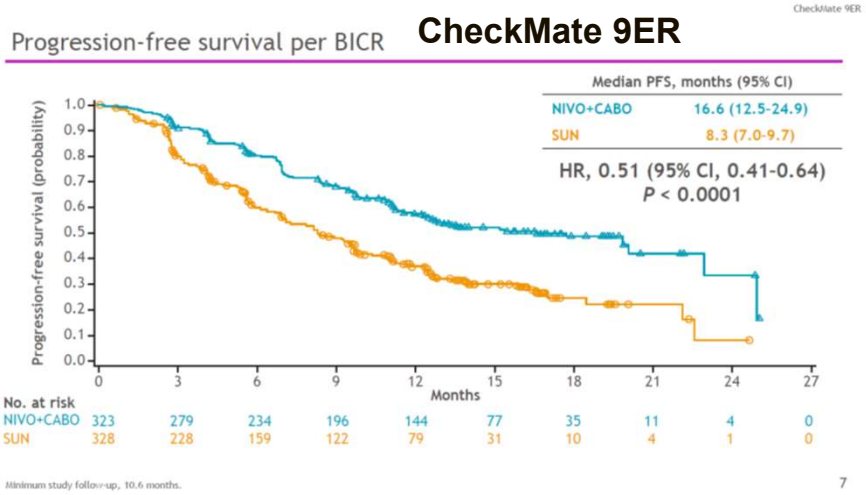
Arance et al. ASCO 2019

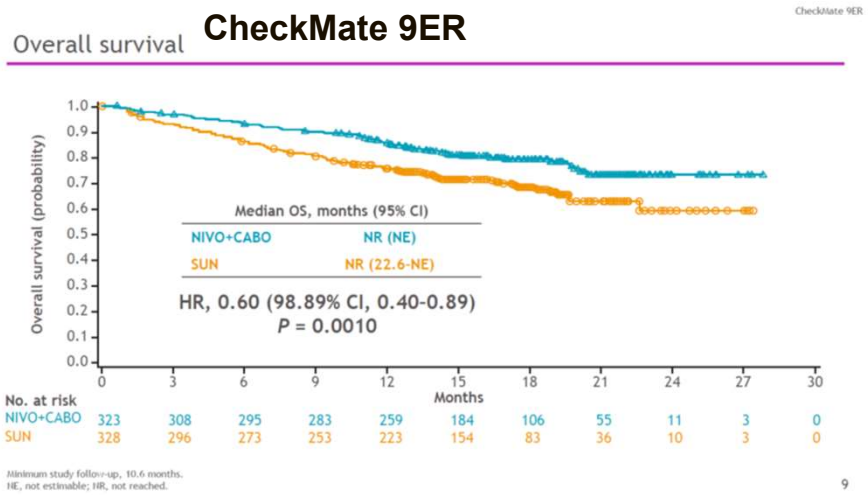
BICR-Confirmed Response by PD on Prior Anti–CTLA-4 + Anti–PD-(L)1

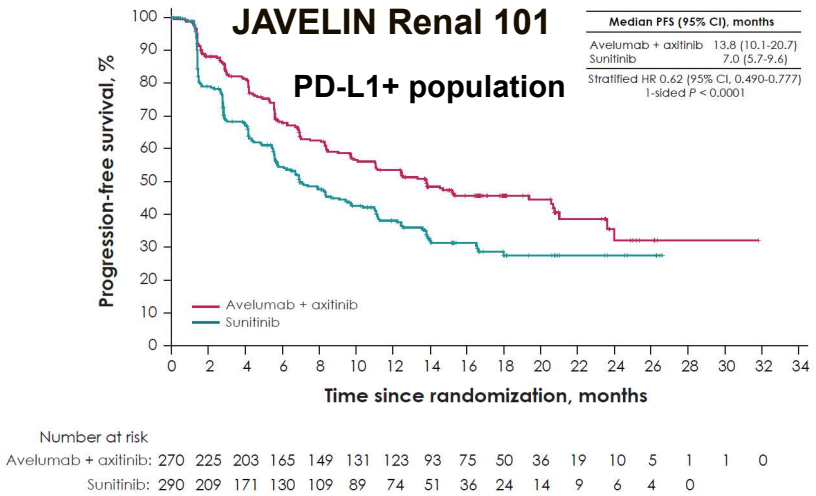
	Total Population N = 103	PD on Prior Anti–CTLA-4 + Anti–PD-(L)1 Yes n = 29	PD on Prior Anti–CTLA-4 + Anti–PD-(L)1 No n = 74
ORR, % (95% CI)	**21.4% (13.9-30.5)**	**31.0% (15.3-50.8)**	**17.6% (9.7-28.2)**
DCR, % (95% CI)	65.0% (55.0-74.2)	62.1% (42.3-79.3)	66.2% (54.3-76.8)
Best overall response, n (%)			
CR	2 (1.9%)	1 (3.4%)	1 (1.4%)
PR	20 (19.4%)	8 (27.6%)	12 (16.2%)
SD	45 (43.7%)	9 (31.0%)	36 (48.6%)
PD	31 (30.1%)	10 (34.5%)	21 (28.4%)
Not assessed[a]	5 (4.9%)	1 (3.4%)	4 (5.4%)

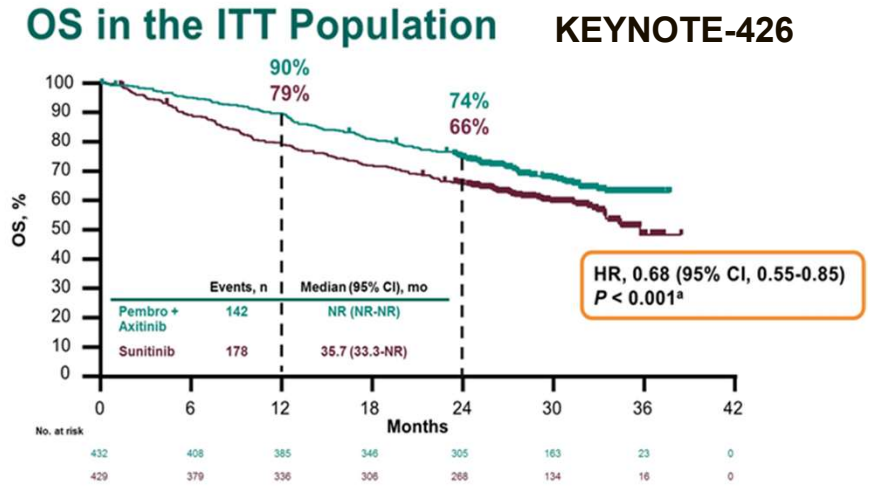
[a]Patients who had no post-baseline imaging assessments.
Data cutoff date: June 10, 2020.

TT plus I-O in RCC



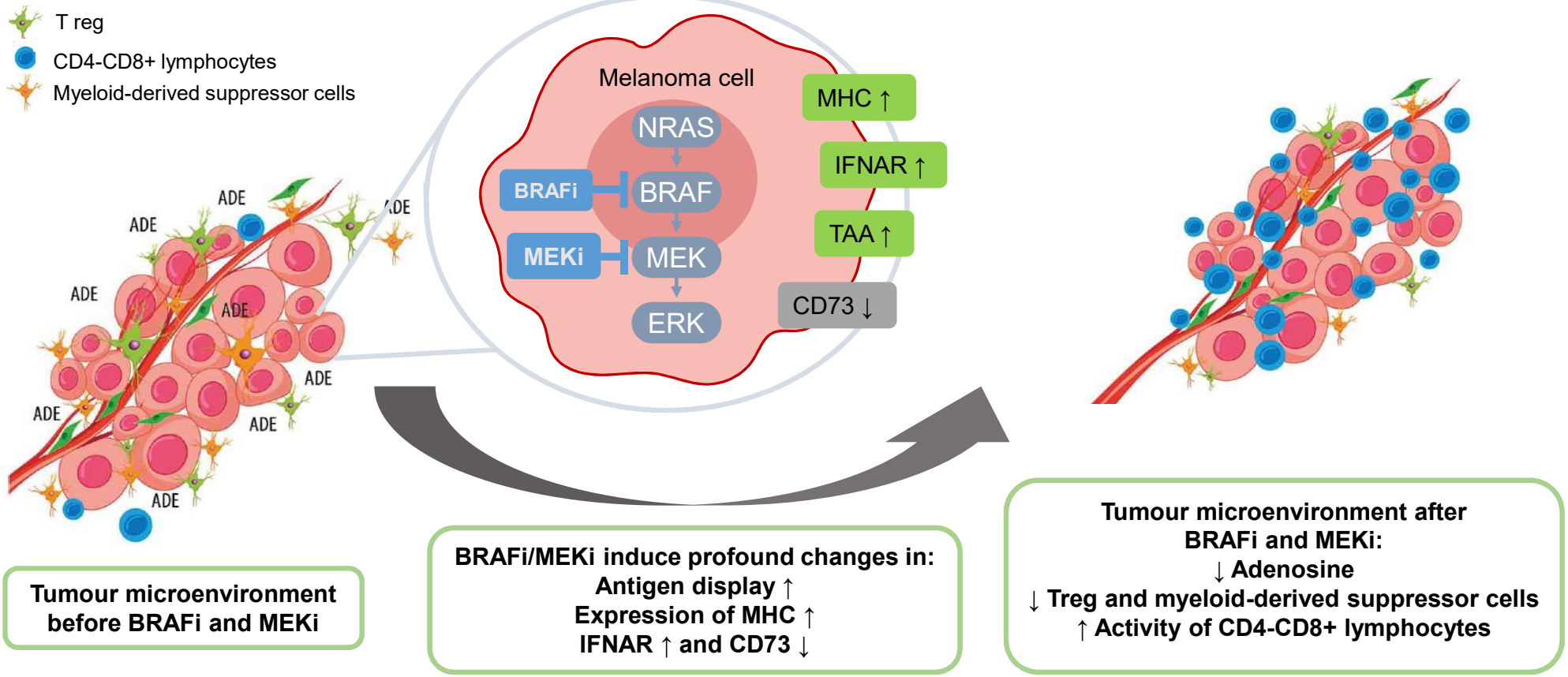






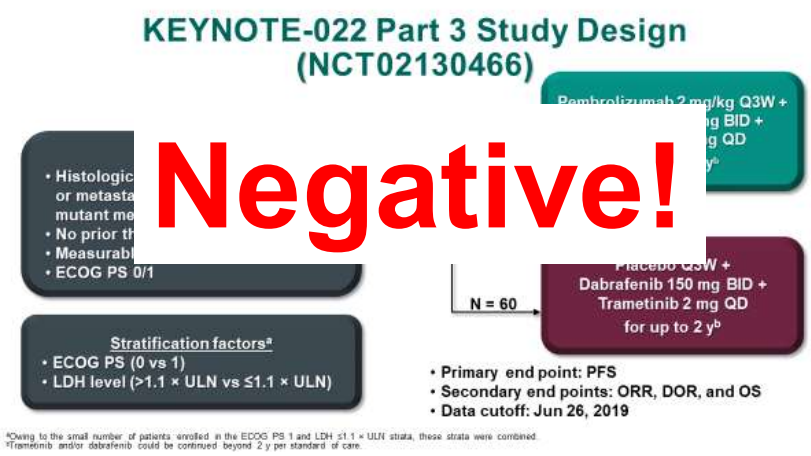
Choueri et al ESMO 2020
Choueri et al Ann Oncol 2020
Elizabeth Plimack, Keynote-426, ASCO 2020

BRAF/MEK inhibitors as immunomodulating agents



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



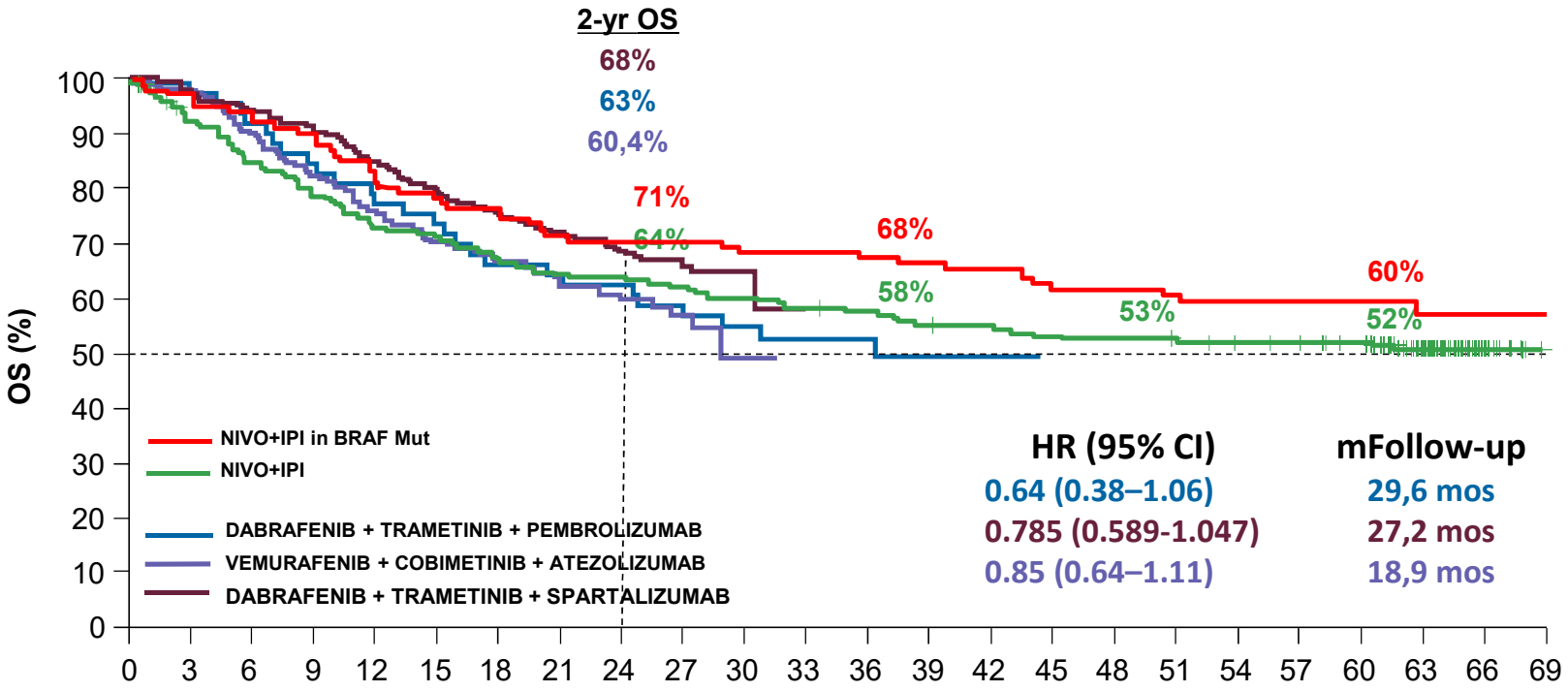
Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With *BRAF*^{V600} Mutation–Positive Advanced Melanoma: Primary 150 Trial

Positive!

Grant A. McA, M.D., Ph.D.,[3] Caroline Robert, go Pereira, M.D.,[7] Thon I.D.,[10] Georgy Moisee nne Uyei, M.D.,[12] Virginia McNally, Ph.D.,[13] Ralf Gutzmer, M.D.,[14] Paolo Ascierto, M.D.[15]

[1]Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russia; [3]First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, Greece; [4]Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; [5]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [6]Department of Chemotherapy and Innovative Technologies, N. N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russia; [7]Hospital das Clínicas, Porto Alegre, Brazil; [8]University Hospital Tübingen, Tübingen, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]N. N. Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; [11]St. Petersburg Oncology Hospital, St. Petersburg, Russia; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Roche Products Ltd., Welwyn Garden City, UK.; [14]Haut-Tumour-Zentrum Hannover (HTZH), Klinik für Dermatologie, Allergologie und Venerologie, Medizinische Hochschule Hannover (MHH), Hannover, Germany; [15]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy.

OS from KEYNOTE-022, IMspire 150 and Combi-I (Triplet arms) and …



Larkin et al. NEJM 2019
Ferrucci et al. SMR 2019
McArthur et al. AACR 2020
Nathan et al. ESMO 2020


BP
60222

Thank You!

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