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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

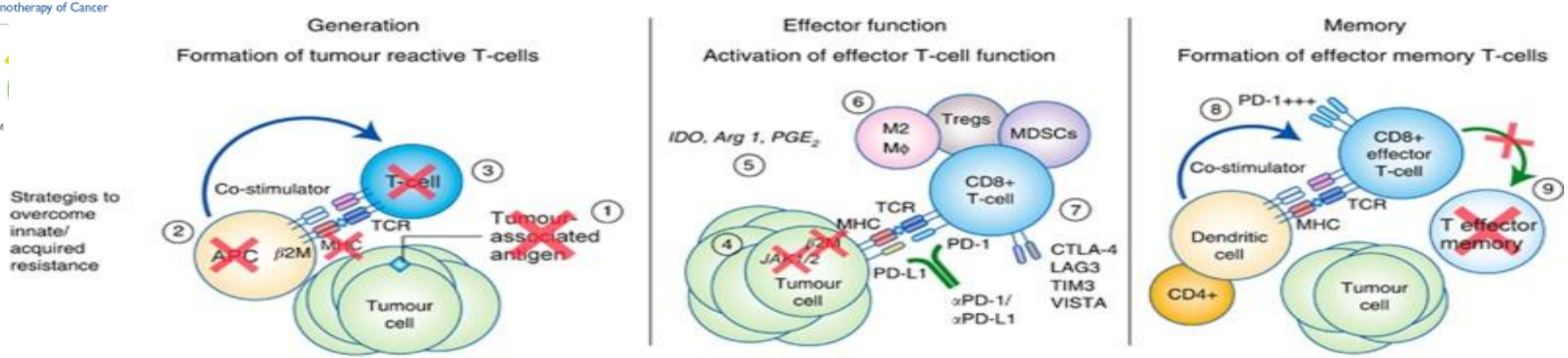
- **Research Support (Clinical Trials):**
  - Millennium, Merck/Celgene, BMS/Lilly
- **Advisory Board/Consultant:**
  - BMS, Lilly, Genentech, Celgene, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Cantargia AB, Amgen, Abbvie, Axiom, PharmaMar, Takeda, Huya Bio, GLG, Daiichi
- **Data and Safety Monitoring Board:**
  - University of Pennsylvania, CAR T Program
  - Takeda
- **Employment:**
  - Fox Chase Cancer Center
- I will discuss non-FDA Approved drugs and combinations.

Resistance to IO

- Primary Resistance
  - No response to IO

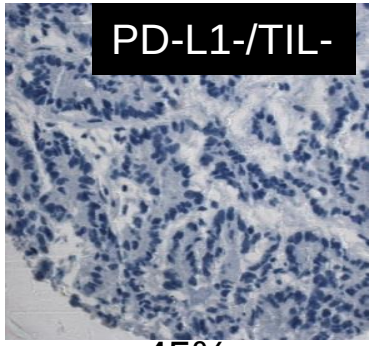
- Acquired Resistance
  - Some response followed by progression
    - Early progression
    - Late progression

Klapper et al. Cancer 2008

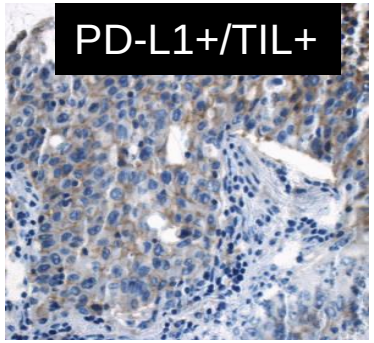


ICI combination	Examples	Potential mechanism(s)
Single/dual ICI therapy	Anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-TIM3, anti-LAG3	(7) Alternate immune checkpoints (8) Severe T-cell exhaustion
ICI + immune stimulating agents	Anti-OX40, anti-CD137/4-1BB, anti-CD40, anti-ICOS, oncolytic Viruses, TLR agonists, vaccines, NK cell activation (anti-KIR)	(1) Lack of sufficient or suitable neo-antigens (2) Impaired processing or presentation of tumour antigens (3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (7) Alternate immune checkpoints
ICI + metabolic inhibitors	IDO inhibitors, adenosine receptor (A2AR) inhibitors	(5) Metabolic/inflammatory mediators (6) Immune suppressive cells
ICI + targeted therapies	BRAF + MEK inhibitors, VEGF inhibitors, EGFR inhibitors, PARP inhibitors, mTOR inhibitors	(3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (7) Alternate immune checkpoints
ICI + epigenetic modifiers	Histone deacetylase inhibitors, hypomethylating agents (e.g., DNA methytransferase inhibitors)	(3) Impaired intratumoural immune infiltration (4) Impaired IFNγ signalling (9) T-cell epigenetic changes
ICI + chemotherapy	Paclitaxel, dacarbazine, carboplatin/paclitaxel, carboplatin/ gemcitabine	(1) Lack of sufficient or suitable neo-antigens
ICI + radiation	Hypofractionated radiation, stereotactic body radiation	(1) Lack of sufficient or suitable neo-antigens

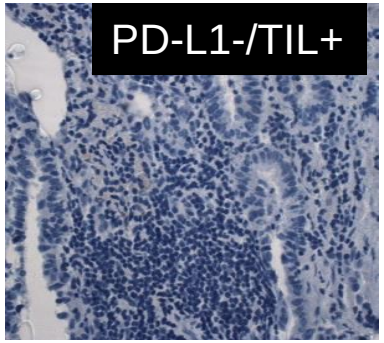
Categories of Tumors Based on Staining for PD-L1 and TILs



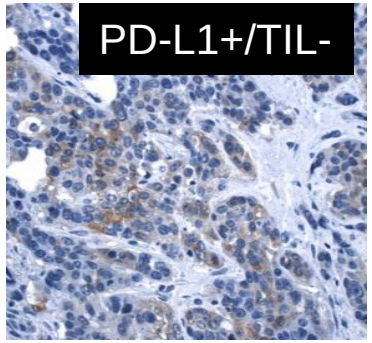
45%
Type I



17%
Type II



26%
Type III



12%
Type IV

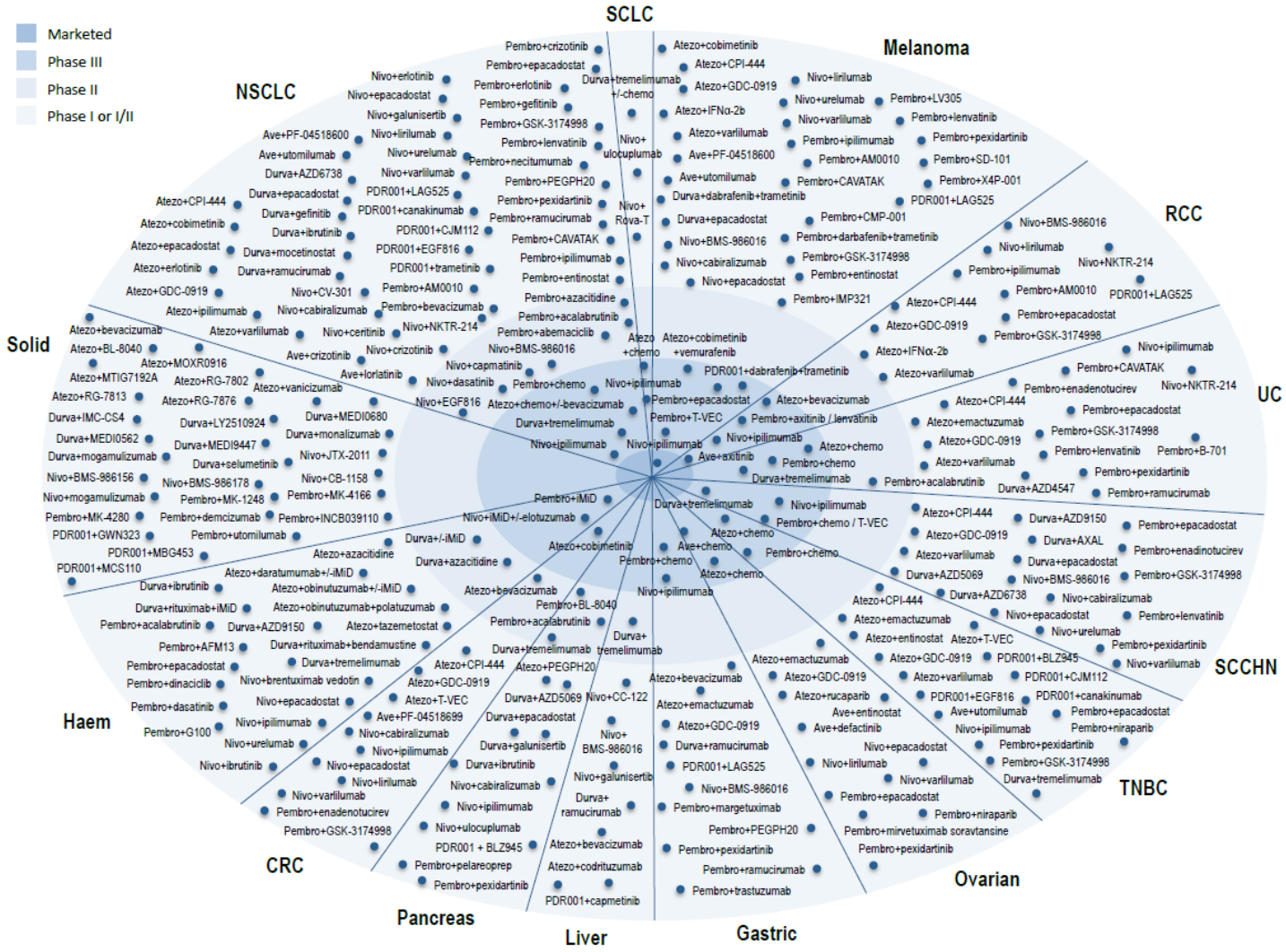
Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy

Subgroup		Type	Tumor Distribution	Possible Resistance Mechanism(s)	Analysis
B7-H1	TIL				
-	-	I	45%	Poor priming of general T cell responses	Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells
				Lack of inflammatory cell recruitment	Chemokine expression in biopsy or FFPE samples
+	+	II	17%	Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways	CD80 expression on TILs, expression of alternate suppressive pathways in TME
-	+	III	26%	Alternate immune suppressive pathways	Expression of select molecules in pathways with roles in evasion of NSCLC immunity
+	-	IV	12%	Intrinsic induction of B7-H1 by oncogenes	Expression of molecules triggering aberrant signaling events

Velcheti et al, 2014.

Clinical Trials

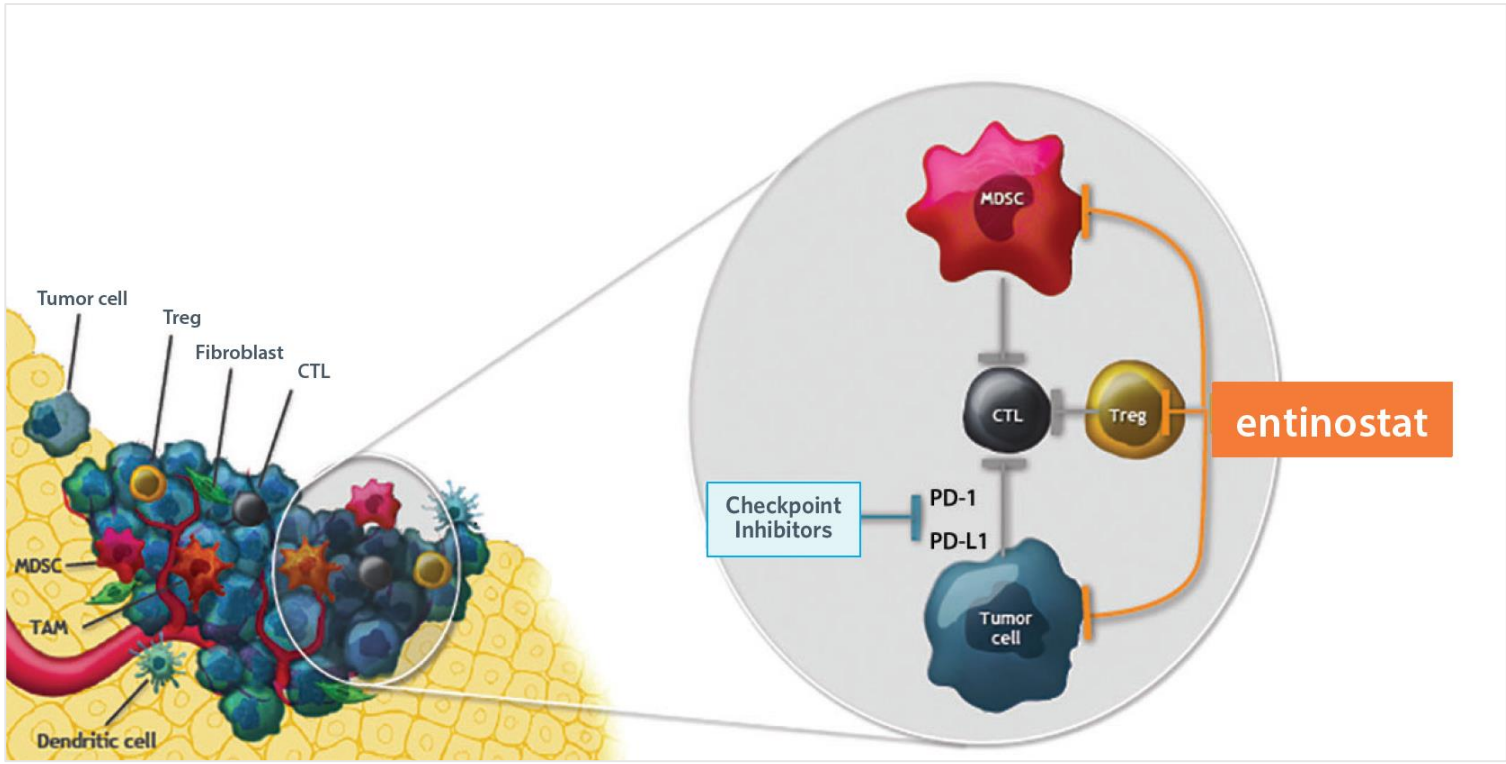
No Phase III Results Yet.



Chen & Mellman, Nature, 2017

Treatment options are limited for patients with NSCLC whose disease has progressed on anti-PD-(L)1 therapy[1]

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor[2]
- ENT leads to downregulation of immunosuppressive cell types in the tumor microenvironment[2]
- Synergy with anti-PD1 inhibition in preclinical models[2]
- Promising activity shown in combination with pembrolizumab in patients with melanoma and lung cancer[3,4]

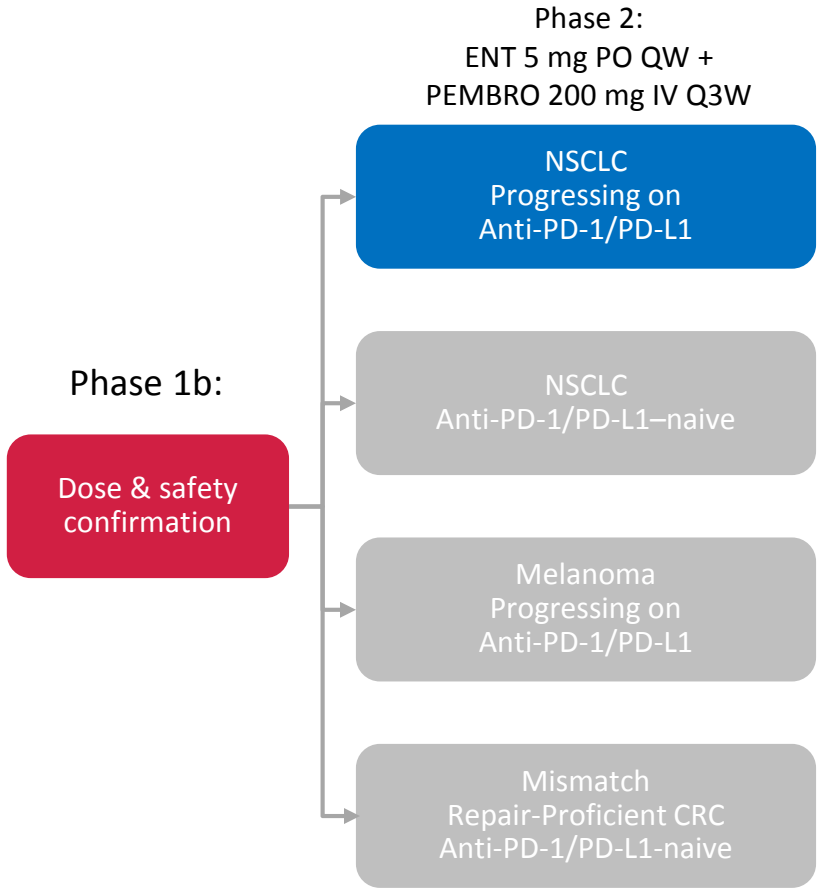


M. Hellman, WCLC 2018

NSCLC, non-small cell lung cancer.

1. Zimmer L, et al. *Eur J Cancer*. 2017;75:47-55. **2.** Orillion A, et al. *Clin Cancer Res*. 2017;23:5187-5201. **3.** Agarwala SS, et al. Presented at ASCO 2018. Abstract 9530. **4.** Gandhi L, et al. Presented at ASCO 2018. Abstract 9036.

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



M. Hellman, WCLC 2018

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

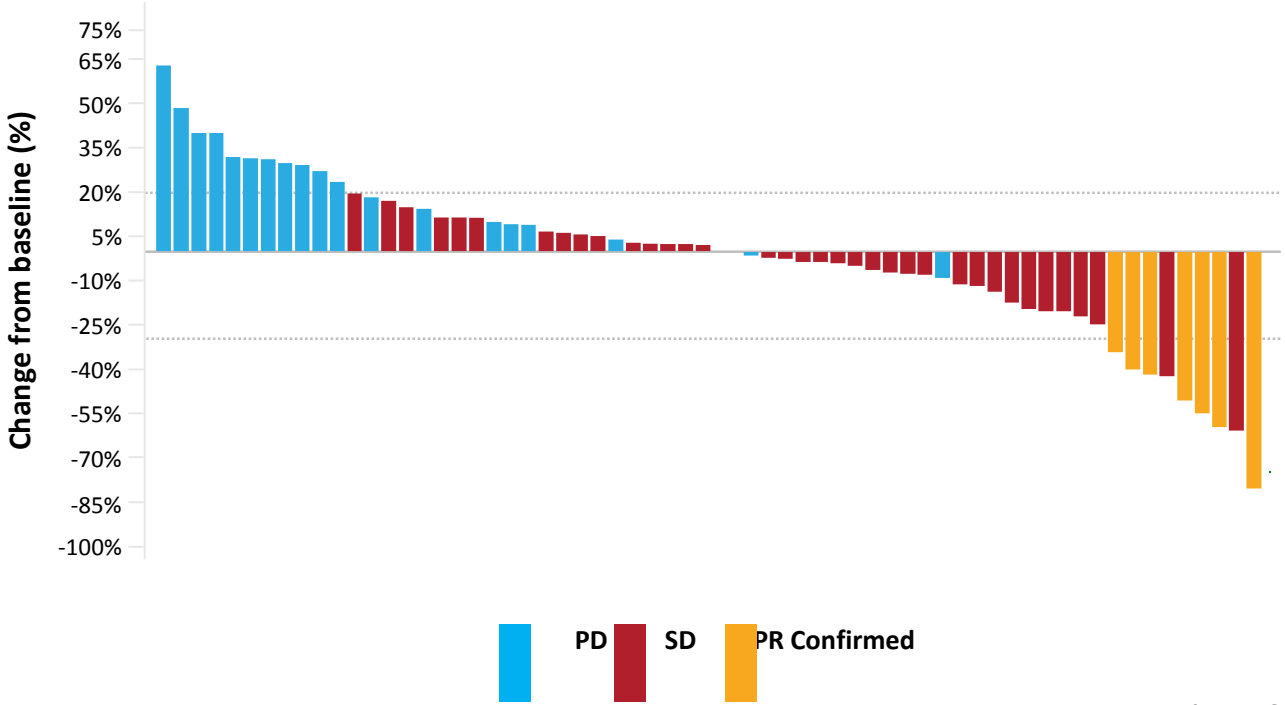
76 patients enrolled (72 efficacy evaluable*), last patient enrolled December 2017

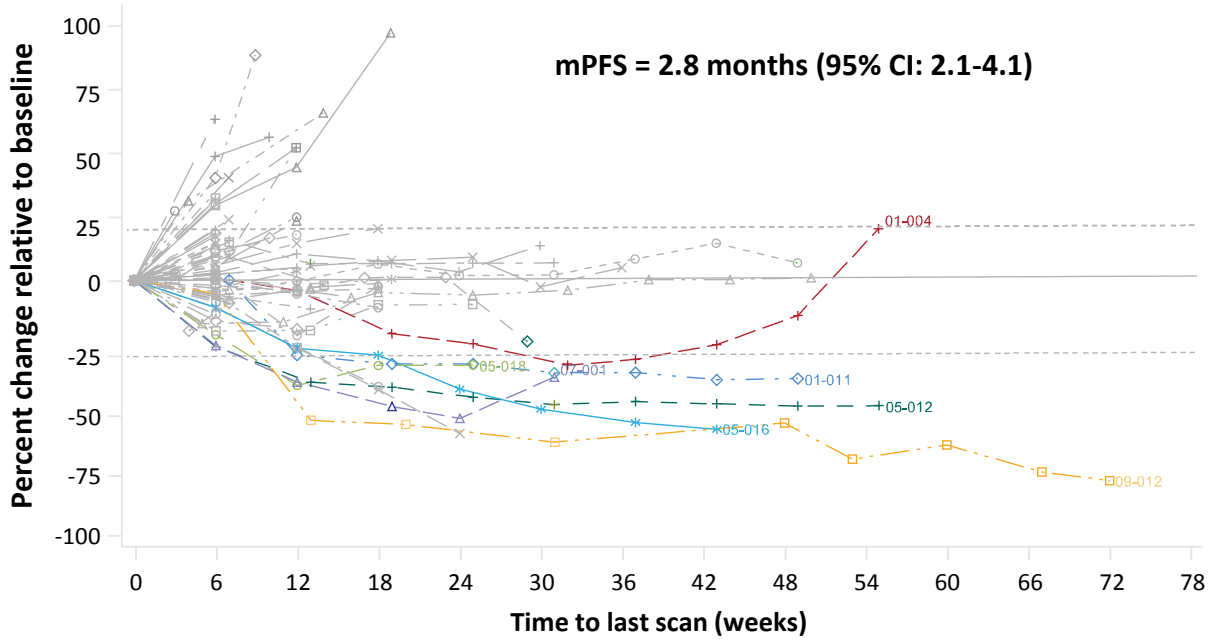
- Sample size was based on single proportion binomial test, assuming a true ORR of 15% & lower threshold of 5%, with 90% power and a 1-sided significance level of 5%.

*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





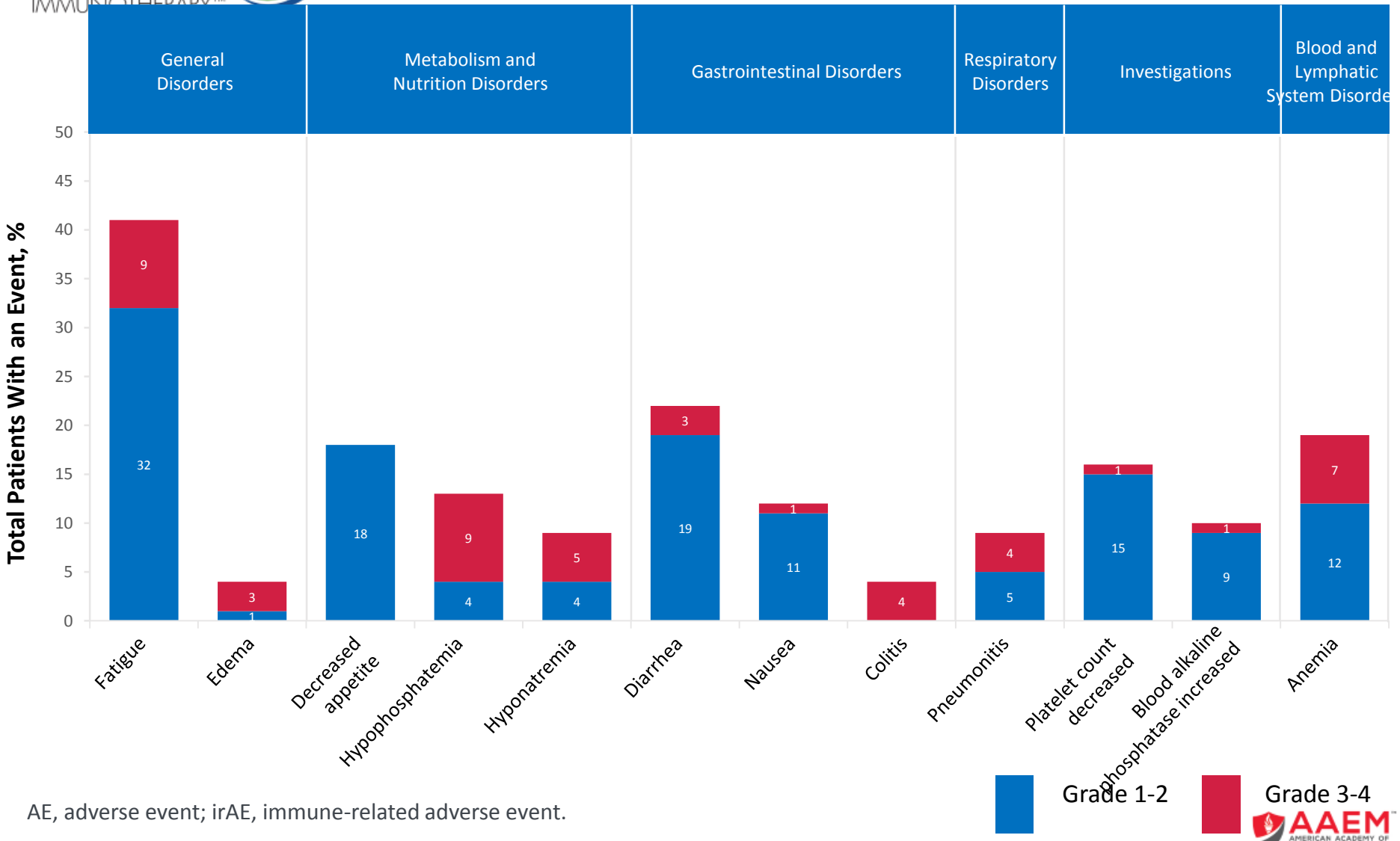
- Objective response rate with ENT + PEMBRO was 10% (7 of 72, 95% CI: 4-19%)
  - Prespecified ORR target not reached; median duration of response was 5.3 months
  - An additional 50% of patients achieved disease stabilization
- Experience similar in PD1-pretreated melanoma (ORR = 18%)[1]

M. Hellman, WCLC 2018

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.

Treatment-related adverse events occurring in ≥ 10% of patients for All Grade or ≥ 2 patients for Grade 3/4

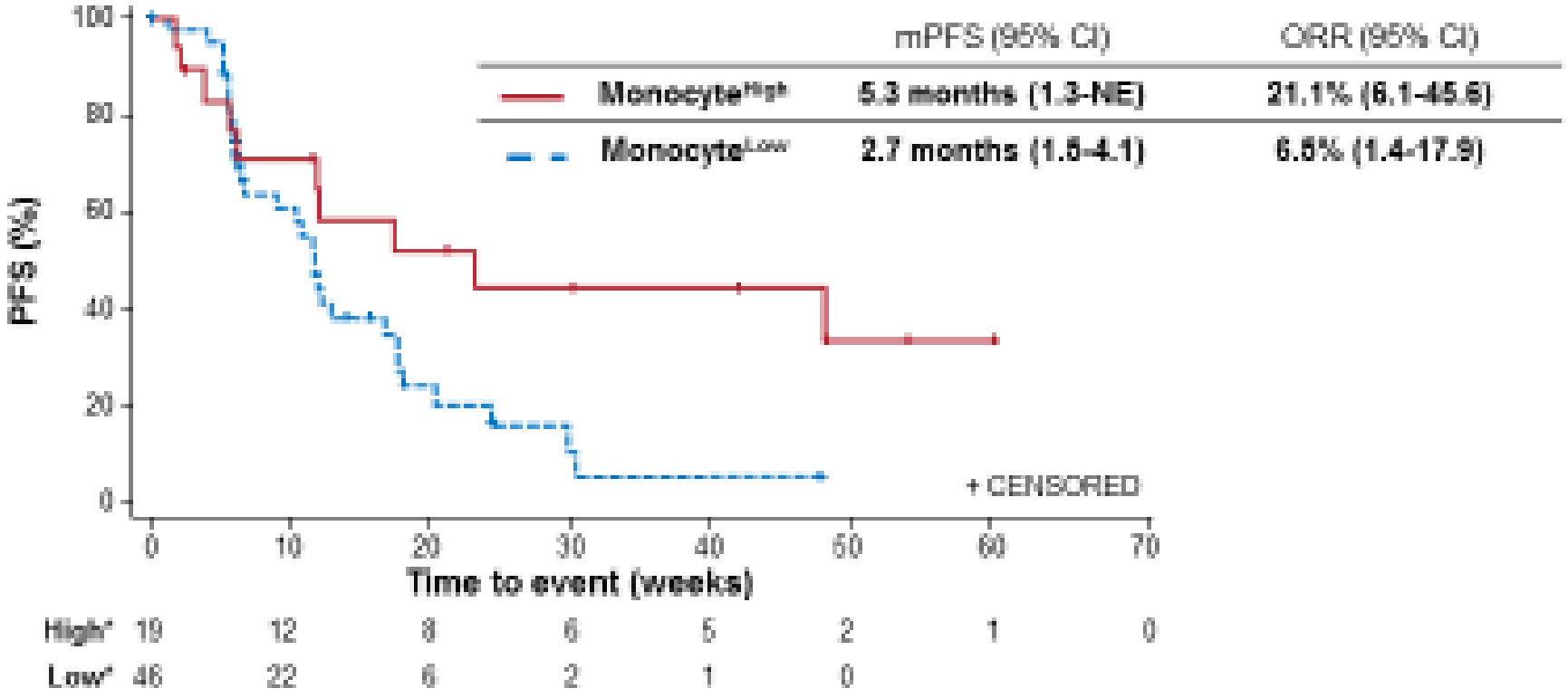


- 7 patients (9.2%) experienced Grade 3/4 related irAEs
  - pneumonitis, 3; colitis, 3; hyperthyroidism, 1
- 23 patients (30.3%) experienced other Grade 3/4 related AEs
- 11 patients (14%) discontinued a study drug due to a treatment-related AE
- 13 patients (17%) required a dose reduction of study drug, of which 11 remained on study

M. Hellman, WCLC 2018

AE, adverse event; irAE, immune-related adverse event.

Higher baseline levels of peripheral CD14+CD16-HLA-DR^{HI} classical monocytes are associated with ORR and PFS benefits

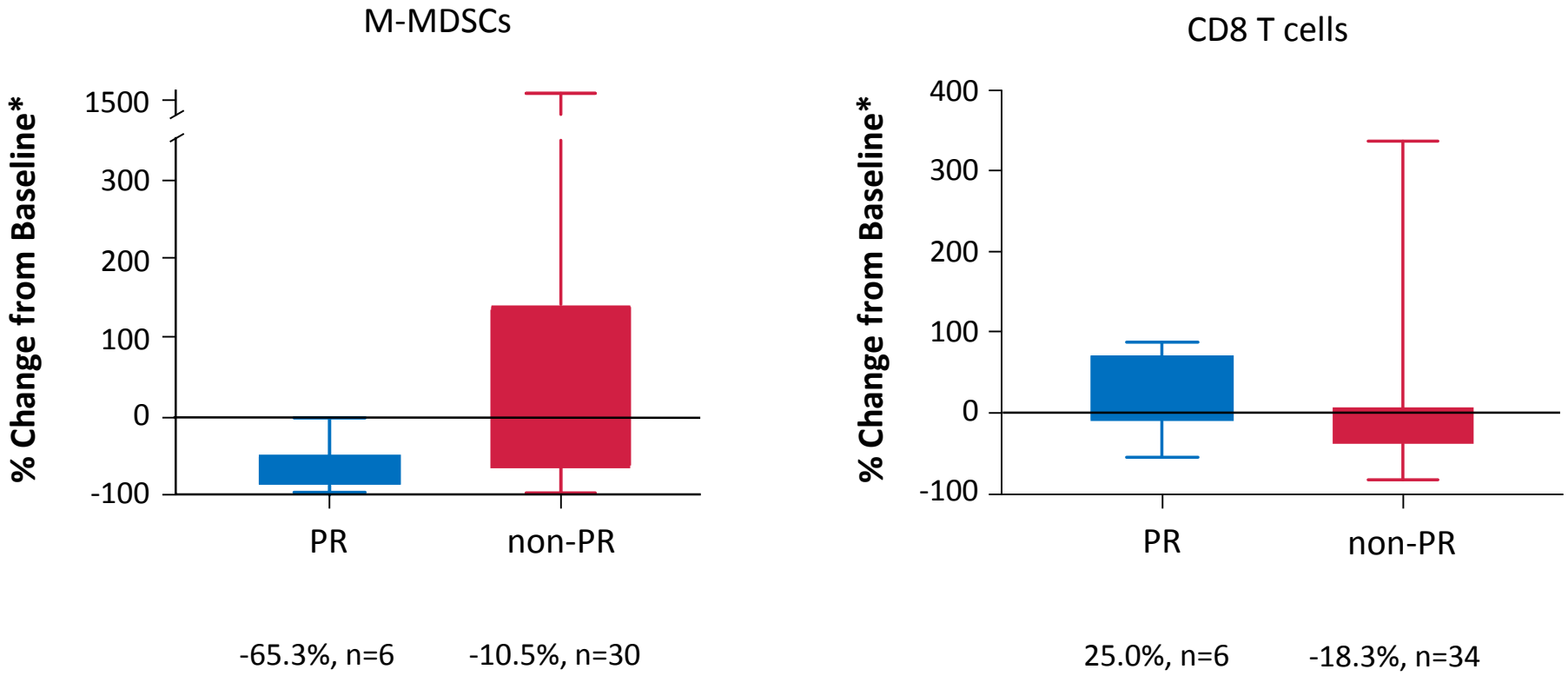


M. Hellman, WCLC 2018

- 26% of patients in the monocyte high group (5 of 19) are ongoing and 2% of patients in the monocyte low group (1 of 46) are ongoing.

*High / low defined by midpoint (13.1% of live PBMCs / ml) of range of peripheral monocyte values from available samples.
CI, confidence interval; NE, not estimable; ORR, objective response rate; mPFS, median progression-free survival.

Reduced circulating MDSCs ($CD14^{+}HLA\text{-}DR^{neg/low}$) associated with clinical responses

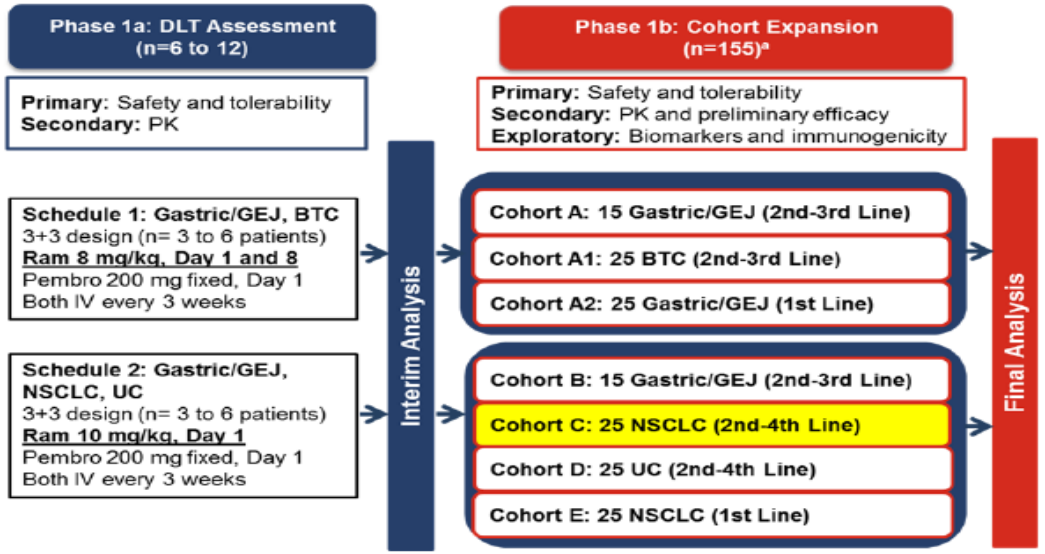


- Circulating MDSC cell reduction consistent with hypothesized entinostat MOA
- Trend in increased CD8+ T cells observed in responding patients

M. Hellman, WCLC 2018

*% change from baseline was measured at C2D15 (5 wks).
MDSCs, myeloid-derived suppressor cells.

Phase Ia/b Trial of Ramucirumab + Pembrolizumab: NSCLC Cohort Update (median follow up 20.1mo)

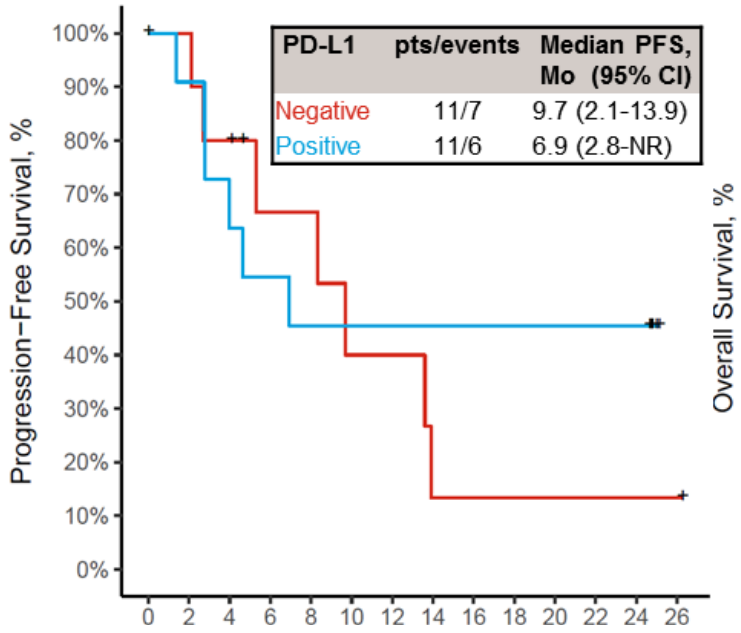


Tumor Response by PD-L1

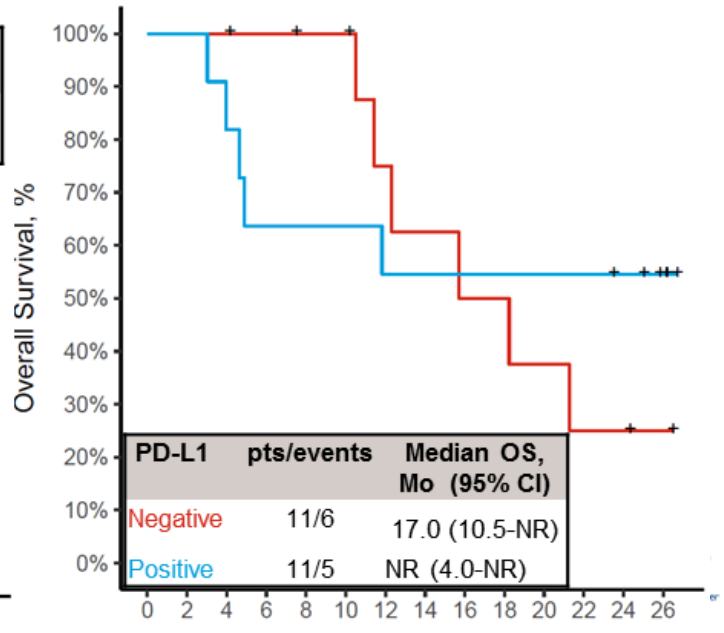
PD-L1 Status	NSCLC (2nd-4th line) TPS <1% n=11	TPS ≥1% n=11
ORR, % (95% CI)	18 (2.3-51.8)	45 (16.7-76.6)
Time to response	2.8 (2.8-2.8)	1.4 (1.3-5.3)
Duration of response	NR (11.1-NR)	NR (NR-NR)
Disease control, % (95% CI)	82 (48.2-97.7)	91 (58.7-99.8)
Duration of stable disease	8.3 (2.7-13.6)	4.0 (2.8-6.9)

- The safety profile of Ramucirumab + Pembrolizumab is consistent with monotherapy treatment for each drug with no additional toxicities
- Phase II efficacy studies of this combination are under development

PFS



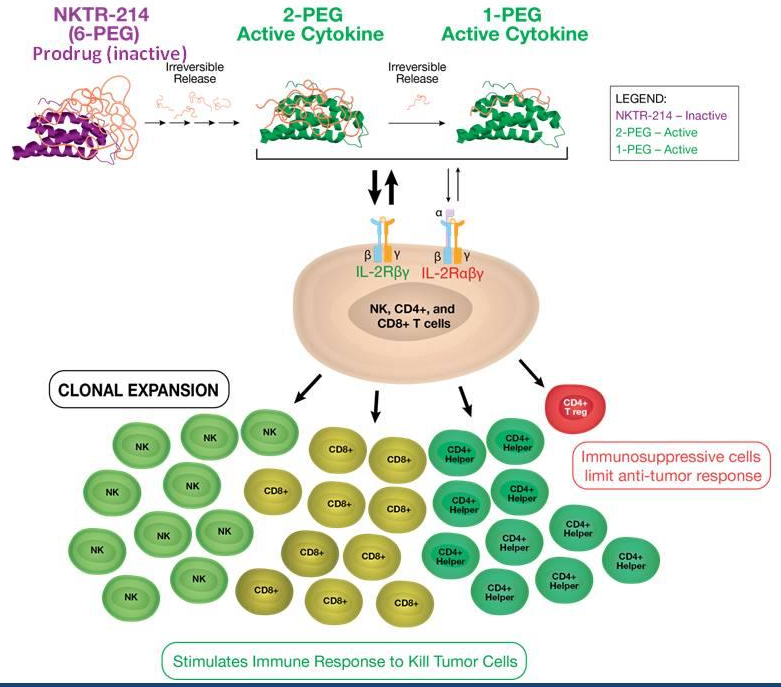
OS



Herbst R, et al. *J Clin Oncol*. 2018;36(suppl): Abstract 3059.

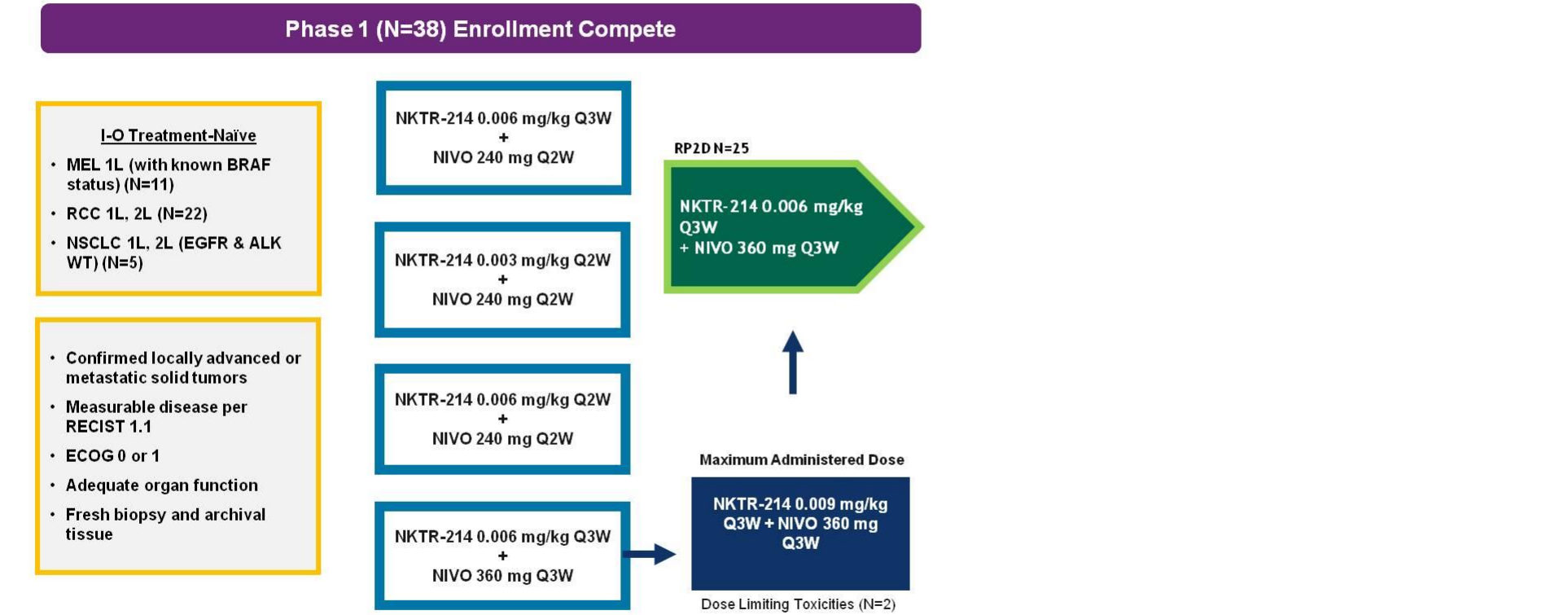
PIVOT-02

NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

PIVOT-02 Study Dose-Escalation in I-O Treatment-Naïve Patients: Enrollment Complete



RP2D, recommended Phase 2 dosing

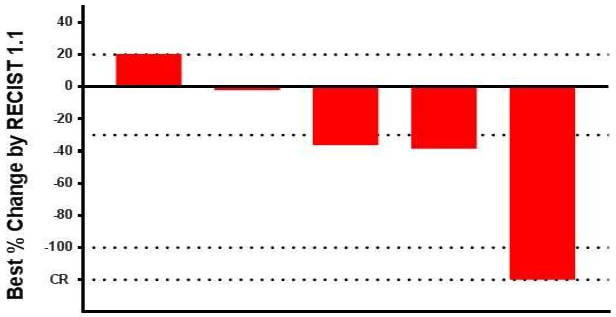
Presented By Adi Diab at 2018 ASCO Annual Meeting

PIVOT-02

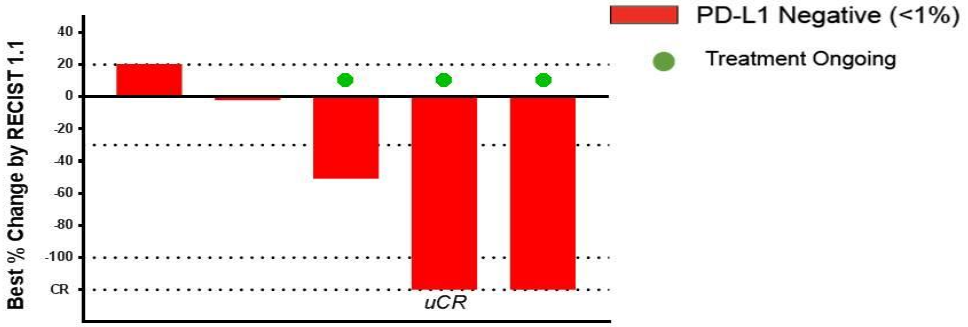
Stage IV IO-Naïve 1-2L NSCLC Dose Escalation Cohort (N=5)
Deepening of Responses Over Time in PD-L1 Negative Patients

Best Overall Response by RECIST (2L): ORR=3/4 (75%); DCR=3/4 (75%)
Best Overall Response by RECIST (1L and 2L): ORR=3/5 (60%); DCR=4/5 (80%)

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)

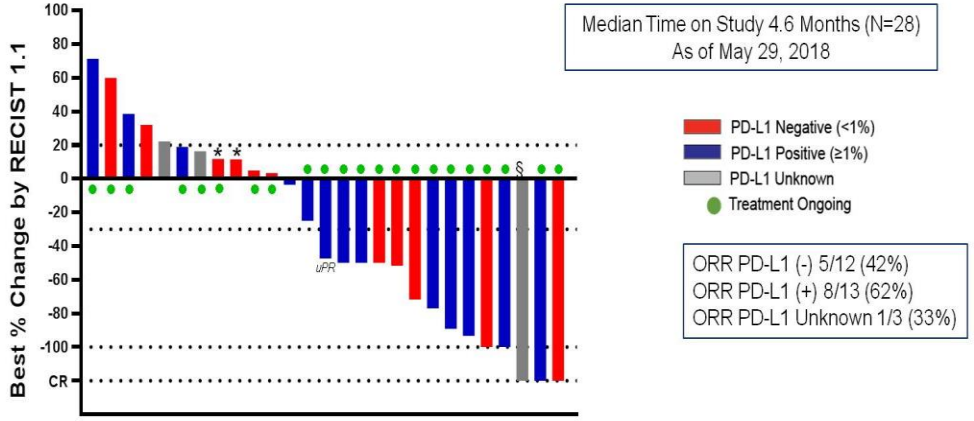


PDL1 positivity for this analysis was 1% or greater. Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria., CR: Complete response, all target and non-target lesions cleared,. "u": Unconfirmed

PIVOT-02

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D: Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=14/28 (50%); DCR=20/28 (71%)



Data cut: May 29, 2018

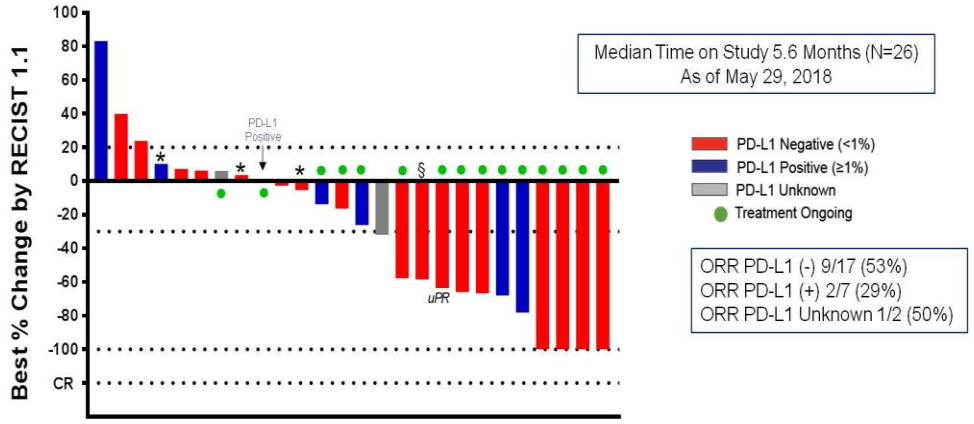
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. -100% is PR for complete clearance of target lesions. CR is a complete response. "u": Unconfirmed. *Best overall response is PD; SD for target lesions but PD due to a new lesion. §Off study treatment with confirmed CR due to patient decision.
One PD-L1(-) patient had PD due to non-target lesions and target lesions were not assessed, therefore 27/28 patients included in waterfall plot..

14

Stage IV IO-Naïve 1L RCC Cohort Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 7/11 (64%)
Stage 2: Best Overall Response ORR=12/26 (46%); DCR=20/26 (77%)



Data cut: May 29, 2018

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria; -100% is PR for complete clearance of target lesions. CR is a complete response, "u": Unconfirmed. *Best overall response is PD (SD for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.

15

Presented By Adi Diab at 2018 ASCO Annual Meeting

PIVOT-02

Immune-Mediated Grade ≥3 AEs at RP2D

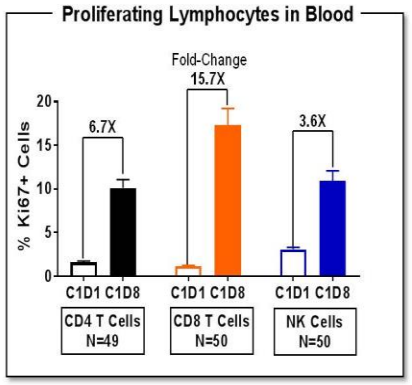
Immune-Mediated Adverse Events	NKTR-214 0.006 q3w + Nivo 360 (N=283)
Any imAE (Grade ≥3)	**10 (3.5%)**
Grade ≥3 imAE Treated with Steroid / Immuno-modulating Medication	**7 (2.5%)**
Pneumonitis*/dyspnea	2 (0.7%)
Skin adverse event	2 (0.7%)
Hepatitis	1 (0.4%)
Colitis	1 (0.4%)
Elevated Lipase	1 (0.4%)
Grade ≥3 Endocrinopathy	**3 (1.1%)**
Diabetes Mellitus Treated with Insulin	1 (0.4%)
Hyperglycemia Treated with Insulin	2 (0.7%)

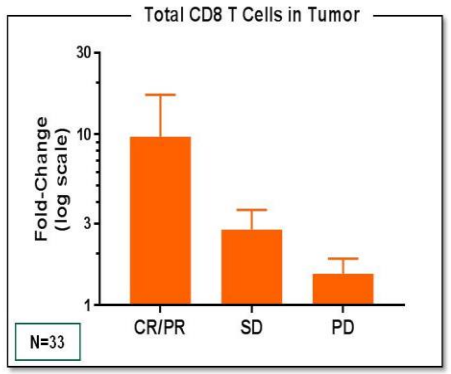
- One treatment-related G5 pneumonitis related to nivolumab in patient with NSCLC pre-treated with carboplatin/pemetrexed and history of brain metastases

Data cut: May 7, 2018

PIVOT-02

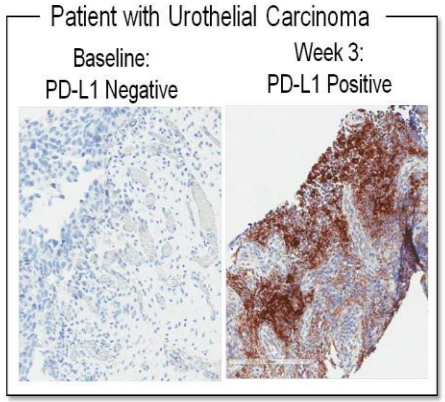
NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood and CD8 T Cells in Tumor

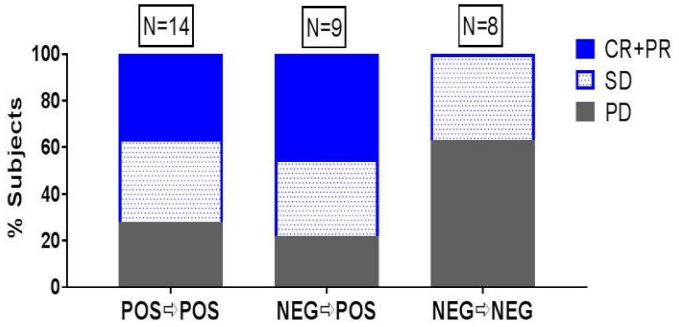




"Proliferating Lymphocytes in Blood" were measured using flow cytometry of fresh whole blood for all patients that the met inclusion criteria and had matched Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) blood collections. Data presented as mean ± standard error. Fold-change calculated for C1D8/C1D1. Ki67 is a marker of proliferation. "Total CD8 T Cells in Tumor" measured using immunohistochemistry using biopsy specimens collected at baseline and week 3. Cells/mm² were counted and fold-change calculated for week3/baseline, data presented as mean ± standard error.

Conversion of PD-L1(-) to PD-L1(+) in Tumor Biopsies from Baseline to Week 3 is Associated with Clinical Benefit



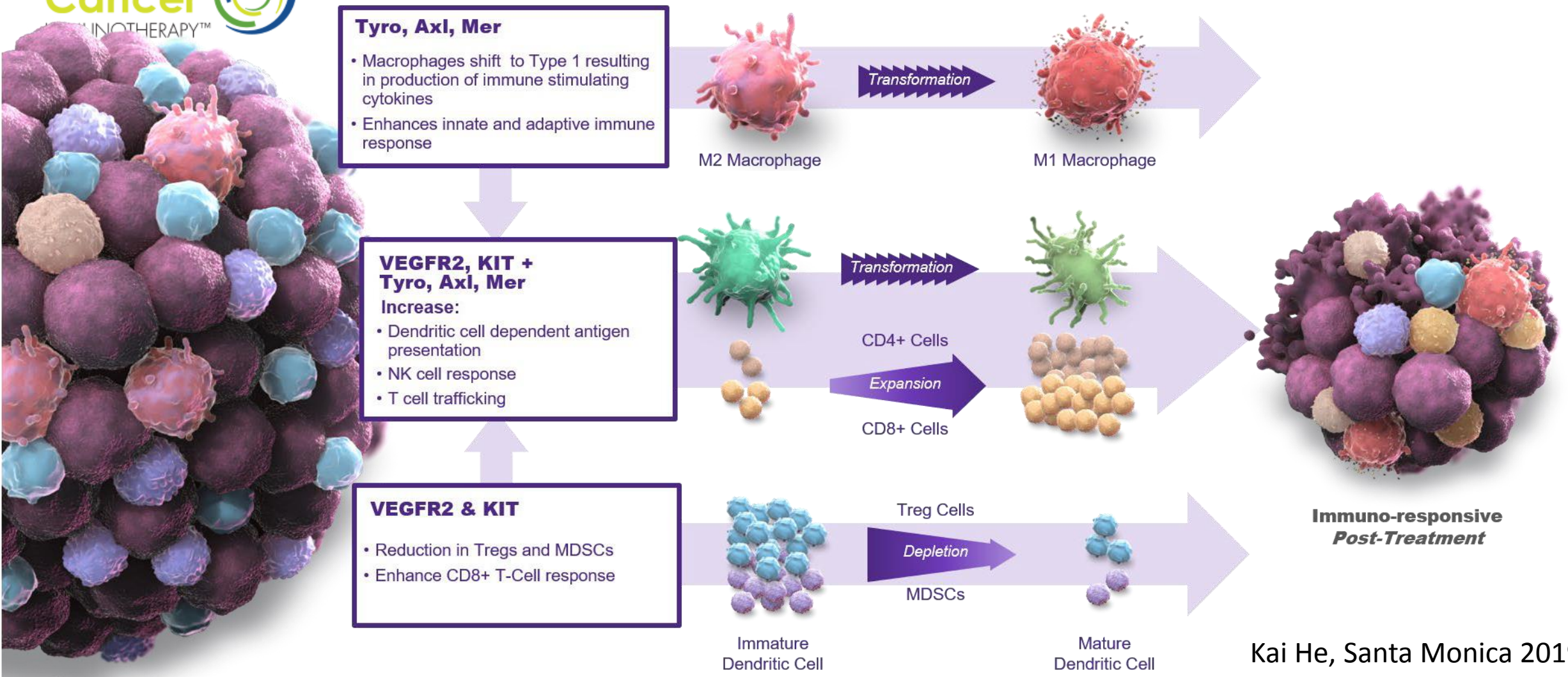


- NKTR-214 + nivolumab can convert PD-L1(-) tumors to PD-L1(+)
  - PD-L1 negative to positive conversion in 9/17 (53%) of patients
- Patients that were PD-L1(+) at baseline, or converted to PD-L1(+) after start of treatment showed greatest clinical benefit

31 patients were available with matched baseline and week 3 results for PD-L1 status. Of these, 17 were PD-L1 negative at baseline. PD-L1 was assessed on tumor cells using a validated 28-8 method. Example image shown for UC patient at baseline and week 3, 20x magnification.

Presented By Adi Diab at 2018 ASCO Annual Meeting

Sitravatinib in the Tumor Microenvironment – Restores Immune Response

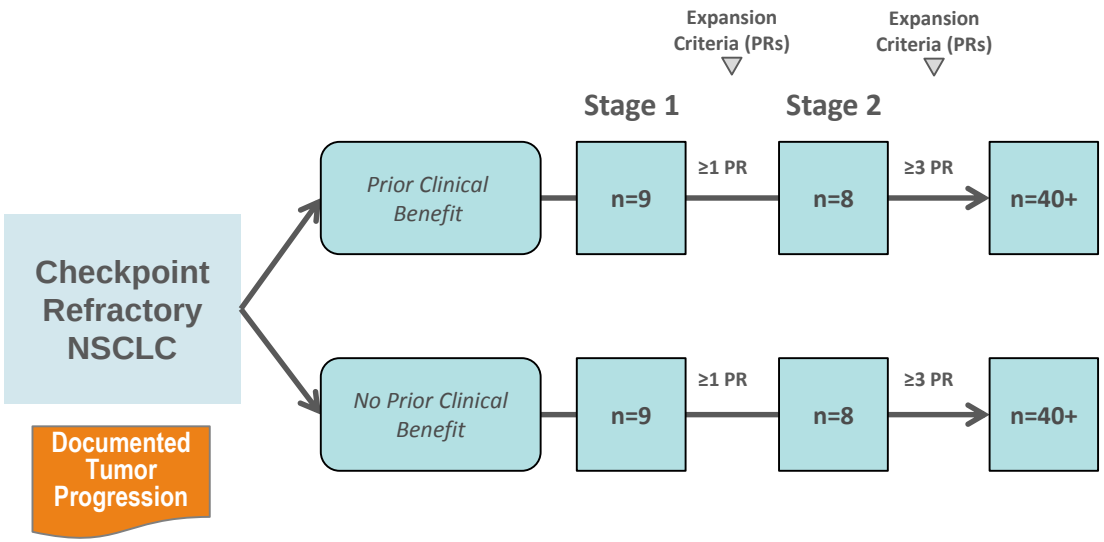


Kai He, Santa Monica 2019

Pircher et al., *Synergies of Targeting Tumor Angiogenesis and Immune Checkpoints.* Int J Mol Sci, 2017. **18**(11).
Garton et al., *Anti-KIT Monoclonal Antibody Treatment Enhances the Antitumor Activity of Immune Checkpoint Inhibitors by Reversing Tumor-Induced Immunosuppression.* Mol Cancer Ther, 2017. **16**(4)
Akalu, Y.T., C.V. Rothlin, and S. Ghosh, *TAM receptor tyrosine kinases as emerging targets of innate immune checkpoint blockade for cancer therapy.* Immunol Rev, 2017. **276**(1)
Graham, D.K., D. DeRyckere, K.D. Davies, and H.S. Earp, *The TAM family.* Nat Rev Cancer, 2014. **14**(12)
Du, W., Huang, H., Sorrelle, N., & Brekken, R. A. (2018). Sitravatinib potentiates immune checkpoint blockade in refractory cancer models. *JCI Insight*, *3*(21).

MRTX-500 Background and Study Design

- Sitravatinib (MGCD516) is an orally available, small molecule inhibitor of a spectrum of related receptor tyrosine kinases (RTKs) including TAM family, VEGFR2 and KIT.
- MRTX-500 is a Phase 2 study evaluating the tolerability and clinical activity of sitravatinib in combination with nivolumab in patients with non-squamous NSCLC who have experienced progression of disease on or after treatment with CIT.
- Patients receive oral sitravatinib once daily (QD) in combination with nivolumab 240/480 mg intravenously every 2/4 weeks, as continuous 28 day cycles.



Key Objectives:

- Objective Response Rate (ORR) by RECIST 1.1.
- Safety, tolerability, pharmacokinetics
- Investigate baseline biomarkers for correlation with clinical outcome parameters:
  - Circulating & tumor cell PD-L1
  - Mutation profile/TMB in ctDNA
  - Circulating & tumor infiltrating immune cell populations & cytokines
  - Gene expression signatures

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MRTX-500 Safety: Most Frequent (≥10%) Treatment-Related (Sitravatinib and/or Nivolumab)*

Adverse Event (Preferred Term)	N=70	
	All Grades n (%)	Grade ≥3 n (%)
Diarrhea	31 (44)	8 (11)
Nausea	28 (40)	0
Fatigue	27 (39)	2 (3)
Decreased appetite	18 (26)	0
Vomiting	18 (26)	1 (1)
Dysphonia	17 (24)	0
Weight decrease	16 (23)	1 (1)
Hypertension	16 (23)	9 (13)
Alanine aminotransferase increase	12 (17)	0
Aspartate aminotransferase increase	10 (14)	0
Hypothyroidism	10 (14)	0
Palmar-plantar erythrodysaesthesia	10 (14)	1 (1)
Stomatitis	10 (14)	1 (1)
Mucosal Inflammation	8 (11)	3 (4)
Lipase increase	4 (6)	2 (3)
Hyponatremia	5 (7)	2 (3)

*Data as of 26-Jun-2018 (Investigators Brochure) – includes all patients CIT-Experienced (N=64) and CIT-Naïve Cohorts (N=6)
12 patients (17%) discontinued due to treatment-related adverse event

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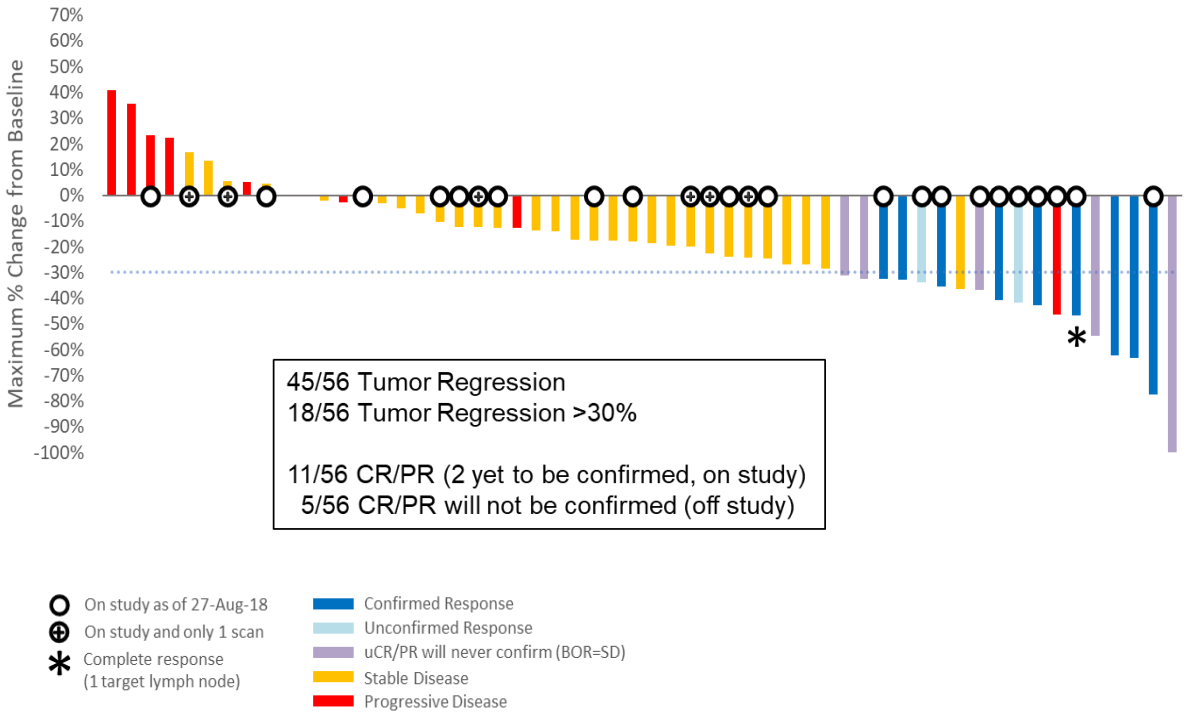
MRTX-500 Clinical Activity
CIT Experienced Cohorts

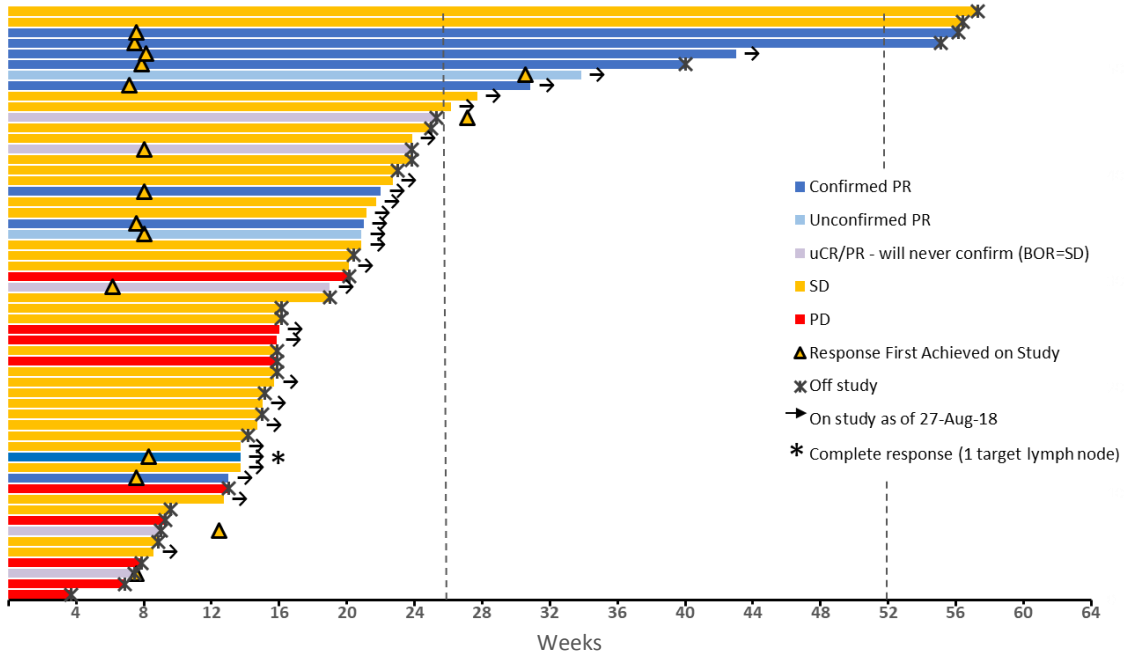
Presented at ESMO 2018

Preliminary Maximum Response
NSCLC Patients Who Failed Prior Checkpoint Therapy
by Best Response, N=56



Study cycles of 28 days, with disease assessment scans every 2 cycles
Data as of 27-Aug-2018

Preliminary Duration of Treatment
NSCLC Patients Who Failed Prior Checkpoint Therapy
by Best Response, N=56



Preliminary Kaplan-Meier Estimates

Median Duration of Response:	9.2 months
Median Progression Free Survival:	6.8 months
Median Overall Survival:	15.1 months

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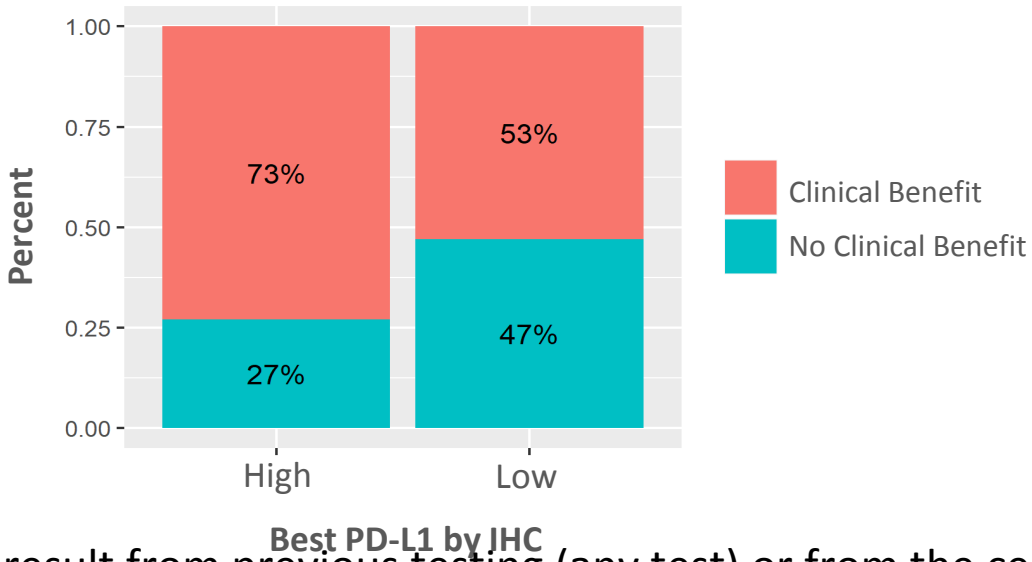
MRTX-500 Biomarker Data: PD-L1 Status
CIT Experienced Cohorts

Clinical Benefit – PD-L1 by IHC



- Highest PD-L1 result from previous testing (any test) or from the central lab (DAKO 28-8) was compared to clinical benefit
- A non-significant trend between PD-L1 high staining and clinical benefit was observed (p-value = 0.45)
- Clinical benefit, including PRs, still observed in PD-L1 low pts and some PD-L1 high pts did not respond

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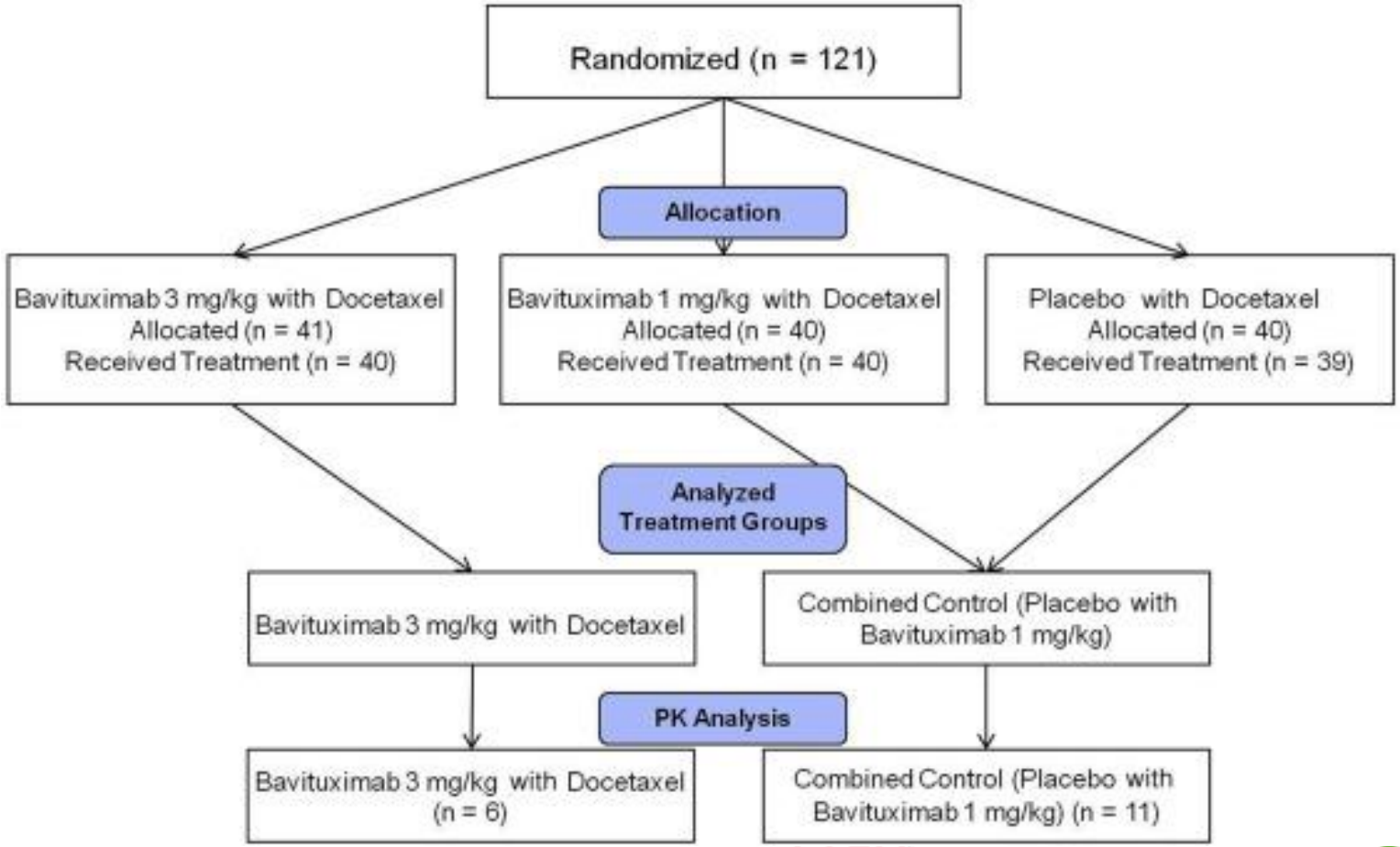
Docetaxel Combined With Bavituximab in Previously Treated, Advanced Nonsquamous NoneSmall-Cell Lung Cancer

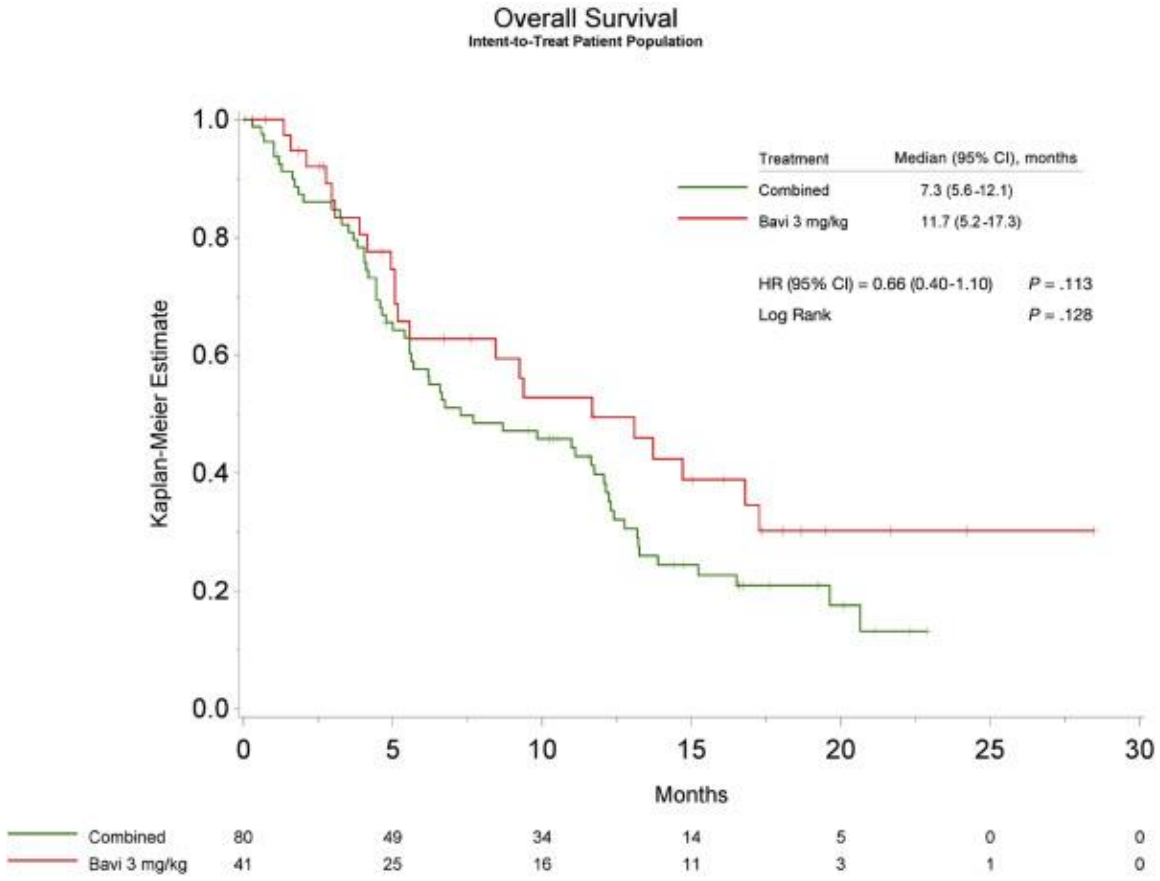
- Bavituximab is a phosphatidylserine-targeting antibody with a selective tumor, vascular-directed immune response.
- Exposed PS on apoptotic cells suppresses immune and inflammatory responses by binding to macrophage PS receptors
- This signals macrophage production of anti-inflammatory cytokines such as TGFb and interleukin (IL)- 10 and preventing dendritic cell maturation and antigen presentation

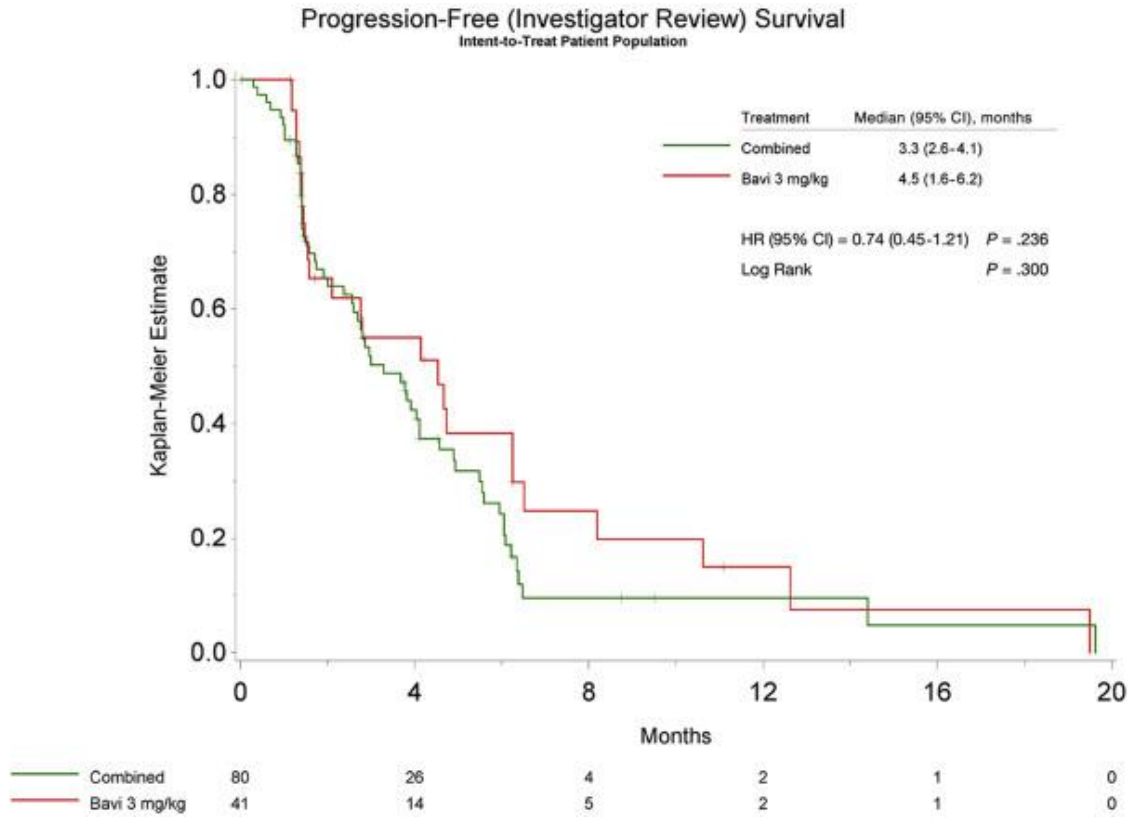
Gerber et al, Clinical Lung Cancer, vol. 17, No. 3

Study Flow Diagram Showing the Randomization and Disposition of Patients



Docetaxel Combined With Bavituximab in Previously Treated, Advanced Nonsquamous Non Small-Cell Lung Cancer





Gerber et al, Clinical Lung Cancer, vol. 17, No. 3

Remarks

- With the use of chemo plus IO in the first line setting there is a need for drugs and combinations that could be effective in chemo and IO refractory patients
- Recognizing mechanisms of resistance to immunotherapy are of significant importance
- Repeat biopsies at the time of progression for conduct of correlative studies is essential
- New promising combinations are under investigation