FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

Oncology Dose-Finding Workshop Part 3

July 20, 2017

W. Washington DC Hotel

Washington, DC

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

Welcome and Workshop Objectives

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Dose-finding and optimization: FDA perspective

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Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
FDA

Scope

- Two dose-finding workshops complete, third today
- Has FDA evolved in its review perspective for evaluating dose justification?

Example #1: Rociletinib

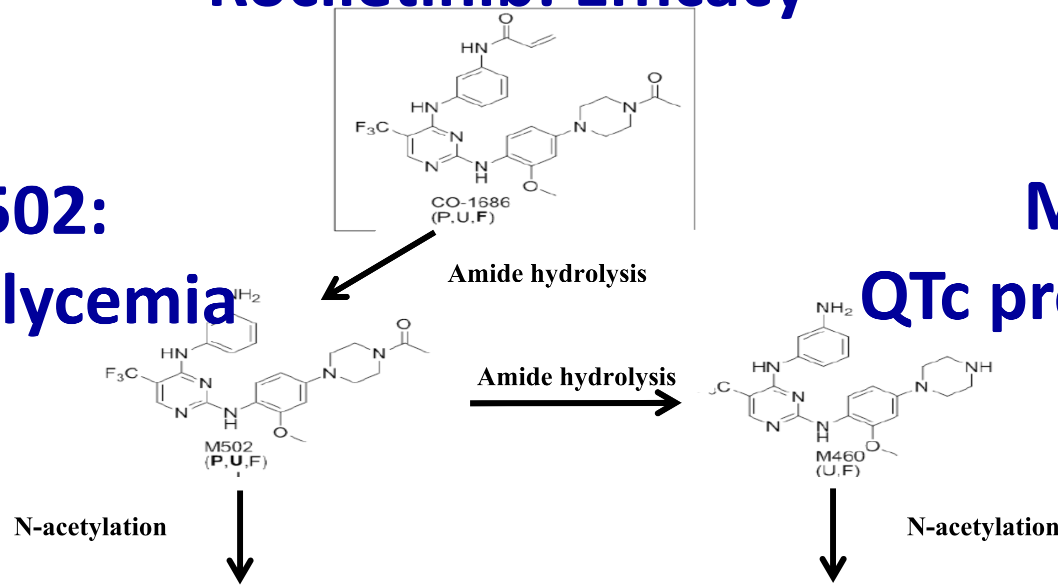
- Marketing application submitted to FDA for treatment of patients with NSCLC with EGFR T790M mutation
- Discussed at April 2016 ODAC

Rociletinib Biotransformation Pathway

Rociletinib: Efficacy

M502: Hyperglycemia

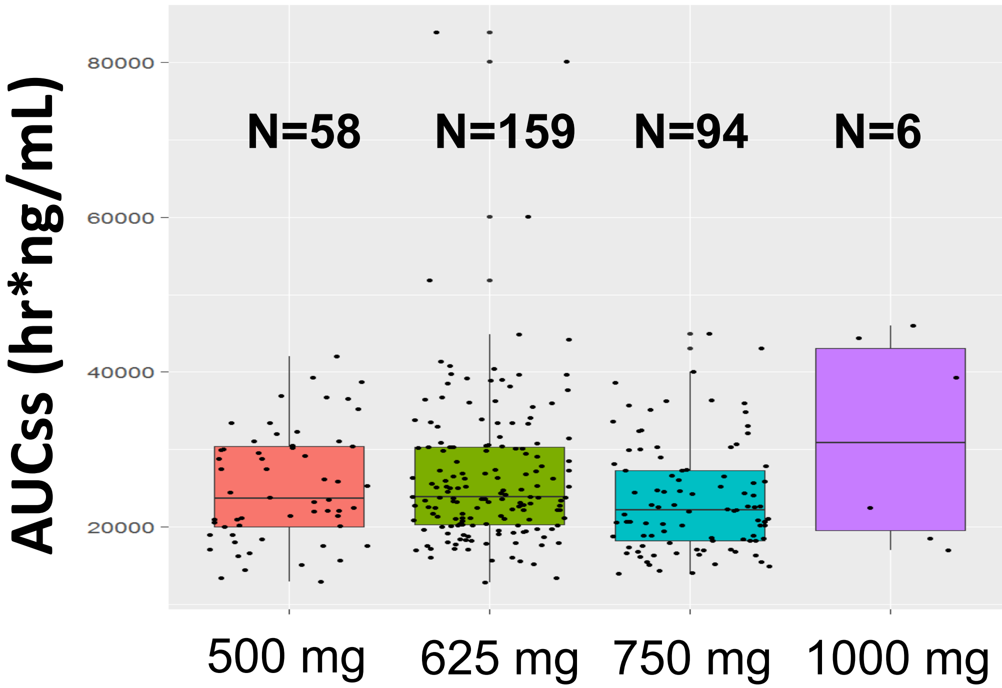
M460: QTc prolongation



$T_{1/2}$ (M502): 20 hours
$T_{1/2}$ (M460): 51 hours

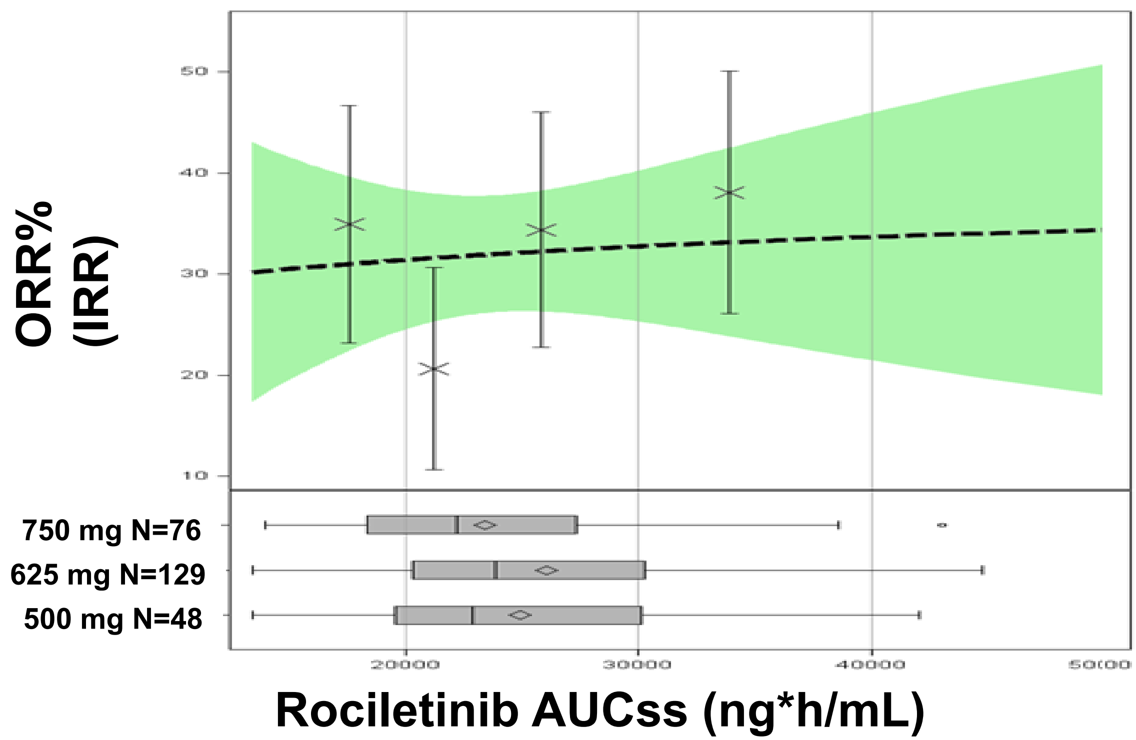
Chao Liu, presentation at 4/2016 ODAC

Population PK: Similar Rociletinib Exposure from 500 to 1000 mg BID



Dose-Exposure is flat

Rociletinib Exposure-Efficacy Relationship



Rociletinib steady-state AUC was derived from population PK analysis

Example #1: Rociletinib

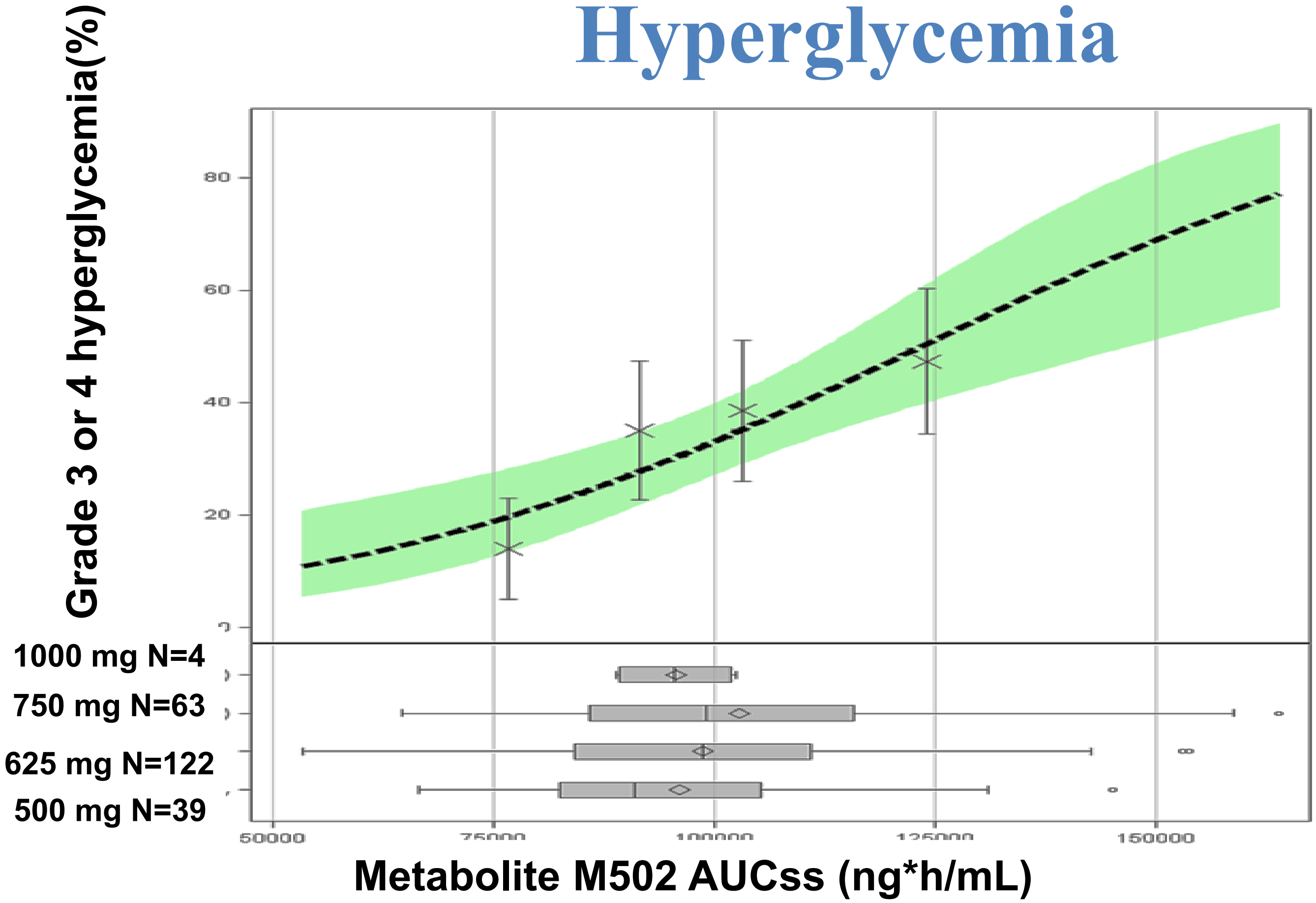
Primary Efficacy Endpoint

Clinical Pharmacology Data

- Dose-exposure flat across doses 500-1000 mg BID
- Exposure-efficacy flat at across doses 500-1000 mg BID

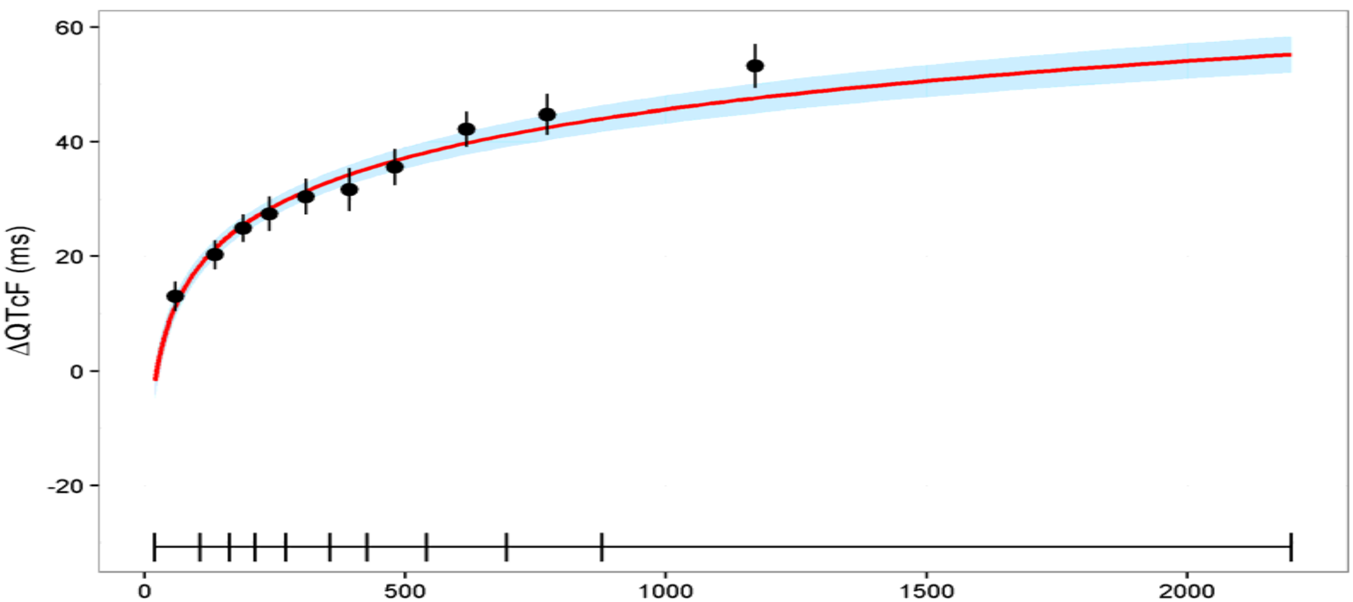
FDA Approach: Pooling of the efficacy data across several dose groups may provide a reasonable estimate of the true effect of rociletinib on tumor response.

M502 Exposure-Safety Relationship: Hyperglycemia



M502 steady-state AUC was derived from population PK analysis

M460 Exposure-Safety Relationship: QTc Prolongation



Metabolite M460 Concentrations (ng/mL)

M460 concentrations were from observed data

Rociletinib: Appropriate Dose based on Available Data?

- **Dose-exposure relationship is flat from 500 to 1000 mg BID**
  – FDA pooled data across different dose levels for safety & efficacy
- **Exposure-efficacy relationship is flat**
  – Patients with higher rociletinib exposure are unlikely to have further benefit
- **Exposure-safety relationship is steep**
  – Patients with higher metabolite exposure are at increased risk for QTc prolongation & hyperglycemia

625 mg BID not adequately supported

Example #2: Nivolumab

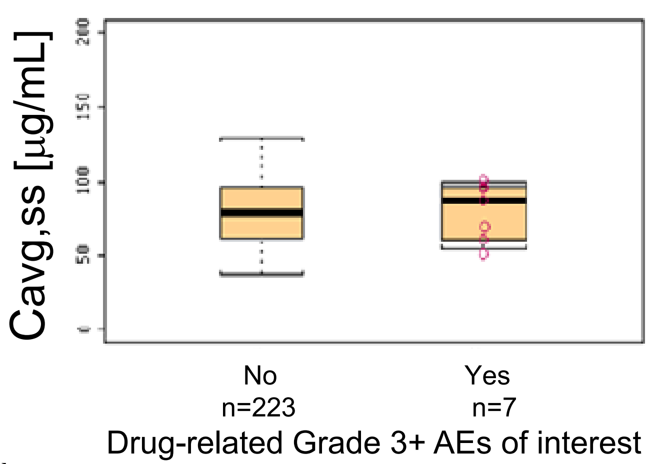
- Received accelerated approval in 2014 for metastatic melanoma at dose of 3 mg/kg q 2 weeks
  - Approval based on analysis of ORR and duration of response for nivolumab arm in a randomized trial
  - Clinical pharmacology data included PK data from 1040 patients enrolled in eight completed and ongoing clinical trials at time of approval
    - Data for E-R analyses for safety (n=640) were collected from three trials
    - Data for E-R analyses for clinical activity (n=206) were collected from two trials

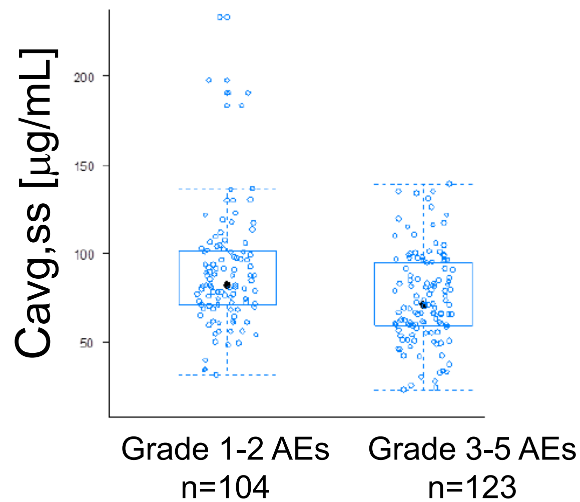
Example #2: Nivolumab

- Exposure-response for efficacy
  - No dose or exposure-efficacy relationship identified in the proposed patient population based on the primary endpoint of ORR
  - A flat exposure-ORR relationship was identified over the dose range of 0.1-10 mg/kg

Example #2: Nivolumab

- Exposure-response for safety
  - no exposure-safety relationships between exposure ($C_{avg,\ ss}$) and time to first Grade 3+ drug related-AEs, AEs leading to discontinuation and all Grade 3+ AEs





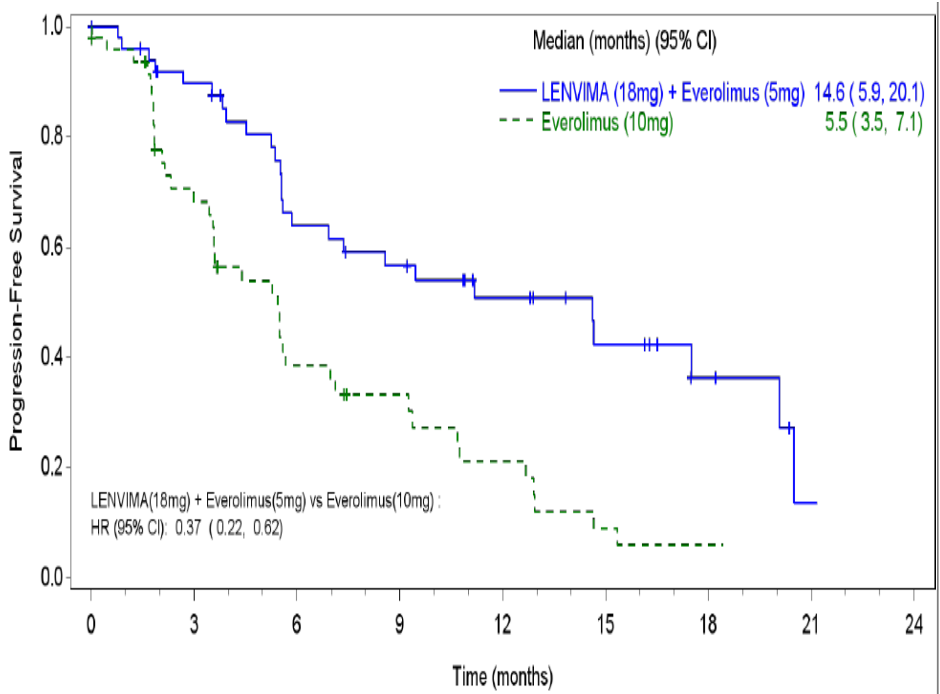
Example #2: Nivolumab

- 9/2016: sBLA approved changing to flat dose for solid tumor indications
  - Based on simulations by the Pop-PK model, overall exposure at 240 mg Q2W flat dose is similar (<6% difference) to 3 mg/kg Q2W dose
  - Small difference in exposure won't have clinically meaningful impact on efficacy and safety as the dose/exposure response relationships for efficacy and safety relatively flat in these three indications
  - Dose-safety relationship appears to be flat for nivolumab from 0.1mg/kg (N=17) up to 10mg/kg (N=95) in the pooled data of RCC, NSCLC and melanoma indications

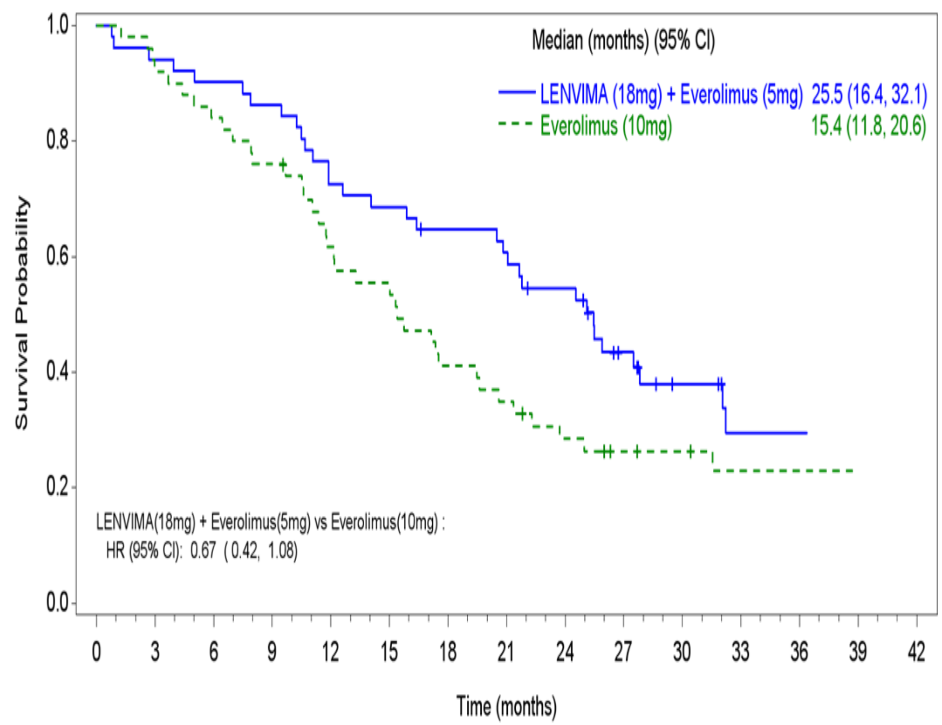
Example #3: Lenvatinib

- Approved 5/2016 for treatment of renal cell carcinoma at 18 mg daily in combination with everolimus

Progression-free survival



Overall survival



Example #3: Lenvatinib

- Issue: 89% of patients required a dose interruption/reduction
- In light of efficacy, approved with a PMR for dose optimization
- What doses should be studied?
  - Use E-R modeling to recommend doses for PMR
  - Challenge for modeling that exposure was not constant over time with dose interruptions/reductions⇒biased E-R relationship

Example #3: Lenvatinib

- Post-marketing requirement:
  - Lenvatinib 14 mg daily with option for up-titration with everolimus 5 mg daily versus lenvatinib 18 mg daily with everolimus 5 mg daily
  - Evaluate the incidence of intolerable grade 2 and grade 3-5 adverse reactions

Summary

- Modeling used in select situations to aid in regulatory decisions
- You will hear about more novel regulatory approaches to initial combination trials submitted to FDA today

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- Lenvatinib Pharmacometrics reviewers
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  - Yaning Wang, Ph.D.

SESSION I:

Immuno-oncology (IO) Overview – Scope of the Problem

Moderator: Amy E. McKee, MD

Speakers:
Robert H. Vonderheide, MD, D Phil
David F. McDermott, MD
Leisha A. Emens, MD, PhD
Joaquim Bellmunt, MD, PhD

Immune vulnerabilities and therapeutic opportunities in pancreatic cancer

Robert H. Vonderheide, MD, DPhil

Abramson Cancer Center
University of Pennsylvania

July 20 2017

Cancer immunotherapy revolution

CTLA-4 antibody

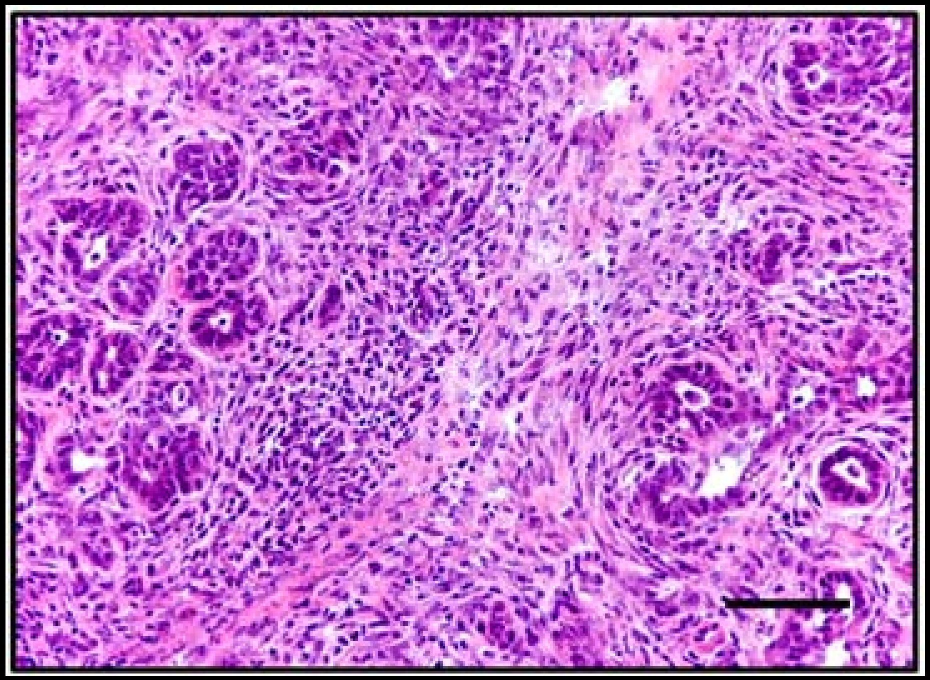
PD-1 antibodies

The NEW ENGLAND JOURNAL of MEDICINE

CART19 T cells

PD-1 plus X

Pancreatic ductal adenocarcinoma is notorious among these immune resistant tumors



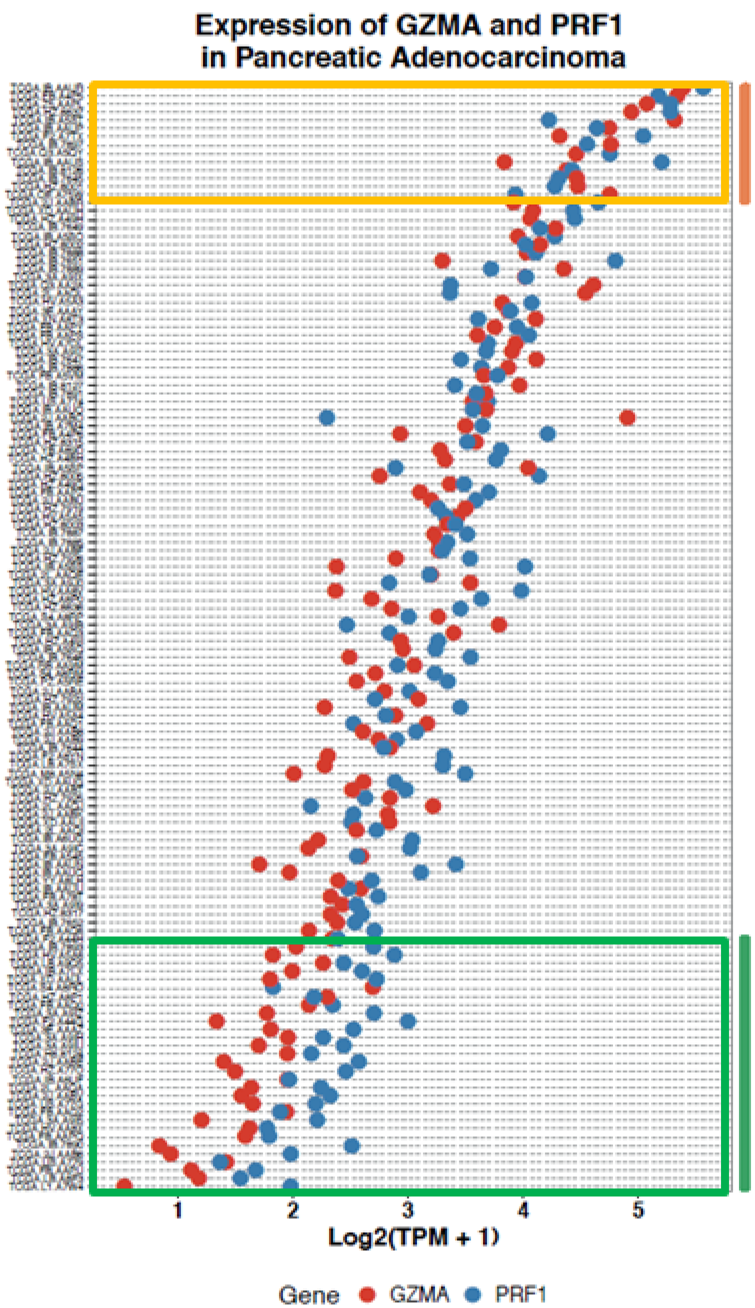
3rd leading cause of cancer death, more than breast ca, yet ever increasing impact of combination chemotherapy

Pancreatic cancer as window to understand immunology in 'cold' tumors

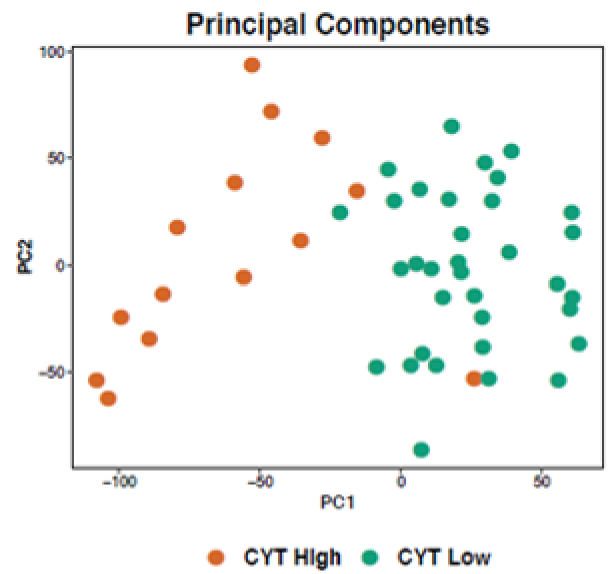
- Effector T cell infiltration into the tumor is poor in most cases
- Prominent myeloid inflammation driven by oncogenic signaling
- Few missense mutations and indels
- Resistant to checkpoint mAb and CARs
- 3 recent vaccine-only randomized clinical trials were negative

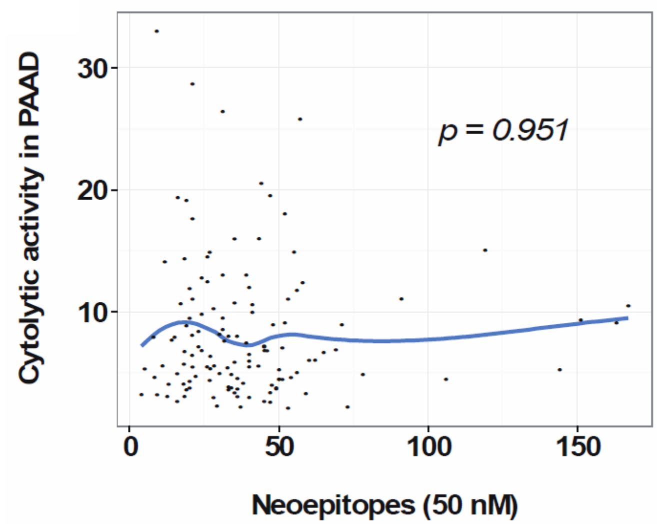
But resected patients whose tumors exhibit relatively high CD8 infiltration survive longer

Vonderheide and Bayne, Curr Opin Immunol, 2013; Johnson et al, CCR, 2017; Thind et al, Therp Adv Gastroenterol, 2017; Ino et al, Br J Cancer, 2013

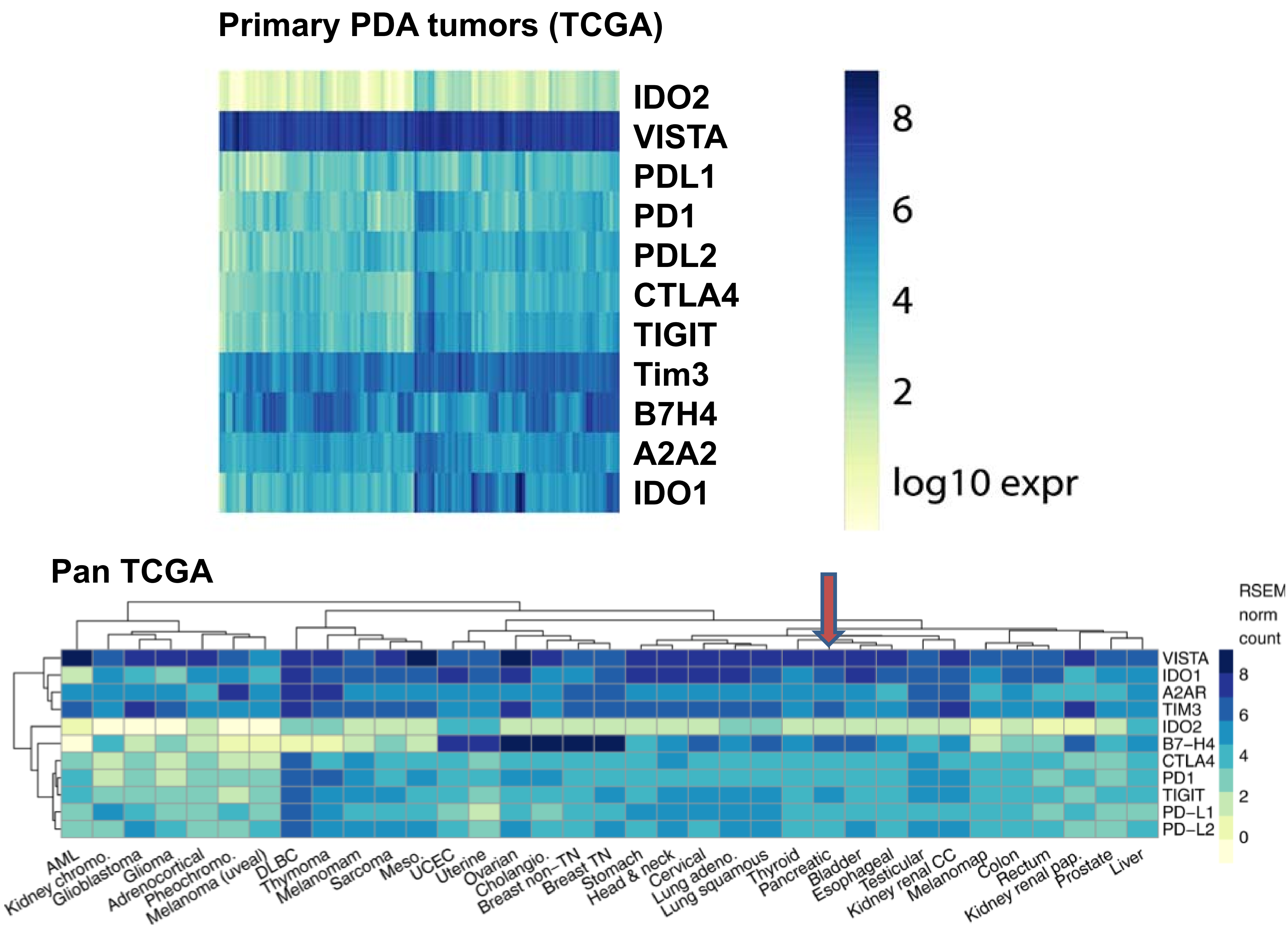


All primary tumors, untreated n=134





Balli et al, Clin Can Res, 2016


Primary PDA tumors (TCGA)
IDO2
VISTA
PDL1
PD1
PDL2
CTLA4
TIGIT
Tim3
B7H4
A2A2
IDO1
8
6
4
2
log10 expr
Pan TCGA
RSEM norm count
VISTA
IDO1
A2AR
TIM3
IDO2
B7-H4
CTLA4
PD1
TIGIT
PD-L1
PD-L2
8
6
4
2
0
AML
Kidney chromo.
Glioblastoma
Glioma
Adrenocortical
Pheochromo.
Melanoma (uveal)
DLBC
Thymoma
Melanomam
Sarcoma
Meso.
UCEC
Uterine
Ovarian
Cholangio.
Breast non-TN
Breast TN
Stomach
Head & neck
Cervical
Lung adeno.
Lung squamous
Thyroid
Pancreatic
Bladder
Esophageal
Testicular
Kidney renal CC
Melanomap
Colon
Rectum
Kidney renal pap.
Prostate
Liver

T cell immunosurveillance in pancreatic cancer?

Young KPC
(<5 weeks)

Kras$^{G12D/+}$ *Trp53*$^{R172H/+}$ *Pdx-1 Cre*

Serial ultrasounds

Moribund or
tumor >1000mm^3

- **CD8** (2.43) $\pm$ **CD4** (GK1.5)
- **IgG2b isotype control** (LTF-2)

Endpoints:

- Tumor burden (serial U/S)
- Survival: age at sac

KPC tumor diagnosed at 15 wks, 8.9 mm^3

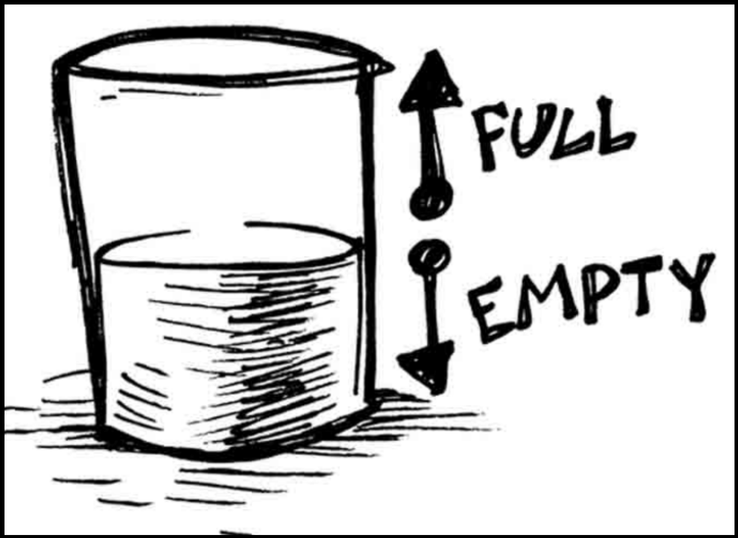
Immunobiology of KPC tumors

- KPC tumors feature low mutational burden, absence of predicted neoepitopes derived from tumor mutations, scant T cell infiltration, and resistance to checkpoint immunotherapy
- Spontaneous tumor progression is identical in the presence or absence of T cells
- Tumors arising in T cell-depleted mice grow unchecked in immune-competent hosts
- Introduction of the neoantigen ovalbumin (OVA) leads to tumor rejection and T cell memory, but not in OVA immune-tolerant mice

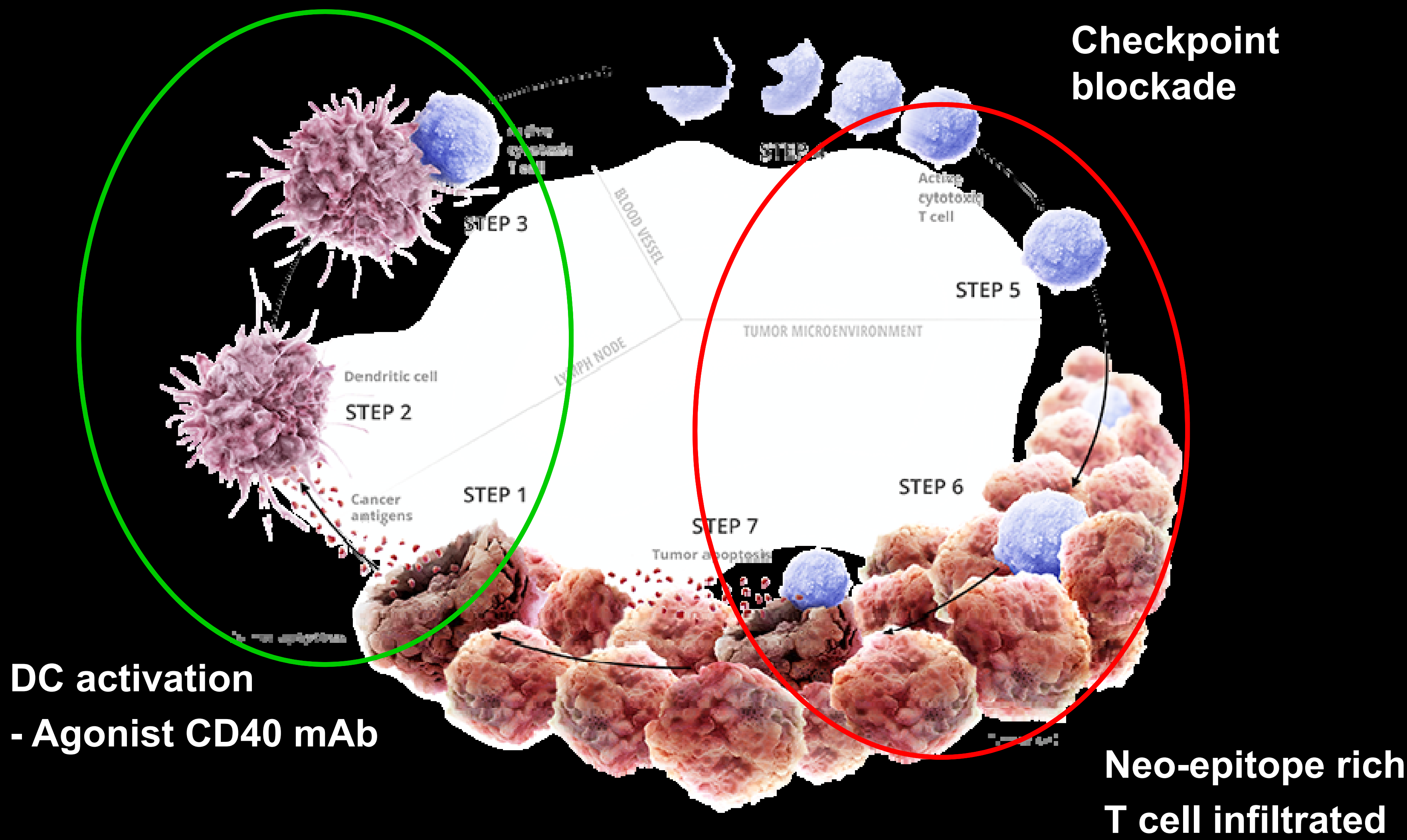
Evans et al, JCI Insight, 2016

Is there a way forward?

- Maybe, in the absence of strong antigens, there is no Darwinian-like pressure from T cells and the underlying pancreatic tumor cells may remain highly susceptible to T cells…. if these can be provoked



Cancer immunity cycle



Adapted from Chen and Mellman. Immunity, 2013.

X plus PD-1

Novel and combination immunotherapy in PDA

FDA approval: PD-1 for MSI-high/dMMR, including PDA

Experimental immunotherapy for PDA:

- BTK inhibitor + Gem/nP
- GVAX/CRS207 +/- PD-1
- CCR2 inhibitor plus chemotherapy
- CXCR4 inhibitor +/- PD-1
- FAK1 inhibitor plus chemotherapy
- SBRT + PD-L1 +/- CTLA4 (RADVAX™)
- Mesothelin- or MUC1-specific CAR T cells
- KrasG12D-specific T cells for HLA-C*08:02
- CD40/Gem/nP +/- PD-1

Johnson et al, CCR, 2017; Thind et al, Therp Adv Gastroenterol, 2017

Agonist CD40 mAb

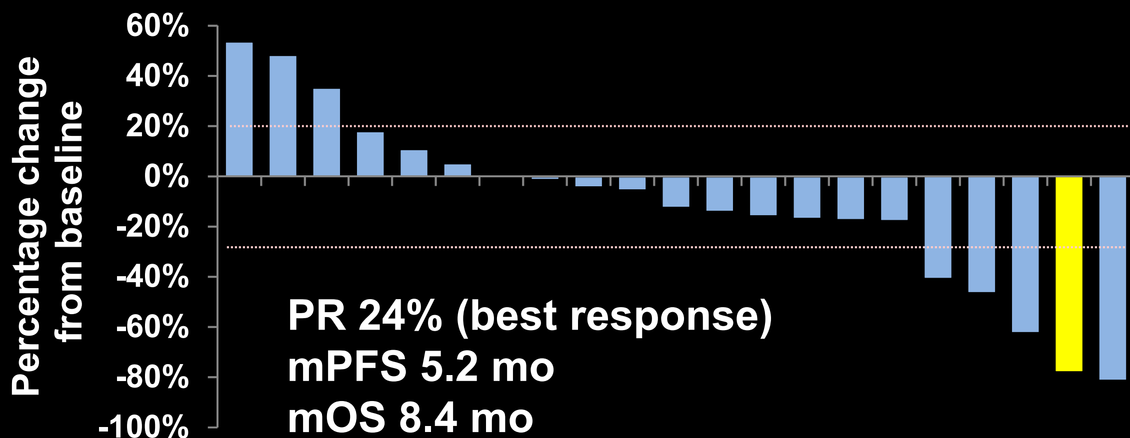
- **Mechanisms**
  - License antigen-presenting cells and activate/prime T cells
  - Re-educate tumor associated macrophages into tumoricidal macrophages
- **Clinical observations so far**
  - Acute activation of antigen presenting cells
  - Mild/moderate, transient CRS and elevation of AST/ALT
  - Multiple CD40 agonists in clinical development now; most still in FIH

Nowak et al, *Cancer Res*, 2003; Beatty et al, *Science*, 2011; Vonderheide and Glennie, *Clin Can Res*, 2013; Beatty et al, *Gastroenterology*, 2015; Winograd et al, *Cancer Immunol Res*, 2015 Long et al, *Cancer Discovery, 2016;* many others

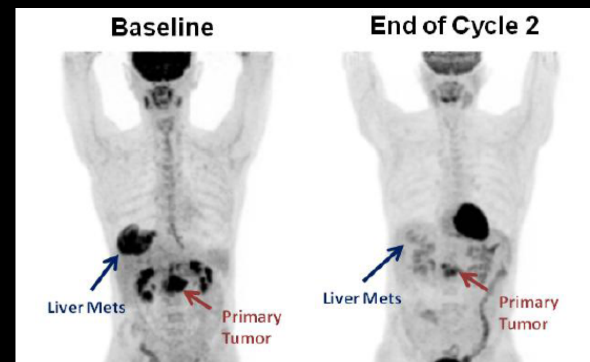
CD40 myths

- Unmanageable and inevitable severe cytokine release syndrome
- Liver failure
- Agonist CD40 mAb require crosslinkg
- No clinical activity

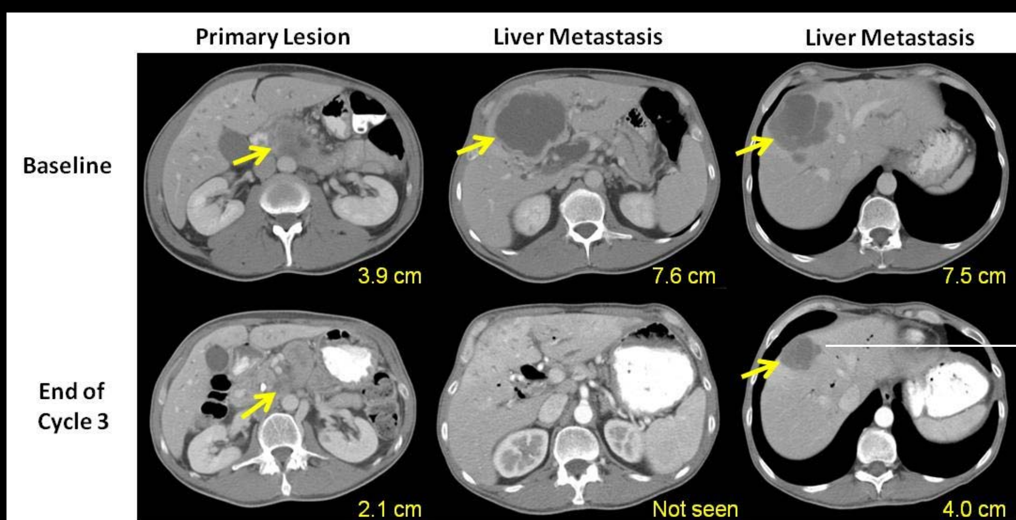
Gemcitabine and agonist anti-CD40 mAb in chemo-naïve metastatic pancreatic carcinoma

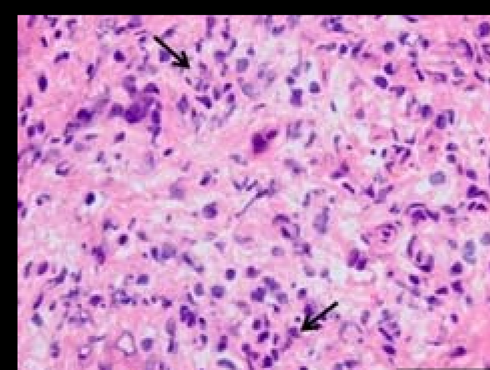


PR 24% (best response)
mPFS 5.2 mo
mOS 8.4 mo



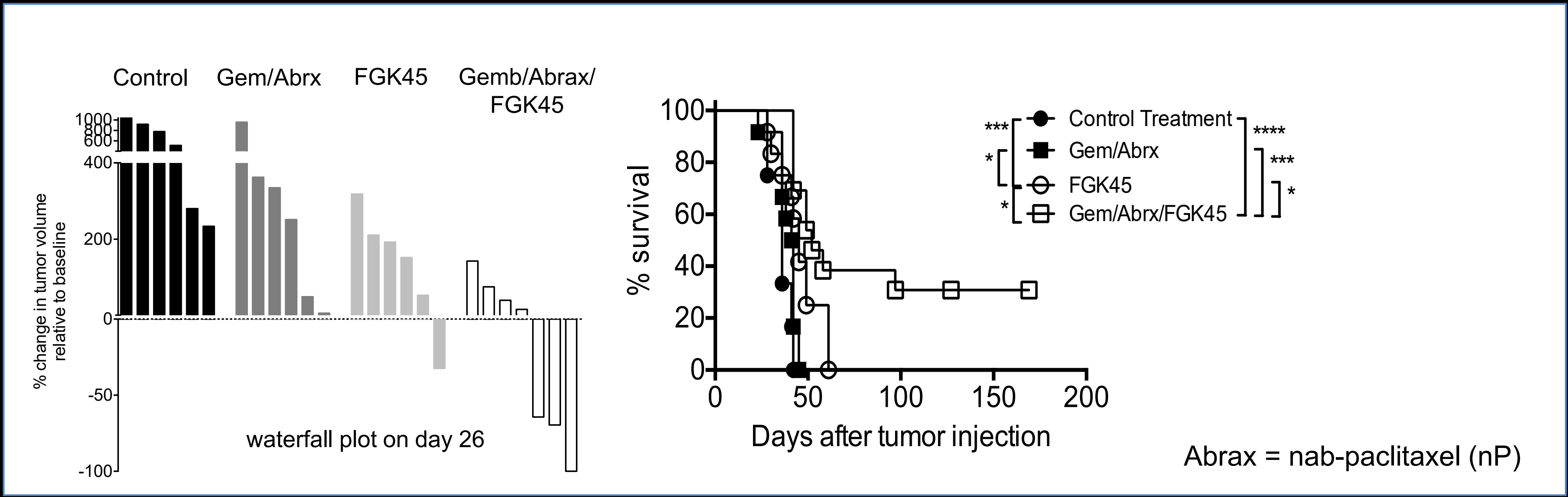
FDG-PET response: 88%





Beatty et al, Science, 2011
Beatty et al, Clin Can Res, 2013

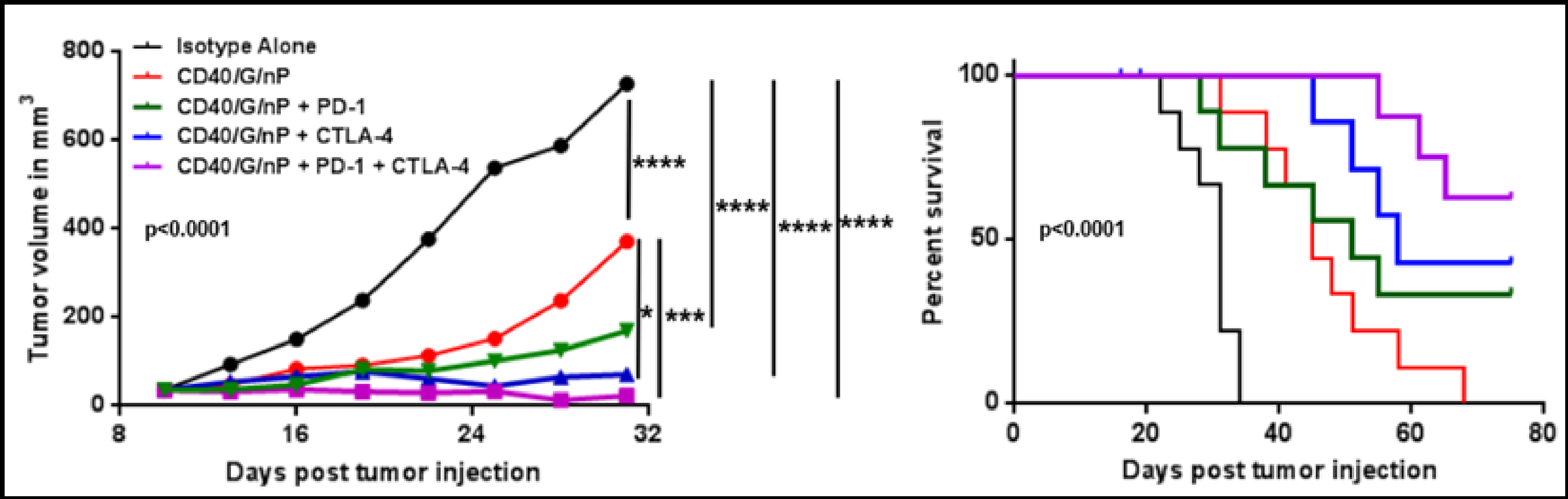
CD40/chemo in KPC model



- **No regressions in T cell-depleted mice or IFNγ KO mice**
- **Dependent on both nP and CD40 for maximal effect**
  - Addition of nP to Gem/CD40 converts mechanism to T cell-dependent, macrophage-independent

Byrne et al, Cell Rep, 2016

CD40/chemo plus checkpoint blockade in PDA

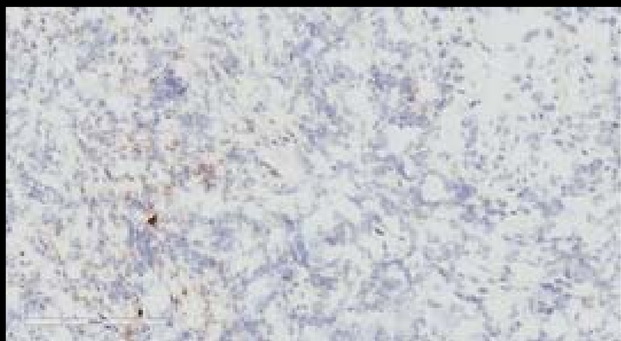


Gem – gemcitabine
nP – nab-paclitaxel (Abraxane)

Winograd et al, Can Immunol Res, 2015

T cell priming to establish responsiveness to checkpoint blockade

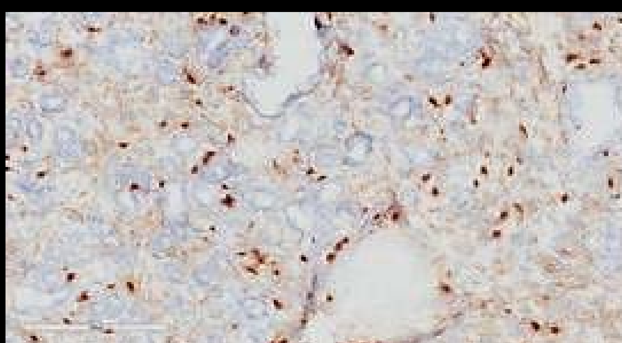
Genetically engineered
KPC mouse model of pancreas cancer
(no classically defined neo epitopes)



CD8 IHC

PD-1, CTLA4, or both → **No tumor response**

Treatment with gemcitabine,
nab-paclitaxel, agonist CD40



PD-1, CTLA4, or both → **Regression**
Improved Survival
Cures
(T cell and BATF dep)

Winograd et al, Cancer Immunol Res, 2015; Byrne and Vonderheide, Cell Reports, 2016

CD40 mAb clinical trials in pancreatic cancer

- **Neoadjuvant/adjuvant Gem/nP + RO7009789 in resectable patients**
  - IND sponsor, Vonderheide
  - Two arm, N=10 pts/arm
  - SU2C-Lustgarten, PanCan, NCI/CITN
  - Penn, Hopkins, U Wash, Case, Wisconsin
  - Primary endpoint: safety and feasibility

- **Gem/nP +/- APX005M +/- nivolumab in naïve metastatic patients**
  - IND sponsor, Parker Institute for Cancer Immunotherapy
  - Overall PI, Vonderheide
  - Three arms, N=35 pts/arm
    - Gem/nP + APX005M
    - Gem/nP + nivolumab
    - Gem/nP + APX005M + nivolumab
  - Primary endpoint: 1 year OS

CD40: special challenges for immune agonists

- Determine optimal schedule
- Optimize route of administration
- Determine role of antibody crosslinking
- Identify combination partners and sequence

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DF/HCC
DANA-FARBER / HARVARD CANCER CENTER

Improving Kidney Cancer Therapy through Novel Clinical Trial Design

David McDermott, MD

Leader, Kidney Cancer Program
Dana-Farber/Harvard Cancer Center
Director, Biologic Therapy and Cutaneous Oncology Programs
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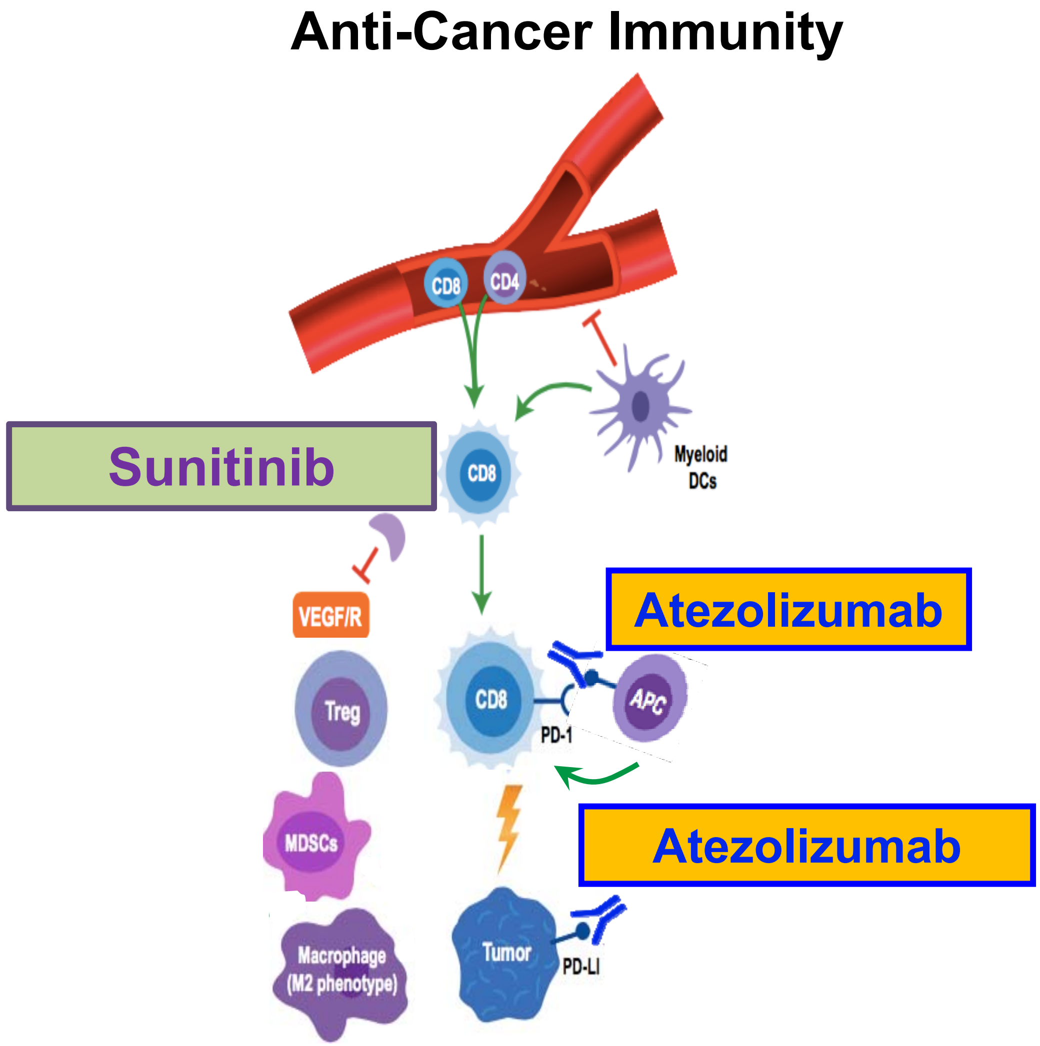
Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-L1 Blockade

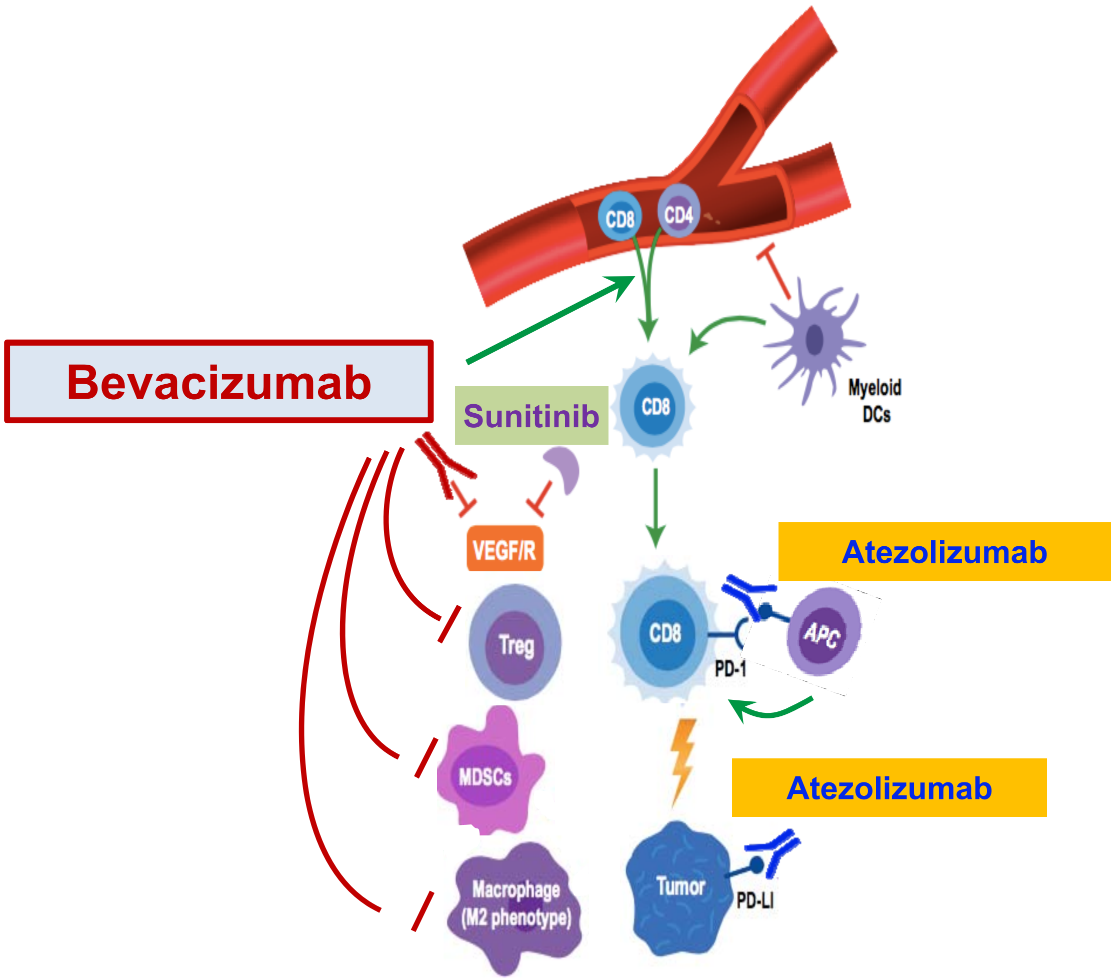


PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.
Finke, *Clin Cancer Res*. 2008; McDermott, *J Clin Oncol*. 2016; Wallin. *Nat Commun*. 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-L1 Blockade

Anti-Cancer Immunity



PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.
Finke, *Clin Cancer Res*. 2008; McDermott, *J Clin Oncol*. 2016; Wallin. *Nat Commun*. 2016.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

First-Line Phase 3 Trials in Advanced RCC

Control	Experimental Arm
Sunitinib	Axitinib + avelumab
Sunitinib	Bevacizumab + atezolizumab
Sunitinib	Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	Axitinib + pembrolizumab
Sunitinib	Nivolumab + ipilimumab

Are these approaches advances in immunotherapy?

PD-1 Ab + Chemo = Improvement in Immunotherapy?

Pembrolizumab (Keytruda) 5-10-2017

On May 10, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA®, Merck and Co., Inc.) in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC).

Approval was based on a cohort (G1) of patients enrolled in an open-label, multicenter, multi-cohort study (KEYNOTE-021). A total of 123 patients with locally advanced or metastatic non-squamous NSCLC and no prior systemic treatment for metastatic disease were enrolled. Patients were randomized to receive either pembrolizumab, 200 mg every 3 weeks, in combination with pemetrexed and carboplatin (PC) for 4 cycles followed by pembrolizumab for a maximum of 24 months (n=60) compared to PC alone (n=63). At the investigator's discretion, patients in both arms may have received pemetrexed as maintenance therapy. Randomization was stratified by PD-L1 tumor expression (tumor proportion score [TPS] <1% vs. TPS ≥1%).

The trial demonstrated an improvement in overall response rate (ORR) and in progression-free survival (PFS) for patients randomized to pembrolizumab plus PC. The ORR was 55% (95% CI: 42-68%) for the pembrolizumab plus

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**

PATIENTS

NSCLC

Treatment Naïve

Open-Label

N=123 pts

Unselected

Primary Endpoint = ORR

RANDOMIZE

ARM A

Carbo + Pem

ARM B

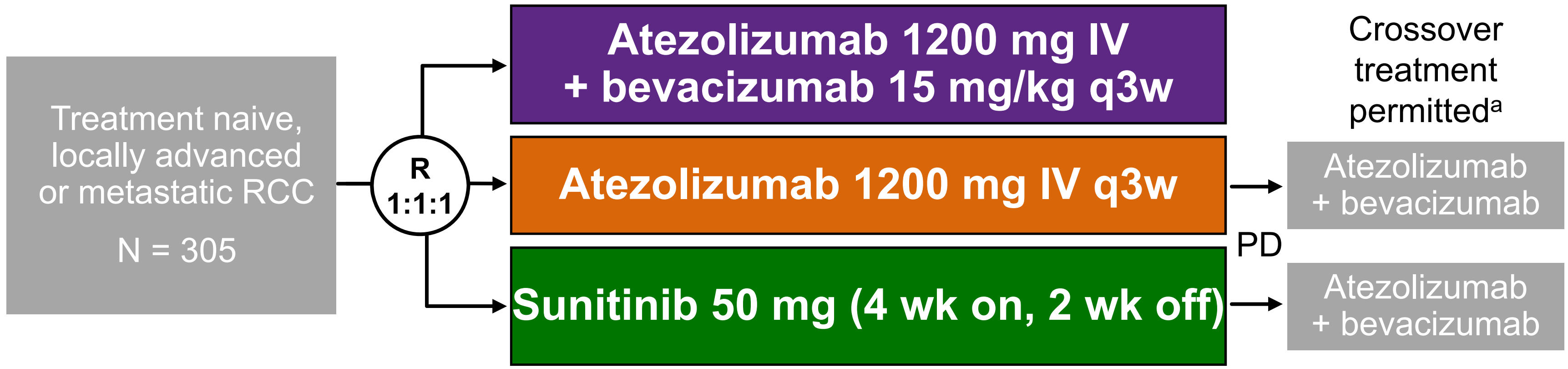
C + P/Pembro

Rational Application of Combination IO Therapy: Lessons Learned from Immotion 150

- **Trial Design**
  - **Proper Controls**
  - **Adequate Size**
- Patient Selection
- Novel Endpoints

IMmotion150 (Phase II) Trial Design

First-Line Treatment



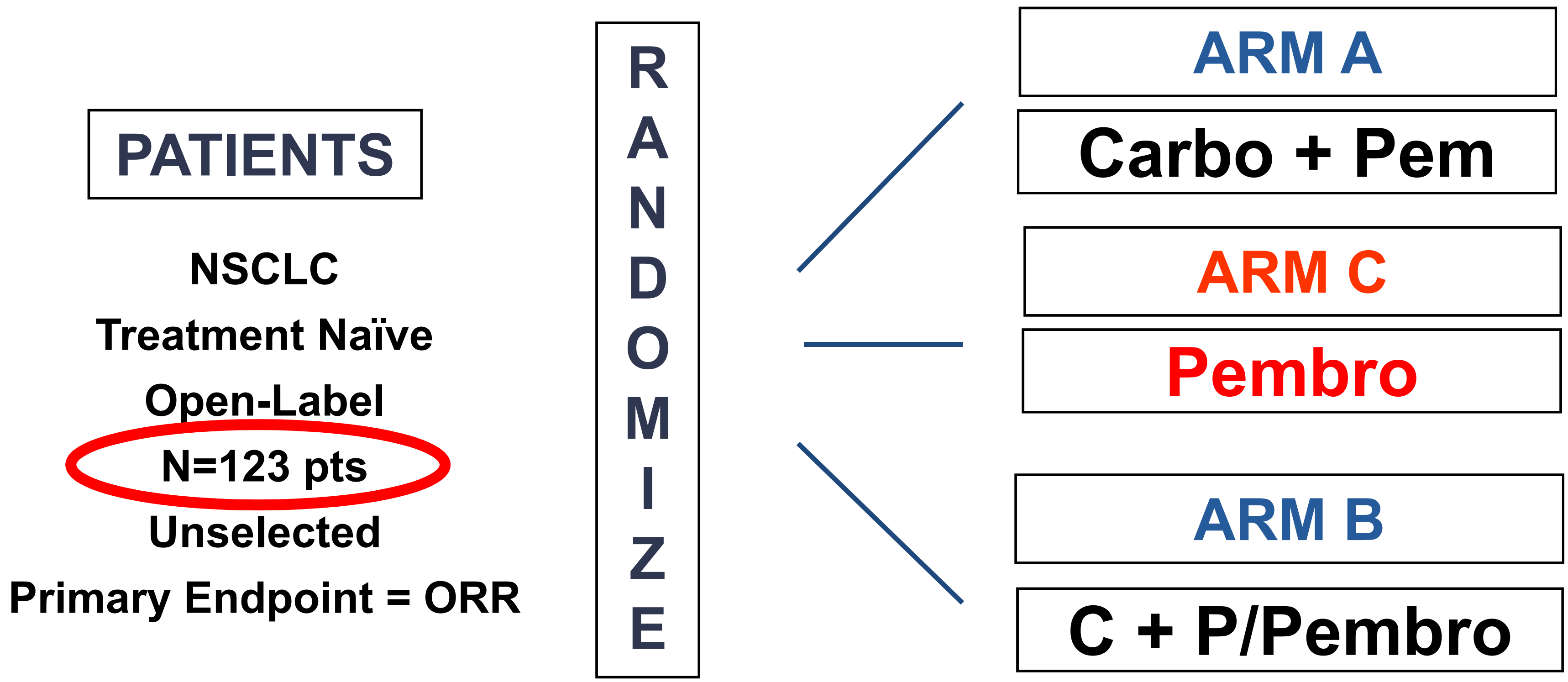
- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Coprimary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with ≥ 1% of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures

IC, tumor-infiltrating immune cells; IRF, independent review facility; ITT, intention-to-treat; TME, tumor microenvironment.
[a] Crossover from atezolizumab monotherapy not allowed in Europe.
McDermott, *JCO* 2016; McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

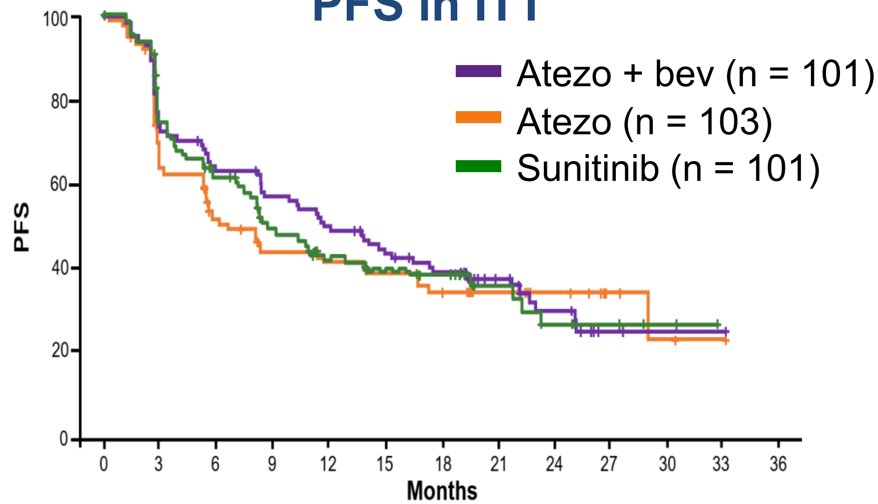
*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**



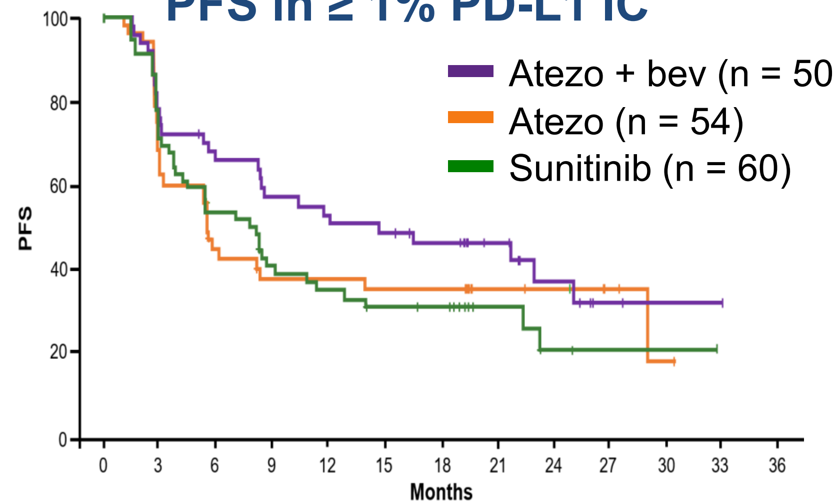
Lancet Oncology 2017

Encouraging Efficacy by PFS of Atezolizumab + Bevacizumab vs Sunitinib in Patients With IC PD-L1 Expression

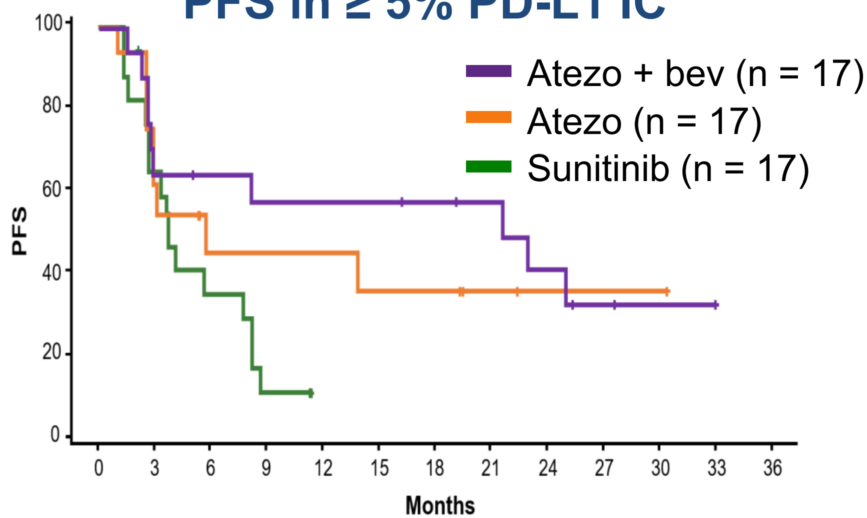
PFS in ITT



PFS in ≥ 1% PD-L1 IC



PFS in ≥ 5% PD-L1 IC



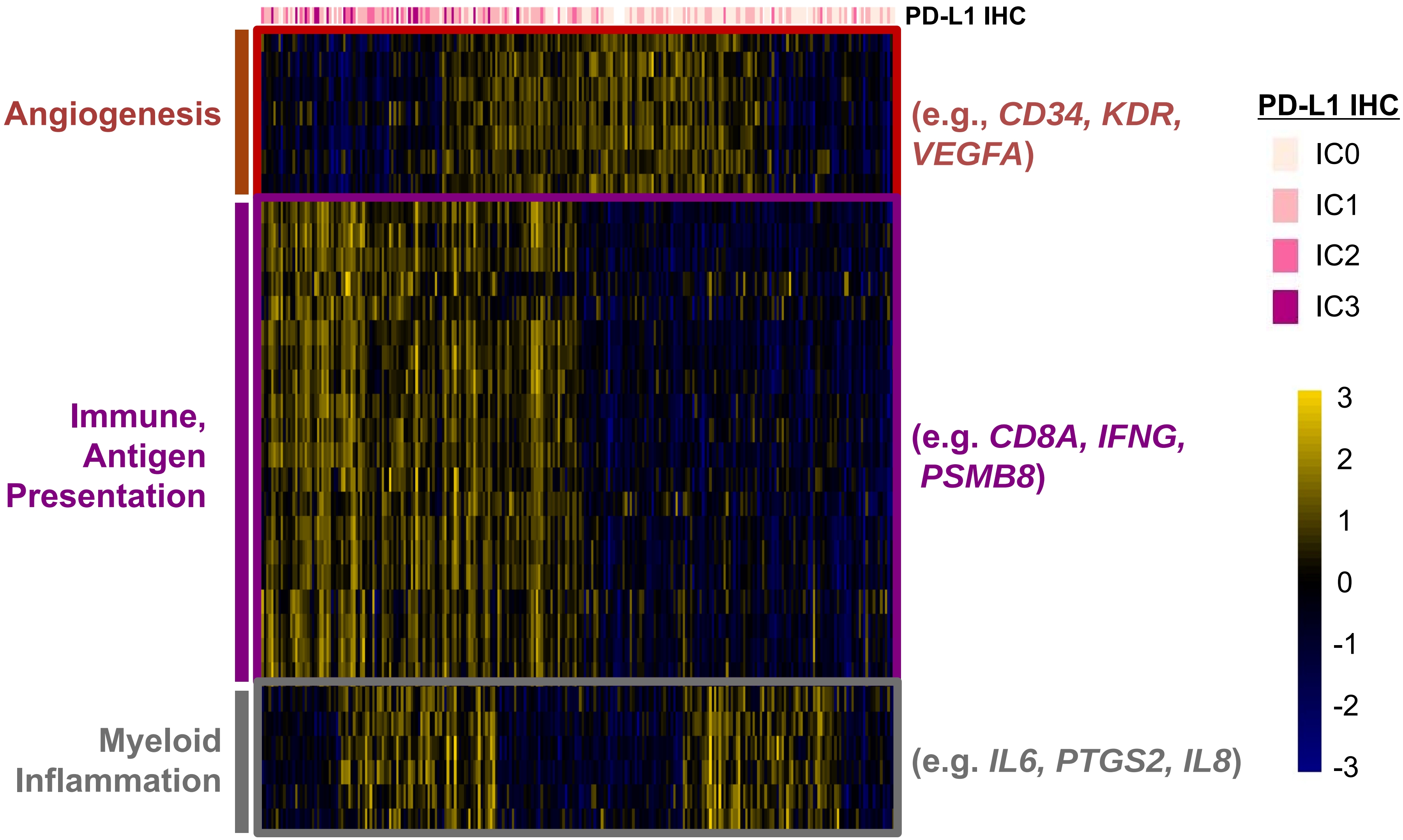
Atezo, atezolizumab; bev, bevacizumab. IRF-assessed PFS.
McDermott, ASCO GU 2017.

Stratified HR (95% CI)			
	ITT	≥ 1% PD-L1 IC	≥ 5% PD-L1 IC
Atezo + bev vs sunitinib	1.00 (0.69, 1.45)	**0.64 (0.38, 1.08)**	**0.34 (0.13, 0.91)**
Atezo vs sunitinib	1.19 (0.82, 1.71)	1.03 (0.63, 1.67)	**0.64 (0.27, 1.54)**

with tumors expressing < 1% PD-L1 on IC and ≥ 1% PD-L1 on IC

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors



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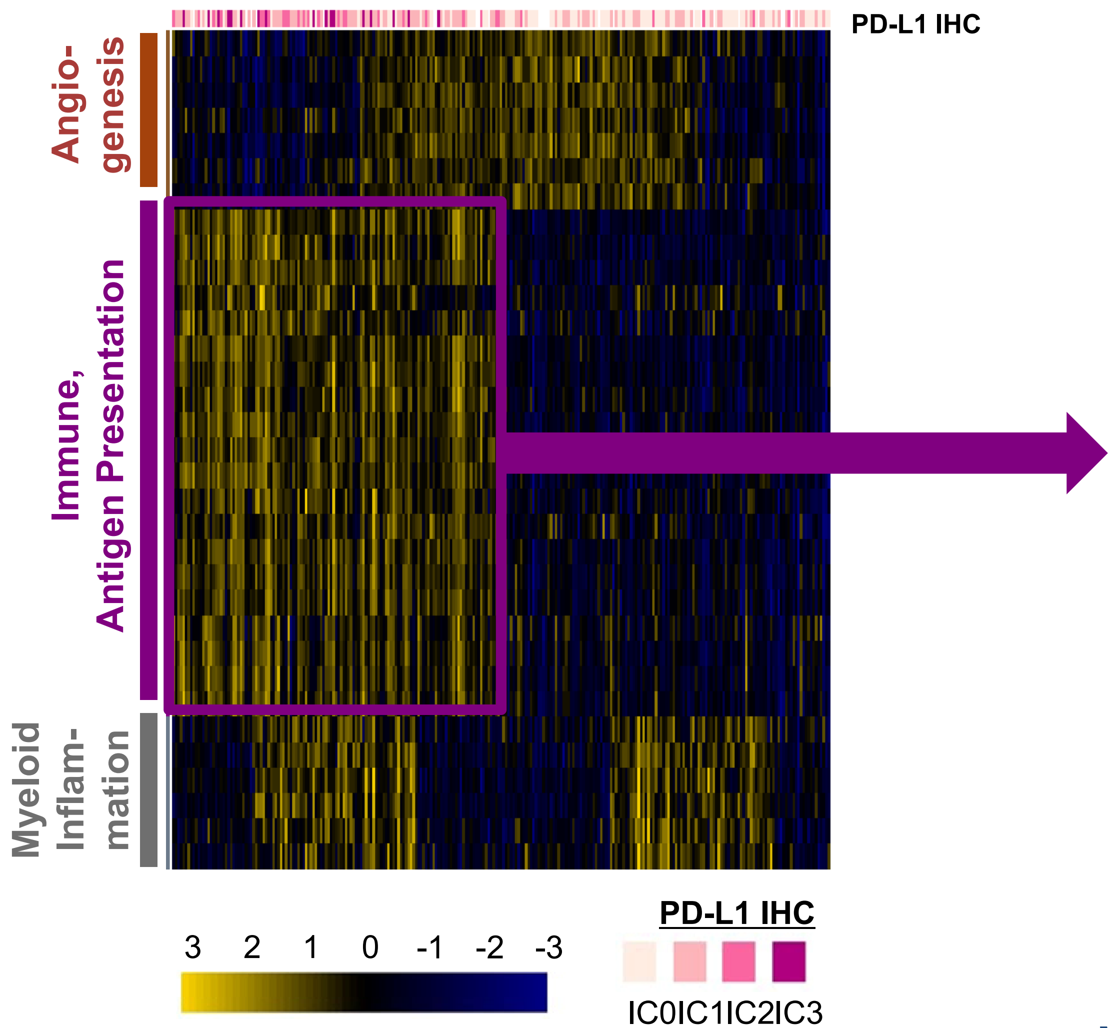
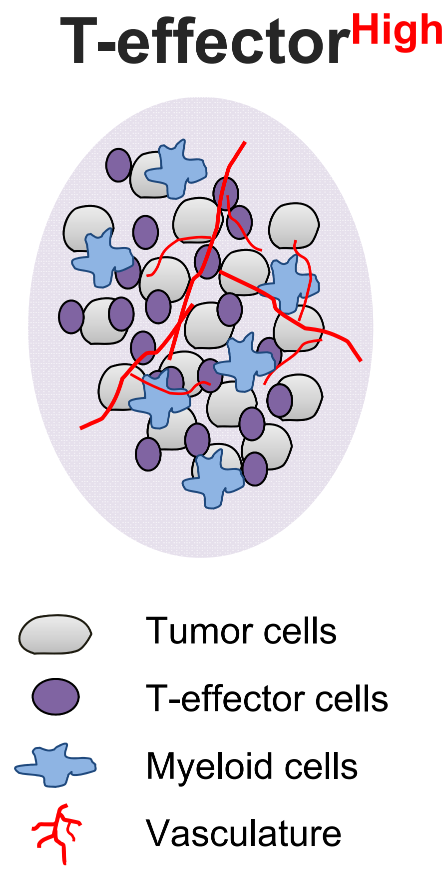
Immune





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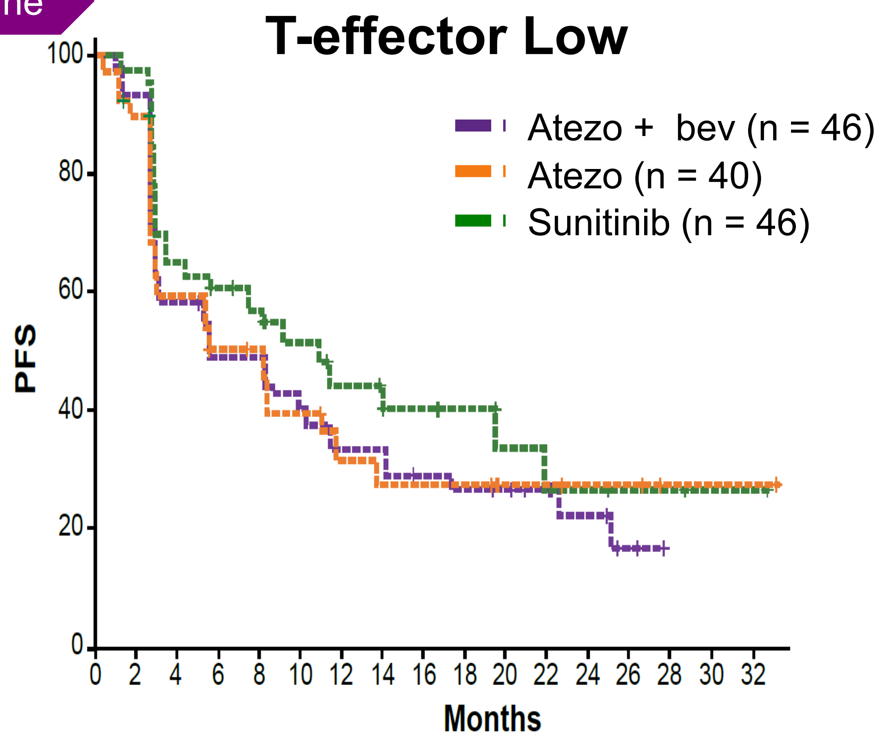
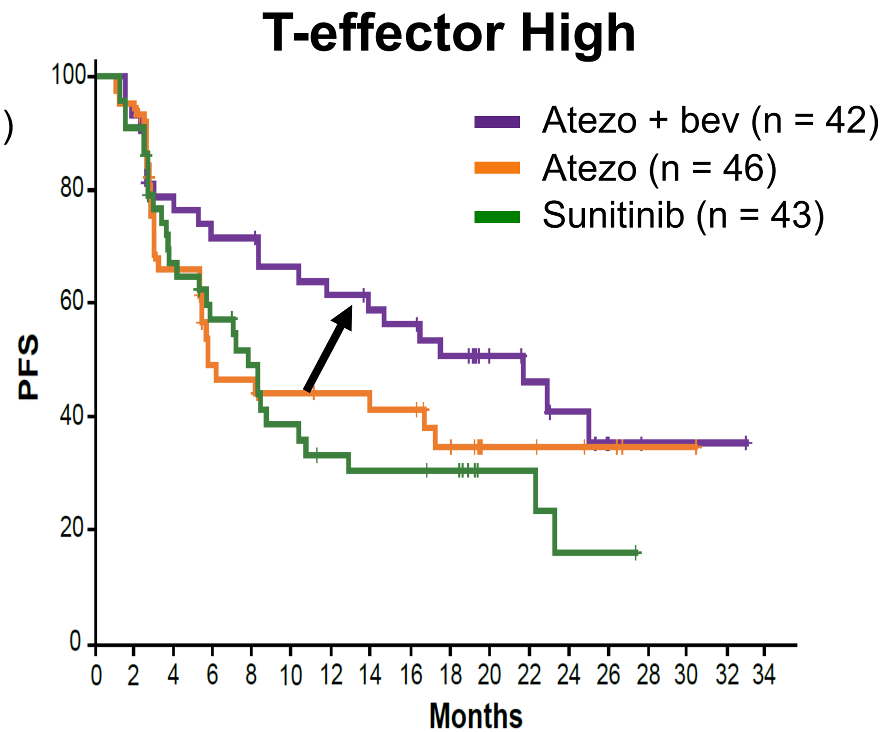
McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Atezolizumab and Bevacizumab Demonstrated Improved PFS vs Sunitinib in the T-Effector^{High} Subset

Immune





HR (95% CI)		
	T-effector Low	**T-effector High**
Atezo + bev vs sunitinib	1.41 (0.84, 2.36)	**0.55 (0.32, 0.95)**
Atezo vs sunitinib	1.33 (0.76, 2.33)	0.85 (0.50, 1.43)

T-effector gene signature: *CD8A, EOMES, PRF1, IFNG, CD274*.
T-effector High: ≥ median expression, T-effector Low: < median expression.

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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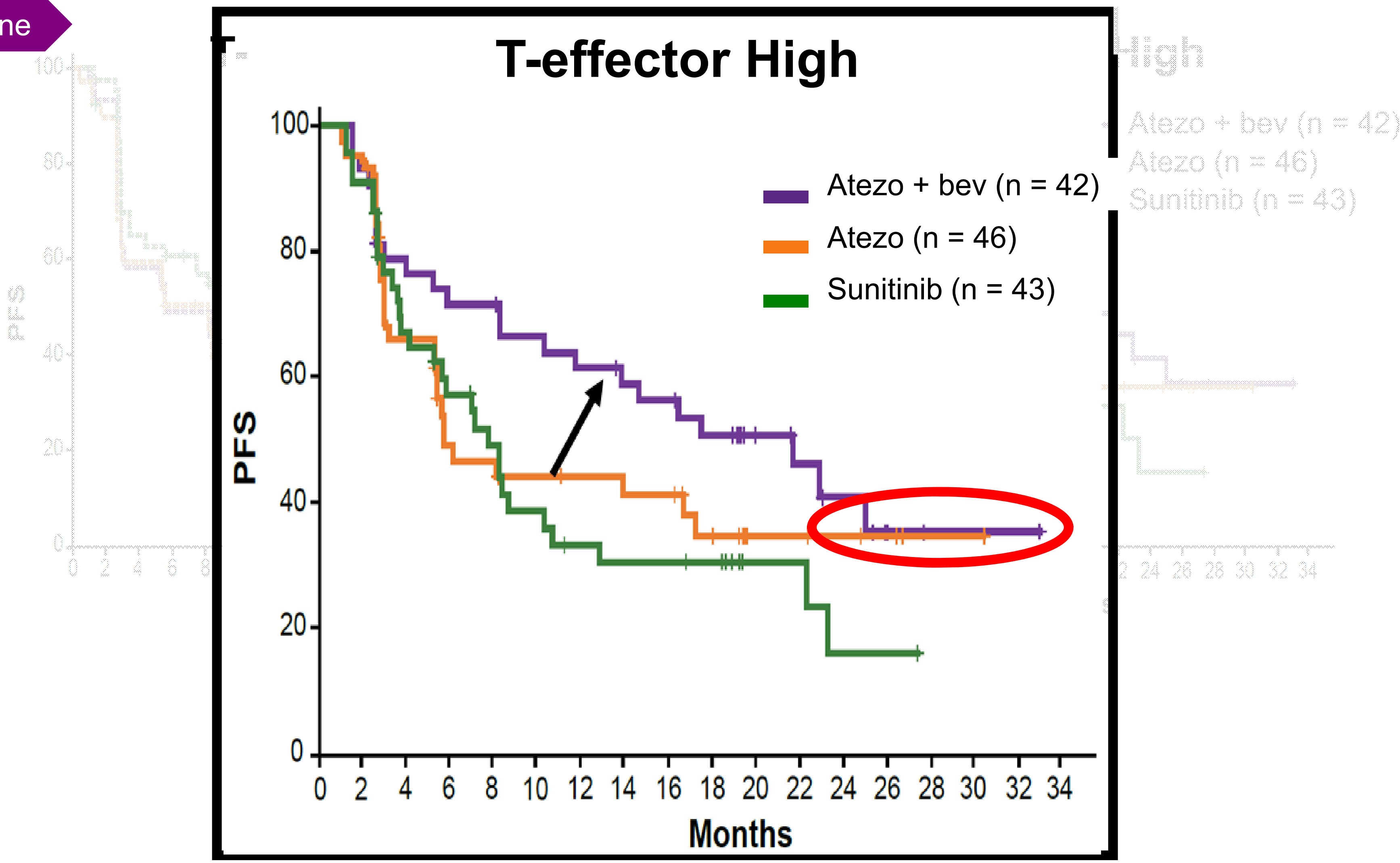

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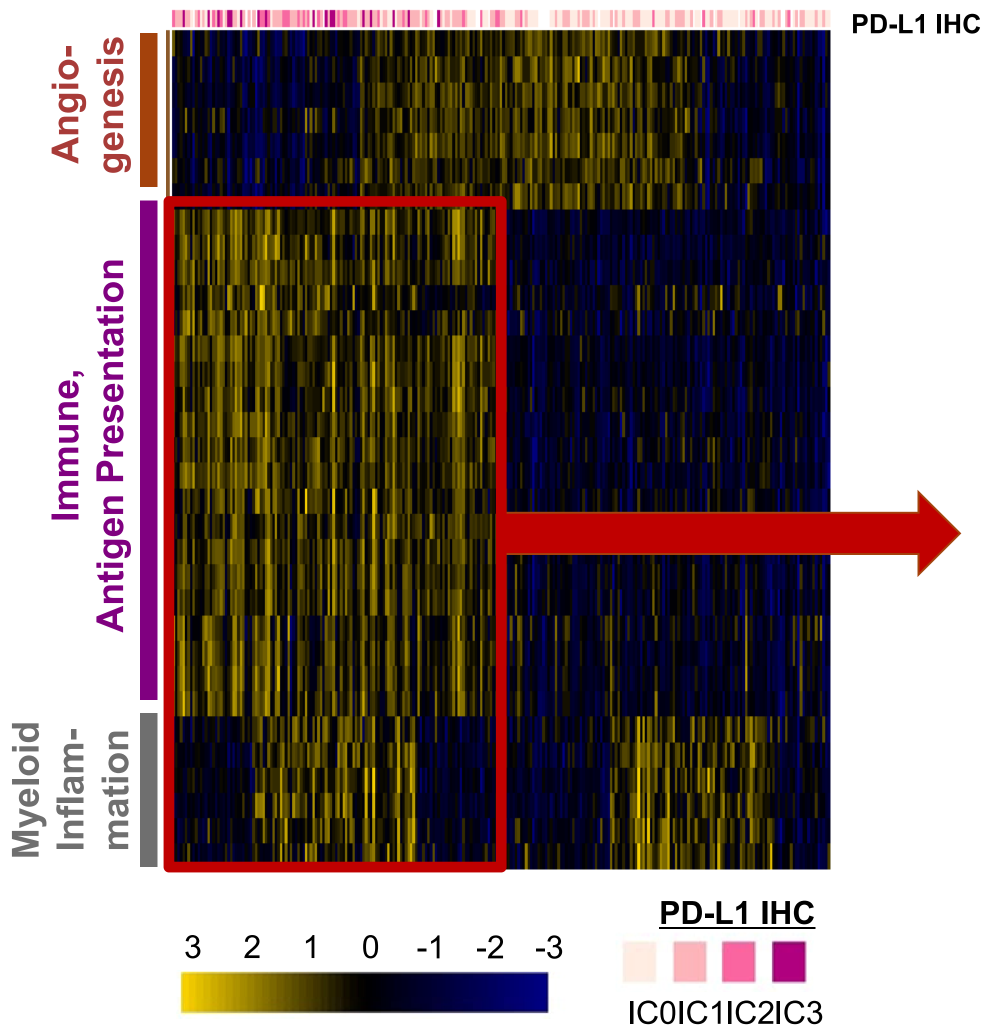
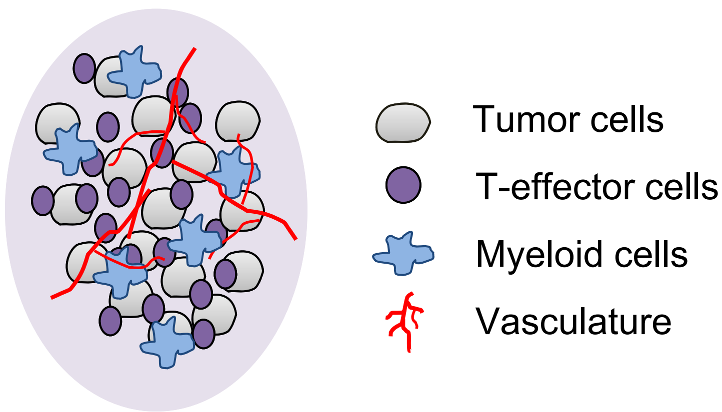
Myeloid Inflammation



T-effector^{High} Subpopulation



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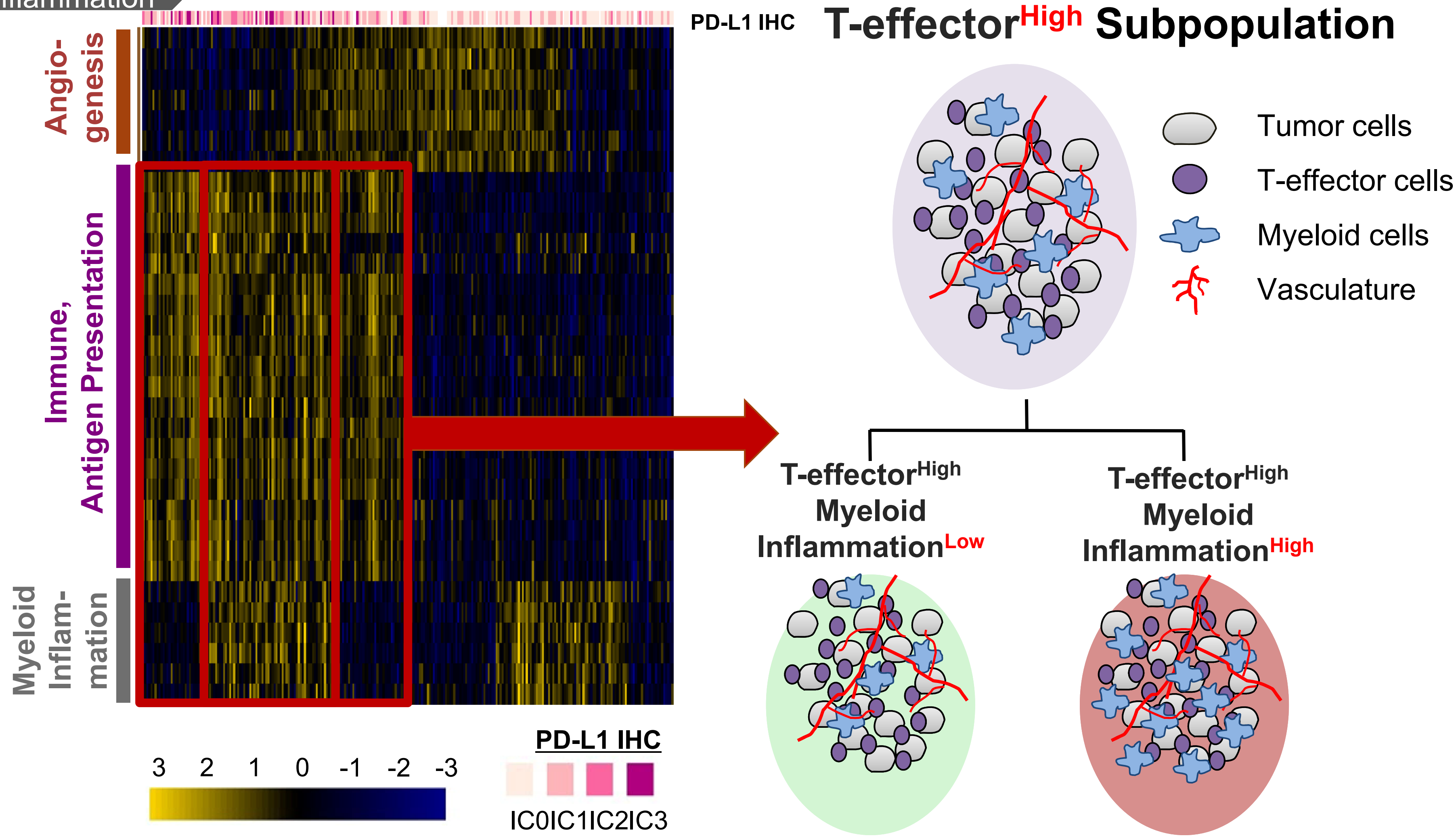

Brauer, *Clin Cancer Res.* 2012; Herbst, *Nature* 2014; Powles, *SITC* 2015; Fehrenbacher, *Lancet* 2016.

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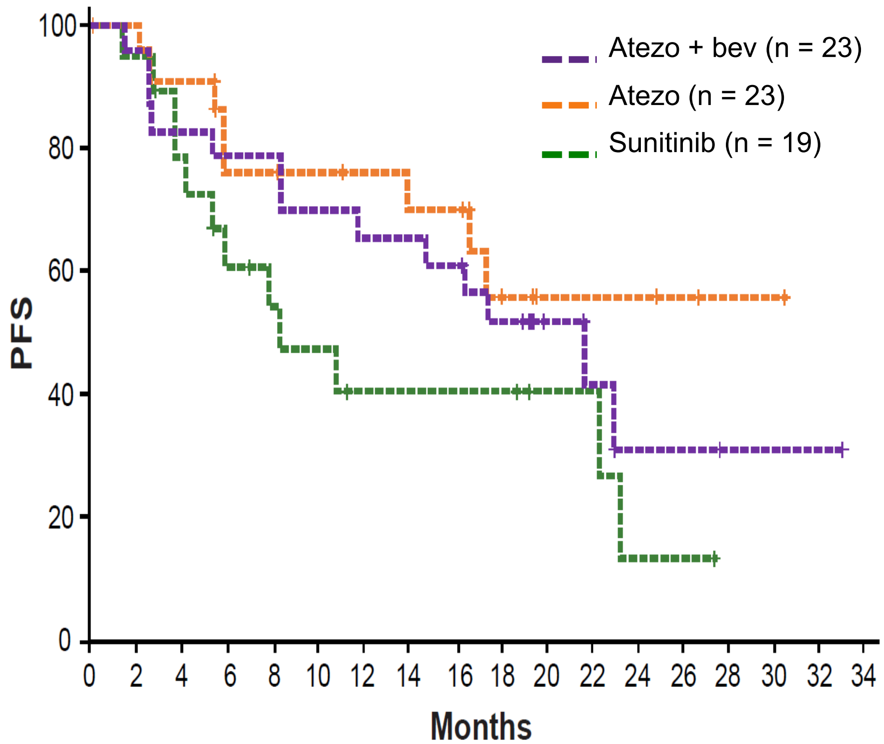
Addition of Bevacizumab to Atezolizumab in 1L Was Associated With Improved Benefit in T-Effector^{High} Myeloid Inflammation^{High} Subgroup

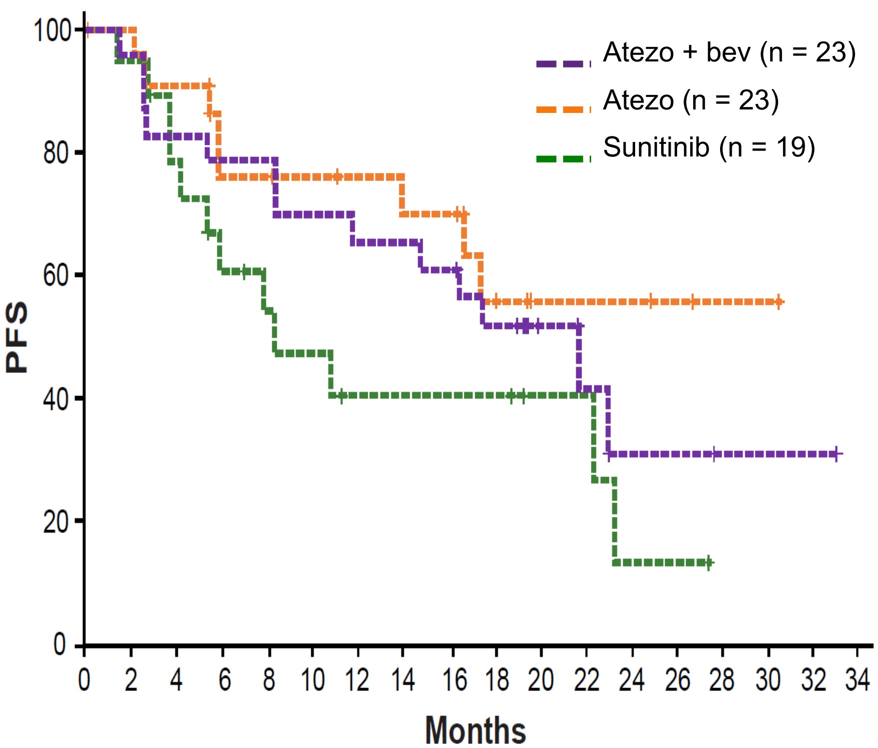
T-effector^{High} Myeloid Inflammation^{Low}



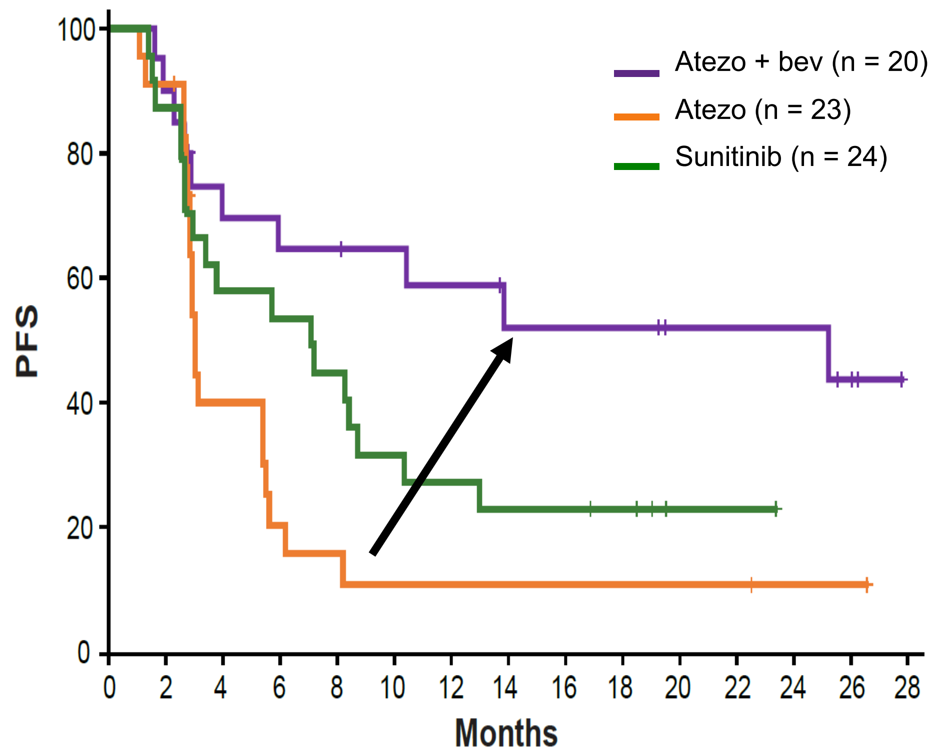
PFS measured by independent review facility.
T-effector gene signature: *CD8A, EOMES, PRF1, IFNG, CD274*.
High, ≥ median expression; low, < median expression. McDermott, AACR 2017.

Addition of Bevacizumab to Atezolizumab in 1L Was Associated With Improved Benefit in T-Effector^{High} Myeloid Inflammation^{High} Subgroup

T-effector^{High} Myeloid Inflammation^{Low}



T-effector^{High} Myeloid Inflammation^{High}



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Rational Application of Combination IO Therapy: Lessons Learned from Immotion 150

- Trial Design

- **Patient Selection**
  - **Impact of RNA Seq**

- Novel Endpoints

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

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NSCLC

Treatment Naïve

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N=123 pts

Unselected

Primary Endpoint = ORR

RANDOMIZE

ARM A

Carbo + Pem

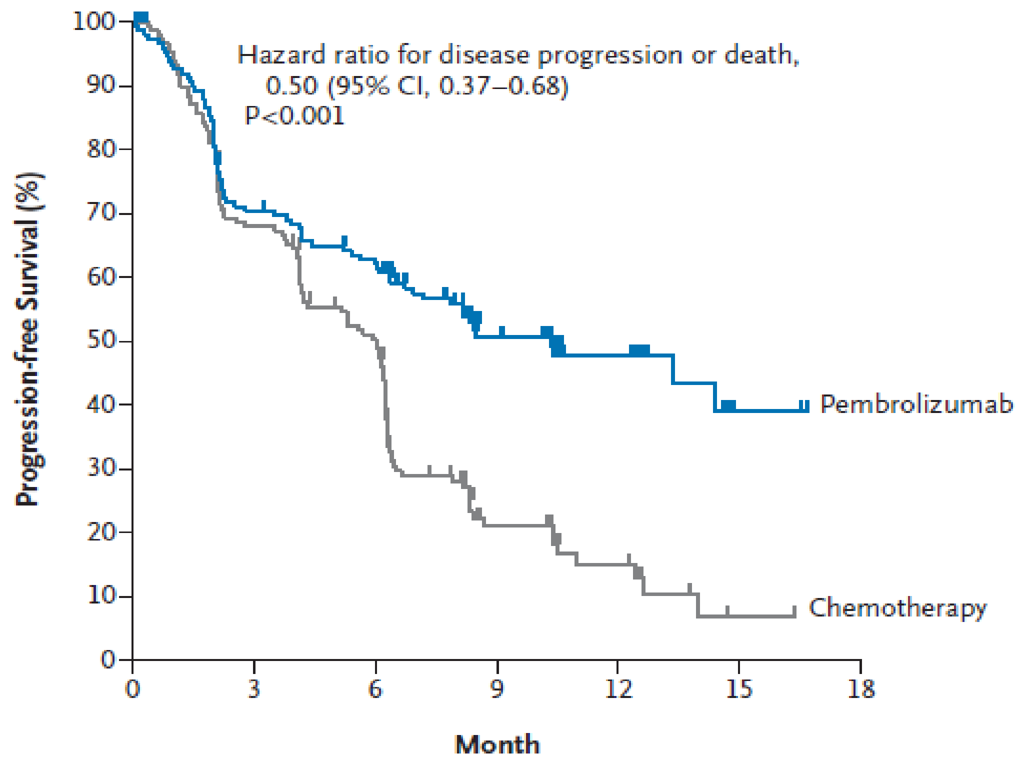
ARM B

C + P/Pembro

Lancet Oncology 2017

The NEW ENGLAND JOURNAL of MEDICINE

A



No. at Risk

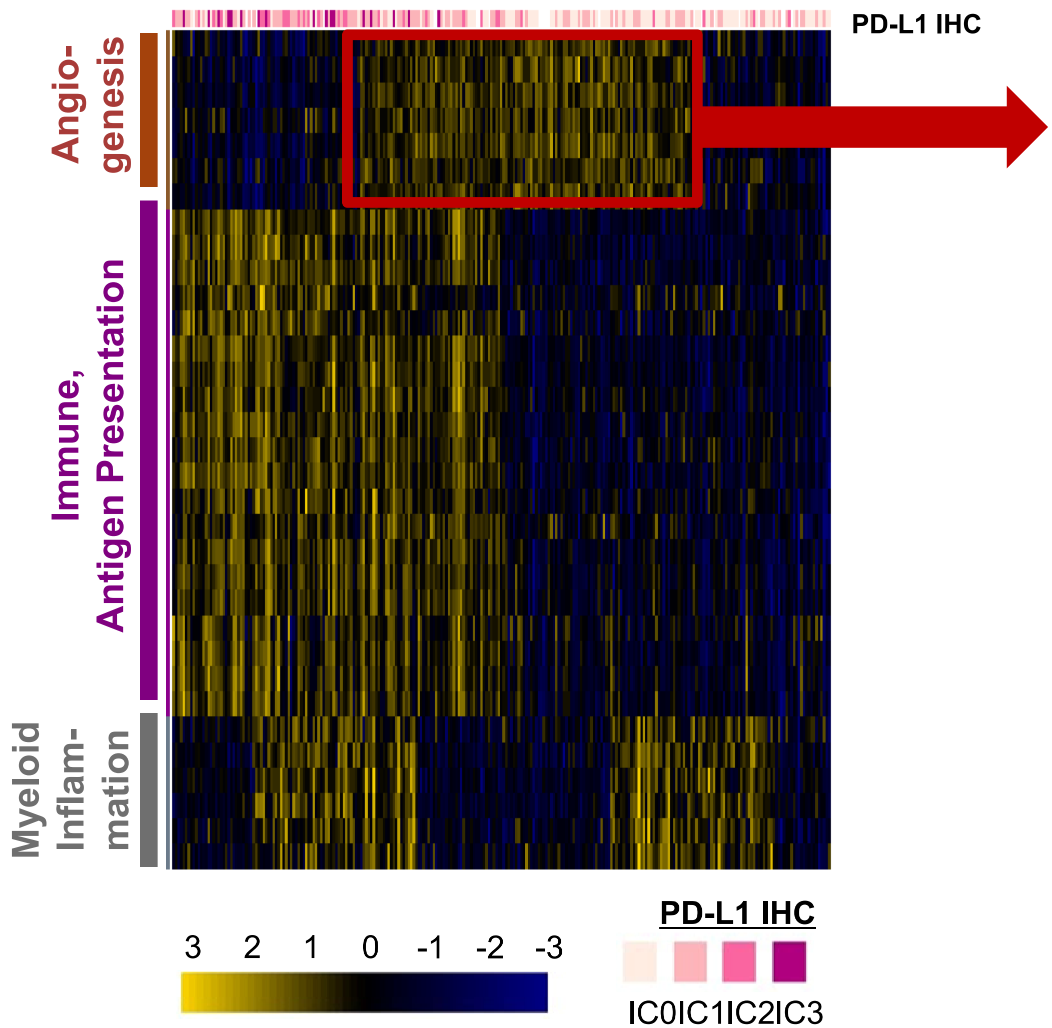
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

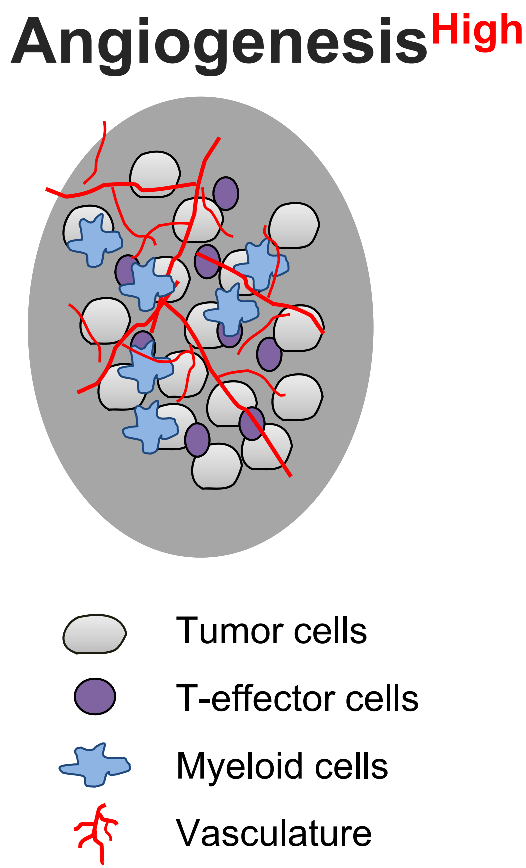
Nivo P3 Trial: Antitumor activity

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)	12.0 (0–27.6+)	12.0 (0–22.2+)
Ongoing response, n/N (%)	45/103 (44)	8/22 (36)

Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

Angiogenesis





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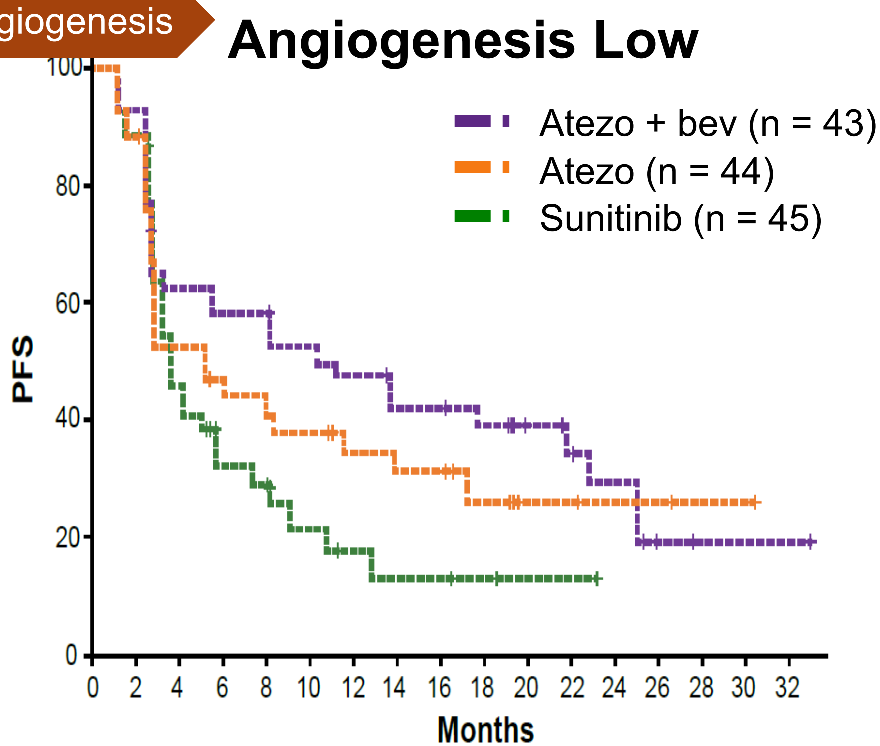
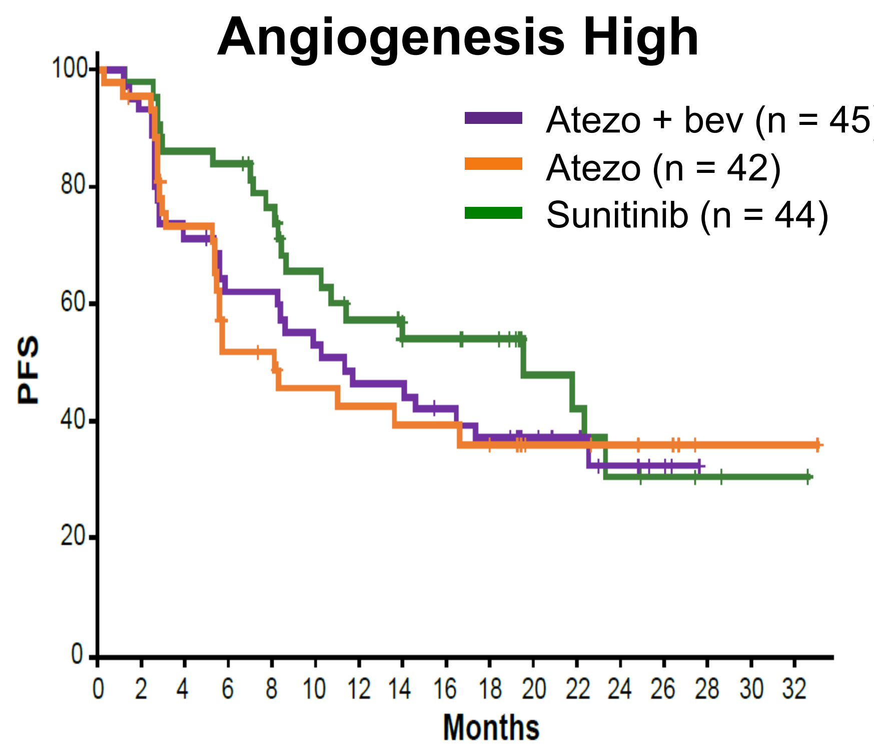
Angiogenesis

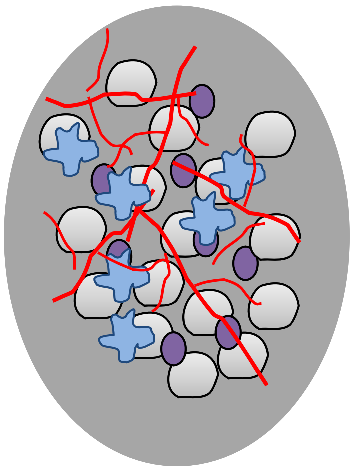




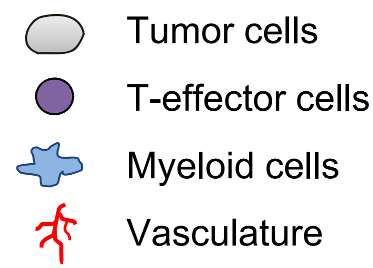
HR (95% CI)		
	Angiogenesis Low	**Angiogenesis High**
Atezo + bev vs sunitinib	0.58 (0.35, 0.98)	**1.36 (0.78, 2.36)**
Atezo vs sunitinib	0.75 (0.45, 1.25)	**1.45 (0.81, 2.60)**

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Molecular Correlates of Differential Response to Atezolizumab ± Bevacizumab vs Sunitinib in mRCC



Angiogenic



Clinical Activity

Sunitinib

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

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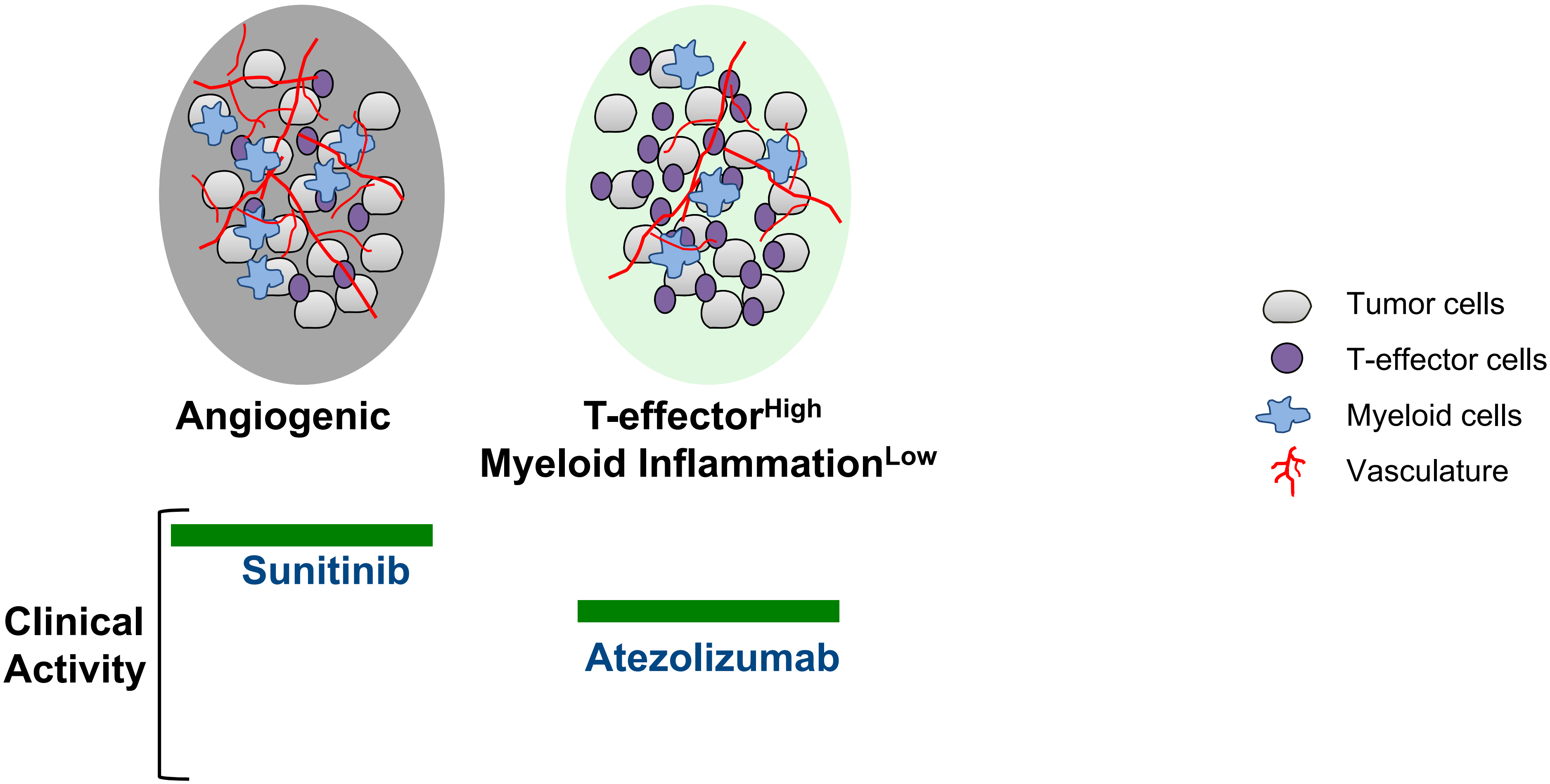

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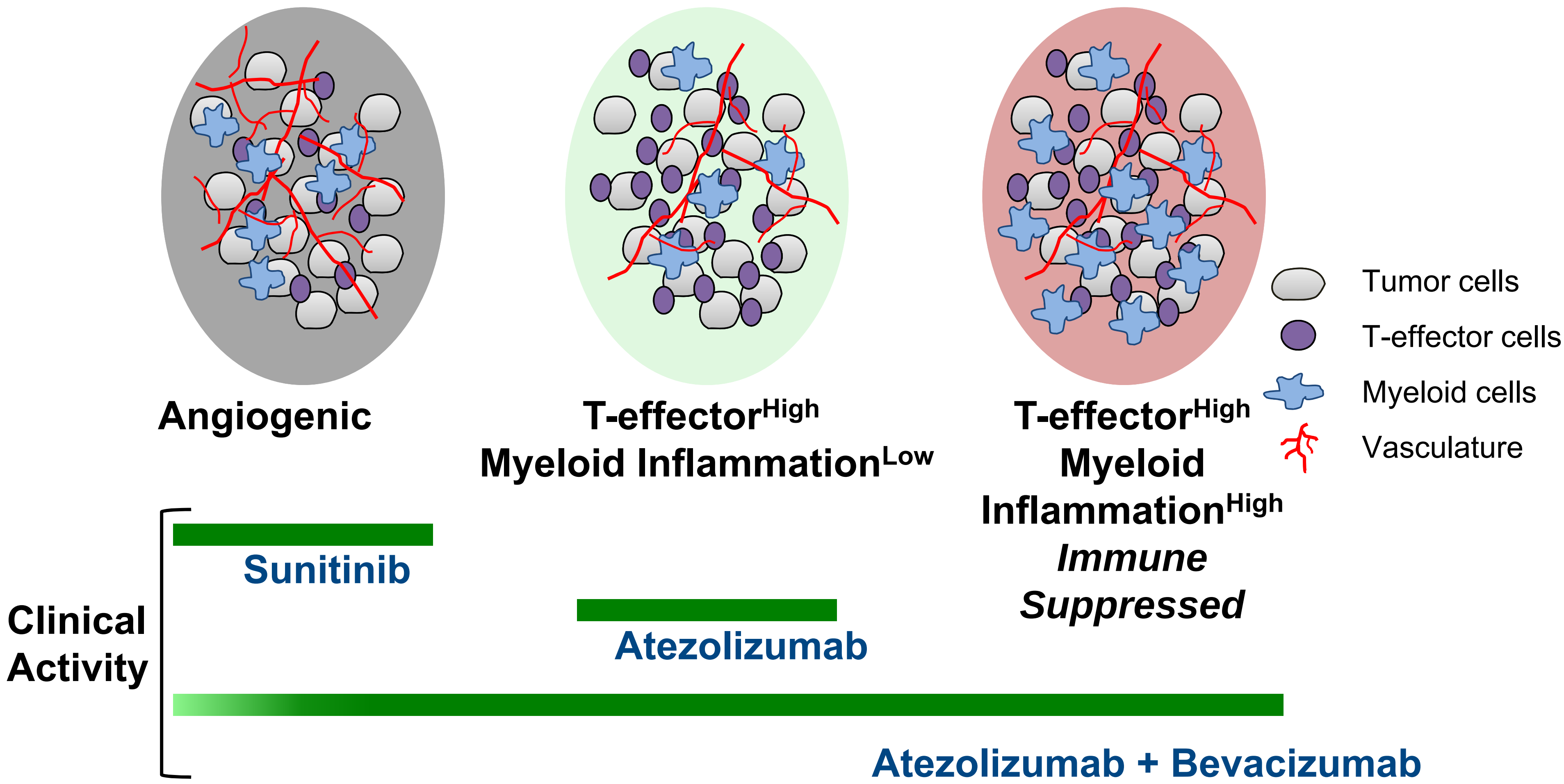

McDermott D, et al. IMmotion150 biomarkers: AACR 2017

Rational Application of Combination IO Therapy: Lessons Learned from Immotion 150

- Trial Design
- Patient Selection
- **Novel Endpoints**
  - **IO not MT or chemo**

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

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Lancet Oncology 2017

Immunotherapy Endpoints?

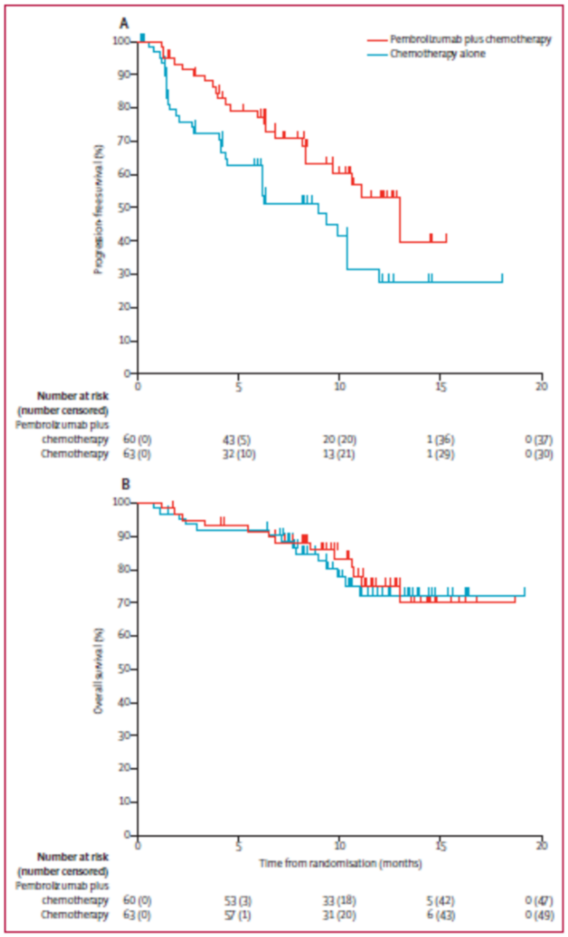


Figure 3: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)**
Progression-free survival assessed per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review in the intention-to-treat population.

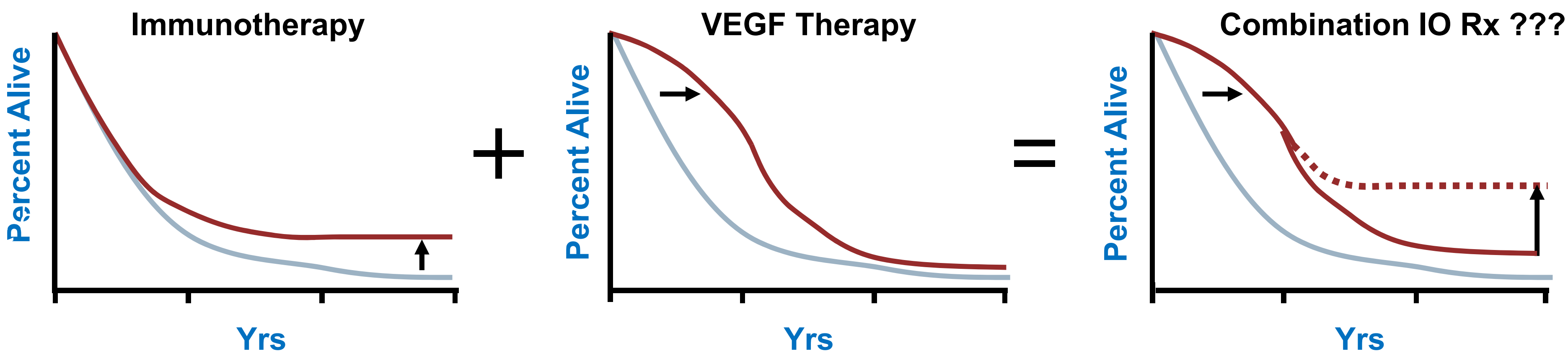
Improved ORR and mPFS

What about OS?

Does the combination regimen improve IO outcomes?

Slide courtesy of R. Sullivan, MGH

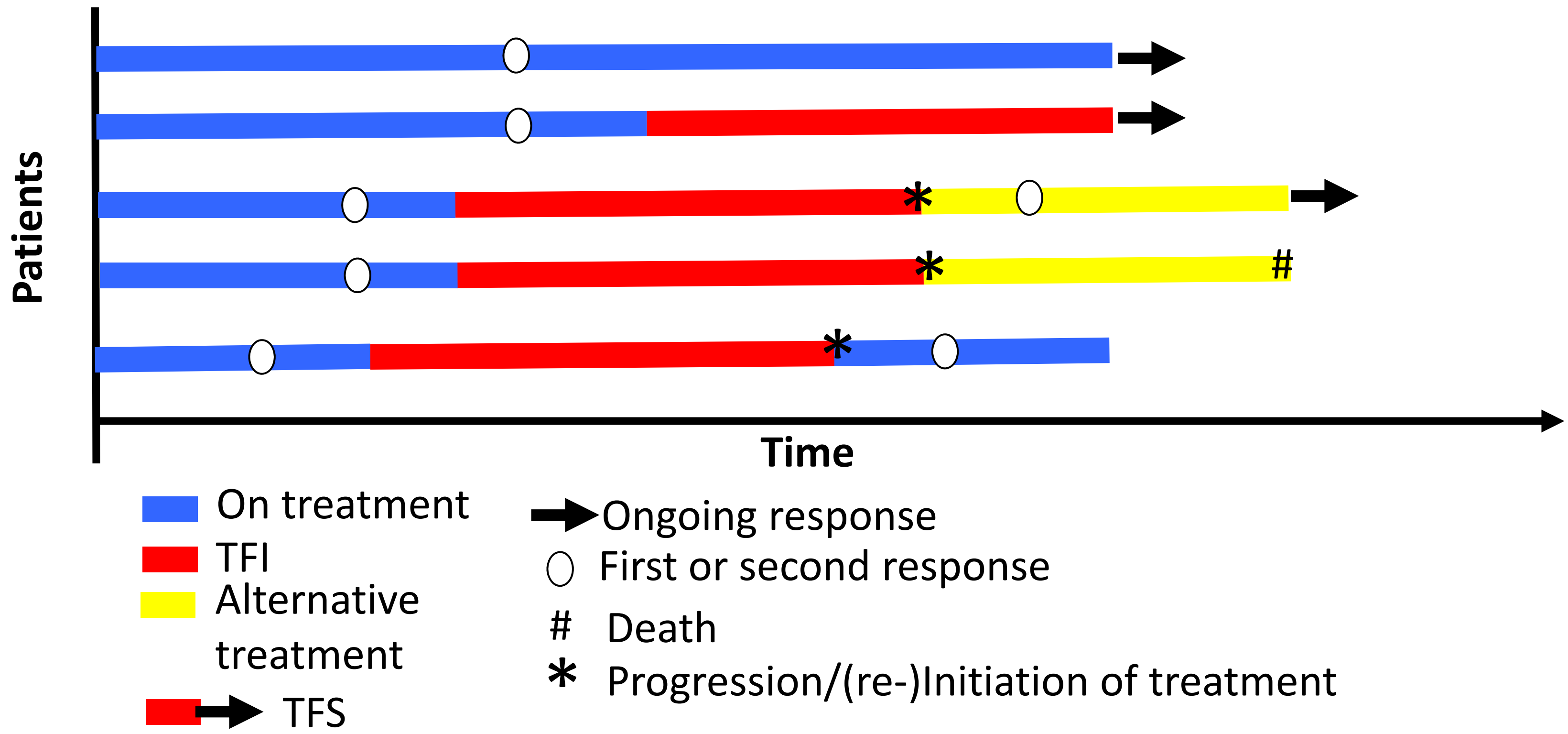
Combining VEGF and PD-1 Blockade:
Is it Immunotherapy?



- If **YES** – combinations with become SOC in front-line
- If **NO** – then many will favor sequence – less toxicity and cost
- Improvements in predictive biomarkers may support sequential single agent approach
- PD-1 + VEGF likely > VEGF <u>but</u> is PD-1 + VEGF > VEGF followed by PD-1?

Slide courtesy of T RIbas

Treatment-free Survival
A New Endpoint?



Izar et al, Cancer 2016

Will Cost Impact Access to Therapy?: Lessons from Melanoma

Regimen cost for "typical" patient (80 kg) with Melanoma in Phase 3 (Checkmate 067)[a]

Drug	Median Doses	Cost
Nivolumab	15	$89,000
Nivolumab + ipilimumab	4	$150,000
Remission	0	0

- Nivolumab: $24.70/mg[b]
- Ipilimumab: $135.18/mg[b]

[a]Larkin J et al. *N Engl J Med.* 2015; 373:23-34.
[b]First quarter 2016, in US dollars.

Conclusions

Rational application of IO Rx in RCC:

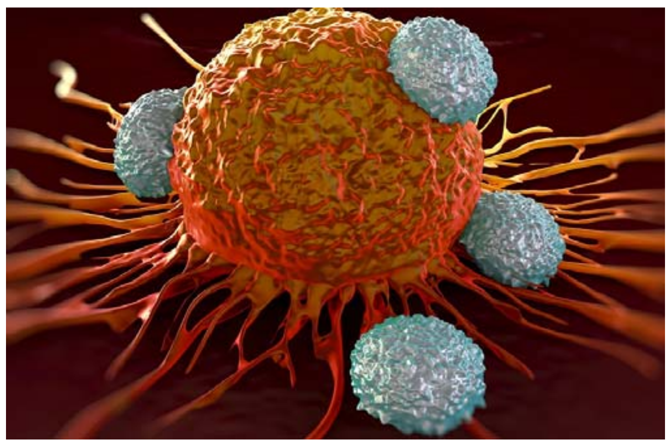
- FDA/NCI/HMO Support for:
  - Innovative Trial Design
  - Novel Endpoints
- Focus on the Goals:
  - Improving Predictive Biomarkers
  - Customizing Appropriate Rx Duration
  - Increasing Remission Rate

Food and no-Drug Administration

Acknowledgements

- Participating study investigators and clinical sites
- The Immotion 150 study was sponsored by F. Hoffmann-La Roche, Ltd
- Genentech Translational Team
  - Mahrukh Huseni, Priti Hegde
- DF/HCC KCP SPORE Colleagues

Provoking Breast Cancer Immunity with Strategic Immunotherapy Combinations



Leisha A. Emens, MD PhD
Bloomberg-Kimmel Institute of Cancer Immunotherapy
Johns Hopkins University School of Medicine

Disclosure Information

I have the following financial relationships to disclose:

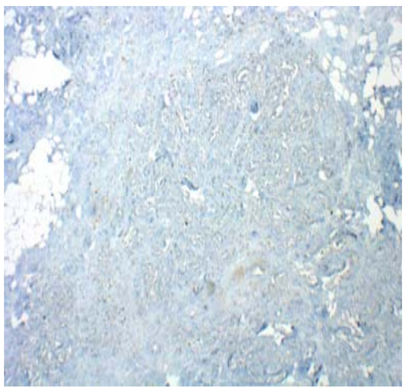
Consultant for: Vaccinex, Celgene, Bristol Meyers Squibb, AstraZeneca, Amgen, Syndax, Molecuvax, eTHeRNA, Peregrine, Bayer, Gritstone

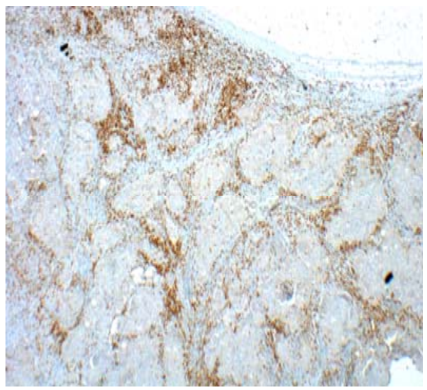
Grant/Research support from: Genentech/Roche, EMD Serono, Maxcyte, Merck, AstraZeneca, Aduro, Corvus

Under a licensing agreement between Aduro Biotech, and the Johns Hopkins University, the University and Dr. Emens are entitled to milestone payments and royalty on sales of a GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

The Immune System and Breast Cancer

Cold **Hot**





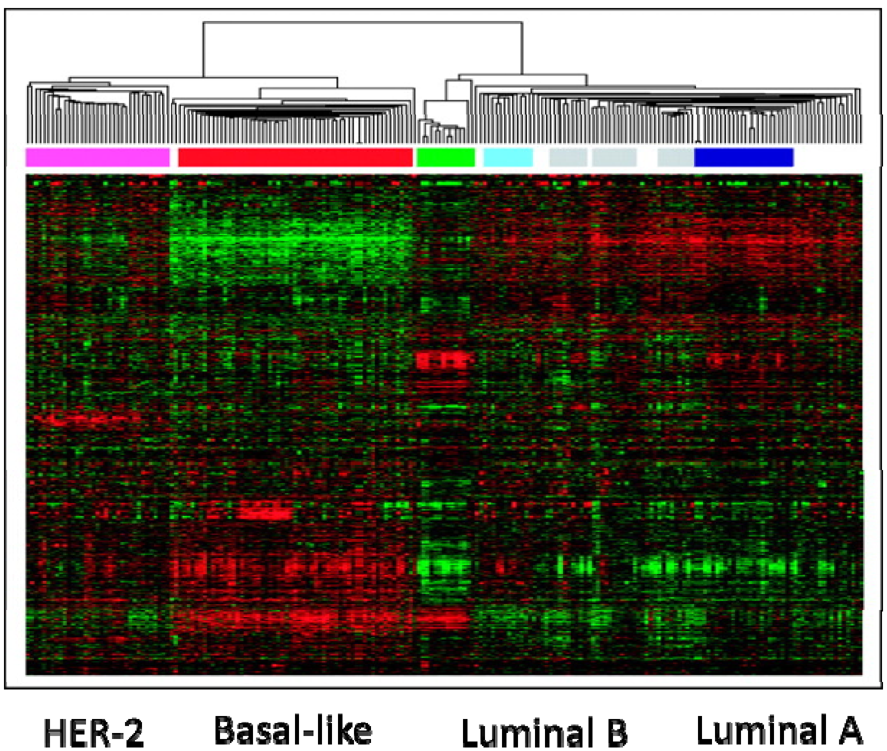
ER+ BC **HER-2+ BC** **TNBC**

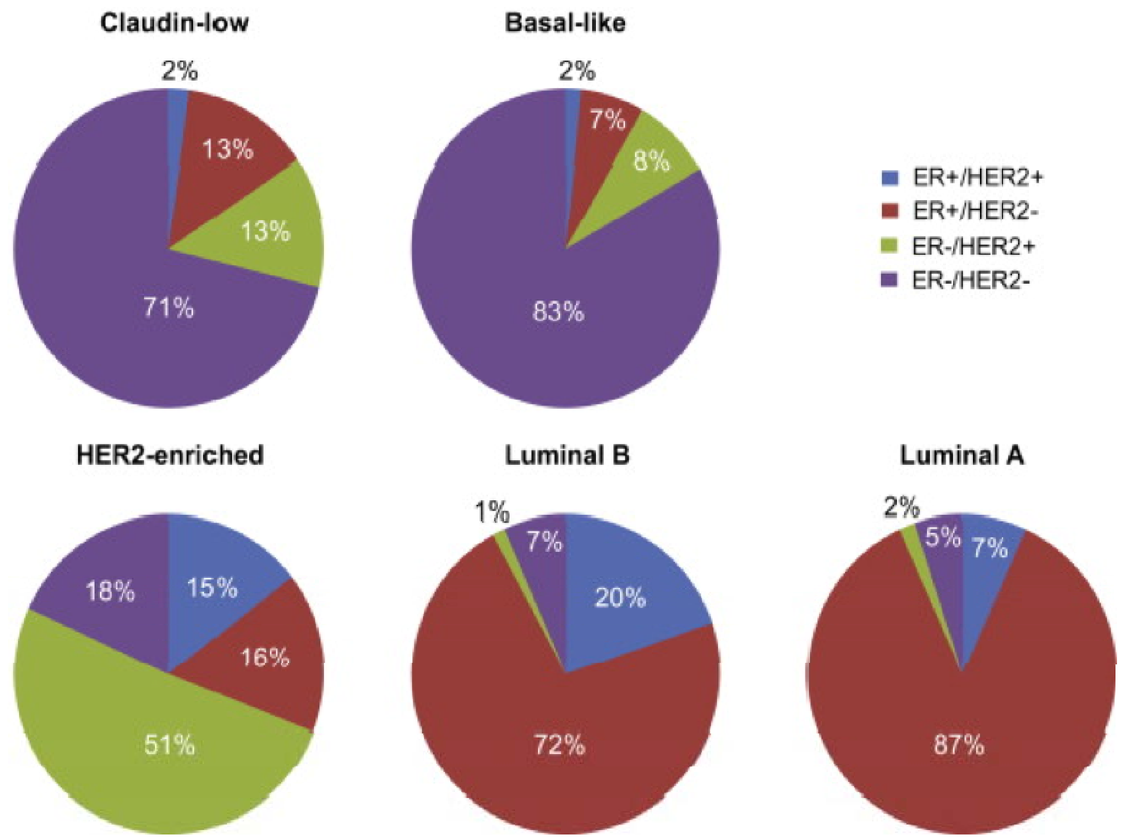
Gajewski TF Semin Oncol 2015 42: 663-71.
Herbst RS et al Nature 2014 515: 568-71.
Chen DS Mellman I Immunity 2013 39: 1-10.
Cimino-Mathews A/Emens LA, unpublished images.

- Poor prognostic factors (ER^{neg}, PR^{neg}, high grade, LN^{+}) are associated with higher T cell infiltrates at diagnosis
- Higher numbers of $CD8^{+}$ TILs and a higher CD8+ T cell/FoxP3+ Treg ratio predict better clinical outcomes (cPR, DFS, OS), except for ER+ BC
- TNBC and HER-2+ breast cancers are high value targets for cancer immunotherapy
  --No approved targeted therapies for TNBC
  --Potentially synergistic targeted therapies in HER-2+ BC
- ER+ breast cancers present the challenge of transforming tumors from cold to hot

Clinical versus Intrinsic Breast Cancer Subtypes

Intrinsic Breast Cancer Subtypes





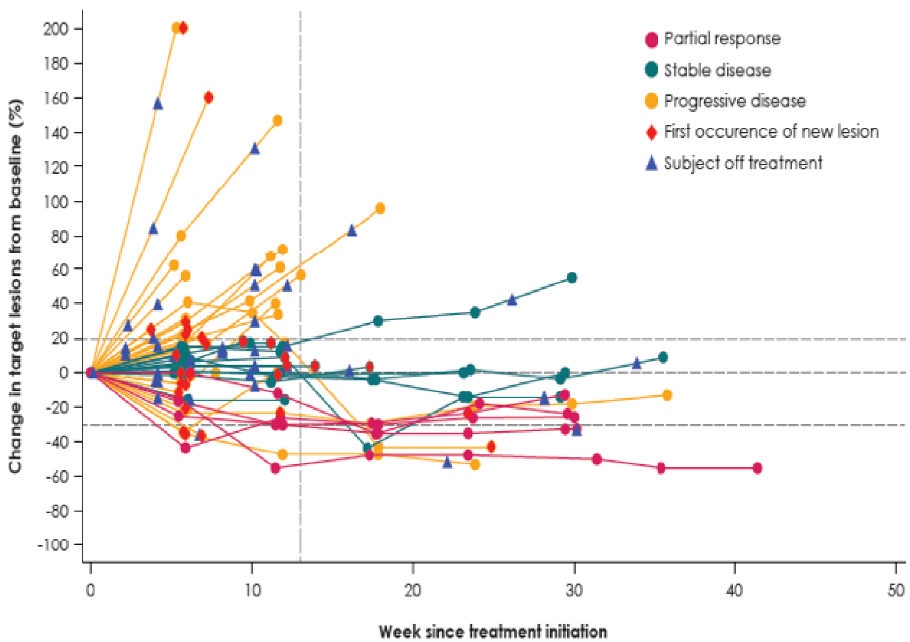
Prat/Perou et al Molec Oncol 2011; 25: 5-23..

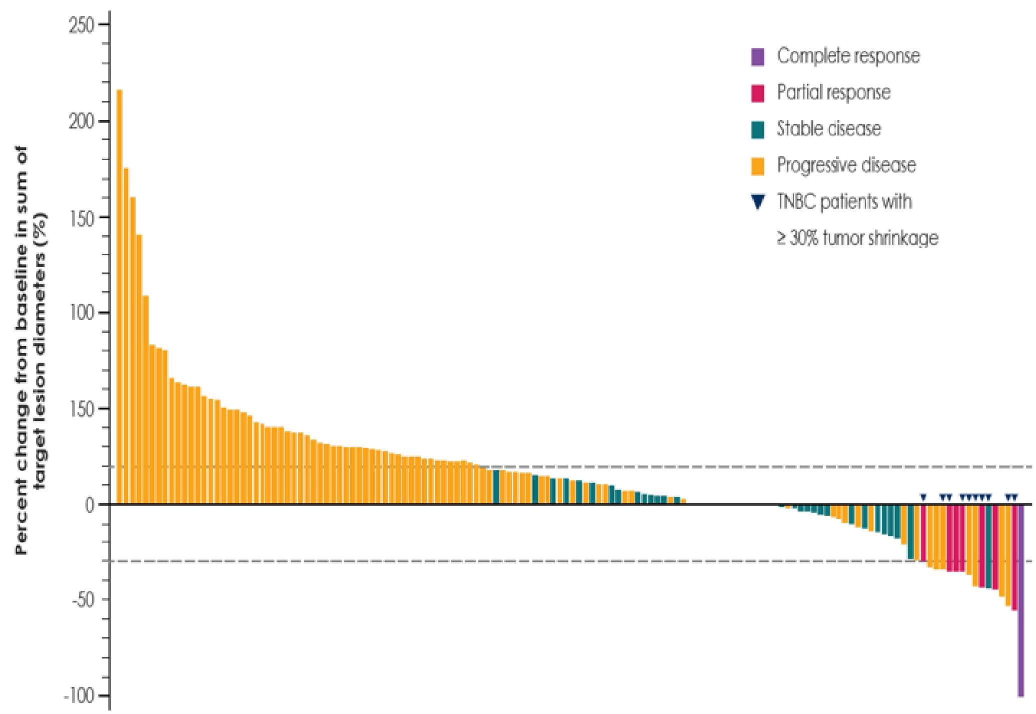
Immunologic Features of Breast Cancer Subtypes

<table>
<tr><th>Breast Cancer Subtype</th><th>Clinical Phenotype</th><th>Immunologic Phenotype</th></tr>
<tr><td>Luminal A</td><td>90% ER+ 89% PR+
14% HER-2+</td><td rowspan="2">Lymphocyte predominant 2.9%
Median stromal TILs 10%
Median intratumoral TILs 1.5%
TILs at Dx not predictive</td></tr>
<tr><td>Luminal B</td><td>98% ER+ 82% PR+
24% HER-2+</td></tr>
<tr><td>HER-2-enriched</td><td>38% ER+ 20% PR+
72% HER-2+</td><td>Lymphocyte predominant 11.1%
Median stromal TILs 15%
Median intratumoral TILs 3%
TILs at Dx predictive of response</td></tr>
<tr><td>Basal-like
(includes 70-80% TNBC)

Kroemer G et al. Nature Med 2015 21: 1128-38.</td><td>8% ER+ 7% PR+
7% HER-2+</td><td>Lymphocyte predominant 10.6%
Median stromal TILs 20%
Median intratumoral TILs 5%
TILs at Dx predictive of response</td></tr>
</table>

Avelumab Activity in Breast Cancer Patients



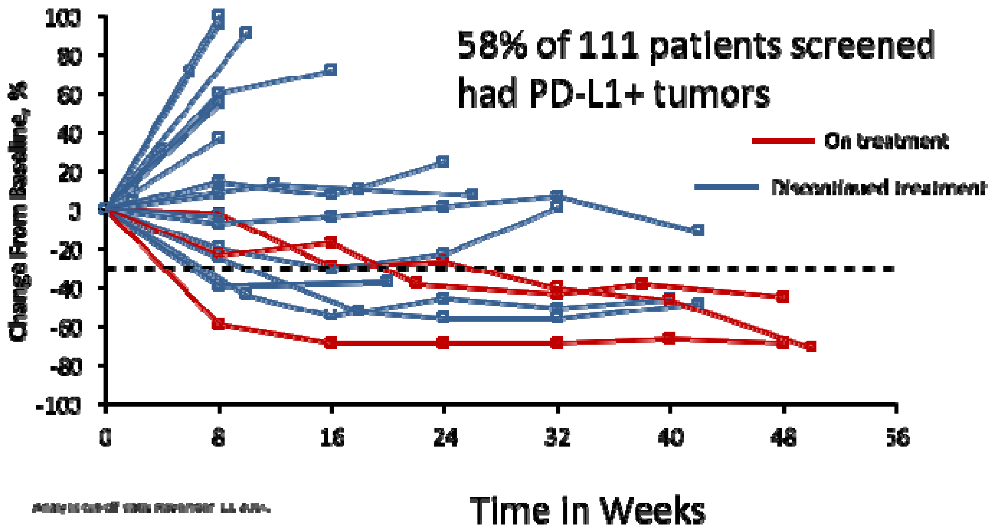


- 168 PD-L1 unselected patients/all BC subtypes
- ORR in breast cancer = 4.8%
- 1 CR, 7 PRs, 39 patients with SD; DCR = 28%

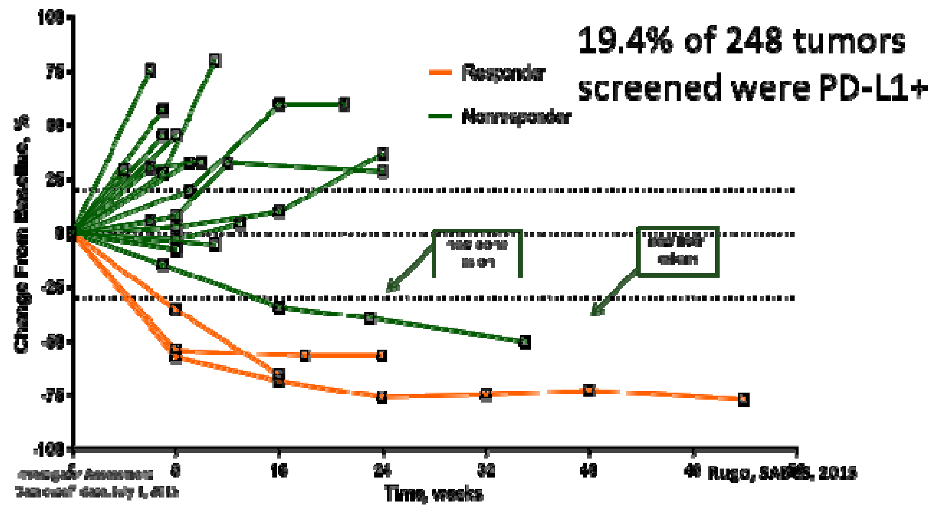
Dirix L et al SABCS 2015

Pembrolizumab Activity in PD-L1+ TNBC and ER+ BC

- ORR: 18.5%; PFS rate at 24 weeks: 23.3% (n= 27)
- 1 CR, 4 PRs, 7 SD, 3 of 5 responses ongoing

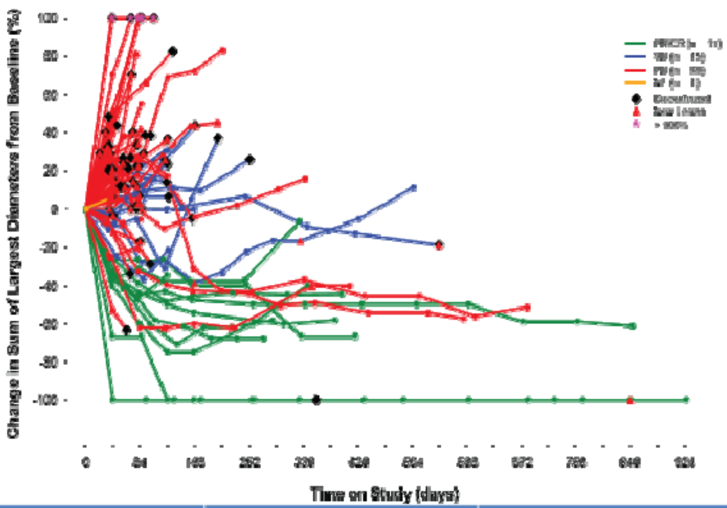


- ORR: 12%; PFS rate at 24 weeks: 20% (n=20)
- No CRs, 3 PRs, evidence of pseudoprogression

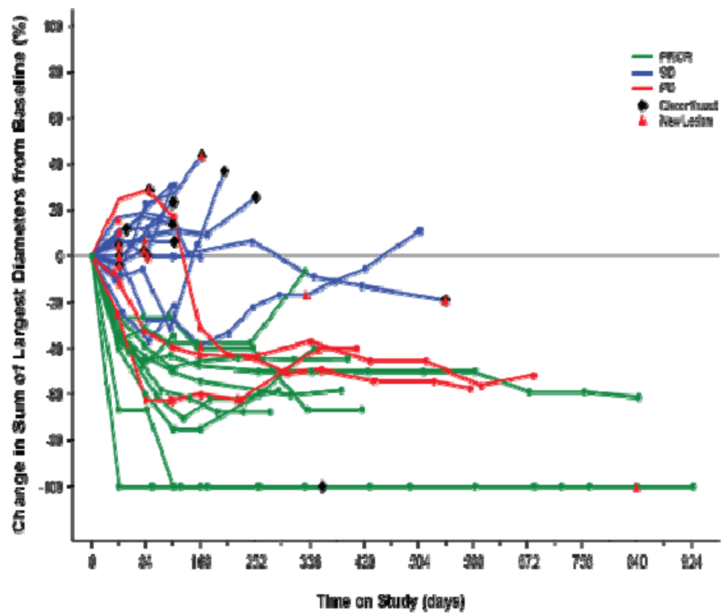


Nanda R et al. JCO 2016;34:2460.
Rugo H et al. SABCS 2015.

Atezolizumab Activity in PD-L1+ TNBC



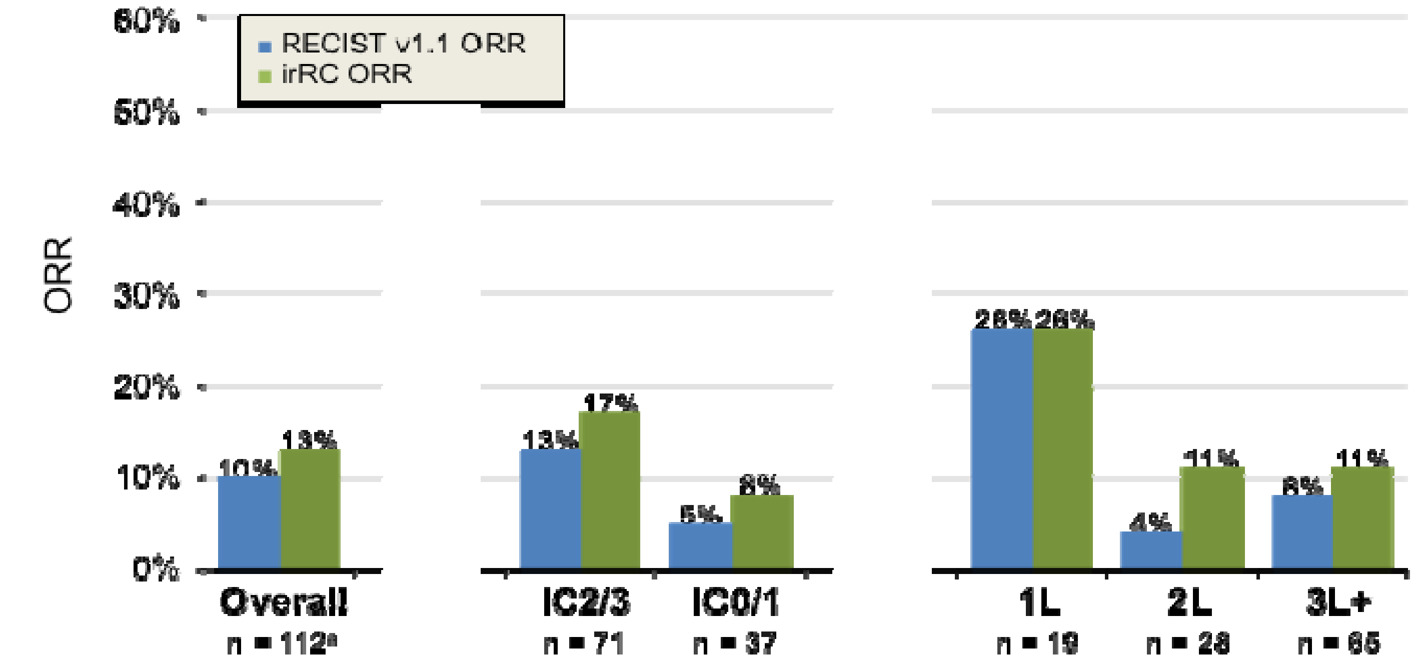
Criteria	Median DOR (range)	Median PFS (95% CI)
RECIST v1.1	21.1 mo (2.8 to 26.5+)	1.4 mo (1.3, 1.6)
irRC	21.1 mo (2.8 to 33.9+)	1.9 mo (1.4, 2.6)



Clinical benefit was observed in some patients with RECIST v1.1 SD or PD status

Schmid P, et al. AACR 2017 Phase Ia Atezolizumab in TNBC

TNBC Response Rates to Atezolizumab by Subgroup



	Overall		IC2/3		IC0/1		1L		2L		3L+	
ORR 95% CI, %[b]	5, 17	6, 21	6, 23	9, 28	1, 18	2, 22	9, 51	9, 51	0, 18	2, 28	3, 17	4, 21

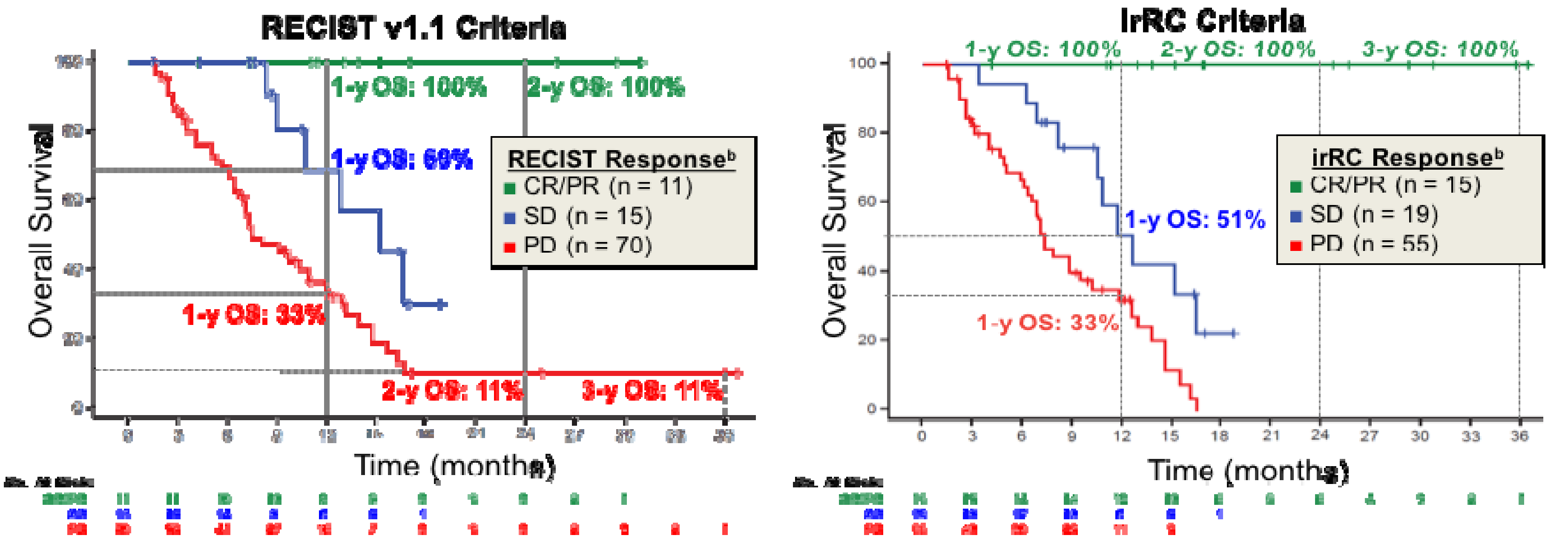
- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab

[a] Objective response–evaluable patients. Four patients had unknown PD-L1 status. Confirmed, investigator-assessed responses are plotted. Patients with missing or unevaluable responses are included (16 per RECIST v1.1 and 23 per irRC). [b] ORR 95% CI was estimated using Clopper-Pearson method. Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

Overall Survival by Response Status

- Median OS was 9.3 mo (95% CI: 7.0, 12.6) in all patients (median follow-up, 15.2 mo)[a]
  - Landmark OS rates (95% CI) were: 41% (31, 51) at 1 year, and 22% (12, 32) at both 2 and 3 years

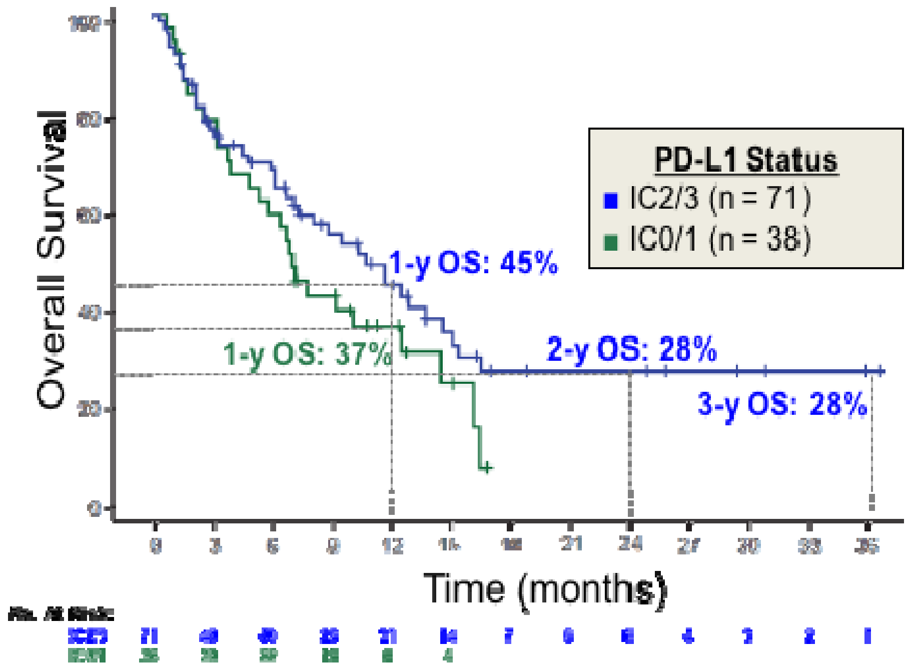


- Pseudo-progression was observed in patients with RECIST PD and long-term OS

[illegible]

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

Overall Survival by PD-L1 Status



	All Pts (n = 113)	PD-L1 Status[a] IC2/3 (n = 71)	IC0/1 (n = 38)
mOS (95% CI)	9.3 mo (7.0, 12.6)	10.7 mo (7.2, 14.7)	7.1 mo (5.1, 12.6)

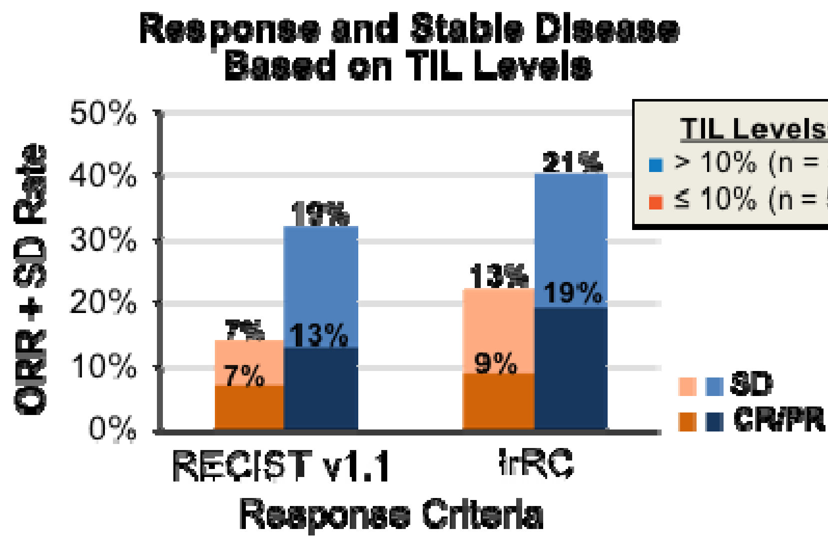
- Longer OS was observed in patients with higher PD-L1 IC status

[a] Four patients had unknown PD-L1 status. Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.5 mo (0.5+ to 19.9) in IC0/1 patients. Data cutoff: March 31, 2016.

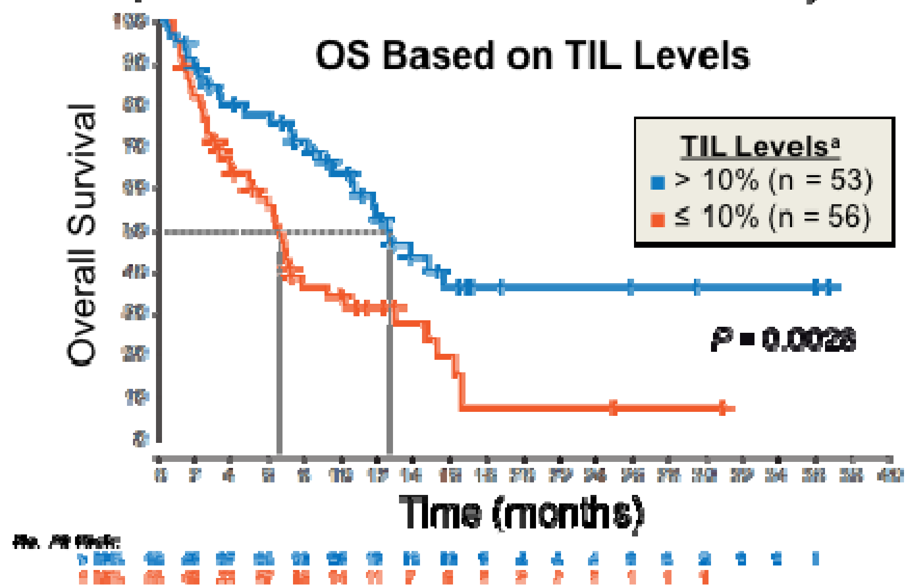
Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

Association of Response and Survival with TILs

- Median TIL infiltration (% tumor area) in tumors from enrolled patients defined the cutoff used for analysis



ORR 95% CI, %				
	0.14	4.22	2.17	6.29



	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

- Higher ORR and longer OS were seen with higher baseline TIL infiltration
- Similar results were observed with CD8 infiltration

[a] Samples unavailable for TIL assessments (5 per RECIST v1.1 and 5 per irRC) are not included. Objective response–evaluable population includes patients with unevaluable response assessments (16 per RECIST v1.1 and 23 per irRC). Log-rank (Mantel-Cox) P value is exploratory. Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

KEYNOTE-086: Phase 2 Study of Pembrolizumab in Metastatic TNBC

Cohort A:
Previously Treated
PD-L1 Unselected

386 patients screened

170 patients enrolled/treated
- **105 PD-L1 positive (61.8%)**
- **64 PD-L1 negative (37.6%)**
- **1 PD-L1 unknown (0.6%)**

PD-L1 is an imperfect biomarker. Context is important.

	Previously Treated Any PD-L1 Expression Cohort A			*First Line PD-L1 Selected*
	All (n=170)	**PD-L1+ (n=105)**	**PD-L1- (n=64)**	***PD-L1+ (n=52)***
ORR, %	**4.7%**	**4.8%**	**4.7%**	***23.1%***
DCR, %	**7.6%**	**9.5%**	**4.6%**	
CR, n	**1**	**1**	**0**	
PR, n	**7**	**4**	**3**	
SD, n	**35**	**22**	**112**	

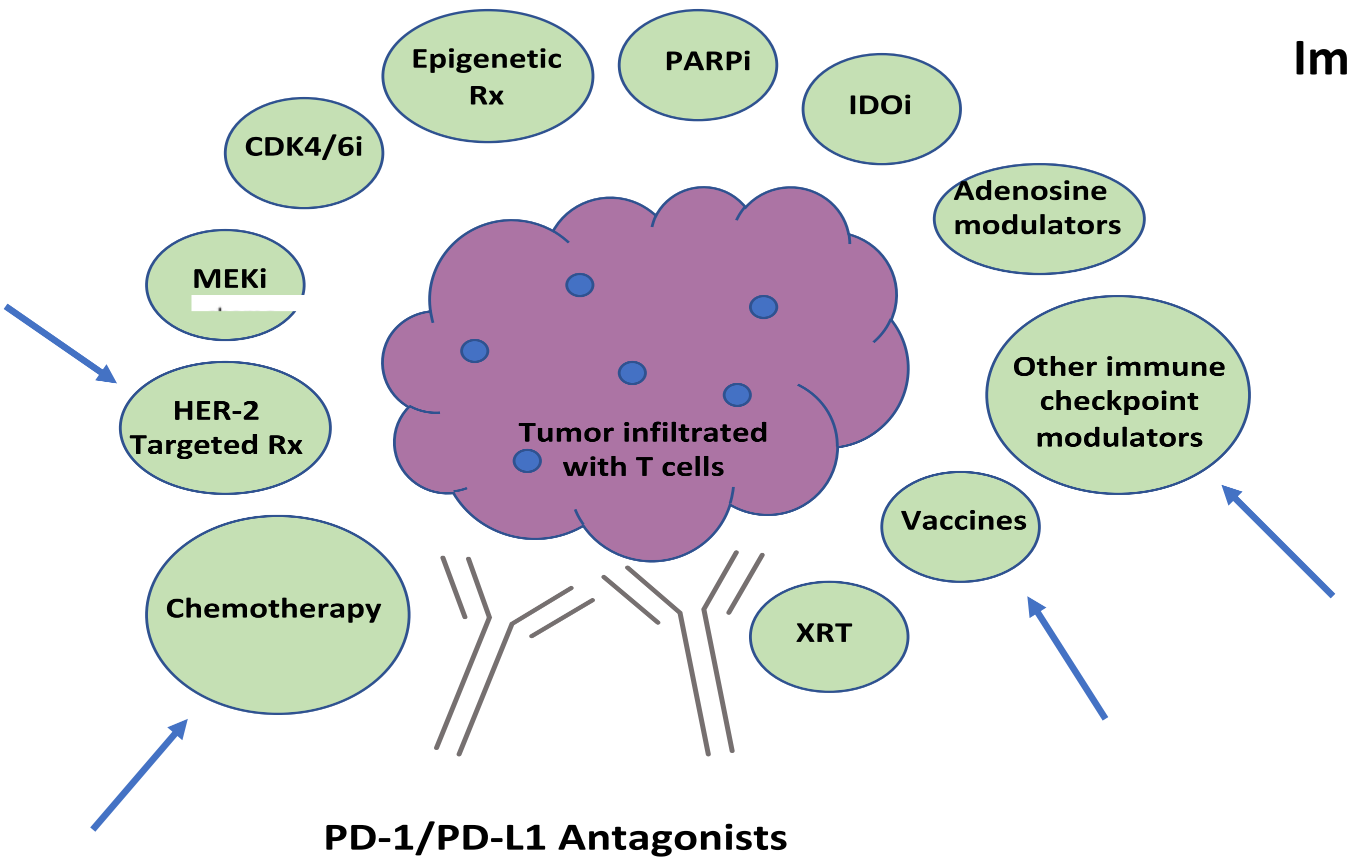
Adams S, ASCO 2017

Two Primary Challenges for the Field

Deepening Responses to Single Agent Immunotherapy

Converting Non-Responders to Responders

Selected Promising Combination Immunotherapies for Breast Cancer



Important Variables:

Drug

Dose

Sequence

Individualization to tumor mutated vs. shared Ags immunoregulation

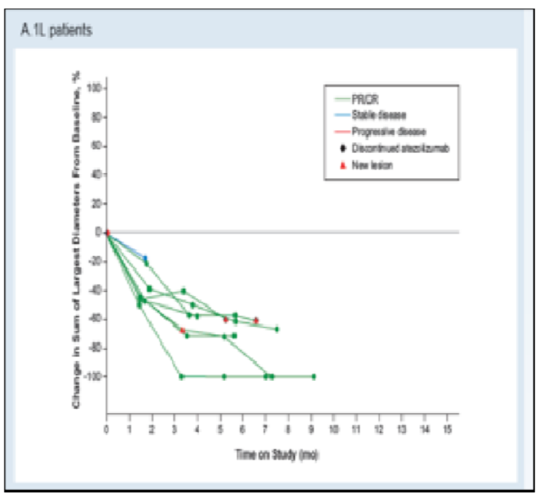
Combination of PD-1/PD-L1 Blockade with Standard Chemotherapy in TNBC

Atezolizumab with Nab-Paclitaxel

Changes in Tumor Burden Over Time with Line of Therapy

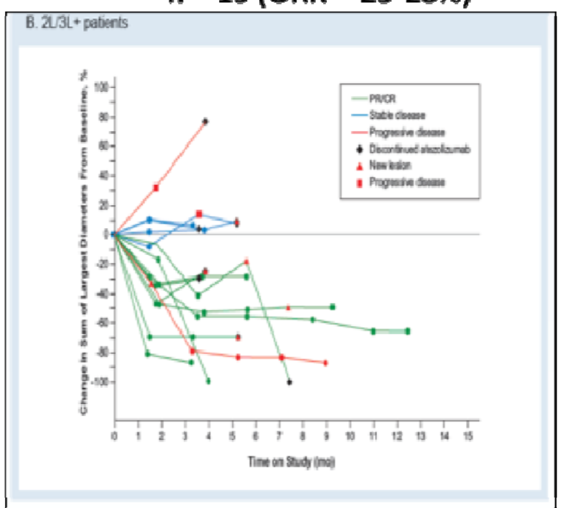
- PD-1 unselected patients
- Atezolizumab 840 mg every 2W; Nab-paclitaxel 100 mg/m² weekly
- Confirmed ORR = 41.7%; 3 pseudoprogressors

n = 9 (ORR ~ 67%)



Adams S, et al, SABCS 2015

n = 15 (ORR ~ 25-28%)



* 11 of 17 responses (65%) continued on treatment at time of data cut off

Taxane+Atezolizumab (ORR 41.7%)

--antigen release
--signal through TLR-4
--augment DC activity/Ag presentation

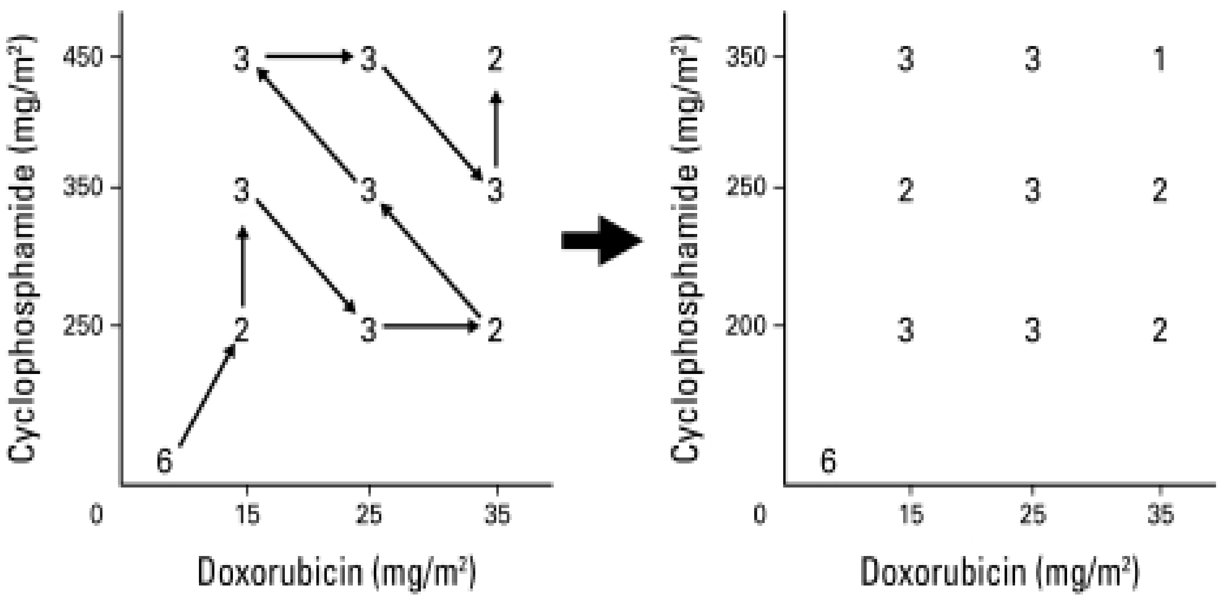
Eribulin+Pembrolizumab (ORR 33.3%)

--antigen release
--decreases Tregs
--decreases M2 macrophages

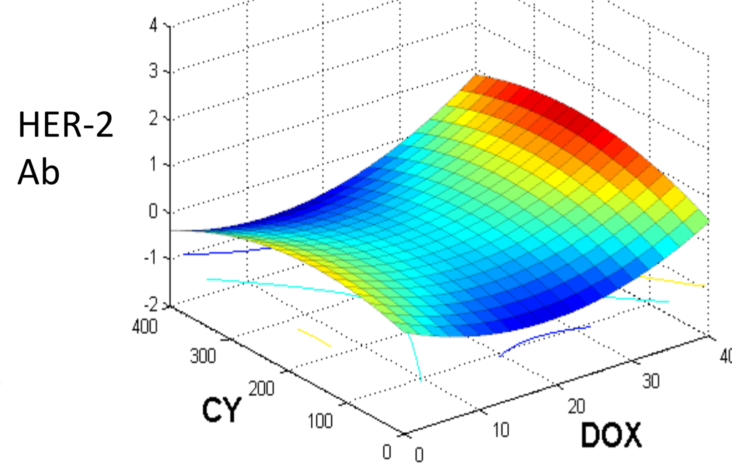
Tolaney S, SABCS 2016

Combination of Vaccination with Low Dose Chemotherapy

Novel Trial Designs to Explore Dose and Schedule



$$y_{u} = \beta_0 + \beta_1 x_{1u} + \beta_2 x_{2u} + \beta_{11} x_{1u}^2 + \beta_{22} x_{2u}^2 + \beta_{12} x_{1u} x_{2u} + e_{u}$$



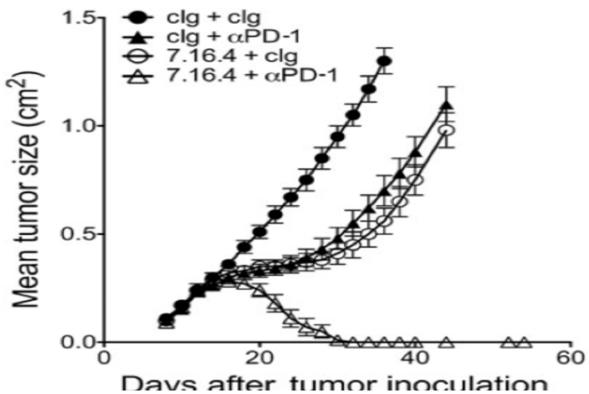
Possible Inputs: dose x dose
dose x schedule

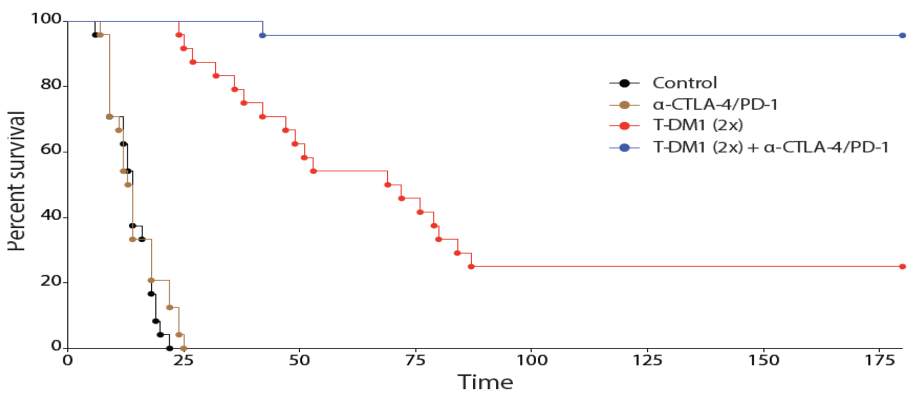
Possible Outputs: immune response
clinical response
toxicity

Emens LA, J Clin Oncol 2009;27: 5911-18

Combination of Immunotherapy with HER-2-directed Therapy

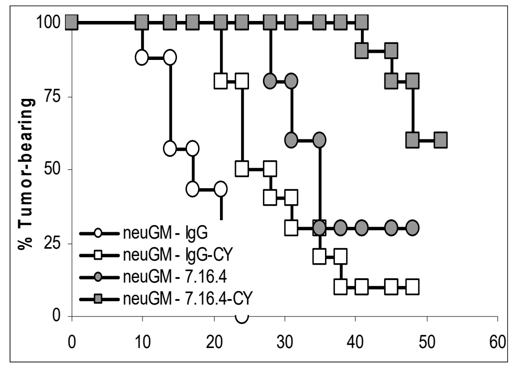
Checkpoint Blockade

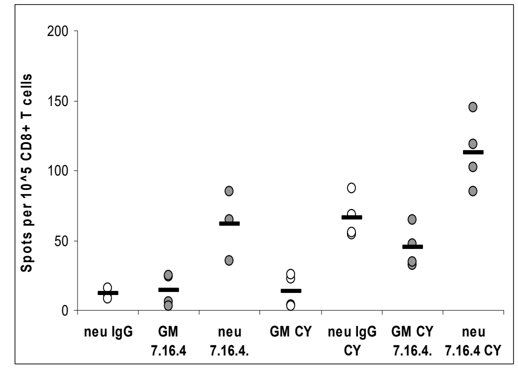


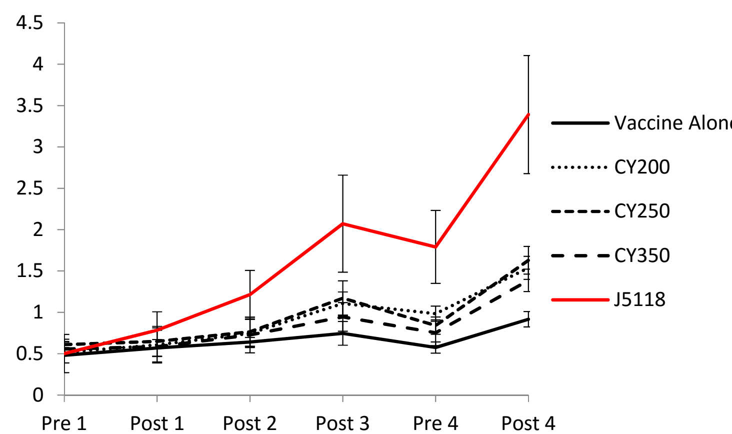


Stagg J et al, PNAS, 2011; 108: 7142-47
Müller P et al, Science Translation Medicine, 2015; 315:315ra188

Vaccination



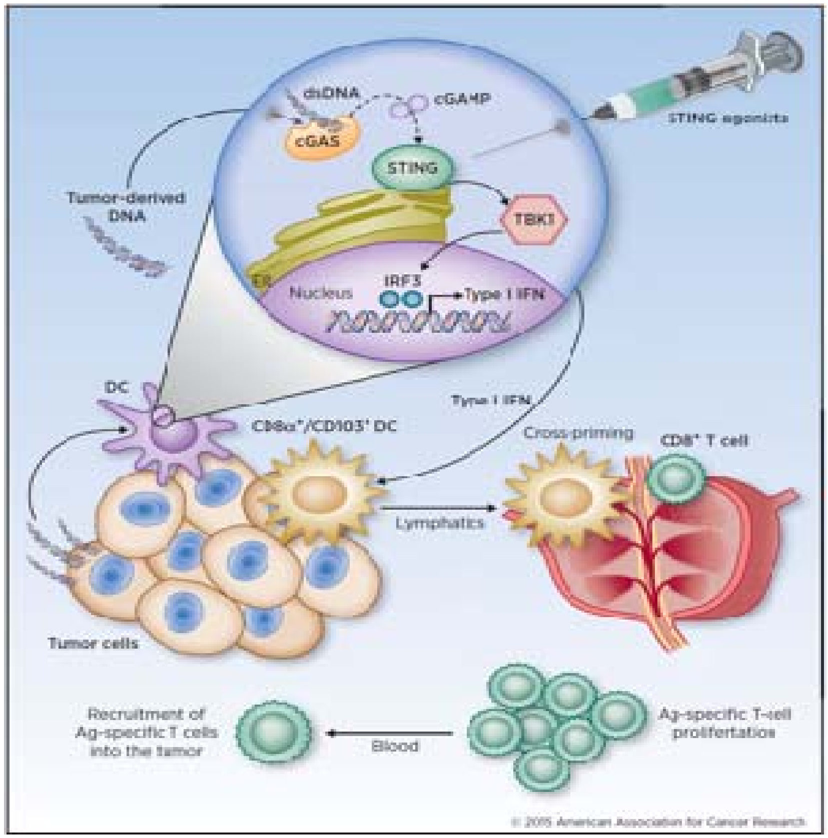




Chen/Emens et al, Cancer Immunol Res 2014; 2: 949-961
Chen/Emens, unpublished data

Intratumoral Vaccination Alone and with Immune Checkpoint Blockade

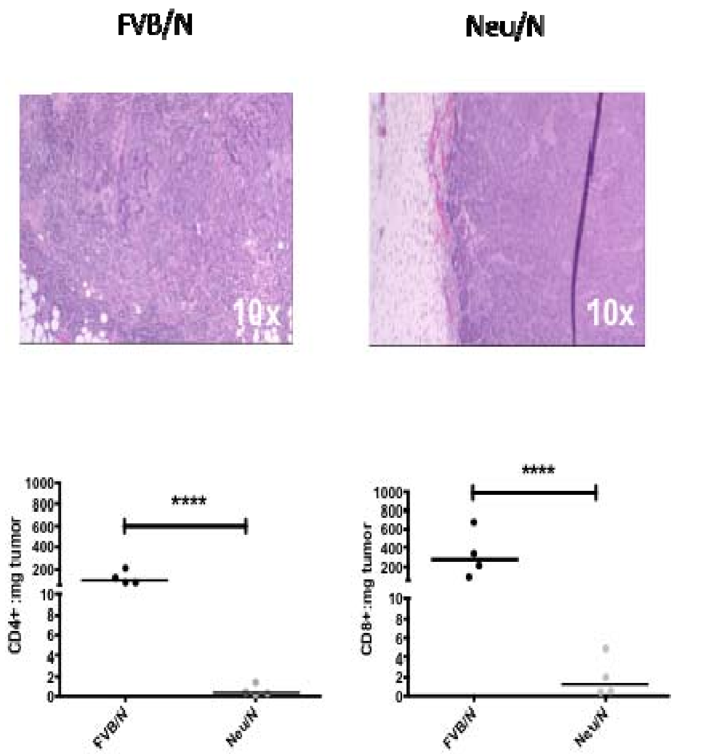
Activating *In Situ* Tumor-Initiated T Cell Priming

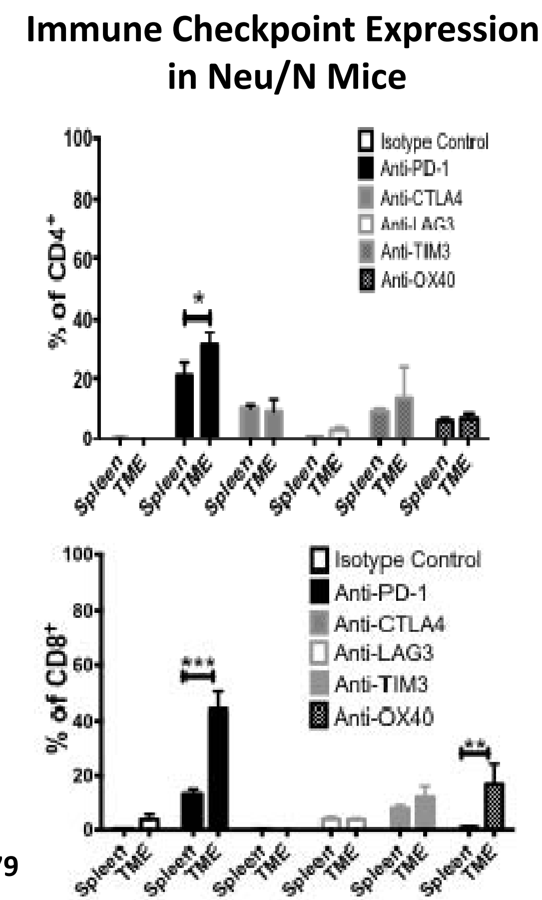


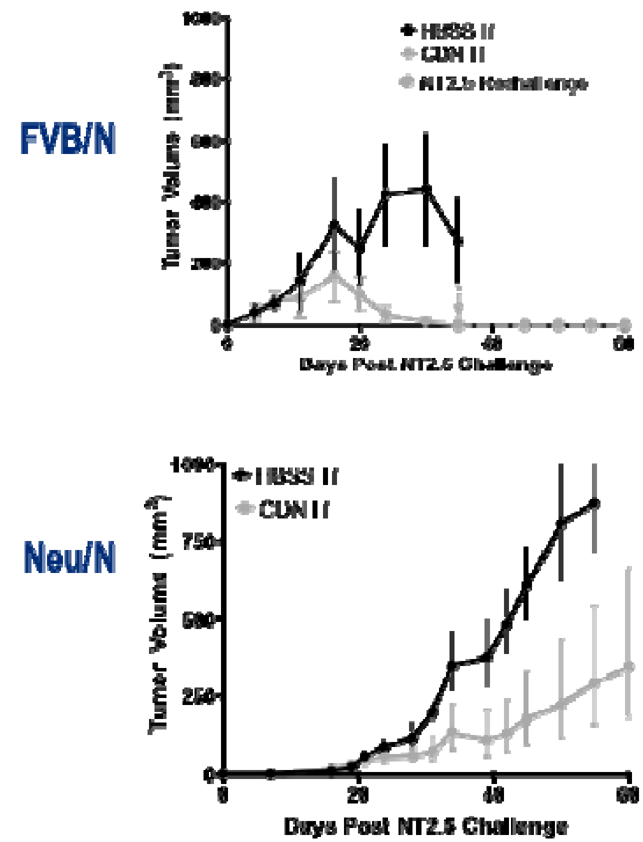
Corrales and Gajewski, Clin. Cancer Res (2015)

- T cell inflamed tumors in humans typically have an IFN-β transcriptional signature
- STING is the critical receptor to activate immune cells, including dendritic cells
- Tumor-derived DNA induces IFN-β by tumor resident DCs through STING signaling
- Intratumoral injection of CDNs induces IFN-β, activating tumor-resident DCs that stimulate tumor specific CD8+ T cell priming

Tumor Inflammation and Response to ADU-S100 in FVB/N and Neu/N Mice

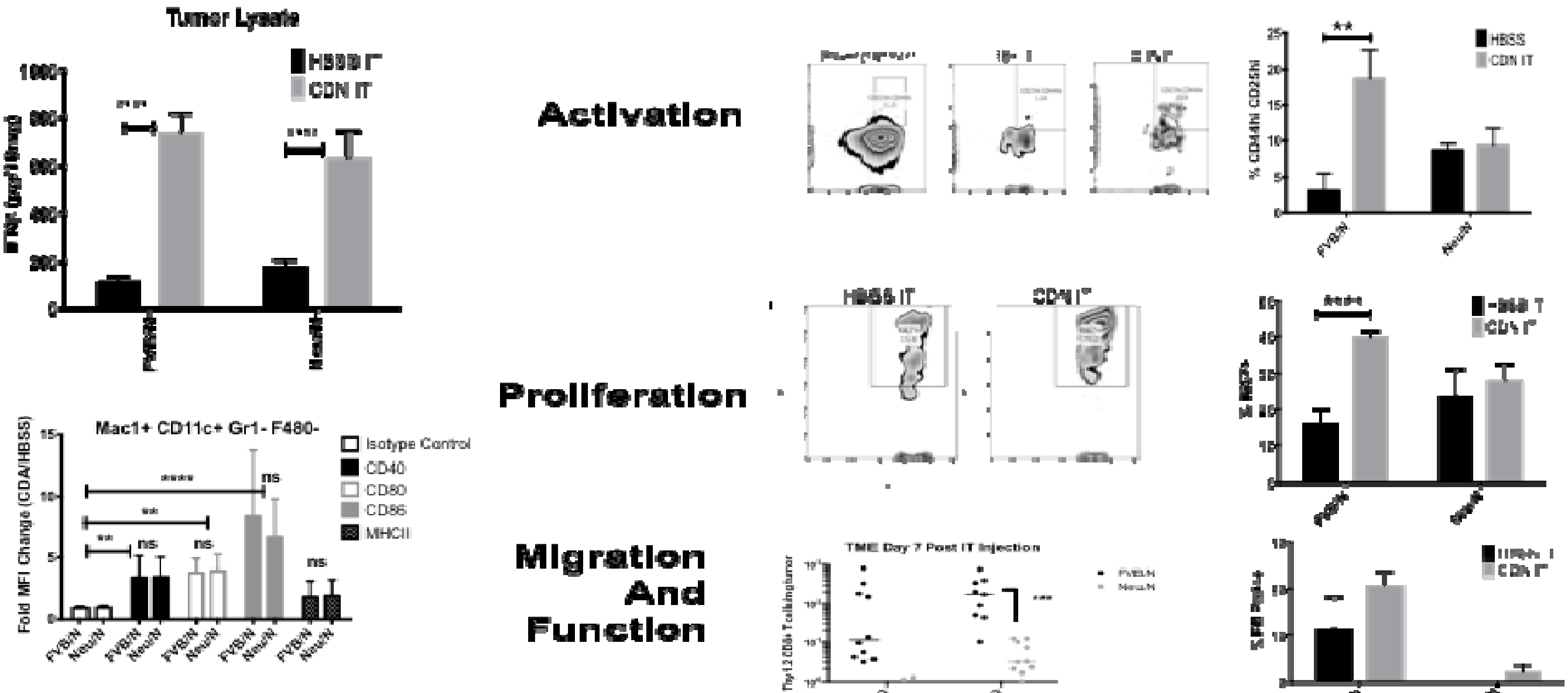






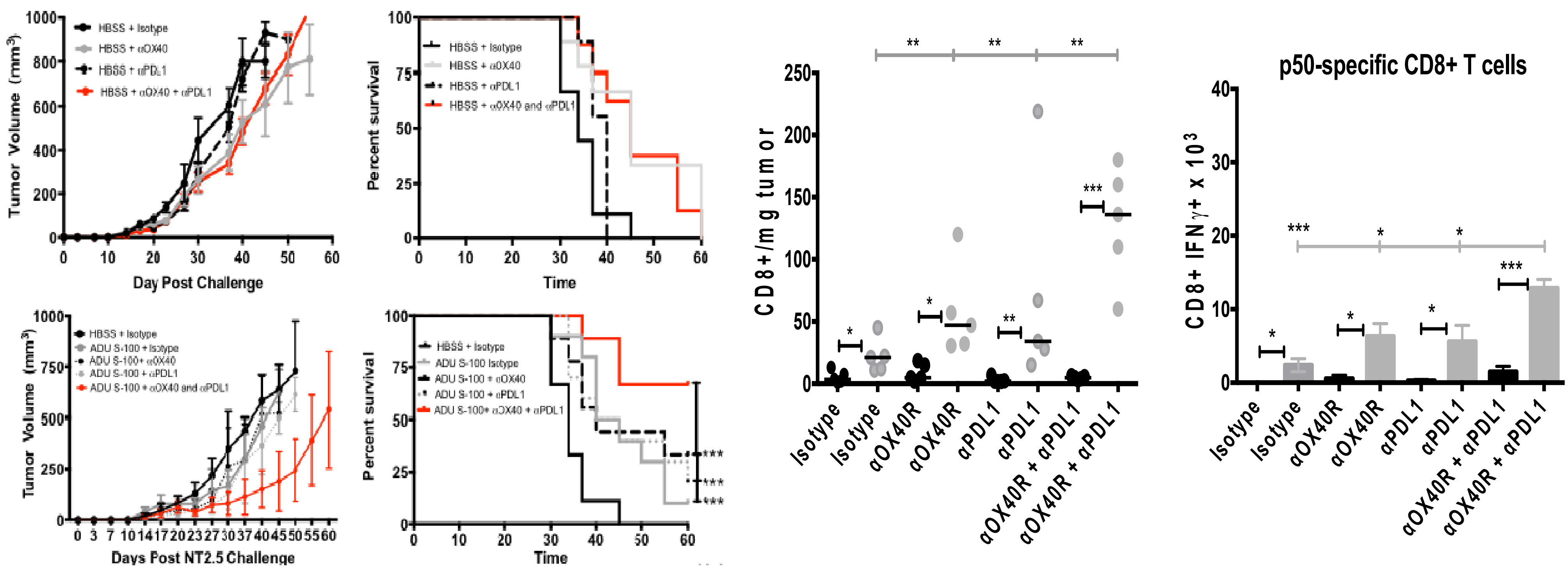
Foote JB/Emens LA, Cancer Immunol Res, 2017;5:468-79

Innate Immune Activation Occurs, But T Cell Priming is Deficient in Neu/N Mice



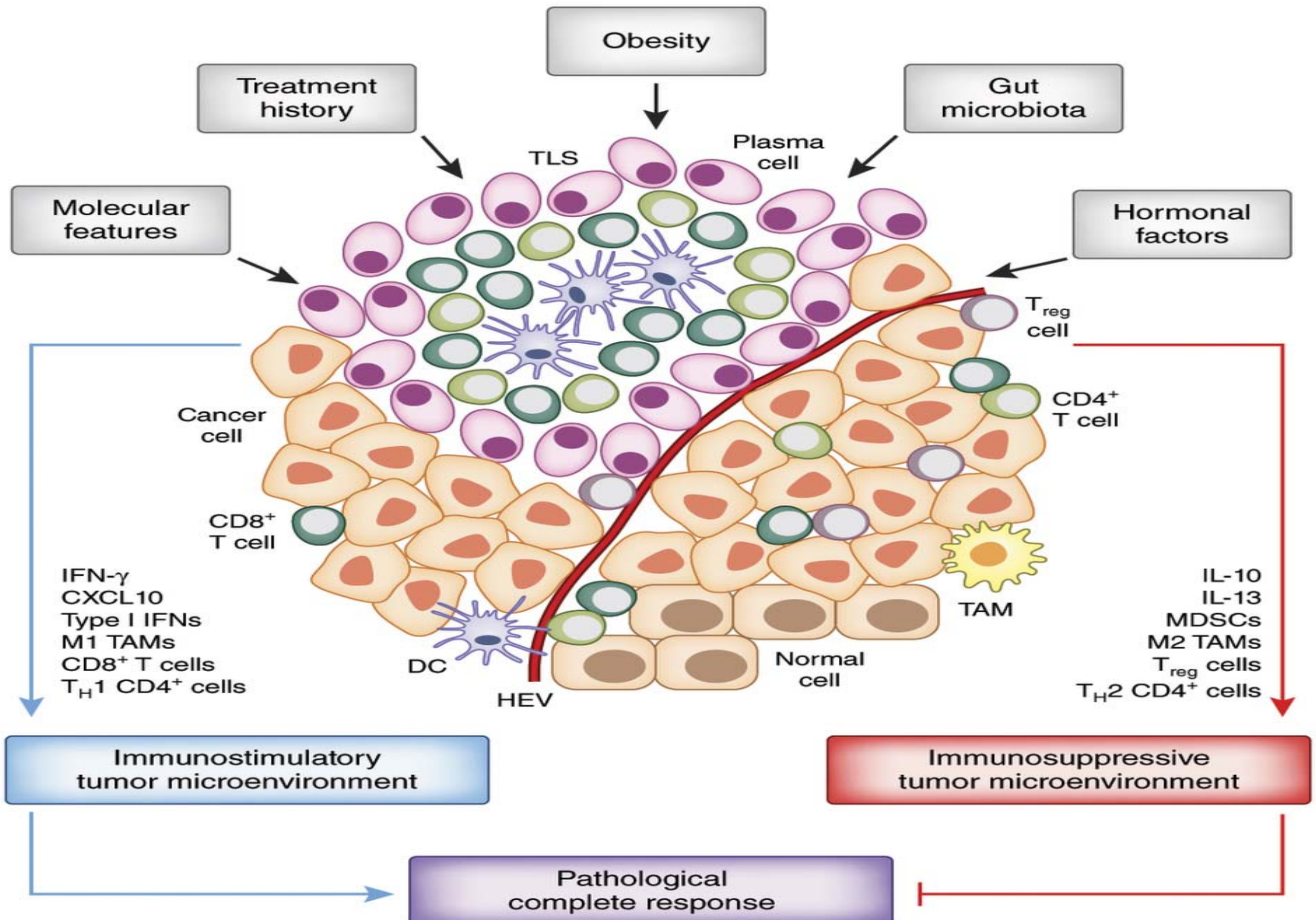
Foote JB/Emens LA, Cancer Immunol Res, 2017;5:468-79

ADU-S100 Combined with PD-L1 Blockade and OX-40 Activation Enhances Tumor-Free Survival and Immunity in Neu/N Mice



Foote JB/Emens LA, Cancer Immunol Res, 2017;5:468-79

Multiple Factors May Influence the Response to Breast Cancer Immunotherapy



Kroemer G et al. Nature Med 2015 21: 1128-38.

Conclusions

- Breast cancer can be immunogenic, most breast tumors are not
- Multiple layers of regulation within the TME shut down tumor immunity
- Vaccines and STING agonists may prime the TME for response to immune checkpoint modulation
- Standard cancer therapies can augment the activity of immunotherapies
- The future is in combination immunotherapies which should have synergistic clinical activity but may come at a toxicity cost
- We need to do smart trials elucidating immunologic mechanisms of response and resistance in patients

Acknowledgements

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- Aduro Colleagues

A special thanks to the patients and families who participate in these clinical trials!

Urothelial Cancer

Strategic Immunotherapy Combinations and sequencies in urothelial cancer

Joaquim Bellmunt, MD PhD

Associate Professor of Medicine

Harvard Medical School/Dana-Farber Cancer Institute

Washington, July 20th 2017

Disclosures

- Advisory role:
  - Genentech, Merck, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenex, Janssen
- Speaker role:
  - Pfizer, Merck, GSK, Novartis, Pierre-Fabre, Astellas
- Research funding:
  - Takeda, Pfizer, Novartis, Sanofi Aventis

Immunotherapy in UC

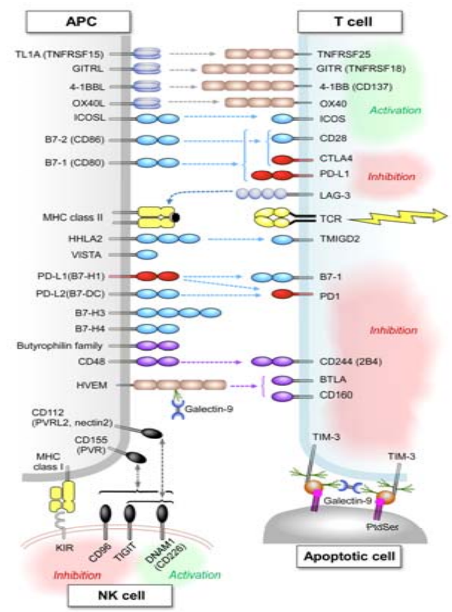
- **<u>Exciting times in the treatment of urothelial carcinoma</u>**

- Immunotherapy is a well tolerated and active treatment for our patients
- → **<u>But only 15-20% of patients derive benefit</u>** and many open questions remain with regards to understanding predicting factors

- The future is combination (or sequential ?)
  - Check-point inhibitors
  - Immune based therapies (vaccines, ADC, Bispecific antibodies, CAR-T cells…)
  - + Targeted agents (cabozantinib, FGFr3 inh..)
  - Combination/ Sequential use of chemo and XRT
  - Customized: Genomically based

1st

- Potential synergistic combos
  - IO/IO
  - IO/+ other immune approaches
    - ADC, BSA, Vaccines
  - IO/targeted therapies

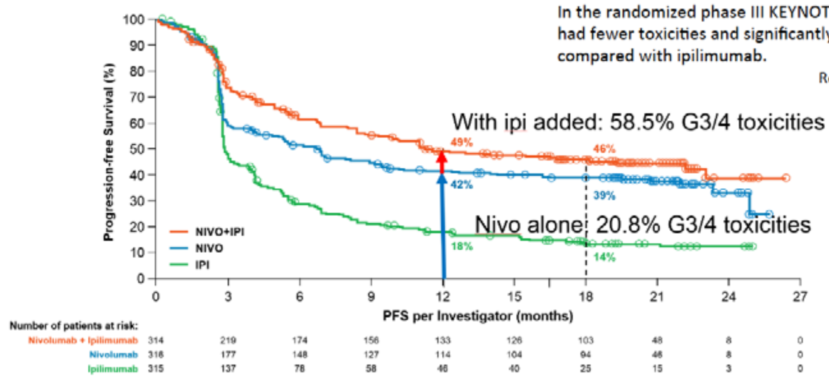


1.- Exhausted Tumor infiltrating lymphocytes express multiple immunoinhibitory receptors:
2.- These are druggable targets for tumor immunotherapy

IO + IO combo vs IO monotherapy (MM and mUC)

In the randomized phase III KEYNOTE-006 study, pembrolizumab had fewer toxicities and significantly improved overall survival compared with ipilimumab.

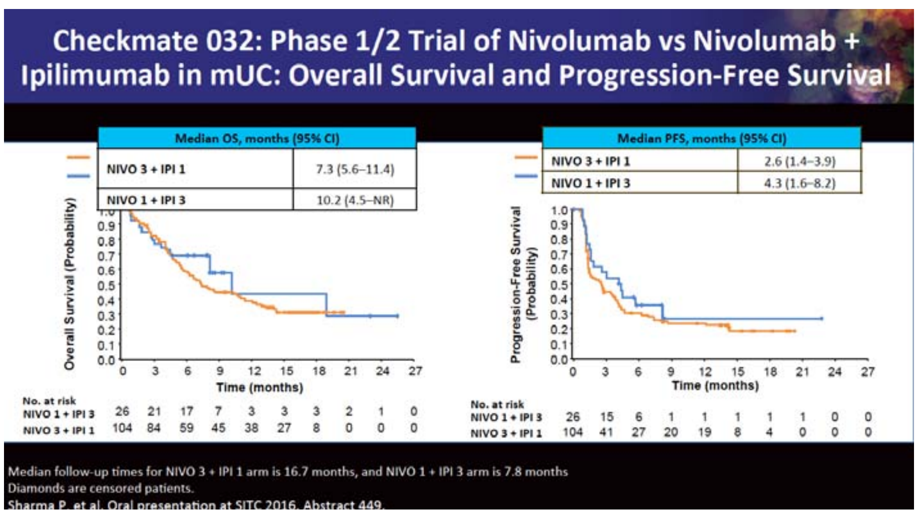
Robert C, et al. *N Engl J Med.* 2015.

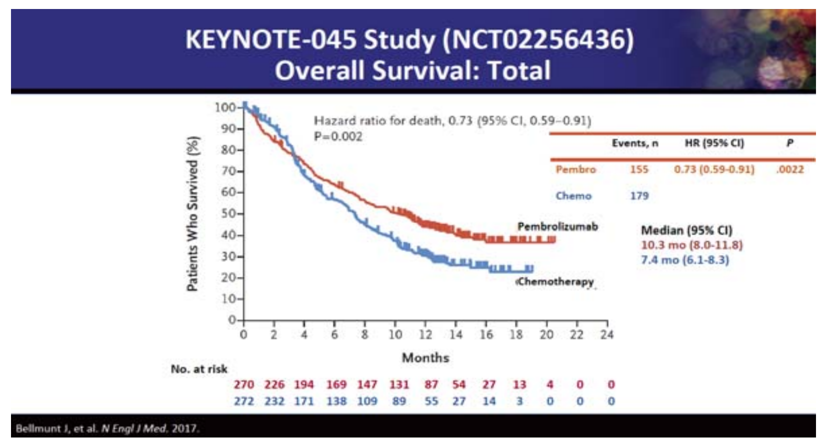


CheckMate 067

- NIVO+IPI and NIVO significantly improved OS and PFS vs. IPI alone in patients with untreated advanced melanoma
- In descriptive analyses, NIVO+IPI resulted in *numerically higher* OS, PFS and ORR vs. NIVO alone
- For NIVO+IPI, median DOR and time to subsequent therapy are still not reached

Larkin J, et al. AACR 2017. Abstract CT075.

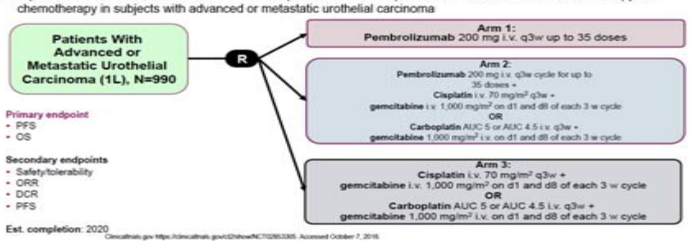




First line trials exploring IO/IO or chemo Immunotherapy given concurrently

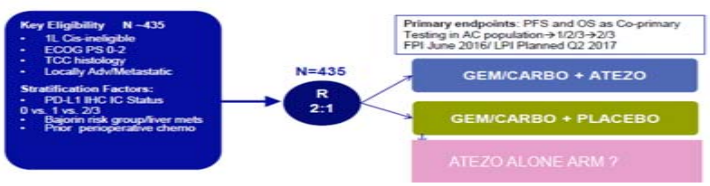
KEYNOTE-361 (ongoing): Study Design

- A phase 3 randomized, controlled clinical trial of pembrolizumab +/- platinum-based combination chemotherapy vs chemotherapy in subjects with advanced or metastatic urothelial carcinoma



Chemotherapy + Immunotherapy in 1st- line "unfit"?

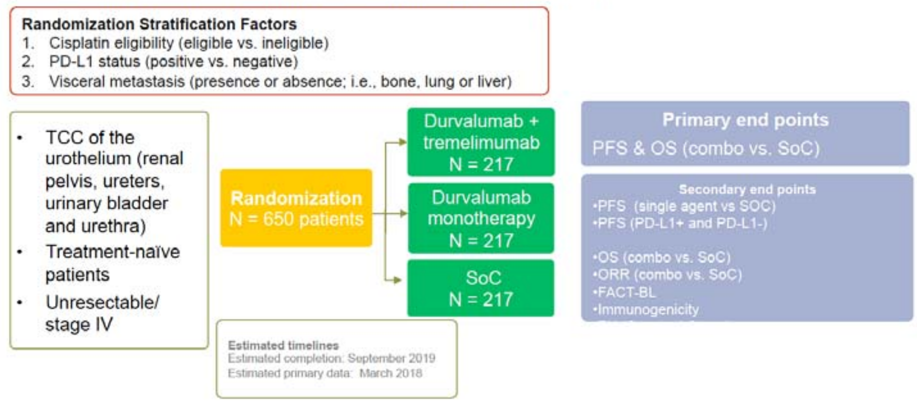
ImVigor 130



FIRST LINE PHASE III

DANUBE Study Design (NCT02516241)

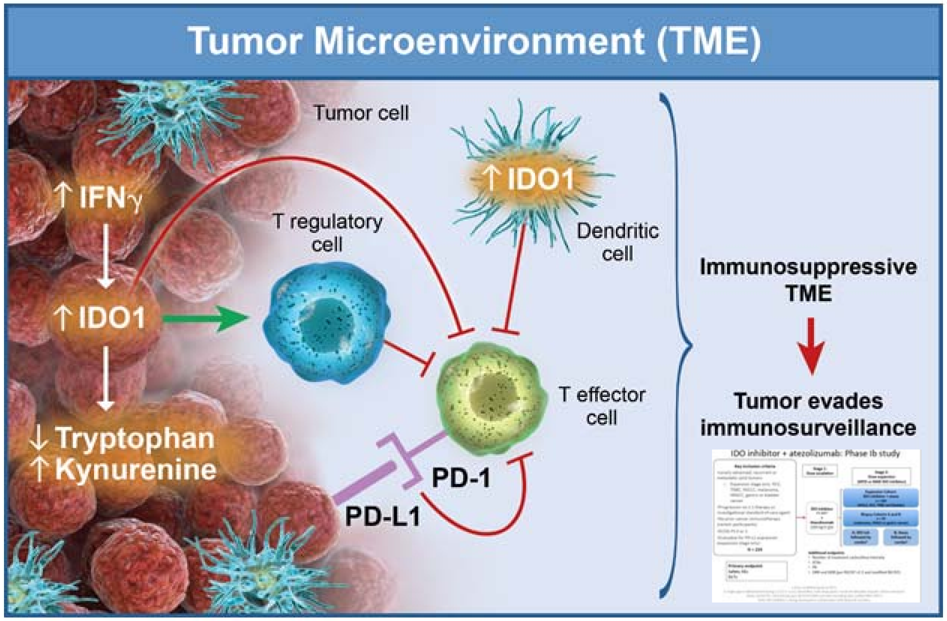
Durvalumab ± Tremelimumab vs SOC in the first-Line Advanced UBC



Study of Nivolumab in Combination With Ipilimumab Compared to the Standard of Care Chemotherapy in Treatment of Patients With Untreated Inoperable or Metastatic Urothelial Cancer (CheckMate901)

DC Smith, ASCO, Jun 2017

IDO1 Enzyme and Epacadostat (oral IDO inhibitor)



- Tumors may evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of IDO1
- IDO1 is an IFNγ-induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway[1]
- Tryptophan depletion and production of kynurenine and other metabolites shift the local immune microenvironment to an immunosuppressive state[1]
- Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment[2]
- Combining epacadostat with a checkpoint inhibitor may improve patient outcomes

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma.

Objective and Study Design

Objective: To report efficacy, safety, and tolerability data for epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma

ECHO-202/KEYNOTE-037* study design:

Phase 1b

Dose Escalation

- Epacadostat 25 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 50 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 100 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 300 mg BID + Pembrolizumab 200 mg Q3W

Safety Expansion

- Epacadostat 50 mg BID + Pembrolizumab 200 mg Q3W
- Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W
- Epacadostat 300 mg BID + Pembrolizumab 200 mg Q3W

Phase 2

Open-Label Cohort Expansion

Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W

Tumor cohorts
Melanoma, SCCHN, urothelial carcinoma, NSCLC† (TPS ≥50%,‡ TPS <50%), RCC,† TNBC, OC, MSI-High CRC,†‡ DLBCL,†‡ GC,‡ HCC‡

Phase 1/2 Urothelial Carcinoma Patients (N=40)

- ≥18 years of age
- Histologically or cytologically confirmed advanced urothelial carcinoma
- Life expectancy >12 weeks
- ECOG PS 0 or 1
- ALT, AST, ALP <2.5 x ULN; conjugated bilirubin <2.0 x ULN
- No previous IDO inhibitor or immune checkpoint inhibitor treatment
- Phase 2: Progression during or following platinum-based chemotherapy or alternative therapy in the adjuvant or advanced disease setting

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; HCC, hepatocellular carcinoma; IDO, indoleamine 2,3 dioxygenase; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer; TPS, tumor proportion score; ULN, upper limit of normal.

Note: GC and HCC cohorts were not yet open for patient enrollment at data cutoff (February 27, 2017).

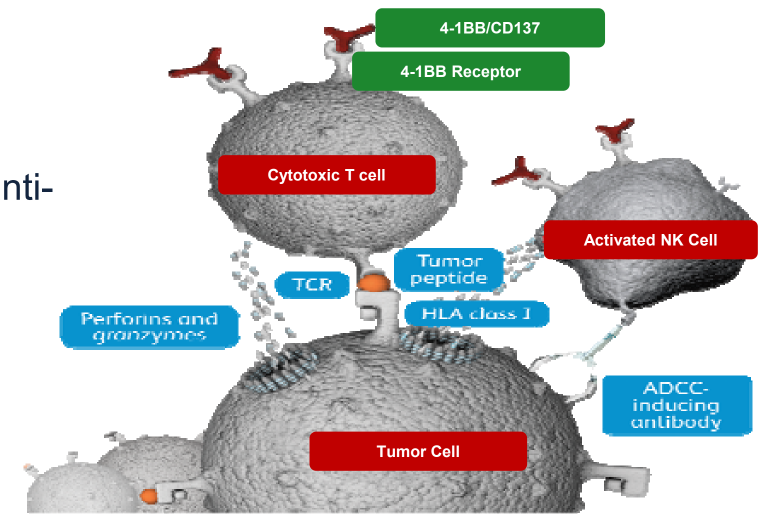
Best Objective Response

Patients, n (%)	Total (N=40)	No. Prior Lines of Treatment: 0*–1 (n=32)	No. Prior Lines of Treatment: ≥2 (n=8)	PD-L1 Expression†: Positive (n=11)	PD-L1 Expression†: Negative (n=8)
ORR (CR+PR)	**14 (35)**	**12 (38)**	**2 (25)**	**7 (64)**	**1 (13)**
CR	3 (8)	3 (9)	0	0	0
PR	11 (28)	9 (28)	2 (25)	7 (64)	1 (13)
SD	7 (18)	7 (22)	0	1 (9)	1 (13)
DCR (CR+PR+SD)	**21 (53)**	**19 (59)**	**2 (25)**	**8 (73)**	**2 (25)**
PD	14 (35)	10 (31)	4 (50)	2 (18)	6 (75)
Not evaluable	5 (13)	3 (9)	2 (25)	1 (9)	0

- **Based on irRECIST: ORR=38% (4 CR, 11 PR); DCR=60% (9 SD)**

CR, complete response; DCR, disease control rate; irRECIST, immune-related RECIST; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
* Enrolled patients who had no prior treatment for advanced urothelial carcinoma received platinum-based treatment in adjuvant/neoadjuvant setting. † Of 21 patients with unknown PD-L1 expression, there were 3 CR, 3 PR, 5 SD, 6 PD, and 4 not evaluable by RECIST.

4-1BB **agonist mAb** Utomilumab (targeting T-cells)



Anti-CD137 (4-1BB) can amplify anti-tumor immune responses by :

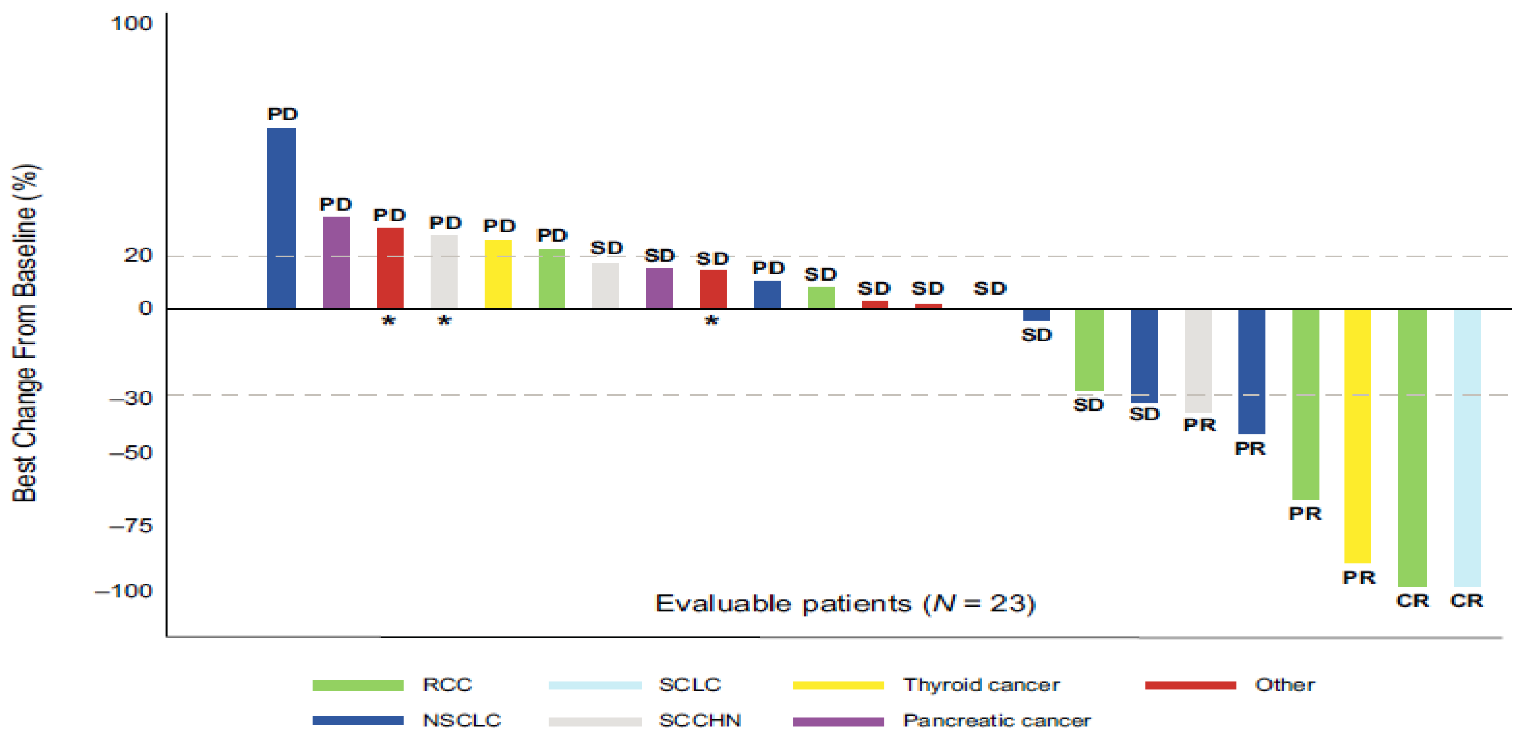
- Alleviating T-Cell exhaustion post-IO therapy:anti-PD-1/L1, anti-CTLA4
- CD8+ T cell activation, proliferation, survival, and tumor killing
- Activation of CD4+ T cells, providing cytokine help for CD8+ T cells and NK cells
- Natural killer cell expansion and antibody dependent cell-mediated cytotoxicity

- Utomilumab is a fully human IgG2 agonist mAb that binds to 4-1BB

- **Phase Ib trial of utomilumab + pembrolizumab**
  - Utomilumab given with pembrolizumab (2.0 mg/kg) on day 1 of 21 day cycles
  - No dose limiting toxicities were seen in the dose range 0.45-5.0 mg/kg
  - In this trial, terminal phase serum half-life of utomilumab was 6-7.5 days across the dose range examined.

Gopal AK, et al. J Clin Oncol 2015:33(suppl); abstr 3004; Tolcher, AW et al. J Clin Onc 2016:34(suppl); abstr 3002

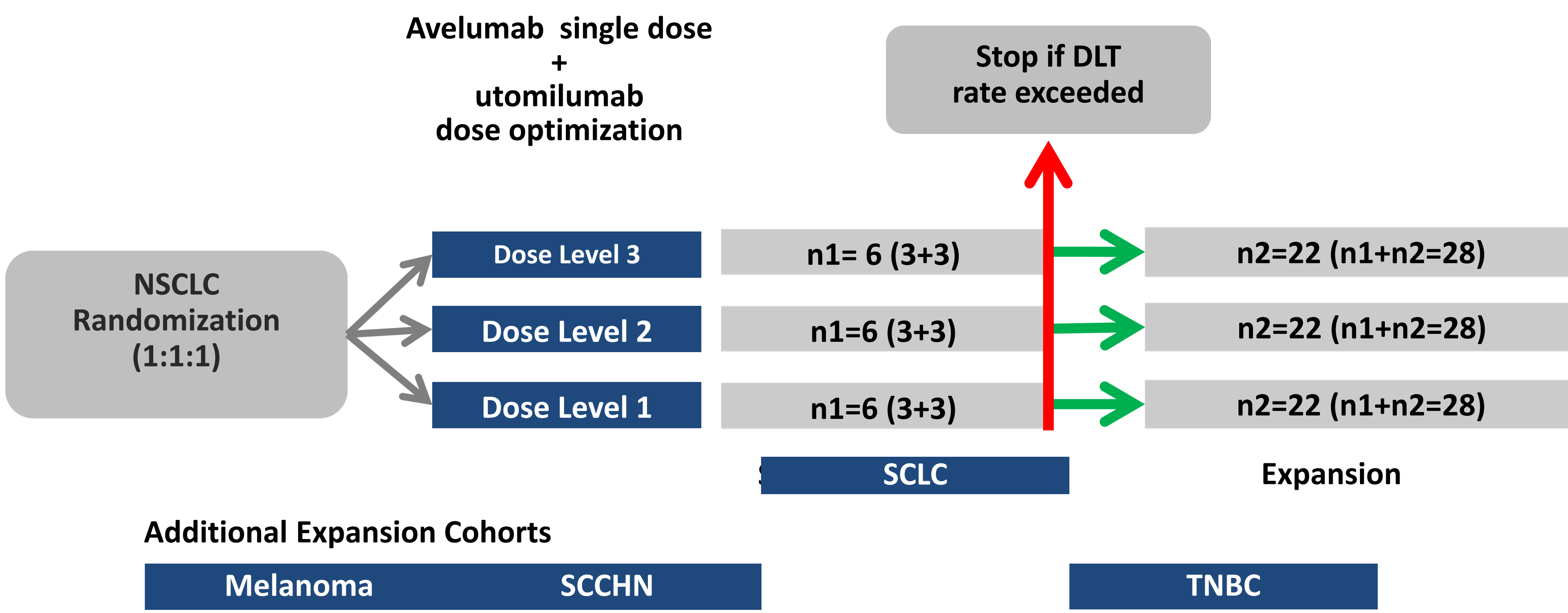
Phase Ib utomilumab + pembrolizumab



Tolcher, AW et al. J Clin Onc 2016:34(suppl); abstr 3002 ; *A. W. Tolcher, M. Sznol, S. Hu-Lieskovan, K. P. Papadopoulos, A. Patnaik, D. W. Rasco, D. Di Gravio, B. Huang, D. Gambhire, Y. Chen, A. D. Thall, N. Pathan, E. V. Schmidt, L. Q. M. Chow*; Phase Ib Study of Utomilumab (PF-05082566), a 4-1BB/CD137 Agonist, in Combination with Pembrolizumab (MK-3475) in Patients with Advanced Solid Tumors, Clin Cancer Res June 22 2017 DOI:10.1158/1078-0432.CCR-17-1243

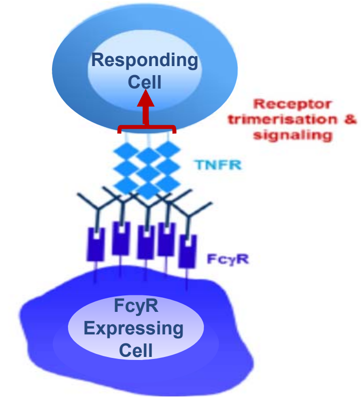
Study B9991004: Avelumab (Anti-PD-L1) + IO Combinations, Phase I/II (starting with utomilumab)

- **Utomilumab 1-h IV infusion q4w**
- **Avelumab 1-h IV infusion q2w**

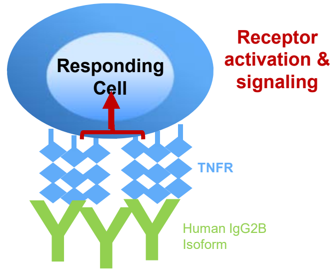


OX40 **agonist mAb** PF-04518600 (targeting T-cells)

- **OX40 (CD134)** is a co-stimulatory receptor that is expressed on **activated CD4+** and **regulatory T cells (Tregs). TCR stimulation in the presence of OX40 co-stimulation leads to an enhanced T cell response against tumor cells**
- OX40 is transiently upregulated during antigen specific priming, with higher expression levels and longer duration on CD4+ T cells than CD8+ T cells
- OX40 signaling can provide co-stimulatory signals to T cells through activation of PI3K and NFκB pathways leading to enhanced cell proliferation, effector functions and memory cell survival, thus overcoming T cell tolerance which is a major obstacle for cancer treatment
- **OX40 agonist antibodies can diminish the inhibitory effect of regulatory T cells in the tumor microenvironment through suppression and/or depletion**
- PF-04518600 is a fully human IgG2 agonist antibody to human OX40 that does not block the endogenous OX40L binding
- *In vivo* it is expected to function via binding to FcγRs and clustering OX40 to activate downstream signaling pathways
- In addition, IgG2 mAbs have been shown to cluster and activate TNFR superfamily members in an FcγR-independent manner because of close proximity of the Fab arms and the hinge region



Low level of target receptor is clustered by antibody bound to FcγRs, driving activating signals to receptor-expressing cells



In humans, the IgG2B isoform can promote clustering of receptors, driving FcγR-independent activating signals.

Diab et al., Ann Oncol (2016) 27 (suppl_6): 1053PD; O. Hamid et al., J Clin Oncol 34, 2016 (suppl; abstr 3079); Wilson NS, et al. Cancer Cell. 2011 Jan 18;19(1):101–13; Kawamata S, et al. *J Biol Chem* 1998;273:5808-5814; Moran AE, et al. *Curr Opin Immunol* 2013;25:230–237; Weinberg AD, et al. *Immunol Rev* 2011;44:218–231; Linch SN, et al. *Front Oncol* 2015;5:34; Bulliard Y, et al. *Immunol Cell Biol* (2014) 92(6):475–80; Redmond WL, et al. *Eur J Immunol* (2009) 39(8):2184–94; Piconese S, et al. *J ExpMed* (2008) 205(4):825–39; Wilson NS, et al. Cancer Cell. 2011 Jan 18;19(1):101-13; White AL, et al. Cancer Cell. 2015 Jan 12; 27(1):138-48

OX40 agonist mAb PF-04518600 Clinical Trials

Title	Phase	Status	Indication(s)	ID Number
A Study Of Avelumab In Combination With Other Cancer Immunotherapies In Advanced Malignancies (JAVELIN Medley)	1b/2	Recruiting	Advanced Cancer Selected tumor types	NCT02554812
Study Of **OX40 Agonist** PF-04518600 **Alone And In Combination With 4-1BB** Agonist PF-05082566	1	Recruiting	Selected advanced solid tumors	NCT02315066

Clinicaltrials.gov as of May 2017

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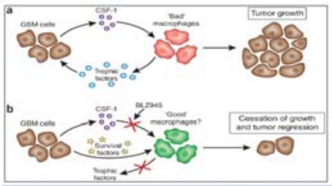
IO +

Anti CSF-1 treatment development

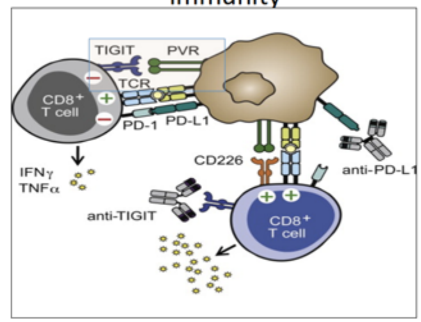


Tumour Assoc. Macrophage infiltration has been identified as an **independent poor prognostic factor** in several cancer types.).

Inhibition of CSF-1 or CSF-1R may have **utility in cancer therapeutics**
Several Clinical trials have been completed or are ongoing in multiples solid tumors in which **macrophages are now being targeted via CSF1R** inhibitors or by blocking mAbs.

Nature Medicine **19**, 1207–1208 (2013)

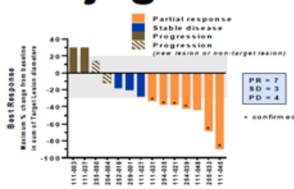
TIGIT: Attacking both innate and adaptive immunity



❑ **TIGIT acts as an inhibitory immune checkpoint** on both **T cells** and **natural killer (NK) cells**, providing an opportunity to target both the adaptive and innate arms of the immune system.

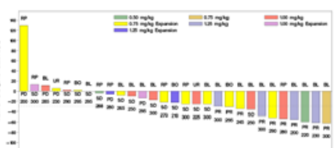
Antibody-drug conjugates

Sacituzumab govitecan (IMMU-132)
- Antibody targeting Trop-2
- Conjugated to SN-38, active metabolite of irinotecan

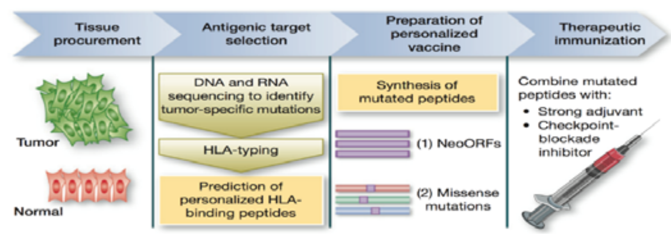


Antibody-drug conjugates (ADCs) deliver cytotoxic selectively to tumor cells.
Generally consist of antibody attached to potent cytotoxic agent
Linker is often key to success: some cleavable, others not
Monoclonal antibody targets tumor antigen, leading to ADC internalization
Once internalized, cytotoxic is liberated

Enfortumab vedotin (ASG-22CE)
- Antibody targets Nectin-4
- Conjugated to MMAE, microtubule inhibitor
- Nectin-4 preferentially expressed on UC



Developing NeoVax: based on multiple coding mutations unique to each pt tumor



- *Safety, feasibility*
- *immune activity*
- *clinical activity*

P. Ott PI (bladder,RCC,melanoma),
Gateway for Cancer Research funded
-Neovax+local subcutaneous IPI

Hacohen et al, Can Imm Res 2013

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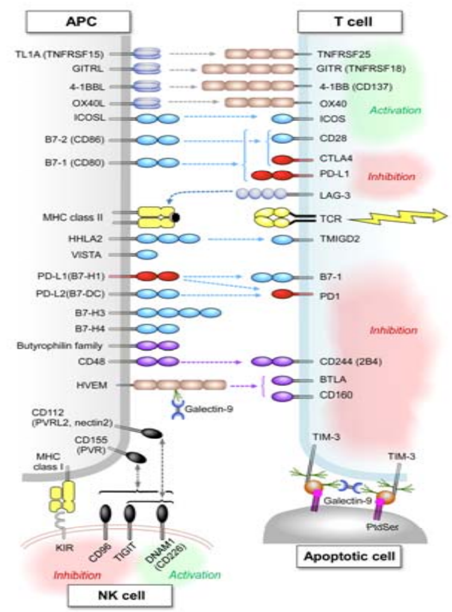
1st

- Potential synergistic combos
  - IO/IO
  - IO/+ other immune approaches
    - ADC, BSA, Vaccines
  - IO/targeted therapies

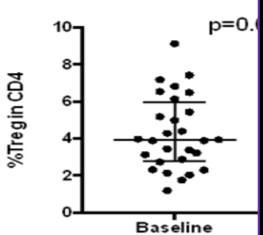


1.- Exhausted Tumor infiltrating lymphocytes express multiple immunoinhibitory receptors:
2.- These are druggable targets for tumor immunotherapy

Changes in immune infiltrating cells in bladder cancer patients treated with cabozantinib

N=28

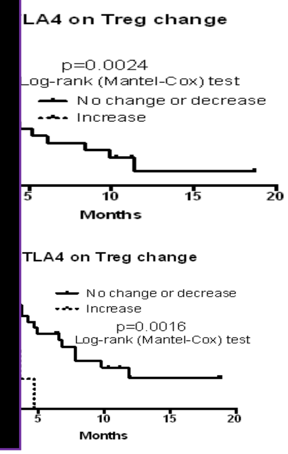
Tregs at baseline ar
with cabozantinib i



Treg PD-1 expression and

Cabozantinib has immunomodulatory properties that may counteract tumor-induced immunosuppression, providing a rationale for combining cabozantinib with immunotherapeutic strategies

CTLA-4 on regulatory T cells and
Free Survival (D) and Overall
al after cabozantinib

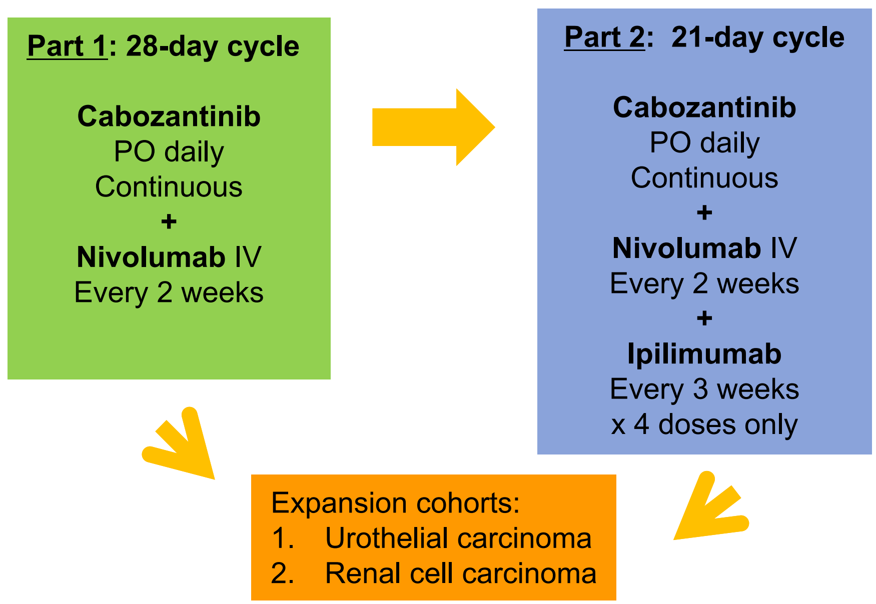


- Treatment with cabozantinib lead to:
- Decrease Tregs among CD4+ T-cells, increase PD-1 expression in Tregs, decrease CTLA-4 expression on Tregs.

Presented by: Andrea B. Apolo ASCO 2014

A Phase I/Expansion Study of Cabozantinib Plus Nivolumab (CaboNivo) Alone or With Ipilimumab (CaboNivoIpi) in Patients With Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

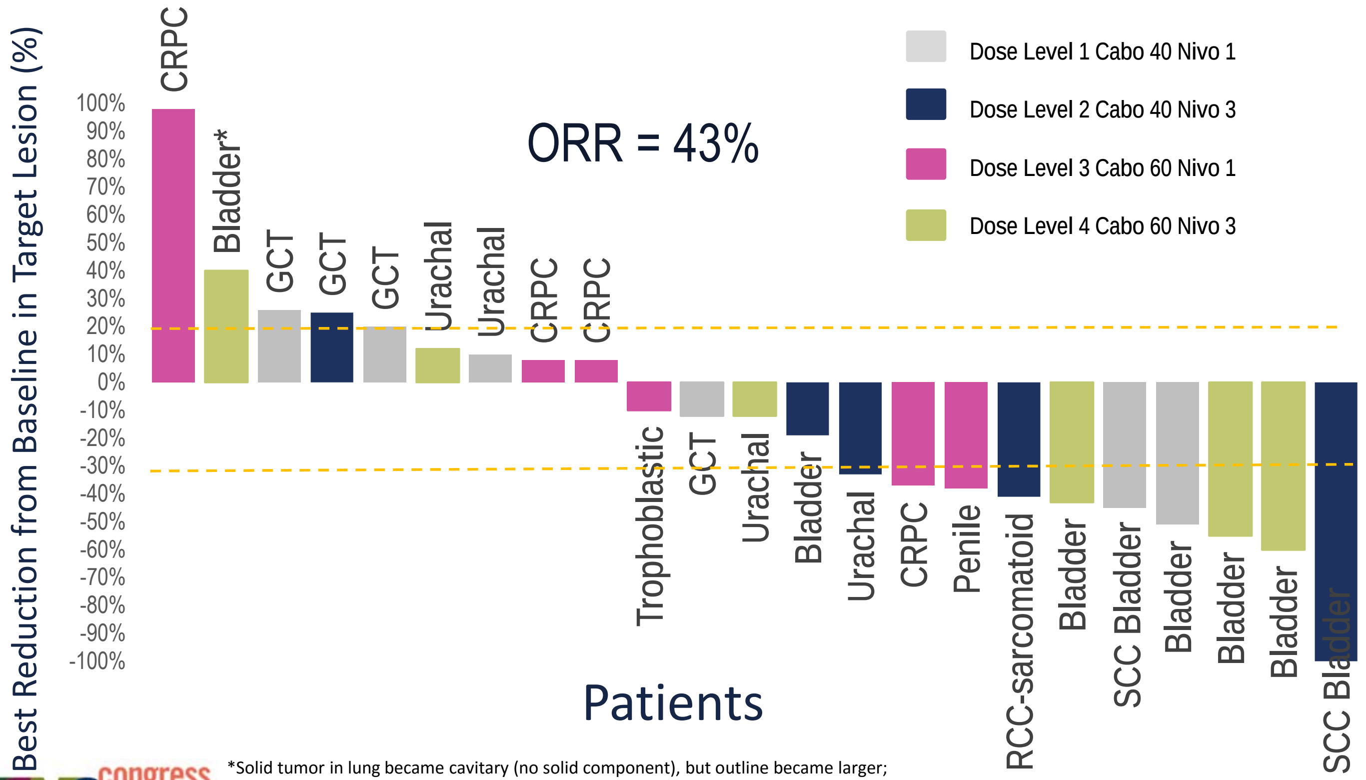
Treatment Schema and Dose Levels



Experimental Therapeutics Clinical Trials Network (ETCTN)

Apolo AB, et al. ESMO 2016 abstract 774PD

Cabozantinib + Nivolumab
Tumor Burden Reduction in Target Lesions



COPENHAGEN 2016 ESMO congress

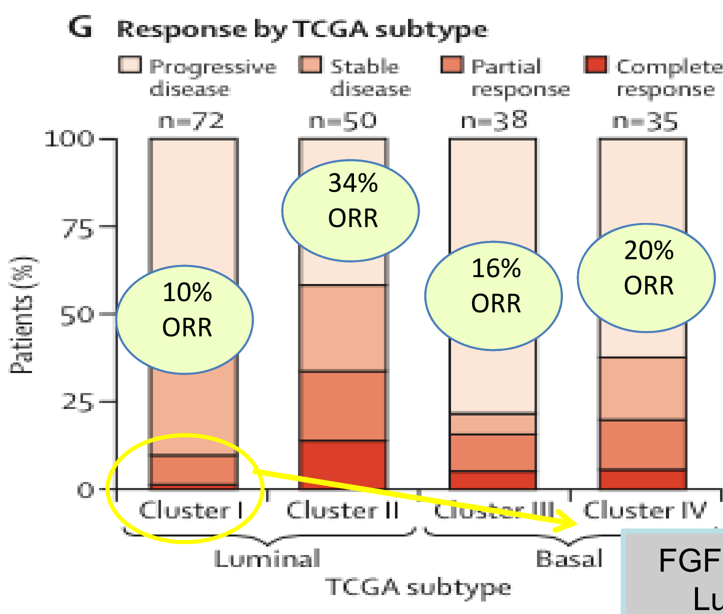
*Solid tumor in lung became cavitary (no solid component), but outline became larger; categorized as stable disease.
CRPC: castration-resistant prostate cancer; GCT: germ cell tumor; ORR: overall response rate; SCC: squamous cell carcinoma; urachal: urachal adenocarcinoma

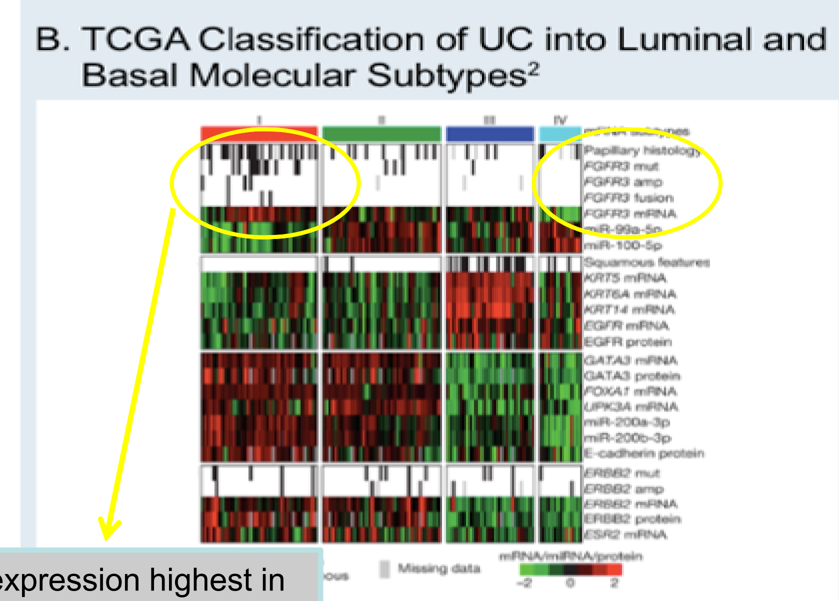
Apolo AB, et al. ESMO 2016 abstract 774PD

It suggest that Combining B-701 and Checkpoint Inhibitor May Provide Benefit

Atezo Ph2 Data Shows the Non-Responders in the "Immune desert" with High FGFR3 Expressions

Atezolizumab Response Rate in Bladder Cancer Sub-types





FGFR3 expression highest in Luminal Cluster I, where responses to Atezo is 10%

J Powles, SITC 30th Annual Meeting 2015 Poster.

Sweis et al 2015: FGFR3 Pathway Associated with Non-inflamed Bladder Tumors and Inversely Correlates with CD8+ T Cells

Rosenberg J et al. Lancet, 2016
Rosenberg J et al. ASCO 2016

Phase 1b Study (Keytruda + B-701) in UCC

Design and Timelines

- **mUC progressed on at least one platinum-based chemo**
- **Atezo naïve**
- **N = up to 12**
- **All comers**
- **PDL1 & FGFR3 + / - assessed retrospectivel y by IHC**

Open-Label On Therapy until Disease Progression

Pembrolizumab + B-701

First 6 patients - Safety Analysis

Pembrolizumab + B-701

Enroll remaining patients

Primary Endpoint:
- Safety and tolerability

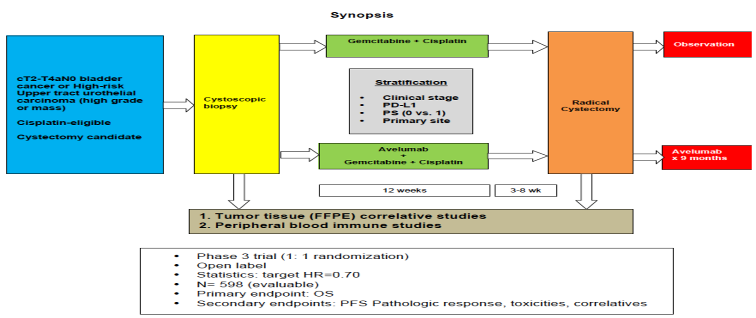
Exploratory Endpoints:
- Objective Response (ORR)
- Progression-free survival (PFS)
- Duration of Response (DOR)
- Overall survival (OS)

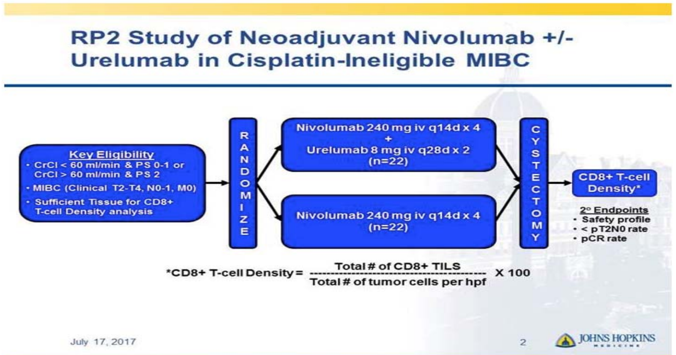
- Investigator study
- FPI ~ September 2016
- Keytruda & B-701 dosing: IV q21days

2nd

- Taking advantage of strategic designs or specific settings
  - **Neoadjuvant paradigm in bladder**
  - Match type trial
  - Concomitant vs Sequential IO/chemo

Neoadjuvant Chemo + Avelumab





Adaptively-randomized neoadjuvant bladder trial

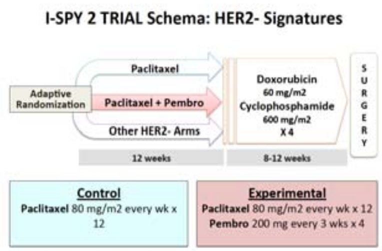
I-SPY 2 Adaptive Randomization

New patient accrues; assess subtype

Randomization
(Probabilities based on performance of each drug within each subtype)

Outcome MRI→pCR model

Update probabilities



I-SPY2 is a biomarker-rich clinical trial with multiple platforms and serial tumor specimens

Studies to identify those most likely to benefit or have complications are ongoing

I-SPY 2 Results Reporting

- The I-SPY 2 Bayesian model generates predictive probability distributions of pCR rates by signature
  - Estimated pCR rates
  - Actual pCR rates not reported; biased by the adaptive randomization
- Format of results presented
  - Estimated mean pCR rates by signature
  - Probability that experimental arm is superior to the control for a given signature
  - Predicted probability of success in a 1:1 randomized 300 patient phase 3 trial

2nd

- Taking advantage of strategic designs or specific settings
  - Neoadjuvant paradigm in bladder
  - **Match type trial**
  - Concomitant vs Sequential IO/chemo

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BISCAY Study: Multi-Drug, Biomarker-Directed, Phase 1b Study in Patients with Metastatic Muscle Invasive Bladder Cancer (MIBC)

- The study will consist of a number of study modules (substudies), each evaluating the safety and tolerability of a specific agent or combination
- The study will evaluate immunotherapy and small molecule targeted therapies
  - AZD4547 (selective FGFR-1,2, and 3 TKI), olaparib (PARP-1/2/3 inhibitor), AZD1775 (Wee1 TKI)

Patients With mMIBC Who Have Progressed on Prior Treatment (N=110)

Module A
- **AZD4547 (PO BID)**
- **Durvalumab (IV Q4W) + AZD4547 (PO BID)**

Module B
- **Durvalumab (IV Q4W) + olaparib (PO BID)**

Module C
- **Durvalumab (IV Q4W) + AZD1775**

Module D
- **Durvalumab (IV Q4W)**

Primary endpoints
- Safety/toxicity/DLT

Secondary endpoints
- PK, ORR, DCR, PFS, DOR

Other endpoints
- Biomarker analysis of blood and tissue

Inclusion criteria
- M/F ≥18; metastatic MIBC; 2nd/3rd line; failed adjuvant/neo-adjuvant chemotherapy <1 yr; 1 lesion ≥10 mm at baseline in the longest diameter suitable for accurate repeated measurement; WHO PS 0-1

Exclusion criteria
- Exposure to immunotherapy, chemotherapy or anticancer agents <4 weeks, radiotherapy <4 wks, or radiotherapy for palliation <2 wks, any study drugs <30 days
- Current or prior immunosuppressive drugs <28 days
- Severe or uncontrolled systemic disease

DLT, dose-limiting toxicity.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02546661. Accessed October 18, 2016.

2nd

- Taking advantage of strategic designs or specific settings
  - Neoadjuvant paradigm in bladder
  - Match type trial
  - **Concomitant vs Sequential IO/chemo**

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Phase II Trial of Gemcitabine + Cisplatin + Ipilimumab in Patients with Metastatic Urothelial Cancer: HCRN GU-148

Matthew D. Galsky, Noah M. Hahn, Costantine Albany, Mark T. Fleming, Alexander Starodub, Przemyslaw Twardowski, Sumanta K. Pal, Ralph J. Hauke, Guru Sonpavde, William K. Oh, Li Wang, Nina Bhardwaj, Sacha Gnjatic, Seunghee Kim-Schulze, Ziyue Liu

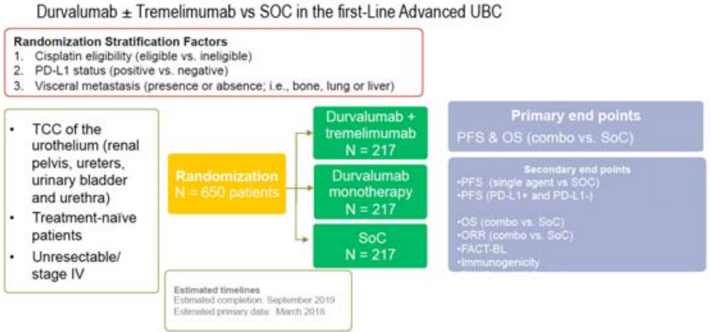
The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins University School of Medicine, Baltimore, MD; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; US Oncology Research, Virginia Oncology Associates, Hampton, VA; Indiana University Health Goshen Center for Cancer Care, Goshen, IN; City of Hope, Duarte, CA; Nebraska Cancer Specialists, Omaha, NE; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; Division of Hematology/Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Mount Sinai Medical Center, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY; Division of Biostatistics, Indiana University, Indianapolis, IN

First line trials exploring IO/IO or chemo Immunotherapy given concurrently

FIRST LINE PHASE III

DANUBE Study Design (NCT02516241)

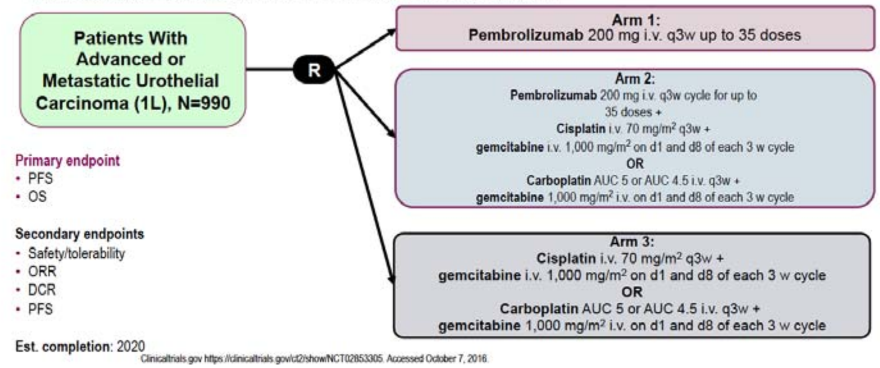
Durvalumab ± Tremelimumab vs SOC in the first-Line Advanced UBC



Study of Nivolumab in Combination With Ipilimumab Compared to the Standard of Care Chemotherapy in Treatment of Patients With Untreated Inoperable or Metastatic Urothelial Cancer (CheckMate901)

KEYNOTE-361 (ongoing): Study Design

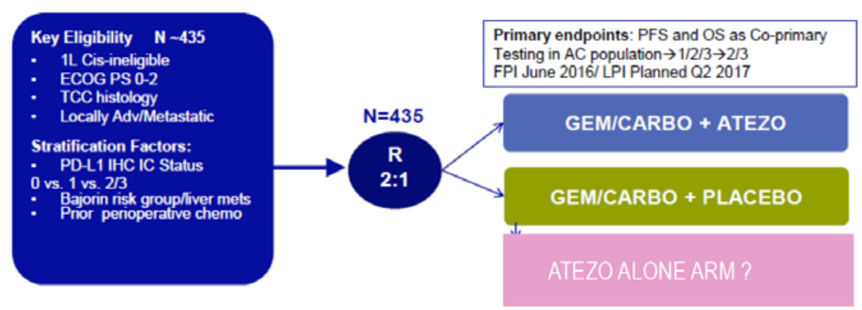
- A phase 3 randomized, controlled clinical trial of pembrolizumab +/- platinum-based combination chemotherapy vs chemotherapy in subjects with advanced or metastatic urothelial carcinoma



Clinicaltrials.gov https://clinicaltrials.gov/ct2/show/NCT02853305. Accessed October 7, 2016.

Chemotherapy + Immunotherapy in 1st- line "unfit"?

ImVigor 130



U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

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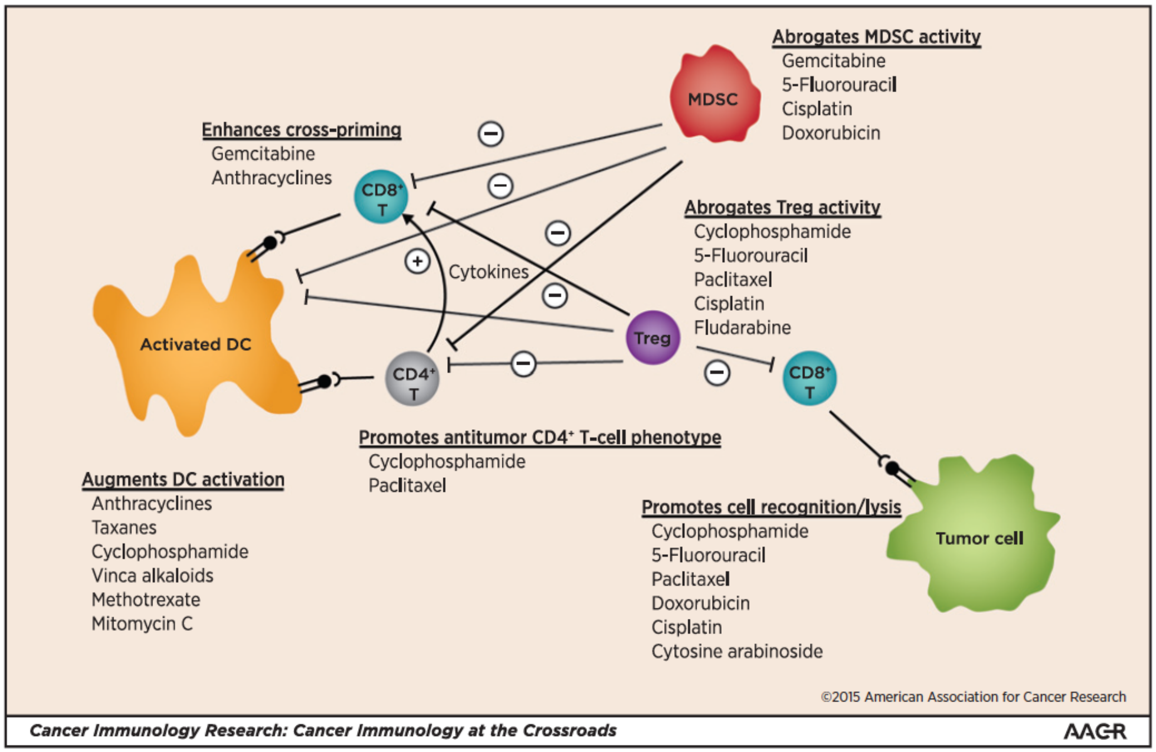
Chemotherapy Can Modulate Distinct Features of Tumor Immunobiology in a Drug-, Dose-, and Schedule Dependent Manner[1]



1.-Chen G, Emens LA. Chemoimmunotherapy: reengineering tumor immunity. Cancer Immunol Immunother 2013;62:203–16.

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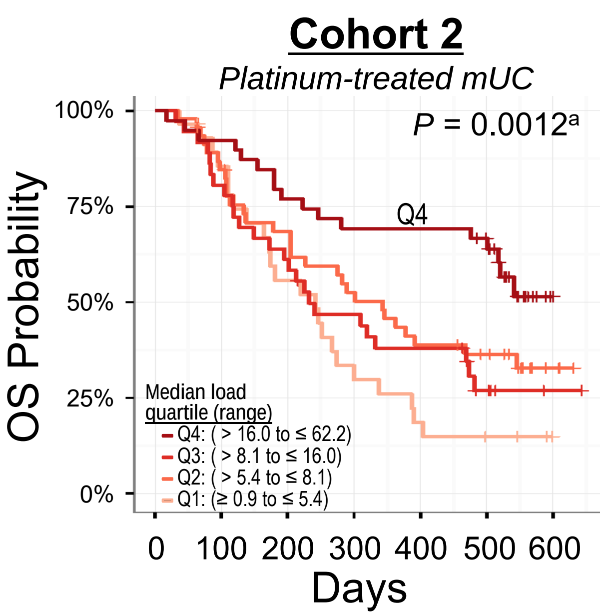
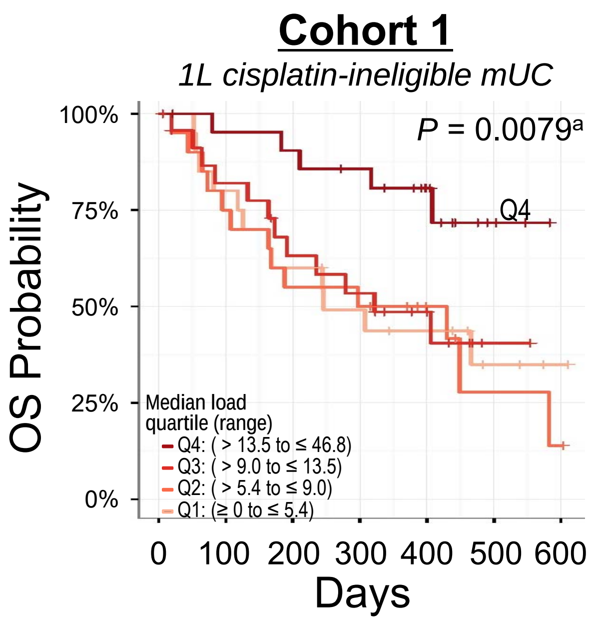
3rd

- Focusing on new genomic findings (ASCO 2017, TCGA 2017)
  - TMB,MMR,DDR

Biomarkers beyond PD-L1: Mutation load is associated with OS in patients treated with atezolizumab





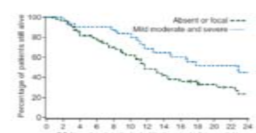
- Mutation load associated with ORR
- Quartile-split mutation load was associated with OS in platinum-treated patients (cohort 2)
- Similar results were seen for 1L cisplatin-ineligible patients (cohort 1)
  - In both cohorts, patients with the highest median mutation load (Q4) had significantly longer OS vs those in Q1-Q3[a]

Rosenberg et al. ASCO 2016

Urothelial Cancer. PD-L1, APOBEC and TMB

Gene	MNC presence (score = 2, 3, 4)		PDL1 MNC presence (score = 2, 3, 4)		Longer OS			PDL1 tumor expression (≥ 5%)	
	P-vlaue		P-vlaue		HR, CI	P-vlaue		P-vlaue	
APOBEC3A	**0.007**	**High Expression**	**0.0009**	**High expression**	**0.45 (CI:0.23–0.86)**	**0.01**	**High expression**	0.87	
APOBEC3B	**0.13**		**0.05**	**Low expression**		0.89		0.18	
APOBEC3C	0.80		0.2			0.6		0.06	
APOBEC3D	**0.05**	**High Expression**	**0.009**	**High expression**	**0.49 (0.25–0.95)**	**0.02**	**High expression**	0.23	
APOCEC3F_a	0.40		0.49			0.43		**0.05**	**Low expression**
APOBEC3F_b	0.46		0.31			0.15		**0.04**	**Low expression**
APOBEC3G	0.59		0.65			0.55		0.47	
APOBEC3H	0.19		**0.06**	**High expression**	**0.36 (0.19–0.71)**	**0.004**	**High expression**	0.8	

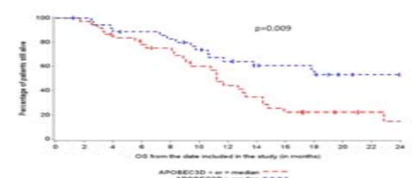
Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma



- Positive PD-L1 expression (score of 2–4) in TIMCs was significantly associated with longer OS (12 versus 23 months) in both univariate (P = 0.04) and multivariable analysis (P = 0.0007) (adjusting for ECOG status and visceral disease)
- PD-L1 expression in tumor cell membrane was not associated with survival (P = 0.45)

Annals of Oncology 00: 1–6, 2015 doi 10.1093/annonc/mdv009

- Correlation with ↑ PD-L1 in TIMCs
- APOBEC3A,D,H
  - ↑ TIMCs
  - ↑ TIMC → PD-L1 expression
  - High mutational burden caused by APOBEC
  - High neo-antigen levels on cc

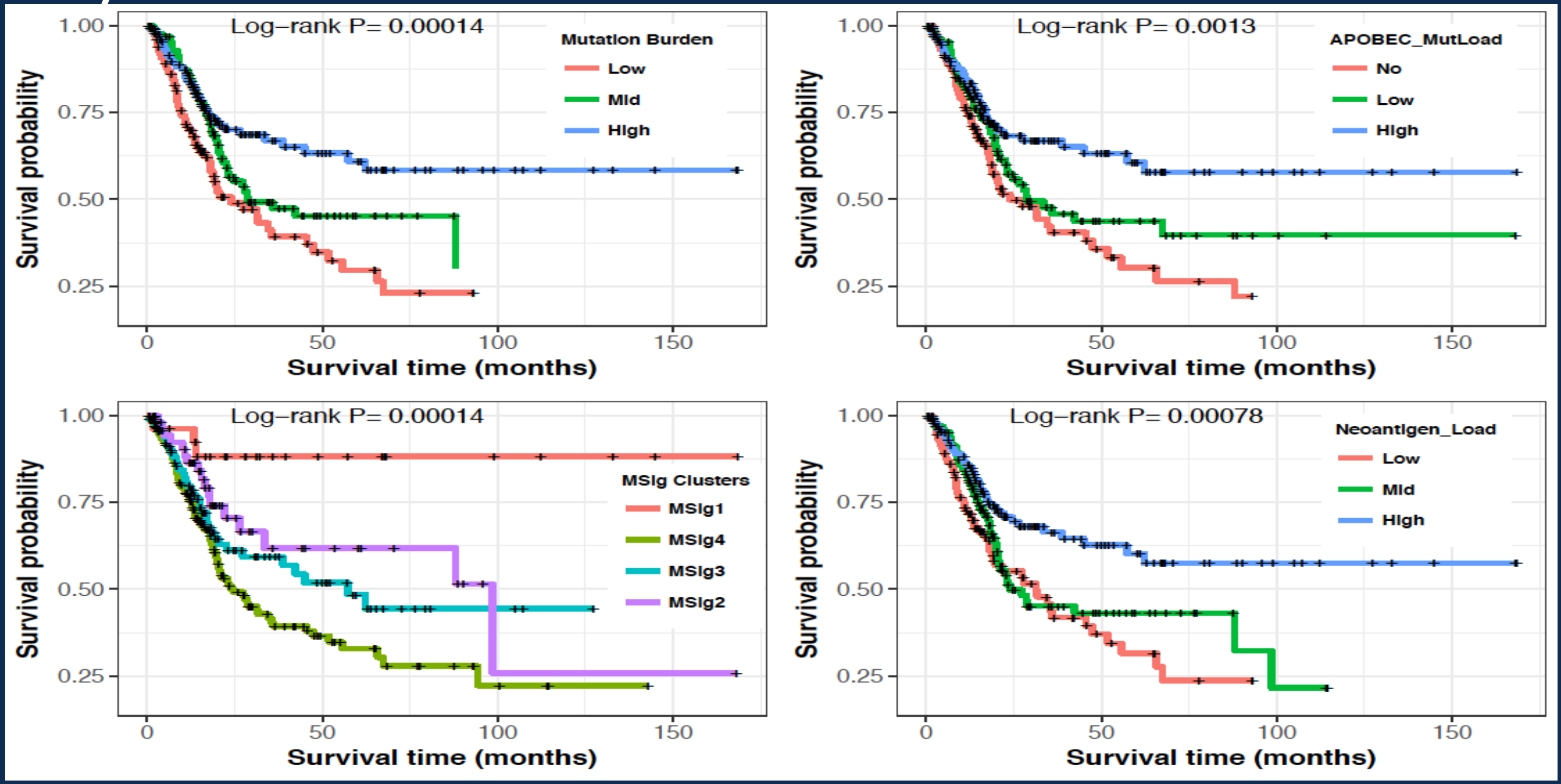


Responsible for chemotherapy response and survival benefit ?

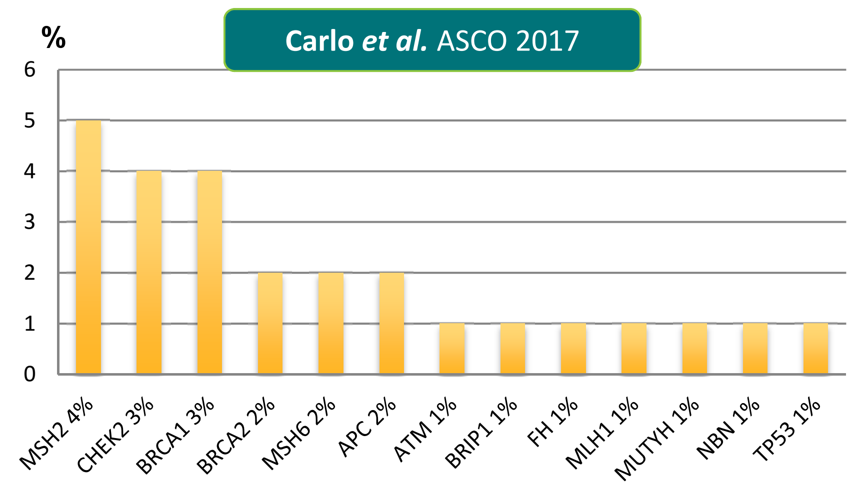
Mullane Scientific Reports 2016

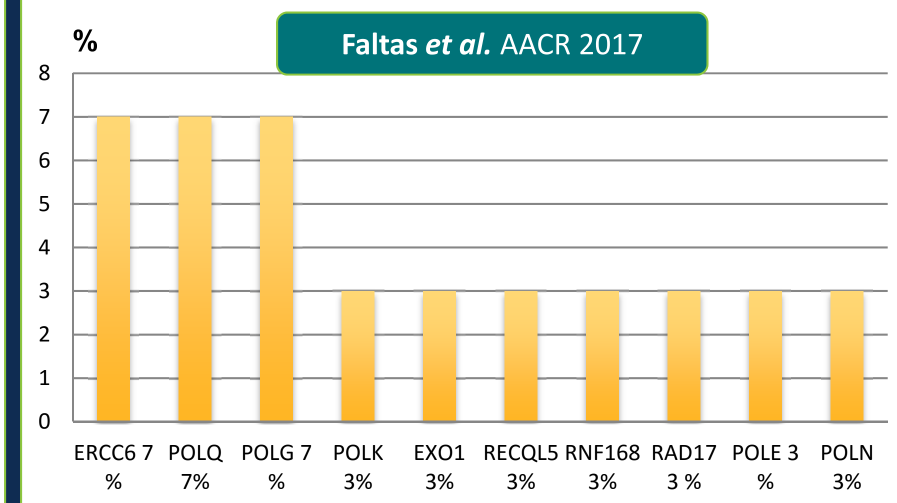
Middlebrooks et al. Nat genet 2016
Mullane SA, Bellmunt J et al . Scientific Reports 2016

Abstract 4500: Comprehensive molecular characterization and analysis of muscle-invasive urothelial carcinomas TCGA 2017 (n=412)



Germline DDR SNVs: common in UC patients





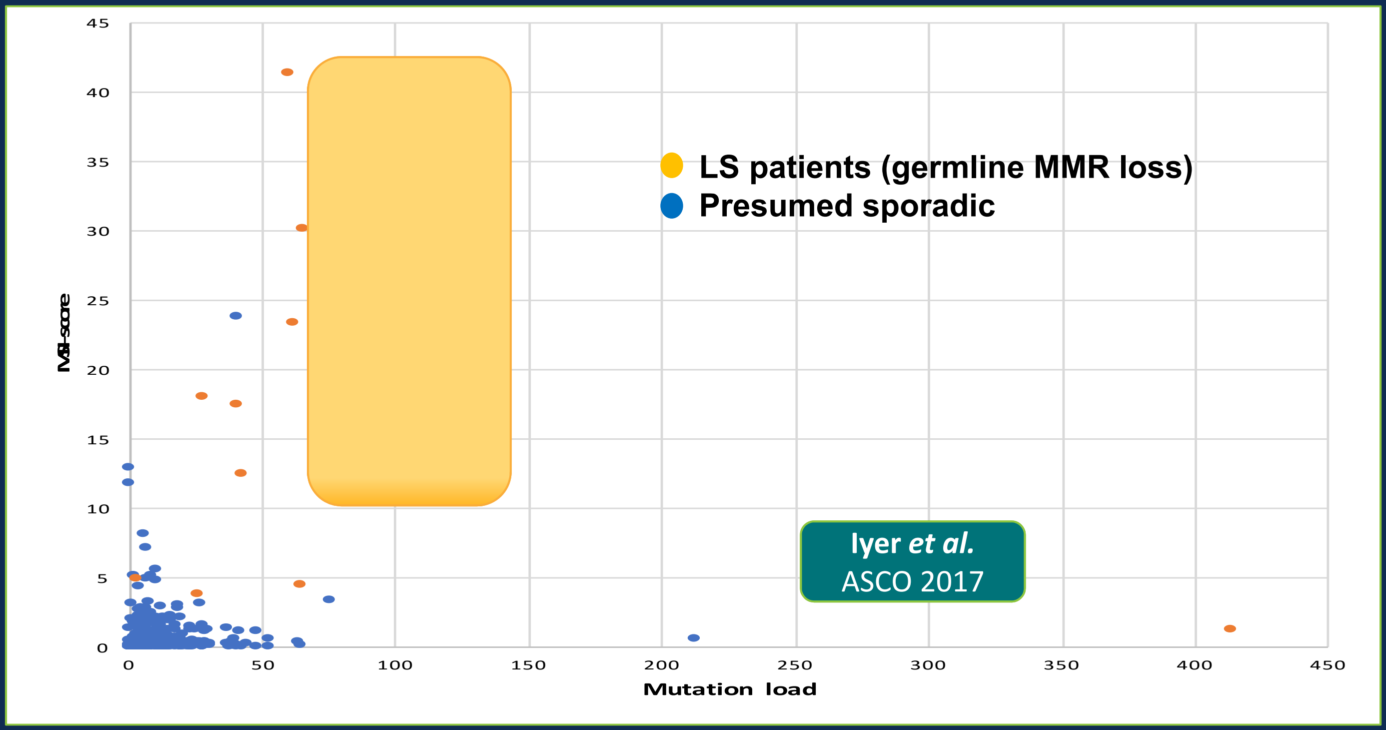
22% germline DDR mutations

MSK-IMPACT (targeted)
UTUC in 31% of cohort

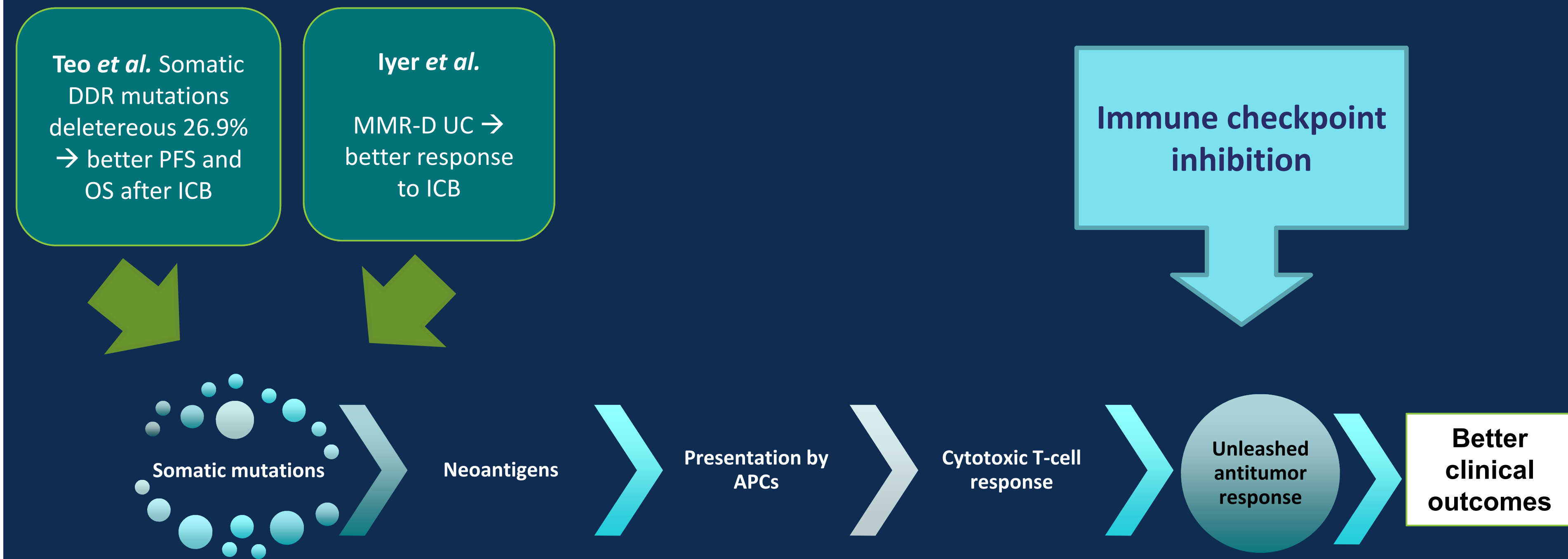
48% germline DDR SNPs

EXaCT-1 (WES)
UTUC in 19% of cohort

Germline MMR mutations in UC: uncommon (3%) but important and may be associated with HNPCC



Somatic mutations and response to immunotherapy



Pembrolizumab indicated for treatment of patients with unresectable / metastatic solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) **(also urothelial cancer)**

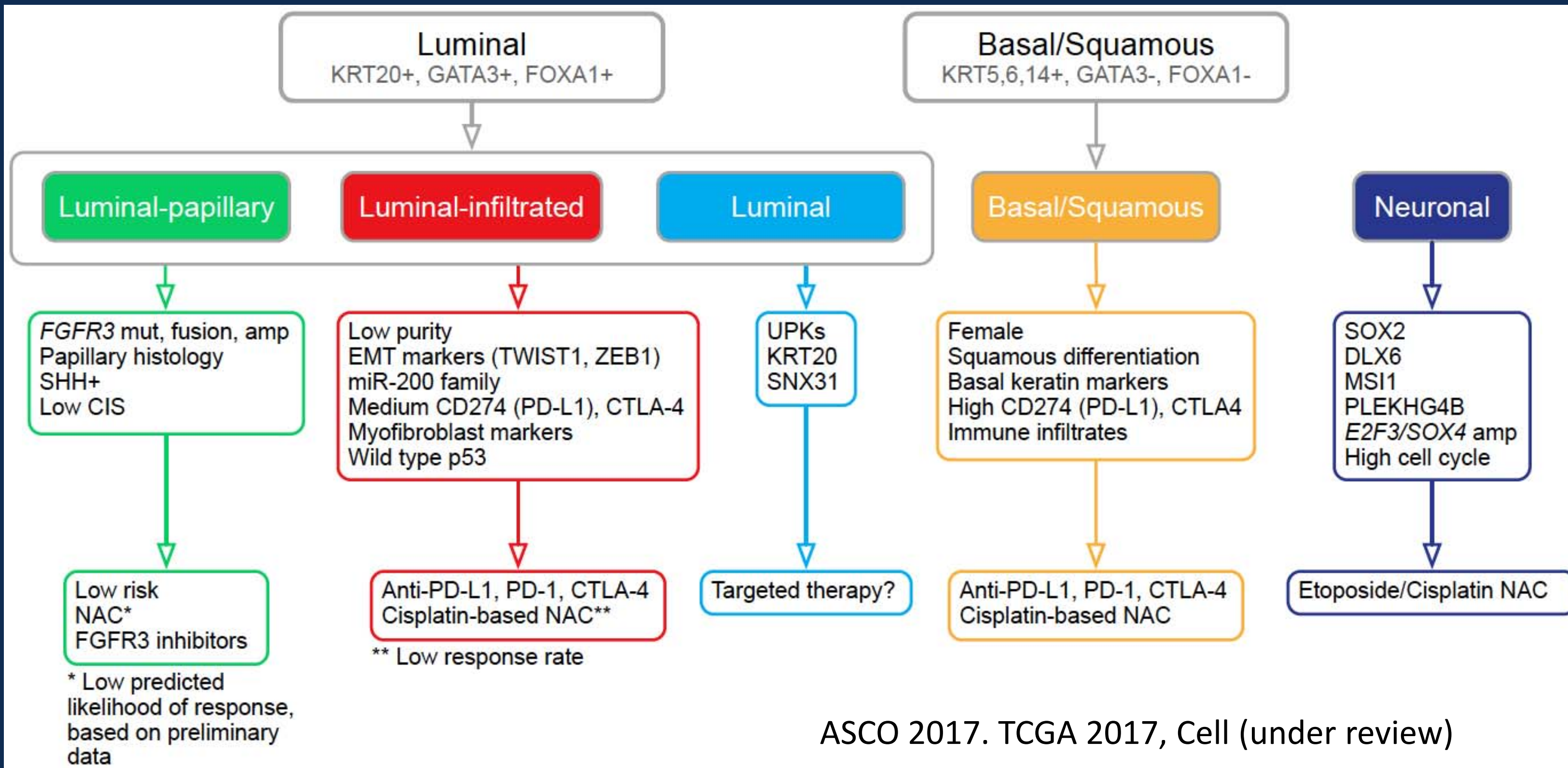
+ PARP inhibitors ?

FDA, May 23rd , 2017

Future treatment paradigm??

Framework for prospective hypothesis testing in clinical trials, as well as for validation in ongoing or completed clinical trials that test, or have tested, treatment strategies

CLASSIFICATION INTO DIFFERENT MOLECULAR SUBTYPES



ASCO 2017. TCGA 2017, Cell (under review)

This slide has been withheld by the presenter.

DANA-FARBER CANCER INSTITUTE BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL

Understanding immunology and genetics has identified groups that respond well to PD-1/PD-L1 therapy

- IO combos with IO, targeted therapies, chemo, vaccines. Sequencies.
- Highly mutated tumors (TMB, MSI, defects in DNA repair)
- Genetically defined groups (TCGA 2017)
- Implement integrated analysis of response- and resistance-associate mutations with mutational signature, clinical annotations, and mutational clonality

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PANEL DISCUSSION - SESSION I

Immuno-oncology (IO) Overview – Scope of the Problem

Moderator: Amy E. McKee, MD

Speakers:
Robert H. Vonderheide, MD, D Phil
David F. McDermott, MD
Leisha A. Emens, MD, PhD
Joaquim Bellmunt, MD, PhD

Panelists:
Daniel S. Chen, MD, PhD
Nolan A. Wages, PhD

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SESSION II:
Key Translational and Design Questions for IO Agents

Moderator: Elizabeth M. Jaffee, MD

Speakers:

Tiffany S. Ricks, PhD

Daniel S. Chen, MD, PhD

Bernard A. Fox, PhD

Nonclinical Safety Evaluation of Novel Cancer Immunotherapy Combinations

Tiffany K. Ricks, PhD
Pharmacology/Toxicology Reviewer
OHOP/FDA

FDA-AACR Oncology Dose Finding Workshop
July 20, 2017

Disclosures

- I have no conflicts of interest to disclose.

ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

- Provides basic nonclinical recommendations for the development of anti-cancer drugs
- To initiate clinical trials for anti-cancer drugs, you typically need 28-day toxicology studies in 2 species
- For biologics, as discussed in ICH S6 and its addendum, a single species is often acceptable if there is only one pharmacologically relevant species
- These studies are the primary data used to determine the acceptability of the proposed starting dose for first-in-human trials

Challenges with Cancer Immunotherapies

- Species relevance; is there a pharmacologically relevant species?
  - Differences in binding or thresholds for immune activation/sensitivity
- Toxicology studies in monkeys generally underpredict human toxicities

Anti-PD-1 Monkey Tox Findings	Anti-PD-1 Human AEs
• Diarrhea • Multi-organ, diffuse WBC infiltration histologically with no demonstrable clinical or clinpath correlates	• Colitis • Pneumonitis • Uveitis • Nephritis • Hepatitis • Hyper- and Hypothyroidism • Hypopituitarism • Hypophysitis • Myositis • Vasculitis

- How to select an appropriate starting dose
  - Recommend using a Minimally Anticipated Biologic Effect Level (MABEL)
- Unique safety concerns, e.g., cytokine release syndrome, aberrant T cell activation, and immune-related AEs
- Combinations of cancer immunotherapies

Special Recognition of Immune-Targeting Drugs

- ICH S9 specifically mentions concerns about using standard methods based on toxicology studies alone to set the starting dose of immune agonists:
  - "For biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally anticipated biologic effect level (MABEL) should be considered."
- Determining a MABEL relies heavily on a variety of pharmacology studies

Calculating a MABEL

- There is no universal approach for determining a FIH dose based on a MABEL
- Useful data inputs:
  - In vitro pharmacology data from target cells from human and toxicology species
  - Concentration-effect data from in vitro and in vivo studies
  - If using animal data, then provide a comparison of
    - Animal-human differences in exposure/drug distribution
    - Animal-human differences in expression level and distribution of target
    - Animal-human differences in affinity of target binding and intrinsic efficacy
    - Duration and reversibility of biologic effect
    - Dose-exposure relationship (PK/PD)

Combinations of Cancer Immunotherapies

ICH S9, Q & A (draft):

- Pharmaceuticals planned for use in combination should be well studied individually in toxicological evaluations
  - Sufficient data to support clinical trials of each drug alone
- Provide data to support biological rationale of the combination
  - In vitro or in vivo data or literature assessment based on mechanistic understanding of target biology
  - May provide additional support for dose selection and safety
- In general, combination toxicology studies are not warranted

Combinations of Cancer Immunotherapies

ICH S9, Q & A (draft):

- If there is sufficient clinical data to support the combination, additional nonclinical data may not be warranted
  - e.g., completed Phase 1 or a monotherapy phase within a Phase 1
- If there is no or very limited clinical experience with one or both products, combination pharmacology studies are often recommended
  - e.g., in vitro cytokine release assay in human PBMCs, in vitro studies examining the potential functional dose response curve of T cells, and in vitro T cell activation assays
  - Include assessment of concentration-response curves for determining EC_{50}, EC_{20}, and EC_{90} to justify combination start dose

Combinations of Cancer Immunotherapies

- Expect overlapping immune-related AEs; other toxicities may be difficult to predict

- Dose reduction is generally recommended relative to single-agent MTD/RP2D

Case Study #1:
2 Products with Clinical Experience

- Sponsor proposed combination of a kinase inhibitor with an anti-PD1 antibody
- Significant clinical experience with both products
- No pharmacology or toxicology studies were submitted to support the combination

Case Study #1: Issue

- Kinase inhibitor has a class-effect of cardiac toxicity
- Findings of severe cardiac inflammation in toxicology studies for the kinase inhibitor
  - Cardiac valvulopathy
  - Severe inflammation of blood vessels and associated mortalities in rats
  - Potential risk for aneurysm
- Clinically, no clear cardiac findings had been noted to date

Case Study #1: Outcome

- Despite the lack of clinical findings to date, there was a concern about the potential of the combination to exacerbate this finding and make it clinically significant
- No additional nonclinical studies requested
- Sponsor was asked to lower starting dose of kinase inhibitor to a dose with a predicted exposure ~20% of that causing cardiac inflammation in nonclinical studies
- Clinical monitoring for cardiovascular changes using echocardiography and ECG

Case Study #2:
Checkpoint inhibitor and anti-PD1 antibody

- Sponsor proposed a first-in-human combination of a checkpoint inhibitor (Drug X) and anti-PD1 antibody
  - Previous clinical experience with anti-PD1 antibody
  - Experience with similar products targeting immune checkpoint

- Proposed 2 cycle lead-in phase with Drug X followed by combination with RP2D of anti-PD1 antibody

Case Study #2:
Checkpoint inhibitor and anti-PD1 antibody

- Provided 3-month toxicology study in monkeys with Drug X alone and in combination with anti-PD1 antibody (not requested)
  - Findings included immune cell infiltration in multiple organs including CNS and kidneys; not dose limiting

- Provided pharmacology data with Drug X alone and in combination with anti-PD1 antibody
  - In vitro antigen recall assay using human T cells and antigen-loaded DCs; observed potent IFN-γ response
  - Syngeneic mouse tumor model; greater anti-tumor activity with combination

Case Study #2: Issues

- Drug X alone had little pharmacodynamic activity but significant increase in activity with anti-PD1 antibody

- Adding RP2D of anti-PD1 antibody to proposed starting dose of Drug X may greatly increase the activity and toxicity

Case Study #2: Outcome

- Sufficient nonclinical data to support combination of Drug X and anti-PD1 antibody
- Reduce start dose of Drug X by 20-fold based on EC_{50} for T cell activation from in vitro combination assay
- Drug X alone was not expected to have any significant clinical activity
- Recommended modifying the protocol so that all dose escalation cohorts receive the combination rather than starting with a 2 cycle lead-in phase

Case Study #3: Novel target

- Immune receptor expressed on T cells and NK cells
  - Associated with impaired T cell-mediated anti-tumor immunity
  - Role of target in immunology and tumor biology is still being explored
  - Multiple ligands; potentially unidentified
  - Role in promotion of Th2 responses
  - Role in Treg maintenance

- Proposed a FIH trial of Drug Y alone and in combination with RP2D of anti-PD-L1 antibody
  - Combination will begin after DLT evaluation of at least 2 dose levels of Drug Y alone
  - Combination start dose will be no higher than monotherapy start dose

Case Study #3: Novel target

- Provided data from pharmacology studies
  - In vitro mixed lymphocyte reaction, in vitro cytokine release, syngeneic murine tumor model with surrogate antibodies

- 4-week toxicology study in monkeys with Drug Y
  - Multi-organ immune cell infiltration
  - Anaphylaxis-like reactions after several infusions at the low dose; resulted in one mortality after 5th dose

- Sponsor did not evaluate activity of mAb on Th2 cells

Case Study #3: Outcome

- Sponsor proposed a starting dose based on mechanism of action and pharmacology and toxicology data
- Requested Sponsor lower starting dose 10-fold
  - Dose predicted to result in a concentration equal to EC_{50} for IFN-γ release in mixed lymphocyte reaction assay
  - Dose still pharmacologically active
- Combination with anti-PD-L1 antibody may proceed after DLT evaluation of 2 cohorts
- Combination start dose should be no higher than monotherapy start dose

Summary

For cancer immunotherapy combinations:

- Toxicology studies of each drug alone
- Data to support the biological rationale and safety of the combination
- If there is sufficient clinical experience, additional nonclinical studies of the combination may not be warranted
- When there is no or very limited clinical experience, combination pharmacology studies are recommended
- Use totality of data including pharmacology data, literature assessment, and experience with similar products

Acknowledgments

- Todd Palmby
- Whitney Helms
- Emily F. Wearne
- Shawna Weis
- John Leighton
- OHOP colleagues

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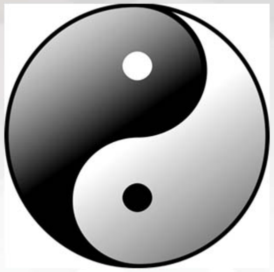
Things We are Looking For When We Receive an IND for an Immunomodulator

*Applies to immune activators and checkpoint inhibitors

- Pharmacology of the targeted pathway
  - Is the target an agonist or antagonist of immune activity?
- Comparative binding assessments with orthologues from animals and humans
- Assessment of **cytokine release potential** with appropriate +/- controls
- Studies using human cells that take into account multiple mechanisms of action
- Receptor Occupancy
- 28-day repeat-dose toxicology study (if there's a pharmacologically relevant species); consider adding immune endpoints



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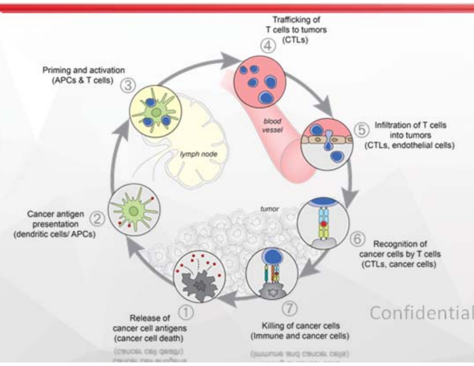
AACR American Association for Cancer Research

FINDING CURES TOGETHER℠

Oncology Dose-Finding Workshop
Part 3
Thursday July 20th, 2017

Next Wave: Considerations for Novel Cancer Immunotherapy Combination Development



Daniel S. Chen MD PhD
Vice President
Global Head of Cancer Immunotherapy
Product Development
Genentech/Roche

Genentech
A Member of the Roche Group

Roche

DISCLOSURES

I am an employee of Genentech,

a member of the Roche group.

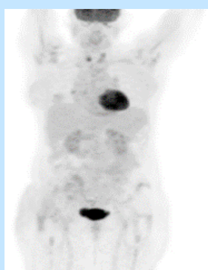
The information presented is solely intended to foster the exchange of scientific and medical information.

CANCER IMMUNOTHERAPY SHOWS TRANFORMATIVE PROMISE

Patient with NSCLC treated with atezolizumab (FIR study)[1]

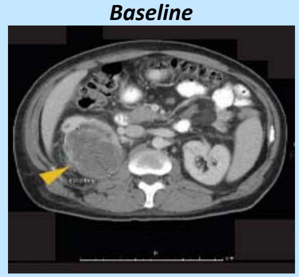
Baseline

Post C2 (Week 6)



Patient with RCC treated with nivolumab (NCT00730639)[2]

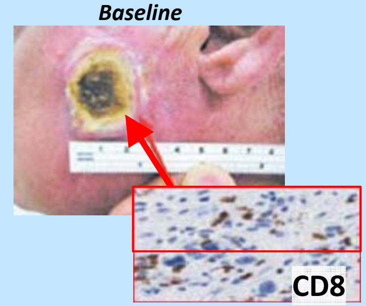
Baseline



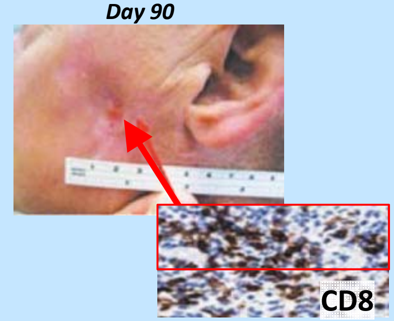
23 months

Patient with melanoma treated with pembrolizumab (KEYNOTE-001)[3]

Baseline



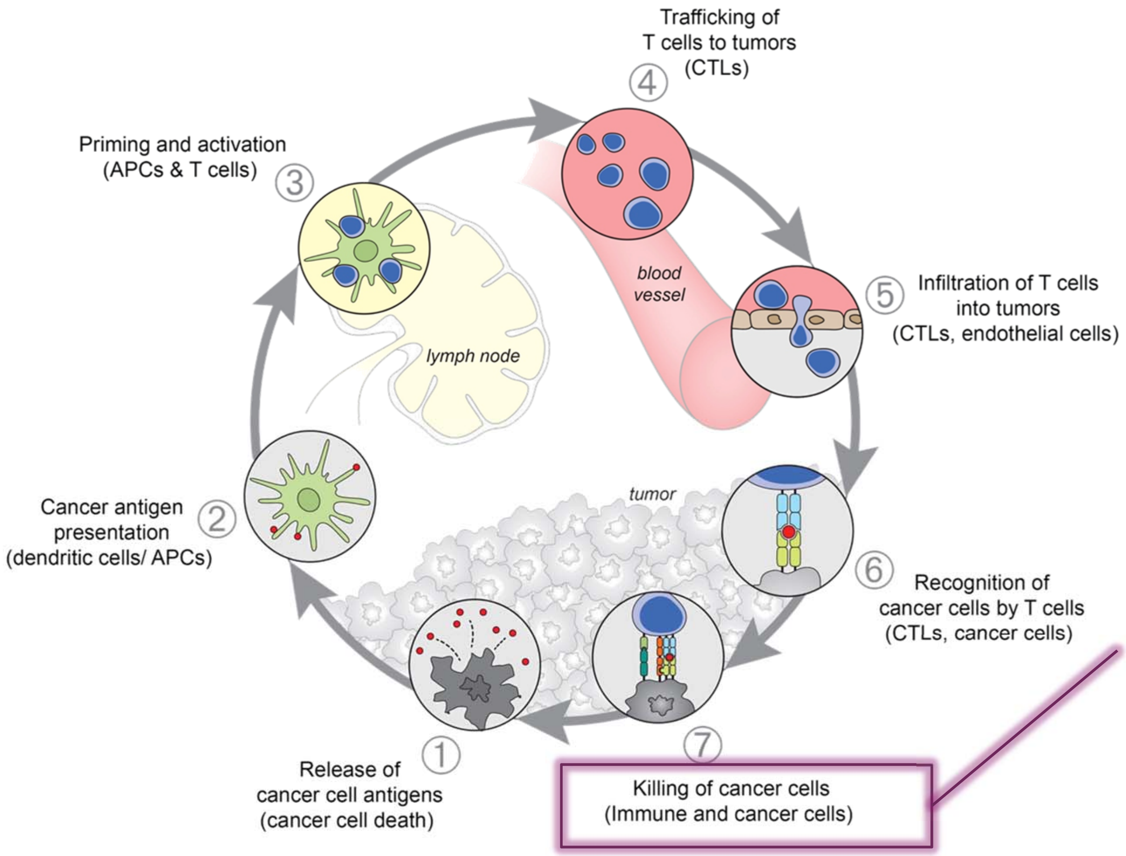
Day 90



1. Chaft, et al. WCLC 2015; 2. McDermott, et al. J Clin Oncol 2015; 3. Hamid, et al. N Engl J Med 2013

Chen DS, FDA-AACR 2017

UNDERSTAND HUMAN CANCER-IMMUNE BIOLOGY
A BIOLOGIC FRAMEWORK: THE CANCER-IMMUNITY CYCLE



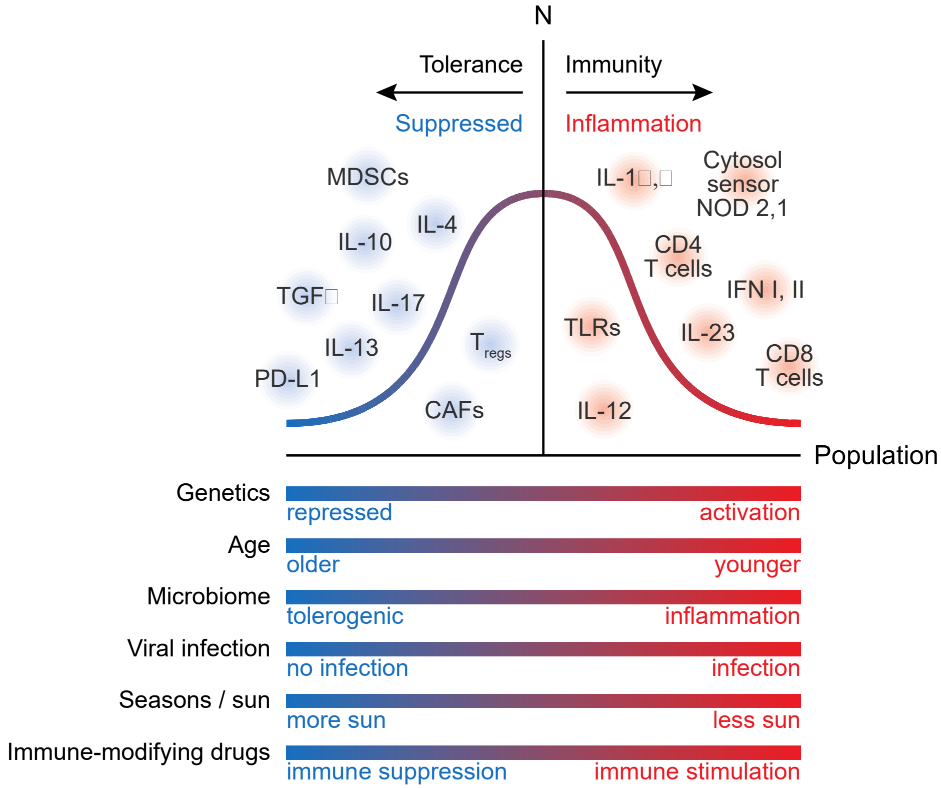
PD-L1 Expressed in the tumor microenvironment

Chen DS, Mellman I. Immunity. 2013.

Chen DS, FDA-AACR 2017

UNIFYING PRINCIPLES: *THE CANCER IMMUNE SET POINT*

$$\int (F_{stim}) - \int (F_{inhib}) \geq 1/\Sigma_{n=1,\,y} (TCR_{affinity} \text{ x frequency})$$

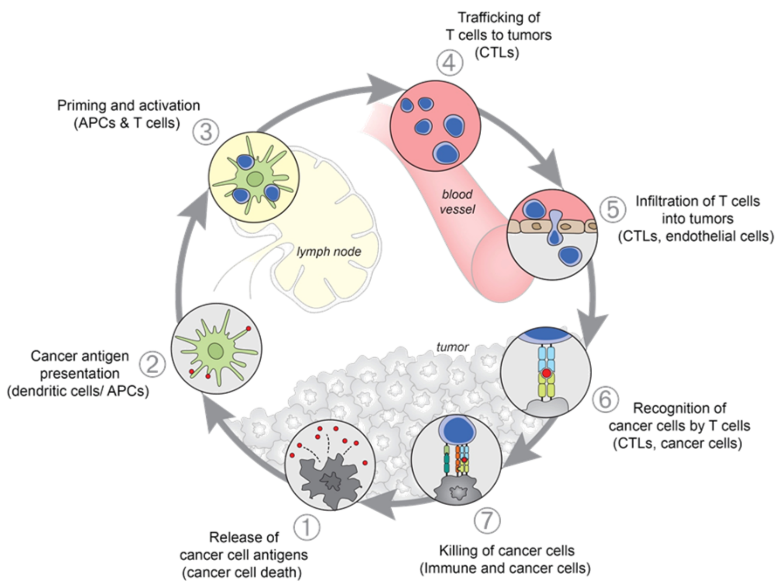


Chen DS, Mellman I. Nature 2017

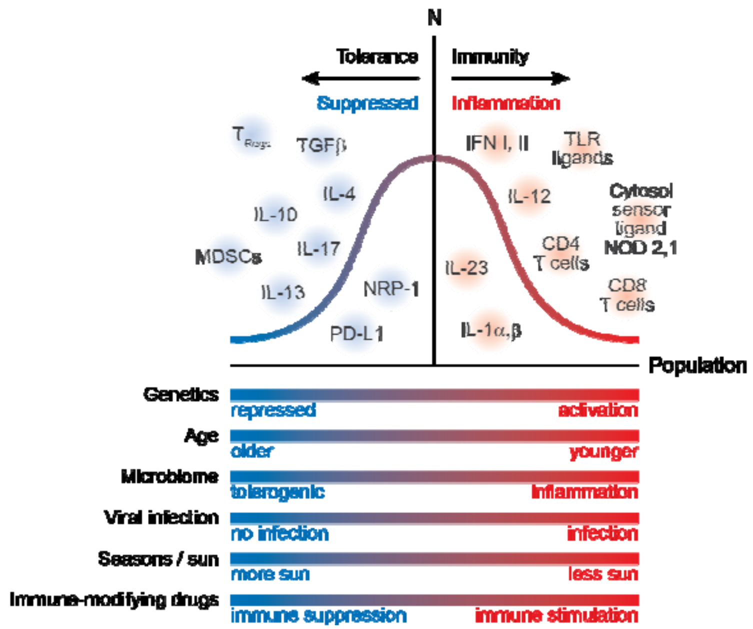
Chen DS, FDA-AACR 2017

IMMUNE BIOLOGY

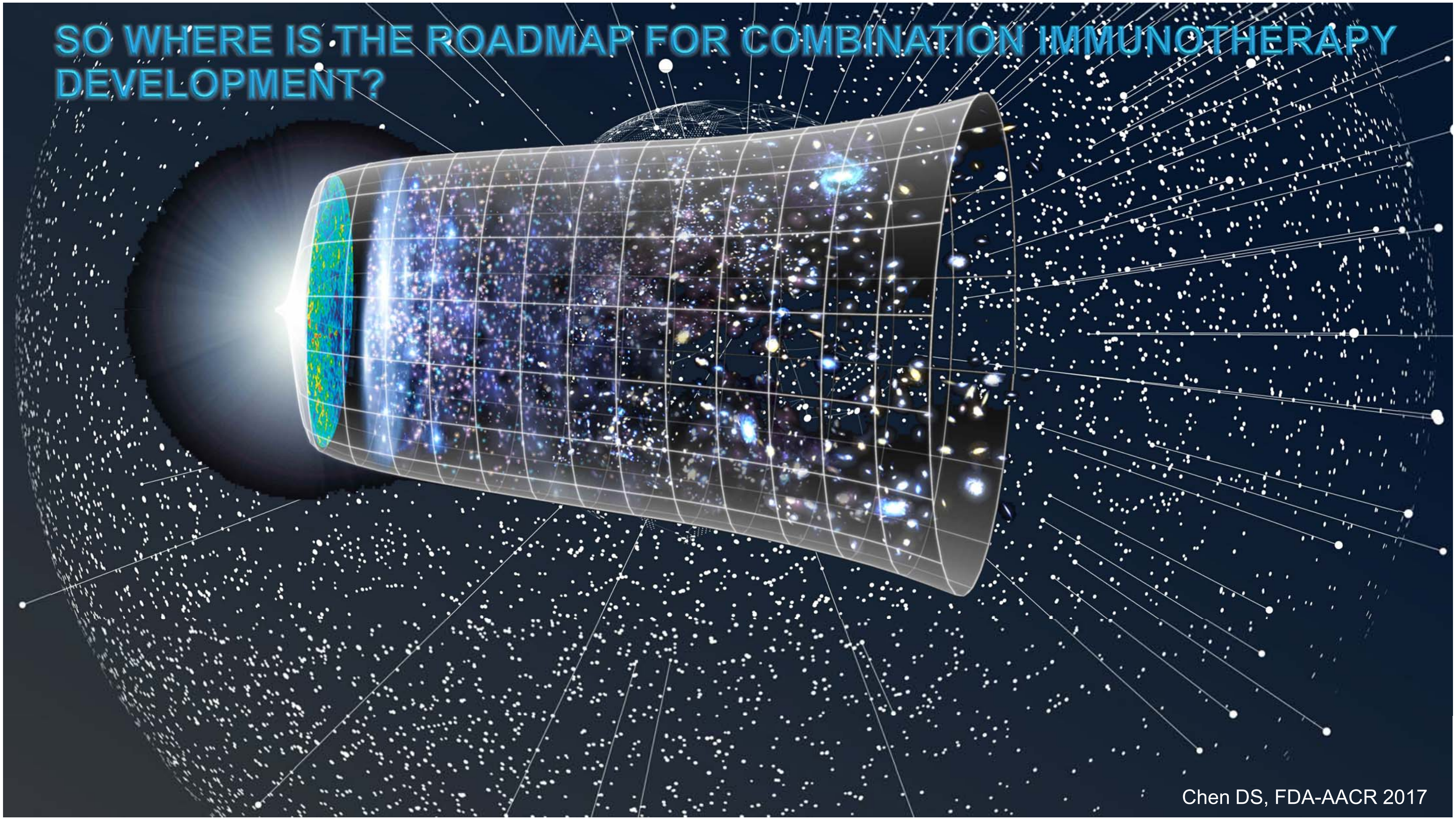
A complex set of tumor, host and environmental factors govern strength, and timing of anti-cancer immune responses

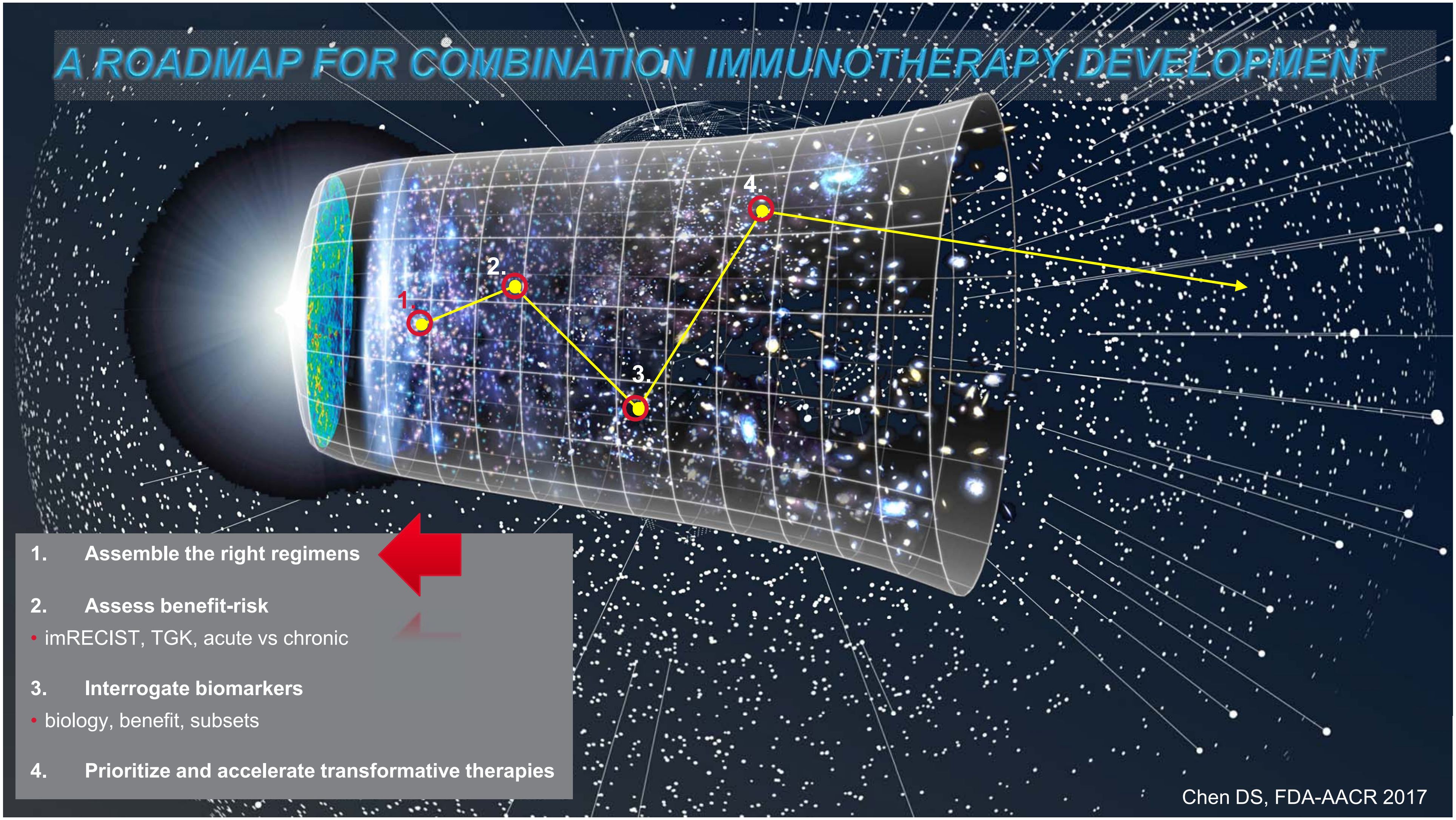


Chen and Mellman. *Immunity* 2013



Chen and Mellman. *Nature 2017*

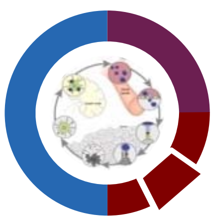

SO WHERE IS THE ROADMAP FOR COMBINATION IMMUNOTHERAPY DEVELOPMENT?
Chen DS, FDA-AACR 2017


A ROADMAP FOR COMBINATION IMMUNOTHERAPY DEVELOPMENT
1.
2.
3.
4.
1. Assemble the right regimens
2. Assess benefit-risk
• imRECIST, TGK, acute vs chronic
3. Interrogate biomarkers
• biology, benefit, subsets
4. Prioritize and accelerate transformative therapies
Chen DS, FDA-AACR 2017

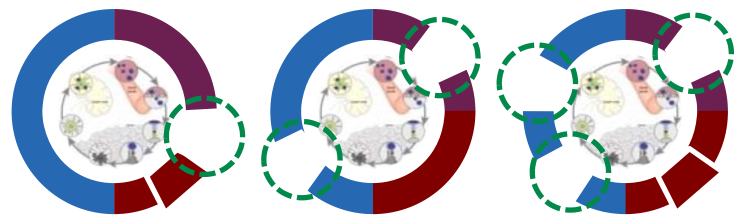
1. RATIONAL COMBINATIONS: BUILDING BLOCKS TO ASSEMBLE EFFECTIVE IMMUNITY

Each individual patient may require 1, 2, 3, 4, etc., of these molecules in combination (or sequentially) to restore cancer immunity

Some patients may only require targeting of negative regulator (aPD-L1 monotherapy) to enable cancer immunity



Some patients will need two or more therapies to enable cancer immunity (e.g., to drive infiltration, boost MHC expression, etc)

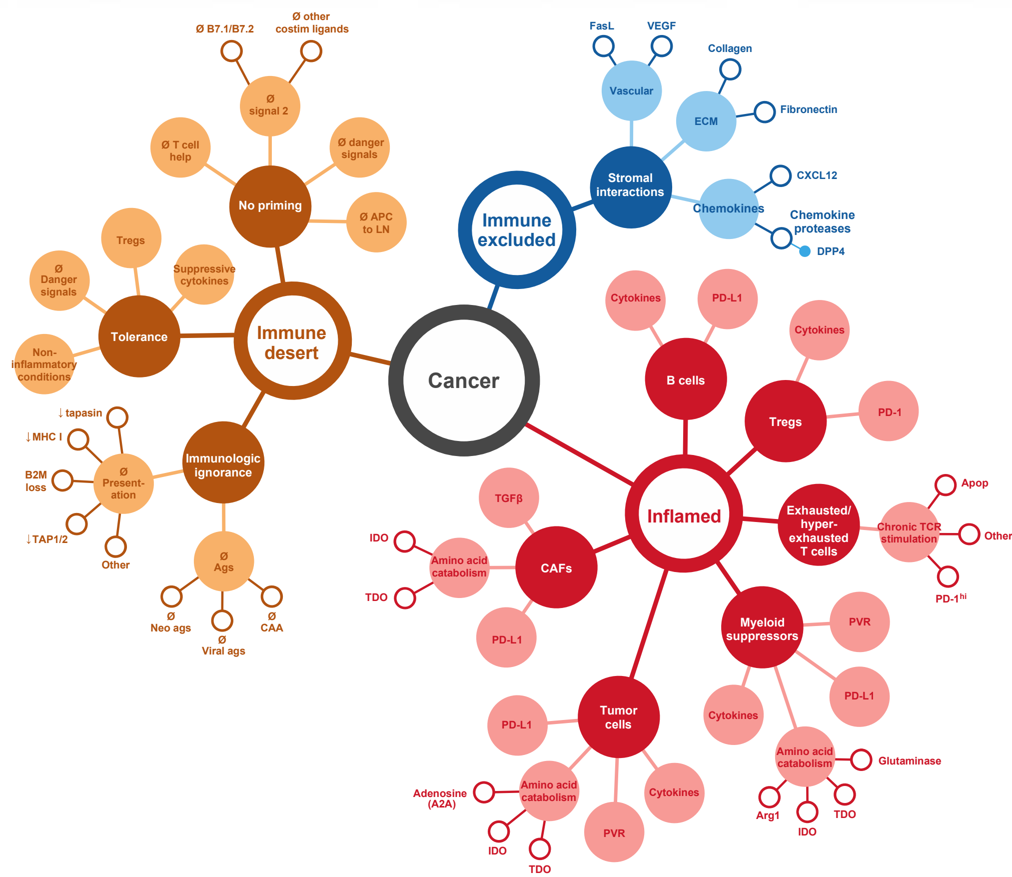


Amanda Nottke

Confidential. Not for distribution.

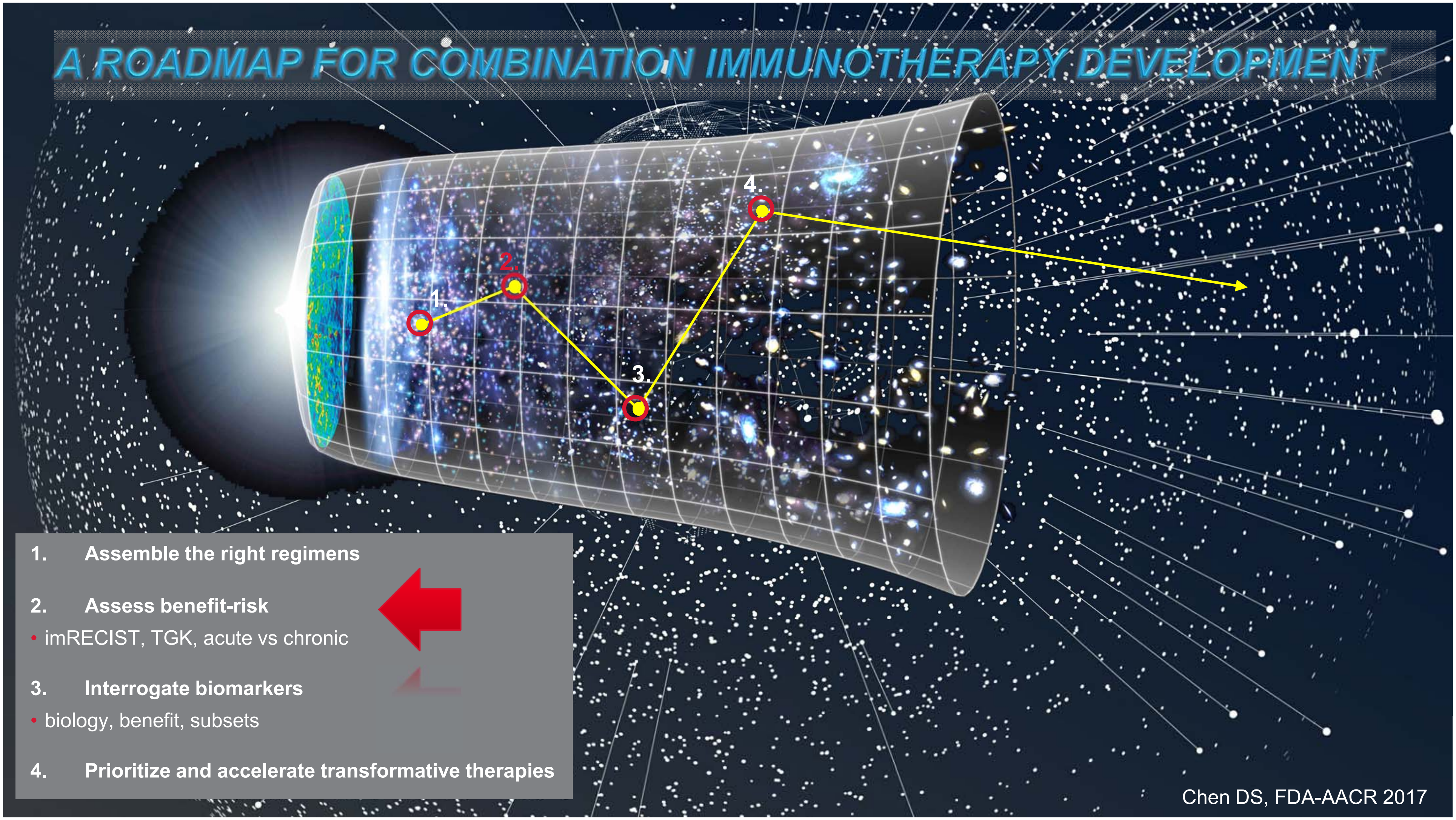
Chen DS, FDA-AACR 2017

1. RATIONAL COMBINATIONS:
ADDRESS THE CANCER IMMUNE PHENOTYPES



Chen and Mellman. *Immunity* 2013

Chen DS, FDA-AACR 2017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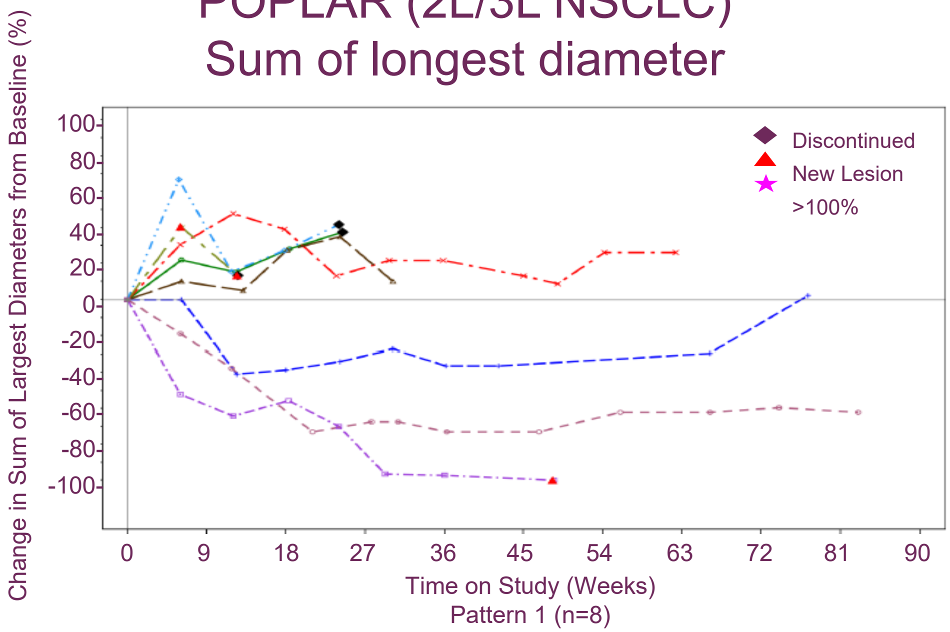
Chen DS, FDA-AACR 2017

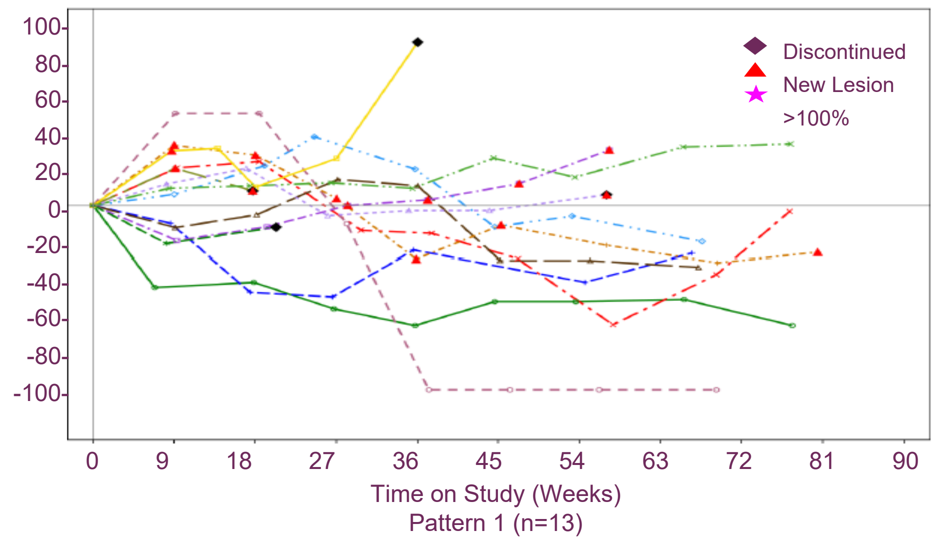
2. ASSESS BENEFIT:
PATTERNS OF RESPONSE WITH IMMUNOTHERAPY

First PD in Target Lesions that later reverts to non-PD

POPLAR (2L/3L NSCLC)
Sum of longest diameter



IMvigor 210 (2L+ mUC)
Sum of longest diameter

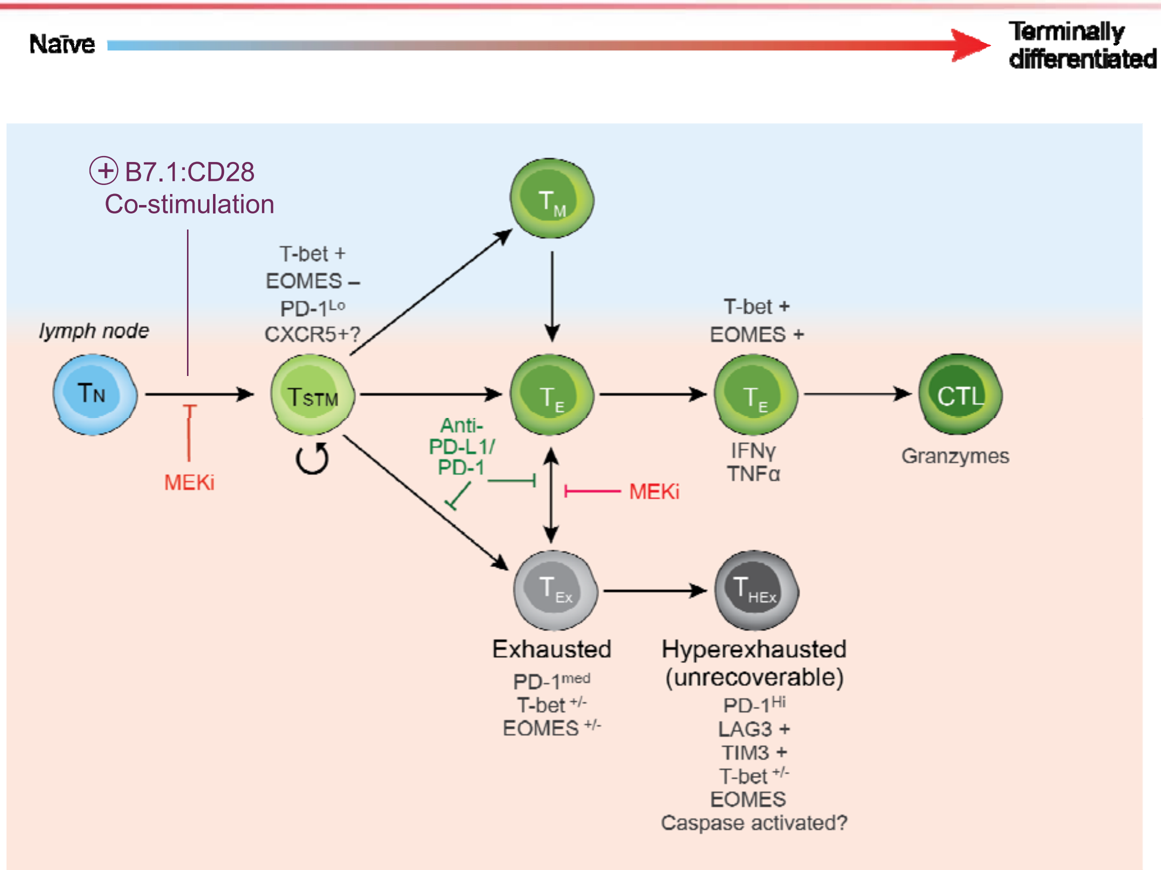


POPLAR: Randomized P2 study of Atezolizumab monotherapy in 2/3L NSCLC
IMvigor210: Atezolizumab P2 study in mUC (bladder cancer)

Ballinger M, Lyons B, Winslow N, Fine G, Chen DS . FDA-AACR IO Drug Development 10 2016

Chen DS, FDA-AACR 2017

2. ASSESS BENEFIT: ACUTE VS CHRONIC?



Chen DS, Mellman I. Nature 2017

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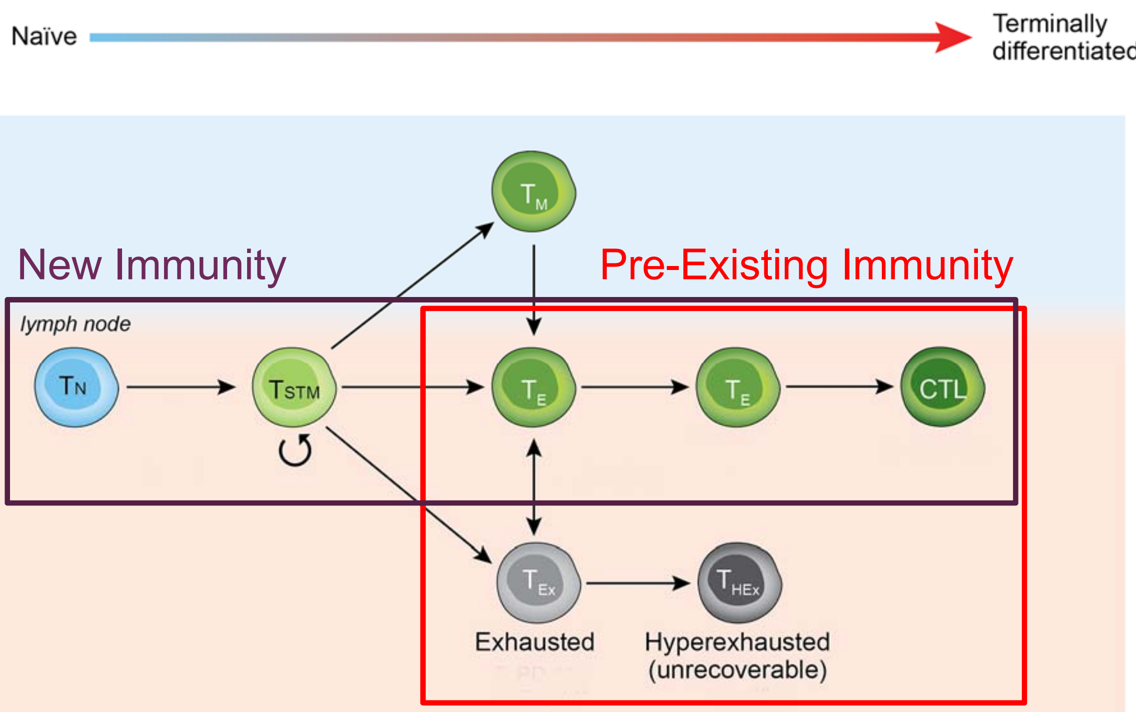
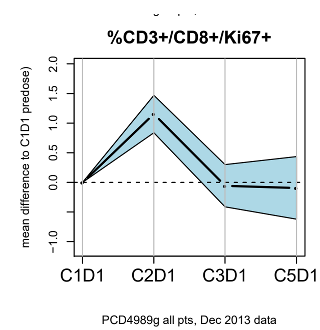


Chen DS, Mellman I. Nature 2017

New Immunity Driven through B7.1?†

Anti-PDL1(atezolizumab)



Herbst et al. Nature 2014

Additional related data published in Das et al. JImmunol 2015

†*as proposed in Chen, Irving, Hodi, CCR 2012*

TARGETING PDL1: NSCLC P3 STUDY (ITT)

Metastatic or locally advanced NSCLC (2L/3L) N = 1225

R 1:1

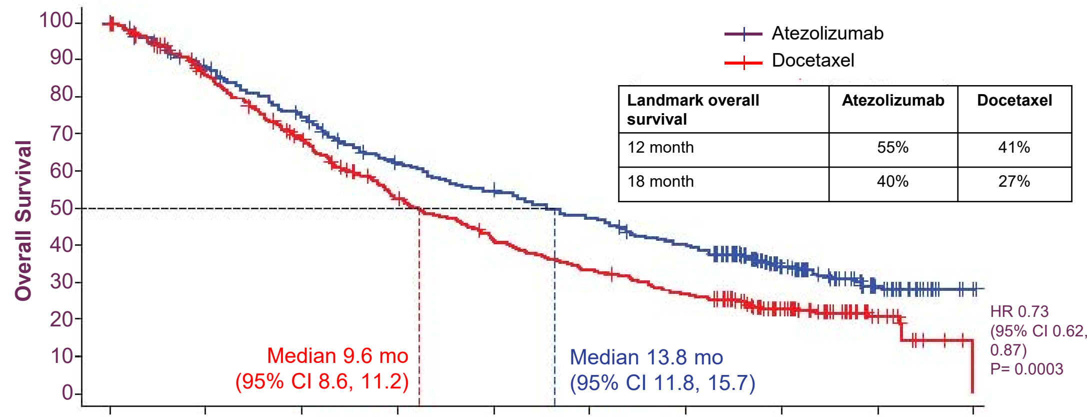
Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m² IV q3w
until disease progression

Primary Endpoints (first 850 enrolled patients):

- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

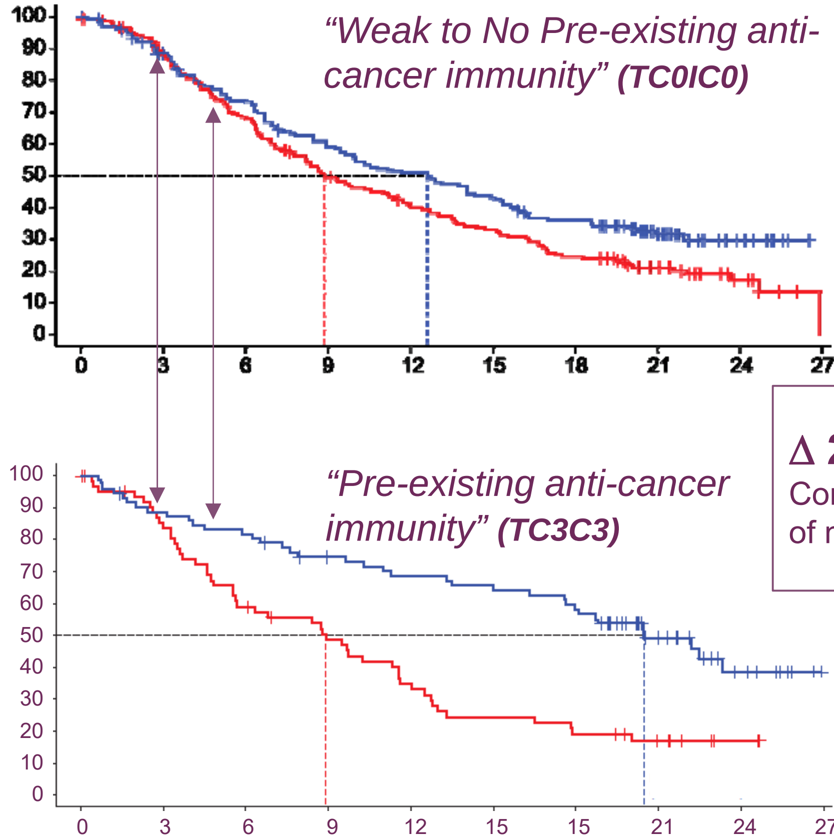


Landmark overall survival	Atezolizumab	Docetaxel
12 month	55%	41%
18 month	40%	27%

No. Patients at Risk
Atezolizumab 425 407 382 333 342 326 305 279 260 248 234 223 218 205 198 188 175 163 157 141 116 74 54 41 28 15 4 1
Docetaxel 425 390 365 336 311 286 263 236 219 195 179 168 151 140 132 123 116 104 98 90 70 51 37 28 16 6 3

Barlesi et al, ESMO 2016; Rittmeyer et al. Lancet 2017

2. ASSESS BENEFIT: IMMEDIATE VS DELAYED?



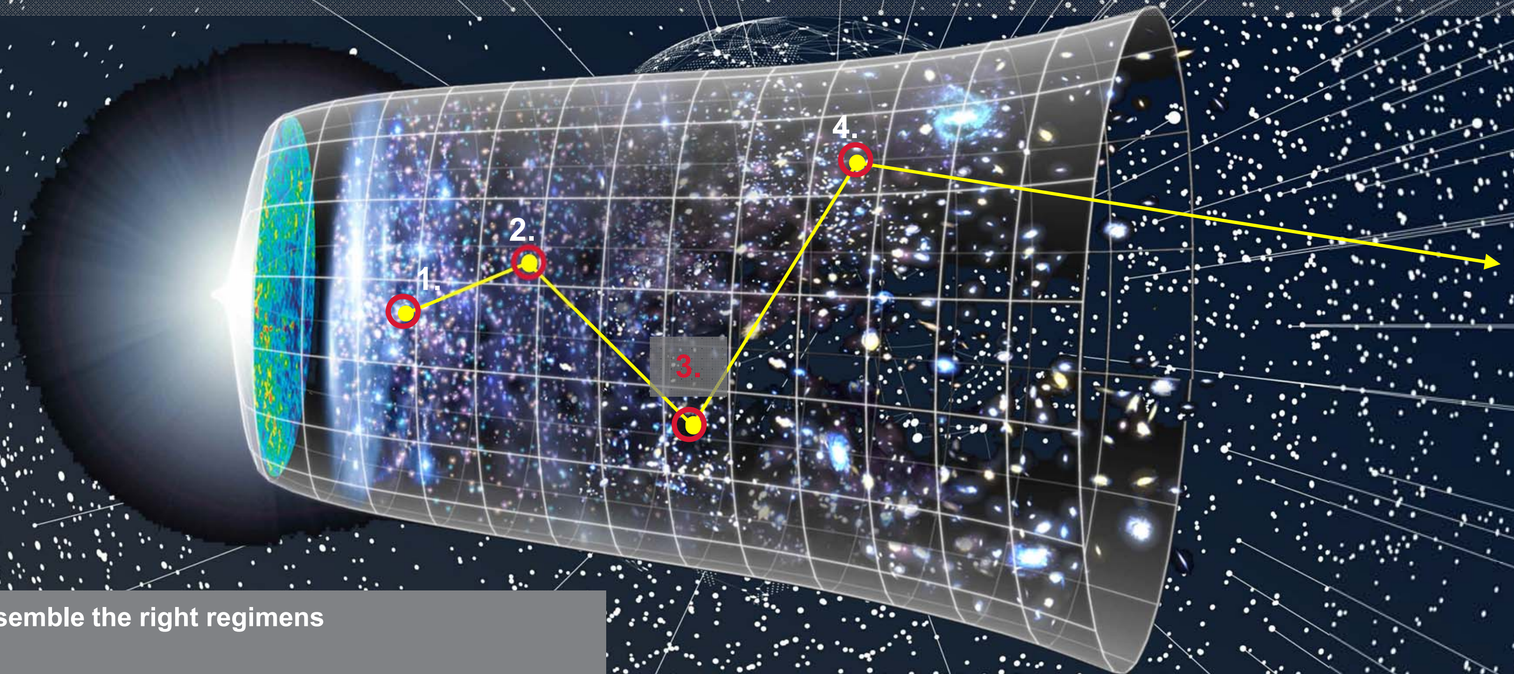
Chen TECENTRIQ 2016 EOY Presentation

Δ 2months:
Consistent with priming of new immunity

Barlesi et al, ESMO 2016; Rittmeyer et al. Lancet 2017

Chen DS, FDA-AACR 2017

A ROADMAP FOR COMBINATION IMMUNOTHERAPY DEVELOPMENT



1. **Assemble the right regimens**

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   - imRECIST, TGK, acute vs chronic

3. **Interrogate biomarkers**
   - biology, benefit, subsets

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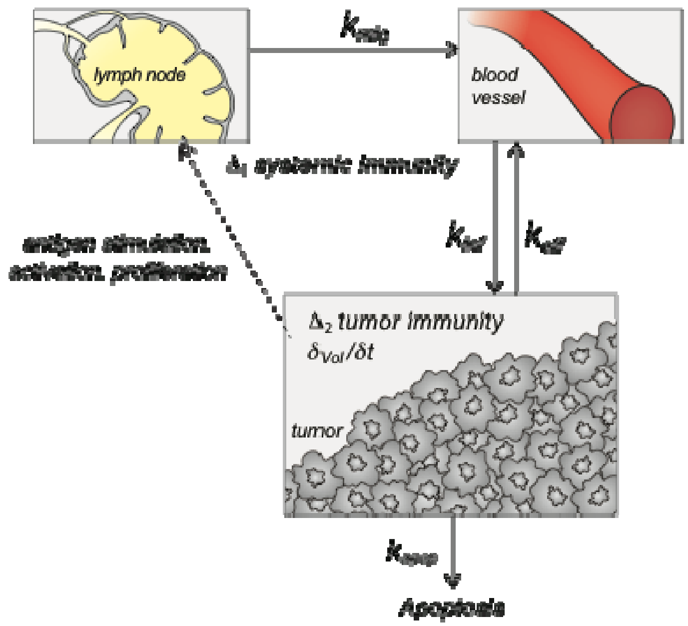
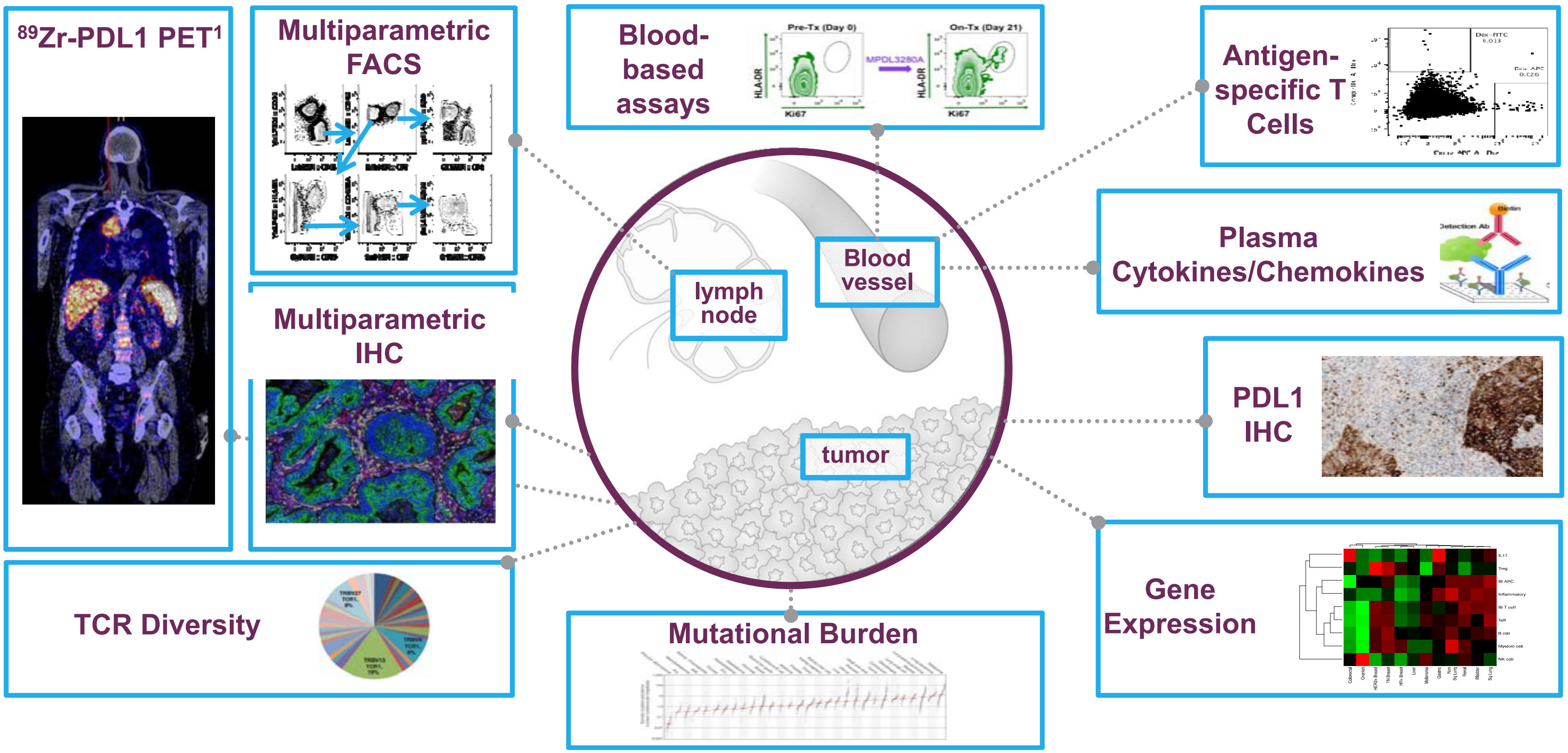
3. IMMUNE BIOMARKER COMPARTMENTS



Chen DS, Mellman I. Nature 2017

3. COMPREHENSIVE CIT BIOMARKER PLATFORM

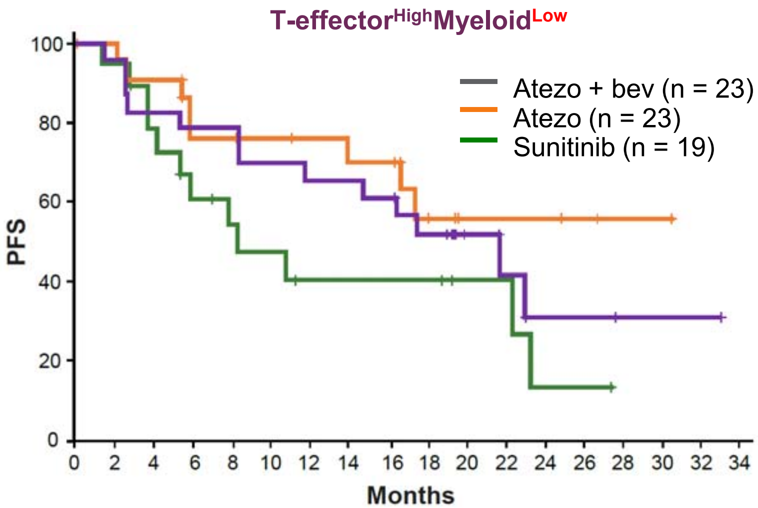


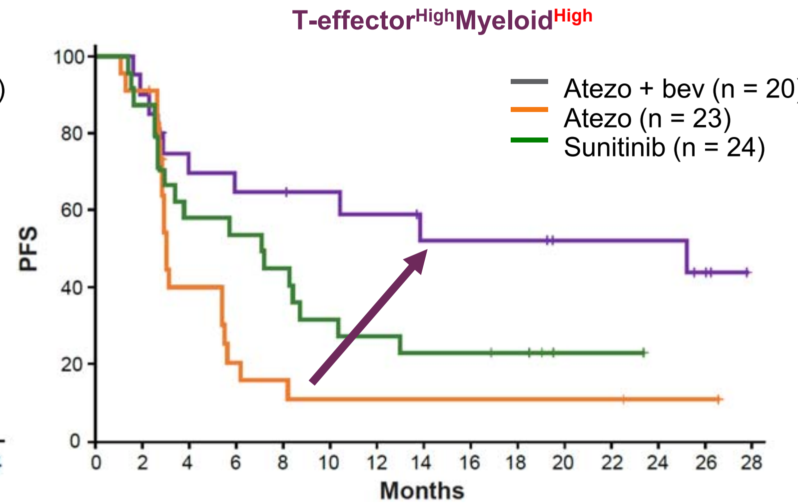
Modified from Chen DS SITC 2015
[1]De Vries, NIH workshop 2016

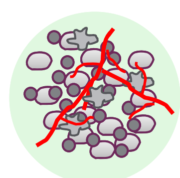
Chen DS, FDA-AACR 2017

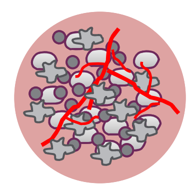
BIOMARKERS MAY IDENTIFY SUBGROUPS DERIVING GREATEST BENEFIT FROM COMBINATIONS: *IMMUNE GENE EXPRESSION*

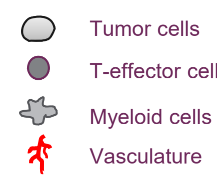
Myeloid Inflammation









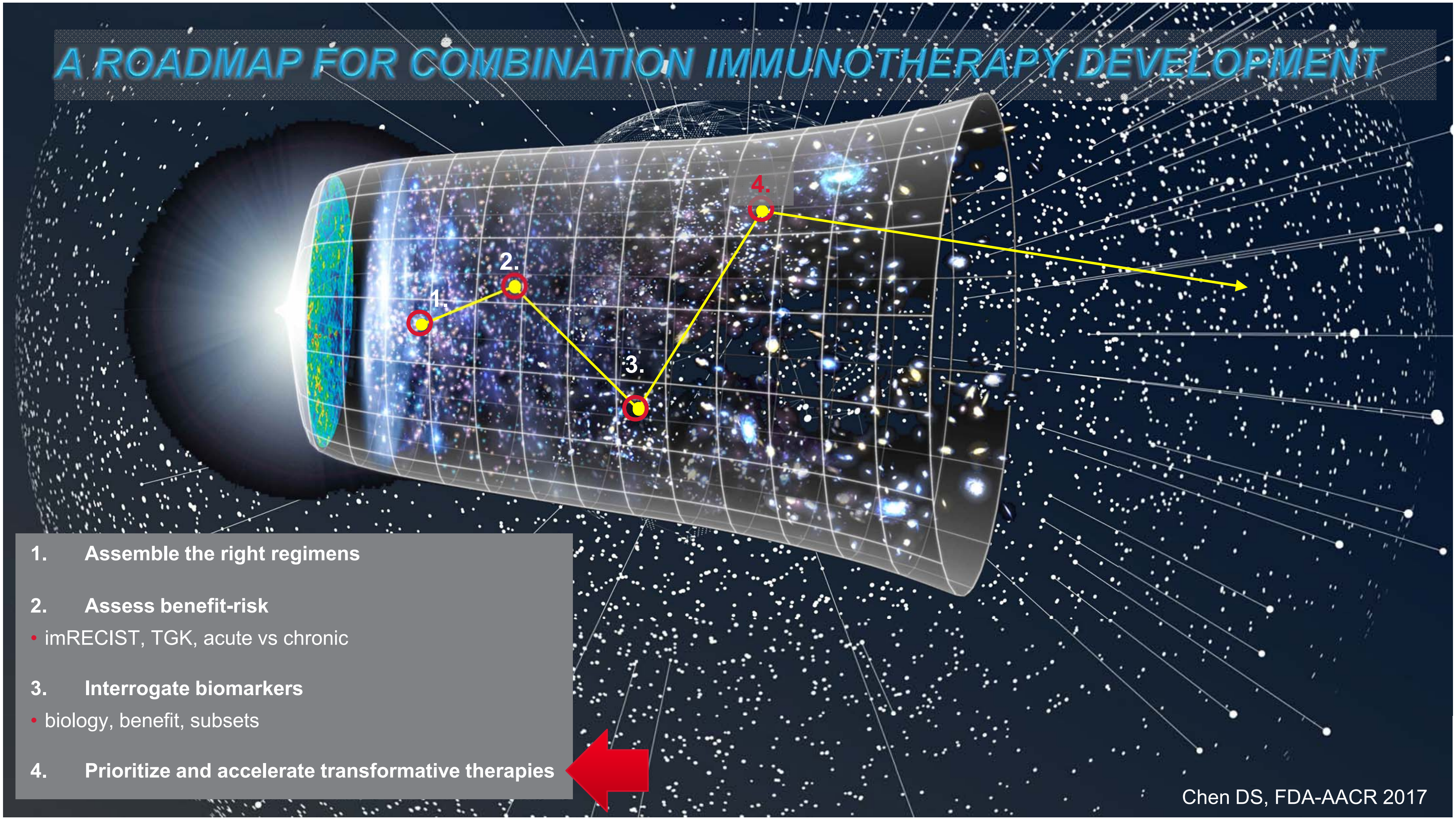


T-effector High

T-effector High
Immune Suppressed

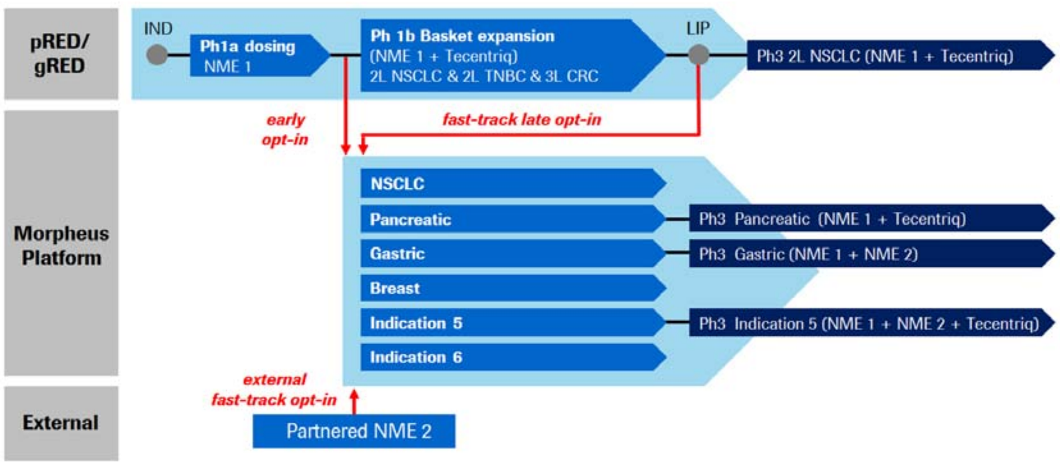
McDermott et. al AACR 2017

Chen DS, FDA-AACR 2017


A ROADMAP FOR COMBINATION IMMUNOTHERAPY DEVELOPMENT
1.
2.
3.
4.
1. Assemble the right regimens
2. Assess benefit-risk
• imRECIST, TGK, acute vs chronic
3. Interrogate biomarkers
• biology, benefit, subsets
4. Prioritize and accelerate transformative therapies
Chen DS, FDA-AACR 2017

4. RAPIDLY PRIORITIZE AND ACCELERATE TRANSFORMATIVE THERAPIES: A NOVEL CIT PLATFORM

FAST & EFFICIENT COMBO DEVELOPMENT



Multi-indication	Multi-basket	Faster and more confident decisions; potential for accelerated	Longitudinal At disease progression patients can reenter other combinations	Adaptable
Indication specific umbrella protocol with SOC control arm	Biomarker defined subgroups for personalized healthcare			Fast-track opt-in for external and internal late-stage NMEs

2017 launch in 4 indications including 11 molecules and 22 first-in-disease combinations

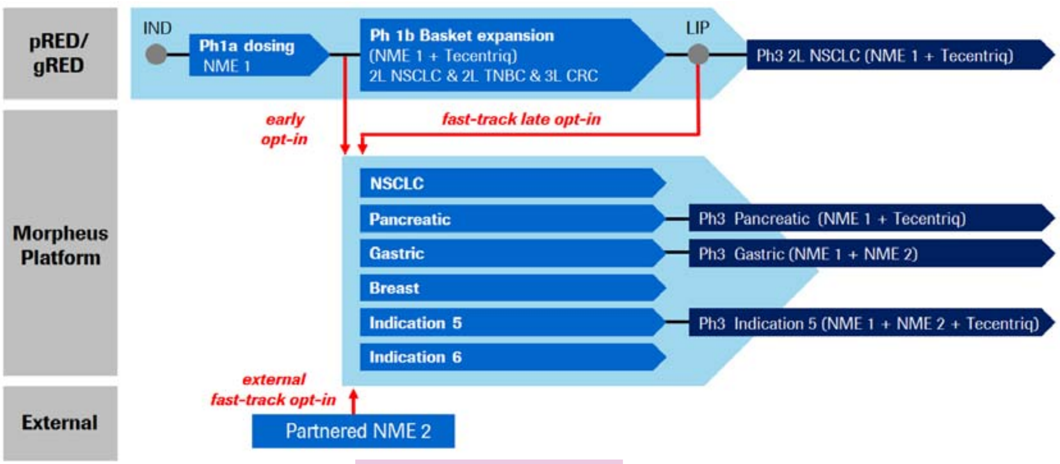
CIT=cancer immunotherapy; IND=new investigational drug application; NME=new molecular entity; LIP=late-stage investment point; SOC=standard of care

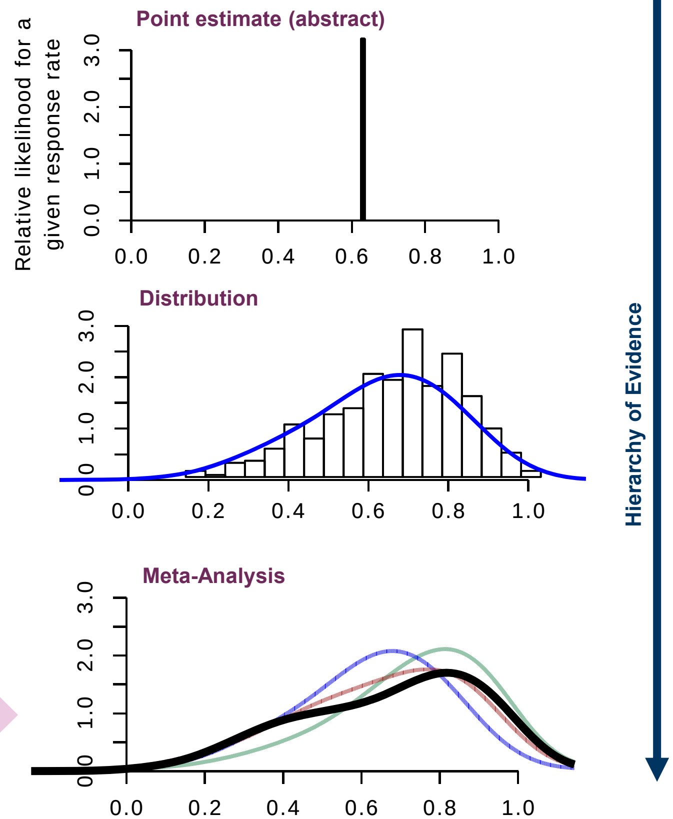
Ed Cha, Bill Grossman, et al.

Chen DS, FDA-AACR 2017

4. RAPIDLY PRIORITIZE AND ACCELERATE TRANSFORMATIVE THERAPIES: *RAPID AND RELIABLE ESTIMATION OF BENEFIT OVER SOC*

FAST & EFFICIENT COMBO DEVELOPMENT



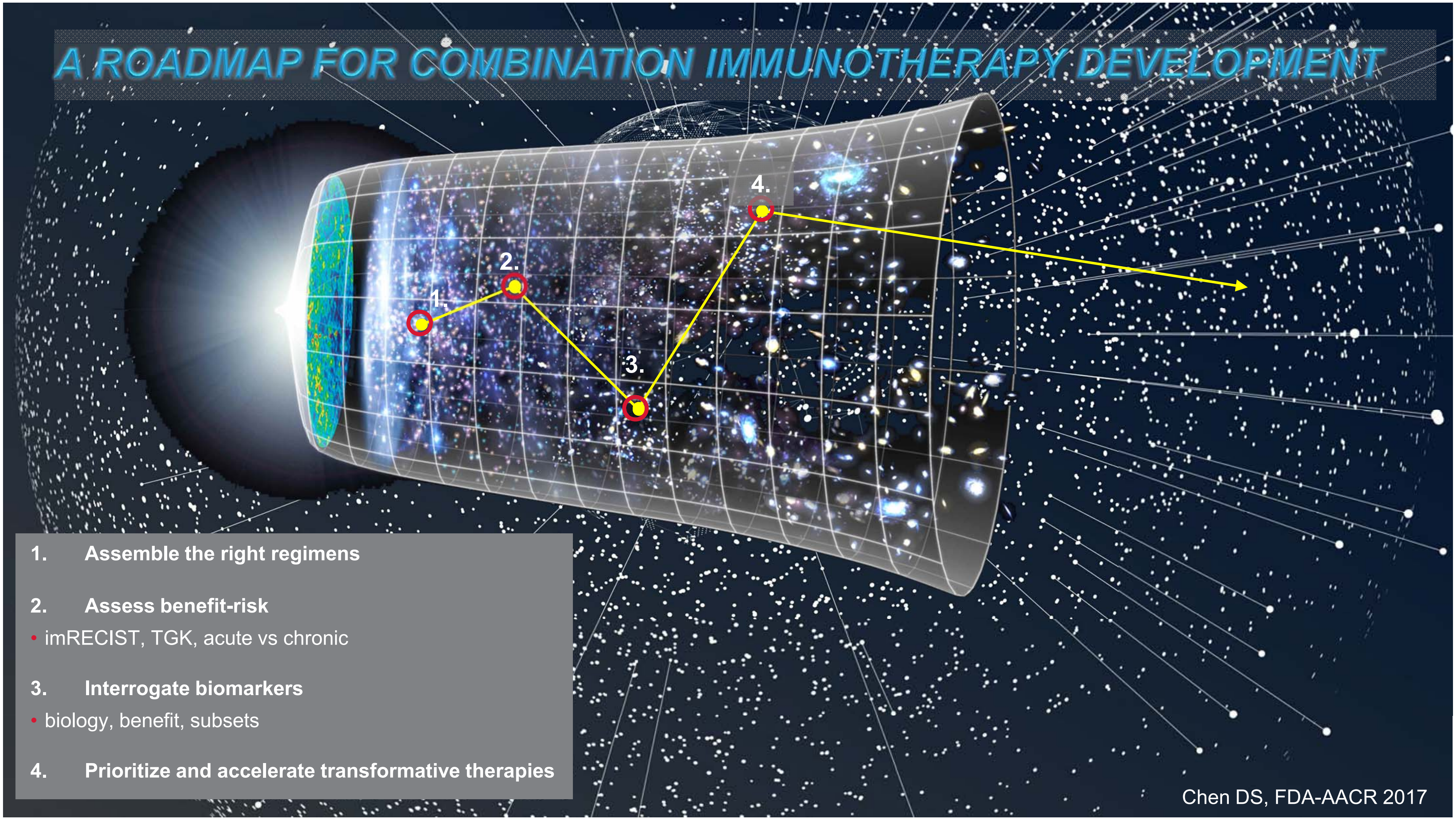


***Real World Data**

- *Create a **synthetic control arm** based on RWD using similar inclusion/exclusion criteria as RCT, with patients treated by the SOC*
- *Outcomes from RWD cohort can complement or replace those from the CT SOC arm*

Contempory randomized Control Arm
+*individual* patient characteristics
+*individual* patient biomarker data
+Real world data* linked to NGS

Chen DS, FDA-AACR 2017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Chen DS, FDA-AACR 2017

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Jean Charles Soria
Omid Hamid
Tom Powles
Naiyer Rizvi
Ignacio Melero
George Coukos
Roy Herbst

Genentech/Roche investigators

Patients and their families

Chen DS, FDA-AACR 2017

Three Important Considerations for Developing Effective Imuno-Oncology Combinations: Immunity, Co-stimulation and Checkpoint Blockade

Bernard A. Fox
Harder Family Chair for Cancer Research
Laboratory of Molecular and Tumor Immunology
Robert W. Franz Cancer Research Center
Earle A. Chiles Research Institute
Providence Portland Medical Center

UbiVac

Molecular Microbiology and Immunology, OHSU

Bernard A. Fox, PhD – COI Disclosures

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Definiens, Research Support, SAB
Immunophotonics, consulting - SAB
Janssen/Johnson & Johnson, Research Support, SAB
MedImmune/AstraZeneca, Research Support, SAB
OncoSec, Research Support
PerkinElmer, Research Support, SAB
PrimeVax, SAB,
Peregrine, Advisory, research support
UbiVac, co-founder, managing Member
Ventana/Roche, Research Support, SAB
Viralytics, Research Support, Advisory

Objectives of the Workshop:

1. To identify best practices regarding patient selection for immune-oncology combinations.
2. **To identify best practices regarding dose selection and optimization for IO combinations –** ***Data to suggest schedule may be important***
3. To discuss the utility of biomarkers as pharmacodynamics endpoints to aid in dose optimization.
4. **To discuss how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of each individual agent –** ***proposed model***
5. To discuss modeling and simulation approaches which take into account nonclinical data and data borrowed from other sources.
6. To discuss novel trial endpoints to define 6. patient benefit.

Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

- Immunity
- Costimulation
- Checkpoint Blockade

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Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

- **Immunity**
- Co-stimulation
- Checkpoint Blockade

1) Do patients have T cells that can recognize their cancer?
2) Do those T cells exhibit cancer destructive properties?
3) Can those T cells Traffick to the Cancer? (Stroma / IM / Tumor)

What do T cells recognize?

- NeoAntigens: important source of “non-tolerized” epitopes
- Viral antigens
- Normal proteins which are over-expressed / selectively expressed

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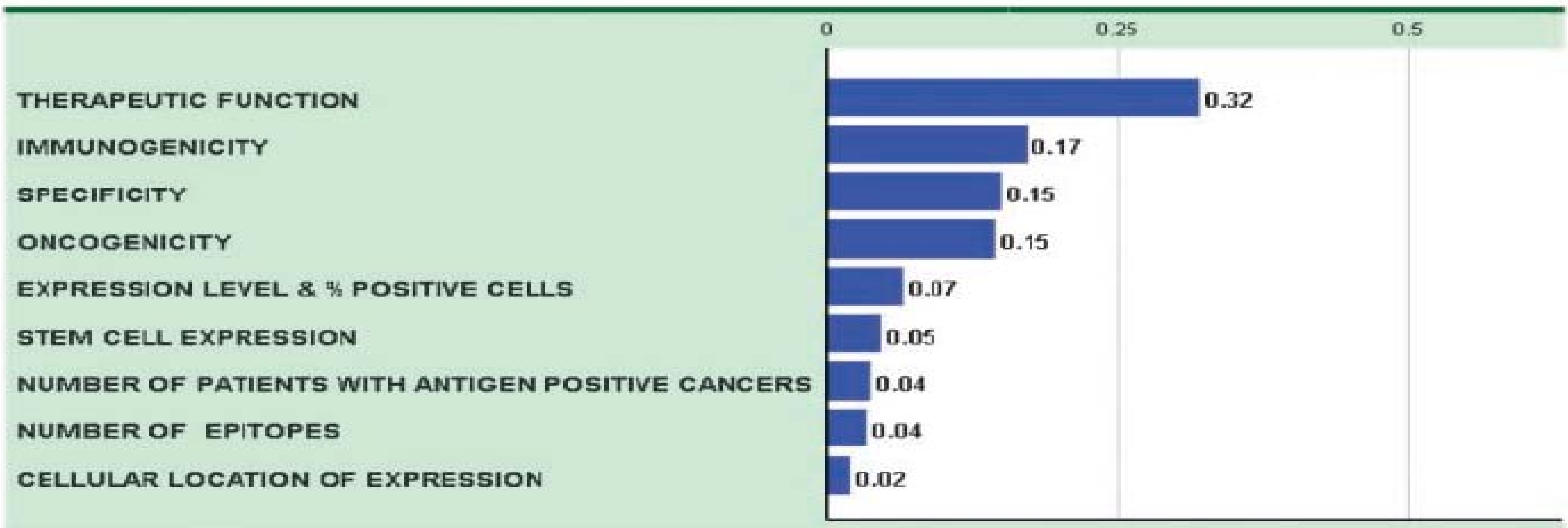
The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

Martin A. Cheever,[1] James P. Allison,[2] Andrea S. Ferris,[3] Olivera J. Finn,[4] Benjamin M. Hastings,[3] Toby T. Hecht,[5] Ira Mellman,[7] Sheila A. Prindiville,[6] Jaye L. Viner,[6] Louis M. Weiner,[8] and Lynn M. Matrisian[6]



Clin Cancer Res 2009;15:5323-5337

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How to Measure what T cells recognize?

Need a functional assay -

- **NeoAntigens and viral antigens:** you have the "mutated" or viral sequence and you can sequence the antigens and test

- **Normal proteins: Where to start?**

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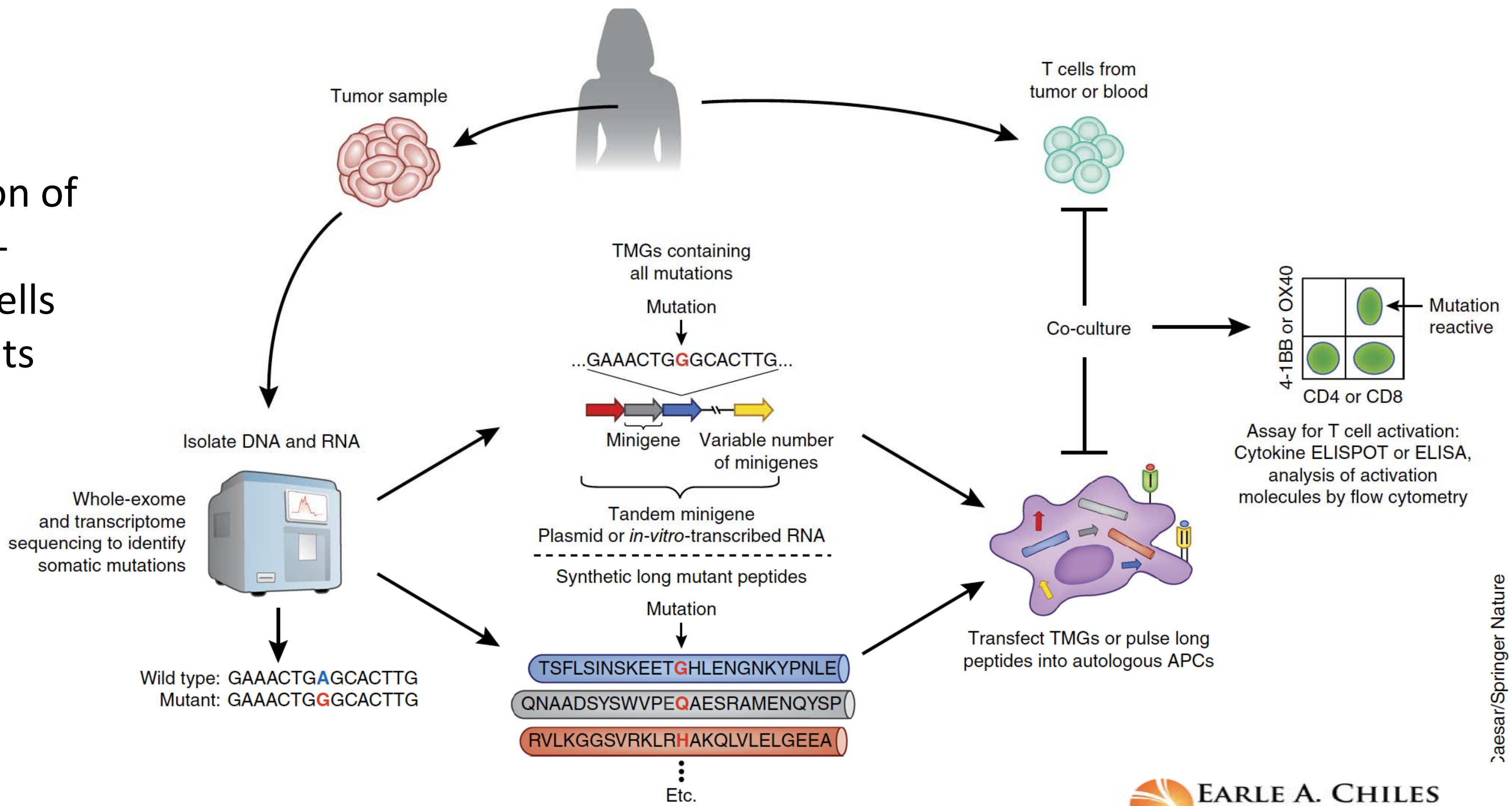
‘Final common pathway’ of human cancer immunotherapy: targeting random somatic mutations

Eric Tran, Paul F Robbins & Steven A Rosenberg

NATURE IMMUNOLOGY VOLUME 18 NUMBER 3 MARCH 2017

Method for Identification of neoantigen-reactive T cells from patients with cancer



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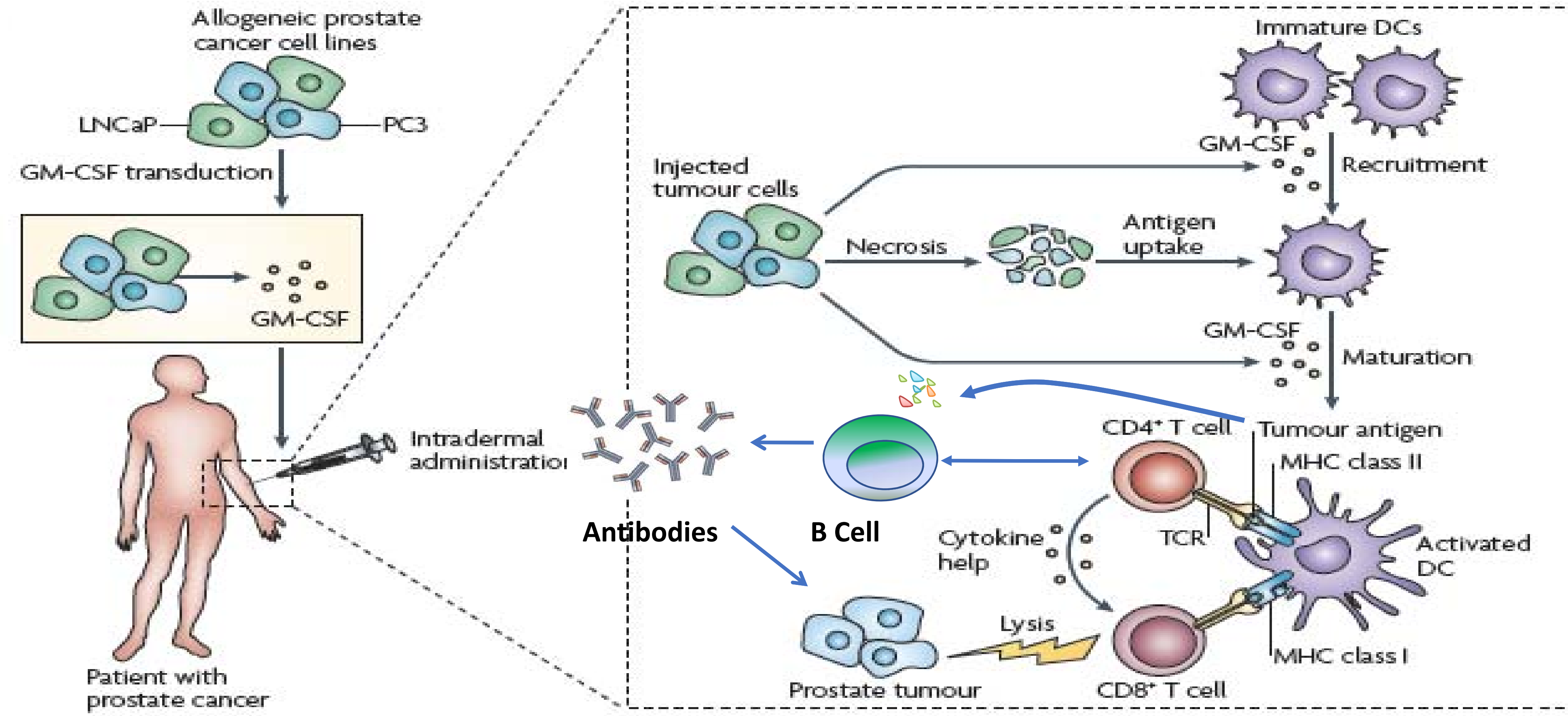
B cells and T cells can have a coordinated response to antigen



Modified from Drake. Nat Rev Immunol. 2010; Goodnow et al, Nature Immunology.

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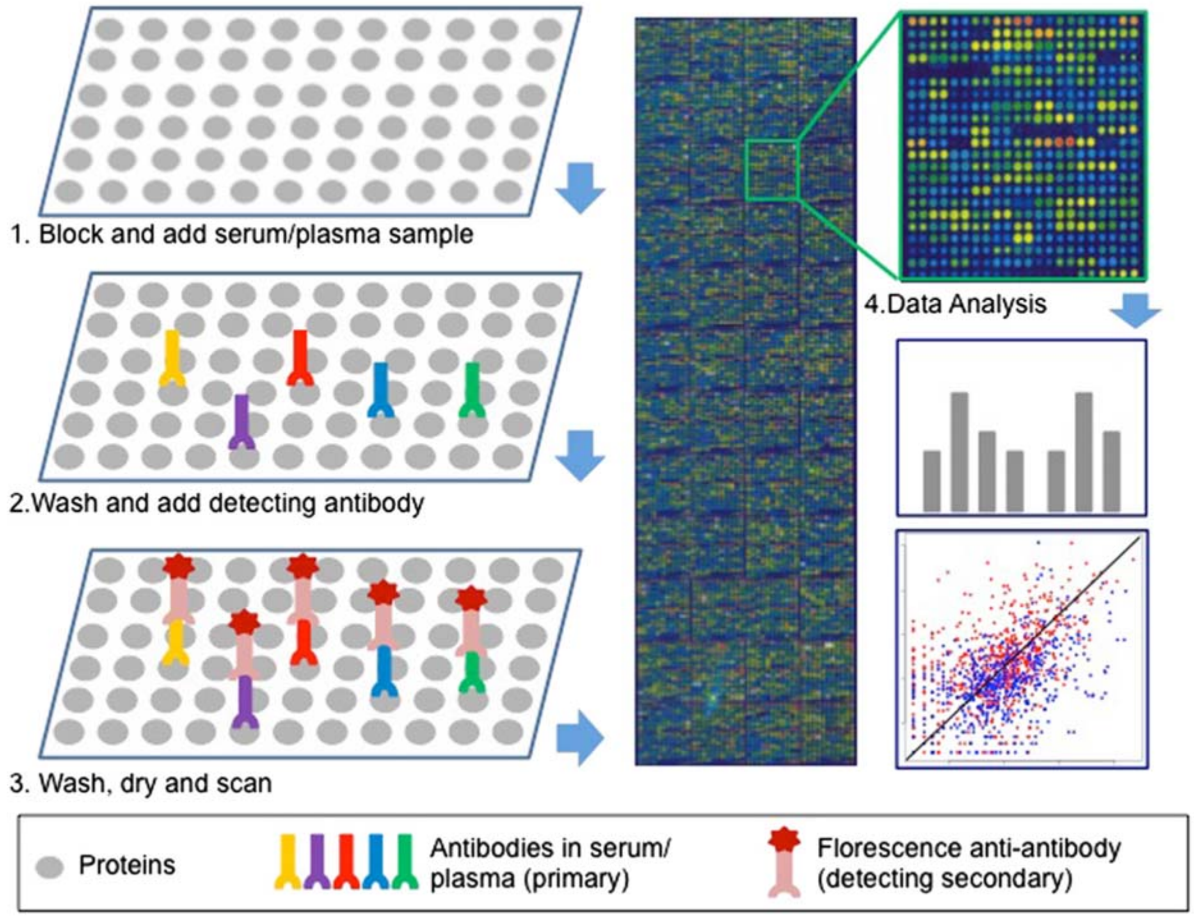
SHORT REPORT Open Access

Immune Monitoring Technology Primer: protein microarray ('seromics')

Jianda Yuan[1*], Ena Wang[2] and Bernard A. Fox[3]

Method for Identifying the development or augmentation of Ab responses against human Proteins

- Invivogen ProtoArray
  9,000 proteins
- CDI HuProt
  19,000 proteins

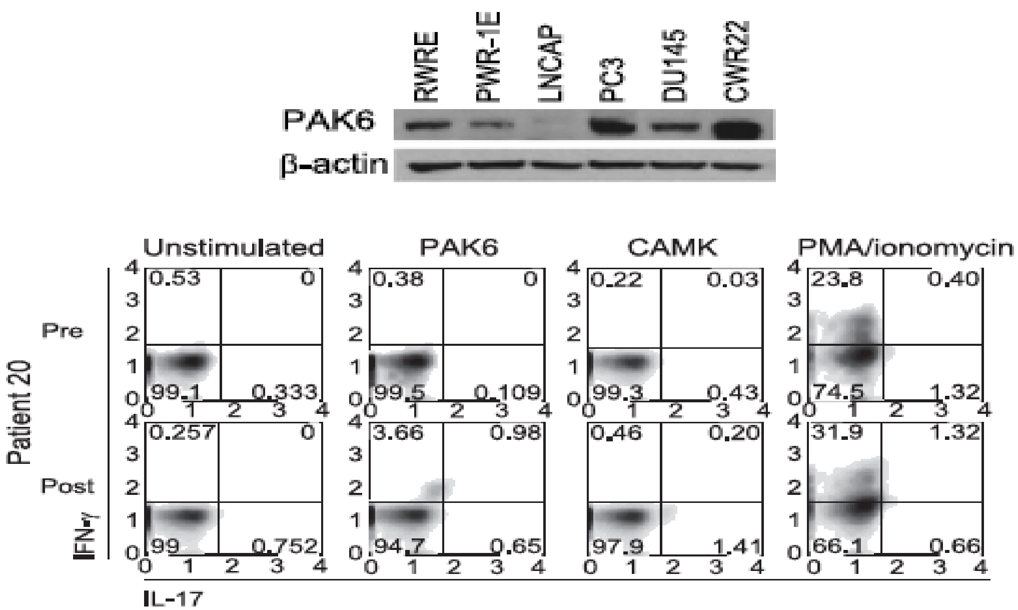


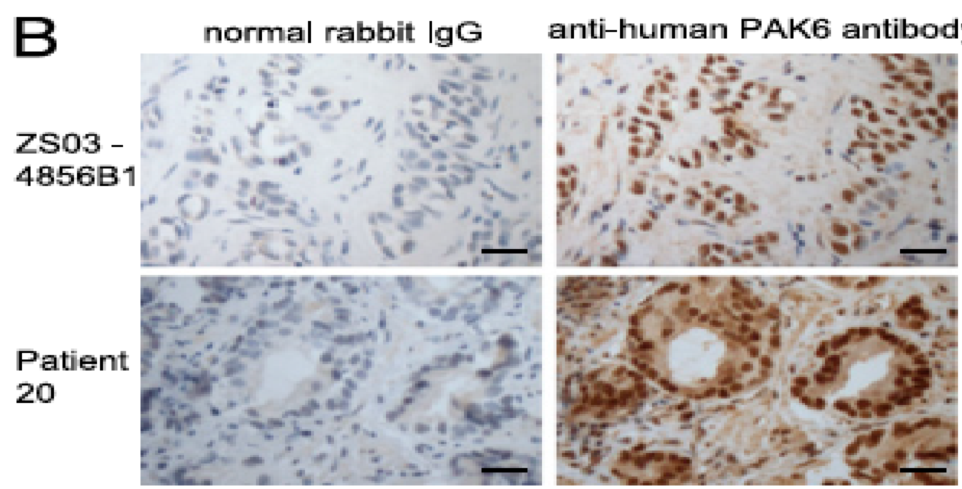
Yuan *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:2

Diversity of Antigen-Specific Responses Induced In Vivo with CTLA-4 Blockade in Prostate Cancer Patients

Serena S. Kwek,* Vinh Dao,* Ritu Roy,† Yafei Hou,* David Alajajian,* Jeffrey P. Simko,‡ Eric J. Small,* and Lawrence Fong*

Published September 5, 2012, doi:10.4049/jimmunol.1201529





Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome

Satyendra C. Tripathi[a], Haley L. Peters[b], Ayumu Taguchi[c], Hiroyuki Katayama[a], Hong Wang[a], Amin Momin[a], Mohit Kumar Jolly[d], Muge Celiktas[a], Jaime Rodriguez-Canales[c], Hui Liu[c], Carmen Behrens[c], Ignacio I. Wistuba[c], Eshel Ben-Jacob[d,1], Herbert Levine[d,2], Jeffrey J. Molldrem[b], Samir M. Hanash[a], and Edwin J. Ostrin[e,2]

	Protein Name	**Uniprot Accession**	**Functional category**	**Peptide**
DFCI032 and HCC2935	Chromosome 19 Open Reading Frame 10	**Q969H8**	cellular protein metabolic process	VIVAKASRTEL
	Catechol O-methyltransferase	**P21964**	Catecholamine metabolism Neurotransmitter degradation	IYKGPGSEAGP
	Cellular retinoic acid-binding protein 2	**P29373**	Transport Signal transduction	LKVLGVNVM
	Proto-oncogene c-Crk	**P46108**	Proto-oncogene Regulation of Rho GTPase activity	YKIHYLDTTTL
	Elongation factor 1-alpha 1	**P68104**	regulation of transcription, DNA-dependent	MLEPSANMPWF IVAAGVGEF PSANMPWFKG
	Glycogen synthase kinase-3 alpha	**P49840**	Signal Transduction	LVDPDTAVLKL
	Hypoxanthine-guanine phosphoribosyltransferase	**P00492**	Purine salvage	FCIPNHYAEDL VFIPHGLIM
	Malate dehydrogenase, mitochondrial	**P40926**	Tricarboxylic acid cycle	FVKSQETECTY
	Peptidyl-prolyl cis-trans isomerase A	**P62937**	RNA-dependent DNA replication	GEPLGRVSFEL FADKVPKTAEN
	60S ribosomal protein L38	**P63173**	regulation of translation	PRKIEEIKDF
	Protein S100-A10	**P60903**	positive regulation of binding cellular response to acid	PSQMEHAMET PLAVDKIMK IAGLTIACNDY
	Transaldolase	**P37837**	pentose-phosphate shunt	LTISPKLLGEL ISPFVGRILD
	Triosephosphate isomerase	**P60174**	Glycolysis gluconeogenesis pentose-phosphate shunt	VDIINAKQ VGGASLKPEF LVGGASLKPEF

Eluted peptides off panel NSCLC lines

Ran protoArrays on sera from recently diagnosed patients with NSCLC

Proteins eliciting autoantibody Reactivity were for peptides presented by HLA class I molecules (NSCLC lines)

Tripathi et al, PNAS 2016

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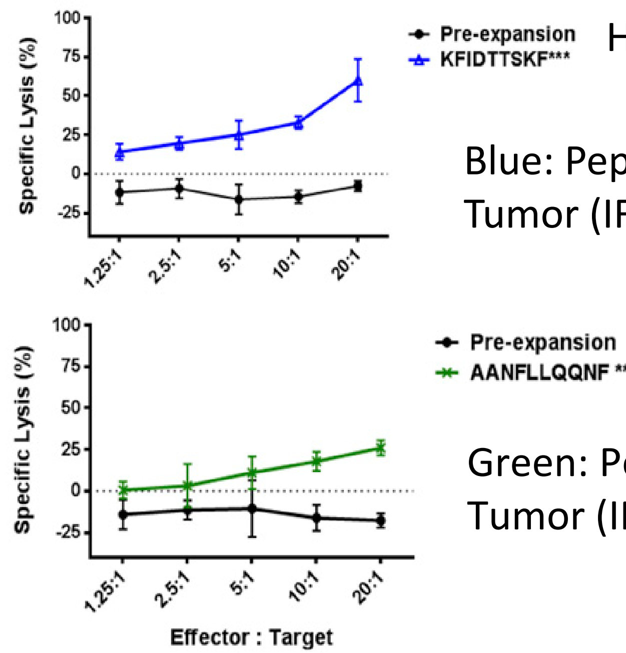

H1299 NSCLC line

Blue: Peptide eluted off Tumor (IFN-γ+)

Green: Peptide eluted off Tumor (IFN-γ-)

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PROVOCATIVE:

- Patients have broad pre-existing anticancer immunity against non-mutated epitopes.
- Once stimulated, with Ag, can exhibit Cytotoxicity

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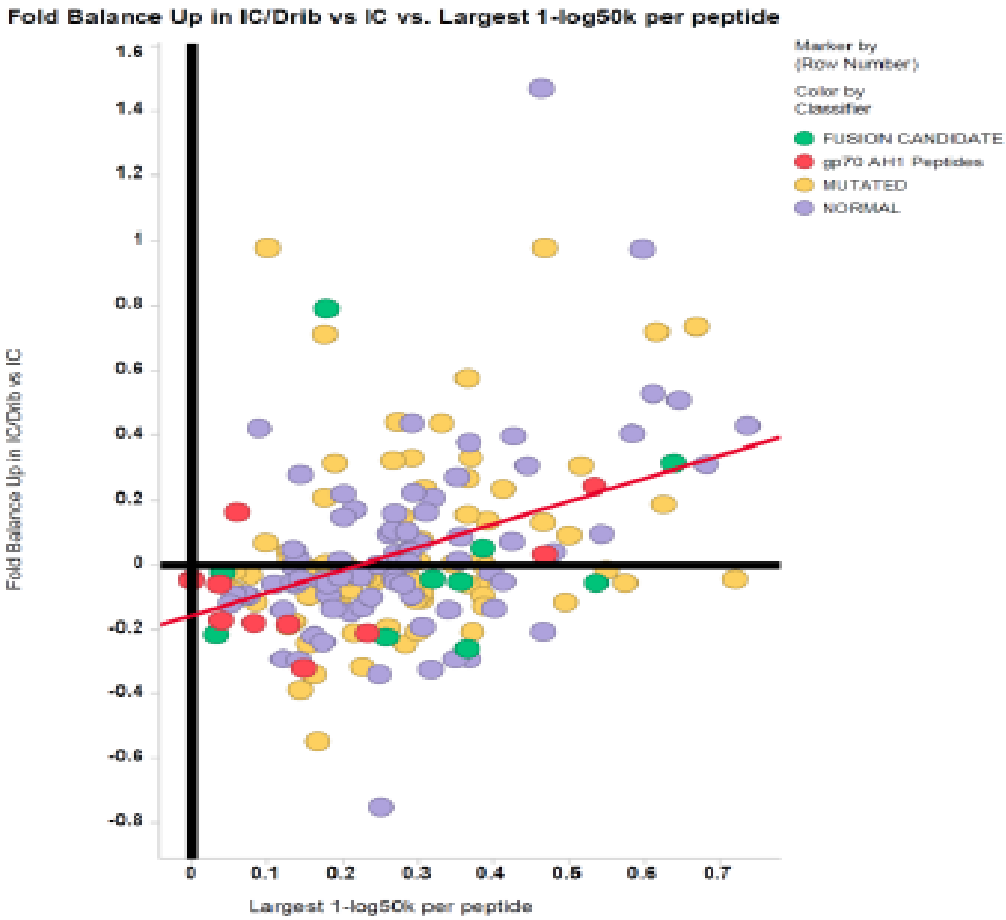

Increasing Maximum MHCI Affinity

DRibble Cancer Vaccine Induces Antibody Responses To Peptides Containing High Affinity Domains for MHC I

Hulett T et al. submitted

Tyler Hulett

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Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

- **Immunity**
- Costimulation
- Checkpoint Blockade

1) Do patients have T cells that can recognize their cancer?
2) Do those T cells exhibit cancer destructive properties?
3) Can those T cells Traffick to the Cancer?

Use TCR analysis to follow Peptide-specific T cells?

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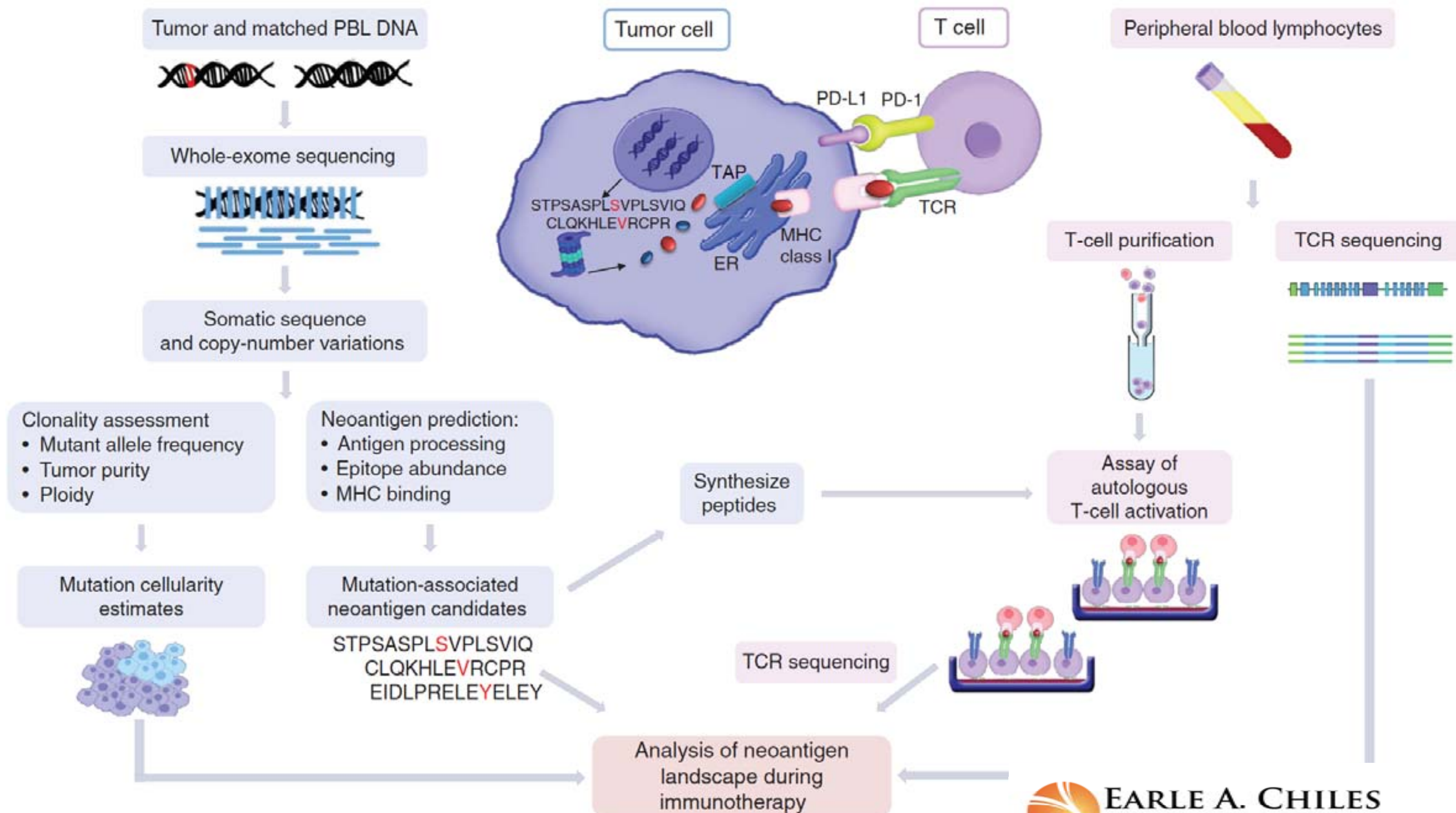
Evolution of Neoantigen Landscape during Immune Checkpoint Blockade in Non-Small Cell Lung Cancer

Valsamo Anagnostou[1,2], Kellie N. Smith[1,2], Patrick M. Forde[1,2], Noushin Niknafs[3], Rohit Bhattacharya[3], James White[1], Theresa Zhang[4], Vilmos Adleff[1], Jillian Phallen[1], Neha Wali[1], Carolyn Hruban[1], Violeta B. Guthrie[3], Kristen Rodgers[5], Jarushka Naidoo[1,2], Hyunseok Kang[1], William Sharfman[1], Christos Georgiades[6], Franco Verde[7], Peter Illei[1,8], Qing Kay Li[8], Edward Gabrielson[1,8], Malcolm V. Brock[1,5], Cynthia A. Zahnow[1], Stephen B. Baylin[1], Robert B. Scharpf[1], Julie R. Brahmer[1,2], Rachel Karchin[3], Drew M. Pardoll[1,2], and Victor E. Velculescu[1,2,3,8]

Anagnostou V Can. Discovery, March 2017

- Use single peptide stimulation to assess the TCR(s) for a single epitope
- Evaluate PBL and Tumor to detect trafficking



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- Checkpoint Blockade

Anti- OX-40 - Activity in “immunogenic” mouse models

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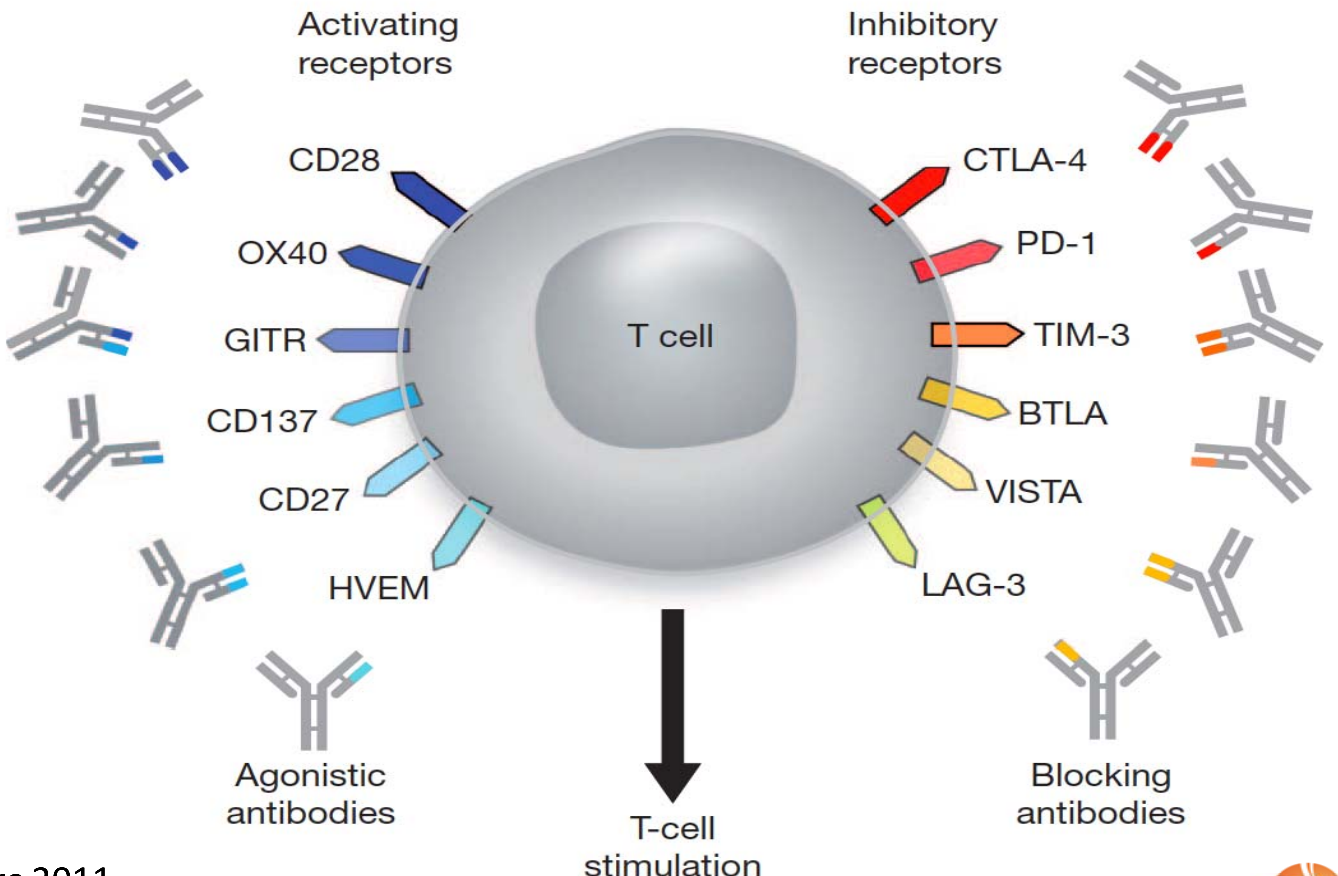
Activating Receptors / Costimulatory Molecules



Mellman et al. *Nature* 2011

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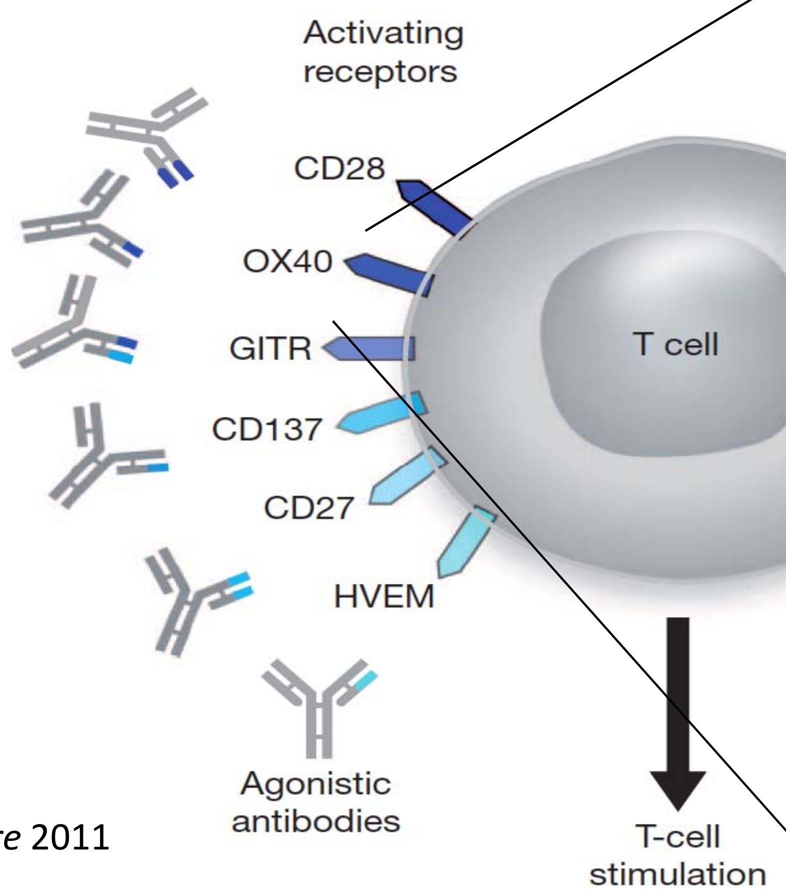
OX40 Costimulatory Receptor



Mellman et al. *Nature* 2011

- Upregulated within 24 hours of TCR stimulation
- Constitutively expressed on T_{reg} cells, but can be expressed on activated $CD8^+$ and $CD4^+$ conventional cells
- Leads to proliferation, activation and survival signaling
- Stimulated by OX40-ligand on APCs (or agonist Abs like OX86)
- Numerous phase I clinical trials

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Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

- Immunity
- **Costimulation**
- Checkpoint Blockade

Anti- OX-40 - Activity in "immunogenic" mouse models
- Augments T & B cell responses
- Reduces "contraction"

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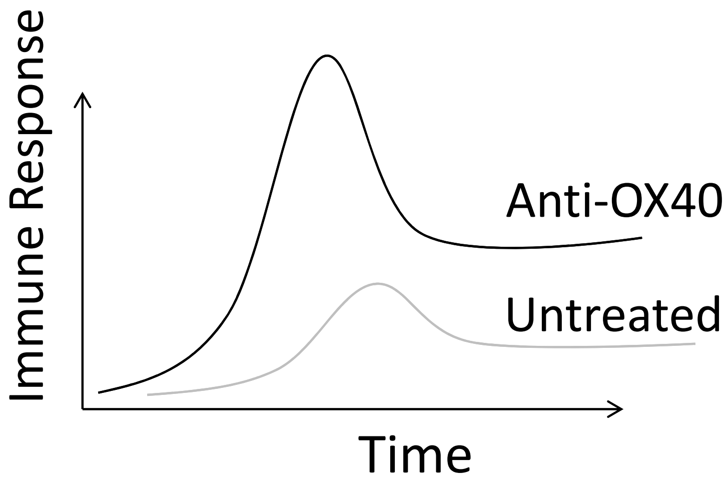
Danger and OX40 Receptor Signaling Synergize to Enhance Memory T Cell Survival by Inhibiting Peripheral Deletion[1]

Joseph R. Maxwell,[2*] Andrew Weinberg,[2†] Rodney A. Prell,[†] and Anthony T. Vella[3*]

Maxwell et al, J. Immunol 2000



OX40 ligation increases IL-2 production and IL-2R expression - enhance CD4 and CD8 T cell effector differentiation and the generation of long-lived memory cells

Redmond et al. Crit Rev Immunol. 2009

INSIGHT: Combine vaccination with anti-OX40 to increase therapeutic efficacy

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Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

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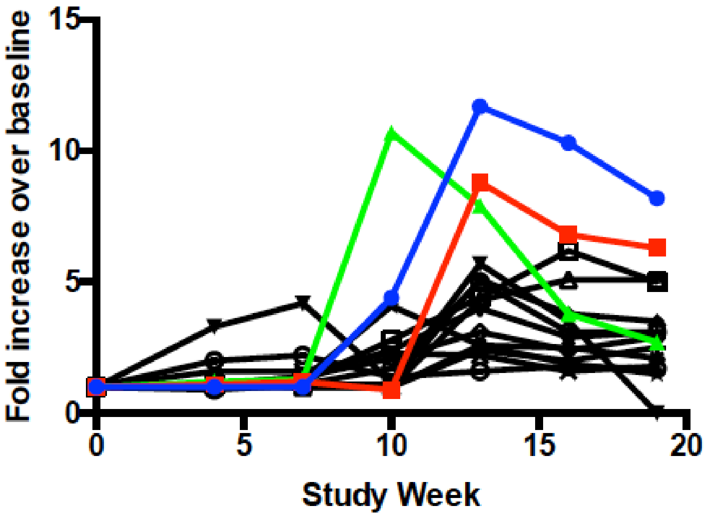
Goal: To discuss how the expectation of the demonstration of the contribution of each agent has to a combination and strategies to isolate the effect of each individual agent.

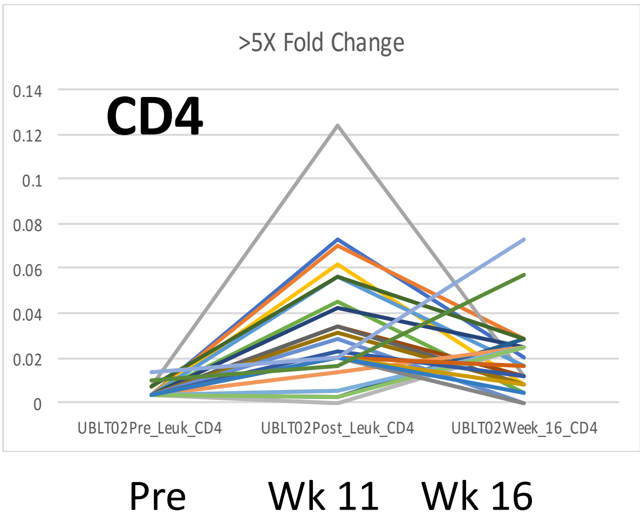
Detection of "Contraction" of B and T cell responses following vaccination –

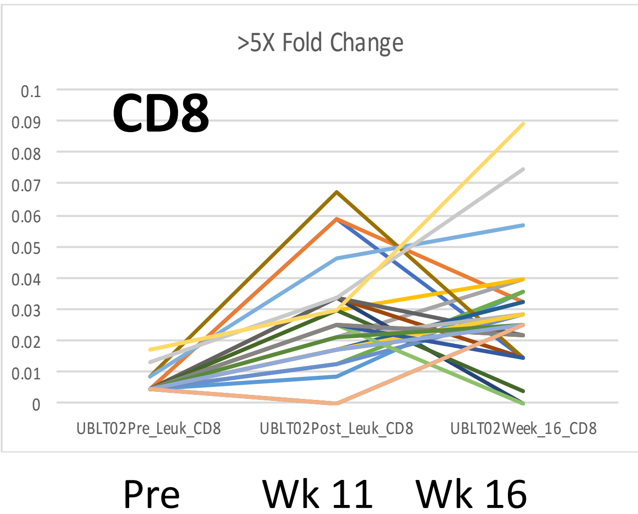
Combination Vaccine Immunotherapy (DRibbles) for Patients With Definitively-Treated Stage III Non-small Cell Lung Cancer – PI: R. Sanborn NCT01909752 2R44CA121612-02A1

Antibody Response



T cell Response





Sanborn R 2016 WLC/IASLC; Paustian C SITC 2016, Fox B 2017 ASCO

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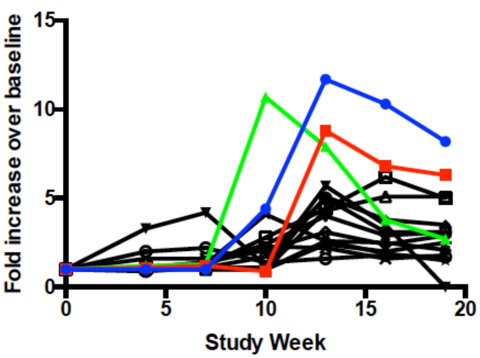
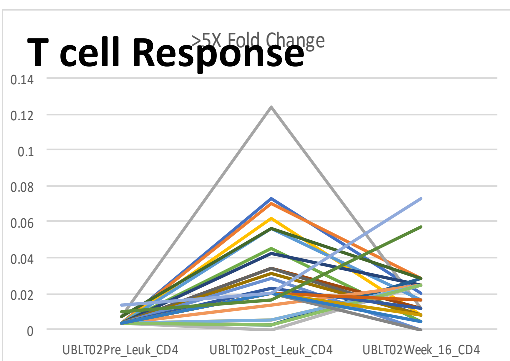
Detection of "Contraction" of B and T cell responses following vaccination: Will anti-OX40 sustain response?

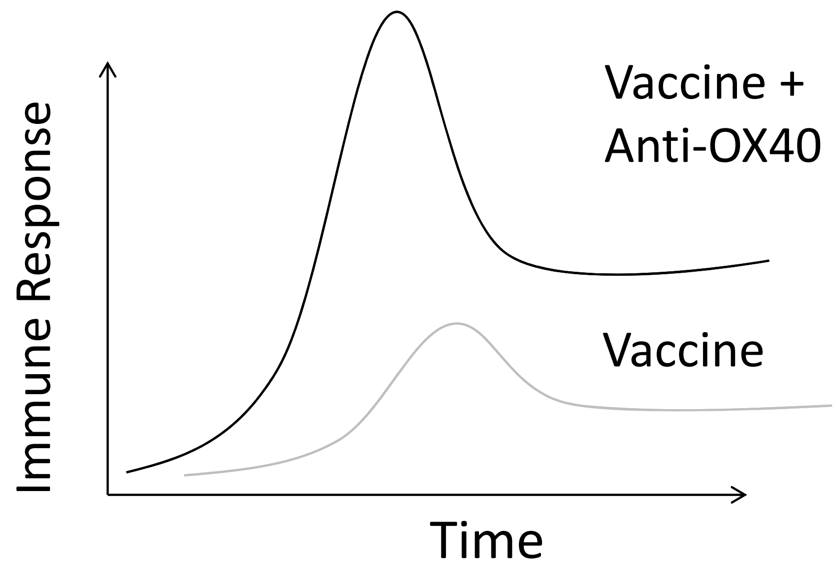
Antibody Response





Pre Wk 11 Wk 16

Evaluate effect of anti-OX40 on pattern of B and T cell responses



Sanborn R. et al, in preparation; Paustian C, et al. in preparation

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Combinational Immunotherapy with Allo-DRibble Vaccines and Anti-OX40 Co-Stimulation Leads to Generation of Cross-Reactive Effector T Cells and Tumor Regression

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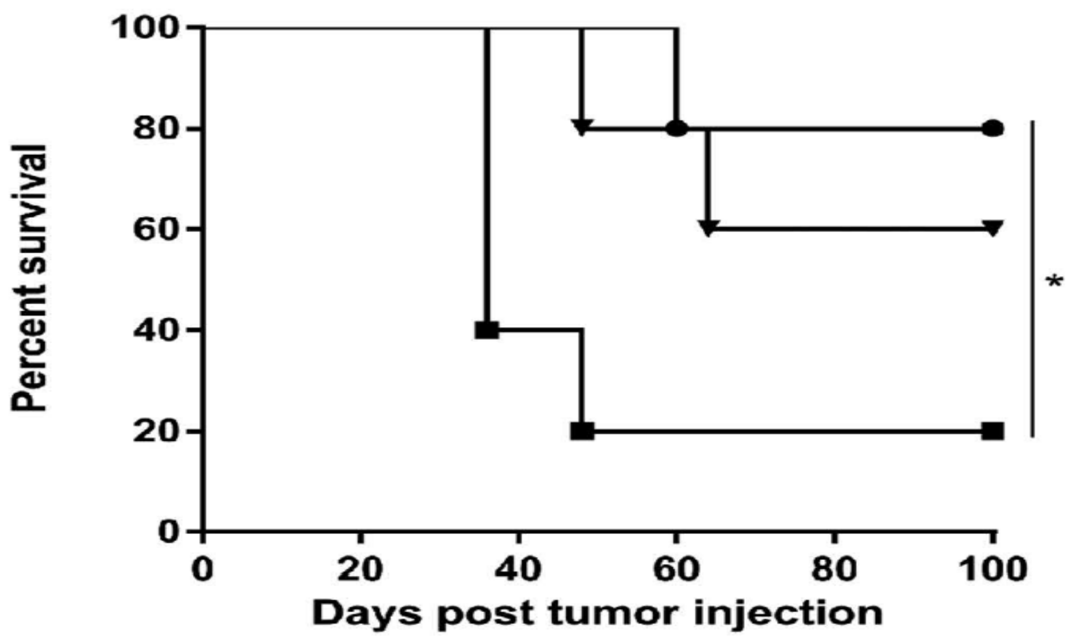
Guangjie Yu[1,2,*], Yuhuan Li[2,*], Zhihua Cui[2], Nicholas P. Morris[2], Andrew D. Weinberg[2], Bernard A. Fox[2], Walter J. Urba[2], Lixin Wang[1] & Hong-Ming Hu[2]

www.nature.com/scientificreports tificreports
SCIENTIFIC REPORTS

SCIENTIFIC REPORTS | 6:37558 | DOI: 10.1038/srep37558

Combining DRibble Vaccine plus anti-OX40 Significantly Increases Therapeutic Effect



Yu G et as, Sci Rep Nov. 2016

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Three Important Considerations for Developing Effective Imuno-Oncology Combinations:

- Immunity
- Costimulation
- **Checkpoint Blockade**

1) Focus on combinations

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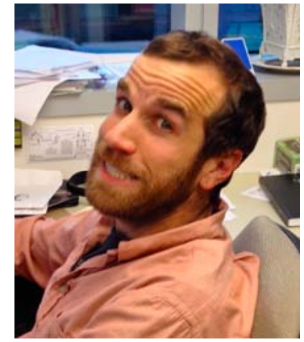
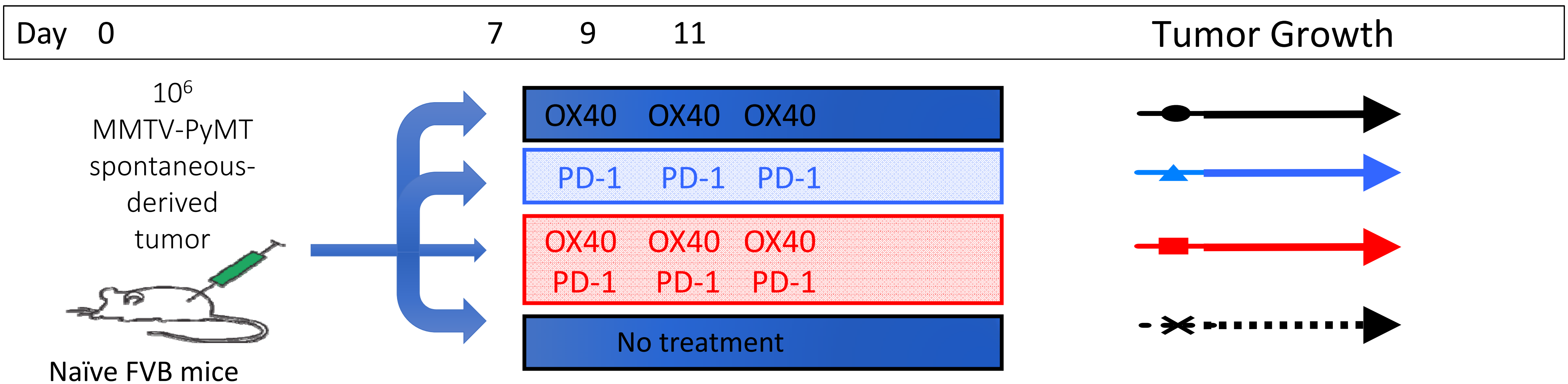
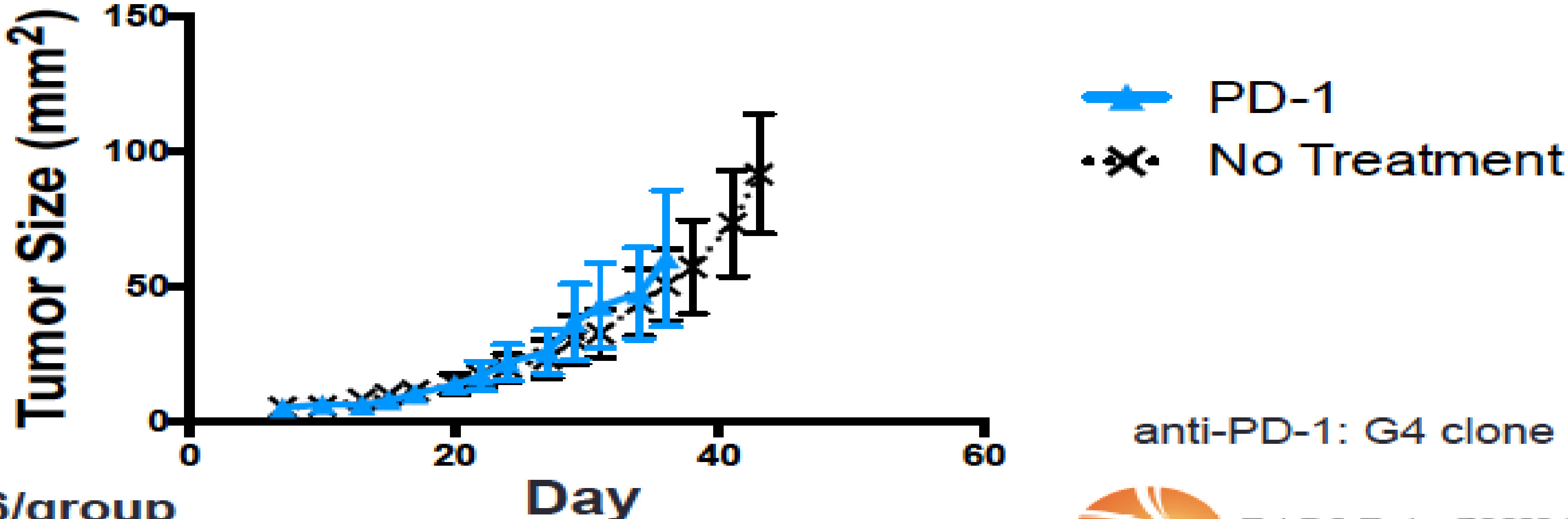
Will PD-1 blockade added to OX40 costimulation impact tumor growth?





Messenheimer D. et al. in press Clin. Can Res. 2017

PD-1 blockade alone has no impact on tumor growth



n = 6/group

anti-PD-1: G4 clone

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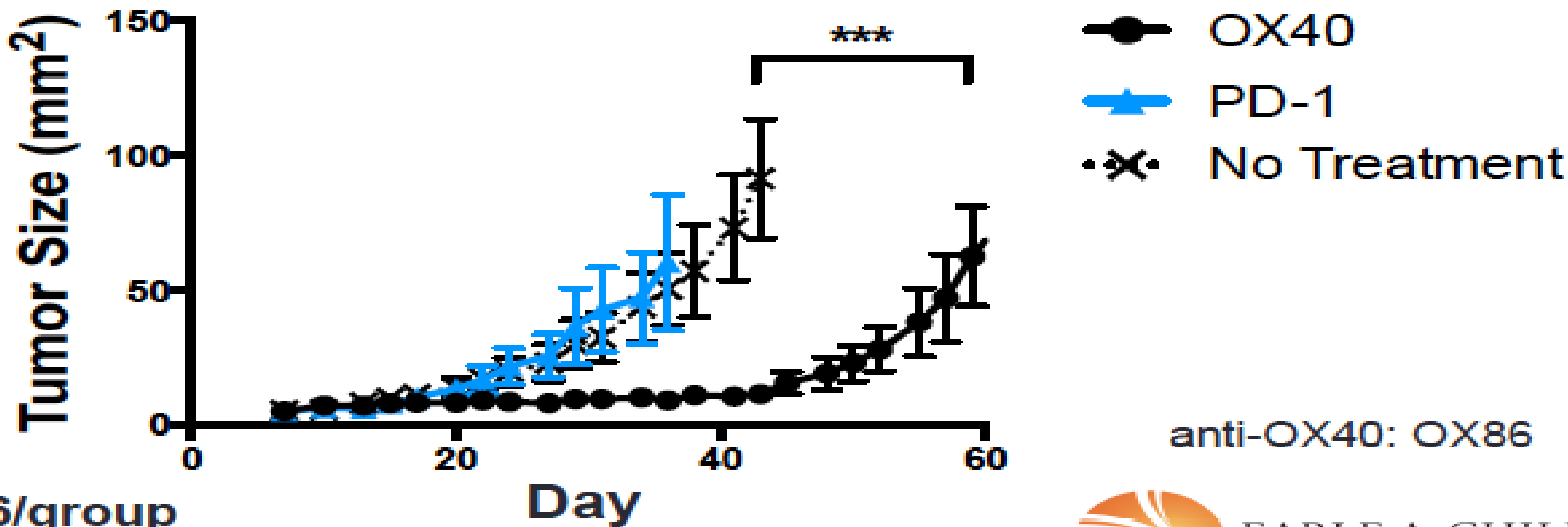
Messenheimer D. et al. in press Clin. Can Res. 2017

OX40 costimulation provides anti-tumor effect



n = 6/group
*** = p < 0.001

anti-OX40: OX86

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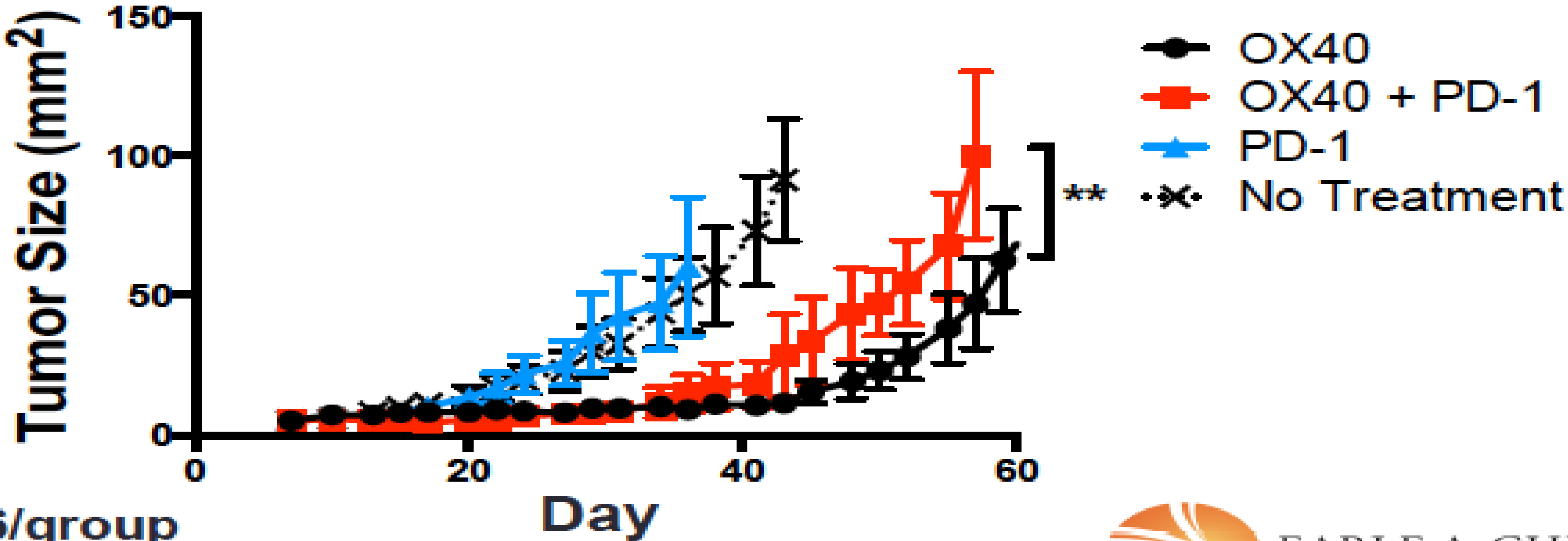
Messenheimer D. et al. in press Clin. Can Res. 2017

Combined treatment does not augment anti-OX40-treated effect



n = 6/group
** = $p < 0.01$

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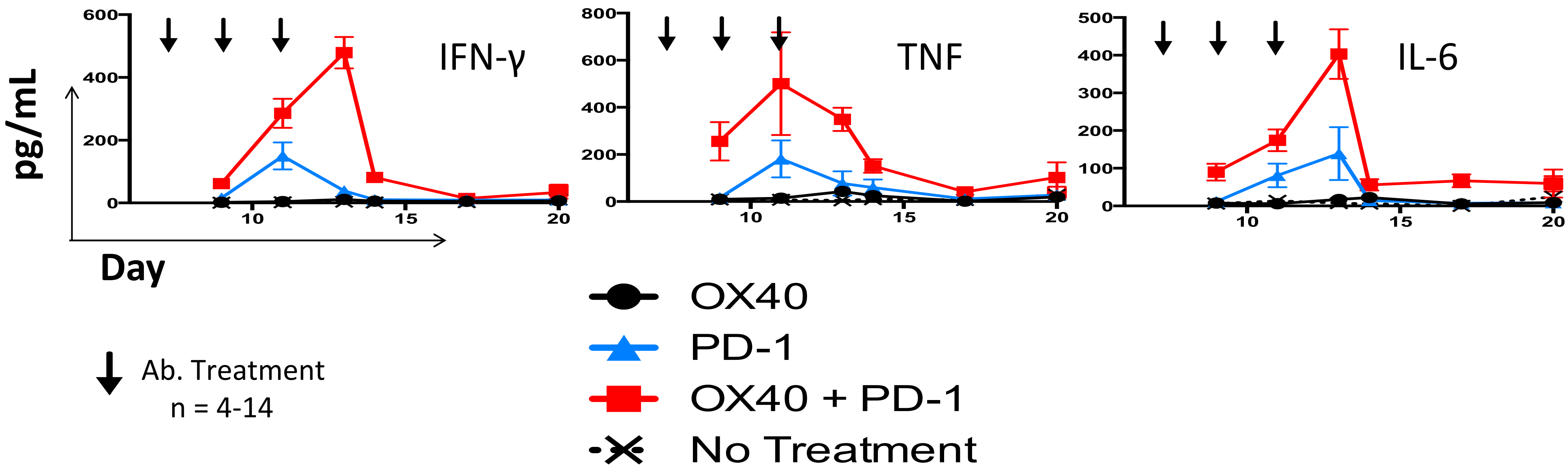
Messenheimer D. et al. in press Clin. Can Res. 2017

Combination of anti-OX40 and anti-PD-1 increases serum cytokines



Messenheimer D. et al. in press Clin. Can Res. 2017

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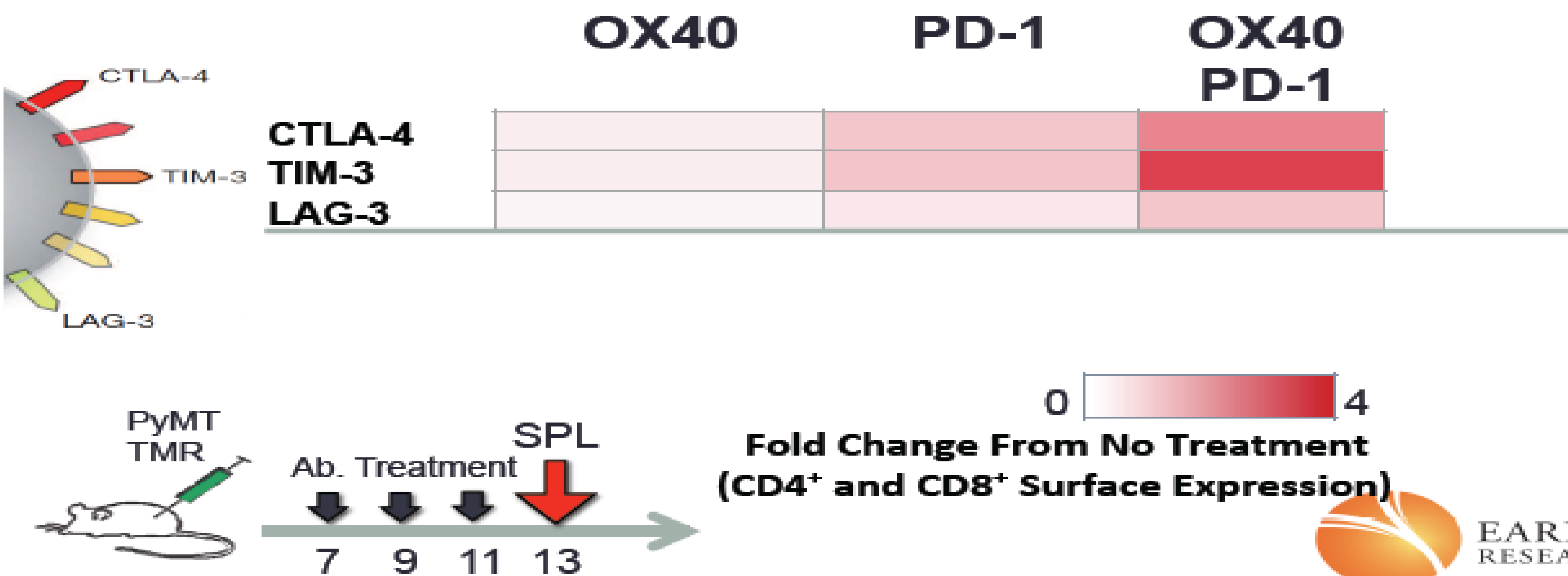
Combination increases inhibitory receptors



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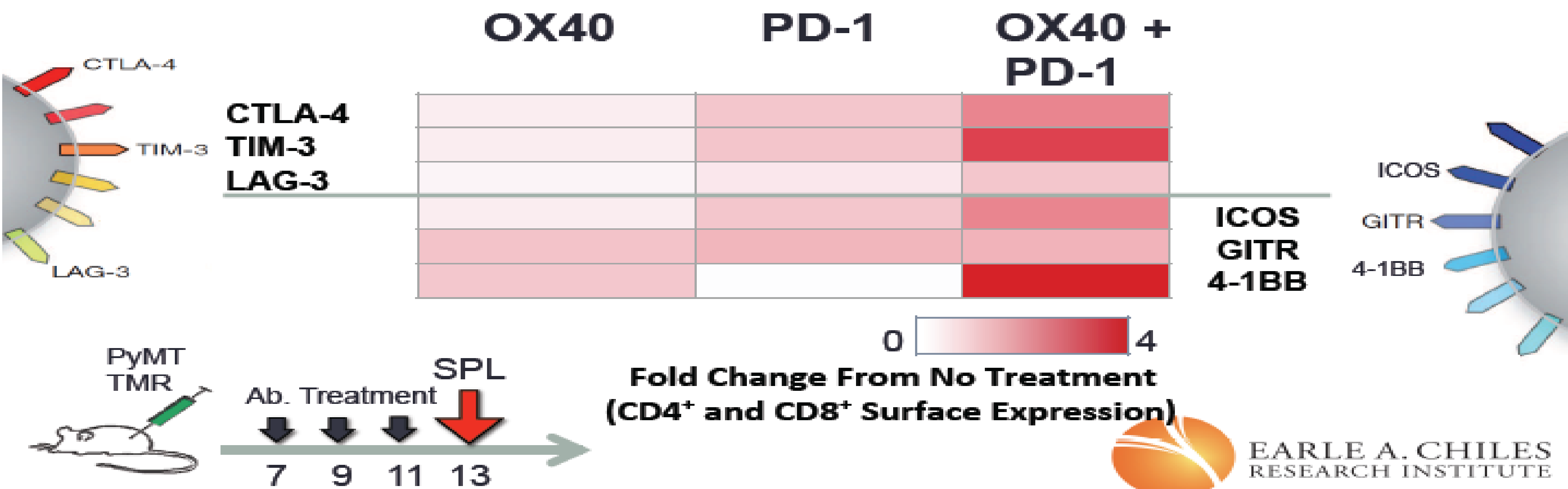
Messenheimer D. et al. in press Clin. Can Res. 2017

Combination increases costimulatory receptors



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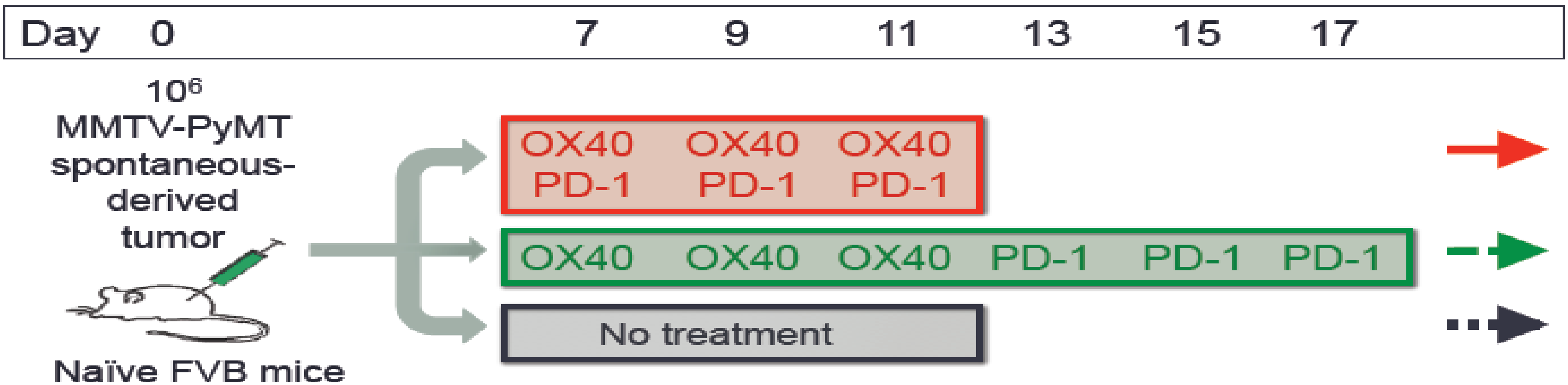
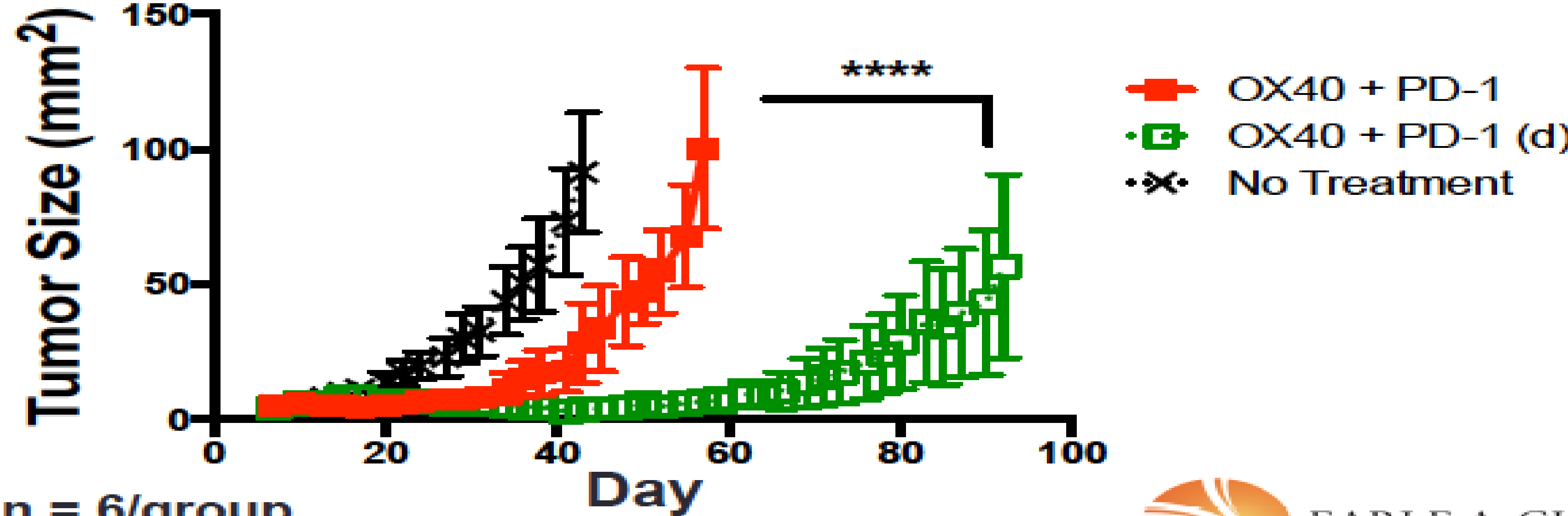
Messenheimer D. et al. in press Clin. Can Res. 2017

Will delayed PD-1 blockade augment OX40 costimulation?



Messenheimer D. et al. in press Clin. Can Res. 2017

Anti-OX40 plus delayed anti-PD-1 is superior to concurrent combination



n = 6/group
**** = p < 0.0001

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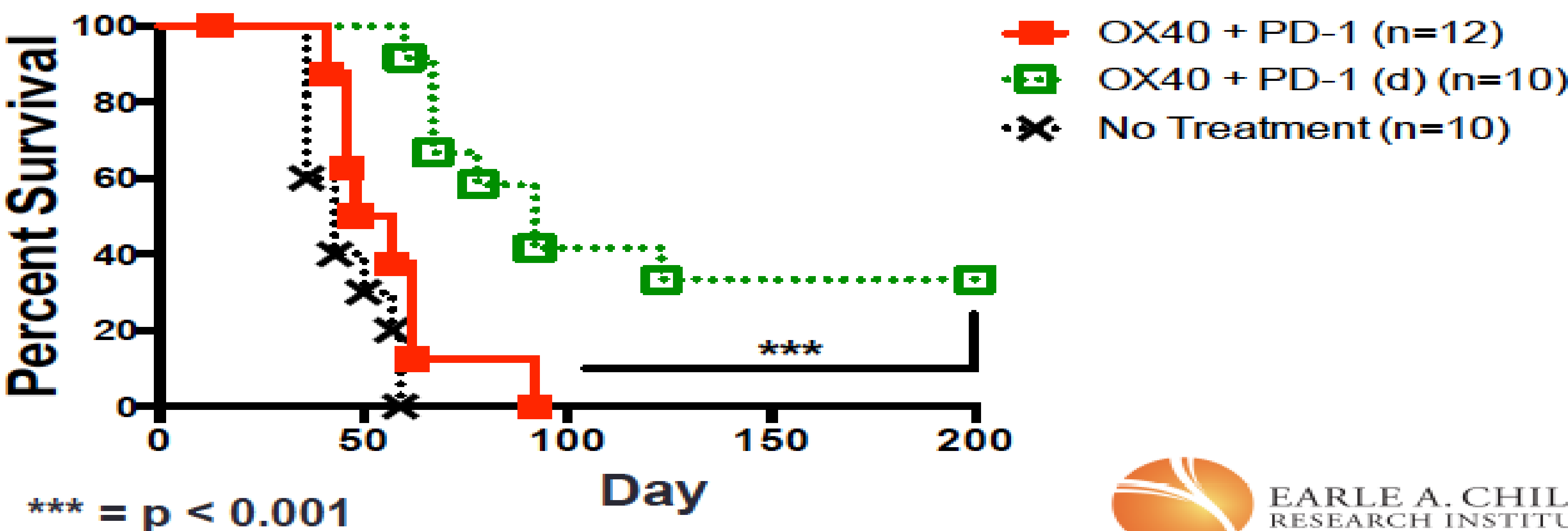
Messenheimer D. et al. in press Clin. Can Res. 2017

AND provides long-term survival



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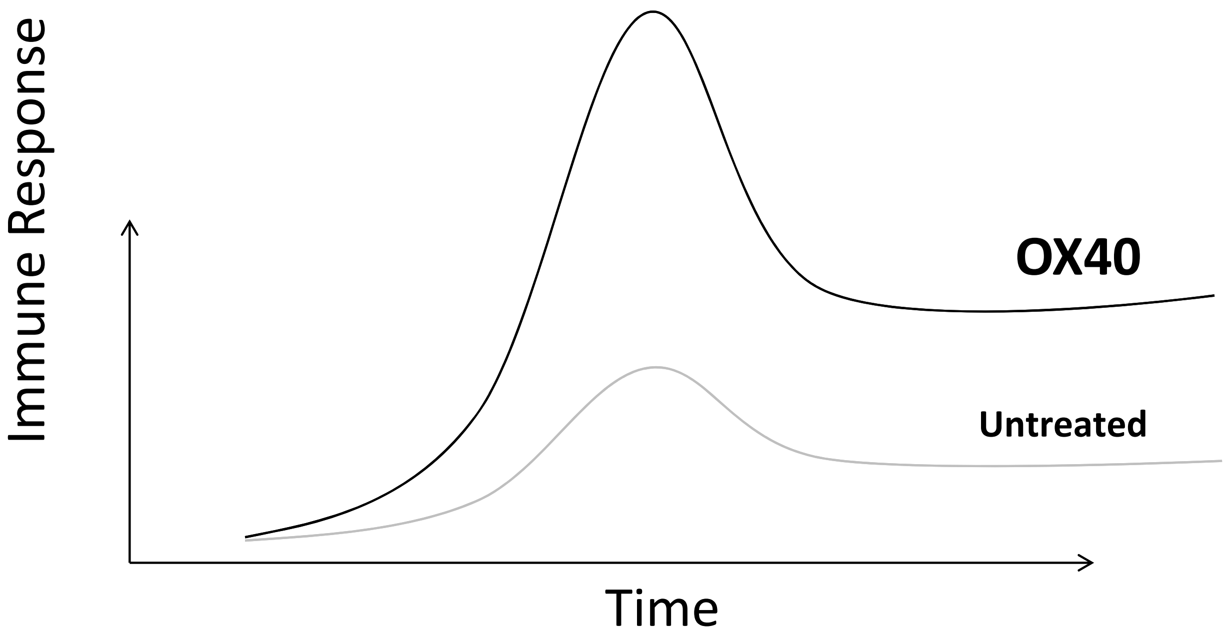
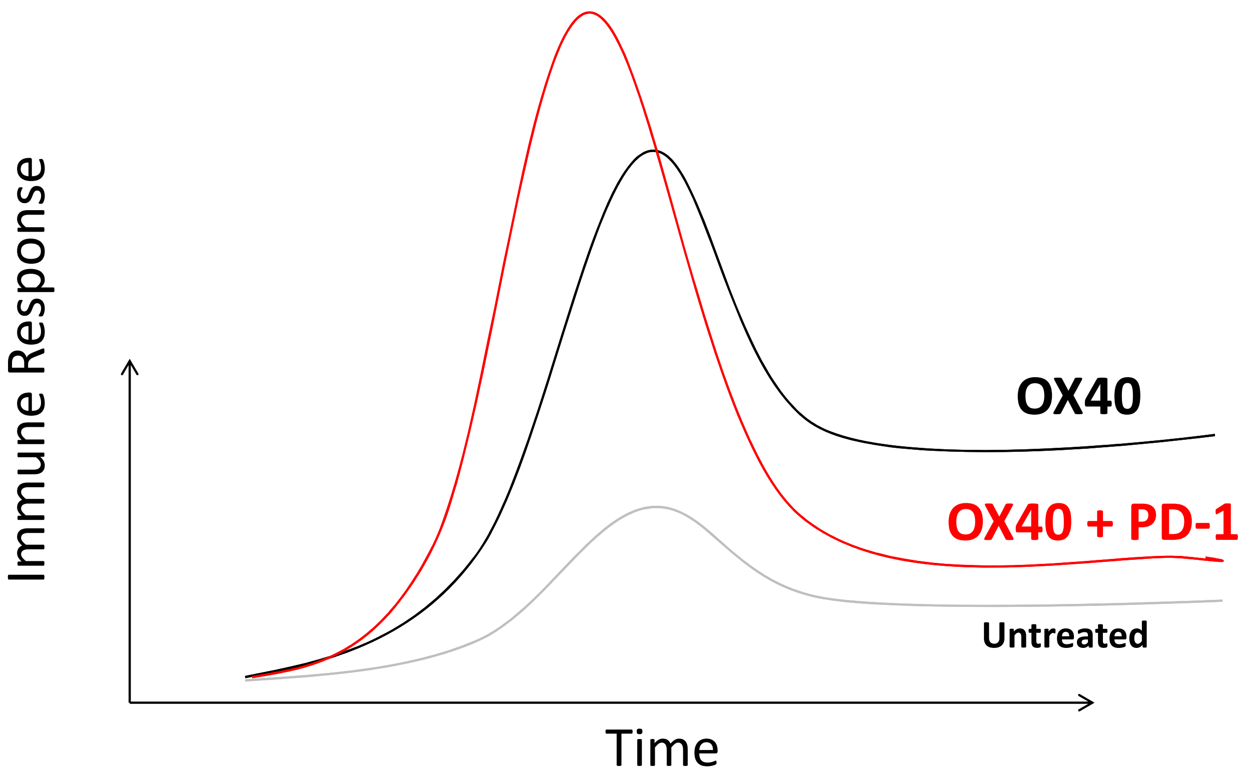
Anti-OX40 provides anti-tumor therapeutic effect



Concurrent anti-OX40 + anti-PD-1 reduces therapeutic effect of anti-OX40 alone

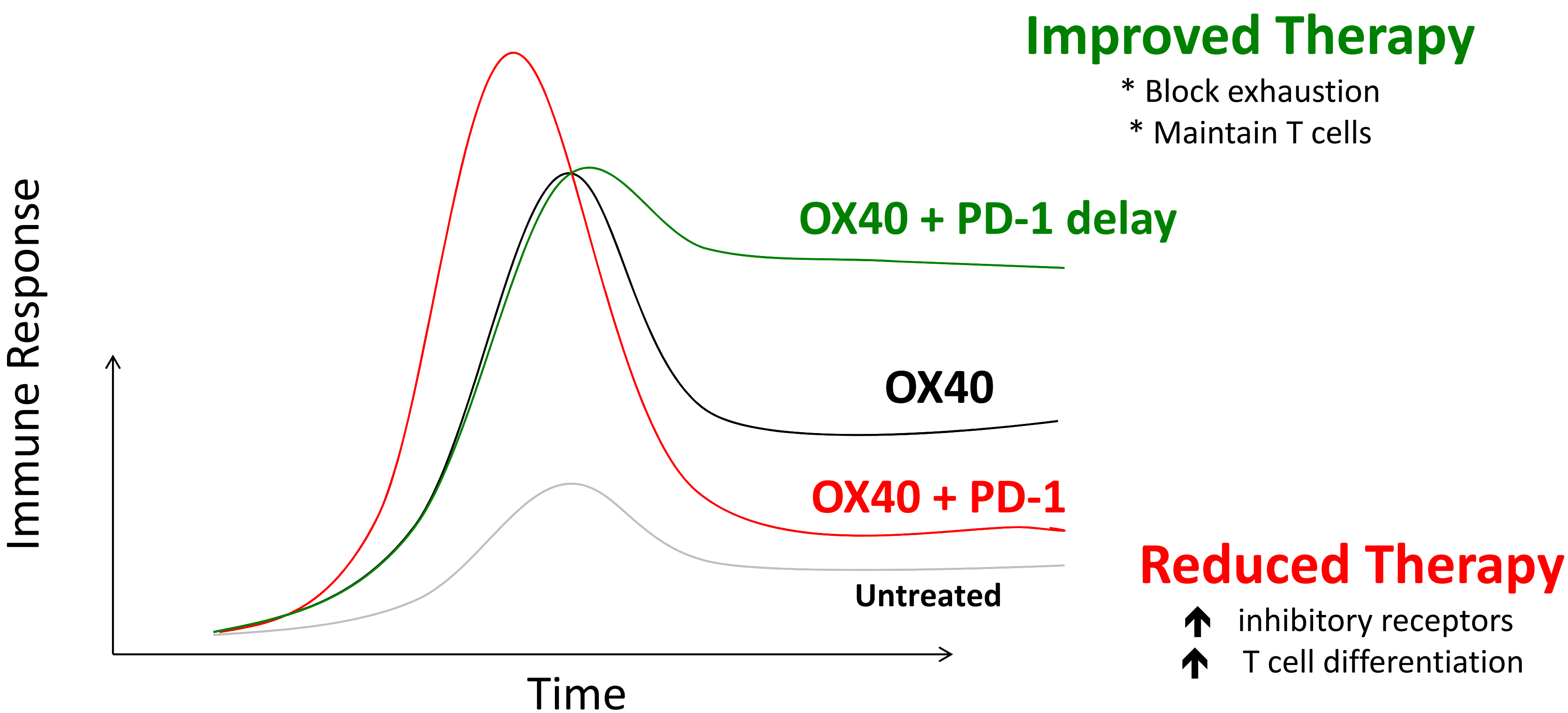


Reduced Therapy

↑ inhibitory receptors

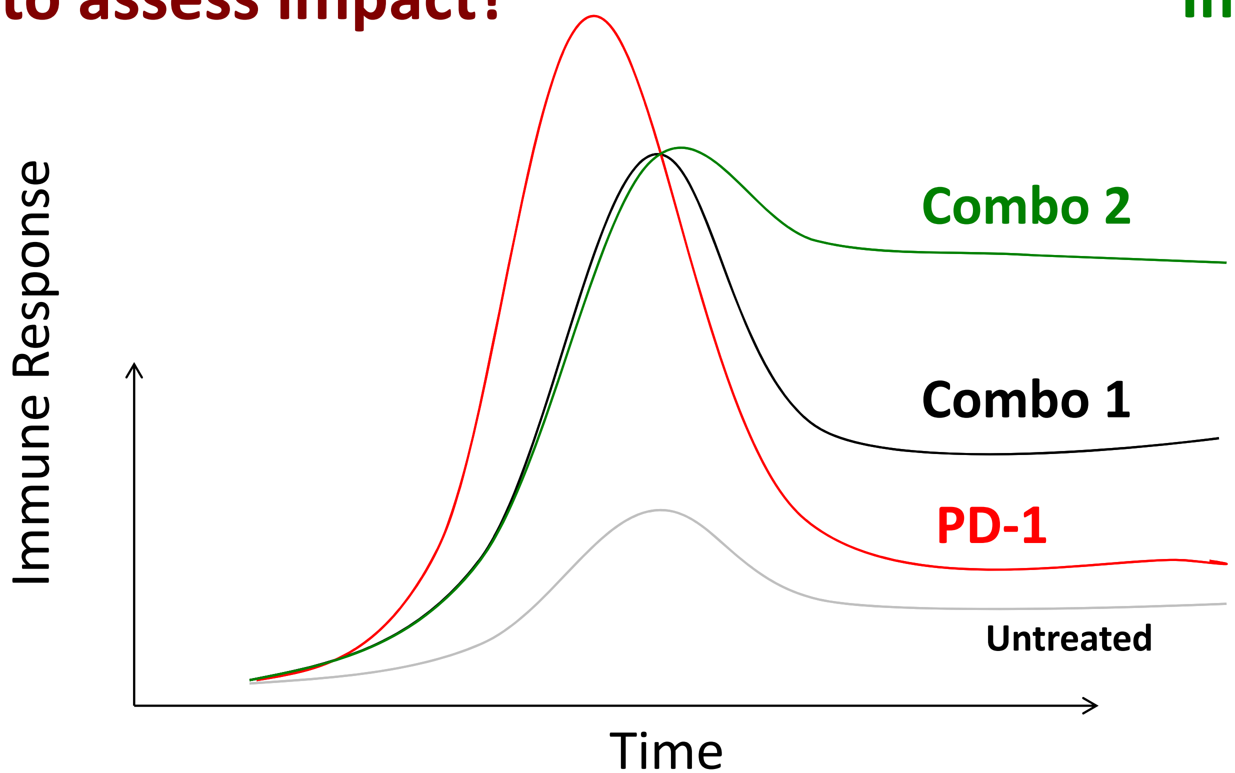
↑ T cell differentiation

Anti-OX40 + delayed anti-PD-1 provides improved therapy



Hypothetical Evaluation of “Effect” of Combination in Clinical Trial

Use Seromics and evaluation of TCR and BCR to assess impact?



Improved Therapy

* Block exhaustion
* Maintain T cells

Reduced Therapy

↑ inhibitory receptors
↑ T cell differentiation

Conclusions

- IgG Ab responses may be useful to identify the scope of immunotherapy induced/augmented immune responses.
- Characterization of “cancer” peptidomes and correlation with IgG Ab responses may provide opportunities to better characterize the scope of the anti-cancer T cell response following immunotherapy.
- TCR characterization of tumor/peptide expanded T cells may provide a way to track trafficking of tumor-specific T cells (ala, Anagnostou et al., Can Discov 2017).
- Vaccines may induce B and T cell immune responses that subsequently contract. Addition of costimulatory or checkpoint inhibitors may increase expansion and reduce contraction – providing a way to monitor contributions of individual agents.

Conclusions

In the transplanted pymt mammary cancer model in FVB mice:

- Anti-OX40 plus **concurrent** anti-PD-1 significantly **reduces therapeutic efficacy** provided by anti-OX40
- Concurrent combination increases serum cytokines and upregulation of **inhibitory and costimulatory receptors**
- Anti-OX40 and **delayed** anti-PD-1 provides significantly **better therapeutic efficacy**, with long term survivors in ~35% of treated mice
- These findings raise the possibility that combination I-O may have unpredicted activity, underscores need for monitoring strategies that evaluate parameters that are predicted to show positive impact of combo

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Patients and their families

Oncologists, pathologist, surgeons and nurses who arrange tumor specimens and administrators and staff who make it happen.

UbiVac
Traci Hilton
Sandra Aung
Andrew Gunderson
Christopher Paustian

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Lynn and Jack Loacker

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American Association for Cancer Research

PANEL DISCUSSION - SESSION II

Key Translational and Design Questions for IO Agents

Moderator: Elizabeth M. Jaffee, MD

Speakers:

Tiffany S. Ricks, PhD
Daniel S. Chen, MD, PhD
Bernard A. Fox, PhD

Panelists:

Marc R. Theoret, MD
R. Todd Bunch, PhD
Leisha A. Emens, MD, PhD
David F. McDermott, MD

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SESSION III:

Considerations for Dose Selection of IO Combination Products

Moderator: Eric H. Rubin, MD

Speakers:

Chao Liu, PhD

Laura L. Fernandes, PhD

Amit Roy, PhD

Eric H. Rubin, MD

Israel Lowy, MD, PhD

René Bruno, PhD

FDA Perspective on Combination Dose-Finding Trials with Immunotherapy in Oncology

Laura L. Fernandes, PhD
Mathematical Statistician OB/OTS/CDER/FDA
Chao Liu, PhD
Clinical Pharmacologist, OCP/OTS/CDER/FDA

FDA-AACR Oncology Dose Finding Workshop Part 3
July 20, 2017

Outline

- Statistical Perspective
  - IO trial methodology
  - Case Examples
- Clinical Pharmacology Perspective
- Summary

Unique Challenges in IO Trials

- Need an efficacy endpoint that is available in a reasonable timeframe
  - Should be able to capture the delayed response
- Need a safety endpoint that captures both short-term and delayed toxicity
- Efficacy and/or toxicity tends to plateau instead of a monotonically increasing function of dose
  - Postel-Vinay, et al. (2009), Jain et al. (2010).
- Seamless designs - monitor both efficacy and toxicity endpoints in the same trial
  - Replacing the Phase Ib trial with a proof of concept trial by enrolling a large cohort followed by a confirmatory phase III trial.

Defining Features Immunotherapy (IO) Combination Trials

- IO agent with a targeted therapy (TKI/VEGF) or chemotherapeutic or another IO agent.
- Toxicity profile of the combination could be additive or overlapping, efficacy profile could be additive, synergistic or in some instances antagonistic/detrimental.
- For example with objective response rate (ORR) as the commonly used efficacy endpoint,
  - **Additivity** – the combination provides an ORR which is equal to the sum of the ORR in the individual agents.
  - **Synergy** – the combination results in an ORR greater than what is expected as a sum of the ORR in the individual agents.
  - **Detrimental** – the combination results in an ORR that is significantly lower than expected from the sum of the ORR in the individual agents.

Approaches to IO Combination Trials

- **Approach 1:** Investigate agents with prior monotherapy indications.
  - Consider different dose level combination anchored around the indicated dosage for the two agents
- **Approach 2:** Combine an approved agent with a first in human (FIH) agent.
  - Fix one agent at the approved dose level and consider different dose levels of the new agent
  - Consider additional dose levels of the approved agent with different dose levels of the new agent
- **Approach 3:** Combine two agents with no prior indications.
  - Study both the agents at different dose level combinations – many different combinations based on the number of dose levels for each of the agents.
- **Approach 4:** Triple combinations!
  - There are numerous possibilities
  - **In all the approaches the resource in terms of patients is limited – need clever ways to optimize and identify combinations that are safe with increased levels of efficacy**

Approaches to IO Combination Trials

- **Algorithmic based**
  - Mimic the ‘3+3’ design by ordering the dose level combinations based on perceived degree of toxicity and assign cohort of patients based on observed toxicities.
- **Model based**
  - Assumes a model for toxicity and efficacy relationships and estimates model parameters after observing patient outcomes of toxicity and efficacy to guide the assignment for the next patient.

Proposed Methods in the Literature

This a list of some of the methods proposed in the literature for combination studies with both safety and efficacy endpoints.

- **Partial Ordering** – Wages & Conaway (2014);
  - Motivated by a melanoma vaccine trial, orders the dose combinations into "zones" based on toxicity
  - Similar methods proposed by Guo & Li (2014), Wages, Slingluff & Petroni (2015)
- **TriCRM Extension** – Mandrekar et al., (2007, 2010)
  - Models three possible outcomes - acceptable toxicity with no efficacy, acceptable toxicity with efficacy and severe toxicity, in the setting of dual agents.
  - Maximize the difference between success and toxicity probabilities to identify the dose combination.
- **Linear Predictor Approach** - Cai, Yuan & Ji (2014)
  - Also proposed by Riviere, Yuan, Dubois & Zohar (2015)
- **Copula-type Regression** - Yin and Yuan (2009)
- Several other methods that jointly model efficacy and toxicity that could be possibly extended to the combination setting - Zhang et al. (2014), Thall et al., (2013)
- Other methods in combination setting modeling toxicity could be possibly extended to include efficacy - Tighiouart et al., (2013), Braun et al., (2010)

Case Example: 1

- **Mel 60,** Phase I/II trial for melanoma vaccine using long-peptides and TLR agonists, evaluating the safety and immunogenicity (Wages, et al., 2015)
- Optimal regimen: will have acceptable toxicity profile as measured by DLTs and a high immunologic response rate (IRR)
- The regimens in the zones are arranged using "partial ordering"
- Efficacy incorporated in the dose assignment rules, model based design
- Ongoing trial, methodology could be adapted to IO drug agents.

Table 1
Available treatment regimens for a study of a long-peptide vaccine (LPV7) plus TLR agonists for resected stage IIB–IV melanoma.

Zone	Regimen	Peptide vaccine	Adjuvant preparation	Dose of TLR agonists
Z_1	d_1	LPV7 + tet	IFA	–
Z_1	d_2	LPV7 + tet	PolyICLC	1 mg
Z_1	d_3	LPV7 + tet	Resquimod	112.5 mcg
Z_2	d_4	LPV7 + tet	IFA + PolyICLC	1 mg/112.5 mcg
Z_2	d_5	LPV7 + tet	IFA + Resquimod	1 mg
Z_2	d_6	LPV7 + tet	PolyICLC + Resquimod	112.5 mcg
Z_3	d_7	LPV7 + tet	IFA + PolyICLC + Resquimod	1 mg/112.5 mcg

Wages et al., Contemporary Clinical Trials.

Case Example: 2

- Nivolumab + Ipilimumab, Wolchok et al.,(2013)
- Metastatic melanoma, both IO agents with complementary mechanisms
- Concurrent and sequenced regimens: Planned four levels of Nivolumab (0.3mg,1mg,3mg, 10mg) and two levels of Ipilimumab (1 mg, 3 mg,10 mg)

	Doses of Nivolumab				
Doses of Ipilimumab		0.3 mg	1 mg	3 mg	10 mg
	1 mg	X	X	Cohort 2a	X
	3 mg	Cohort 1	**Cohort 2**	Cohort 3	~~Cohort 4~~
	10 mg	X	X	X	~~Cohort 5~~

- Studied three dose levels of Nivolumab (0.3g, 1mg, 3mg) and two dose levels of Ipilimumab (0.3 mg, 3 mg) with a dose-escalation plan with a '3+3' algorithmic design.
- All of the combinations not explored.

Case Example: 2

- Results: 33 patients in sequenced regimen (Ipilimumab followed by Nivolumab) and 53 patients in concurrent regimen.

Dose (mg/kg)	Grade 3/4 AE*	ORR
Nivolumab 0.3 + Ipilimumab 3	9/14 (64%)	3/14 (21%)
Nivolumab 1 + Ipilimumab 3	14/17 (82%)	9/17 (53%)
Nivolumab 3 + Ipilimumab 1	11/15 (69%)	6/15 (40%)
Nivolumab 3 + Ipilimumab 3	4/6 (67%)	3/6 (50%)

*Wolchok et al., *AE regardless of causality*.

- Concurrent therapy had a better response than sequential option
- Efficacy not incorporated in the dose-escalation rules.
- Nivolumab 3mg + Ipilimumab 1mg chosen as the optimal combination for mMelanoma. This is different from the indication for NSCLC.
- Additional PK/PD perspective will be presented by Dr. Liu

Features of Current Designs

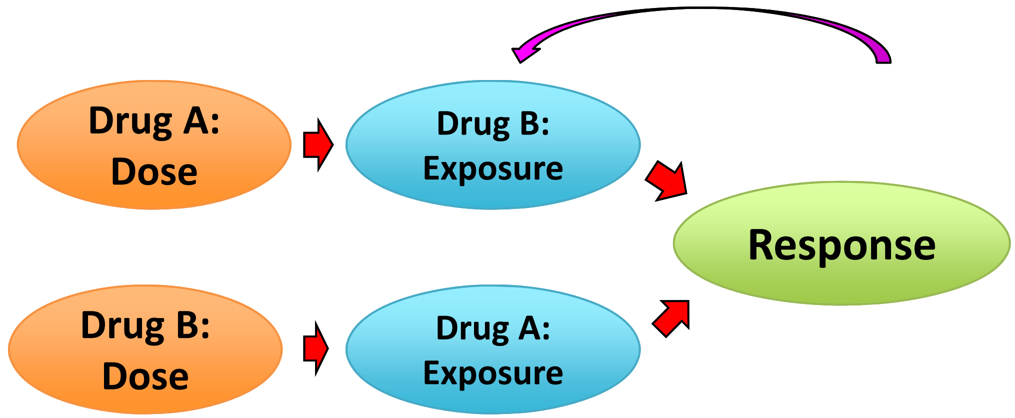
Algorithmic Designs

- Popular and easy to understand and implement
- All combinations are not explored
- “Escalation” is hard to define
- Does not use the information from all the patients in the trial to inform decision on the current cohort of patients
- Does not use efficacy to guide the patient assignment

Model Based Designs

- Incorporate both efficacy and toxicity and information from all patients
- Various prior knowledge can be incorporated in the model building
- Models could become complex, and require additional logistics in setting up the model, prior information in ordering etc.

General Picture: Clinical Pharmacology Perspective

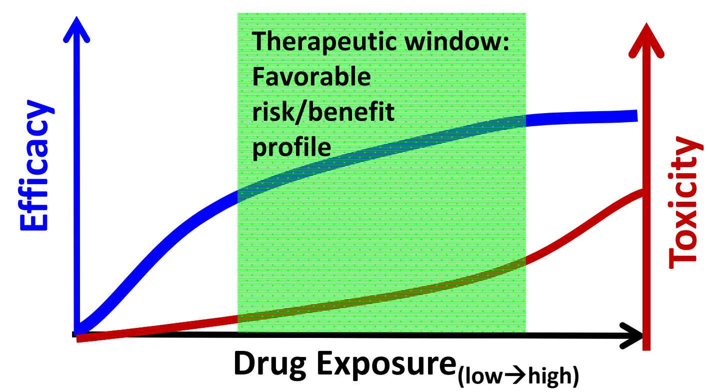


- Pharmacodynamics
- Efficacy
- Safety

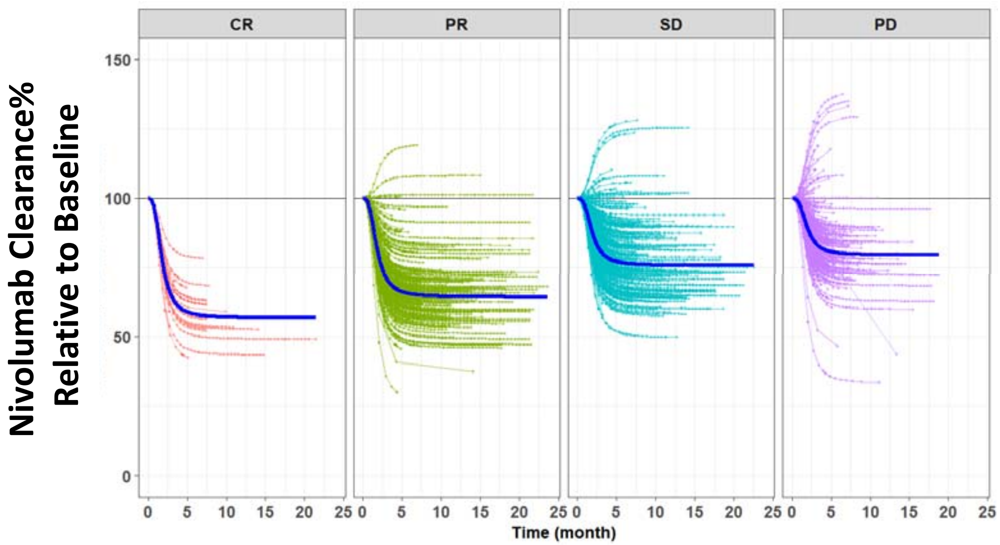
Factors affecting drug exposure

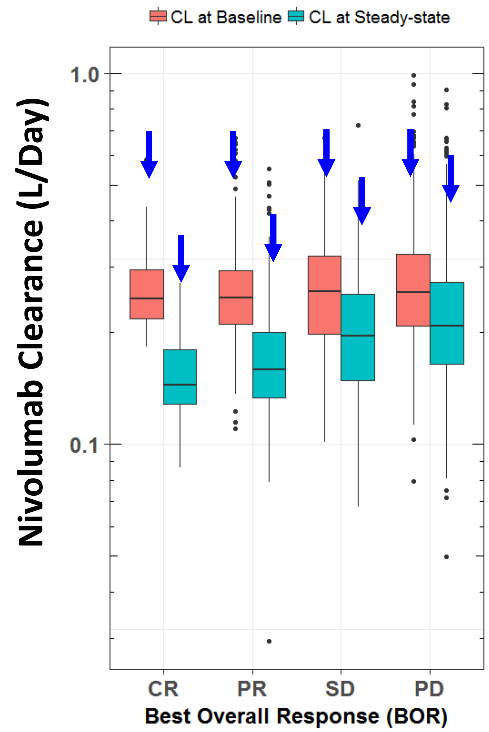
- ***Intrinsic factors:***
  - -Body weight
  - -Immunogenicity
  - -Organ function
  - -Genetic polymorphisms
  - -Other physiological conditions
- ***Extrinsic Factors:***
  - -Drug characteristics
  - -Concomitant medication

Exposure-Response (E-R)



Reduced Clearance with Improving Disease Status in Immuno-oncology products: Nivolumab





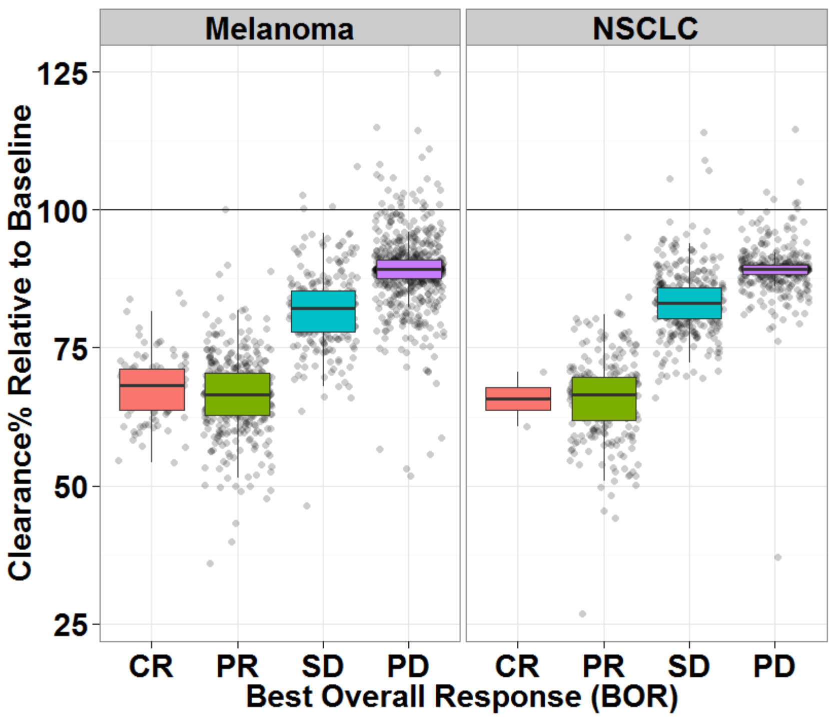
Clearance: Body's capacity to remove the drugs

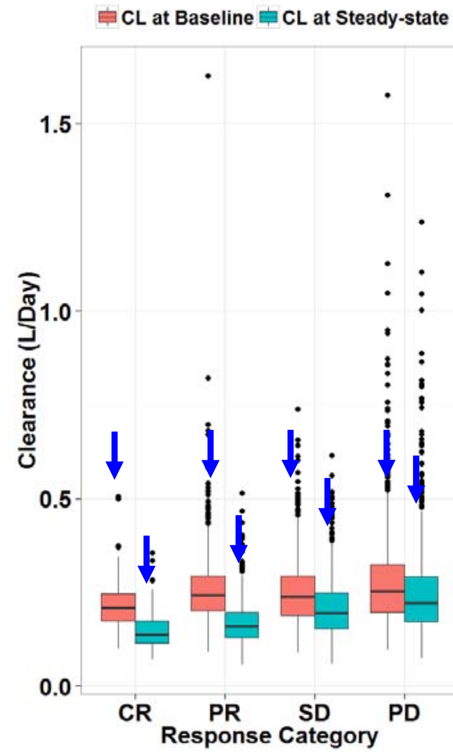
$$\textit{Exposure (AUC)} = \frac{\textit{Dose}}{\textit{Clearance}}$$

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

Liu C. Clin Pharmacol Ther. 2017 May;101(5):657-666.

Reduced Clearance with Improving Disease Status in Immuno-oncology products: Pembrolizumab





Changes of clearance over time were also observed at other approved PD-1 or PD-L1 inhibitors.

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

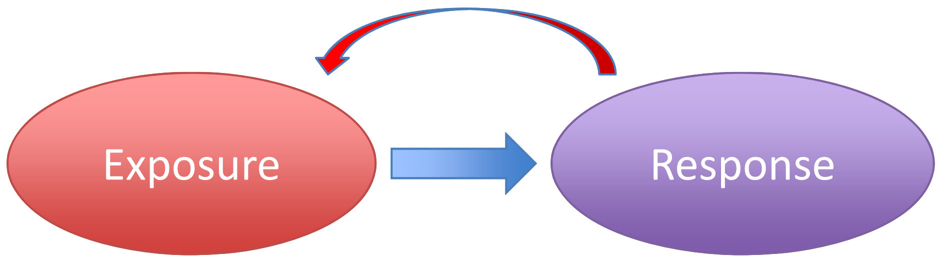
Wang Y, 7th American Conference on Pharmacometrics (ACoP7)
H Li et al. J Pharmacokinet Pharmacodyn. 2017.

Potential Mechanisms of Change of Clearance

Elevated catabolism of protein including mAbs in late stage cancer patients

- **Cancer cachexia**
  - Many cancer patients suffer from cancer cachexia
    - Weight loss is caused by a negative energy balance
      - Decreased food intake, increased energy expenditure, or both
  - Cancer patients were reported to have a *50-70%* higher whole body protein turnover rates. *(Fearon et. al. Cancer Res. 1988, 48, 2590-95)*
- **Systemic Inflammation**
  - Cancer-associated symptoms, in particular the progressive loss of weight and lean tissue, are manifestations of a chronic ongoing systemic inflammatory response. *(Roxburgh & McMillan. Br J Cancer. 2014 Mar 18; 110(6): 1409–1412.)*
- **Other physiological changes**

Implication for I-O combination therapy



Exposure-Response Analysis

- Simple regression analysis using steady-state exposure as the independent variable will lead to incorrect inference on causality.
- Appropriate methods that estimate the E-R relationship can minimize this bias[1].

Pharmacokinetics Profiles

- Higher efficacy with the combination agents might result in a greater magnitude of change in the clearance reduction when compared to the individual monotherapy setting.

[1]*Liu C. Clin Pharmacol Ther. 2017 May;101(5):657-666.*

Other Clinical Pharmacology Considerations on the I-O combination dose selection

- **Immunogenicity**
  - Immunogenicity profile of I-O products could be distinct at combination settings as compared to monotherapy
- **Drug-drug Interaction**
  - Potential for cytokine-mediated alterations in drug metabolism

"Wishlist" for Combination IO Trials

- Conduct trials that
  - incorporate model based designs to identify optimal dose combinations
  - incorporate the both early and delayed toxicities
  - characterize the PK/PD variability and account for patient heterogeneity
  - study the sequencing of the drugs
- Conduct adequate dose exploration before commencing trials to support registration
  - Various dose level/dosing regimens with reasonably wide dose range
- Collect PK from clinical studies
- Explore D-R and E-R relationship for PD/efficacy and safety
  - Potential drug-disease interaction should be taken into account in the E-R analysis

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- Jiang Liu

Tumor Growth Rate - OS Models to Inform Drug Development Decisions

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FDA-AACR Oncology Dose Finding Workshop
Part 3, Washington DC,
July 20, 2017

Outline

Dose selection in oncology drug development

Drug-disease modeling framework

- Tumor kinetic models
- Tumor growth inhibition (TGI) metrics
- TGI-survival models

Growth rate vs. OS in NSCLC

A framework to help decisions in early Phase Ib combination studies

Conclusions so far

Dose selection in oncology

Expedited programs

- Little learning from early clinical trials to inform late studies
- New treatments approved based on early (Phase I) studies

Dose and dosing schedules selection based on MTD, biomarker responses or target exposure based on preclinical studies

No (or few) dose-ranging studies

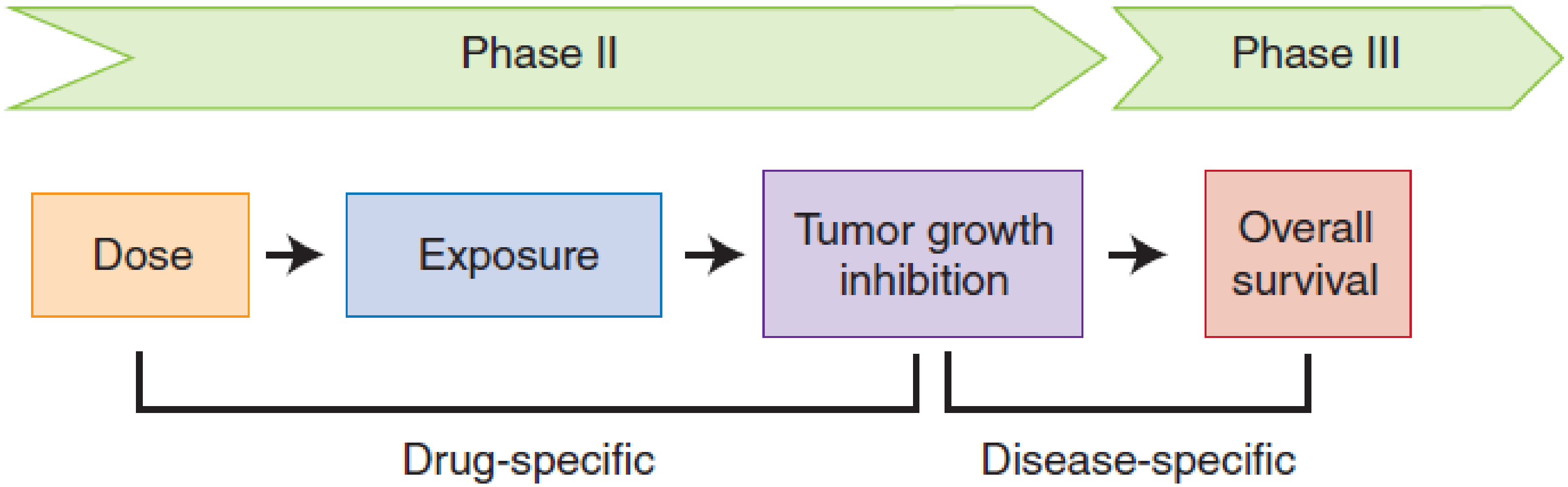
- Primary clinical endpoints (ORR, PFS) poorly informative

Given the number of new treatments and combinations… we need to be creative in term of designs and endpoints

Model-based tumor growth inhibition endpoints may offer an alternative

- More sensitive than classical endpoints to assess treatment effect

Drug-disease modeling framework



Bruno *et al*. *Clin Pharmacol Ther*, **93**:303-5, 2013

Models-based tumor growth inhibition (TGI) metrics are used as biomarkers to capture treatment effect and predict for OS benefit in ‘drug-independent’ TGI-OS models.

Is this paradigm working for cancer immunotherapy ?

TGI – Overall Survival models

Drug independent, disease specific (platform) model

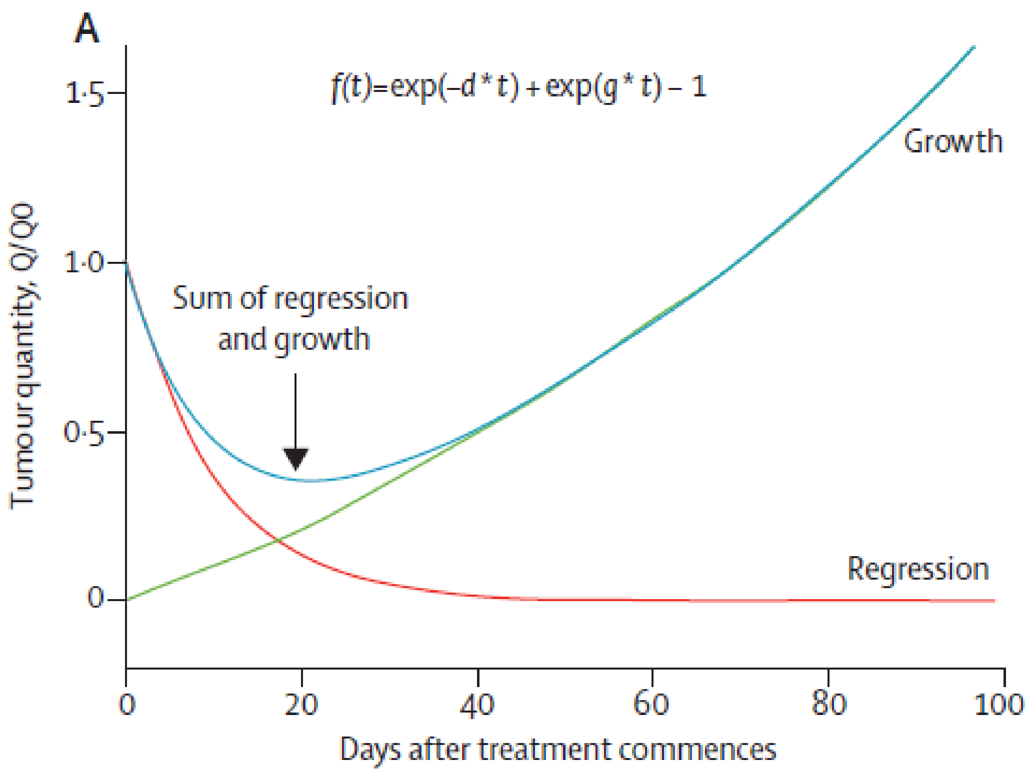
- Survival time distribution is estimated (parametric model) as a function of prognostic factors and predictors.
- TGI metrics are used as a biomarker to capture drug effect on OS
- Historical studies (preferably Phase III) can be used to develop the models
- **Overall survival models have been developed for many solid and hematologic tumors, a few models for PFS are available too**
  - Reviewed by Bruno et al. Clin. Pharmacol. Ther. 95, 386-393, 2014
- **Many companies** are implementing this approach to support early clinical development
- **Regulatory attention** on this approach is also rapidly evolving (e.g. FDA presented an integrated TGI-OS analysis of PD-1 data at the FDA-AACR: Immuno-oncology Drug Development Workshop, October 14, 2016)

A few cases of external evaluations are available

- External evaluations is critical to establish model robustness and treatment independence

Tumor growth rate: On-treatment growth rate

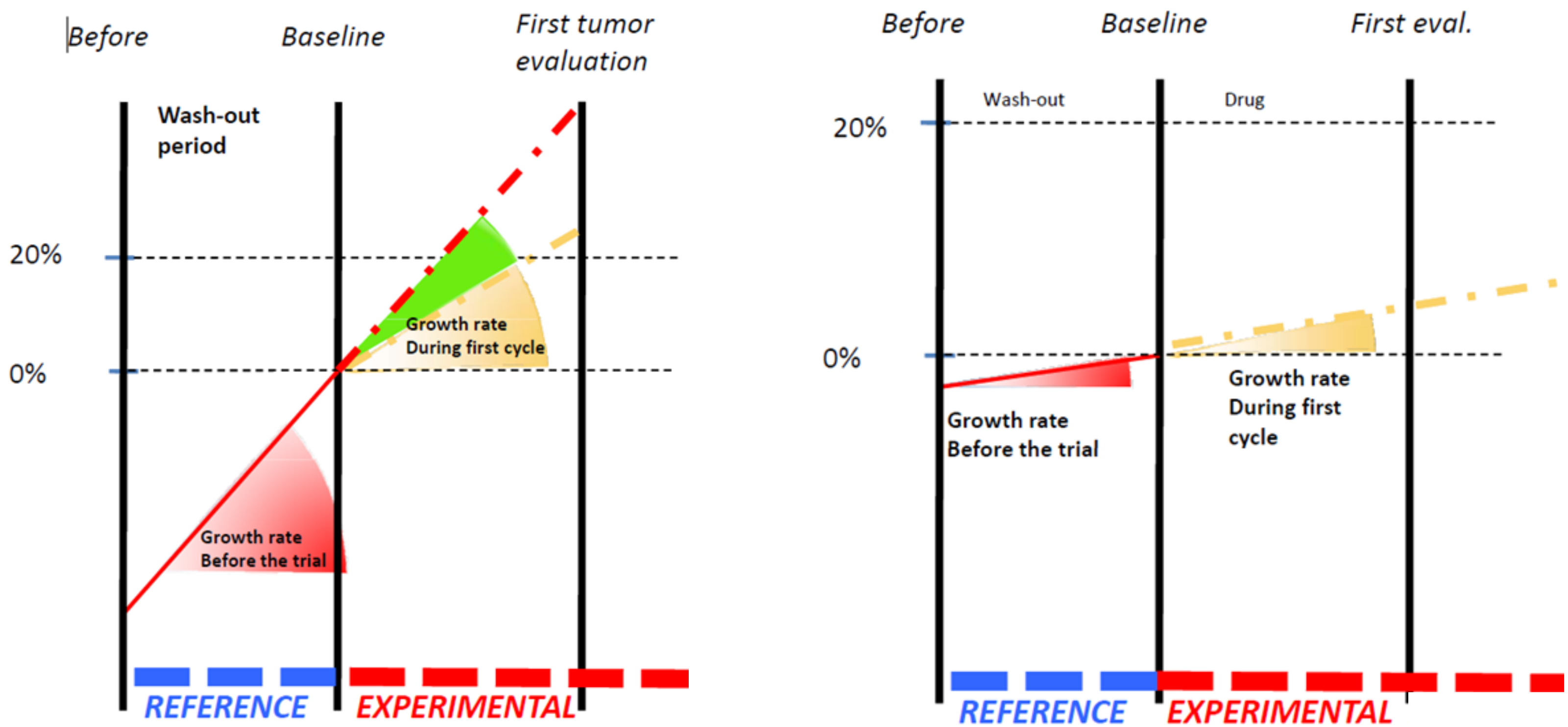
On-treatment growth is predictive of OS



Stein et al. CCR 17:907-17, 2011
Wilkerson et al. Lancet Oncol 18:143-54, 2017

Tumor growth rate: Pre-treatment vs. on-treatment growth rate

The comparison of pre-treatment and on-treatment growth is critical for RECIST data interpretation and signal finding in early studies



Ferté et al. Clin Cancer Res 20:246-252, 2014

Growth Rate vs. OS in NSCLC

Atezolizumab POPLAR Phase II study

Bruno et al, Am Conf Pharmacomet (ACoP7), Seattle, Oct 2016

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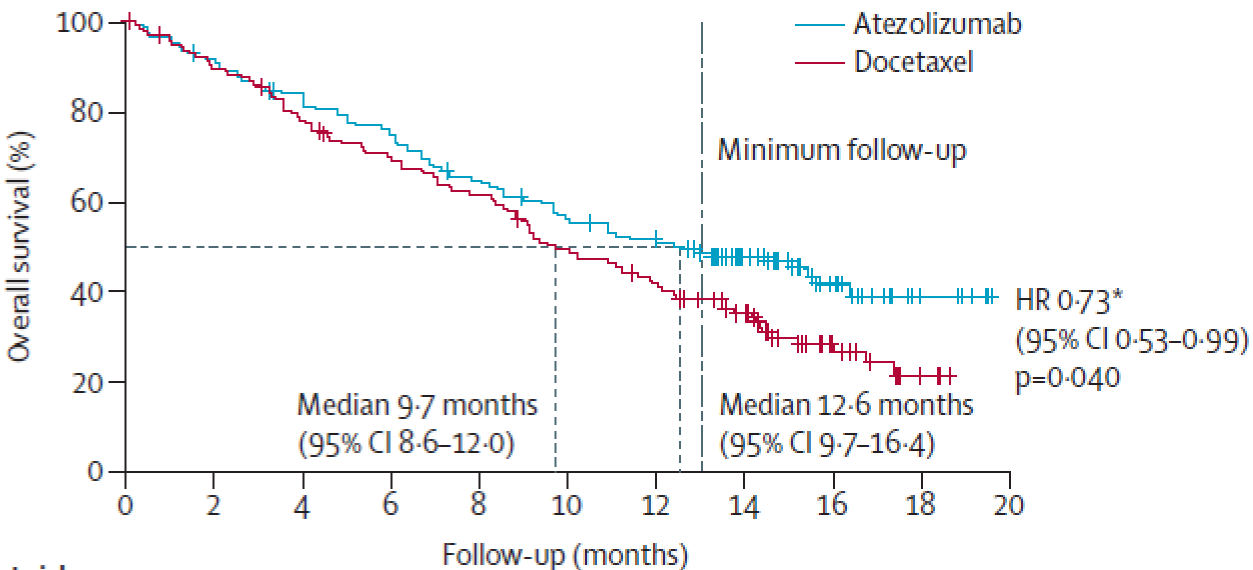
POPLAR study

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

*Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artal-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group**

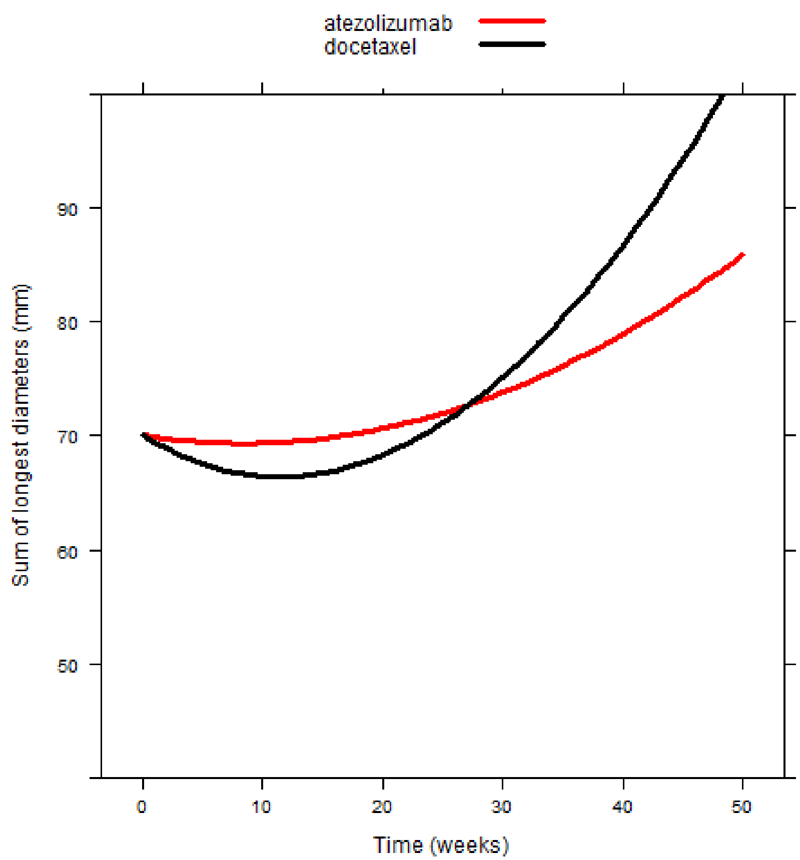
A Intention to treat



Number at risk											
Atezolizumab	144	131	117	106	90	78	69	42	20	7	0
Docetaxel	143	123	106	92	82	65	54	39	17	3	0

Lancet 2016; 387: 1837–46

Typical TGI profiles: more shrinkage in docetaxel and slower growth (KG) in atezolizumab arm



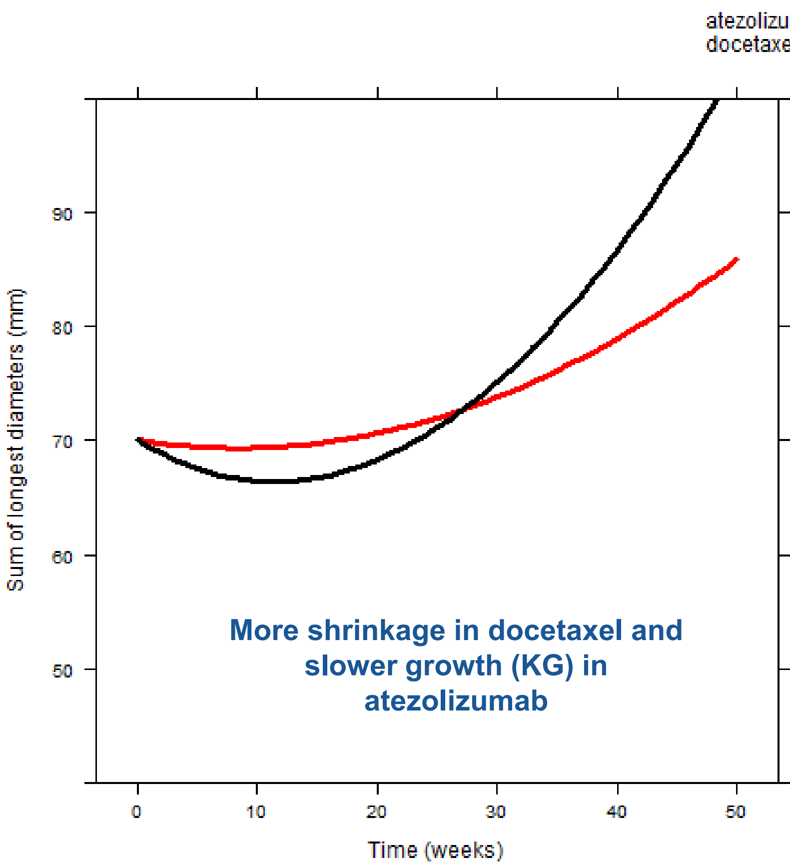
Bi-exponential model: more shrinkage in docetaxel arm, slower growth in atezolizumab arm (Stein et al, CCR 17:907-17, 2011)

Growth rate (KG) : 3.4 months longer tumor doubling time in atezolizumab arm

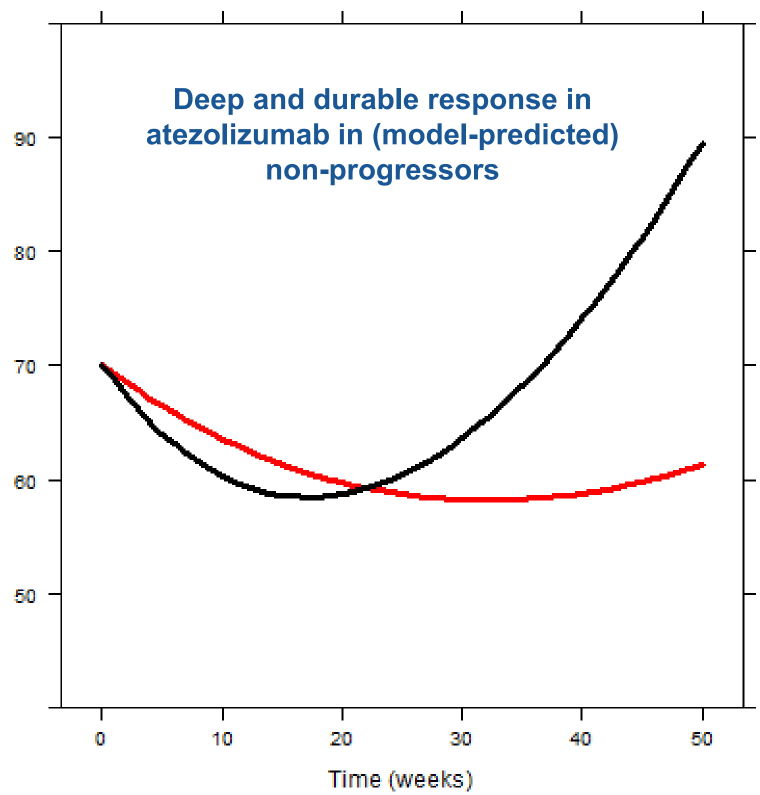
No major evidence of delayed responses or pseudo-progressions in POPLAR data based on target lesions

Bruno et al, ACoP7, Seattle, Oct 2016

Typical TGI profiles: Deep and durable response in atezolizumab arm in (model-predicted) non-progressors at week 6



All patients



Patients with model-predicted SLD at week 6 < model-predicted SLD at time 0 (start of treatment) (n=83 patients (67.5%) in docetaxel, n=73 patients (56.6%) in atezolizumab)

OS Model: POPLAR

Final OS lognormal model

	Value	Std. Error	z	p
(Intercept)	1.224	0.600	2.04	0.041
# Met sites	-0.163	0.0528	-3.09	0.002
Albumin	0.0519	0.0102	5.11	3.22e-07
logKG	-0.752	0.0875	-8.59	8.38e-18
Log(scale)	-0.338	0.0639	-5.29	1.23e-07

SE=standard error of parameter estimate; z=Wald statistic; p=Wald test ($\chi 2$); Scale=standard deviation of log(OS)

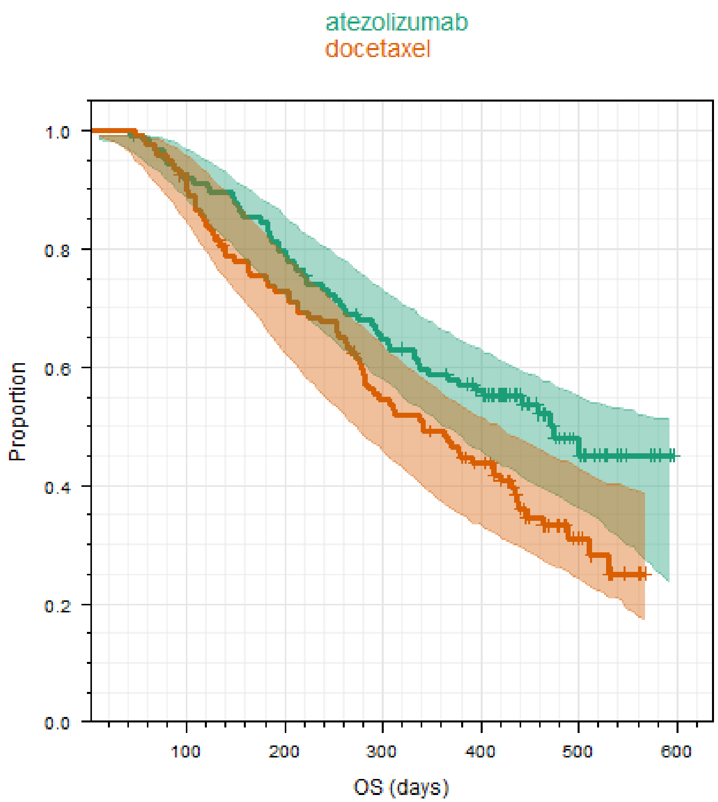
Negative sign in parametric model: survival probability decrease with covariate increase

Probability of death decrease with log(KG)

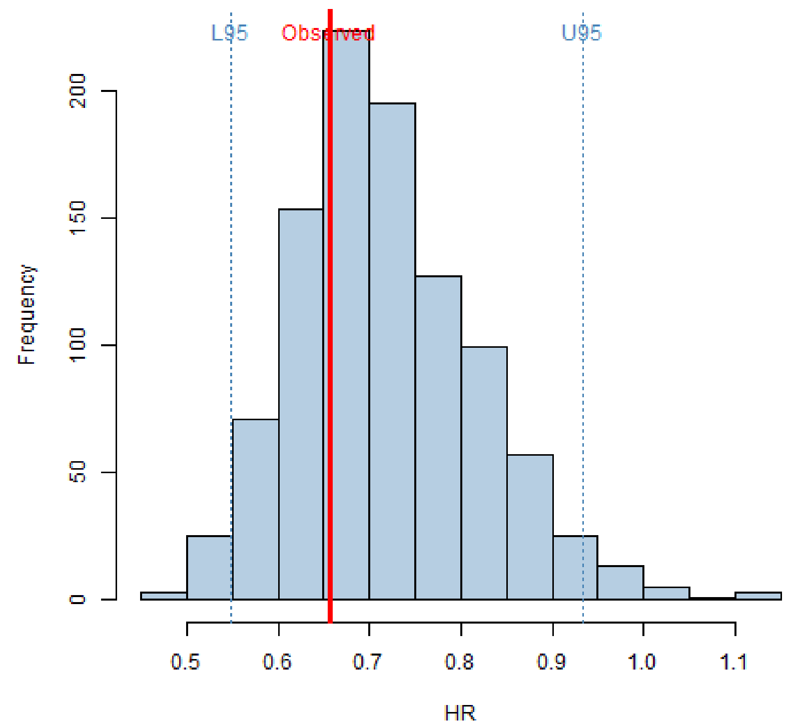
Treatment effect no longer in the multivariate model.
Difference in logKG explains treatment effect.

Bruno et al, ACoP7, Seattle, Oct 2016

Model qualification to predict atezolizumab effect (HR) over docetaxel in POPLAR (95% prediction intervals vs. observed)



Areas= 95% prediction interval of survival distributions; Lines=Observed Kaplan-Meier distributions with censored data (crosses)



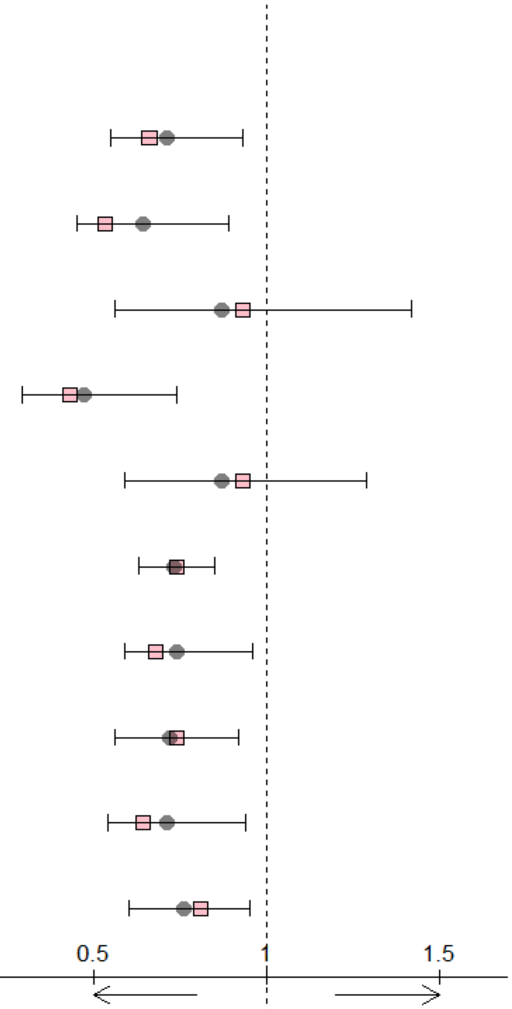
Histogram=HR distribution over 1000 replicates; Dotted vertical lines=lower and upper limits of the 95% prediction interval; solid vertical line=observed HR

Difference in KG across arms captures OS benefit with atezolizumab

Bruno et al, ACoP7, Seattle, Oct 2016

TGI-OS POPLAR model prediction of the atezolizumab to docetaxel hazard ratio in POPLAR and OAK

Study	Population	Observed	Predicted (95% PI)
POPLAR	All	0.66	0.71 (0.55,0.93)
	TC123IC123	0.53	0.64 (0.45,0.89)
	TC0IC0	0.93	0.87 (0.56,1.42)
	High Teff	0.43	0.47 (0.29,0.74)
	Low Teff	0.93	0.87 (0.59,1.29)
OAK	All	0.74	0.73 (0.63,0.85)
	TC123IC123	0.68	0.74 (0.59,0.96)
	TC0IC0	0.74	0.72 (0.56,0.92)
	High Teff	0.64	0.71 (0.54,0.94)
	Low Teff	0.81	0.76 (0.60,0.95)



Model predictions (dots) and 95% prediction interval (1000 replicates, bars) with observed (squares)

TC/IC: PD-L1 expression in tumor/tumor-infiltrating immune cells
Teff: T-effector and interferon-γ gene signature

Lancet 2016; 387: 1837–46

A framework to help decisions in early Phase Ib combination studies

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Decision framework - KG as an exploratory endpoint

Decisions often rely on ORR (or PFS) in small cohorts of patients in non-randomized Phase Ib studies

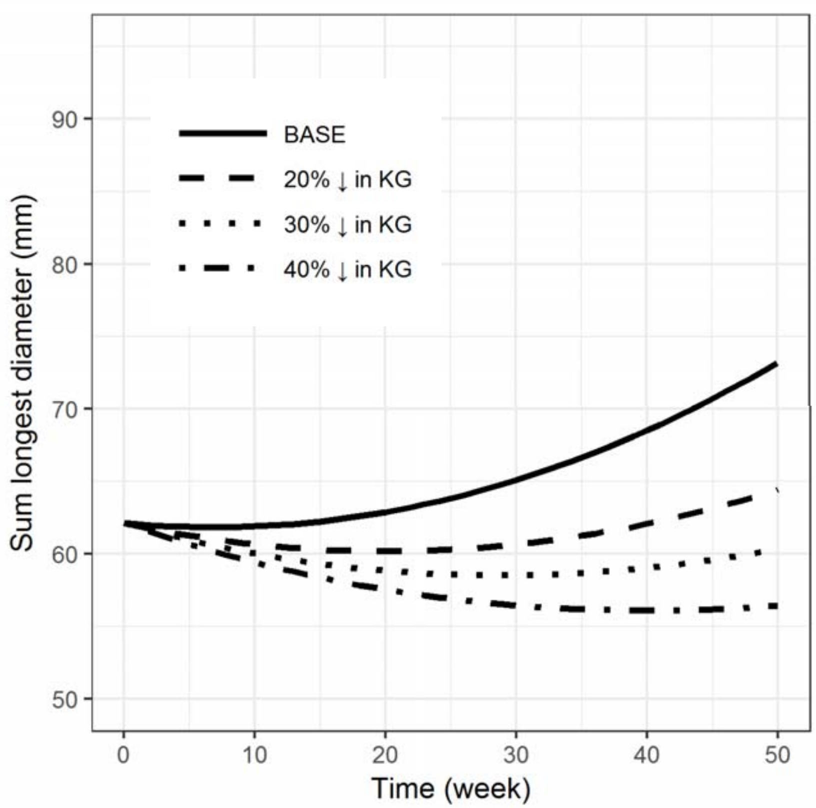
Use the TGI model to generate predictions of single agent profiles and KG adjusted to patients characteristics

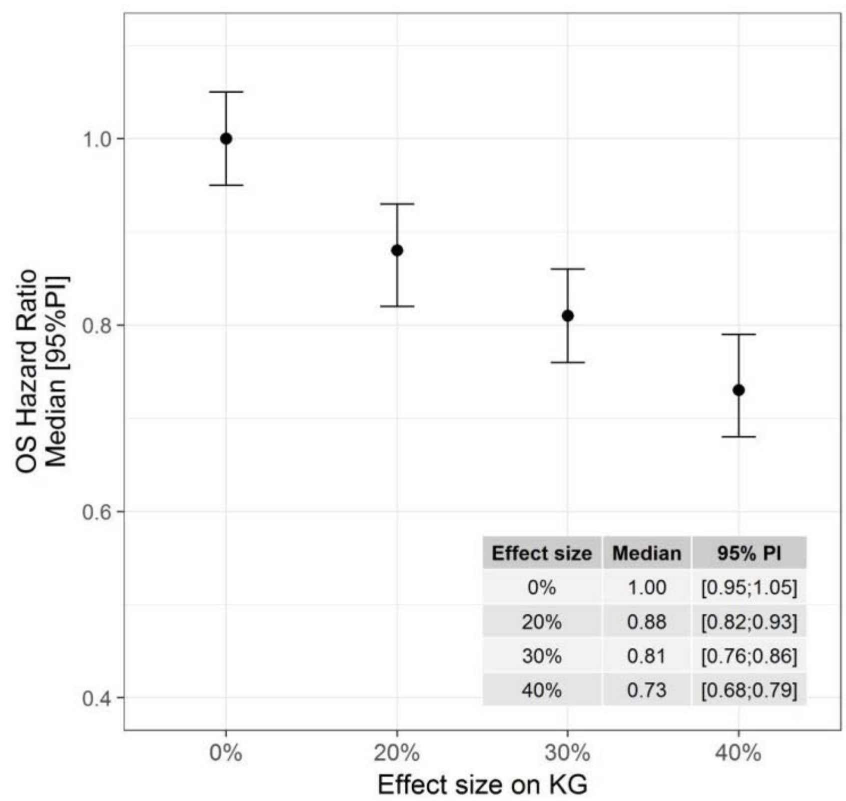
- Compare with observed profiles and KG in patients receiving combination treatments with single agent
  - Identify signal (or absence of signal) of increased efficacy (slower KG) in small cohorts of patients in Phase Ib studies
    - Select best combination (go/no go)
    - Assess dose (exposure) response

Use the OS model to quantify the expected magnitude of OS improvement (HR vs. single agent)

- Select dose to achieve desired product profile

Expected impact of combinations on TGI profile and HR





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Conclusions so far

Concluding remarks

TGI-Survival modeling methodology is pretty well established

- Many tumor types across a wide range of therapeutic agents
- Model-based on-treatment growth rate seems to be a robust predictor of OS
- It's working for immunotherapies (NSCLC, mUC…)

External validation of models is critical to convince development teams and facilitate implementation

On-treatment growth rate has potential as an alternative endpoint to evaluate efficacy in early cancer immunotherapy studies

- To support early clinical study design
- To help prioritize and select the most promising combination therapies
- To help select best dose/schedule to achieve desired product profile

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POPLAR study patients and investigators

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- Wan-Ting (Alyse) Lin, Rui Zhu, Kari Morrissey, Pascal Chanu, Helen Winter, Sandhya Girish, Amita Joshi

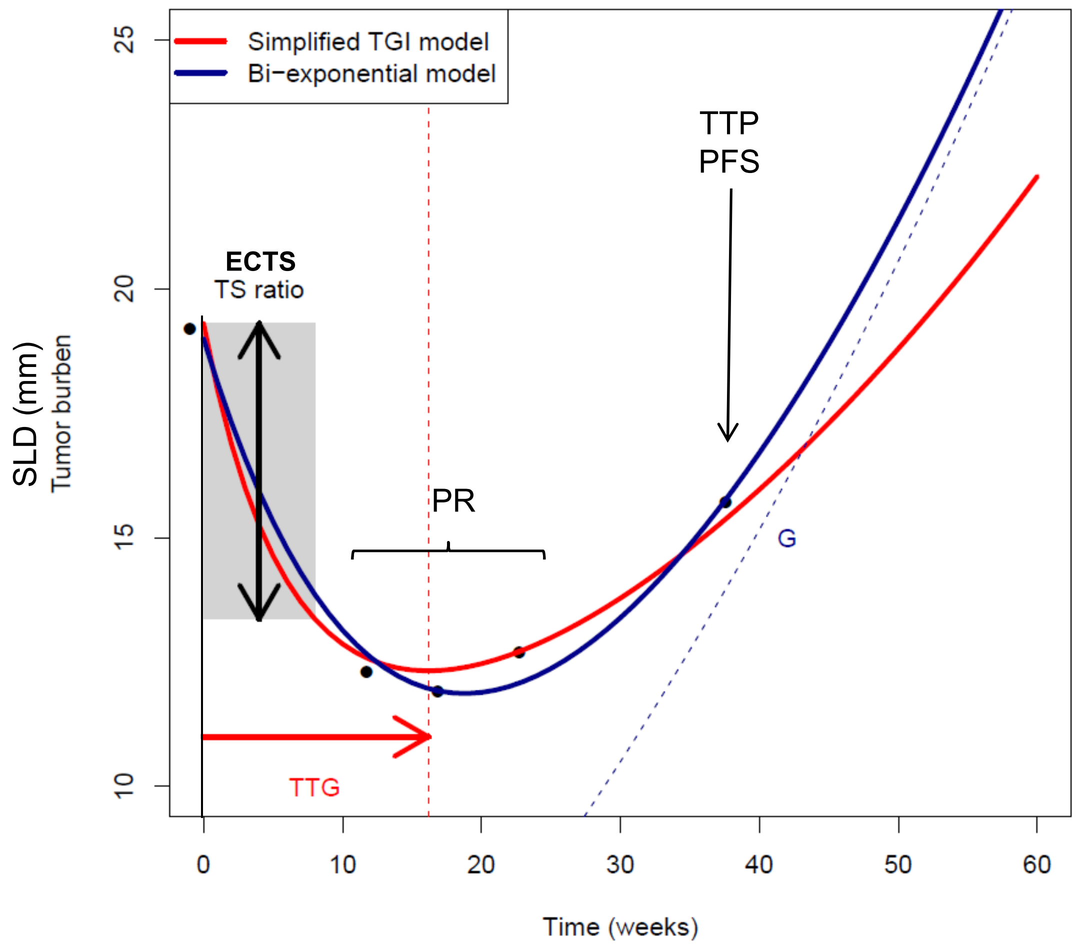
Genentech, Biomarkers, Biostatistics and Clinical

- Marcin Kowanetz, Pei He, Marcus Ballinger, Dan Chen

Atezolizumab Project Team

Backups

Tumor growth inhibition metrics



Claret *et al*. *J Clin Oncol*, **31**:2110-2114, 2013

SLD: sum of longest diameters of target lesions (RECIST)

PR: partial response
TTP: time to progressive disease
PFS: progression free survival

Metrics:
- ECTS: early change in tumor size (TS ratio)
- Maximum change in tumor size
- TTG: time to growth
- G: growth rate
- Full (relative change) profile

POPLAR study

Open-label, Phase II randomized controlled trial POPLAR in patients with advanced NSCLC who progressed on post-platinum chemotherapy (Fehrenbacher et al, Lancet 387, 1837-1846, 2016)

287 patients randomized (Aug 2013 - March 2014)

- Atezolizumab: 144 patients, 129 (89.6%) are TGI evaluable*
- Docetaxel: 143 patients, 123 (86.0%) are TGI evaluable*

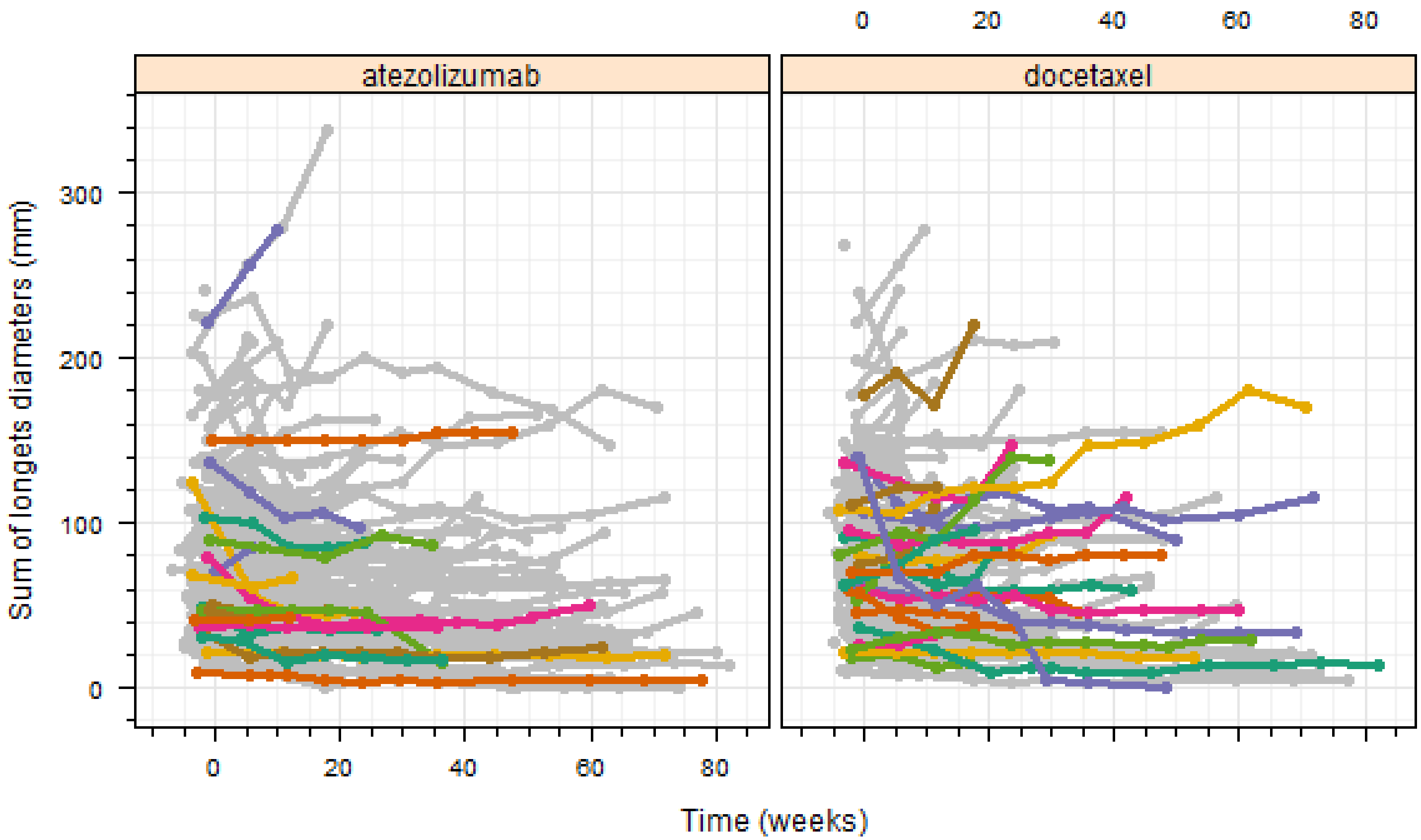
Median OS (intention-to-treat population)

- Atezolizumab: 12.6 months (95% CI 9.7–16.4)
- Docetaxel: 9.7 months (8.6–12·0)

Hazard ratio: 0.73 (p=0.040)

* patient evaluable for TGI if at least one post-baseline tumor size measurement

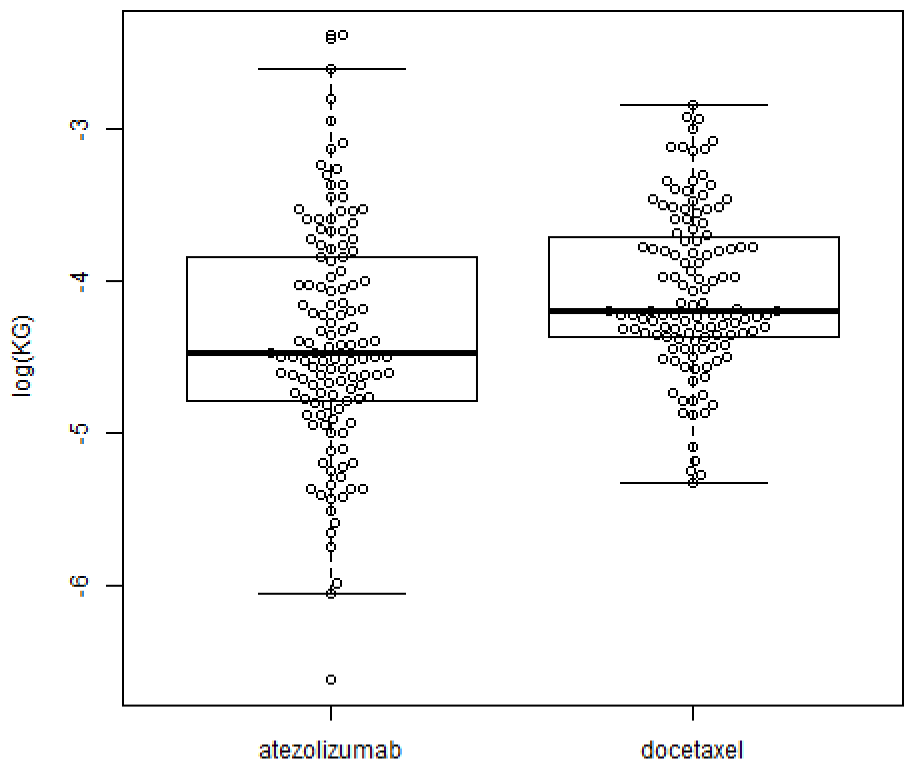
TGI data



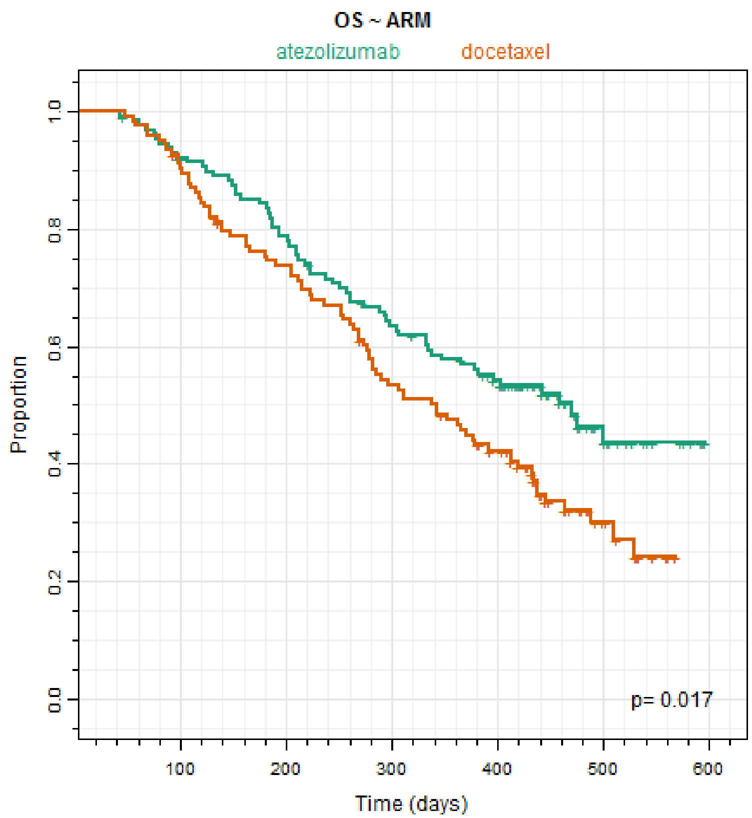
All profiles in grey, 50 patients taken at random are colored

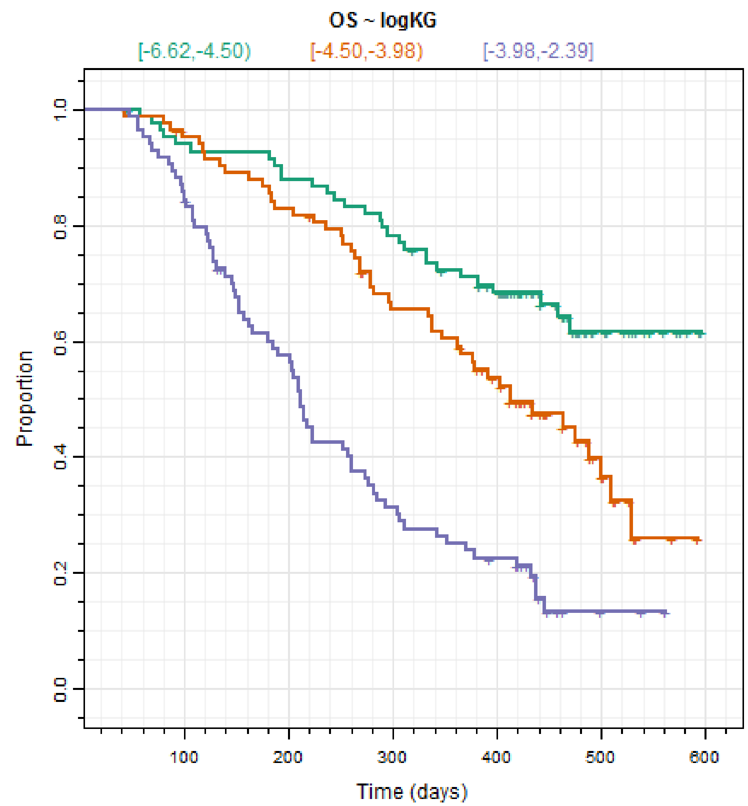
Distribution of individual KG estimates in the two arms

Slower KG in atezolizumab Arm



OS by arms and by tertiles of logKG





Univariate cox analysis

Selected for backward elimination

	Score	p	N	Sign
logKG	69.4	0	252	+
# Met sites	28.2	0	252	+
ALP	20.2	0	247	+
ALBU	20.1	0	244	-
Baseline SLD	14.2	2e-04	252	+
Never Smoker	6.8	0.0092	252	-
ECOG>0	6.1	0.0139	252	+
Atezolizumab	5.7	0.0173	252	-
Non squamous	4.5	0.0346	252	-
Female	3.9	0.0495	252	-
EGFR	3.8	0.0514	249	+
YSM	3.7	0.0545	252	-
TC123 IC123	1.9	0.1688	252	-
Serum Creatinine	1	0.3284	249	-
IC3	1	0.3195	252	-
TC23 IC23	1	0.3098	252	-
AST	0.5	0.4787	247	-
AGE	0.4	0.546	252	-
Total protein	0.4	0.5067	246	-
LDH	0.3	0.6126	246	+
BWT	0.3	0.5997	249	-
TC3	0.2	0.6468	252	-

positive sign in Cox model: hazard tends to increase with covariate

Score=difference in -2*log-likelihood between model with covariate and model with intercept only; p=log-likelihood ratio test; N=number of patients with non-missing covariate

BMS Experience in I-O Combination Dose Selection: IPI + NIVO

Amit Roy

FDA-AACR Workshop on I-O Combination Dose Selection

20-July-2017

Bristol-Myers Squibb

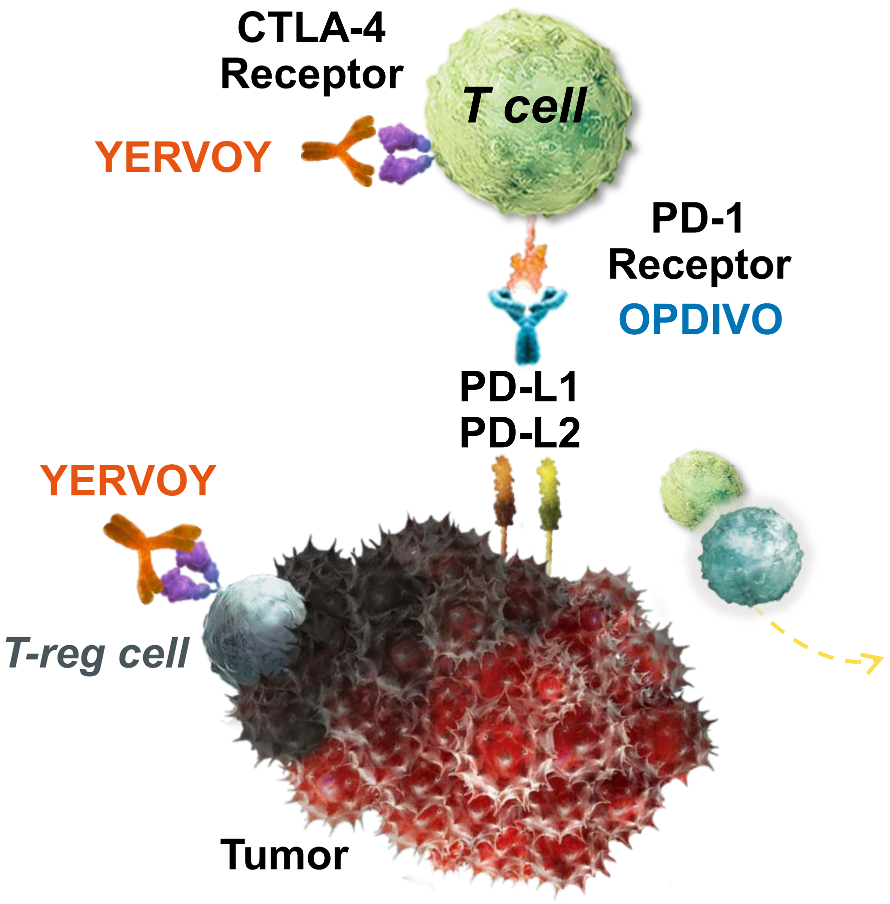
Scientific Rationale for Combining nivolumab (anti-PD-1) and ipilimumab (anti-CTLA4)

Complementary MoAs that work together to maximize anti-tumor immunologic responses

YERVOY (ipilimumab)
Injection for intravenous infusion

YERVOY blocks CTLA-4 to:

- **Help stimulate T-cell activation and proliferation**
- **Deplete T-reg cells and reverse immune-suppression**
  - **Efficacy of CTLA-4 Ab in mouse tumor models dependent on Fc receptor binding Ab isotype**



OPDIVO (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

OPDIVO blocks PD-1 to:

- **Help stimulate T-cell activation and proliferation**
- **Reactivate quiescent T-cells within the tumor**

Memory T cell

Some activated T cells become memory cells that can support subsequent immune responses by recognizing the tumor antigen

Selby, M. *et al*., Cancer Imm Res 2013

Bristol-Myers Squibb

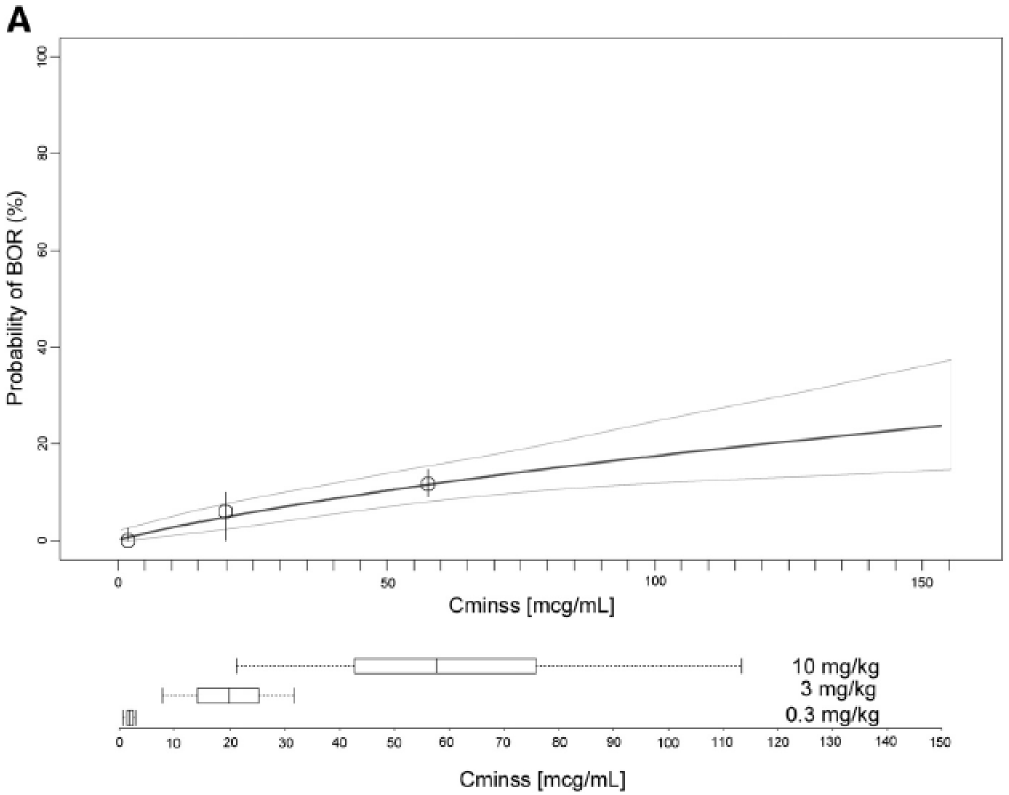
Background

- Ipilimumab monotherapy 3 mg/kg Q3W (4 doses) monotherapy is approved for the treatment of advanced melanoma
- Nivolumab monotherapy is approved for several indications, including advanced melanoma, RCC, and NSCLC
  - Initial approval in the US was for 3 mg/kg Q2W*
- The IPI+NIVO combination doses for advanced melanoma, RCC, and NSCLC were selected based on data from 3 Ph1 studies
- Safety and efficacy first evaluated in a Phase 1b study (CA209-004)
  - Ipilimumab, 3mg/kg Q3wk x 4 (approved dose/schedule)
    - Ipi was core component of regimen
    - Various Nivo doses added to Ipi core

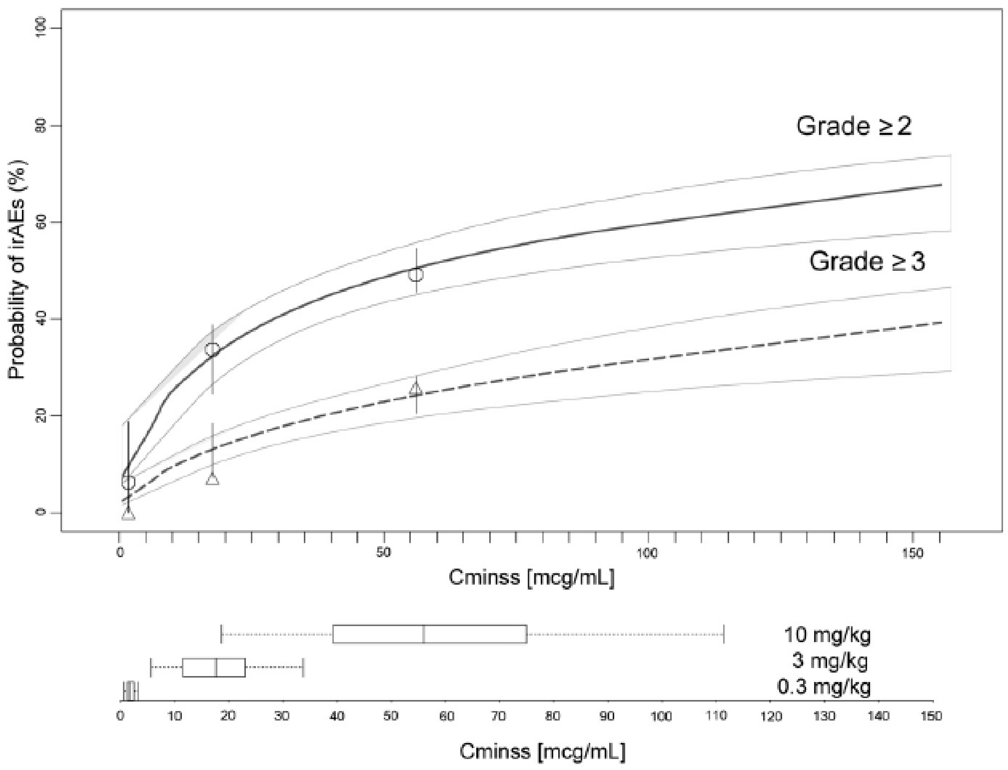
* Subsequently changed to 240 mg Q2W

Ipilimumab Exposure-Response of Efficacy and Safety: Advanced Melanoma

Probability of Objective Tumor Response* vs Cminss



Probability of Immune-Related AEs vs Cminss



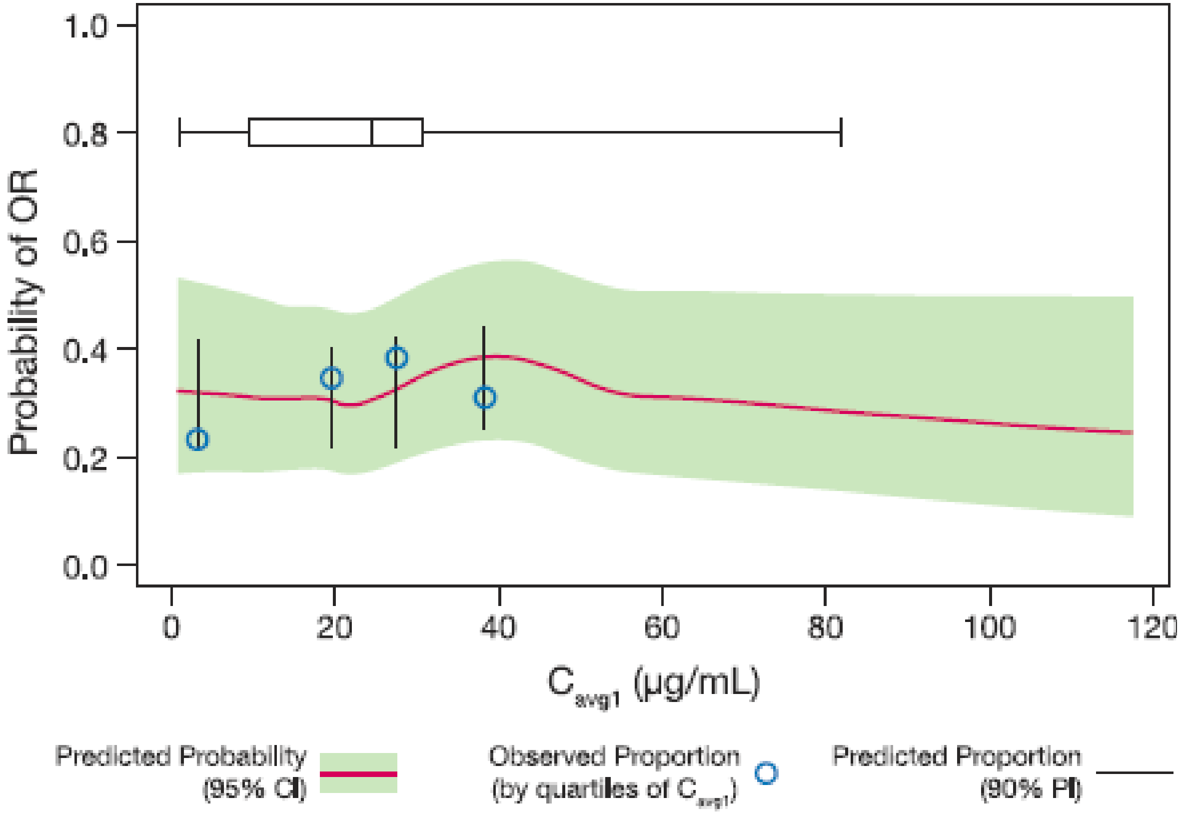
*BOR: Best Overall Response of CR or PR by modified WHO Criteria

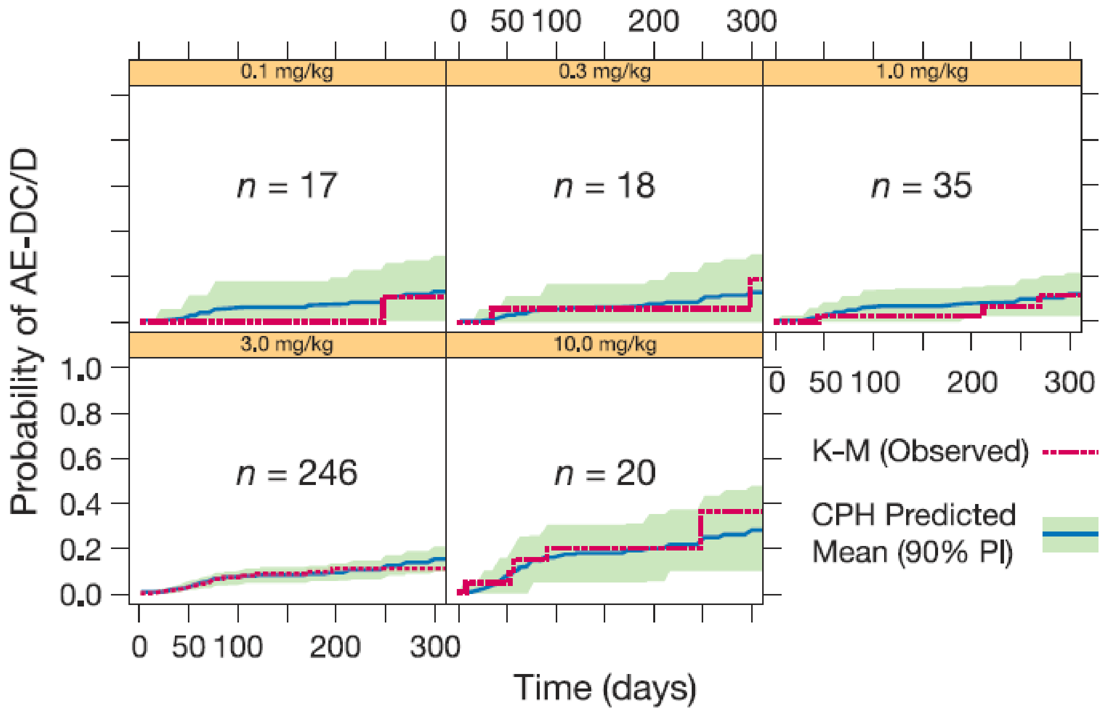
Probability of tumor response and risk of safety events increase with increasing ipilimumab dose and exposure

Feng Y et al, CCR, 2015

Bristol-Myers Squibb

Nivolumab Exposure-Response of Efficacy and Safety: Advanced Melanoma



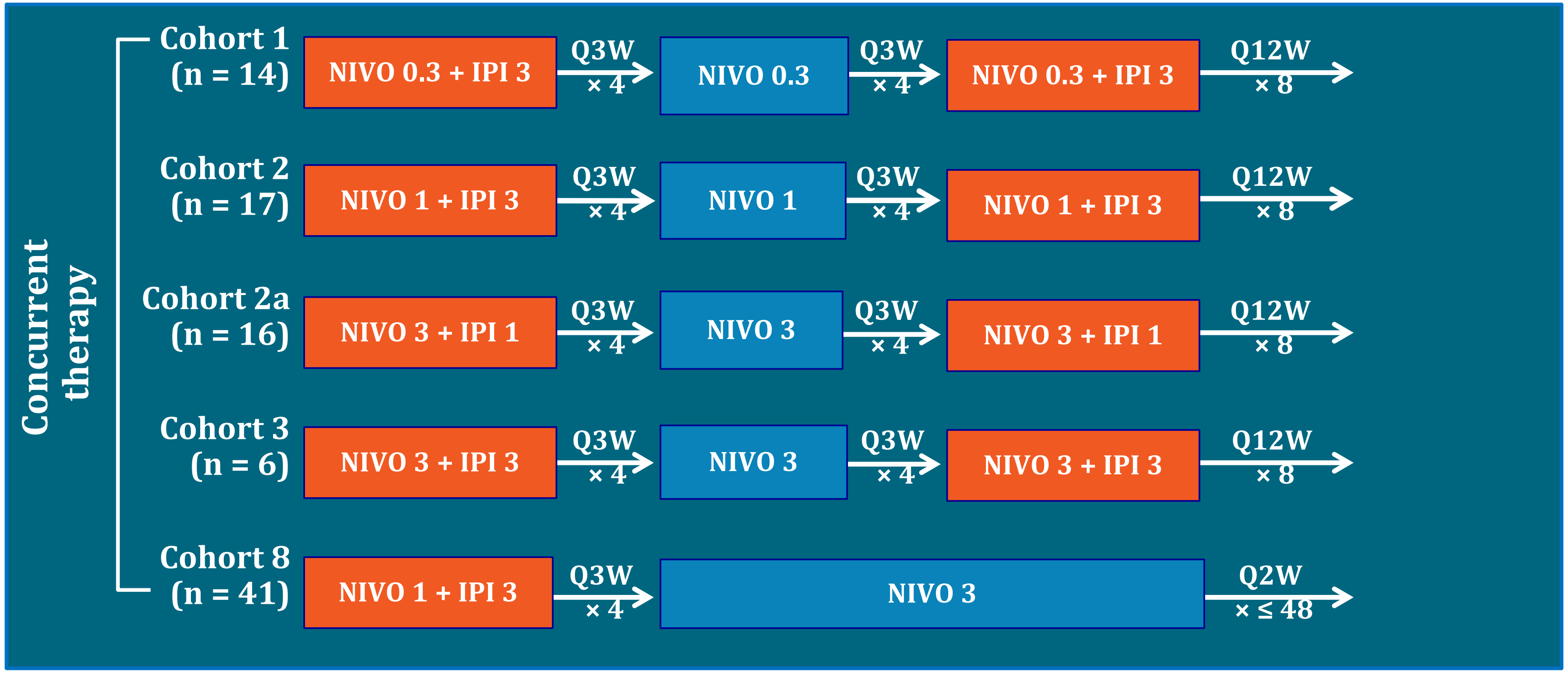


Nivolimab E-R of tumor response and safety is relatively flat in melanoma
Nivolumab 3 mg/kg Q2W was investigated in pivotal studies in advanced melanoma

Wang X et al, CPT:PSP, 2016
Agrawal S, FDA-AACR Oncology Dose Finding Workshop, 2016

Bristol-Myers Squibb

Design of Ph1b Study of NIVO + IPI in Advanced Melanoma (CA209-004)



- ***Dose escalation cohorts (1,2, and 3) enrolled sequentially (3+3 design), and evaluated increasing doses of NIVO***
- ***Cohort 2a (reduced dose of IPI) added after Cohort 3 was determined to exceed MTD***
- ***Cohort 8 added as an expansion Cohort with NIVO monotherapy in maintenance period***

All dose units are mg/kg.
IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks; Q3W, every 3 weeks; Q12W, every 12 weeks.

1. Adapted from Kluger HM, et al. Presented at SMR 2014.
2. Wolchok JD, et al. *N Engl J Med* 2013;369:122-133.
3. Feltquate D, FDA-AACR Workshop: I-O Development

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Selected Efficacy and Safety Data for N1/I3 and N3/I1 Cohorts in CA209-004

Safety	N1/I3 (Cohort 2) (n=17)		N3/I1 (Cohort 2a) (n=16)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	100	65	81	44
Treatment-related AEs leading to discontinuation, %	24		19	

Efficacy	N1/I3 (Cohort 2) (n=17)	N3/I1 (Cohort 2a) (n=16)
ORR	47	50

- ***Tumor response and safety was similar for N1/I3 and N3/I1, but sample size is relatively small***
- ***N1I3 was selected for further evaluation, given the understanding of monotherapy dose/exposure-response***

1. Wolchok et al. *N Engl J Med* 2013;369:122-133.
2. Larkin et al. *N Engl J Med* 2015;373:23-34.
3. Kluger et al. Presented at SMR 2014. Adapted from Postow M, et al. Presented at Melanoma Bridge 2015
4. Feltquate, Presented at FDA-AACR I-O Development Workshop, October 2016

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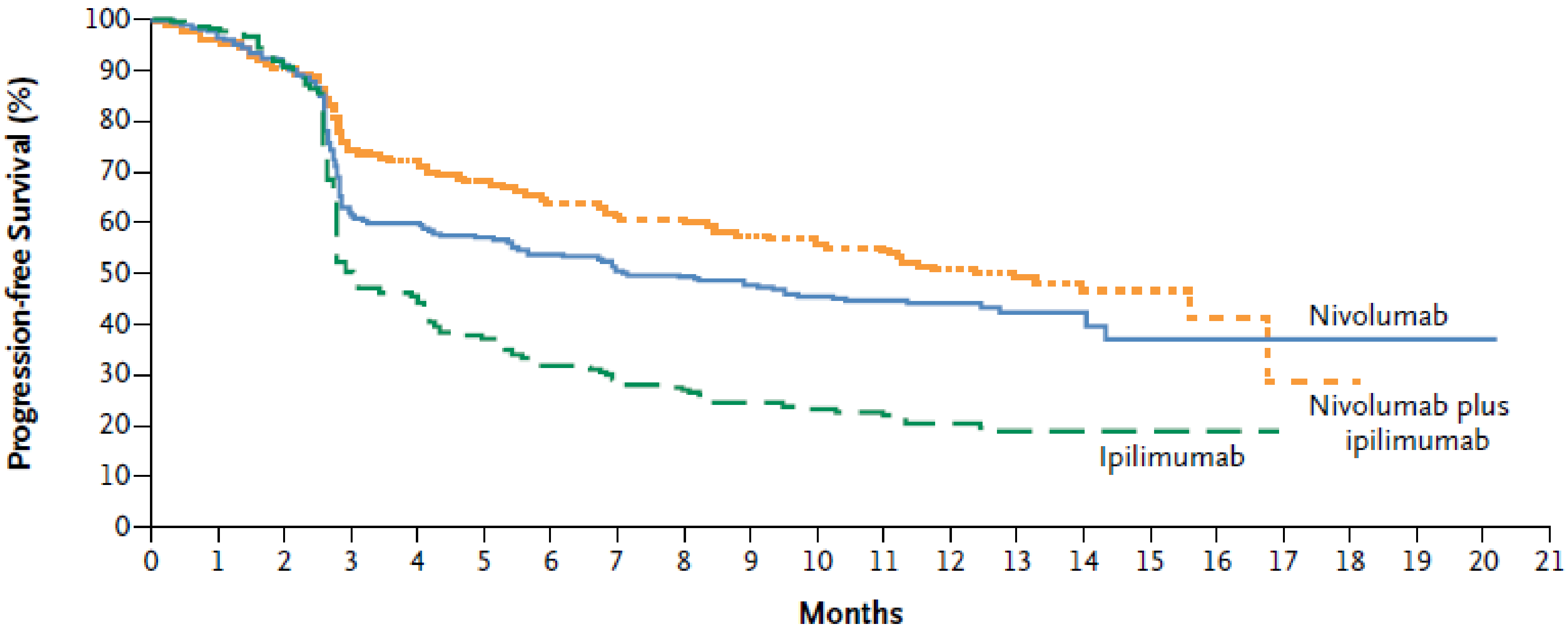
PFS in Ph3 Study of IPI+NIVO, IPI, and NIVO (CA209-067)

A **Intention-to-Treat Population**



No. at Risk

Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

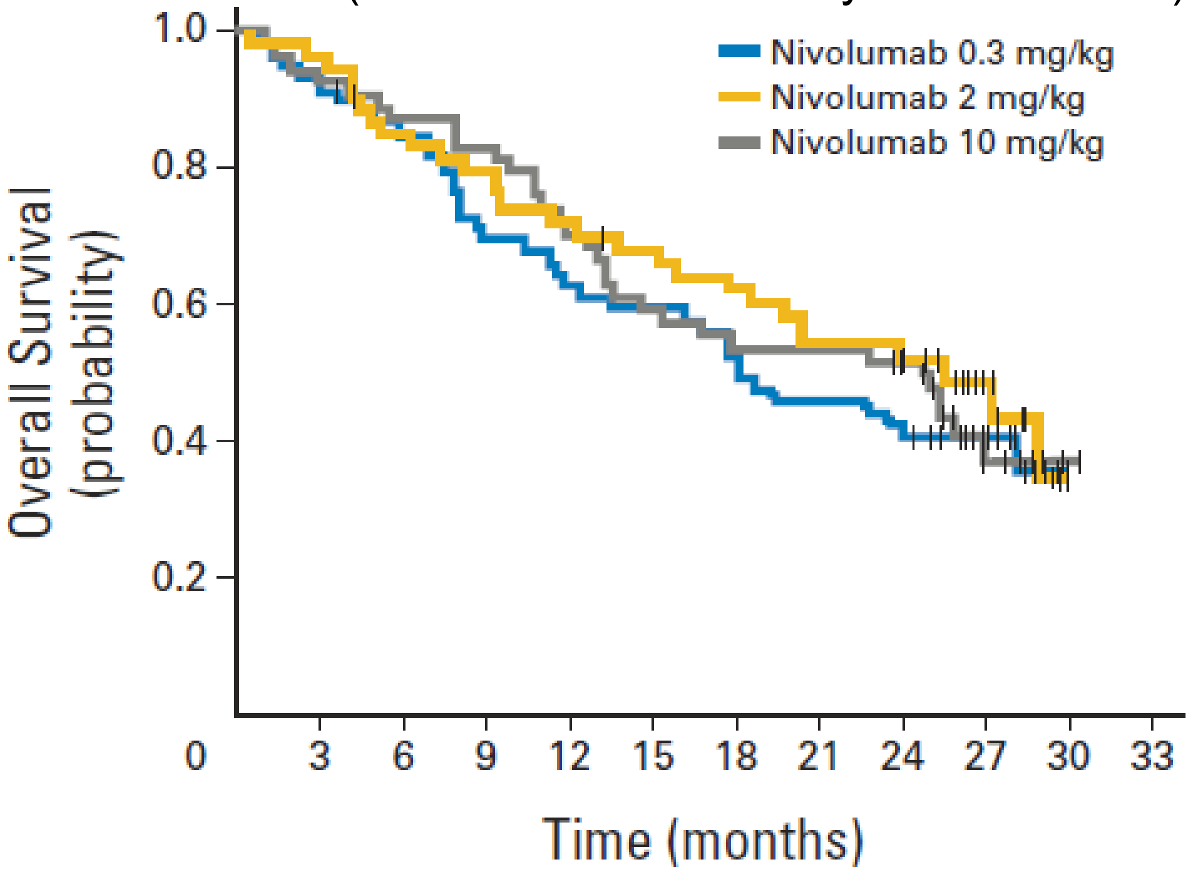
N1I3 had longer PFS than N3 or I3

Larkin, J et al., NEJM (2015)

Bristol-Myers Squibb

Nivolumab Monotherapy Dose-Response in 2L RCC

Kaplan-Meier of OS, Dose Level
(Randomized Ph2 Study of NIVO Q3W)

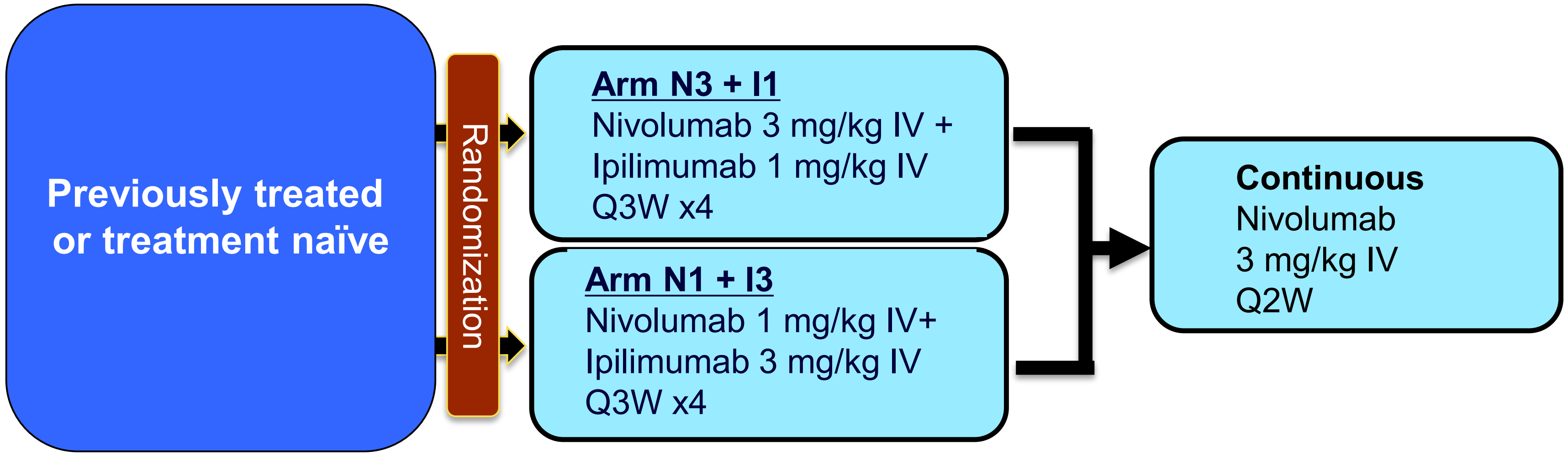


Nivolumab dose-response is flat over a wide range of doses
Nivolumab 3 mg/kg Q2W was investigated in pivotal studies in RCC

Motzer RJ, et al. (2015). Journal of Clinical Oncology, 33(13), 1430-1437.

Bristol-Myers Squibb

Design of Phase Ib Study of NIVO + IPI in Advanced RCC (CA209-016)



Randomized study with robust sample size

Feltquate D, Presented at FDA-AACR I-O Development Workshop, October 2016

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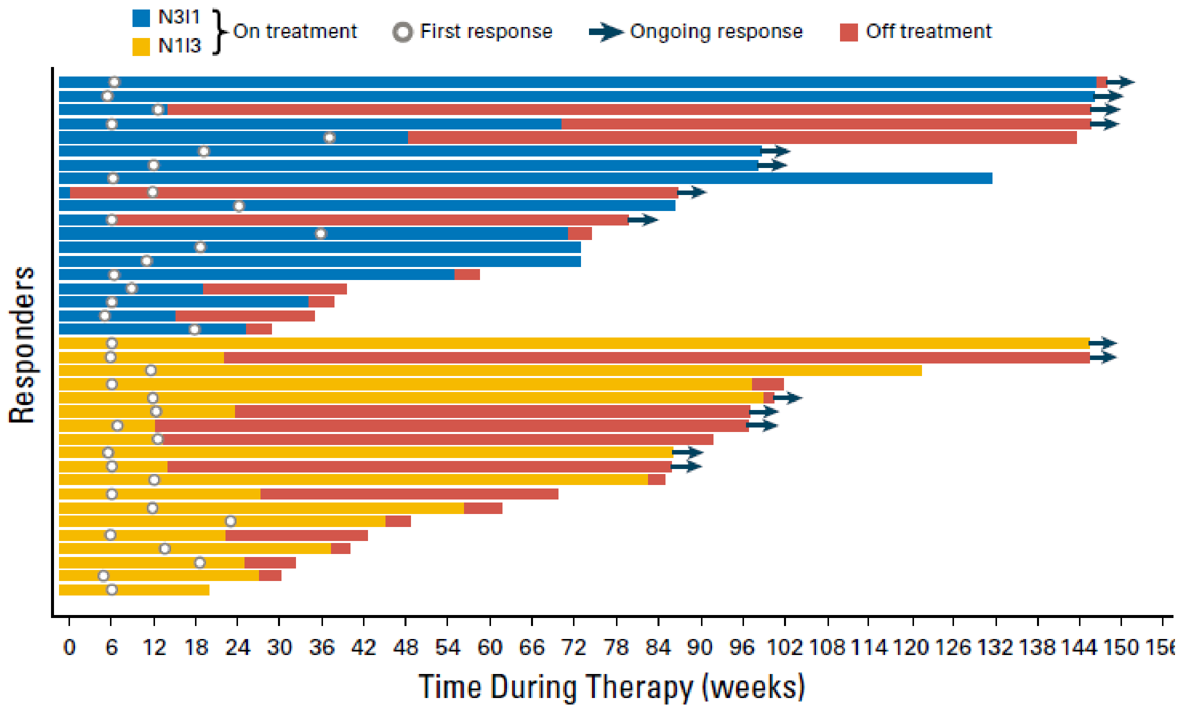
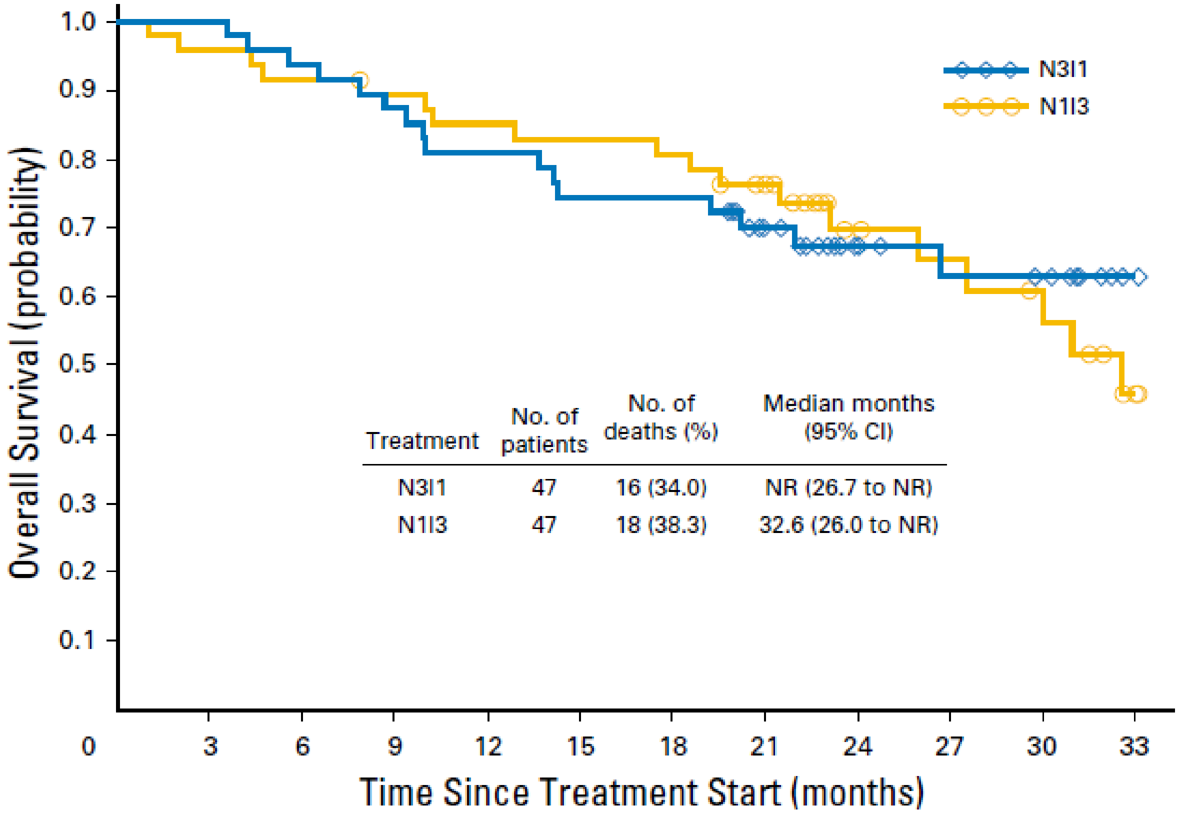
Efficacy for N1/I3 and N3/I1 Cohorts in CA209-016



	Median time to response, weeks (range)	Median duration of response, weeks (95% CI)
N3I1	11.1 (5.3 to 37.1)	88.7 (37.1 to NR)
N1I3	7.0 (5.1 to 23.1)	85.9 (35.1 to NR)



No. at risk												
N3I1	47	47	44	41	38	35	35	27	17	14	13	6
N1I3	47	45	43	41	39	38	37	29	17	15	12	7

Efficacy was similar with N1/I3 and N3/I1

Hammers et al., JCO 2017

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Selected Data for N1/I3 and N3/I1 Cohorts in CA209-016

Safety	N1/I3 (n=47)		N3/I1 (n=47)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	95.7	61.7	91.5	38.3
Treatment-related AEs leading to discontinuation, %	27.7		10.6	

Efficacy	N1/I3 (n=47)	N3/I1 (n=47)
ORR	40.4	40.4

- ***N3/I1 has similar anti-tumor activity but safer profile than N1/I3***
- ***N3/I1 selected to be tested in pivotal study***

Hammers et al,JCO 2017.

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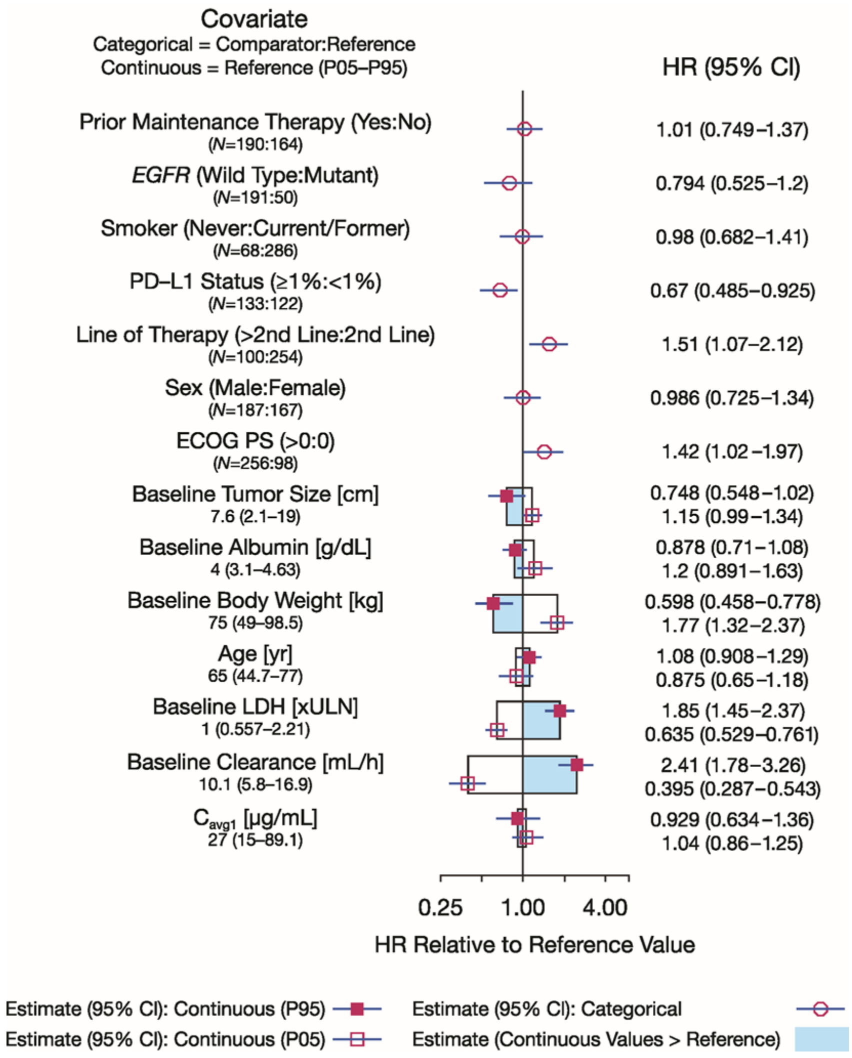
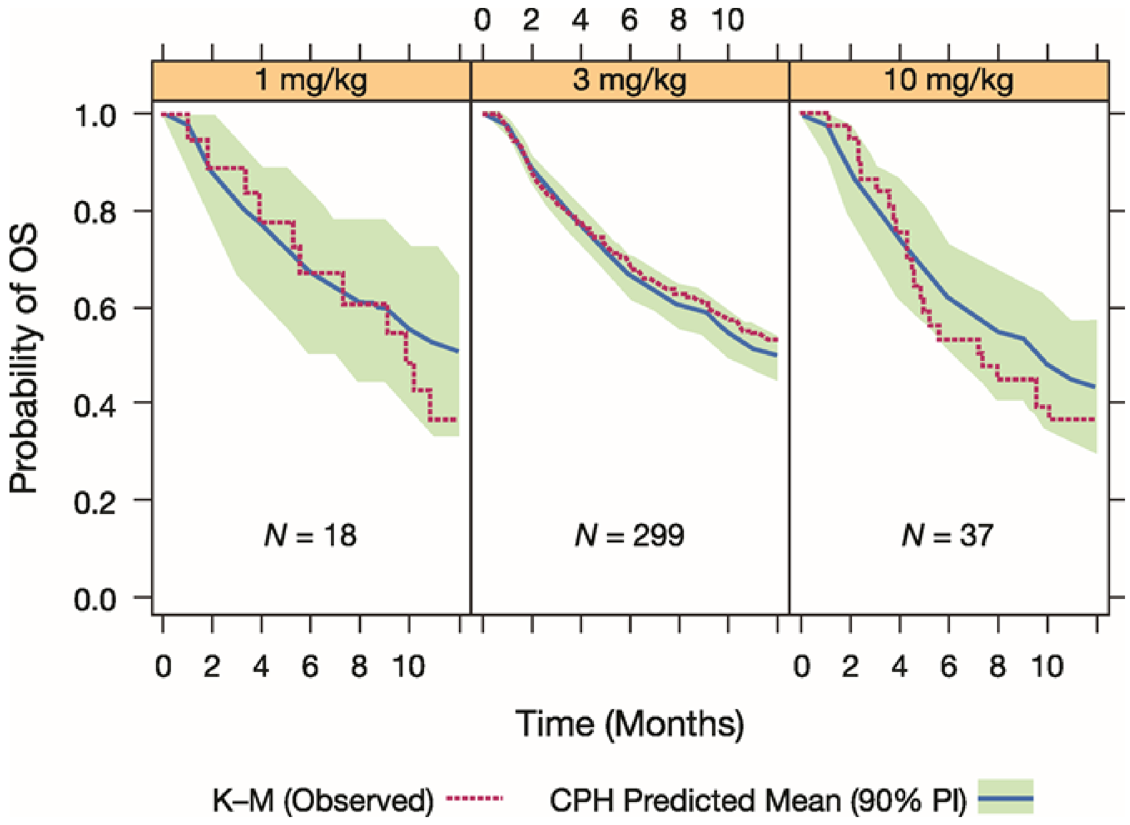
Nivolumab Exposure-Response of OS: NSQ-NSCLC





E-R of OS is relatively flat over a dose range of 1 to 10 mg/kg Q2W
Nivolumab 3 mg/kg Q2W was investigated in NSCLC pivotal studies

Feng Y, ASCPT, 2016 (Accepted for publication in CCR)

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Initial Ipi/Nivo cohorts for NSCLC evaluated in a Phase 1b Study (CA209-012)

Stage IIIB/IV NSCLC (any histology); no prior chemotherapy for advanced disease; ECOG PS 0 or 1

Squamous	Non-squamous	Squamous	Non-squamous
Nivo 1 mg/kg IV Q3W + Ipi 3 mg/kg IV Q3W (four 21-day cycles)	Nivo 1 mg/kg IV Q3W + Ipi 3 mg/kg IV Q3W (four 21-day cycles)	Nivo 3 mg/kg IV Q3W + Ipi 1 mg/kg IV Q3W (four 21-day cycles)	Nivo 3 mg/kg IV Q3W + Ipi 1 mg/kg IV Q3W (four 21-day cycles)

Nivo 3 mg/kg IV Q2W
until PD or unacceptable toxicity[a]

Primary endpoints: safety and tolerability
Secondary endpoints: ORR (RECIST v1.1)[b] and PFS rate at 24 wks
Exploratory endpoints: OS; efficacy by PD-L1 expression

Feltquate D, Presented at FDA-AACR I-O Development Workshop, October 2016

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Selected Data for Initial I/N and N Cohorts from Phase 1b NSCLC Study

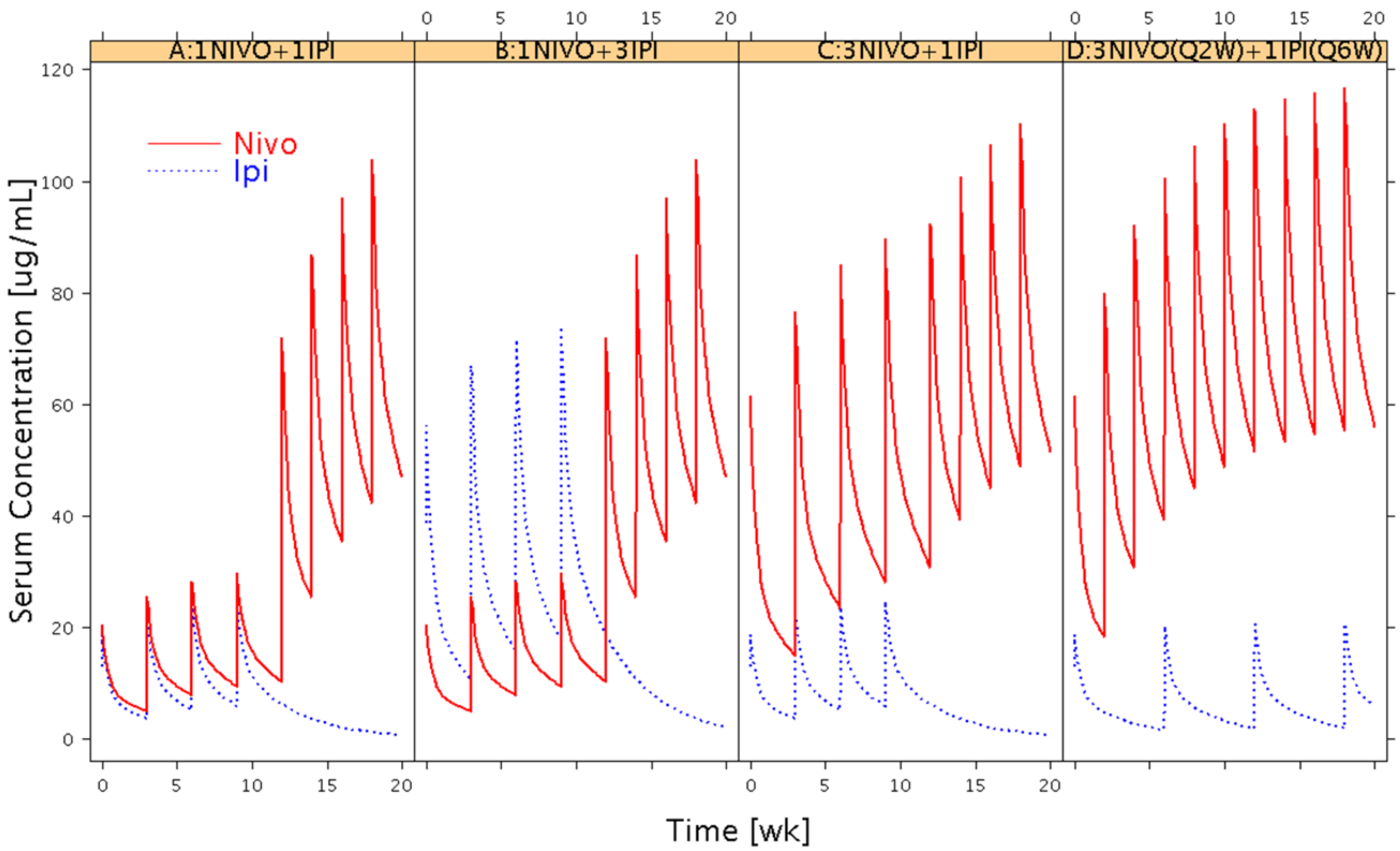
Safety	N1/I3 (n=24)		N3/I1 (n=25)		N3 (n=52)		N1/I1 (n=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AEs, %	92	58	84	49	71	19	52	15
Treatment-related AEs leading to discontinuation (DC), %	38		32		10		6	

Efficacy	N1/I3 (n=24)	N3/I1 (n=25)	N3 (n=52)	N1/I1 (n=31)
ORR, %	13	20	23	16

- *Majority of AEs leading to DC occurred after 1 or 2 treatments*
- *Lower anti-tumor activity than Nivo mono possibly due to early discontinuation*
- *Additional cohort of N1/I1 added later*

Feltquate D, Presented at FDA-AACR I-O Development Workshop, October 2016

NIVO and IPI Concentration-Time Profiles: Alternative Combination Regimens



Less frequent IPI dosing may alleviate toxicity

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2nd Generation Ipi/Nivo Combo is much more tolerable with greater clinical activity than the original schedule

	Nivo 3 Q2W + Ipi 1 Q12W (n=38)		Nivo 3 Q2W + Ipi 1 Q6W (n=39)		Nivo 3 Q2W (n=52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	82	37	72	33	71	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10

	Nivo 3 Q2W + Ipi 1 Q12W (n=38)	Nivo 3 Q2W + Ipi 1 Q6W (n=39)	Nivo 3 Q2W (n=52)
All-Comers, ORR, %	47	39	23
PD-L1+ (>1%), ORR, %	57	57	28

[a]Antonia SJ, et al. Presentation at CMSTO 2014; Adapted from Hellmann MD, et al. Presentation at ASCO. 2016_3001

Feltquate D, Presented at FDA-AACR I-O Development Workshop, October 2016

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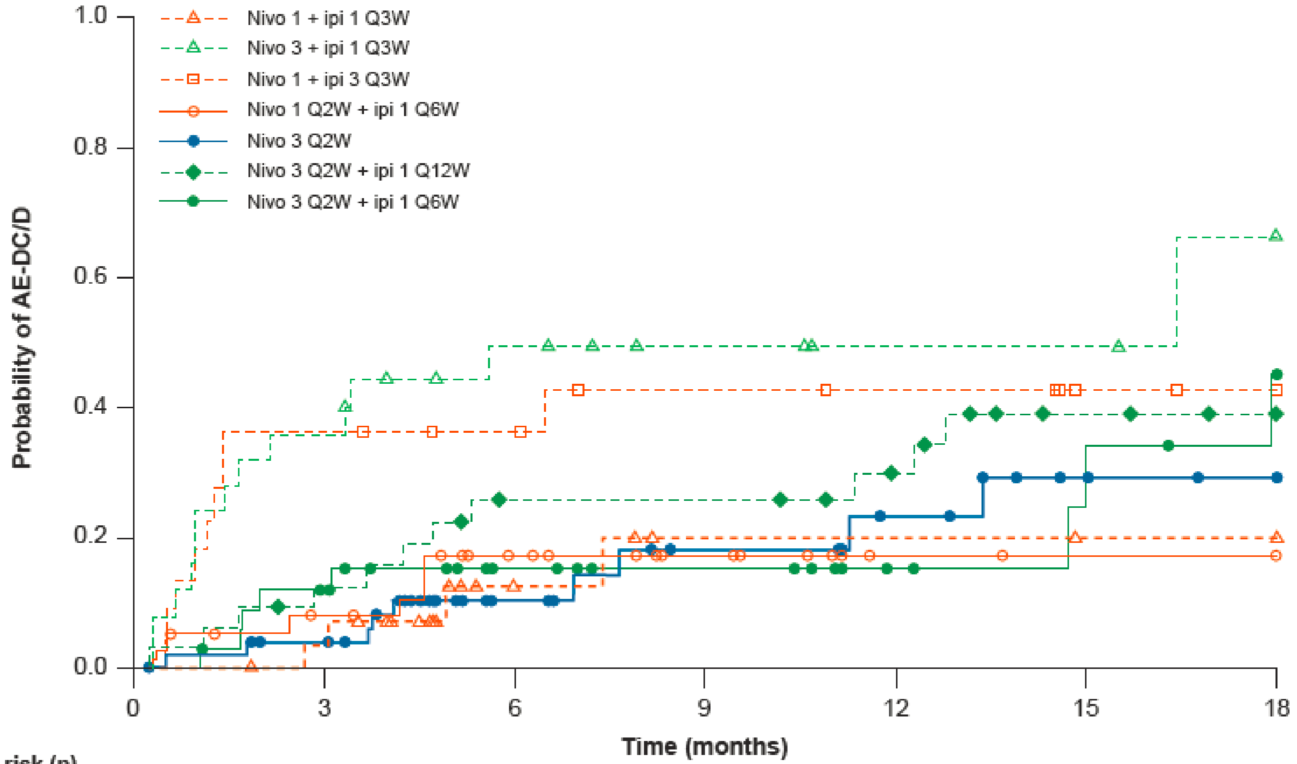
Dose-Response of Safety* in CA209-012 (Selected Cohorts)



Patients at risk (n)

Nivo 1 + ipi 1 Q3W	29	27	12	9	9	8	8
Nivo 3 + ipi 1 Q3W	25	16	10	6	4	4	2
Nivo 1 + ipi 3 Q3W	22	14	11	8	7	4	3
Nivo 1 Q2W + ipi 1 Q6W	38	32	20	14	8	7	7
Nivo 3 Q2W	52	47	28	19	14	9	7
Nivo 3 Q2W + ipi 1 Q12W	32	27	20	20	16	10	8
Nivo 3 Q2W + ipi 1 Q6W	34	28	18	15	10	7	5

* AE-DC/D: Adverse events leading to discontinuation or death

Zhao X et al. ASCPT 2017

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Summary and Conclusions

- Combinations of IO-IO agents such as Ipi/Nivo are feasible to administer
- Evaluation of different dose/schedules of IO-IO combinations benefit from larger sample sizes and randomized evaluation
- Systematic evaluation of dose/schedule for IO-IO combinations by tumor type may be needed as optimal/maximal effects may vary by tumor type
- Model-based analyses can inform which doses/schedules should be tested

Acknowledgements

- David Feltquate
- BMS Oncology Drug Development Teams
- Investigators
- BMS Clinical Pharmacology & Pharmacometrics Group

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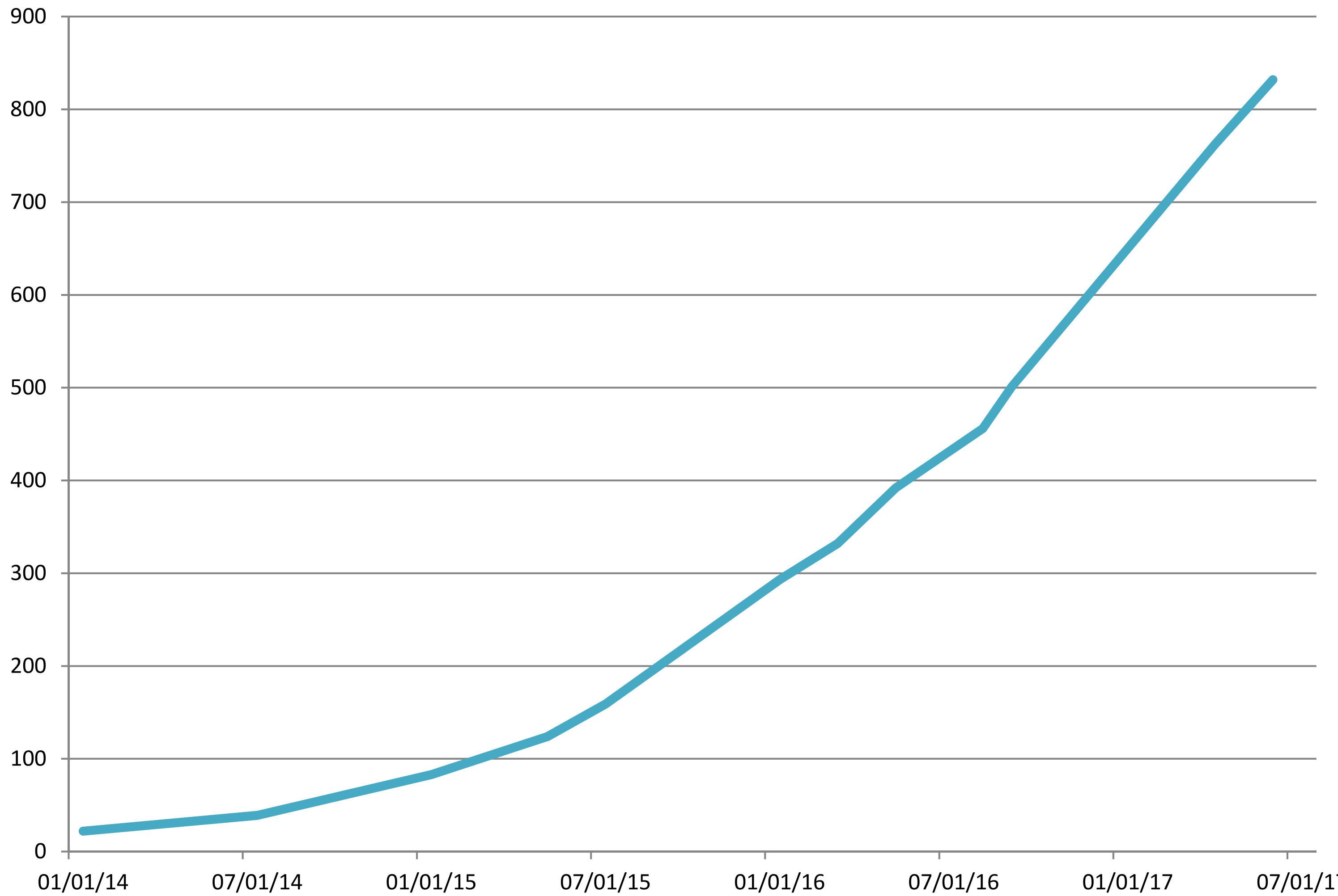
Approaches to Dose-Finding for Combinations with Immuno-Oncology Agents

Eric H. Rubin, M.D.

Merck Research Laboratories

Large Number of Combination Studies of PD-1/PD-L1 Antibodies



Considerations for Dose Selection in Combinations

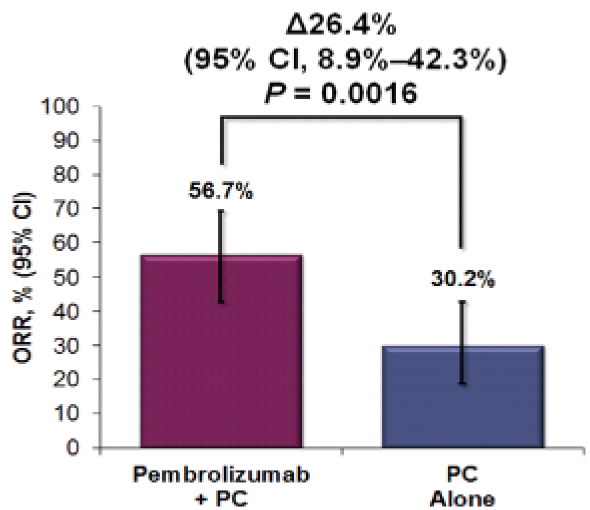
- Many possible variables to alter
  - Dose for drug A
  - Dose for drug B
  - Schedule for drug A
  - Schedule for drug B
    - Mismatched schedules (e.g. Q2W and Q3W) create inconvenience for patients
- Even if select only 2 doses and 2 schedules for each drug, there are 16 possible cohorts to investigate
  - With a minimum of 3-6 patients per cohort = possibly at least 48 patients, depending on occurrence of DLTs
  - With a typical 1 month DLT assessment time, at least 16 months to identify a preliminary RPTD, again depending on occurrence of DLTs
- Simple approaches involve “fixing” dose and schedule of one of the drugs

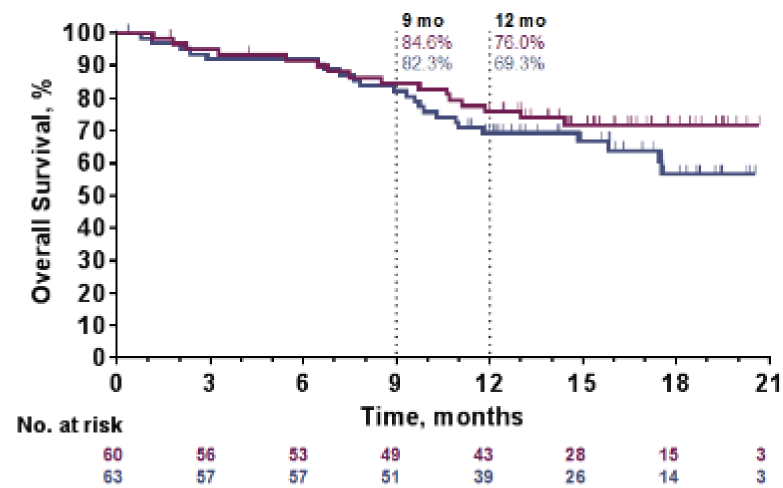
Approach to Determination of Dose for a Drug Combined with Pembrolizumab

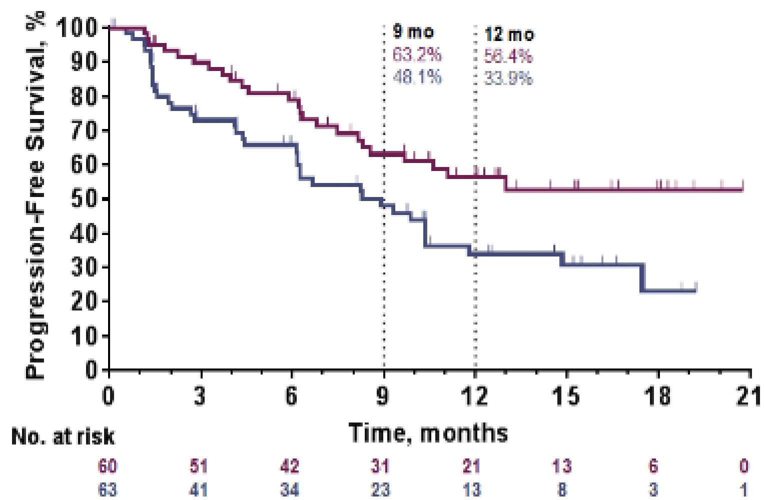
- Pembrolizumab dose fixed at 200 mg Q3W
- Current results indicate that many, but not all combinations are tolerable with the recommended monotherapy dose for the combination agent

Keynote 21G - Example of Chemotherapy Combination with Pembrolizumab

Pembro dose 200 mg, standard doses of pem and carbo – established as tolerable in cohort C of Keynote 21







- Combination approved based on significant improvement in ORR and PFS
- Trend toward OS benefit emerging despite a high rate of crossover (75%)

Variations in Approach to Determination of Combination Doses

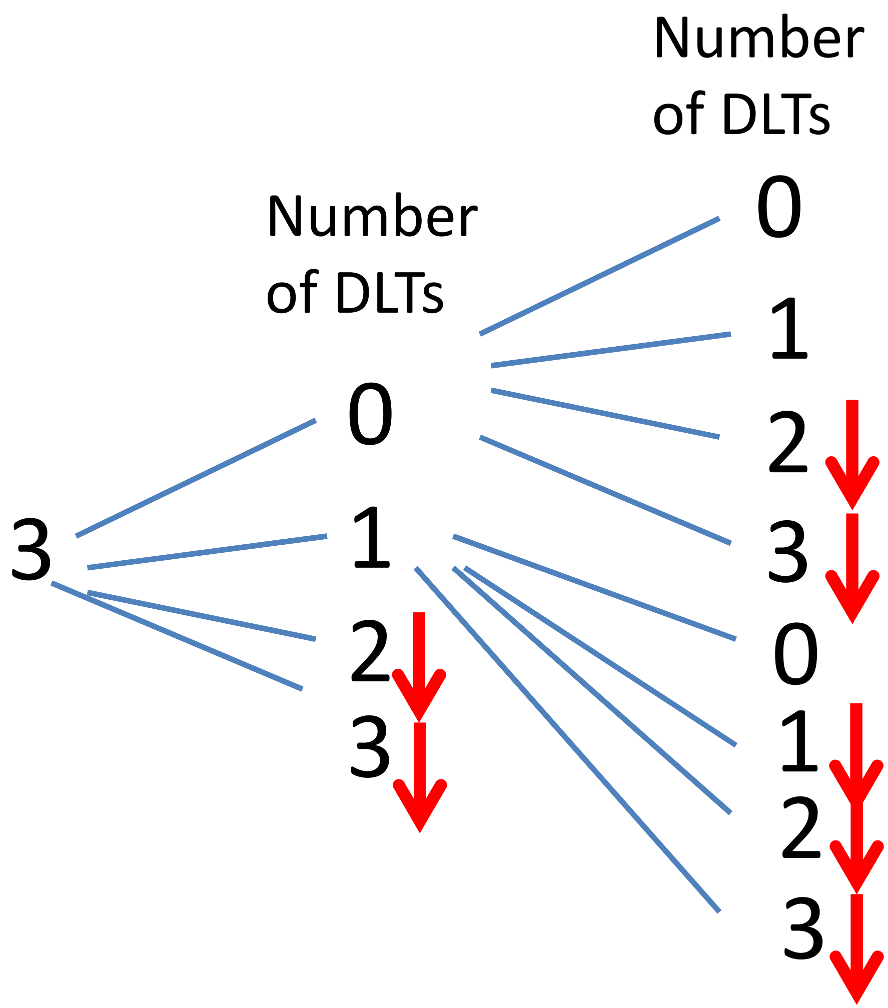
- Company A – small molecule A
  - No MTD identified yet with monotherapy administration of Drug A
  - 3+3 up and down DLT approach, “standard” DLT criteria
  - Starting dose of molecule A based on clinical safety and pharmacodynamic data, RPTD for monotherapy Drug A not yet identified
  - Maximum administered dose specified in case no MTD
    - Rationale for selection of maximum administered dose not provided
  - “The RP2D will be based on all available data including DLT data and an assessment of X-inducible genes and safety and tolerability data”
  - “The sponsor may also choose to investigate lower dose level(s) and enroll 3 or more additional patients prior to Phase 2 “
- This approach has the usual risk of selection of a non-tolerable RPTD based on the small numbers 3+3 approach

Risk of 3+3 in Combination Dose Finding

- Development of drug A was based on an MTD approach and the monotherapy RPTD has a 25% DLT rate - using the 3 + 3 approach, what is the chance of selecting a dose lower than the monotherapy RPTD in combination with drug B simply due to DLTs arising from drug A?

  A. 20%
  B. 50%
  C. 80%

3 + 3 Algorithm



10 possible outcomes

7 result in selecting a lower dose

With underlying DLT rate of 25% for drug A, probability of selecting a lower dose for drug A in combination based on that rate alone is 53%

Variations in Approach to Determination of Combination Doses - 2

- Company B – small molecule B
  - No MTD identified with monotherapy administration of Drug B
  - 6+6 up and down approach, “standard” DLT criteria
  - Starting dose of molecule B based on RPTD of monotherapy Drug B
    - One dose level -1 specified in case recommended monotherapy dose not tolerated in combination with pembro
    - No dose escalation

- Better than 3+3 but still risk in selecting a non-tolerable RPTD based on 6 patients

Preferred Approach to Determination of Combination Doses

- Company C – monoclonal antibody Drug C
  - No MTD identified yet with monotherapy administration of Drug C
  - "A Toxicity Probability Interval design with a target DLT rate of 30% will be applied to identify an MTD of Drug C in combination with pembrolizumab"
  - "standard" DLT criteria
  - Starting dose based on preclinical data and preceding monotherapy cohort data
  - Maximum administered dose specified in case no MTD
    - Rationale for selection of maximum administered dose not provided
  - "The totality of the data will be considered before deciding on the dose(s) to carry forward to Part B and the escalation schedule may be adjusted based on pharmacodynamics (PD), PK, and safety data emerging throughout the study. "

Table 1 Dose Escalation and Confirmation Rules Based on the Modified Toxicity Probability Interval Design

	Number of Subjects Treated at Current Dose											
Number of Toxicities	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
7					DU	DU	DU	DU	DU	DU	DU	D
8						DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU
10								DU	DU	DU	DU	DU
11									DU	DU	DU	DU
12										DU	DU	DU
13											DU	DU
14												DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate ⤡ 30%
Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.05{03TFYL}, {03RRDF}, {03FL3C}

Yuan Ji, Ping Liu, Yisheng Li and B. Nebiyou Bekele
A modified toxicity probability interval method for dose-finding trials
Clin Trials, October 2010

Advantages of Use of TPI

- DLT probability rate can be adjusted based on expected rates for each drug administered as monotherapy, but is generally below 35%
  - A Bayesian calculation is used to derive rules for dose decisions, which are pre-specified
  - 3+3 ignores dosage history other than previous cohort, does not allow re-escalation, and MTD is not a dose with any particular probability of DLT

- Typical TPI approach: dose-finding stops once 14 patients are enrolled at a given dose that meets or is below the targeted DLT rate

DLT Criteria in Combination Studies

- Combination of Drug A with an approved dose + an experimental agent Drug B
- What about severe toxicities that are attributed to Drug A?
  - "After all, every drug has side effects and sometimes they are severe"
  - Should these NOT be counted as DLTs?
    - Could affect dose-finding if a patient uniquely susceptible to severe toxicity from Drug A is enrolled by chance

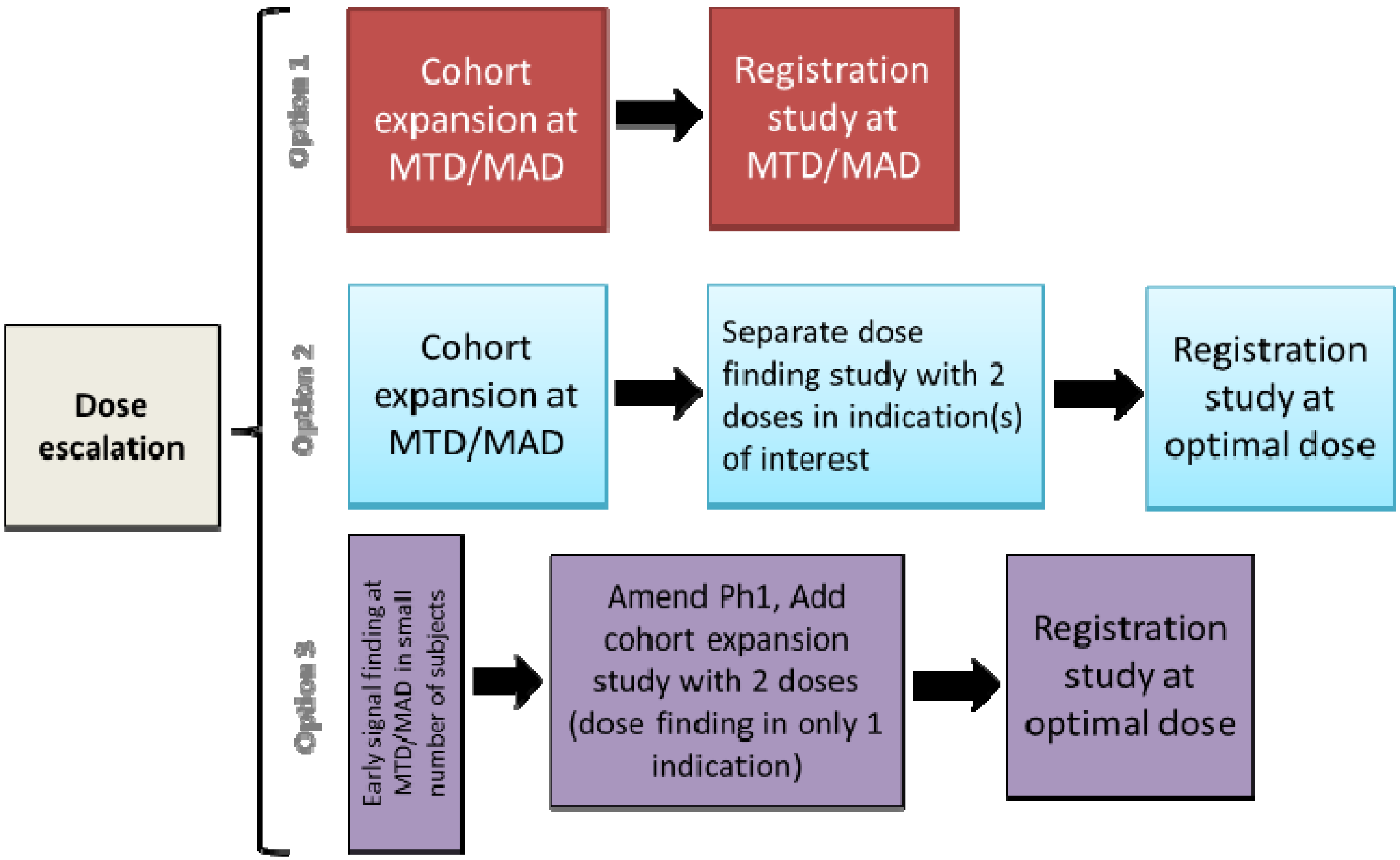
DLT Criteria in Combination Studies

- What about severe toxicities that are attributed to Drug A?
  - On the other hand, other than an infusion reaction that occurs immediately after Drug A, can we really be sure that an observed DLT originates only from Drug A?
  - NO! Toxicities that are well-known for Drug A may still be enhanced (more frequent and/or severe) with co-administration of Drug B

DLT Criteria in Combination Studies

- What about severe toxicities that are attributed to Drug A?
  - This is another reason to avoid small numbers and the 3+3 approach
  - Adaptive approaches such as Toxicity Probability Interval can account for “chance” enrollment of susceptible patients and provide greater confidence that the identified RPTD for the combination is tolerable

Trial Design Approach to Determination of Combination Doses*



*Dose is fixed for one drug

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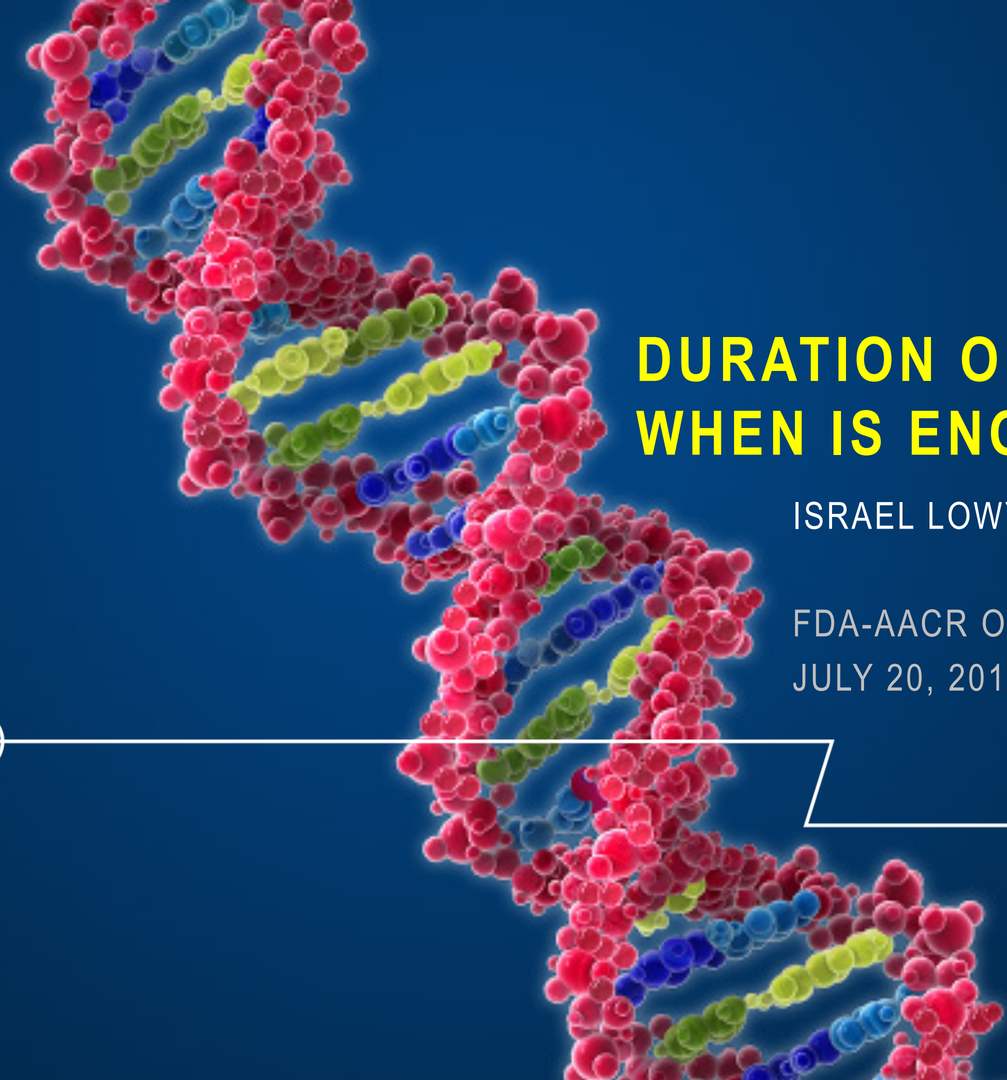


REGENERON

SCIENCE TO MEDICINE®

DURATION OF ANTI-PD-1 TREATMENT: WHEN IS ENOUGH, ENOUGH?

ISRAEL LOWY, MD PhD; REGENERON PHARMACEUTICALS

FDA-AACR ONCOLOGY DOSE FINDING WORKSHOP
JULY 20, 2017 WASHINGTON, DC

Disclaimer:
The views expressed in this presentation are those of the speaker, and do not necessarily represent an official position of Regeneron Pharmaceuticals

GOAL: PROMOTE DISCUSSION OF OPTIMAL DURATION OF TREATMENT IN THE AGE OF (REASONABLY) WELL TOLERATED IMMUNOTHERAPY

- How did we arrive at typical dosing plan for PD-1/PD-L1 blockade: to progression or up to 24 months
  - Establishment of current effective doses and durations of therapy in immunotherapy: development has been less than perfectly systematic
  - IL-2, ipilimumab (anti-CTLA-4), PD-1/PD-L1 blockade – monotherapy and in combinations
  - Balancing empiricism and scientific rationale with pressures to speed to market
- What would optimization mean?
  - What is an acceptable operational definition?
  - Does optimization matter?
- How to define biological criteria to support optimization?

MOVING FROM THE CLASSIC (CHEMO/RADIATION) TREATMENT PARADIGM IN ONCOLOGY TO AN IMMUNE THERAPEUTIC PERSPECTIVE

- Kill proliferating tumor cells with cytotoxic agents for as long as patient tolerates or until progression occurs
  - Leeway for discontinuation of therapy in setting of occasional durable complete responses
  - Reflects rarity of ability to effectively eradicate or induce long term control
- Approach established before immune competence recognized as an important factor in tumor control
  - For therapies that enable the immune system – perhaps treatment could stop after a clinically meaningful response has been elicited and/or stabilized
  - Even classic therapies rely upon a competent anti-tumor immune system for full activity – radiation and chemotherapy
- Analogy to requirements for treatment success in infectious diseases – it’s the host too, not just the bug/tumor
  - Defined courses of treatment with anti-microbials rarely eradicate organisms, but reduce burden so that immune system can contain the pathogens (e.g. pulmonary MTb in immunocompetent host; strep throat and PCN)
  - Immunosuppressed patients typically require higher, more intense dosing that can be open ended (or at least suppressive/prophylactic) therapy because there is no effective immune response to contain the organism
- Given the ability to augment anti-tumor immune competence of patients with current therapies, a consideration of defined courses rather than open-ended is appropriate, and may be in best interest of patients

A BRIEF COURSE OF IMMUNOTHERAPY CAN RESULT IN DURABLE OS - …ALTHOUGH THE BREVITY OF DOSING WAS ALSO DRIVEN BY TOLERABILITY

HIGH-DOSE IL-2 TREATMENT OF METASTATIC MELANOMA 2111

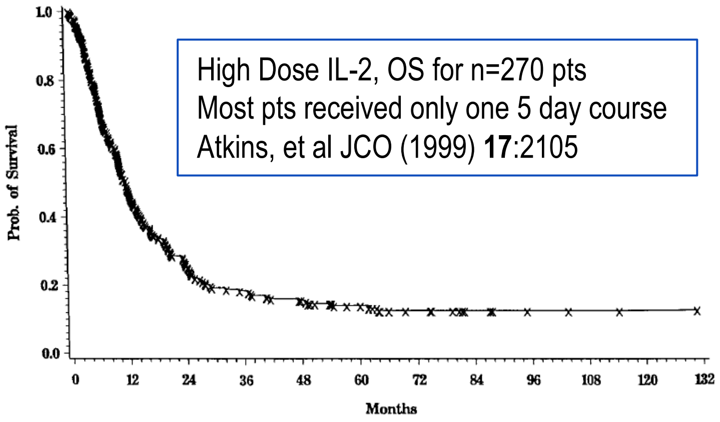


Fig 2. Kaplan-Meier plot of survival for the whole study population (270 patients).

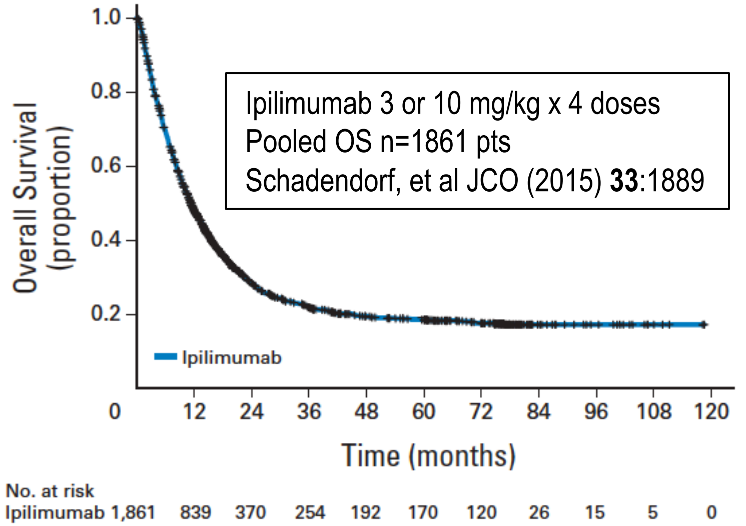


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

HISTORY OF CURRENT DOSING PARADIGMS: SOME IPILIMUMAB (MDX-010) EARLY DRUG DEVELOPMENT TRIVIA…

- The original **dose** of 3 mg/kg first tested, and then taken into phase 3 was chosen because the serum level (from preclinical toxicology studies) corresponded to an IC50 for interfering with CTLA-4 binding to CD80/CD86…
- The original **schedule** of q3 weeks x 4 was chosen to correspond with the gp100 vaccination schedule that Steve Rosenberg had established in prior studies
- Formal dose ranging studies (up to 10 mg/kg) were performed only well after the phase 3 was underway, and little to nothing was done to explore dosing intervals or durations…leaving the **nagging question at the time**: *should one have dosed higher and longer?*
- The dose ranging studies did show better ORR with ipi at higher doses (10 mg/kg), but at a cost of higher toxicity, and the long term survival curves do not suggest a markedly better OS outcome
- One approach to duration of dosing was to add q12 week "booster" doses of ipi…this was incorporated in some trial designs but has fallen by the wayside

HISTORY OF CURRENT DOSING PARADIGM – PD-1/PD-L1 BLOCKADE

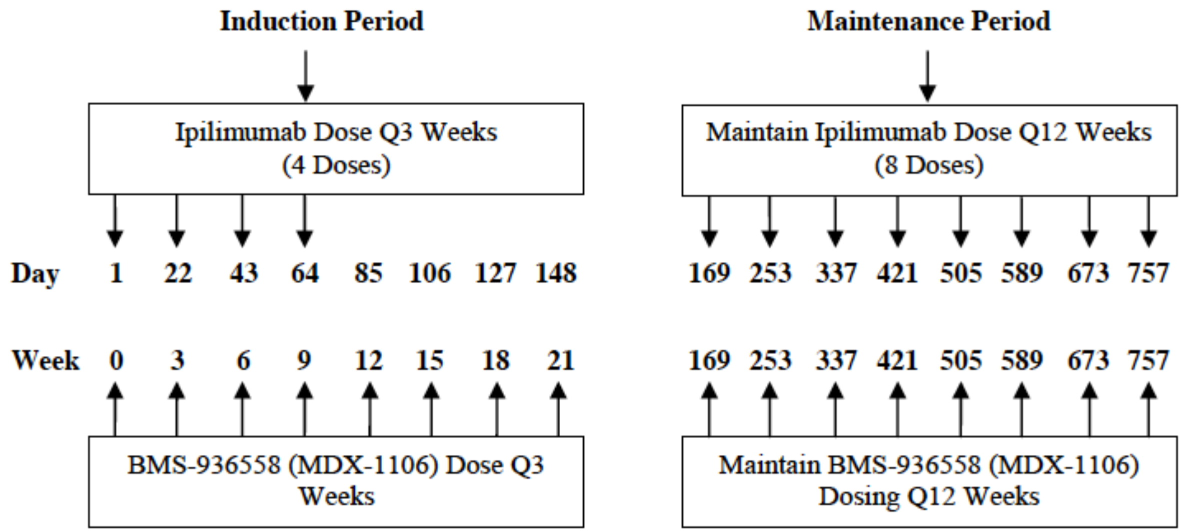
- FIH study of nivolumab [MDX-1106, Brahmer et al (2010) **28**:3167] treated the first patient in 2006, and allowed for up to 3 doses to provide for time for immune response to emerge
- In planning the next, and larger repeat dose studies for both anti-PD-1 (MDX-1106) and anti-PD-L1 (MDX-1105), the decision was made to dose for up to two years:
  - No one would ever wonder if dosing duration was sufficiently tested prior to larger trials
  - The ***plan*** was: based on emergence of time to efficacy, the duration would be rolled back...
  - In fact, this was tried at the outset of the initial combination study of anti-CTLA-4 and anti-PD-1, initiated in 2009
  - The remarkably successful results, along with the relatively mild safety profile seen in the two multi-dose studies led to a stampede into the current IO era, and many studies simply copied the original designs described in:
    - Anti-PD-1: Topalian et al NEJM (2012); **366**: 2443; Anti-PD-L1: Brahmer et al NEJM (2012); **366**:2455
  - As a result – nearly all studies have duration of therapy of up to 2 years or until progression

DUE TO PROMISING EFFICACY, DOSING DURATION OF ANTI-PD-1 (NIVO) WAS SHORTENED WHEN ORIGINALLY COMBINED WITH ANTI-CTLA-4 (IPI)

Anti-PD-1 Monoclonal Antibody
BMS-936558

CA209004 (MDX110604)
Clinical Protocol

Figure 2: Dosing Scheme (Concurrent Regimens: Cohorts 1-5)



Note: At visits where both study drugs will be administered, BMS-936558 (MDX-1106) will be administered first.

- Study initiated in 2009
- Nivo "induction" was originally planned for only 6 months
- More doses were added to the then fashionable q12 week "booster" dose of ipi for 8 more doses – although not really believed necessary
- Subsequent modifications led to the pivotal study design: no booster ipi, reverted to q 2 wk nivo up to 2 years.

Wolchok et al NEJM (2013) **369**:122

PROS AND CONS OF OPEN ENDED TREATMENT (IF TOLERABLE) (CURRENT VARIATIONS: UNTIL PROGRESSION OR ~ 2 YEARS)

PROS:

- ”If it ain’t broke, don’t fix it”
- Physician/Patient anxiety: “I am doing great, why stop?”
- Durability of responses after discontinuation not established in prospective studies
  - Is it clear when one could stop?
  - No randomized discontinuation trials to date to guide therapy

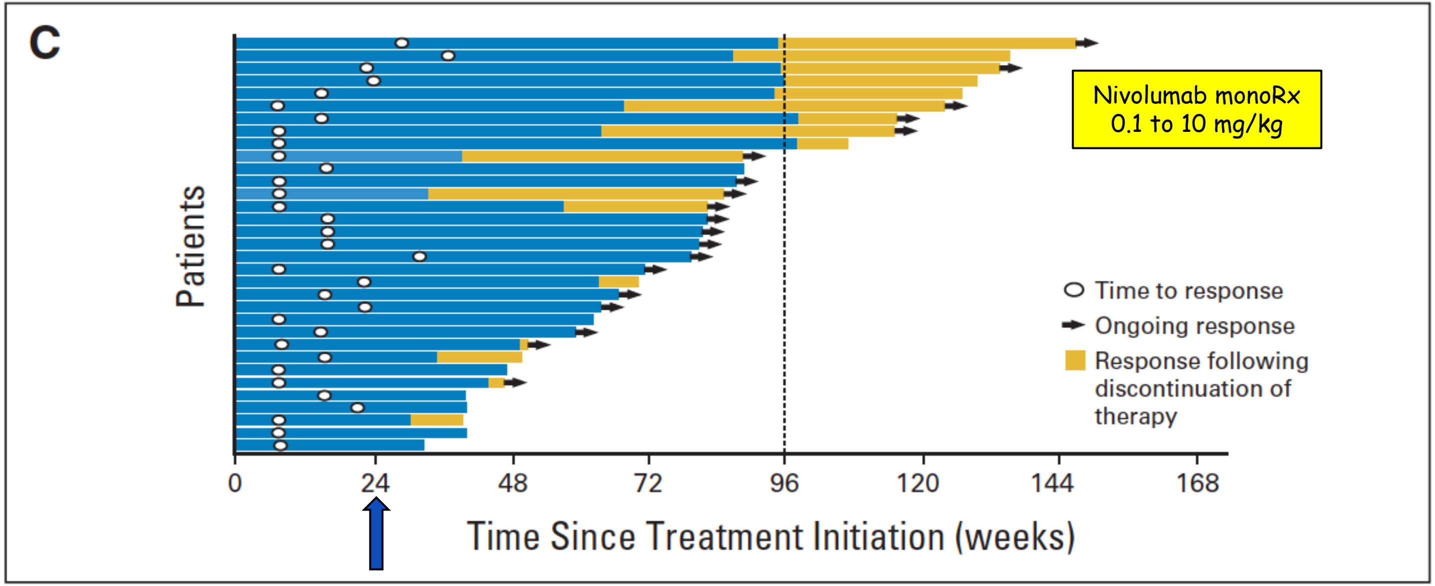
CONS:

- More is not always better or smarter:
  - Burdensome to patient and health care system
  - Significant late emergent irAEs do occur
    - Piling on additional agents adds new toxicities
  - No data to suggest that duration of response, once it occurs, is enhanced by longer course of therapy
  - Relapse/progression ON treatment implies resistance, whereas shorter courses and late relapse leave option for effective retreatment
- Biologic paradigm of immune control and emerging data suggests durability
  - Response kinetics across multiple studies and indications suggest 6-12 month Rx is sufficient
  - Follow up of patients discontinued for AEs supports durability

WHAT ARE THE DATA AND THE ARGUMENTS FOR A SHORTER DURATION?

- Across various tumor types, most responses to monotherapy PD-1/PD-L1 blockade emerge by 6 months, and the vast majority are clearly stabilized by 12 months
  - Even if one stopped treatment at 12 months, one would have significant levels of antibody for another 2 months, and in the case of anti-PD-1, persistent receptor occupancy for additional 2-5 months
- The kinetics of tumor decline are accelerated and deeper in the setting of additive/synergistic combinations
- No biologic rationale to suspect that response durability would be compromised by shorter treatment
- Emerging data support durability based on:
  - Patients completing a 2 year course
  - Patients with a response/stable disease who needed to stop treatment due to emergence of irAE
  - Patients treated prospectively for shorter durations

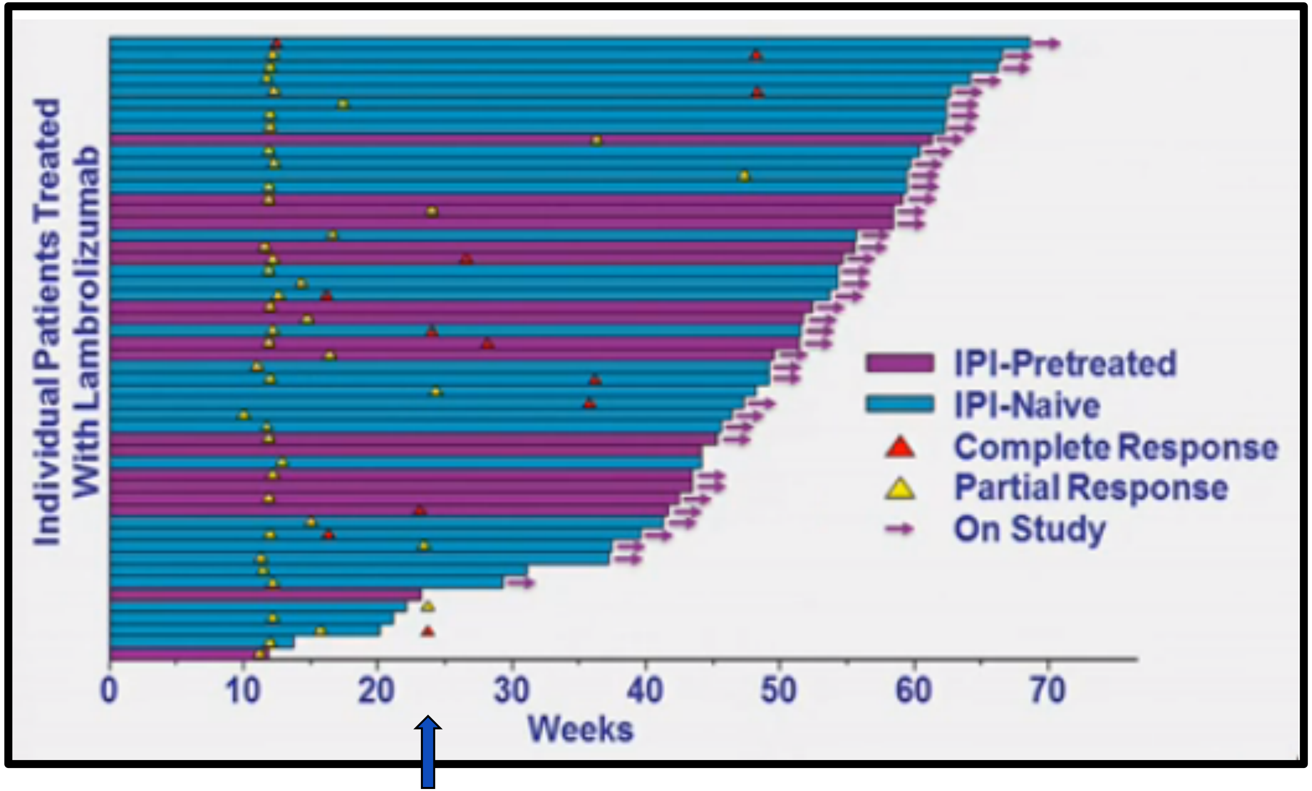
MAJORITY OF RESPONSES EMERGE BEFORE 24 WEEKS
DO WE NEED TO TREAT FOR 2 YRS?



- Topalian SL, Sznol M, et al "Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab" JCO 2014 Mar 3 Epub

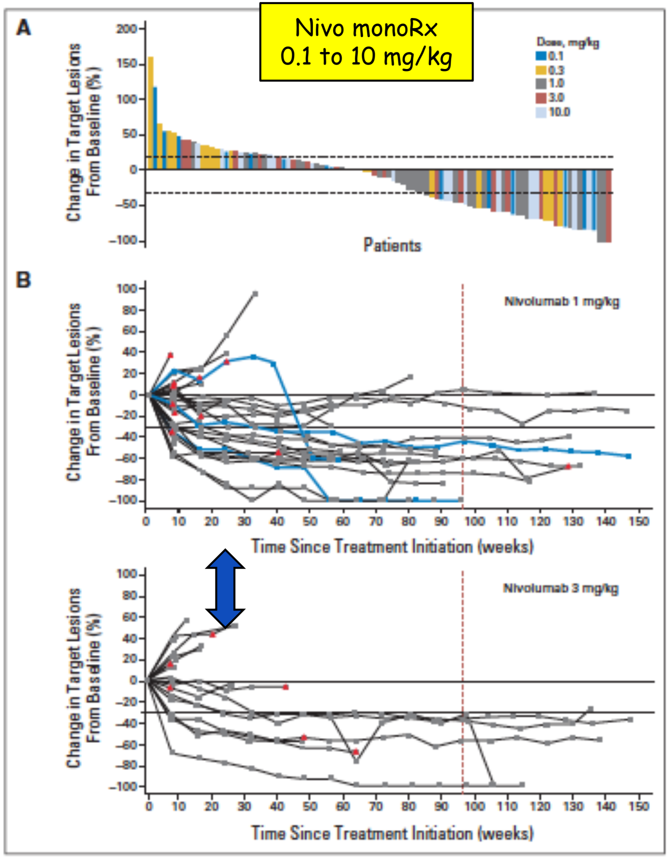
ASCO 2013 PEMBROLIZUMAB (MK-3475): PHASE 1 MELANOMA

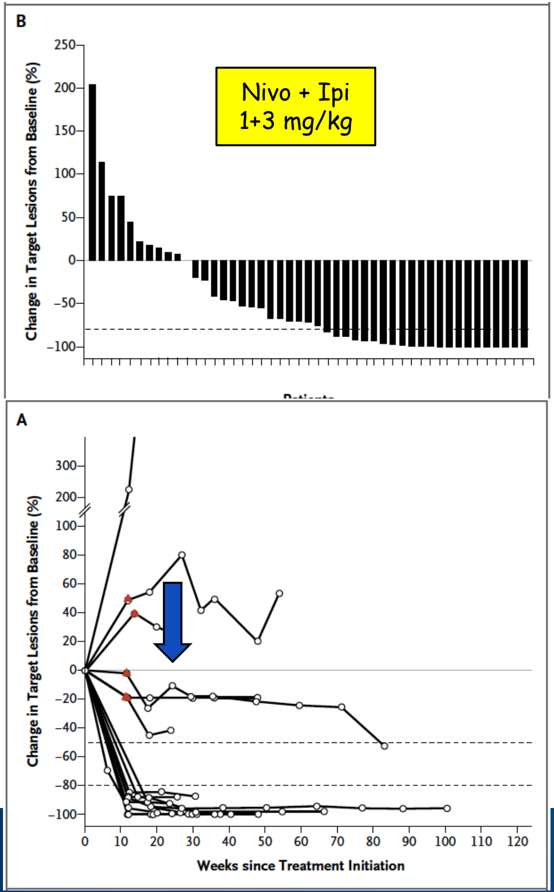
TIME TO RESPONSE AND ON-STUDY DURATION



Independent central review, RECIST 1.1

SPEED TO RESPONSE AND DEPTH INCREASED WITH COMBO (AND ANTI-PD-1 INDUCTION ONLY TO SIX MONTHS)

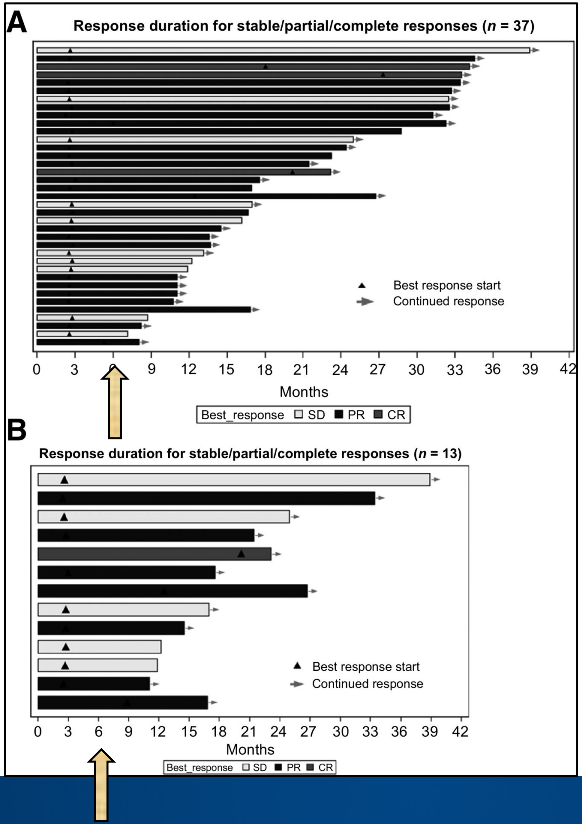




PHASE I/II STUDY OF METASTATIC MELANOMA PATIENTS WHO HAD PROGRESSED AFTER IPILIMUMAB, TREATED WITH NIVOLUMAB FOR SIX MONTHS

- Dosing based on first combo ipi-nivo study
- Nivolumab 3 mg/kg q 2wk for 24 wks, then only q 12 wks for 72 wks (6 additional doses)
- Similar response rates and time to response (TTR) seen in this (small) study as seen in full q2wk dosing paradigms

Swimmer's plots for ipilimumab-refractory patients receiving nivolumab.

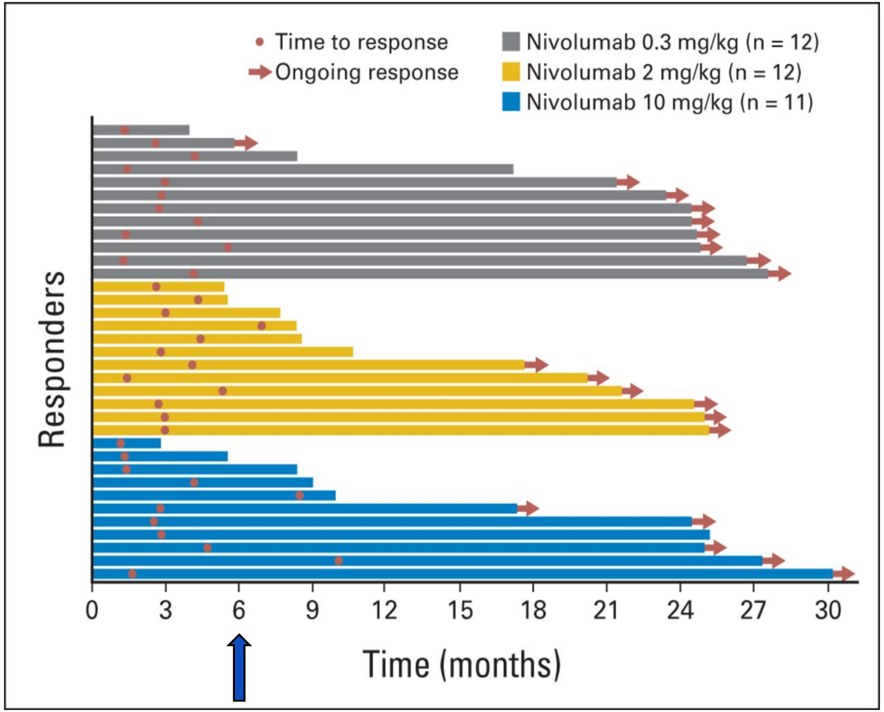


Jeffrey Weber et al. Cancer Immunol Res 2016;4:345-353

NIVOLUMAB FOR METASTATIC RENAL CELL CARCINOMA: RESULTS OF A RANDOMIZED PHASE II TRIAL

- Dose ranging: 0.3, 2, or 10 mg/kg q 3 wk to progression
  - (96 weeks of dosing = 32 doses of nivolumab)
- Response Rate
  - 20%, 22%, 20%
- Numbers of doses
  - 6 (1-29), 7.5 (1-32), 8 (1-31)
- Time to Response
  - 2.8, 3.0, and 2.8 mos
- **Duration of Response**
  - **NR, NR, 22.4 mos**
- PFS/irPFS (exploratory)
  - 2.7/4.3, 4.0/5.4 and 4.2/6.9 mos
- OS
  - 18.2, 25.5, and 27.4 mos (overlapping 80% CI)

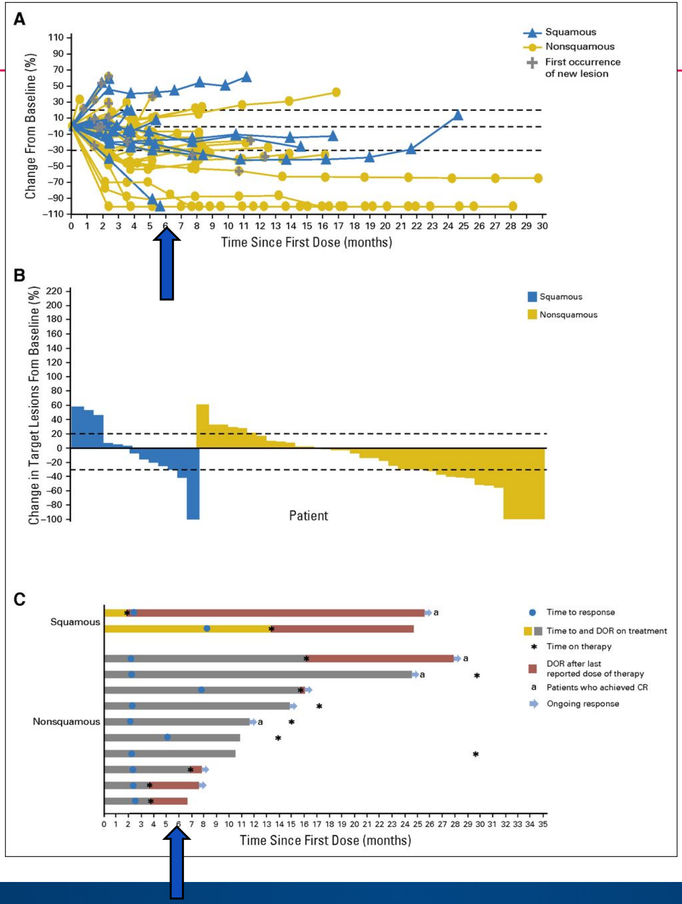
Duration of response in patients who achieved objective response by dose treatment arm.



Robert J. Motzer et al. JCO 2015;33:1430-1437

NIVOLUMAB MONOTHERAPY FOR FIRST-LINE TREATMENT OF ADVANCED NON-SMALL-CELL LUNG CANCER (CM12)

- 3 mg/kg q 2 wk until progression or toxicity
- Improved response rate and OS with patients with any degree of PD-L1 +
  - (>= 1% by BMS assay)



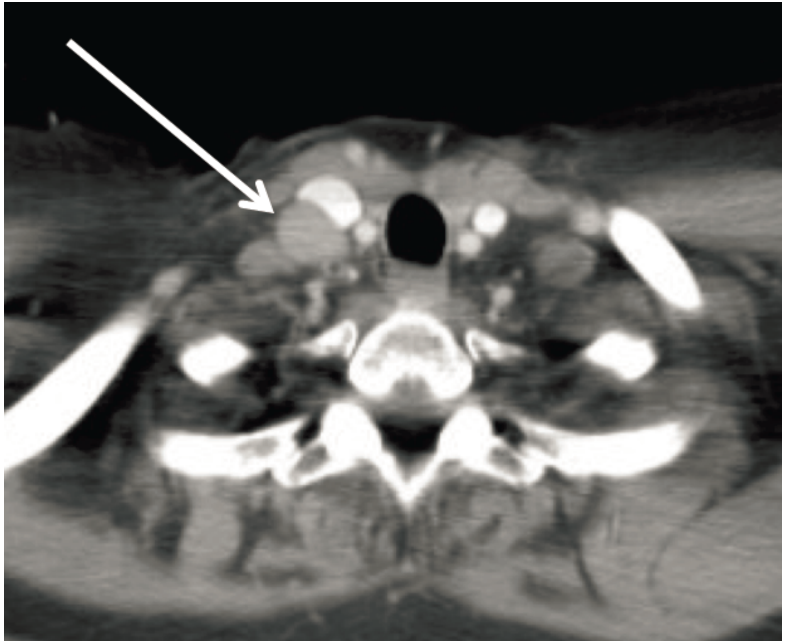
Scott Gettinger et al. JCO 2016;34:2980-2987

REGENERON ANTI-PD-1 PROGRAM (REGN2810): IN OUR FIH ACROSS A VARIETY OF COHORTS, WE HAVE SET THE DOSING DURATION TO ~1YR

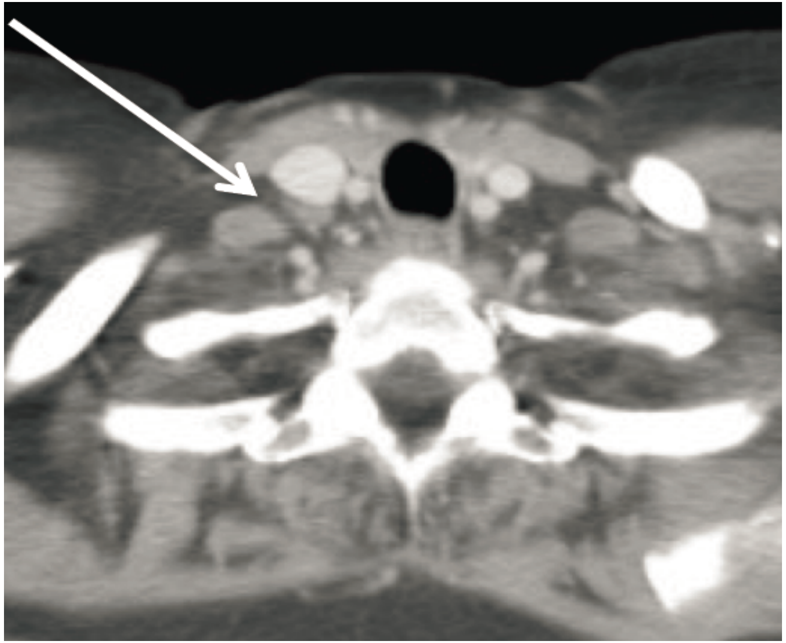
- Typically, after 48 weeks of dosing, patients enter 6 month follow up off treatment
  - Patients that progress/relapse during the follow up are eligible for renewal of treatment
- For the first 16 patients that entered post-treatment follow-up at 48 weeks, responses have been maintained in all but one patient throughout the six months.
  - This patient was successfully restarted on treatment and responding
  - As we accrue more patients completing 48 weeks, this will provide a cohort to assess durablity
- In general, we have also seen most responses established within the first 6 months
  - Example of cohorts with metastatic or locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC) presented at ASCO2017
- Nonetheless, some of our phase 3 studies have been planned to dose out to 2 years…
  - Just in case ☹
  - Concern would patients seek treatment elsewhere?

A PATIENT WITH CERVICAL CANCER DEVELOPED PROGRESSION DURING FOLLOW-UP, AND SUBSEQUENT RESPONSE WITH RE-TREATMENT

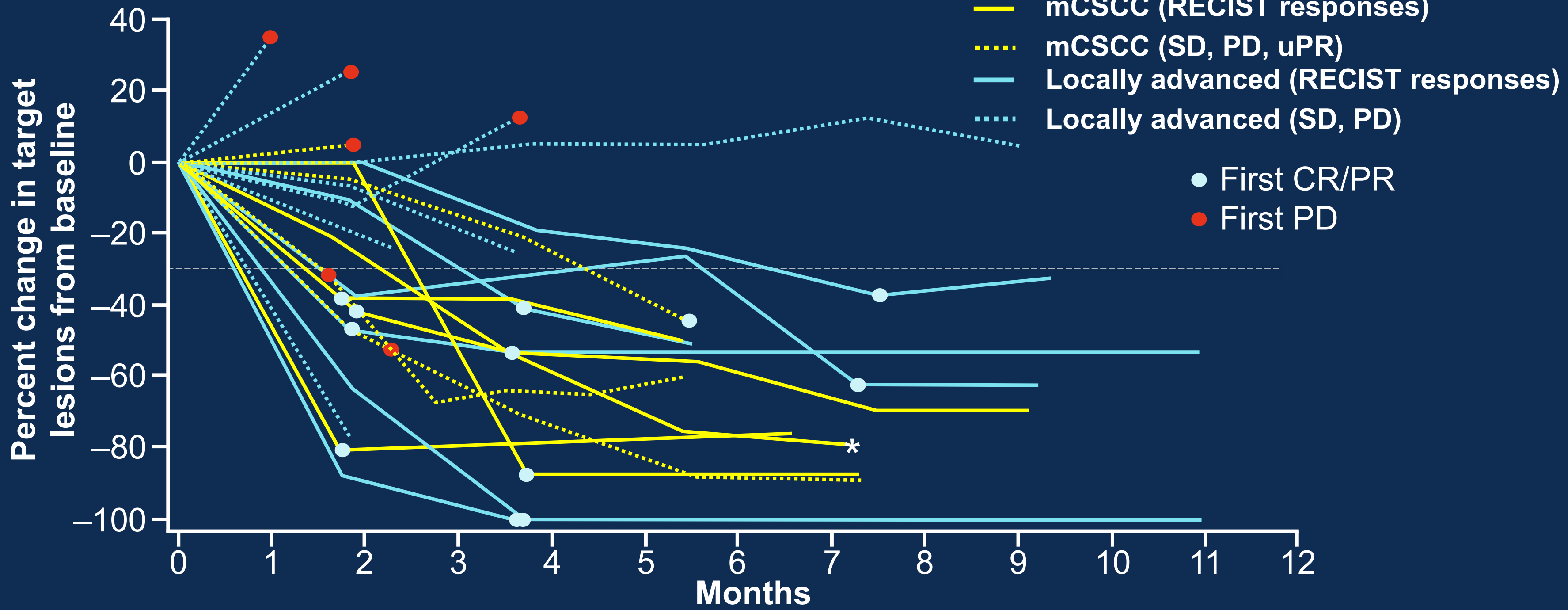
14 Dec 2016, progression off treatment



28 Feb 2017, after 8 weeks of re-treatment



REGN2810 Produced Rapid, Deep and Durable Tumor Reductions in Target Lesions (Both Cohorts of CSCC)

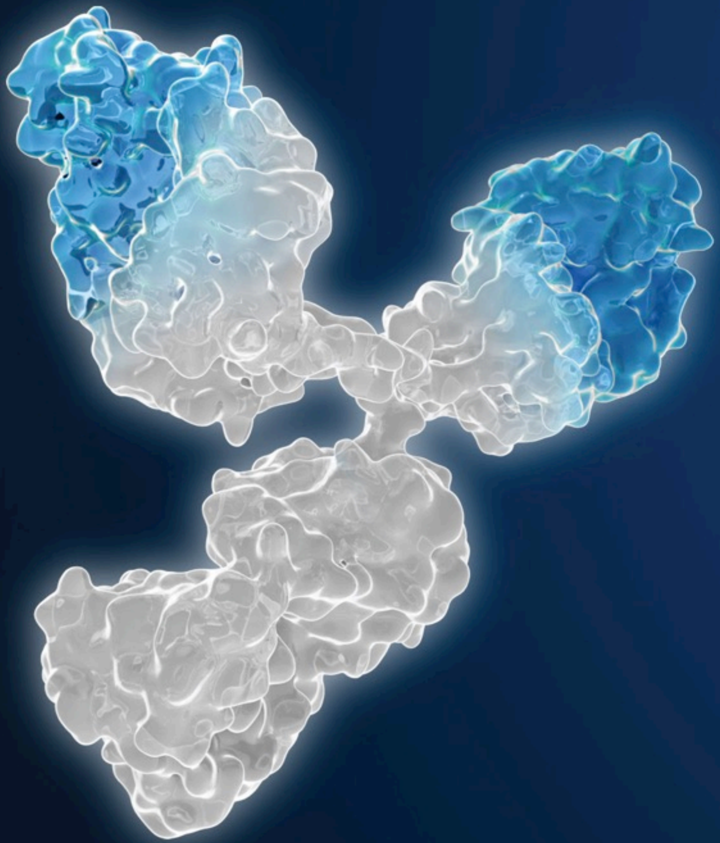


*Patient progressed at subsequent assessment; however, the sum of target lesions are not evaluable.
CR, complete response; mCSCC, metastatic cutaneous squamous cell carcinoma;
PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors;
uPR, unconfirmed partial response; SD, stable disease

Data cut-off date: 27 April 2017

DISCUSSION POINTS

- What is an acceptable operational definition for optimal treatment duration?
  - Stability of response demonstrated for X months on treatment?
  - Difference between complete response and SD/PR for establishing criterion?
- Does optimization of duration of treatment matter?
  - Is this an important aspect of treatment to address?
  - Is their appetite for doing controlled studies to establish efficacy of shorter courses of therapy?
  - Can we identify biological correlates of optimization?– a signature that indicates the tumor is under control…



THANK YOU

REGENERON

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AACR American Association for Cancer Research

PANEL DISCUSSION - SESSION III:

Considerations for Dose Selection of IO Combination Products

Moderator: Eric H. Rubin, MD

Speakers:
Chao Liu, PhD
Laura L. Fernandes, PhD
Amit Roy, PhD
Eric H. Rubin, MD
Israel Lowy, MD, PhD
René Bruno, PhD

Panelists:
Qi Liu, PhD
Lei Nei, PhD
Marc R. Theoret, MD
Nolan A. Wages, PhD