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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consulting Fees: Idera, Regeneron, Apexigen, Evolveimmune, Johnson and Johnson, Glaxo-Smith Kline , Alligator, Verastem , Agenus , Rubius, Bristol-Myers , Genentech-Roche, Boston Pharmaceuticals , Nextcure, Servier, Adaptimmune, Immunocore, Dragonfly, Pierre-Fabre, Molecular Partners , Boehringer Ingelheim, Torque-Repertoire, Innate pharma, Nektar, Pieris, Numab, Abbvie, Astra Zeneca, Adaptive Biotechnologies, Actym, Amphivena

- Ownership interest less than 5%: Adaptive Biotechnologies, Actym, Amphivena, Torque-Rertoire, Nextcure, Evolveimmune, Johnson & Johnson, Glaxo-Smith Kline

- I will be discussing non-FDA approved indications during my presentation.

Spectrum of PD-1/PD-L1 Antagonist Activity

Approved (single agent or combination)

- **Melanoma**
- **Merkel cell**
- **Squamous Cell Ca of Skin**
- **NSCLC – adenocarcinoma and squamous cell**
- **Small cell lung cancer**
- **Head and neck cancer**
- **Renal cancer (clear cell)**
- **Bladder**
- **Gastric and gastroesophageal junction**
- **Hepatocellular carcinoma**
- **Triple negative breast cancer**
- **Cervical Cancer**
- **Endometrial Cancer (with lenvatinib)**
- **MMR-repair deficient tumors (colon, cholangiocarcinoma)**
- **TMB- high tumors**
- **Hodgkin lymphoma**
- **Refractory primary mediastinal large B-cell lymphoma (PMBCL)**

Active:

- Basal Cell Carcinoma
- Renal (non-clear cell)
- Ovarian
- Thymoma
- Mesothelioma
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (cutaneous T-cell lymphomas, peripheral T-cell lymphoma)
- Prostate cancer (with ipilimumab)

Minimal to no activity

- MMR+ (MSS) colon cancer
- Myeloma
- Pancreatic cancer

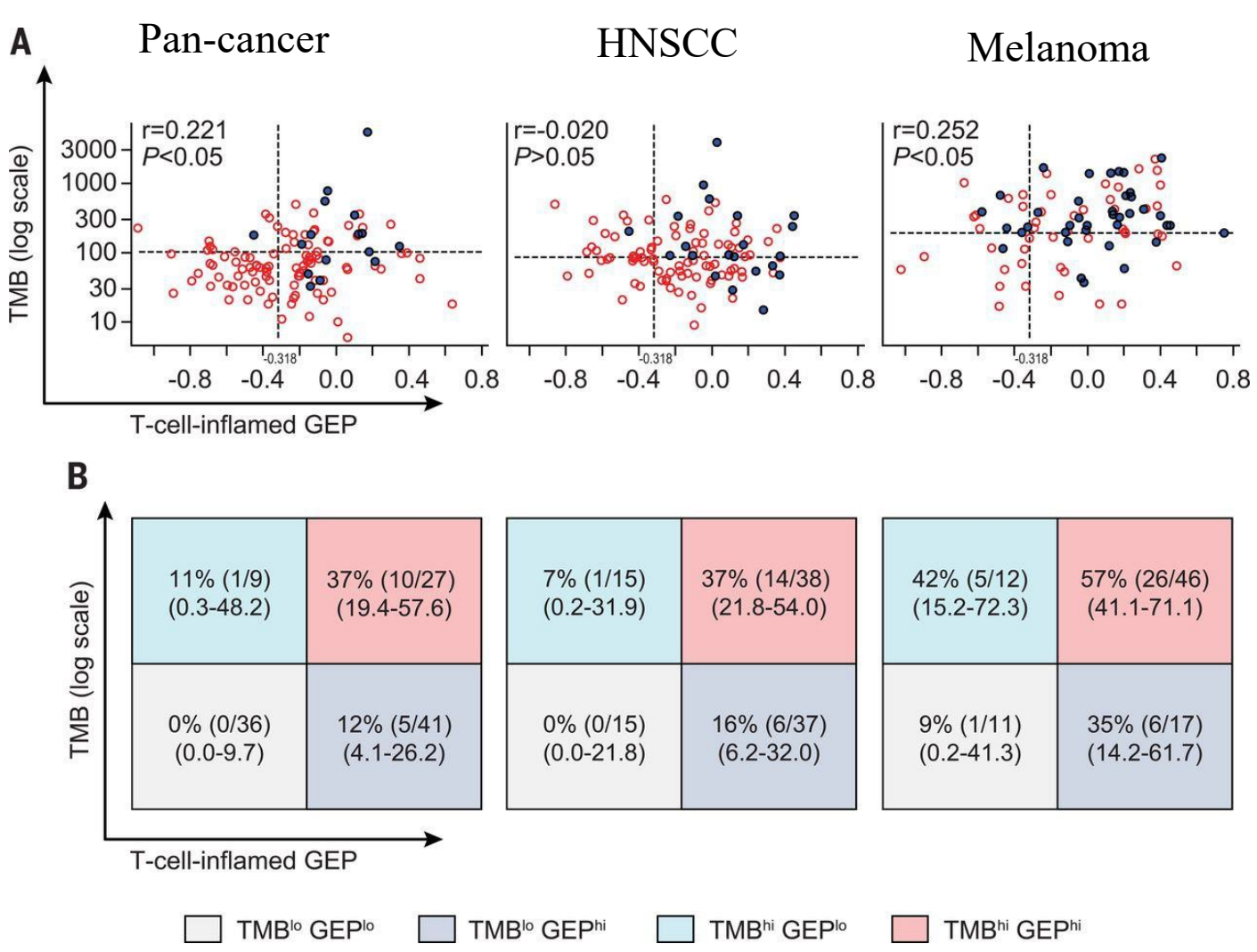
Approved Anti-PD-1 agents

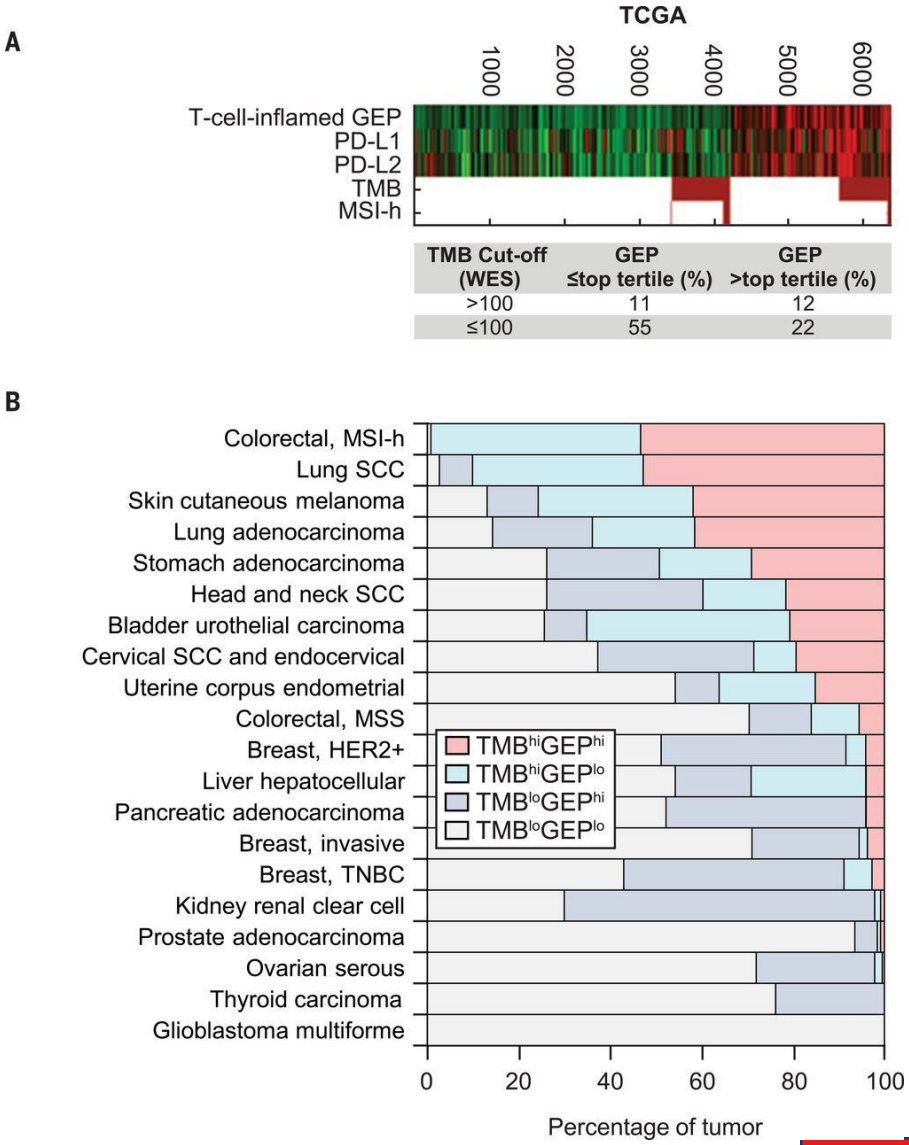
•Nivolumab, Pembrolizumab, Cemiplimab

Approved Anti-PD-L1 agents

- Atezolizumab, Durvalumab, Avelumab

Joint relationship of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts.





TMB Cut-off (WES)	GEP ≤top tertile (%)	GEP >top tertile (%)
>100	11	12
≤100	55	22

Published by AAAS

Razvan Cristescu et al. Science 2018;362:eaar3593

Science
AAAS

No T-cells
No response → Why?

↓

No priming
Exclusion of T-cells from tumor? → Why? →

No or few antigens (low mutation burden)
Genetic inability to respond to antigens
Necessary APC/DC not present (BATF+)
Tumor suppresses or inhibits DC/APC migration/activation
Other (microbiome, etc) suppresses or inhibits DC/APC migration/activation
Inadequate activation of APC/DC (or not enough)
Expression of T-cell exclusion molecules
Missing or suppressed T-cell chemokines

Ag specific T-cells present,
No response → Why? →

Not enough T-cells
T-cells not 'strong' enough – affinity/exhaustion
T-cells need something else – cytokines/co-stimulation
T-cells not replenished from outside tumor
Hostile environment – low oxygen/glucose
Inhibitory cytokines or other soluble molecules
Other inhibitory ligand-receptor checkpoints
Inhibitory cells – Treg/Macrophages/MDSC
Tumor can't be recognized – beta2 microglobulin or MHC loss

Summary of Immune Checkpoint Inhibitor Non-Response or Resistance

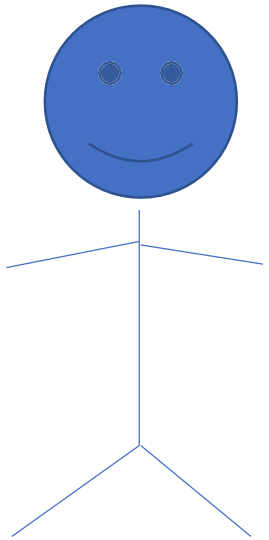
- Genetic component (HLA heterozygosity, other)?
- Low tumor mutation burden
- **Lower microbiome diversity/presence or absence of bacterial species**
- Increased/stabilized beta catenin
- STK11/LKB1 mutation
- **Failure of Sting activation**
- **PTEN loss (dependent on VEGF)**
- **Increased VEGF**
- Tumor Hypoxia
- IPRES signature/angiogenesis/ETM transition
- **Increase in Myeloid cell signature**
- Increased peripheral complement activation, wound healing, acute phase reactants
- **Tumor/TME metabolism (glucose)**
- ***Induction of T-cell regulatory mechanisms (IDO, Tim-3, other immune checkpoints) or T-cell exhaustion***
- Increase in tumor DNA copy number loss (immune related genes) (Roh et al., Sci. Transl. Med. 9, March 2017)
- JAK mutations (IFN-γ pathway signaling) (Zaretsky et al, NEJM)
- Beta-2 microglobulin/HLA loss

→ Priming – Minimal to no T-cell response

→ Exclusion/Traffic signals?
Or lack of/inadequate activation of tumor APC

→ Feedback negative regulation +/- lack of additional agonist signals

→ Tumor cell or T-cell insensitivity



* Odds for benefit and quality of benefit

Biomarker 1* for PD-1/PD-L1 pathway

Optimal anti-tumor response

Biomarker 3 for maximal effect – stop therapy, no further therapy

Biomarker 2

Sub- optimal anti-tumor response

Add therapy X to PD-1/PD-L1 blockade

No anti-tumor response

Add therapy X/Y/Z to PD-1/PD-L1 blockade

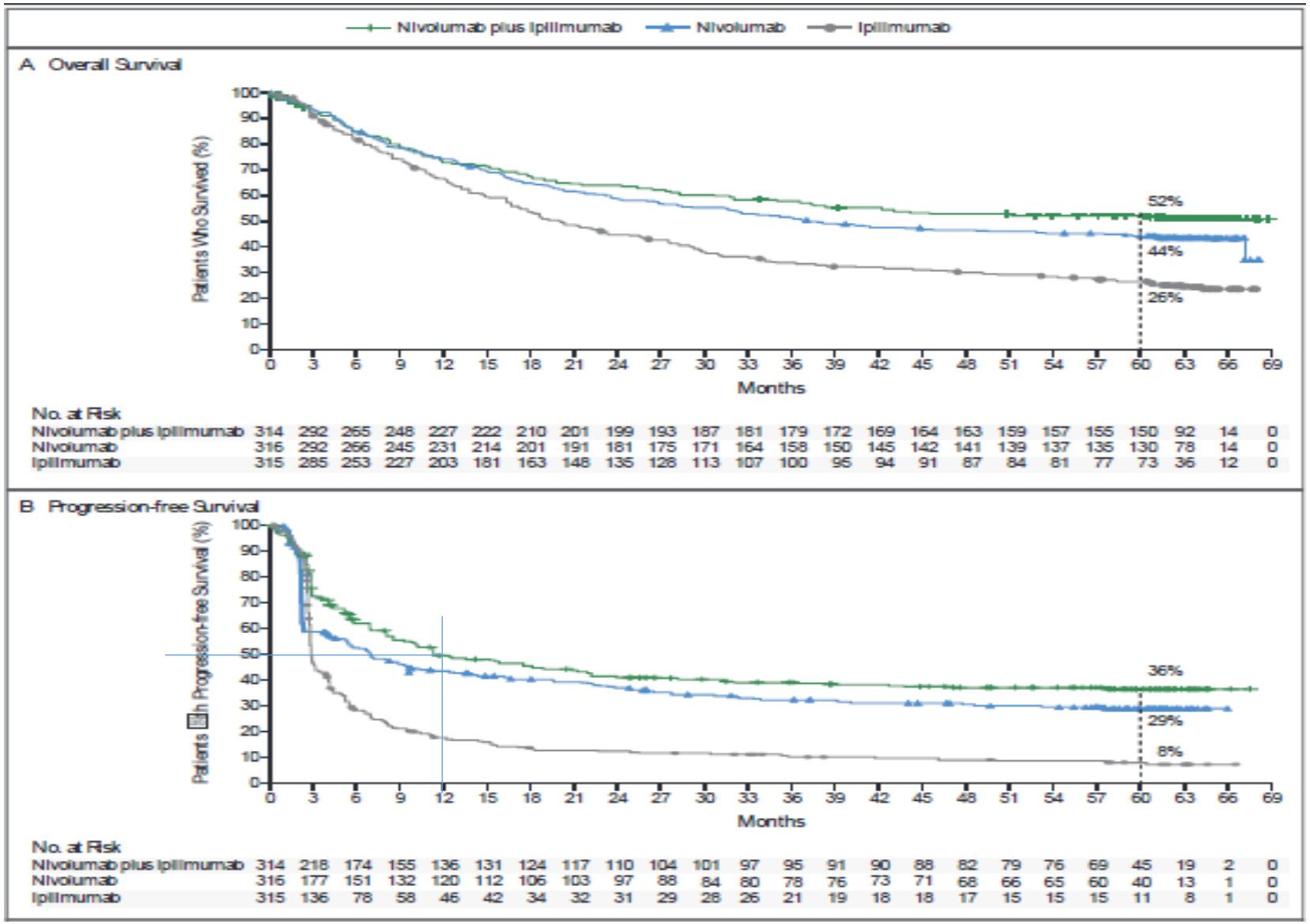
Immune therapy X/Y/Z without PD-1/PD-L1 blockade

Biomarker x1, x2, x3 for alternative therapies

Alternative non-immune therapy

Biomarker 1 and Biomarker 2 could be assessed early post-treatment

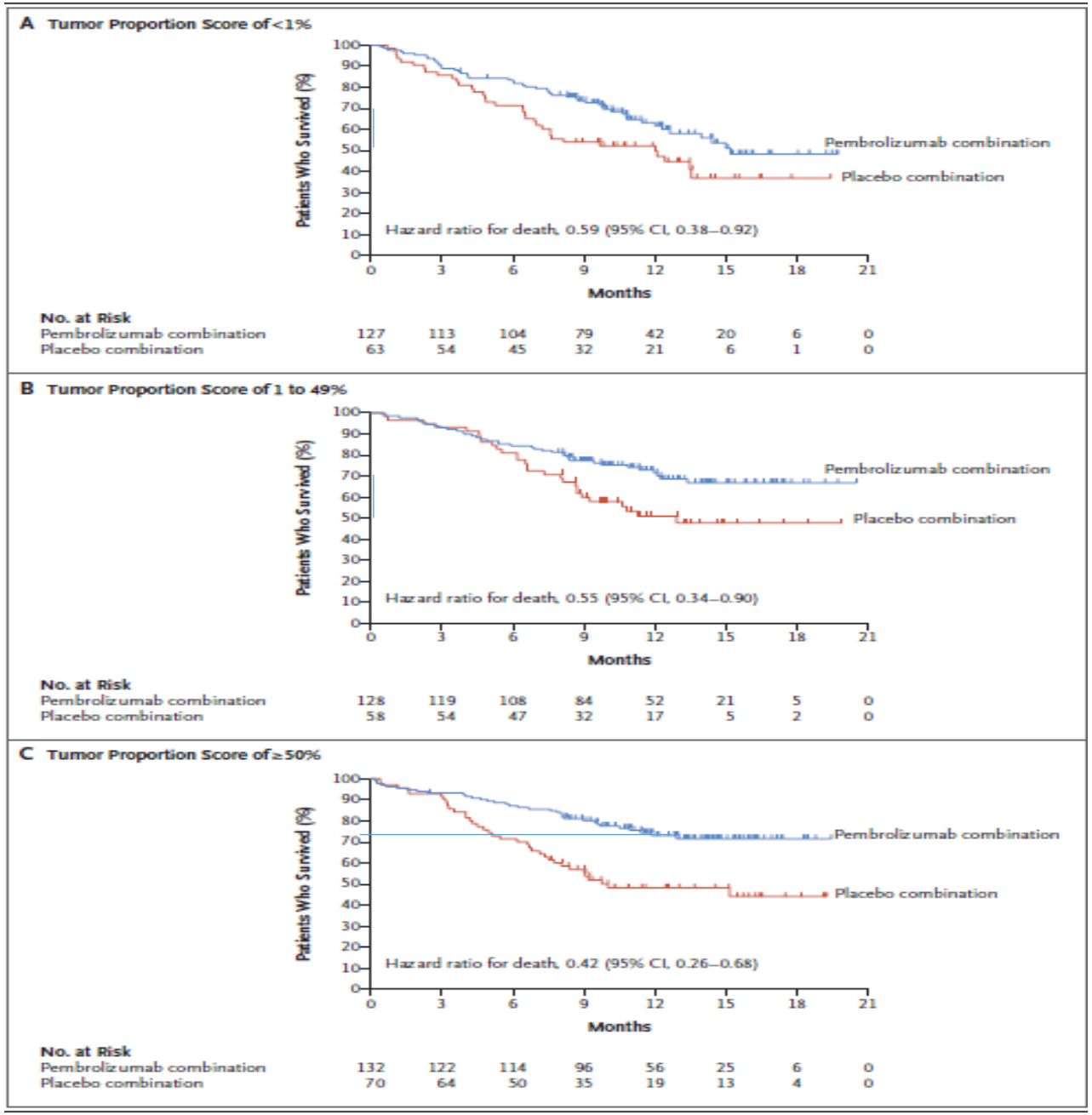
CA209-067: Metastatic Melanoma, anti-CTLA-4 + anti-PD-1 or Anti-PD-1 vs anti-CTLA-4: Five-Year Survival Data



Larkin et al

DOI: 10.1056/NEJMoa1910836

Anti-CTLA-4 + anti-PD-1 approved in multiple indications



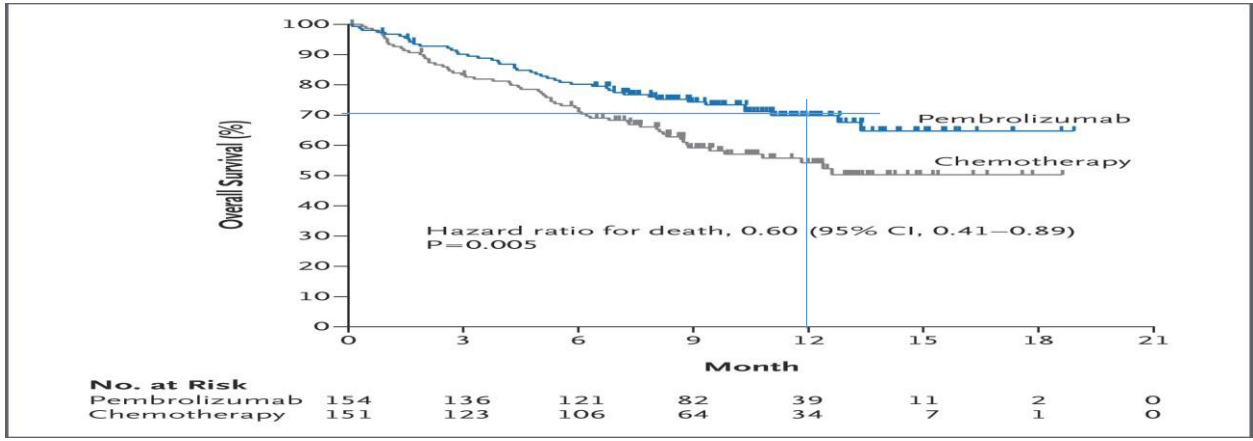
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

This article was published on April 16, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1801005

Pembrolizumab in PD-L1 high NSCLC



PD-L1 in predicting pembrolizumab response in NSCLC

Lancet 2019; 393: 1819–30
Published Online
April 4, 2019
http://dx.doi.org/10.1016/
S0140-6736(18)32409-7

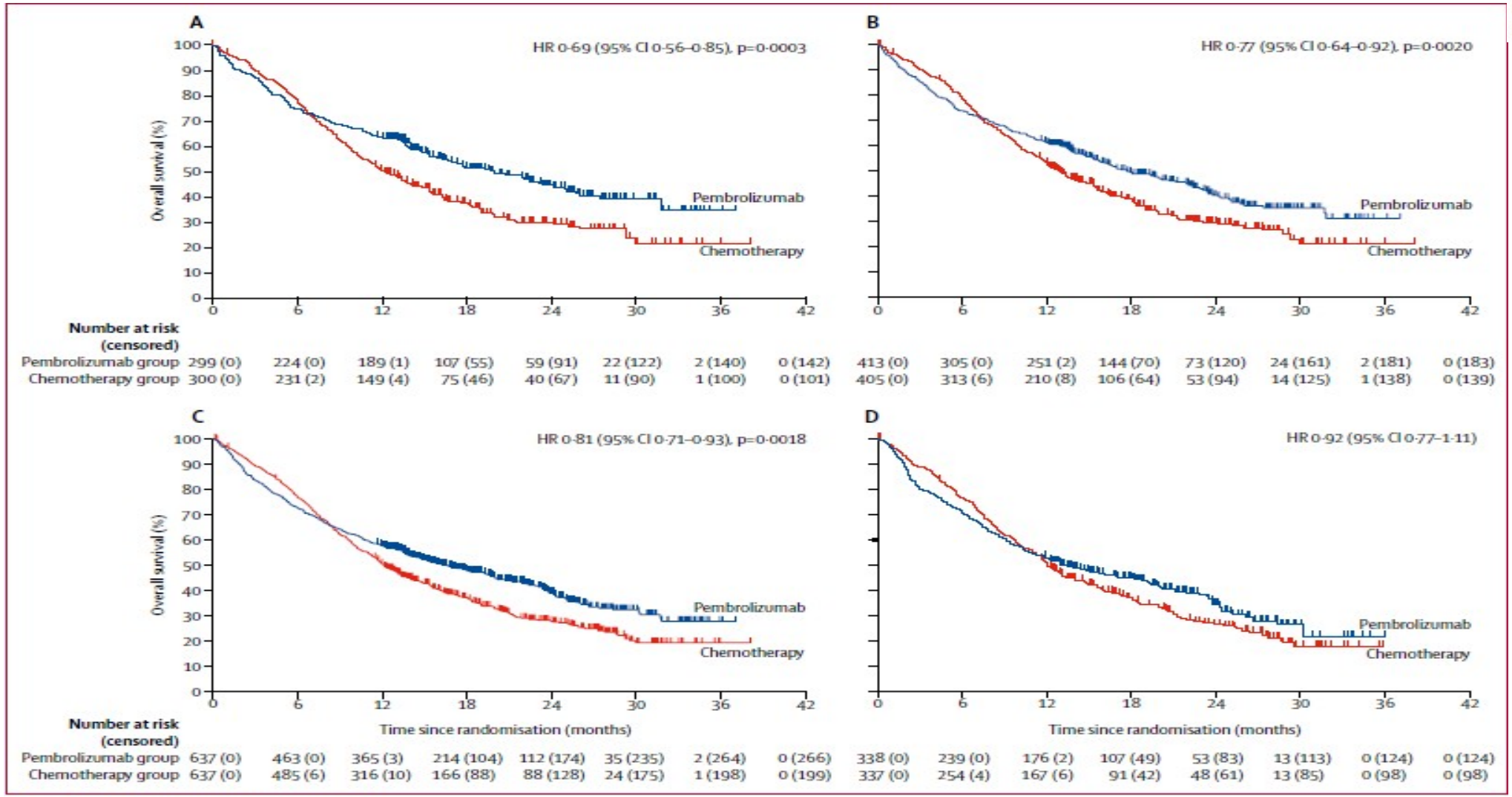
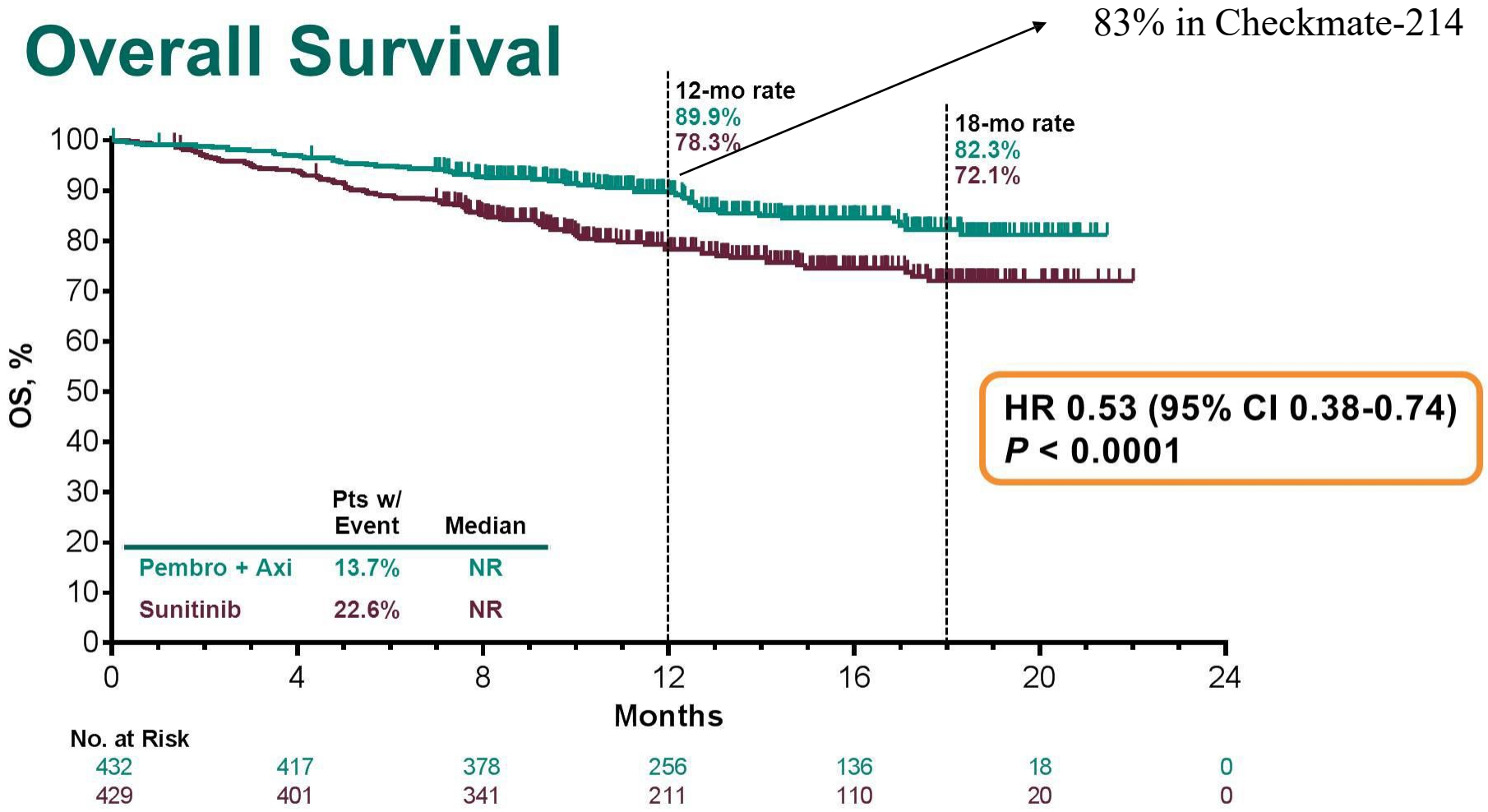


Figure 2: **Kaplan-Meier estimates of overall survival**
(A) PD-L1 TPS 50% or greater population. (B) PD-L1 TPS 20% or greater population. (C) PD-L1 TPS 1% or greater population. (D) PD-L1 TPS 1–49% population (exploratory analysis). Tick marks indicate censoring of the data at the last time the patient was known to be alive. HR=hazard ratio. PD-L1=programmed death ligand 1. TPS=tumour proportion score.

N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714. [Epub ahead of print]

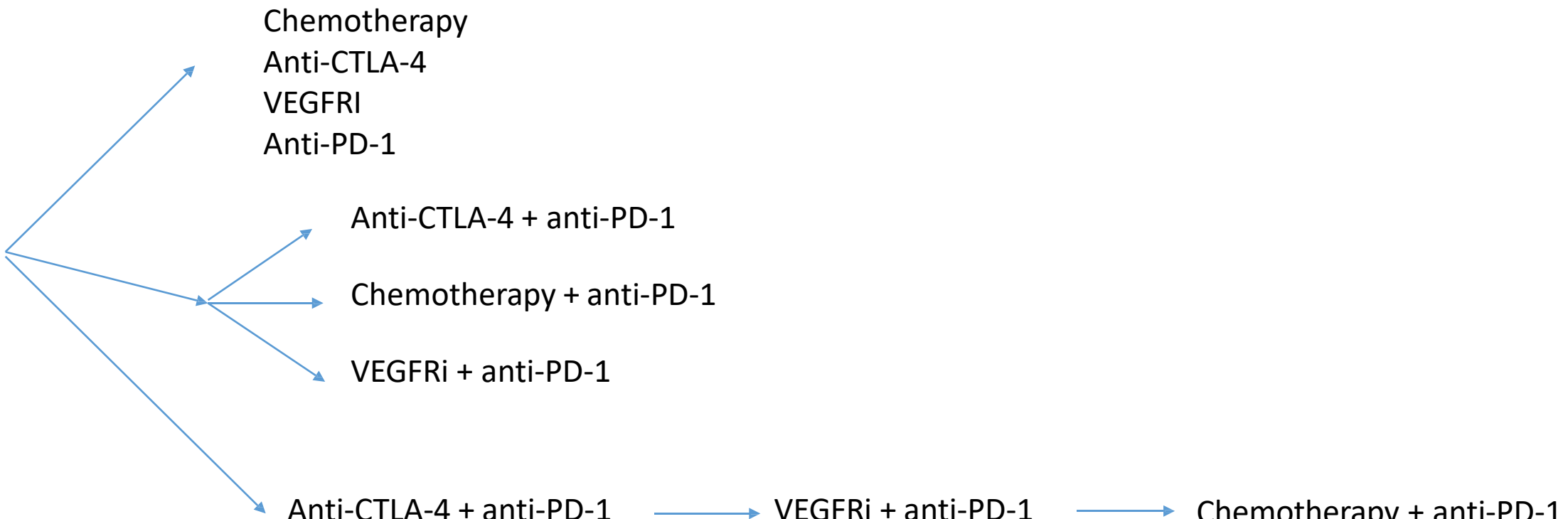
Keynote-426: Pembro/axitinib versus sunitinib



Data cutoff date: Aug 24, 2018.

Other VEGRi combinations: **Atezolizumab + bevacizumab in HCC Pembrolizumab + lenvatinib in endometrial**

Challenge of Combinations Disease X



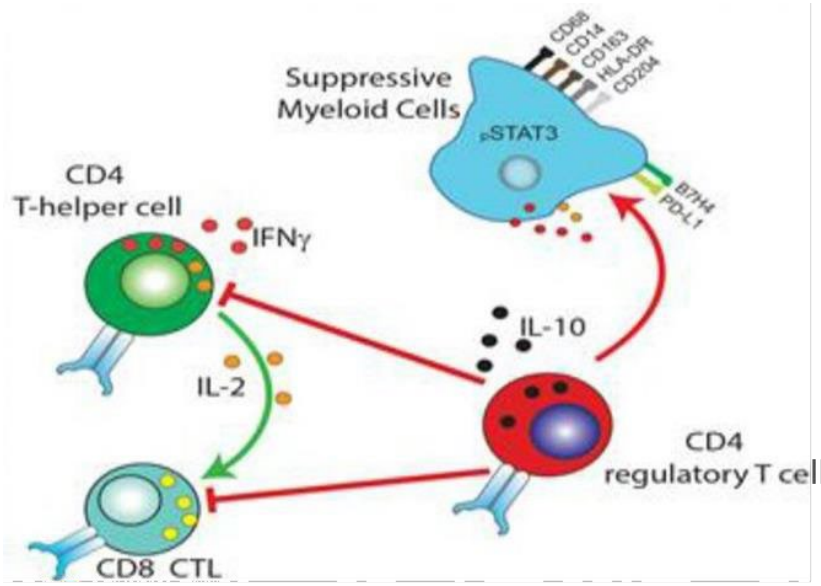
What mechanisms are being addressed by combinations?

- Anti-CTLA-4
  - CTLA-4 inhibition increases TCR repertoire, increases T-cell proliferation and tumor T-cell infiltration
  - Anti-CTLA-4 may increase availability of CD80/CD86 for co-stimulation
  - Anti-CTLA-4 may inhibit/reduce Treg within tumor
- Chemotherapy
  - Reduces Tumor bulk – Improves T-cell: tumor target ratio
  - Separate mechanism of kill – 'synergize' with T-cell mechanism of killing
  - Reduces T-cell inhibitory substances produced by tumor
  - Modify/reduce Treg + MDSC inhibition
  - Alters tumor barriers (vasculature/pressure) to T-cell penetration
  - Kills tumor cells in a manner that increases their recognition by T-cells and APC (vaccination)
  - Induce DNA damage and STING activation
  - Alters T-cell signaling/gene expression to produce T-cell attractants
- VEGFRi (next slide)
  - Effects on vasculature and T-cell traffic

VEGFRi produce immunomodulatory effects; but may differ depending on the individual agent

Cabozantinib – MER-TKi

Regulatory T cells suppress or downregulate induction and proliferation of effector T cells (e.g. CD4 and CD8)

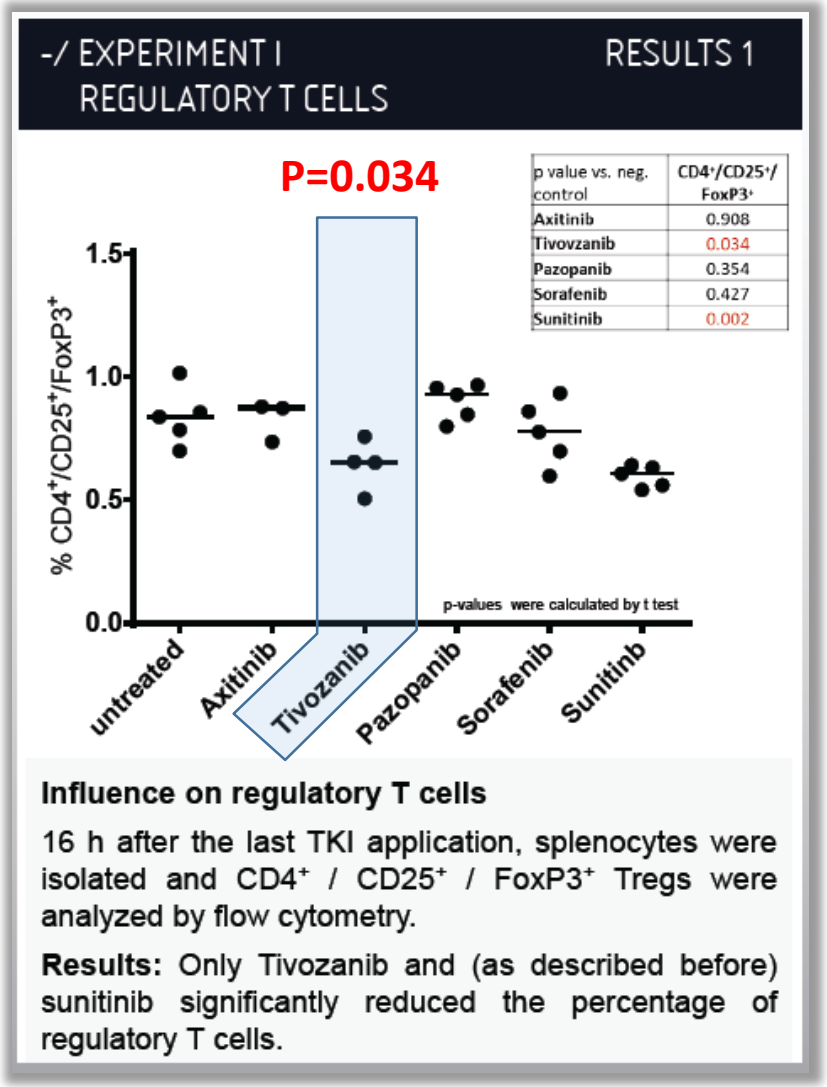


Other Immune effects:

-Changes in MDSC populations

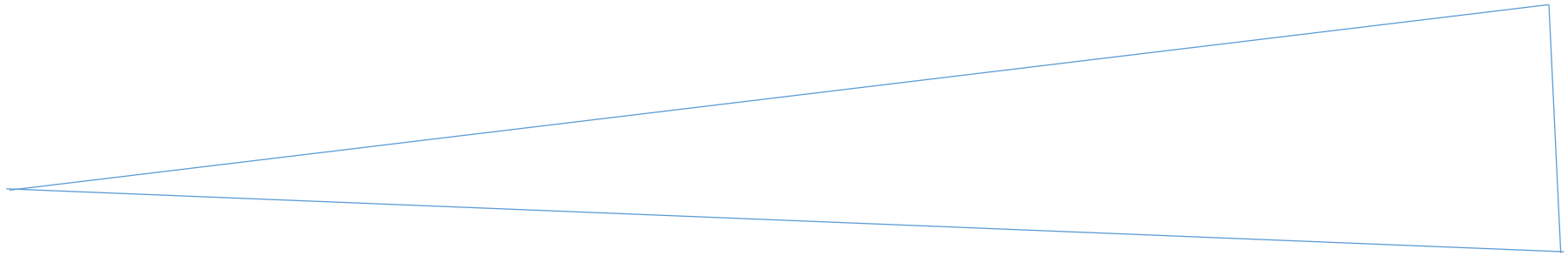
-Induce T-cell attracting chemokines within tumor

-Block inhibitory effects of VEGF on dendritic cells



Pawlowski N et al. AACR 2013. Poster 3971.

Improving immunotherapy



Low T-cell

Vaccines, neoantigen, intratumoral therapies
Inhibit T-cell exclusion pathways
Adoptive cell therapies – CAR-T, TCRs against developmental Ag
CD3 bispecific engagers
Innate (non-T cell dependent) immunity –
NK, macrophage, MDSC modulation
Microbiome modulators

High T-cell

- Inhibit other immune checkpoints, LAG3, TIM3, TIGIT
- Inhibit suppressive immune populations
- Block suppressive soluble ligands
- Increase co-stimulation and expand population participating in antitumor effect – CD40, cytokines, agonist of co-stim receptors
- Adoptive cell therapy – TIL
- Alter metabolism or hypoxia

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

Diab et al, ASCO 2018

Table 3. Best Overall Response in Patients Progressing on Anti-PD-1 Therapy (N=21)

Best overall tumor response	Response rate (RECIST v1.1), N=26
Complete response (CR)	2 of 21 (9.5%)*
Partial response (PR)	6 of 21 (28.6%)
Stable disease (SD)	7 of 21 (33.3%)
Progressive disease (PD)	6 of 21 (28.6%)
Not yet assessed	5
Overall response rate (CR, uCR, or PR)	8 of 21 (38.1%)
Disease control rate (CR, PR, or SD)	15 of 21 (71.4%)

As of 9 May 2018.

*One CR unconfirmed.

ILLUMINATE-204 Responders: Baseline Characteristics (n=8)

- Age range: 62 to 91 years
- Stage IV: 6 out of 8 (75%)
  - M1c: 3, including 1 with liver metastases
- $BRAF^{V600}$ mutation: 4
- Elevated LDH: 1
- Prior recurrent/metastatic ipilimumab treatment: 2

Cell

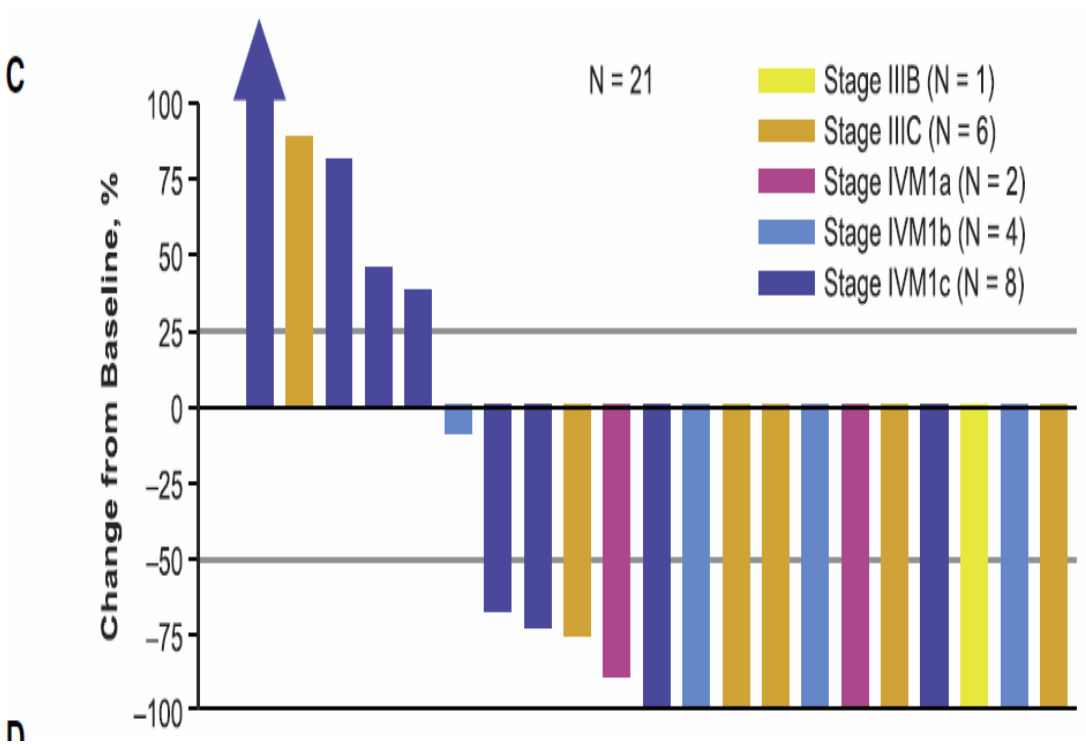
Ribas et al http://dx.doi.org/10.1016/j.cell.2017.08.027

Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy

Table 1. Best Overall Response[a]

	Talimogene Laherparepvec Plus Pembrolizumab (N = 21)	
	Total[b]	Confirmed[b]
Patients with a response	15	13
Response rate, % (95% CI)	71 (48–89)	62 (38–82)
Best overall response, n (%)		
Complete response	8 (38)	7 (33)
Partial response	7 (33)	6 (29)
Stable disease[c]	1 (5)	3 (14)
Progressive disease	5 (24)	5 (24)
Disease control rate, n (%)	16 (76)	16 (76)

[a]Response was evaluated per immune-related response criteria by investigators; data cutoff was August 31, 2016.
[b]Responses were confirmed by a subsequent assessment at least 4 weeks later.
[c]A best overall response of stable disease required an evaluation of stable disease no earlier than 77 days after enrollment.



Tvec + ipilimumab increased ORR vs ipilimumab alone in metastatic melanoma

A Systemically Administered, Conditionally Active TLR8 Agonist for the Treatment of HER2-Expressing Tumors

Kara Moyes, Ty Brender, Sean W. Smith, Hengyu Xu, Ben Setter, Li-Qun Fan, Rebecca Brunette, Justin Killebrew, Phil Tan, Craig Coburn, Robert DuBose, Peter Baum, Valerie Odegard

Silverback Therapeutics, Seattle, WA

SBT6050 is Designed for Systemic Administration with TME-Localized Activity

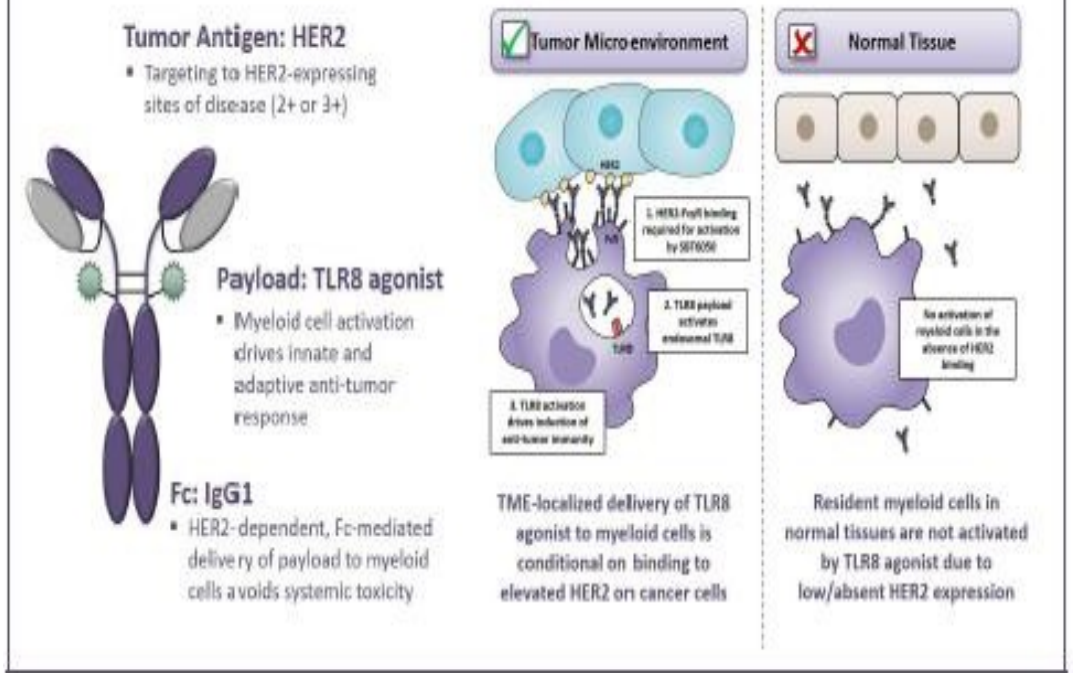
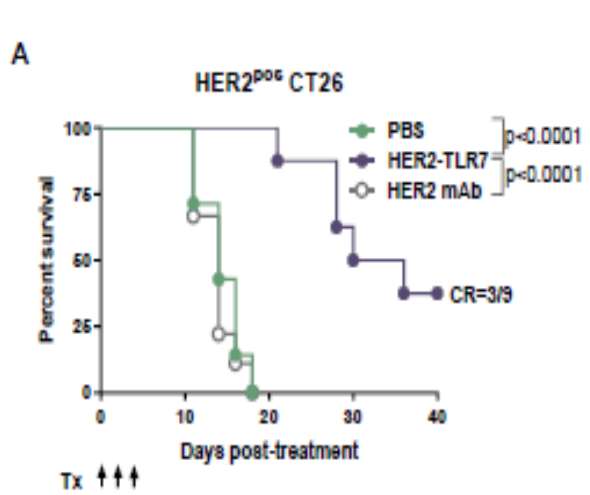
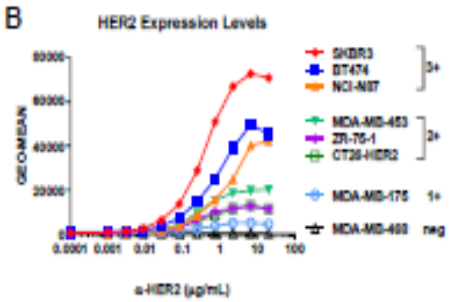


Figure 4: HER2-TLR7 Monotherapy Results in Tumor Clearance Without Significant Systemic Cytokine Release





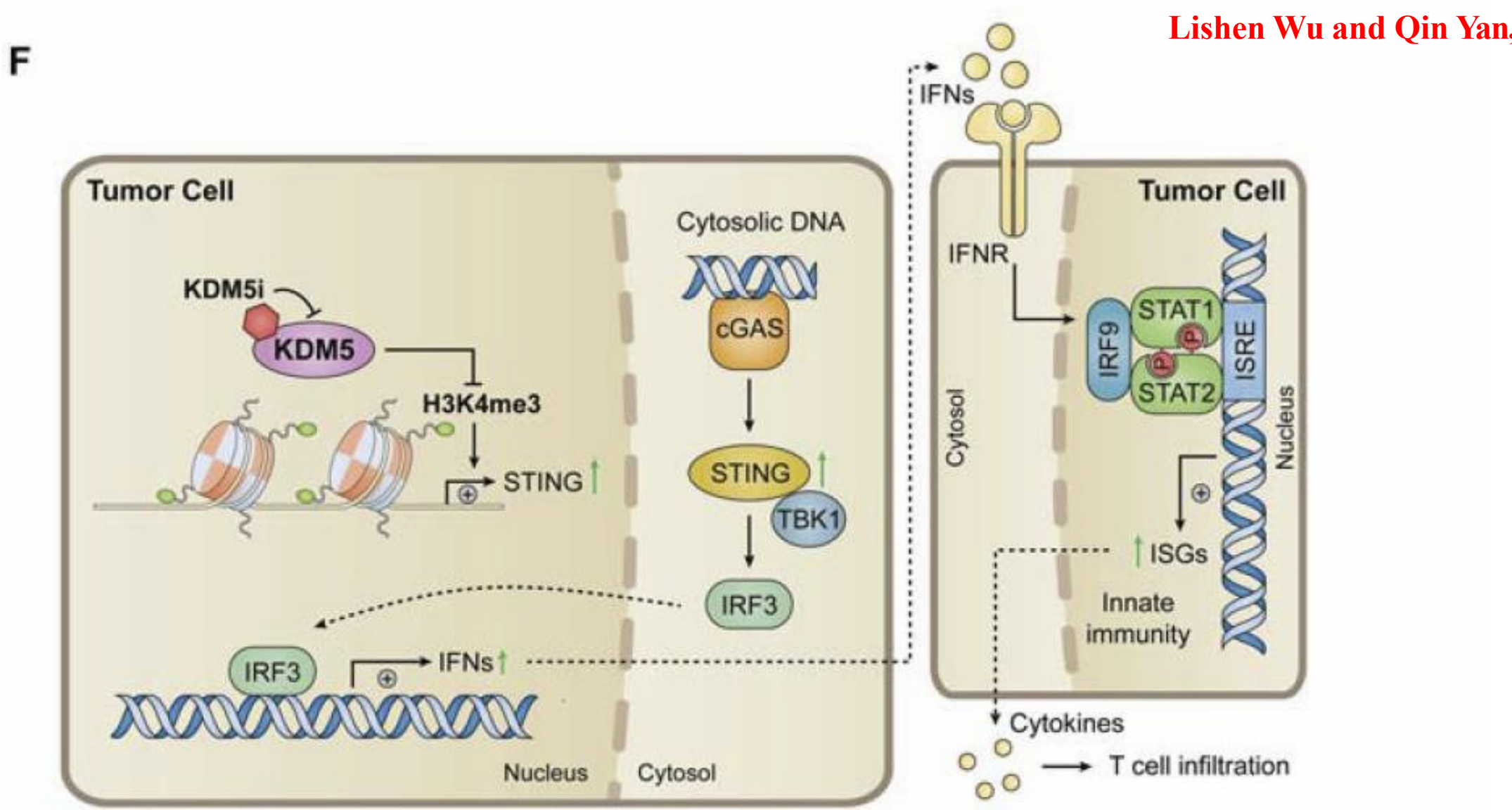
C

Cytokine/ Chemokine	HER2-TLR7 (pg/mL)	PBS (pg/mL)
IL-6	ND	ND
IL-10	ND	ND
TNFα	ND	ND
IL-1β	ND	ND
MCP-1	60	ND

Mice bearing subcutaneous HER2pos CT26 tumors were treated intravenously with HER2-TLR7 at 5 mg/kg, unconjugated HER2 mAb at 5 mg/kg, or PBS; CR=Complete Response (A). Relative HER2 expression of cell lines determined by flow cytometry (B). Cytokine/chemokine expression as assessed in blood drawn 24 hours after dosing; ND=Not Detected (C).

Inhibitors of KDM5 upregulate STING in Tumor cells

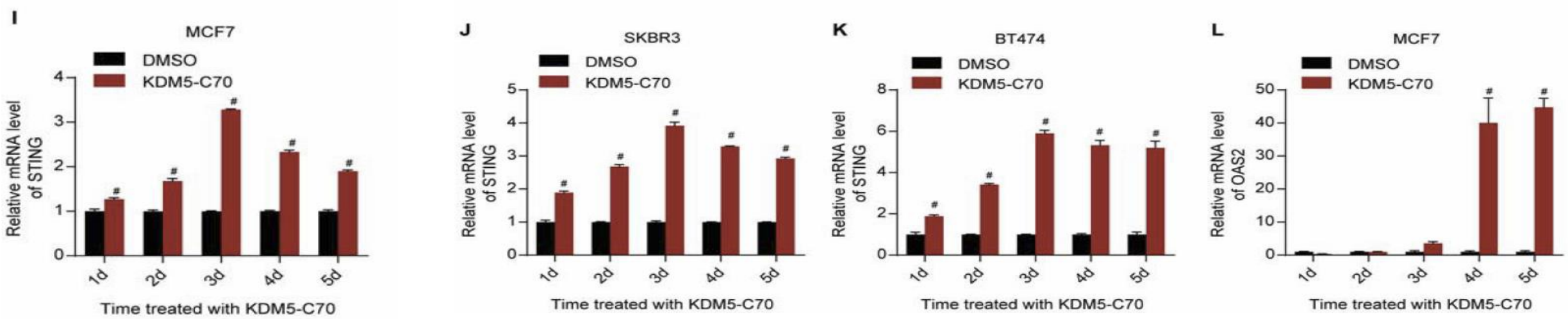
Lishen Wu and Qin Yan, Yale



PLOS Biology | https://doi.org/10.1371/journal.pbio.2006134 August 6, 2018

KDM5 histone demethylases repress immune response via suppression of STING

Lizhen Wu[1☯], Jian Cao[1☯], Wesley L. Cai[1], Sabine M. Lang[1], John R. Horton[2], Daniel J. Jansen[3], Zongzhi Z. Liu[1], Jocelyn F. Chen[1], Meiling Zhang[1], Bryan T. Mott[3], Katherine Pohida[3], Ganesha Rai[3], Stephen C. Kales[3], Mark J. Henderson[3], Xin Hu[3], Ajit Jadhav[3], David J. Maloney[3], Anton Simeonov[3], Shu Zhu[4], Akiko Iwasaki[5,6], Matthew D. Hall[3], Xiaodong Cheng[2], Gerald S. Shadel[1,7,8], Qin Yan[1]*



STING induction in 4 breast cancer cell lines treated with 1uM KDM5i

PLOS Biology | https://doi.org/10.1371/journal.pbio.2006134 August 6, 2018

Agonistic CD40 Antibodies and Cancer Therapy

Robert H. Vonderheide[1] and Martin J. Glennie[2]

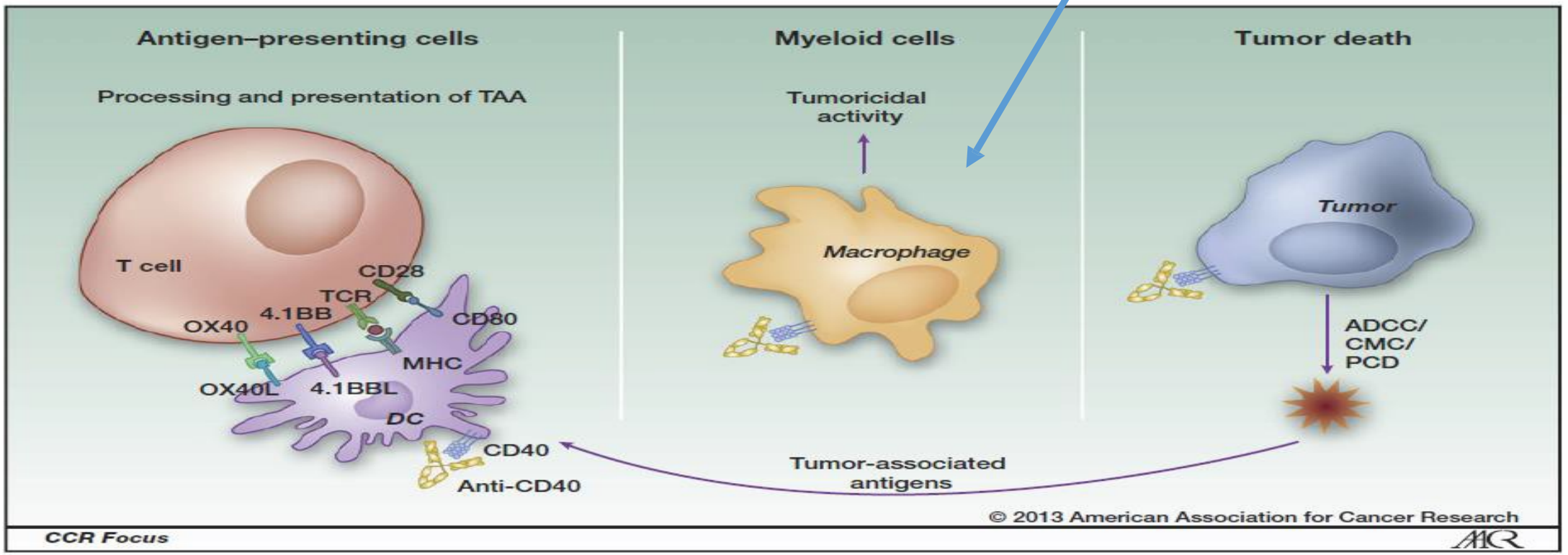
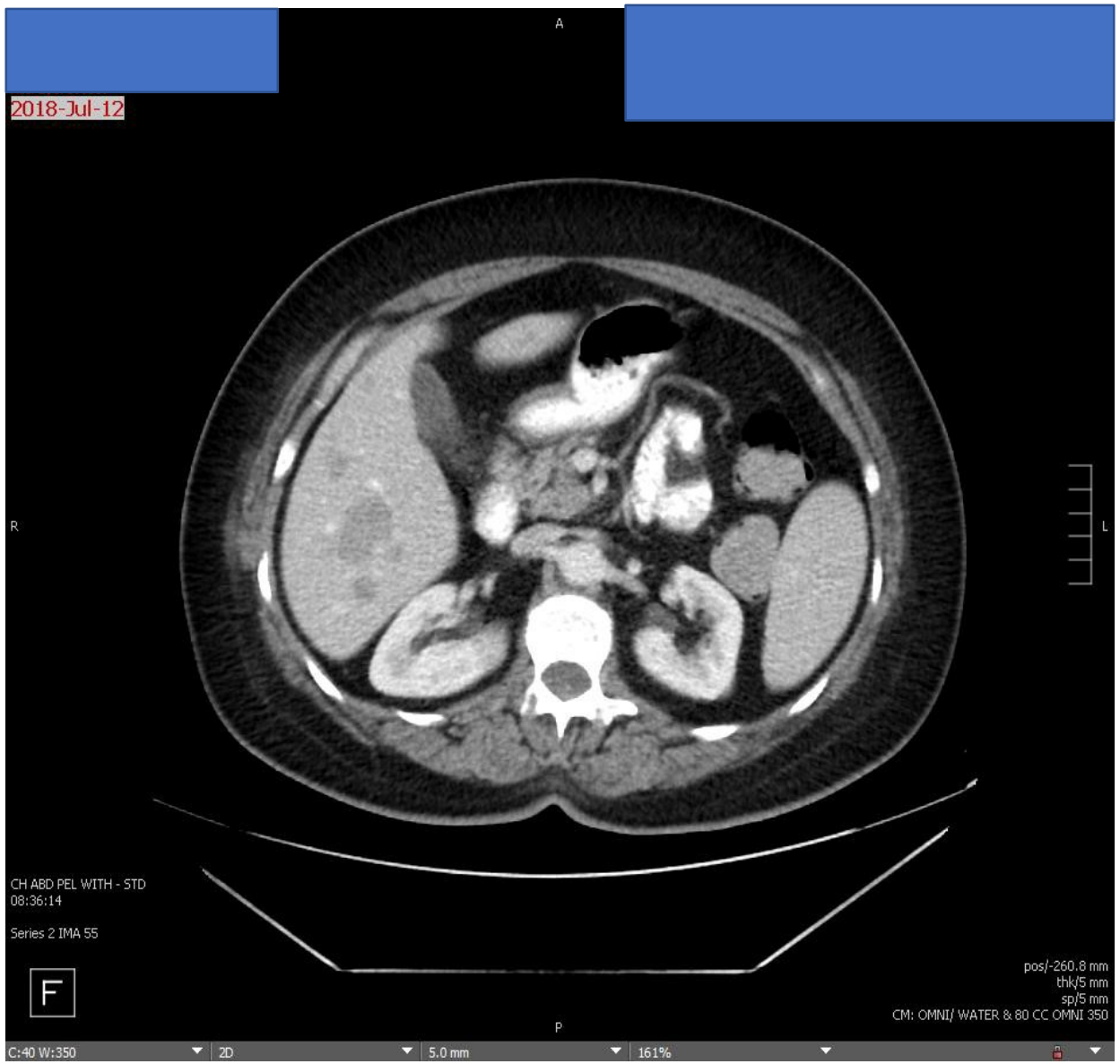
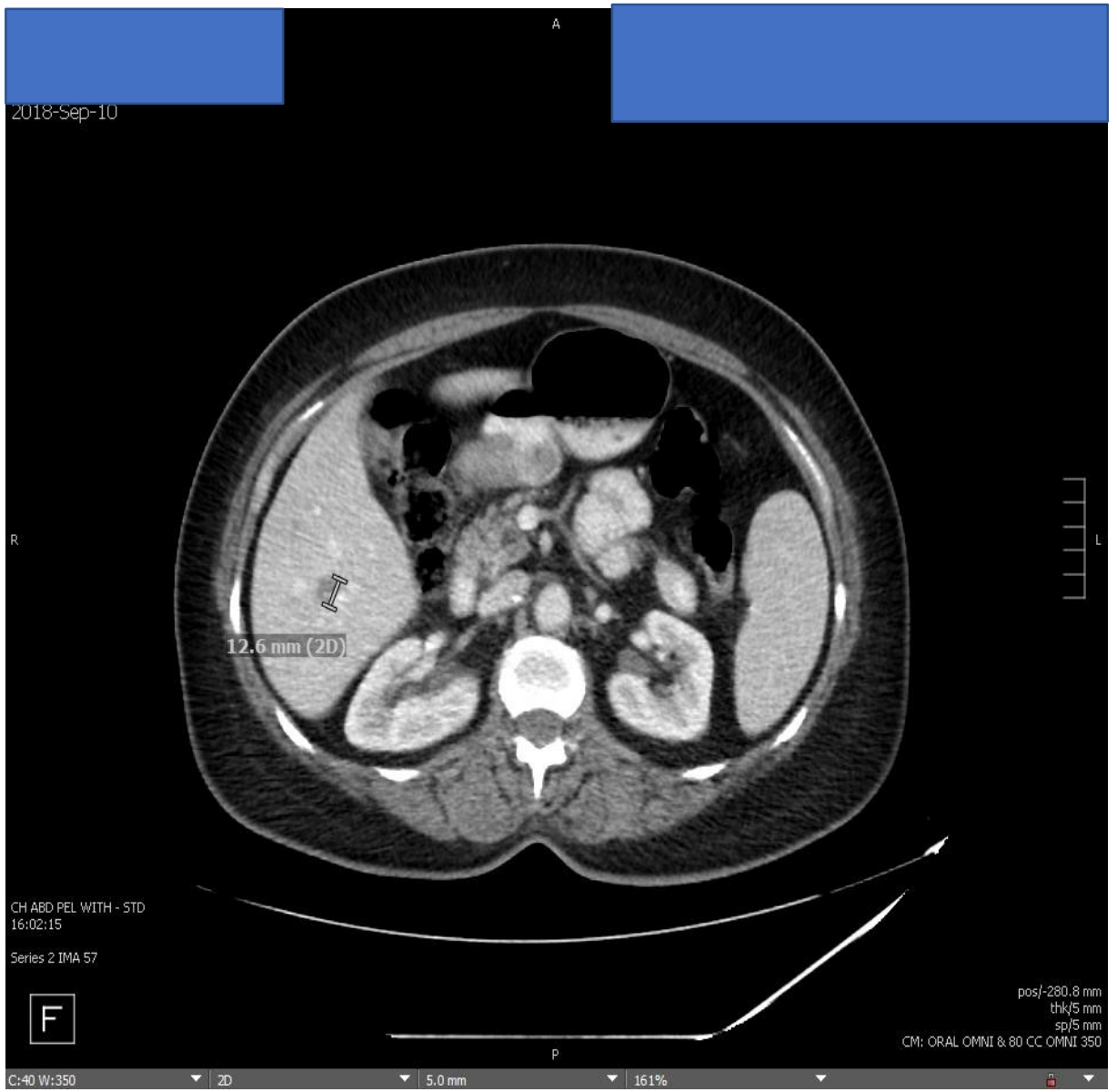


Figure 1. Potential mechanisms of action of agonistic CD40 mAb on various immune effectors. The primary consequence of CD40 mAb is to activate DC (often termed licensing; first panel) and potentially myeloid cells and B cells (not shown) and increase their ability to process and present tumor-associated antigens (TAA) to local cytotoxic T lymphocytes (CTL). Work from numerous model systems suggests that DC are the most potent in conducting this function and shows that only in tumors which are relatively immunogenic and hence have sufficient ongoing immune recognition will control be established with this treatment. Recent data from genetic tumor models now underscore the ability of agonistic CD40 mAb to generate tumoricidal myeloid cells (middle) when CTL responses cannot be established. Finally, agonistic CD40 mAb can have a cytotoxic effect on tumor by initiating ADCC, CMC, or programmed cell death (PCD; third panel; tumor). It is not clear to what extent anti-CD40 mAb can promote cell death in solid tumors, but hematologic malignancies are susceptible to killing. TAA released from dead and dying tumor cells [panel 3 (tumor)] have the potential to be cross-primed by APC and presented to CTL (panel 1) without the need for T-cell help.

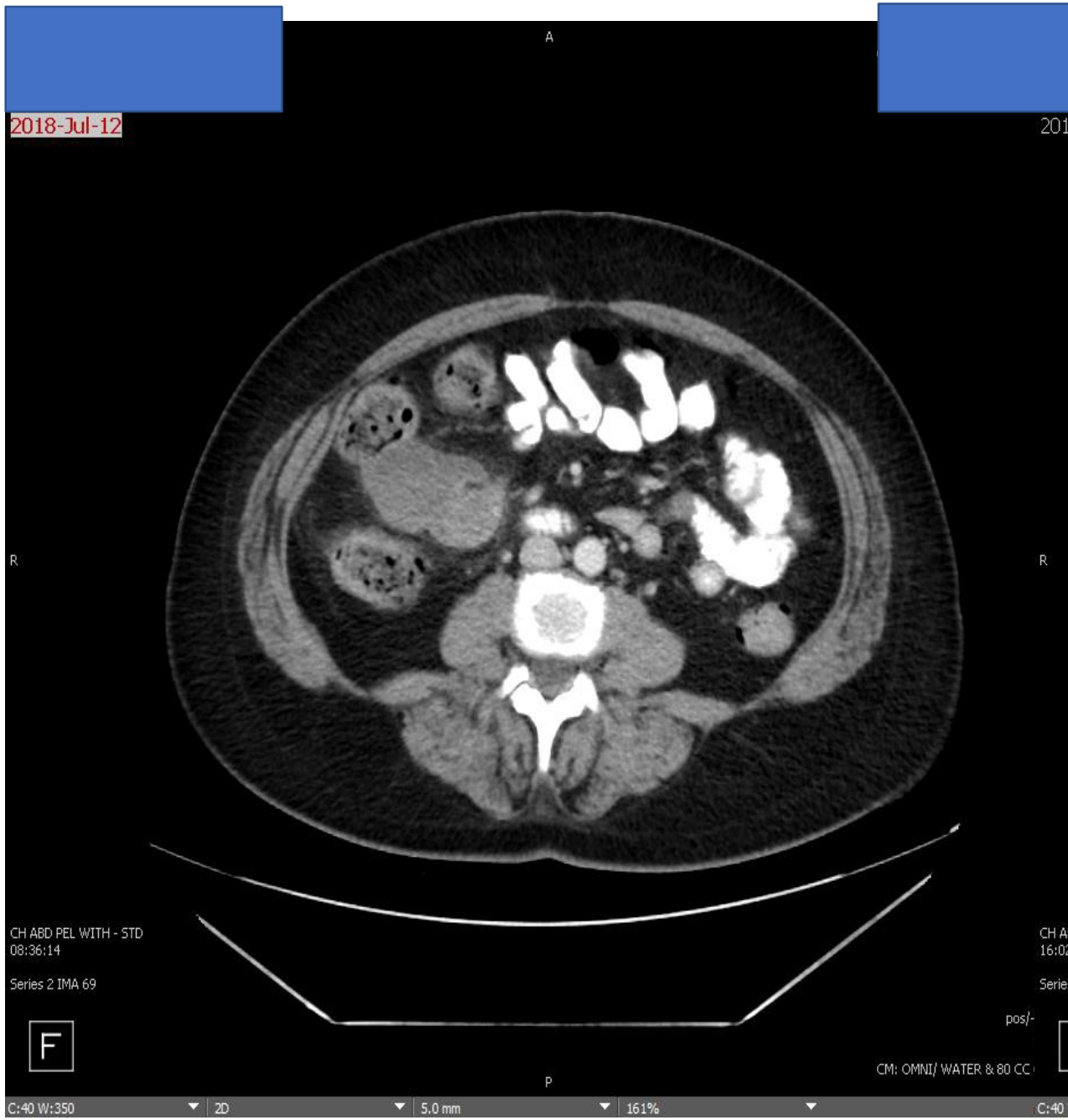
Clin Cancer Res; 19(5); 1035–43. ©2013 AACR.

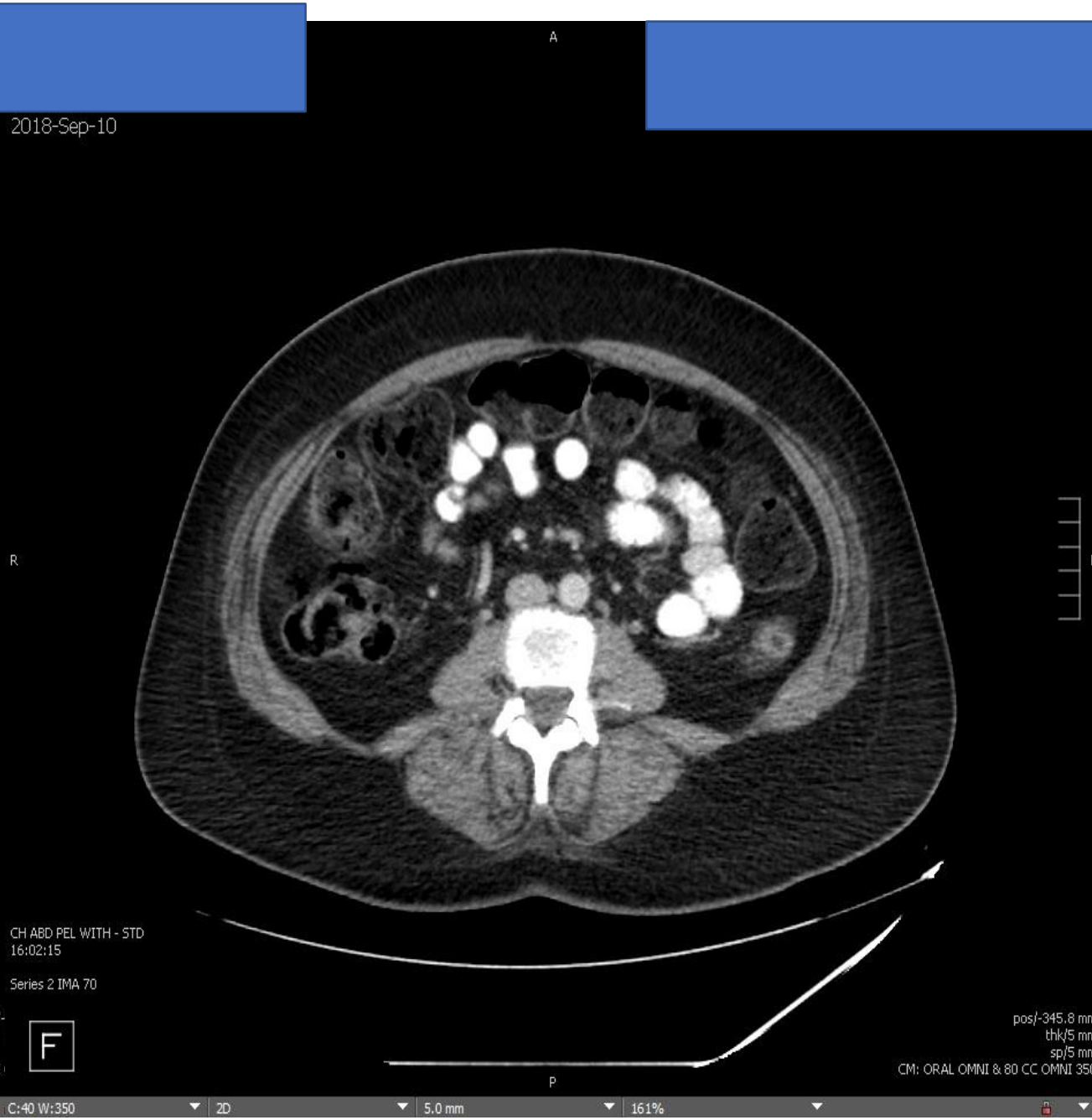
Response to Apexigen anti-CD-40 + Nivo in Metastatic Melanoma with Acquired Ipi/Nivo ->Nivo Resistance





Response to anti-CD-40 + Nivo in Metastatic Melanoma with Acquired Ipi/Nivo ->Nivo Resistance

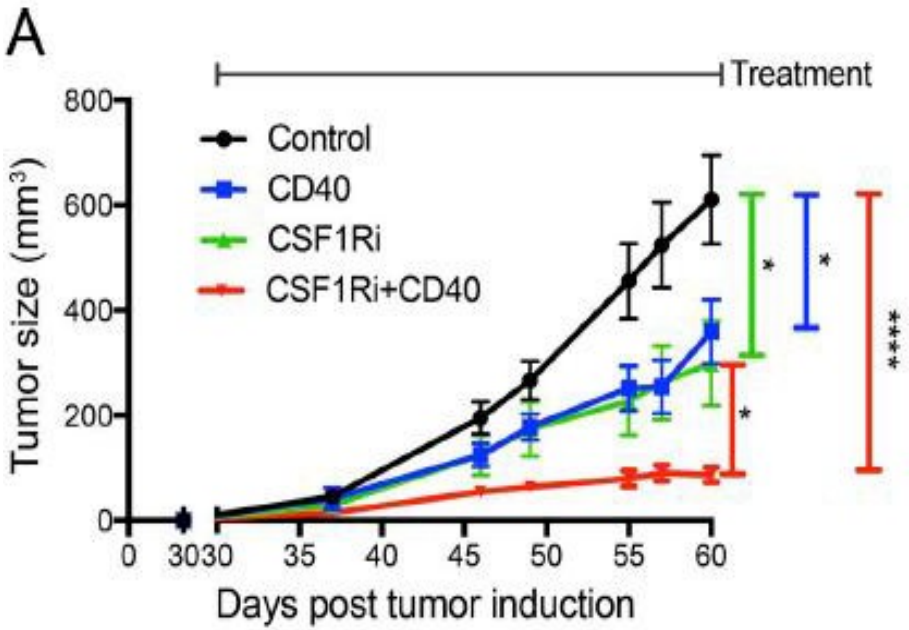


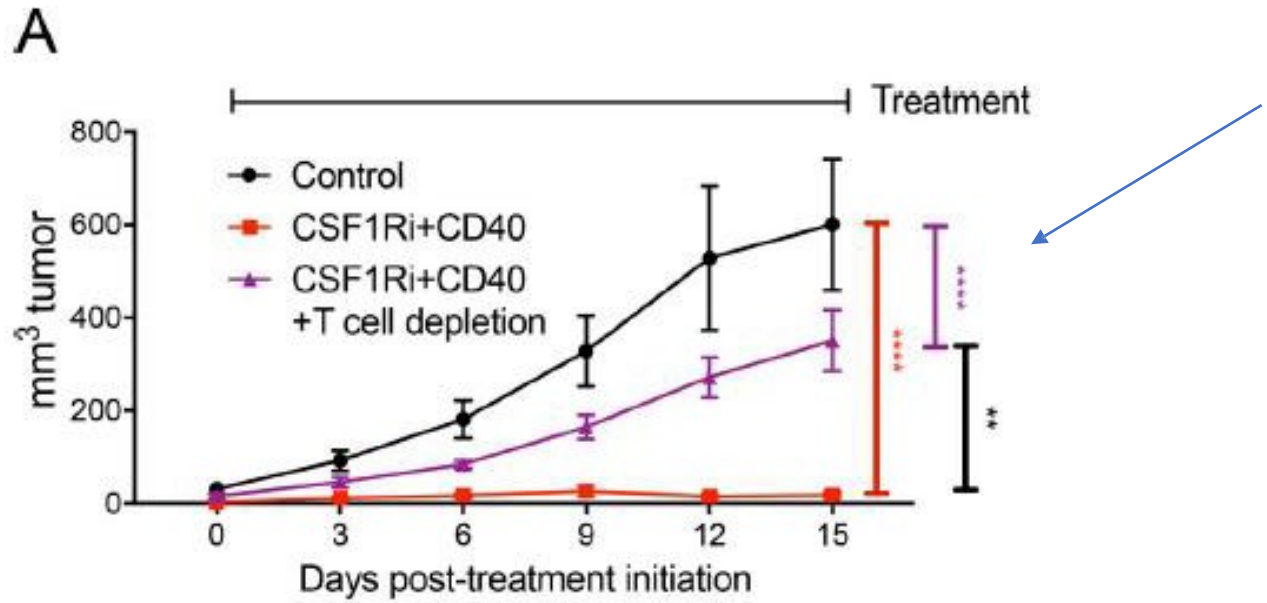


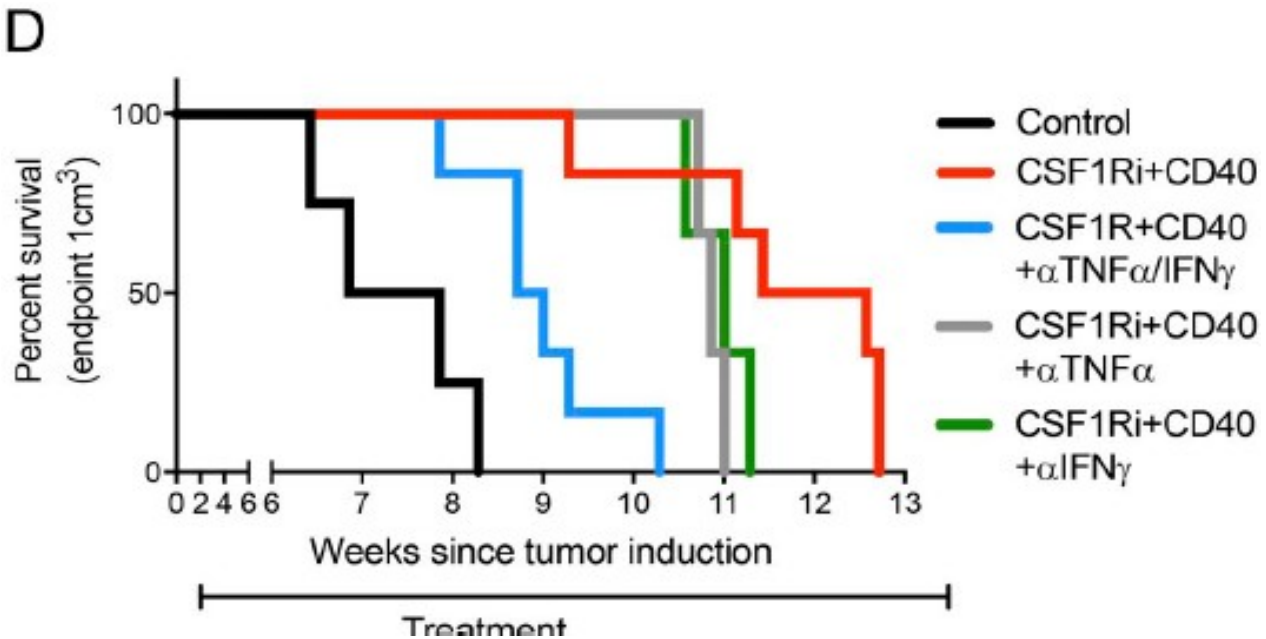
Other Targets for Macrophage/MDSC Modulation

- PI3K-gamma
- CD47
- MER-TK
- ILT2 or ILT4/HLA-G
- GM-CSF
- CSF-1R
- PD-1H
- Siglec-15
- TIM-3

Combinations targeting Macrophages/MDSC – component of non-T cell mediated immunity







The Rockefeller University Press
J. Exp. Med. 2018 Vol. 215 No. 3 877–893
https://doi.org/10.1084/jem.20171435

ADP-A2M4 (MAGE-A4) IN PATIENTS WITH SYNOVIAL SARCOMA

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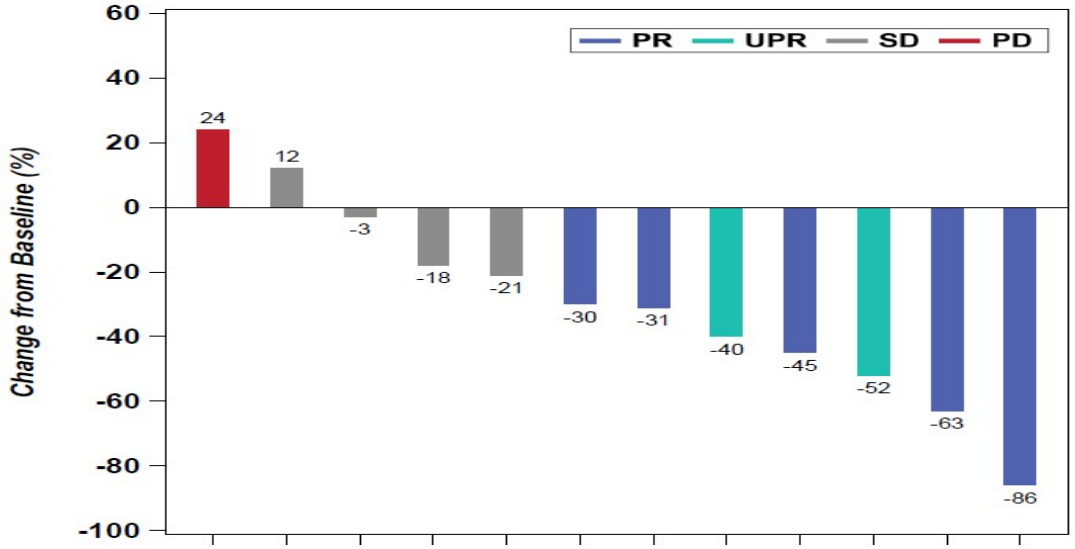
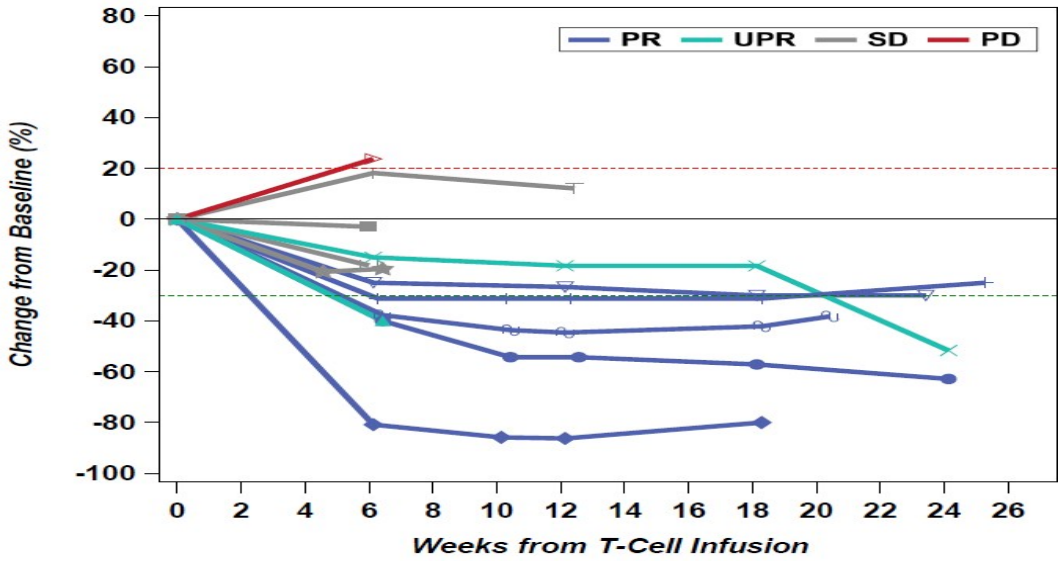
ADP-A2M4 SPEAR T-CELLS INDUCE CLINICAL RESPONSES

Best overall response in 12 patients* with post-baseline assessments

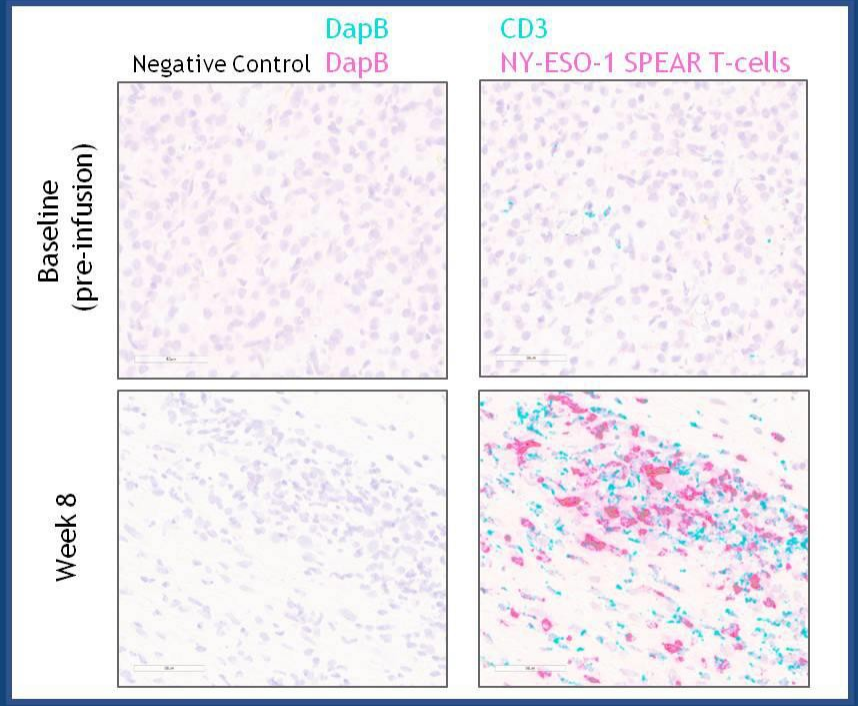




BARCELONA 2019 ESMO congress

*13th treated patient did not have post-baseline assessment at time of data cut off

Patient 11129: NY-ESO-1 SPEAR T-cells are Infiltrating the Tumor



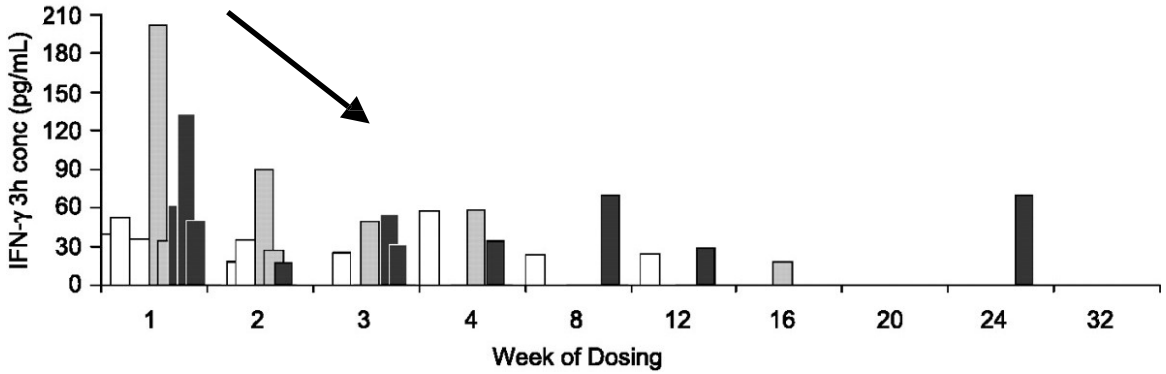
Cytokines – Current Trends

- Re-engineering
  - IL-2 - eliminating CD25 binding
  - IL-18 – mutant to eliminate binding to auto-regulatory IL-18BP
  - Pegylation – pro-drug to change PK, possibly receptor binding, biodistribution
- Novel cytokines (new functions)?
  - PEG- IL-10
- Combinations
  - With ligand-receptor inhibitory or co-stimulatory signals
  - Other modulators (vaccines, IT TLR)
  - Cytokine + cytokine
- Targeting to tumor or APC
  - FAP-IL-2v or CEA-IL-2v
  - Bispecifics (PD-L1/IL-15)
  - Masked cytokines (pro-drugs, tumor-specific activation)
  - Triggered production by CAR-T or other engineered adoptively transferred cells
  - IL-15 and IL-12 backpacks for ACT
- In vitro for cell expansion in ACT protocols

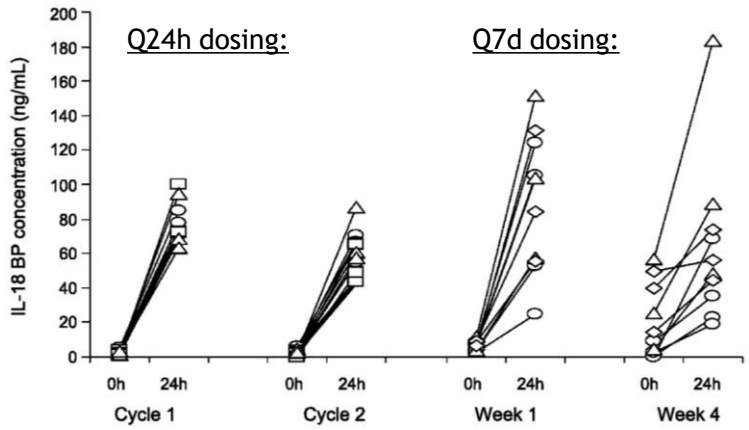
Clinical experience with rIL-18 therapy: Safe, well-tolerated, but ineffective through Ph2

Aaron Ring, Yale

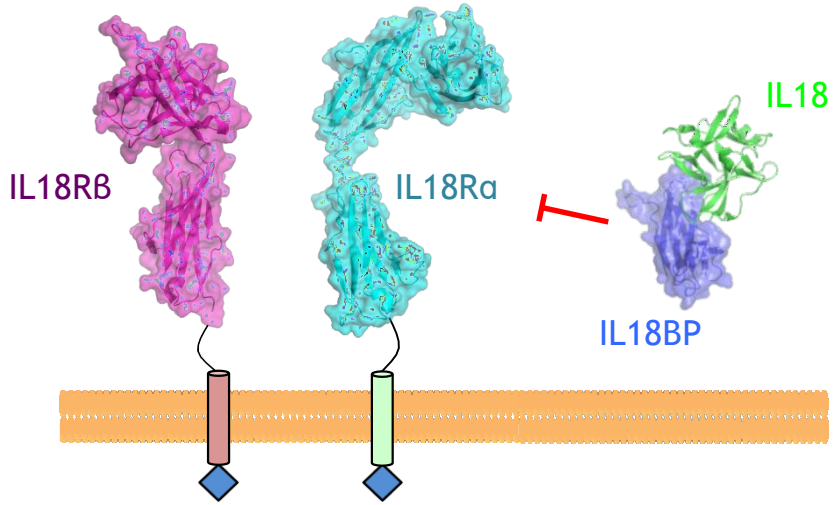
IL-18 PD activity wanes with repeated dosing



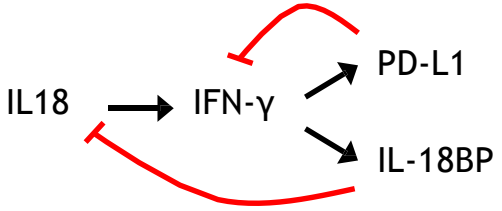
Corresponding to a massive systemic **upregulation of IL-18BP**:

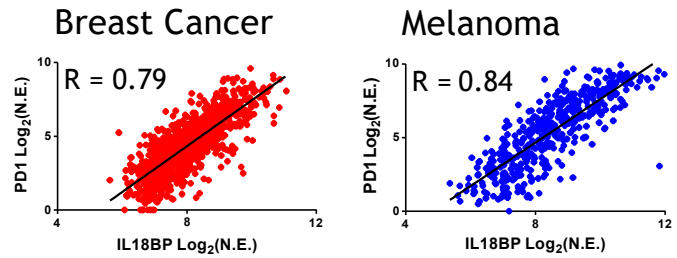


IL-18BP is a potent (2 pM) soluble decoy receptor that antagonizes IL-18



And is part of a negative feedback loop downstream of IFN-γ:



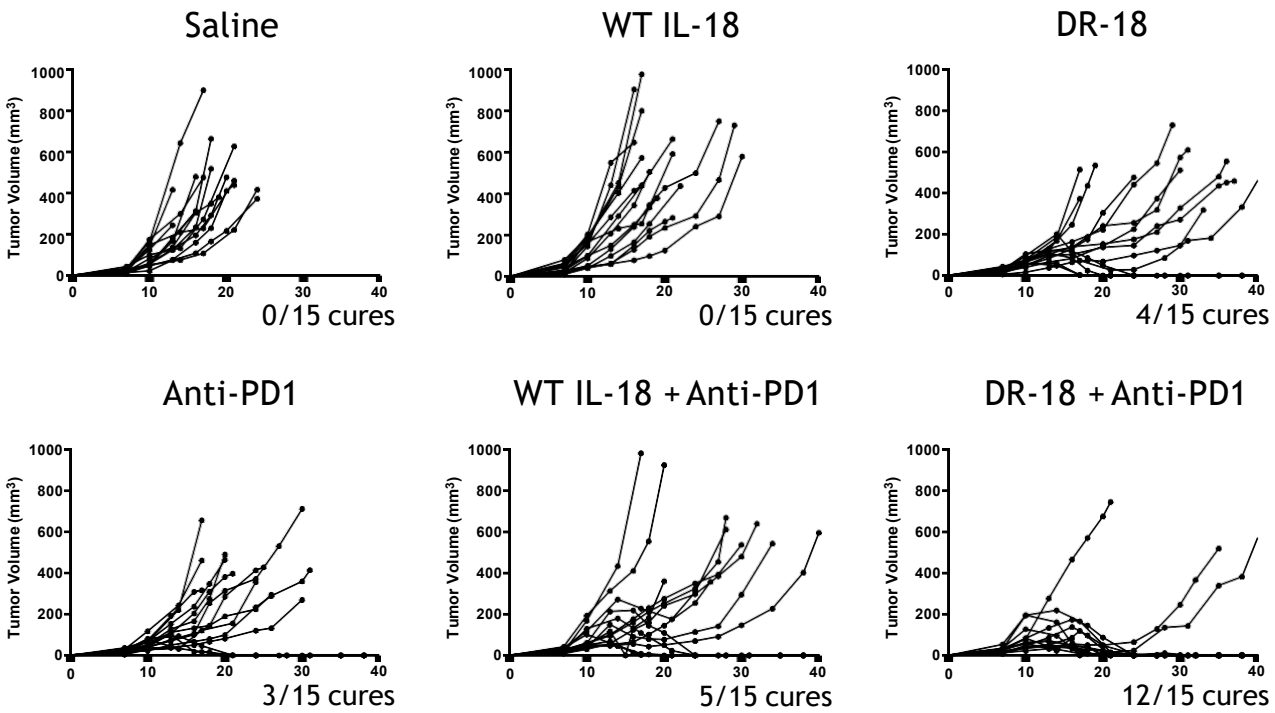


Hypothesis: IL-18BP is a soluble "immune checkpoint" and major barrier to the efficacy of IL-18 (and possibly other I/O agents)

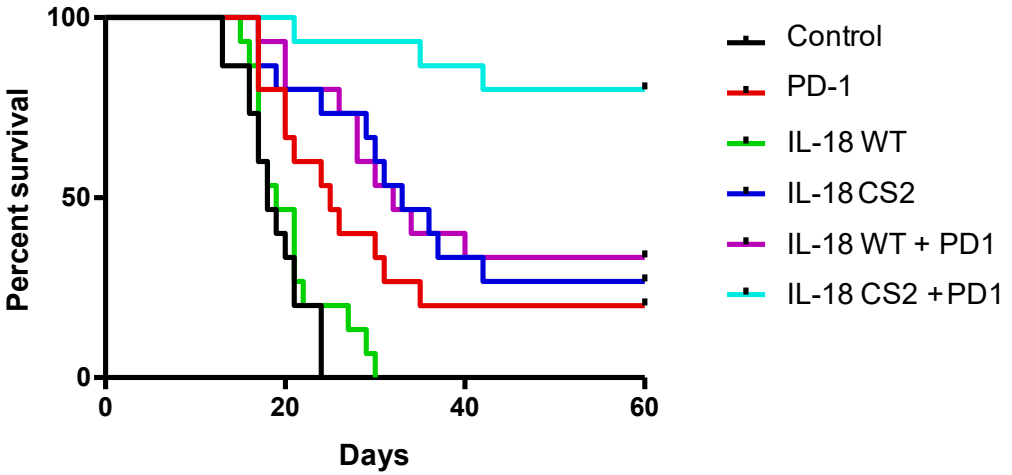
Robertson et al., Clinical Cancer Research, 2006| Robertson et al., Clinical Cancer Research, 2008

DR-18 is effective as a single agent and in combination with anti-PD1 antibodies

Yummer1.7 melanoma treatment model
Representative tumor growth spider plots:



Combined survival data (15 mice/group):



- Similar efficacy observed with MC38 and CT26 tumor models
- Treatment effect dependent upon CD8 and CD4 cells and IFN-g
- Cured mice show resistance to engraftment upon re-challenge with original tumor.

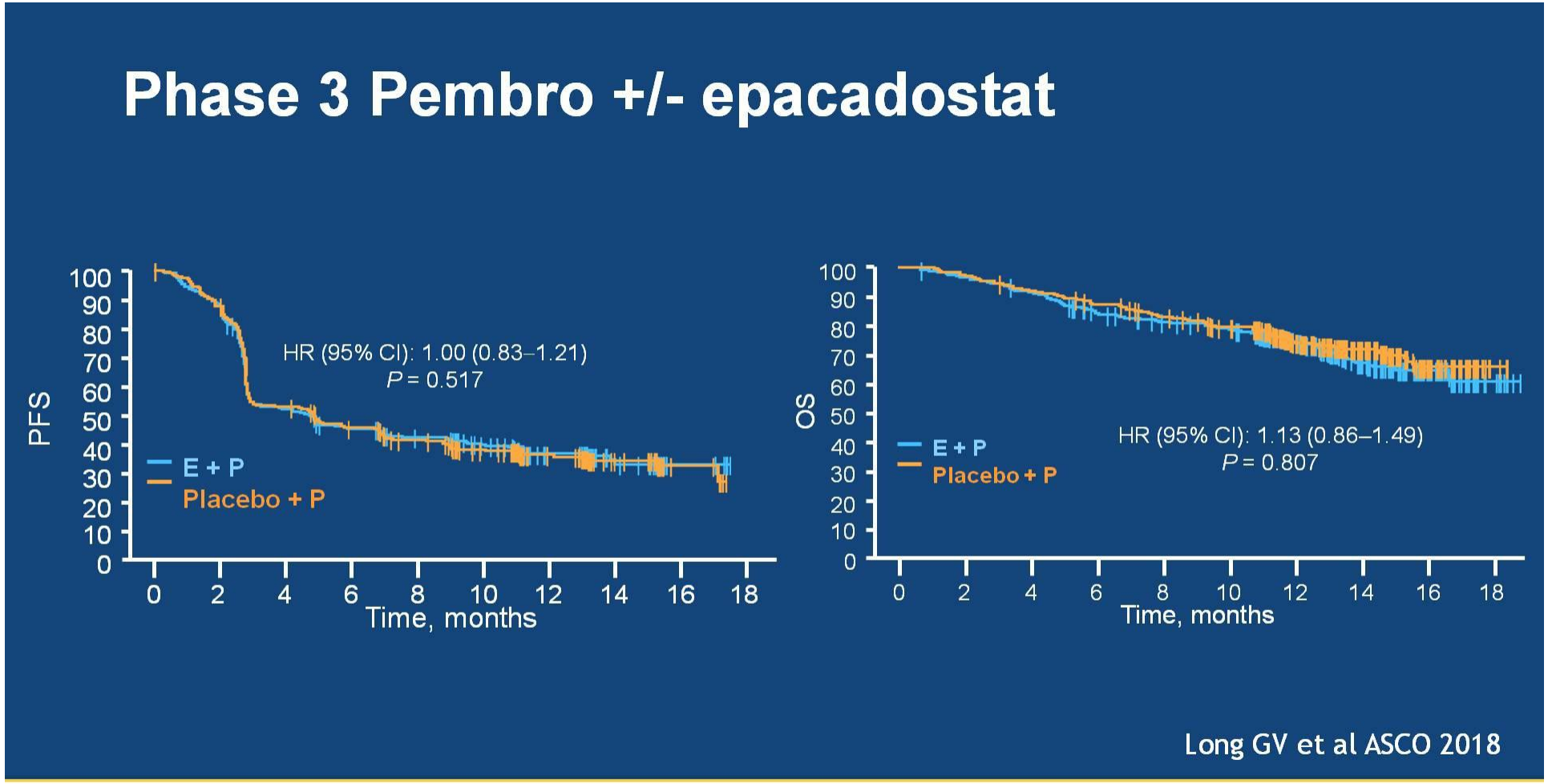
Aaron Ring, Yale

Too many inhibitory pathways for T-cells

- LAG-3
- TIM-3
- TIGIT, PVRIG
- SIGLEC-15
- NKG2A
- Vista
- (hypoxia) CD39/CD73/adenosine-A2AR pathway
- TGF-beta
- IDO

Which ones are critical and in which settings?

Promising IDOi Combination Data in Phase 2 Not Confirmed by Phase 3 Trial

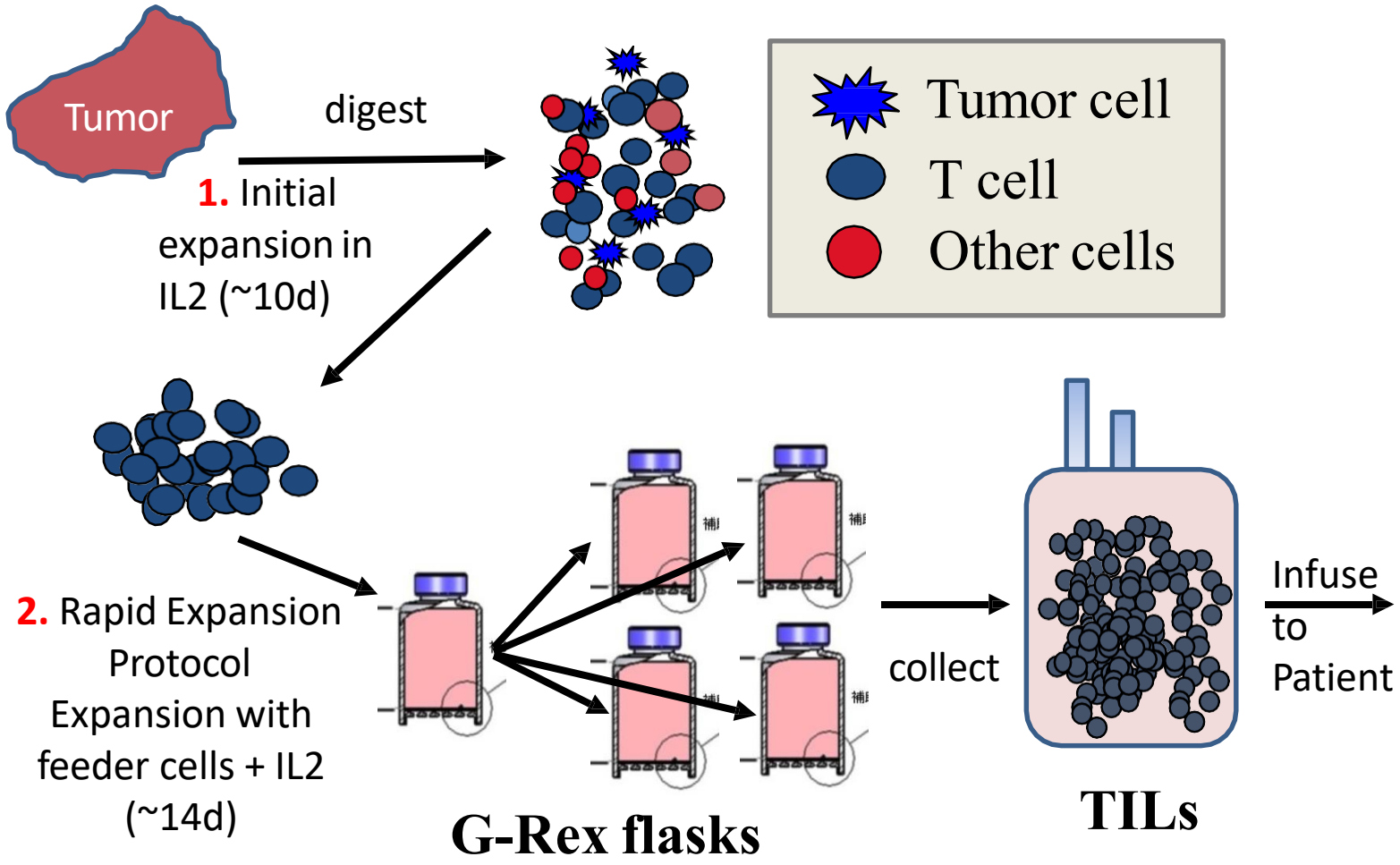


Presented By Alexander Menzies at 2018 ASCO Annual Meeting

Trends in bispecific development

- Multiple molecular constructs including ‘artificial’ Ab-like molecules
- Many potential combinations, multiple options for valency
- Two major approaches
  - Combine immunologic targets
    - Depends on proving bispecific activity > sum of individual components
    - 2 inhibitory targets (LAG3/PD-1), inhibitory + cytokine (PD-L1/IL-15), inhibitory + costimulatory (PD-L1/4-1BB), stimulatory (CD40/4-1BB)
  - Use bispecific to target to tumor
    - Her2, FAP, mesothelin, CD19, CD22, CD33, others
    - Immune molecules - CD3, 4-1BB, CD40, IL-2v, NK-activating molecules
  - ADCs are related but not usually immune modulatory

TIL Production



C-144-01 Cohort 2 Efficacy

RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	2 (3.0)
Partial Response	22 (33.3)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable[1]	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 26.9+

- After a median study follow-up of 18.7 months, median DOR was still not reached (range 2.2, 26.9+)
- Response was seen regardless of location of tumor resected
- Mean number of TIL cells infused: 27.3 x 10^9

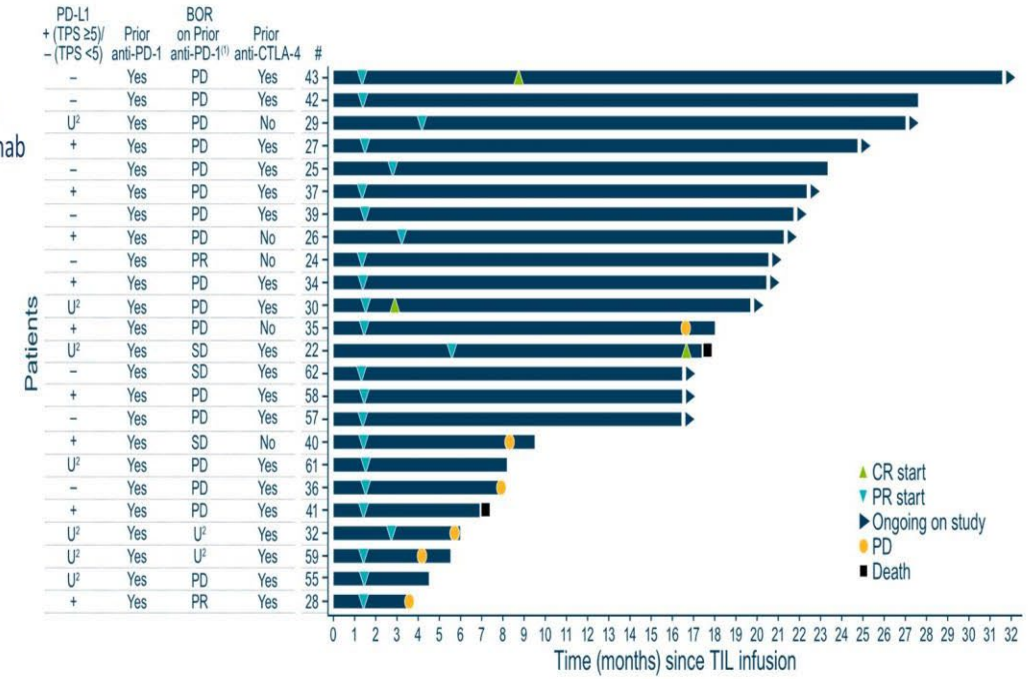
[1] NE due to not reaching first assessment.

C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

79% of responders had received prior ipilimumab

Responses deepen over time



[1] BOR is best overall response on prior anti-PD-1 immunotherapy
[2] U: unknown
[3] Patient 22 BOR is PR

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

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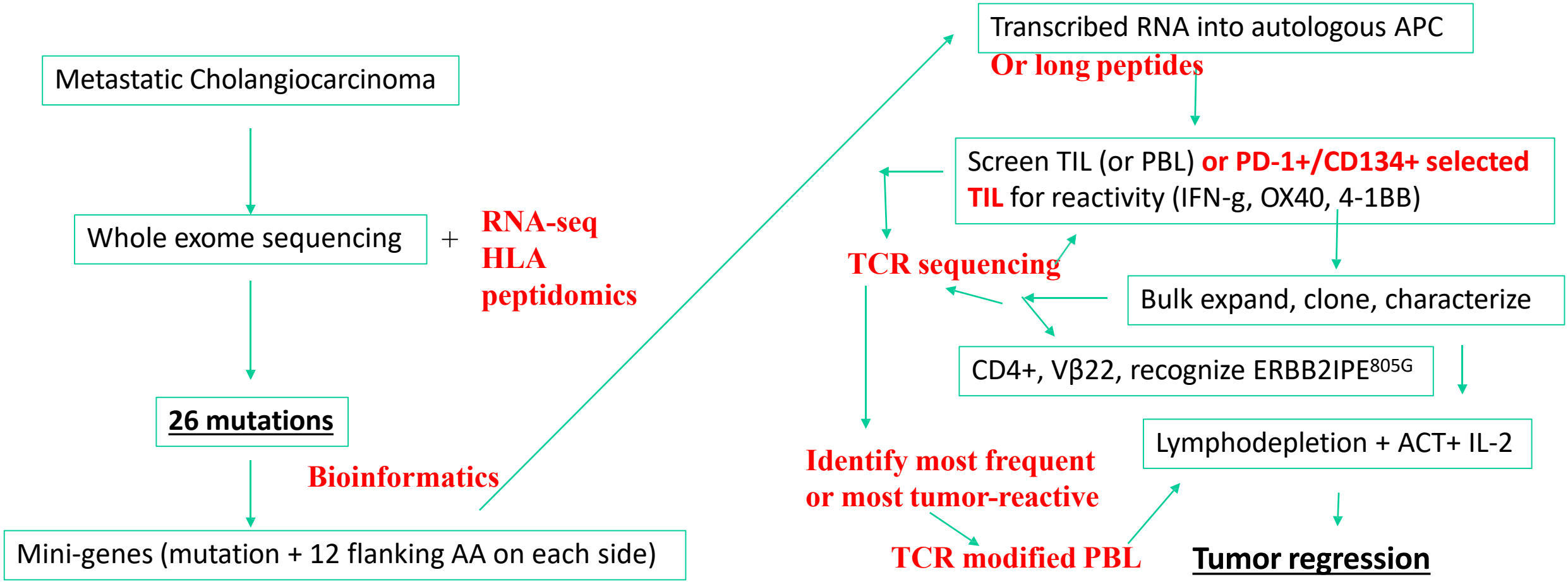
John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1]
Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1]‡



And Finally:

- Movement of immune therapies to the adjuvant and neoadjuvant setting
- Prospective identification and therapeutic intervention to prevent I-O toxicity
  - Biomarkers
  - Blockade of cytokines and cell subsets dispensable for anti-tumor effect