Combination Immunotherapy Approaches

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Complete Disclosure

- Consulting:
  Agenus, Dendreon, NexImmune, ImmunExcite, Janssen, Lilly, Merck, Pierre Fabre, Roche / Genentech

- Patents
  Amplimmune, BMS, Janssen

- Stockholder
  Compugen, NexImmune, Potenza, Tizona

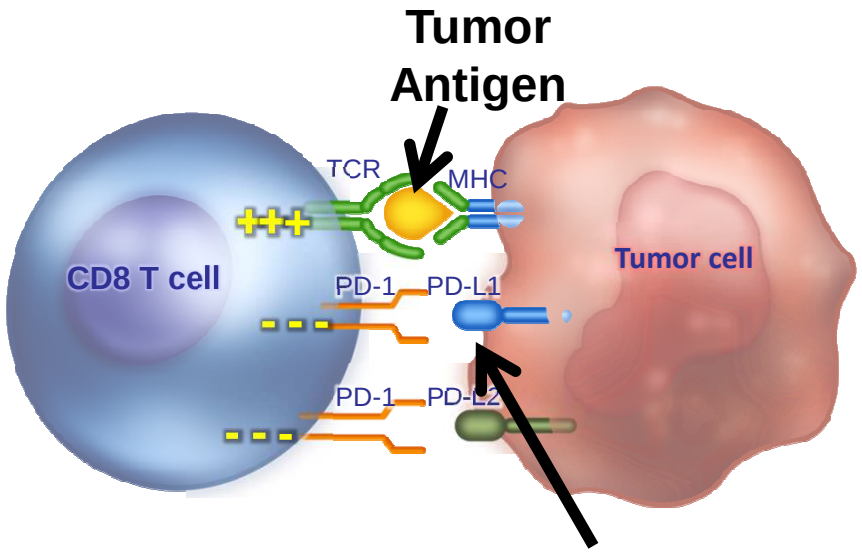
- Sponsored Research Agreement
  BMS, Janssen, Aduro Biotech

Several of the Agents Discussed are NOT FDA-approved for use in cancer treatment

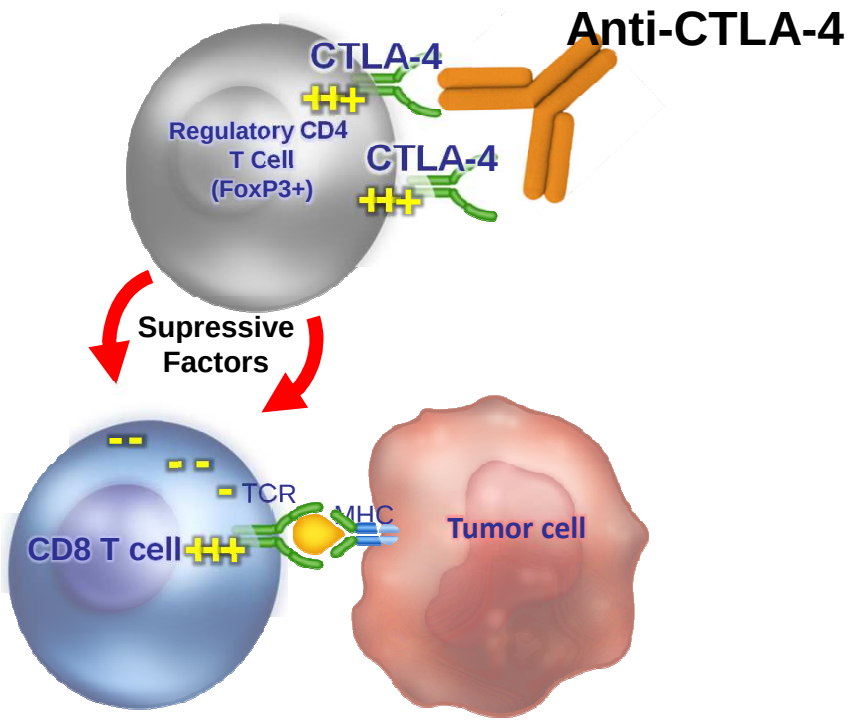
- Immunotherapy + Immunotherapy
  - Combined Checkpoint Blockade
  - Checkpoint + Agonist*
  - Checkpoint + Vaccine*
- Immunotherapy + Conventional Agent
  - + Hormonal Therapy
  - + Chemotherapy
  - + VEGF Inhibition
- Immunotherapy + Myeloid / Stromal Agent
  - + CSF-1R inhibition
  - + IDO inhibition
- Immunotherapy + Immune Activator
  - + Cancer Vaccine
  - + Intratumoral Activator

IO / IO

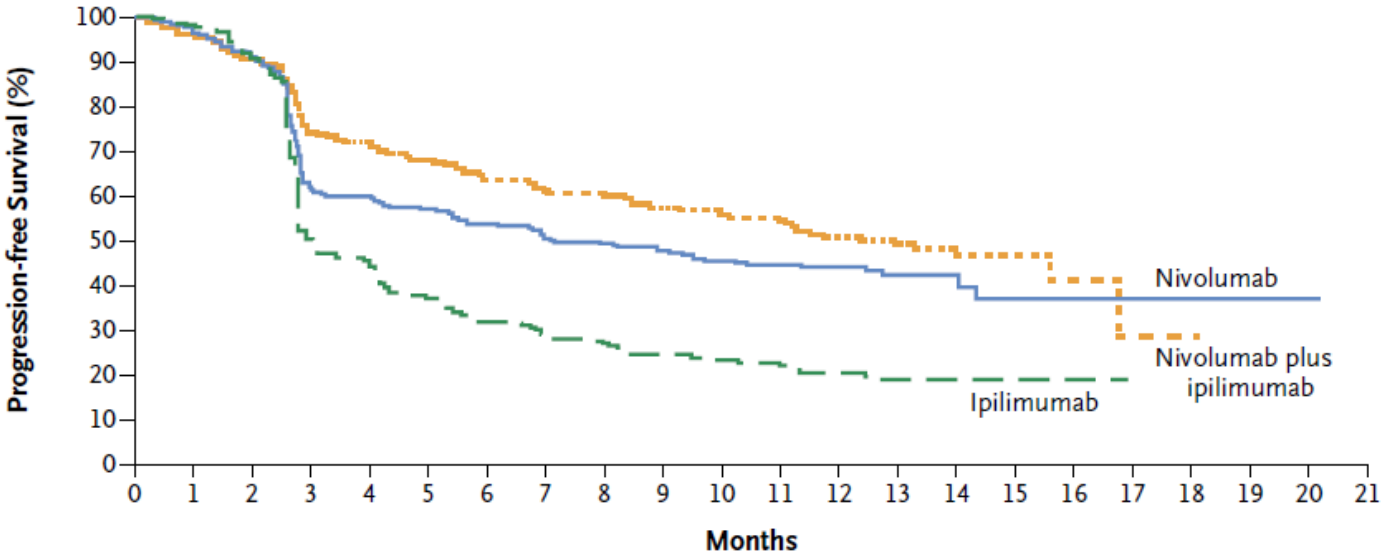
Biological Rationale:
Anti-PD-1 and Anti-CTLA-4 Act on Different Cell Types



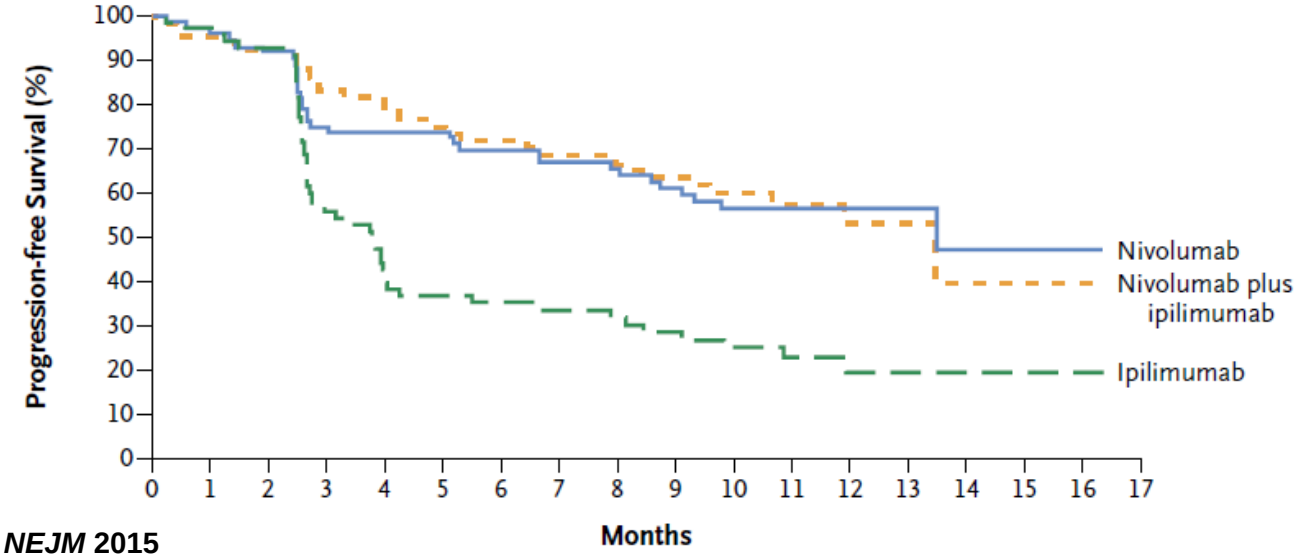
PD-L1 Expression on Tumor Cells OR Myeloid Cells SENDS a Negative Signal



Clinical Validation: Additive Effects on PFS

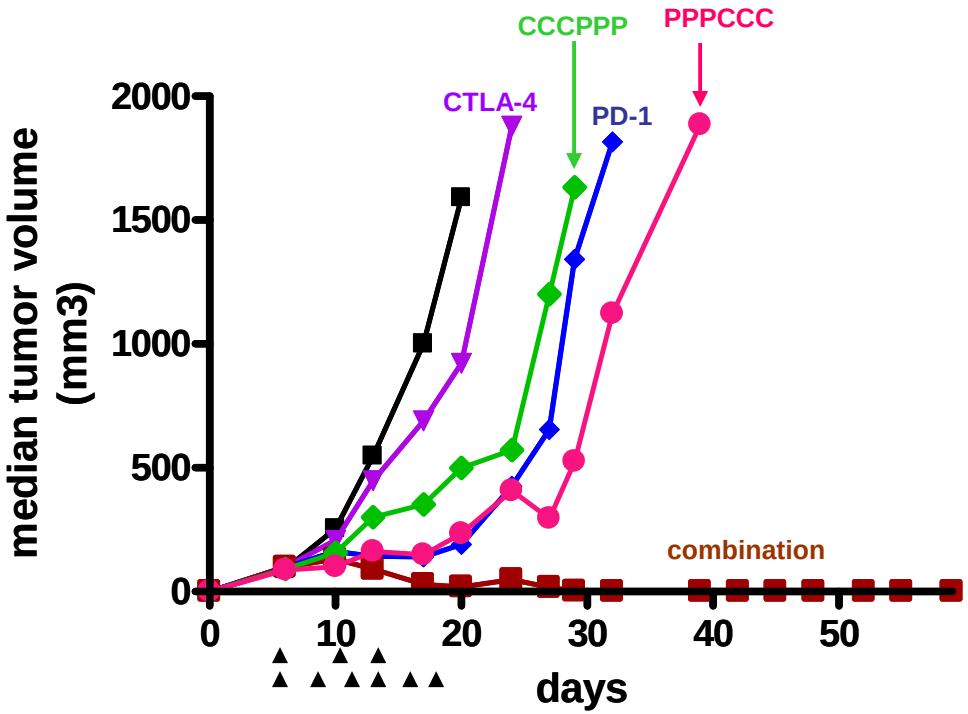


Patients with PD-L1–Positive Tumors



Larkin J et al, *NEJM* 2015

Animal Studies Showed Clear Synergy



injected on d0 with 2 x 10^6 cells
dosing d7,10,13 @ 10 mg/kg
or d6,9,11,13,16,18 @ 10 mg/kg

- Control
- α CTLA-4
- α PD-1
- α PD-1 + α CTLA-4
- CCCPPP
- PPPCCC

Courtesy of A. Korman

Toxicity Additive / Ipilimumab Driven

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	Cohort 1 (N=14)		Cohort 2 (N=17)		Cohort 2a (N=16)		Cohort 3 (N=6)		All Patients in Concurrent-Regimen Group (N=53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number of patients (percent)									
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)
Endocrinopathy	1 (7)	0	3 (18)	0	1 (6)	0	2 (33)	1 (17)	7 (13)	1 (2)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hyperthyroidism	0	0	1 (6)	0	0	0	1 (17)†		2 (4)†	0
Thyroid-function results abnormal	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Hepatic disorder	4 (29)	3 (21)	5 (29)	3 (18)	2 (12)	1 (6)	1 (17)	1 (17)	12 (23)	8 (15)
Aspartate aminotransferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (12)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)
Alanine aminotransferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (12)	0	1 (17)	1 (17)	11 (21)	6 (11)
Gastrointestinal disorder	5 (36)	1 (7)	6 (35)	2 (12)	6 (38)	2 (13)	3 (50)	0	20 (38)	5 (9)
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)
Renal disorder	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Acute renal failure	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)
Renal failure	0	0	1 (6)	1 (6)	0	0	0	0	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Skin disorder	10 (71)	1 (7)	14 (82)	0	10 (62)	1 (6)	3 (50)	0	37 (70)	2 (4)
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0
Urticaria	0	0	0	0	1 (6)	0	0	0	1 (2)	0
Blister	0	0	1 (6)	0	0	0	0	0	1 (2)	0
Infusion-related reaction	0	0	1 (6)	0	0	0	0	0	1 (2)	0

* Only the highest grade of event was counted for each patient. Adverse events that require more frequent monitoring or intervention with immune suppression or hormone replacement are listed, according to a prespecified list of terms from the *Medical Dictionary for Regulatory Activities*, version 15.1. The dose levels in the cohorts were as follows: cohort 1 received 0.3 mg of nivolumab per kilogram of body weight and 3 mg of ipilimumab per kilogram, cohort 2 received 1 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram, cohort 2a received 3 mg of nivolumab per kilogram and 1 mg of ipilimumab per kilogram, and cohort 3 received 3 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram. The doses in cohort 3 exceeded the maximum doses that were associated with an acceptable level of adverse events, and the doses in cohort 2 were identified as the maximum doses that were associated with an acceptable level of adverse events. The numbers reported for the specific adverse events within an organ category may be greater than the total number reported for the organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.

† Data include one patient with an event of unknown grade.

Hepatitis

Colitis

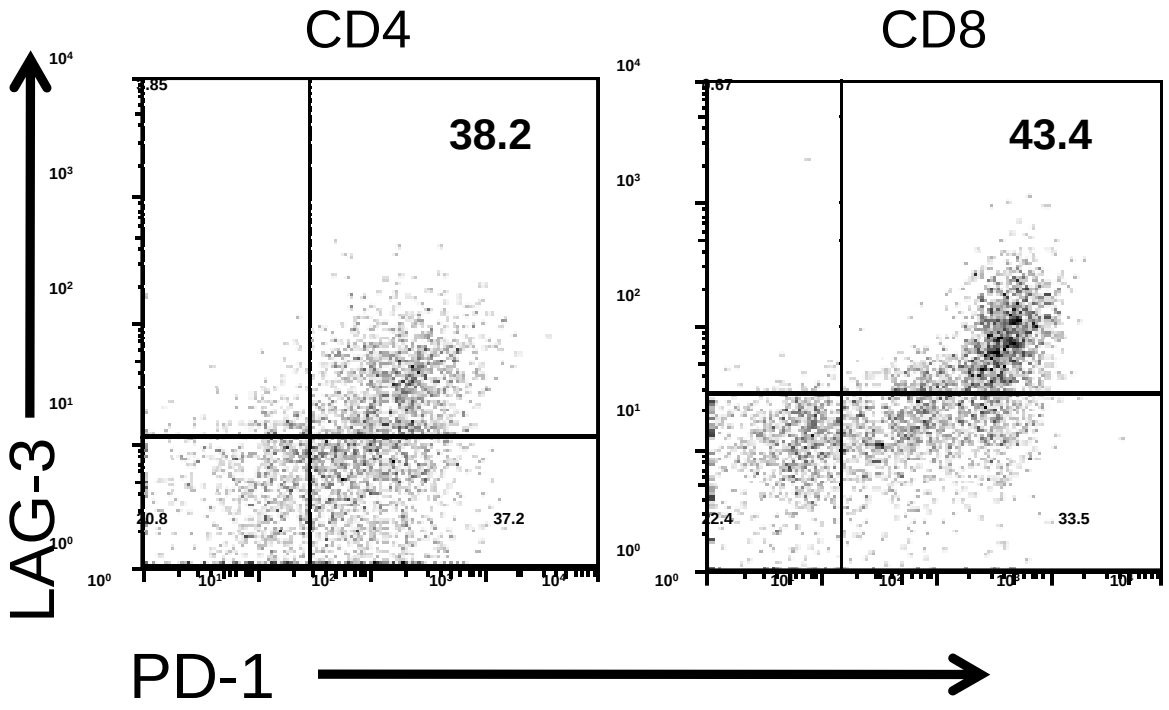
Nephritis

Dermatitis

The NEW ENGLAND JOURNAL of MEDICINE

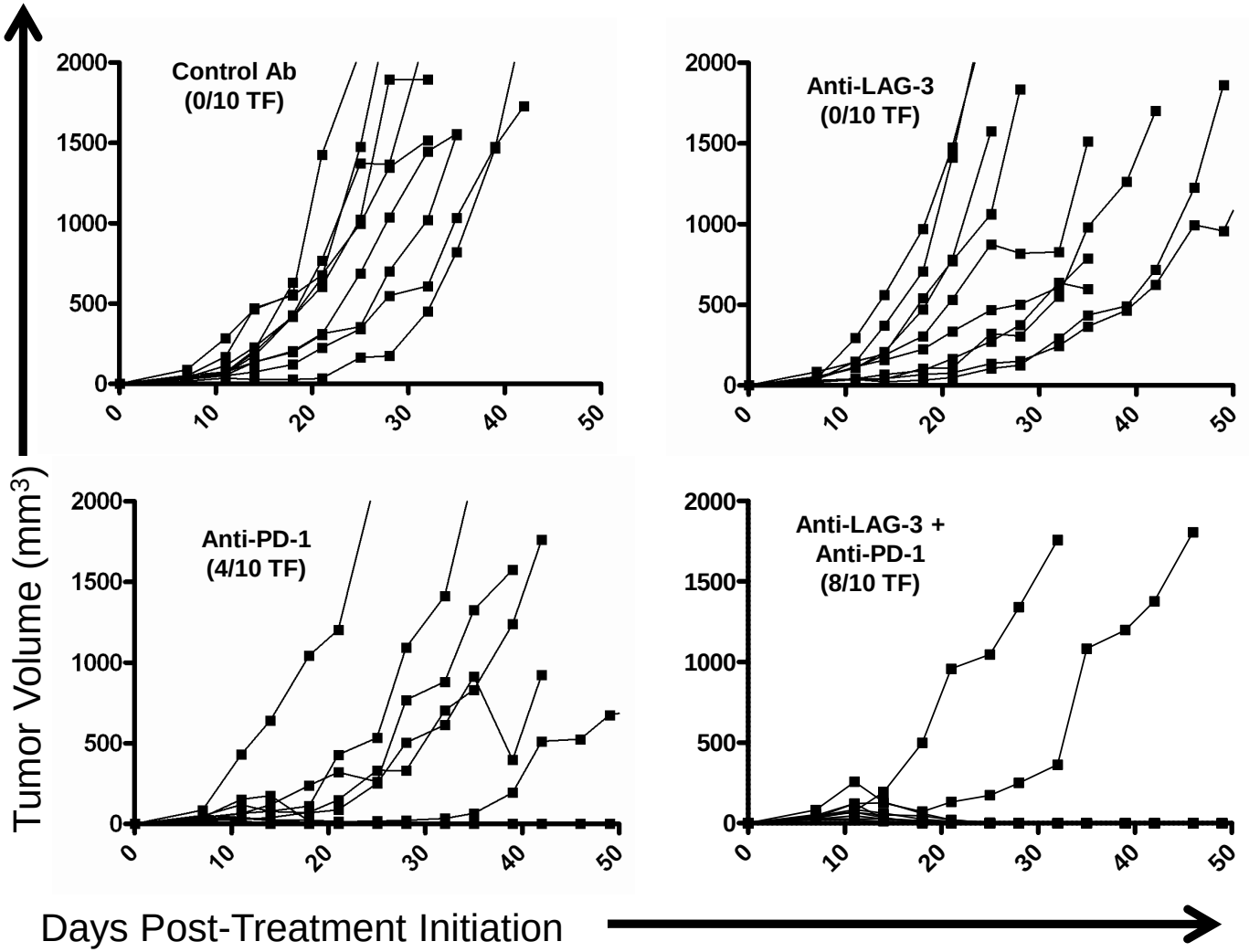
Wolchok JD et al. N Engl J Med 2013;369:122-133

Biological Rationale:
Targeting Multiple Checkpoint Molecules on the SAME Cell



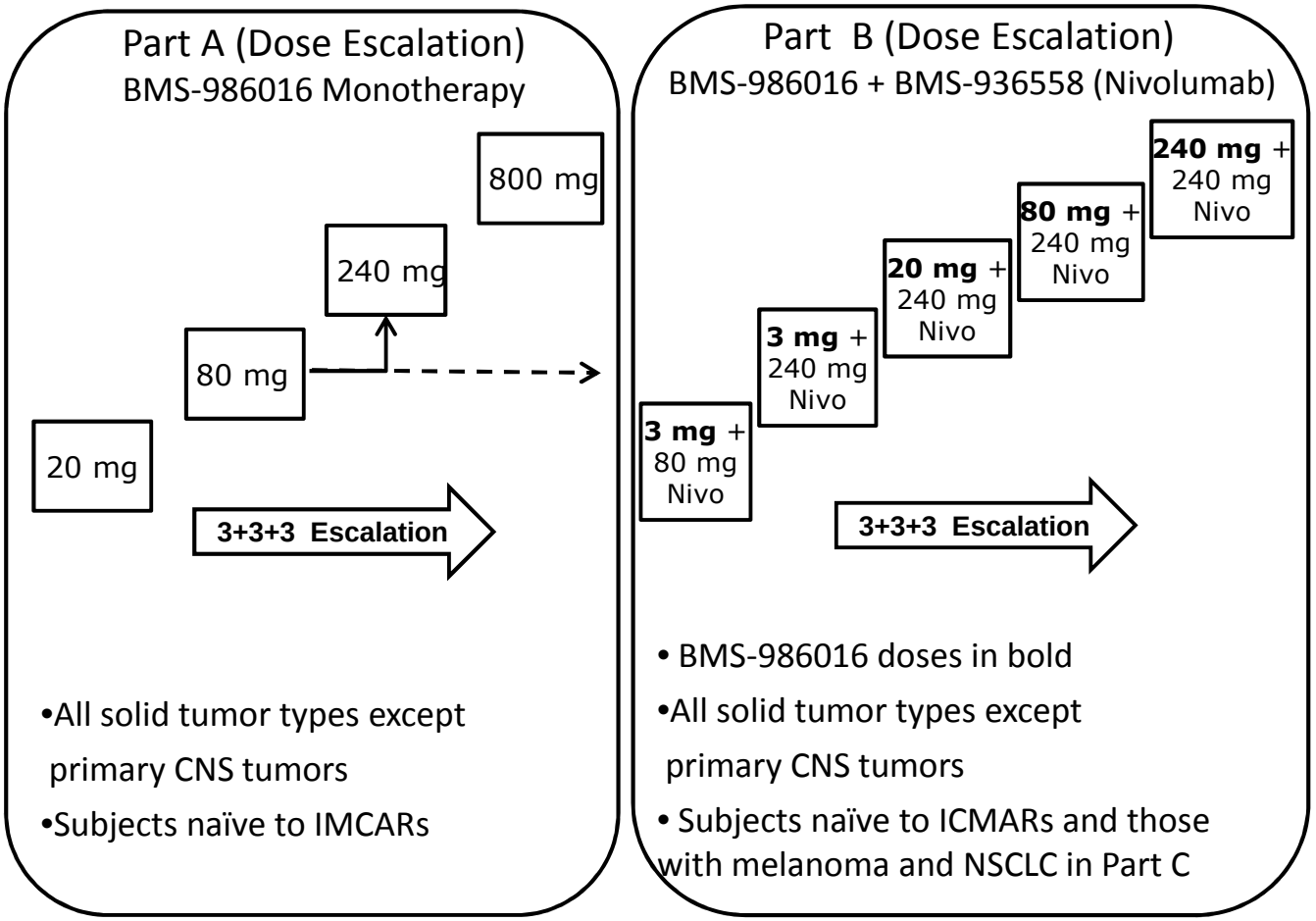
Woo, Goldberg, Drake and Vignali. *Cancer Research 2013*

Animal Studies Show Clear Synergy



Day 7 Staged MC38 – Similar Results in Staged SA1N

CA224-020 Study Schematic



Courtesy of Andres Gutierez, BMS

IO + Conventional Agent

The NEW ENGLAND JOURNAL of MEDICINE

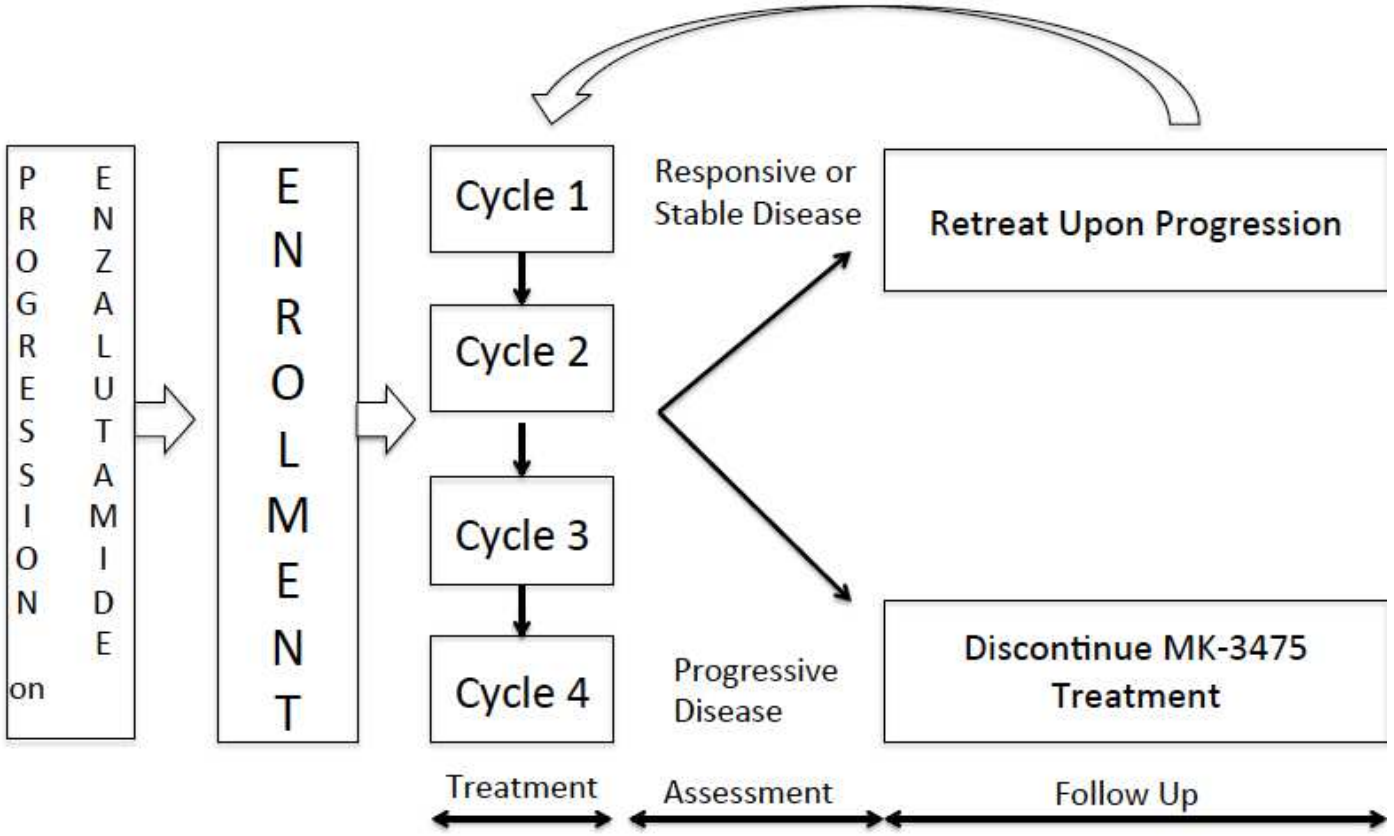
ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

"No objective responses were observed in patients with colorectal or prostate cancer."

Adding Checkpoint Inhibition to Enzalutamide Progressors



PI: Dr. Julie Graff – Oregon Health Sciences University

Responder Details

Responder	Cycle 1	PSA (ng/ml) every 3-weeks and nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI
1	April 2015	**70.65** → 11.11 → 1.18 → 0.11 → **0.08**	Yes (lymph)	PR	present
2	October 2015	**46.09** → 41.22 → 12.99 → 9.89 → **0.02**	No	n/a	n/a
3	January 2016	**2502.75** → 1.26 → 0.07 →0.01 → **<0.01**	Yes (liver)	PR	absent
4	March 2016	**82.43** → 17.34 → 0.3 → **0.01**	No	n/a	n/a
5	June 2016	**250** → 88.69 → 5.1 → 0.43 → **0.18***	Yes (liver)	PR	pending

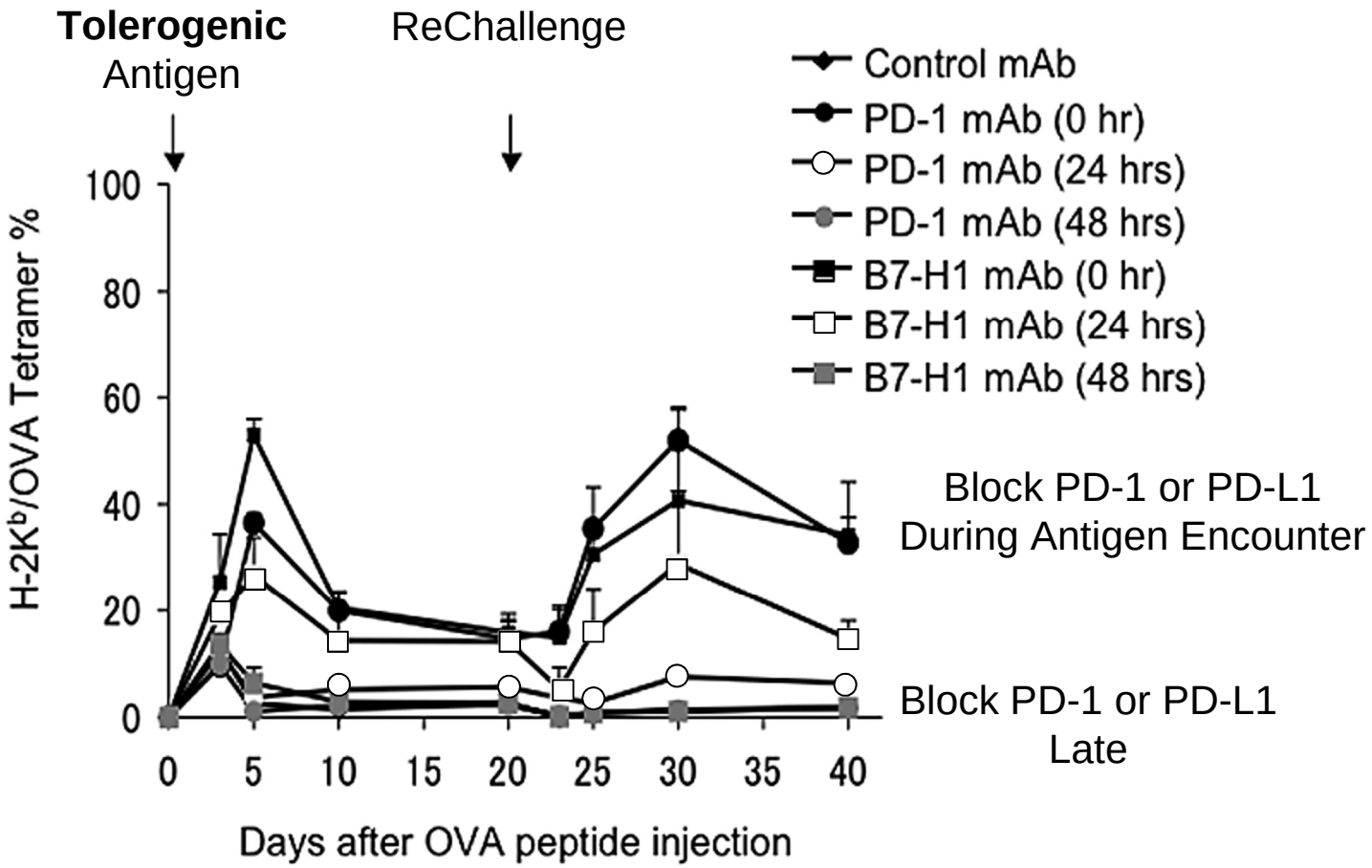
None of the responders have relapsed.

J Graff ESMO 2016

Potential Immunological Effects of Conventional Chemotherapy

- Immunogenic Cell Death
  - Release of tumor antigens
  - Presentation of tumor antigens
  - Likely depends on chemotherapy agent and dose
- Destruction of Immuno-Suppressive Populations
  - Myeloid Derived Suppressor Cells
  - M2 macrophages
- Homeostatic Proliferation -> Acquisition of Effector Function

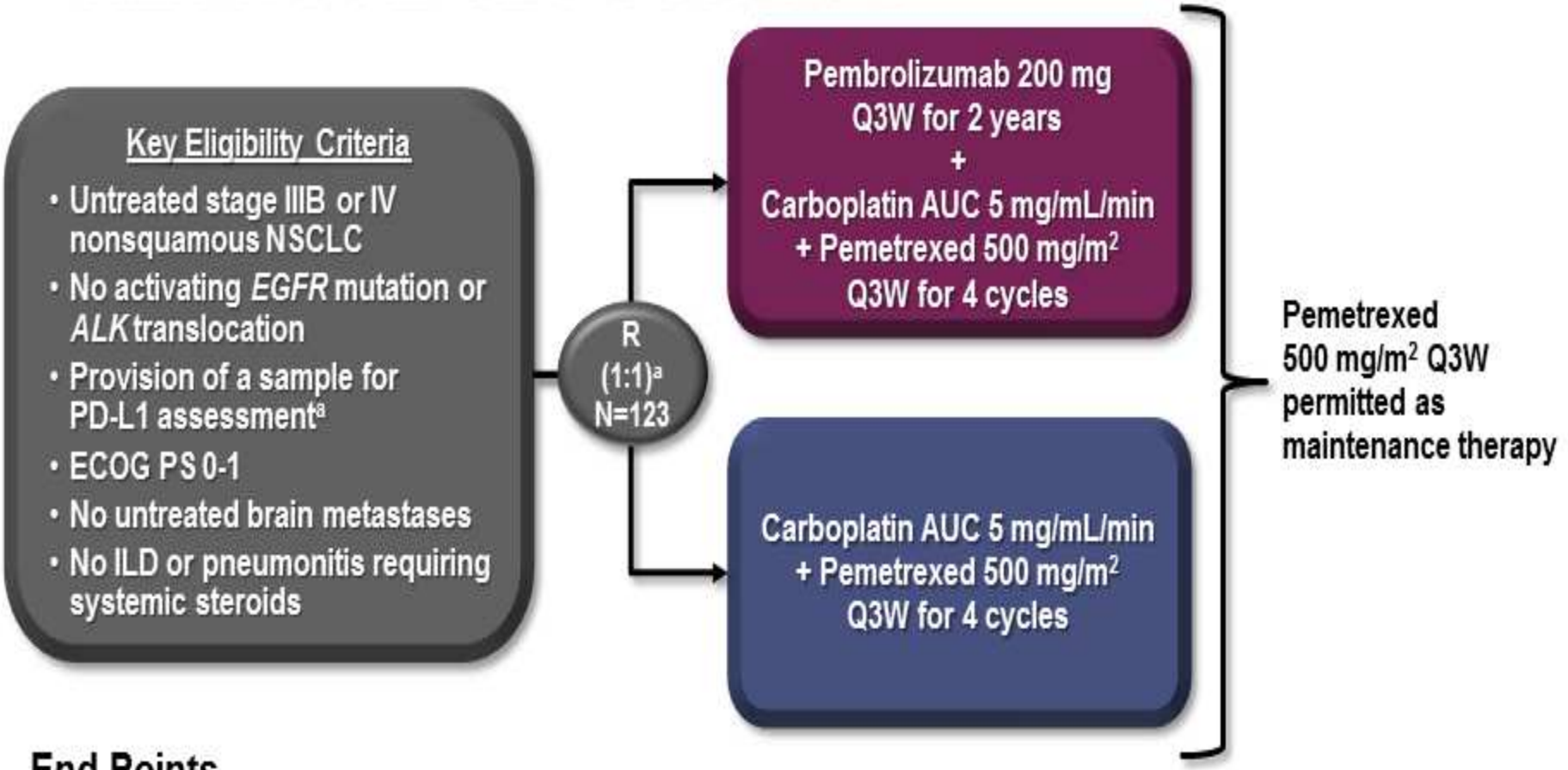
Rationale For Chemotherapy / IO Combinations: Programming the Immunological Outcome of Antigen Encounter



Tsushima F et al. Blood 2007;110:180-185

CJ Langer. ESMO 2016.

KEYNOTE-021 Cohort G



End Points

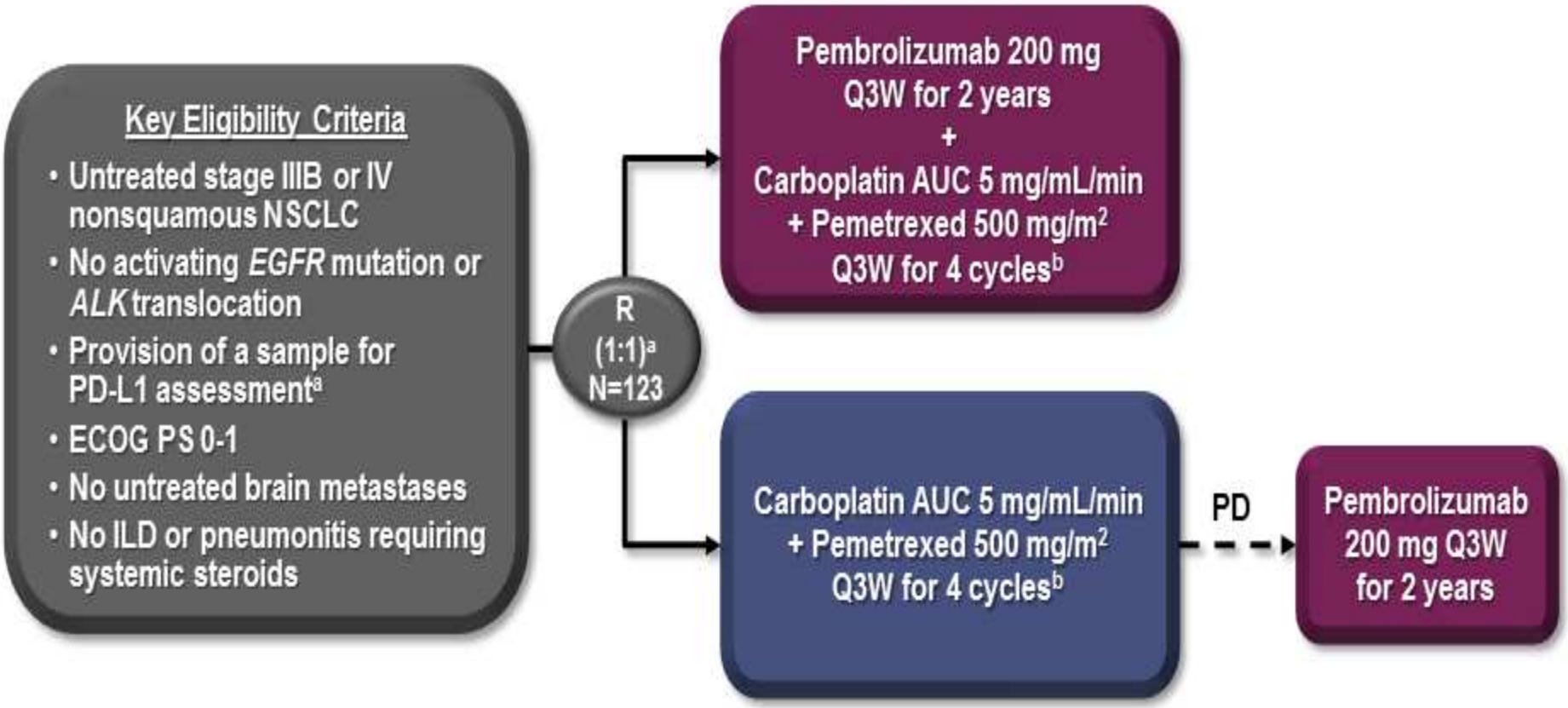
Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

KEYNOTE-021 Cohort G



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

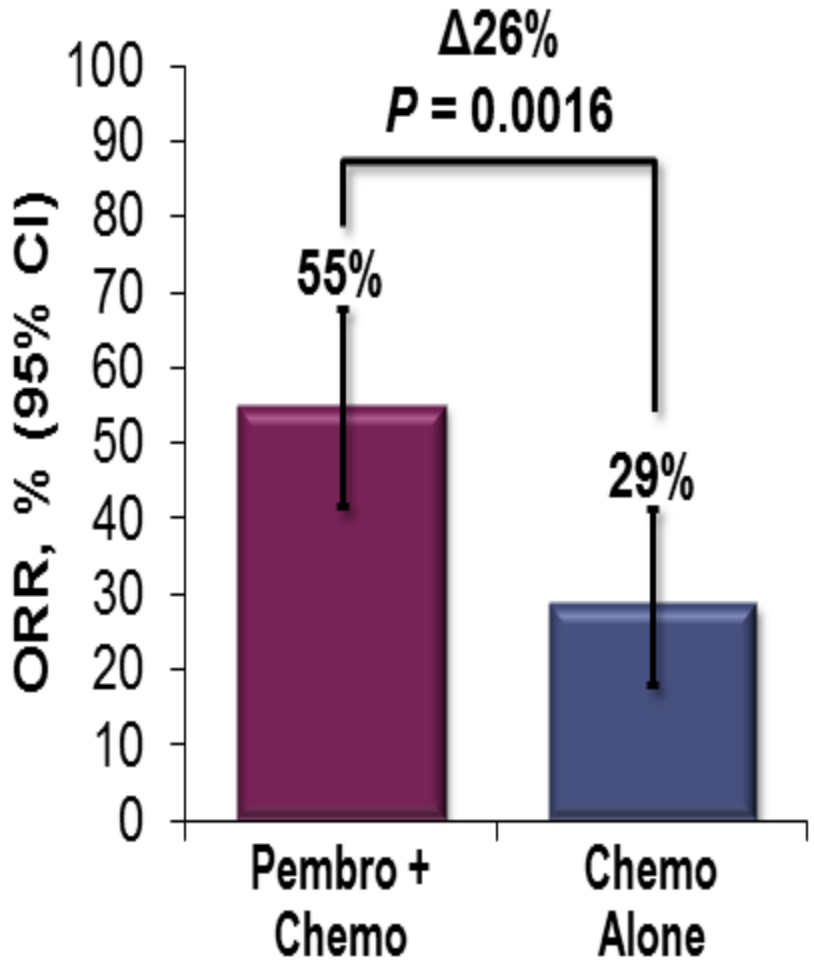
PD=progressive disease.

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

[b]Indefinite maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.

CJ Langer. ESMO 2016.

Confirmed Objective Response Rate
(RECIST v1.1 by Blinded, Independent Central Review)



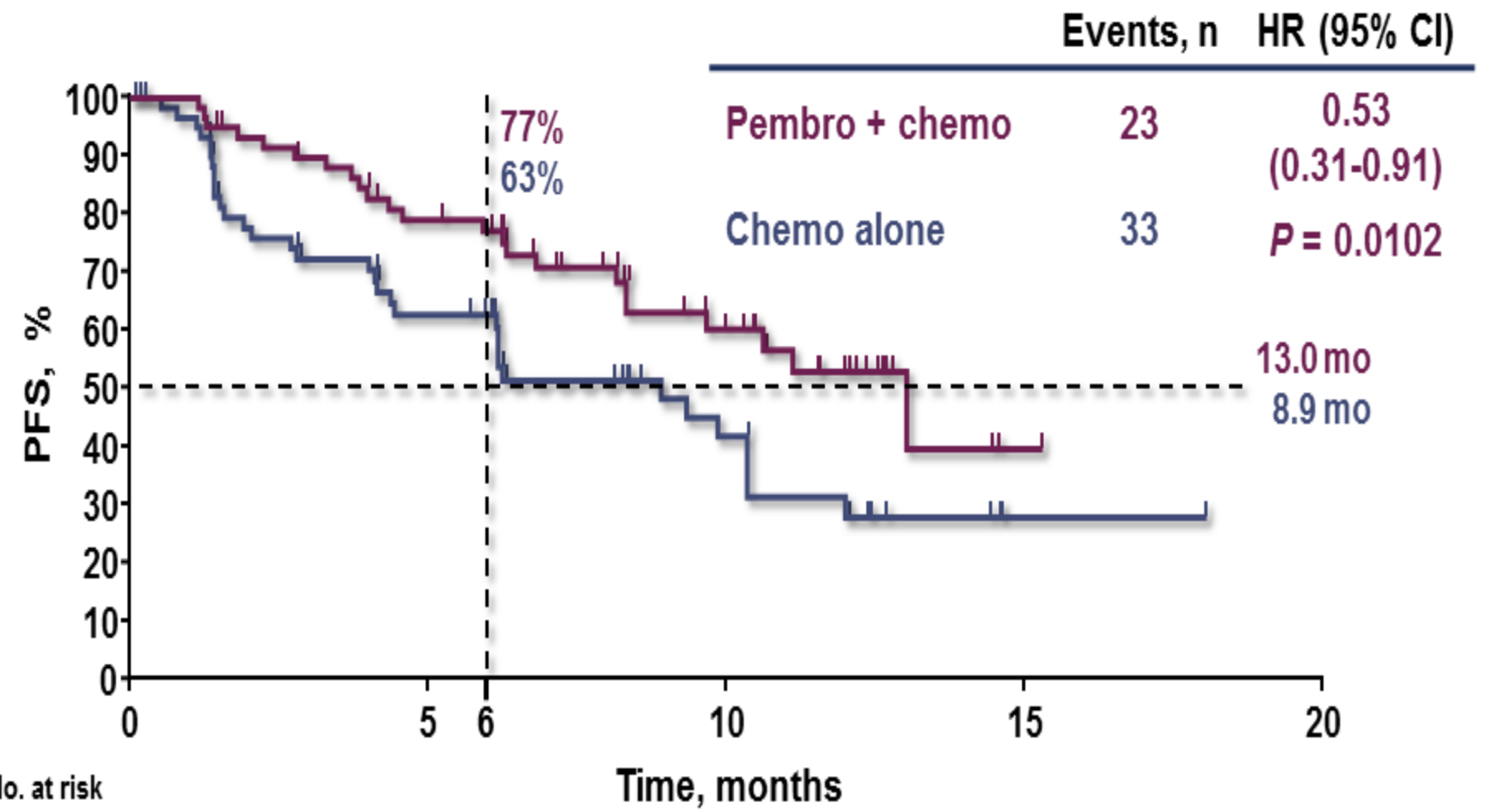
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

Data cut-off: August 8, 2016.

Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)

CJ Langer. ESMO 2016.



Data cut-off: August 8, 2016.

CJ Langer. ESMO 2016.

Best Overall Response
(RECIST v1.1 by Blinded, Independent Central Review)

Best response, n (%)	Pembro + Chemo N = 60	Chemo Alone N = 63
Complete response[a]	0	0
Partial response[a]	33 (55)	18 (29)
Stable disease	20 (33)	26 (41)
Progressive disease	2 (3)	11 (17)
Not evaluable[b]	5 (8)	8 (13)

[a]Confirmed responses only.

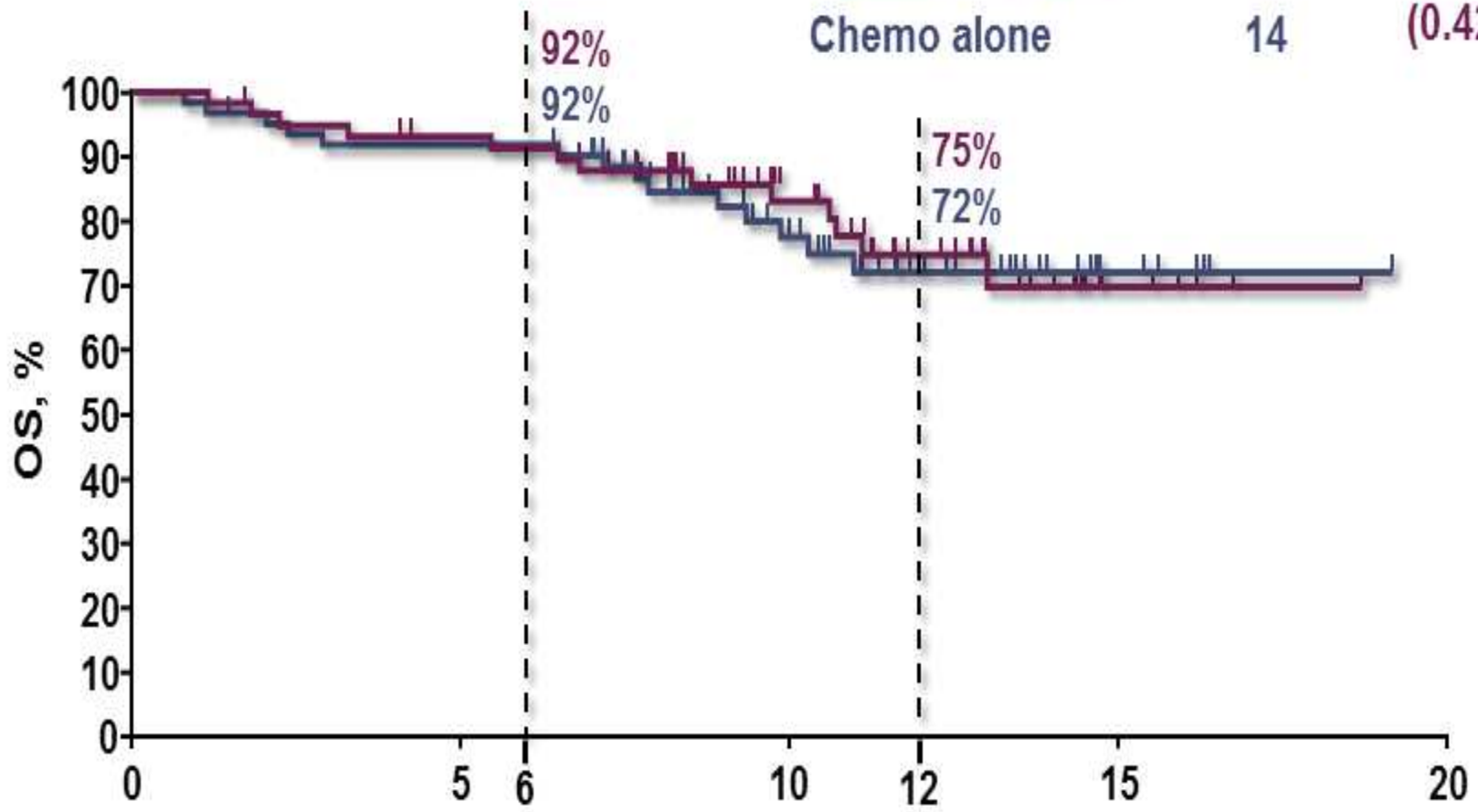
[b]No postbaseline scan performed or a baseline or postbaseline scan not evaluable per RECIST v1.1 by blinded, independent central review.

Data cut-off: August 8, 2016.

CJ Langer. ESMO 2016.

Overall Survival

	Events, n	HR (95% CI)
Pembro + chemo	13	0.90 (0.42-1.91)
Chemo alone	14	



No. at risk

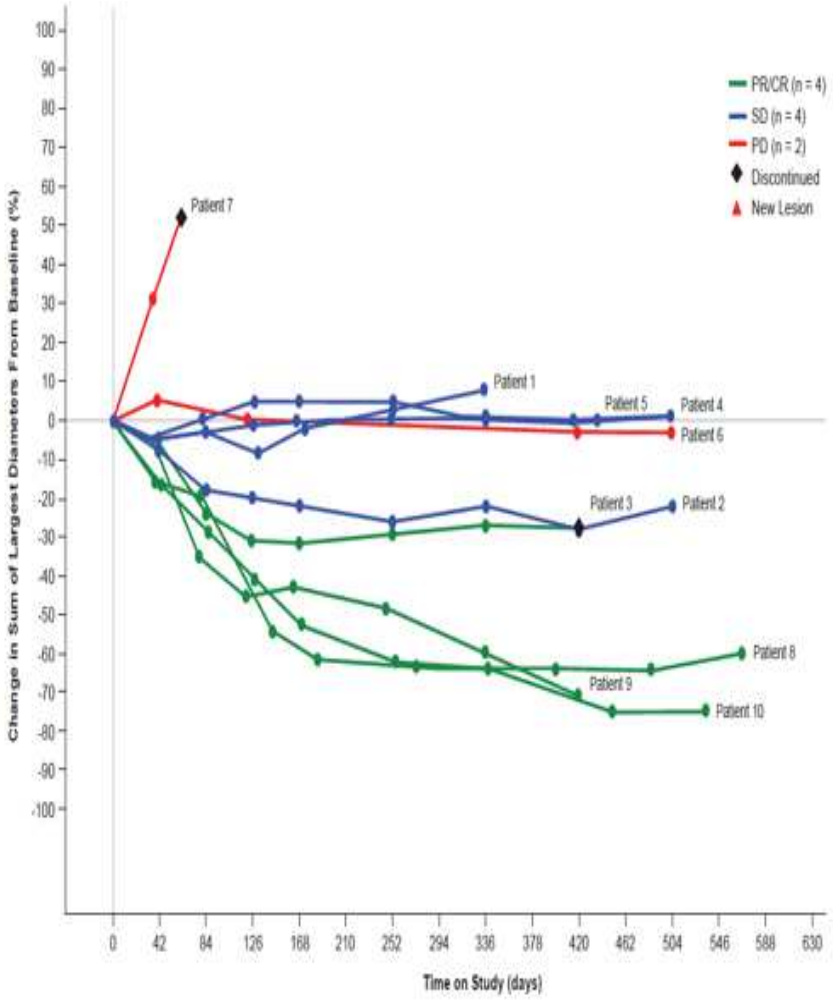
60	53	33	5	0
63	57	31	6	0

Data cut-off: August 8, 2016.

Potential Immunological Effects of VEGF Inhibition

- Normalize Tumor Vasculature -> Permit T Cell Immigration Into Tumor Bed
- VEGF Promotes Inhibitory Dendritic Cells / Myeloid Suppressor Cells
- Anti-Tumor Effects of VEGF Inhibition -> Immunogenic Cell Death

PD-L1 Ab (atezolizumab) + VEGF Ab (bevacizumab)



- **40%** Overall Response Rate (ORR)

  − *Historical response rates with atezolizumab and bevacizumab are ~15% and ~9%, respectively*

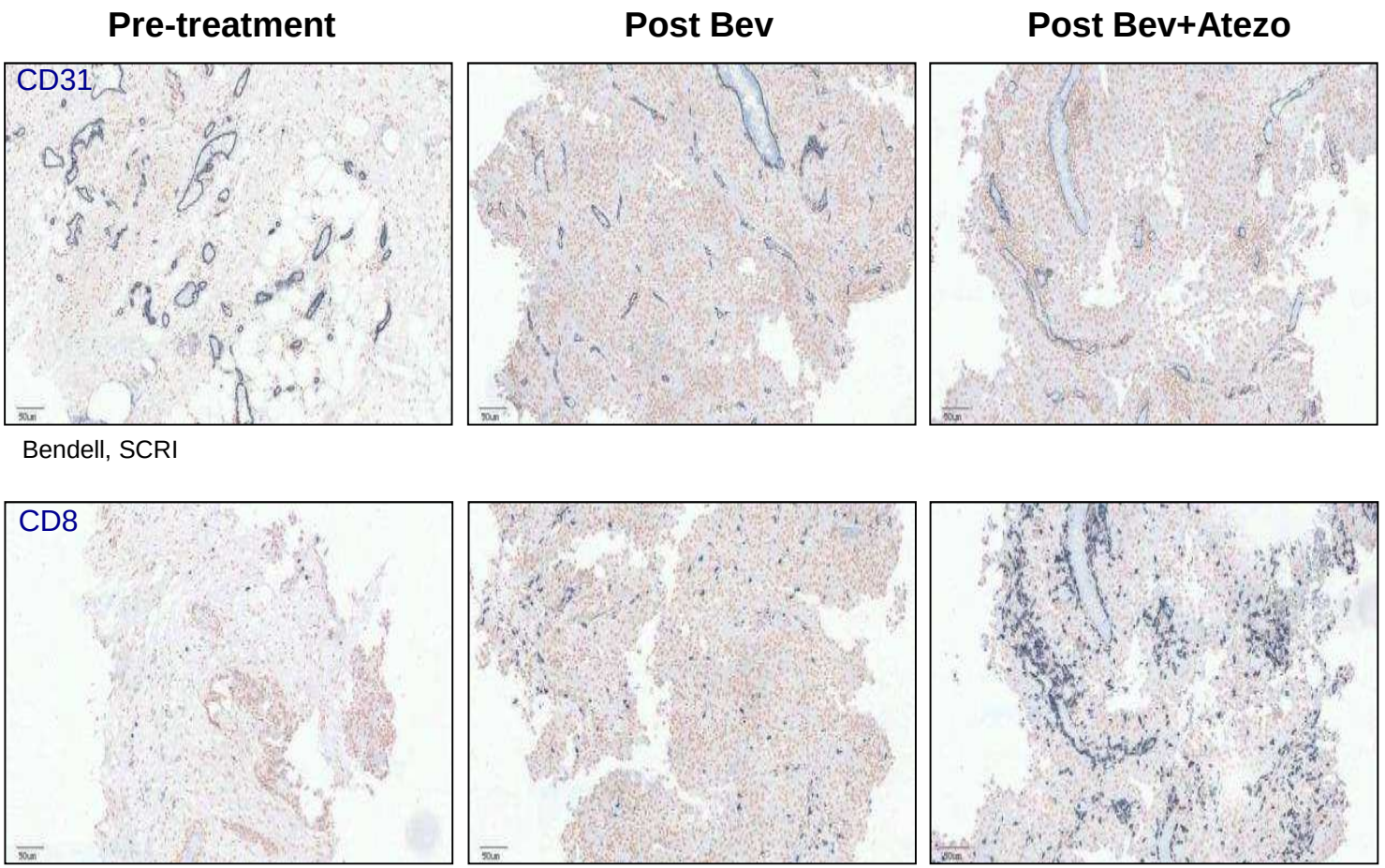
- Combination is **well-tolerated**
- **6 of 10** patients still on study after 15 months

Investigator-assessed unconfirmed response per RECIST v1.1.
IC, immune cells; IHC 3: ≥ 10% tumor-infiltrating ICs positive for PD-L1; IHC 2: ≥ 5% and < 10% tumor ICs positive for PD-L1; IHC 1: ≥ 1% and < 5% tumor ICs positive for PD-L1; IHC 0: < 1% tumor ICs positive for PD-L1.
Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff July 7, 2014.

Wallin et al, Nat Comm, 2016

Increases in CD8⁺ T cells are observed with treatments

Patient 3, Female, 62 years old

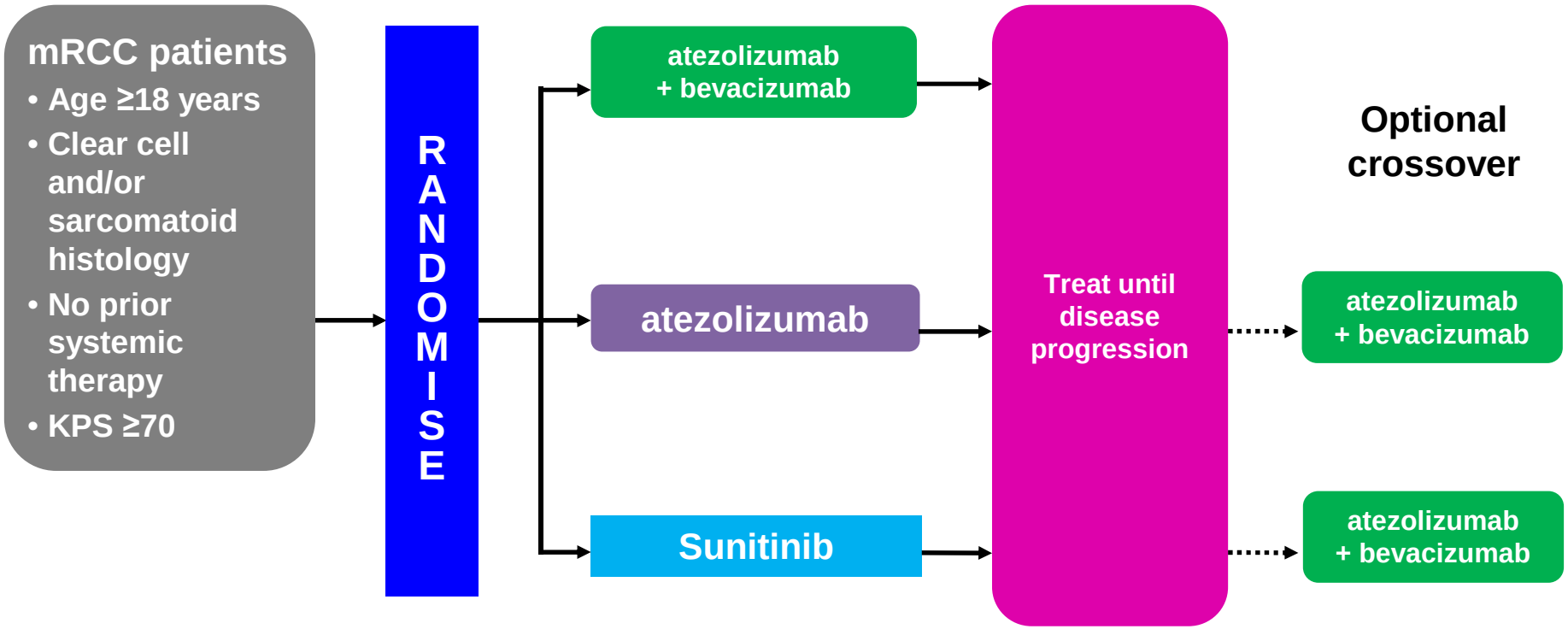


Bendell, SCRI

- **83%** (5/6) of **bev + atezo** RCC patients had increases in tumor CD8⁺ T cells
- **11%** (1/9) of RCC patients had increased tumor CD8⁺ T cells following **monotherapy atezo** (PCD4989g)

Wallin et al, Nat Comm, 2016

Ongoing phase II trial of atezolizumab + bevacizumab vs atezolizumab vs sunitinib in Kidney Cancer



- **Estimated enrolment:** 300
- **Estimated completion date:** February 2016
- **Primary endpoint:** PFS (per central review)
- **Secondary endpoints:** OS, ORR, DOR, OS, safety

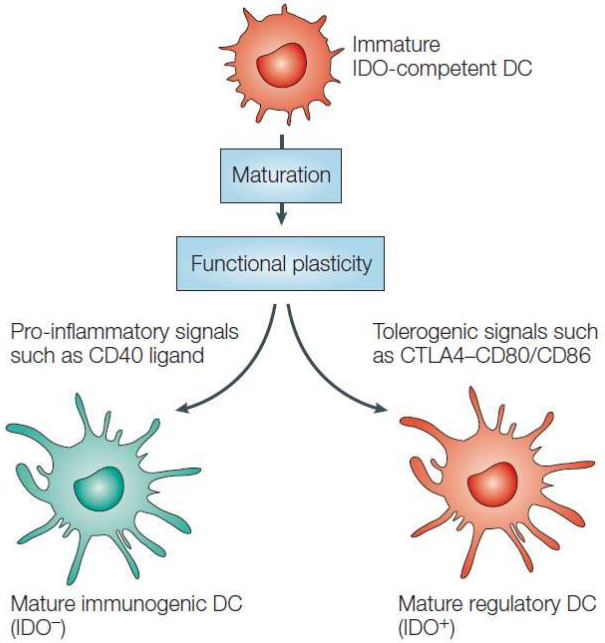
NCT01984242. Available at http://www.clinicaltrials.gov (Accessed May 2015).

First Line Treatment of RCC is Likely to Be a Combination Regimen

- Ipilimumab / Nivolumab vs. Sunitinib
- Atezolizumab / Bevicizumab vs. Sunitinib
- Avelumab / Axitinib vs. Sunitinib
- Pembrolizumab / Axitinib vs. Sunitinib

IO + Stromal Targeting

Targeting the Tumor MicroEnvironment (TME): IDO Inhibition



Preliminary results from a phase 1/2 study of epacadostat (INCB024360) in combination with pembrolizumab in patients with selected advanced cancers

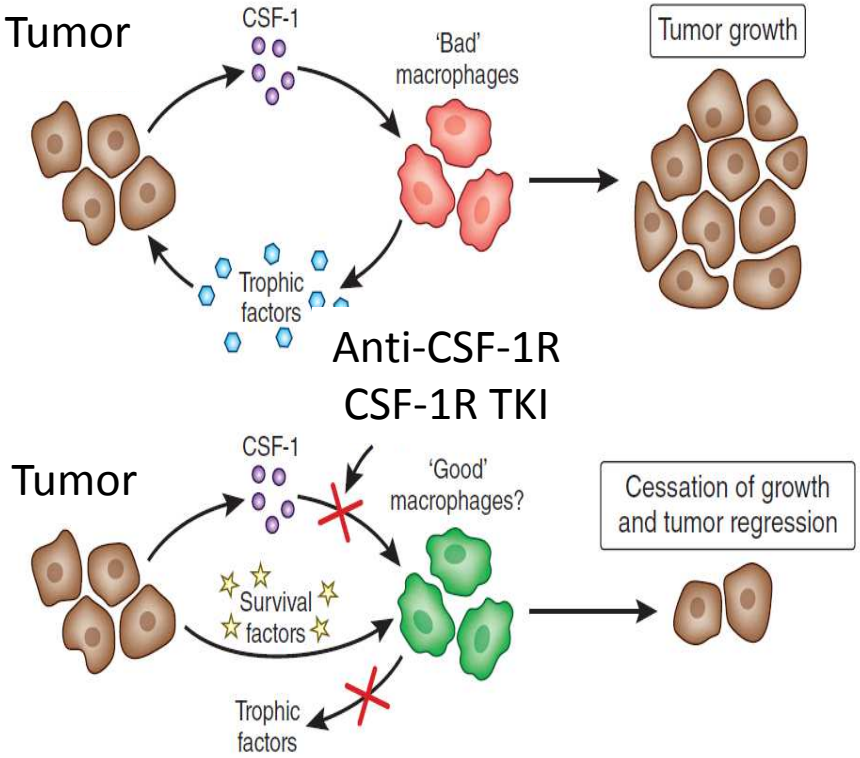
Evaluable patients*, n (%)	Melanoma (n=7)	RCC (n=5)	TCC (n=2)	NSCLC (n=2)	EA (n=2)	SCCHN (n=1)
ORR (CR+PR)	4 (57)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
CR	2 (29)	0	0	0	0	0
PR	2 (29)	2 (40)	1 (50)	1 (50)	1 (50)	1 (100)
SD	2 (29)	2 (40)	0	1 (50)	0	0
DCR (CR+PR+SD)	6 (86)	4 (80)	1 (50)	2 (100)	1 (50)	1 (100)
PD	1 (14)	0	1 (50)	0	0	0
Not assessable	0	1 (20)	0	0	1 (50)	0

*Patients with ≥ 1 post-baseline response assessment or discontinued from study or died before response could be assessed.

Mellors and Munn, *Nat. Rev. Immunol.* (2004)

Gangadhar TC et al, *JITC* 2015

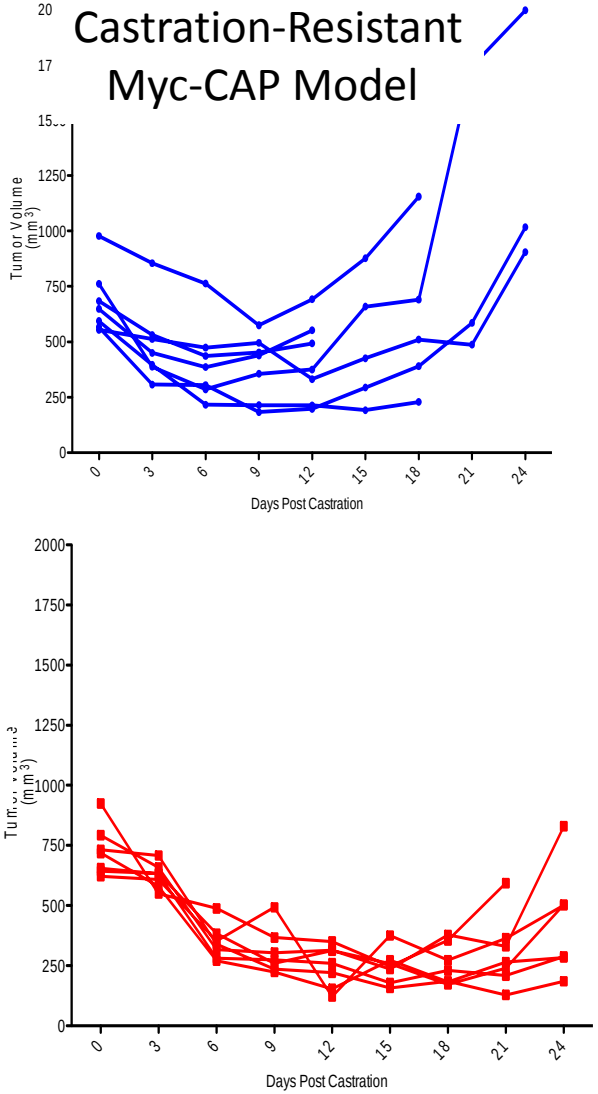
Targeting the Tumor MicroEnvironment (TME): Targeting Suppressive Myeloid Cells / Macrophages



Pyontek et al, *Nat. Med.* (2013)

Isotype

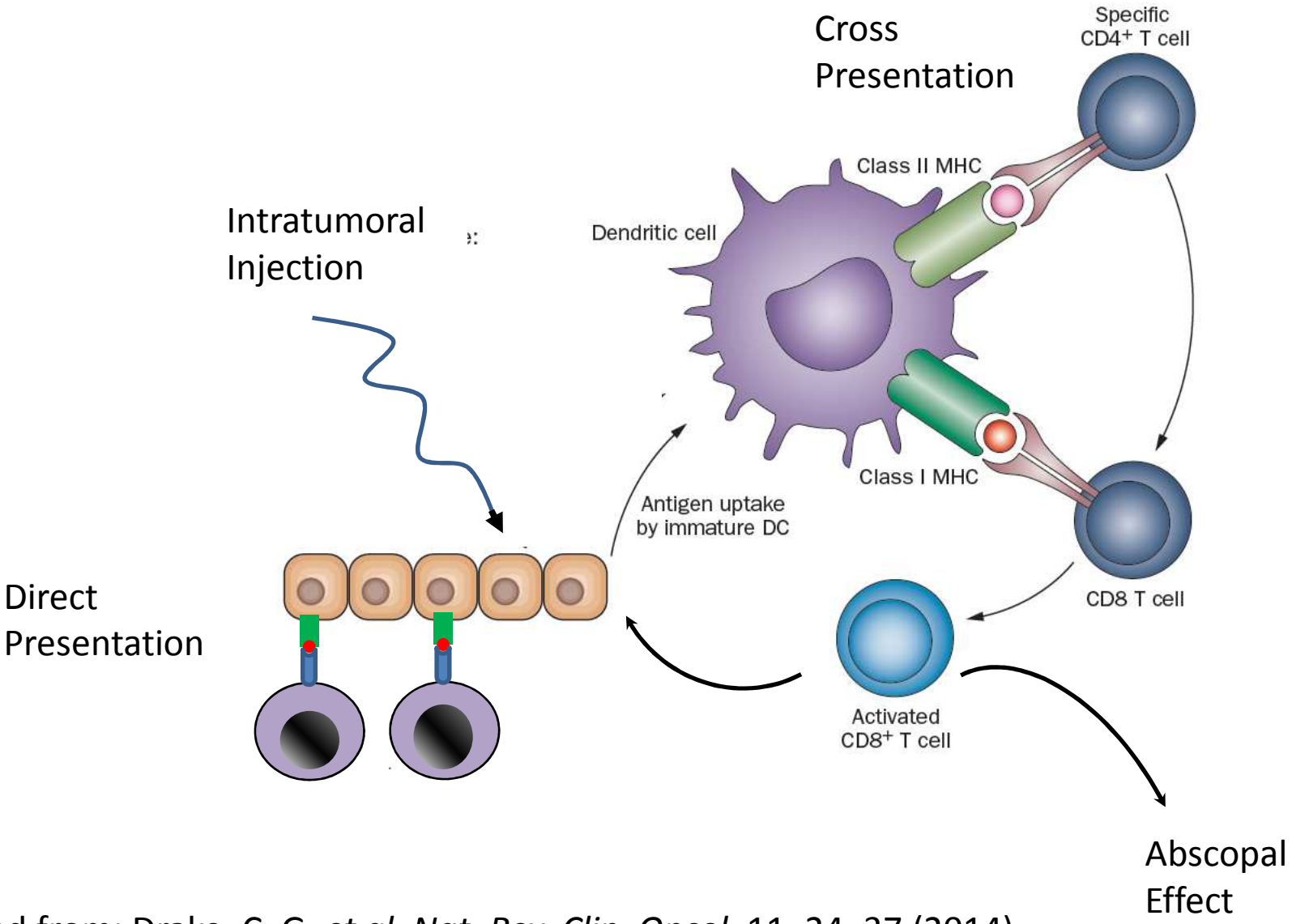
Anti-CSF-1R



Lopez-Bujanda and Drake, Unpublished

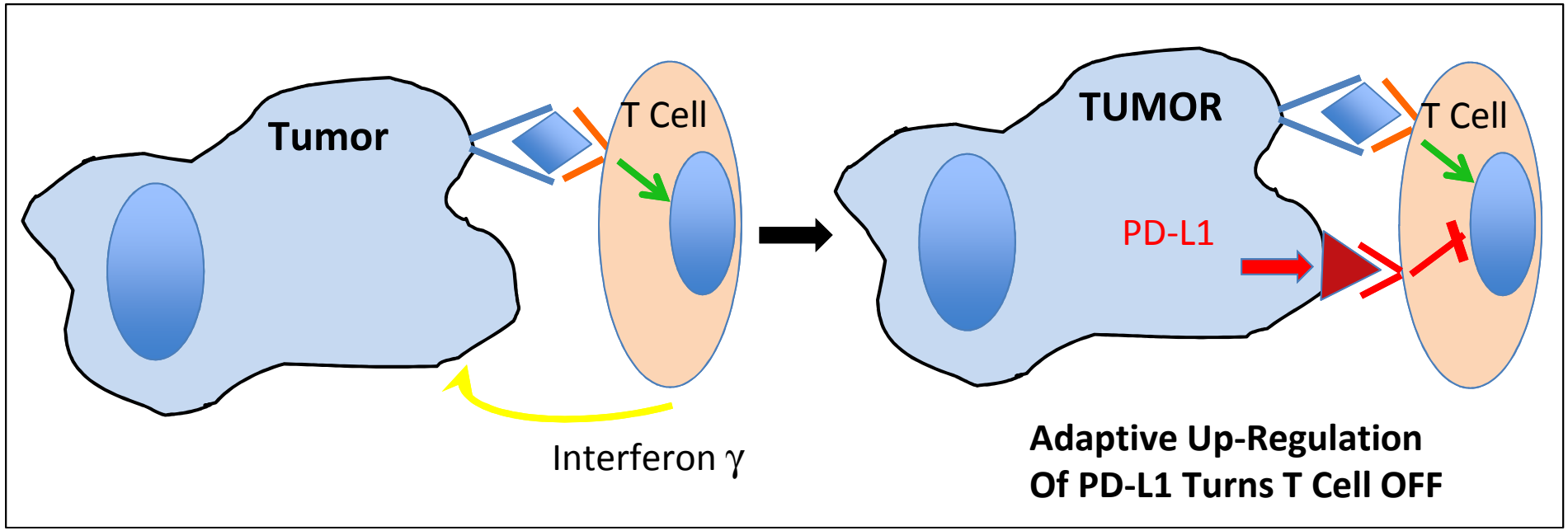
IO + Intratumoral Activator

Intratumoral Injection and the "Abscopal Effect"



Modified from: Drake, C. G. *et al. Nat. Rev. Clin. Oncol*. 11, 24–37 (2014)

What's Different in 2016?
Adaptive Immune Resistance



Pardoll and Drake JEM 2012

Vectors

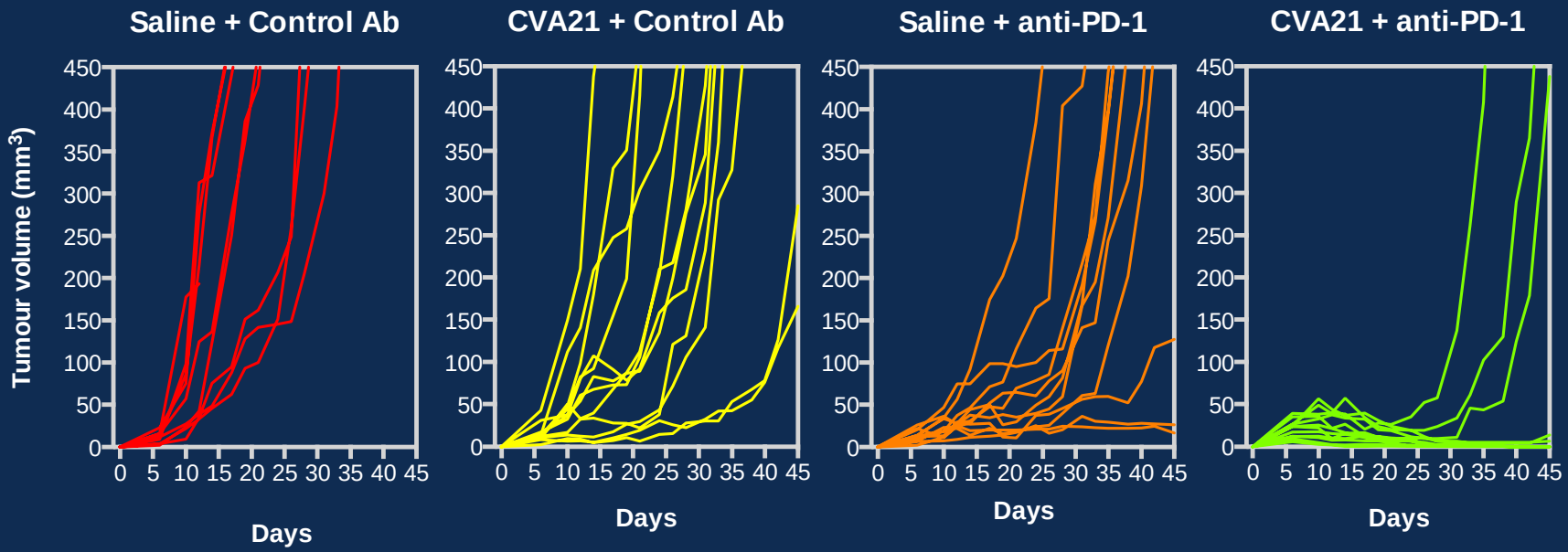
- Oncolytic Viruses (HSV-1, Reovirus, Vaccinia)
  - T-Vec (+ GM-CSF)
- Coxsackie Virus
  - Cavatak (naked)
- Adenovirus
  - Prostatak (+ herpes virus thymidine kinase gene)
- Alpha-Gal glycosphingolipid
  - U Mass
- Plasmid DNA
  - OncoSec
- TLR Agonists
  - Too many to count !
- STING agonists (cyclic dinucleotides)
- Bacteria (BCG)
  - Daily, in your local urology clinic

Payload

- TH1 Cytokines:
  - IL-2, IL-12, TNF-alpha
- DC Activators / Attractants
  - GM-CSF, CD40L
- Type I IFN's
  - IFN-beta
- Allo-MHC

Preclinical Rationale

- Pre-clinical evidence of enhanced antitumor activity using a combination of CVA21 and PD-1 blockade



- Oncolytic and immunotherapeutic activities of CVA21 warrant further clinical evaluation of CVA21 in combination with other immunotherapeutic agents (ie. immune checkpoint inhibitor strategies anti-CTLA-4 or anti-PD-1) or targeted small molecules (ie. BRAF and MEK kinase inhibitors)

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- PCW Foundation
- Dept Urology

Slides

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There are over 750 Cancer Immunotherapy combination studies currently listed on clinical trials.gov:

- **How will we as a community deal with this vast quantity of trials and agents?**
- **How will we prioritize what to move forward into pivotal studies?**
- **What if 20 combination regimens are approved - is there room in clinical oncology practice for 20 new regimens?**