Clinical Activity and Safety of Anti-Programmed Death-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) in Patients (pts) With Previously Treated, Metastatic Renal Cell Carcinoma (mRCC)

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Disclosures

- Advisory Board Participation
  - Bristol-Myers Squibb
  - Prometheus Labs
  - Genentech
  - Pfizer

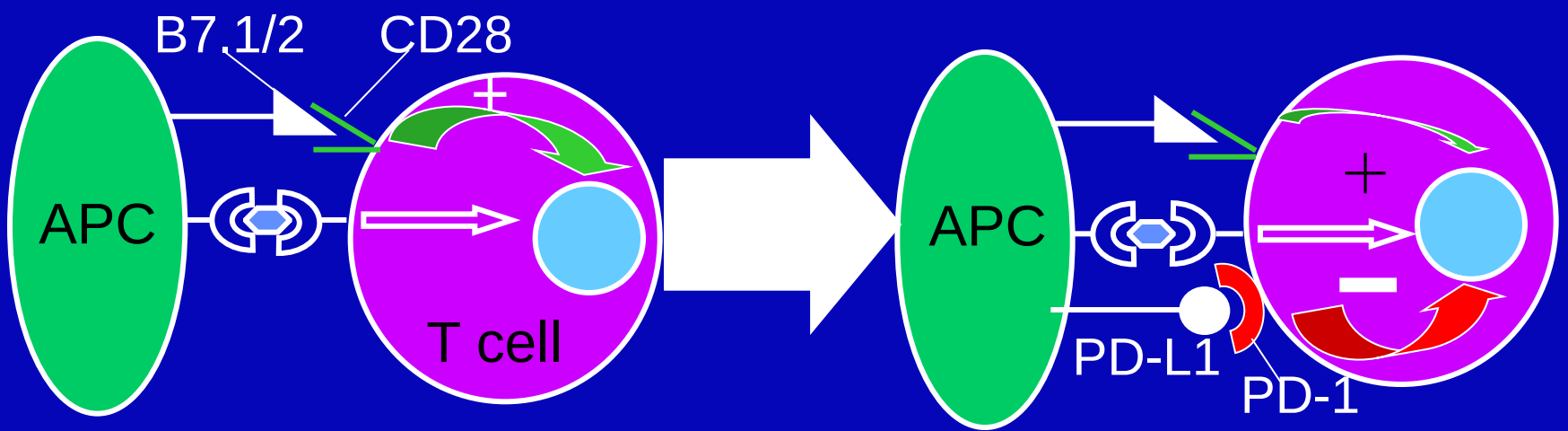
- Research Funding
  - Prometheus Labs

Six Years of Impressive Progress

Setting		Phase III	Alternative
1st-Line Therapy	Good or Intermediate Risk*	Sunitinib Pazopanib	**HD IL-2**
		Bevacizumab + IFNα	
	Poor Risk*	Temsirolimus	Sunitinib
2nd-Line Therapy	Prior Cytokine	Sorafenib	Sunitinib or Bevacizumab
	Prior VEGFR Inhibitor	Everolimus Axitinib	Clinical Trials
	Prior mTOR Inhibitor	Clinical Trials	

Does Immunotherapy have any role?

PD-1/PD-L1: Immune Checkpoint Pathway



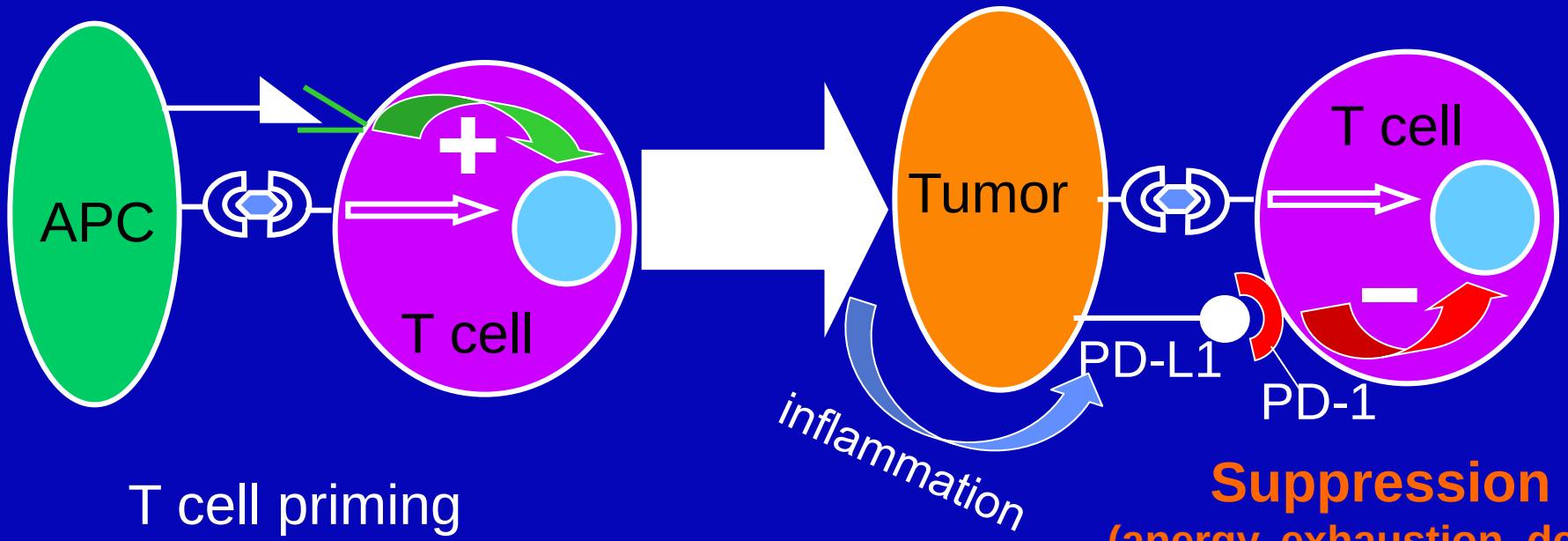
T cell priming

Suppression
(anergy, exhaustion, death)

- There are positive and negative signal pathways that regulate T cells
- The Programmed Death (PD)-1/PD-L1 ligand pathway is an immune checkpoint that suppresses activated T cells and promotes tolerance[1]

[1]Park J-J, et al. *Blood.* 2010;116:1291-8.

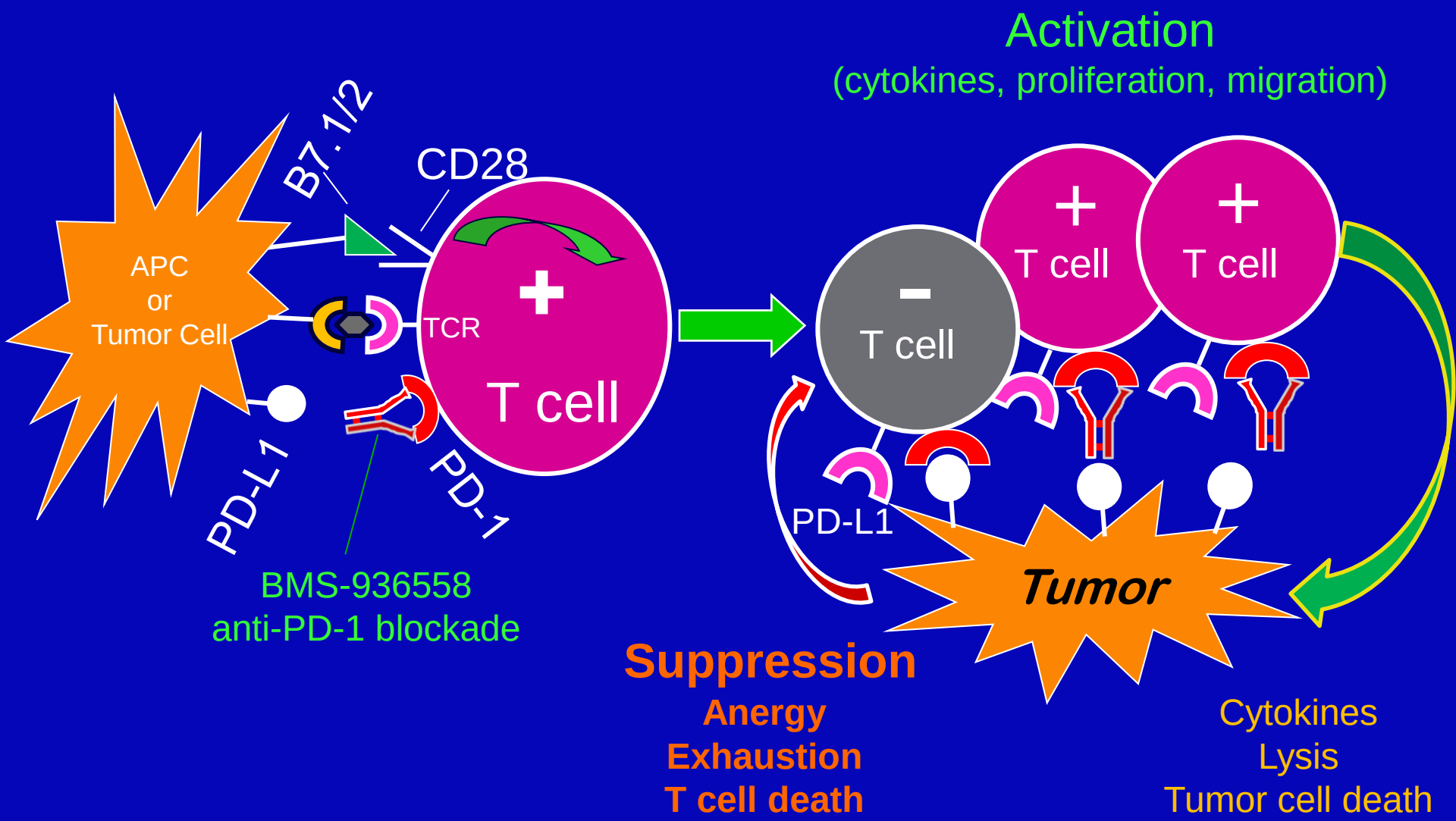
PD-1/PD-L1: Pathway: Tumor cells – T cells



- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)[1,2]
- In RCC, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, including[3]:
  - More aggressive disease
  - Shorter survival

[1]Topalian et al. *Curr Opin Immunol 2012,* [2]Taube JM, et al. *Science Transl Med.* 2012;4:127ra37. [3]Thompson RH, et al. *PNAS* 2004.

Anti-PD-1: Blocking T cell Suppression



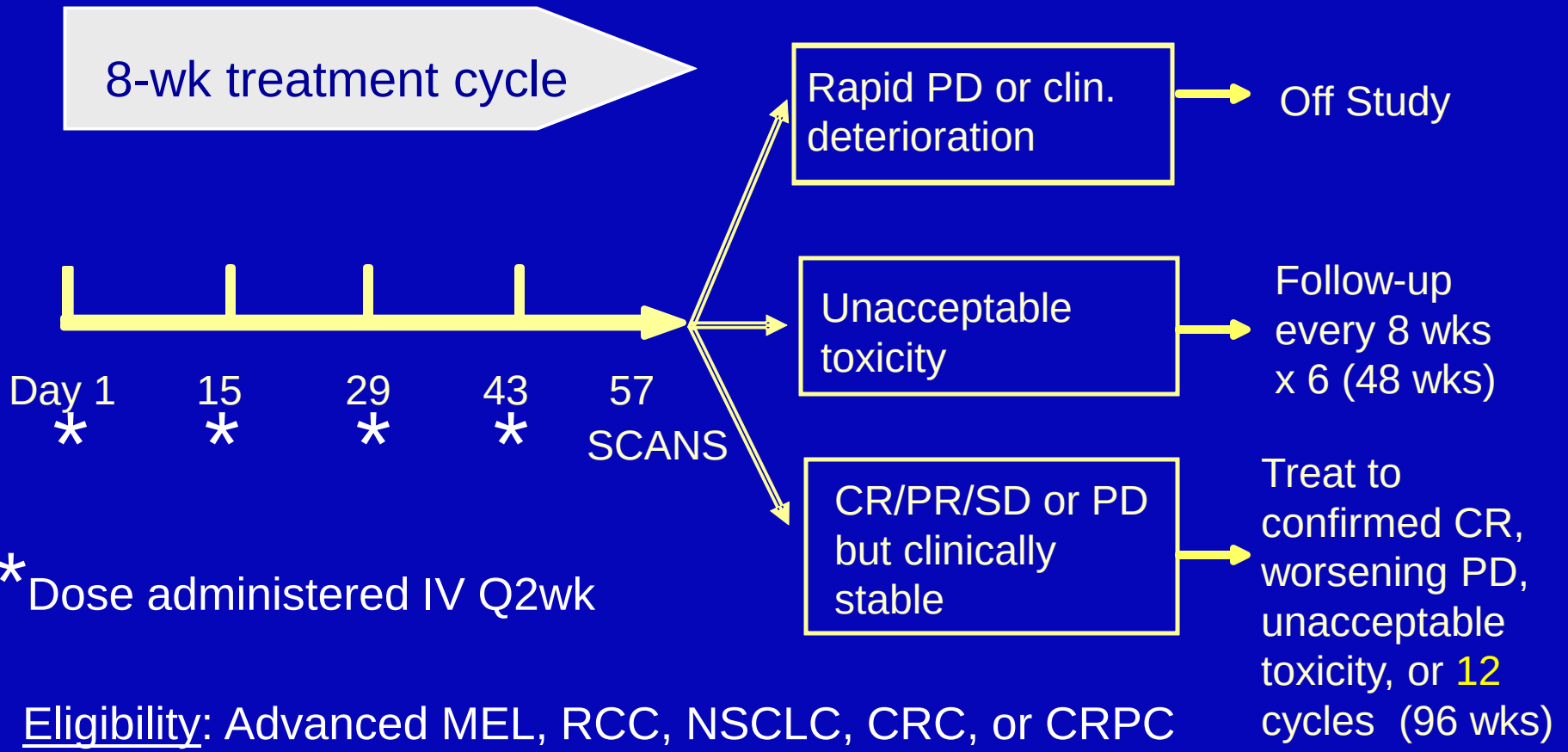
Keir ME et al, *Annu Rev Immunol* 2008; Pardoll DM, *Nat Rev Cancer* 2012

BMS-936558 (MDX-1106/ONO-4538)

- **Fully human IgG4 anti-human PD-1-blocking Ab[1]**
- **No known Fc function (ADCC, CDC)**
- **High affinity for PD-1 (KD ~3 nM), blocks binding of both PD-L1 (B7-H1) and PD-L2 (B7-DC)**
- **In the first-in-human, single-dose, dose-escalation study, BMS-936558 exhibited a manageable safety profile and preliminary evidence of clinical activity in patients with treatment-refractory solid tumors[1]**

[1]Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167-75.

Study Design: Phase I Multi-dose Regimen



*Dose administered IV Q2wk

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

Study Objectives and Summary

- **Primary**
  - **Assessment of safety and tolerability of BMS-936558**
- **Secondary/Exploratory objectives include preliminary efficacy of BMS-936558 and pharmacokinetics**
- **Accrual completed Dec. 2011; patient assessment ongoing (N=304)**
- **A maximum tolerated dose was not identified at doses up to 10 mg/kg**
- **There was no apparent relationship between drug dose and AE frequency in all treated patients**
- **Antitumor activity was seen in NSCLC, melanoma and RCC[1]**

[1]Topalian S, et al. NEJM 2012;366:2443-2454.

RCC Cohorts

- Dose Expansion
  - 16 patients enrolled at 10 mg/kg followed by
  - 18 patients enrolled at 1 mg/kg
  - Assessment of antitumor activity
  - Assessment of safety and tolerability of BMS-936558

- Current analysis for patients as of July 3, 2012
  - Safety results are presented for the overall (N=304) and RCC (n=34) populations
  - Clinical activity is presented for the RCC population

Baseline Characteristics of RCC Patients

Baseline Characteristic	n=34
Median age, (range), yr	58 (35-74)
Male, no. (%)	26 (76)
ECOG PS, no. (%)	
0	13 (38)
1	21 (62)
Lesions at baseline, no. (%)	
Bone	10 (29)
Liver	9 (26)
Lung	30 (88)
Lymph node	28 (82)
Other	20 (59)

- **>40% received 3 or more prior therapies**
- **>70% received anti-angiogenic therapy**

BMS-936558-Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3-4	
	Tot Pop*,†	RCC	Tot Pop	RCC
	No. (%) of Patients, All Doses			
Any adverse event	220 (72)	29 (85)	45 (15)	7 (21)
Fatigue	78 (26)	14 (41)	5 (2)	—
Rash	41(14)	9 (27)	—	—
Diarrhea	36 (12)	5 (15)	3 (1)	—
Pruritus	31 (11)	6 (18)	1 (0.3)	1 (3)
Nausea	24 (8)	2 (6)	1 (0.3)	—
Appetite ↓	24 (8)	3 (9)	—	—
Hemoglobin ↓	18 (6)	2 (6)	1 (0.3)	—
Pyrexia	16 (5)	3 (9)	—	—

*AEs occurring in ≥5% of the total population.

† Drug-related renal failure/nephritis occurred in 1% of the total population, with no grade 3-4 drug-related events, based on an analysis on July 3, 2012

‡The most common grade 3-4 AEs were respiratory system disorders (2 pts) and hypophosphatemia (2 pts). An additional 10 grade 3-4 drug-related AEs were observed and one or more occurred in a single patient.

Summary of Key Safety Results

- In the total treated patient population across all tumor types:
  - Grade 3-4 drug-related AEs occurred in 15%
  - Discontinuation of treatment due to drug-related AE occurred in 18/304 (6%) of patients
  - Three drug-related deaths occurred in patients with pneumonitis (2 with NSCLC and 1 with CRC)
- In RCC patients:
  - Safety profile was similar to the total treated patient population
  - Grade 3-4 drug-related AEs occurred in 21% of pts

Clinical Activity of BMS-936558 in RCC Patients

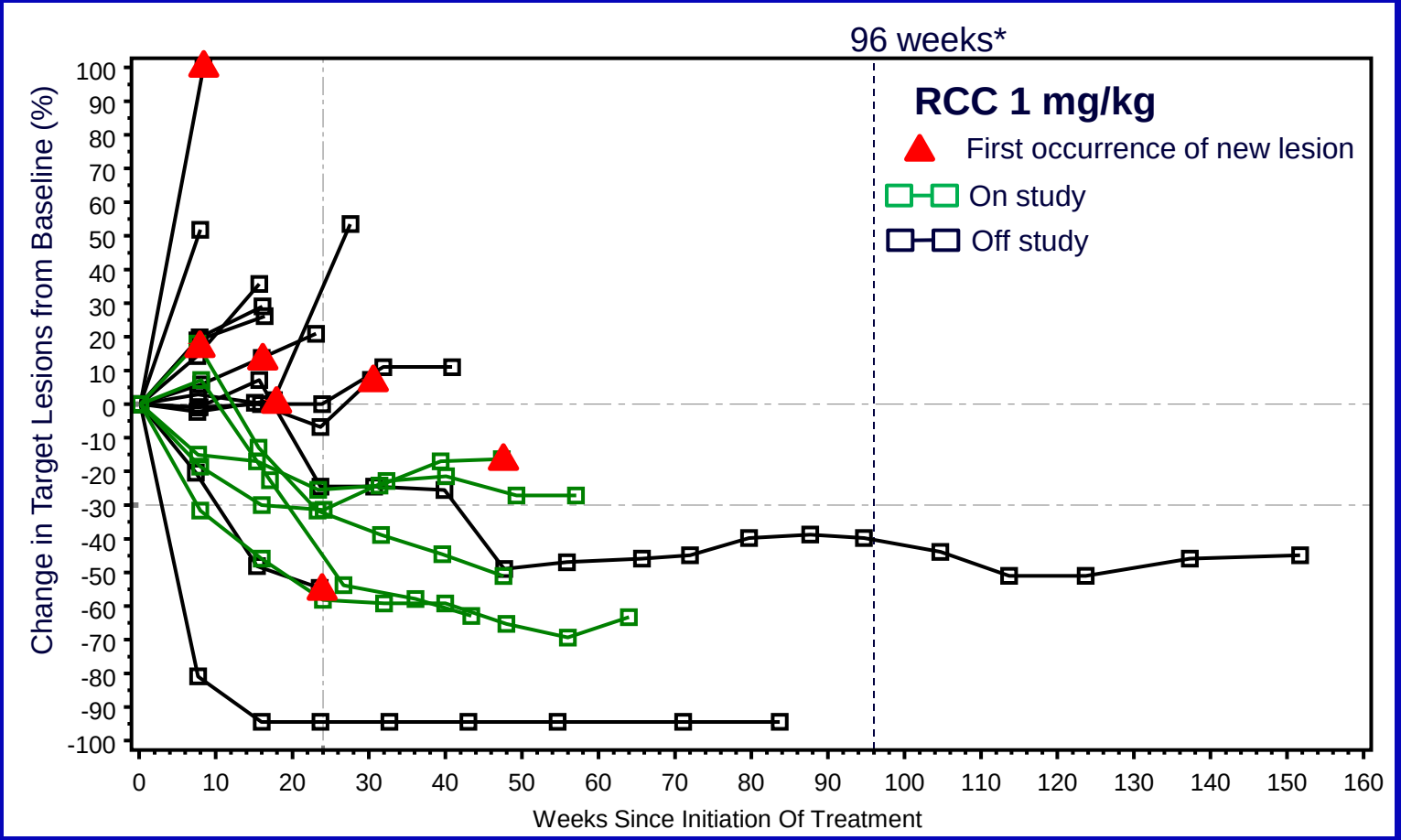
Population	Dose (mg/kg)	Patients (n)	Median Duration of Response Months (95% CI)	ORR n (%)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL RCC	1, 10	34	—	10 (29)	9 (27)	58
RCC	1	18	12.9 (9.2 – NE)	5 (28)	4 (22)	50
	10	16	12.9 (8.4 – NE)	5 (31)*	5 (31)	67

*One CR

NE, currently not estimable by Kaplan-Meier due to insufficient follow-up

- ORR was assessed using modified RECIST v1.0
- 3 additional RCC patients had a nonconventional pattern of response and were not classified as responders by the conventional RECIST

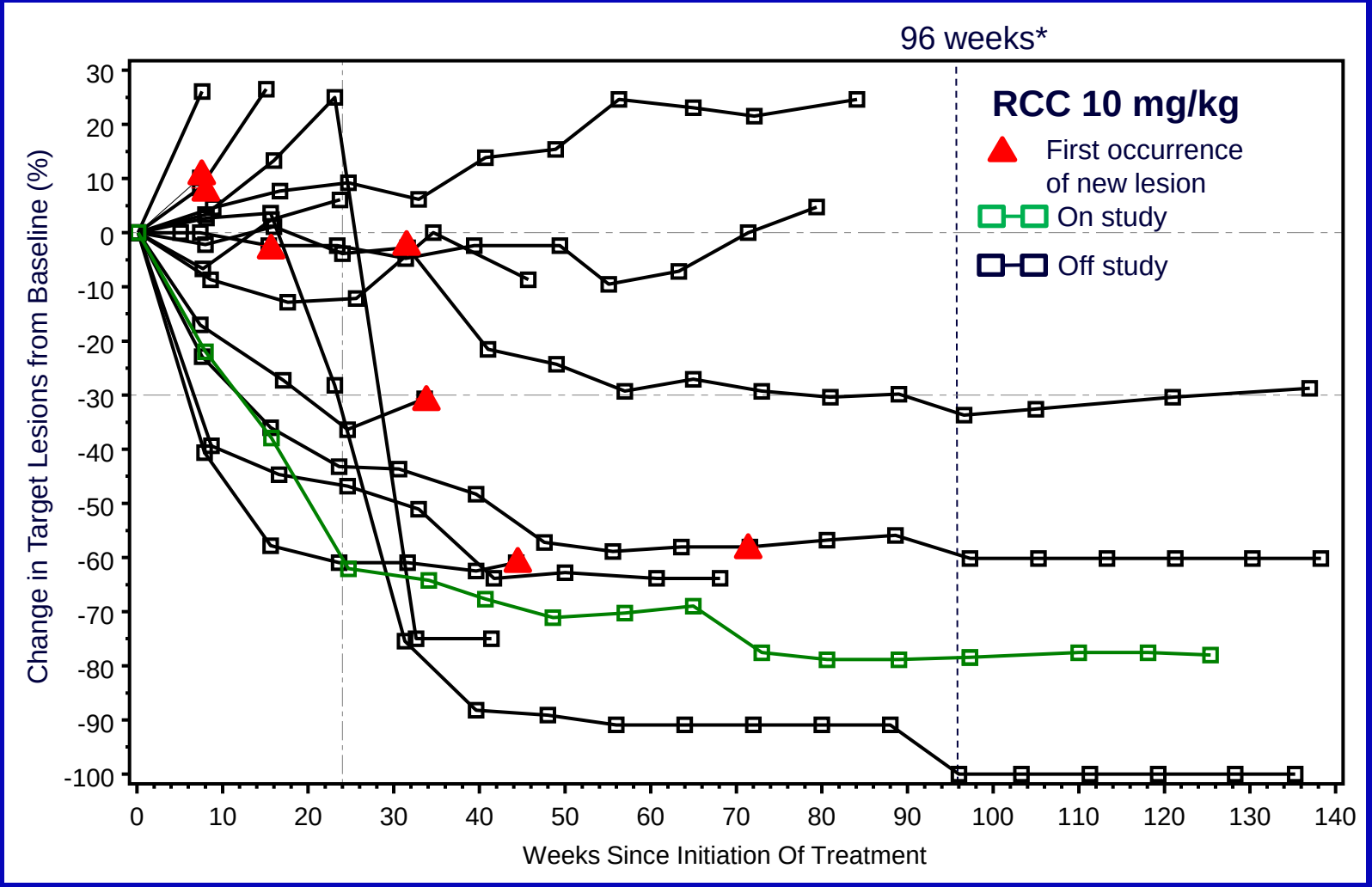
Changes in Target Lesions Over Time in RCC Patients Treated With 1 mg/kg BMS-936558



* line represents the protocol-specified maximum duration of active therapy (96 weeks)

- **Shorter study duration in 1 mg/kg cohort is consistent with enrollment occurring after the 10 mg/kg cohort (except for the 2 pts enrolled during dose escalation)**

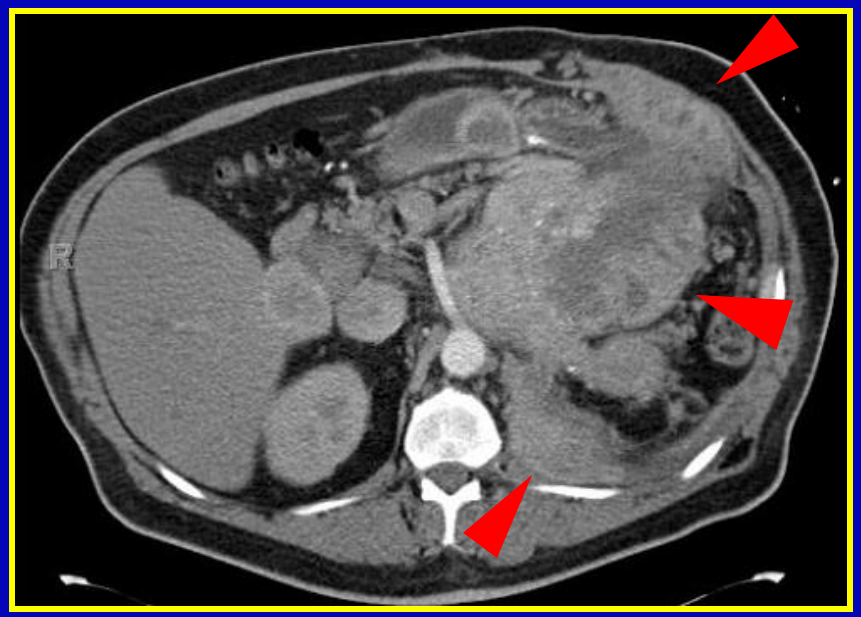
Changes in Target Lesions Over Time in RCC Patients Treated With 10 mg/kg BMS-936558



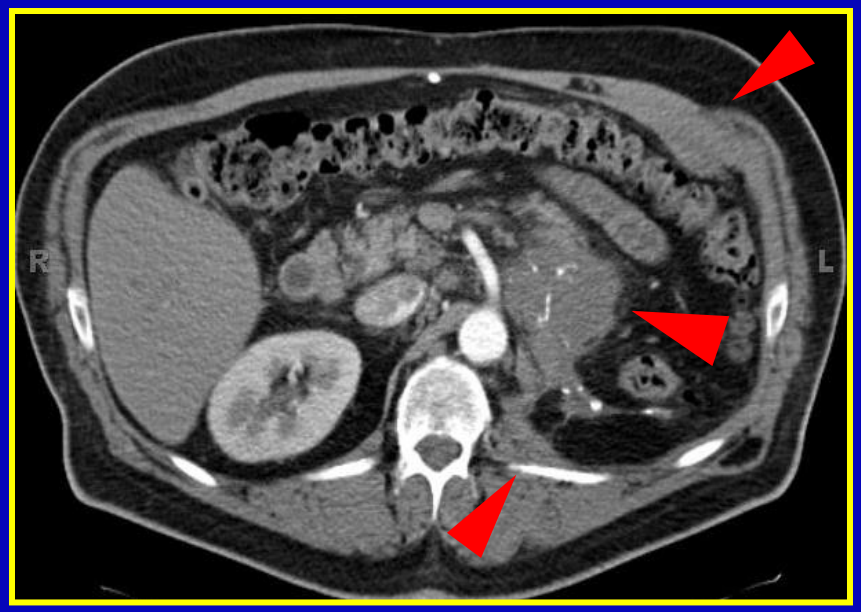
* line represents the protocol-specified maximum duration of active therapy (96 weeks)

Partial Regression of Metastatic RCC in a Patient Treated with 1 mg/kg BMS-936558

Pretreatment



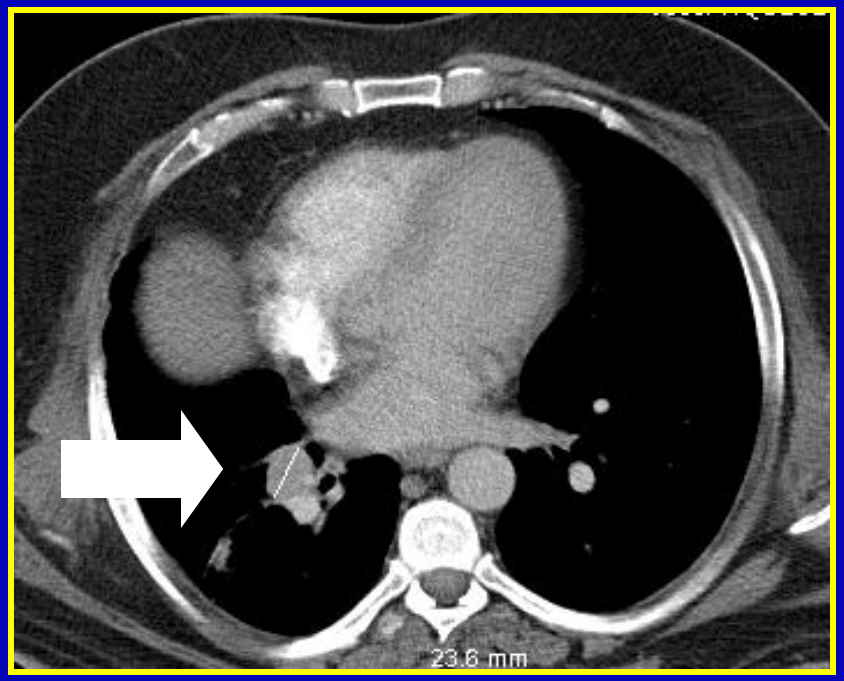
6 months

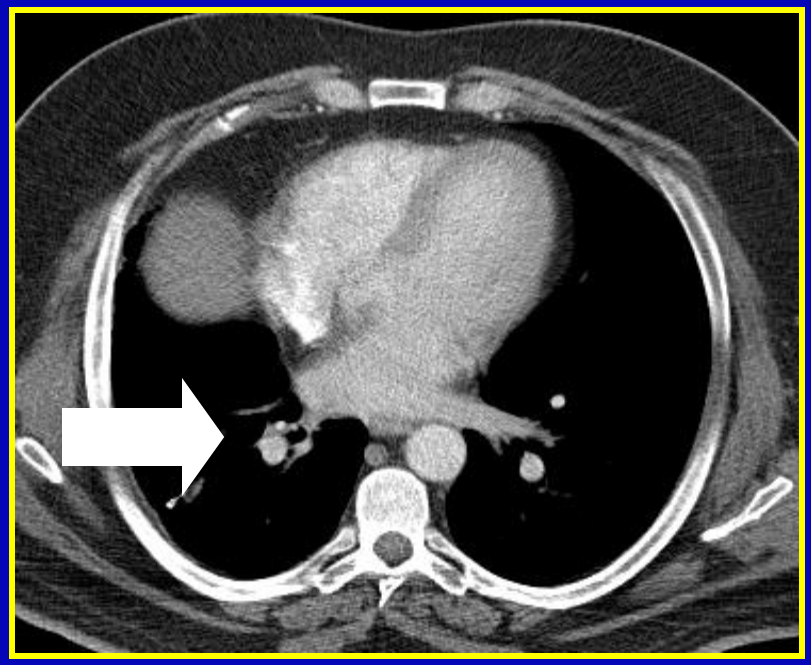


- 57-year-old patient had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Currently in cycle 6 with ongoing PR

Courtesy of C. Drake, Johns Hopkins Univ

Partial Regression of Metastatic RCC in a Patient Treated with 1 mg/kg BMS-936558: Durable Benefit off Therapy



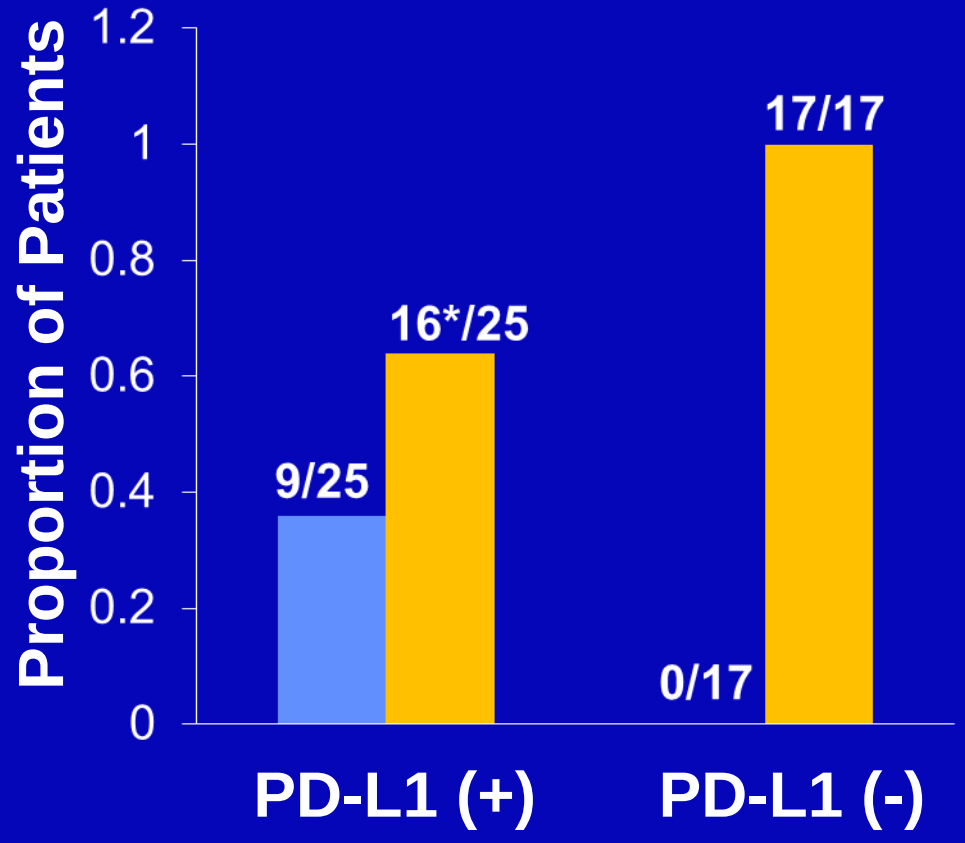


- 48-year-old patient with low volume but poorly differentiated mRCC
- Developed progressive disease after sunitinib, sorafenib, and thoracic surgery
- Therapy held after 3 cycles due to near CR
- Response has continued for 3 years, while off therapy

Courtesy of M. Sznol, Yale Cancer Center

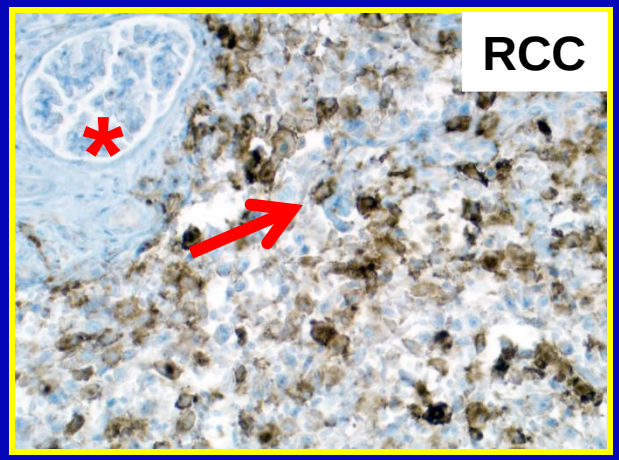
Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies with Clinical Outcomes

PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 pts



CR/PR
Non-responders

P=0.006



Patient samples: 18 MEL,10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

* 2 pts still under evaluation

Topalian et al NEJM, 2012

Summary

- BMS-936558 can be administered safely in an outpatient setting to pretreated RCC patients, while demonstrating durable clinical benefit
- Blockade of the PD-1 pathway may represent an important, new target for RCC immunotherapy
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes is being further explored
- Clinical registration trials of BMS-936558 in patients with RCC are planned

Acknowledgments

- The patients and their families
- The study sites enrolling patients to the trial
- Support for this work from Bristol-Myers Squibb and Ono Pharmaceutical Company, Ltd.
- All authors contributed to and approved the presentation; medical writing assistance in the preparation of the slides was provided by StemScientific funded by Bristol-Myers Squibb

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