Clinical Activity and Safety of Anti-Programmed Death-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) in Patients (pts) With Advanced Melanoma (MEL)

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Disclosures

- Dr. Jeffrey A. Sosman has the following disclosures:
  - Consults and participates on advisory boards for for Roche- Genentech, Millennium Pharmaceuticals, and GlaxoSmithKline
  - Receives research funding from Bristol-Myers Squibb, Millennium Pharmaceuticals, Roche-Genentech, and GlaxoSmithKline

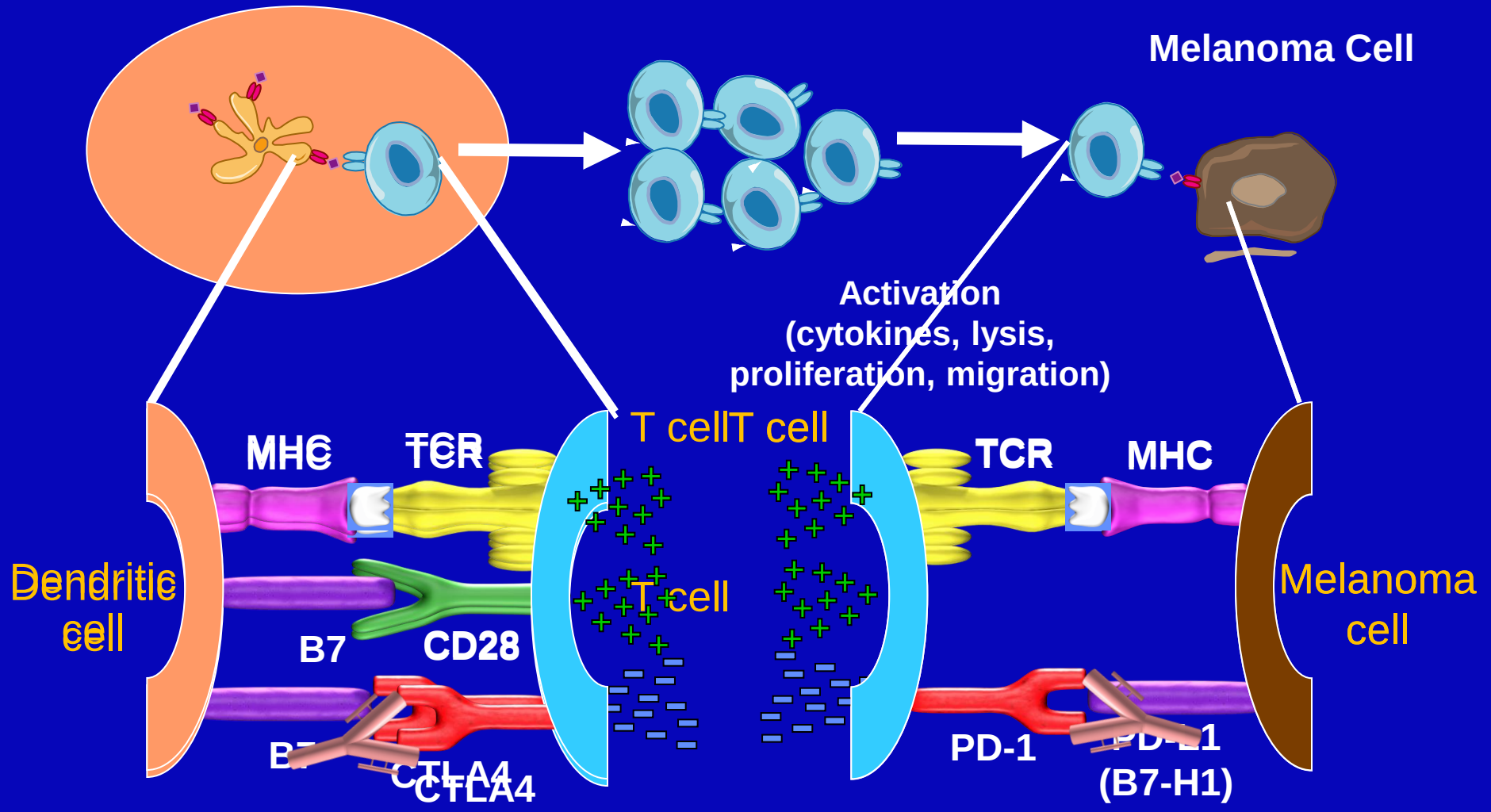
Role of PD-1 Pathway in Cancer

- **PD-1 expression on tumor-infiltrating lymphocytes (TILs)**
  - **Associated with decreased cytokine production and effector function[1]**
- **PD-1 expression and melanoma[2]**
  - **Patients with stage IV disease had significantly higher levels of PD-1 on peripheral CD8+/CD4+ T-cells than did healthy controls**
  - **PD-1 expression on CD8+ TILs increases as disease progresses**
- **PD-L1 expression and melanoma**
  - **PD-L1 tumor expression may correlate with adaptation to immune attack and response to therapeutic PD-1 blockade[3,4]**

[1]Ahmadzadeh M, et al. *Blood.* 2009;114:1537-44. [2]Hino R, et al. *Cancer.* 2010;116:1757-66. [3]Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167-75. [4]Taube JM, et al. *Science Transl Med.* 2012;4:127ra37

Role of PD-1 in Suppressing Antitumor Immunity

Differences between blocking CTLA4/B7 and blocking PD-1/PD-L1

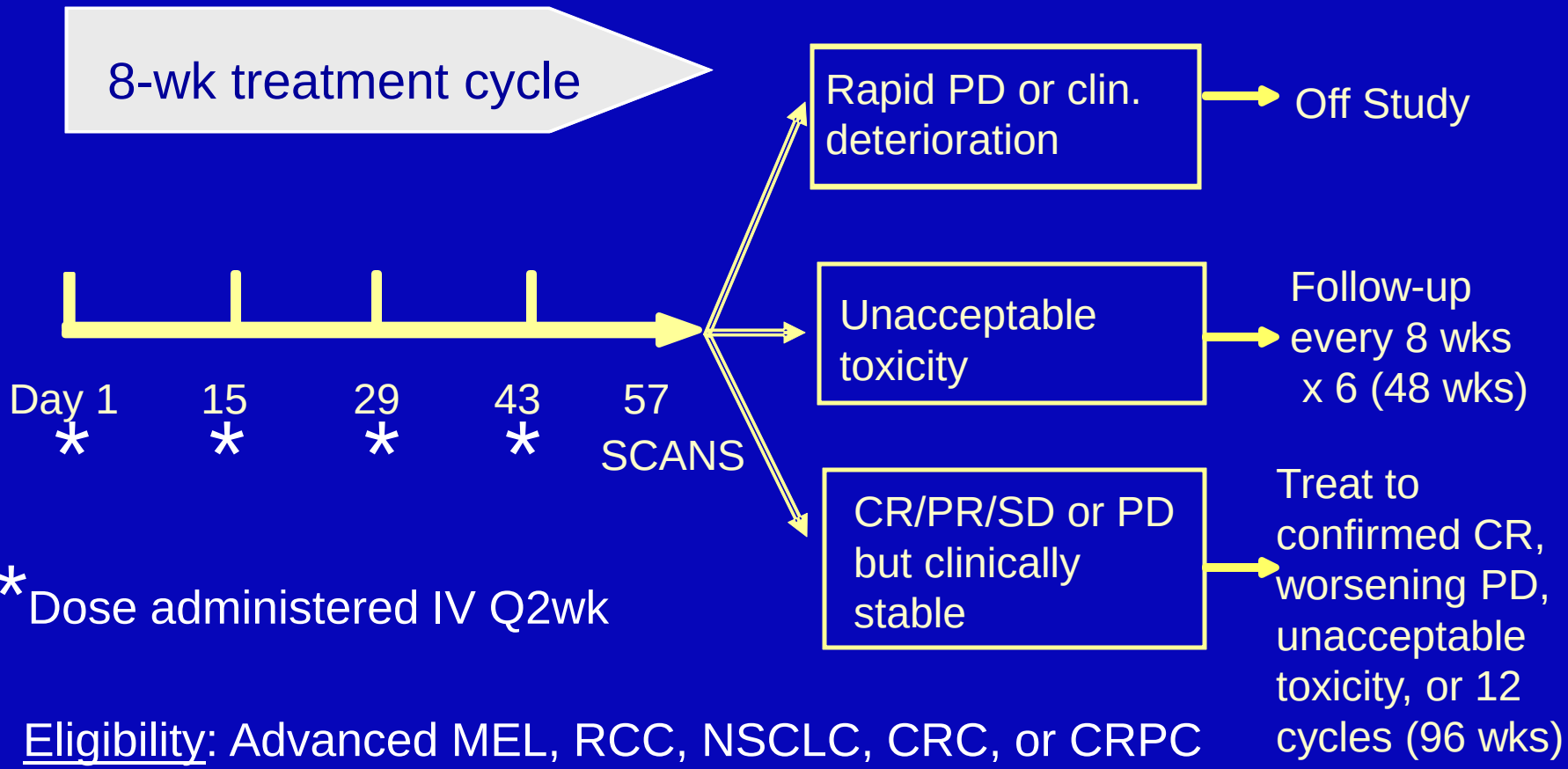


BMS-936558 (MDX-1106/ONO-4538)

- Fully human IgG4 anti-human PD-1 blocking Ab[1]
- No known Fc function (ADCC, CDC)
- High affinity for PD-1 (K_D ~3 nM), blocks binding of both PD-L1 (B7-H1) and PD-L2 (B7-DC)
- Manageable safety profile and preliminary evidence of clinical activity in patients with treatment-refractory solid tumors[1]

[1]Brahmer J, 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 Conduct

- Primary
  - Assessment of safety and tolerability of BMS-936558
- Secondary/Exploratory objectives include preliminary efficacy and pharmacokinetics
- Accrual completed (Dec. 2011); patient assessment ongoing
- Current analysis for patients as of July 3, 2012
  - 304 patients (107 with MEL) were evaluable for safety
  - 294 patients (106 with MEL) were evaluable for clinical activity

Baseline Characteristics For MEL Cohort

Characteristic	n=107
Median age, years (range)	61 (29 – 85)
Male, n (%)	72 (67)
ECOG PS, n (%)	
0	66 (62)
1	37 (35)
2	3 (3)

- Approximately 25% received 3 or more prior therapies

BMS-936558–Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3–4	
	Tot Pop*,**,†	MEL	Tot Pop	MEL‡
	No. (%) of Patients, All Doses			
Any adverse event	220 (72)	88 (82)	45 (15)	22 (21)
Fatigue	78 (26)	33 (31)	5 (2)	2 (2)
Rash	41(14)	24 (22)	—	—
Diarrhea	36 (12)	19 (18)	3 (1)	2 (2)
Pruritus	31 (10)	15 (14)	1 (0.3)	—
Nausea	24 (8)	9 (8)	1 (0.3)	1 (1)
Appetite ↓	24 (8)	7 (7)	—	—
Hemoglobin ↓	18 (6)	6 (6)	1 (0.3)	1 (1)
Pyrexia	16 (5)	5 (5)	—	—

*AEs occurring in ≥5% of the total population

**** Pneumonitis occurred in <5 % of the total population**

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

‡Common grade 3–4 AEs also included lymphopenia (3 pts) and abdominal pain and lipase increased (2 each). An additional 27 grade 3–4 drug-related AEs were observed and a single patient could exhibit one or more of these AEs

Summary of Key Safety Results

- For the entire study group, the maximum tolerated dose was not reached at doses up to 10 mg/kg
- Grade 3-4 drug-related AEs occurred in 21% (n=22) of all treated melanoma patients; the most common were lymphopenia (n=3), fatigue (2), diarrhea (2), abdominal pain (2), and lipase increased (2)
- There was no apparent relationship between drug dose and AE frequency in all treated patients and in melanoma patients
- Grade 2 pneumonitis was reported in 1 melanoma patient; 3 drug-related deaths (2 NSCLC, 1 CRC) occurred in patients with pneumonitis

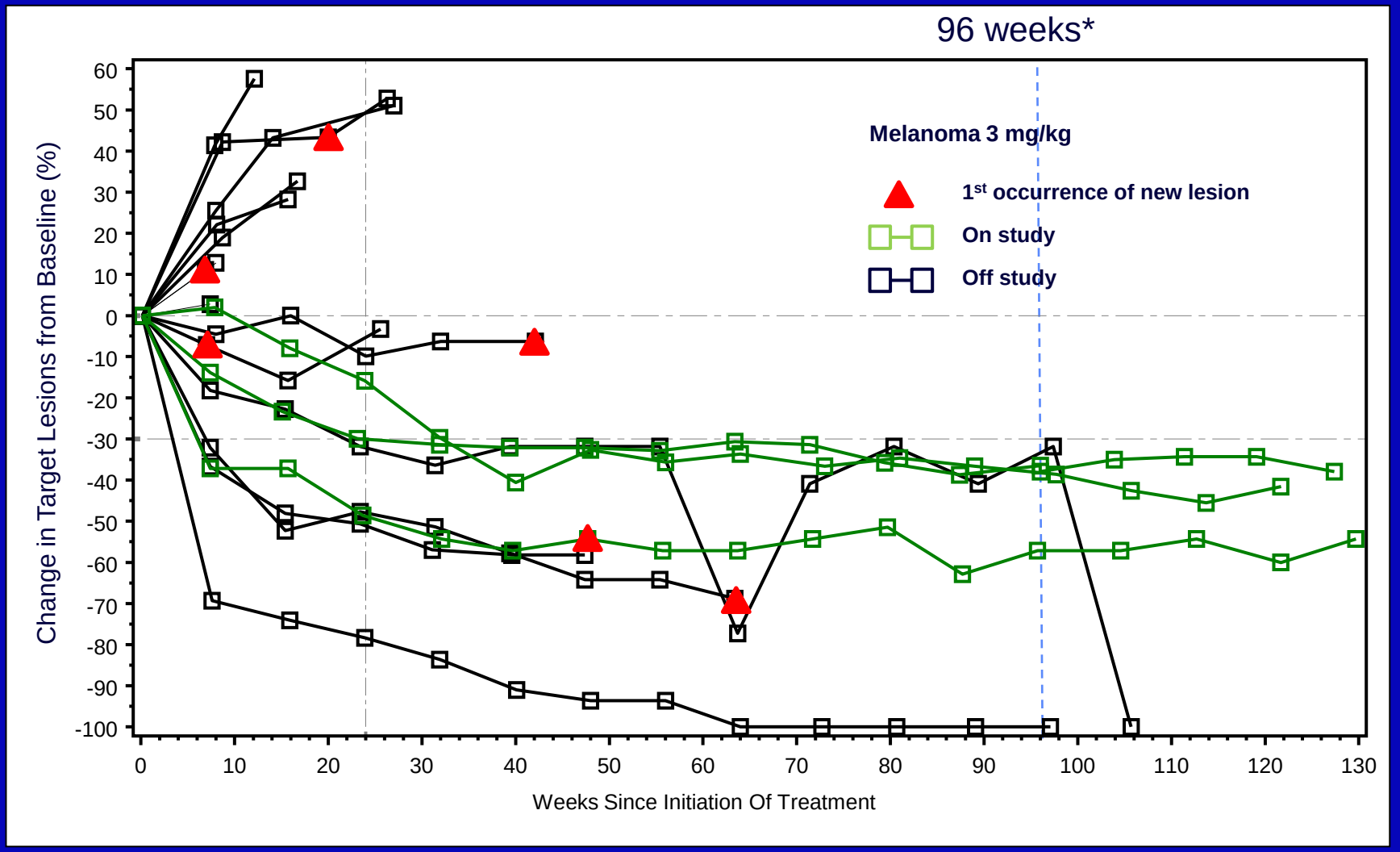
Clinical Activity of BMS-936558 in Melanoma Patients

Population	Dose (mg/kg)	Pts n	ORR n (%)	Median Duration of Response (95%CI)	Individual Pt Responses	PFSR at 24 wk (%)
All MEL	0.1-10	106	33 (31)	—	Range: 1.8+ to 25.7	42
MEL	0.1	17	6 (35)	NE	3.7+, 4.2+, 5.6, 5.6, 5.6+, 11.2+	41
	0.3	18	5 (28)	NE	1.8+, 4.2, 7.4+, 7.6+, 9.2+	33
	1	34	11 (32)	24 months (22.9 – NE)	1.9+, 5.5+, 7.5, 7.5, 11.1+, 13.4+, 18.4+, 22.9, 23.2+, 24, 24.9+	48
	3	17	7 (41)	NE	9.2+, 9.3, 11.1, 12.9, 18.8+, 22+, 22.4+	55
	10	20	4 (20)	25.7 months (17.0 – 25.7)	17, 18+, 24.6+, 25.7	30

NE, not currently estimable

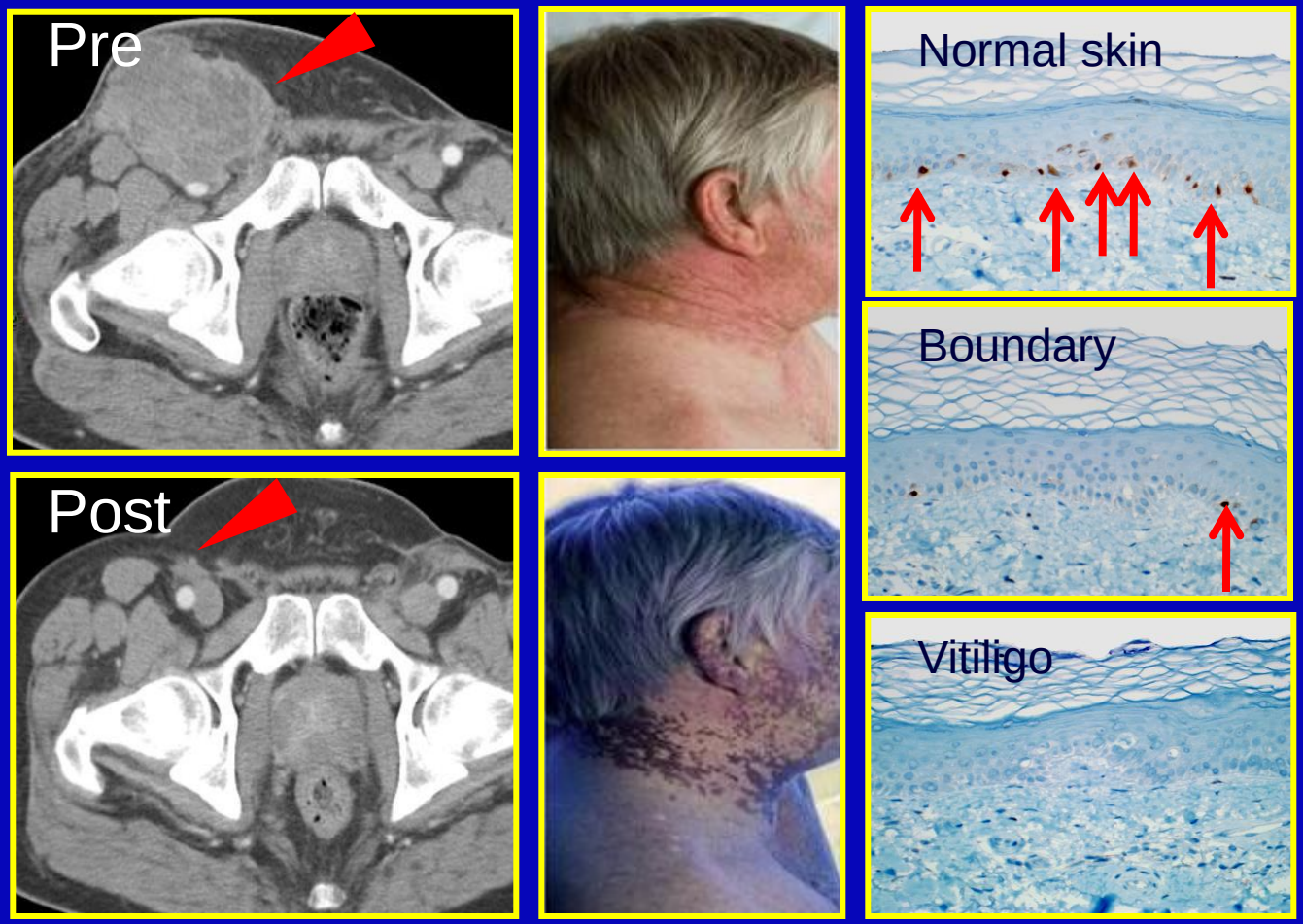
- ORR was assessed using modified RECIST v1.0
- 4 additional MEL patients had an unconventional pattern of response and were not classified as responders by the conventional RECIST
- Of 33 patients with OR (all dose levels)
  - 29 initiated treatment ≥1 year prior to July 3, 2012 and 16 had response lasting ≥1 year
  - 4 initiated treatment <1 year prior to July 3, 2012 and 4 had responses ranging from 1.8 to 5.5 months

Changes in Target Lesions Over Time in Melanoma Patients (3mg/kg)



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

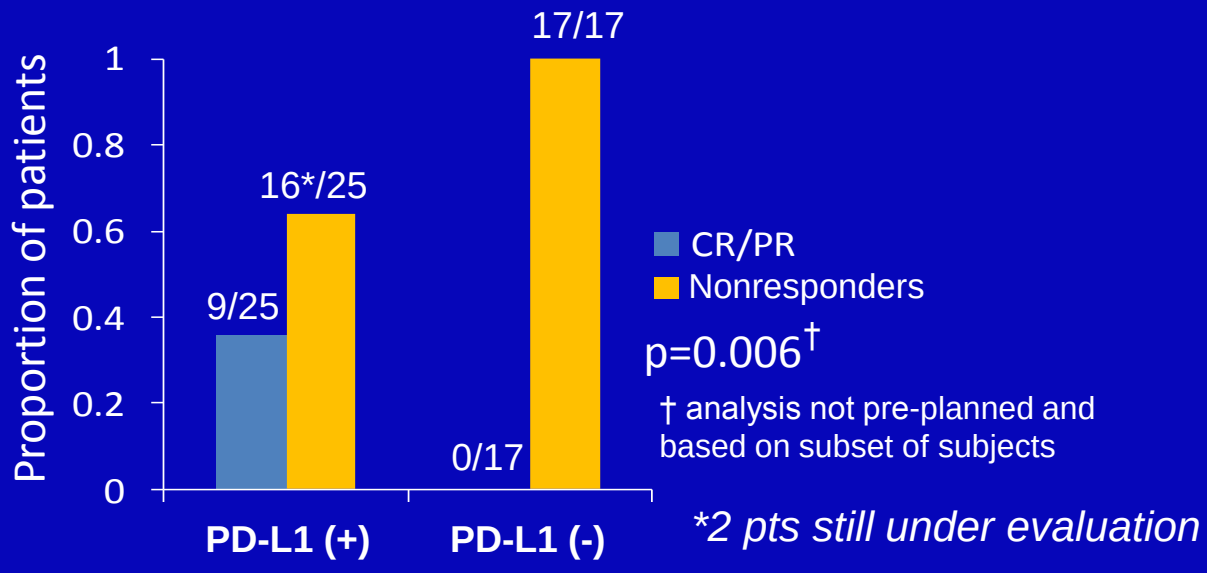
Complete Regression of Metastatic Melanoma (BMS-936558, 3 mg/kg) Associated With Vitiligo



History: 62-year-old male had previously developed PD following IL-2, temozolomide, and multiple surgeries.

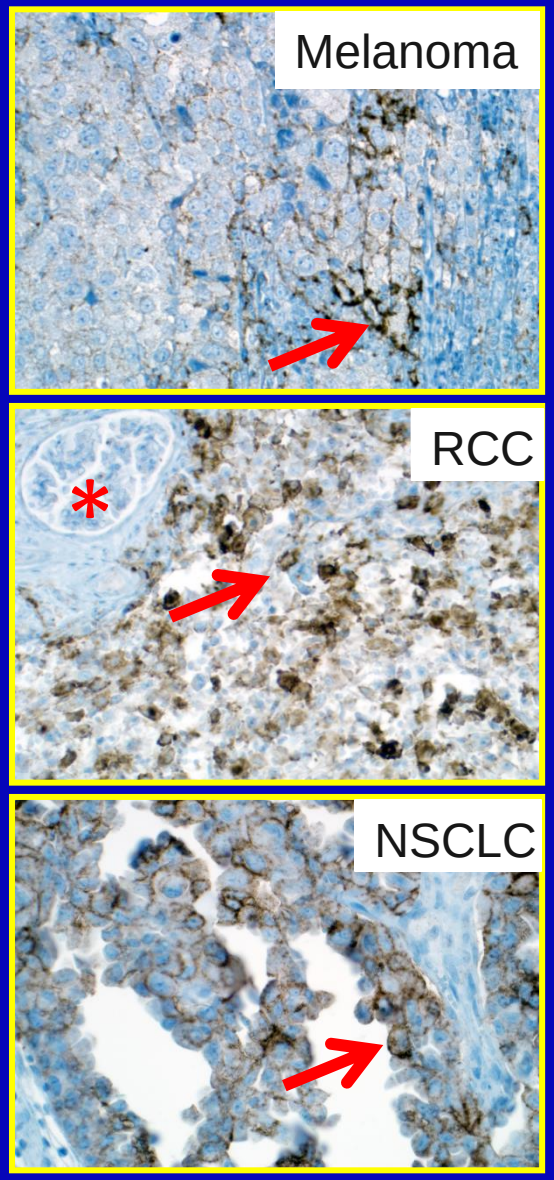
Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes

42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.



**2 pts still under evaluation*

Association Between Pretreatment Tumor PD-L1 Expression and Clinical Response			
Response Status	**PD-L1 Positive no. (%)**	**PD-L1 Negative no. (%)**	**Total no. (%)**
CR/PR	**9 (36)**	**0**	**9 (21)**
Nonresponder	**16* (64)**	**17 (100)**	**33 (79)**
All Patients	**25**	**17**	**42**



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

Summary

- BMS-936558 can be administered safely in an outpatient setting to patients with advanced melanoma, with durable clinical benefit
- Objective responses were observed within each dose cohort (0.1 – 10 mg/kg)
- Responses are durable and are ongoing in a majority of patients
- Blockade of the PD-1 pathway may represent a new immune therapy for patients with melanoma
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored
- Registration trials of BMS-936558 in patients with melanoma are planned

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