# Clinical Activity and Safety of Anti-PD-1 (BMS-936558, MDX-1106) in Patients with Advanced Non-Small-Cell Lung Cancer

**J.R. Brahmer,**[1] L. Horn,[2] S.J. Antonia,[3] D. Spigel,[4] L. Gandhi,[5] L.V. Sequist,[6] J.M. Wigginton,[7] D. McDonald,[7] G. Kollia,[7] A. Gupta,[7] S. Gettinger[8]

[1]Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD; [2]Vanderbilt-Ingram Cancer Center, Nashville, TN; [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Massachusetts General Hospital Cancer Center, Boston, MA; [7]Bristol-Myers Squibb, Princeton, NJ; [8]Yale University School of Medicine, New Haven, CT

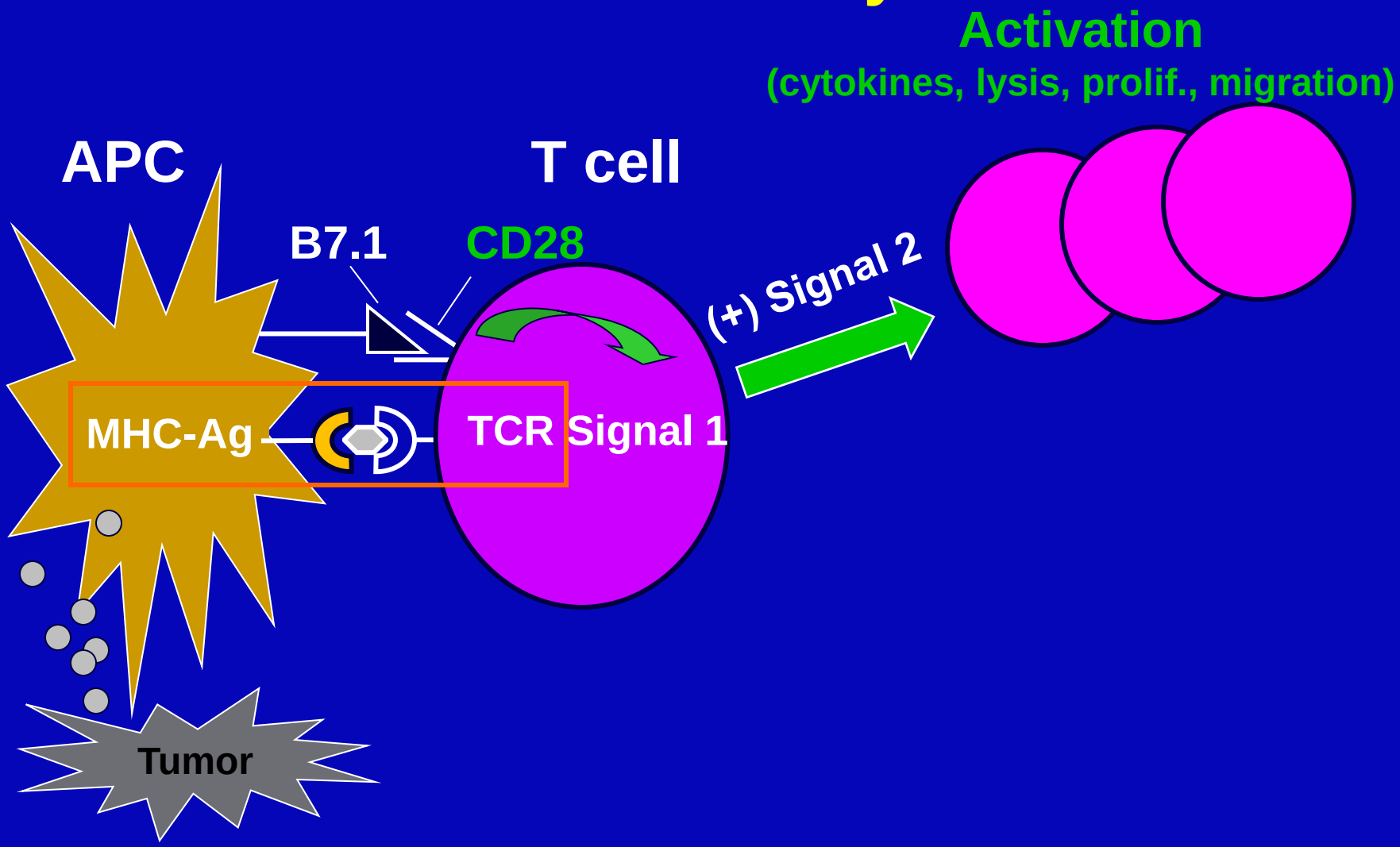
# Background

## Immunotherapy in NSCLC:

- Immunotherapy historically not successful in NSCLC
- Resurgence of interest over past decade
- Vaccines
- Check-point inhibitors:
  - Preliminary evidence of activity with CTLA-4 and chemotherapy [1,2]

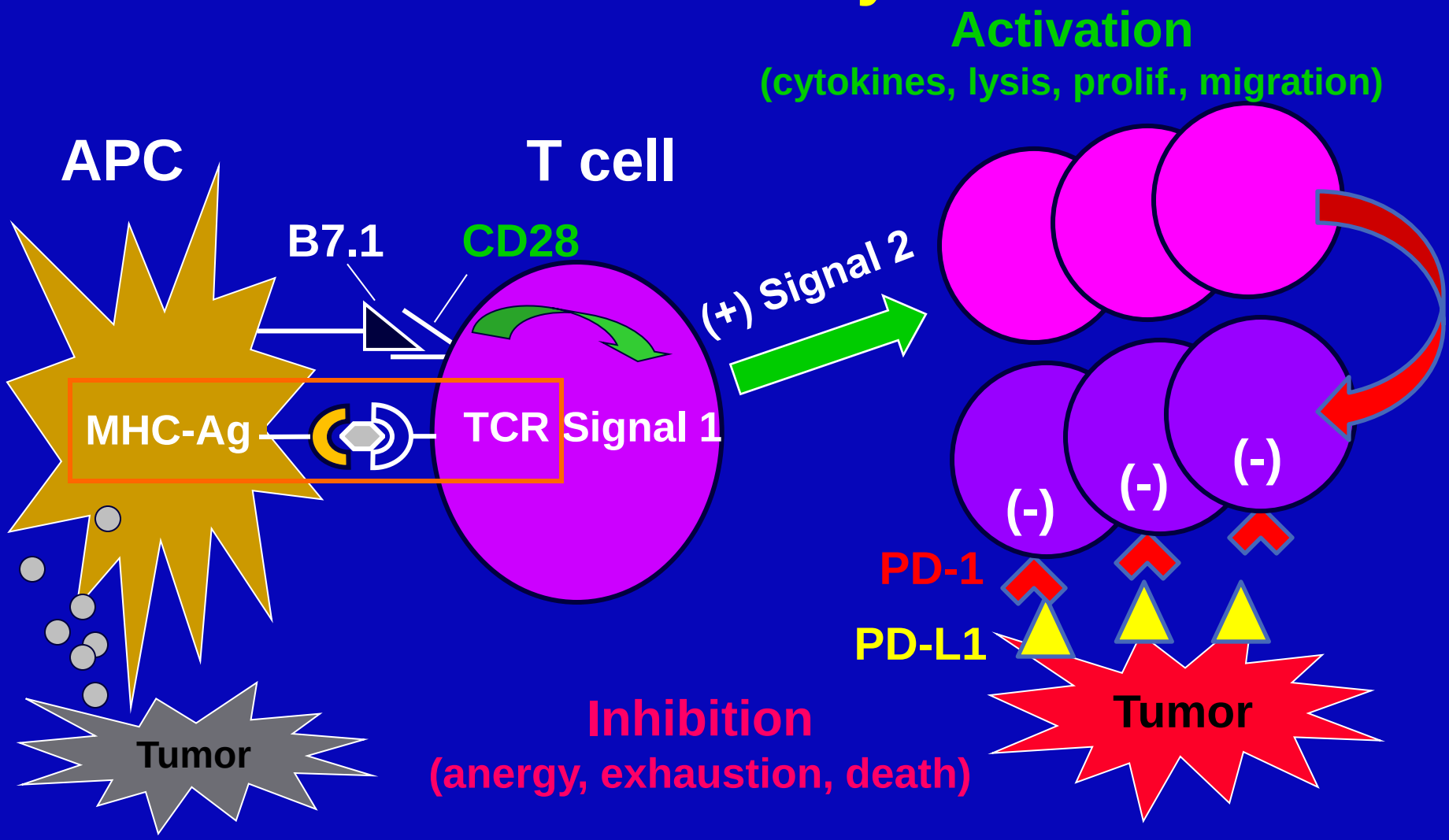
[1]Lynch TJ, et al. J Clin Oncol. 2012. [2]Genova C, et al. Expert Opin Biol Ther 2012.

# Role of PD-1 in Suppressing Antitumor Immunity



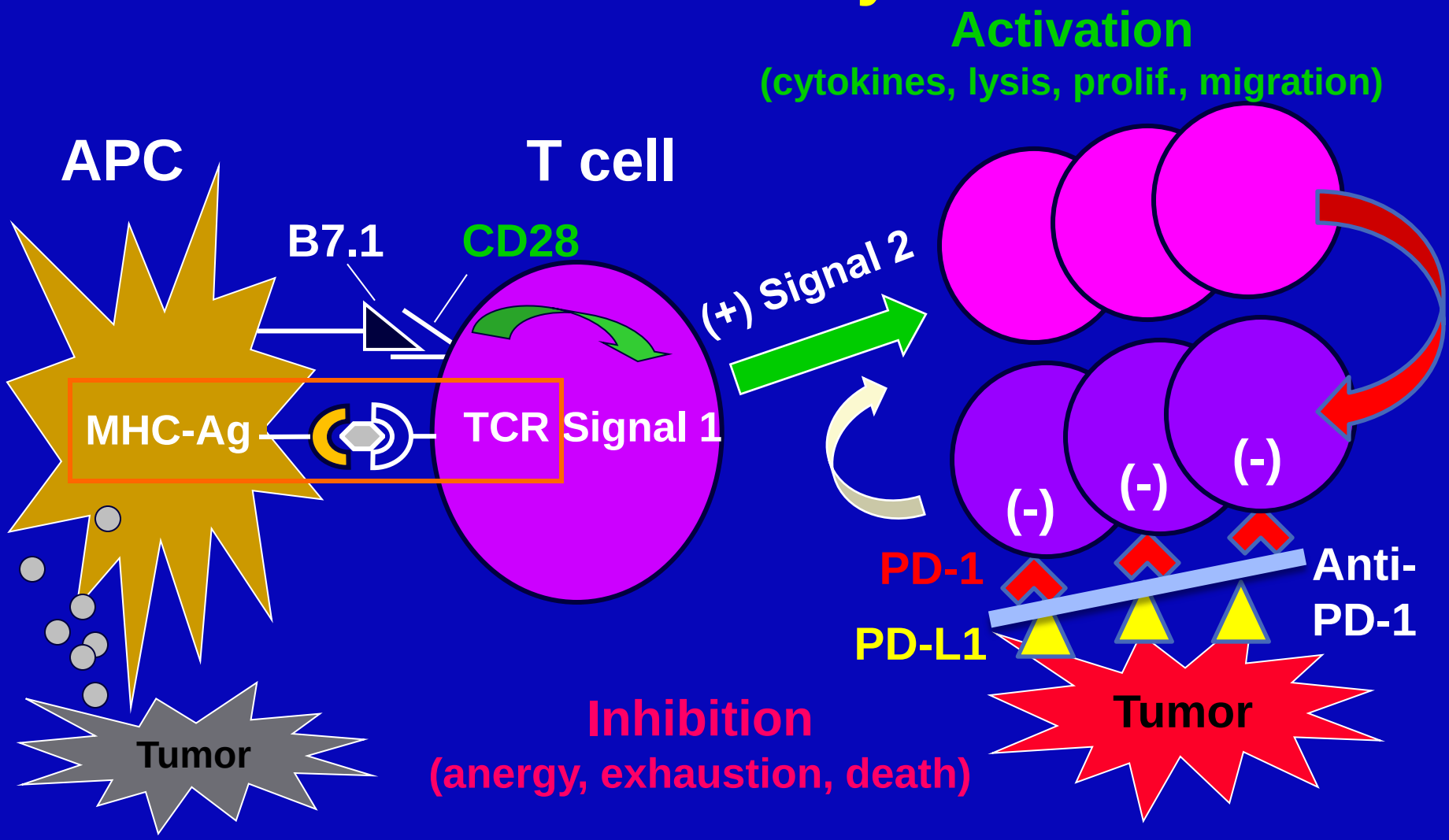

*Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012*

# Role of PD-1 in Suppressing Antitumor Immunity




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

# Role of PD-1 in Suppressing Antitumor Immunity




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

# Role of PD-1 Pathway in NSCLC

- PD-1 expression on tumor infiltrating lymphocytes (TILs) in NSCLC has shown:
  - Decreased cytokine production and decreased effector function[1,2]
- PD-L1 expression noted in NSCLC[2,3]
- Increase of PD-L1 expression on tumor cells correlated with a decrease in the number of TILs in the same region[4]
- Preliminary correlation of PD-L1 expression by tumor cells with response to PD-1 blockade[5]

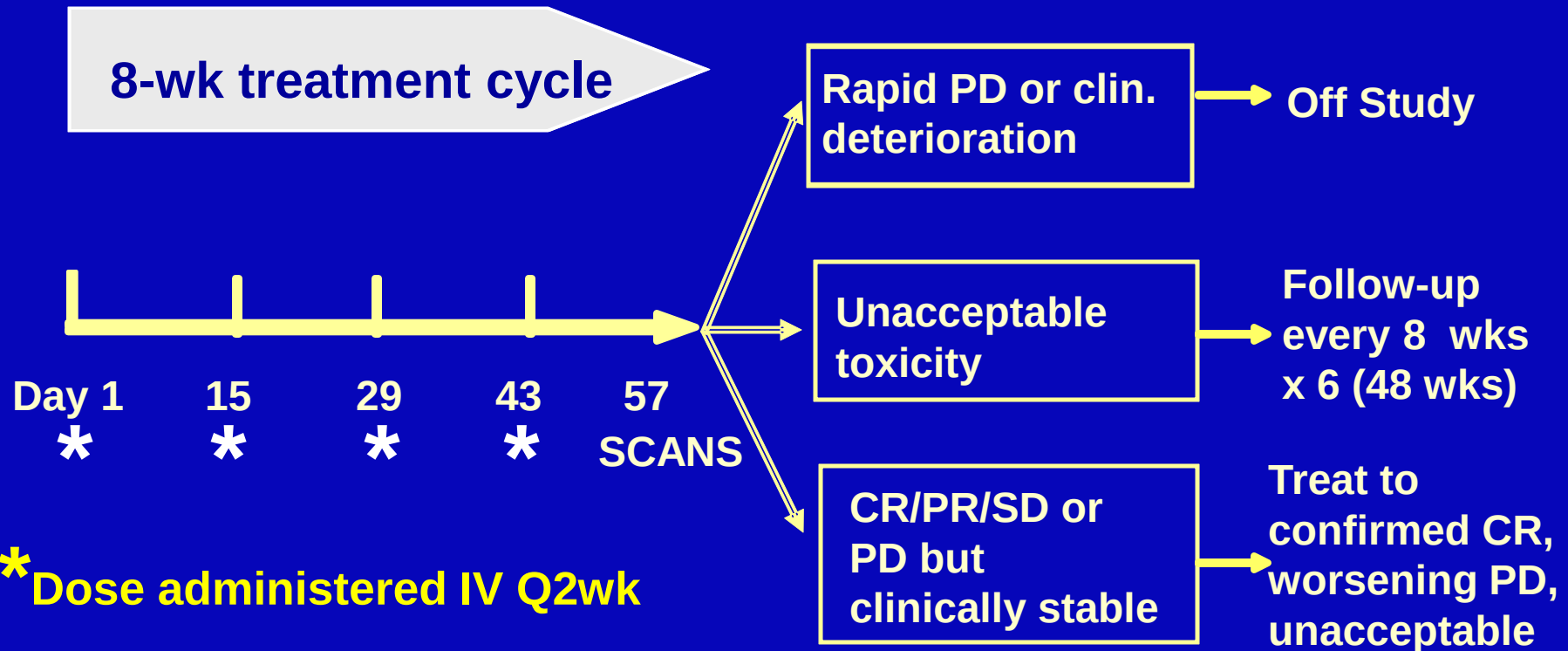
[1]Ahmadzadeh M, et al. Blood 2009;114:1537-44. [2]Zhang Y, et al. Cell Mol Immunol 2010;7:389-95. [3]Mu C-Y et al. Med Oncol 2010. [4]Konishi J, et al. Clin Cancer Res 2004;10:5094-100. [5]Brahmer J, et al. J Clin Oncol 2010;28:3167-75

# 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 in a first-in-human, single-dose, dose-escalation study[1]

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

# Study Design: Phase I Multi-dose Regimen




*Dose administered IV Q2wk

Doses tested for NSCLC: 1, 3, 10 mg/kg

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
  - Assessment of antitumor activity
  - Pharmacodynamic evaluation
- Accrual completed (Dec. 2011); patient assessment ongoing
- Current analysis for patients treated through Feb. 2012
  - 296 patients (122 with NSCLC) were evaluable for safety
  - 236 patients (76 with NSCLC) were evaluable for clinical activity

# Baseline Characteristics

| Baseline Characteristic | n=122 |
|---|---|
| Median age (range), yr | 65 (38-85) |
| Male, no. (%) | 74 (61) |
| Tumor histology, no. (%)* | |
| Squamous | 47 (39) |
| Non-squamous | 73 (60) |
| ECOG PS, no. (%)† | |
| 0-1 | 117 (96) |
| 2 | 2 (2) |
| Number of prior therapies, no. (%)‡ | |
| 1-2 | 49 (40) |
| ≥3 | 67 (55) |
| Nature of prior therapy, no. (%) | |
| Platinum-based chemotherapy | 115 (94) |
| Tyrosine-kinase inhibitor | 41 (34) |
| Radiotherapy | 40 (33) |

*Unknown: 2 (2%). †Not reported: 3 (2%). ‡Not reported: 6 (5%).

# BMS-936558-Related Adverse Events

| Drug-Related Adverse Event | All Grades | | Grades 3-4 | |
|---|---|---|---|---|
| | Tot Pop* | NSCLC | Tot Pop | NSCLC† |
| | No. (%) of Patients, All Doses | | | |
| Any adverse event | 207 (70) | 78 (64) | 41 (14) | 10 (8) |
| Fatigue | 72 (24) | 22 (18) | 5 (2) | 2 (2) |
| Rash | 36 (12) | 5 (4) | — | — |
| Diarrhea | 33 (11) | 7 (6) | 3 (1) | 1 (1) |
| Pruritus | 28 (9) | 6 (5) | 1 (0.3) | — |
| Nausea | 24 (8) | 9 (7) | 1 (0.3) | — |
| Appetite ↓ | 24 (8) | 12 (10) | — | — |
| Hemoglobin ↓ | 19 (6) | 10 (8) | 1 (0.3) | — |
| Pyrexia | 16 (5) | 7 (6) | — | — |

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

† The most common grade 3-4 AEs were fatigue, pneumonitis, and elevated AST (2 pts each). An additional 16 grade 3-4 drug-related AEs were observed and one or more occurred in a single patient.

# Summary of Key Safety Results

- 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 or NSCLC patients
- In the total patient population across all tumor types:
  - Grade 3-4 drug-related AEs occurred in 14% of patients
  - Grade 1-2 pneumonitis was noted in 6 (2%) patients
  - Three drug-related deaths occurred in patients with pneumonitis (2 with NSCLC and 1 with CRC)
- In NSCLC patients:
  - Grade 3-4 drug-related AEs occurred in 8% of patients
  - Grade 1-2 pneumonitis was noted in 4 (3%) patients

# Clinical Activity of BMS-936558 in NSCLC Patients

| Pop | Dose (mg/kg) | Pts n | ORR n (%) | Duration of Response (mo) | SD ≥24 wk n (%) | PFSR at 24 wk (%) |
|---|---|---|---|---|---|---|
| ALL NSCLC | 1-10 | 76 | 14 (18) | 1.9+ to 30.8+ | 5 (7) | 26 |
| NSCLC | 1 | 18 | 1 (6) | 9.2+ | 1 (6) | 16 |
| | 3 | 19 | 6 (32) | 1.9+ to 30.8+ | 2 (11) | 41 |
| | 10 | 39 | 7 (18) | 3.7 to 14.8+ | 2 (5) | 24 |

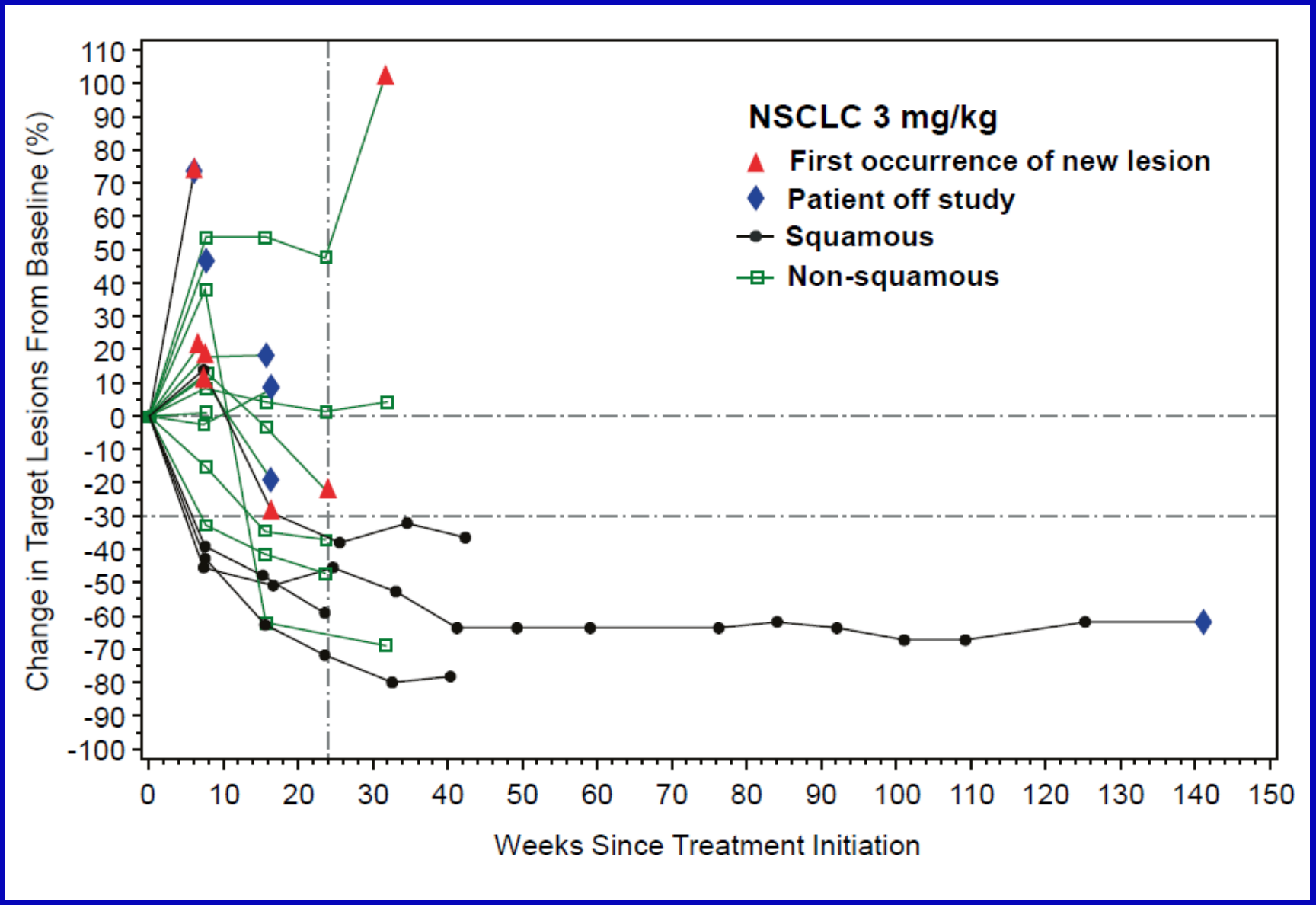
- ORR was assessed using modified RECIST v1.0
- 3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation

# Clinical Activity by Histology, Efficacy Population

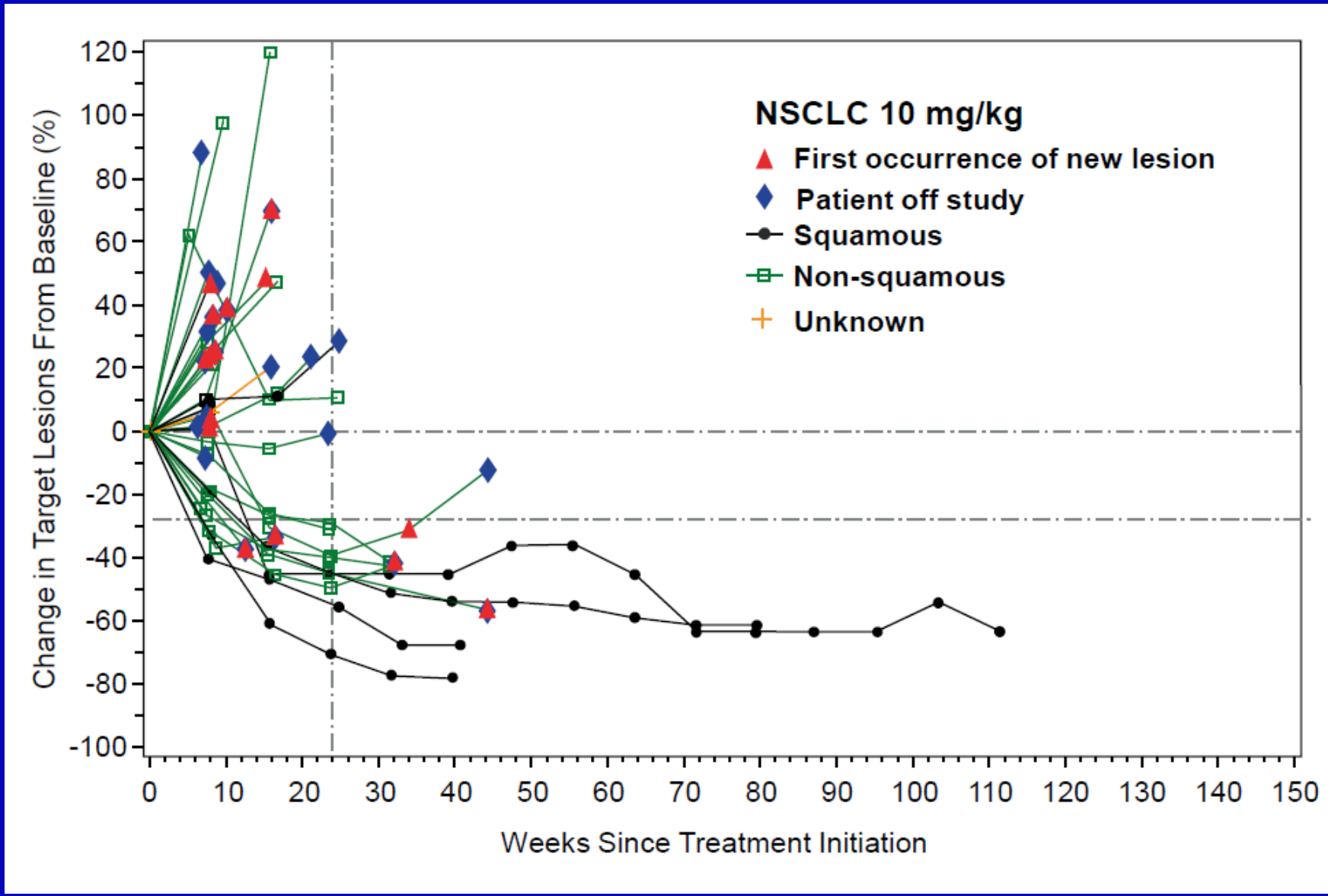
| Parameter | BMS-936558 Dose, mg/kg | | |
|---|---|---|---|
| | 1 | 3 | 10 |
| **ORR, No. patients* (%)** | | | |
| Squamous | 0<br>n=5 | 3 (50)<br>n=6 | 3 (43)<br>n=7 |
| Non-squamous | 0<br>n=12 | 3 (23)<br>n=13 | 4 (13)<br>n=31 |
| **SD ≥24 wk, No. patients (%)** | | | |
| Squamous | 0 | 0 | 0 |
| Non-squamous | 1 (8) | 2 (15) | 2 (6) |
| **PFSR at 24 wk, (%)** | | | |
| Squamous | 0 | 50 | 43 |
| Non-squamous | 14 | 37 | 21 |

*1 patient of unknown histology who received 1mg/kg had an OR.

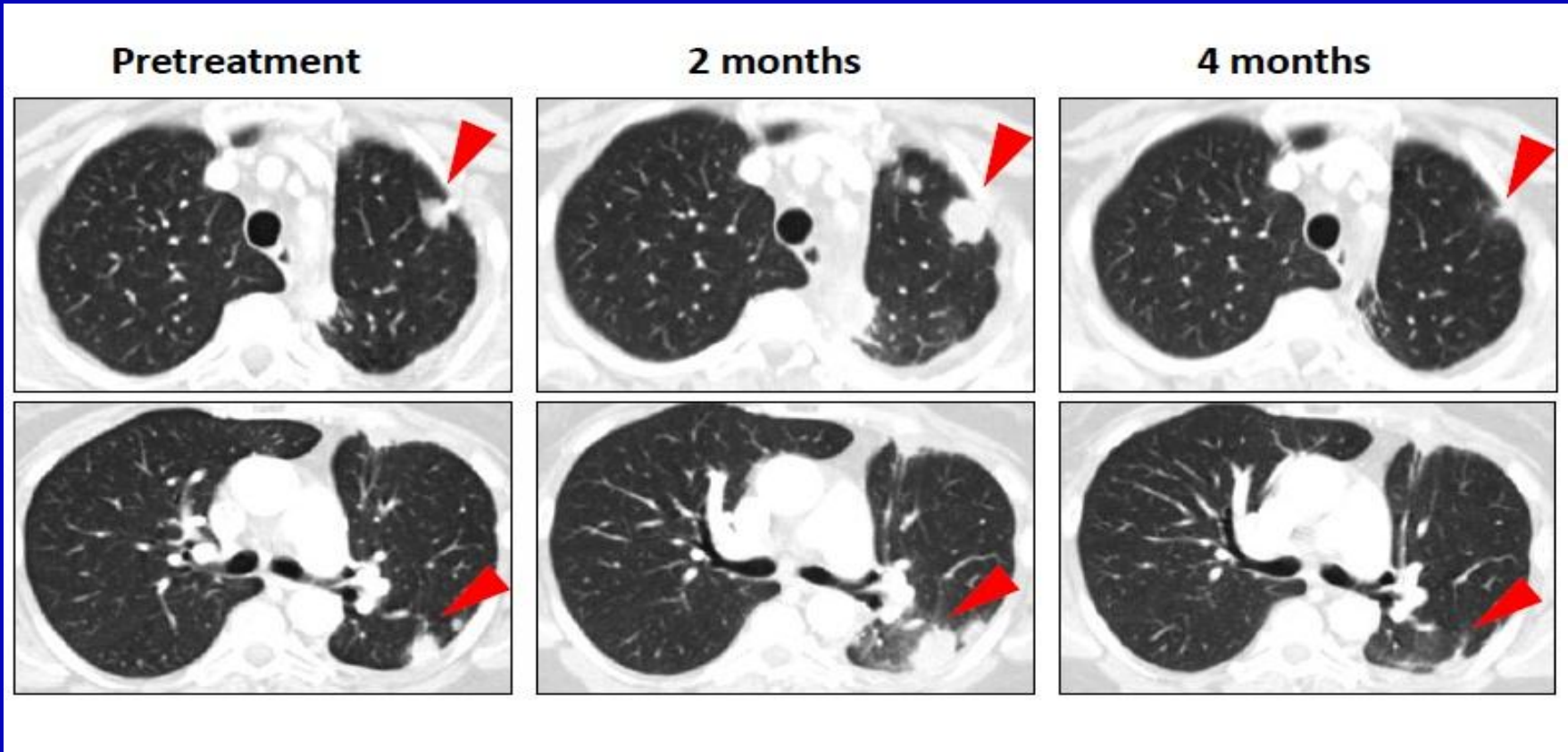
# Changes in Target Lesions Over Time in NSCLC Patients



# Changes in Target Lesions Over Time in NSCLC Patients



# Response of Metastatic NSCLC (BMS-936558, 10mg/kg)




- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx ‘04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

# Conclusions

- BMS-936558 can be administered safely in an outpatient setting to heavily pretreated NSCLC patients
- Durable clinical benefit was seen in both squamous and non-squamous NSCLC
- These findings support the importance of the PD-1 pathway in NSCLC therapy across different histologies
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored
- Clinical registration trials of BMS-936558 in patients with NSCLC are planned

# Acknowledgments


- The patients and their families
- The study sites enrolling patients to the trial
- Alan Korman and colleagues of Bristol-Myers Squibb (BMS) who developed BMS-936558
- Support for this work from BMS, Ono Pharmaceutical Company, Ltd., and grants from the NIH and the Melanoma Research Alliance
- All authors contributed to and approved the presentation; assistance in the preparation of the slides was provided by Susan Leinbach, a professional medical writing consultant, funded by Bristol-Myers Squibb

# Principal Investigators Participating on the Study

Dr. S.J. Antonia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Dr. J.R. Brahmer, Sidney Kimmel Comprehensive Cancer Center at John Hopkins, Baltimore, MD

Dr. R.D. Carvajal, Memorial Sloan-Kettering Cancer Center, New York, NY

Dr. F.S. Hodi, Dana-Farber Cancer Institute, Boston, MA

Dr. D.P. Lawrence, Massachusetts General Hospital Cancer Center, Boston, MA

Dr. P. Leming, The Christ Hospital, Cincinnati, OH

Dr. D. McDermott, Beth Israel Deaconess Medical Center, Boston, MA

Dr. D. Mendelson, Pinnacle Oncology Hematology, Scottsdale, AZ

Dr. J.D. Powderly, Carolina BioOncology Institute, Huntersville, NC

Dr. D.C. Smith, University of Michigan, Ann Arbor, MI

Dr. J. Sosman, Vanderbilt University Medical Center, Nashville, TN

Dr. D.R. Spigel, Sarah Cannon Research Institute / Tennessee Oncology, PLLC, Nashville, TN

Dr. M. Sznol, Yale Cancer Center, New Haven, CT