Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Non-Small Cell Lung Carcinoma

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The Angeles Clinic and Research Institute

Advances in Cancer Immunotherapy™ - Los Angeles
June 19, 2015

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Society for Immunotherapy of Cancer

Disclosures

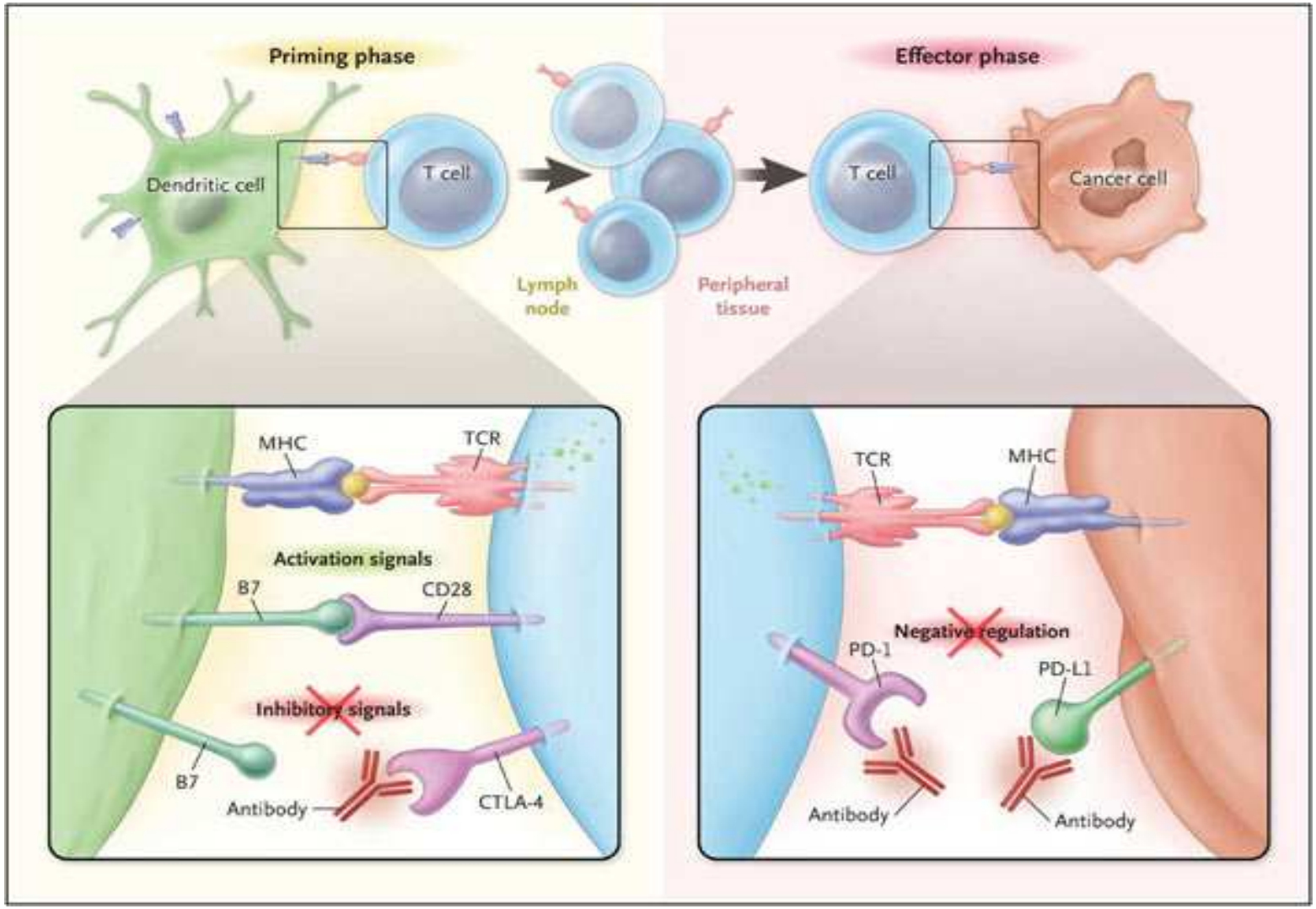
- Speaker’s Bureau: Bristol Myers Squibb

Background

- Non-small cell lung cancer (NSCLC) remains the leading cause of cancer related mortality worldwide
- Despite recent advances in the treatment of lung cancer, the prognosis of patients with lung cancer remains poor .
- There is a need for new therapeutic strategies to improve lung cancer patients' survival.
- Lung cancer is historically not known to be an immunogenic-mediated malignancy
- However, studies show increased tumor-infiltrating lymphocytes in lung cancer patients correlate with improved survival

Approaches to Immunotherapy

- Interleukin-2
- Interferon
- Vaccines
- Tumor infiltrating lymphocytes
- CTLA4-inhibitors
- Anti PD-1/anti PD-L1 antibodies



Ribas A. NEJM 2012 June 28; 366(26):2517-9

Immune checkpoint inhibitors

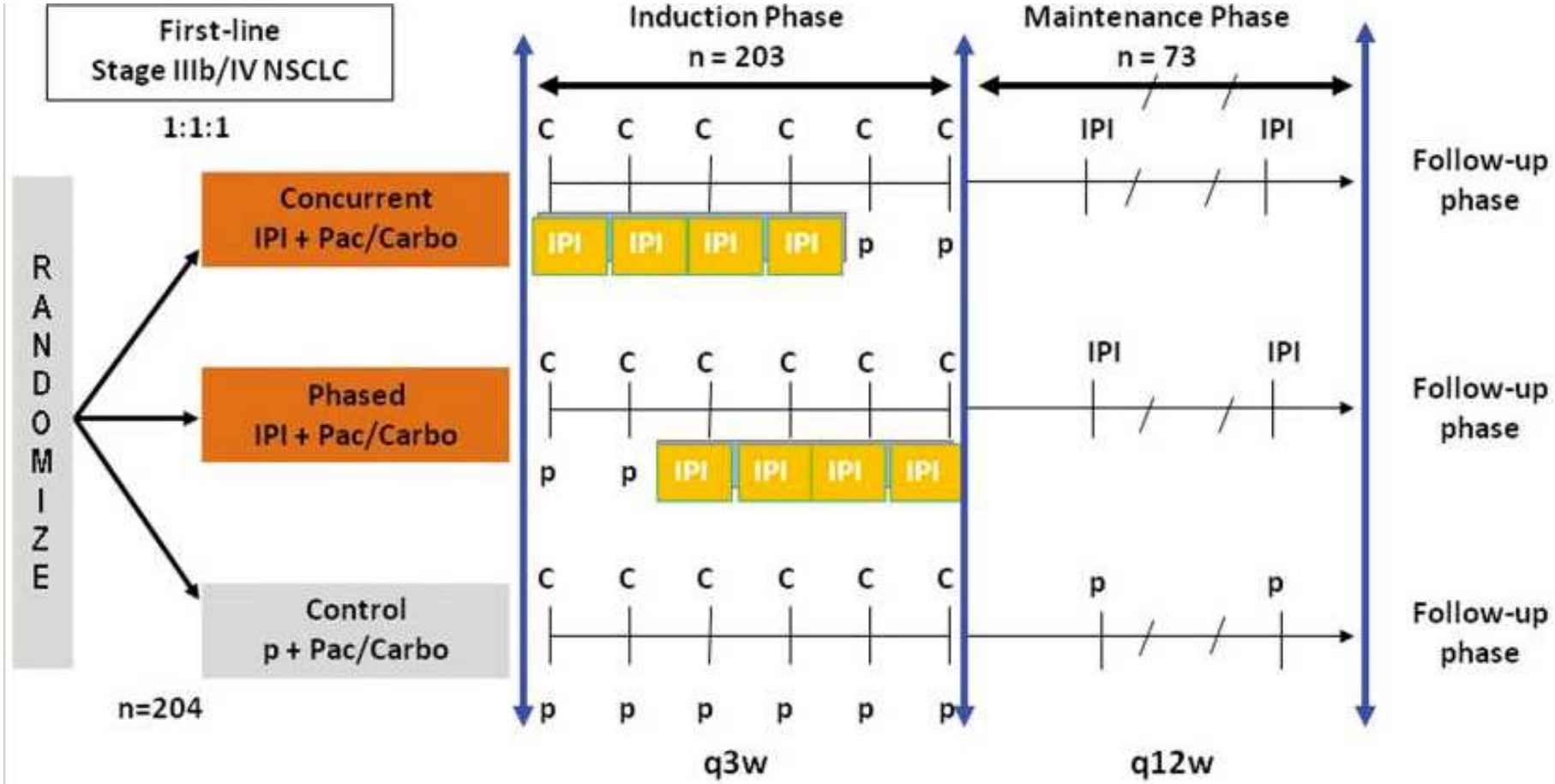
- CTLA-4 inhibitors
  - Ipilimumab
  - Tremelimumab

- Anti PD-1 antibodies
  - Pembrolizumab
  - Nivolumab
  - AMP-514

- Anti PD-L1 antibodies
  - Medi4736
  - atezolizumab (MPDL3280A)
  - Avelumab(MSB0010718C)

CTLA-4 inhibitors

Randomized Phase II Study of Ipilimumab and Chemotherapy in Advanced NSCLC



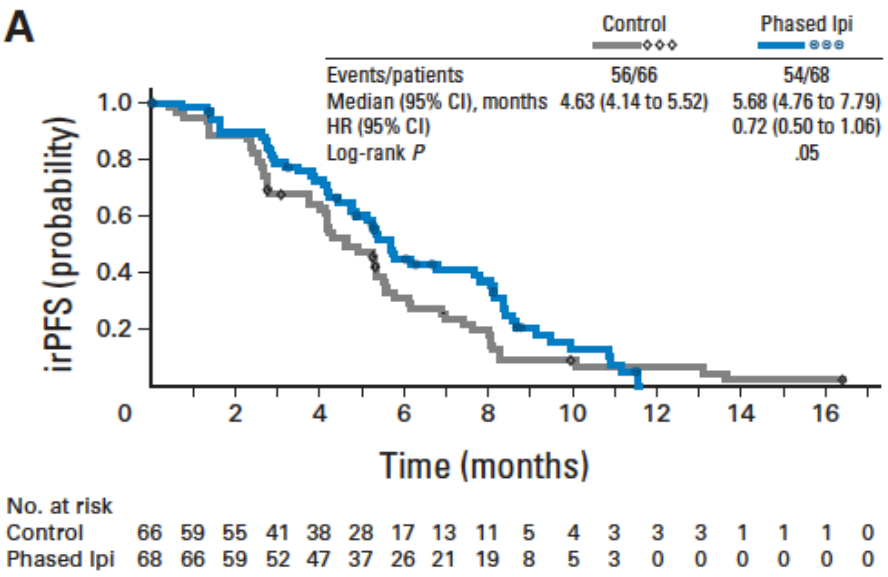
IPI, Ipilimumab (10 mg IV) ; C, Chemotherapy (Pac /Carbo); p, Placebo

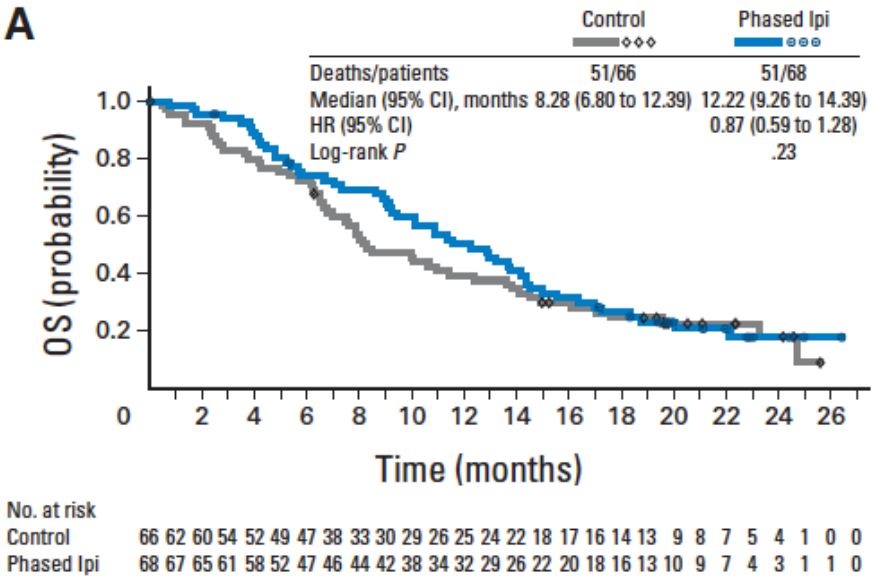
Cx regimen: Pac (175 mg/m^2)/Carbo (AUC=6) prior to start of ipilimumab

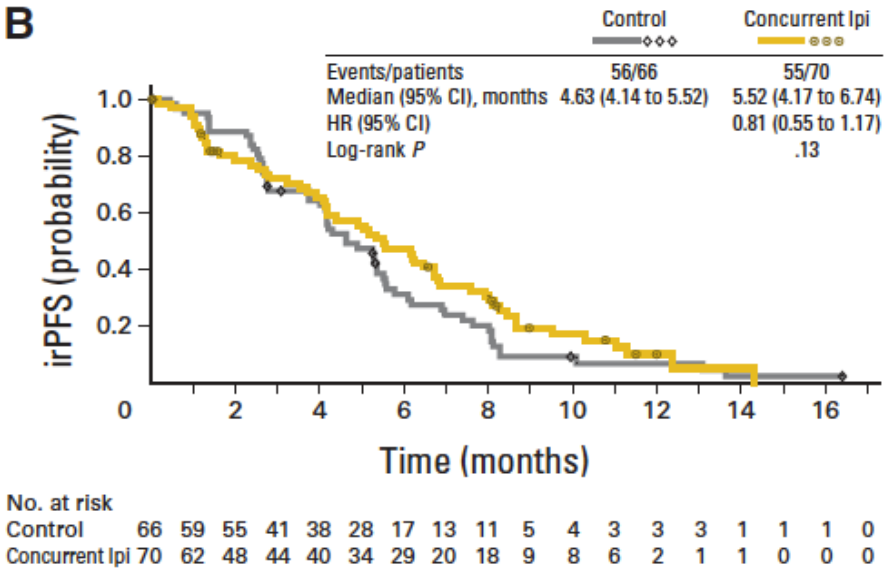
Primary endpoint:
Immune-related PFS

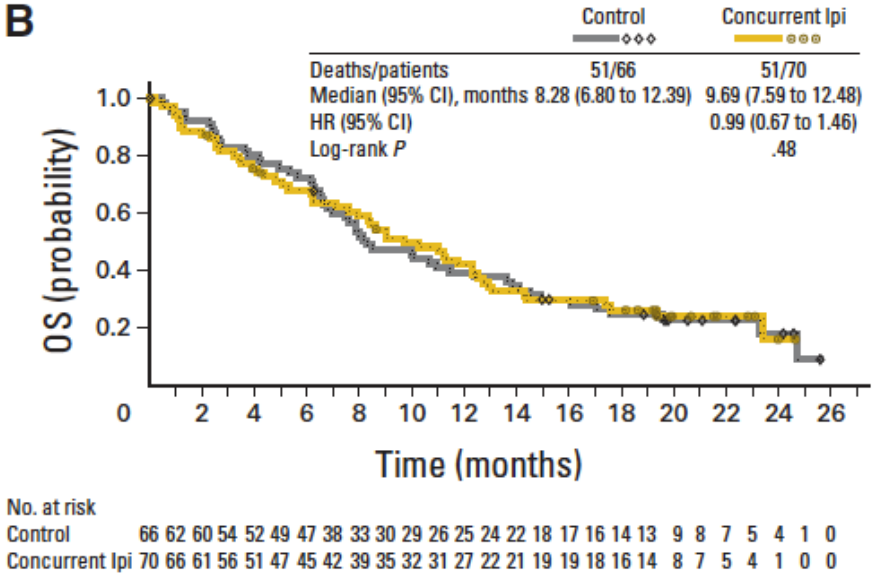
Lynch T et al. JCO 30, 2012

Randomized Phase II of Ipilimumab and Chemotherapy in Advanced NSCLC









Lynch T et al. JCO 30, 2012

Randomized Phase II of Ipilimumab and Chemotherapy in Advanced NSCLC – Results by Histology

irPFS	All	Squamous	Non-squamous
Carbo-taxol	4.6		
Phased ipi	5.7 (HR 0.72)	HR 0.55	HR 0.82
Concurrent ipi	5.5 (HR 0.81)	HR 0.85	HR 0.77

Survival			
Carbo-taxol	8.3		
Phased ipi	12.2 (HR 0.87)	HR 0.48	HR 1.17
Concurrent ipi	9.7 (HR 0.99)	HR 1.02	HR 0.96

Lynch T et al. JCO 30, 2012

Randomized phase II clinical trial comparing tremelimumab (CP-675,206) with best supportive care (BSC) following first-line platinum-based therapy in patients (pts) with advanced non-small cell lung cancer (NSCLC).

- Pts treated with ≥4 cycles of first-line platinum-based therapy resulting in either stable disease (SD) or response per RECIST were eligible and were randomized 3-6 weeks after prior therapy.

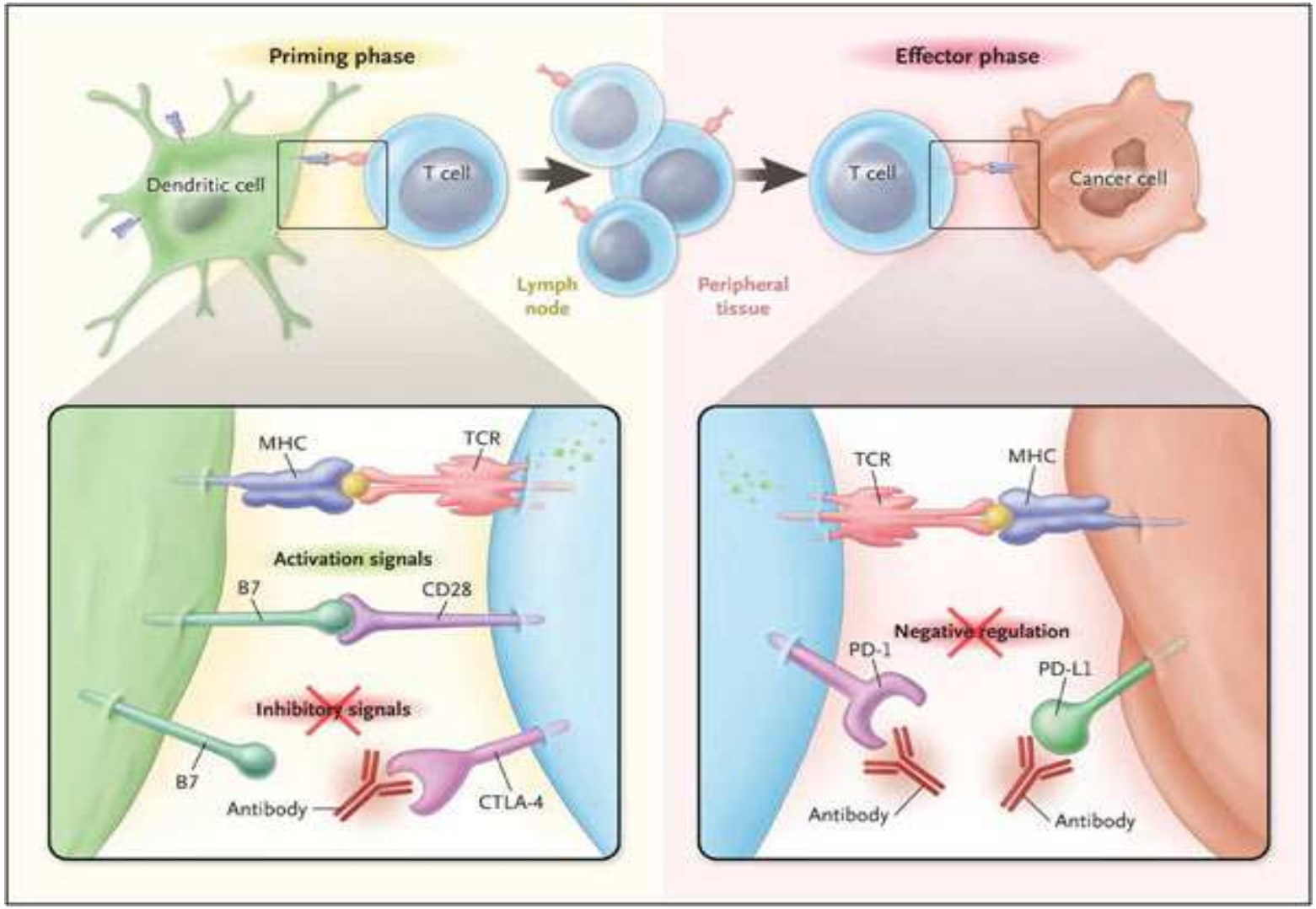
- Pts received 15 mg/kg IV tremelimumab Q90D or BSC until disease progression

- Eighty-seven pts received tremelimumab (n=44) or BSC (n=43).

- Among pts receiving tremelimumab, there were 2 (4.8%) partial responses and 7 (16.6%) SDs, compared with 0 and 6 (14.3%) pts receiving BSC, respectively

Zatloukal et al, ASCO 2009 abstract 8071

Disappointing results with single agent CTLA-4 inhibitors



Ribas A. NEJM 2012 June 28; 366(26):2517-9

Anti PD-1 antibody

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.

Topalian S et a. NEJM 2012

Nivolumab (BMS-936558/MDX-1106) Human Anti-PD-1 Antibody

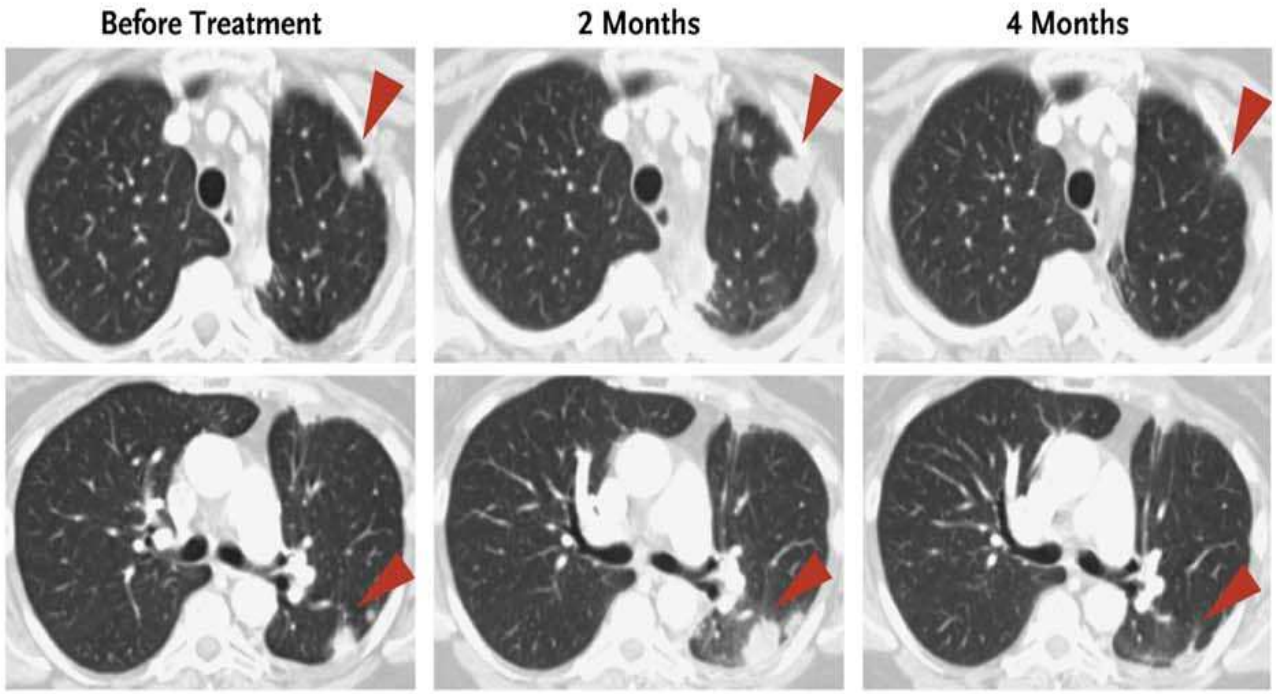
- IgG4 – no ADCC/CDCC activity
- High affinity binding to human PD-1 (K_D ~ 3 nM)
- Blocks binding of PD-1 to PD-L1 (B7-H1) and PD-L2 (B7-DC)
- *In vitro*, BMS-936558
  - Augments cytokine production/proliferation
    - Human allogeneic mixed lymphocyte reaction (MLR)

Phase 1 study assessing the safety, anti-tumor activity and pharmacokinetics of BMS-936558, a fully human IgG4-monoclonal antibody directed against PD-1

- Given IV every 2 weeks
- Patients received treatment for up to 2 years
- Dose escalation study(0.1 to 10 mg/kg)
- Maximum tolerated dose was not reached
- A total of 296 patients with advanced solid tumors:
  - Melanoma(104 patients)
  - NSCLC(122)
  - Renal-cell cancer(34)
  - Castration-resistant prostate cancer(17)
  - Colorectal cancer(19)

- Responses seen in:
  - melanoma: 19-41% response rates
  - lung cancer:
    - 6/18(33%): squamous histology
    - 7/56(12%): nonsquamous histology
  - renal-cell cancer: 24-31% response rates
- No objective responses observed in patients with colorectal or prostate cancer
- Patients with PD-L1 negative tumors did not have a response.
- Disease progression was the most common cause of death

D Patient with Non–Small-Cell Lung Cancer



Topalian S et a. NEJM 2012

CHECKMATE 017

A multinational, multicenter, open-label, randomized phase 3 study of nivolumab compared to docetaxel in patients with metastatic squamous NSCLC With progression on or after platinum-based chemotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

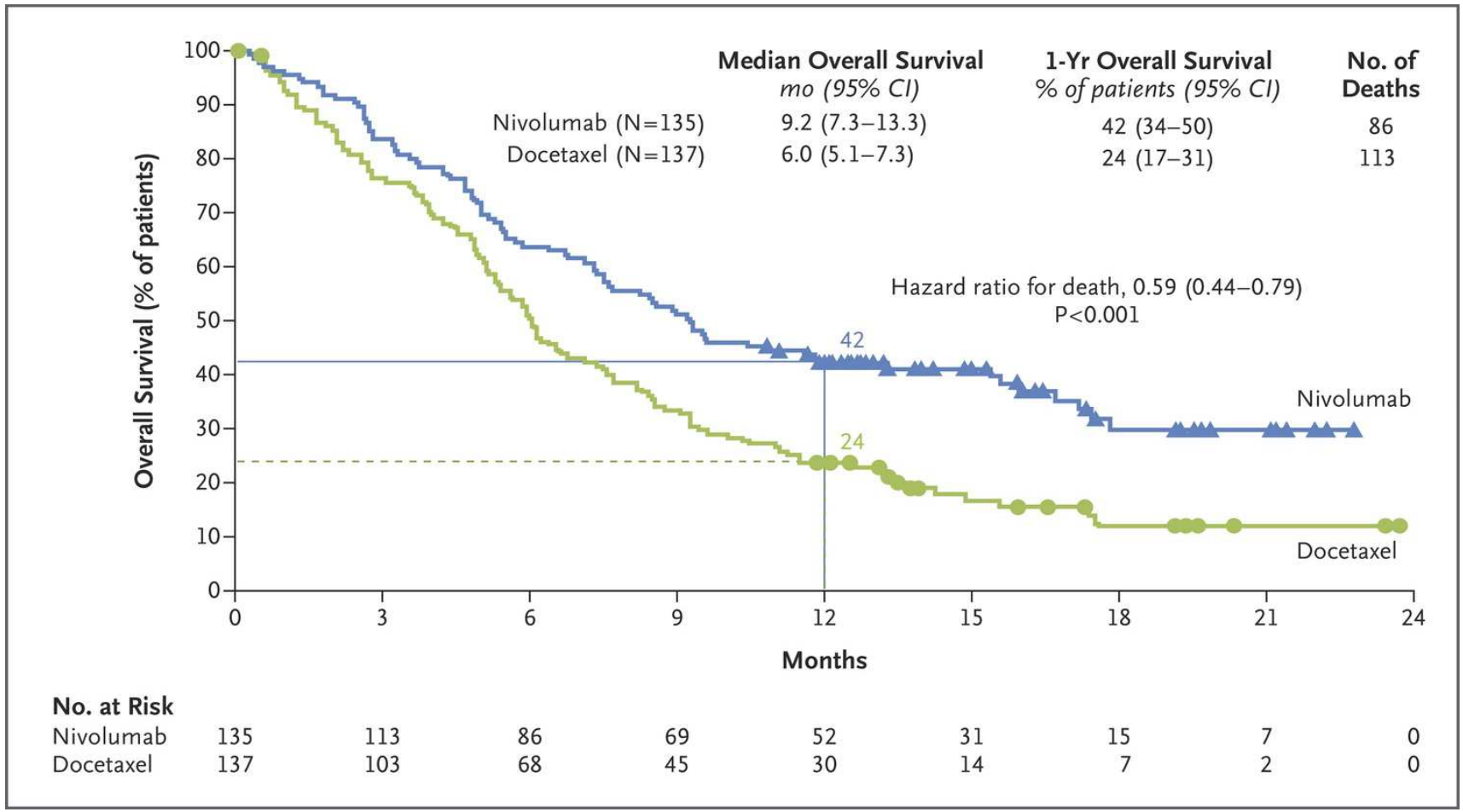
- Randomly assigned 272 patients to receive nivolumab, at a dose of 3 mg per kilogram of body weight every 2 weeks, or docetaxel, at a dose of 75 mg per square meter of body-surface area every 3 weeks

- Primary endpoint: overall survival

- Trial stopped early for meeting its end point

- Median overall survival: 9.2 months with nivolumab vs. 6.0 months with docetaxel

- Hazard ratio: 0.59



Brahmer J et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504627

Nivolumab approved in treatment of patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy

Phase III, randomized trial (CheckMate 057) of nivolumab versus docetaxel in advanced non-squamous cell NSCLC.

- randomized 582 patients with advanced nonsquamous NSCLC after the failure of platinum-based doublet chemotherapy to nivolumab at 3 mg/kg IV every 2 weeks (n = 292) or docetaxel at 75 mg/m2 intravenously every 3 weeks (n = 290).

- Primary endpoint: overall survival

- The study was stopped early after an independent monitoring panel determined the primary endpoint of improved OS had been reached.

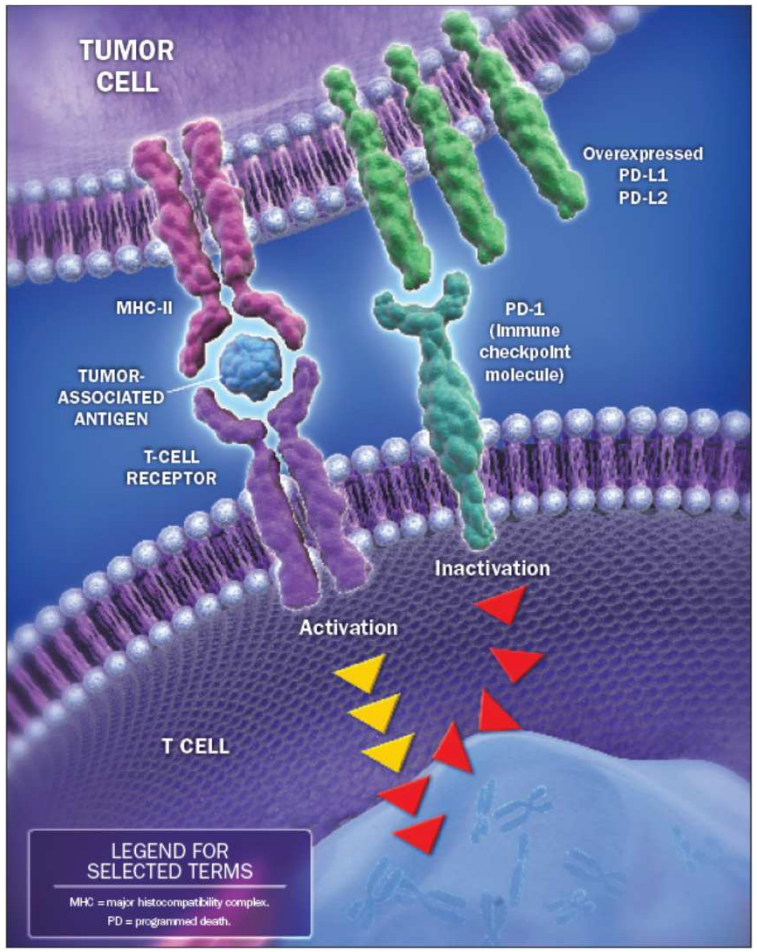
J Clin Oncol. 2015;33 (suppl; abstr LBA109). ASCO 2015

- ORR was 19% with the PD-1 inhibitor compared with 12% with chemotherapy

- In PD-L1–positive patients (PD-L1 expression on ≥1% of tumor cells), median OS was improved by 41% among 123 individuals treated with nivolumab versus 123 patients who received docetaxel (median OS = 17.2 months vs 9.0 months; HR = 0.59).

J Clin Oncol. 2015;33 (suppl; abstr LBA109). ASCO 2015

PD-1 Pathway and Pembrolizumab



- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function[1]
- PD-L1 expression on tumor cells and macrophages suppresses immune surveillance → neoplastic growth[2]
- Pembrolizumab is a humanized monoclonal IgG4 antibody
  - Binds to PD-1 with high affinity
  - Prevents PD-1 from binding to PD-L1 and PD-L2
  - Robust antitumor activity and manageable in multiple advanced malignancies[a]

1. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704; 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64.

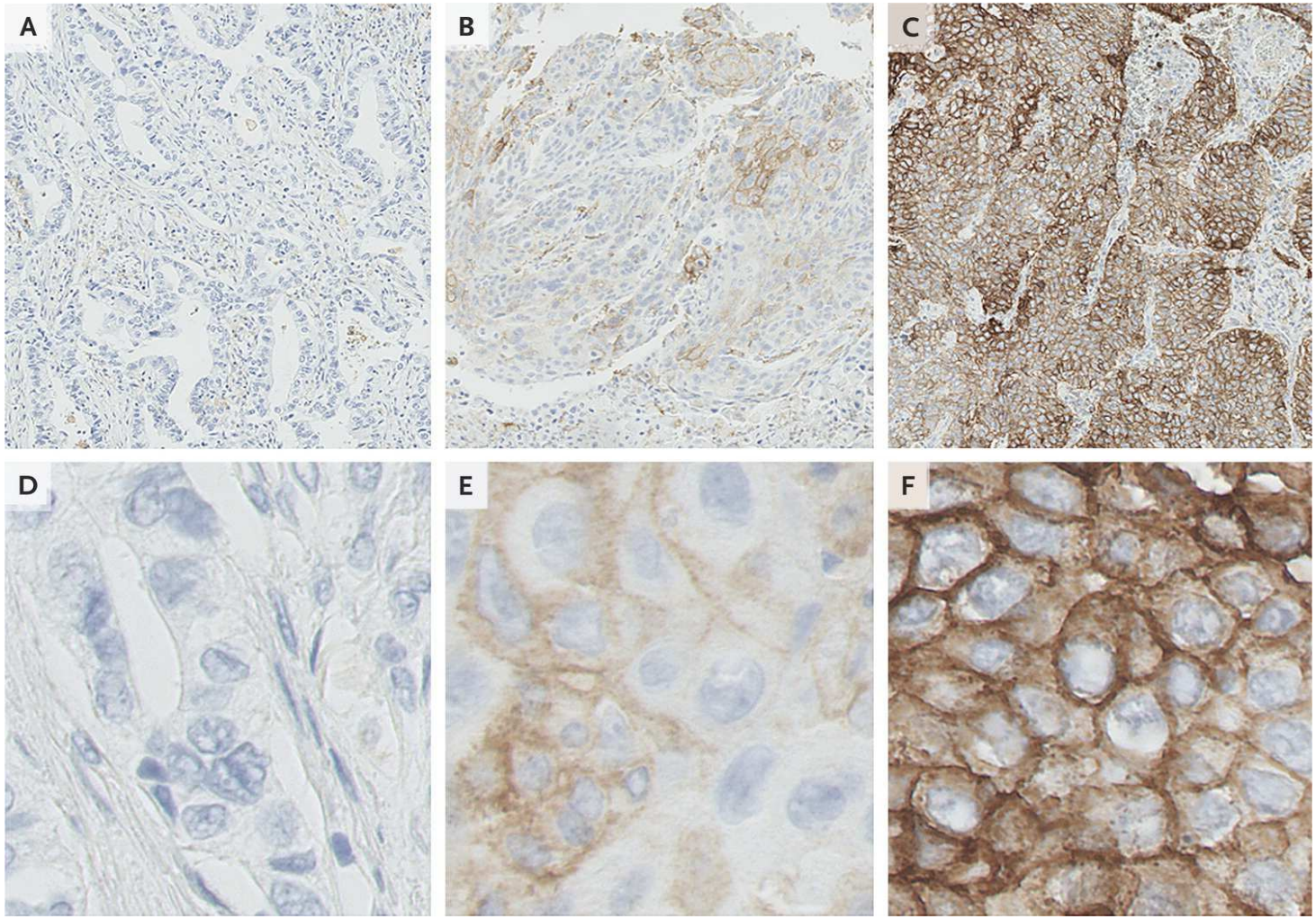
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

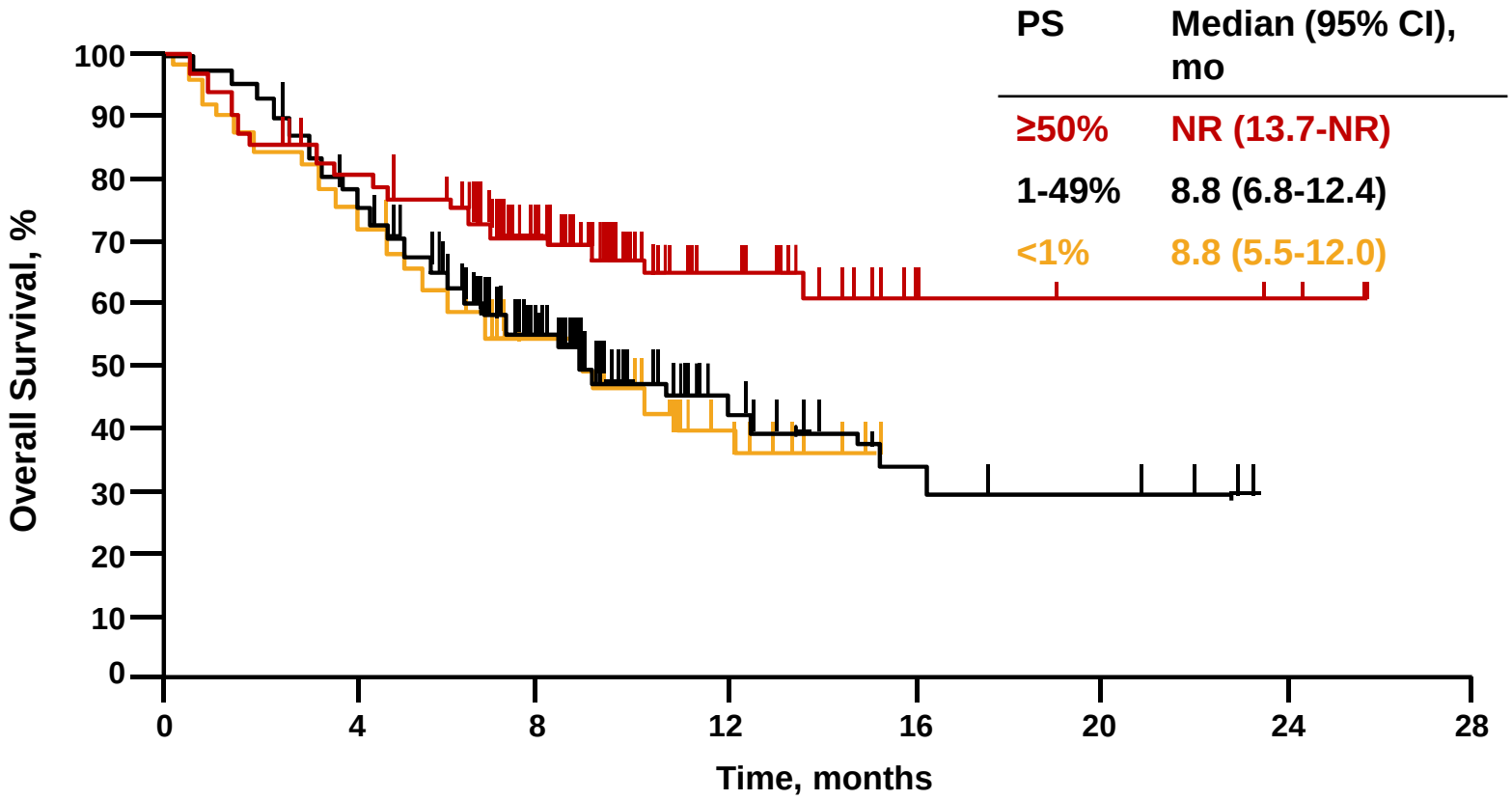
Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

Garon EB et al. N Engl J Med 2015;372:2018-2028.



Garon EB et al. N Engl J Med 2015;372:2018-2028.

OS by PD-L1 Expression, All CTA-Evaluable Patients[a]



n at risk

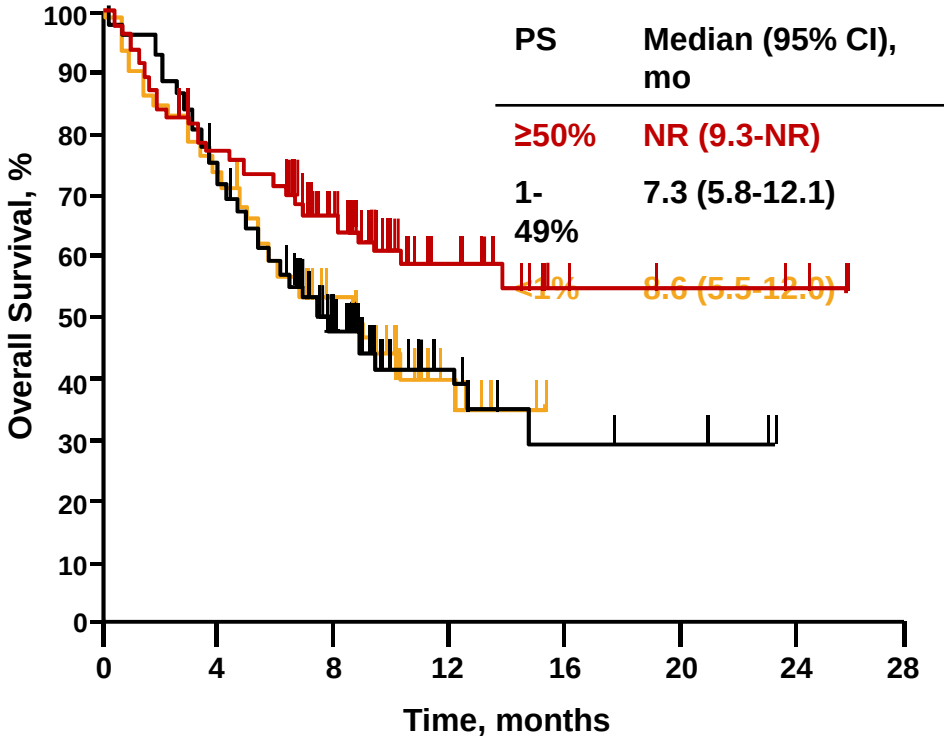
PS ≥50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

[a]Assessed in all patients whose samples were stained within 6 months of cutting.
Analysis cut-off date: August 29, 2014.

Garon et al AACR 2015

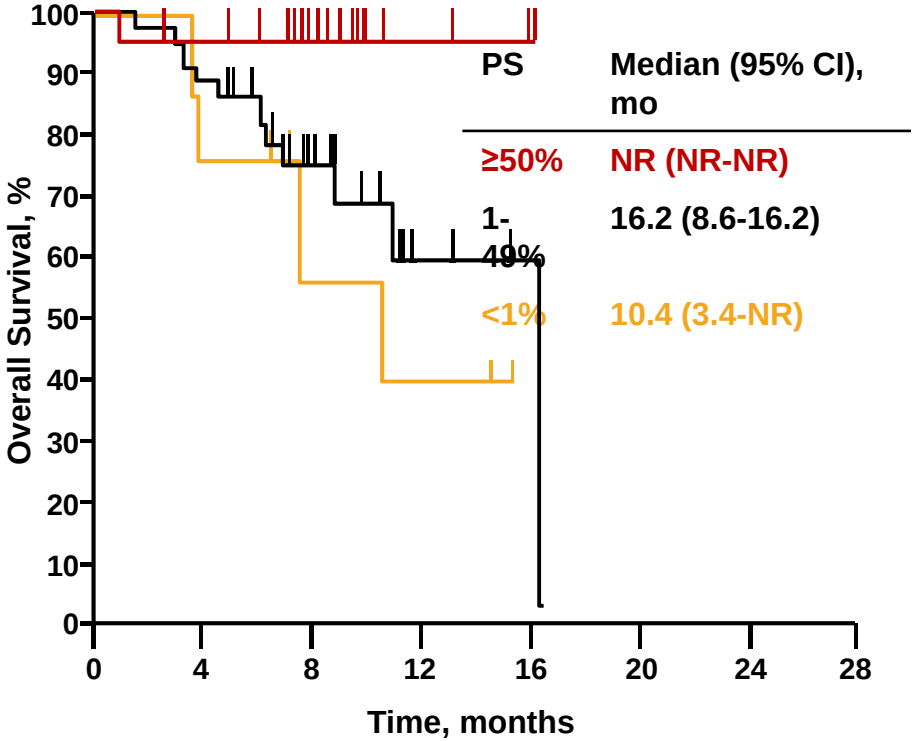
OS by PD-L1 Expression, CTA-Evaluable Patients by Prior Treatment[a]

Previously Treated



n at risk							
99	74	45	18	5	4	3	0
127	89	43	12	5	4	0	0
68	49	30	6	0	0	0	0

Treatment Naive



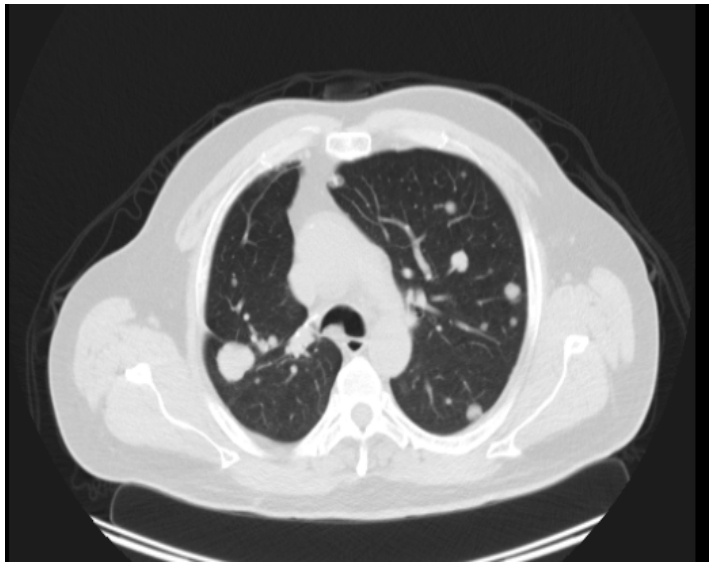
n at risk							
20	18	11	4	0	0	0	0
34	30	15	3	1	0	0	0
8	6	3	2	0	0	0	0

[a]Assessed in all patients whose samples were stained within 6 months of cutting.
Analysis cut-off date: August 29, 2014.

Garon et al AACR 2015

Patient #1

- 61 y/o male with remote smoking history diagnosed with locally advanced lung adenocarcinoma in 2011
- 3 cycles of neoadjuvant cisplatin and pemetrexed
- Right upper lobectomy in May 2012
- No adjuvant chemotherapy
- November 2012→new pulmonary nodules
- Dec 2012-Feb 2013→Dendritic vaccine trial
- June 2013→Present for trial evaluation



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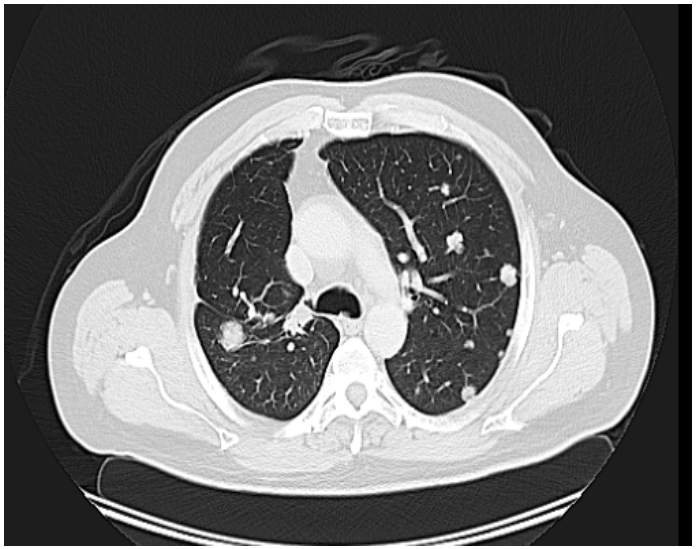

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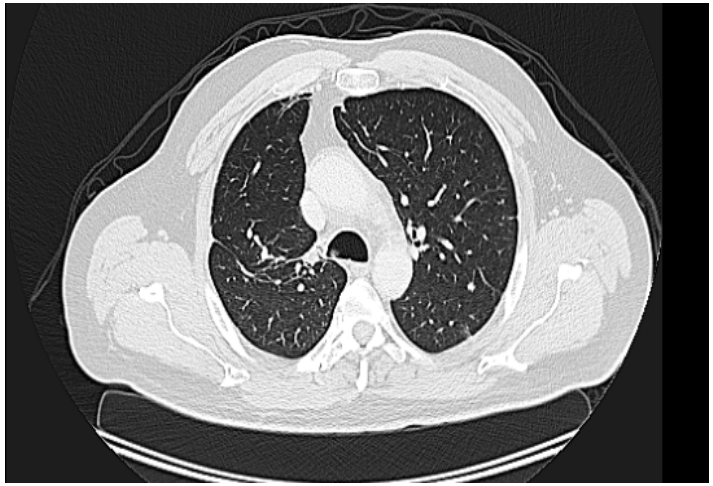

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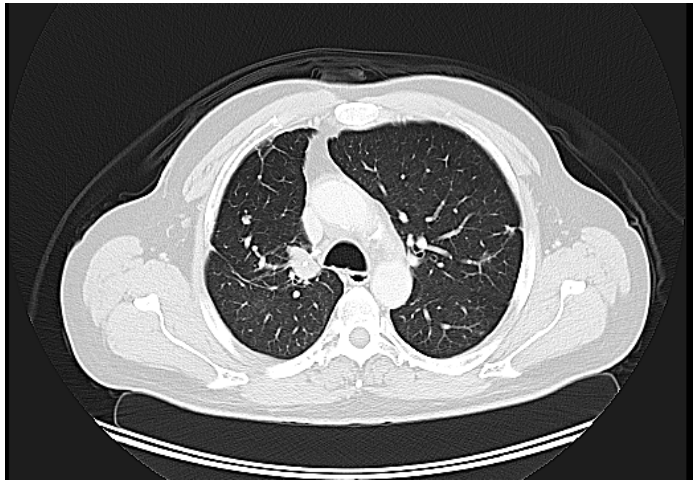

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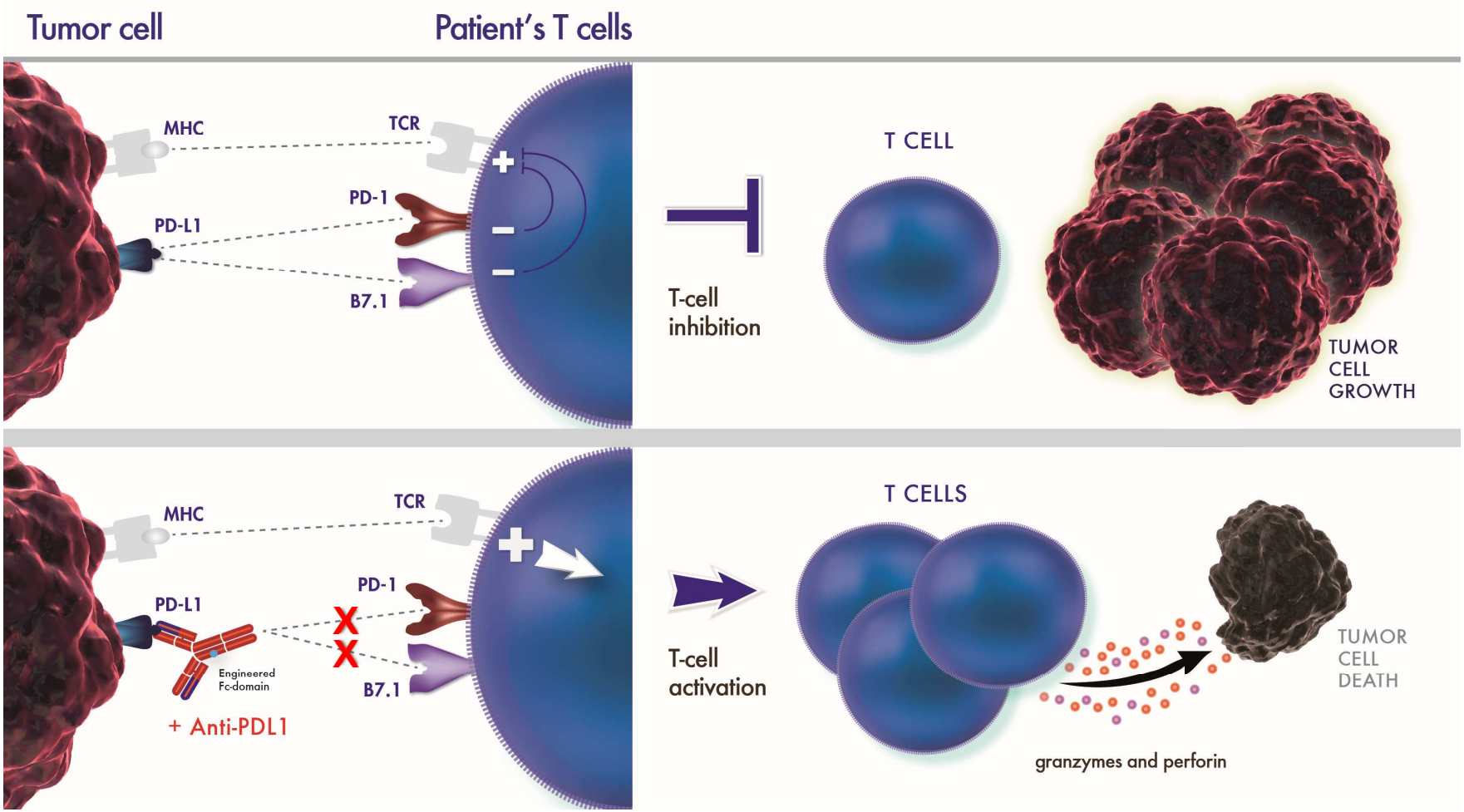
Anti PD-L1 antibody

Atezolizumab(MPDL3280A) Inhibits the Binding of PD-L1 to PD-1 and B7.1

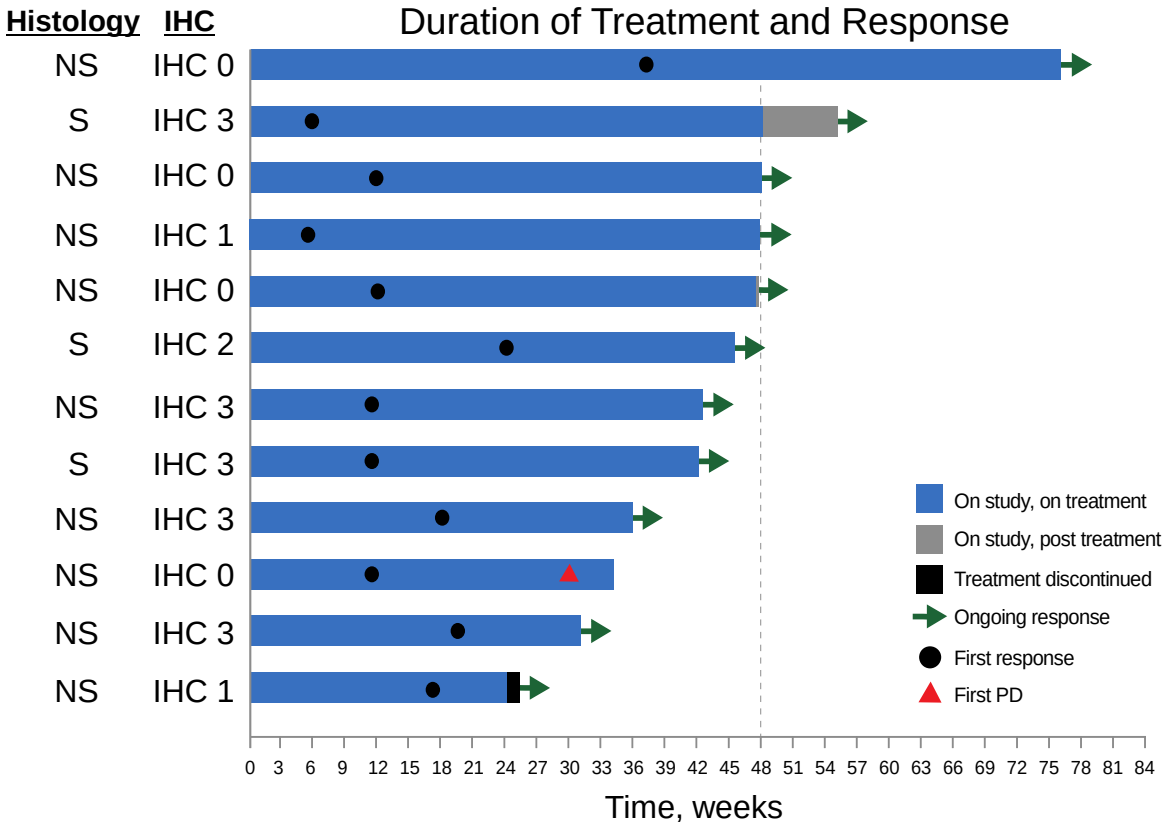


- Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
- Binding to PD-L1 leaves PD-1/PD-L2 interaction intact

Clinical Activity

Best Response by PD-L1 IHC Status, Histology and Duration of Treatment and Response – NSCLC

PD-L1 Status[b] (n = 53)	ORR[a]	PD Rate
IHC 3 (n = 6)	**83%** (5/6)	**17%** (1/6)
IHC 2 and 3 (n = 13)	**46%** (6/13)	**23%** (3/13)
IHC 1/2/3 (n = 26)	**31%** (8/26)	**38%** (10/26)
All patients (IHC 0/1/2/3 and 7 patients with diagnostic unknown; n = 53)	**23%** (12/53)	**40%** (21/53)



IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.

[a] ORR includes investigator-assessed unconfirmed and confirmed (u/c) PR per RECIST 1.1.

[b] PD-LI status determined using proprietary Genentech Roche IHC.

Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff Apr 30, 2013.

NS, nonsquamous.
S, squamous.

Horn et al. WCLC 2013

Clinical activity, safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study.

- 88 NSCLC pts were safety- and efficacy-evaluable
- Majority of pts had 3 lines of therapy
- ORRs, DOR, PFS and OS were assessed by PD-L1 status
- Pts with PD-L1 expression of TC3 or IC3 (n = 20) had an ORR of 45% (95% CI, 23-68%) vs 14% (95% CI, 6-25%) for pts with PD-L1 expression of TC 0/1/2 and IC 0/1/2 (n = 58)

Horn et al. J Clin Oncol 33, 2015 (suppl; abstr 8029) ASCO 2015

MEDI4736: anti PD-L1 antibody

- MEDI4736 (M) is a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with high affinity and selectivity

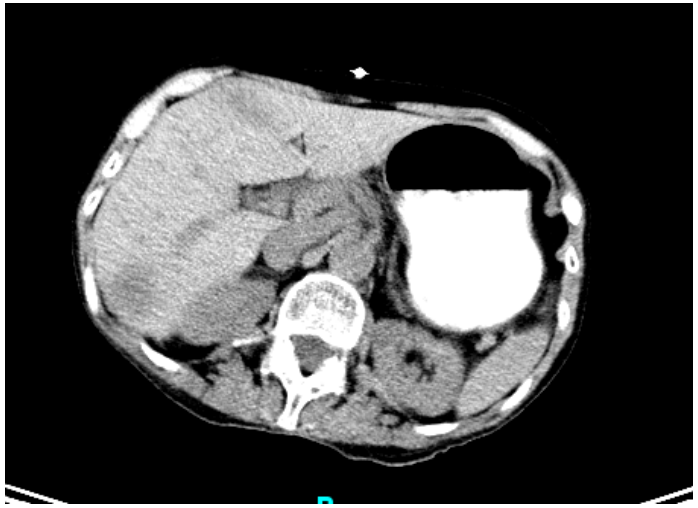
Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC)

- 198 pts (116 non-squamous and 82 squamous histology; mean age 64 [range 26–87] enrolled.
- 149 pts were evaluable for response with ≥24 wks of follow-up
- ORR was 14% (23% in PD-L1+)
- DCR at 24 wks was 24%.
- ORR was higher in squamous (21%) than non-squamous pts (10%).
- Responses were durable with 76% ongoing

Rizvi et al. ASCO 2015

Patient #2

- 66 y/o female with 57 pack year smoking history
- Diagnosed with locally advanced poorly differentiated lung adenocarcinoma in 9/2013
- Initially treated with carboplatin/paclitaxel with radiation→did not tolerate due to toxicity
- Second line gemcitabine→disease progression with mets to the liver
- Third line pemetrexed→further progression
- January 2014: present for a clinical trial evaluation



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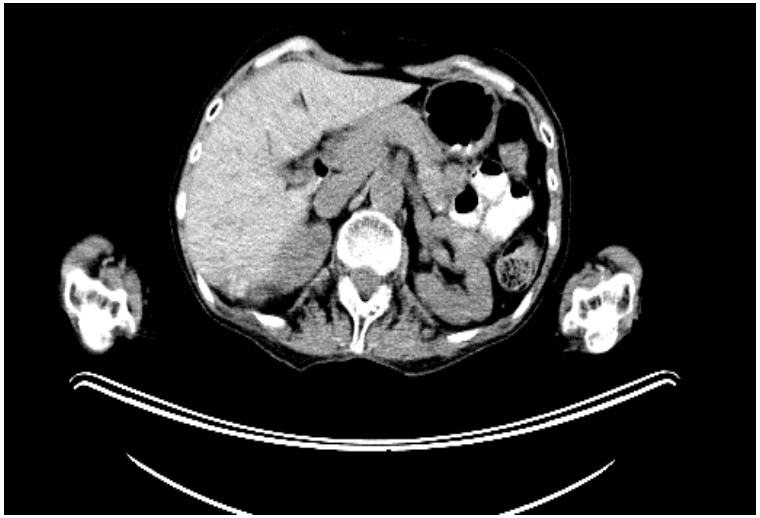

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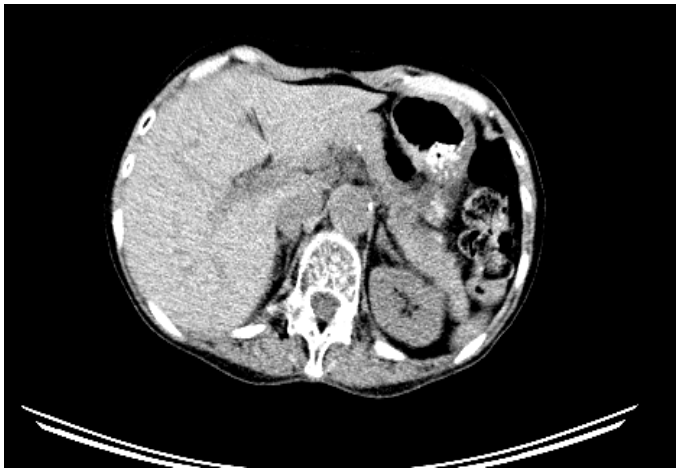

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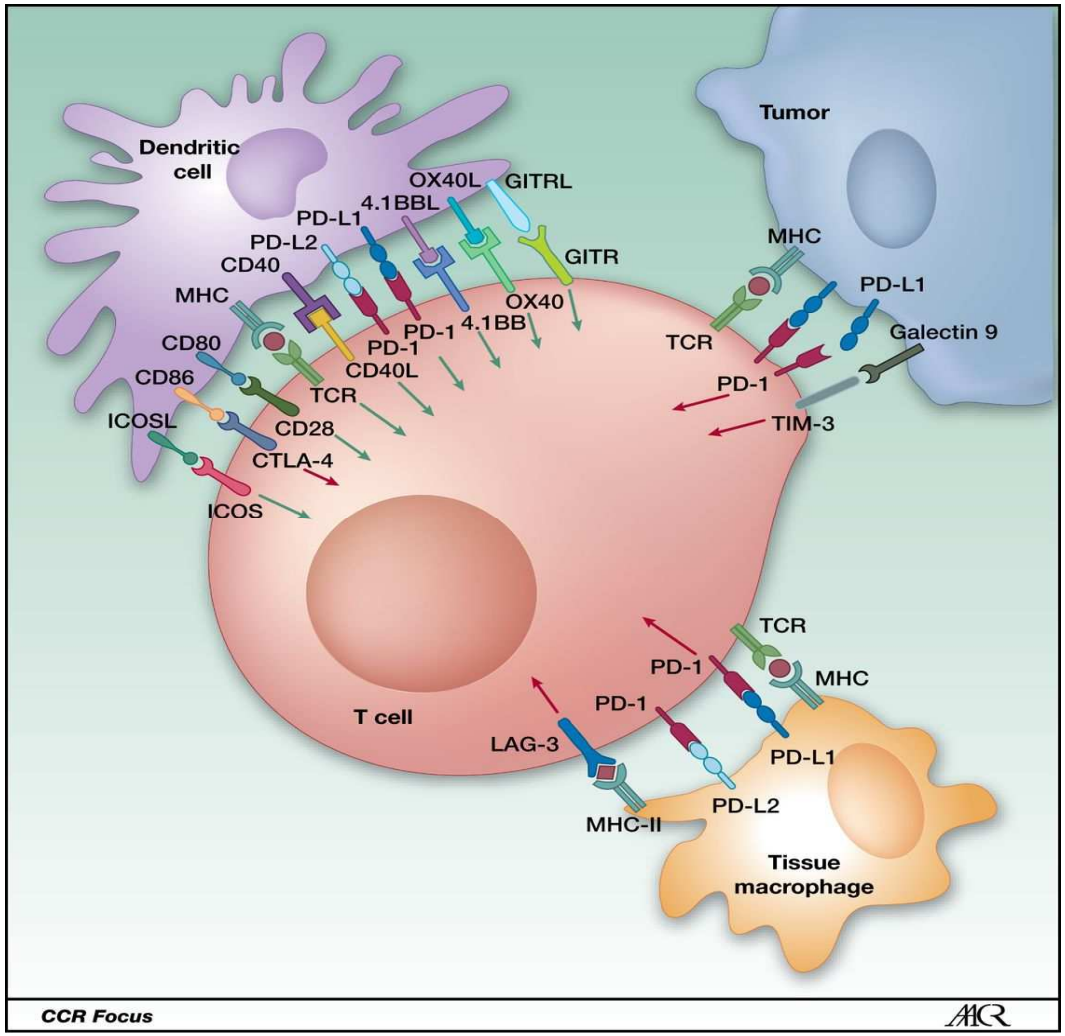
Costimulatory and coinhibitory ligand–receptor interactions between a T cell and a dendritic cell, a tumor cell, and a macrophage, respectively, in the tumor microenvironment.



Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309

Clinical Cancer Research
AACR American Association for Cancer Research

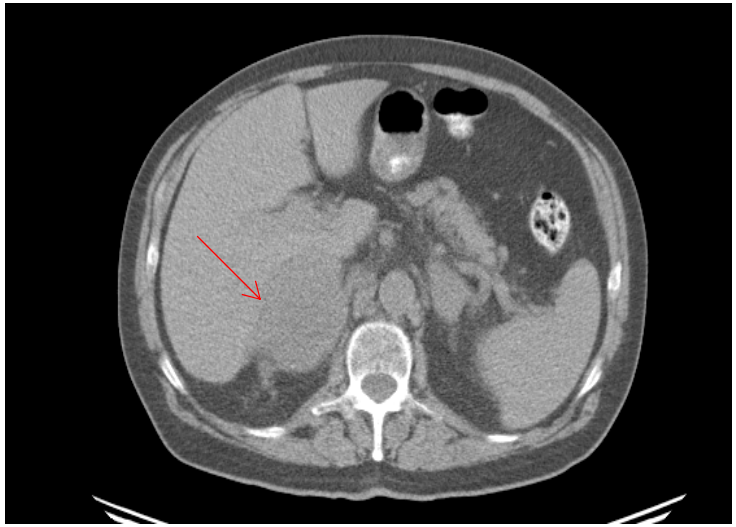
Combination Immunotherapy

Phase 1b Study of MEDI4736, a Programmed Cell Death Ligand-1 (PD-L1) Antibody, in Combination with Tremelimumab, a Cytotoxic T-lymphocyte-associated Protein-4 (CTLA-4) Antibody, in Patients with Advanced Non-small Cell Lung Cancer (NSCLC)

- Ongoing, Phase 1b dose escalation and dose expansion study
- Evaluating different doses of Tremelimumab and MEDI4736
- Currently in dose expansion
- Combination trials: management of toxicity

Patient #3

- 70 y/o male with 44 pack year smoking history with Hx of COPD
- August 2013: presented with shortness of breath
- Diagnosed with stage IV lung adenocarcinoma
- Initially treated with 4 cycles of cisplatin and gemcitabine→progression
- July 2014: presented for trial evaluation



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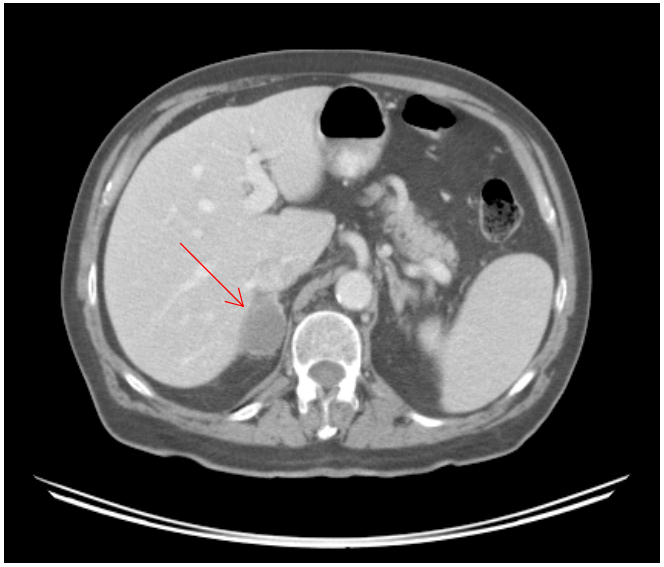

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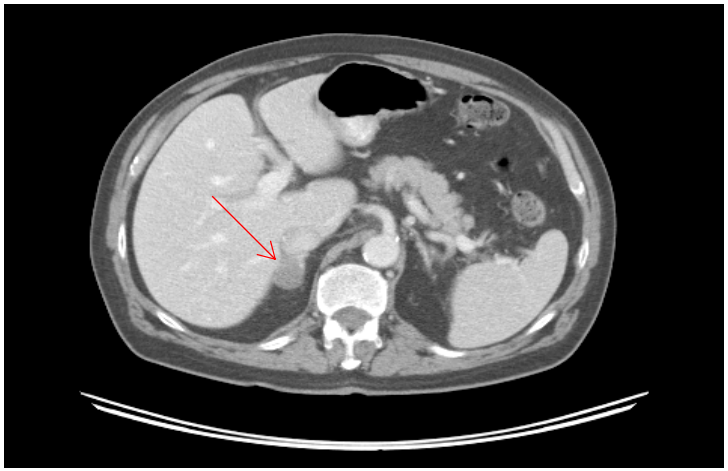

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Phase 1 Study of Pembrolizumab Plus Ipilimumab as Second-Line Therapy for Advanced Non-Small Cell Lung Cancer: KEYNOTE-021 Cohort D

- Stage IIIB/IV NSCLC that recurred after ≤ 2 prior regimens received pembro + IPI every 3 wk for 4 cycles followed by maintenance pembro
- Primary end point was safety and incidence of dose-limiting toxicities (DLTs) in the first 3 wk of dosing
- 18 patients enrolled
- 8 patients discontinued therapy
- No treatment related grade 4 event
- 3 grade 3 events: adrenal insufficiency, drug eruption, and maculopapular rash
- ORR: 39%, DCR: 83%
  - CR: 1 pt,, PR: 6 pts, SD: 8 pts, PD: 3 pts
- Response irrespective of PD-L1 status

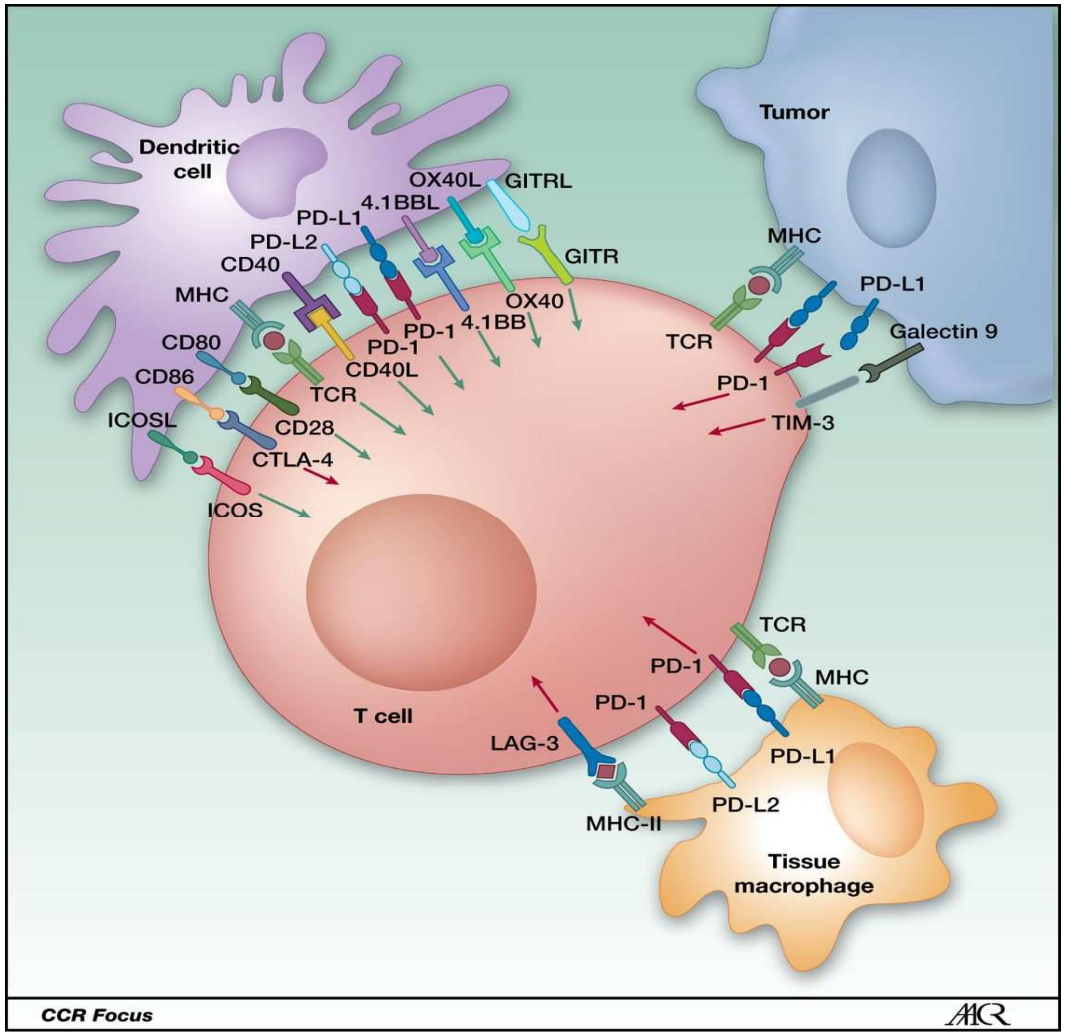
Patnaik, A et al. ASCO 2015

Can we predict who is going to respond?

- PD-L1 testing as a marker
- Correlation of response of PD-L1 expression and response to immunotherapy
- No standardized PD-L1 testing assay

Future direction

- Other combination trials
  - Anti CCR4+anti PD-L1 or Tremelimumab
  - Anti PD-1 antibody + IDO inhibitor
- Anti PD-1 or anti PD-L1 antibody refractory patients
- Combination chemotherapy
- Novel Agents
  - OX40
  - TIM3
  - LAG3
  - CD137
  - GITR



Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309

Clinical Cancer Research
AACR American Association for Cancer Research

Lessons and Take Home Messages

- Immunotherapy has a role in the treatment of NSCLC
- Agents tolerated well
- Potential for durable responses
- Offers options for treatment in a disease that has few therapeutic options