# Targeting the Immune System to Improve Patient Outcomes in

# Advanced
# NSCLC

A CME-certified **Oncology Exchange** Activity

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Oncology

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# Disclosures

The steering committee and faculty reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

**John Powderly II MD, CPI:** *Consultant:* Amplimmune, AstraZeneca, Bristol-Myers Squibb, Genentech, Merck; *Research:* Amplimmune, AstraZeneca, Bristol-Myers Squibb, CellDex, EMD Serono, Genentech, Imclone/Lilly, InCyte, Macrogenics; *Speaker/Speaker's Bureau:* Bristol-Myers Squibb, Dendreon, Merck; *Shareholder:* BioCytics (Founder), BlueBird Bio, Juno, Kite Pharmaceuticals, Lion Biotech

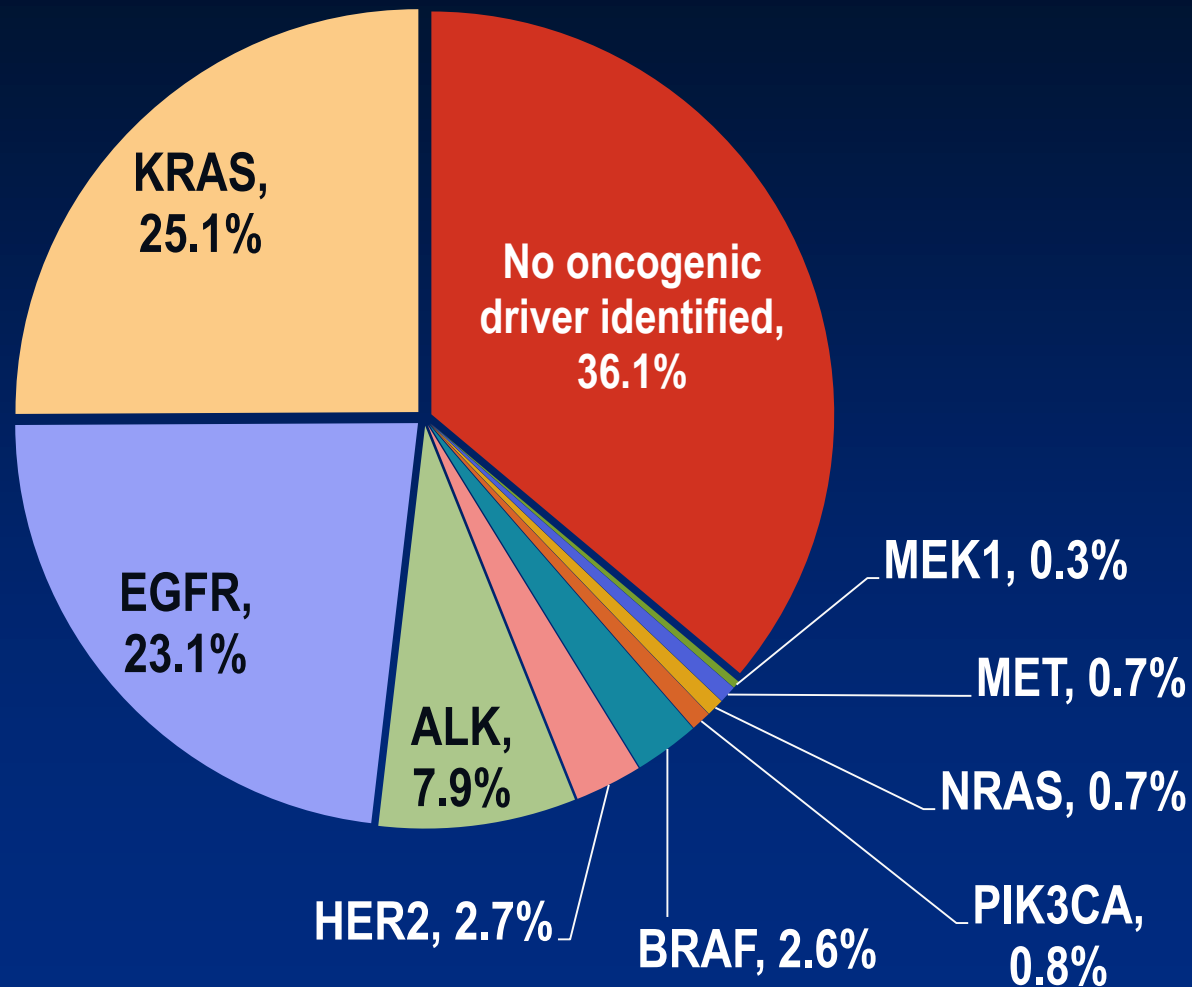**Suresh S. Ramalingam, MD:** *Consultant:* AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Lilly, Merck

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**Latha Shivakumar, PhD, CHCP; Blair St. Amand; Jay Katz, CHCP; Ashley Marostica:** Nothing to disclose
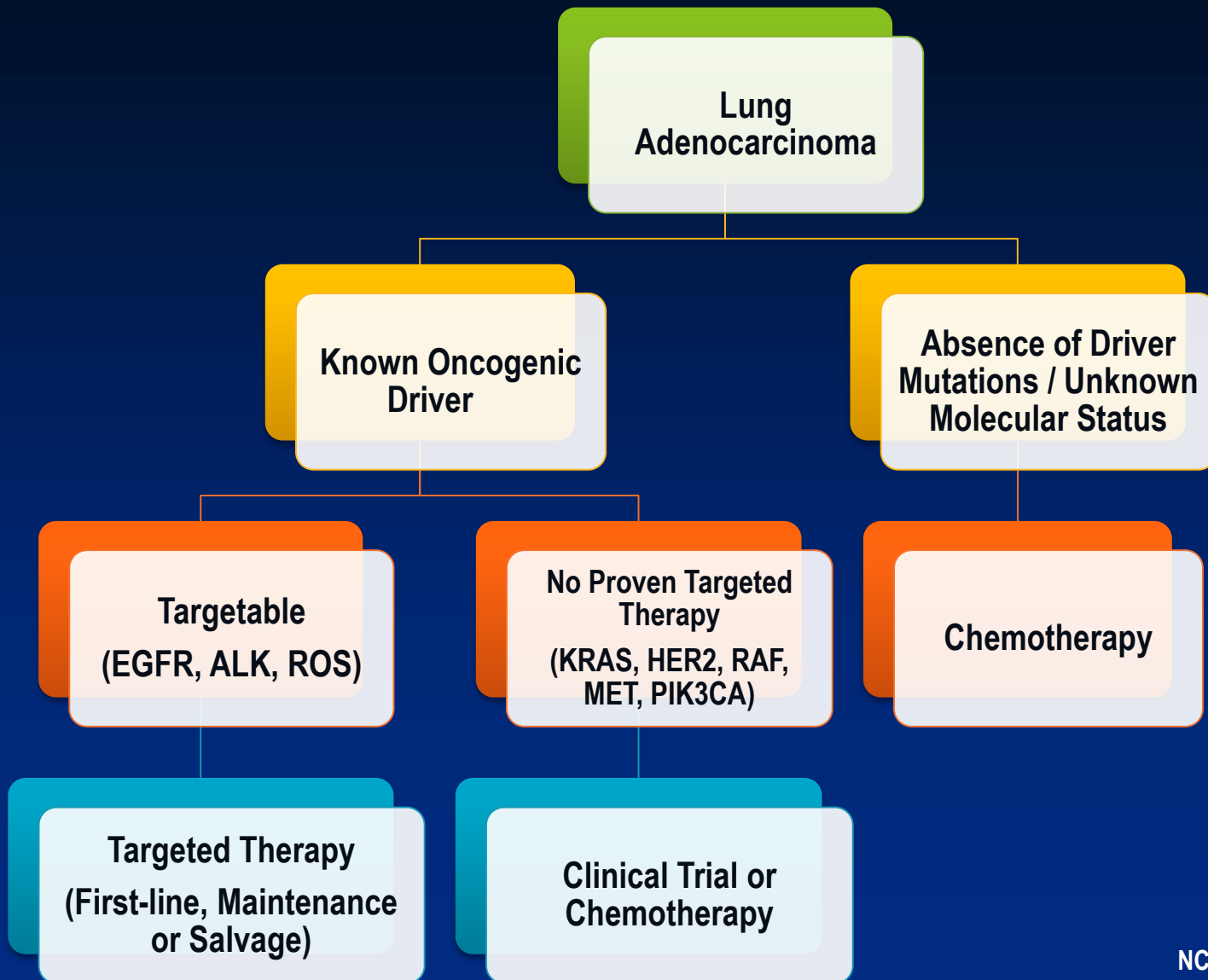
# Learning Objectives

- Evaluate mechanisms of action of immunotherapies in advanced NSCLC

- Assess emerging data for immune checkpoint inhibitors in advanced NSCLC

- Discuss the role of biomarkers in patient selection for immunotherapies

- Educate patients with NSCLC about promising immunotherapeutic agents and clinical trial opportunities

# Lung Cancer Mutation Consortium: Incidence of Driver Mutations



- No oncogenic driver identified, 36.1%
- KRAS, 25.1%
- EGFR, 23.1%
- ALK, 7.9%
- HER2, 2.7%
- BRAF, 2.6%
- PIK3CA, 0.8%
- NRAS, 0.7%
- MET, 0.7%
- MEK1, 0.3%

Sholl LM et al. *J Thorac Oncol.* 2015;10:768-777.

# Treatment Algorithm For Advanced NSCLC



NCCN v7.2015.

# Immunotherapies Beyond Frontline Therapy

# 2013 *Science* "Breakthrough of the Year"; 2014 Special *Nature* Edition

# Immunotherapy: Basic Approaches

- Immunization
  - Utilize cancer vaccines to promote antitumor immunity
- Passive
  - Activated immune cells to enhance antitumor immunity
- Non-specific
  - Promote effector cells against tumor cells
  - Inhibit regulatory cells

DeVita VT Jr et al. Eds. *Cancer: Principles & Practice of Oncology. 9th ed.* Philadelphia, PA: LWW; 2011.

# Tumor Immune Evasion

- Immune system is exponentially more adaptable than tumor

- Vaccines are *the* greatest success story of modern medicine by eradicating infectious diseases

- So, why haven't cancer vaccines worked?

  - **Infections**

    - Discriminate self from *non*-self (obvious)

  - **Tumors**

    - Discriminate self from *altered*-self (subtle)

- Self-tolerance = Self-preservation

  - 98% anti-self lymphocytes undergo apoptosis

  - Remaining T-cells >90% tolerizing surveillance

  - Our immune system balance favors self-tolerance

# Antitumor Immunity

- Major requisites
  - Recognition of tumor-related protein(s) as foreign
  - Mount an appropriate immune response
- Both steps involve a number of well-regulated events
- Failure of one or more steps aids tumor progression and metastasis

Swann JB, Smyth MJ. *J Clin Invest.* 2007;117:1137-1146.

# CTLA-4 and PD-1/PD-L1: The Brakes on T cell Activation



T-cell receptor: Antigen-MHC



CD28: B7

IL-2
IFN



CTLA-4: B7

PD-1: PD-L1



Vaccine?

# Immune Checkpoint CTLA-4

- CTLA-4 "Cytotoxic T Lymphocyte Antigen 4," receptor expressed on T cells

  - James Allison, PhD discovered in 1990s

  - Most important inhibitory receptor (tolerance) during antigen presentation in lymph nodes

  - Double gene knockout mouse model: Develop lymphoproliferative disease and fulminant auto-immunity toxicity and die by 6 weeks of life

  - Human polymorphisms are associated with familial tendency towards autoimmune diseases

  - Ipilimumab first checkpoint inhibitor developed, anti-CTLA-4 mAb

# Tumor Immunotherapy CTLA-4 vs PD-1/PD-L1
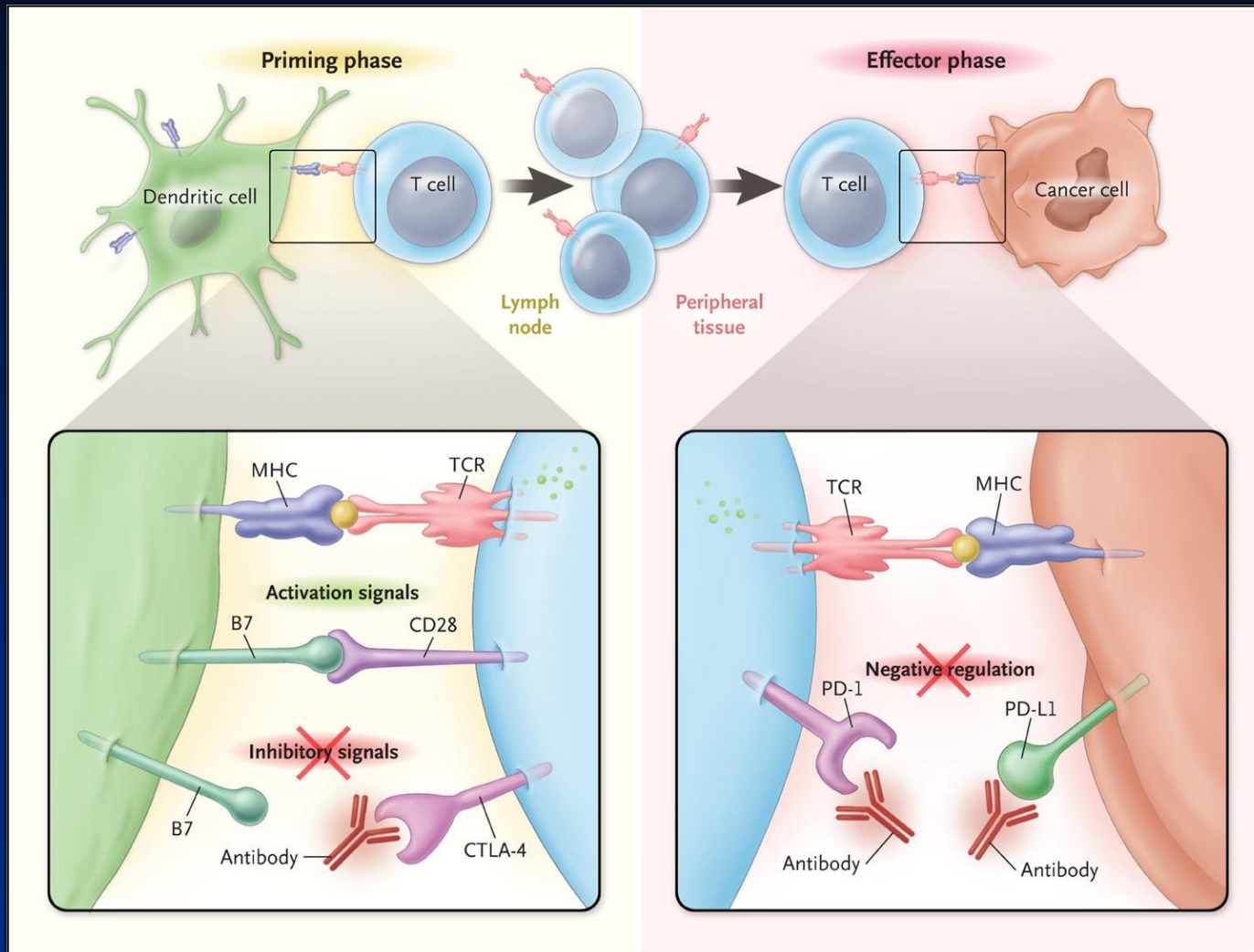
# Immune Checkpoint: PD-1/PD-L1
## PD = "Programmed Death"

- PD-1 receptor (on lymphocytes) has two ligands: PD-L1 and PDL2

- PD-L1 ligand:
  - Expressed on immune cells and dynamically expressed in tissue (and tumors) during inflammation
  - PD-L1 "shield for tumors to hide from immune cells"
  - During inflammation, interferon gamma will upregulate PD-L1 expression

- PD-1/PD-L1 axis: Most important "break" (tolerance) at peripheral site of inflammation

- PD-1 or PD-L1:
  - Pharmacologic blockade of either PD-1 or PD-L1, overcomes "tolerance" and enables activated T cells to destroy tumors
  - Double gene knockout mouse model developed mild tendency towards auto-immunity with inflammatory stimuli

- **Nivolumab and pembrolizumab:** first anti-PD-1 mAbs developed and FDA approved

# Placenta and Tumors Express PD-L1 to Evade Immune Recognition

**Placenta**
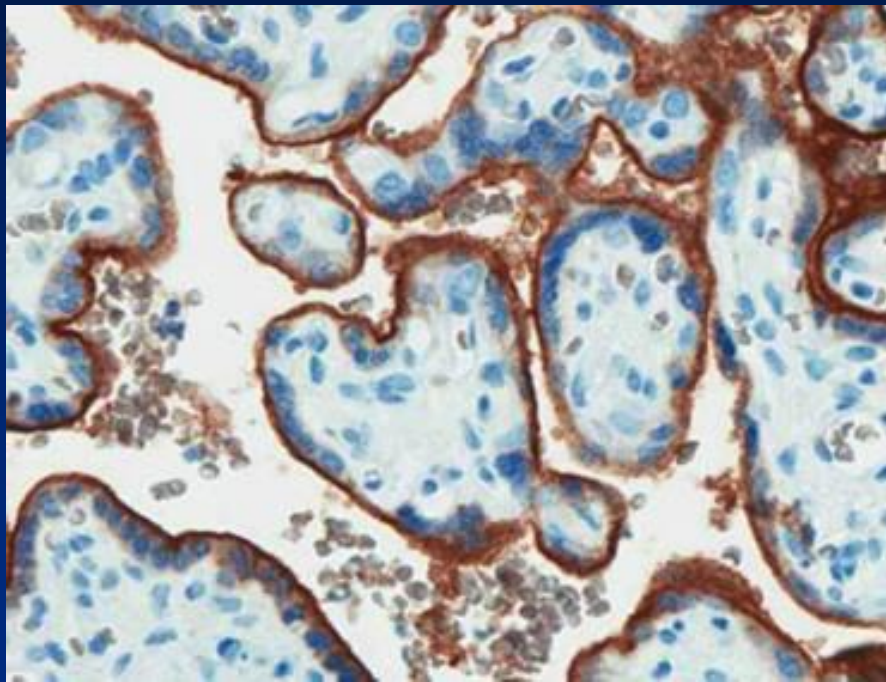
**Tumor**
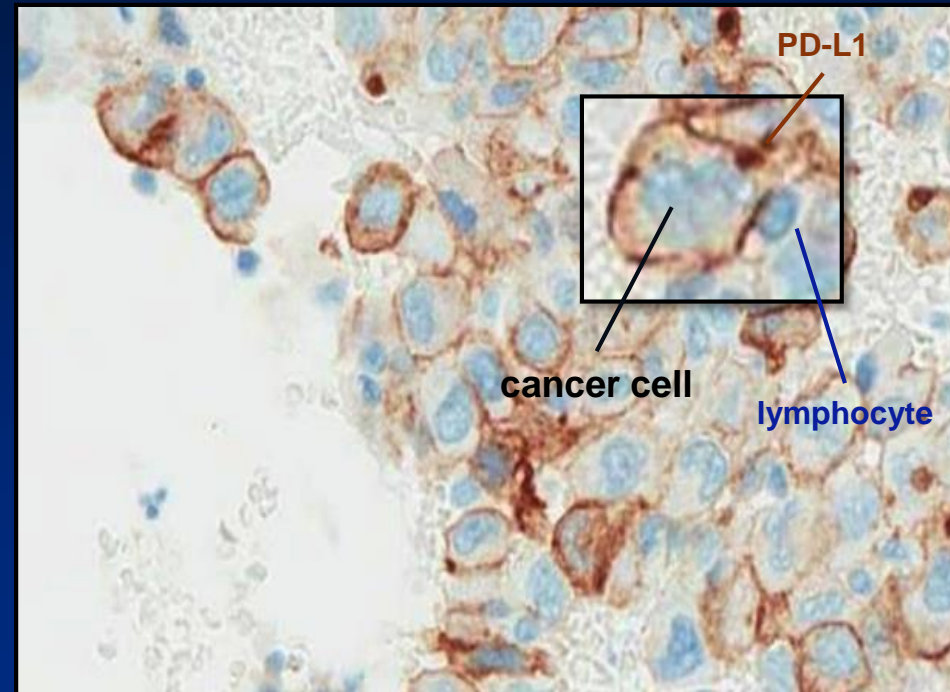
# Lung Cancer Immunotherapy



Somatic mutation frequencies in different tumors[1]
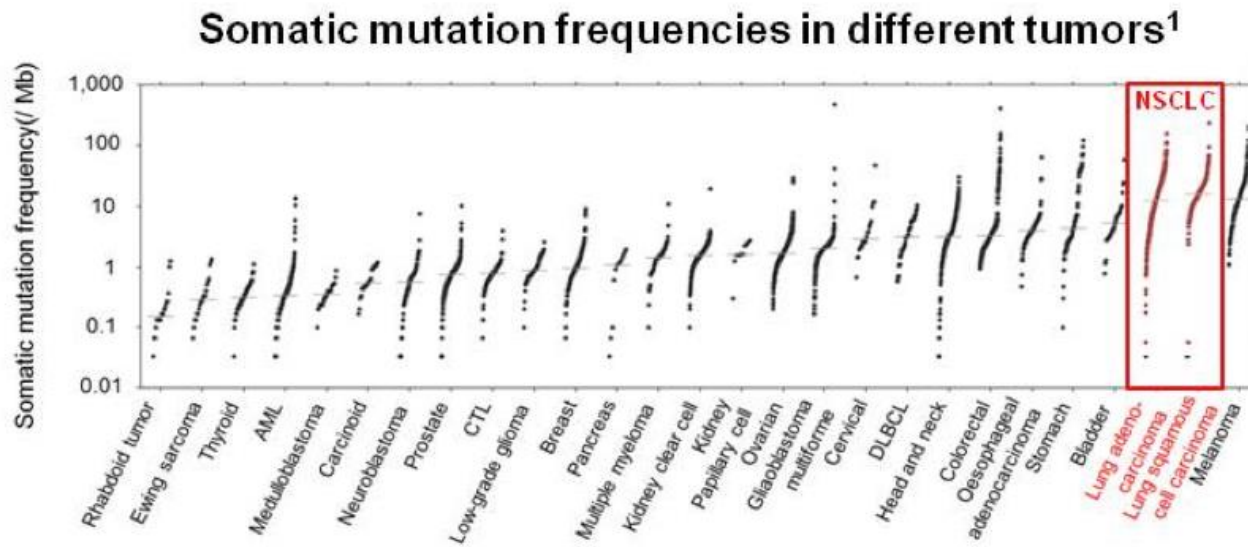
- High rates of somatic mutations in lung cancer may contribute to increased immunogenicity[2]
- Therapies targeting the PD-L1/PD-1 pathway will alter the treatment of NSCLC

# Checkpoint Blockade: Drugs in Development

| Anti-CTLA-4 | Anti-PD-L1 | Anti-PD-1 |
|---|---|---|
| **Ipilimumab** (Fully human IgG1) FDA Approved 2011 | **MDX-1105,** (Fully human IgG4); Phase I | **MDX-1106, Nivolumab,** (Fully human IgG4)   FDA-approved Melanoma & Squamous Lung |
| **Tremelimumab** (Fully human IgG2); Phase III | **MPDL3280A, RG7446, Atezolizumab**; Phase II-III | **CT-011 Pidilizumab** (Humanized IgG1); Phase II |
| | **MEDI4736, Durvalumab**; Phase III | **MK3475 Pembrolizumab** (formerly Lambrolizumab) (Humanized  IgG4) FDA-approved 2014 – Melanoma |
| | **MSB0010718C, Avelumab;** Phase I-II | **AMP-224** (B7-DC/IgG1fusion protein); Phase I-II |
| | | **MEDI0680, AMP514**; Phase I |

# Case Presentation 1: Mrs. RDB

Mrs. RDB is a 61-year-old African American female presenting with cough in 2005.

- Imaging showed dominant LUL mass with bilateral lung mets and sclerotic bone mets

- Bronchoscopy Bx: squamous cell lung carcinoma (stage IV)

- PMH: Tobacco 1 ppd x 45 years (quit 2 years prior), HTN, DM

# Case Presentation 1: Mrs. RDB (cont.)

- Treatment
  - Aug 2005: carbo/vinorelbine x 4 months, with >50% reduction by Feb 2006
    - Monthly zoledronic acid
  - Dec 2006: Progressed
    - 2nd-line gemcitabine/vinorelbine x 4 months
  - May 2007: Progressed LLL, RUL, mediastinal LAD, and new bone mets
  - ? Option 3rd-line treatment

# Polling Question

Which third-line treatment option would you choose for this patient in 2015?

1. Docetaxel

2. EGFR-targeted therapy

3. VEGFR-targeted therapy

4. PD-1 mAb

# Case Presentation 1: Mrs. RDB (cont.)

May 2007: Informed Consent PD-1 mAb trial (MDX-1106 001, phase I study, nivolumab)

- Single dose nivolumab 1 mg/kg (lowest dose cohort, 1st lung patient ever dosed)

  - Grade 1 rash, grade 1 diarrhea, grade 1 elevated amylase/lipase, tumor pain flare

- 8-week restaging: 41% RECIST partial response

  - ANA converted from neg to + 1:160

- 12 week "confirmatory" scan showed new spine met (mixed response)

  - Re-challenged with nivolumab at 16 weeks, but progressed.

# MDX-1106 001: *Phase I Study of Single-agent Anti-PD-1 (MDX-1106, nivolumab) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates*



May 2007      July 2007

Brahmer JR et al. *J Clin Oncol.* 2010;28:3167-3175.

# Case Presentation 2: Mr. JN

Mr. JN is a 69-year-old Caucasian male who presented in 2006 with cough. Imaging showed RUL mass.

- Jan 2006:  RUL lobectomy: path squamous cell carcinoma (with mixed adenocarcinoma components) T3N0, stage IIB. Declined adjuvant chemo.

- Jan 2008: New R adrenal mass 5x4 cm, Bx: adenocarcinoma (stage IV)

- April 2008: R adrenalectomy, Path 4.5 cm poorly differentiated carcinoma (EGFR wild-type)

- June 2008: CT scan – NED

# Case Presentation 2: Mr. JN (cont.)

- June 2008: gemcitabine/carbo/bevacizumab x 1 cycle

  – Prolonged thrombocytopenia, transfusions

- Aug 2008: switched to carbo/pac/bevacizumab x 3 cycles

  – Taxane induced dermatitis

- Feb 2009: Progression L adrenal mass 5.5 cm (hypermetabolic on PET)

# Case Presentation 2: Mr. JN (cont.)

- Feb 2009: Informed Consent MDX-1106 003 (phase Ib)

  – Nivolumab 3 mg/kg Q2 weeks x 2 years

  – Baseline ANA + 1:40, CRP +, rheum factor +, vitiligo,

  – Adverse events:

    - COPD exacerbation x 2, Rx steroids

    - RML pneumonia,  Rx Abx

    - Corneal herpetic outbreak

    - Squamous skin cancers x 3, each resected

- Feb 2011: completed 2 years of nivolumab

# Case Presentation 2: Mr. JN (cont.)

- July 2015: Ongoing durable partial response

- PD-1 nivolumab

- Longest PD-1 lung survivor (> 6 years)

February 2009                                        September 2009



28.5 mm
23.2 mm
120 mm
120 mm
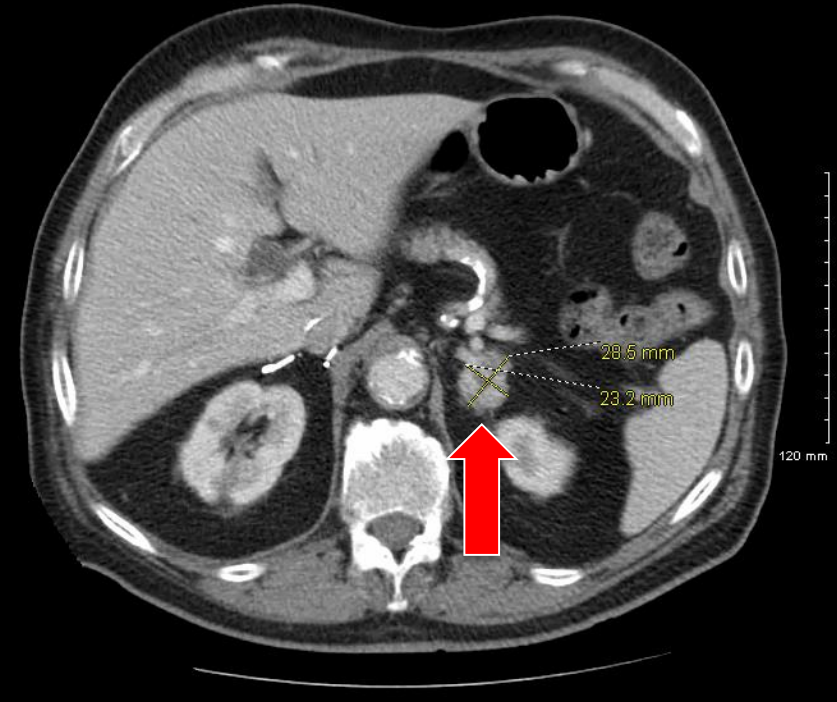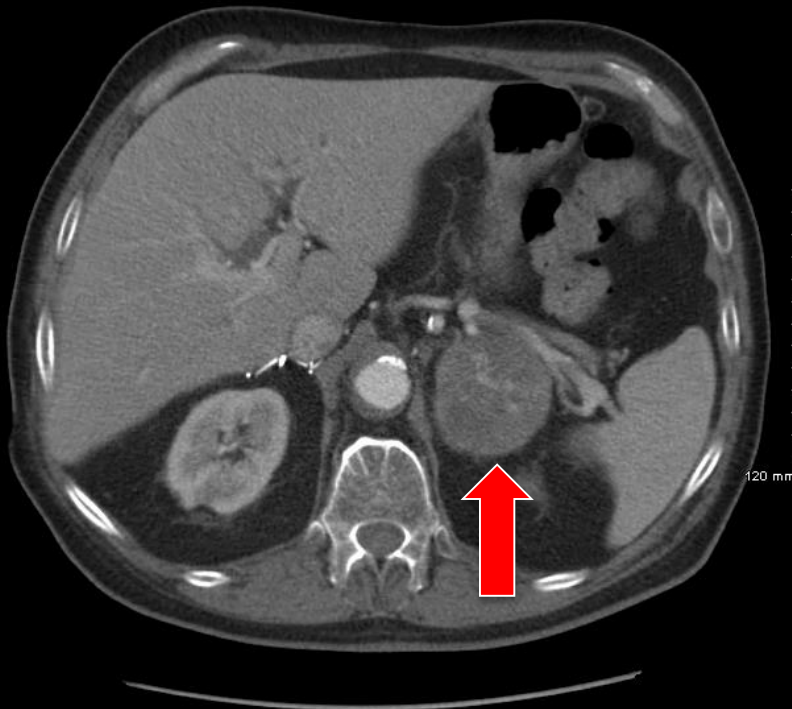
# Polling Question

Which of the following grade 3-4 adverse events is most likely seen in a patient with advanced NSCLC receiving anti-PD-1 antibody?

1. Pneumonitis

2. Febrile neutropenia

3. Dehydration

4. Rash

# PD-1 Blockade in Lung Cancer

# Nivolumab Phase I: Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

- Phase Ib, 296 patients with solid tumors stage IV

  - Rx monotherapy mAb Q2 weeks (4 doses over a 8 week cycle) up to 12 cycles until PD or CR

  - Cumulative objective response (RECIST)

    - Melanoma: 28%

    - Renal Cell Cancer: 27%

    - Non-small Cell Lung Cancer: 18%

  - 65% of responders were durable >1 year

  - Drug-related Aes: 14% (fatigue, cough, fever, rash, diarrhea, nausea)

    - Drug-related grade 3-4 toxicity: 11%

    - Grade 3-4 pneumonitis: 1%, including 3 deaths from pneumonitis (2 NSCLC, 1 renal)

    - MTD not reached; 5% of patients stopped therapy due to AEs

  - Among 42 archived tumors, response correlated with PD-L1 tumor expression ($P$=0.006)

Topalian SL et al. *N Engl J Med.* 2012;366:2443-2454.

# CheckMate 017: Nivolumab vs Docetaxel 2nd-line Squamous Cell Lung Cancer: *FDA-approved March 2015*

- Phase III, randomized 272 patients

  – Docetaxel vs nivolumab 3 mg/kg Q2w

- Interim analysis:

  – Median OS 6 months vs 9 months

  – 1 year OS: 22% vs 42%

  – 41% reduction risk of death

  – Hazard ratio 0.59 ($P<0.001$)

- ORR nivo: 27%, of which 63% durable

- ORR docetaxel: 12%, of which 33% durable



**Figure 1:  Overall Survival - Trial 2**
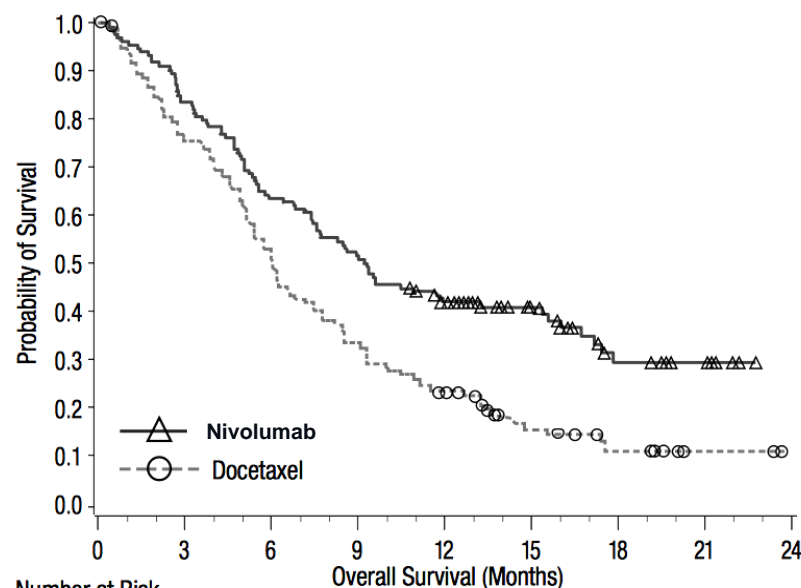
| Number at Risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| OPDIVO | 135 | 113 | 86 | 69 | 52 | 31 | 15 | 7 | 0 |
| Docetaxel | 137 | 103 | 68 | 45 | 30 | 14 | 7 | 2 | 0 |

Brahmer J et al. *N Engl J Med.* 2015;373:123-135.

# CheckMate 017: OS and PFS According to PD-L1 Expression Level

Unstratified Hazard Ratio (95% CI)

| | Nivolumab | Docetaxel | | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| **Overall Survival** | **No. of patients** | | | |
| ≥1% | 63 | 56 | | 0.69 (0.45-1.05) |
| <1% | 54 | 52 | | 0.58 (0.37-0.92) |
| ≥5% | 42 | 39 | | 0.53 (0.31-0.89) |
| <5% | 75 | 69 | | 0.70 (0.47-1.02) |
| ≥10% | 36 | 33 | | 0.50 (0.28-0.89) |
| <10% | 81 | 75 | | 0.70 (0.48-1.01) |
| Not quantifiable at baseline | 18 | 29 | | 0.39 (0.19-0.82) |
| **Progression-free Survival** | **No. of patients** | | | |
| ≥1% | 63 | 56 | | 0.67 (0.44-1.01) |
| <1% | 54 | 52 | | 0.66 (0.43-1.00) |
| ≥5% | 42 | 39 | | 0.54 (0.32-0.90) |
| <5% | 75 | 69 | | 0.75 (0.52-1.08) |
| ≥10% | 36 | 33 | | 0.58 (0.33-1.02) |
| <10% | 81 | 75 | | 0.70 (0.49-0.99) |
| Not quantifiable at baseline | 18 | 29 | | 0.45 (0.23-0.89) |

Nivolumab Better ← → Docetaxel Better



| | Nivolumab (n=131) | | Docetaxel (n=129) | |
|---|---|---|---|---|
| | **Any Grade** | **Grade 3 or 4** | **Any Grade** | **Grade 3 or 4** |
| **Any Event** | 58% | 7% | 86% | 55% |

Treatment-related grade 3/4 adverse events reported in at least 5% of patients:
pneumonitis, fatigue, decreased appetite, leukopenia

Brahmer J et al. *N Engl J Med.* 2015;373:123-135.

# CheckMate 063: Nivolumab 3$^{rd}$-line Squamous NSCLC

- 117 patients, (open label, 3$^{rd}$-line)
  - Included patients regardless of PD-L1 status
  - Nivolumab 3 mg/kg IV Q 2 weeks
  - Objective Response Rate (ORR) = 15%
    - Of which 76% were durable

FDA Package Insert for Nivolumab.

# CheckMate 063: Overall Survival (all Treated Patients)



| DBL | Median follow-up, mos (range) | Median OS, mos (95% CI) | 1-yr OS rate, % (95% CI) | 18-mo OS rate, % (95% CI) | Events, n/N |
|---|---|---|---|---|---|
| July 2014 | 8.0 (0.0, 17.3) | 8.2 (6.1, 10.9) | 41 (32, 50) | – | 72/117 |
| June 2015 | 8.0 (0.0, 26.8) | 8.1 (6.1, 10.9) | 39 (30, 48) | 27 (19, 35) | 90/117 |

**Number of patients at risk:**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| July 2014 DBL 117 | 93 | 68 | 51 | 28 | 5 | 0 | | | |
| June 2015 DBL117 | 93 | 69 | 54 | 45 | 38 | 30 | 24 | 6 | 0 |
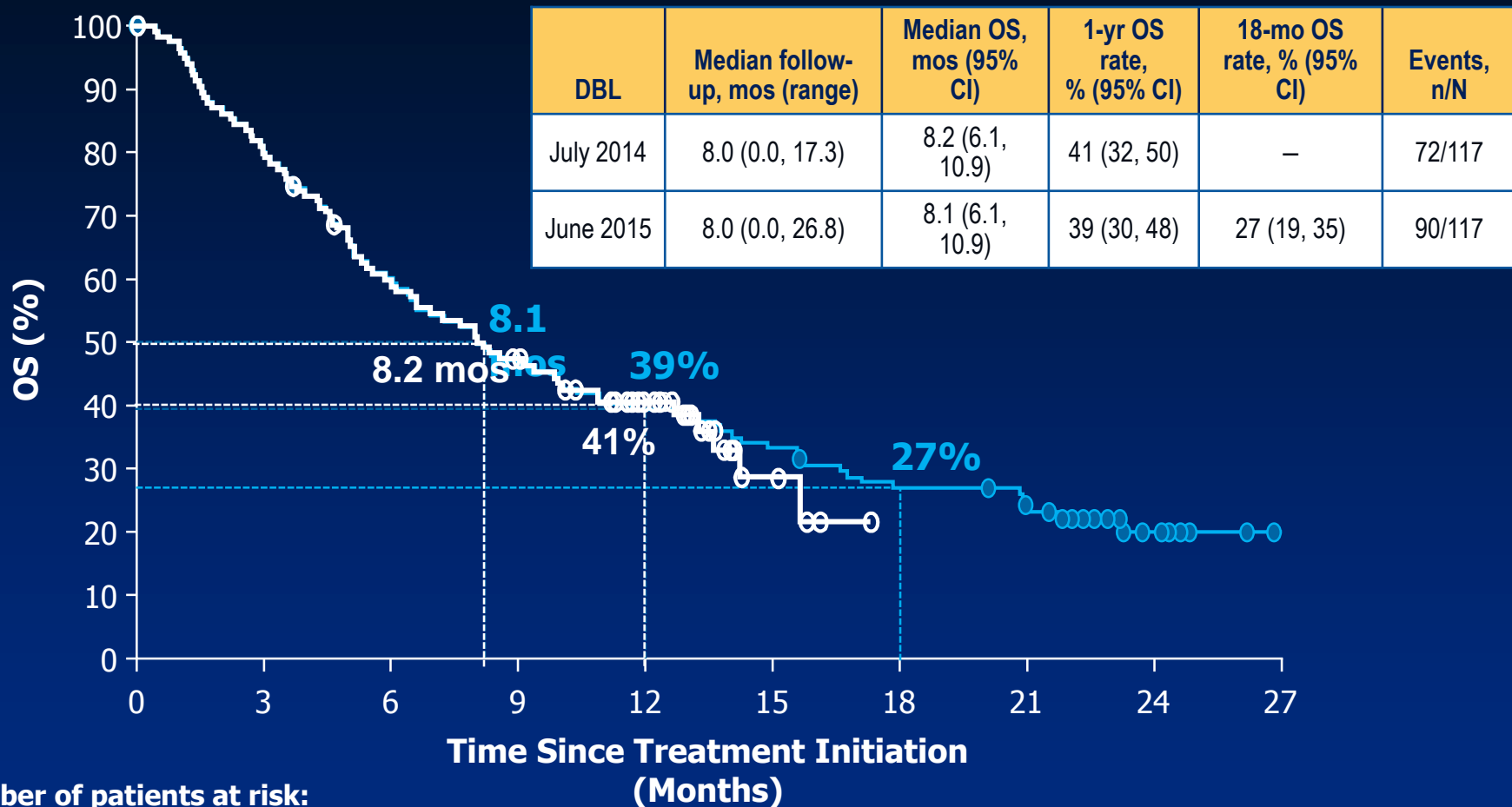
Data are based on July 2014 and June 2015 DBLs. Symbols represent censored observations

# CheckMate 057: Nivolumab vs Docetaxel 2nd-line Non-squamous NSCLC

- Phase III, 582 patients randomized

- Nivolumab 3 mg/kg Q2W vs docetaxel 75 mg/m$^2$ Q3

- Primary endpoint OS

- Trial stopped early by DSMC, met its primary endpoints at interim analysis



|  | Nivolumab (n=292) | Docetaxel (n=290) |
|---|---|---|
| ORR | 19% | 12% |
| P-value | 0.0246 | |
| Median DOR, mos | 17.2 | 5.6 |

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

# CheckMate 057: Nivolumab vs Docetaxel 2nd-line Non-squamous NSCLC

## Treatment Effect on OS in Predefined Subgroups

| | N | Unstratified HR (95% CI) |
|---|---|---|
| Overall | 582 | 0.75 (0.62, 0.91) |
| **Age Categorization (years)** | | |
| <65 | 339 | 0.81 (0.62, 1.04) |
| ≥65 and <75 | 200 | 0.63 (0.45, 0.89) |
| ≥75 | 43 | 0.90 (0.43, 1.87) |
| **Gender** | | |
| Male | 319 | 0.73 (0.56, 0.96) |
| Female | 263 | 0.78 (0.58, 1.04) |
| **Baseline ECOG PS** | | |
| 0 | 179 | 0.64 (0.44, 0.93) |
| ≥1 | 402 | 0.80 (0.63, 1.00) |
| **Smoking Status** | | |
| Current/Former Smoker | 458 | 0.70 (0.56, 0.86) |
| Never Smoked | 118 | 1.02 (0.64, 1.61) |
| **EGFR Mutation Status** | | |
| Positive | 82 | 1.18 (0.69, 2.00) |
| Not Detected | 340 | 0.66 (0.51, 0.86) |
| Not Reported | 160 | 0.74 (0.51, 1.06) |

0.25   0.5   1.0   2.0   4.0

Nivolumab ← → Docetaxel
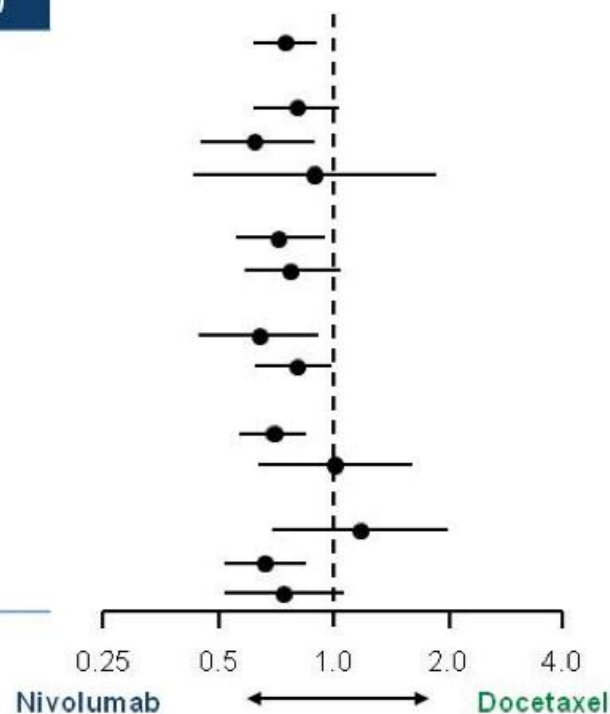
All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

Paz-Ares L et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract LBA109).
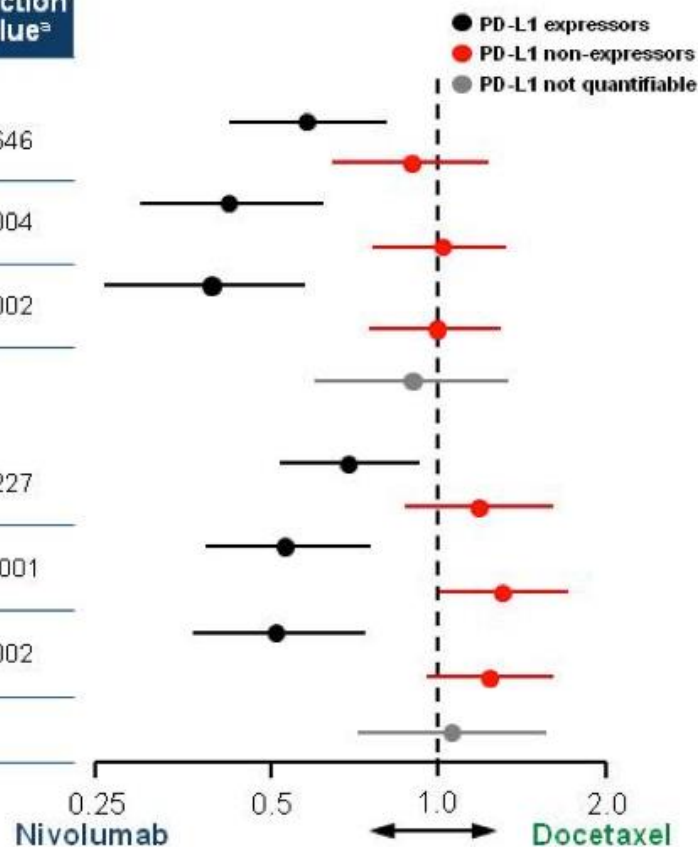
# CheckMate 057: Nivolumab vs Docetaxel 2nd-line <u>Non-squamous</u> NSCLC

## OS and PFS Hazard Ratios by Baseline PD-L1 Expression

| PD-L1 expression level | Nivolumab n | Docetaxel n | Unstratified HR (95% CI) | Interaction P-value[a] |
|---|---|---|---|---|
| **OS** | | | | |
| ≥1% | 123 | 123 | 0.59 (0.43, 0.82) | 0.0646 |
| <1% | 108 | 101 | 0.90 (0.66, 1.24) | |
| ≥5% | 95 | 86 | 0.43 (0.30, 0.63) | 0.0004 |
| <5% | 136 | 138 | 1.01 (0.77, 1.34) | |
| ≥10% | 86 | 79 | 0.40 (0.26, 0.59) | 0.0002 |
| <10% | 145 | 145 | 1.00 (0.76, 1.31) | |
| Not quantifiable at baseline | 61 | 66 | 0.91 (0.61, 1.35) | |
| **PFS** | | | | |
| ≥1% | 123 | 123 | 0.70 (0.53, 0.94) | 0.0227 |
| <1% | 108 | 101 | 1.19 (0.88, 1.61) | |
| ≥5% | 95 | 86 | 0.54 (0.39, 0.76) | <0.0001 |
| <5% | 136 | 138 | 1.31 (1.01, 1.71) | |
| ≥10% | 86 | 79 | 0.52 (0.37, 0.75) | 0.0002 |
| <10% | 145 | 145 | 1.24 (0.96, 1.61) | |
| Not quantifiable at baseline | 61 | 66 | 1.06 (0.73, 1.56) | |

- ● PD-L1 expressors
- ● PD-L1 non-expressors
- ● PD-L1 not quantifiable

[a]Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction.

0.25   0.5   1.0   2.0
Nivolumab ← → Docetaxel

# CheckMate 057: Nivolumab vs Docetaxel 2nd-line Non-squamous NSCLC

## Treatment-related AEs Reported in ≥10% of Patients

| | Nivolumab (n = 287) | | Docetaxel (n = 268) | |
|---|---|---|---|---|
| | Any Grade, % | Grade 3–4,[a] % | Any Grade, % | Grade 3–4,[a] % |
| **Total patients with an event** | 69 | **10** | 88 | **54** |

## Treatment-related Select AEs

| | Nivolumab (n = 287) | | Docetaxel (n = 268) | |
|---|---|---|---|---|
| | Any Grade | Grade 3–4[a] | Any Grade | Grade 3–4[a] |
| **Endocrine, %** | | | | |
| Hypothyroidism | 7 | 0 | 0 | 0 |
| **Gastrointestinal, %** | | | | |
| Diarrhea | 8 | 1 | 23 | 1 |
| **Hepatic, %** | | | | |
| ALT increased | 3 | 0 | 1 | <1 |
| AST increased | 3 | <1 | 1 | 0 |
| **Pulmonary, %** | | | | |
| Pneumonitis | 3 | 1 | <1 | <1 |
| **Skin, %** | | | | |
| Rash | 9 | <1 | 3 | 0 |
| Pruritus | 8 | 0 | 1 | 0 |
| Erythema | 1 | 0 | 4 | 0 |
| **Hypersensitivity/Infusion reaction, %** | | | | |
| Infusion-related reaction | 3 | 0 | 3 | <1 |

- Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention

Includes events reported in ≥2.5% of patients.
[a]No grade 5 events were reported at DBL;1 grade 5 event for nivolumab was reported post-DBL.

Paz-Ares L et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract LBA109).

# KEYNOTE-001: Pembrolizumab for Treatment of NSCLC

- **FDA Approved October 2015 for 2nd line NSCLung, if PDL1 +**

- 495 patients, phase IB study
  - Allowed front-line and prior chemo-treated patients
  - Randomized 2 mg/kg Q3w vs 10 mg/kg Q3w
  - Recent Bx required, training vs validation group: PD-L1+ >50% expression

- Results: ORR 19.4% (of which 84% durable)
  - Similar efficacy 2 mg/kg vs 10 mg/kg
  - If PD-L1 +, **ORR 45.2%**
  - If smoker, ORR 22.5% vs 10.3% never smoker

- Toxicity: fatigue, pruritis, decreased appetite
  - No clear difference between 2 mg/kg vs 10 mg/kg
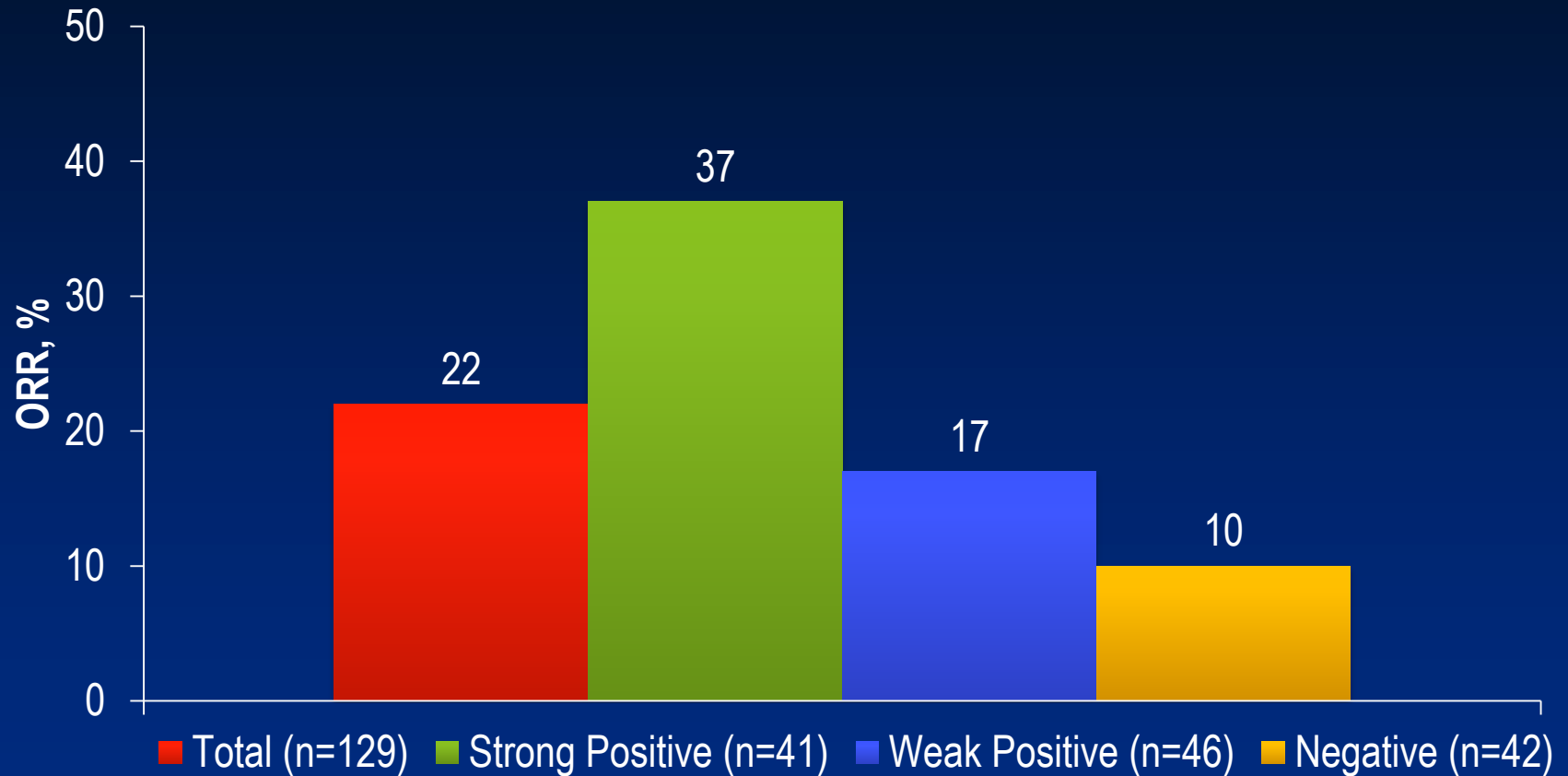  - 9% grade 3-5 treatment AEs, 1 patient pneumonitis death

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

# KEYNOTE-001: Pembrolizumab for Treatment of NSCLC
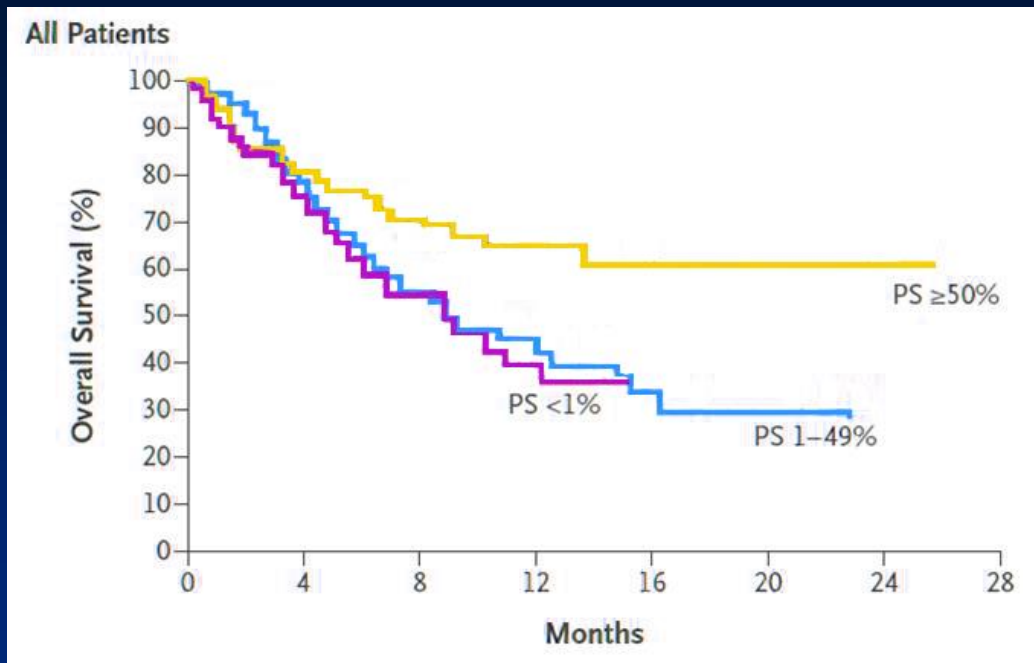


| Select Adverse Events – Occurring in >4% of patients (*n* = 495) | Any Grade | Grade 3-5 |
|---|---|---|
| | No. of patients (%) | |
| Fatigue | 96 (19.4) | 4 (0.8) |
| Pruritus | 53 (10.7) | 0 |
| Decreased appetite | 52 (10.5) | 5 (1.0) |
| Rash | 48 (9.7) | 1 (0.2) |
| Arthralgia | 45 (9.1) | 2 (0.4) |
| Diarrhea | 40 (8.1) | 3 (0.6) |
| Nausea | 37 (7.5) | 4 (0.8) |
| Hypothyroidism | 34 (6.9) | 1 (0.2) |
| Asthenia | 24 (4.8) | 5 (1.0) |
| Anemia | 21 (4.2) | 0 |
| Dyspnea | 21 (4.2) | 19 (3.8) |
| Pyrexia | 21 (4.2) | 3 (0.6) |

PS = proportion score % positivity
of PD-L1 membrane staining on tumor

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

# Pembrolizumab: Response Rate by Level of PD-L1 Expression



Garon EB et al. *N Engl J Med.* 2015;372:2018-2028.
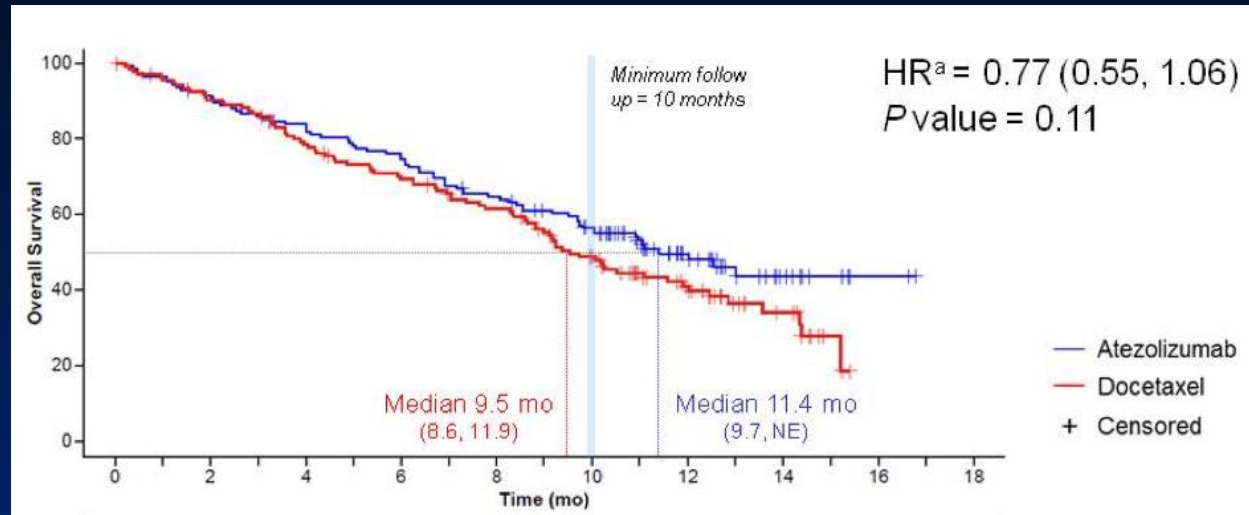
# PD-L1 Blockade

# Efficacy, Safety, and Predictive Biomarker Results from Phase II Atezolizumab (MPDL3280a) vs Docetaxel 2nd/3rd-line NSCLC

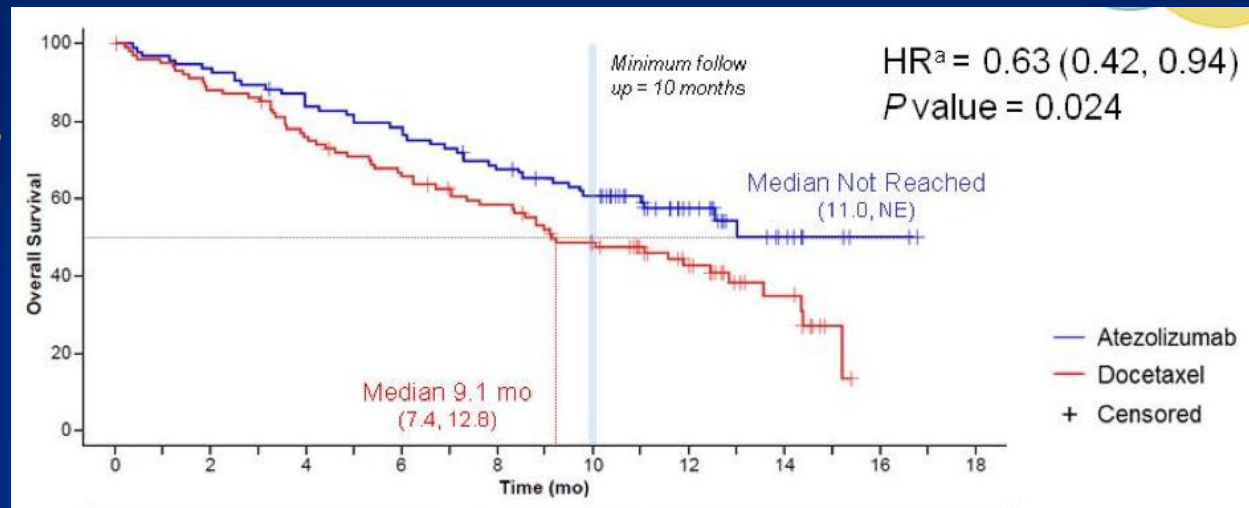*POPLAR Study (Interim Analysis)*

**ITT Interim OS (n=287)**



**PD-L1 Expression Subgroups**

**TC 1/2/3 or IC 1/2/3 Interim OS (n=195)**



Spira AI et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract 8010).

# MEDI4736 (Durvalumab) PD-L1 mAb
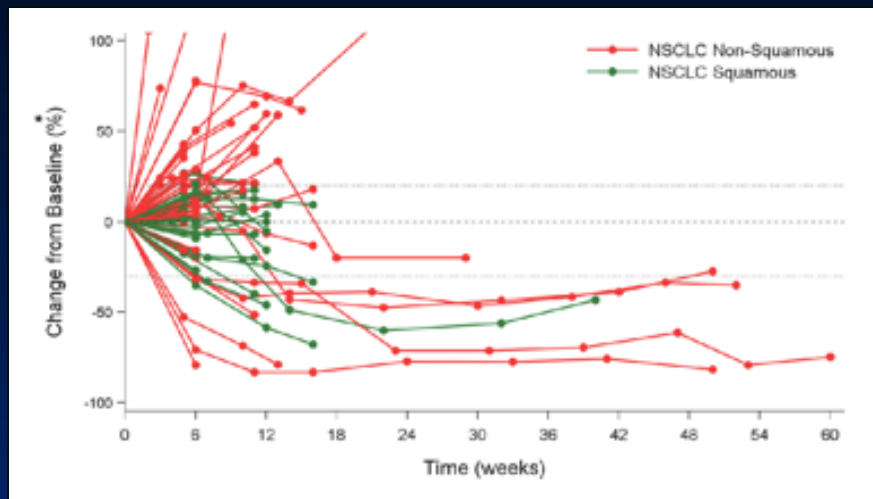


| | MEDI4736 10 mg/kg q2w | MEDI4736 All doses |
|---|---|---|
| **RECIST Response[b]** | | |
| Response evaluable[c] | 13% (6/47) | 16% (9/58) |
| PD-L1+ | 39% (5/13) | 25% (5/20) |
| PD-L1- | 5% (1/19) | 3% (1/29) |
| **Disease Control Rate[d]** | | |
| Response evaluable[c] | 30% (14/47) | 35% (20/58) |
| PD-L1+ | 54% (7/13) | 45% (9/20) |
| PD-L1- | 32% (6/19) | 24% (7/29) |

Segal NH et al. Presented at: American Society of Clinical Oncology, 2014 Annual Meeting; (Abstract 3002).
Brahmer J et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract 8112).

# Correlates and Biomarkers

- Presence of tumor infiltrating lymphocytes

- Auto-immunity

- PD-L1 expression: on tumor and immune cells

- Mutation load (mutanome)

  - Carcinogen exposure

  - Smoking status

  - Hypermutators (BRCA, Lynch syndrome)

  - Viral-mediated tumors

# PD-L1 Tumor Expression

- Distinct mechanisms of PD-L1 expression

  – Interferon gamma induced dynamic upregulation in the inflammatory tumor microenvironment ("adaptive resistance")

  – Oncogenic driver mutations that constitutively express PD-L1

  – Epithelial to mesenchymal transformation (EMT) of the carcinoma phenotype

# Predictive Correlates of Response to Anti-PD-L1 mAb MPDL3280a (Atezolizumab) in Cancer Patients

- Phase I trial of 277 patients, of whom 177 had biopsy and evaluable response
  - 28 paired biopsies
  - Immune mediated grade 3-4 events = 1% (no grade 3-4 pneumonitis)
- Results:
  - PD-L1 expression was more common on TIL, macrophages, and dendritic cells than on tumors
- RECIST response associated with:
  - High levels PD-L1 on immune cells ($P$=0.007), but not tumor PD-L1 expression
  - T helper type 1 (Th1) gene expression
  - CTLA-4 expression
  - Absence of fractalkine CX3CL1
  - NSCLC trend favoring smokers (42% vs 10%)
- Suggests the PD-L1 mAb blockade is most effective in:
  - Pre-existing immunity ("immune competence")
  - Re-invigorates anti-tumor response ("overcomes peripheral tolerance")

Herbst RS et al. *Nature.* 2014;515:563-567.

# Mutational Landscape Determines Sensitivity to PD-1 Blockade in NSCLC

- Background: PD-1 and PD-L1 best responses appear in melanoma and lung cancer (which have high carcinogen exposure)

- 34 lung patients on Pembro study had cancer exome gene sequence

  – >300 "nonsynonymous mutations" (meaning alter protein sequence) associated with:

    - Improved ORR, durable clinical benefit, and PFS

    - "Molecular smoking signature" (C-to A transversions)

    - Higher neo-antigen burden

    - DNA repair enzyme pathway mutations ("hypermutated tumors")

  – Concluded: genomic landscape (mutational burden "mutanome") enables response to PD-1 therapy

Rizvi NA et al. *Science.* 2015;348:124-128.

# PD-L1 as a Predictive Immune Biomarker: Assays, Sample Collection, and Analyses in NSCLC Studies

| | Pembrolizumab Merck | Nivolumab Bristol-Myers Squibb | MPDL3280A Roche/Genentech | MEDI4736 AstraZeneca |
|---|---|---|---|---|
| **PD-L1 Assay** | • Prototype or clinical trial IHC assay (22C3 Ab)[1] | • Dako automated IHC assay (28-8 Ab)[3,4] | • Ventana automated IHC assay | • 1st generation or Ventana automated IHC (BenchMark ULTRA) assay (Ventana PD-L1 (SP263) clone)[7,8] |
| **Sample Source and Collection** | • Surface expression of PD-L1 on tumor specimen* <br><br> • Ph I: Fresh tissue <br> • Ph II/III: Archival or fresh tissue[2] | • Surface expression of PD-L1 on tumor cells* <br><br> • Archival[4] or fresh tissue | • Surface expression of PD-L1 on TILs[5] <br><br> • Archival or fresh tissue | • Surface expression of PD-L1 on TILs <br><br> • PhI: Fresh tissue |
| **Definition of Positivity†** | **IHC Staining:** <br> • Strong vs weak expression[2] <br> • PD-L1 expression required for NSCLC for enrollment[2] <br>   • Note that one arm of KEYNOTE 001 trial requires PD-L1− tumors[1] <br><br> **Tumor PD-L1 expression:**[1] <br> • ≥50% PD-L1+ cut-off: 32% (41/129) <br> • 1-49% PD-L1+ cut-off: 36% (46/129) | **IHC Staining:** <br> • Strong vs weak expression[3,4] <br> • Patients not restricted in PD-L1 status in 2nd- & 3rd-line[4] <br> • Ph III 1st-line trial in PD-L1+[3] <br><br> **Tumor PD-L1 expression:**[4] <br> • 5% PD-L1+ cut-off: 49% (33/68)[4] | **IHC Staining intensity (0, 1, 2, 3):** <br> • IHC 3 (≥10% PD-L1+): Ph III trial[5] <br> • IHC 2,3 (≥5% PD-L1+)[5] <br> • IHC 1,2,3 (≥1% PD-L1+)[5] <br> • IHC 1, 0, or unknown <br> • PD-L1 expression required for NSCLC for enrollment <br><br> **TIL PD-L1 expression:**[5,6] <br> • IHC 3 (≥10% PD-L1+): 11% (6/53) <br> • PD-L1 low (IHC 1, 0): 75% (40/53) | **IHC Staining intensity:** <br> • Not presented to date[7,8,9] <br><br><br><br><br><br> **TIL PD-L1 expression:** <br> • Not presented to date[7,8,9] |

# Combination Checkpoints

# Immune Modulatory Receptors

Turning Up the Activating    Blocking the Inhibiting



Activating    Inhibiting
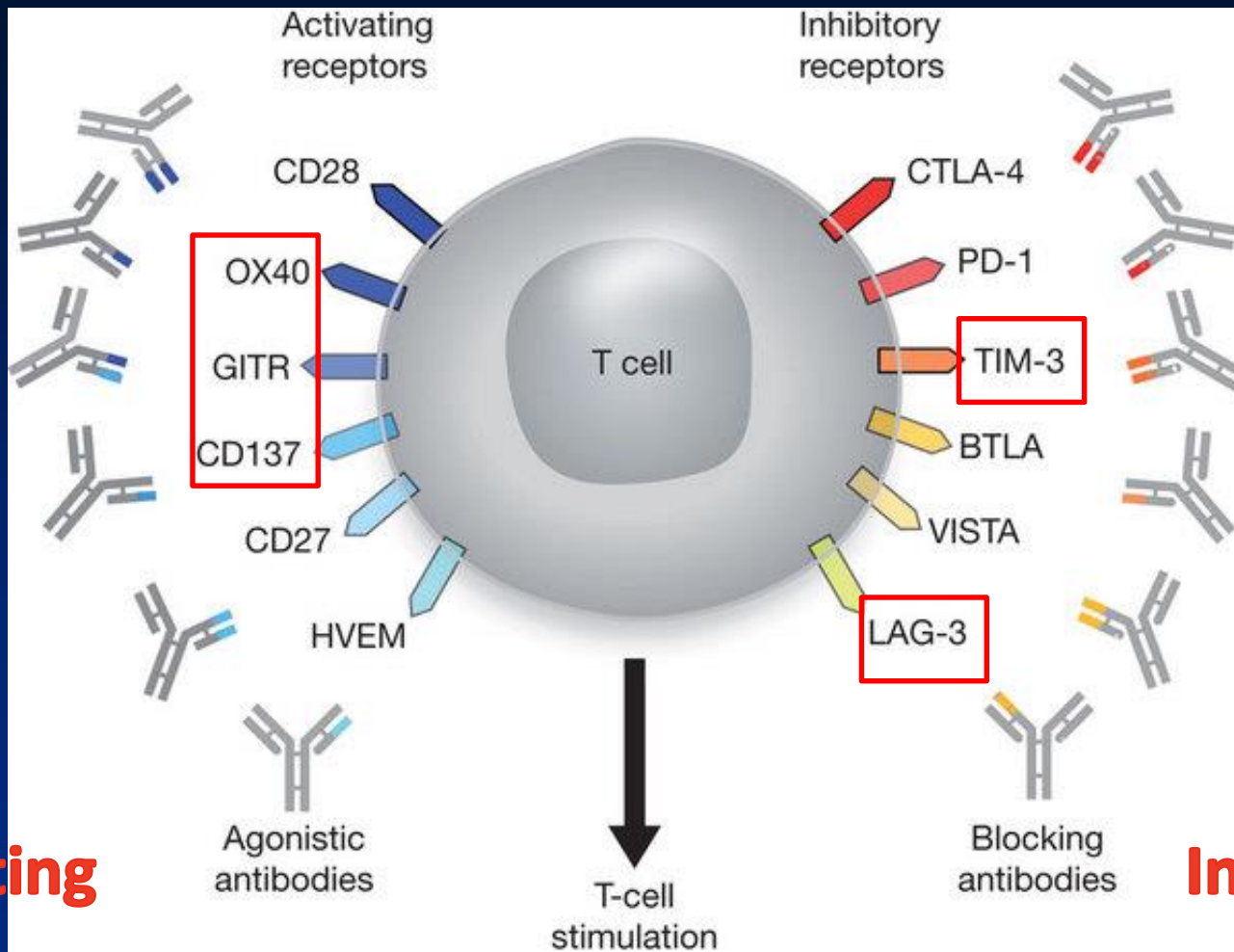
# Keynote-021 Cohort D: Phase I Pembrolizumab + Ipilimumab as 2nd-line NSCLC



Change From Baseline in Tumor Size
(RECIST v1.1, Investigator Review)

Pembrolizumab 10 mg/kg + ipilimumab 1 or 3 mg/kg
Pembrolizumab 2 mg/kg + ipilimumab 1 mg/kg

71% of patients showed decrease in target lesion burden

Patnaik A et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract 8011).
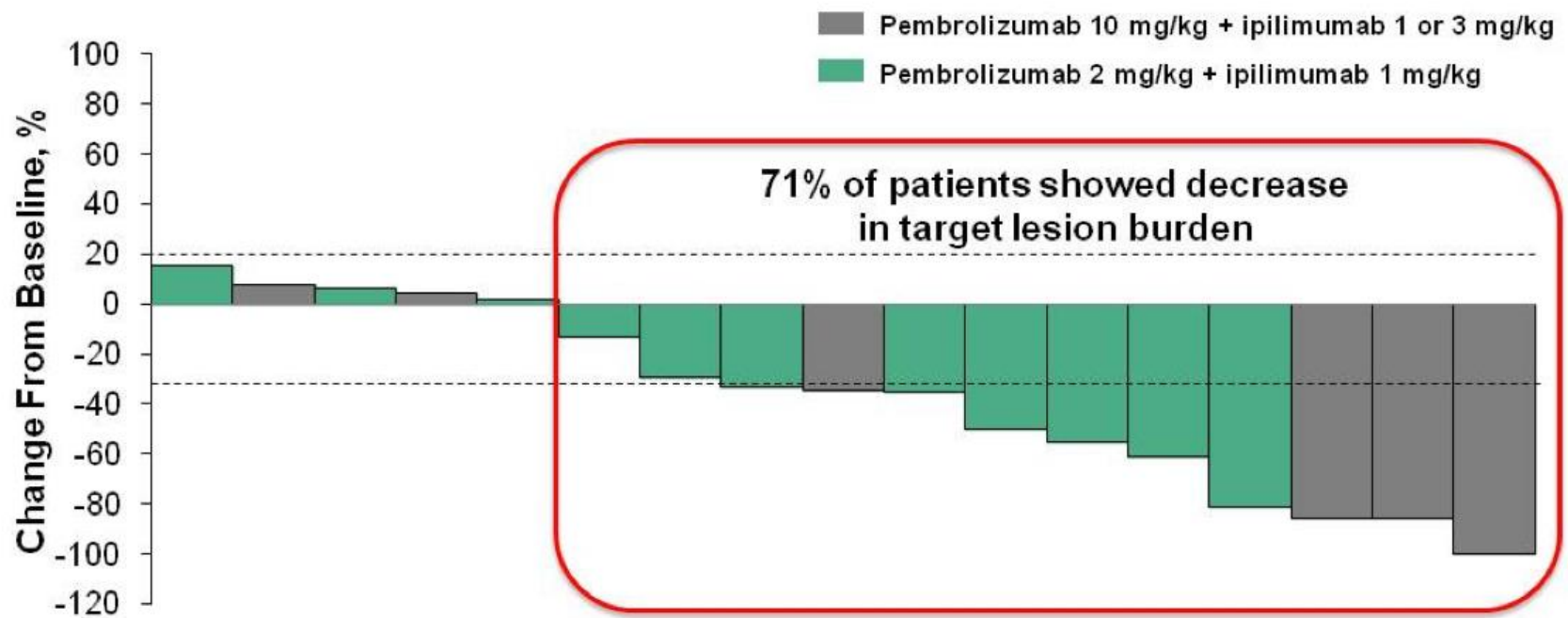
# Case Presentation 3

- A 61-year-old male presented with left lateral chest pain

- Work-up revealed a left upper-lobe lung mass measuring 2.5 lung mass and an erosive lesion in the left 5th rib

- Enlarged left hilar lymph node

- PET scan was positive at the left lung mass, hilum, left 5th rib, T9 and T12 spine

# Case Presentation 3: Work-up

- Biopsy of the rib lesion was positive for squamous cell lung carcinoma

- Medical history included hypertension and hyperlipidemia

- Former smoker with a 40 pack years smoking history

- ECOG PS = 1

# Case Presentation 3 (cont.)

# Polling Question

The patient receives palliative radiotherapy for the rib lesion. What systemic therapy would you recommend?

1. Platinum-based doublet chemotherapy

2. Single agent cytotoxic chemotherapy

3. Immunotherapy, such as anti-PD-1 therapy

4. Targeted EGFR TKI therapy

# First-line Immunotherapy for NSCLC

# Pembrolizumab as 1st-line therapy for NSCLC

n = 101

**Key Eligibility Criteria**
- Metastatic NSCLC
- Treatment-naïve
- PD-L1+ve
- ECOG PS 0 or 1
- Adequate organ function

R A N D O M I Z E

1:1

Pembrolizumab 10 mg/kg Q2W until PD or unacceptable toxicity

Pembrolizumab 10 mg/kg Q3W* until PD or unacceptable toxicity

*11 patients randomized to 2 or 10 mg/kg Q3W

**Endpoints**
- Primary: AE, DLTs, RR
- Secondary: pharmacokinetics, pharmacodynamics, PFS, OS, DOR

- PD-L1 expression was assessed by IHC (22C3 antibody)
- Response assessed every 9 week by RECIST 1.1

Rizvi NA et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract 8026).

# KEYNOTE-001: Efficacy

| | All treated    (n = 101) | PD-L1 Staining | | |
| --- | --- | --- | --- | --- |
| | | ≥50%         (n = 27) | 1%-49%         (n = 52) | <1%         (n = 12) |
| ORR, % (95% CI) | 27 (18-37) | 51.9 (32-71) | 17.3 (8-30) | 8.3 (0.2-39) |
| DCR, % | NA | 77.8 | 63.5 | 66.7 |
| PFS<br>　median, months (95% CI)<br>　6-month rate, % | 6.1 (4.1-9.1)<br>NA | 12.5 (8.0-NR)<br>77.0 | 4.2 (3.1-6.4)<br>44.4 | 3.5 (2.1-NR)<br>25.0 |
| OS<br>　median, months (95% CI)<br>　6-month rate, % | NR (16.2-NR)<br>NA | NR (17.8-NR)<br>92.6 | 16.2 (10.7 – NR)<br>80.4 | 10.4 (3.4-NR)<br>75.0 |

- ORRs were similar across dosage groups
- Among patients with squamous histology, ORRs were 100%, 23%, and 0% for those with ≥50% (n = 1), 1%-49% (n = 13), and <1% (n = 5) PD-L1 staining, respectively
- Among patients with non-squamous histology, ORRs were 52%, 16%, and 14% for those with ≥50% (n = 25), 1%-49% (n = 37), and <1% (n = 7) PD-L1 staining, respectively

# KEYNOTE-001: PFS By Biomarker Status



Figure 5. Kaplan-Meier estimates of PFS (A) and OS (B) in the total population and by PD-L1 expression level.

Rizvi NA et al. Presented at: American Society of Clinical Oncology, 2015 Annual Meeting; (Abstract 8026).
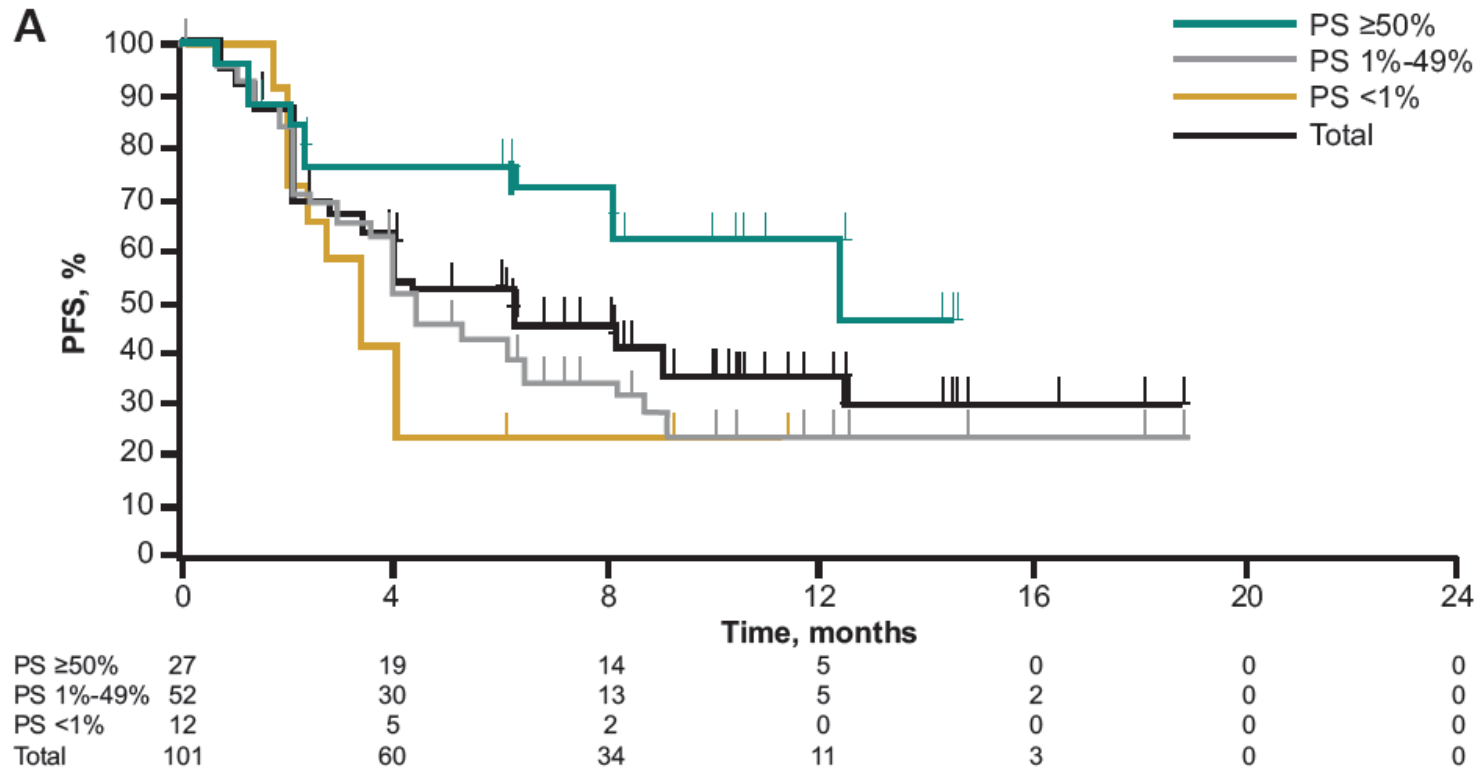
# KEYNOTE-001: Survival by Biomarker Status



Figure 5. Kaplan-Meier estimates of PFS (A) and OS (B) in the total population and by PD-L1 expression level.
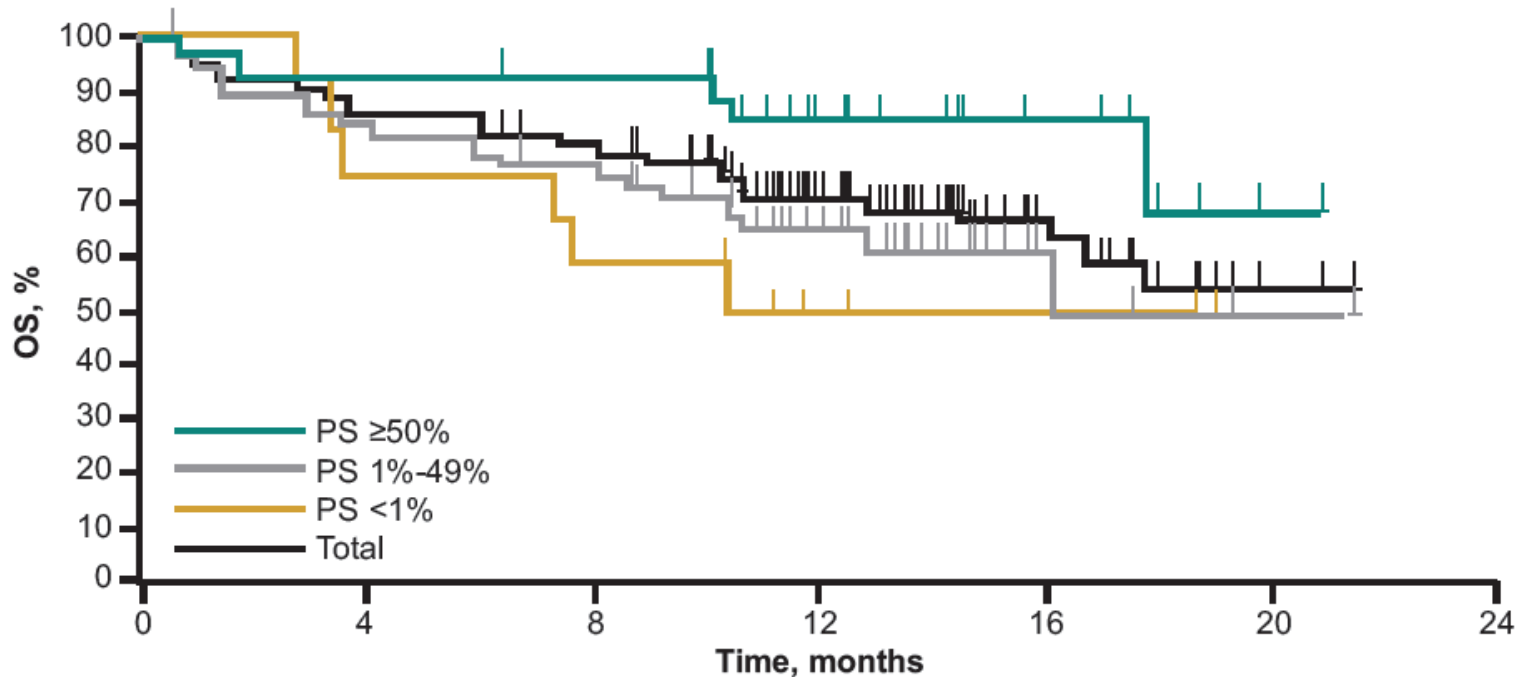
# KEYNOTE-001: Pembrolizumab for Treatment of NSCLC

- 495 patients, phase IB study
  - Allowed front-line and prior chemo-treated patients
  - Randomized 2 mg/kg Q3w vs 10 mg/kg Q3w
  - Recent Bx required, training vs validation group: PD-L1+ >50% expression

- Results: ORR 19.4% (of which 84% durable)
  - Similar efficacy 2 mg/kg vs 10 mg/kg
  - If PD-L1 +, ORR 45.2%
  - If smoker, ORR 22.5% vs 10.3% never smoker

- Toxicity: fatigue, pruritis, decreased appetite
  - No clear difference between 2 mg/kg vs 10 mg/kg
  - 9% grade 3-5 treatment AEs, 1 patient pneumonitis death

# KEYNOTE-001: Pembrolizumab for Treatment of NSCLC
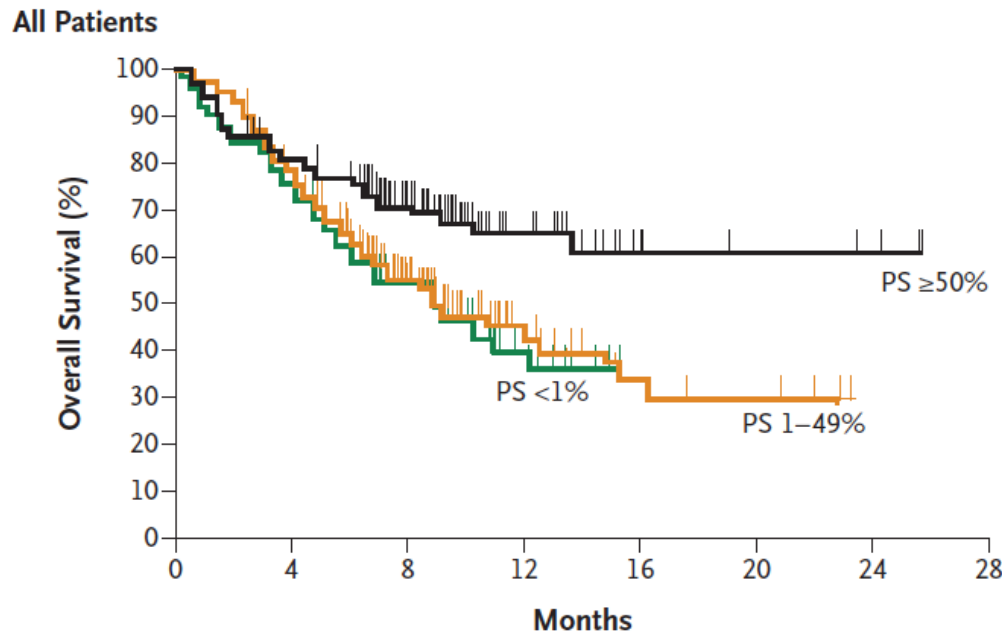


**All Patients**

PS ≥50%

PS <1%

PS 1−49%

PS = proportion score % positivity
of PD-L1 membrane staining on tumor

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

**Table 1. Adverse Events in 495 Patients in the Treated Population.***

| Adverse Event | Any Grade | Grade 3–5 |
|---|---|---|
| | *no. of patients (%)* | |
| Fatigue | 96 (19.4) | 4 (0.8) |
| Pruritus | 53 (10.7) | 0 |
| Decreased appetite | 52 (10.5) | 5 (1.0) |
| Rash | 48 (9.7) | 1 (0.2) |
| Arthralgia | 45 (9.1) | 2 (0.4) |
| Diarrhea | 40 (8.1) | 3 (0.6) |
| Nausea | 37 (7.5) | 4 (0.8) |
| Hypothyroidism | 34 (6.9) | 1 (0.2) |
| Asthenia | 24 (4.8) | 5 (1.0) |
| Anemia | 21 (4.2) | 0 |
| Dyspnea | 21 (4.2) | 19 (3.8) |
| Pyrexia | 21 (4.2) | 3 (0.6) |
| Decreased weight | 19 (3.8) | 2 (0.4) |
| Dry skin | 18 (3.6) | 0 |
| Pneumonitis† | 18 (3.6) | 9 (1.8) |
| Elevation in aspartate aminotransferase | 15 (3.0) | 3 (0.6) |
| Vomiting | 14 (2.8) | 3 (0.6) |
| Dermatitis acneiform | 13 (2.6) | 0 |
| Myalgia | 13 (2.6) | 0 |
| Cough | 12 (2.4) | 0 |
| Elevation in alanine aminotransferase | 11 (2.2) | 2 (0.4) |
| Chills | 10 (2.0) | 0 |
| Constipation | 10 (2.0) | 2 (0.4) |
| Infusion-related reaction | 15 (3.0) | 1 (0.2) |

# Pembrolizumab: Response Rate by Level of PD-L1 Expression



ORR, %

| | |
|---|---|
| Total (n=129) | 22 |
| Strong Positive (n=41) | 37 |
| Weak Positive (n=46) | 17 |
| Negative (n=42) | 10 |

Garon EB et al. *N Engl J Med.* 2015;372:2018-2028.
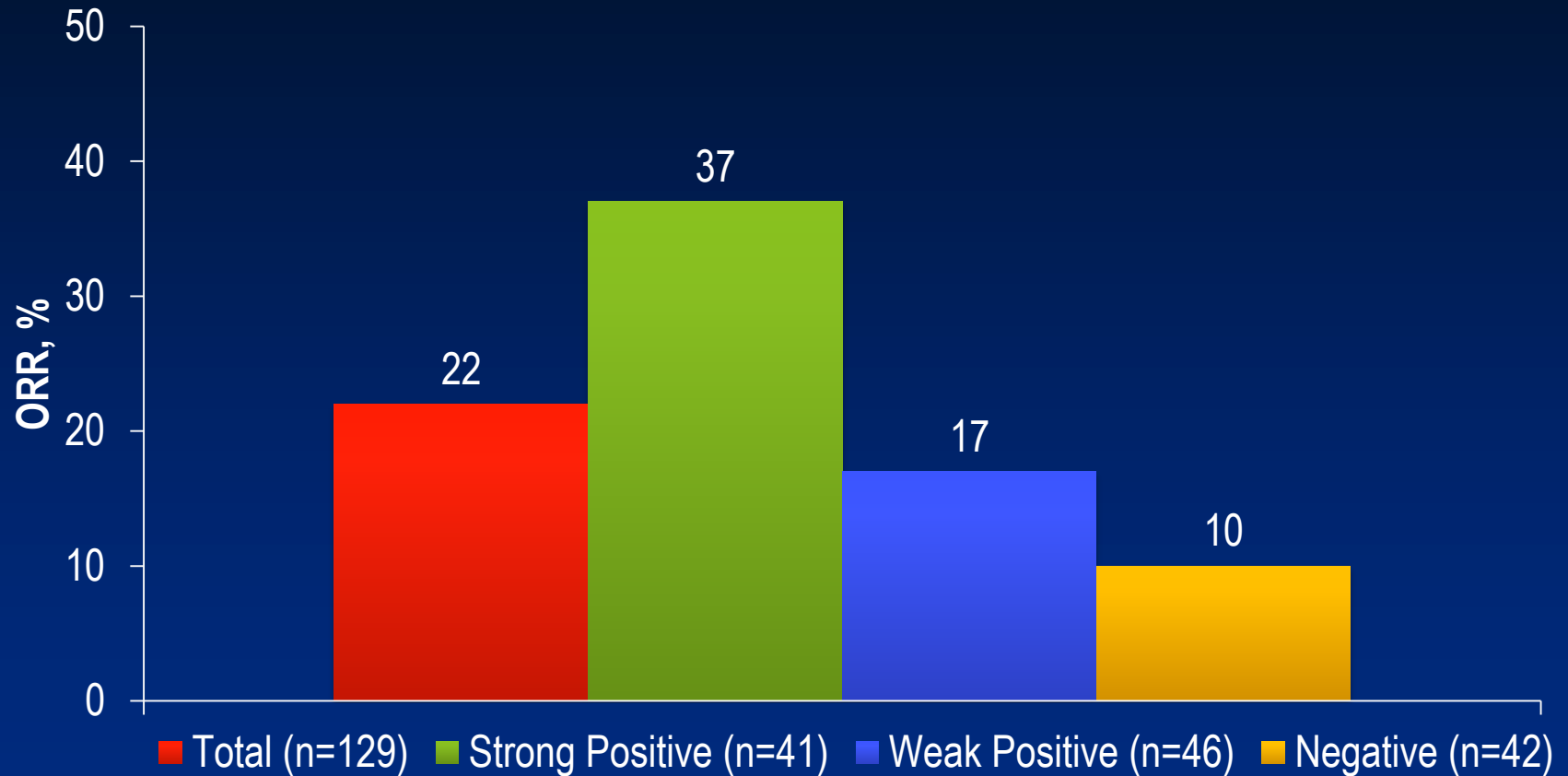
# Nivolumab in Advanced NSCLC: Front-line Therapy

**Key Eligibility Criteria**
- Stage IIIB/IV NSCLC
- ECOG PS 0 or 1
- Chemo-naïve except Arms D, K, L
- Life expectancy ≥ 3 mo

**Endpoints**
- Primary: safety, tolerability
- Secondary: ORR, 24-week PFS
- Exploratory: OS

RANDOMIZE

1:1

Arm F: Nivolumab monotherapy (any) (n = 52)

Arm K: Nivolumab monotherapy (squamous)

Arm L: Nivolumab monotherapy (nonsquamous)

Nivolumab was dosed at 3 mg/kg IV Q2W until progression or unacceptable toxicity (post-progression treatment was permitted per protocol)

- There are multiple arms in this trial with nivolumab combinations
- Only results for Arm F are reported
- Prior radiotherapy must have been completed at least 2 wk prior to study entry
- Response (RECIST v1.1) was evaluated overall by histology and by tumor PDL1 expression (PDL1+: ≥1% tumor cells expressing PDL1)

Gettinger SN et al. *J Clin Oncol.* 2014;32:5s (suppl; abstr 8024).

# Nivolumab in Advanced NSCLC Correlation of Outcomes with PD-L1 Expression



Figure 3. OS in pts with NSCLC treated with NIVO monotherapy
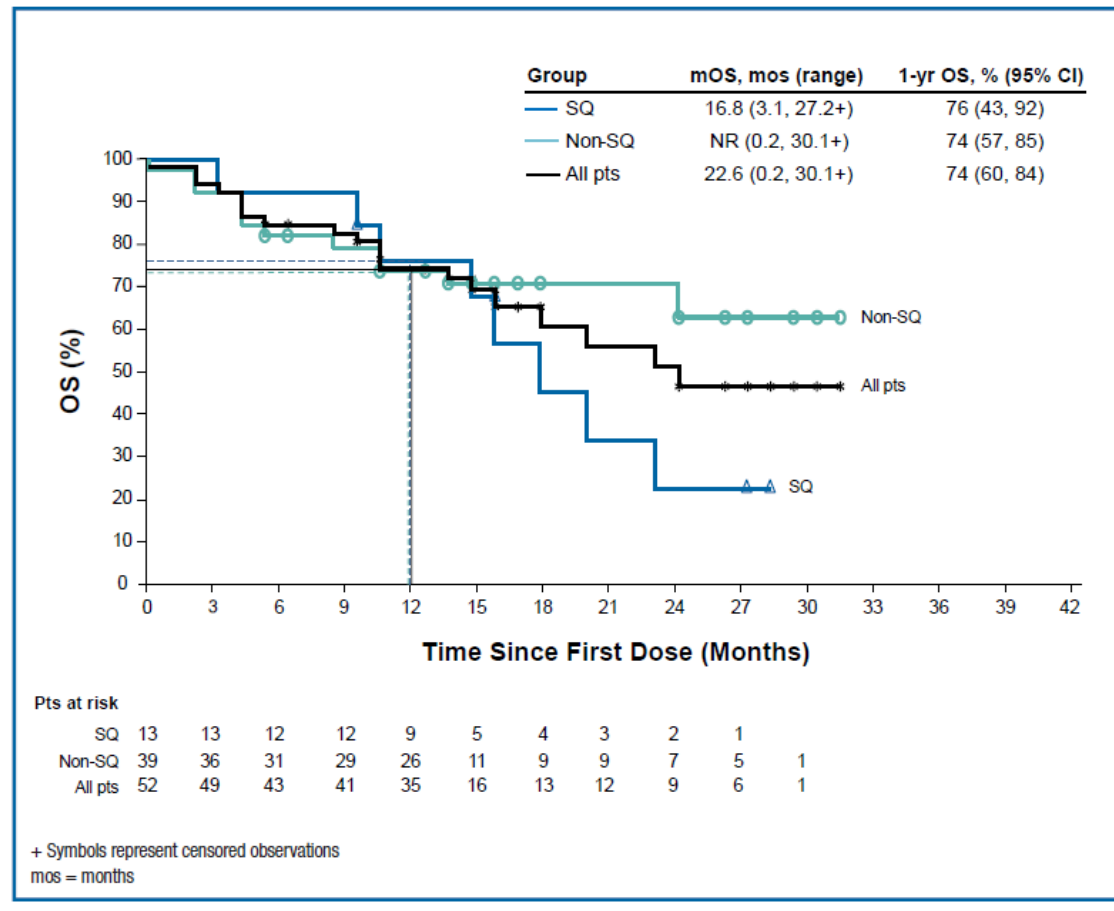
# Polling Question

A patient with NSCLC is interested in receiving an immune checkpoint inhibitor as first-line therapy. Which of the following would you advise?

1. Monotherapy with an immune checkpoint inhibitor
2. Combination with chemotherapy
3. Immune checkpoint inhibitor for 4 cycles followed immediately by chemotherapy
4. Chemotherapy for 4 cycles followed immediately by immune checkpoint inhibitor
5. Currently available data are limited regarding the role of immune checkpoint inhibitor as first-line therapy outside of clinical trials

# Chemotherapy + PD-1/PDL-1 Inhibition

# Phase I/II KEYNOTE-021: Pembrolizumab + Chemotherapy

**Induction**  **Maintenance**

**Key Eligibility Criteria**
- Stage IIIB/IV NSCLC
- No prior systemic therapy
- ≥1 measurable lesion by RECIST v1.1 criteria
- ECOG PS 0 or 1
- Any PD-L1 status
- Wild-type *EGFR* and *ALK*-negative translocation status
- No active/history of autoimmune disease

n = 49 (NCT 308)

**R A N D O M I Z E**

**1:1**

**Cohort A**

**Any histology, n = 25**

Pembrolizumab 2 or 10 mg/kg Q3W + carboplatin AUC 6 + paclitaxel 200 mg/m$^2$ for 4 cycles

Pembrolizumab

**Cohort C**

**Nonsquamous without EGFR mutation or with ALK translocation only, n = 24**

Pembrolizumab 2 or 10 mg/kg Q3W + carboplatin AUC 5 + pemetrexed 500 mg/m$^2$ for 4 cycles

Pembrolizumab + pemetrexed

**Endpoints**
- Primary: PFS, ORR, RP2D
- Secondary: OS

- DLT observation was the first 3 weeks after initial dosing
- Response was assessed by RECIST v1.1 every 6 weeks for the first 18 weeks, every 9 weeks for year 1, and every 12 weeks until year 2 by investigator assessment and central review
- As of March 31, 2015, 49 patients were treated

# KEYNOTE-021: Efficacy

## Best Overall Response Rate per RECIST v1.1 by Investigator Review

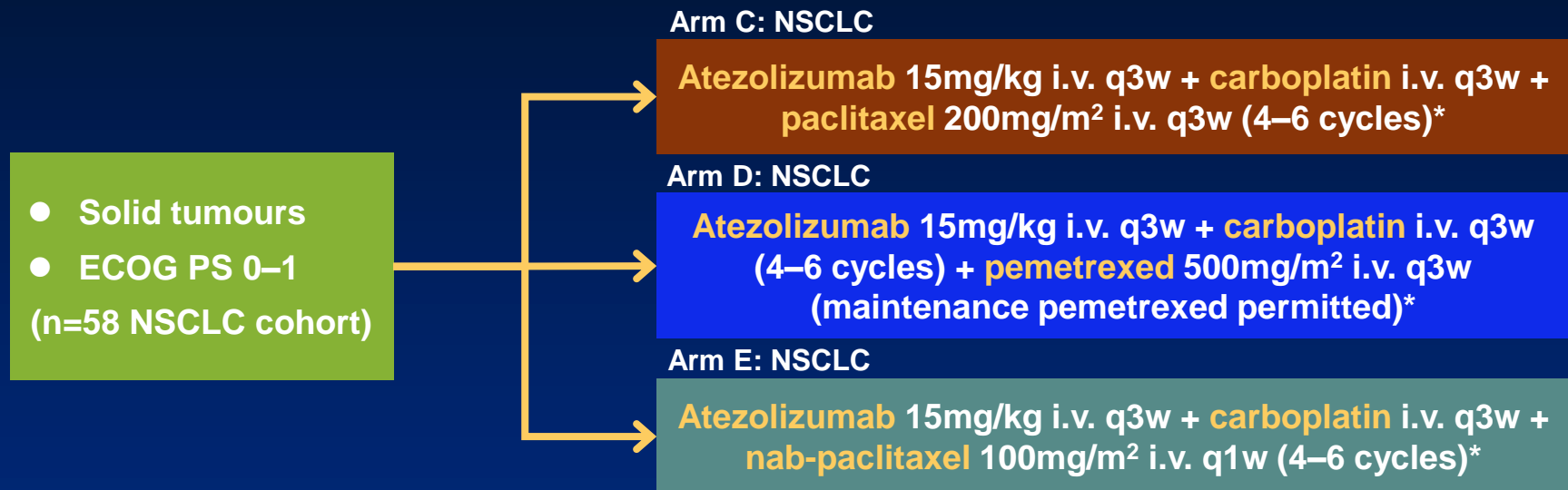| | Cohort A | | | Cohort C | | |
|---|---|---|---|---|---|---|
| | Pembro 10 mg/kg Q3W + paclitaxel + carboplatin (n = 12) | Pembro 2 mg/kg Q3W + paclitaxel + carboplatin (n = 13) | Cohort A Total n = 25 | Pembro 10 mg/kg Q3W + pemetrexed + carboplatin (n = 12) | Pembro 2 mg/kg Q3W + pemetrexed + carboplatin (n = 12) | Cohort C Total n = 24 |
| ORR, n (%) [95% CI] | 2 (17) [2-48] | 5 (38) [14-68] | 7 (28) [12-49] | 9 (75) [43-74] | 5 (42) [15-72] | 14 (58) [37-78] |
| DCR, n (%) [95% CI] | 9 (75) [6-57] | 12 (92) [64-100] | 21 (84) [64-96] | 12 (100) [74-100] | 12 (100) [74-100] | 24 (100) [86-100] |
| Best overall response, n (%) | | | | | | |
| CR | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| PR | 2 (17) | 5 (38) | 7 (28) | 9 (75) | 5 (42) | 14 (58) |
| SD | 7 (58) | 7 (54) | 14 (56) | 3 (25) | 7 (58) | 10 (42) |
| PD | 3 (25) | 1 (8) | 4 (16) | 0 (0) | 0 (0) | 0 (0) |

- 21/25 patients in Cohort A (88%) and all 24 patients in Cohort C (100%) experienced a decrease from baseline in size of their target lesion
- At the time of analysis, 7/7 responders in Cohort A, and 8/14 responders in Cohort C remained in response
  - 16/25 patients in Cohort A and 16/24 patients in Cohort C remained on treatment

# KEYNOTE-021: Safety

## Grade 3-4 Treatment-Related Adverse Events

| Adverse Event, n (%) | Cohort A | | Cohort C | |
|---|---|---|---|---|
| | Pembro 10 mg/kg Q3W + paclitaxel + carboplatin (n = 12) | Pembro 2 mg/kg Q3W + paclitaxel + carboplatin (n = 13) | Pembro 10 mg/kg Q3W + pemetrexed + carboplatin (n = 12) | Pembro 2 mg/kg Q3W + pemetrexed + carboplatin (n = 12) |
| Any | 3 (25) | 5 (38) | 5 (42) | 4 (33) |
| ALT increased | 0 (0) | 0 (0) | 1 (8) | 1 (8) |
| Anemia | 1 (8) | 1 (8) | 0 (0) | 1 (8) |
| AST increased | 0 (0) | 0 (0) | 1 (8) | 2 (17) |
| Atrial fibrillation | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| Colitis | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| Diarrhea | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| Drug eruption | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| Fatigue | 1 (8) | 0 (0) | 0 (0) | 0 (0) |
| Febrile neutropenia | 0 (0) | 2 (15) | 0 (0) | 0 (0) |
| Hypertension | 1 (8) | 0 (0) | 0 (0) | 0 (0) |
| Hyponatremia | 0 (0) | 0 (0) | 1 (8) | 0 (0) |
| Infectious pleural effusion | 0 (0) | 1 (8) | 0 (0) | 0 (0) |
| Leukopenia | 0 (0) | 1 (8) | 0 (0) | 0 (0) |
| Neutropenia | 0 (0) | 1 (8) | 0 (0) | 0 (0) |
| Rash | 1 (8) | 0 (0) | 0 (0) | 0 (0) |
| Urticaria | 0 (0) | 1 (8) | 0 (0) | 0 (0) |
| WBC count decreased | 0 (0) | 1 (8) | 0 (0) | 0 (0) |

# Atezolizumab (MPDL3280A) combined with platinum-based chemotherapy in NSCLC: Phase Ib GP28328 study design and endpoints

**Solid tumours**
**ECOG PS 0–1**
(n=58 NSCLC cohort)

**Arm C: NSCLC**
Atezolizumab 15mg/kg i.v. q3w + carboplatin i.v. q3w + paclitaxel 200mg/m$^2$ i.v. q3w (4–6 cycles)*

**Arm D: NSCLC**
Atezolizumab 15mg/kg i.v. q3w + carboplatin i.v. q3w (4–6 cycles) + pemetrexed 500mg/m$^2$ i.v. q3w (maintenance pemetrexed permitted)*

**Arm E: NSCLC**
Atezolizumab 15mg/kg i.v. q3w + carboplatin i.v. q3w + nab-paclitaxel 100mg/m$^2$ i.v. q1w (4–6 cycles)*

*supportive care (including steroids if necessary) was permitted, at the investigators' discretion; atezolizumab was given until loss of clinical benefit

- Primary endpoint: safety (including dose-limiting toxicities)

- Secondary endpoints: pharmacokinetics; best overall response; objective response rate (ORR); duration of response (DOR); progression-free survival (PFS)

- Date of cut-off: 10 Feb 2015; Median safety follow-up: 128.5 days (4.2 months)

Camidge DR et al. Presented at 2015 WCLC.

# Grade 3/4 Treatment-Related AEs* in ≥3% of patients

| AE, n (%) | Arm C – cb/pac (n=14) | Arm D – cb/pem (n=24) | Arm E – cb/nab (n=20) | All NSCLC patients (n=58) |
|---|---|---|---|---|
| Neutropenia | 4 (28.6) | 8 (33.3) | 7 (35.0) | 19 (32.8) |
| Anemia | 2 (14.3) | 2 (8.3) | 4 (20.0) | 8 (13.8) |
| Fatigue | 1 (7.1) | 2 (8.3) | 2 (10.0) | 5 (8.6) |
| Neutrophil count decreased | 1 (7.1) | 1 (4.2) | 2 (10.0) | 4 (6.9) |
| Platelet count decreased | 0 (0) | 3 (12.5) | 1 (5.0) | 4 (6.9) |
| Alanine aminotransferase increased | 0 (0) | 1 (4.2) | 2 (10.0) | 3 (5.2) |
| Aspartate aminotransferase increased | 0 (0) | 1 (4.2) | 2 (10.0) | 3 (5.2) |
| Dehydration | 1 (7.1) | 2 (8.3) | 0 (0) | 3 (5.2) |
| Thrombocytopenia | 0 (0) | 2 (8.3) | 1 (5.0) | 3 (5.2) |
| Hypokalemia | 0 (0) | 1 (4.2) | 1 (5.0) | 2 (3.4) |
| Leukopenia | 0 (0) | 2 (8.3) | 0 (0) | 2 (3.4) |
| Nausea | 0 (0) | 0(0) | 2 (10.0) | 2 (3.4) |

- One patient in Arm D had a grade 5 event possibly related to treatment (systemic candida)

*includes AEs attributed to chemotherapy and/or atezolizumab; data cut-off: 10 Feb 2015

Camidge DR et al. Presented at 2015 WCLC.

# Summary of Response by RECIST v1.1 (Response-Evaluable Patients)

| | Arm C – cb/pac (n=8) | Arm D – cb/pem (n=17) | Arm E – cb/nab (n=16) | All NSCLC patients (n=41) |
|---|---|---|---|---|
| Overall response, n (ORR %) | 4 (50.0) | 13 (76.5) | 9 (56.3) | 26 (63.4) |
| [95% CI for ORR] | [15.7–84.3] | [50.1–93.2] | [29.9–80.3] | [46.9–77.9] |
| Complete response, n (%) | 0 (0) | 0 (0) | 4 (25.0) | 4 (9.8) |
| Partial response, n (%) | 4 (50.0) | 13 (76.5) | 5 (31.3) | 22 (53.7) |
| Stable disease, n (%) | 4 (50.0) | 1 (5.9) | 4 (25.0) | 9 (22.0) |
| Progressive disease, n (%) | 0 (0) | 2 (11.8) | 2 (12.5) | 4 (9.8) |
| Missing or unevaluable, n (%) | – | 1 (5.9) | 1 (6.3) | 2 (4.9) |

- Data are preliminary; ~25 patients will be included in each arm for final analysis

*censored; data cut-off: 10 Feb 2015

Camidge DR et al. Presented at 2015 WCLC.

# Extent of Response and Changes in Tumor Burden by Treatment Arm



Data cut-off: 10 Feb 2015; SLD, sum of longest diameters

# Duration of Individual Patient Responses* at Time of Interim Analysis
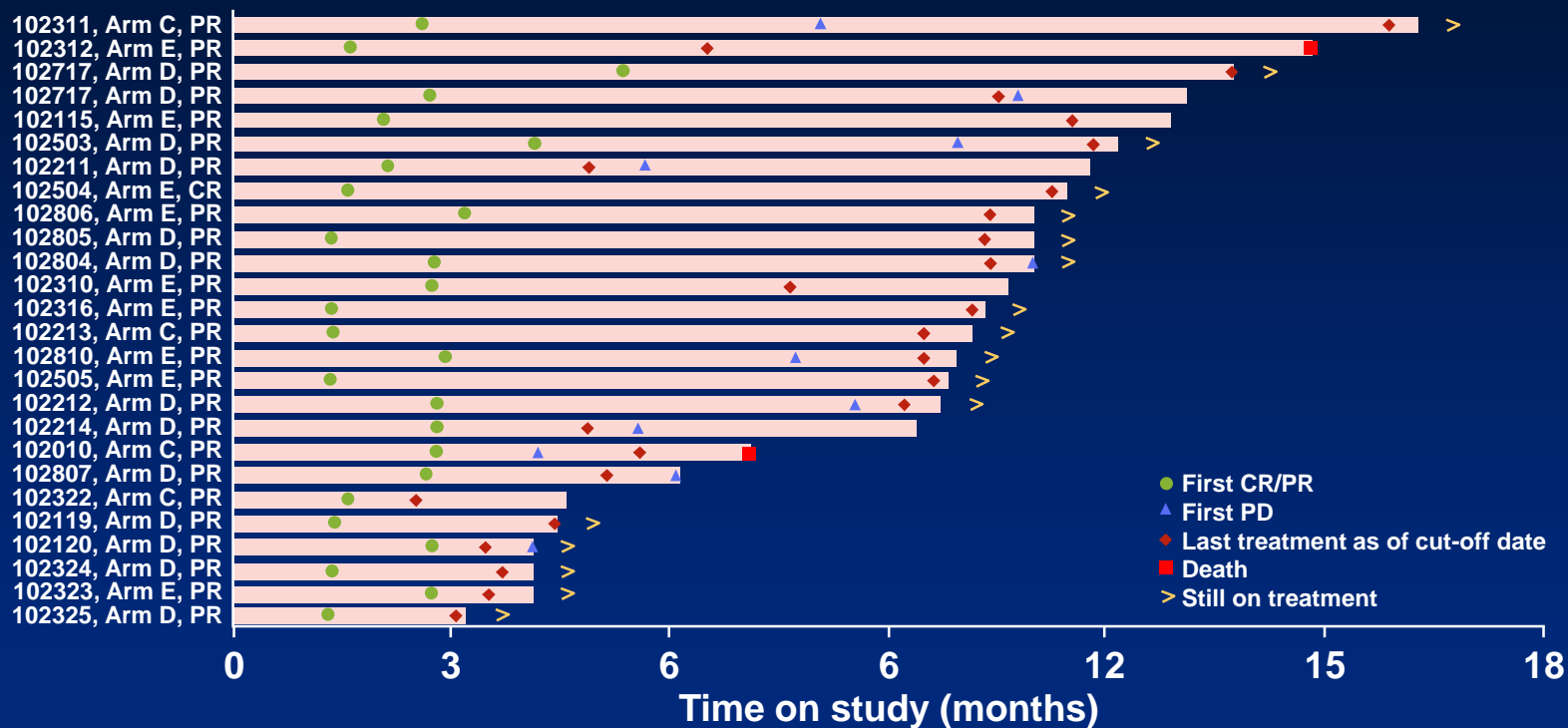


**Data cut-off: 10 Feb 2015; *investigator-assessed, unconfirmed responses**

Camidge DR et al. Presented at 2015 WCLC.

# Case Presentation 3 (cont.)

- The patient enrolled in a clinical trial and received pembrolizumab as first-line therapy.

- He achieved near complete resolution of the left lung mass and had no new lesions (PR)

- 6 months later, the patient developed dyspnea and was hospitalized for pneumonia

- Diagnosis of drug-induced pneumonitis was made and pembrolizumab was discontinued

- Patient was followed on close surveillance after recovery from pneumonia

- 14 months later (from diagnosis of NSCLC), he developed disease progression and is on combination chemotherapy

# First-line PD-1 Blockade in NSCLC

# Ipilimumab + Nivolumab 1st Line Lung

- Phase IB, front-line lung cancer, n = 49
  - ORR 19% (PD-L1+), 14% (PD-L1-)
  - PFS 24 weeks 47% (PD-L1+), 29% (PD-L1-)
  - Drug related grade 3%-4% AEs = 49%



Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline[a] and B) PFS

[a]Only includes patients with baseline target lesion and at least one post-baseline target lesion assessment with non-missing value

Antonia SJ et al. *J Clin Oncol.* 2014;32:5s (suppl; abstr 8023).
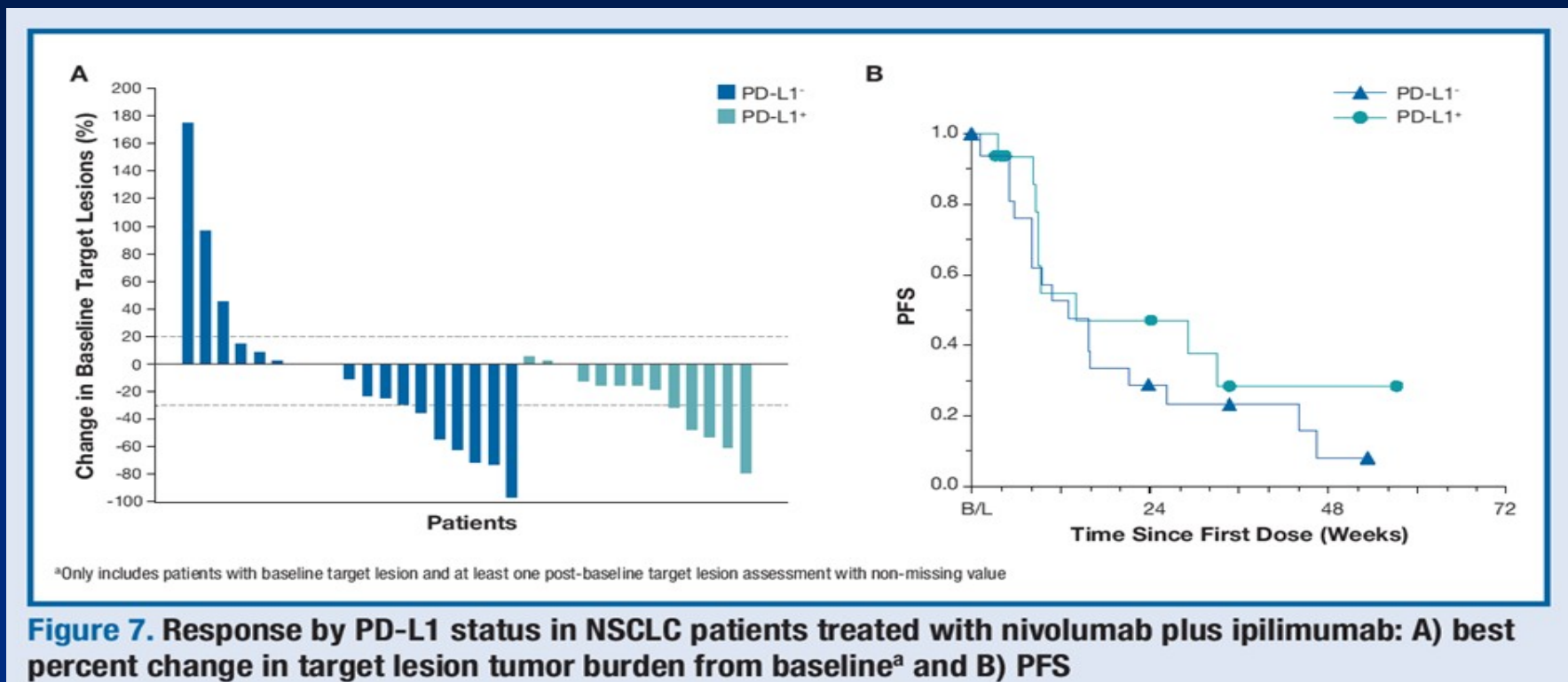
# CheckMate 012 Study Design: Nivolumab Plus Ipilimumab in First-line NSCLC

Stage IIIB/IV NSCLC (any histology); no prior chemotherapy for advanced disease; ECOG PS 0 or 1

| Nivo 1 mg/kg IV Q3W x 4<br>+<br>Ipi 1 mg/kg IV Q3W x 4 | Nivo 1 mg/kg IV Q2W<br>+<br>Ipi 1 mg/kg IV Q6W | Nivo 3 mg/kg IV Q2W<br>+<br>Ipi 1 mg/kg IV Q12W | Nivo 3 mg/kg IV Q2W<br>+<br>Ipi 1 mg/kg IV Q6W |

**Nivo 3 mg/kg IV Q2W until disease progression or unacceptable toxicity[a]**

**Until disease progression or unacceptable toxicity[a]**

**Primary endpoint:** safety and tolerability
**Secondary endpoints:** ORR (RECIST v 1.1) and PFS rate at 24 wks
**Exploratory endpoints:** OS; efficacy by PD-L1 expression

[a]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit

Rizvi et al, WCLC 2015

# Summary of Efficacy

| | Nivo 1 + Ipi 1 Q3W (n = 31) | Nivo 1 Q2W + Ipi 1 Q6W (n = 40) | Nivo 3 Q2W + Ipi 1 Q12W (n = 38) | Nivo 3 Q2W + Ipi 1 Q6W (n = 39) | Nivo 3 Q2W[a] (n = 52) |
|---|---|---|---|---|---|
| **Confirmed ORR, % (95% CI)** | **13** (4, 30) | **25** (13, 41) | **39** (24, 57) | **31** (17, 48) | **23** (13, 37) |
| **Confirmed DCR, % (95% CI)** | 55 (36, 73) | 58 (41, 73) | 74 (57, 87) | 51 (35, 68) | 50 (36, 64) |
| **Best overall response, %** | | | | | |
| Complete response | 0 | 0 | 0 | 0 | 8 |
| Partial response | 13 | 25 | 39 | 31 | 15 |
| Unconfirmed partial response | 3 | 3 | 5 | 8 | 0 |
| Stable disease | 42 | 33 | 34 | 21 | 27 |
| Progressive disease | 35 | 30 | 13 | 26 | 38 |
| Unable to determine | 6 | 10 | 8 | 15 | 12 |
| **PFS rate at 24 wks, % (95% CI)** | 55 (36, 71) | NC | 63 (44, 76) | NC | 41 (27, 54) |
| **Median PFS, mos (95% CI)** | 10.6 (2.1, 16.3) | 4.9 (2.8, ) | 8.0 (4.2, ) | 8.3 (2.6, ) | 3.6 (2.3, 6.6) |
| **Median OS, mos (95% CI)** | NR (11.5, ) | NR (8.9, ) | NR | NR (8.7, ) | 22.6 (14.9, ) |
| **Median length of follow-up, mos (range)** | 16.6 (1.8–24.5) | 6.2 (0.4–13.1) | 8.4 (0.9–12.3) | 7.7 (1.1–12.2) | 14.3 (0.2–30.1) |

- Median DOR was not reached in any arm
- Unconventional immune-related responses were observed in arms Nivo 3 Q2W + Ipi 1 Q12W (n = 2), Nivo 3 Q2W + Ipi 1 Q6W (n = 1) and Nivo 3 Q2W (n = 3)

NR: the time point at which the percent of survivors drops below 50% has not been reached due to insufficient number of events and/or follow up.
[a]Results for Nivo 3 Q2W are reported based on a March 2015 DBL

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# Efficacy by Tumor PD-L1 Expression

| | ≥1% PD-L1 expression | | | | <1% PD-L1 expression | | | |
|---|---|---|---|---|---|---|---|---|
| | Nivo 1 + Ipi 1 Q3W (n = 12) | Nivo 1 Q2W + Ipi 1 Q6W (n = 21) | Nivo 3 Q2W + Ipi 1 Q12W (n = 21) | Nivo 3 Q2W + Ipi 1 Q6W (n = 23) | Nivo 1 + Ipi 1 Q3W (n = 13) | Nivo 1 Q2W + Ipi 1 Q6W (n = 7) | Nivo 3 Q2W + Ipi 1 Q12W (n = 9) | Nivo 3 Q2W + Ipi 1 Q6W (n = 7) |
| ORR, % | 8 | 24 | 48 | 48 | 15 | 14 | 22 | 0 |
| mPFS, wks (95% CI) | 11.5 (7.1, ) | 21.1 (11.4, ) | 34.6 (15.9, 35.3) | NR (15.4, ) | 34.0 (8.9, ) | NR (10.1, ) | 23.1 (4.0, ) | 10.3 (7.4, 12.7) |
| PFS rate at 24 wks, % (95% CI) | 42 (15, 67) | 40 (18, 61) | 74 (48, 88) | 65 (42, 81) | 57 (25, 80) | NC | 39 (9, 69) | 0 |

- PD-L1 expression was measured using the Dako/BMS automated IHC assay[1,16]
  - Fully validated with analytical performance having met all predetermined acceptance criteria for sensitivity, specificity, precision, and robustness
- All patients had available pretreatment tumor samples; 76% (113/148) had samples evaluable for PD-L1 expression
- Median DOR was not reached in any arm, regardless of PD-L1 expression

NR: the time point at which the percent of survivors drops below 50% has not been reached due to insufficient number of events and/or follow up

Rizvi et al, WCLC 2015

# KEYNOTE 42 Trial

Advanced NSCLC
No Prior Therapy
PS 0/1
n=1240 Pts

PDL-1 Positive

Pembrolizumab
200 mg Q 21 days

Platinum-based
chemotherapy

Primary endpoint: Overall Survival

NCT02220894

# CheckMate 026 Trial

Advanced NSCLC
No Prior Therapy
PS 0/1
n=535 Pts

PDL-1 Positive

Nivolumab
3 mg/kg Q 2 weeks

Platinum-based
chemotherapy

Primary endpoint: PFS

NCT02041533

# Conclusions

- Immune checkpoint inhibitors are active as monotherapy in 1$^{st}$-line treatment of advanced NSCLC

- Combination of PD-1/PDL-1 inhibitors with platinum-based chemotherapy appears safe, based on early experience

**Targeting the Immune System to Improve Patient Outcomes in Advanced NSCLC**

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