ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- No relevant financial relationships to disclose

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Presentation Outline

- Background: Checkpoint inhibitors for the treatment of lung cancer
- Overview of clinical trial results that lead to current FDA approval of immunotherapies for the treatment of advanced/refractory, advanced/treatment naïve, and locally advanced NSCLC
- Discussion of predictive biomarkers of immune checkpoint blockade therapy
- Case studies

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FDA-approved Checkpoint Inhibitors for use in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

2008
Nivolumab FIH trial initiated

2012
Checkmate 017 and 057 initiated
Pembrolizumab FIH trial initiated

2015 (March)
Nivolumab FDA approved in 2nd line Sq NSCLC

2015 (Fall)
Nivolumumab Approved in Fall for 2nd line Non-sq NSCLC
Pembrolizumab FDA approved in 2nd line NSCLC (PD-L1 > 50%)

2016 (Fall)
Pembrolizumab FDA approved 1st line NSCLC (PD-L1 > 50%)
Pembrolizumab FDA approved in 2nd line NSCLC (PDL1 > 1%)
Atezolizumab FDA approved 2nd line NSCLC

2017 (May)
Pembrolizumab + Pemetrexed and Carboplatin FDA approved 1st line NSCLC
2017 (July)
Durvalumab FDA Breakthrough Therapy Designation for Stage III NSCLC

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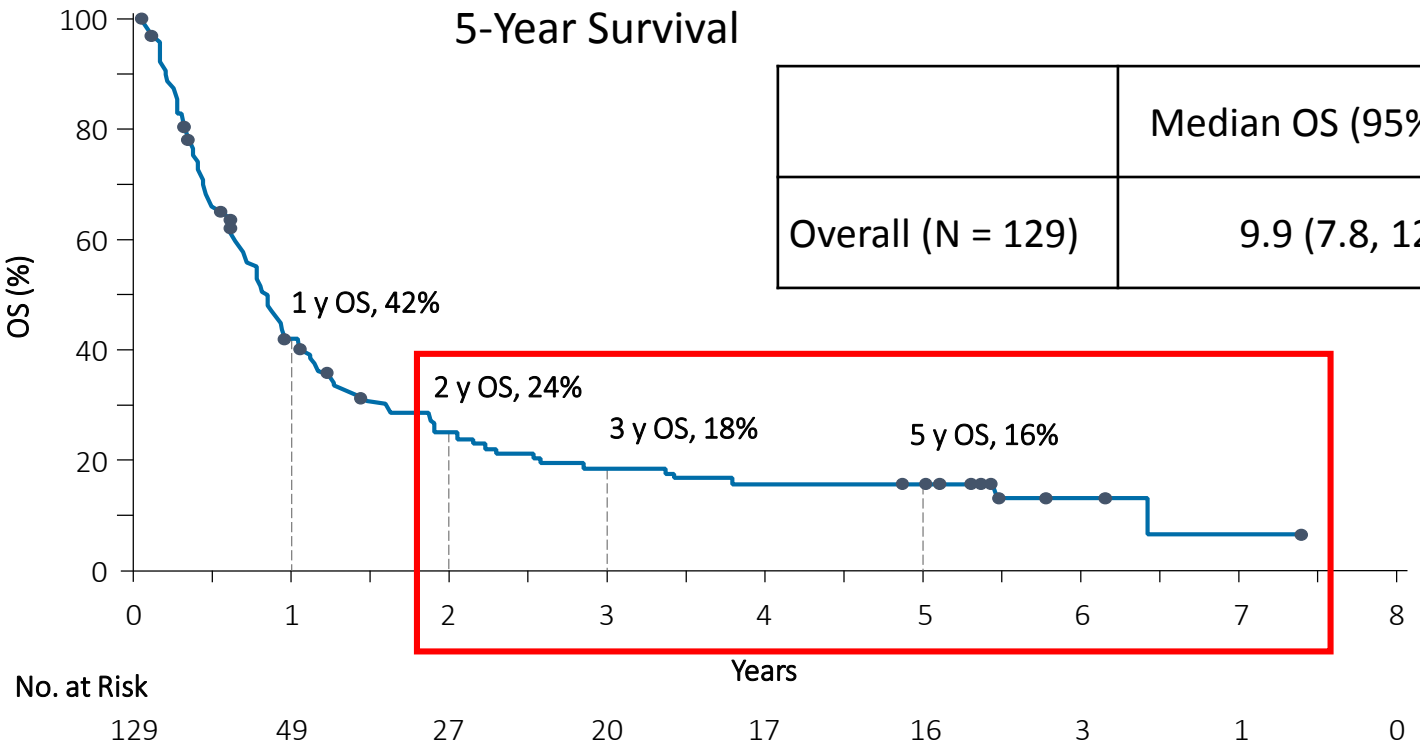
CA209-003: Nivolumab in Heavily Pretreated Advanced NSCLC (NCT00730639)

Phase 1, 5-Year Update



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

Brahmer et al, AACR 2017

NCI SEER data, Lung and Bronchus Cancer, 2014

- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor
- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%

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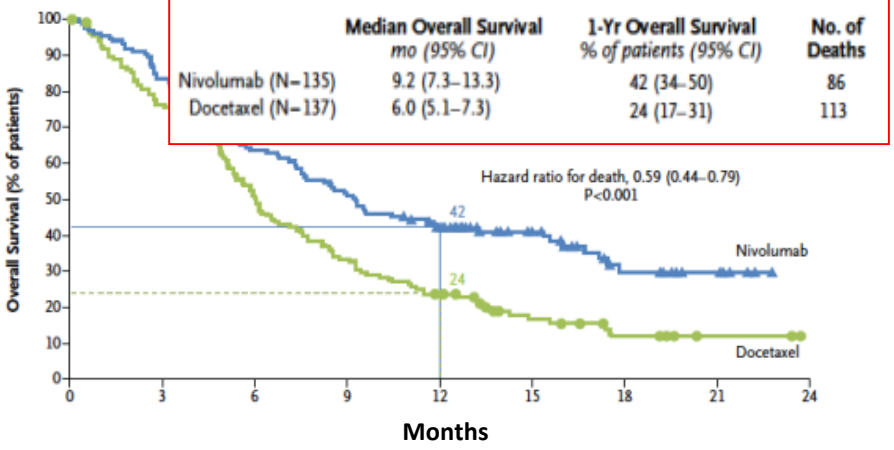
PD1/PD-L1 Inhibitors increase *Overall Survival* in 2L Advanced NSCLC

CHECKMATE 017 – Squamous Cell

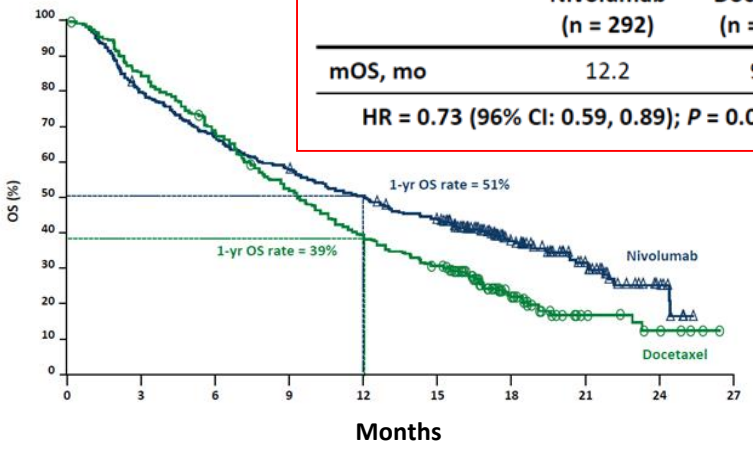
	Median Overall Survival *mo (95% CI)*	1-Yr Overall Survival *% of patients (95% CI)*	No. of Deaths
Nivolumab (N–135)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N–137)	6.0 (5.1–7.3)	24 (17–31)	113



CHECKMATE 057 – Non-squamous cell

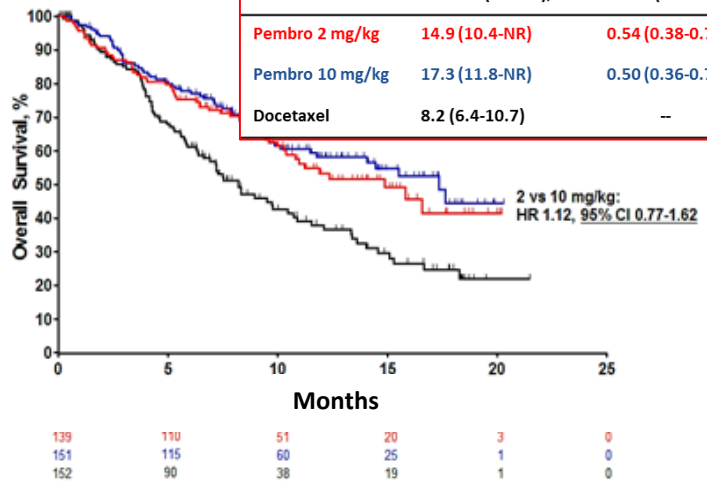
	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015



KEYNOTE 010 (TPS ≥ 1%) - NSCLC

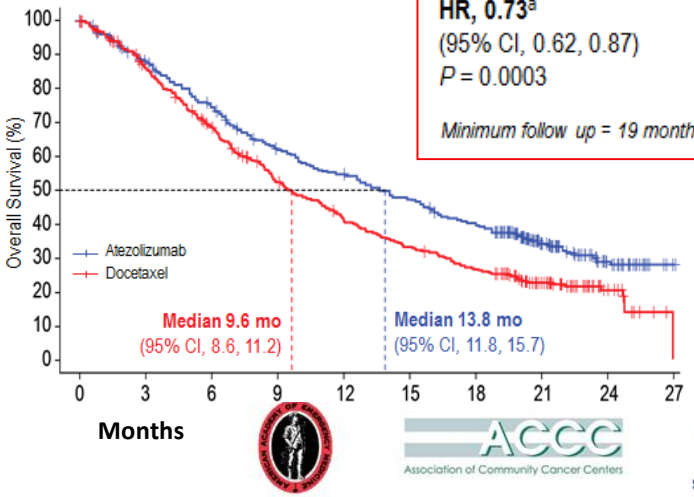
Treatment Arm	Median (95% CI), mo	HR* (95% CI)	P
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	--	--



OAK - NSCLC

HR, 0.73[a]
(95% CI, 0.62, 0.87)
P = 0.0003

Minimum follow up = 19 months



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Brahmer NEJM 2015; Borghaei, NEJM 2015; Herbst Lancet 2016; Rittmeyer Lancet 2017

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Toxicities in 2/3L Randomized trials

	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Keynote 010
Related Grade 3-5 AEs	15%	8%	11%	13-16%
Discontinuation due to related AEs	5%	6%	6%	4-5%
Pneumonitis AEs	1%	5%	3%	4-5%

Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

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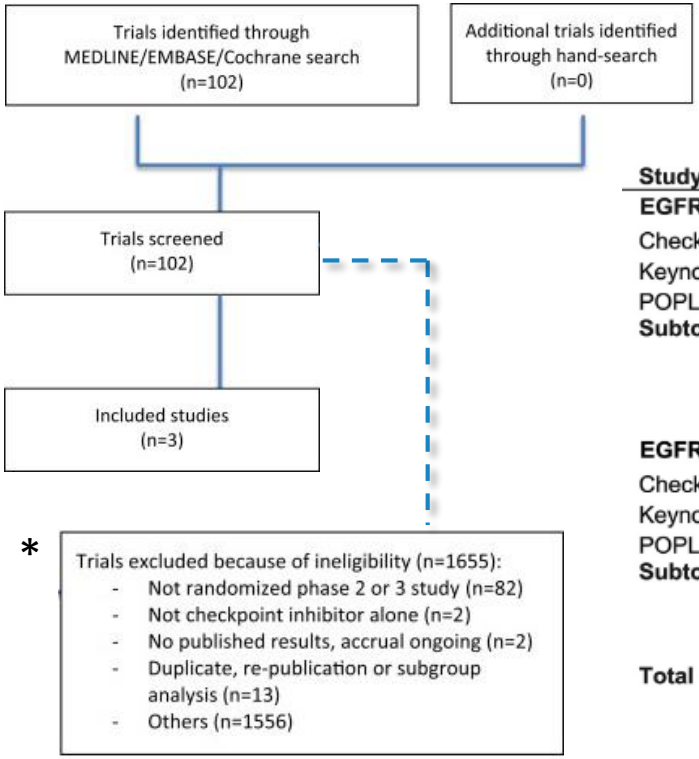
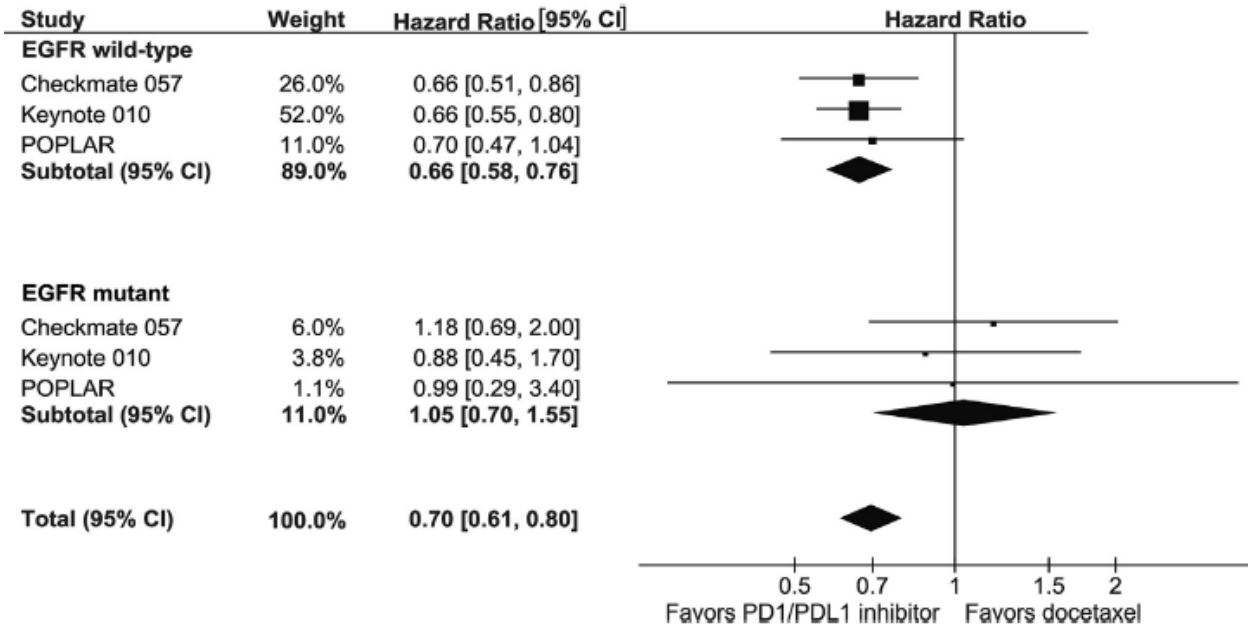
Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

A Meta-Analysis: CM-057, KN-010, POPLAR





CK Lee et al., JTO 2016

FDA-approved Checkpoint Inhibitors in 2nd Line Setting for Advanced NSCLC

FDA-Approved Agents in 2nd Line Setting for Advanced NSCLC

- Nivolumab (PD-1)
- Pembrolizumab (PD-1)
- Atezolizumab (PD-L1)

- PD-L1 testing is **not necessary**

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What about **1st line** setting in untreated advanced NSCLC patients?

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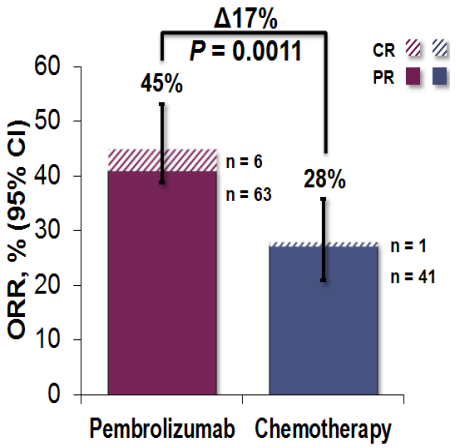
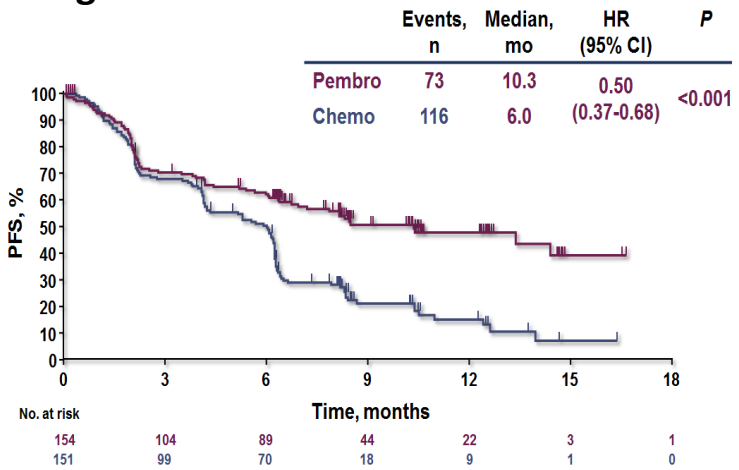
KEYNOTE-024: Pembrolizumab versus Chemotherapy for PD-L1 Positive NSCLC

Efficacy, Survival; PD-L1 > 50%

Objective Response Rate

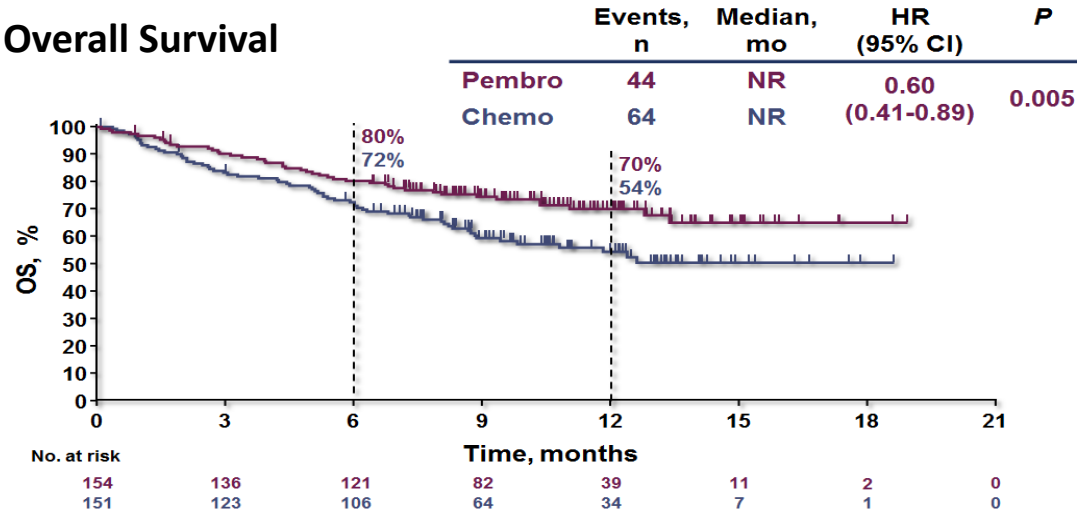


Progression-Free Survival



Reck M et al, ESMO 2016, NEJM 2016

Overall Survival



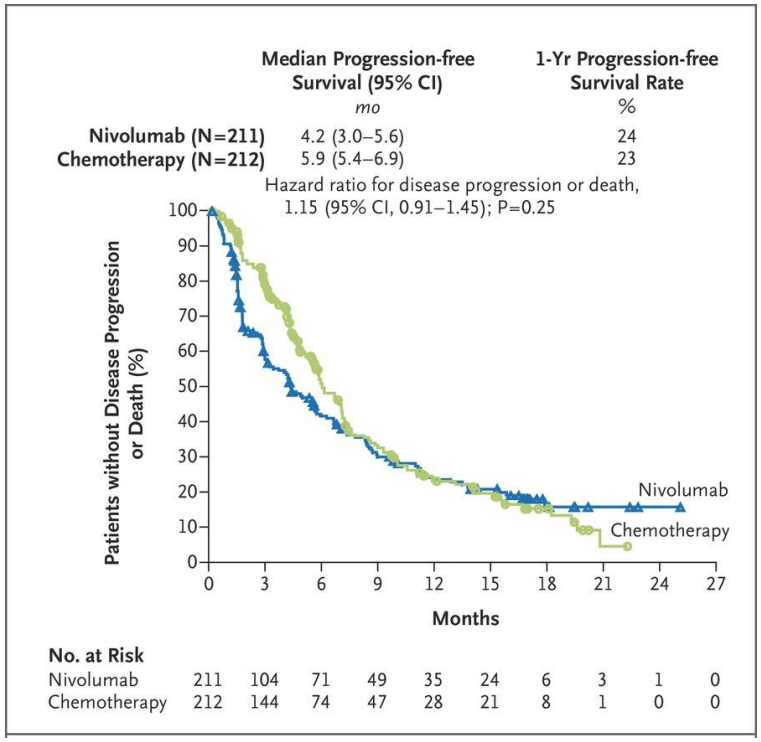
FDA-approved as 1st Line if PD-L1 >50%

50% cross-over from chemotherapy arm

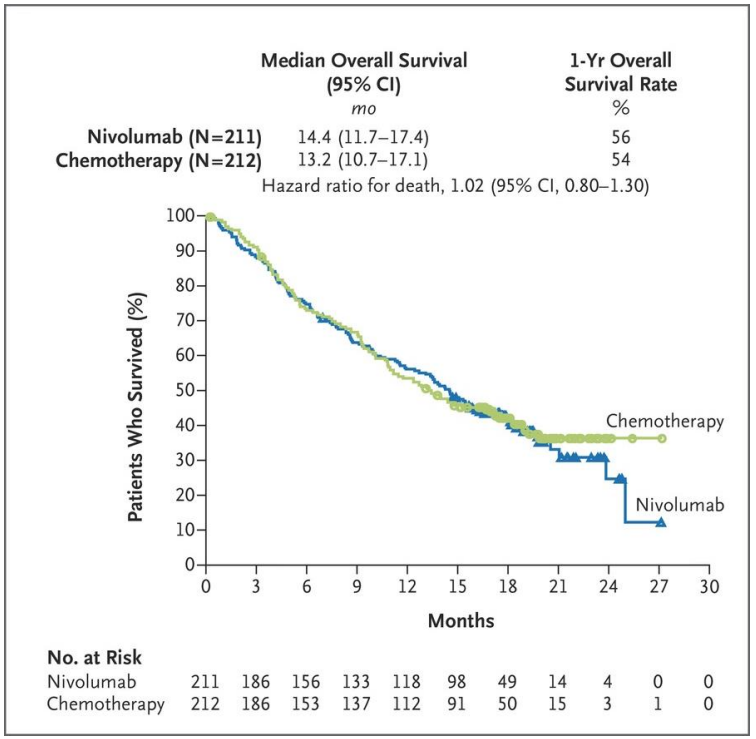
Checkmate-026: Nivolumab versus Chemotherapy for NSCLC

No PD-L1 Selection

Progression-Free Survival



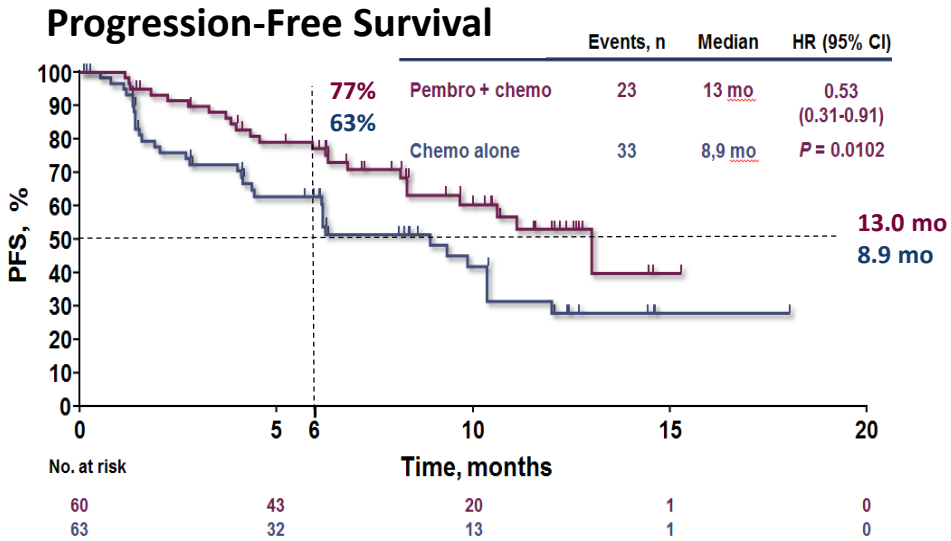
Overall Survival

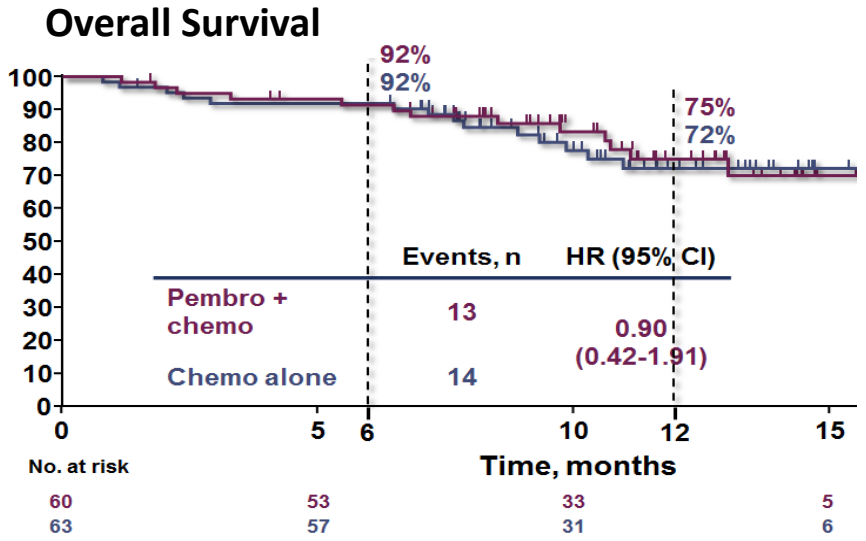


Carbone D et al,, NEJM 2017

Nivolumab CANNOT be used as 1st Line

KEYNOTE 021: Carboplatin and Pemetrexed +/- Pembrolizumab for adv. NSCLC (Open Label): *Progression Free and Overall Survival*





Langer, et al Lancet Oncology 2016
Borghaei, ESMO 2017

Clear ORR and PFS benefit; No OS advantage

- ORR 55% with pembro + PC vs 29% with PC (P = 0.0016)
- Median PFS improved by 4.1 months; PFS HR: 0.53; No difference for OS (crossover; immature data)
- Estimated rate of OS at 12 months: 75% (Combo) vs 72% (CT)
- In CT arm, **cross-over is 51%** to PD-L1 therapies (pembro & others)

Updated (ESMO '17):

- ORR 57% with pembro + PC vs 32% with PC (P = 0.0029)
- PFS significantly improved with pembro + PC vs PC (HR, 0.54; 95% CI, 0.33–0.88; P = 0.0067)
  - Median (95% CI) PFS of 19.0 (8.5–NR) mo vs 8.9 (95% CI, 6.2–11.8) mo
- mOS: Not reached for Pembro + PC (22.8–NR) mo; 20.9 for PC (14.9–NR) mo
  - OS HR: 0.59 (P = 0.0344)

KEYNOTE 189: Platinum-based CT +/- pembrolizumab for 1L metastatic NSCLC

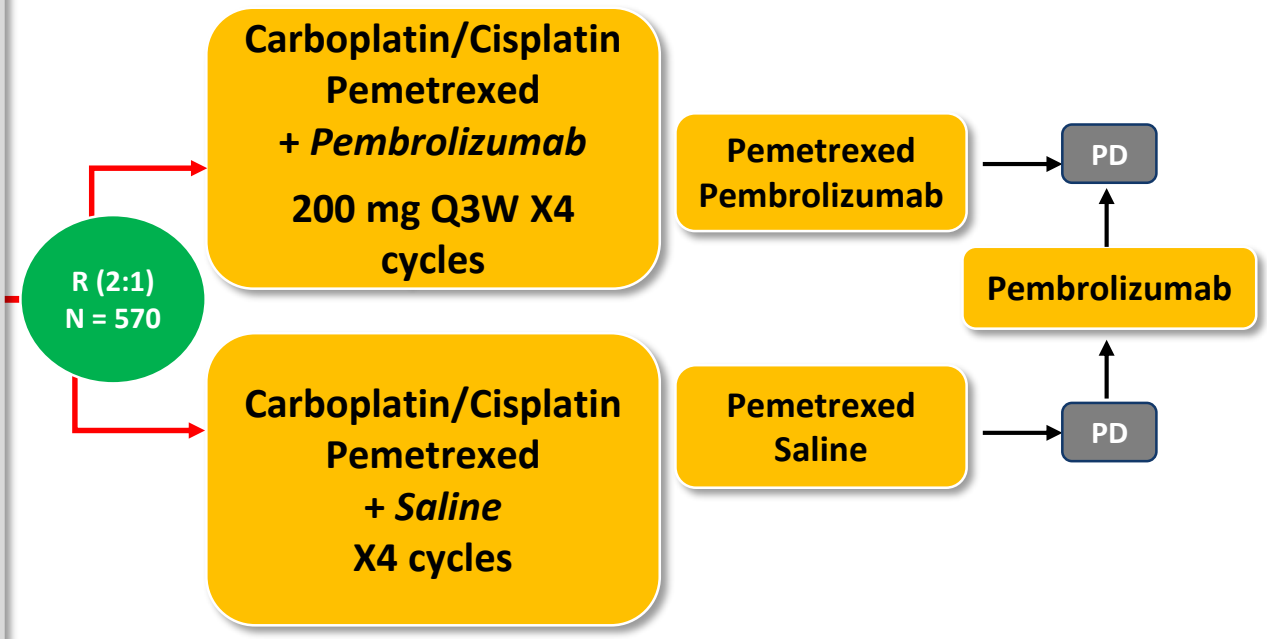
Phase 3 Safety and Efficacy study design

Patients

- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

Stratification

- PDL1 prop score: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin



Primary Endpoint: PFS – target HR 0.7 and OS
Secondary Endpoints: ORR, DOR, AEs
Exploratory Endpoints: QoL
*Completed Accrual: February, 2017

FDA-approved Checkpoint Inhibitors in 2nd Line Setting for Advanced NSCLC

- Only **Pembrolizumab** (PD-1) alone is FDA-approved in first line setting for advanced NSCLC with **PD-L1 > 50% (22C3 assay), EGFR/ALK wild type**

- Await results of KEYNOTE 189: Chemotherapy + Pembrolizumab vs Chemotherapy + Placebo

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Immune checkpoint blockade in **locally advanced** NSCLC?

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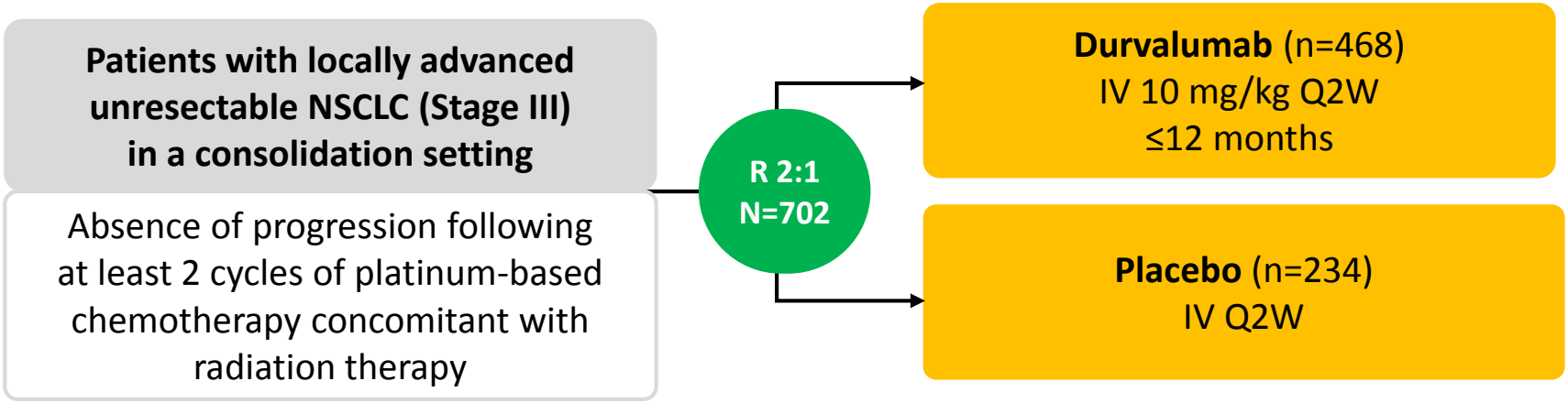
PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

Phase 3, randomized, double-blind, placebo-controlled trial (NCT02125461)



1. In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
2. NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
3. Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
4. Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

Primary endpoints: PFS, OS

Secondary endpoints: ORR, DoR, DSR, Safety/tolerability, PK, immunogenicity, QoL

Results: Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer; PFS was significantly longer with durvalumab than with placebo.

DoR = duration of response; DSR = deep sustained response;
NSCLC = non-small cell lung cancer; ORR = objective response rate;
OS = overall survival; PFS = progression-free survival;
PK = pharmacokinetics; Q2W = every 2 weeks; QoL = quality of life.

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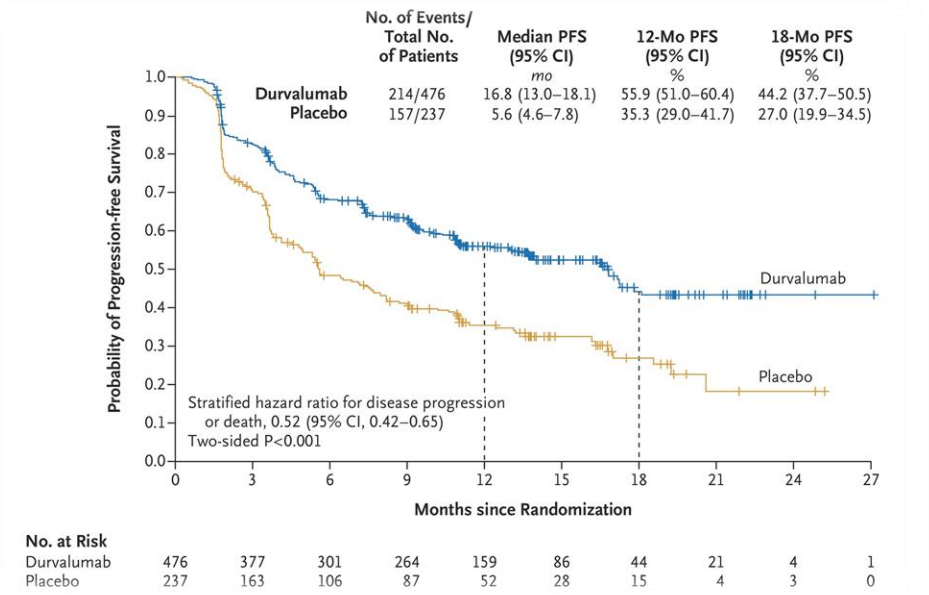
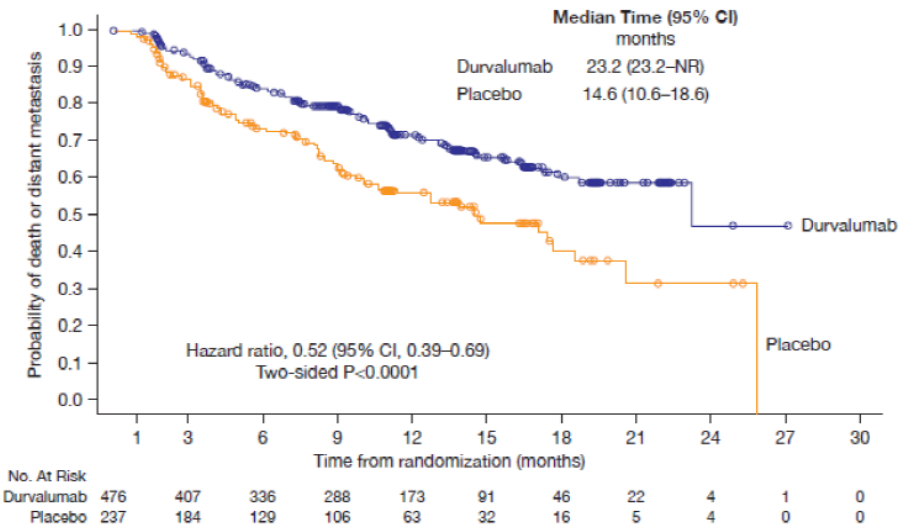
Progression Free Survival



Time to Death or Distant Metastasis



Clear advantages in PFS and time to death/metastasis

Antonia et al., NEJM 2017

- ORR 28.4% Durvalumab vs 16.0% Placebo (P<0.001)
- Median PFS 16.8 mo Durvalumab vs 5.6 mo Placebo (P<0.001)
- Median time to death/metastasis 23.2 mo Durvalumab vs 14.6 mo Placebo (HR 0.52, 95% CI 0.39 – 0.69; P<0.001)

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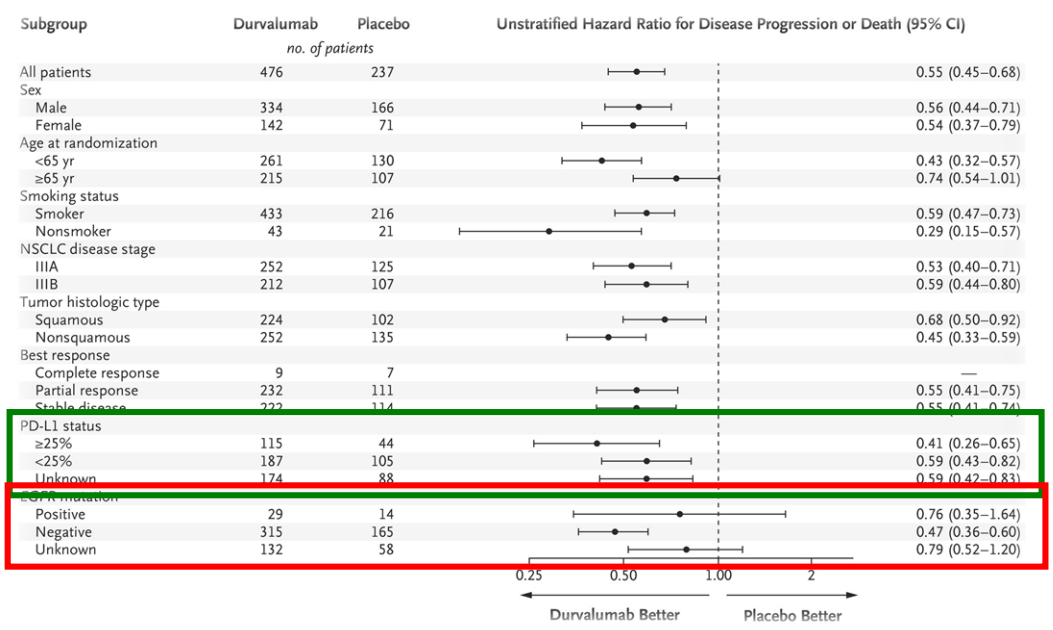

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

- Favors Durvalumab *regardless* of PD-L1 status
- Favors Durvalumab in EGFR mutant *negative* population
- Pneumonitis and Hypothyroidism higher in Durvalumab group
  – mostly low grade events

Antonia et al., NEJM 2017

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EA5142: ANVIL – Adjuvant Nivolumab after Surgical Resection and Adjuvant CT in NSCLC

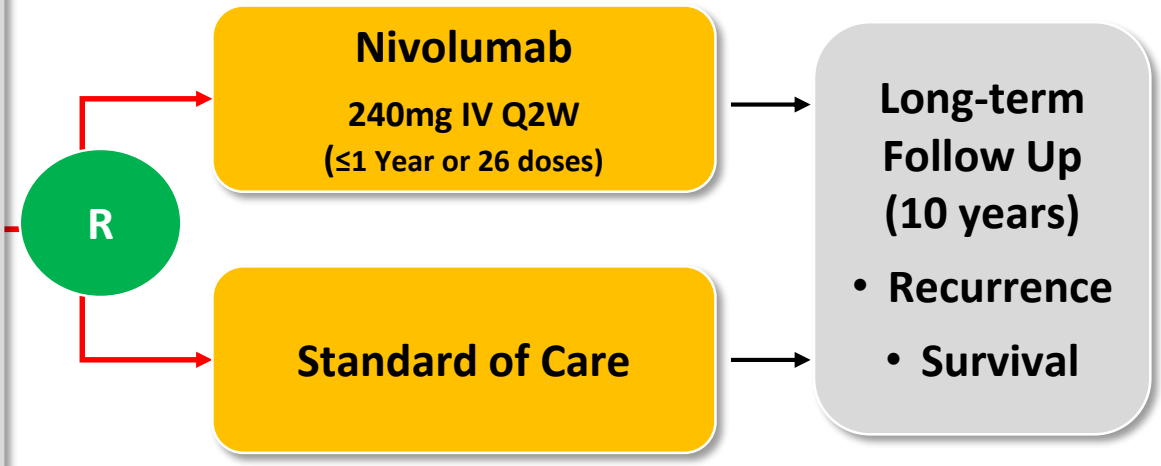
Study Design – ALCHEMIST Screening (NCT02194738)

Key Eligibility Criteria

- Patient registered to ALCHEMIST screening trial (A151216)
- EGFR/ALK wildtype (if non-squamous)
- No contraindication to nivolumab

Stratification

- Stage IB (≥4cm)/IIA vs IIB/IIIA
- Squamous vs. non-squamous*
- No prior adjuvant treatment vs. chemotherapy vs. chemotherapy + radiation
- PD-L1 positive** (≥1%) vs. Negative (<1%)



Chaft JE et al, ASCO Annual Meeting *2017*

Primary endpoints: DFS and OS in all patients

- ANVIL plans to enroll 714 patients to detect co-primary endpoints of a 30% improvement in OS and/or a 33% reduction in DFS favoring nivolumab.
- EA5142 is currently open at over 400 centers nationwide.

*Adenosquamous grouped as non-squamous
**PD-L1+ defined as ≥ 1% by IHC
Accrual Goal = 714 patients

FDA-approved Checkpoint Inhibitors in 2nd Line Setting for Advanced NSCLC

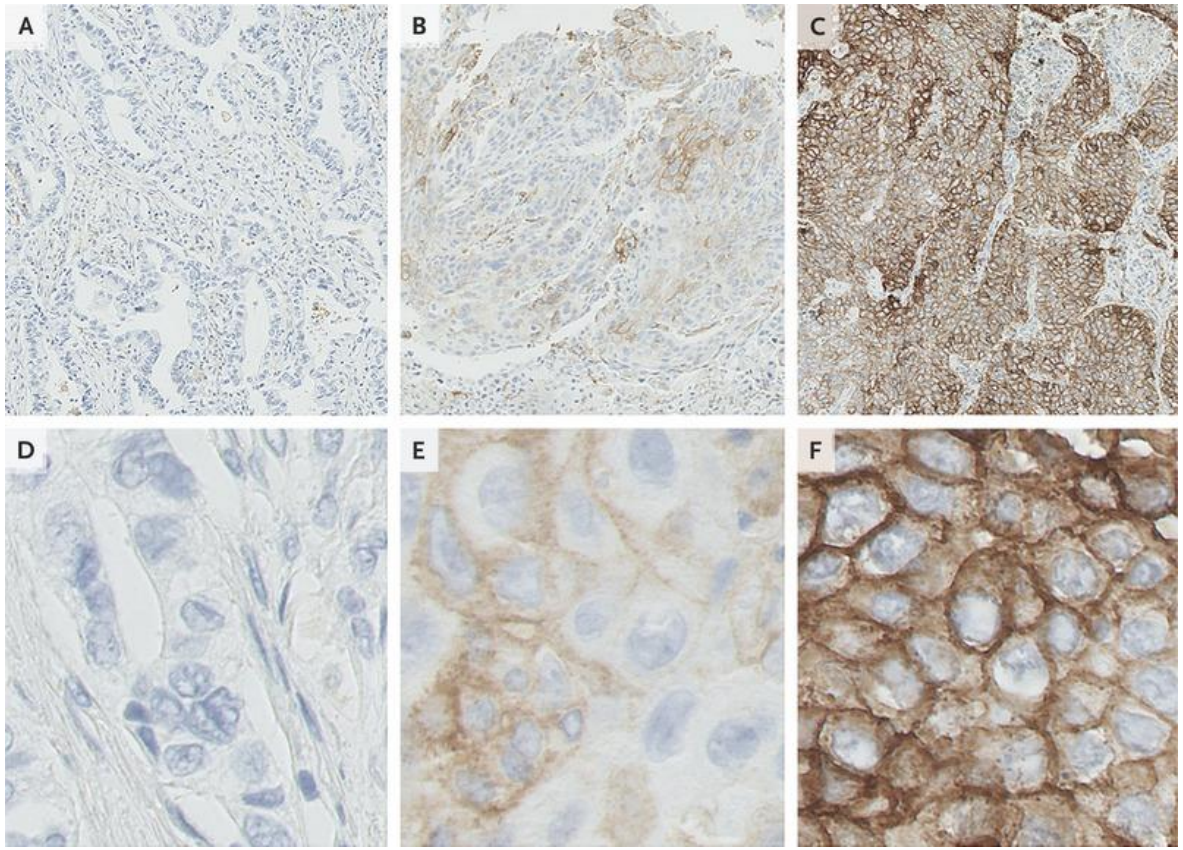
- **Durvalumab** (PD-L1) is FDA-approved following concurrent chemoradiation for locally advanced NSCLC (Feb 2018)

- PD-L1 testing is **not necessary**

PD-L1 staining of NSCLC with increasing levels of expression

PD-L1 IHC

- Percentage of neoplastic cells showing membranous staining of PD-L1 proportion score (PS)
- Need > 100 cancer cells in order to calculate PS

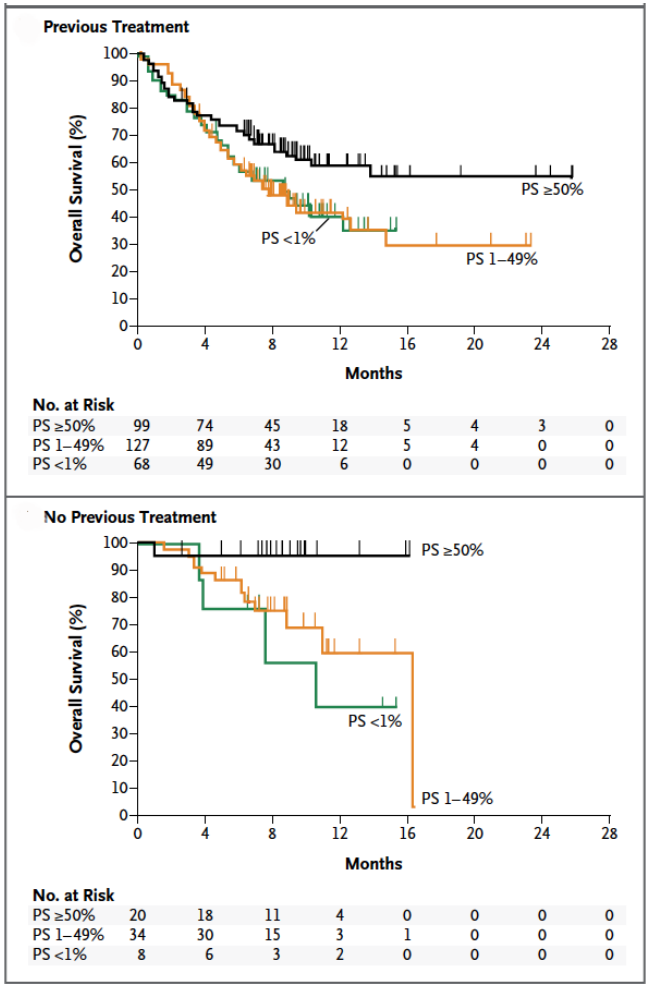


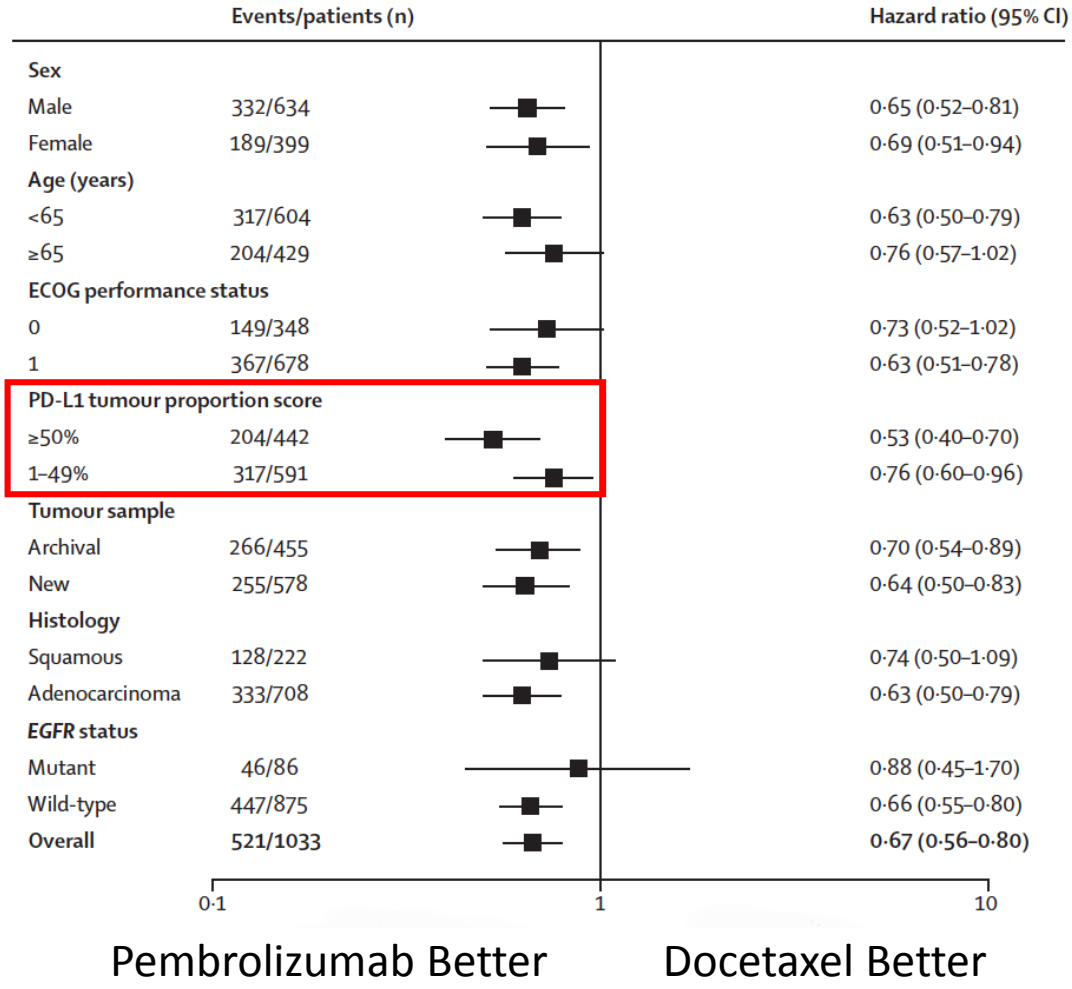
PS <1% PS 1-49% PS ≥50%

Garon EB et al, N Engl J Med 2015

PD-L1 and Outcomes – Pembrolizumab (22C3)

Overall Survival





Garon et al., NEJM, 2015; Herbst et al, Lancet 2015

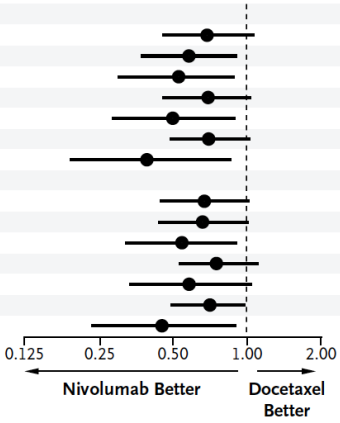
PD-L1 and Outcomes – Nivolumab (28-8)

2nd Line SCC

Brahmer et al., NEJM, 2015

Overall and Progression-free Survival According to PD-L1 Expression Level

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥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			
≥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)



1st Line NSCLC

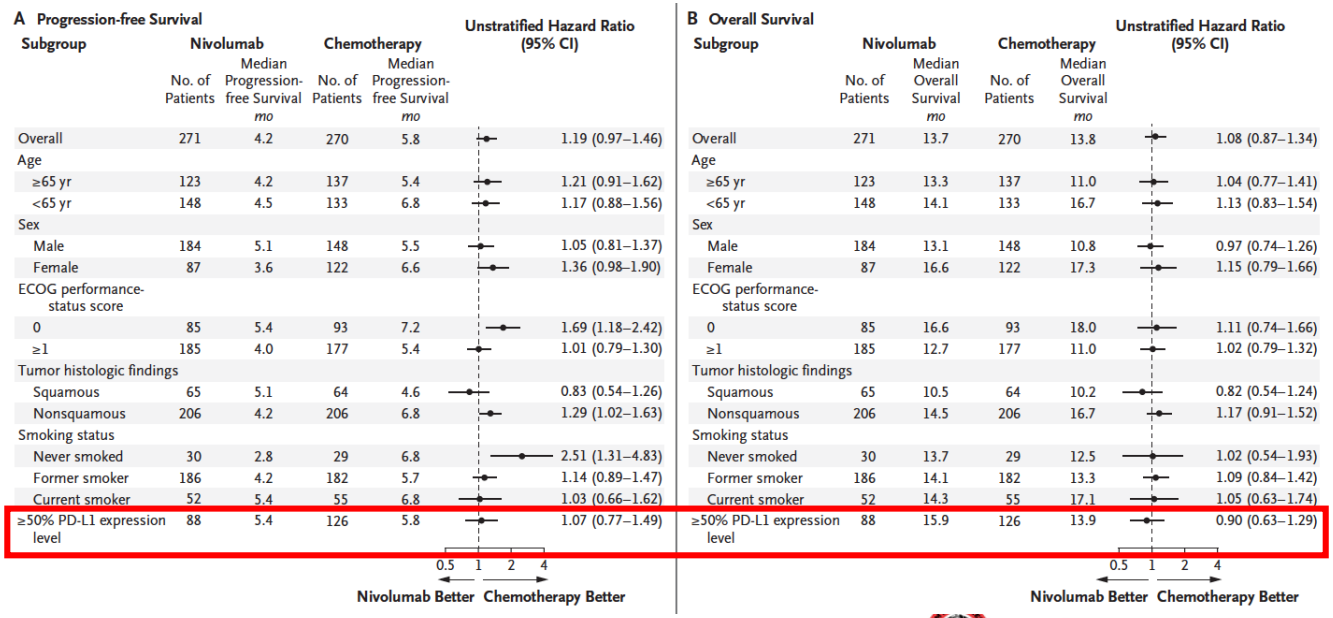
Carbone et al, NEJM 2017

A Progression-free Survival

Subgroup	Nivolumab No. of Patients	Nivolumab Median Progression-free Survival *mo*	Chemotherapy No. of Patients	Chemotherapy Median Progression-free Survival *mo*	Unstratified Hazard Ratio (95% CI)
Overall	271	4.2	270	5.8	1.19 (0.97–1.46)
Age					
≥65 yr	123	4.2	137	5.4	1.21 (0.91–1.62)
<65 yr	148	4.5	133	6.8	1.17 (0.88–1.56)
Sex					
Male	184	5.1	148	5.5	1.05 (0.81–1.37)
Female	87	3.6	122	6.6	1.36 (0.98–1.90)
ECOG performance-status score					
0	85	5.4	93	7.2	1.69 (1.18–2.42)
≥1	185	4.0	177	5.4	1.01 (0.79–1.30)
Tumor histologic findings					
Squamous	65	5.1	64	4.6	0.83 (0.54–1.26)
Nonsquamous	206	4.2	206	6.8	1.29 (1.02–1.63)
Smoking status					
Never smoked	30	2.8	29	6.8	2.51 (1.31–4.83)
Former smoker	186	4.2	182	5.7	1.14 (0.89–1.47)
Current smoker	52	5.4	55	6.8	1.03 (0.66–1.62)
≥50% PD-L1 expression level	88	5.4	126	5.8	1.07 (0.77–1.49)

B Overall Survival

Subgroup	Nivolumab No. of Patients	Nivolumab Median Overall Survival *mo*	Chemotherapy No. of Patients	Chemotherapy Median Overall Survival *mo*	Unstratified Hazard Ratio (95% CI)
Overall	271	13.7	270	13.8	1.08 (0.87–1.34)
Age					
≥65 yr	123	13.3	137	11.0	1.04 (0.77–1.41)
<65 yr	148	14.1	133	16.7	1.13 (0.83–1.54)
Sex					
Male	184	13.1	148	10.8	0.97 (0.74–1.26)
Female	87	16.6	122	17.3	1.15 (0.79–1.66)
ECOG performance-status score					
0	85	16.6	93	18.0	1.11 (0.74–1.66)
≥1	185	12.7	177	11.0	1.02 (0.79–1.32)
Tumor histologic findings					
Squamous	65	10.5	64	10.2	0.82 (0.54–1.24)
Nonsquamous	206	14.5	206	16.7	1.17 (0.91–1.52)
Smoking status					
Never smoked	30	13.7	29	12.5	1.02 (0.54–1.93)
Former smoker	186	14.1	182	13.3	1.09 (0.84–1.42)
Current smoker	52	14.3	55	17.1	1.05 (0.63–1.74)
≥50% PD-L1 expression level	88	15.9	126	13.9	0.90 (0.63–1.29)



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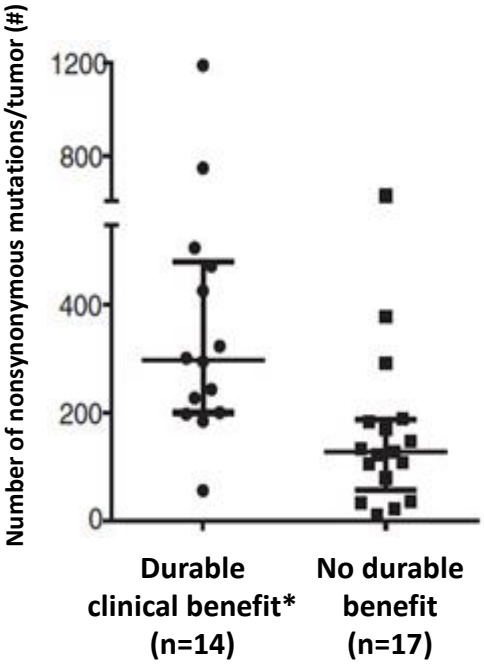
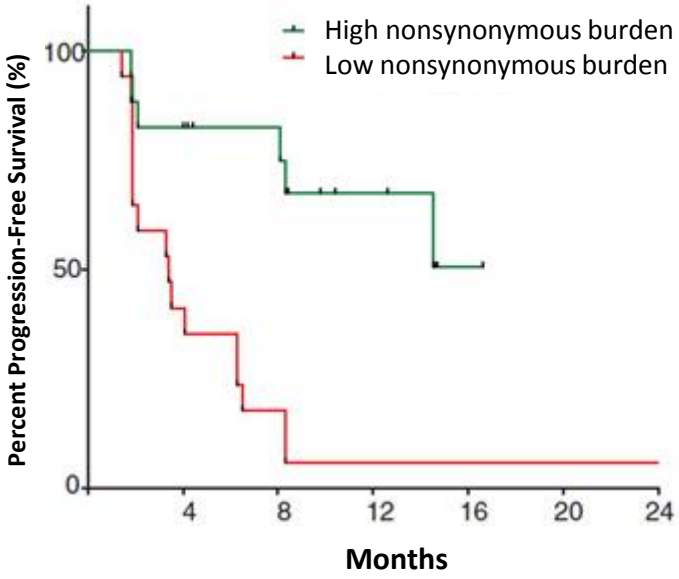
Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC

Data for All Sequenced Tumors



*Partial or stable response lasting > 6 mo



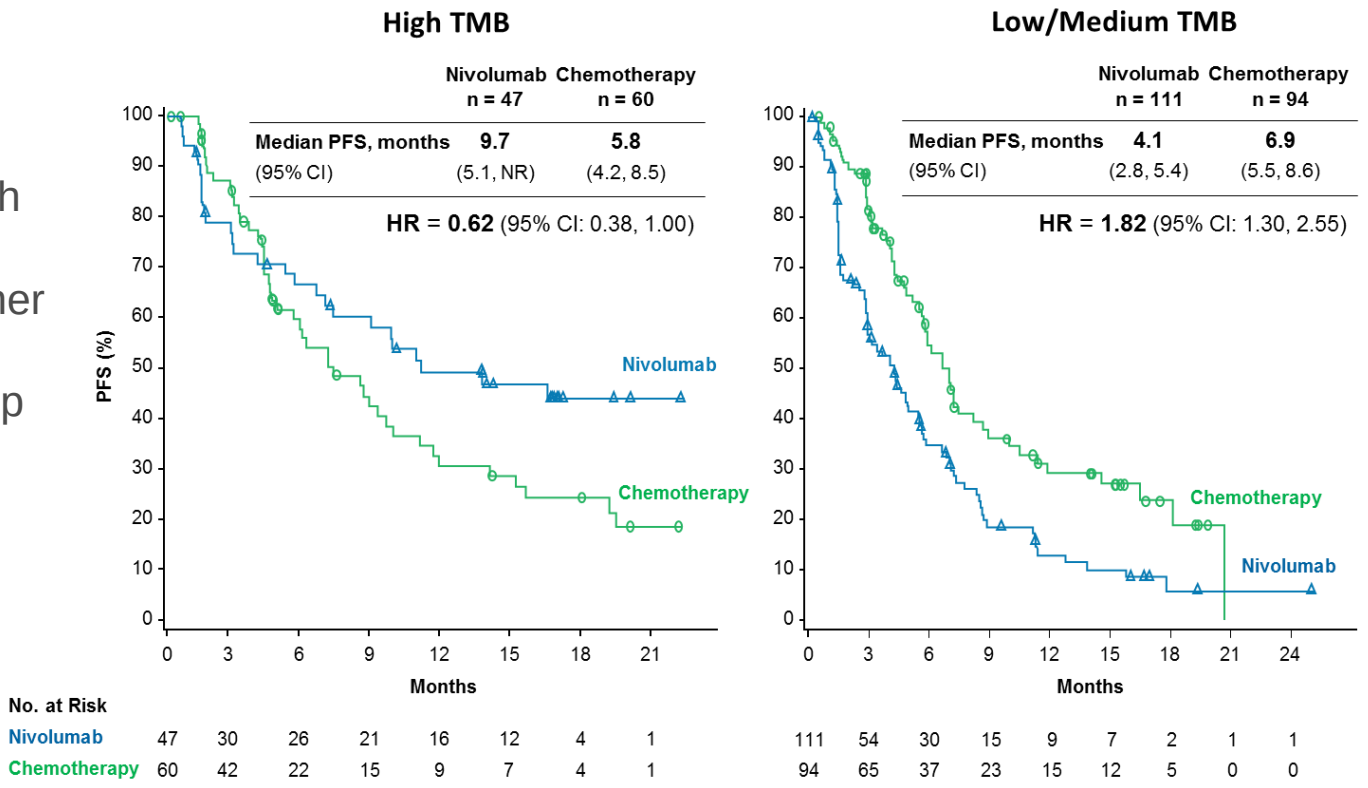
Rizvi N et al, Science, 2015

- Whole-exome sequencing of NSCLCs treated with pembrolizumab
- In two independent cohorts, higher nonsynonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit (left panel), and progression-free survival (right panel)

CheckMate 026 Subgroup: First-line Nivolumab versus chemotherapy in PD-L1 positive NSCLC (>1%)

Phase 3, Open label trial

Among the patients with a high TMB, the response rate was higher in the nivolumab group vs. chemotherapy group and progression-free survival was longer



Carbone et al., NEJM 2017

Immune Checkpoint Blockade Summary

Stage III

Durvalumab after chemoradiation

Stage IV

1st Line

- **Pembrolizumab**
  - if PD-L1 > 50%
  - EGFR/ALK/ROS1/ BRAF wild type
- **TKI**
  - if mutant EGFR/ ALK/ROS1/BRAF
- **Platinum Doublet Chemotherapy**
  - All others

2nd Line

- **Pembrolizumab**
- **Nivolumab**
- **Atezolizumab**
  - If pembroizumab not given in 1st line
  - PD-L1 status not necessary
- **Platinum Doublet Chemotherapy**
  - If pembroizumab or TKI given in 1st line

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Case Study: 1

Patient Background:

- 58-year-old female
- Never smoker with bilateral lung metastases
- Biopsy shows
  - adenocarcinoma,
  - EGFR mutation (L858R) and
  - PD-L1 is 90% positive (22C3 assay)

What do you recommend?

1. Erlotinib 150 mg po qd
2. Pembrolizumab
3. Pembrolizumab + pemetrexed and carboplatin combination

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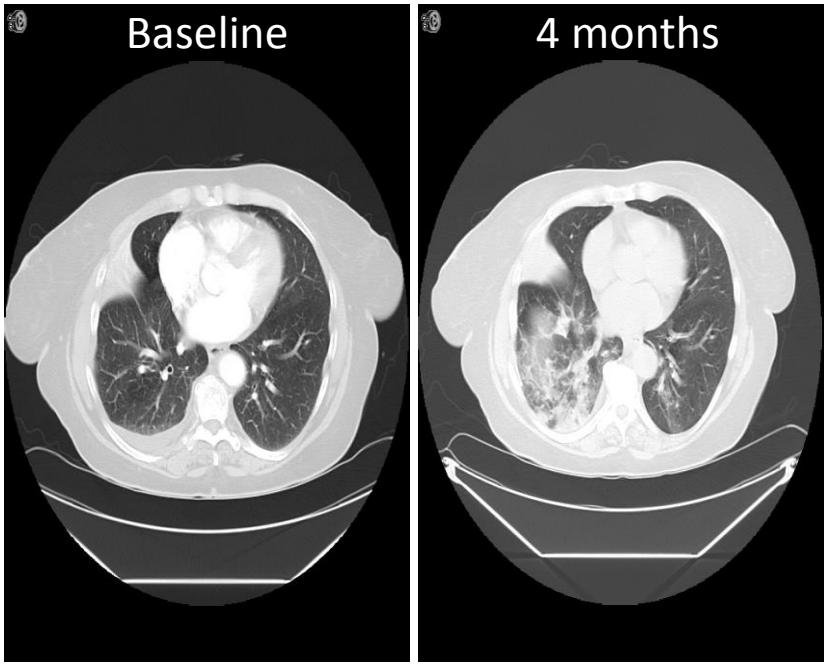
Case Study: 2

Patient Background

- 70-year-old female ex-smoker with NSCLC
- Treatment response to anti-PD-1 antibody presents with increasing cough, SOB and new decline in O2 sat to 82%.

What is your management recommendation ?

1. Continue anti-PD-1 antibody
2. Continue anti-PD-1 with dose reduction
3. Hold anti-PD-1 for 2 weeks
4. Discontinue anti-PD-1 and start prednisone 40 mg po qd
5. Discontinue anti-PD-1 and admit for IV steroids



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Thank you!

Questions?

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