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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
- I will not be discussing non-FDA approved indications during my presentation.

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Presentation Outline

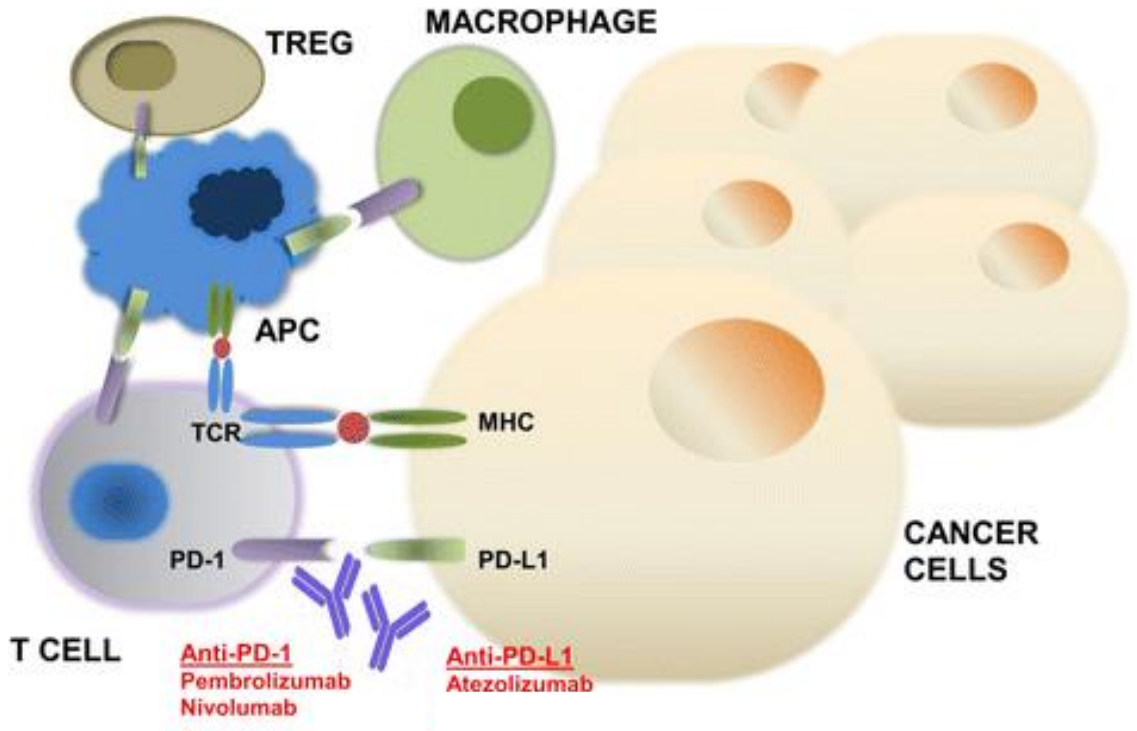
- Background: Checkpoint inhibitors for the treatment of lung cancer
- Overview of clinical trial results that lead to current FDA approval of immunotherapies for the treatment of advanced/refractory and advanced/treatment naïve NSCLC
- Ongoing study evaluating the role of immunotherapies for early-stage/locally advanced NSCLC
- Overview of clinical trial results evaluating immunotherapies for refractory SCLC
- Case studies

Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

Checkpoint inhibitors for the treatment of metastatic disease

- PD-1 acts as “off-switch” for T-Cells allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells



Gong J, Journal for ImmunoTherapy of Cancer, 2018

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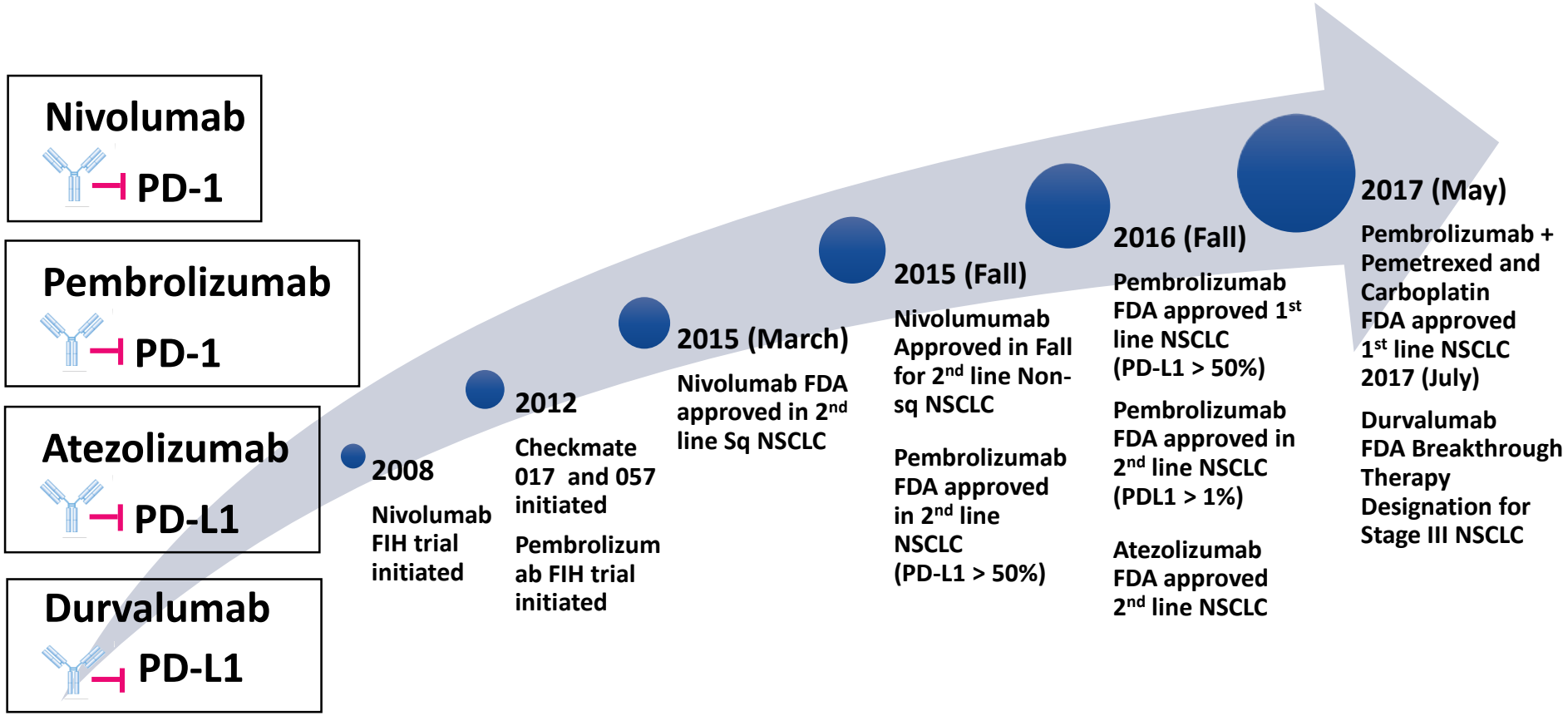
FDA-approved Checkpoint Inhibitors for use in NSCLC



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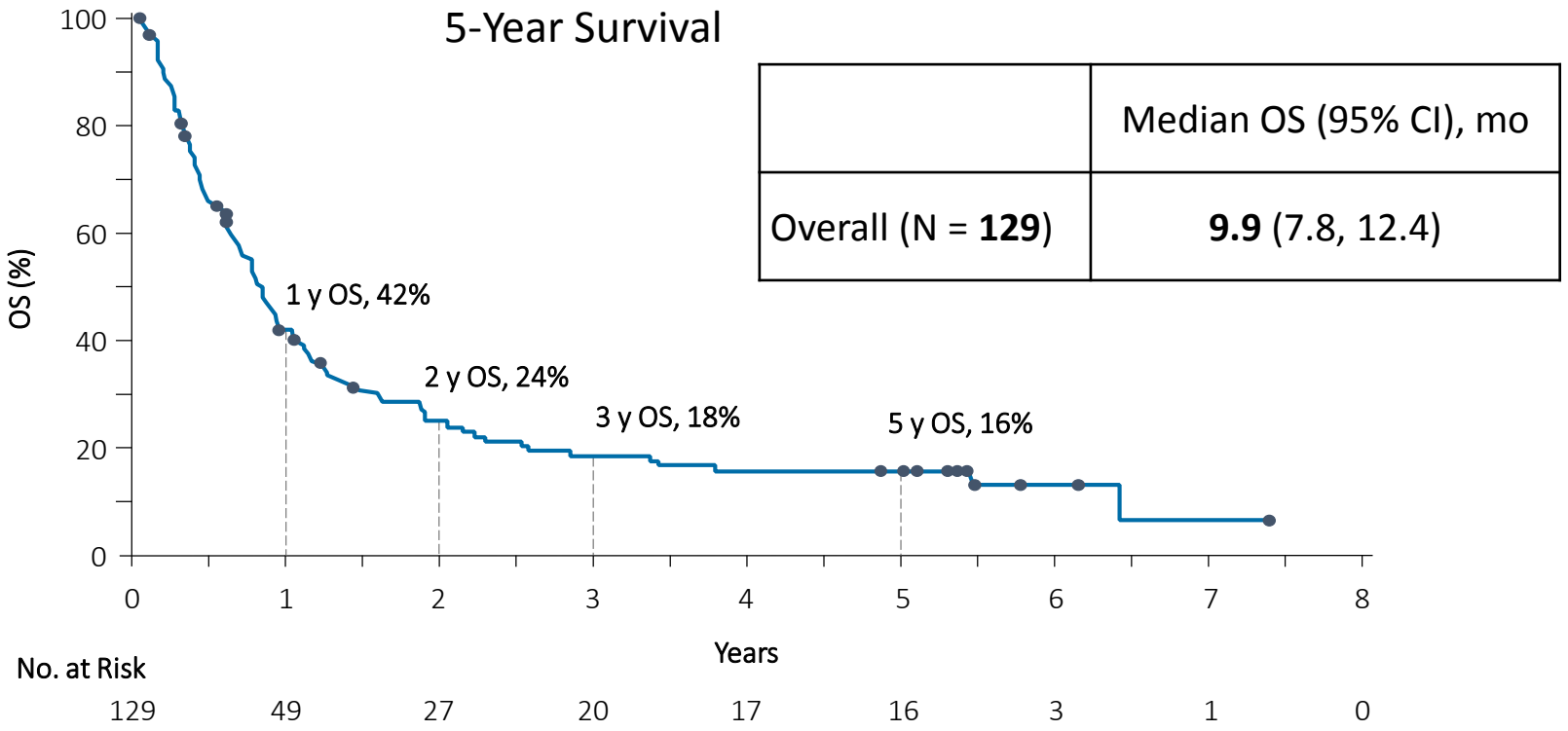
CA209-003: Nivolumab in Heavily Pretreated Advanced NSCLC (NCT00730639)

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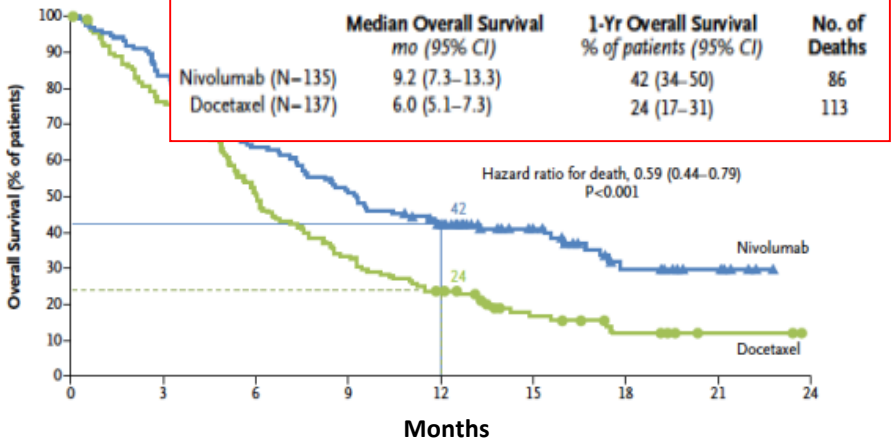
PD1/PD-L1 Inhibitors increase *Overall Survival* in 2L Advanced NSCLC

CHECKMATE 017 (squamous)

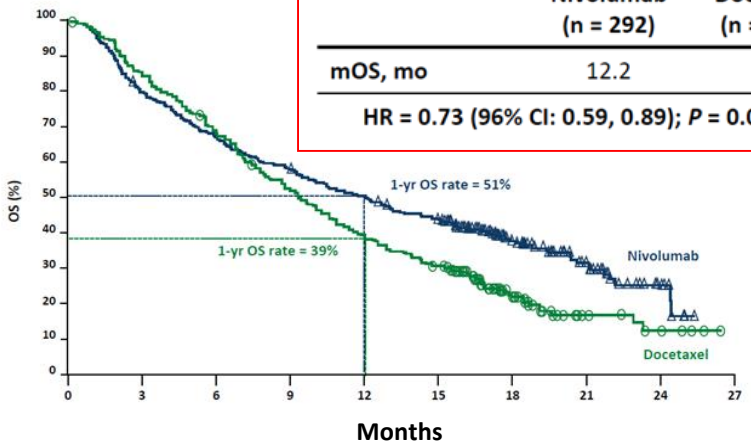
	Median Overall Survival *mo (95% CI)*	1-Yr Overall Survival *% of patients (95% CI)*	No. of Deaths
Nivolumab (N–135)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N–137)	6.0 (5.1–7.3)	24 (17–31)	113



CHECKMATE 057 (non-squamous)

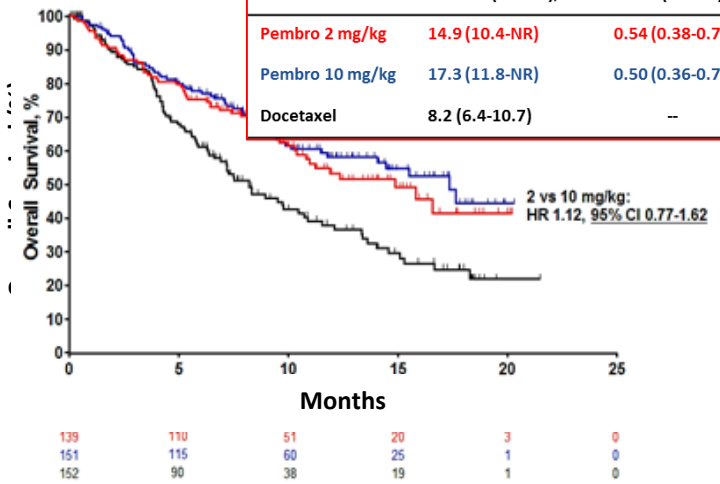
	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

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



KEYNOTE 010 (TPS ≥ 1%)

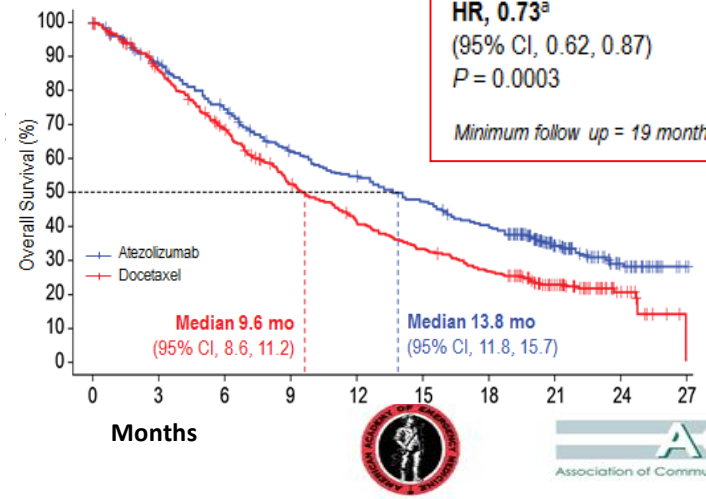
Treatment Arm	Median (95% CI), mo	HR* (95% CI)	P
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	--	--



OAK

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

Minimum follow up = 19 months



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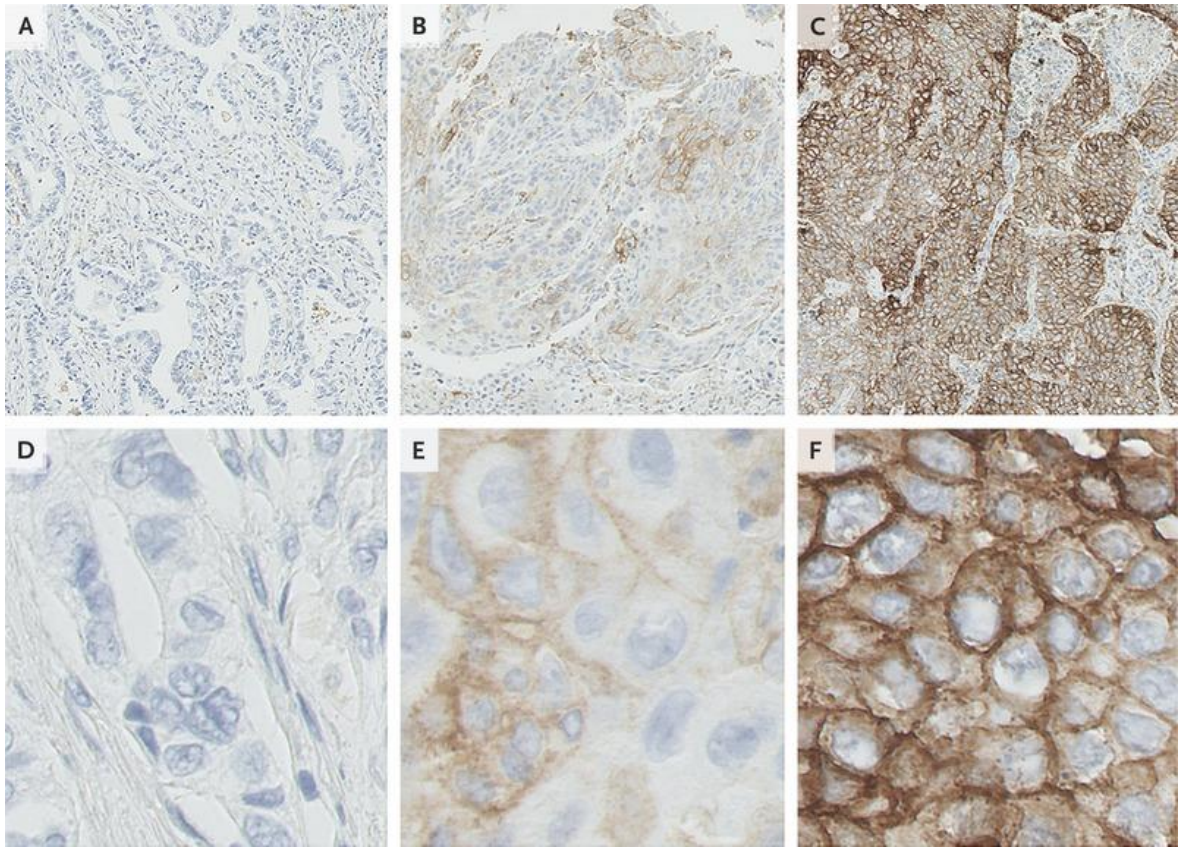
Brahmer NEJM 2015; Borghaei, NEJM 2015; Herbst Lancet 2016; Rittmeyer Lancet 2017

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%

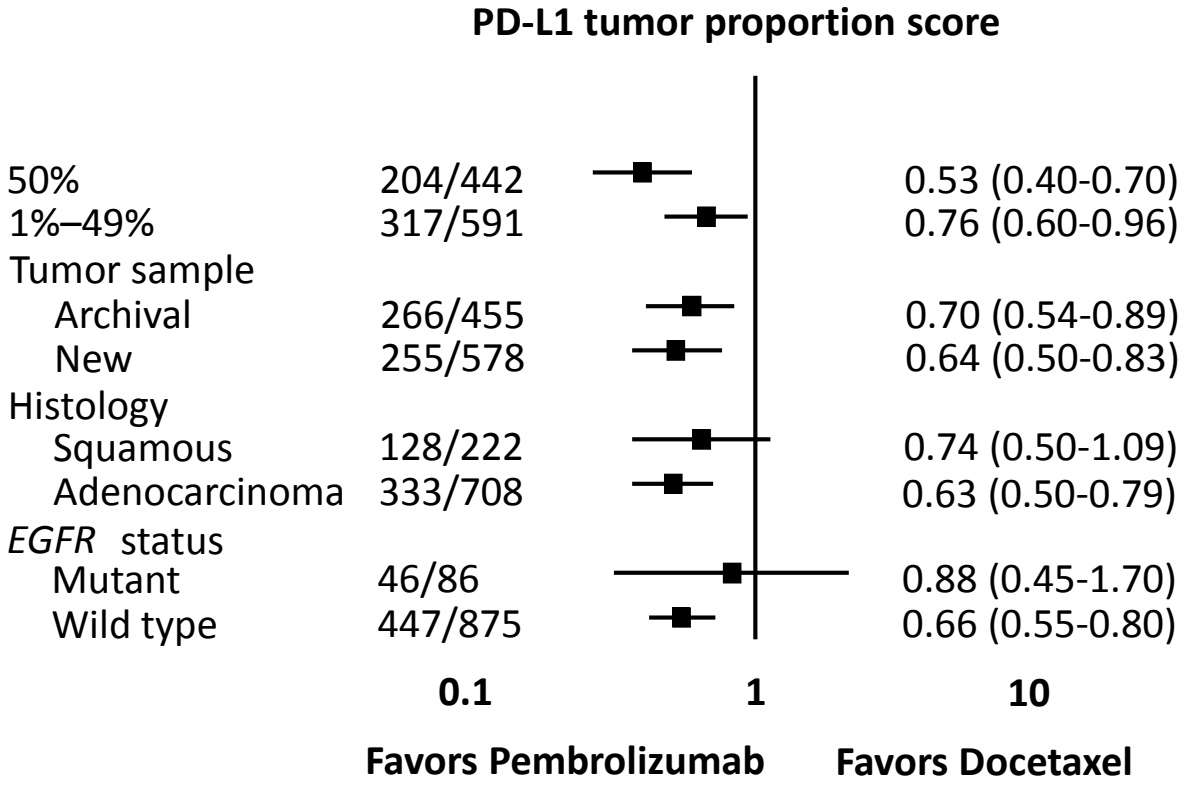
Garon EB et al, N Engl J Med 2015

KEYNOTE 010: Pembrolizumab versus Docetaxel for previously treated, PD-L1-positive, advanced NSCLC

Phase 2/3 randomized, controlled trial

Study Design

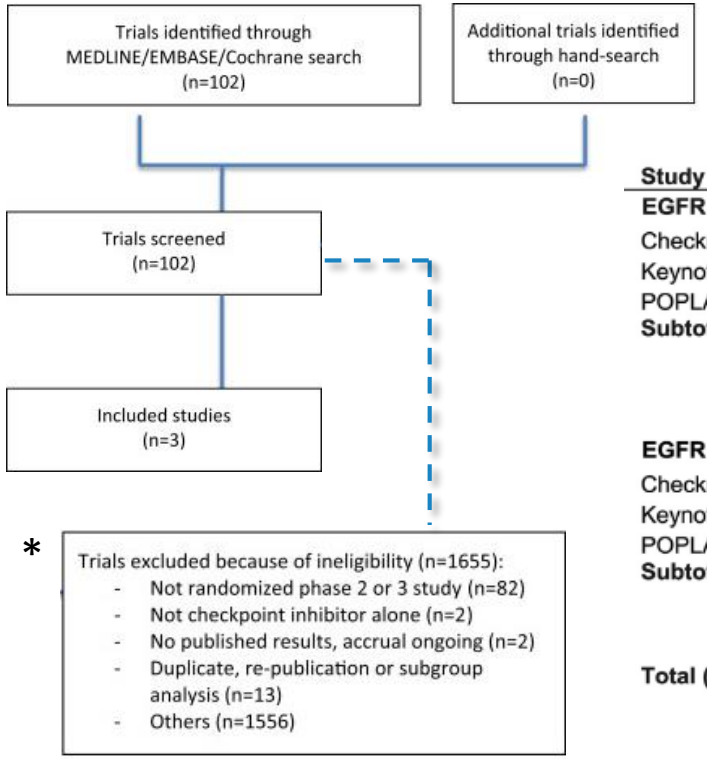
- Second-line in advanced NSCLC
- PD-L1 ≥1%
- Pembrolizumab 2mg/kg, 10mg/kg, or Docetaxel
- Primary endpoints: OS, PFS

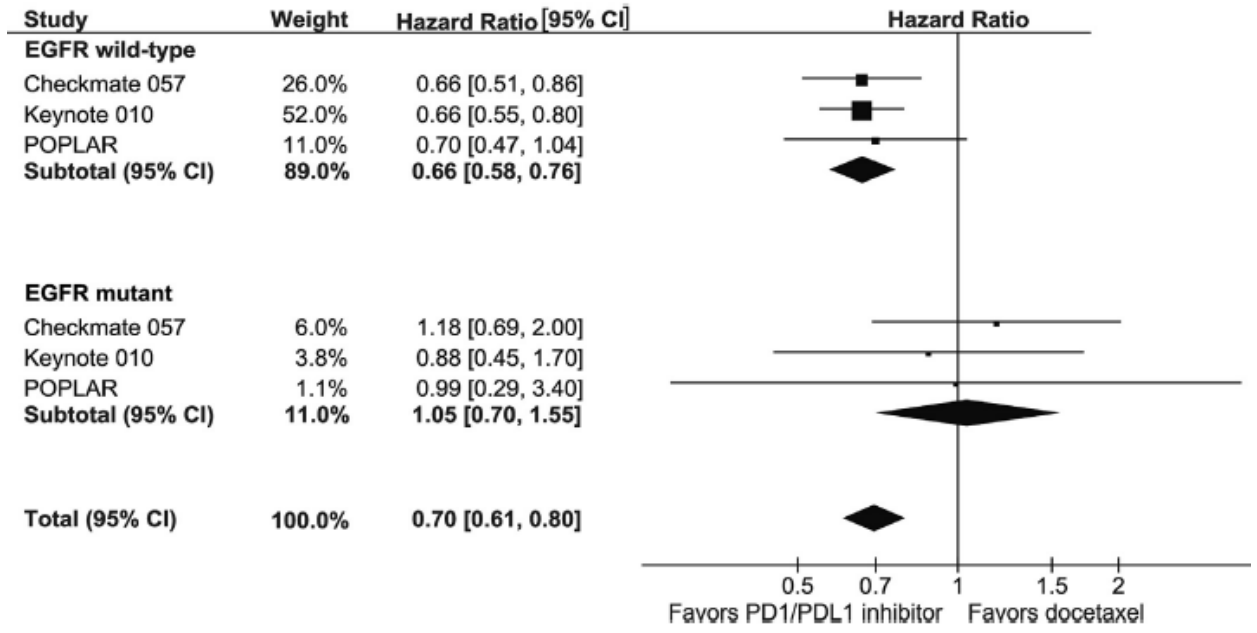


Herbst et al, Lancet 2015

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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





CK Lee et al., JTO 2016

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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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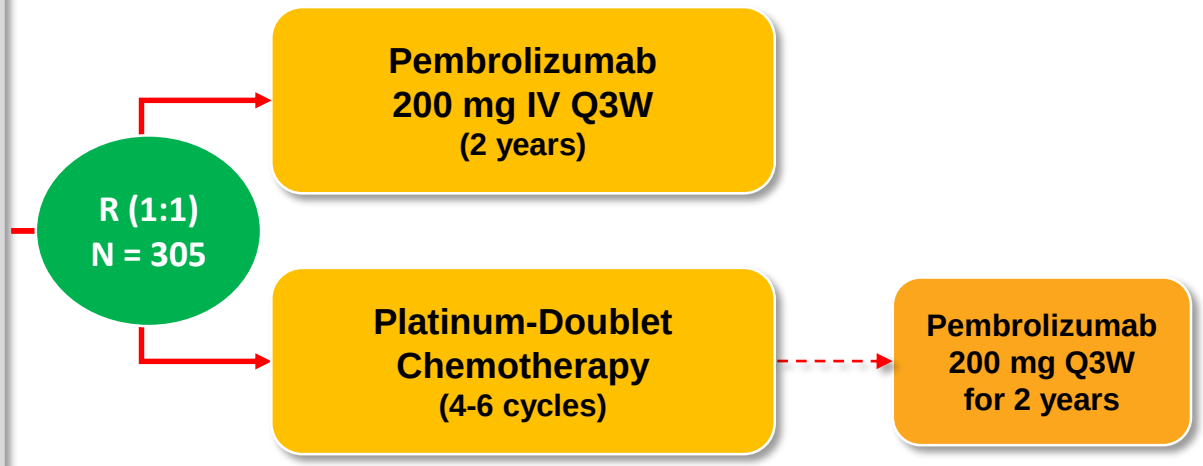
KEYNOTE-024: 1L Pembrolizumab versus Chemotherapy for PD-L1 High NSCLC

Study Design (NCT02142738)

Key Eligibility Criteria

- ***Untreated*** stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, Safety

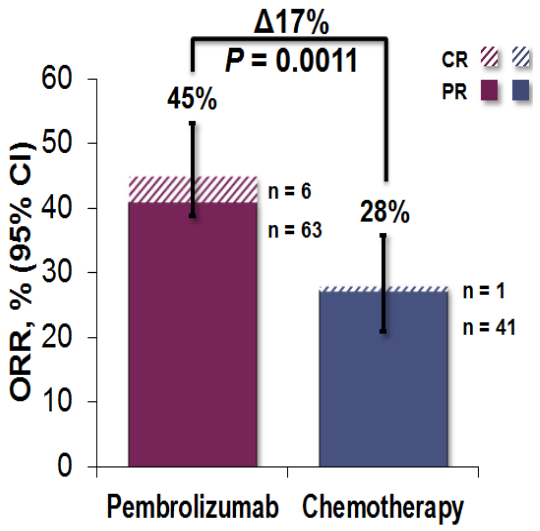
Exploratory: DOR

Reck M et al, ESMO 2016, NEJM 2016

KEYNOTE-024: 1L Pembrolizumab versus Chemotherapy for PD-L1 High NSCLC

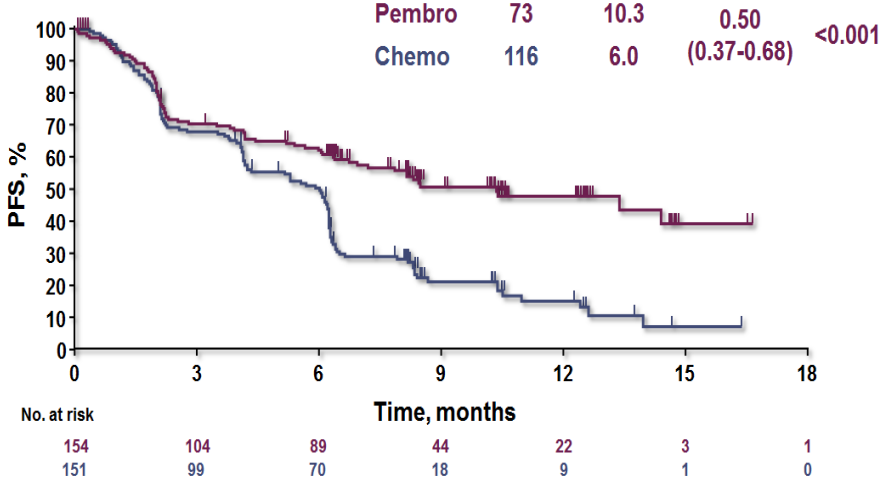
Efficacy

Objective Response Rate



Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



***Imaging every 9 weeks**

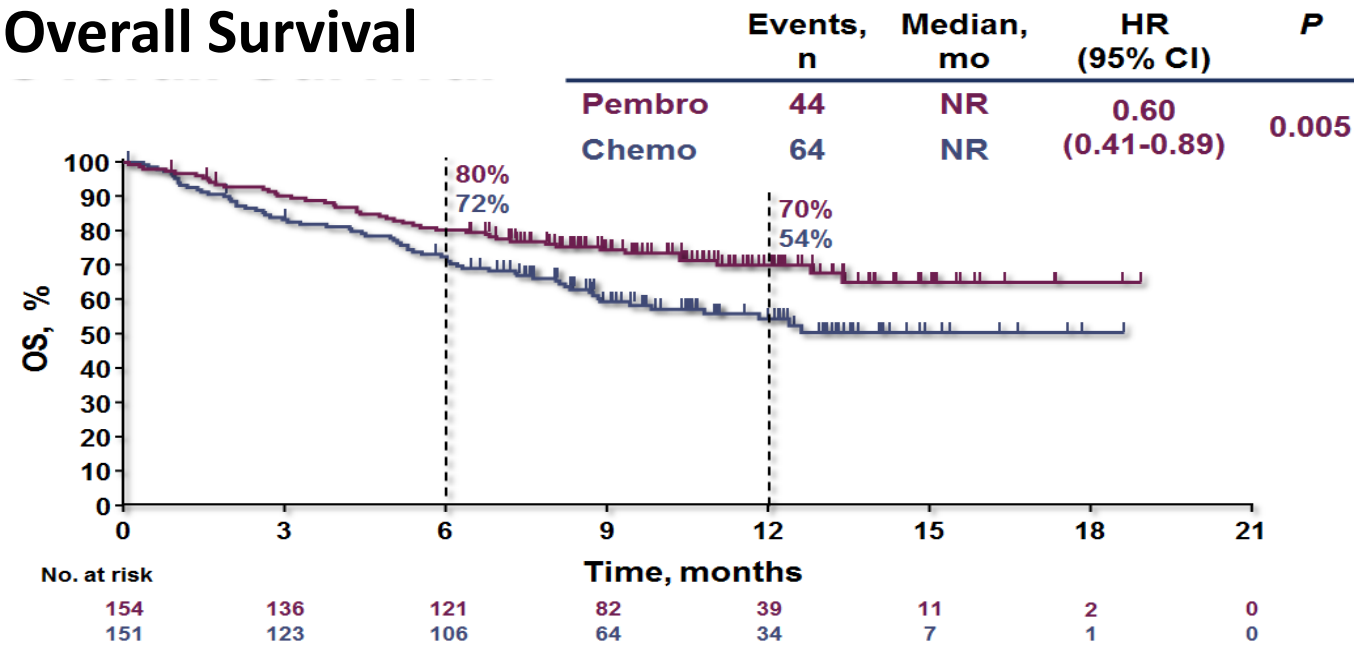
Reck M et al, ESMO 2016, NEJM 2016

Clear and strong signal of activity

- ORR is improved, control arm performs as expected (based on other phase III trials)
  - 45% ORR is the one of best RRs ever reported in 1st line setting (and with monotherapy!)
  - Time to Response: Pembrolizumab = Chemotherapy
- PFS is improved by 4.3 months (HR of 0.50)
  - Improvement of PFS in most subgroups (except female/never smokers - lower mutational load?)
  - Strongest signal of PFS observed in SqCC (HR: 0.35)

KEYNOTE-024: 1L Pembrolizumab versus Chemotherapy for PD-L1 High NSCLC

Overall Survival



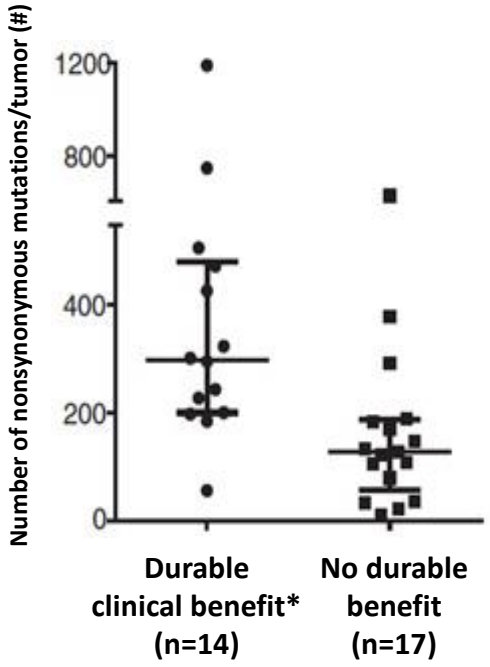
Reck M et al, ESMO 2016, NEJM 2016

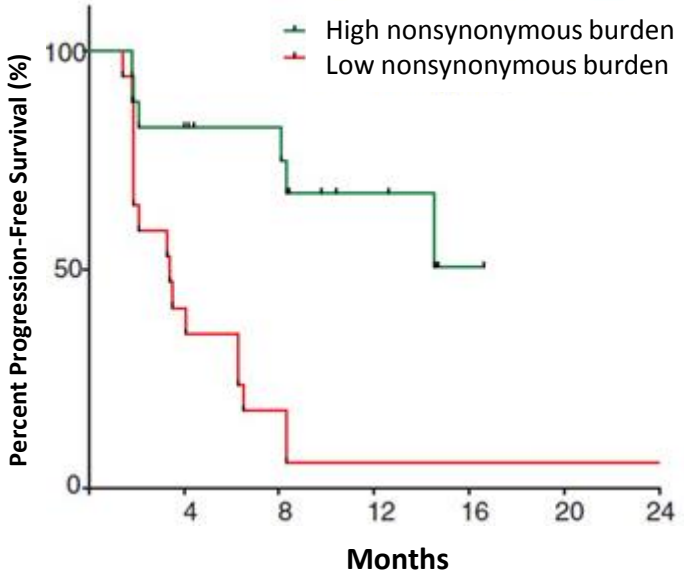
Survival benefit

- Estimated Overall Survival at 12 months: 70% (Pembrolizumab) vs 54% (Chemotherapy)
- Hazard Ratio for death: 0.60
- Significantly longer OS in Pembrolizumab group despite cross-over in 50% of patients in control arm (60% if you count crossover to any PD-1 inhibitor)
- Median OS not reached in either group

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)

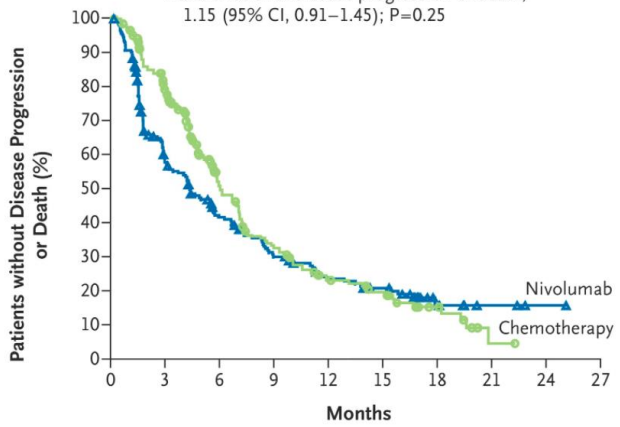
CHECKMATE-026: 1L Nivolumab versus Chemotherapy for PD-L1 Positive NSCLC

Survival

Progression-Free Survival

	Median Progression-free Survival (95% CI) *mo*	1-Yr Progression-free Survival Rate %
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25

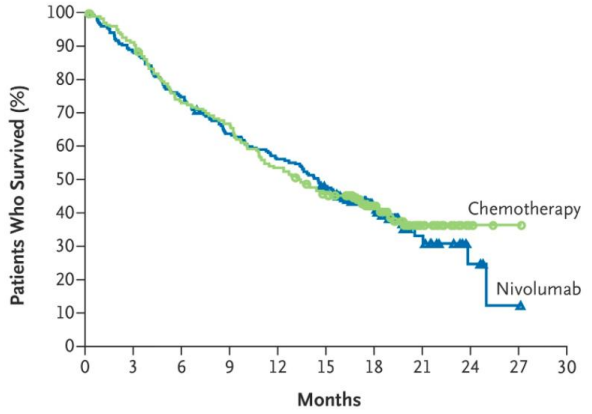


No. at Risk										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Overall Survival

	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate %
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



No. at Risk											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Carbone DP et al, NEJM 2017

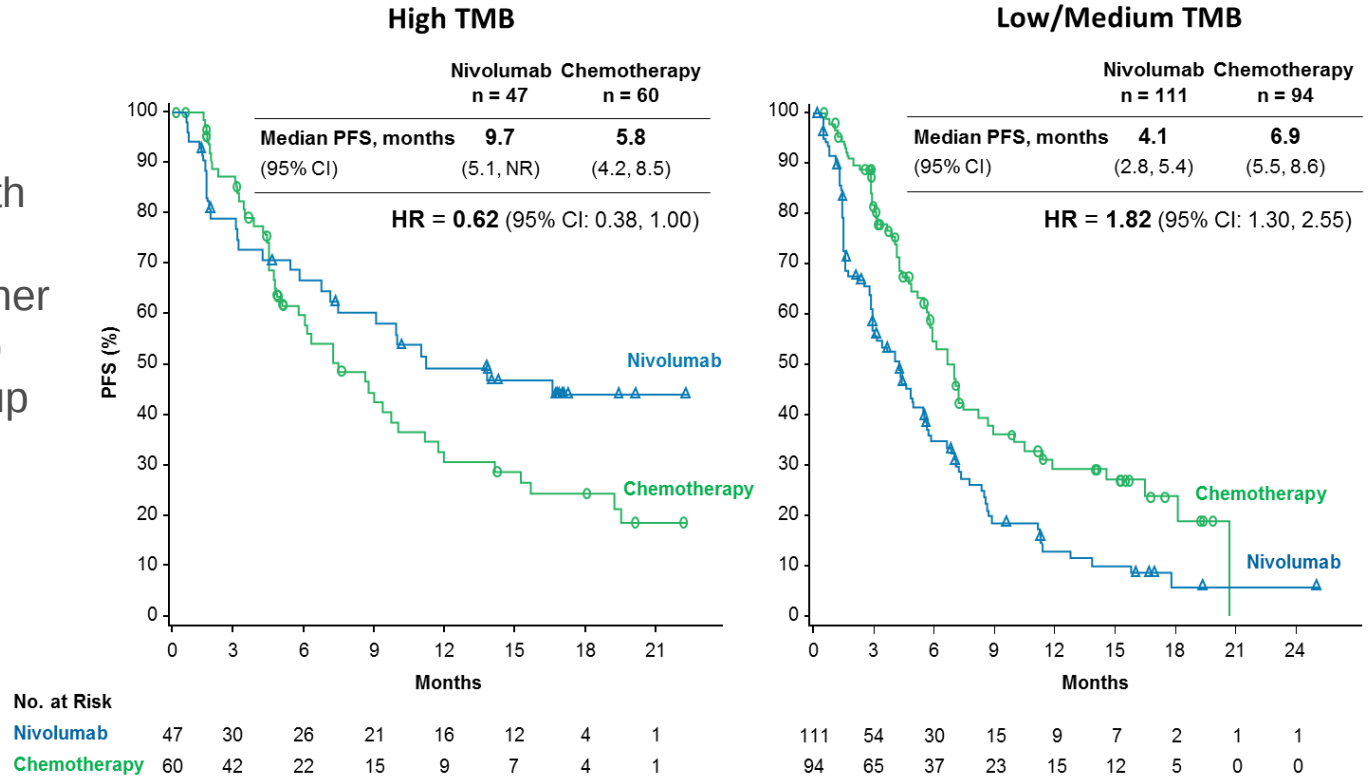
No survival benefit

- 423 patients with PD-L1-positive (≥5% by 28-8 clone)
- Higher proportion of PD-L1 >50% in chemo arm (74.1%) compared to nivo arm (53.2%)
- Fewer never smokers in KEYNOTE-024 (3%) vs. CHECKMATE-026 (11%)
- Subgroup analysis of PD-L1>50% patients also showed no benefit of nivolumab (HR 0.90, 95% CI 0.63-1.29

CheckMate 026 Subgroup: First-line Nivolumab versus chemotherapy in PD-L1 positive NSCLC

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



Peters, et al., AACR 2017

KEYNOTE 021G: Front-line Carboplatin and Pemetrexed +/- Pembrolizumab for Adv. Non-squamous NSCLC

Phase 2 Cohort G, Randomized, Open-label

Key Eligibility Criteria

- ***Untreated*** stage IIIB or IV nonsquamous NSCLC
- No activating EGFR mutation/ALK translocation
- Provision of a sample for PD-L1 assessment[a]
- ECOG PS 0-1
- No untreated brain mets
- No ILD or pneumonitis requiring systemic steroids

R (1:1)[a]
N = 123

Pembrolizumab 200 mg Q3W for 2 years
+
Carboplatin AUC 5 mg/mL/min
+ **Pemetrexed** 500 mg/m2 Q3W for 4 cycles[b]

Carboplatin AUC 5 mg/mL/min
+ **Pemetrexed** 500 mg/m2 Q3W for 4 cycles[b]

PD

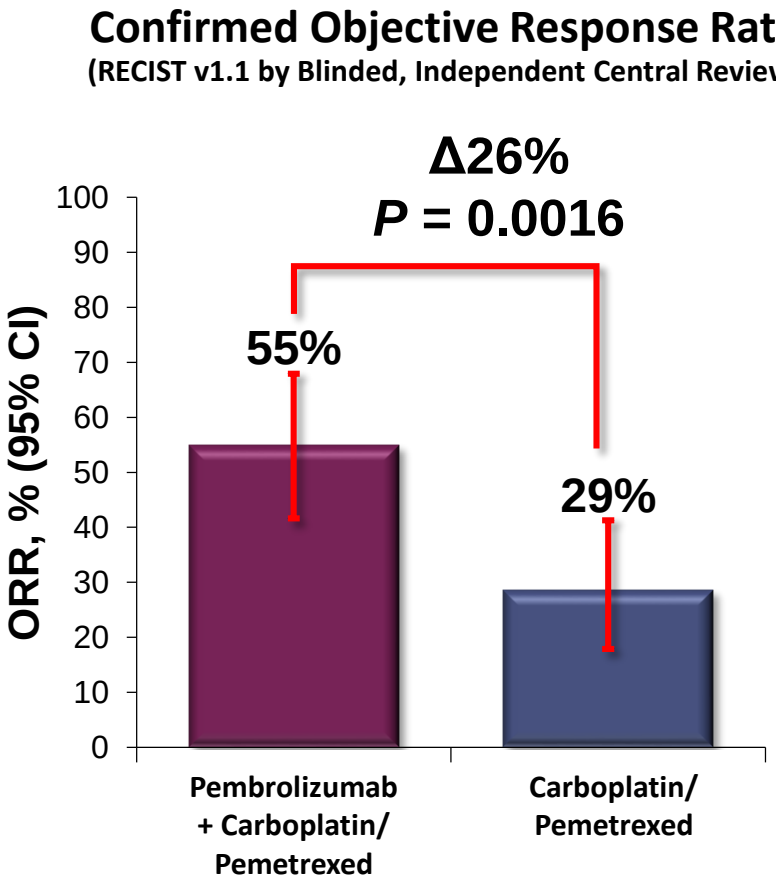
Pembrolizumab 200 mg Q3W for 2 years

Langer, et al Lancet Oncology 2016

Primary Endpoints: ORR (RECIST v1.1 per blinded, independent central review)
Secondary Endpoints: PFS, OS, safety, relationship between antitumor activity and PD-L1 TPS

KEYNOTE 021G: Carboplatin and Pemetrexed +/- Pembrolizumab for adv. NSCLC

Confirmed Objective Response Rate



Data cut-off: August 8, 2016

	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

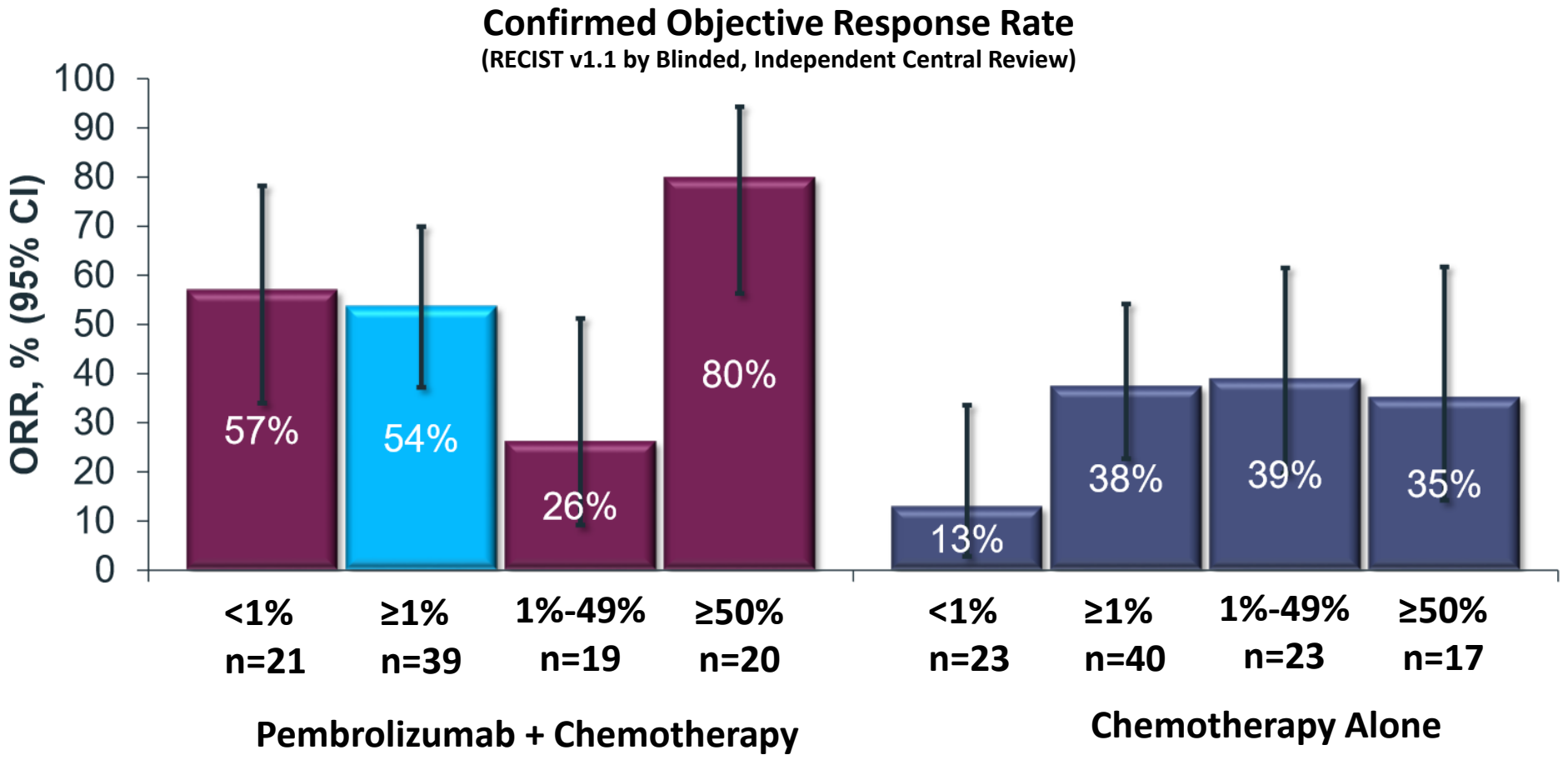
DOR = duration of response; TTR = time to response

[a]Alive without subsequent disease progression

Langer, et al Lancet Oncology 2016

KEYNOTE 021G: Carboplatin and Pemetrexed +/- Pembrolizumab for adv. NSCLC

Confirmed Objective Response Rate

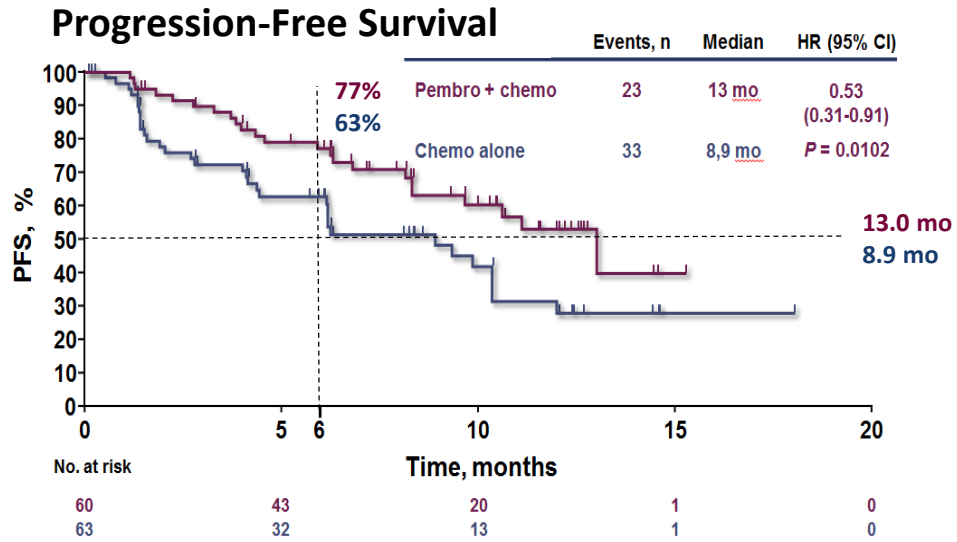


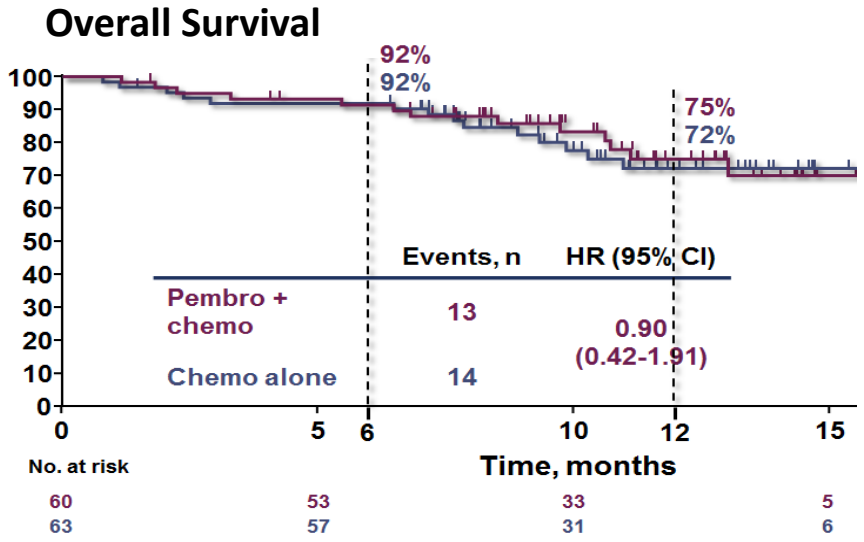
Langer, et al Lancet Oncology 2016

Data cut-off: August 8, 2016

KEYNOTE 021G: Carboplatin and Pemetrexed +/- Pembrolizumab for adv. NSCLC

Progression Free and Overall Survival





Langer, et al Lancet Oncology 2016
Borghaei, ESMO 2017

Clear PFS benefit; No OS advantage

- 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 (95% CI, 7%–41%; 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

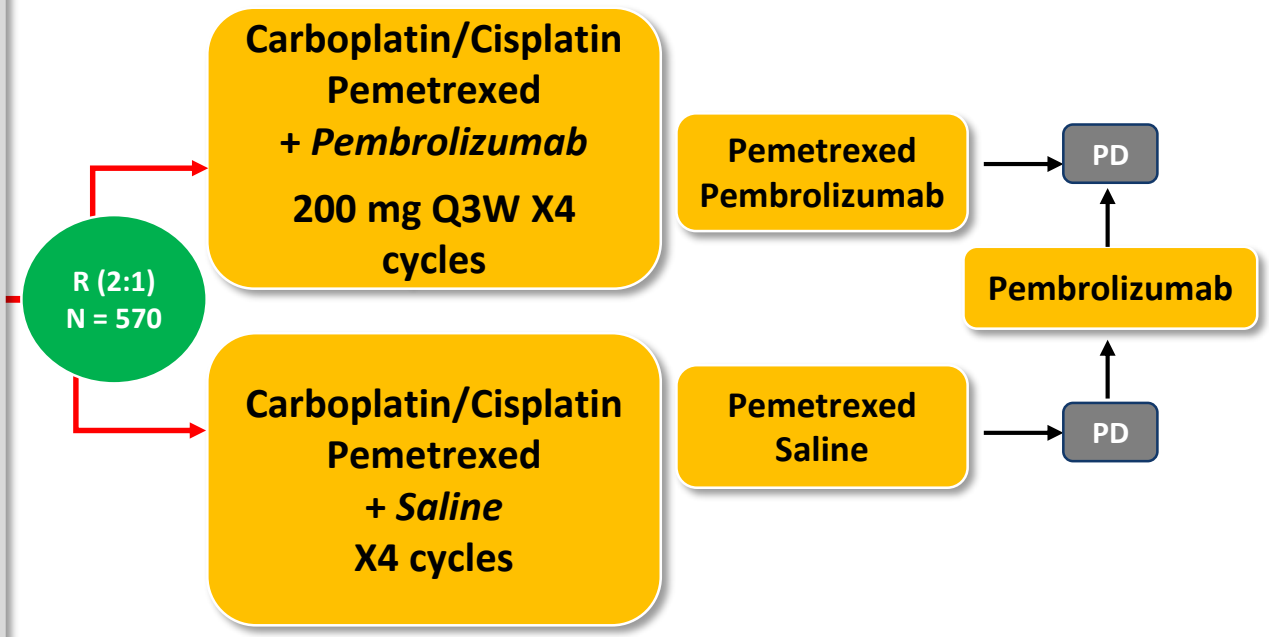
Phase 3 Safety and Efficacy study design

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

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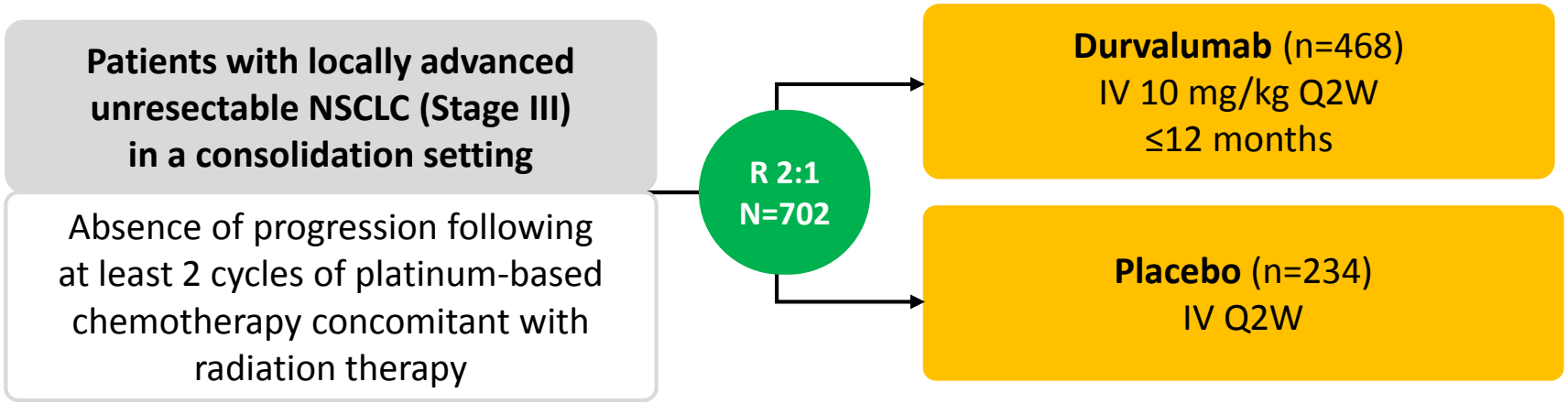
PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

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.

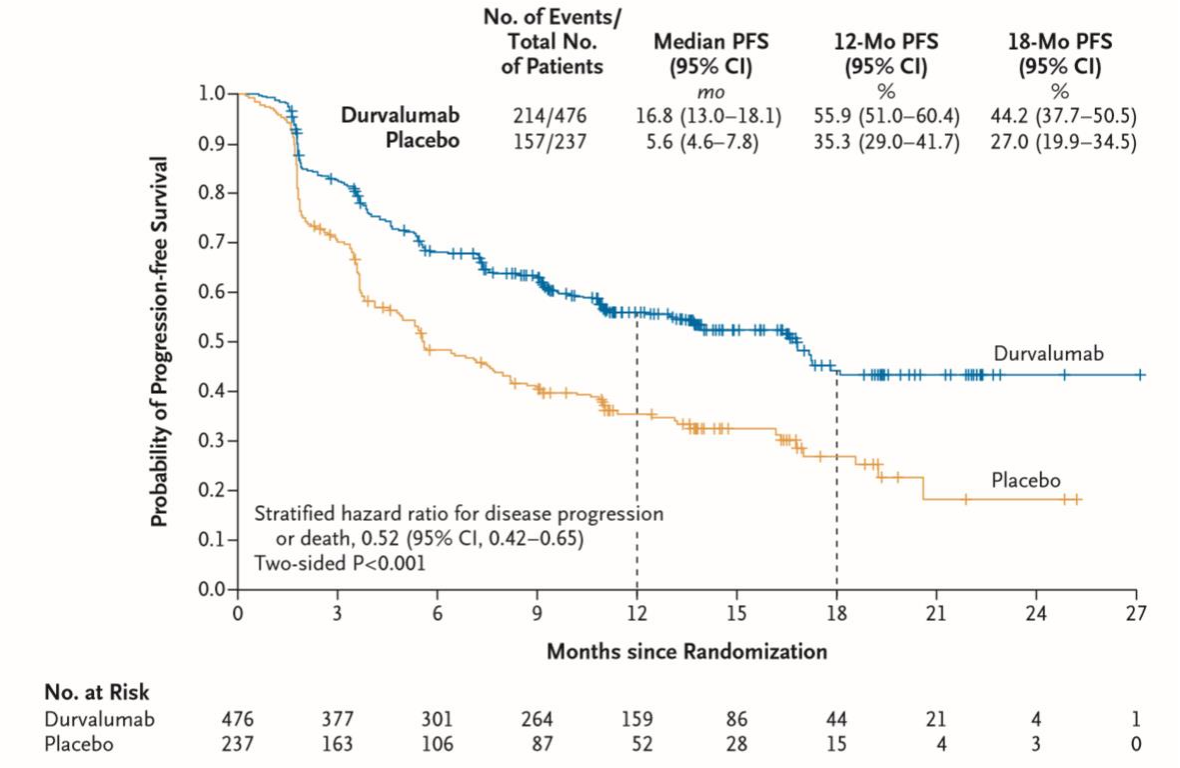
Primary endpoints: PFS, OS

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

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.

PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

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



Antonia et al., NEJM 2017

<u>Any Grade 3/4 AE:</u>
Durvalumab: 29.9%
Placebo: 26.1%

Grade 3/4
<u>Pneumonitis:</u>
Durvalumab: 3.4%
Placebo: 2.6%

Results: Durvalumab after chemoradiotherapy improved PFS (16.8 months) compared to Placebo (5.6 months) (HR 0.52, 95% CI, 0.42-0.65, p<0.001)

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

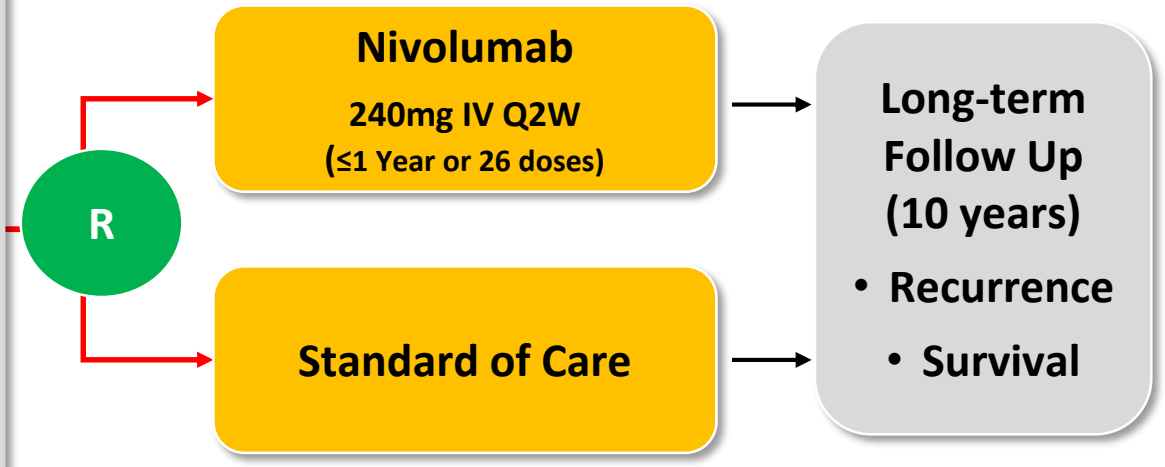
Study Design – ALCHEMIST Screening (NCT02194738)

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

CheckMate 032: Nivolumab +/- Ipilumumab in Recurrent Small Cell Lung Cancer (SCLC)

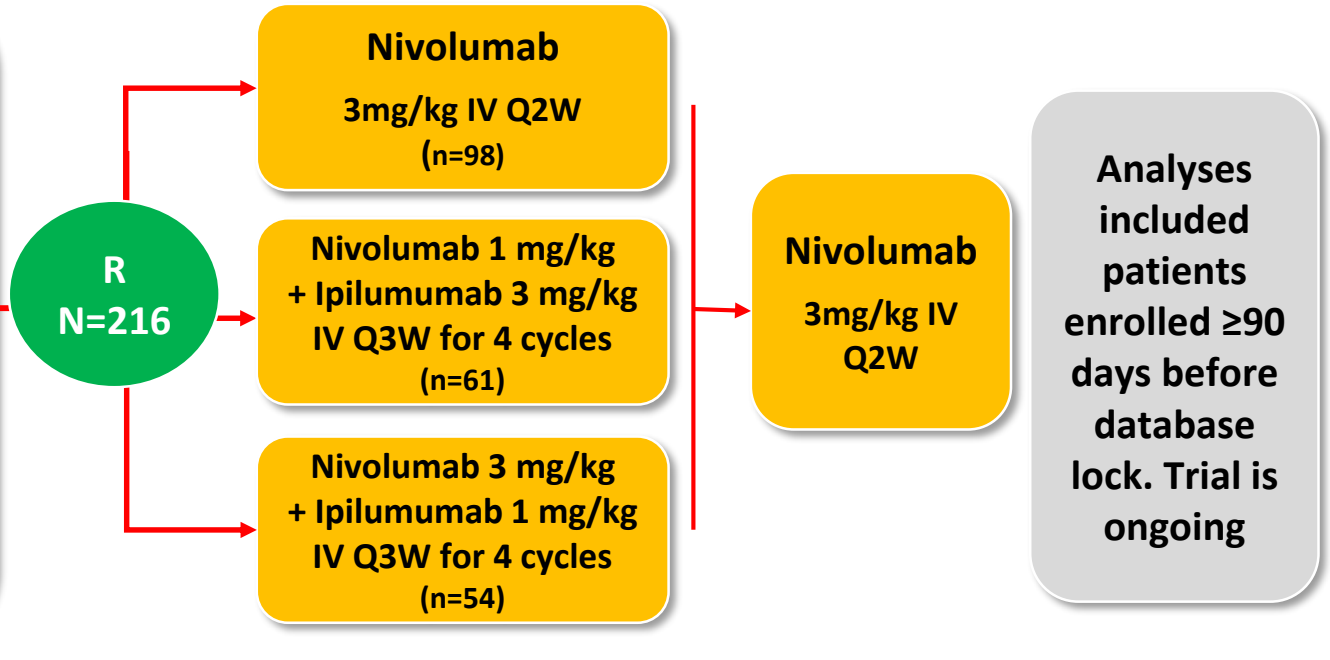
Phase 1/2 Study Design

Key Eligibility Criteria

- SCLC with progressive disease after ≥1 prior line of therapy
- Including first-line platinum based regimen

Stratification

- Unselected by PD-L1 expression



Antonia S. et al. ASCO Annual Meeting 2016, Lancet Oncology 2016

Primary endpoint: ORR

Secondary endpoints: Safety, OS, PFS, biomarkers

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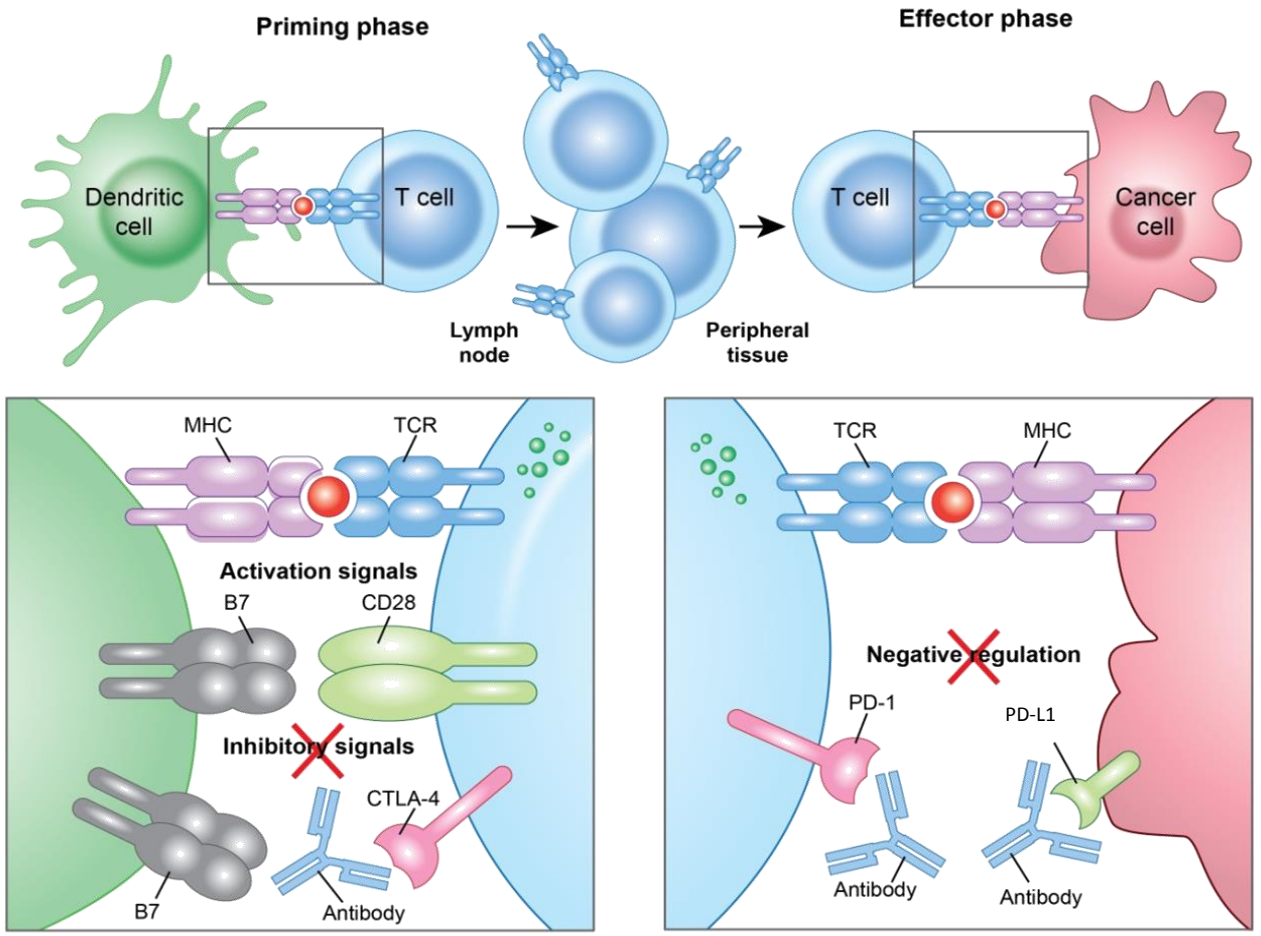
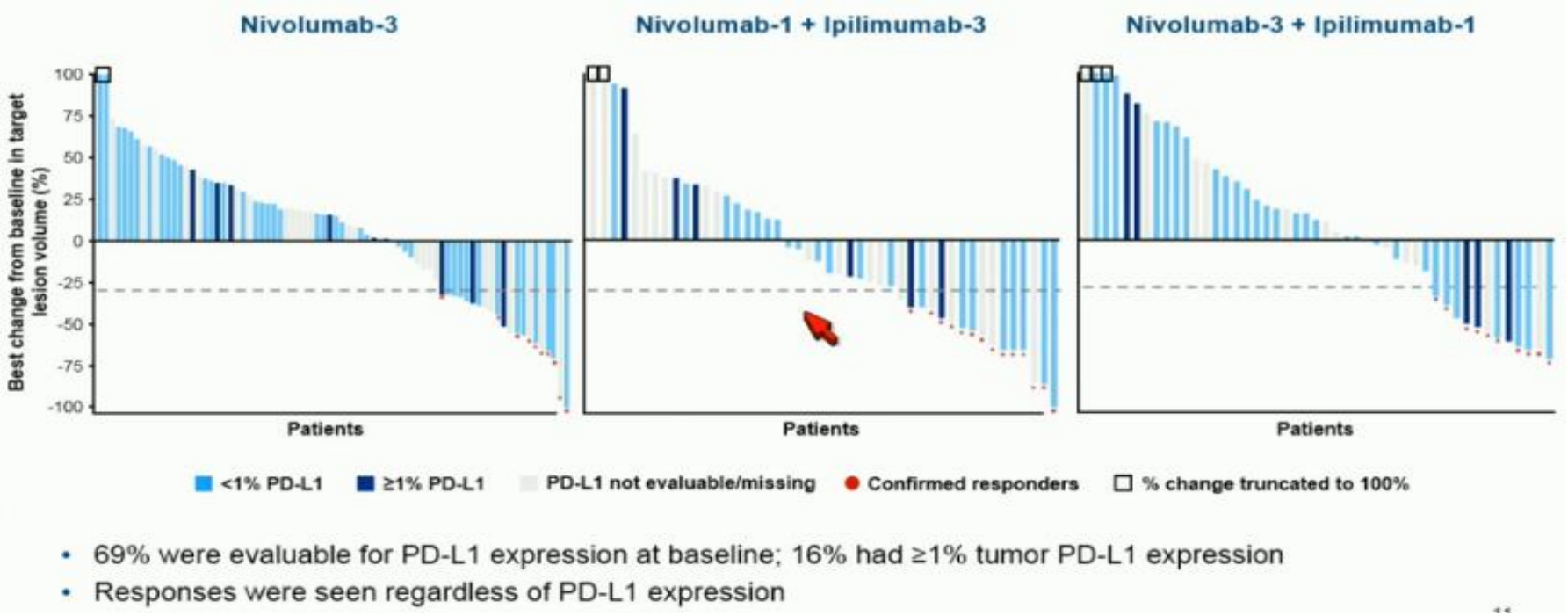
Combination Immune checkpoint blockade



Ribas A, NEJM, 2012

CheckMate 032: Nivolumab +/- Ipilumumab in Recurrent SCLC

Tumor Responses by PDL-1 Expression



Objective Response Rate (ORR)

- 10% nivolumab 3 mg/kg
- 23% nivolumab 1 mg/kg plus ipilimumab 3 mg/kg
- 19% nivolumab 3 mg/kg plus ipilimumab 1 mg/kg

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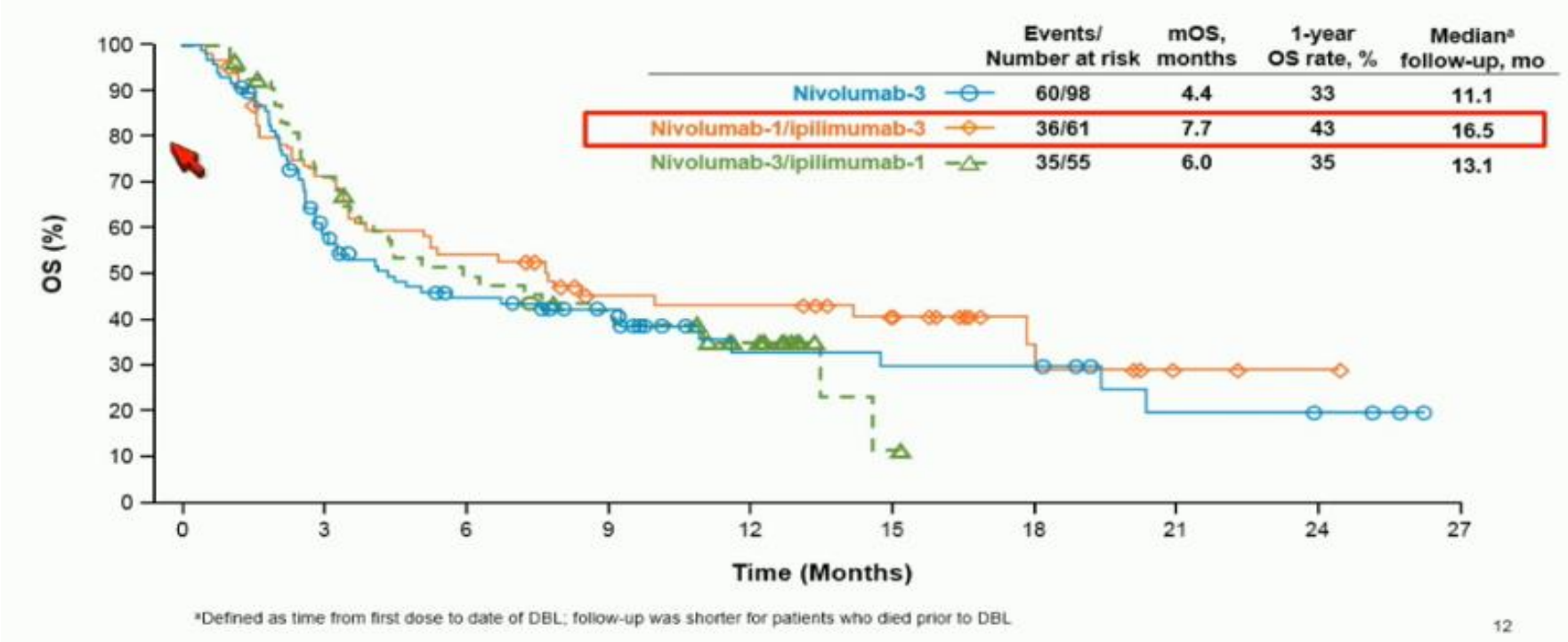
CheckMate 032: Nivolumab +/- Ipilumumab in Recurrent SCLC

N-1/I-3 Prolongs OS



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TMB: A Potential Biomarker of Response to Combined IO Agents in SCLC Patients

- Association of high TMB and clinical benefit from N ± I in patients with SCLC was evaluated in an exploratory analysis of CheckMate 032 (NCT01928394)
  - Patients were equally divided into TMB tertiles (low, medium, and high).
- In TMB-evaluable patients treated with nivolumab (n=133), ORR, PFS, and OS improved in the high TMB cohort vs the medium and low TMB cohorts
  - ORR: 21.3% vs 6.8% and 4.8%;
  - 1-year PFS: 21.2% vs 3.1% and not calculable;
  - 1-year OS: 35.2% vs 26.0% and 22.1%.
- Similar benefits were seen in TMB-evaluable patients treated with N+I (n=78) in the high vs medium and low TMB cohorts:
  - ORR: 46.2% vs 16.0% and 22.2%;
  - 1-year PFS: 30.0% vs 8.0% and 6.2%;
  - 1-year OS 62.4% vs 19.6% and 23.4%

Rizvi N et al. 2017 WCLC

*Tumor Mutational Burden

- Total number of nonsynonymous somatic mutations
- 211 (53% of ITT population) had an evaluable TMB result for these analyses

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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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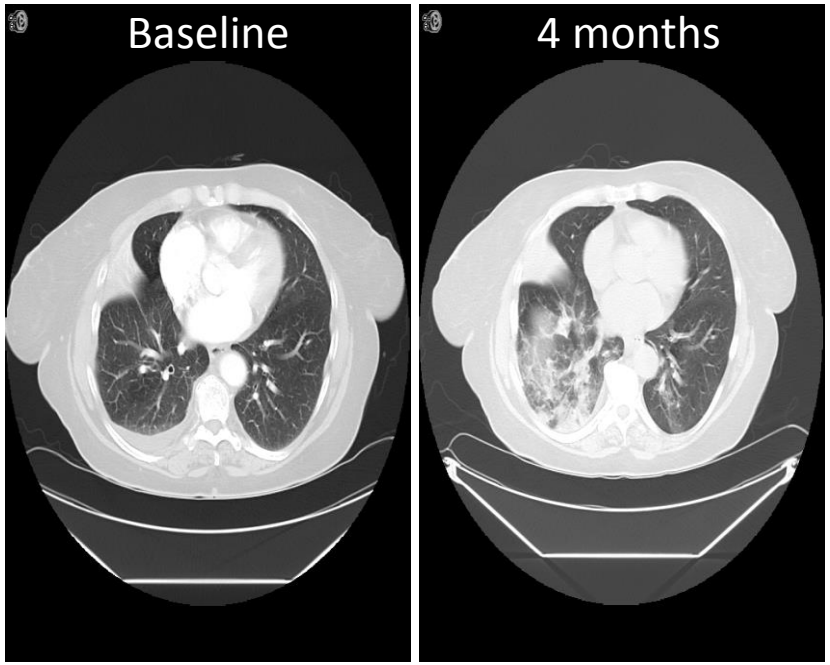
Case Study: 2

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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