ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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Leader, Thoracic Oncology Program
University of Wisconsin

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- Genentech, Inc., Takeda Pharmaceutical Company Limited, Consulting Fees
- I *will not* be discussing non-FDA approved indications during my presentation.

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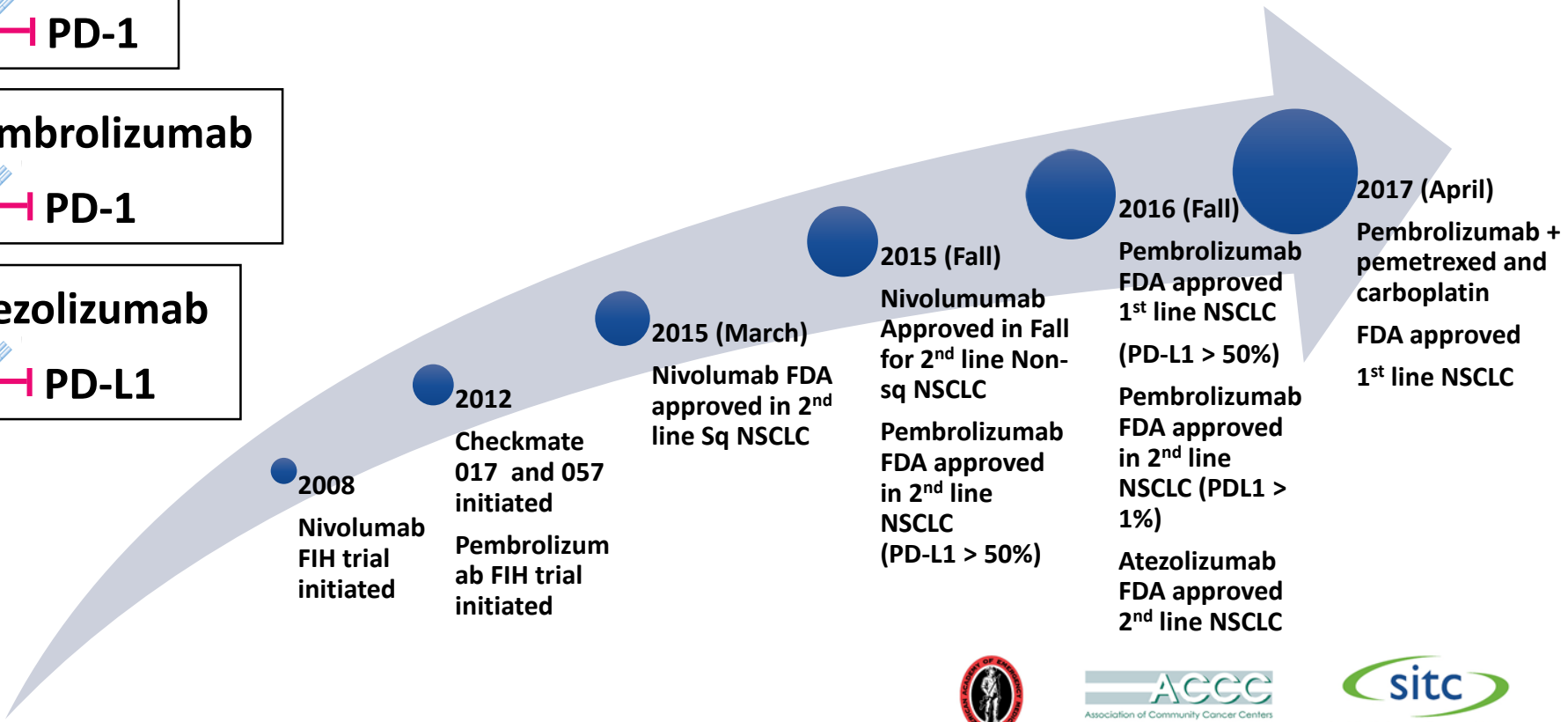
Immune checkpoint inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1



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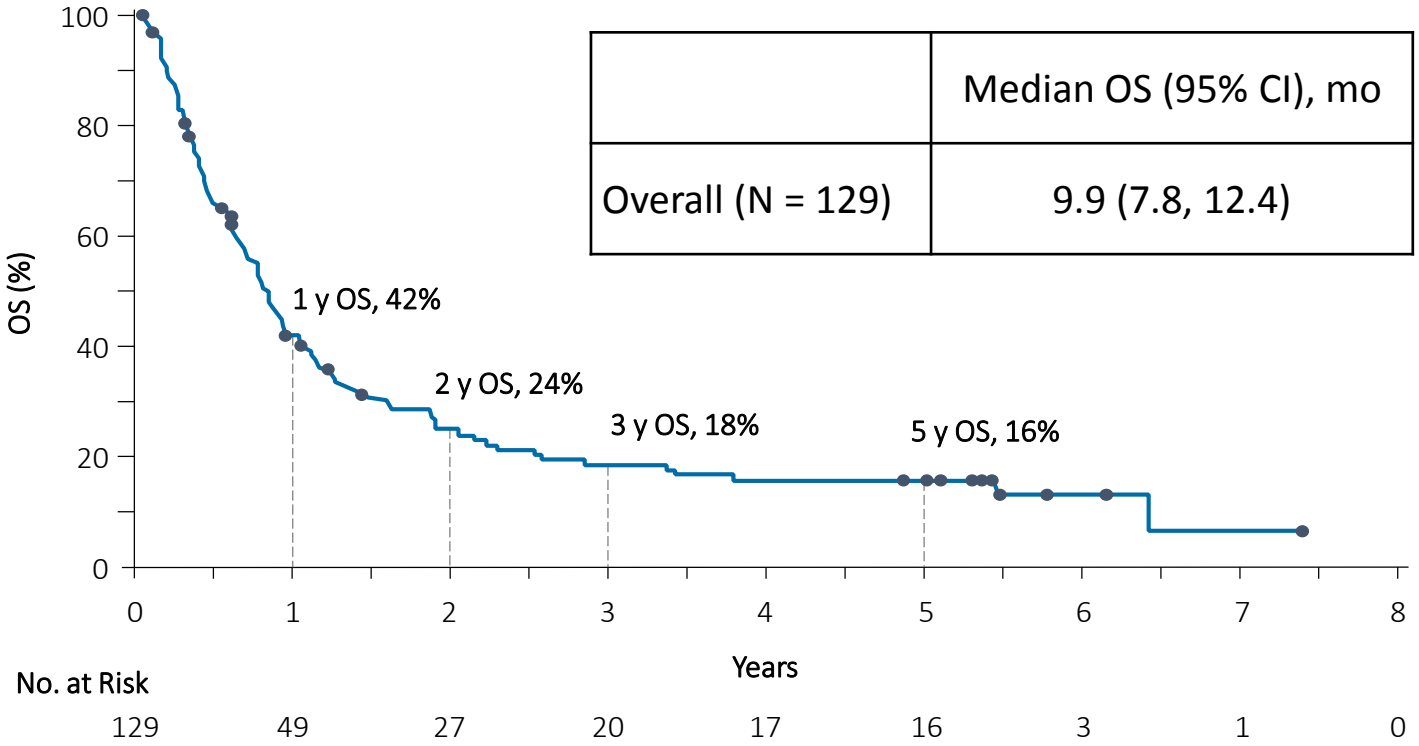
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

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



Brahmer et al, AACR 2017

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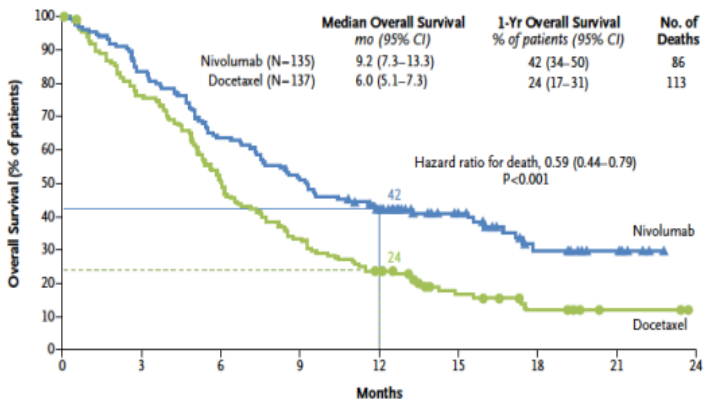
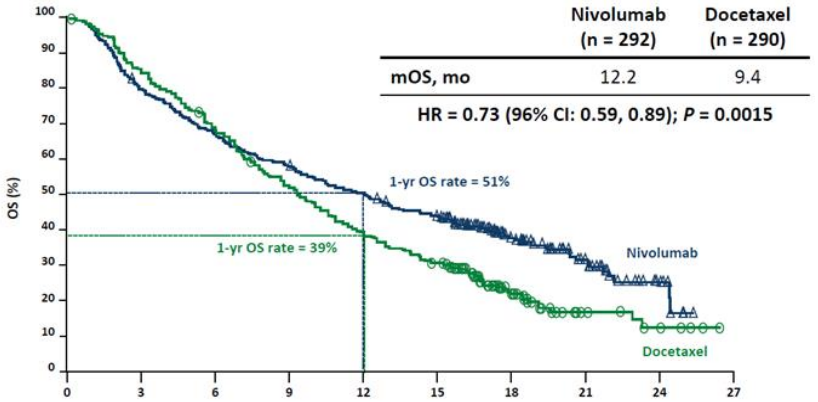
PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

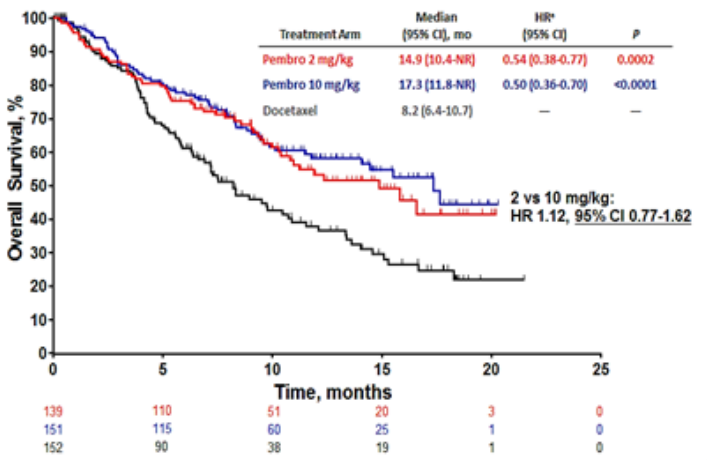
CHECKMATE 017



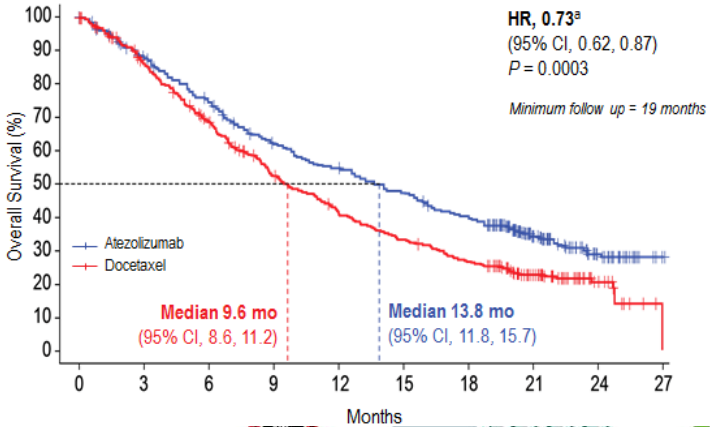
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)



OAK



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

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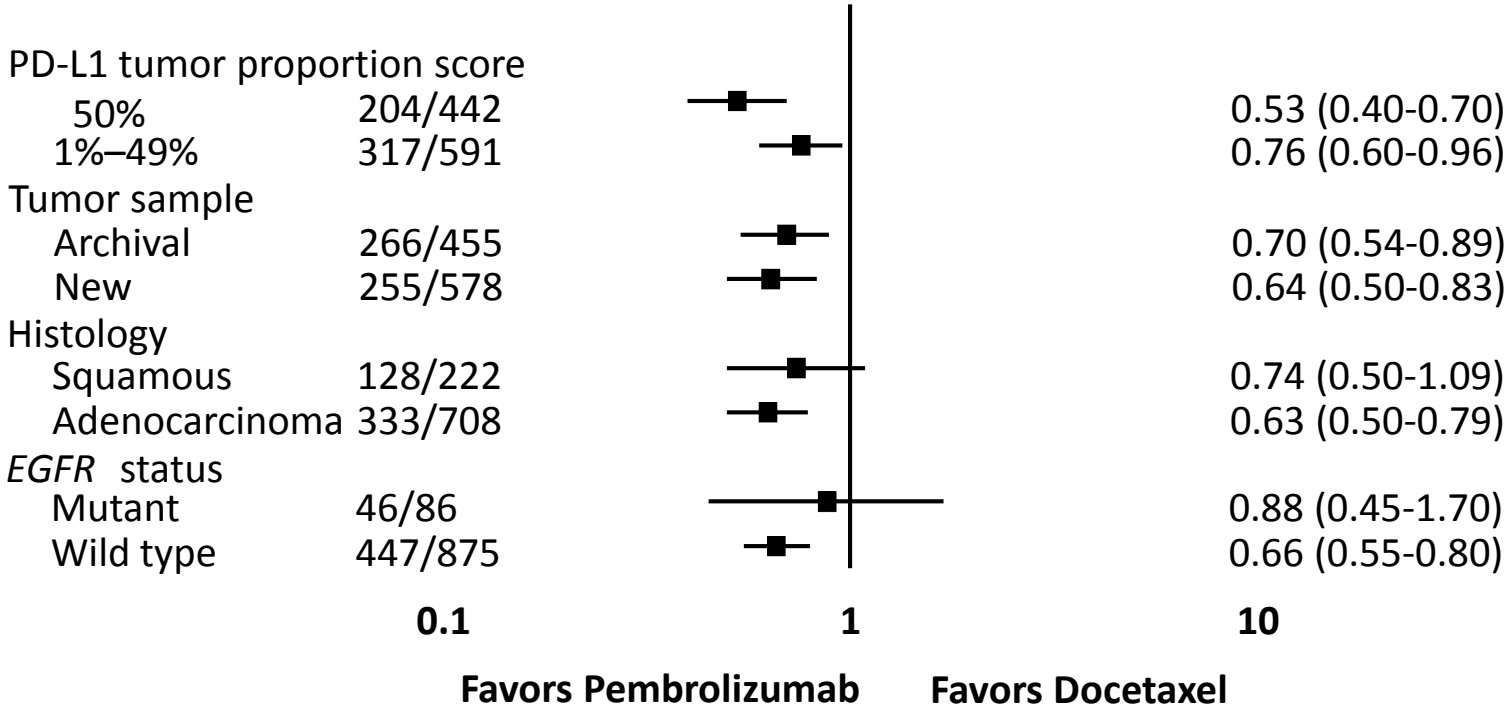
KEYNOTE 010: Pembrolizumab approval ≥ 2nd line (PD-L1 ≥ 1%)



Herbst et al, Lancet 2015

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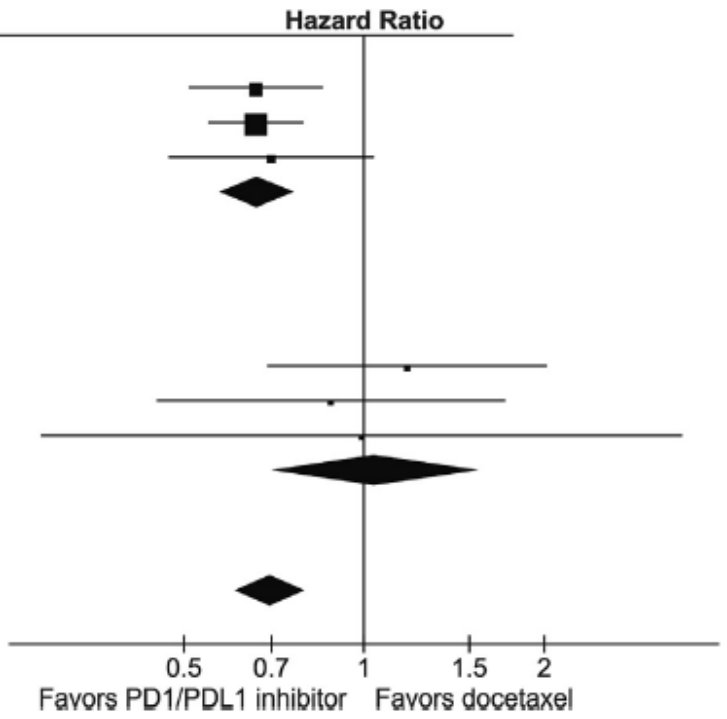
EGFRm PD-(L)-1 meta-analysis

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



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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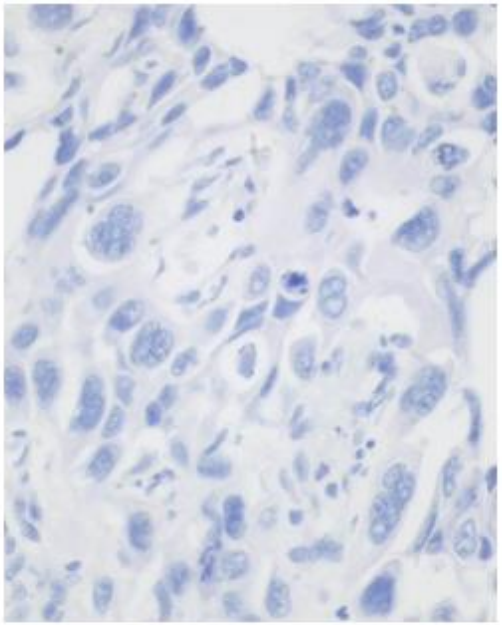
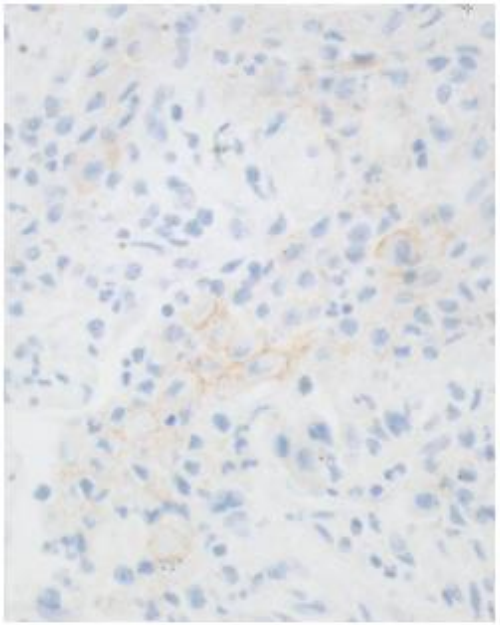
PD-L1 selection to bridge the gap?



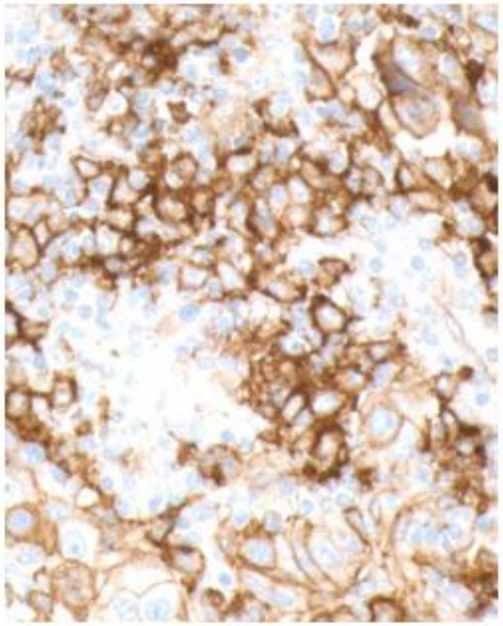
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



PD-L1 = 100% positive

Strong Positive (50%-100%)

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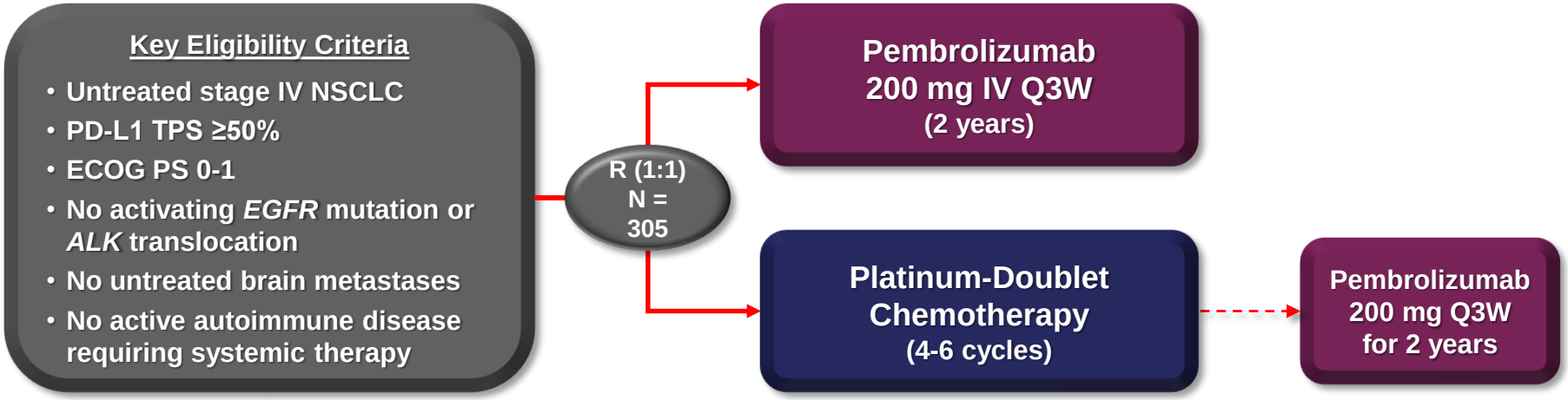
KEYNOTE-024 Study Design (NCT02142738)



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 10/16

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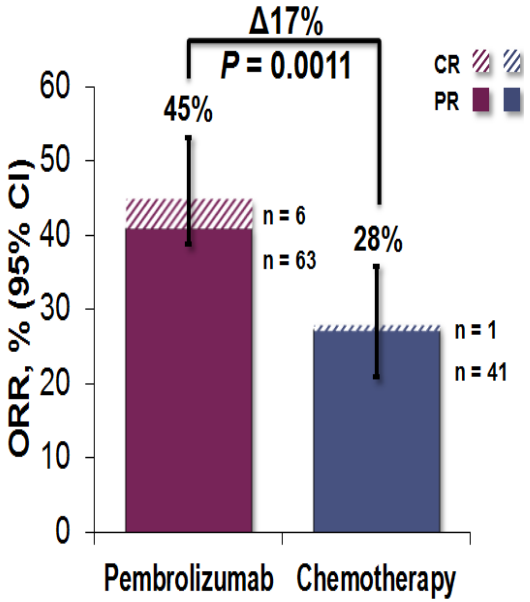
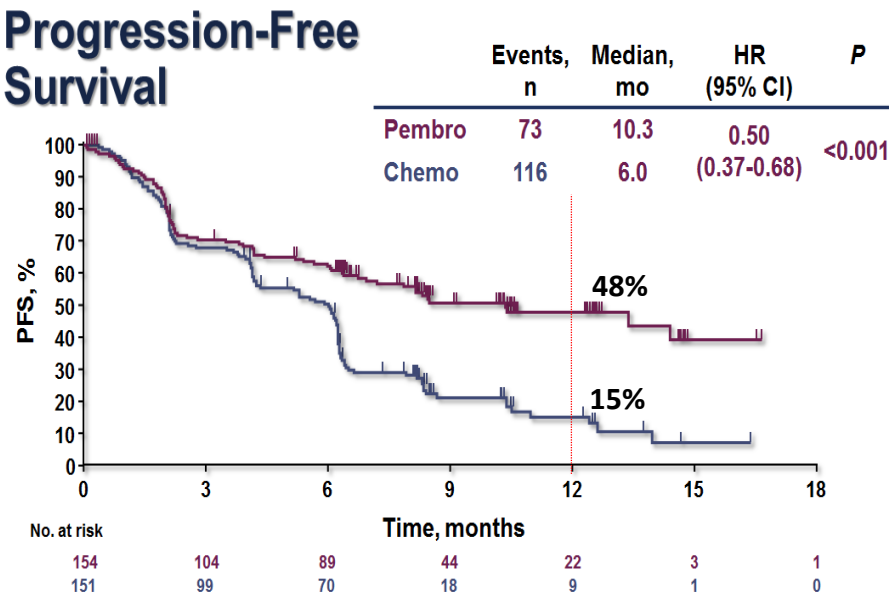
Efficacy data: Keynote 24



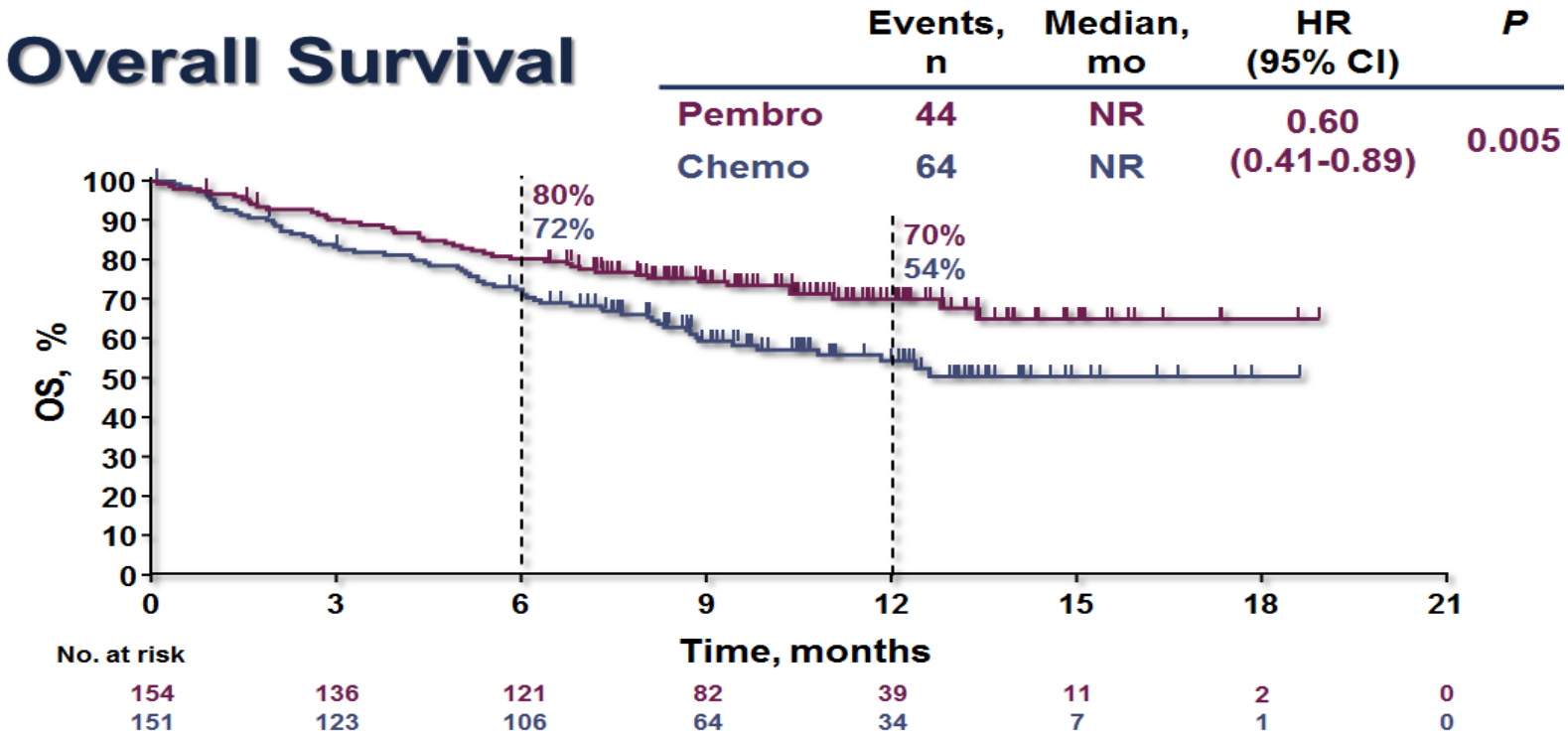


imaging every 9 weeks

- Clear and strong signal of activity
  - → ORR is improved, with a control arm that 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 is identical between Pembro and Chemo
  - → PFS is improved by 4.3 months (HR of 0.50)
  - → Improvement of PFS in all subgroups (except female/never smokers => lower mutational load ?)
  - → Strongest signal of PFS benefit observed in SqCC (HR of 0.35)

Reck M et al, ESMO 2016, NEJM 10/16

Keynote 24: Survival data



Clearcut survival benefit

- **Estimated rate of OS @ 12 months: 70% (Pembro) vs 54% (CT)**
- **HR for death: 0.60**
- **Despite cross-over in 50% of patients on the control arm**

Reck M et al, ESMO 2016, NEJM 10/16

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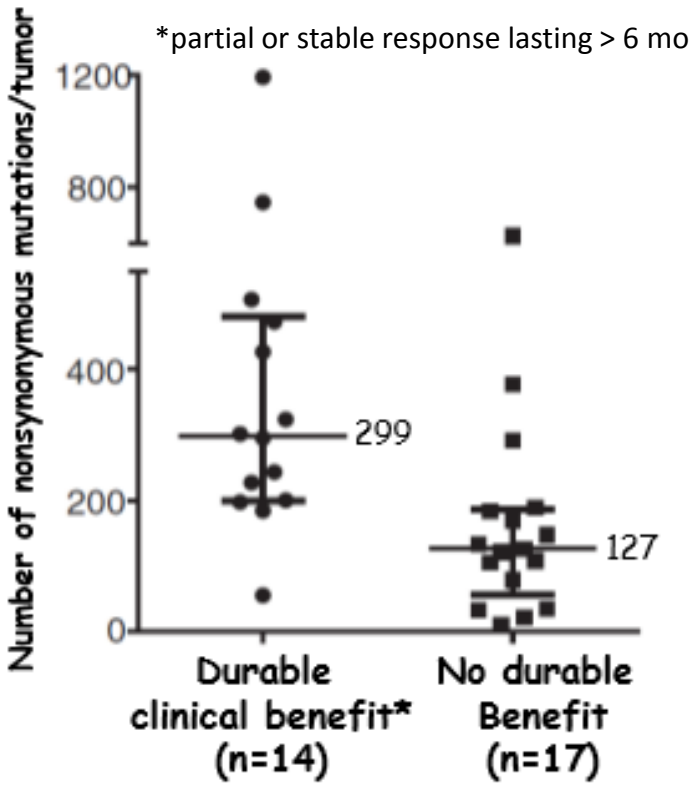
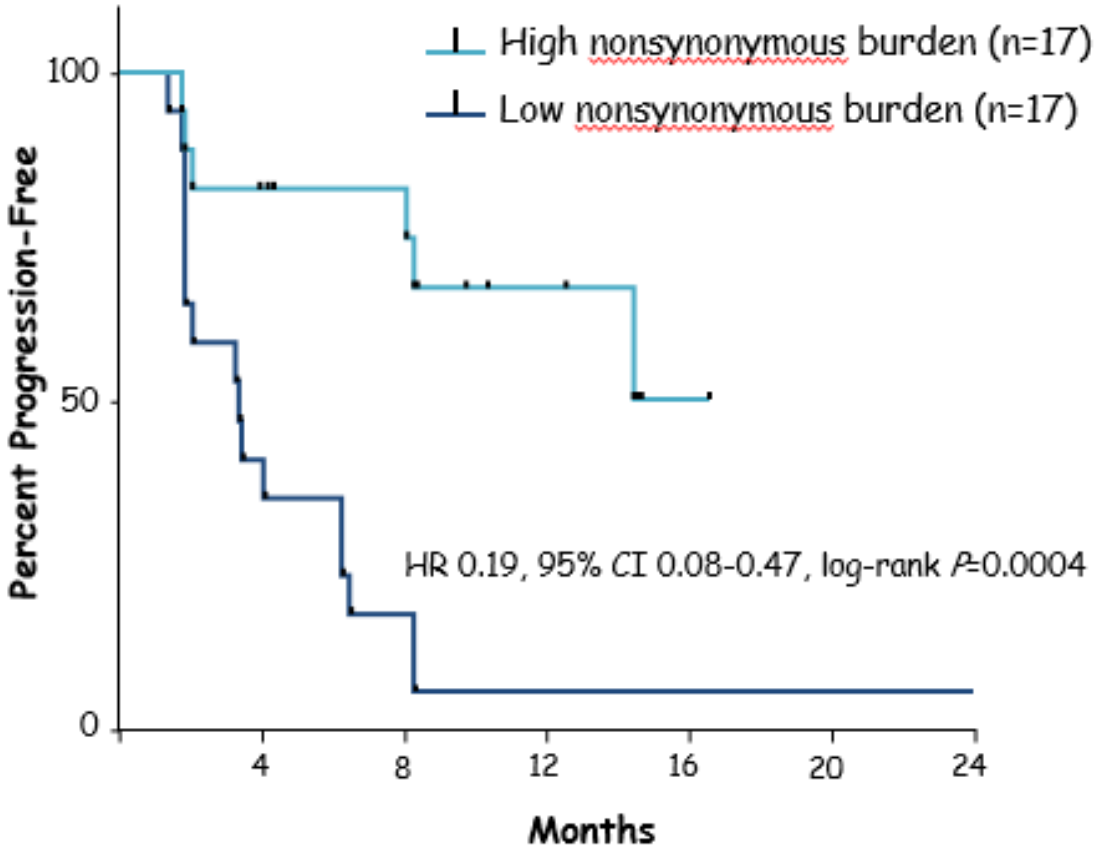
Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



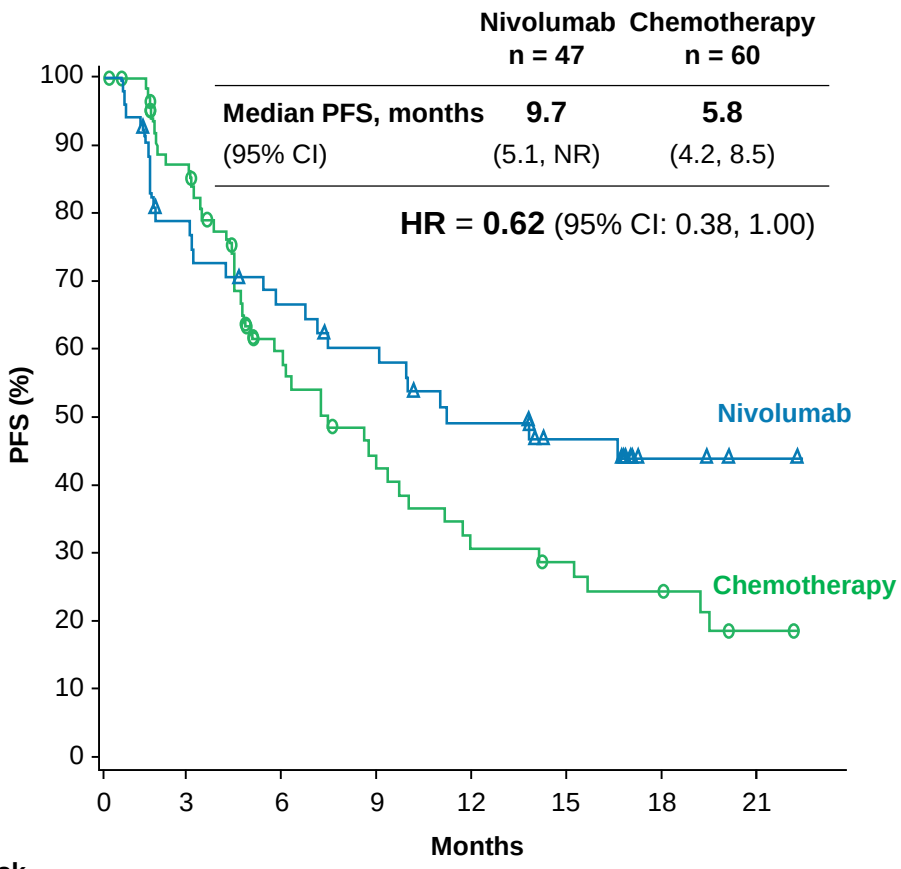


Rizvi N et al, Science 2015:348(6230):124-128

PFS by Tumor Mutation Burden Subgroup CheckMate 026 TMB Analysis

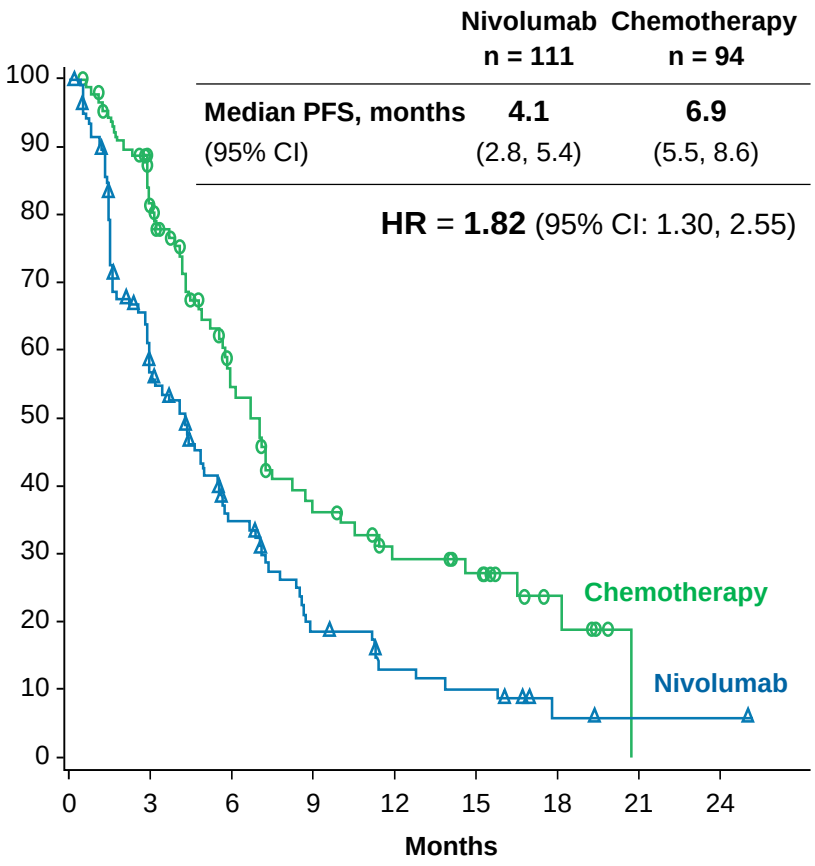
Nivolumab in First-line NSCLC

High TMB



No. at Risk								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB

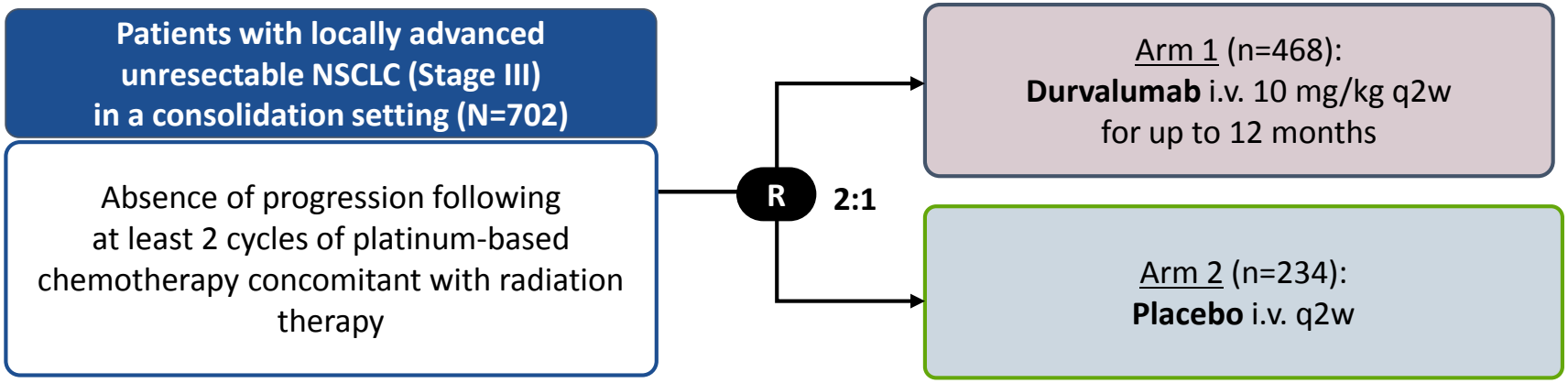


Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

Peters, et al., AACR 2017

PACIFIC (NCT02125461/D4191C00001): Study Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)



Primary endpoints
- PFS, OS

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

Est. completion: 2017
FPD[4] Q2 14
LPCD: Q2 16

DoR = duration of response; DSR = deep sustained response; FPD, first patient dosed; i.v. = intravenous; LPCD = last patient commenced dosing; 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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PACIFIC (NCT02125461/D41[illegible]001): Study Design

- Phase 3, randomized, double-blind, placebo-co[illegible], global study (26 countries)

Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting (N=702)

Absence of progression followi[illegible] at least 2 cycles of platinum [illegible] chemotherapy concomitant [illegible] therap[illegible]

Arm 1 (n=468): **[illegible]valumab** i.v. 10 mg/kg q2w for up to 12 months

Arm 2 (n=234): **Placebo** i.v. q2w

Primary endpoi[illegible]
- PFS, OS

Second[illegible]
- O[illegible]
- [illegible]
- PK[illegible]

Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

Est. completion: 2017
FPD[4] Q2 14
LPCD: Q2 16

DoR = duration of [illegible]; DSR = deep sustained response; FPD, first patient dosed; i.v. = intravenous; LPCD [illegible]tient commenced dosing; NSCLC = non-s[illegible]ll cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; q2w = every 2 weeks; QoL = quality of life.

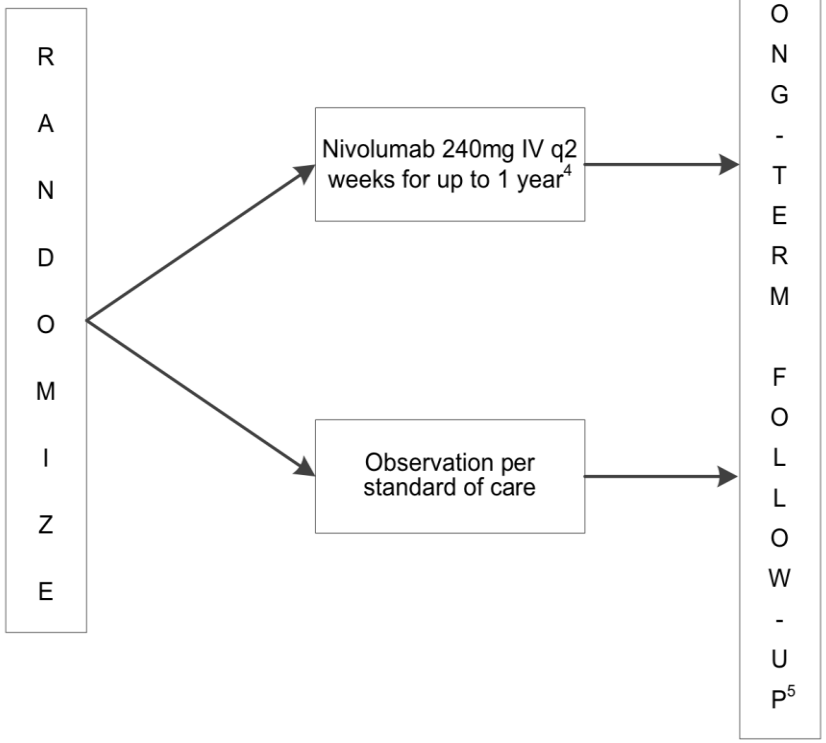
EA5142: ANVIL – Adjuvant Nivolumab in Resected NSCLC

<u>Eligibility</u>

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

<u>Stratification</u>

- Stage AJCC 7th edition: IB (≥ 4cm)/IIA vs IIB/IIIA
- Histology: squamous vs. non-squamous (adenosquamous should be grouped as non-squamous)
- Prior adjuvant treatment for lung cancer (none vs. chemotherapy vs. chemotherapy + radiation)
- PD-L1 status: positive (≥ 1%) vs. negative (< 1%)/non-evaluable) membranous expression determined centrally



Cycle = 2 weeks (14 days)
Accrual Goal = 714 patients

1. If Stage 1B, then tumor must be ≥ 4cm
2. Adenosquamous should be grouped as non-squamous
3. PD-L1+ is defined as ≥ 1% by IHC
4. Maximum number of doses is 26
5. Patients will be followed for recurrence and survival for 10 years

Co-primary endpoints: DFS and OS in all patients

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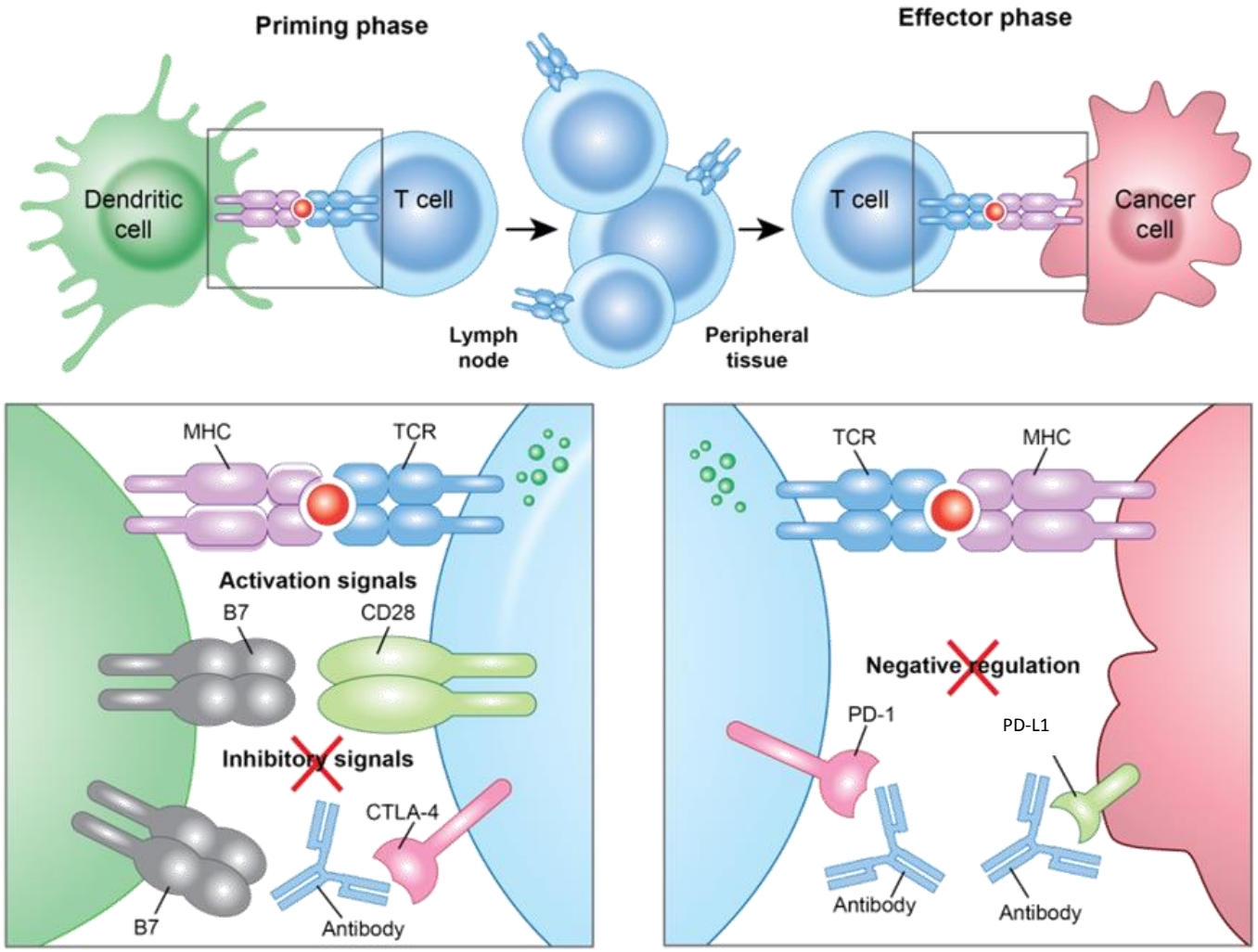
Combination Immune checkpoint blockade



Engl J Med 2012; 366:2517-2519.

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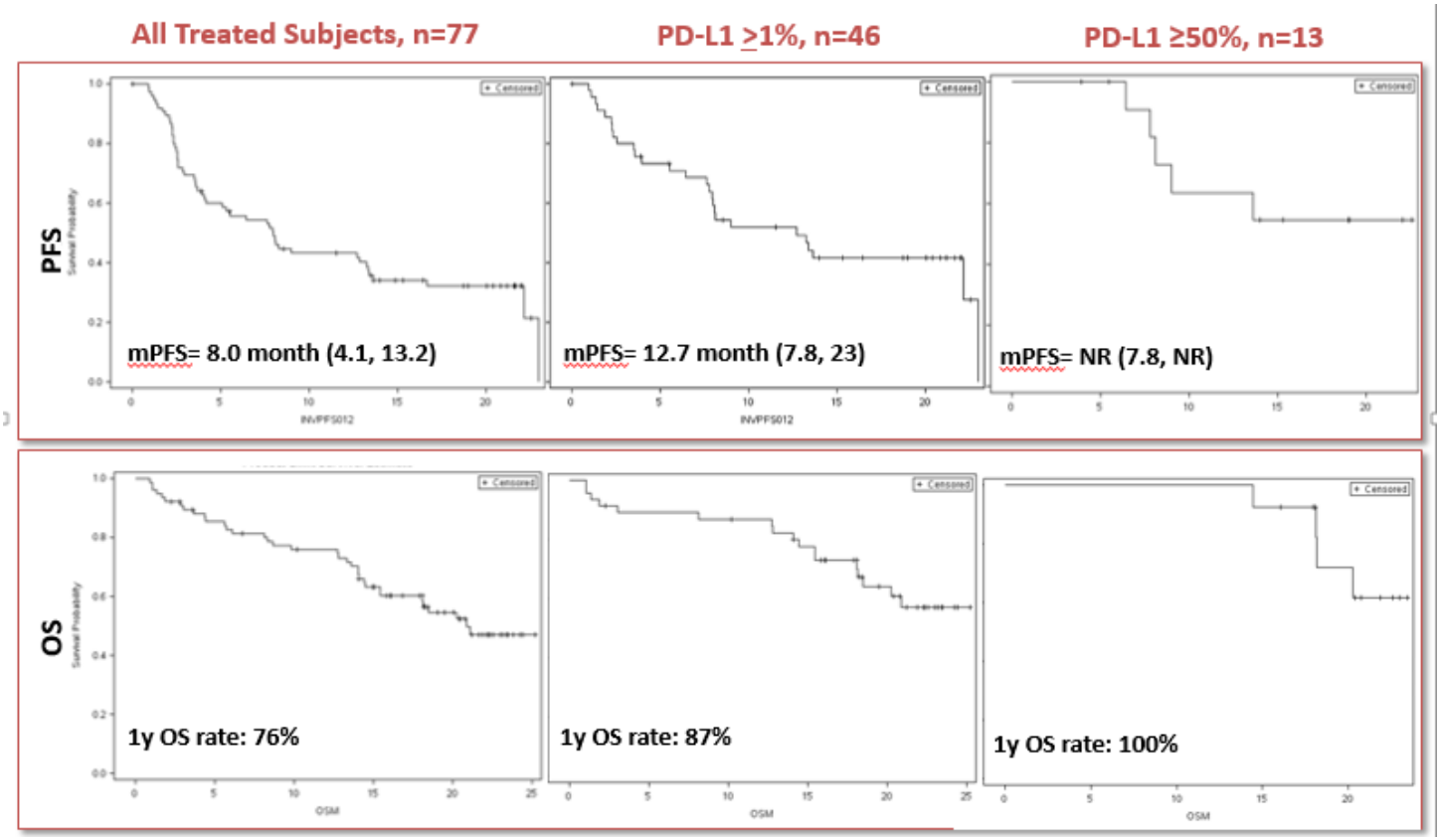
Ipilimumab: CTLA-4

Nivolumab: PD-1

Combination I-O (IPI/NIVO) potential in first line ?



CheckMate 012
Goldman, et al, ASCO Annual Meeting, 2017

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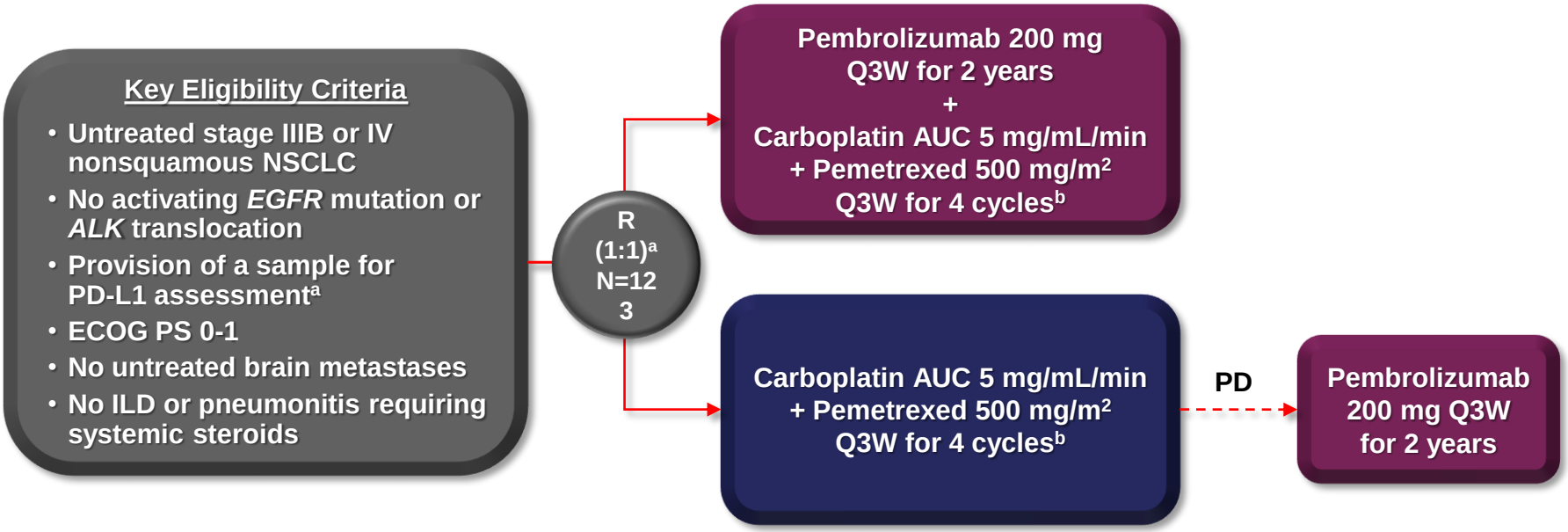
KEYNOTE-021 Cohort G



End Points

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

Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer, et al Lancet Oncology 2016

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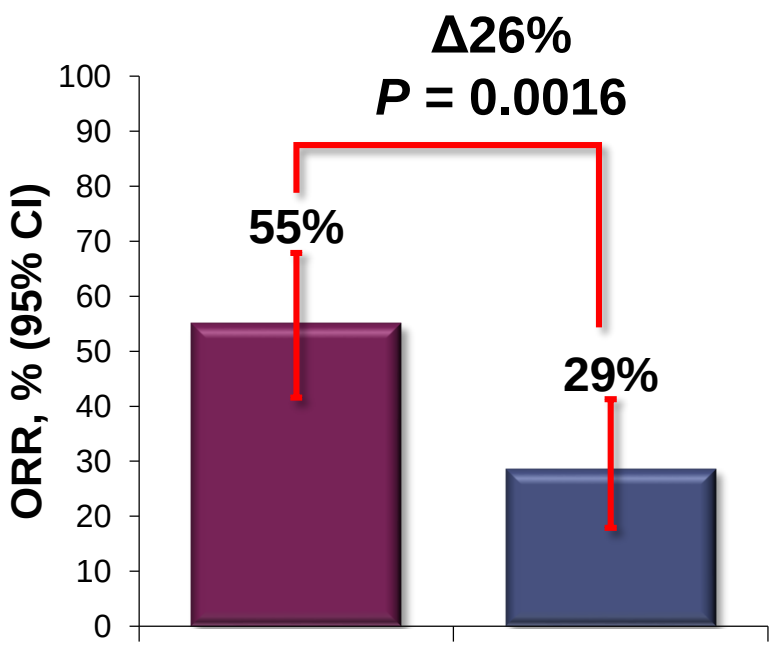
Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



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

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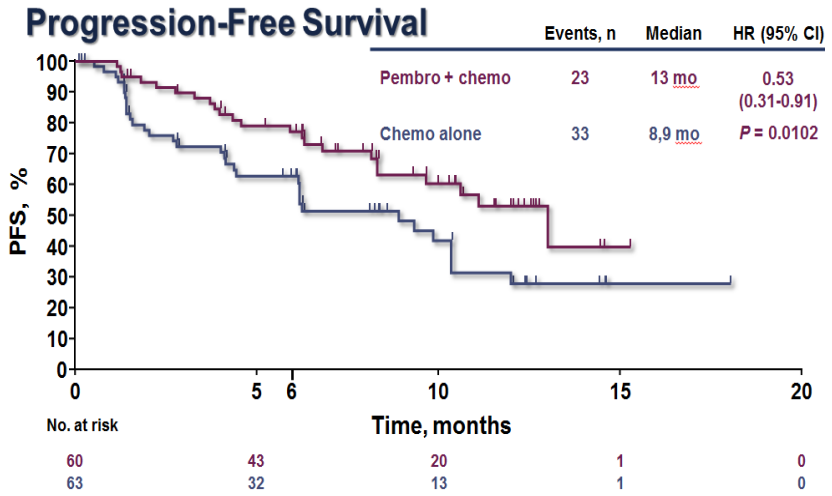
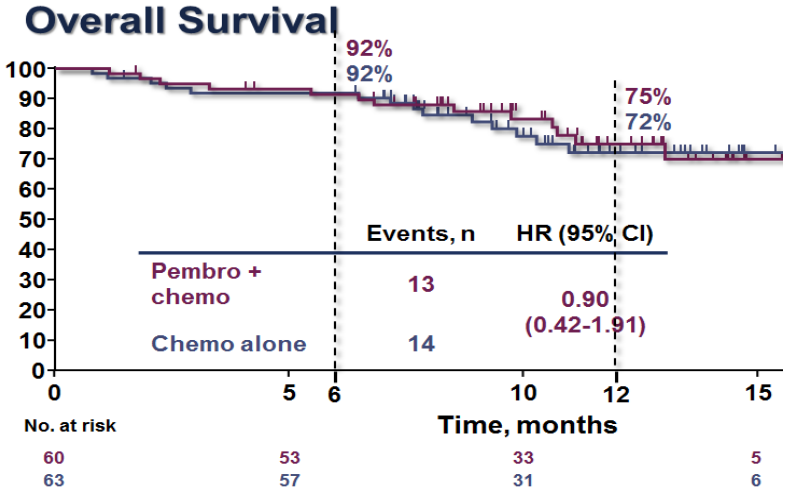
COPENHAGEN 2016 ESMO congress

PFS and OS Survival data





Clear PFS benefit and no OS advantage

- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Langer, et al Lancet Oncology 2016

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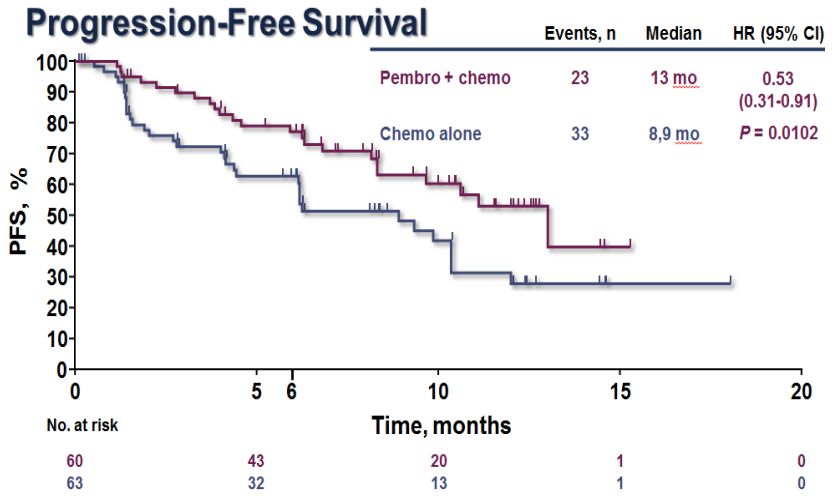
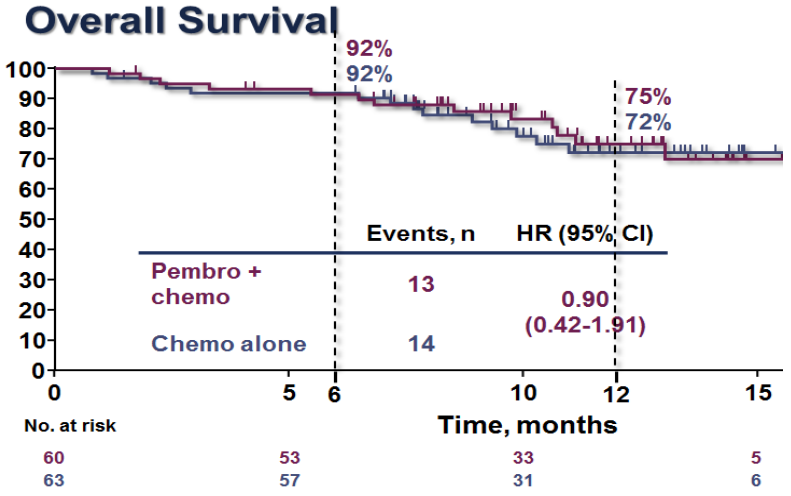
PFS and OS Survival data





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Updated (ASCO '17):

- RR: 57% vs 30.5%
- PFS HR has dropped to 0.5 from 0.53, Median now NR vs 8.9
- OS HR has dropped to 0.69 from 0.9 with dip in p value from 0.37 to 0.13 (1yr OS 76% vs 69%)

Langer, et al Lancet Oncology 2016,
Papadimitrikopolou, ASCO 2017

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Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

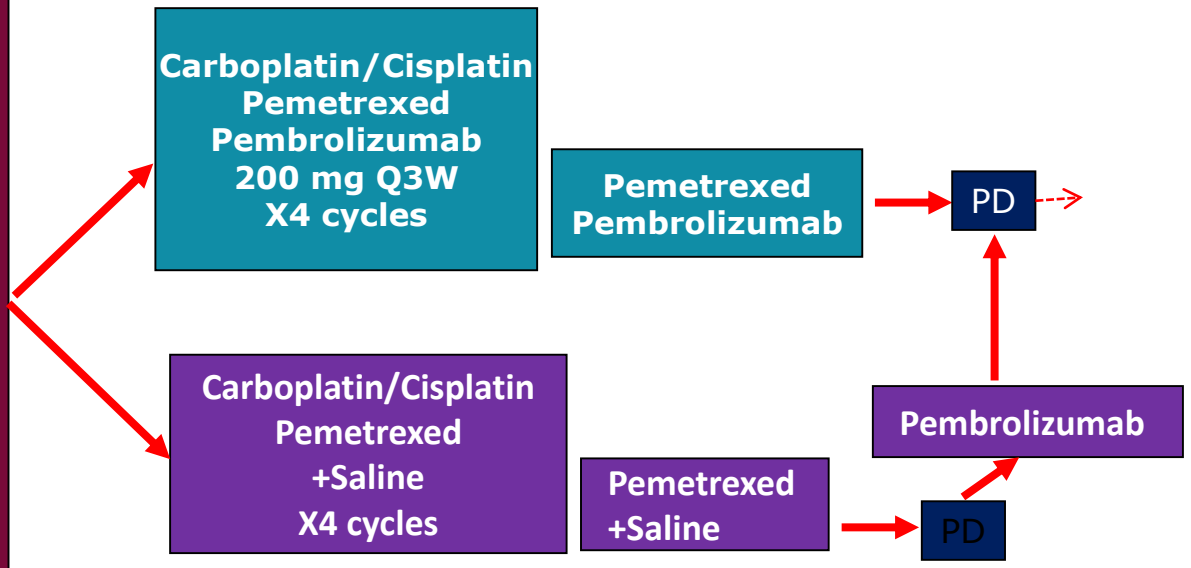
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

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

RANDOMIZATION

2:1

N=570



Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

Study Design

Keynote A Clinical Trial for Non-Small Cell Lung Cancer 189

Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
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Stratify:
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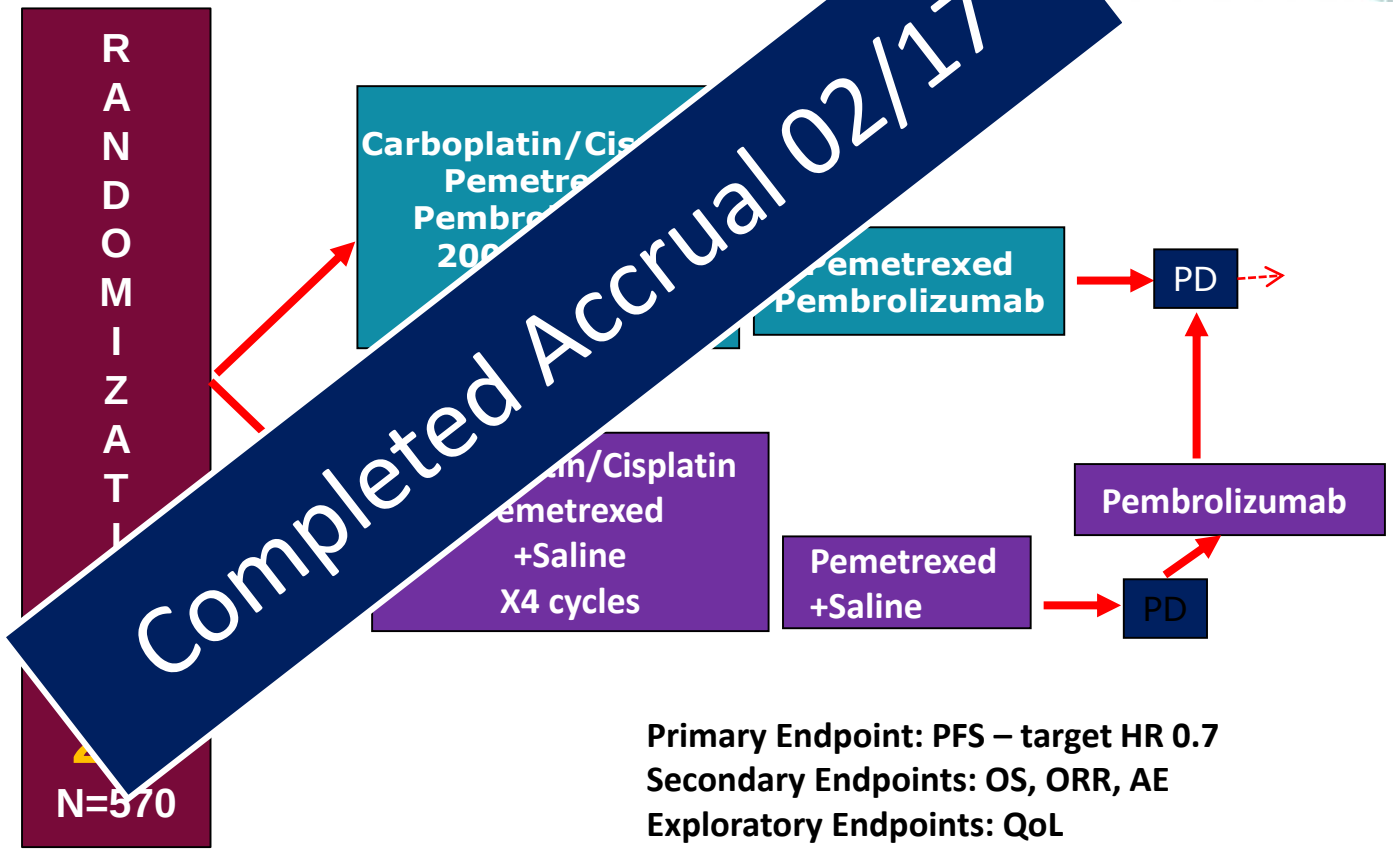
- cisplatin vs carboplatin



Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

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Phase 3 first-line combination trials in advanced NSCLC (all PD-L1 unselected)

Treatment	N*	Arms			Primary endpoint
Checkmate 227[1]	1980	Nivolumab, ipilimumab	Nivolumab	Plt-doublet chemotherapy	OS
MYSTIC[2]	1092	Durvalumab, tremelimumab	Durvalumab	SOC Plt-based chemotherapy	PFS
NEPTUNE[3]	800	Durvalumab, tremelimumab	SOC Plt-based chemotherapy	-	OS
IMpower 130[4]	550	Atezolizumab, nab-paclitaxel/carboplatin	nab-paclitaxel/carboplatin	-	PFS
IMpower 150[5]	1200	Atezolizumab, paclitaxel/carboplatin, bevacizumab	Atezolizumab, paclitaxel/carboplatin	Paclitaxel/ carboplatin, bevacizumab	PFS
IMpower 131[6]	1200	Atezolizumab, nab-paclitaxel/carboplatin	Atezolizumab, paclitaxel/carboplatin	Nab-paclitaxel/carboplatin	PFS

*Estimated enrolment

Plt, platinum; SOC, standard of care

1. NCT02477826; 2. NCT02453282; 3. NCT02542293; 4. NCT02367781; 5. NCT02366143; 6. NCT02367794

ADVANCES IN Cancer IMMUNOTHERAPY™

Case Study #1

A 58-year-old female never smoker with bilateral lung mets, 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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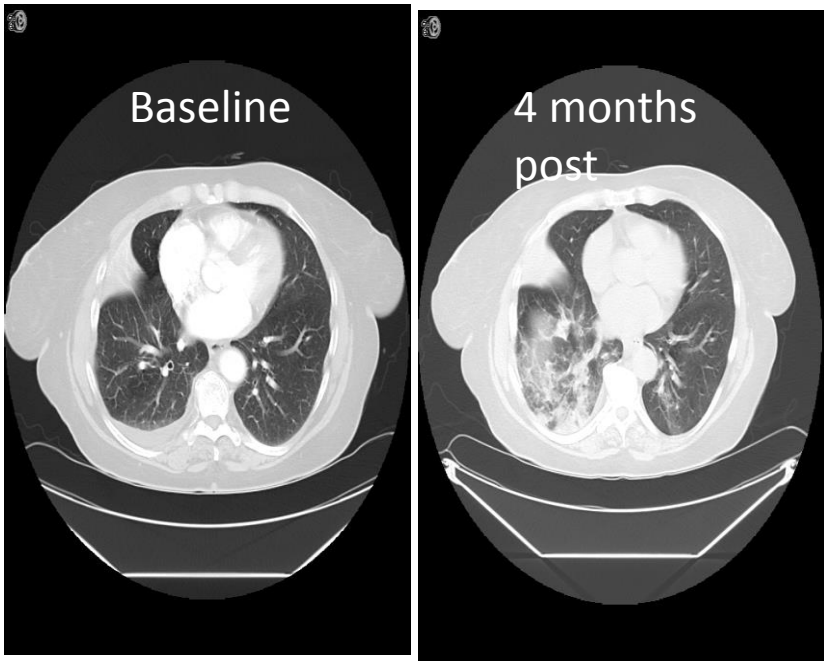
Case Study #2

A 70-year-old female ex-smoker with NSCLC with 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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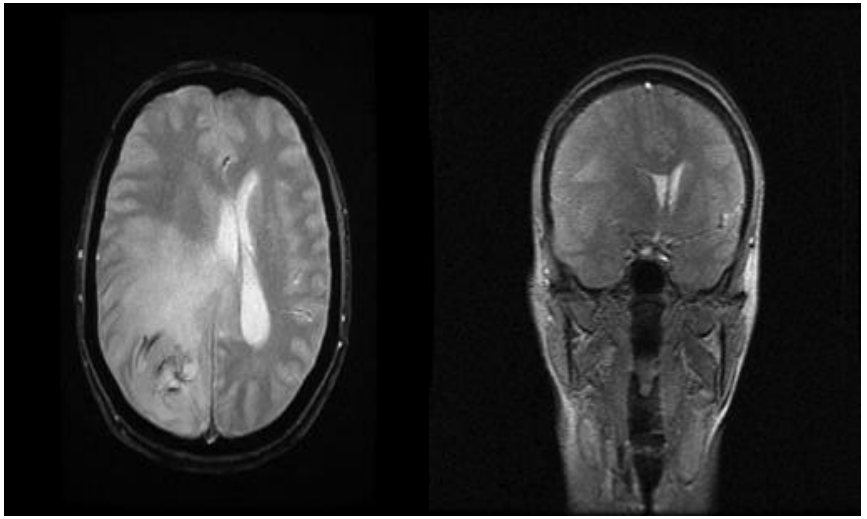
Case Study #3

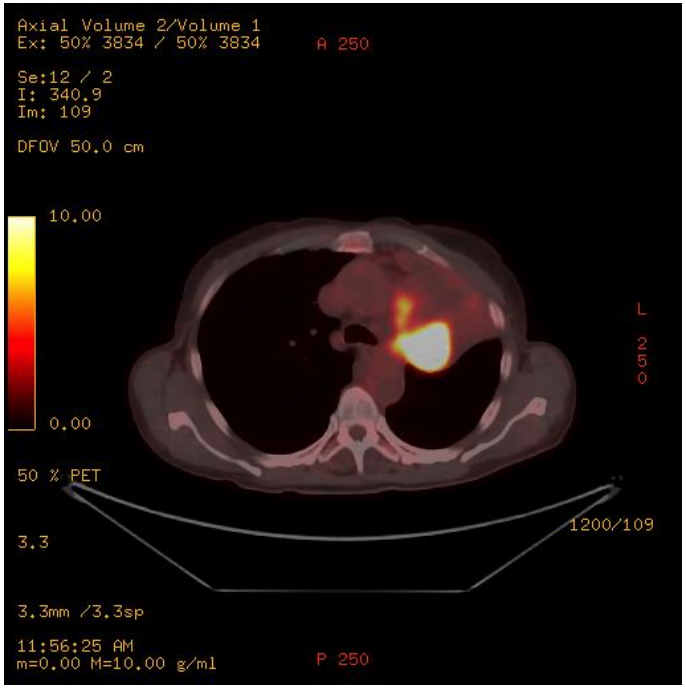
51 yo female, smoker, presented with 1-week of headaches, and diplopia. On exam was found to have esotropia and right 6th nerve palsy.
Patient underwent right parietal craniotomy for resection of an intra-axial supratentorial tumor on 4/11/15, followed by post-op radiation. Pathology showed adenocarcinoma. Genomic testing showed KRAS mutation: Gly13Asp (c.38G>A) in codon 13. Tumor PD-L1 60%. What is (are) the recommended systemic treatment option (s)?

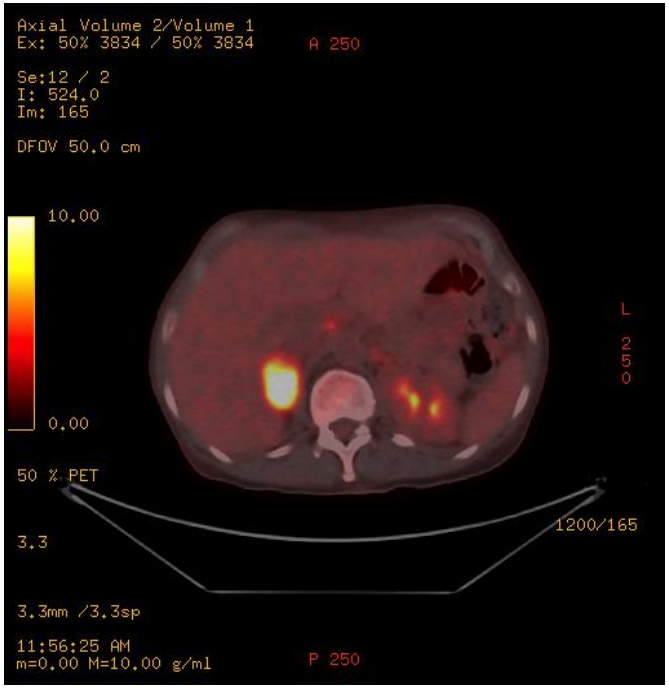


1. Carboplatin/pemetrexed
2. Carboplatin/paclitaxel/ Bevacizumab
3. Pembrolizumab
4. Pembrolizumab/carboplatin/ pemetrexed

Case Study #4

70 yo female, smoker, diagnosed with stage IV squamous cell carcinoma of the left hilum. She enrolled on MYSTIC trial and was randomized to durvalumab/tremelimumab. She received 4 cycles of durvalumab/tremelimumab. She obtained near CR after 2 cycles.





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Case Study #4

She developed grade 3 diarrhea/colitis and grade 2 hepatitis in September 2016. This required management with prednisone and she responded well. She subsequently developed hypothyroidism and was started on levothyroxine. In December of 2016, she developed fatigue and bilateral leg weakness. Labs showed Na 125-130. She underwent extensive work-up which did not show evidence of progression. Work-up was also negative for paraneoplastic disorder, neurologic disorder or myopathy.

What is the best next step?

1. No further work-up is needed.
2. This is likely deconditioning, and patient should be referred to PT/rehab.
3. Additional work-up is recommended. What would you order?
4. Hospice referral, given her functional decline, she is not a candidate for further treatment upon progression.