ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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American Academy of Emergency Medicine

ACCC
Association of Community Cancer Centers

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Disclosures

- Travel and Consulting Fees: Mirati, Roche, Ariad, Abbvie, Lilly
- I will not be discussing non-FDA approved indications during my presentation.

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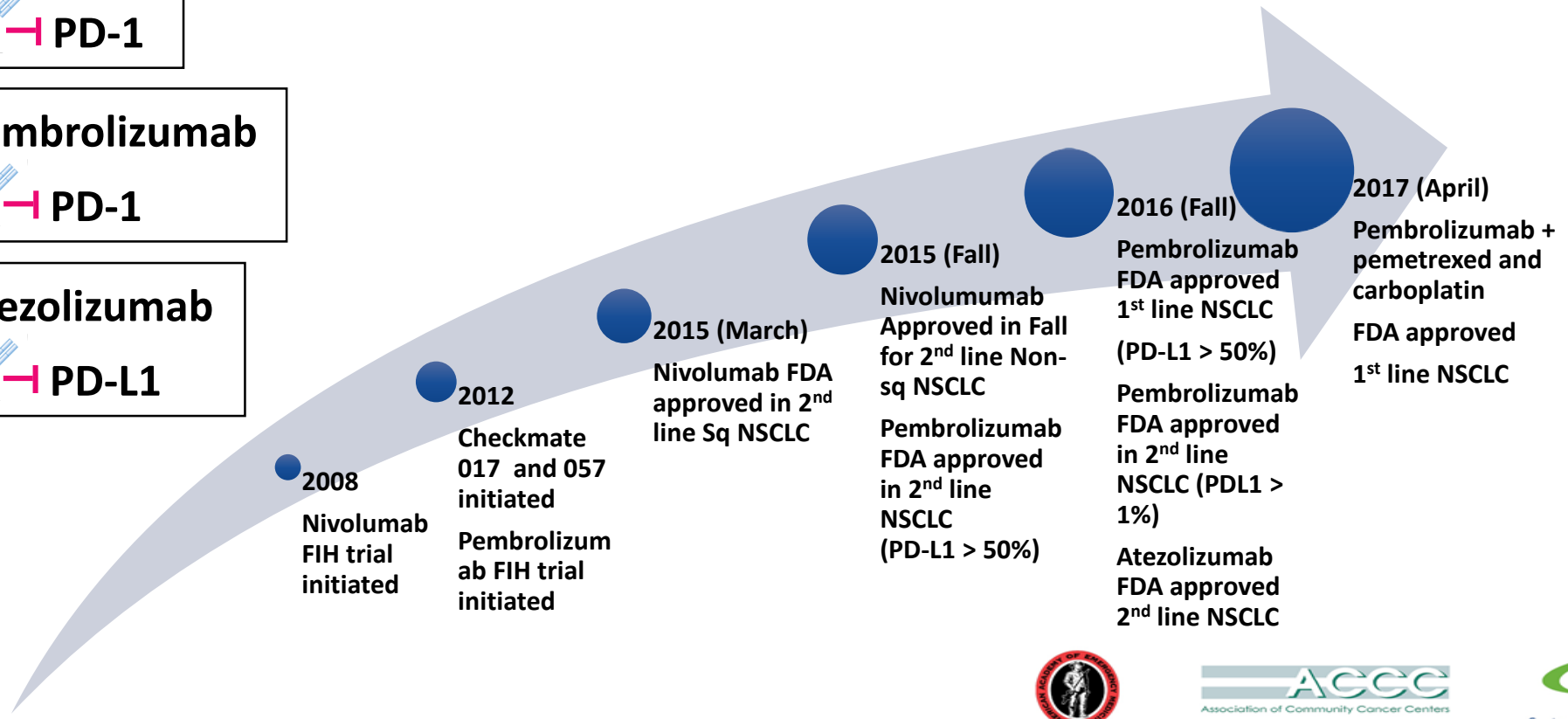
Immune checkpoint inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1



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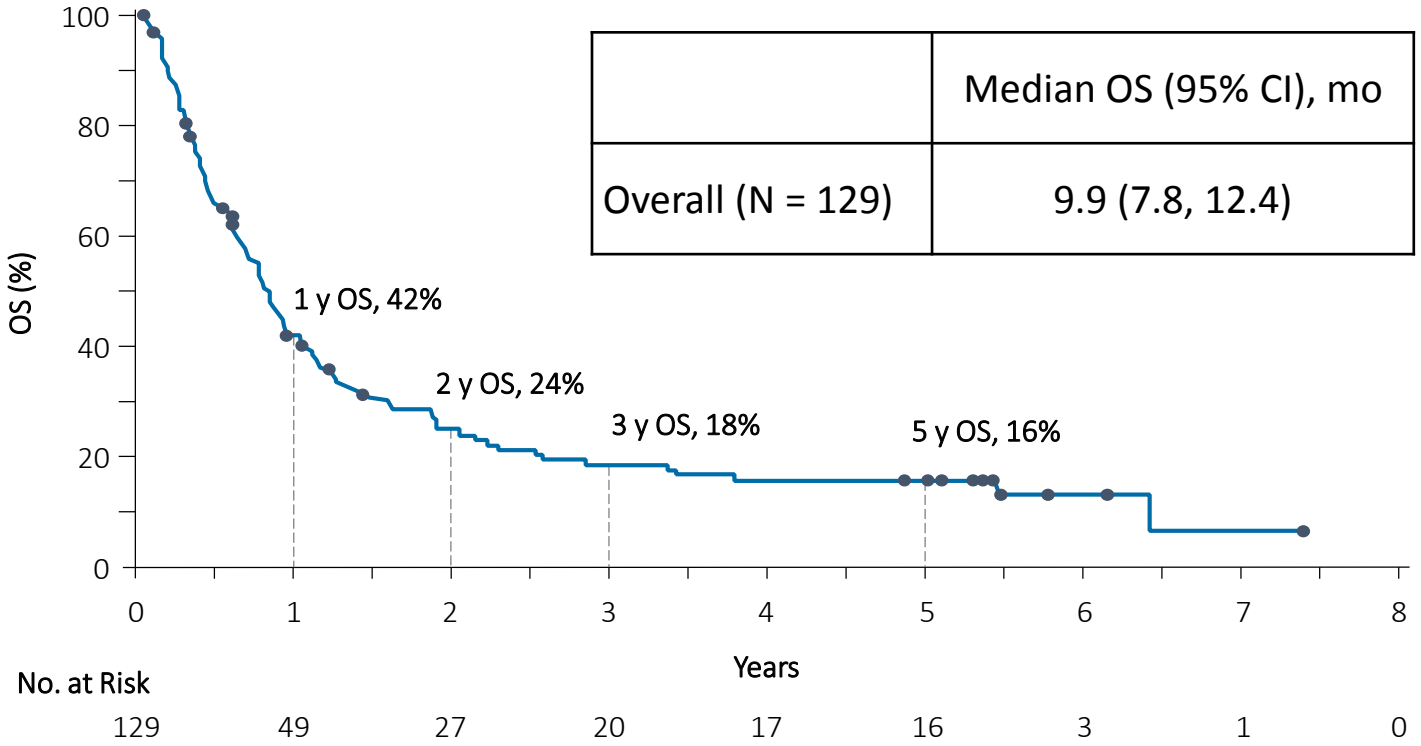
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

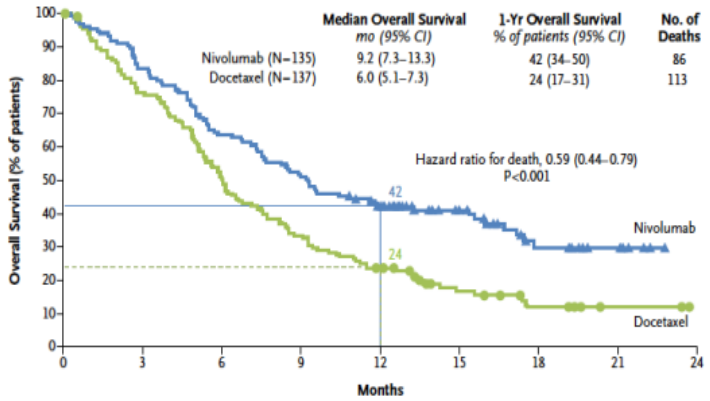
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)



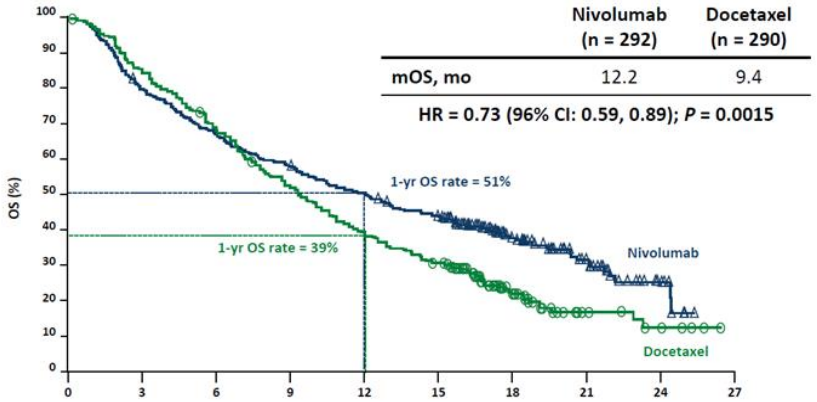
Brahmer et al, AACR 2017

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

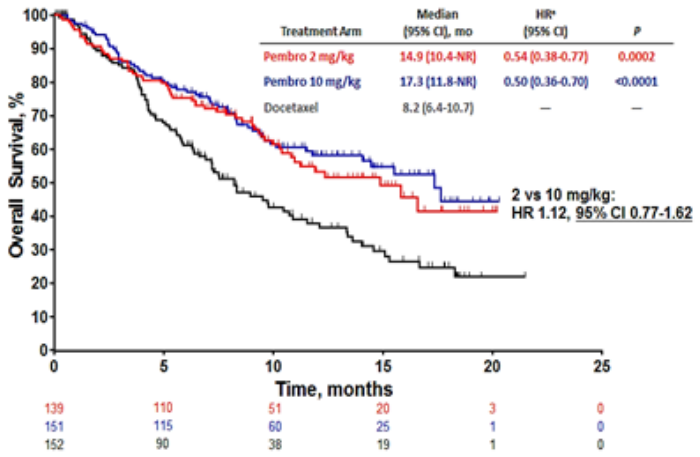
CHECKMATE 017



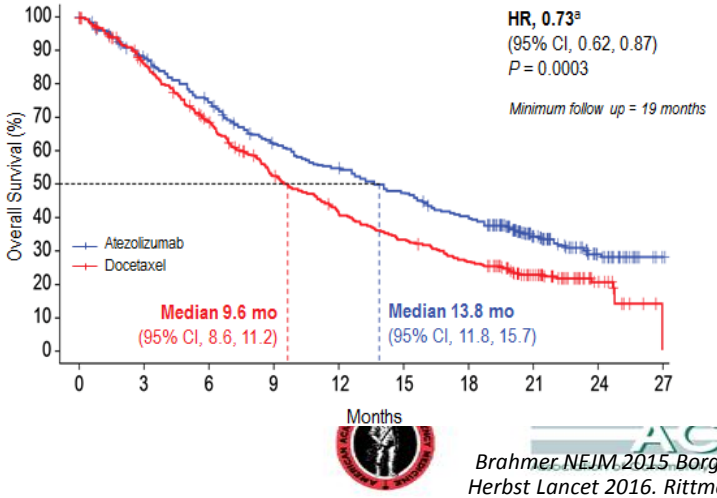
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)

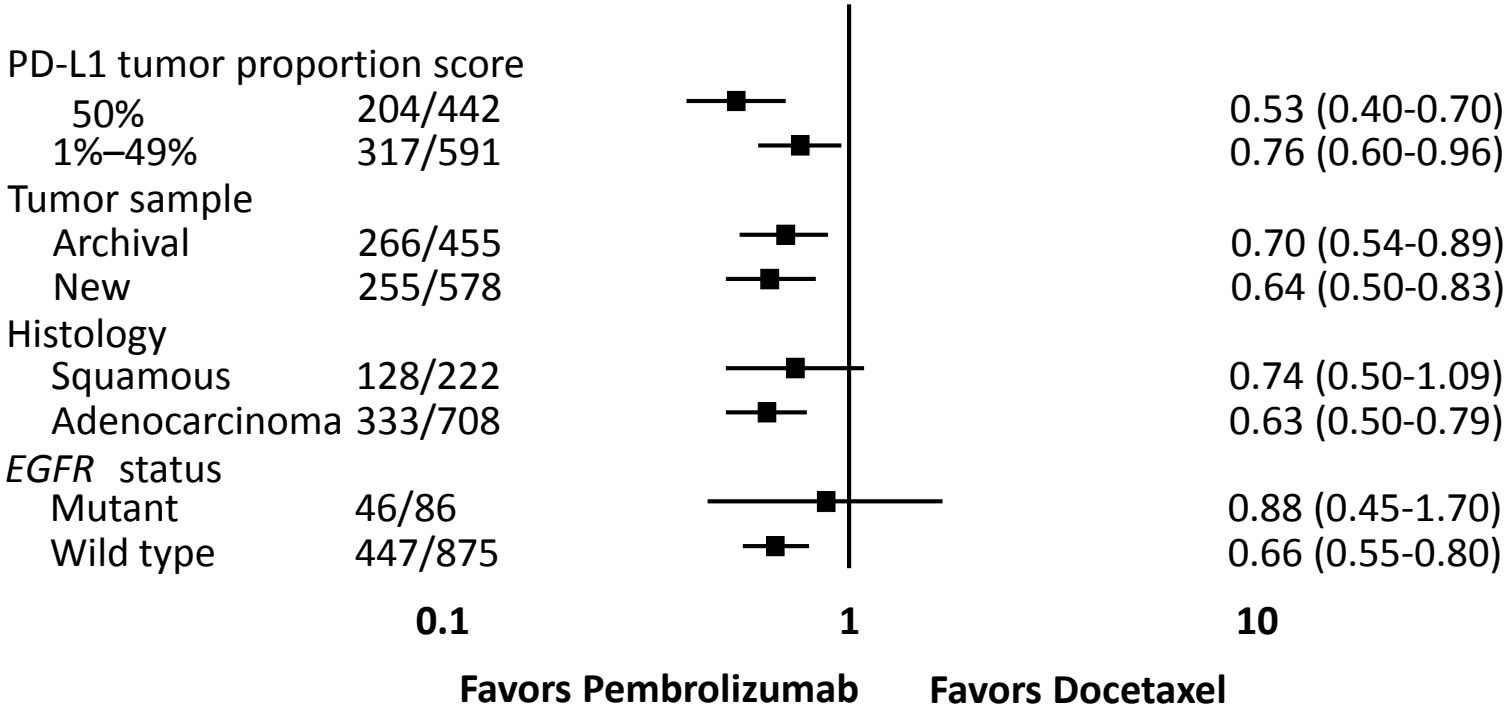


OAK



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

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



Herbst et al, Lancet 2015

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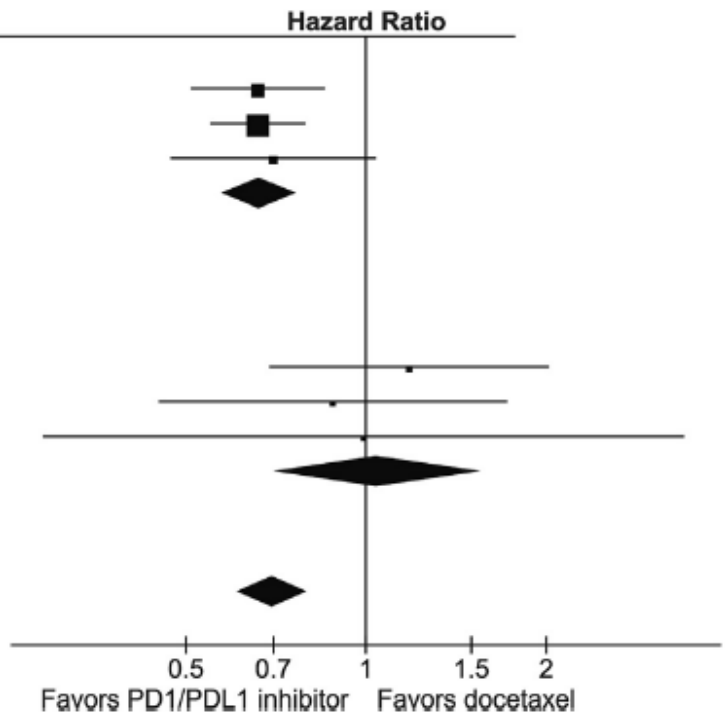
EGFRm PD-(L)-1 meta-analysis

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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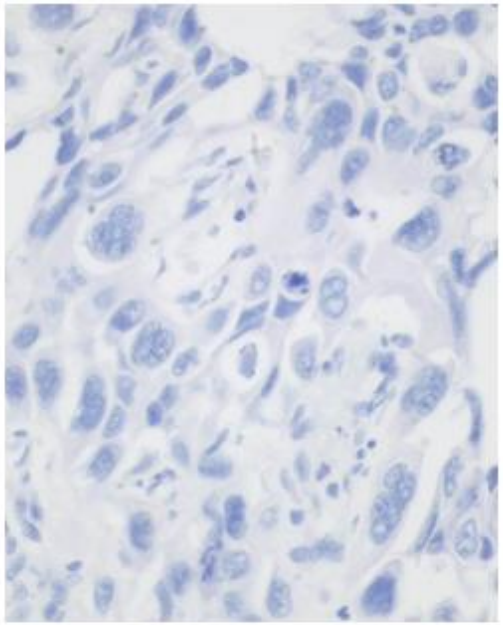
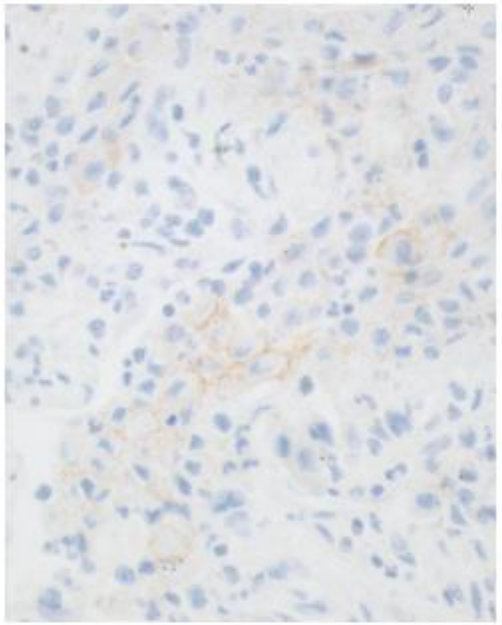
PD-L1 selection to bridge the gap?



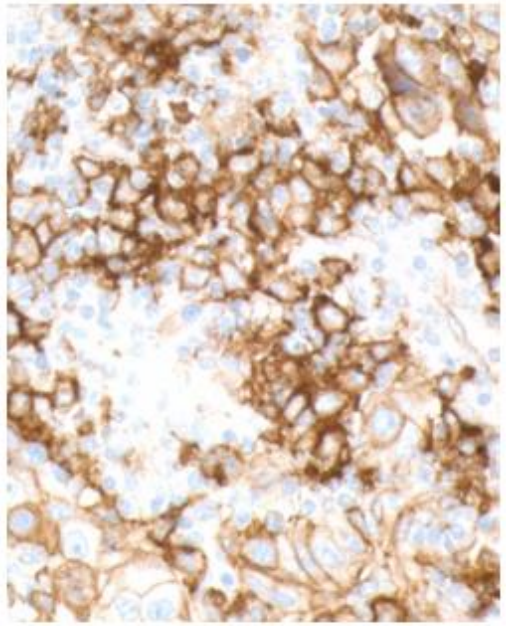
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



PD-L1 = 100% positive

Strong Positive (50%-100%)

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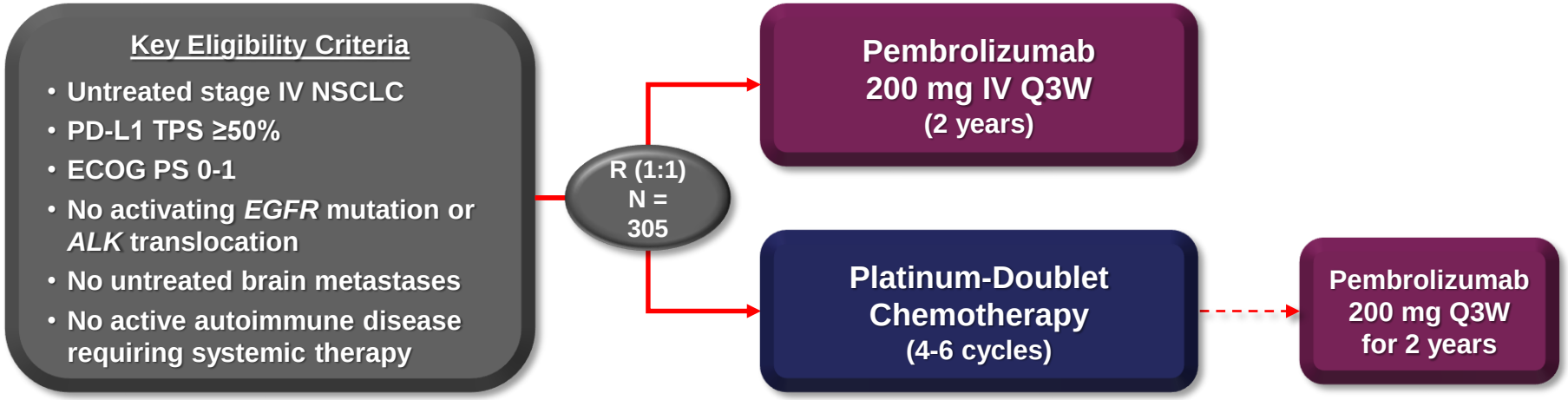
KEYNOTE-024 Study Design (NCT02142738)



Key End Points

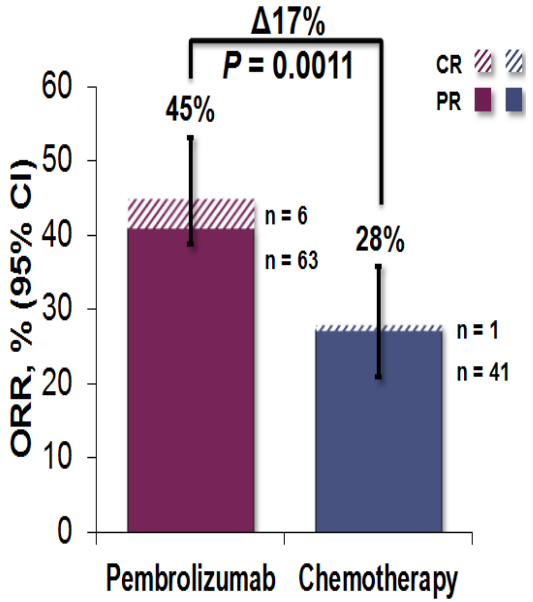
Primary: PFS (RECIST v1.1 per blinded, independent central review)

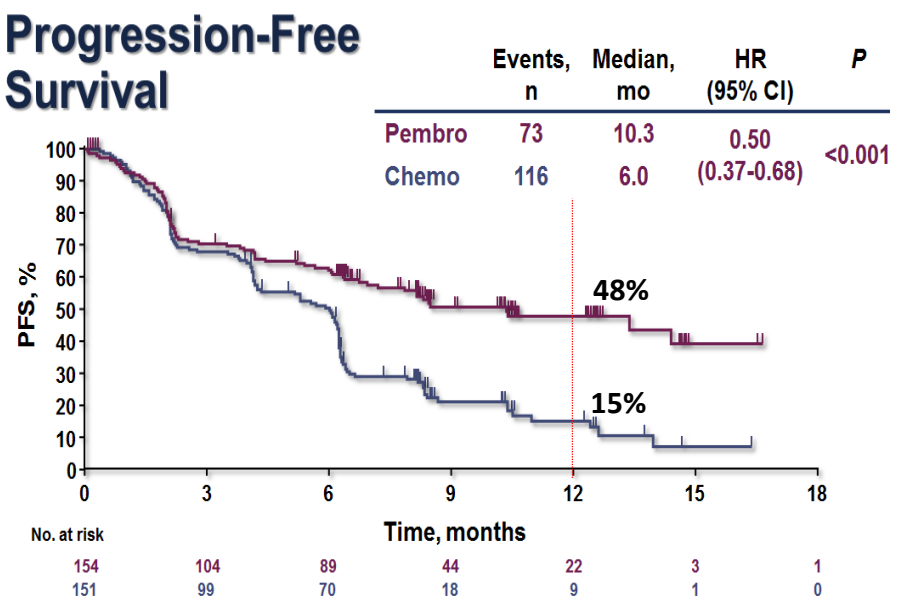
Secondary: OS, ORR, safety

Exploratory: DOR

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

Efficacy data: Keynote 24



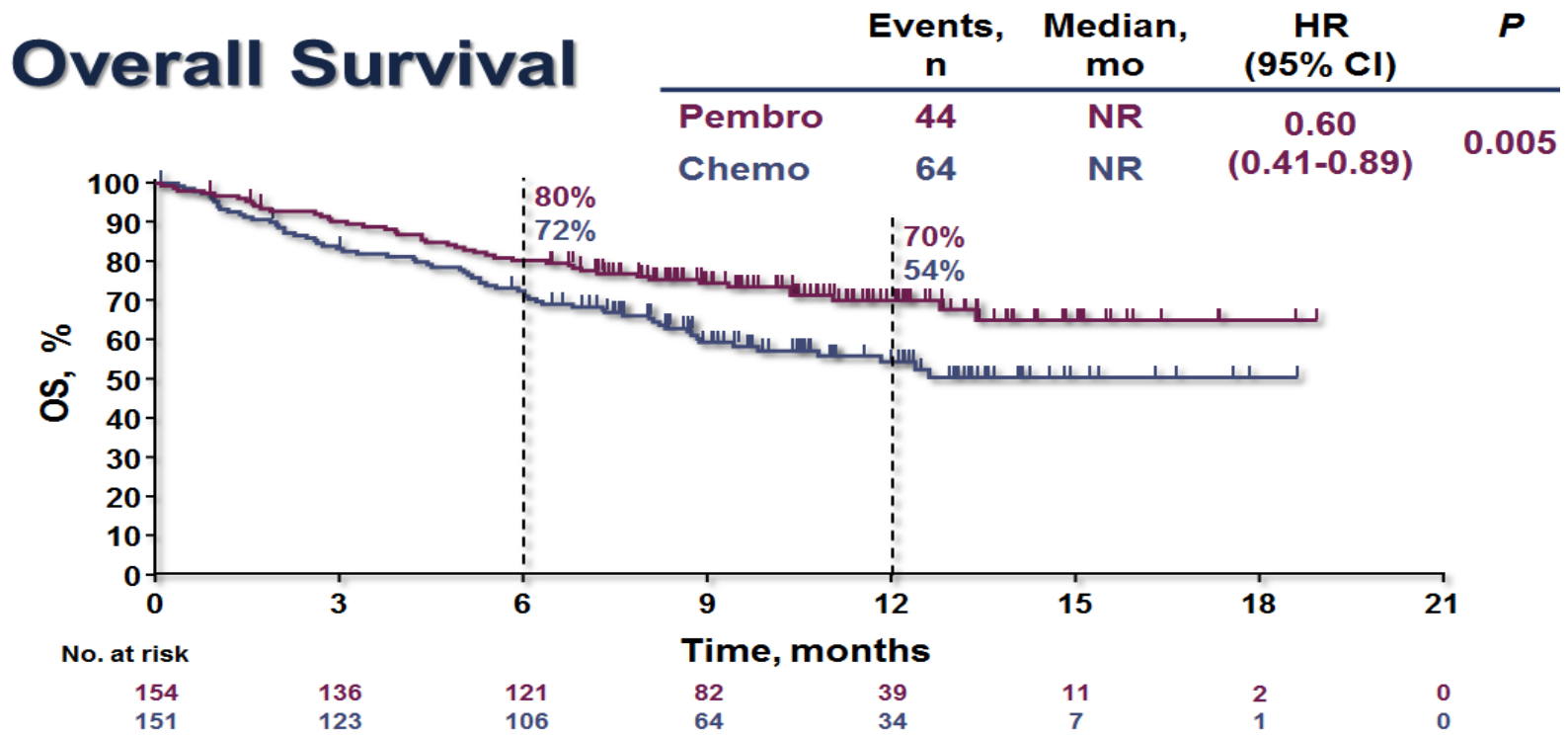


imaging every 9 weeks

- 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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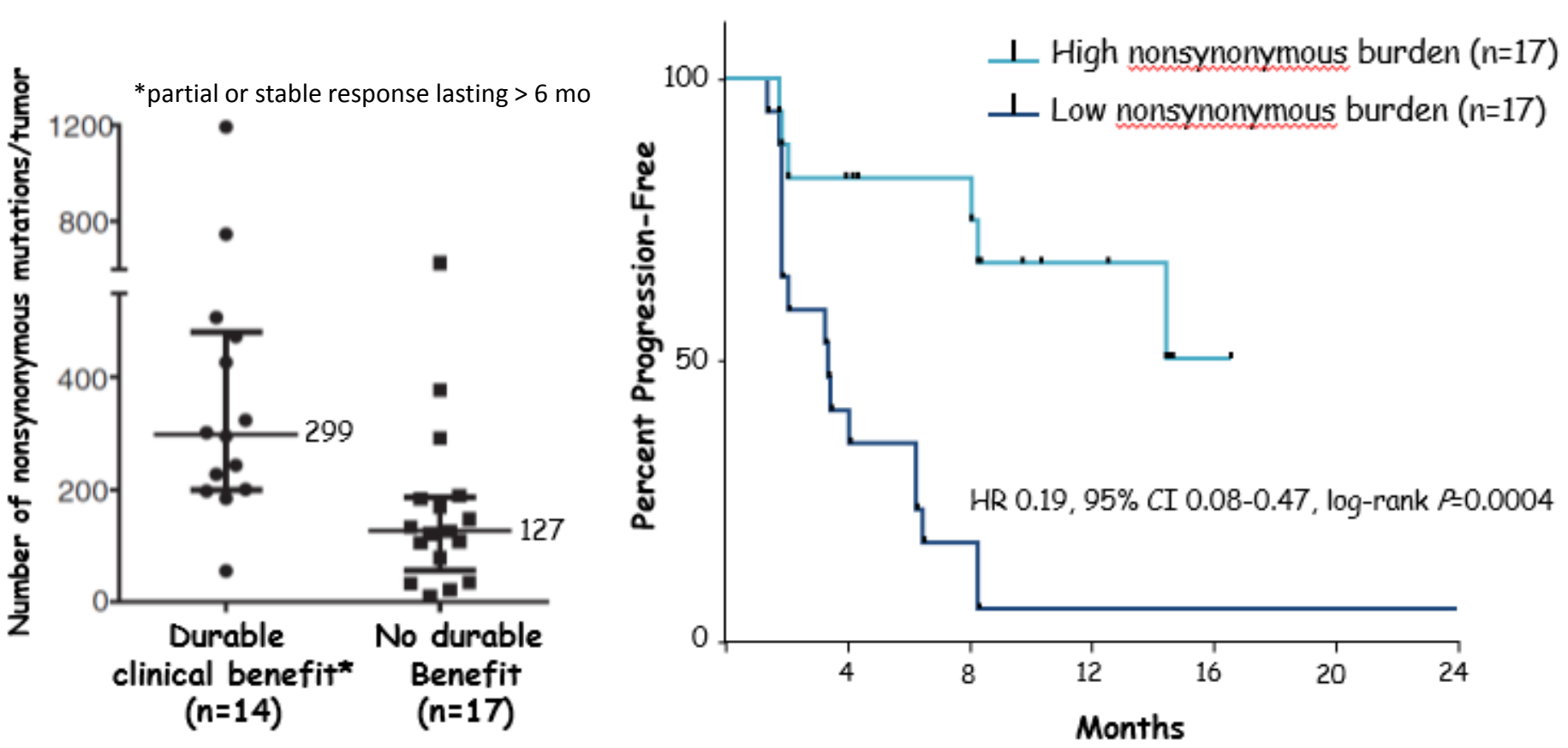
Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



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

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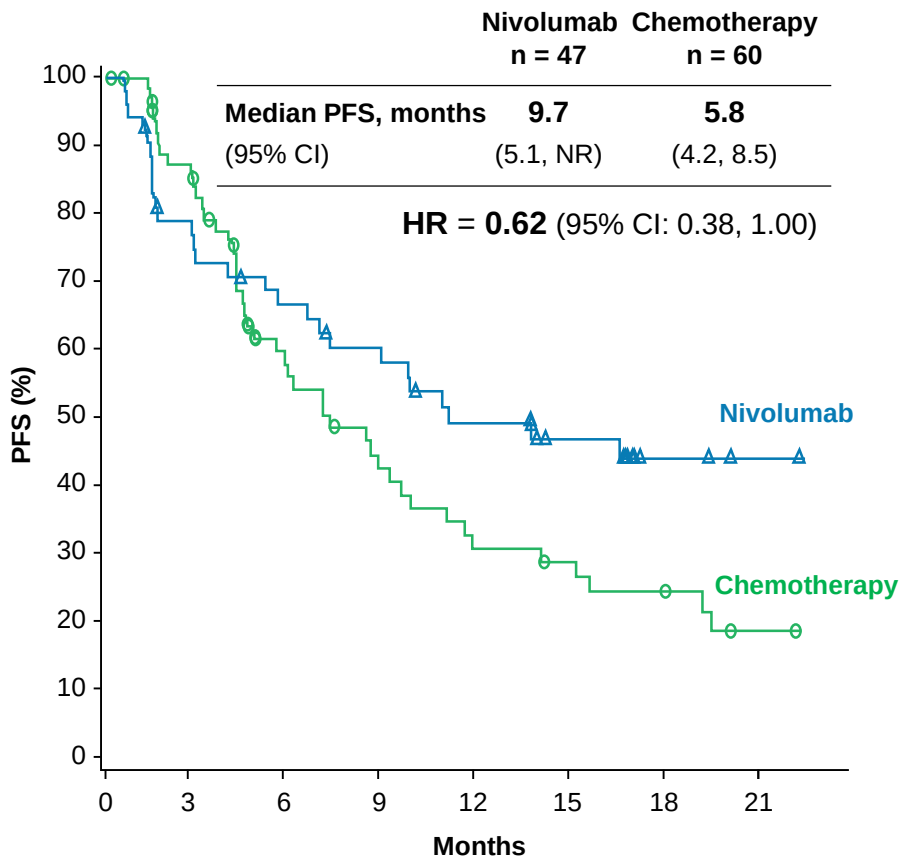
PFS by Tumor Mutation Burden Subgroup CheckMate 026 TMB Analysis

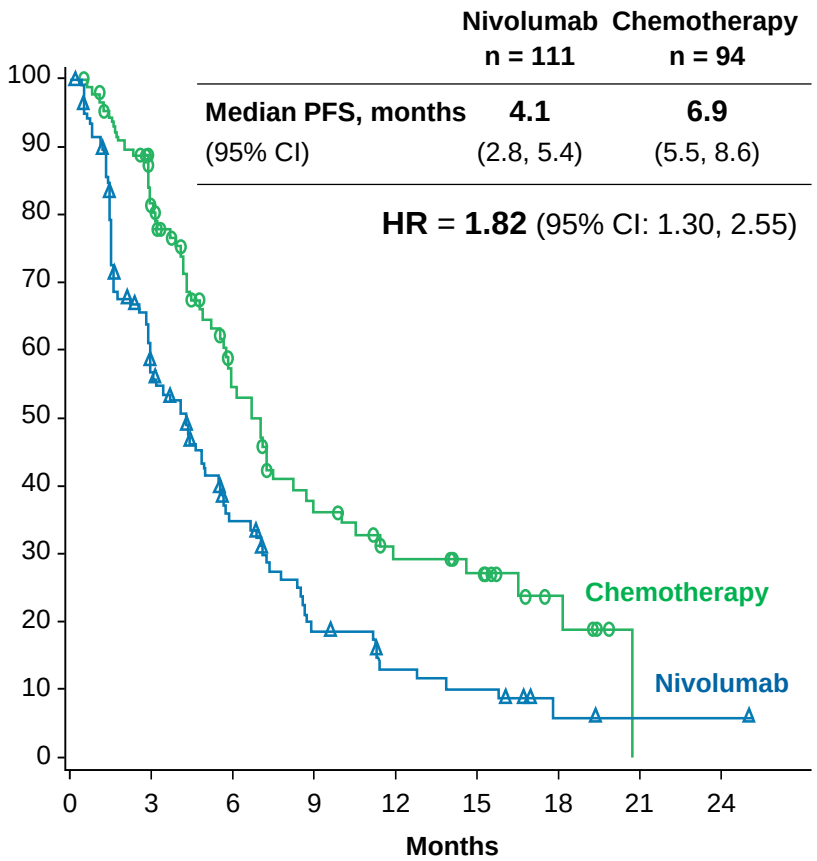
Nivolumab in First-line NSCLC

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

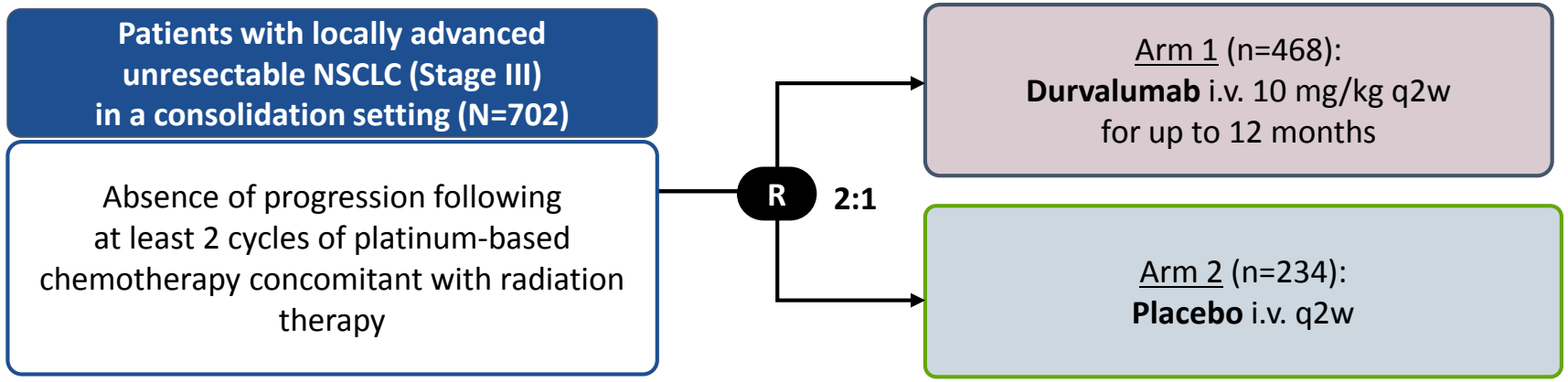


111	54	30	15	9	7	2	1	1	
94	65	37	23	15	12	5	0	0	

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.

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

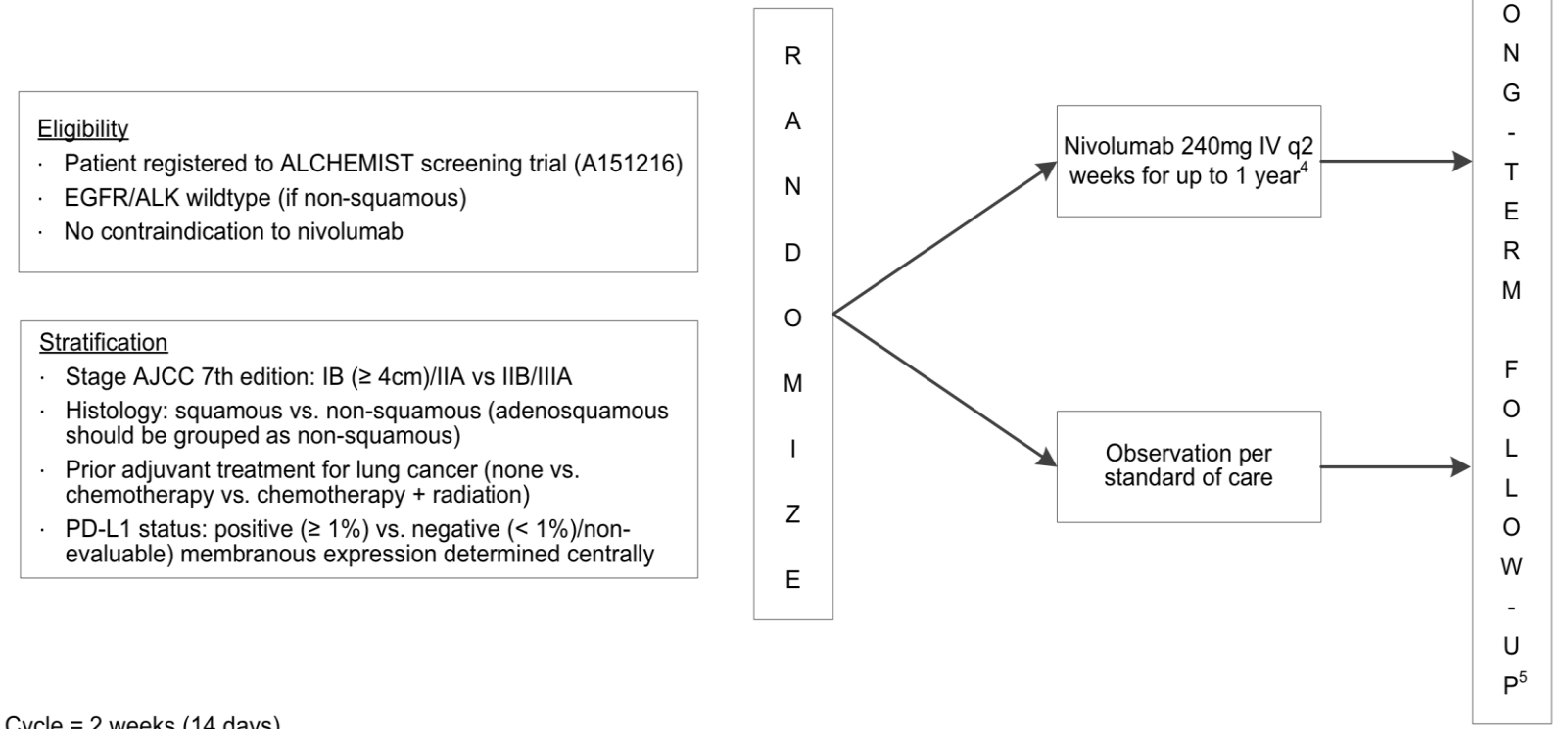
Second[illegible]
- [illegible]
- [illegible]
- PK[illegible]

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

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

DoR = duration of [illegible] = 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



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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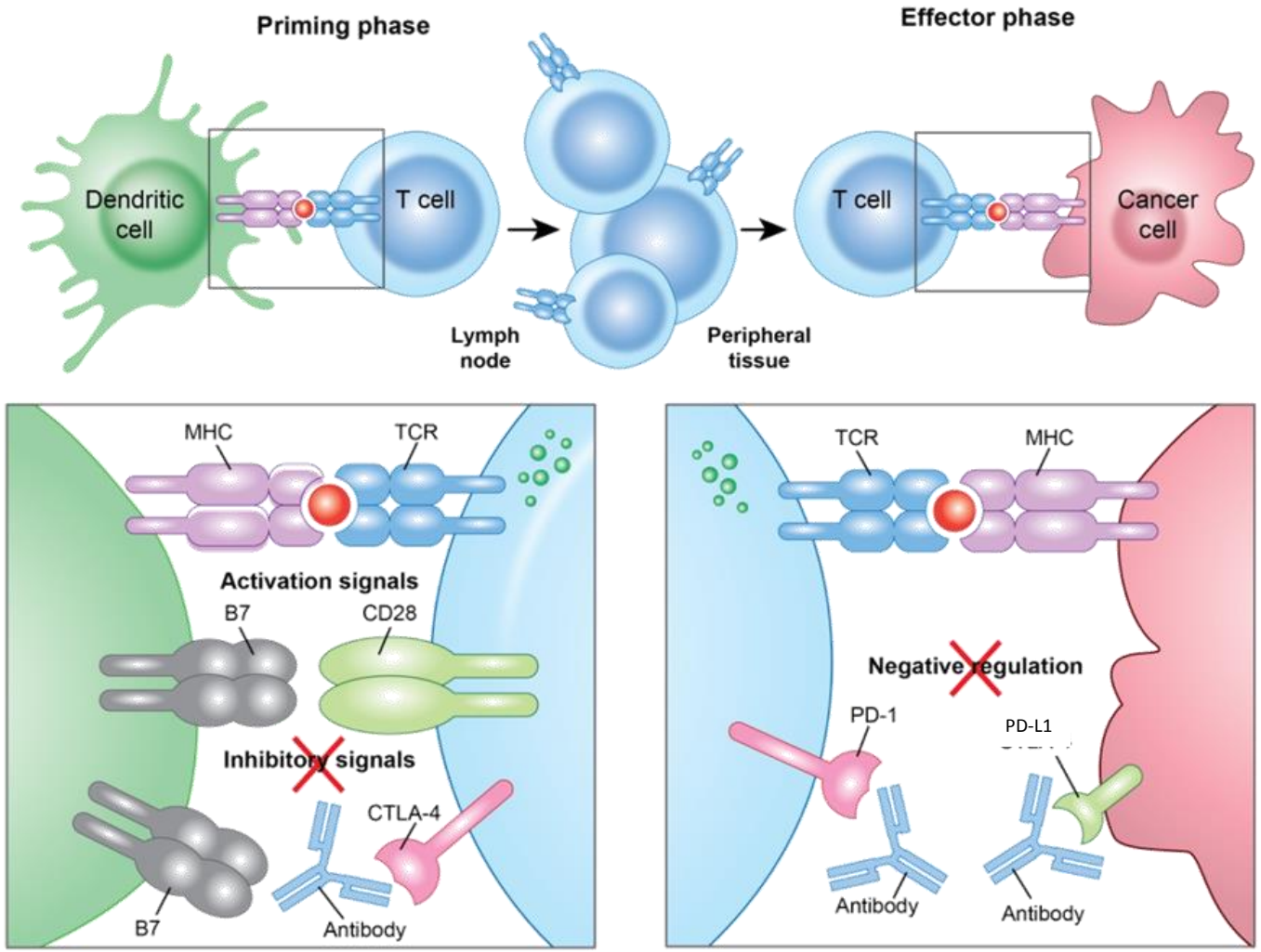
Combination
Immune checkpoint blockade



Ribas A, N Engl J Med 2012; 366:2517-2519.

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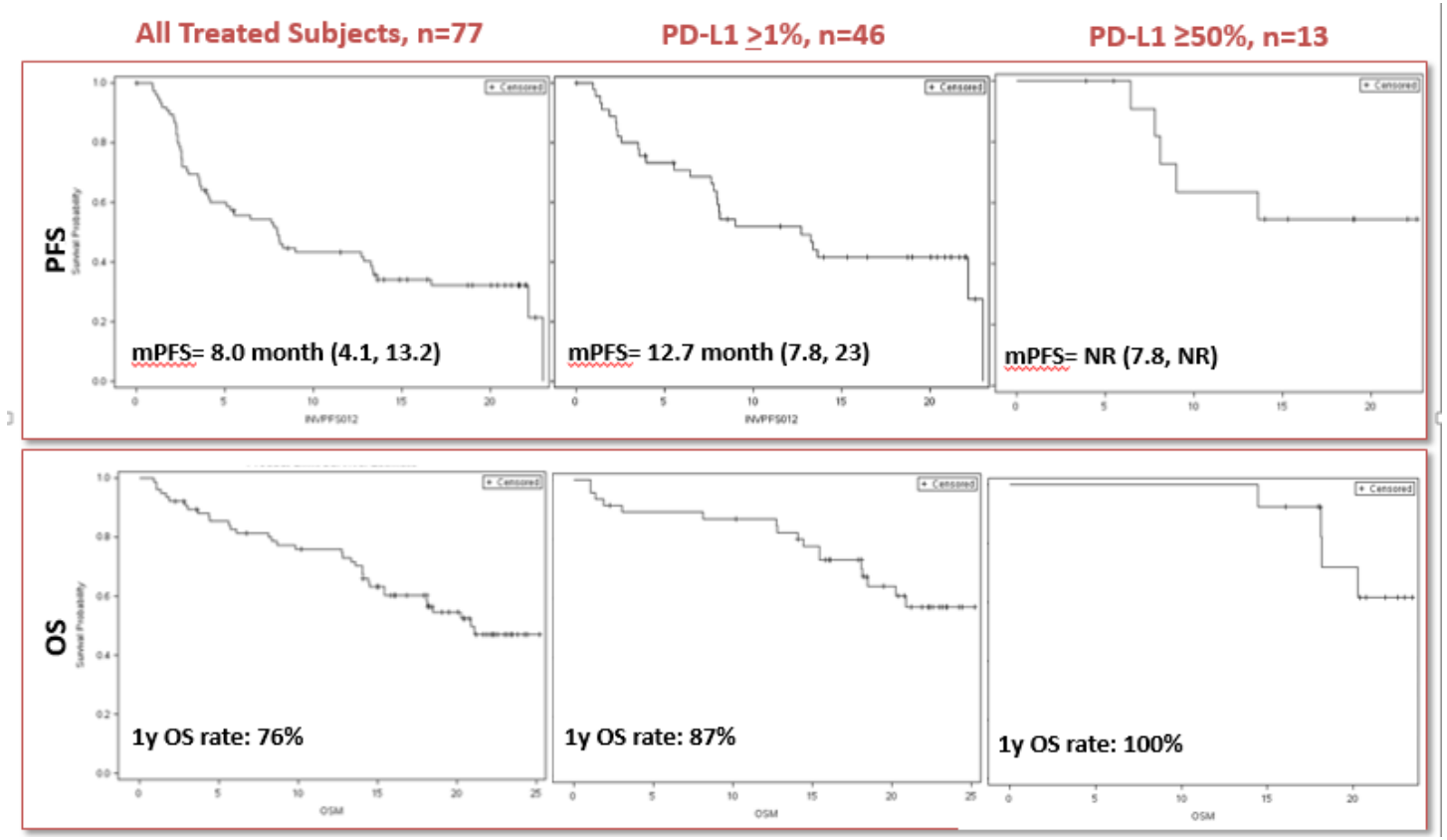
Ipilimumab: CTLA-4

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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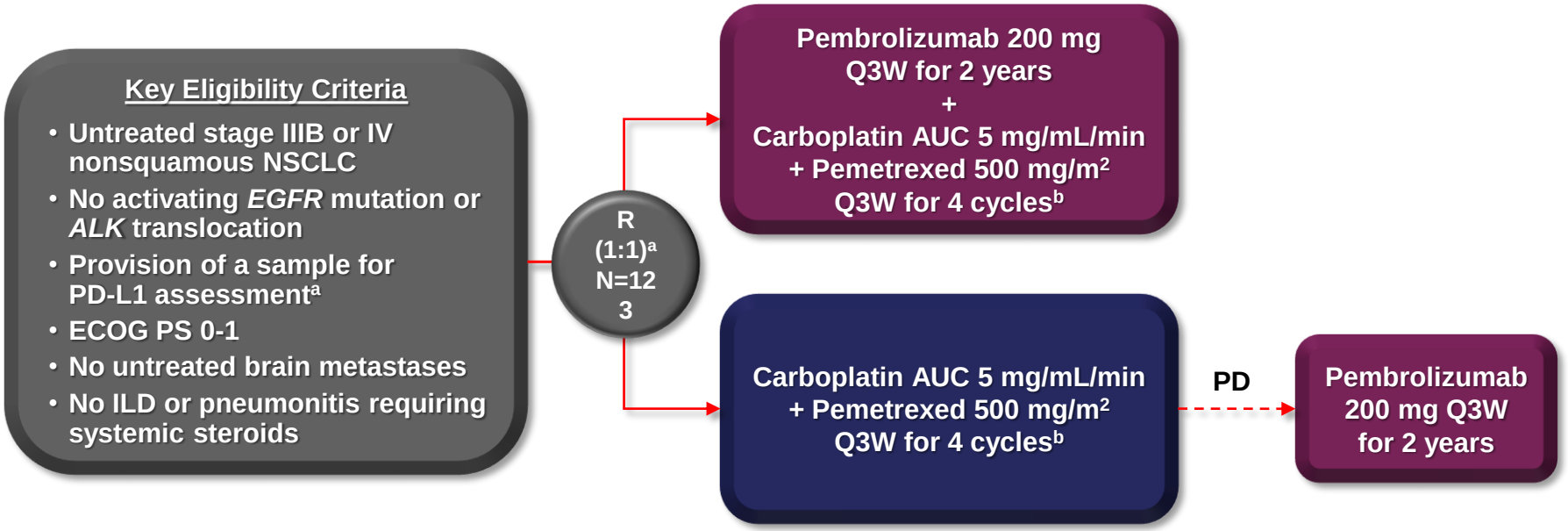
KEYNOTE-021 Cohort G



End Points

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

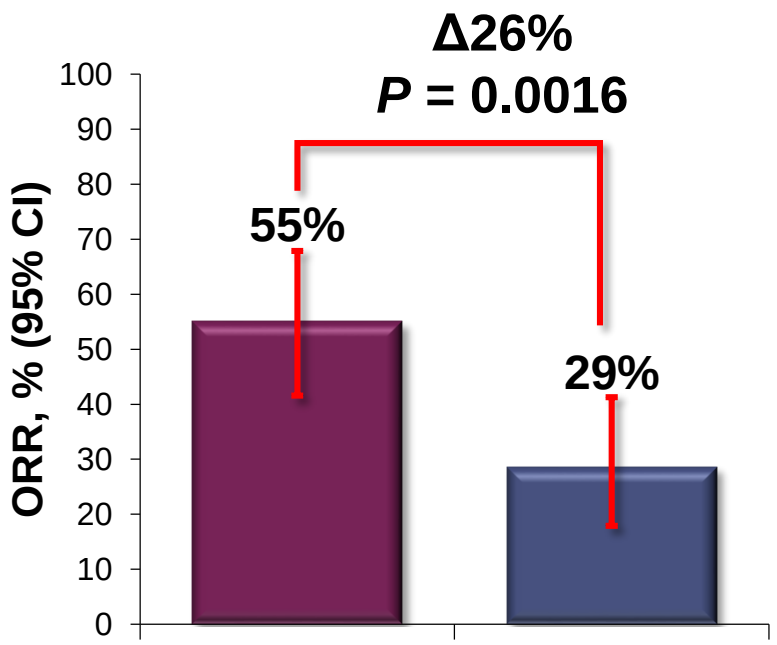
Key secondary: PFS

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

Langer, et al Lancet Oncology 2016

Confirmed Objective Response Rate

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



Data cut-off: August 8, 2016.

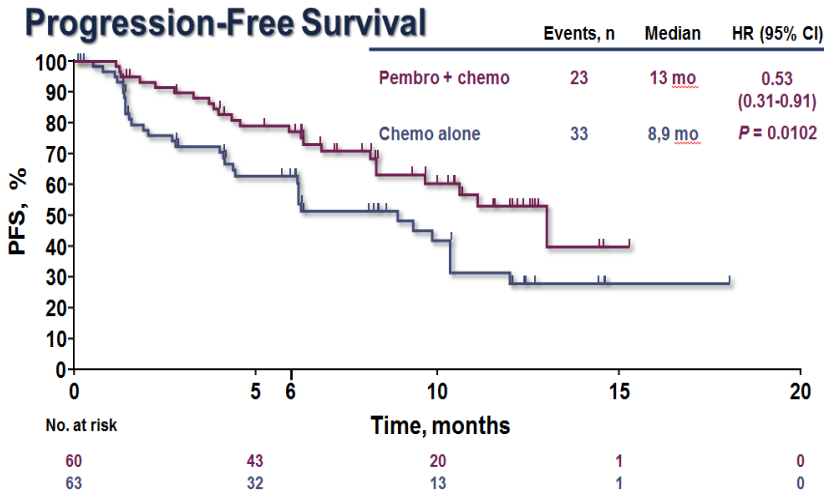
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response, [a] n (%)	29 (88)	14 (78)

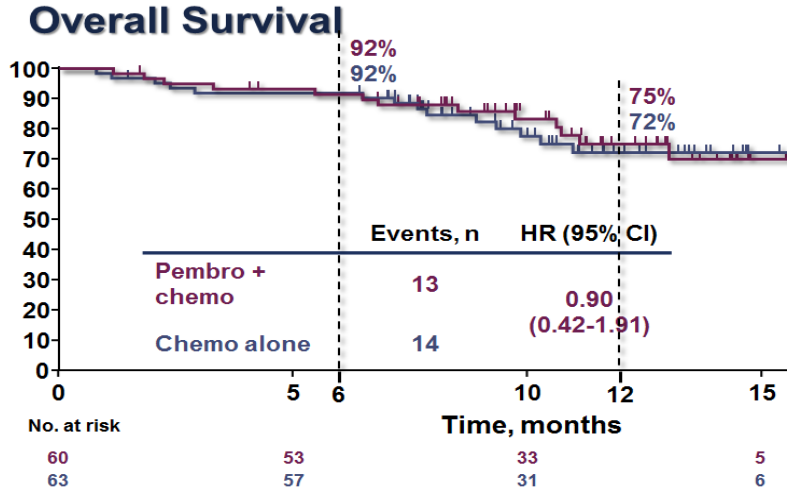
DOR = duration of response; TTR = time to response.

[a]Alive without subsequent disease progression.

Langer, et al Lancet Oncology 2016

PFS and OS Survival data



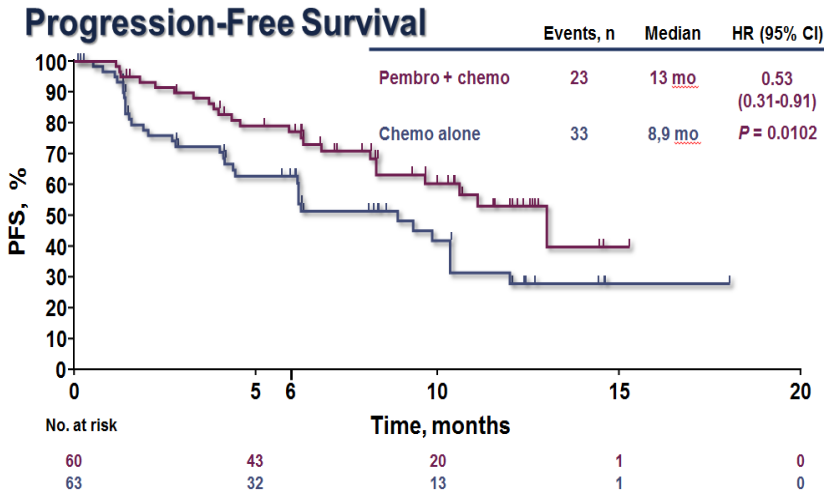


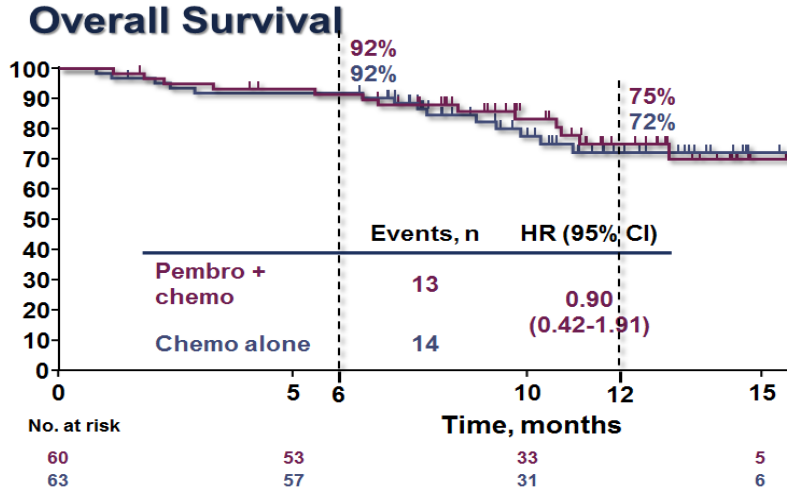
Clear PFS benefit and no OS advantage

- 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

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

Study Design

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

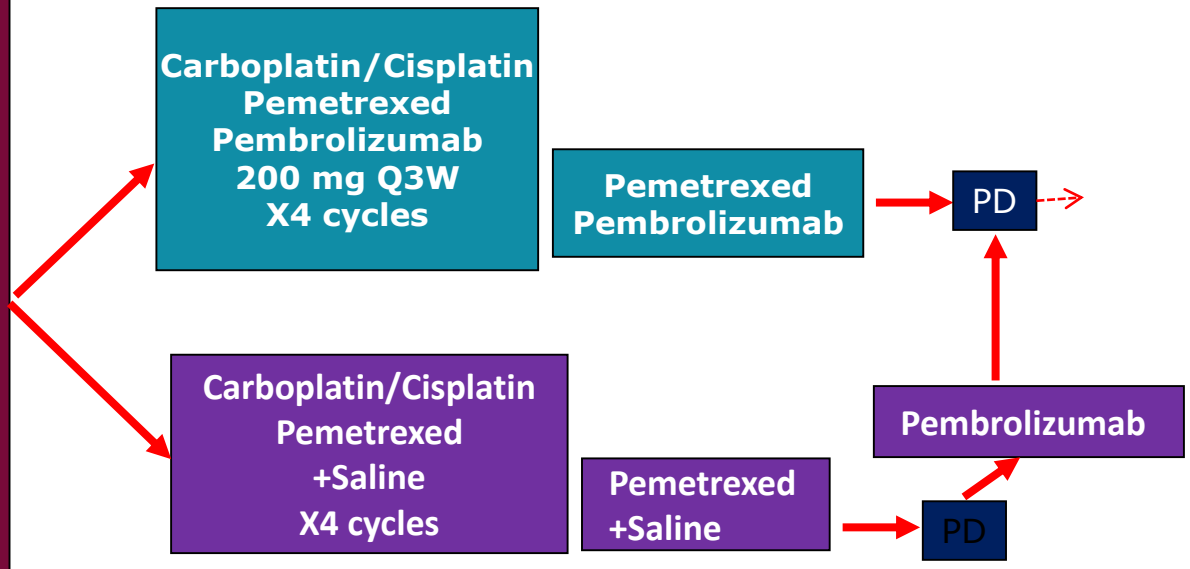
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

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
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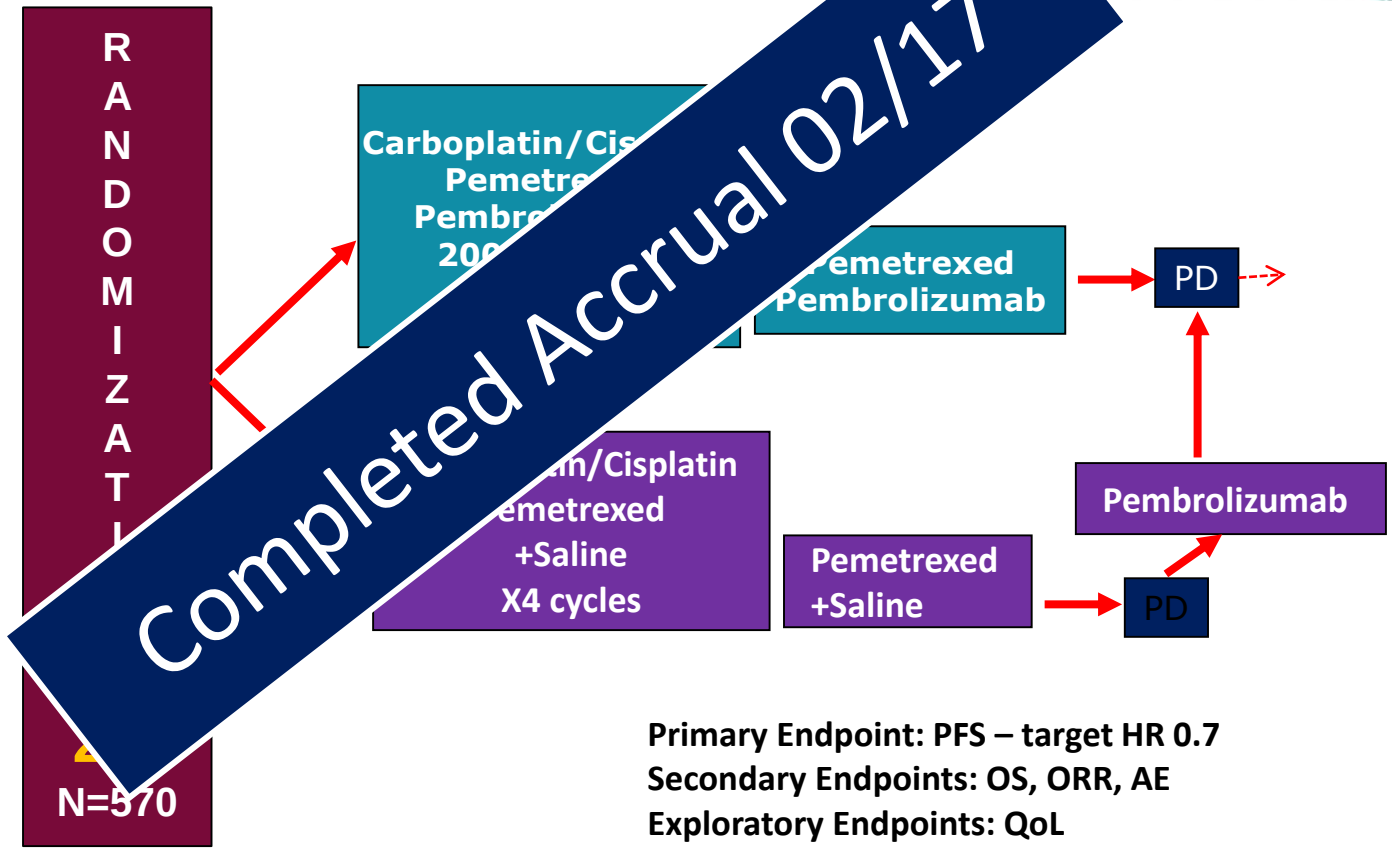

Primary Endpoint: PFS – target HR 0.7
Secondary Endpoints: OS, ORR, AE
Exploratory Endpoints: QoL

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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

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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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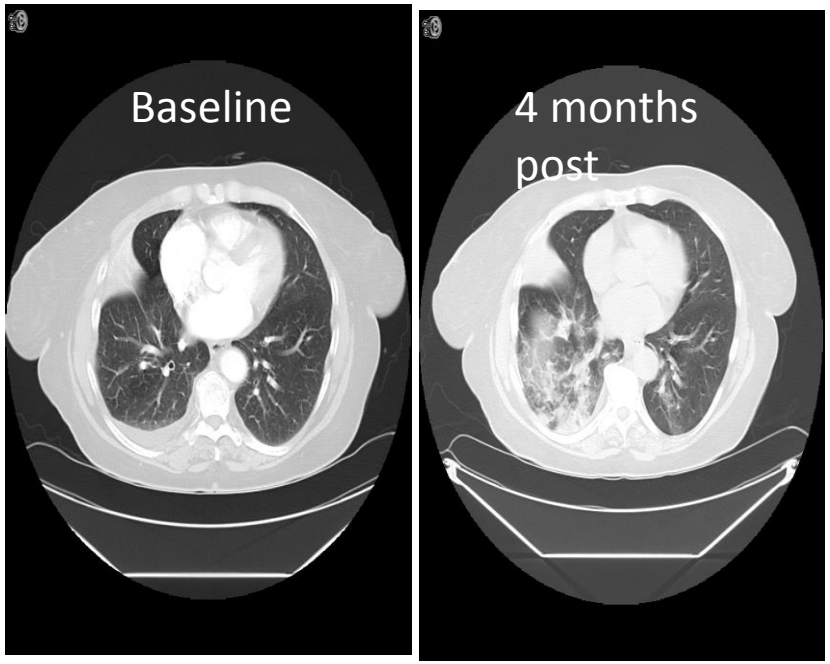
Case Study #2

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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