ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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ACCC Association of Community Cancer Centers

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Disclosures

- Consultant and/or Speaker:
  - AbbVie
  - BMS
  - Celgene
  - EMD Serono
  - Merck
  - Pfizer
  - Roche
- Research funding
  - BMS
  - Merck
- I will not be discussing non-FDA approved indications during my presentation.

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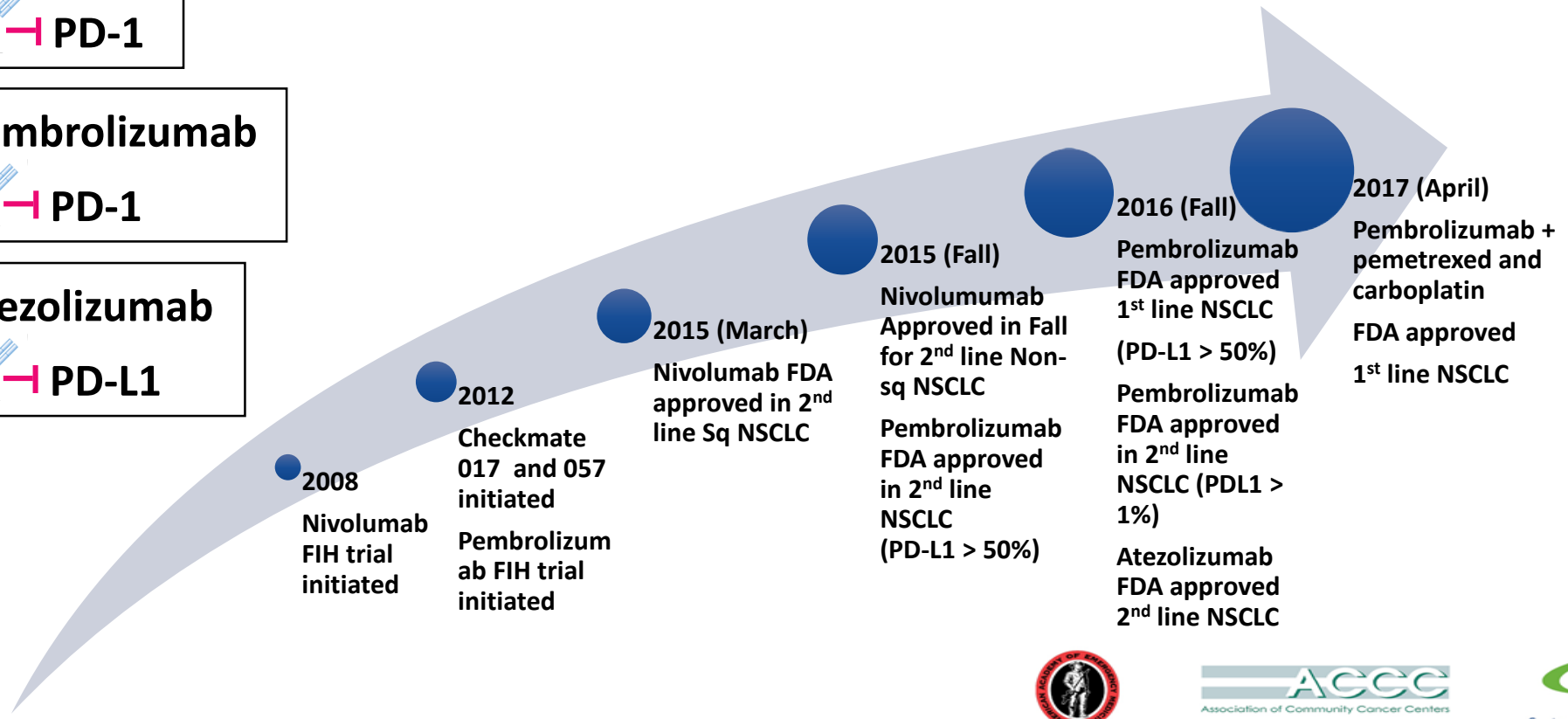
Immune checkpoint inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1



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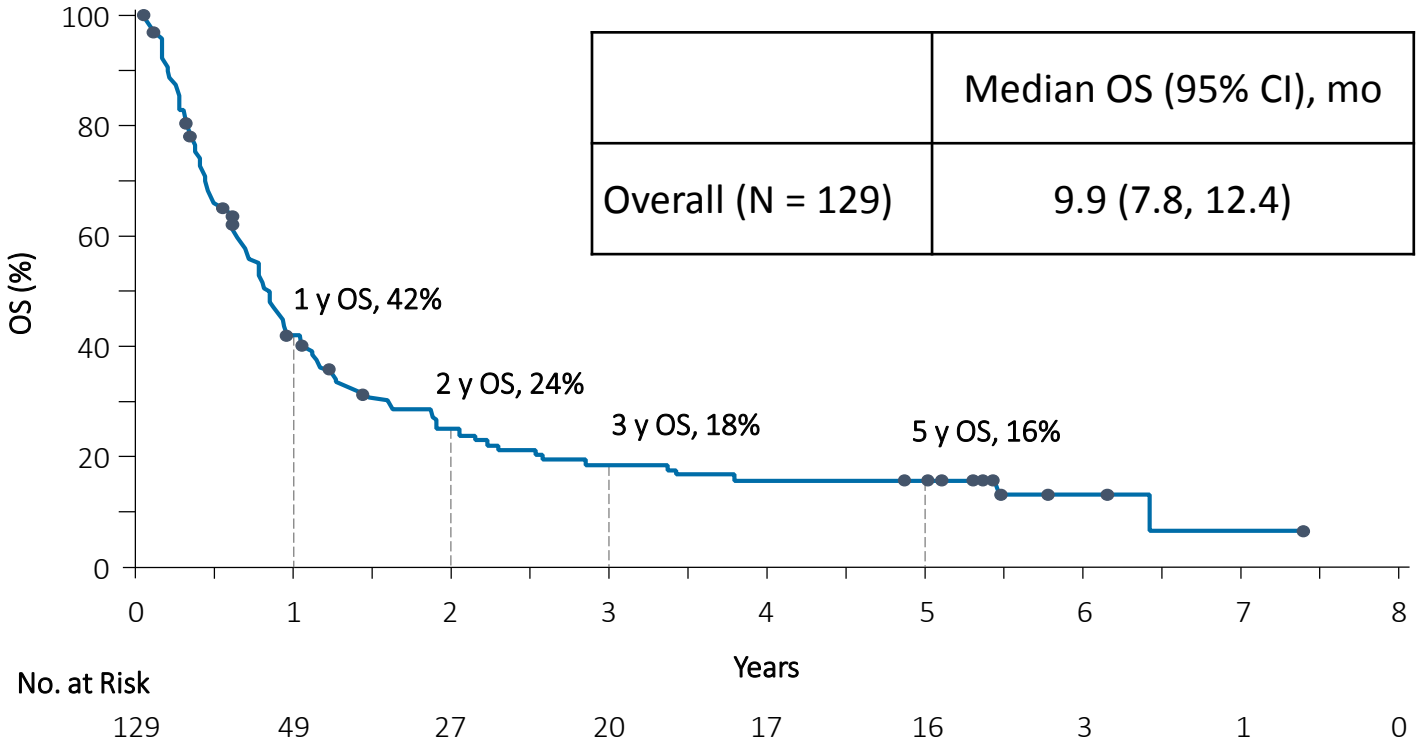
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

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



Brahmer et al, AACR 2017

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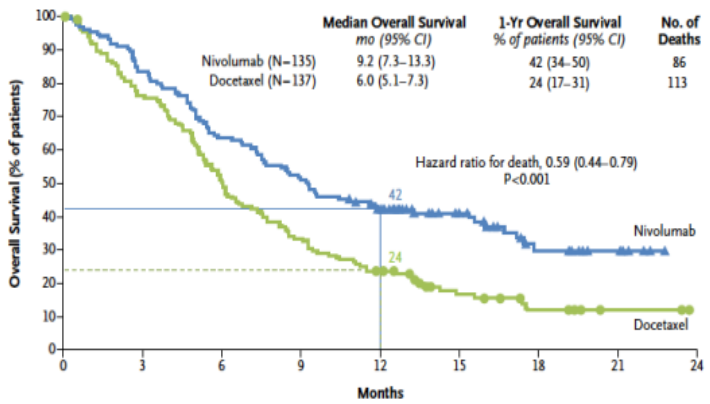
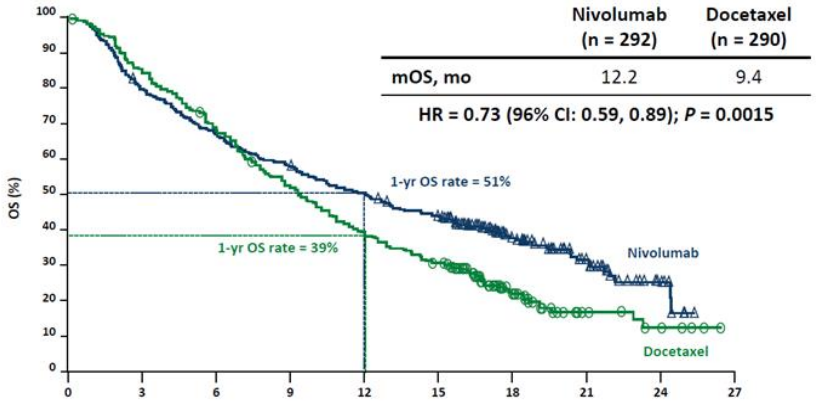
PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

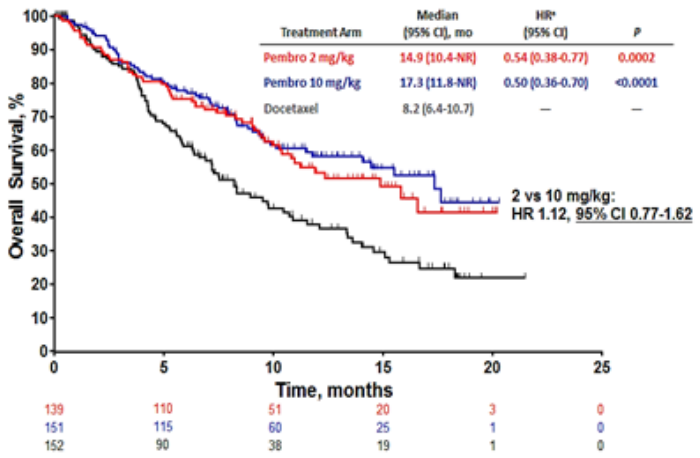
CHECKMATE 017



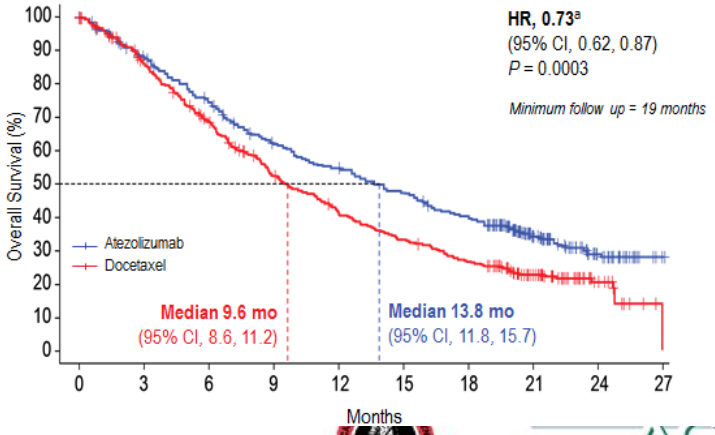
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)



OAK



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

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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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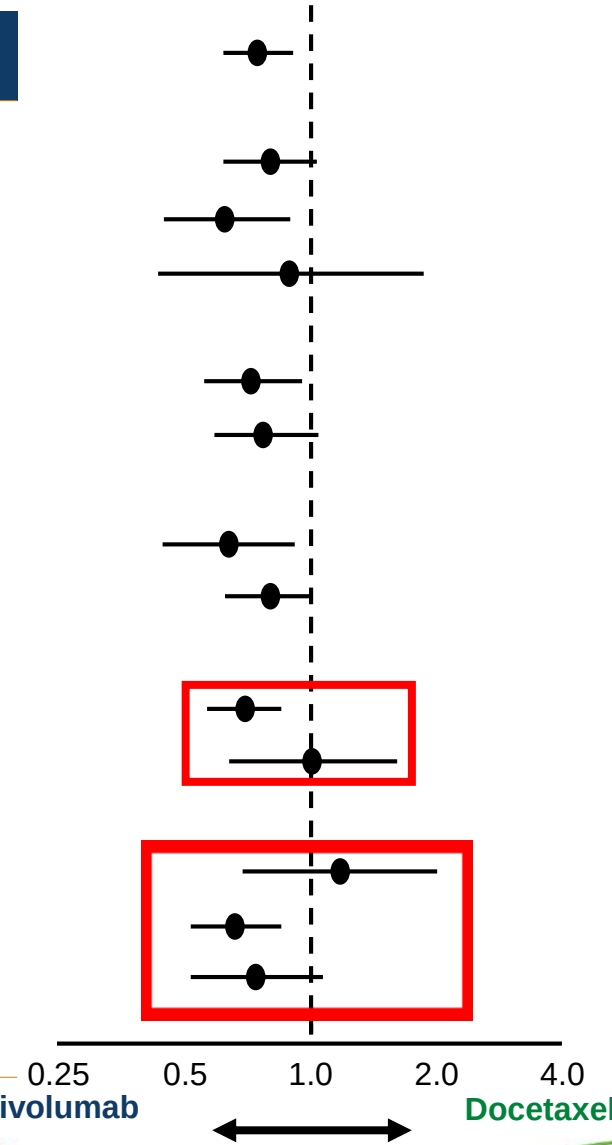
Predefined Subgroups Checkmate 57

	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)



All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

Borghaei H, Paz-Ares L, Horn L, Spigel D, Steins M, Ready N et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2015;373(17):1627-1639.

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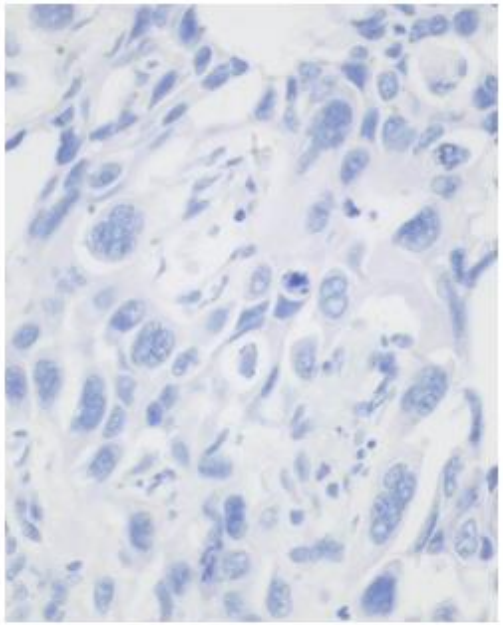
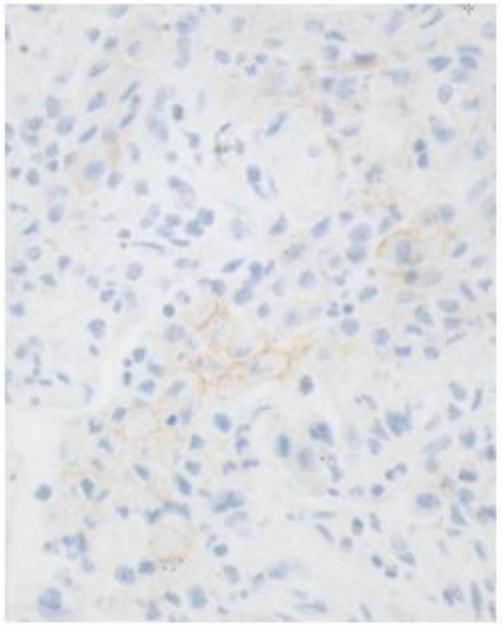
PD-L1 selection to bridge the gap?



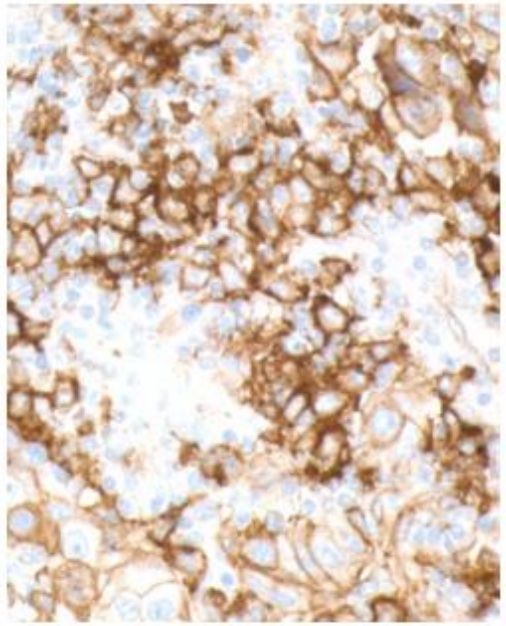
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



PD-L1 = 100% positive

Strong Positive (50%-100%)

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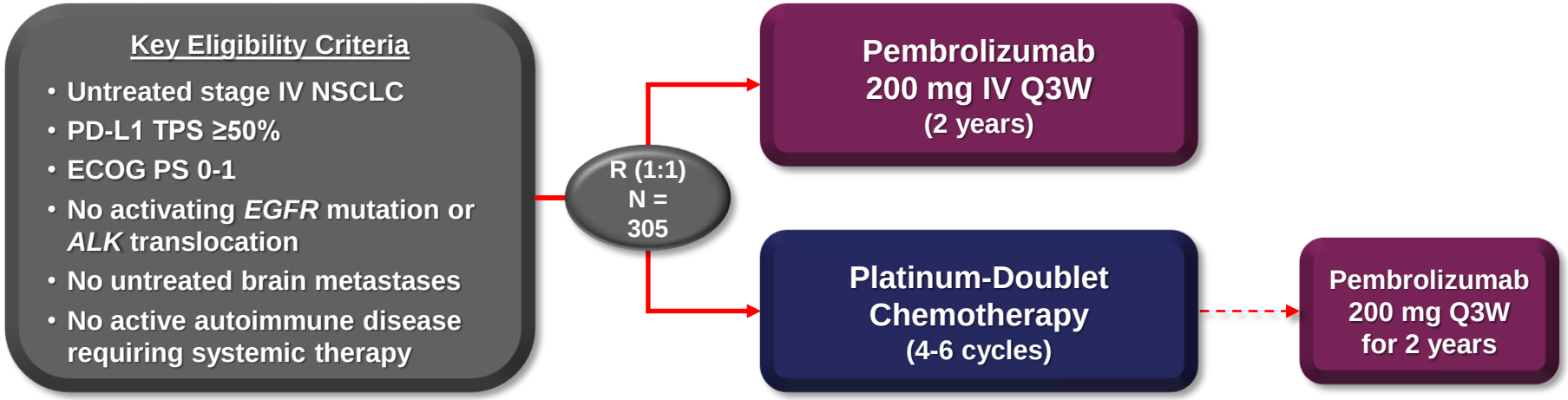
KEYNOTE-024 Study Design (NCT02142738)



Key End Points

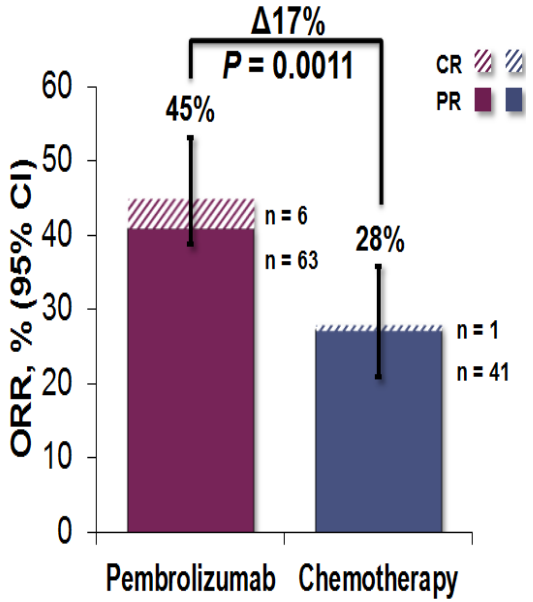
Primary: PFS (RECIST v1.1 per blinded, independent central review)

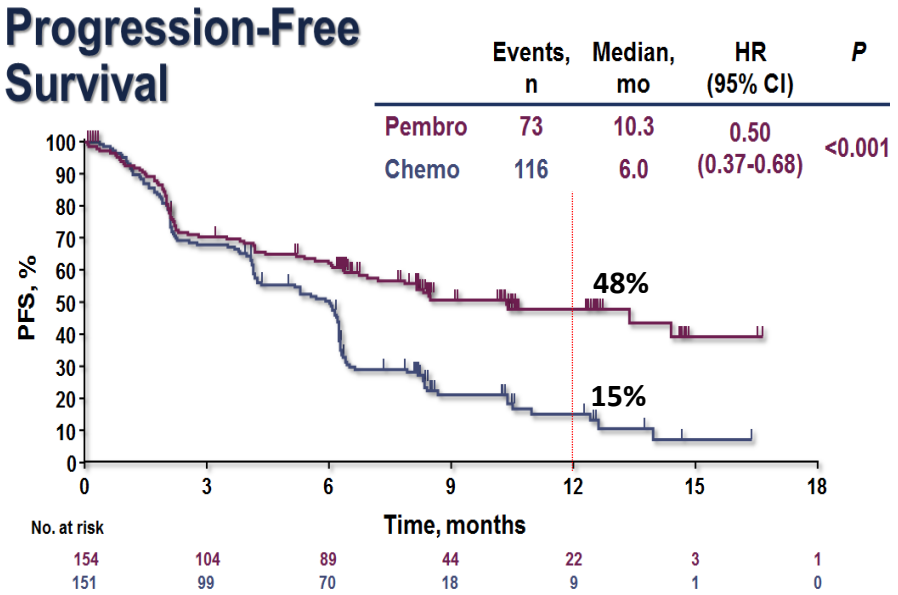
Secondary: OS, ORR, safety

Exploratory: DOR

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

Efficacy data: Keynote 24



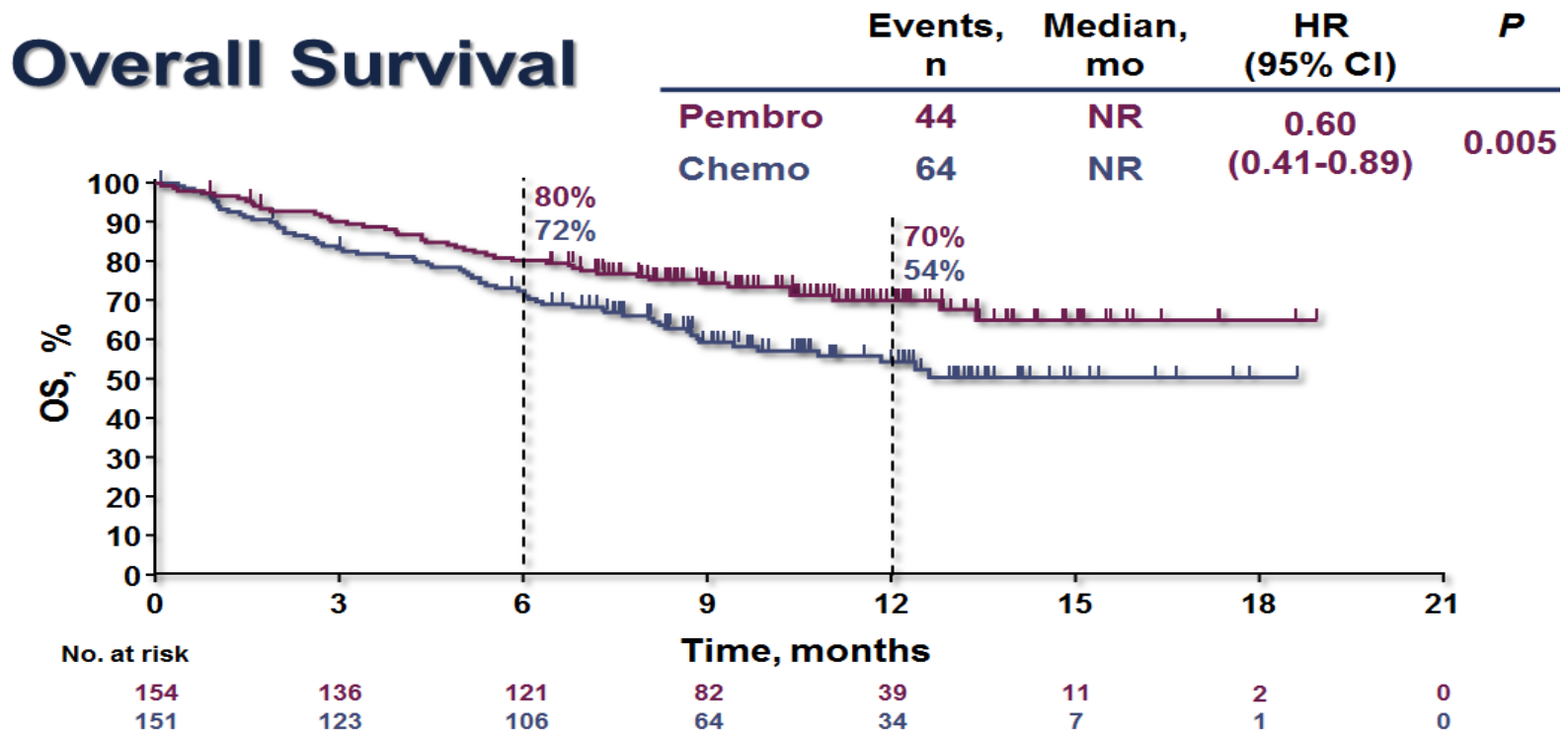


imaging every 9 weeks

- 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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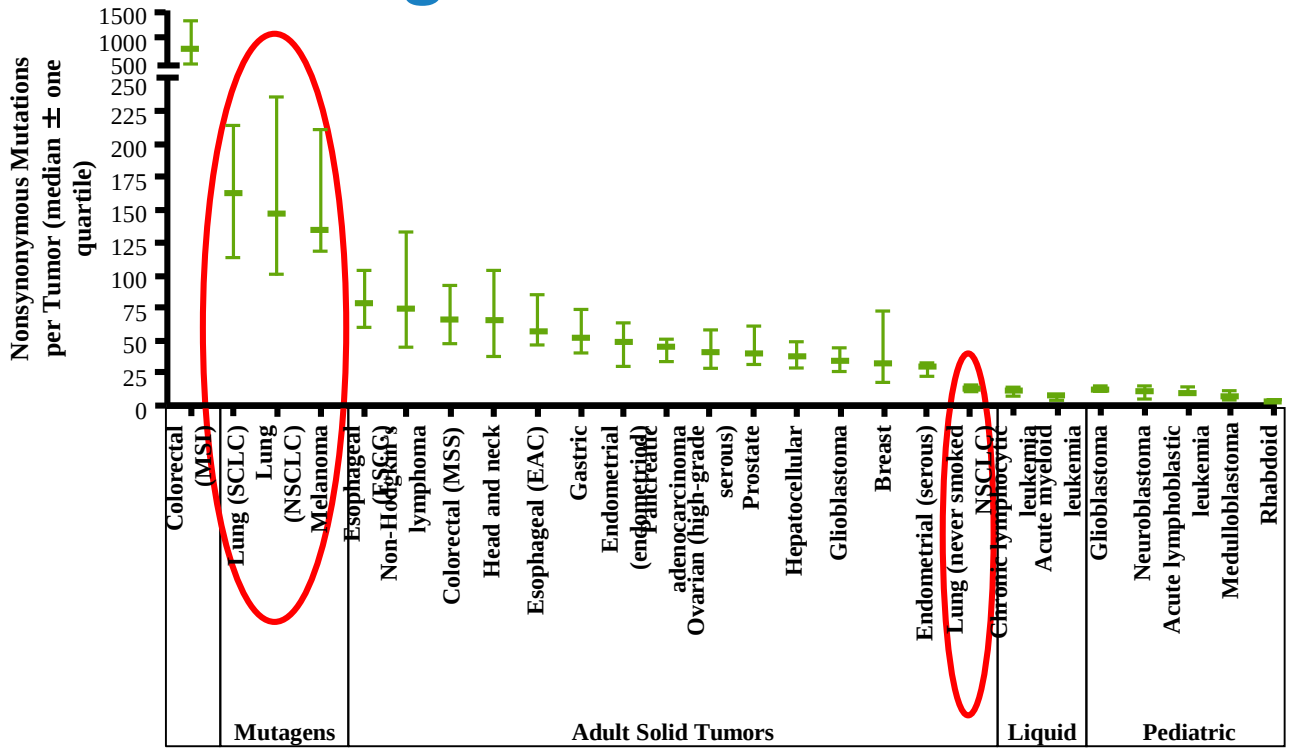
PD-(L)1 antibodies active in tumors known to have high mutation burden

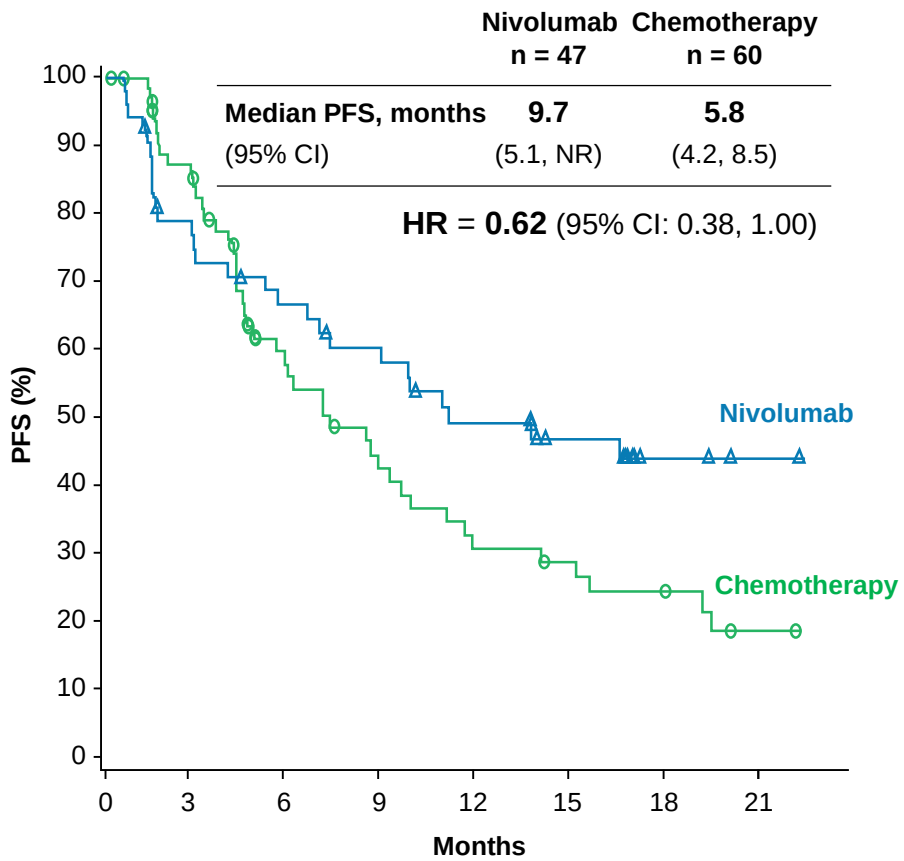


Vogelstein B, et al. *Science*. 2013.

PFS by Tumor Mutation Burden Subgroup CheckMate 026 TMB Analysis

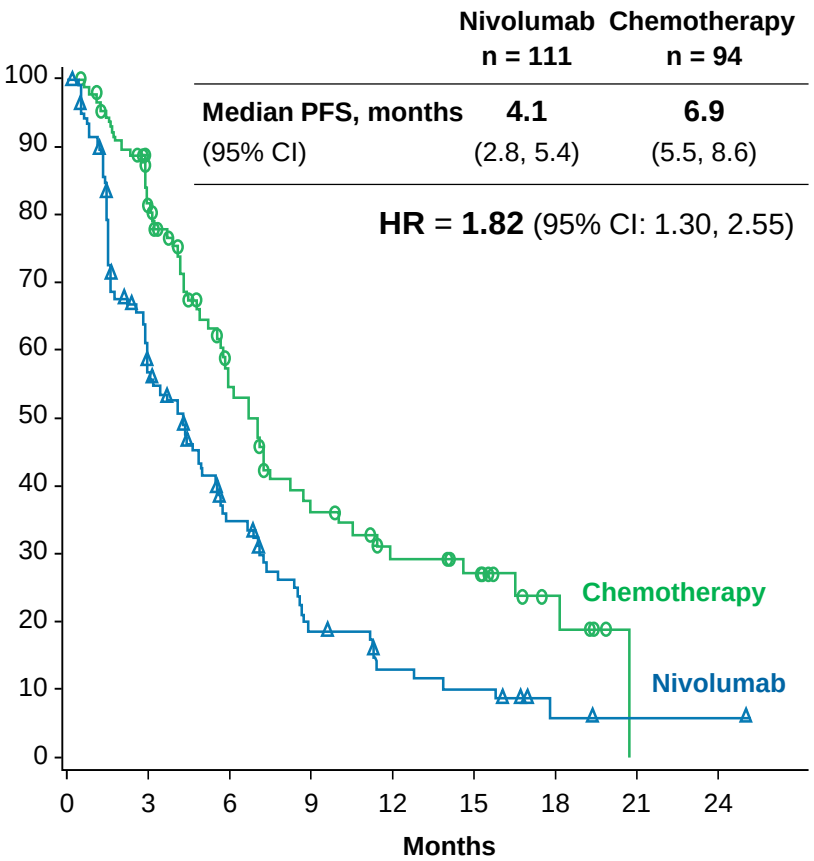
Nivolumab in First-line NSCLC

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

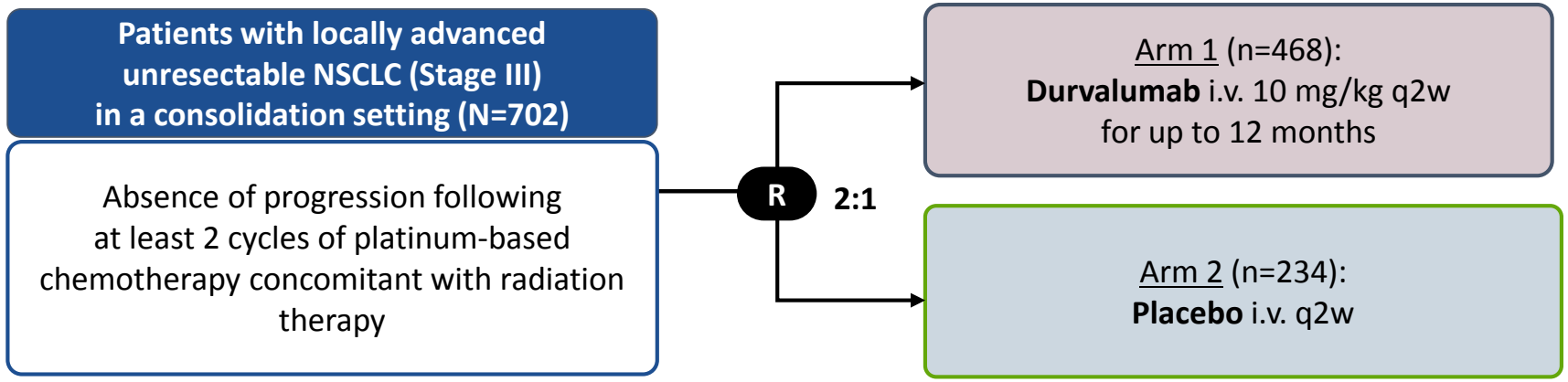


111	54	30	15	9	7	2	1	1	
94	65	37	23	15	12	5	0	0	

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.

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Safety Summary*

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	142 (29.9)	61 (26.1)
Grade 5	21 (4.4)	13 (5.6)
Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs, n (%)	322 (67.8)	125 (53.4)
SAEs, n (%)	136 (28.6)	53 (22.6)
Any-grade immune-mediated AEs, n (%)	115 (24.2)	19 (8.1)
Grade 3/4	16 (3.4)	6 (2.6)

*Two patients randomized to placebo received at least one dose of durvalumab and were considered part of the durvalumab arm for safety reporting.

Safety analysis set. AE, adverse event; SAE, serious adverse event

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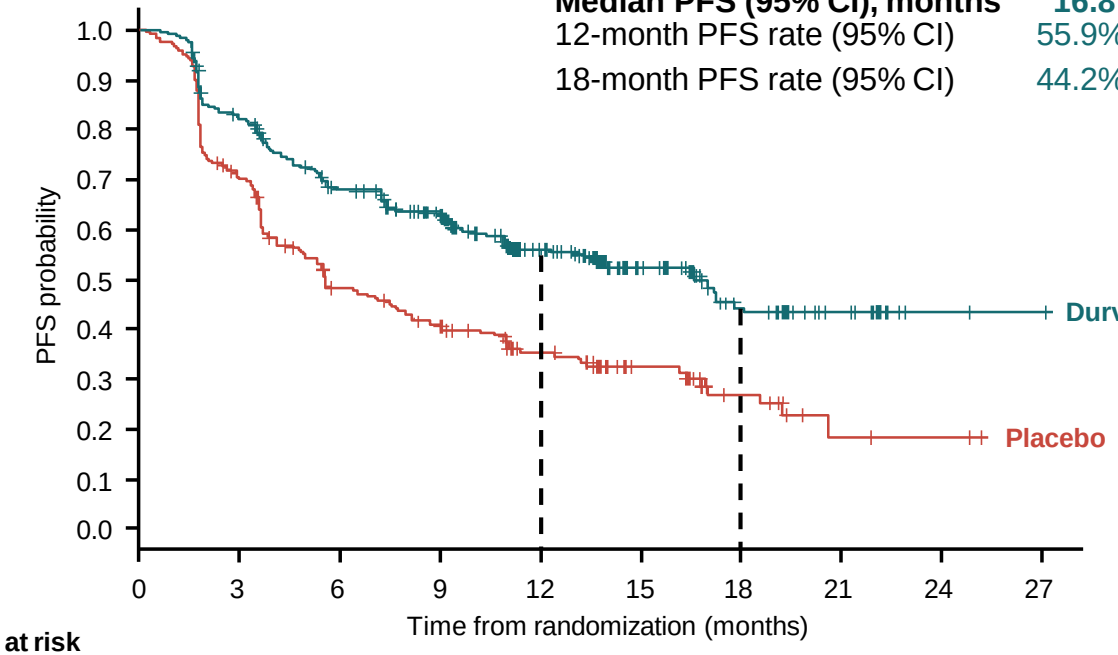
Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65) Two-sided P<0.0001

PFS by BICR (Primary Endpoint; ITT)

	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)



No. at risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

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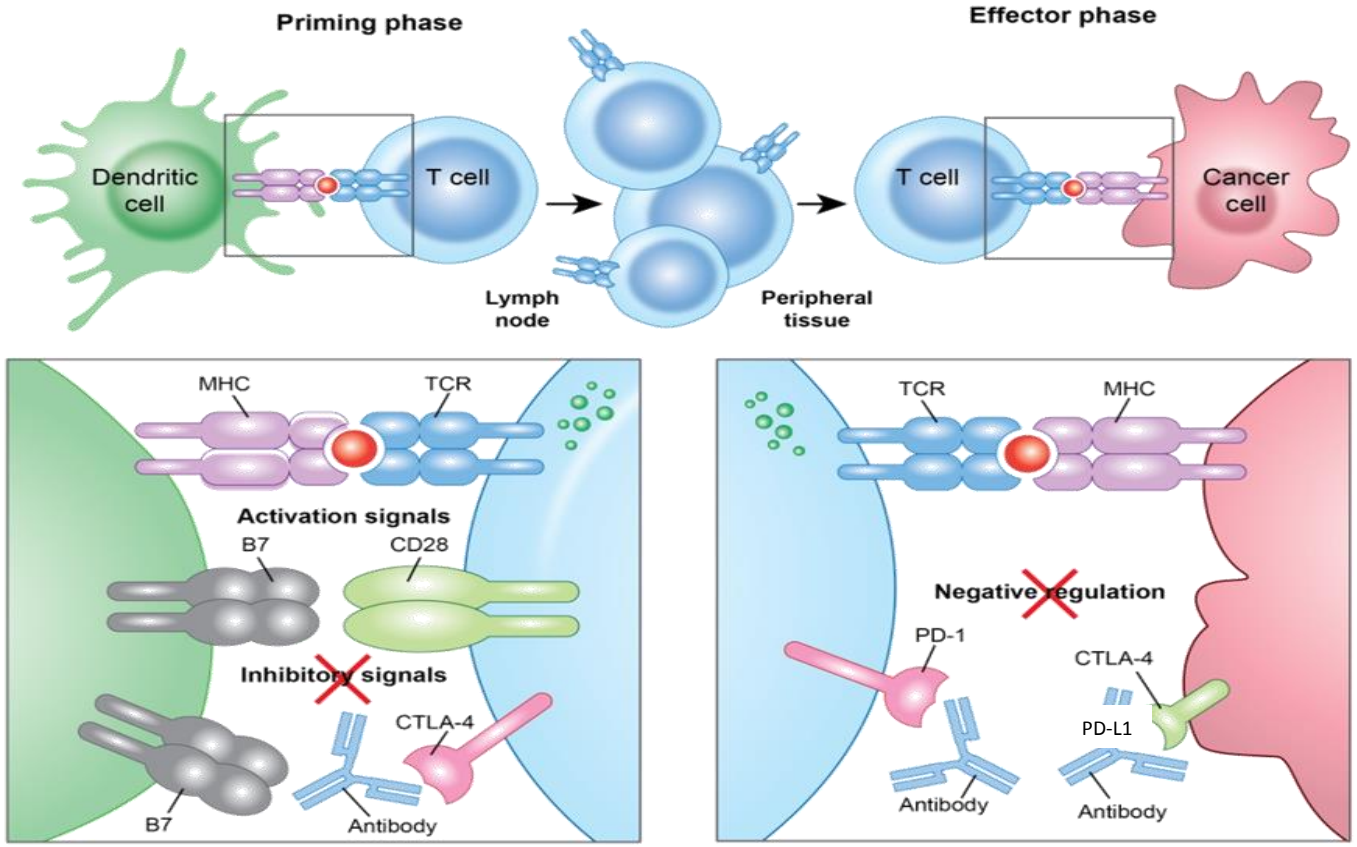
Combination Immune checkpoint blockade



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

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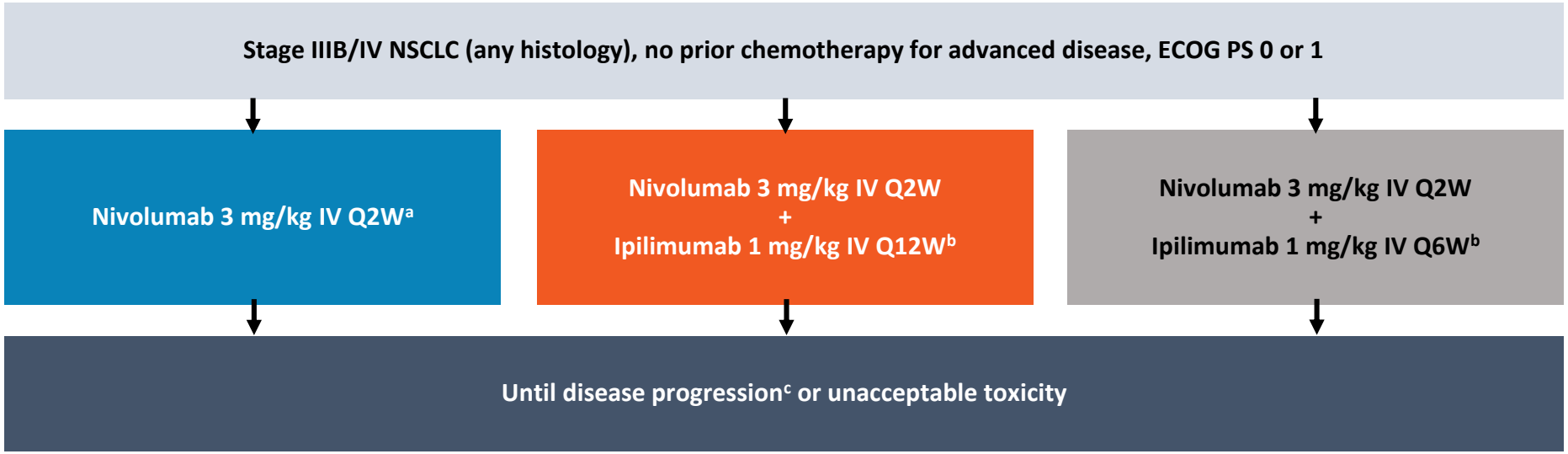
Phase 1 CheckMate 012 Study Design: First-Line Nivolumab ± Ipilimumab in NSCLC



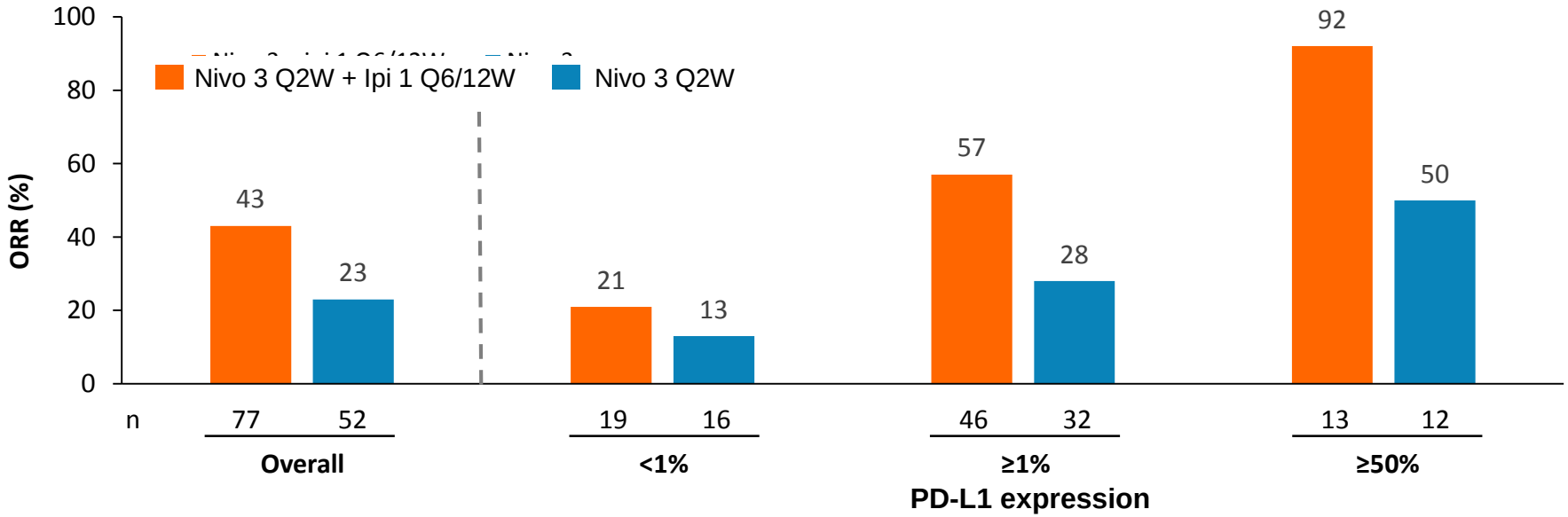
Primary endpoint: safety and tolerability
Secondary endpoints: ORR (RECIST v1.1) and PFS rate at 24 weeks assessed by investigators
Exploratory endpoints: OS, efficacy by PD-L1 expression

- Updated data[d] presented here are based on median follow-up durations of 22 months (monotherapy) and 16 months (combination cohorts)
  - Overall additional follow-up relative to previous reports: monotherapy, +~18 months;[1] combination cohorts, +6 months[2]

ClinicalTrials.gov number NCT01454102; [a]Treatment allocation not randomized; [b]Treatment allocation randomized; earlier cohorts evaluated other dosing schedules/regimens[2] [c]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
[d]Based on a September 2016 database lock

1. Gettinger S, et al. *J Clin Oncol* 2016;34:2980–2987; 2. Hellmann MD, et al. *Lancet Oncol* 2016 Dec 5. [Epub ahead of print].

Nivolumab ± Ipilimumab ORR by Tumor PD-L1 Expression
CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC



- 5 CRs (10%) were achieved in the nivolumab monotherapy cohort (1 in a patient with tumor PD-L1 expression <1%)
- 6 CRs (8%) were achieved in the nivolumab + ipilimumab cohorts[a] (3 in patients with tumor PD-L1 expression <1%)

Based on a September 2016 database lock; [a]3 determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation

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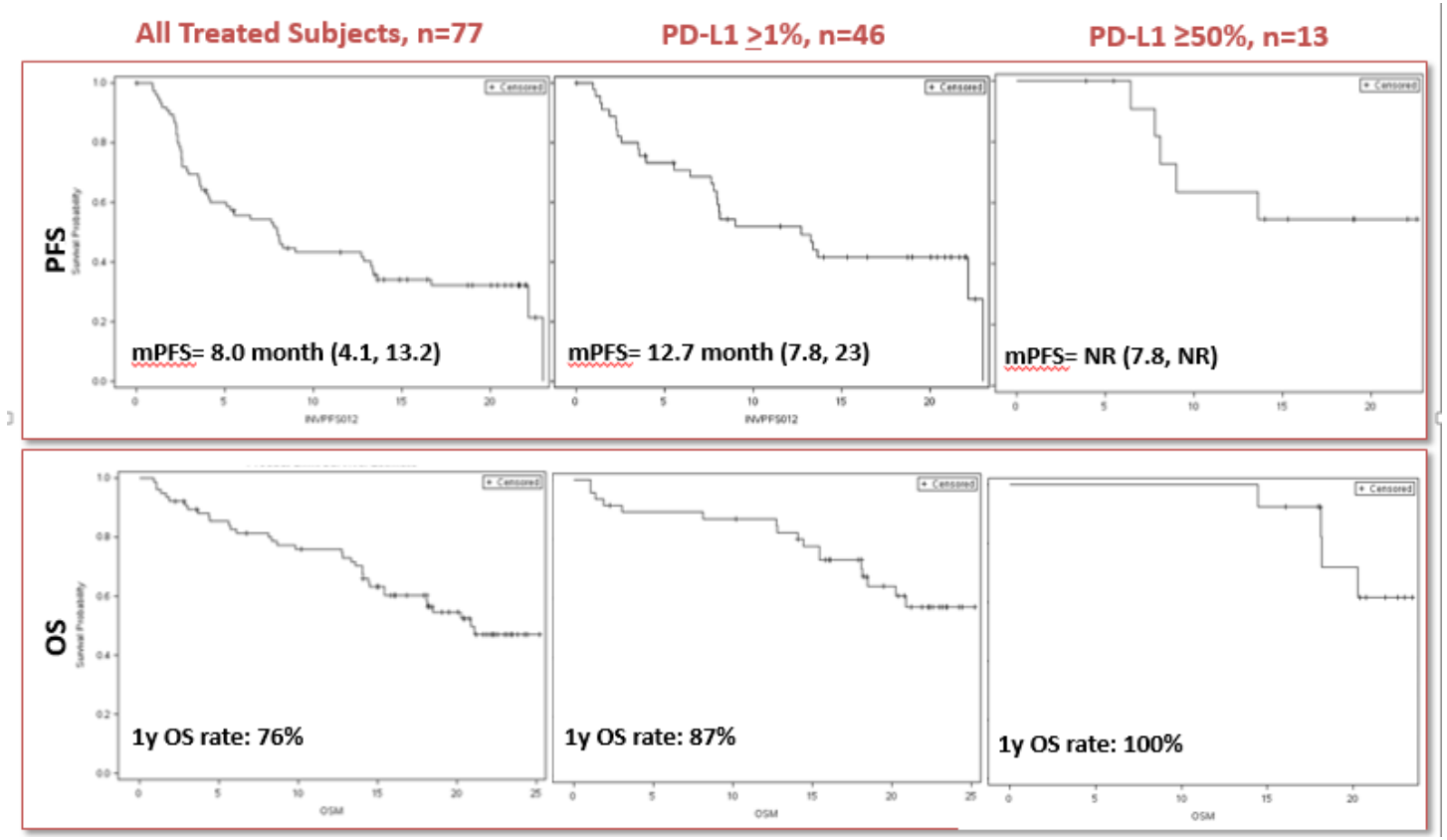
Ipilimumab: CTLA-4

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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Study Design

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

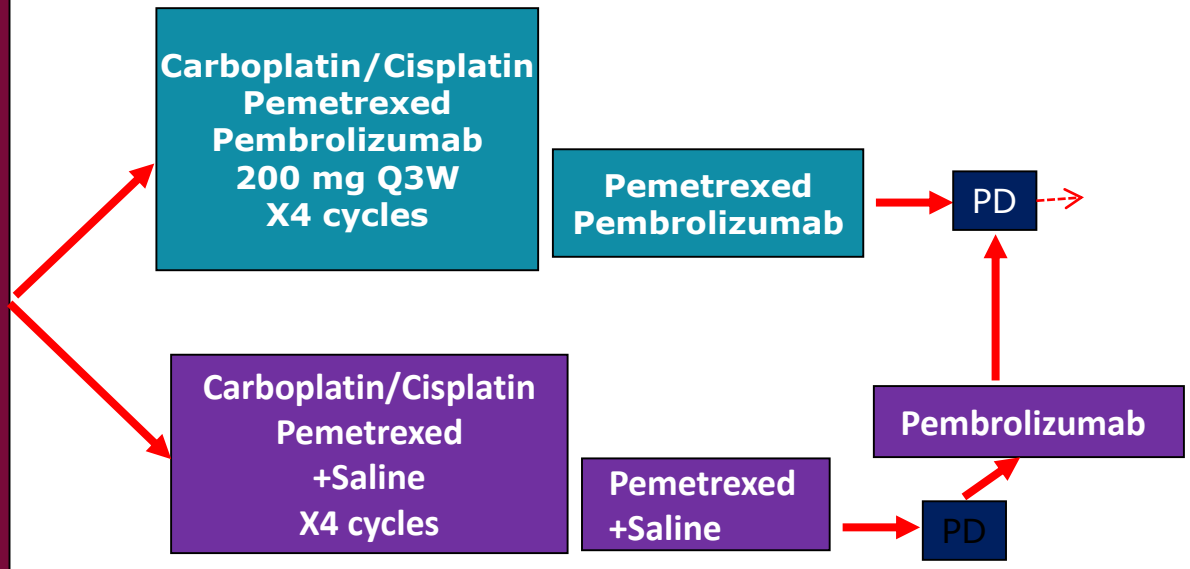
Patients:
- Metastatic non-squamous NSCLC
- First line metastatic treatment
- Measurable disease
- ECOG PS 0-1
- Tissue for biomarker available
- EGFR wild type
- EML4/ALK fusion negative
- No active CNS metastases

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

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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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Conclusions Immune Therapy Lung Cancer

- PD1 checkpoint has transformed lung cancer therapy
- PD1 Ab standard of care most 2nd line advanced lung cancer
- Pembrolizumab is new standard for advanced lung cancer PDL1 > 50%
- Durvalumab after CRT for stage lung cancer
- Five year survival for phase 1 nivolumab 15%
- Not where we need to be but there is hope!
- Need predictive biomarkers of efficacy and toxicity
- Combination immune therapy has great promise
- Need more clinical and translational research

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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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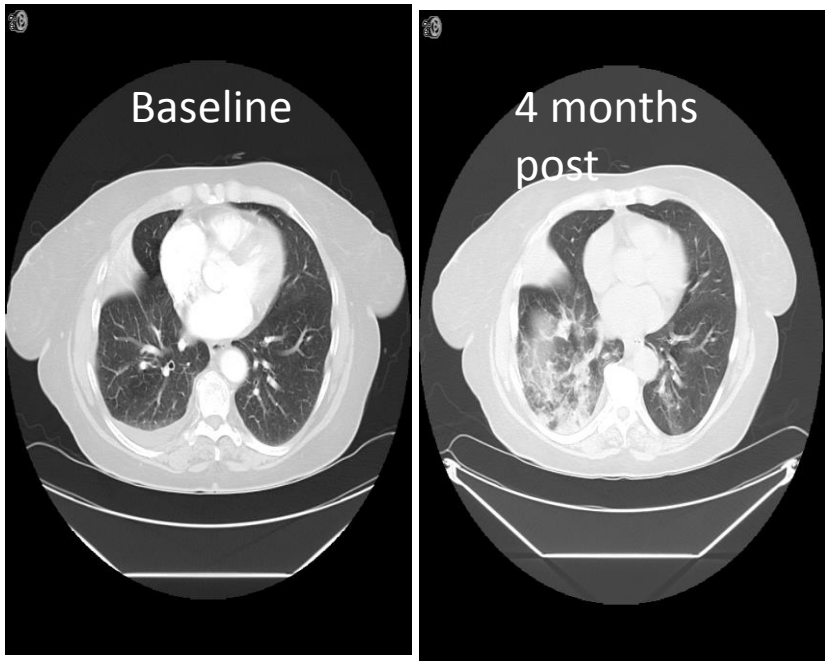
Case Study #2

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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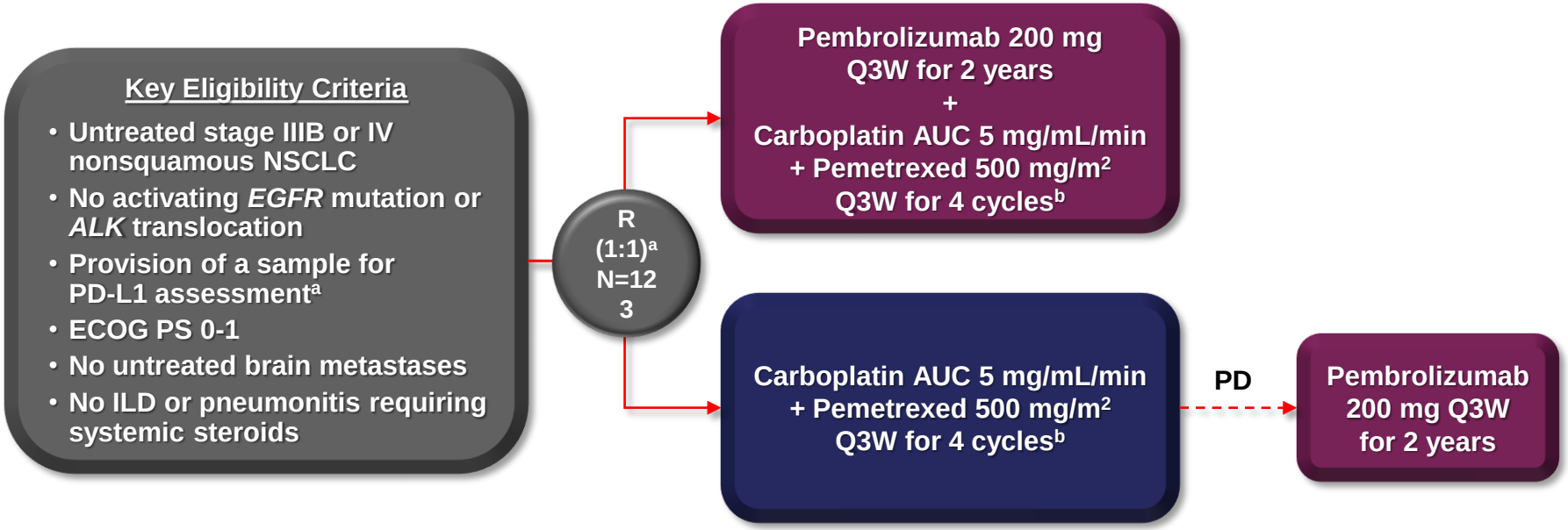
KEYNOTE-021 Cohort G



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

[a] Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

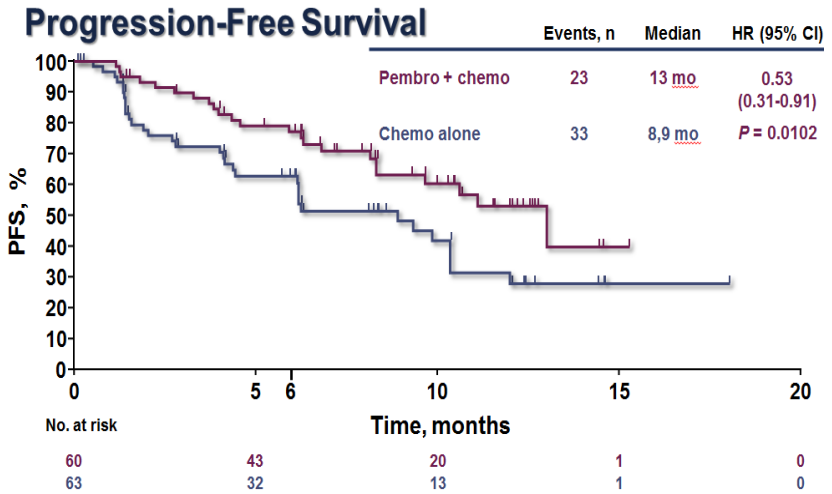
[b] Indefinite maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.

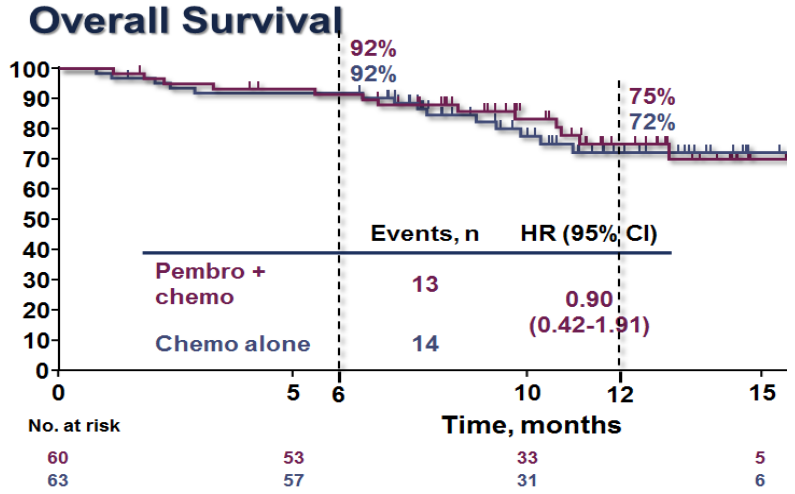
PD=progressive disease.

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

PFS and OS Survival data





Clear PFS benefit and no OS advantage

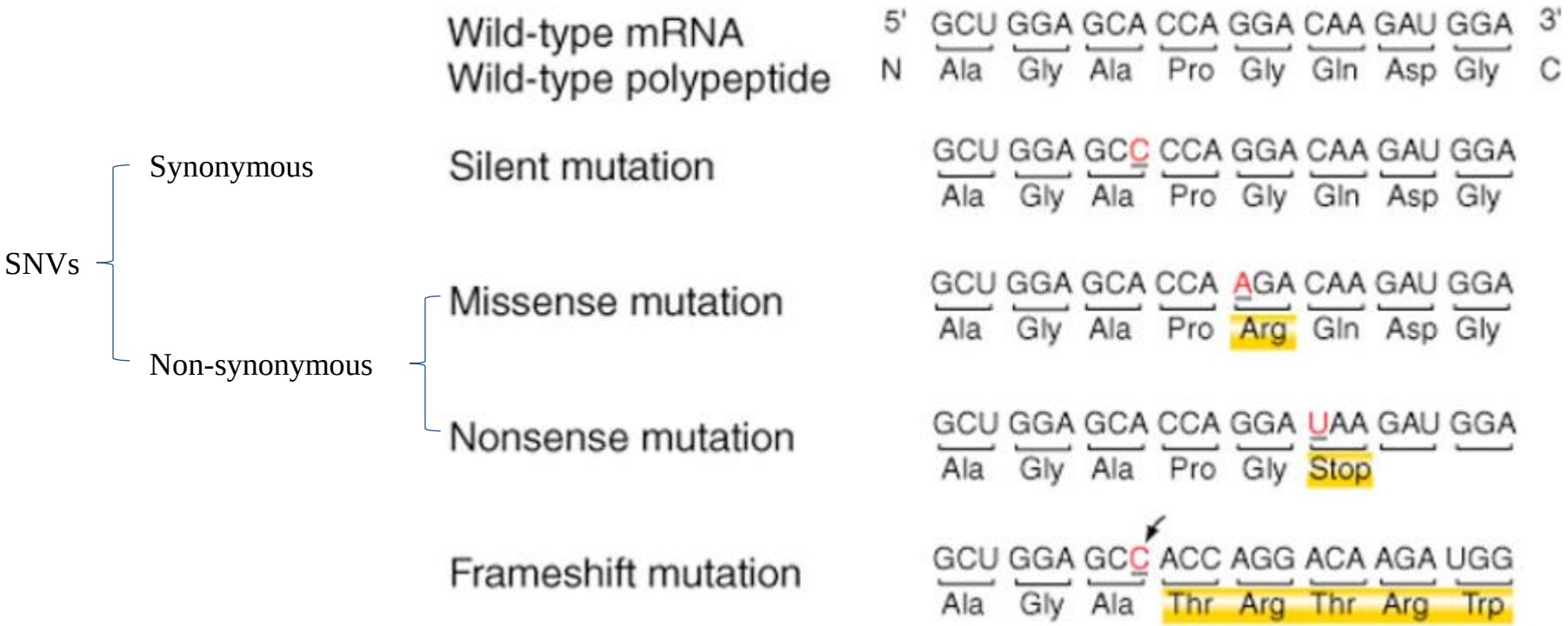
- Median PFS improved by 4.1 months
- PFS HR is 0.53
- No difference for OS (crossover; immature data……..)
- Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
- In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others)

Updated (ASCO ‘17):

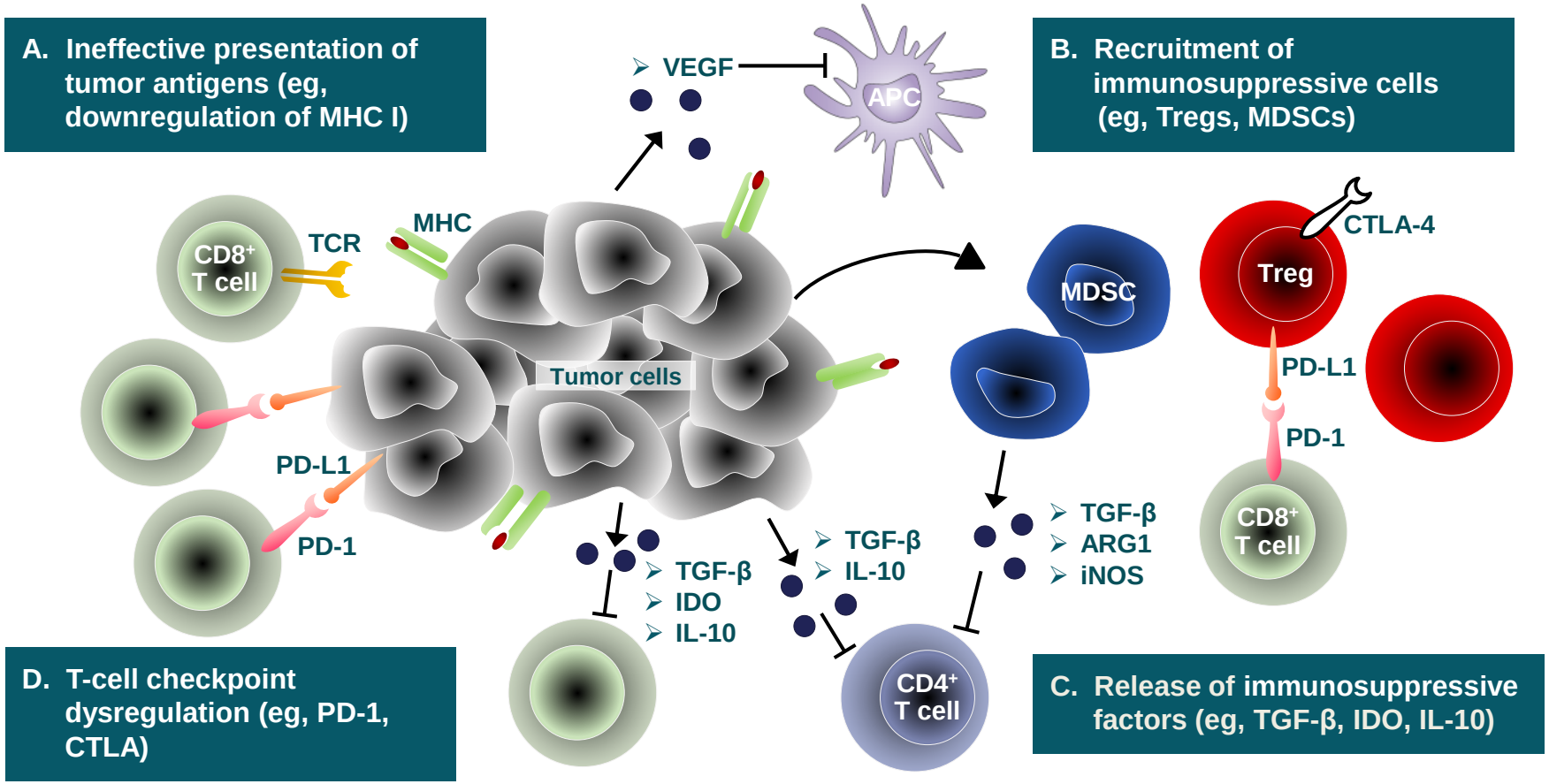
- RR: 57% vs 30.5%
- PFS HR has dropped to 0.5 from 0.53, Median now NR vs 8.9
- OS HR has dropped to 0.69 from 0.9 with dip in p value from 0.37 to 0.13 (1yr OS 76% vs 69%)

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

What mutations to “count” in TMB



Tumors use complex and frequently overlapping mechanisms to escape the immune system



ARG1=arginase 1; CTLA-4=cytotoxic T-lymphocyte associated antigen-4; IDO=indoleamine 2,3-dioxygenase; IL=interleukin; iNOS=inducible nitric oxide synthase; MDSC=myeloid-derived suppressor cell; PD-1=programmed death-1; PD-L1=programmed death ligand 1; TCR=T-cell receptor; TGF-β=transforming growth factor beta; VEGF=vascular endothelial growth factor.

Vesely MD et al. Ann Rev *Immunol*. 2011;29:235–271.