

ADVANCES IN
Cancer
IMMUNOTHERAPY™



Immunotherapy for the Treatment of Lung Cancer

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Society for Immunotherapy of Cancer

Disclosures

- Bristol-Myers Squibb, Ariad Pharmaceuticals, Inc., Consulting Fees; Bristol-Myers Squibb, Contracted Research
- I may be discussing non-FDA approved indications during my presentation.

Immune checkpoint inhibitors in NSCLC

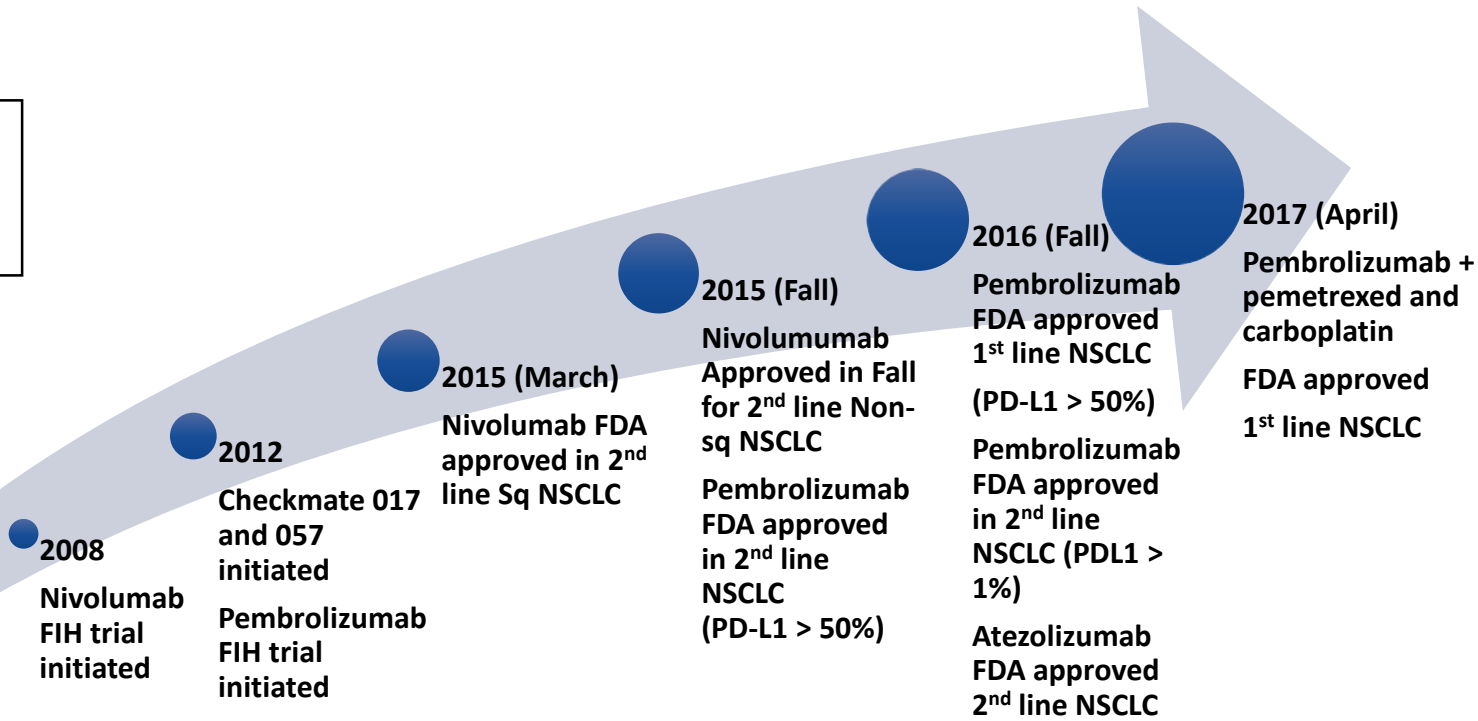
Nivolumab



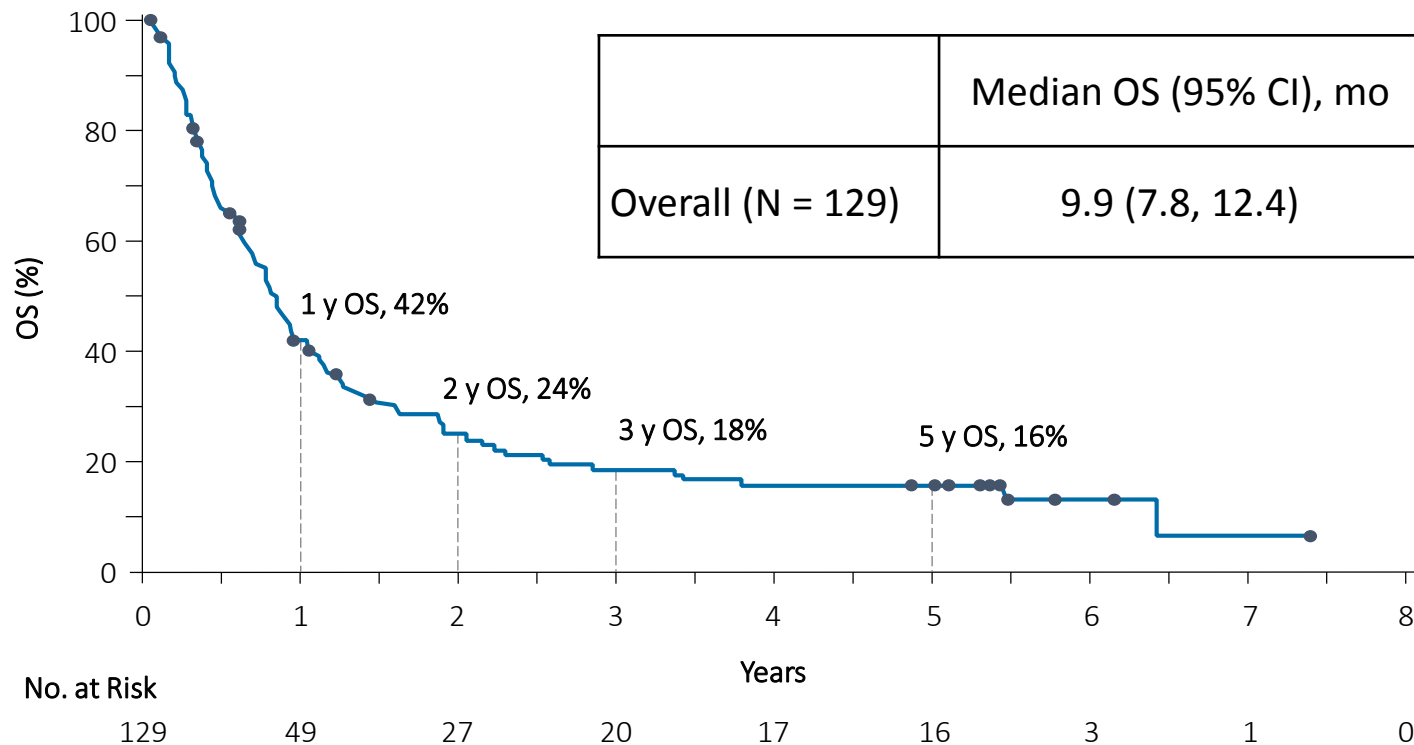
Pembrolizumab



Atezolizumab



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

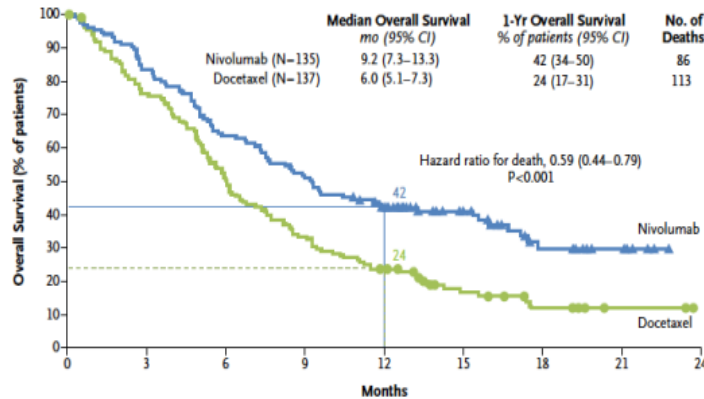


Brahmer et al, AACR 2017

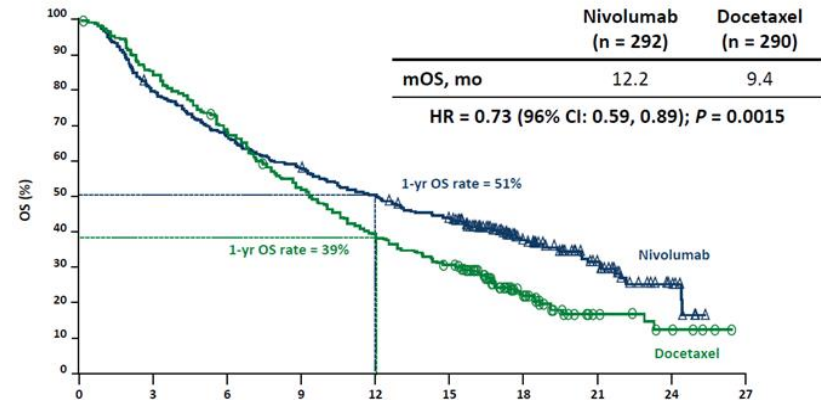


PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

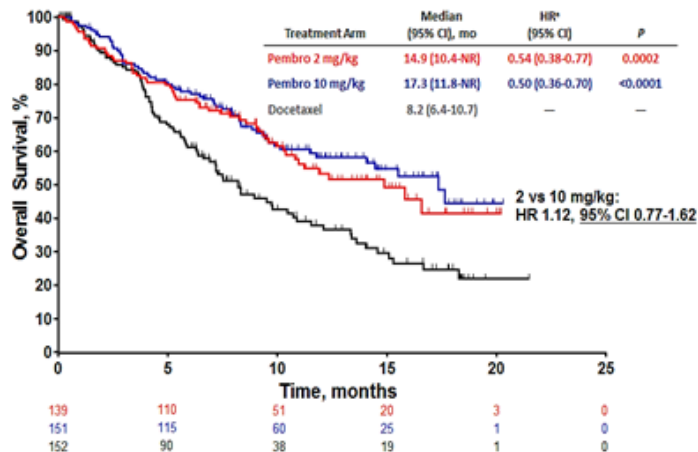
CHECKMATE 017



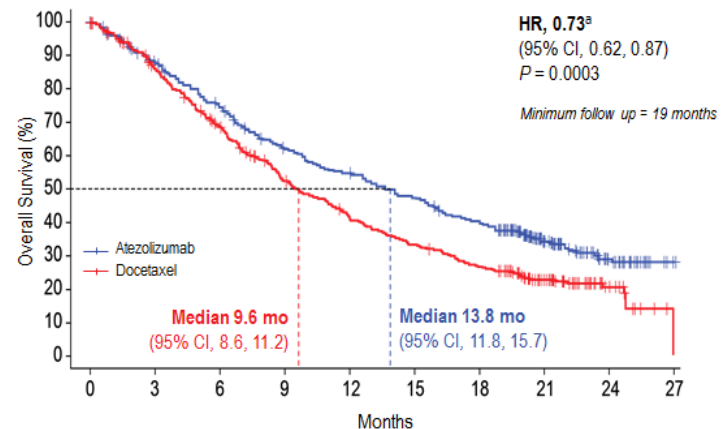
CHECKMATE 057



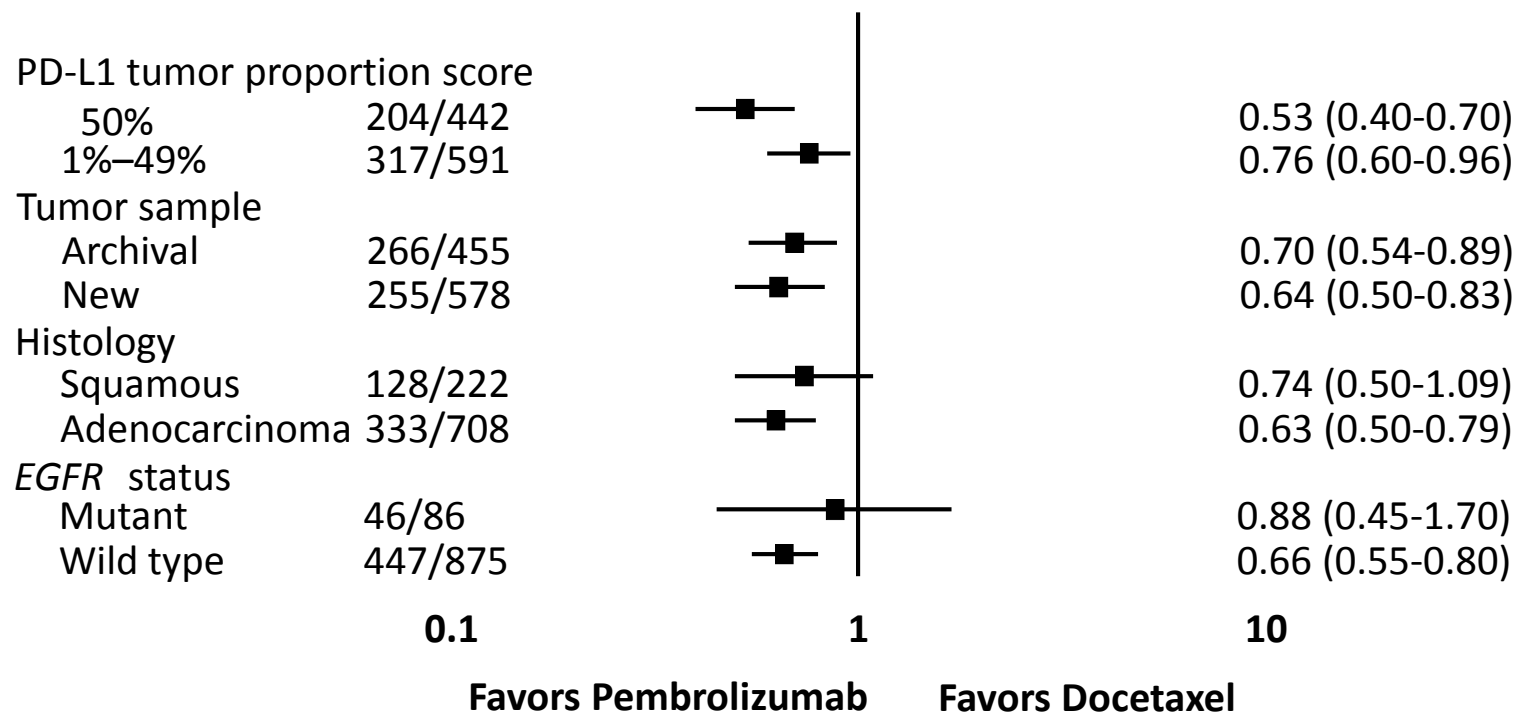
KEYNOTE 010 (TPS ≥ 1%)



OAK

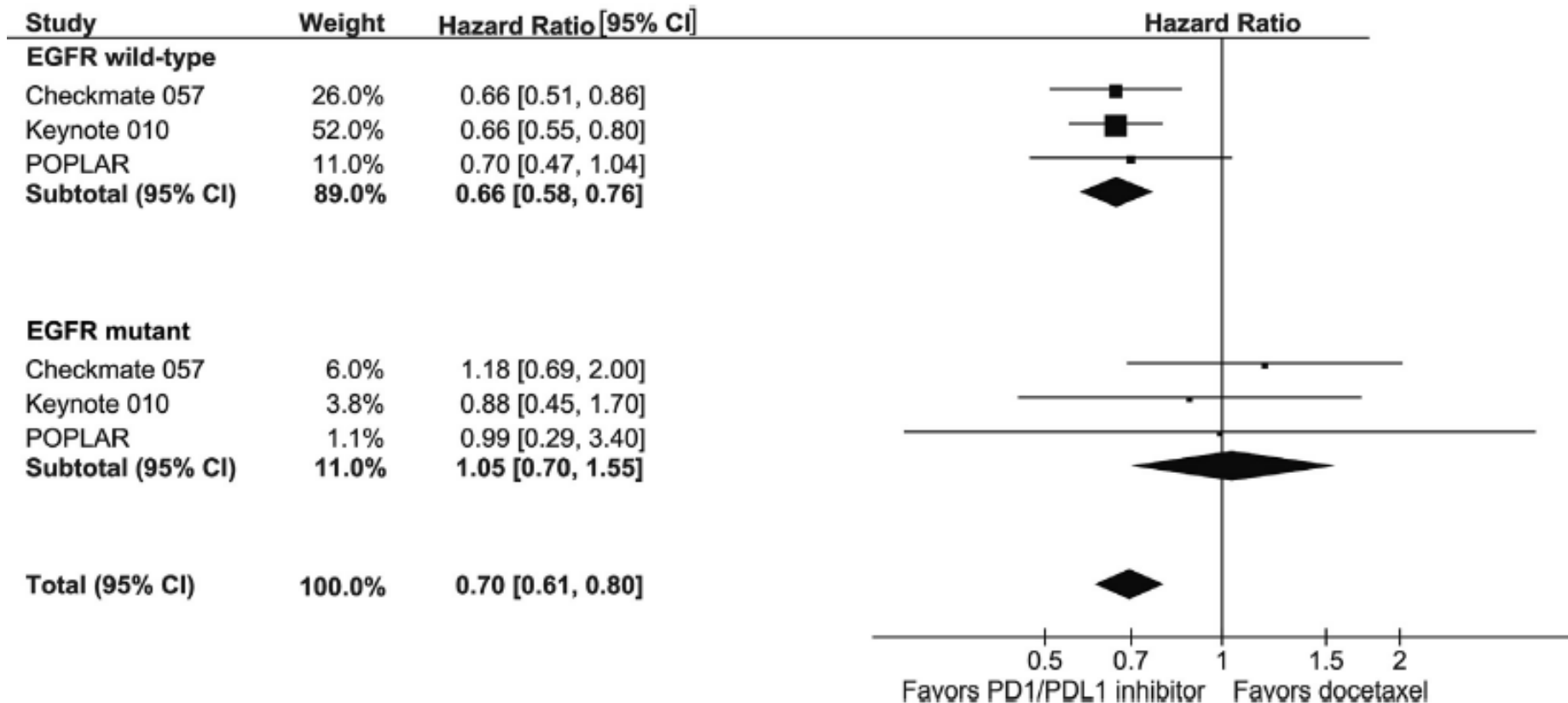


KEYNOTE 010: Pembrolizumab approval ≥ 2nd line (PD-L1 ≥ 1%)



Herbst et al, Lancet 2015

EGFRm PD-(L)-1 meta-analysis



CK Lee et al., *JTO* 2016



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

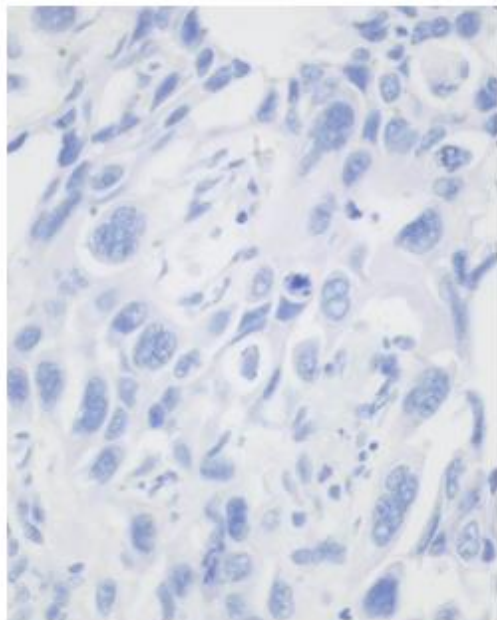
Borghaei, et al., *NEJM* 2015

Herbst, et al., *Lancet* 2015

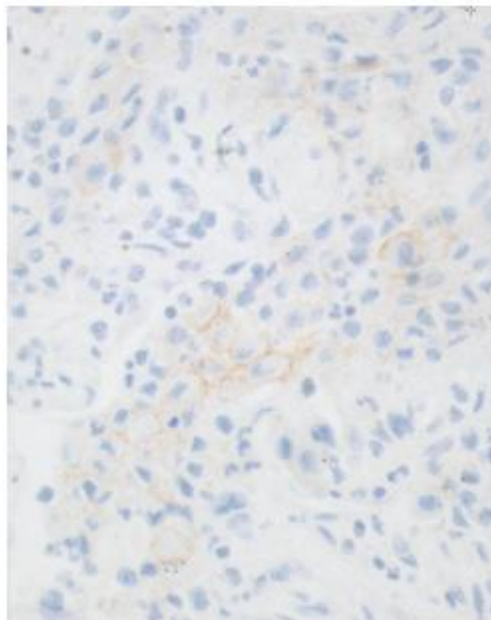




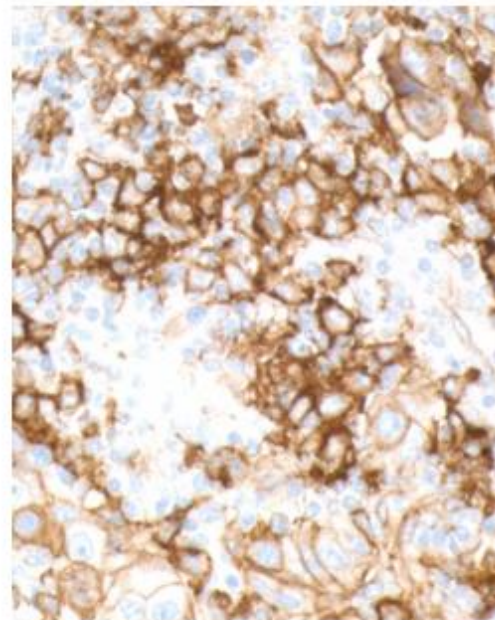
PD-L1 selection to bridge the gap?



PD-L1 = 0% positive
Negative



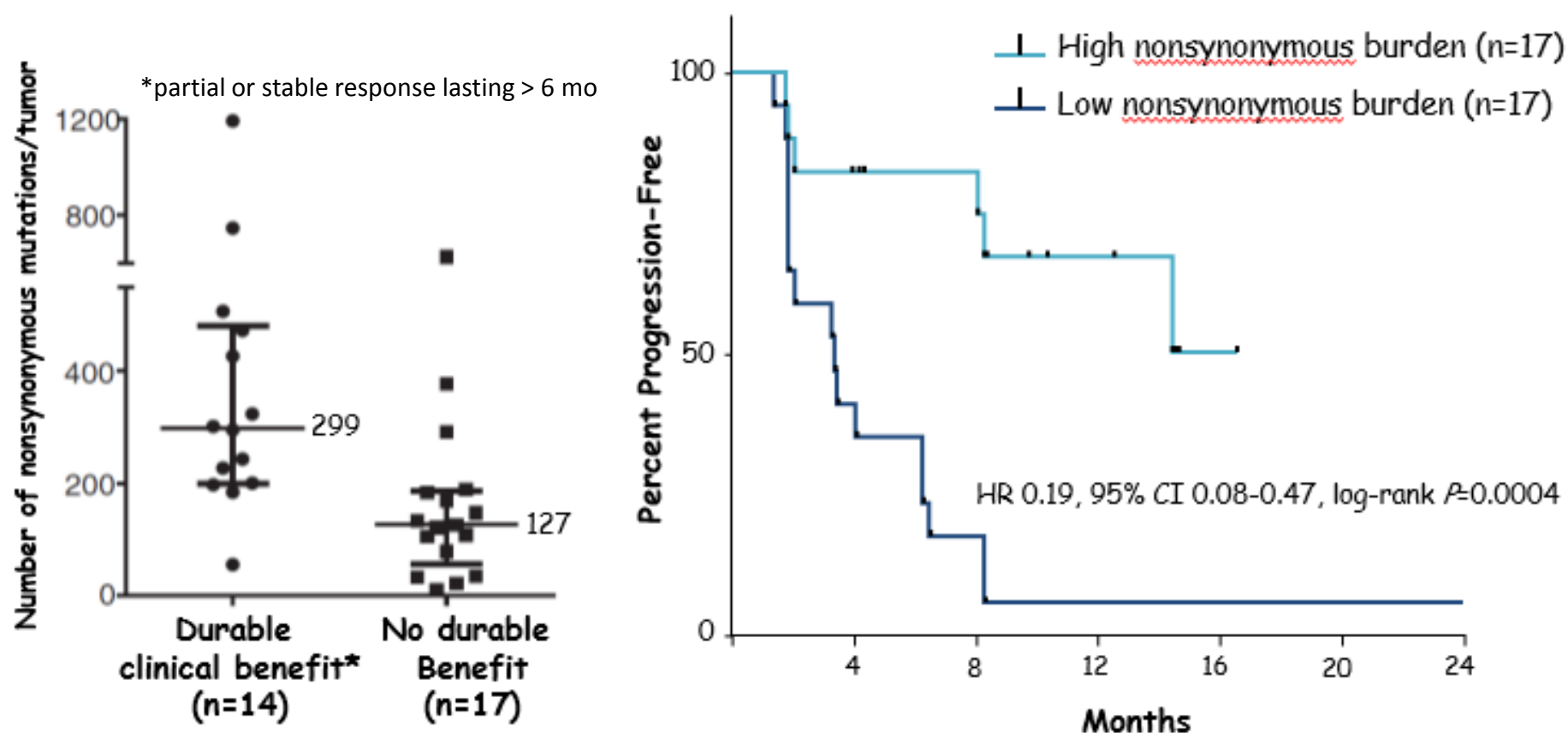
PD-L1 = 2% positive
Weak Positive
(1%-49%)



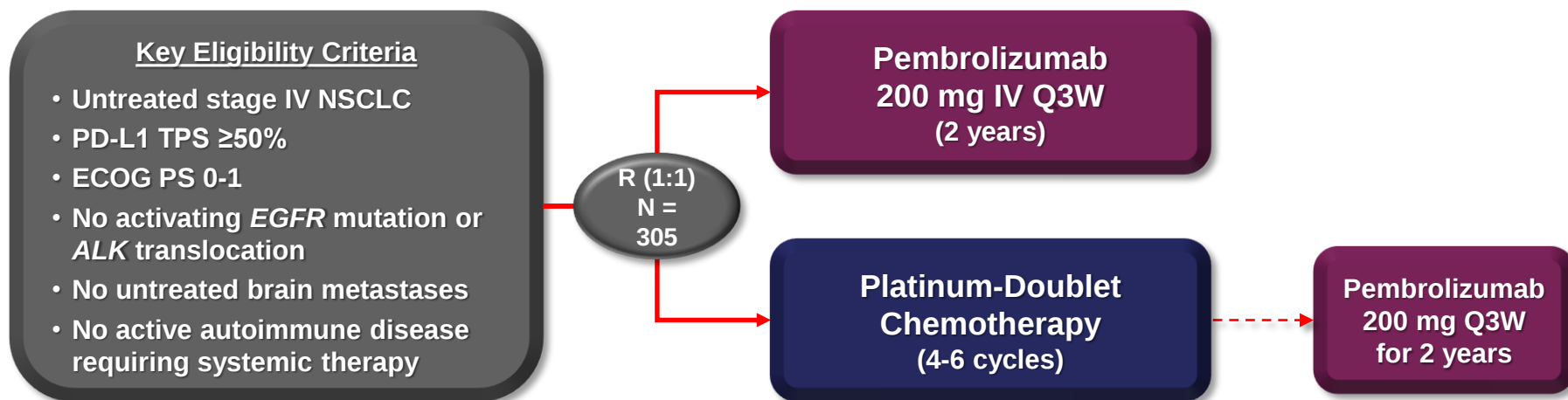
PD-L1 = 100% positive
Strong Positive
(50%-100%)



Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



KEYNOTE-024 Study Design (NCT02142738)



Key End Points

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

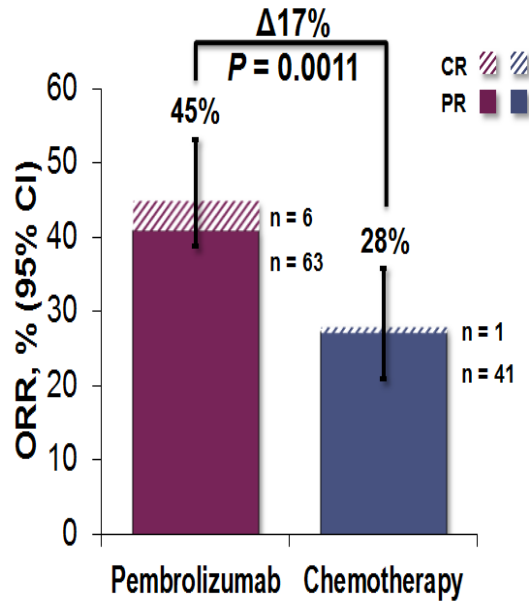
Secondary: OS, ORR, safety

Exploratory: DOR

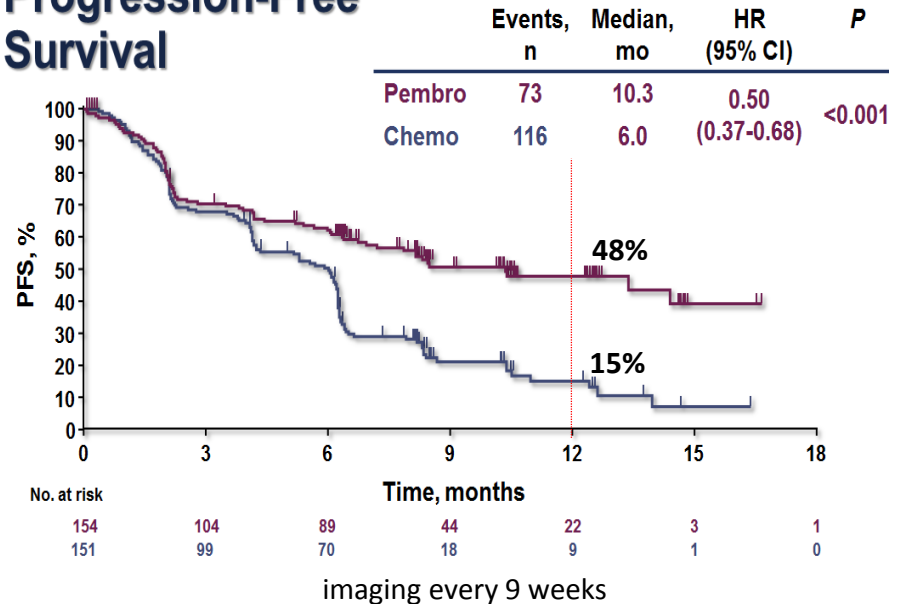
Reck M et al, ESMO 2016, NEJM 10/16



Efficacy data: Keynote 24



Progression-Free Survival



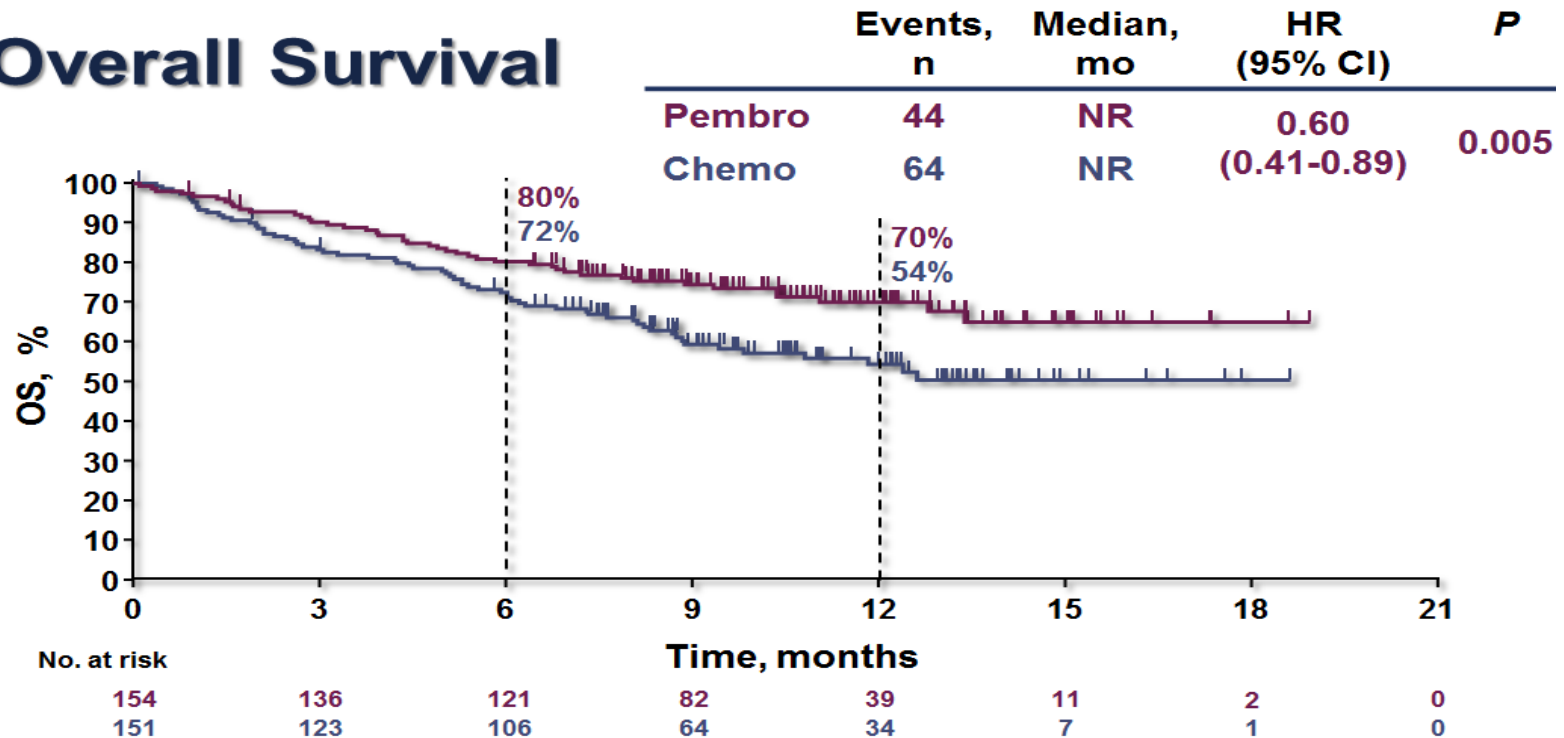
❖ Clear and strong signal of activity

- 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)



Keynote 24: Survival data

Overall Survival



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

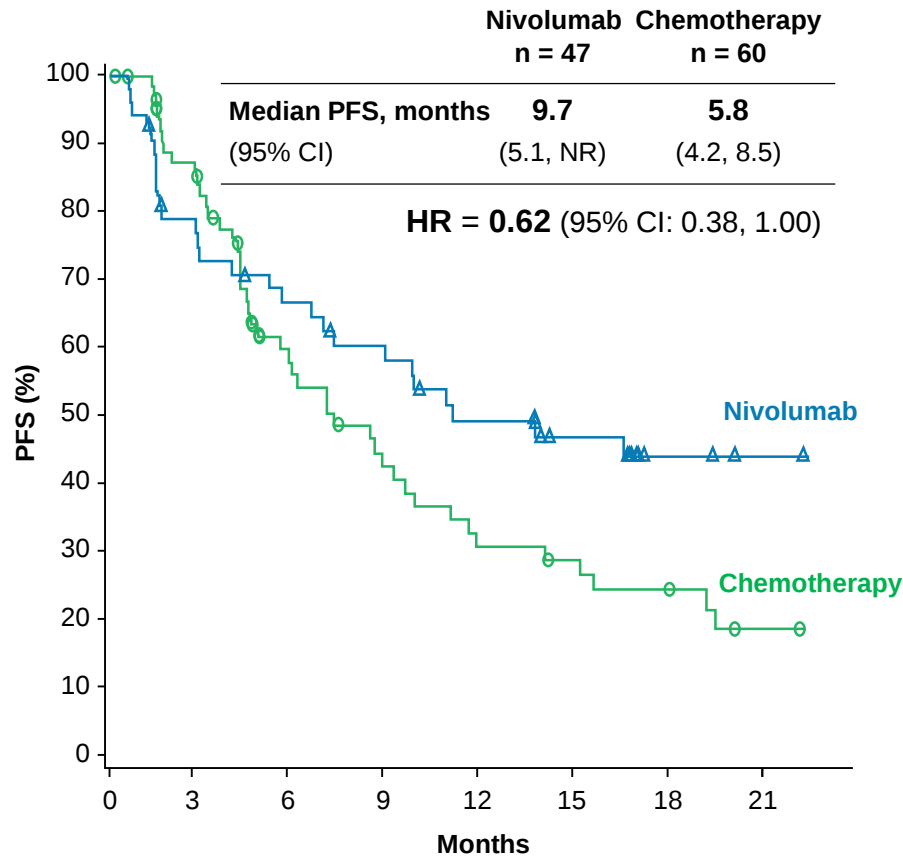


PFS by Tumor Mutation Burden

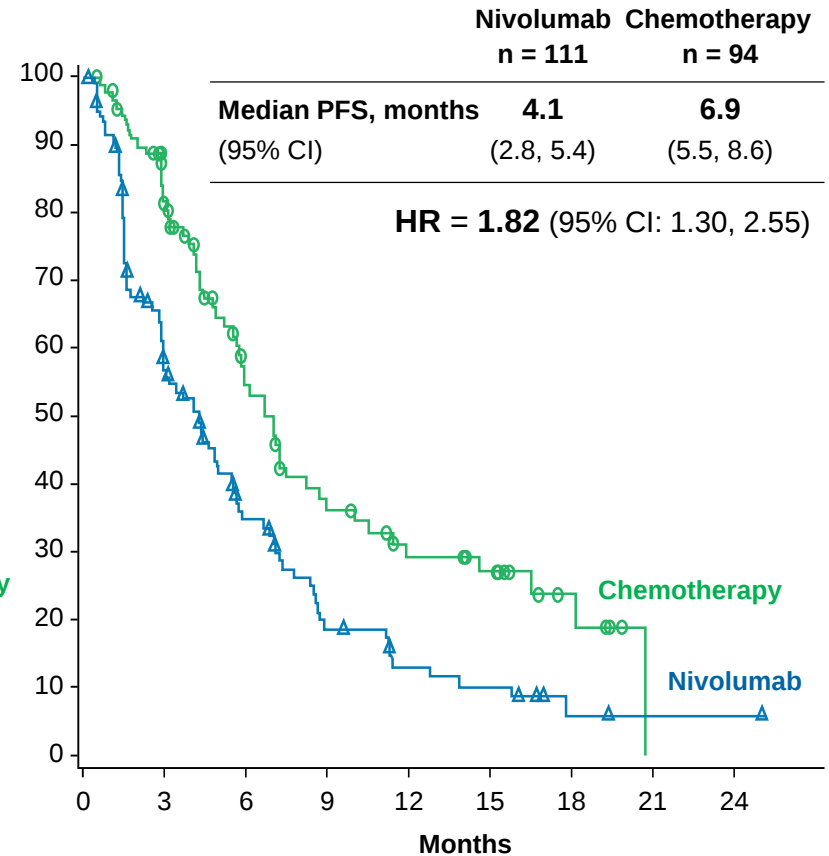
Subgroup CheckMate 026 TMB Analysis

Nivolumab in First-line NSCLC

High TMB



Low/medium TMB



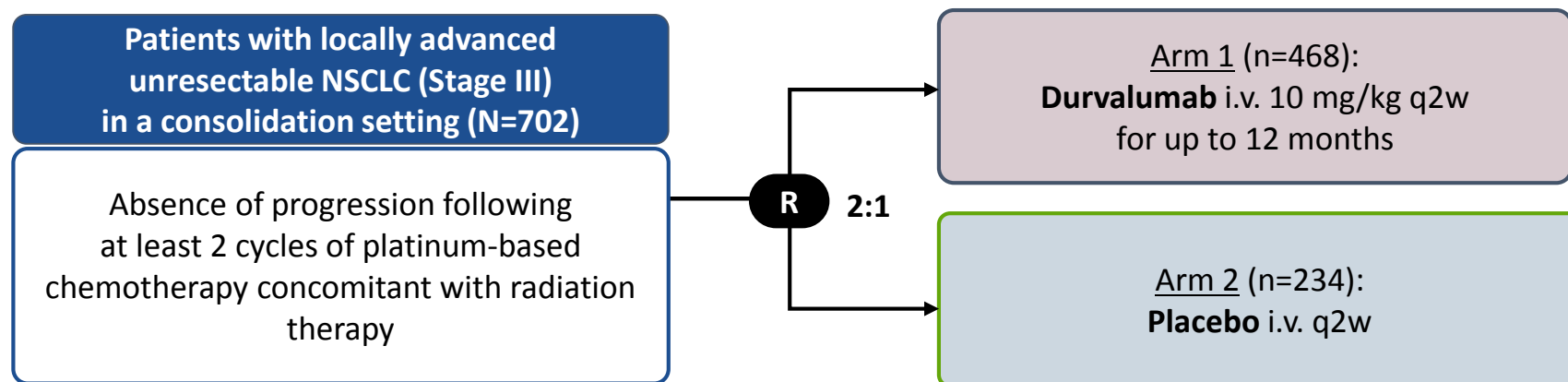
No. at Risk

Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

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

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

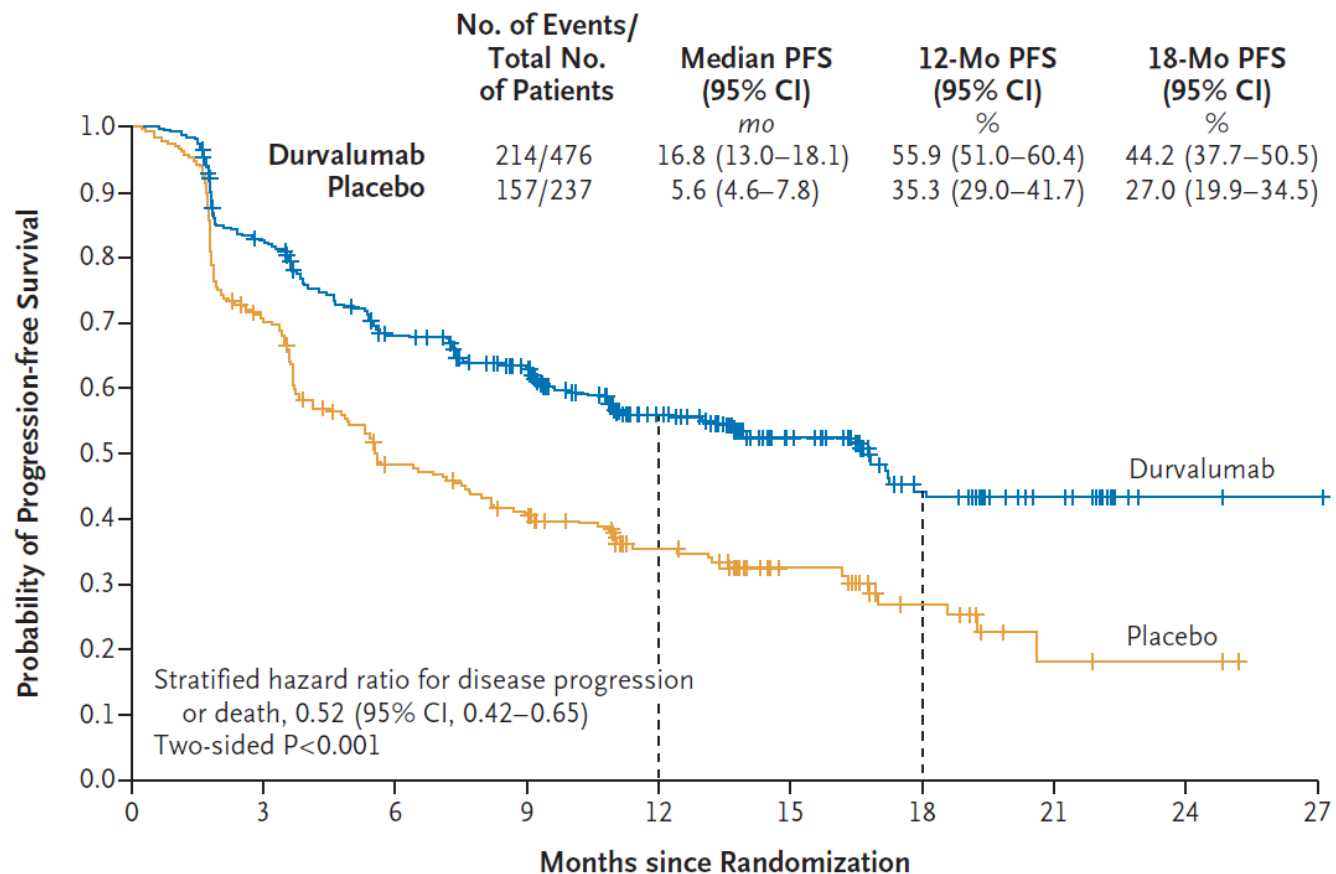
Est. completion: 2017
FPD⁴ Q2 14
LPCD: Q2 16



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/D4191C00001):



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



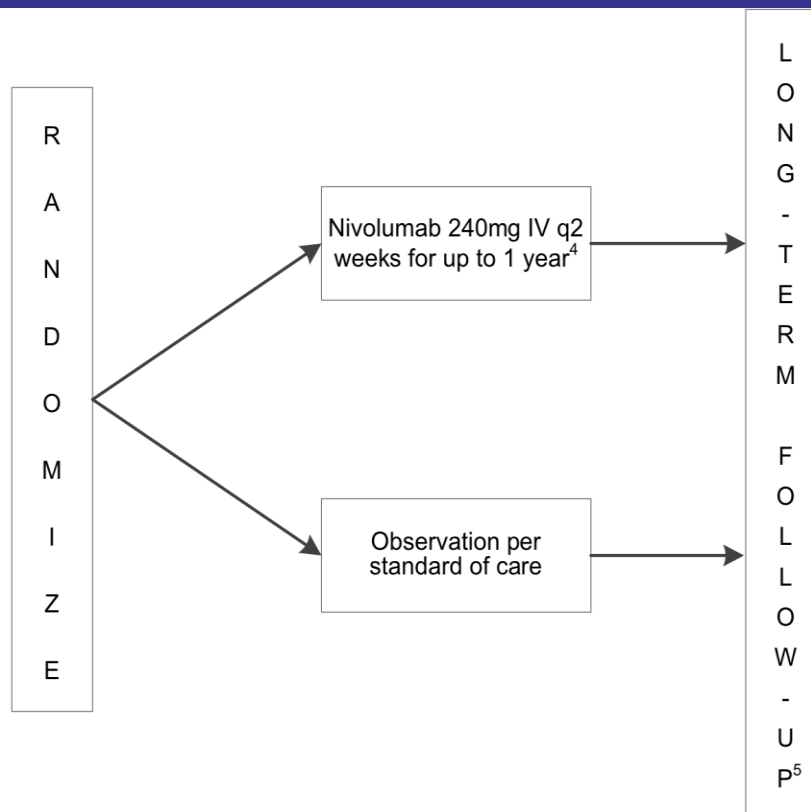
EA5142: ANVIL – Adjuvant Nivolumab in Resected NSCLC

Eligibility

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

Stratification

- Stage AJCC 7th edition: IB (≥ 4 cm)/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 ($\geq 1\%$) vs. negative ($< 1\%$)/non-evaluable) membranous expression determined centrally



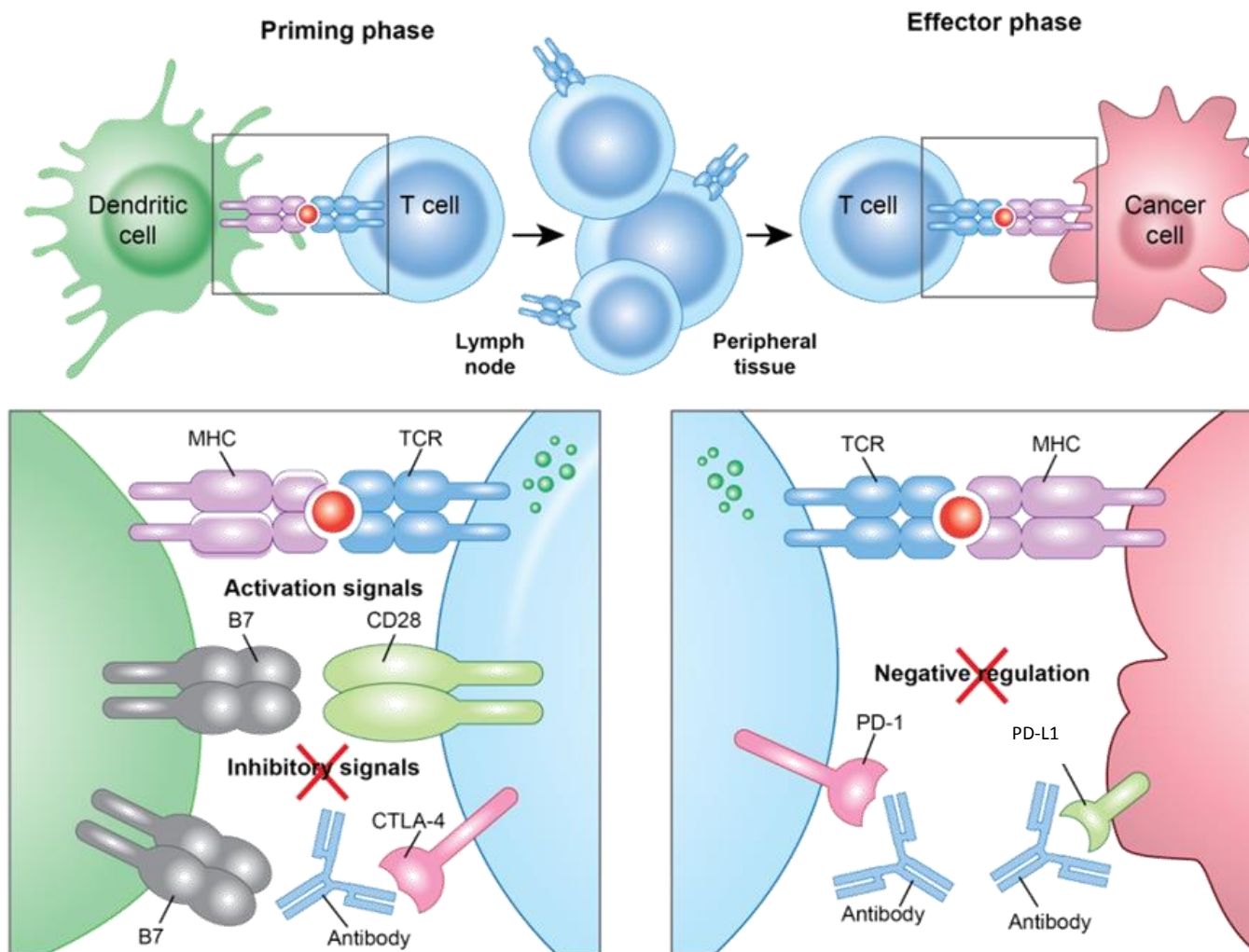
Cycle = 2 weeks (14 days)

Accrual Goal = 714 patients

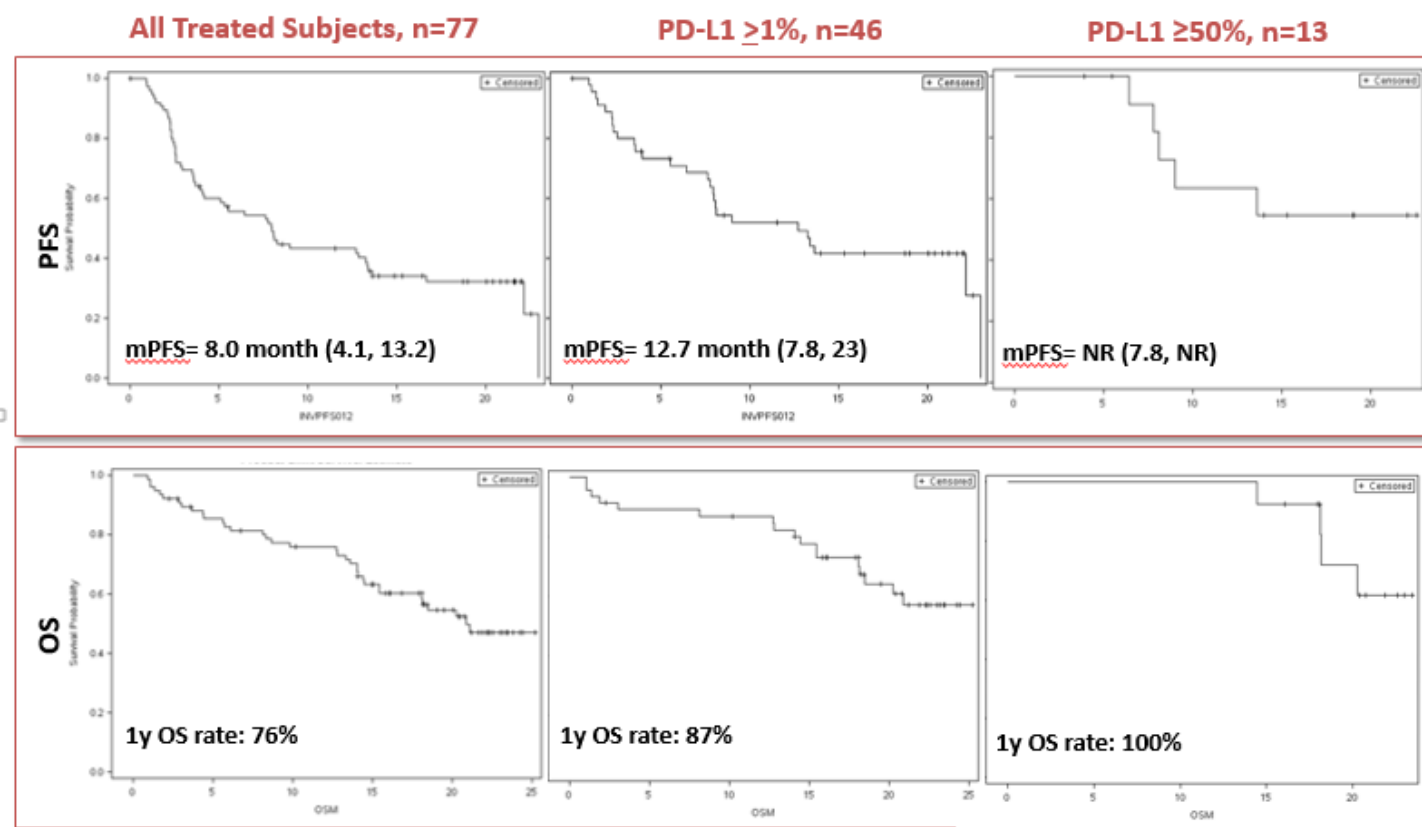
1. If Stage 1B, then tumor must be ≥ 4 cm
2. Adenosquamous should be grouped as non-squamous
3. PD-L1+ is defined as $\geq 1\%$ by IHC
4. Maximum number of doses is 26
5. Patients will be followed for recurrence and survival for 10 years

Co-primary endpoints: DFS and OS in all patients

Combination Immune checkpoint blockade



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



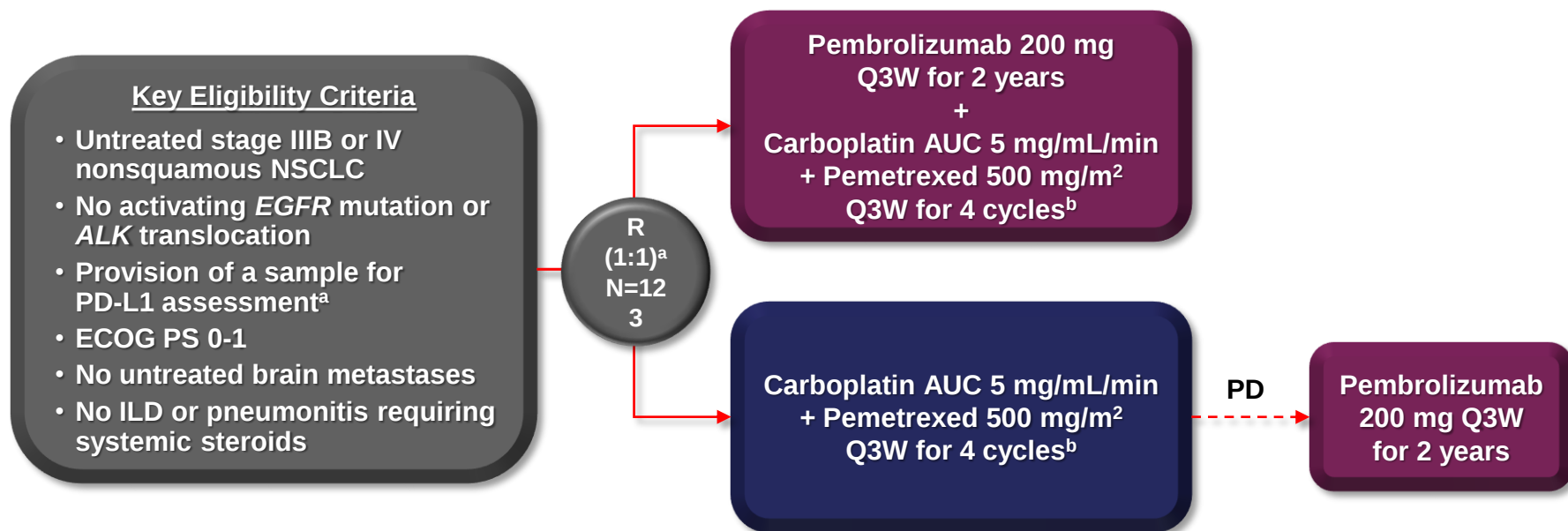
CheckMate 012

Goldman, et al, ASCO Annual Meeting, 2017

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KEYNOTE-021 Cohort G



End Points

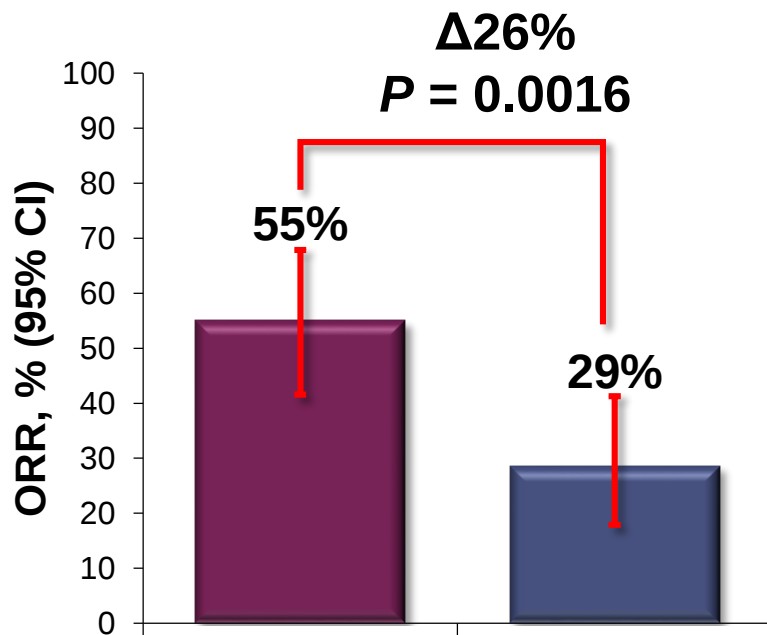
Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

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

Confirmed Objective Response Rate

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



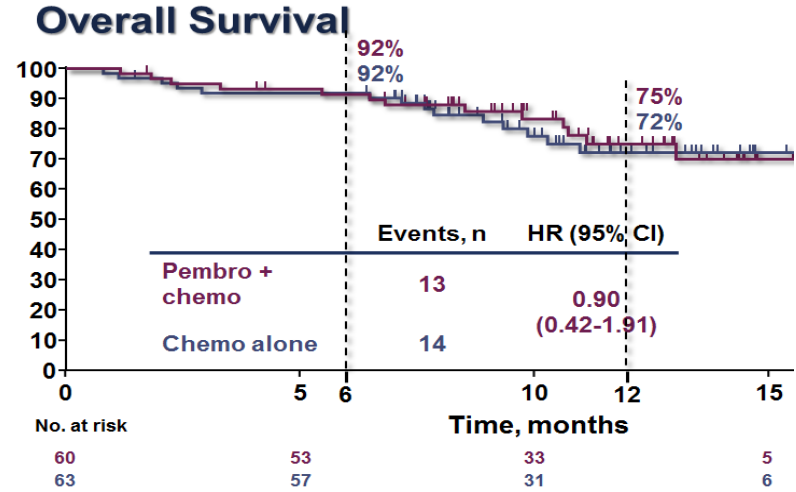
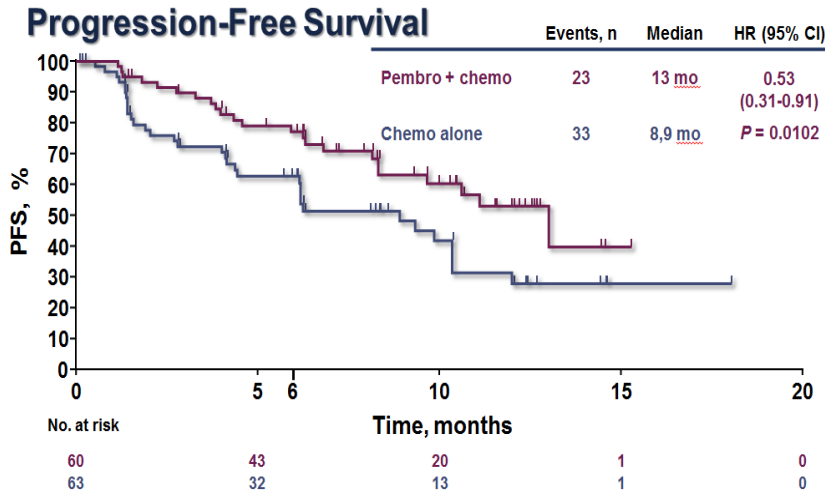
Data cut-off: August 8, 2016.

	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.

^aAlive without subsequent disease progression.

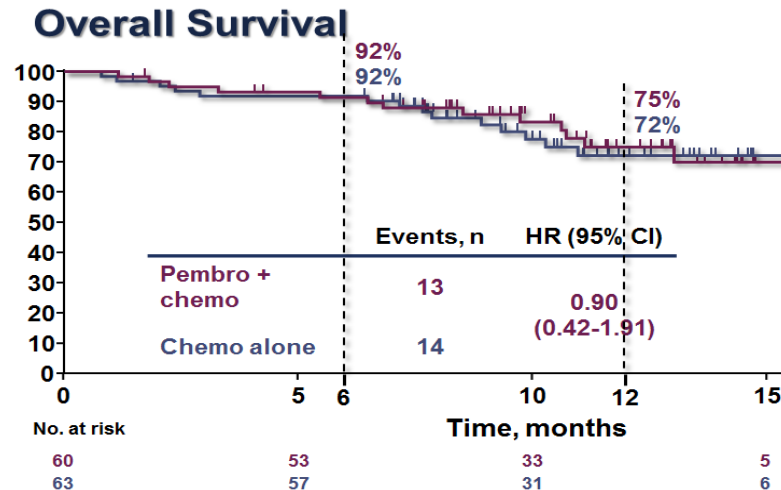
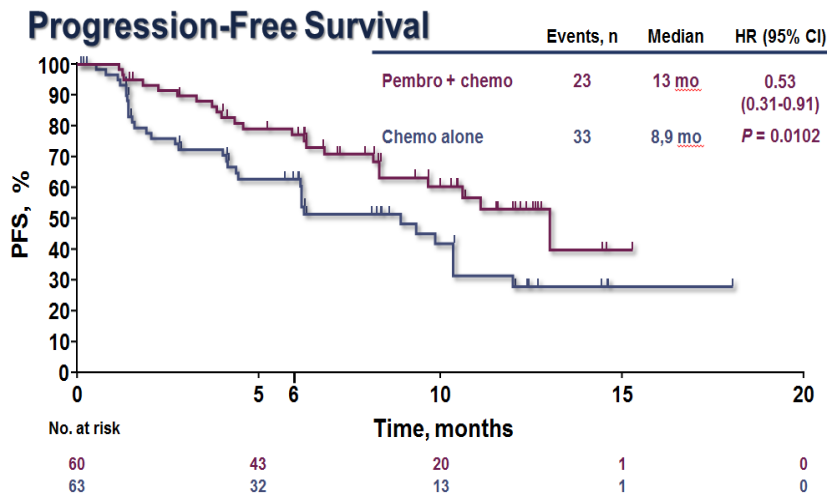
PFS and OS Survival data



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)

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%)

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

Stratify:

- PDL1 prop score: $\geq 1\%$, $< 1\%$
- Smoking status
- cisplatin vs carboplatin

R
A
N
D
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M
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Z
A
T
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O
N

2:1
N=570

**Carboplatin/Cisplatin
Pemetrexed
Pembrolizumab
200 mg Q3W
X4 cycles**

**Pemetrexed
Pembrolizumab**

PD

**Carboplatin/Cisplatin
Pemetrexed
+Saline
X4 cycles**

**Pemetrexed
+Saline**

PD

Pembrolizumab

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

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- First line metastatic treatment
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R
A
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O
N

N=570

Completed Accrual 02/17

Carboplatin/Cisplatin
Pemetrexed
Pembrolizumab
200mg

Pemetrexed
Pembrolizumab

PD

Carboplatin/Cisplatin
Pemetrexed
+Saline
X4 cycles

Pemetrexed
+Saline

PD

Pembrolizumab

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

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

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

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

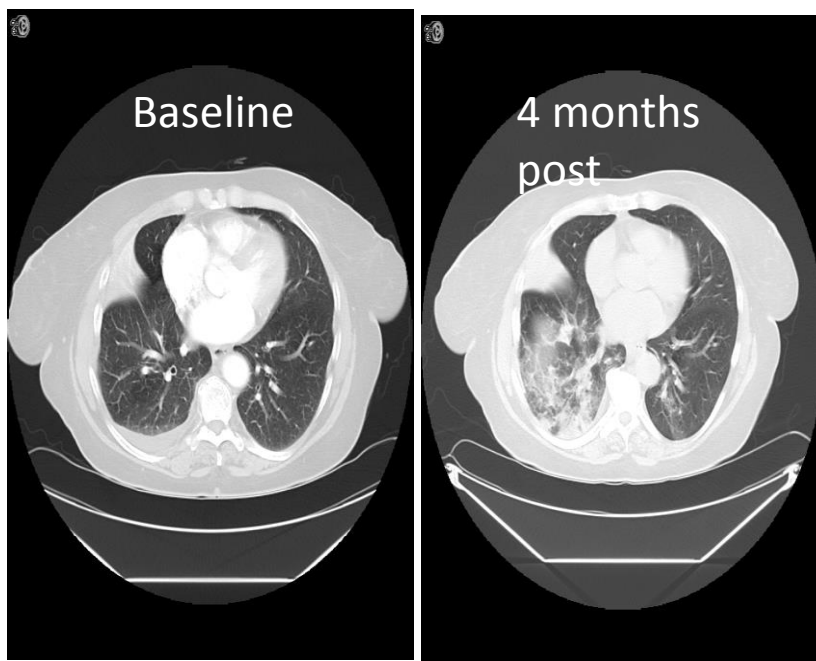
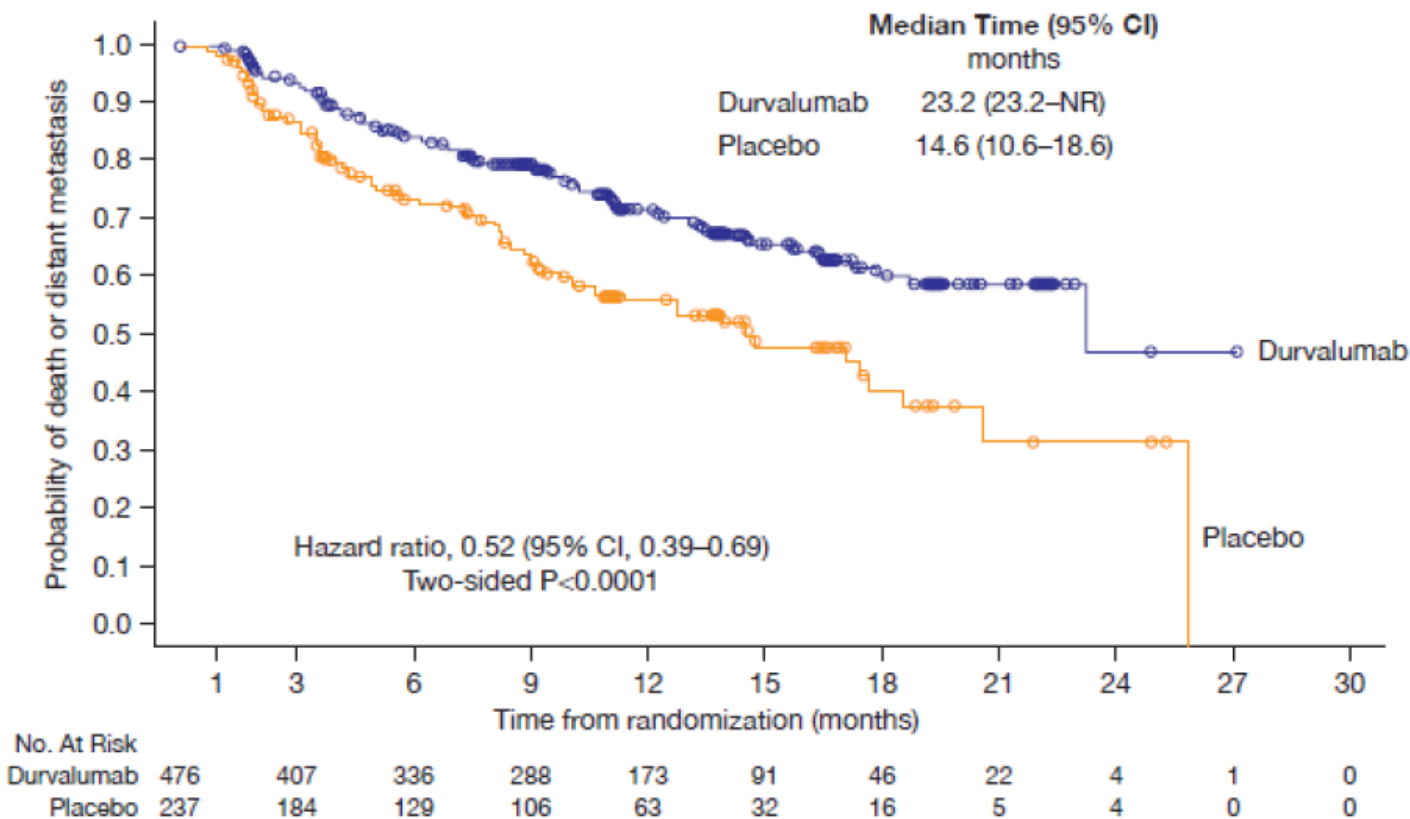




Figure S3. Time to Death or Distant Metastasis in the Intention-to-Treat Population (BICR).



Anti-PD-1 Better tolerated than Chemo (PhIII)

	BMS 057 (Non-Squam)				BMS 017 (Squam)				KN010 (PD-L1+)			
	Nivolumab (n = 287)		Docetaxel (n = 268)		Nivolumab (n = 131)		Docetaxel (n = 129)		Pembro 2/ 10 (n = 682)		Docetaxel (n = 309)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Tx-related AEs, %	69	10	88	54	59	8	87	58	63/ 66	13/ 16	81	35
Tx-related AEs leading to d/c, %	5	4	15	7	5	3	10	7	4/ 5		10	
Tx-related deaths, %	<1		<1		0		2		1/ 1		2	

Anti-PD/PDL1 as Backbone to Combination Tx?

Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
- Chemotherapy - Radiation/ Ablation - EGFR/ ALK TKI - Anti-VEGF/ VEGFR inhibitor - Vasc Disrupt Agent - Hypomethylating Agent - HDAC inhibitor - SPK Inhibitor - C-Met inhibitor - Glutaminase inhibitor - Dasatinib - Vaccine - Gene therapy - IL15 agonist - PEG IL10 - TGFβR1 inhibitor - Anti-CD27 - Ant-CXCR4 - Anti-CSF-1R - IDO-1 inhibitor - Anti-CTLA4 - Anti-LAG - Anti-TIM-3 - Anti-KIR	- Chemotherapy - Radiation - EGFR/ ALK TKI - Anti-VEGF/VEGFR inhibitor - Hyomethylating Agent - HDAC inhibitor - CDK Inhibitor - BTK inhibitor - PI3K Inhibitor - KIT/CSF1R/FLT3 Inh - FGFR inhibitor - JAK1 Inhibitor - CRM1 Inhibitor - FAK Inhibitor - Anti-EGFR - Anti-CEACAM1 - PEG hyaluronidase - Vaccine - Oncolytic - PEG IL10 - Anti-CSF-1 - IDO1 Inhibitor - Anti-CTLA4 - Anti-B7-H3	- Chemotherapy - Radiation - EGFR/ ALK TKI - Anti-VEGF/Ang-2 - MEK Inhibitor - Vaccine - Adoptive Cell Therapy - Anti-CEA/CD3 - Anti-CEA/ IL-2 - Anti-OX40 - Anti-CD40 - Anti-CD27 - Anti-CSF-1 - Adenosine A2A Inhibitor - IDO-1 Inhibitor - Anti-CTLA4 - Anti-TIGIT	- Chemotherapy - Radiation - EGFR/ALK TKI - VEGFR Inhibitor - BTK Inhibitor - MEK Inhibitor - HAD Inhibitor - PARP Inhibitor - WEE1 Inhibitor - ATR Inhibitor - Anti-OX40 - CXCR4 Inhibitor - CSF - Anti-CD73 - Anti-CCR4 - Anti-CSF1R - Anti-NKG2A - Adenosine A2a Inhibitor - IDO1 Inhibitor - Anti-CTLA4 - Anti-PD1
		Avelumab: ALK inhibitor (crizotinib and lorlatinib), Anti-41BB, Anti-OX40	

