Emerging Therapeutic Landscape in Advanced Non-small Cell Lung Cancer (NSCLC): A New Immunotherapy Paradigm

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Langer Disclosures: Past 12 months

- Grant/Research Support:
  - Genentech, OSI (Astellas), Merck, GlaxoSmithKline, Nektar, Advantagene, Clovis; Ariad; Inovio, Threshold, AZ, Celgene, MGA
- DSMC:
  - Lilly, Amgen, Synta, Agennix, SWOG, Peregrine, Incyte, AbbVie
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CheckMate 017 & 057: Nivolumab in Previously Treated Metastatic *Squamous and Nonsquamous* NSCLC

CheckMate-017 Squamous	Nivolumab (n = 135)	Docetaxel (n = 137)	Hazard ratio	*p*-value
Median OS	9.2 mo	6.0 mo	0.59	0.00025
Median PFS	3.5 mo	2.8 mo	0.62	0.0004
ORR	20%	9%	—	0.0083

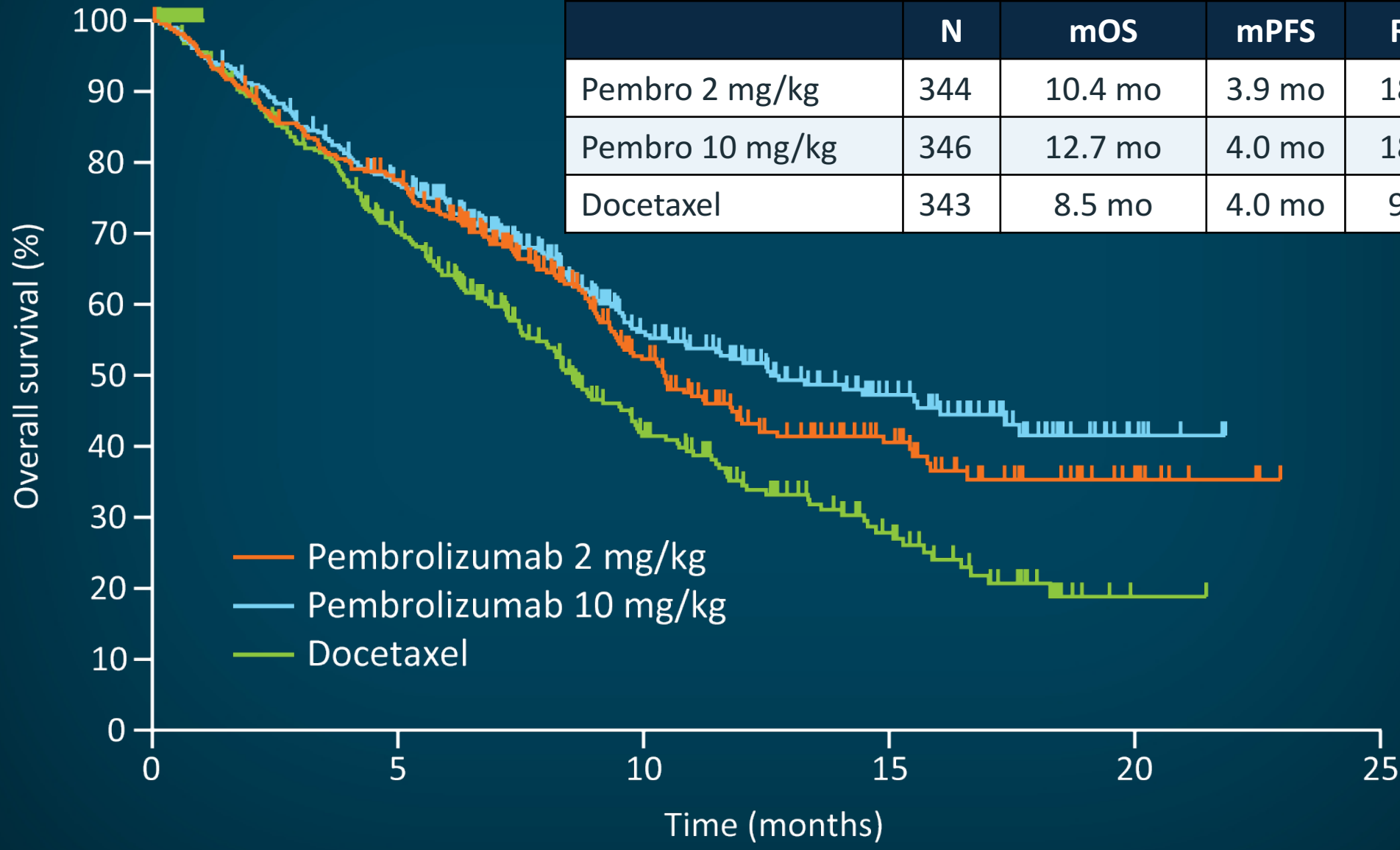
CheckMate-057 Nonsquamous	Nivolumab (n = 292)	Docetaxel (n = 290)	Hazard ratio	*p*-value
Median OS	12.2 mo	9.4 mo	0.73	0.002
Median PFS	2.3 mo	4.2 mo	0.92	0.39
ORR	19%	12%	—	0.02

Nivolumab was associated with greater efficacy than docetaxel across all end points in subgroups defined according to prespecified levels of tumor-membrane expression (≥1%, ≥5%, and ≥10%) of the PD-1 ligand

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35. Borghaei H et al. N Engl J Med. 2015;373(17):1627-39.

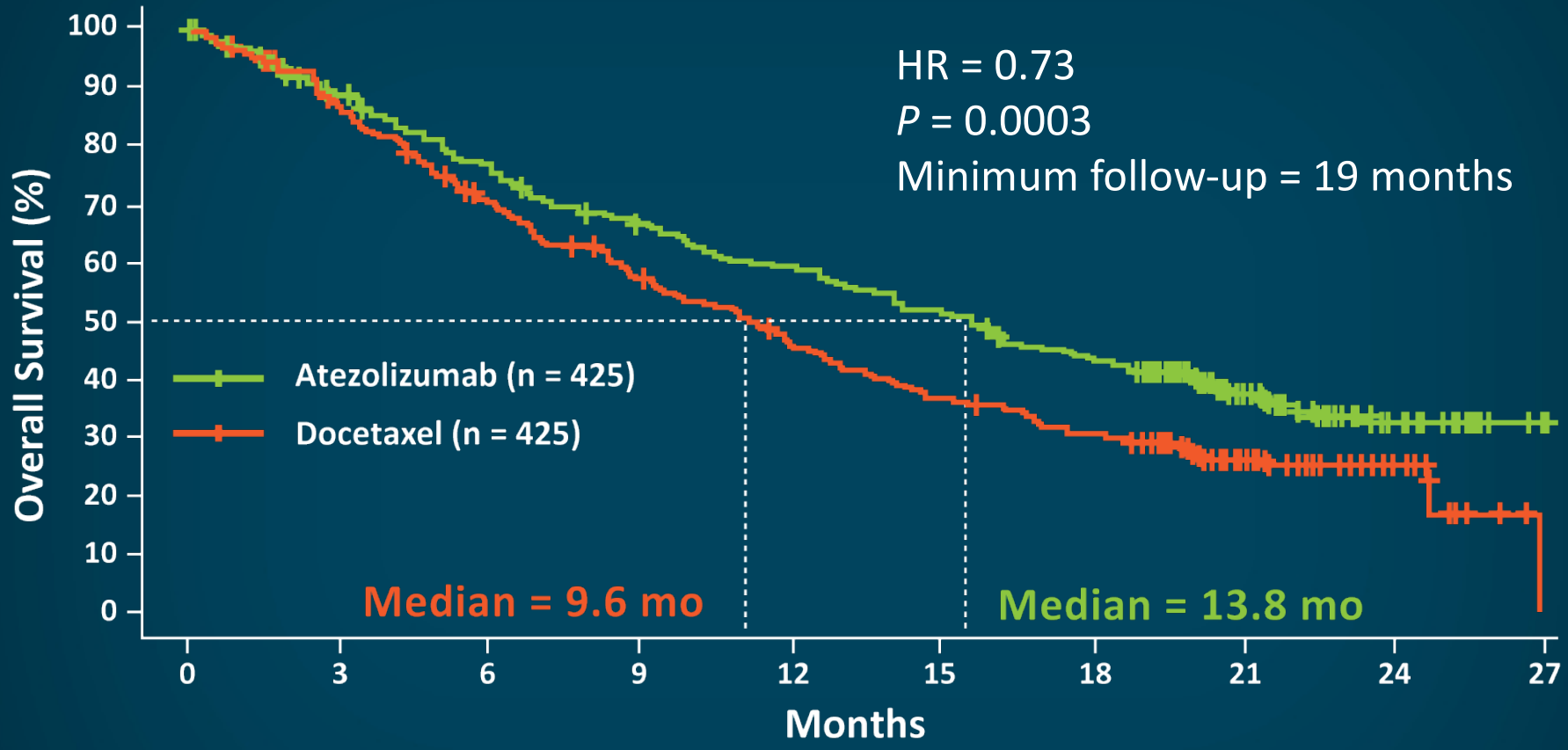
KEYNOTE-010: Pembrolizumab versus Docetaxel in Advanced NSCLC (TPS≥1%)

	N	mOS	mPFS	RR
Pembro 2 mg/kg	344	10.4 mo	3.9 mo	18%
Pembro 10 mg/kg	346	12.7 mo	4.0 mo	18%
Docetaxel	343	8.5 mo	4.0 mo	9%



Herbst RS et al. *Lancet* 2016;387(10027):1540-50.

OAK: A Phase III Study of Atezolizumab versus Docetaxel in 2L/3L NSCLC (ITT Population)



- OS was improved regardless of PD-L1 expression levels
- There was pronounced benefit in patients with ≥50% PD-L1 expression
- OS benefit was observed in all subgroups except EGFR mutation-positive disease

Barlesi F et al. *Proc ESMO* 2016;Abstract LBA44_PR.

Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

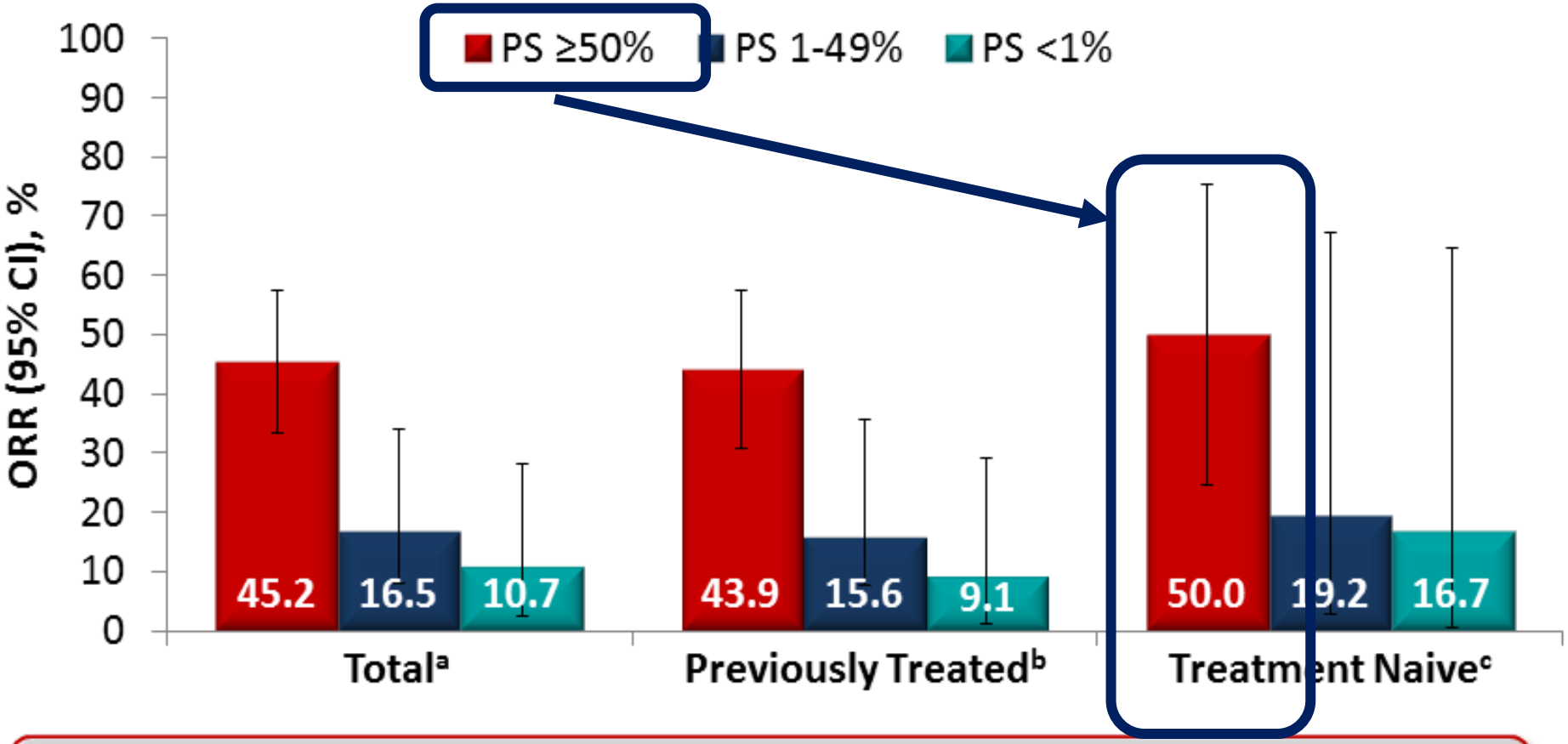
KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

June 16, 2016 06:45 AM Eastern Daylight Time

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive KEYTRUDA.

"We believe that the KEYNOTE-024 results have the potential to change the therapeutic paradigm in first-line treatment of non-small-cell lung cancer."

ORR by PD-L1 Proportion Score: CTA-Evaluable Validation Set Patients With Measurable Disease



When measurable disease is NOT required, the ORR (95% CI) in the PS ≥50% subgroups are: **42.3%, 41.0%, and 47.1%** in the total, previously treated, and treatment-naive populations[d]

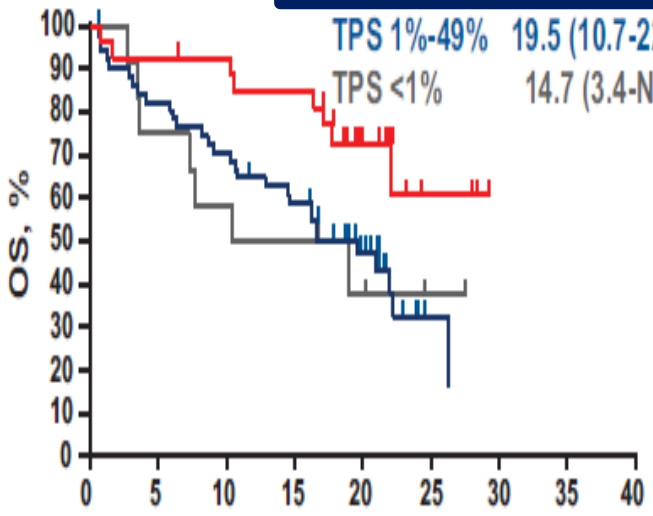
[a]n = 73, 103, and 28, respectively. [b]n = 57, 77, and 22, respectively. [c]n = 16, 26, and 6, respectively. [d]n = 78, 61, and 17, respectively.
ORR was assessed per RECIST v1.1 by central review in the biomarker-evaluable population (ie, patients with measurable disease per RECIST v1.1 by central review at baseline whose slides were cut within 6 months of staining and for which a proportion score could be assigned).
Analysis cut-off date: August 29, 2014.

Longterm OS in KN 001 in Tx-naïve NSCLC Pts Based on PDL1 Status

E

Frontline

	Median, mo (95% CI)	18-mo Rate, %	24-mo Rate, %
TPS ≥50%	NR (22.1-NR)	72.7	60.6
TPS 1%-49%	19.5 (10.7-22.2)	50.1	32.5
TPS <1%	14.7 (3.4-NR)	50.0	37.5



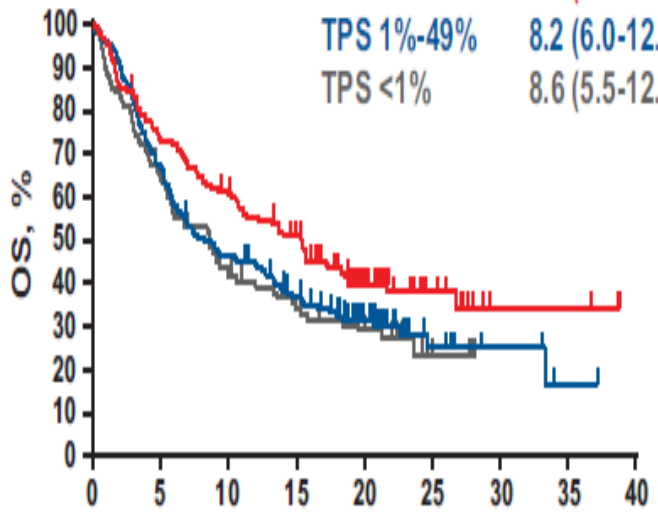
No. at risk

27	25	24	22	11	3	0	0	0
52	42	36	29	16	2	0	0	0
12	9	7	6	3	1	0	0	0

F

2nd Line

	Median, mo (95% CI)	18-mo Rate, %	24-mo Rate, %
TPS ≥50%	15.4 (10.6-18.5)	43.4	38.0
TPS 1%-49%	8.2 (6.0-12.7)	32.9	28.2
TPS <1%	8.6 (5.5-12.0)	31.7	23.5

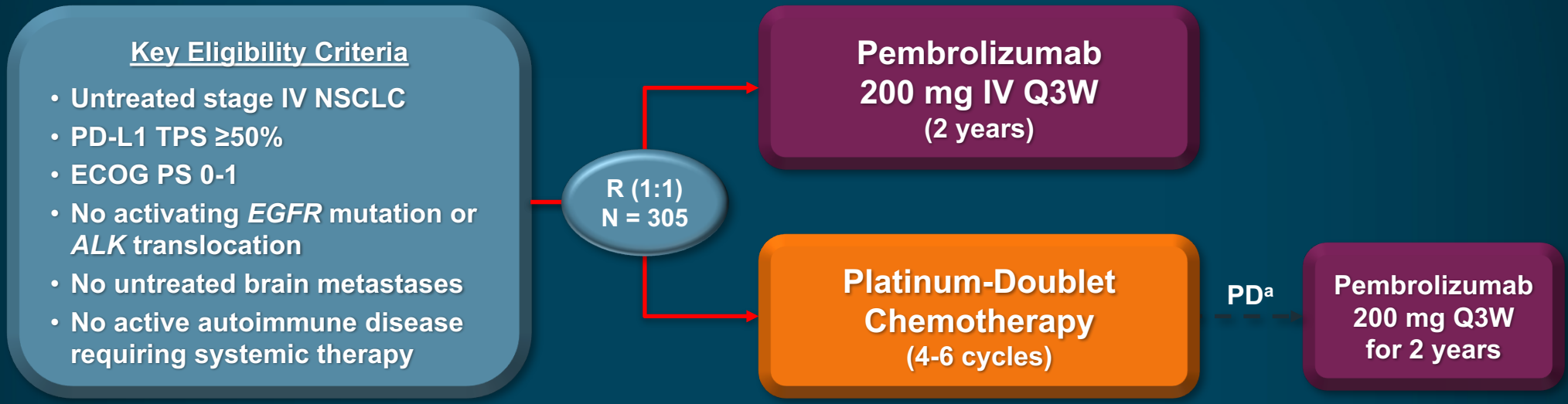


No. at risk

138	100	81	65	34	13	3	3	0
168	112	77	57	33	8	4	1	0
90	57	36	28	21	3	0	0	0

Hui et al ASCO 2016

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

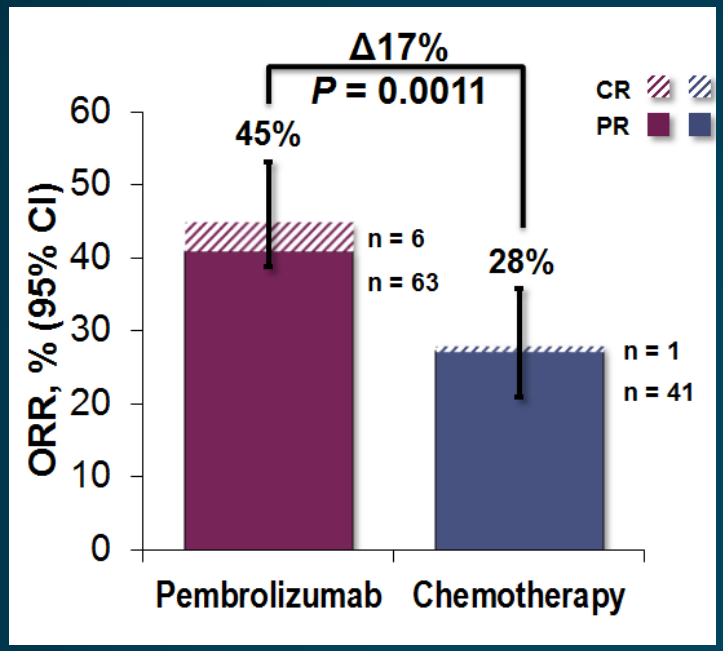
Primary: PFS (RECIST v1.1 per blinded, independent central review)

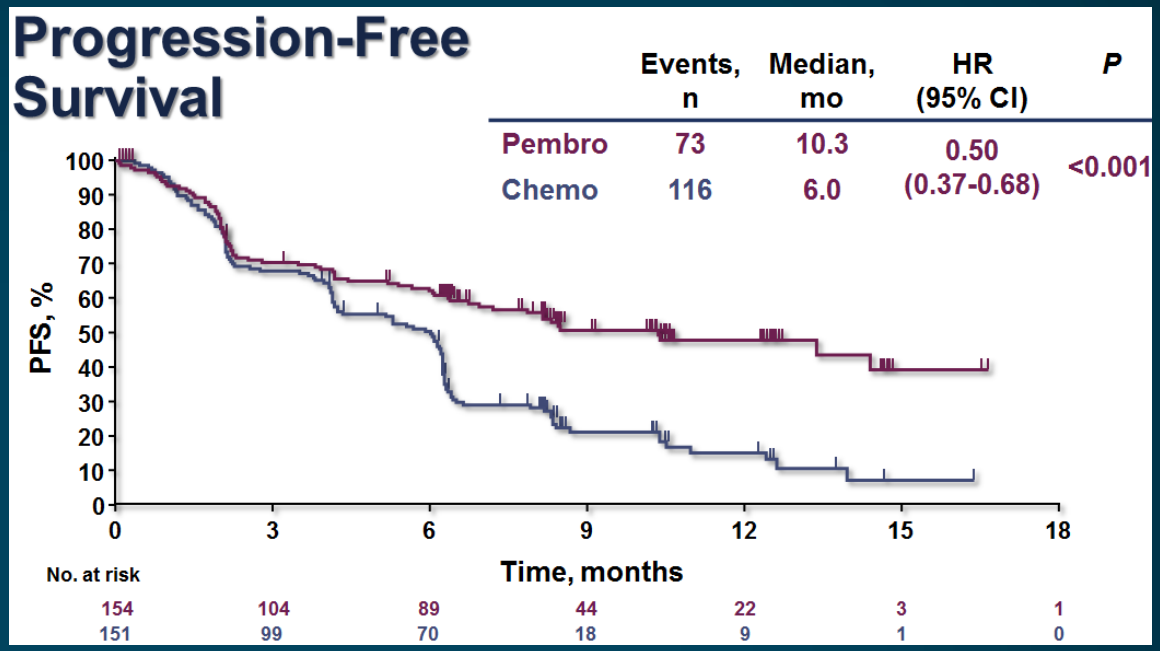
Secondary: OS, ORR, safety

Exploratory: DOR

[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.

Efficacy data: KEYNOTE- 24

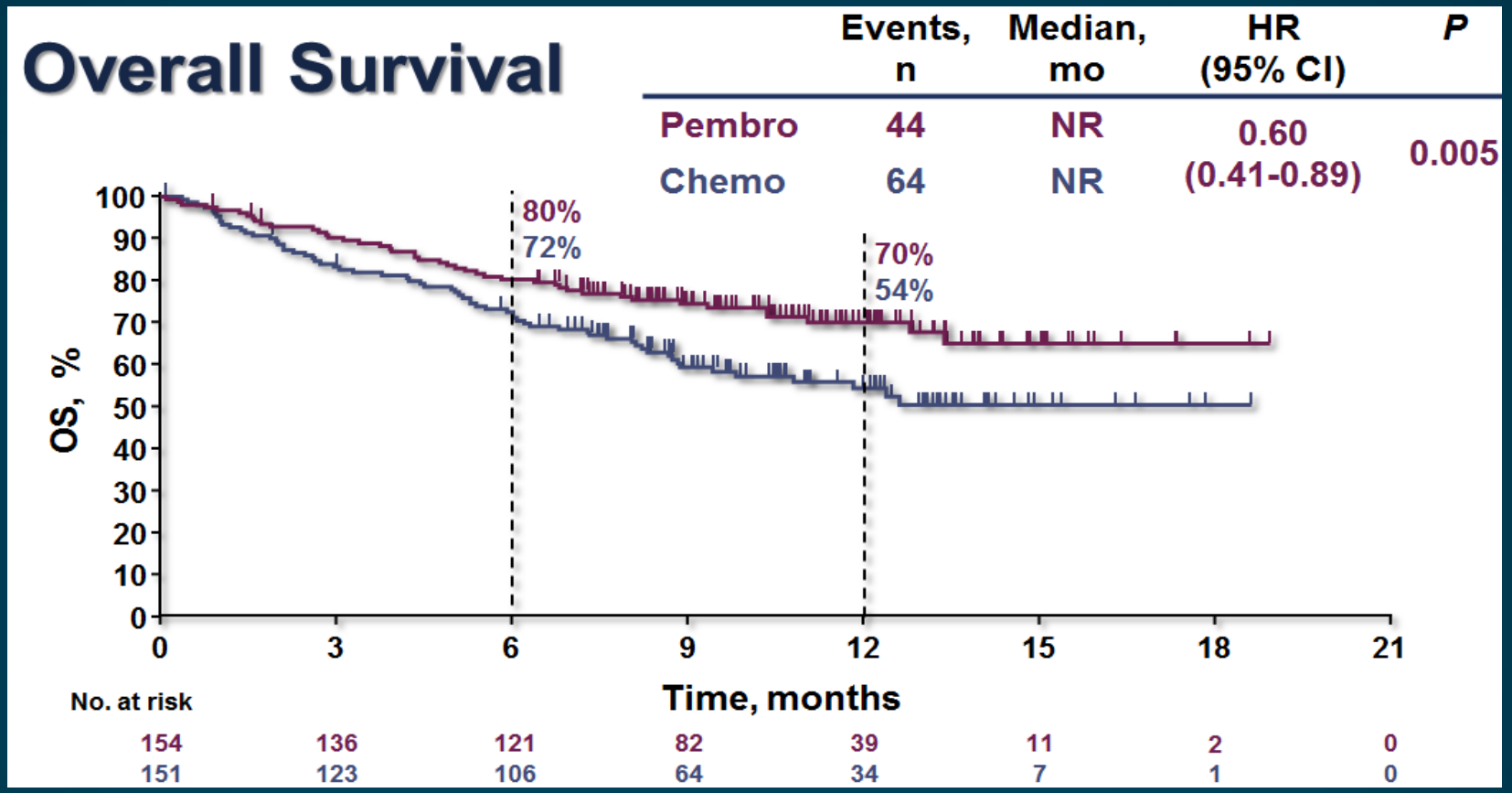




imaging was every 9 weeks

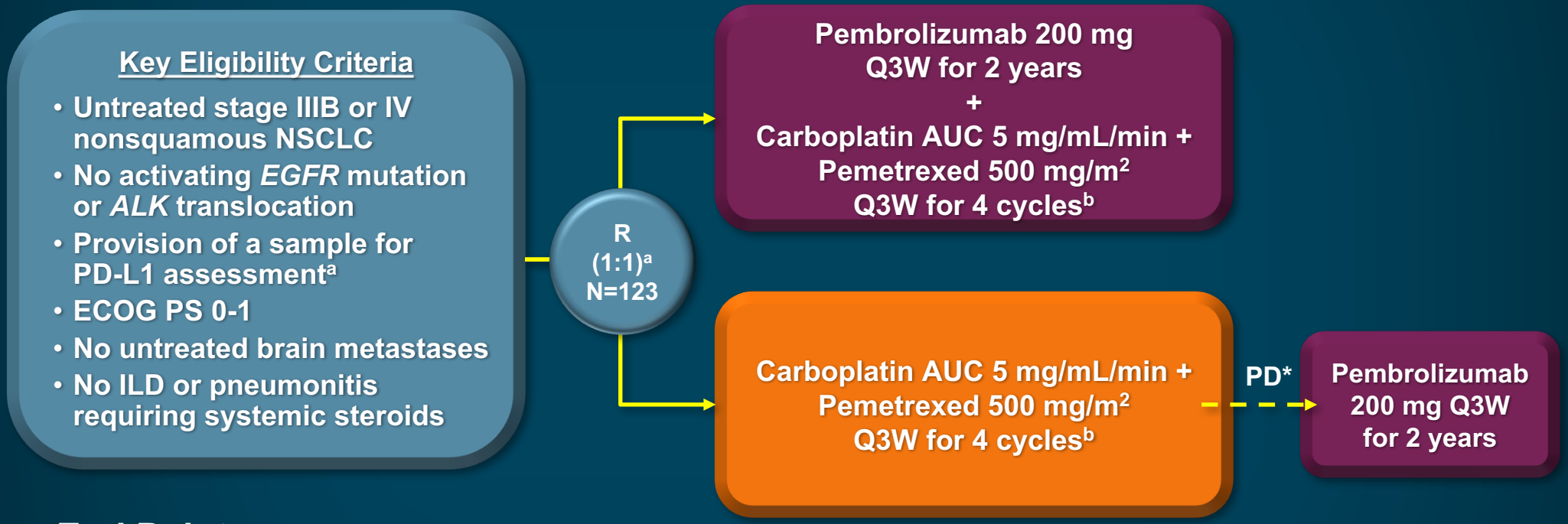
- Clear and strong signal of activity
  - → ORR is improved, with a control arm that performs as expected (based on other phase III trials)
  - → 45% ORR is the one of best RRs ever reported in 1st line setting (and with monotherapy !)
  - → Time to Response is identical between Pembro and Chemo
  - → 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)

KEYNOTE 24: Survival data



- **Clearcut survival benefit for NSCLC pts with PDL1 ≥ 50%**
  - 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

KEYNOTE-021 Cohort G:
Pem/Carbo +/- Pembrolizumab



End Points

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

Key secondary: PFS

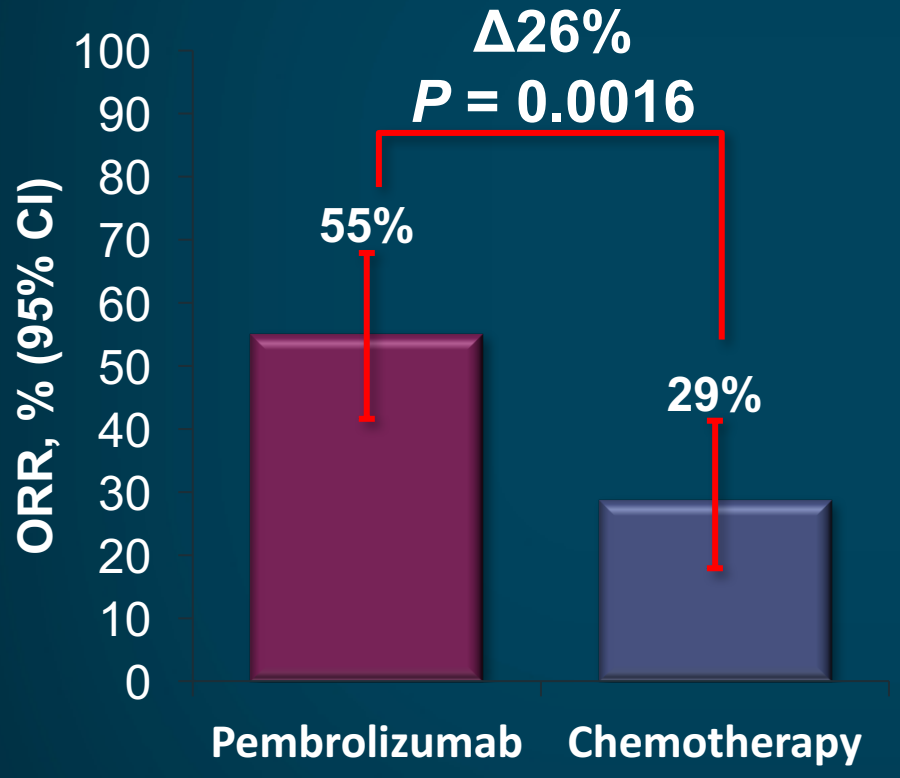
Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

* 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.

Langer et al, Lancet Oncology, 2016

Confirmed Objective Response Rate

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



	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)

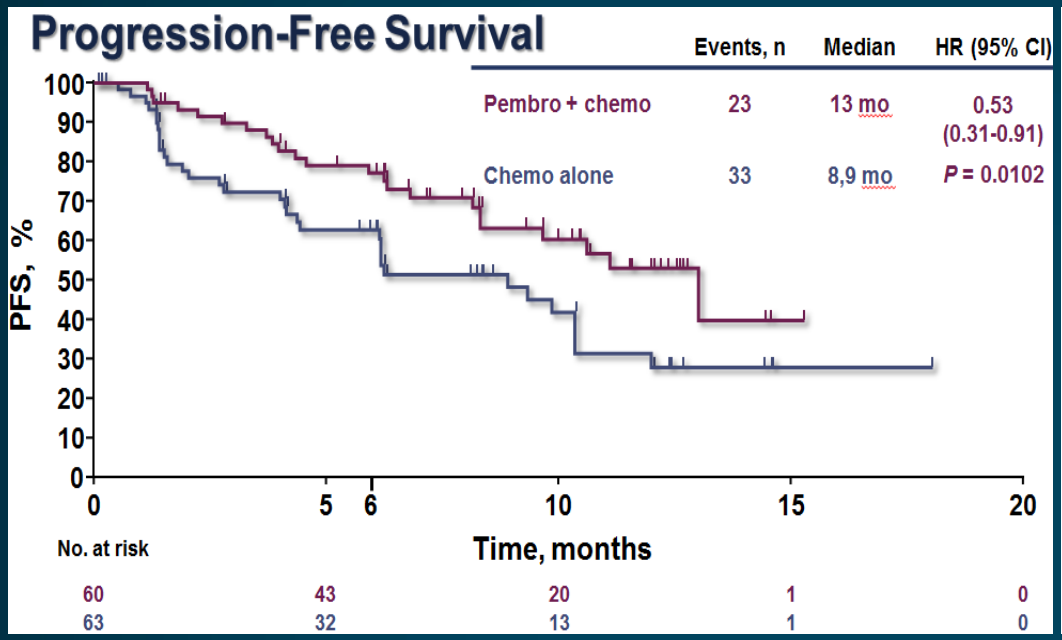
Data cut-off: August 8, 2016.

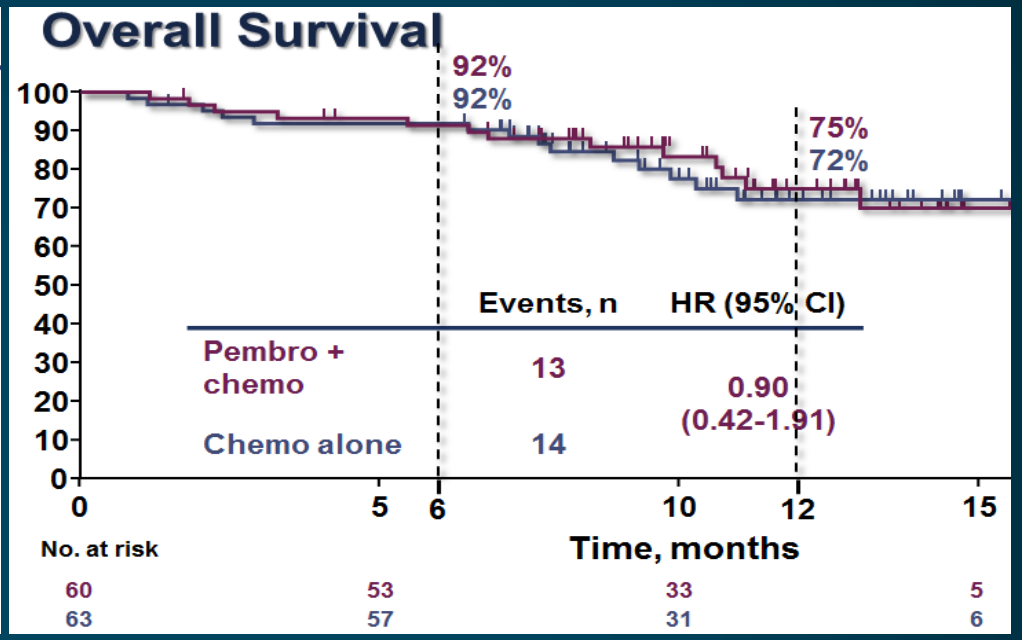
DOR = duration of response; TTR = time to response.

[a]Alive without subsequent disease progression.

Langer et al, Lancet Oncology, 2016

PFS and OS Survival data



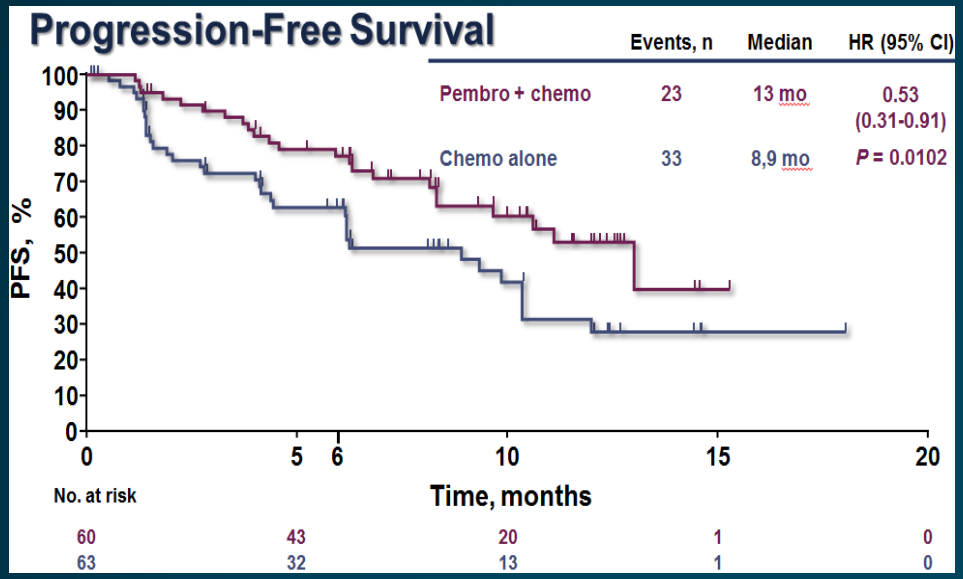


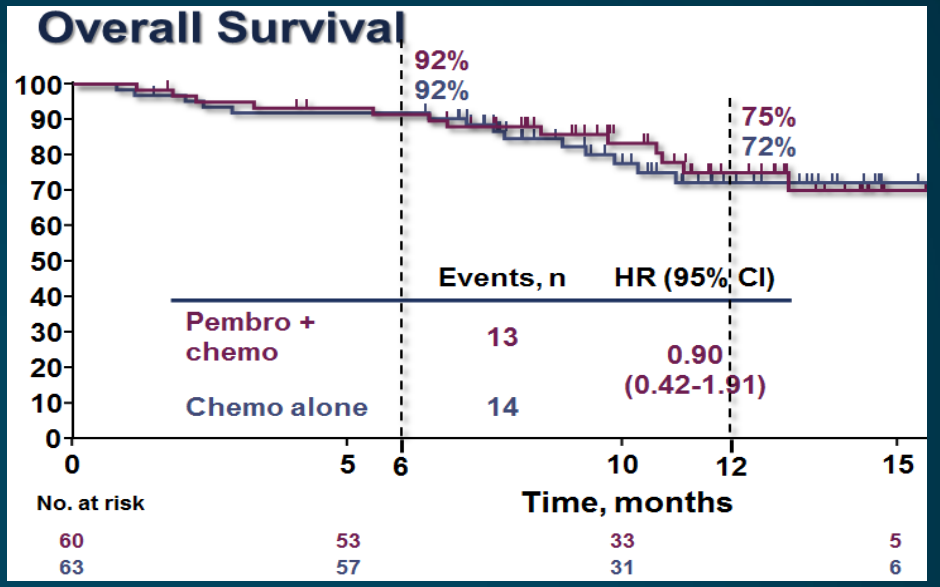
- Clear PFS benefit and no OS advantage
  - Median PFS improved by 4.1 months
  - PFS HR is 0.53
  - No difference for OS
  - Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
  - In CT arm cross-over is 51% to PD-(L)1 therapies (pembro & others), but > 70% in those eligible

COPENHAGEN 2016 ESMO congress

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, with drop in p value from 0.369 to 0.13
  - 1 yr OS 76% vs 69%

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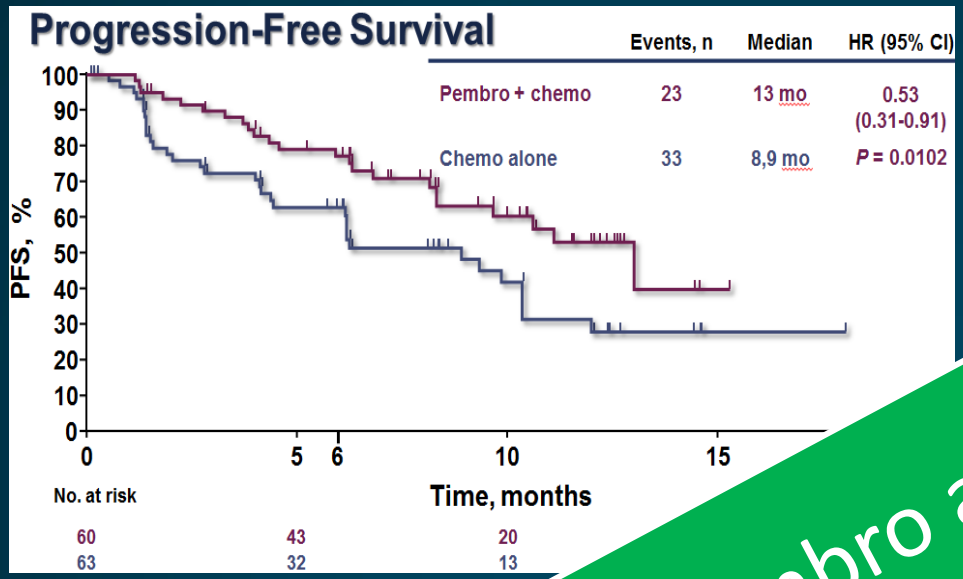
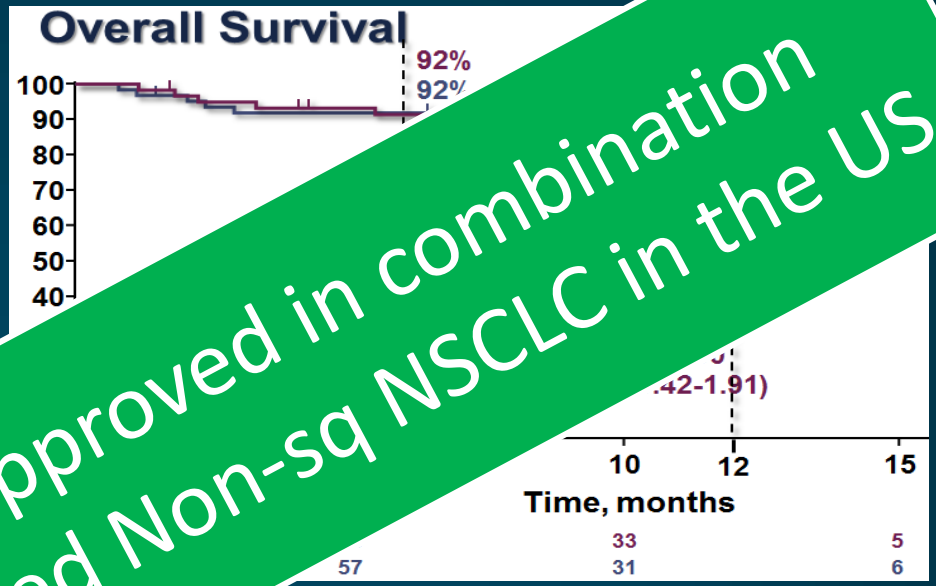
Langer et al, Lancet Oncology, 2016

PFS and OS Survival data





As of 05/09/17, Pembro approved in combination with Pem/Carbo in Advanced Non-sq NSCLC in the US

- Clear PFS benefit and p
  - Median PFS
  - PFS
  - s: 75% (Combo) vs 72% (CT)
  - to PD-(L)1 therapies (pembro & others), but > 70% in
  - 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, with drop in p value from 0.369 to 0.13
  - 1 yr OS 76% vs 69%

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Langer et al, Lancet Oncology, 2016

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: ≥1%, <1%
- Smoking status
- cisplatin vs carboplatin

RANDOMIZATION

2:1

N=570

Carboplatin/Cisplatin
Pemetrexed
Pembrolizumab
200 mg Q3W
X4 cycles

Pemetrexed
Pembrolizumab

PD → *Follow*

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

Study Design

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RANDOMIZAT

N=570

Carboplatin/Cis
Pemetre
Pembro
200

emetrexed
Pembrolizumab

PD → Follow

/Cisplatin
emetrexed
+Saline
X4 cycles

Pemetrexed
+Saline

PD

Pembrolizumab

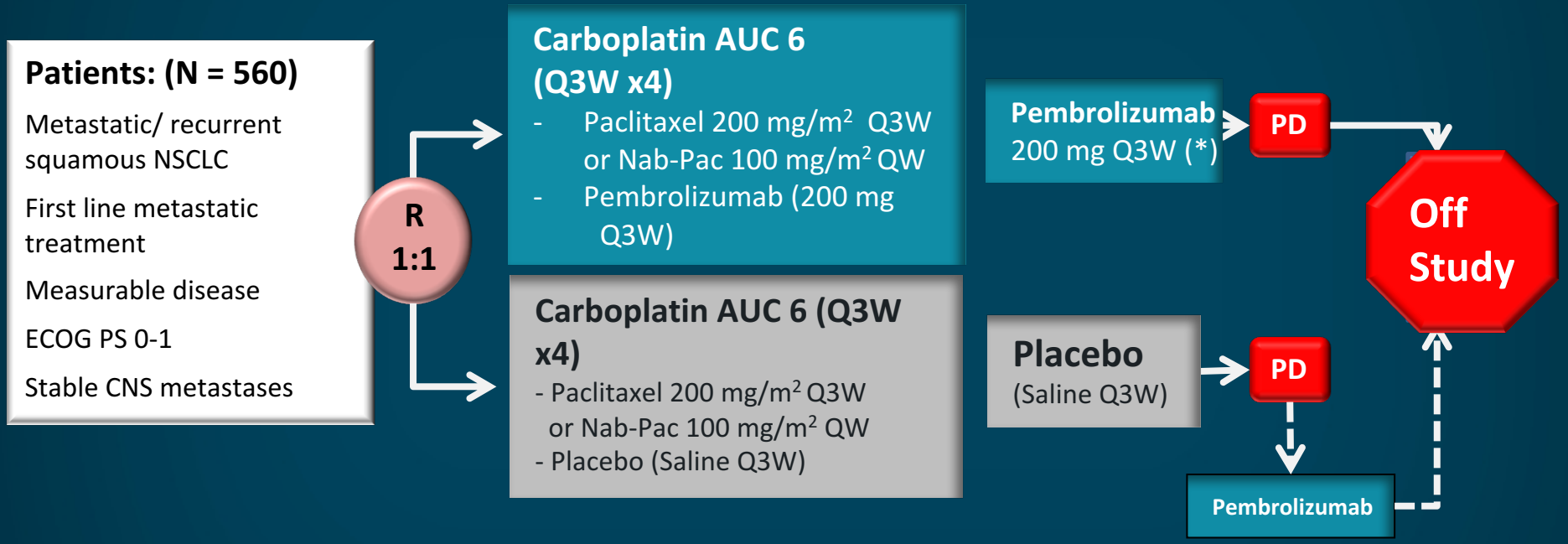
Completed Accrual 02/17

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

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

KEYNOTE 407 (Squamous NSCLC)

First line pembrolizumab + chemotherapy (carboplatin + paclitaxel/nab-paclitaxel) combination study



- **Primary Endpoint:** Overall and Progression-Free Survival
- **Secondary Endpoints:** ORR, AE
- **Exploratory Endpoints:** QoL

Stratify:

PDL1 TPS score: ≥1% vs <1%

Paclitaxel vs nab-paclitaxel

* Up to 2 years

First- and Second-Line Treatment of Metastatic NSCLC (After KEYNOTE-024)