Immune Checkpoint Inhibitors for Lung Cancer

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Non-Small Cell Lung Cancer

- PD-1/PD-L1 Inhibitors in second-line therapy
  - Nivolumab
  - Pembrolizumab
  - Atezolizumab
- PD-L1 expression as a biomarker
- First-line treatment
  - PD-1 inhibitor versus chemotherapy
  - Chemotherapy +/- PD-1 inhibitors
  - Nivolumab +/- ipilimumab
- Consolidation treatment
  - Durvalumab

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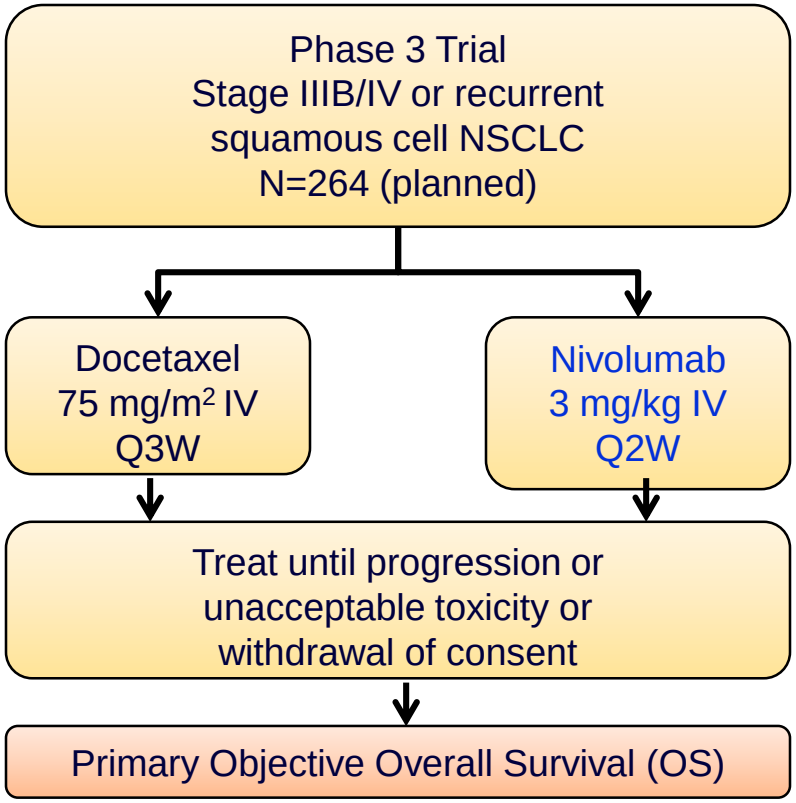
Phase III - CheckMate 017
2nd Line Nivolumab vs. Docetaxel in SCC



Key Eligibility Criteria

- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

Primary Endpoints

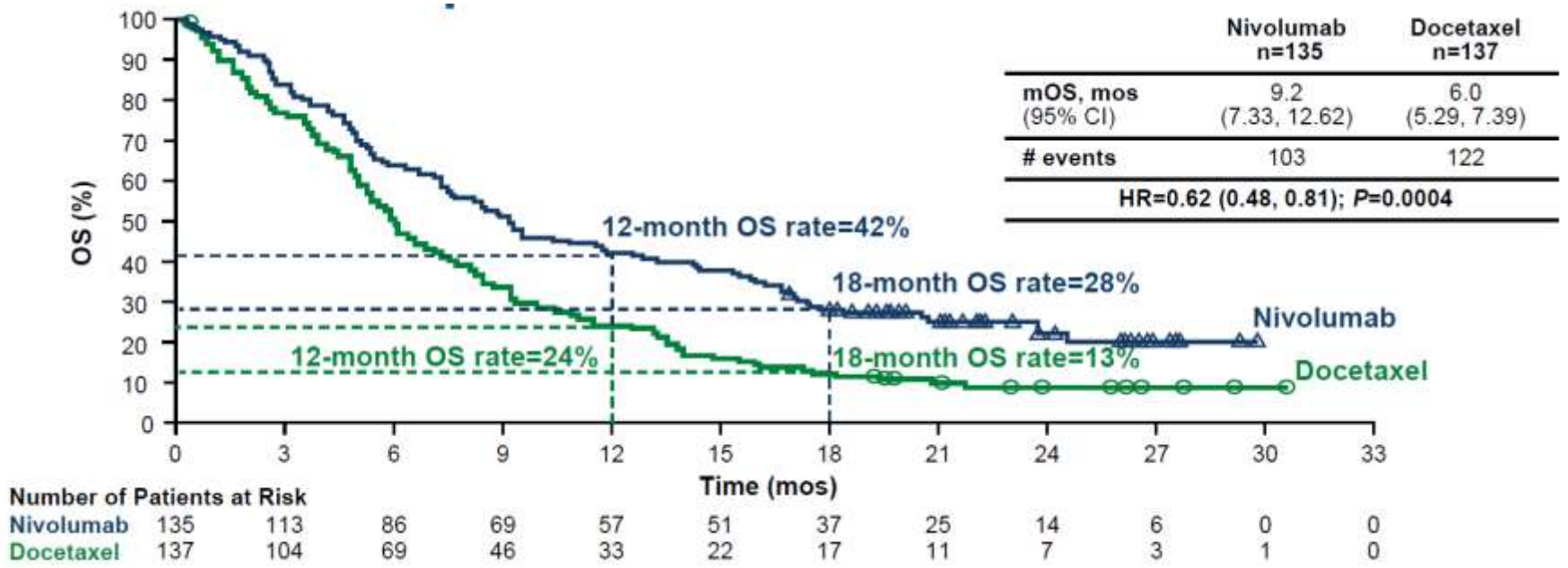
- OS

Secondary Endpoints

- PFS and ORR
- ORR and OS in PD-L1+ vs PD-L1– subgroups
- Duration of OR
- Time to OR
- Proportion of patients exhibiting disease-related symptom progression per Lung Cancer Symptom Scale

Phase III - CheckMate 017
2nd Line Nivolumab vs. Docetaxel in SCC

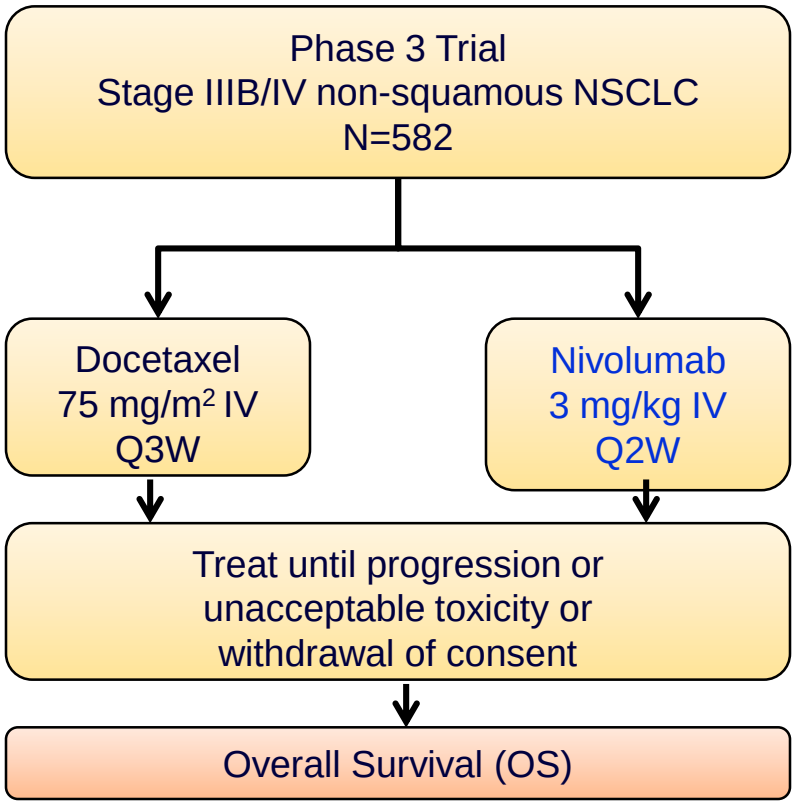
Overall Survival



	Nivolumab n=135	Docetaxel n=137
mOS, mos (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR=0.62 (0.48, 0.81); *P*=0.0004		

Reckamp K et al, IASLC 2015

Phase III - CheckMate 057
Nivolumab vs. Docetaxel in Non-SCC



Key Eligibility Criteria

- Stage IIIB/IV non-squamous NSCLC
- Prior Pt-containing chemotherapy (2nd-line) required: additional TKI therapy allowed (3rd-line)
- Patient may have received continuous or switch maintenance with pemetrexed, erlotinib, or bevacizumab post–Pt-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

Primary Endpoint

- OS

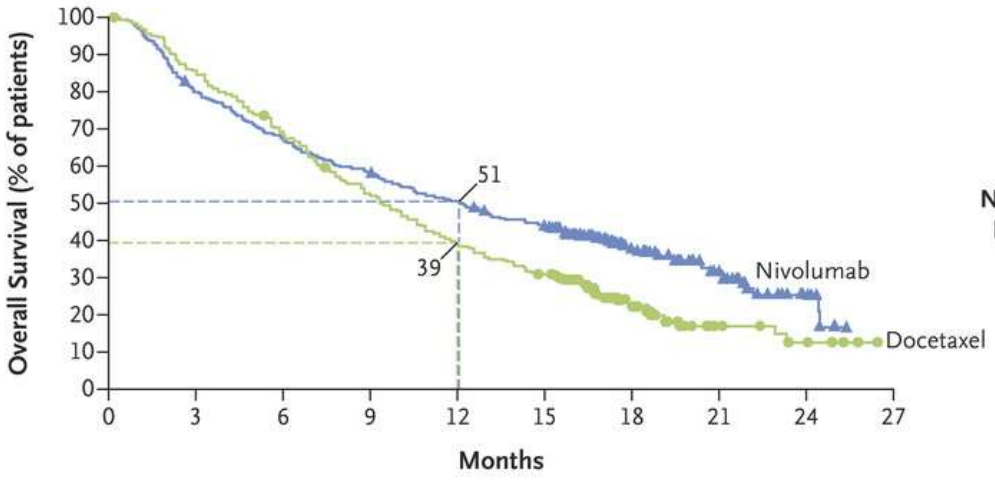
Secondary Endpoints

- PFS
- ORR
- QoL

Borghaei H et al. N Engl J Med 2015;373:1627-1639.

Phase III - CheckMate 057
2nd Line Nivolumab vs. Docetaxel in Non-SCC

Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

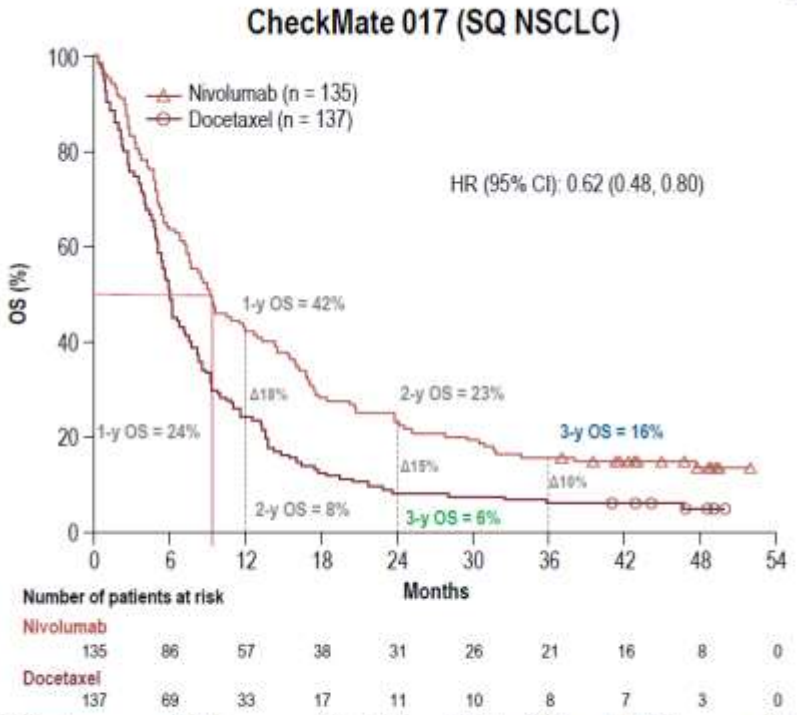
Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

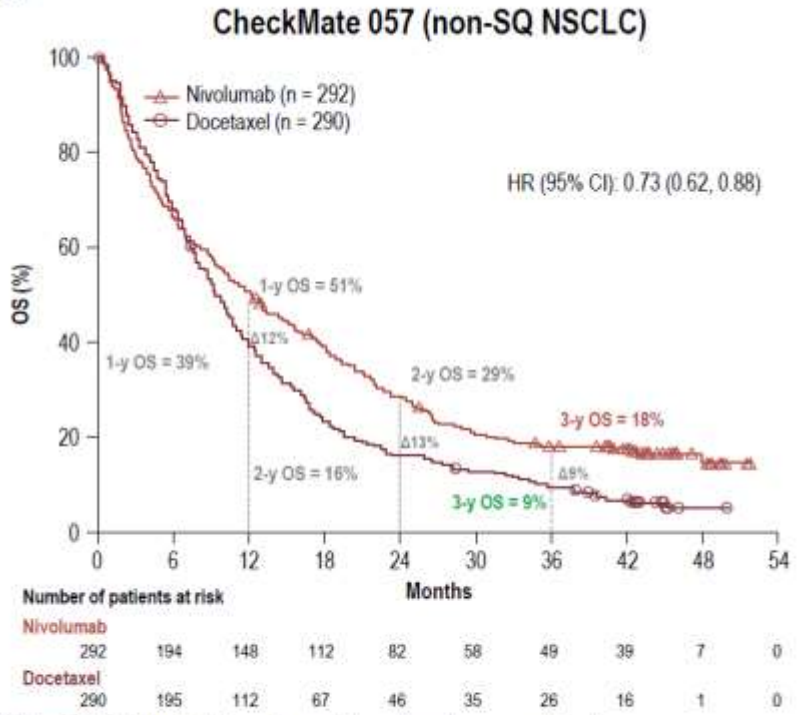
No. at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Borghaei H et al. N Engl J Med 2015;373:1627-1639.

Phase III - CheckMate 017 and 057
Long-Term Overall Survival

OS Data

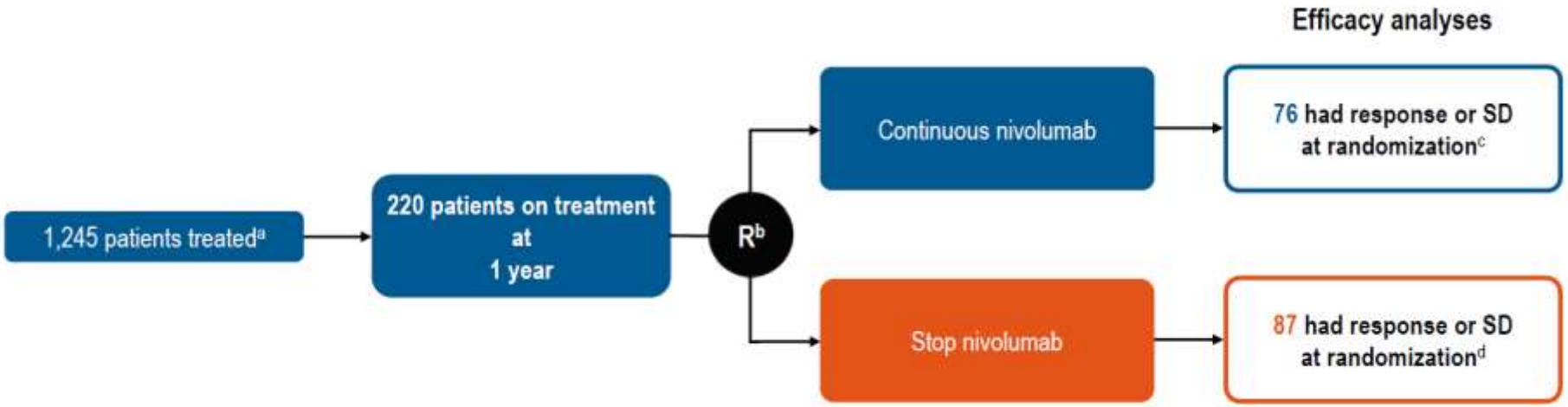




- 3-year OS rates were 16% versus 6% in CheckMate 017 and 18% versus 9% in CheckMate 057 with nivolumab and docetaxel, respectively
- Of the 3-year survivors treated with docetaxel, the majority received subsequent immunotherapy, either during crossover to nivolumab or as post-study treatment (CheckMate 017: 75% [6/8 patients]; CheckMate 057: 73% [19/26 patients])

ESMO 2017

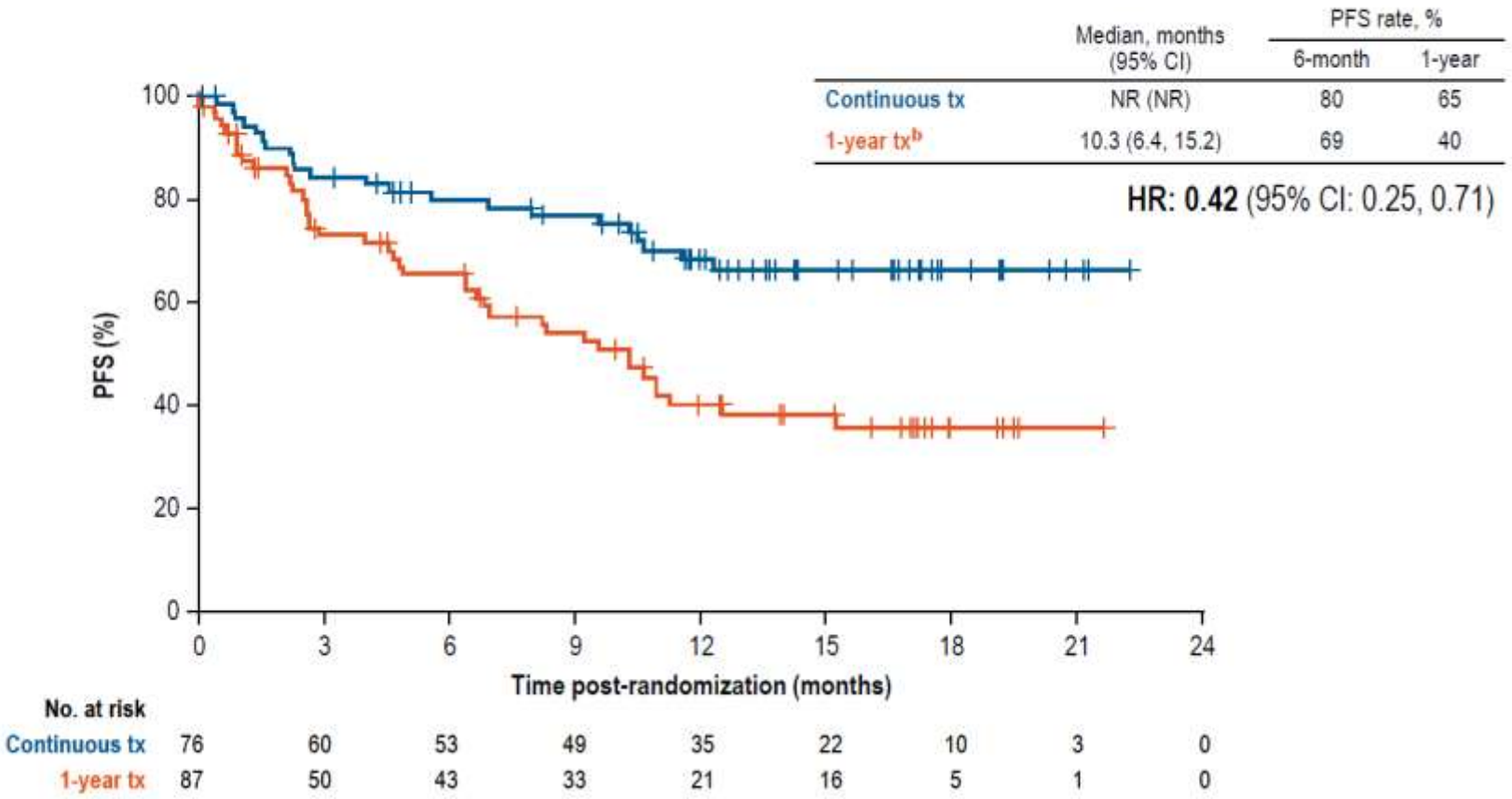
Phase III - CheckMate 153
Nivolumab Continuous vs. 1 Year



Spiegel et al. ESMO 2017.

Phase III - CheckMate 153
Nivolumab Continuous vs. 1 Year

PFS FROM RANDOMIZATION



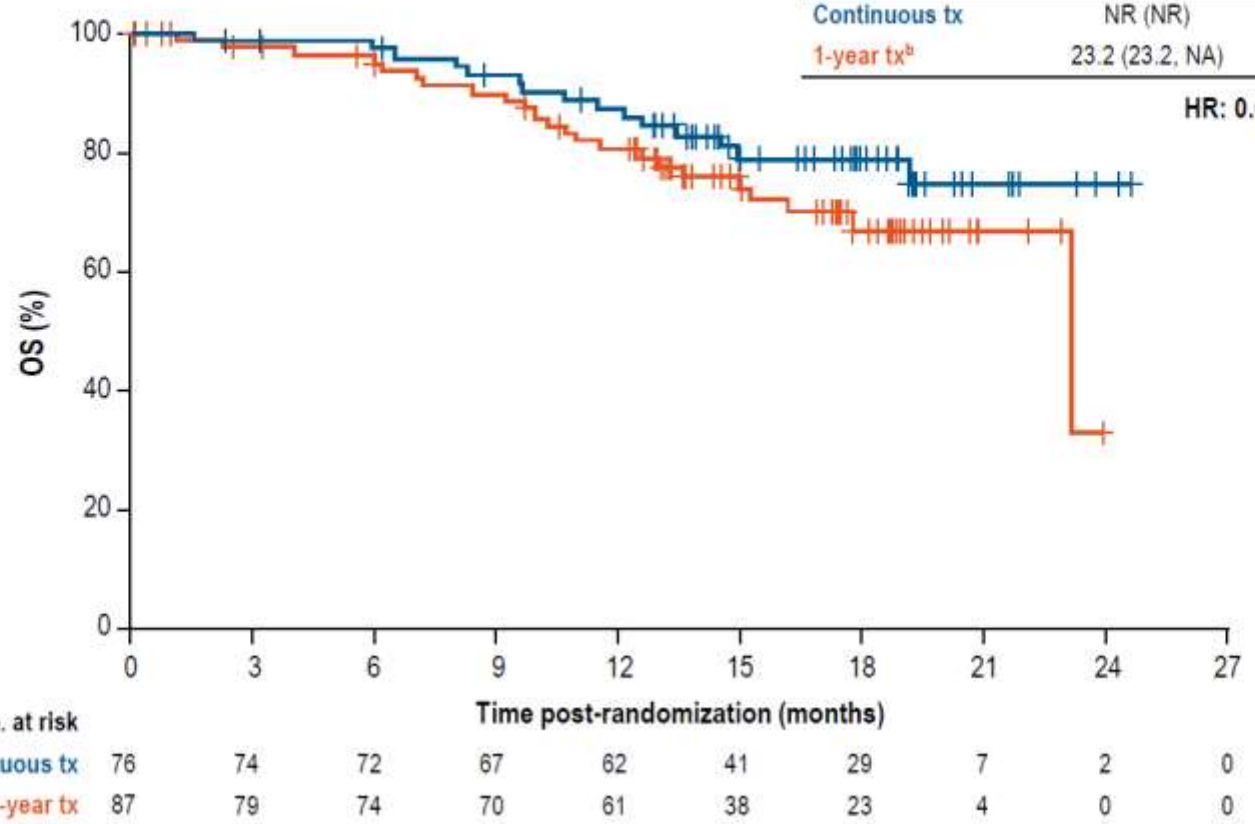
Spiegel et al. ESMO 2017.

Phase III - CheckMate 153
Nivolumab Continuous vs. 1 Year

OS FROM RANDOMIZATION

	Median, months (95% CI)	OS rate, % 6-month	OS rate, % 1-year
Continuous tx	NR (NR)	97	88
1-year tx[b]	23.2 (23.2, NA)	95	81

HR: 0.63 (95% CI: 0.33, 1.20)



Spiegel et al. ESMO 2017.

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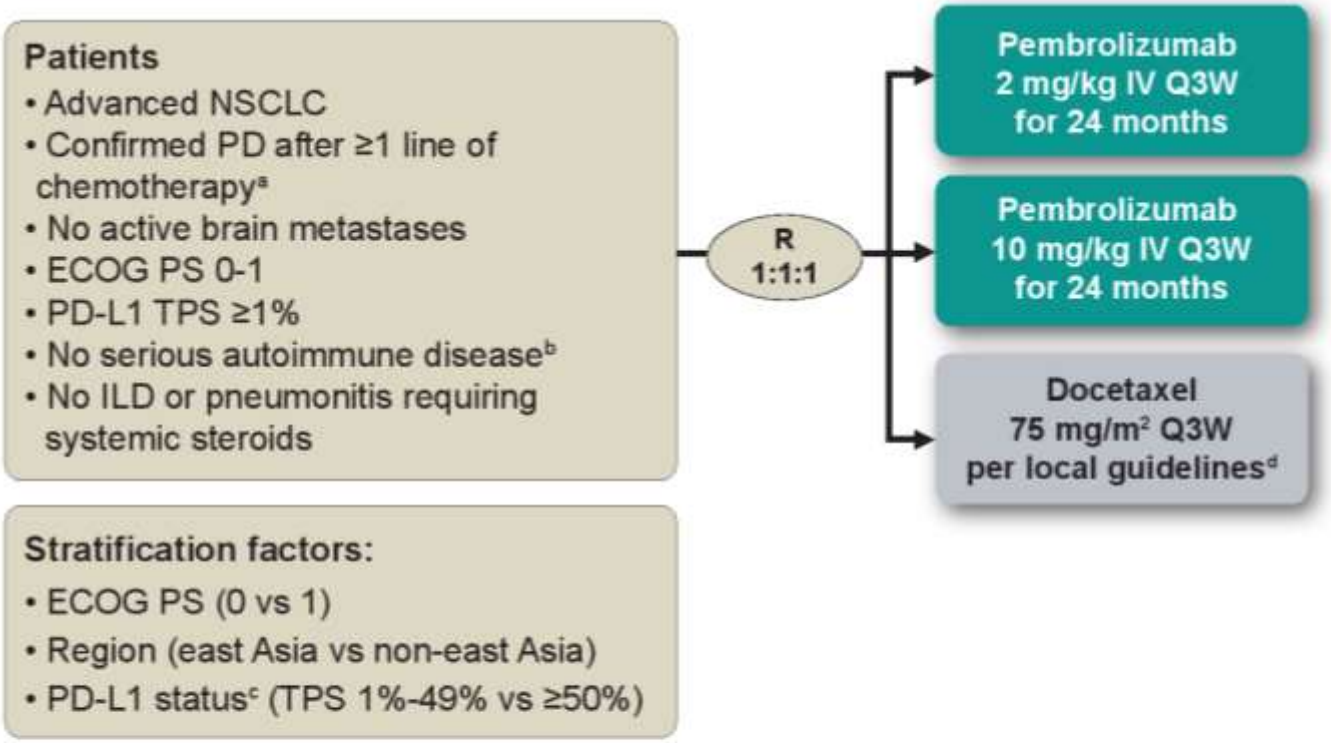
Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC



[a]Prior therapy must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients whose tumors had an EGFR sensitizing mutation or an ALK translocation.

[b]No active or documented history of any autoimmune disease or syndrome that required systemic steroids or immunosuppressive agents, excluding patients with vitiligo, resolved childhood asthma/atopy, or those that required inhaled steroids or local steroid injections.

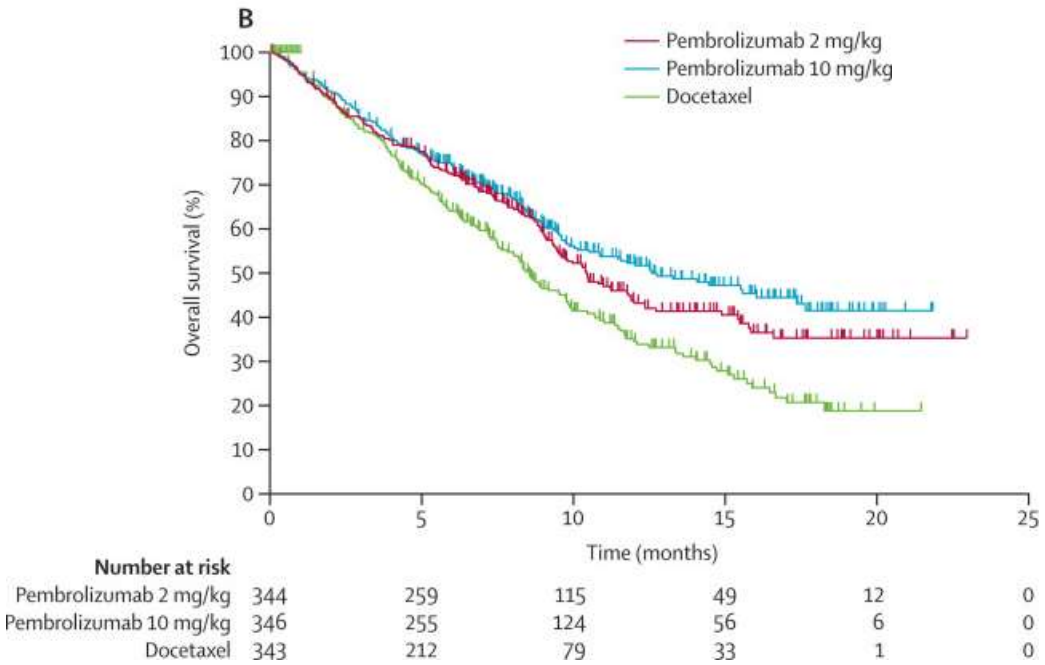
[c]Based on results from KEYNOTE-0013 and added after 441 patients enrolled to ensure equal distribution of TPS ≥50% and 1%-49% in subsequently enrolled patients.

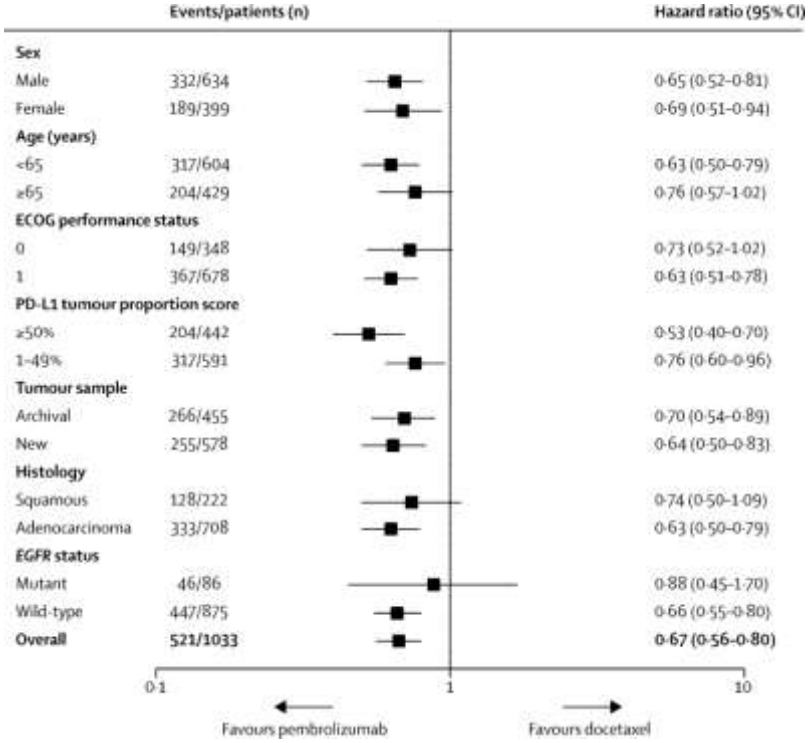
[d]Patients received the maximum number of cycles permitted by the local regulatory authority.

ECOG PS = Eastern Cooperative Oncology Group performance status; ILD = interstitial lung disease; PD = progressive disease; R = randomized.

Herbst et al. Lancet 2015

Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC





Median overall survival:

Docetaxel: 8.5 months
Pembrolizumab 2 mg/kg: 10.4 months (HR=0.71, 95% CI 0.58-0.88; p=0.0008)
Pembrolizumab 10 mg/kg: 12.7 months (HR=0.61, 95% CI 0.49-0.75; p<0.0001)

Herbst et al. Lancet 2015

Phase II/III - Keynote 010
Pembrolizumab vs. Docetaxel in NSCLC – TPS 1-49%

Figure 2. Kaplan-Meier estimates of OS in the PD-L1 TPS 1%-49% stratum.

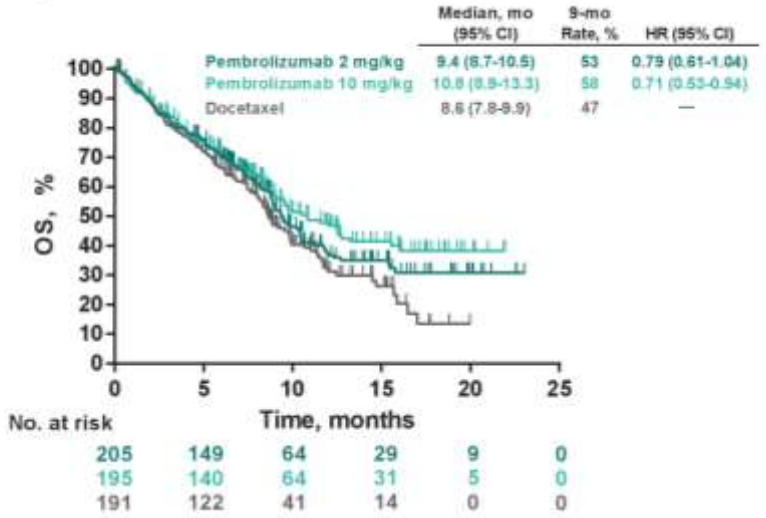


Table 2. ORR and DOR per RECIST v1.1 by independent central review in the PD-L1 TPS 1%-49% Stratum

	Pembrolizumab 2 mg/kg n = 205	Pembrolizumab 10 mg/kg n = 195	Docetaxel n = 191
ORR, % (95% CI)	10 (6-15)	10 (6-15)	10 (6-16)
DOR, median (range), wk	46 (9+ to 87+)	45 (13+ to 74+)	26 (6+ to 31)
Ongoing response,* %	65	65	35

*Responders who are alive, progression free, did not initiate new anticancer therapy, and were not lost to follow-up

Garon et al. ASCO 2016

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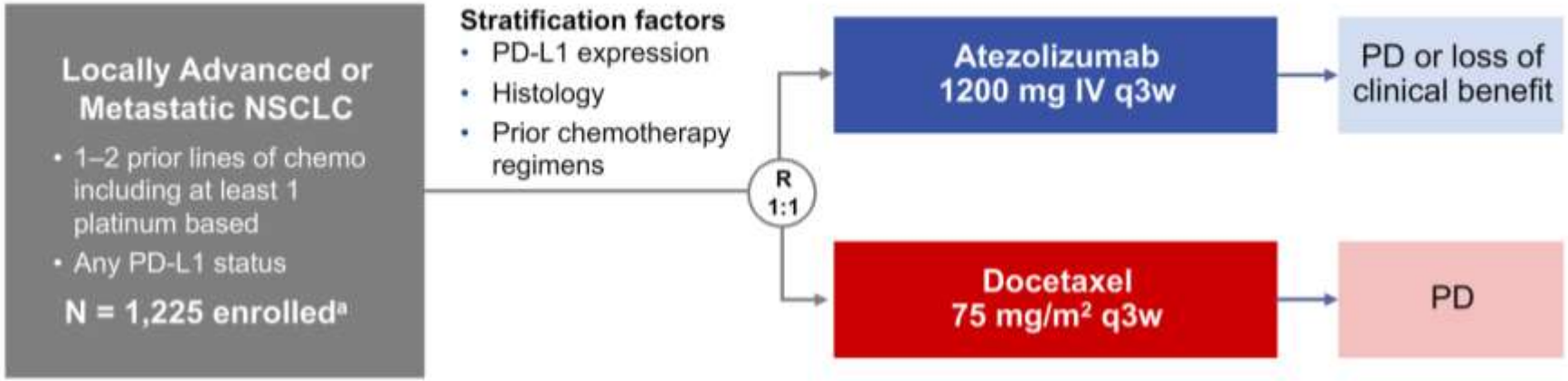
Phase III - OAK
Atezolizumab vs. Docetaxel in NSCLC



Primary Endpoints (first 850 enrolled patients):

- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
TC, tumor cells; IC, tumor-infiltrating immune cells.

ESMO congress 6

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

Barlesi et al. ESMO 2016

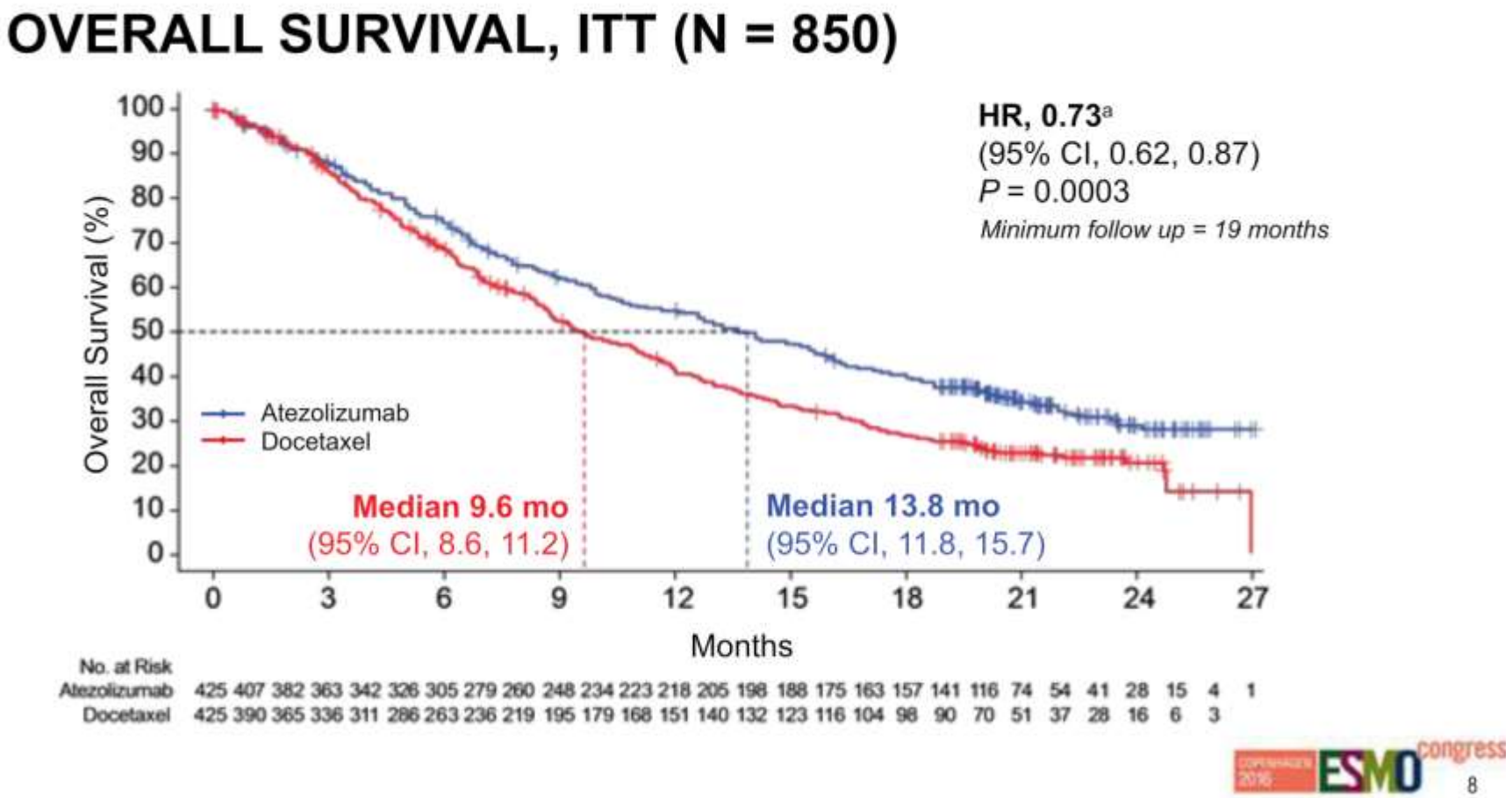
PHASE III - OAK
ATEZOLIZUMAB VS. DOCETAXEL IN NSCLC

BASELINE CHARACTERISTICS, ITT (N = 850)

Characteristics	Atezolizumab n = 425	Docetaxel n = 425
Median age, y	63 y	64 y
≥ 65 y	45%	49%
Male	61%	61%
Histology		
Nonsquamous	74%	74%
Squamous	26%	26%
ECOG PS, 0 / 1	37% / 64%	38% / 62%
No. of prior therapies, 1 / 2	75% / 25%	75% / 25%
History of tobacco use		
Never	20%	17%
Current / Previous	14% / 66%	16% / 67%
CNS mets, Yes / No	9% / 91%	11% / 89%
Known EGFR status		
Mutant / Wild type	10% / 75%	10% / 73%

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

Phase III - OAK
Atezolizumab vs. Docetaxel in NSCLC



[a]Stratified HR.

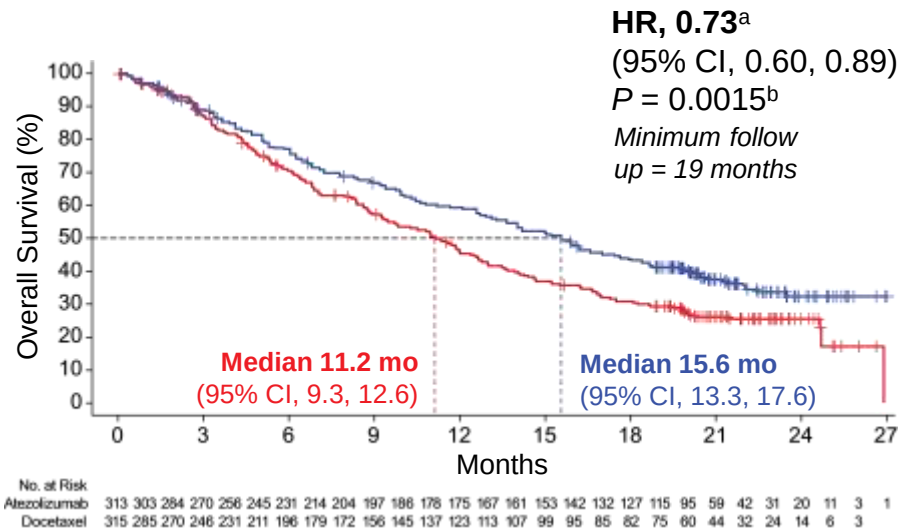
Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

Barlesi et al. ESMO 2016

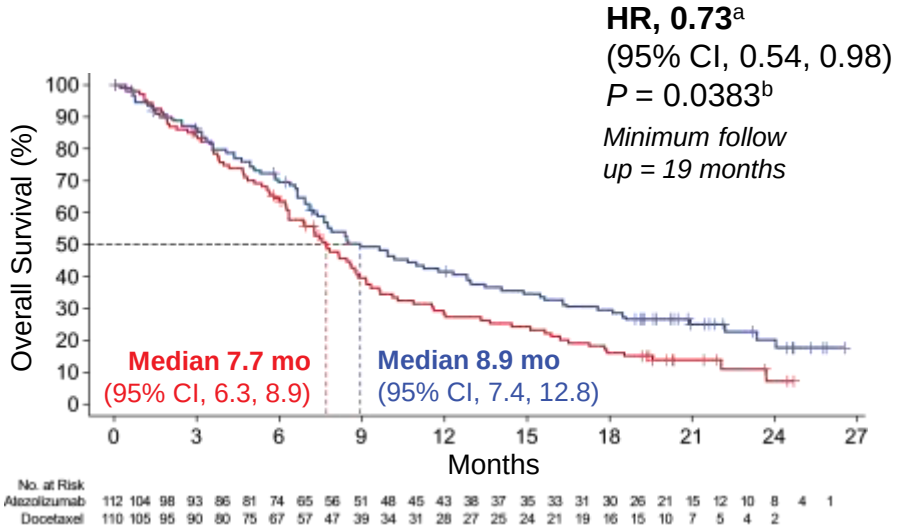
PHASE III - OAK
ATEZOLIZUMAB VS. DOCETAXEL IN NSCLC

OS BY HISTOLOGY

Non-squamous



Squamous



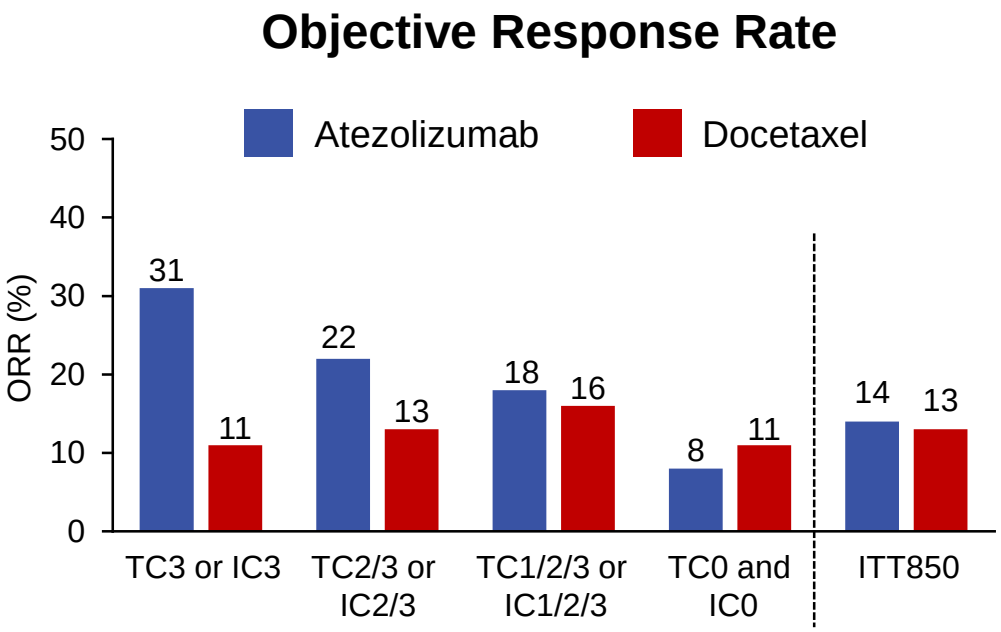
Atezolizumab
Docetaxel

[a]Unstratified HRs.
[b]*P* values for descriptive purpose only.
Histology information from eCRF.
OS, overall survival.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

PHASE III - OAK
ATEZOLIZUMAB VS. DOCETAXEL IN NSCLC

ORR AND DOR



Duration of Response		
	Atezolizumab	Docetaxel
ITT	n = 58	n = 57
Ongoing response	52%	18%
Median (mo)	**16.3**	**6.2**
TC1/2/3 or IC1/2/3	n = 43	n = 36
Ongoing response	47%	11%
Median (mo)	**16.0**	**6.2**
TC0 and IC0	n = 14	n = 21
Ongoing response	71%	29%
Median (mo)	**NE**	**6.2**

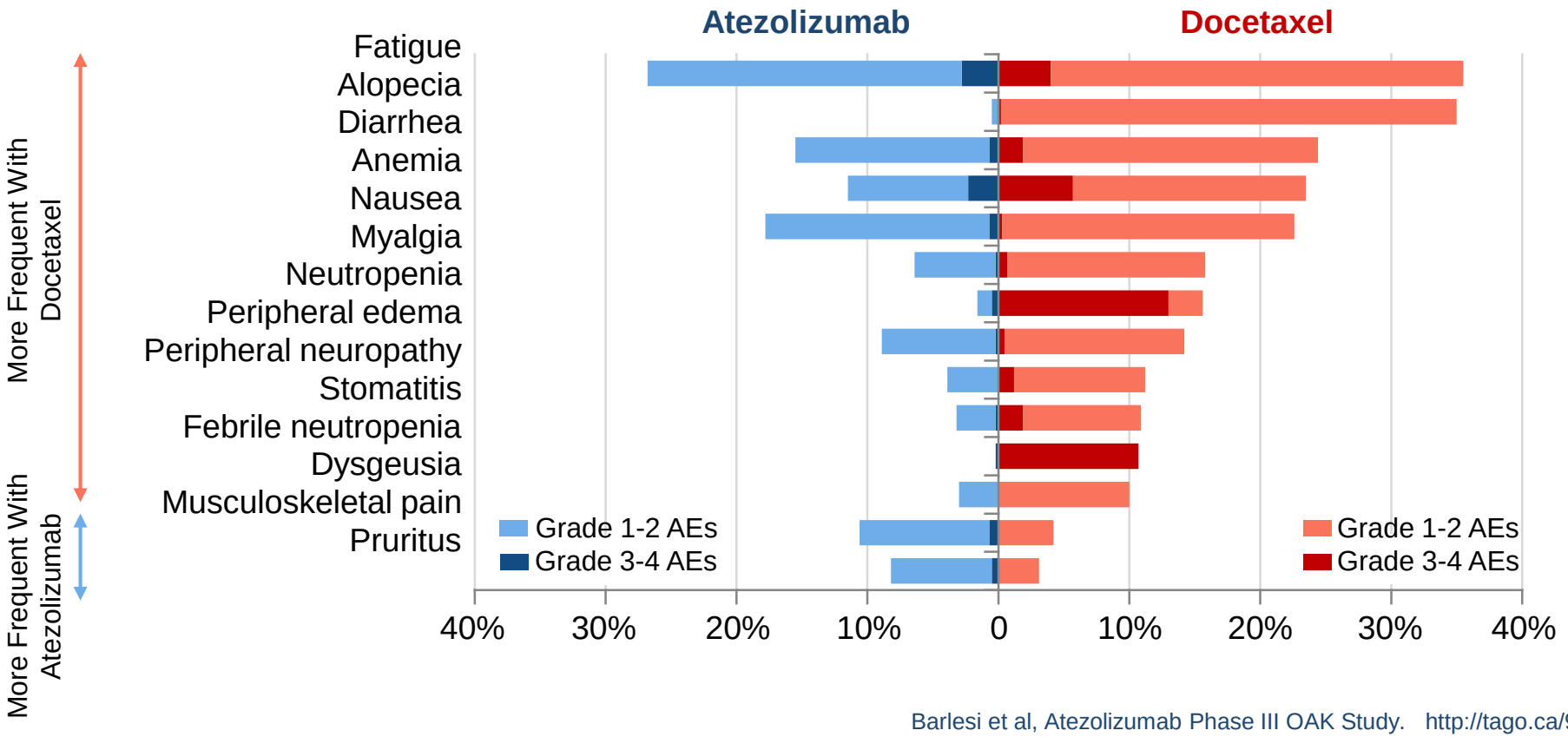
Confirmed investigator-assessed ORR per RECIST v1.1.
DOR, duration of response; NE, not estimable; ORR, objective response rate.
TC, tumor cells; IC, tumor-infiltrating immune cells.

Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

PHASE III - OAK
ATEZOLIZUMAB VS. DOCETAXEL IN NSCLC

ALL CAUSE AEs

>5% DIFFERENCE BETWEEN ARMS



Barlesi et al, Atezolizumab Phase III OAK Study. http://tago.ca/9Hh

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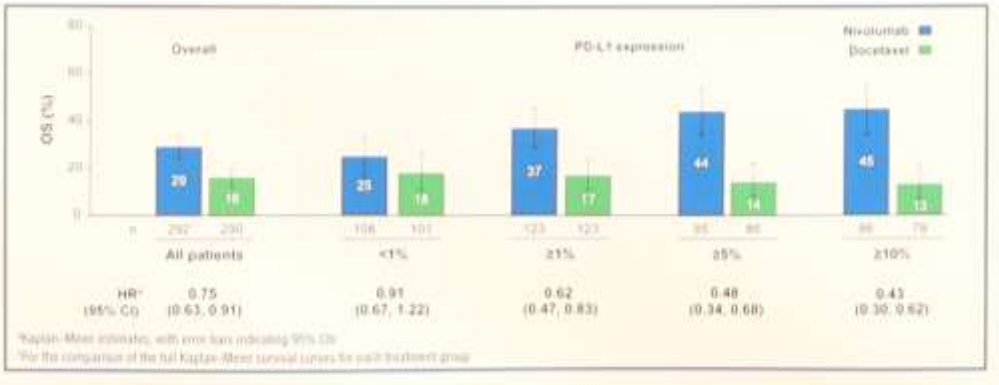
Efficacy According to PD-L1

Phase III - CheckMate 057
2-year Overall Survival – Non-Squamous NSCLC



Borghaei H et al. ASCO 2016.

Phase III - CheckMate 017
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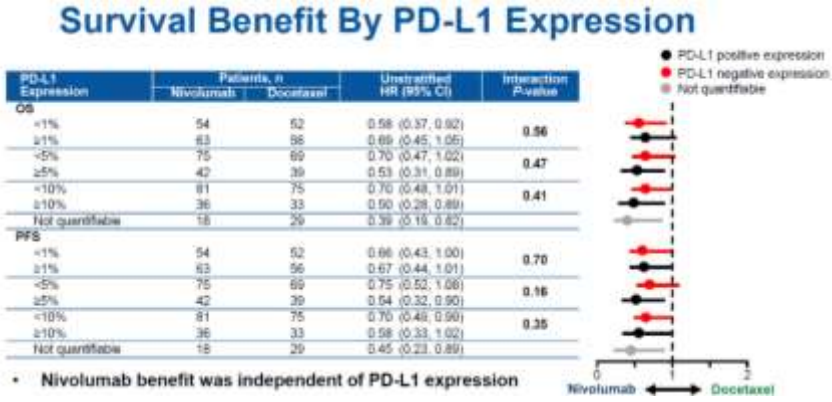
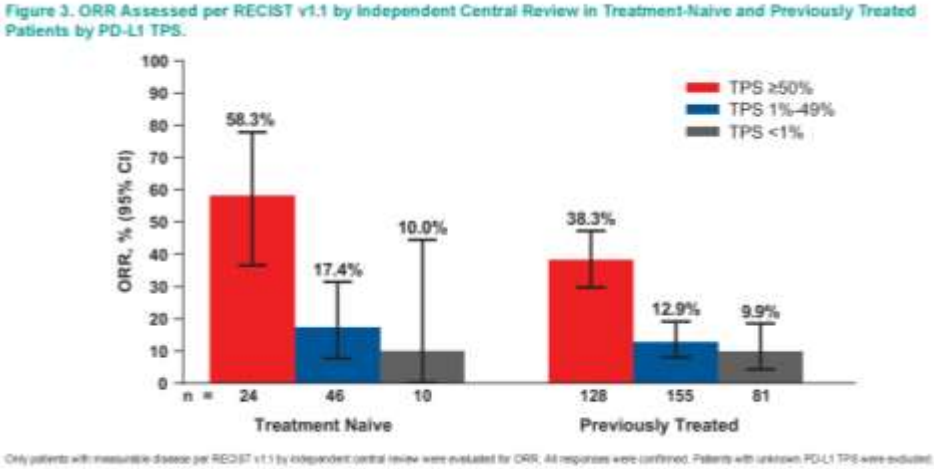


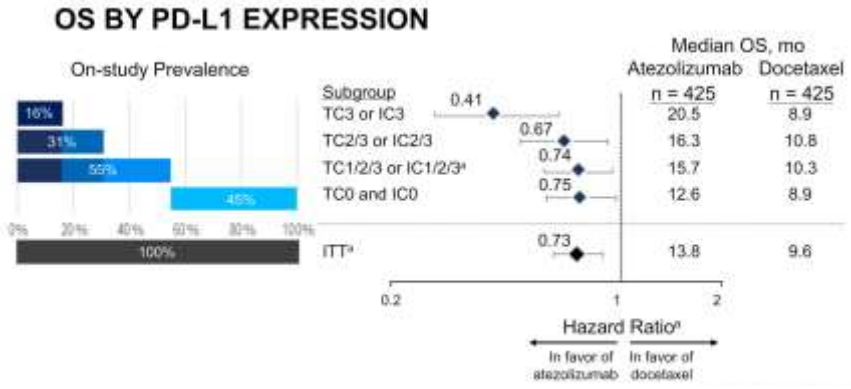
Reckamp K et al, IASLC 2015

Phase I - Keynote 001
Pembrolizumab in NSCLC



Garon EB et al. N Engl J Med 2015;372:2018-2028; Hui et al. ASCO 2016.

Phase III - OAK
Atezolizumab versus Docetaxel in NSCLC



[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Barlesi et al. ESMO 2016

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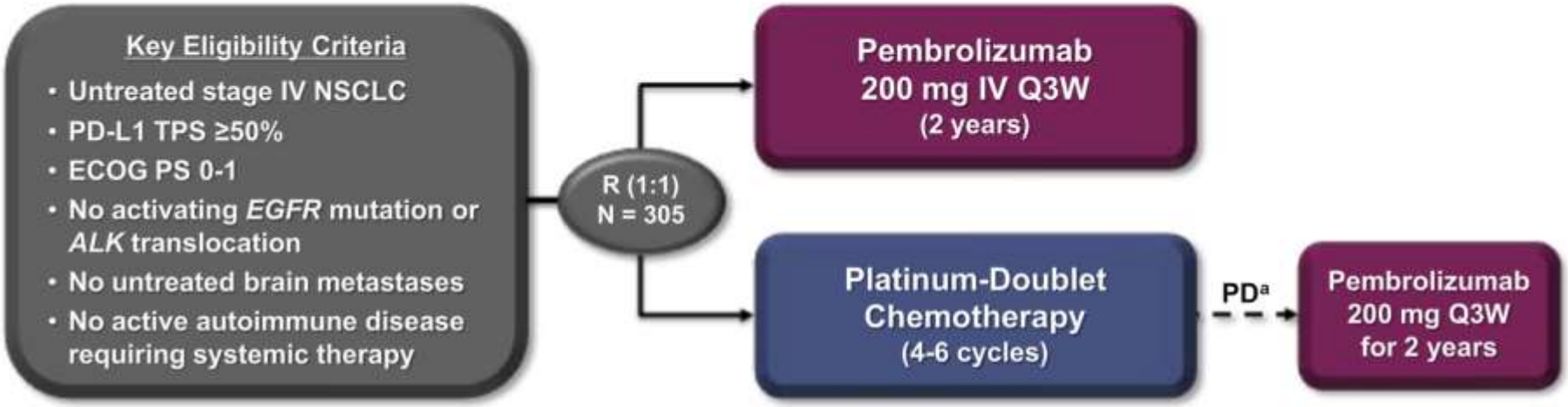
Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

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

Secondary: OS, ORR, safety

Exploratory: DOR

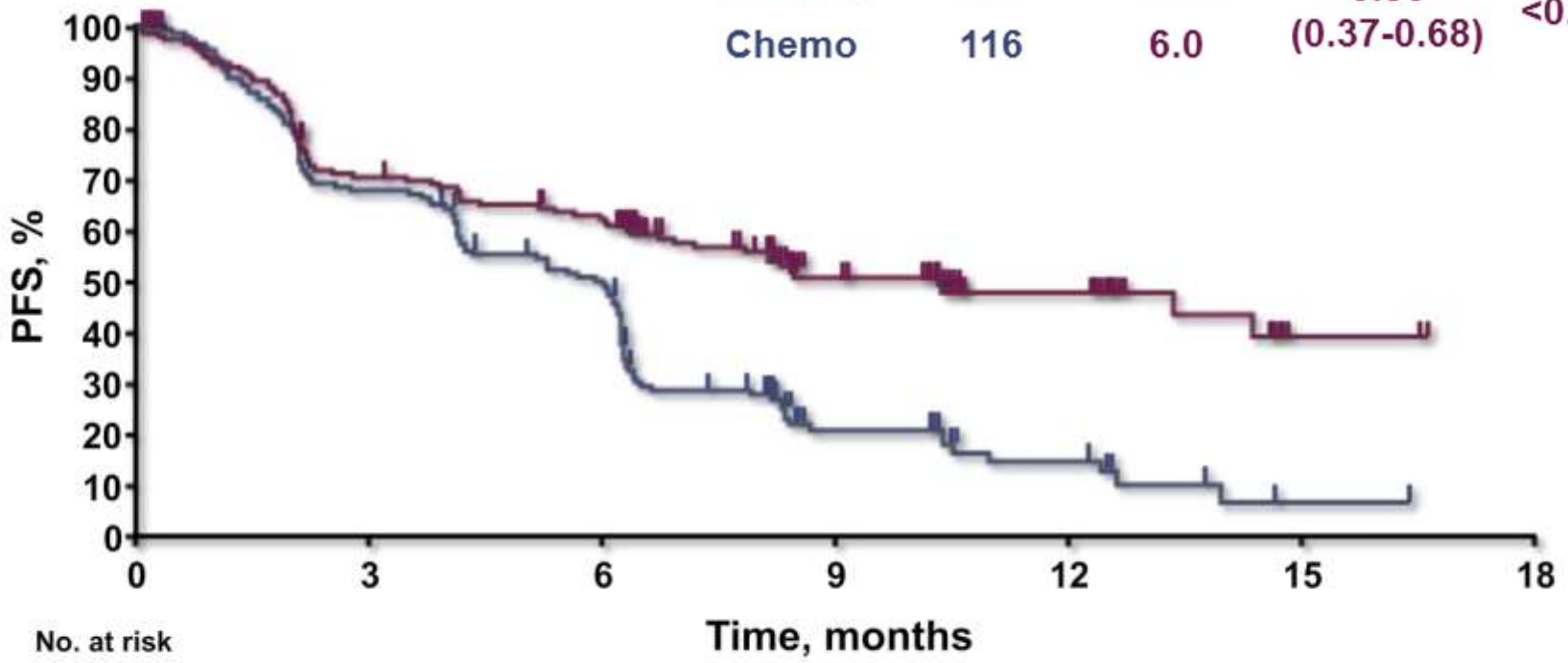
*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



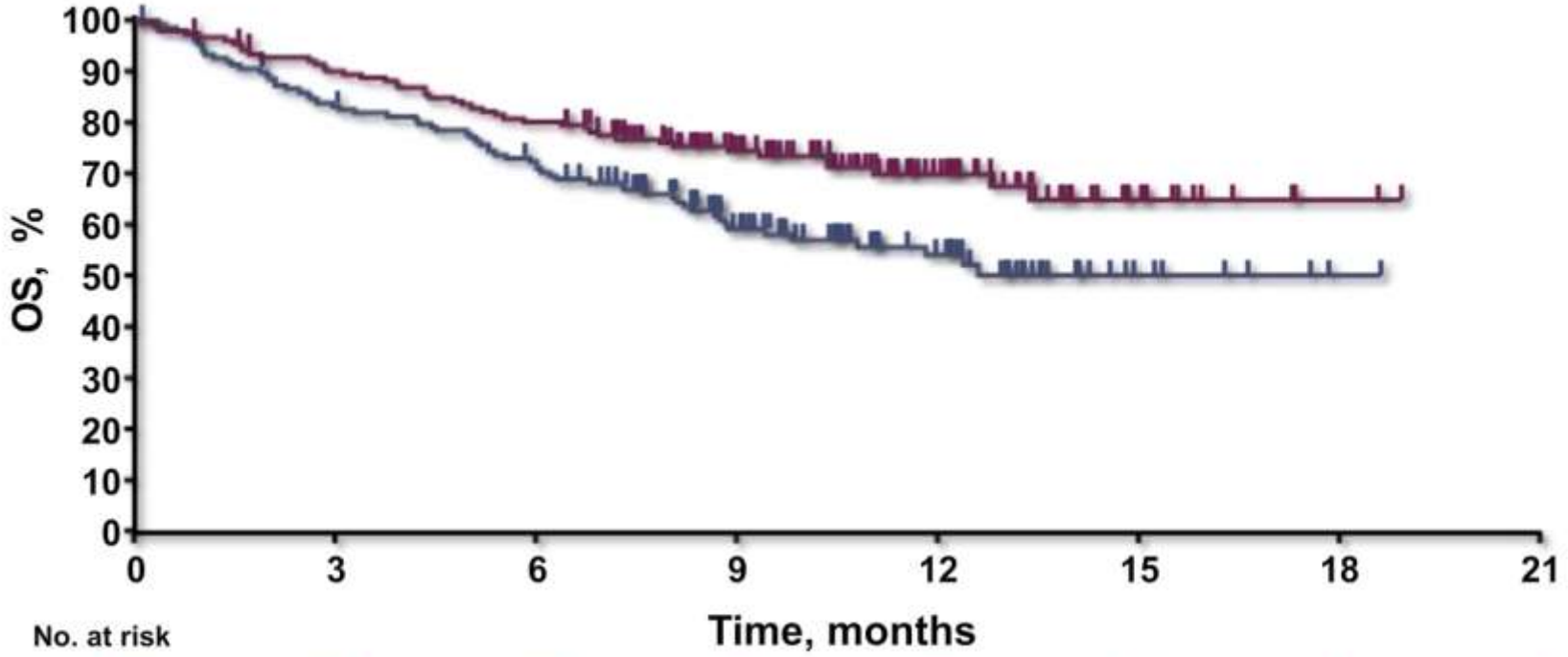
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab

Overall Survival

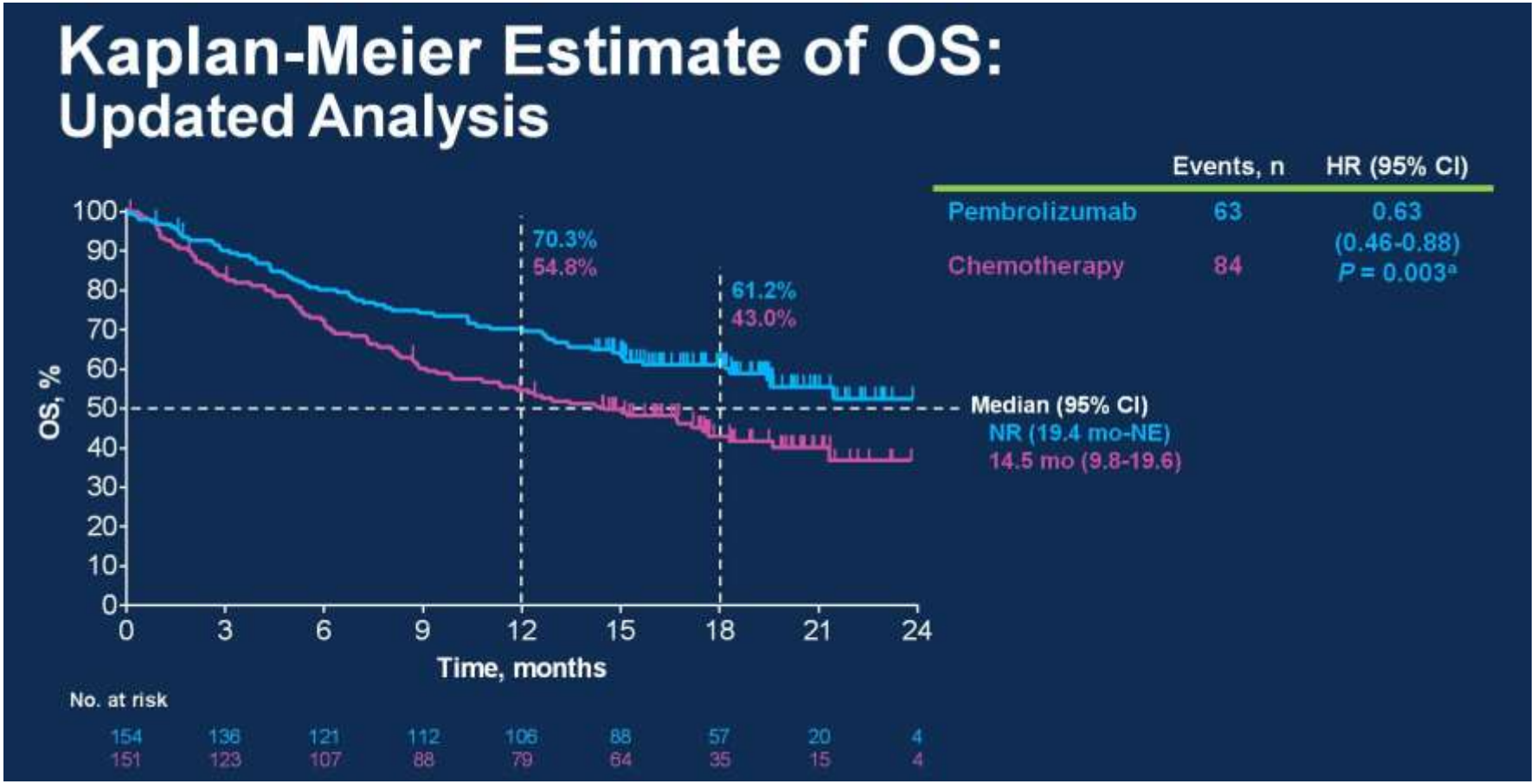
	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Data cut-off: May 9, 2016.

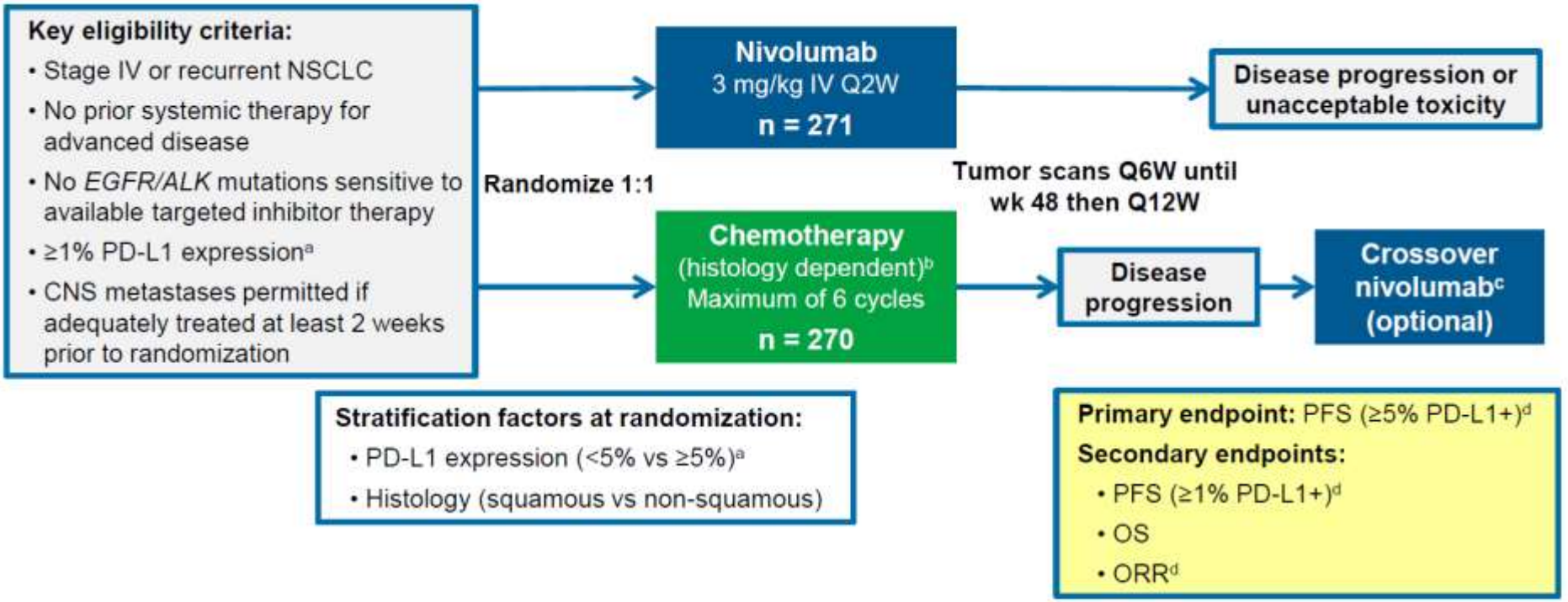
Reck et al. ESMO 2016; NEJM 2016

Phase III - Keynote 024
First-line Platinum Doublet vs. Pembrolizumab



Brahmer et al., ASCO 2017

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab



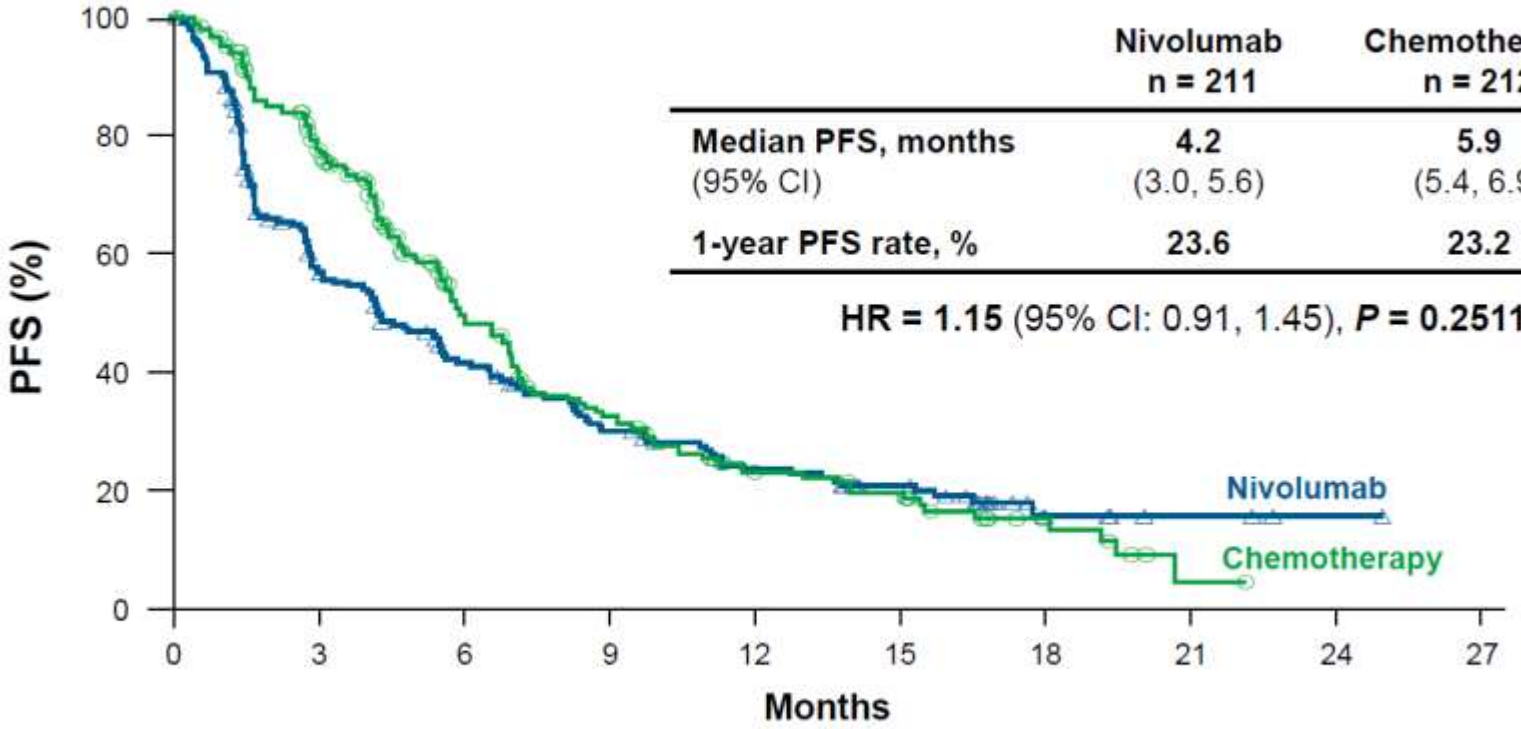
[a]Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review
[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review

Socinski et al. ESMO 2016;

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab

Primary Endpoint (PFS per IRRC in ≥5% PD-L1+)

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months (95% CI)	**4.2** (3.0, 5.6)	**5.9** (5.4, 6.9)
1-year PFS rate, %	**23.6**	**23.2**

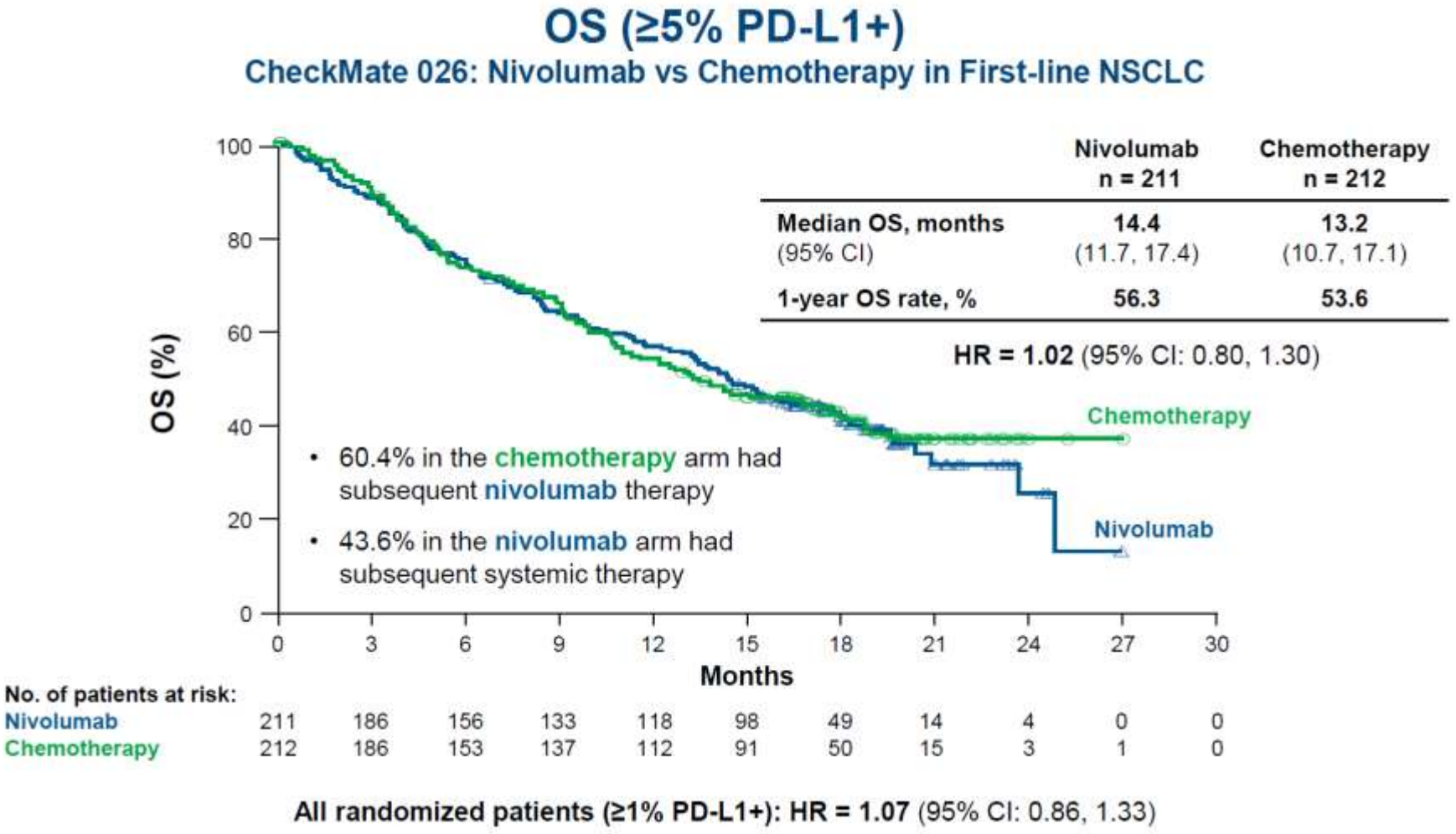
HR = 1.15 (95% CI: 0.91, 1.45), ***P* = 0.2511**

No. of patients at risk:										
Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

Socinski et al. ESMO 2016;

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab



All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

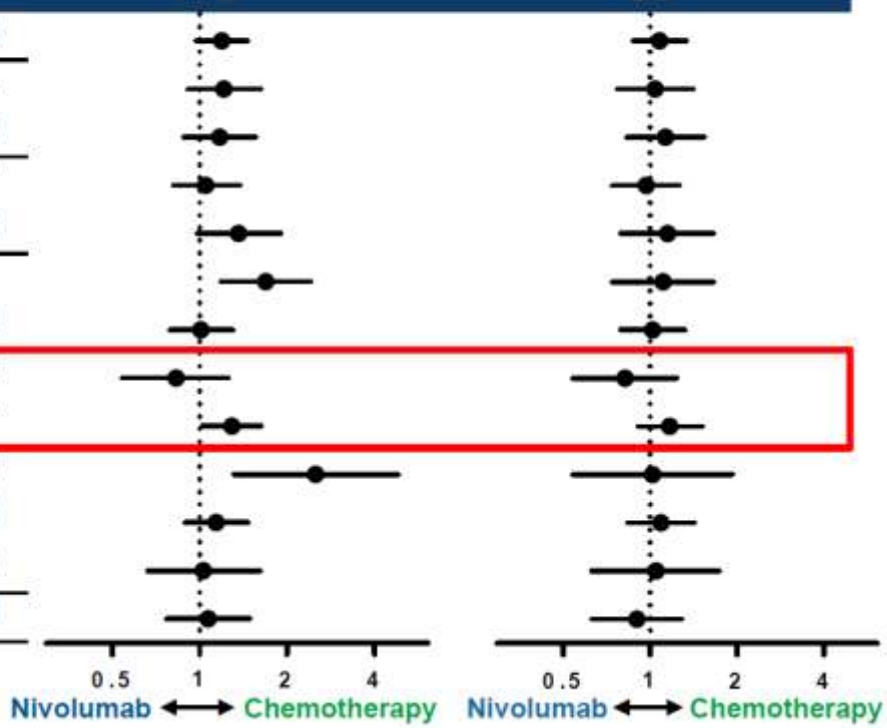
Socinski et al. ESMO 2016;

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab

PFS and OS Subgroup Analyses (All Randomized Patients)

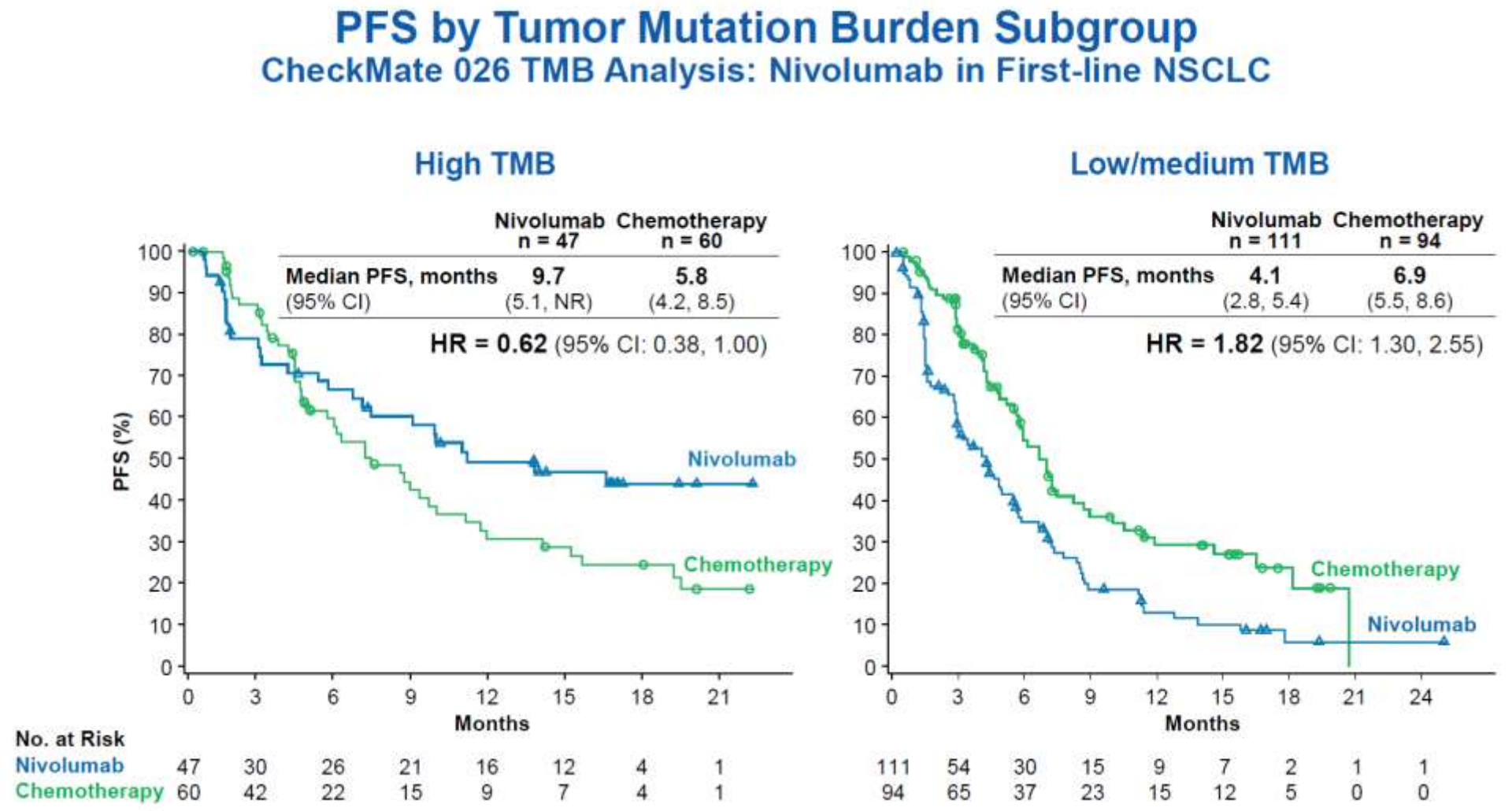
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

Subgroup	Patients, n		Unstratified HR	
	Nivolumab	Chemotherapy	PFS	OS
Overall	271	270	1.19	1.08
≥65 years	123	137	1.21	1.04
<65 years	148	133	1.17	1.13
Male	184	148	1.05	0.97
Female	87	122	1.36	1.15
ECOG PS = 0	85	93	1.69	1.11
ECOG PS ≥1	185	177	1.01	1.02
Squamous	65	64	0.83	0.82
Non-squamous	206	206	1.29	1.17
Never smoker	30	29	2.51	1.02
Former smoker	186	182	1.14	1.09
Current smoker	52	55	1.03	1.05
≥50% PD-L1+	88	126	1.07	0.90



Socinski et al. ESMO 2016;

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab

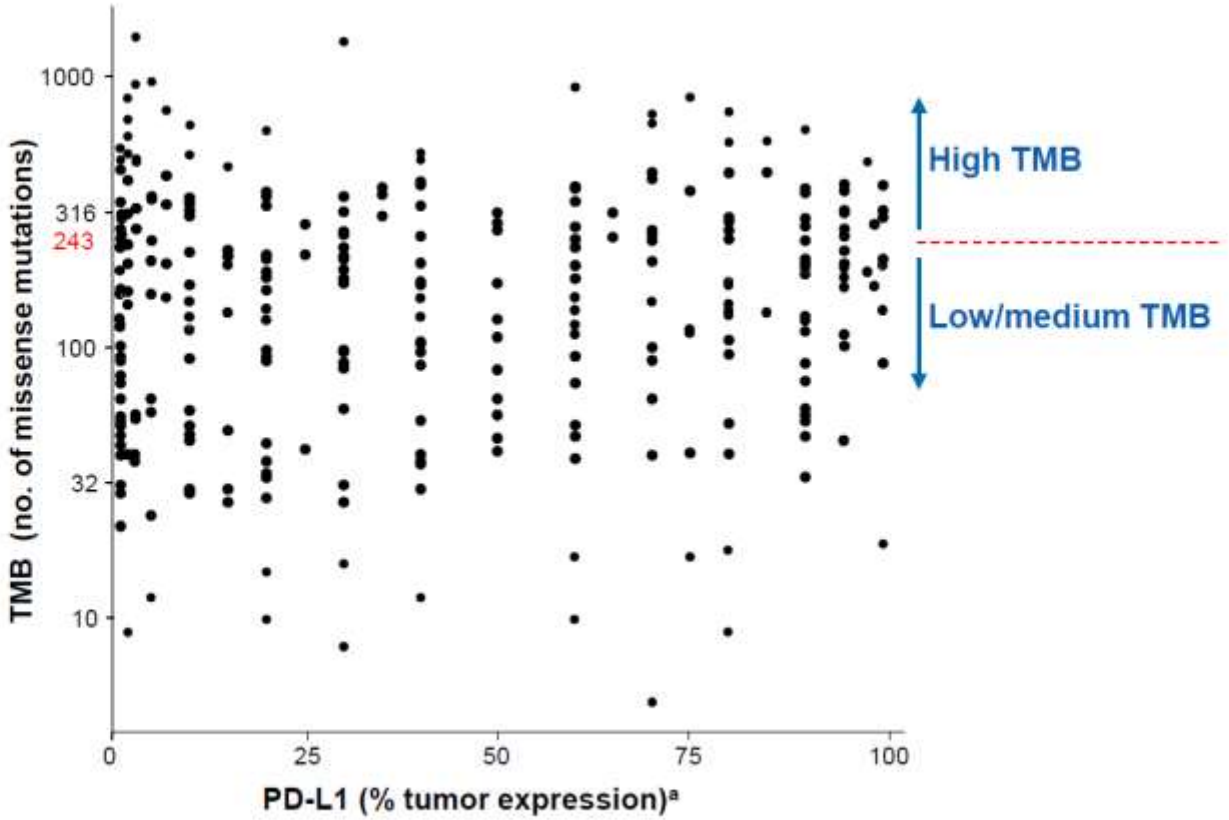


Peters et al. AACR 2017

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab

Analysis of the Association Between TMB and PD-L1 Expression[a]

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

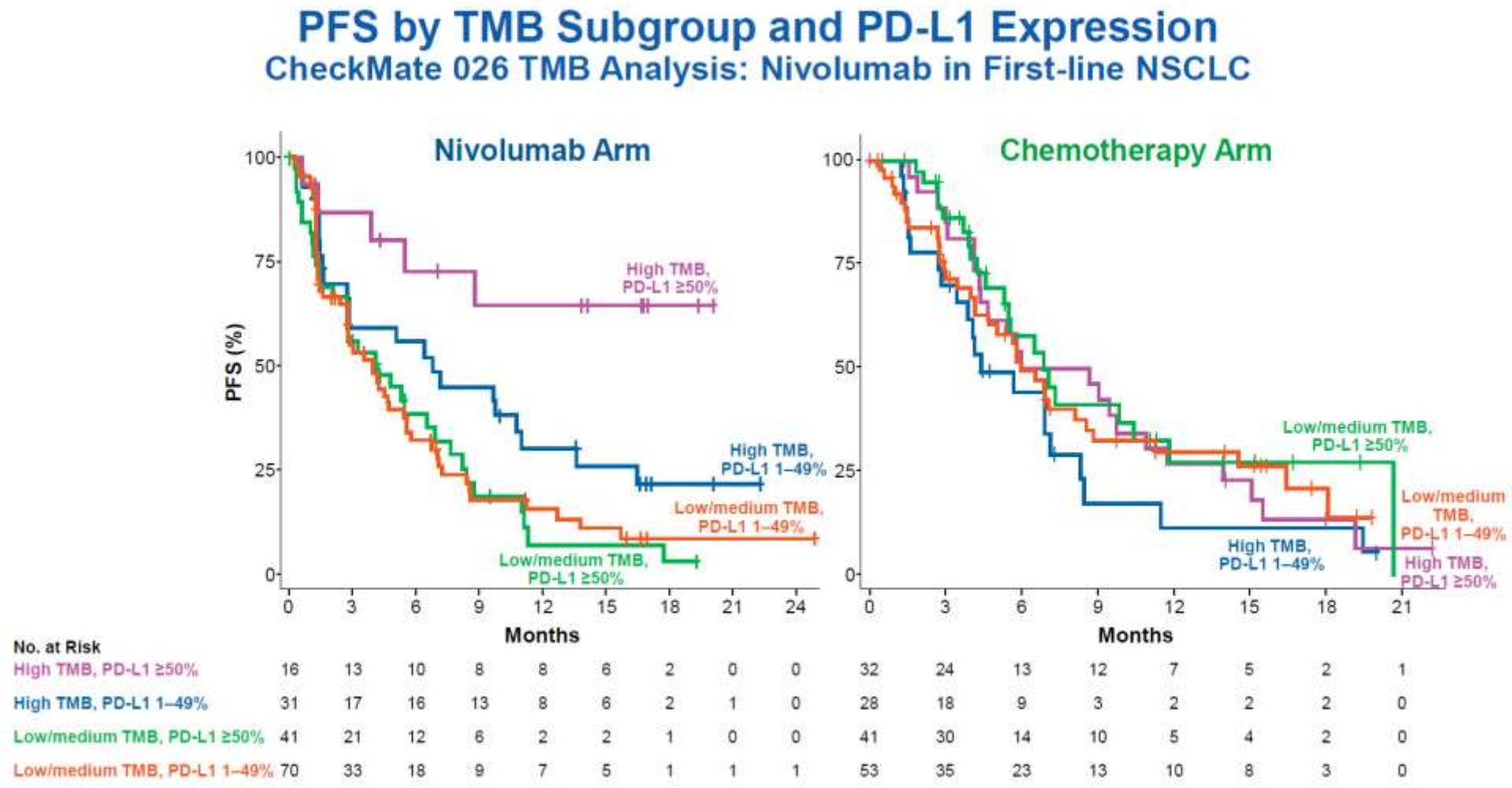


- There was no association between TMB and PD-L1 expression in patients with ≥1% PD-L1 tumor expression

[a]All patients had ≥1% PD-L1 tumor expression

Peters et al. AACR 2017

Phase III - Checkmate 026
First-line Platinum Doublet vs. Nivolumab

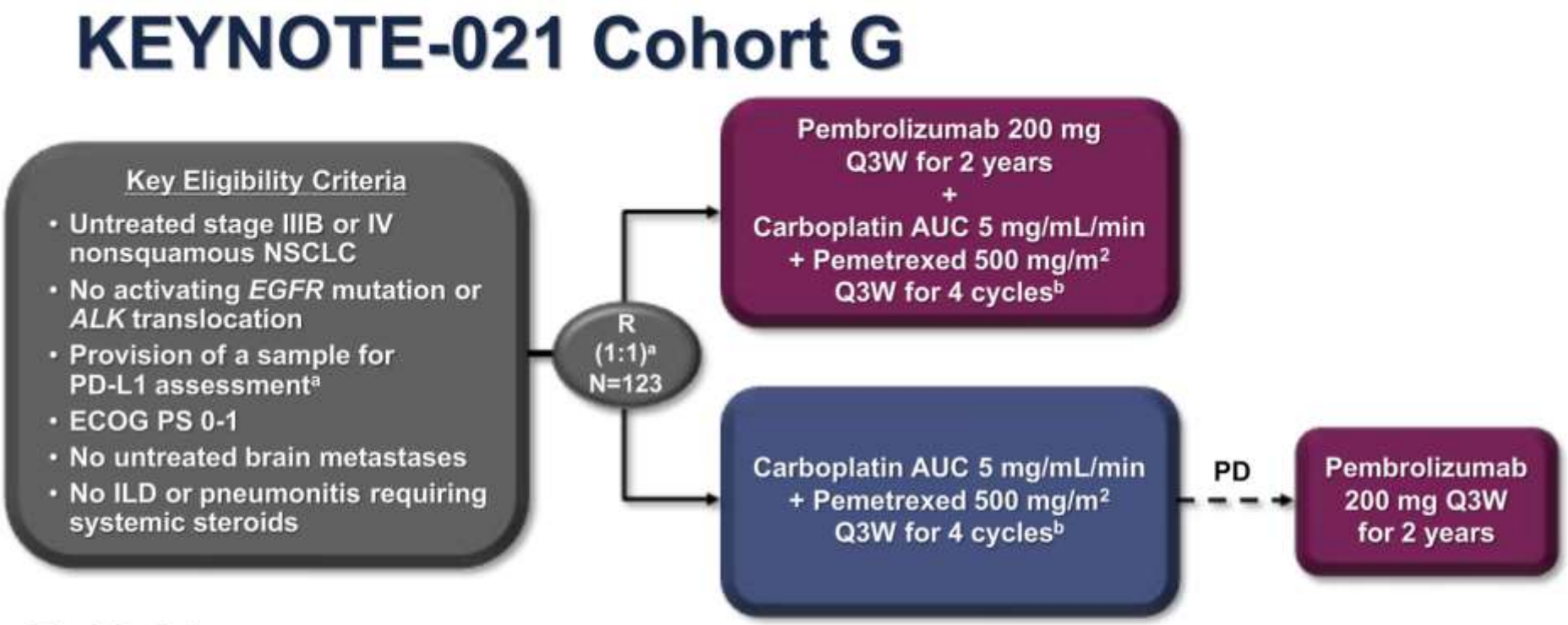


Peters et al. AACR 2017

Non-Small Cell Lung Cancer

- PD-1/PD-L1 Inhibitors in second-line therapy
  - Nivolumab
  - Pembrolizumab
  - Atezolizumab
- PD-L1 expression as a biomarker
- First-line treatment
  - PD-1 inhibitor versus chemotherapy
  - Chemotherapy +/- PD-1 inhibitors
  - Nivolumab +/- ipilimumab
- Consolidation treatment
  - Durvalumab

Phase II - Keynote 021
First-line Carboplatin / Pemetrexed ± 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

PD=progressive disease.

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

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

Langer et al. ESMO 2016; Lancet Oncol 2016

Phase II - Keynote 021
First-line Carboplatin / Pemetrexed ± Pembrolizumab

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

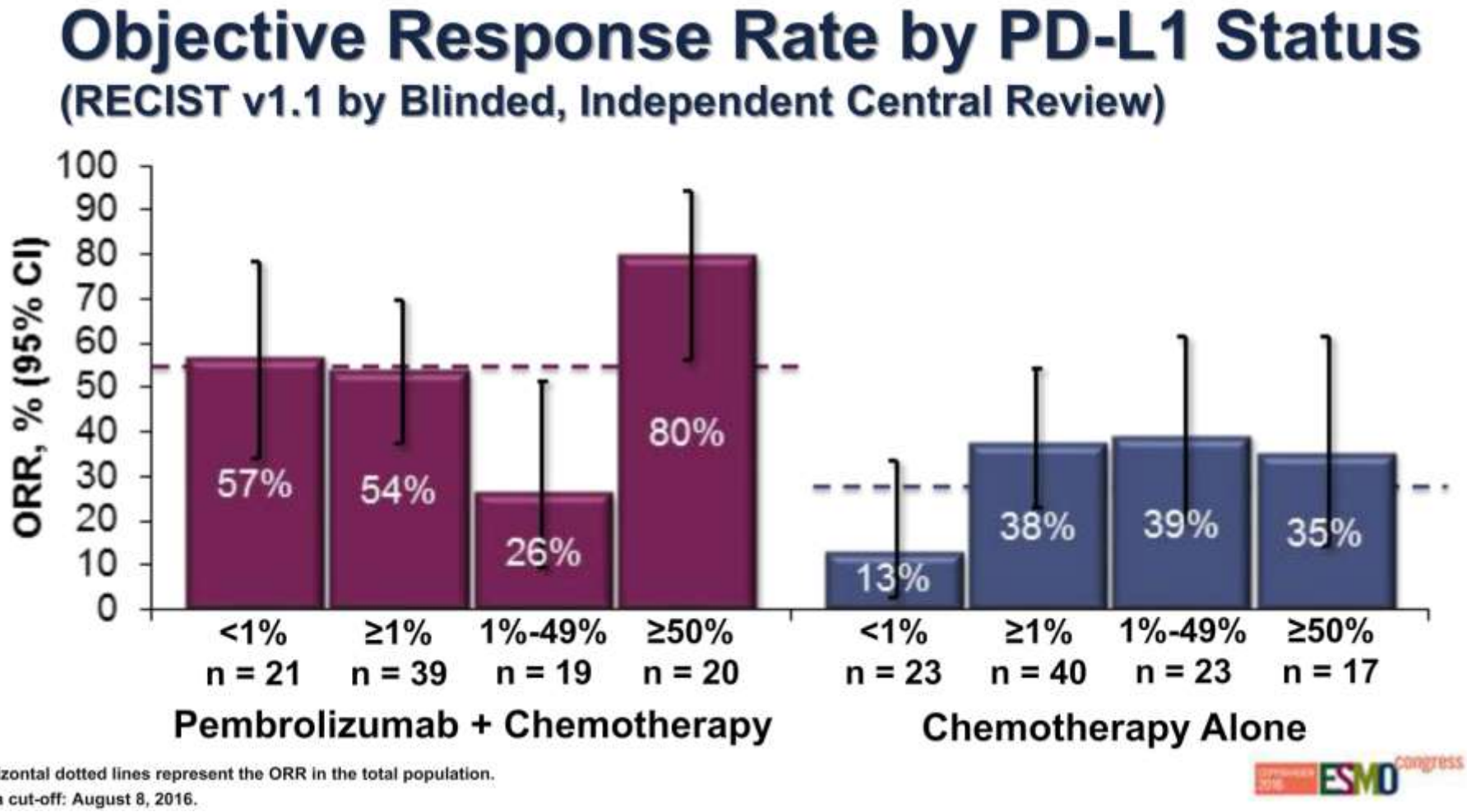
Best response, n (%)	Pembro + Chemo N = 60	Chemo Alone N = 63
Complete response[a]	0	0
Partial response[a]	33 (55)	18 (29)
Stable disease	20 (33)	26 (41)
Progressive disease	2 (3)	11 (17)
Not evaluable[b]	5 (8)	8 (13)

[a]Confirmed responses only.
[b]No postbaseline scan performed or a baseline or postbaseline scan not evaluable per RECIST v1.1 by blinded, independent central review.
Data cut-off: August 8, 2016.

COPENHAGEN 2016 ESMO congress

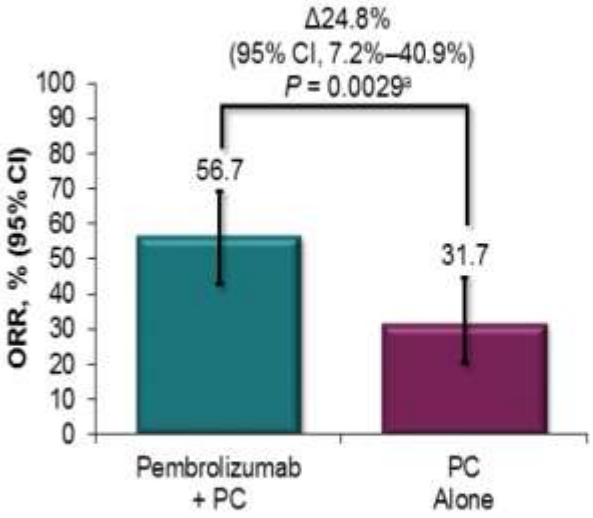
Langer et al. ESMO 2016; Lancet Oncol 2016

Phase II - Keynote 021
First-line Carboplatin / Pemetrexed ± Pembrolizumab

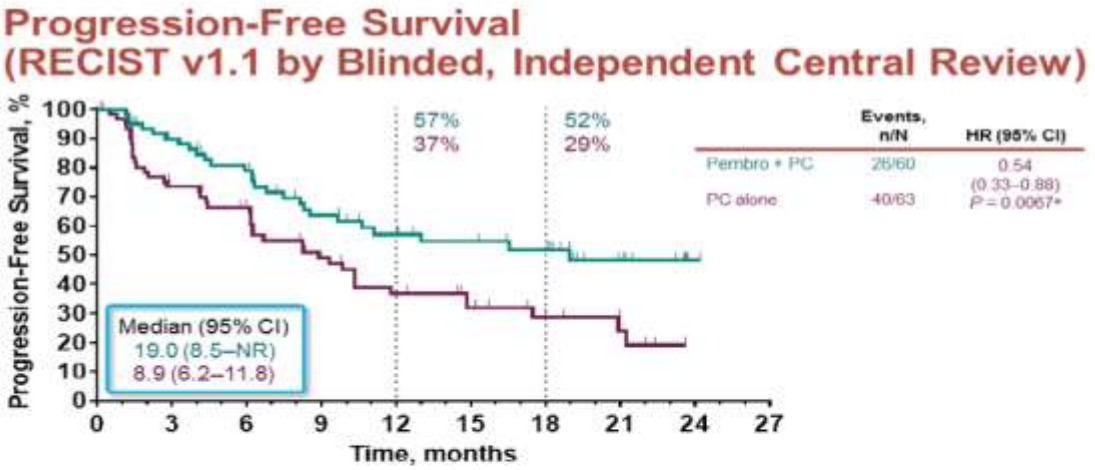


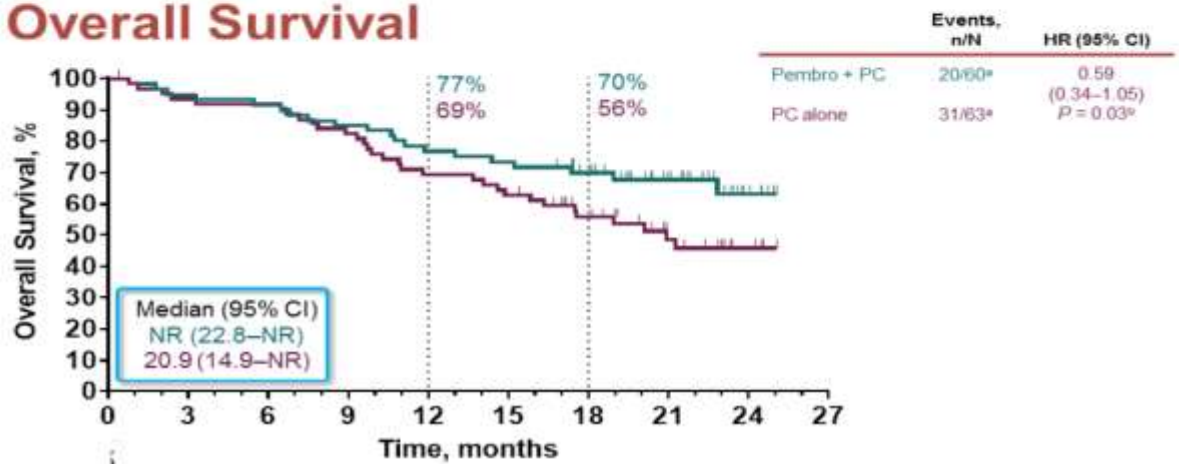
Langer et al. ESMO 2016; Lancet Oncol 2016

Phase II - Keynote 021
First-line Carboplatin / Pemetrexed ± Pembrolizumab



Borghaei ESMO 2017





Borghaei et al. ESMO 2017

Non-Small Cell Lung Cancer

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  - Pembrolizumab
  - Atezolizumab
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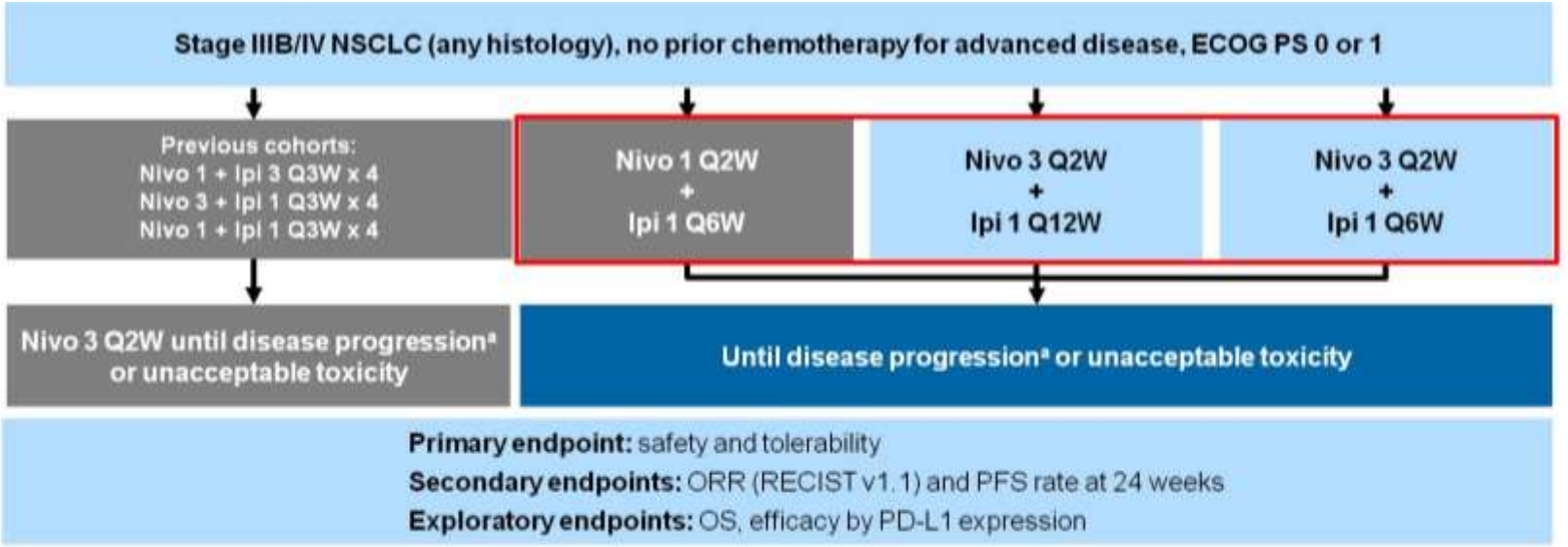
- First-line treatment
  - PD-1 inhibitor versus chemotherapy
  - Chemotherapy +/- PD-1 inhibitors
  - Nivolumab +/- ipilimumab
- Consolidation treatment
  - Durvalumab

Phase I - Checkmate 012
First-line Ipilimumab / Nivolumab



- The safety and tolerability of the nivolumab–ipilimumab combination was improved with less frequent ipilimumab dosing[5]
- Schedules with nivolumab 3 mg/kg also showed increased clinical efficacy in a previous analysis[5]
- Here, we report longer follow-up on nivolumab 3 mg/kg plus ipilimumab schedules[b]

[a]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit
[b]February 2016 database lock
Ipilimumab and nivolumab dosing are shown in mg/kg IV (eg, nivo 1 = nivolumab 1 mg/kg IV)

Hellman et al. ASCO 2016

Phase I - Checkmate 012
First-line Ipilimumab / Nivolumab

Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

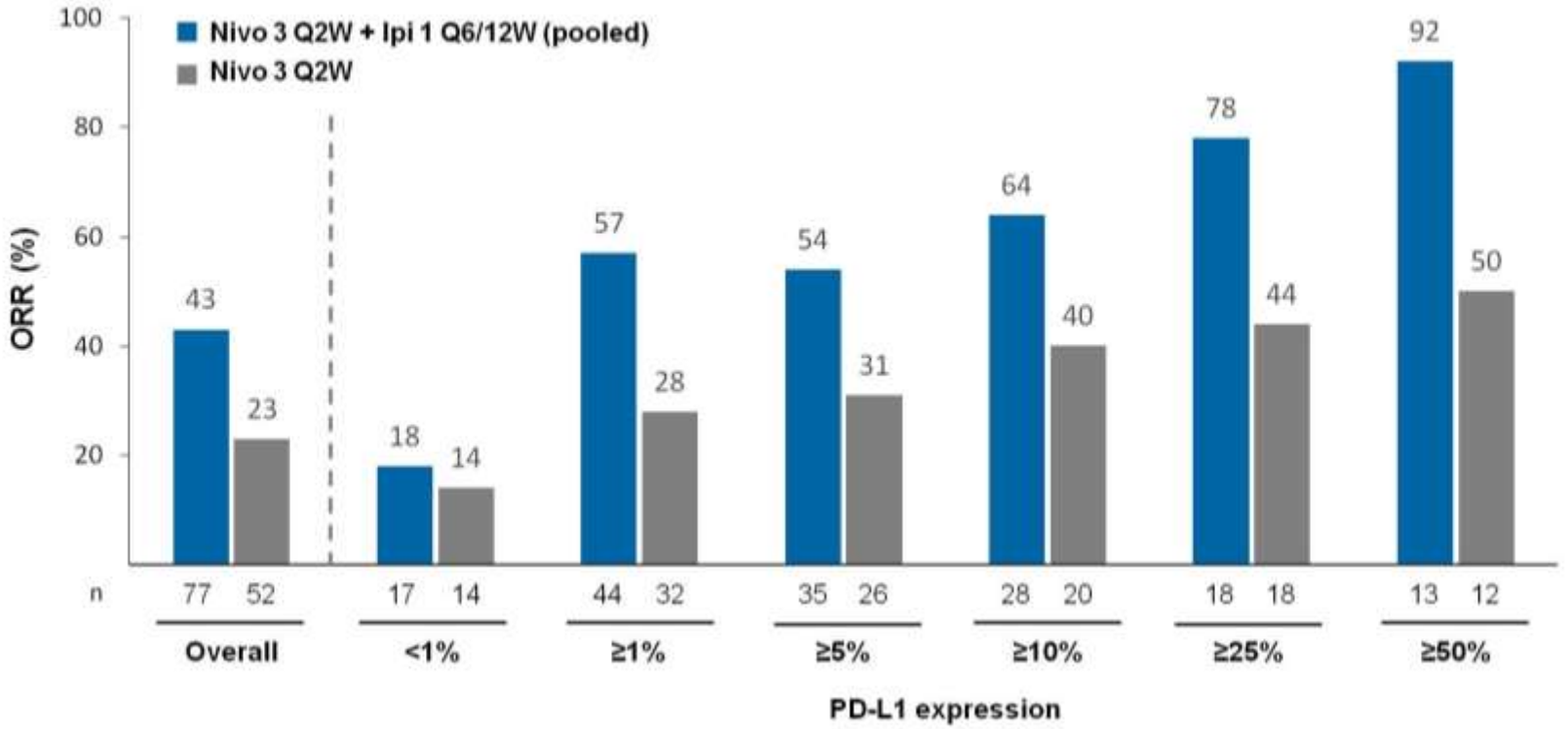
NC = not calculated (when >25% of patients are censored); NR = not reached

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

Hellman et al. ASCO 2016

Phase I - Checkmate 012
First-line Ipilimumab / Nivolumab

Efficacy Across All Tumor PD-L1 Expression Levels



Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

Hellman et al. ASCO 2016

Phase I - Checkmate 012
First-line Ipilimumab / Nivolumab

Safety Summary

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W (n = 52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	82	37	72	33	71	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab[6]

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

Hellman et al. ASCO 2016

Non-Small Cell Lung Cancer

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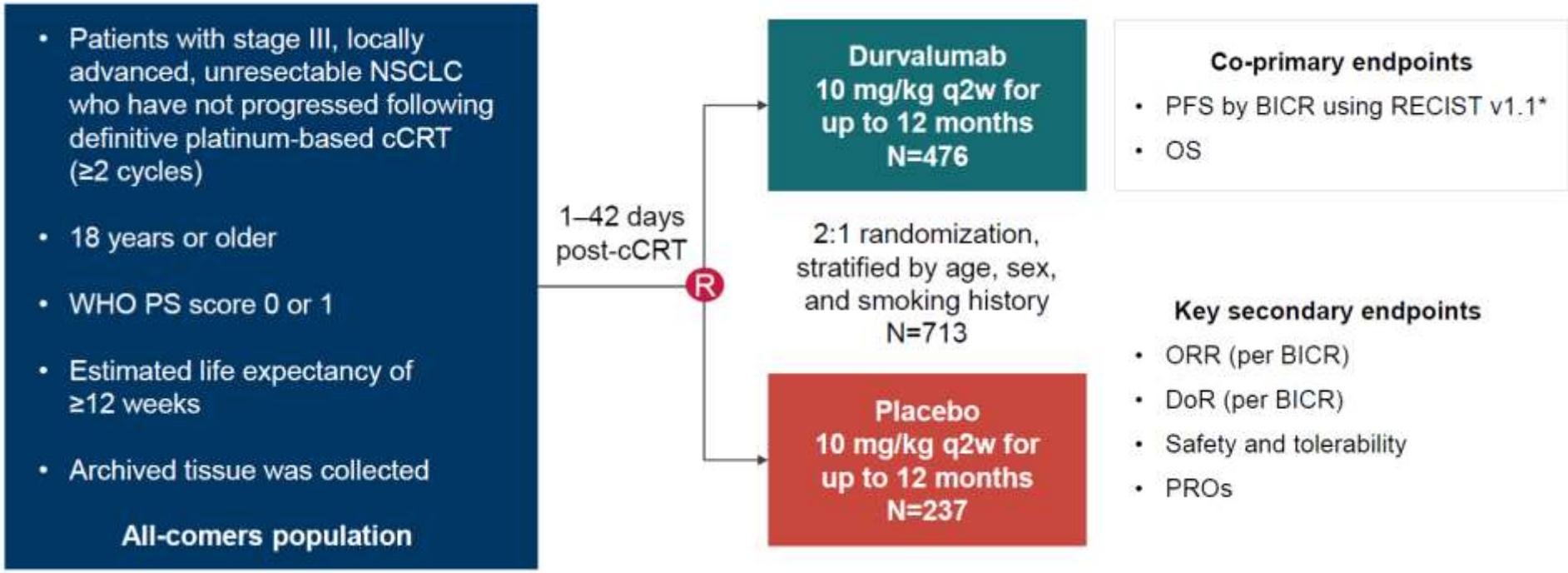
  - Durvalumab

Phase III - PACIFIC
Durvalumab vs. Placebo Consolidation



Paz Ares et al. ESMO 2017; NEJM 2017

Phase III - PACIFIC
Durvalumab vs. Placebo Consolidation

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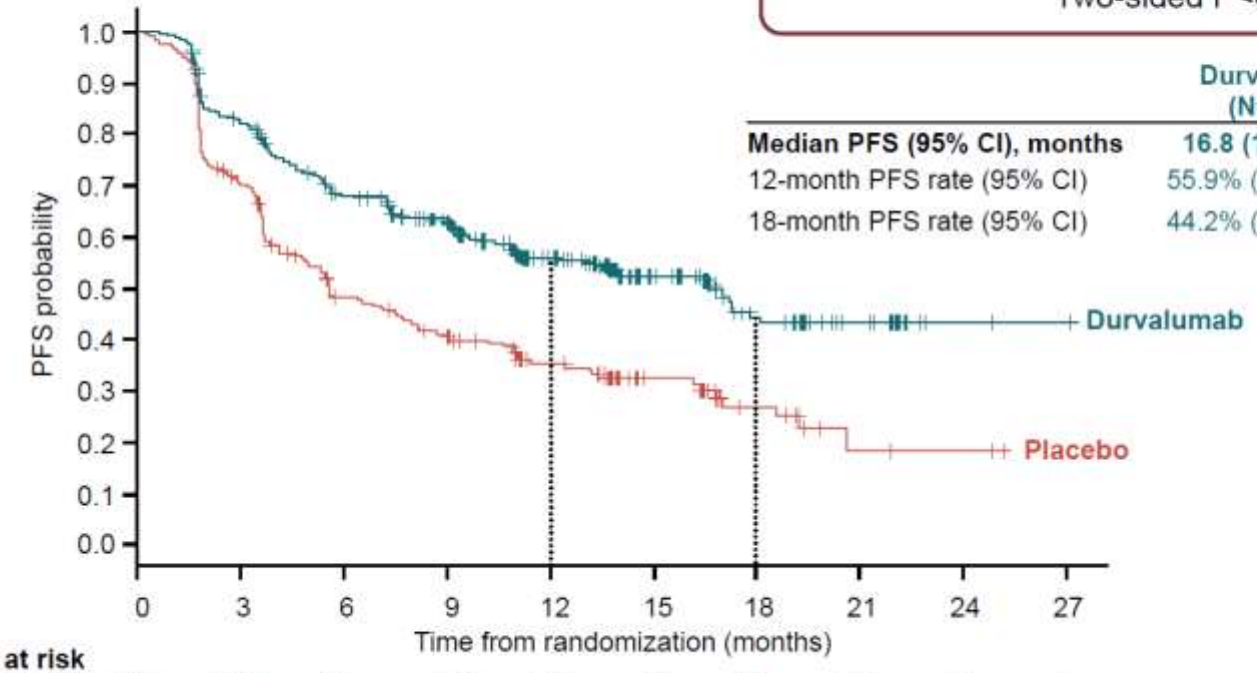
PFS by BICR (Primary Endpoint; ITT)

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

	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

Interim Analysis

Median follow-up:

14.5 months

(range 0.2–29.9)

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

Paz Ares et al. ESMO 2017; NEJM 2017

Summary

- PD-(L)1 inhibitors are now the standard treatment option for patients progressing after platinum-based therapies
    - Improved survival compared to docetaxel
    - Improved side effect profile compared to docetaxel
- PD-L1 expression determination in the second-line setting is only required for pembrolizumab use
- PD-L1 expression predicts for greater benefit from PD-(L)1 inhibitors
- Pembrolizumab first-line is the new standard of care for patients with TPS ≥ 50%
- Carboplatin, pemetrexed and pembrolizumab first-line is na option for selected patients
- Durvalumab should become a new standard consolidation therapy after chemoXRT in stage III NSCLC