Immunotherapy in the clinic. Lung Cancer

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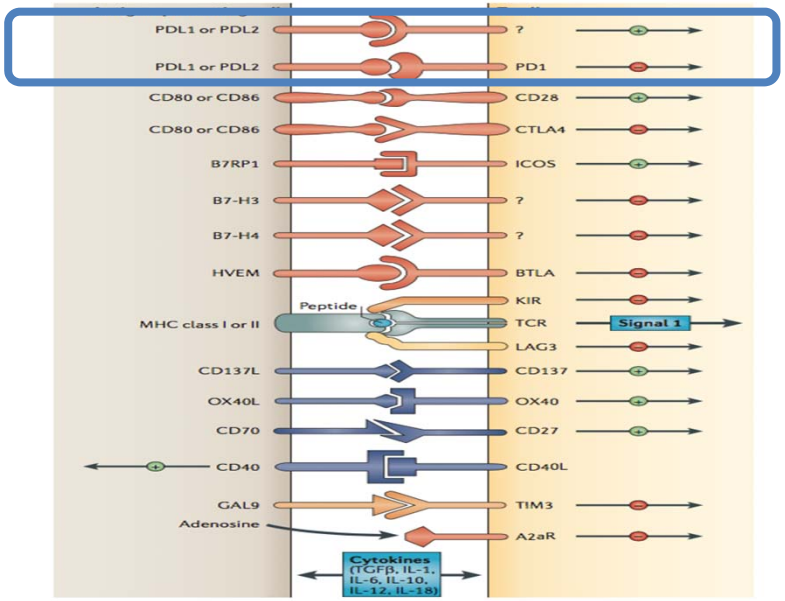
- **Agenda**
  - Where we come from?
  - Immunotherapy in Second line
  - Immunotherapy in First line
  - Future strategies:
    - Combos
    - Early stage

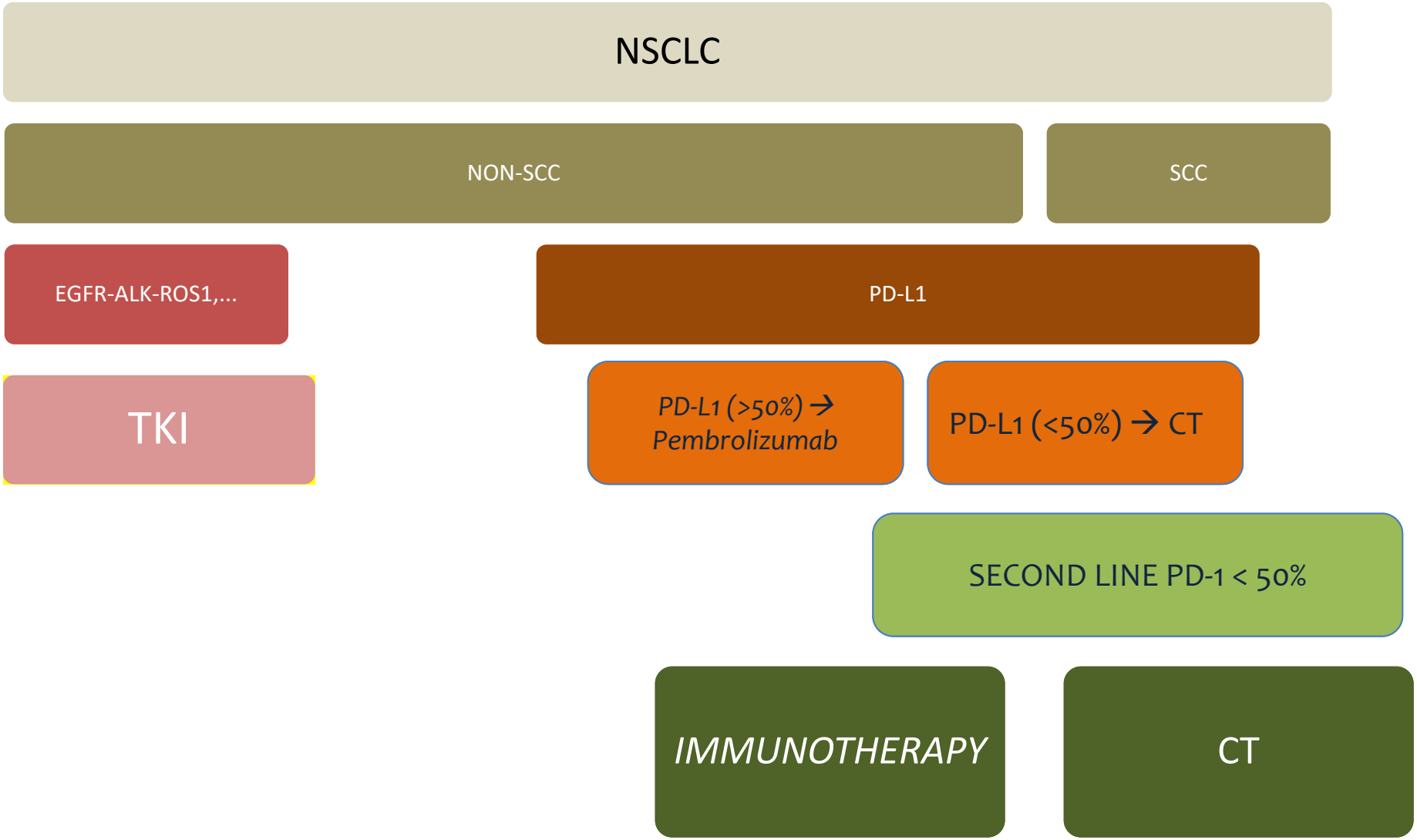
Where we come from in NSCLC?

WT NSCLC — **Platinum doublet** — **Docetaxel**

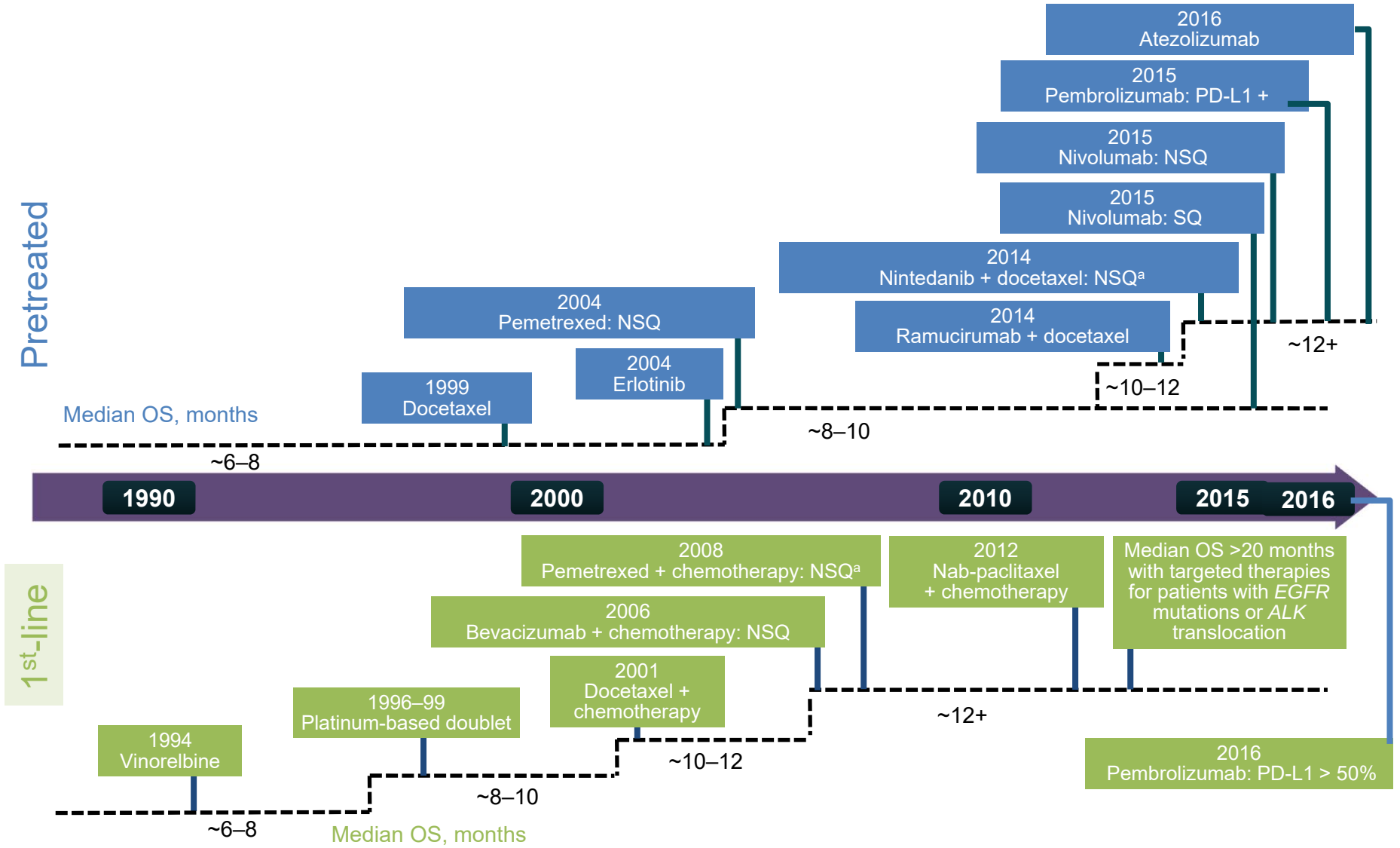


Inhibition of one Immune Checkpoint...

Where are we now in NSCLC?



NSCLC: OS improvements



[a]Adenocarcinoma only. ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-squamous; OS=overall survival; SQ=squamous.

Stinchcombe TE, F1000Prime Rep. 2014;6:117; Giotrif US Prescribing Information; Alimta US Prescribing Information; Avastin US Prescribing Information; Taxotere US Prescribing Information; Tarveva US Prescribing Information; Socinski MA, et al. *J Clin Oncol.* 2012;30:2055–2062; Opdivo US Prescribing Information; Cyramza US Prescribing Information; Vargatef SmPC; Paz-Ares L, et al. Presented at ASCO 2015, Abstract LBA109; Schiller J, et al. *New Engl J Med.* 2002;346:92–98.

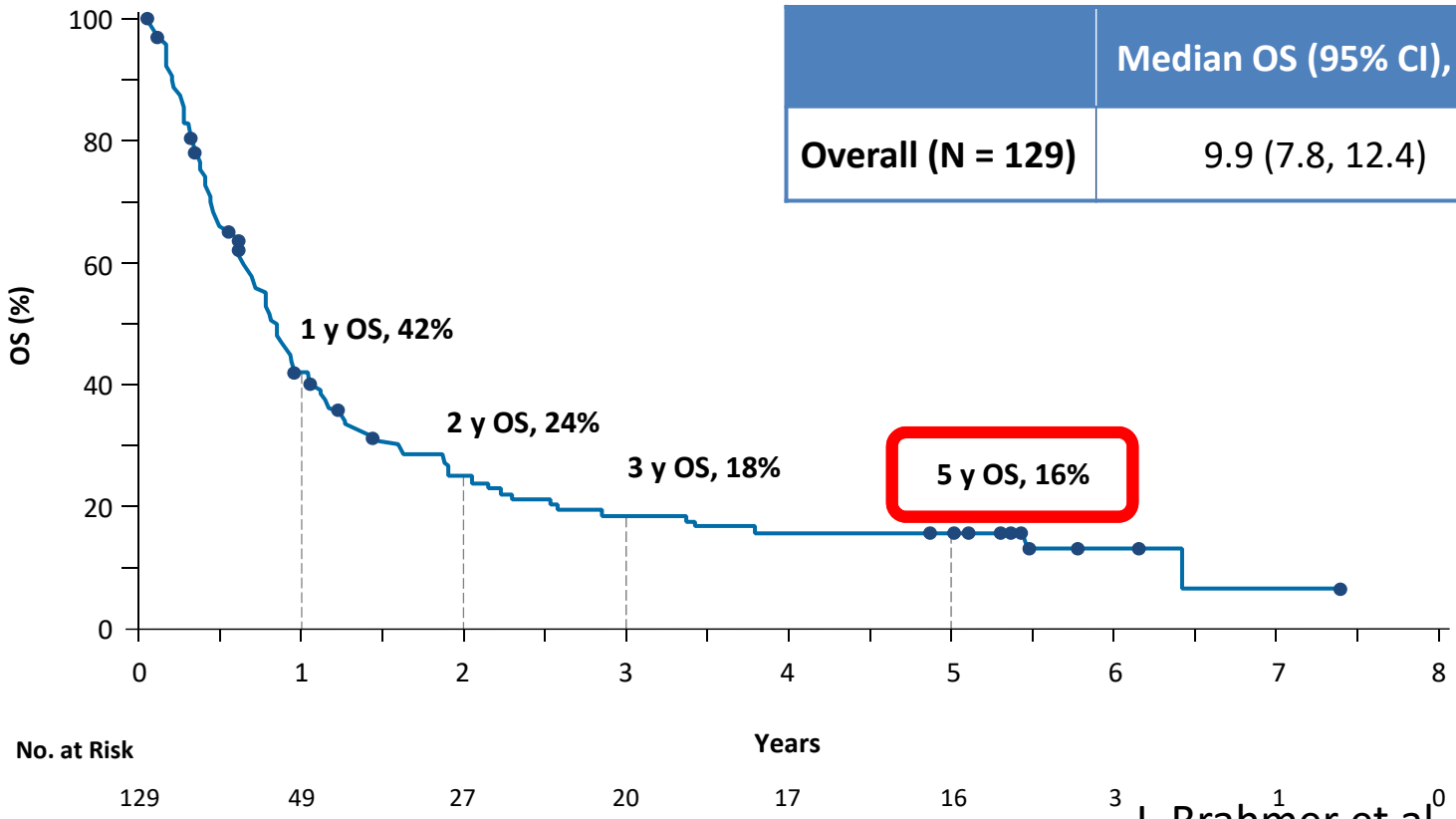
IO IN SECOND LINE NSCLC

- **NIVOLUMAB**
- **PEMBROLIZUMAB**
- **ATEZOLIZUMAB**

NIVOLUMAB

5-Year OS in phase 1 CA209-003 trial

has improved long term OS in patients with heavily pretreated metastatic



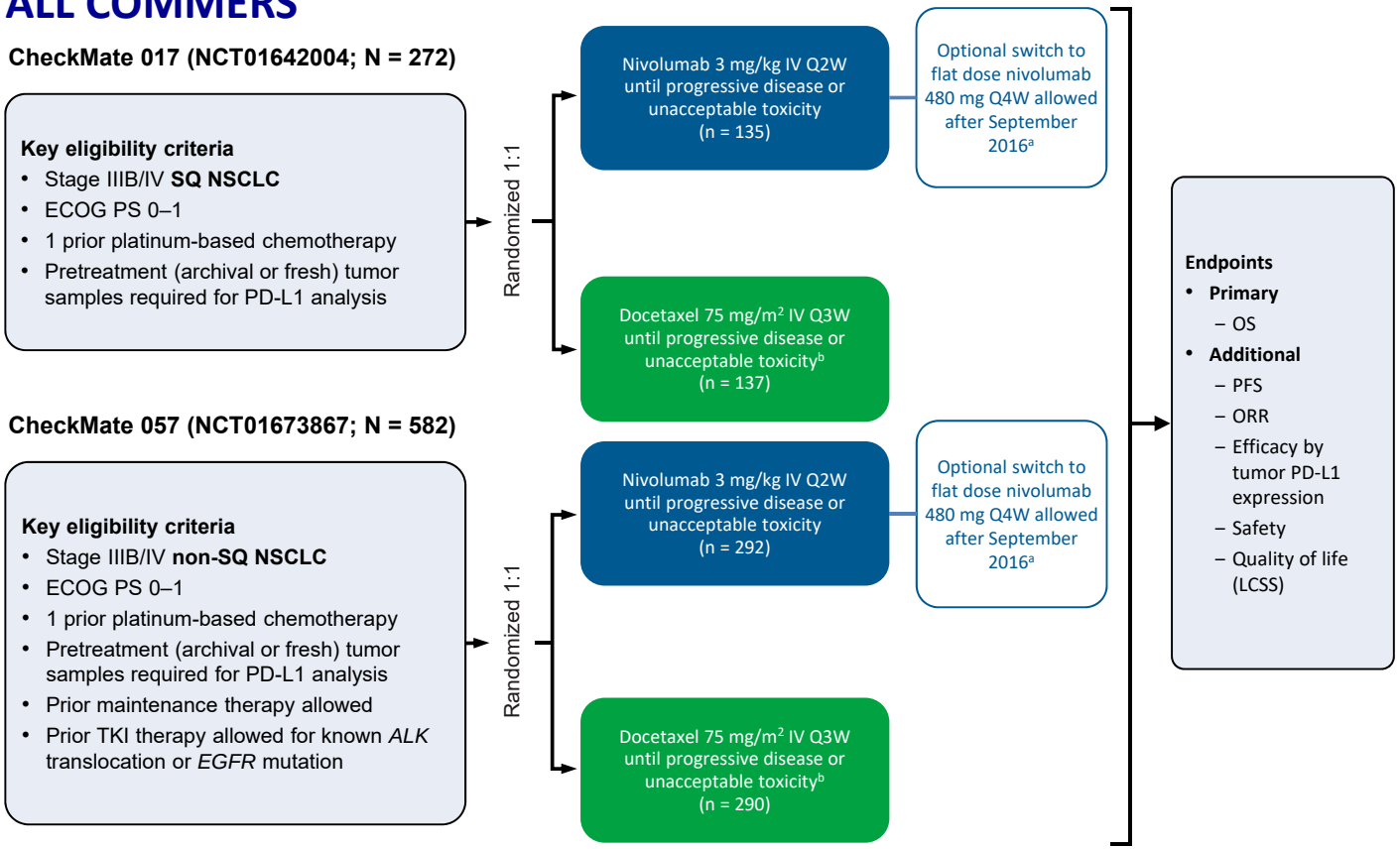
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

J. Brahmer et al. AACR 2017

[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Nivolumab. CheckMate 017 and 057

ALL COMMERS

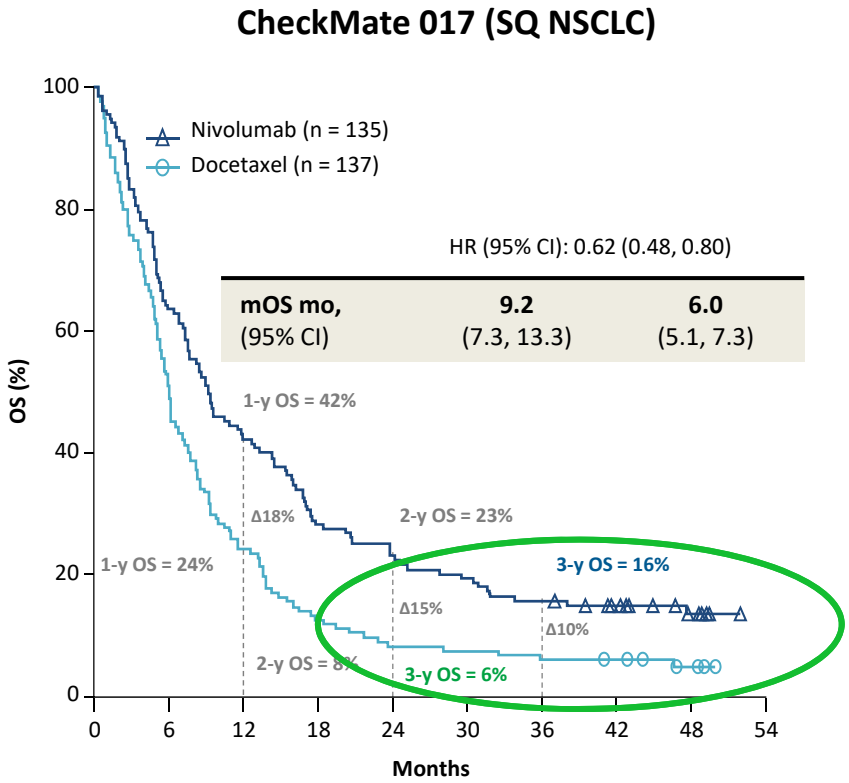


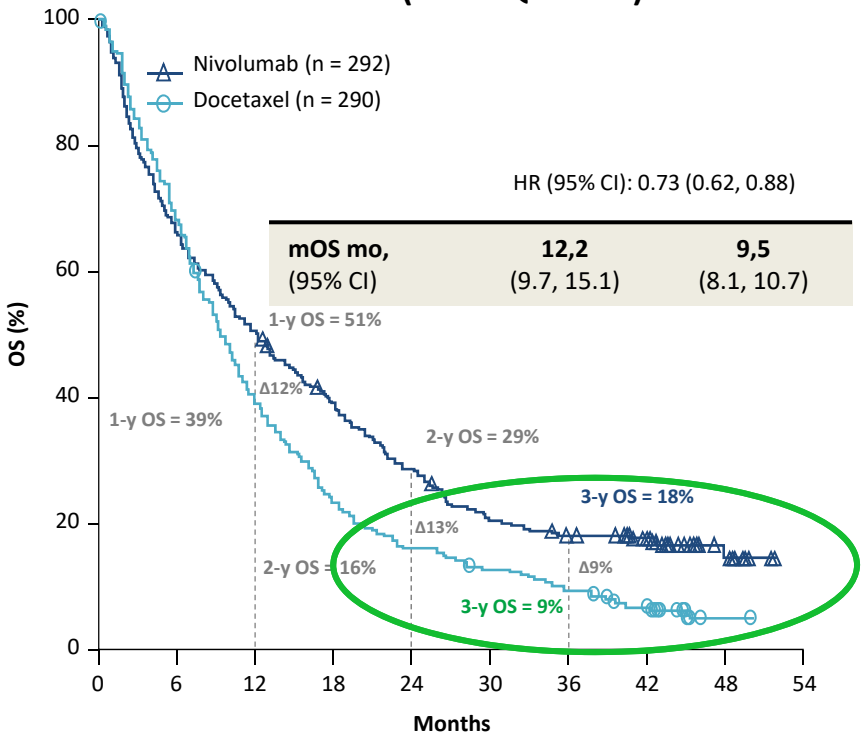
[a]The protocols of both studies were amended in September 2016, when minimum follow-up was approximately 2.5 years, allowing patients to switch to nivolumab 480 mg Q4W starting 2 weeks after their last 3-mg/kg Q2W dose; [b]After completion of the primary analyses,[3,4] patients in the docetaxel arms who ended treatment at any time during the studies were allowed to cross over to nivolumab

ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; IV = intravenous; LCSS = Lung Cancer Symptom Scale; ORR = objective response rate; PFS = progression-free survival; Q3W = every 3 weeks; TKI = tyrosine kinase inhibitor

FELIP E. ESMO 2017

CheckMate 017 and 057. OS (3 years' minimum follow-up)





CI = confidence interval; HR = hazard ratio

FELIP E. ESMO 2017

QoL with Nivolumab

Significantly better safety profile than CT

CheckMate 017. LCSS Average Symptom Burden Index: Mean Change From Baseline While on Treatment

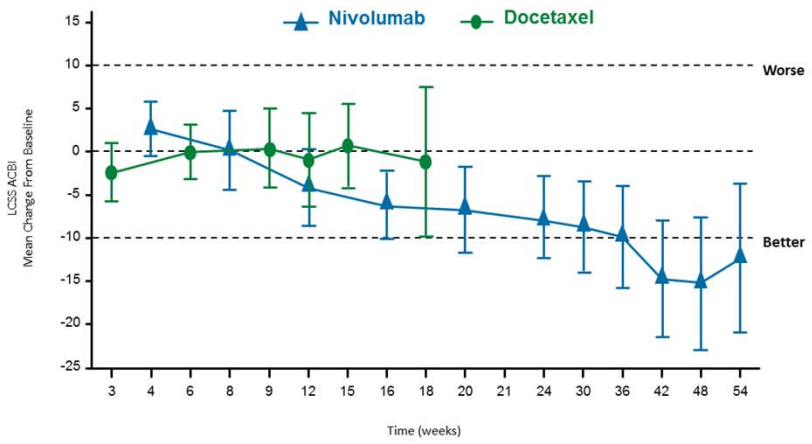
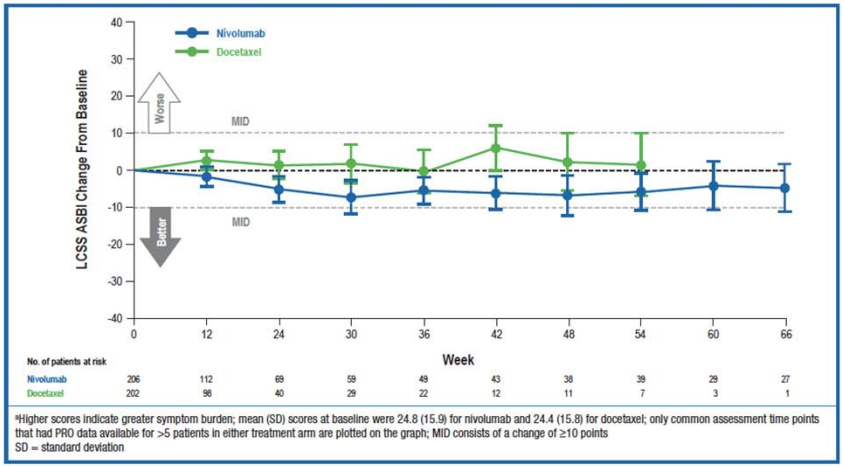
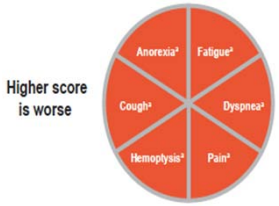


Figure 5. LCSS ASBI change from baseline means and 95% confidence intervals (on treatment)[a]



[a]Higher scores indicate greater symptom burden; mean (SD) scores at baseline were 24.8 (15.9) for nivolumab and 24.4 (15.8) for docetaxel; only common assessment time points that had PRO data available for >5 patients in either treatment arm are plotted on the graph; MID consists of a change of ≥10 points
SD = standard deviation

Lung Cancer Symptom Scale as a Marker of Treatment Benefit With Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC From CheckMate 057



Gralla ASCO 2016

Pembrolizumab. KEYNOTE-001

The NEW ENGLAND JOURNAL of MEDICINE

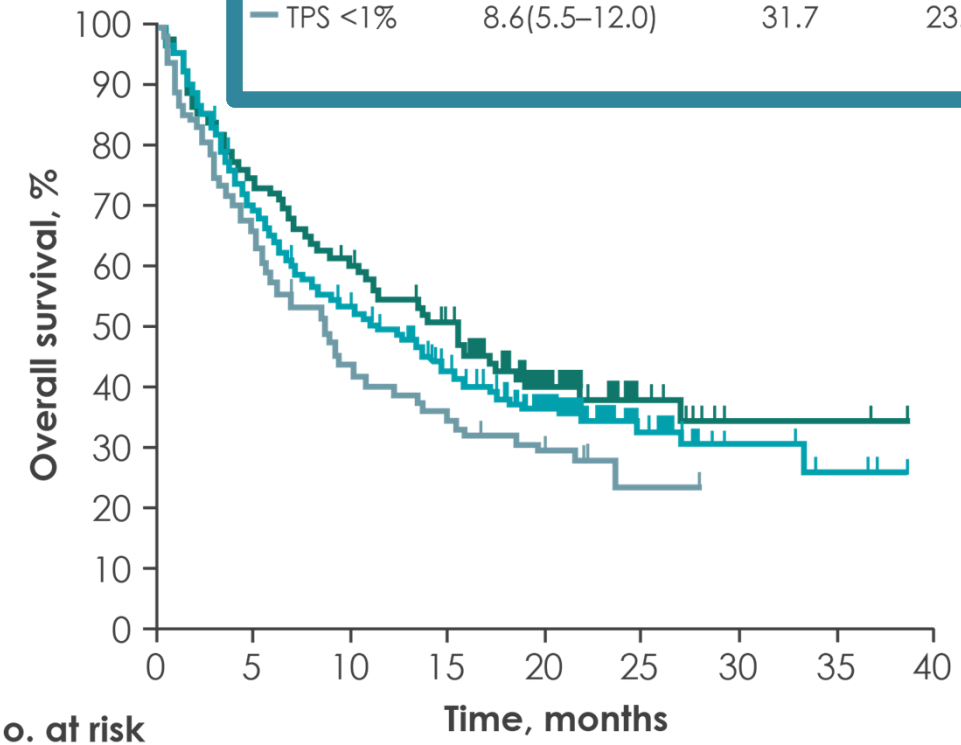
ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D.,

Median follow-up: 23.1m

	Median, mo (95% CI)	18-month rate, %	24-month rate, %
TPS ≥50%	15.4(10.6–18.5)	43.4	38.0
TPS ≥1%	11.3(8.3–14.0)	37.7	32.8
TPS <1%	8.6(5.5–12.0)	31.7	23.5



Analysis data cut-off: September 18, 2015.

Patients with unknown PD-L1 TPS were excluded.

CI: confidence interval; OS: overall survival; mo: months; PD-L1: programmed cell death ligand 1; TPS: tumour proportion score; NR: not reached.

Adapted from Hui R *et al*. Presented at ASCO 2016. Poster 9026.

KEYNOTE-010

PD-L1 > 1%


THE LANCET Articles

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Patients

- Advanced NSCLC
- Confirmed **PD after ≥1 line** of chemotherapy[a]
- No active brain metastases
- ECOG PS 0-1
- **PD-L1 TPS ≥1%** (22C3 Ab)
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

R
1:1:1

- **Pembrolizumab** 2 mg/kg IV Q3W for 24 months
- **Pembrolizumab** 10 mg/kg IV Q3W for 24 months
- **Docetaxel** 75 mg/m^2 Q3W per local guidelines[c]

Stratification factors:

- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status[b] (TPS ≥50% vs 1%-49%)

End points in the TPS ≥50% stratum and TPS ≥1% population

- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

ClinicalTrials.gov, NCT01905657.

[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]Added after 441 patients enrolled based on results from KEYNOTE-001 (Garon EB et al. *N Engl J Med*. 2015;372:2018-28).

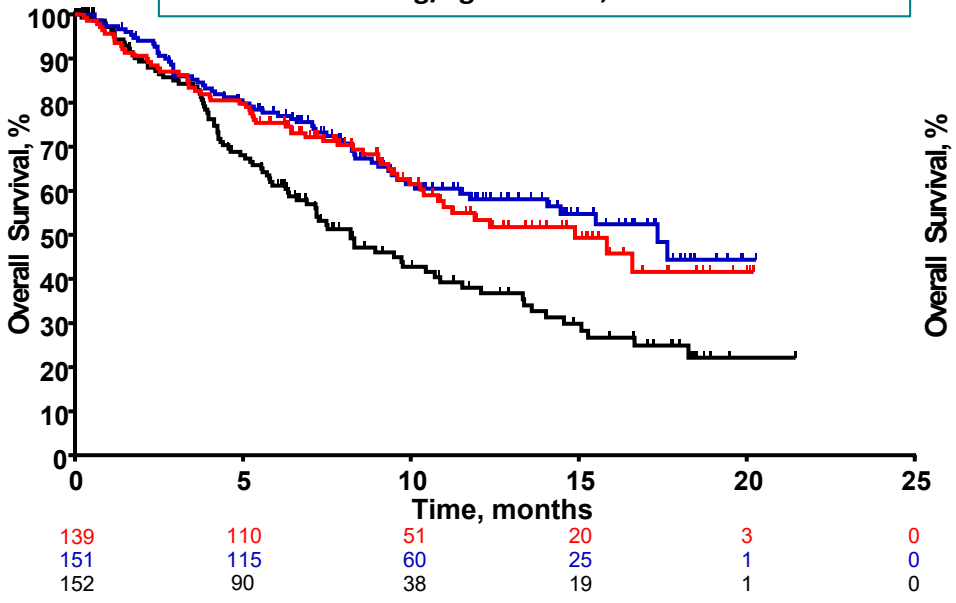
[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

KEYNOTE-010. OS

OS, PD-L1 TPS ≥50% Stratum

Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	—	—

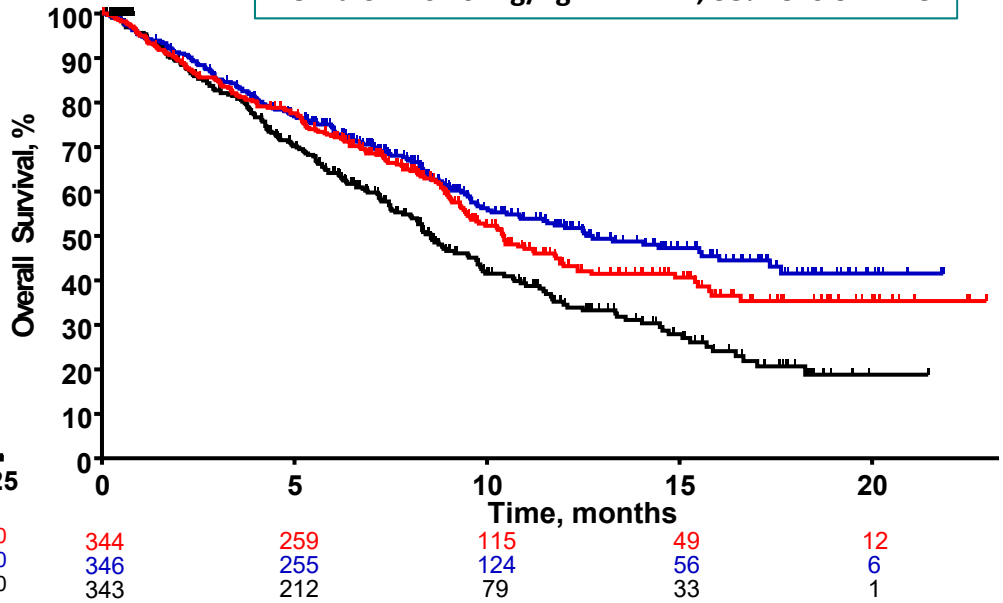
Pembro 2 vs 10 mg/kg: HR 1.12, 95% CI 0.77-1.62



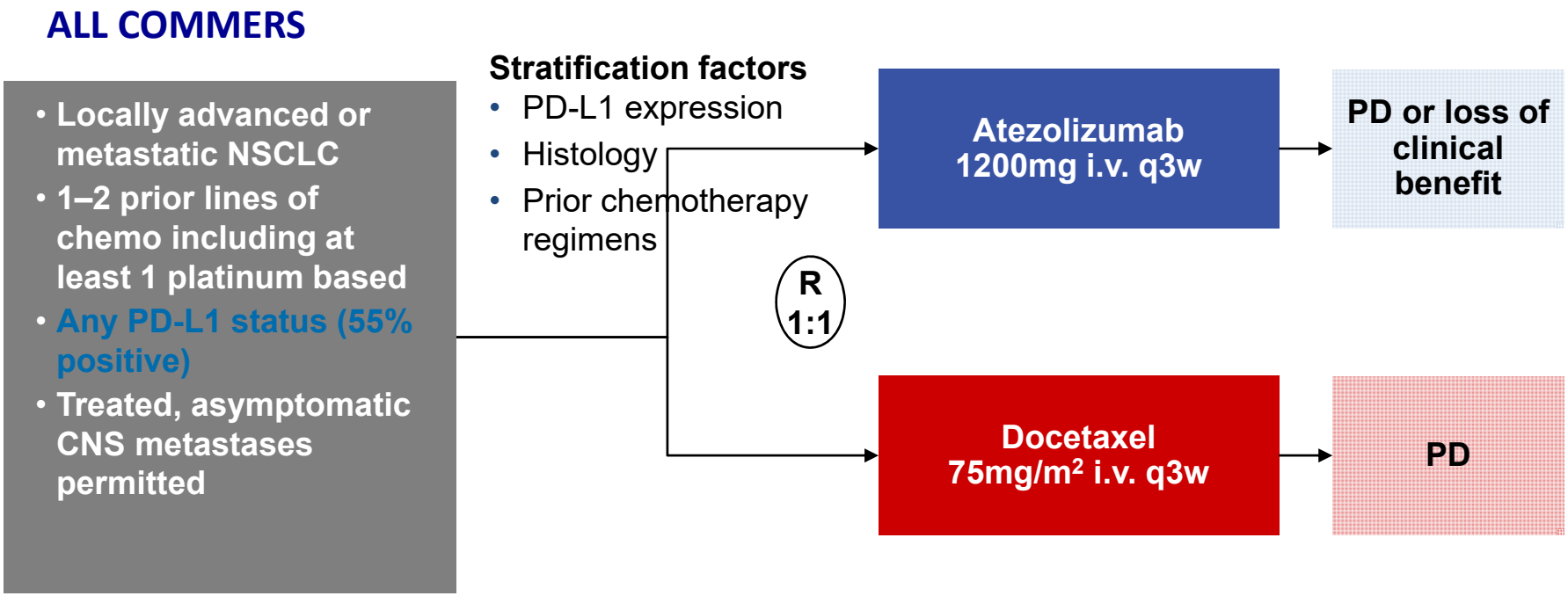
OS, PD-L1 TPS ≥1% (Total Population)

Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

Pembro 2 vs 10 mg/kg: HR 1.17, 95% CI 0.94-1.45



Atezolizumab. OAK trial



Primary Endpoints OS in the ITT population

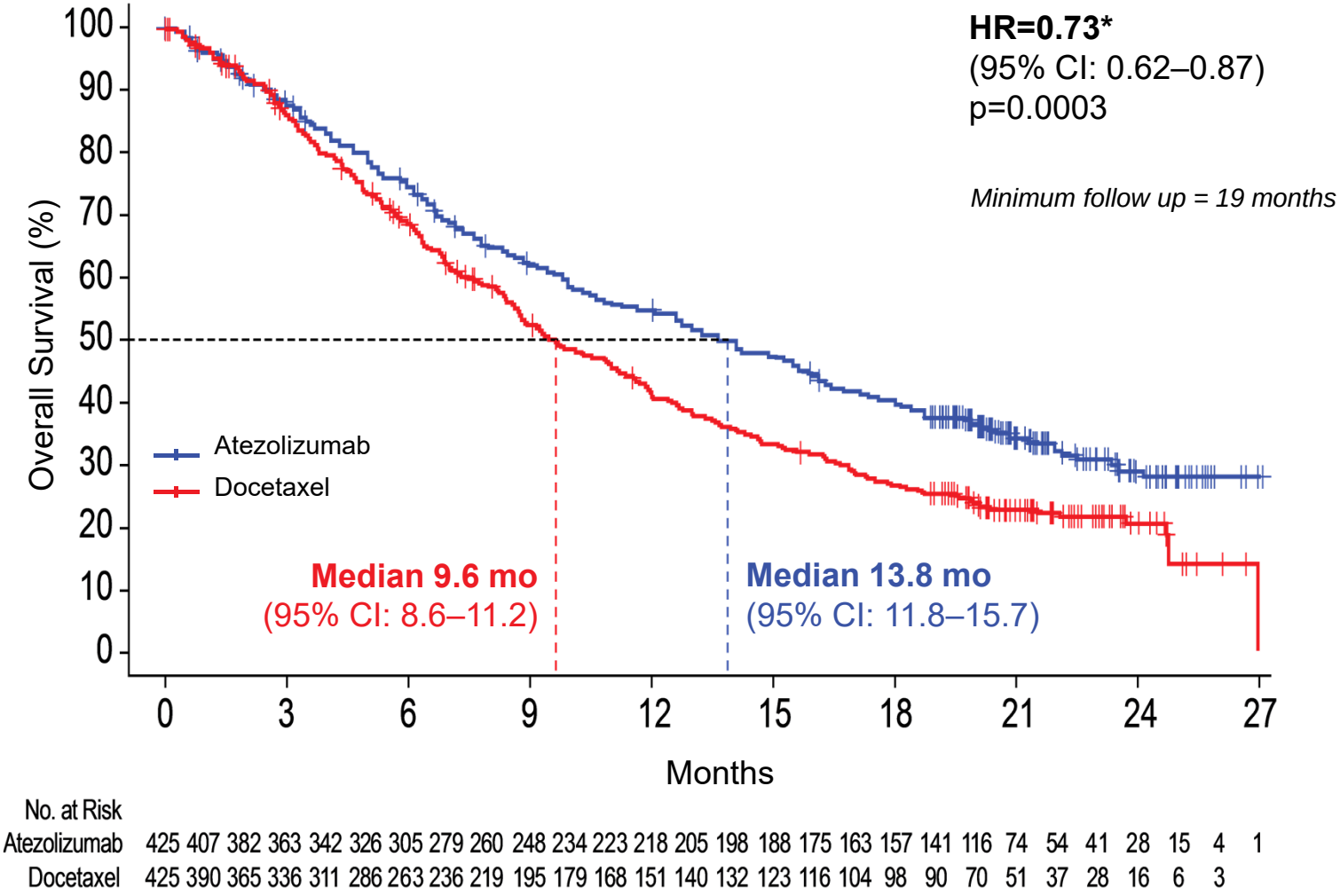
- OS in patients with PD-L1 expression on ≥1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, safety

*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)

NCT02008227; GO28915
Barlesi, et al. ESMO 2016 (Abs LBA44); Rittmeyer, et al. Lancet 2017

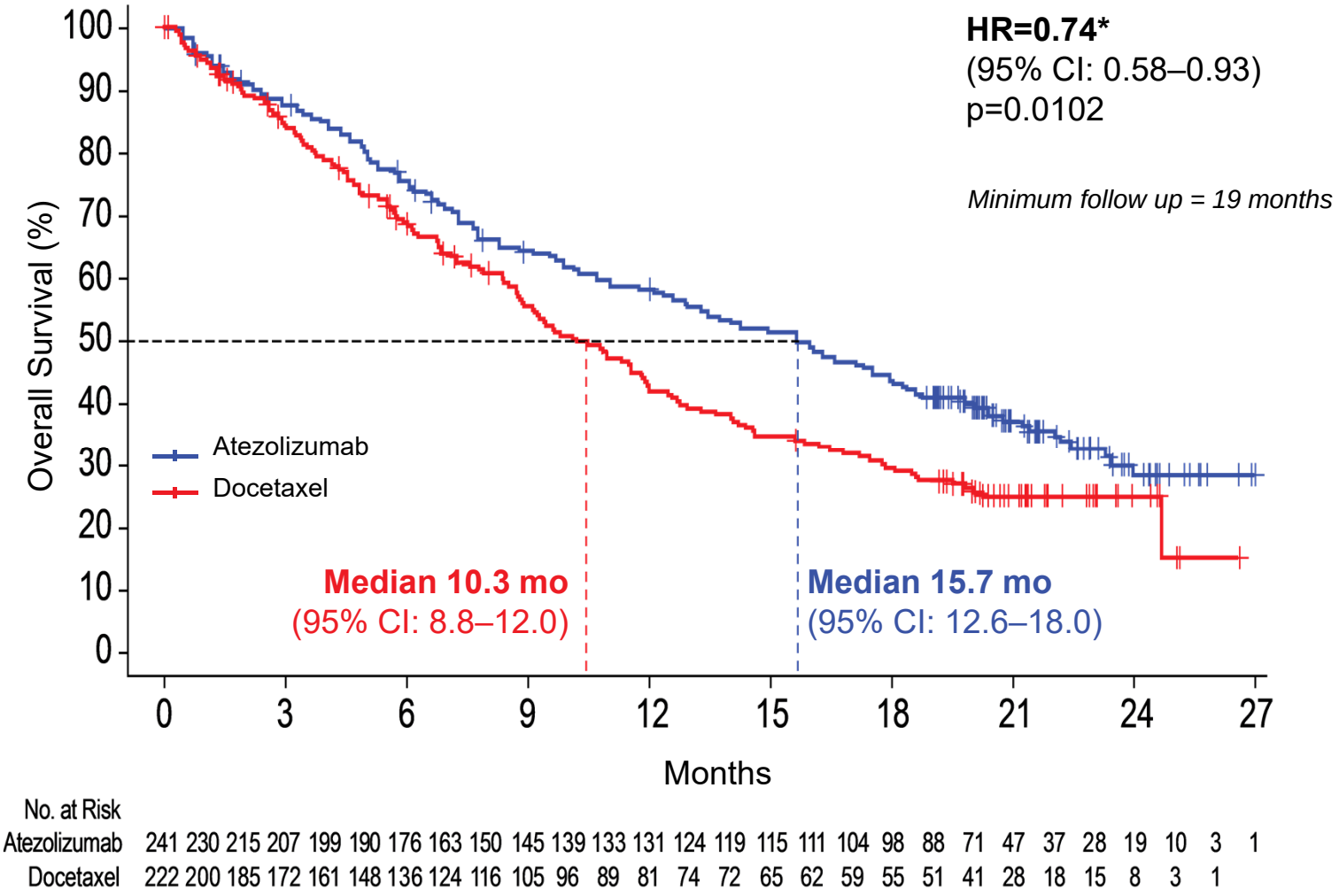
OAK trial. OS (ITT population)



*Stratified HR

Barlesi, et al. ESMO 2016 (Abs LBA44); Rittmeyer, et al. Lancet 2017

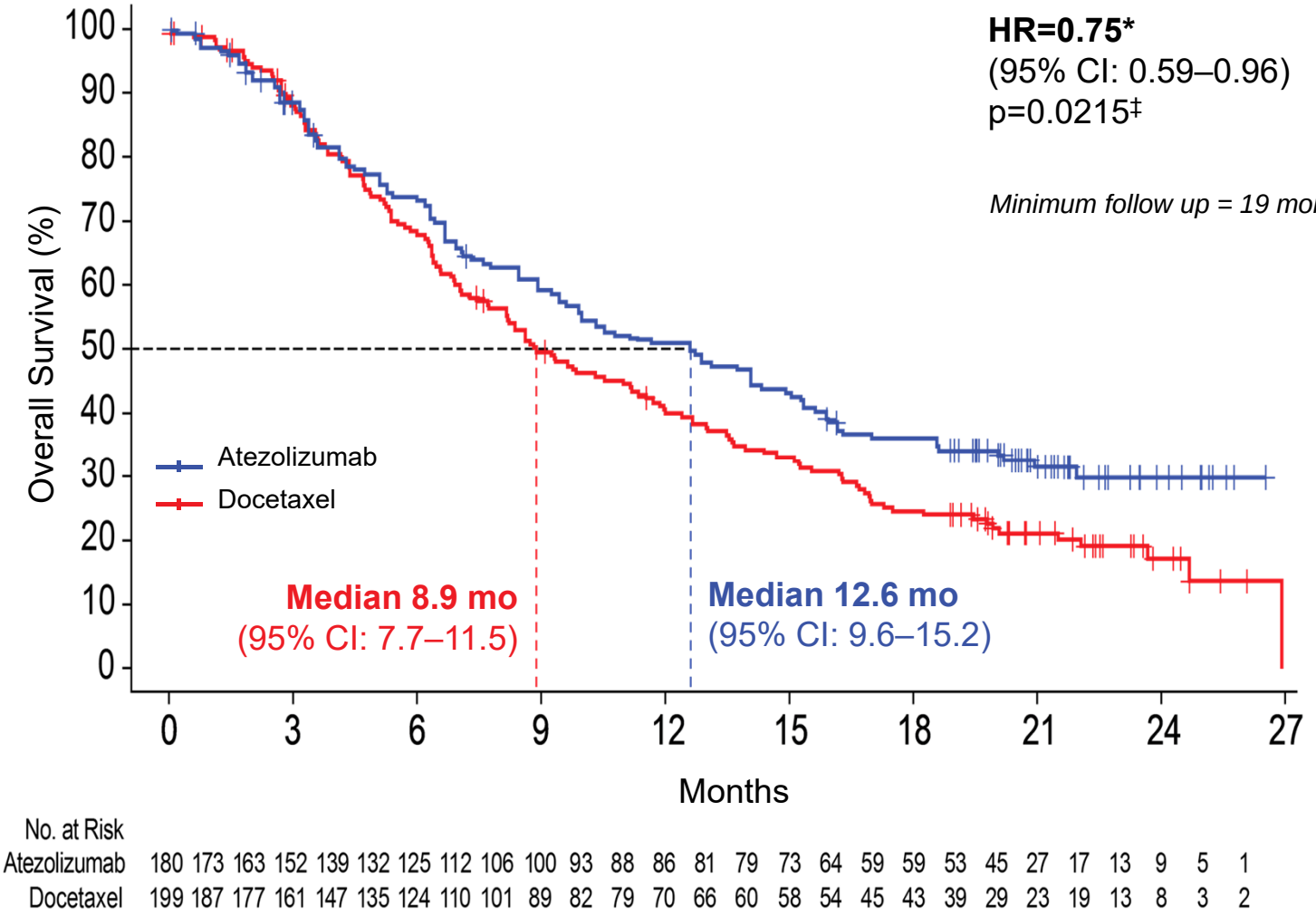
OAK trial. OS in PD-L1 ≥1%



*Stratified HR

Barlesi, et al. ESMO 2016 (Abs LBA44); Rittmeyer, et al. Lancet 2017

OAK trial. OS in PD-L1 <1%

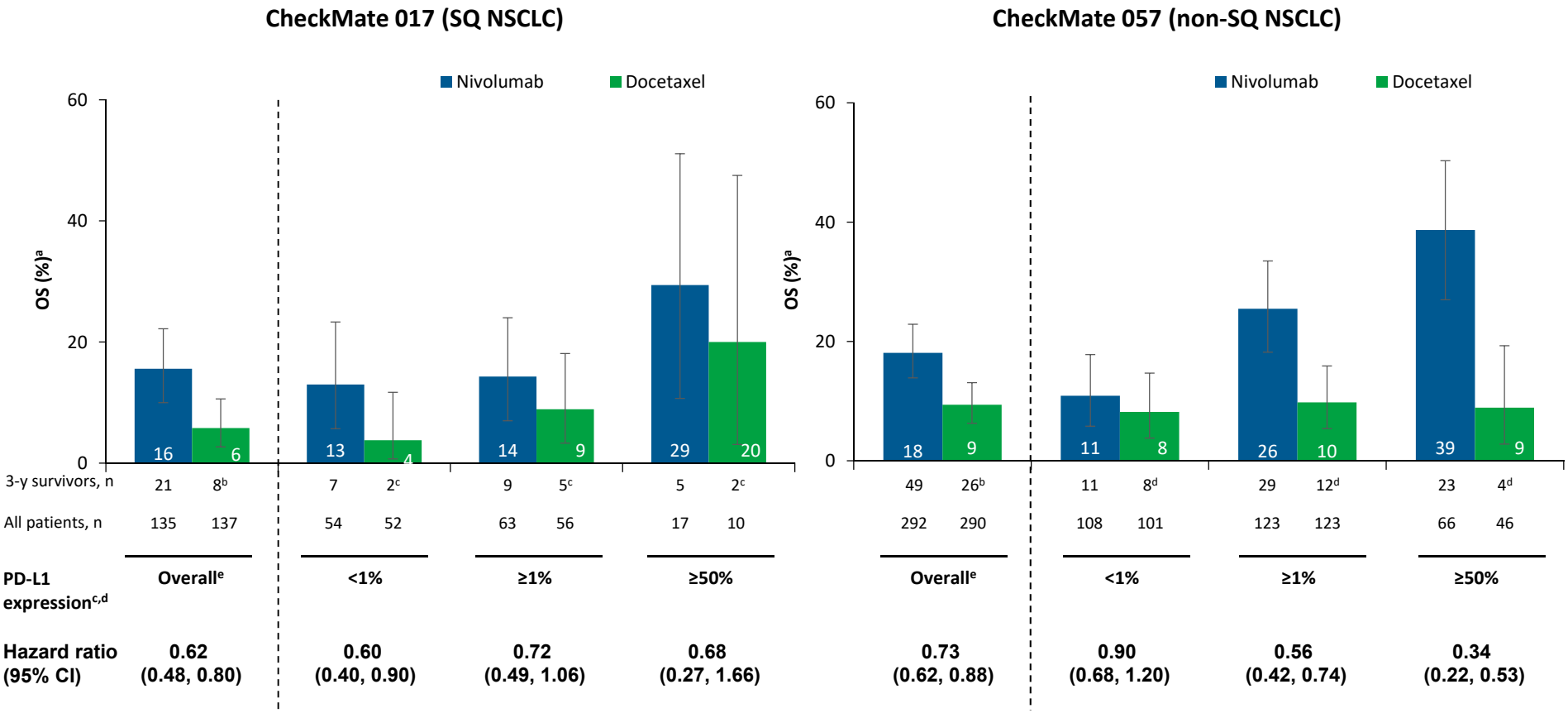


*Unstratified HR
‡P value for descriptive purpose only

Barlesi, et al. ESMO 2016 (Abs LBA44); Rittmeyer, et al. Lancet 2017

What‘s the impact of PD-L1 expression?

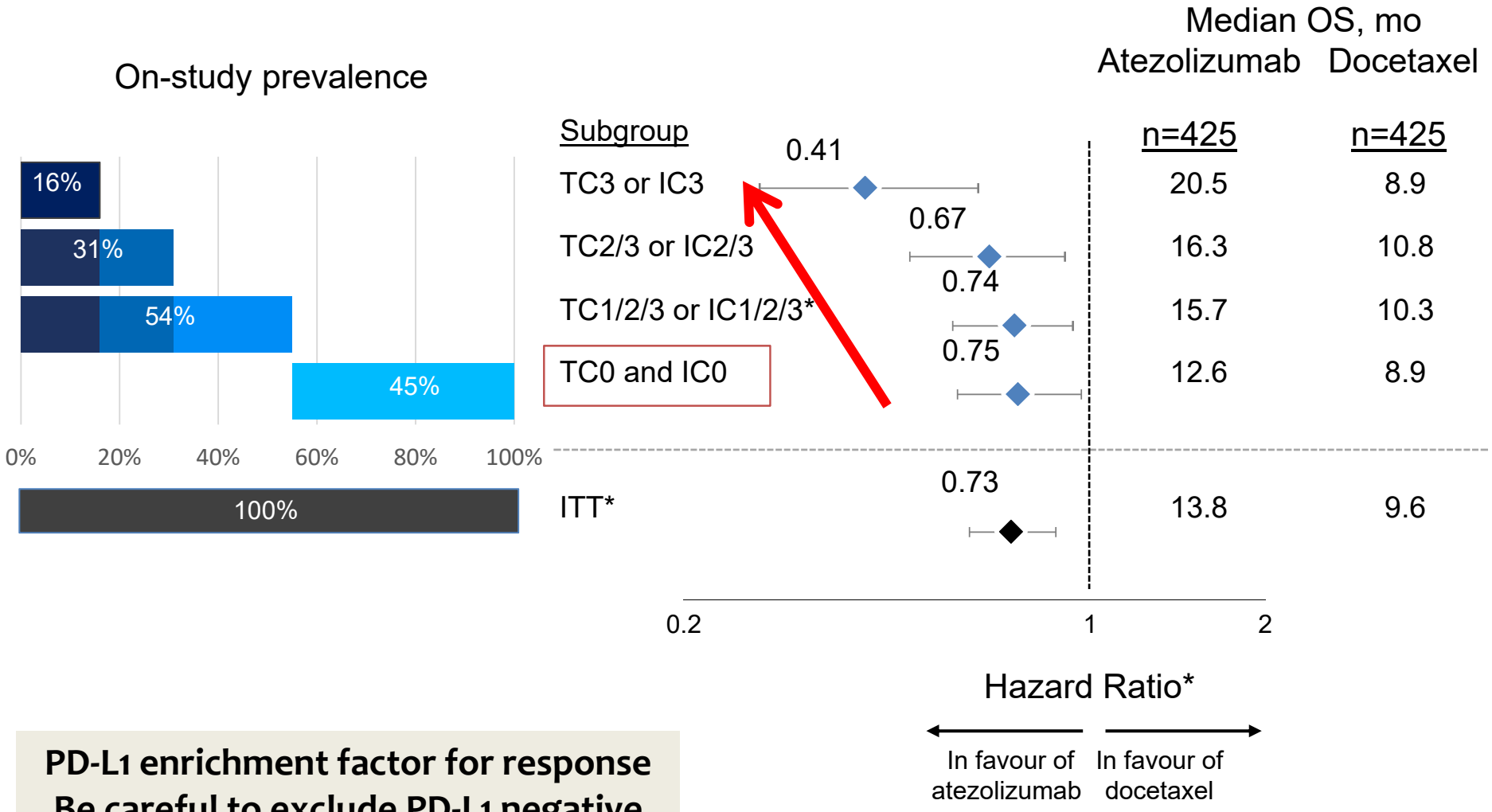
Nivolumab. 3-year OS, overall and by PD-L1



[a]Kaplan-Meier estimates, with error bars indicating 95% CIs; [b]Of the 3-year survivors treated with docetaxel (n = 34) in CheckMate 017 and CheckMate 057, 25 (74%) received subsequent immunotherapy, either during crossover to nivolumab or as post-study treatment; [c]Of the 3-year survivors treated with docetaxel in CheckMate 017 who had <1%, ≥1%, or ≥50% PD-L1 expression levels, 2, 4, and 2 patients, respectively, received subsequent immunotherapy; [d]Of the 3-year survivors treated with docetaxel in CheckMate 057 who had <1%, ≥1%, or ≥50% PD-L1 expression levels, 5, 8, and 4 patients, respectively, received subsequent immunotherapy; [e]Overall population includes those with no quantifiable PD-L1 expression (CheckMate 017: nivolumab, n = 18 [3-y OS, 28%] and docetaxel, n = 29 [3-y OS, 3%]; CheckMate 057: nivolumab, n = 61 [3-y OS, 15%] and docetaxel, n = 66 [3-y OS, 10%])

FELIP E. ESMO 2017

OAK trial. OS by PD-L1 expression



PD-L1 enrichment factor for response
Be careful to exclude PD-L1 negative

*Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for subgroups

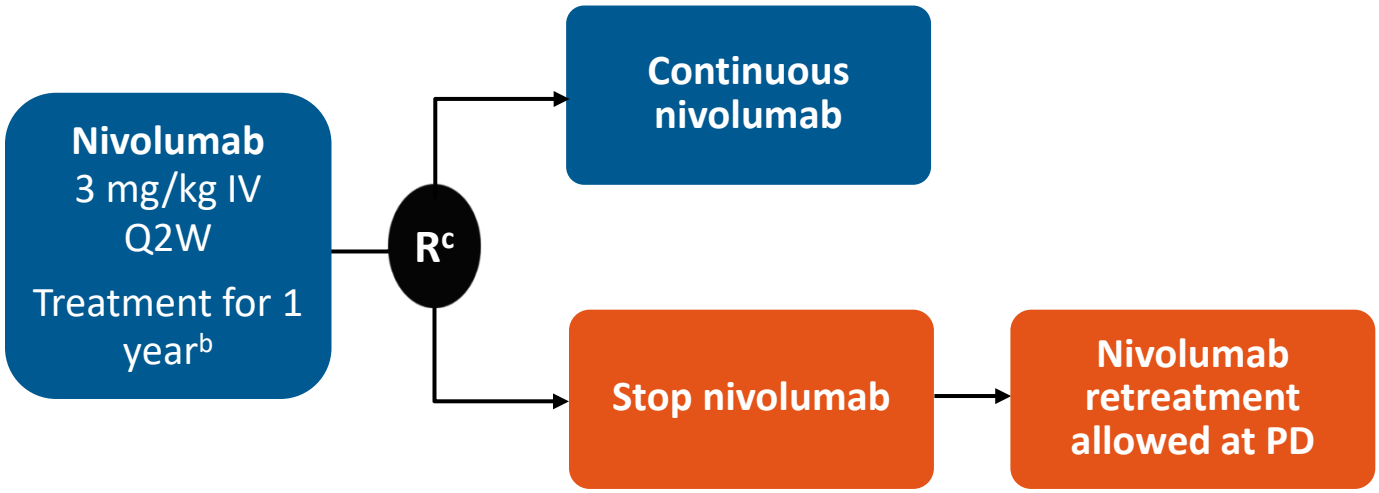
Barlesi, et al. ESMO 2016 (Abs LBA44); Rittmeyer, et al. Lancet 2017

How long to treat?

CheckMate 153: Continuous vs 1-Year Nivolumab

Key eligibility criteria

- Advanced/ metastatic NSCLC
- ≥1 prior systemic therapy[a]
- ECOG PS 0–2
- Treated CNS metastases allowed



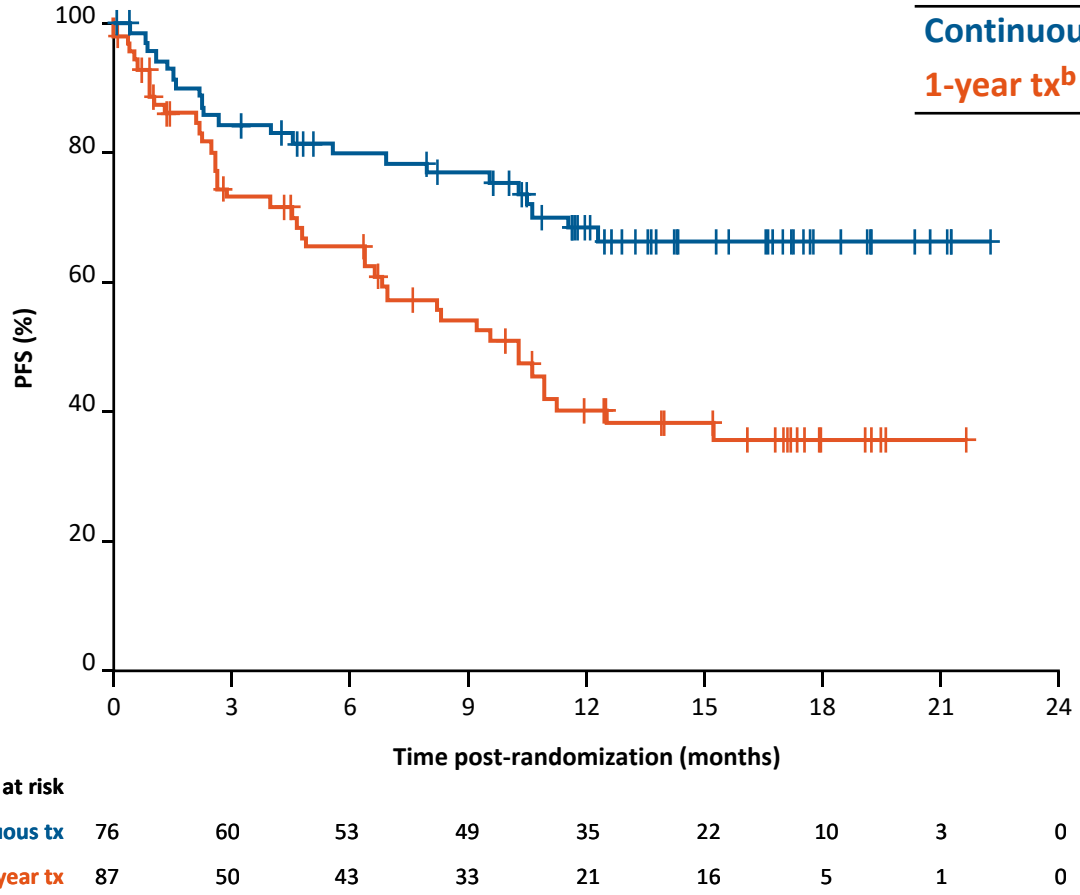
Exploratory endpoints[d]: safety/efficacy[e] with continuous vs 1-year treatment, efficacy, other (eg, biomarkers, PK)

- At database lock (May 15, 2017), minimum/median follow-up time post-randomization was 10.0/14.9 months

[a]Conventional systemic therapies, excluding immuno-oncology therapies; [b]Treatment until PD, unacceptable toxicity, or withdrawal of consent; treatment beyond investigator-assessed PD permitted; [c]All patients on treatment at 1 year were randomized regardless of response status; [d]Primary endpoint was incidence of high-grade select treatment-related AEs[1,2]; [e]Responses were investigator-assessed every 8 weeks ± 5 days from week 9

1. Hussein M, et al. Oral presentation at IASLC 16th World Conference on Lung Cancer; September 6–9, 2015; Denver, CO, USA. Abstract ORAL02.02. 2. Waterhouse D, et al. Poster presentation at ASCO Annual Meeting; June 3–7, 2016; Chicago, IL, USA. Abstract 3059.

CheckMate 153: PFS from Randomization



	Median, months (95% CI)	PFS rate, % 6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

- Improvement inPFS irrespective of response (CR/PR or SD)
- Trend in OS (HR 0.63)
- *Some stabilizations by reexposure*

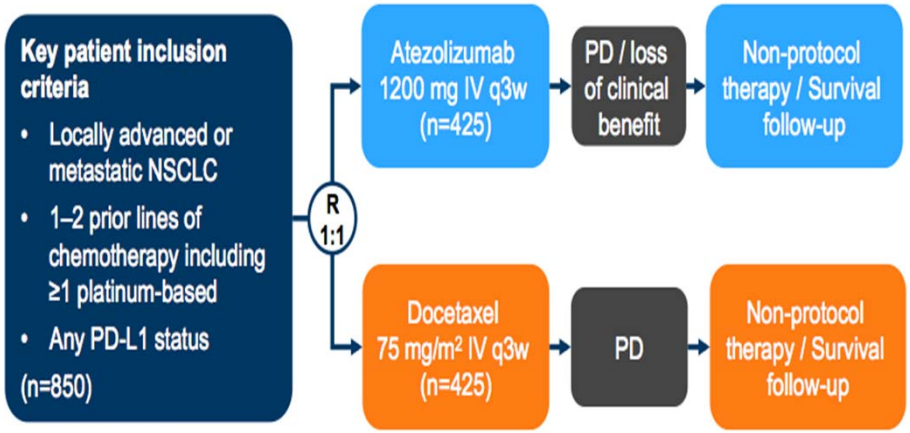
[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

SPIGEL, ESMO 2017

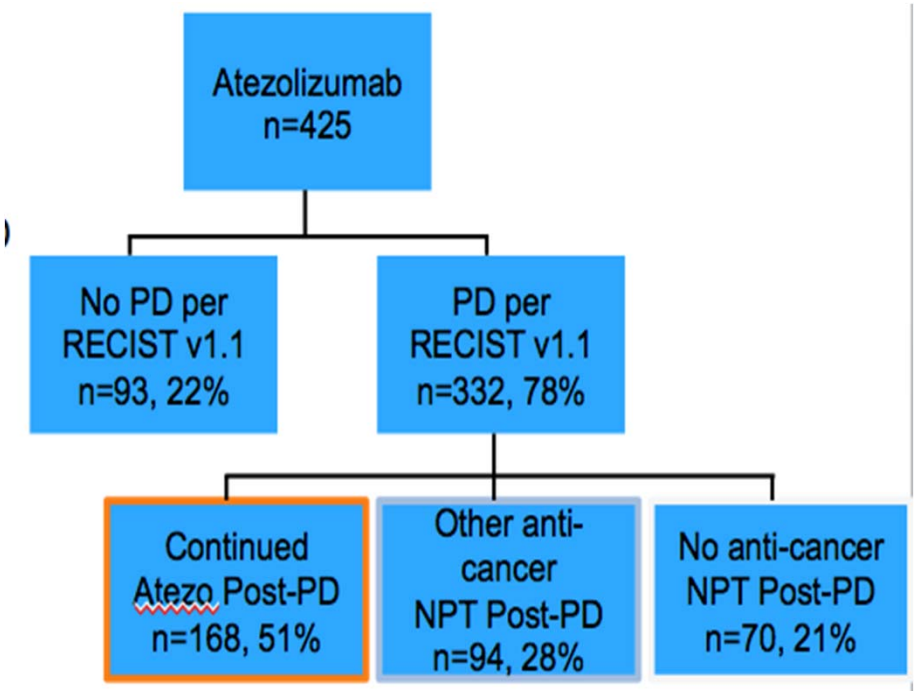
Treatment beyond progression

Treatment beyond progression

Oak – Exploratory Analysis



	Atezo Post-PD	Other Post PD	No Treatment Post PD
Number	168 (51%)	94 (28%)	70 (21%)
Median OS	12.7 m (9.3 ; 14.9)	8.8 m (6.0 ; 12.1)	2.2 m (1.9 ; 3.4)
18 m OS	37%	20%	9%

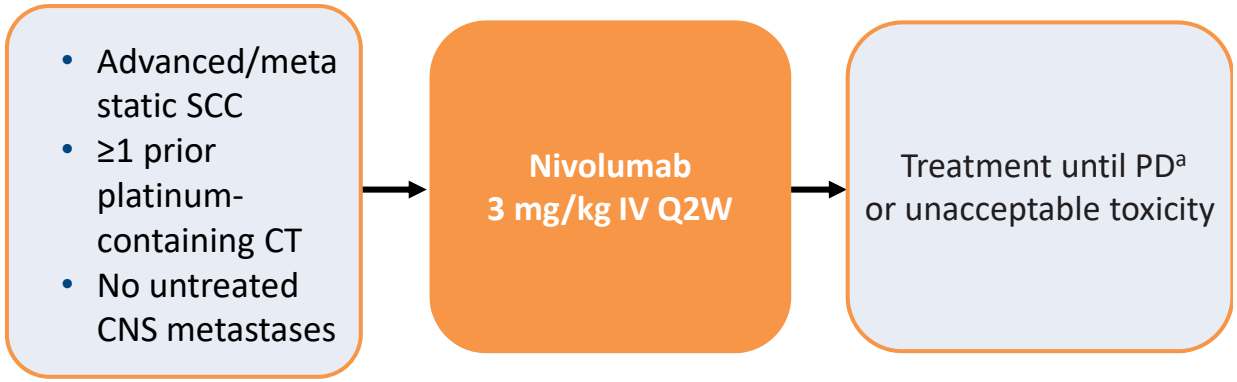


NEED FOR RANDOMIZED CLINICAL TRIAL

Gandara D et al, ASCO 2017; abstract 9001

PS-2 & elderly

CheckMate 171



TRAE	All patients (N = 809)		≥70 years (n = 279)		ECOG PS 2 (n = 98)	
	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)	Any grade, n (%)	Grade 3–4, n (%)
TRAEs	403 (50)	95 (12)	155 (56)	38 (14)	45 (46)	6 (6)
Serious TRAEs	60 (7)	41 (5)	19 (7)	13 (5)	4 (4)	2 (2)
TRAEs leading to discontinuation	45 (6)	31 (4)	16 (6)	12 (4)	5 (5)	4 (4)

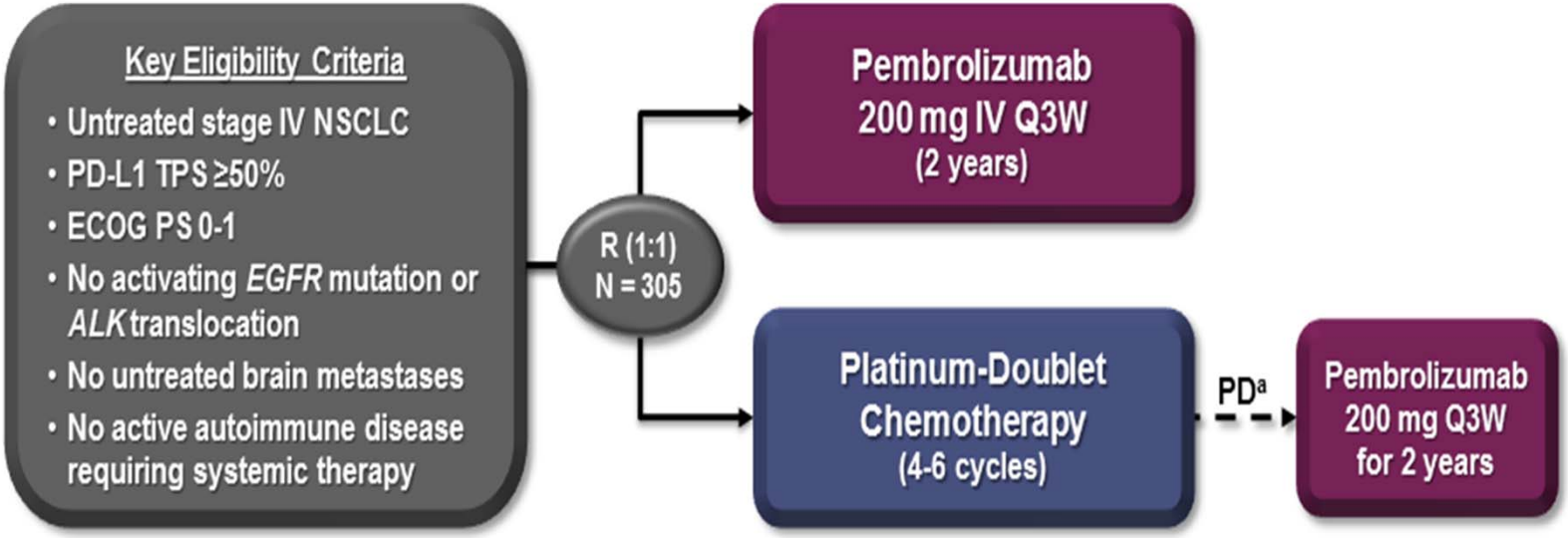
	All patients	≥70 years	ECOG PS 2
Median OS, months (95% CI)	9.9 (8.7, 13.1)	11.2 (7.6, NA)	5.4 (3.9, 8.3)
3-month OS rate, % (95% CI)	81 (78, 83)	78 (73, 83)	65 (54, 74)
6-month OS rate, % (95% CI)	67 (63, 70)	66 (59, 71)	46 (34, 57)
RESPONSE RATE	14%	14%	11%

POPAT, ESMO 2017

IO IN FIRST LINE NSCLC

- **MONOTHERAPY: Pembro, Nivo**
- **COMBINATIONS**
  - **IO-IO**
  - **IO-CT**

KEYNOTE-024. PD-L1> 50%



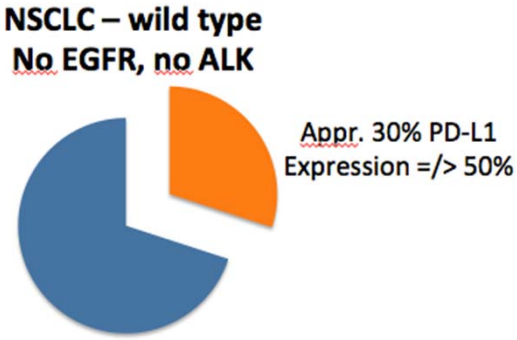
Key End Points

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

Secondary: OS, ORR, safety

Exploratory: DOR

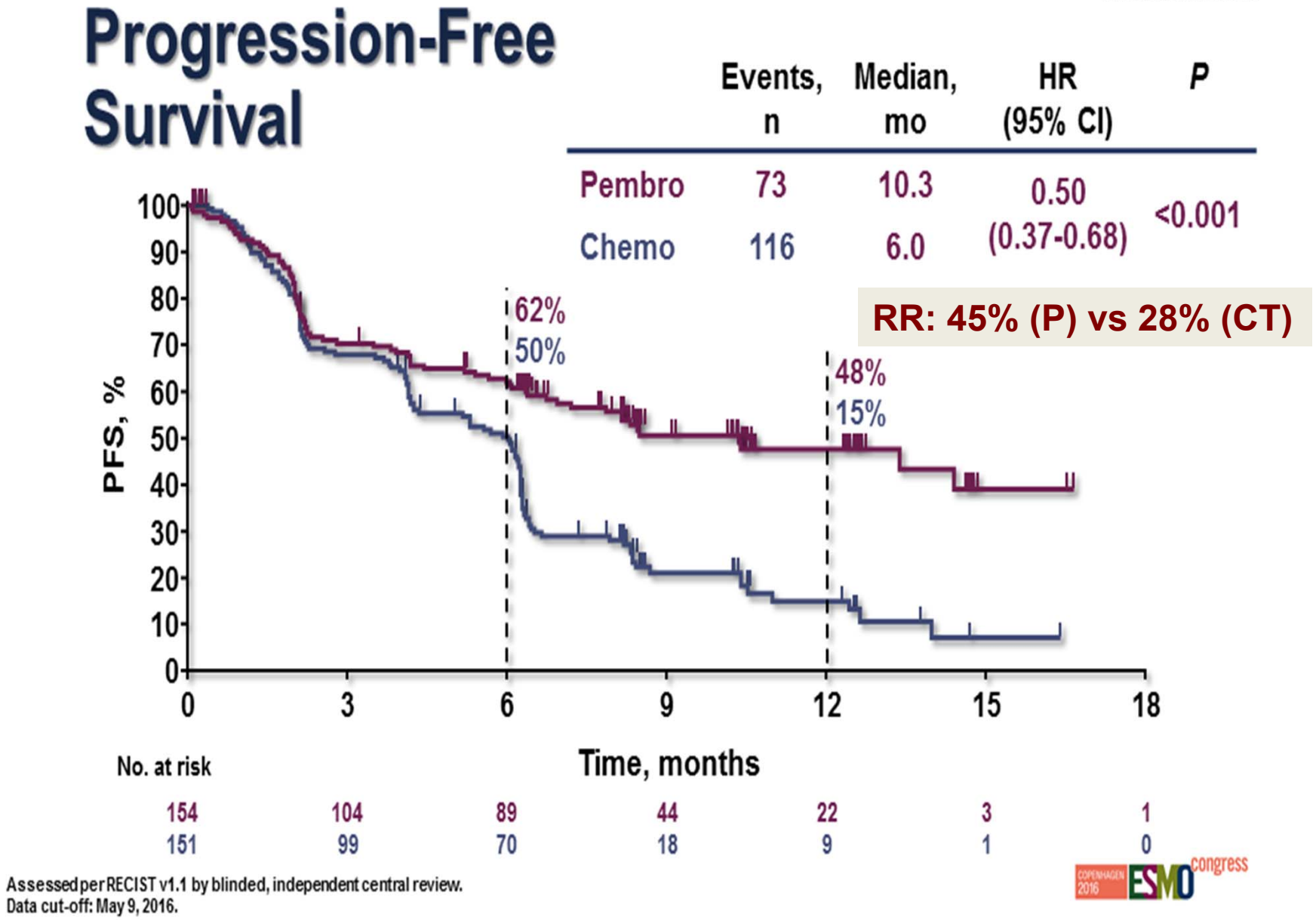
[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.



M. Reck et al. ESMO 2016

KEYNOTE-024. PFS

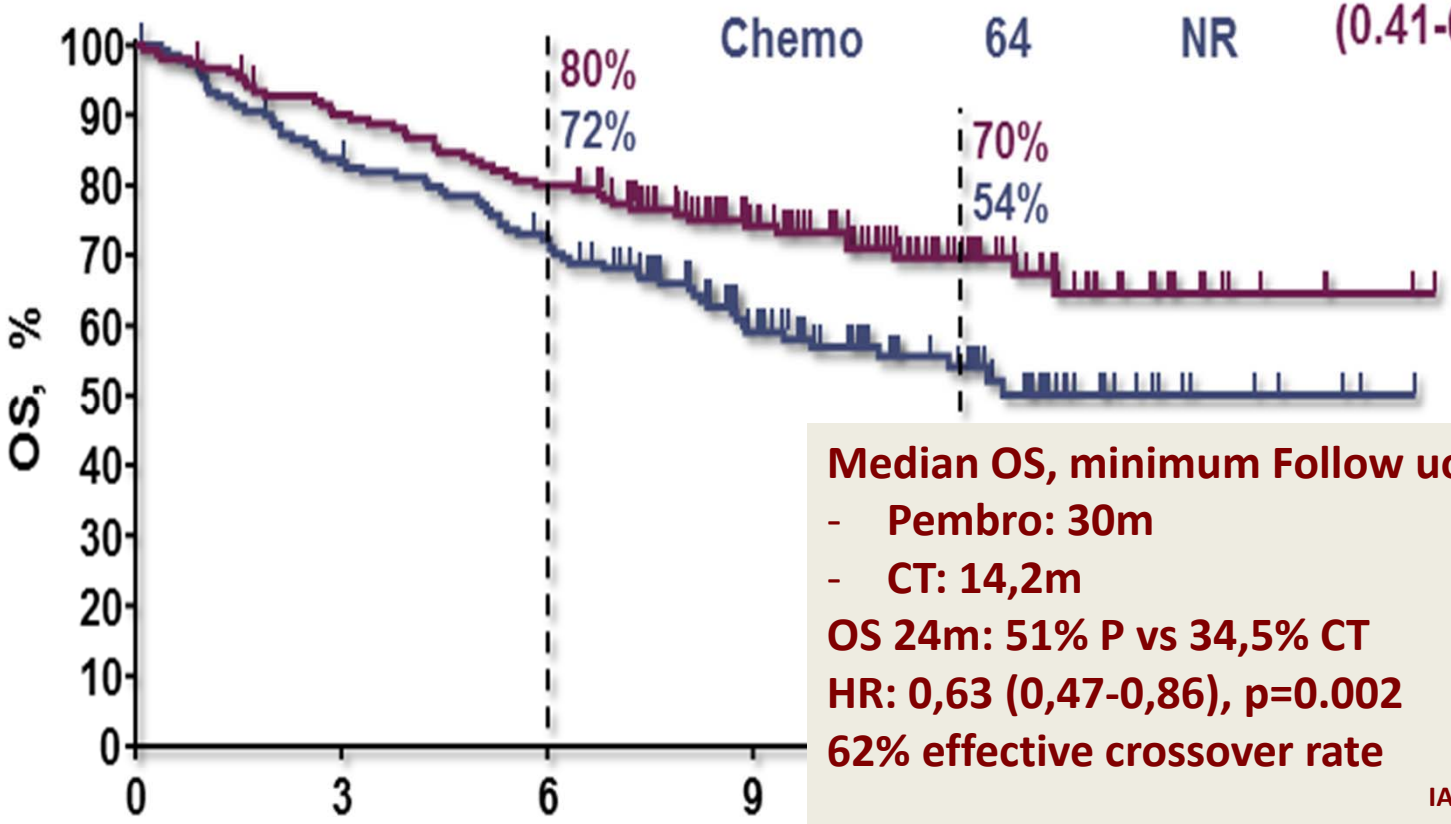
M Reck. ESMO 2016.



KEYNOTE-024. OS

M Reck. ESMO 2016.

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



Median OS, minimum Follow uo 25 months

- **Pembro: 30m**
- **CT: 14,2m**

OS 24m: 51% P vs 34,5% CT

HR: 0,63 (0,47-0,86), p=0.002

62% effective crossover rate

IASCL 2017, Brahmer J.

DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

Exposure and AE Summary

	Pembrolizumab N = 154	Chemotherapy N = 150
Exposure, median (range)	7.0 mo (1 d-18.7 mo)	3.5 mo (1 d-16.8 mo)
Treatment-related AEs, n (%)	113 (73)	135 (90)
Grade 3-4	40 (26)	77 (51)
Serious	33 (21)	31 (21)
Led to discontinuation	11 (7)	16 (11)
Led to death	1 (<1)	3 (2)

Data cut-off: May 9, 2016.

CheckMate 026
PD-L1> 1%

CheckMate 026: A Phase 3 Trial of Nivolumab vs Investigator's Choice of Platinum-Based Doublet Chemotherapy as First-line Therapy for Stage IV/ Recurrent Programmed Death Ligand 1–Positive NSCLC

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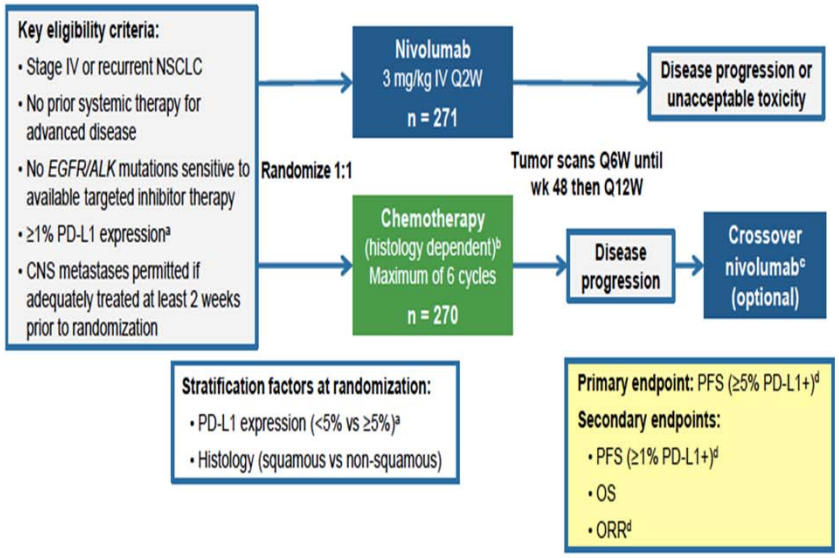
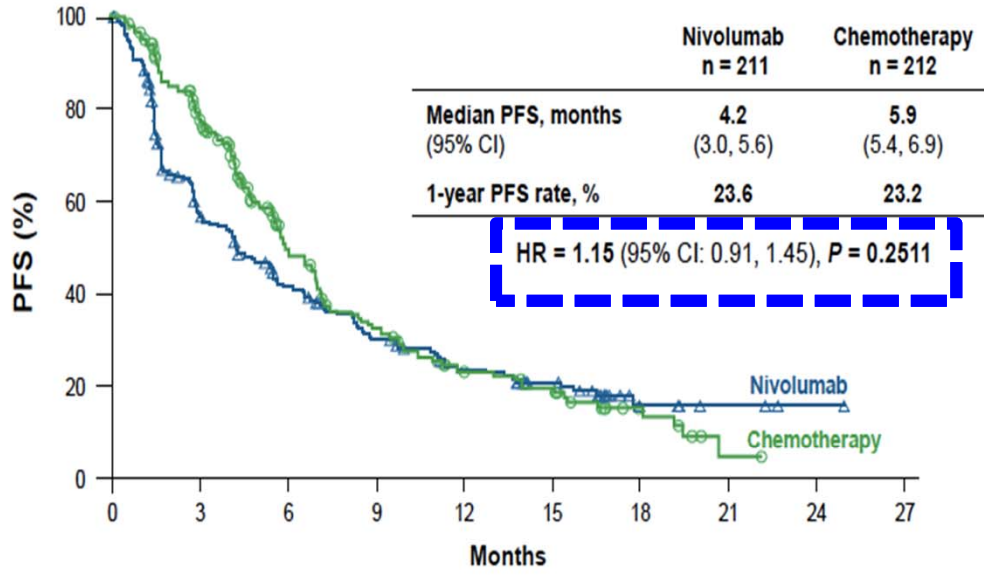


Overall Survival (≥5% PD-L1+)	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	14.4 (11.7, 17.4)	13.2 (10.7, 17.1)
1-year OS rate, %	56.3	53.6

HR = 1.02 (95% CI: 0.80, 1.30)

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

CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC

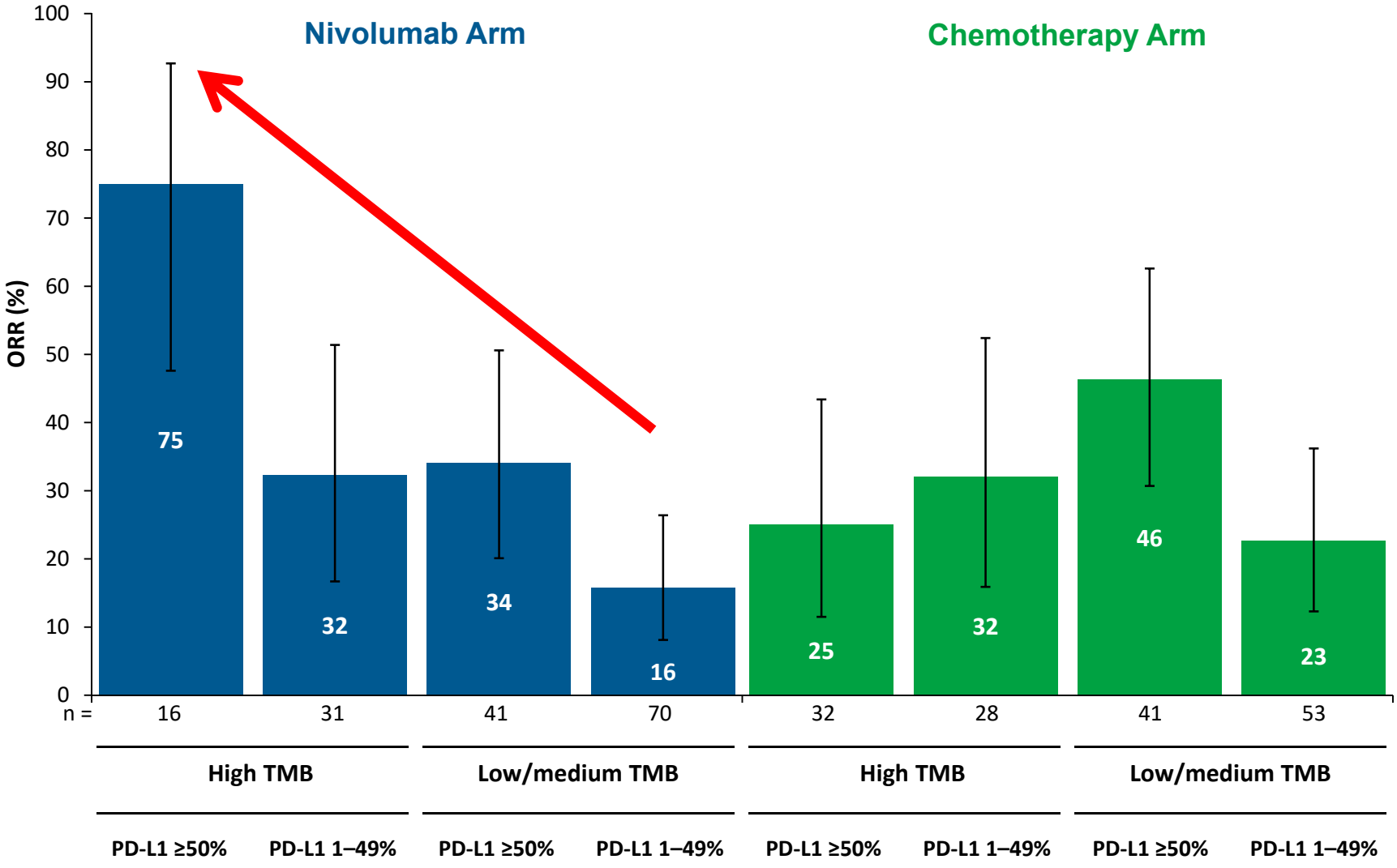


No. of patients at risk:

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)

ORR by TMB Subgroup and PD-L1 Expression
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC



[a]ORR was 45.6% in patients with ≥50% PD-L1 expression in the nivolumab arm of the TMB-evaluable population

S. PETERS. AACR2017

IO-IO Combinations

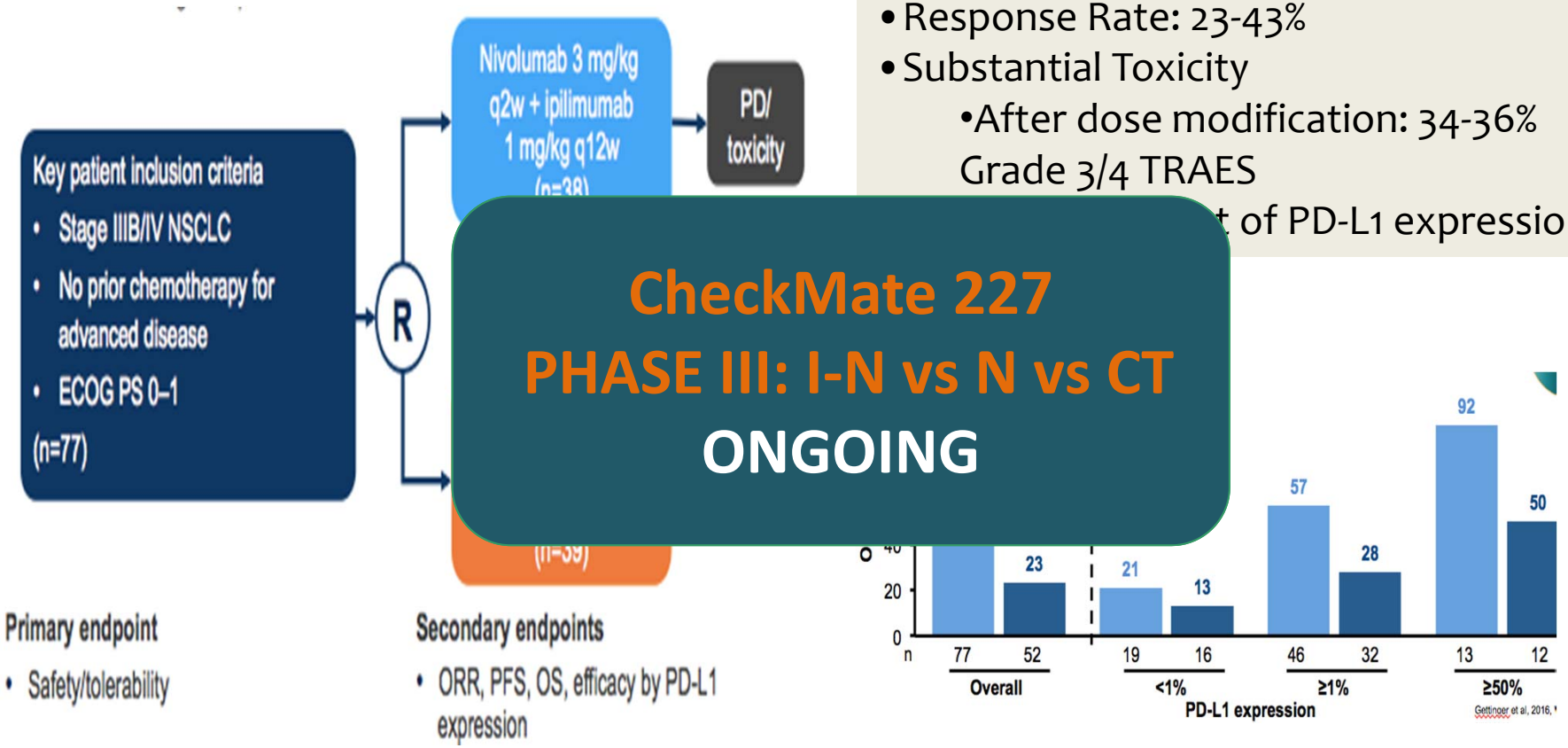
Phase 1 CheckMate 012: first-line Nivolumab + Ipilimumab

Hellmann M, ASCO 2016

- Response Rate: 23-43%
- Substantial Toxicity
  - After dose modification: 34-36%

Grade 3/4 TRAES

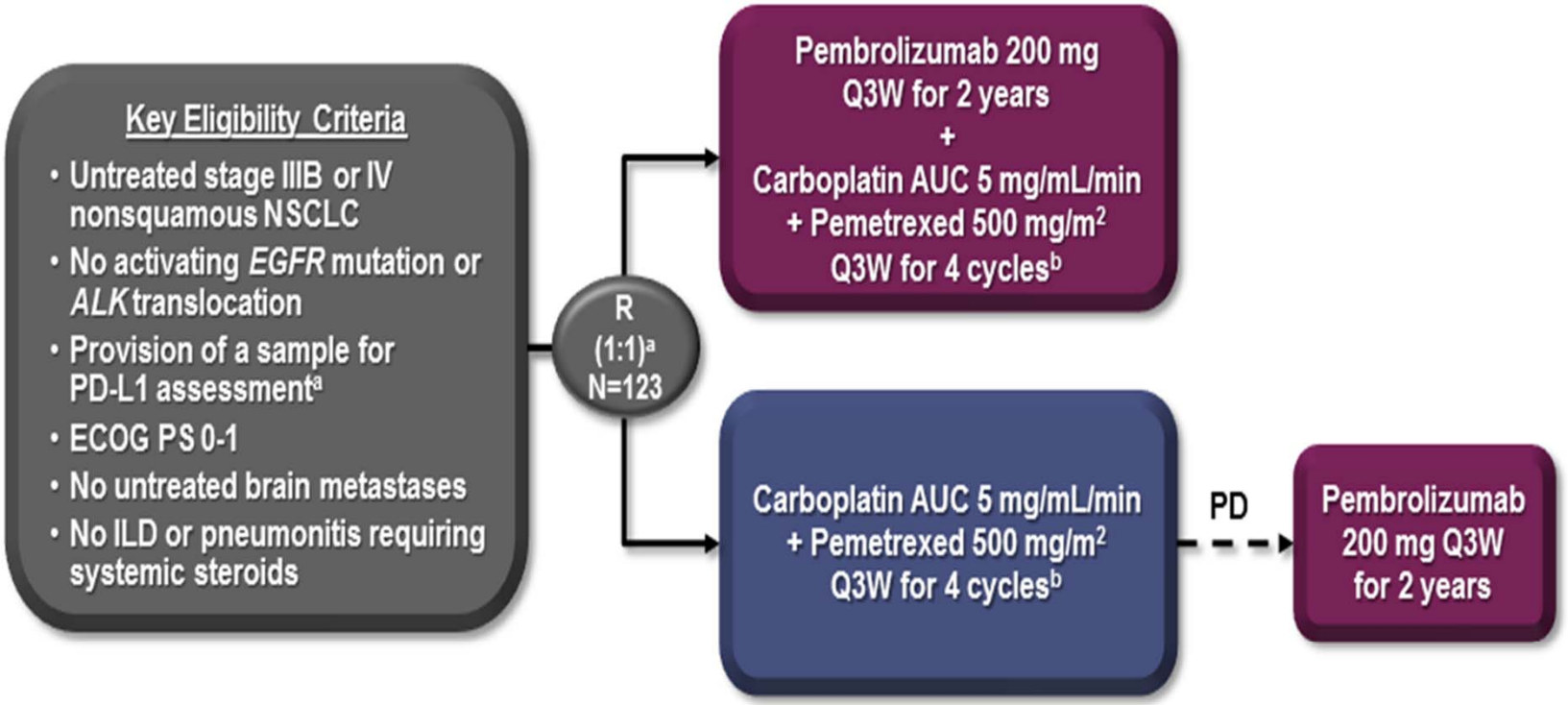
t of PD-L1 expression:



IO-CT Combinations

CJ Langer. ESMO 2016.

KEYNOTE-021 phase 2 trial



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.

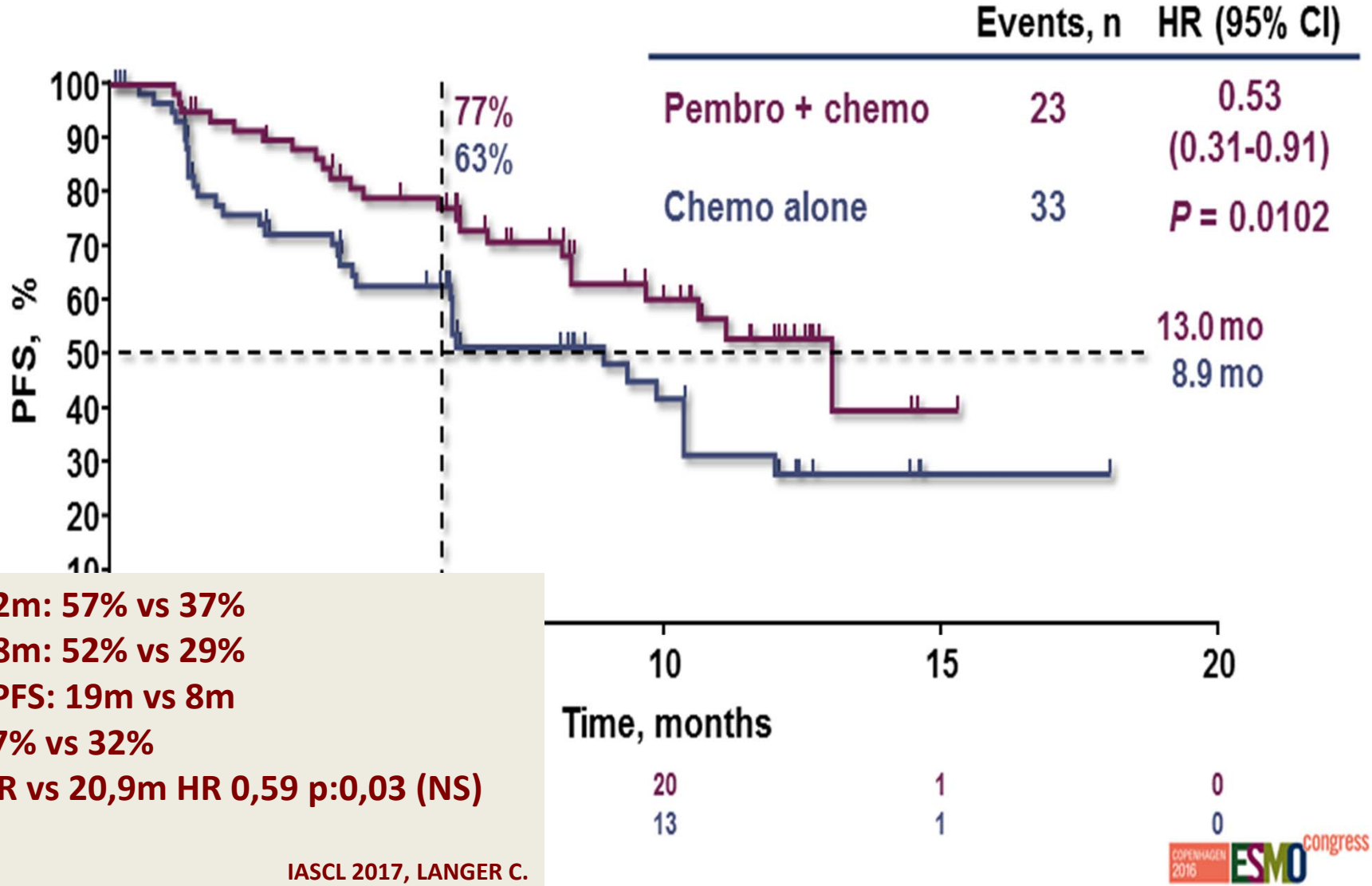
[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

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

COPENHAGEN 2016 ESMO congress

Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)

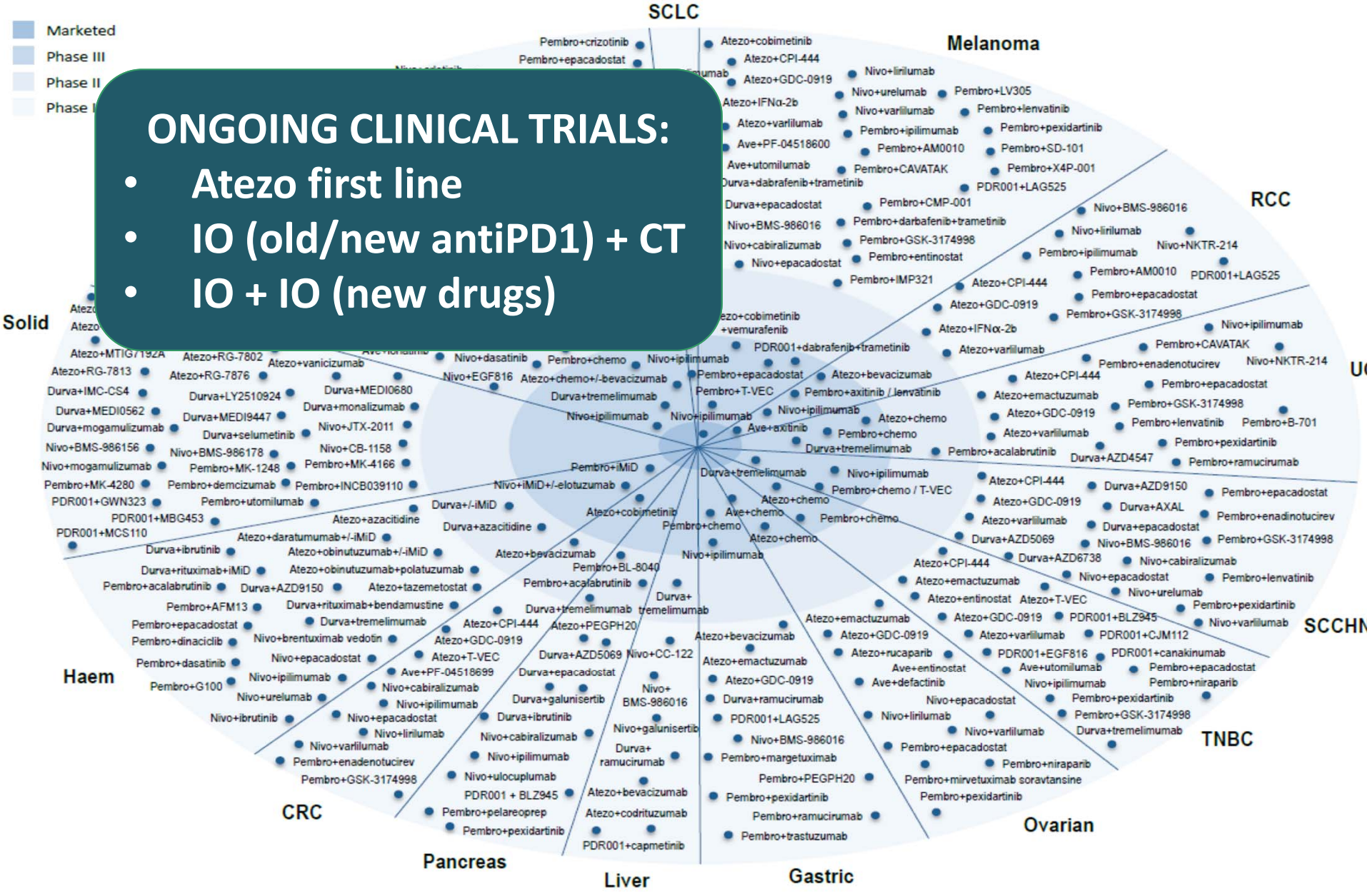
CJ Langer. ESMO 2016.



PFS 12m: 57% vs 37%
PFS 18m: 52% vs 29%
Med PFS: 19m vs 8m
RR: 57% vs 32%
OS: NR vs 20,9m HR 0,59 p:0,03 (NS)

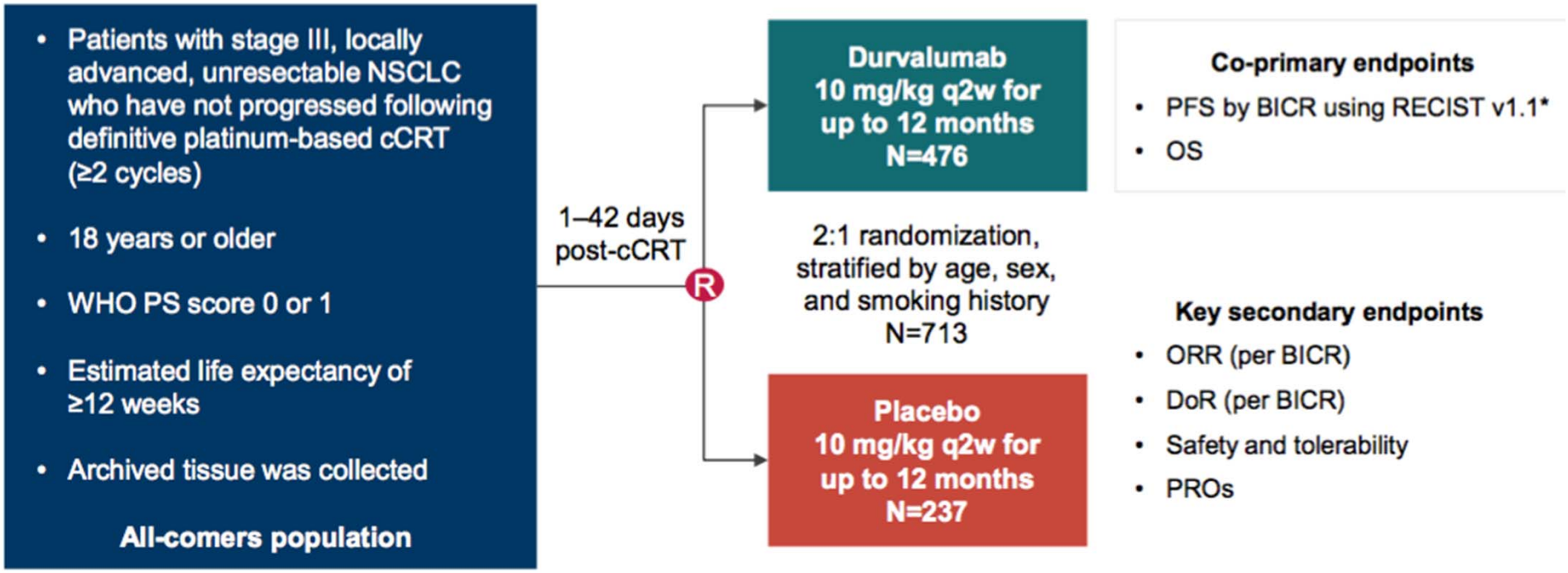
IASCL 2017, LANGER C.

Cancer immunotherapy-based combination Studies underway in 2016. Chen et al, Nature 18:2017



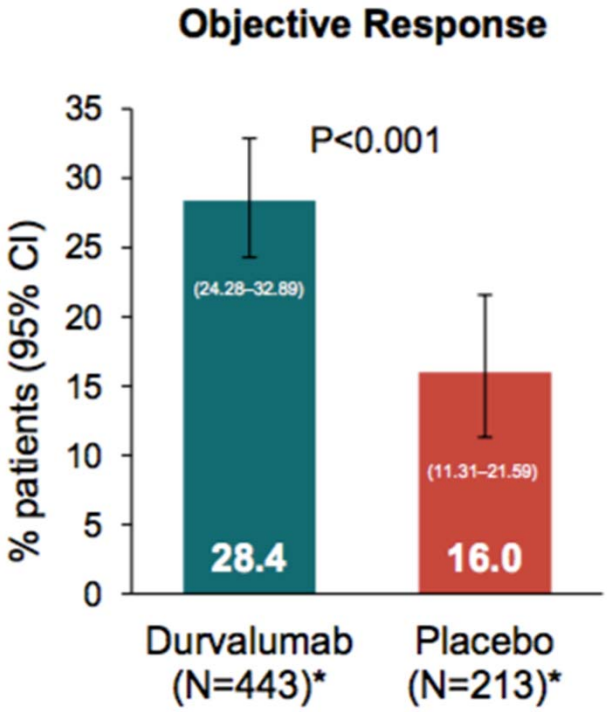
Early stage

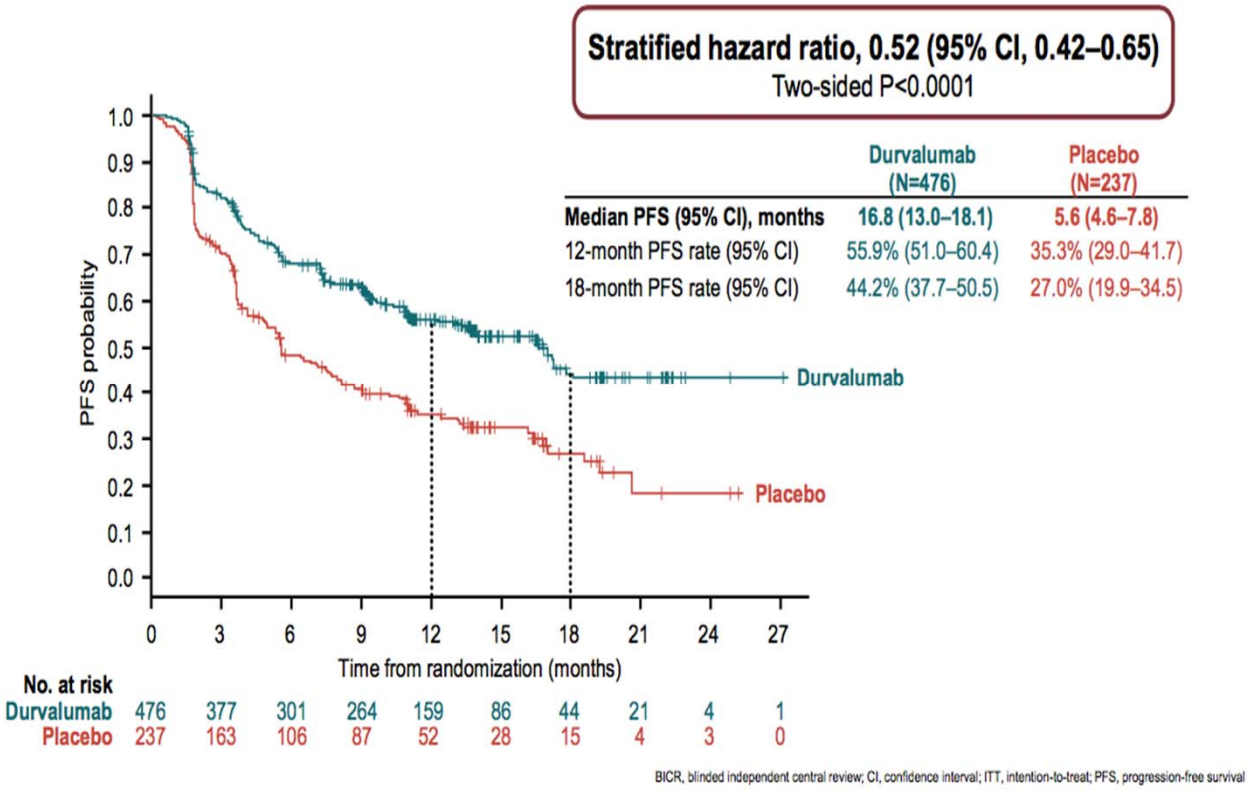
Pacific trial. Loc advanced NSCLC



Paz-Ares. ESMO 2017

Pacific trial





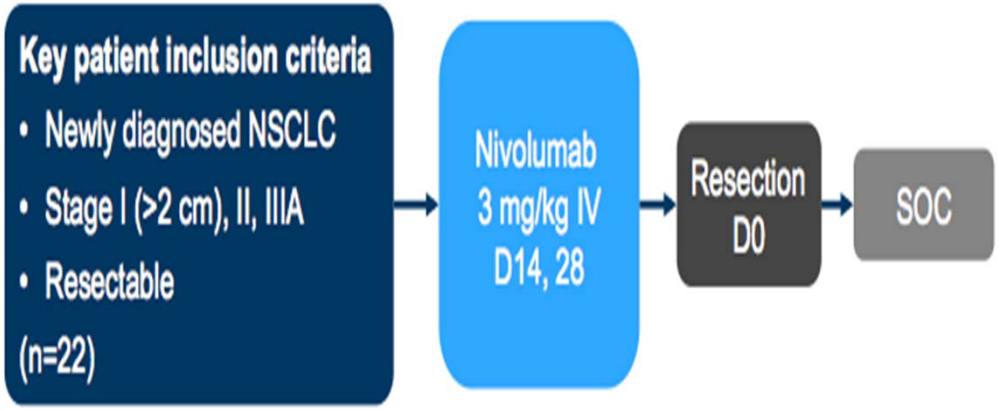
BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

Durvalumab did not negatively affect QoL

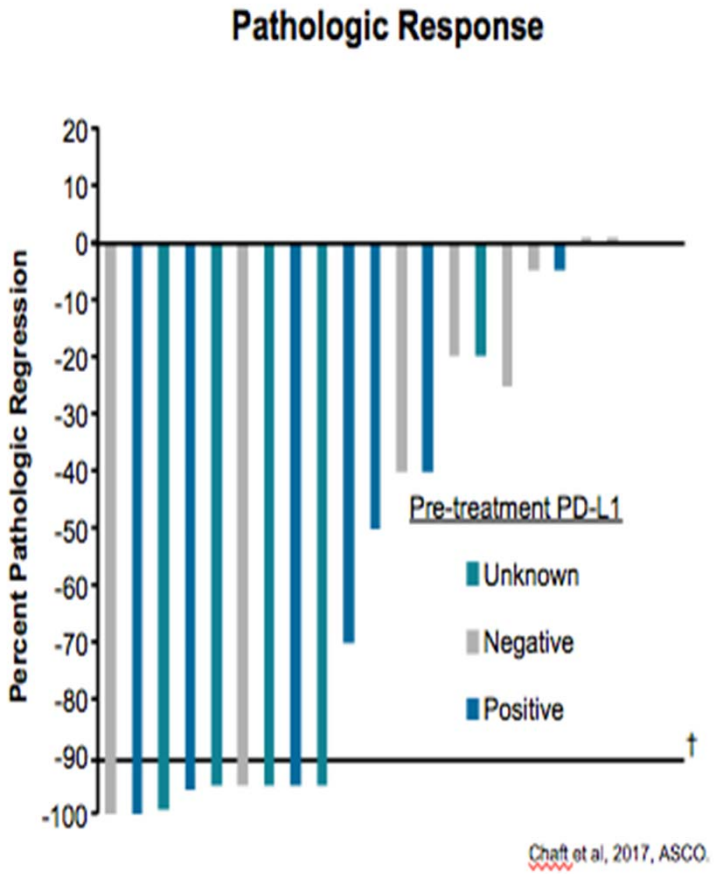
IASLC 2017

Paz-Ares. ESMO 2017

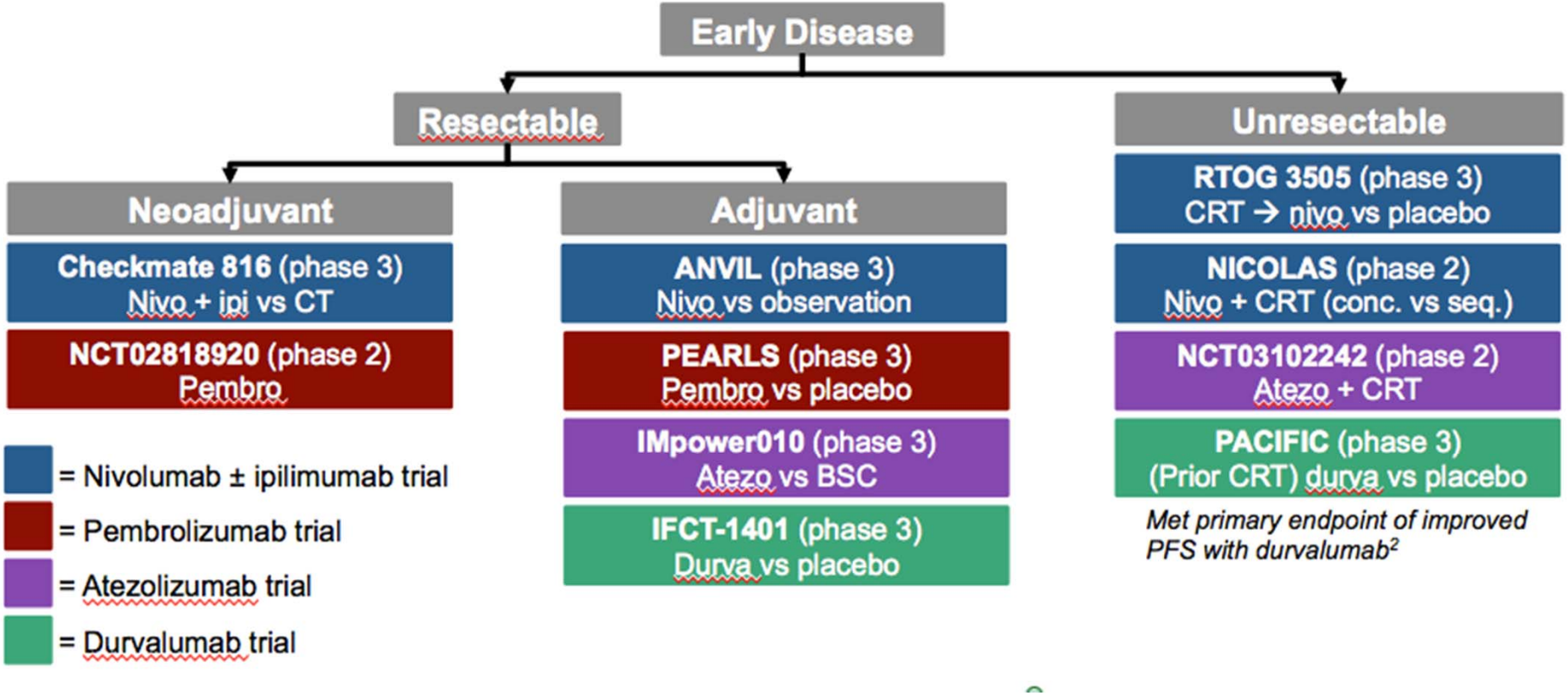
CheckMate 159



- 10% PR, 85% SD
- Major Pathological Response (<10% viable tumor cells): 43% (9/21)
- No impact of PD-L1 expression
- No delay of surgery



Current trials in early stage



Final comments

- Confirmed objective and symptomatic efficacy in pretreated patients → long term survivors for the fist time!
- Superior efficacy in selected untreated patients
- Upfront combinations to be determined: IO-IO, IO-CT
- Several remaining questions: biomarkers, special population, early stage, SCLC,...

Immunotherapy in the clinic. Lung Cancer

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20 octubre 2017
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