Recent update in lung cancer treatment “Immunotherapy”

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정치영

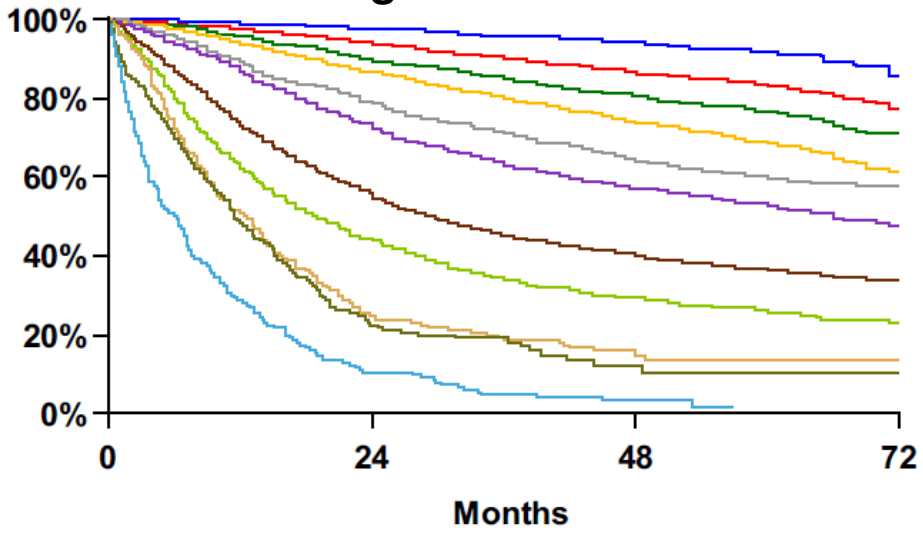
Contents

- **Immunotherapy in NSCLC**
  : immune checkpoint inhibitors
  anti-PD-1, anti-PD-L1, anti-CTLA4

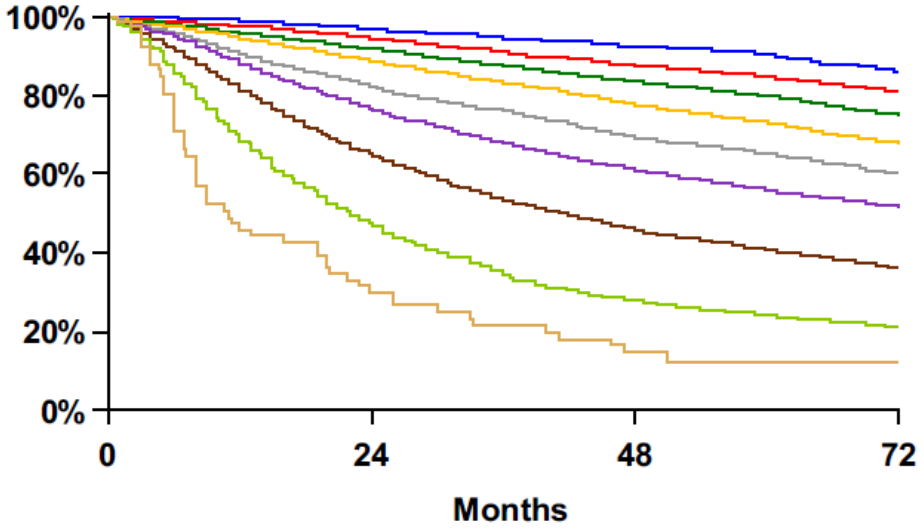
- **Recent clinical update**
  : phase II/III
  : subsequent, first-line, stage III Tx

Overall survival: TNM 8th edition (1999-2010)

Clinical stage



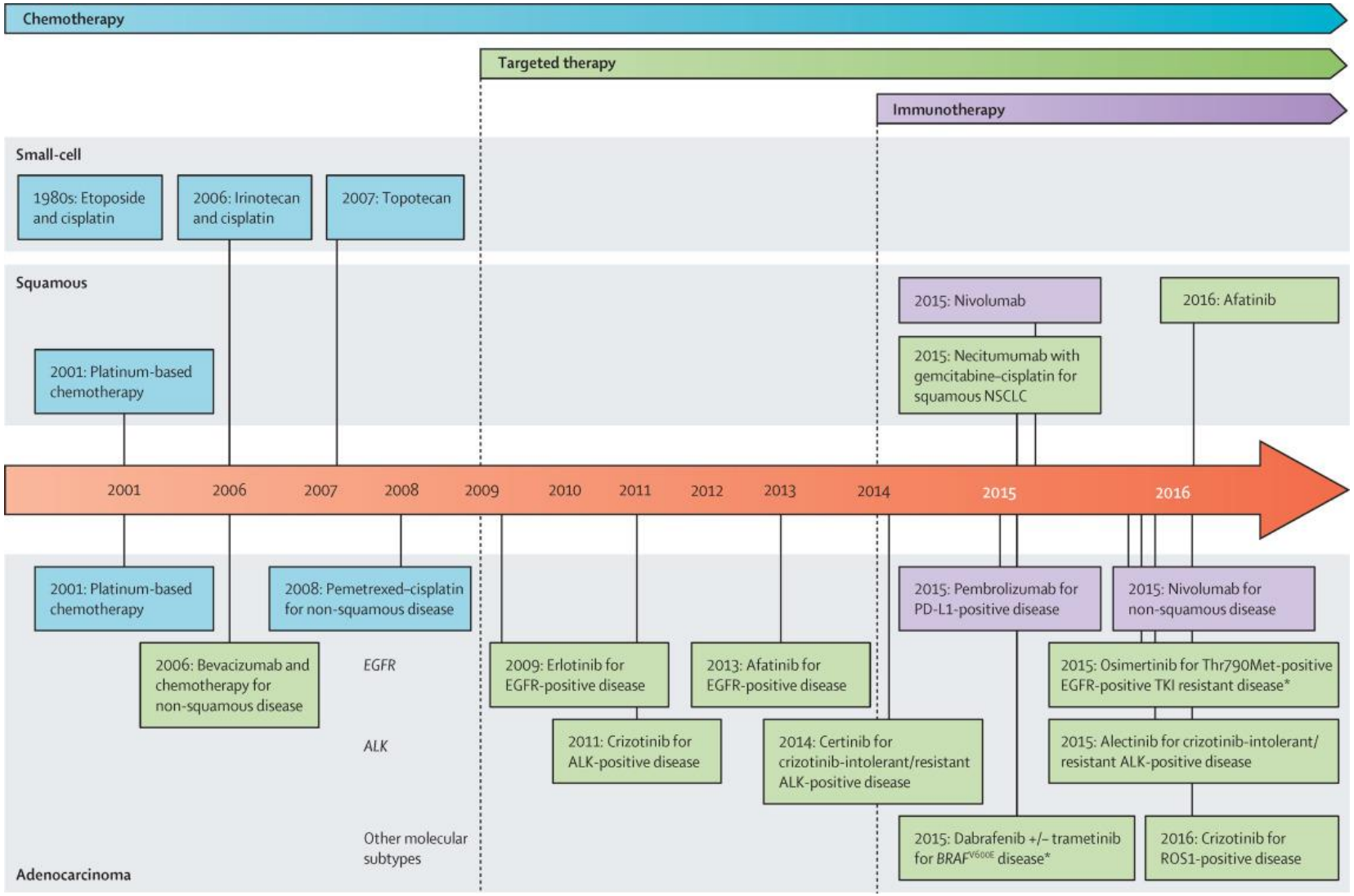
Pathologic stage



5-year survival

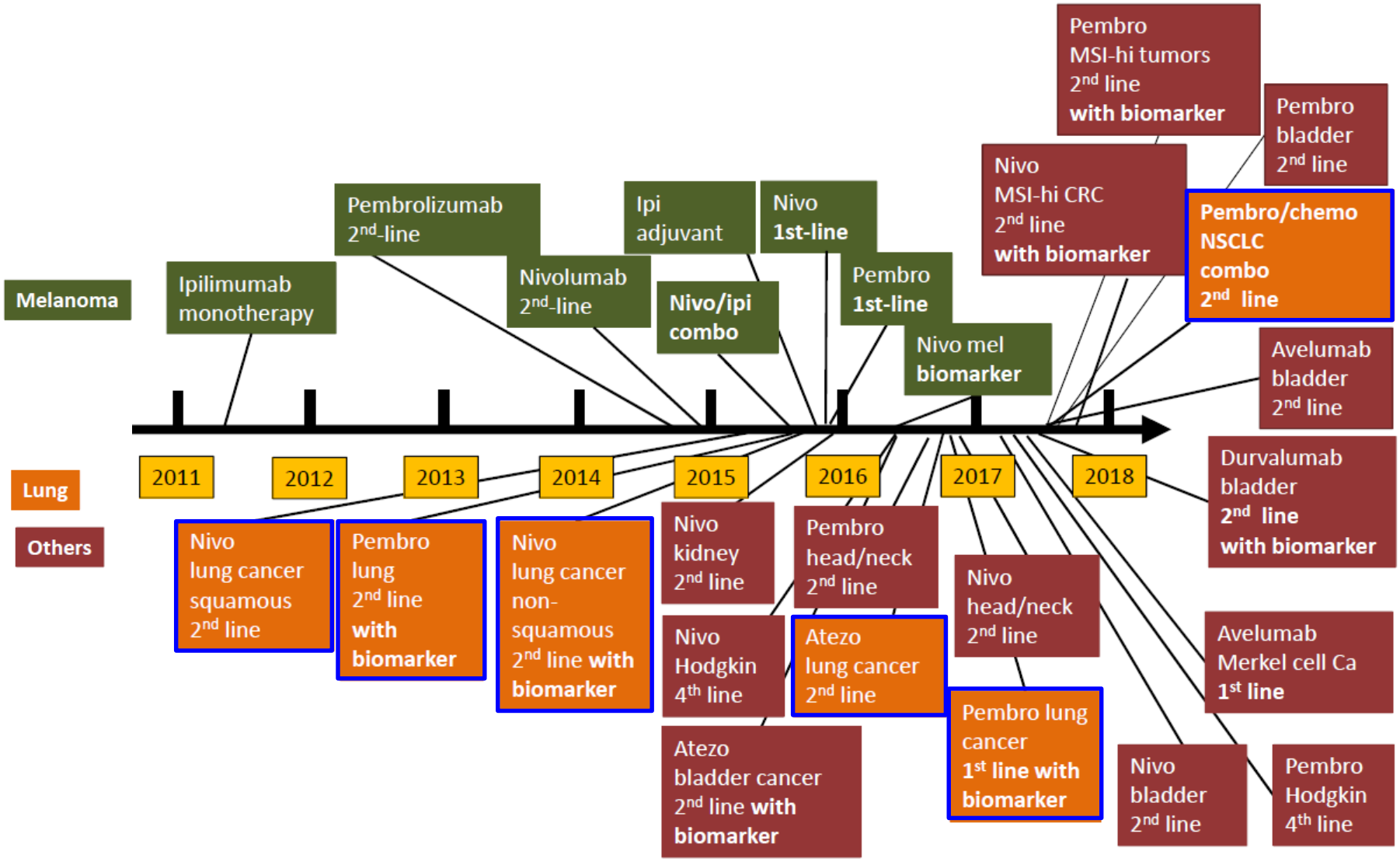
Stage	Clinical	Pathologic
IA1	92%	90%
IA2	83%	85%
IA3	77%	80%
IB	68%	73%
IIA	60%	65%
IIB	53%	56%
IIIA	36%	41%
IIIB	26%	24%
IIIC	13%	12%
IVA	10%	
IVB	0%	

Timeline of key therapeutic advances for advanced lung cancer



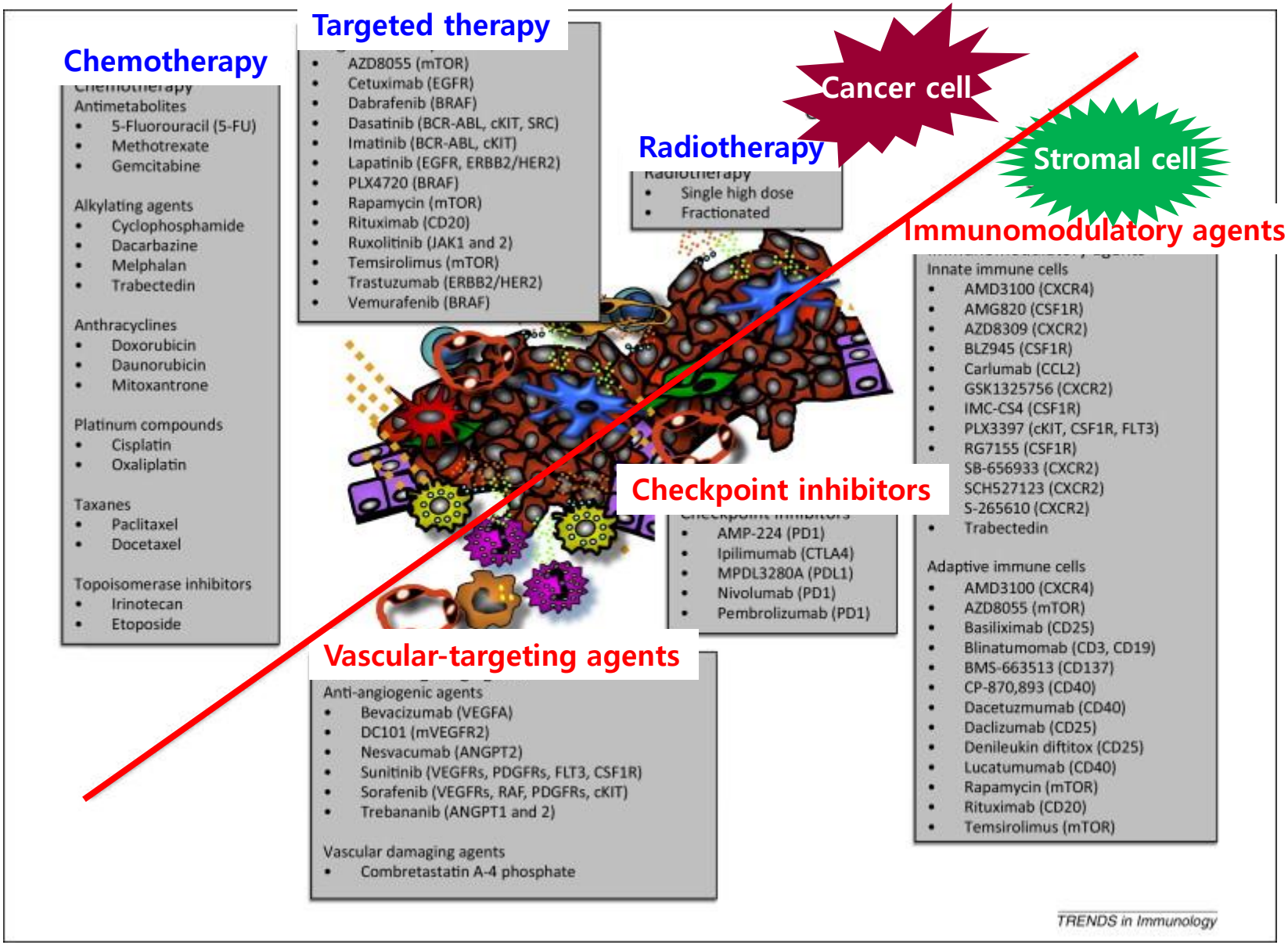
Lancet Oncol 2016;17:e347–62.

Immune checkpoint inhibitors: FDA approvals



Topalian S. ESMO 2017

Categories of anticancer therapies and their targets



Trends Immunol 2015;36:198-216.

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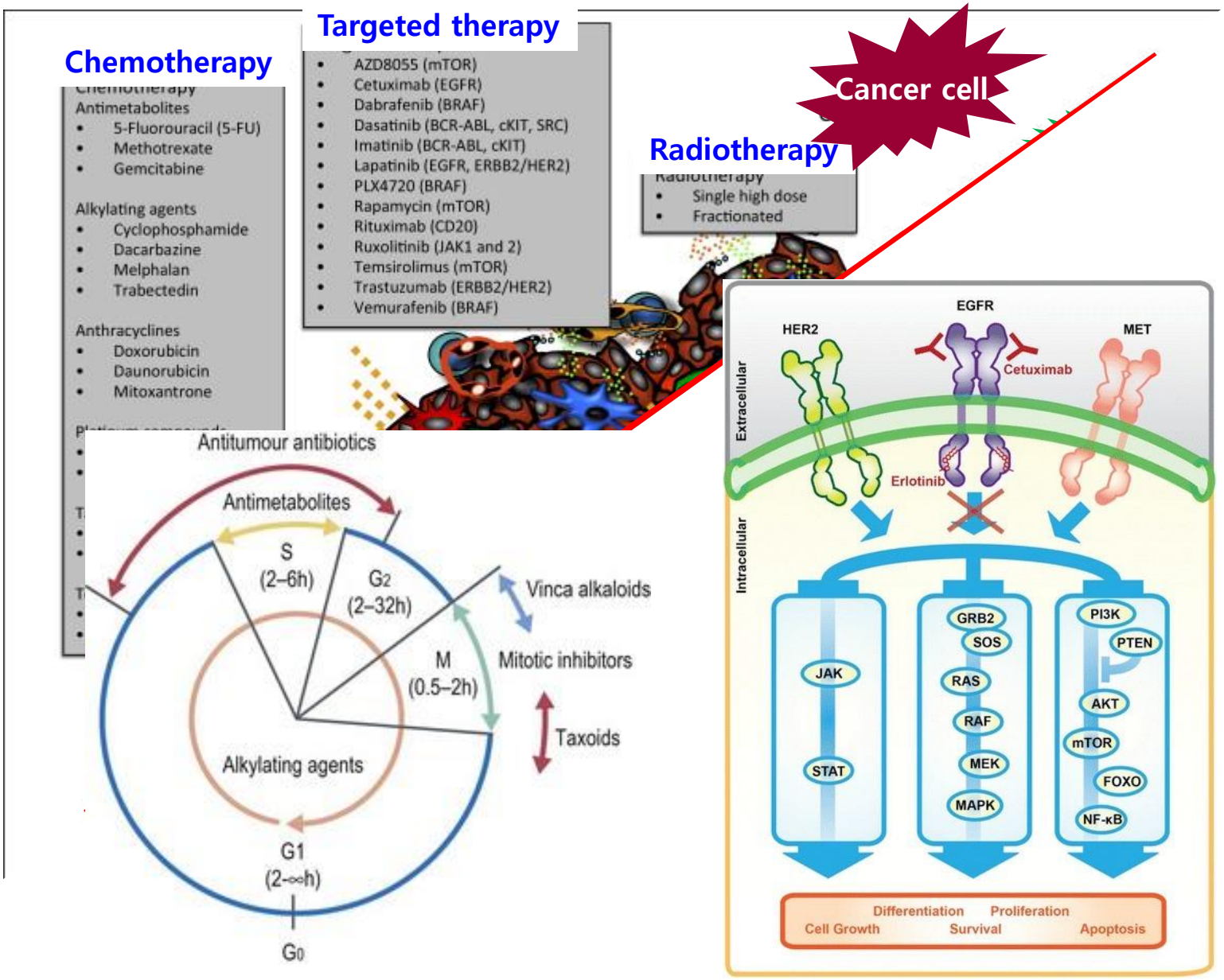

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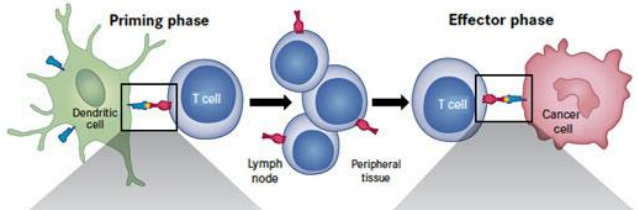
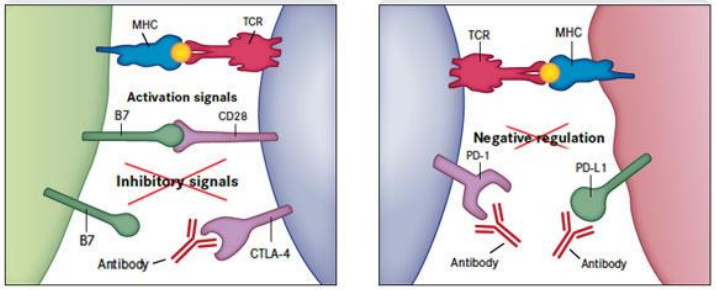
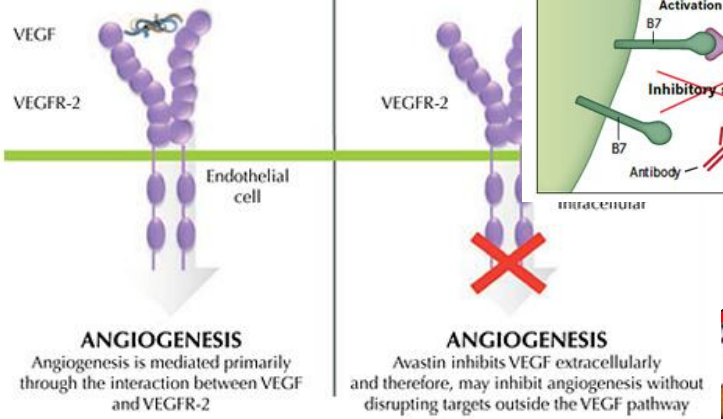






Stromal cell

Immunomodulatory agents

Innate immune cells
- AMD3100 (CXCR4)
- AMG820 (CSF1R)
- AZD8309 (CXCR2)
- BLZ945 (CSF1R)
- Carlumab (CCL2)
- GSK1325756 (CXCR2)
- IMC-CS4 (CSF1R)
- PLX3397 (cKIT, CSF1R, FLT3)
- RG7155 (CSF1R)
- SB-656933 (CXCR2)
- SCH527123 (CXCR2)
- S-265610 (CXCR2)
- Trabectedin

Adaptive immune cells
- AMD3100 (CXCR4)
- AZD8055 (mTOR)
- Basiliximab (CD25)
- Blinatumomab (CD3, CD19)
- BMS-663513 (CD137)
- CP-870,893 (CD40)
- Dacetuzmumab (CD40)
- Daclizumab (CD25)
- Denileukin diftitox (CD25)
- Lucatumumab (CD40)
- Rapamycin (mTOR)
- Rituximab (CD20)
- Temsirolimus (mTOR)

Checkpoint inhibitors

- AMP-224 (PD1)
- Ipilimumab (CTLA4)
- MPDL3280A (PDL1)
- Nivolumab (PD1)
- Pembrolizumab (PD1)

Vascular-targeting agents

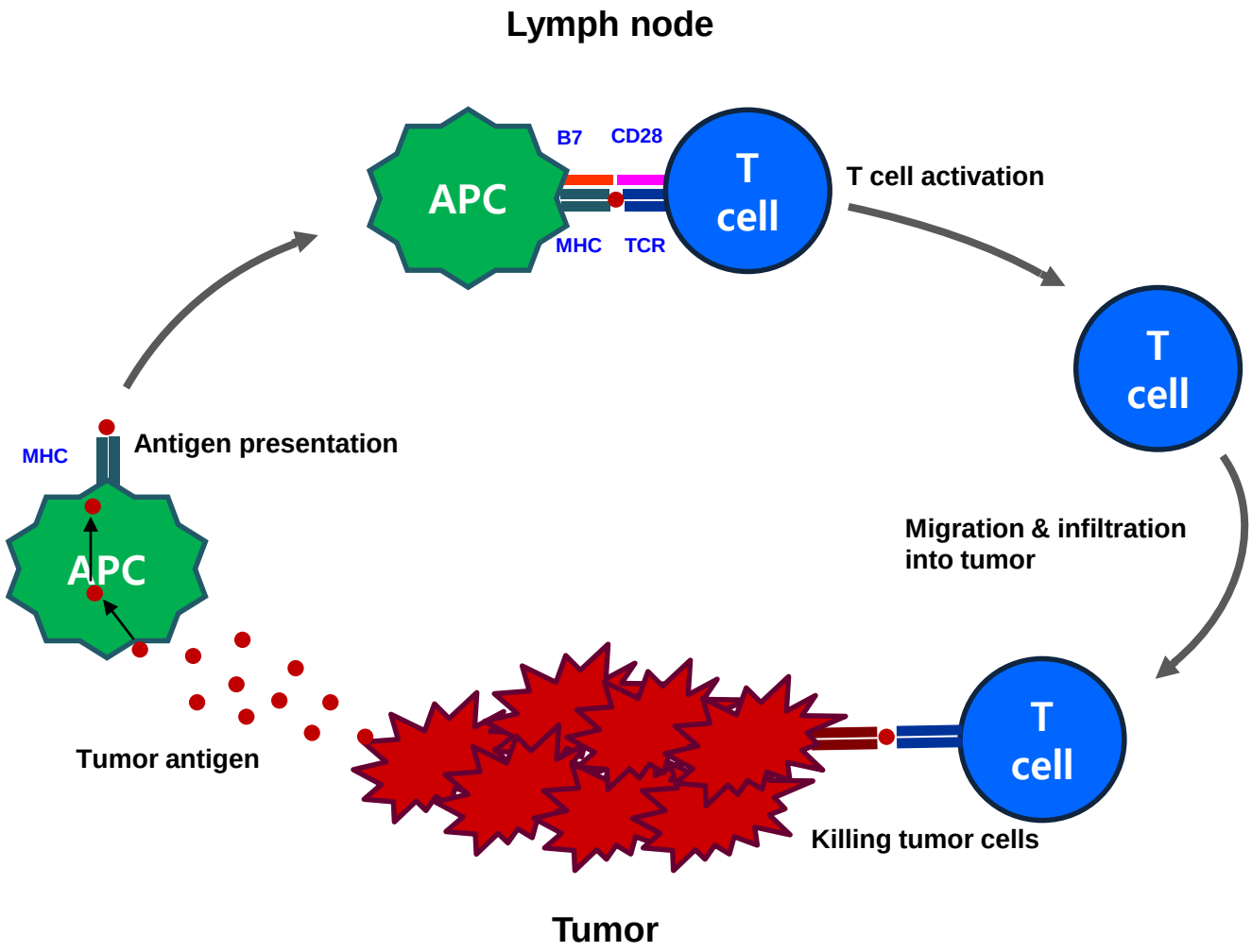
Anti-angiogenic agents
- Bevacizumab (VEGFA)
- DC101 (mVEGFR2)
- Nesvacumab (ANGPT2)
- Sunitinib (VEGFRs, PDGFRs, FLT3, CSF1R)
- Sorafenib (VEGFRs, RAF, PDGFRs, cKIT)
- Trebananib (ANGPT1 and 2)

Vascular damaging agents
- Combretastatin A-4 phosphate

TRENDS in Immunology

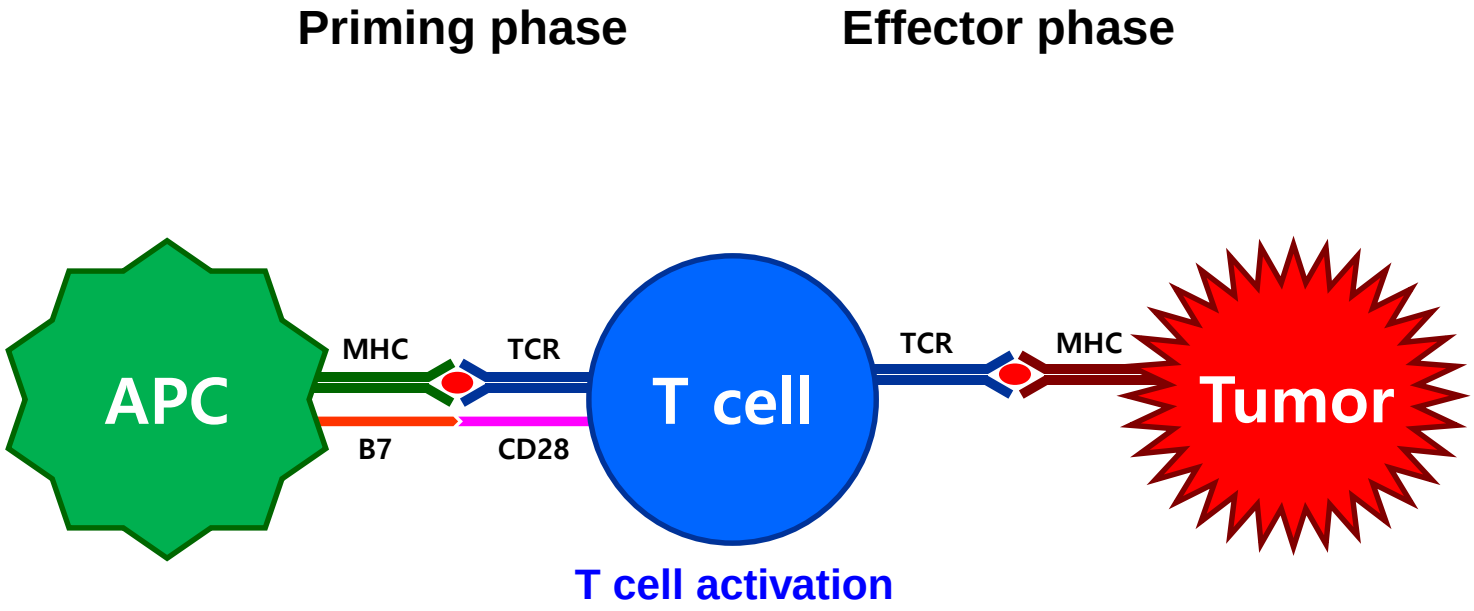
Trends Immunol 2015;36:198-216.

Cancer-immunity cycle



Jung CY, Antonia SJ. Tuberc Respir Dis 2018;81:29-41.

Immune system activation & checkpoint inhibitors



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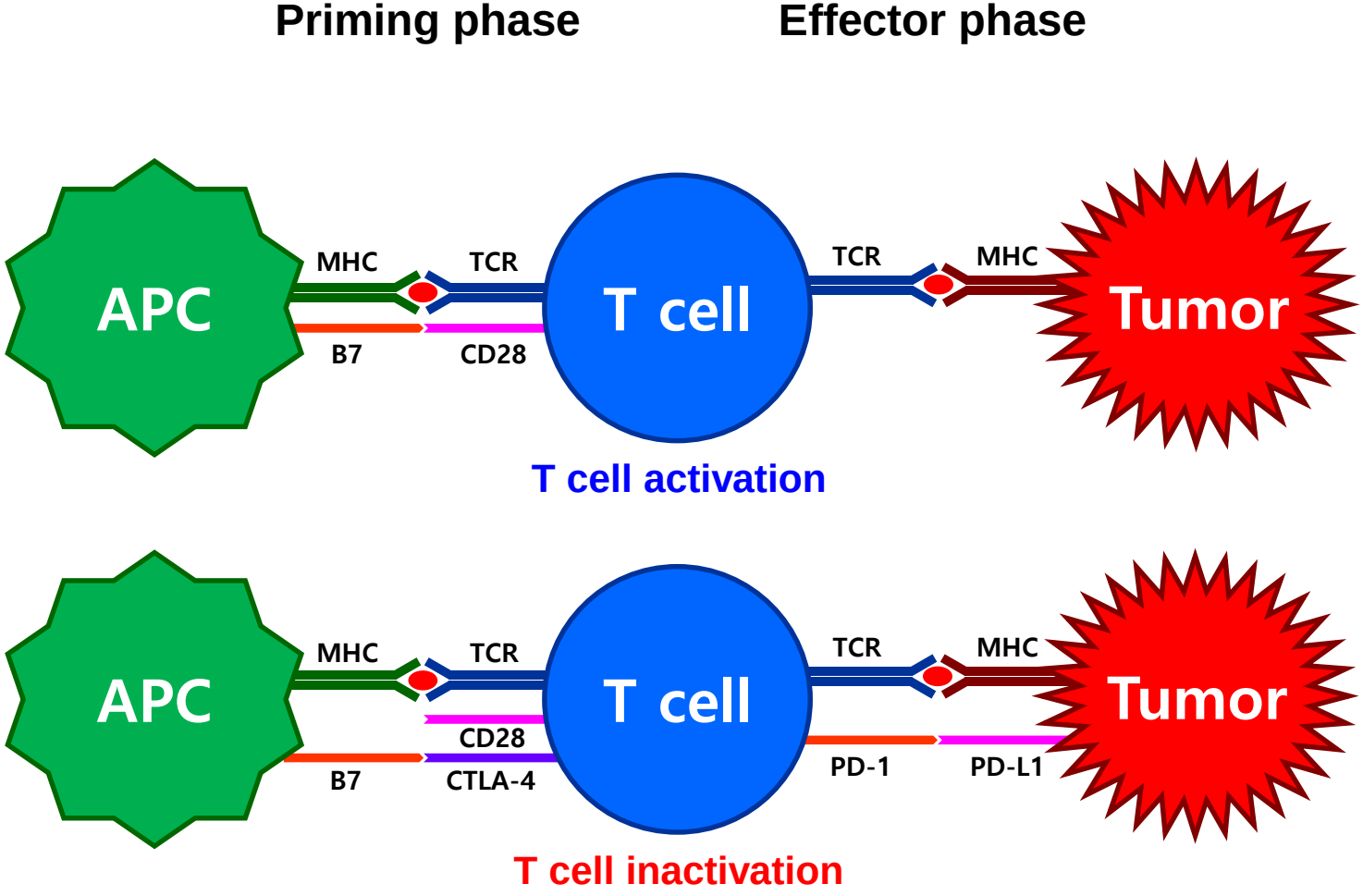

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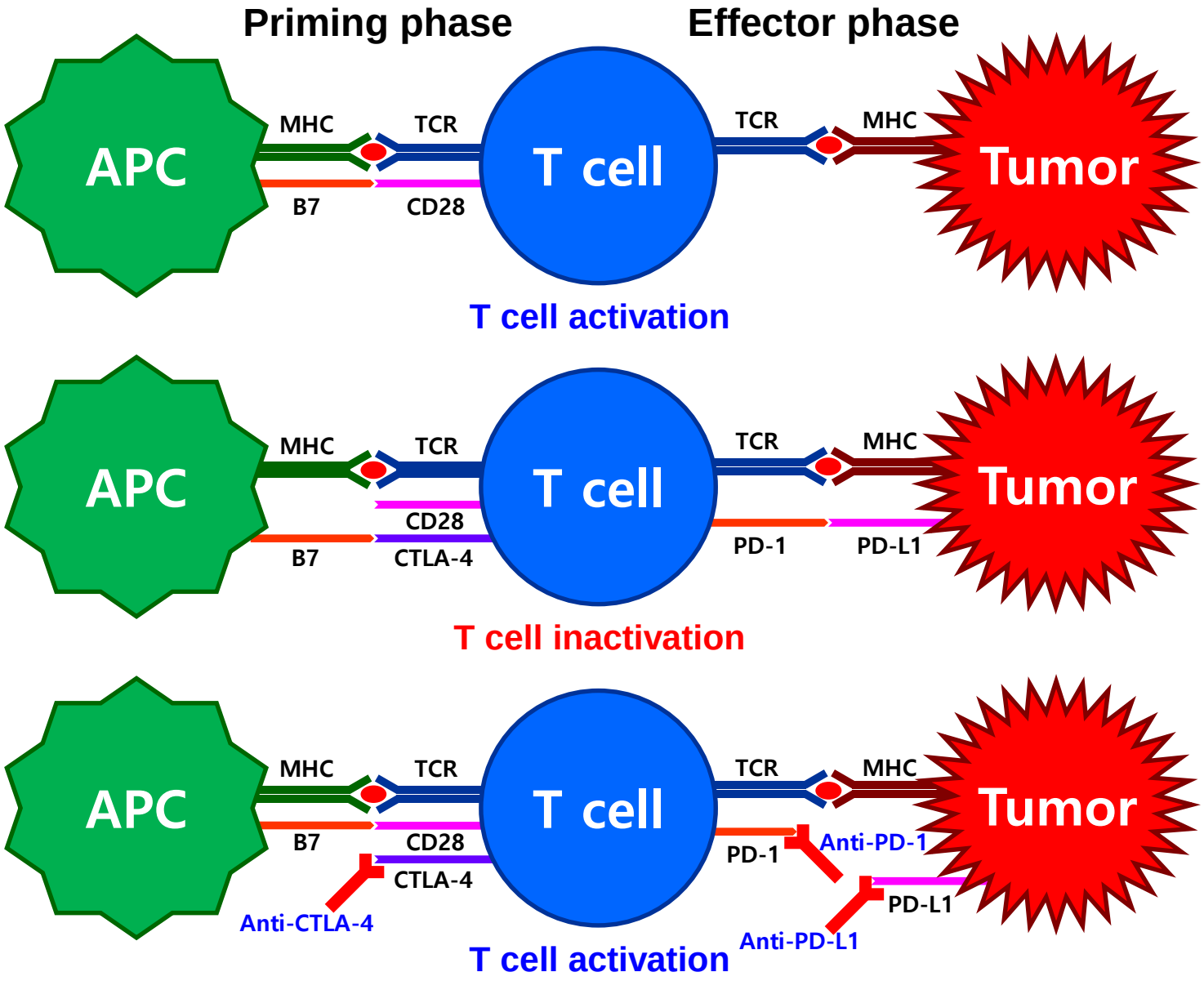
Immune system activation & checkpoint inhibitors



Jung CY, Antonia SJ. Tuberc Respir Dis 2018;81:29-41.

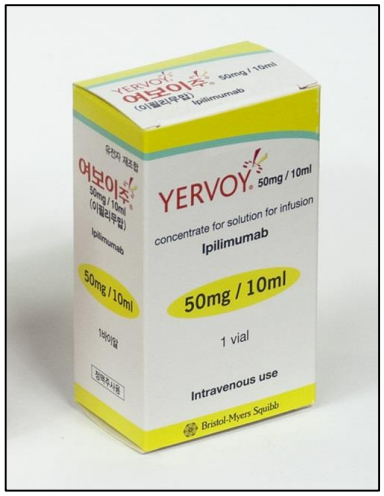
Immune checkpoint inhibitors

Anti-PD-1

Nivolumab

Pembrolizumab

Anti-CTLA-4



Ipilimumab

Anti-PD-L1

Atezolizumab

Durvalumab

Avelumab

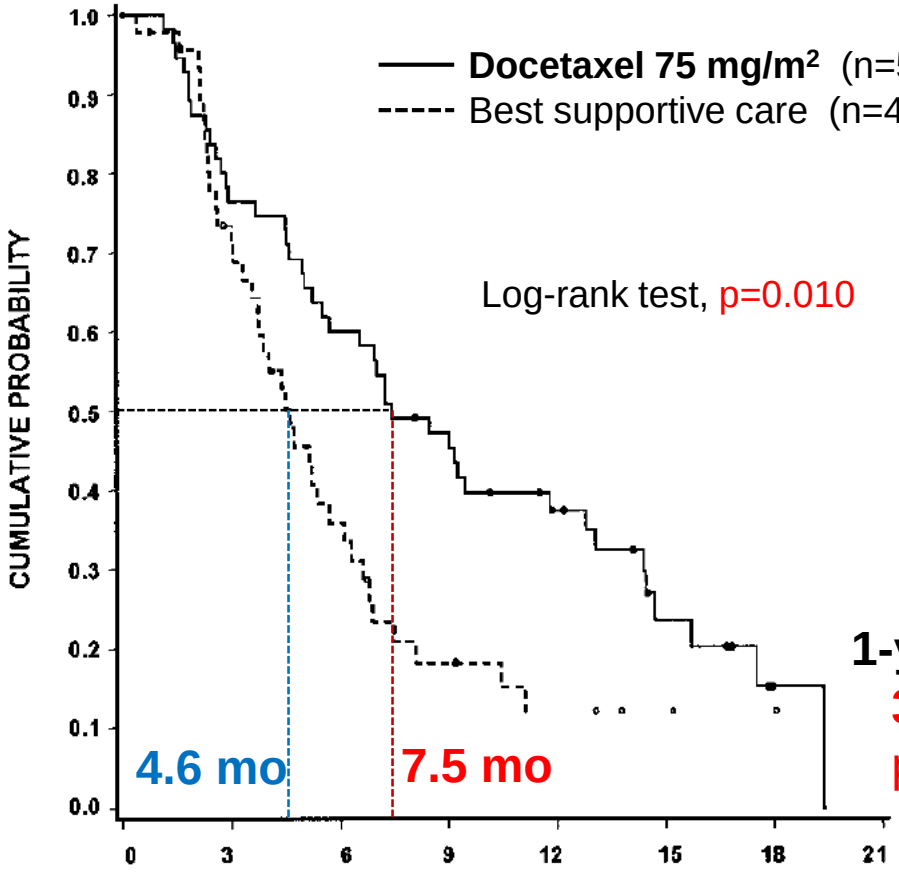
Subsequent treatment

Monotherapy vs. Docetaxel

Standard of care: ≥ 2L chemotherapy for advanced NSCLC

Docetaxel vs. best supportive care

Overall survival



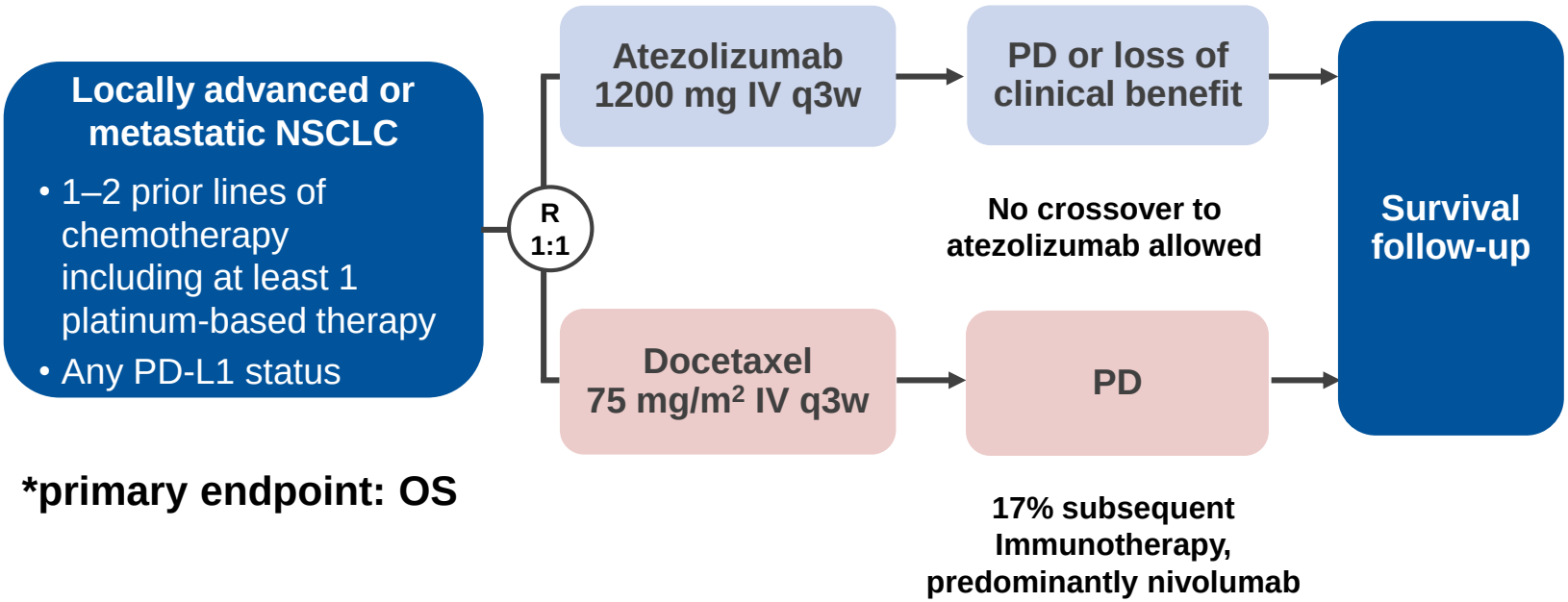
1-yr survival:
37% vs. **12%**
p=0.003

ORR: 7.1%

Shepherd FA, et al. J Clin Oncol 2000;18:2095-103.

Atezolizumab: phase III, 2L/3L NSCLC
OAK

Study design



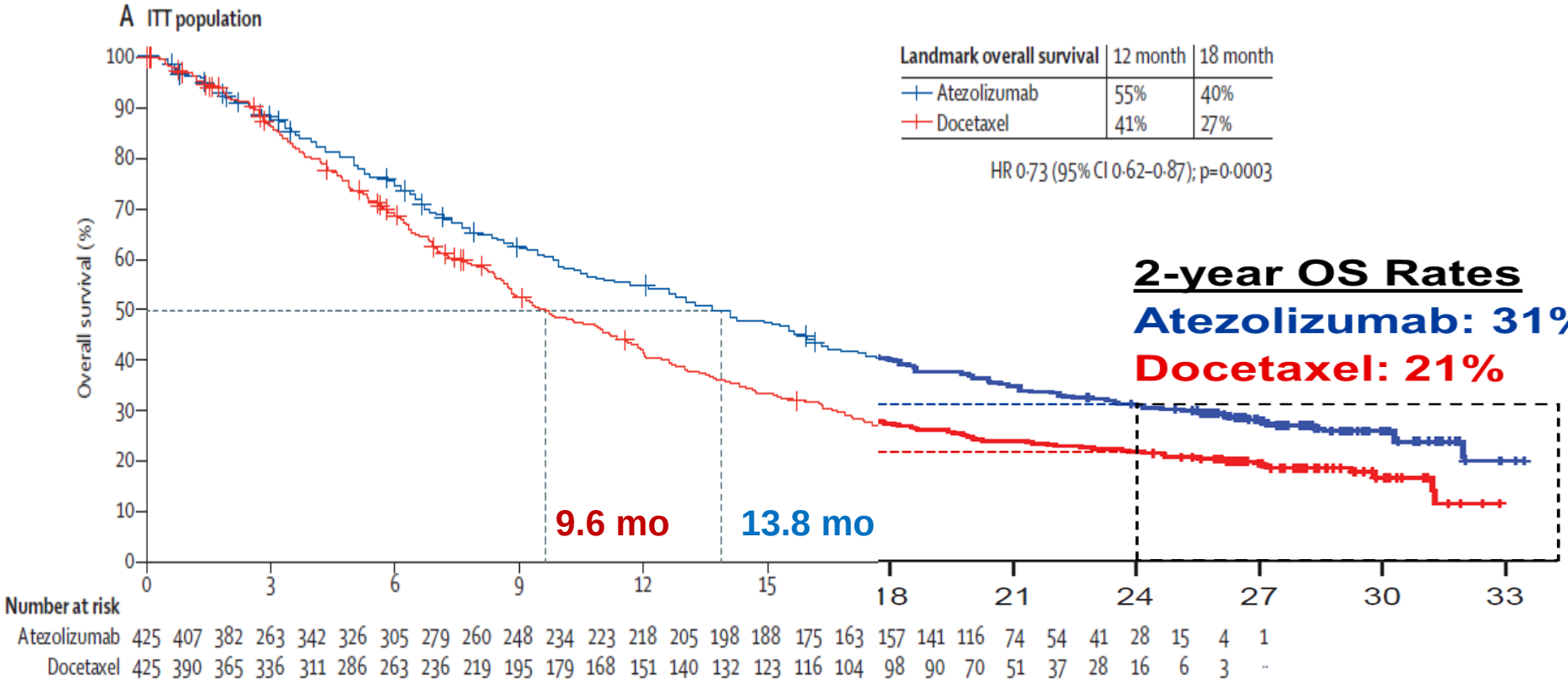
***primary endpoint: OS**

Rittmeyer A, et al. Lancet 2017;389:255–65.

Atezolizumab: phase III, 2L/3L NSCLC

OAK

OS (primary endpoint)



ORR: 14% vs. 13%

WCLC 2017

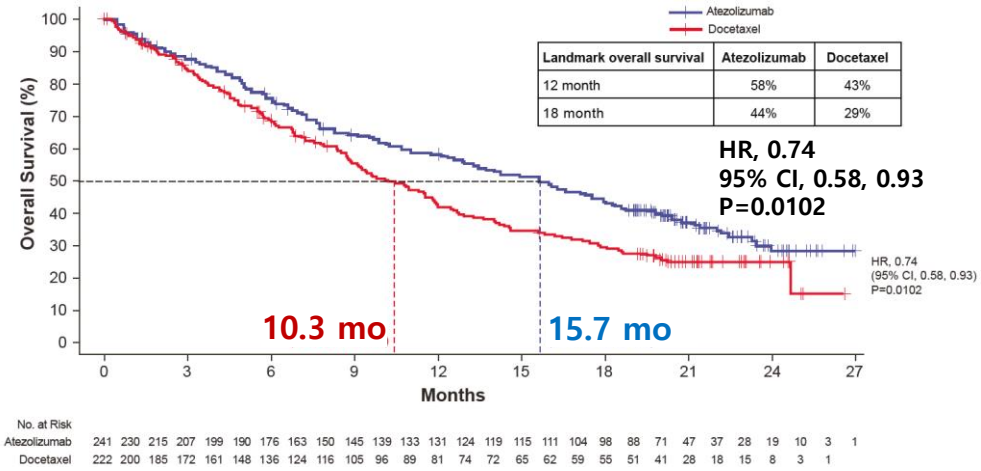
Rittmeyer A, et al. Lancet 2017;389:255–65.

Atezolizumab: phase III, 2L/3L NSCLC

OAK

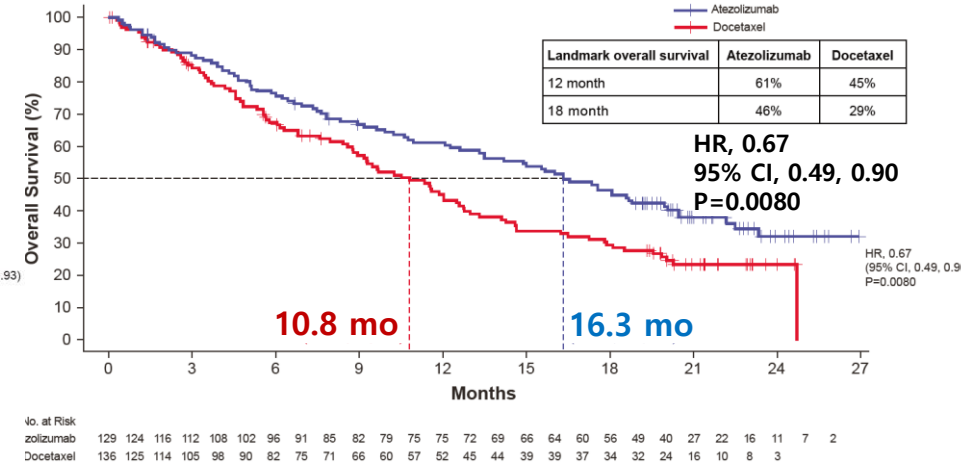
OS by PD-L1 expression

TC1/2/3 or IC1/2/3 (Co-primary endpoint)



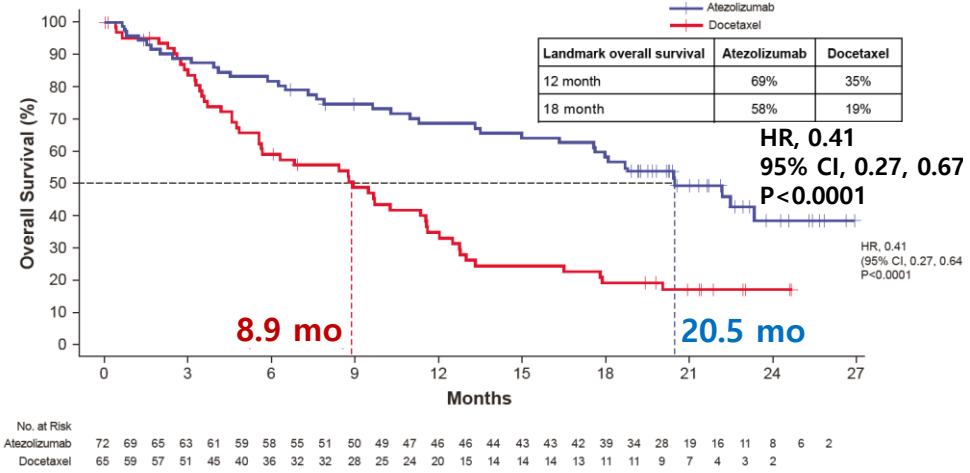
Landmark overall survival	Atezolizumab	Docetaxel
12 month	58%	43%
18 month	44%	29%

TC2/3 or IC2/3



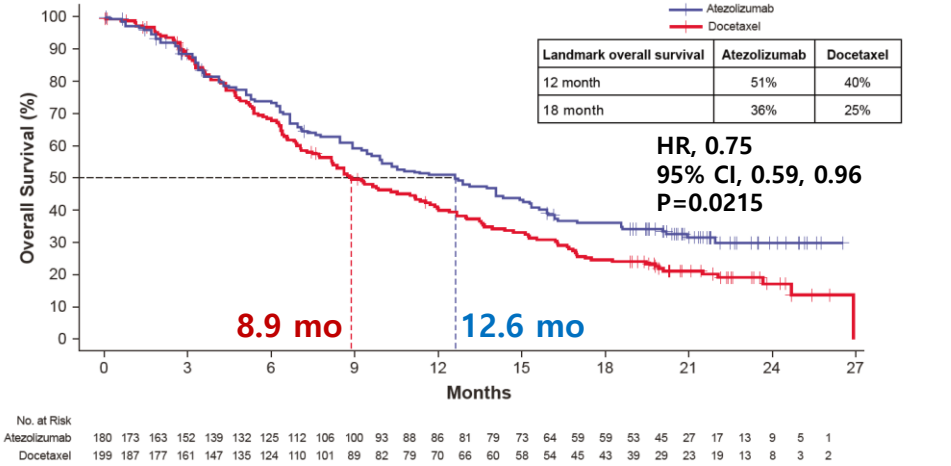
Landmark overall survival	Atezolizumab	Docetaxel
12 month	61%	45%
18 month	46%	29%

TC3 or IC3



Landmark overall survival	Atezolizumab	Docetaxel
12 month	69%	35%
18 month	58%	19%

TC0 and IC0



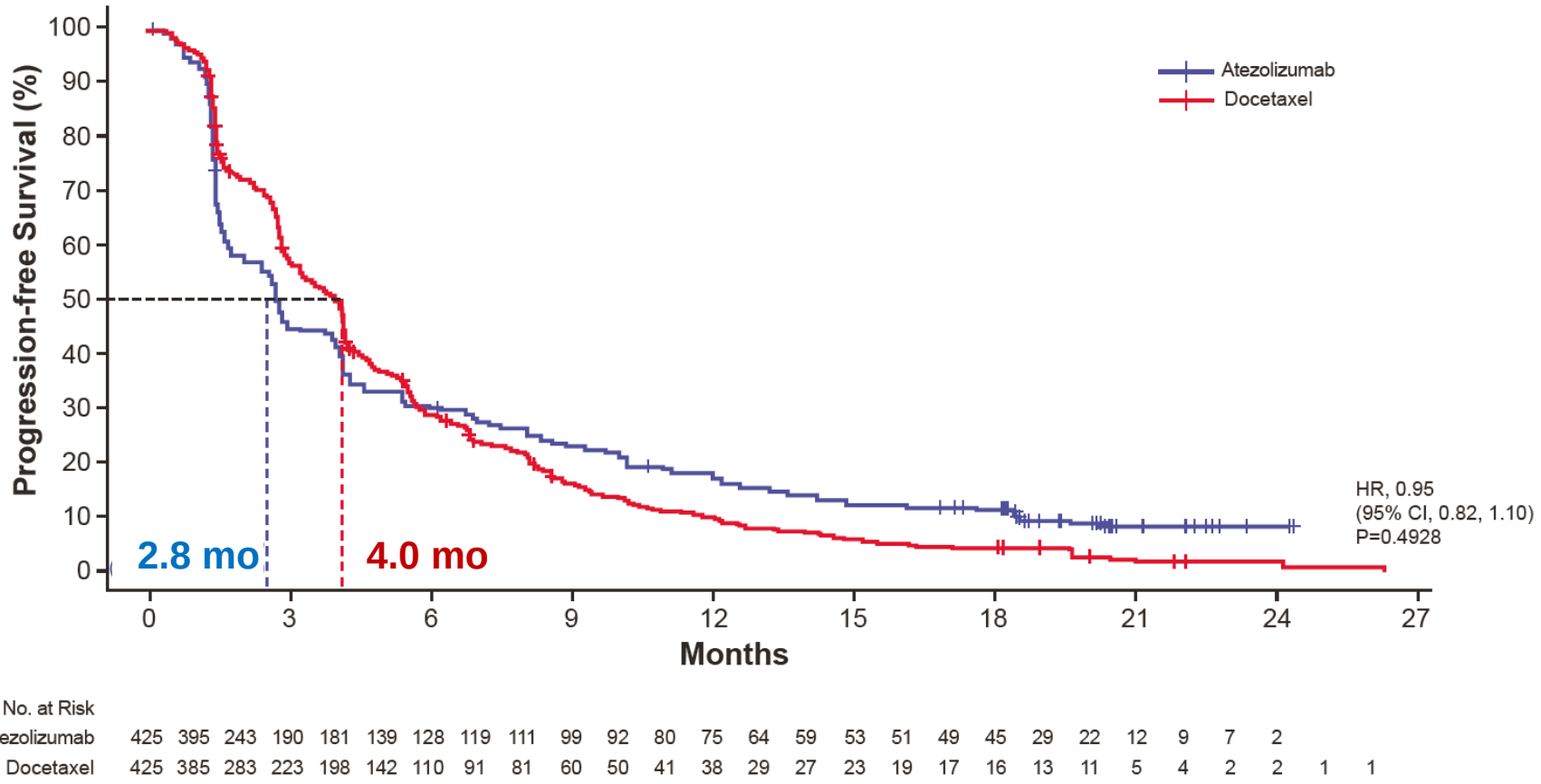
Landmark overall survival	Atezolizumab	Docetaxel
12 month	51%	40%
18 month	36%	25%

Rittmeyer A, et al. Lancet 2017;389:255–65.

Atezolizumab: phase III, 2L/3L NSCLC

OAK

PFS



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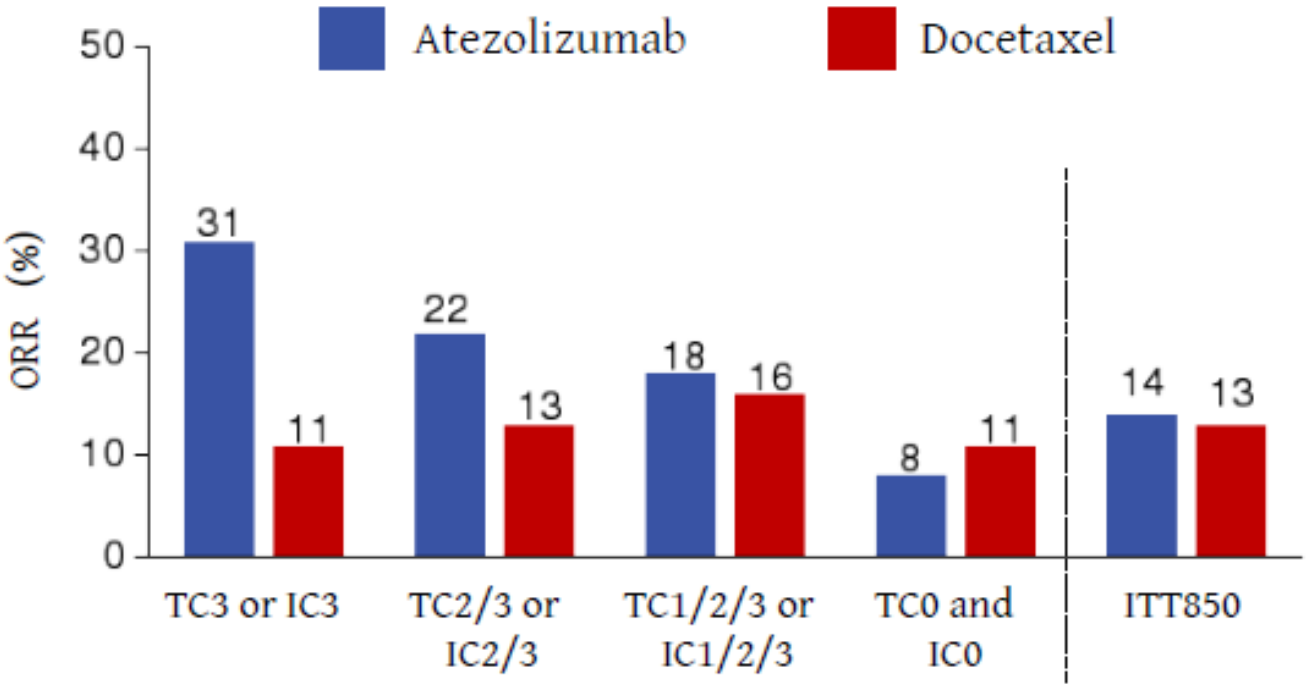
Atezolizumab: phase III, 2L/3L NSCLC
OAK

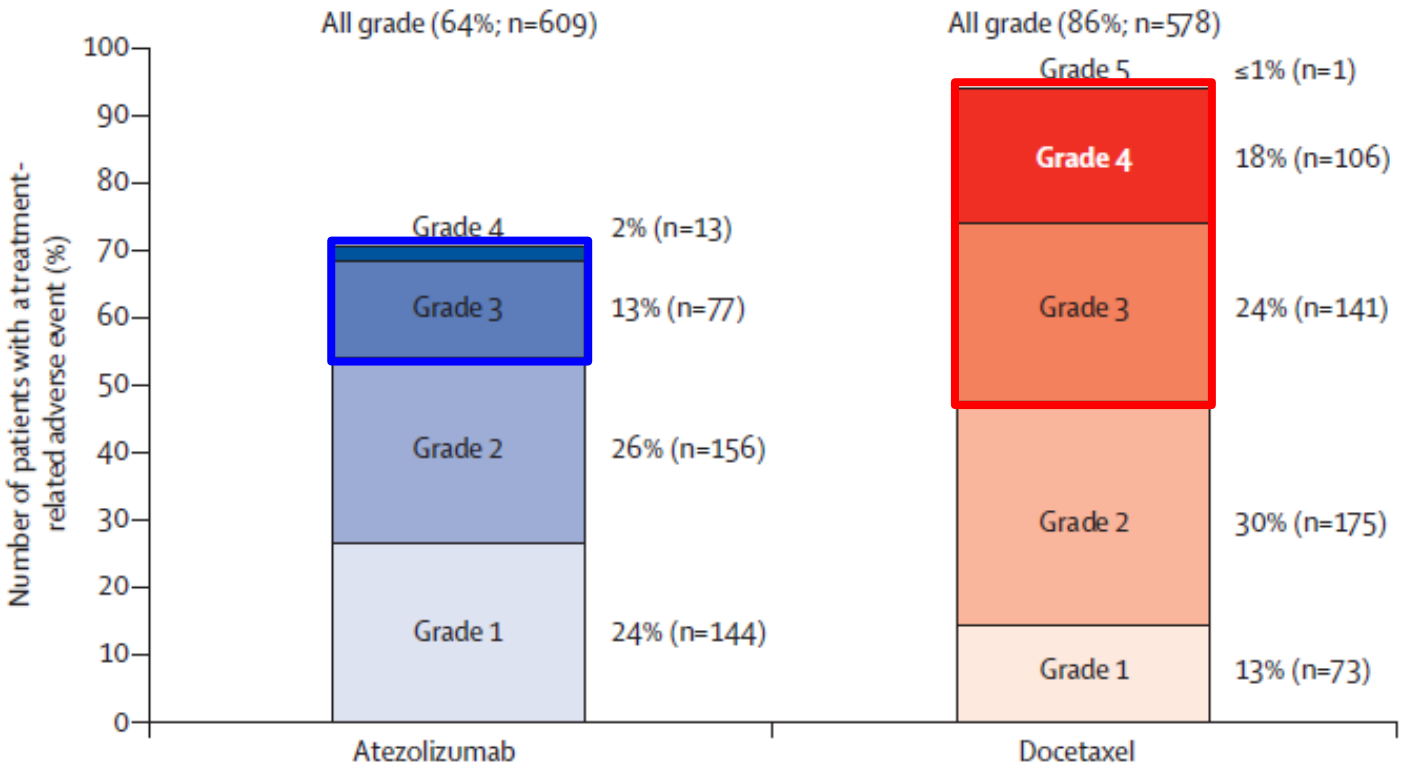
Objective response rate



Rittmeyer A, et al. Lancet 2017;389:255–65.

Atezolizumab: phase III, 2L/3L NSCLC
OAK

Treatment-related AEs



Rittmeyer A, et al. Lancet 2017;389:255–65.

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

Study design

- NSCLC patients (Stage IIIB/IV)
- ≥2 prior systemic treatment regimens including 1 platinum-based CT
- Recent (≤3 months) tumour biopsy and archived tumour tissue block for PD-L1 testing

N=1980 screened

Durvalumab i.v. 10 mg/kg q2w up to 12 months

Cohort 1 (n=111)
EGFR mutation/*ALK* alteration
PD-L1 high (≥25% tumour cells)
And PD-L1 low (<25%)

Cohort 2 (n=265)
EGFR/*ALK* wild-type
PD-L1 high (≥25% tumour cells)
and PD-L1 low (<25%)

Cohort 3 (n=68)
EGFR/*ALK* wild-type
PD-L1 high (≥90% tumour cells)

Cohorts were independent;
Cohorts 2 and 3 enrolled sequentially

Primary endpoint:
- **ORR**

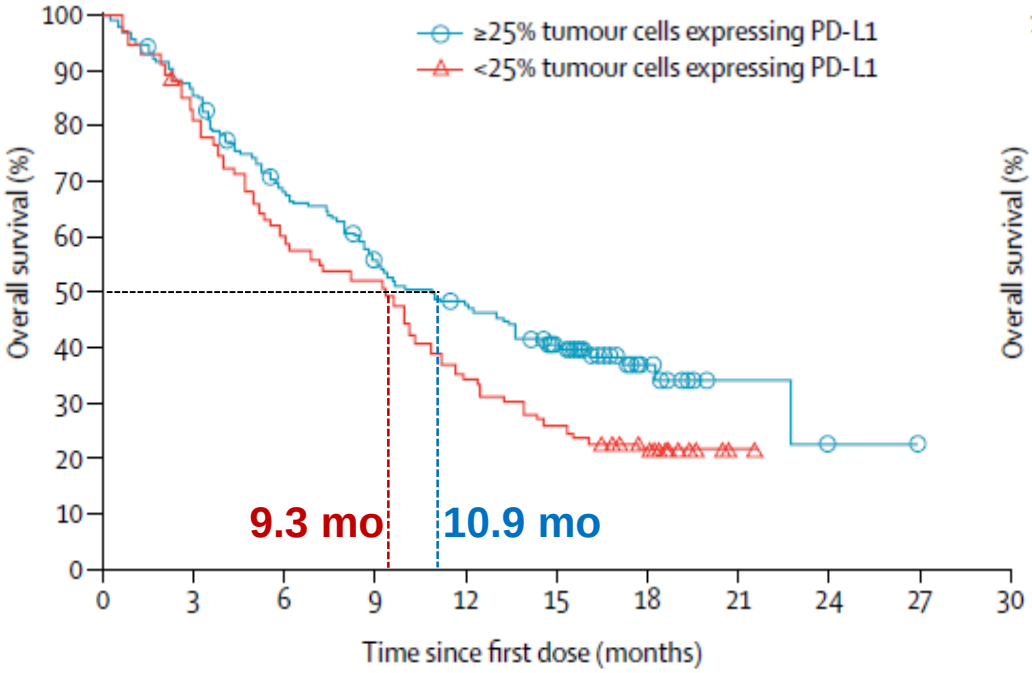
Secondary endpoints:
- DoR, PFS, DCR, OS
- Safety
- PK
- Immunogenicity

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

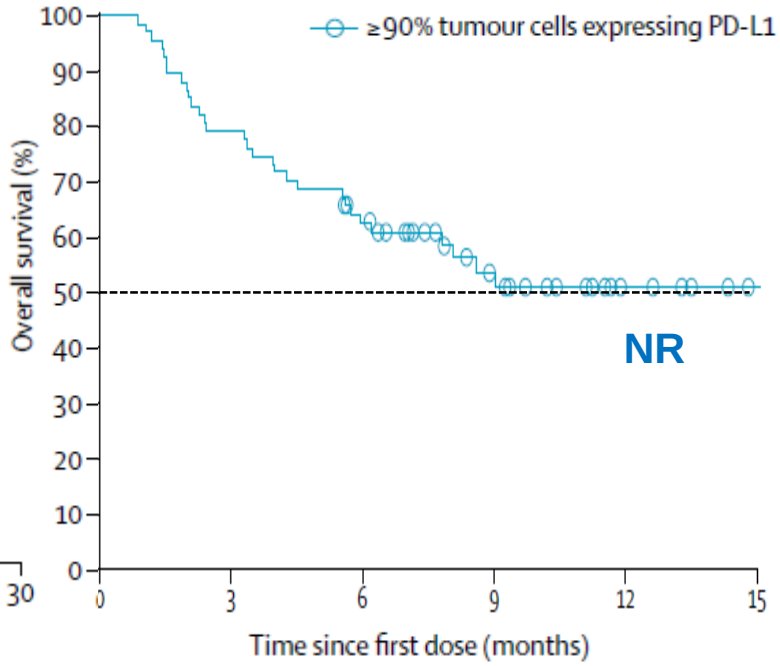
OS (EGFR-/ALK-)

Cohort 2
(PD-L1 < 25% vs ≥ 25%)



ORR: 7.5% vs. 16.4%

Cohort 3
(PD-L1 ≥ 90%)



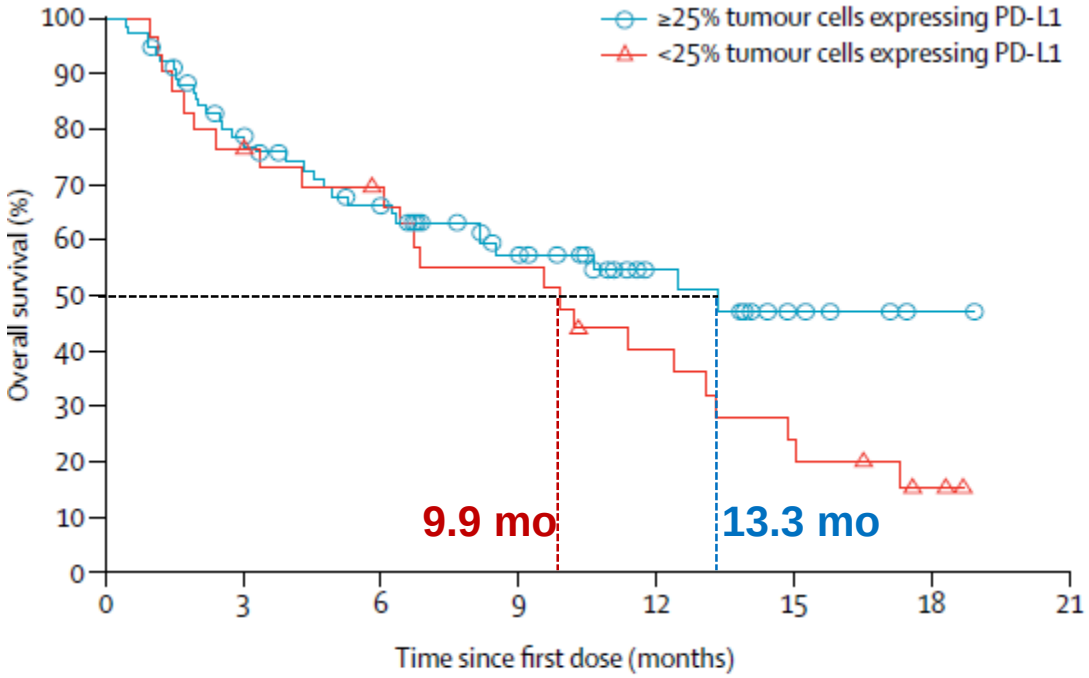
ORR: 30.9%

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

OS (EGFR+/ALK+)

Cohort 1
(PD-L1 < 25% vs ≥ 25%)



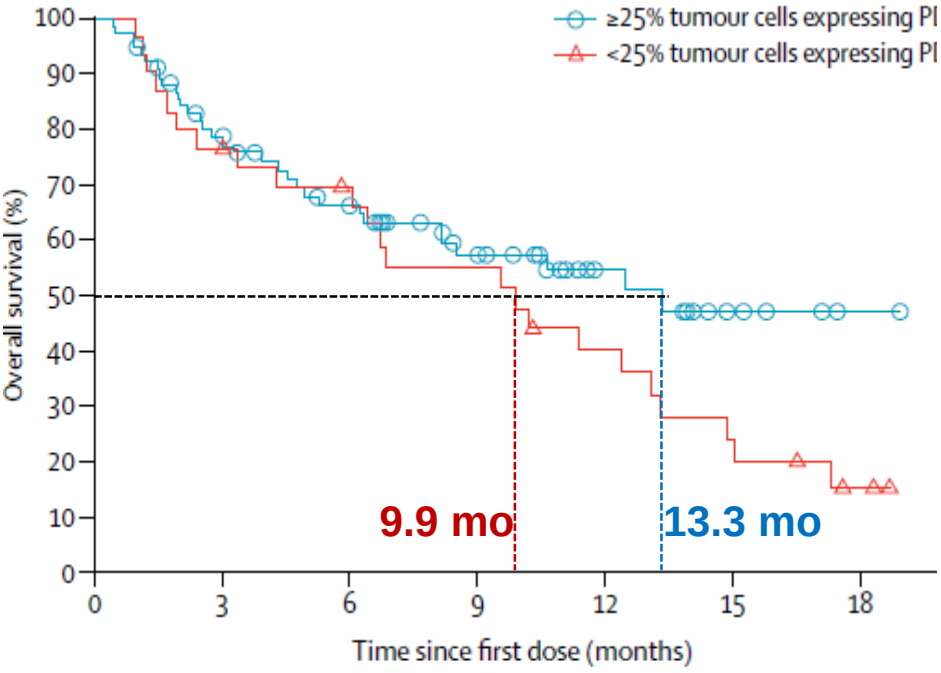
ORR: 3.6% vs. 12.2%

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

OS (EGFR+/ALK+)

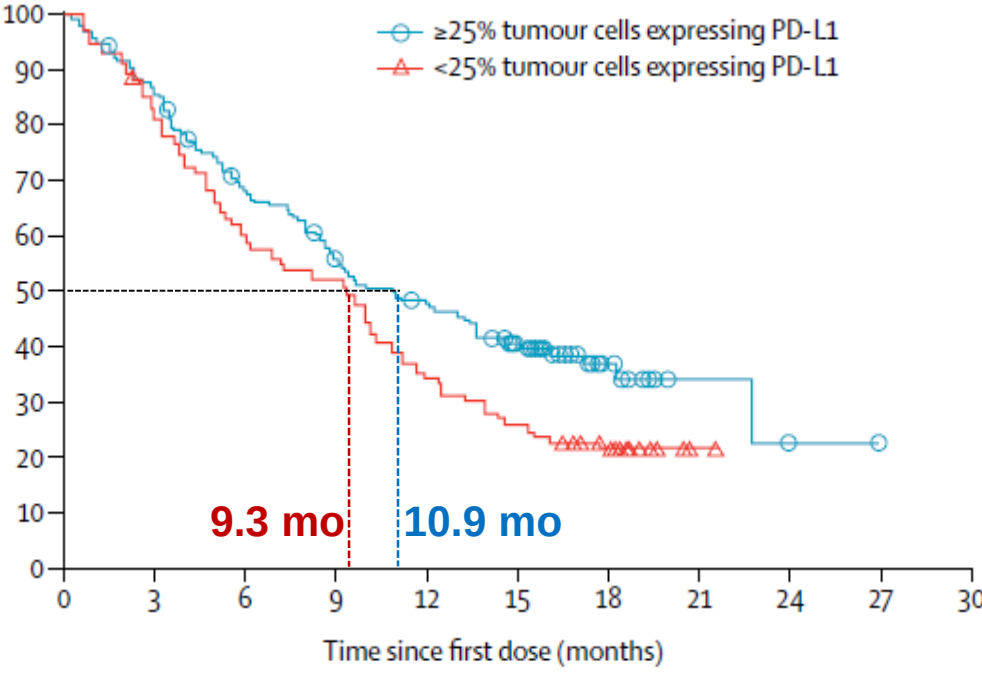
Cohort 1
(PD-L1 < 25% vs ≥ 25%)



ORR: 3.6% vs. 12.2%

OS (EGFR-/ALK-)

Cohort 2
(PD-L1 < 25% vs ≥ 25%)



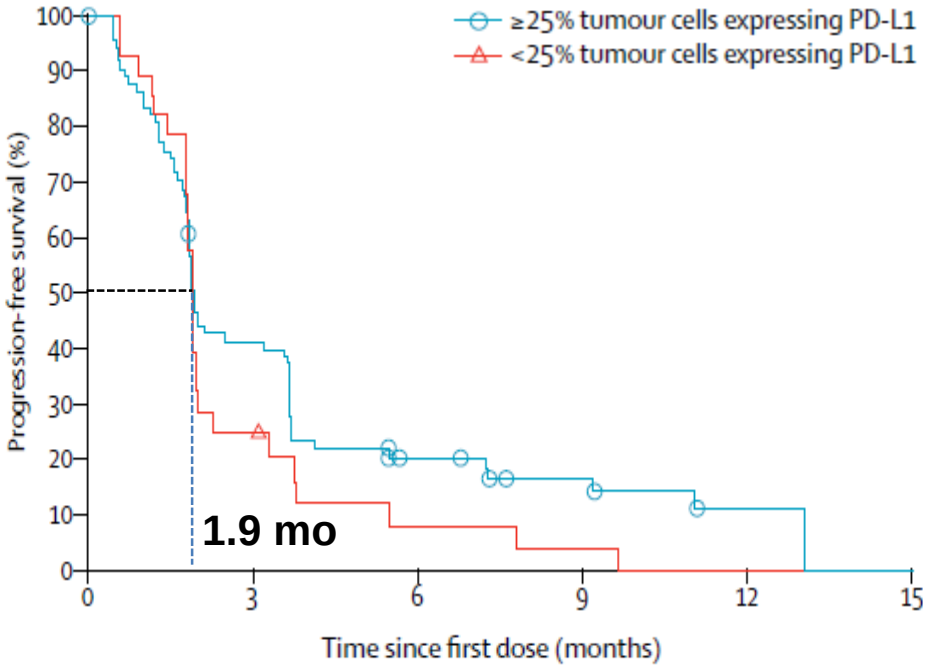
ORR: 7.5% vs. 16.4%

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

PFS (EGFR+/ALK+)

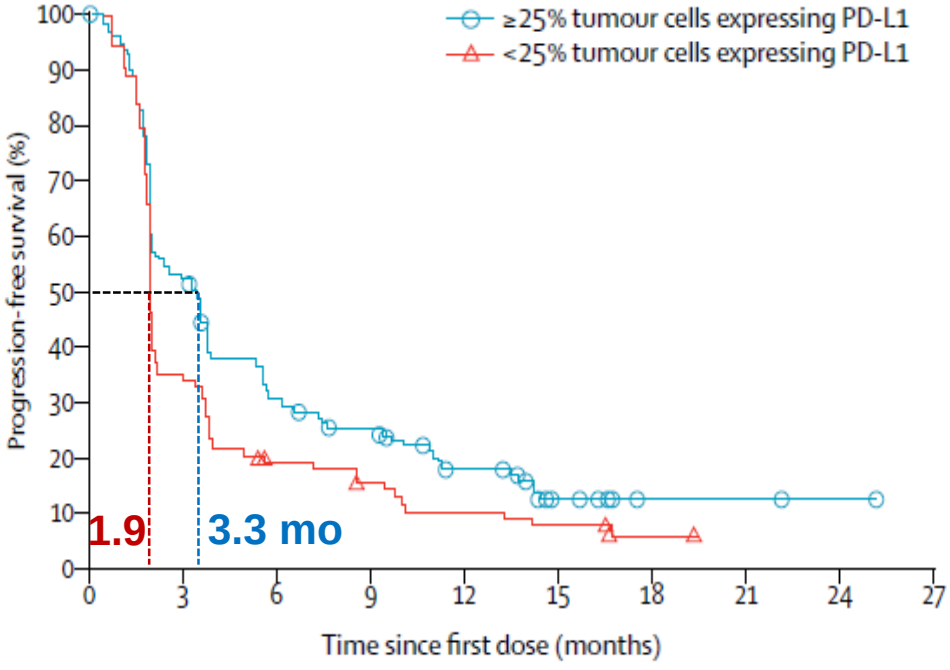
Cohort 1
(PD-L1 < 25% vs ≥ 25%)



ORR: 3.6% vs. 12.2%

PFS (EGFR-/ALK-)

Cohort 2
(PD-L1 < 25% vs ≥ 25%)



ORR: 7.5% vs. 16.4%

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Durvalumab: phase II, ≥ 3L NSCLC
ATLANTIC

Immune-mediated AEs

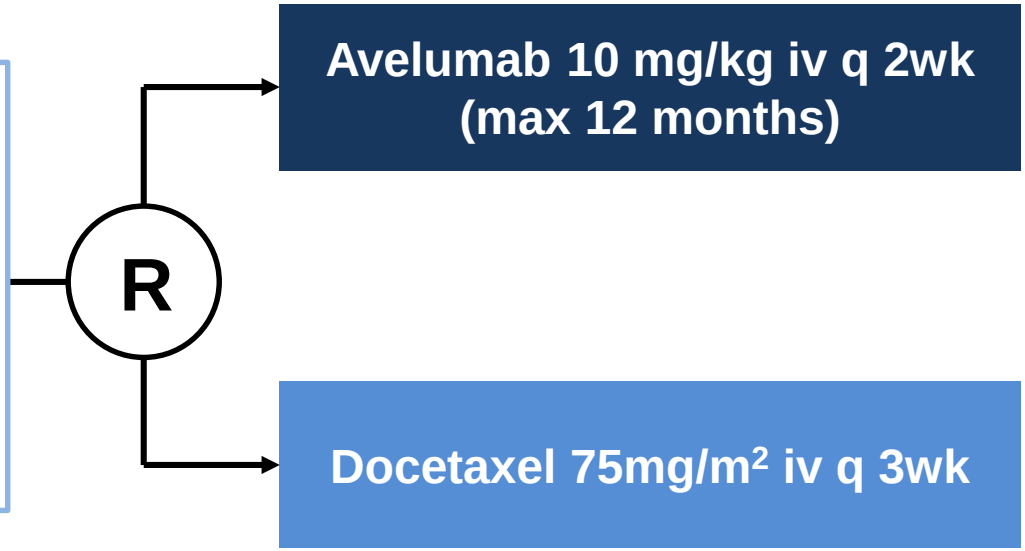
	Cohort 1, *EGFR+/ALK+* (n=111)		Cohort 2, *EGFR−/ALK−*† (n=265)		Cohort 3, *EGFR−/ALK−*† (≥90%‡; n=68)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Any event§	13 (12%)	1 (1%)	22 (8%)	5 (2%)	9 (13%)	5 (7%)
Adrenal insufficiency	0	0	1 (<1%)	1 (<1%)	0	0
Colitis	0	0	1 (<1%)	0	1 (1%)	0
Dermatitis	1 (1%)	0	2 (1%)	1 (<1%)	0	0
Diarrhoea	1 (1%)	0	1 (<1%)	0	0	1 (1%)
Hyperthyroidism	3 (3%)	0	4 (2%)	0	3 (4%)	0
Hypophysitis	0	0	0	0	0	1 (1%)
Hypothyroidism	11 (10%)	0	13 (5%)	0	8 (12%)	0
Pneumonitis	1 (1%)	1 (1%)	3 (1%)	2 (1%)	2 (3%)	0
Rash	0	0	1 (<1%)	0	1 (1%)	1 (1%)
Select hepatic events	0	0	0	1 (<1%)	0	2 (3%)

Garassino MC, et al. Lancet Oncol 2018 Mar 12 (Epub)

Avelumab: phase III, ≥ 2L NSCLC
JAVELIN Lung 200

Study design

- Stage IIIB/IV or recurrent NSCLC who have experienced disease progression
- ECOG 0-1
- PD-L1 test
- EGFR & ALK wild in Non SQ



N=750
Primary endpoint: OS

Avelumab: phase III, ≥ 2L NSCLC
JAVELIN Lung 200

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MERCK KGAA, DARMSTADT, GERMANY, AND PFIZER PROVIDE UPDATE ON PHASE III JAVELIN LUNG 200 TRIAL OF AVELUMAB MONOTHERAPY IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

February 15, 2018

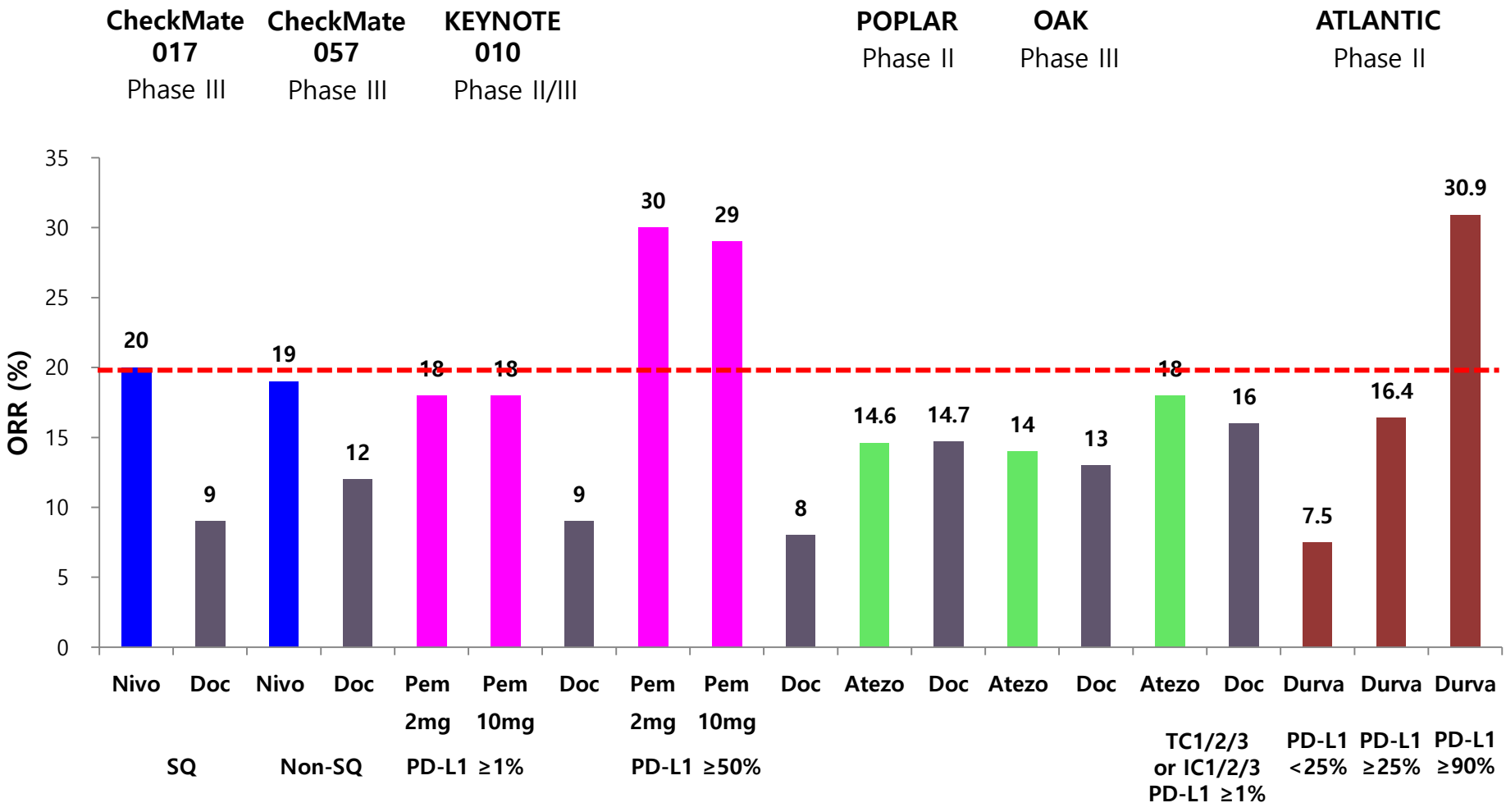
Avelumab: phase III, ≥ 2L NSCLC
JAVELIN Lung 200

Overall survival

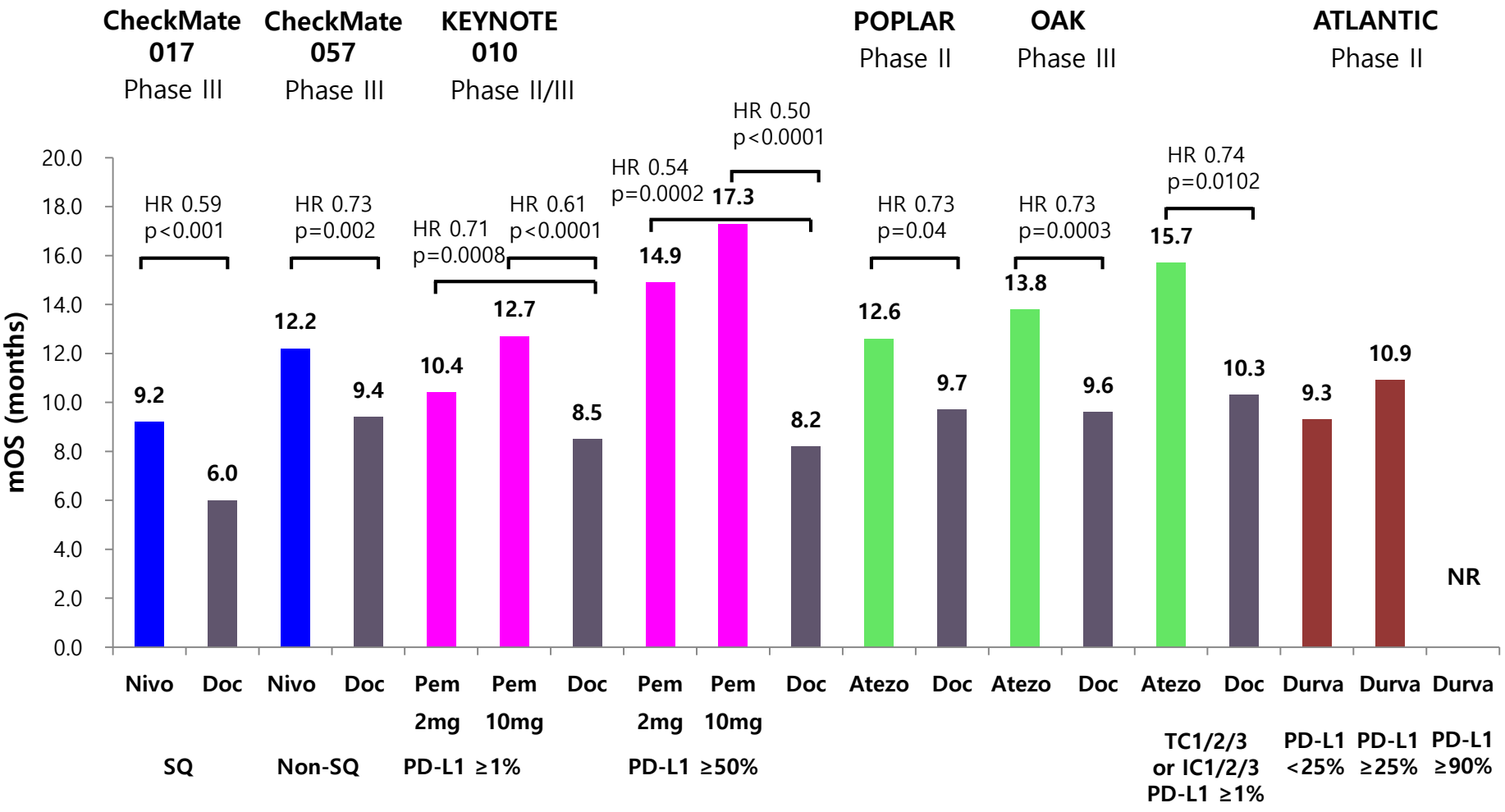
PD-L1	HR	95% CI	*p*-value	
PD-L1 ≥ 1%	**0.90**	**0.72-1.12**	**0.1627**	
PD-L1 ≥ 50%	0.67	0.51-0.89	0.0052	40%
PD-L1 ≥ 80%	0.59	0.42-0.83	0.0022	30%

*** Docetaxel group: 26.4% subsequent immune checkpoint inhibitors**

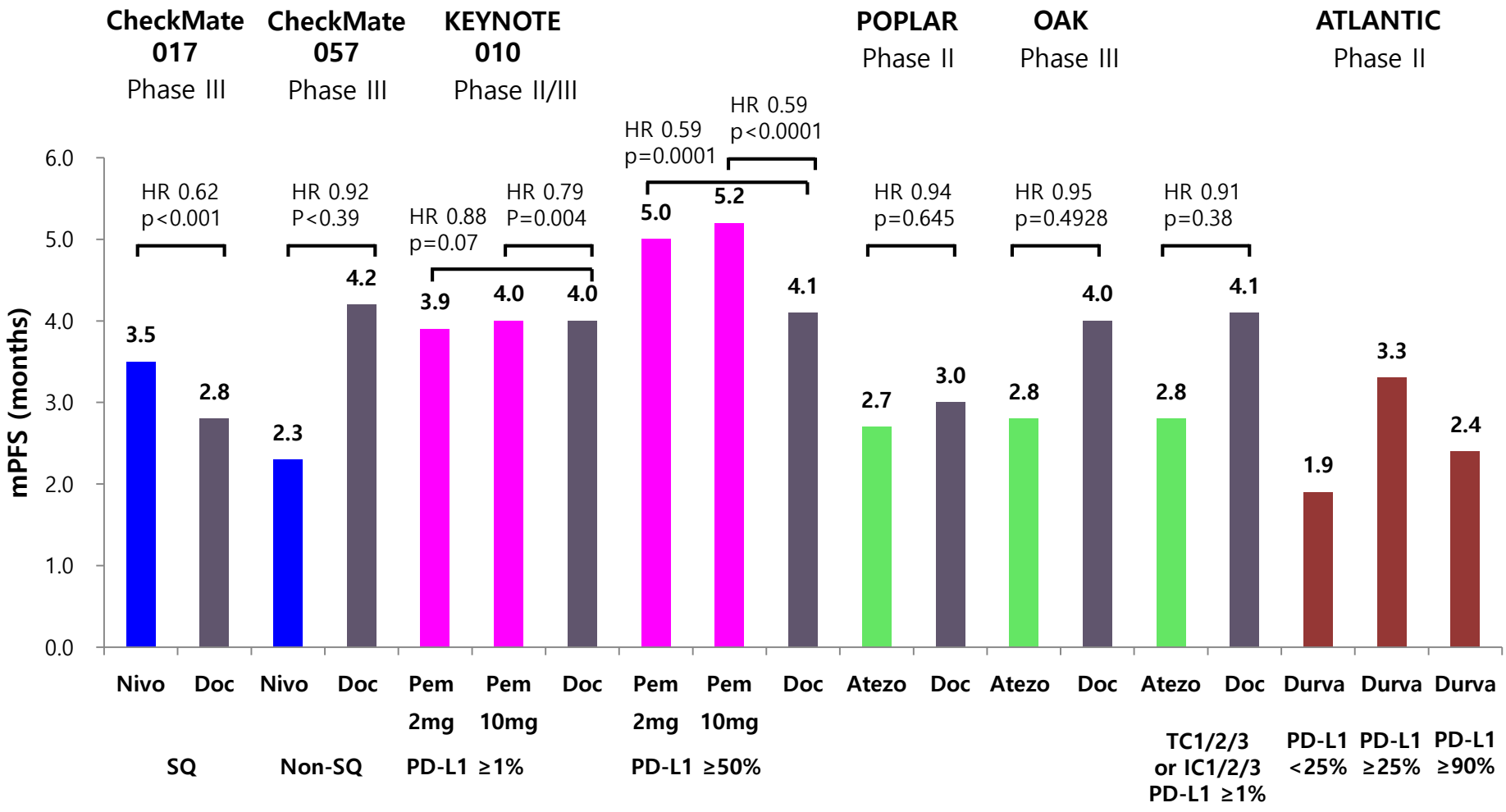
Subsequent treatment: ORR



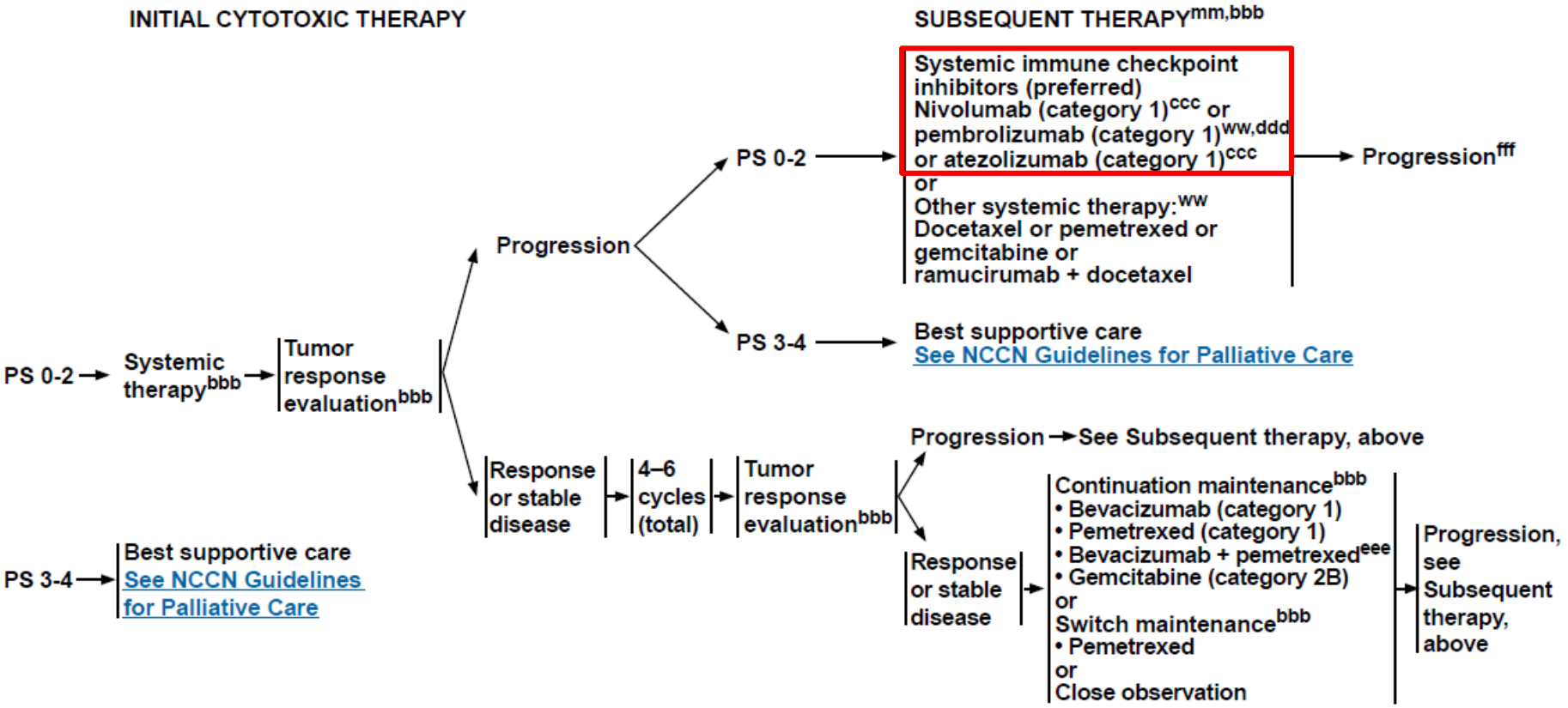
Subsequent treatment: OS



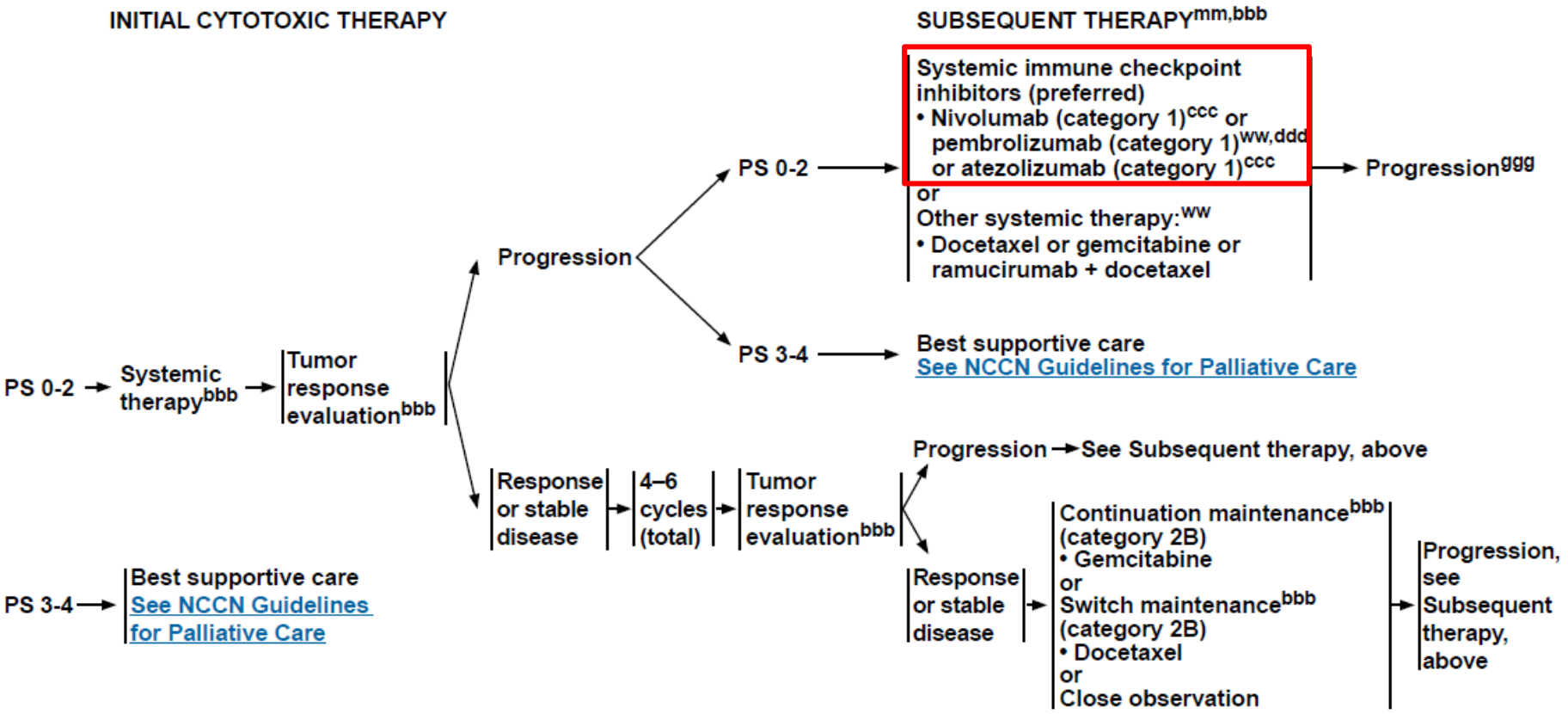
Subsequent treatment: PFS



ADENOCARCINOMA, LARGE CELL, NSCLC NOS



SQUAMOUS CELL CARCINOMA



요양급여 적용기준

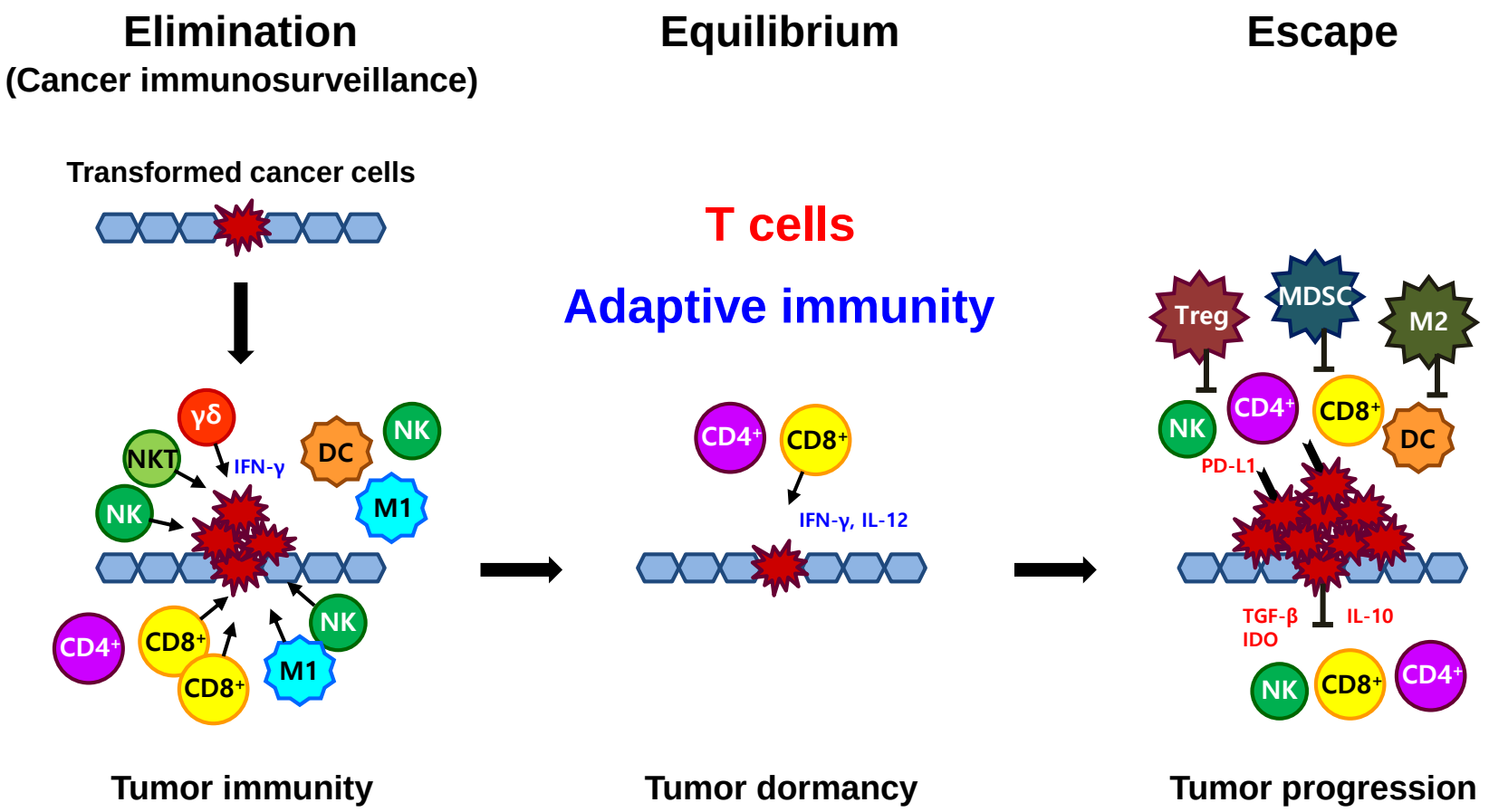
	Nivolumab (Opdivo®)	Pembrolizumab (Keytruda®)	Atezolizumab (Ticentriq®)
PD-L1 발현 양성	≥ 10% SP263 28-8	≥ 50% 22C3	≥ 5% SP142 (TC/IC)
이전 백금기반 화학요법에 실패한(2차 이상) stage IIIB 이상			

EGFR 또는 ALK 변이가 확인된 환자는 이러한 변이에 대한 승인된 치료를 투여한 후 질병 진행이 확인되고, 이전 백급기반 화학요법에도 실패한 경우

이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함.

급여인정 기간: 1년까지(단, 질병진행시 중단) 급여인정 하되, 1년 내에 최적의 투여 기간에 대한 임상결과 미 발표시 자동 연장하여 최대 2년으로 함.

Cancer immunoediting



Jung CY, Antonia SJ. Tuberc Respir Dis 2018;81:29-41.

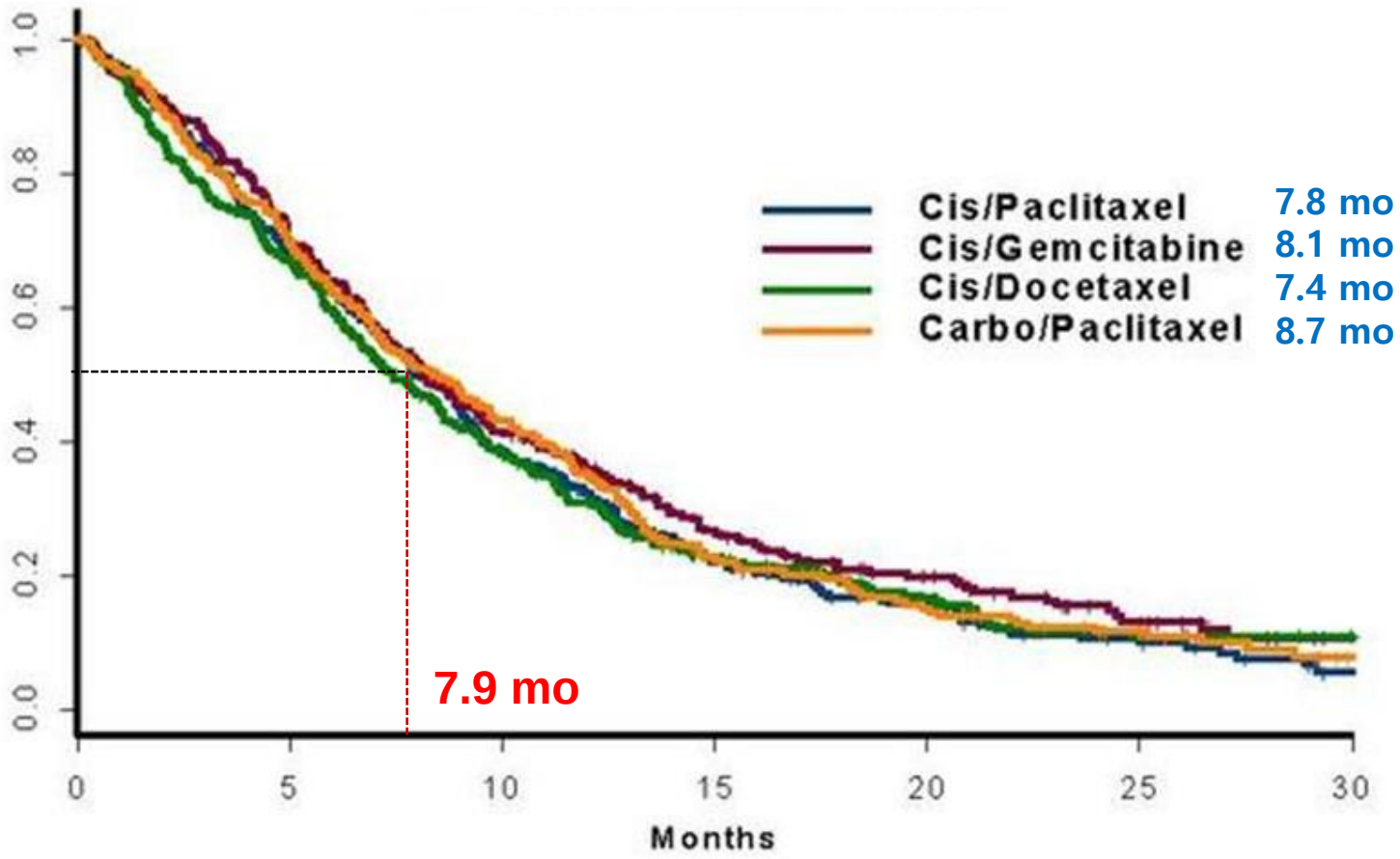
First-line treatment

Monotherapy vs. platinum-doublet CTx

Standard of care: 1L chemotherapy for advanced NSCLC

ECOG 1594: Platium doublet CTx

Overall survival

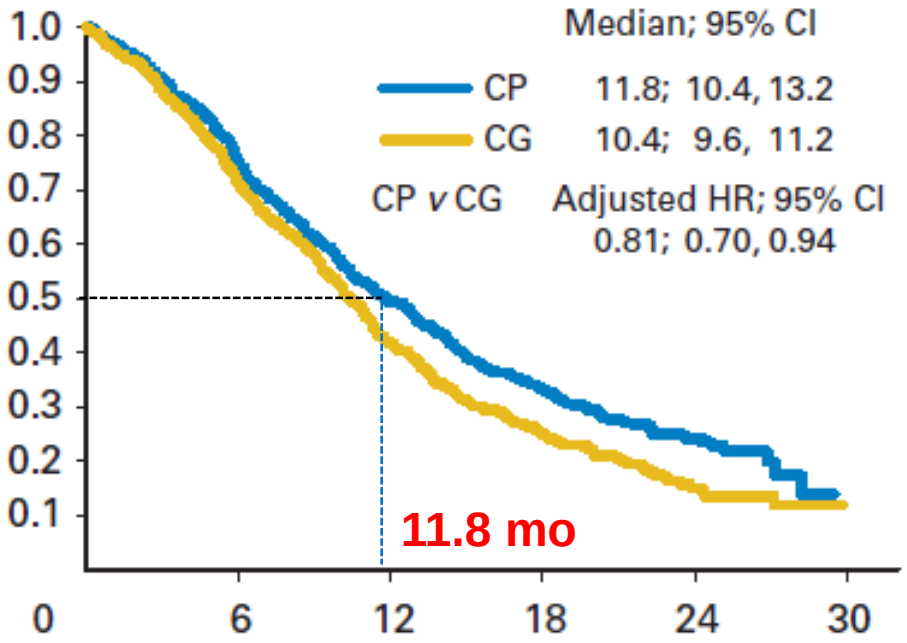


ORR: 19%, mTTP: 3.6 mo

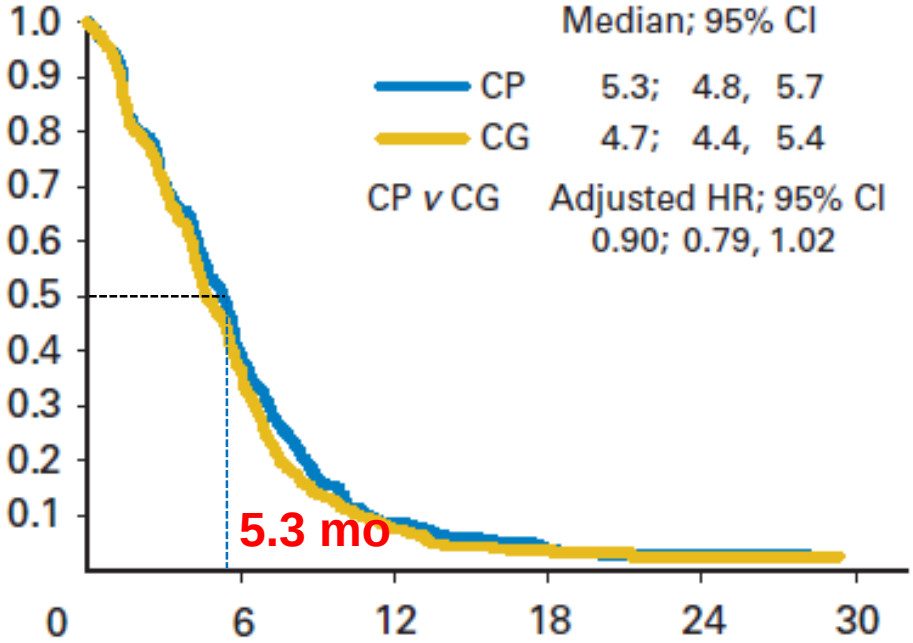
Schiller JH, et al. N Engl J Med 2002;346:92-8.

Standard of care: 1L chemotherapy for advanced Non-SQ
JMDB: Pemetrexed+cisplatin

Overall survival



Progression free survival



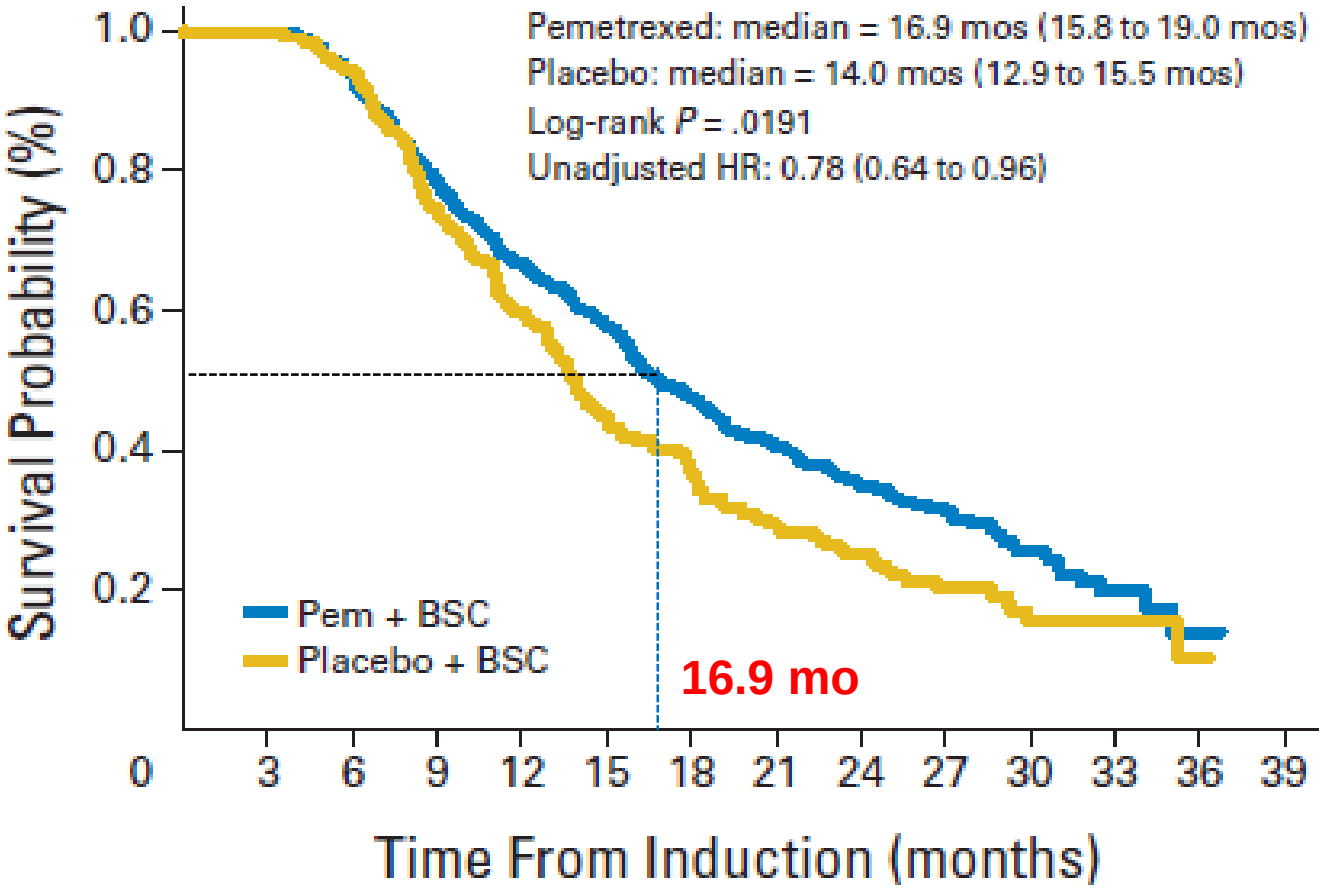
ORR: 30.6% vs. 28.2% (all patients)

Scagliotti GV, et al. J Clin Oncol 2008;26:3543-51.

Standard of care: 1L pemetrexed maintenance for Non-SQ

PARAMOUNT

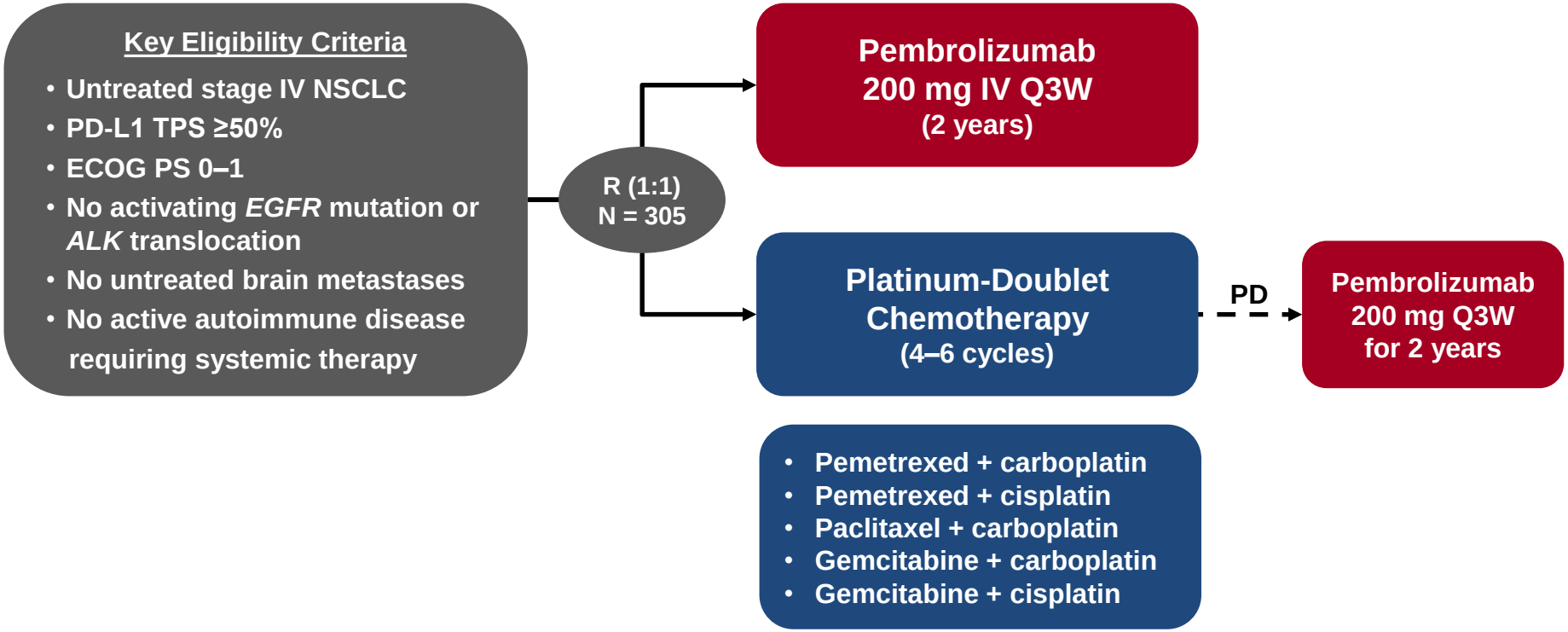
Overall survival



Paz-Ales L, et al. Lancet Oncol 2012;13:247-55.
Paz-Ales L, et al. J Clin Oncol 2013;31:2895-902.

Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%) KEYNOTE-024

Study design

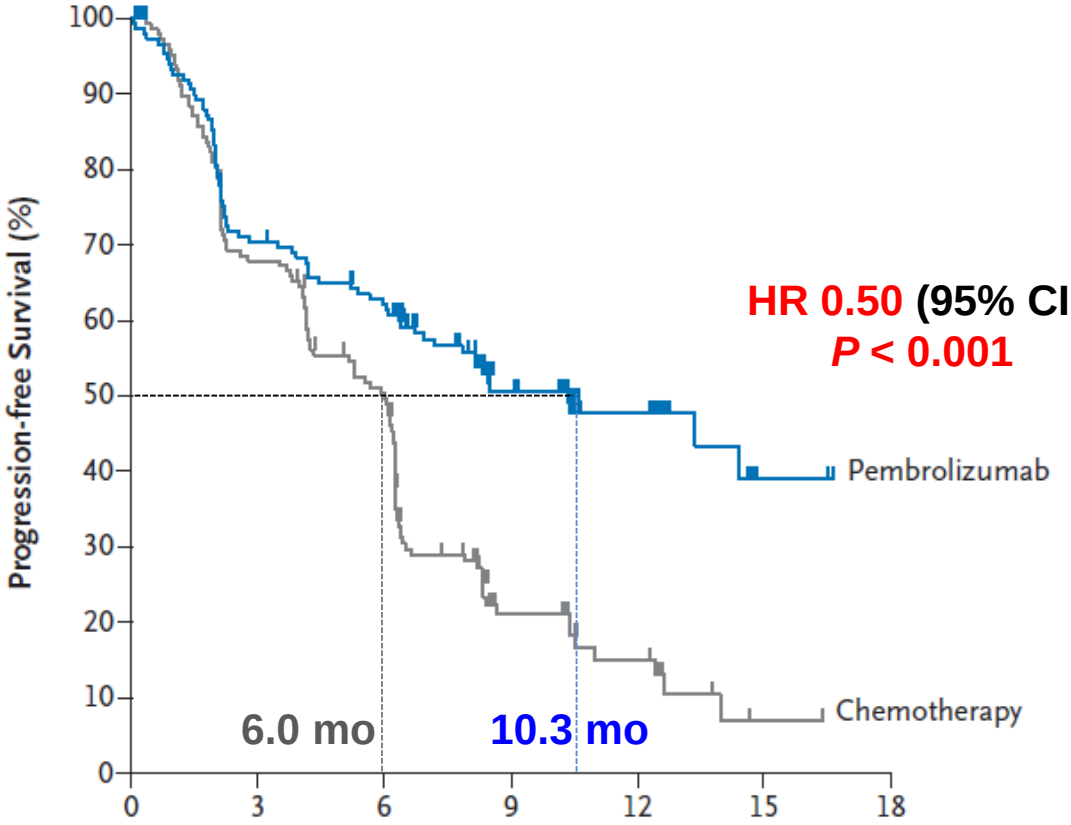


Reck M, et al. N Engl J Med 2016;375:1823-33.

Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%)

KEYNOTE-024

PFS (primary endpoint)



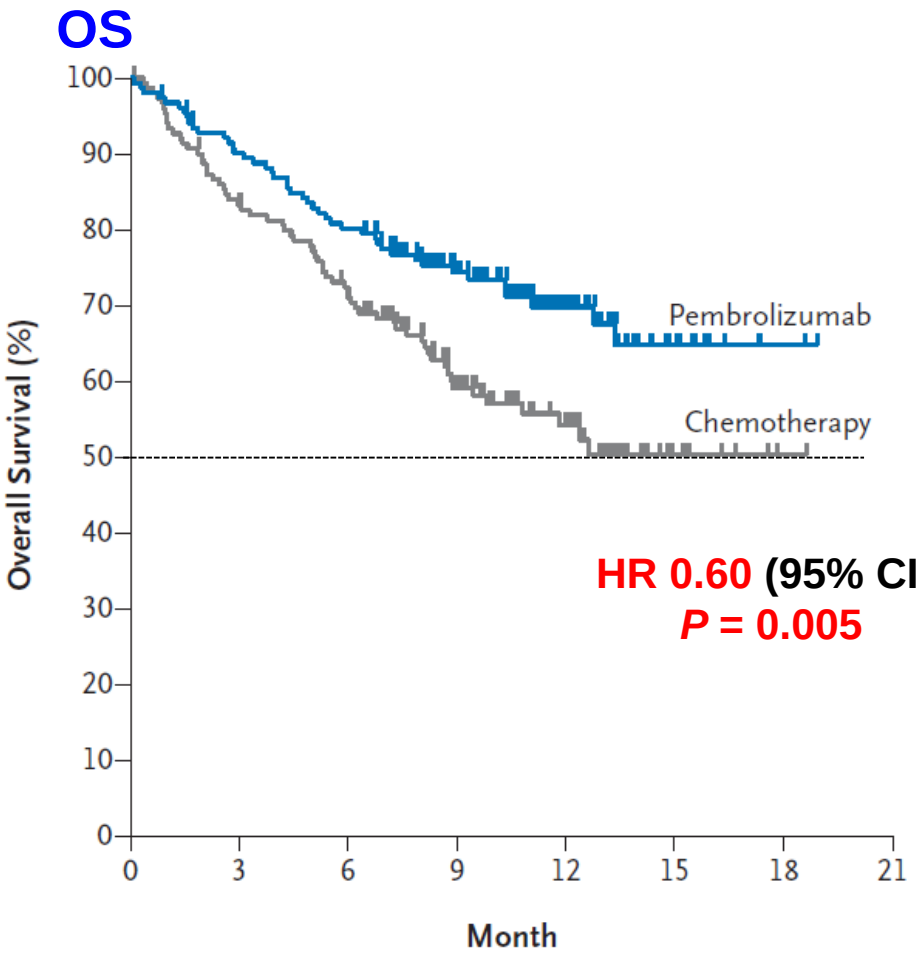
HR 0.50 (95% CI, 0.37-0.68)
***P* < 0.001**

ORR: 44.8% vs. 27.8%

No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

Reck M, et al. N Engl J Med 2016;375:1823-33.

Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%)
KEYNOTE-024

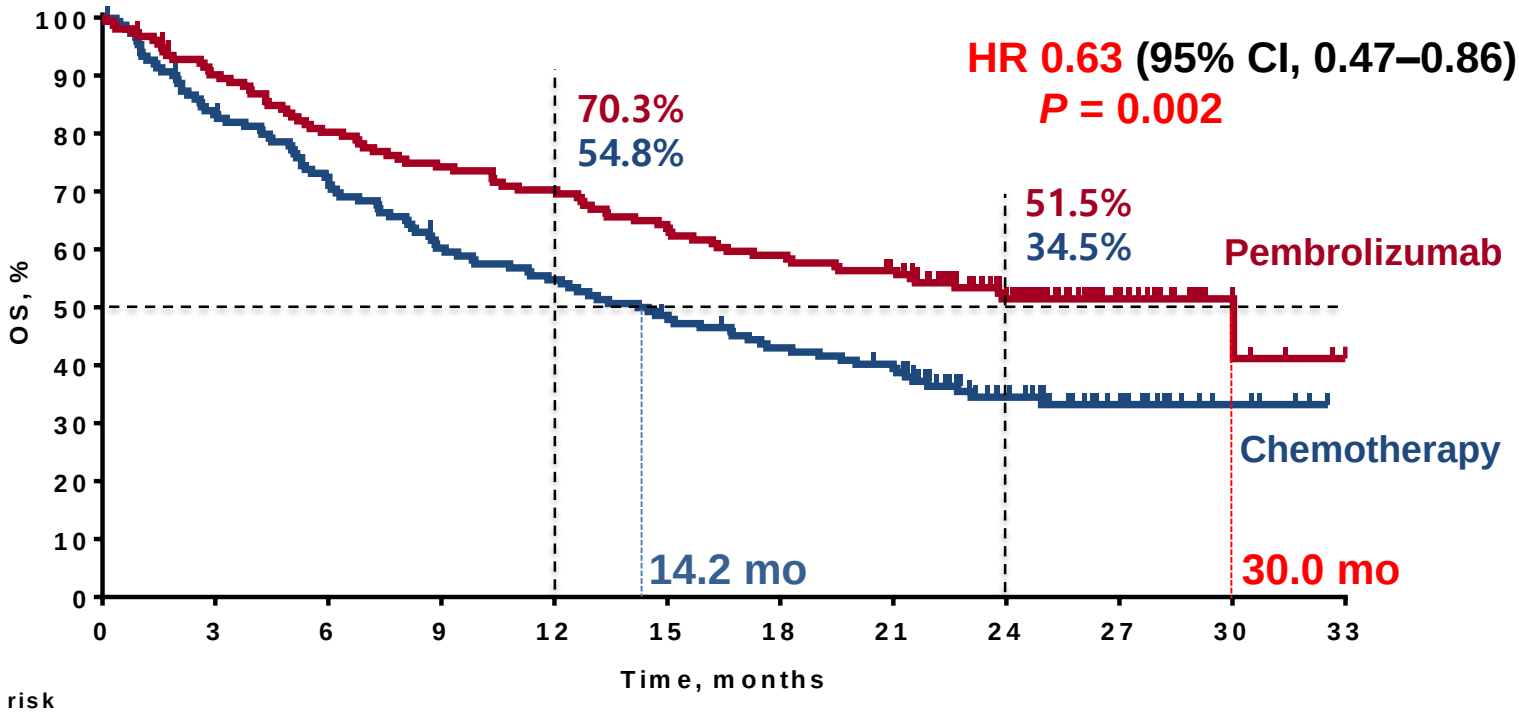


HR 0.60 (95% CI, 0.41-0.89)
***P* = 0.005**

Reck M, et al. N Engl J Med 2016;375:1823-33.

Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%)
KEYNOTE-024

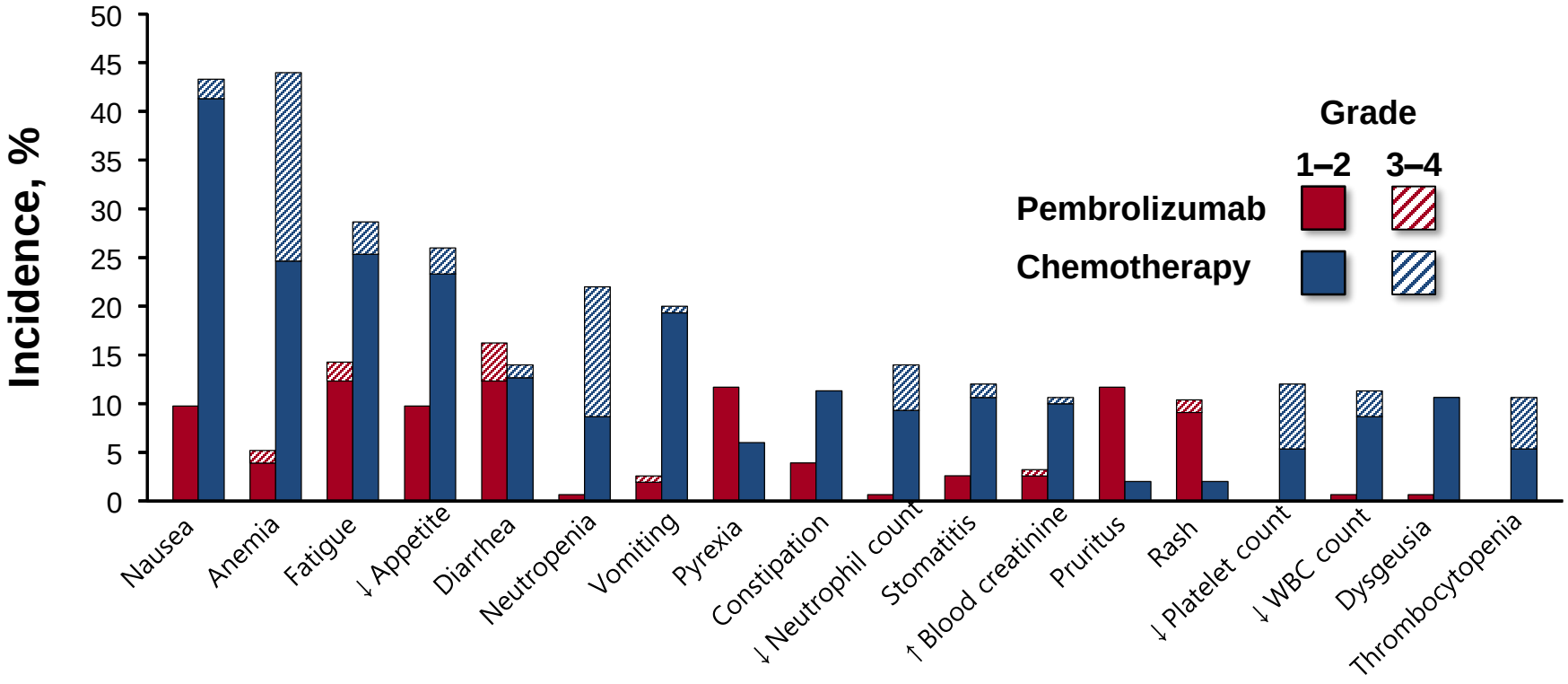
OS (updated analysis)



* CTx group cross over: **62.3%** (**82 Pembrolizumab**, 12 other anti-PD-1)

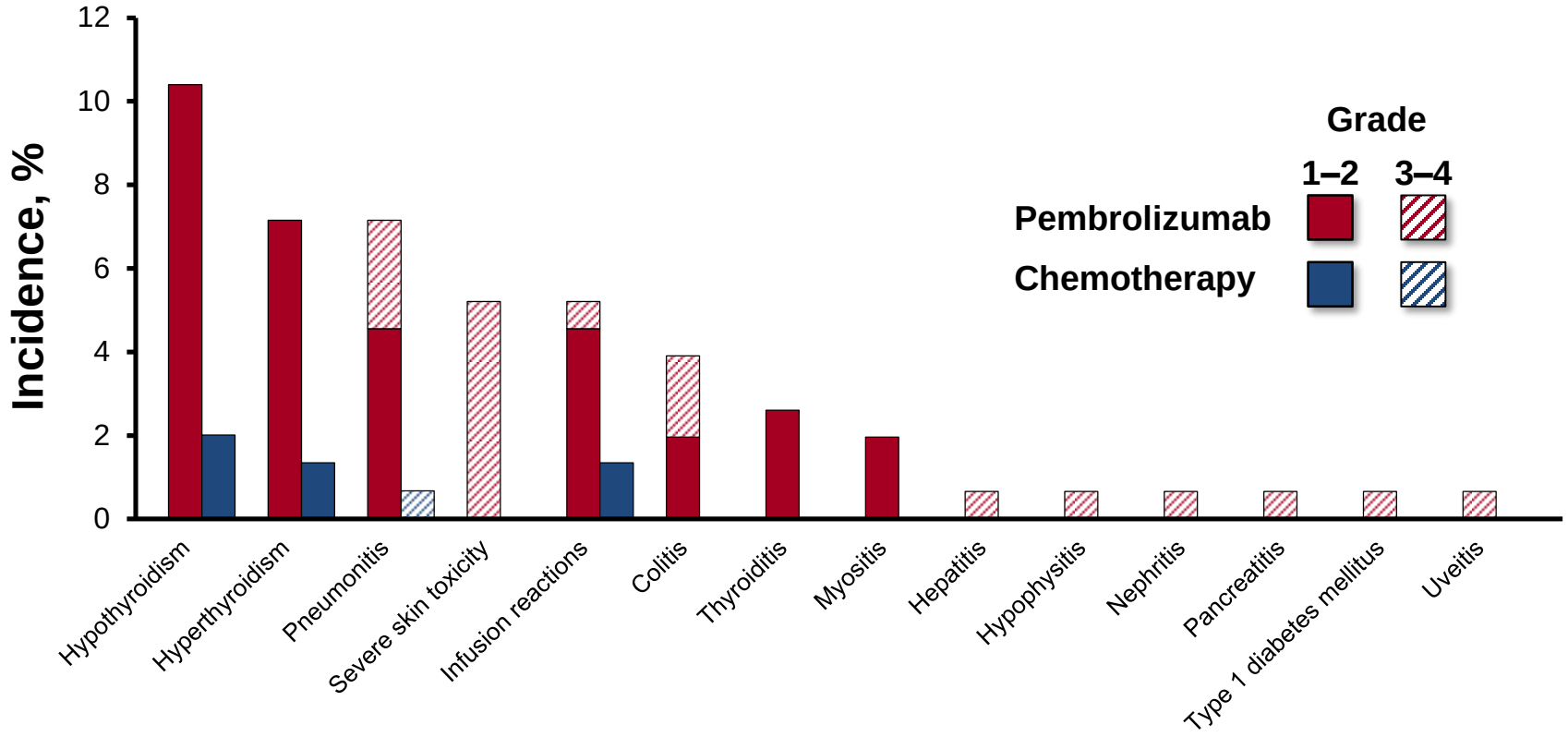
Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%)
KEYNOTE-024

Treatment-related AEs (≥ 10%)



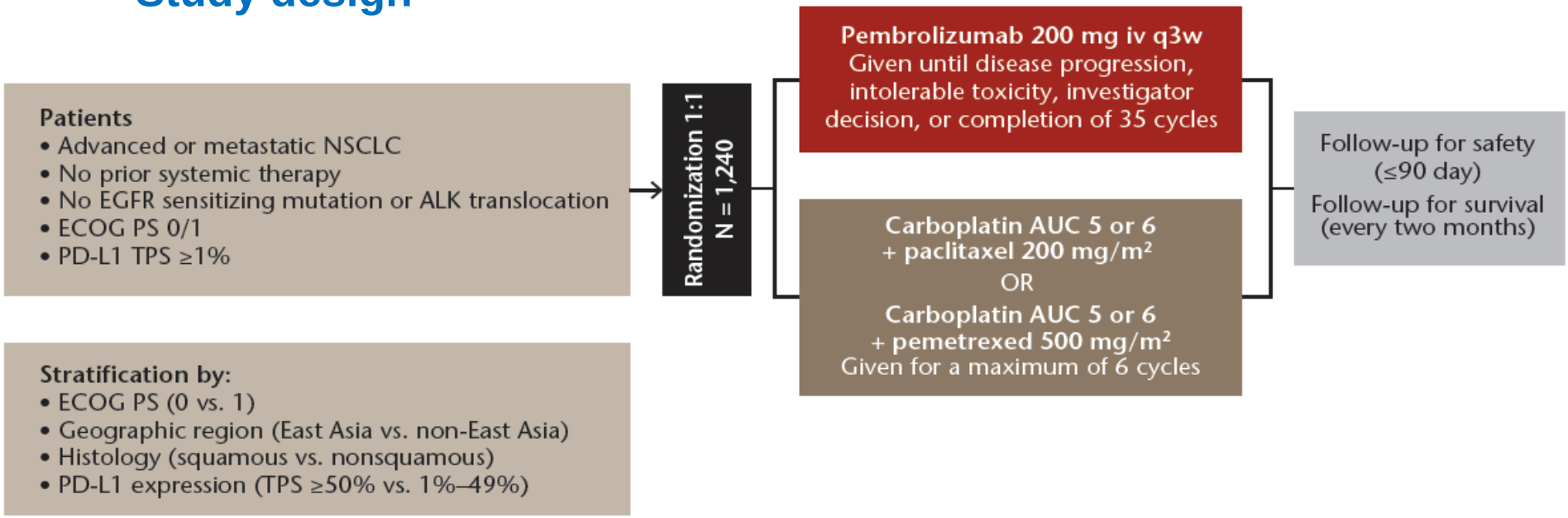
Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 50%)
KEYNOTE-024

Immune-mediated AEs



Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 1%)
KEYNOTE-042

Study design



ALK = anaplastic lymphoma kinase; AUC = area under concentration-time curve; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; iv = intravenous; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; q3w = every three weeks; TPS = tumour proportion score

Pembrolizumab: phase III, 1L NSCLC (PD-L1 ≥ 1%)
KEYNOTE-042

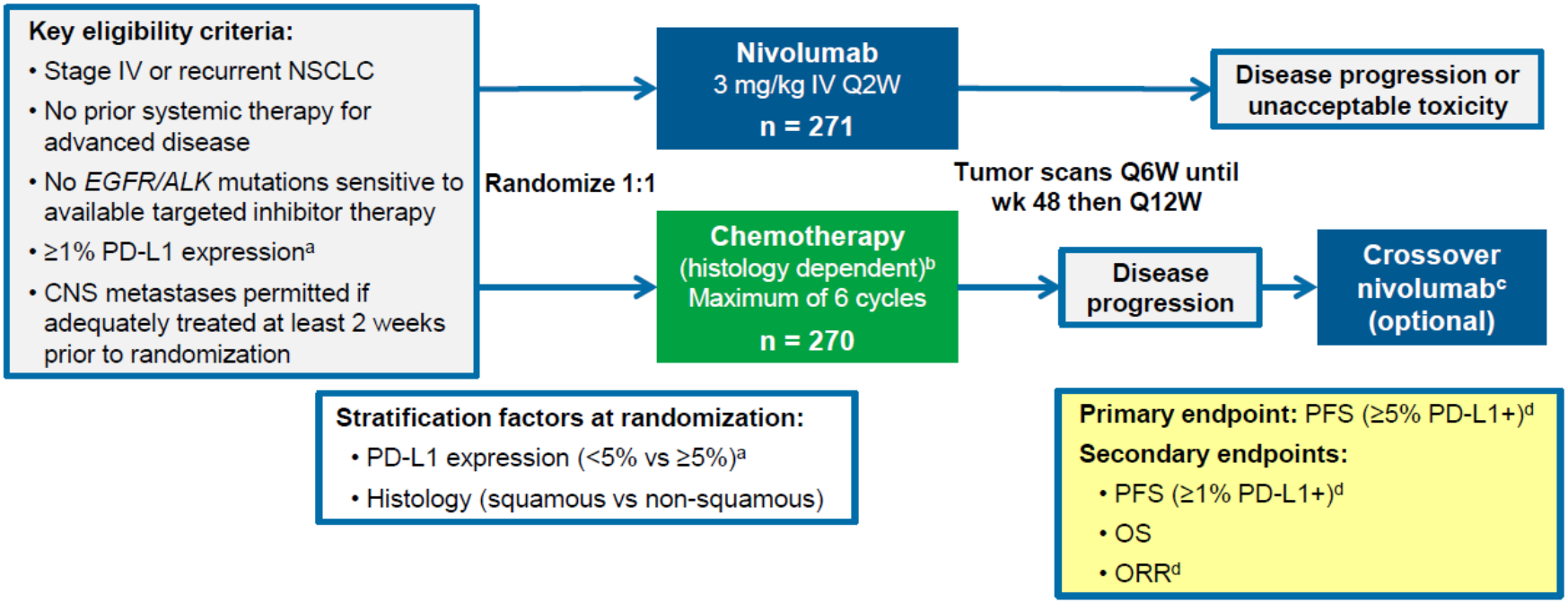
Published on *Merck Newsroom Home* (http://www.mrknewsroom.com) on 4/9/18 6:45 am EDT

KEYTRUDA® (pembrolizumab) Monotherapy Met Primary Endpoint in Phase 3 KEYNOTE-042 Study, Significantly Improving OS as First-Line Therapy in Locally Advanced or Metastatic NSCLC Patients Expressing PD-L1 in at Least 1 Percent of Tumor Cells

Release Date:
Monday, April 9, 2018 6:45 am EDT

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

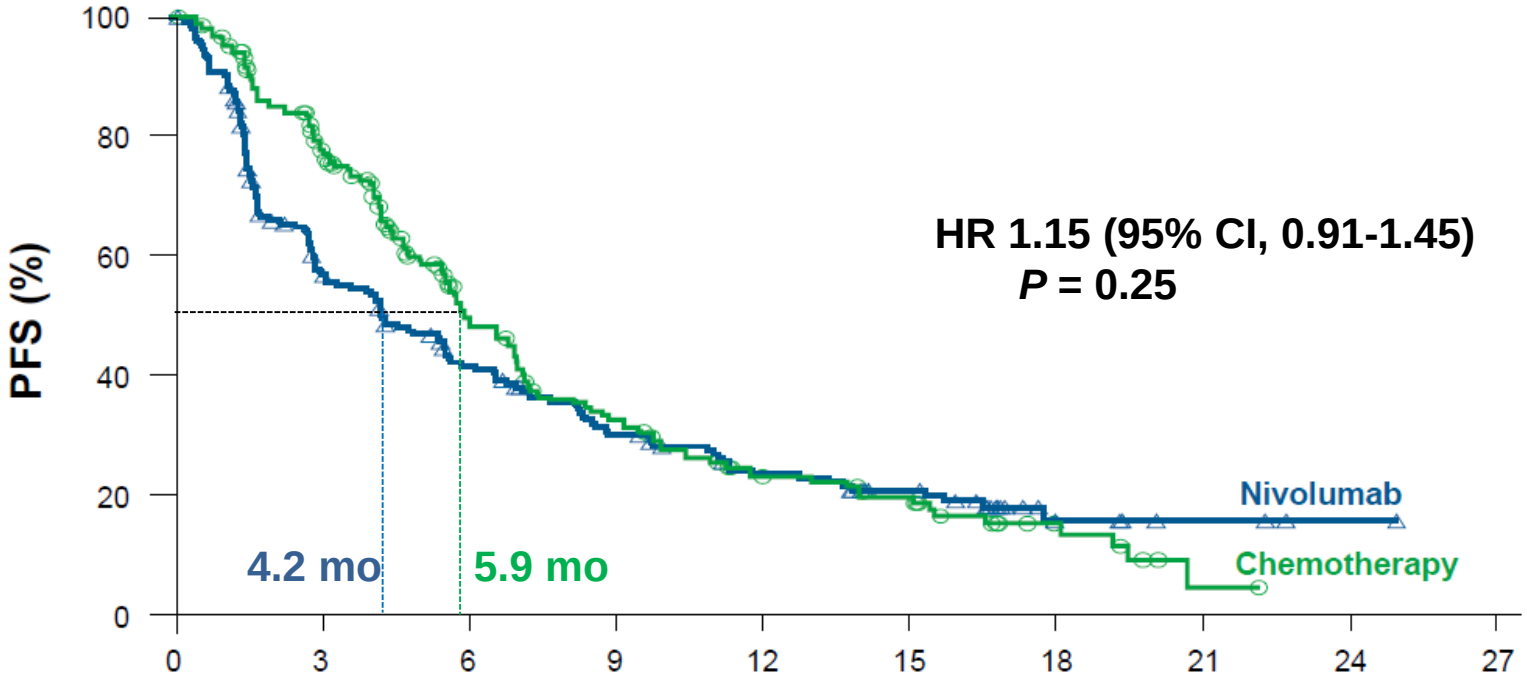
Study design



Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

PFS (primary endpoint)



HR 1.15 (95% CI, 0.91-1.45)
***P* = 0.25**

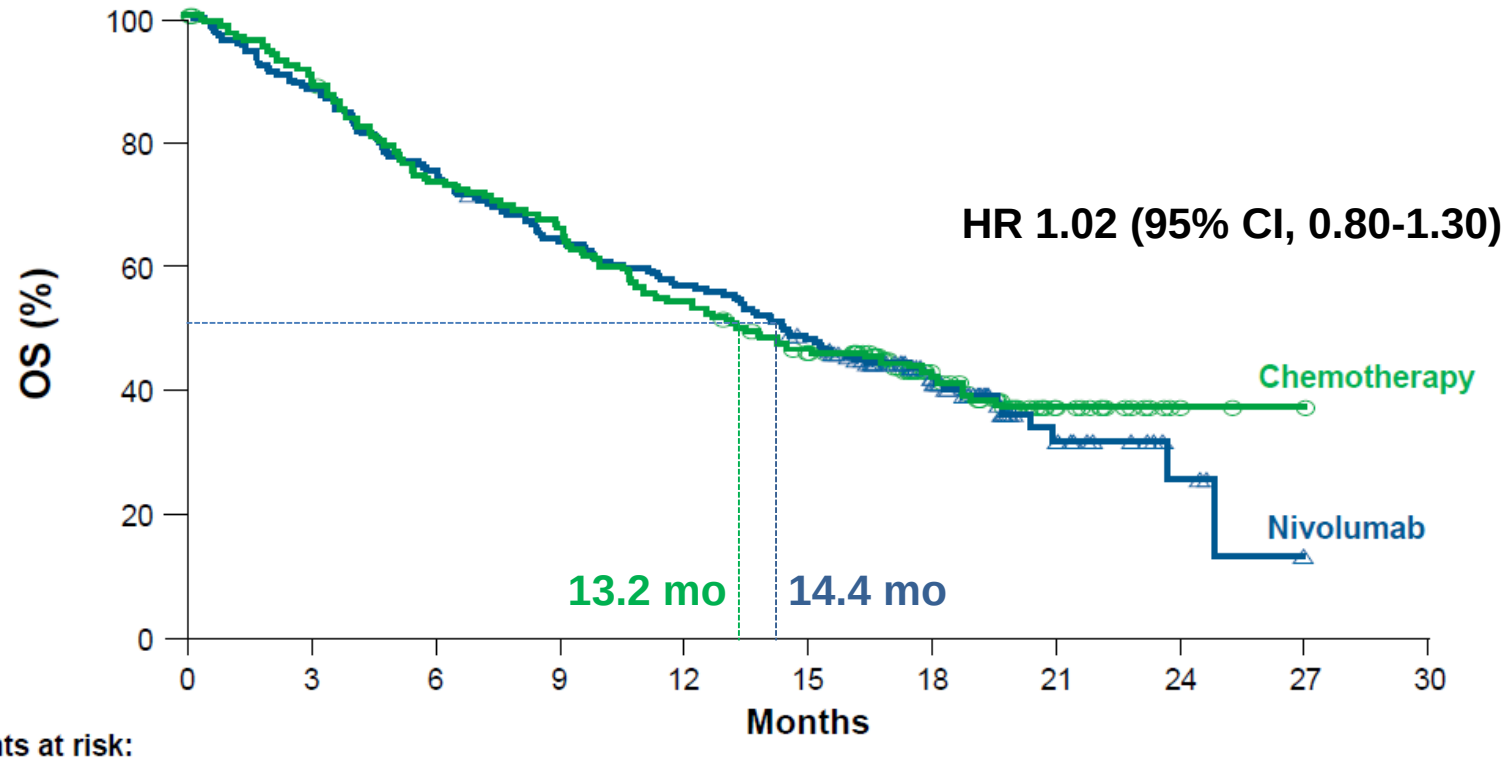
ORR: 26% vs. 33%

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

Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

OS



No. of patients at risk:											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

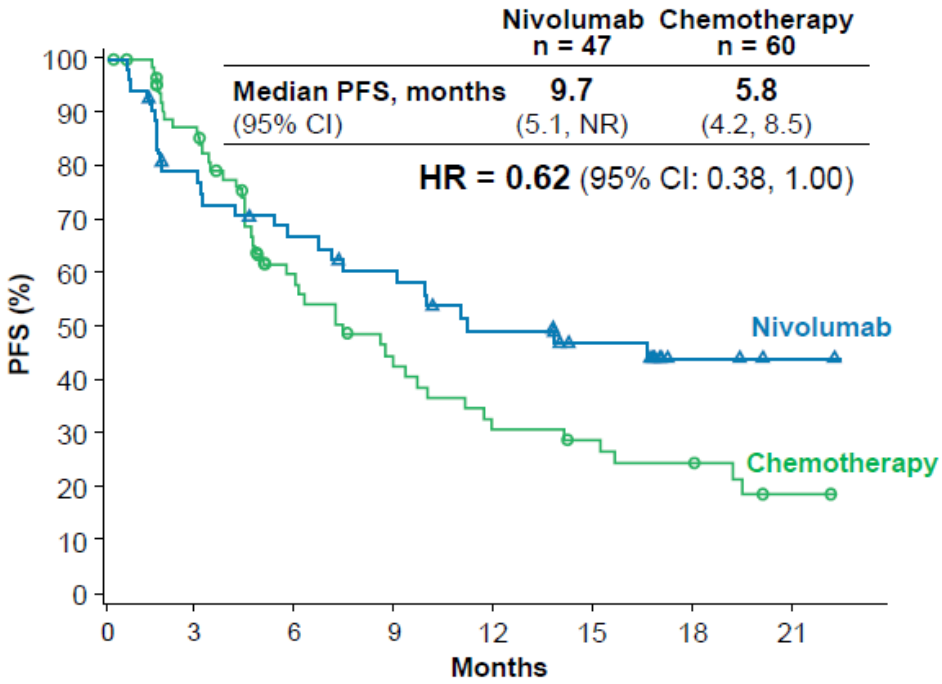
- Cross over Chemotherapy arm: **60.4% Nivolumab**
  Nivolumab arm: **43.6% Chemotherpay**

Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

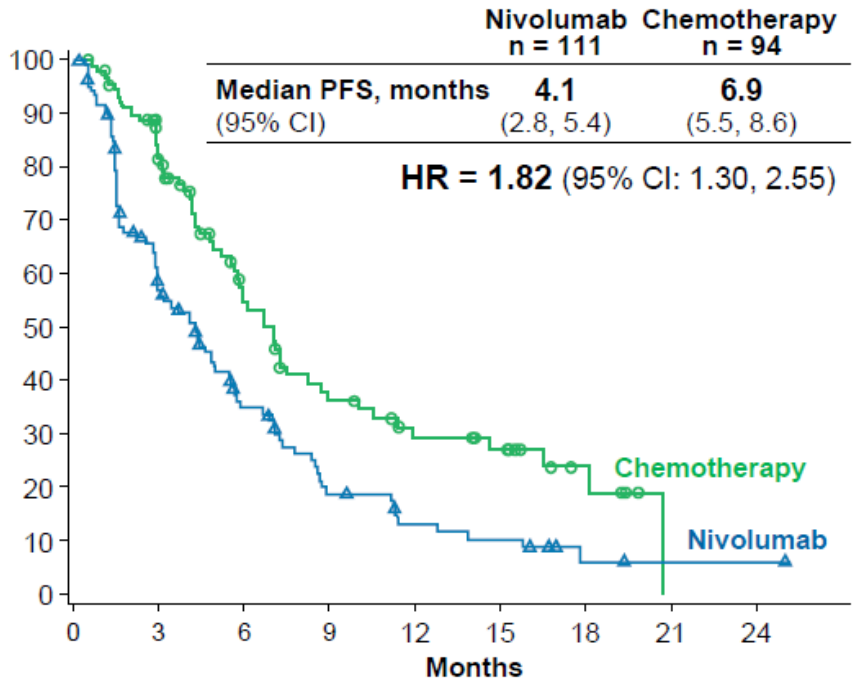
PFS by tumor mutation burden

High TMB



ORR: 47% vs. 28%

Low/medium TMB

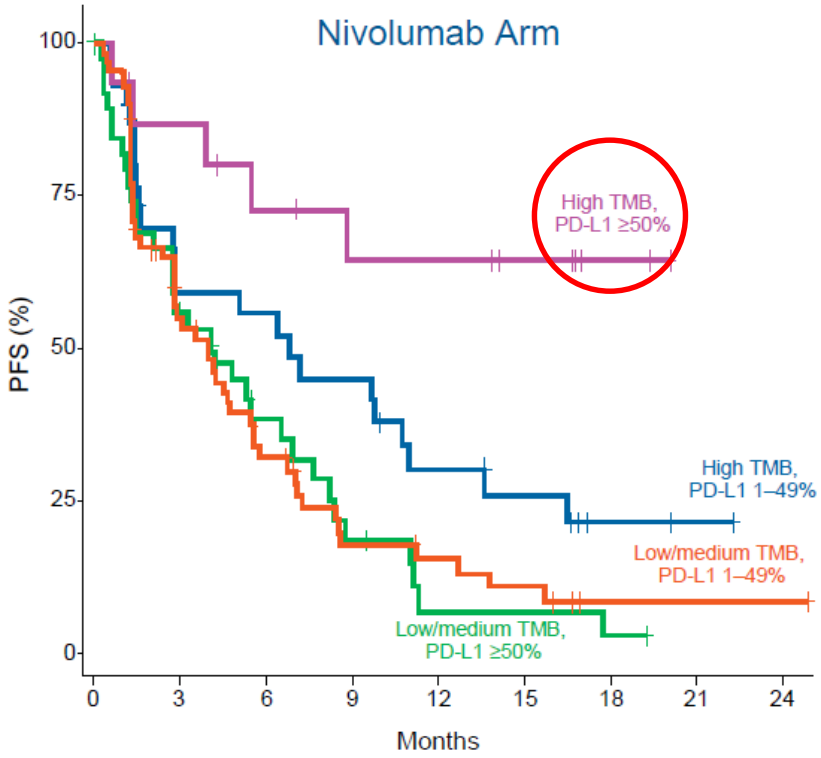


ORR: 23% vs. 33%

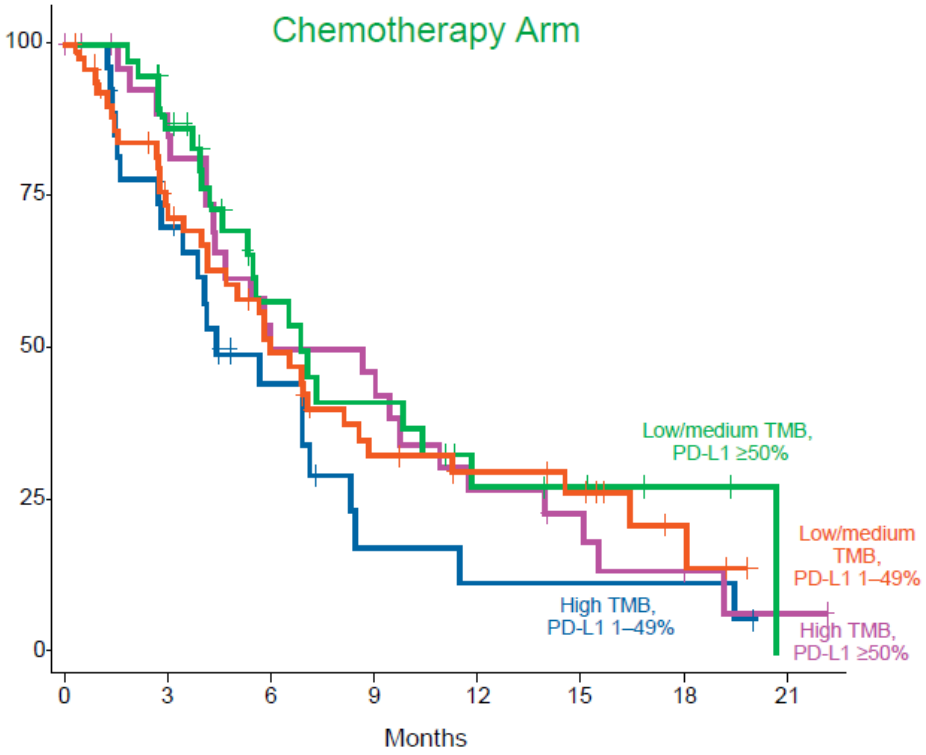
Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

PFS by TMB & PD-L1 expression



ORR: 75% vs. 32/34% vs. 16%



ORR: 25% vs. 32/46% vs. 23%

AACR 2017

Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

Treatment-related AEs

	Nivolumab (n = 267)		Chemotherapy (n = 263)	
Treatment-related AEs, %	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any AEs	71.2	17.6	92.4	50.6
SAEs	17.2	13.1	18.3	15.6
AEs leading to discontinuation	9.7	7.9	13.3	6.5
Treatment-related deaths, n (%)	2 (0.7)[b]		3 (1.1)[c]	
Most frequent treatment-related AEs,[d] %				
Fatigue	21.0	1.1	35.4	5.3
Diarrhea	13.9	1.1	12.9	1.9
Decreased appetite	12.0	0.4	27.8	1.5
Nausea	11.6	0.4	48.3	1.9
Vomiting	5.6	0	22.8	1.9
Constipation	3.4	0	11.0	0
Anemia	3.4	0.4	43.0	17.5
Asthenia	3.0	0	10.6	1.5
Thrombocytopenia	0.7	0.4	14.4	8.4
Neutropenia	0	0	18.3	11.0

Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Nivolumab: phase III, 1L NSCLC (PD-L1 ≥ 5%)
CheckMate 026

Imbalance in the characteristics

	Nivolumab (n = 271)	Chemotherapy (n = 270)
Median age, years (range)	63.0 (32, 89)	65.0 (29, 87)
Female, %	32.1	45.2
Selected sites of metastases (lesions), %		
Brain	12.2	13.3
Liver	19.9	13.3
Median sum of target lesion diameters, mm (range)	82.5 (14, 218)	68.0 (15, 272)
PD-L1 expression, %		
≥5%	76.8	77.8
≥25%	48.7	60.7
≥50%	32.5	46.7
≥75%	20.7	27.4
Tumor mutation burden, n (%)		
Low	62 (39.2)	41 (26.6)
Medium	49 (31.0)	53 (34.4)
High	47 (29.7)	60 (39.0)

Carbone DP, et al. N Engl J Med 2017;376:2415-26.

KEYNOTE-024 vs. CheckMate 026

	KEYNOTE-024	CheckMate 026
PD-L1 cut-off	50% (22C3)	5% (28-8)
PD-L1 testing	after metastatic diagnosis (new)	within 6 months (archive)
Never smokers	3%	11%
Prior radiotherapy	-	37.6%

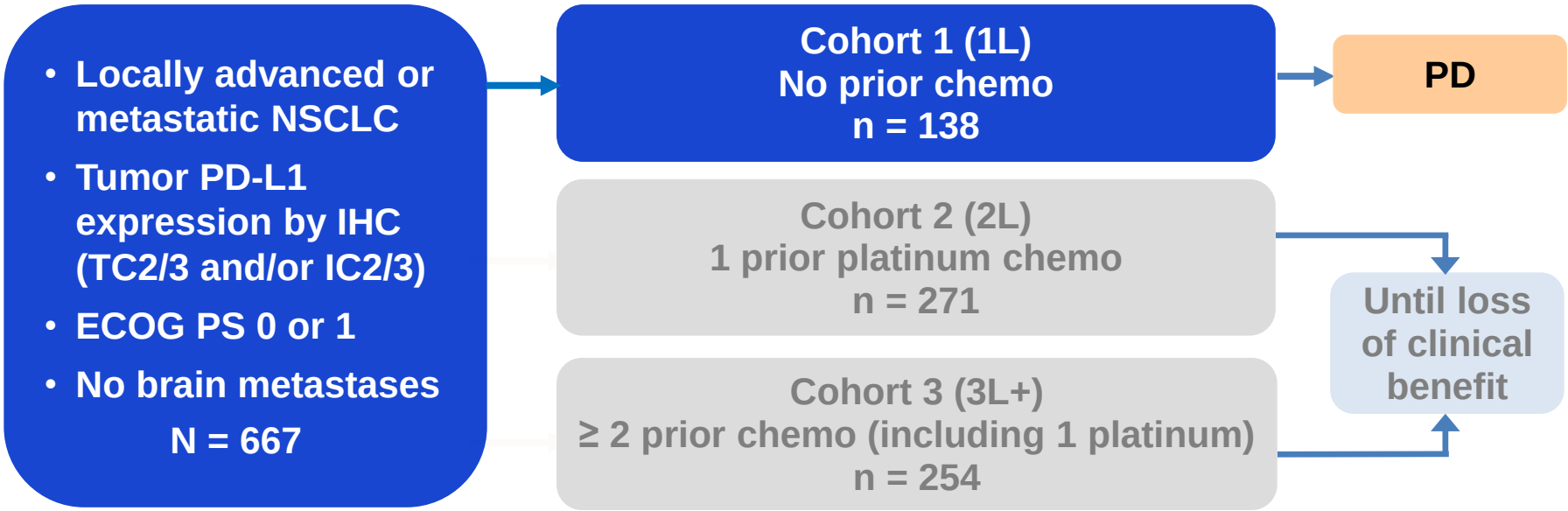
Remon J, et al. BMC Med 2017;15:55.
Carbone DP, et al. N Engl J Med 2017;376:2415-26.

Atezolizumab: phase II, 1L NSCLC (TC2/3 or IC2/3)

BIRCH

PD-L1 ≥ 5%

Study design



*EGFR/ALK(+), after progression

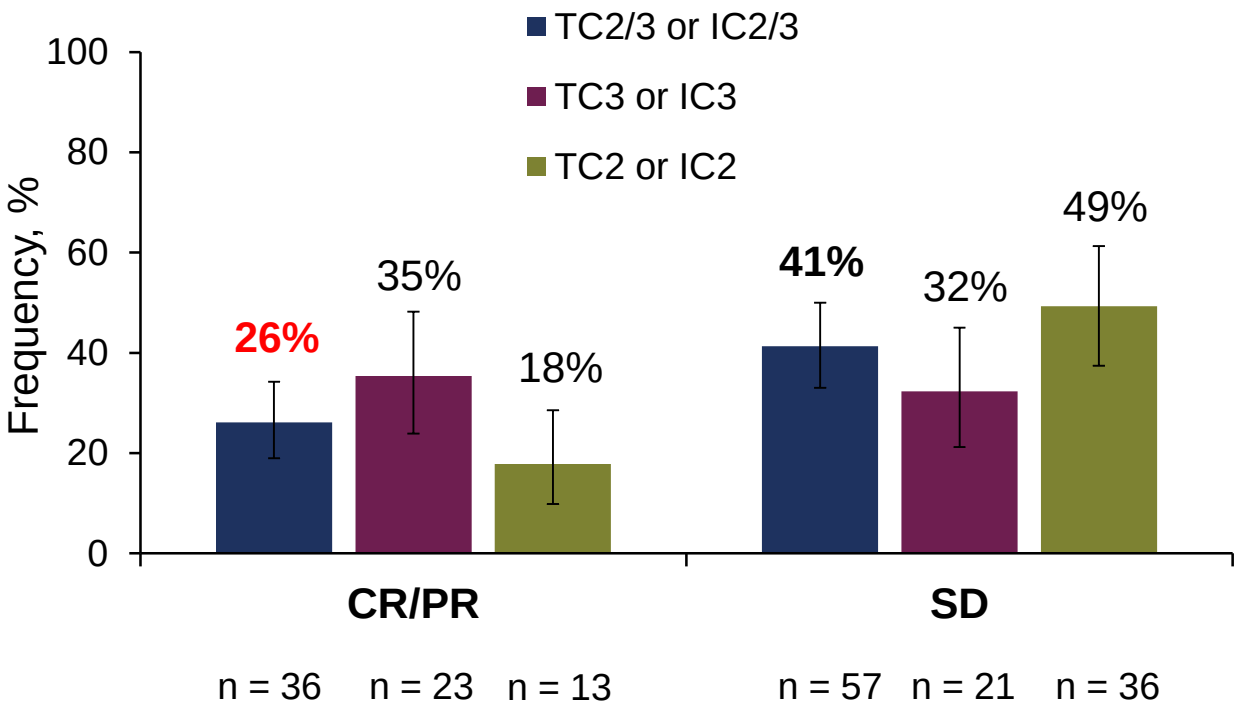
Peter S, et al. J Clin Oncol 2017;35:2781-9.

Atezolizumab: phase II, 1L NSCLC (TC2/3 or IC2/3)

BIRCH

PD-L1 ≥ 5%

ORR (primary endpoint)



WCLC 2017

Peter S, et al. J Clin Oncol 2017;35:2781-9.

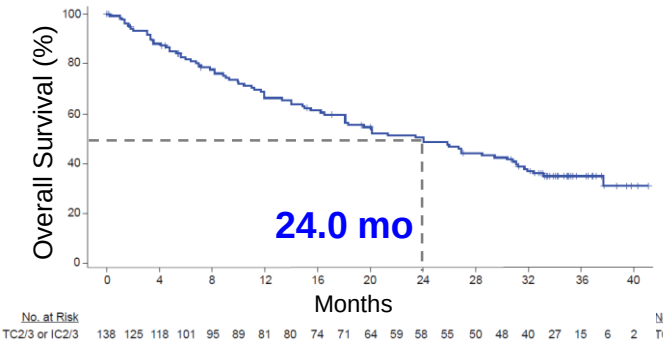
Atezolizumab: phase II, 1L NSCLC (TC2/3 or IC2/3)

BIRCH

PD-L1 ≥ 5%

OS (median OS, 24-mo OS rate)

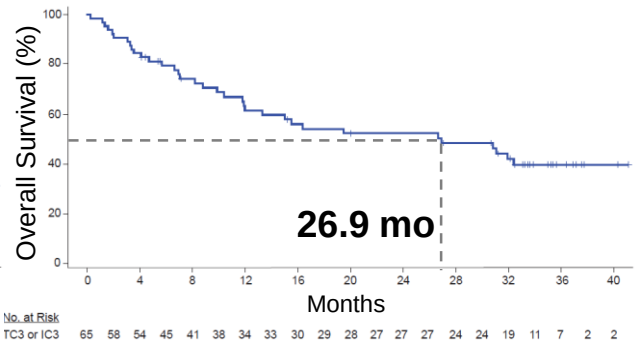
TC2/3 or IC2/3
n = 138



24-mo OS rate = 50%

mPFS 7.6 mo

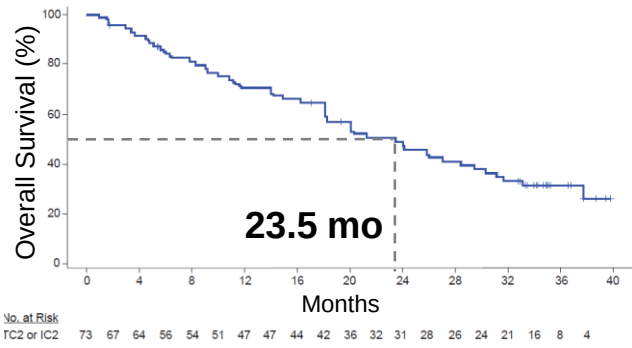
TC3 or IC3
n = 65



24-mo OS rate = 52%

mPFS 7.3 mo

TC2 or IC2
n = 73



24-mo OS rate = 49%

mPFS 7.6 mo

WCLC 2017

Peter S, et al. J Clin Oncol 2017;35:2781-9.

Atezolizumab: phase II, 1L NSCLC (TC2/3 or IC2/3)

BIRCH

PD-L1 ≥ 5%

Adverse events

Safety Summary	N = 138 n (%)
Total patients with ≥ 1 AE	126 (91%)
Grade 5 AEs	2 (1%)
AEs leading to dose interruption	40 (29%)
Treatment-related AEs	85 (62%)
Treatment-related Grade 5 AEs	0
Treatment-related AEs leading to atezolizumab withdrawal	6 (4%)
Serious AEs	48 (35%)

Treatment-Related Adverse Events (≥ 5%)	All Grade (%)	Grade 3–4 (%)
Fatigue	17%	1%
Diarrhea	10%	1%
Decreased appetite	10%	0
Nausea	10%	0
Pruritus	9%	0
Rash	8%	1%
Asthenia	7%	1%
Pyrexia	7%	0
Arthralgia	6%	0
Dry skin	6%	0
Hypothyroidism	6%	0
Constipation	5%	0
Headache	5%	0

- **Atezolizumab monotherapy was generally well-tolerated**

WCLC 2017

Peter S, et al. J Clin Oncol 2017;35:2781-9.

Atezolizumab: ongoing phase III trials

IMpower110 LUNG	*Phase III 1L in non-squamous NSCLC* *Atezolizumab vs carbo/cis + pem*	Monotherapy
IMpower111 LUNG	*Phase III 1L in squamous NSCLC* *Atezolizumab vs carbo/gem or cis/gem*	Monotherapy
IMpower130 LUNG	*Phase III 1L in non-squamous NSCLC* *Atezolizumab + carbo/nab-pac*	Combo
IMpower131 LUNG	*Phase III 1L in squamous NSCLC* *Atezolizumab + carbo/pac or carbo/nab-pac*	Combo
IMpower132 LUNG	*Phase III 1L in non-squamous NSCLC* *Atezolizumab + carbo or cis/pem*	Combo
IMpower150 LUNG	*Phase III 1L in non-squamous NSCLC* *Atezolizumab + carbo/pac ± bev*	Combo
IMpower010 LUNG	*Phase III adjuvant in non-squamous NSCLC* *Atezolizumab vs BSC*	Adjuvant monotherapy

Avelumab: phase III, 1L NSCLC
JAVELIN Lung 100

KEY ELIGIBILITY CRITERIA

- Recurrent/metastatic stage IV NSCLC
- First-line treatment setting
- PD-L1+ tumor
- EGFR/ALK negative

TARGET ENROLLMENT

- N=1,095, including n=469 with high-expression PD-L1+ tumors

Stratification factors:
Histology (squamous vs non-squamous) and tumor PD-L1 expression

ARM A

Avelumab 10 mg/kg IV Q2W

ARM B*

Investigator's choice of platinum doublet chemotherapy IV Q3W

ARM C†

Avelumab 10 mg/kg weekly for 12 weeks, then Q2W thereafter

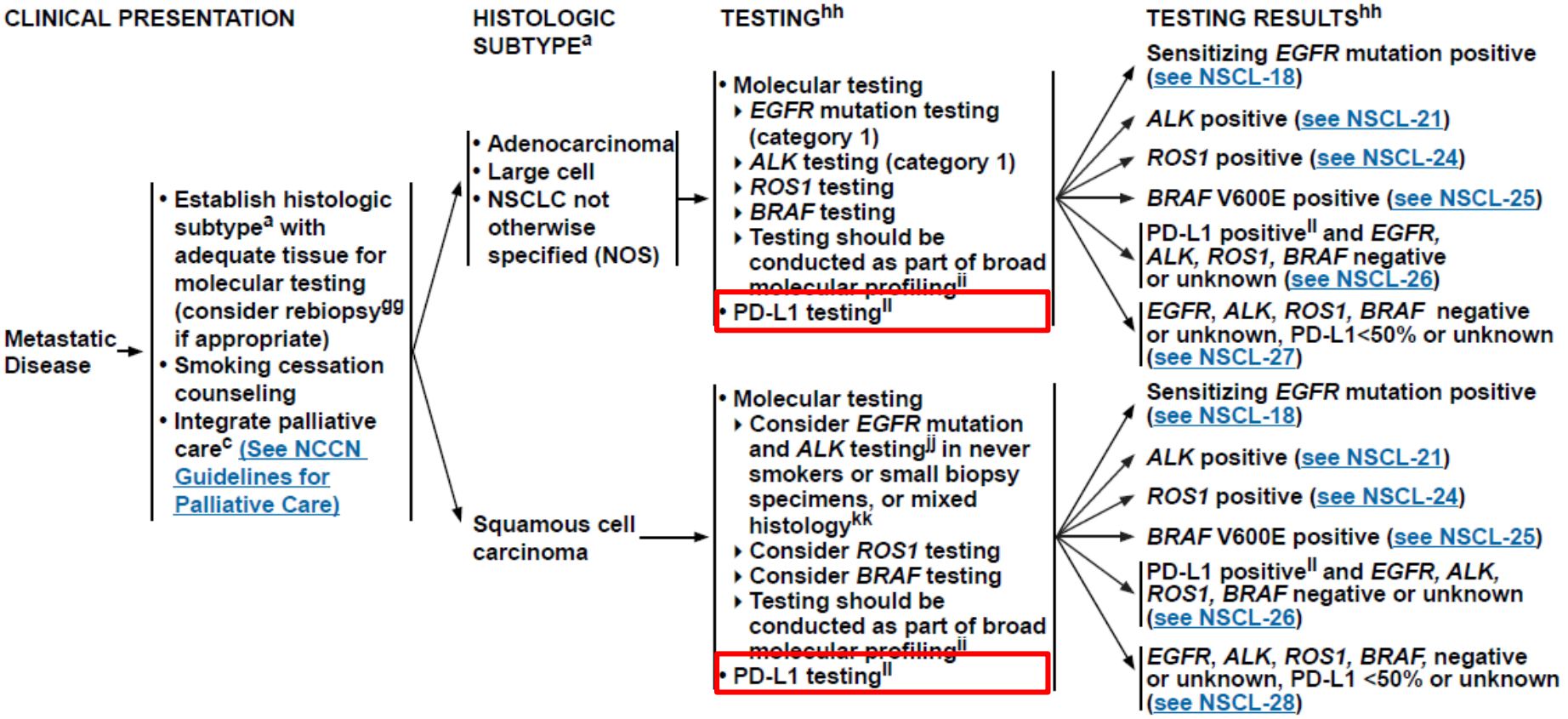
Treatment until disease progression, unacceptable toxicity, or withdrawal, or until a maximum of 6 cycles of chemotherapy

CO-PRIMARY ENDPOINTS

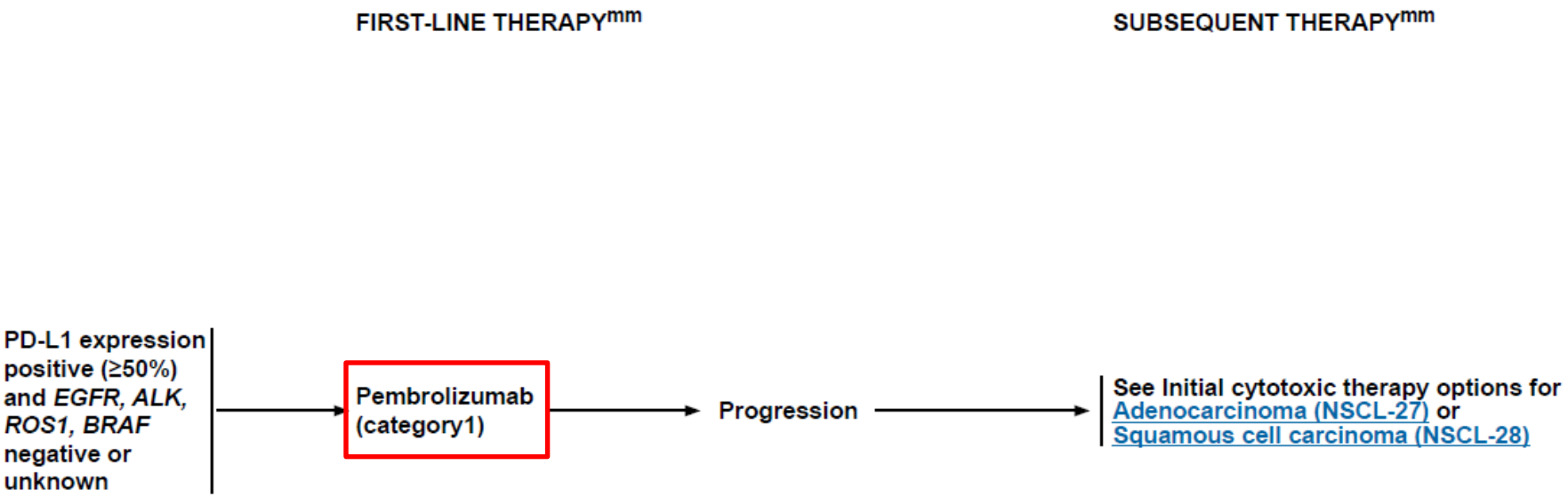
Progression-free survival and overall survival

SECONDARY ENDPOINTS

- Best overall response
- Duration of response
- Avelumab PK and immunogenicity
- Patient-reported outcomes
- Safety and tolerability


CLINICAL PRESENTATION
HISTOLOGIC SUBTYPE[a]
TESTING[hh]
TESTING RESULTS[hh]
Metastatic Disease
• Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[gg] if appropriate)
• Smoking cessation counseling
• Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)
• Adenocarcinoma
• Large cell
• NSCLC not otherwise specified (NOS)
Squamous cell carcinoma
• Molecular testing
▸ EGFR mutation testing (category 1)
▸ ALK testing (category 1)
▸ ROS1 testing
▸ BRAF testing
▸ Testing should be conducted as part of broad molecular profiling[ii]
• PD-L1 testing[ll]
• Molecular testing
▸ Consider EGFR mutation and ALK testing[jj] in never smokers or small biopsy specimens, or mixed histology[kk]
▸ Consider ROS1 testing
▸ Consider BRAF testing
▸ Testing should be conducted as part of broad molecular profiling[ii]
• PD-L1 testing[ll]
Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)
PD-L1 positive[ll] and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1<50% or unknown (see NSCL-27)
Sensitizing EGFR mutation positive (see NSCL-18)
ALK positive (see NSCL-21)
ROS1 positive (see NSCL-24)
BRAF V600E positive (see NSCL-25)
PD-L1 positive[ll] and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
EGFR, ALK, ROS1, BRAF, negative or unknown, PD-L1 <50% or unknown (see NSCL-28)

PD-L1 EXPRESSION POSITIVE[hh]



TARGETED THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 2)

Subsequent Therapy

- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

Sensitizing *EGFR* Mutation

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Gefitinib[3,4]
  - Osimertinib[5]
- Subsequent therapy
  - Osimertinib[6]

***ALK* Rearrangement**

- First-line therapy
  - Alectinib[7,8]
  - Ceritinib[9]
  - Crizotinib[10,11]
- Subsequent therapy
  - Alectinib[12,13]
  - Brigatinib[14]
  - Ceritinib[15]

***ROS1* Rearrangement**

- First-line therapy
  - Ceritinib[16]
  - Crizotinib[17]

***BRAF* V600E Mutation**

- First-line therapy
  - Dabrafenib/trametinib[18]
- Subsequent therapy
  - Dabrafenib/trametinib[19,20]

PD-L1 Expression

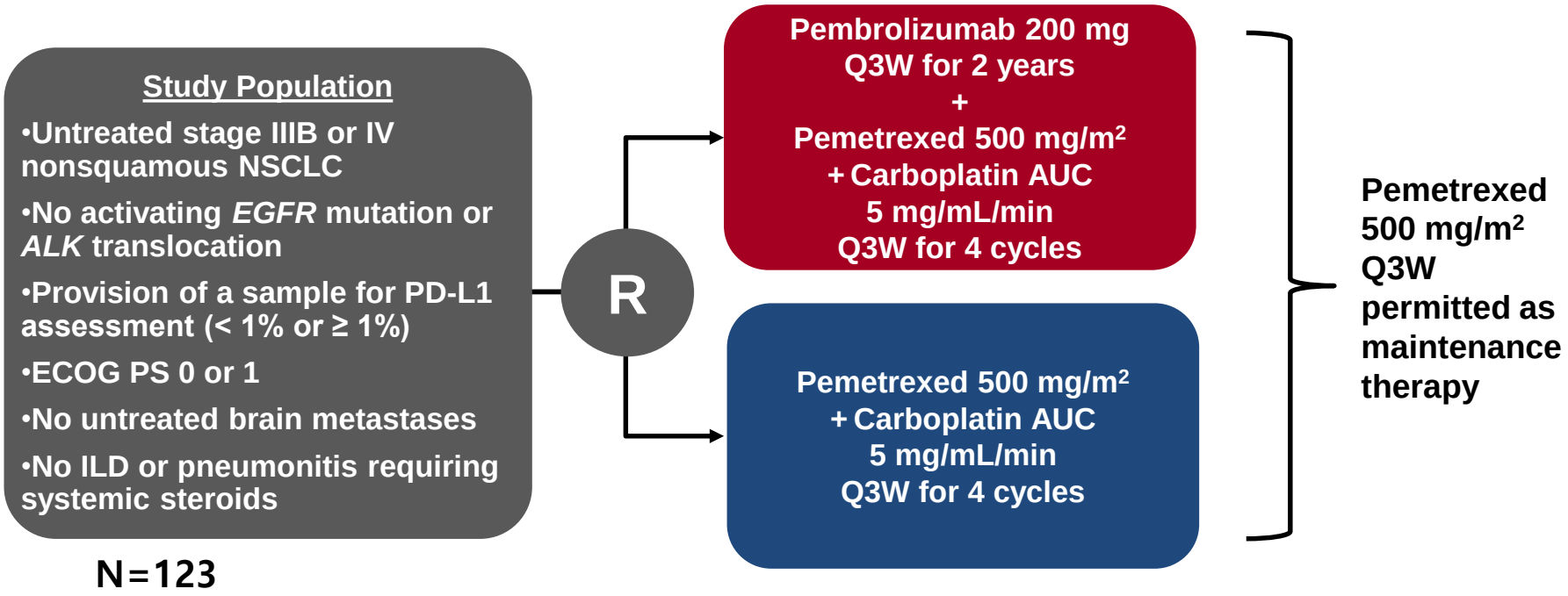
- First-line therapy
  - Pembrolizumab[21,22]
- Subsequent therapy
  - Atezolizumab[23]
  - Nivolumab[24,25]
  - Pembrolizumab[26]

First-line treatment

Combination vs. platinum-doublet CTx

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

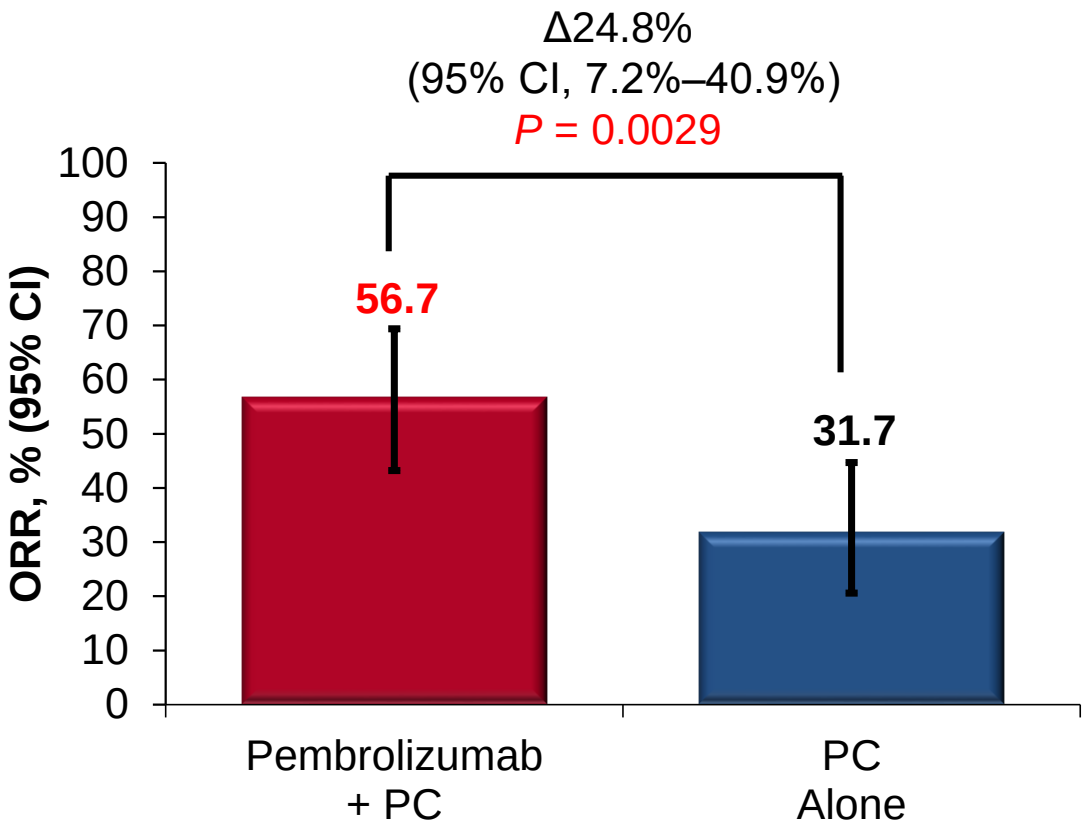
Study design



Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

ORR (primary endpoint)

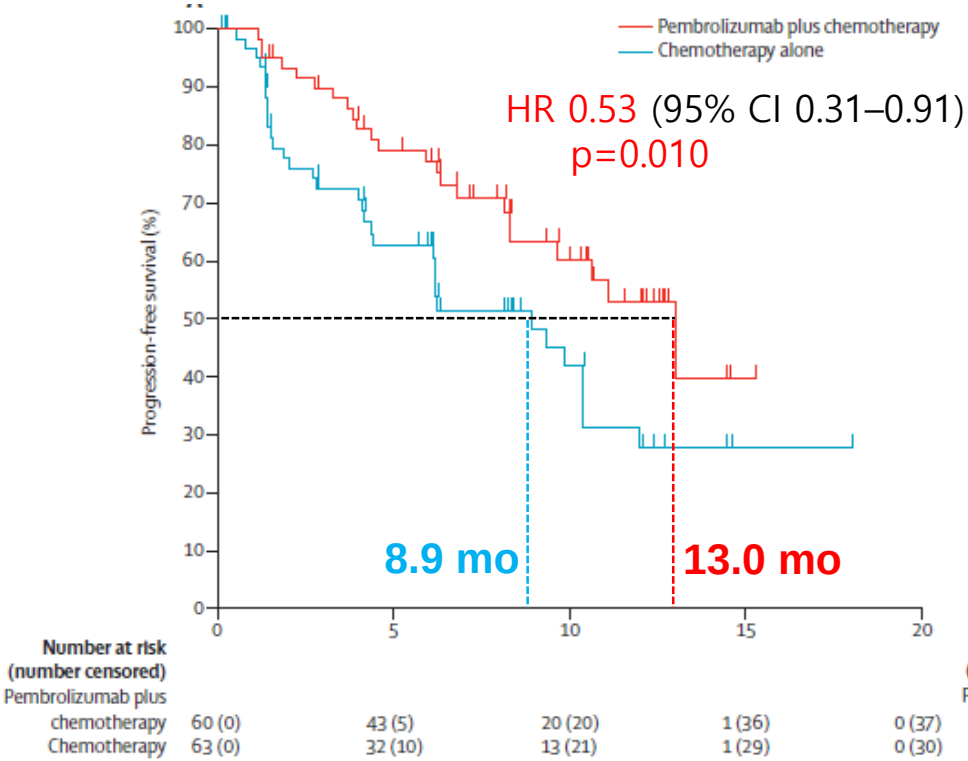


WCLC 2017

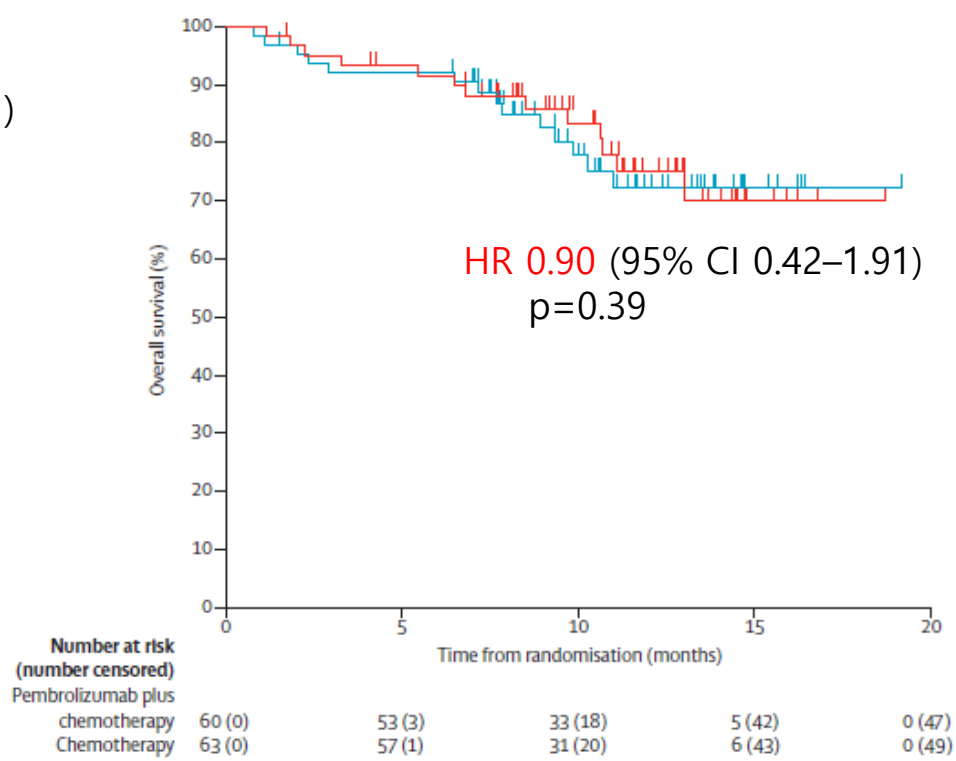
Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

PFS



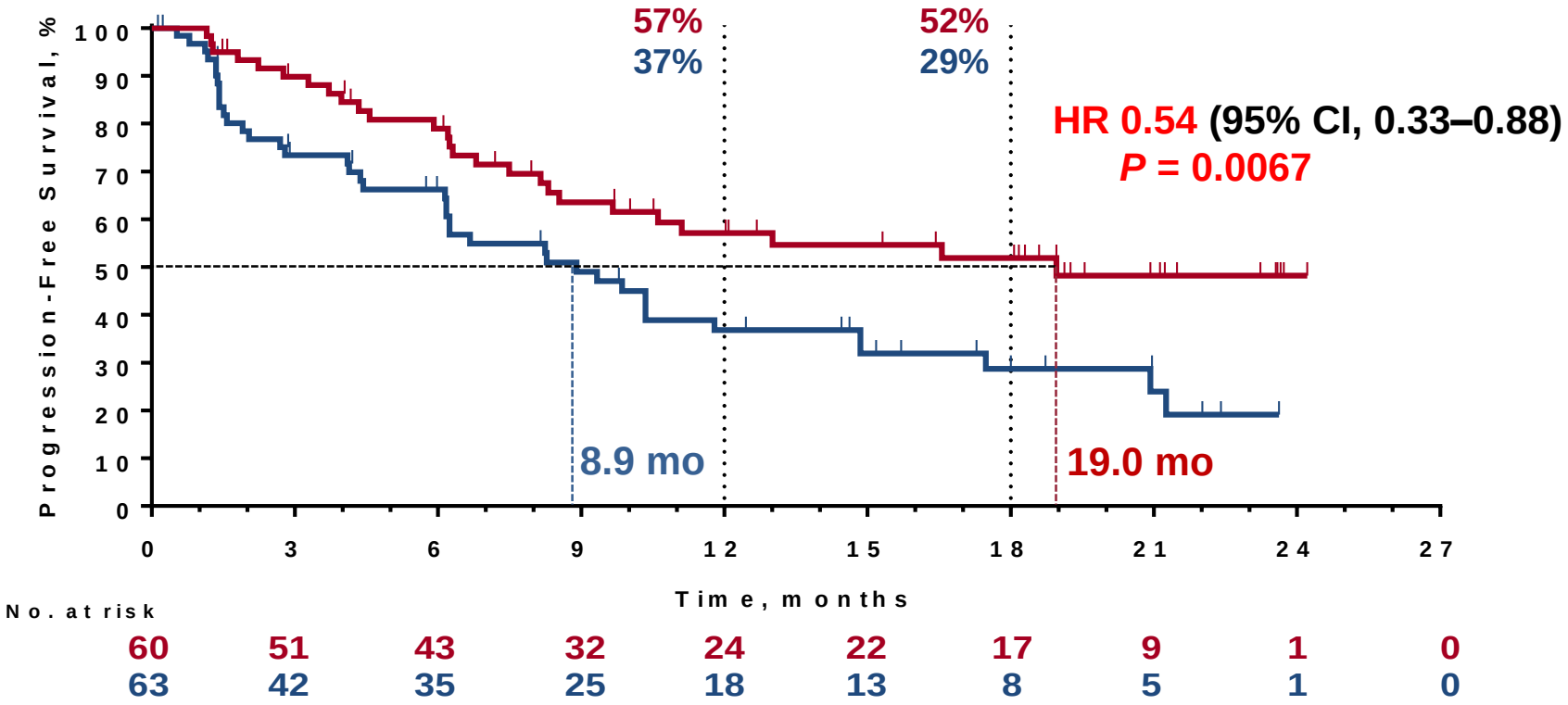
OS



Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

PFS (update analysis)

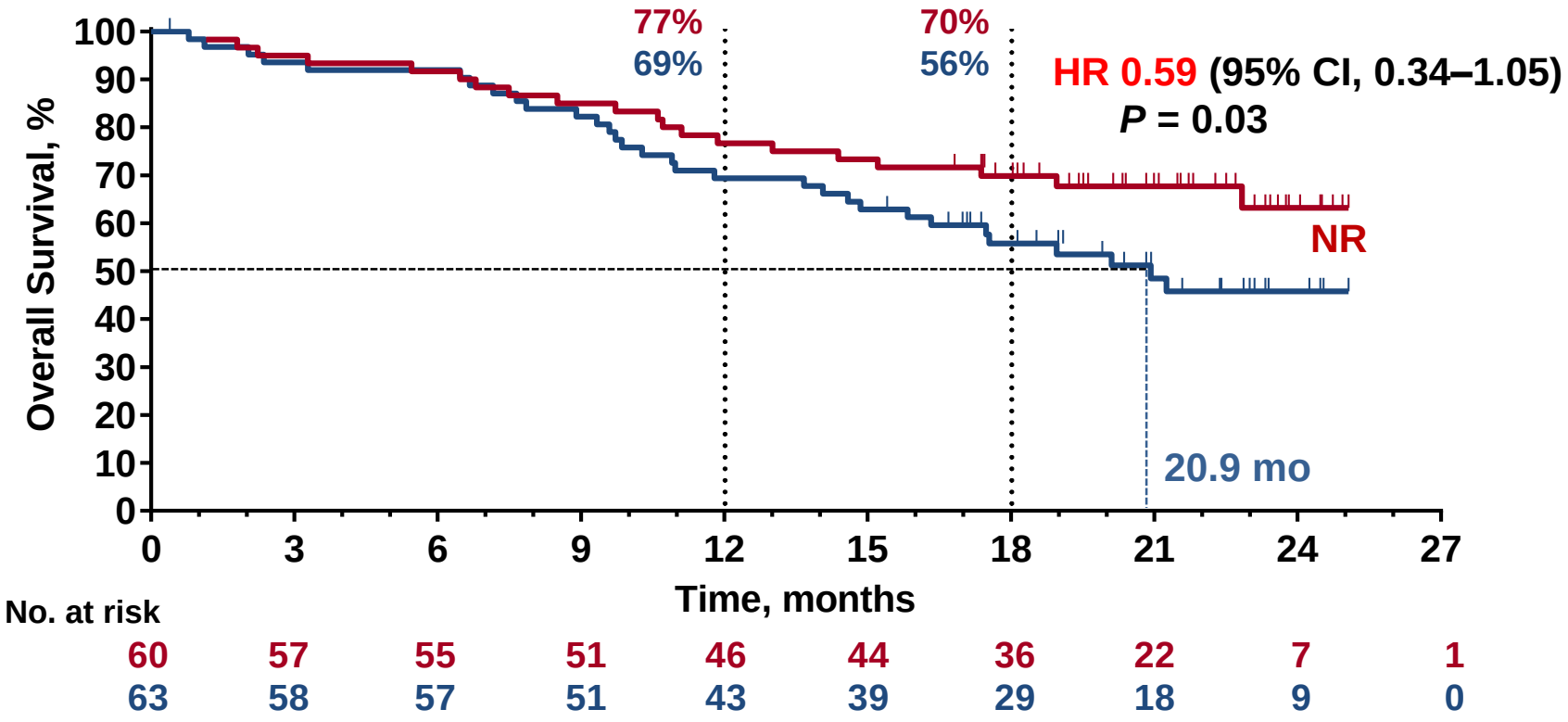


WCLC 2017

Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

OS (update analysis)



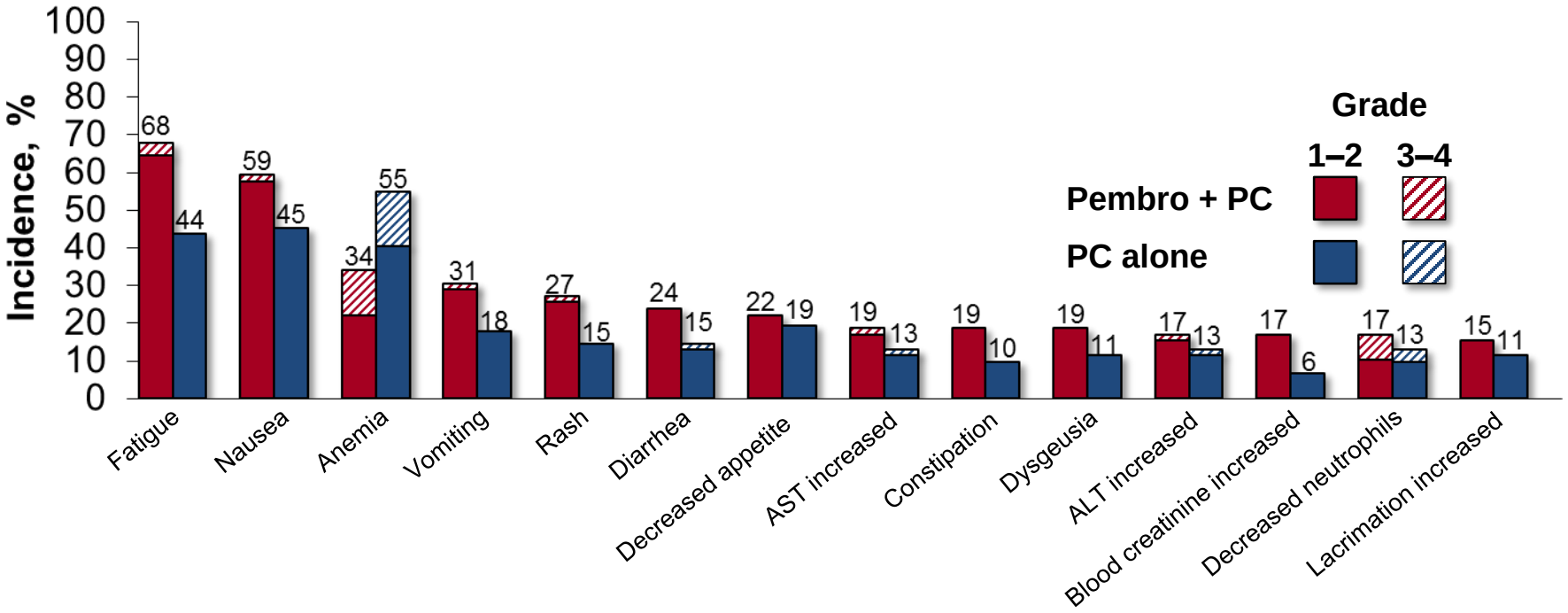
• Cross over Chemotherapy arm: **75% pembrolizumab or others**

WCLC 2017

Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem/Carbo: phase II, 1L Non-SQ
KEYNOTE-021 cohort G

Adverse events



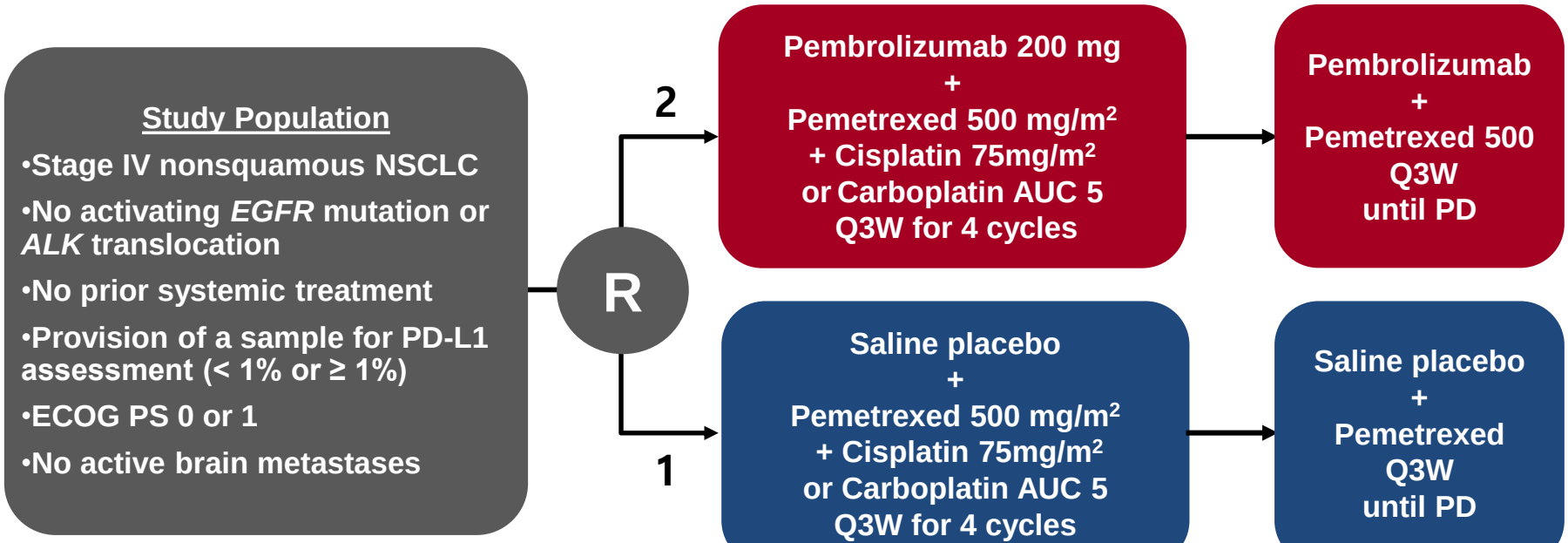
Treatment-related AEs: 41% vs. 29%

WCLC 2017

Langer CJ, et al. Lancet Oncol 2016;17:1497-1508.

Pembrolizumab+Pem-Cis/Carbo: phase III, 1L Non-SQ
KEYNOTE-189

Study design



*Primary endpoints: PFS, OS

Pembrolizumab+Pem-Cis/Carbo: phase III, 1L Non-SQ
KEYNOTE-189

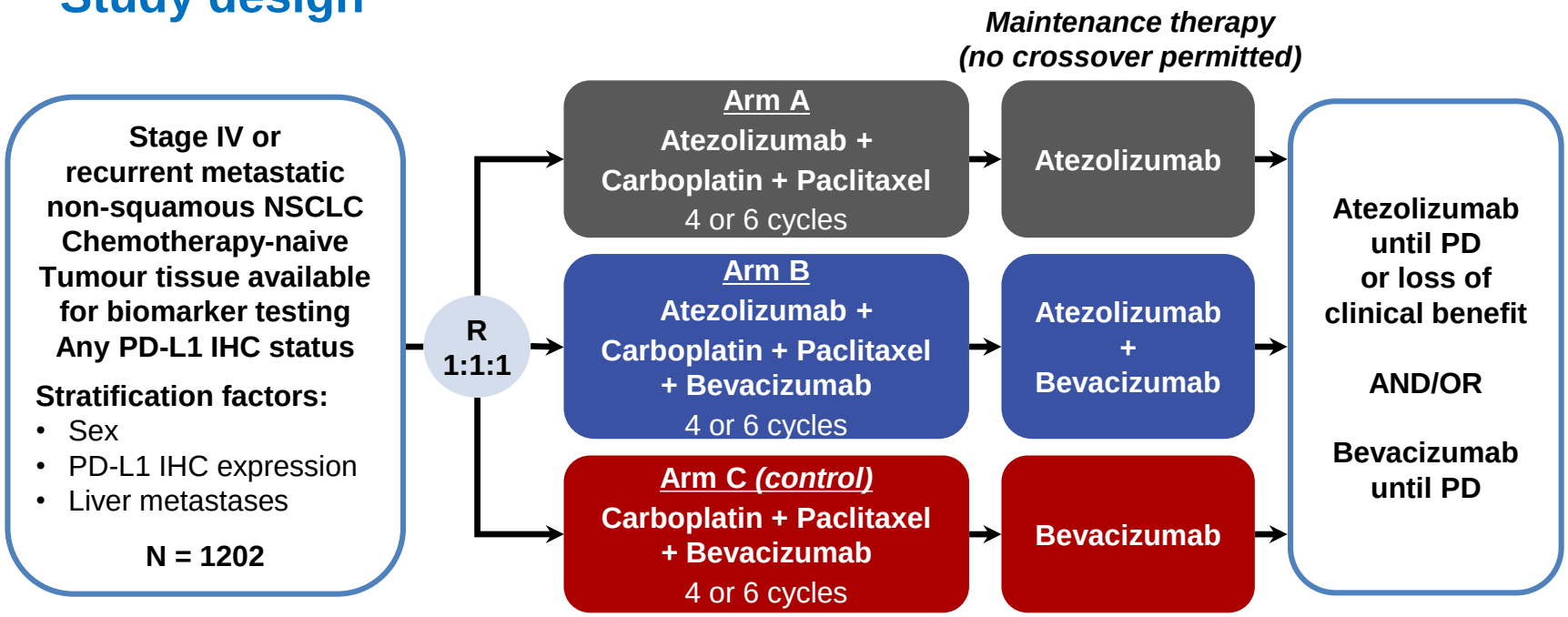
Published on *Merck Newsroom Home* (http://www.mrknewsroom.com) on 1/16/18 6:45 am EST

Merck's KEYTRUDA(R) (pembrolizumab) Significantly Improved Overall Survival and Progression-Free Survival as First-Line Treatment in Combination with Pemetrexed and Platinum Chemotherapy for Patients with Metastatic Nonsquamous Non-Small Cell Lung...

Release Date:
Tuesday, January 16, 2018 6:45 am EST

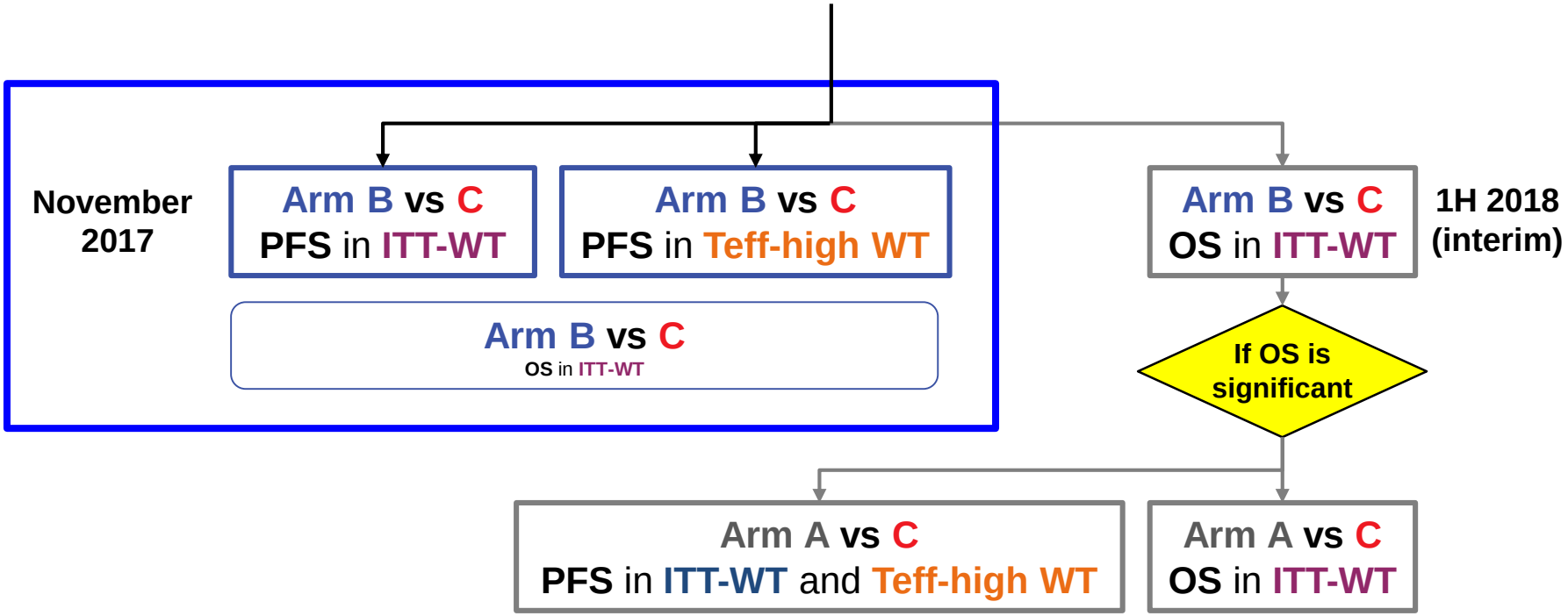
Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ
IMpower150

Study design



Reck M, et al. ESMO immuno-oncology congress 2017

Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ
IMpower150



Arm A: atezo + CP

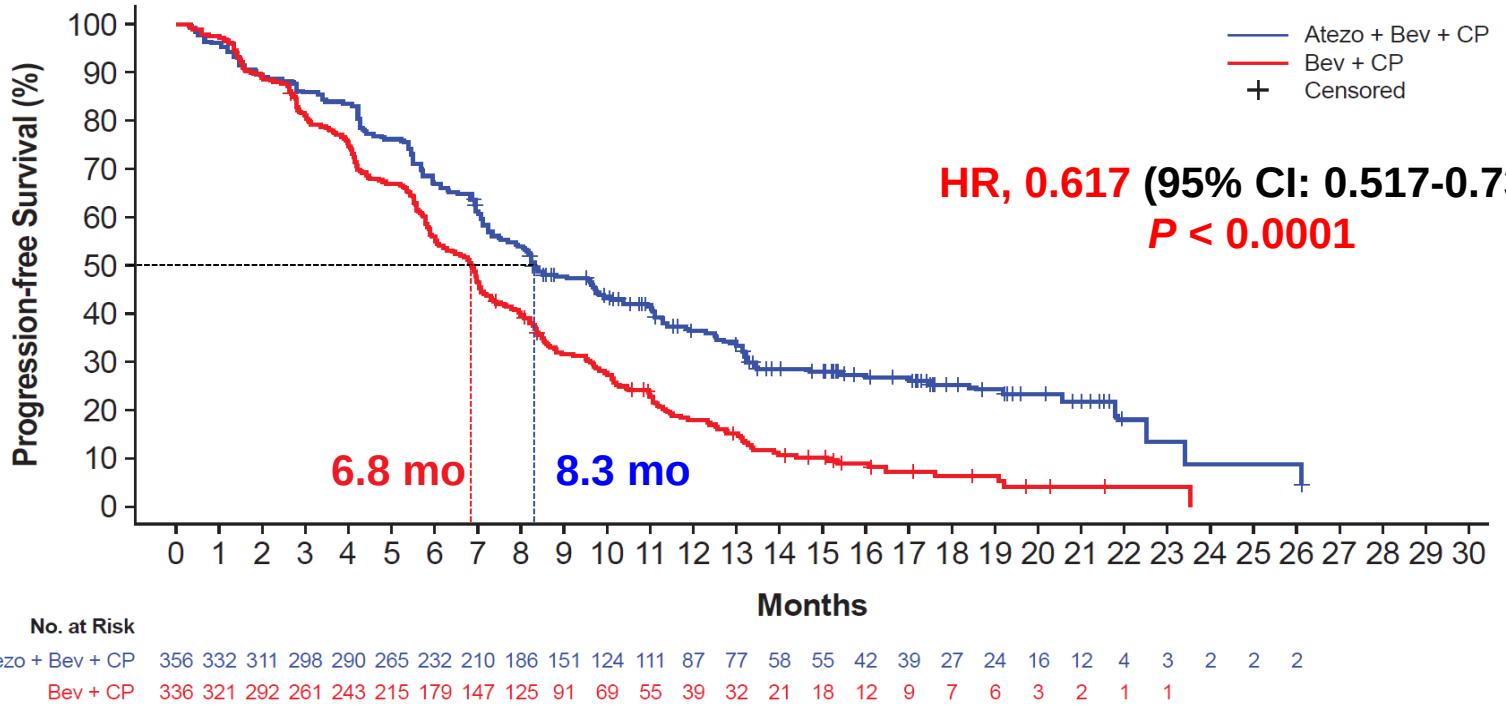
Arm B: atezo + bev + CP

Arm C: bev + CP *(control)*

Reck M, et al. ESMO immuno-oncology congress 2017

Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ
IMpower150

PFS in ITT-WT

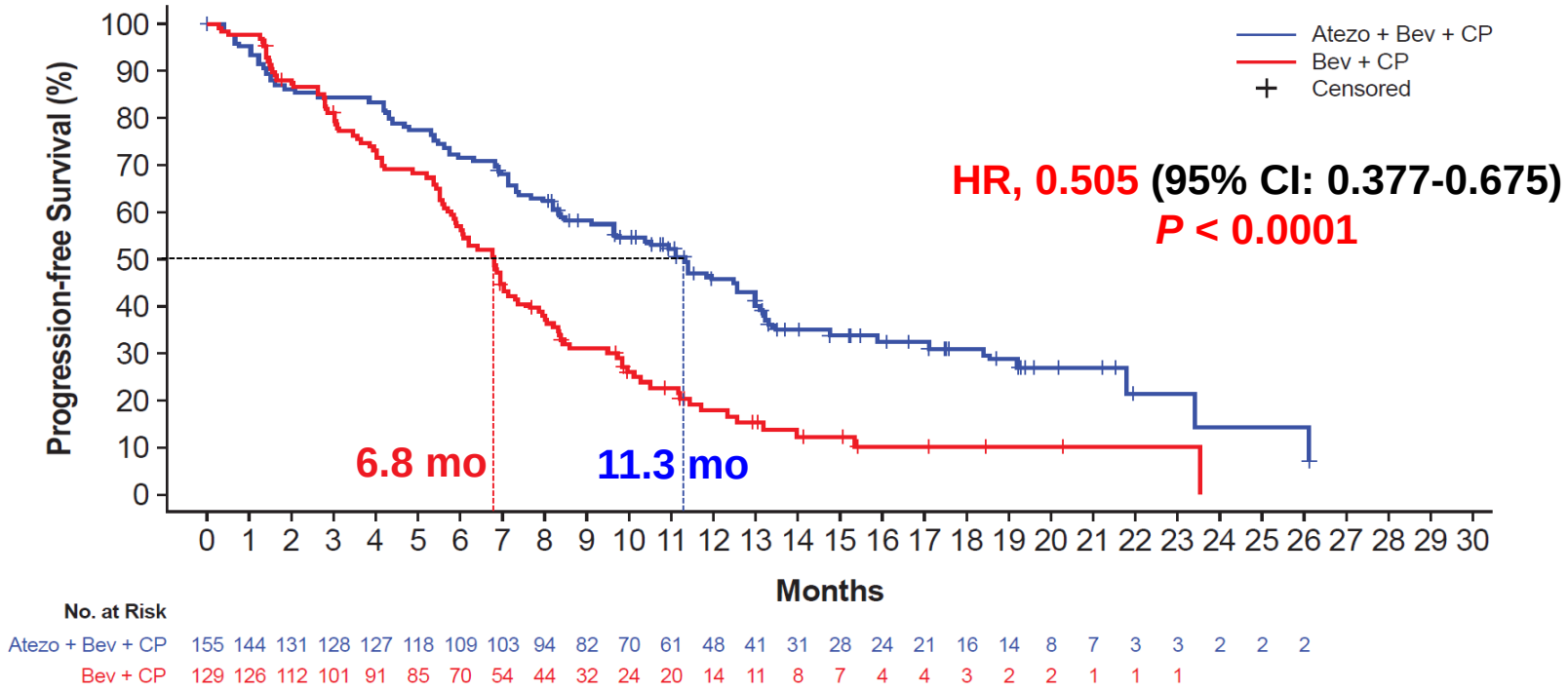


ORR: 64% vs. 48%

Reck M, et al. ESMO immuno-oncology congress 2017

Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ
IMpower150

PFS in Teff-high-WT

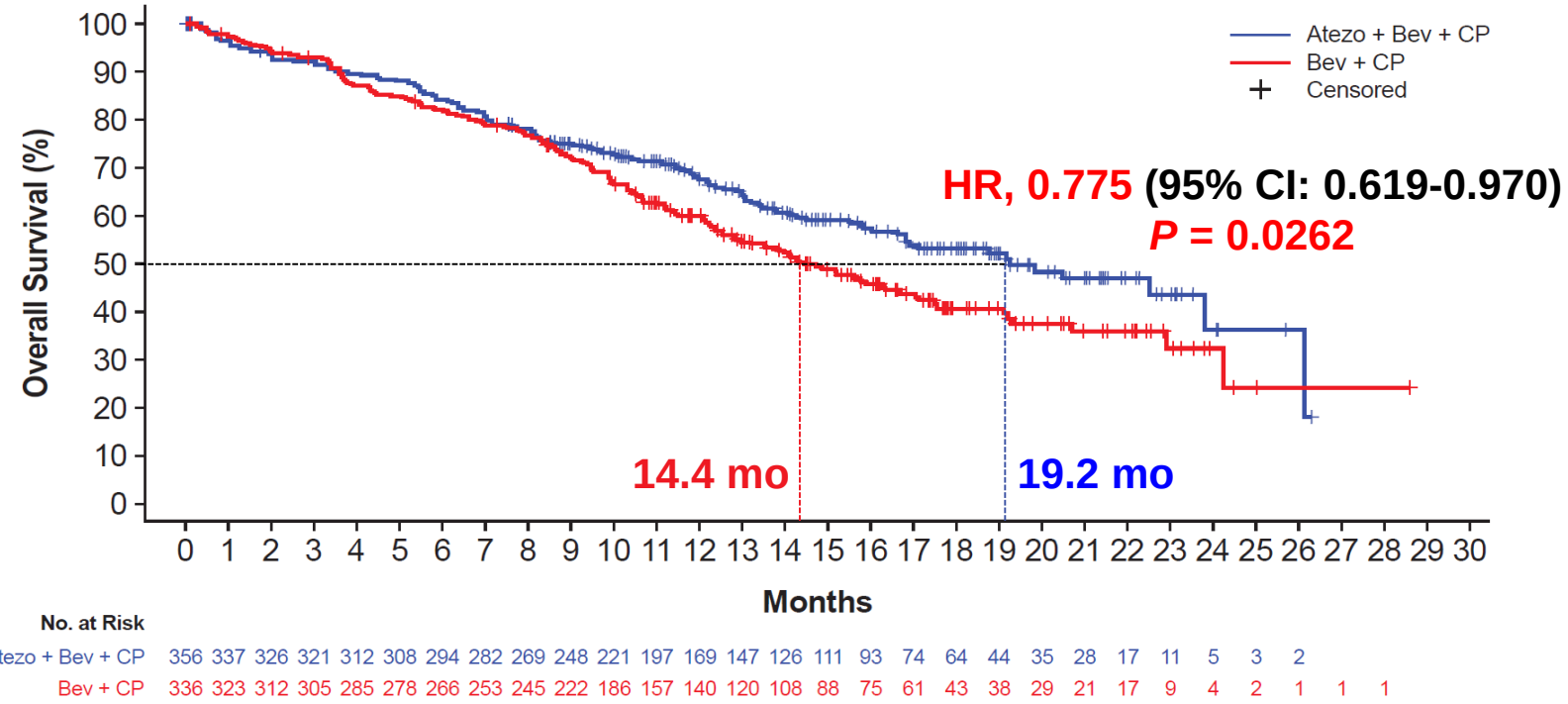


ORR: 69% vs. 54%

Reck M, et al. ESMO immuno-oncology congress 2017

Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ
IMpower150

OS in ITT-WT (not mature)



ORR: 64% vs. 48%

Reck M, et al. ESMO immuno-oncology congress 2017

Atezolizumab+bevacizumab+PC: phase III, 1L Non-SQ IMpower150

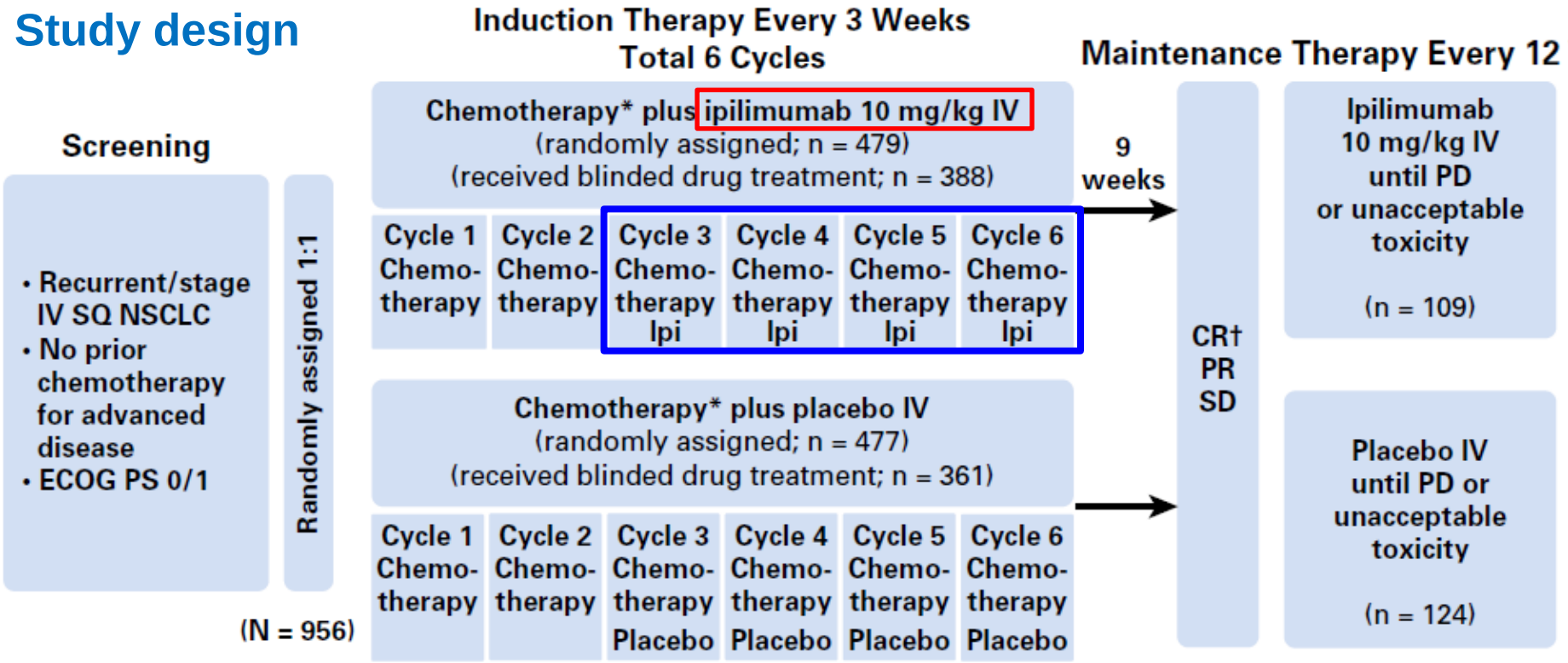
Immune-related AEs of special interest in ≥ 5 patients across arms

	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
AEs of special interest, n (%)	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	114 (29%)	14 (4%)	113 (29%)	9 (2%)	52 (13%)	2 (1%)
Hepatitis	39 (10%)	12 (3%)	54 (14%)	19 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	34 (9%)	10 (3%)	47 (12%)	16 (4%)	29 (7%)	3 (1%)
Hypothyroidism	30 (8%)	1 (<1%)	50 (13%)	1 (<1%)	15 (4%)	0
Infusion-related reactions	16 (4%)	3 (1%)	13 (3%)	2 (1%)	11 (3%)	3 (1%)
Pneumonitis	21 (5%)	7 (2%)	11 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	9 (2%)	5 (1%)	2 (1%)	2 (1%)
Severe cutaneous reaction	3 (1%)	3 (1%)	4 (1%)	0	1 (<1%)	0
Adrenal insufficiency	2 (1%)	0	2 (1%)	1 (<1%)	3 (1%)	1 (<1%)
Pancreatitis	2 (1%)	2 (1%)	5 (1%)	2 (1%)	0	0

Reck M, et al. ESMO immuno-oncology congress 2017

Ipilimumab+Pac/Carbo: phase III, 1L Squamos NSCLC

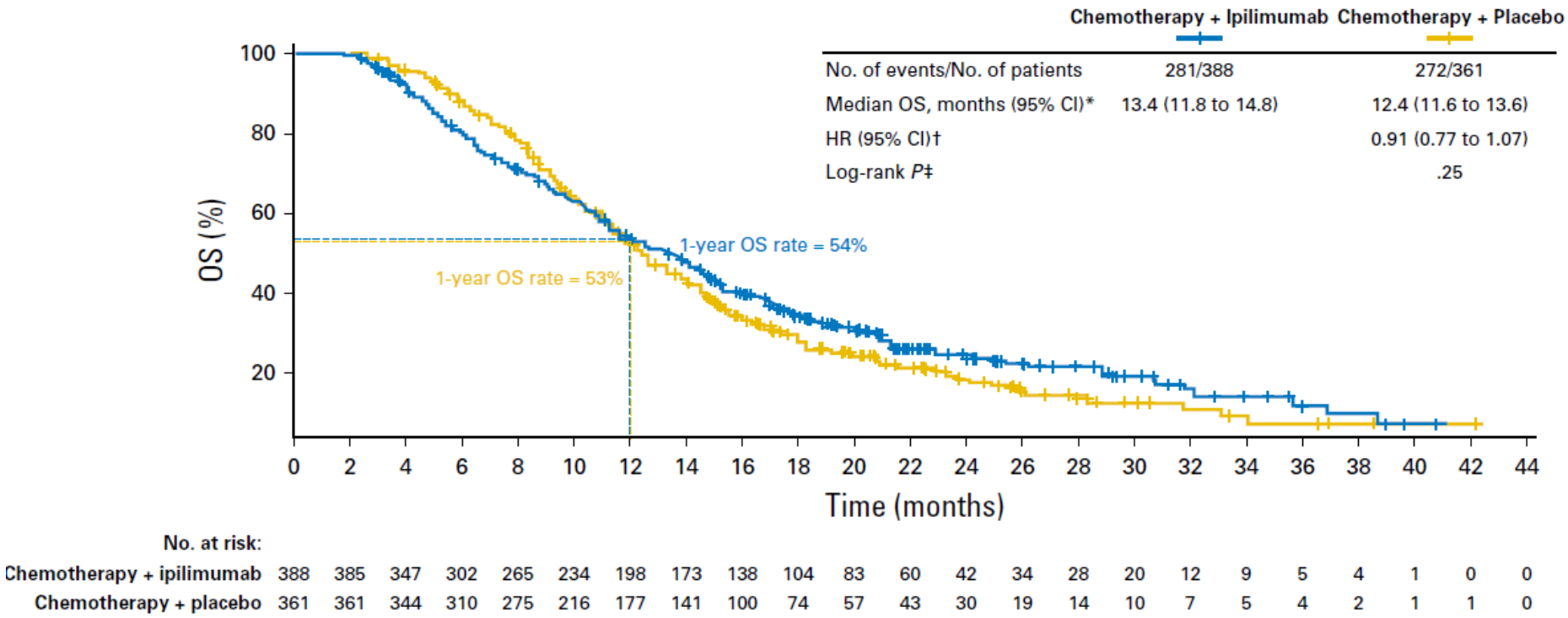
Study design



Govindan R, et al. J Clin Oncol 2017;35:3449-57.

Ipilimumab+Pac/Carbo: phase III, 1L Squamos NSCLC

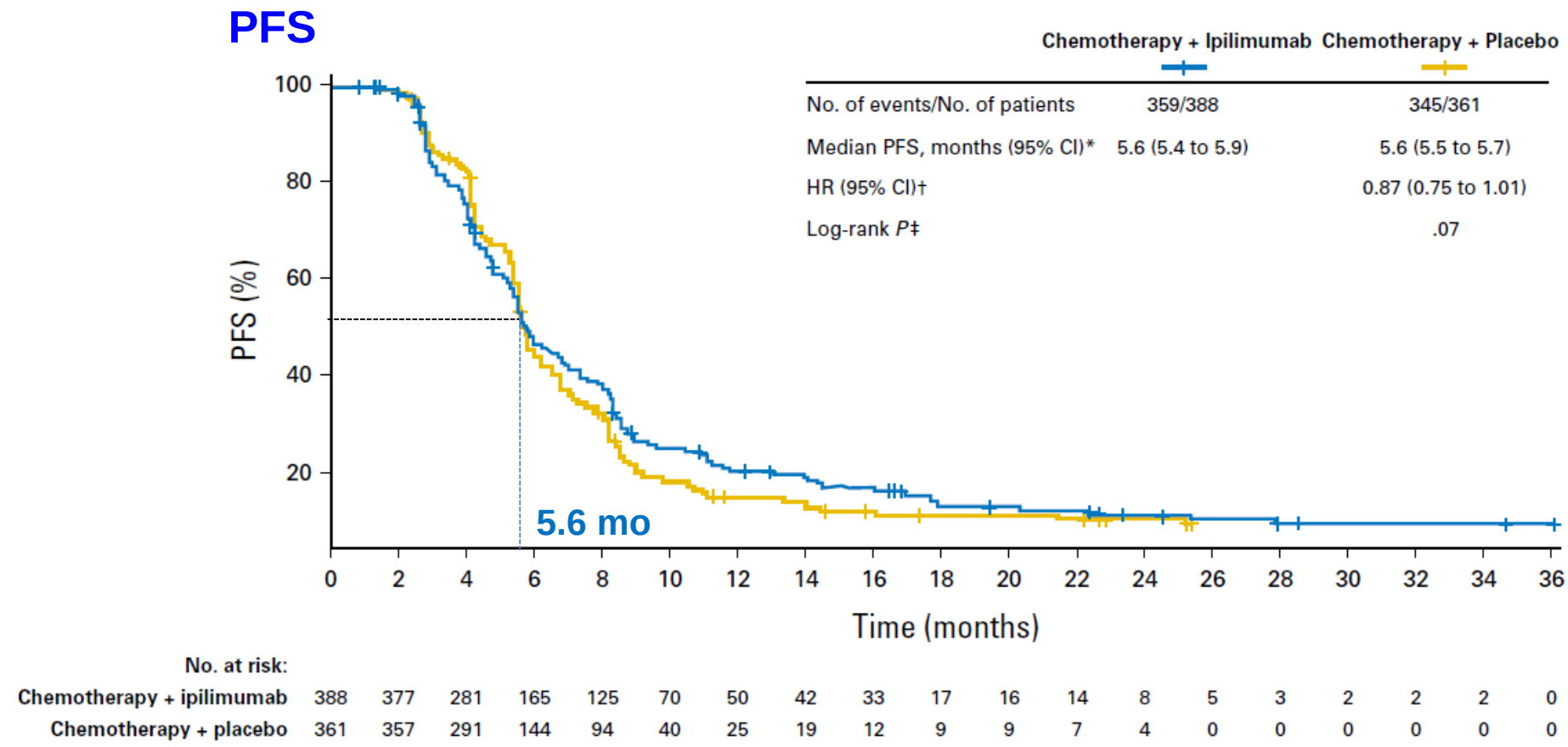
OS (primary endpoint)



ORR: 44% vs. 47%

Govindan R, et al. J Clin Oncol 2017;35:3449-57.

Ipilimumab+Pac/Carbo: phase III, 1L Squamos NSCLC



ORR: 44% vs. 47%

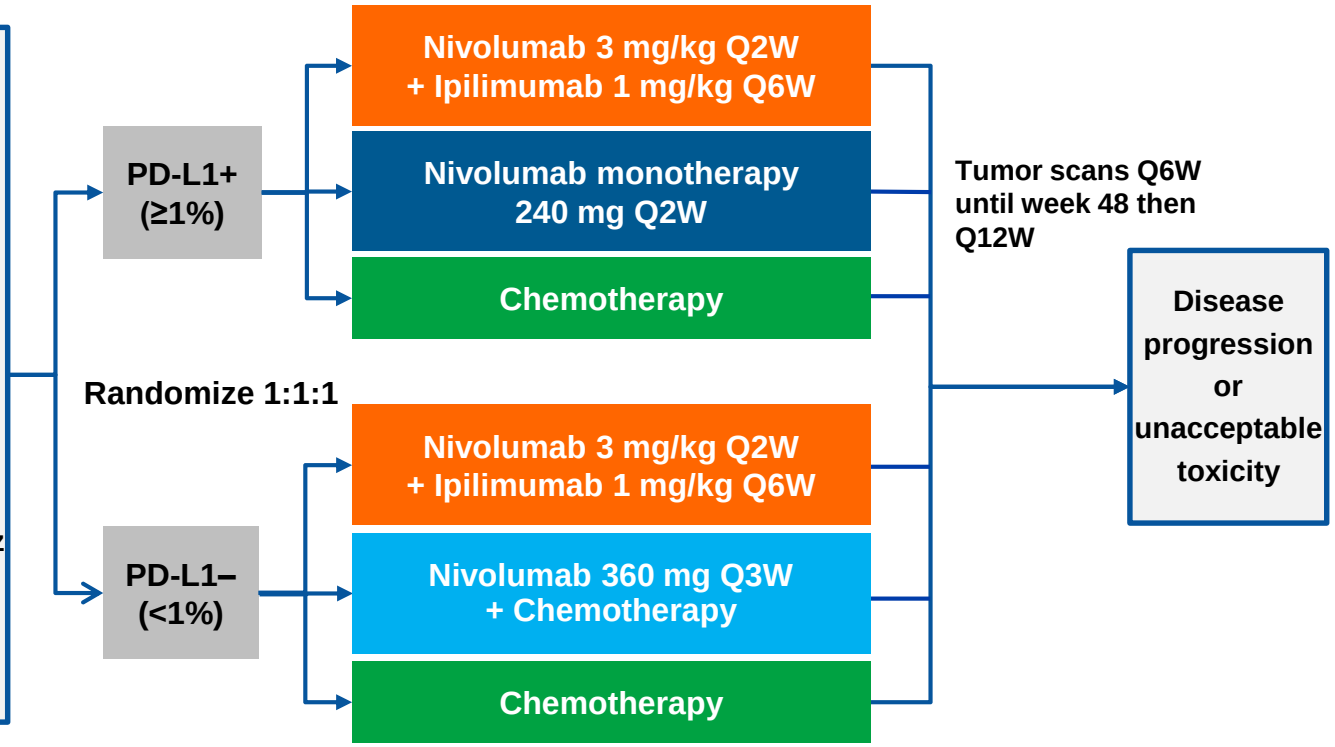
Govindan R, et al. J Clin Oncol 2017;35:3449-57.

Nivolumab+Ipilimumab: phase III, 1L NSCLC
CheckMate 227

Study design

Key eligibility criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- CNS metastases permitted if adequately treated ≥2 weeks prior to randomization

Stratification factor at randomization:
- Histology (squamous vs non-squamous)



***Primary endpoints: PFS, OS**

Nivolumab+Ipilimumab: phase III, 1L NSCLC
CheckMate 227

Bristol-Myers Squibb

Press Release

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Pivotal Phase 3 CheckMate -227 Study Demonstrates Superior Progression-Free Survival (PFS) with the Opdivo Plus Yervoy Combination Versus Chemotherapy in First-Line Non-Small Cell Lung Cancer (NSCLC) Patients with High Tumor Mutation Burden (TMB)

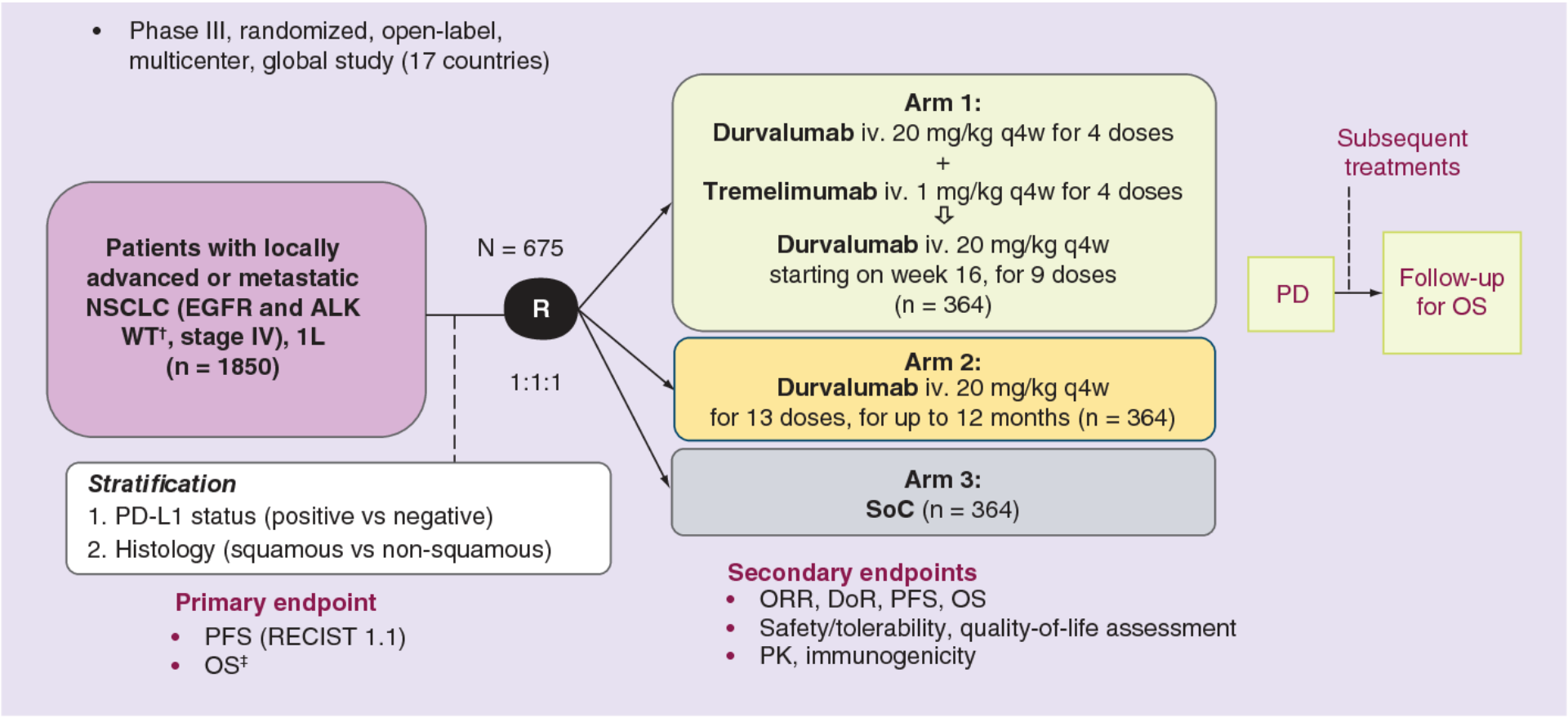
First and only Phase 3 trial to evaluate and show a highly statistically significant PFS benefit with an I-O/I-O combination in first-line NSCLC patients with high TMB, regardless of PD-L1 expression

Results will be shared with regulatory authorities and presented at a future congress

Trial will continue as planned to assess the Opdivo plus Yervoy combination for the other co-primary endpoint of overall survival in patients whose tumors express PD-L1

MONDAY, FEBRUARY 5, 2018 6:59 AM EST

Durvalumab+Tremelimumab: phase III, 1L NSCLC
MYSTIC



Durvalumab+Tremelimumab: phase III, 1L NSCLC
MYSTIC

AstraZeneca

AstraZeneca Websites | Global site

What science can do | Our science | Our focus areas | Our company | Careers | Investors | Partnering | Media | Sustainability

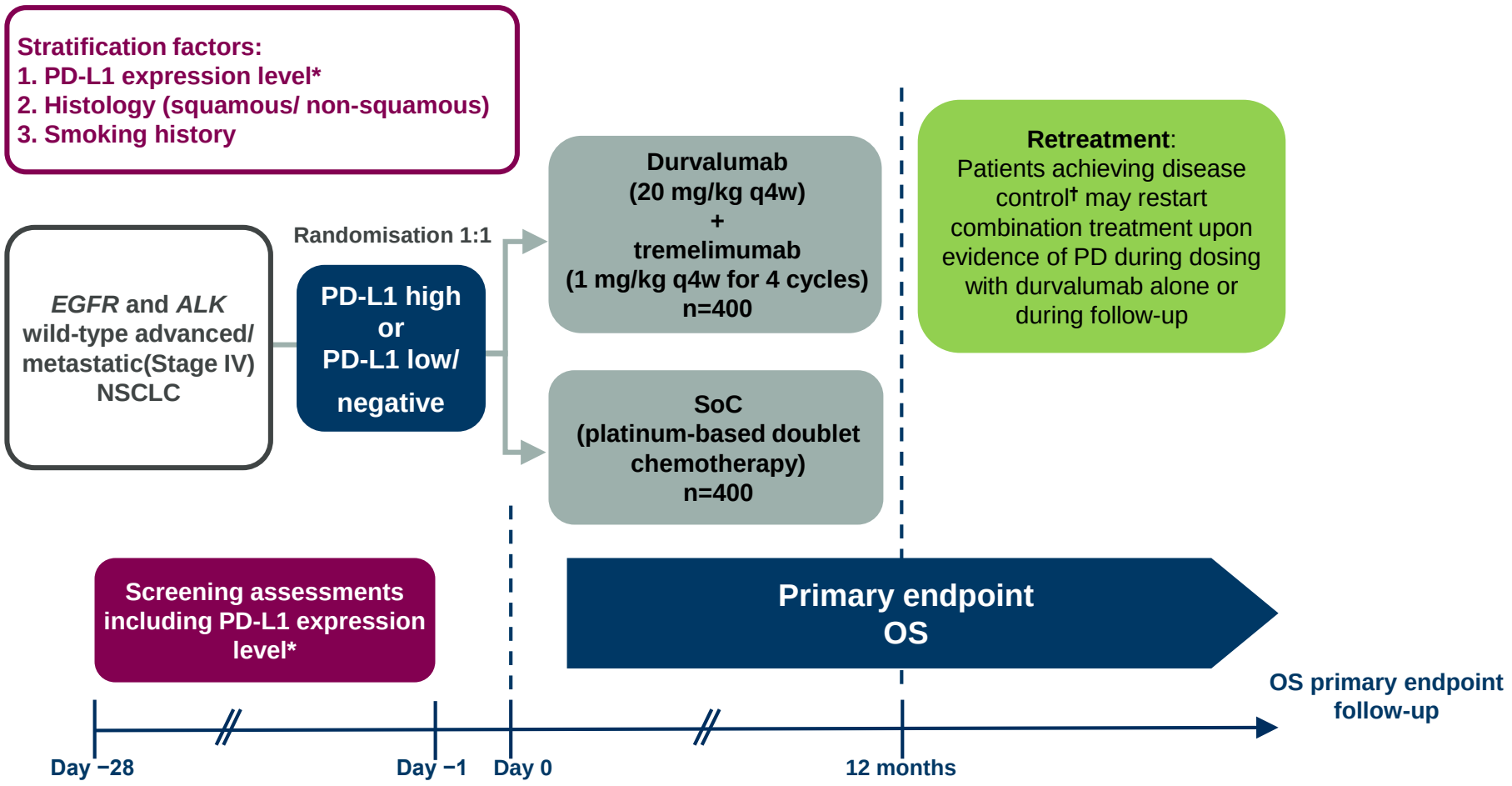
AstraZeneca reports initial results from the ongoing MYSTIC trial in Stage IV lung cancer

PUBLISHED
27 July 2017

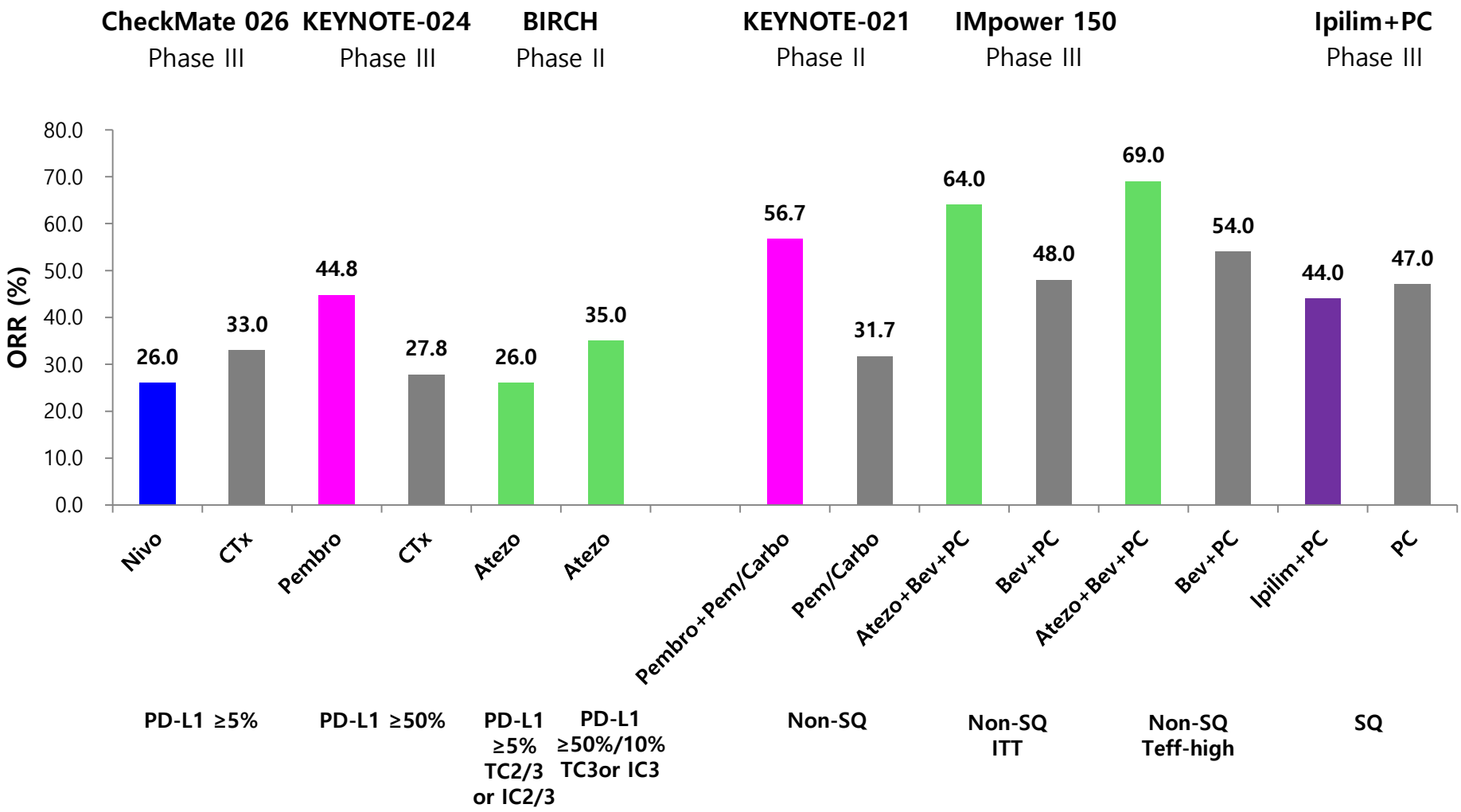
Imfinzi plus tremelimumab combination did not meet a primary endpoint of progression-free survival compared to chemotherapy

The MYSTIC trial continues as planned to assess the additional primary endpoints of overall survival for Imfinzi monotherapy and for the Imfinzi plus tremelimumab combination

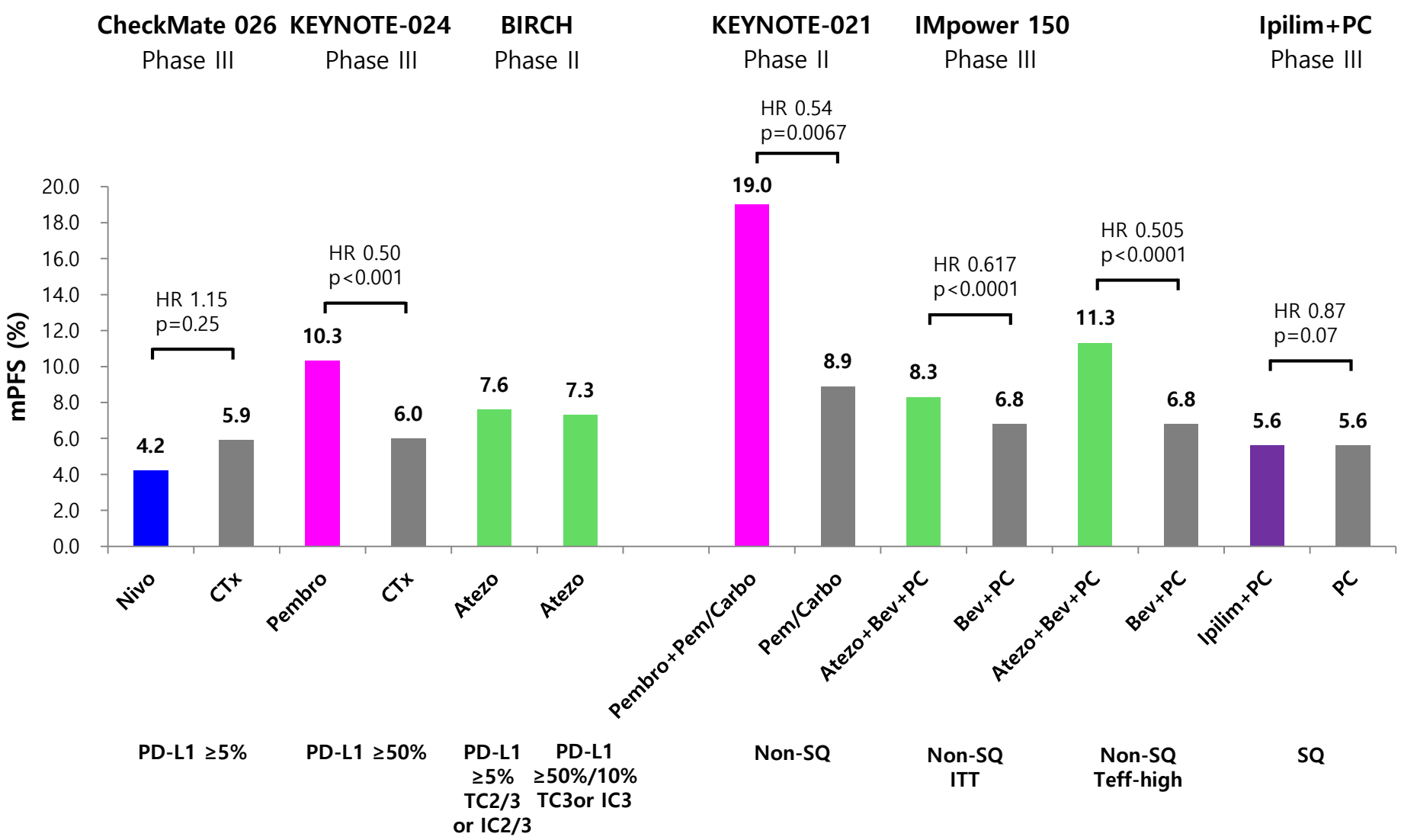
Durvalumab+Tremelimumab: phase III, 1L NSCLC
NEPTUNE



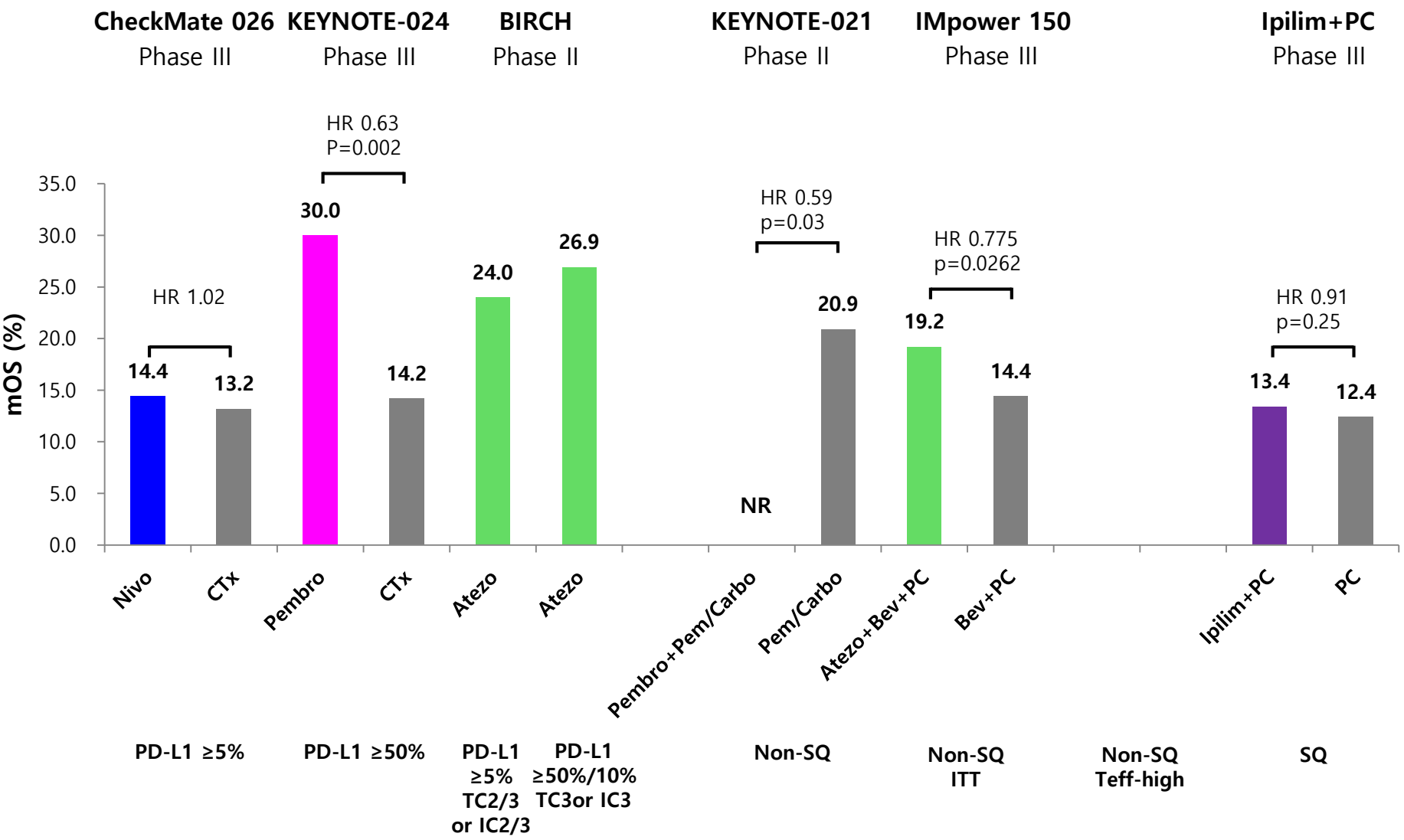
First-line treatment: ORR



First-line treatment: PFS



First-line treatment: OS



SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)*,**

Initial Cytotoxic Therapy Options

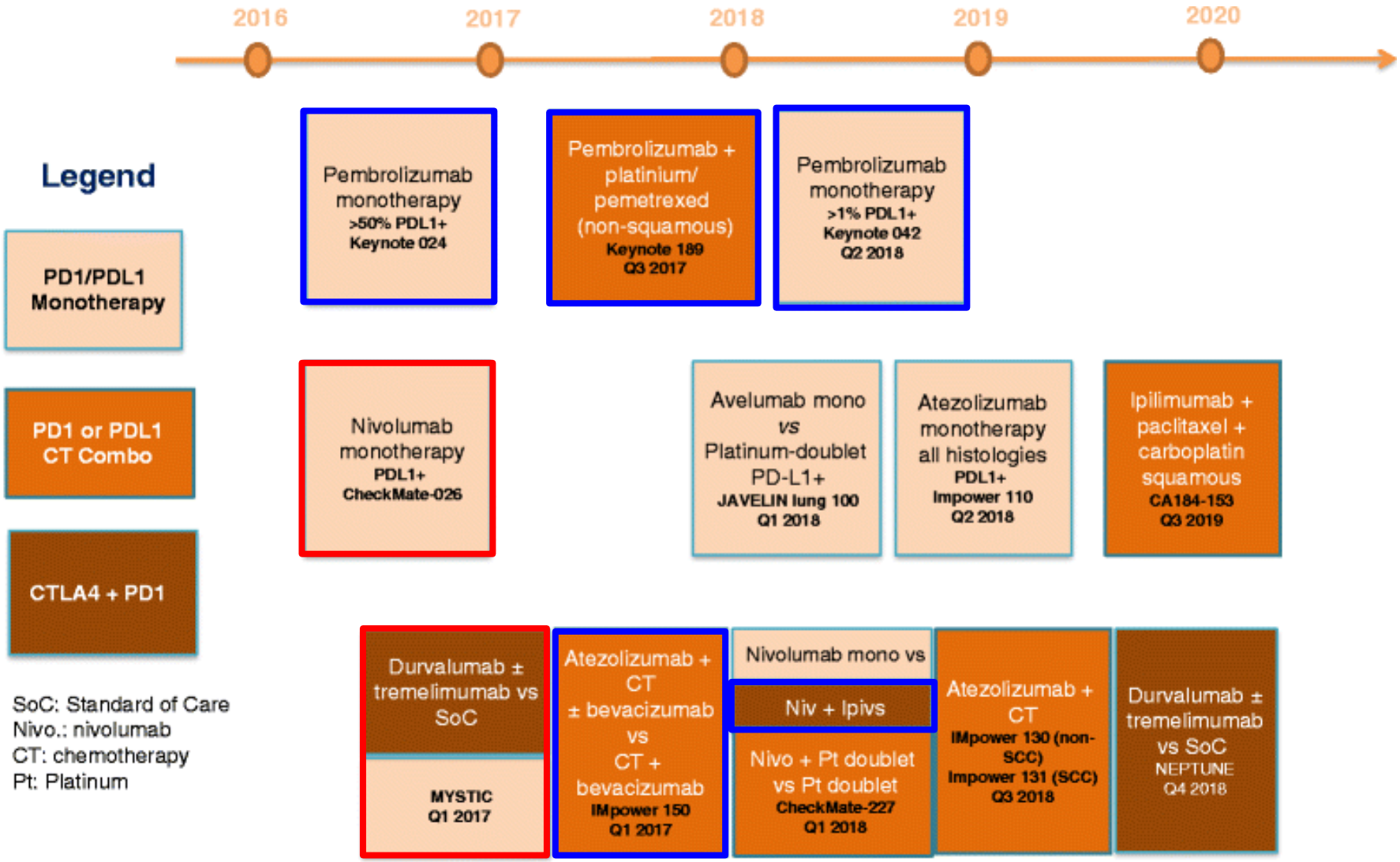
Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)

- Bevacizumab/carboplatin/paclitaxel (category 1)[1,†,‡,#]
- Bevacizumab/carboplatin/pemetrexed[2,†,‡,#]
- Bevacizumab/cisplatin/pemetrexed[3,†,‡,#]
- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/pemetrexed (category 1)[10]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[11]
- Cisplatin/gemcitabine (category 1)[9,12]
- Cisplatin/paclitaxel (category 1)[13]
- Cisplatin/pemetrexed (category 1)[12]
- Gemcitabine/docetaxel (category 1)[14]
- Gemcitabine/vinorelbine (category 1)[15]
- Pembrolizumab/carboplatin/pemetrexed[16,¶]

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel[17]
- Carboplatin/albumin-bound paclitaxel[18,19]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/pemetrexed[10]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]
- Pemetrexed[28]

Upcoming randomized trials of 1st line NSCLC



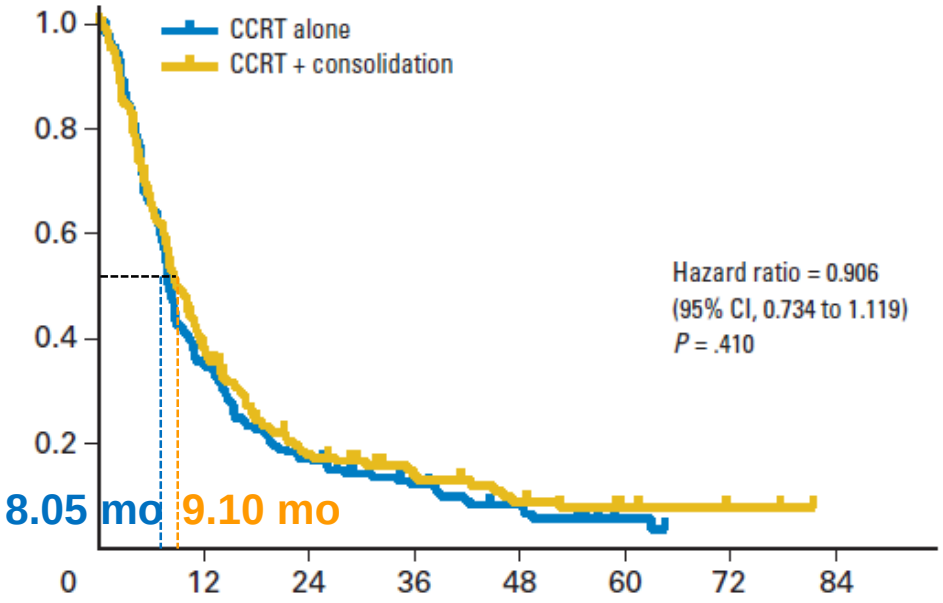
BMC Med 2017;15:55.

Stage III treatment

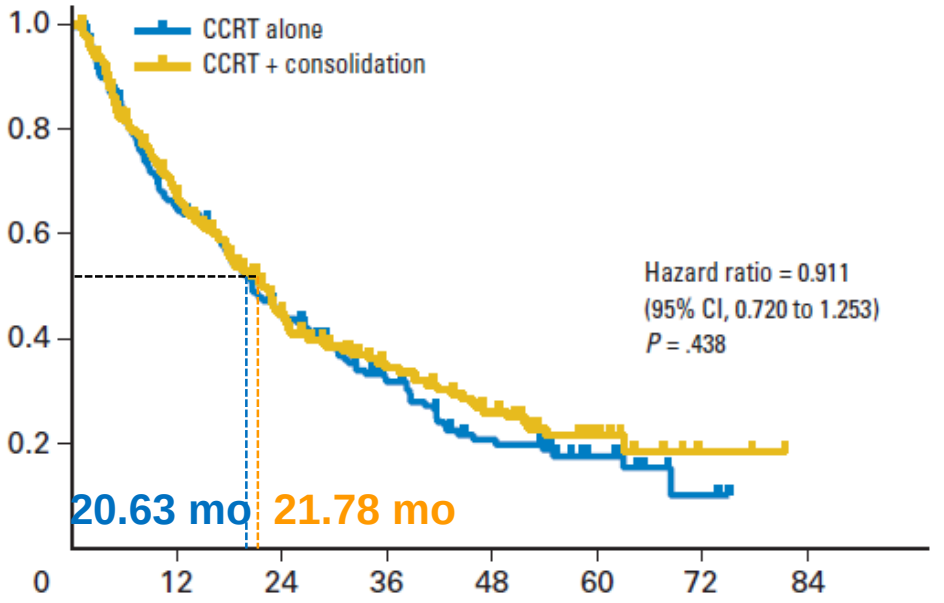
CCRT+consolidation vs. CCRT

Standard of care: locally advanced & unresectable NSCLC
CCRT+consolidation vs. CCRT

Progress free survival



Overall survival

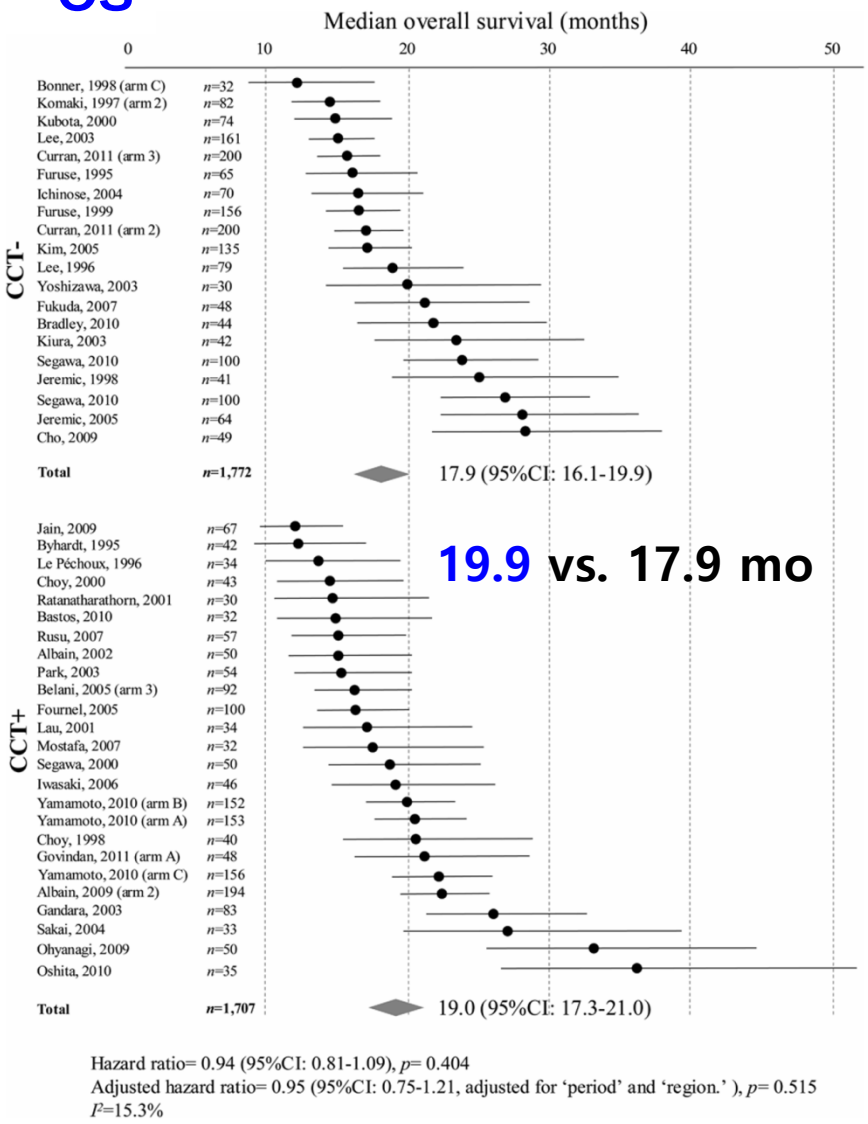


Ahn JS, et al. J Clin Oncol 2015;33:2660-6.

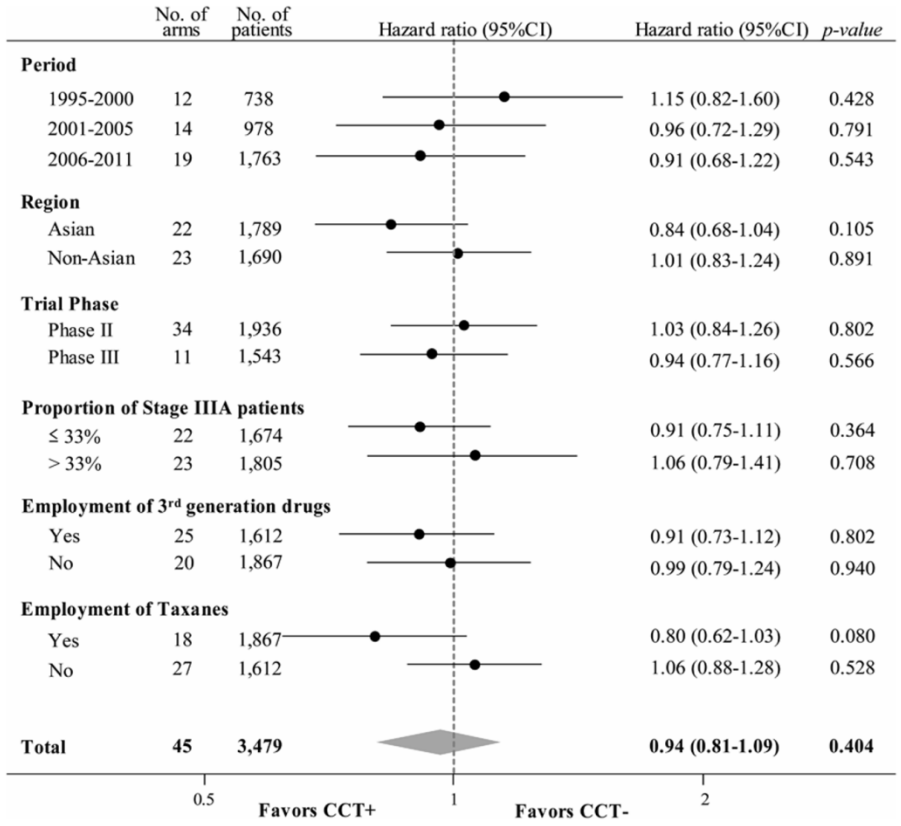
Standard of care: locally advanced & unresectable NSCLC

CCRT+consolidation vs. CCRT

OS



19.9 vs. 17.9 mo



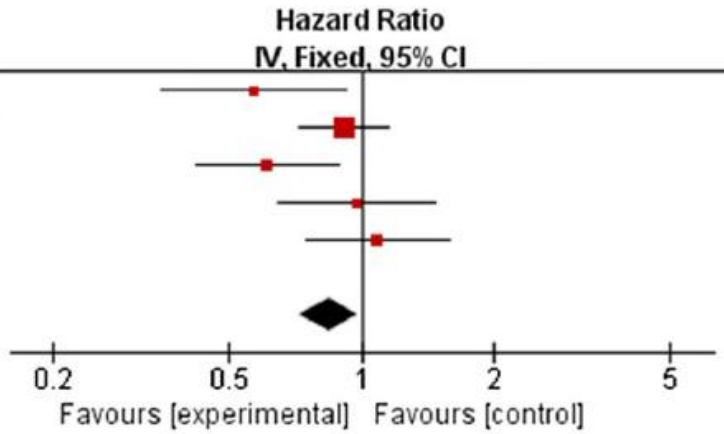
Tsujino K, et al. Int J Thorac Oncol 2013;8:1181–9.

Standard of care: locally advanced & unresectable NSCLC
CCRT+consolidation vs. CCRT

OS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hasan Mutlu 2015	-0.5621	0.2488	9.9%	0.57 [0.35, 0.93]
Jin Seok Ahn 2015	-0.0932	0.12	42.5%	0.91 [0.72, 1.15]
Lipin Liu 2015	-0.4943	0.1904	16.9%	0.61 [0.42, 0.89]
Nasser Hanna 2008	-0.0202	0.2095	13.9%	0.98 [0.65, 1.48]
S. I. Jalal 2011	0.0862	0.1907	16.8%	1.09 [0.75, 1.58]
Total (95% CI)			**100.0%**	**0.85 [0.73, 0.99]**

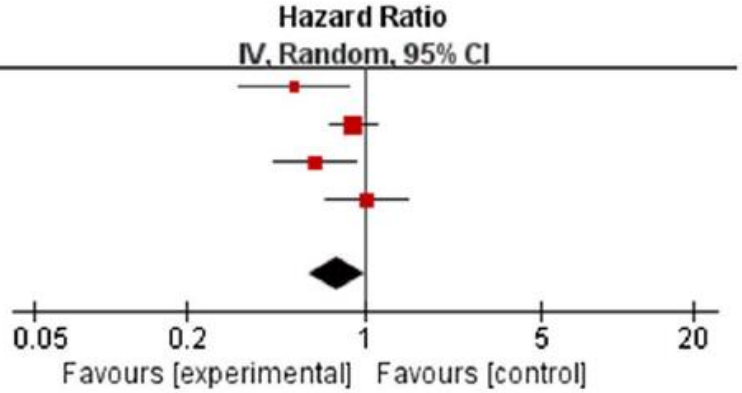
Heterogeneity: Chi² = 8.11, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 2.13 (P = 0.03)



PFS

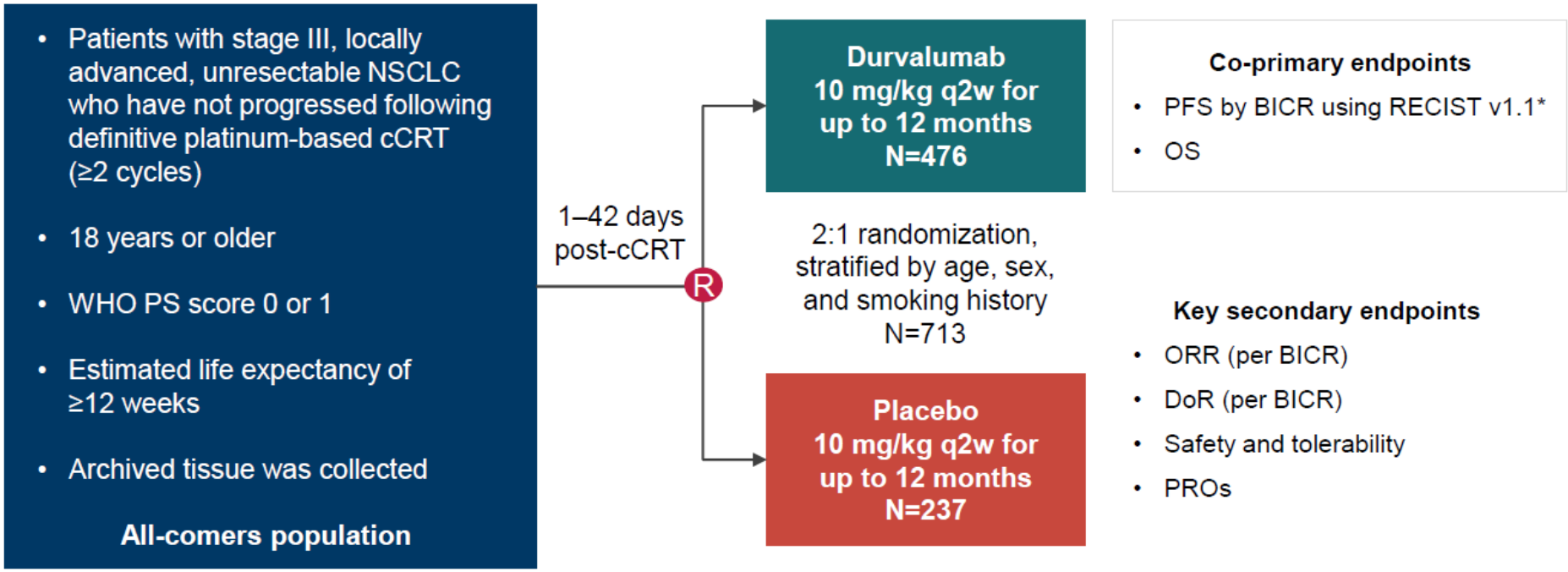
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Hasan Mutlu 2015	-0.6349	0.2574	17.0%	0.53 [0.32, 0.88]
Jin Seok Ahn 2015	-0.0987	0.1074	35.7%	0.91 [0.73, 1.12]
Lipin Liu 2015	-0.4463	0.1912	23.7%	0.64 [0.44, 0.93]
Nasser Hanna 2008	0.0198	0.1921	23.6%	1.02 [0.70, 1.49]
Total (95% CI)			**100.0%**	**0.78 [0.60, 1.02]**

Heterogeneity: Tau² = 0.04; Chi² = 6.70, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 1.84 (P = 0.07)



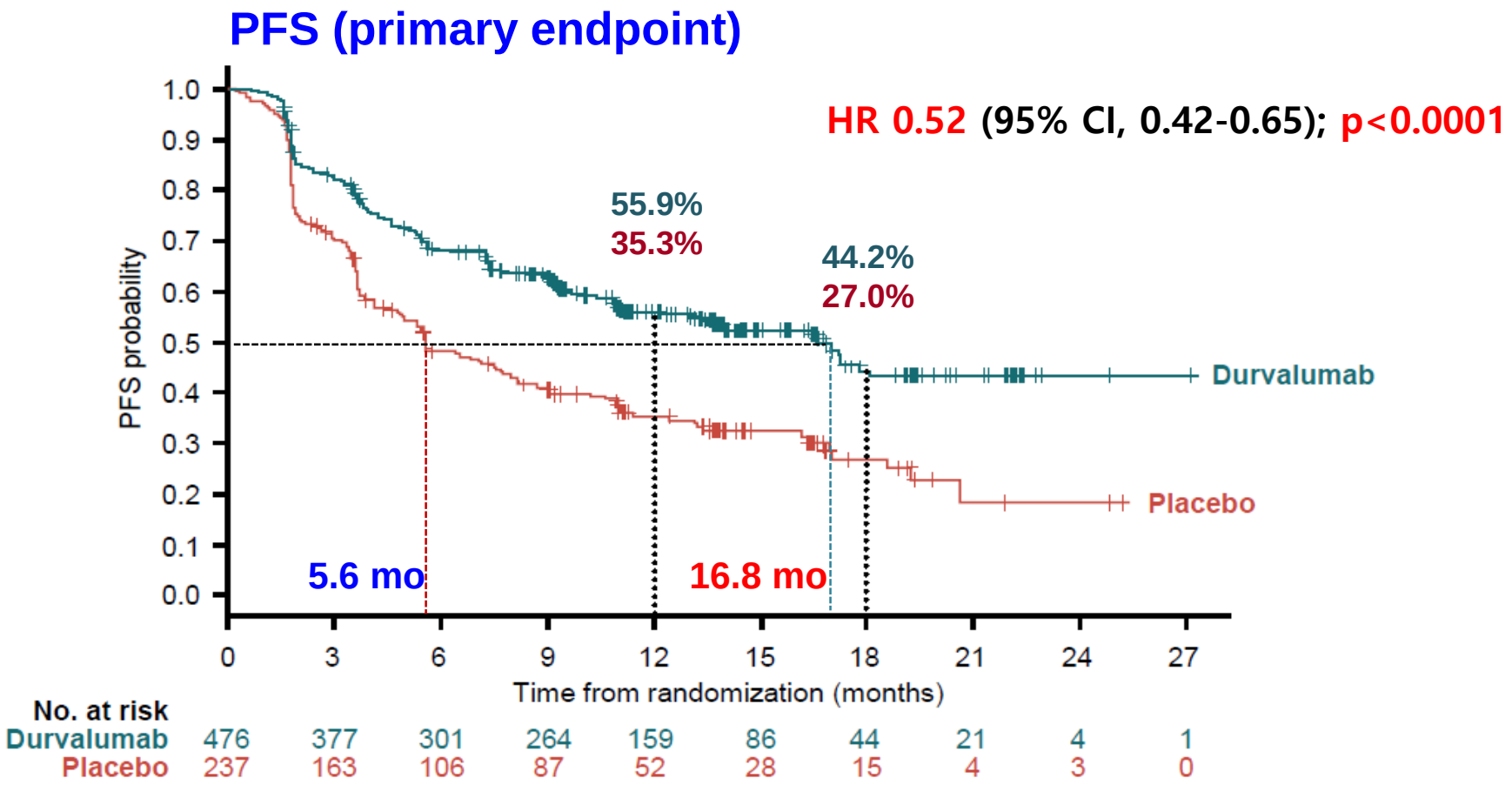
Wang S, et al. Int J Clin Oncol 2017;22:229–36.

Durvalumab: phase III, stage III unresectable NSCLC
PACIFIC



Antonia SJ. et al. N Engl J Med 2017;377:1919-29.

Durvalumab: phase III, stage III unresectable NSCLC
PACIFIC

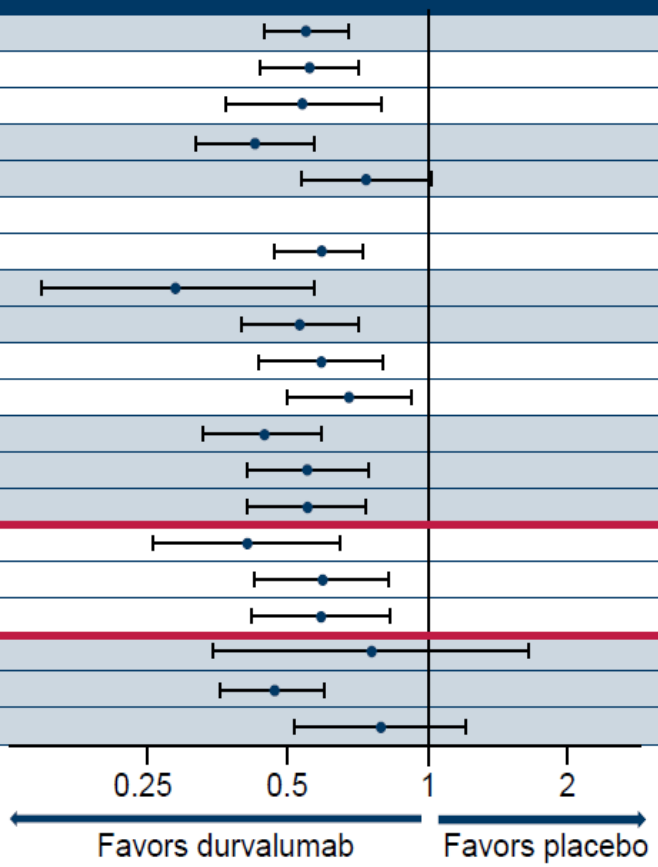


Antonia SJ. et al. N Engl J Med 2017;377:1919-29.

Durvalumab: phase III, stage III unresectable NSCLC
PACIFIC

PFS: subgroup analysis

		Durvalumab No. of patients	Placebo No. of patients	Unstratified HR* (95% CI)
	All patients	476	237	0.55 (0.45–0.68)
Sex	Male	334	166	0.56 (0.44–0.71)
	Female	142	71	0.54 (0.37–0.79)
Age at randomization	<65 years	261	130	0.43 (0.32–0.57)
	≥65 years	215	107	0.74 (0.54–1.01)
Smoking status	Smoker	433	216	0.59 (0.47–0.73)
	Non-smoker	43	21	0.29 (0.15–0.57)
Disease stage	Stage IIIA	252	125	0.53 (0.40–0.71)
	Stage IIIB	212	107	0.59 (0.44–0.80)
Histology	Squamous	224	102	0.68 (0.50–0.92)
	Non-squamous	252	135	0.45 (0.33–0.59)
Best response to cCRT	CR	9	7	–
	PR	232	111	0.55 (0.41–0.75)
	SD	222	114	0.55 (0.41–0.74)
PD-L1 status	≥25%	115	44	0.41 (0.26–0.65)
	<25%	187	105	0.59 (0.43–0.82)
	Unknown	174	88	0.59 (0.42–0.83)
EGFR status	Mutant	29	14	0.76 (0.35–1.64)
	Wild-type	315	165	0.47 (0.36–0.60)
	Unknown	132	58	0.79 (0.52–1.20)



Antonia SJ. et al. N Engl J Med 2017;377:1919-29.

Durvalumab: phase III, stage III unresectable NSCLC
PACIFIC

Adverse events

	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)

Pneumonitis (grouped terms) or radiation pneumonitis, n (%)*	Durvalumab (N=475)	Placebo (N=234)
Any grade	161 (33.9)	58 (24.8)
Grade 3/4	16 (3.4)	6 (2.6)
Grade 5	5 (1.1)	4 (1.7)
Leading to discontinuation	30 (6.3)	10 (4.3)

Antonia SJ. et al. N Engl J Med 2017;377:1919-29.

NCCN Guidelines Version 3.2018
Non-Small Cell Lung Cancer

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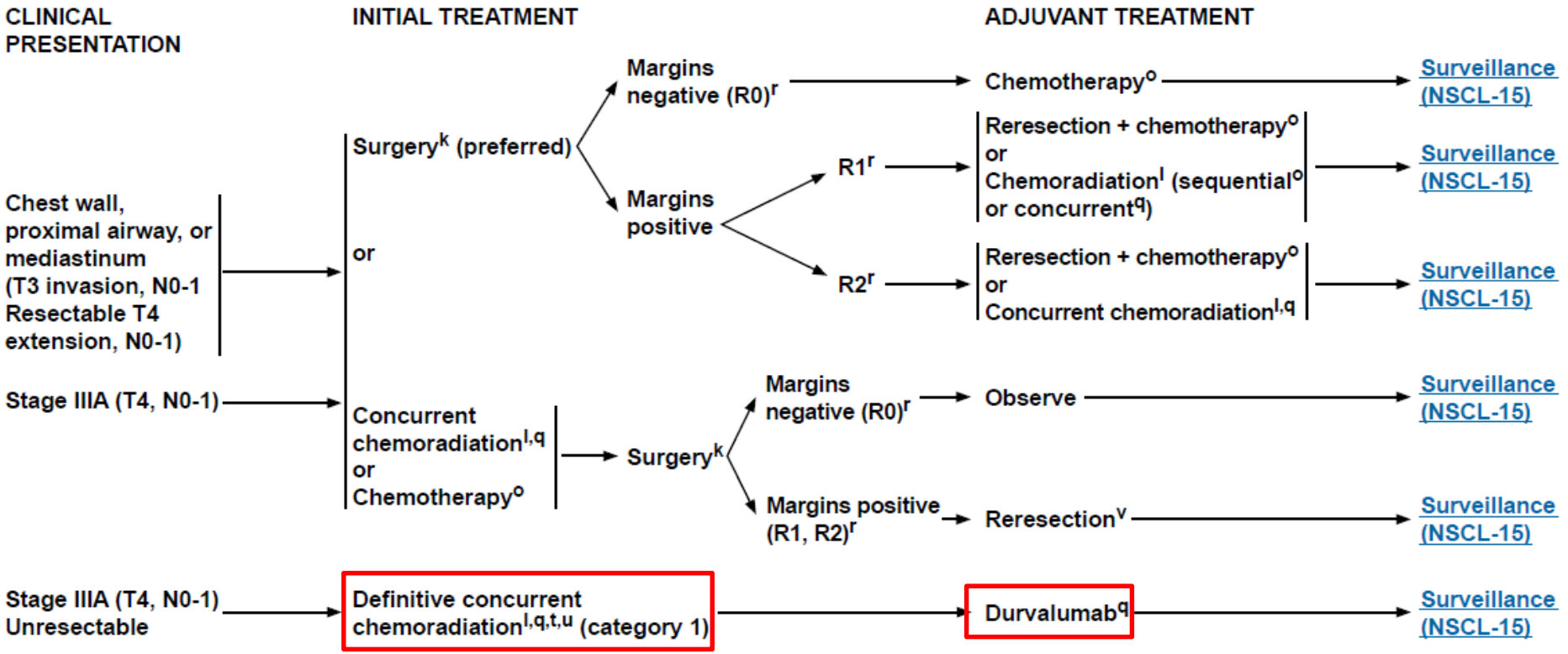
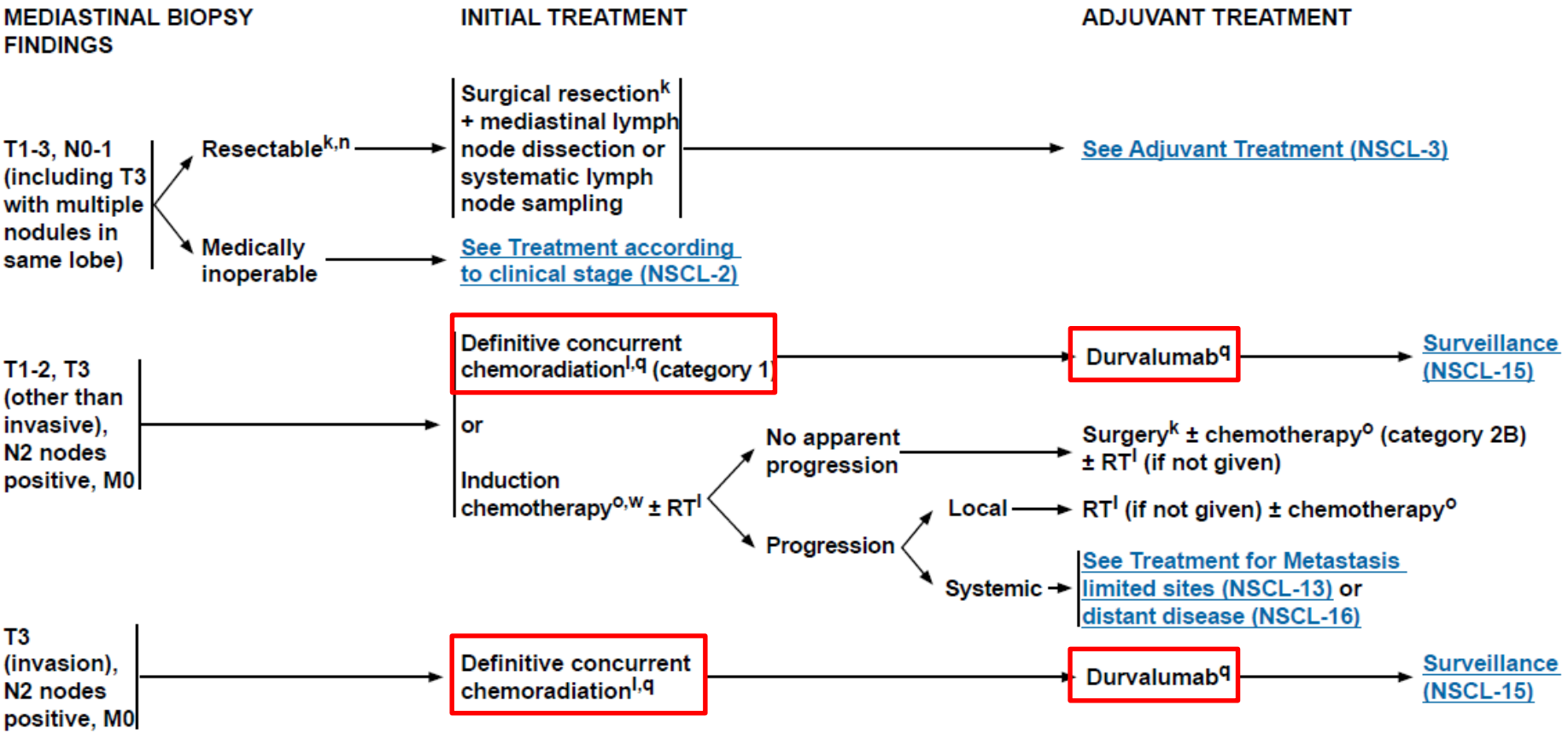
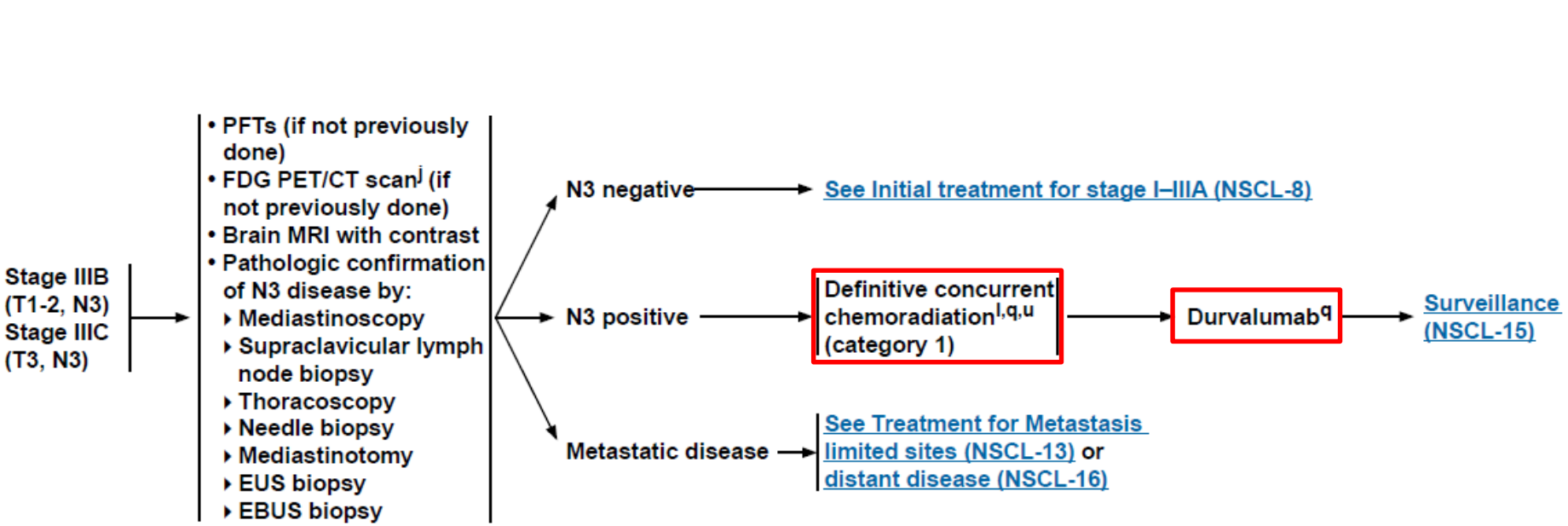
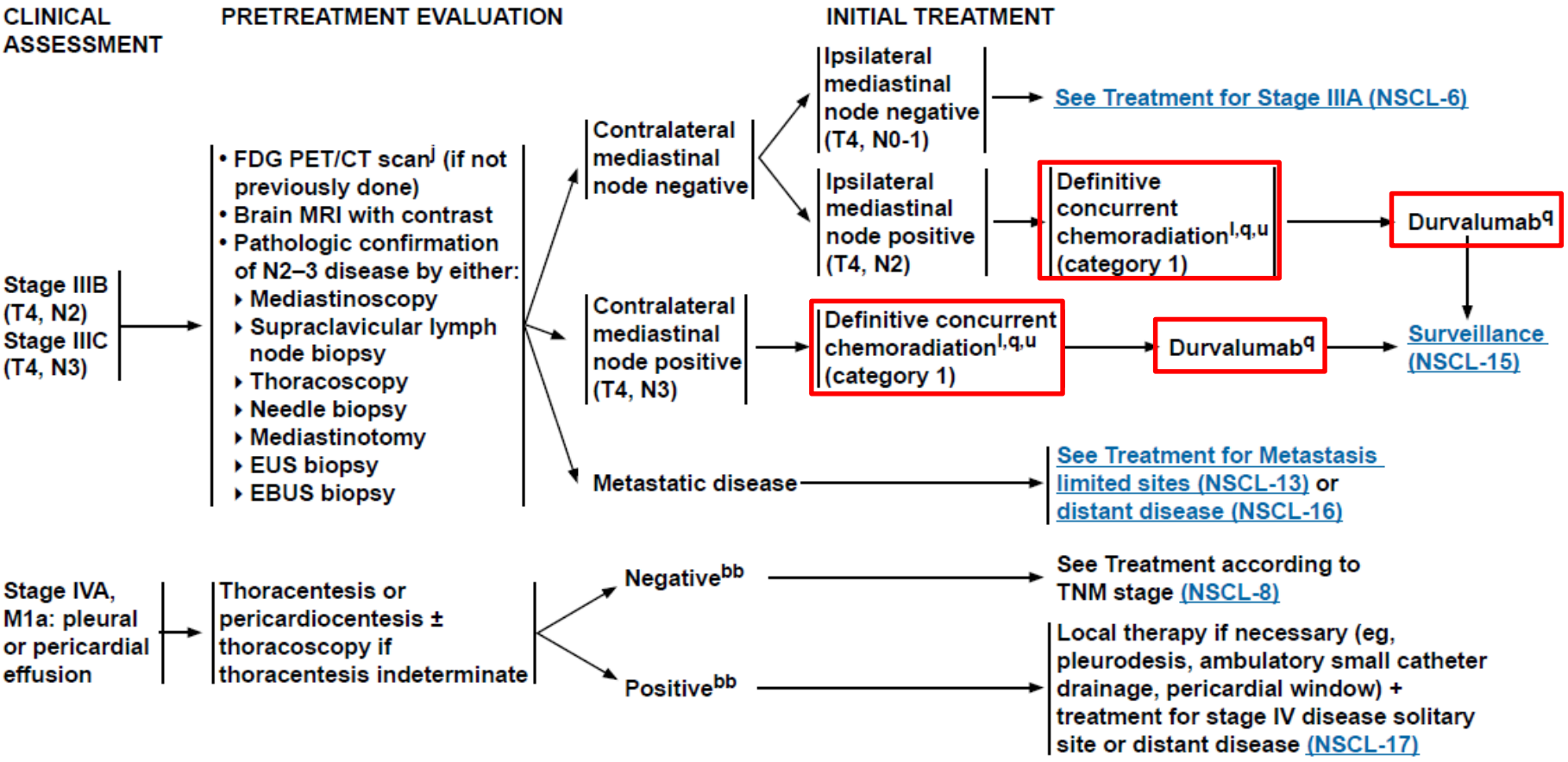



MEDIASTINAL BIOPSY FINDINGS
INITIAL TREATMENT
ADJUVANT TREATMENT
T1-3, N0-1 (including T3 with multiple nodules in same lobe)
Resectable[k,n]
Surgical resection[k] + mediastinal lymph node dissection or systematic lymph node sampling
See Adjuvant Treatment (NSCL-3)
Medically inoperable
See Treatment according to clinical stage (NSCL-2)
T1-2, T3 (other than invasive), N2 nodes positive, M0
Definitive concurrent chemoradiation[l,q] (category 1)
Durvalumab[q]
Surveillance (NSCL-15)
or
Induction chemotherapy[o,w] ± RT[l]
No apparent progression
Surgery[k] ± chemotherapy[o] (category 2B) ± RT[l] (if not given)
Progression
Local
RT[l] (if not given) ± chemotherapy[o]
Systemic
See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)
T3 (invasion), N2 nodes positive, M0
Definitive concurrent chemoradiation[l,q]
Durvalumab[q]
Surveillance (NSCL-15)


CLINICAL ASSESSMENT
PRETREATMENT EVALUATION
INITIAL TREATMENT
Stage IIIB (T1-2, N3)
Stage IIIC (T3, N3)
• PFTs (if not previously done)
• FDG PET/CT scan[j] (if not previously done)
• Brain MRI with contrast
• Pathologic confirmation of N3 disease by:
▸ Mediastinoscopy
▸ Supraclavicular lymph node biopsy
▸ Thoracoscopy
▸ Needle biopsy
▸ Mediastinotomy
▸ EUS biopsy
▸ EBUS biopsy
N3 negative
See Initial treatment for stage I–IIIA (NSCL-8)
N3 positive
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Surveillance (NSCL-15)
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)


CLINICAL ASSESSMENT
PRETREATMENT EVALUATION
INITIAL TREATMENT
Stage IIIB (T4, N2) Stage IIIC (T4, N3)
• FDG PET/CT scan[j] (if not previously done)
• Brain MRI with contrast
• Pathologic confirmation of N2–3 disease by either:
Mediastinoscopy
Supraclavicular lymph node biopsy
Thoracoscopy
Needle biopsy
Mediastinotomy
EUS biopsy
EBUS biopsy
Contralateral mediastinal node negative
Ipsilateral mediastinal node negative (T4, N0-1)
See Treatment for Stage IIIA (NSCL-6)
Ipsilateral mediastinal node positive (T4, N2)
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Surveillance (NSCL-15)
Contralateral mediastinal node positive (T4, N3)
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)
Stage IVA, M1a: pleural or pericardial effusion
Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate
Negative[bb]
See Treatment according to TNM stage (NSCL-8)
Positive[bb]
Local therapy if necessary (eg, pleurodesis, ambulatory small catheter drainage, pericardial window) + treatment for stage IV disease solitary site or distant disease (NSCL-17)

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

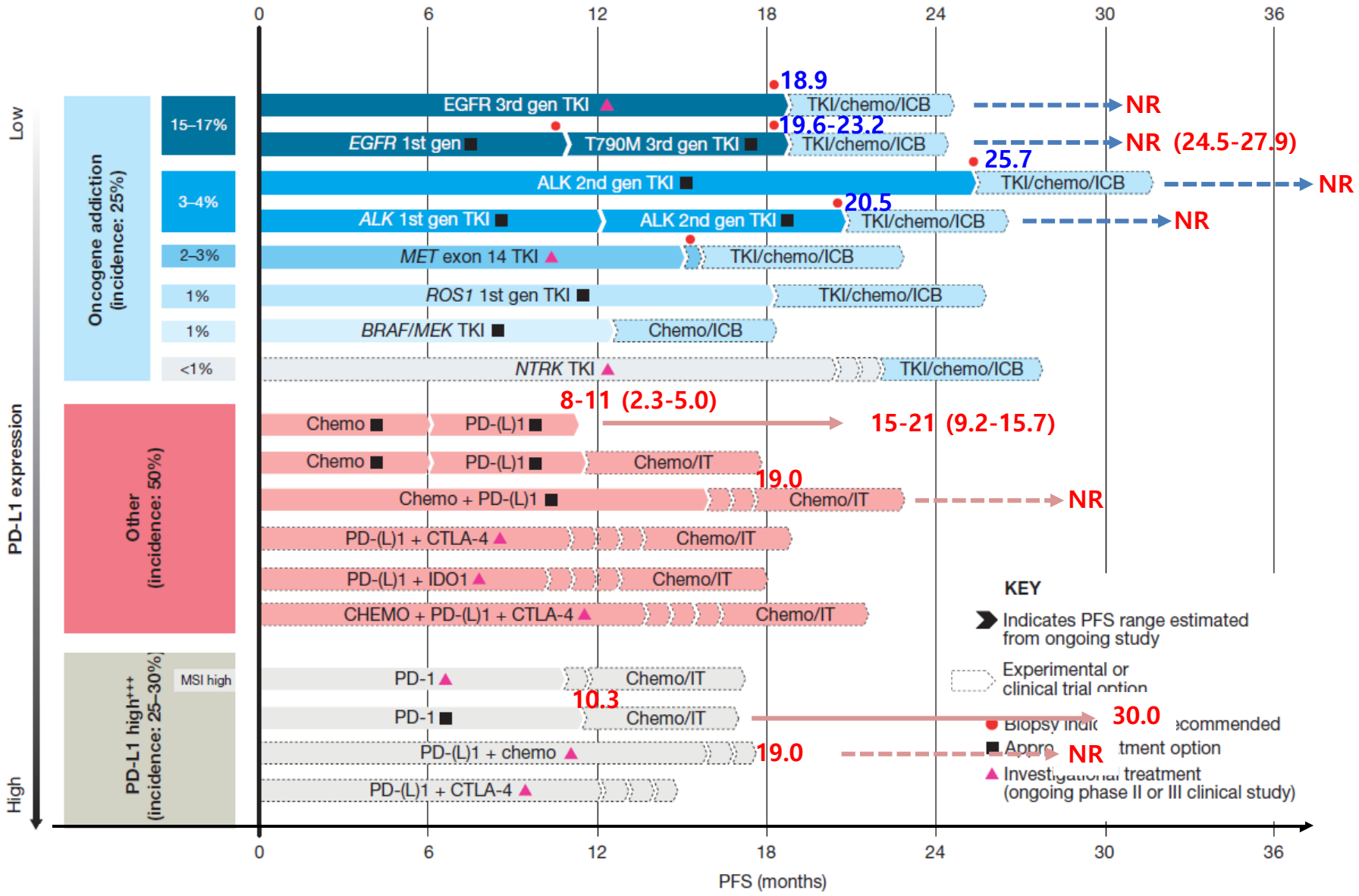
- **Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5, 29–33; concurrent thoracic RT[a,b,*,†]**
- **Cisplatin 100 mg/m² days 1 and 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT[b,*,†]**
- **Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)[*,†]**
- **Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d,e] (nonsquamous)[*,†] ± additional 4 cycles of pemetrexed 500 mg/m²[†]**
- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[f,*,†] ± additional 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6[†]**

Consolidation Therapy for Patients with Unresectable Stage III NSCLC, PS 0-1, and No Disease Progression After 2 or More Cycles of Definitive Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months[h]

*Regimens can be used as preoperative/adjuvant chemotherapy/RT.
†Regimens can be used as definitive concurrent chemotherapy/RT.

Current and investigative treatment options for advanced NSCLC



Nature 2018;553:446-454.

Summary

- **Immune checkpoint inhibitors, esp. anti-PD-1/PD-L1**
  : have become the standard of care
  in advanced NSCLC

- **≥ 2L Tx, nivolumab, pembrolizumab, atezolizumab**
  : safer & more effective than docetaxel

- **1L Tx monotherapy, pembrolizumab**
  : should be considered, with PD-L1≥ 50%

Summary

- **1L Tx combination**

  I-O + CTx

  : pembrolizumab+pem-cis/carbo

  will be a standard of care in non-SQ NSCLC

  : atezolizumab+bev+pacl/carbo in non-SQ NSCLC

  I-O + I-O

  : nivolumab+ipilimumab

- **Unresectable stage III, after CCRT**

  : durvalumab may be an effective consolidation Tx