Squamous Cell Carcinoma: What are the Standards and Potential Pathways in Development

Dr. Luis Corrales-Rodríguez
Oncología Médica

Centro de Investigación y Manejo del Cáncer (CIMCA)
Servicio de Oncología-Hospital San Juan de Dios-CCSS

San José, Costa Rica

Luis Corrales-Rodriguez, MD

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PAPERS

Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials

Non-small Cell Lung Cancer Collaborative Group

BMJ 1995;311:899-909

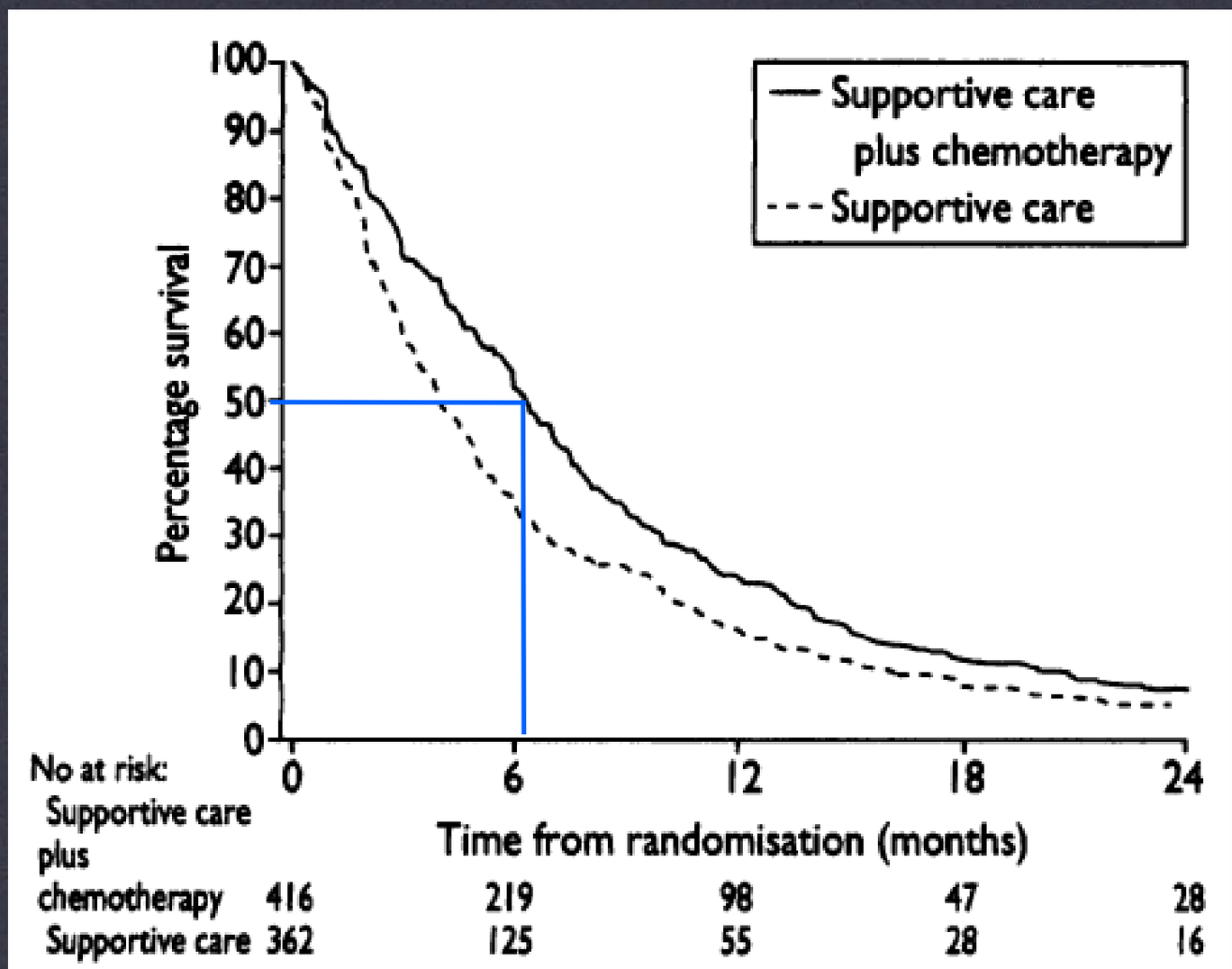


FIG 8—*Survival in trials of supportive care versus supportive care plus chemotherapy (only trials using regimens based on cisplatin)*

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

Stratification Variables

Performance status: 0 or 1 vs. 2
Weight loss in previous 6 mo: <5% vs. >5%
Disease stage: IIIB vs. IV or recurrent disease
Presence or absence of brain metastases

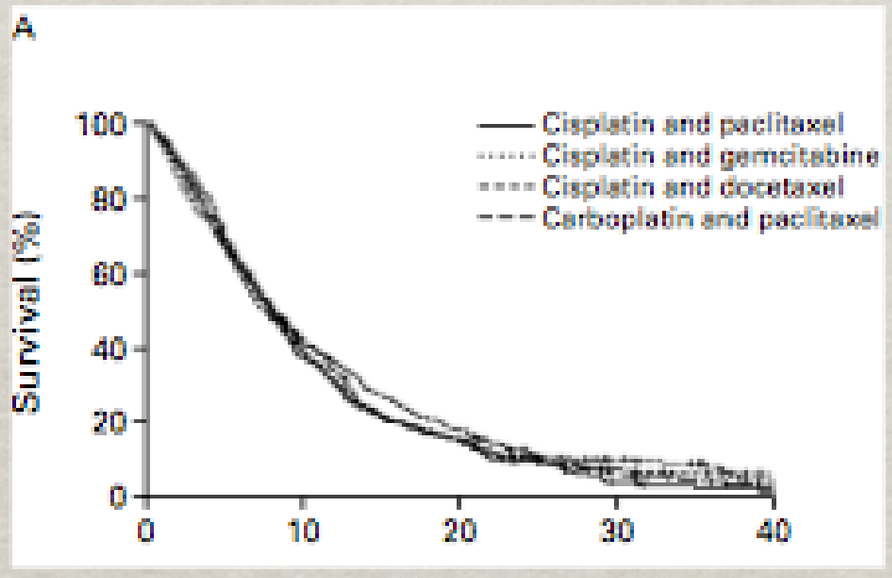
Regimens

Cisplatin plus paclitaxel
paclitaxel, 135 mg/m² over 24-hr period on day 1
cisplatin, 75 mg/m² on day 2
3-wk cycle

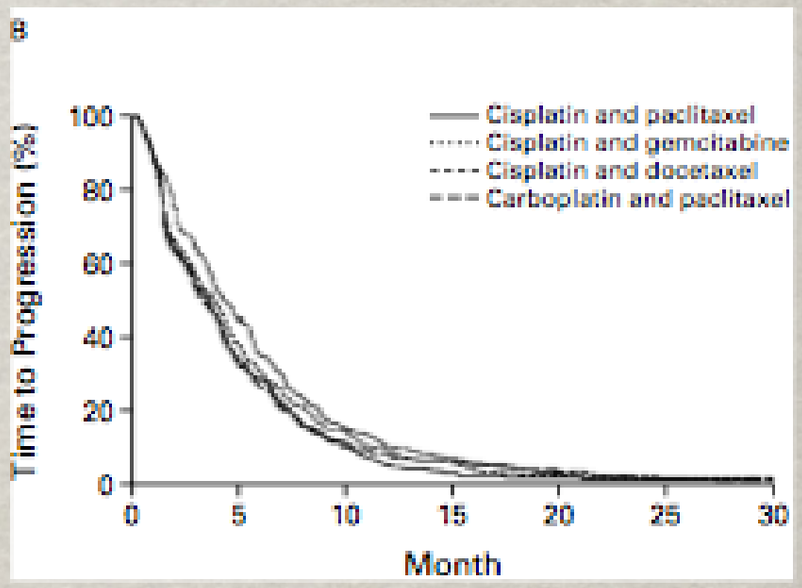
Cisplatin plus gemcitabine
gemcitabine, 1000 mg/m² on days 1, 8, and 15
cisplatin, 100 mg/m² on day 1
4-wk cycle

Cisplatin plus docetaxel
docetaxel, 75 mg/m² on day 1
cisplatin, 75 mg/m² on day 1
3-wk cycle

Carboplatin plus paclitaxel
paclitaxel, 225 mg/m² over 3-hr period on day 1
carboplatin, AUC 6.0 mg/ml/min on day 1
3-wk cycle



Overall Survival



Time to progression

Schiller J et al. NEJM 2002; 346:92-8

Treatment according to histology

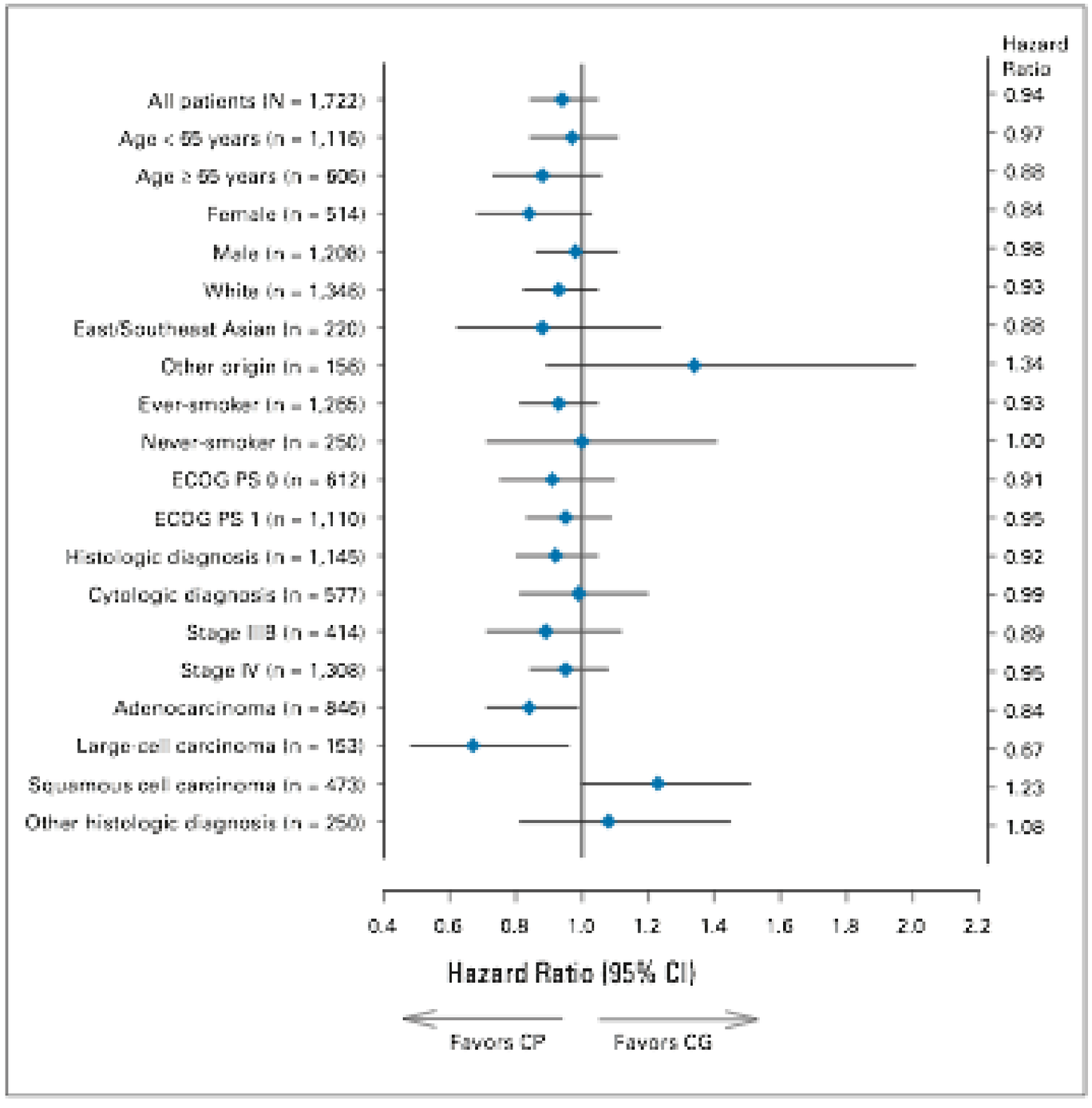


Fig 3. Survival hazard ratios (cisplatin/pemetrexed over cisplatin/gemcitabine) in groups according to baseline characteristics. Results based on Cox adjusted analyses for Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, sex, and basis for diagnosis (histologic v cytologic). In the analysis by group, pertaining to each of these four covariates, the variable predicting the group was excluded from the model. Three patients were missing ECOG PS and are excluded from the Cox adjusted analyses; 209 patients were missing smoking status. CP, cisplatin/pemetrexed; CG, cisplatin/gemcitabine.

Scagliotti G et al. J Clin Oncol 2008;26:3543–3551

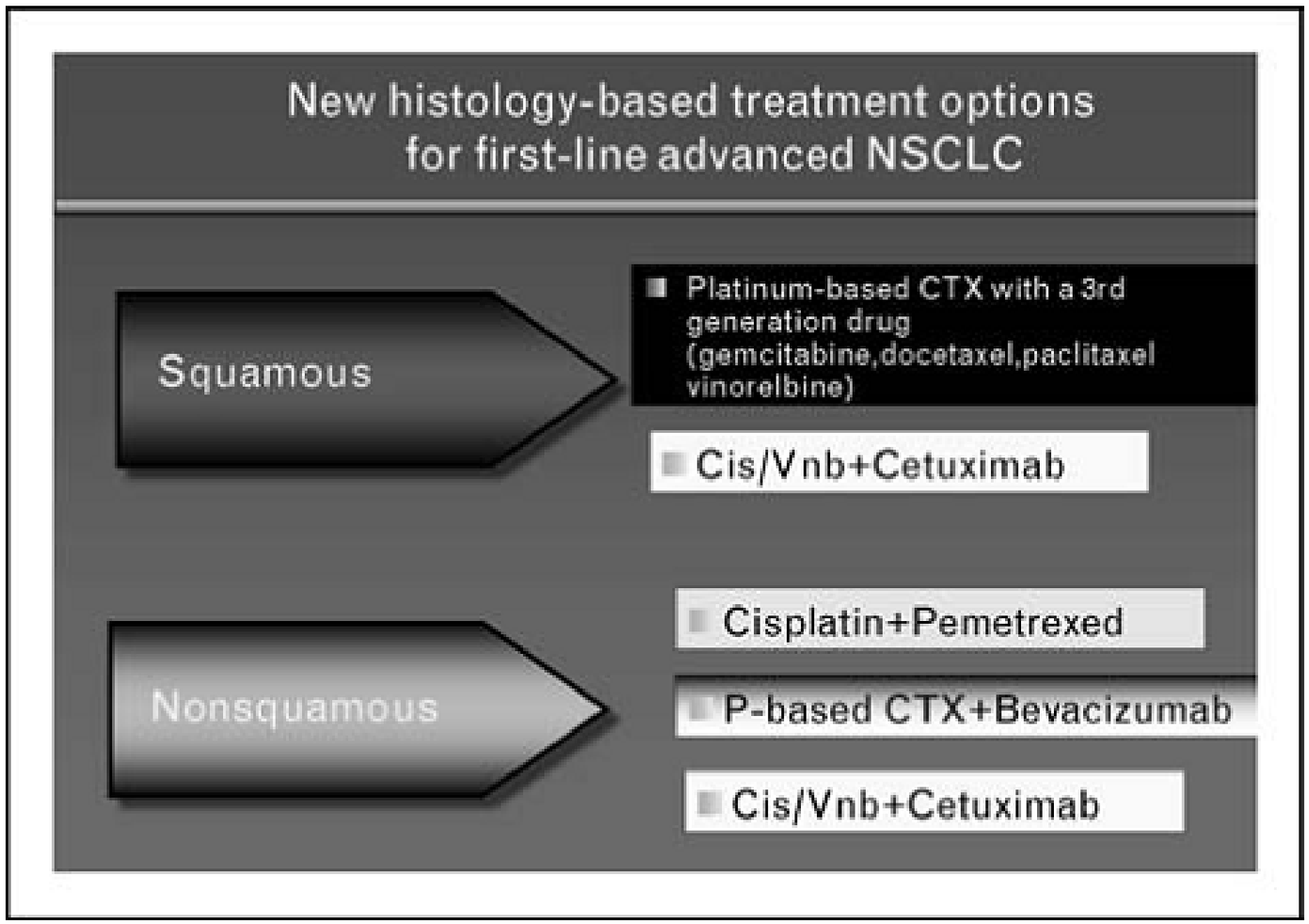
Treatment according to histology

EDITORIAL COMMENT

Histology-based treatment: a new scenario in the management of advanced nonsmall cell lung cancer

Cesare Gridelli

Figure 1 Histology-based therapeutic options for advanced nonsmall cell lung cancer



Gridelli C. Current Opinion in Oncology 2009,21:97–98

NSCLC

72%

Non squamous

28%

Squamous

62%

Non squamous

29.8%

EGFR

(1-2%)

ROS1

6.9%

EML4-alk

Data EMOT-Hospital San Juan de Dios 2017

First Line

- Chemotherapy +/- antiEGFR McAb
- Immunotherapy

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)*,**,§

Initial Cytotoxic Therapy Options

Squamous Cell Carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[11]
- Cisplatin/gemcitabine (category 1)[9,12]
- Cisplatin/paclitaxel (category 1)[13]
- Gemcitabine/docetaxel (category 1)[14]
- Gemcitabine/vinorelbine (category 1)[15]

Squamous Cell Carcinoma (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]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]

*Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

§Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Carboplatin/Albumin-Bound Paclitaxel vs Carboplatin/Paclitaxel in Advanced NSCLC

Stratified by stage (IIIb vs IV), age (< 70 yrs vs > 70 yrs), sex, histology (squamous vs nonsquamous), geographic region

Pts with stage IIIb/IV NSCLC, ECOG PS 0-1, no previous chemotherapy for metastatic disease (N = 1050)

21-day cycles

Albumin-bound Paclitaxel 100 mg/m^2 on Days 1, 8, 15 + **Carboplatin AUC 6 on Day** 1
No premedication

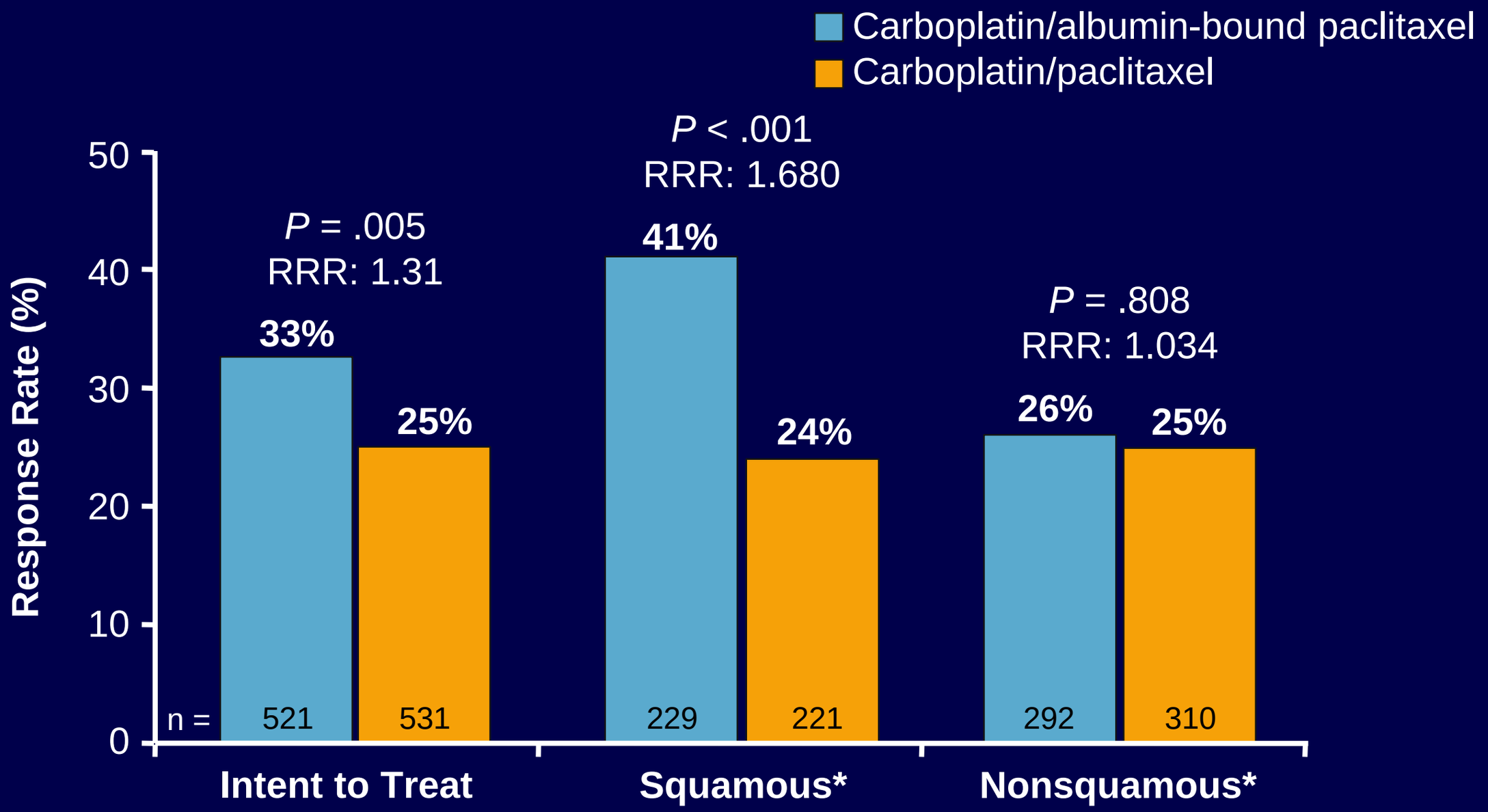
Paclitaxel 200 mg/m^2 on Day 1 + **Carboplatin AUC 6 on Day 1**
Premedication: dexamethasone, antihistamines

Phase III
Primary endpoint: ORR
Secondary endpoints: PFS, OS, safety

Socinski MA, et al. J Clin Oncol. 2012;30:2055-2062.

Slide credit: clinicaloptions.com

Carboplatin/Albumin-Bound Paclitaxel vs Carboplatin/Paclitaxel: Response



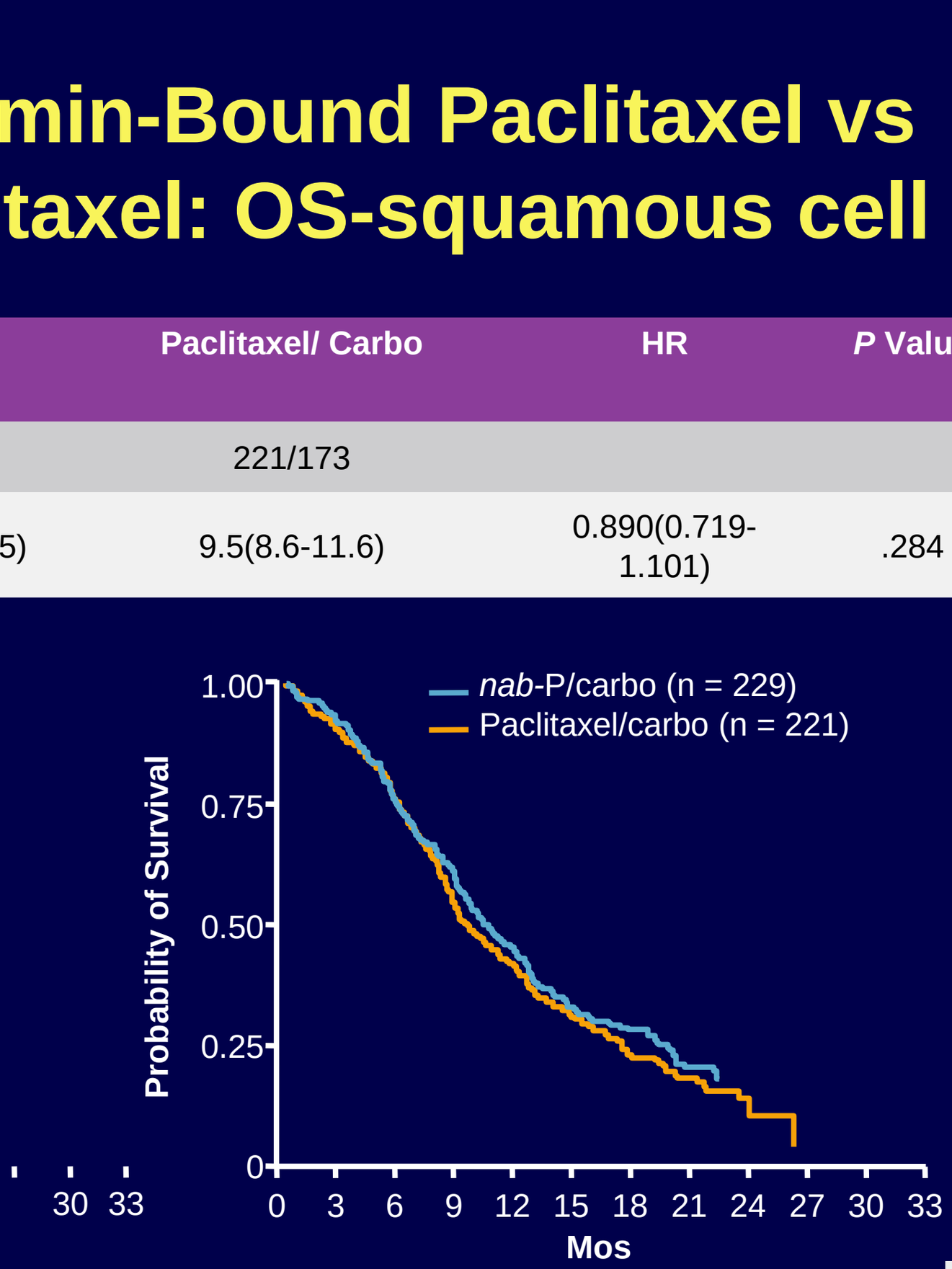
*Not a prespecified endpoint. Interaction *P* value for histology = .036

Socinski MA, et al. J Clin Oncol. 2012;30:2055-2062.

Slide credit: clinicaloptions.com

Carboplatin/Albumin-Bound Paclitaxel vs Carboplatin/Paclitaxel: OS-squamous cell

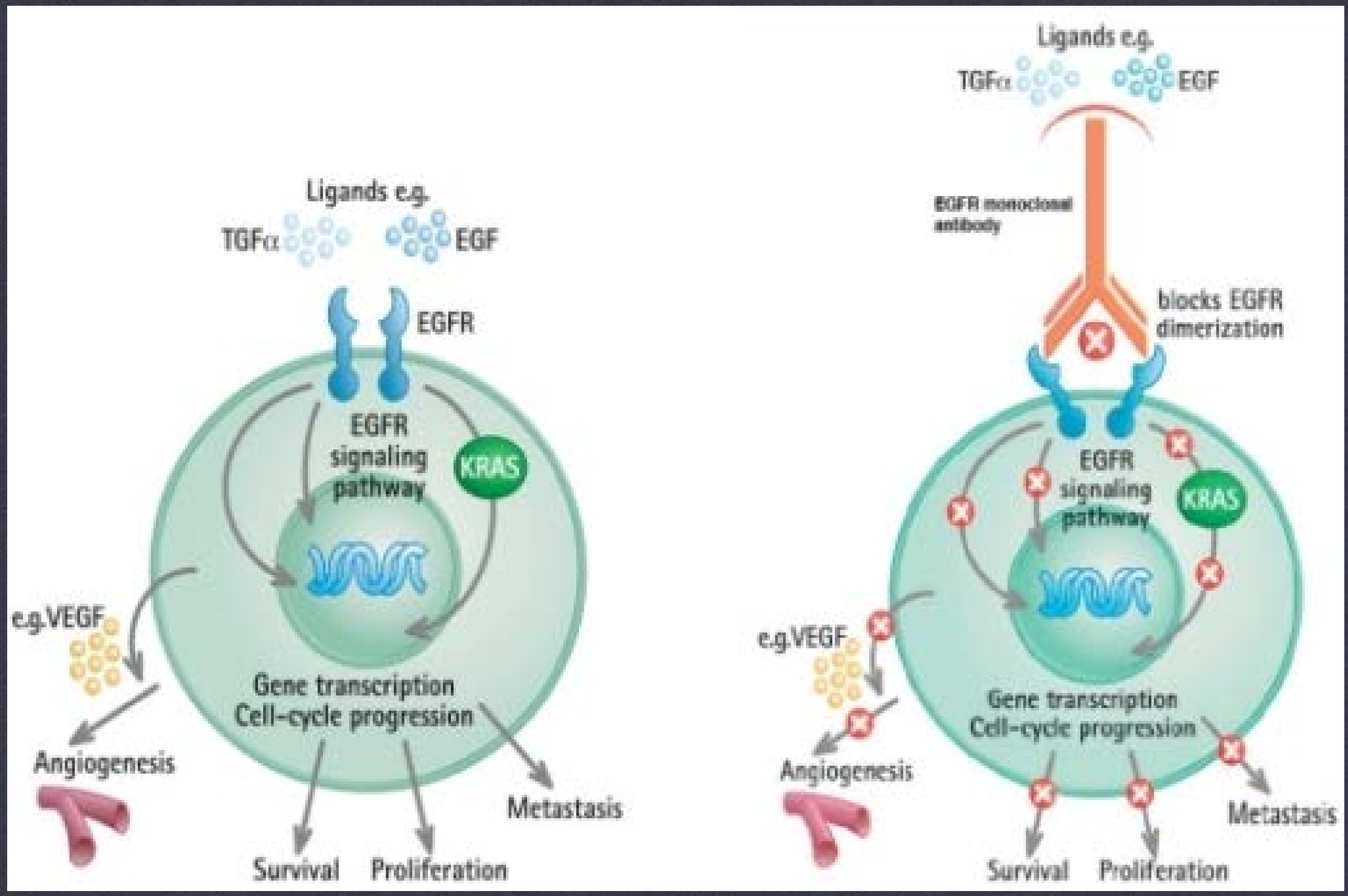
Squamous Cell	*nab*-P/ Carbo	Paclitaxel/ Carbo	HR	*P* Value
N/events	229/170	221/173		
Median OS, mos (95% CI)	10.7(9.4-12.5)	9.5(8.6-11.6)	0.890(0.719-1.101)	.284



Socinski MA, et al. J Clin Oncol. 2012;30:2055-2062.

Slide credit: clinicaloptions.com

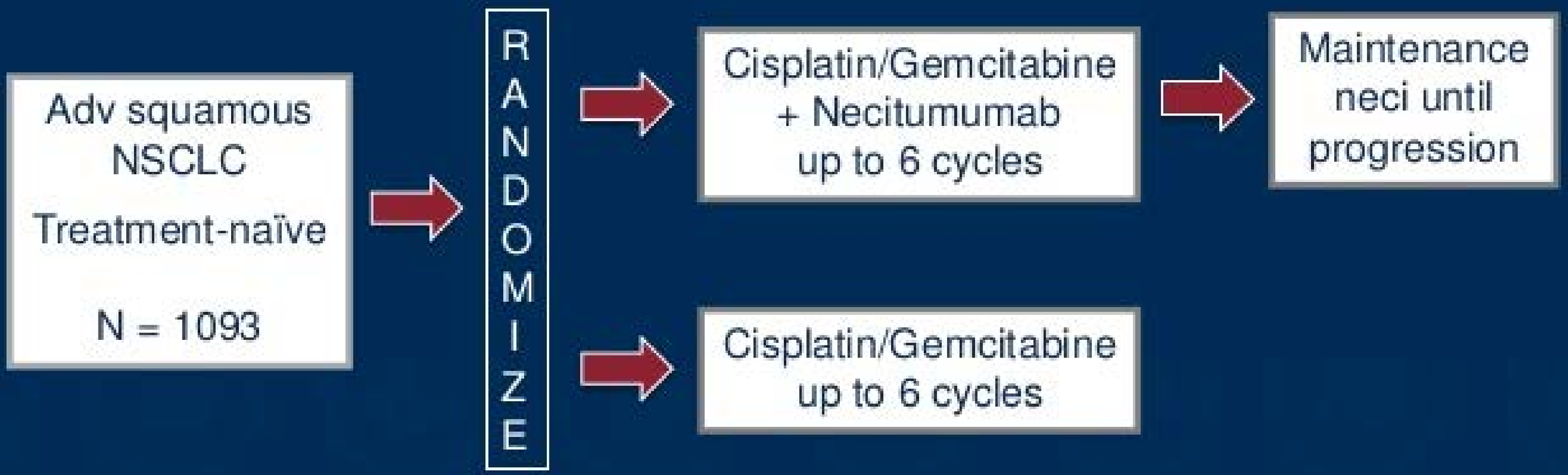
AcMc anti EGFR



Soulières D, Greer W, Magliocco AM, Huntsman D, Young S, Tsao MS, Kamel-Reid S - Curr Oncol (2010)

SQUIRE: Chemotherapy +/- Necitumumab for First Line Adv Squamous NSCLC

- Necitumumab (Neci) (IMC-11F8) is a human IgG1 anti-EGFR monoclonal antibody



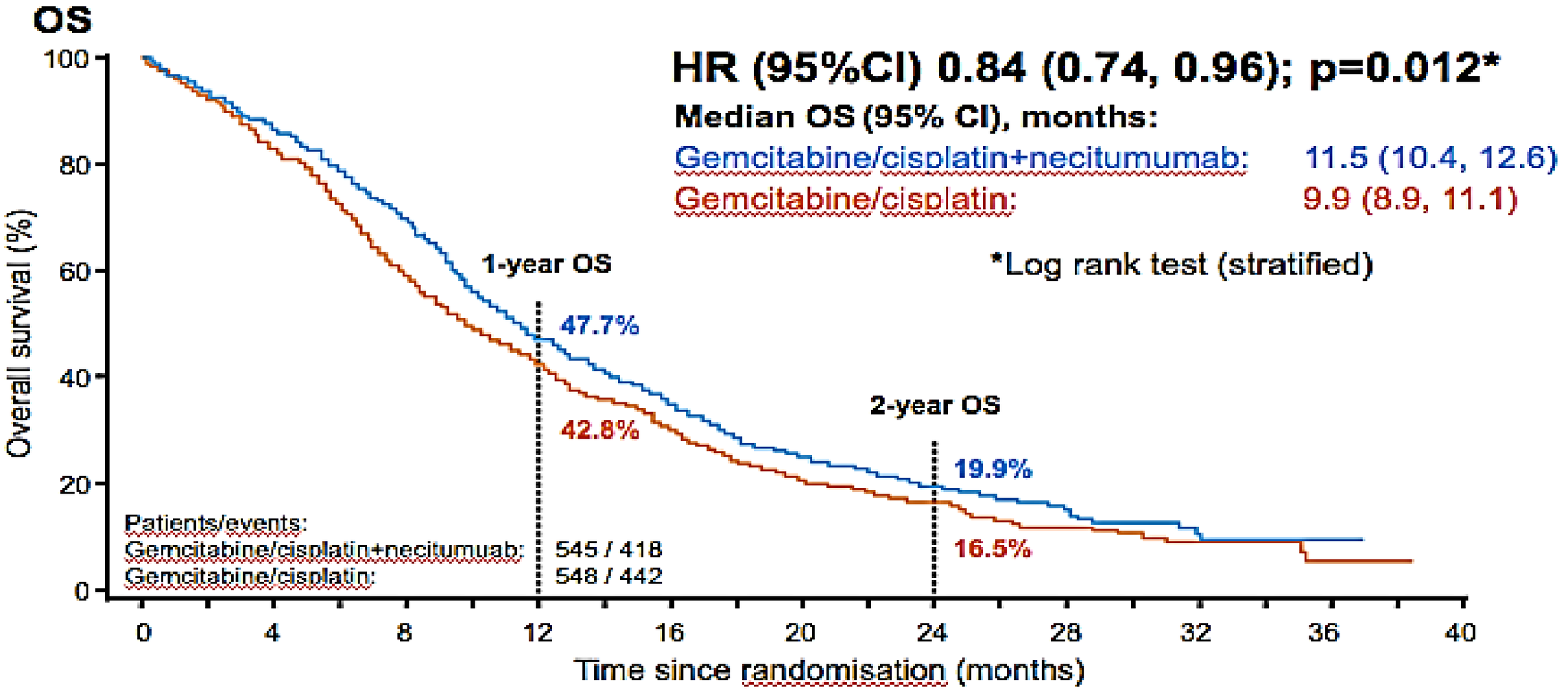
Primary endpoint: OS

Cisplatin 75 mg/m2 IV day 1 q21 days
Gemcitabine 1250 mg/m2 IV days 1, 8 q21 days

Necitumumab 800 mg/kg IV days 1, 8 q21 days

Thatcher, A#8008

SQUIRE



HR (95%CI) 0.84 (0.74, 0.96); p=0.012*

Median OS (95% CI), months:

Gemcitabine/cisplatin+necitumumab: 11.5 (10.4, 12.6)

Gemcitabine/cisplatin: 9.9 (8.9, 11.1)

*Log rank test (stratified)

- **Benefit in ORR, PFS (0.85) and OS (HR 0.84)**

Thatcher et al. *J Clin Oncol*. 2014;32(suppl 5). Abstract 8008.

KEYNOTE-024 Study Design (NCT02142738)

Key Eligibility Criteria

- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0–1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

Pembrolizumab 200 mg IV Q3W (2 years)

Platinum-Doublet Chemotherapy[a] (4–6 cycles)

PD[c]

Pembrolizumab 200 mg Q3W for 2 years

End Points

Primary: PFS (RECIST v1.1, blinded independent central review)
Key secondary: OS
Secondary: ORR, safety
Exploratory: DOR

- Pemetrexed + carboplatin[b]
- Pemetrexed + cisplatin[b]
- Paclitaxel + carboplatin
- Gemcitabine + carboplatin
- Gemcitabine + cisplatin

[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only.
[c]Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

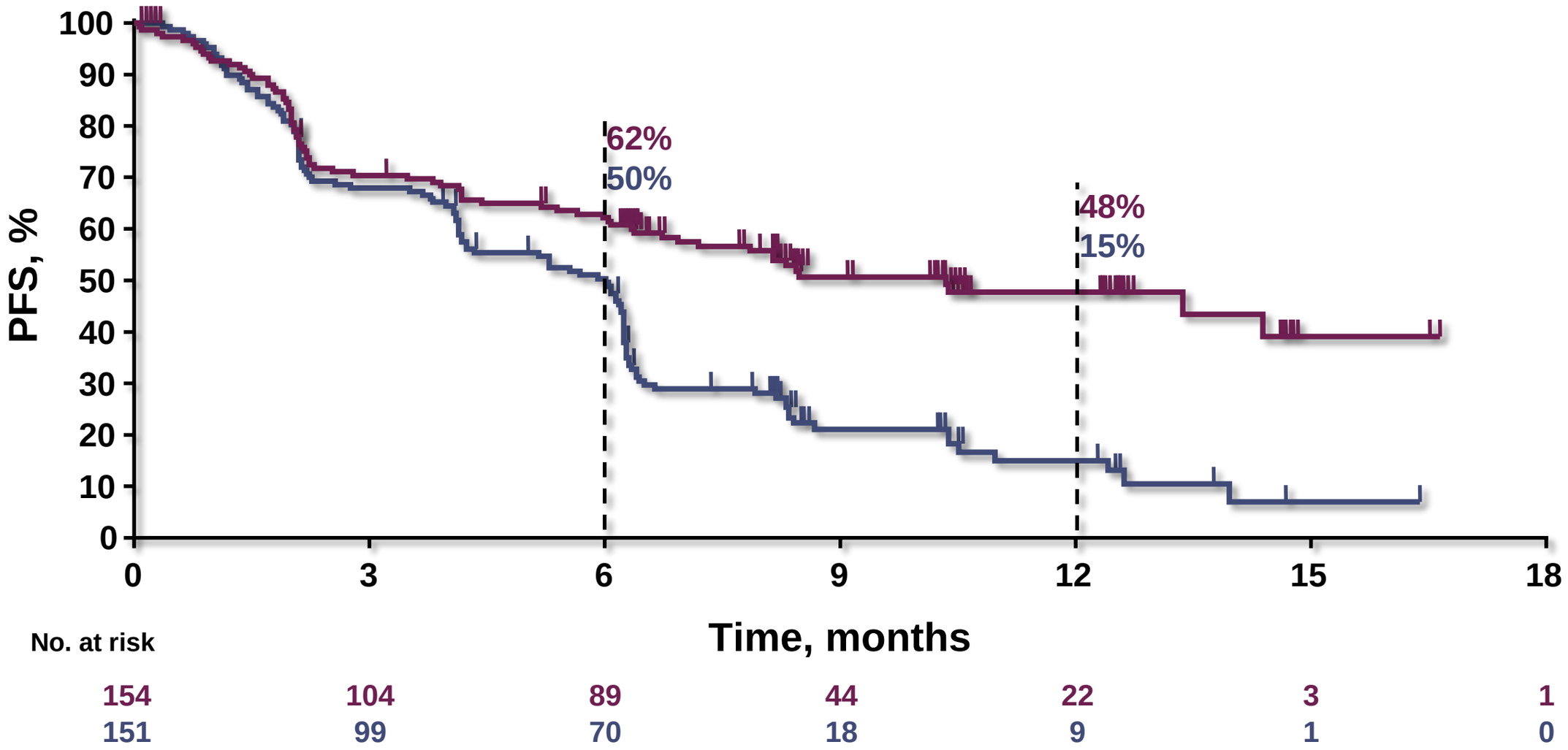
Baseline Characteristics

	Pembrolizumab N = 154	Chemotherapy N = 151
Age, years, median (range)	64.5 (33–90)	66.0 (38–85)
Male, n (%)	92 (59.7)	95 (62.9)
ECOG PS 1, n (%)	99 (64.3)	98 (64.9)
East Asian enrollment site, n (%)	21 (13.6)	19 (12.6)
Squamous histology, n (%)	29 (18.8)	26 (17.2)
Current/former smoker, n (%)	149 (96.8)	132 (87.4)
Treated brain metastases, n (%)	18 (11.7)	10 (6.6)
Prior neoadjuvant therapy, n (%)	3 (1.9)	1 (0.7)
Prior adjuvant therapy, n (%)	6 (3.9)	3 (2.0)

Reck M, et al. N Engl J Med. 2016;375:1823-1833.

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.

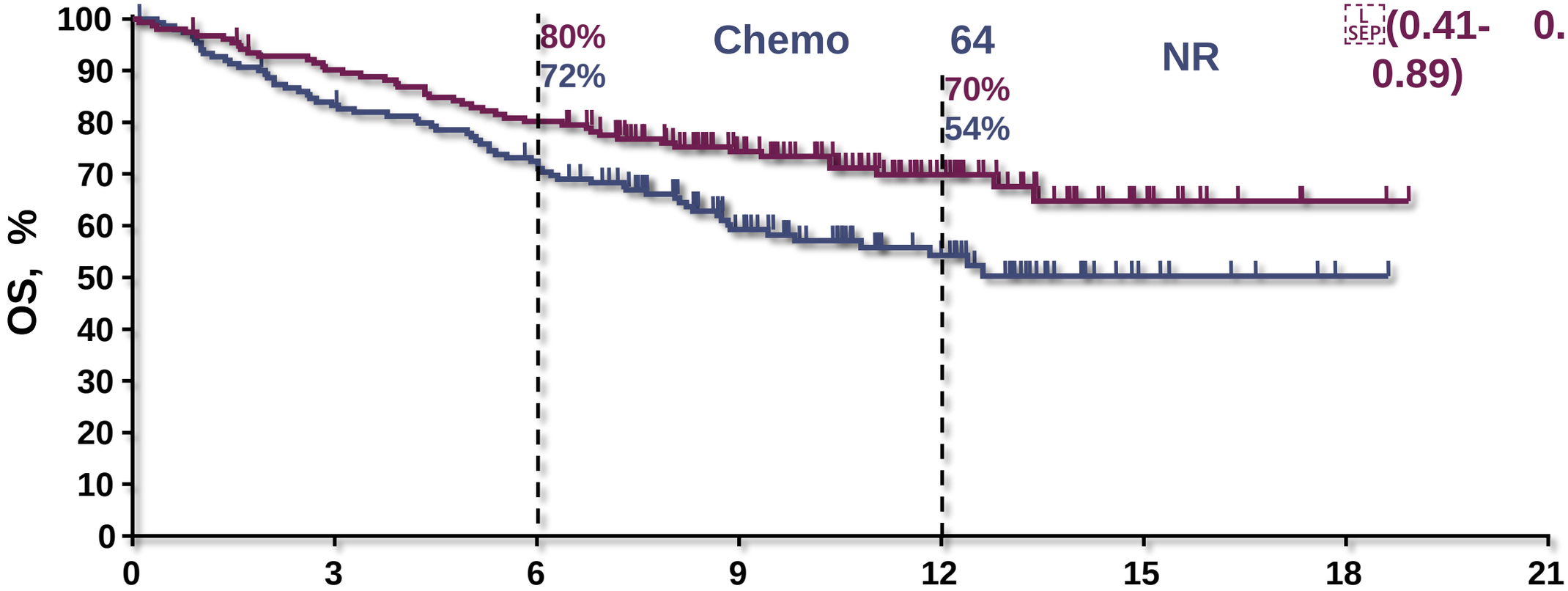
Reck M, et al. N Engl J Med. 2016;375:1823-1833.

Overall Survival

OS benefit as first-line therapy for advanced NSCLC with PD-L1 TPS ≥50% compared to platinum-based chemotherapy (HR, 0.63; 95% CI, 0.47–0.86; nominal P = 0.002)

WCLC 2017

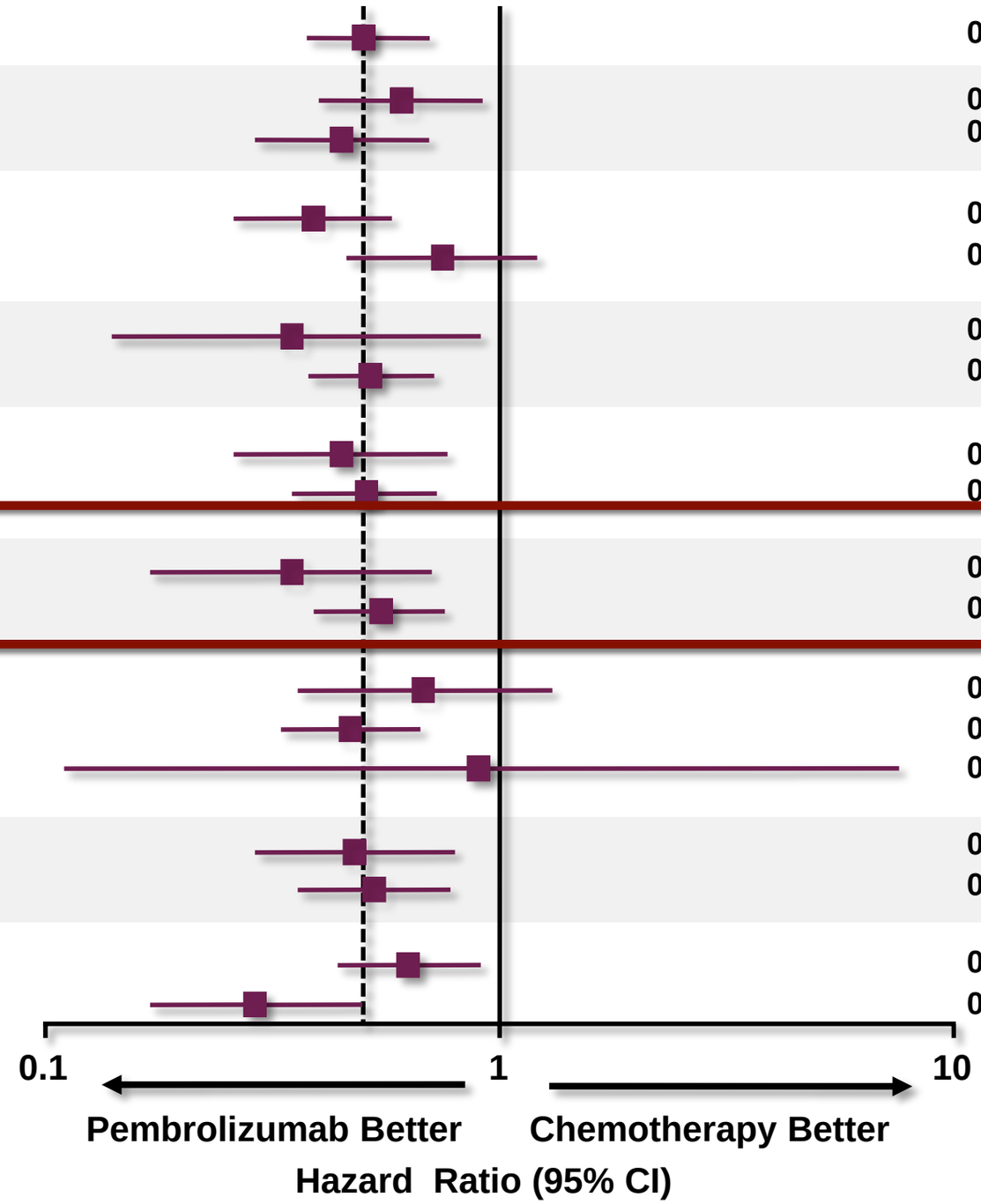
	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Data cut-off: May 9, 2016.

Progression-Free Survival in Subgroups

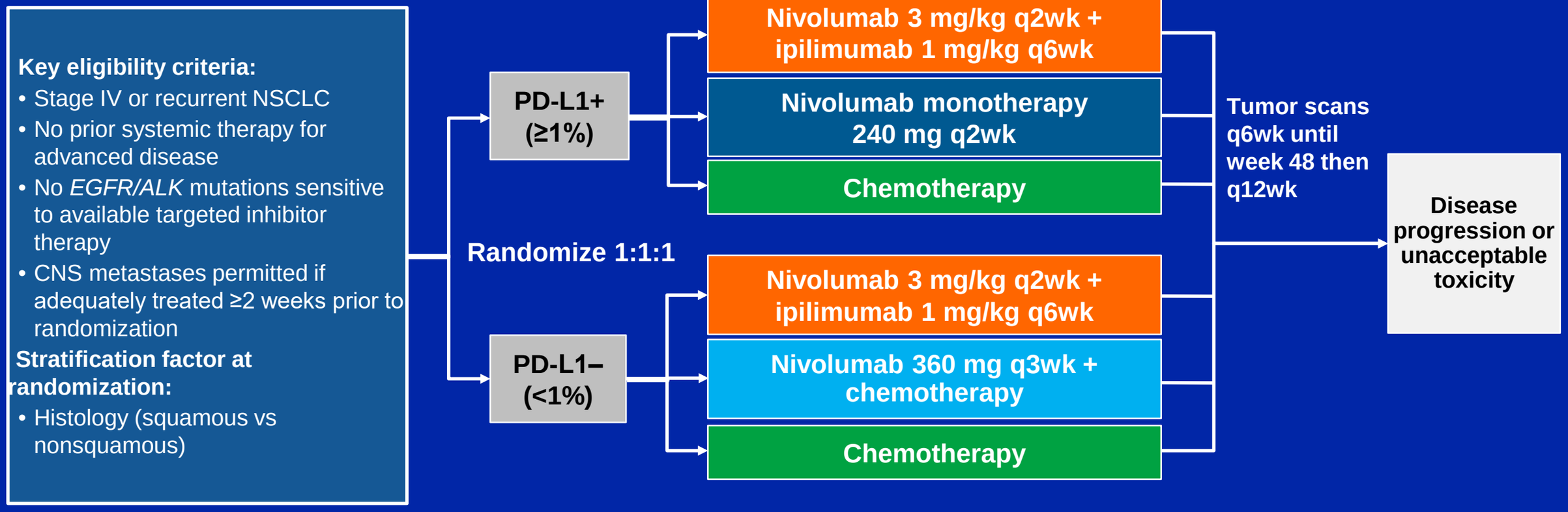
Overall	**Overall (N = 305)**	**0.50 (0.37-0.68)**
Age	**<65 years (n = 141)**	**0.61 (0.40-0.92)**
	≥65 years (n = 164)	**0.45 (0.29-0.70)**
Sex	**Male (n = 187)**	**0.39 (0.26-0.58)**
	Female (n = 118)	**0.75 (0.46-1.21)**
Enrollment region	**East Asia (n = 40)**	**0.35 (0.14-0.91)**
	Non-east Asia (n = 265)	**0.52 (0.38-0.72)**
ECOG PS	**0 (n = 107)**	**0.45 (0.26-0.77)**
	1 (n = 197)	**0.51 (0.35-0.73)**
Histology	**Squamous (n = 56)**	**0.35 (0.17-0.71)**
	Nonsquamous (n = 249)	**0.55 (0.39-0.76)**
Smoking status	**Current (n = 65)**	**0.68 (0.36-1.31)**
	Former (n = 216)	**0.47 (0.33-0.67)**
	Never (n = 24)	**0.90 (0.11-7.59)**
PD-L1 TPS	**50%-74% (n = 113)**	**0.48 (0.29-0.80)**
	75%-100% (n = 190)	**0.53 (0.36-0.78)**
Chemotherapy regimen	**With pemetrexed (n = 199)**	**0.63 (0.44-0.91)**
	Without pemetrexed (n = 106)	**0.29 (0.17-0.50)**



Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

Reck M, et al. N Engl J Med. 2016;375:1823-1833.

CheckMate 227: A Phase III Trial of Nivolumab Alone or in Combination with Ipilimumab or Chemotherapy



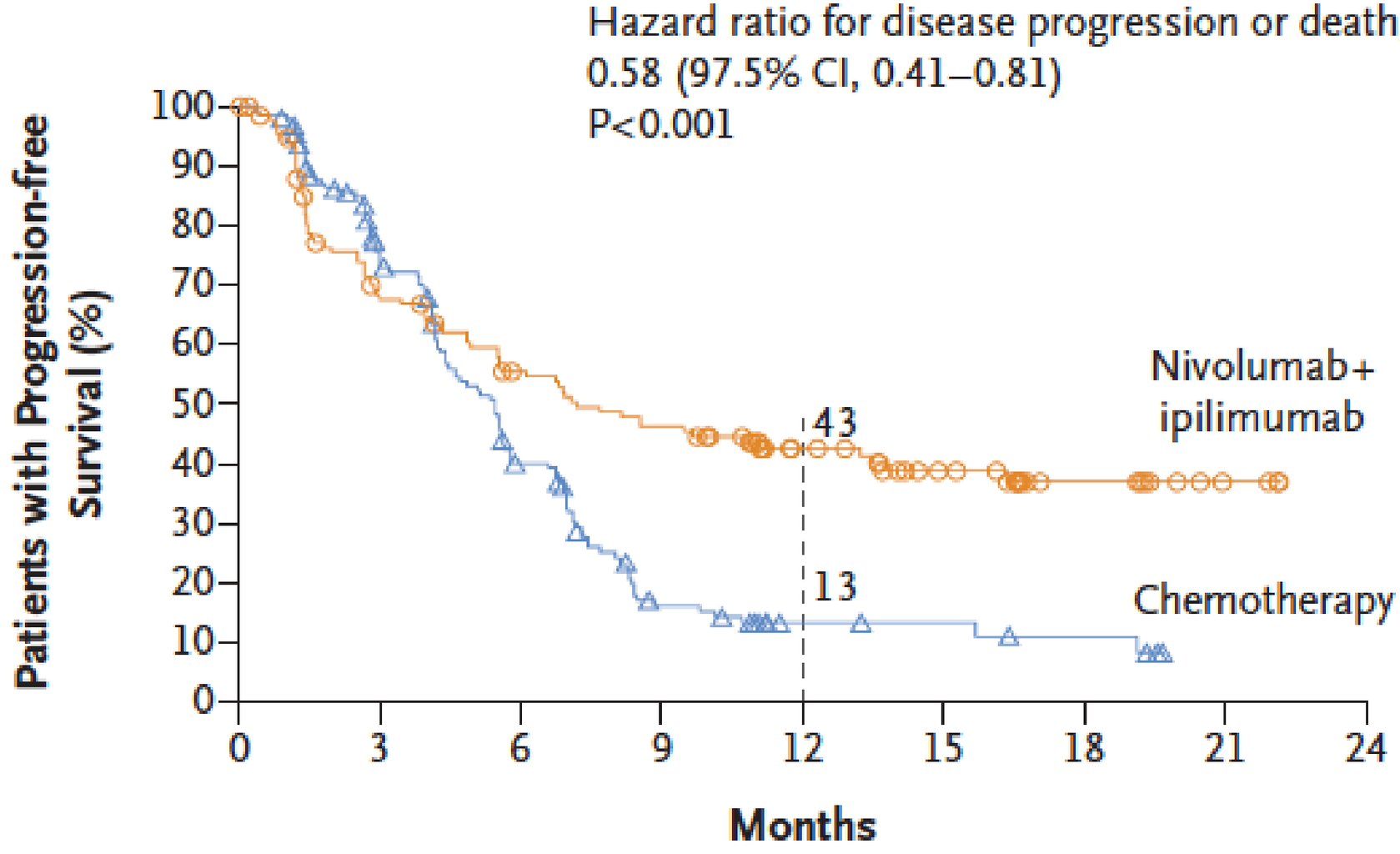
January 19, 2017: Company stated that it would NOT ask for accelerated approval of this combination based on (unknown to us) data available at the time.

http://investor.bms.com/investors/news-and-events/press-releases/press-release-details/2017; www.clinicaltrials.gov. Accessed March 2017

Table 1. Baseline Characteristics of Patients with a High Tumor Mutational Burden.*

Characteristic	Nivolumab plus Ipilimumab (N = 139)	Chemotherapy (N = 160)
Age — yr		
Median	64	64
Range	41–87	29–80
Age category — no. (%)		
<65 yr	73 (52.5)	83 (51.9)
≥65 to <75 yr	53 (38.1)	63 (39.4)
≥75 yr	13 (9.4)	14 (8.8)
Sex — no. (%)		
Male	98 (70.5)	106 (66.2)
Female	41 (29.5)	54 (33.8)
Region — no. (%)		
North America	14 (10.1)	16 (10.0)
Europe	77 (55.4)	87 (54.4)
Asia	21 (15.1)	32 (20.0)
Rest of world†	27 (19.4)	25 (15.6)
ECOG performance-status score — no. (%)†		
0	56 (40.3)	49 (30.6)
1	82 (59.0)	110 (68.8)
≥2	1 (0.7)	1 (0.6)
Smoking status — no. (%)		
Current or former smoker	130 (93.5)	146 (91.2)
Never smoked	7 (5.0)	11 (6.9)
Unknown	2 (1.4)	3 (1.9)
Tumor histologic type — no. (%)		
Squamous	45 (32.4)	55 (34.4)
Nonsquamous	94 (67.6)	105 (65.6)
PD-L1 expression level — no. (%)		
<1%	38 (27.3)	48 (30.0)
≥1%	101 (72.7)	112 (70.0)

A Progression-free Survival



No. at Risk

Nivolumab + ipilimumab	139	85	66	55	36	24	11	3	0
Chemotherapy	160	103	51	17	7	6	4	0	0

High TMB

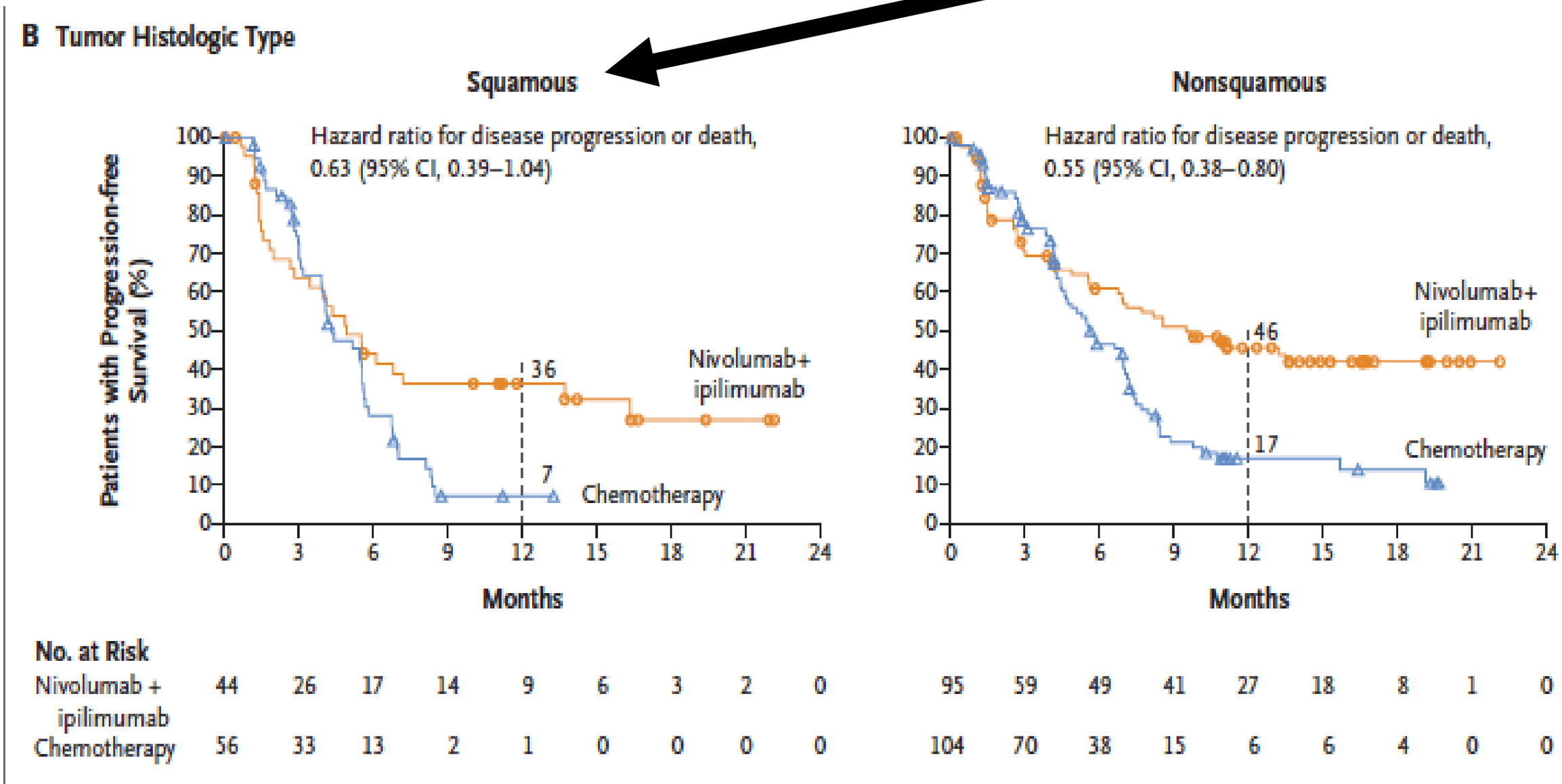


Figure 3. Progression-free Survival among Patients with a High Tumor Mutational Burden According to Tumor PD-L1 Expression and Histologic Type.

A high tumor mutational burden was defined as at least 10 mutations per megabase. The circles (for nivolumab plus ipilimumab) and triangles (for chemotherapy) indicate censored data.

Additional lines of treatment

Chemotherapy
Immunotherapy
Other treatments

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)*,**,§

Initial Cytotoxic Therapy Options

Squamous Cell Carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[11]
- Cisplatin/gemcitabine (category 1)[9,12]
- Cisplatin/paclitaxel (category 1)[13]
- Gemcitabine/docetaxel (category 1)[14]
- Gemcitabine/vinorelbine (category 1)[15]

Squamous Cell Carcinoma (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]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]

*Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Immunotherapy

CheckMate 017 (NCT01642004) — Study Design

Stage IIIb/IV SQ NSCLC

1 prior PT-DC, ECOG PS 0–1, pretreatment (archival or fresh) tumor samples required for PD-L1 analysis

N=272

Nivolumab
3 mg/kg IV Q2W
n=135
Until PD or unacceptable toxicity

Randomize
1: 1

Stratification factors:
region, prior paclitaxel use

Docetaxel
75 mg/m^2 IV Q3W
n=137
Until PD or unacceptable toxicity

Primary endpoint: OS[a]

Additional endpoints: ORR (investigator-assessed), PFS[a] (investigator-assessed), correlation between PD-L1 expression and efficacy, safety,[b] quality of life (LCSS)

- Updated safety and longer-term survival (18 months) are reported here
- At the time of analysis, 13% of patients in the nivolumab arm were continuing treatment vs no patients in the docetaxel arm

[a]Updated based on August 2015 database lock (DBL). [b]Updated based on June 2015 DBL

CheckMate 017: OS by PD-L1 Expression in Squamous NSCLC

1% PD-L1 Expression Level

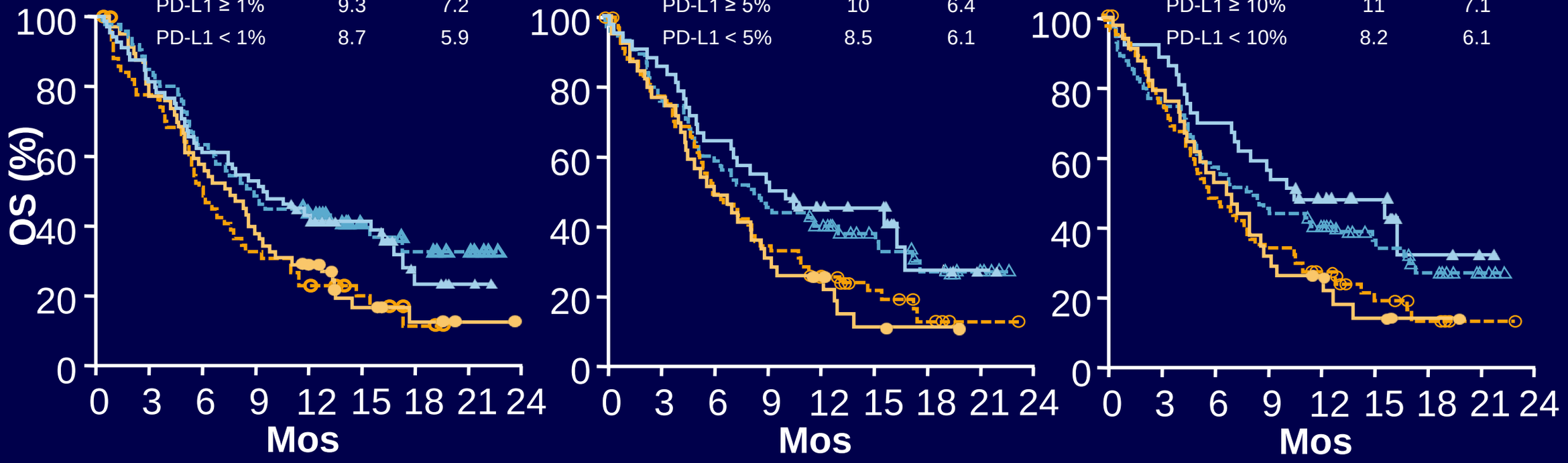
	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 1%	9.3	7.2
PD-L1 < 1%	8.7	5.9

5% PD-L1 Expression Level

	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 5%	10	6.4
PD-L1 < 5%	8.5	6.1

10% PD-L1 Expression Level

	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 10%	11	7.1
PD-L1 < 10%	8.2	6.1

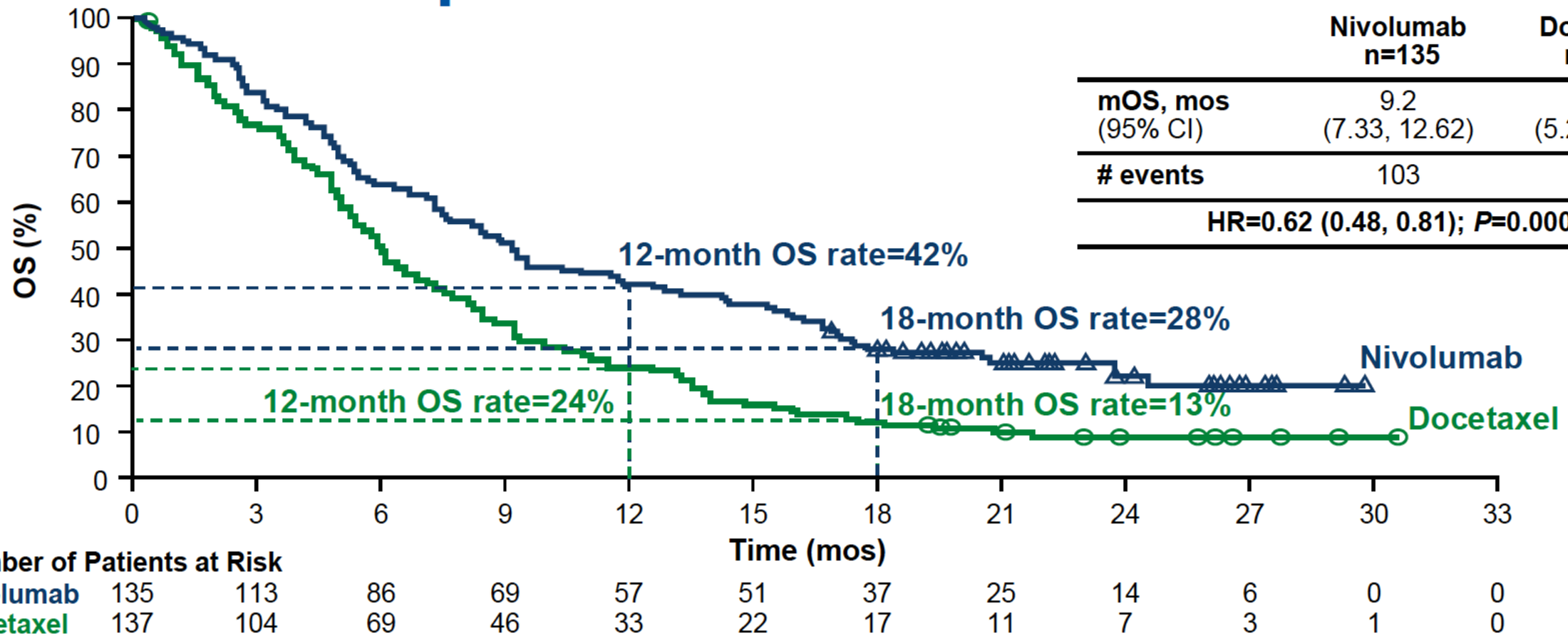


Brahmer J, et al. N Engl J Med. 2015;373:123-135.

Slide credit: clinicaloptions.com

Updated 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		



Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 months

Based on August 2015 DBL.
Symbols refer to censored observations.

KEYNOTE-010: trial design

Patients
- Advanced NSCLC
- Confirmed PD after ≥1 line of chemotherapy[a]
- No active brain metastases
- ECOG PS 0–1
- PD-L1 TPS ≥1%
- 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%)

Endpoints stratified by TPS ≥50% *vs.* ≥1%
- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

ClinicalTrials.gov identifier: NCT01905657.

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

[b]Added after 441 patients had been enrolled, following results from KEYNOTE-001 (Garon EB *et al. N Engl J Med* 2015;372:2018–2028).

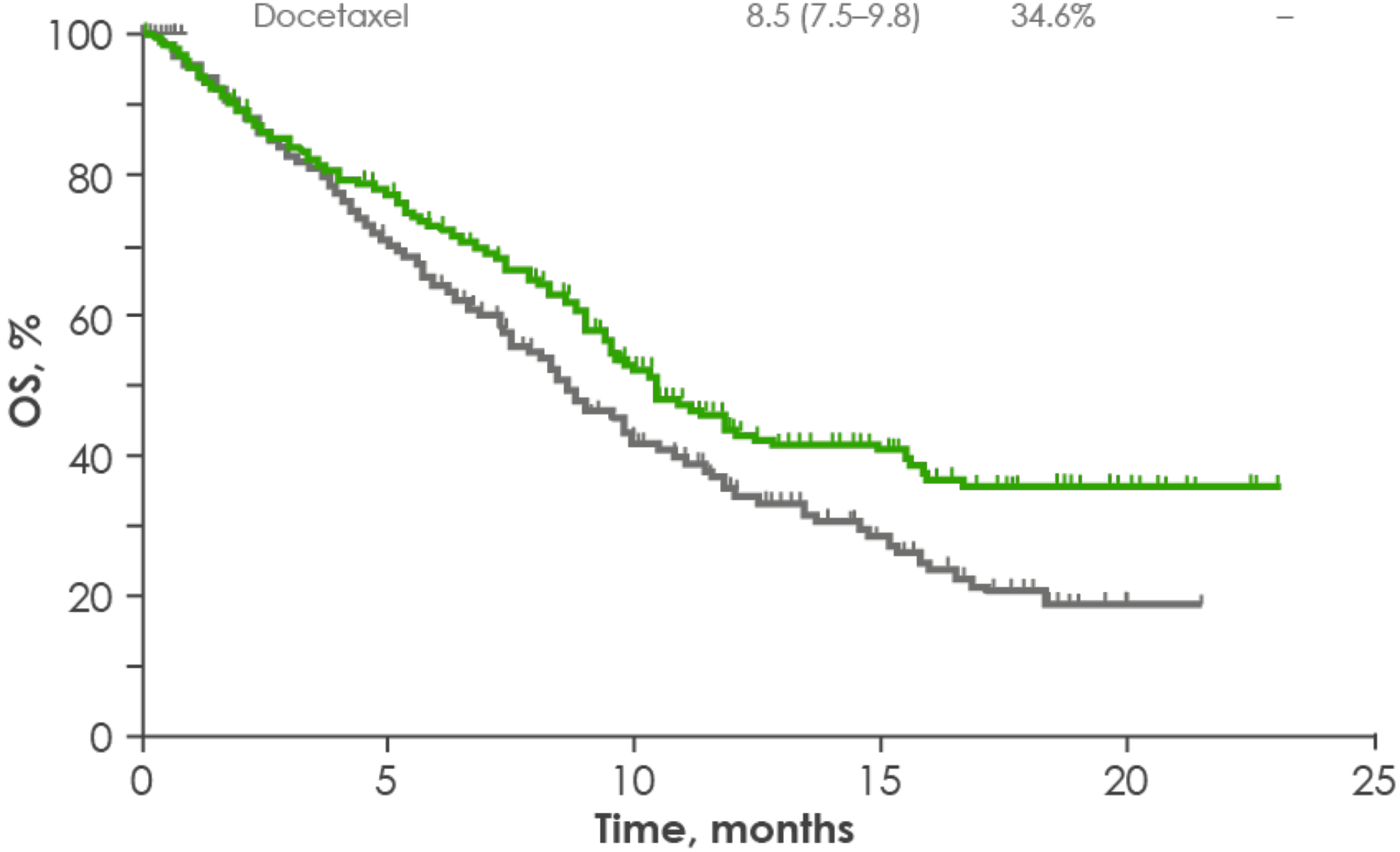
[c]Patients who discontinued docetaxel after receiving the maximum number of cycles approved by the local authorities were considered to have completed study treatment.

ECOG PS: Eastern Cooperative Oncology Group performance status; ILD: interstitial lung disease; IV: intravenous;
NSCLC: non-small-cell lung cancer; ORR: overall response rate; OS: overall survival; PD: progressive disease;
PD-L1: programmed cell death ligand 1; PFS: progression-free survival; Q3W: every 3 weeks; TPS: tumour proportion score.

Herbst RS et al. *Lancet* 2016; 387: 1540–1550 (and online appendix).

KEYNOTE-010: overall survival
All patients (PD-L1 TPS ≥1%)

Treatment arm		Median OS (95% CI), months	OS at 1 year	HR (95% CI)	p value
Pembrolizumab	2 mg/kg	10.4 (9.4–11.9)	43.2%	0.71 (0.58–0.88)	0.0008
Docetaxel		8.5 (7.5–9.8)	34.6%	–	–



Patients at risk, n

344	259	115	49	12	0
343	212	79	33	1	0

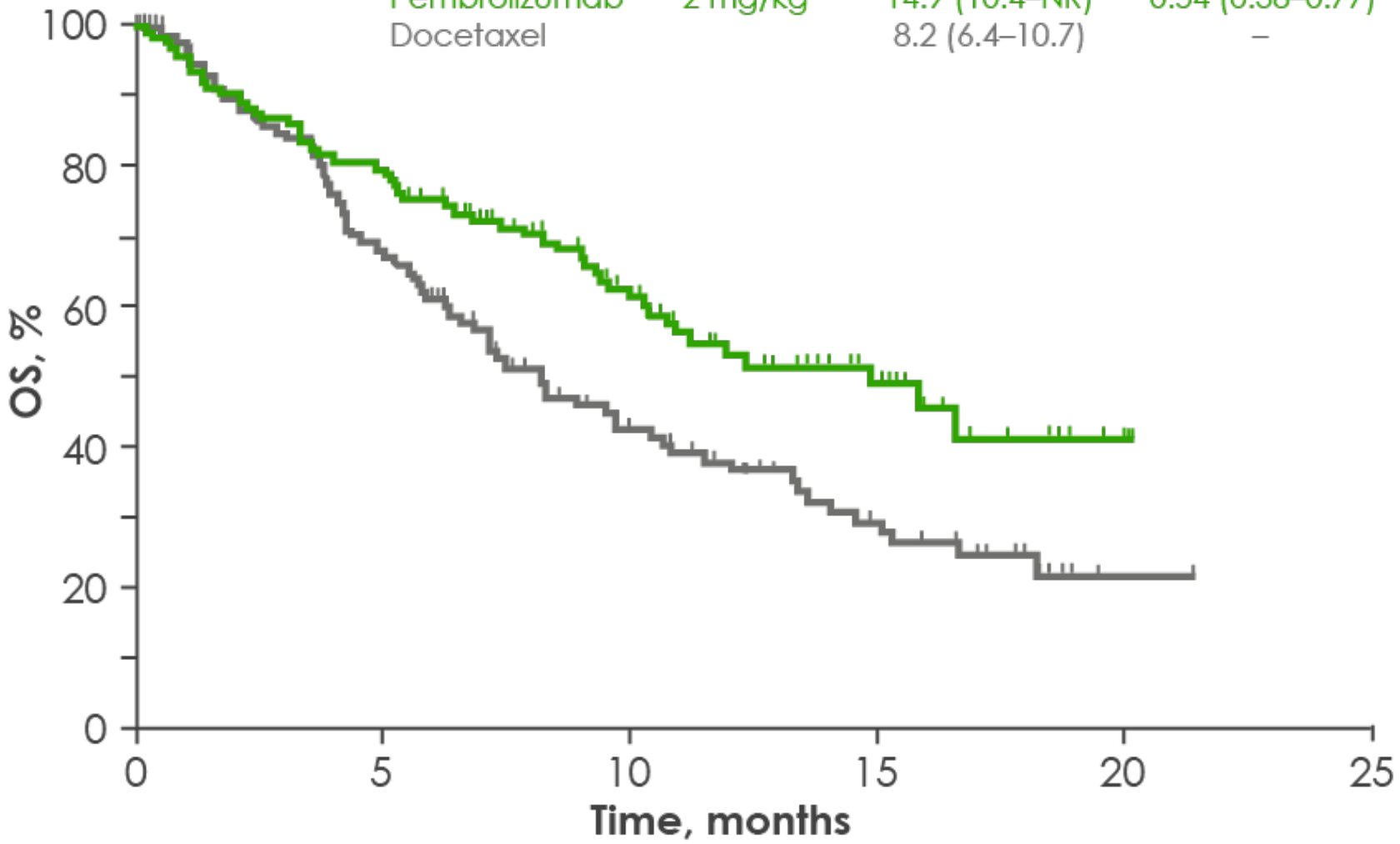
Analysis cut-off date: September 30, 2015.

CI: confidence interval; HR: hazard ratio; OS: overall survival; PD-L1: programmed cell death ligand 1; TPS: tumour proportion score.

Adapted from Herbst RS et al. *Lancet* 2016; 387: 1540–1550 (and online appendix).

KEYNOTE-010: overall survival
Patients with PD-L1 TPS ≥50%

Treatment arm		Median OS (95% CI), months	HR[a] (95% CI)	p value
Pembrolizumab	2 mg/kg	14.9 (10.4–NR)	0.54 (0.38–0.77)	0.0002
Docetaxel		8.2 (6.4–10.7)	–	–



Patients at risk, n

139	110	51	20	3	0
152	90	38	19	1	0

Analysis cut-off date: September 30, 2015.

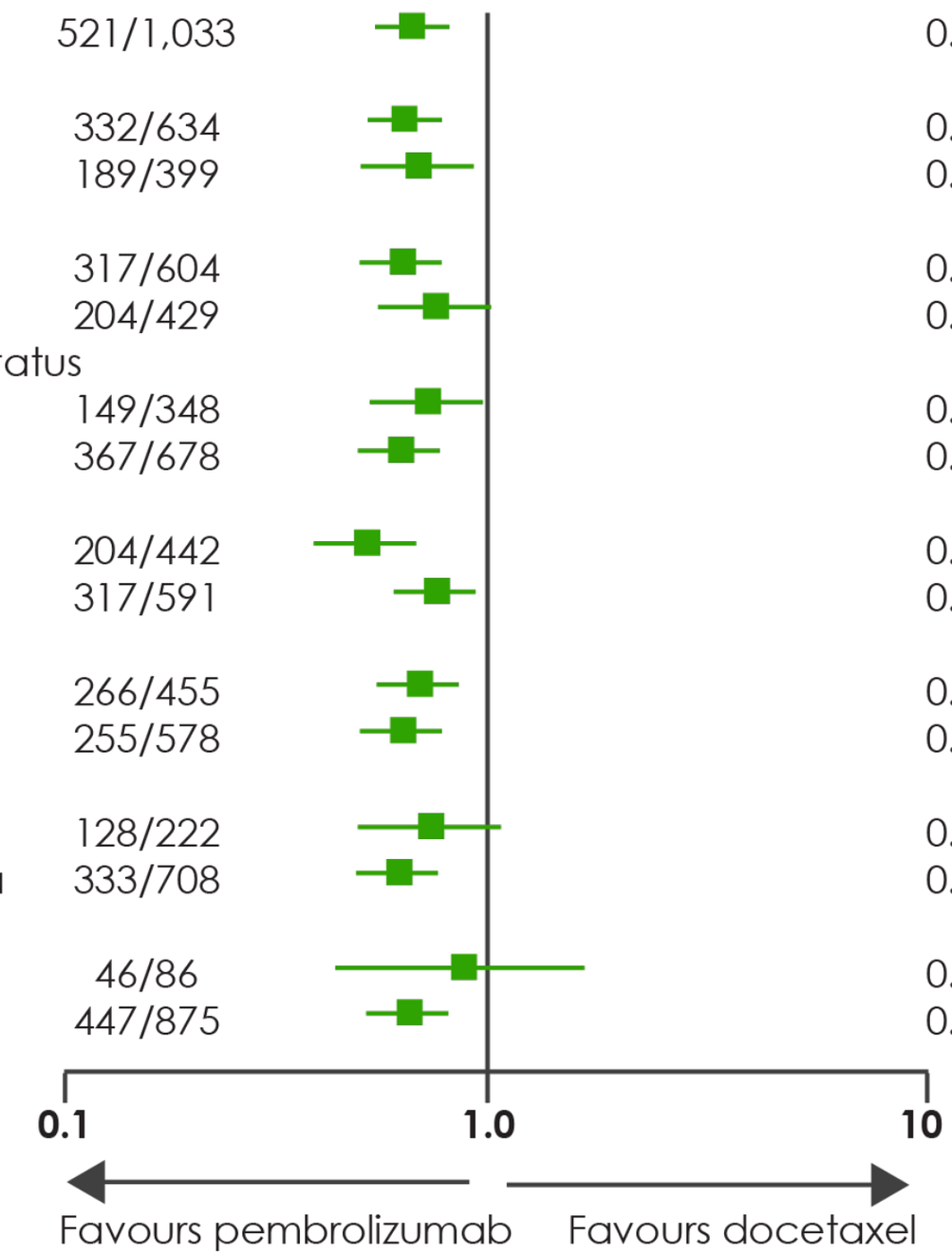
[a]Difference for pembrolizumab *vs* docetaxel.

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

Adapted from Herbst RS et al. *Lancet* 2016; 387: 1540–1550 (and online appendix).

KEYNOTE-010: overall survival in key subgroups All patients (PD-L1 TPS ≥1%)

Supgroup	Events, n/patients, n	Hazard ratio (95% CI)
Overall	521/1,033	0.67 (0.56–0.80)
Sex		
Male	332/634	0.65 (0.52–0.81)
Female	189/399	0.69 (0.51–0.94)
Age		
<65 years	317/604	0.63 (0.50–0.79)
≥65 years	204/429	0.76 (0.57–1.02)
ECOG performance status		
0	149/348	0.73 (0.52–1.02)
1	367/678	0.63 (0.51–0.78)
PD-L1 TPS		
≥50%	204/442	0.53 (0.40–0.70)
1–49%	317/591	0.76 (0.60–0.96)
Tumour sample		
Archival	266/455	0.70 (0.54–0.89)
New	255/578	0.64 (0.50–0.83)
Histology		
Squamous	128/222	0.74 (0.50–1.09)
Adenocarcinoma	333/708	0.63 (0.50–0.79)
EGFR status		
Mutant	46/86	0.88 (0.45–1.70)
Wild type	447/875	0.66 (0.55–0.80)



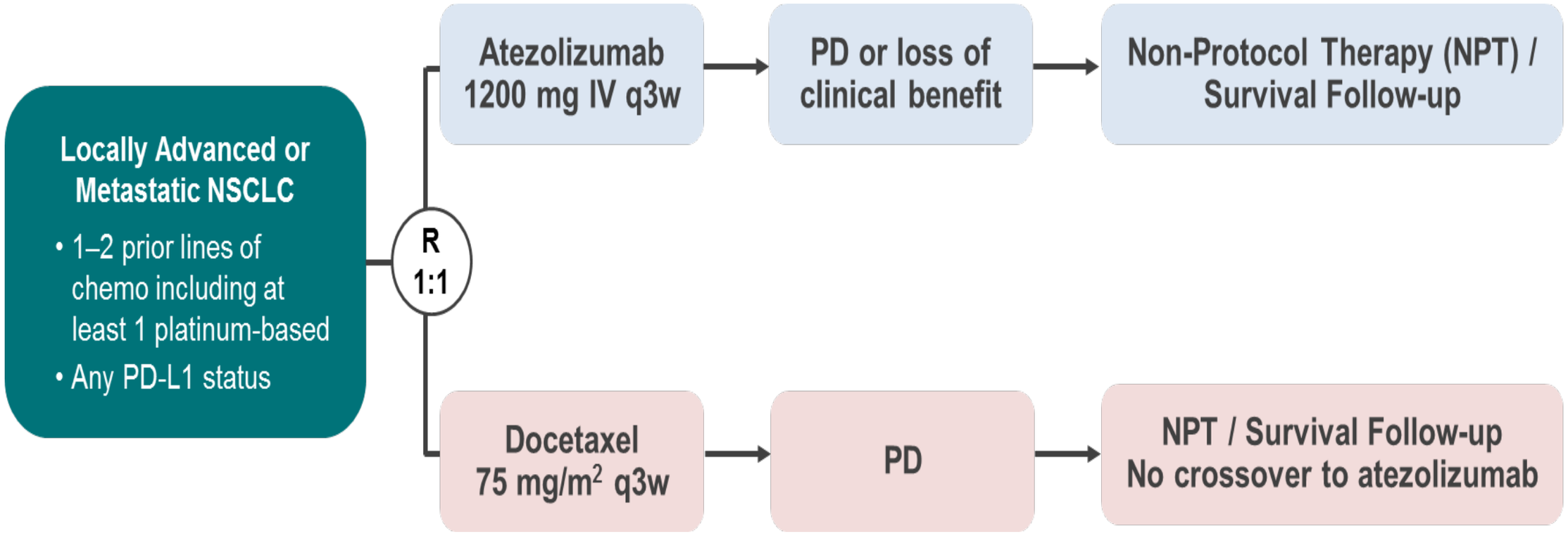
Analysis cut-off date: September 30, 2015.

[a]Data for pembrolizumab groups pooled.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: programmed cell death ligand 1; TPS: tumour proportion score.

Herbst RS et al. *Lancet* 2016; 387: 1540–1550 (and online appendix).

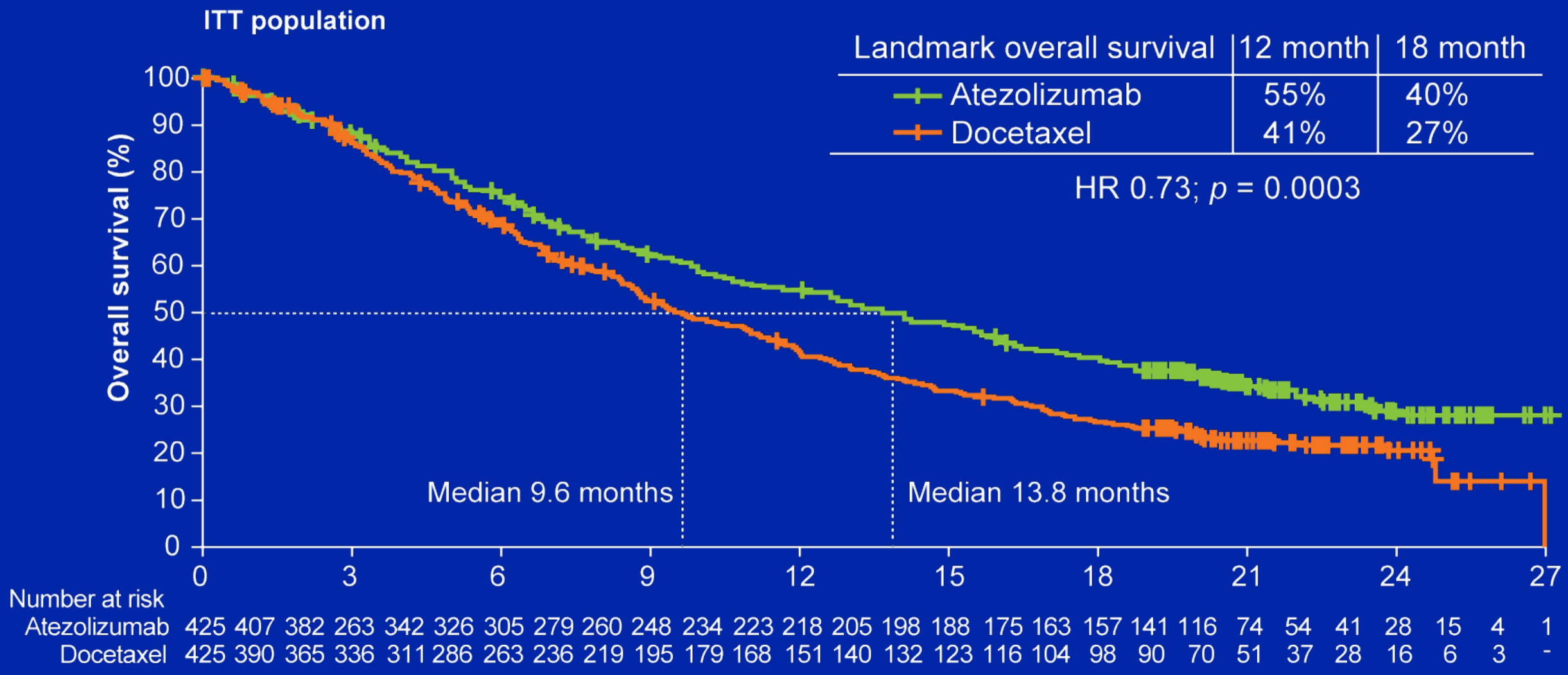
OAK: Ph III Randomized Study in 2L+ NSCLC



- **Primary endpoint (first 850 enrolled patients): OS in the ITT population**
- **Treatment Beyond Progression (TBP) allowed in the atezolizumab arm as long as patients were felt to be experiencing continued clinical benefit (per investigator) and no severe toxicity based on protocol defined criteria**

Gandara DR et al. OAK: Atezolizumab treatment beyond disease progression.

OAK: Atezolizumab versus Docetaxel in NSCLC



Landmark overall survival	12 month	18 month
Atezolizumab	55%	40%
Docetaxel	41%	27%

HR 0.73; p = 0.0003

Rittmeyer A et al. *Lancet* 2017;389(10066):255-65.

OS

	N=850	HR	Median OS, months: Atezo	Median OS, months: Docetaxel
ITT	100%	0.74	13.8	9.6
Age				
<65	53%	0.80	13.2	10.5
≥65	47%	0.66	14.1	9.2
Gender				
Male	61%	0.79	12.6	9.2
Female	39%	0.64	16.2	11.2
Histology				
Non-squamous	74%	0.73	15.6	11.2
Squamous	26%	0.73	8.9	7.7
Prior therapy				
1	75%	0.71	12.8	9.1
2	25%	0.80	15.2	12.0
PD-L1 expression				
TC ≥50% or IC ≥10%	16%	0.41	20.5	8.9
TC or IC ≥5%	31%	0.67	16.3	10.8
TC or IC ≥1%	54%	0.74	15.7	10.3

In a complementary and retrospective analysis of the TC and IC <1% subgroup, median OS was 12.6 months with Atezolizumab (95% CI, 9.6, 15.2) vs 8.9 months with docetaxel (95% CI, 7.7, 11.5) (HR=0.75; 95% CI, 0.59, 0.96)

Rittmeyer A et al. *Lancet* 2017;389(10066):255-65.

Other treatments

Targeted Approaches to Anti-VEGF Therapy

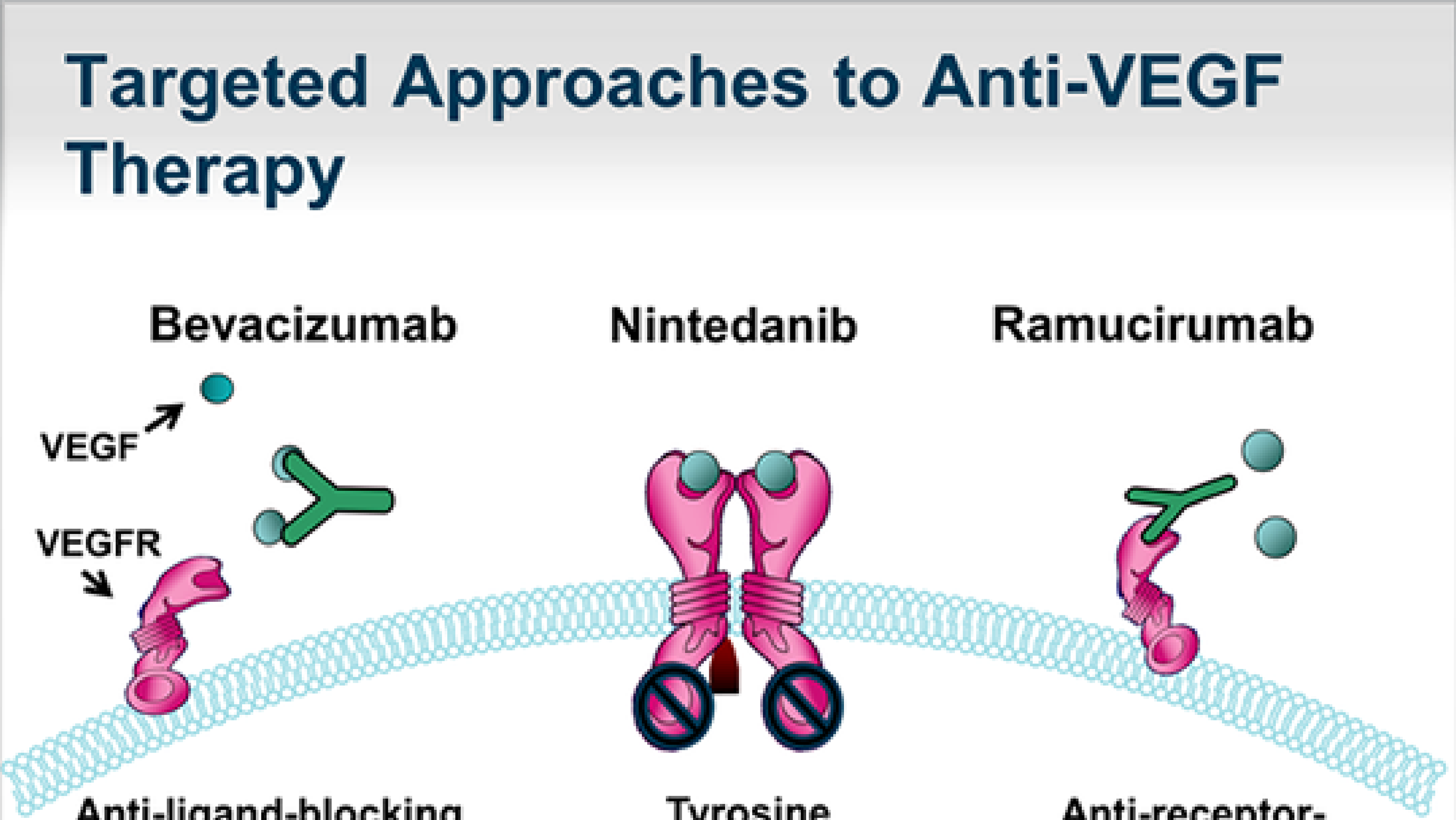
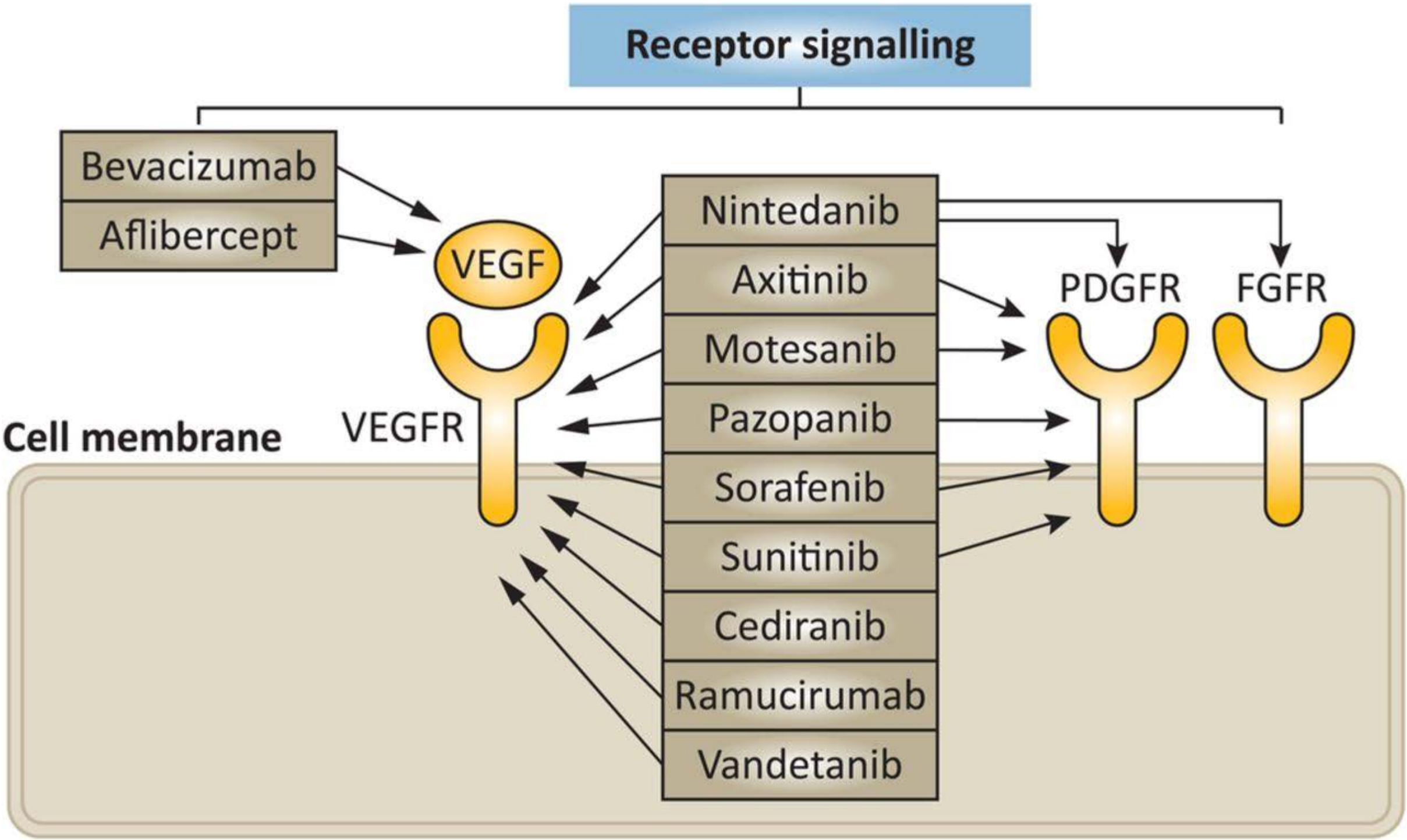


Image courtesy of C. Langer, MD.


Receptor signalling
Bevacizumab
Aflibercept
VEGF
Nintedanib
Axitinib
Motesanib
Pazopanib
Sorafenib
Sunitinib
Cediranib
Ramucirumab
Vandetanib
PDGFR
FGFR
VEGFR
Cell membrane

REVEL: Docetaxel +/- Ramucirumab as Second Line Therapy for Adv NSCLC

- Ramucirumab (RAM) is a human IgG1 monoclonal antibody, specifically binding to the extracellular domain of VEGFR-2
- Approved in previously treated gastric cancer

Adv NSCLC
(any histology)

Prior platinum-based chemo
Prior bev allowed

N = 1253

RANDOMIZE

Docetaxel 75 mg/m2 +
Ramucirumab 10 mg/kg
IV Q21 days

Docetaxel 75 mg/m2 +
Placebo
IV Q21 days

Treat until PD or prohibitive toxicity

Primary endpoint: OS

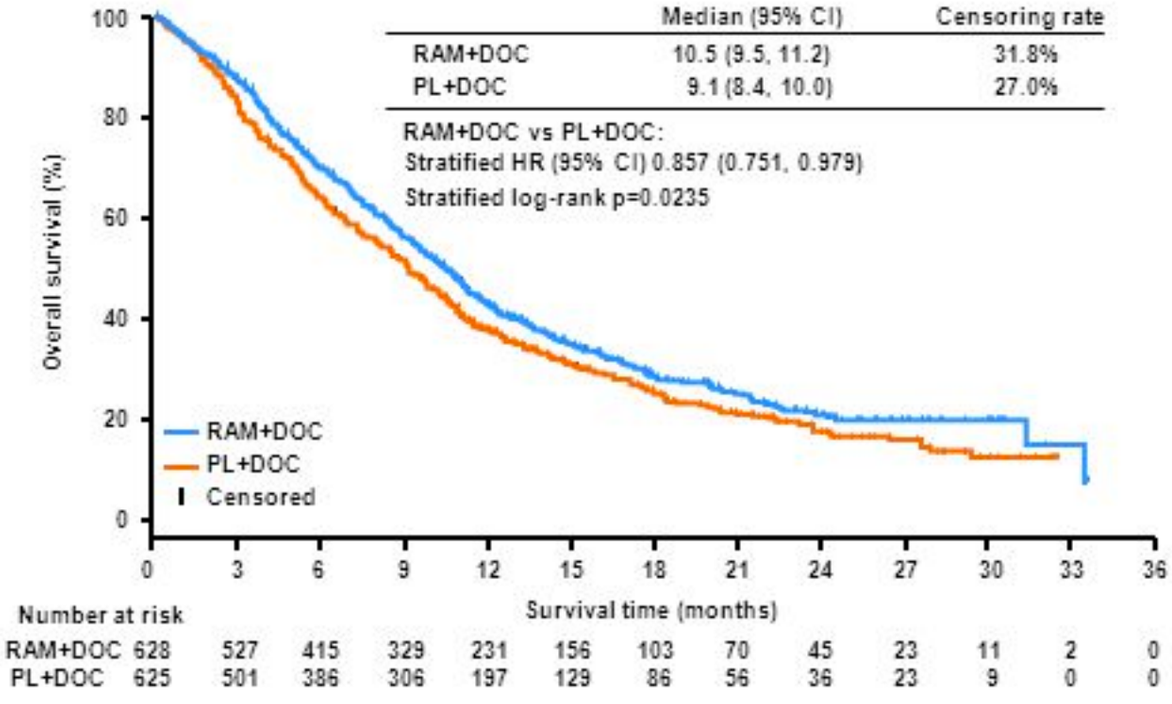
Squamous 25% DR vs 27% DP

Perol, A#LBA-8006

LBA8006^: REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line treatment of stage IV non-small cell lung cancer (NSCLC) following disease progression after one prior platinum-based therapy – Perol M et al

- **Key results**
  - Ramucirumab+docetaxel significantly improved survival over placebo+docetaxel

OS



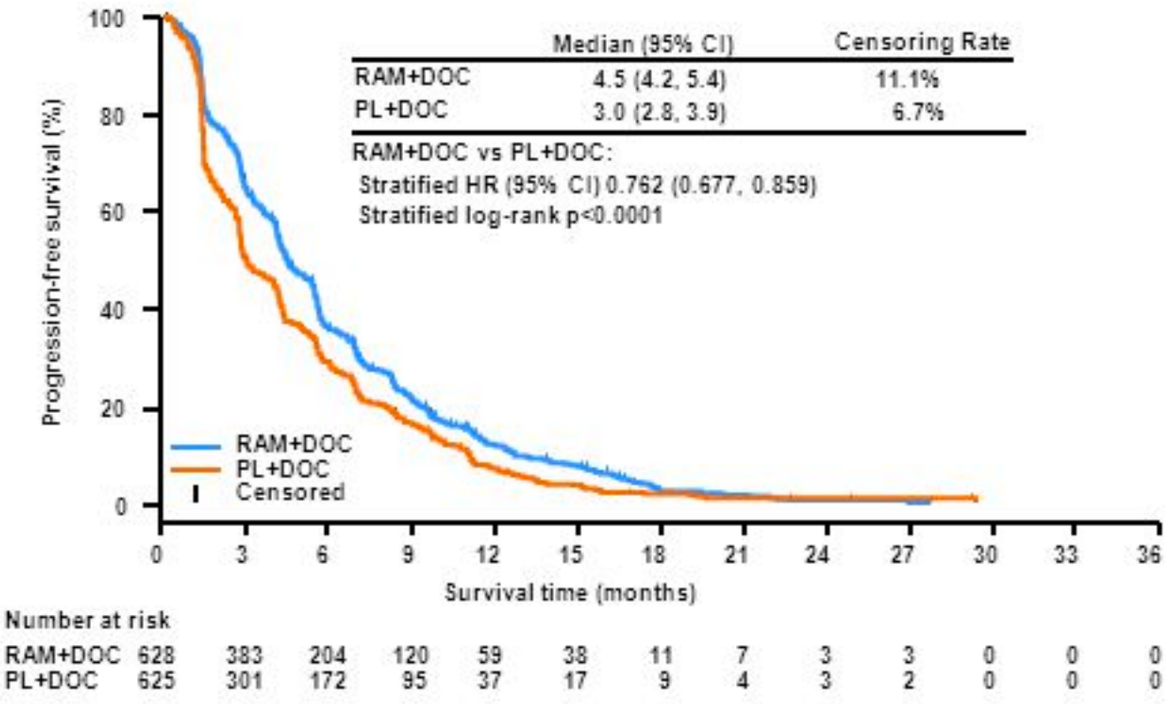
	Median (95% CI)	Censoring rate
RAM+DOC	10.5 (9.5, 11.2)	31.8%
PL+DOC	9.1 (8.4, 10.0)	27.0%

RAM+DOC vs PL+DOC:
Stratified HR (95% CI) 0.857 (0.751, 0.979)
Stratified log-rank p=0.0235

Number at risk

RAM+DOC	628	527	415	329	231	156	103	70	45	23	11	2	0
PL+DOC	625	501	386	306	197	129	86	56	36	23	9	0	0

PFS



	Median (95% CI)	Censoring Rate
RAM+DOC	4.5 (4.2, 5.4)	11.1%
PL+DOC	3.0 (2.8, 3.9)	6.7%

RAM+DOC vs PL+DOC:
Stratified HR (95% CI) 0.762 (0.677, 0.859)
Stratified log-rank p<0.0001

Number at risk

RAM+DOC	628	383	204	120	59	38	11	7	3	3	0	0	0
PL+DOC	625	301	172	95	37	17	9	4	3	2	0	0	0

RAM, ramucirumab; DOC, docetaxel

Pérol et al. J Clin Oncol 2014; 32 (suppl 5; abstr LBA8006^)

LUX-Lung 8: Afatinib vs Erlotinib Study Design

Stratified by East Asian vs non-East Asian

SCC of the lung (stage IIIB/IV)[1]; progressed after ≥ 4 cycles of a first-line platinum doublet; ECOG PS 0-1; adequate organ function

(N = 795)

Afatinib 40 mg* QD
(n = 398)

Erlotinib 150 mg† QD
(n = 397)

*Dose escalation to 50 mg and dose reduction to 30 or 20 mg permitted.
†Dose reduction to 100 or 50 mg permitted.
Tumor assessment at baseline, Wks 8, 12, 16; every 8 wks thereafter.

- Primary endpoint: PFS by independent review
- Secondary endpoints: OS, ORR, DCR, tumor shrinkage, PRO, safety

Soria JC, et al. Lancet Oncol. 2015;16:897-907.

Slide credit: clinicaloptions.com

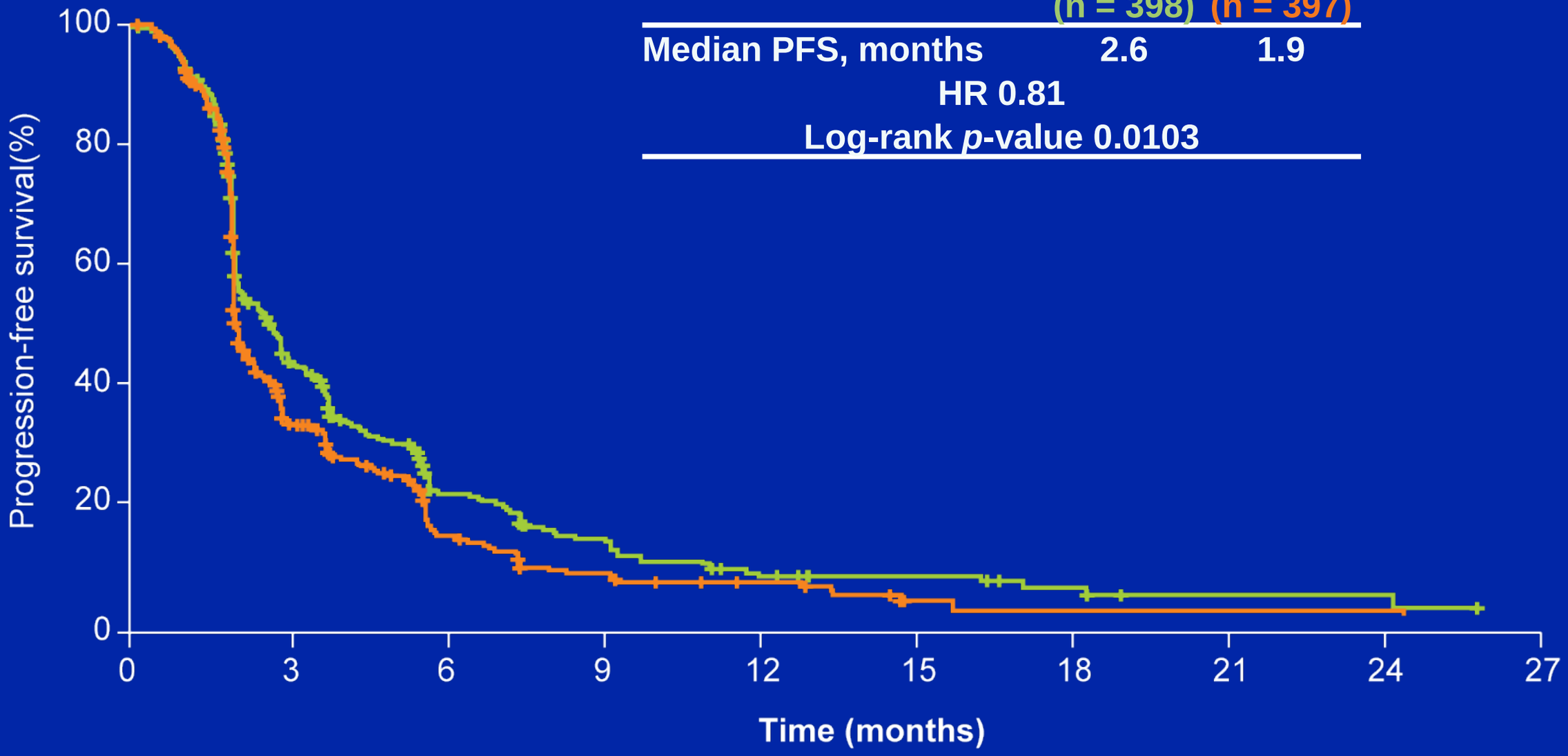
Características demográficas

		Afatinib‡‡	Erlotinib‡‡	Total
Aletorizados		335	334	669
ECOG*, %	0	33	35	34
	1	66	65	66
Masculinos, %		85	84	85
Raza (para estratificación), %	Non-East Asian	78	78	78
	East Asian	22	23	22
Edad mediana, años		65	64	65
Tabaquismo, %	No fumadores	8	3	5
	Ex-fumadores†	7	6	7
	Fumador	85	91	88
Mediana diagnóstico, años		0.7	0.8	0.8
Etapa clínica‡, %	IIIB	13	12	12
	IV	88	87	87
Histología§, %	Células escamosas	96	96	96
	Mixto¶	5	3	4
Quimioterapia previa, %	Doble-platino	100	100	100
Mejor respuesta a primera línea de quimioterapia**, %	RC/RP	47	46	46
	EE	41	43	42
	Desconocido	13	11	12

RC, respuesta completa; RP, respuesta parcial; EE, enfermedad estable; *<1% fueron ECOG PS 2; †<15 paquetes años y pararon >1 año antes del diagnóstico; ‡<1% etapa IIIA; §<1% no diferenciado (considerados como histología escamoso); ¶considerado a ser histologíae scamosa; **<1% presentan progresión de la enfermedad; ‡‡los porcentajes pueden no sumar 100 debido al redondeo

LUX-Lung 8: Progression-Free Survival with Second-Line Afatinib versus Erlotinib in Squamous Cell Carcinoma of the Lung

	Afatinib (n = 398)	Erlotinib (n = 397)
Median PFS, months	2.6	1.9
HR 0.81		
Log-rank *p*-value 0.0103		

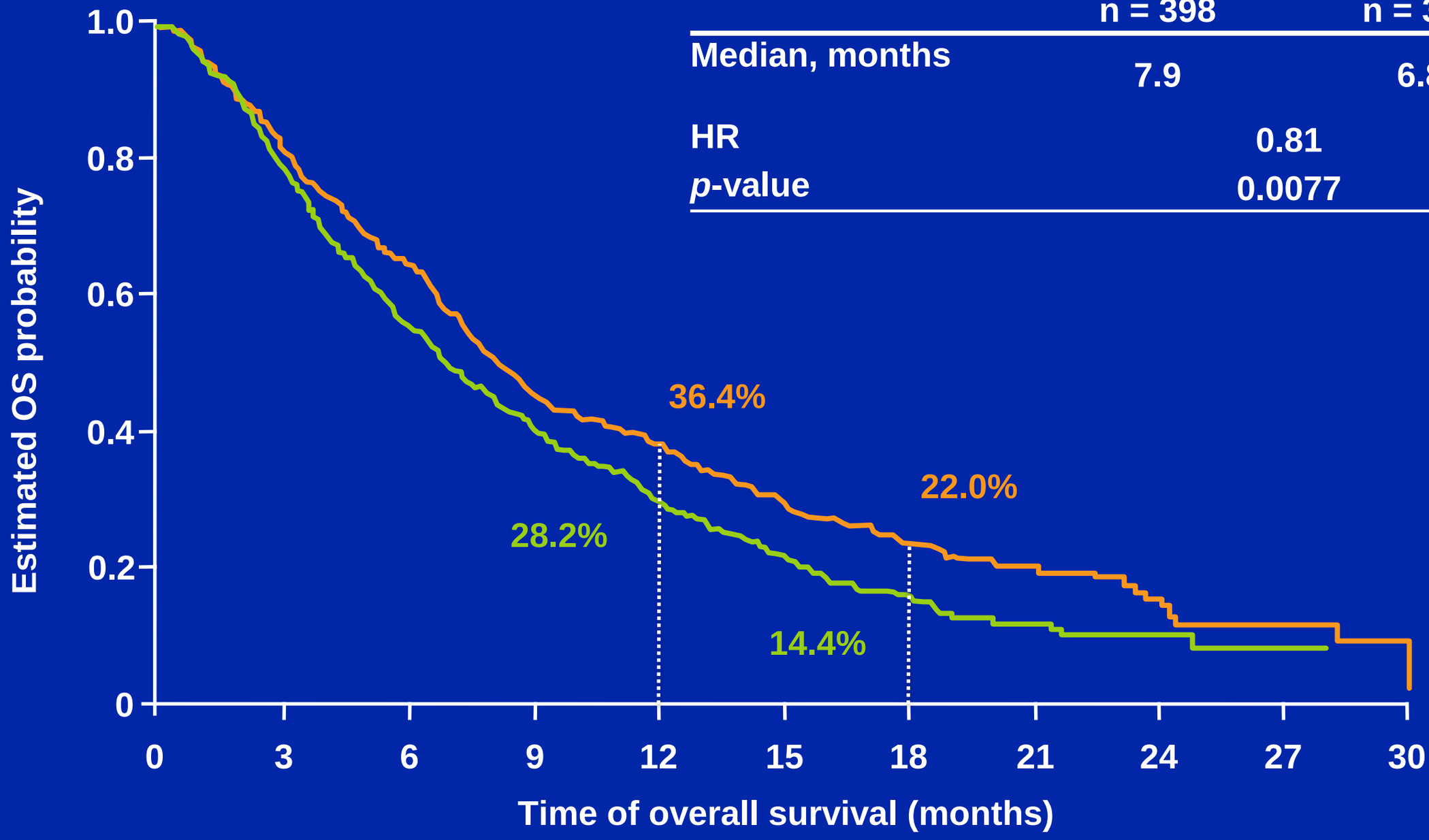


Median follow-up time: 18.4 months

Soria JC et al. *Lancet Oncol* 2015;16(8):897-907.

LUX-Lung 8 Primary Analysis: Overall Survival

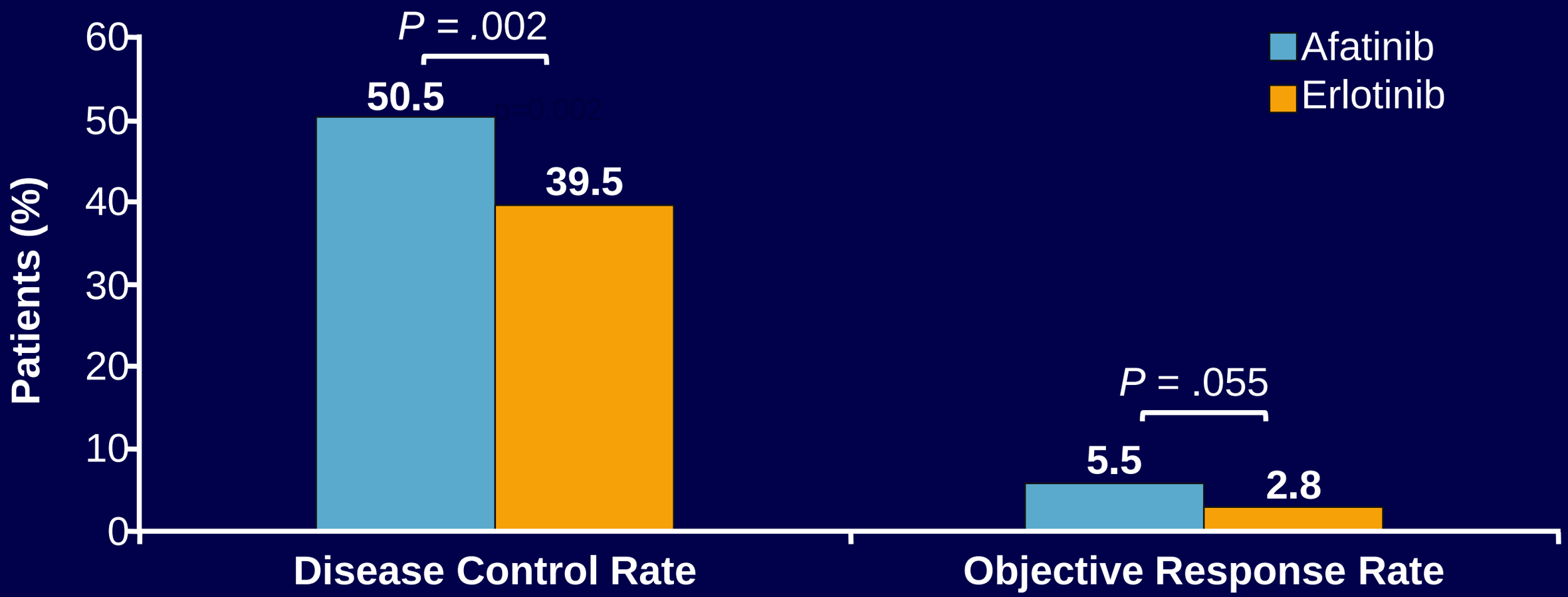
	Afatinib n = 398	Erlotinib n = 397
Median, months	7.9	6.8
HR	0.81	
p-value	0.0077	



Median follow-up time: 18.4 months

Soria JC et al. *Lancet Oncol* 2015;16(8):897-907.

LUX-Lung 8: Response

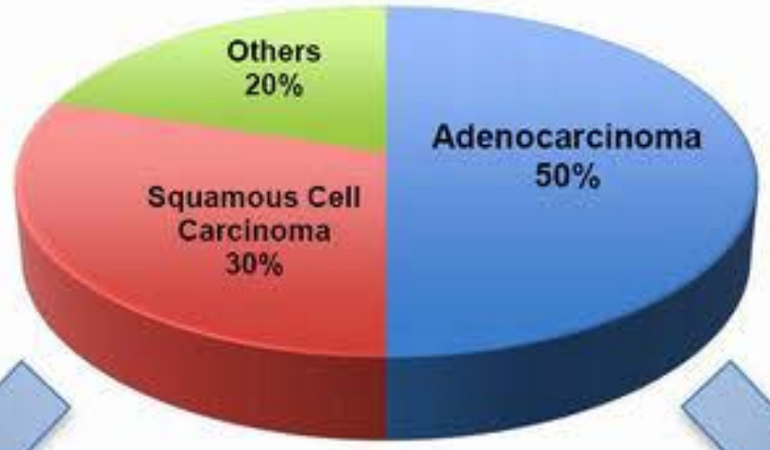


- Duration of response was 7.29 mos for afatinib and 3.71 mos for erlotinib

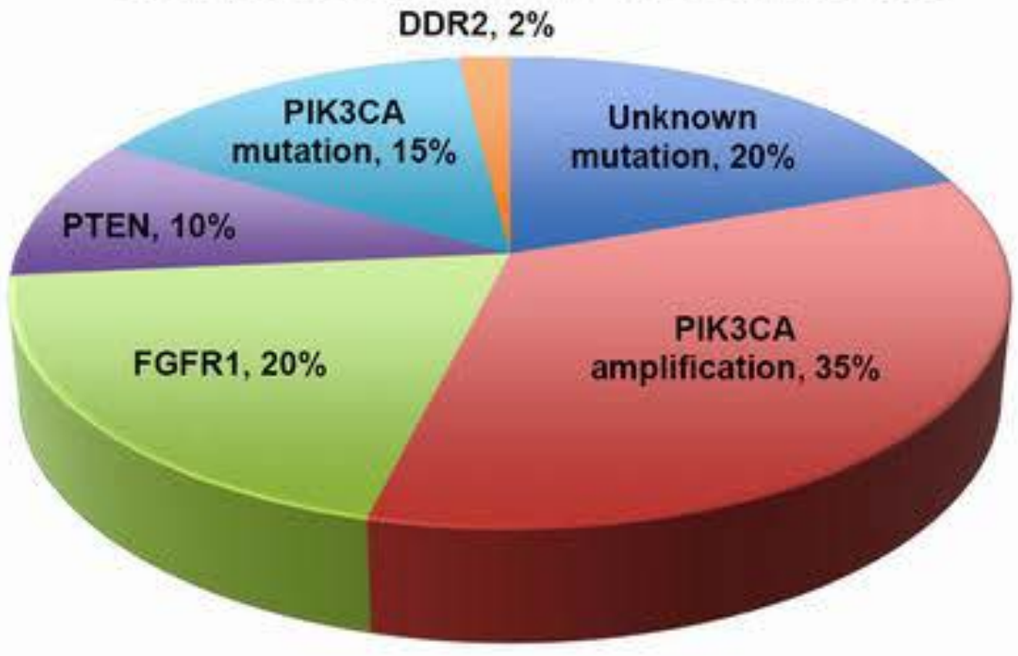
Soria JC, et al. Lancet Oncol. 2015;16:897-907.

Slide credit: clinicaloptions.com

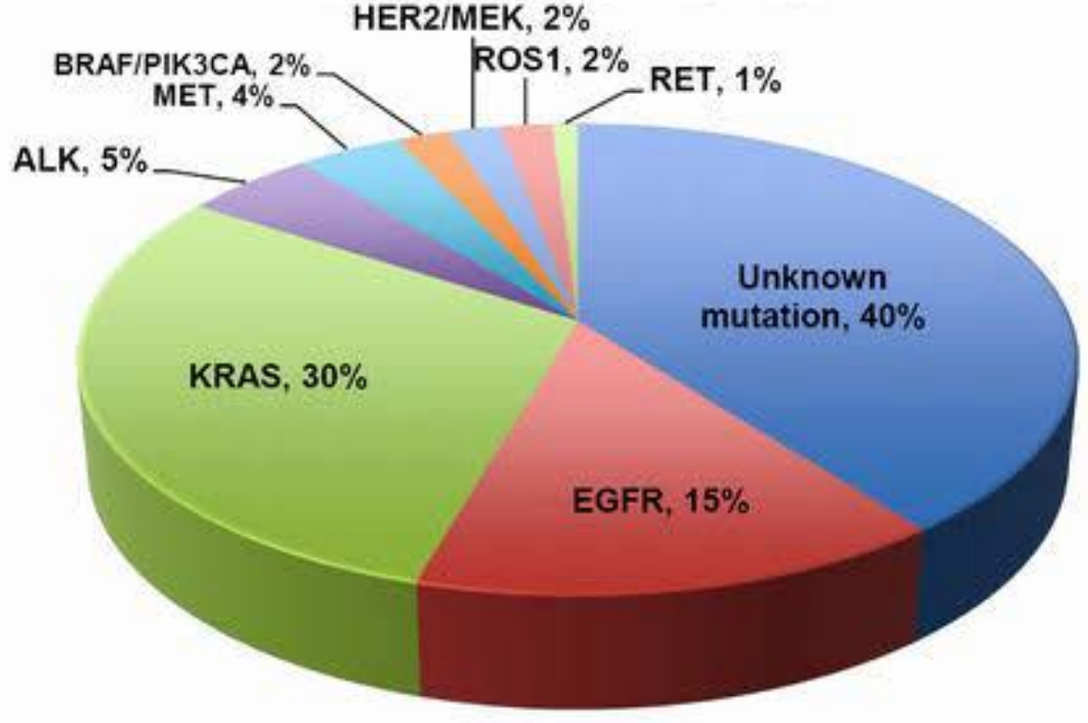
NSCLC by histology



Squamous Cell Carcinoma

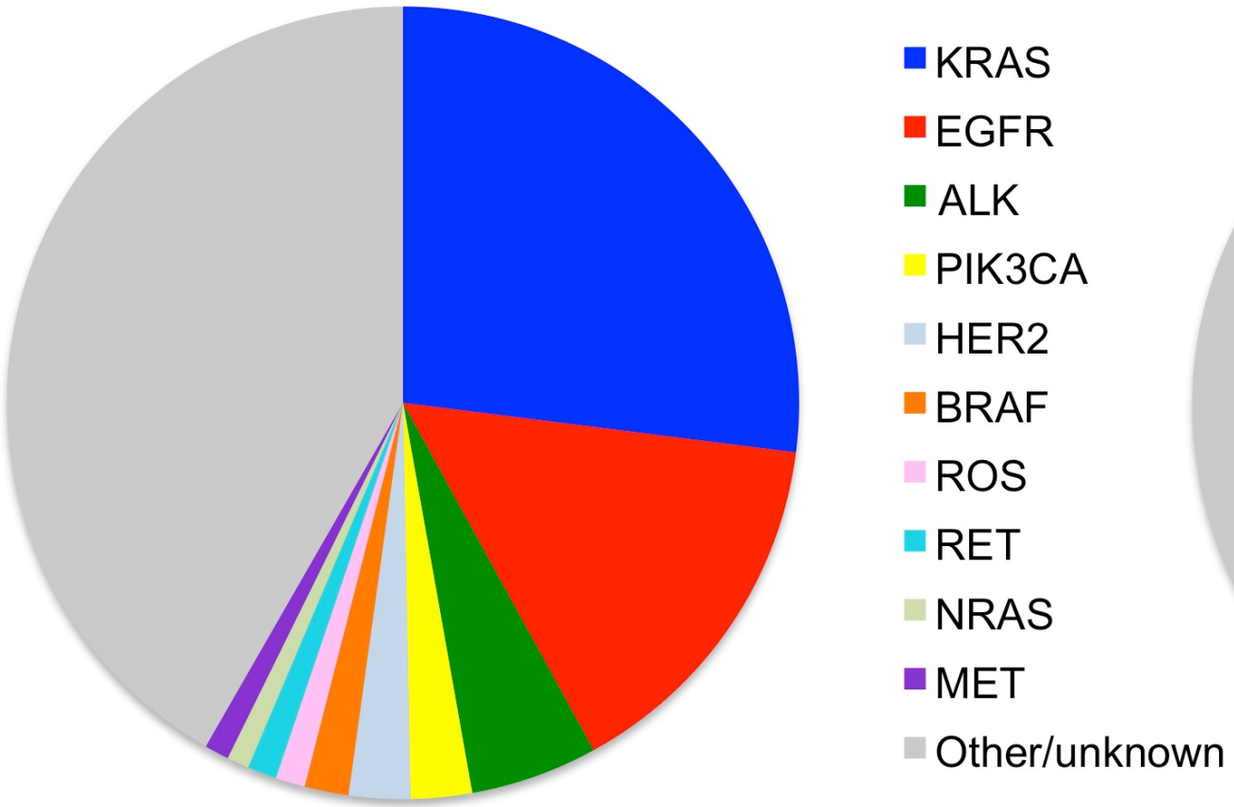


Adenocarcinoma

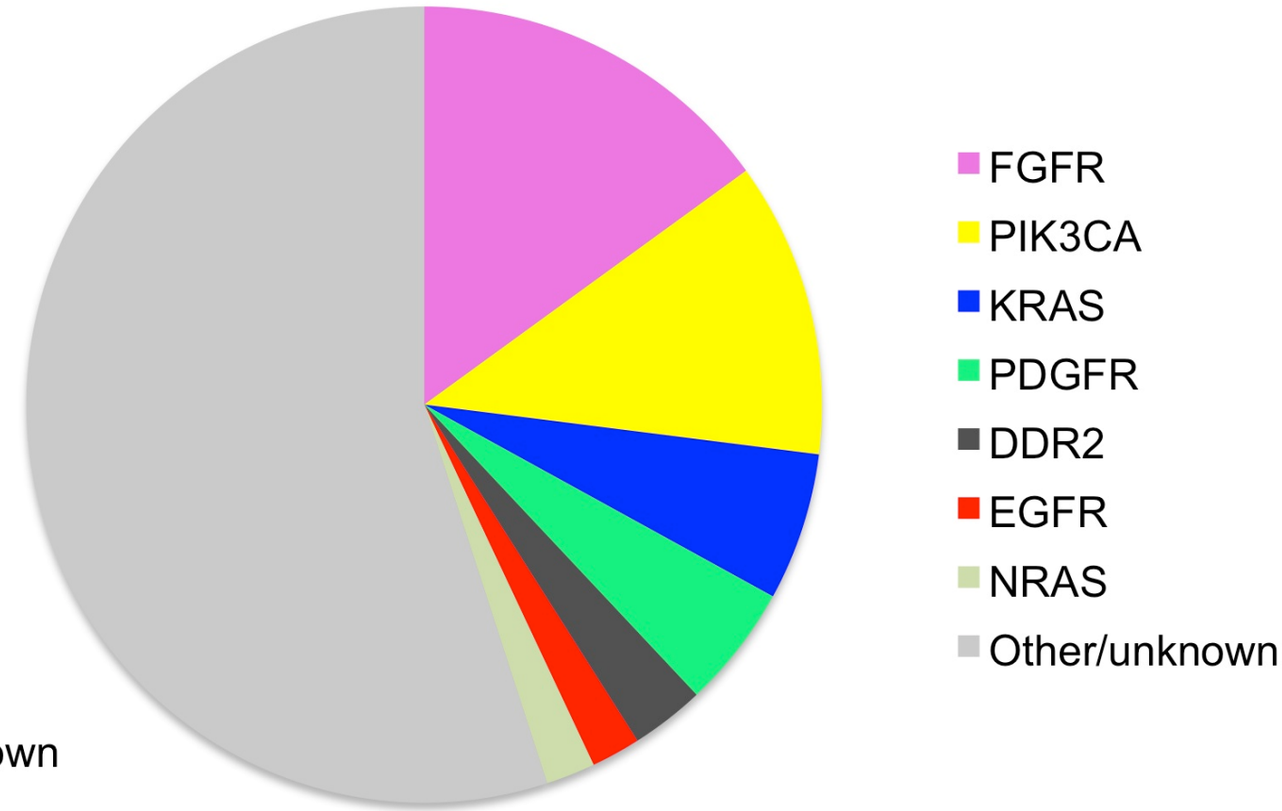


Genetic Profiles by Histologic Subtype

Oncogenic drivers differ between adenocarcinomas and squamous cell carcinomas



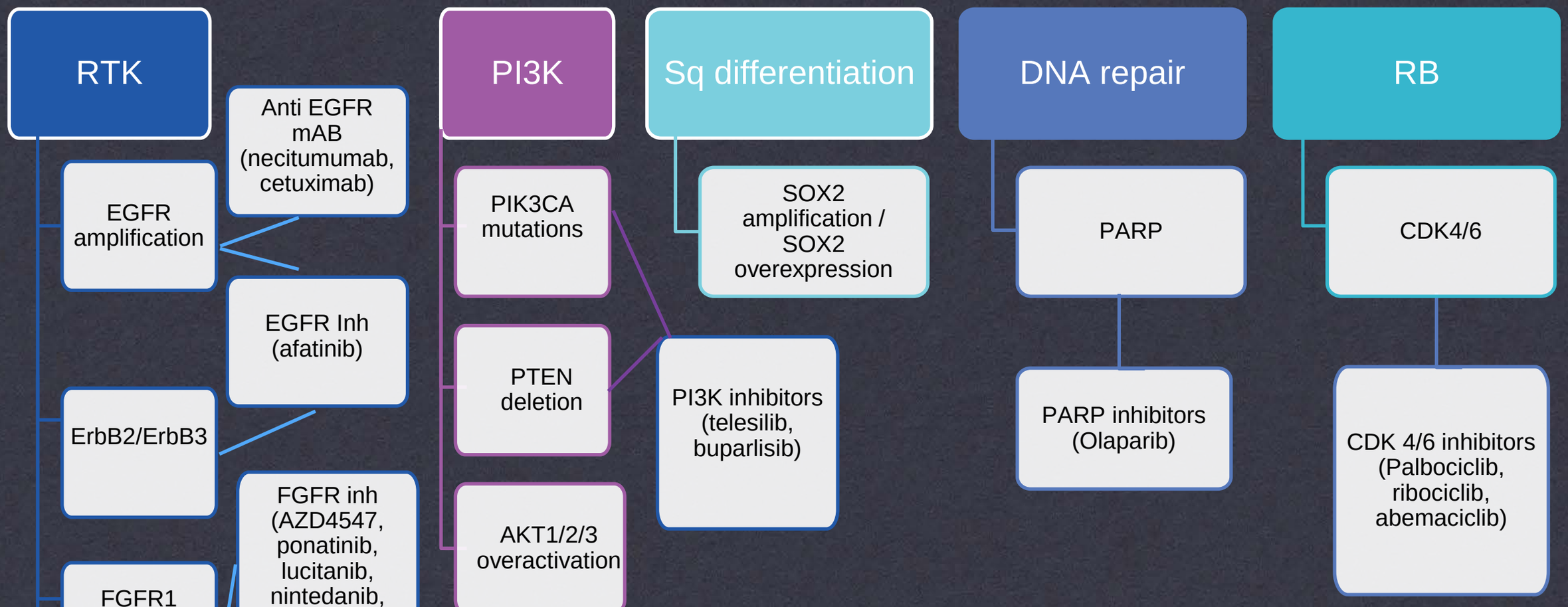
Adenocarcinoma



Squamous cell carcinoma

Sequist et al., Ann Oncol 22:2616, 2011; Bergethon et al., JCO Jan 3, 2012; Weiss et al., Sci Transl Med 2:62ra93. 2010; Kris et al., WCLC 2011; Hammerman et al., Cancer Discovery 1:78, 2011; AJ Iafrate, personal communication

Selected potential target pathways in squamous NSCLC[1,2]



AKT, alpha serine/threonine-protein kinase; CDK4/6, cyclin-dependent kinase 4/6; DDR2, discoidin domain receptor tyrosine kinase 2; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; PARP, polyadenosine diphosphate (ADP)–ribose polymerase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; PI3K, phosphoinositide-3-kinase; PTEN, phosphatase and tensin homolog; RB, retinoblastoma; RTK, receptor tyrosine kinase; SOX, SRY-related HMG box

1. Shtivelman E et al. *Oncotarget* 2014;5:1392–433; 2. Stead LF et al. *PLoS One* 2013;8:e78823

Thank you!

corrales@cimcacr.com

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Centro de Investigación
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