Squamous Cell Carcinoma Standard and Novel Targets.

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Squamous Cell Carcinoma: Standard and Novel Targets

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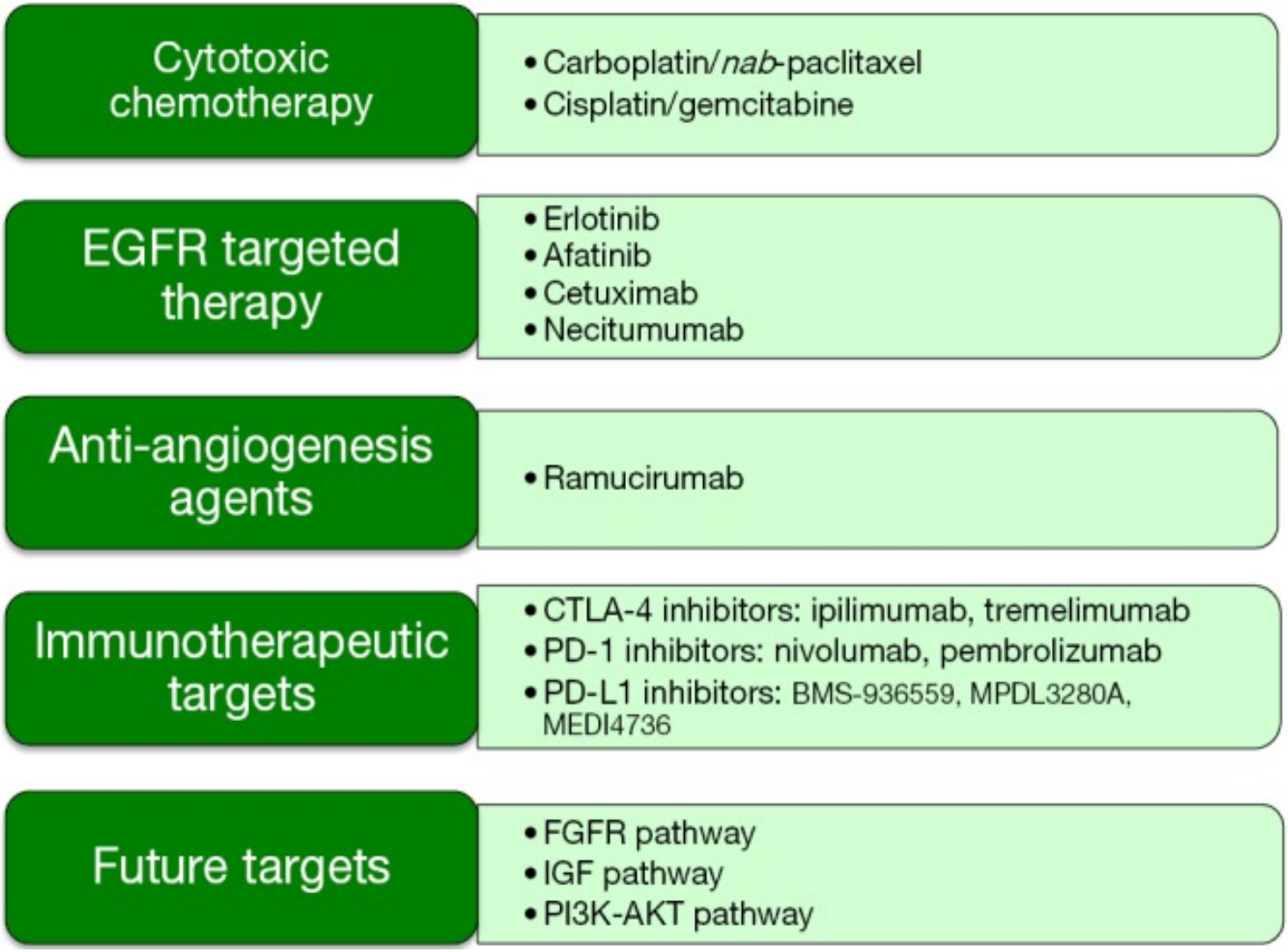
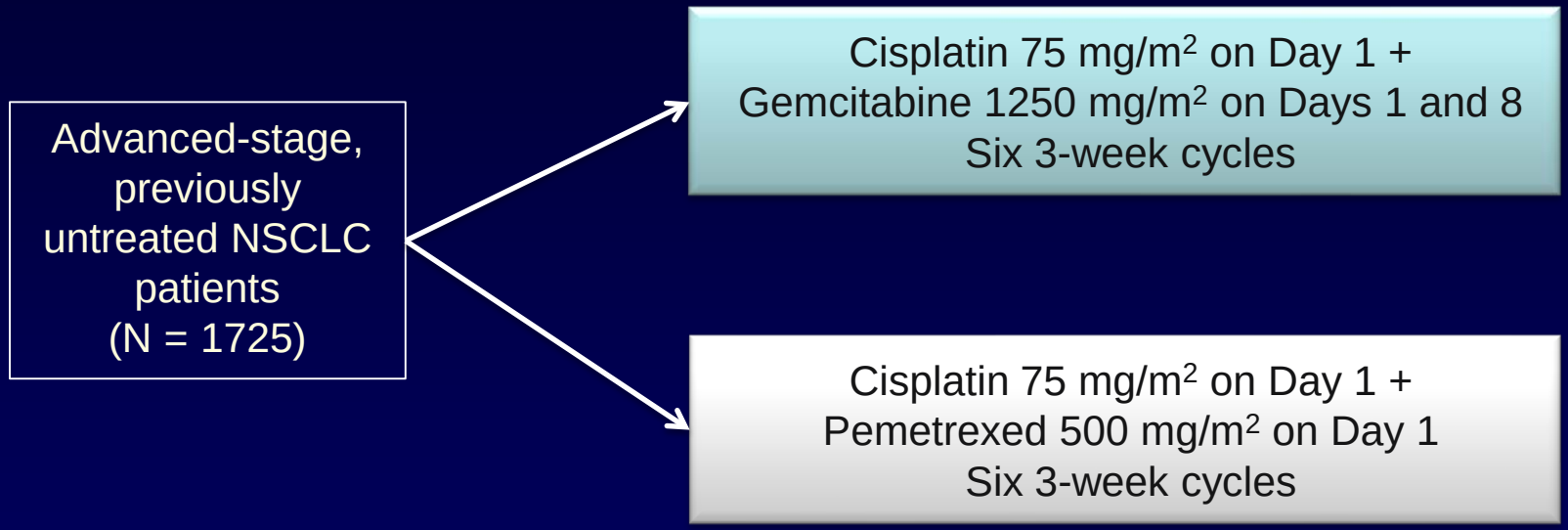
Review of current and potential future therapies for squamous cell carcinoma (SCC) of the lung.

Derman, et al Transl Lung Cancer Res. 2015 Oct; 4(5): 524–532.



First Line Treatment options For Metastatic Squamous Cell Carcinoma of the Lung

Phase III Study: Gemcitabine + Cisplatin vs. Pemetrexed + Cisplatin as First-line Therapy

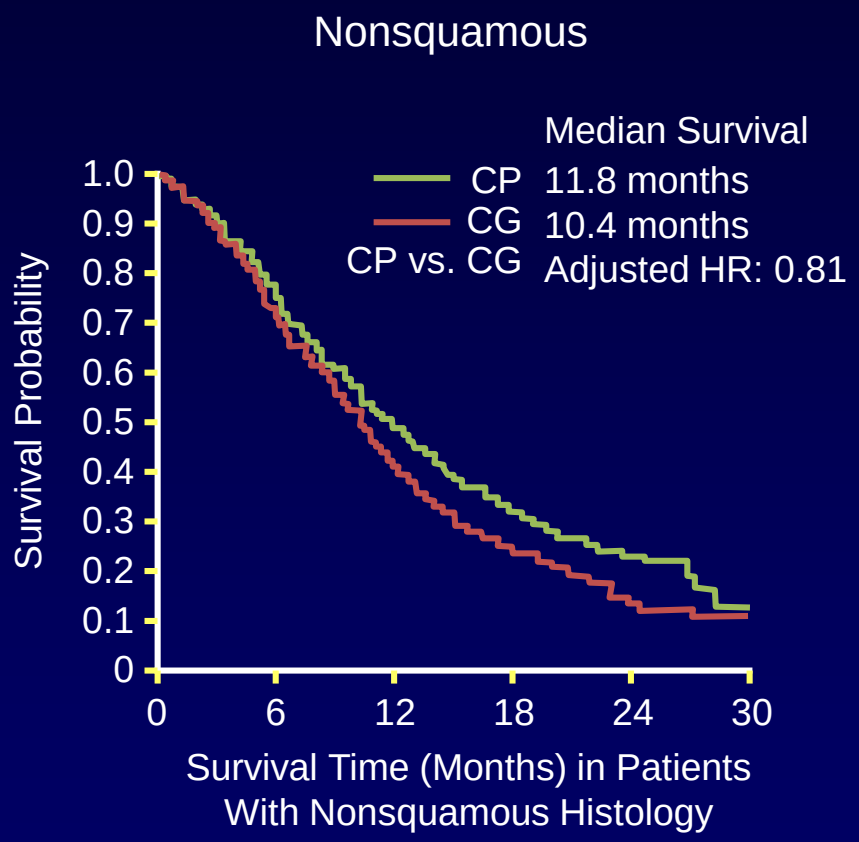


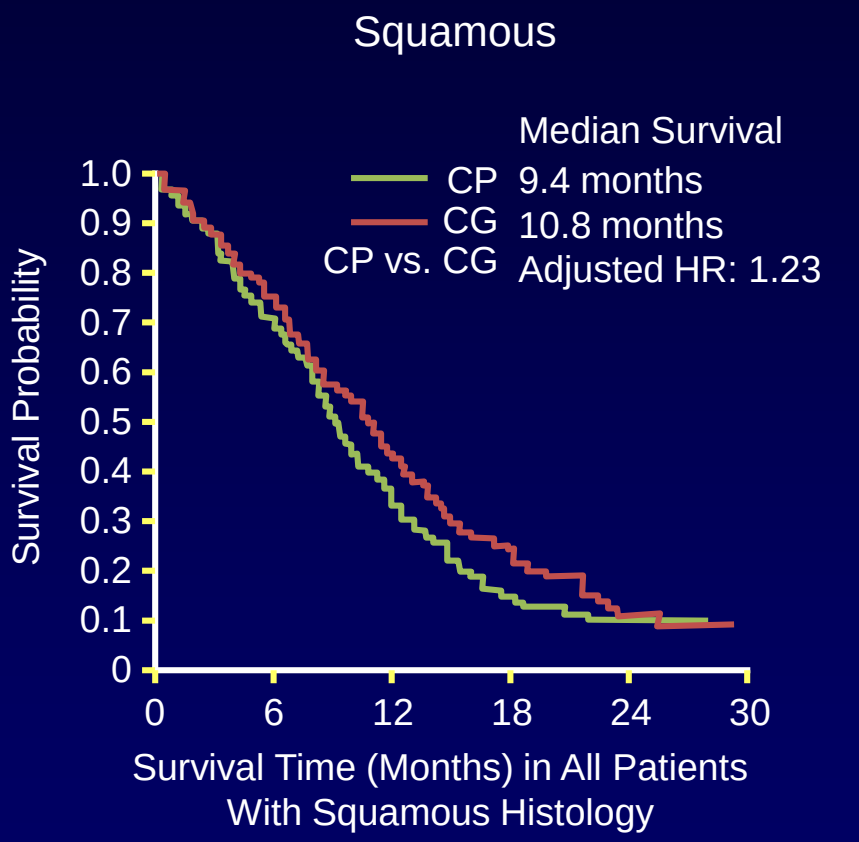
Stratified by:

- ECOG performance score (0 vs. 1)
- Disease stage (IIIB vs. IV)
- Brain metastases (yes vs. no)
- Sex (male vs. female)
- Pathologic diagnosis (histologic vs. cytologic)
- Treatment center

Scagliotti GV, et al. *J Clin Oncol*. 2008;26:3543-3551.

CP vs. CG in Advanced NSCLC: OS by Histology

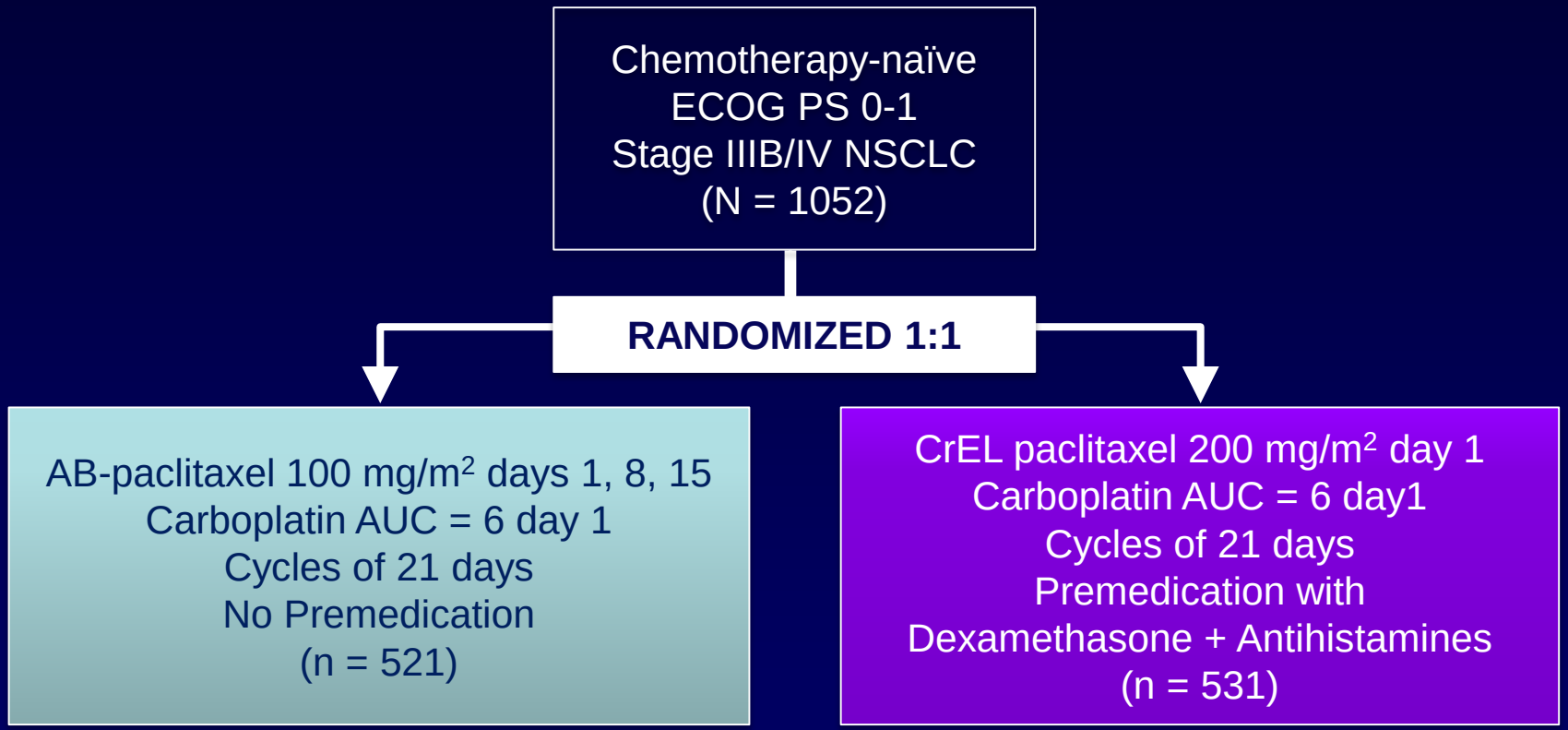




Scagliotti GV, et al. *J Clin Oncol.* 2008;26:3543-3551.

Albumin-Bound Paclitaxel + Carboplatin vs. Cremophor EL Paclitaxel + Carboplatin in Advanced NSCLC

Study Design

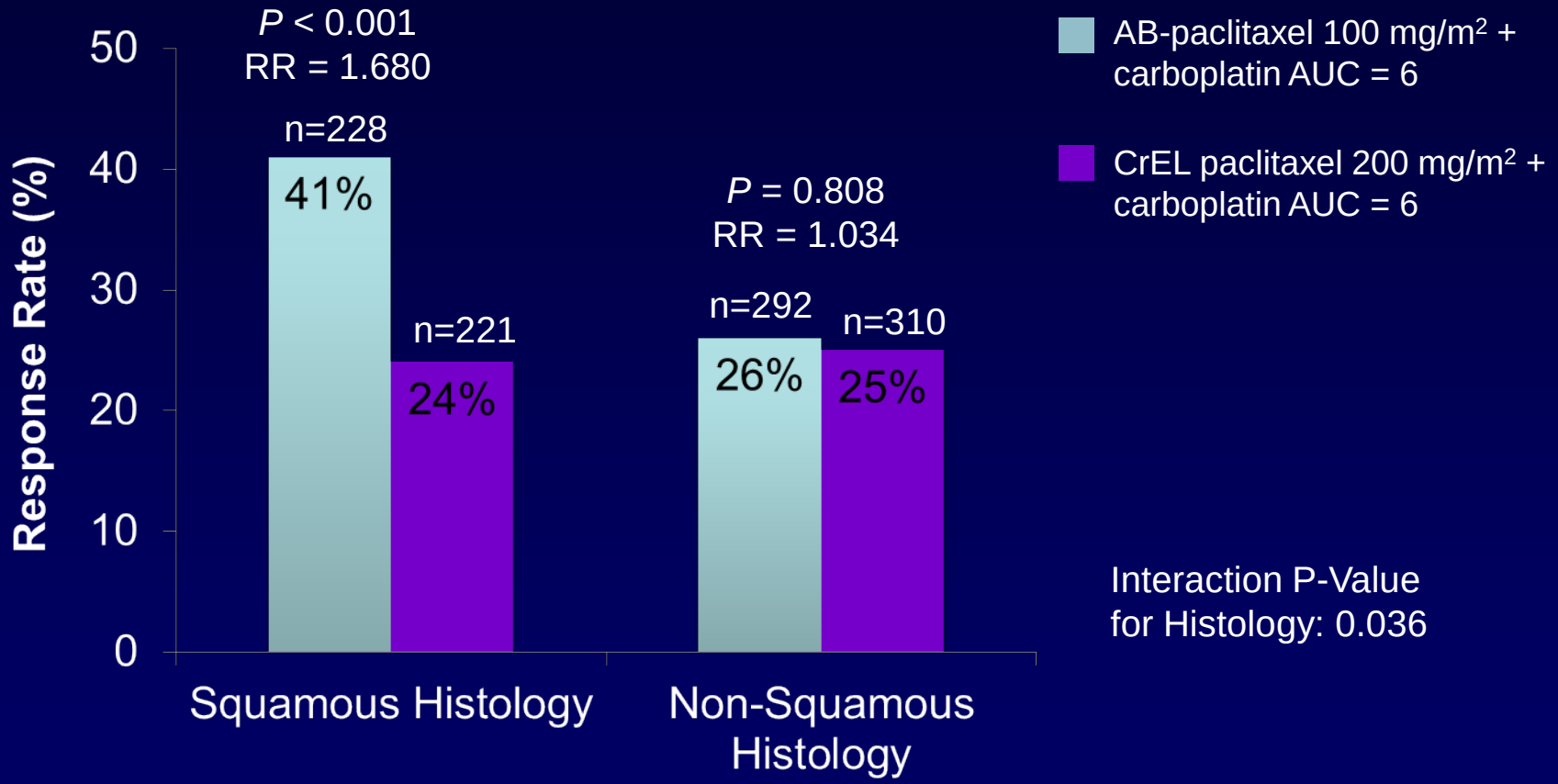


Socinski MA et al. ASCO. 2011 [Abstract 7551].

AB, albumin-bound; CrEL, Cremophor® EL; ECOG, Eastern Cooperative

Albumin-Bound Paclitaxel + Carboplatin vs. Cremophor EL Paclitaxel + Carboplatin in Advanced NSCLC

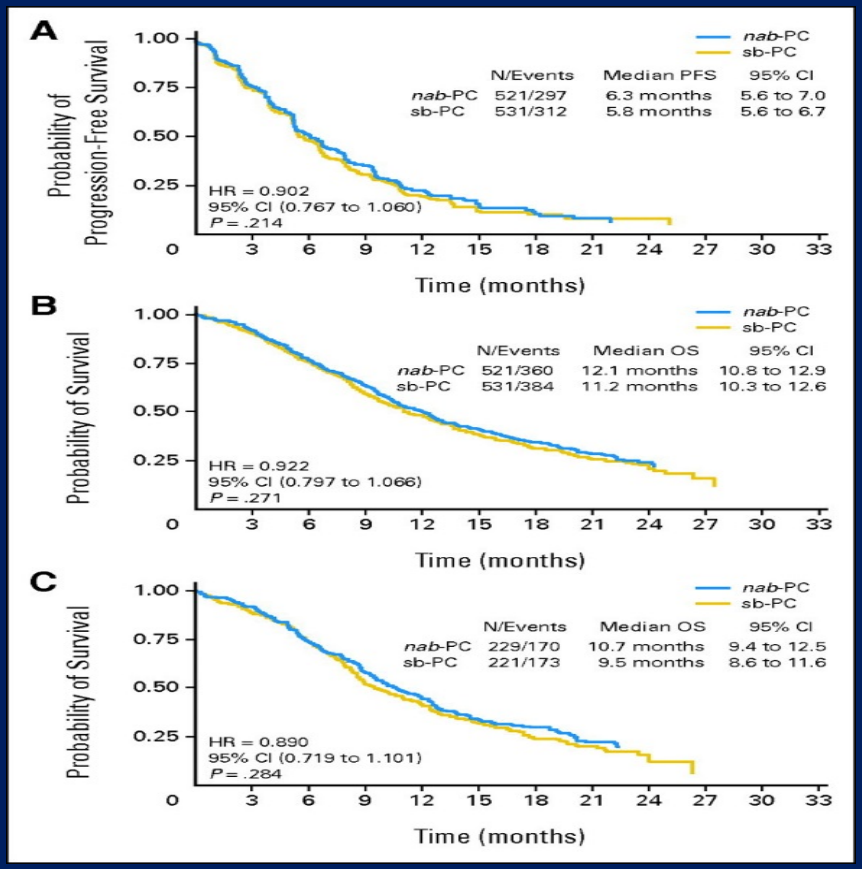
Results: ORR, Stratified by Histology[a]



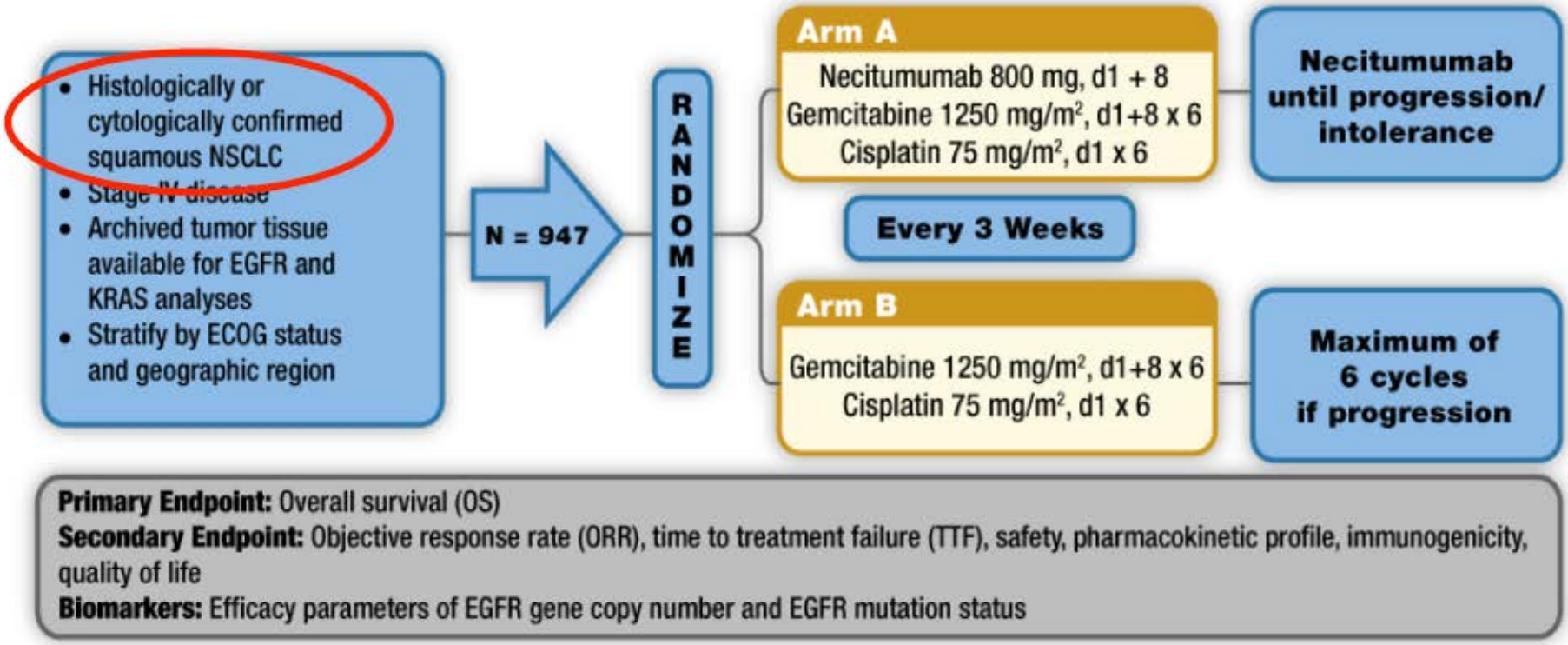
[a] Not a pre-specified endpoint.

Socinski MA et al. ASCO. 2011 [Abstract 7551].

PFS (A), OS (B) in the ITT population as well as OS (C) in squamous Cell Carcinoma for CnP vs CP



SQUIRE (CP11-0806): Phase III Trial of Necitumumab plus Gemcitabine and Cisplatin in SqCC NSCLC

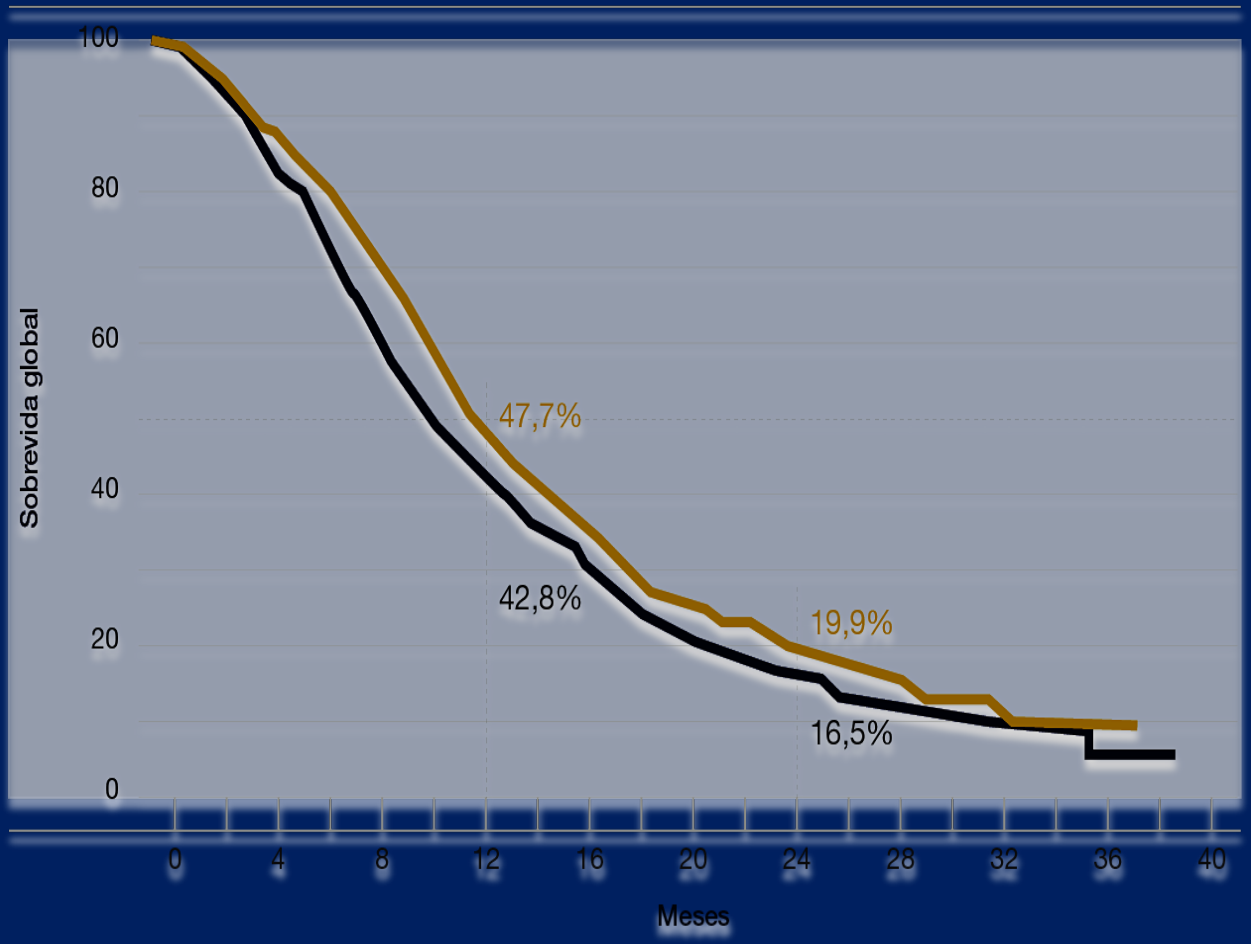


Patient selection was not based in EGFR expression

Tatcher N, J Clin Oncol 32:5s, 2014 (suppl; abstr 8008)

SQUIRE: Phase III Trial of Necitumumab plus Gem/Cis in SqCC NSCLC: OS

SOBREVIDA GLOBAL



Median OS (m)	
Gem-Cis + Necitumumab	**11,5**
Gem-Cis	9,9
HR	0,84
IC 95%	0,74-0,96
p value	**0,012**

Tatcher N, J Clin Oncol 32:5s, 2014 (suppl; abstr 8008)

SQUIRE: Phase III Trial of Necitumumab plus Gem/Cis in SqCC NSCLC: Conclusions

- SQUIRE is the largest phase III trial exploring the first line treatment of squamous cell lung cancer

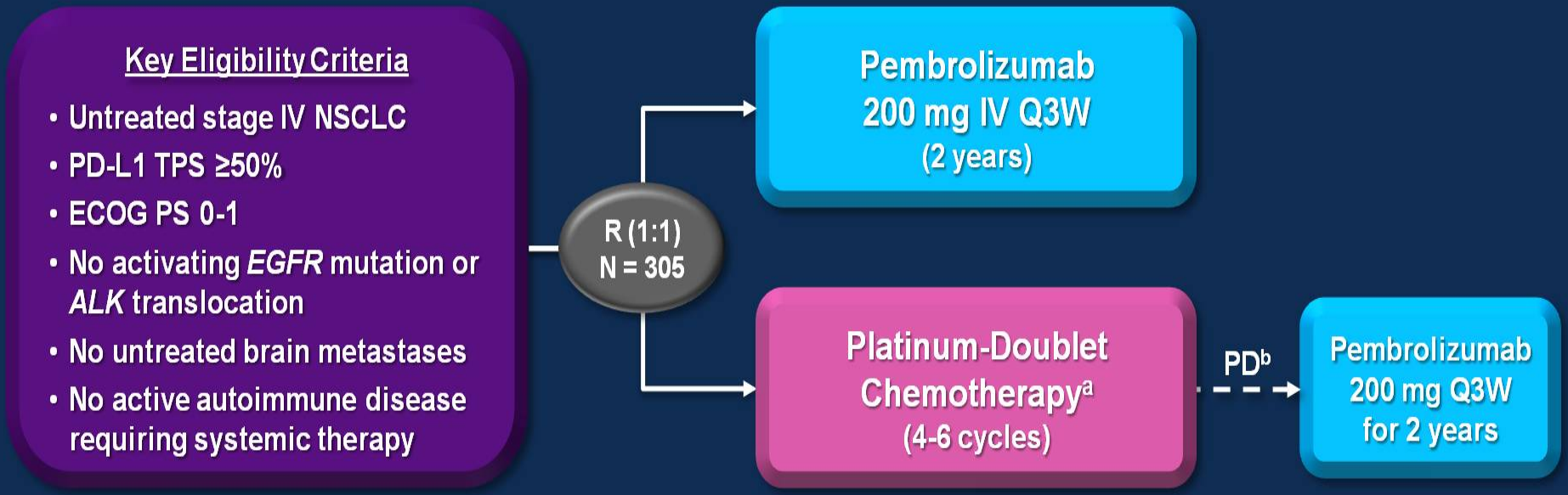
- The study reached its primary endpoint (OS: 11.5 vs. 9.9m; p=0.012)
- However, minimal delta in PFS and no difference in ORR.
- The combination of Necitumumab, Gemcitabine and Cisplatin had a manageable toxicity profile.
- New therapeutic alternative for squamous cell lung cancer.

Tatcher N, J Clin Oncol 32:5s, 2014 (suppl; abstr 8008)

Black Box warning for Necitumumab

- Cardiopulmonary arrest or sudden death occurred in 15 (3%) of 538 patients treated with Necitumumab plus gemcitabine and cisplatin as compared to 3 (0.6%) of 541 patients treated with gemcitabine and cisplatin alone in Study 1
- Twelve of the 15 patients died within 30 days of the last dose of Necitumumab and had comorbid conditions including history of coronary artery disease (n=3), hypomagnesemia (n=4), chronic obstructive pulmonary disease (n=7), and hypertension (n=5).
- Eleven of the 12 patients had an unwitnessed death.
- Hypomagnesemia occurred in 83% of 461/538 patients with available laboratory results treated with Necitumumab as compared to 70% of 457/541 patients with available laboratory results treated with gemcitabine and cisplatin alone in Study 1.

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

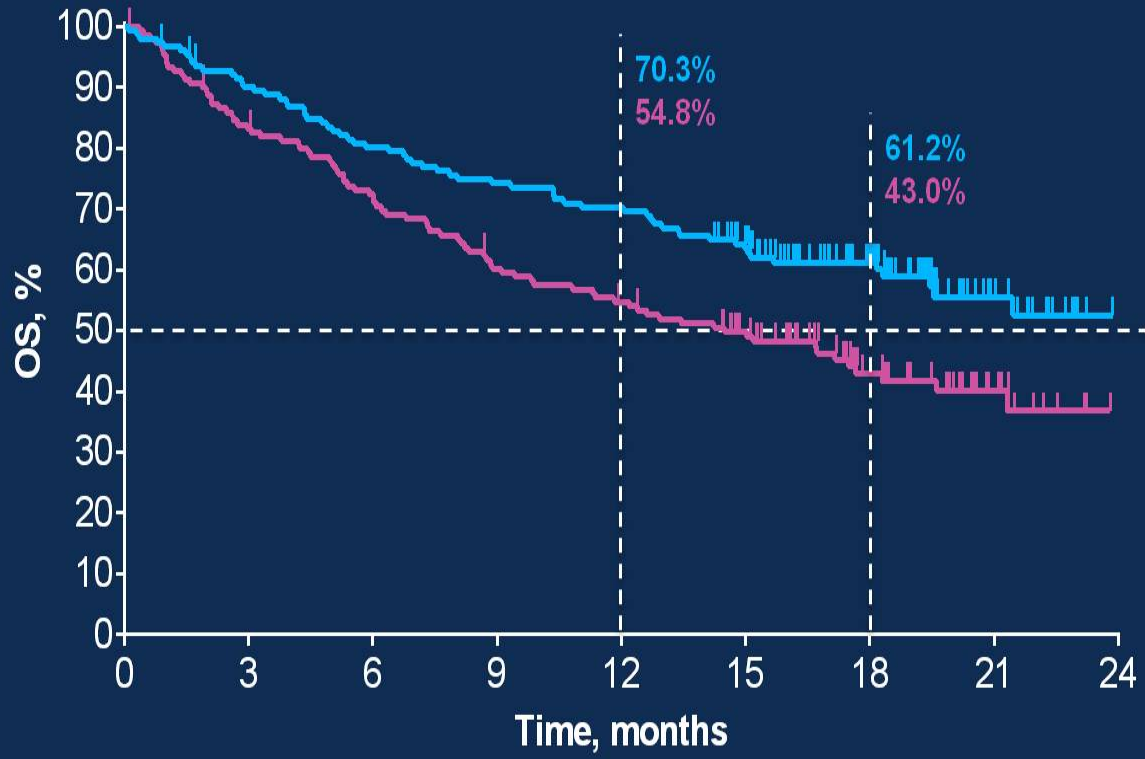
Primary: PFS (RECIST v1.1, blinded independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR, PFS2

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

Kaplan-Meier Estimate of OS: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab	63	0.63 (0.46-0.88)
Chemotherapy	84	$P = 0.003$[a]

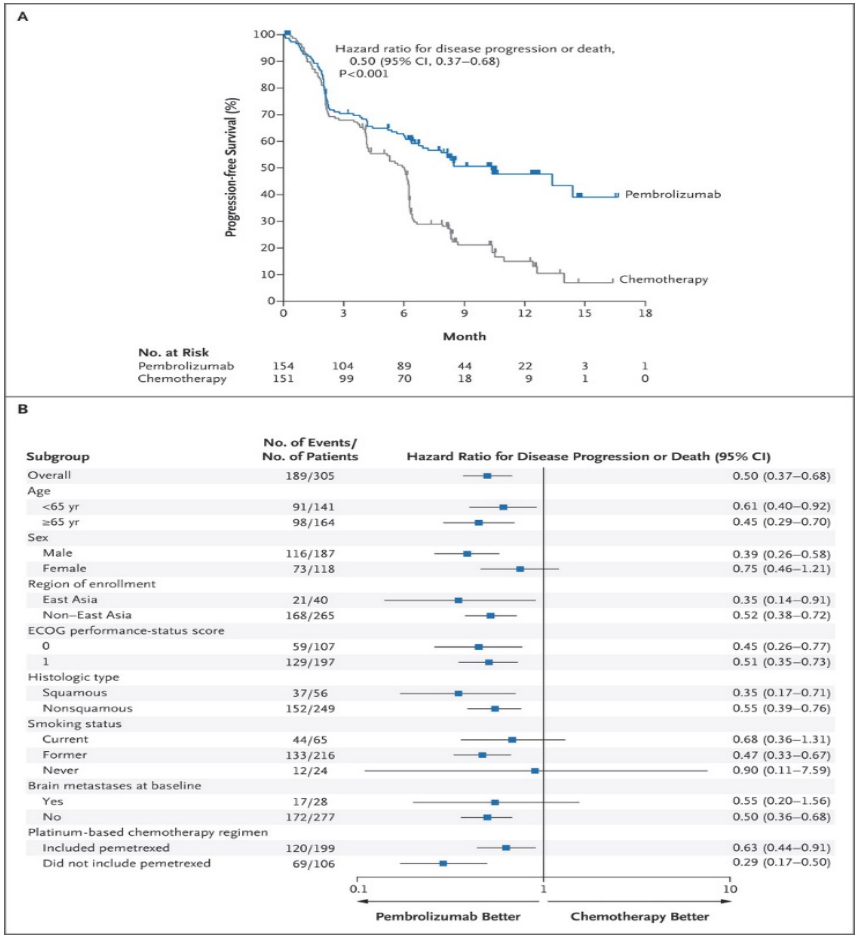
Median (95% CI)
NR (19.4 mo-NE)
14.5 mo (9.8-19.6)

No. at risk

154	136	121	112	106	88	57	20	4
151	123	107	88	79	64	35	15	4

[a]Nominal *P* value.
Data cutoff: Jan 5, 2017.

Subset Analysis For Squamous Cell Carcinoma in Keynote 024



What is New at ASCO 2018 regarding Metastatic Squamous Cell Carcinoma of the Lung?

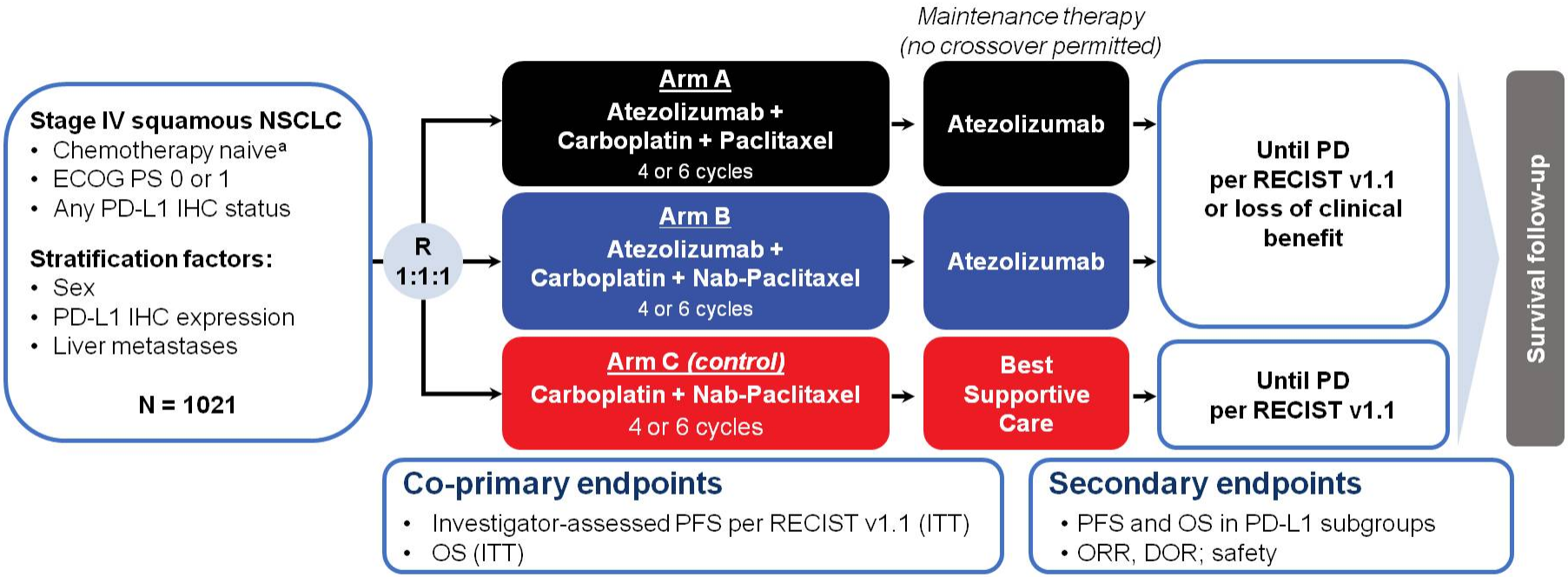
IMpower131: Primary PFS and Safety Analysis of a Randomized Phase III Study of Atezolizumab + Carboplatin + Paclitaxel or Nab-Paclitaxel vs Carboplatin + Nab-Paclitaxel as 1L Therapy in Advanced Squamous NSCLC

Robert Jotte,[1,2] Federico Cappuzzo,[3] Ihor Vynnychenko, [4] Daniil Stroyakovskiy,[5] Delvys Rodriguez Abreu,[6] Maen Hussein,[7] Ross Soo,[8] Henry J. Conter,[9] Toshiyuki Kozuki,[10] Carlos da Silva,[11] Vilma Graupner,[12] Shawn W. Sun,[13] Ray Lin,[13] Helen Jessop,[12] Marcin Kowanetz,[13] Tien Hoang,[13] Alan Sandler,[13] Mark A. Socinski[14]

[1]Rocky Mountain Cancer Centers, Denver, CO; [2]US Oncology, Houston, TX; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [4]Sumy State University, Sumy, Ukraine; [5]Moscow City Oncology Hospital, Moscow Healthcare Department, Moscow Oblast, Russia; [6]Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Spain; [7]Sarah Cannon Research Institute/Florida Cancer Specialists, Lady Lake, FL; [8]Department of Haematology-Oncology, National University Hospital, Singapore; [9]William Osler Health System, Brampton, ON, Canada; [10]Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [11]Fundação Pio XII Institution – Cancer Hospital of Barretos, Barretos, São Paulo, Brazil; [12]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [13]Genentech, Inc., South San Francisco, CA; [14]Florida Hospital Cancer Institute, Orlando, FL

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

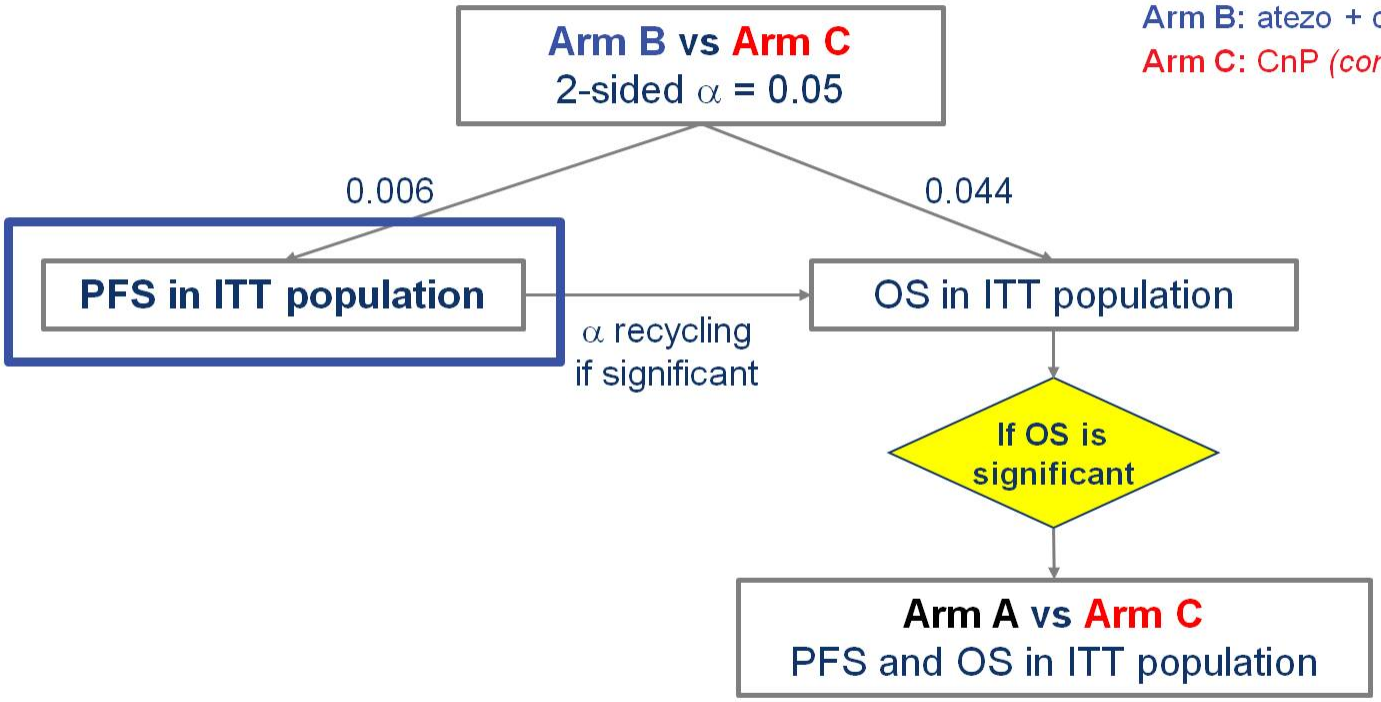
IMpower131: Study Design



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.
[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.
[b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

IMpower131: Statistical Testing Plan

Arm A: atezo + carbo + pac (CP)
Arm B: atezo + carbo + nab-pac (CnP)
Arm C: CnP *(control)*



Data cutoff: January 22, 2018.
atezo, atezolizumab; carbo, carboplatin; nab-pac, nab-paclitaxel; pac, paclitaxel.

Baseline Characteristics in the ITT Population

Baseline Characteristics	Arm A: Atezo + CP (N = 338)	Arm B: Atezo + CnP (N = 343)	Arm C (control): CnP (N = 340)
Age, median (range), years	66 (43-85)	65 (23-83)	65 (38-86)
Sex, male, n (%)	278 (82)	279 (81)	278 (82)
Race, n (%)			
Asian	34 (10)	41 (12)	37 (11)
White	290 (86)	289 (84)	290 (85)
Other/unknown	11 (4)	13 (4)	13 (4)
ECOG PS, 0, n (%)	109 (32)	115 (34)	110 (32)
Tobacco use history,[a] n (%)			
Current or former smoker	308 (91)	311 (91)	216 (93)
Never smoker	30 (9)	32 (9)	23 (7)
Liver metastases, yes, n (%)	66 (20)	70 (20)	69 (20)
PD-L1 expression,[b] n (%)			
High (TC3 or IC3)	53 (16)	53 (15)	48 (14)
Low (TC1/2 or IC1/2)	114 (34)	129 (38)	121 (36)
Negative (TC0 and IC0)	170 (50)	160 (47)	171 (50)

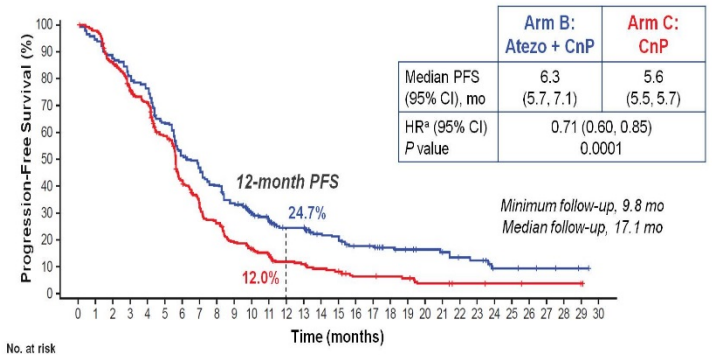
TC3 or IC3 (high) = TC ≥ 50% or IC ≥ 10% PD-L1+; TC1/2 or IC1/2 (low) = TC ≥ 1% and < 50% or IC ≥ 1% and < 10% PD-L1+; TC0 and IC0 (negative) = TC and IC < 1% PD-L1+.

IC, tumor-infiltrating immune cell; TC, tumor cell.

[a] One patient in Arm C had unknown tobacco use history status. [b] PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

IMpower 131: PFS and OS
Atezo + Chemo vs Chemo Alone

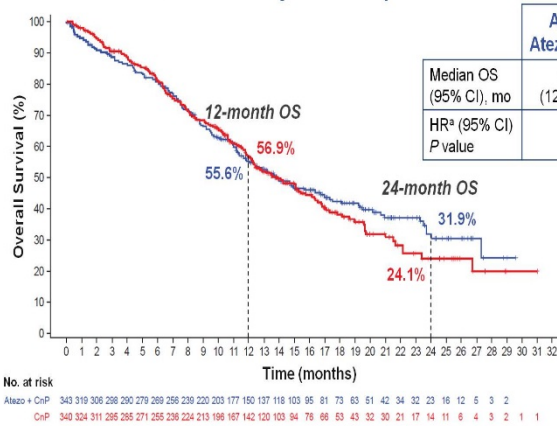
INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI) *P* value	0.71 (0.60, 0.85) 0.0001	

Data cutoff: January 22, 2018.
INV, investigator. [a] Stratified HR.

First Interim OS in the ITT Population (Arm B vs Arm C)

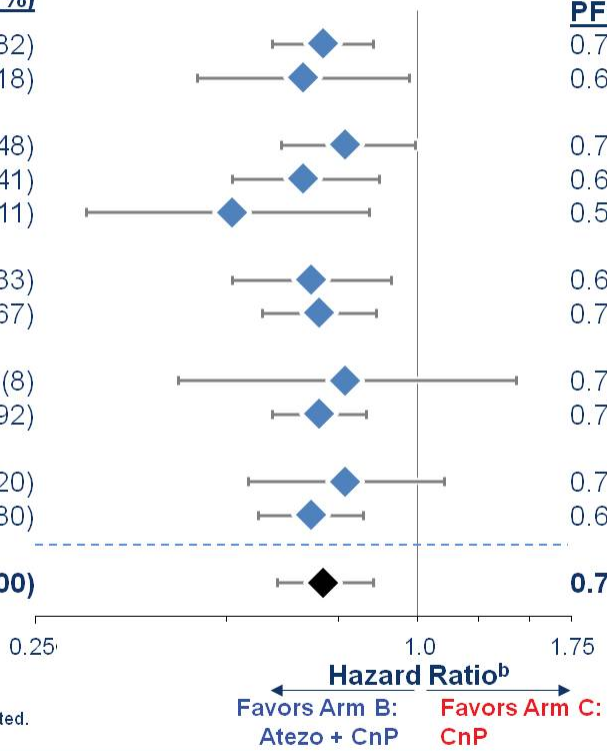


	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	

Data cutoff: January 22, 2018.
[a] Stratified HR.

INV-Assessed PFS in Clinical Subgroups

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo	
			Arm B	Arm C
Male	557 (82)	0.71 (0.59, 0.85)	6.3	5.6
Female	126 (18)	0.66 (0.45, 0.97)	6.5	5.6
< 65 years	326 (48)	0.77 (0.61, 0.99)	6.0	5.6
65-74 years	279 (41)	0.66 (0.51, 0.87)	6.0	5.6
75-84 years[a]	77 (11)	0.51 (0.30, 0.84)	7.0	5.6
ECOG PS 0	225 (33)	0.68 (0.51, 0.91)	7.2	5.7
ECOG PS 1	456 (67)	0.70 (0.57, 0.86)	5.8	5.5
Never smoker	55 (8)	0.77 (0.42, 1.43)	8.3	5.3
Current or former smoker	627 (92)	0.70 (0.59, 0.83)	6.2	5.6
Liver metastases	139 (20)	0.77 (0.54, 1.10)	5.5	4.2
No liver metastases	544 (80)	0.68 (0.56, 0.82)	7.0	5.6
ITT population	**683 (100)**	**0.71 (0.60, 0.85)**	**6.3**	**5.6**



Data cutoff: January 22, 2018.
[a] One patient in Arm C was aged ≥ 85 years; thus, an HR cannot be calculated.
[b] Stratified HR for ITT; unstratified HRs for all other subgroups.

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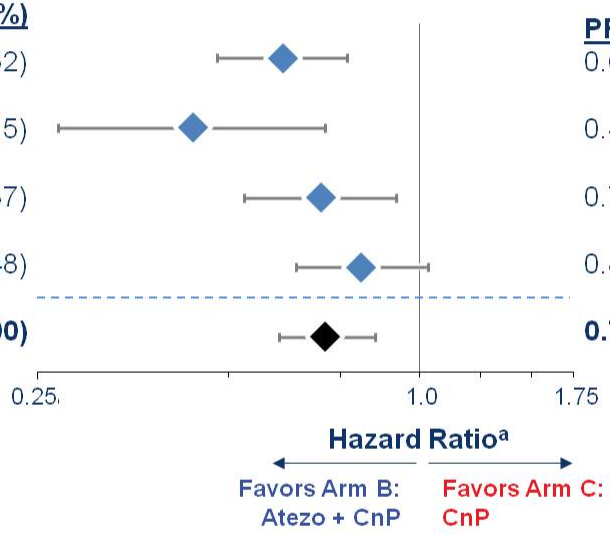
INV-Assessed PFS in PD-L1 Subgroups

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo	
			Arm B	Arm C
PD-L1 positive (TC1/2/3 or IC1/2/3)	351 (52)	0.61 (0.48, 0.77)	7.0	5.6
PD-L1 high (TC3 or IC3)	101 (15)	0.44 (0.27, 0.71)	10.1	5.5
PD-L1 low (TC1/2 or IC1/2)	250 (37)	0.70 (0.53, 0.92)	6.0	5.6
PD-L1 negative (TC0 and IC0)	331 (48)	0.81 (0.64, 1.03)	5.7	5.6
ITT population	**683 (100)**	**0.71 (0.60, 0.85)**	**6.3**	**5.6**

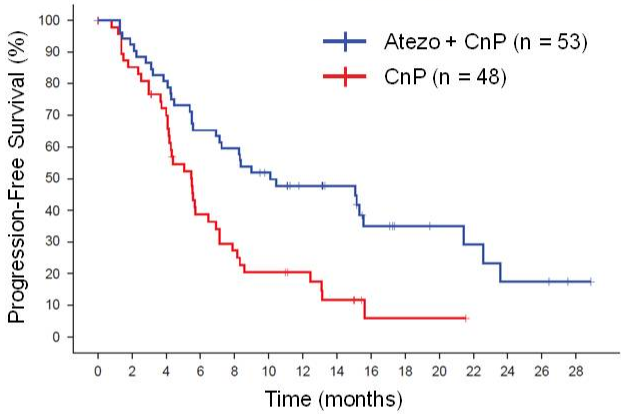


- **PFS benefit was observed with atezolizumab + CnP (Arm B) vs CnP (Arm C) across all PD-L1 subgroups**

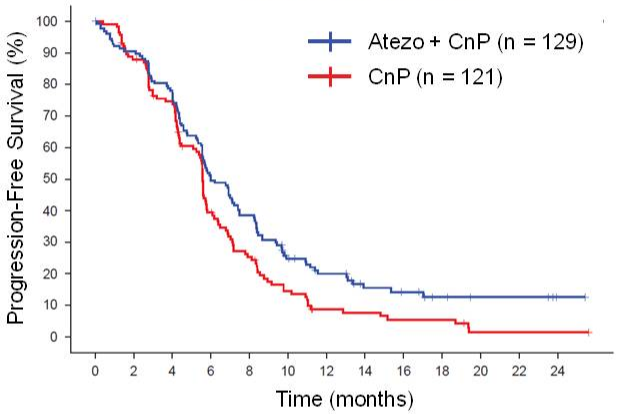
Data cutoff: January 22, 2018.
[a] Stratified HR for ITT; unstratified HRs for all PD-L1 subgroups.

INV-Assessed PFS in PD-L1 Subgroups (Arm B vs Arm C)

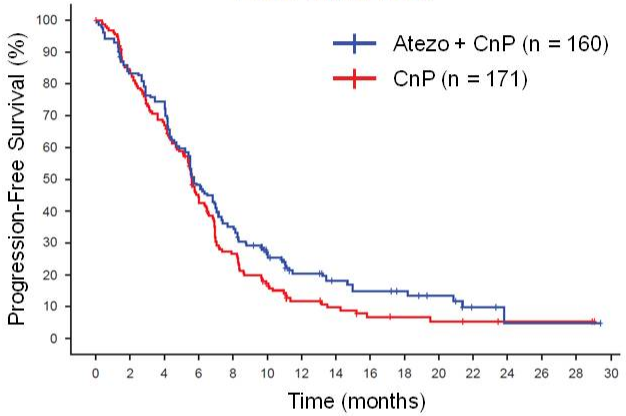
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0



	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month PFS	48%	20%	20%	9%	20%	12%
Median PFS, mo	10.1	5.5	6.0	5.6	5.7	5.6
HR[a] (95% CI)	0.44 (0.27, 0.71)		0.70 (0.53, 0.92)		0.81 (0.64, 1.03)	

Data cutoff: January 22, 2018.
[a] Unstratified HR.

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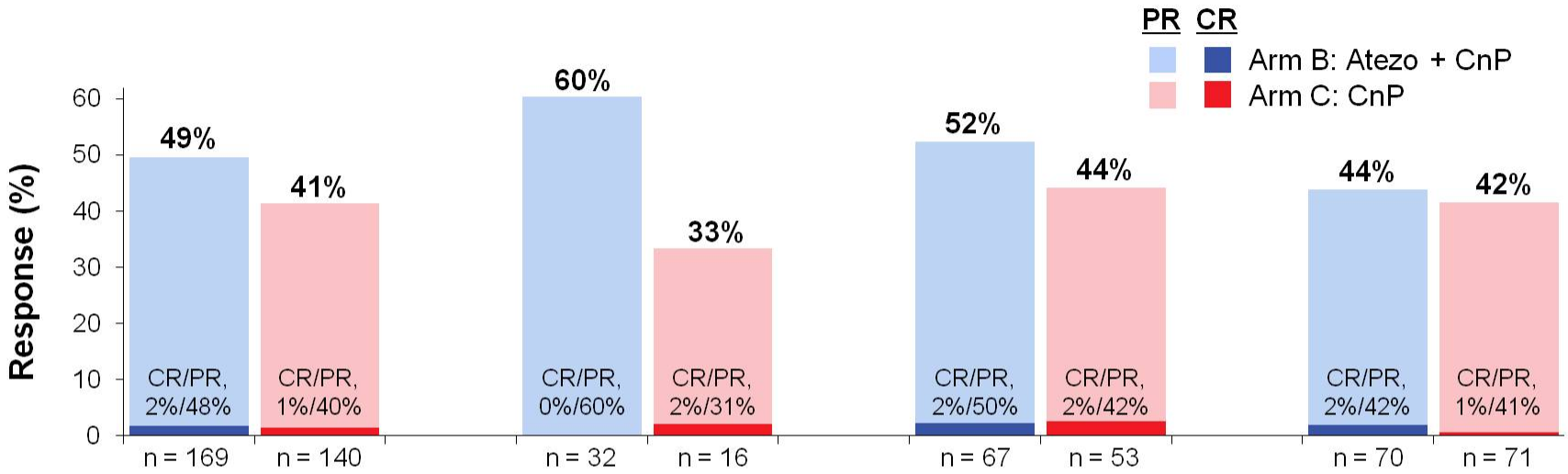
Confirmed Objective Response Rate and Duration of Response



	ITT Population		PD-L1 High (TC3 or IC3)		PD-L1 Low (TC1/2 or IC1/2)		PD-L1 Negative (TC0 and IC0)	
Median DOR (range), mo	7.2 (1.7-28.1+)	5.2 (2.1-27.6+)	18.7 (1.7-26.0)	5.3 (2.8-14.1)	6.9 (2.6-22.4)	5.0 (2.6-24.3)	6.9 (1.9-28.1)	5.2 (2.1-27.6)
Ongoing response, n (%)	54 (32)	23 (16)	17 (53)	4 (25)	17 (25)	6 (11)	20 (29)	13 (18)

Data cutoff: January 22, 2018.
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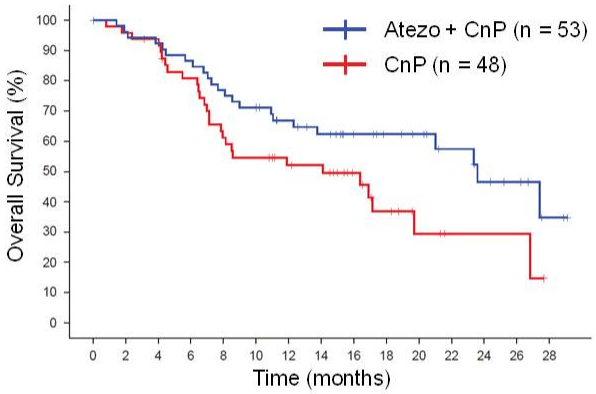
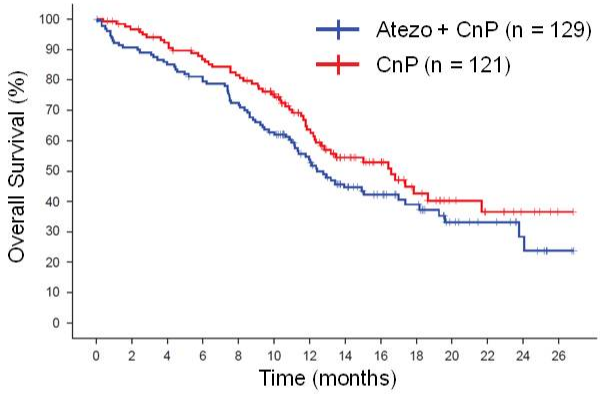
First Interim OS in PD-L1 Subgroups (Arm B vs Arm C)

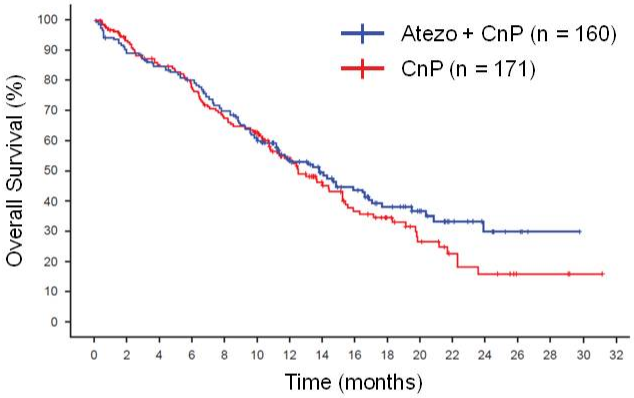
PD-L1 High
TC3 or IC3



PD-L1 Low
TC1/2 or IC1/2



PD-L1 Negative
TC0 and IC0



	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month OS	67%	52%	54%	64%	53%	53%
24-month OS	47%	30%	28%	37%	30%	16%
Median OS, mo	23.6	14.1	12.4	16.6	13.8	12.5
HR[a] (95% CI)	0.56 (0.32, 0.99)		1.34 (0.95, 1.90)		0.86 (0.65, 1.15)	

Data cutoff: January 22, 2018.
[a] Unstratified HR.

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Subsequent Cancer Therapies

n (%)	Arm B: Atezo + CnP (N = 343)	Arm C (control): CnP (N = 340)
Total no. of patients with ≥ 1 treatment	109 (31.8)	190 (55.9)
Immunotherapy	18 (5.2)	143 (42.1)
Nivolumab	12 (3.5)	123 (36.2)
Pembrolizumab	4 (1.2)	15 (4.4)
Atezolizumab	2 (0.6)	4 (1.2)
Ipilimumab	1 (0.3)	3 (0.9)
Durvalumab	0	2 (0.6)
Other	0	3 (0.9)
Chemotherapy	97 (28.3)	79 (23.2)
Targeted therapy	20 (5.8)	18 (5.3)

Data cutoff: January 22, 2018.

Safety Summary

	Arm B: Atezo + CnP (N = 334)	Arm C (control): CnP (N = 334)
Treatment duration, median (range), mo		
Atezolizumab	6.7 (0-30)	NA
Carboplatin	2.6 (0-7)	2.4 (0-7)
Paclitaxel/nab-paclitaxel	3.0 (0-7)	2.8 (0-7)
All-cause AE, n (%)	332 (99)	324 (97)
Grade 3-4	243 (73)	220 (66)
Grade 5	31 (9)	14 (4)
Treatment-related AE, n (%)	316 (95)	303 (91)
Grade 3-4	227 (68)	190 (57)
Grade 5	4 (1)	3 (1)
Serious AE, n (%)	152 (46)	96 (29)
Treatment-related serious AE	68 (20)	35 (10)
AEs of special interest, n (%)	162 (49)	71 (21)
Grade 3-4	39 (12)	8 (2)
Grade 5	1 (< 1)	0
AE leading to any treatment withdrawal, n (%)	97 (29)	58 (17)
AE leading to any dose interruption or modification, n (%)	258 (77)	219 (66)

Data cutoff: January 22, 2018.

Immune-Related AEs of Special Interest in ≥ 5 Patients Across Arms

	Arm B: Atezo + CnP (N = 334)		Arm C (control): CnP (N = 334)	
AEs of Special Interest, n (%)	**All Grade**	**Grade 3-4**	**All Grade**	**Grade 3-4**
Rash	74 (22)	6 (2)	39 (12)	1 (< 1)
Hepatitis	58 (17)	18 (5)	29 (9)	4 (1)
Laboratory abnormalities[a]	58 (17)	18 (5)	27 (8)	3 (1)
Hypothyroidism	34 (10)	2 (1)	3 (1)	0
Pneumonitis	23 (7)	4 (1)	5 (1)	3 (1)
Hyperthyroidism	11 (3)	1 (< 1)	1 (< 1)	0
Infusion-related reaction	2 (1)	0	0	0
Colitis	6 (2)	4 (1)	0	0
Diabetes mellitus	4 (1)	3 (1)	1 (< 1)	0

Data cutoff: January 22, 2018.
[a] One patient in Arm B had Grade 5 abnormal hepatic function.

Summary

- IMpower131 met the co-primary endpoint of investigator-assessed PFS with atezolizumab + CnP (Arm B) vs CnP (Arm C) in the ITT population
- PFS benefit in Arm B vs Arm C was observed across all PD-L1–expressing subgroups and was enriched in subgroups with higher PD-L1 expression
- Atezolizumab + CnP has a manageable safety profile consistent with known safety risks of the individual therapies; no new safety signals were identified
- OS continues to be followed, with the next interim OS analysis anticipated later in 2018

KEYNOTE-407: Phase 3 Study of Carboplatin-Paclitaxel/Nab-Paclitaxel With or Without Pembrolizumab for Metastatic Squamous NSCLC

Luis Paz-Ares,[1] Alexander Luft,[2] Ali Tafreshi,[3] Mahmut Gümüş,[4] Julien Mazières,[5] Barbara Hermes,[6] Filiz Çay Senler,[7] Andrea Fülöp,[8] Jeronimo Rodriguez Cid,[9] Shunichi Sugawara,[10] Ying Cheng,[11] Silvia Novello,[12] Balazs Halmos,[13] Yue Shentu,[14] Xiaodong Li,[14] Gregory M Lubiniecki,[14] Bilal Piperdi,[14] Dariusz Kowalski[15]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Leningrad Regional Clinical Hospital, St. Petersburg, Russia; [3]Wollongong Hospital, Wollongong, NSW, Australia; [4]Kartal Research and Training Hospital, Istanbul, Turkey; [5]Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [6]Universitätskinikum Tübingen, Tuebingen, Germany; [7]Ankara University, Ankara, Turkey; [8]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [9]Oncology Center, Medica Sur Hospital, Mexico City, Mexico; [10]Sendai Kousei Hospital, Sendai, Japan; [11]Cancer Hospital of Jilin Province, Changchun, China; [12]University of Turin, Orbassano, Italy; [13]Albert Einstein College of Medicine, Bronx, NY, USA; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland

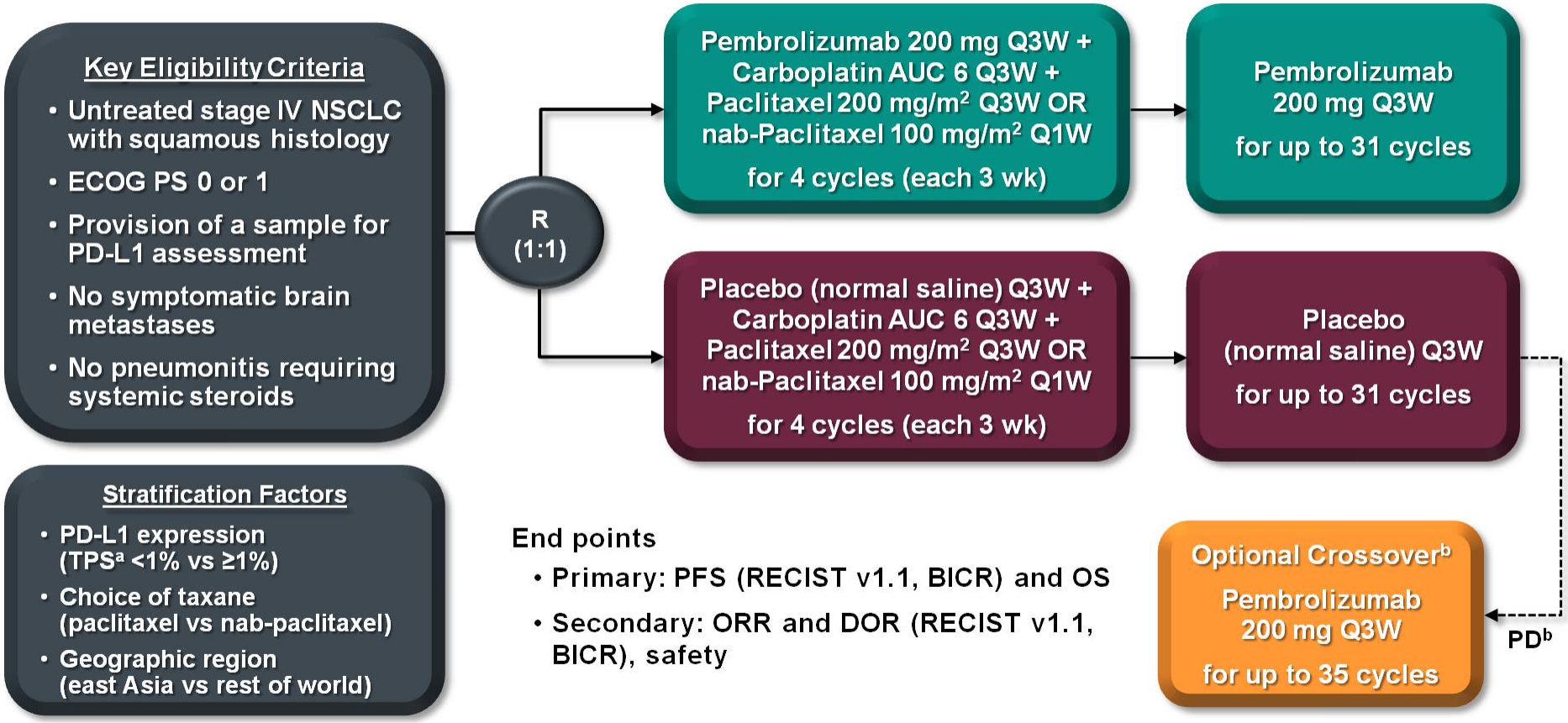
Presented By Luis Paz-Ares at 2018 ASCO Annual Meeting

Pembrolizumab and First-Line Treatment of Metastatic NSCLC

- Pembrolizumab: anti–PD-1 monoclonal antibody with antitumor activity against lung cancer and several other tumors, as well as a favorable safety profile
- As monotherapy: significantly improves OS over platinum-doublet chemotherapy for metastatic NSCLC with PD-L1 TPS ≥50%, with a benefit observed for both squamous and nonsquamous histology[1]
- In combination with pemetrexed and platinum: significantly improves OS over pemetrexed and platinum alone and has a manageable safety profile for metastatic nonsquamous NSCLC, irrespective of PD-L1 TPS[2]
- Evaluation of pembrolizumab plus chemotherapy in metastatic squamous NSCLC is a logical next step

1. Reck M et al. *N Engl J Med* 2016;375:1823-33.
2. Gandhi L et al. *N Engl J Med* 2018;378:2078-92.

KEYNOTE-407 Study Design (NCT02775435)



BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Statistical Considerations

- Planned enrollment: 560 patients
  - Actual enrollment: 559 patients
- Study has at least 90% power for PFS and 85% power for OS with a target HR of 0.70
- Protocol specified 3 interim analyses (IA) before the final analysis
- Overall alpha for study: strictly controlled at one-sided 2.5% using the graphical method of Mauer and Bretz

Analysis	End Points	Planned Timing
IA1	ORR	~200 patients followed for ~28 wk
IA2	PFS and OS	~332 PFS events
IA3	PFS and OS	~415 PFS events
Final	OS	~361 deaths

Second Interim Analysis

- First analysis of PFS and OS
- Planned to occur after **~332 PFS events** observed
- Statistical methods
  - Difference in OS and PFS: stratified log-rank test
- Data cutoff date: Apr 3, 2018
  - External DMC meeting: May 21, 2018
  - Patients with a PFS event: 349
  - Superiority thresholds (one-sided): 0.008 for PFS, 0.0029 for OS
  - Median follow-up[a]: 7.8 months (range, 0.1-19.1)

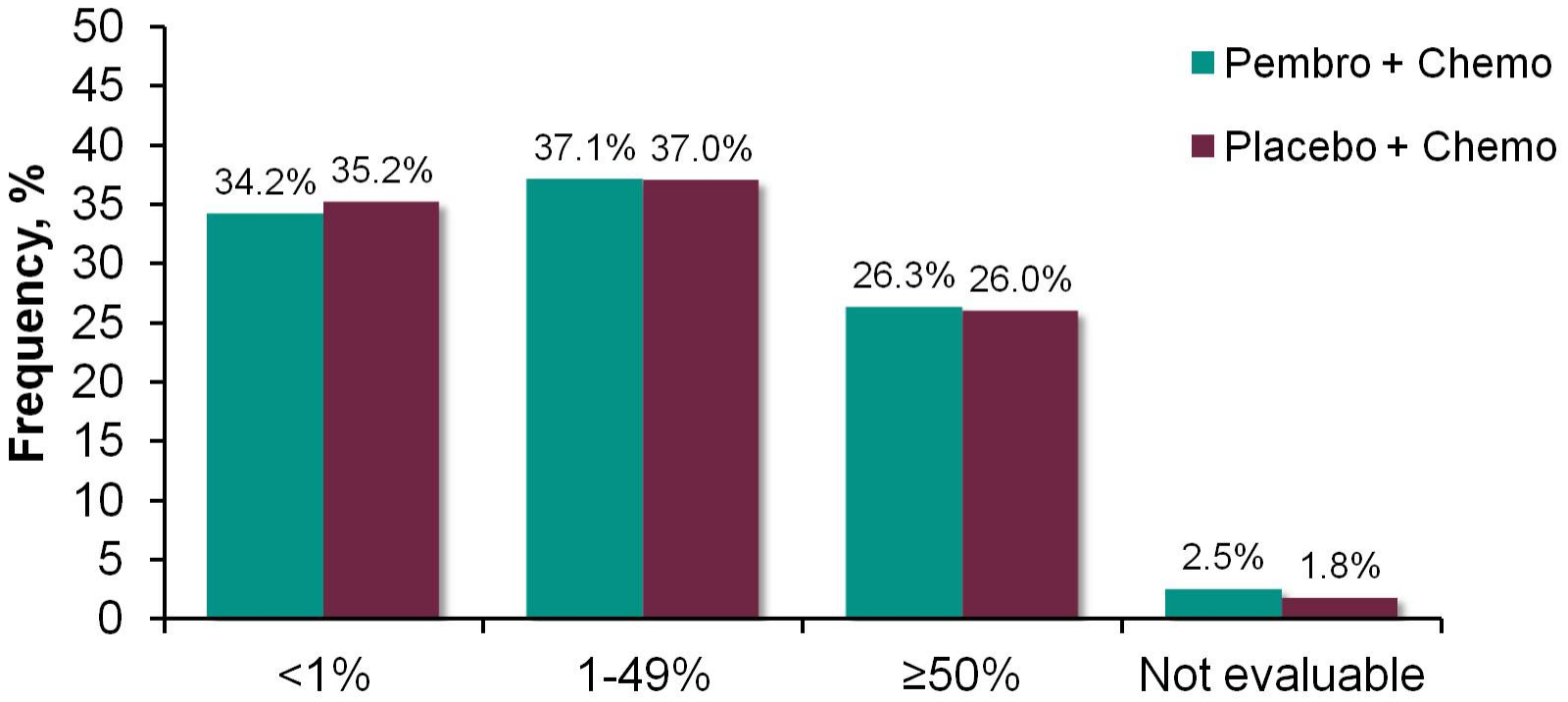
All interim analyses reviewed by external, independent data monitoring committee. [a]Defined as the time from randomization to the date of death or data cut-off, whichever occurred first.

Baseline Characteristics at IA2

	Pembro + Chemo (N = 278)	Placebo + Chemo (N = 281)
Age, median (range), years	65.0 (29-87)	65.0 (36-88)
Men	220 (79.1%)	235 (83.6%)
ECOG PS 1	205 (73.7%)	191 (68.0%)
Stable brain metastases	20 (7.2%)	24 (8.5%)
Former/current smoker	256 (92.1%)	262 (93.2%)
Enrolled in east Asia	54 (19.4%)	52 (18.5%)
PD-L1 TPS ≥1%	176 (63.3%)	177 (63.0%)
Paclitaxel chosen as taxane	169 (60.8%)	167 (59.4%)
Prior thoracic radiation	17 (6.1%)	22 (7.8%)
Prior (neo)adjuvant therapy	5 (1.8%)	8 (2.8%)

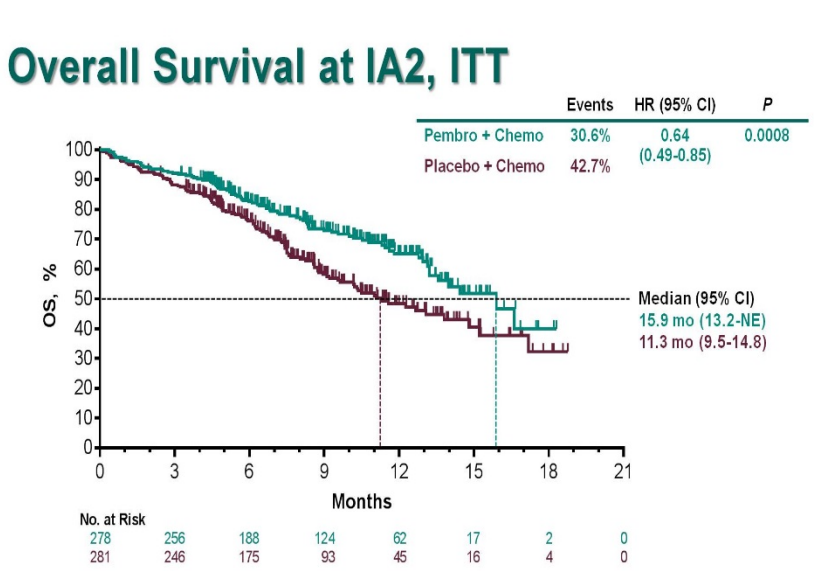
Data cutoff date: Apr 3, 2018.

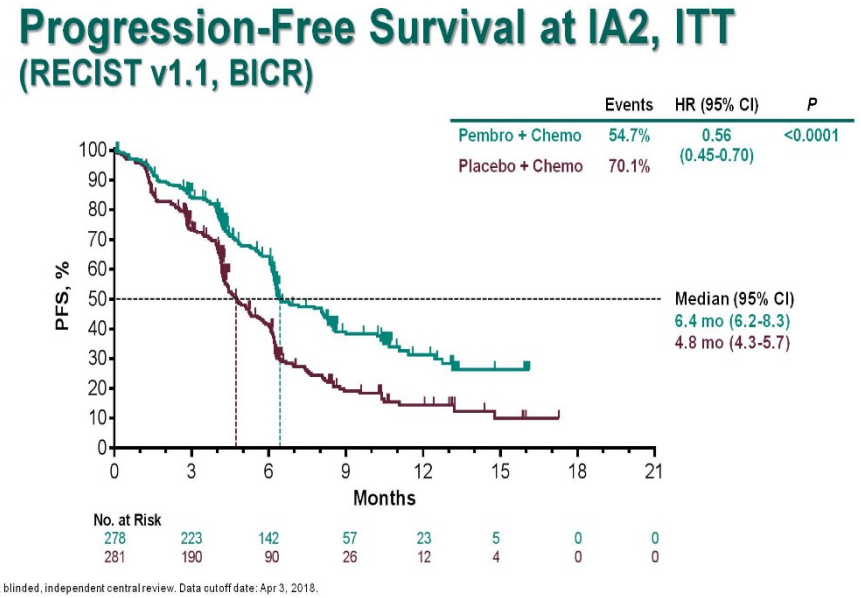
Frequency of PD-L1 TPS Categories



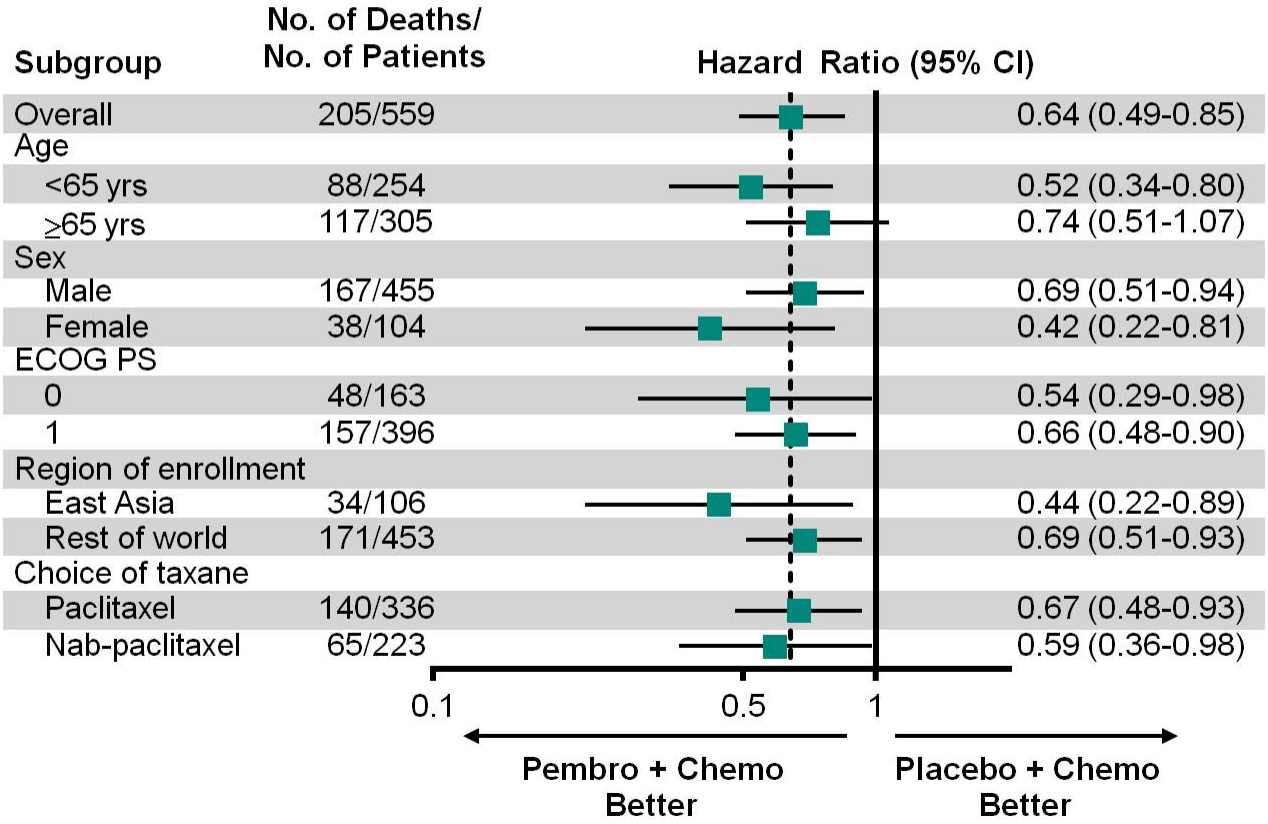
Not evaluable refers to specimens with an inadequate number of tumor cells or no tumor cells seen; these patients were included in the PD-L1 TPS <1% group for randomization stratification but excluded from analyses of efficacy by TPS. Data cutoff date: Apr 3, 2018.

Keynote#407 OS and PFS
Pembro + Chemotherapy vs. Chemotherapy alone



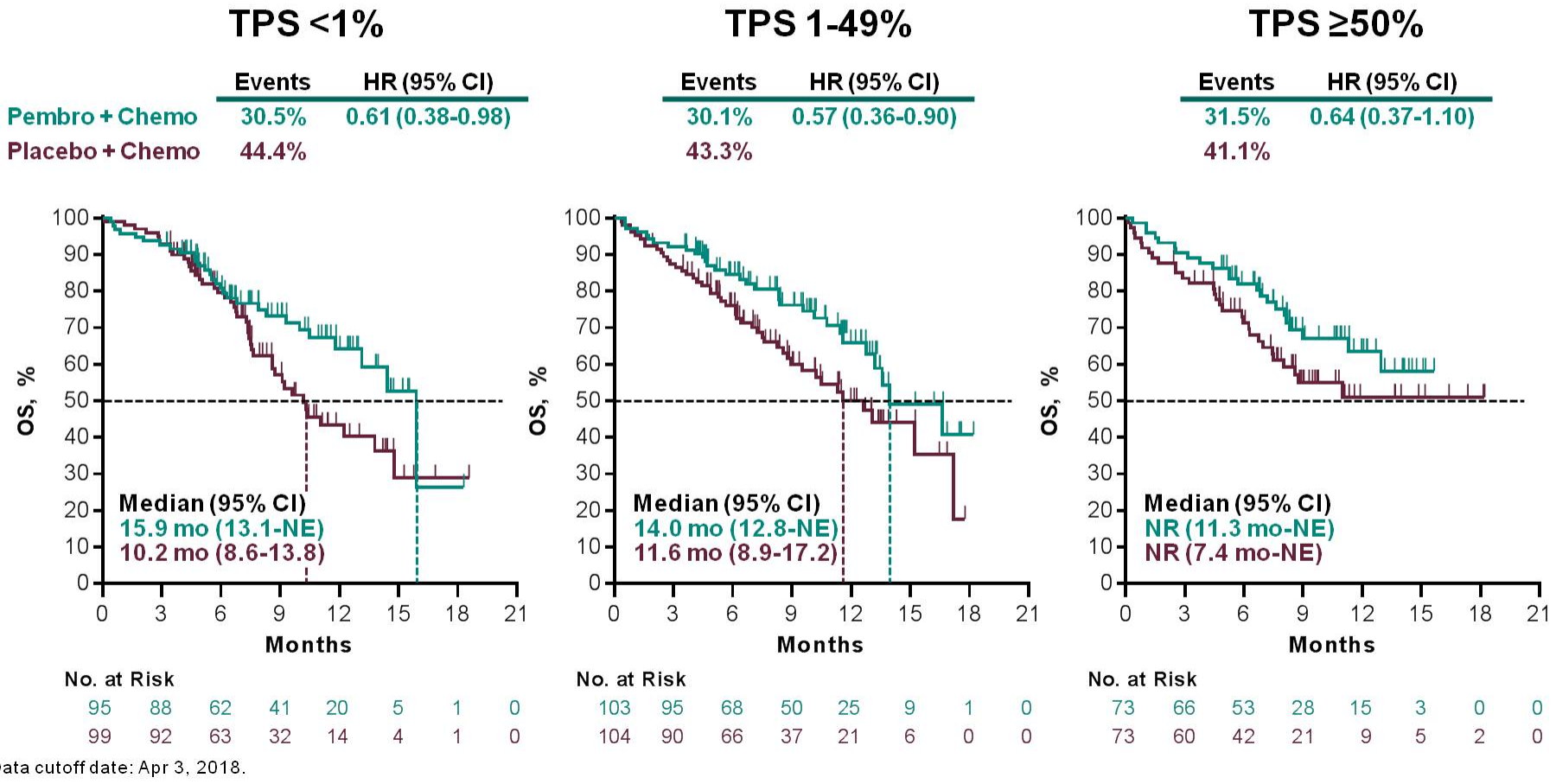


Overall Survival at IA2 in Key Subgroups



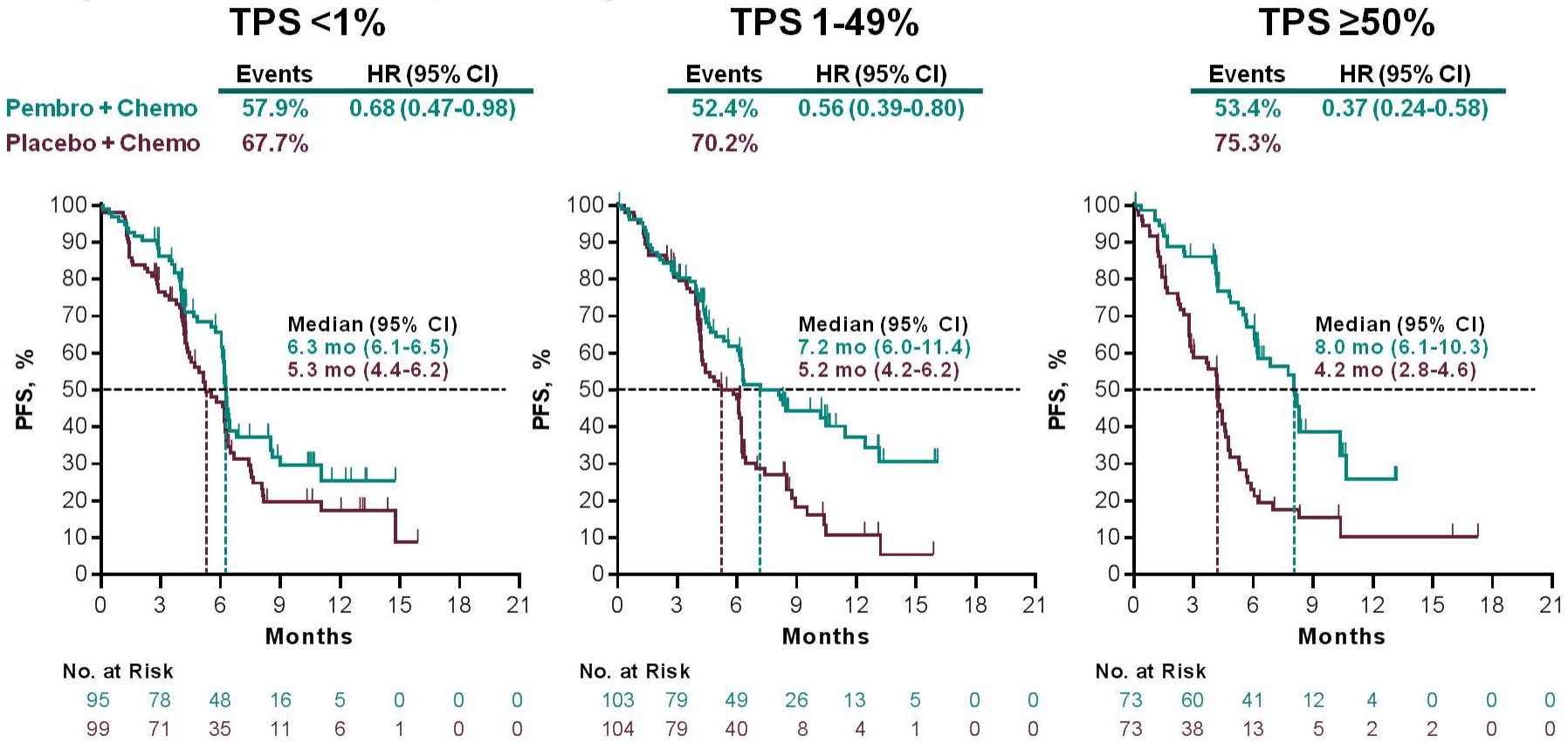
Data cutoff date: Apr 3, 2018.

Overall Survival at IA2 by PD-L1 TPS



Data cutoff date: Apr 3, 2018.

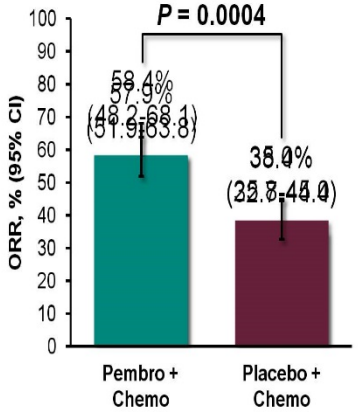
Progression-Free Survival by PD-L1 TPS (RECIST v1.1, BICR)



BICR, blinded, independent central review. Data cutoff date: Apr 3, 2018.

Keynote#407 ORR and DOR: Pembro + Chemo vs. Chemo alone

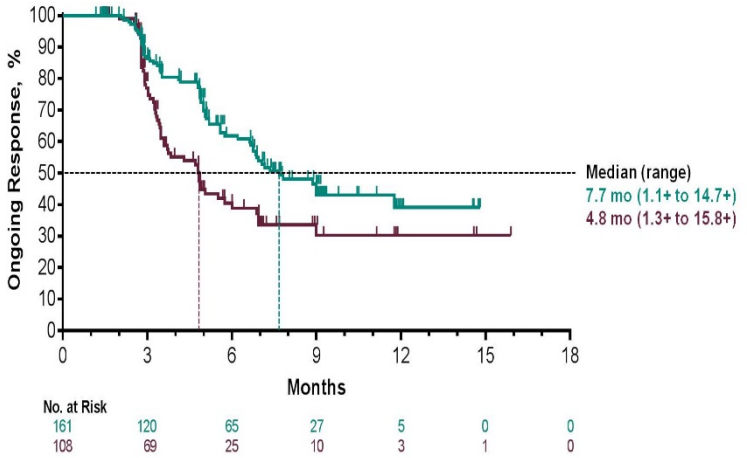
Objective Response Rate at IA2
(RECIST v1.1 by BICR)



Best Response	Pembro + Chemo (N = 278)	Placebo + Chemo (N = 281)
Complete response	4 (1.4%)	2 (0.7%)
Partial response	157 (56.5%)	102 (36.3%)
Stable disease	76 (27.3%)	104 (37.0%)
Progressive disease	17 (6.1%)	36 (12.8%)
Not evaluable[a]	6 (2.2%)	5 (1.8%)
Not assessed[b]	16 (5.8%)	32 (11.4%)

[a]Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR. [b]Patients who did not have ≥1 post-baseline imaging assessment.
Includes confirmed responses only. Detailed statistical comparison of ORR at IA2. Data cutoff date: Apr 3, 2018.

Duration of Response at IA2
(RECIST v1.1, BICR)



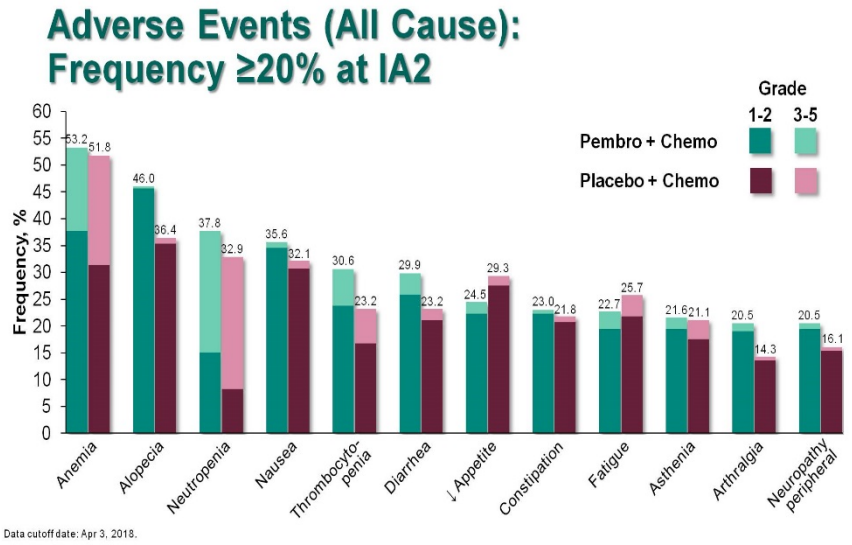
Includes confirmed responses only.
Data cutoff date for initial response: Apr 3, 2018.

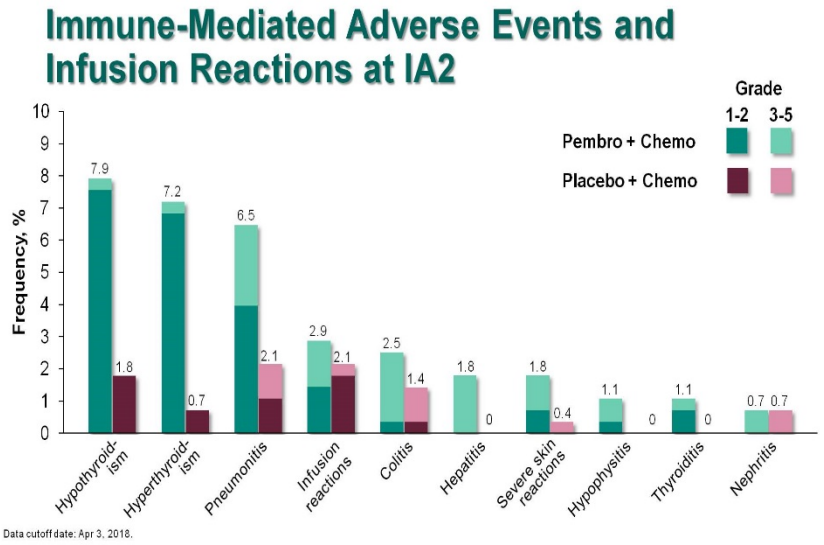
Exposure to Study Treatment at IA2

	Pembro + Chemo N = 278	Placebo + Chemo N = 280
Treatment duration, mean (SD)	6.3 mo (4.1)	4.7 mo (3.5)
Treatment cycles		
Mean (SD)	9.3 (5.8)	7.3 (5.0)
Median (range)	8 (1-27)	6 (1-27)
4 doses of carboplatin, n (%)	219 (78.8%)	205 (73.2%)
4 doses of paclitaxel, n (%)	133/169 (78.7%)	119/167 (71.3%)
5-11 doses of nab-paclitaxel, n (%)	72/109 (66.1%)	73/113 (64.6%)
12 doses of nab-paclitaxel, n (%)	25/109 (22.9%)	24/113 (21.2%)
≥5 doses of pembrolizumab or placebo, n (%)	214 (77.0%)	189 (67.5%)

Data cutoff date: Apr 3, 2018.

Keynote #407 Adverse effects: Pembro + Chemo vs. Chemo Alone





Summary and Conclusions

- Pembrolizumab plus chemotherapy significantly improved OS (HR 0.64) over chemotherapy alone
  - Benefit was observed irrespective of PD-L1 TPS: HR 0.61 for TPS <1%, 0.57 for TPS 1-49%, and 0.64 for TPS ≥50%
- PFS (HR 0.56) and ORR (*P* = 0.0004) were also improved with pembrolizumab plus chemotherapy and responses were more durable
- AE frequency and severity were mostly similar between arms
  - Observed events consistent with known safety profiles of pembrolizumab and chemotherapy, with no new safety signals identified
  - Rates of discontinuation due to AEs were higher in the pembrolizumab plus chemotherapy arm, but generally low overall
  - Immune-mediated AEs were more frequent in the pembrolizumab arm, with frequency and severity consistent with those observed for pembrolizumab monotherapy
- Data suggest pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel should become a new standard-of-care for first-line treatment of metastatic squamous NSCLC, irrespective of PD-L1 expression

Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced/Metastatic NSCLC With a PD-L1 TPS ≥1%: Open-Label, Phase 3 KEYNOTE-042 Study

Gilberto Lopes,[1] Yi-Long Wu,[2] Iveta Kudaba,[3] Dariusz M Kowalski,[4] Byoung Chul Cho,[5] Hande Z Turna,[6] Gilberto Castro, Jr,[7] Vichien Srimuninnimit,[8] Konstantin K. Laktionov,[9] Igor Bondarenko,[10] Karou Kubota,[11] Gregory M Lubiniecki,[12] Jin Zhang,[12] Debra Kush,[12] Tony Mok[13]

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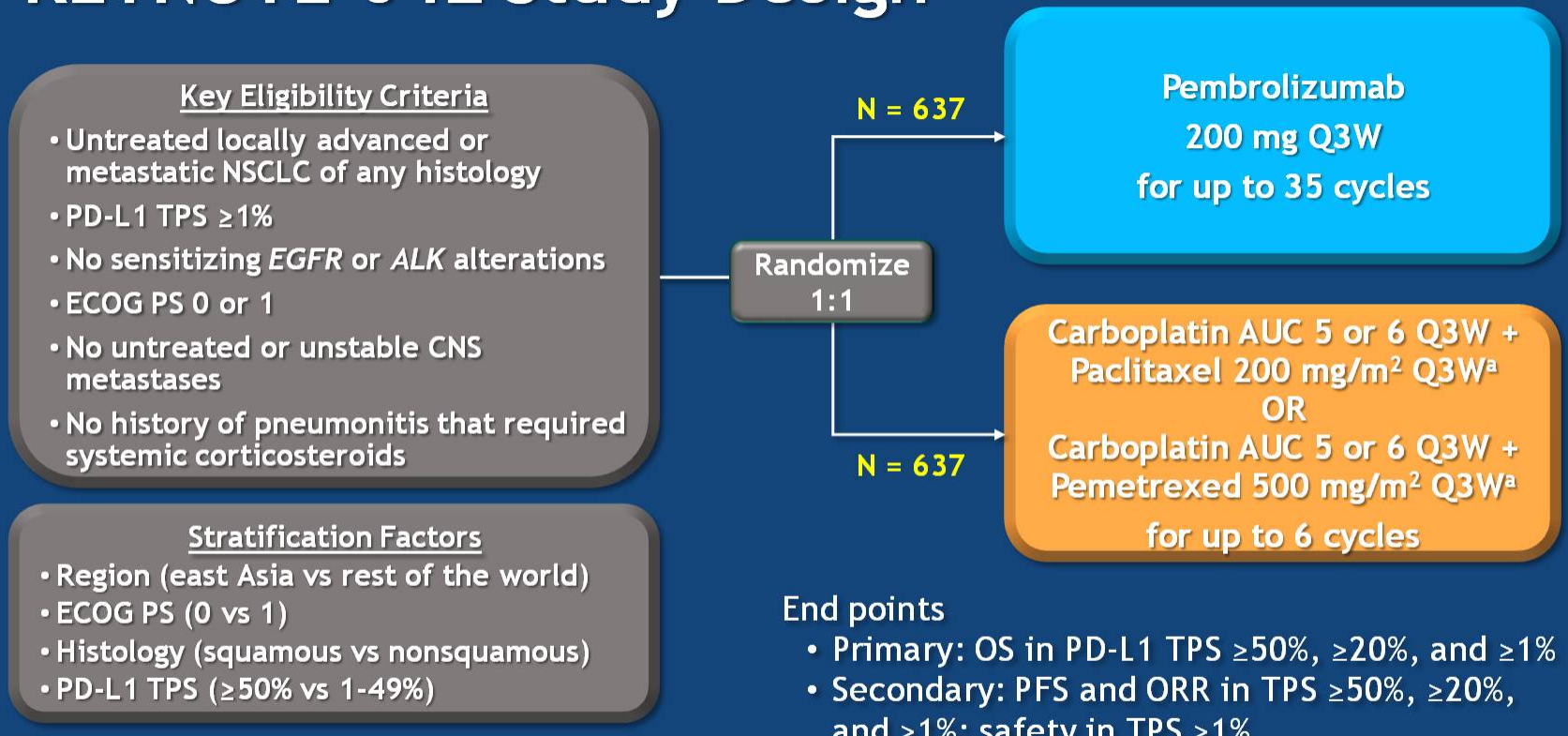
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Gilberto Lopes

Presented By Gilberto Lopes at 2018 ASCO Annual Meeting

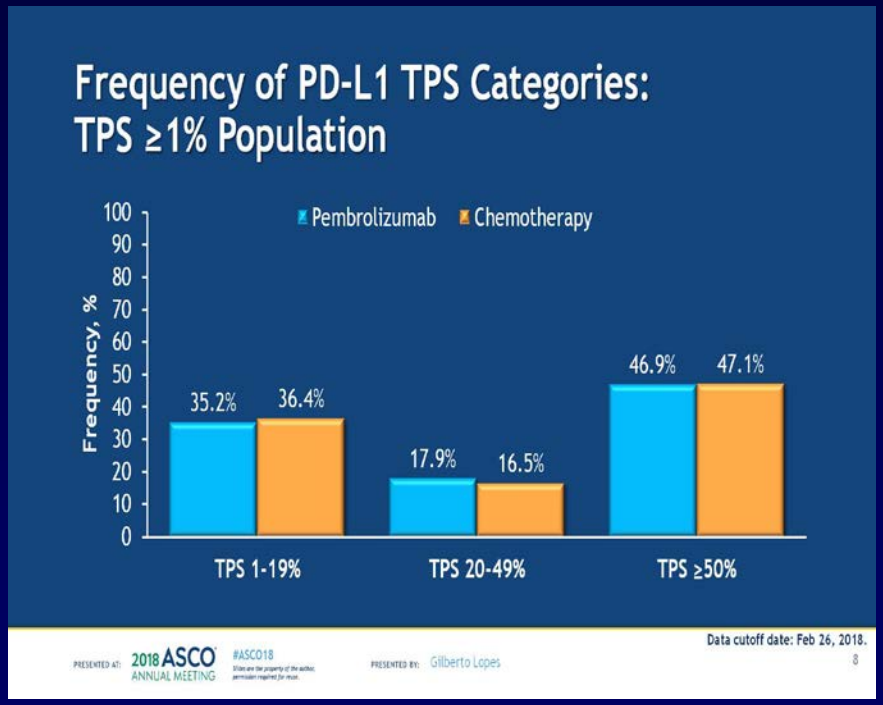
KEYNOTE-042 Study Design

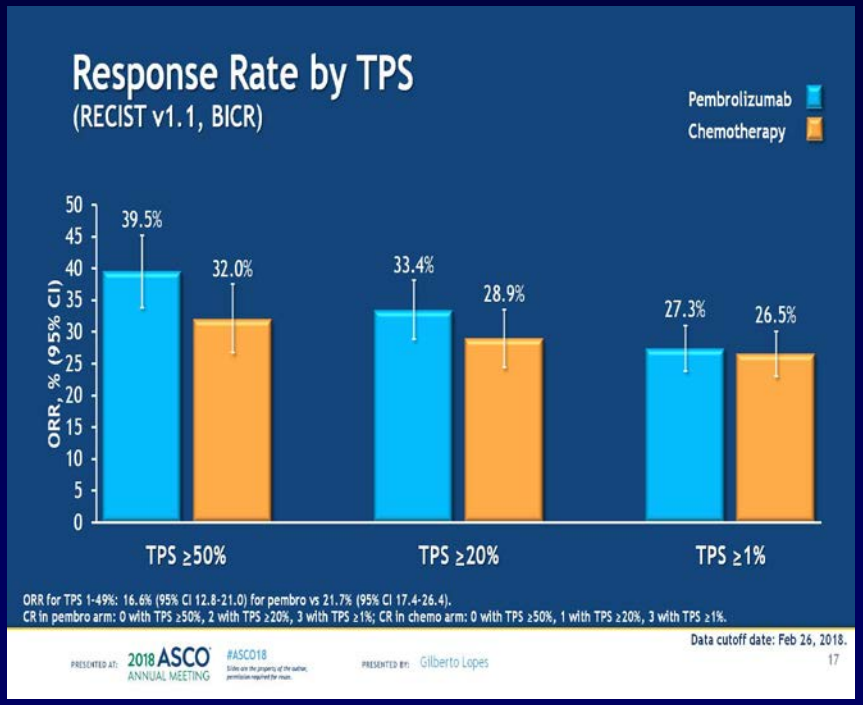


End points
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

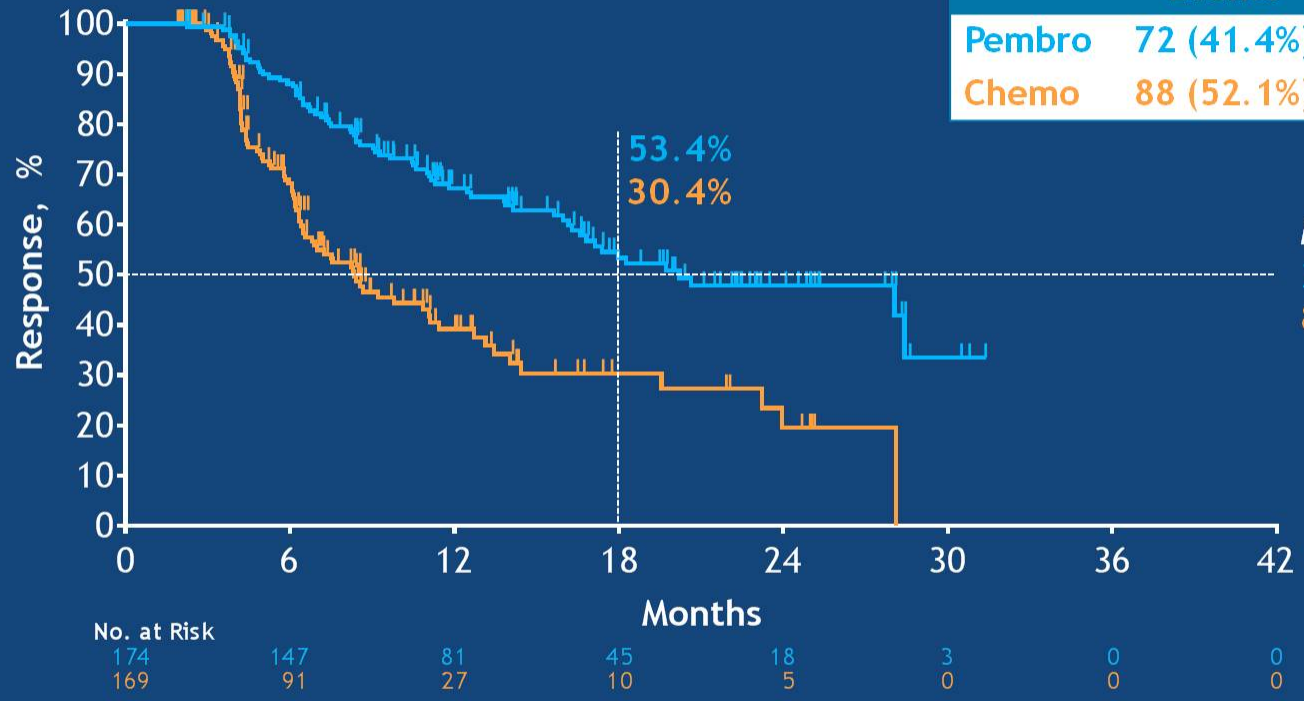
[a]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

Frequency and Response Rate for PDL1 TPS >1%





Duration of Response: TPS ≥1%
(RECIST v1.1, BICR)



	Events
Pembro	72 (41.4%)
Chemo	88 (52.1%)

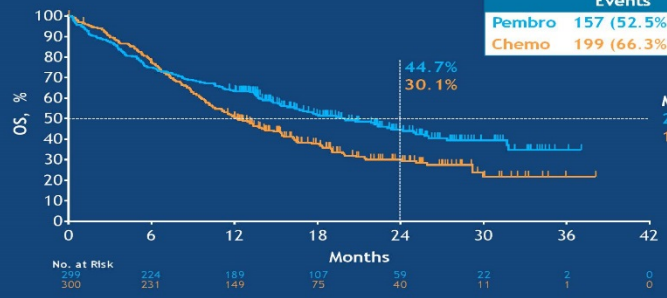
Median (range)
20.2 mo (2.1+ to 31.2+)
8.3 mo (1.8+ to 28.1)

Median DOR for pembro vs chemo: 20.2 mo vs 10.8 mo for TPS ≥50%, 20.2 mo vs 8.3 mo for TPS ≥20%, and 17.4 mo vs 8.2 mo for TPS 1-49%.

Data cutoff date: Feb 26, 2018.

Presented By Gilberto Lopes at 2018 ASCO Annual Meeting

Overall Survival: TPS ≥50%



	Events	HR (95% CI)	P
Pembro	157 (52.5%)	0.69 (0.56-0.85)	0.0003
Chemo	199 (66.3%)		

Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Progression-Free Survival: TPS ≥50%
(RECIST v1.1, BICR)

	Events	HR (95% CI)	P
Pembro	221 (73.9%)	0.81 (0.67-0.99)	0.0170[a]
Chemo	233 (77.7%)		

Median (95% CI)
7.1 mo (5.9-9.0)
6.4 mo (6.1-6.9)

[a]Protocol-specified significance boundary not met. BICR, blinded independent central review.

Overall Survival: TPS ≥20%

	Events	HR (95% CI)	P
Pembro	230 (55.7%)	0.77 (0.64-0.92)	0.0020
Chemo	266 (65.7%)		

Median (95% CI)
17.7 mo (15.3-22.1)
13.0 mo (11.6-15.3)

Progression-Free Survival: TPS ≥20%
(RECIST v1.1, BICR)

	Events	HR (95% CI)
Pembro	317 (76.8%)	0.94 (0.80-1.11)
Chemo	314 (77.5%)	

Median (95% CI)
6.2 mo (5.1-7.8)
6.6 mo (6.2-7.3)

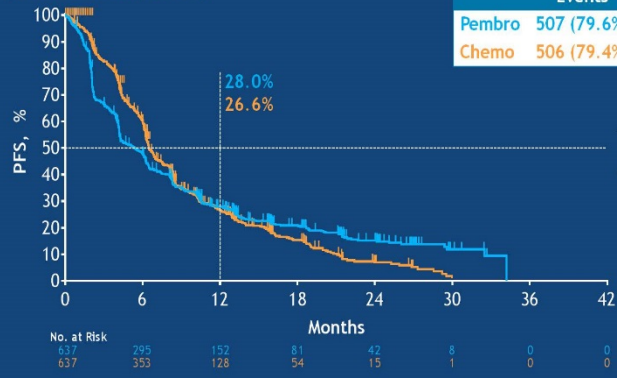
ormal comparison of pembrolizumab vs chemotherapy not performed based on hierarchical testing strategy.

Overall Survival: TPS ≥1%

	Events	HR (95% CI)	P
Pembro	371 (58.2%)	0.81 (0.71-0.93)	0.0018
Chemo	438 (68.8%)		

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

Progression-Free Survival: TPS ≥1%
(RECIST v1.1, BICR)



	Events	HR (95% CI)
Pembro	507 (79.6%)	1.07 (0.94-1.21)
Chemo	506 (79.4%)	

Median (95% CI)
5.4 mo (4.3-6.2)
6.5 mo (6.3-7.0)

Formal comparison of pembrolizumab vs chemotherapy not performed based on hierarchical testing strategy.

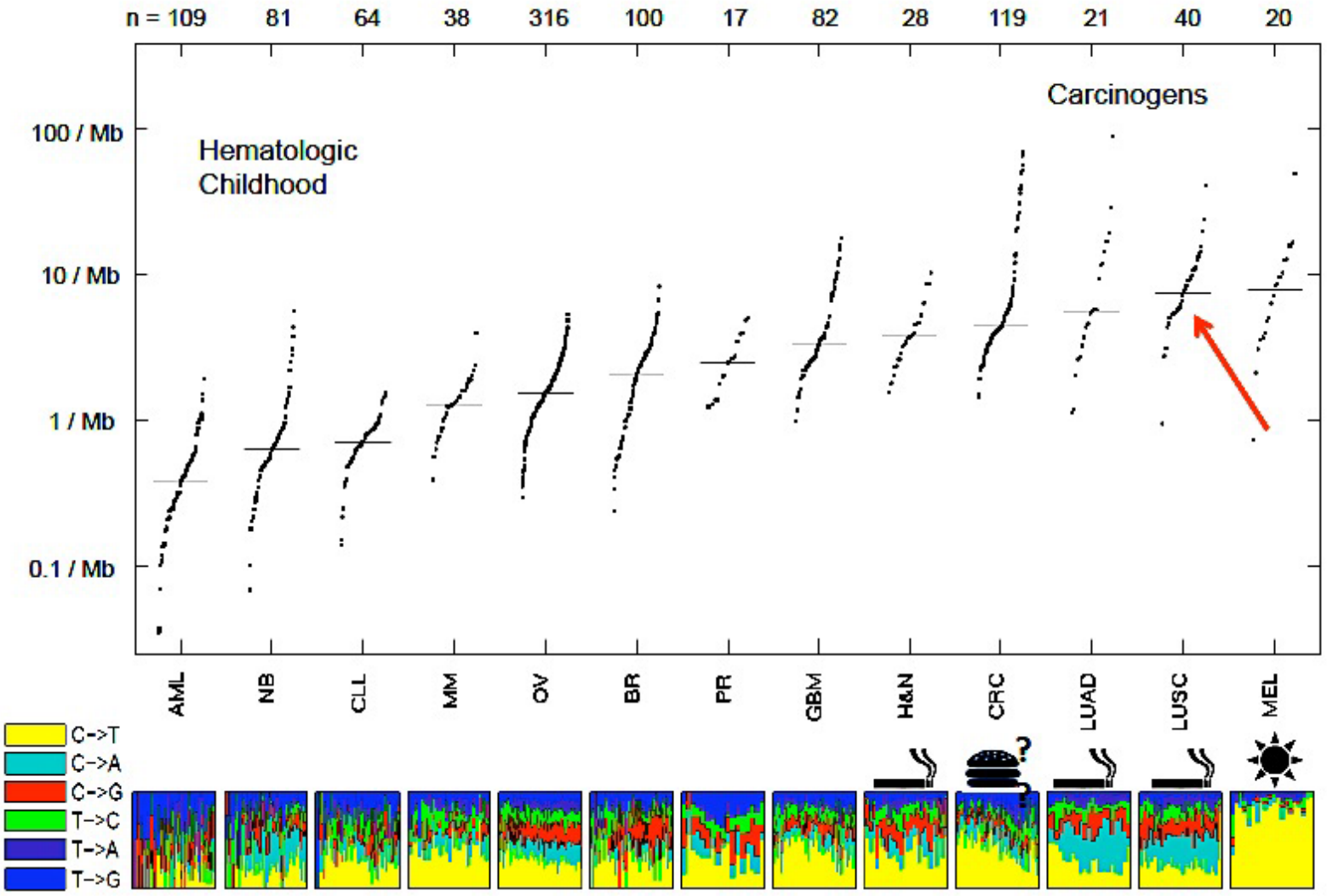
Summary and Conclusions

- Pembrolizumab significantly improved OS over platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC with PD-L1 TPS ≥50%, ≥20%, and ≥1%
  - HR (95% CI) of 0.69 (0.56-0.85), 0.77 (0.64-0.92), and 0.81 (0.71-0.93), respectively
  - Greater magnitude of benefit for pembrolizumab at higher levels of PD-L1 expression is consistent with previous studies of pembrolizumab monotherapy in metastatic NSCLC
  - In an exploratory analysis of TPS 1-49% population, HR (95% CI) was 0.92 (0.77-1.11)
- No significant PFS benefit for pembrolizumab at this analysis
  - Based on recommendation of external data monitoring committee, study is continuing to evaluate PFS based on additional follow-up
- Duration of response longer in patients treated with pembrolizumab than chemotherapy at all levels of PD-L1 expression

Summary and Conclusions

- Despite longer exposure, frequency of treatment-related AEs was lower with pembrolizumab
  - Safety profile consistent with that previously observed for pembrolizumab
  - Better safety profile of pembrolizumab suggests it is an appropriate treatment option for any level of PD-L1 positivity
- Keynote 042 is the first study with a primary endpoint of OS to demonstrate superiority of pembrolizumab over platinum-based chemotherapy in patients with previously untreated advanced or metastatic NSCLC without EGFR mutations or ALK translocations and with a PD-L1 TPS ≥1%
- These data confirm and potentially extend the role of pembrolizumab monotherapy as a standard first-line treatment for patients with PD-L1-expressing tumors

Comparative Rate of Mutations Across Different Tumor Types



Getz G, and Lawrence M, Broad Institute, MIT

2018 ASCO ANNUAL MEETING

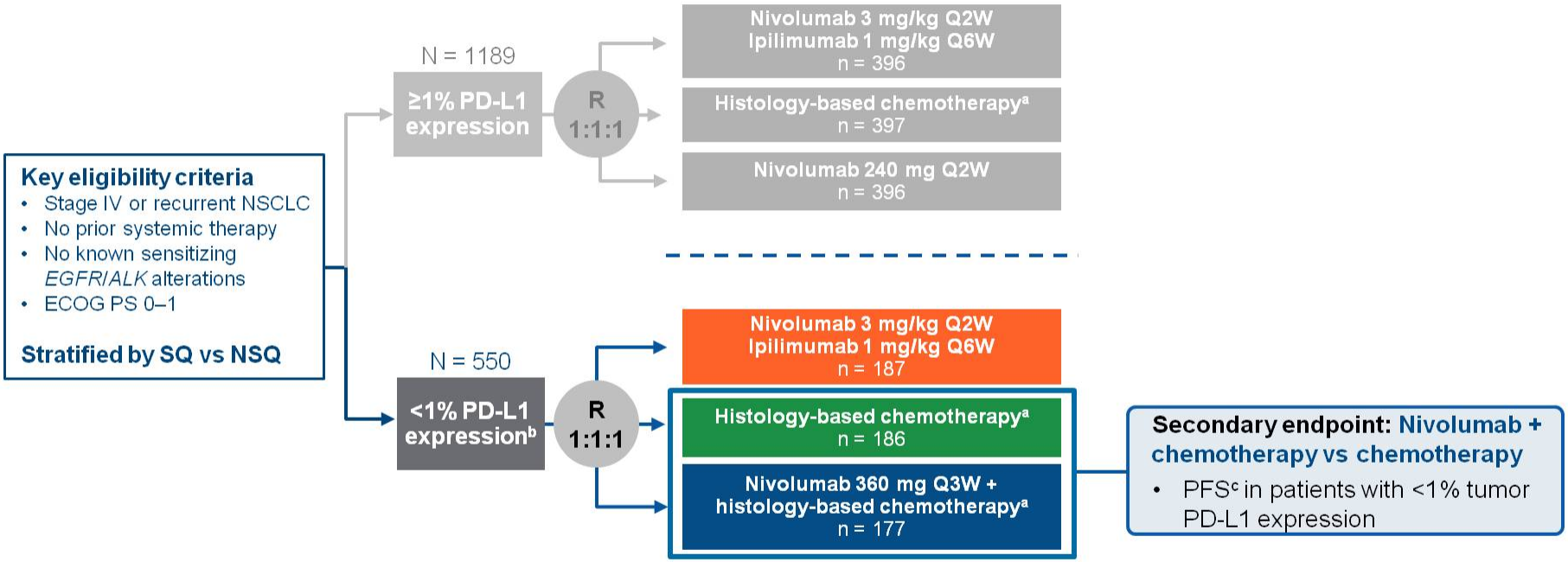
Nivolumab + Ipilimumab, Nivolumab + Chemotherapy, and Chemotherapy in Chemo-Naive Patients With Advanced Non-Small Cell Lung Cancer and <1% Tumor PD-L1 Expression: Results From CheckMate 227

Hossein Borghaei,[1] Matthew D. Hellmann,[2] Luis Paz-Ares,[3] Suresh S. Ramalingam,[4] Martin Reck,[5] Kenneth J. O'Byrne,[6] Prabhu Bhagavatheeswaran,[7] Faith Nathan,[7] Julie Brahmer[8]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Hospital Universitario Doce de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [5]LungenClinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany; [6]Princess Alexandra Hospital Brisbane, Queensland, Australia; [7]Bristol-Myers Squibb, Princeton, NJ, USA; [8]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

2018 ASCO Annual Meeting, June 1–5, Chicago, IL

CheckMate 227 Part 1 Study Design



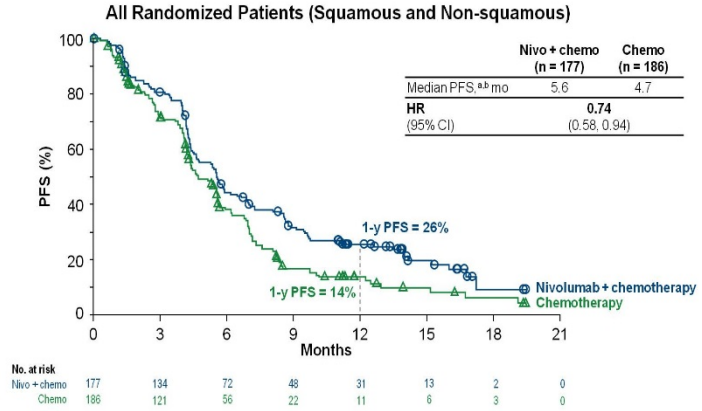
- Co-primary endpoints: OS in PD-L1–selected populations and PFS[c] in TMB-selected populations treated with nivolumab + ipilimumab vs chemotherapy

Database lock: January 24, 2018; minimum follow-up: 11.2 months

[a]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤4 cycles; [b]One patient was randomized with <1% tumor PD-L1 expression in IVRS, but was subsequently found to have ≥1% tumor PD-L1 expression; [c]Per BICR

PFS, ORR and DOR: Nivolumab + Chemotherapy vs Chemotherapy in Patients With <1% Tumor PDL1 Expression

PFS: Nivolumab + Chemotherapy vs Chemotherapy in Patients With <1% Tumor PD-L1 Expression

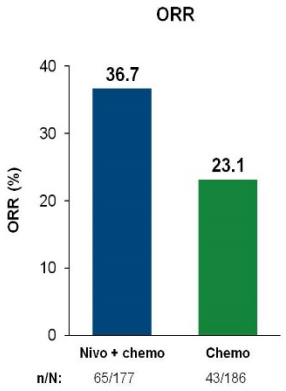


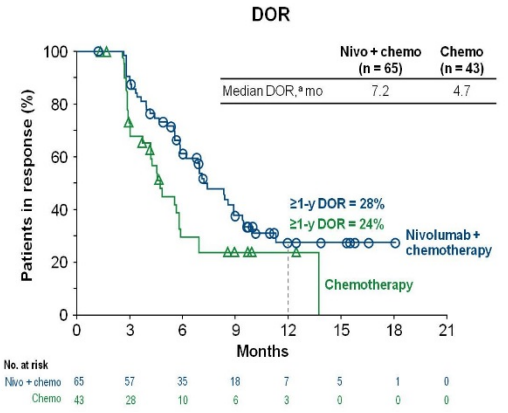
	Nivo + chemo (n = 177)	Chemo (n = 186)
Median PFS,[a,b] mo	5.6	4.7
HR (95% CI)	0.74 (0.58, 0.94)	

[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

ORR and DOR in Patients With <1% Tumor PD-L1 Expression



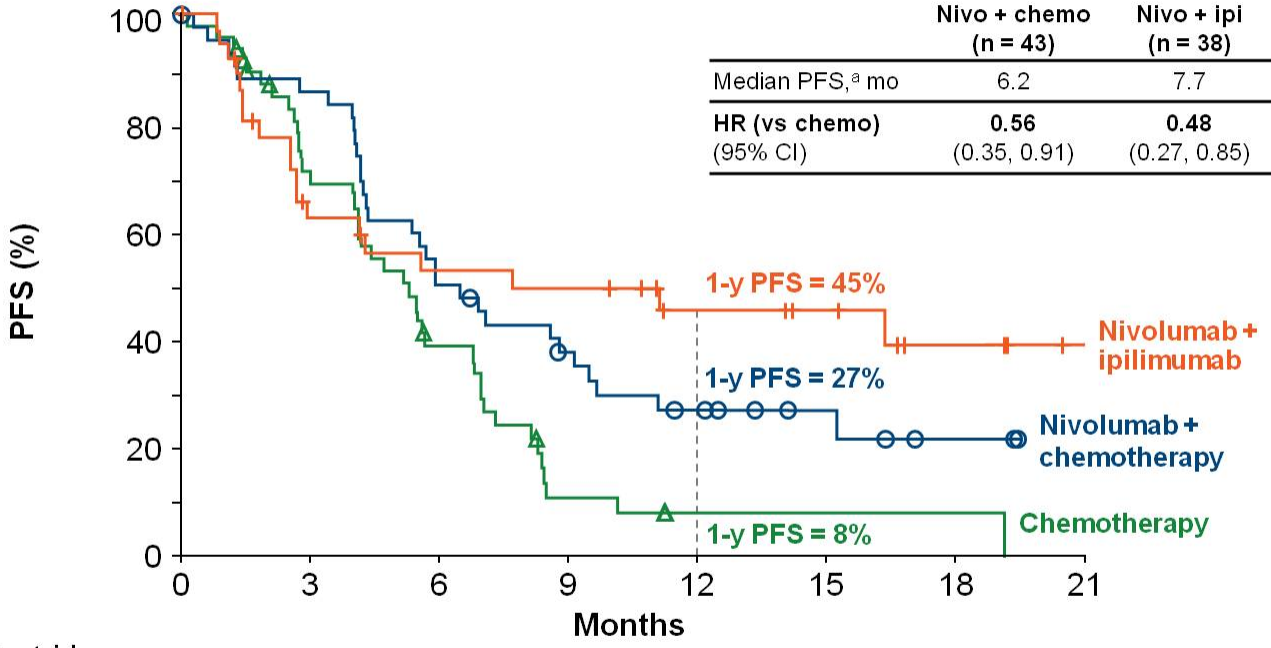


	Nivo + chemo (n = 65)	Chemo (n = 43)
Median DOR,[a] mo	7.2	4.7

DOR per BICR; ORR was 25.1% (n/N: 47/187), median DOR was 18.0 mo (95% CI: 12.2, NR), and ≥1-y DOR was 72% in the nivo + ipi arm
[a]95% CI: nivo + chemo (5.9, 9.4 mo), chemo (3.7, 5.8 mo)

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 43)	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS,[a] mo	6.2	7.7	5.3
HR (vs chemo) (95% CI)	**0.56** (0.35, 0.91)	**0.48** (0.27, 0.85)	

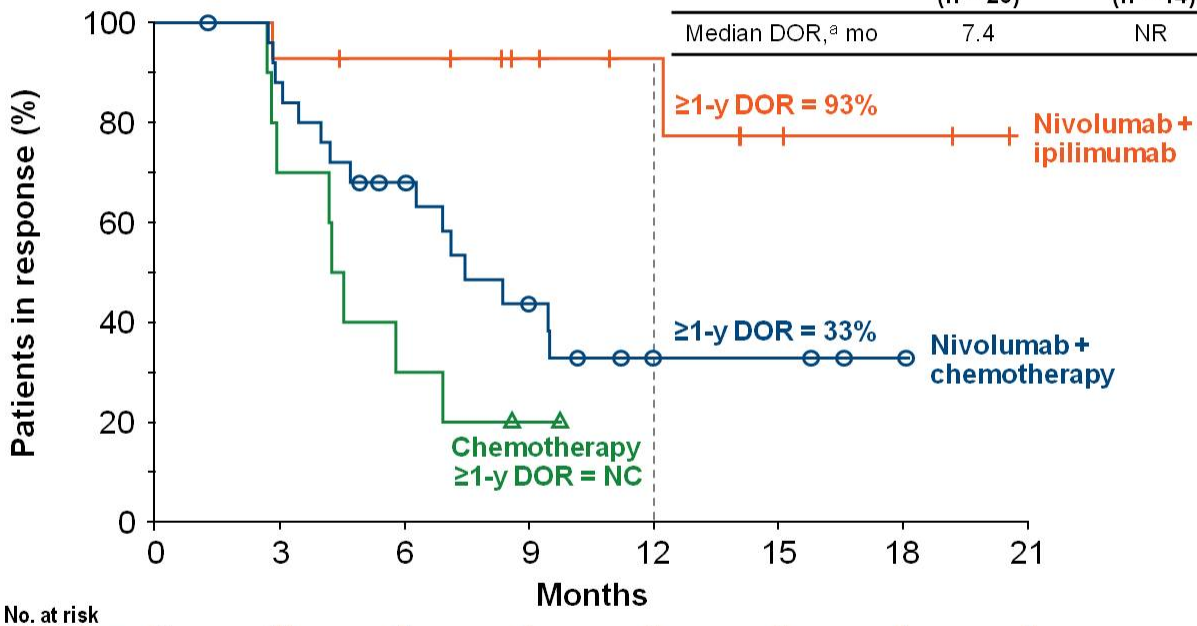


Exploratory analysis

[a]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo)

DOR: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab in Patients With TMB ≥10 mut/Mb and <1% Tumor PD-L1 Expression

	Nivo + chemo (n = 26)	Nivo + ipi (n = 14)	Chemo (n = 10)
Median DOR,[a] mo	7.4	NR	4.4



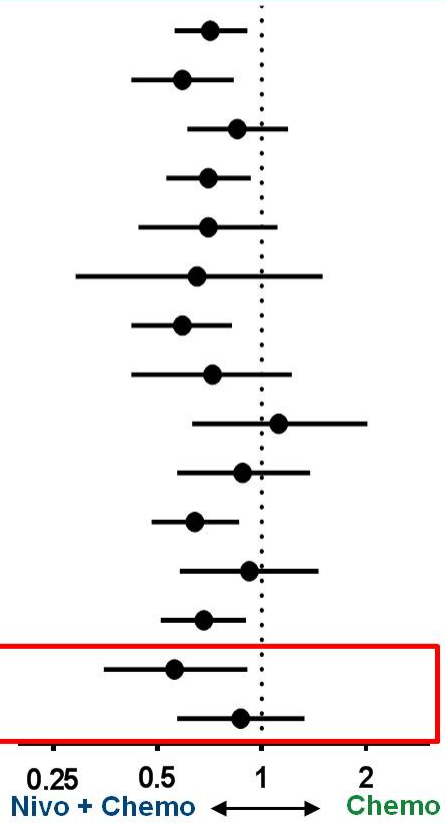
- ORR was 60.5% with nivo + chemo, 36.8% with nivo + ipi, and 20.8% with chemo

Exploratory analysis

[a]95% CI: nivo + chemo (4.6, NR mo), nivo + ipi (12.2, NR mo), chemo (2.7, 6.9 mo)

PFS Subgroup Analyses in Patients With <1% Tumor PD-L1 Expression

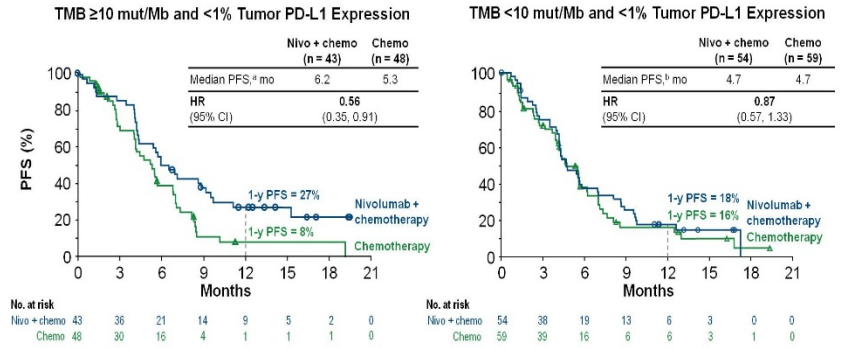
Subgroup	Nivo + chemo n	Chemo n	Unstratified HR
Overall	177	186	0.71
<65 years	91	98	0.59
≥65 years	86	88	0.85
Male	130	125	0.70
Female	47	61	0.70
North America	25	15	0.65
Europe	90	92	0.59
Asia	36	43	0.72
Rest of world	26	36	1.12
ECOG PS 0	59	57	0.88
ECOG PS 1	117	127	0.64
Squamous	43	46	0.92
Non-squamous	134	140	0.68
TMB high (≥10 mut/Mb)	43	48	0.56
TMB low (<10 mut/Mb)	54	59	0.87



PFS: Nivolumab vs. Chemotherapy vs. Nivolumab + Ipilumumab by TMB

CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

PFS: Nivolumab + Chemotherapy vs Chemotherapy By TMB



- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

[a]95% CI: nivo + chemo (4.3, 9.1 mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), chemo (3.9, 6.2 mo)

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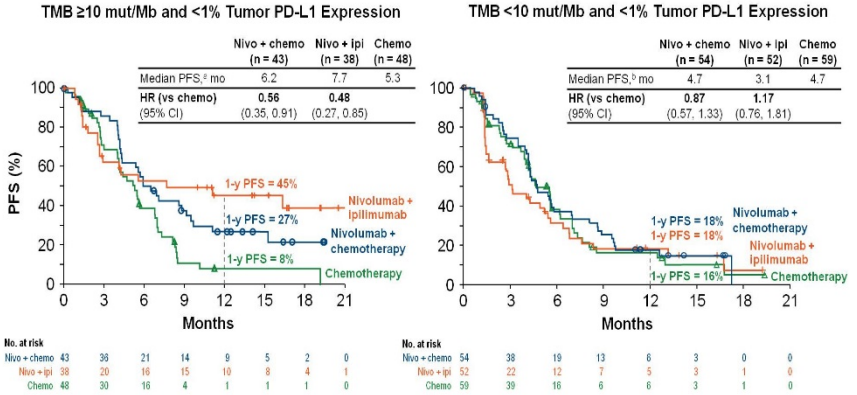
CheckMate 227: Nivo + Ipi, Nivo + Chemo, and Chemo in 1L NSCLC With <1% Tumor PD-L1 Expression

PFS: Nivolumab + Chemotherapy and Nivolumab + Ipilimumab By TMB



Exploratory analysis

[c]95% CI: nivo + chemo (4.3, 9.1 mo), nivo + ipi (2.7, NR mo), chemo (4.0, 6.8 mo); [b]95% CI: nivo + chemo (4.2, 6.9 mo), nivo + ipi (1.6, 5.4 mo), chemo (3.9, 6.2 mo)

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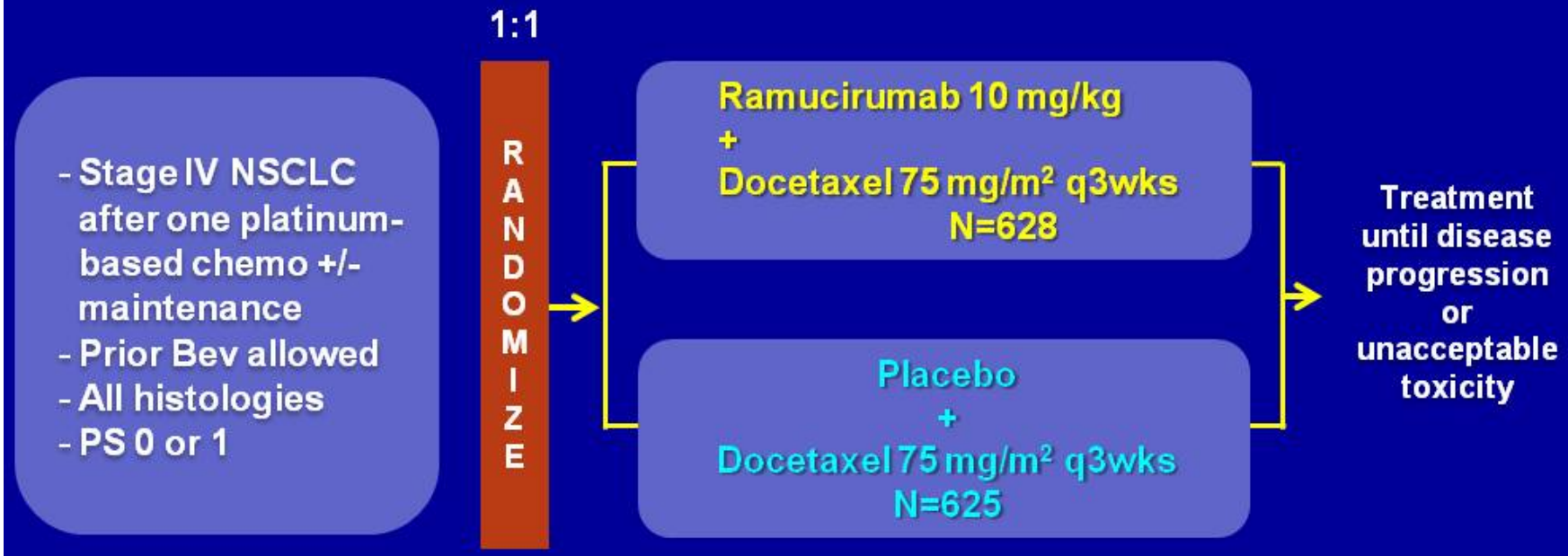
Summary: Nivolumab + Ipilimumab and Nivolumab + Chemotherapy in 1L NSCLC With <1% Tumor PD-L1 Expression

- Nivolumab + chemo vs chemo PFS HR was 0.74 (95% CI: 0.58, 0.94)[a] in patients with <1% PD-L1 expression,[b] consistent with other PD-(L)1 + chemo studies
- TMB testing may be clinically relevant to select patients for IO + chemo in addition to IO + IO
  - In patients with <1% PD-L1 expression, PFS benefit from nivolumab + chemo vs chemo was enhanced with high TMB (≥10 mut/Mb)
  - Patients with low TMB (<10 mut/Mb) and <1% PD-L1 did not appear to have PFS benefit from nivolumab in combination with either chemo or ipilimumab
- Responses were more durable and 1-year PFS rates were higher with nivolumab + ipilimumab vs nivolumab + chemo in patients with high TMB (≥10 mut/Mb) and <1% PD-L1 expression
- There were fewer grade 3–4 TRAEs with nivolumab + ipilimumab than nivolumab + chemo

[a]NSQ PFS HR = 0.68 (95% CI: 0.51, 0.90); [b]NSQ and SQ

Second Line Options for Squamous Cell Carcinoma of the Lung

REVEL: Study Design



Stratification factors:

- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

Primary endpoint: **Overall Survival**

Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

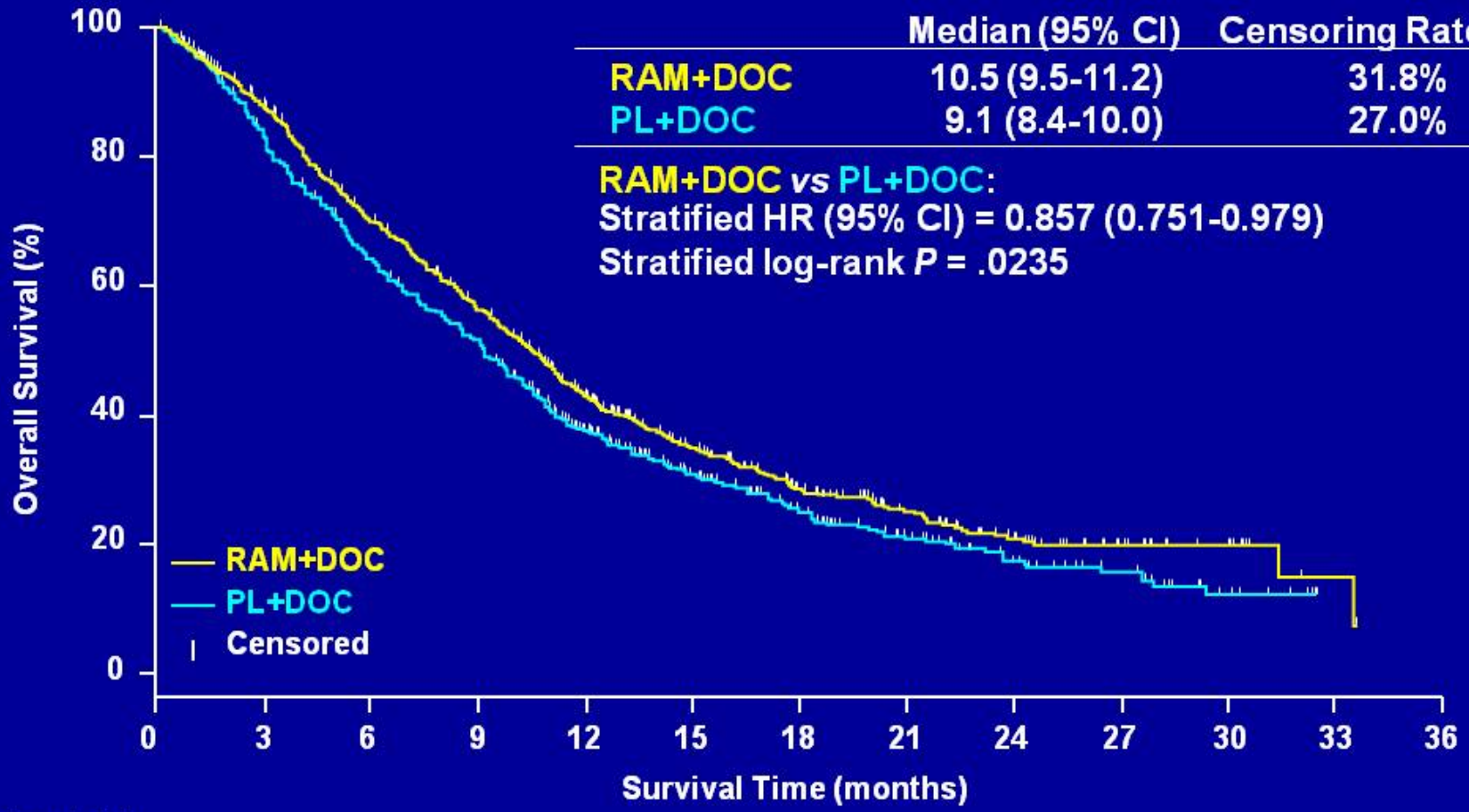
Abbreviations: Bev=bevacizumab; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=objective response rate; PFS=progression-free survival; ROW=rest of the world; q3wks=every 3 weeks.

Overall Survival

ITT Population

	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%

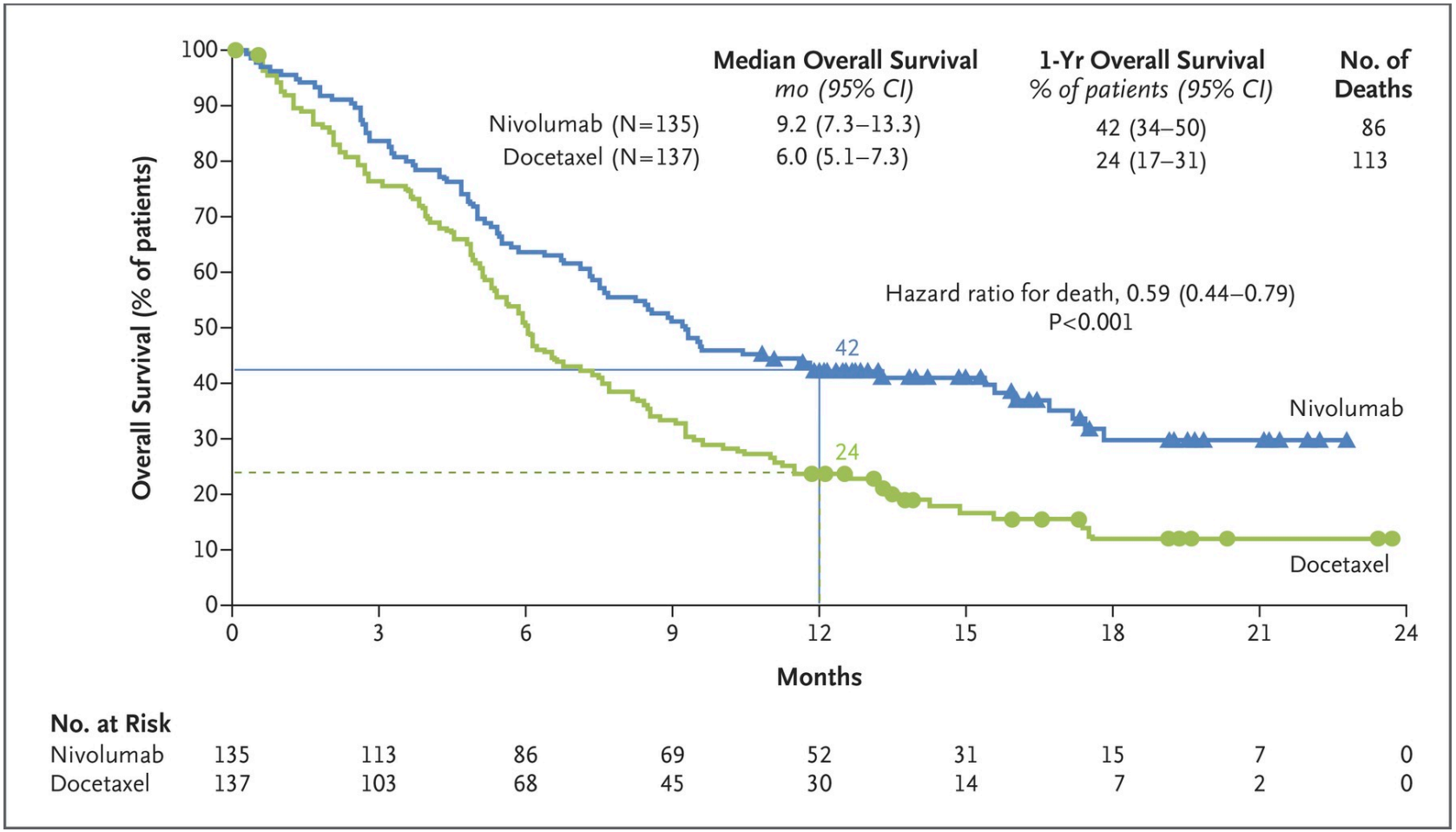
RAM+DOC *vs* PL+DOC:
Stratified HR (95% CI) = 0.857 (0.751-0.979)
Stratified log-rank *P* = .0235



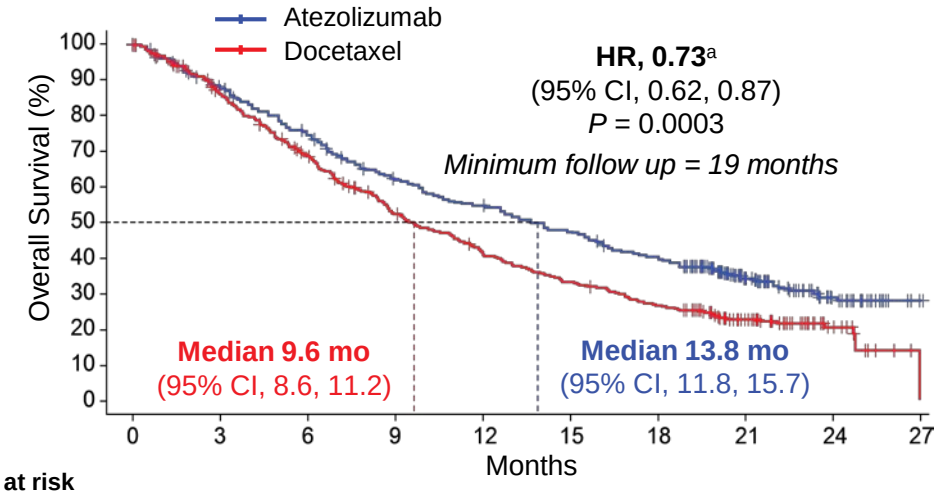
Number at risk

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

OS for Nivolumab vs. Docetaxel as second line option in squamous Cell carcinoma, Checkmate 017.

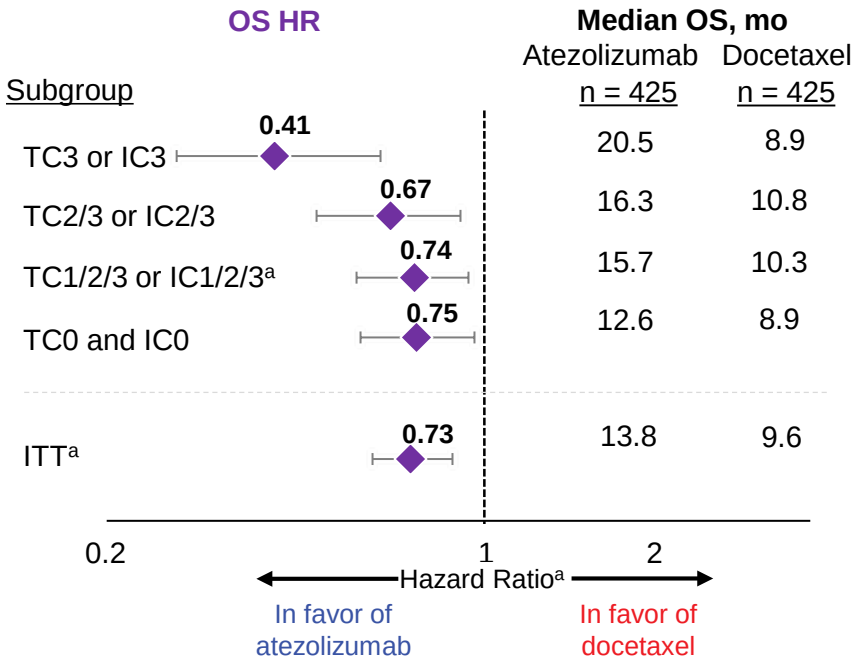


Atezolizumab: Overall survival, ITT (n = 850) and PD-L1 subgroups



No. at risk

Atezolizumab	425	363	305	248	218	188	157	74	28	1
Docetaxel	425	336	263	195	151	123	98	51	16	0

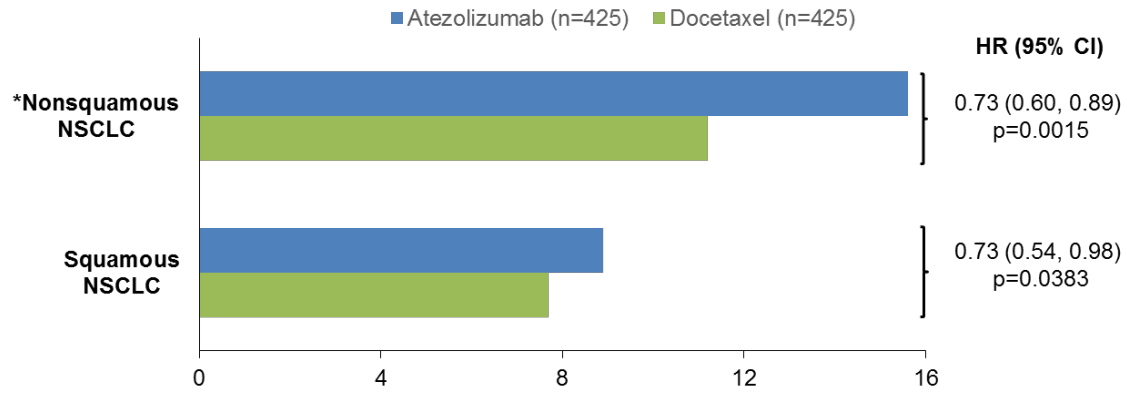


[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.
Barlesi et al. ESMO 2016 LBA44

Gadgeel et al., WCLC 2016

Atezolizumab Survival Benefit by Histology Compared to Docetaxel

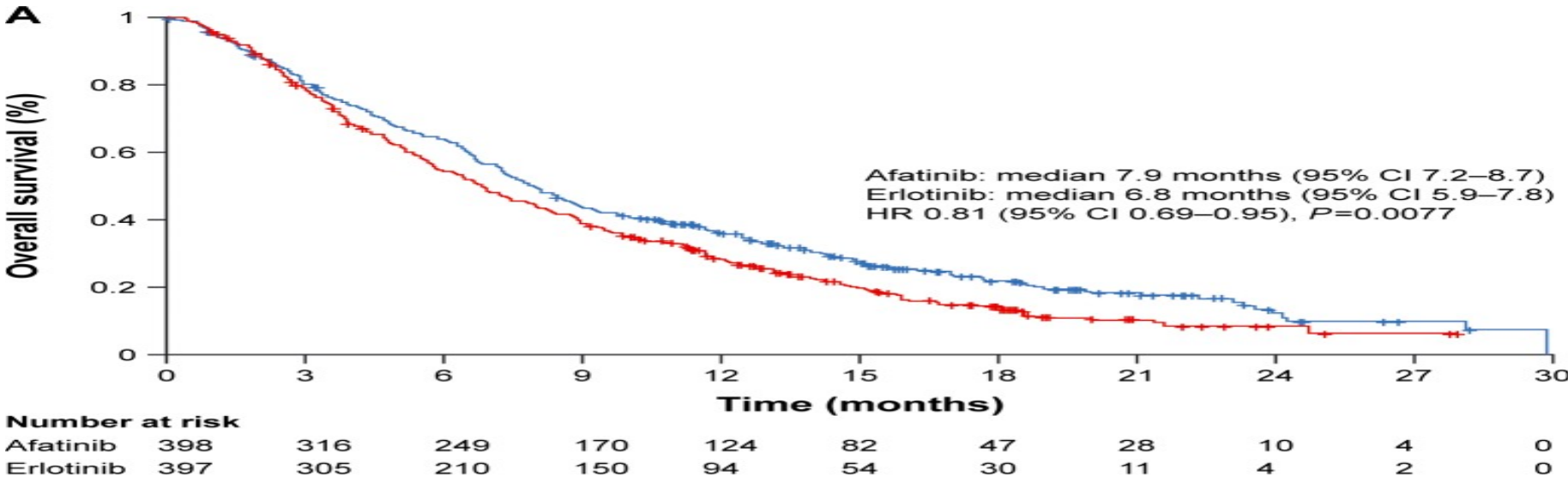
OS results from OAK: a randomized Phase III clinical trial:[2]

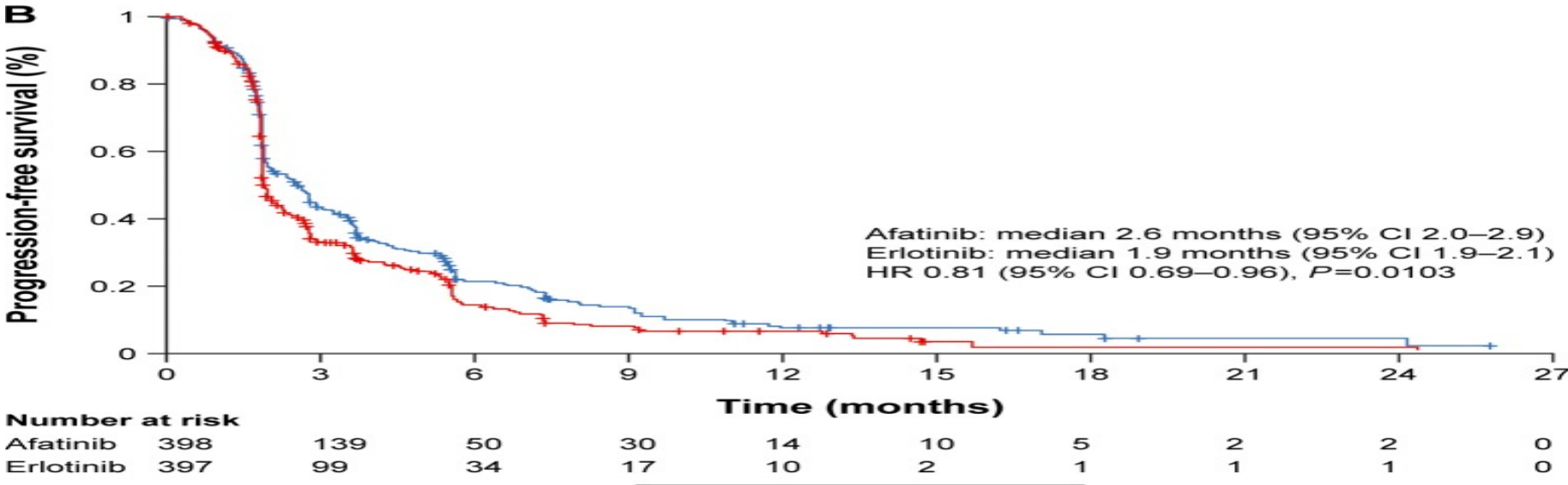


‡There are 4 main pathological types of lung cancer (adeno-, squamous cell, small cell and large cell carcinoma). For reasons of clinical consequences, different pathological types of lung cancer are sometimes grouped into a category (non-small cell carcinoma or nonsquamous non-small cell carcinoma) when it is necessary or useful to consider them in the same way, even if the tumors are pathologically different

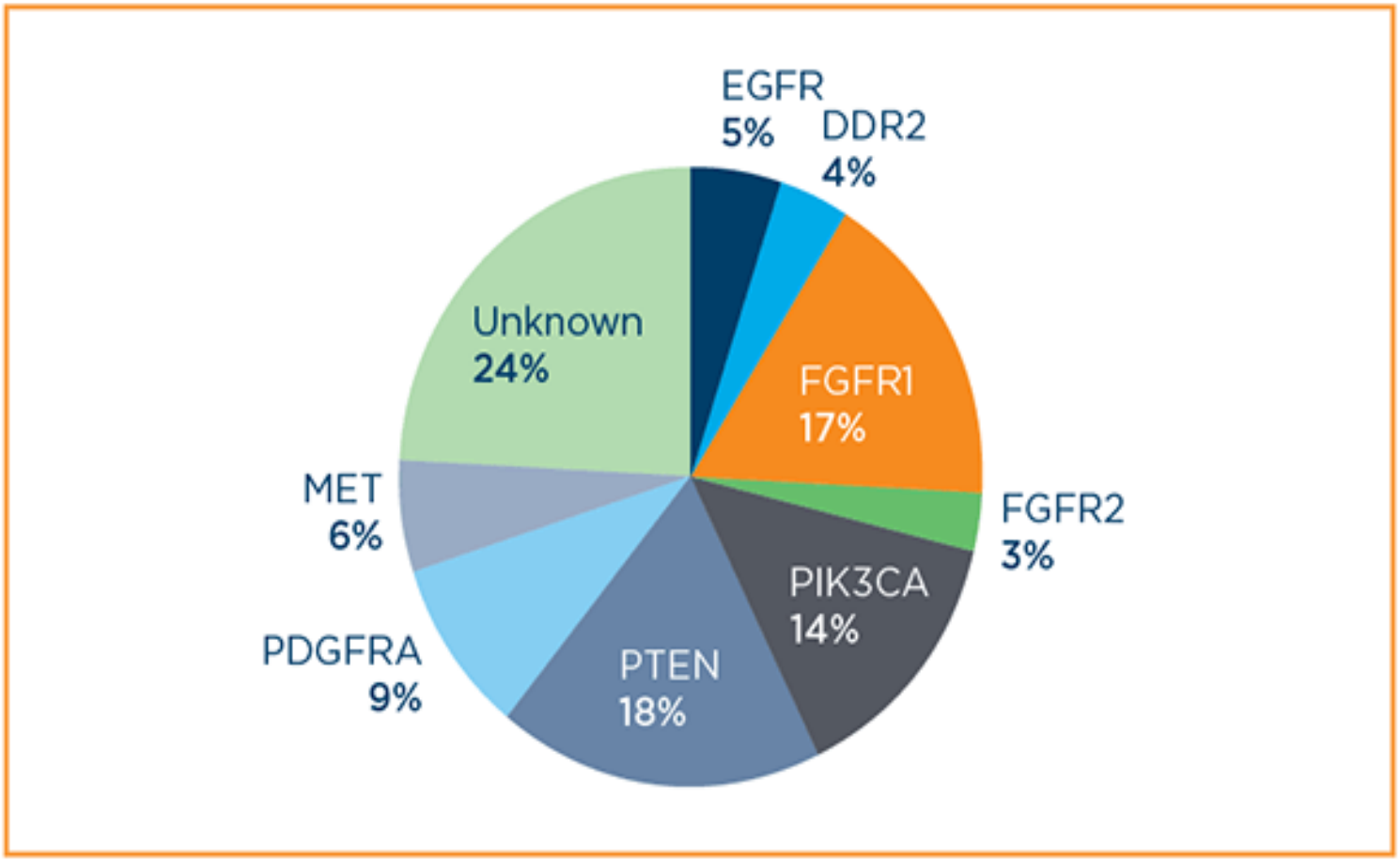
Gadgeel et al., WCLC 2016

Afatinib vs. Erlotinib as second line options for Squamous Cell carcinoma of the lung

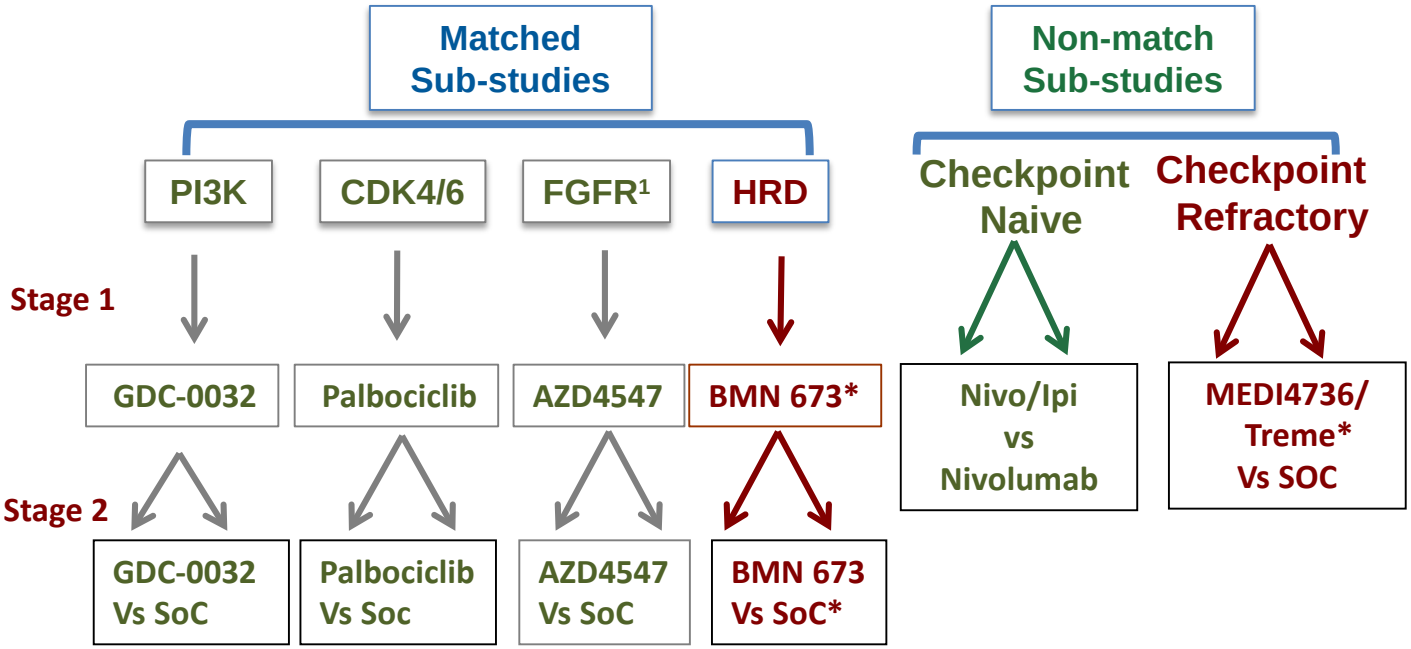




DRIVER MUTATIONS IN SQUAMOUS CELL LUNG CANCER



LUNG-MAP Schema



- **Lung-MAP amended to 2nd line therapy & beyond to accommodate Nivolumab approval**
- **Pre-screening added back**
- **Eligibility criteria broadened; *Sub-studies in development**

Gadgeel et al., WCLC 2016

Thank You