Place of immunotherapy in the treatment of NSCLC

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im. Eugenii i Janusza Zeylandów

Niniejszy wykład powstał dzięki wsparciu firmy MSD.
Wszelkie poglądy zawarte w niniejszej prezentacji odzwierciedlają wyłącznie opinie autora i nie stanowią reklamy produktów leczniczych w świetle ustawy „Prawo farmaceutyczne”.

Introduction

Lung cancer– last century disease

"On one point, however, there is complete consensus of opinion and that is that primary malignant neoplasms of the lung are among the rarest form of disease."

Adler J. Primary malignant growths of the lung and bronchi, Longmans. New York ***1912****.*

BRONCHOGENIC CARCINOMA HAS BECOME one of the most important and most lethal lesions to which civilized man is heir.

Ochsner A. The ethiology of bronchogenic carcinoma. Dis., Chest. ***1964****; 45: 586–590.*

Statistics

- **20%** of all cancer-related deaths are due to lung cancer

- Mortality from lung cancer **higher** than from colon, breast and prostate cancer combined

Non small cell lung cancer stage III

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
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Overall Survival with Durvalumab versus Placebo after Chemoradiotherapy in Stage III NSCLC: Updated Results from PACIFIC

Scott J. Antonia[1], Augusto Villegas[2], Davey Daniel[3], David Vicente[4], Shuji Murakami[5], Rina Hui[6], Takayasu Kurata[7], Alberto Chiappori[1],
Ki Hyeong Lee[8], Maike de Wit[9], Byoung Chul Cho[10], Maryam Bourhaba[11], Xavier Quantin[12], Takaaki Tokito[13], Tarek Mekhail[14], David Planchard[15], Young-Chul Kim[16], Christos S. Karapetis[17], Sandrine Hiret[18], Gyula Ostoros[19], Kaoru Kubota[20], Jhanelle E. Gray[1],
Luis Paz-Ares[21], Javier de Castro Carpeño[22], Corinne Faivre-Finn[23], Martin Reck[24], Johan F. Vansteenkiste[25], David R. Spigel[26], Catherine Wadsworth[27], Giovanni Melillo[28], Maria Taboada[29], Phillip A. Dennis[28], Mustafa Özgüroğlu[30]

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PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

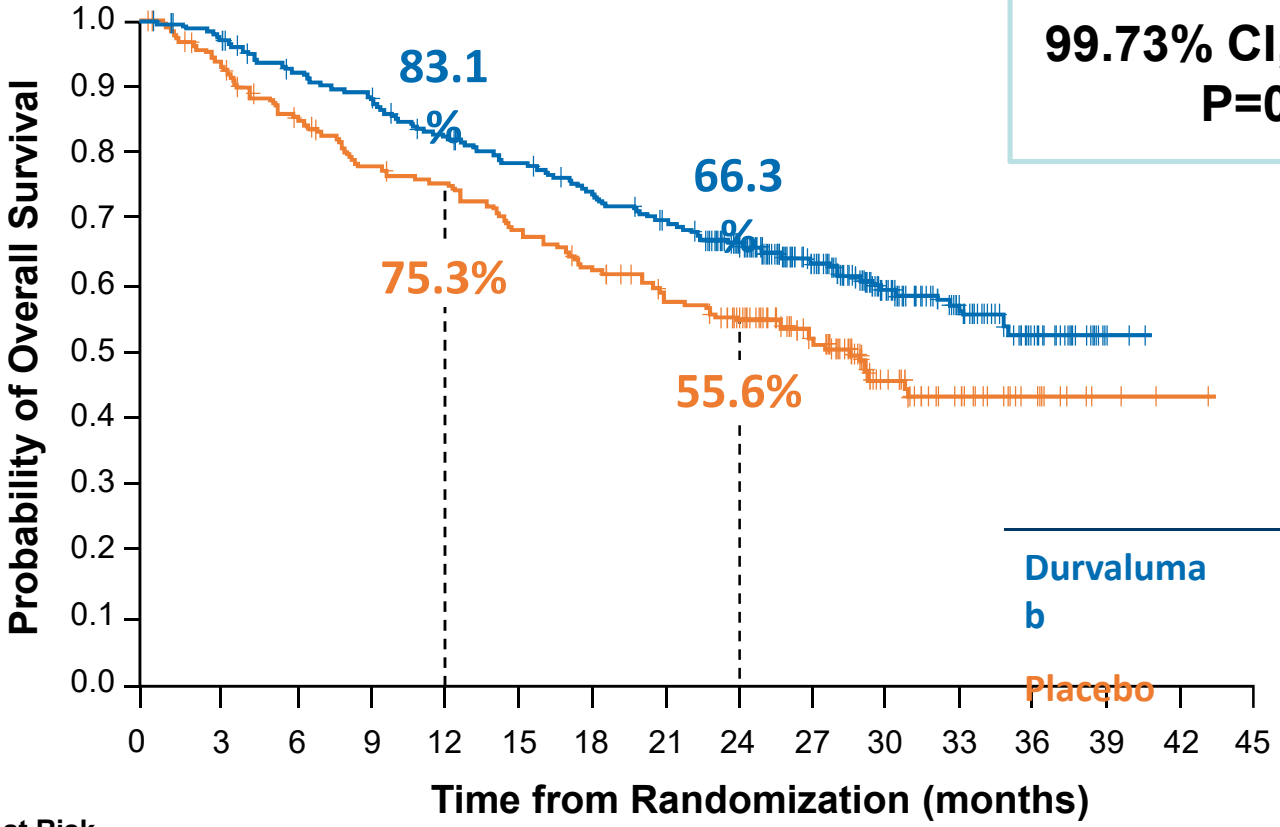
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*Using the Ventana SP263 immunohistochemistry assay

†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis.

ClinicalTrials.gov number: NCT02125461

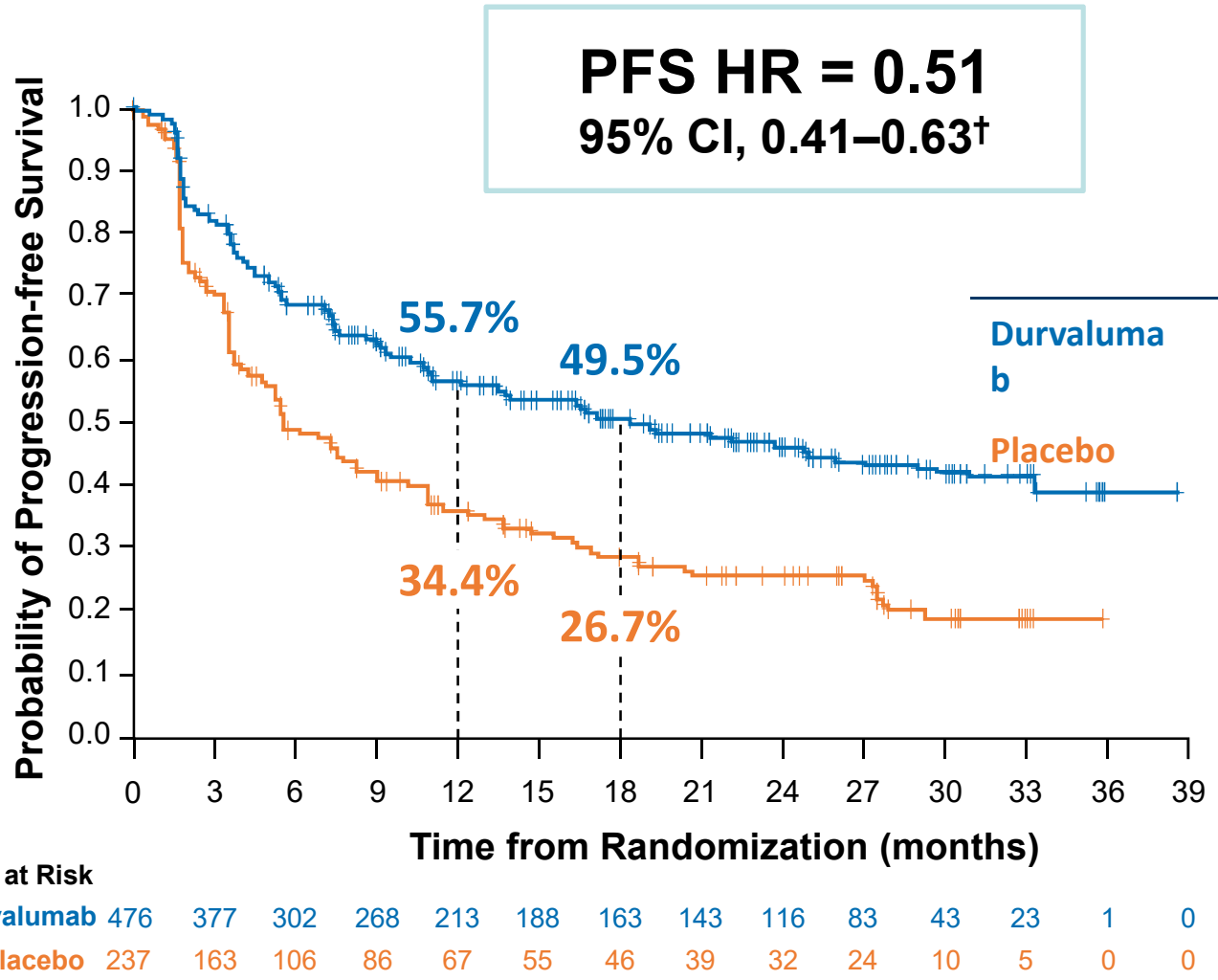
Overall Survival* (ITT)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

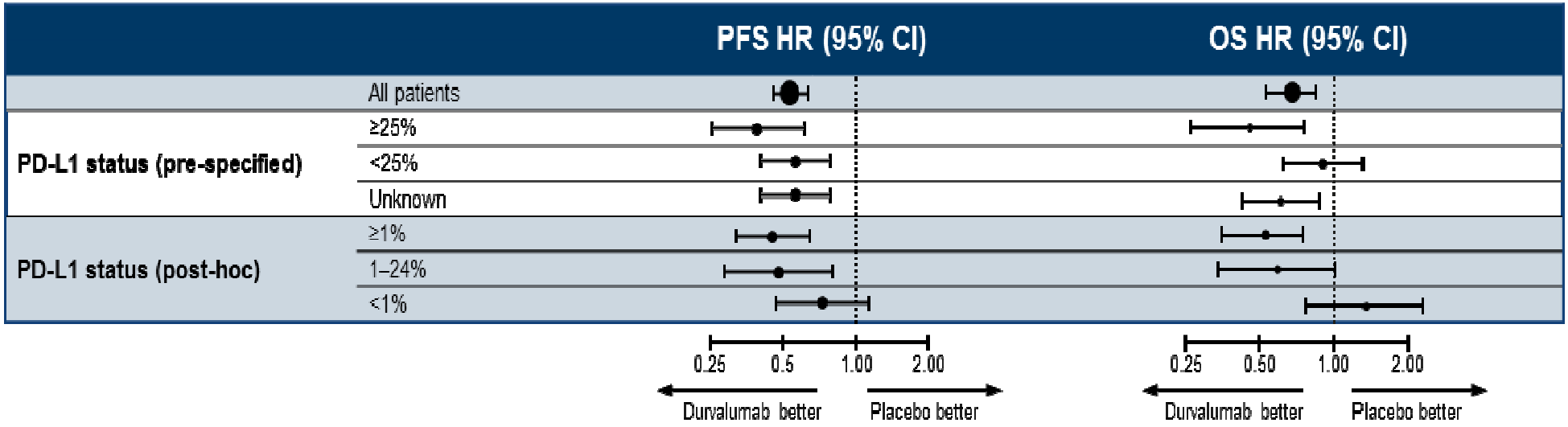
	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvaluma b	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

Updated Progression-free Survival by BICR* (ITT)



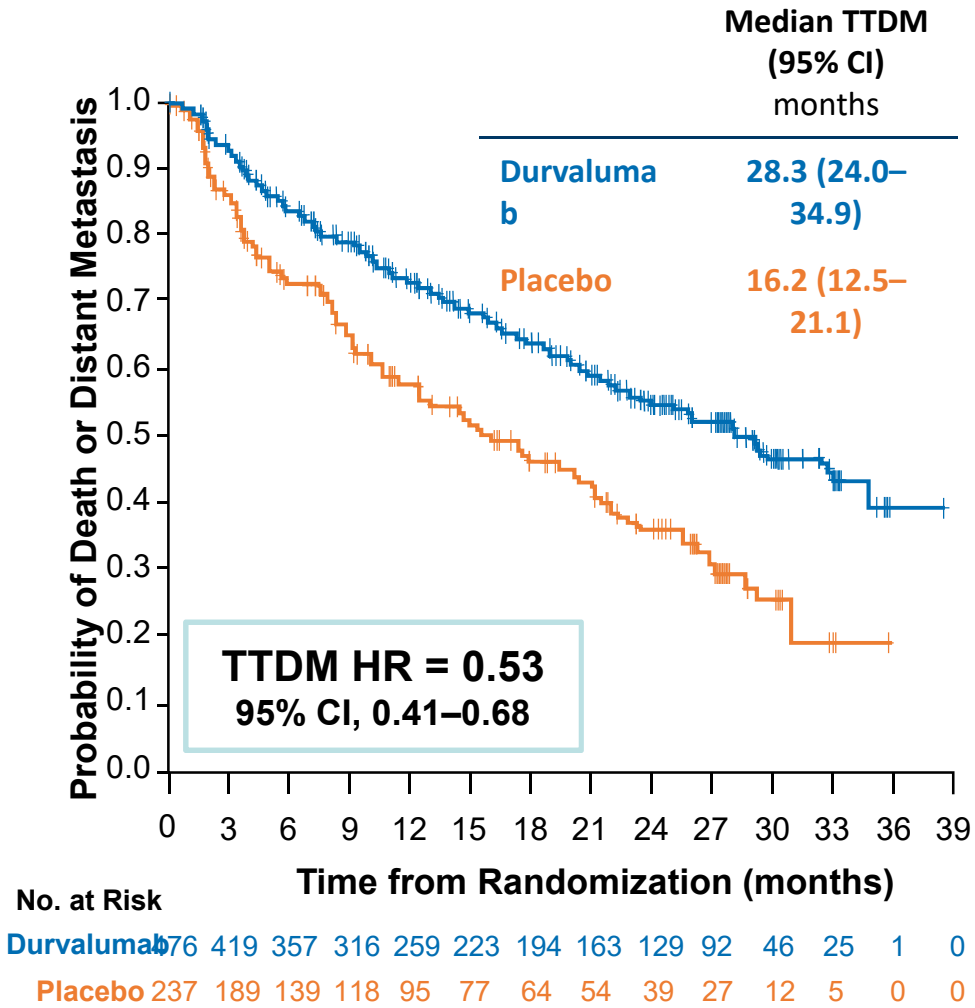
	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvaluma b	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

Subgroup Analysis by PD-L1 Status



- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

Updated Time to Death or Distant Metastasis (TTDM) by BICR* (ITT)



Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

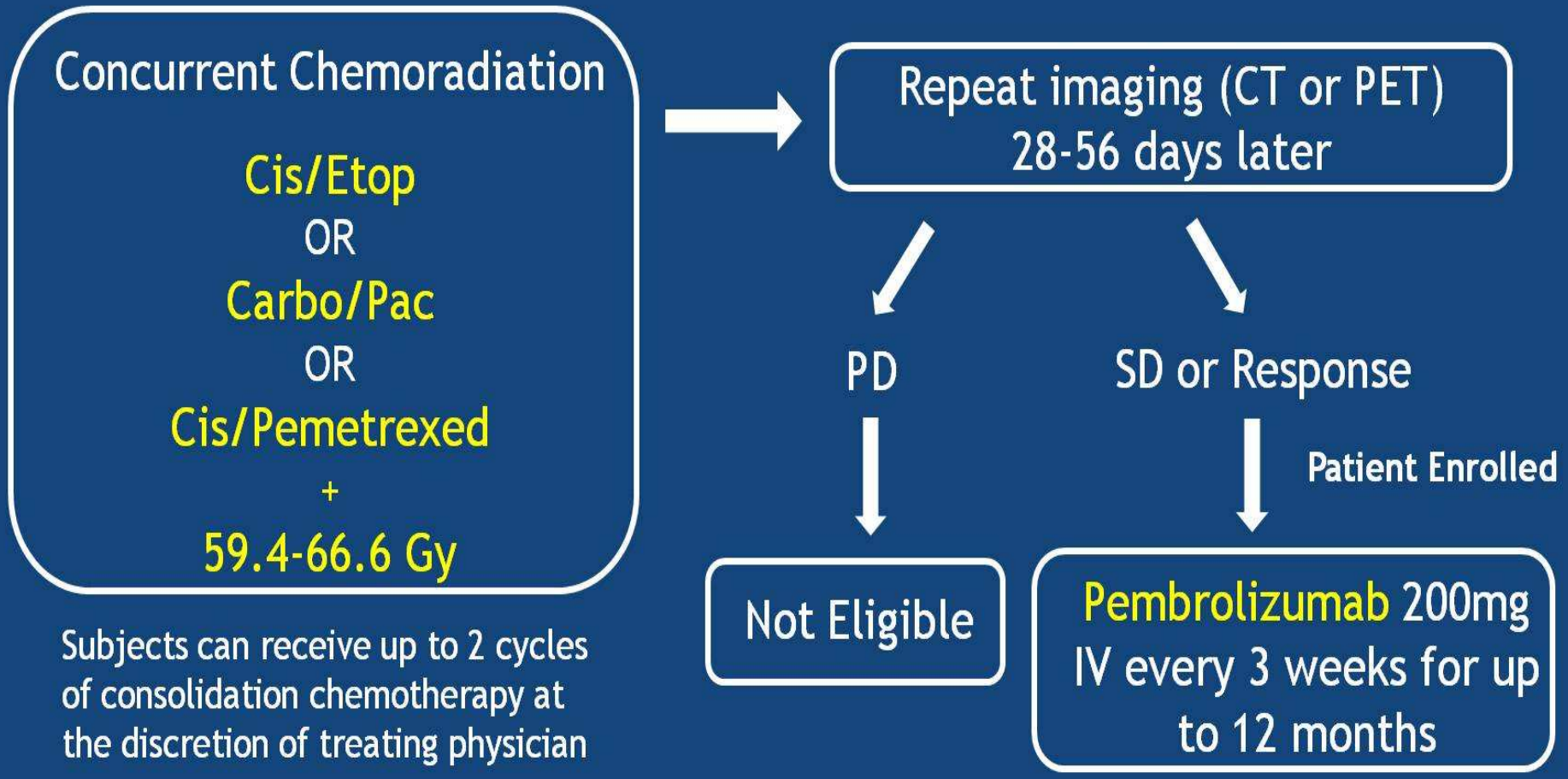
Phase II Trial of Concurrent Chemoradiation with Consolidation Pembrolizumab in Patients with Unresectable Stage III NSCLC

Hoosier Cancer Research Network LUN 14-179

Greg Durm[1], Sandra Althouse[2], Ahad Sadiq[3], Shadia Jalal[1], Salma Jabbour[4], Robin Zon[5], Goetz Kloecker[6], William Fisher[7], Karen Reckamp[8], Ebenezer Kio[9], Robert Langdon[10], Bamidele Adesunloye[11], Ryan Gentzler[12], and Nasser Hanna[1]

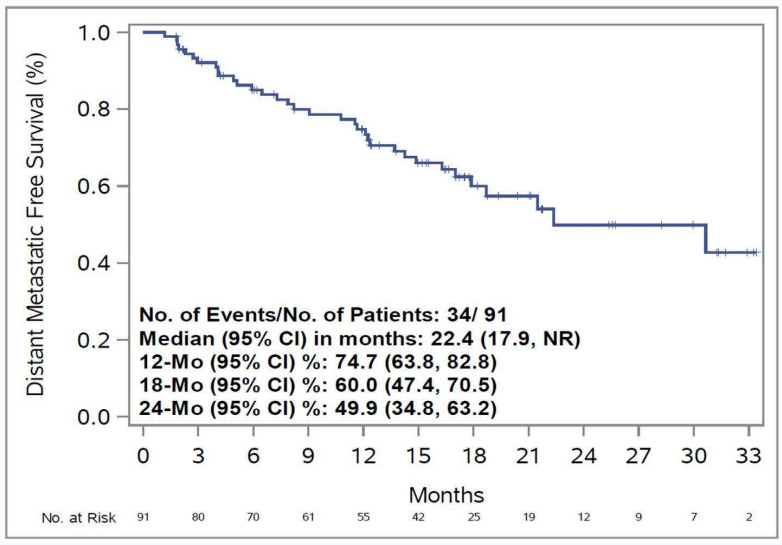
[1] Indiana University Simon Cancer Center, [2] Indiana University Department of Biostatistics, [3] Fort Wayne Medical Oncology and Hematology, [4] Rutgers Cancer Institute of New Jersey, [5] Michiana Hematology/Oncology, [6] University of Louisville James Graham Brown Cancer Center, [7] IU Health Ball Memorial Hospital, [8] City of Hope Comprehensive Cancer Center, [9] Goshen Center for Cancer Care, [10] Nebraska Methodist Hospital, [11] IU Health Arnett Cancer Center, [12] University of Virginia Cancer Health System

Consolidation Pembrolizumab Following CCRT for Unresectable Stage III NSCLC: LUN 14-179

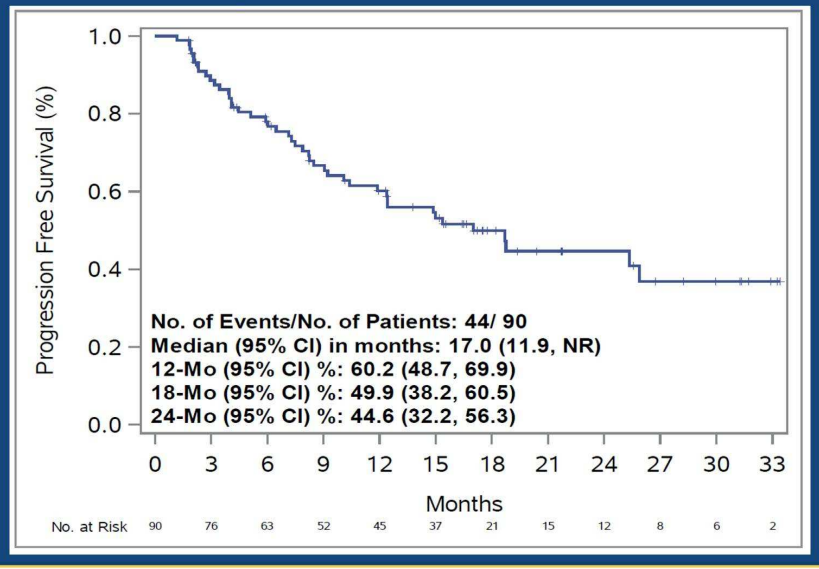


Subjects can receive up to 2 cycles of consolidation chemotherapy at the discretion of treating physician

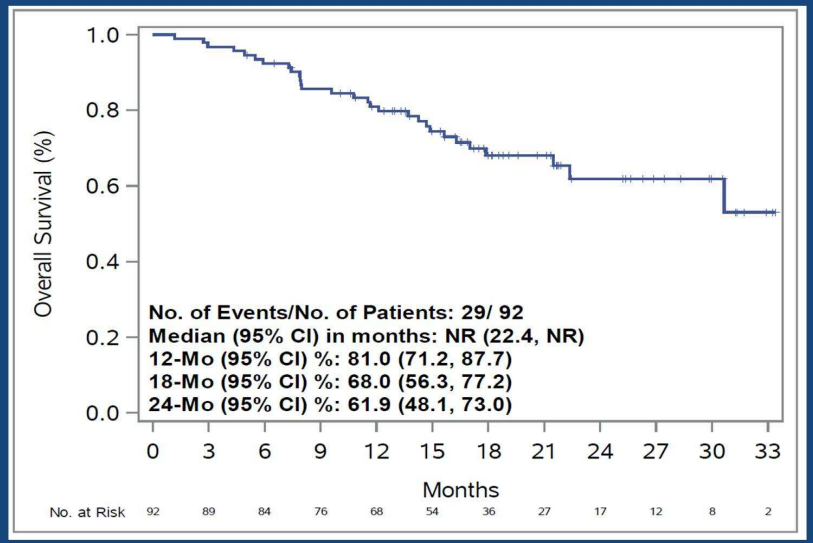
Time to Metastatic Disease or Death



Progression Free Survival



Overall Survival



Conclusions

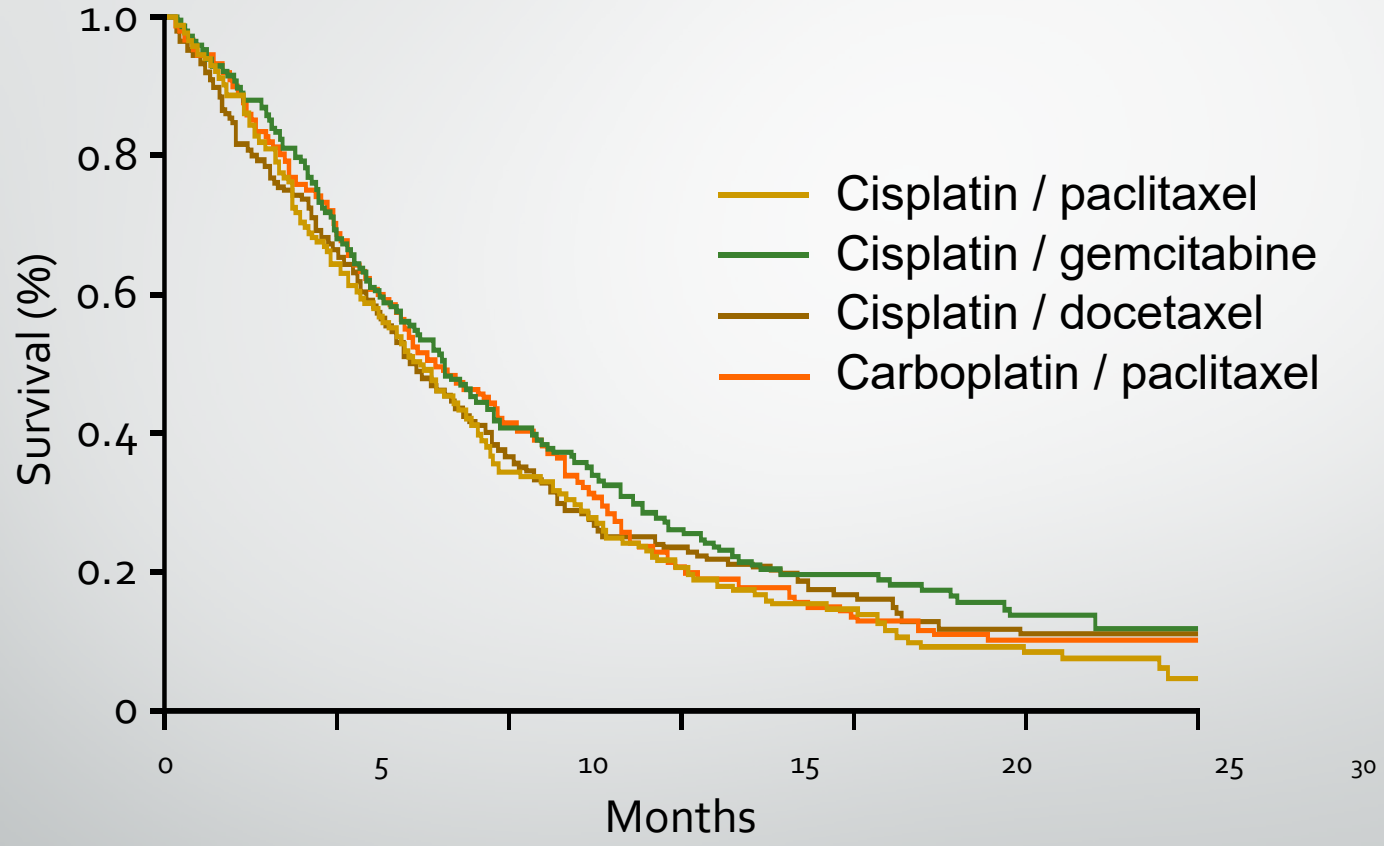
- This trial confirms that consolidation Pembrolizumab following CCRT in stage III NSCLC is feasible and safe in the majority of patients
- Consolidation Pembrolizumab following CCRT substantially improves TMDD and PFS compared to historical control
- Preliminary OS data is promising and suggests a major improvement in survival for this patient population

Stage III conclusions

- Consolidation immunotherapy after definitive radiochemotherapy in stage III NSCLC showed positive results both in PFS and OS
- First drug durvalumab is registered in this indication
- Other immunotherapeutics are evaluated in this setting
- There are ongoing trials in sequential radiochemotherapy

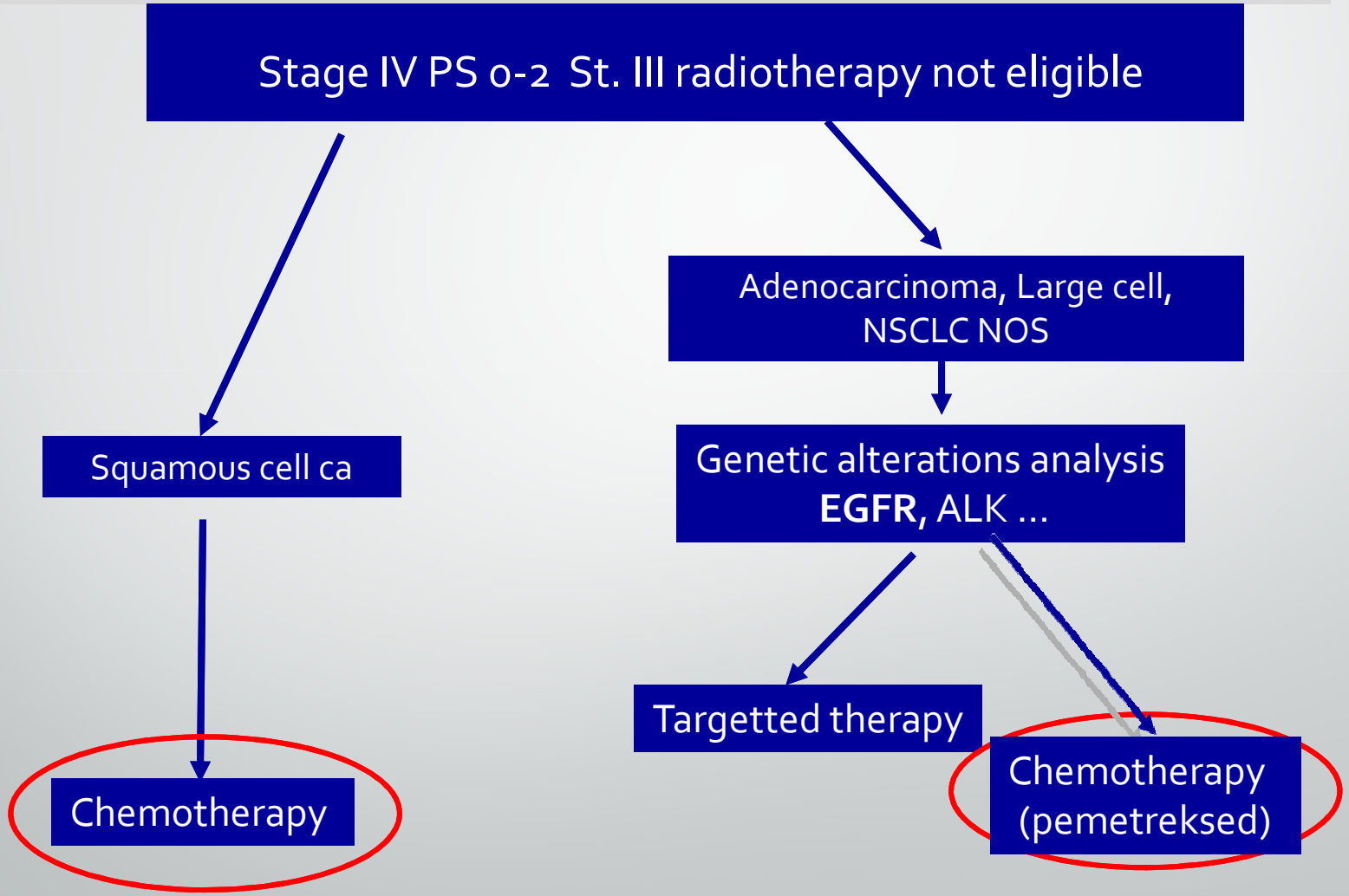
Non small cell lung cancer stage III C and IV

E1594: chemotherapy plateau in advanced NSCLC



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

Advanced NSCLC algorithm before immunotherapy



Non small cell lung cancer stage IV first line monotherapy

COPENHAGEN 2016 ESMO congress

KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%

Martin Reck,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Melanie A. Leiby,[14] Gregory M. Lubiniecki,[14] Yue Shentu,[14] Reshma Rangwala,[14] and Julie R. Brahmer[15] on behalf of the KEYNOTE-024 investigators

[1]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; [9]Southern Medical Day Care Centre, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, London, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

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IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

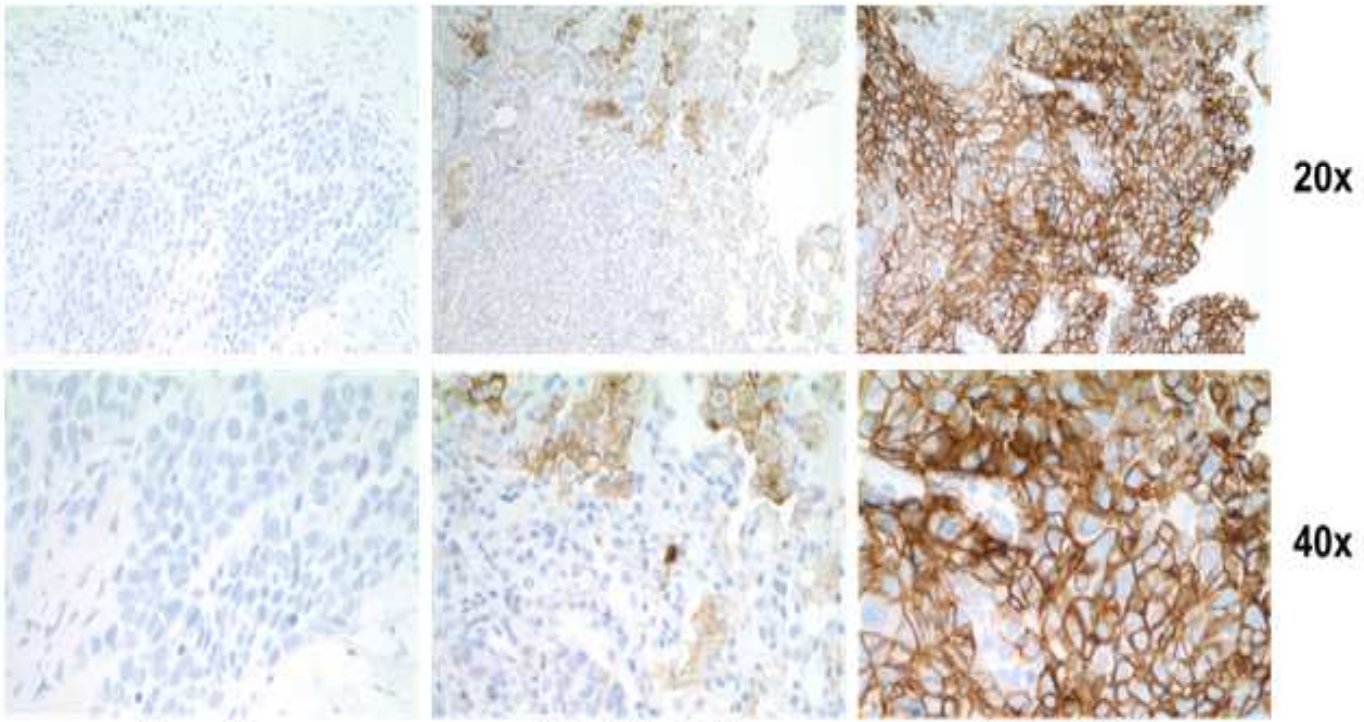
Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Antonio Riccio,[14] Jing Yang,[14] M. Catherine Pietanza,[14] Martin Reck[15]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; [9]Southern Medical Day Care Centre, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, Sutton, Surrey, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany.

IASLC 2017

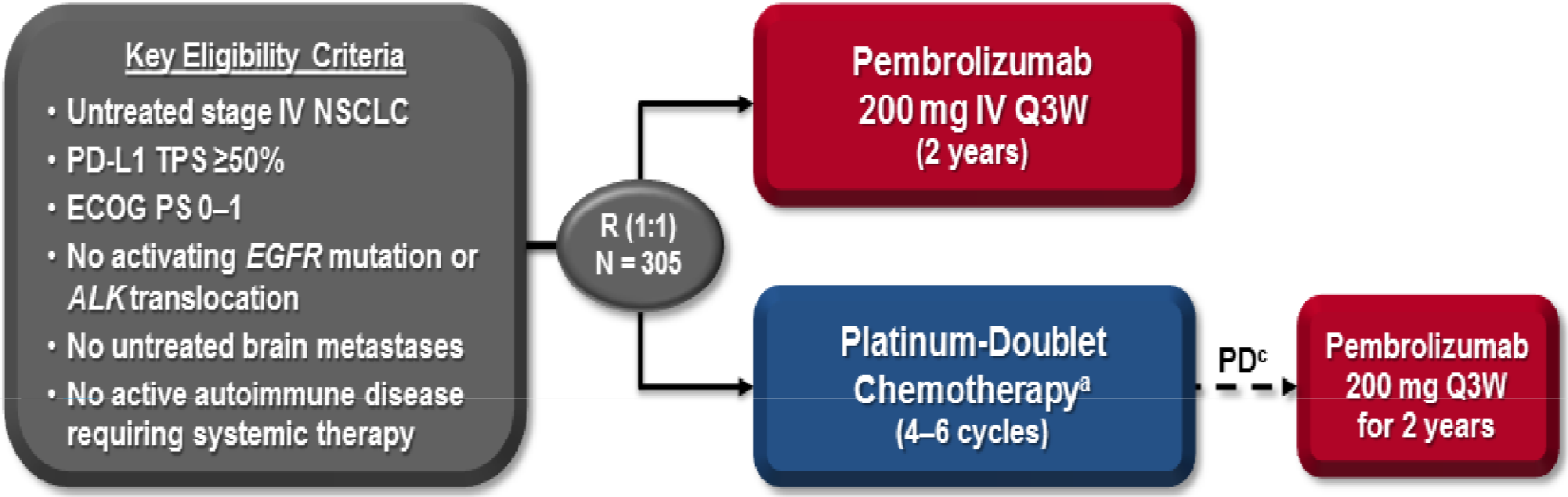
PD-L1 Expression and Pembrolizumab

- PD-L1 TPS cutpoint of 50% was identified in KEYNOTE-001 using independent training and validation sets[1]
- FDA-approved and CE-marked companion diagnostic: PD-L1 IHC 22C3 pharmDx (Dako)



1. Garon EB et al. *N Engl J Med.* 2015;372:2018-2028.
PD-L1 staining images from Herbst RS et al. *J Clin Oncol*, 2016;34(15_suppl): abstr 3030.

KEYNOTE-024 Study Design (NCT02142738)



End Points

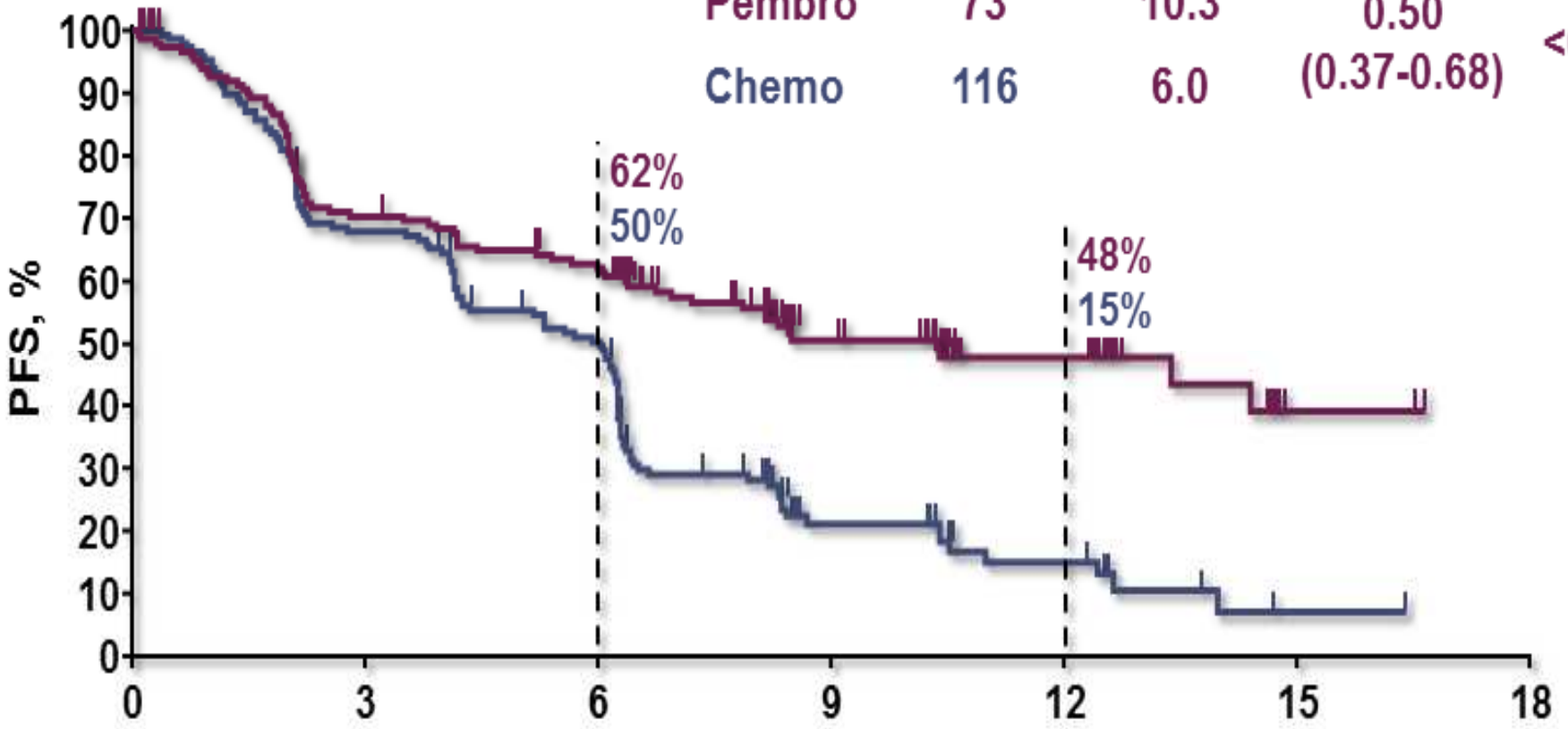
Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

[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.

M Reck. ESMO 2016.

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		

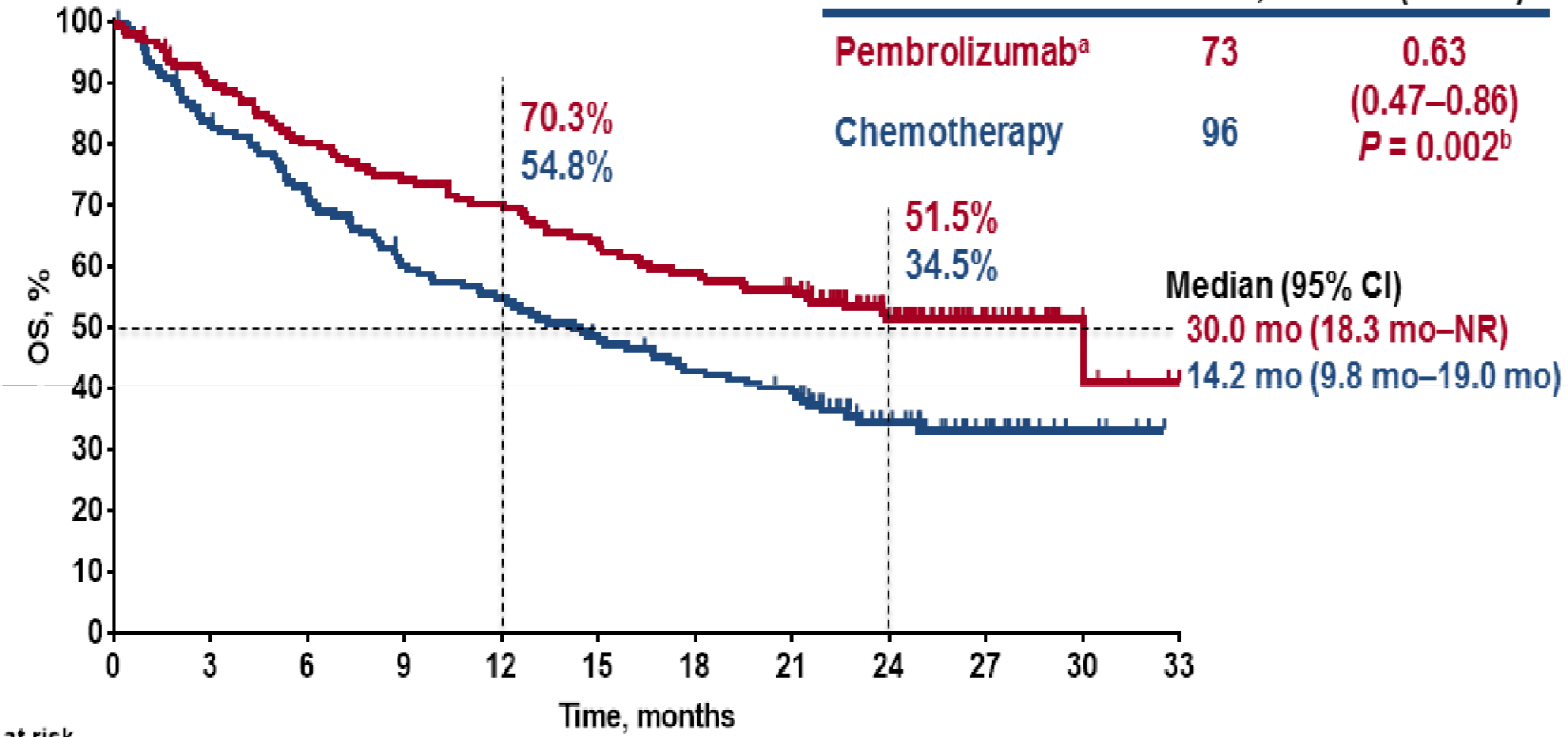


No. at risk

154	104	89	44	22	3	1
151	99	70	18	9	1	0

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

Overall Survival: Updated Analysis



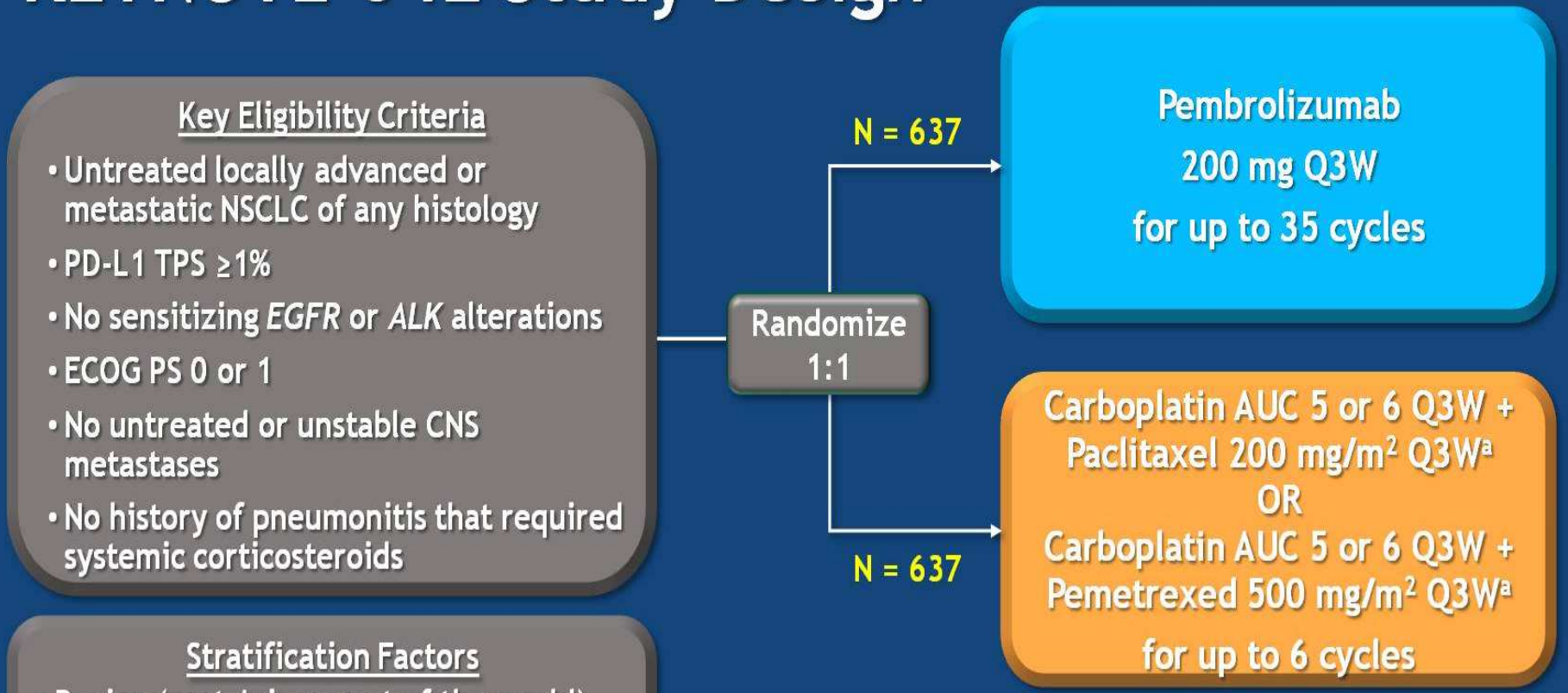
[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

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]

[1]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [2]Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guandong, China; [3]Riga East Clinical University - Latvian Oncology Center, Riga, Latvia; [4]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [5]Yonsei Cancer Center, Seoul, South Korea; [6]Instanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; [7]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [8]Siriraj Hospital, Bangkok, Thailand; [9]NN Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [11]Nippon Medical School Hospital, Tokyo, Japan; [12]Merck & Co., Inc., Kenilworth, NJ, USA; [13]The Chinese University of Hong Kong, Shatin, Hong Kong PRC

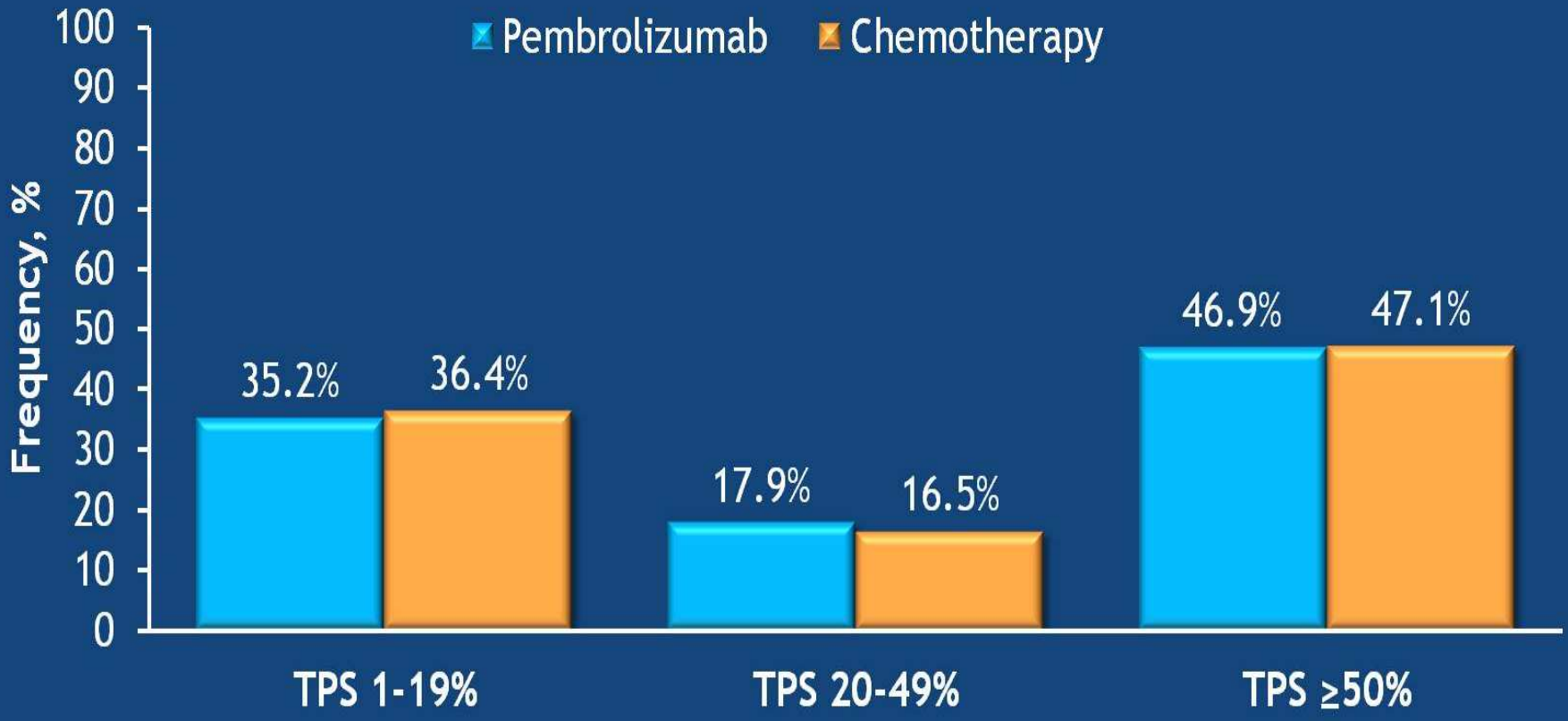
KEYNOTE-042 Study Design



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.

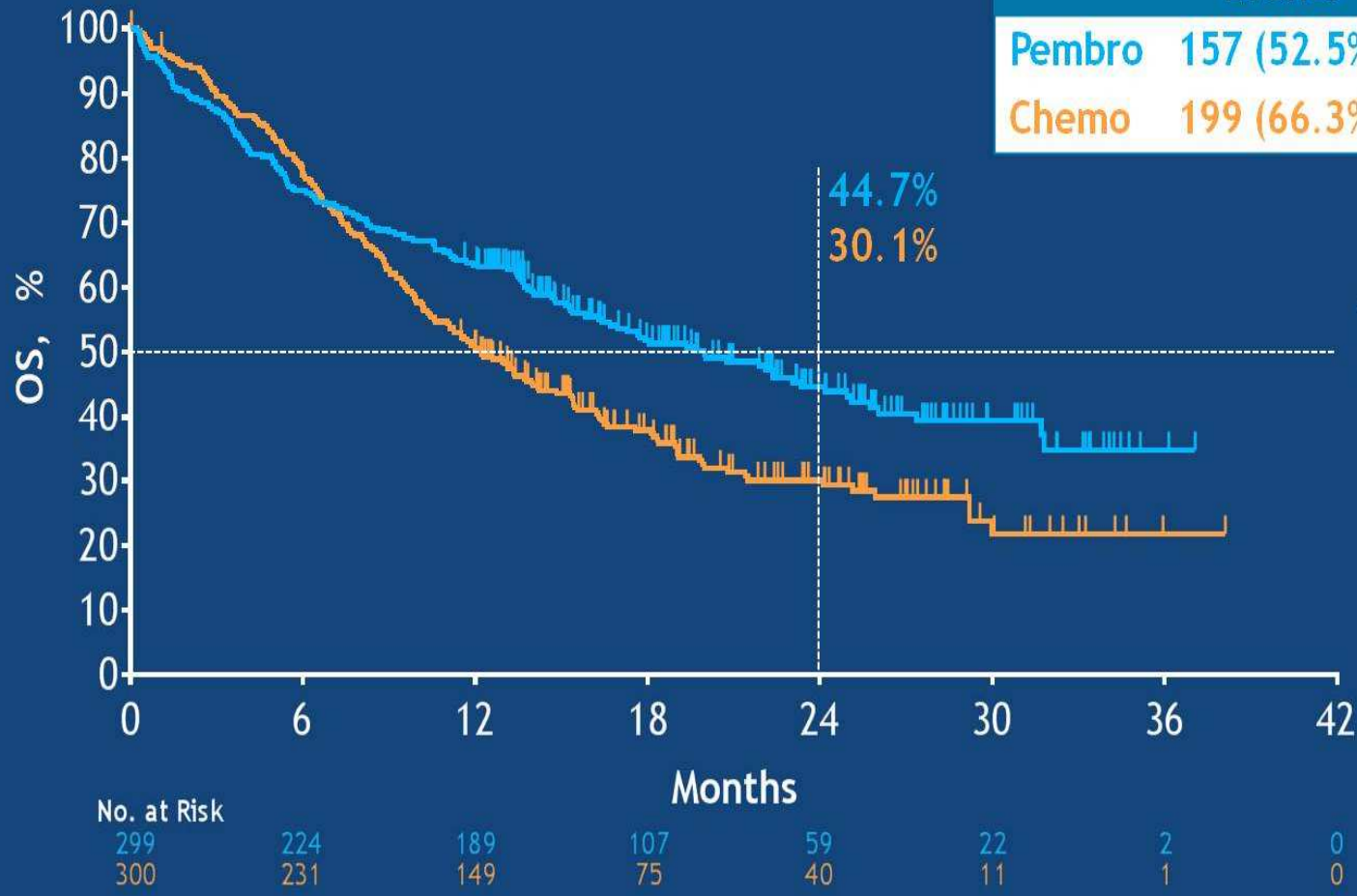
Frequency of PD-L1 TPS Categories: TPS ≥1% Population



Data cutoff date: Feb 26, 2018.

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%)		

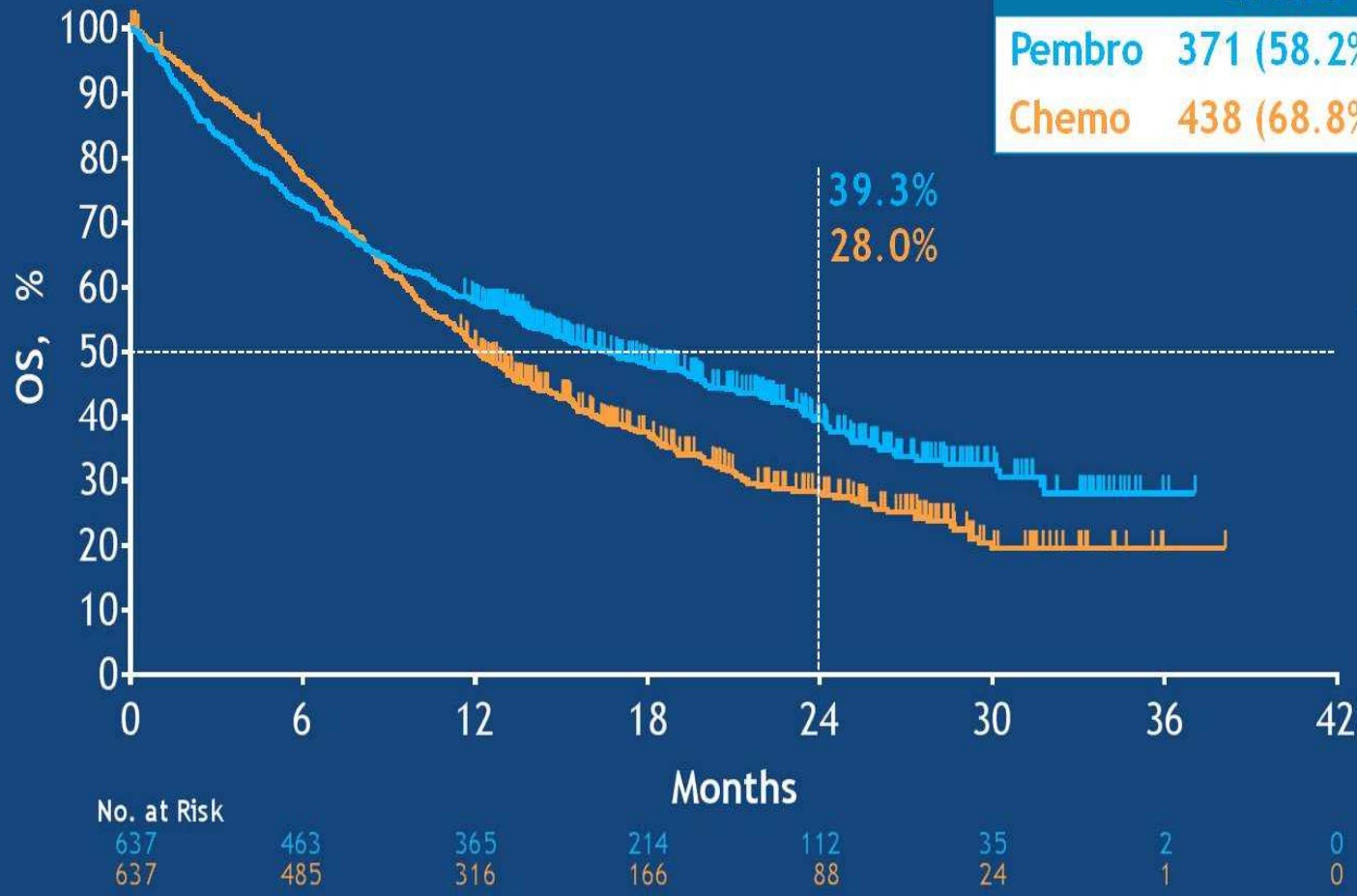


Median (95% CI)
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

Data cutoff date: Feb 26, 2018.

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%)		

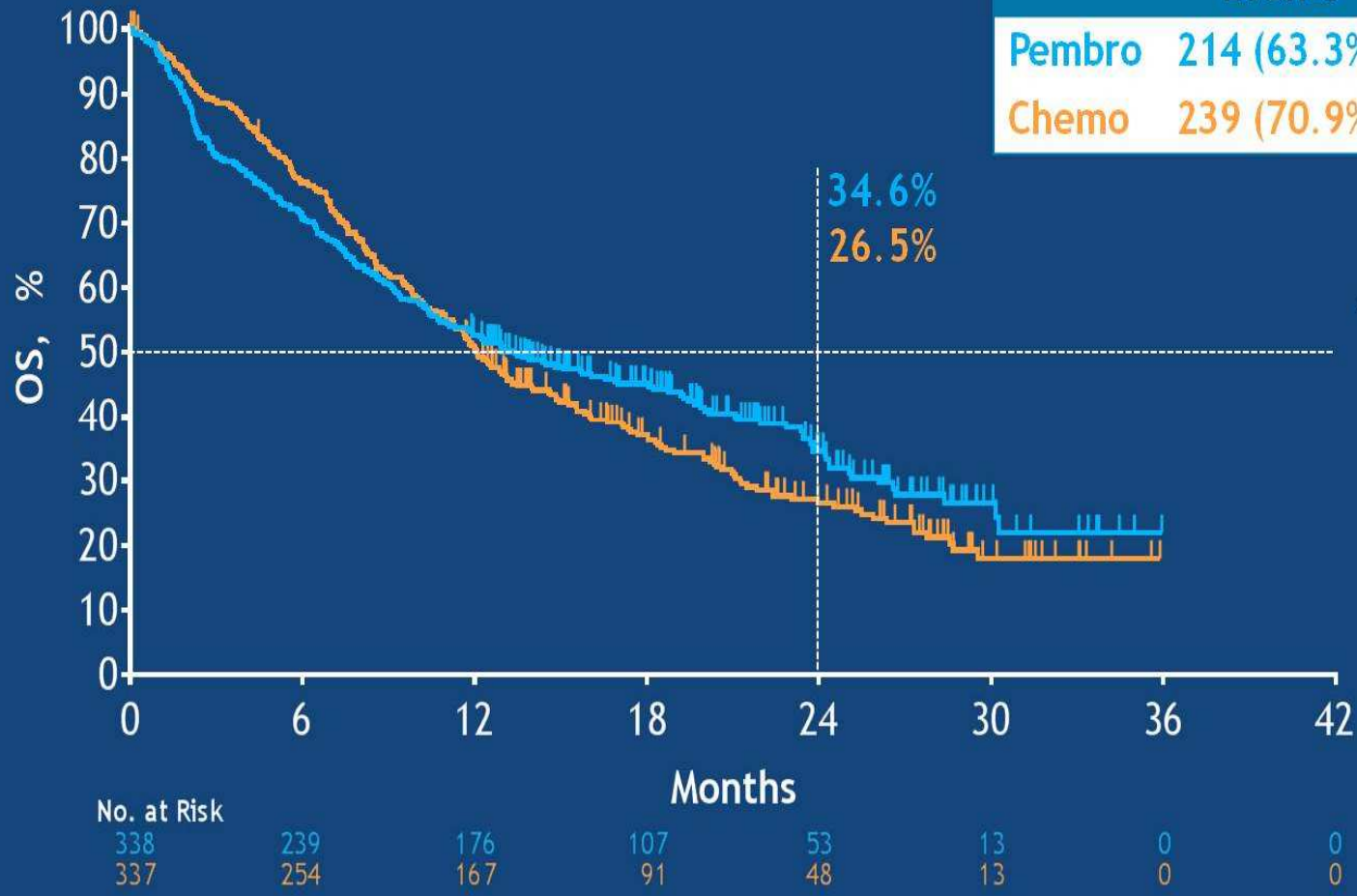


Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

Data cutoff date: Feb 26, 2018.

Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

	Events	HR (95% CI)
Pembro	214 (63.3%)	0.92 (0.77-1.11)
Chemo	239 (70.9%)	



Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

[a]No alpha allocated to this comparison.

Checkmate 026:
Phase III Nivolumab vs Chemotherapy in First-line NSCLC[1]

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
- ≥1% PD-L1[a]
- CNS metastases if treated prior to randomization, with return to baseline for at least 2 weeks prior to randomization

Stratification factors at randomization:
- PD-L1 expression (<5% vs ≥5%)[a]
- Histology (squamous vs nonsquamous)

R 1:1

Nivolumab
3 mg/kg IV Q2W
n=271

PT-DC
(Histology dependent)[b]
Maximum of 6 cycles
n=270

Disease progression or unacceptable toxicity

Tumor scans Q6W until wk 48 then Q12W

Disease Progression

Crossover nivolumab[c] (optional)

Primary Endpoint:
- PFS (≥5% PD-L1+)[d]

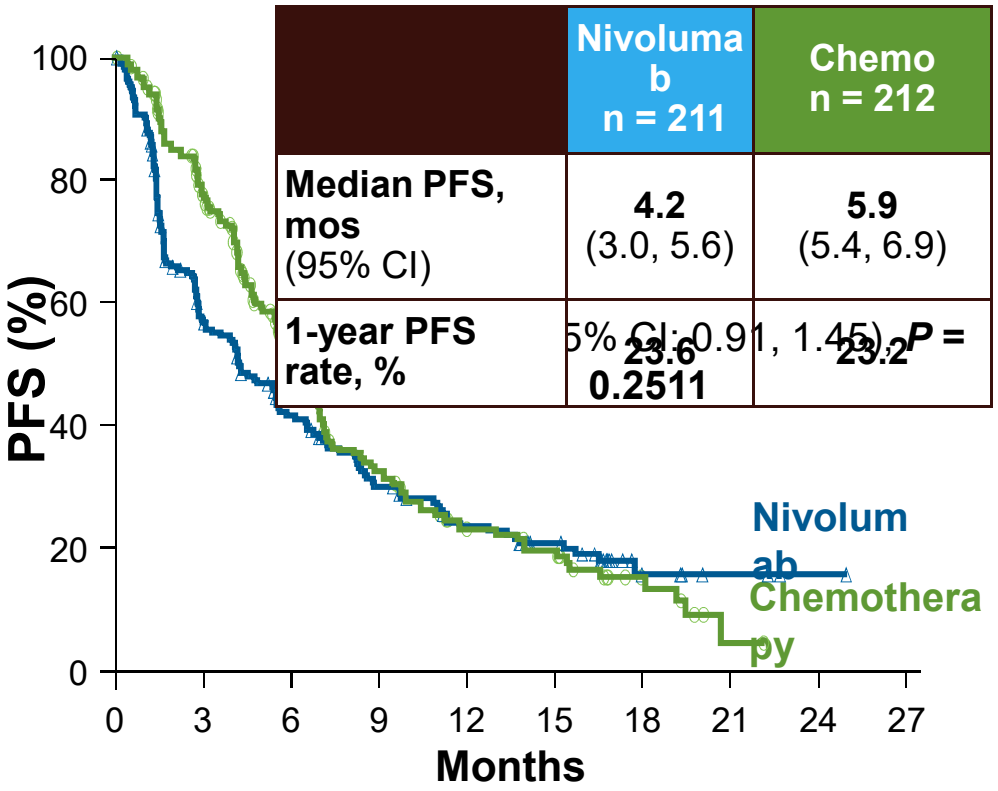
Secondary Endpoints:
- PFS (≥1% PD-L1+)[d]
- OS (≥1% PD-L1+ and ≥5% PD-
- ORR (≥5% PD-L1+)[d]

Nivolumab is currently not approved for 1L advanced/metastatic NSCLC.

[a]Dako 28-8 validated; archival samples obtained ≤6 months before enrollment were permitted. [b]Squamous: Gemcitabine 1250 mg/m² + cisplatin 75 mg/m²; Gemcitabine 1000 mg/m² + carboplatin AUC 5; Paclitaxel 200 mg/m² + carboplatin AUC 6. Non-squamous: Pemetrexed 500 mg/m² + cisplatin 75 mg/m²; Pemetrexed 500 mg/m² + carboplatin AUC 6--option for pemetrexed maintenance therapy. [c]No washout required before crossover. [d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review.

1. Socinski M et al. Oral presentation at ESMO 2016. 2. Hellmann MD et al. Oral presentation at ASCO 2016. 3001.

Checkmate 026: PFS and OS (≥5% PD-L1+)



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

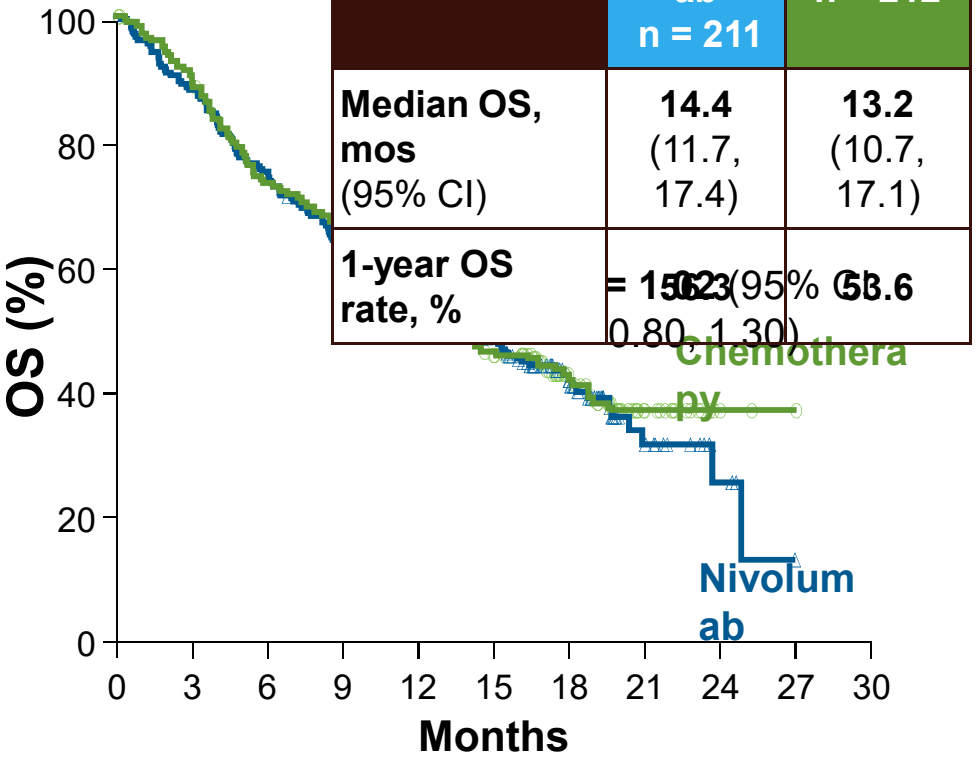
5% CI: 0.91, 1.45), ***P* = 0.2511**

No. of patients at risk:

Nivo	211	104	71	49	35	24	6	3	1	0
Chemo	212	144	74	47	28	21	8	1	0	0

All randomized patients (≥1% PD-L1+)

HR = 1.17 (95% CI: 0.95, 1.43)



	Nivolumab n = 211	Chemo n = 212
Median OS, mos (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.2**	**53.6**

= 1562(95% C
0.80, 1.30)

No. of patients at risk:

Nivo	211	186	156	133	118	98	49	14	4	0	0
Chemo	212	186	153	137	112	91	50	15	3	1	0

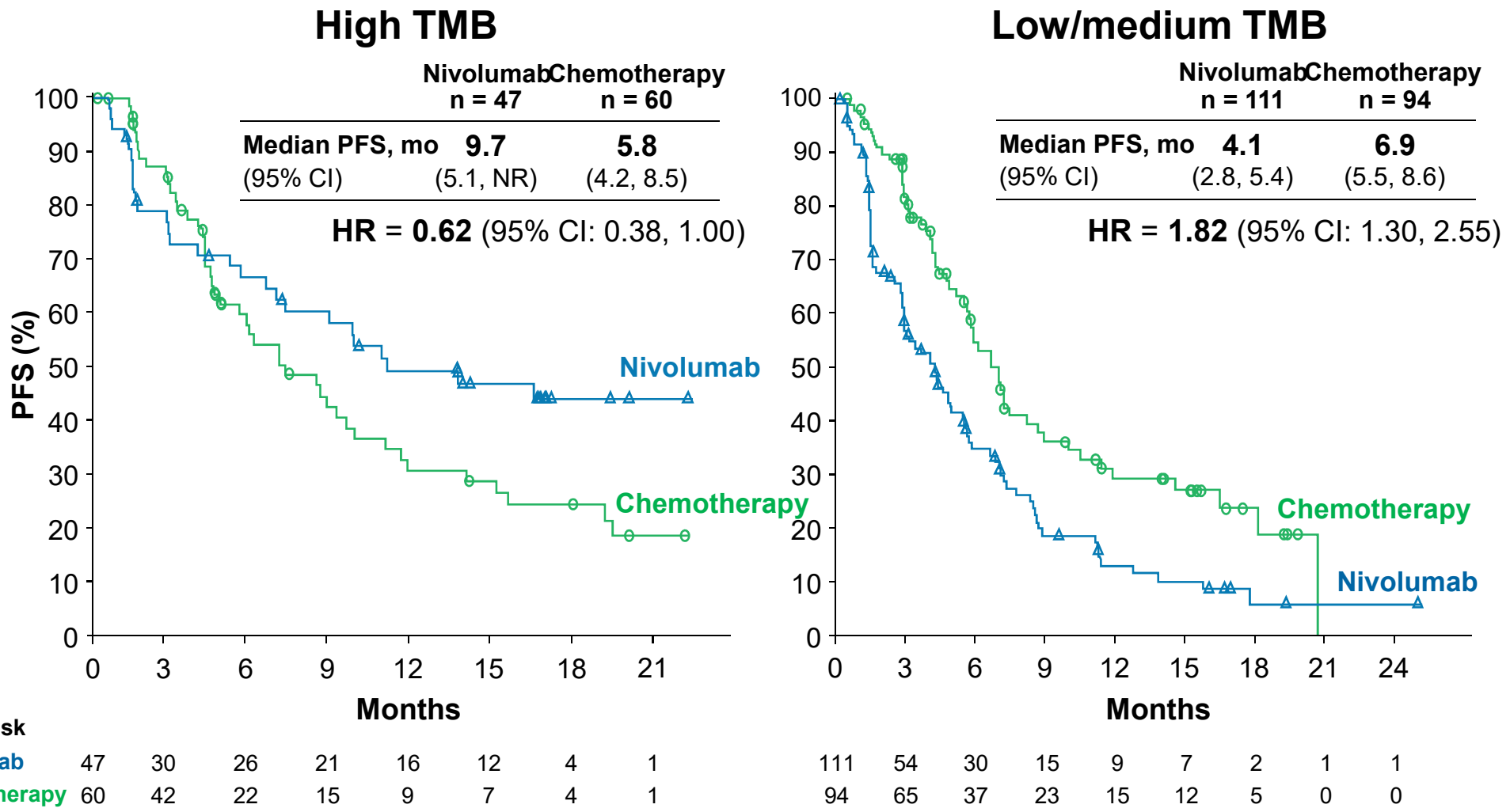
All randomized patients (≥1% PD-L1+)

HR = 1.07 (95% CI: 0.86, 1.33)

CI=confidence interval; HR=hazard ratio; mos=months; OS=overall survival; PFS=progression-free survival; PD-L1=programmed death ligand 1.

Socinski M et al. Oral presentation at ESMO 2016.

Tumor Mutation Burden As a Predictive Biomarker for Nivolumab in NSCLC: CheckMate 026



Non small cell lung cancer stage IV first line combination therapy

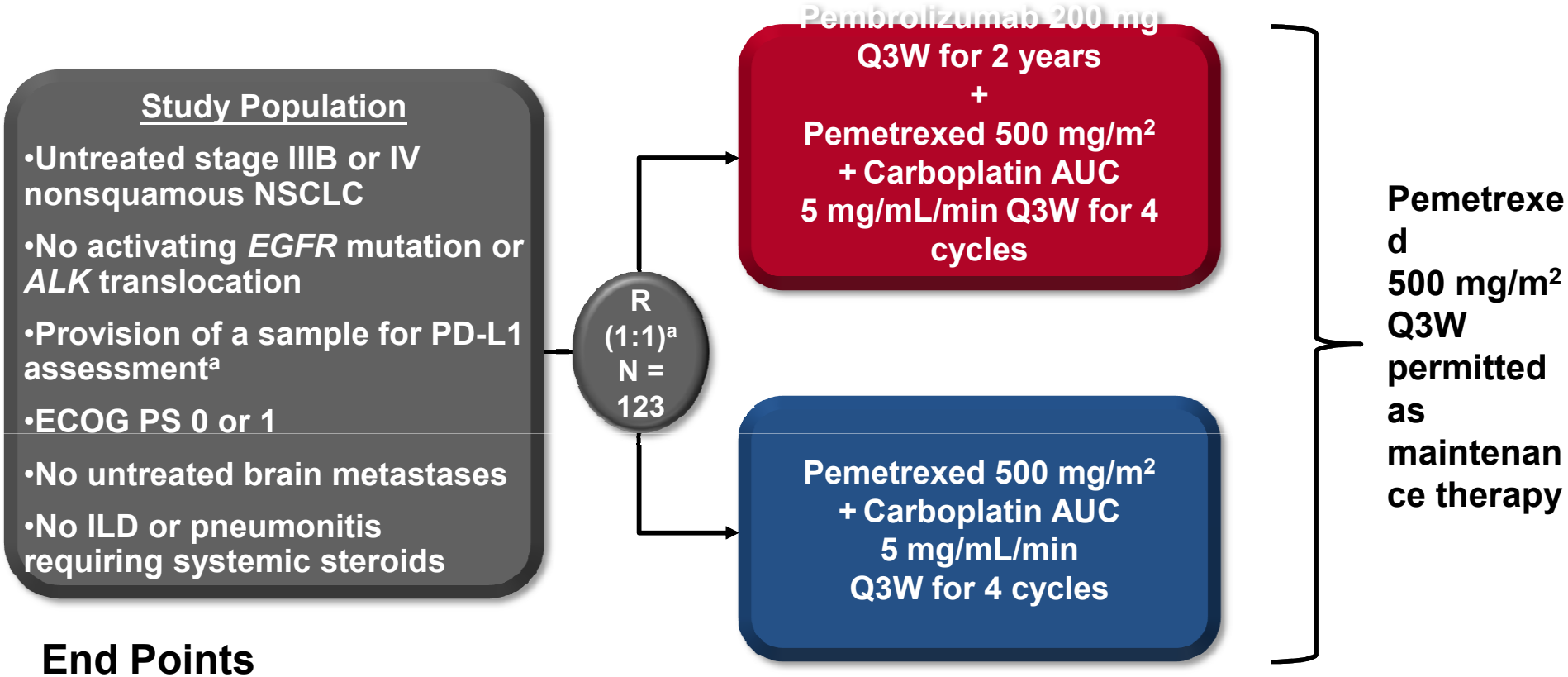
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Pemetrexed-Carboplatin plus Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC: KEYNOTE-021 Cohort G Update

Hossein Borghaei,[1] Corey J. Langer,[2] Shirish Gadgeel,[3] Vassiliki A. Papadimitrakopoulou,[4] Amita Patnaik,[5] Steven F. Powell,[6] Ryan D. Gentzler,[7] Renato G. Martins,[8] James P. Stevenson,[9] Shadia I. Jalal,[10] Amit Panwalkar,[11] James Chih-Hsin Yang,[12] Matthew Gubens,[13] Lecia V. Sequist,[14] Mark M. Awad,[15] Joseph Fiore,[16] Sanatan Saraf,[16] Harry Raftopoulos,[16*] Leena Gandhi[15]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; [6]Sanford Health, Sioux Falls, SD, USA; [7]University of Virginia, Charlottesville, VA, USA; [8]Seattle Cancer Care Alliance, Seattle, WA, USA; [9]Cleveland Clinic, Cleveland, OH, USA; [10]Indiana University School of Medicine, Indianapolis, IN, USA; [11]Sanford Roger Maris Cancer Center, Fargo, ND, USA; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]University of California San Francisco, San Francisco, CA, USA; [14]Massachusetts General Hospital, Boston, MA, USA; [15]Dana-Farber

KEYNOTE-021 Cohort G

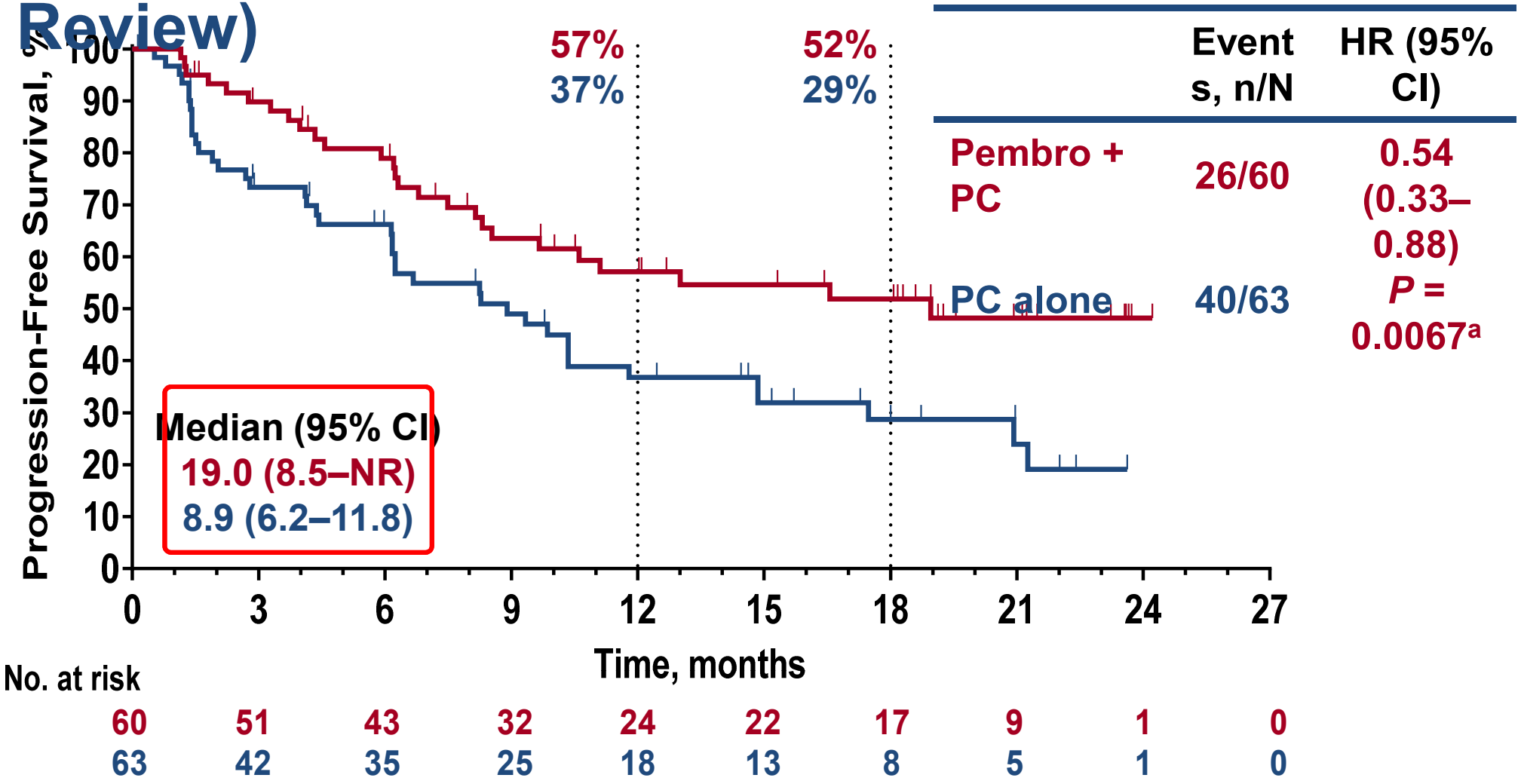


End Points

- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all *P* values are nominal (one-sided $P < 0.025$)

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

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

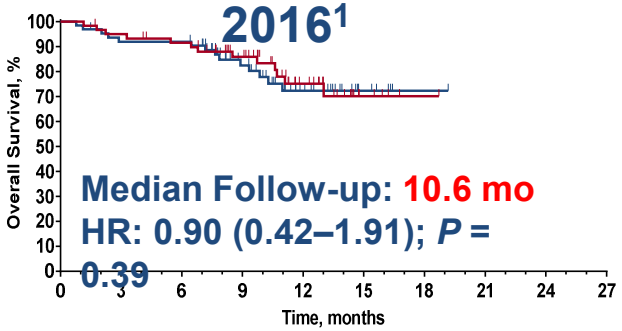


	Events, n/N	HR (95% CI)
Pembro + PC	26/60	0.54 (0.33–0.88)
PC alone	40/63	*P* = 0.0067[a]

[a]P value is descriptive (one-sided P < 0.025).
Data cut-off: May 31, 2017.

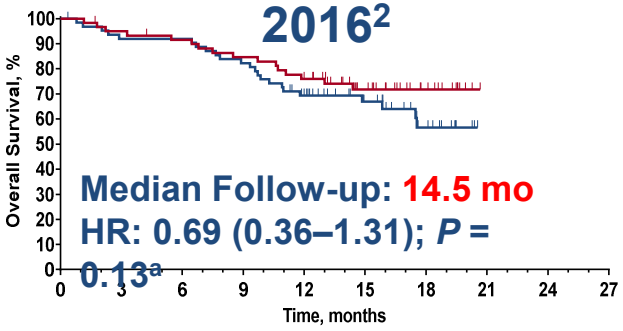
Overall Survival

Data Cut-off: August 8, 2016[1]



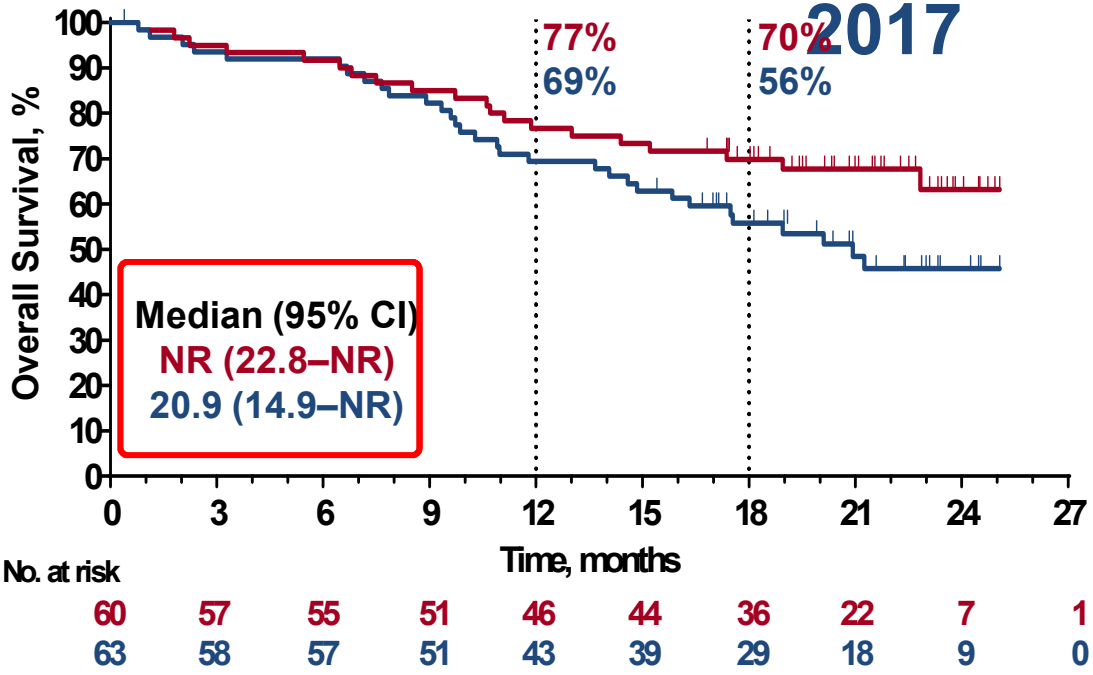
Median Follow-up: 10.6 mo
HR: 0.90 (0.42–1.91); *P* = 0.39

Data Cut-off: December 31, 2016[2]



Median Follow-up: 14.5 mo
HR: 0.69 (0.36–1.31); *P* = 0.13[a]

Data Cut-off: May 31, 2017



Median Follow-Up: 18.7 mo

	Events, n/N	HR (95% CI)
Pembro + PC	20/60[b]	0.59 (0.34–1.05)
PC alone	31/63[b]	*P* = 0.03[a]

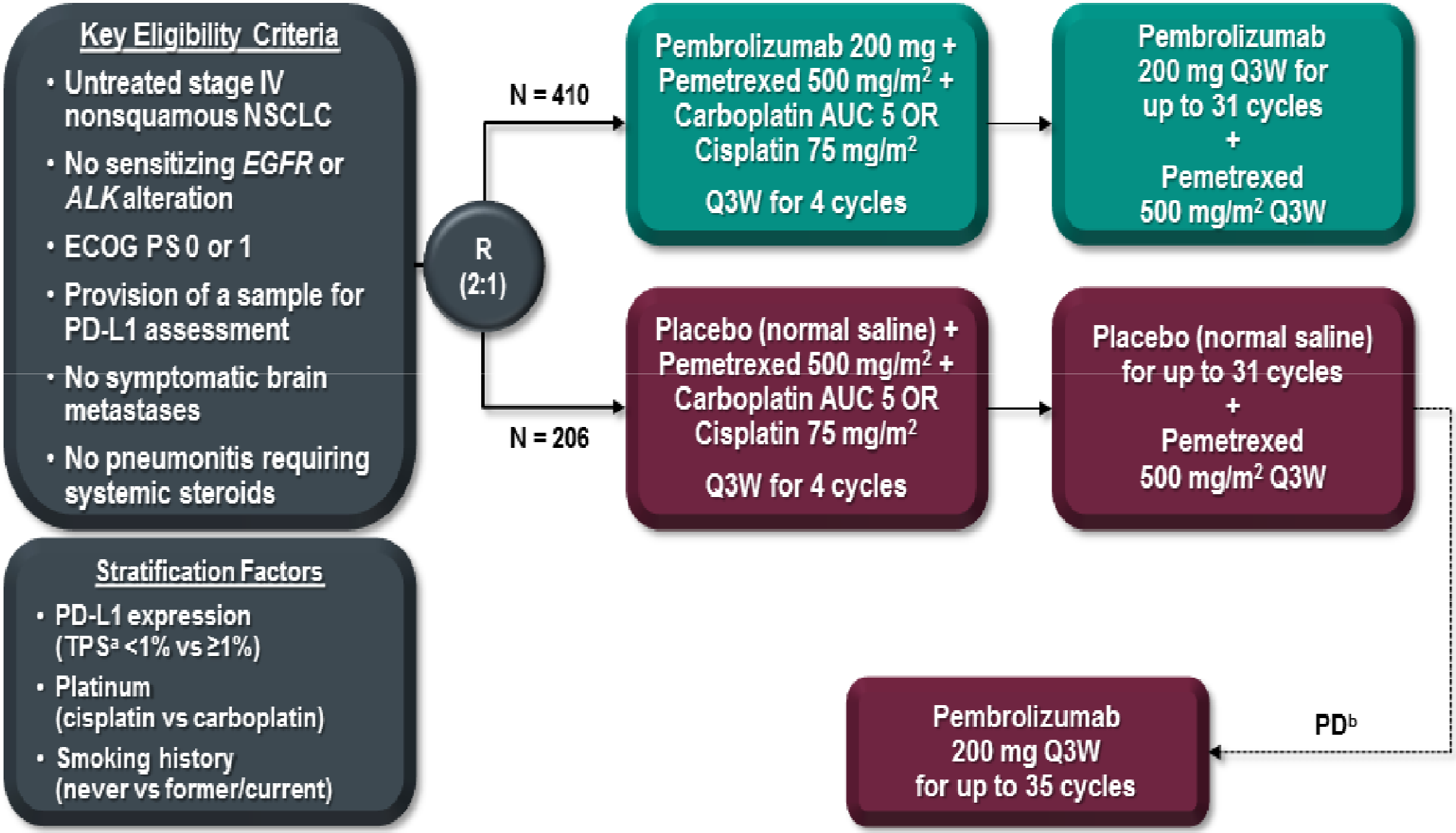
1. Langer CJ, et al. Lancet Oncol. 2016;17(11):1497-1508. 2. Papadimitrakopoulou VA, et al. 2017. J Clin Oncol. 35(suppl): abstract 9094.

KEYNOTE-189: Randomized, Double-Blind, Phase 3 Study of Pembrolizumab or Placebo plus Pemetrexed and Platinum as First-Line Therapy for Metastatic NSCLC

Leena Gandhi, Delvys Rodríguez-Abreu, Shirish Gadgeel, Emilio Esteban, Enriqueta Felip, Flávia De Angelis, Manuel Domine, Philip Clingan, Maximilian J. Hochmair, Steven Powell, Susanna Yee-Shan Cheng, Helge G. Bischoff, Nir Peled, Francesco Grossi, Ross R. Jennens, Martin Reck, Rina Hui, Edward B. Garon, Michael Boyer, Belén Rubio-Viqueira, Silvia Novello, Takayasu Kurata, Jhanelle E. Gray, John Vida, Ziwen Wei, Jing Yang, Harry Raftopoulos, M. Catherine Pietanza, Marina C. Garassino

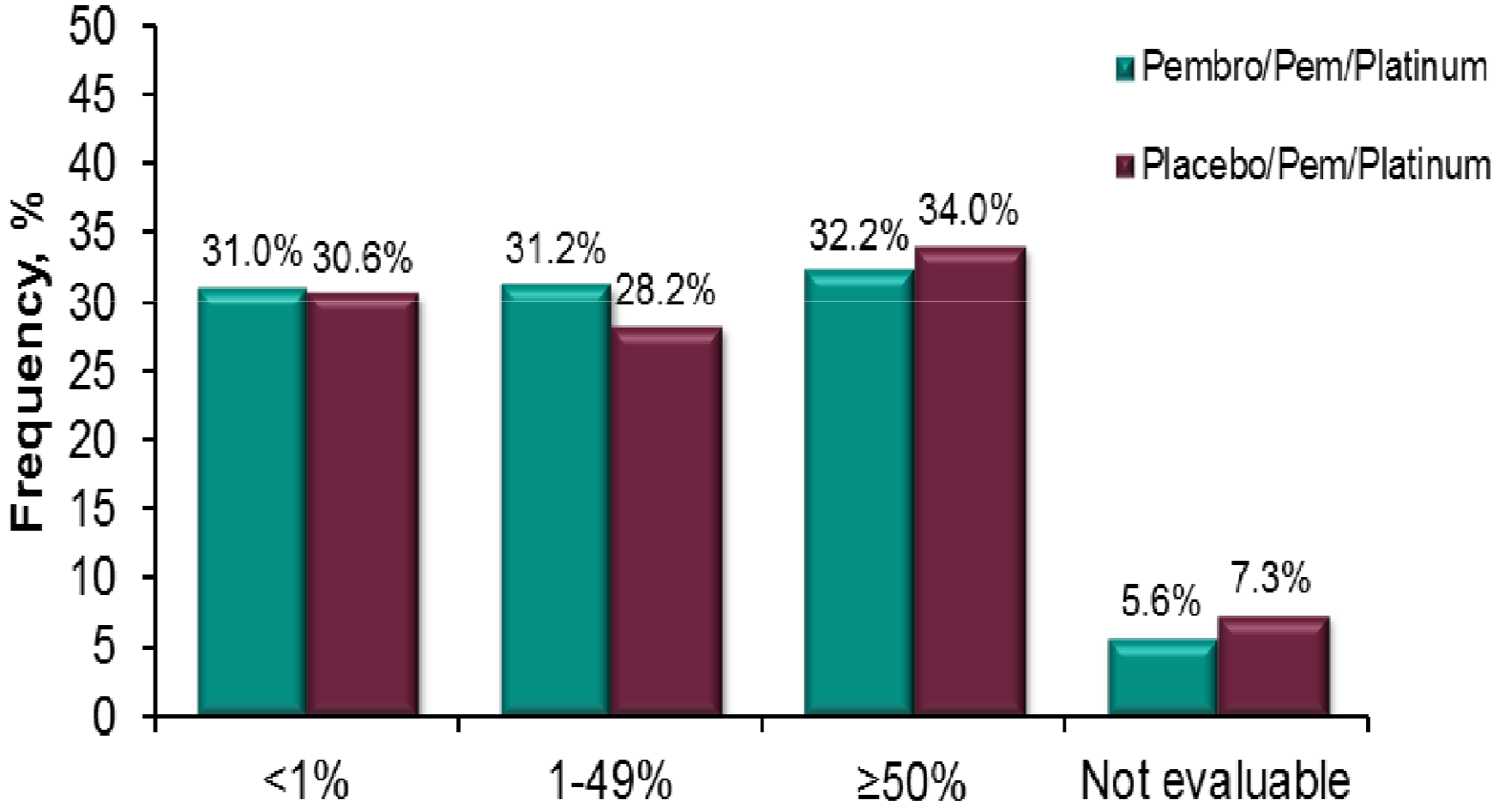
Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)



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

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: Nov 8, 2017.

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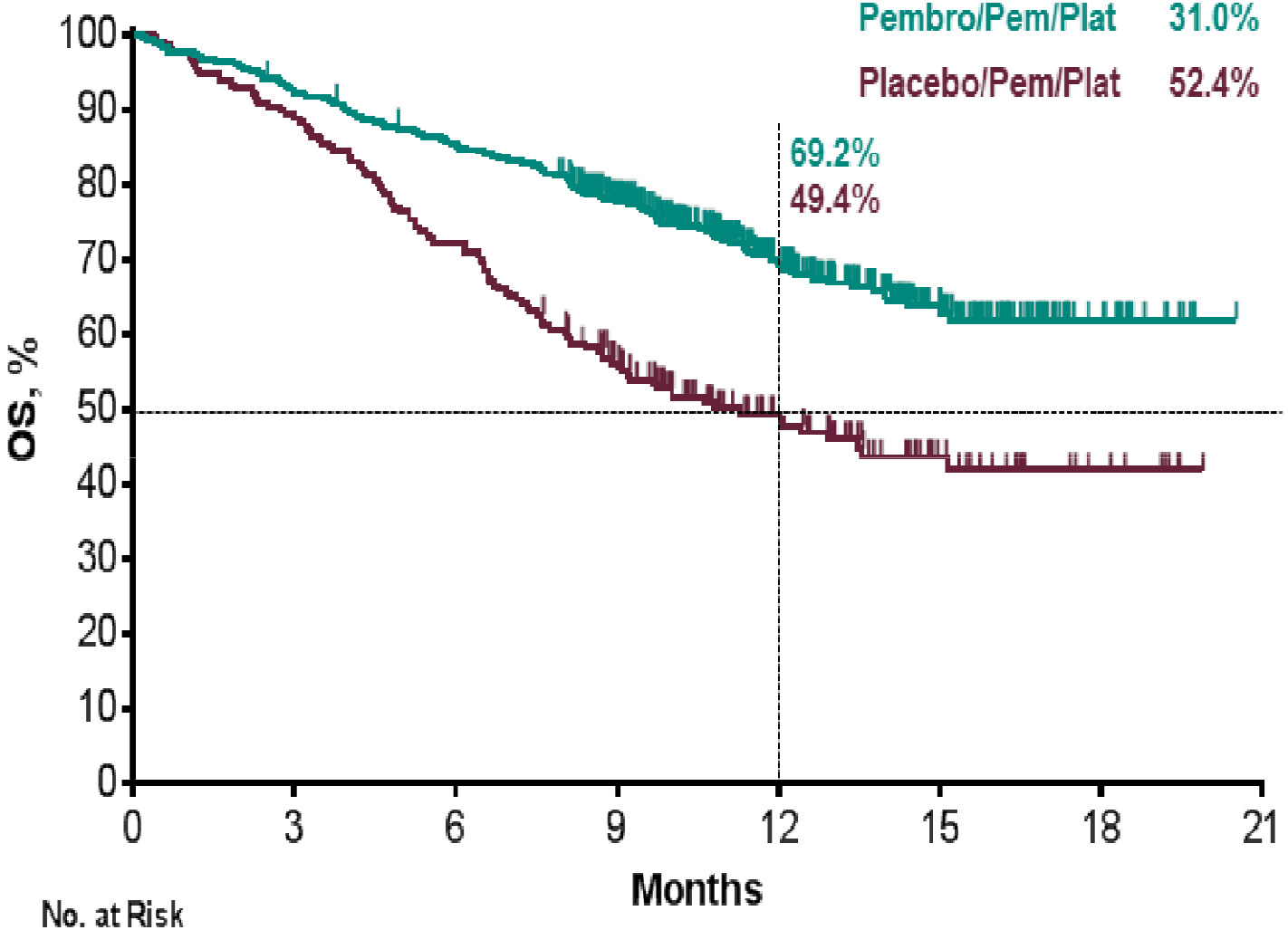
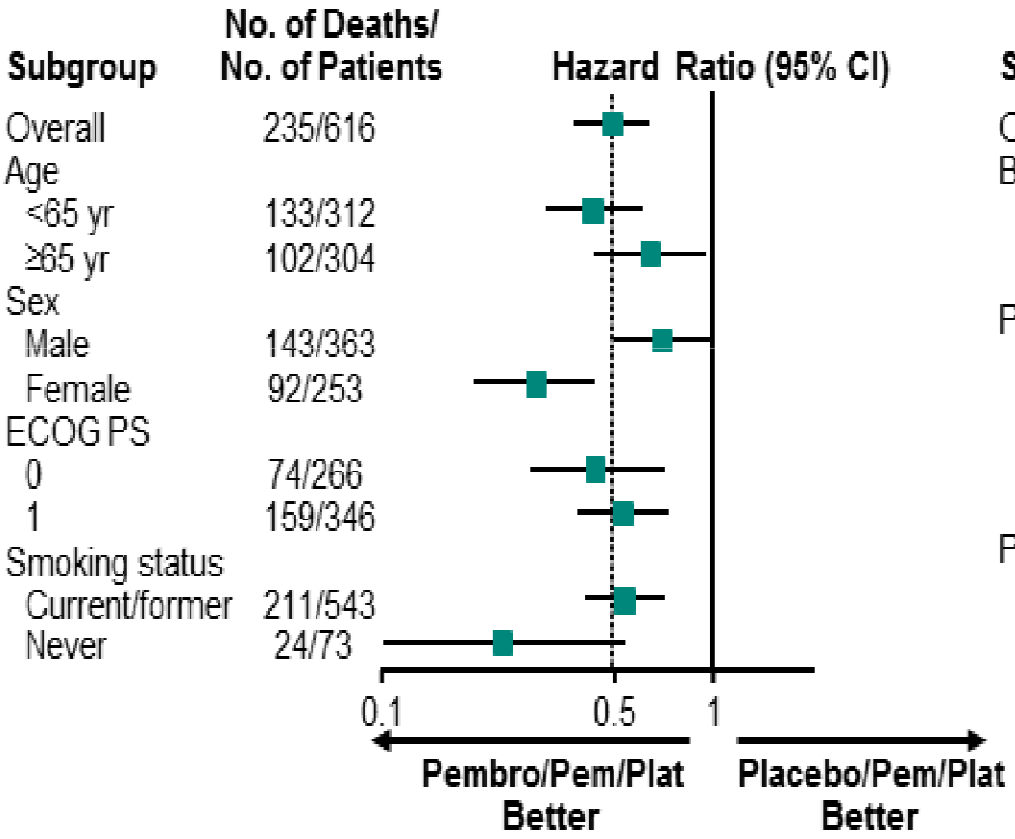
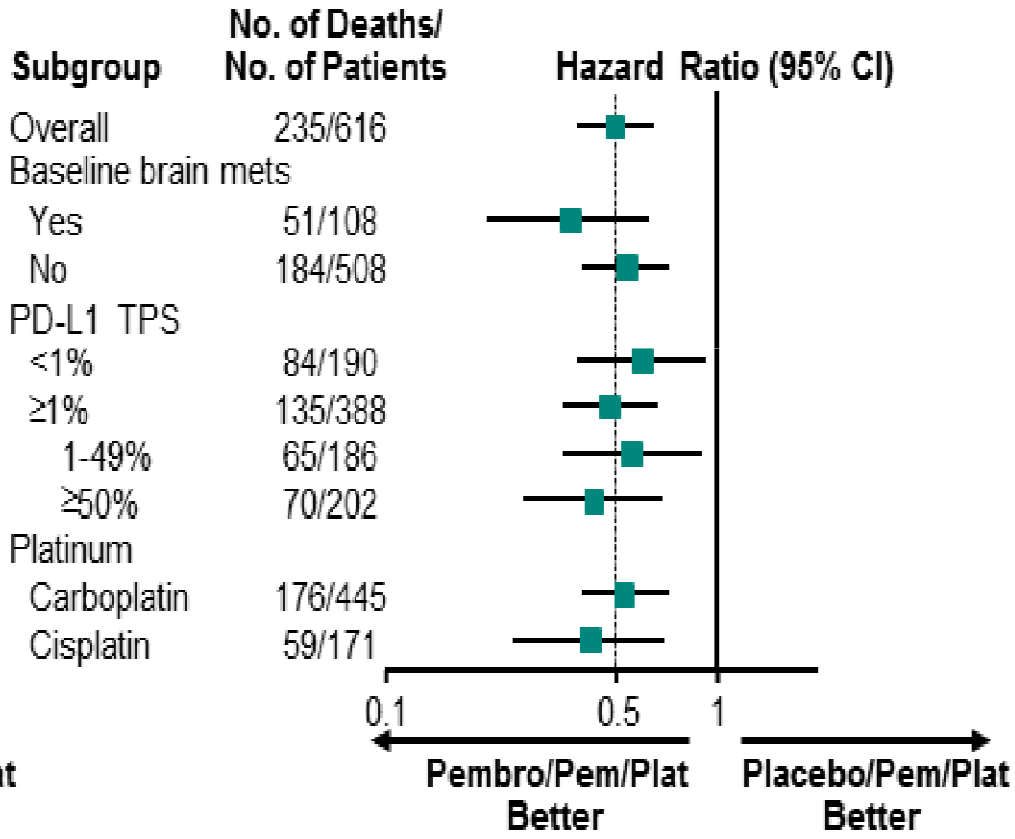
Overall Survival, ITT



Data cutoff date: Nov 8, 2017.

Overall Survival in Key Subgroups



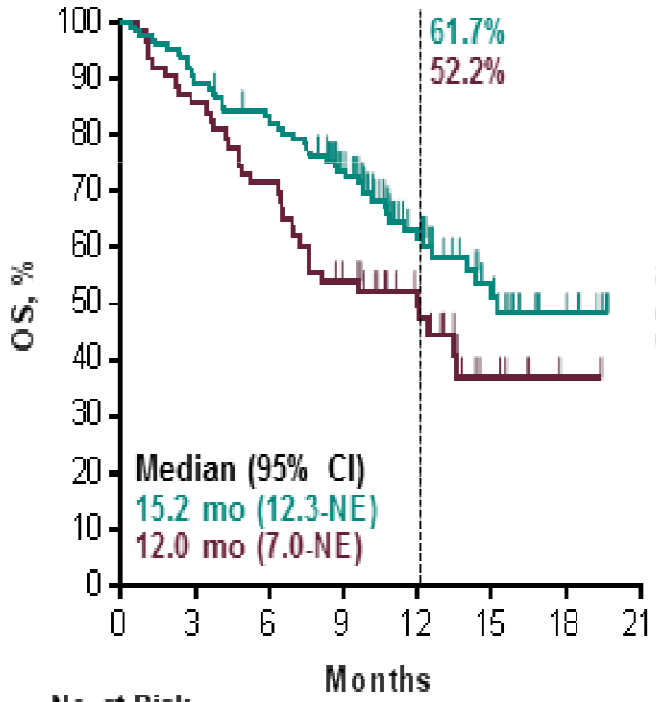


Data cutoff date: Nov 8, 2017.

Overall Survival by PD-L1 TPS

TPS <1%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	38.6%	0.59 (0.38-0.92)	0.0095
Placebo/Pem/Plat	55.6%		

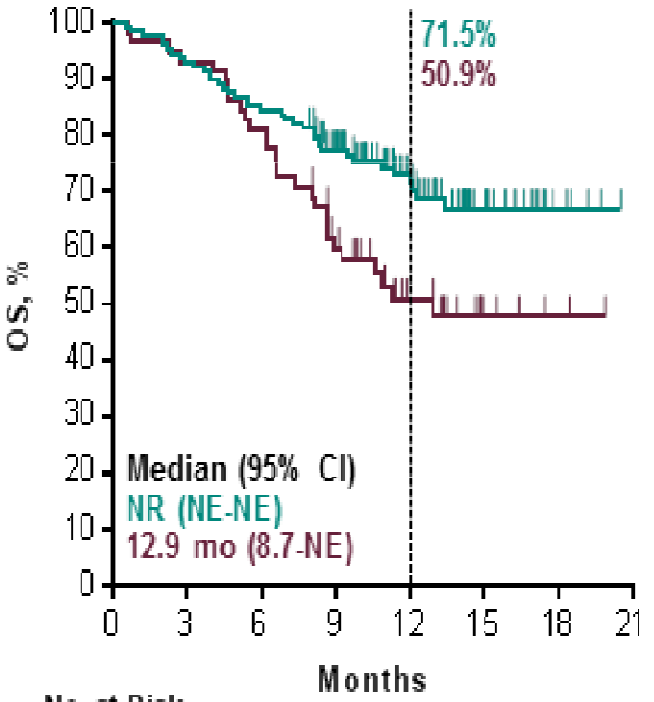


No. at Risk

127	113	104	79	42	20	6	0
63	54	45	32	21	6	1	0

TPS 1-49%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	28.9%	0.55 (0.34-0.90)	0.0081
Placebo/Pem/Plat	48.3%		

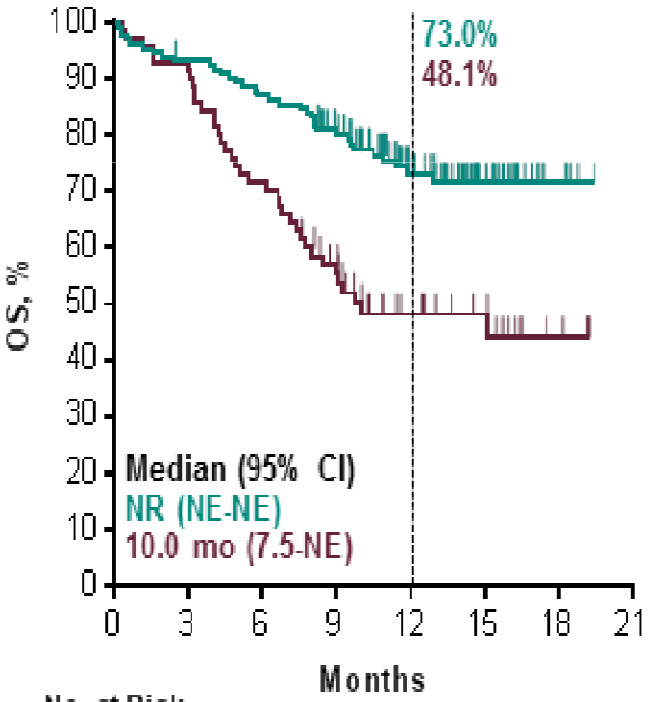


No. at Risk

128	119	108	84	52	21	5	0
58	54	47	32	17	5	2	0

TPS ≥50%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	25.8%	0.42 (0.26-0.68)	0.0001
Placebo/Pem/Plat	51.4%		

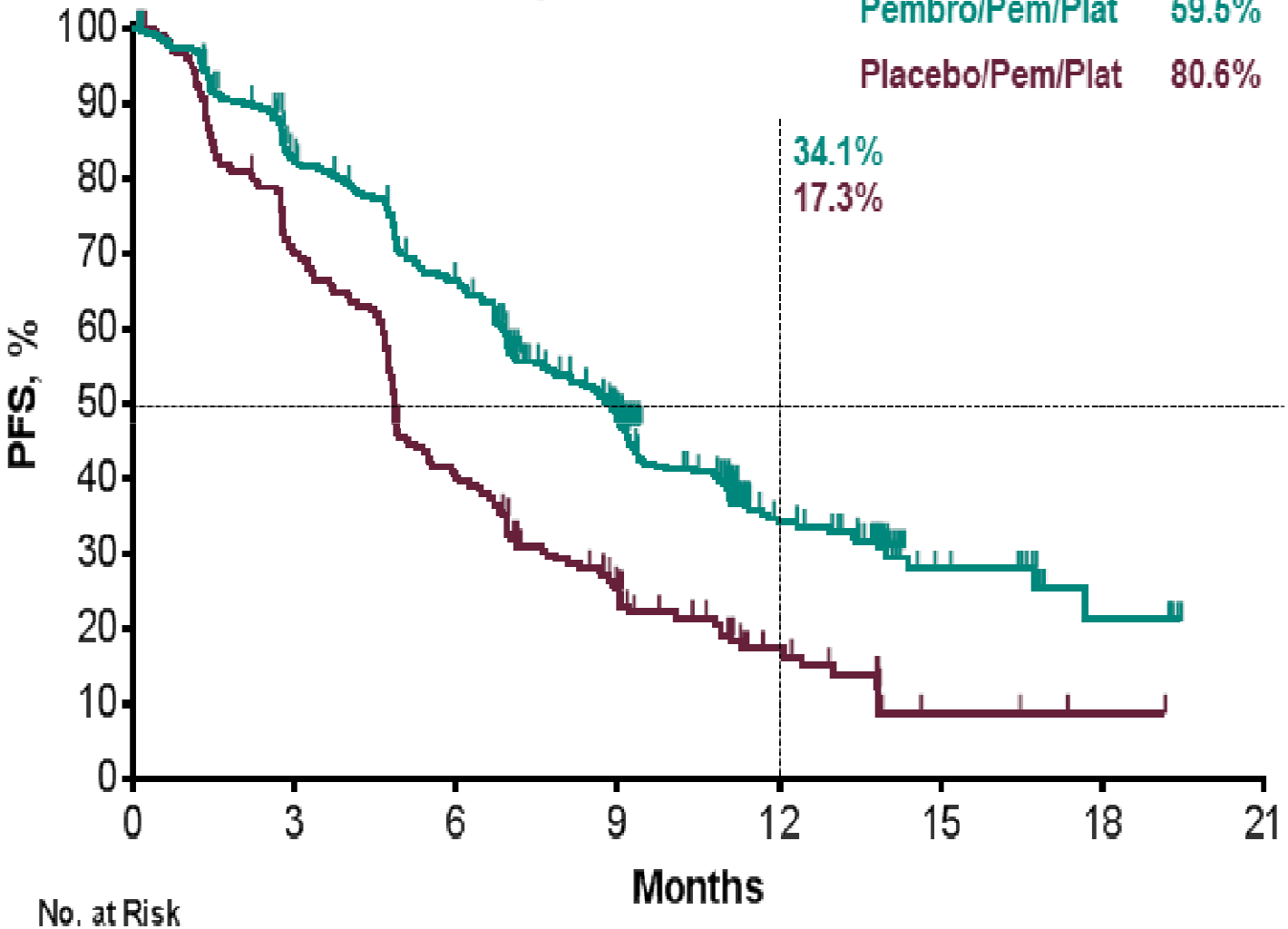


No. at Risk

132	122	114	96	56	25	6	0
70	64	50	35	19	13	4	0

[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Progression-Free Survival, ITT (RECIST v1.1, BICR)



	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	59.5%	0.52 (0.43-0.64)	<0.00001
Placebo/Pem/Plat	80.6%		

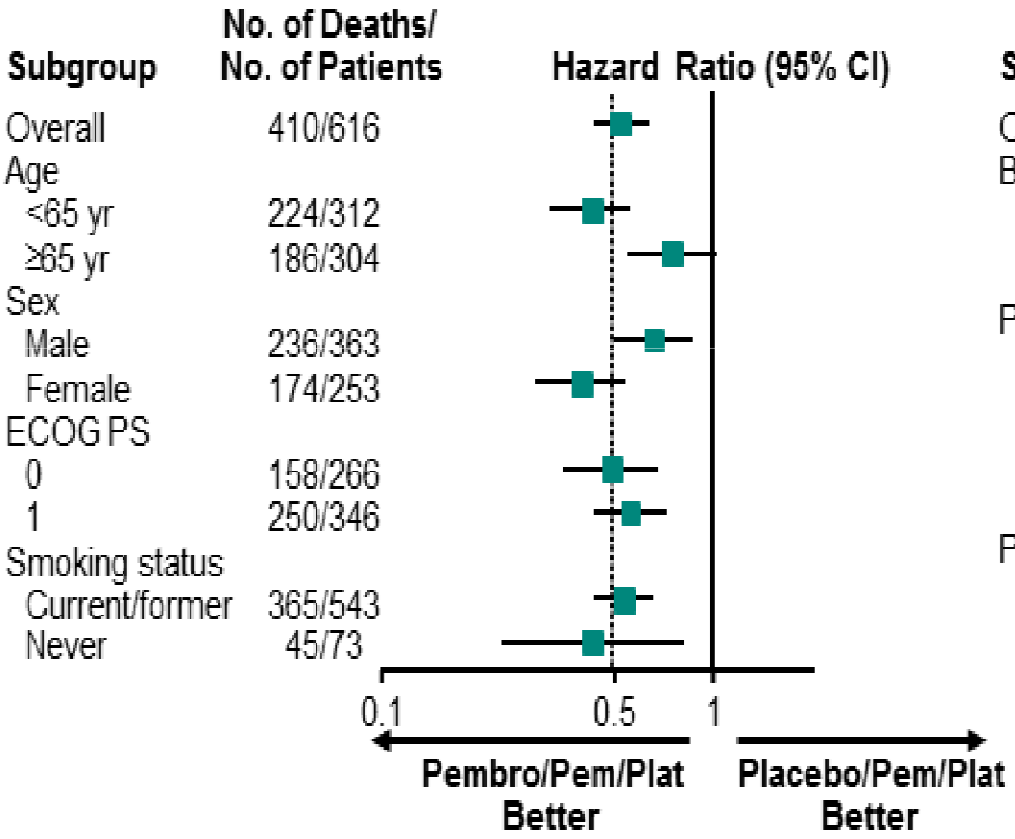
Median (95% CI)
8.8 mo (7.6-9.2)
4.9 mo (4.7-5.5)

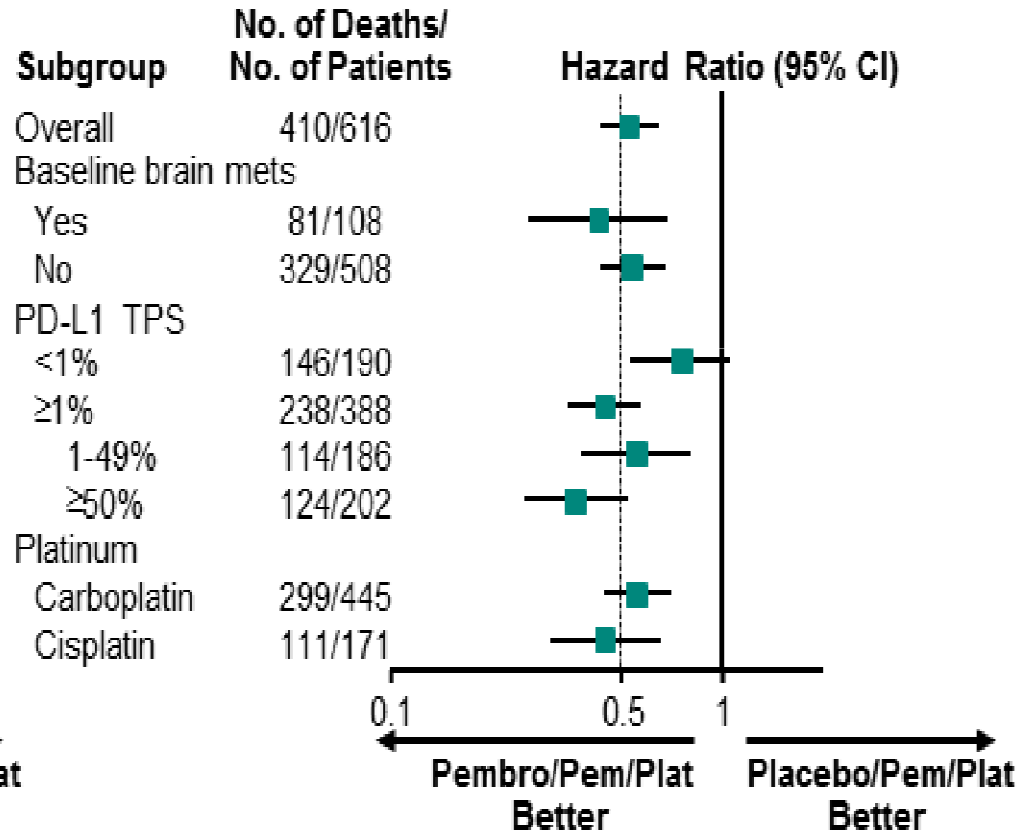
No. at Risk

410	322	256	149	60	17	5	0
206	141	80	40	16	3	1	0

BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

Progression-Free Survival in Key Subgroups (RECIST v1.1, BICR)





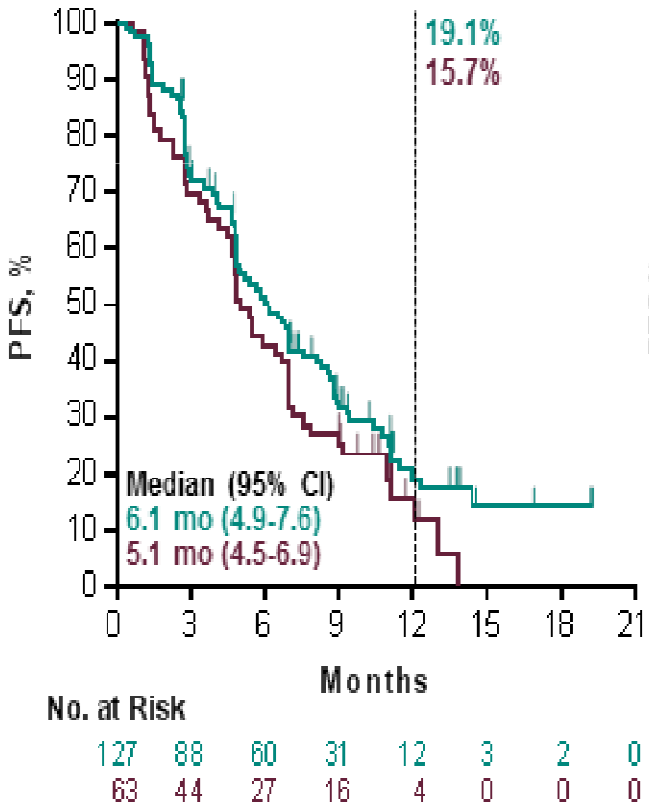
BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

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

Gandhi KN189
AACR 2018

TPS <1%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	72.4%	0.75 (0.53-1.05)	0.0476
Placebo/Pem/Plat	85.7%		

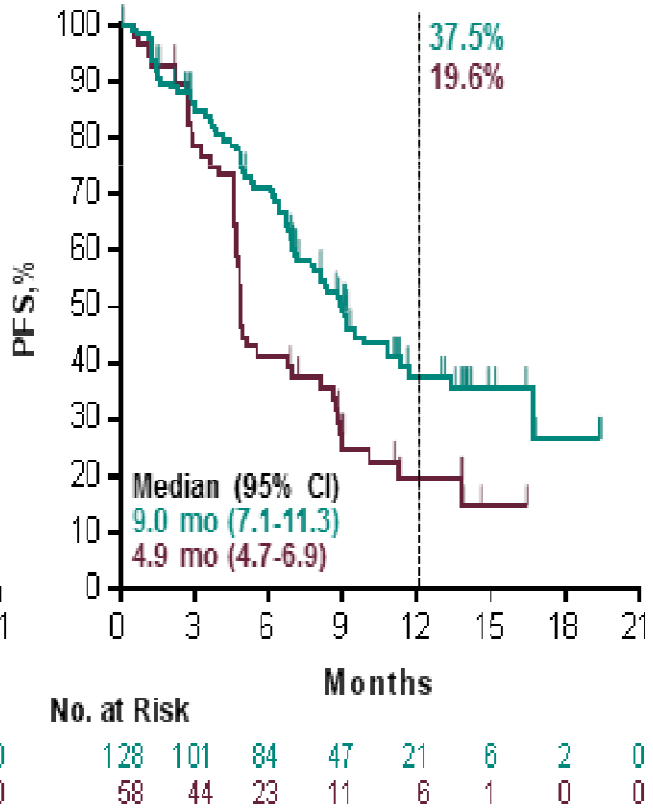


No. at Risk

127	88	60	31	12	3	2	0
63	44	27	16	4	0	0	0

TPS 1-49%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	54.7%	0.55 (0.37-0.81)	0.0010
Placebo/Pem/Plat	75.9%		

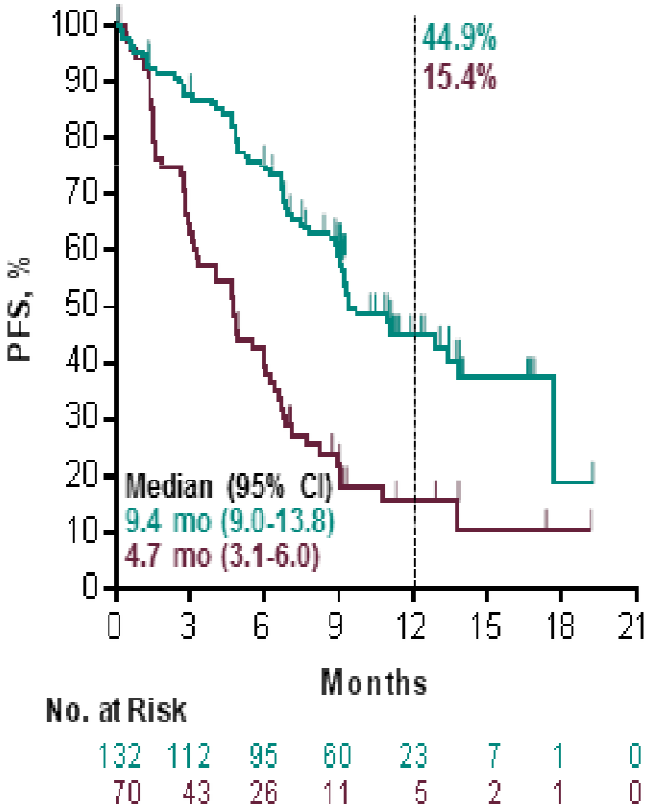


No. at Risk

128	101	84	47	21	6	2	0
58	44	23	11	6	1	0	0

TPS ≥50%

	Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	51.5%	0.36 (0.25-0.52)	<0.00001
Placebo/Pem/Plat	80.0%		

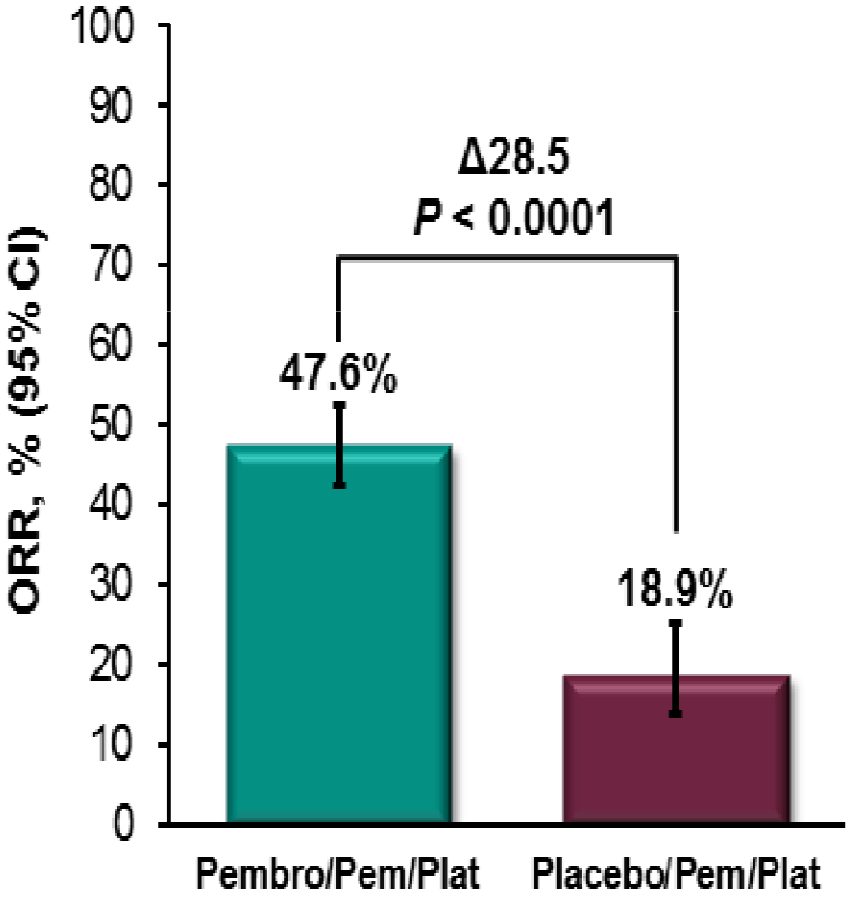


No. at Risk

132	112	95	60	23	7	1	0
70	43	26	11	5	2	1	0

[a]Nominal and one-sided. BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

Response Rate and Duration, ITT (RECIST v1.1, BICR)

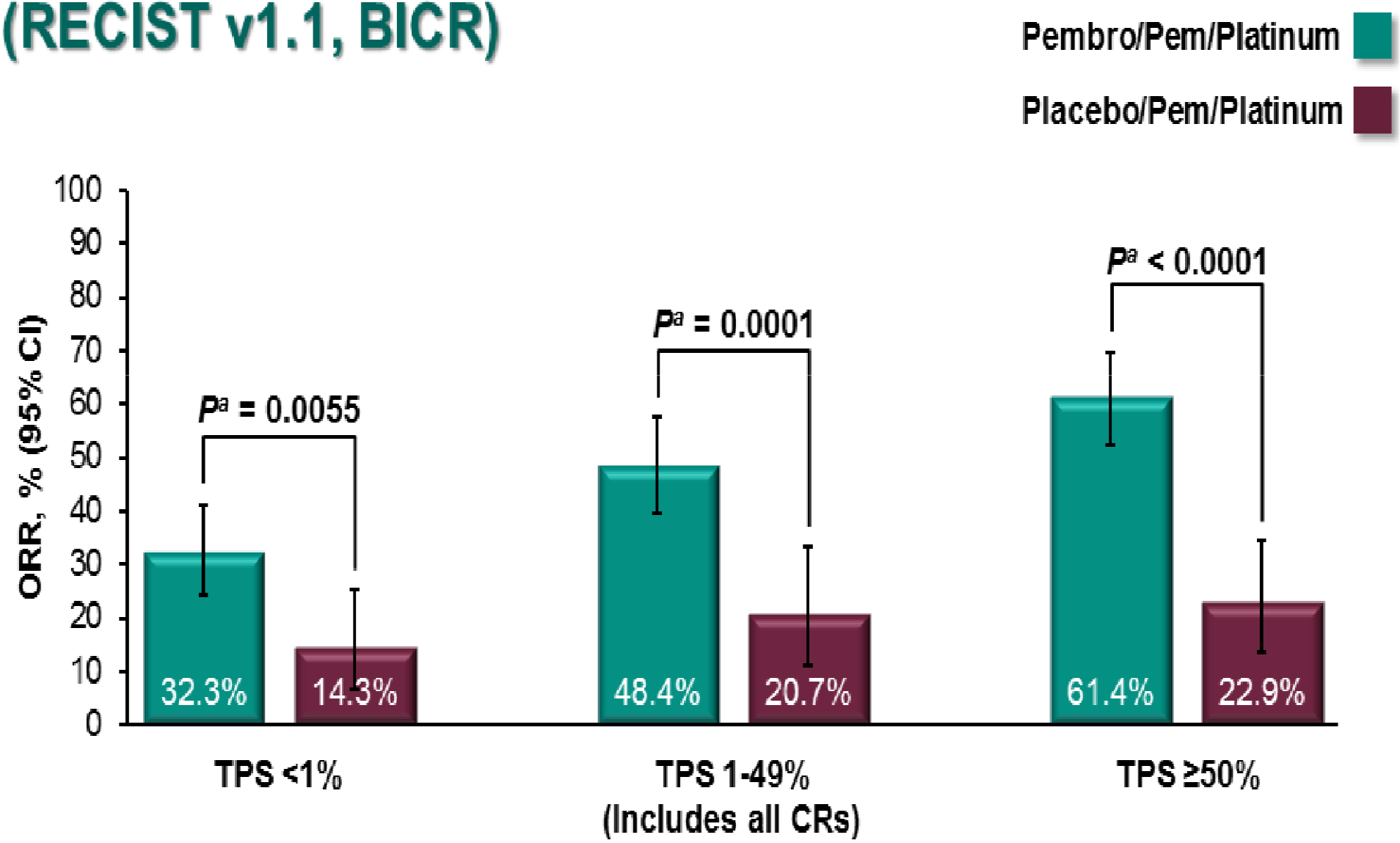


Best Response,[a] n (%)	Pembro/ Pem/Plat (N = 410)	Placebo/ Pem/Plat (N = 206)
CR	2 (0.5%)	1 (0.5%)
PR	193 (47.1%)	38 (18.4%)
SD	152 (37.1%)	106 (51.5%)
PD	36 (8.8%)	36 (17.5%)

Duration of response, mo	Pembro/ Pem/Plat (N = 195)	Placebo/ Pem/Plat (N = 39)
Median	11.2	7.8
Range	1.1+ to 18.0+	2.1+ to 16.4+

[a]An additional 27 (6.6%) patients in the pembro/pem/plat arm and 25 (12.1%) in the placebo/pem/plat arm did not have ≥2 evaluable sets of radiographic images.
BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

Response Rate by PD-L1 TPS (RECIST v1.1, BICR)



[a]Nominal and one-sided.
BICR, blinded, independent central review. Data cutoff date: Nov 8, 2017.

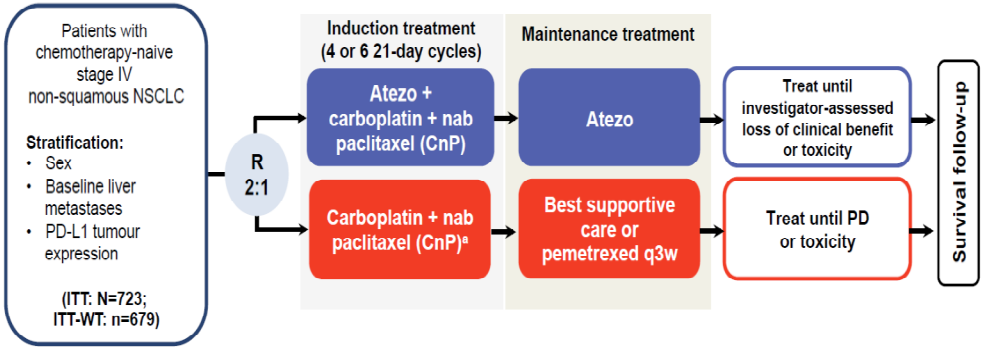
IMpower130: efficacy and safety from a randomised phase 3 study of carboplatin and nab-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC

Federico Cappuzzo,[1] Michael McCleod,[2] Maen Hussein,[3] Alessandro Morabito,[4] Achim Rittmeyer,[5] Henry J. Conter,[6] Hans-Georg Kopp,[7] Davey Daniel,[8] Steven McCune,[9] Tarek Mekhail,[10] Alona Zer,[11] Niels Reinmuth,[12] Ahad Sadiq,[13] Venice Archer,[14] Tania Ochi Lohmann,[15] Lijia Wang,[16] Marcin Kowanetz,[17] Wei Lin,[18] Alan Sandler,[19] Howard West[20]

[1]Dipartimento di Oncologia Medica, Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [2]Sarah Cannon Research Institute / Florida Cancer Specialists, Fort Myers, FL, USA; [3]Sarah Cannon Research Institute / Florida Cancer Specialists, Leesburg, FL, USA; [4]Thoracic Medical Oncology, Istituto Nazionale Tumori, IRCCS "Fondazione G. Pascale", Naples, Italy; [5]Department of Thoracic Oncology, Lungenfachklinik Immenhausen, Immenhausen, Germany; [6]Department of Medicine, William Osler Health System, Ontario, Canada; [7]Robert Bosch Centrum für Tumorerkrankungen (RBCT), Klinik Schillerhöhe, Stuttgart, Germany; [8]Tennessee Oncology, Chattanooga, TN, USA; [9]Northwest Georgia Oncology Centers, Marietta, GA, USA; [10]Florida Hospital Cancer Institute, Orlando, FL, USA; [11]Thoracic Oncology Unit, Rabin Medical Center, Tel Aviv University, Israel; [12]Thoracic Oncology, Asklepios Clinics Munich-Gauting, Gauting, Germany; [13]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [14]Roche Products Limited, Welwyn Garden City, UK; [15]PD Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Biostatistics, Genentech, Inc., South San Francisco, CA, USA; [17]Oncology Biomarker Development, Genentech, Inc., South San Francisco, CA, USA;[18]Clinical Science, Genentech, Inc., South San Francisco, CA, USA; [19]Clinical Science, Genentech, Inc., South San Francisco, CA, USA; [20]Thoracic Oncology Program, Swedish Cancer Institute, Seattle, WA, USA

esmo.org

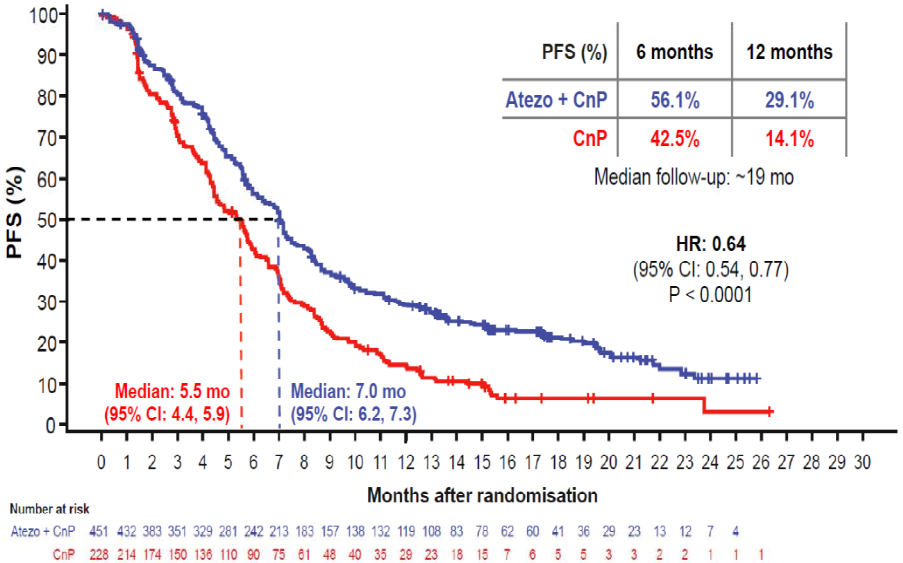
IMpower130 study design



- **Co-primary endpoints:** investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with *EGFR* or *ALK* genomic alterations
- **Key secondary endpoints:** OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

Atezo 1200 mg IV q3w; carboplatin area under the curve 6 mg/mL/min q3w; nab-paclitaxel 100 mg/m² IV days 1, 8, 15.
PD-L1 status tested with VENTANA SP142 IHC assay. Data cut-off: 15 March 2018.
[a] Crossover to receive atezo at PD was permitted only for patients enrolled to protocol versions 1–4.

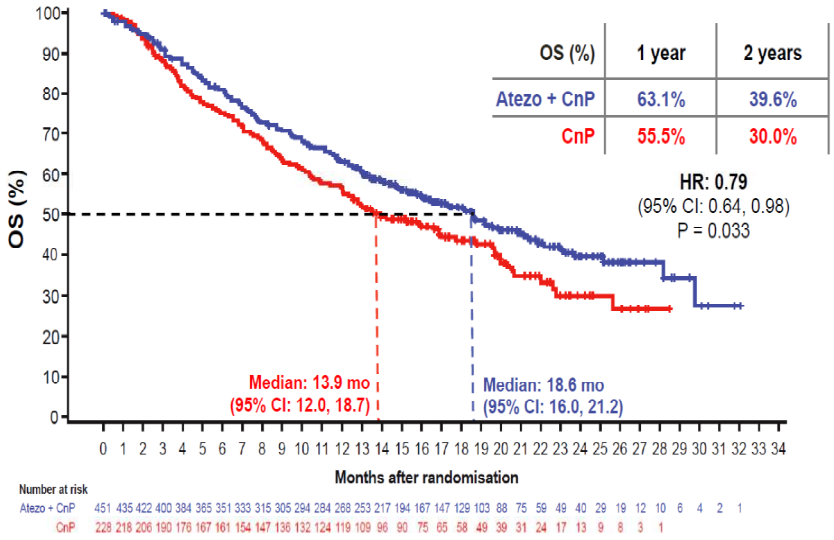
Investigator-assessed PFS (ITT-WT)



PFS (%)	6 months	12 months
Atezo + CnP	56.1%	29.1%
CnP	42.5%	14.1%

Median follow-up: ~19 mo

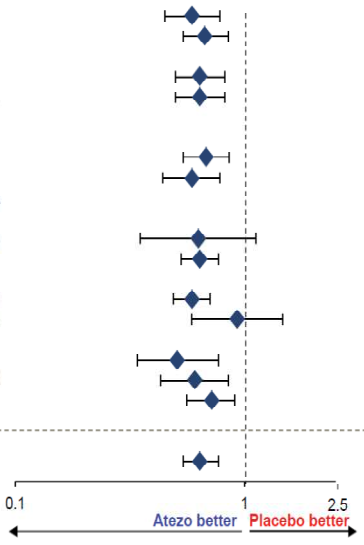
OS (ITT-WT)



OS (%)	1 year	2 years
Atezo + CnP	63.1%	39.6%
CnP	55.5%	30.0%

PFS in key subgroups (ITT-WT)

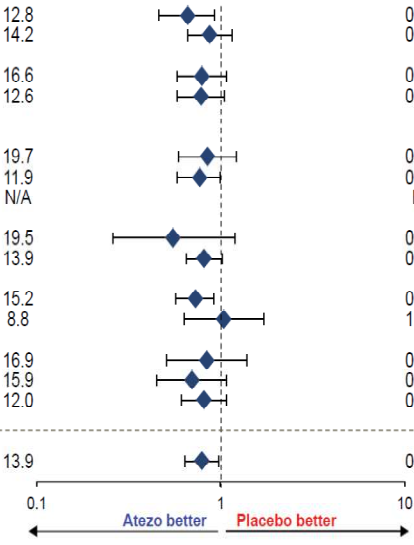
Population	n (%)	Median PFS (mo) Atezo + CnP	CnP	HR (95% CI)
Female	279 (41.1)	7.4	4.8	0.59 (0.45, 0.78)
Male	400 (58.9)	6.4	5.6	0.67 (0.54, 0.85)
<65 years	341 (50.2)	6.8	5.5	0.64 (0.5, 0.82)
≥65 years	338 (49.8)	7.2	5.3	0.64 (0.5, 0.82)
ECOG PS[a]				
0	280 (41.3)	7.9	5.6	0.59 (0.44, 0.78)
1	397 (58.6)	6.1	5.0	0.68 (0.54, 0.86)
2	1 (0.1)	N/A	N/A	N/A (N/A, N/A)
Never smoker	65 (9.6)	8.1	4.6	0.63 (0.35, 1.12)
Current/previous smoker	614 (90.4)	6.9	5.5	0.64 (0.53, 0.77)
No liver mets at enrolment	579 (85.3)	7.3	5.6	0.59 (0.49, 0.71)
Liver mets at enrolment	100 (14.7)	4.2	4.4	0.93 (0.59, 1.47)
PD-L1-high (TC3 or IC3)	130 (19.1)	6.4	4.6	0.51 (0.34, 0.77)
PD-L1-low (TC1/2 or IC1/2)	193 (28.4)	8.3	6.0	0.61 (0.43, 0.85)
PD-L1-negative (TC0 and IC0)	356 (52.4)	6.2	4.7	0.72 (0.56, 0.91)
ITT-WT	679 (100)	7.0	5.5	0.64 (0.54, 0.77)



Stratified HR for ITT-WT; unstratified HR for all other subgroups.
[a] One patient had an unknown ECOG PS.

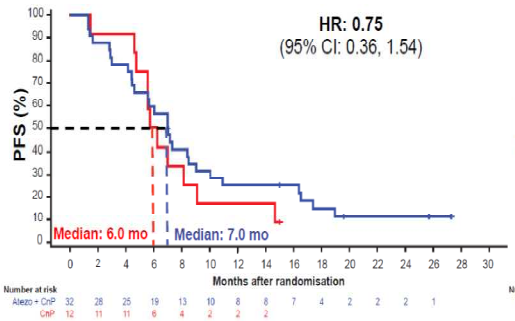
OS in key subgroups (ITT-WT)

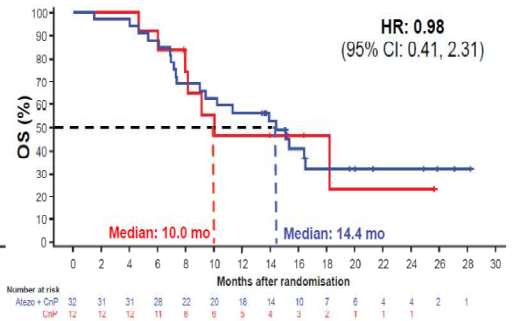
Population	n (%)	Median OS (mo) Atezo + CnP	CnP	HR (95% CI)
Female	279 (41.1)	21.4	12.8	0.66 (0.46, 0.93)
Male	400 (58.9)	16.0	14.2	0.87 (0.66, 1.15)
<65 years	341 (50.2)	19.2	16.6	0.79 (0.58, 1.08)
≥65 years	338 (49.8)	16.1	12.6	0.78 (0.58, 1.05)
ECOG PS[a]				
0	280 (41.3)	20.8	19.7	0.85 (0.59, 1.22)
1	397 (58.6)	15.2	11.9	0.77 (0.58, 1.00)
2	1 (0.1)	N/A	N/A	N/A (N/A, N/A)
Never smoker	65 (9.6)	28.2	19.5	0.55 (0.26, 1.19)
Current/previous smoker	614 (90.4)	18.1	13.9	0.81 (0.65, 1.02)
No liver mets at enrolment	579 (85.3)	21.1	15.2	0.73 (0.57, 0.92)
Liver mets at enrolment	100 (14.7)	10.0	8.8	1.04 (0.63, 1.72)
PD-L1-high (TC3 or IC3)	130 (19.1)	17.3	16.9	0.84 (0.51, 1.39)
PD-L1-low (TC1/2 or IC1/2)	193 (28.4)	23.7	15.9	0.70 (0.45, 1.08)
PD-L1-negative (TC0 and IC0)	356 (52.4)	15.2	12.0	0.81 (0.61, 1.08)
ITT-WT	679 (100)	18.6	13.9	0.79 (0.64, 0.98)



Stratified HR for ITT-WT; unstratified HR for all other subgroups.
[a] One patient had an unknown ECOG PS.

Investigator-assessed PFS and OS in *EGFR*/*ALK*-positive subgroup





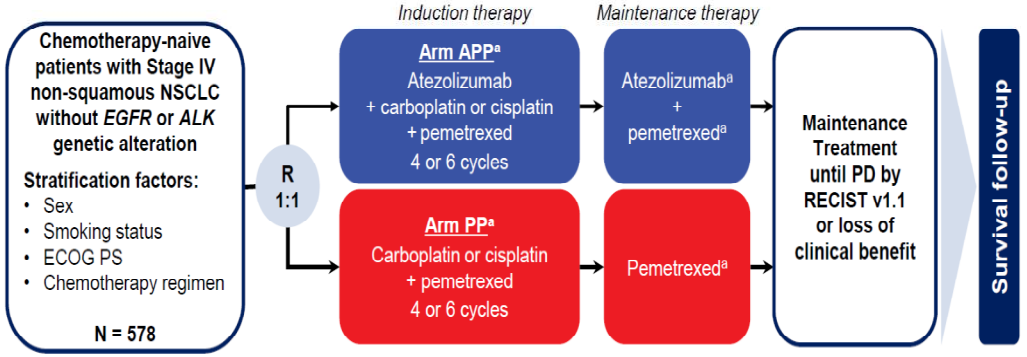
IMpower132: efficacy of atezolizumab + carboplatin/cisplatin + pemetrexed as 1L treatment in key subgroups with stage IV non-squamous NSCLC

Fabrice Barlesi,[1] Makoto Nishio,[2] Manuel Cobo,[3] Nicola Steele,[4] Victor Paramonov,[5] Barbara Parente,[6] Rachel Dear,[7] Henri Berard,[8] Nir Peled,[9] Lasika C. Seneviratne,[10] Editta Baldini,[11] Satoshi Watanabe,[12] Koichi Goto,[13] Diana Mendus,[14] Hina Patel,[14] Yu Deng,[14] Marcin Kowanetz,[14] Tien Hoang,[14] Wei Lin,[14] Vassiliki A. Papadimitrakopoulou[15]

[1]Aix-Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; [2]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [3]Hospital Regional Universitario Carlos Haya, Málaga, Spain; [4]The Beatson West of Scotland Cancer Centre, Glasgow, UK; [5]Cherkassy Regional Oncology Dispensary, Cherkassy, Ukraine; [6]CUF Porto Hospital, Porto, Portugal; [7]The Kinghorn Cancer Centre, St. Vincent's Hospital, Sydney, Australia; [8]Hôpital d'Instruction des Armées (HIA) Sainte-Anne, Toulon, France; [9] The Cancer Institute, Soroka Medical Center and Ben-Gurion University, Beer-Sheva, Israel; [10]Los Angeles Cancer Network, Los Angeles, CA, USA; [11]Ospedale San Luca, Lucca, Italy; [12]Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [13]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [14]Genentech, Inc, South San Francisco, CA, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

esmo.org

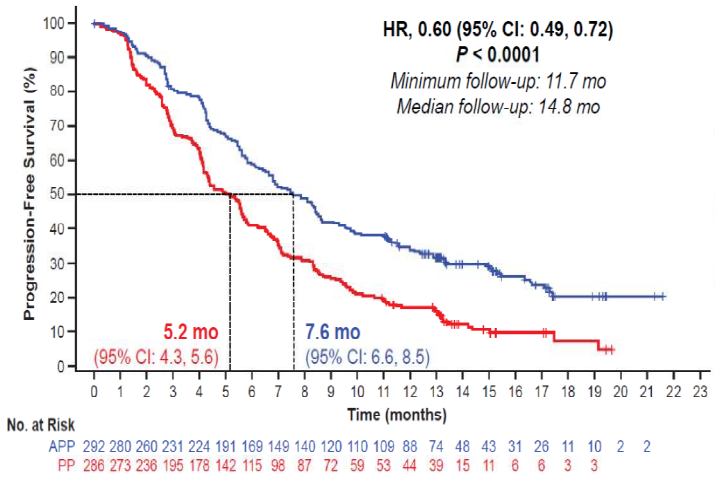
IMpower132 study design



- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker[b] subgroup analyses

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
[a] Atezolizumab: 1200 mg IV q3w, carboplatin: AUC 6 mg/mL/min IV q3w, cisplatin: 75 mg/m² IV q3w, pemetrexed: 500 mg/m² IV q3w.
[b] Biomarker-evaluable tissue not mandatory for enrolment and was available from 60% of patients. NCT02657434.
Data cutoff: May 22, 2018.

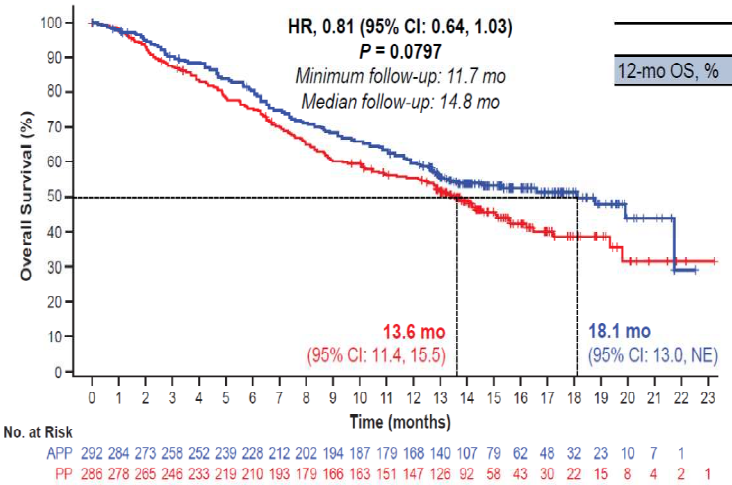
PFS in the ITT population[1]



	APP	PP
6-mo PFS, %	59%	41%
12-mo PFS, %	34%	17%
ORR, %	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
Data cutoff: May 22, 2018.
1. Papadimitrakopoulou VA, et al. WCLC, 2018.

Interim OS analysis in the ITT population[1]

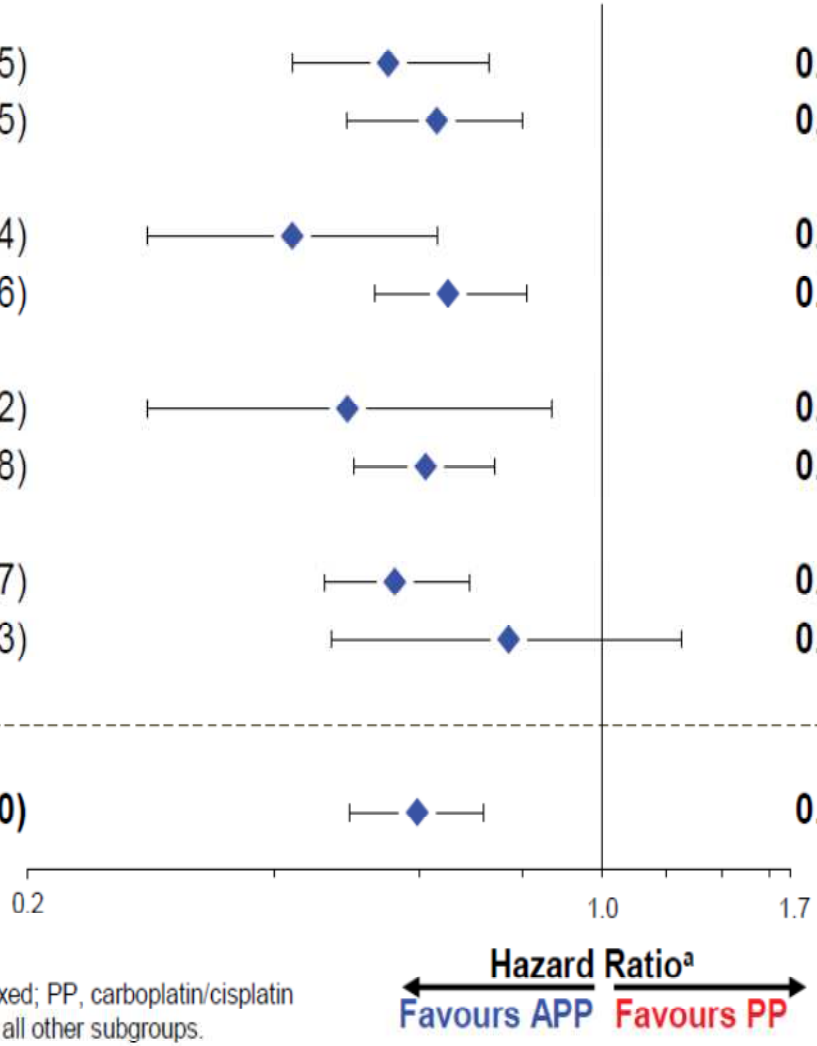


	APP	PP
12-mo OS, %	59.6%	55.4%

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.
Data cutoff: May 22, 2018. Frequency of OS events: 44% and 49% in arms APP and PP respectively.
1. Papadimitrakopoulou VA. WCLC, 2018.

PFS in key patient subgroups[1]

Subgroup	n (%)	HR (95% CI)[a]	Median PFS, mo	
			APP	PP
≥ 65 years	258 (45)	**0.55** (0.42, 0.73)	8.4	5.6
< 65 years	320 (55)	**0.63** (0.49, 0.80)	6.9	4.4
Asian	136 (24)	**0.42** (0.28, 0.63)	10.2	5.3
Non-Asian	442 (76)	**0.65** (0.53, 0.81)	6.9	5.0
Never smoker	67 (12)	**0.49** (0.28, 0.87)	8.6	5.5
Current or former smoker	511 (88)	**0.61** (0.50, 0.74)	7.5	5.1
No liver metastases	505 (87)	**0.56** (0.46, 0.69)	8.4	5.5
Liver metastases	73 (13)	**0.77** (0.47, 1.25)	4.4	4.0
ITT population	**578 (100)**	**0.60 (0.49, 0.72)**	**7.6**	**5.2**



APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed. [a] Stratified HR for ITT; unstratified for all other subgroups.
Data cutoff: May 22, 2018.

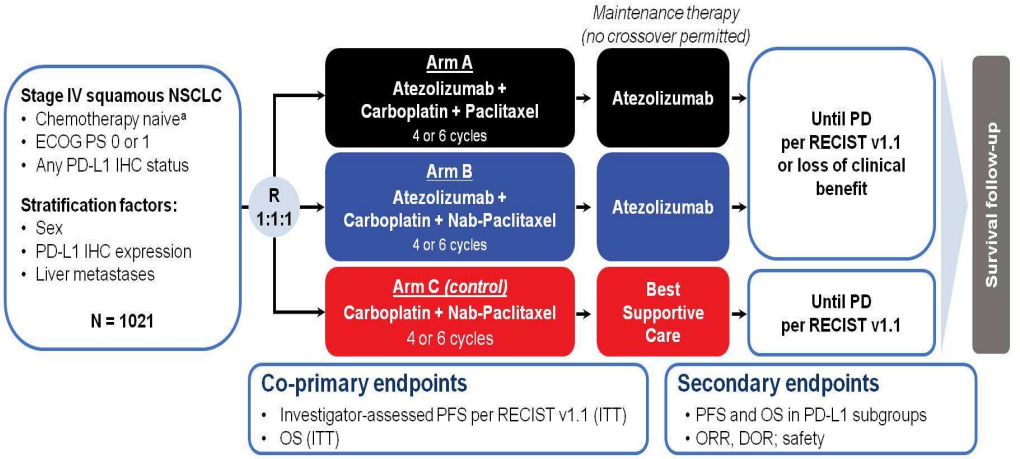
1. Papadimitrakopoulou VA, et al. WCLC 2018.

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]

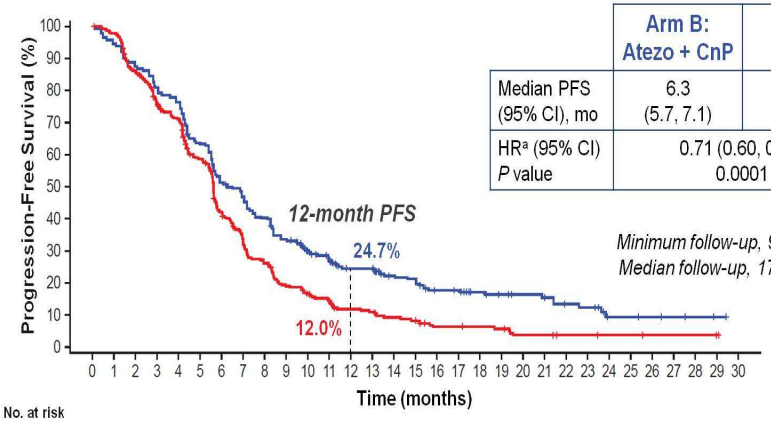
[1]Rocky Mountain Cancer Centers, Denver, CO; [2]US Oncology, Houston, TX; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [4]Sumy State University, Sumy, Ukraine; [5]Moscow City Oncology Hospital, Moscow Healthcare Department, Moscow Oblast, Russia; [6]Complejo Hospitalario Universitario 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

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.

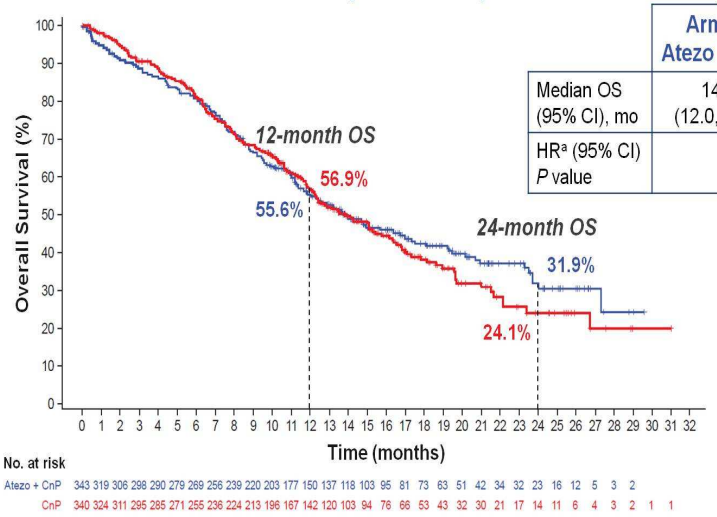
INV-Assessed PFS in the ITT Population (Arm B vs Arm C)



	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)

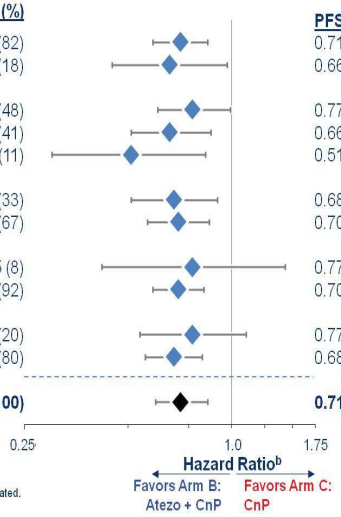


	Arm B: Atezo + CnP	Arm C: CnP
Median OS (95% CI), mo	14.0 (12.0, 17.0)	13.9 (12.3, 16.4)
HR[a] (95% CI) *P* value	0.96 (0.78, 1.18) 0.6931	

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

INV-Assessed PFS in Clinical Subgroups

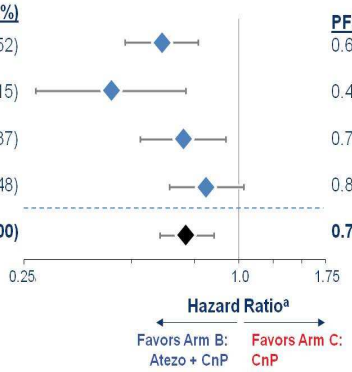
Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo Arm B	Median PFS, mo Arm C
Male	557 (82)	0.71 (0.59, 0.85)	6.3	5.6
Female	126 (18)	0.66 (0.45, 0.97)	6.5	5.6
< 65 years	326 (48)	0.77 (0.61, 0.99)	6.0	5.6
65-74 years	279 (41)	0.66 (0.51, 0.87)	6.0	5.6
75-84 years[a]	77 (11)	0.51 (0.30, 0.84)	7.0	5.6
ECOG 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.

INV-Assessed PFS in PD-L1 Subgroups

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo Arm B	Median PFS, mo 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**

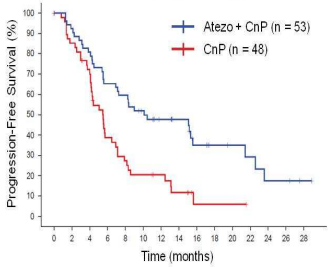


- **PFS benefit was observed with atezolizumab + CnP (Arm B) vs CnP (Arm C) across all PD-L1 subgroups**

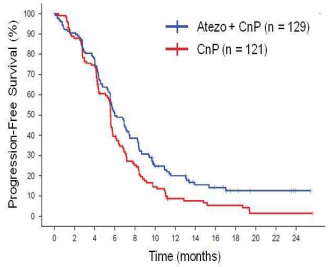
Data cutoff: January 22, 2018.
[a] Stratified HR for ITT; unstratified HRs for all PD-L1 subgroups.

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

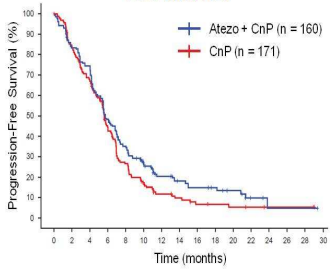
PD-L1 High — *TC3 or IC3*



PD-L1 Low — *TC1/2 or IC1/2*



PD-L1 Negative — *TC0 and IC0*

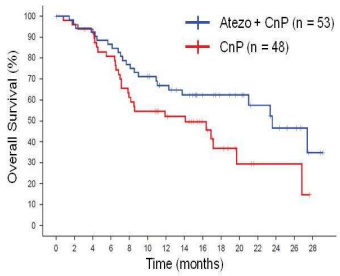


	Atezo + CnP	CnP	Atezo + CnP	CnP	Atezo + CnP	CnP
12-month PFS	48%	20%	20%	9%	20%	12%
Median PFS, mo	10.1	5.5	6.0	5.6	5.7	5.6
HR[a] (95% CI)	0.44 (0.27, 0.71)		0.70 (0.53, 0.92)		0.81 (0.64, 1.03)	

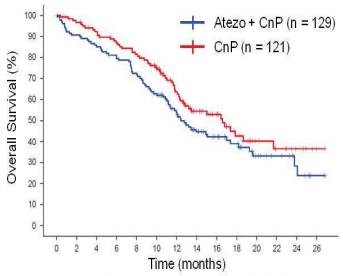
Data cutoff: January 22, 2018.
[a] Unstratified HR.

First Interim OS in PD-L1 Subgroups (Arm B vs Arm C)

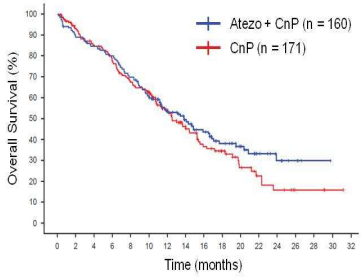
PD-L1 High — *TC3 or IC3*



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.

Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)

ESMO ASIA CONGRESS 2017

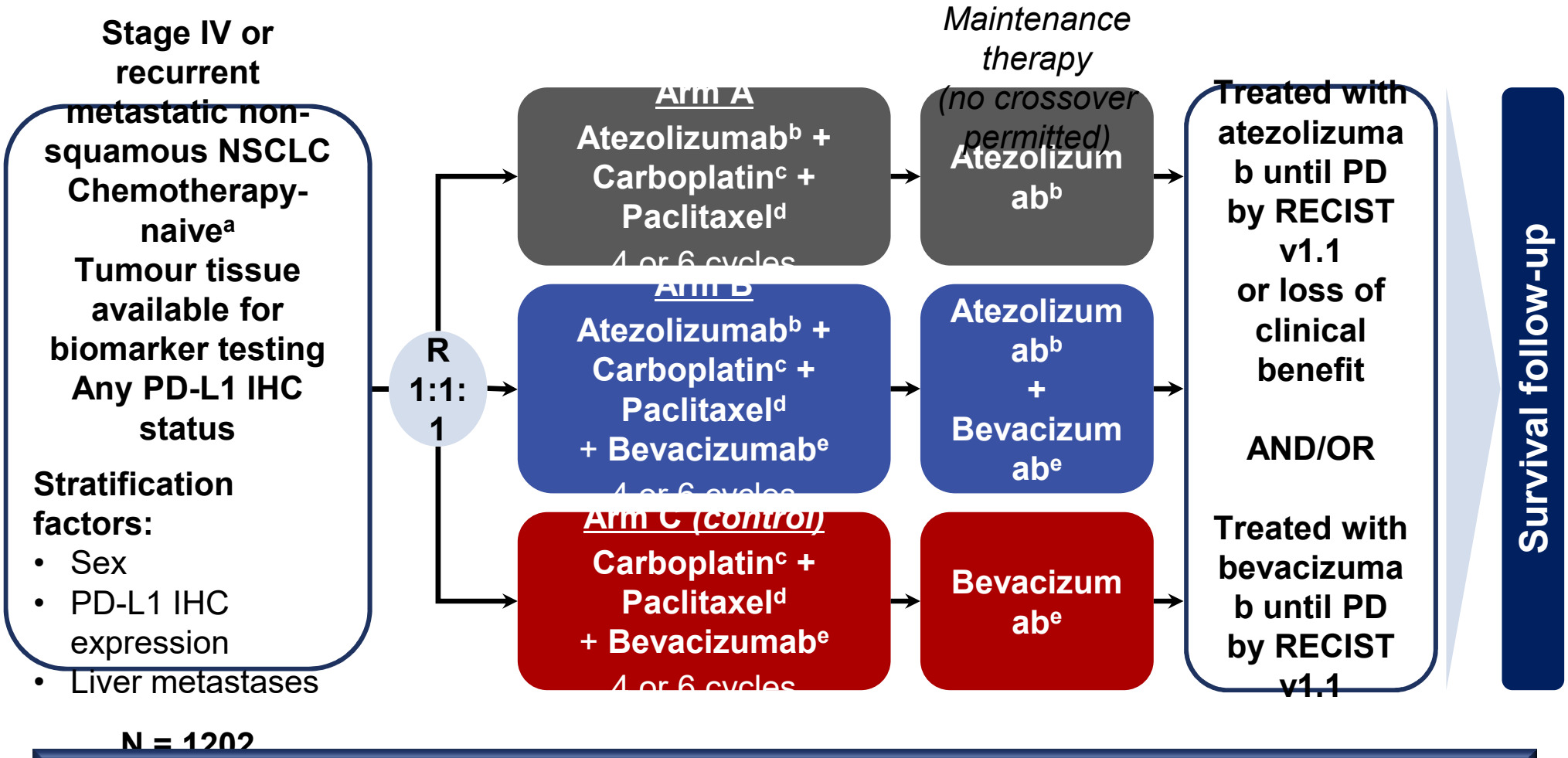
Martin Reck,[1] Mark A. Socinski,[2] Federico Cappuzzo,[3] Francisco Orlandi,[4] Daniil Stroyakovskii,[5] Naoyuki Nogami,[6] Delvys Rodríguez-Abreu,[7] Denis Moro-Sibilot,[8] Christian A. Thomas,[9] Fabrice Barlesi,[10] Gene Finley,[11] Claudia Kelsch,[12] Anthony Lee,[12] Shelley Coleman,[12] Yijing Shen,[12] Marcin Kowanetz,[12] Ariel Lopez-Chavez,[12] Alan Sandler,[13] Robert Jotte[13]

[1]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany;

[2]Florida Hospital Cancer Institute, Orlando, FL, USA; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy;

[4]Instituto Nacional del Torax, Santiago, Chile; [5]Moscow City Oncology Hospital, Moscow, Russia; [6]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [7]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [8]Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France; [9]New England Cancer Specialists, Scarborough, ME, USA; [10]Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; [11]Allegheny Cancer Center, Pittsburgh, PA, USA; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Rocky Mountain Cancer Centers, Denver, CO, USA

IMpower150 study design

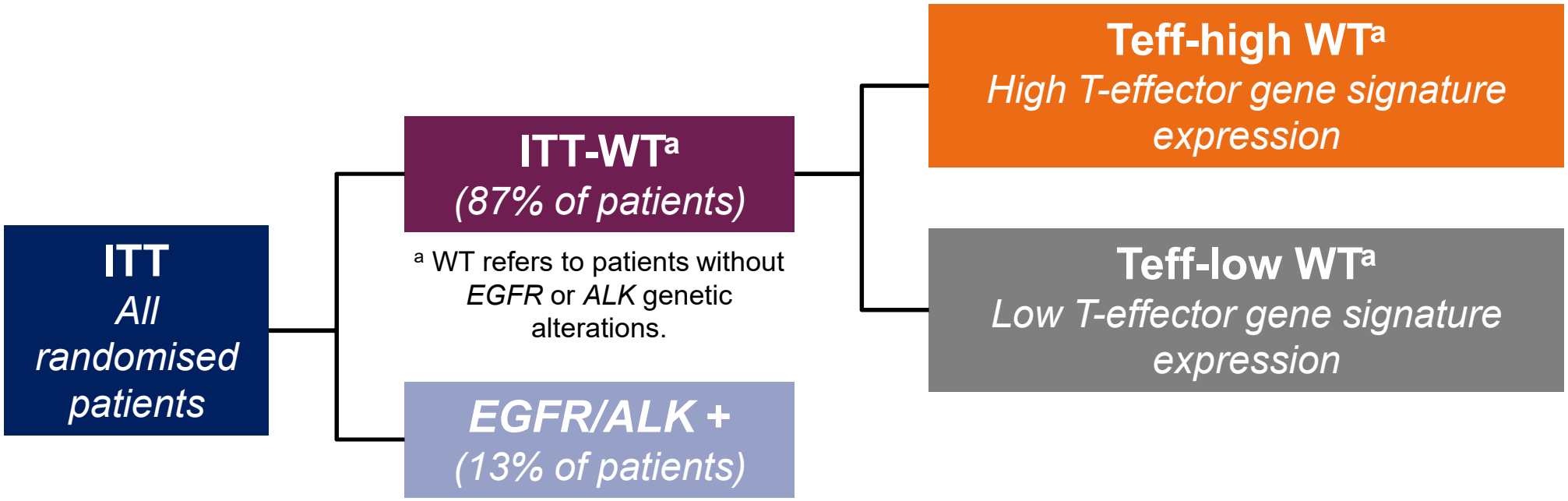


The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w.
[d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

IMpower150 study populations and objectives



[a] WT refers to patients without *EGFR* or *ALK* genetic alterations.

1 Co-primary objectives

- Investigator-assessed **PFS** in **ITT-WT**
- Investigator-assessed **PFS** in **Teff-high WT**
- **OS** in **ITT-WT**

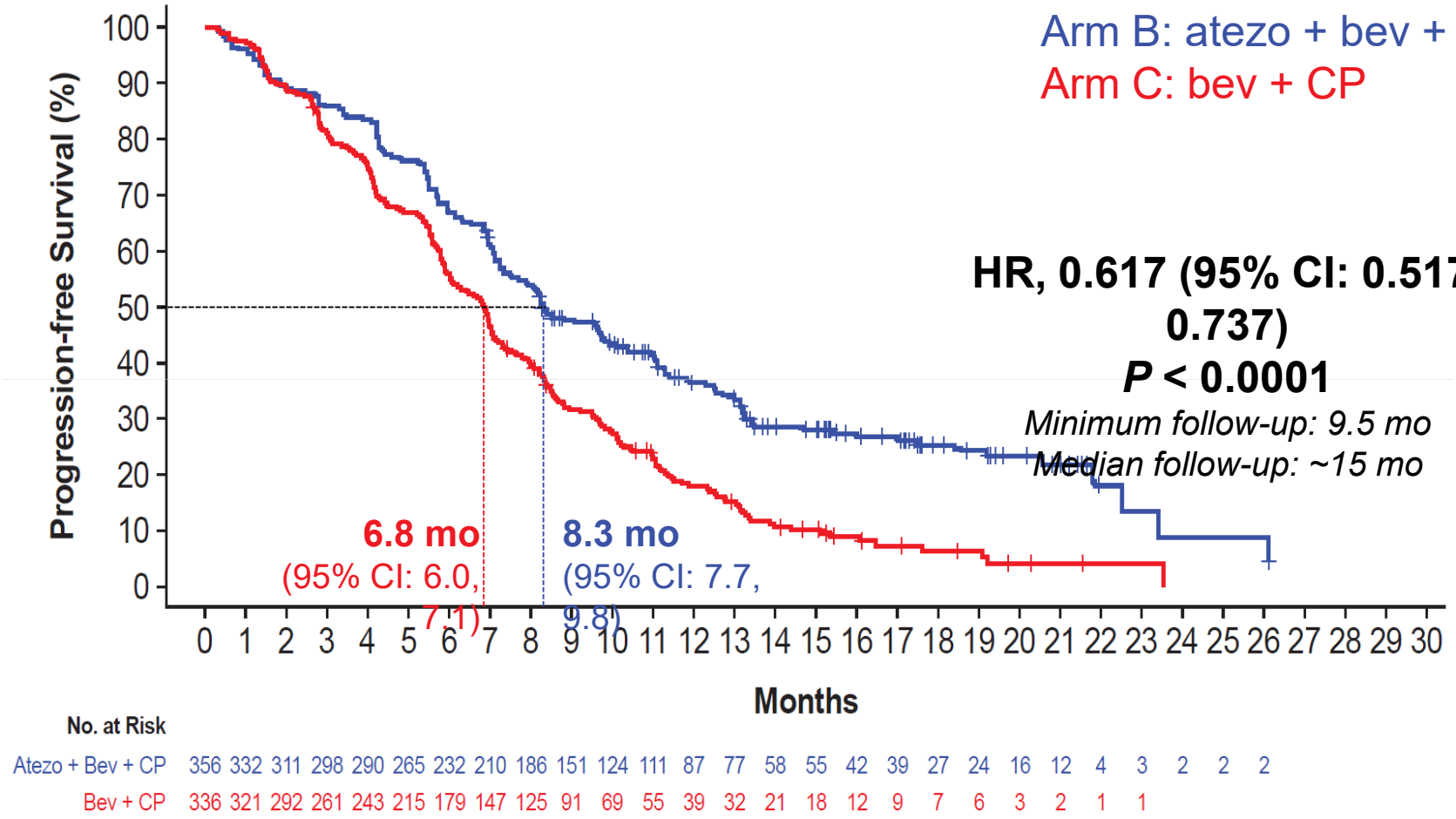
2 Key secondary objectives

- Investigator-assessed **PFS** and **OS** in **ITT**
- Investigator-assessed **PFS** in PD-L1 IHC subgroups
- Independent review facility (IRF)-assessed **PFS**
- **ORR** and **DOR** per RECIST v1.1
- **Safety** in **ITT**

The T-effector (Teff) gene signature is defined by expression of *PD-L1*, *CXCL9* and *IFNγ* and is a surrogate of both PD-L1 IHC expression and pre-existing immunity (Kowanetz M, et al. WCLC, 2017).

Reck M, et al. IMpower150 PFS analysis.

INV-assessed PFS in ITT-WT (Arm B vs Arm C)

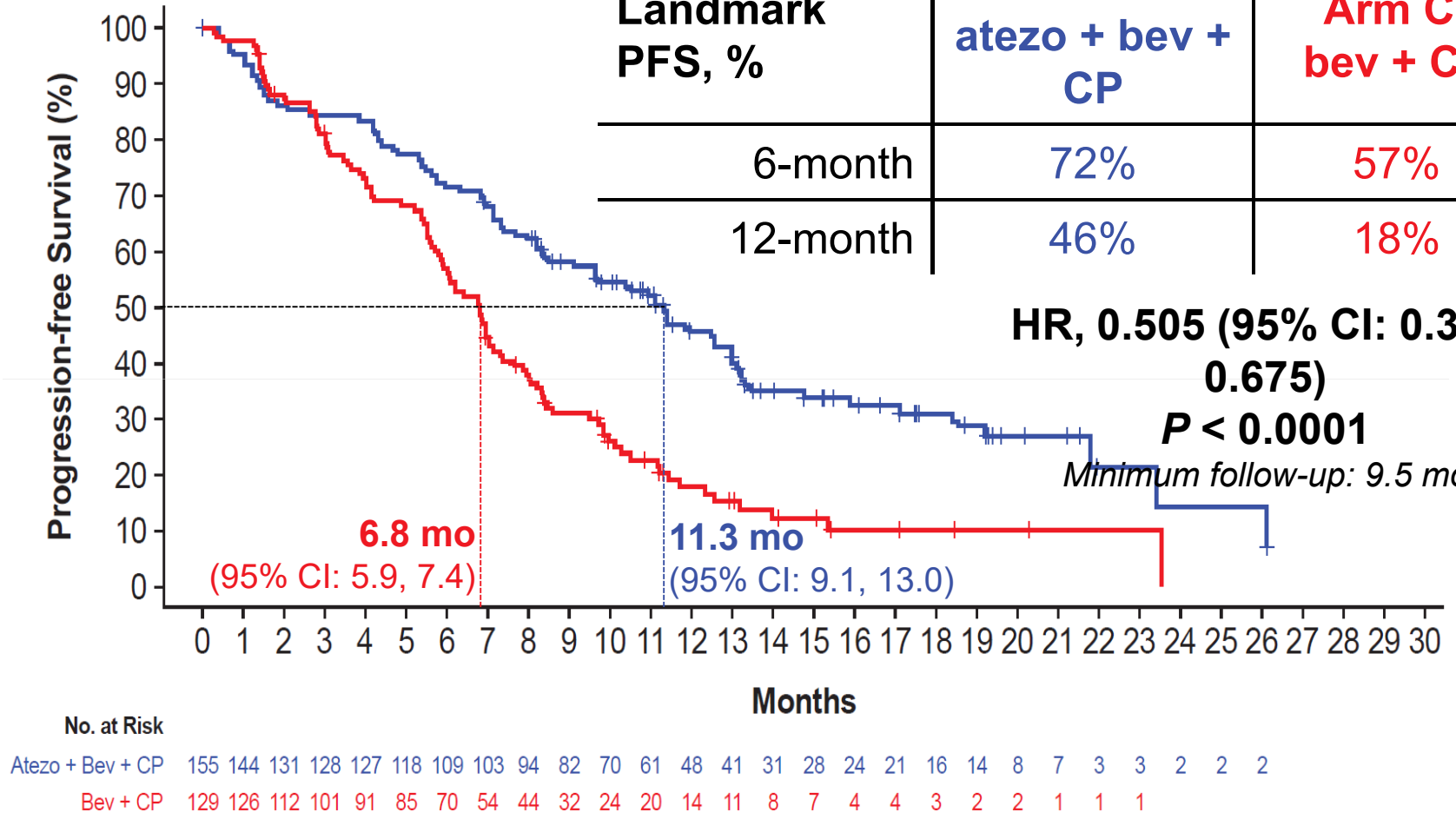


INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

INV-assessed PFS in Teff-high WT (Arm B vs Arm C)

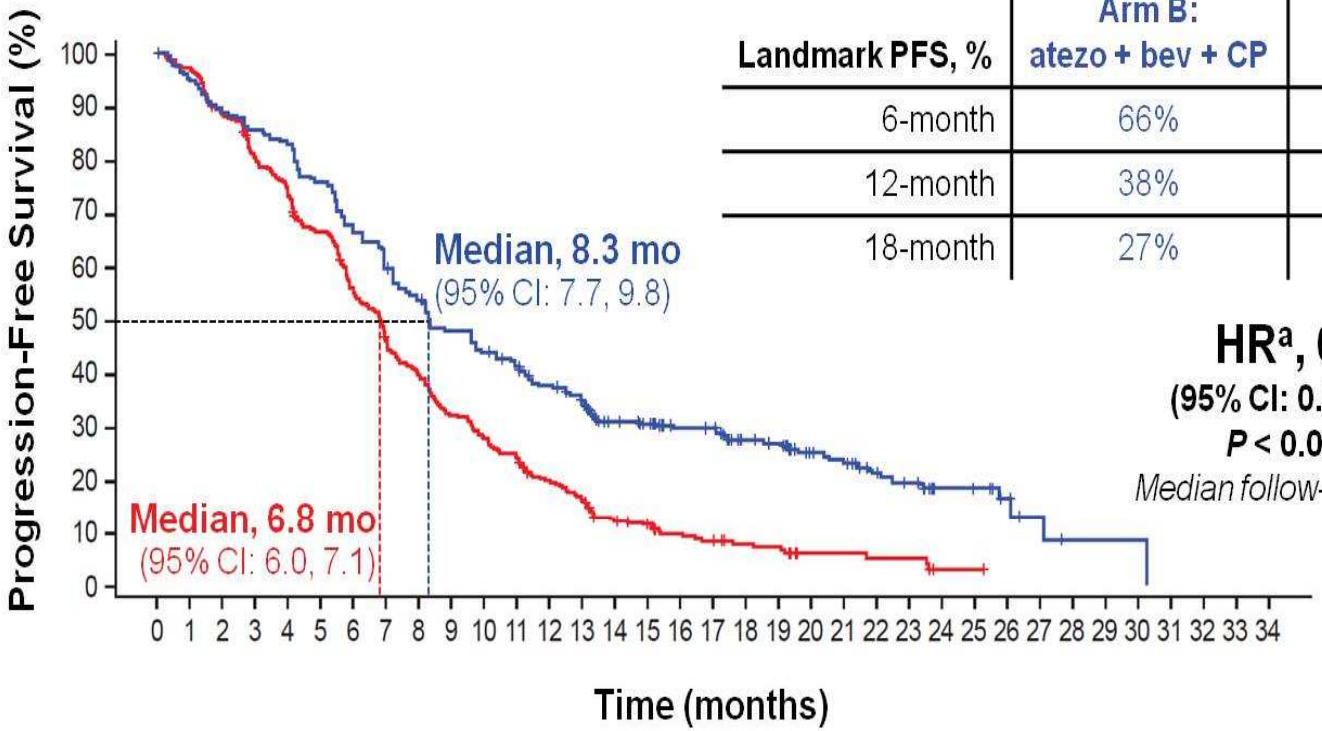
Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	72%	57%
12-month	46%	18%



INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

Updated PFS Analysis in the ITT-WT (Arm B vs Arm C)



Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

HR[a], 0.59
(95% CI: 0.50, 0.70)
***P* < 0.0001[b]**
Median follow-up: ~20 mo

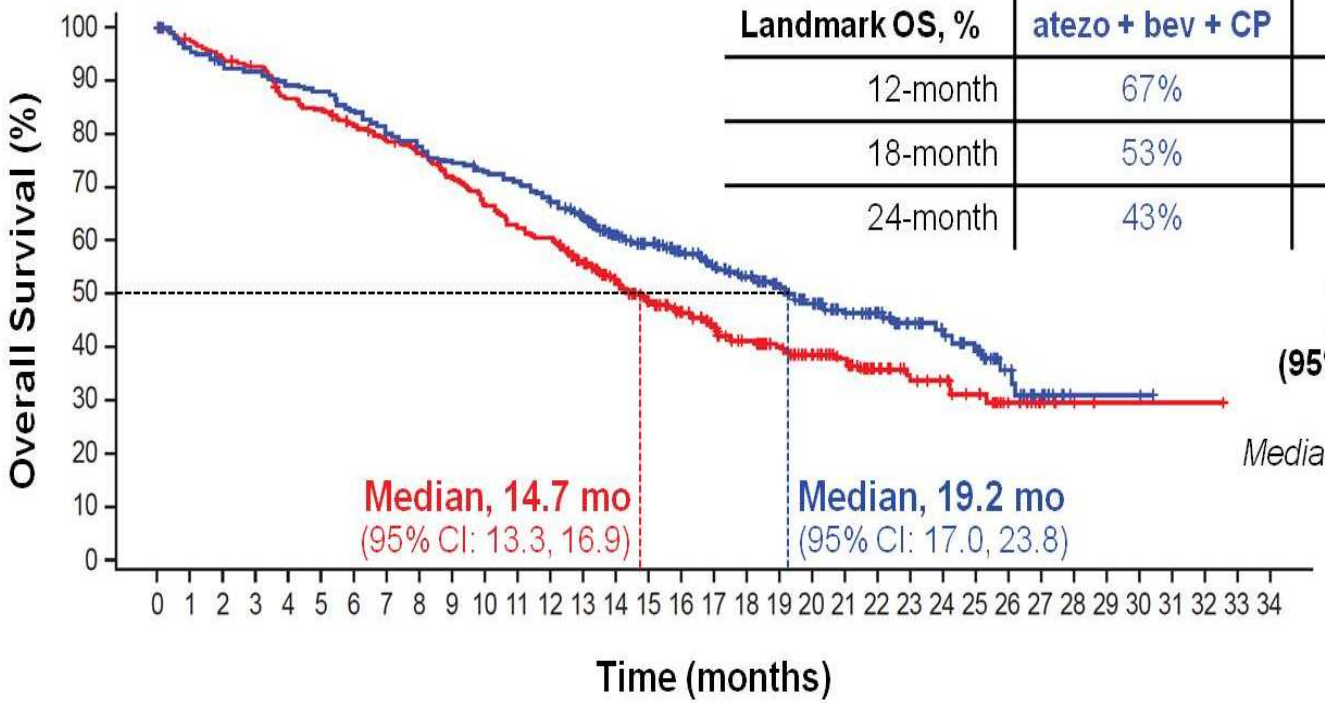
No. at Risk																														
Atezo+Bev+CP	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev+CP	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

- Statistically significant and clinically meaningful PFS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was previously observed[1] and continued to improve with additional follow-up

[a] Stratified HR. [b] For descriptive purposes only. Data cutoff: January 22, 2018

1. Reck M, et al. ESMO IO 2017 [abstract LBA1_PR].

OS in the ITT-WT (Arm B vs Arm C)



Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

No. at Risk

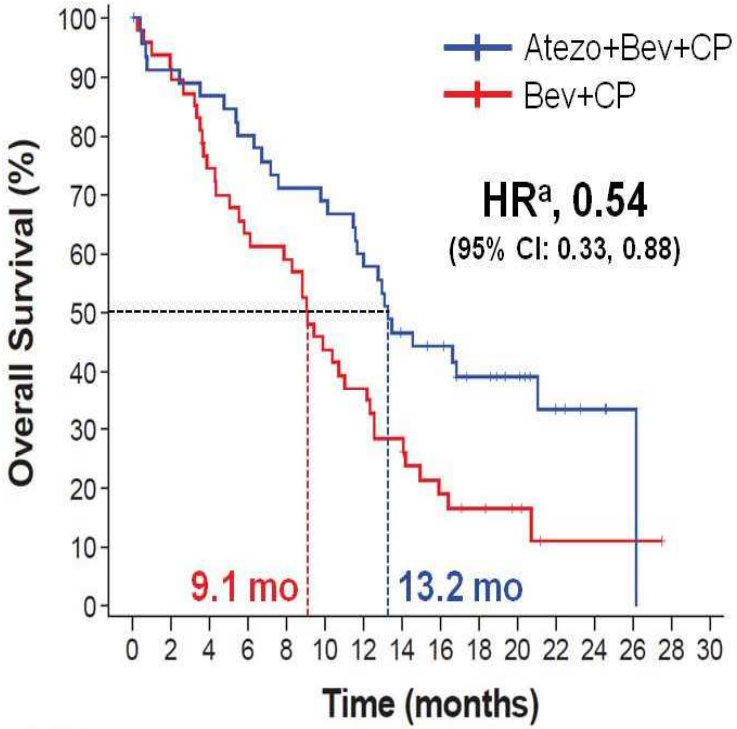
Atezo+Bev+CP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bev+CP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

- Statistically significant and clinically meaningful OS benefit with atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy was observed

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

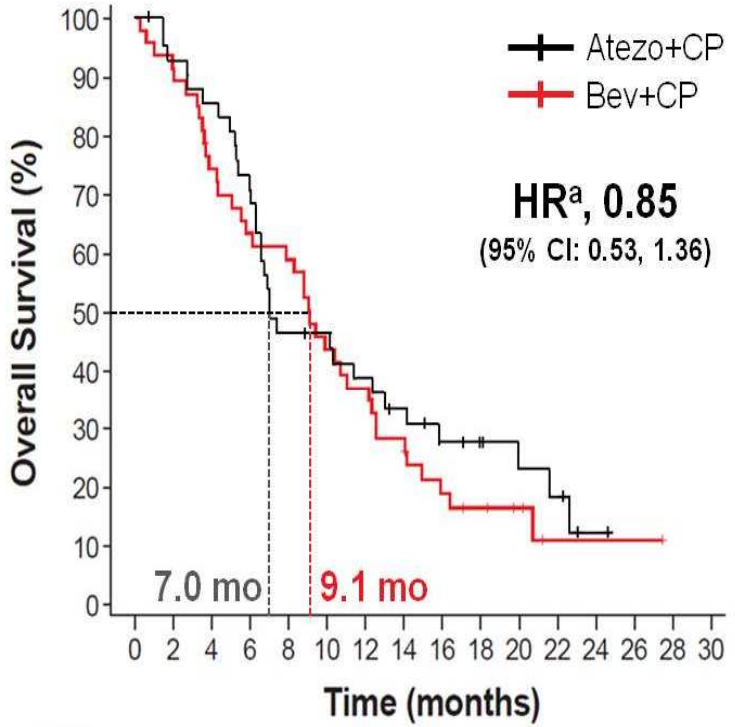
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of Patients With Liver Metastases in the ITT-WT

Arm B vs Arm C



No. at Risk														
Atezo+Bev+CP	47	41	39	36	32	31	26	20	18	13	10	5	3	1
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1

Arm A vs Arm C

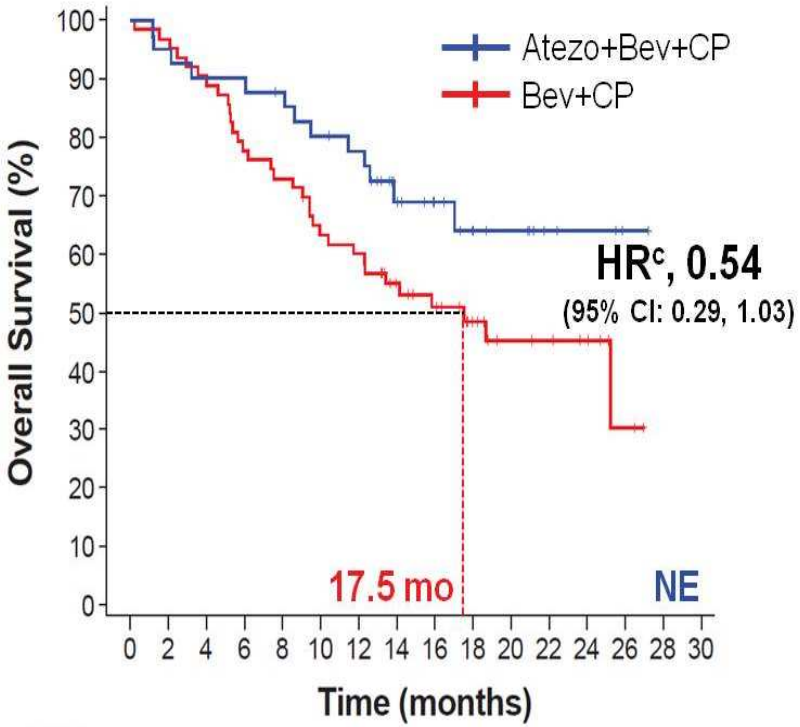


No. at Risk														
Atezo+CP	42	38	35	28	19	18	15	12	9	7	5	4	1	
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1

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

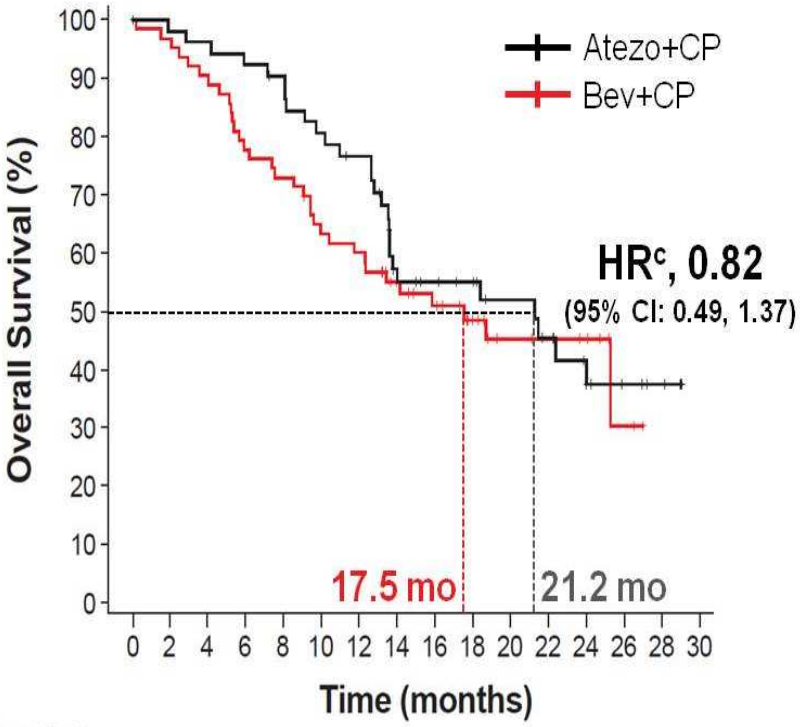
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients[a]

Arm B[b] vs Arm C



No. at Risk														
Atezo+Bev+CP	41	39	37	37	35	32	30	20	15	11	9	5	4	2
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

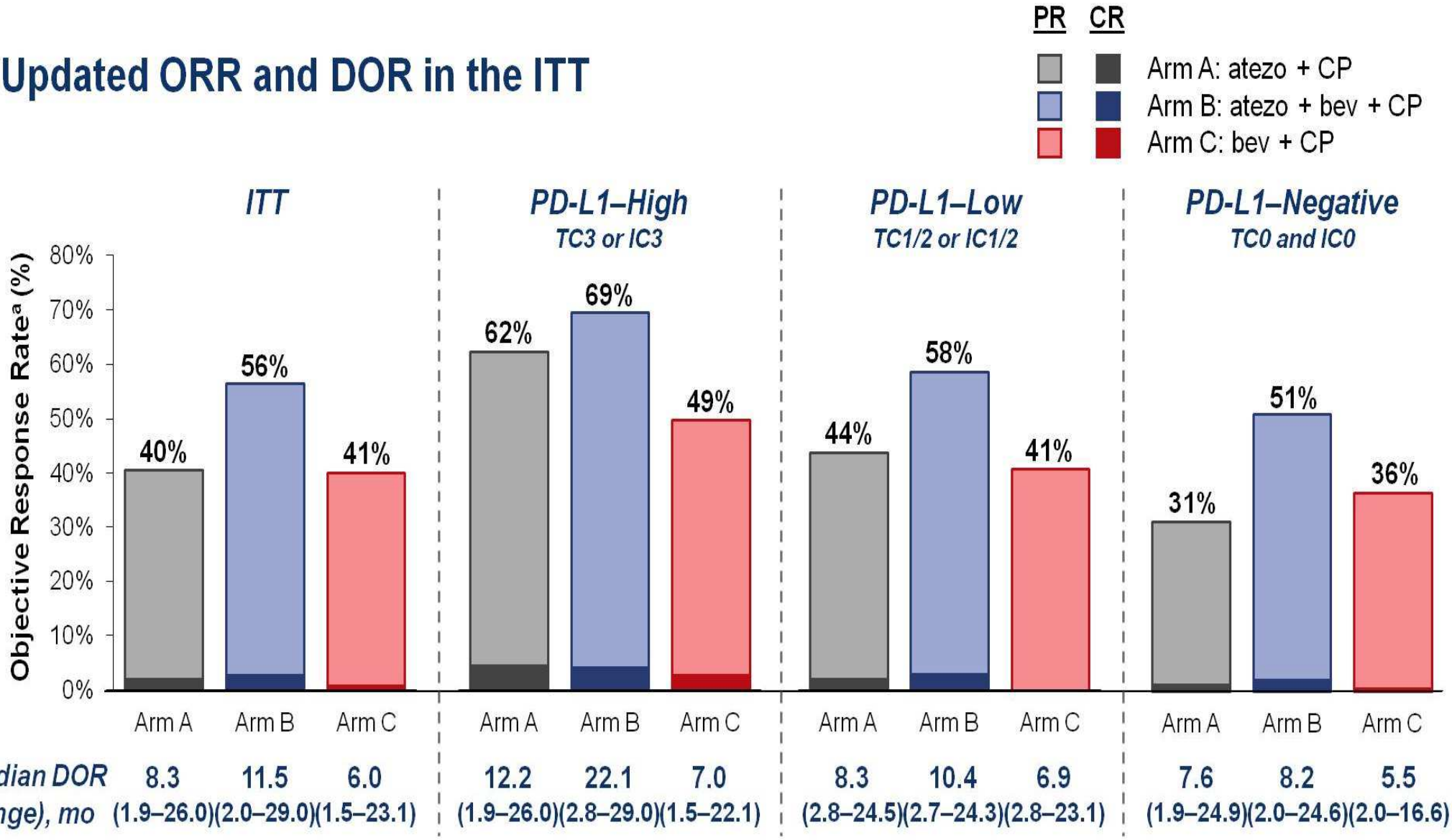
Arm A vs Arm C



No. at Risk														
Atezo+CP	53	51	50	48	46	41	37	24	22	20	16	13	8	6	4
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab. [c] Unstratified HR.
Data cutoff: January 22, 2018

Updated ORR and DOR in the ITT



[a] Investigator-assessed, confirmed per RECIST v1.1.
Data cutoff: January 22, 2018

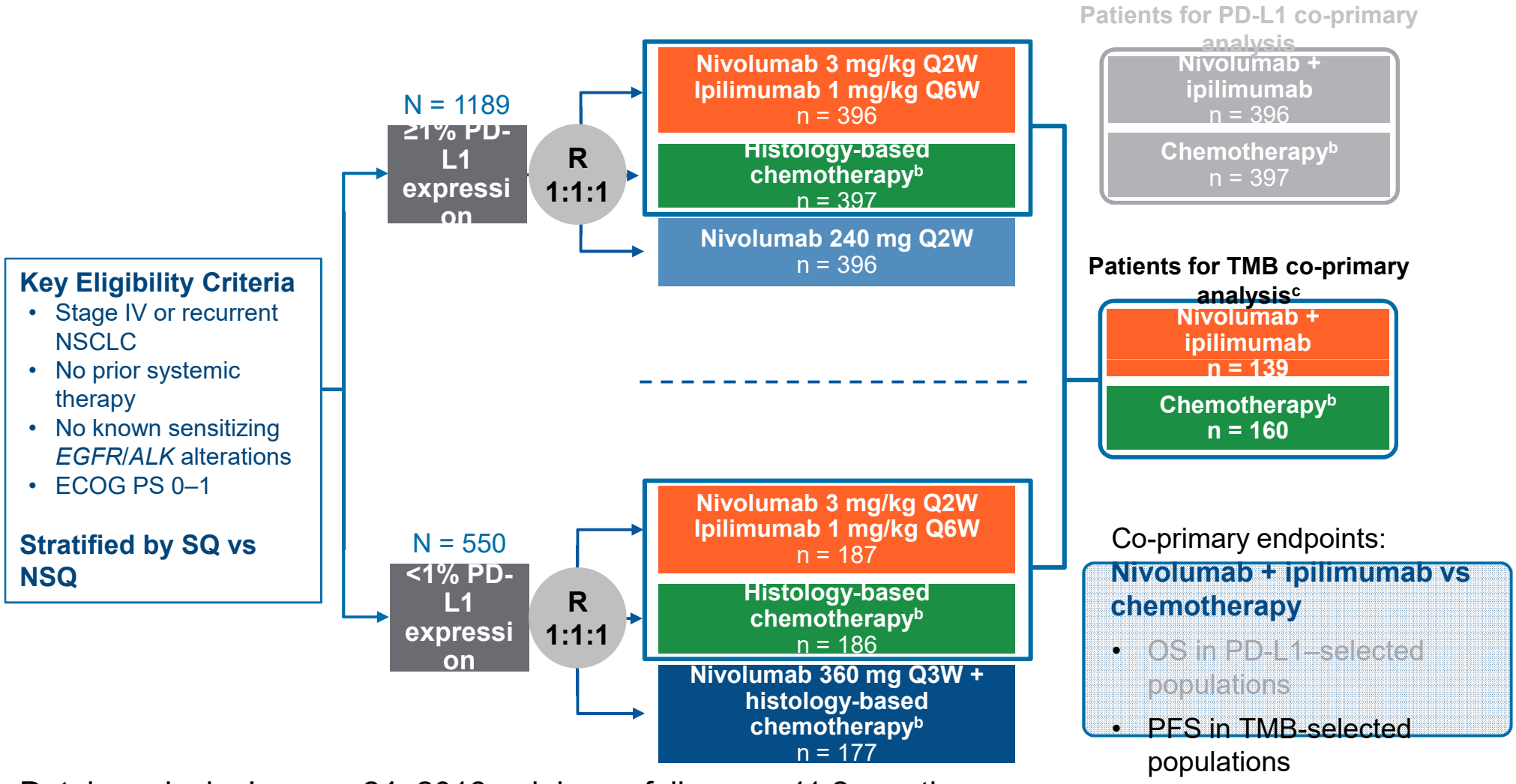
AACR ANNUAL MEETING 2018
American Association for Cancer Research
CHICAGO, IL
1506PL1802060-01; 04.2018
CheckMate 227
CT077

Nivolumab + Ipilimumab vs Platinum-Doublet Chemotherapy as First-line Treatment for Advanced Non-Small Cell Lung Cancer: Initial Results From CheckMate 227

Matthew D. Hellmann,[1] Tudor-Eliade Ciuleanu,[2] Adam Pluzanski,[3] Jong Seok Lee,[4] Gregory A. Otterson,[5] Clarisse Audigier-Valette,[6] Elisa Minenza,[7] Helena Linardou,[8] Sjaak Burgers,[9] Pamela Salman,[10] Hossein Borghaei,[11] Suresh S. Ramalingam,[12] Julie Brahmer,[13] Martin Reck,[14] Kenneth J. O'Byrne,[15] William J. Geese,[16] George Green,[16] Han Chang,[16] Joseph Szustakowski,[16] Prabhu Bhagavatheeswaran,[16] Diane Healey,[16] Yali Fu,[16] Faith Nathan,[16] Luis Paz-Ares[17]

[1]Memorial Sloan Kettering Cancer Center Hospital, New York, NY, USA; [2]Prof. Dr. Ion Chiricuta Institute of Oncology and Universitatea de Medicina si Farmacie Iuliu Hatieganu, Cluj-Napoca, Romania; [3]Centrum Onkologii–Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland; [4]Seoul National University Bundang Hospital, Seoul, South Korea; [5]The Ohio State University, Columbus, OH, USA; [6]Hôpital Sainte Musse, Toulon, France; [7]Ospedale Santa Maria della Misericordia, Perugia, Italy; [8]First Department of Oncology, Metropolitan Hospital, Athens, Greece; [9]Antoni Van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands; [10]Fundación Arturo López Pérez, Santiago, Chile; [11]Fox Chase Cancer Center, Philadelphia, PA, USA; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [14]LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [15]Princess Alexandra Hospital, Brisbane, QLD, Australia; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]Hospital Universitario 12 de Octubre, Centro Nacional de Investigaciones Oncológicas, Universidad Complutense, & CiberOnc, Madrid, Spain

CheckMate 227 Part 1 Study Design[a]



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

[a]NCT02477826 [b]**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; [c]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mut/Mb

Nivolumab + Ipilimumab Using FoundationOne CDx™

- Retrospective testing from CheckMate 026, 012, and 568 informed selection of the TMB cutoff (≥10 mut/Mb)[1–3]
- ORR increased in patients with higher TMB, and plateaued at TMB ≥10 mut/Mb

CheckMate 568:

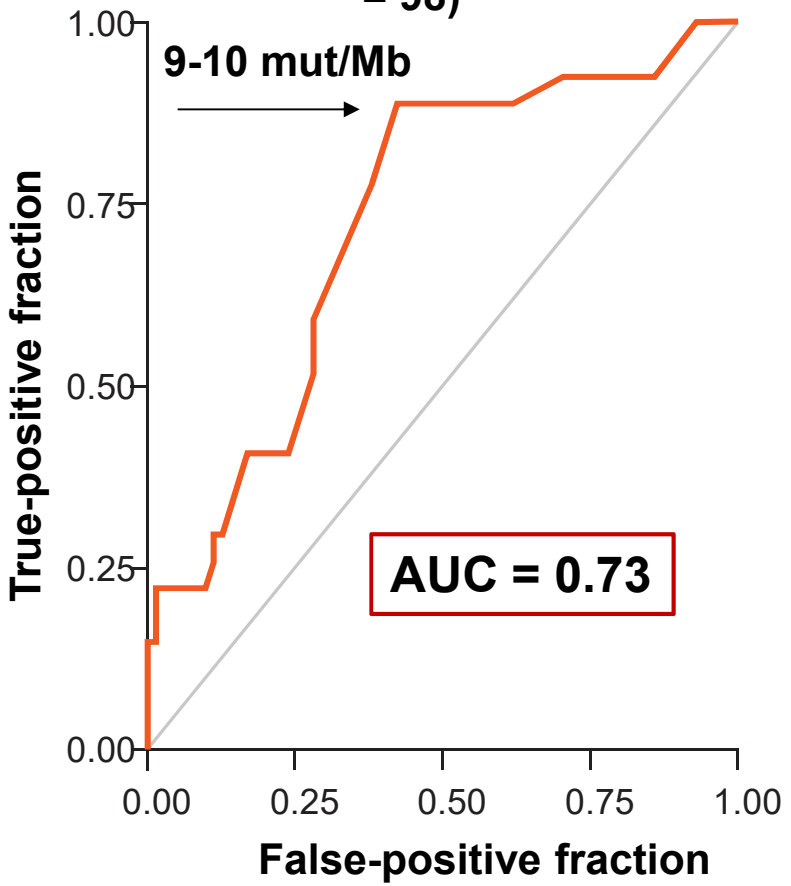
Phase 2 study of nivolumab + ipilimumab in 1L NSCLC

Tumor Mutational Burden (TMB) as a Biomarker for Clinical Benefit From Dual Immune Checkpoint Blockade With Nivolumab + Ipilimumab in First-line Non-Small Cell Lung Cancer: Identification of TMB Cutoff From CheckMate 568

Ramalingam S, et al.

Date: April 16, 2018 Time: 12:05 – 12:25pm

CheckMate 568: ROC for TMB by ORR irrespective of tumor PD-L1 expression (n = 98)



1. Carbone DP, et al. *N Engl J Med* 2017:376;2415–2426; 2. Hellmann MD, et al. *Cancer Cell* 2018. doi: https://doi.org/10.1016/j.ccell.2018.03.018. Epub; 3. Ramalingam S, et al. Presented at AACR Annual Meeting; April 14–18, 2018; Chicago, IL, USA. CT078.

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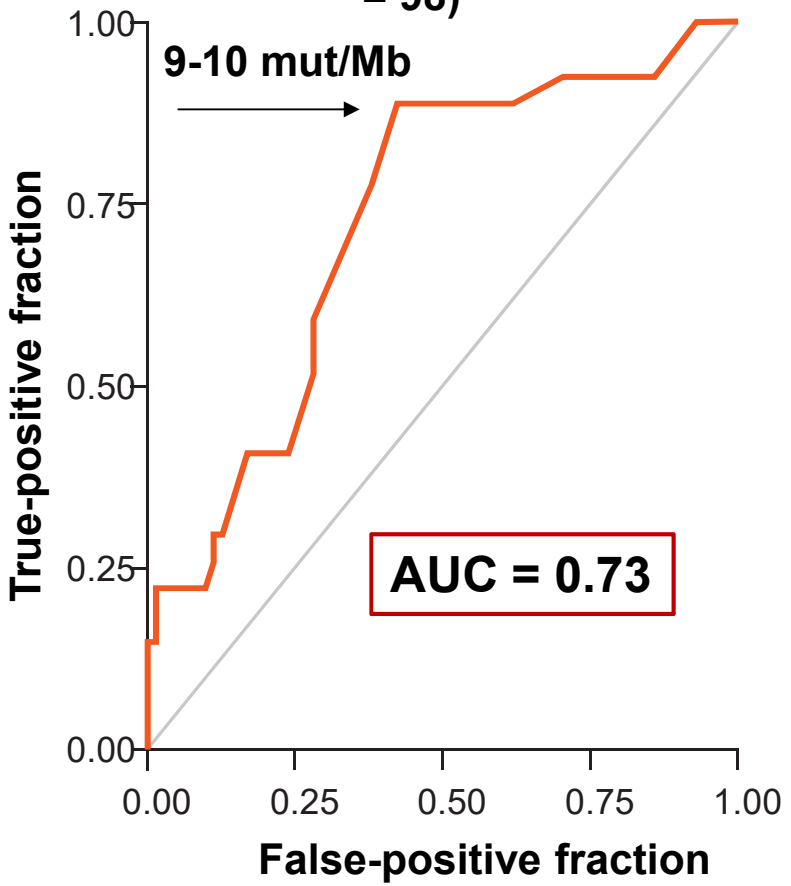

1. Carbone DP, et al. *N Engl J Med* 2017:376;2415–2426; 2. Hellmann MD, et al. *Cancer Cell* 2018. doi: https://doi.org/10.1016/j.ccell.2018.03.018. Epub; 3. Ramalingam S, et al. Presented at AACR Annual Meeting; April 14–18, 2018; Chicago, IL, USA. CT078.

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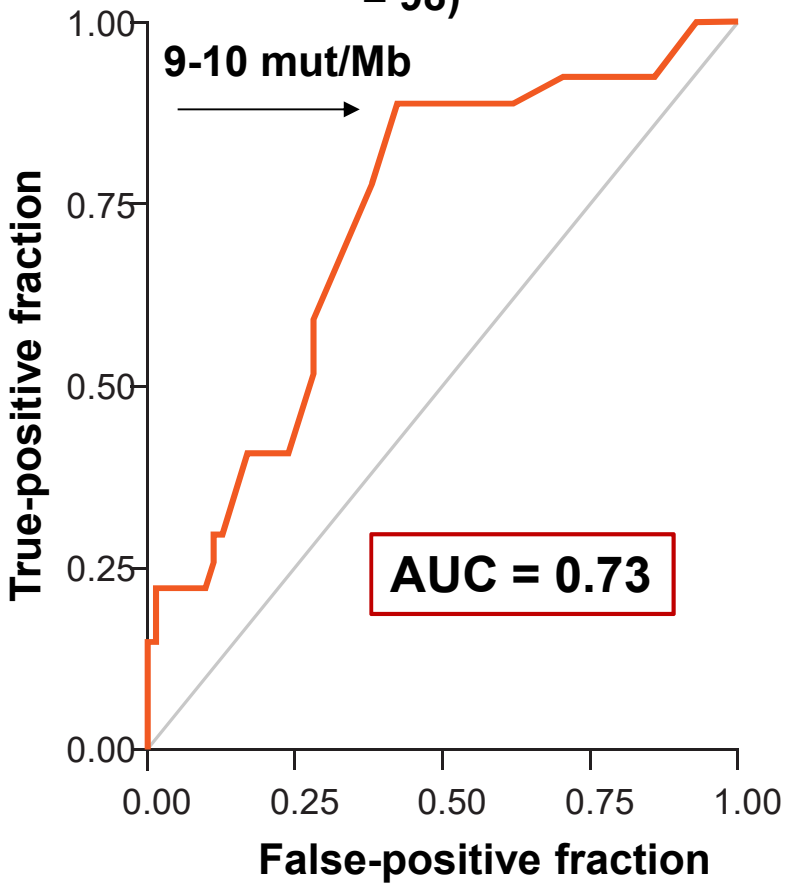
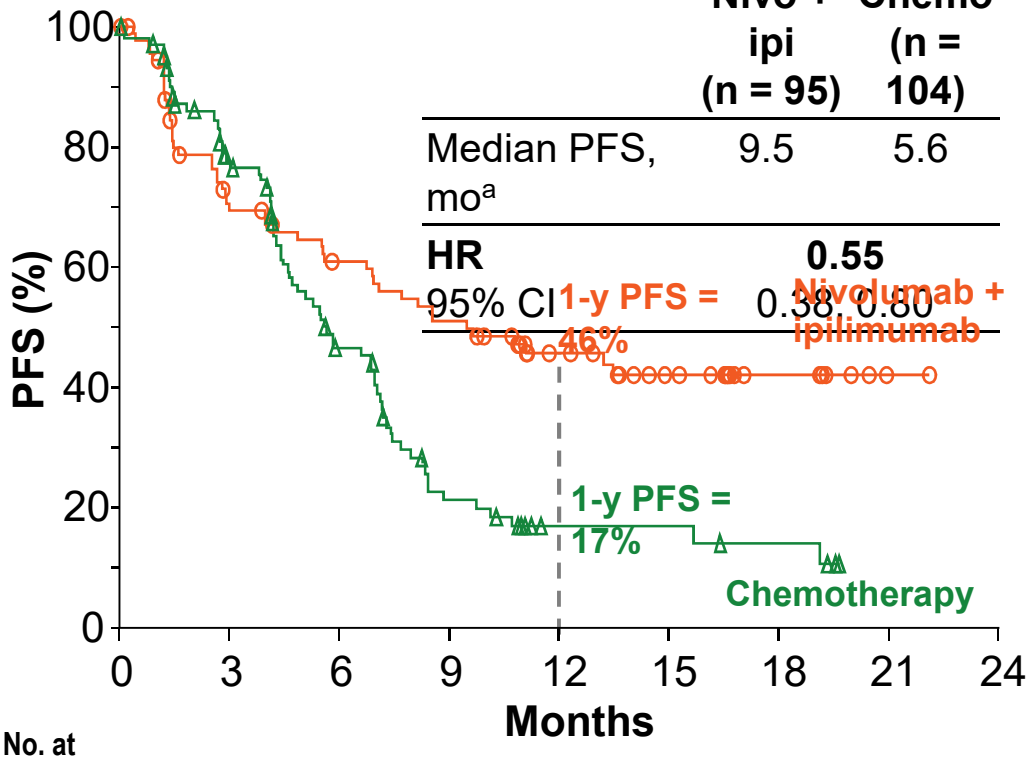


1. Carbone DP, et al. *N Engl J Med* 2017:376;2415–2426; 2. Hellmann MD, et al. *Cancer Cell* 2018. doi: https://doi.org/10.1016/j.ccell.2018.03.018. Epub; 3. Ramalingam S, et al. Presented at AACR Annual Meeting; April 14–18, 2018; Chicago, IL, USA. CT078.

PFS in Patients With High TMB (≥10 mut/Mb) by Tumor Histology

Non-squamous

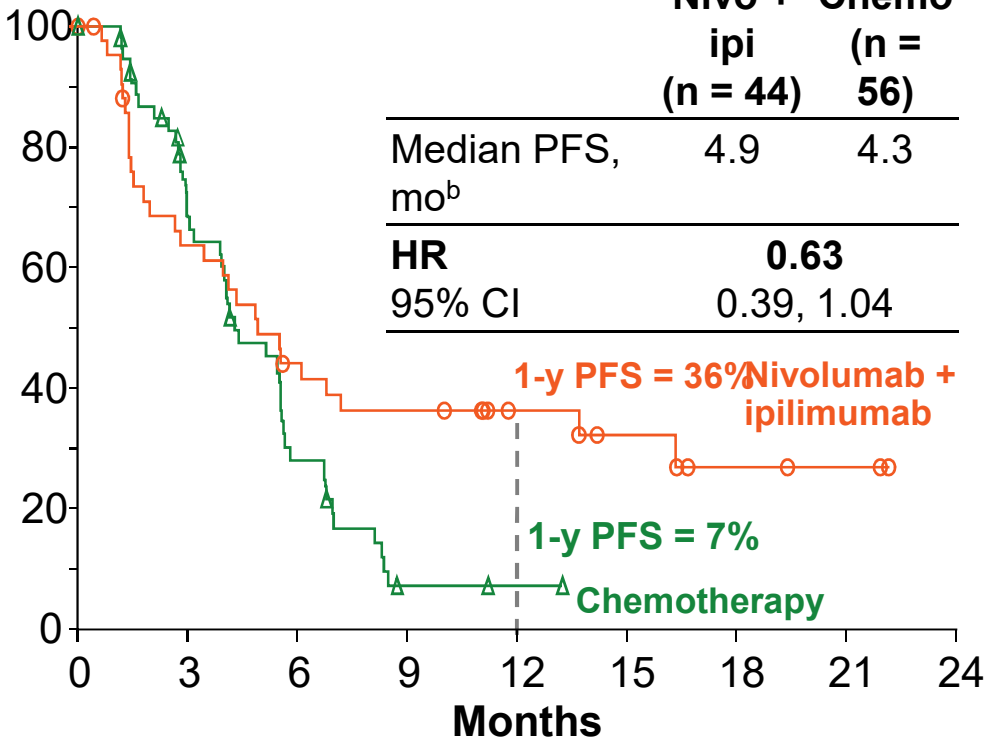
	Nivo + ipi (n = 95)	Chemo (n = 104)
Median PFS, mo[a]	9.5	5.6
HR	0.55	
95% CI	0.38, 0.80	



No. at risk									
Nivo + ipi	95	59	49	41	27	18	8	1	0
Chemo	104	70	38	15	6	6	4	0	0

Squamous

	Nivo + ipi (n = 44)	Chemo (n = 56)
Median PFS, mo[b]	4.9	4.3
HR	0.63	
95% CI	0.39, 1.04	

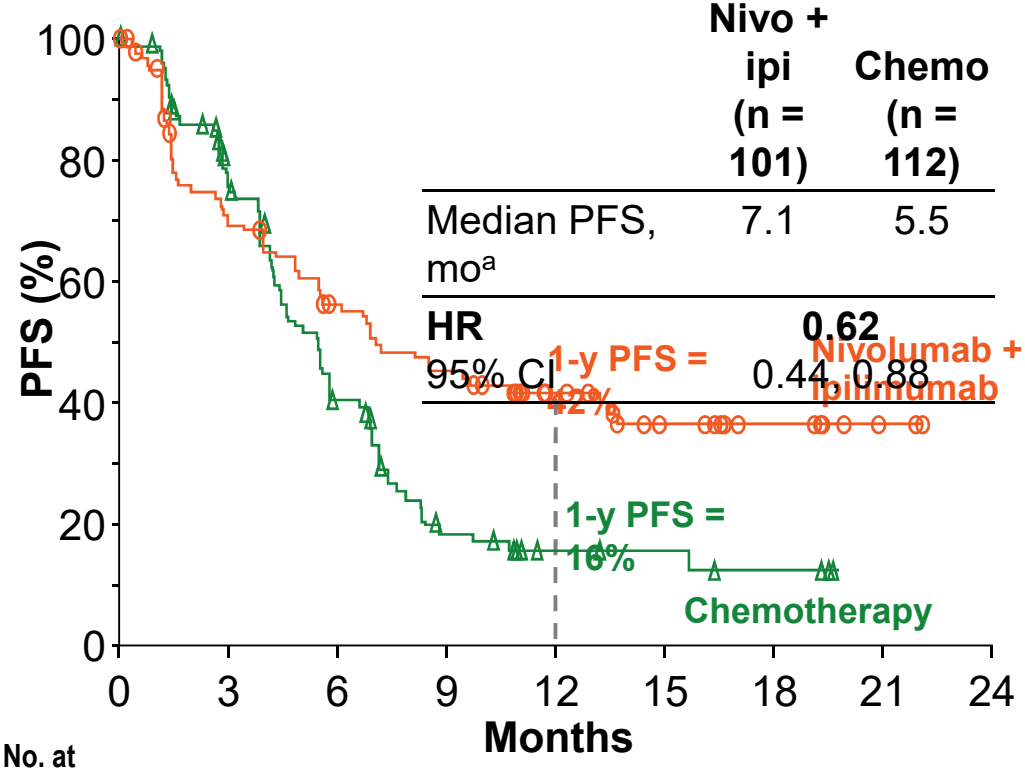


No. at risk									
Nivo + ipi	44	26	17	14	9	6	3	2	0
Chemo	56	33	13	2	1	0	0	0	0

[a]95% CI: nivo + ipi (5.6 mo, NR), chemo (4.5, 7.0 mo); [b]95% CI: nivo + ipi (2.7, 13.7 mo), chemo (3.2, 5.6 mo)

PFS in Patients With High TMB (≥10 mut/Mb) by Tumor PD-L1 Expression

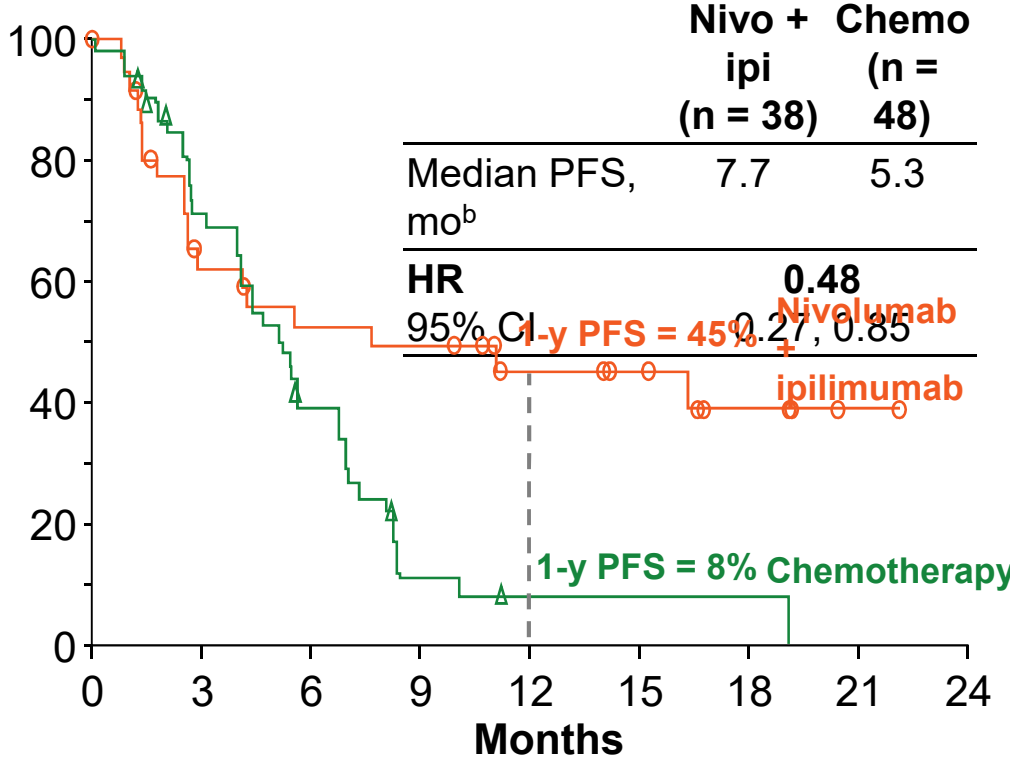
≥1% PD-L1 expression



	Nivo + ipi (n = 101)	Chemo (n = 112)
Median PFS, mo[a]	7.1	5.5
HR	0.62	
95% CI	0.44, 0.88	

No. at risk									
Nivo + ipi	101	65	50	40	26	16	7	2	0
Chemo	112	73	35	13	6	5	3	0	0

<1% PD-L1 expression

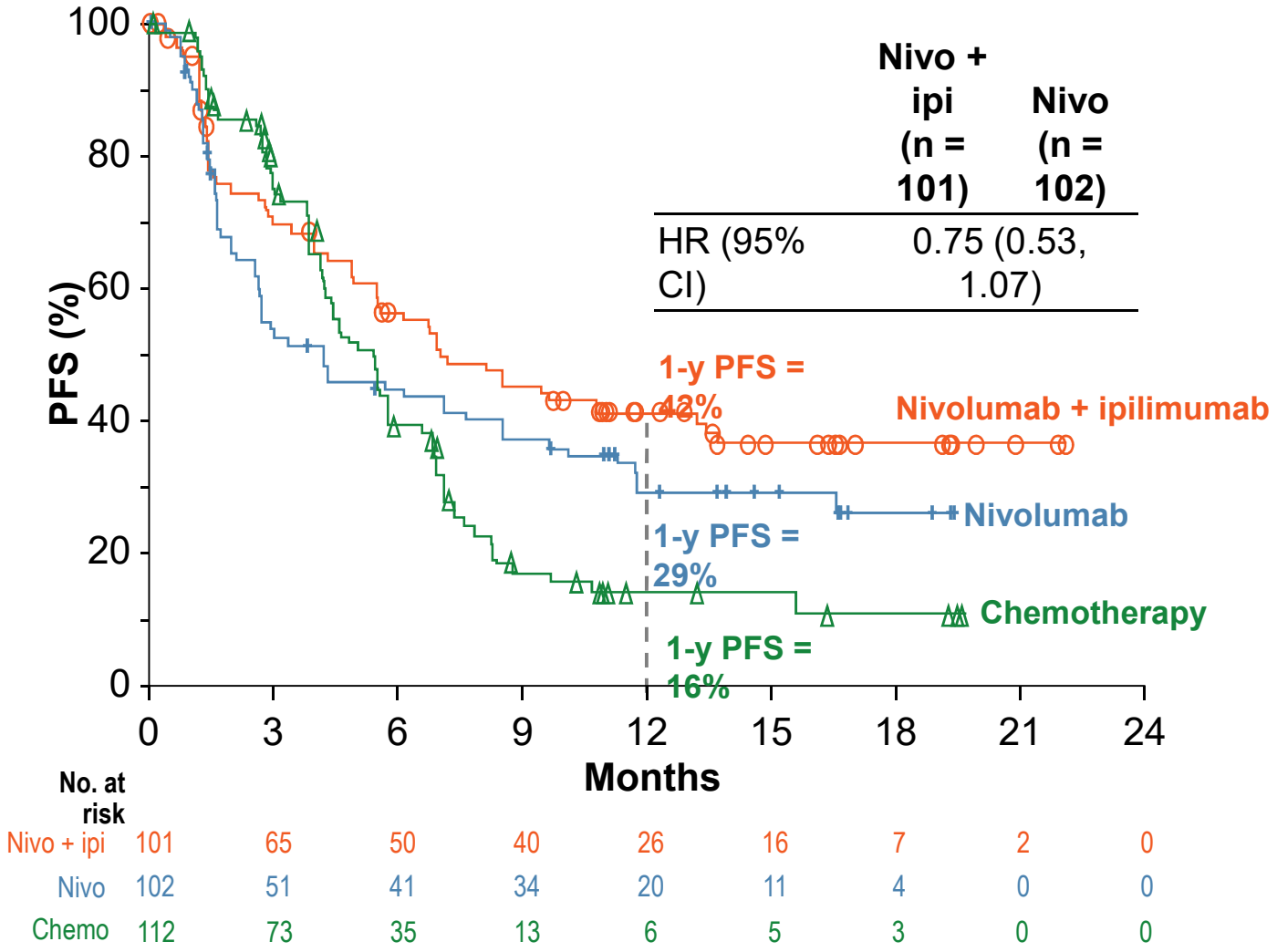


	Nivo + ipi (n = 38)	Chemo (n = 48)
Median PFS, mo[b]	7.7	5.3
HR	0.48	
95% CI	0.27, 0.85	

Nivo + ipi	38	20	16	15	10	8	4	1	0
Chemo	48	30	16	4	1	1	1	0	0

[a]95% CI: nivo + ipi (5.5, 13.5 mo), chemo (4.3, 6.6 mo); [b]95% CI: nivo + ipi (2.7 mo, NR), chemo (4.0, 6.8 mo)

Patients With High TMB (≥10 mut/Mb) and ≥1% PD-L1 Expression



Non small cell lung cancer second line

Checkmate 017 and 057: STUDY DESIGNS

Checkmate 017 (NCT01642004; N=272)

Key eligibility criteria

- Stage IIIB/IV **SQ NSCLC**
- ECOG PS 0–1
- One prior platinum-based chemotherapy
- Pretreatment (archival or fresh) tumor samples required for PD-L1 analysis

Randomize 1:1

- **Nivolumab** 3 mg/kg IV Q2W until PD or unacceptable toxicity **(n=135)**
- **Docetaxel** 75 mg/m² IV Q3W until PD or unacceptable toxicity **(n=137)**

Checkmate 057 (NCT01673867; N=582)

- Stage IIIB/IV **non-SQ NSCLC**
- ECOG PS 0–1
- One prior platinum-based chemotherapy
- Pretreatment (archival or fresh) tumor samples required for PD-L1 analysis
- Prior maintenance therapy allowed
- Prior TKI therapy allowed for known *ALK* translocations or *EGFR* mutations

Randomize 1:1

- **Nivolumab** 3 mg/kg IV Q2W until PD or unacceptable toxicity **(n=292)**
- **Docetaxel** 75 mg/m² IV Q3W until PD or unacceptable toxicity **(n=290)**

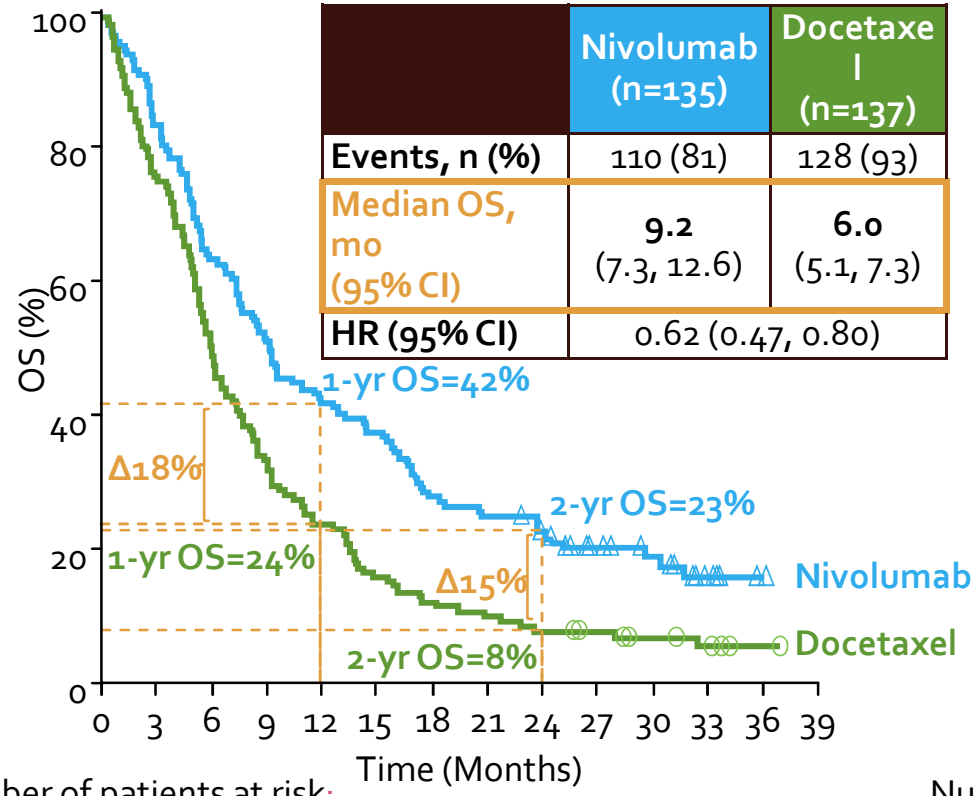
Endpoints

- **Primary**
  - OS
- **Additional**
  - ORR
  - PFS
  - Efficacy by tumor PD-L1 expression
  - Safety
  - Quality of life (LCSS)

Borghaei H et al. Poster presentation at ASCO 2016. 9025.

Checkmate 017 and 057: Kaplan-Meier Estimates of OS

Checkmate 017 (SQ NSCLC)

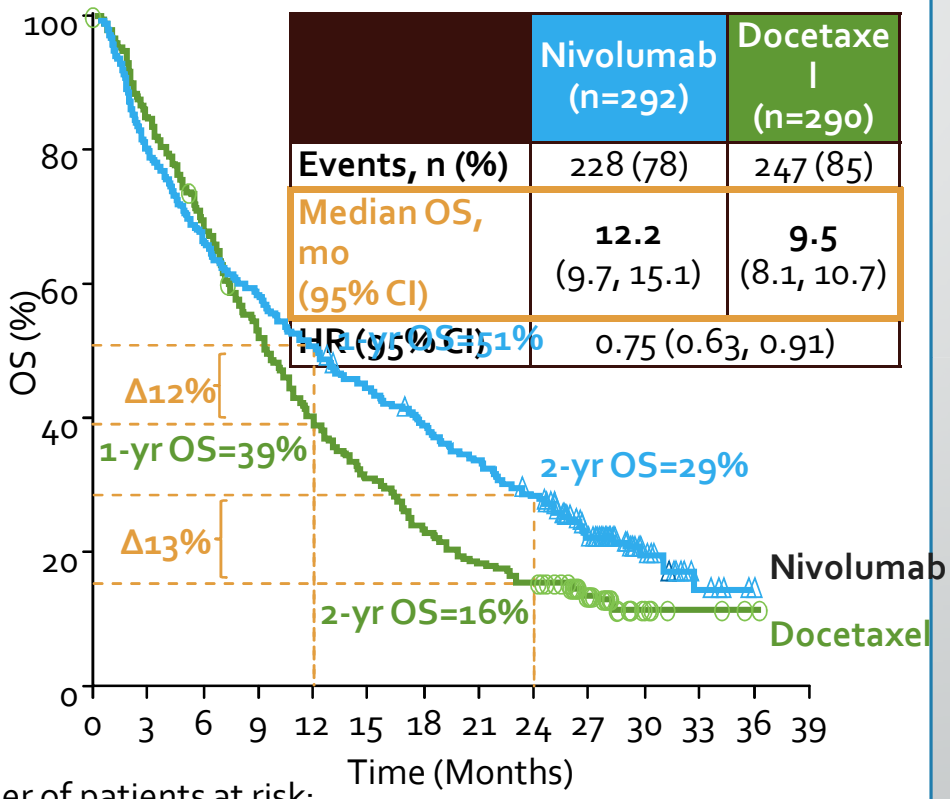


	Nivolumab (n=135)	Docetaxel (n=137)
Events, n (%)	110 (81)	128 (93)
Median OS, mo (95% CI)	**9.2** (7.3, 12.6)	**6.0** (5.1, 7.3)
HR (95% CI)	0.62 (0.47, 0.80)	

Number of patients at risk:

Nivolumab	135	113	86	69	57	51	38	34	29	19	14	7	1	0
Docetaxel	137	104	69	46	33	22	17	14	11	9	6	4	1	0

Checkmate 057 (non-SQ NSCLC)



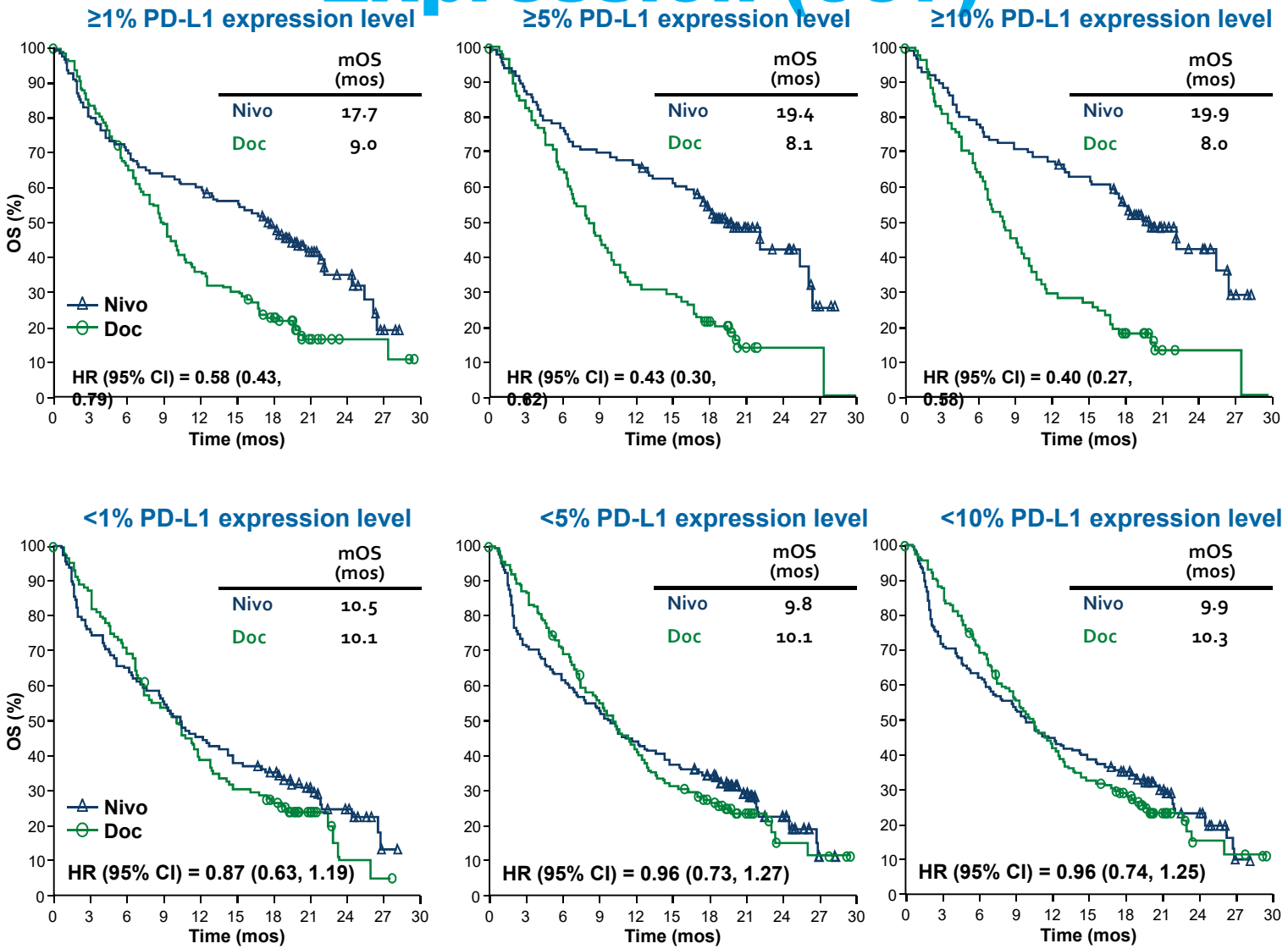
	Nivolumab (n=292)	Docetaxel (n=290)
Events, n (%)	228 (78)	247 (85)
Median OS, mo (95% CI)	**12.2** (9.7, 15.1)	**9.5** (8.1, 10.7)
HR (95% CI)	0.75 (0.63, 0.91)	

Number of patients at risk:

Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

Based on February 2016 DBL. Symbols refer to censored observations. Minimum follow-up for survival: 24.2 months.
Borghaei H et al. Poster presentation at ASCO 2016. 9025.

Overall Survival by PD-L1 Expression (057)



Based on a July 2, 2015 DBL. Symbols represent censored observations.

KEYNOTE-010: Phase 2/3 Study of Pembrolizumab (MK-3475) vs Docetaxel for PD-L1–Positive NSCLC After Platinum-Based Therapy

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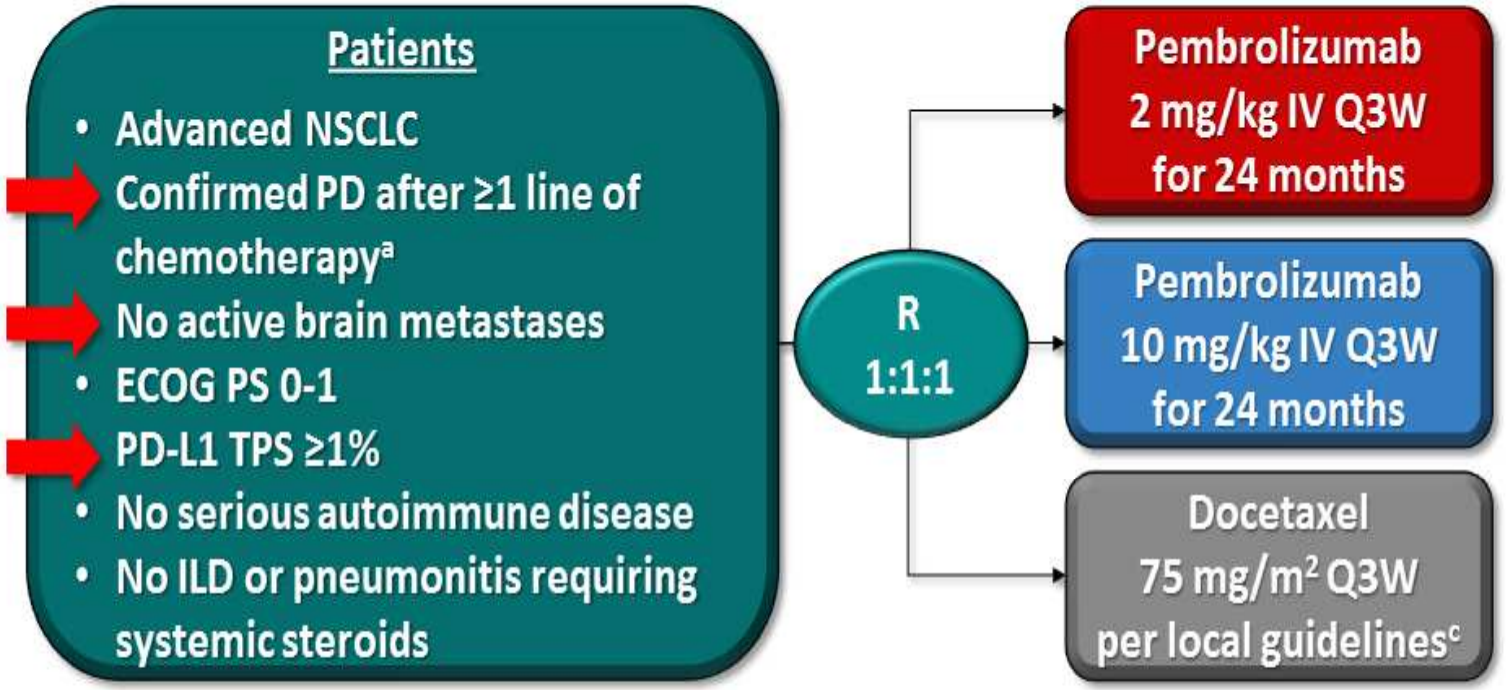
SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

RS Herbst. Presented December 20, 2015.

KEYNOTE-010 Study Design



Stratification factors:

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

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

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

ClinicalTrials.gov, NCT01905657.

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

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

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

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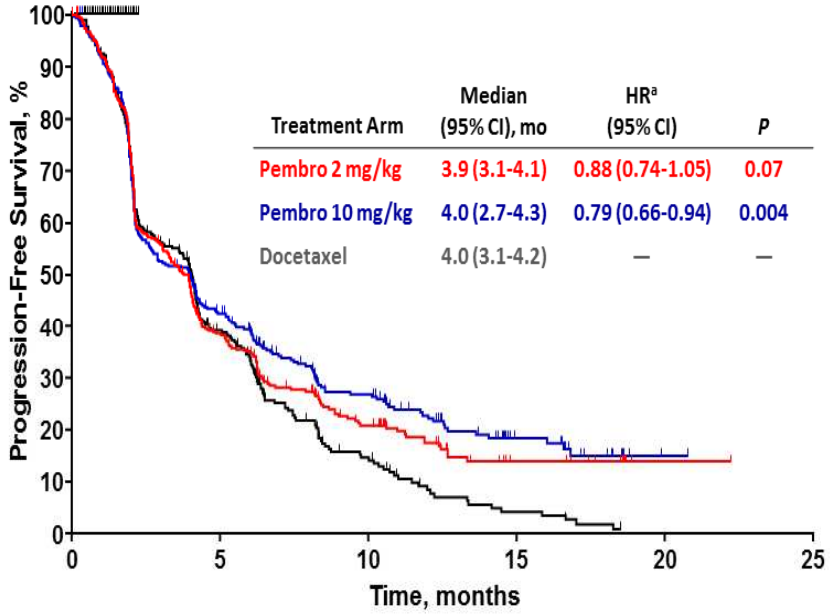
PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥1%



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	3.9 (3.1-4.1)	0.88 (0.74-1.05)	0.07
Pembro 10 mg/kg	4.0 (2.7-4.3)	0.79 (0.66-0.94)	0.004
Docetaxel	4.0 (3.1-4.2)	—	—

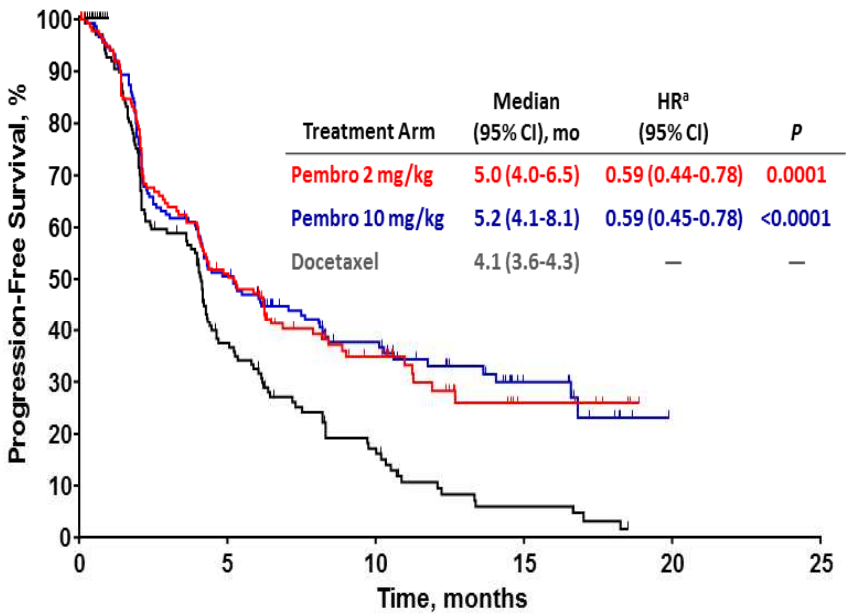
344	122	46	12	1	0
346	137	60	19	1	0
343	103	27	6	0	0

Analysis cut-off date: September 30, 2015.

*Comparison of pembrolizumab vs docetaxel.

RS Herbst. Presented December 20, 2015.

PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥50%



Treatment Arm	Median (95% CI), mo	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	5.0 (4.0-6.5)	0.59 (0.44-0.78)	0.0001
Pembro 10 mg/kg	5.2 (4.1-8.1)	0.59 (0.45-0.78)	<0.0001
Docetaxel	4.1 (3.6-4.3)	—	—

139	66	29	6	0	0
151	72	36	12	0	0
152	45	17	5	0	0

lysis cut-off date: September 30, 2015.

*Comparison of pembrolizumab vs docetaxel.

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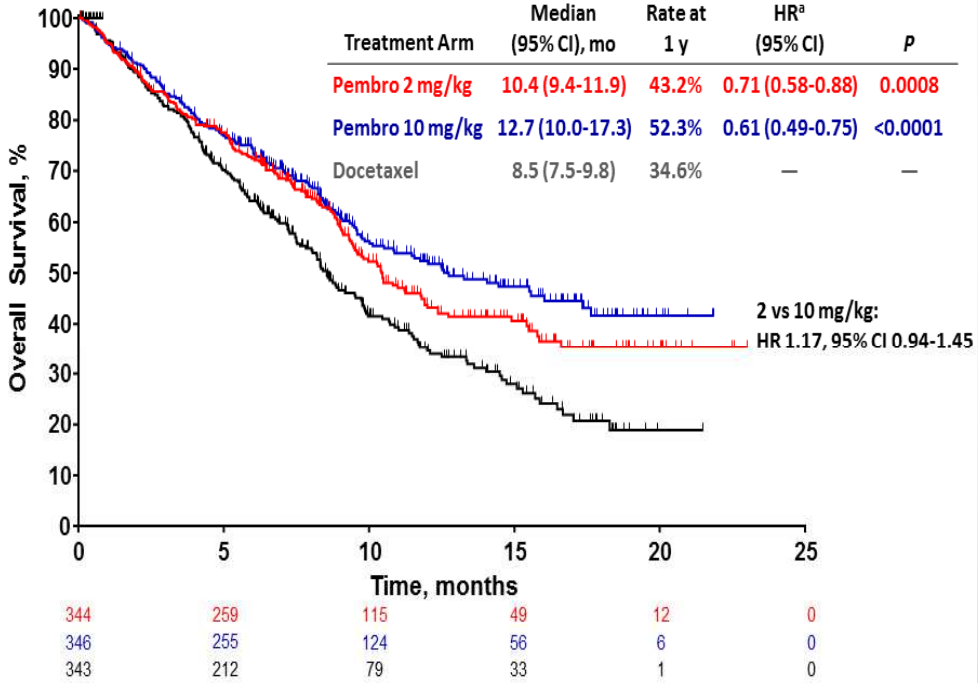
OS, PD-L1 TPS ≥1% (Total Population)



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

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

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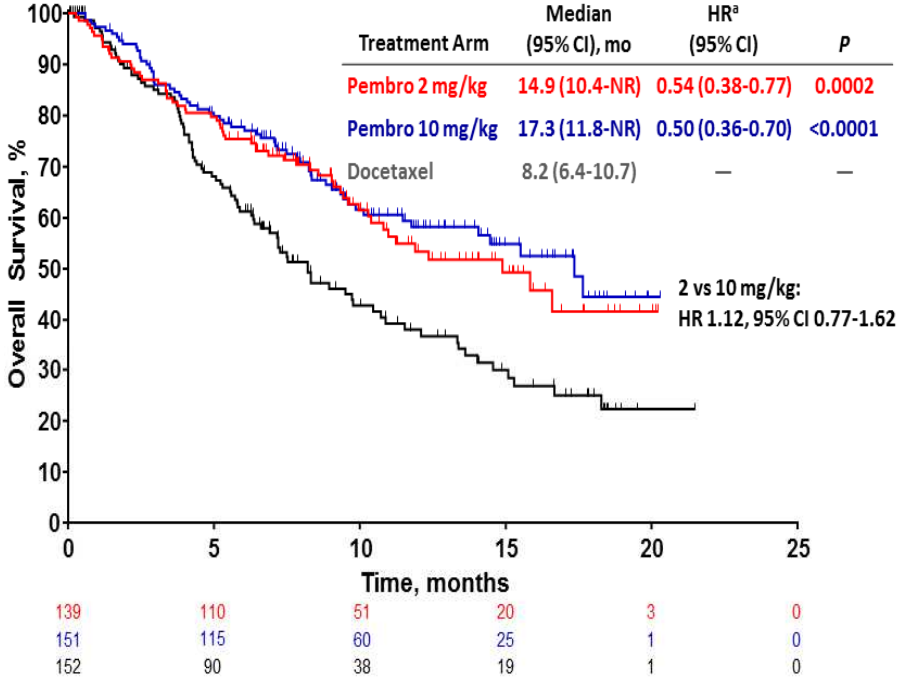
Analysis cut-off date: September 30, 2015.

[a]Comparison of pembrolizumab vs docetaxel.

RS Herbst. Presented December 20, 2015.

OS, PD-L1 TPS ≥50% Stratum



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

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

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Analysis cut-off date: September 30, 2015.

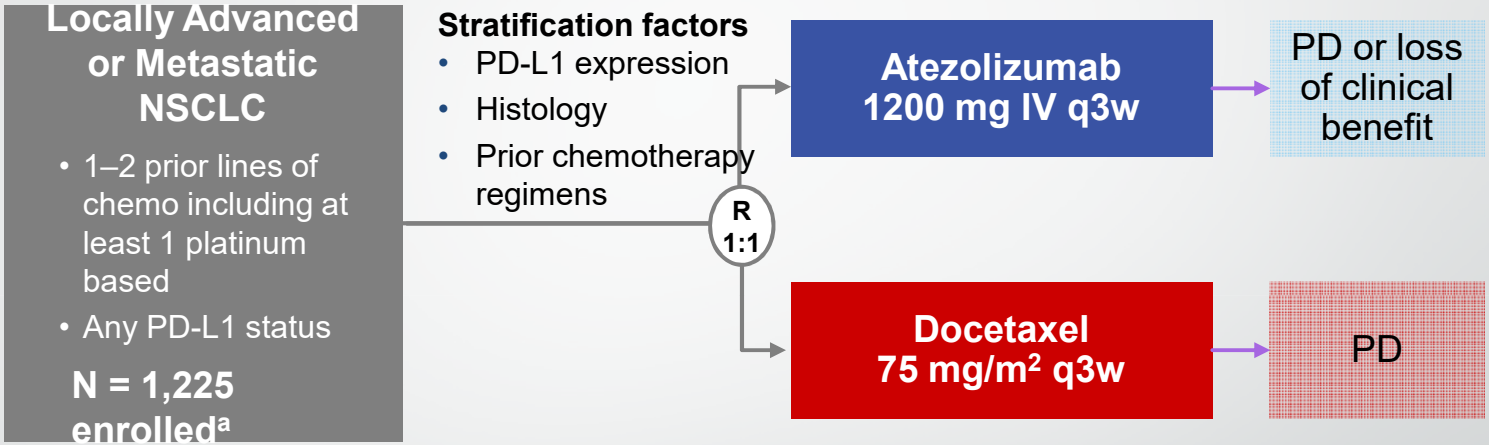
[a]Comparison of pembrolizumab vs docetaxel.

OAK (Abstract LBA44) Content presented at ESMO

Efficacy, safety and predictive biomarker results from OAK, a randomized phase III study comparing atezolizumab with docetaxel in patients with advanced NSCLC

Barlesi, et al.

Phase III OAK study design



Primary Endpoints (first 850 enrolled patients):

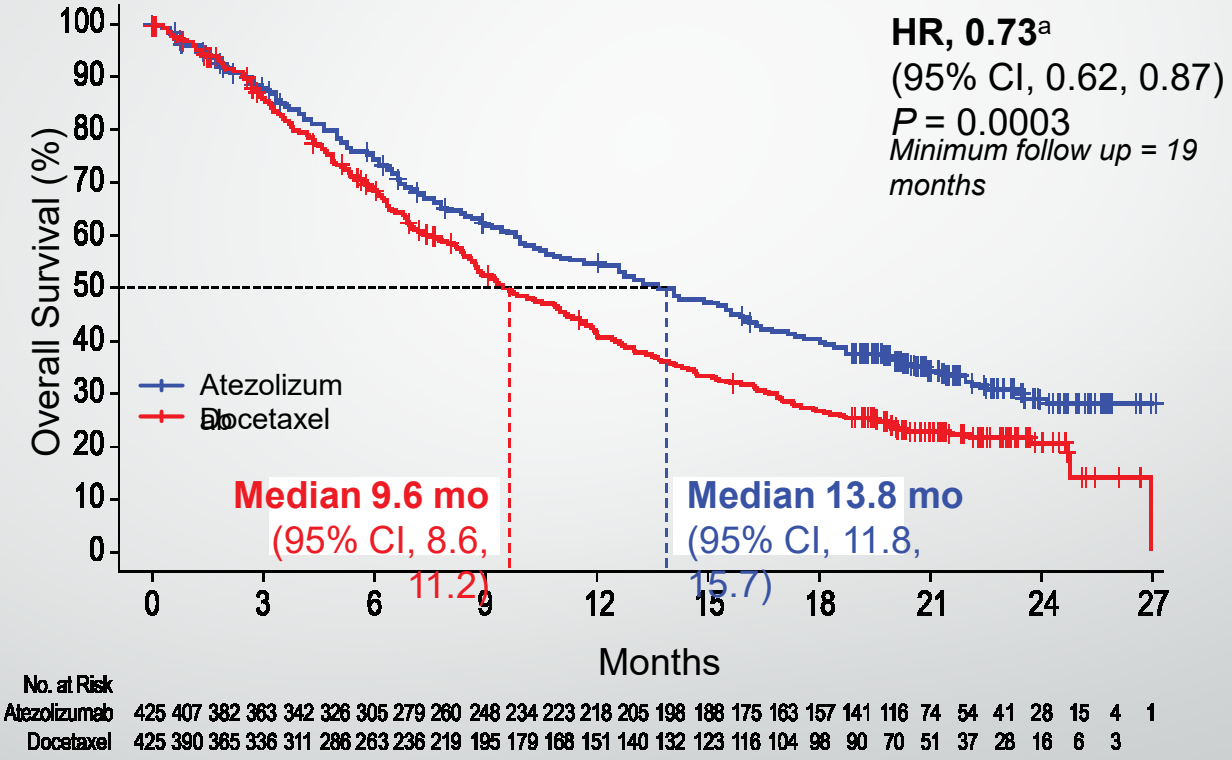
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

Secondary Endpoints: ORR, PFS, DoR, Safety

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

- Barlesi et al, Atezolizumab Phase III OAK Study

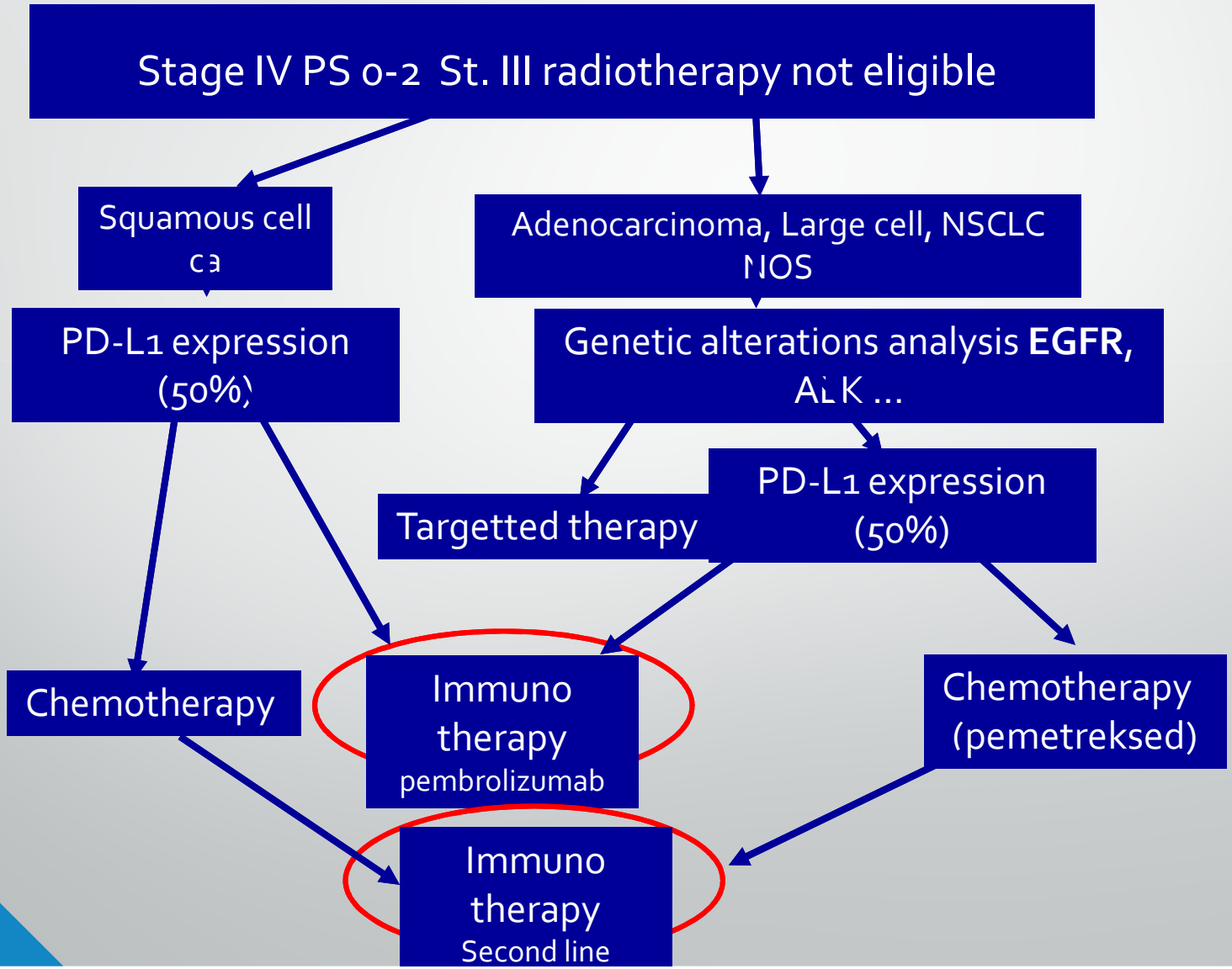
Overall survival, ITT (n = 850)



[a]Stratified HR.

- Barlesi et al, Atezolizumab Phase III OAK Study

Advanced NSCLC algorithm

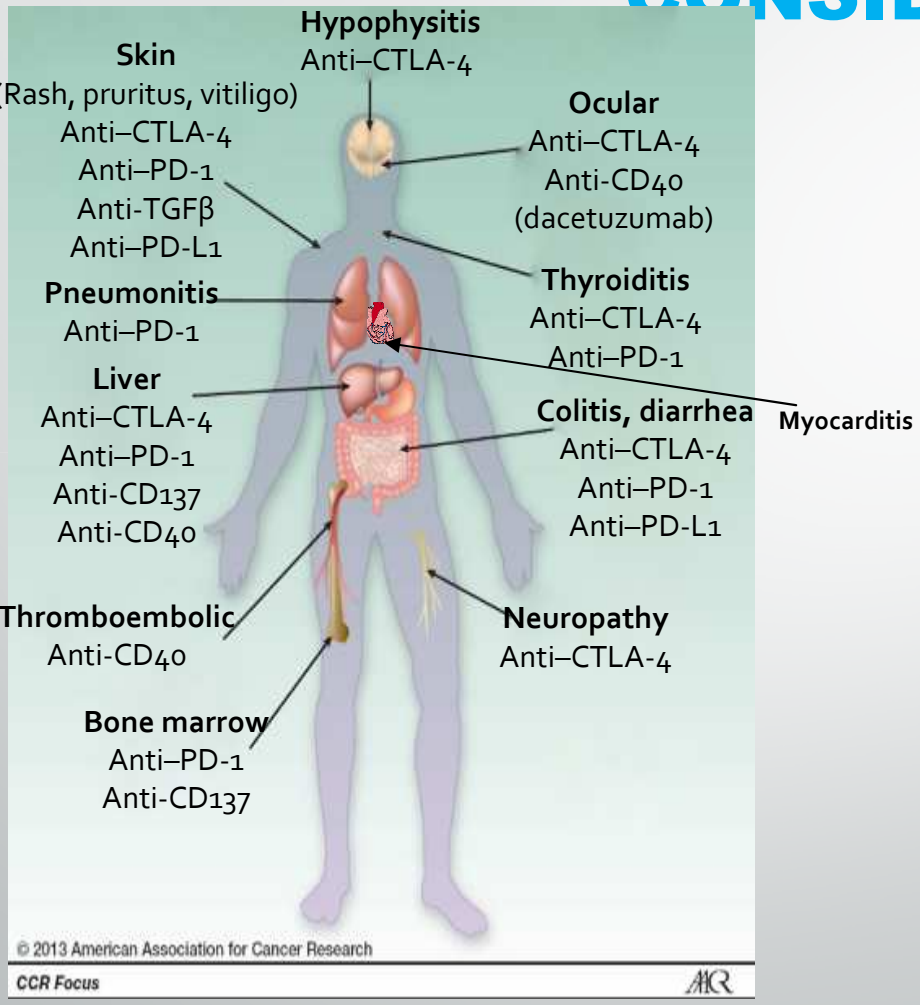


Stage IV conclusions

- First line immunotherapy with pembrolizumab in PD-L1 positive NSCLC became standard of care
- First line immunochemotherapy in new option in non squamous NSCLC despite of PD-L1 expression
- Combination of anti PD-L1 and anti CTLA-4 showed promising results in selected population
- Therapy consisting of chemo, immuno and antiangiogenic therapy showed promising result

DARK SIDE OF THE FORCE

RARE BUT NEW Immune-Related Adverse Reactions With I-O Therapies HAVE TO BE CONSIDERED

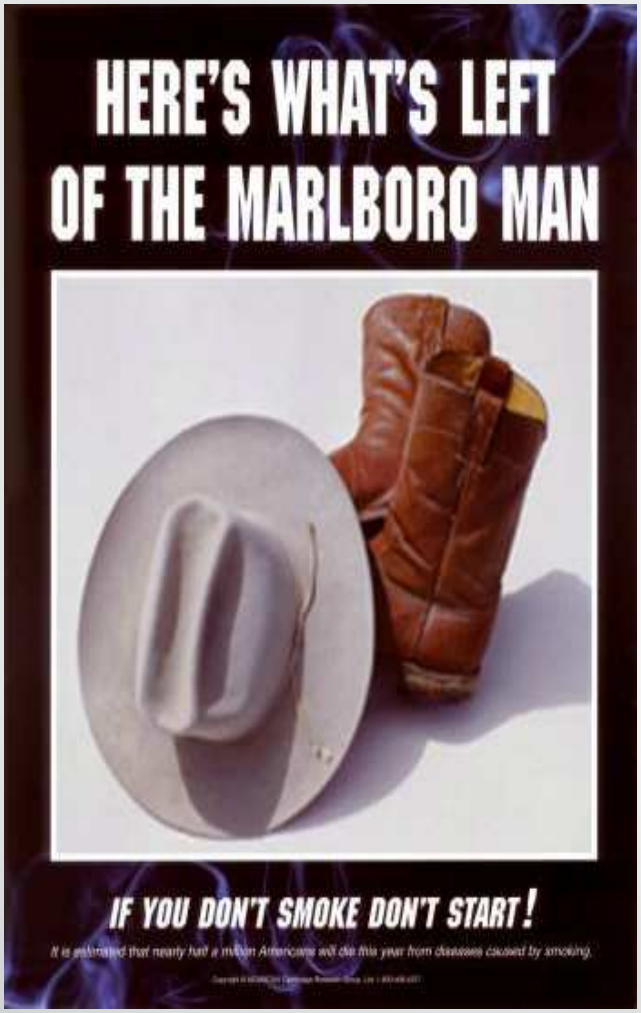


- Be aware of these side effects and carefully control symptoms
- Educate patients for early recognition
- Monitor regularly: liver enzymes, fT_3, fT_4, TSH and blood count
- Grade II: withhold treatment
  Grade III, IV: immediately start IV corticosteroids

CD=cluster of differentiation; CTLA-4=cytotoxic T-lymphocyte antigen 4; fT_3=free triiodothyronine; fT_4=free thyroxine; I-O=immuno-oncology; IV=intravenous; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; TGFβ=Transforming growth factor beta; TSH=thyroid stimulating hormone.
Melero I et al; *Clin Cancer Res* 2013;19:997-1008.

Conclusions

- Consolidation immunotherapy after definitive radiochemotherapy in stage III NSCLC showed positive results both in PFS and OS
- First line immunotherapy of pembrolizumab in PD-L1 positive NSCLC became standard of care
- Immunochemotherapy is new option in non-squamous wild type NSCLC
- Second line immunotherapy has firm place in second line therapy of NSCLC for patient previously treated with chemo only


HERE'S WHAT'S LEFT
OF THE MARLBORO MAN
IF YOU DON'T SMOKE DON'T START!

Thank You