Actualités des congrès 2018 : nouveaux acquis en immunothérapie

24 Mai 2019

Angoulême

Alain Vergnenègre, OUTC,

CHU Limoges

SURVIE ACTUALISÉE DE L'ESSAI PACIFIC
DURVALUMAB *VS PLACEBO*
APRÈS CHIMIO-RADIOTHÉRAPIE DES STADES III

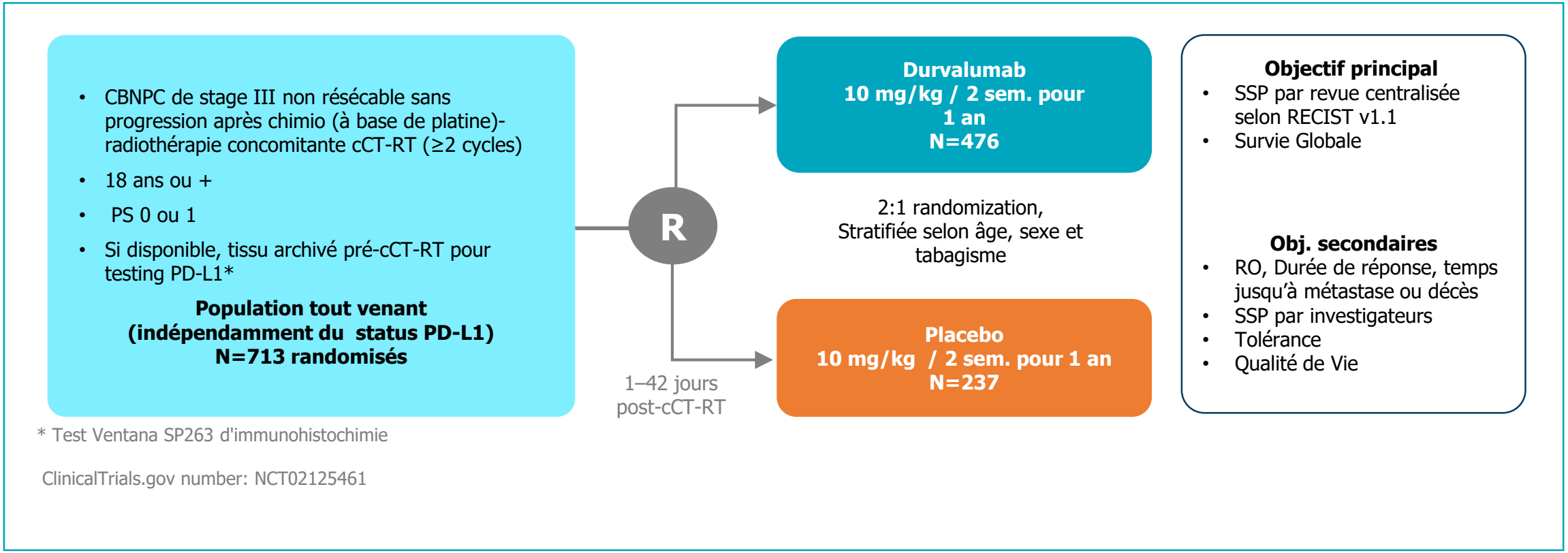
Antonia S.* et al. - *WCLC® 2018 - Abs.# PL02.01

SURVIE actualisée de l'essai PACIFIC

Contexte :

- L'essai de phase III PACIFIC a modifié les pratiques pour les stades III traités par CT-RT concomitante en démontrant un bénéfice de SSP du Durvalumab *vs* *placebo* en consolidation (SSP de 16,8 *vs* 5,6 mois Antonia SJ. *NEJM* 2017)

Design de l'essai PACIFIC



* Test Ventana SP263 d'immunohistochimie

ClinicalTrials.gov number: NCT02125461

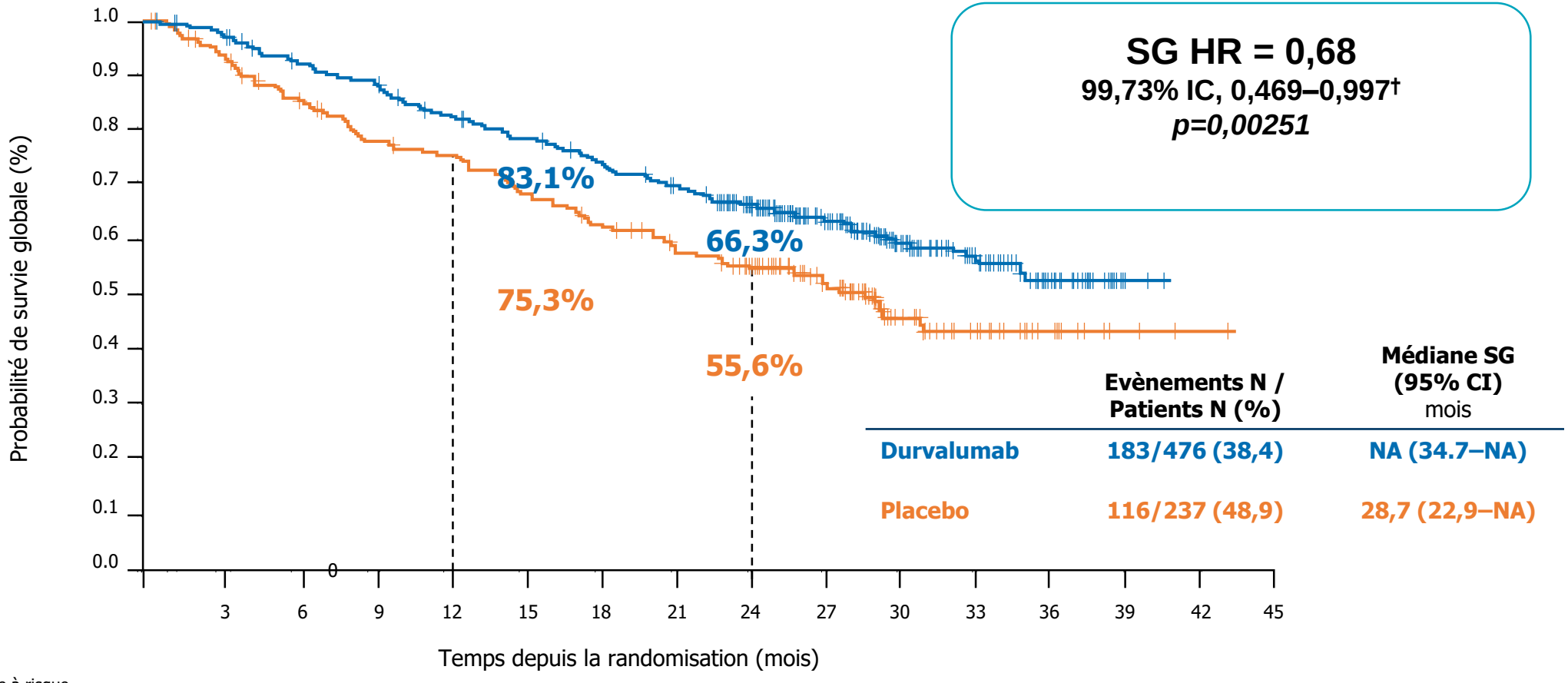
SURVIE actualisée de l'essai PACIFIC

Résultats présentés en session plénière

- **Actualisation de la SSP et du temps médian jusqu'à métastases ou décès**
- **Données de SG**
- toxicités

		Publication *NEJM* 2017	WCLC® 09/2018
Survie Sans Progression (SSP) (mois)	bras *placebo*	5,6	5,6
	bras Durvalumab	16,8	17,2 HR 0.51
SSP à 2 ans (%)	bras *placebo*		26,7%
	bras Durvalumab		49,5%

SURVIE actualisée de l'essai PACIFIC Survie globale



SG HR = 0,68
99,73% IC, 0,469–0,997†
p=0,00251

	Evènements N / Patients N (%)	Médiane SG (95% CI) mois
Durvalumab	183/476 (38,4)	NA (34.7–NA)
Placebo	116/237 (48,9)	28,7 (22,9–NA)

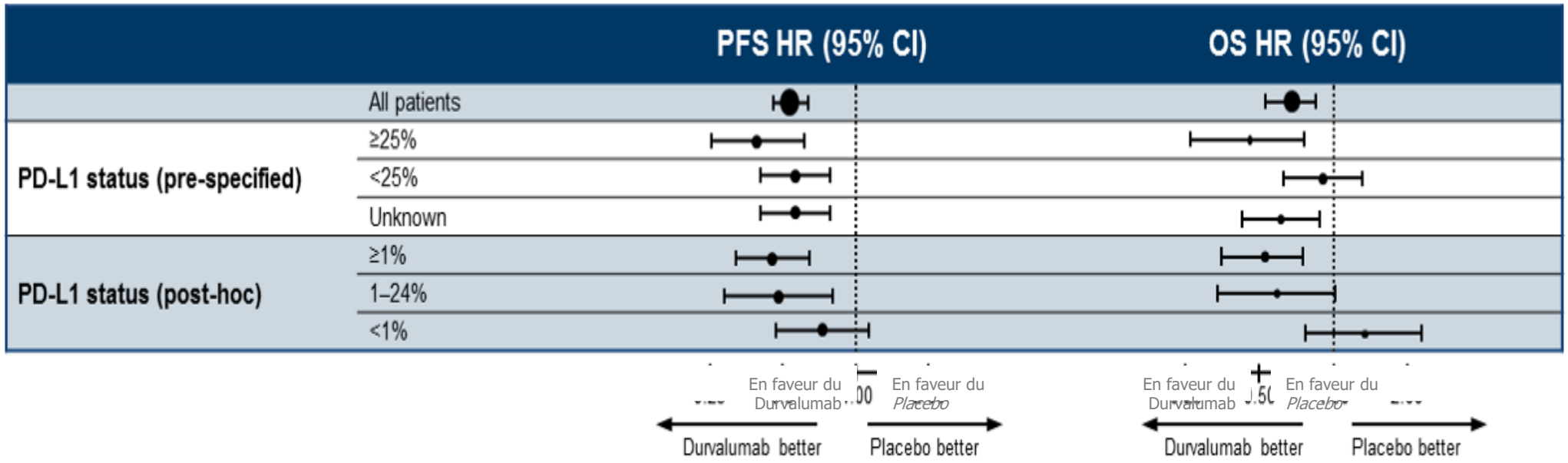
Nombre à risque

Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

SURVIE actualisée de l'essai PACIFIC

SSP et SG en fonction du statut PD-L1

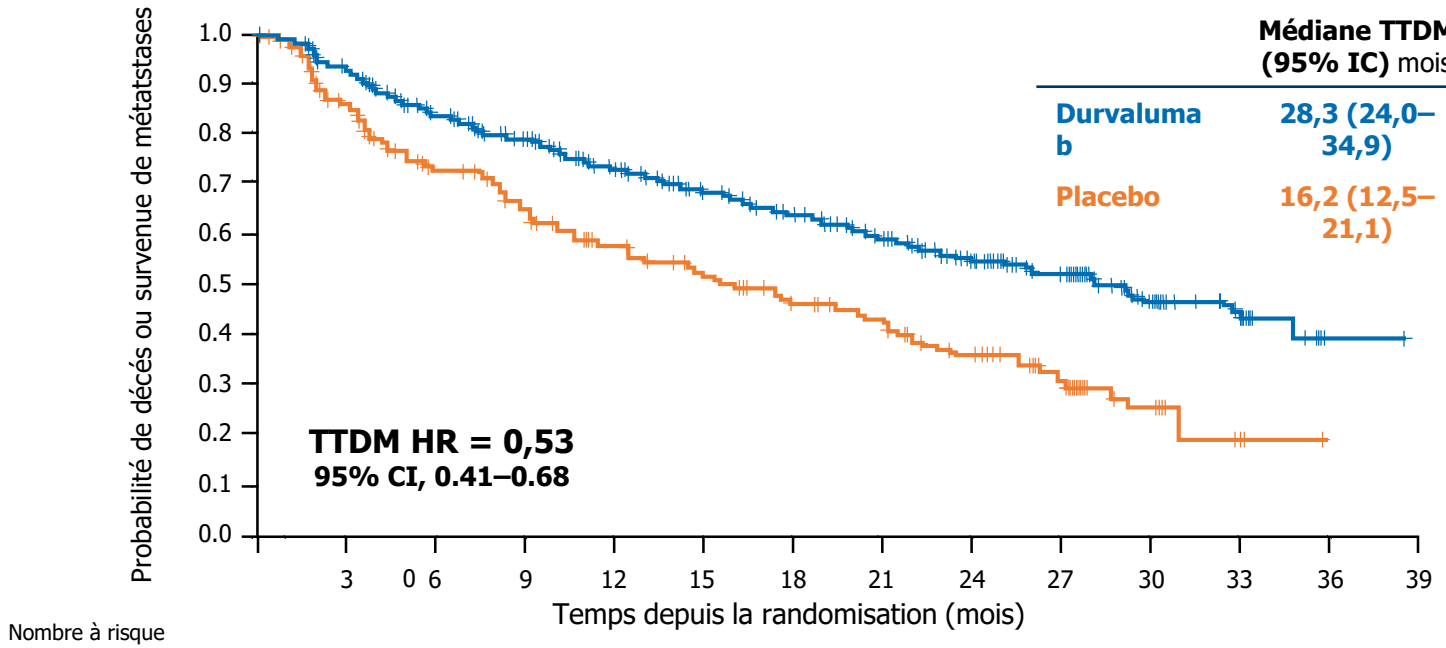
- NB : la recherche PD-L1 n'était pas obligatoire à l'inclusion
- PD-L1 déterminé sur matériel obtenu AVANT la CT-RT
- Statut PD-L1 inconnu chez 37% des patients
- Analyses prévues pour le statut PD-L1 ≥ ou < 25%
- Analyses non prévues initialement pour le statut PD-L1 ≥ ou < 1 %



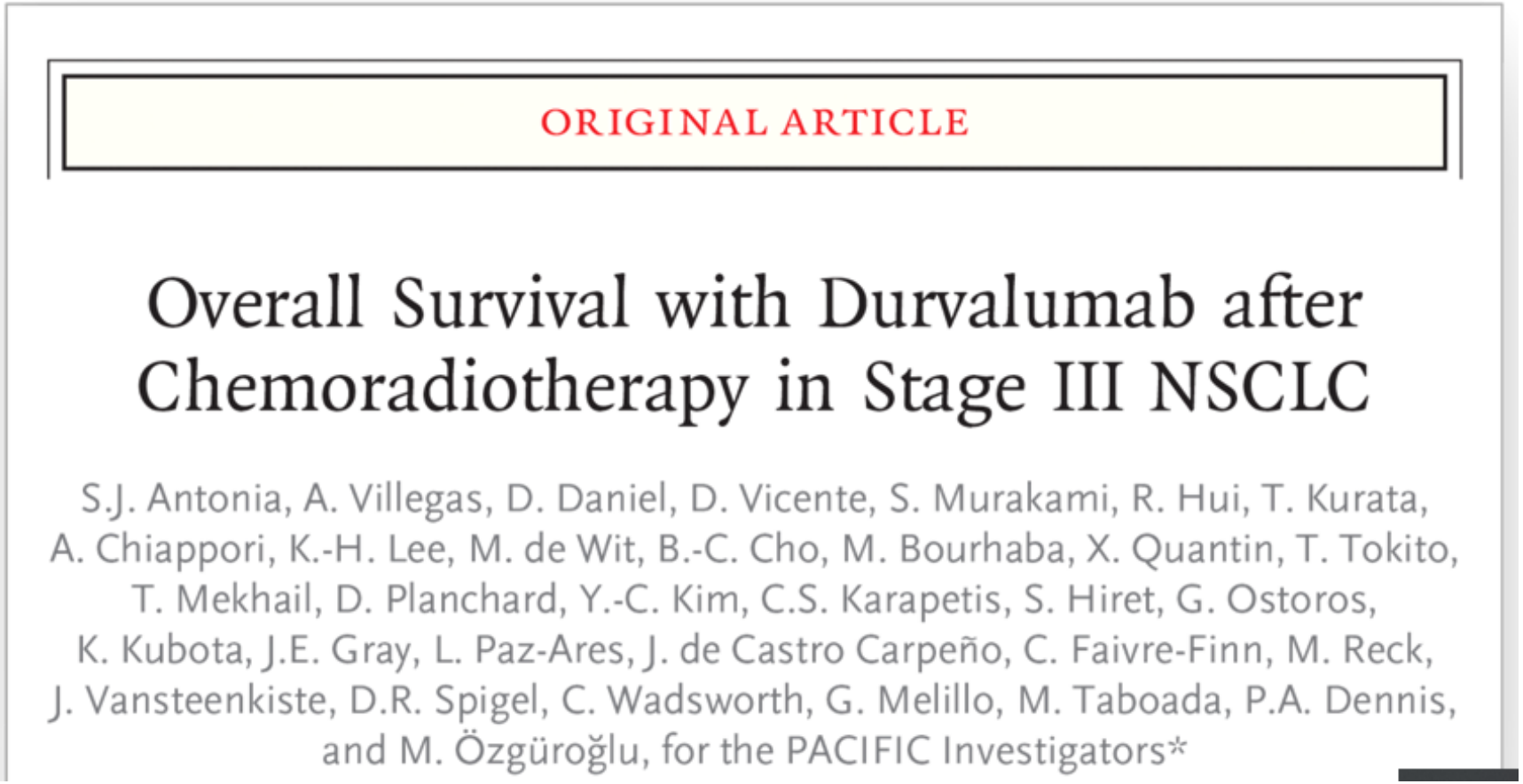
SURVIE actualisée de l'essai PACIFIC

Temps jusqu'au décès ou survenue de métastases (TTDM)

- Données *NEJM* 2017 : durvalumab *vs placebo*= 23,2 *vs* 14,6 mois HR 0,52
- Données actualisées WCLC® 2018 : **28,3 *vs* 16,2 HR 0,53**



SURVIE actualisée de l'essai PACIFIC



ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.-H. Lee, M. de Wit, B.-C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

Durvalumab en consolidation après CT-RT concomitante
= nouveau standard pour les stades III non résécables

Etude PACIFIC : analyse en sous-groupes : problématique des pneumopathies

Vansteenkiste JF et al. - WCLC® 2018 - Abs.# MA05.02

Résultats

	Durvalumab N=107	observation N=115
Pneumopathie tout grade	**33,6%**	**24,9%**
Temps médian jusqu'à survenue/ fin de RT	**73 jours (20-433)**	**76,5 jours (24-280)**
Durée de la pneumopathie	**64 jours (3-568)**	**57 jours (5-187)**
Pneumopathie en tant que cause d'arrêt de traitement / toutes causes	**25,6% / 10,2%**	**18,6% / 6,8%**

Vansteenkiste JF. et al.- WCLC® 2018 – Abs.# MA05.02

Résultats

Analyse multivariée du risque de survenue de pneumopathie

		Odds ratio	95% IC
Sexe	Homme *vs* Femme	0,77	0,47–1,27
Âge à la randomisation		1,01	0,98–1,03
Statut tabagique	Fumeur *vs* Non-fumeur	0,67	0,42–1,07
Stade de la maladie	IIIA vs. IIIB	1,39	0,89–2.17
Histologie	épidermoïde *vs* Non-Epidermoïde	**0,53**	**0,33–0,83**
Meilleure réponse à RT/CT	RC *vs* SM	0,88	0,12–4,22
	RP *vs* SM	1,00	0,65–1,54
WHO PS	0 *vs* 1	**0,64**	**0,42–0.98**
Region	Asiatique *vs* Non-Asiatique	**5,40**	**3,16–9,43**
Temps entre RT et randomisation	<14 *vs* ≥14 jours	1,24	0,76–2,00
CT d'induction préalable	Oui *vs* Non	0,60	0,35–1,01
BPCO pré existante	Oui *vs* Non	0,73	0,44–1,20

Vansteenkiste JF et al.- WCLC® 2018 – Abs.# MA05.02

Conclusion

- Survenue identique de pneumopathies grade 3-4 dans le bras Durvalumab (3,4%) et *placebo* (2,6%), avec délai de survenue et durée identiques dans les deux bras
- Pas d'incidence sur la délivrance du traitement
- Pas de lien avec la dose de RT ou l'existence préalable d'une BPCO. La chimiothérapie d'induction pourrait avoir un rôle protecteur
- En analyse multivariée, l'histologie épidermoïde (OR 0,53) et le PS 0 (OR 0,64) ressortent comme ayant un risque inférieur alors que l'origine ethnique asiatique (OR 5,40) est associée à un sur risque (y compris dans le groupe placebo ce qui semble être une complication non liée au traitement)

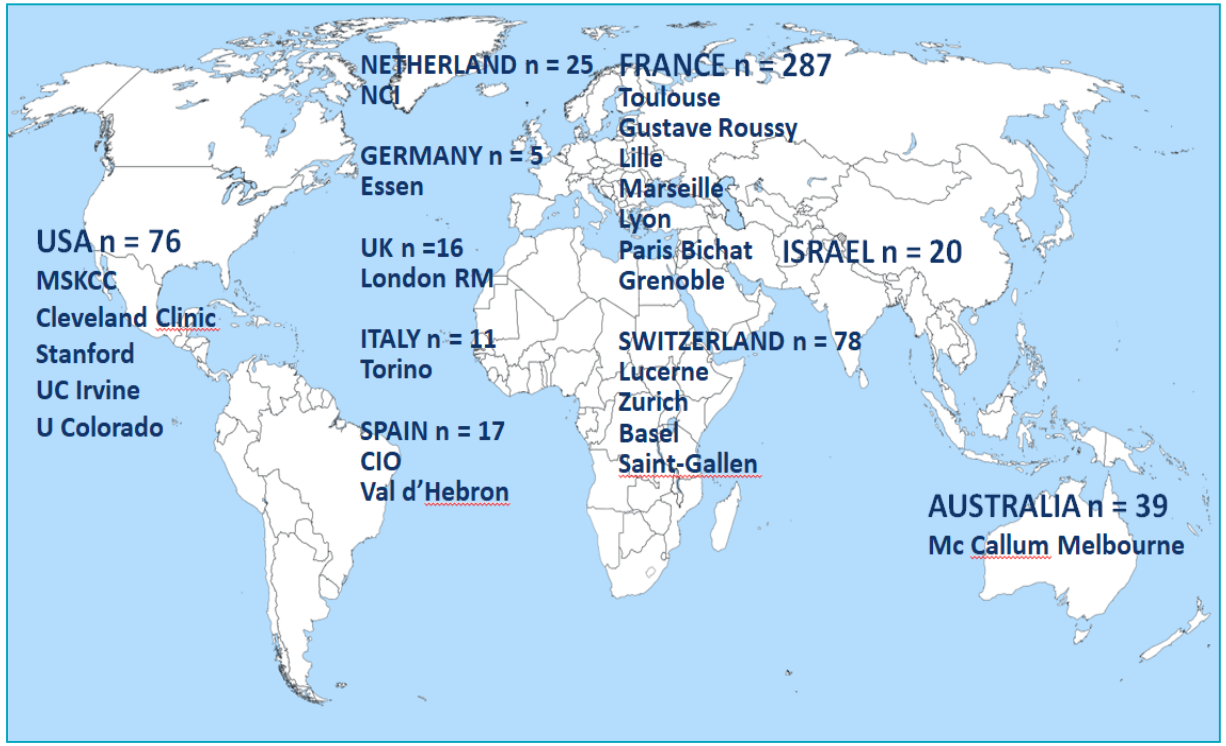
Vansteenkiste JF. et al.- WCLC® 2018 – Abs.# MA05.02

Immunothérapie pour les CBNPC avec driver oncogénique

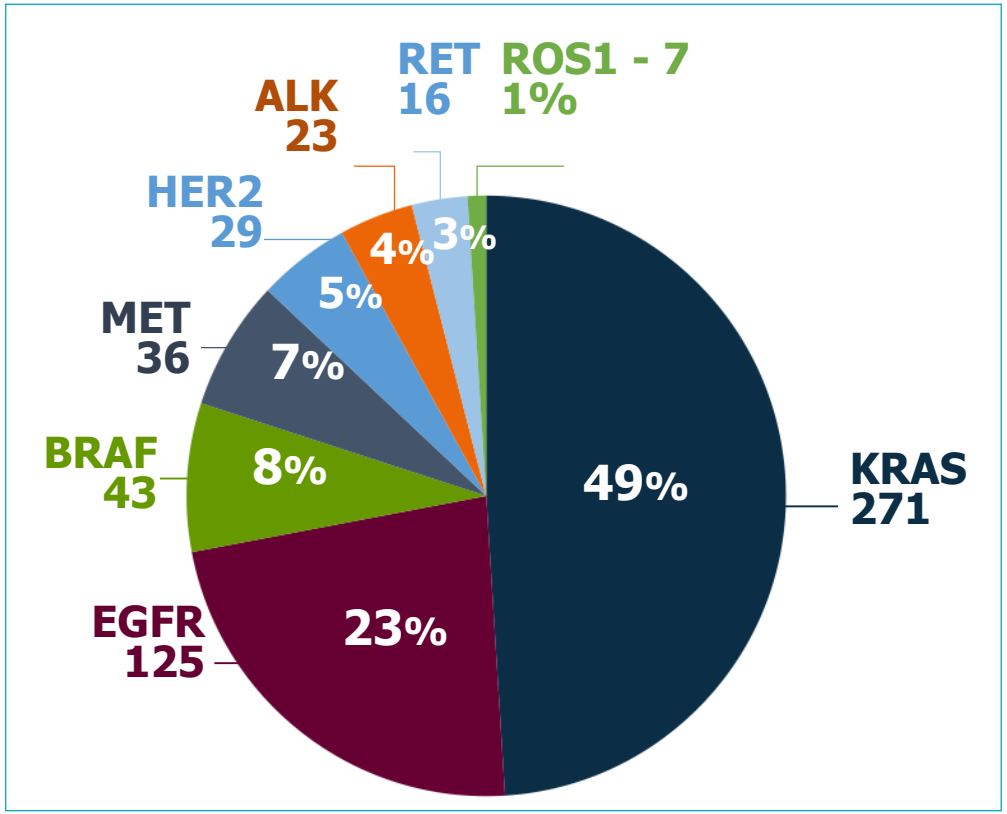
Actualisation du registre IMMUNOTARGET

Gautschi O. **et al.** ***- WCLC® 2018 – Abs.# MA04.03***

Centres/patients (Total = 574)



Mutations driver (Total = 550) (n/%)

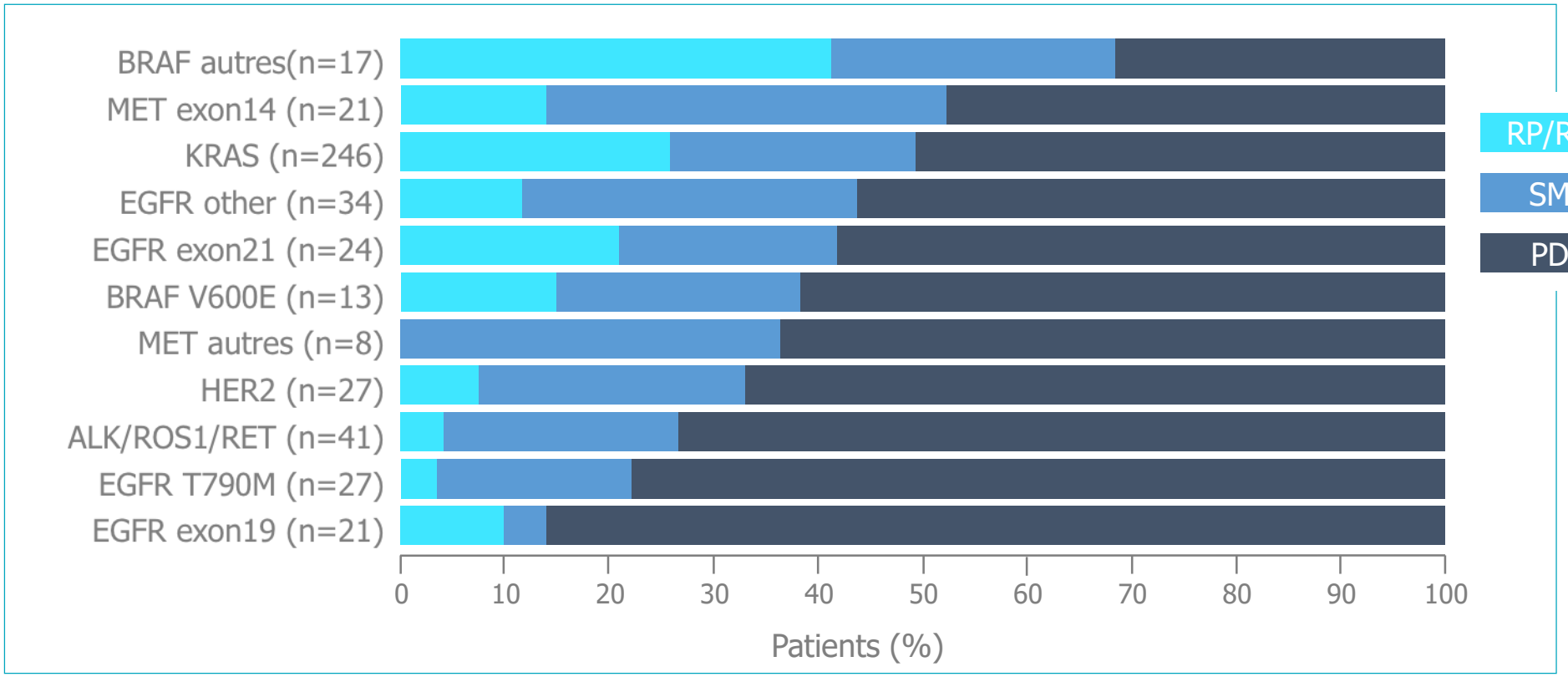


Data cutoff : Avril 2018

- Plus de patients (466) ont reçu du nivolumab ou du pembrolizumab (48) et ont été traités par immunothérapie en 2ème et 3ème ligne (67%)
- Le nombre médian de cycles était de 5 (range 1-68)
- 50 (11%) pts ont eu un grade 3-5 de toxicité
- Médiane de survie globale 13,3 mois, médiane SSP 2,8 mois depuis le début de l'immunothérapie

Figures adaptées de : *Mazières et al., ASCO® 2018 (Abs.# 9010)*

Réponses en fonction des sous-types moléculaires (RECIST1.1)



Les taux de réponse et de contrôle sont meilleurs pour les sous-groupes BRAFnon600/KRAS que pour les ALK/ROS1/RET et les EGFRdel19

Gautschi O. et al. - WCLC® 2018 - Abs.# MA04.03

Associations entre réponse et tabagisme/PD-L1

Le tabagisme reste un facteur prédictif de réponse
PD-L1 peut être un facteur prédictif pour les EGFR mutés

Gautschi O. et al. - WCLC® 2018 - Abs.# MA04.03

CBNPC MÉTASTATIQUE
SANS ADDICTION ONCOGÉNIQUE

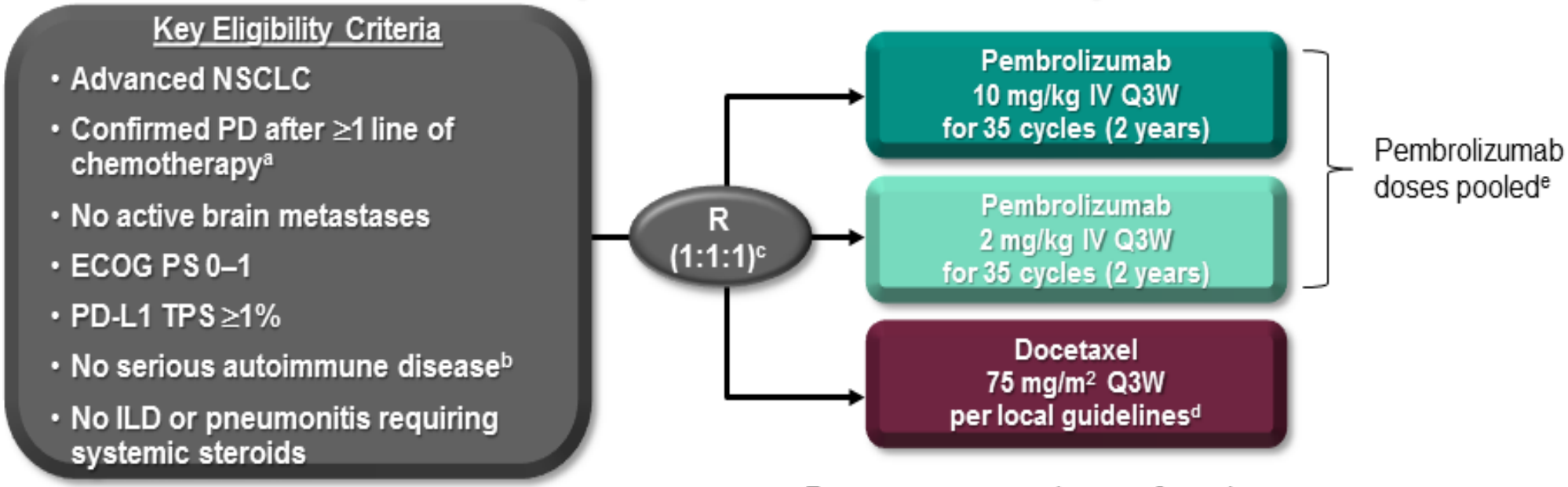
Long-Term Follow-Up in the KEYNOTE-010 Study of Pembrolizumab for Advanced NSCLC, Including in Patients Who Completed 2 Years of Pembrolizumab and Patients Who Received a Second Course of Pembrolizumab

Roy S. Herbst,[1] Edward B. Garon,[2] Dong-Wan Kim,[3] Byoung Chul Cho,[4] José Luis Pérez Gracia,[5] Ji-Youn Han,[6] Catherine Dubos Arvis,[7] Margarita Majem,[8] Martin Forster,[9] Isabella Monnet,[10] Silvia Novello,[11] Zsuzsanna Szalai,[12] Matthew A. Gubens,[13] Wu-Chou Su,[14] Giovanni Luca Ceresoli,[15] Ayman Samkari,[16] Erin Jensen,[16] Gregory M. Lubiniecki,[16] Paul Baas[17]

[1]Yale School of Medicine, New Haven, CT, USA; [2]David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica, CA, USA; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Clinica Universidad de Navarra, Pamplona, Spain; [6]National Cancer Center (Korea), Goyang-si, Republic of Korea; [7]Centre François Baclesse, Caen, France; [8]Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; [9]University College Hospital, London, UK; [10]Centre Hospitalier Intercommunal Créteil, Créteil, France; [11]University of Turin, Azienda Ospedaliero-Universitaria San Luigi, Orbassano, Italy; [12]Petz Aladár Megyei Oktató Kórház, Gyor, Hungary; [13]University of California, San Francisco, San Francisco, CA, USA; [14]National Cheng Kung University Hospital, Tainan, Taiwan; [15]Cliniche Humanitas Gavazzeni, Bergamo, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]The Netherlands Cancer Institute and The Academic Medical Hospital Amsterdam, Amsterdam, Netherlands

R Herbst. ESMO IO 2018.

KEYNOTE-010 (NCT01905657)



Dual primary efficacy endpoints: OS and PFS (RECIST version 1.1, independent central review)

Secondary endpoints: Included ORR and DOR

- Response assessed every 9 weeks; survival assessed every 2 months after treatment ended
- Treatment decisions and eligibility for second-course treatment based on irRECIST, by investigator review

DOR, duration of response; ILD, interstitial lung disease; IV, intravenous; R, randomization.

[a]Must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients with an *EGFR*-sensitizing mutation or an *ALK* translocation.

[b]No active or documented history of any autoimmune disease or syndrome that required systemic steroids or immunosuppressive agents, excluding patients with vitiligo, resolved childhood asthma/atopy, or those requiring inhaled steroids or local steroid injections.

[c]Randomization was stratified by ECOG PS (0 vs 1), region (East Asia vs non–East Asia), and PD-L1 status (TPS ≥50% vs 1%–49%).

[d]Patients received the maximum number of cycles permitted by the local regulatory authority. After the primary analysis, crossover from docetaxel to pembrolizumab was allowed for patients with disease progression.

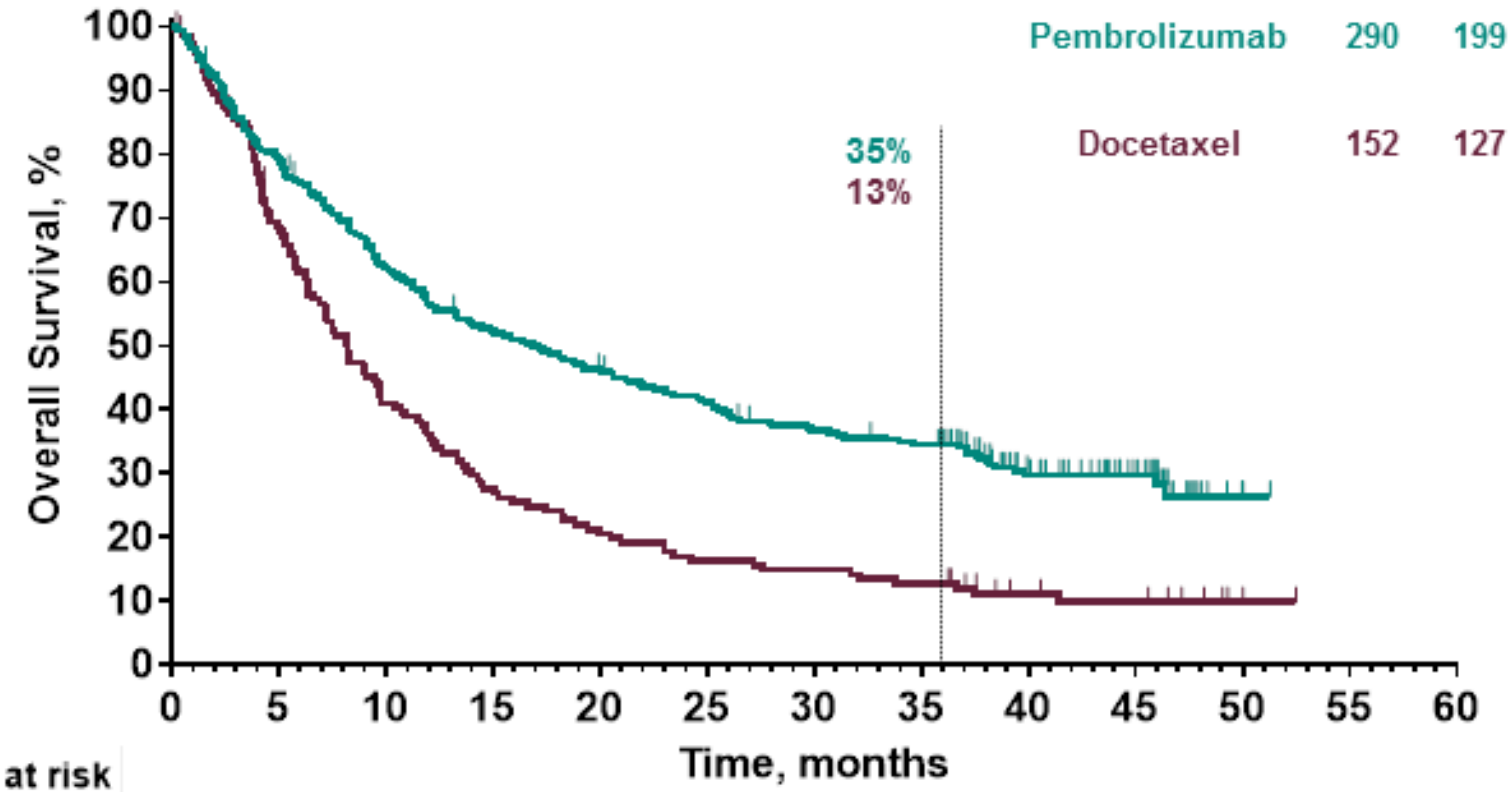
[e]No differences in OS were observed between the 2 mg/kg and 10 mg/kg pembrolizumab dose groups in the primary analysis;[1] therefore, pembrolizumab doses were pooled for this analysis.

1. Herbst R, et al. *Lancet*. 2016;387:1540-1550.

R Herbst. ESMO IO 2018.

Kaplan-Meier Estimates of OS
PD-L1 TPS ≥50% Population

	n	Events, n (%)	Median OS, mo (95% CI)	HR (95% CI)
Pembrolizumab	290	199 (69)	16.9 (12.3–21.4)	0.53 (0.42–0.66) *P*<0.00001
Docetaxel	152	127 (84)	8.2 (6.4–9.8)	

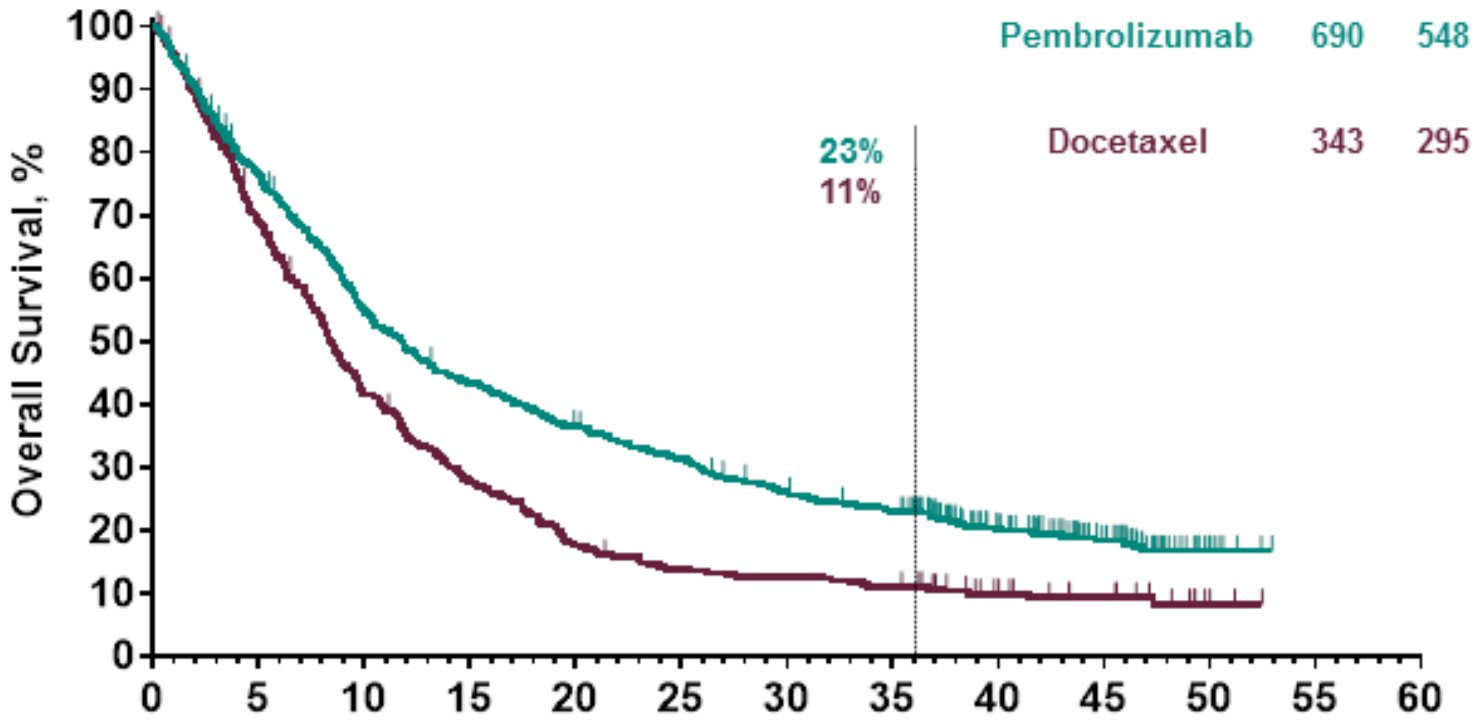


No. at risk													
Pembrolizumab	290	229	178	149	131	115	101	94	50	26	1	0	0
Docetaxel	152	97	58	39	29	23	21	18	10	8	1	0	0

Data cutoff: March 16, 2018.

Kaplan-Meier Estimates of OS
PD-L1 TPS ≥1% Population

	n	Events, n (%)	Median OS, mo (95% CI)	HR (95% CI)
Pembrolizumab	690	548 (79)	11.8 (10.4–13.1)	0.69 (0.60–0.80) *P*<0.00001
Docetaxel	343	295 (86)	8.4 (7.6–9.5)	



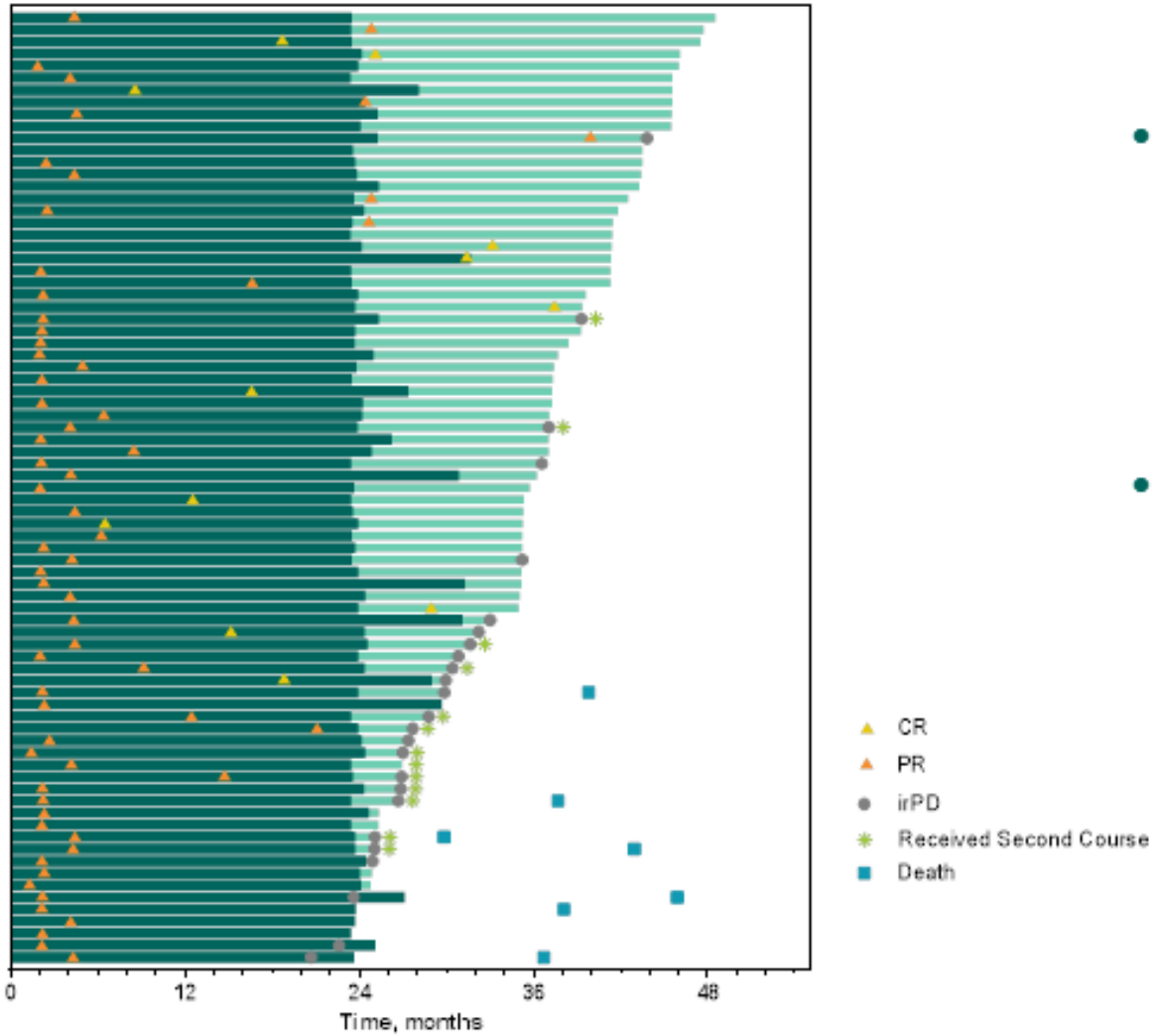
No. at risk													
Pembrolizumab	690	523	374	295	248	211	171	151	86	45	5	0	0
Docetaxel	343	226	135	90	57	44	40	35	20	13	2	0	0

Data cutoff: March 16, 2018.

Treatment Duration and Time to Response (I)

35 cycles (2 Years) of Pembrolizumab Completed[a]

R Herbst, ESMO IO 2018.

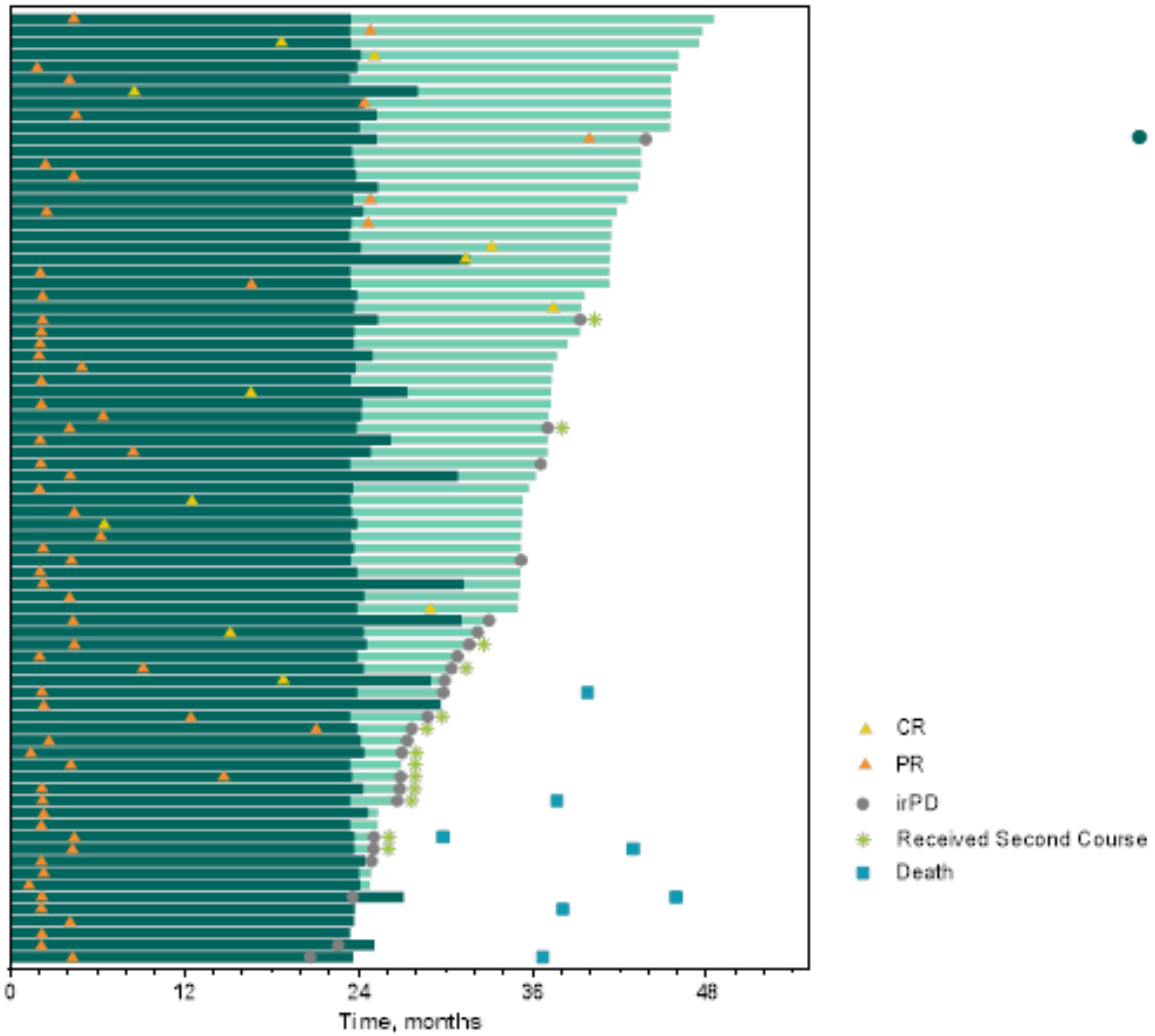


- 75 of 79 patients (95%) had CR or PR as best response per RECIST version 1.1 by independent central review
  - 48 patients (64%) had ongoing response
  - Median (range) duration of response: NR (4 to 46+) months
- 72 patients (91%) remained alive

CR, complete response; PR, partial response. [a]Bar lengths indicate duration of treatment (dark green) and months of follow-up (light green). Follow-up was defined as date of progression or date of the last investigator assessment the patient was alive. Data cutoff: March 16, 2018.

Treatment Duration and Time to Response (II)

35 cycles (2 Years) of Pembrolizumab Completed[a]

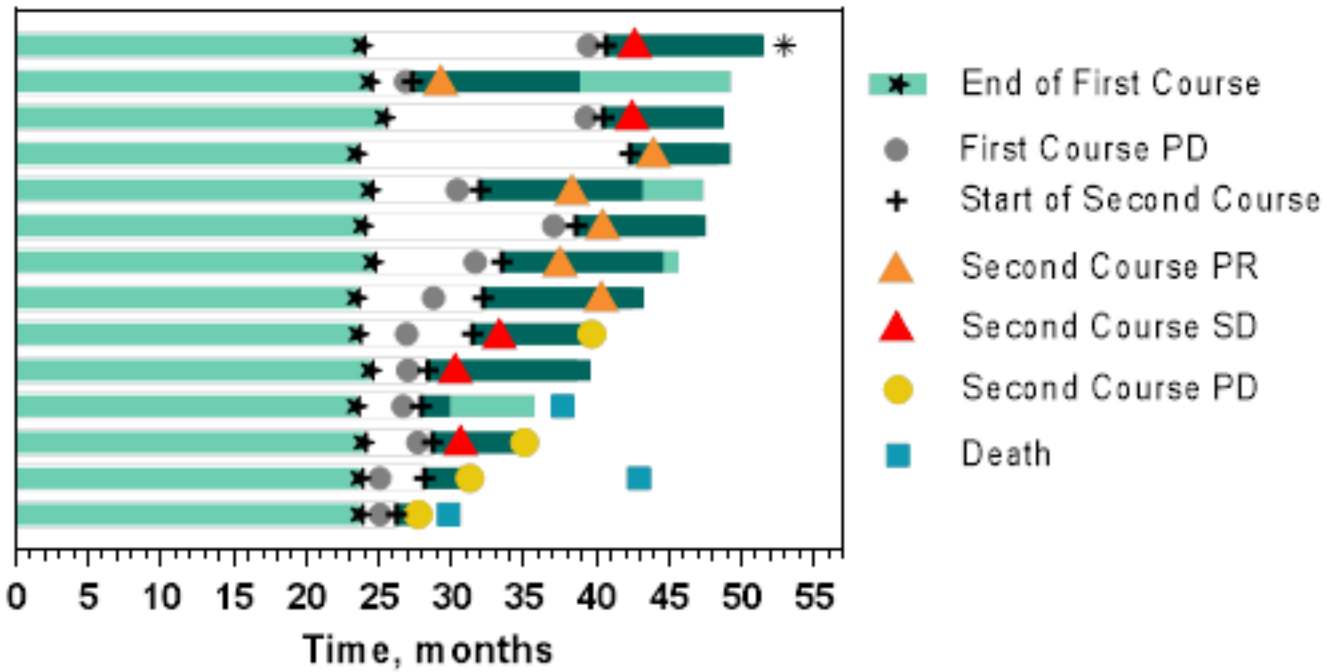


- 25 patients (32%) had confirmed irPD and 1 unconfirmed irPD per irRC by investigator review after stopping 35 cycles or 2 years of pembrolizumab
  - 13 patients completed second-course pembrolizumab (10 alive)
  - 6 patients received no further therapy yet (all alive)
  - 4 patients received chemotherapy (2 alive)
  - 2 patients received TKIs (one with *EGFR* mutation, both alive)

irPD, disease progression, per irRC; TKIs, tyrosine kinase inhibitors. [a]Bar lengths indicate duration of treatment (dark green) and months of follow-up (light green). Follow-up was defined as date of progression or date of the last investigator assessment the patient was alive. Data cutoff: March 16, 2018.

Treatment Duration and Time to Response

Patients Who Received Second-Course Treatment[a]



- In total, 14 patients started a second course of pembrolizumab after 35 cycles or 2 years of pembrolizumab treatment and subsequently having irPD per irRC by investigator review[b]
- Of these 14 patients, 6 (43%) had PR and 5 (36%) had SD during second course treatment per RECIST version 1.1 by independent central review
  - 5 patients (36%) completed 17 cycles
  - 11 patients (79%) remained alive

SD, stable disease.

[a]Bar lengths indicate duration of second course treatment (dark green) and months of second-course follow up (light green bar following dark green bar). Follow up was defined as the date of progression or last investigator assessment the patient was alive. CR and PR are per RECIST version 1.1 by independent central review; PD is per irRC by investigator review.

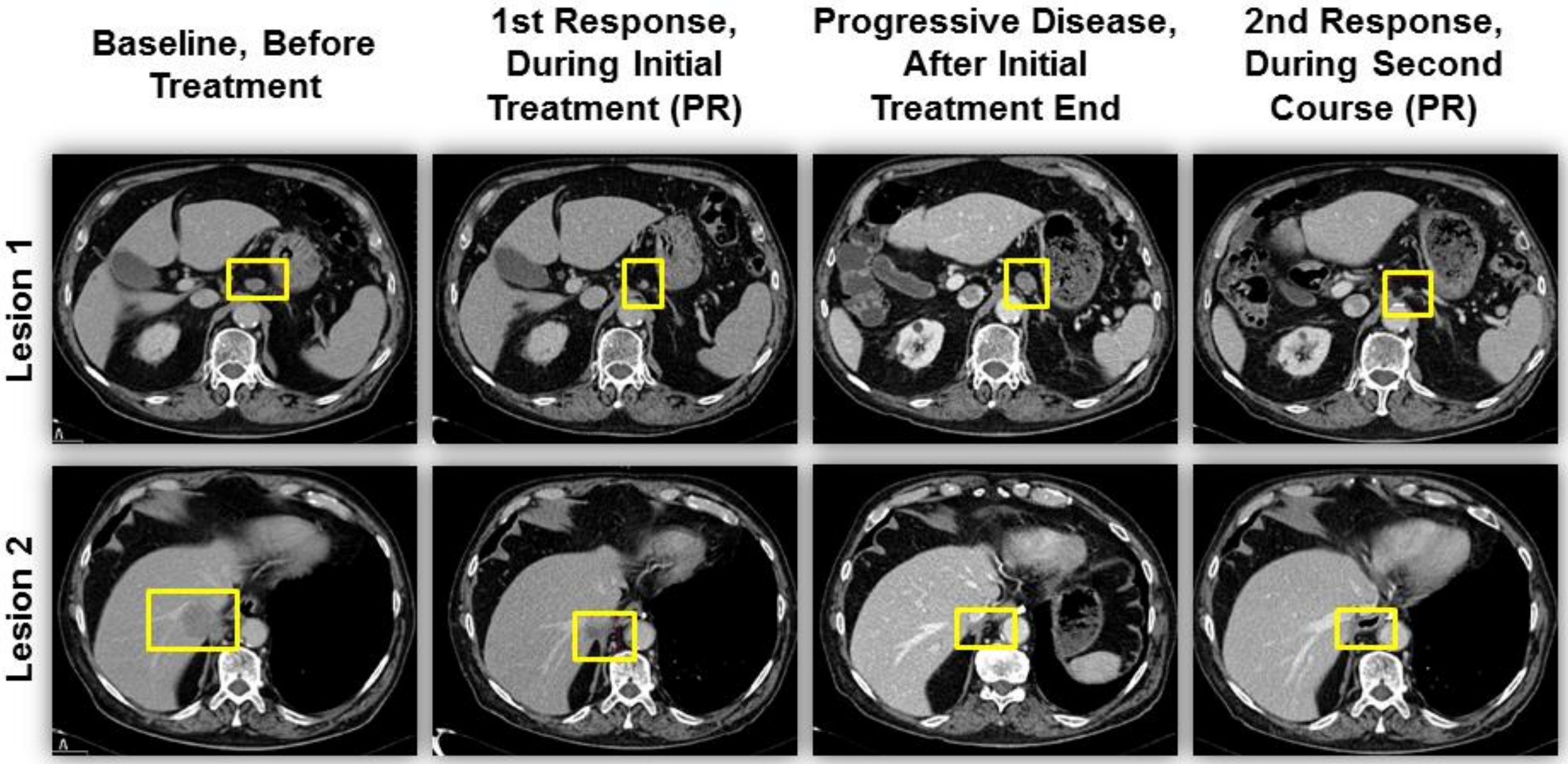
[b]One patient who received a second course of pembrolizumab did not meet eligibility criteria for having completed 35 cycles or 2 years of first course pembrolizumab (indicated with asterisk). One further patient had unconfirmed disease progression in first course. Data cutoff: March 16, 2018.

Case 1

- **Demographics**: 76 year-old, white male
- **Clinical**:
  - ECOG: 0
  - Former smoker (18 pack-years)
  - 1 prior line of therapy (carboplatin/pemetrexed)
  - Past medical history: hypertension, multinodular goiter, diverticulitis, superficial bladder carcinoma
- **Tumor**:
  - Adenocarcinoma
  - No activating *EGFR* mutation/*ALK* translocation
  - PD-L1 TPS ≥50%
  - Stage IV: Tx, N3, M1 (abdominal cavity, liver, and lymph node)
- **Treatment**
  - **Initial treatment**: Received 35 cycles (~2 y) of initial course → 7 months later PD
  - **Second course**: Received 17 cycles (~1 y) of second course (PR during second course)
- **AEs during treatment**: all AEs were grade 1/2, except 1 grade 3 event of pneumothorax; no immune-mediated AEs and infusion reactions reported

Case 1 Tumor Response

R Herbst. ESMO IO 2018.



Conclusions

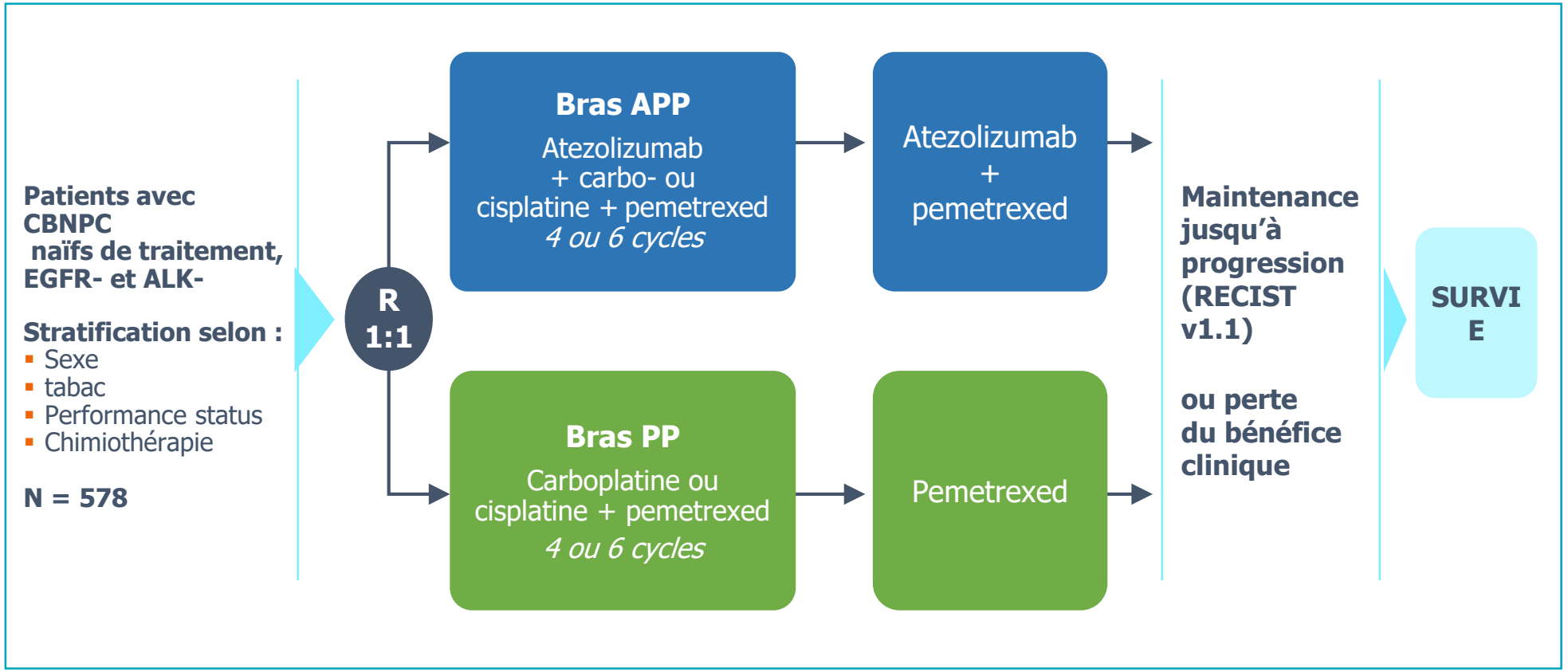
- With 42.6 months of follow-up, pembrolizumab continued to prolong OS vs docetaxel in patients with previously treated, PD-L1–expressing advanced NSCLC
- Pembrolizumab had a favorable and manageable long-term safety profile
- 2 years of pembrolizumab treatment provided durable response and long term disease control
  - 64% of patients who completed 35 cycles or 2 years of pembrolizumab had ongoing response at median follow-up of 43 months
  - A majority of patients who had irPD[a] after stopping pembrolizumab were able to receive a second course of treatment and had long term disease control

[a]Includes 1 patient who had unconfirmed disease progression in first course.

IMPOWER 132 : SSP et tolerance d'Atezolizumab + Carboplatine/Cisplatine + Pemetrexed en 1ère ligne de traitement des CBNPC métastatiques

Papadimitrakopoulou V. et al.- WCLC® 2018 – Abs.# OA05-07

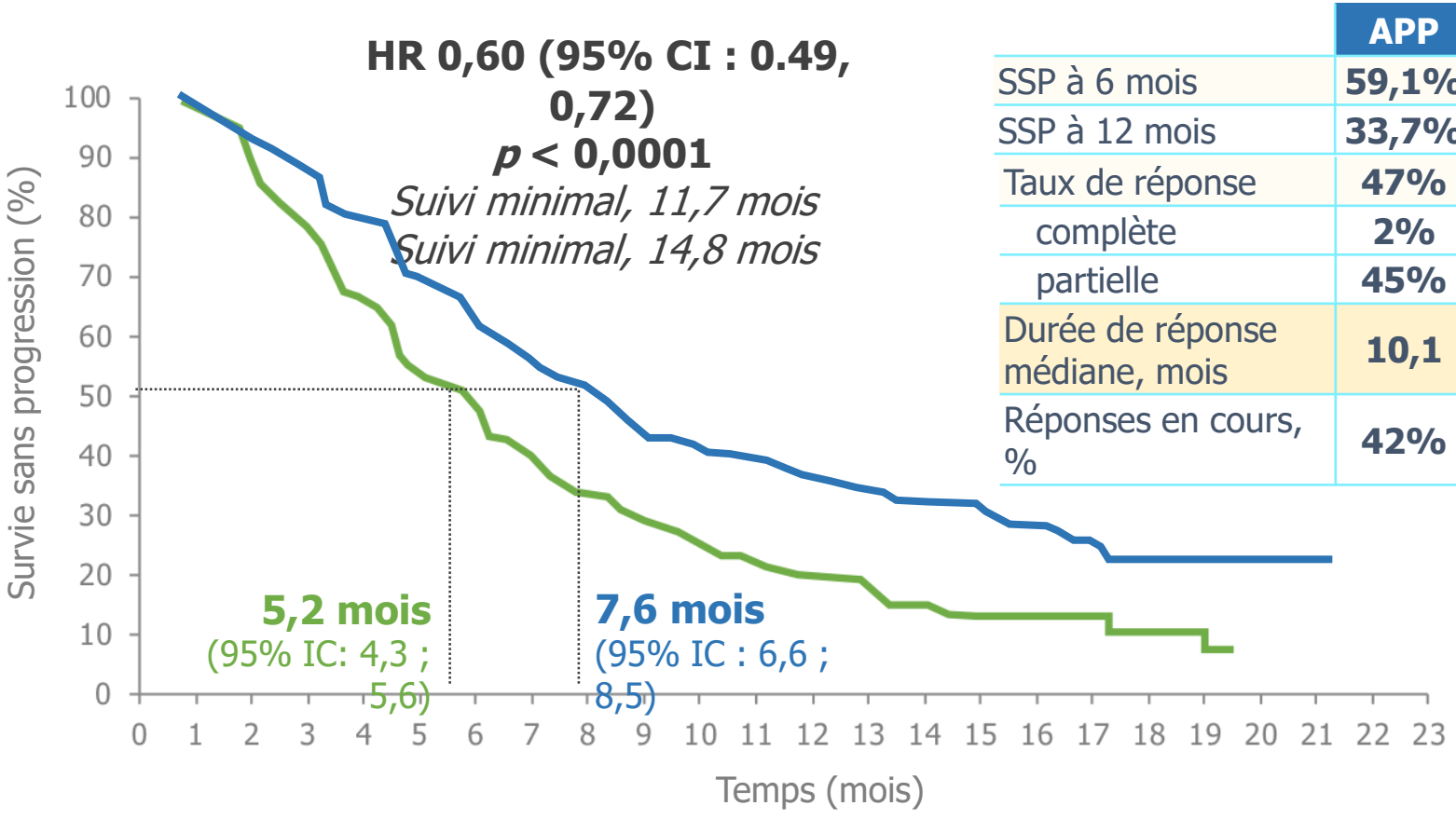
IMpower 132 : Design de l'étude



Co-objectifs primaires : SSP et SG, Objectifs secondaires : Taux de réponse, durée de réponse, PRO, tolérance

Papadimitrakopoulou V. et al.- WCLC® 2018 – Abs.# OA05-07

Objectifs : SSP, taux de réponse, durée de réponse

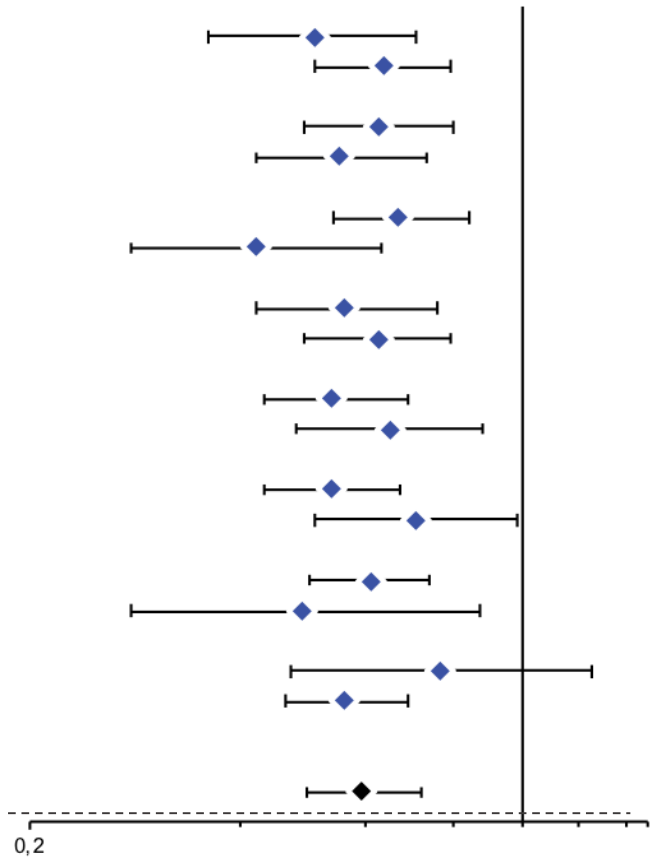


	APP	PP
SSP à 6 mois	**59,1%**	**40,9%**
SSP à 12 mois	**33,7%**	**17,0%**
Taux de réponse	**47%**	**32%**
complète	**2%**	**1%**
partielle	**45%**	**32%**
Durée de réponse médiane, mois	**10,1**	**7,2**
Réponses en cours, %	**42%**	**30%**

Papadimitrakopoulou V. et al.- WCLC® 2018 – Abs.# OA05-05

SSP : analyse en sous-groupe

Sous-groupe	n (%)	HR (IC 95%)	SSP médiane, mois	
			APP	PP
Femme	194 (34)	0,51 (0,36–0,71)	8,3	5,3
Homme	384 (66)	0,64 (0,51–0,79)	7,5	4,9
< 65 ans	320 (55)	0,63 (0,49–0,80)	6,9	4,4
≥ 65 ans	258 (45)	0,55 (0,42–0,73)	8,4	5,6
Caucasien	396 (69)	0,67 (0,54–0,84)	6,9	4,9
Asiatique	136 (24)	0,42 (0,28–0,63)	10,2	5,3
ECOG PS 0	240 (42)	0,56 (0,42–0,76)	8,6	5,8
ECOG PS 1	336 (58)	0,63 (0,49–0,79)	6,8	4,4
Carboplatine	352 (61)	0,54 (0,43–0,69)	8,1	5,5
Cisplatine	226 (39)	0,65 (0,48–0,88)	7,1	4,4
4 cycles	387 (67)	0,54 (0,43–0,67)	7,8	4,5
6 cycles	191 (33)	0,71 (0,51–0,98)	7,6	5,6
Fumeur ou ancien fumeur	511 (88)	0,61 (0,50–0.74)	7,5	5,1
Non-fumeur	67 (12)	0,49 (0,28–0,87)	8,6	5,5
Métastases hépatiques	73 (13)	0,77 (0,47–1,25)	4,4	4,0
Pas de métastase hépatique	505 (87)	0,56 (0,46–0,69)	8,4	5,5
ITT population	**578 (100)**	**0,60 (0,49–0,72)**	**7,6**	**5,2**



Papadimitrakopoulou V. et al.- WCLC® 2018 – Abs.# OA05-05

Conclusions

L'ajout d'Atezolizumab à un doublet de chimiothérapie de type Platine + Pemetrexed

→augmente la survie sans progression
→a un profil de tolérance acceptable

Données de survie globale en cours, non matures

Papadimitrakopoulou V. et al.- WCLC® 2018 – Abs.# OA05-05

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

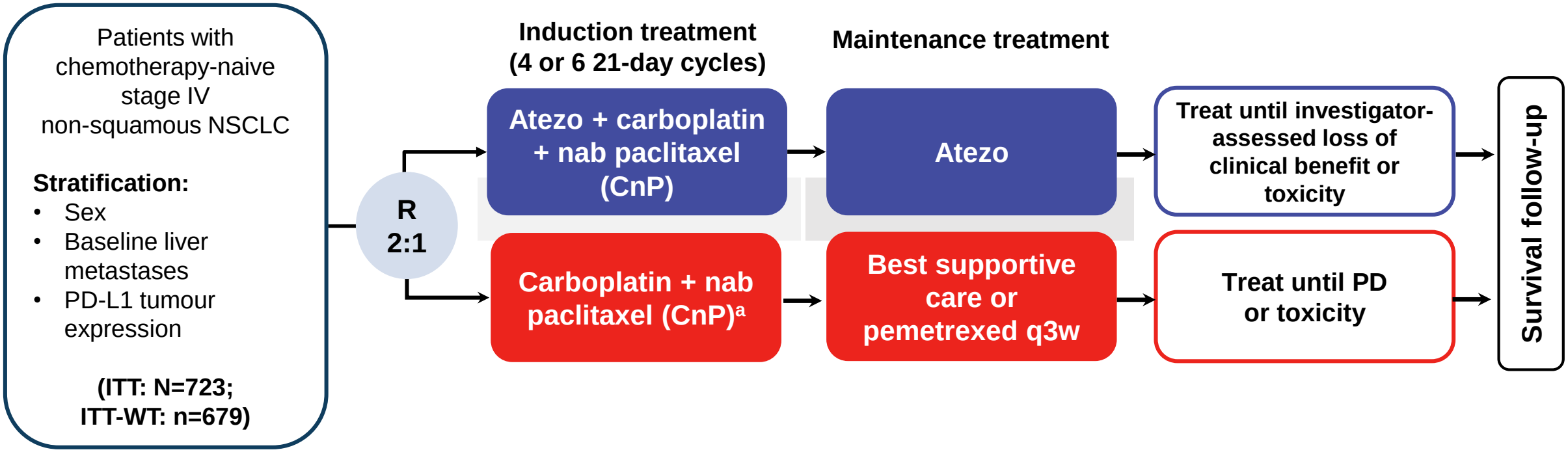
MUNICH 2018 ESMO congress

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

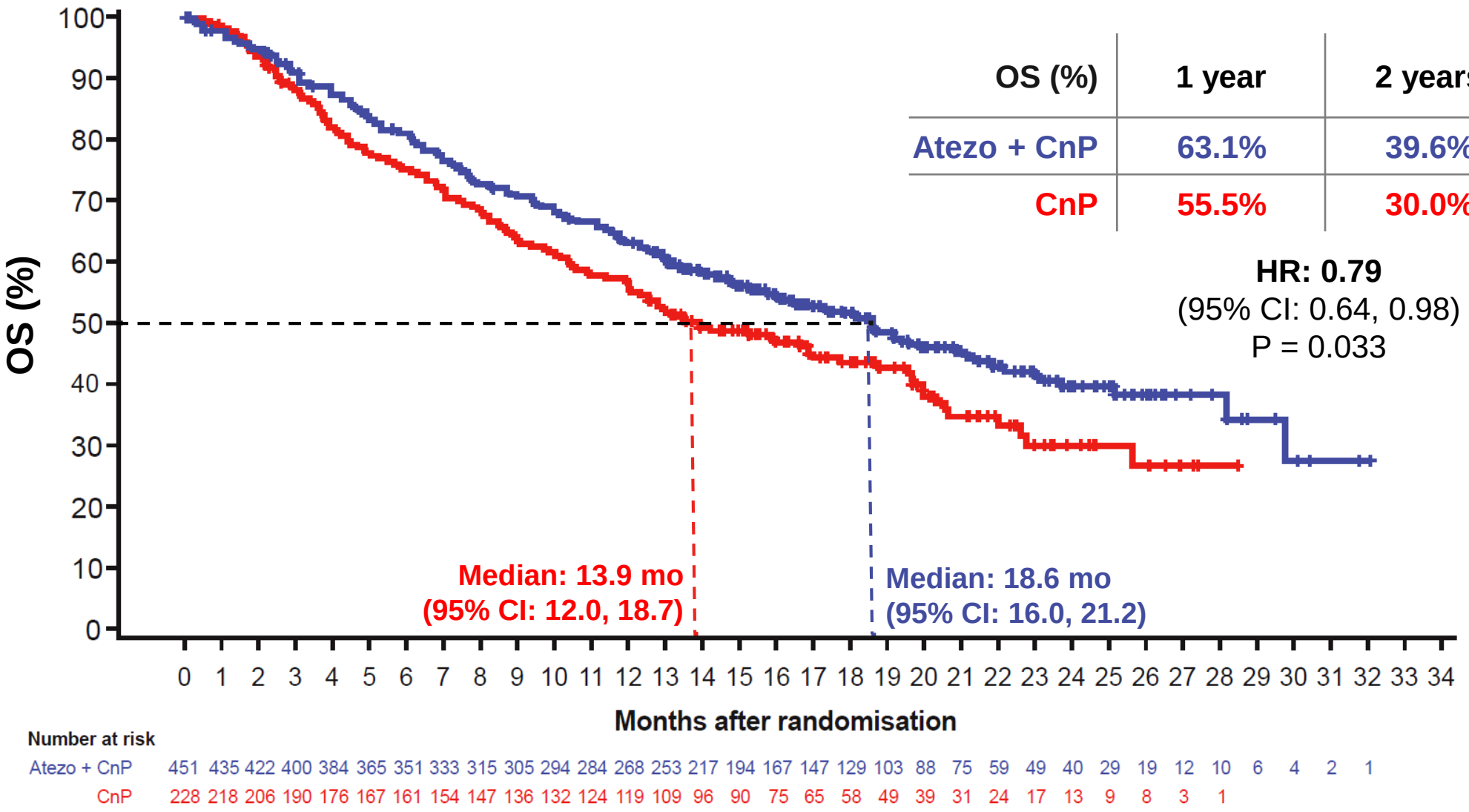
IMpower130 study design



- **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/m^2 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.

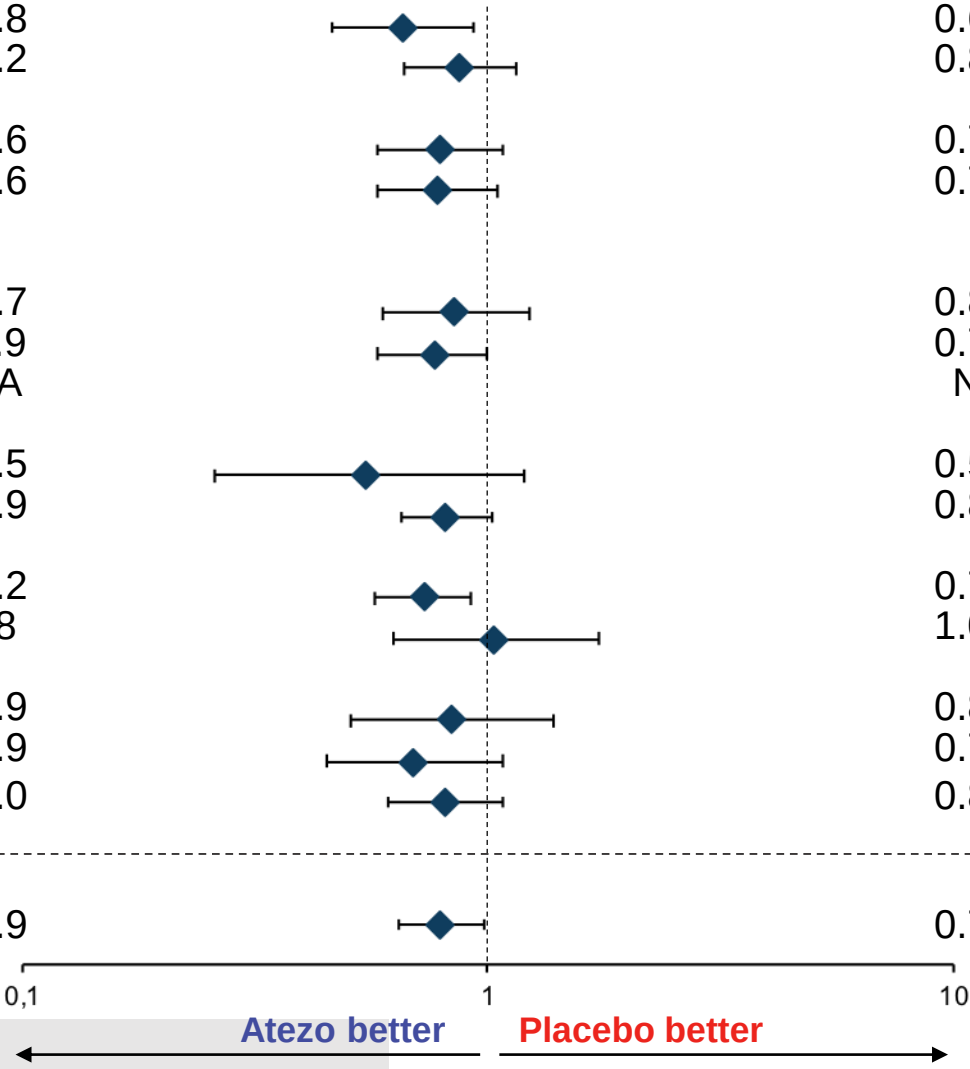
OS (ITT-WT)



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

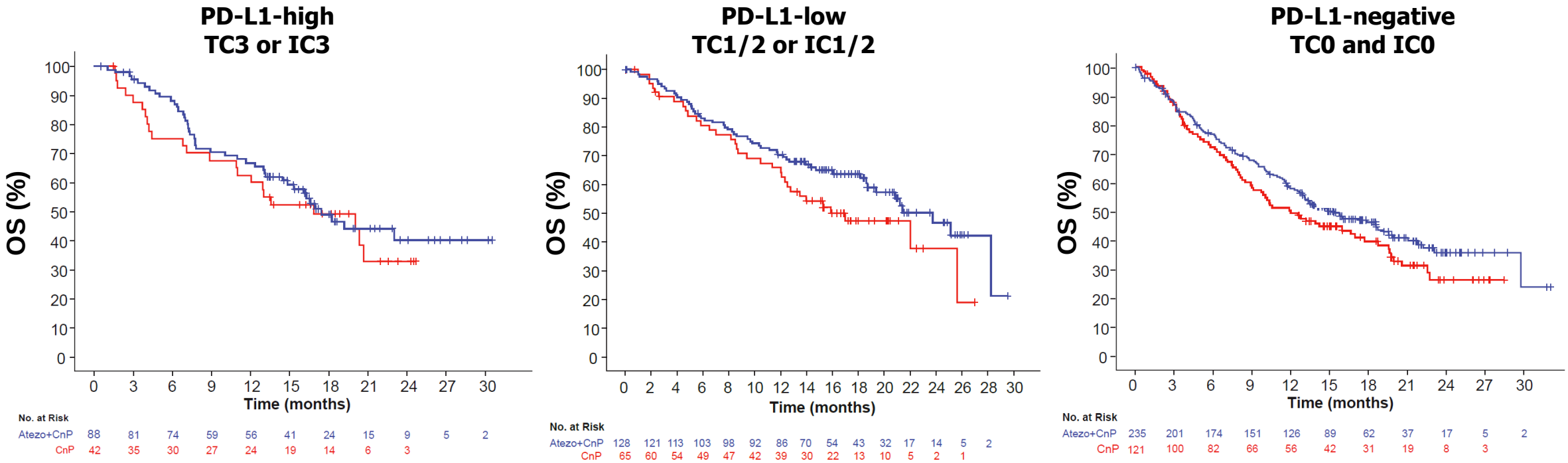
OS in key subgroups (ITT-WT)

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.

OS by baseline PD-L1 status (ITT-WT)



	Atezo + CnP (n=88)	CnP (n=42)	Atezo + CnP (n=128)	CnP (n=65)	Atezo + CnP (n=235)	CnP (n=121)
Median OS, mo (95% CI)	17.3 (14.78, N/A)	16.9 (10.94, N/A)	23.7 (18.63, N/A)	15.9 (12.32, 25.63)	15.2 (12.88, 19.15)	12.0 (8.97, 17.71)
HR (95% CI)	0.84 (0.51, 1.39)		0.70 (0.45, 1.08)		0.81 (0.61, 1.08)	

Summary and conclusions

- IMpower130 met its co-primary PFS and OS endpoints and demonstrated a statistically significant and clinically meaningful benefit of 4.7 months' OS (and 1.5 months' PFS) for atezo plus chemotherapy in the ITT-WT population, compared with chemotherapy alone
  - OS and PFS benefits were observed across all PD-L1 subgroups
  - Outcomes in patients with *EGFR* or *ALK* genomic alterations suggest treatment benefit was mostly driven by the ITT-WT population
- Atezo plus chemotherapy had a safety profile consistent with AEs associated with
single-agent therapy; no new safety signals were identified
- The IMpower130 results support atezo plus chemotherapy as a treatment option for patients with advanced non-squamous NSCLC, regardless of PD-L1 status

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

KEYNOTE-189 Study Design (NCT02578680)

Key Eligibility Criteria

- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors

- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410

Pembrolizumab 200 mg + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

N = 206

Placebo (normal saline) + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

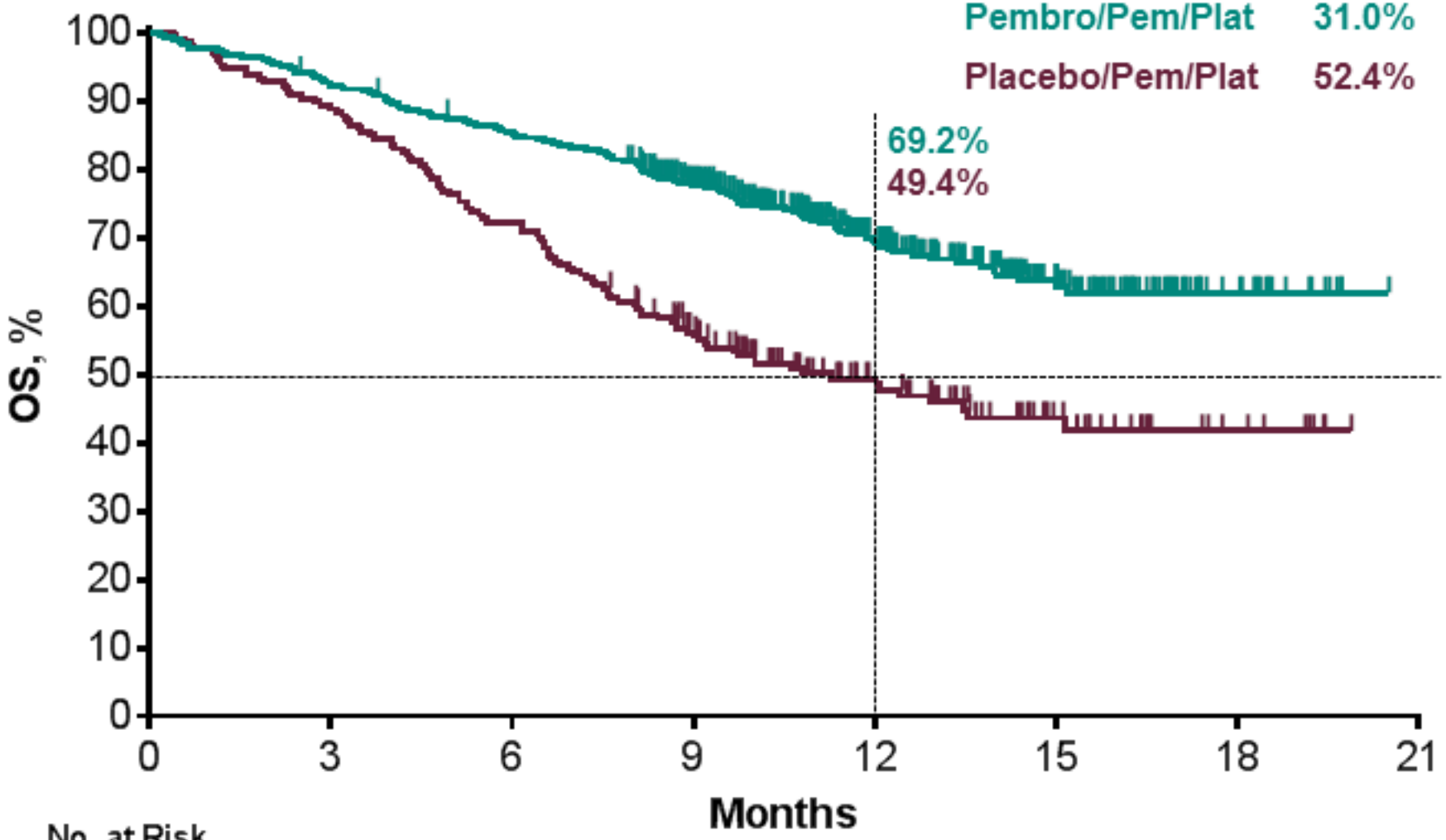
Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

PD[b]

Pembrolizumab 200 mg Q3W for up to 35 cycles

[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.

Overall Survival, ITT



	Events	HR (95% CI)	*P*
Pembro/Pem/Plat	31.0%	0.49 (0.38-0.64)	<0.00001
Placebo/Pem/Plat	52.4%		

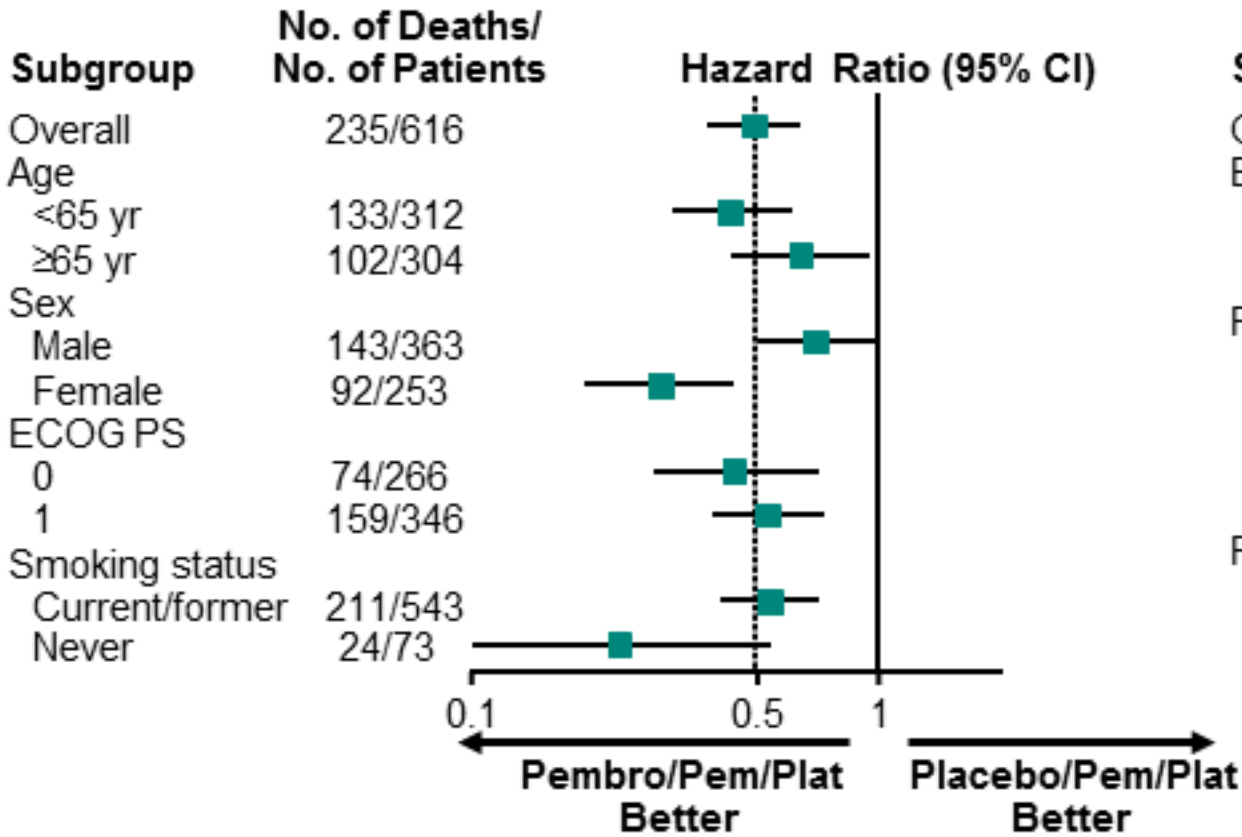
Median (95% CI)
NR (NE-NE)
11.3 mo (8.7-15.1)

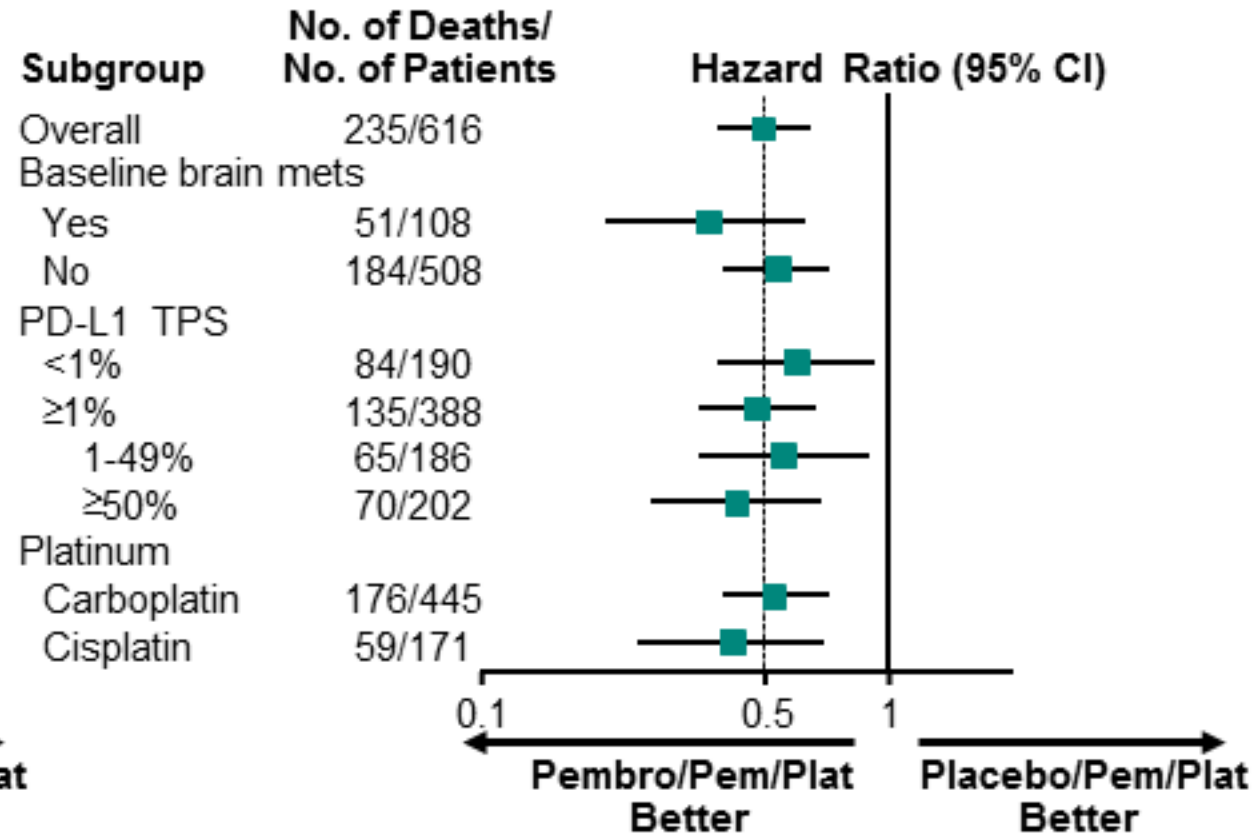
No. at Risk

410	377	347	278	163	71	18	0
206	183	149	104	59	25	8	0

Data cutoff date: Nov 8, 2017.

Overall Survival in Key Subgroups



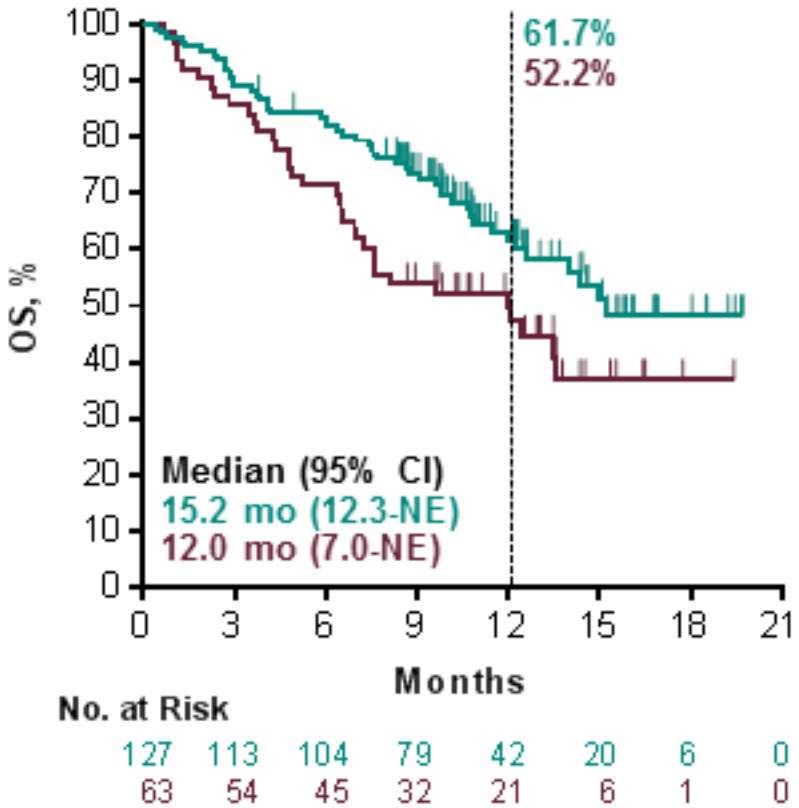


Data cutoff date: Nov 8, 2017.

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%		

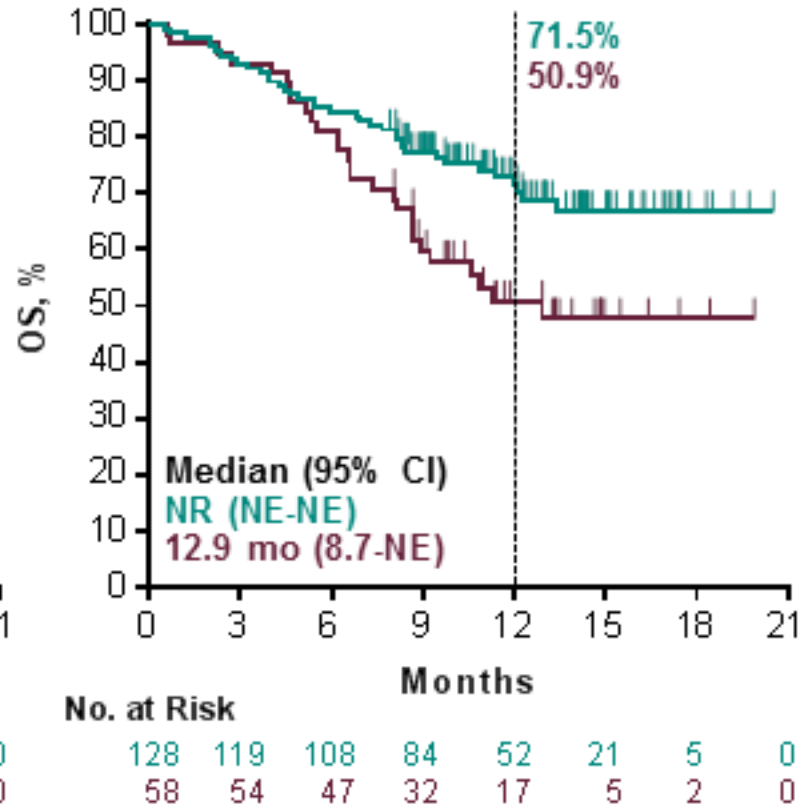


No. at Risk

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%		

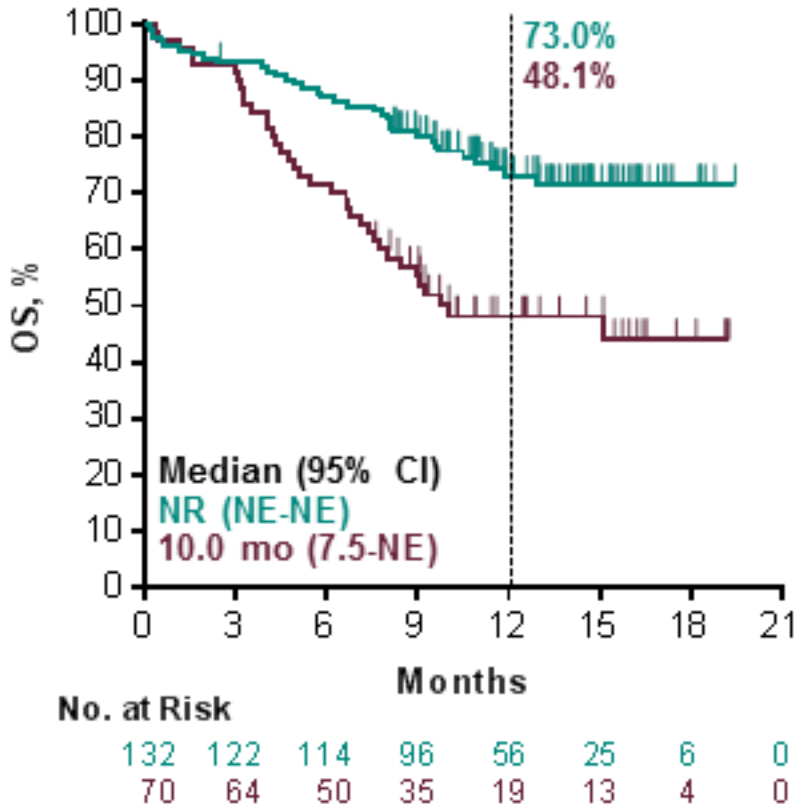


No. at Risk

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.

Summary of Adverse Events

	Pembro/Pem/Platinum N = 405	Placebo/Pem/Platinum N = 202
All cause	404 (99.8%)	200 (99.0%)
Grade 3-5	272 (67.2%)	133 (65.8%)
Led to death	27 (6.7%)	12 (5.9%)
Led to discontinuation		
All treatment[a]	56 (13.8%)	16 (7.9%)
Any treatment	112 (27.7%)	30 (14.9%)
Immune mediated	92 (22.7%)	24 (11.9%)
Grade 3-5	36 (8.9%)	9 (4.5%)
Led to death	3 (0.7%)	0

[a]Includes patients who discontinued pembrolizumab or placebo, pemetrexed, and carboplatin for an adverse event at any time and patients who discontinued pembrolizumab or placebo and pemetrexed for an adverse event after completing 4 cycles of platinum.
Data cutoff date: Nov 8, 2017.

Conclusions

- Adding pembrolizumab to pemetrexed and platinum induction therapy and pemetrexed maintenance therapy significantly improves OS, PFS, and ORR in patients with untreated metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* alterations
- Pembrolizumab plus pemetrexed and platinum has a manageable safety profile
- Pembrolizumab plus pemetrexed and platinum may be a new standard of care for first-line treatment of metastatic nonsquamous NSCLC, irrespective of PD-L1 expression

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

Immunothérapie en 1ère ligne dans le CBNPC
État des lieux en fonction de l'histologie

Bradbury P. et al.- WCLC® 2018 – ISS03

Pembrolizumab en 1ère ligne dans le CBNPC selon l'histologie

Essai	Non épidermoïde	Epidermoïde	Statut PD-L1	Résultats
KEYNOTE-024*	**Pembro *vs* pem/platine ou pacli/carbo ou gem/platine**		**PD-L1 ≥ 50%**	SSP **10,3 *vs* 6** HR **0.5 (0.37-0.68)** SG **30 *vs* 14,2** HR **0.63 (0.47-0.86)**
KEYNOTE-042*	**Pembro *vs* pem/platine ou pacli/carbo**		**PD-L1 ≥ 1%**	SG **chez PD-L1≥ 50%; 20%; ≥ 1%** HR **0.69 (0.56-0.85);** HR **0.77 (0.64-0.92);** HR **0.81 (0.71-0.93)**
KEYNOTE-189* N=616	**Pembro/pem/platine *vs* Pem/platine**		**Tout PD-L1**	SPP **5.6 *vs* 4.9** HR **0.52** *p*<0.00001 SG **NA *vs* 11.3** HR **0.49 (0.38-0.64)**
KEYNOTE-407* N=559		**Pembro/pacli ou nab-pacli/carbo *vs* pacli ou nab-pacli/carbo**	**Tout PD-L1**	SPP **6.4 *vs* 4.8** HR **0.56** *p<0.001* SG **15,9 *vs* 11,3** HR **0.64 (0.49-0.85)**

** Cross over autorisé, pembro : pembrolizumab, gem : gemcitabine, pem : pemetrexed, pacli : paclitaxel , NA : non atteinte*

Bradbury P. et al.- WCLC® 2018 – ISS03

** Cross over autorisé, pembro : pembrolizumab, gem : gemcitabine, pem : pemetrexed, pacli : paclitaxel , NA : non atteinte*

Nivolumab +/- ipilumumab en 1ère ligne dans le CBNPC selon l'histologie

Essai	Non épidermoïde	Epidermoïde	Statut PD-L1	Résultats
CheckMate 026*	**Nivo *vs* chimio à base de platine (CT platine)**		**PD-L1 ≥ 5%**	SSP **4,2 *vs* 5,9** HR **1.15 (0.91-1.45)** SG **14,4 *vs* 13,2** HR **1.02 (0.8-1.3)**
CheckMate 227	**Nivo +/- ipi *vs* CT platine selon histologie**		**Charge Mutationnelle élevée (high TMB)**	**Nivo + Ipi *vs* chimio** SSP **7.2 *vs* 5.5** HR **0.58 (0.41-0.81)** SSP **à 1 an 42,6 *vs* 13,2%** **TMB faible** HR **1.07 (0.84-1.35)**
	pem/platine+pem maintenance	**Gem/platine**		
	Nivo + CT platine *vs* chimio selon histologie		**PD-L1 <1%**	SSP HR **0.74 (0.58-0.94)** **High TMB HR 0.56 (0.35-0.91)** **Faible TMB HR 0.87 (0.57-1.33)**

** Cross over autorisé, nivo : nivolumab, ipi : ipilimumab, beva : bevacizumab, gem : gemcitabine, pem : pemetrexed, pacli : paclitaxel*

Bradbury P. et al.- WCLC® 2018 – ISS03

Atezolizumab en 1ère ligne dans le CBNPC selon l'histologie

Essai	Non épidermoïde	Epidermoïde	Statut PD-L1	Résultats
IMpower131 N=684		**Carbo/pacli ou nab-pacli/Atezo *vs* carbo/(nab)/pacli**	**Tout PD-L1**	**Bras B *vs* C** SSP **6.3 *vs* 5.6** HR **0.71 (0.61-0.85)** SSP **à 1 an : 24,7% *vs* 12%** SG **14 *vs* 13.9** HR **0.96** *p*=0.69
IMpower150 N=800	**Carbo/pacli/Atezo +/- beva *vs* carbo/pacli/beva**			**Bras B *vs* C** SSP **8,3 *vs* 6,8** HR **0.59 (0.50-0.70)** SG **19,2 *vs* 14,7** HR **0.78 (0.64-0.96)**
IMpower132 N=578	**Platine/pem/Atezo *vs* platine/pem**		**Tout PD-L1**	SSP **7,6 *vs* 5,2** HR **0.6 *p*<0.0001** SG **18,1 *vs* 13,6** HR **0.81 *p*=0.079**

Atezo : atezolizumab, gem : gemcitabine, pem : pemetrexed, pacli : paclitaxel, beva : bevacizumab,

CBNPC MÉTASTATIQUE SANS ADDICTION ONCOGÉNIQUE EN DEUXIEME LIGNE

3èmes Rencontres d'Oncologie Thoracique en Nouvelle-Aquitaine - 24 mai 2019

Avelumab *vs* docetaxel pour le traitement des CBNPC métastatiques au-delà de la 1Ère ligne : Étude de phase 3 JAVELIN-Lung 200

Barlesi F. et al.- WCLC® 2018 – Abs.# OA05-05

JAVELIN Lung 200 : Design de l'étude

CBNPC de stade III/IV en progression après une chimio. à base de sel de platine

Patients pour l'analyse primaire (PD-L1+) :
N=529
(PD-L1 ≥ 1% cellules tumorales)

Tous les patients :
N=792

R
1:1

Avelumab
10 mg/kg – 2 semaines
PD-L1+ : n=264
Tous les patients: n=396

Traitement jusqu'à progression ou toxicité inacceptable ou retrait de consentement

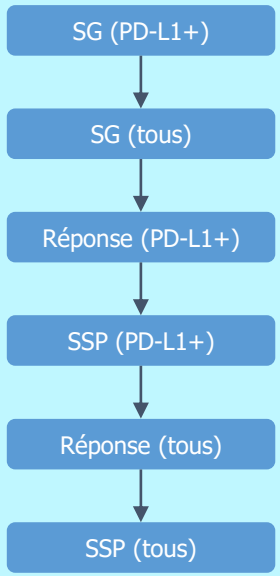
Docetaxel
75 mg/m^2 – 3 semaines
PD-L1+ : n=265
Tous les patients: n=396

Stratification:
- PD-L1+ *vs* PD-L1–
- Histologie épidermoïde *versus* non-épidermoïde

Objectif primaire :
SG (population PD-L1+)

Objectifs secondaires :
SG (tous les patients), réponse, SSP, qualité de vie, tolérance

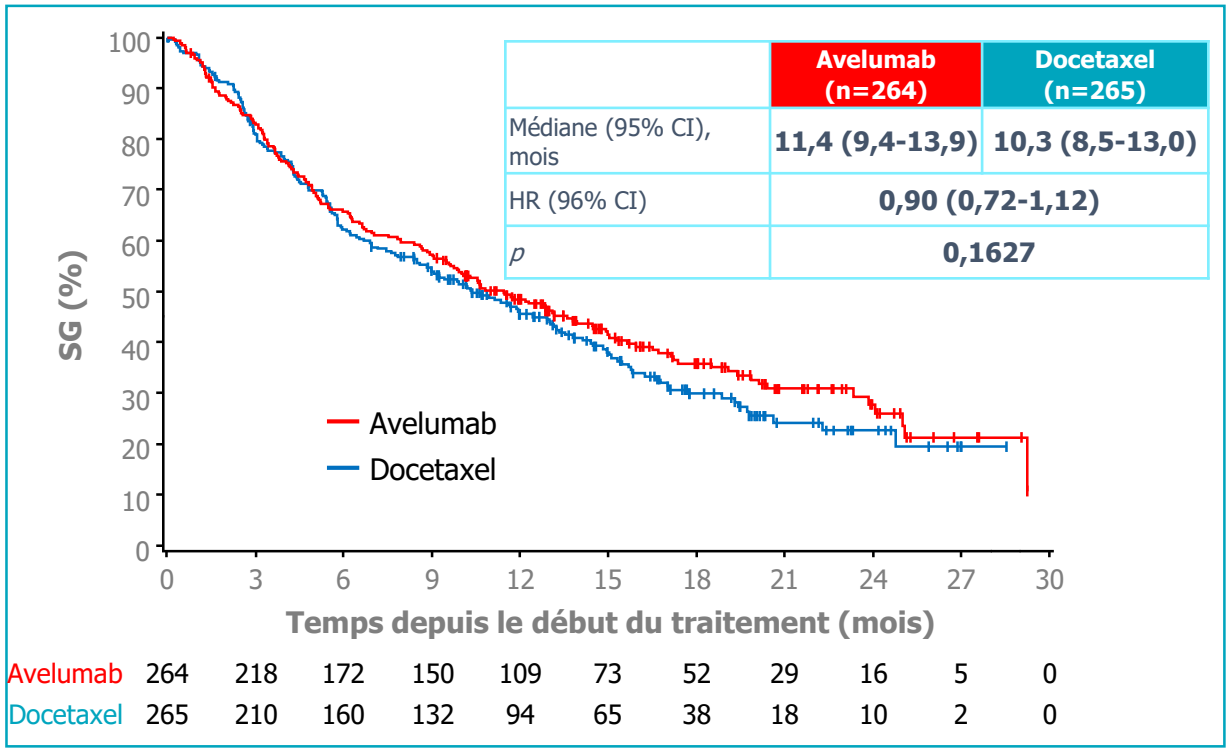
Ordre d'analyse



L'expression de PD-L1 sur les cellules tumorales a été établie avec l'anticorps 73-10.
Un seuil de ≥ 80% avec 73-10 équivaut à ≥ 50% avec 22C3

Barlesi F. et al.- WCLC® 2018 – Abs.# OA05-05

Objectif principal : SG chez les PD-L1+



	Avelumab (n=264)	Docetaxel (n=265)
Médiane (95% CI), mois	**11,4 (9,4-13,9)**	**10,3 (8,5-13,0)**
HR (96% CI)	**0,90 (0,72-1,12)**	
p	**0,1627**	

N'ont pas reçu le traitement

- → Avelumab : **2** (1%) ;
- → Docetaxel : **20** (8%)

On reçu une immunothérapie ultérieure

- → Avelumab : **15** (6%) ;
- → Docetaxel : **70** (26%)

On reçu un traitement anticancéreux

- → Avelumab : **105** (40%) ;
- → Docetaxel : **126** (48%)

◉ **SG médiane chez tous les patients (PD-L1+ ou PD-L1−)**

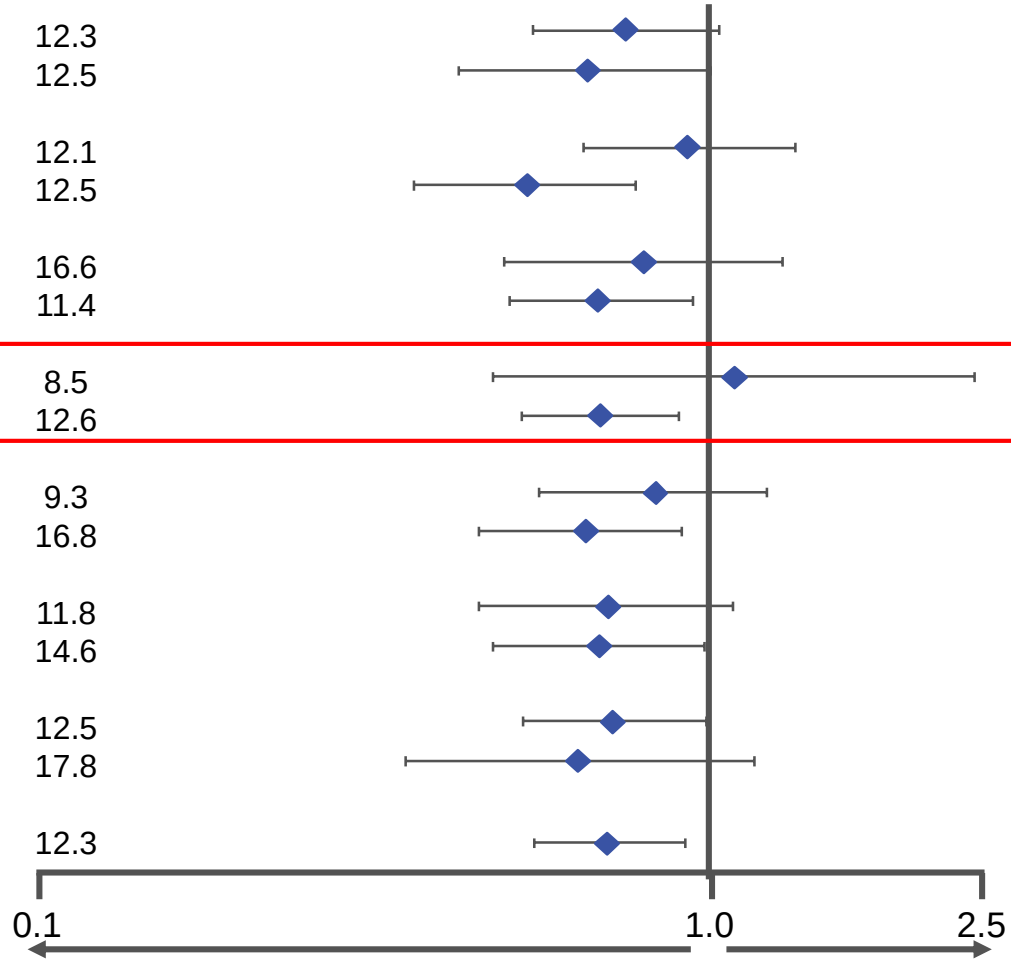
- → Avelumab : **10,5 mois (95% IC : 9,2-12,9)**
- → Docetaxel : **9,9 mois (95% IC : 8,1-11,8)**
  - **HR 0,90 (96% IC : 0.75-1.08)**
  - ***p=0,1175***

3èmes Rencontres d'Oncologie Thoracique en Nouvelle-Aquitaine - 24 mai 2019

Barlesi F. et al.- WCLC® 2018 – Abs.# OA05-05

Overall survival in key subgroups

Subgroup	No. of patients (%)	Median overall survival (months)		Hazard ratio for death (95% CI)[a]
		Placebo	Atezolizumab	
Male	261 (65)	10.9	12.3	0.74 (0.54, 1.02)
Female	142 (35)	9.5	12.5	0.65 (0.42, 1.00)
< 65 years	217 (54)	11.5	12.1	0.92 (0.64, 1.32)
≥ 65 years	186 (46)	9.6	12.5	0.53 (0.36, 0.77)
ECOG PS 0	140 (35)	12.4	16.6	0.79 (0.49, 1.27)
ECOG PS 1	263 (65)	9.3	11.4	0.68 (0.50, 0.93)
Brain metastases	35 (9)	9.7	8.5	1.07 (0.47, 2.43)
No brain metastases	368 (91)	10.4	12.6	0.68 (0.52, 0.89)
Liver metastases	149 (37)	7.8	9.3	0.81 (0.55, 1.20)
No liver metastases	254 (63)	11.2	16.8	0.64 (0.45, 0.90)
bTMB < 10 mut/mb	139 (34)	9.2	11.8	0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb	212 (53)	11.2	14.6	0.68 (0.47, 0.97)
bTMB < 16 mut/mb	271 (67)	9.9	12.5	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb	80 (20)	11.9	17.8	0.63 (0.35, 1.15)
ITT (N = 403)	403 (100)	10.3	12.3	0.70 (0.54, 0.91)



bTMB (blood tumour mutational burden) assessed as reported in Gandara DR, *et al. Nat Med,* 2018.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT. From *The New England Journal of Medicine*, Horn L, et al, First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer, Epub ahead of print. Copyright © 2018. Massachusetts Medical Society. Reprinted with permission.

T Mok, et al. IMpower133 https://bit.ly/2JZp0E6

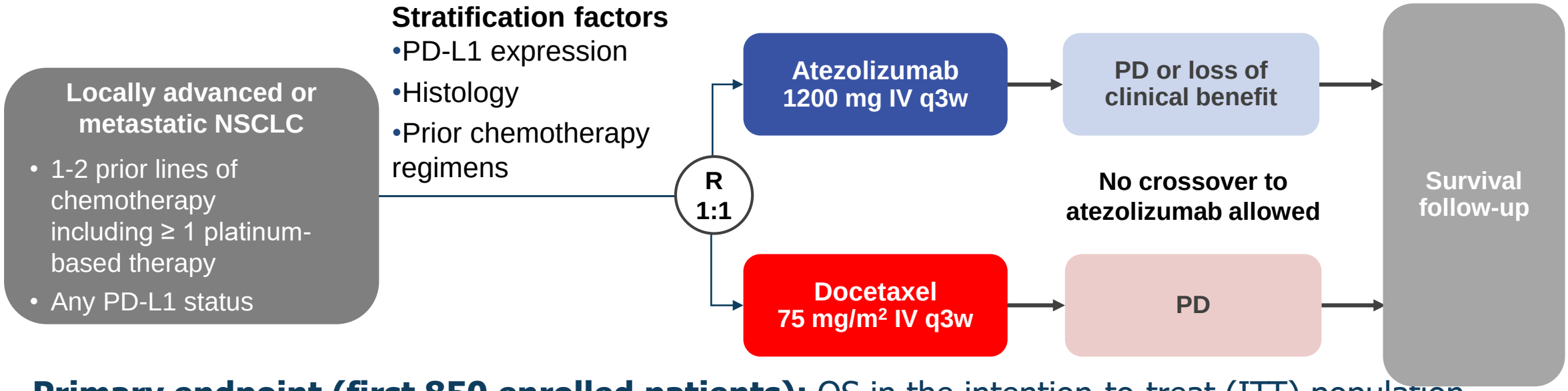
MUNICH 2018 ESMO congress

FAST PROGRESSION IN PATIENTS TREATED WITH A CHECKPOINT INHIBITOR VS CHEMOTHERAPY IN OAK, A PHASE III TRIAL OF ATEZOLIZUMAB VS DOCETAXEL IN 2L+ NSCLC

David R. Gandara,[1] Martin Reck,[2] Stefanie Morris,[3] Andres Cardona,[3] Diana Mendus[4], Marcus Ballinger,[4] Achim Rittmeyer[5]

[1]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [2]German Center for Lung Research, LungenClinic, Grosshansdorf, Germany; [3]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [4]Genentech, Inc., South San Francisco, CA, USA; [5]Lungenfachklinik Immenhausen, Immenhausen, Germany

OAK Fast Progressor Post Hoc Analysis



Primary endpoint (first 850 enrolled patients): OS in the intention-to-treat (ITT) population

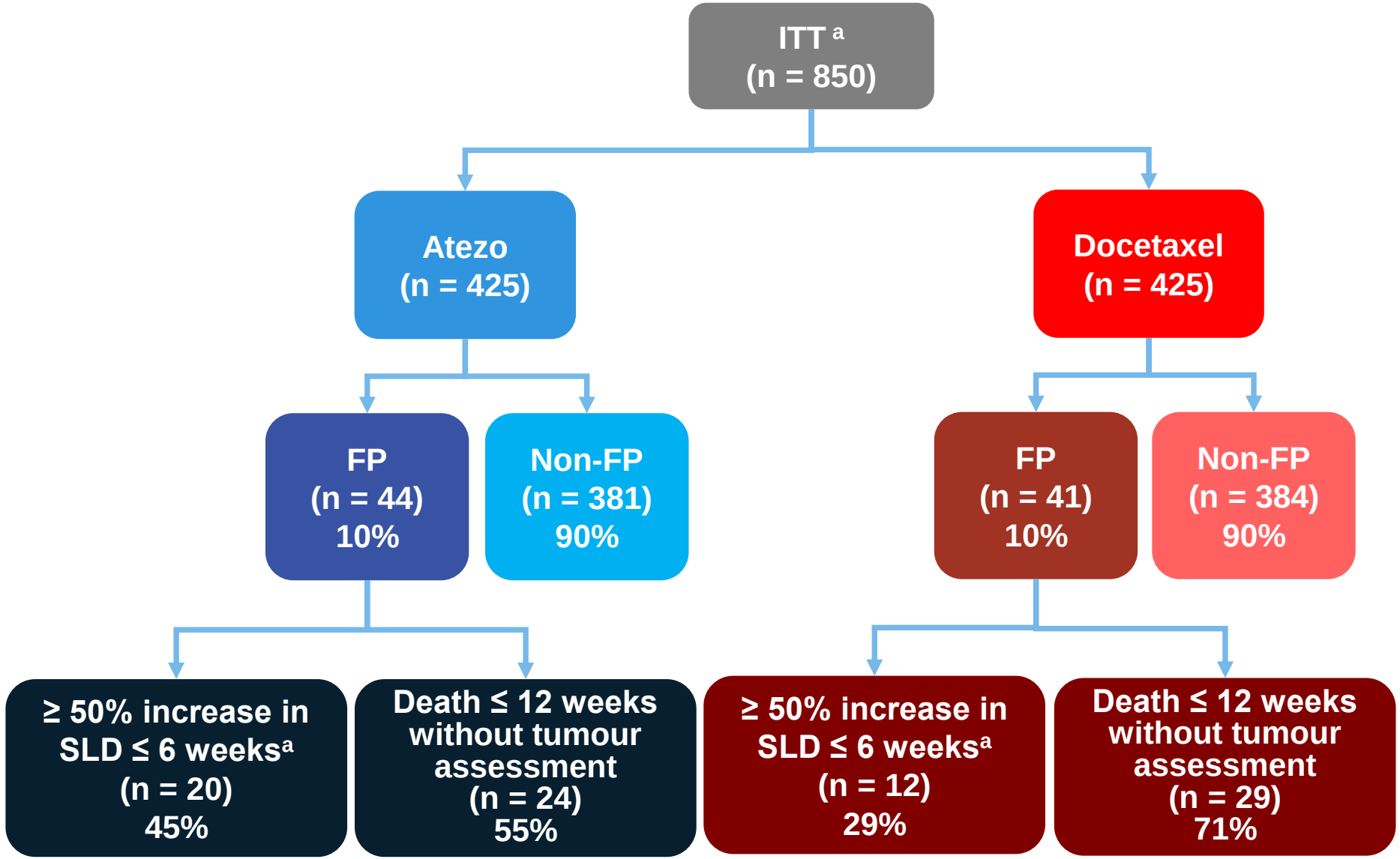
Fast progressors were defined as patients treated with atezolizumab or docetaxel and experienced:

- ≥ 50% increase in the sum of long diameters (SLD) within 6 weeks from baseline ***or***
- Death due to disease progression within 12 weeks from baseline for patients without a response assessment

Separately, OS was evaluated according to baseline factors potentially prognostic for FP

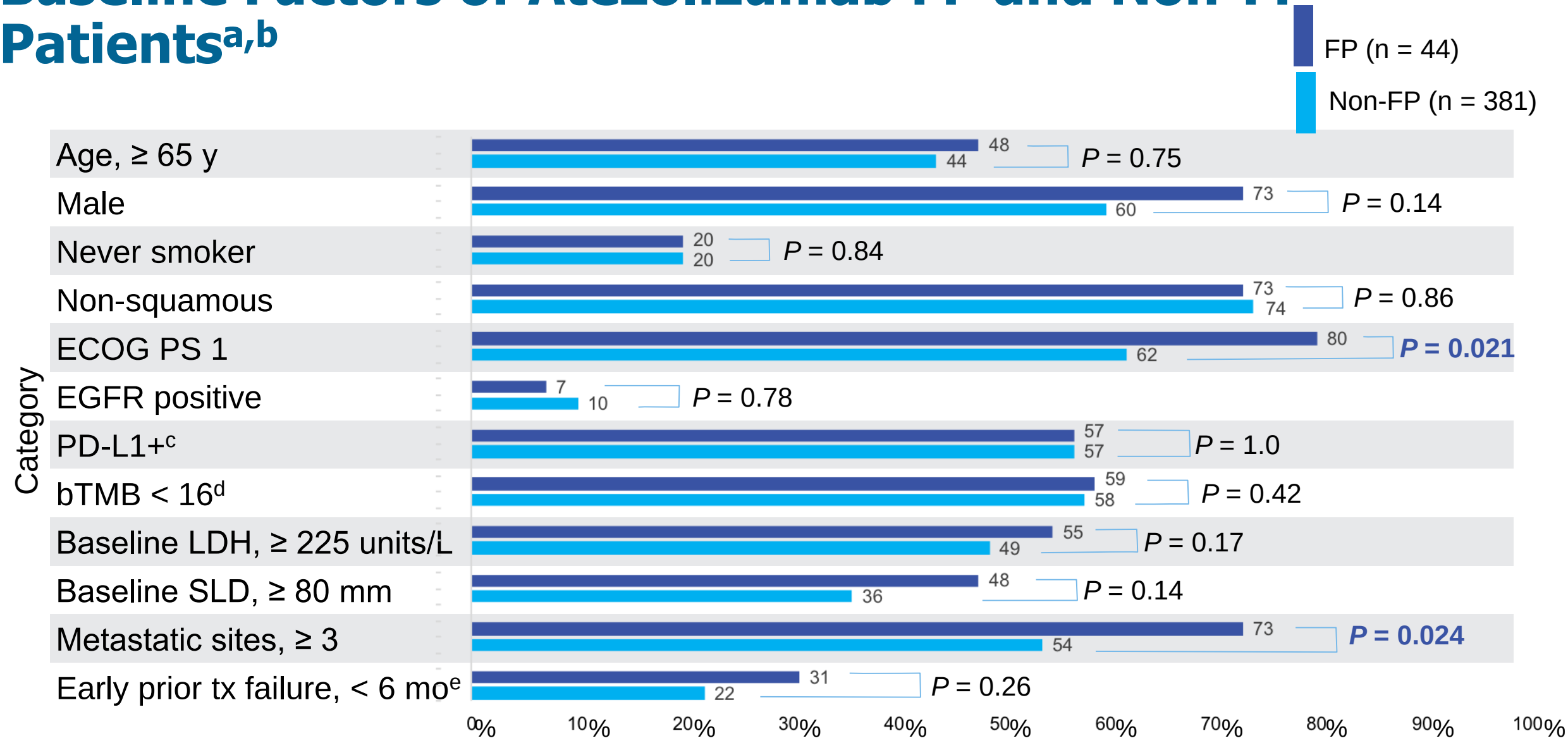
1. Rittmeyer A. *Lancet*. 2017;389(10066):255-265.

OAK Fast Progressor Patient Population



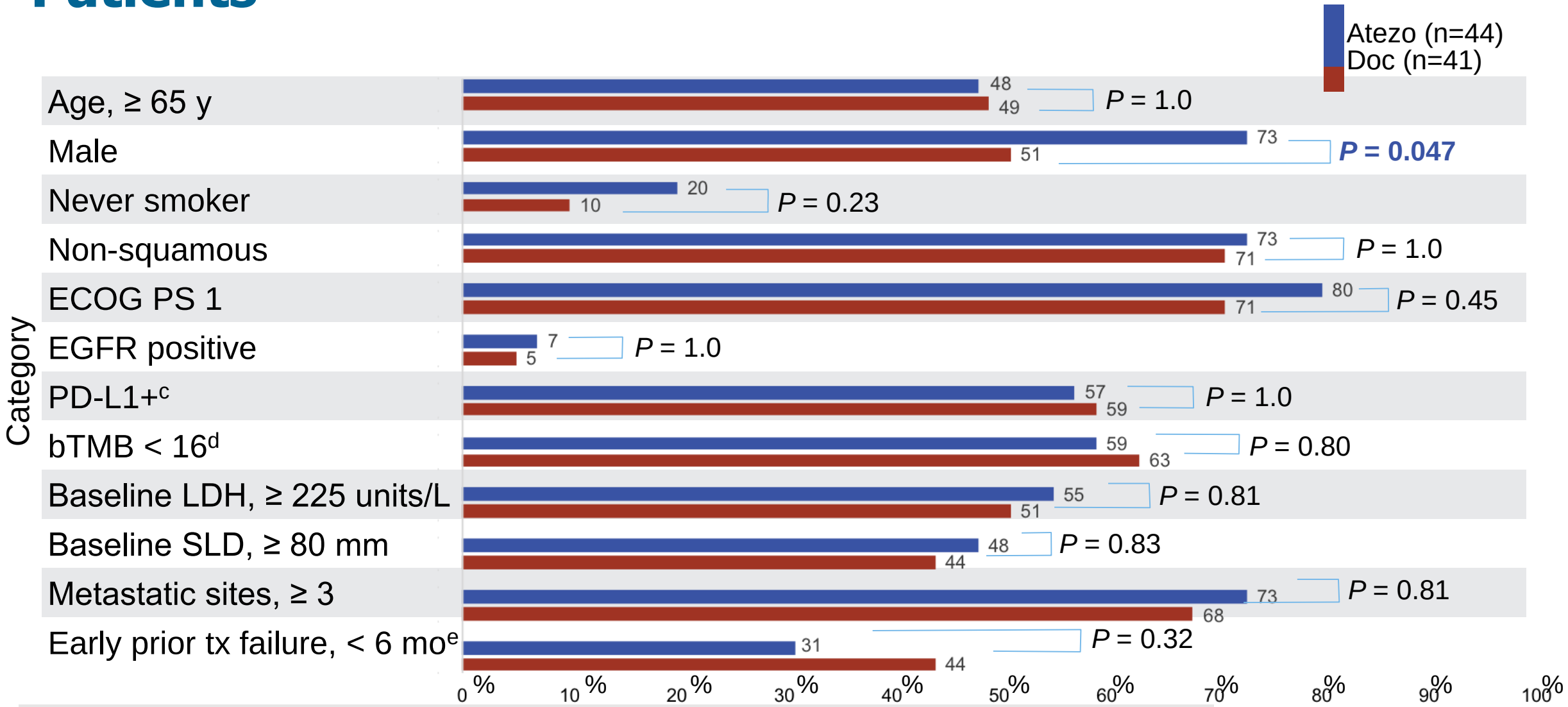
[a] ≥ 50% increase in the SLD within 6 weeks from baseline.

Baseline Factors of Atezolizumab FP and Non-FP Patients[a,b]



[a] *P* values calculated by Fisher test and not adjusted for multiplicity. [b] Percentages may not sum to 100 due to rounding or missing values. [c] Number of unknown in non-FP group: atezolizumab, n = 4; docetaxel, n = 4. [d] Missing, n = 101. [e] Includes only patients with 1 prior treatment.

Baseline Factors of Atezolizumab FP and Docetaxel FP Patients[a,b]



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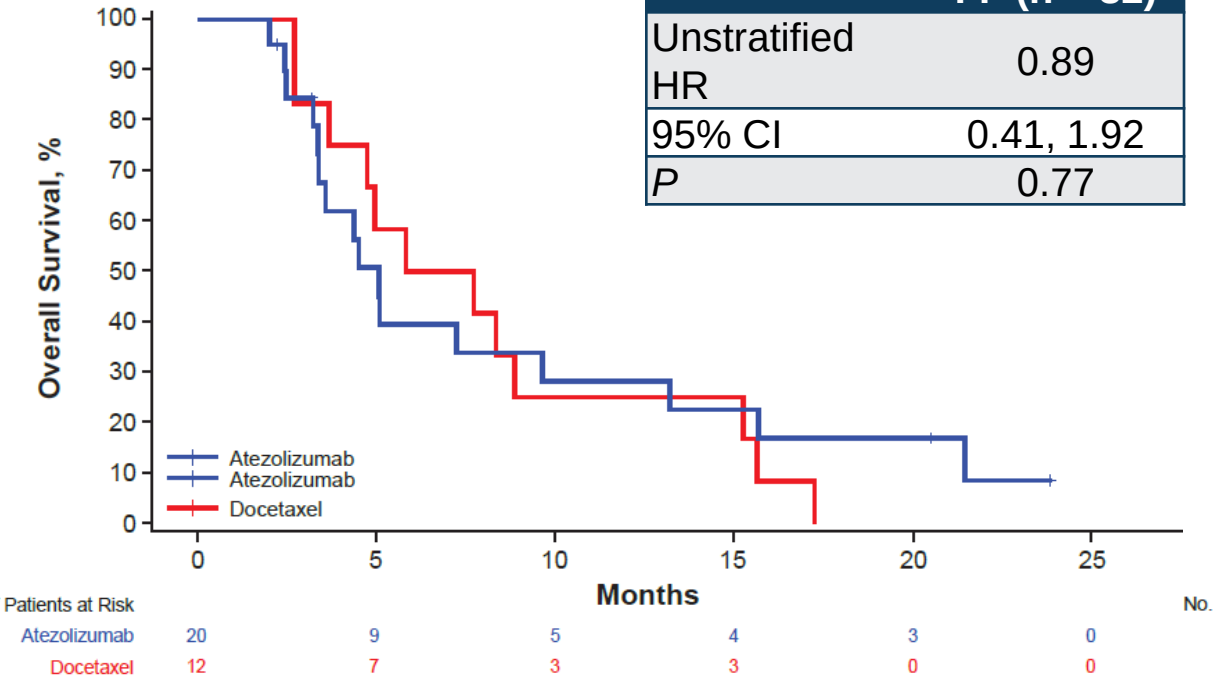
OS Landmark Analysis at Week 6 in Patients With ≥ 50% Increase in SLD[a]

≥ 50% increase in SLD at week 6

	FP (n = 32)
Unstratified HR	0.89
95% CI	0.41, 1.92
P	0.77

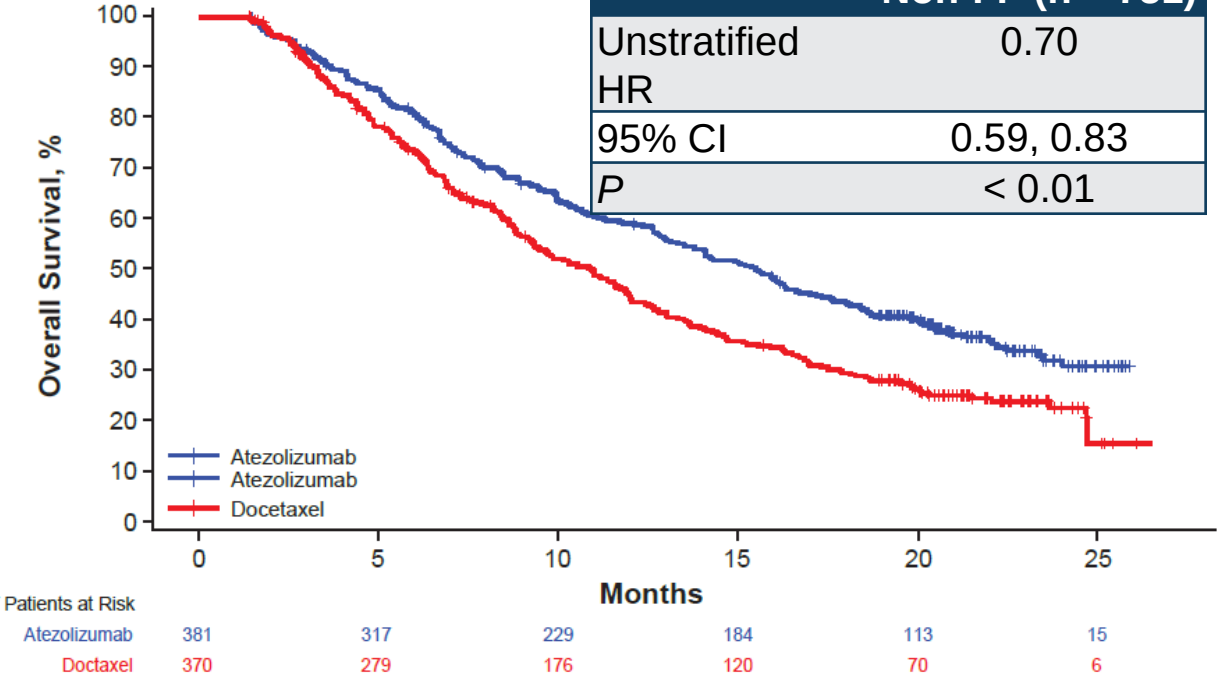


No. of Patients at Risk

Atezolizumab	20	9	5	4	3	0
Docetaxel	12	7	3	3	0	0

< 50% increase in SLD at week 6

	Non-FP (n = 751)
Unstratified HR	0.70
95% CI	0.59, 0.83
P	< 0.01



No. of Patients at Risk

Atezolizumab	381	317	229	184	113	15
Doctaxel	370	279	176	120	70	6

OS among subgroup of FP patients with ≥ 50% increase in SLD at week 6 was similar in the atezolizumab and docetaxel arms, OS among the non-FP subgroup was similar to the ITT population

[a] Patients without a tumour assessment were excluded.

Conclusions

Similar rates of FP occurred in the atezolizumab and docetaxel arms

Characteristics and outcomes of patients with FP were similar for atezolizumab vs docetaxel

- FP in the atezolizumab arm was associated with ≥ 3 metastatic sites and ECOG PS
  but not other baseline factors
- OS was similar for atezolizumab vs docetaxel in patients experiencing radiographic FP

OS benefit with atezolizumab vs docetaxel was observed in all sub-groups, including those expected to be prognostic for aggressive disease, as well as those factors which were not

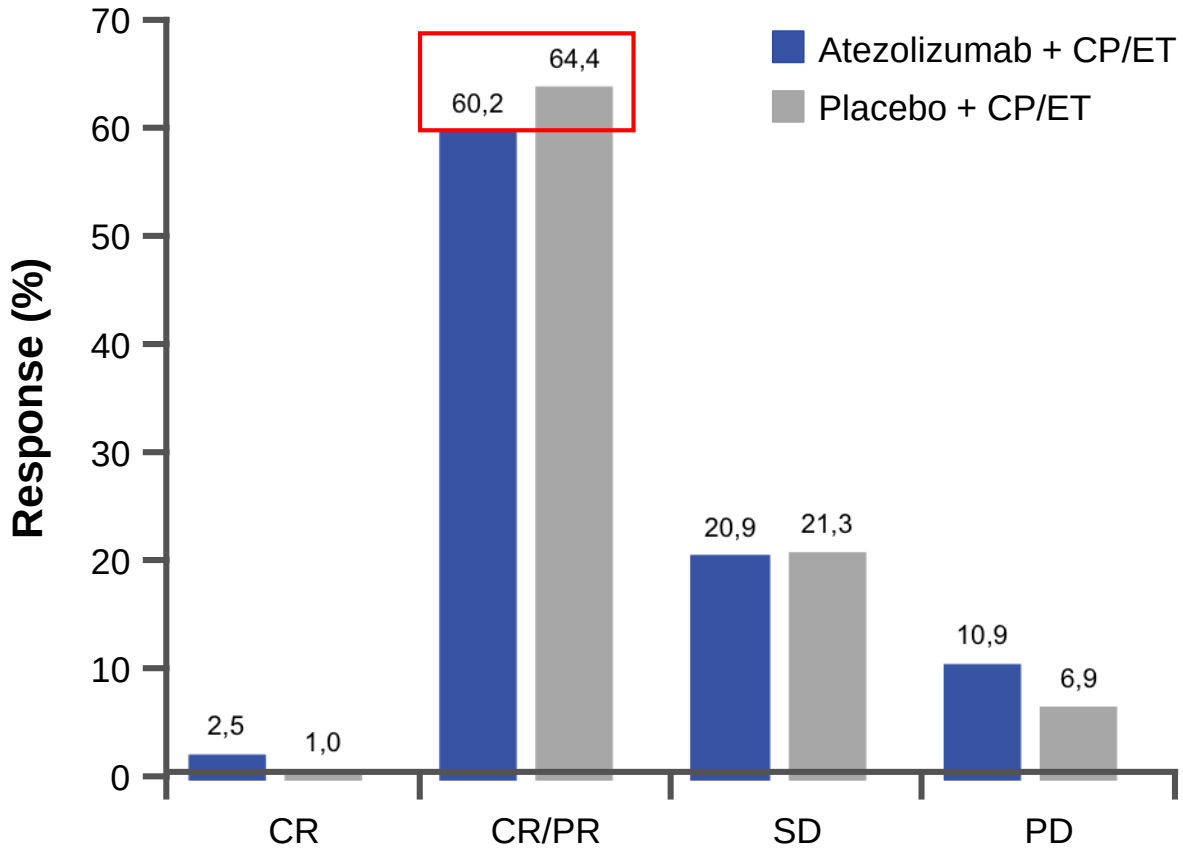
CB APC PREMIERE LIGNE

IMpower133: Primary efficacy and safety + CNS-related adverse events in a Ph1/3 study of first-line atezolizumab + carboplatin + etoposide in extensive stage SCLC (ES-SCLC)

T. S. K. Mok,[1] M. Reck,[2] L. Horn,[3] S. Lam,[4] D. S. Shames,[5] J. Liu,[6] F. Kabbinavar,[4] W. Lin,[4] A. Sandler,[4] S. V. Liu[7]

[1]State Key Laboratory of South China, The Chinese University of Hong Kong, Sha Tin, HK; [2]Thoracic Oncology, Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research (ARCN), Grosshansdorf, DE; [3]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, US; [4]Product Development - Oncology, Genentech, Inc., South San Francisco, CA, US; [5]Oncology Biomarker Development, Genentech, Inc., South San Francisco, CA, US; [6]Product Development - Oncology, Roche (China) Holding, Shanghai, CN; [7]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, US

Confirmed objective response and duration of response



Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration — months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]	18 (14.9)	7 (5.4)

[a] Censored. [b] At clinical cut-off date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.
Data derived from *The New England Journal of Medicine*, Horn L, et al, First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer, Epub ahead of print.

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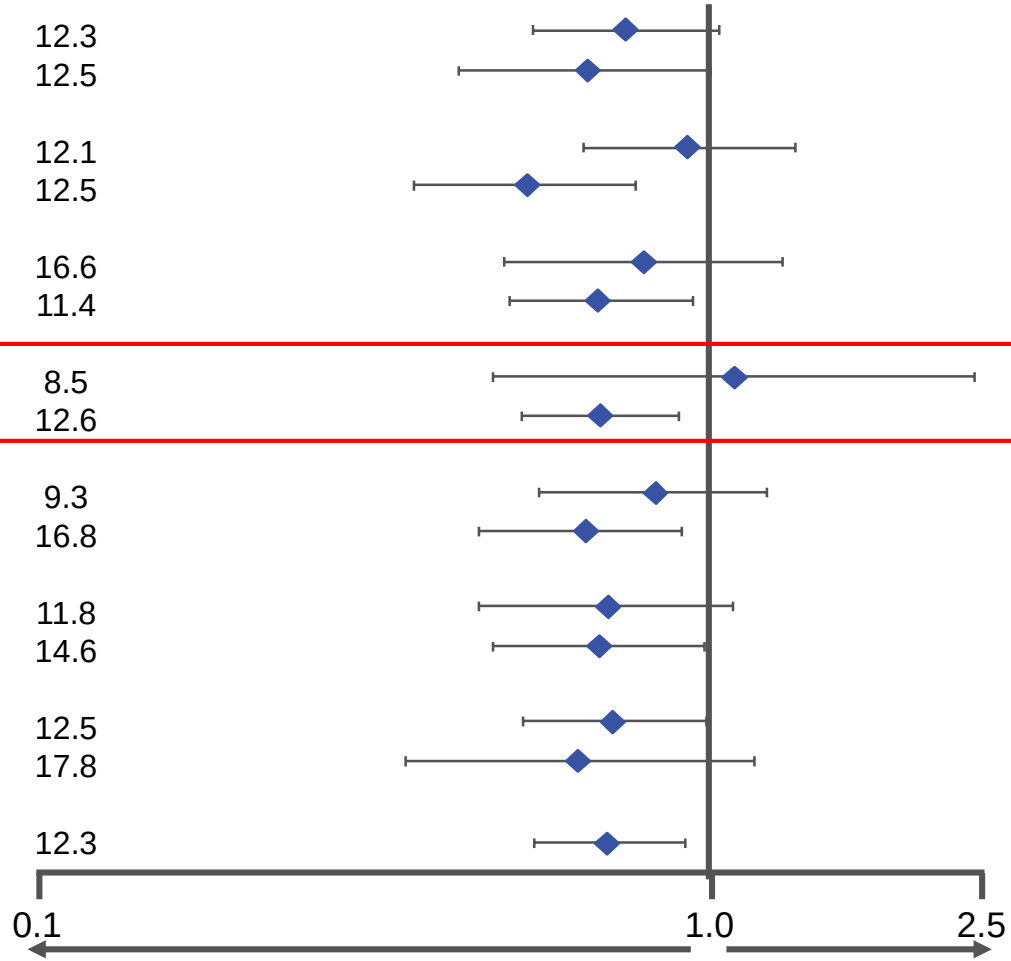

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Questions en suspens, conclusions….

Résistance primaire?

Réintroduction

- Toxicité
- Après résistance secondaire
- Après résistance primaire
- Après traitement de consolidation pour les stades localisés

Comment sélectionner les patients? **On ne sait pas**

Comment réintroduire? **On ne sait pas**