19th Annual
ADVANCES IN ONCOLOGY 2018
September 28-29, 2018

ADVANCES IN ONCOLOGY CONFERENCE

KIMPTON SAWYER HOTEL

New Developments in Lung Cancer Therapeutics

Karen Kelly, MD
Professor of Medicine
Associate Director for Clinical Research
Jennifer Rene Harmon Tegley and Elizabeth Erica Harmon
Endowed Chair in Cancer Clinical Research
UC Davis Comprehensive Cancer Center

Relevant Financial Relationships in The Past Twelve Months by Presenter or Spouse/Partner

- Advisor: AbbVie, AstraZeneca, Genentech, Janssen, Lilly, Merck, Pfizer, Regeneron
- Honoraria: None
- Research: AbbVie, EMD Serono, Genentech, Lycera, Regeneron, Transgene
- Royalty: UpToDate Author

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

2018

A HISTORIC YEAR FOR LUNG CANCER THERAPIES

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

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*

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csőszi, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, and M. Reck, for the IMpower150 Study Group*

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

The NEW ENGLAND JOURNAL of MEDICINE

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*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer

D.R. Camidge, H.R. Kim, M.-J. Ahn, J.C.-H. Yang, J.-Y. Han, J.-S. Lee, M.J. Hochmair, J.Y.-C. Li, G.-C. Chang, K.H. Lee, C. Gridelli, A. Delmonte, R. Garcia Campelo, D.-W. Kim, A. Bearz, F. Griesinger, A. Morabito, E. Felip, R. Califano, S. Ghosh, A. Spira, S.N. Gettinger, M. Tiseo, N. Gupta, J. Haney, D. Kerstein, and S. Popat

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab plus Chemotherapy for First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer

Leora Horn, M.D., Aaron S. Mansfield, M.D., Aleksandra Szczęsna, M.D., Libor Havel, M.D., Maciej Krzakowski, M.D., Ph.D., Maximilian J. Hochmair, M.D., Florian Huemer, M.D., György Losonczy, M.D., Ph.D., Melissa L. Johnson, M.D., Makoto Nishio, M.D., Ph.D., Martin Reck, M.D., Tony Mok, M.D., Sivuonthanh Lam, Pharm.D., David S. Shames, Ph.D., Juan Liu, Ph.D., Beiying Ding, Ph.D., Ariel Lopez-Chavez, M.D., Fairooz Kabbinavar, M.D., Wei Lin, M.D., Alan Sandler, M.D., and Stephen V. Liu, M.D., for the IMpower133 Study Group*

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

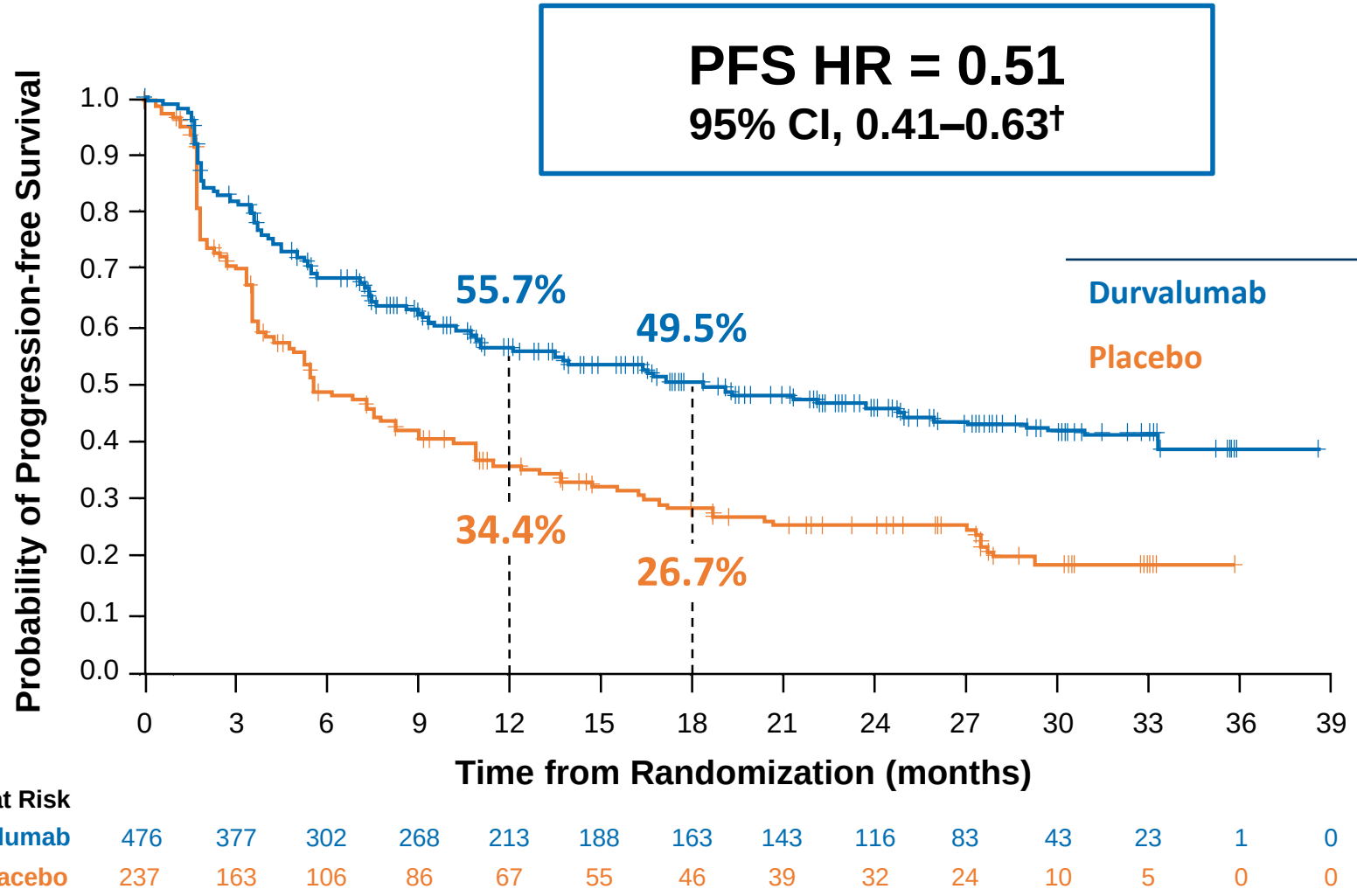
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*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

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Updated Progression-free Survival by BICR* (ITT)

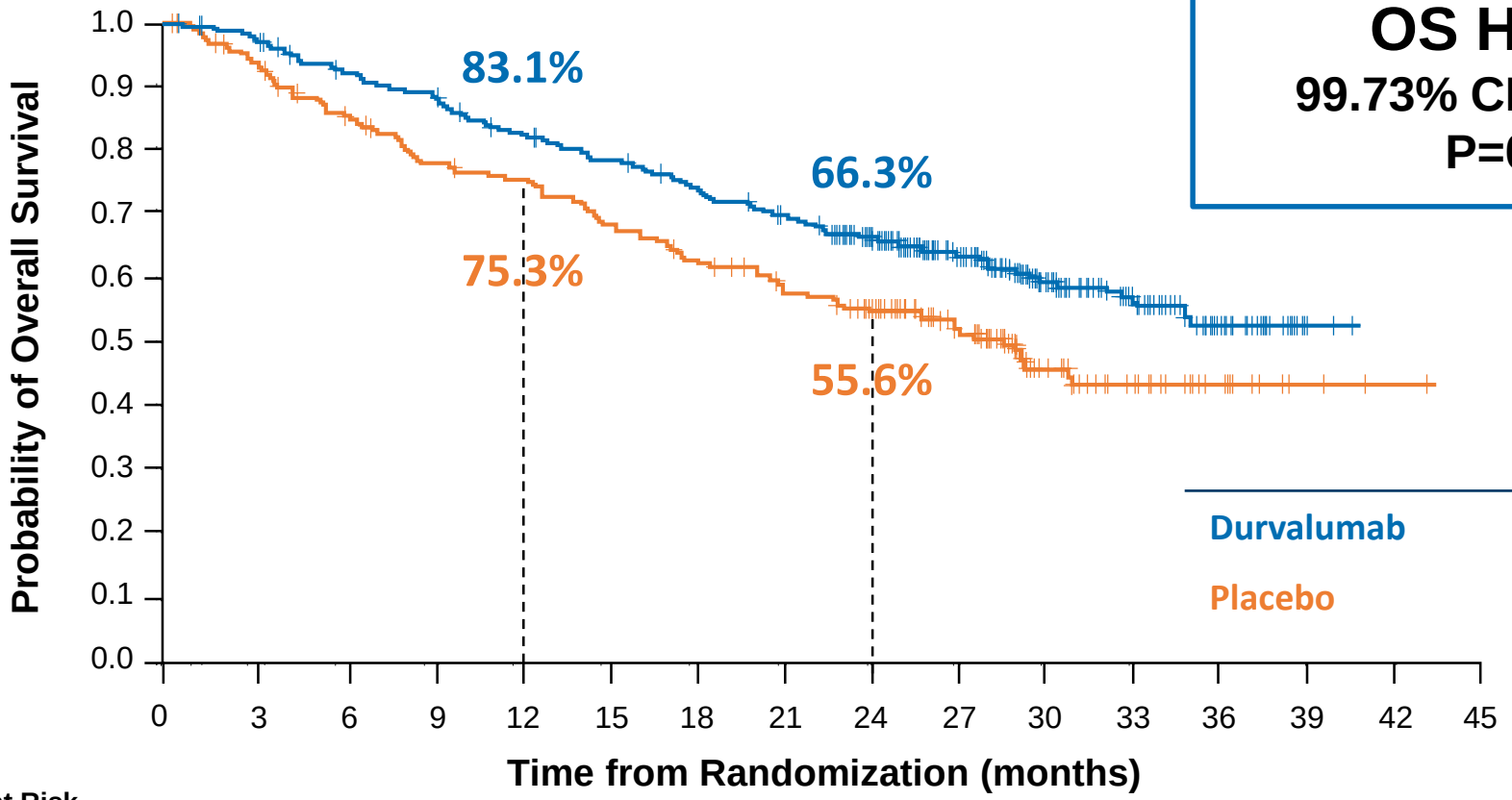


	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)

Antonia, SJ et al, WCLC 2018, abstr PL02.01

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
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

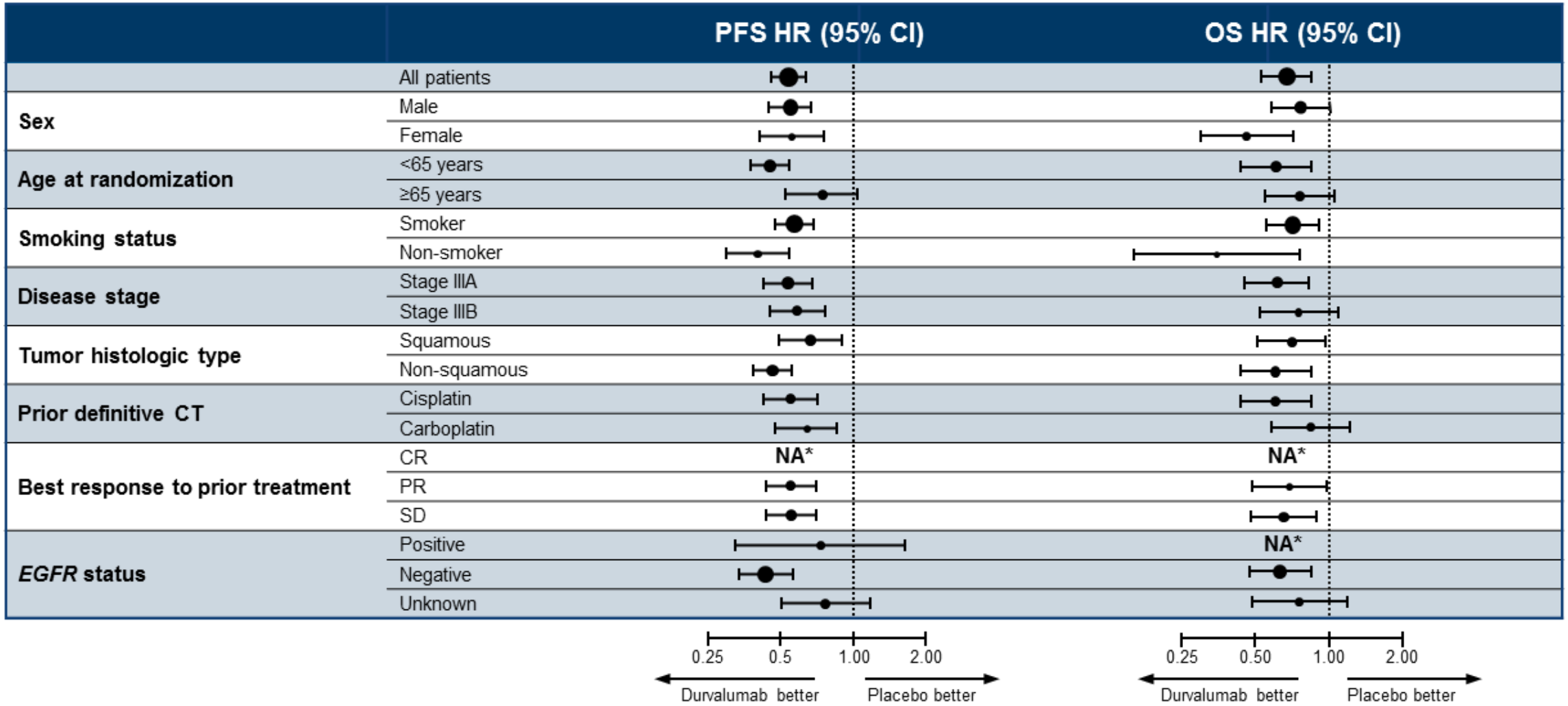
No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Progression-free and Overall Survival by Subgroup (ITT)



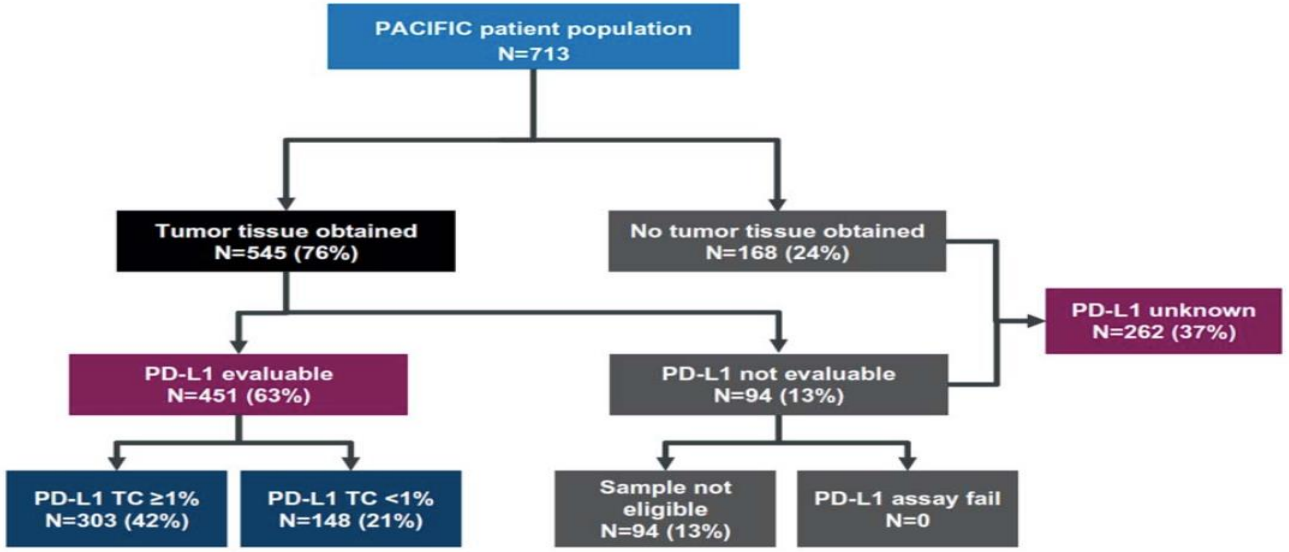
*Not calculated if subgroup has <20 events

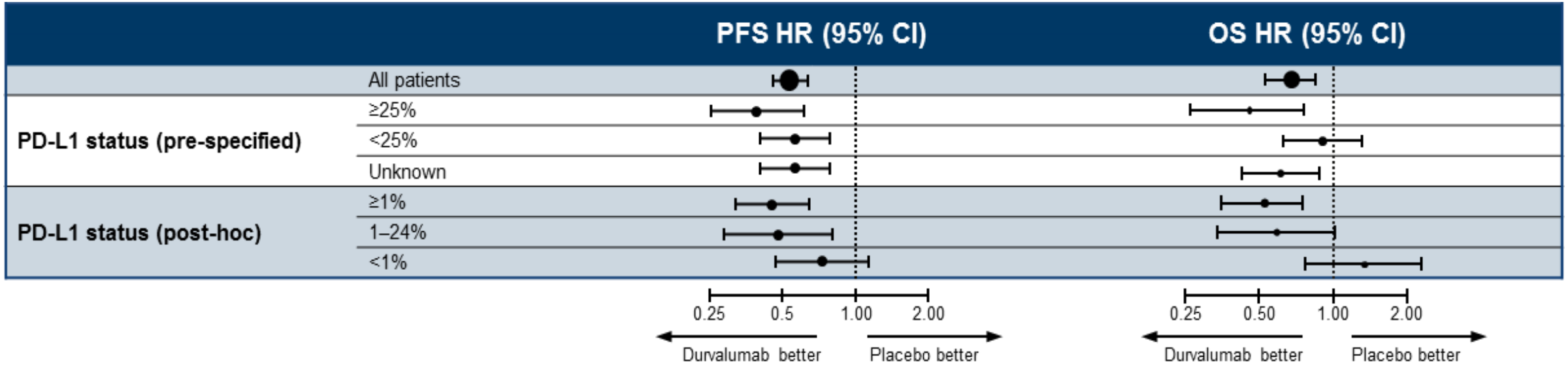
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

NA, not available

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Subgroup Analysis by PD-L1 Status

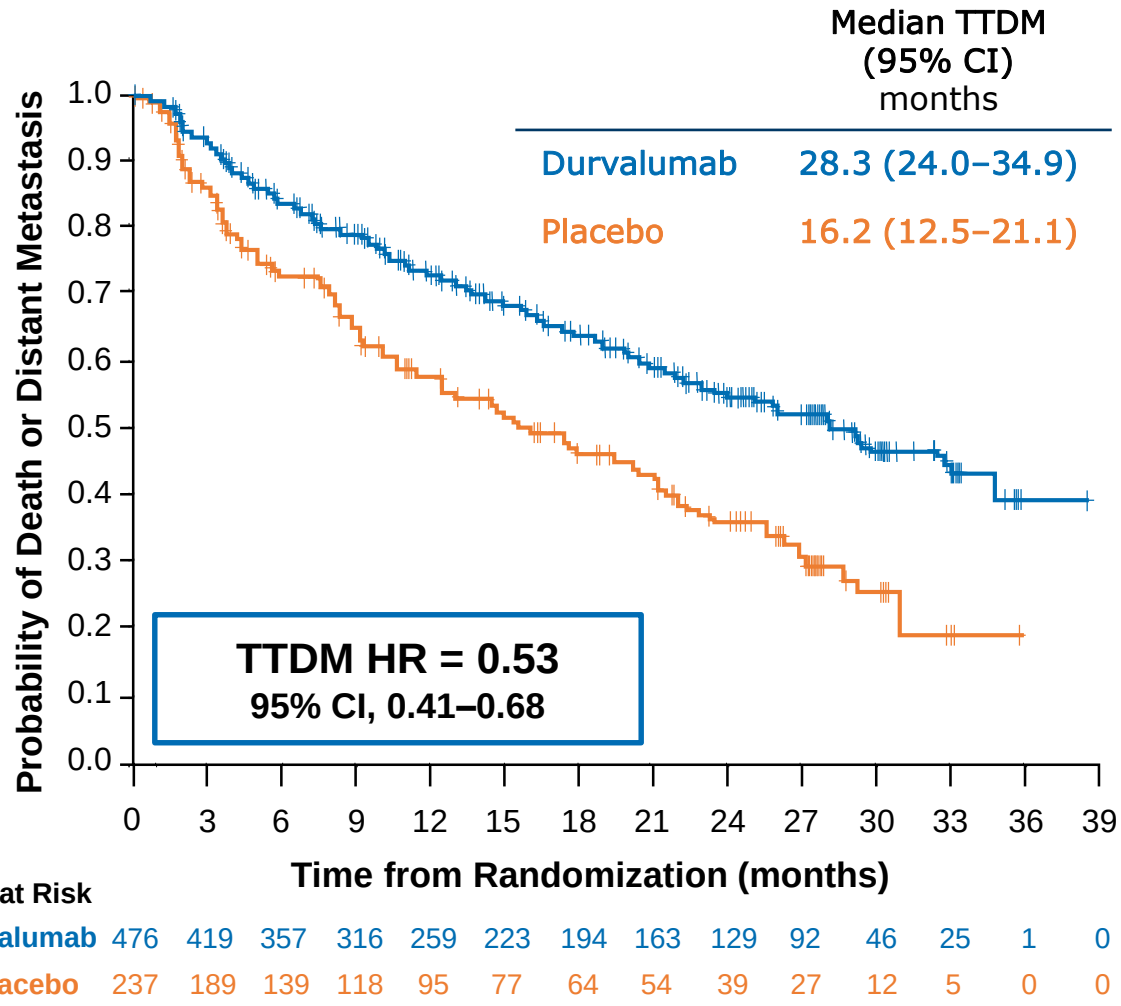




Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

Antonia, SJ et al, WCLC 2018, abstr PL02.01

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



*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†A patient may have had more than one new lesion site

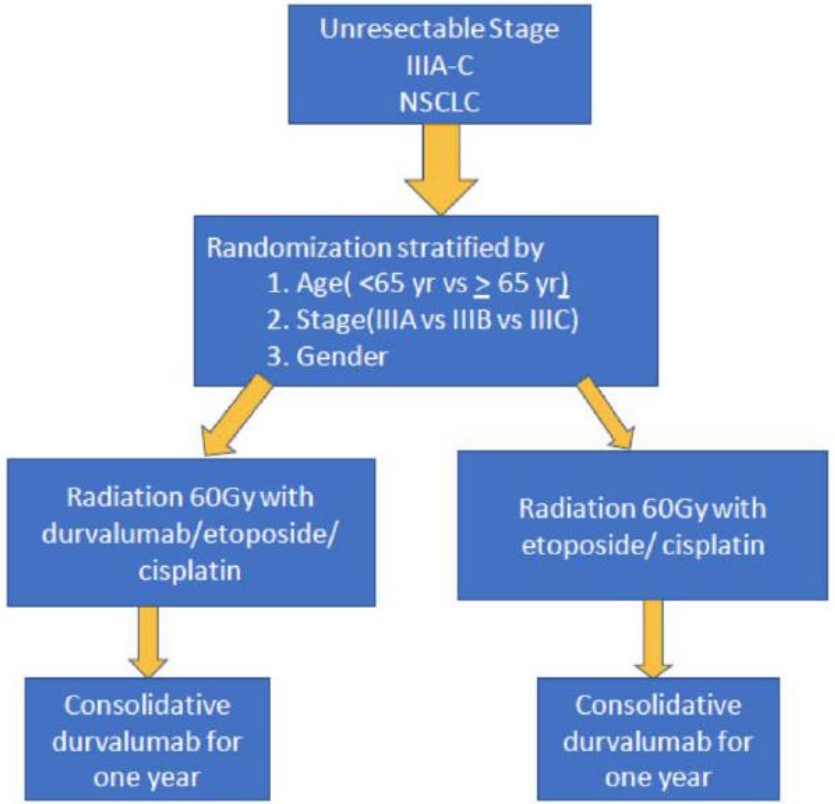
Updated Incidence of New Lesions by BICR* (ITT)

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)

Antonia, SJ et al, WCLC 2018, abstr PL02.01

Future Immunotherapy Trials (in Development)
Unresectable Stage III NSCLC

Phase II ECOG EA5181
Cyclic Chemotherapy



Phase III SWOG S1910
Weekly Chemotherapy

Phase III (n=644 randomized)

STRATIFY

Stage
1. II/IIIA
2. IIIB/IIIC

Histology
1. Squamous
2. Non-squamous

Age
1. <65
2. ≥65

R

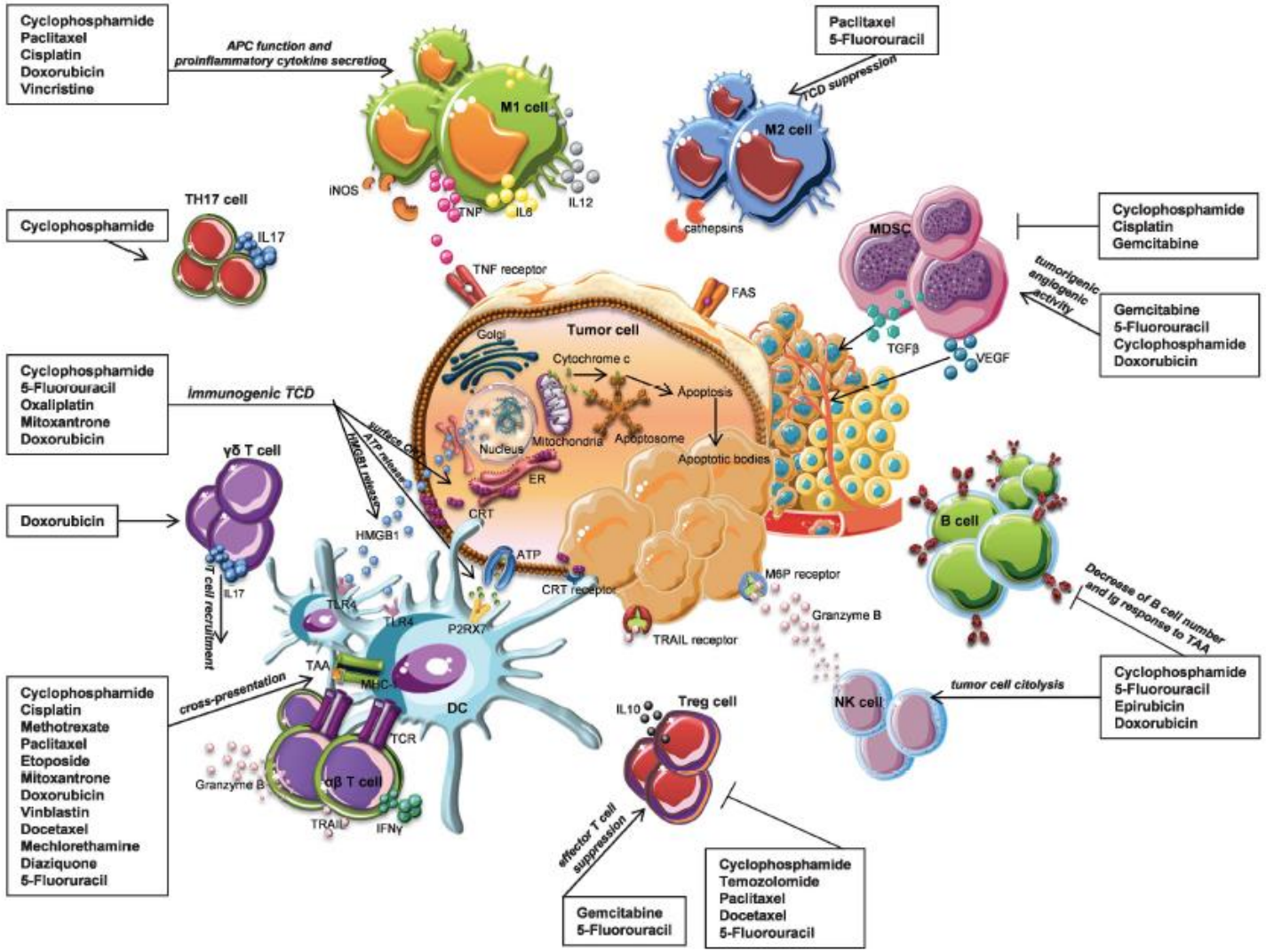
Investigational arm
Atezo + CRT → consolidation atezo

SoC arm
CRT → consolidation atezo

- CRT = standard chemoradiation therapy, 60 Gy in 30 fractions
- Carboplatin AUC 2.0 / Paclitaxel 50 mg/m² concurrent CRT
- Atezo = atezolizumab, 1200 mg IV Q3wk given for up to 1 year

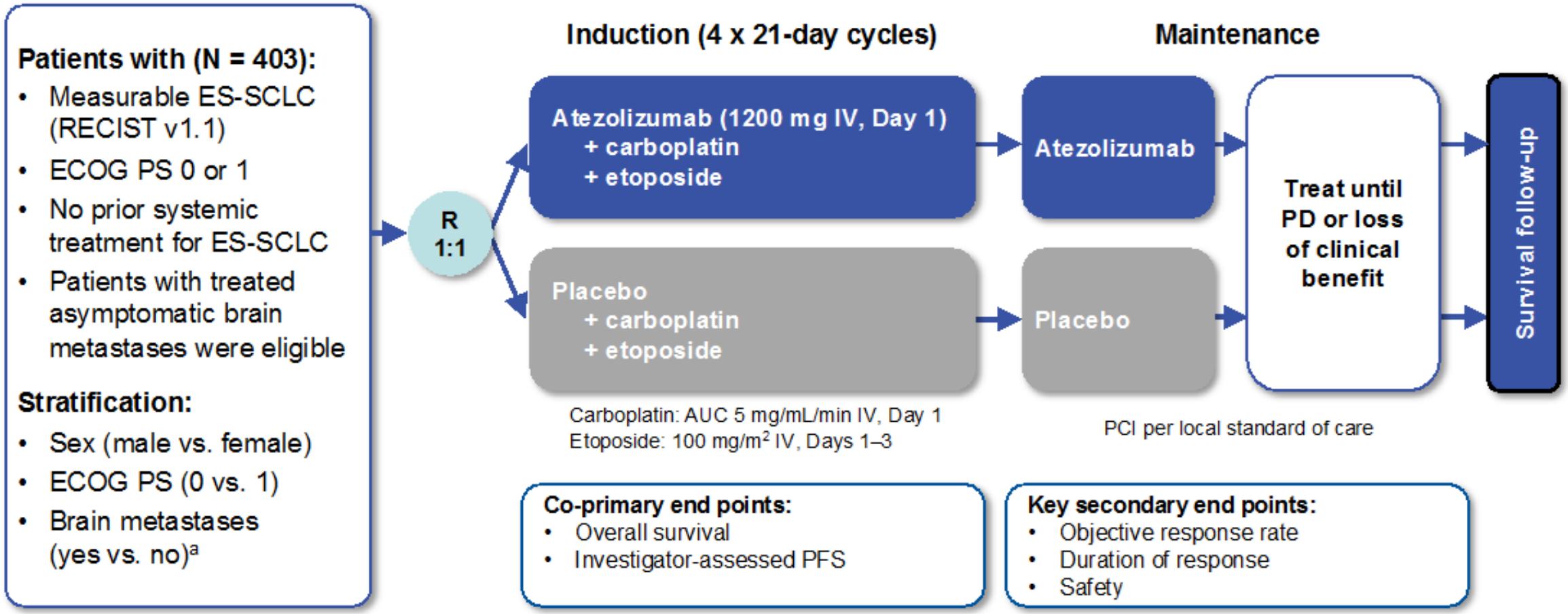
Rationale for Combining Chemotherapy and Immunotherapy

How can chemotherapy enhance an immune response?



Braccio L et all 2014

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Liu, SV et al, WCLC 2018, abstr PL02.07

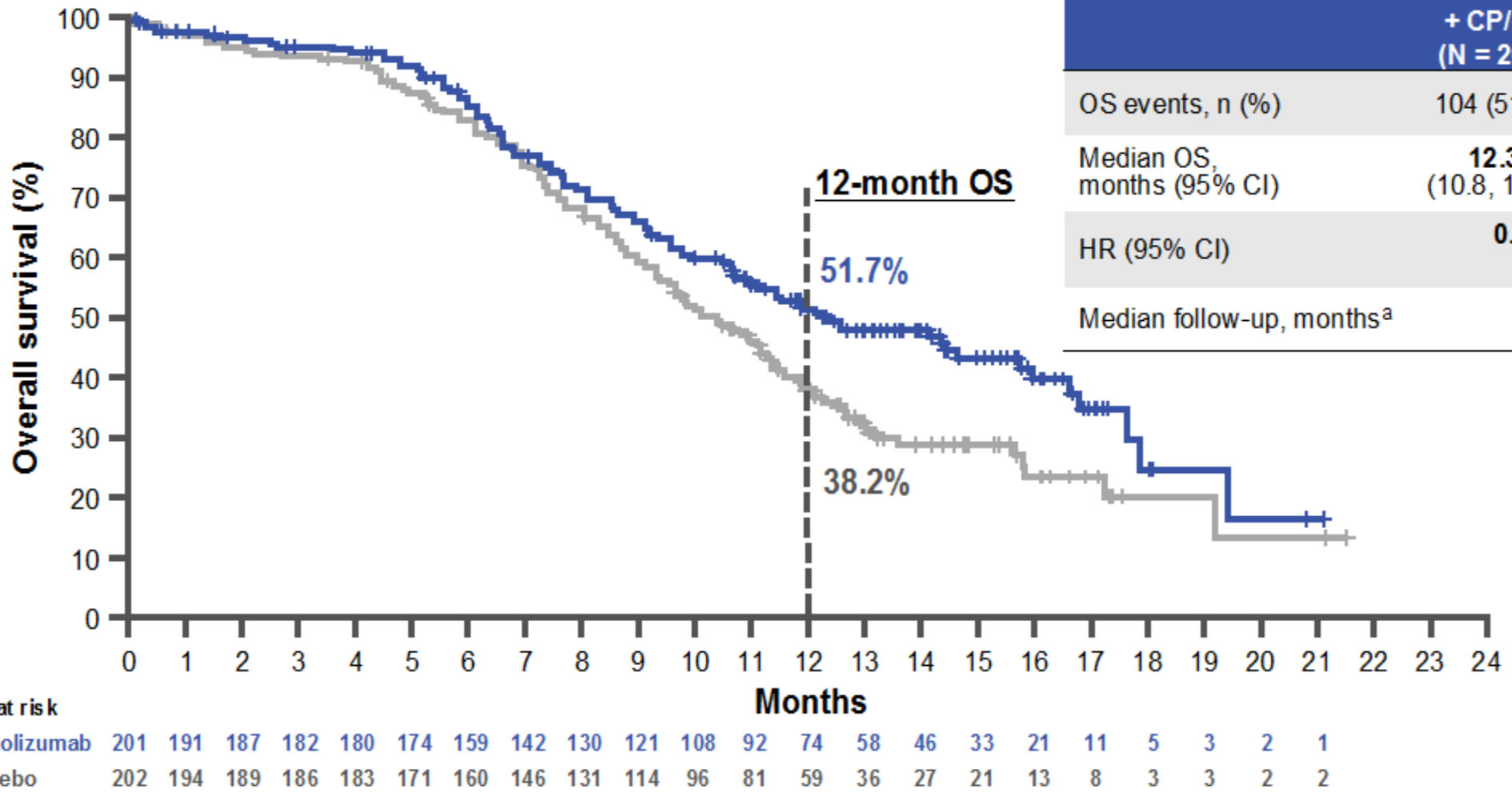
Baseline Characteristics

Characteristic	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Median age (range) — years	64 (28–90)	64 (26–87)
Age group — no. (%)		
< 65 years	111 (55)	106 (52)
≥ 65 years	90 (45)	96 (48)
Male sex — no. (%)[a]	129 (64)	132 (65)
Smoking status[b]		
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Race — no. (%)		
White	163 (81)	159 (79)
Asian	33 (16)	36 (18)
Other	5 (2)	7 (3)
ECOG PS — no. (%)[a]		
0	73 (36)	67 (33)
1	128 (64)	135 (67)
Brain metastases — no. (%)[a]		
Yes	17 (8)	18 (9)
Liver metastases — no. (%)		
Yes	77 (38)	72 (36)

Clinical data cutoff date: April 24, 2018. [a] Data reported per electronic case report form. [b] Nine patients in the atezolizumab group and three patients in the placebo group have never smoked. CP/ET, carboplatin + etoposide.

Liu, SV et al, WCLC 2018, abstr PL02.07

Overall Survival



	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

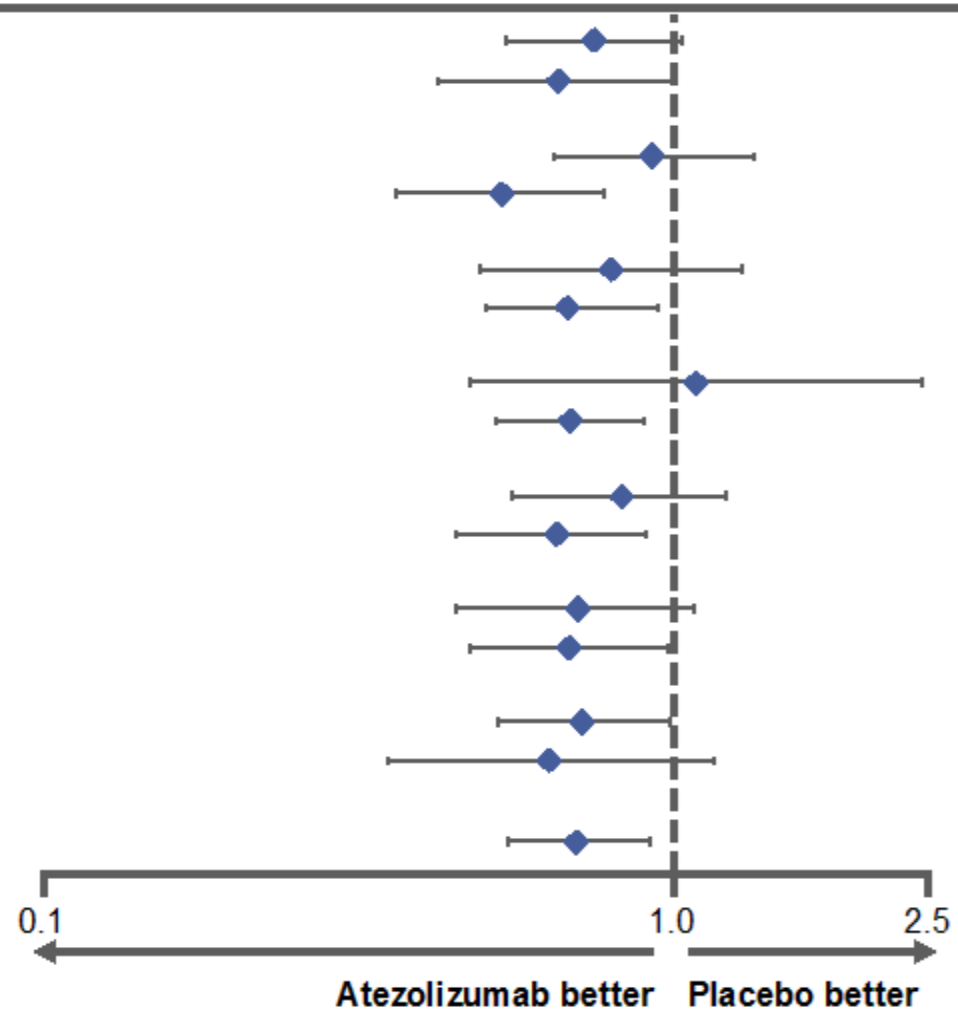
No. at risk																						
Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Liu, SV et al, WCLC 2018, abstr PL02.07

Overall survival in key subgroups

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

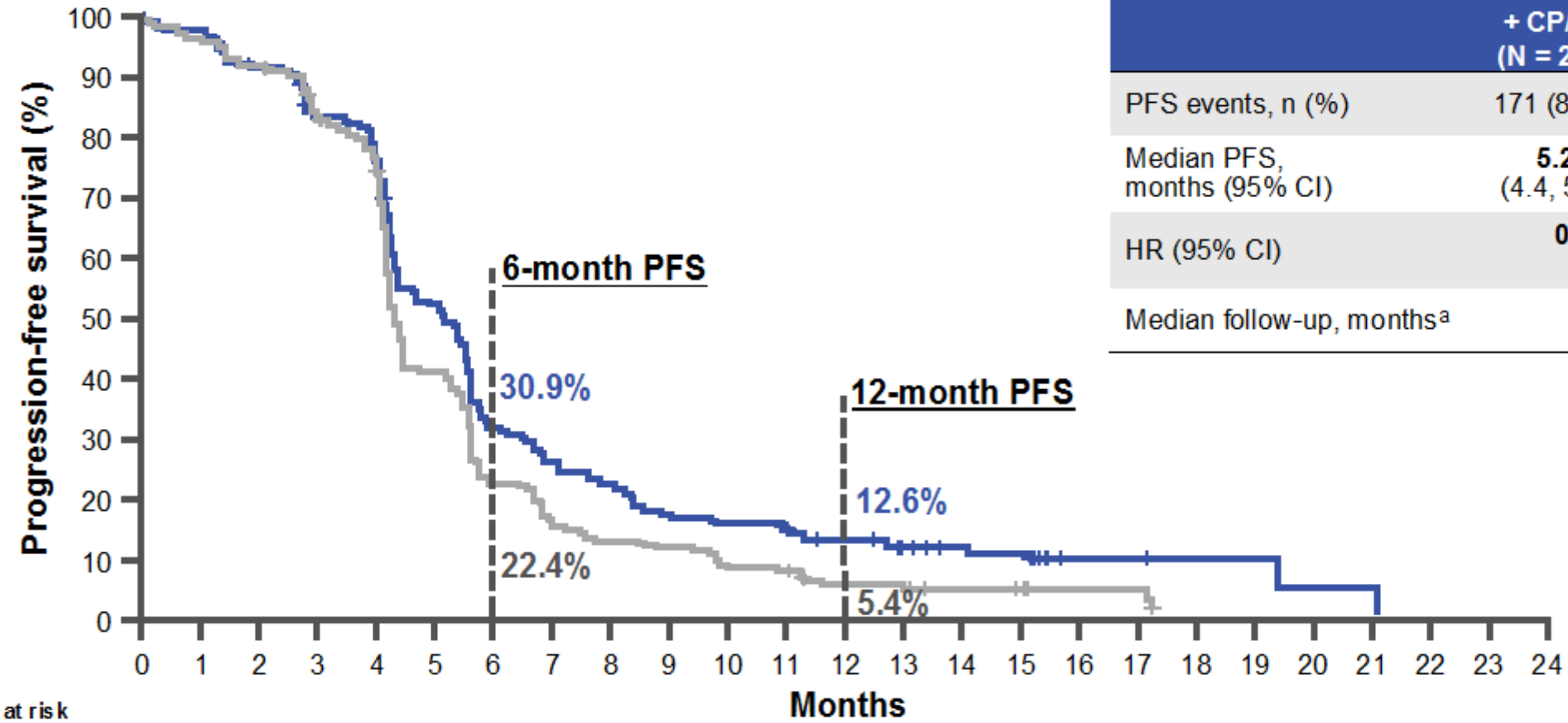


Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med*, 2018.

[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Liu, SV et al, WCLC 2018, abstr PL02.07

Investigator-assessed progression-free survival



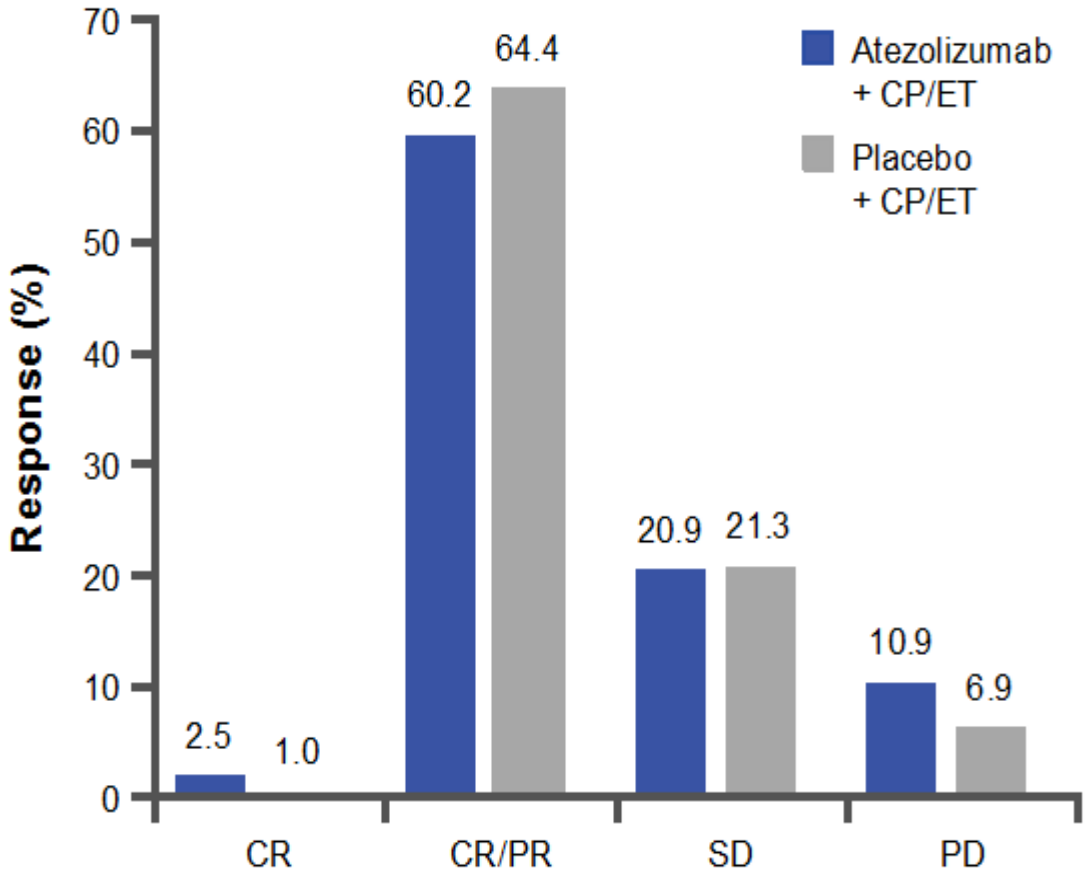
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

No. at risk																						
Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Liu, SV et al, WCLC 2018, abstr PL02.07

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 cutoff date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Liu, SV et al, WCLC 2018, abstr PL02.07

Subsequent treatments

	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Total number of patients with at least one treatment	104 (51.7)	116 (57.4)
Line of therapy — no. (%)		
Second	101 (50.2)	116 (57.4)
Third	29 (14.4)	38 (18.8)
Fourth	3 (1.5)	15 (7.4)
Therapy type — no. (%)		
Chemotherapy/non-anthracycline	81 (40.3)	88 (43.6)
Chemotherapy/anthracycline	31 (15.4)	46 (22.8)
Immunotherapy	6 (3.0)	15 (7.4)
Other	2 (1.0)	2 (1.0)
Targeted therapy	2 (1.0)	1 (0.5)

Clinical data cutoff date: April 24, 2018.

Liu, SV et al, WCLC 2018, abstr PL02.07

Most frequently observed AEs

Treatment-related AEs — no. (%) > 5% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0

Immune-related AEs — no. (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

Clinical data cutoff date: April 24, 2018.

Liu, SV et al, WCLC 2018, abstr PL02.07

Summary

- IMpower133 is the first study in over 20 years to show a clinically meaningful improvement in OS over the current standard-of-care in 1L ES-SCLC
- The addition of atezolizumab to carboplatin and etoposide provided a significant improvement in OS and PFS, compared with carboplatin and etoposide alone in 1L ES-SCLC
  - mOS: 12.3 vs. 10.3 months; HR: 0.70 (p = 0.0069); 12-month OS: 51.7% vs. 38.2%
  - mPFS: 5.2 vs. 4.3 months; HR: 0.77 (p = 0.017); 12-month PFS: 12.6% vs. 5.4%
- The safety profile of atezolizumab plus carboplatin and etoposide was as expected with no new findings
  - Rates of hematologic side effects were similar between treatment groups
  - Administration of atezolizumab did not compromise the ability to deliver standard carboplatin plus etoposide
  - The incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy[1–3]
- **These data suggest that atezolizumab plus carboplatin and etoposide is a new standard of care for the first-line treatment of ES-SCLC**

1. Rittmeyer A, et al. *Lancet*, 2017. 2. Cortinovis D, et al. *Ann Oncol*, 2017 (Suppl. 5). 3. Fehrenbacher L, et al. *Lancet*, 2016.

What is next?

Phase	RX	Line of Rx	Trail Name	Stage	Sponsor
Phase 3	CT/RT then nivo/ipi vs no maintenance	1st line	Stimuli	LD	ETOP
Phase 3	CT/RT + atezo Vs CT/RT	1st line		LD	ECOG-ACRIN
Phase 3	EP vs Pembro/EP	1st line	Keynote 604	ED	Merck
	Nivo+/- ipi	maintenance	Checkmate 331	ED	BMS
Phase 3	EP vs EP+Durva+treme	1st line	Caspian	ED	AZ/Medimmune

Squamous Cell NSCLC

Trial	Patients	PFS	OS
KN 407 (Pembro/Carb/Pac or nab-Pac vs Carb/Pac or nab-Pac)	559	6.4 vs 4.8 m HR 0.56 P<0.001	15.9 vs 11.3 HR 0.64 p=0.0008
IMpower 131 (Atezo/Carb/nab-Pac vs Carb/nab-Pac)	684	6.3 vs 5.6 m HR 0.71 p=0.001	14.0 vs 13.9 HR 0.96 p=0.69

- Efficacy independent from PD-L1 status
- Increased AE rates but no increase of immune related AEs
- Differences in trial populations (e.g. PD-L1 status, post progression immunotherapies)

Jotte RM, et al. J Clin Oncol 2018;36(suppl):Abstr LBA9000; Paz-Ares LG, et al. J Clin Oncol 2018;36(suppl):Abstr 105

Non Squamous NSCLC

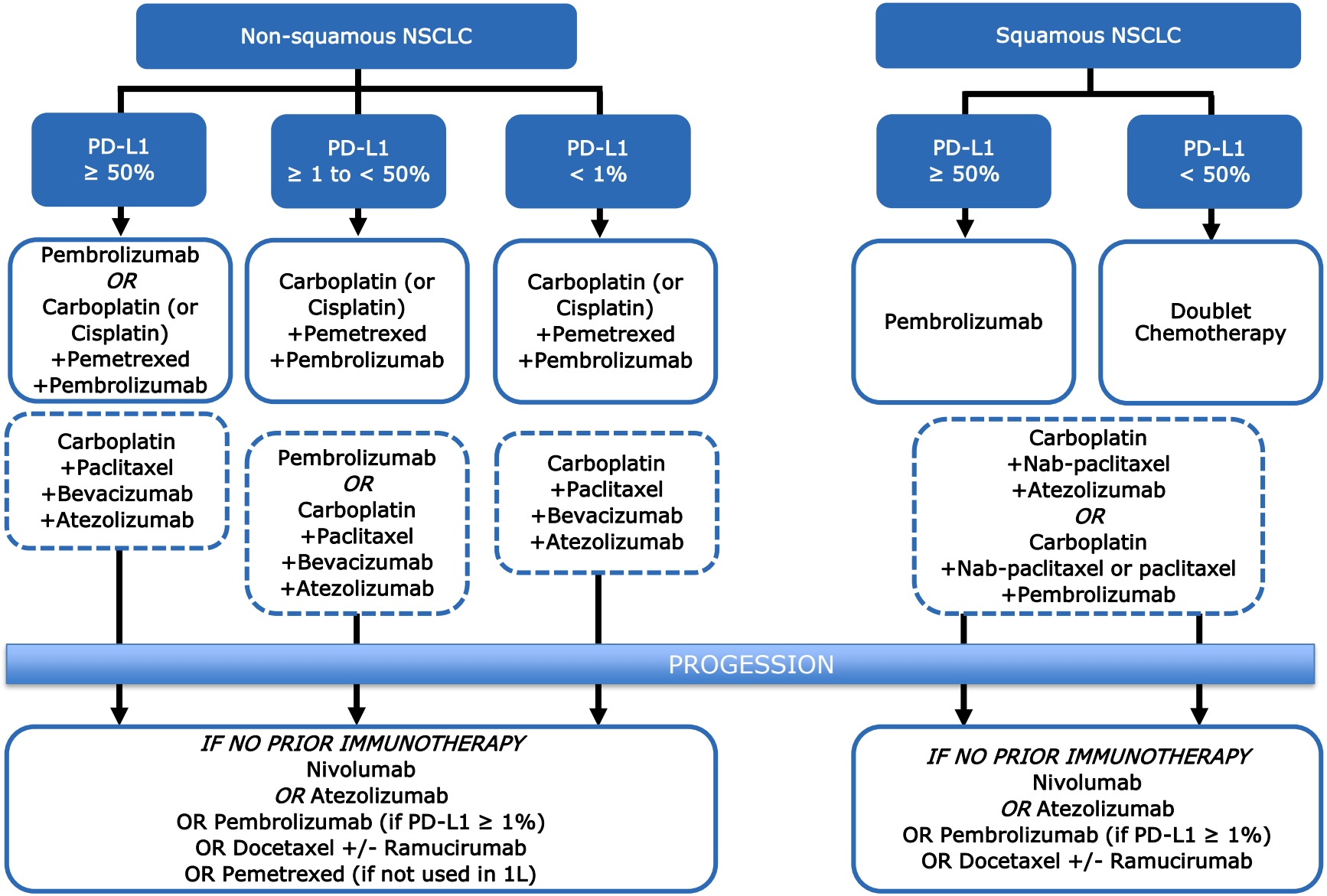
Trial	Patients	PFS	OS
KN 189 (Pembro/Cis or Carb/Pem vs Cis or Carb/Pem)		p<0.00001	p<0.00001
IMpower 150 Atezo/Bev/Carb/Pac vs Bev/Carb/Pac	800	8.3 vs 6.8 m HR 0.59 p<0.0001	19.2 vs 14.7 m HR 0.78 p=0.016

Pemetrexed + Carboplatin + Pembrolizumab received full FDA approval August 2018

- Efficacy independent from PD-L1 status
- Increased AE rates but no increase of immune related AEs

Ghandi L et al, NEJM 2018; Socinski MA, et al. NEJM 2018

Immunotherapy for Advanced NSCLC post-ASCO 2018

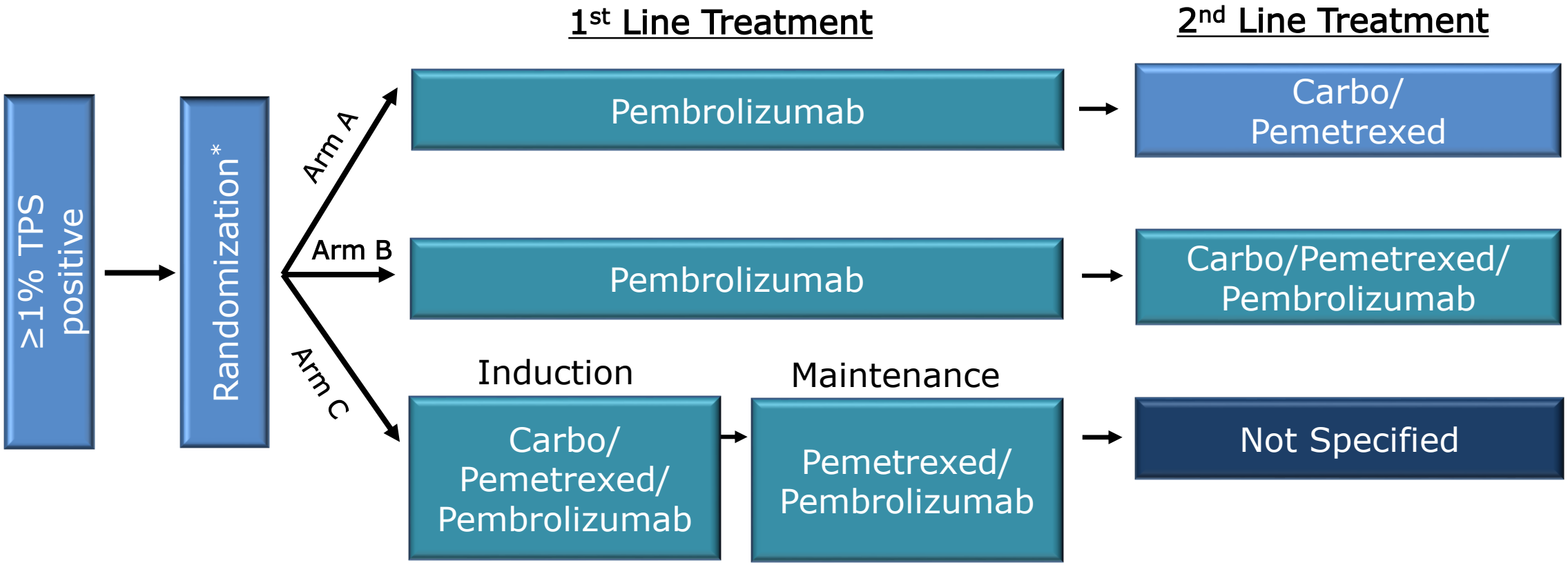


Immune Checkpoint Inhibitors (ICI)

- How long do we give ICI therapy?
- What is the optimal sequence of ICI with chemotherapy?
- Do patients benefit from retreatment with an ICI?
- Are there better predictive markers?
- Are there meaningful differences between ICI?

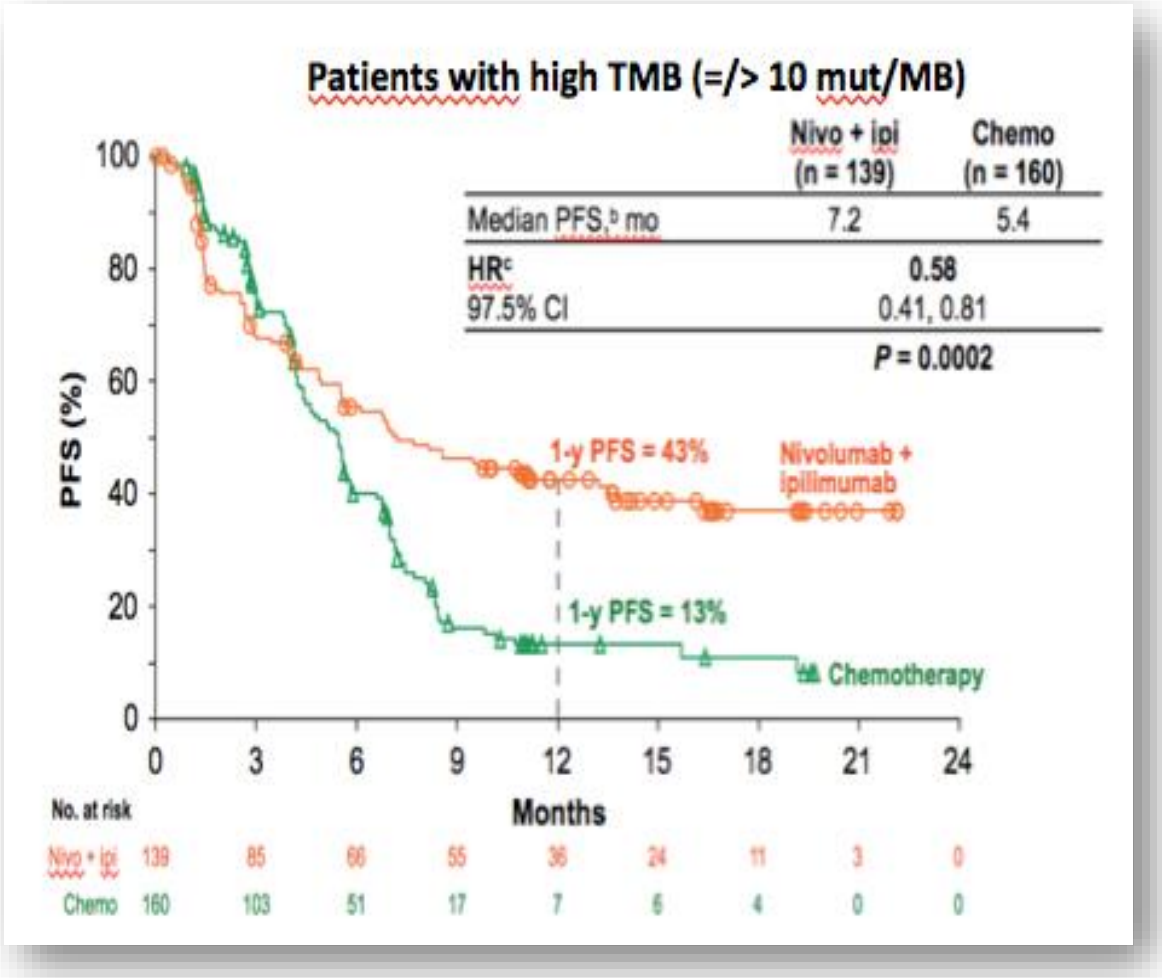
Sequential vs. Combination Therapy: INSIGNA (SWOG/ECOG trial)

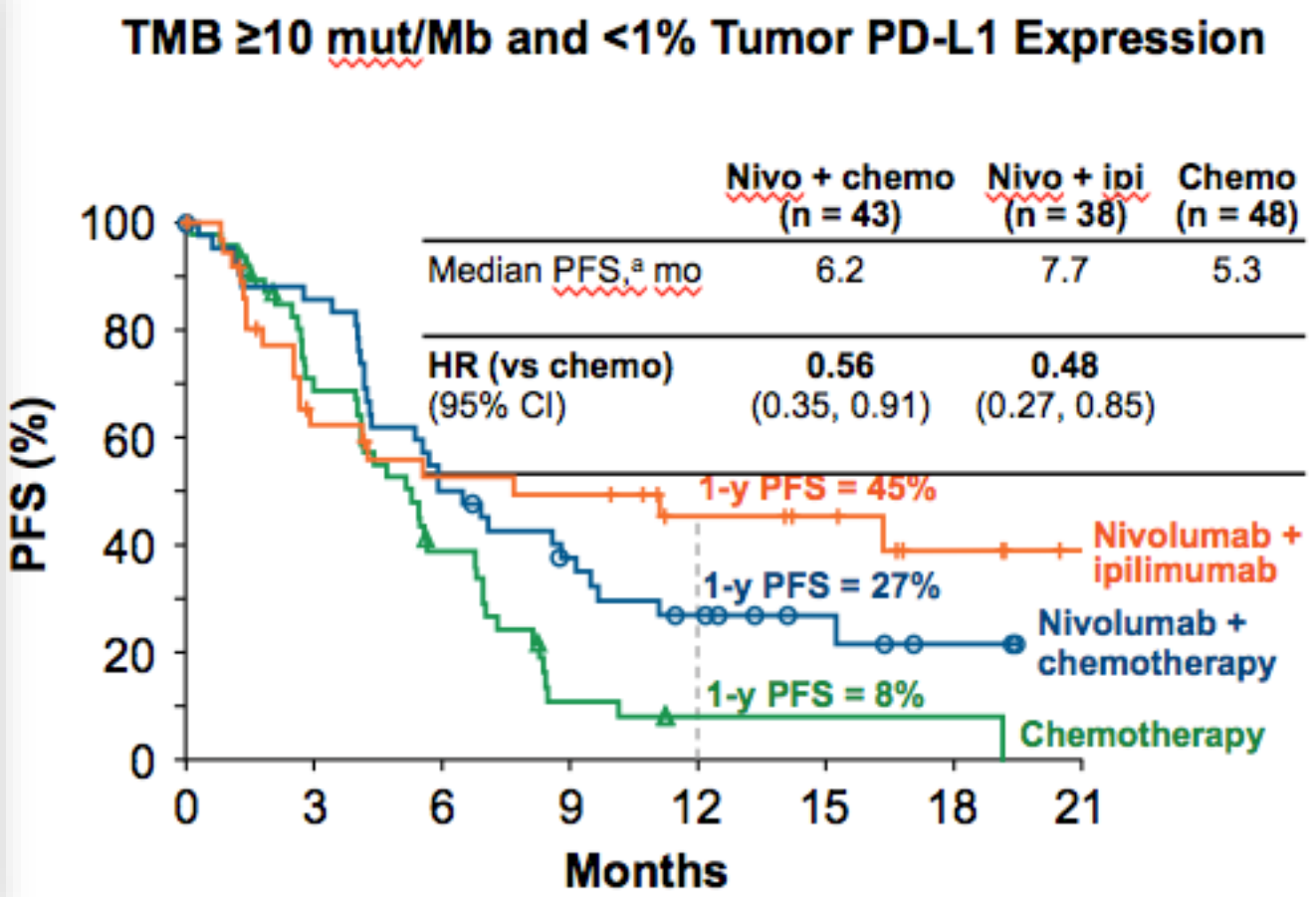
Randomized, Phase III Study of Firstline **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis



SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

CM227 part 1 – PD-L1 < 1%
Combination of PD-L1 and TMB as potential predictive marker

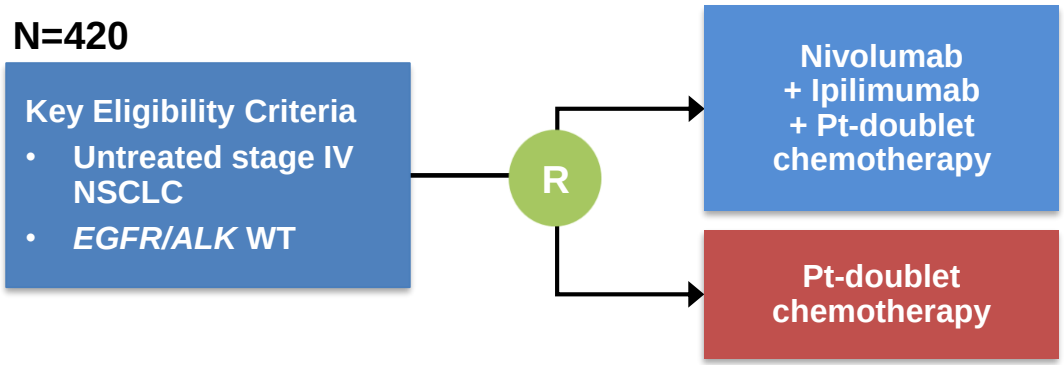




Borghaei H, et al. J Clin Oncol 2018;36(suppl):Abstr 9001

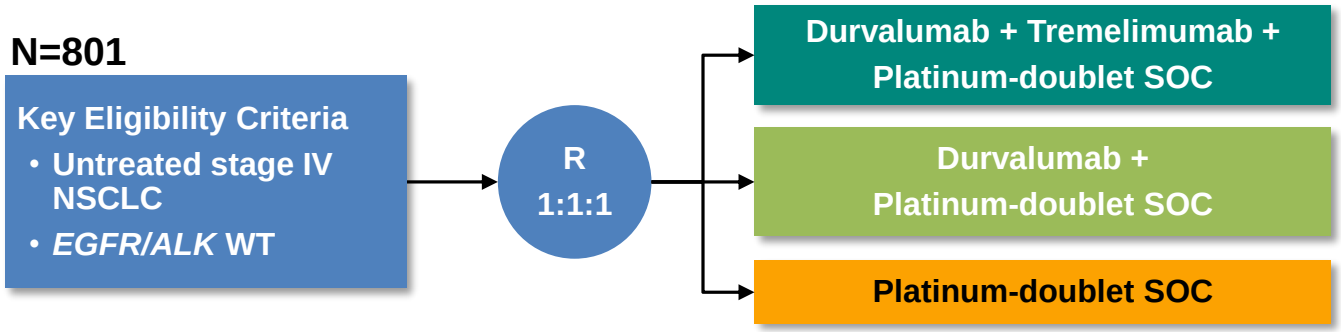
Trials of PD-(L)1 + CTLA-4 + Chemo Combinations in 1L NSCLC

Checkmate 9LA



Primary endpoints: OS

POSEIDON



Primary endpoints: PFS

EGFR-mutated Lung Cancer 2018

Increasing Therapeutic Options in the First-Line Setting

Osimertinib FDA approved for first line therapy April 2018 based on the results from FLAURA

- Superior PFS
- Trend toward improvement in OS
- Mild toxicity profile
- Treat/delay brain metastases

Gefitinib, erlotinib and afatinib FDA approved

EGFR-mutated Lung Cancer 2018

Increasing Therapeutic Options in the First-Line Setting

Trials	Agents	Primary PFS endpoint
ARCHER 1050	Dacomitinib vs Gefitinib	.7-0.74) P<0.0001
NEJ026	Erlotinib + Bevacizumab Vs. Erlotinb	HR 0.61 (0.42-0.88) P=0.016
NEJ009	Gefitinib + Chemotherapy Vs Gefitinib	HR 0.49 (0.39-0.63) P<0.001

FDA approved 9-27-18

Tony S. Mok, MD ASCO 2018, Abstract 9004

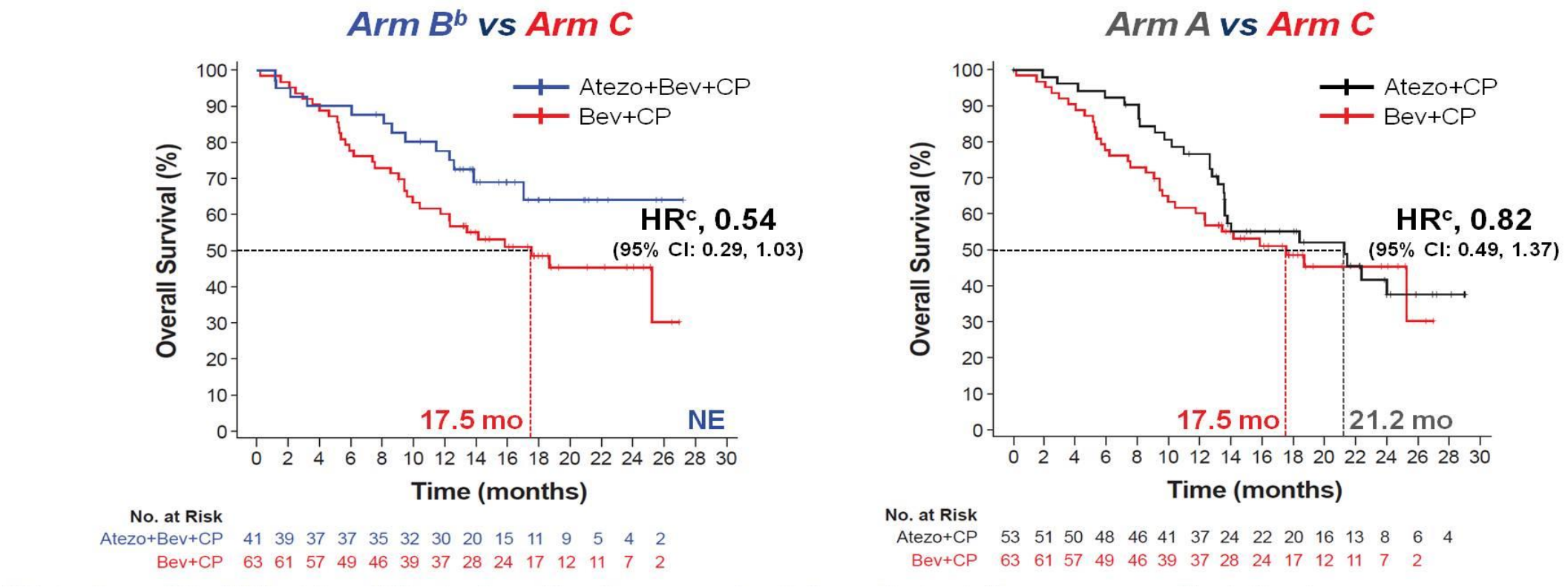
EGFR-mutated Lung Cancer 2018

Increasing Therapeutic Options after EGFR-TKIs

Combination Therapy

IMpower 150

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

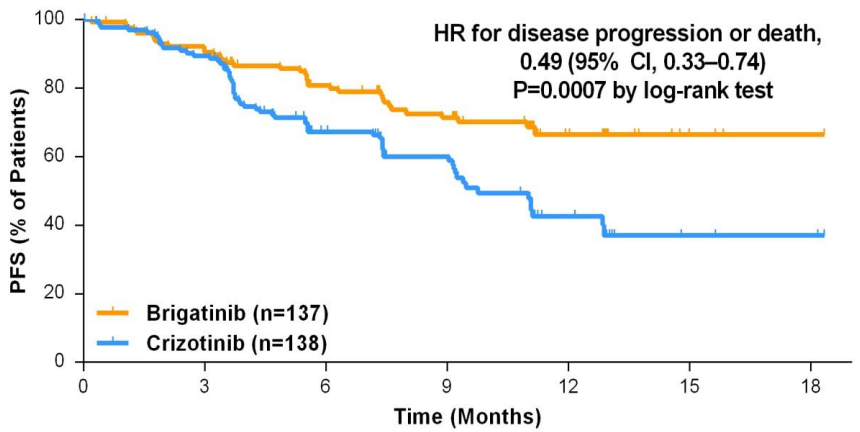


Presented By Mark Socinski at 2018 ASCO Annual Meeting

Therapies for Actionable Mutations 2018

Adenocarcinoma

BRAF V600E+	RET Fusions	ROS1 gene rearrangement	ALK+ gene rearrangement	EGFR+ L858R, del 19	EGFR+ L8612, G719X, S768I	HER2 Neu	MET Exon 14 Mutations
Dabrafenib + Trametinib OR Doublet Chemotherapy OR Chemo-Immunotherapy	Doublet Chemo OR Chemo Immunotherapy	Crizotinib OR Ceritinib	Alectinib OR Crizotinib OR Ceritinib	Erlotinib OR Gefitinib OR Afatinib OR Osimertinib OR Dacomitinib	Afatinib	Doublet Chemo ± Herceptin Chemo-Immunotherapy	Crizotinib OR Doublet Chemo OR Chemo-Immunotherapy
		Entrectinib	Brigatinib				
PROG							
Doublet Chemotherapy OR Chemo-Immunotherapy OR Dabrafenib + Trametinib	Cabozantinib Alectinib Vandetanib	Doublet Chemo OR Chemo-Immunotherapy	Alectinib OR Ceritinib OR Brigatinib	Chemo-Immunotherapy			Crizotinib OR Doublet Chemo OR Chemo-Immunotherapy
	LOX 292 BLU-667	Lorlatinib/ Cabozantinib	Lorlatinib	Carboplatin/ Pemetrexed/ Bevacizumab/ Atezolizumab			



NELSON – trial ISRCTN 63545820

- Randomized Controlled Trial
- Recruitment through population-based registries
- CT screening vs. no screening
- Different screening intervals
- Volume & Volume Doubling Time of nodules
- Central reading of CT images
- Expert causes of death committee &
- Follow up through national registries

Trial, initially powered (80%) for high risk **males**, to detect a lung cancer mortality reduction of ≥ 25% at 10 years after randomization (individual FU)

And includes a small subgroup of women (16%)

de Koning, et al, WCLC 2018, abstr PL02.05

NELSON – trial ISRCTN 63545820

	Year 1	Year 2	Year 4	Year 6.5	Year 10
Screen arm n=7,900	CT screening	CT screening	CT screening	CT screening	
					
	n=7,557 95.6% uptake	n=7,295 92.3% uptake	n=6,922 87.6% uptake	n=5,279 66.8% uptake	
Control arm n=7,892	**Usual care (no screening)**				

NATIONAL LINKAGES
- Statistics Netherlands/ Belgium
- Dutch/ Belgium Cancer Registry
- Centre for Genealogy

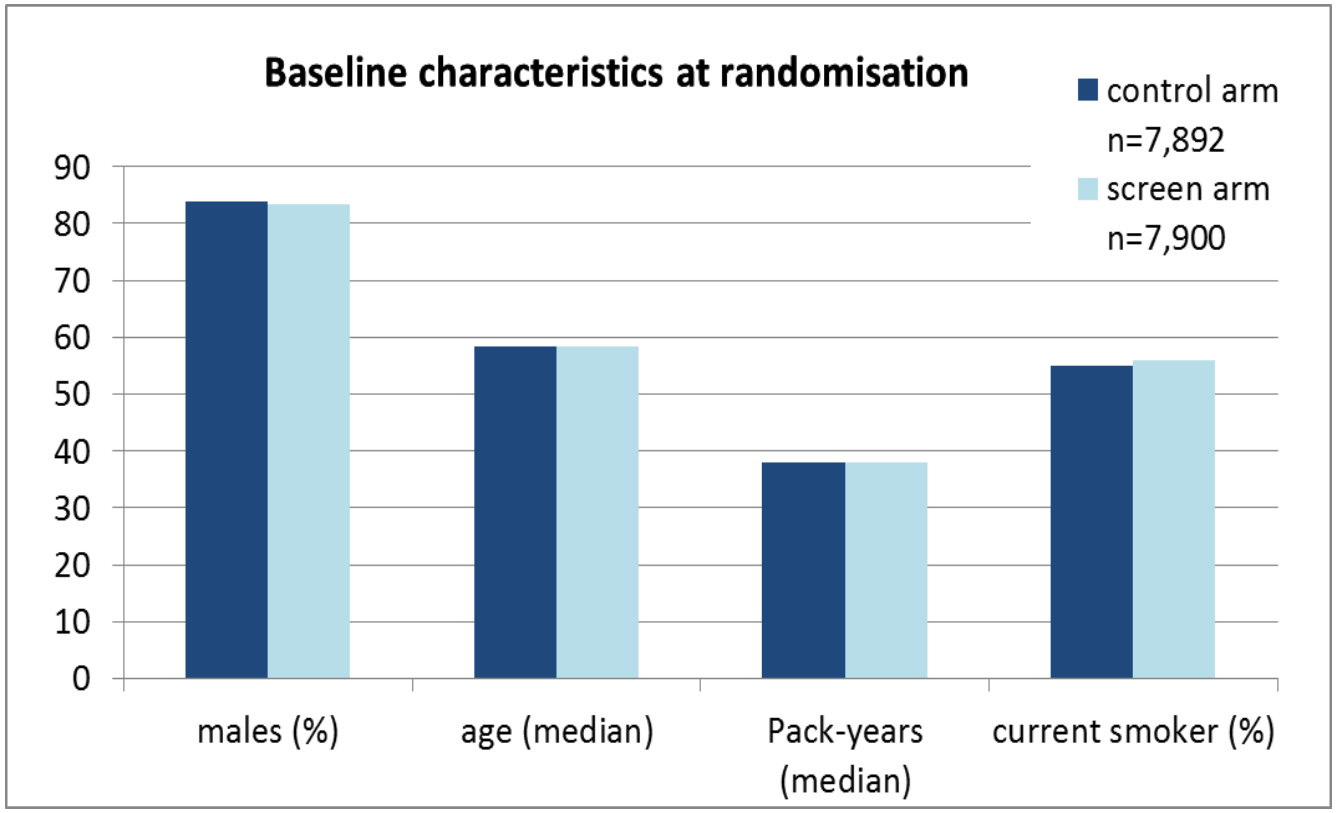
CAUSE OF DEATH REVIEW

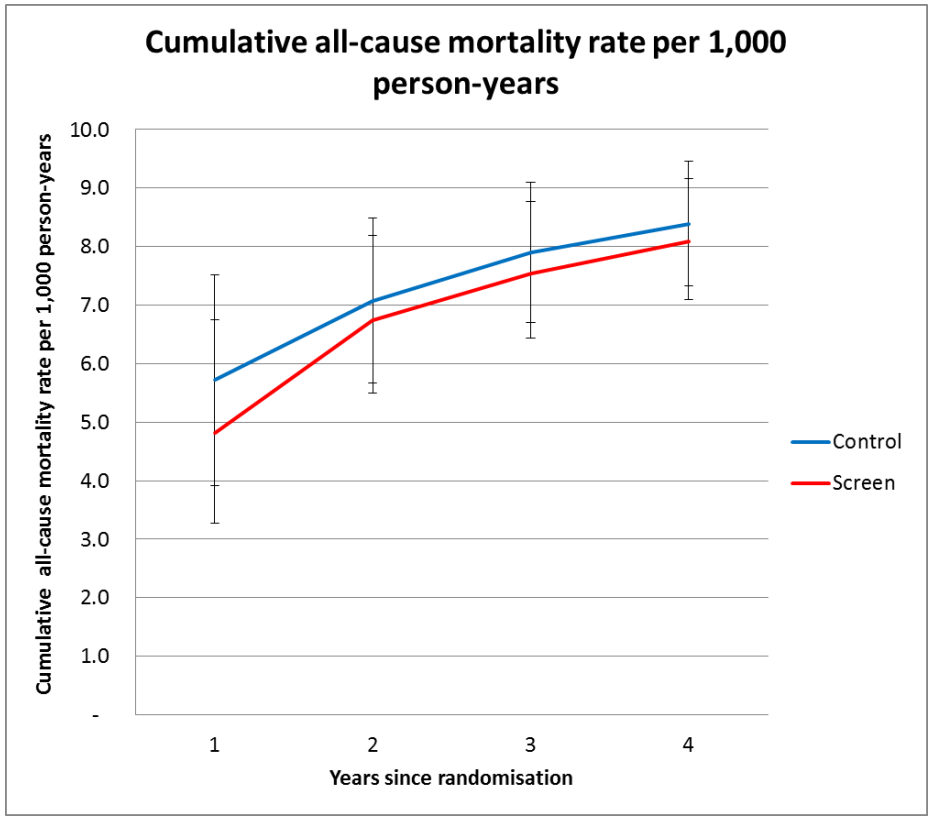
Ever smokers age 50 -70 years
≥15 cig/day for ≥ 25 years or ≥10 cig/day for ≥ 30 years
Smoked within 10 years

Enrollment: 1/28/2004 – 12/18/2006
Follow-up to 12/31/2015

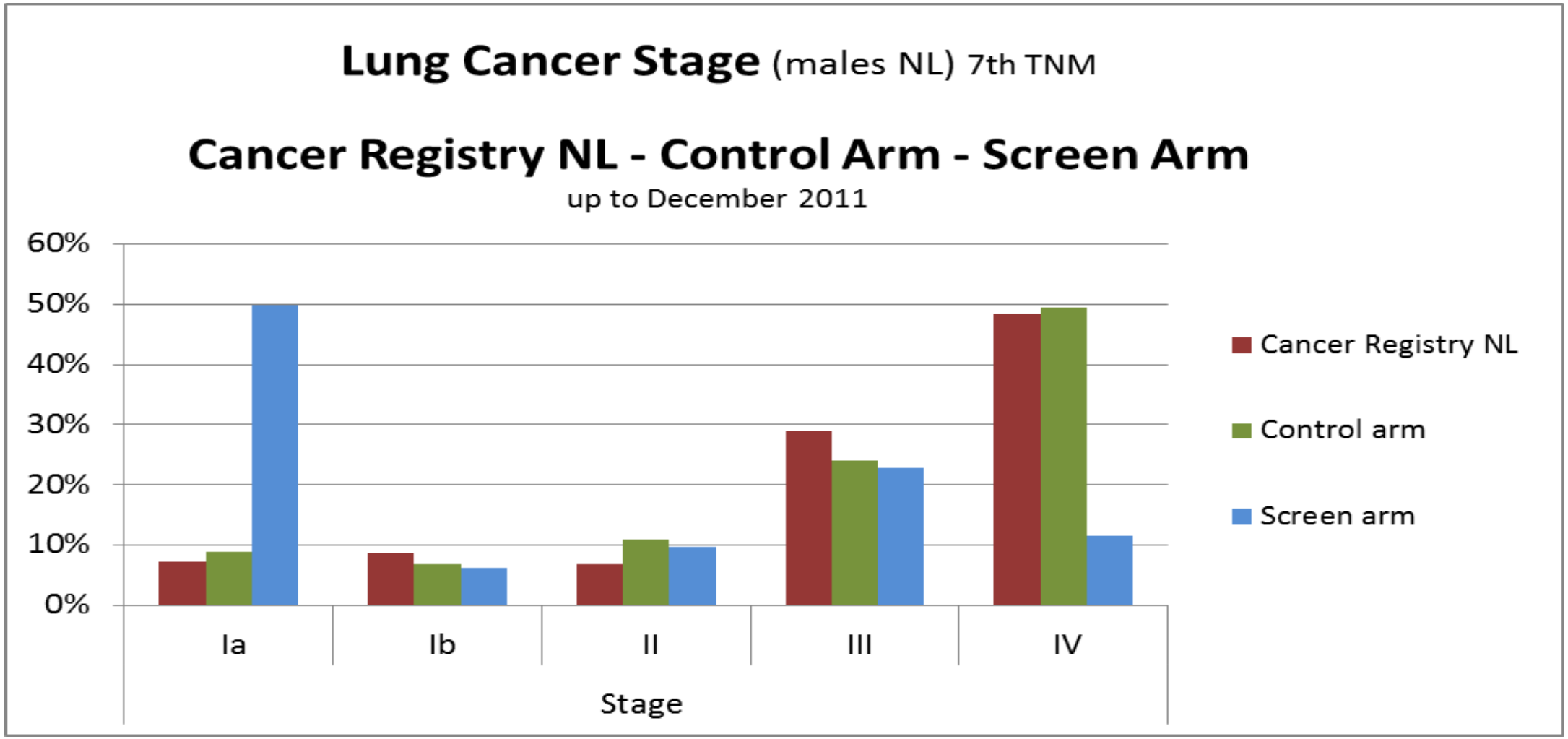
de Koning, et al, WCLC 2018, abstr PL02.05

NELSON - trial ISRCTN 63545820





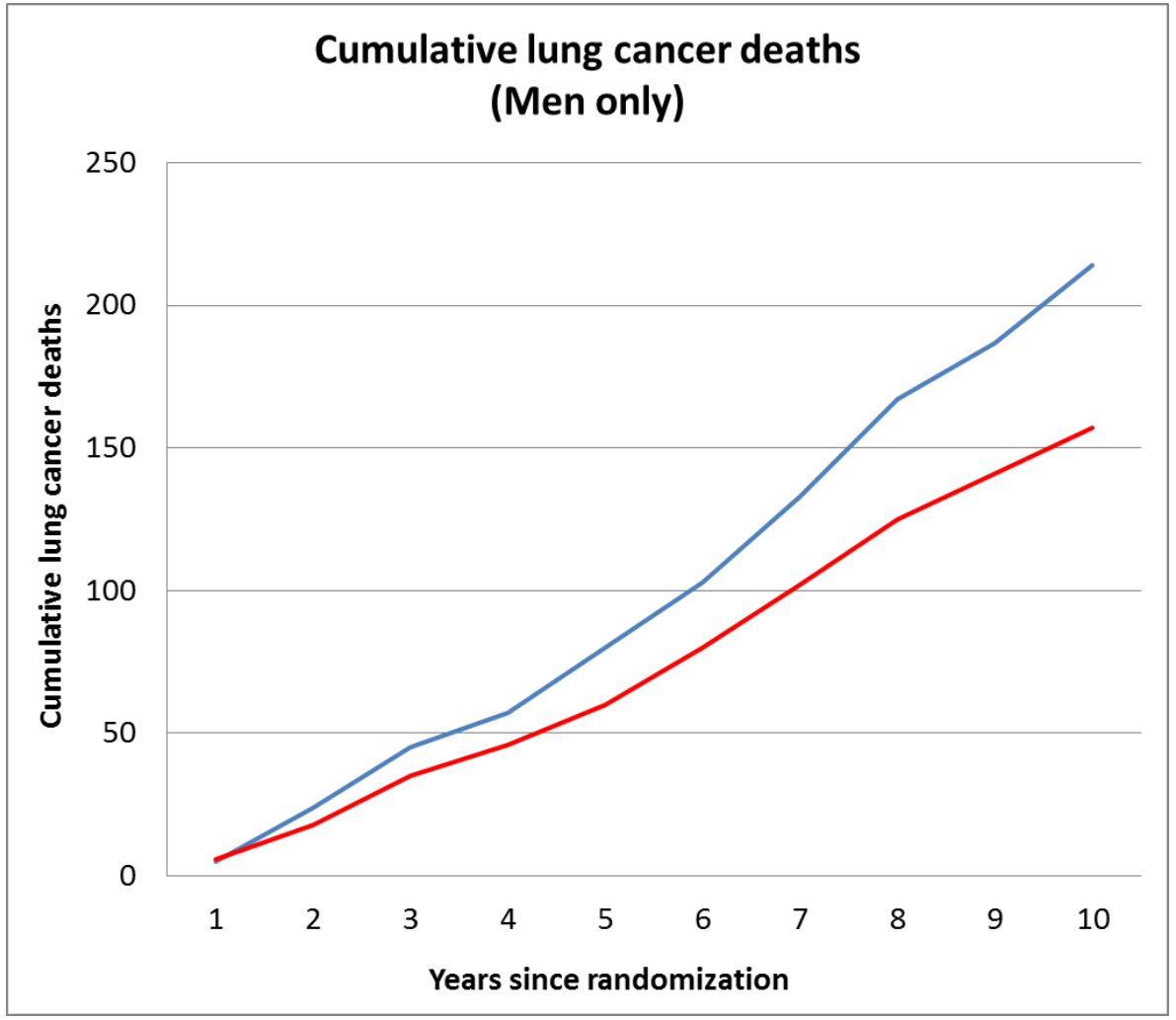
NELSON – trial ISRCTN 63545820



Yousaf-Khan et al., in preparation

de Koning, et al, WCLC 2018, abstr PL02.05

NELSON - trial ISRCTN 63545820



Control Arm:
214 Lung Cancer Deaths

Screen Arm:
157 Lung Cancer Deaths

NELSON - trial ISRCTN 63545820

Lung Cancer Mortality Rate Ratio (95% CI)	Year 8	Year 9	Year 10
MALES	**0.75** P=0.015 (0.59-0.95)	**0.76** P=0.012 (0.60-0.95)	**0.74** P=0.003 (0.60-0.91)
FEMALES	**0.39** P=0.0037 (0.18-0.78)	**0.47** P=0.0069 (0.25-0.84)	**0.61** P=0.0543 (0.35-1.04)

26% mortality reduction with screening in men

39% to 61% mortality reduction in women (only 16% of the study)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

FU 94% complete year 10

Summary

- Chemotherapy + Immune Checkpoint Inhibitor is the Standard of Care for the first line treatment of all patients with advanced lung cancer regardless of histology.
  (The only exception is for patients with actionable mutations who should receive the appropriate TKI).

- Immune checkpoint inhibitors improve survival for patients with unresectable Stage III NSCLC.

- Two randomized trials (NLST and NELSON) confirm the benefits of CT screening in reducing mortality from lung cancer.

Question

Chemotherapy plus an immune checkpoint inhibitor is an appropriate treatment for untreated, advanced stage NSCLC patients except:

1. Adenocarcinoma histology
2. Squamous cell carcinoma
3. Adenocarcinoma with an EGFR mutation
4. Small cell carcinoma
5. Patients with rapidly progressing disease

Question

Chemotherapy plus an immune checkpoint inhibitor is an appropriate treatment for untreated, advanced stage NSCLC patients except:

1. Adenocarcinoma histology
2. Squamous cell carcinoma
3. Adenocarcinoma with an EGFR mutation
4. Small cell carcinoma
5. Patients with rapidly progressing disease

Answer: 3

Rationale: Patients with EGFR mutated tumors should receive an EGFR-TKI