YIR On Demand
Lung

Benjamin Levy, MD
Assistant Professor
Johns Hopkins School of Medicine
Clinical Director
Johns Hopkins Sidney Kimmel
Comprehensive Cancer Center
Baltimore, Maryland
Sibley Memorial Hospital
Washington, DC

Research
To Practice®

Module 1: Mutations and Genomic Alterations in Non-Small Cell Lung Cancer (NSCLC)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

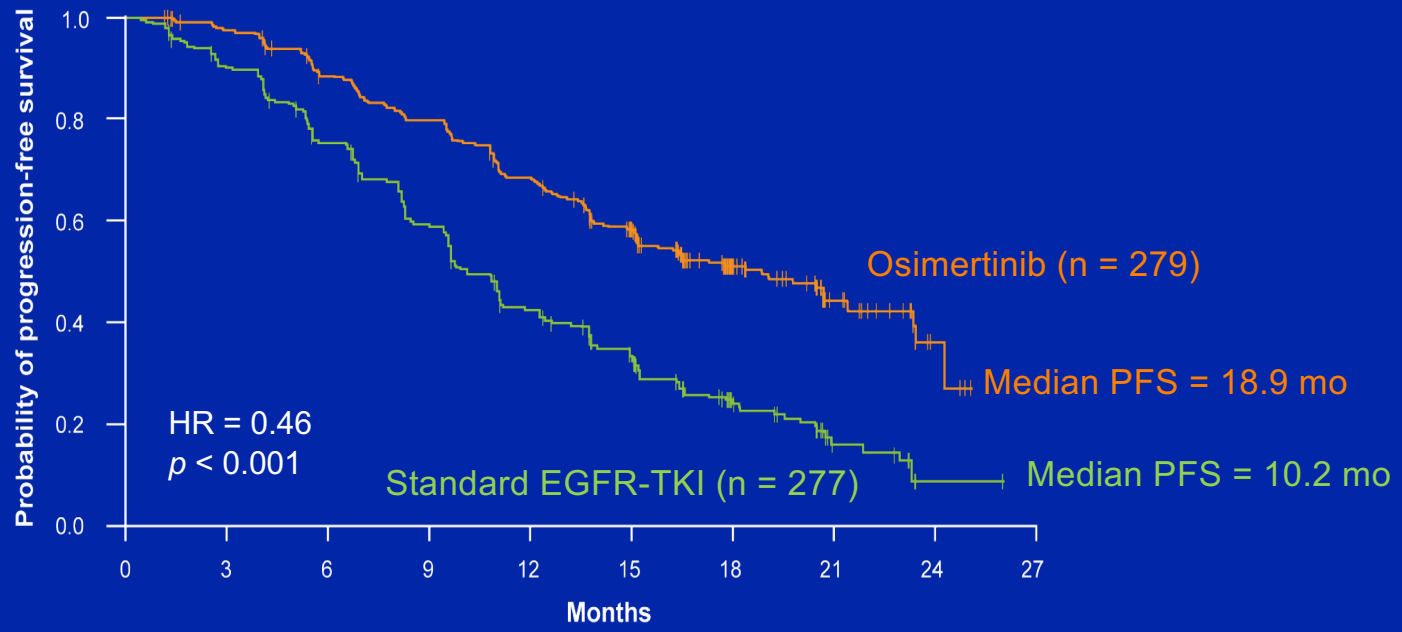
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

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*

N Engl J Med 2018;378(2):113-25.

FLAURA: Osimertinib for Patients with EGFR Mutation-Positive NSCLC

Primary endpoint: PFS for patients with EGFR exon 19 del or L858R mutation



Overall survival data were immature at interim analysis; 18-mo survival rate 83% vs 71% (HR 0.63, *p* = NS)

Soria JC et al. *N Engl J Med* 2018;378(2):113-25.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

Yi-Long Wu, Myung-Ju Ahn, Marina Chiara Garassino, Ji-Youn Han, Nobuyuki Katakami, Hye Ryun Kim, Rachel Hodge, Paramjit Kaur, Andrew P. Brown, Dana Ghiorghiu, Vassiliki A. Papadimitrakopoulou, and Tony S.K. Mok

J Clin Oncol 2018;[Epub ahead of print].

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste

J Clin Oncol 2018;[Epub ahead of print].

CNS Efficacy of Osimertinib in Patients with EGFR Mutation-Positive Advanced NSCLC from the AURA3 and FLAURA Trials

AURA3[1]	Full-analysis set (cFAS)		Evaluable for response (cEFR)	
Clinical variable	Osimertinib (n = 75)	Platinum/pem (n = 41)	Osimertinib (n = 30)	Platinum/pem (n = 16)
CNS ORR	40%	17%	70%	31%
Median CNS DoR	8.9 mo	5.7 mo	8.9 mo	5.7 mo

FLAURA[2]	Full-analysis set		Evaluable for response	
Clinical variable	Osimertinib (n = 61)	EGFR TKIs (n = 67)	Osimertinib (n = 22)	EGFR TKIs (n = 19)
CNS ORR	66%	43%	91%	68%
Median CNS DoR	Not reached	14.4 mo	15.2 mo	18.7 mo

cFAS = measurable/nonmeasurable baseline CNS lesions; cEFR = ≥1 measurable baseline CNS lesion

[1] Wu YL et al. *J Clin Oncol* 2018;[Epub ahead of print]; [2] Reungwetwattana T et al. *J Clin Oncol* 2018;[Epub ahead of print].

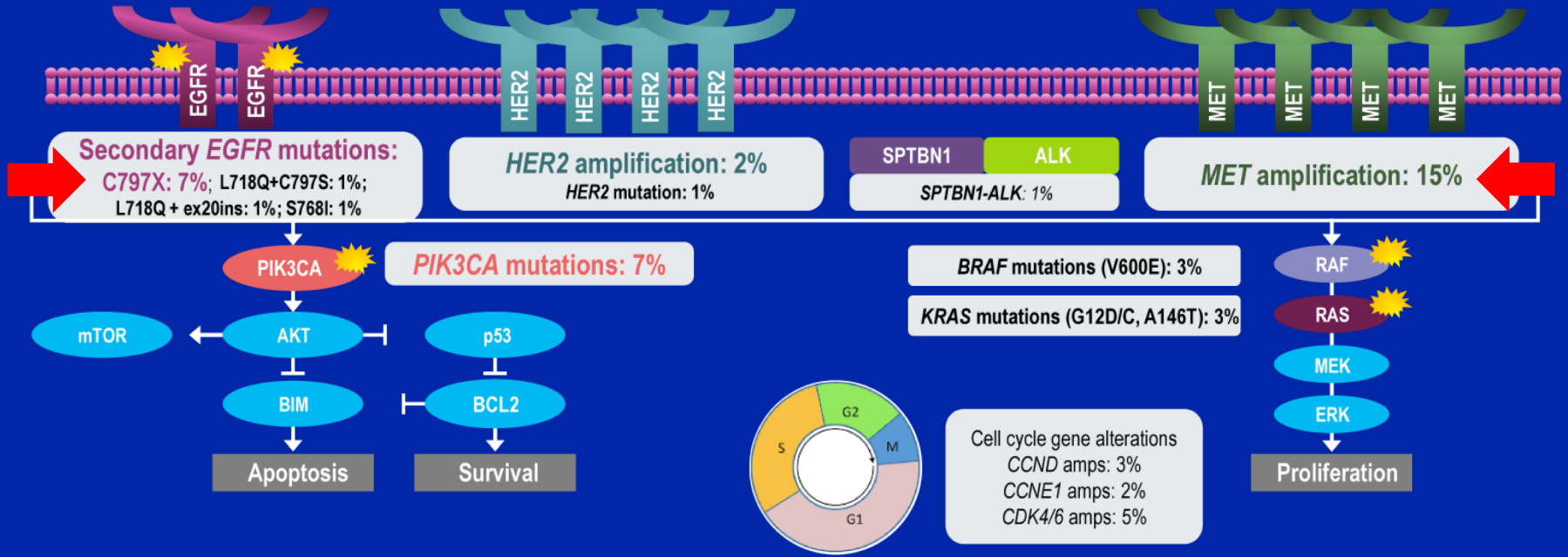
Mechanisms of Acquired Resistance to First-Line Osimertinib: Preliminary Data from the Phase III FLAURA Study

Ramalingam SS et al.

Proc ESMO 2018;Abstract LBA50.

FLAURA: Candidate Acquired Resistance Mechanisms with Osimertinib

- In 91 plasma samples, the most common acquired resistance mechanisms in the comparator EGFR-TKI group were EGFR T790M (47%), MET amplification (4%) and HER2 amplification (2%)
- No osimertinib-treated patients showed evidence of T790M-mediated acquired resistance



Ramalingam SS et al. *Proc ESMO* 2018;Abstract LBA50.

An Open-Label, Multicenter, Phase II Single Arm Trial of Osimertinib in NSCLC Patients with Uncommon EGFR Mutation (KCSG-LU15-09)

Cho JH et al.
Proc WCLC 2018;Abstract OA10.05.

KCSG-LU15-09: Osimertinib for Patients with NSCLC with Uncommon EGFR Mutations

	Osimertinib in patients with uncommon EGFR mutations		
	G719A/C/D/S/X	L861Q	S7681
ORR, n (%)	10/19 (52.6%)	7/9 (77.8%)	3/8 (37.5%)

- Median progression-free survival = 8.2 mo
- Median duration of response = 9.8 mo

Cho JH et al. *Proc WCLC* 2018;Abstract OA10.05.

The NEW ENGLAND JOURNAL of MEDICINE

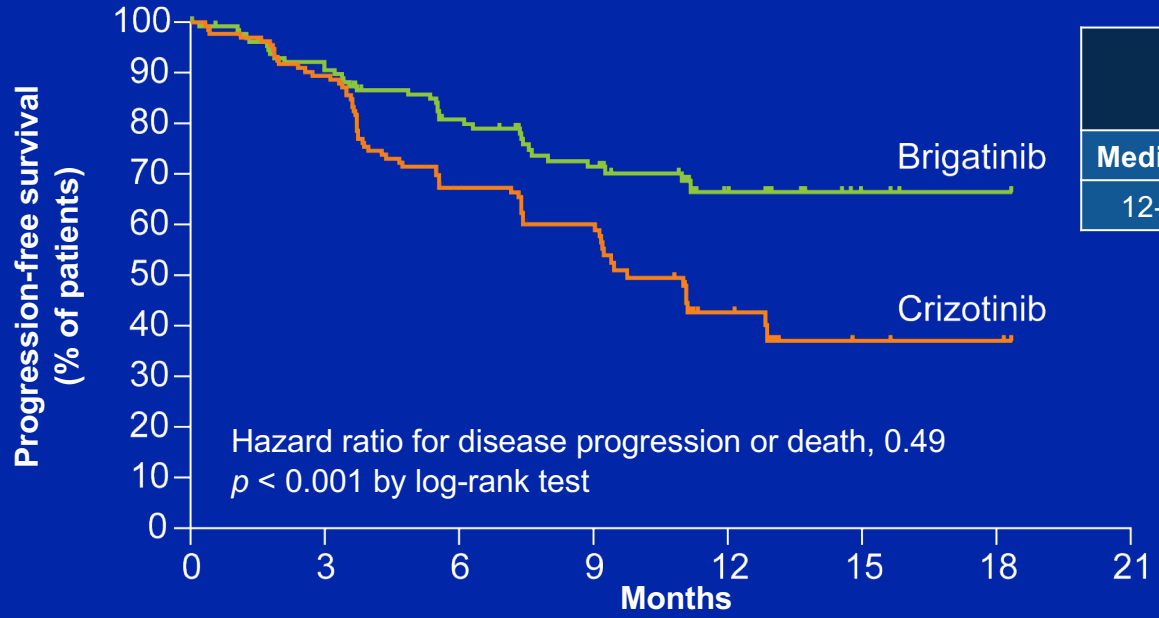
ORIGINAL ARTICLE

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

N Engl J Med 2018;[Epub ahead of print].

ALTA-1L: Progression-Free Survival with Brigatinib versus Crizotinib for ALK-Positive NSCLC

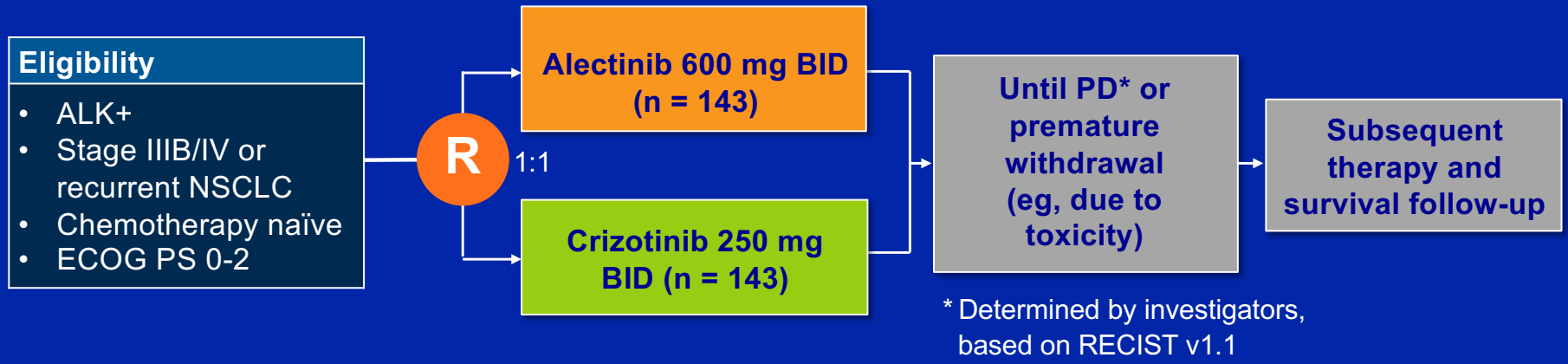


	Brigatinib (N = 137)	Crizotinib (N = 138)
Median PFS, months	**NR**	**9.8**
12-month PFS	67%	43%

- The confirmed objective response rate was 71% with brigatinib and 60% with crizotinib.
- The confirmed rate of intracranial response among patients with measurable lesions was 78% with brigatinib and 29% with crizotinib.
- No new safety concerns were noted.

Camidge DR et al. *N Engl J Med* 2018;[Epub ahead of print].

ALEX Phase III Trial Design



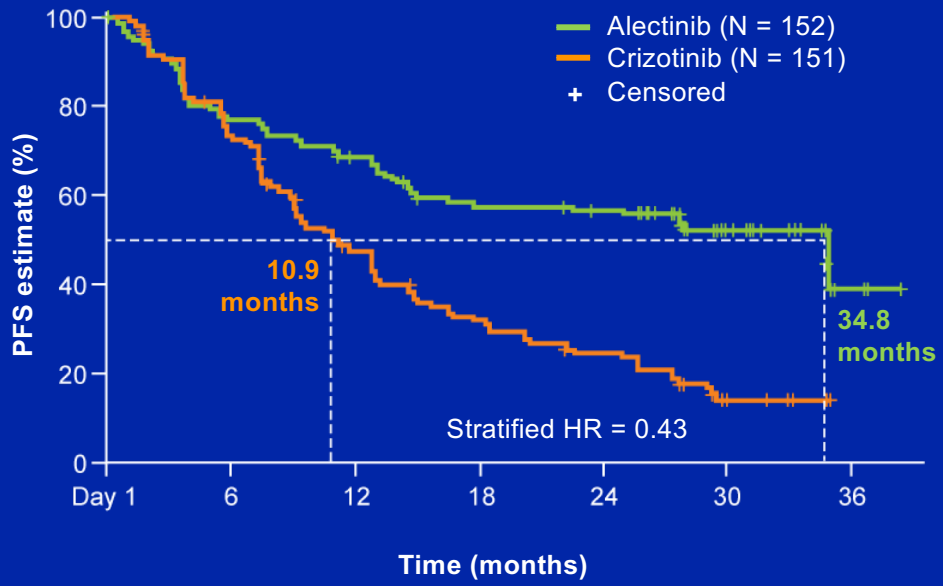
In comparison to crizotinib, alectinib improved both PFS (HR = 0.47, $p < 0.001$) and OS (HR = 0.76, $p = 0.24$)

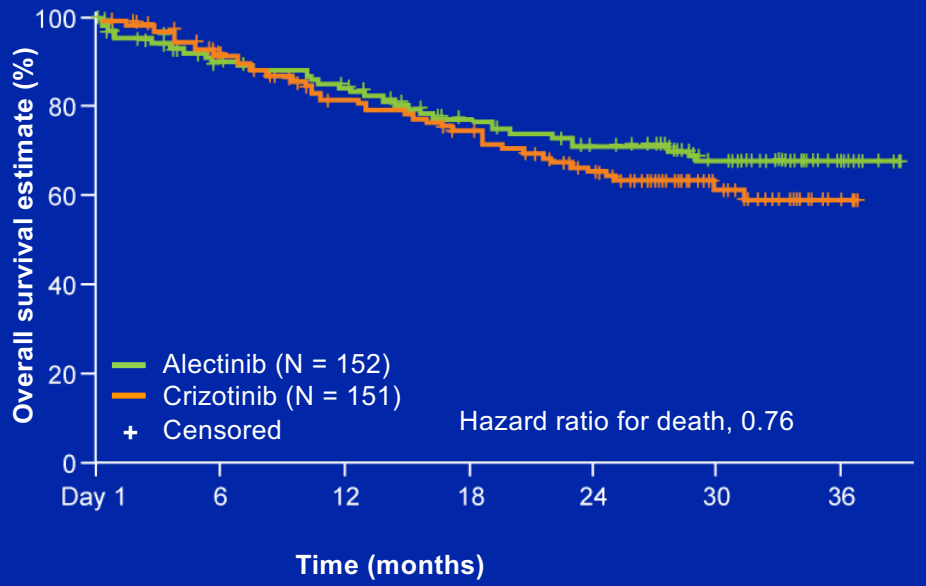
Peters S et al. *N Engl J Med* 2017;377:829-38.

Updated Efficacy and Safety Data from the Global Phase III ALEX Study of Alectinib (ALC) vs Crizotinib (CZ) in Untreated Advanced ALK+ NSCLC

Camidge DR et al.
Proc ASCO 2018;Abstract 9043.

ALEX: Updated PFS and OS Outcomes in the ITT Population





Camidge DR et al. *Proc ASCO* 2018;Abstract 9043.

FDA Approves Lorlatinib for Second- or Third-Line Treatment of Metastatic NSCLC with ALK Rearrangement

Press Release – November 2, 2018

"On November 2, 2018, the Food and Drug Administration granted accelerated approval to lorlatinib for patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

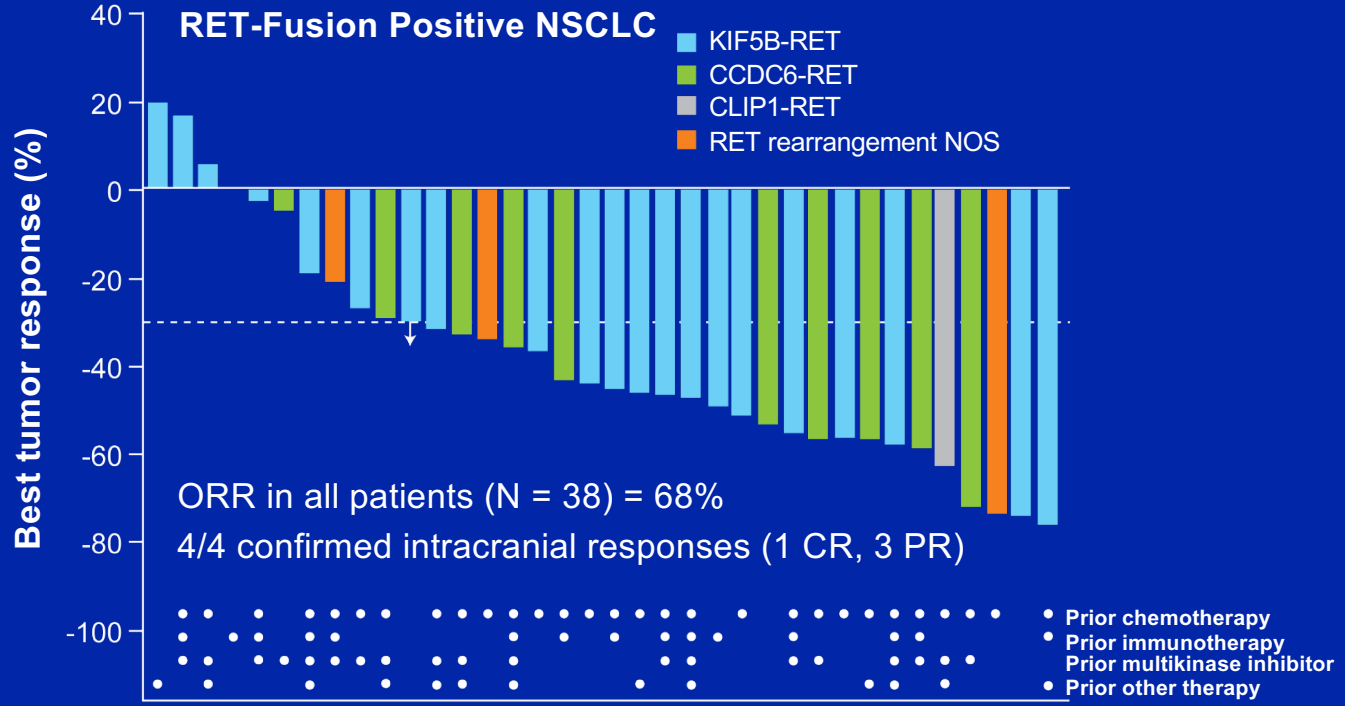
Approval was based on a subgroup of 215 patients with ALK-positive metastatic NSCLC, previously treated with one or more ALK kinase inhibitors, enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter study (Study B7461001; NCT01970865). The major efficacy measures were overall response rate (ORR) and intracranial ORR, according to RECIST 1.1, as assessed by an independent central review committee."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm625027.htm

Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with RET Fusion+ Non-Small Cell Lung Cancer

Oxnard GR et al.
Proc WCLC 2018;Abstract OA12.07.

LIBRETTO-001: Phase I Results with LOXO-292 in RET Fusion- Positive NSCLC



- Dose exploration ongoing at 200 mg BID; most treatment-emergent AEs were Grade 1
- 4 patients experienced treatment-related AEs Grade ≥3: Diarrhea, increased ALT/AST, tumor lysis syndrome (DLT @ 240 mg BID), thrombocytopenia (DLT @ 240 mg BID)

Oxnard GR et al. *Proc WCLC* 2018;Abstract OA12.07.

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

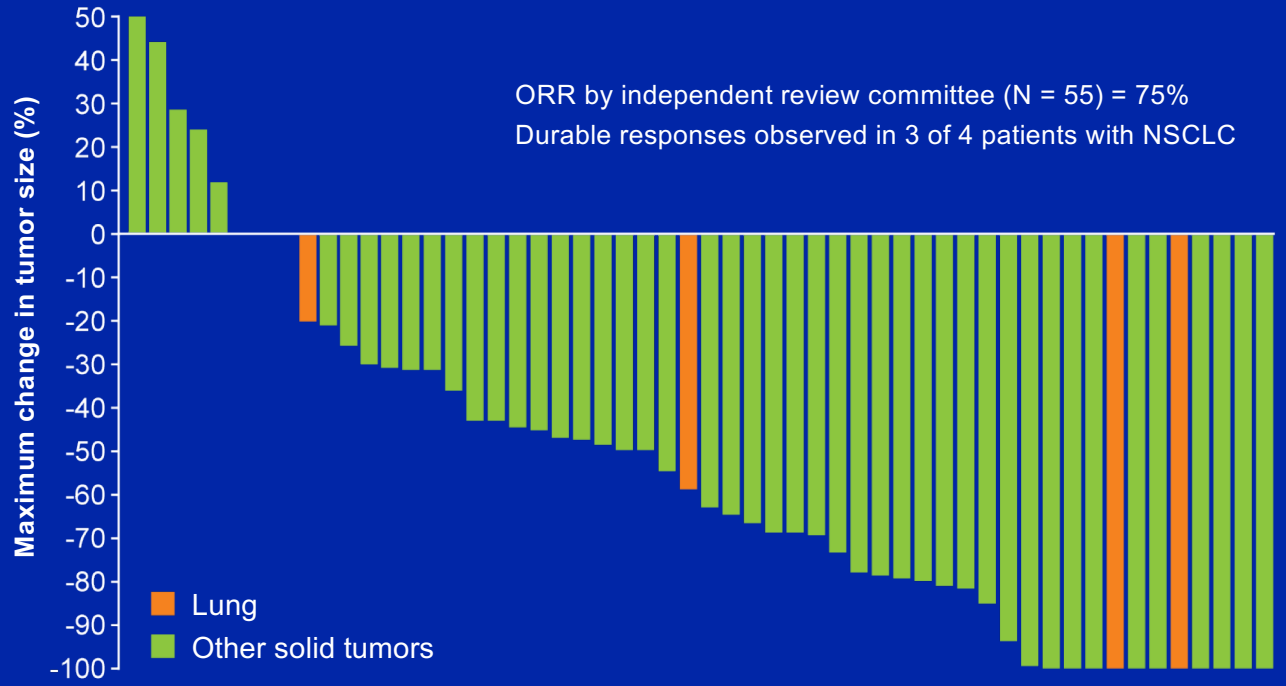
Alexander Drilon, M.D., Theodore W. Laetsch, M.D., Shivaani Kummar, M.D., Steven G. DuBois, M.D., Ulrik N. Lassen, M.D., Ph.D., George D. Demetri, M.D., Michael Nathenson, M.D., Robert C. Doebele, M.D., Ph.D., Anna F. Farago, M.D., Ph.D., Alberto S. Pappo, M.D., Brian Turpin, D.O., Afshin Dowlati, M.D., et al.

N Engl J Med 2018;378(8):731-39.

Rapid, Robust and Durable Responses to Larotrectinib in Patients with TRK Fusion Non-Small Cell Lung Cancer

Farago AF et al.
Proc WCLC 2018;Abstract P1.13.40.

Combined Analysis of 3 Clinical Trials of Larotrectinib in TRK Fusion-Positive Solid Tumors



- Larotrectinib was well tolerated in patients with NSCLC
  - Primarily Grade 1 AEs reported, except for one Grade 2 adverse event (decreased neutrophil count)
- No progressive CNS events observed in patients with previously treated NSCLC harboring NTRK gene fusions

Farago AF et al. *Proc WCLC* 2018;Abstract P1.13.40.

FDA Approves Larotrectinib for Solid Tumors with NTRK Gene Fusions

Press Release – November 26, 2018

"On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

This is the second tissue-agnostic FDA approval for the treatment of cancer.

Approval was based on data from three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626720.htm

Module 2: Immunotherapeutic Approaches in NSCLC

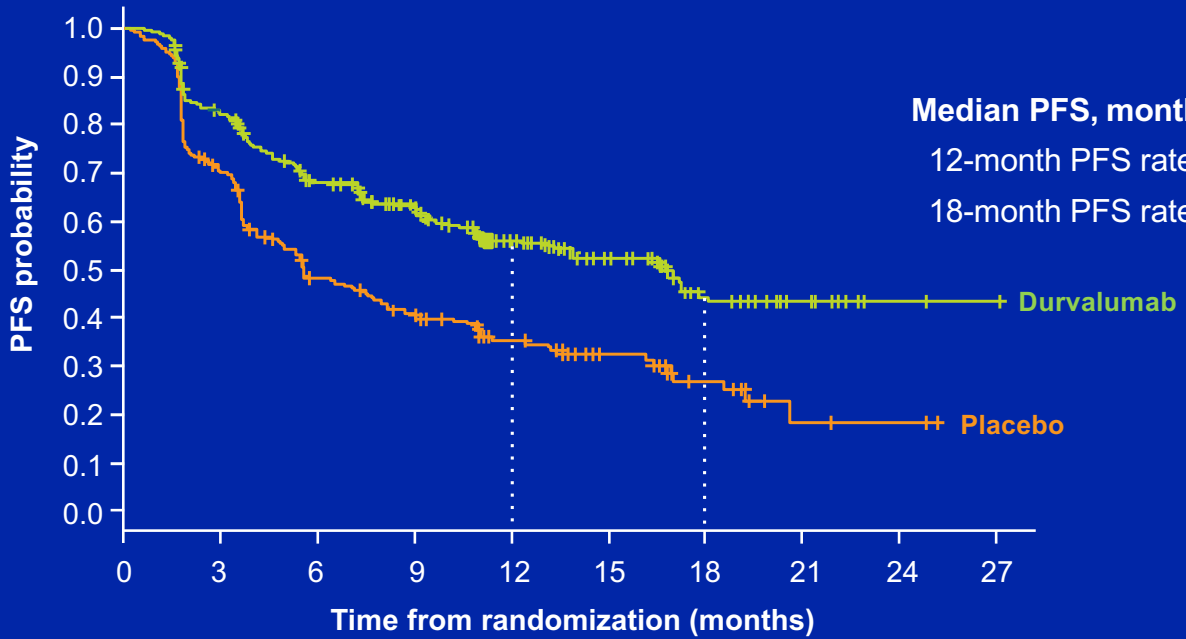
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, 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. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

PACIFIC: PFS by Blinded Independent Central Review in the Intent-to-Treat Population (Primary Endpoint)



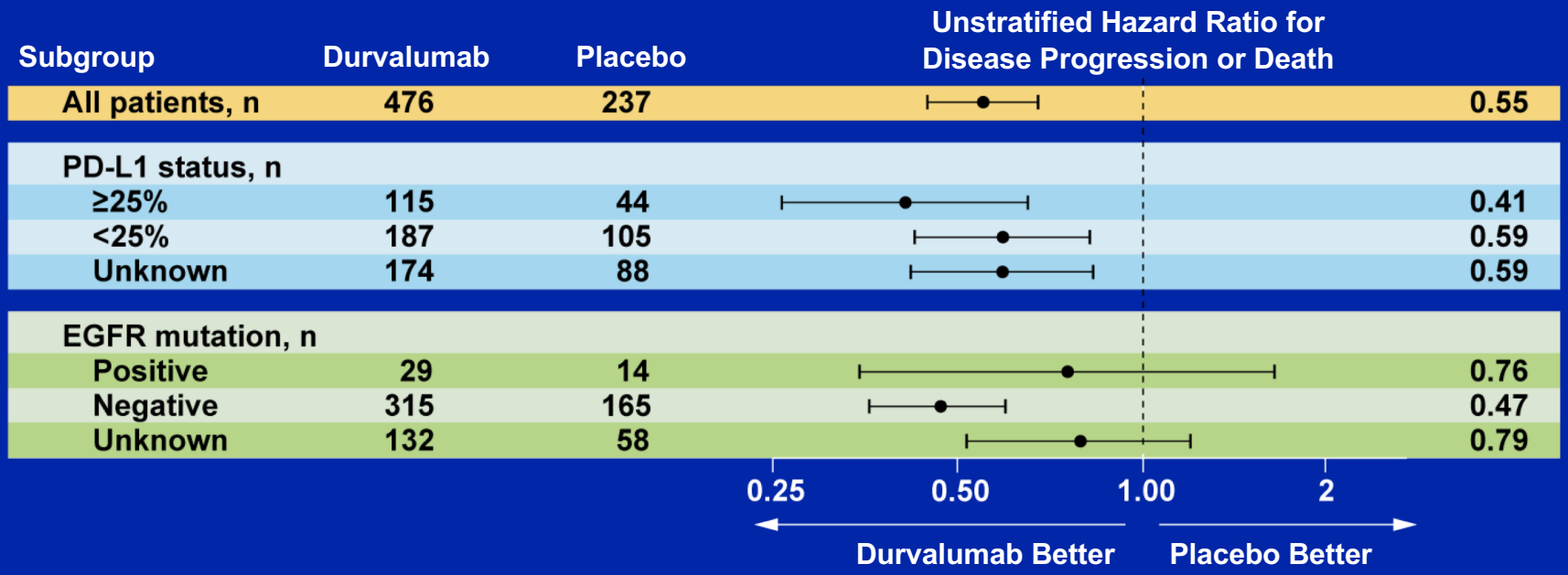
	Durvalumab (N = 476)	Placebo (N = 237)
Median PFS, months	**16.8**	**5.6**
12-month PFS rate	55.9%	35.3%
18-month PFS rate	44.2%	27.0%

Stratified hazard ratio, 0.52
Two-sided $p < 0.001$

- No new safety signals were observed, and the most common Grade 3 or 4 adverse event associated with durvalumab compared to placebo was pneumonia (4.4% and 3.8%, respectively).
- OS data were immature at the time of this analysis.

Antonia SJ et al. *N Engl J Med* 2017;377(20):1919-29.

PACIFIC: PFS by PD-L1 Expression and EGFR Mutation Status



- No significant between-group differences ($p < 0.05$) were noted in either PD-L1 expression or EGFR mutation status

Antonia SJ et al. *N Engl J Med* 2017;377(20):1919-29.

The NEW ENGLAND JOURNAL of MEDICINE

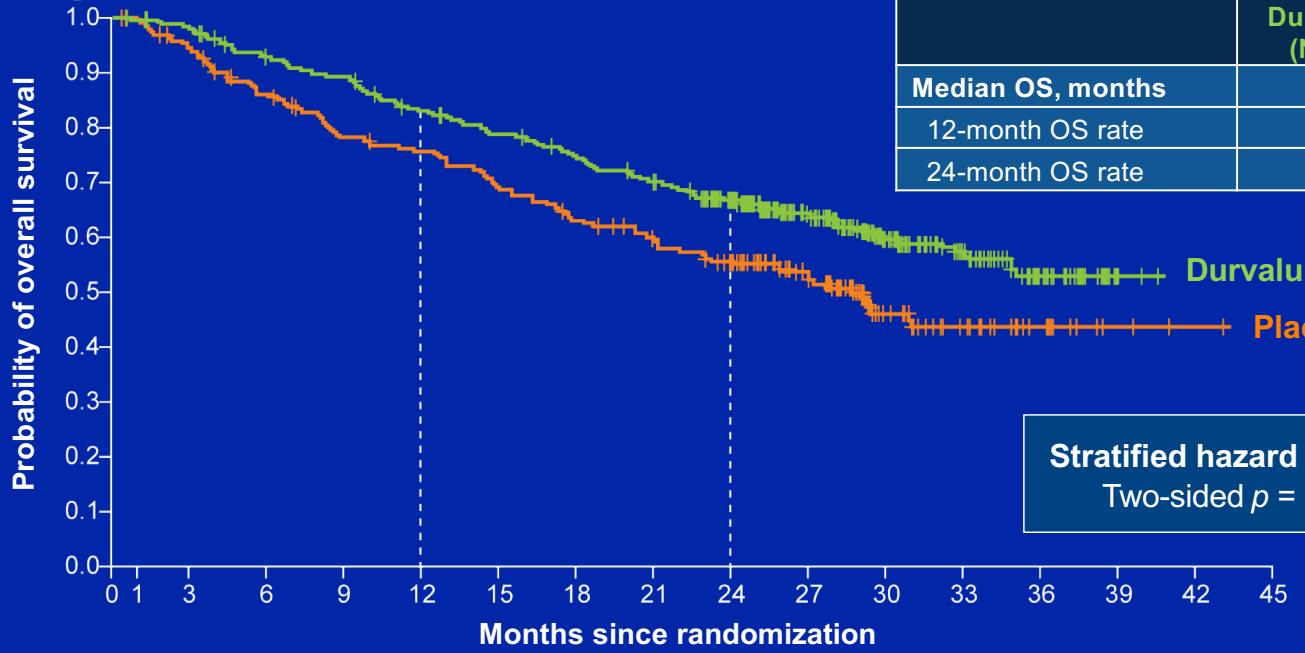
ORIGINAL ARTICLE

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*

N Engl J Med 2018;[Epub ahead of print].

PACIFIC: Overall Survival in the Intention-to-Treat Population



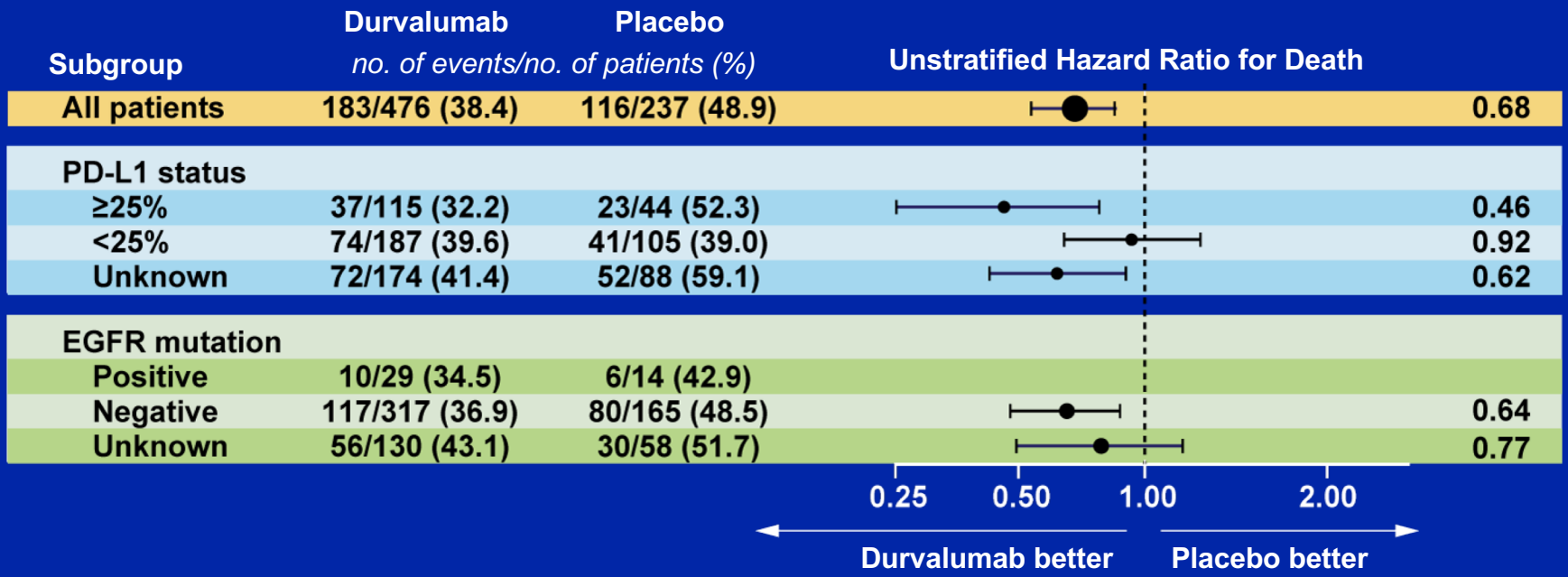
	Durvalumab (N = 476)	Placebo (N = 237)
Median OS, months	**NR**	**28.7**
12-month OS rate	83.1%	75.3%
24-month OS rate	66.3%	55.6%

Stratified hazard ratio, 0.68
Two-sided $p = 0.0025$

- A total of 30.5% of the patients in the durvalumab group and 26.1% of those in the placebo group had Grade 3 or 4 adverse events of any cause.
- 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen due to adverse events.

Antonia SJ et al. *N Engl J Med* 2018;[Epub ahead of print].

PACIFIC: OS by PD-L1 Expression and EGFR Mutation Status



Antonia SJ et al. *N Engl J Med* 2018;[Epub ahead of print].

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

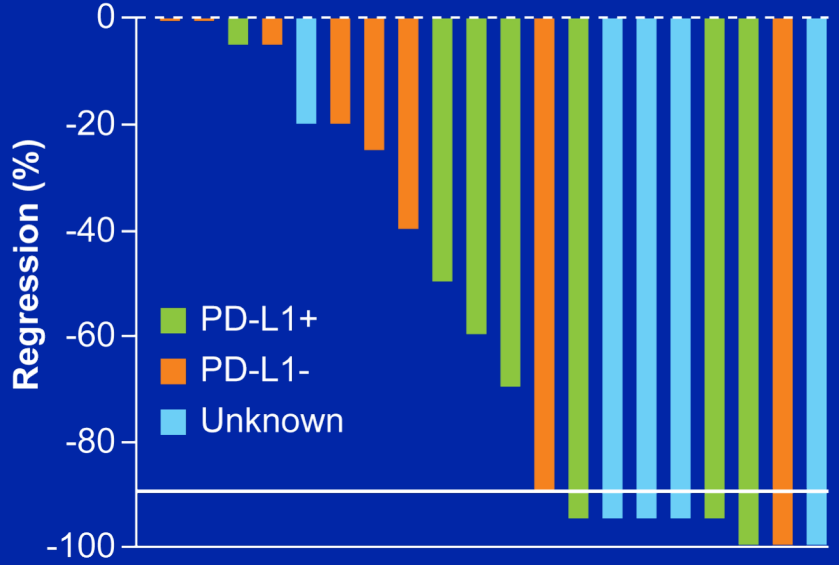
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

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

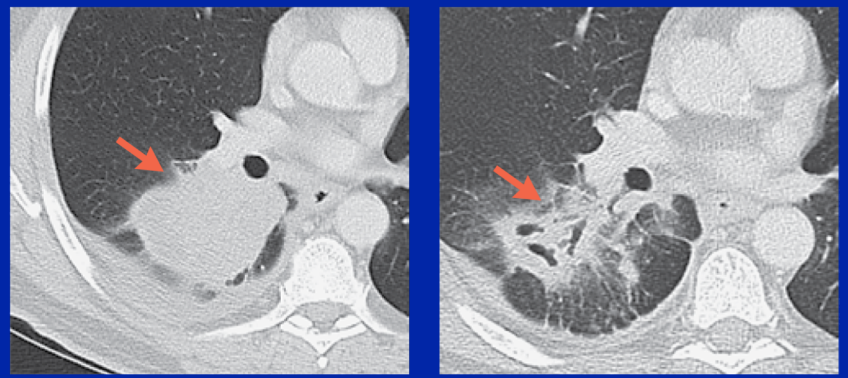
N Engl J Med 2018;378(21):1976-86.

Pilot Study of Neoadjuvant Nivolumab in Resectable NSCLC

- 2 preoperative doses of nivolumab administered every 2 weeks in patients with untreated, surgically resectable early (Stage I, II, or IIIA) NSCLC, with surgery planned ~4 weeks after first dose



Patient 1: Smoker, Stage IIB squamous lung cancer



Pretreatment imaging
8-cm primary tumor

Week 4 (before surgery)
35% shrinkage with tumor cavitation

- Treatment-related AEs of any grade occurred in 5/22 (23%) patients; only 1 event was Grade ≥3

Forde PM et al. *N Engl J Med* 2018;378(21):1976-86.

Pembrolizumab (Pembro) versus Platinum-Based Chemotherapy (Chemo) as First-Line Therapy for Advanced/Metastatic NSCLC with a PD-L1 Tumor Proportion Score (TPS) ≥1%: Open-Label, Phase 3 KEYNOTE-042 Study

Lopes G et al.

Proc ASCO 2018;Abstract LBA4.

KEYNOTE-042: Phase III Results of First-Line Pembrolizumab in Advanced/Metastatic NSCLC (TPS ≥1%)

Primary analysis: Median OS in PD-L1 TPS ≥50%, ≥20% and ≥1%			
Patient subgroup	**Pembrolizumab**	**Chemotherapy***	**HR (*p*-value)**
TPS ≥50% (n = 299; 300)	20.0 mo	12.2 mo	0.69 (0.0003)
TPS ≥20% (n = 413; 405)	17.7 mo	13.0 mo	0.77 (0.0020)
TPS ≥1% (n = 637; 637)	16.7 mo	12.1 mo	0.81 (0.0018)
TPS ≥1%-49% (n = 338; 337)[a]	13.4 mo	12.1 mo	0.92 (—)

* Carboplatin/paclitaxel or carboplatin/pemetrexed up to 6 cycles; [a] Exploratory analysis

- Duration of response was longer in patients who received pembrolizumab than in those who received chemotherapy, at all PD-L1 levels examined.
- At the time of this analysis, no significant PFS benefit was observed with pembrolizumab compared to chemotherapy.

Lopes G et al. *Proc ASCO* 2018;Abstract LBA4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

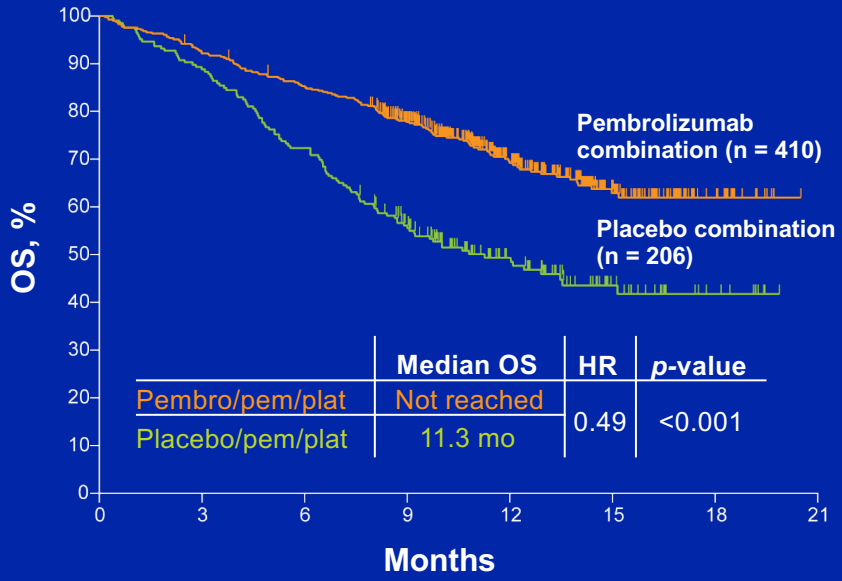
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

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*

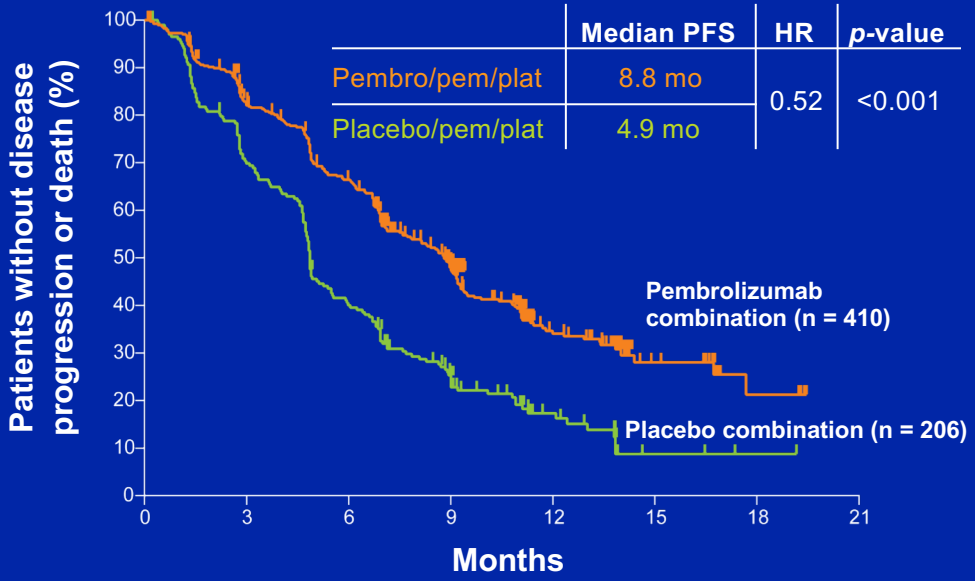
N Engl J Med 2018;378(22):2078-92.

KEYNOTE-189: OS and PFS Results (Primary Endpoint Analyses)

Overall Survival, ITT



Progression-Free Survival, ITT



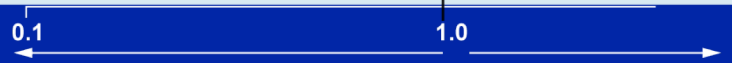
- Response rate (pembro combination vs placebo combination): 47.6% vs 18.9% ($p < 0.001$)

Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

KEYNOTE-189: OS and PFS Results by PD-L1 Expression

Overall Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death
Overall	235/616	0.49
PD-L1 tumor proportion score		
<1%	84/190	0.59
≥1%	135/388	0.47
1-49%	65/186	0.55
≥50%	70/202	0.42

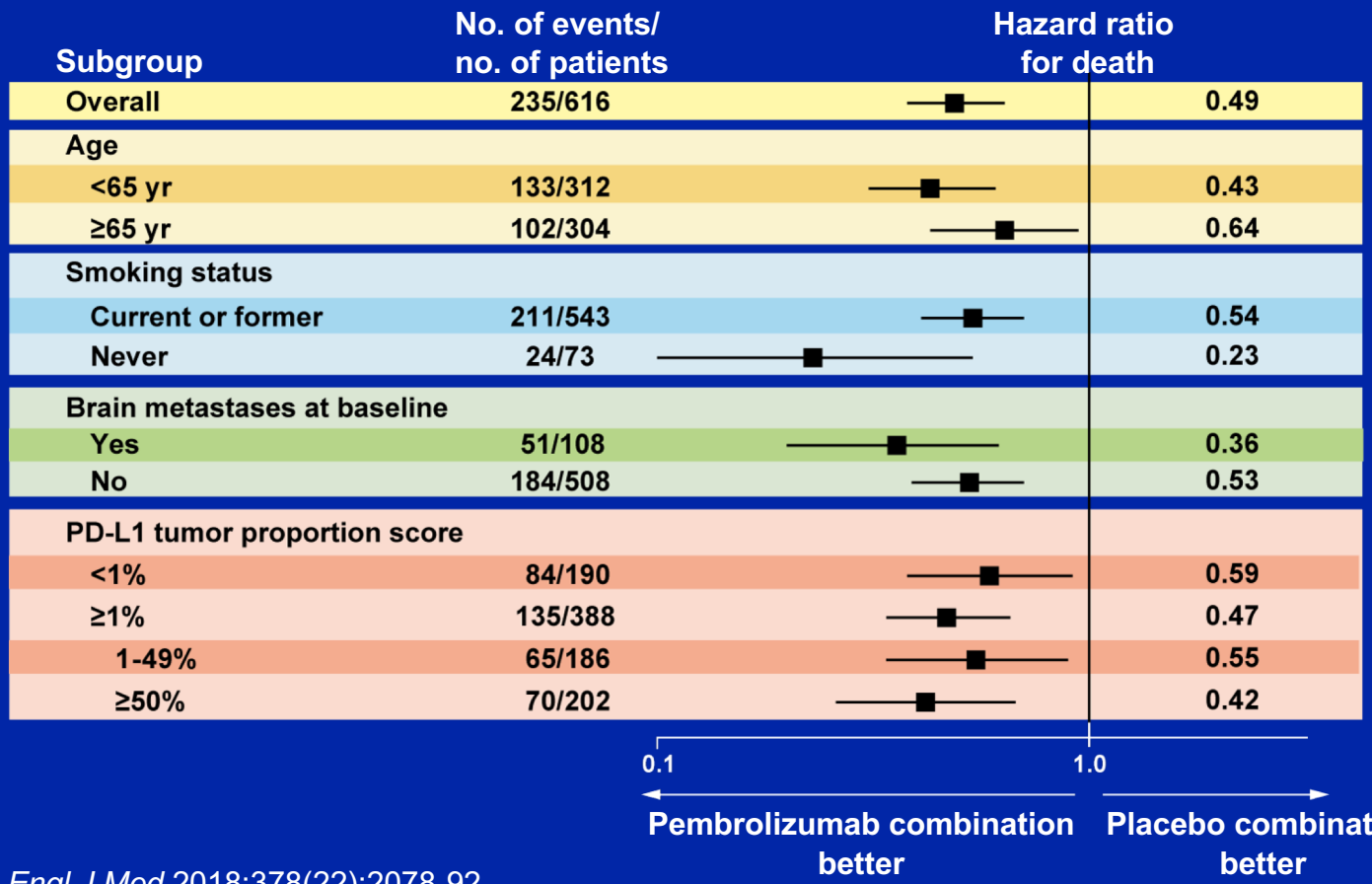


Progression-Free Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death
Overall	410/616	0.52
PD-L1 tumor proportion score		
<1%	146/190	0.75
≥1%	238/388	0.44
1-49%	114/186	0.55
≥50%	124/202	0.36

Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

KEYNOTE-189: OS According to Baseline Characteristics



Gandhi L et al. *N Engl J Med* 2018;378(22):2078-92.

The NEW ENGLAND JOURNAL of MEDICINE

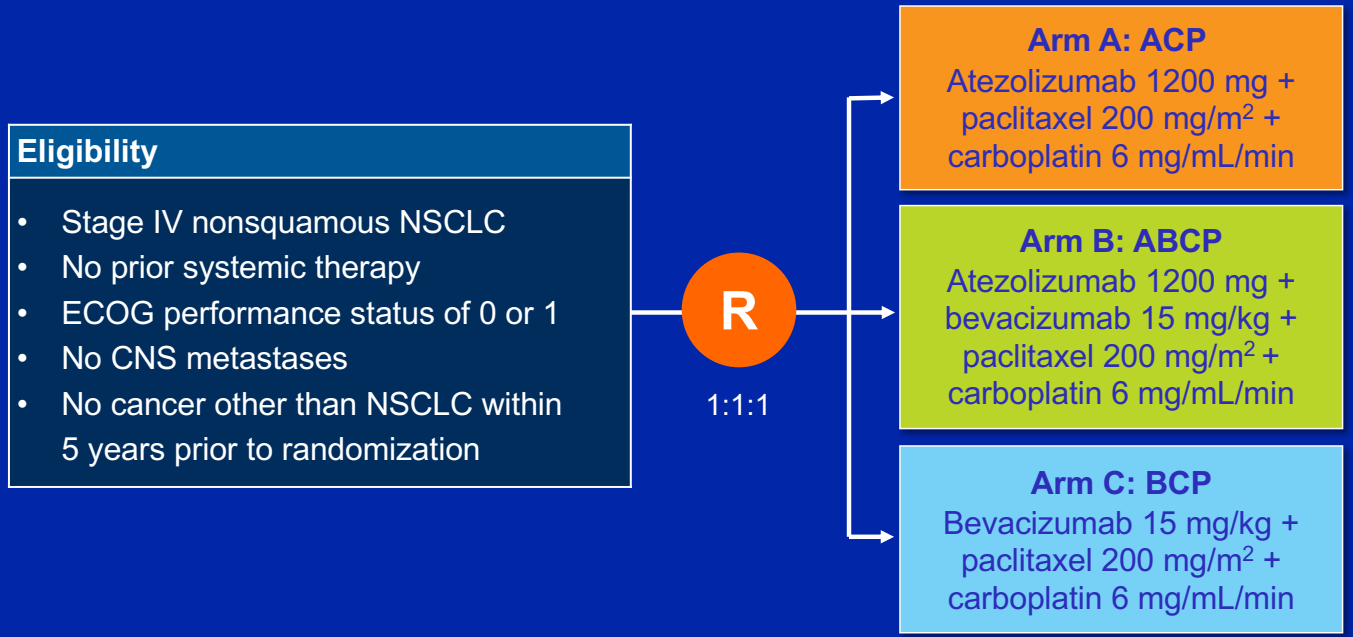
ORIGINAL ARTICLE

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*

N Engl J Med 2018;378(24):2288-301.

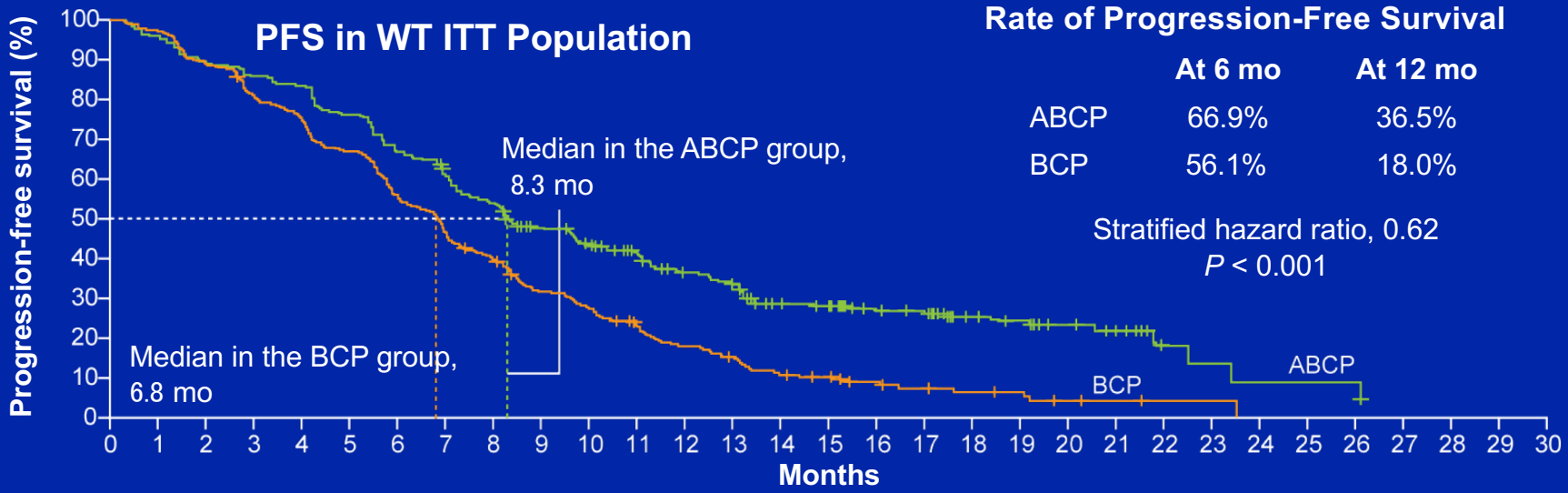
IMpower150: A Phase III Trial of Atezolizumab with Bevacizumab and Chemotherapy in mNSCLC



Coprimary endpoints: PFS based on investigator assessment (per RECIST 1.1) and overall survival

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: PFS Results of First-Line Atezolizumab with Bevacizumab and Chemotherapy in Metastatic Nonsquamous NSCLC



Rate of Progression-Free Survival

	At 6 mo	At 12 mo
ABCP	66.9%	36.5%
BCP	56.1%	18.0%

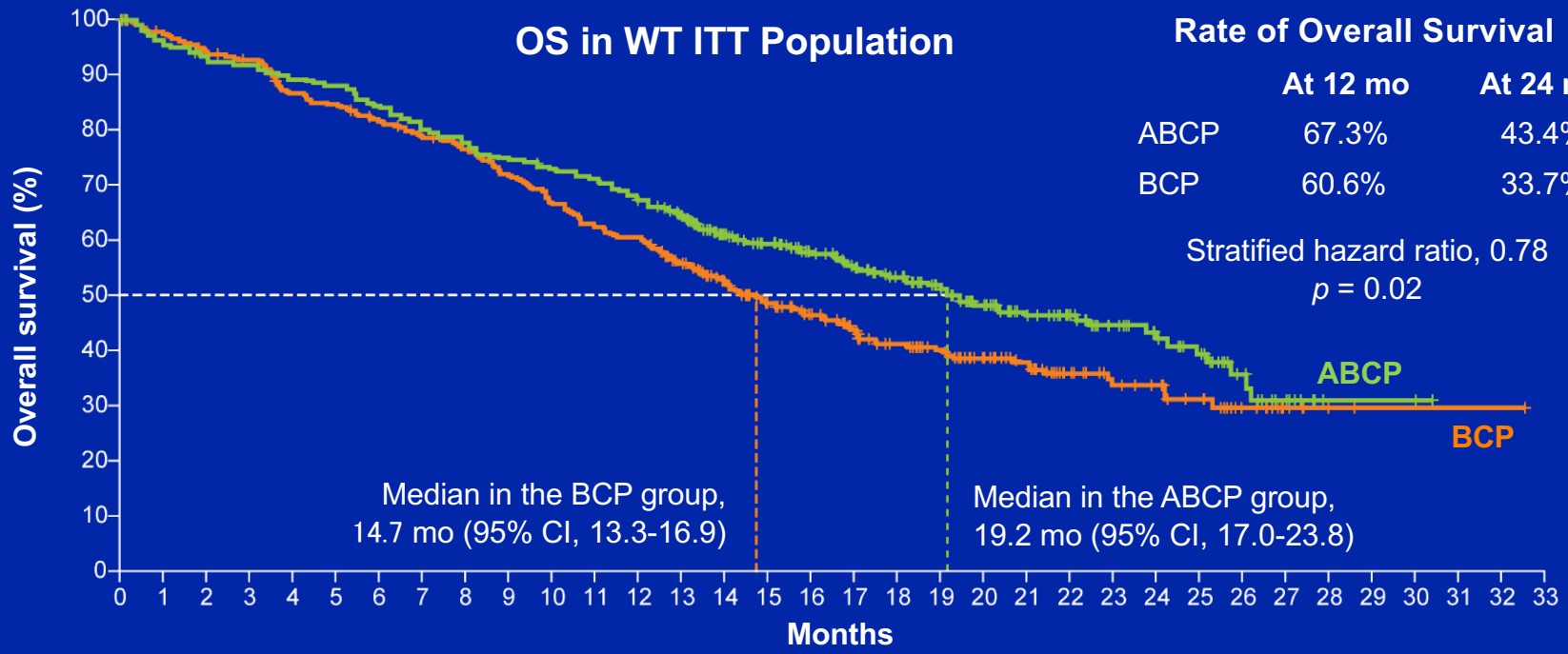
Stratified hazard ratio, 0.62
$P < 0.001$

WT = wild type; ABCP = atezolizumab + BCP; BCP = bevacizumab/carboplatin/paclitaxel

- Median PFS was significantly longer in the ABCP vs BCP group in the effector T-cell (Teff)-high WT population:
  - 11.3 mo vs 6.8 mo (HR 0.51, $p < 0.001$)
- PFS was also higher in the ABCP arm for the entire ITT population, patients with low or negative PD-L1 expression and patients with low Teff gene signatures

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: Interim Analysis of Overall Survival



Rate of Overall Survival

	At 12 mo	At 24 mo
ABCP	67.3%	43.4%
BCP	60.6%	33.7%

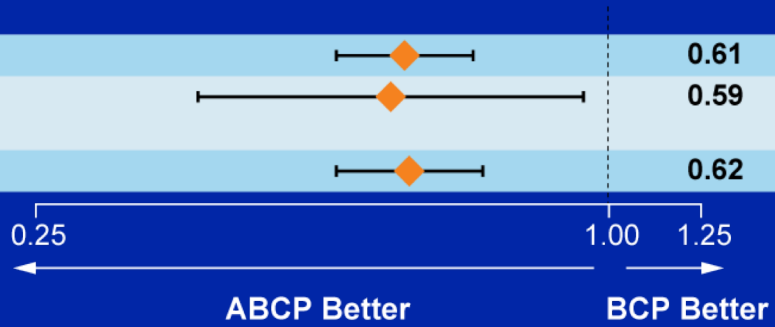
Stratified hazard ratio, 0.78
p = 0.02

WT = wild type; ABCP = atezolizumab + BCP; BCP = bevacizumab/carboplatin/paclitaxel

Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower150: Efficacy of First-Line Atezolizumab with Bevacizumab and Chemotherapy in mNSCLC with Activating Mutations

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61
Patients with EGFR or ALK genetic alterations	108 (14)	9.7	6.1	0.59
WT population	692 (87)	8.3	6.8	0.62



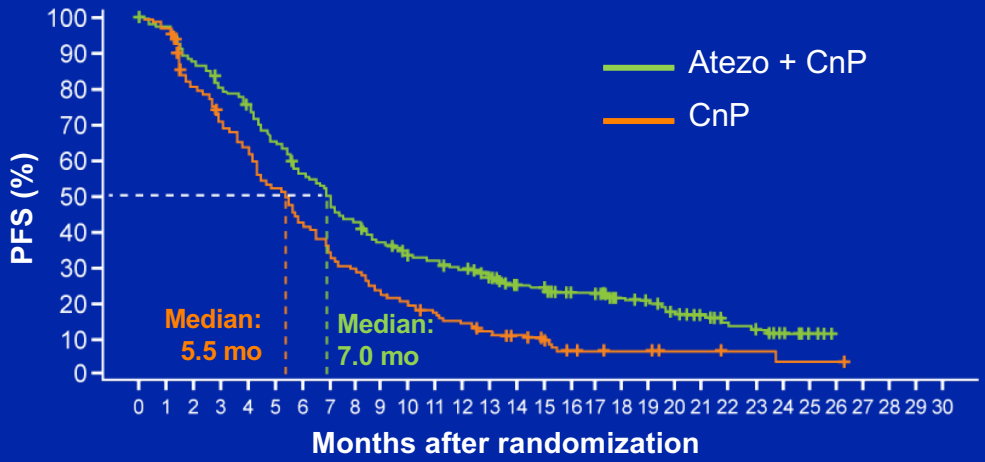
- The addition of atezolizumab to bevacizumab and chemotherapy as first-line treatment resulted in a significant improvement in PFS and OS, regardless of PD-L1 expression and EGFR or ALK genetic alteration status.
- Safety profile of ABCP was consistent with previously reported safety risks of the individual medicines.

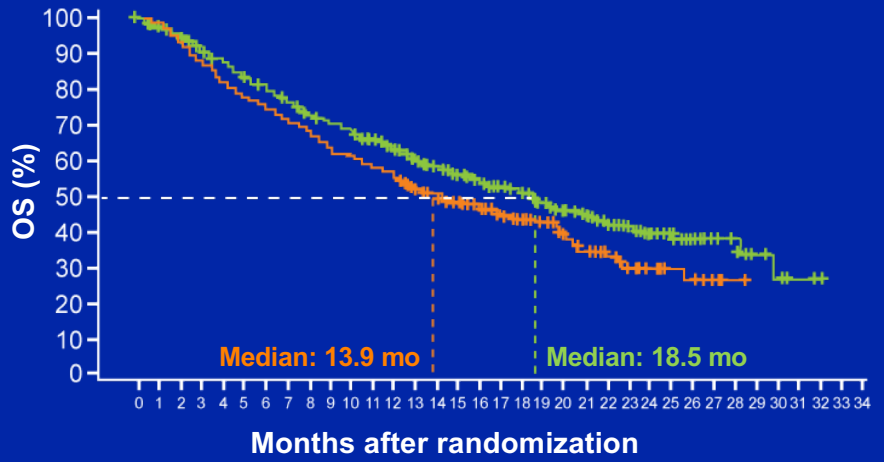
Socinski MA et al. *N Engl J Med* 2018;378(24):2288-301.

IMpower130: Progression-Free Survival (PFS) and Safety Analysis from a Randomised Phase 3 Study of Carboplatin + *Nab*-Paclitaxel (CnP) with or without Atezolizumab (Atezo) as First-Line (1L) Therapy in Advanced Non-Squamous NSCLC

Cappuzzo F et al.
Proc ESMO 2018;Abstract LBA53.

IMpower130: PFS and OS of CnP with or without Atezo in the Intention-to-Treat Wild-Type (ITT-WT) Population





PFS (ITT-WT)	6-month	1-year	HR	*p*-value
Atezo + CnP	56.1%	29.1%	0.64	$p < 0.0001$
CnP	42.5%	14.1%		

OS (ITT-WT)	1-year	2-year	HR	*p*-value
Atezo + CnP	63.1%	39.6%	0.79	$p = 0.033$
CnP	55.5%	30.0%		

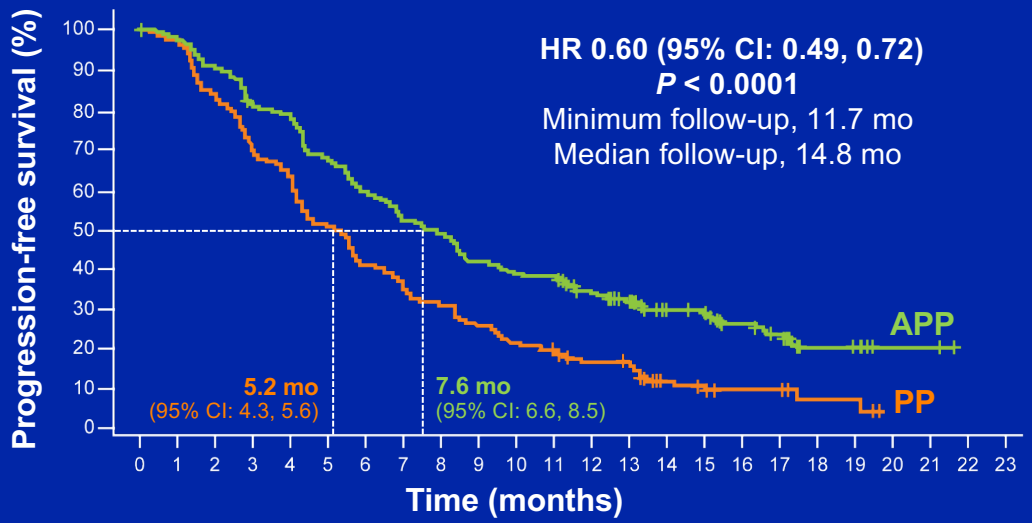
- Outcomes in patients with EGFR or ALK genomic alterations suggest treatment benefit was mostly driven by the ITT-WT population
- Atezo with chemotherapy had a safety profile consistent with the AEs associated with single-agent therapy; no new safety signals were identified

Cappuzzo F et al. *Proc ESMO* 2018;Abstract LBA53.

IMpower132: PFS and Safety Results with 1L Atezolizumab + Carboplatin/Cisplatin + Pemetrexed in Stage IV Non-Squamous NSCLC

Papadimitrakopoulou VA et al.
Proc WCLC 2018;Abstract OA05.07.

IMpower132: Efficacy and Safety Results with First-Line Atezolizumab and Chemotherapy in Metastatic Nonsquamous NSCLC



	APP	PP
6-mo PFS	59.1%	40.9%
12-mo PFS	33.7%	17.0%
	APP	**PP**
ORR	47%	32%
CR	2%	1%
PR	45%	32%
Median DOR, mo	10.1	7.2
Ongoing response, %	42%	30%

APP = atezolizumab + PP; PP = pemetrexed + cisplatin or carboplatin

- At interim analysis, median OS was 18.1 mo with APP and 13.6 mo with PP (HR 0.81; $p = 0.0797$).
- No new safety signals were identified with the APP combination; the safety profile is consistent with known safety risks of the individual therapies.

Papadimitrakopoulou VA et al. *Proc WCLC* 2018;Abstract OA05.07.

The NEW ENGLAND JOURNAL of MEDICINE

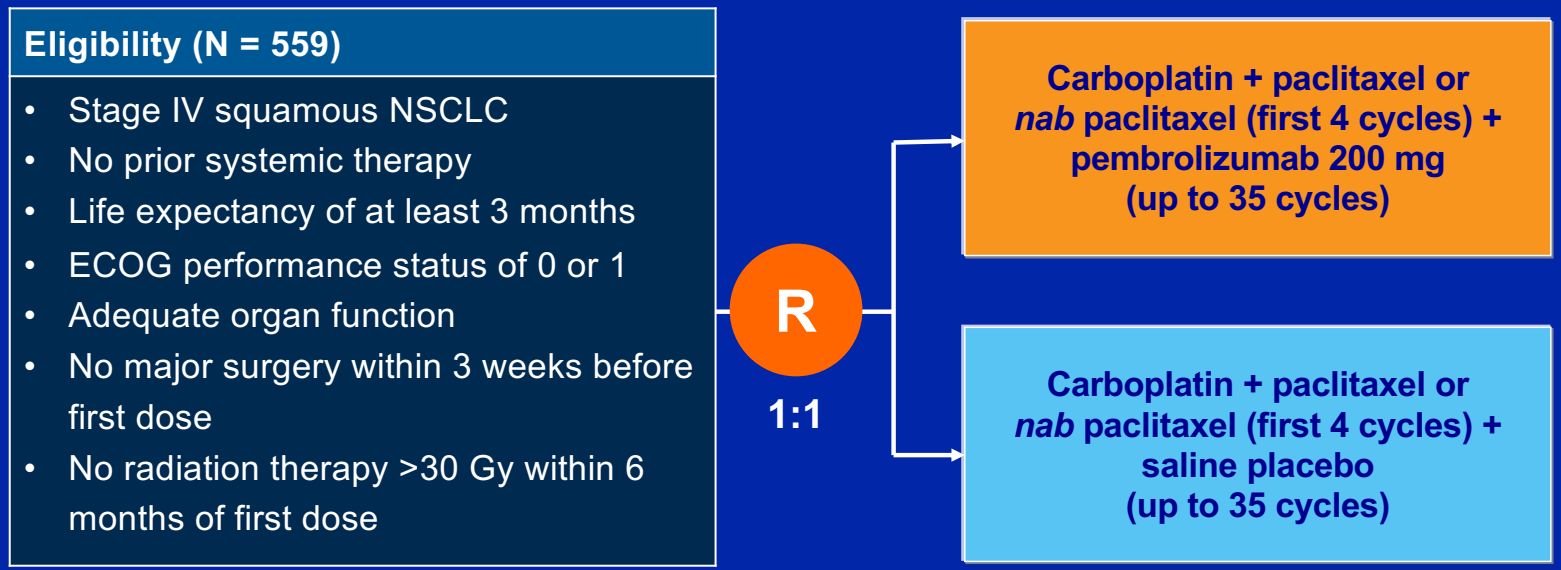
ORIGINAL ARTICLE

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*

N Engl J Med 2018;[Epub ahead of print].

KEYNOTE-407: A Phase III Trial of First-Line Pembrolizumab with Chemotherapy for Advanced Squamous NSCLC



Coprimary endpoints: PFS and OS

www.clinicaltrials.gov. NCT02775435; Paz-Ares L et al. *N Engl J Med* 2018;[Epub ahead of print].

KEYNOTE-407: Second Interim Analysis of First-Line Pembrolizumab with Chemotherapy in Advanced Squamous NSCLC

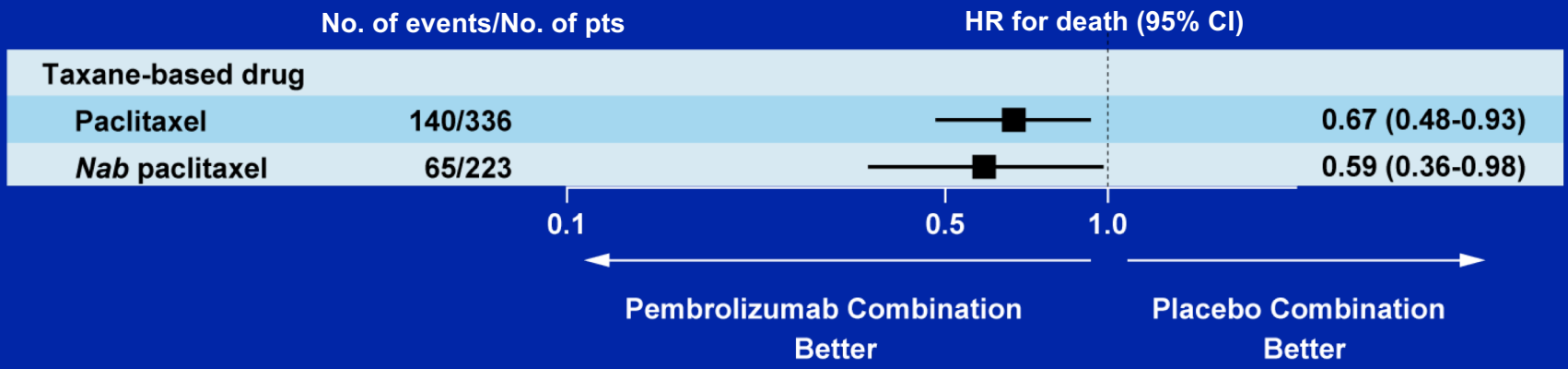
Coprimary endpoints: PFS and OS in ITT	Pembrolizumab + chemotherapy* (n = 278)	Placebo + chemotherapy* (n = 281)	HR (*p*-value)
Median PFS	6.4 mo	4.8 mo	0.56 (<0.0001)
Median OS	15.9 mo	11.3 mo	0.64 (0.0008)

* Chemotherapy = carboplatin with paclitaxel or *nab* paclitaxel

- PFS and OS benefit with pembrolizumab with chemotherapy was observed irrespective of PD-L1 TPS.
- ORR and DoR were greater with pembrolizumab with chemotherapy than with chemotherapy alone.
- Observed toxicities were consistent with the known safety profiles of the individual agents, and no new safety signals were identified:
  - Grade 3-5 immune-mediated AEs (pembrolizumab vs placebo arms): 10.8% vs 3.2%
  - 2 deaths occurred due to pneumonitis (1 on each treatment arm)

Paz-Ares LG et al. *N Engl J Med* 2018;[Epub ahead of print].

KEYNOTE-407: Impact of Choice of Taxane on Outcomes



- The treatment effect was similar between the patients who received paclitaxel and those who received *nab* paclitaxel.

Paz-Ares L et al. *N Engl J Med* 2018;[Epub ahead of print].

FDA Approves Pembrolizumab in Combination with Chemotherapy for First-Line Treatment of Metastatic Squamous NSCLC

Press Release – October 30, 2018

"On October 30, 2018, the Food and Drug Administration approved pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC).

Approval was based on KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to pembrolizumab 200 mg or placebo in combination with carboplatin, and investigator's choice of either paclitaxel every 3 weeks or nab-paclitaxel weekly on a 3-week cycle for 4 cycles followed by pembrolizumab or placebo. Patients continued pembrolizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 24 months."

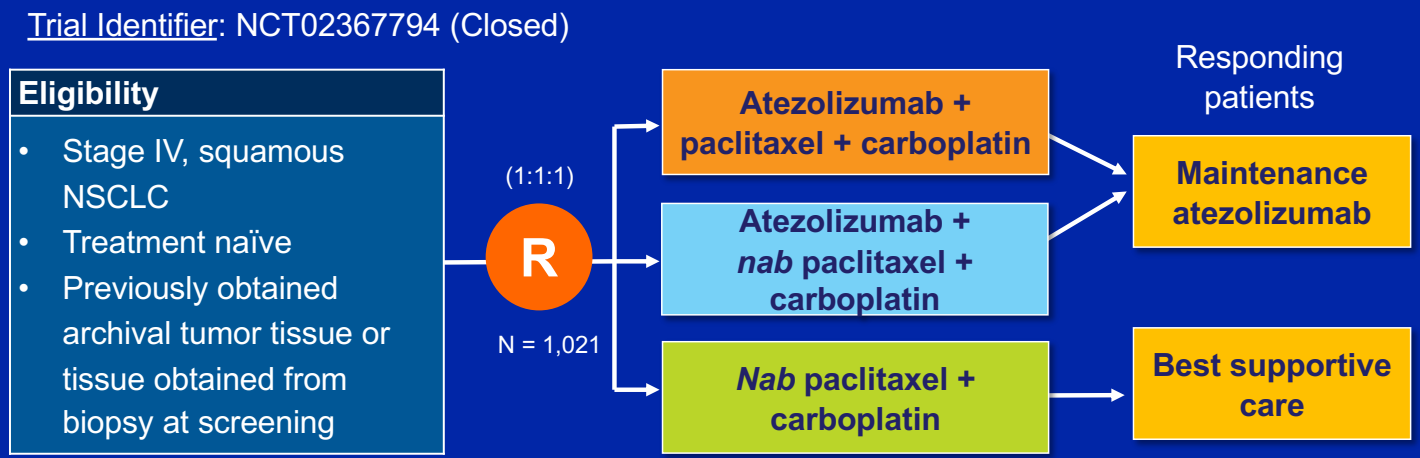
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm624659.htm

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

Jotte RM et al.

Proc ASCO 2018;Abstract LBA9000.

IMpower131: A Phase III Trial of First-Line Atezolizumab with Chemotherapy Compared to Chemotherapy Alone for Squamous Cell NSCLC



www.clinicaltrials.gov. Accessed May 2018; Jotte RM et al. *Proc ASCO* 2018;Abstract LBA9000.

IMpower131: First-Line Atezolizumab with Chemotherapy in Advanced Squamous NSCLC

Coprimary endpoints: PFS and OS in ITT	Atezolizumab + *nab*-P/carboplatin (n = 343)	*nab*-P/carboplatin (n = 340)	HR (*p*-value)
Median PFS	6.3 mo	5.6 mo	0.71 (0.0001)
Median OS	14.0 mo	13.9 mo	0.96 (0.6931)
PFS and OS in PD-L1 high	(n = 53)	(n = 48)	
Median PFS	10.1 mo	5.5 mo	0.44 (-)
Median OS	23.6 mo	14.1 mo	0.56 (-)

- PFS benefit with atezolizumab and *nab*-paclitaxel/carboplatin was observed across all PD-L1-expressing subgroups; next interim OS analysis anticipated later in 2018.
- Atezolizumab with *nab*-paclitaxel/carboplatin had a manageable safety profile consistent with the known risks of the individual therapies.

Jotte RM et al. *Proc ASCO* 2018;Abstract LBA9000.

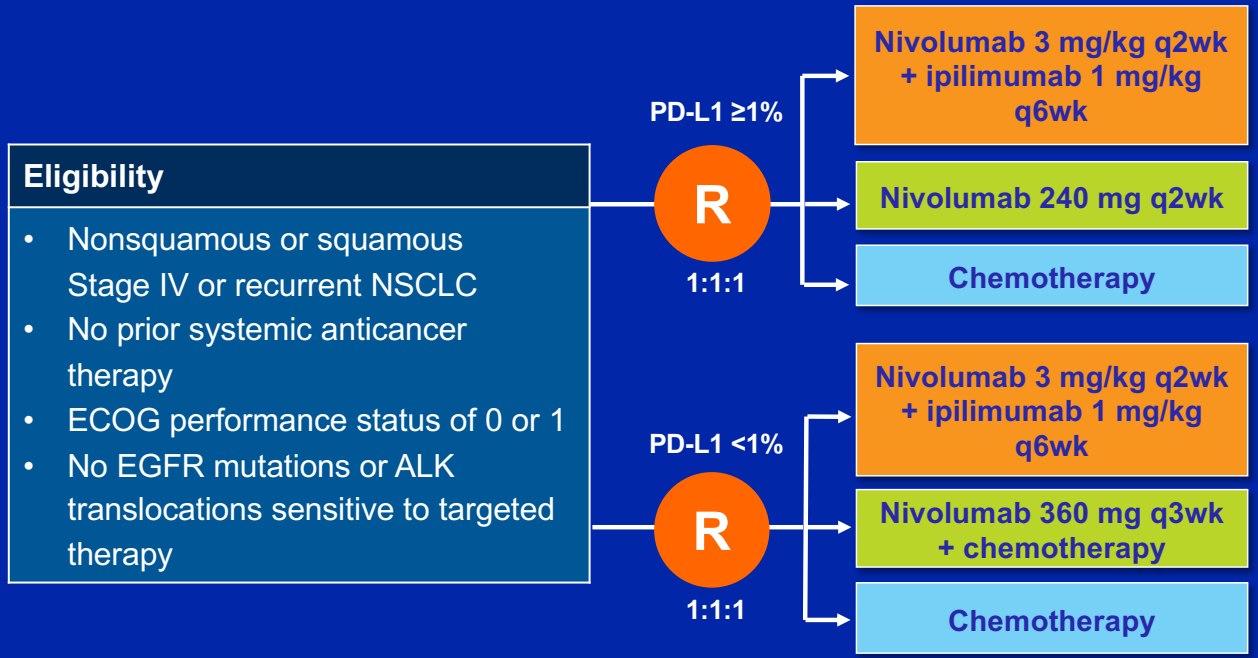
Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden[1]

Nivolumab (Nivo) + Platinum-Doublet Chemotherapy (Chemo) vs Chemo as First-Line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC) with <1% Tumor PD-L1 Expression: Results from CheckMate 227[2]

[1] Hellmann MD et al.
N Engl J Med 2018;378(22):2093-104.

[2] Borghaei H et al.
Proc ASCO 2018;Abstract 9001.

CheckMate 227: Nivolumab and Ipilimumab in NSCLC with a High Tumor Mutational Burden

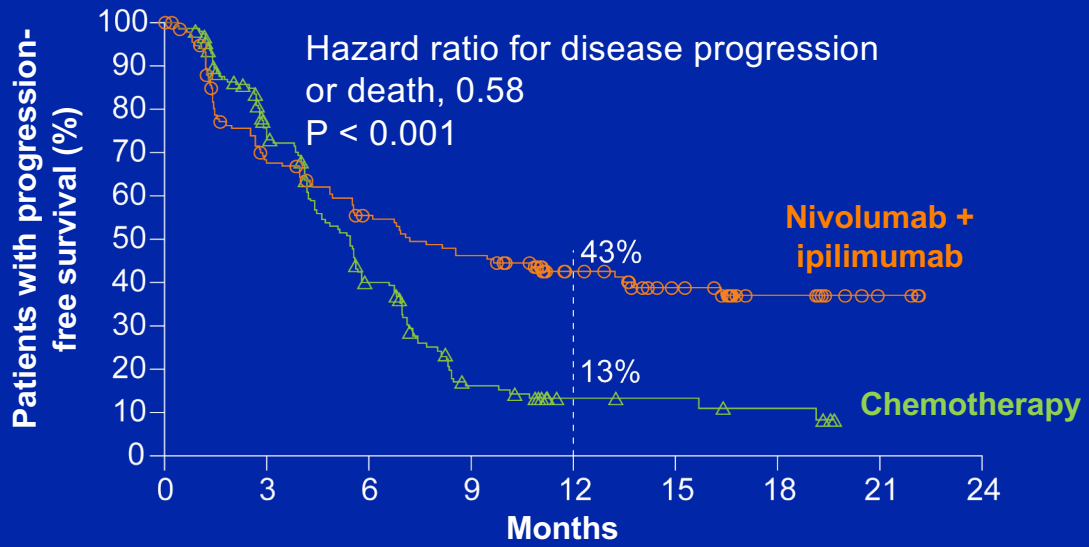


Coprimary endpoints: OS in PD-L1-selected populations and PFS in tumor mutational burden-selected populations

Borghaei H et al. *Proc ASCO* 2018;Abstract 9001.

CheckMate 227: First-Line Nivolumab with Ipilimumab in Metastatic NSCLC

Coprimary endpoint for nivolumab + ipilimumab versus chemotherapy arms: PFS in high tumor mutational burden (TMB) population (≥10 mut/Mb)[1]



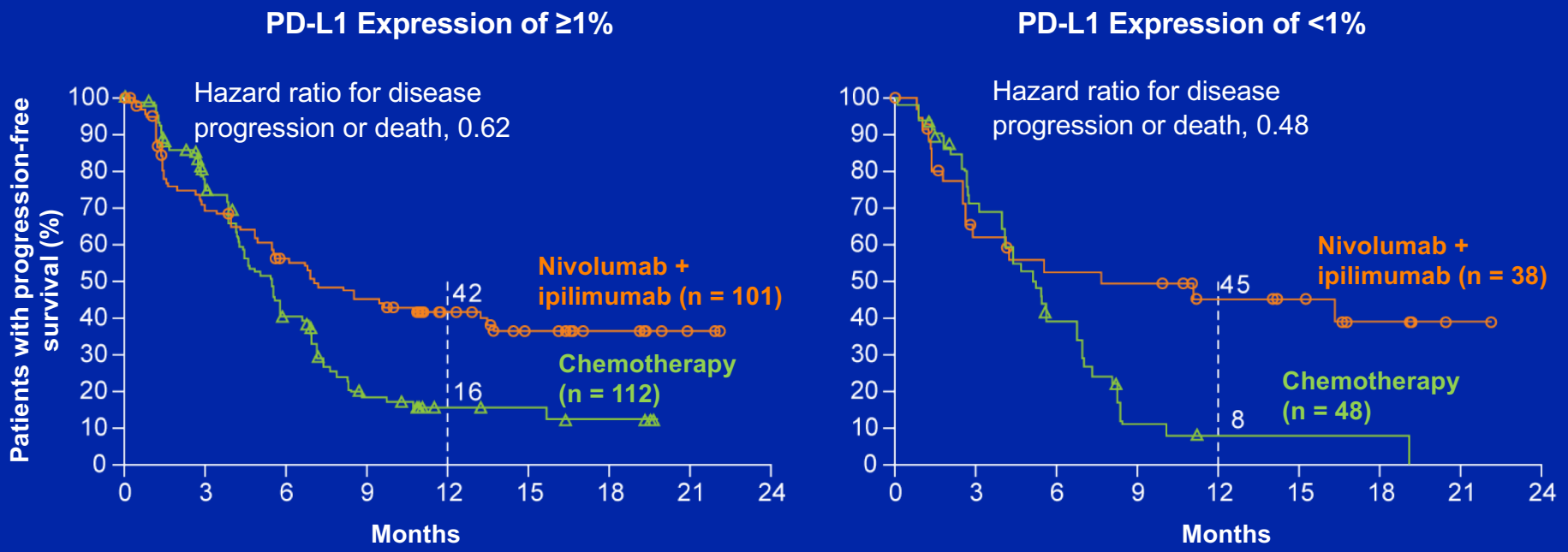
	Nivolumab + ipilimumab (n = 139)	Chemotherapy (n = 160)
Median PFS	7.2 mo	5.5 mo
HR (*p*-value)	0.58 (<0.001)	

Secondary endpoint for nivolumab + chemotherapy (n = 177) versus chemotherapy arms (n = 186): PFS in patients with <1% PD-L1 TPS[2]

- Median PFS: 5.6 mo vs 4.7 mo (HR 0.74)
- PFS benefit was enhanced in patients with high TMB

[1] Hellmann MD et al. *N Engl J Med* 2018;378(22):2093-104; [2] Borghaei H et al. *Proc ASCO* 2018;Abstract 9001.

CheckMate 227: PFS for Patients with High TMB by PD-L1 Expression



PFS was similar in the nivolumab/ipilimumab and chemotherapy groups among patients with low TMB.

Hellmann MD et al. *N Engl J Med* 2018;378(22):2093-104.

CheckMate 227: Treatment-Related Adverse Events in Metastatic NSCLC

Adverse events (Grade 3 or 4)	Nivolumab and ipilimumab (N = 576)	Nivolumab (N = 391)	Chemotherapy (N = 570)
Any Grade 3 or 4	31%	19%	36%
Any serious event	18%	8%	11%
Leading to discontinuation of treatment	12%	7%	5%
Rash	2%	1%	0%
Diarrhea	2%	1%	1%
Anemia	2%	1%	11%
Neutropenia	0%	0%	10%

Hellmann MD et al. *N Engl J Med* 2018;378(22):2093-104.

Tumor Mutational Burden (TMB) as a Biomarker for Clinical Benefit from Dual Immune Checkpoint Blockade with Nivolumab (Nivo) + Ipilimumab (ipi) in First-Line (1L) Non-Small Cell Lung Cancer (NSCLC): Identification of TMB Cutoff from CheckMate 568

Ramalingam SS et al.

Proc AACR 2018;Abstract CT078.

CheckMate 568: Identification of TMB Cutoff to Select Patients for First-Line Nivolumab with Ipilimumab in Metastatic NSCLC

- In CheckMate 568, 288 patients with chemotherapy-naïve Stage IV NSCLC received nivo 3 mg/kg q2wk + ipi 1 mg/kg q6wk for up to 2 years.
- An appropriate TMB cutoff associated with enhanced efficacy was determined with receiver operating characteristic (ROC) curves.

Patient group	ORR
Overall	27%
TMB <5 mut/Mb	4%
TMB <10 mut/Mb	10%
TMB ≥10 mut/Mb	44%
TMB ≥15 mut/Mb	39%

Chosen as cutoff to define population for coprimary efficacy endpoint in CheckMate 227

Ramalingam SS et al. *Proc AACR* 2018;Abstract CT078.

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

J Clin Oncol 2018;36(17):1714-68.

ASCO Guideline: Management of IRAEs in Patients Receiving Immune Checkpoint Inhibitor Therapy

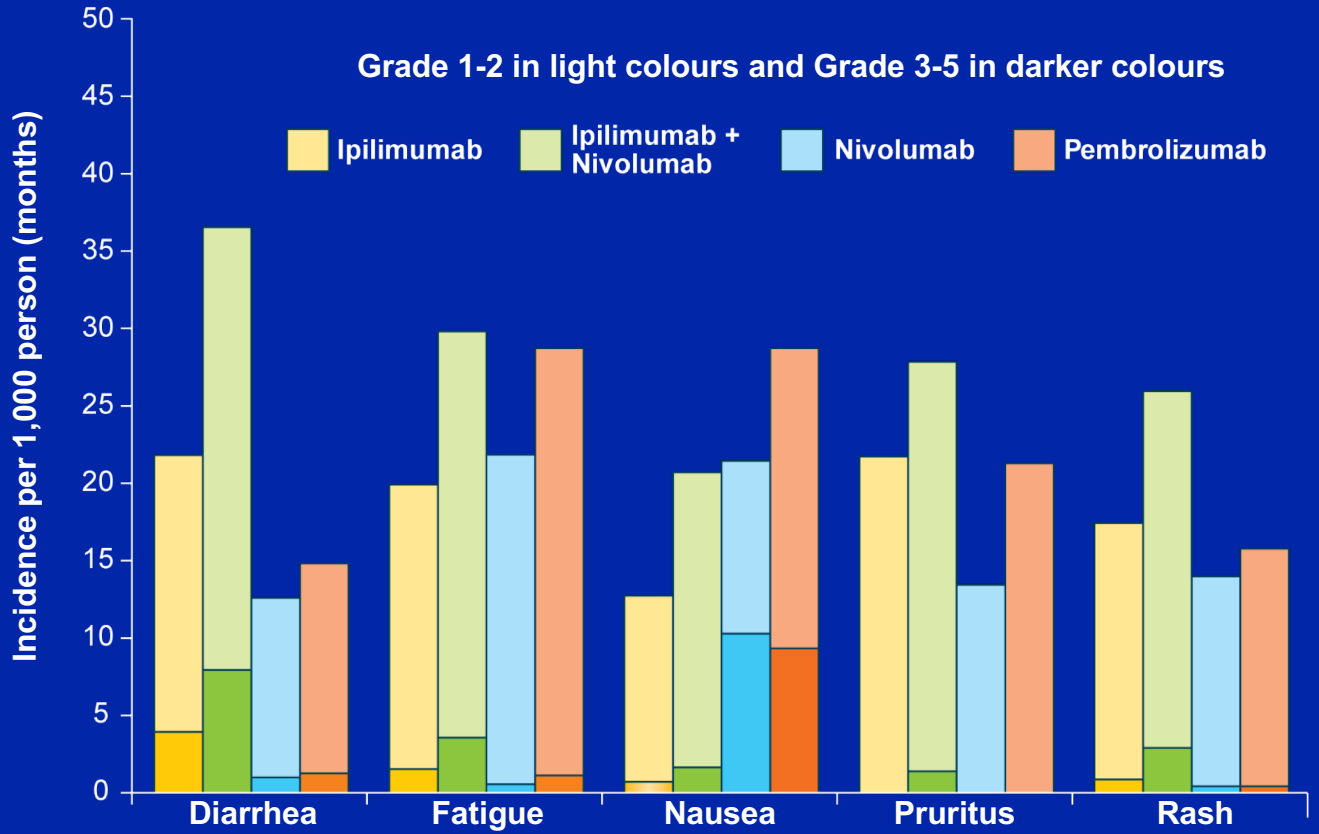
Toxicity grade	General recommendations
Grade 1	• Continue with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
Grade 2	• Therapy may be suspended and resumed when symptoms revert to grade 1 or less. • Corticosteroids may be administered.
Grade 3	• Suspension of therapy and the initiation of high-dose corticosteroids. • Corticosteroids should be tapered over the course of at least 4 to 6 weeks. • Some refractory cases may require infliximab or other immunosuppressive therapy.
Grade 4	• Permanent discontinuation is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

Brahmer JR et al. *J Clin Oncol* 2018;36(17):1714-68.

Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination

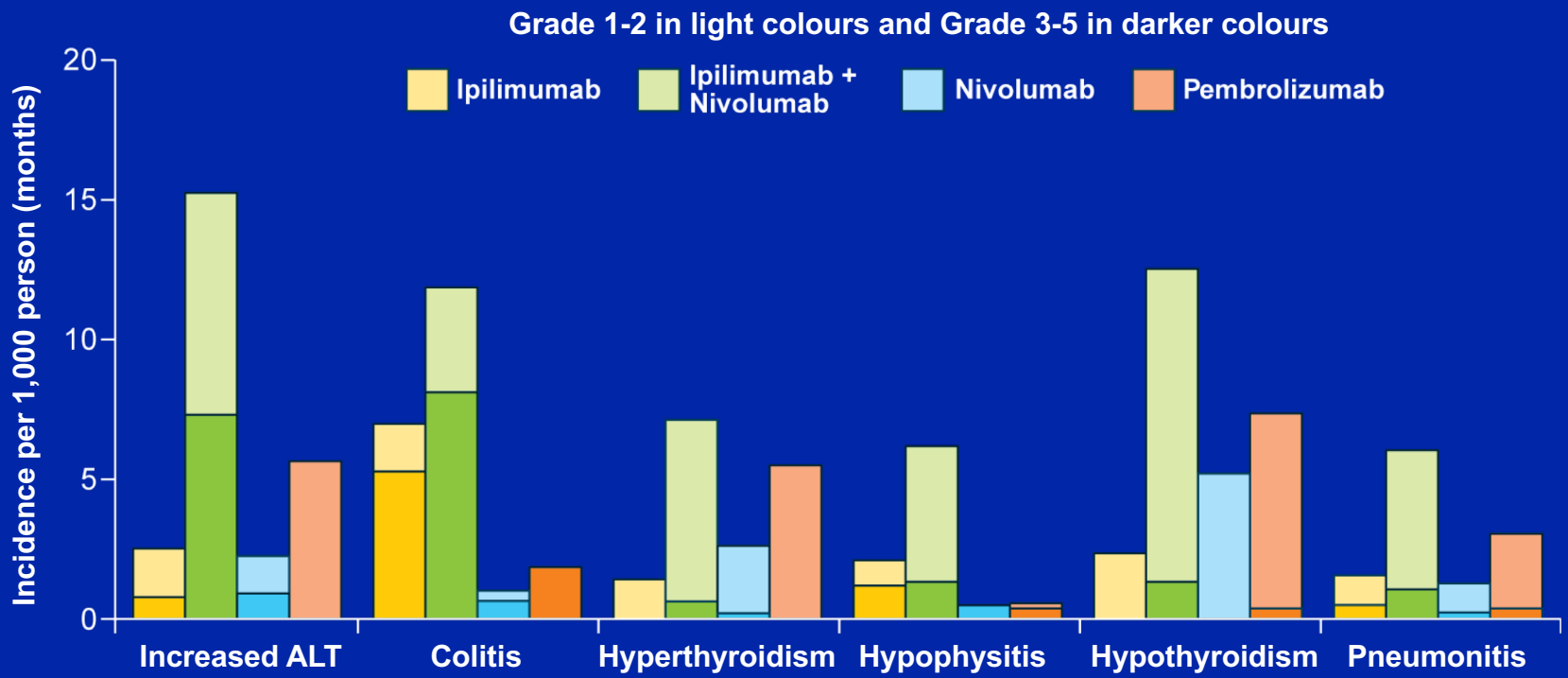
Celine Boutros[1], Ahmad Tarhini[2], Emilie Routier[1], Olivier Lambotte[3–5], Francois Leroy Ladurie[6], Franck Carbonnel[4,7], Hassane Izzeddine[8], Aurelien Marabelle[9], Stephane Champiat[10], Armandine Berdelou[11], Emilie Lanoy[12], Matthieu Texier[12], Cristina Libenciuc[1], Alexander M. M. Eggermont[1,4], Jean-Charles Soria[4,9,10], Christine Mateus[1] and Caroline Robert[1,4,10]

Common Adverse Events with Checkpoint Inhibitors Alone and in Combination



Boutros C et al. *Nat Rev Clin Oncol* 2016;13:473-86.

Adverse Events of Special Interest with Checkpoint Inhibitors



Boutros C et al. *Nat Rev Clin Oncol* 2016;13:473-86.

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

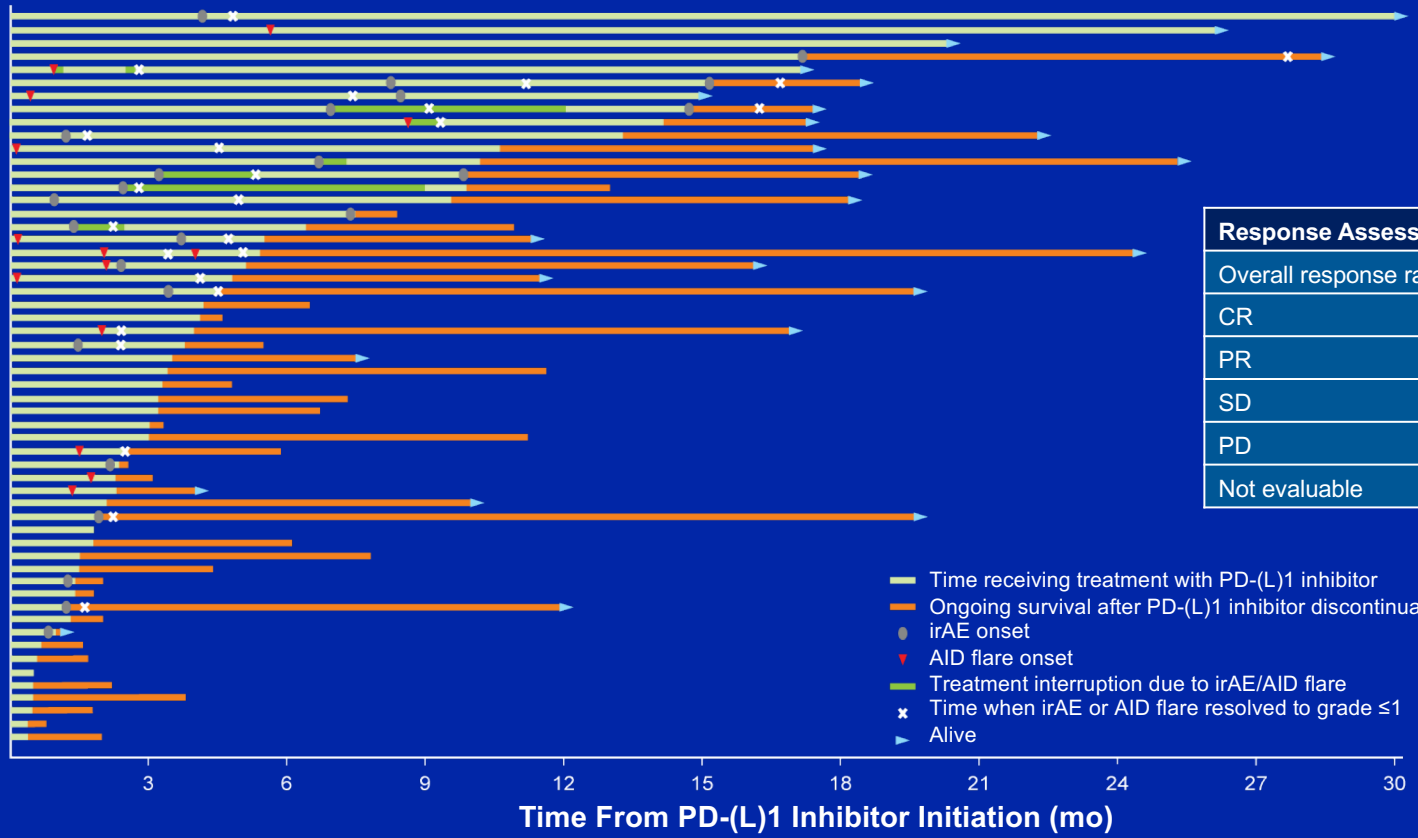
RAPID COMMUNICATION

Safety of Programmed Death–1 Pathway Inhibitors Among Patients With Non–Small-Cell Lung Cancer and Preexisting Autoimmune Disorders

Giulia C. Leonardi, Justin F. Gainor, Mehmet Altan, Sasha Kravets, Suzanne E. Dahlberg, Lydia Gedmintas, Roxana Azimi, Hira Rizvi, Jonathan W. Riess, Matthew D. Hellmann, and Mark M. Awad

J Clin Oncol 2018;36(19):1905-12.

Safety of PD-1 or PD-L1 Inhibitors Among Patients with NSCLC and Preexisting Autoimmune Disorders



Response Assessment	n = 56
Overall response rate	22%
CR	0
PR	11 (22%)
SD	15 (31%)
PD	23 (47%)
Not evaluable	7

Leonardi GC et al. *J Clin Oncol* 2018;36(19):1905-12.

PD-1 Blockade in HIV-Infected Patients with Lung Cancer: A New Challenge or Already a Strategy?

Lavolé A et al.
Ann Oncol 2018;29(4):1065-66.

PD-1 Blockade in HIV-Infected Patients with Lung Cancer

- Ten consecutive patients living with HIV/AIDS, suffering from NSCLC and treated with nivolumab after receiving platinum-based doublet chemotherapy were analyzed from a prospective database of 270 patients followed in the national CANCERVIH network between 2014 and December 2016.
  - Predominantly adenocarcinoma subtype (70%)
  - All patients had EGFR and ALK wild-type tumors
- Statistical analyses on CD4 cell counts performed.
- At nivolumab introduction, plasma HIV load (pVL) was undetectable.
- HIV-related parameters were not altered with a sustained undetectable pVL and stable CD4 counts after three or four perfusions of nivolumab.

Lavolé A et al. *Ann Oncol* 2018;29(4):1065-66.

VOLUME 36 · NUMBER 28 · OCTOBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

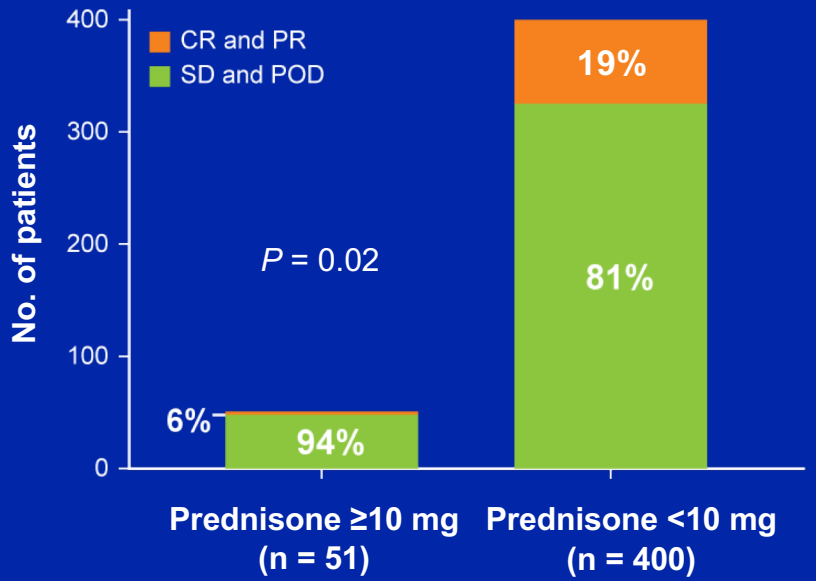
ORIGINAL REPORT

Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non–Small-Cell Lung Cancer

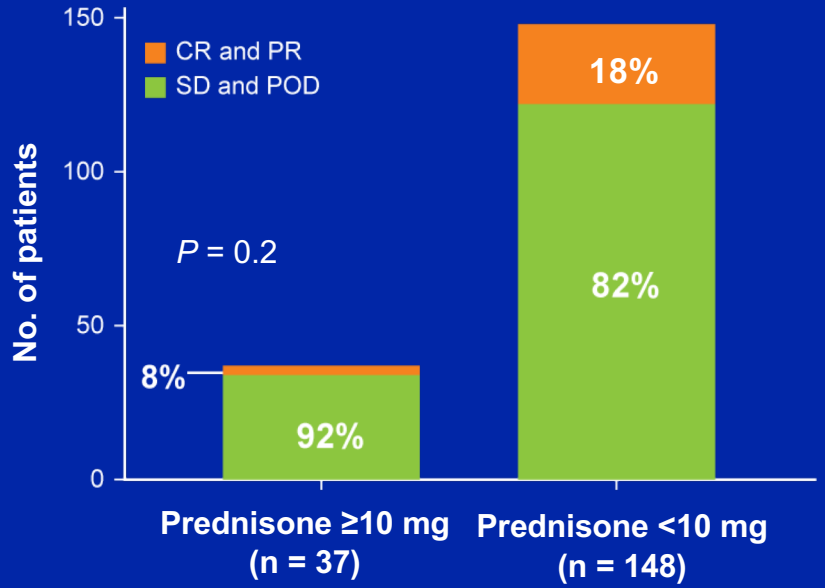
Kathryn C. Arbour, Laura Mezquita, Niamh Long, Hira Rizvi, Edouard Auclin, Andy Ni, Gala Martínez-Bernal, Roberto Ferrara, W. Victoria Lai, Lizza E.L. Hendriks, Joshua K. Sabari, Caroline Caramella, Andrew J. Plodkowski, Darragh Halpenny, Jamie E. Chaft, David Planchard, Gregory J. Riely, Benjamin Besse, and Matthew D. Hellmann

J Clin Oncol 2018;36(28):2872-78.

Impact of Baseline Steroids on Response to PD-1/PD-L1 Blockade in Patients with NSCLC



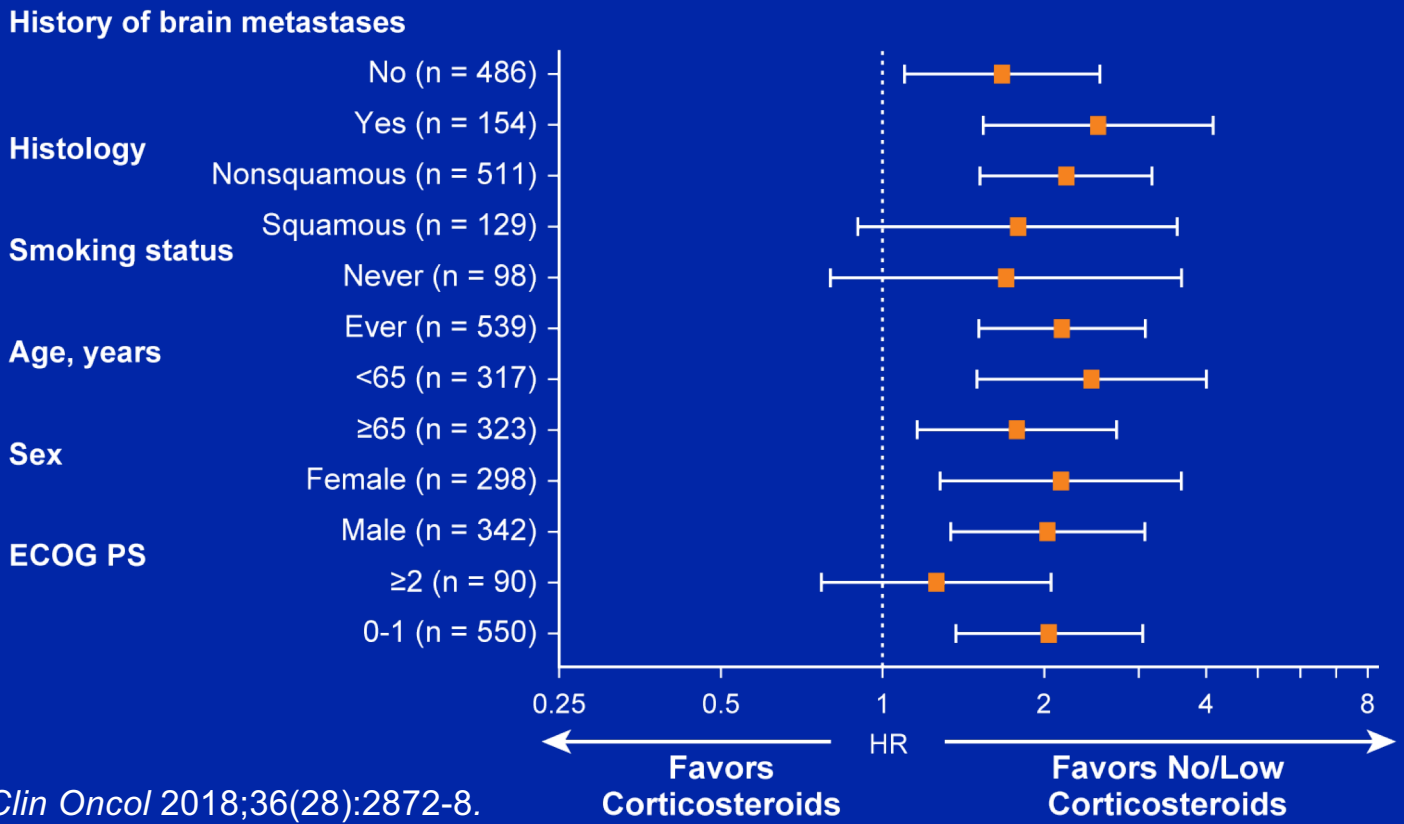
Patients treated at Memorial Sloan Kettering Cancer Center



Patients treated at Gustave Roussy Cancer Center

Arbour KC et al. *J Clin Oncol* 2018;36(28):2872-8.

Effect of Baseline Corticosteroid Use on Efficacy of PD-L/PD-L1 Blockade: Subgroup Analysis of Independent Prognostic Factors for OS in the Pooled Cohort



Arbour KC et al. *J Clin Oncol* 2018;36(28):2872-8.

Module 3: Management of Small Cell Lung Cancer (SCLC)

The NEW ENGLAND JOURNAL of MEDICINE

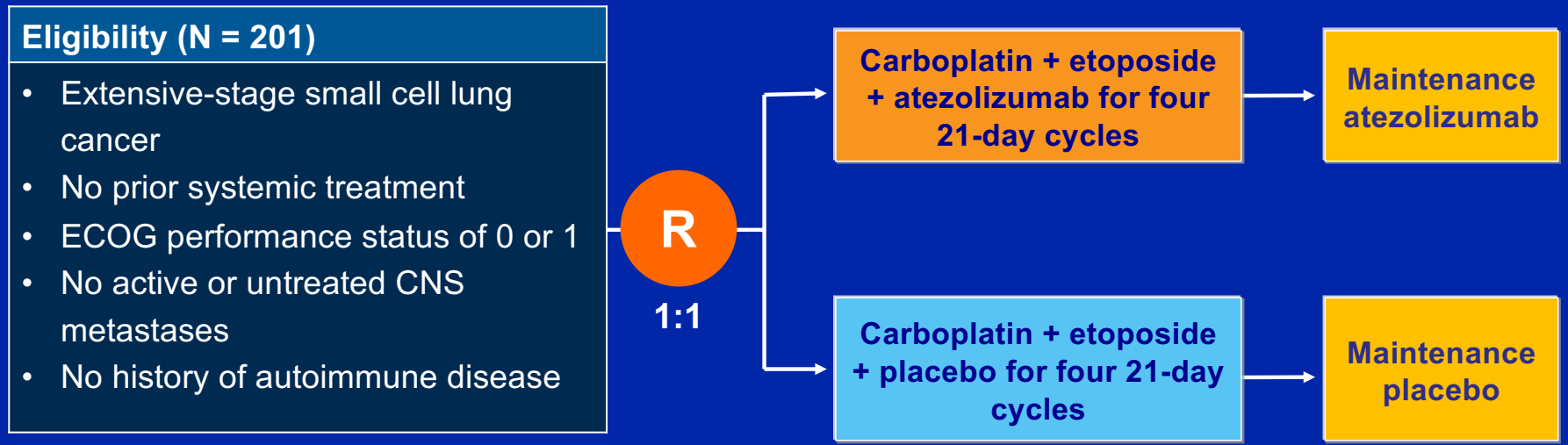
ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*

N Engl J Med 2018;[Epub ahead of print]

IMpower133: A Phase III Trial Evaluating Atezolizumab with Carboplatin and Etoposide in Extensive-Stage SCLC

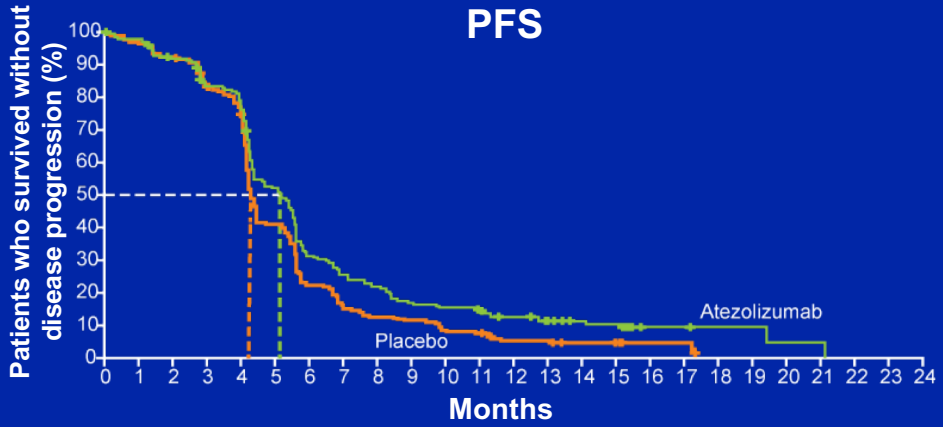


Primary endpoints: Duration of progression-free survival by the investigator using RECIST v1.1 and overall survival

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

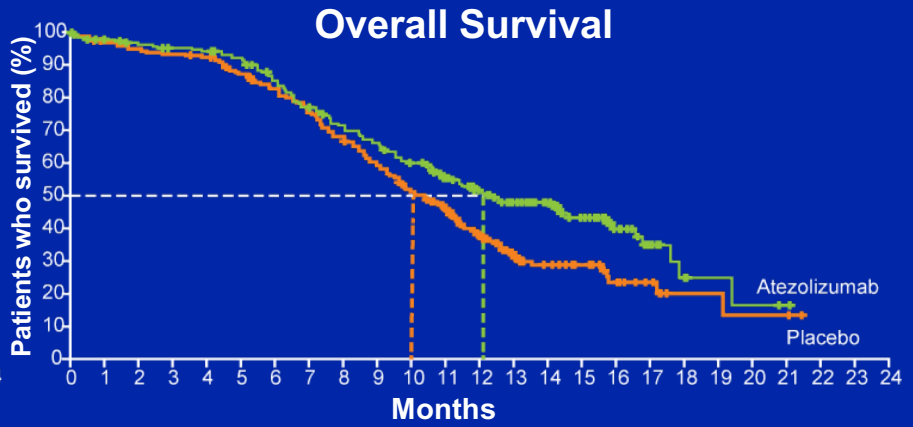
IMpower133: Survival Outcomes with First-Line Atezolizumab and Chemotherapy for Extensive-Stage Small Cell Lung Cancer

PFS



	Median PFS	12-mo PFS	HR	*p*-value
Atezolizumab	5.2 mo	12.6%	0.77	0.02
Placebo	4.3 mo	5.4%		

Overall Survival



	Median OS	12-mo OS	HR	*p*-value
Atezolizumab	12.3 mo	51.7%	0.70	0.007
Placebo	10.3 mo	38.2%		

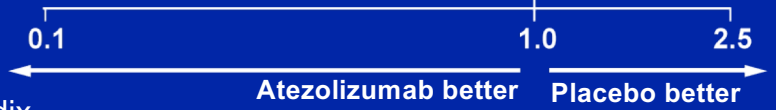
- The safety profile of atezolizumab + carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents; no new findings were observed.

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

IMpower133: OS and PFS by Tumor Mutational Burden

Subgroup	No. of patients (%)	Median overall survival (mo)		Hazard ratio for death
		Atezolizumab	Placebo	
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68
<16 mutations/Mb	271 (67)	12.5	9.9	0.71
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63
Intention-to-treat population	403 (100)	12.3	10.3	0.70

Subgroup	No. of patients (%)	Median progression-free survival (mo)		Hazard ratio
Tumor mutational burden				
<10 mutations/Mb	139 (34)	4.3	4.2	0.78
≥10 mutations/Mb	212 (53)	5.5	4.4	0.69
<16 mutations/Mb	271 (67)	5.2	4.3	0.73
≥16 mutations/Mb	80 (20)	5.6	4.3	0.68
Intention-to-treat population	403 (100)	5.2	4.3	0.77



Horn L et al. *N Engl J Med* 2018;[Epub ahead of print]:Appendix

IMpower133: Adverse Events Related to First-Line Atezolizumab and Chemotherapy for Extensive-Stage SCLC

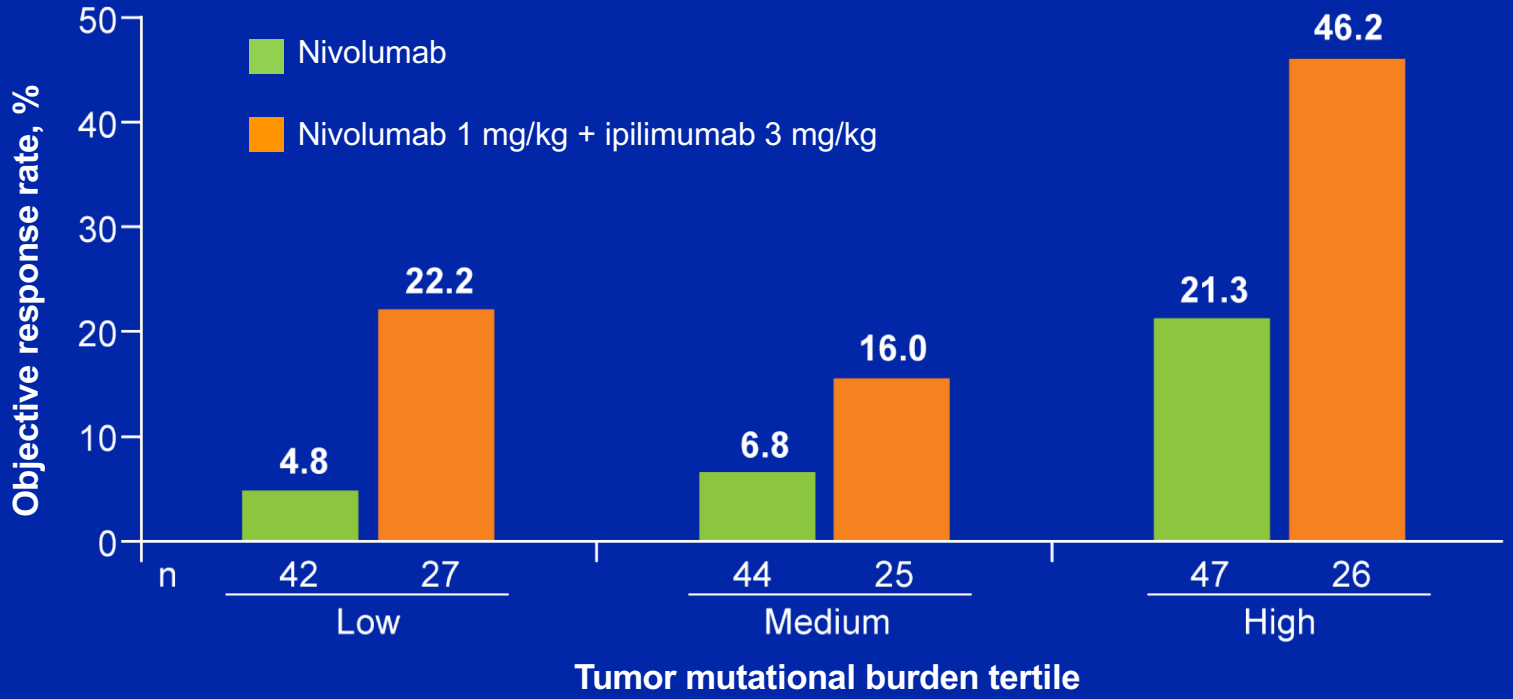
	Atezolizumab (N = 198)		Placebo (N = 196)	
	Grade 3 or 4	Grade 5	Grade 3 or 4	Grade 5
Any adverse event	57%	2%	56%	2%
Neutropenia	23%	1%	25%	0%
Anemia	14%	0%	12%	0%
Thrombocytopenia	10%	0%	8%	0%
Leukopenia	5%	0%	4%	0%
Diarrhea	2%	0%	1%	0%
Febrile neutropenia	3%	0%	6%	0%
Infusion-related reaction	2%	0%	1%	0%

Horn L et al. *N Engl J Med* 2018;[Epub ahead of print].

Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer

Hellmann MD et al.
Cancer Cell 2018;33(5):853-61.

CheckMate 032: Tumor Mutational Burden (TMB) and Efficacy of Nivolumab Alone and in Combination with Ipilimumab



Hellmann MD et al. *Cancer Cell* 2018;33(5):853-61.

FDA Grants Nivolumab Accelerated Approval for Third-Line Treatment of Metastatic Small Cell Lung Cancer

Press Release – August 16, 2018

"On August 16, 2018, the Food and Drug Administration granted accelerated approval to nivolumab for patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.

Approval was based on demonstration of a durable overall response rate (ORR) in a subgroup of patients from CheckMate-032 (NCT01928394), a multicenter, open-label trial in patients with metastatic solid tumors. This subgroup comprised 109 patients with metastatic SCLC, with disease progression after platinum-based therapy and at least one other prior line of therapy, regardless of tumor PD-L1 status.

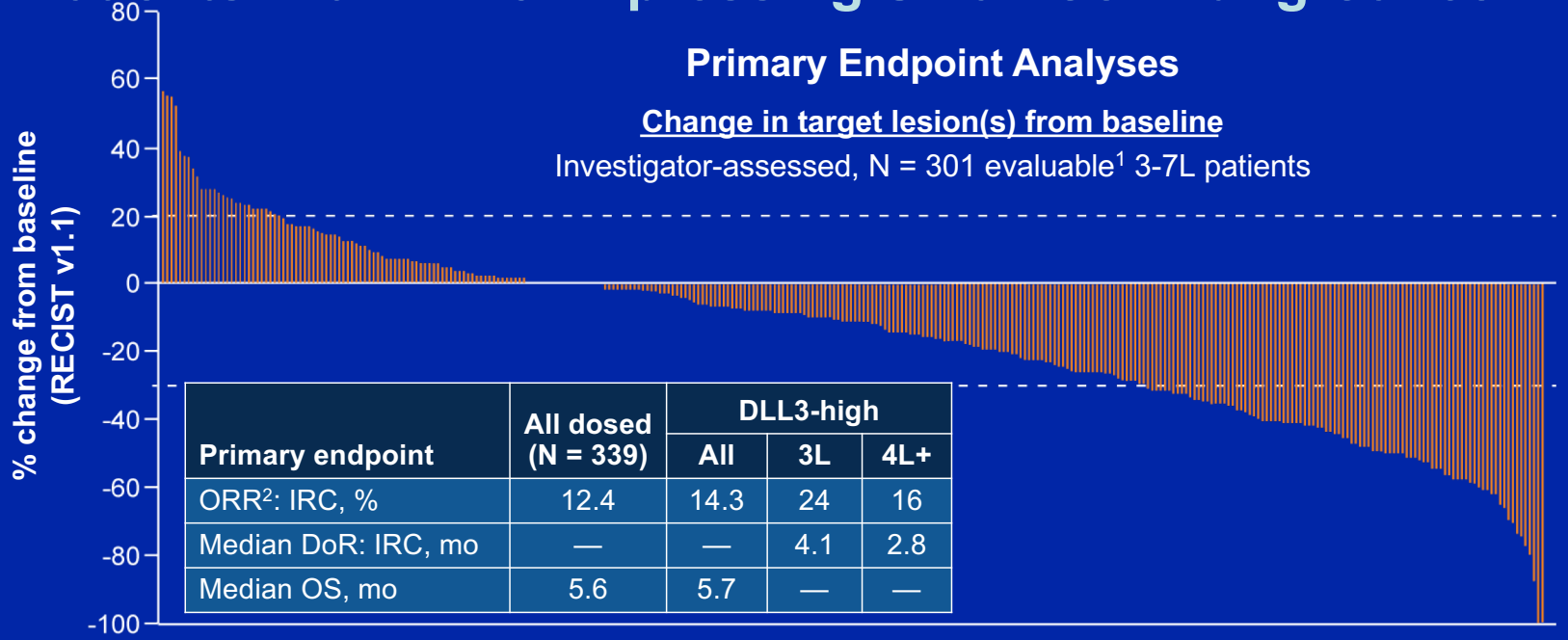
The recommended dose and schedule of nivolumab for this indication is 240 mg every 2 weeks over 30 minutes."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617370.htm

Efficacy and Safety of Rovalpituzumab Tesirine in Patients with DLL3-Expressing, ≥3rd Line Small Cell Lung Cancer: Results from the Phase 2 TRINITY Study

Carbone DP et al.
Proc ASCO 2018;Abstract 8507.

TRINITY: Phase II Results of Rovalpituzumab Tesirine in Patients with DLL3-Expressing Small Cell Lung Cancer



Primary endpoint	All dosed (N = 339)	DLL3-high		
		All	3L	4L+
ORR[2]: IRC, %	12.4	14.3	24	16
Median DoR: IRC, mo	—	—	4.1	2.8
Median OS, mo	5.6	5.7	—	—

[1] Patients who had a baseline scan and at least 1 follow-up scan with an evaluable response; [2] Confirmed CR + PR per RECIST v1.1

- Adverse events were generally manageable. However, important identified risks were pleural/pericardial effusion, edema and photosensitivity.

Carbone DP et al. *Proc ASCO* 2018;Abstract 8507.