Νεότερα στοιχεία στη θεραπεία του καρκίνου του πνεύμονα

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Lung Cancer Remains Major Global Health Burden

* Lung cancer is one of the most common cancers and the leading cause of cancer deaths worldwide
  * **New cases:** US **234.030** in 2018 Global **1.8M** in 2012
  * **Deaths:** US **154.050** in 2018 Global **1.7M** in 2015
* **5-year US survival rates**
  * Overall: **18.6%**
  * Metastatic: **4.7%**
* **NSCLC is 80% to 85% of lung cancers**

Biopsy: Establish Diagnosis, Determine Histologic Subtype, Biomarker Testing

* Histologic subtyping
  * Squamous or nonsquamous?
* **For molecular testing:**
  * Primary tumors and metastatic lesions equally suitable
  * Bone biopsy suboptimal due to decalcification and degradation of DNA
  * Liquid biopsies (cell-free DNA in plasma) when tissue not available

- Determination of *EGFR* and *BRAF* V600E mutations, *ALK* and *ROS1* rearrangements indicated in all nonsquamous cancers
- For squamous NSCLC, consider molecular testing in young, never, or light smokers or if biopsy specimen is small or has mixed histology
- Determination of PD-L1 expression indicated in all NSCLC

Recent Developments With Immunotherapy for Patients With Advanced NSCLC

AACR American Association for Cancer Research
ANNUAL MEETING
2017 WASHINGTON, DC

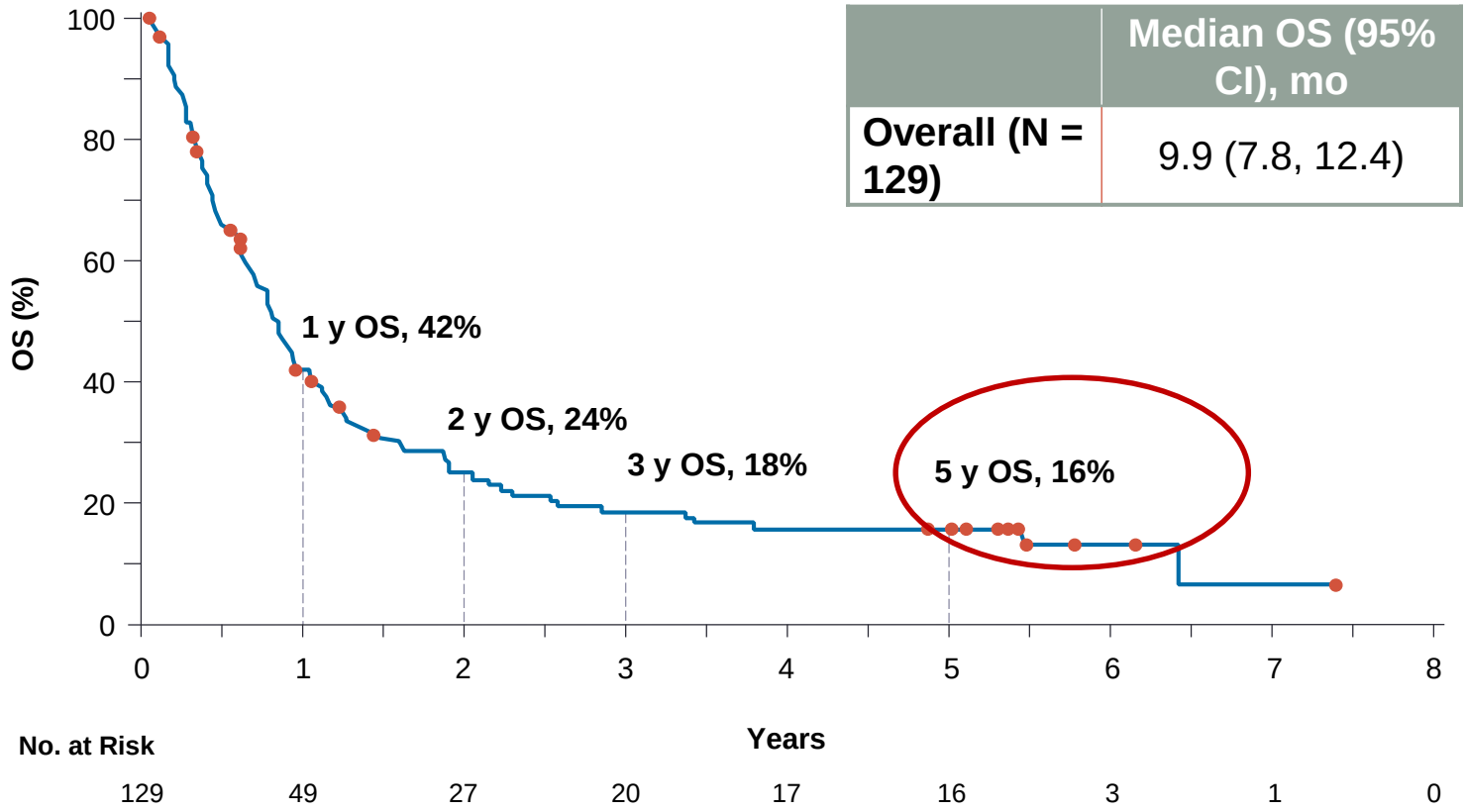
Five-Year Follow-up From the CA209-003 Study of Nivolumab in Previously Treated Advanced Non-Small Cell Lung Cancer: Clinical Characteristics of Long-term Survivors

Julie Brahmer,[1] Leora Horn,[2] David Jackman,[3] David Spigel,[4] Scott Antonia,[5] Matthew Hellmann,[6] John Powderly,[7] Rebecca Heist,[8] Lecia Sequist,[8] David C. Smith,[9] Philip Leming,[10] William J. Geese,[11] Dennis Yoon,[11] Ang Li,[11] Scott Gettinger[12]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [5]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Carolina BioOncology Institute, Huntersville, NC, USA: [8]Massachusetts General Hospital, Boston, MA, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]The Christ Hospital Cancer Center, Cincinnati, OH, USA; [11]Bristol-Myers Squibb, Princeton, NJ, USA; [12]Yale Cancer Center, New Haven, CT, USA

5-Year Estimates of OS[a]
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

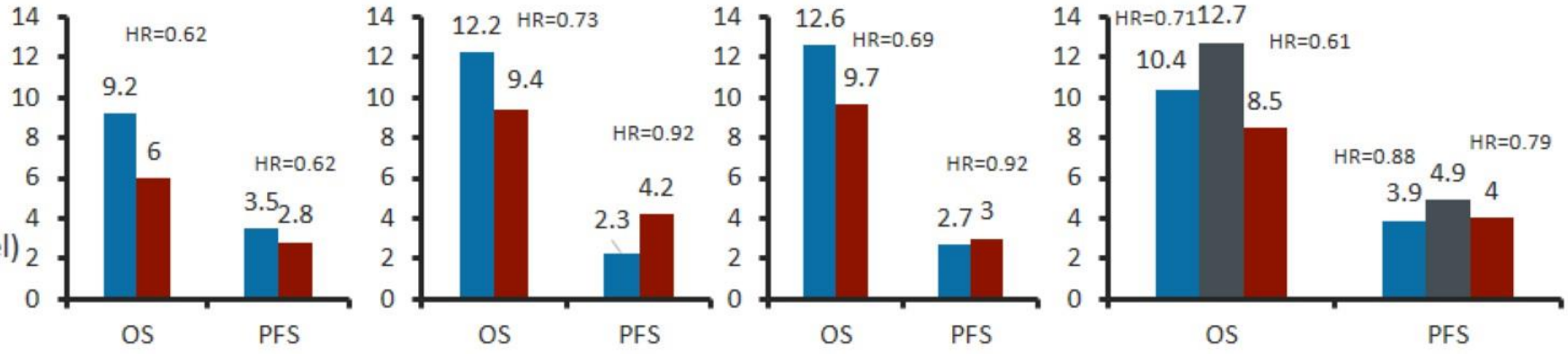


[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Immune Checkpoint Inhibitors in NSCLC

	CheckMate 017[a] Nivolumab vs docetaxel N=272	CheckMate 057[b] Nivolumab vs docetaxel N=582	Poplar[c] Atezolizumab vs docetaxel N=287	KEYNOTE-010[d] Pembrolizumab vs docetaxel N=1034
Histology	Squamous: 100%	Nonsquamous: 100%	Squamous: 34% Nonsquamous: 66%	PD-L1≥1% Squamous: 21% Nonsquamous: 70%

OS and PFS (HR vs docetaxel)

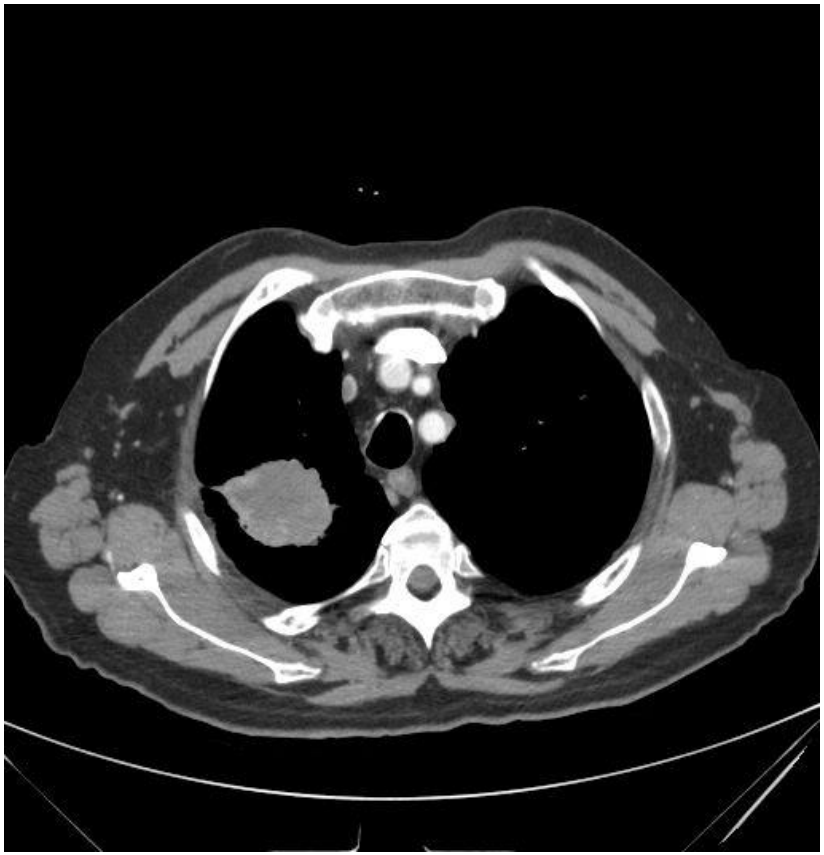


ORR	20%	9%	20%	9%	19%	12%	18%	18%	9%
G3-≥4 AEs	8%	56%	10%	54%	12%	40%	13%	16%	35%

a. Brahmer J, et al. *N Engl J Med.* 2015;373:123-135; b. Borghaei H, et al. *N Engl J Med.* 2015;373:1627-1639; c. Fehrenbacher L, et al. *Lancet.* 2016;387:1837-1846; d. Herbst RB, et al. *Lancet*. 2016;387:1540-1550.

Medscape EDUCATION

adeno-ca nivolumab 3rd line



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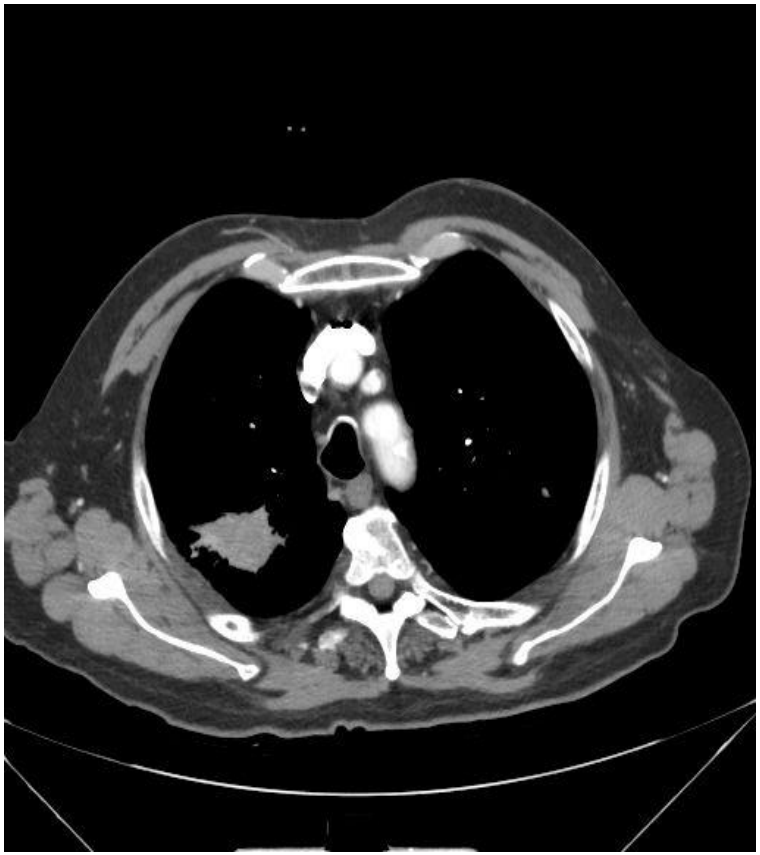

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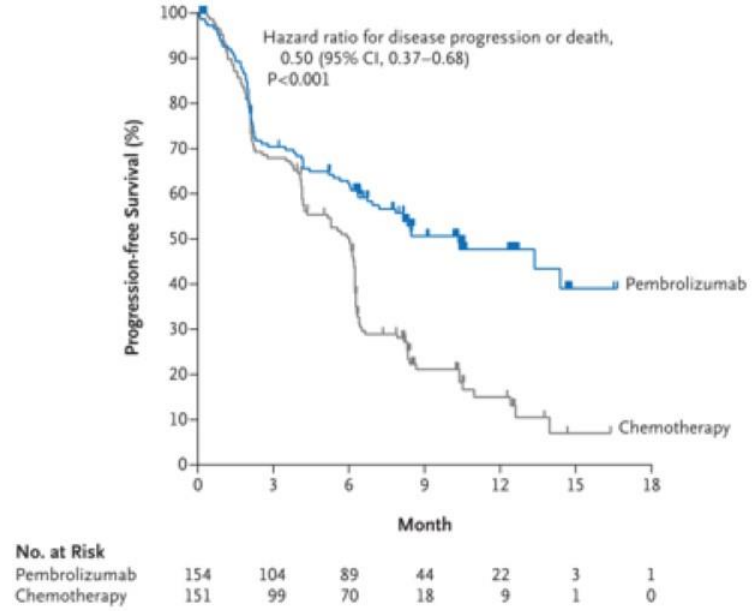
KEYNOTE-024: Pembrolizumab

Phase 3 trial in patients with and no previous systemic therapy for metastatic disease

- PD-L1 expression of ≥50%

Pembrolizumab vs chemotherapy demonstrated:

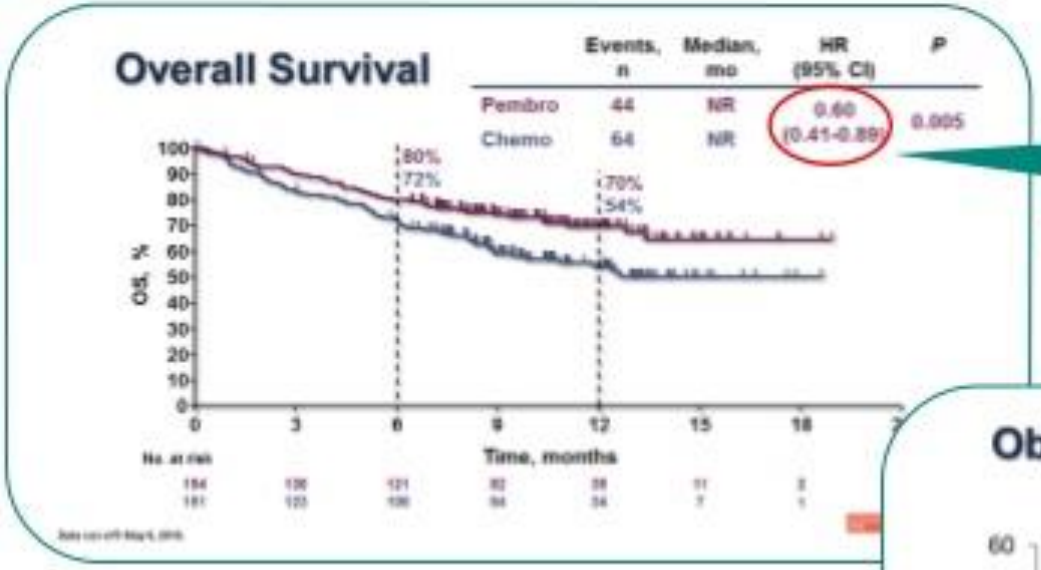
- Longer median PFS (10.3 vs 6.0 mo)
- Improved 6-mo OS (80.2% vs 72.4%, *P* =.005
- Increased ORR (44.8% vs 27.8%)
- Fewer TRAEs
  - Any grade (73.4% vs 90.0%)
  - Grade 3-5 (26.6% vs 53.3%)



From *N Engl J Med*, Reck M, et al., Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer, 375., 1823-1833. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

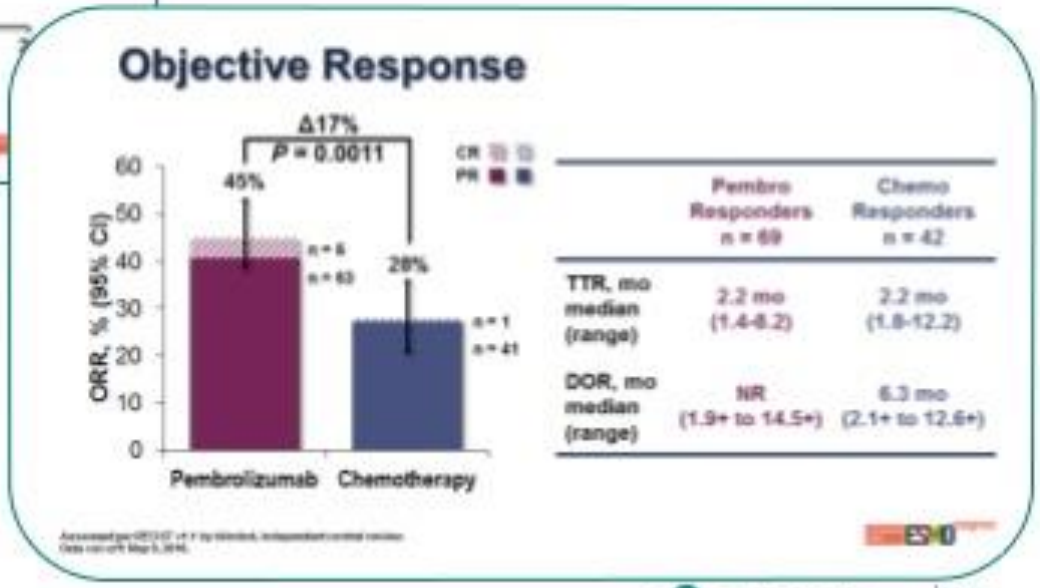
Reck M, et al. *N Engl J Med.* 2016;375:1823-1833.

KEYNOTE-024 Overall Survival and Objective Response



40% risk reduction of death

50% crossover in ITT population
54% crossover excluding ongoing pts



MERCK Be well 125 YEARS

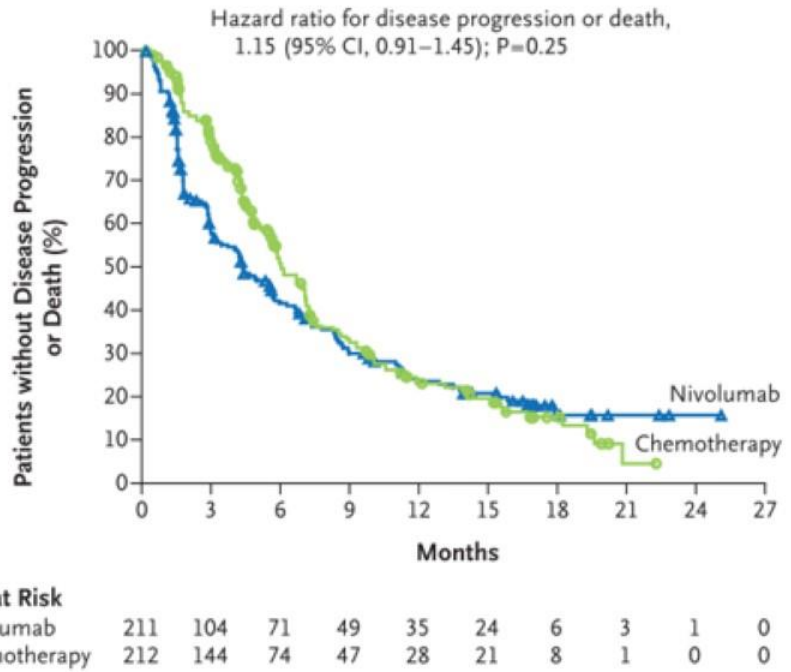
CheckMate 026: Nivolumab

Phase 3 trial in patients with no previous systemic therapy for advanced or metastatic disease

- PD-L1 expression of ≥1% (primary analysis of patients with ≥5%)

Nivolumab vs chemotherapy demonstrated:

- Similar PFS (4.2 mo vs 5.9 mo)
- Similar OS (14.4 mo vs 13.2 mo, HR = 1.02)
- Decreased ORR (26% vs 33%)
- Similar time to response (2.8 mo vs 2.6 mo)
- Longer DoR (12.1 mo vs 5.7 mo)
- Fewer TRAEs
  - Any grade: 71% vs 92%
  - Grade 3/4: 18% vs 51%



From *N Engl J Med*, Carbone DP, et al., First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer, 376., 2415-2426. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Carbone DP, et al. *N Engl J Med.* 2017;376:2415-2426.

Why Combine Chemotherapy With Immunotherapy?

* Cytotoxic agents enhance antigen presentation and immunogenic cell death[1]
* Chemotherapy disrupts immune evasion mechanisms in the tumor microenvironment[2,3]
* Dose, schedule, and drug dependent[4,5]

1. Zitvogel L, et al. Immunity. 2013;39:74-88. 2. Mouw KW, et al. Cancer Discov. 2017;7:675-693.
3. Fukumura D, et al. Nat Rev Clin Oncol. 2018;15:325-340. 4. Emens LA, et al. Curr Opin Mol Ther. 2001;3:77-84.
5. Chen G, Emens LA. Cancer Immunol Immunother. 2013;62:203-216.

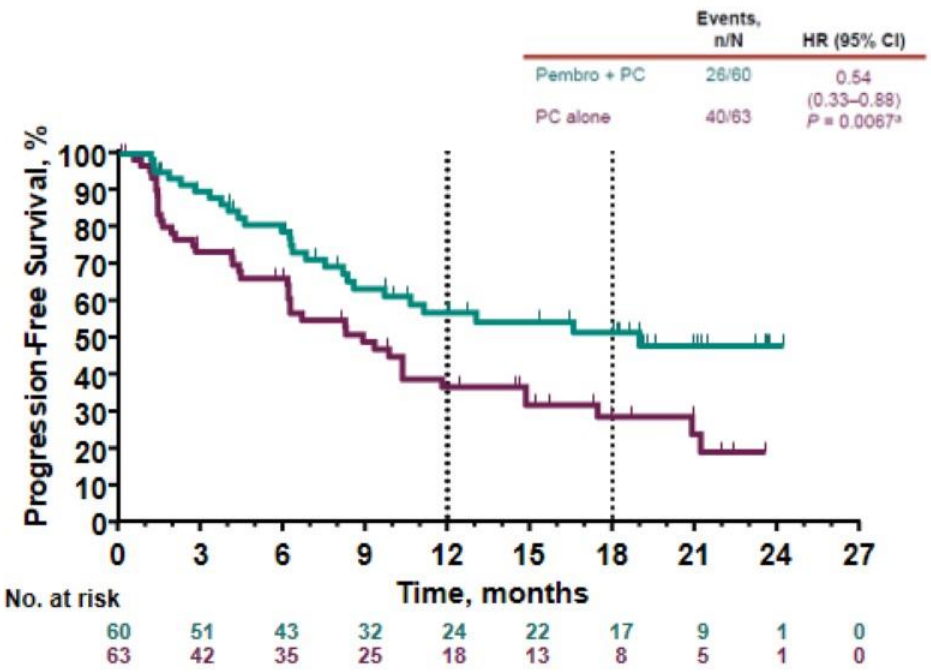
KEYNOTE-021 Cohort G: Pembrolizumab + Chemotherapy

Phase 1/2 trial in patients without *EGFR* mutations or *ALK* translocations

- Non-SCC histology only
- Median follow-up: 18.7 mo

Combination vs chemotherapy shows:

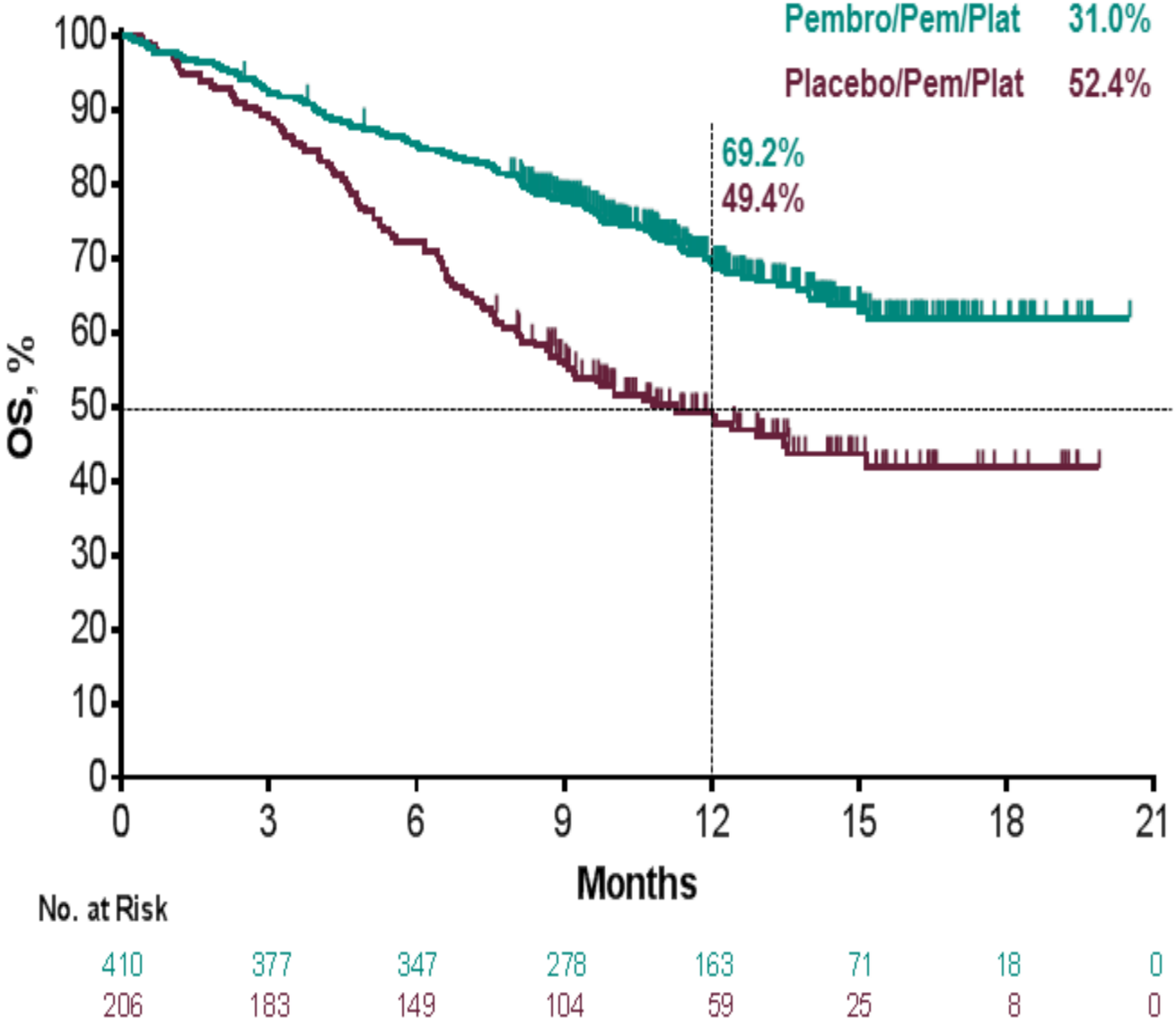
- Longer mPFS (19.0 vs 8.9 mo)
- Nonsignificant increase in mOS (NR [22.8, NR] vs 20.9 mo [14.9, NR])
- Greater ORR (56.7% vs 31.7%)
- Similar duration of response (medians NR)
- More frequent TRAEs
  - Any grade: 93% vs 92%
  - Grade 3/5: 41% vs 29%



Borghaei H, et al. ESMO 2017. Reproduced with permission from Hossein Borghaei.

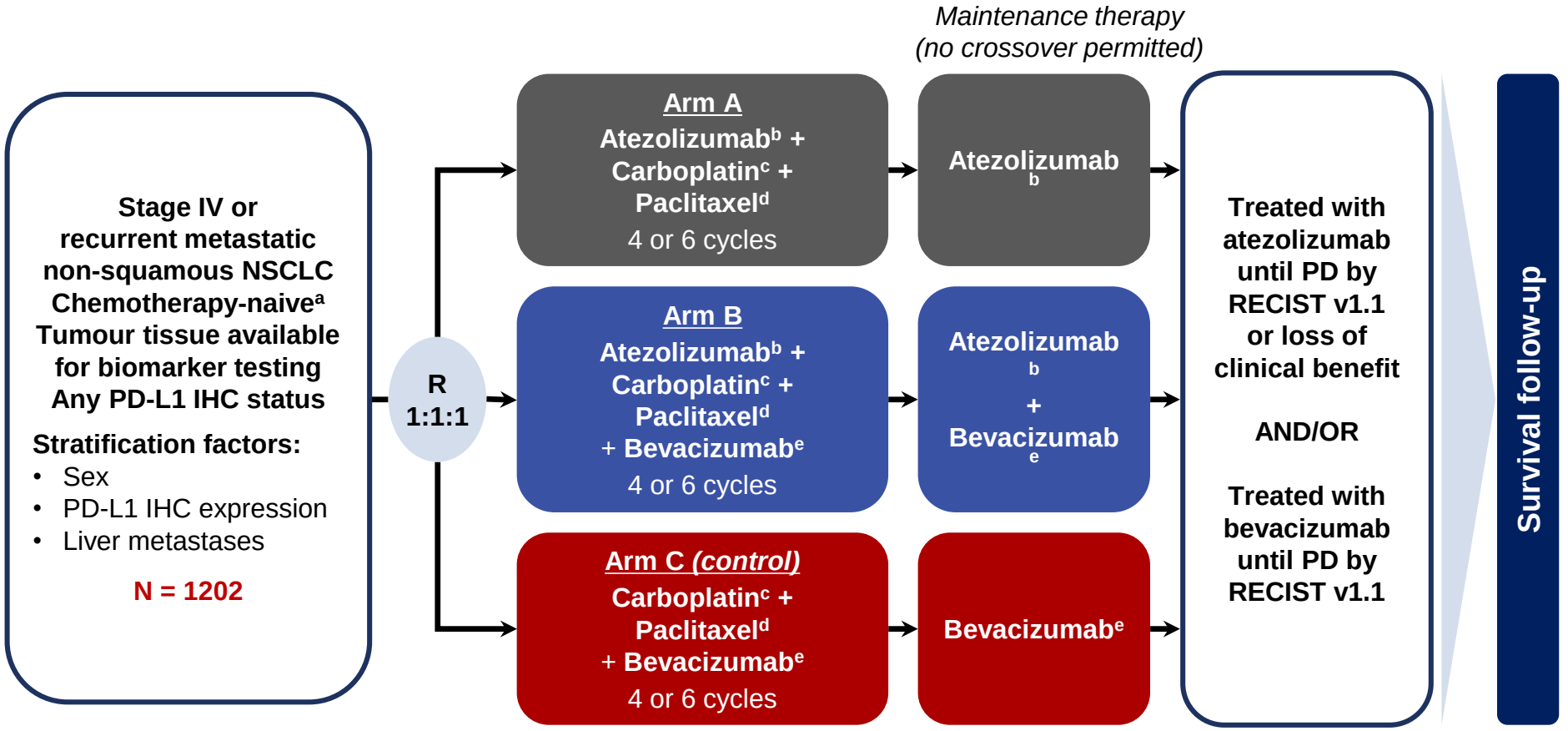
Borghaei H, et al. ESMO 2017.

Overall Survival, ITT



Data cutoff date: Nov 8, 2017.

IMpower150 study design



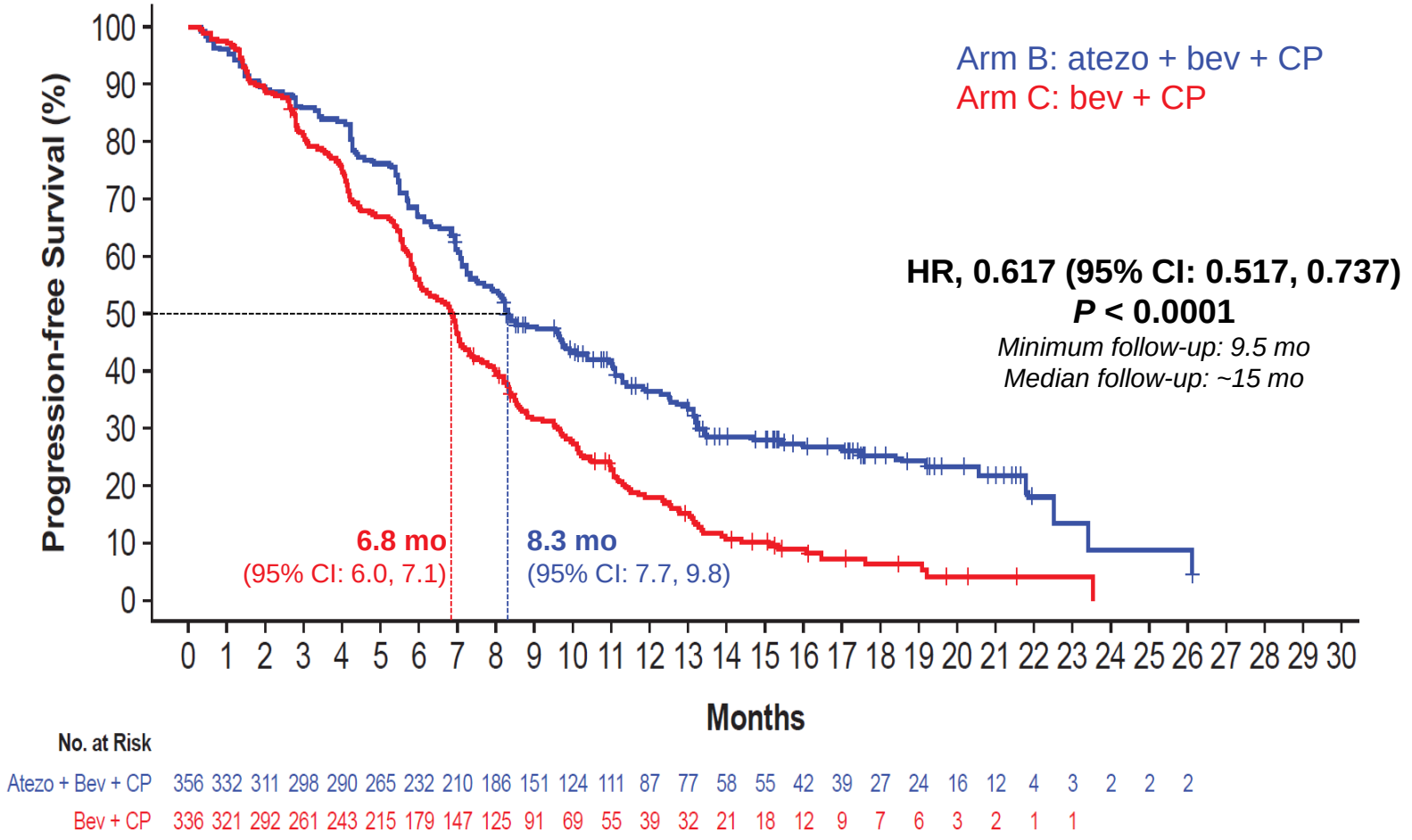
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

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

Reck M, et al. IMpower150 PFS analysis.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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

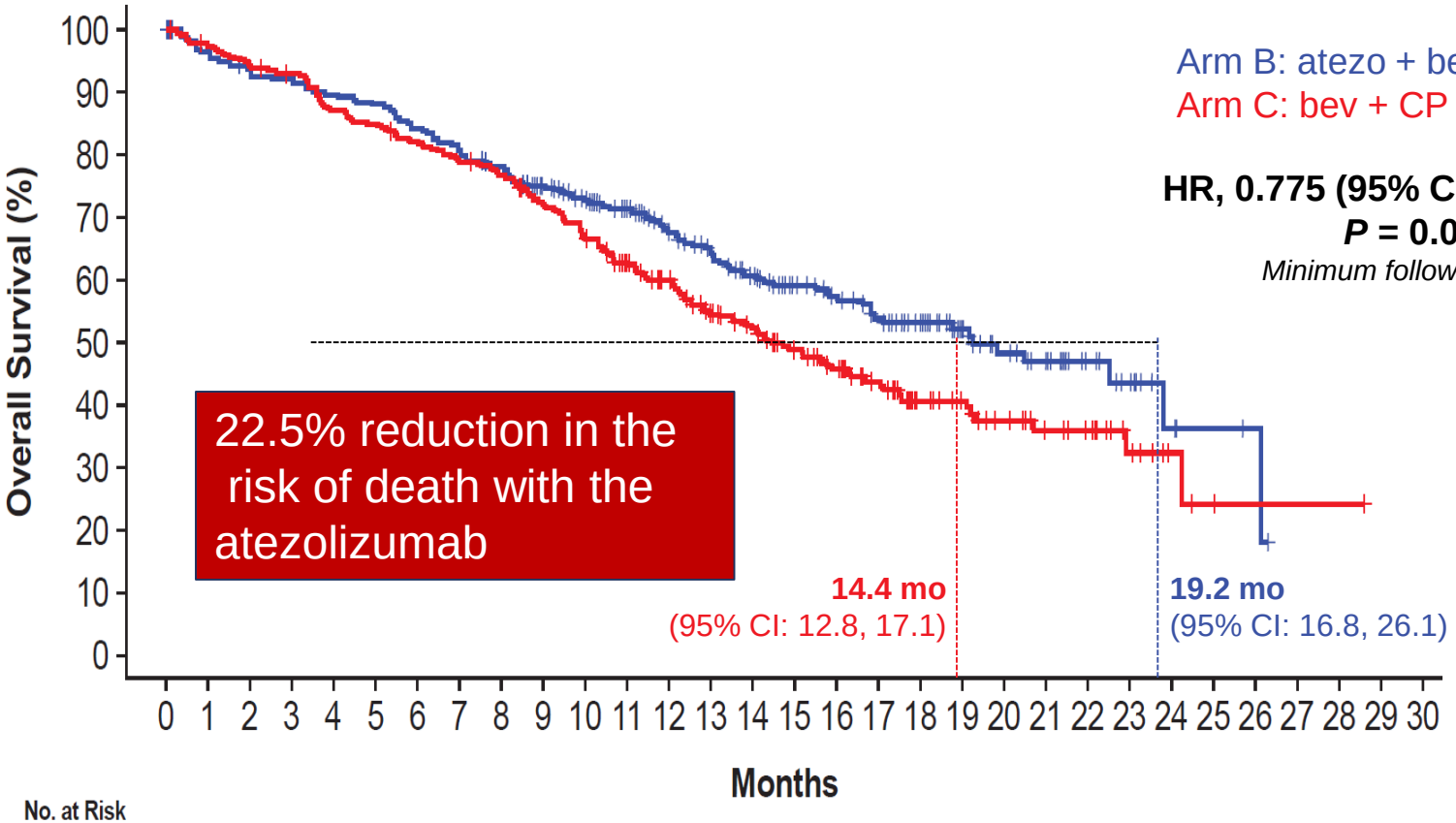


INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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



No. at Risk

Atezo + Bev + CP	356	337	326	321	312	308	294	282	269	248	221	197	169	147	126	111	93	74	64	44	35	28	17	11	5	3	2
Bev + CP	336	323	312	305	285	278	266	253	245	222	186	157	140	120	108	88	75	61	43	38	29	21	17	9	4	2	1	1	1

Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Safety summary

	Arm A: atezo + CP (n = 400)	Arm B: atezo + bev + CP (n = 393)	Arm C (*control*): bev + CP (n = 394)
Median doses received (range), n			
Atezolizumab	10 (1-37)	12 (1-38)	NA
Bevacizumab	NA	10 (1-38)	8 (1-33)
All cause AE, n (%)	389 (97%)	385 (98%)	390 (99%)
Grade 3-4	226 (57%)	242 (62%)	230 (58%)
Grade 5	10 (3%)	23 (6%)	21 (5%)
Treatment-related AE, n (%)	372 (93%)	371 (94%)	376 (95%)
Grade 3-4	170 (43%)	219 (56%)	188 (48%)
Grade 5[a]	3 (1%)	11 (3%)	9 (2%)
Serious AE, n (%)	155 (39%)	165 (42%)	134 (34%)
Treatment-related serious AE	77 (19%)	100 (25%)	76 (19%)
AEs of special interest, n (%)[b]	184 (46%)	199 (51%)	108 (27%)
Grade 3-4	37 (9%)	45 (11%)	13 (3%)
Grade 5	2 (1%)	0	0
AE leading to withdrawal from any treatment	56 (14%)	128 (33%)	98 (25%)
AE leading to dose interruption or modification	203 (51%)	235 (60%)	189 (48%)

[a] Including fatal haemorrhagic AEs: Arm C: haemoptysis n = 1, pulmonary haemorrhage n = 2; Arm B haemoptysis n = 3, pulmonary haemorrhage n = 2, haemorrhage intracranial n = 1; Arm A: haemoptysis n = 1, haemorrhage intracranial n = 1.
[b] Investigator text for AEs encoded using MedDRA v20.1.

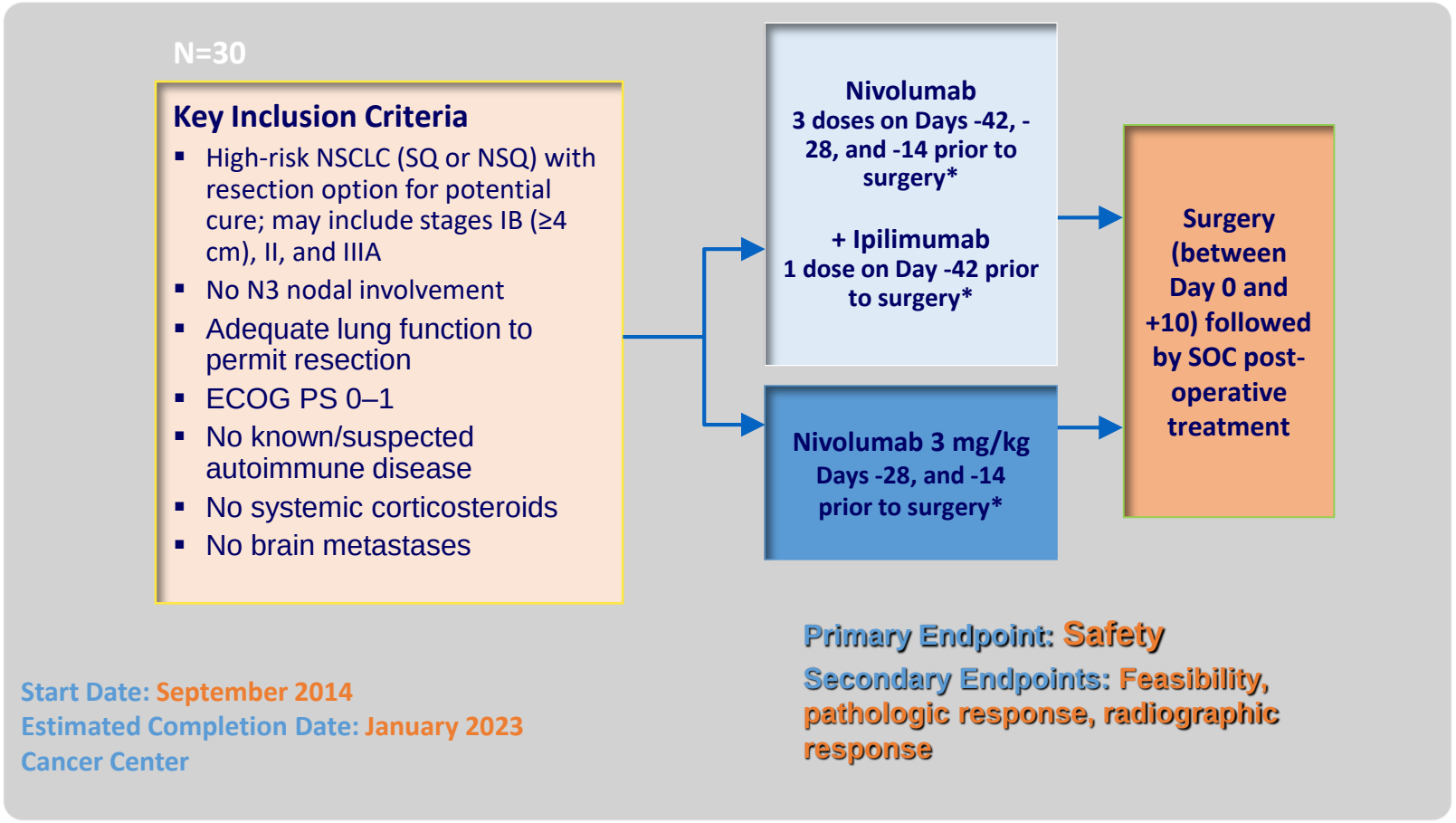
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

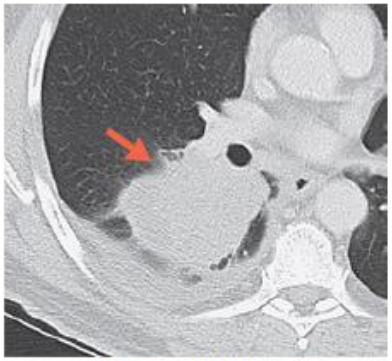
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NCT02259621: Nivolumab With or Without Ipilimumab

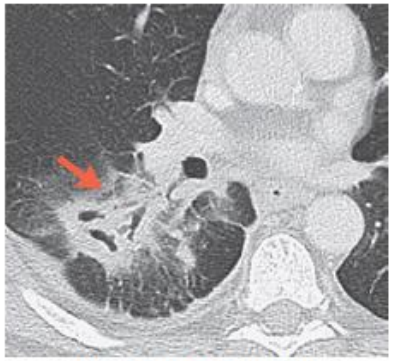
A phase 2 trial to evaluate nivolumab alone or nivolumab plus ipilimumab as neoadjuvant therapy for early stage, resectable NSCLC



Chaft JE et al. ASCO 2017- AACR 2018

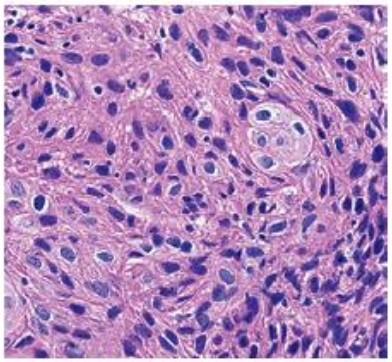


Pretreatment Imaging

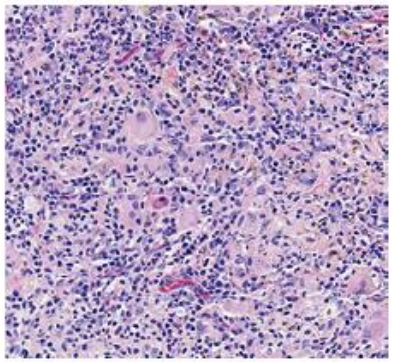


Week 4 (before surgery)

Chest-CT of a 62-year-old male smoker
with stage IIB squamous lung cancer before and after the administration of nivolumab
35% shrinkage with associated tumor cavitation

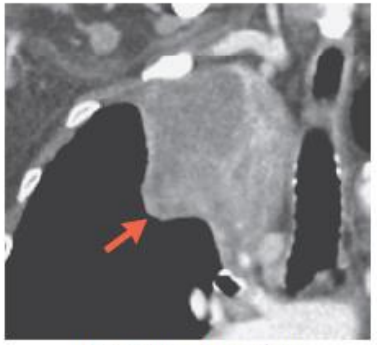


Pretreatment Tumor Biopsy

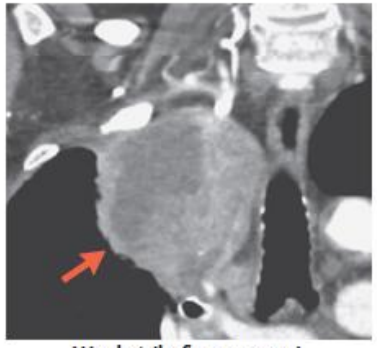


Resection Specimen

100% pathological regression of the primary tumor
but had residual lymph-node metastases
in the resection specimen



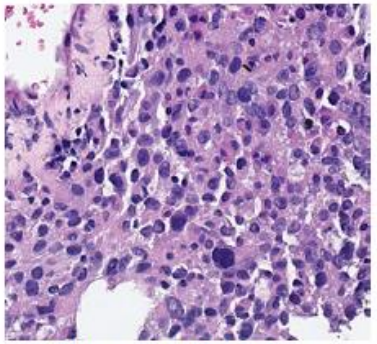
Pretreatment Imaging



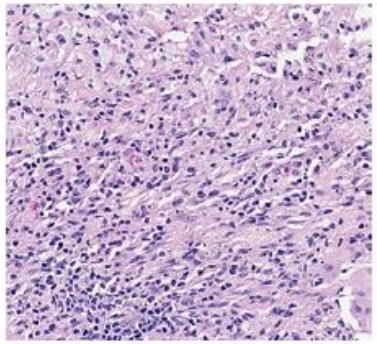
Week 4 (before surgery)

Chest-CT of a 78-year-old female former smoker with stage IIIA lung adeno-ca

in the post-treatment specimen
there was 90% tumor regression.



Pretreatment Tumor Biopsy



Resection Specimen

MADRID 2017 ESMO congress

PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

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

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

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

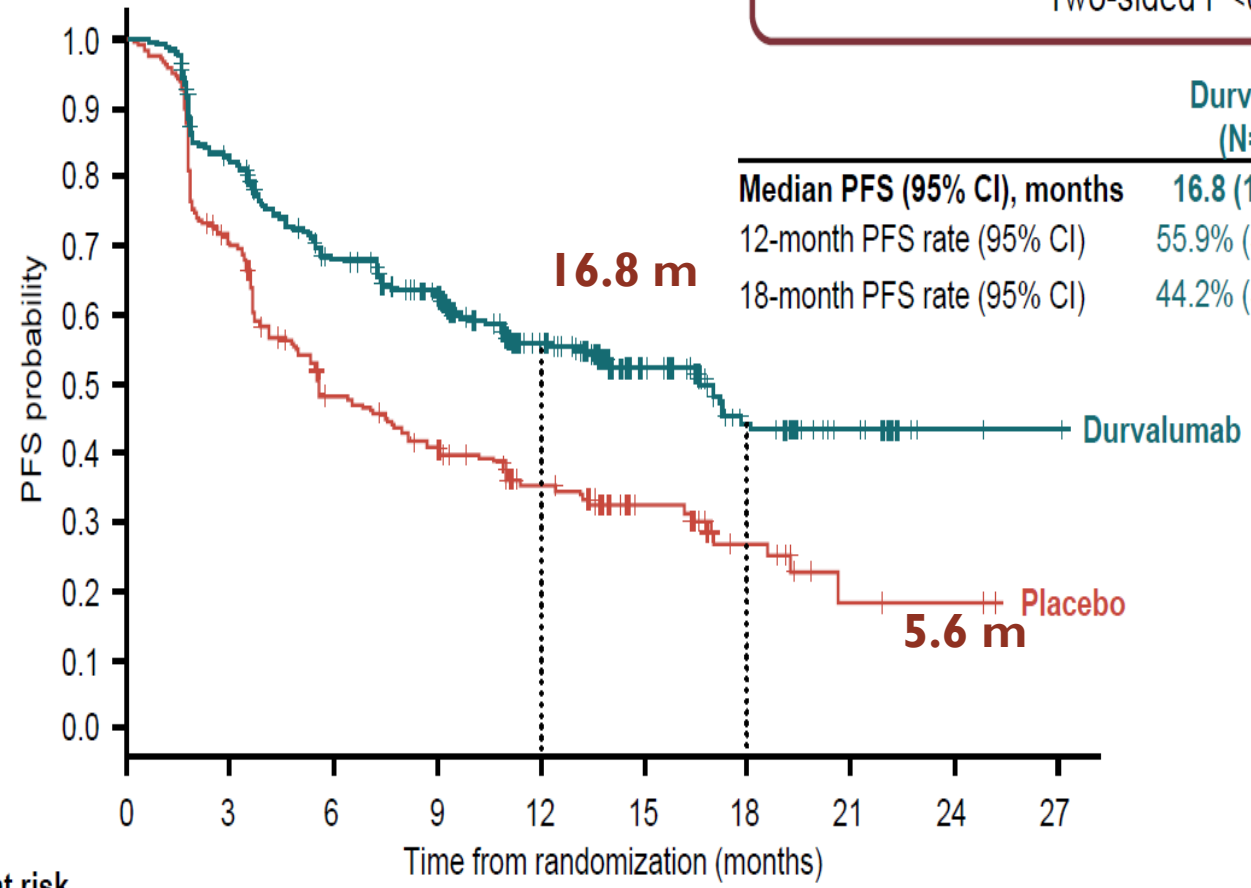
*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.

ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

PFS by BICR (Primary Endpoint; ITT)

Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)
Two-sided P<0.0001

	Durvalumab (N=476)	Placebo (N=237)
Median PFS (95% CI), months	**16.8 (13.0–18.1)**	**5.6 (4.6–7.8)**
12-month PFS rate (95% CI)	55.9% (51.0–60.4)	35.3% (29.0–41.7)
18-month PFS rate (95% CI)	44.2% (37.7–50.5)	27.0% (19.9–34.5)

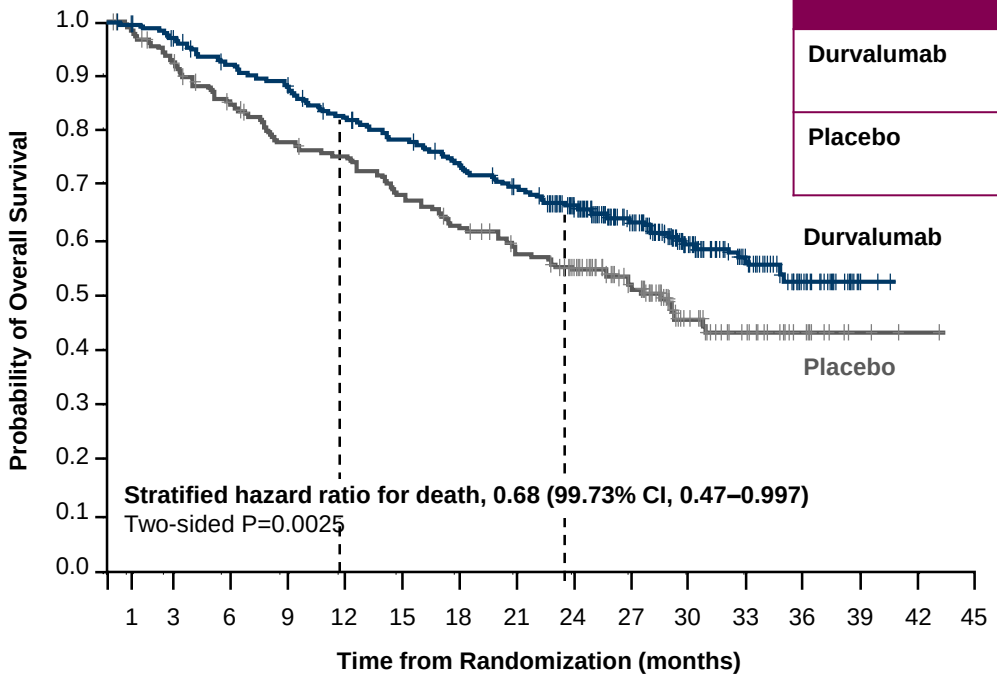


No. at risk									
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

PACIFIC: Overall Survival – in the ITT Population[a,b]

	No. of events / No. of patients	Median OS (95% CI), months	12-mo OS (95% CI) %	24-mo OS (95% CI) %
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)

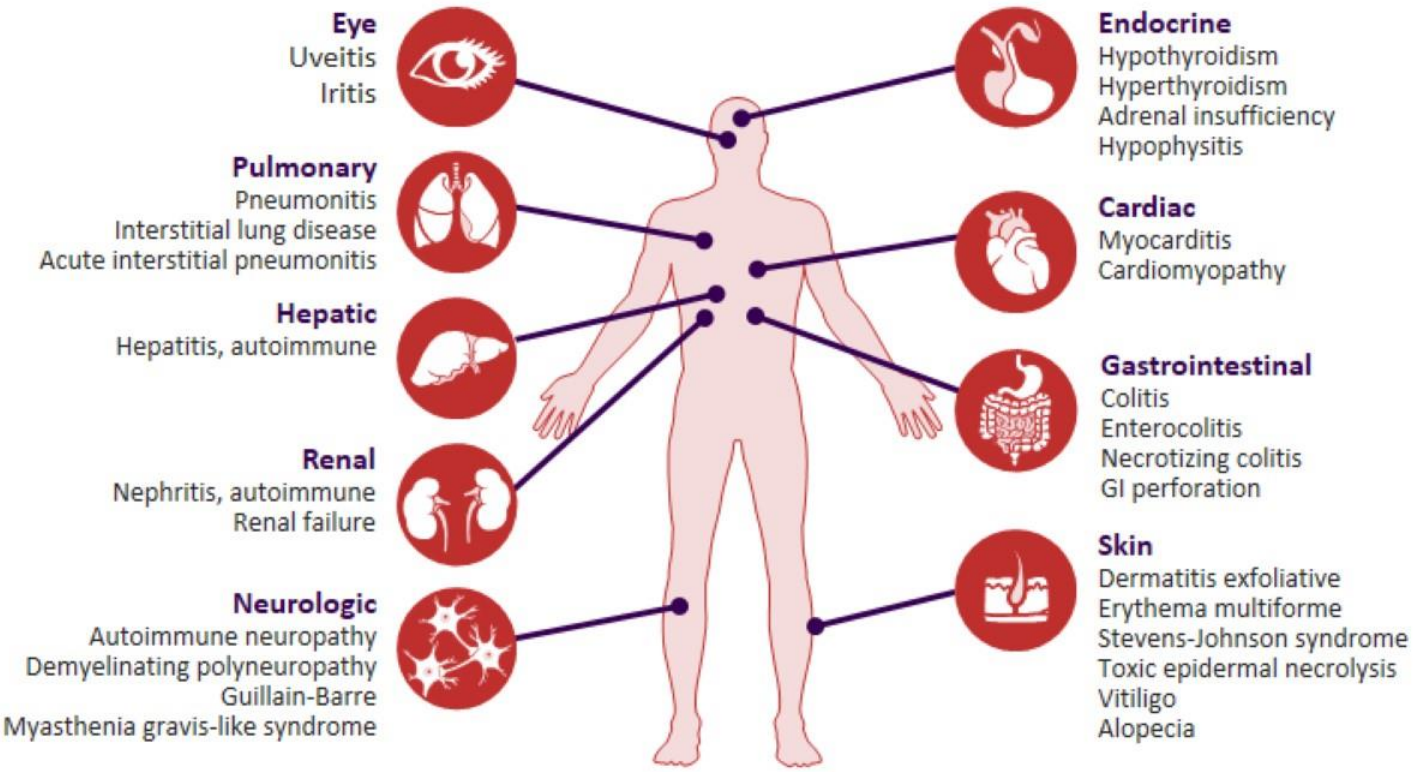


No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

ITT = intent to treat; ; mo = months; NR = not reached; OS = overall survival
[a]Median duration of follow-up for OS was 25.2 months (range 0.2-43.1).
[b]Data cutoff for the first planned OS interim analysis occurred after 299 events (61% of the target 491 events).

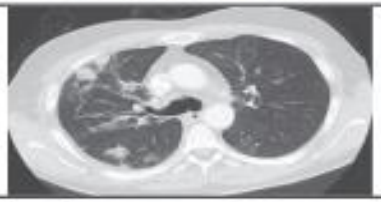
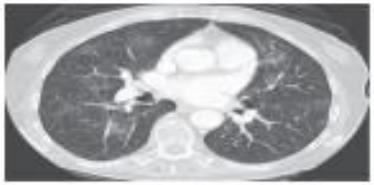
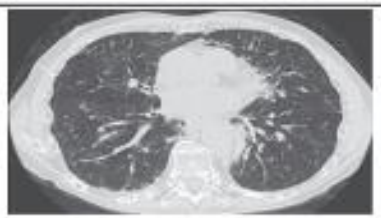
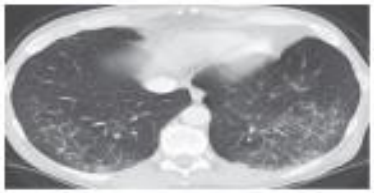
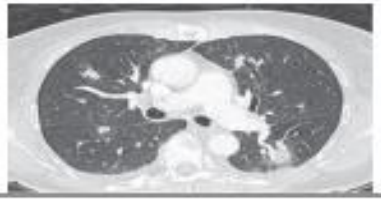
1.Antonia SJ, et al. Article and supplementary appendix online ahead of print. *N Eng J Med*. 2018.

The Breadth of imAEs



Champiat S, et al. *Ann Oncol*. 2016;27:559-574; Friedman CF, et al. *JAMA Oncol*. 2016;2:1346-1353.

Pneumonitis With Anti–PD-1/PD-L1 Therapy

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

NSCLC landscape

- New therapeutic options for patients with advanced NSCLC
- 1st L
  - Pembrolizumab in patients with PD-L1 ≥ 50%
  - Pembrolizumab + Platinum-based CMT (PD-L1 ≥1%)
  - Atezolizumab +Platinum-based CMT + bevacizumab
  - Targeted therapies (patients with *EGFR* mutation or *ALK* rearrangement)

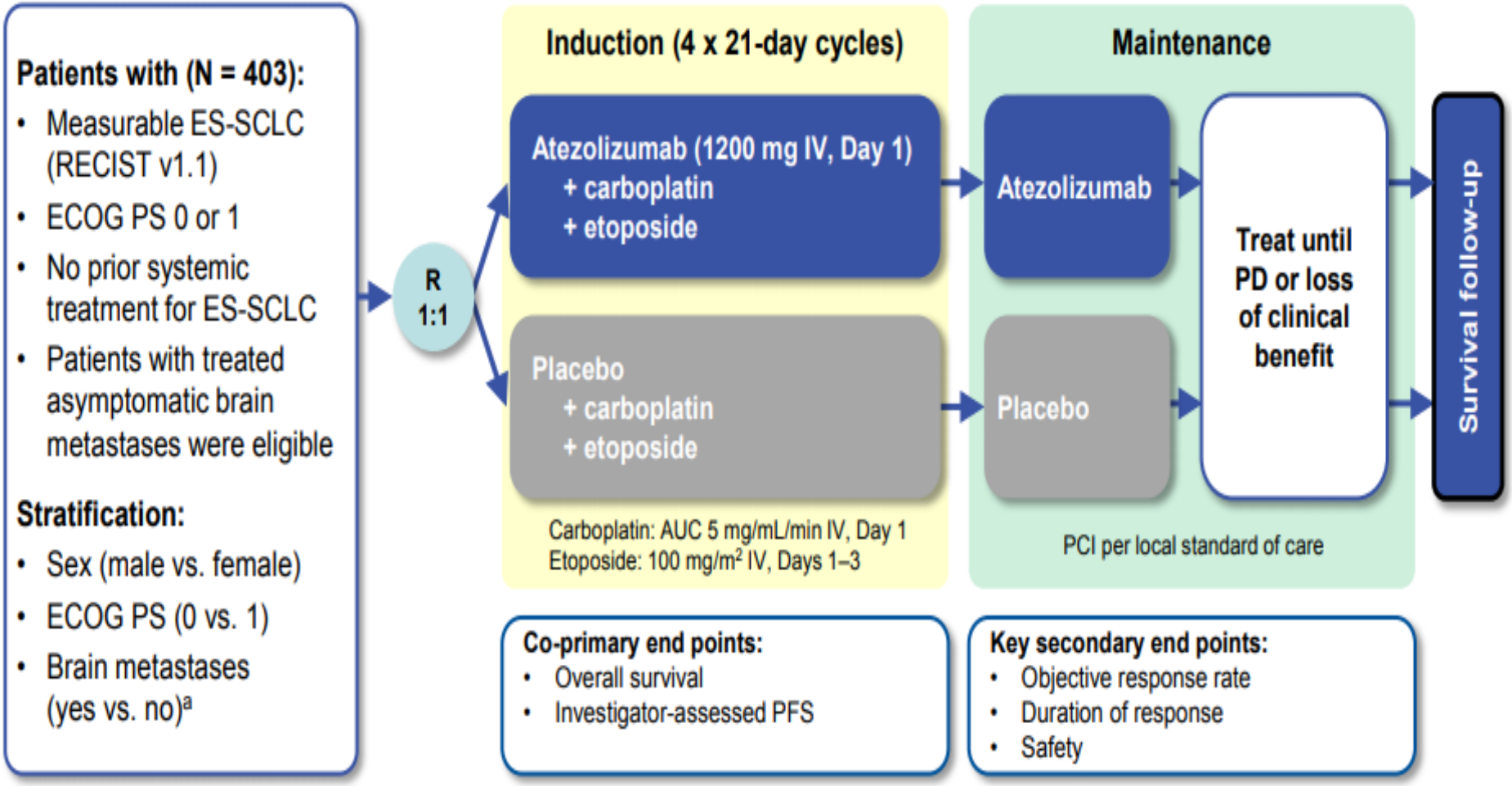
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

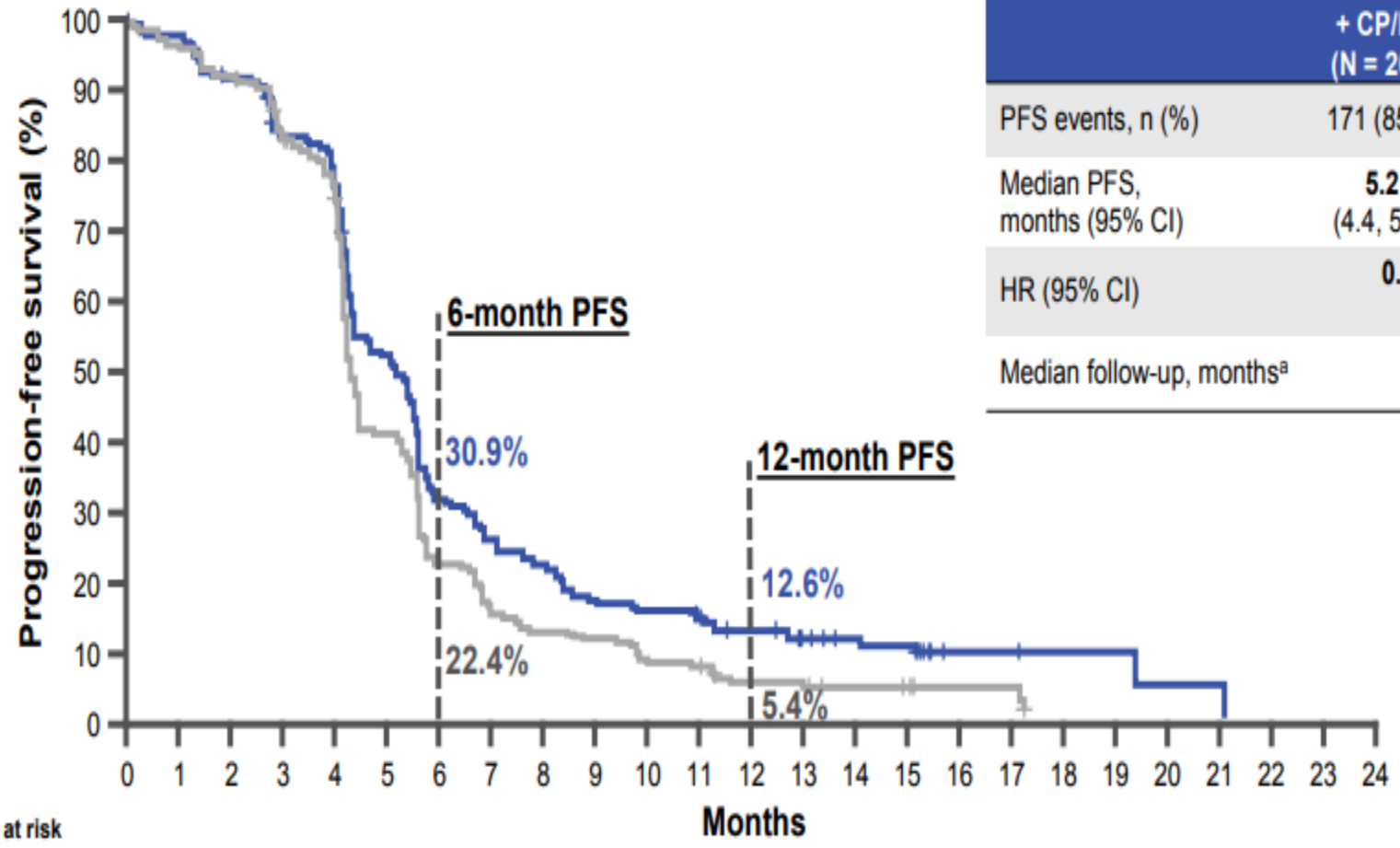
Leora Horn, M.D., Aaron S. Mansfield, M.D., Aleksandra Szczęsna, M.D., Libor Havel, M.D., Maciej Krzakowski, M.D., Ph.D., Maximilian J. Hochmair, M.D., Florian Huemer, M.D., György Losonczy, M.D., Ph.D., Melissa L. Johnson, M.D., Makoto Nishio, M.D., Ph.D., Martin Reck, M.D., Tony Mok, M.D., Sivuonthanh 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*

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.

Investigator-assessed progression-free survival

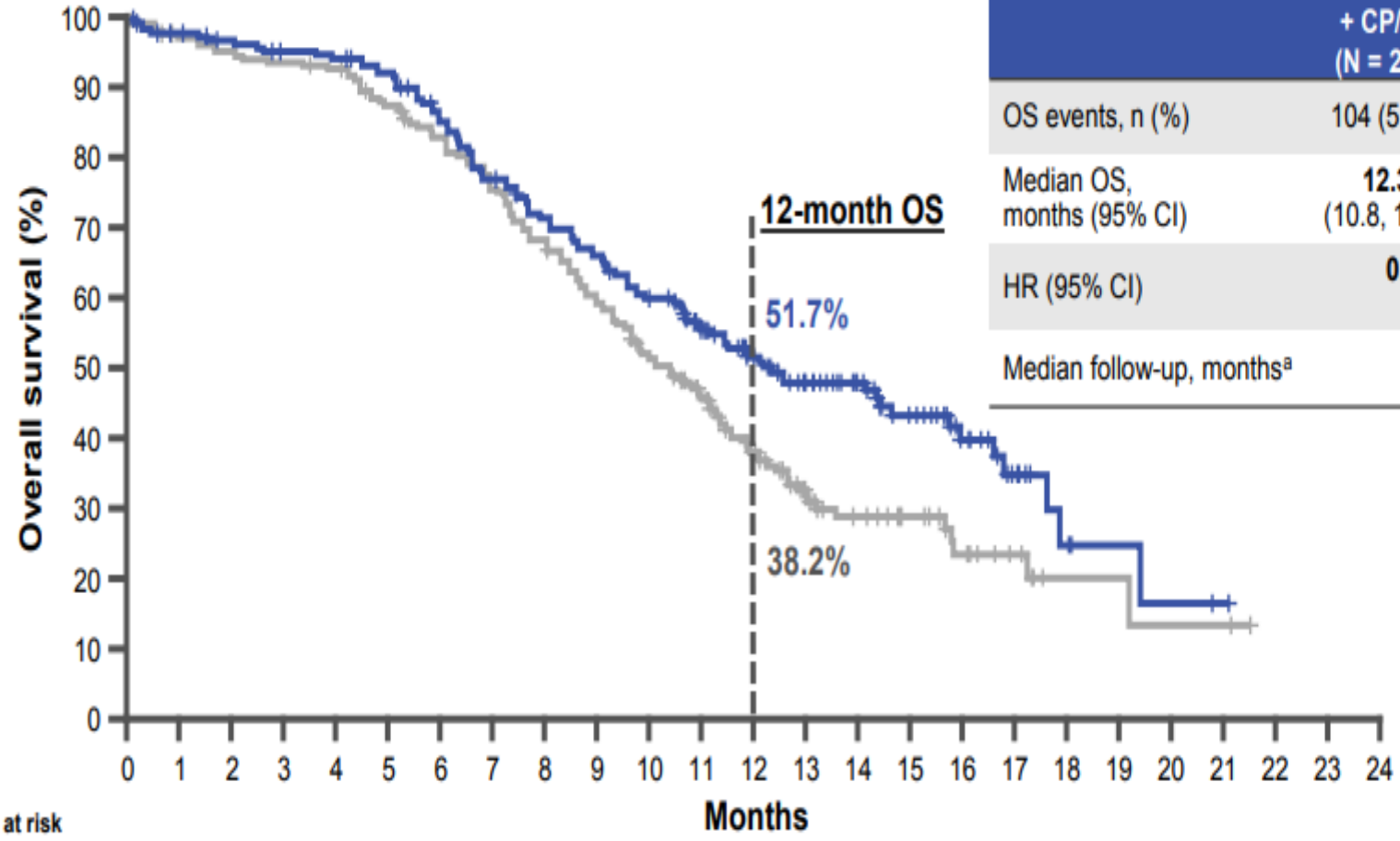


	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

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.

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.

Safety summary

Patients — no. (%)	Atezolizumab + CP/ET (N = 198)	Placebo + CP/ET (N = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	133 (67.2)	125 (63.8)
Treatment-related AEs[a]	188 (94.9)	181 (92.3)
Serious AEs	74 (37.4)	68 (34.7)
Immune-related AEs	79 (39.9)	48 (24.5)
AEs leading to withdrawal from any treatment[a]	22 (11.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	21 (10.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 21)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 30)
  - Chemotherapy: 4 doses for carboplatin; 12 doses for etoposide (same for both treatment groups)

Clinical data cutoff date: April 24, 2018. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.
[a] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component. AE, adverse event.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