Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, January 11, 2020, 8:00 AM – 4:00 PM
Houston, Texas

Faculty

Tanios Bekaii-Saab, MD
Johanna Bendell, MD
Bruce D Cheson, MD
Robert L Coleman, MD
Charles G Drake, MD, PhD
Harry P Erba, MD, PhD
Erika Hamilton, MD
Sara Hurvitz, MD
Mark Levis, MD, PhD
Stephen V Liu, MD, PhD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
Philip A Philip, MD, PhD, FRCP
Gregory J Riely, MD, PhD
Sonali M Smith, MD

Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Cheson, Nastoupil and Smith*

Module 2 — Breast Cancer: *Drs Hamilton and Hurvitz*

Module 3 — Acute Leukemias: *Drs Erba and Levis*

Module 4 — Gastrointestinal Cancers: *Drs Bekaii-Saab, Bendell and Philip*

Module 5 — Genitourinary Cancers: *Drs Drake and Oh*

Module 6 — Lung Cancer: *Drs Liu and Riely*

Module 7 — Gynecologic Cancers: *Drs Coleman and Moore*

Stephen V Liu, MD, PhD
Associate Professor of Medicine
Georgetown University Hospital
Washington, DC

Disclosures

Advisory Committee	Apollomics Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, G1 Therapeutics, Genentech, Heron Therapeutics, Ignyta Inc, Janssen Biotech Inc, Lilly, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc, Takeda Oncology
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Data and Safety Monitoring Board/Committee	Taiho Oncology Inc

Gregory J Riely, MD, PhD
Associate Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Disclosures

Contracted Research	Merck, Mirati Therapeutics, Novartis, Pfizer Inc, Roche Laboratories Inc, Takeda Oncology

Lung Cancer — Drs Liu and Riely

Targeted Therapy in NSCLC

Immune Checkpoint Inhibitors (ICIs) in Patients with Locally Advanced NSCLC

ICIs in Patients with SCLC

Integration of ICIs into Therapy for Metastatic NSCLC

Targetable Oncogenic Drivers

EGFR sensitizing
- Gefitinib[4]
- Erlotinib[4]
- Afatinib[4]
- Osimertinib[4]
- Necitumumab[4]
- Rociletinib[3]

ALK
- Crizotinib[4]
- Alectinib[4]
- Ceritinib[4]
- Lorlatinib[2]
- Brigatinib[2]

MET
- Crizotinib[2]
- Cabozantinib[2]

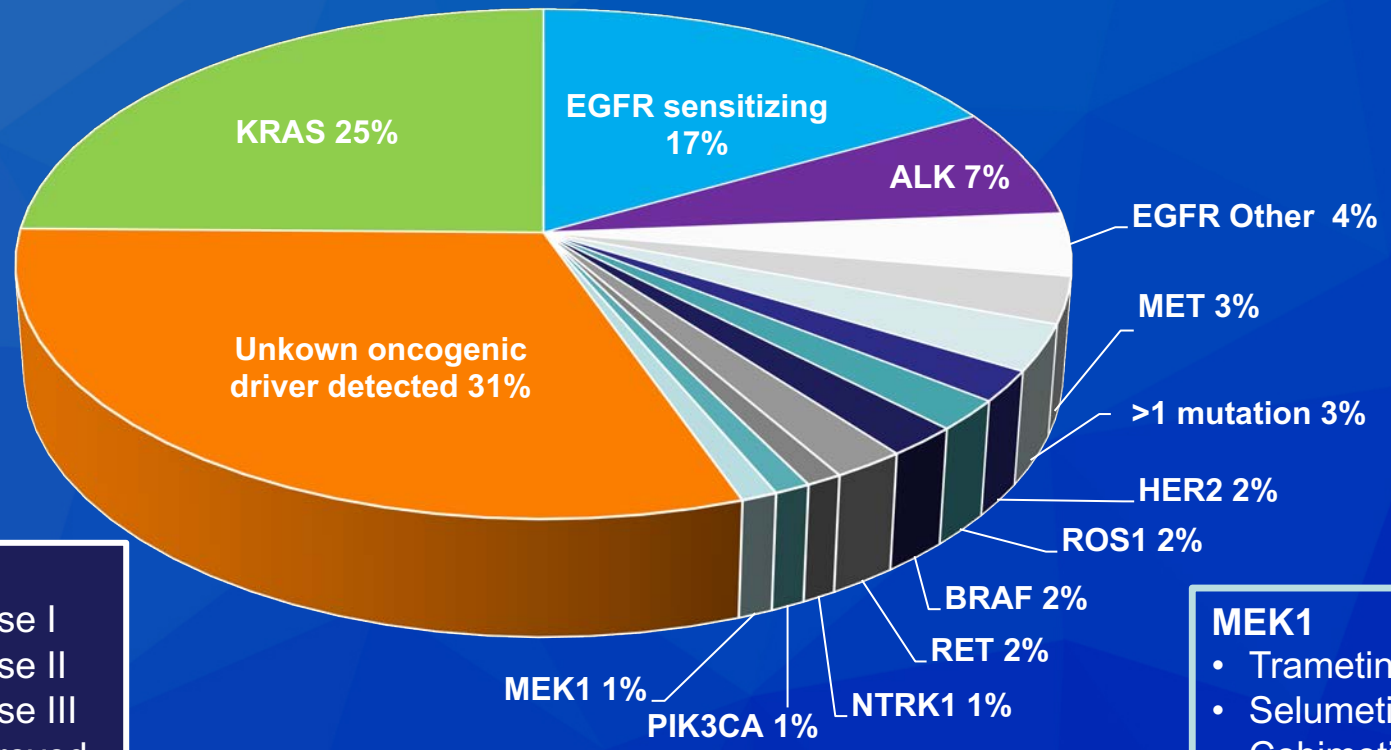
HER2
- Trastuzumab emtansine[2]
- Afatinib[2]
- Dacomitinib[2]

ROS1
- Crizotinib[4]
- Cabozantinib[2]
- Ceritinib[2]
- Lorlatinib[2]
- DS-6051b[1]

BRAF
- Vemurafenib[2]
- Dabrafenib[2]

RET
- Cabozantinib[2]
- Alectinib[2]
- Apatinib[2]
- Vandetanib[2]
- Ponatinib[2]
- Lenvatinib[2]

NTRK1
- Entrectinib[2]
- LOXO-101[2]
- Cabozantinib[2]
- DS-6051b[1]



KEY
1 - Phase I
2 - Phase II
3 - Phase III
4 - Approved

MEK1
- Trametinib[2]
- Selumetinib[3]
- Cobimetinib[1]

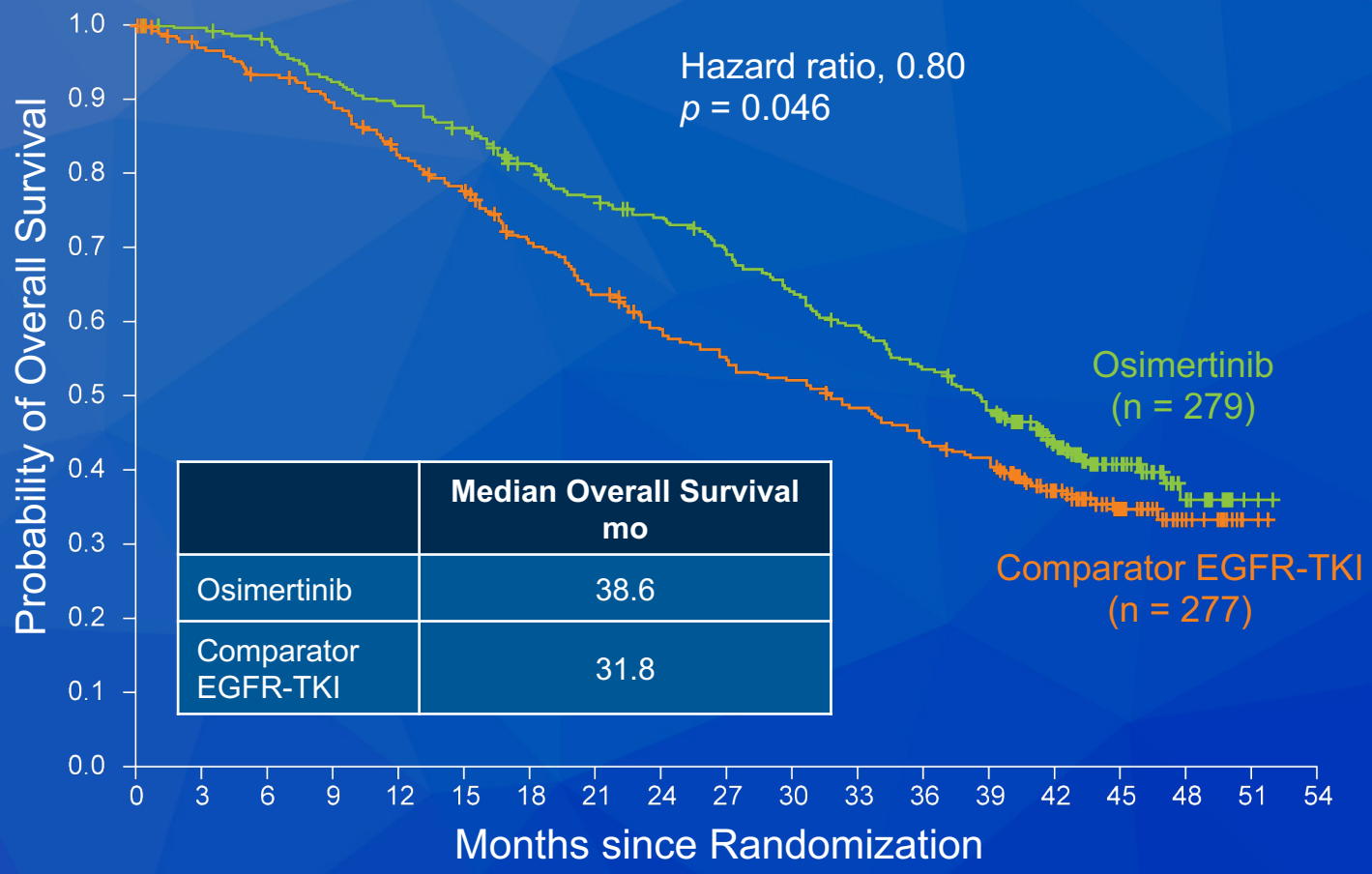
PIK3CA
- LY3023414[2]
- PQR 309[1]

Presented By Frances Shepherd at 2019 ASCO Annual Meeting.

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

Ramalingam SS et al.
N Engl J Med 2020;382(1):41-50.

FLAURA: Final OS Analysis



	Median Overall Survival mo
Osimertinib	38.6
Comparator EGFR-TKI	31.8

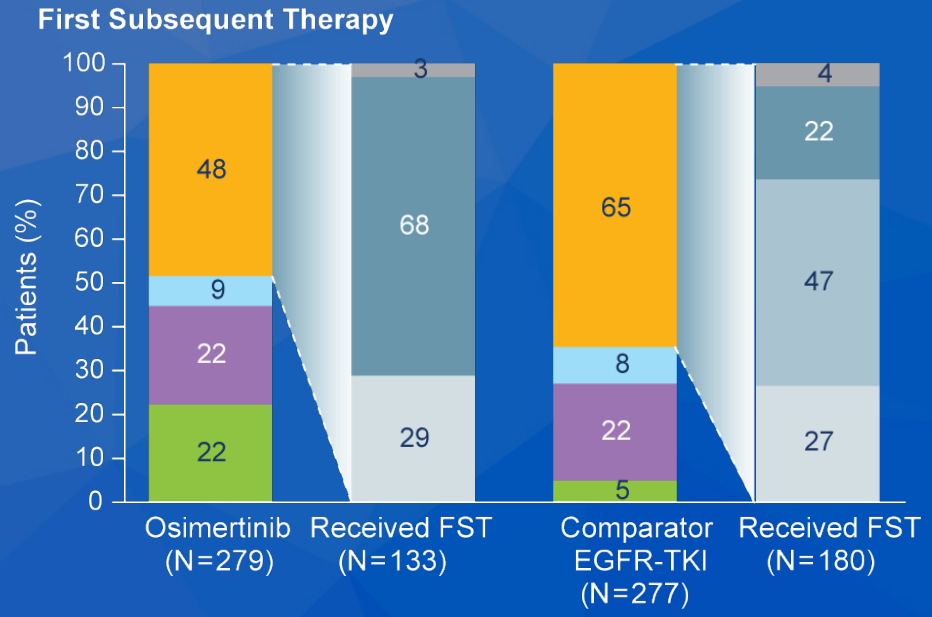
OS	Osimertinib (n = 279)	EGFR-TKI (n = 277)
12-mo OS	89%	83%
24-mo OS	74%	59%
36-mo OS	54%	44%
Pts continuing to receive first-line trial drug	**n = 279**	**n = 277**
At 12 mo	70%	47%
At 24 mo	42%	16%
At 36 mo	28%	9%

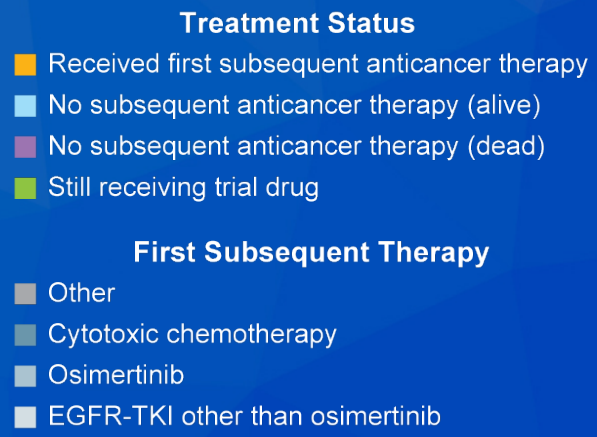
Comparator EGFR-TKI = erlotinib or gefitinib

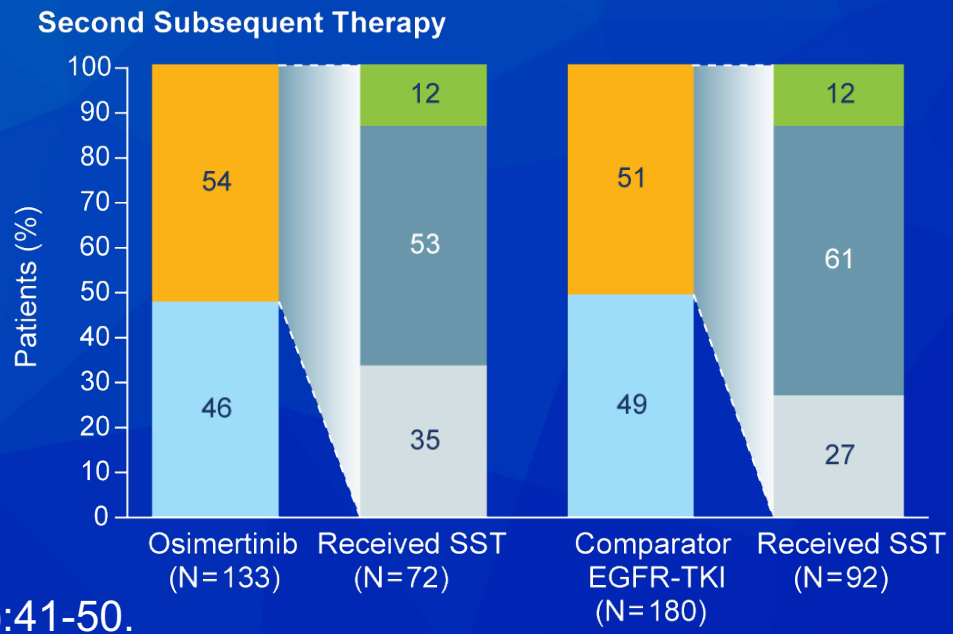
- The overall survival benefit with osimertinib as compared with the comparator EGFR-TKIs was consistent across most predefined subgroups, with varying magnitude of benefit.

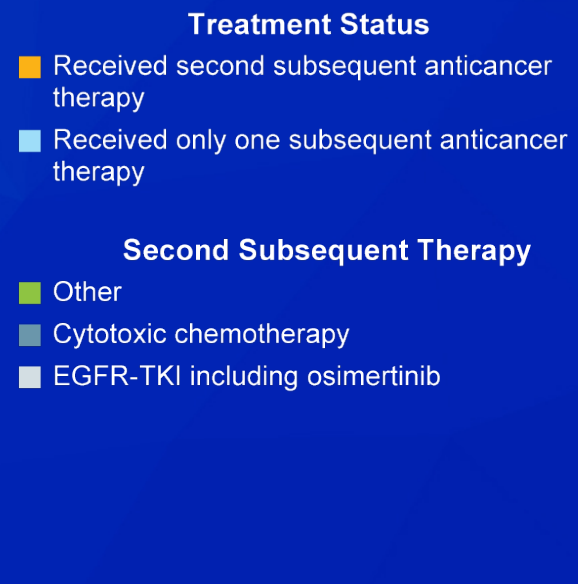
Ramalingam SS et al. *N Engl J Med* 2020;382(1):41-50.

FLAURA: Summary of First and Second Subsequent Therapies Received









Ramalingam SS et al. *N Engl J Med* 2020;382(1):41-50.

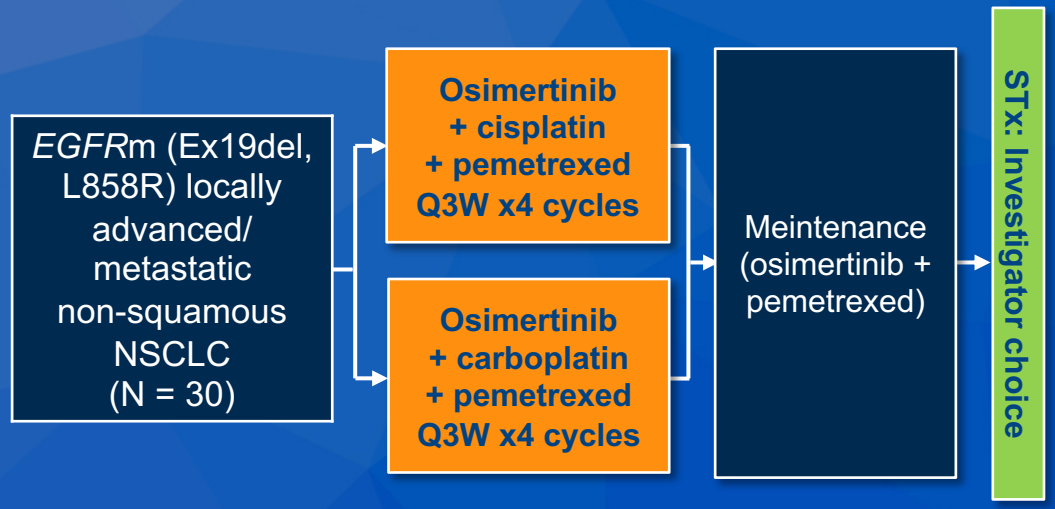
Osimertinib plus Platinum/Pemetrexed in Newly-Diagnosed Advanced EGFRm-Positive NSCLC; The Phase 3 FLAURA2 Study

Jänne PA et al.

Proc IASLC 2019;Abstract OA07.01.

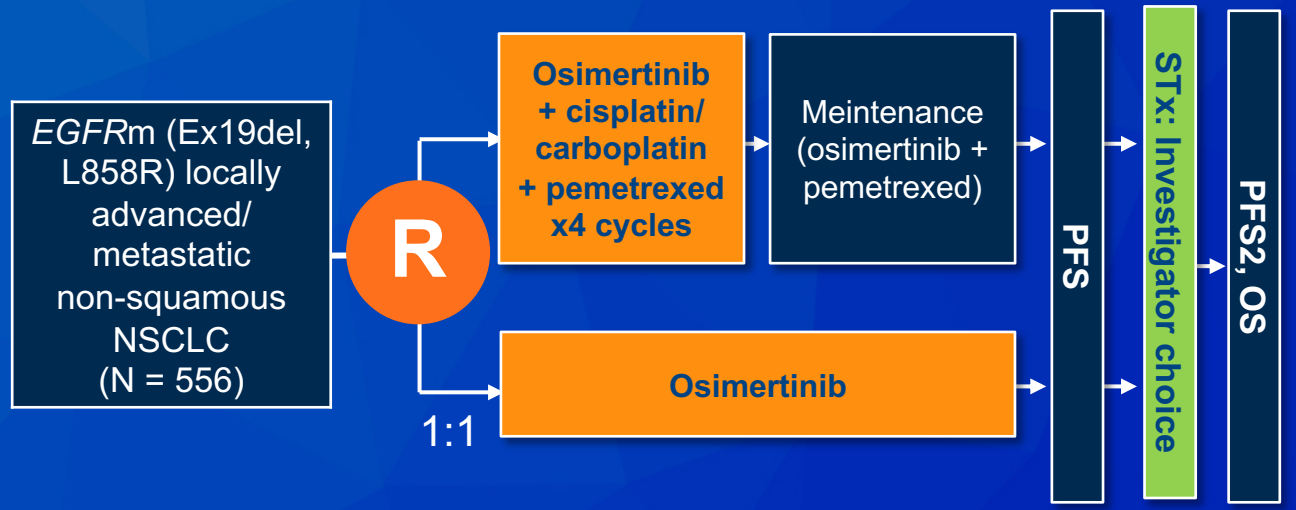
FLAURA2: Safety Run-In and Randomized Phase Designs

Study design: Safety run-in phase



- Osimertinib at a dose of 80 mg QD during induction and maintenance
- Selection of cisplatin or carboplatin is the Investigator's choice
- Safety parameters as primary endpoints

Study design: Randomized phase



- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritized over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue EGFR mutation test at enrollment
- Planned to involve approximately 248 sites in 27 countries

AE = adverse event; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation; Ex19del = exon 19 deletion; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death on a subsequent treatment; Q3W = every 3 weeks; QD = once daily; STx = subsequent treatment; WHO = World Health Organization

Jänne PA et al. *Proc IASLC* 2019;Abstract OA07.01.

Editorial — Dr Neal

EGFR-mutant metastatic NSCLC tumors are exquisitely sensitive to EGFR TKI therapy. For many years, erlotinib, gefitinib, or afatinib were the preferred first-line therapy, prior to starting chemotherapy or immunotherapy. However, more than half of tumors developed acquired resistance with EGFR T790M mutations, which can be overcome with second-line osimertinib, a third-generation EGFR TKI. In 2017, this standard of care changed when the FLAURA trial showed improvement in progression-free survival with first-line osimertinib compared with gefitinib or erlotinib. This year at ASCO, further analysis confirmed a statistically significant overall survival benefit of first-line osimertinib, further solidifying the role of this drug in the initial treatment of patients with EGFR-mutant NSCLC. Since chemo can be effective after progression on EGFR TKI therapy, and other clinical trials using chemotherapy together with TKI showed improvement in PFS, the ongoing FLAURA2 trial will test whether the combination of chemotherapy and osimertinib is superior to osimertinib alone, and results are awaited.

Osimertinib for Patients (pts) with Leptomeningeal Metastases (LM) Associated with EGFRm Advanced NSCLC: The AURA LM Study

Ahn M et al.

Proc ELCC 2019;Abstract 105O.

The AURA LM Study: Osimertinib for Patients with LM Associated with EFGRm Advanced NSCLC

	Patients with LM (n = 22)
Median PFS	11.1 mo
Median OS	18.8 mo
Median duration of response (DoR)	Not reached
Objective response rate (ORR)	55%
Complete or partial response	27%

Graphical assessment of longitudinal analysis showed similar non-CNS and LM responses in AURA LM and BLOOM LM pts.

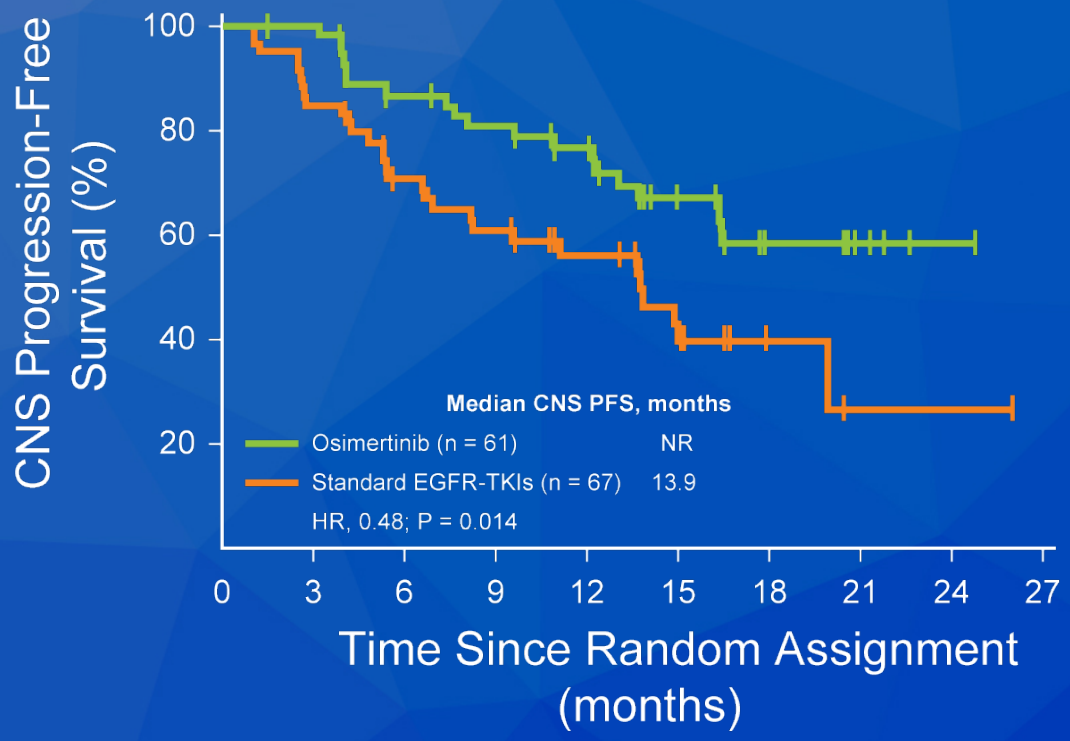
Ahn M et al. *Proc ELCC* 2019;Abstract 105O.

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

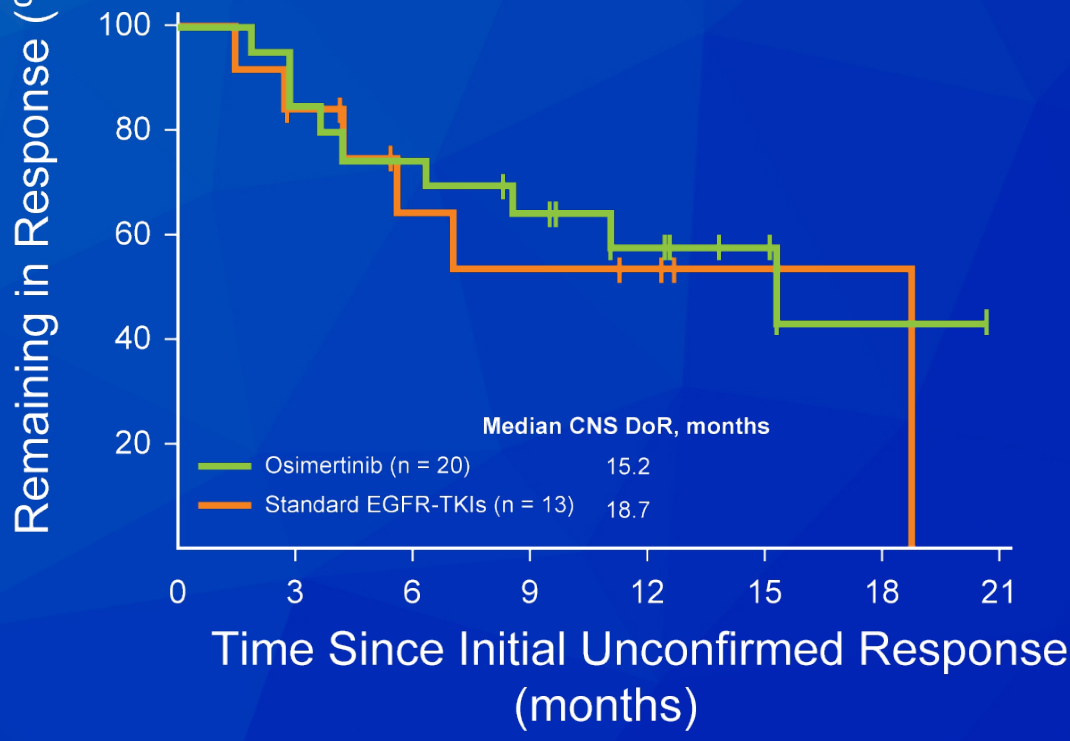
Reungwetwattana T et al.
J Clin Oncol 2018;[Epub ahead of print].

FLAURA: CNS PFS and Duration of CNS Response

CNS PFS (full analysis set)



CNS DoR (evaluable for response set)

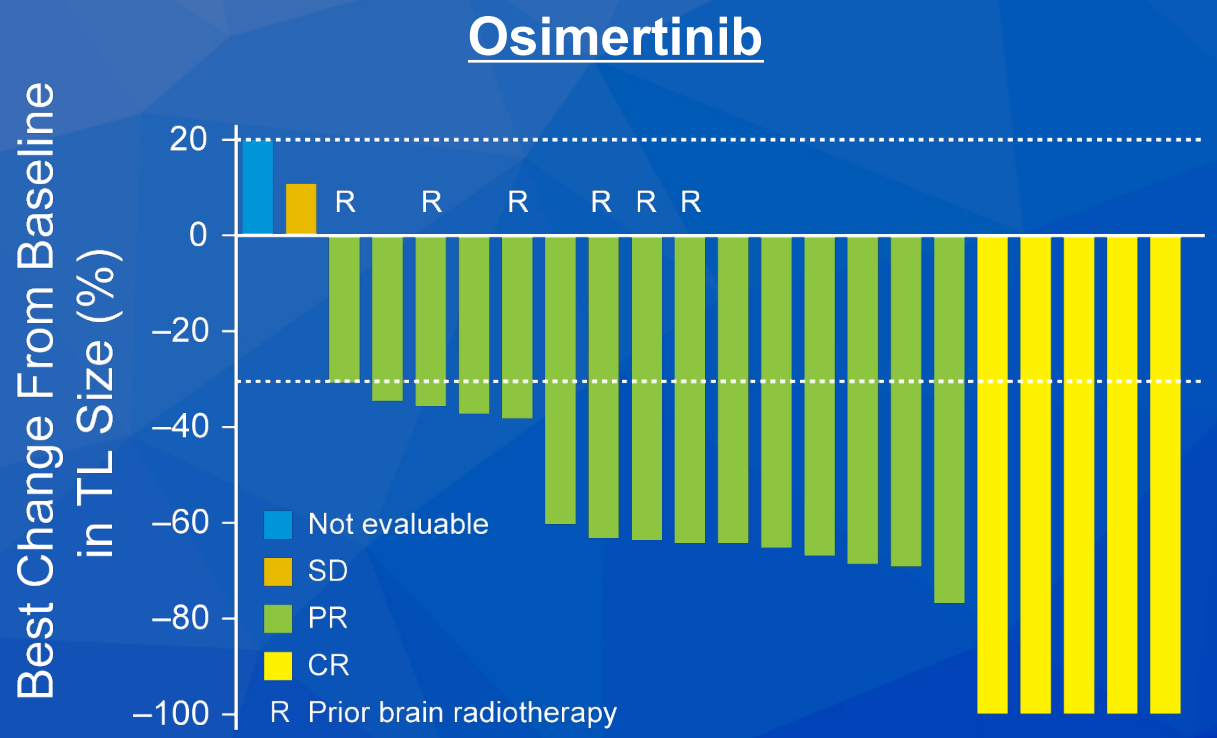


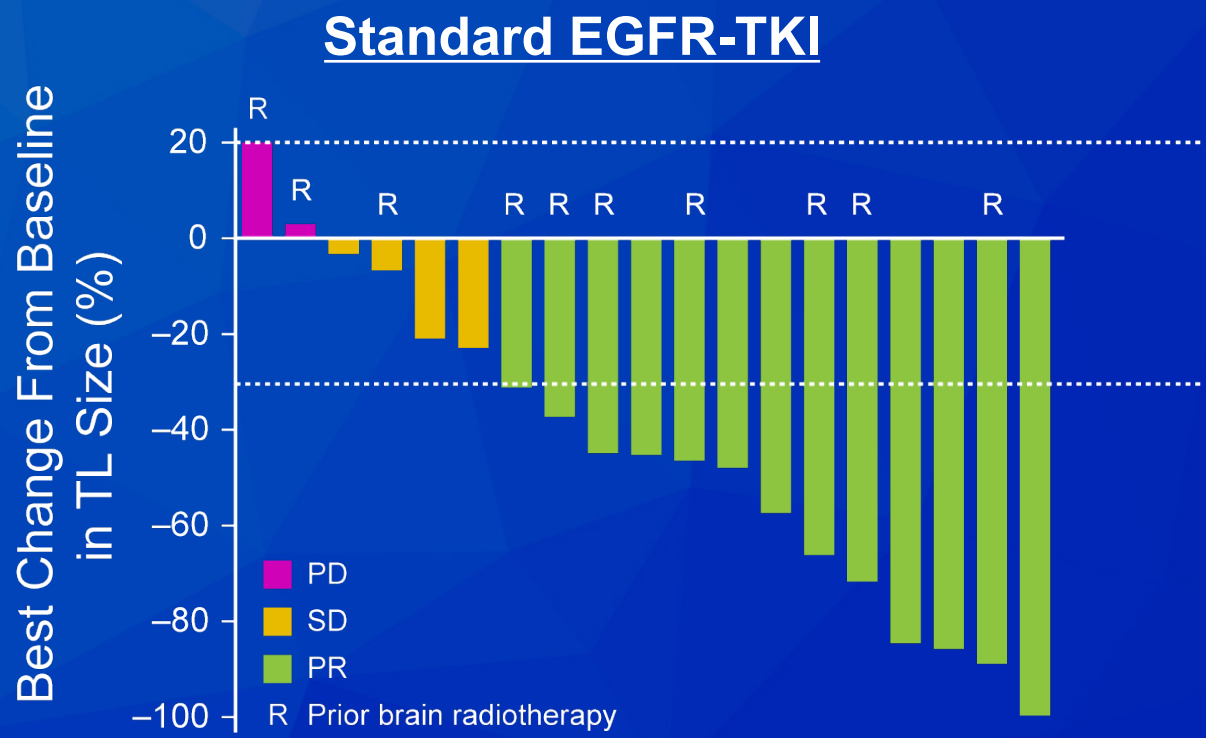
- CNS ORR (full analysis set)
  - Osimertinib = 40/61 (66%)
  - EGFR TKI = 29/67 (43%)

- CNS ORR (evaluable for response set)
  - Osimertinib = 20/22 (91%)
  - EGFR TKI = 13/19 (68%)

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

FLAURA: Best Change from Baseline in Target Lesion (TL) Size





- Benefit with osimertinib was seen irrespective of prior brain radiotherapy.

- CNS DCR (Full Analysis Set)
  - Osimertinib = 55/61 (90%)
  - EGFR-TKI = 56/67 (84%)
    - Odds ratio = 1.8; *p* = 0.269

- CNS ORR (Evaluable for Response Set)
  - Osimertinib = 21/22 (95%)
  - EGFR-TKI = 17/19 (49%)
    - Odds ratio = 2.5; *p* = 0.462

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

Editorial — Dr Neal

EGFR-mutant metastatic NSCLC tumors are exquisitely sensitive to EGFR TKI therapy, but many patients with EGFR-mutant NSCLC initially have brain metastases or develop them over the course of their disease. The early-generation EGFR TKIs erlotinib, gefitinib, and afatinib have modest penetration into the CNS, although this was somewhat less than systemic exposure. First-line treatment with the third-generation EGFR TKI, osimertinib, was superior to erlotinib or gefitinib in the phase III FLAURA study. Some patients were allowed on this study with previously untreated, measurable brain metastases to assess the effect in the CNS directly. Among these patients, osimertinib shrunk the metastases more than 90% of the time, compared with less than 70% of the time for gefitinib or erlotinib. Additionally, patients treated with osimertinib had a lower risk of progression in the CNS, and a longer time to progression overall (including the CNS). This demonstrates that osimertinib has superior efficacy in the brain than prior drugs.

Editorial — Dr Neal (continued)

In addition to solid “parenchymal” brain mets, some patients with EGFR-mutant NSCLC develop tumor growing in the cerebrospinal fluid and around the brain surfaces, called leptomeningeal carcinomatosis. Historically this has been difficult to treat with chemotherapy or radiation, and because of this, these patients have generally been excluded from clinical trials. It was previously demonstrated by the BLOOM study that some patients with active, symptomatic leptomeningeal disease who received 160 mg daily of osimertinib had clinical benefit. In the AURA LM study, patients with leptomeningeal disease were allowed onto the AURA osimertinib studies using 80 mg daily of osimertinib, and were found to have clinically meaningful responses, suggesting that osimertinib can also be effective in treating leptomeningeal disease.

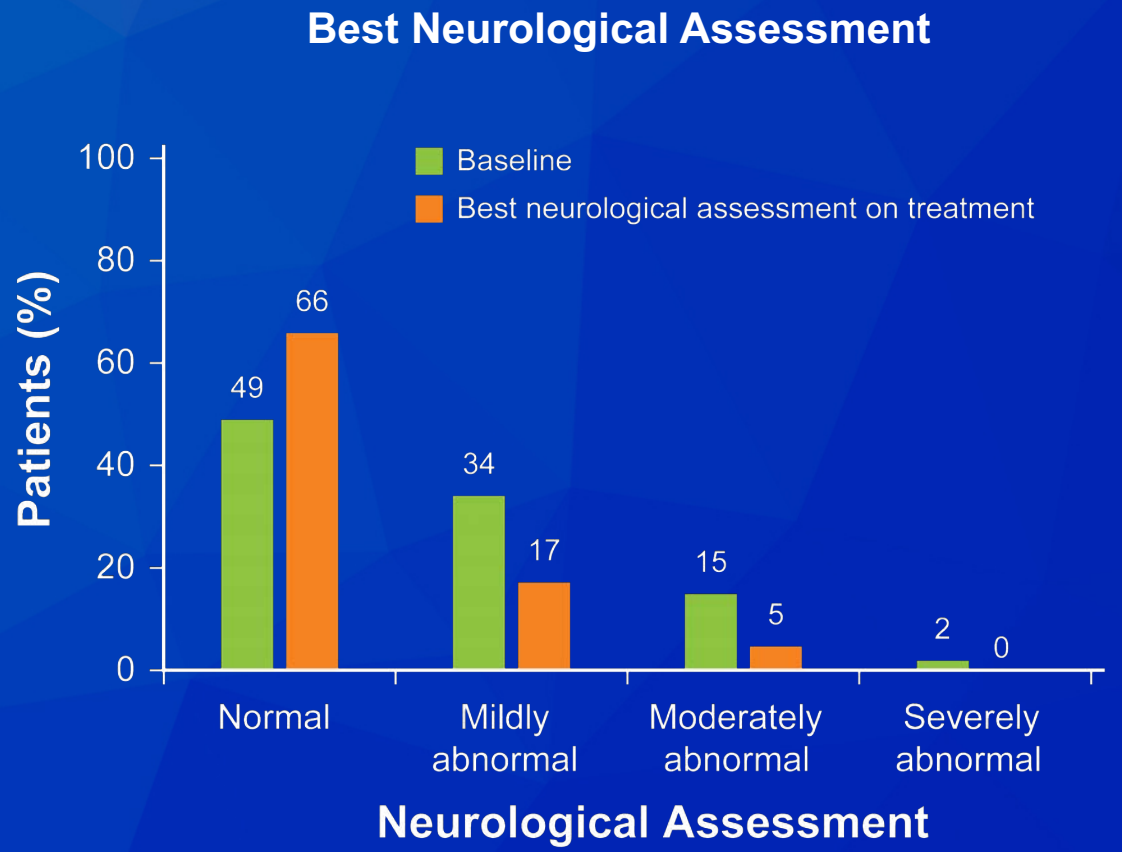
Osimertinib in Patients with Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

Yang JCH et al.
J Clin Oncol 2019;[Epub ahead of print].

BLOOM: Efficacy of Osimertinib in NSCLC with EGFR Mutation and Leptomeningeal Metastases (LM)

Response	LM by BICR (n = 37)	LM by INV (n = 41)	CNS by INV (n = 12)	Non-CNS by INV (n = 38)	Overall by INV (n = 41)
ORR	62%	27%	58%	45%	41%
CR	32%	2%	0	0	0
DCR at 12 wks	9%	78%	83%	71%	73%
Median DoR	15.2 mo	18.9 mo	11 mo	8.3 mo	8.3 mo

ORR = Objective response rate; DCR = disease control rate; DoR = duration of response; BICR = blinded central independent review; INV = investigator



- Median PFS by INV = 8.6 mo with 78% maturity
- Median OS by INV = 11.0 mo with 68% maturity

Yang JCH et al. *J Clin Oncol* 2019;[Epub ahead of print].

Editorial – Dr Riely

This was the recent publication of a study that we have been talking about for some time. This study explored the value of osimertinib in patients with EGFR mutation and leptomeningeal disease who had progressed on a prior 1st-/2nd-generation EGFR TKI. Studies of leptomeningeal disease are pretty uncommon, so the endpoints are not as clear for this disease setting (i.e., do you use radiographic response, clinical response, or cytologic response?). Using central review of radiographic criteria, they demonstrated a 62% response rate, with an impressive median duration of response of 15 months. However, to illustrate the challenge of radiographic endpoints in leptomeningeal disease, with the same group of patients, using investigator assessment, they saw a 27% leptomeningeal response rate and a 19-month median duration of response. Perhaps a more useful endpoint is how patients did clinically.

Editorial – Dr Riely

In this study, they saw neurologic improvement in 12/21 (57%) patients (the subgroup who had neurologic symptoms at baseline). Recently a group called RANO, which began with setting response standards in brain cancers, has developed standard criteria for response in leptomeningeal disease that can hopefully help the field move forward.

Another aspect of this study worth commenting upon was the dose of osimertinib used, 160 mg (which is double the standard dose of osimertinib). In the phase I study of osimertinib, there was efficacy and tolerability seen across a broad range of doses from 20 mg daily all the way up to 240 mg daily. In this study, they elected to use a higher dose with the idea that higher doses would increase efficacy in the CNS. With this higher dose, 22% of patients had adverse events that led to discontinuation. More recently, we saw publication of another series of patients who received osimertinib for leptomeningeal disease (Ahn et al, *Journal of Thoracic Oncology* 2019).

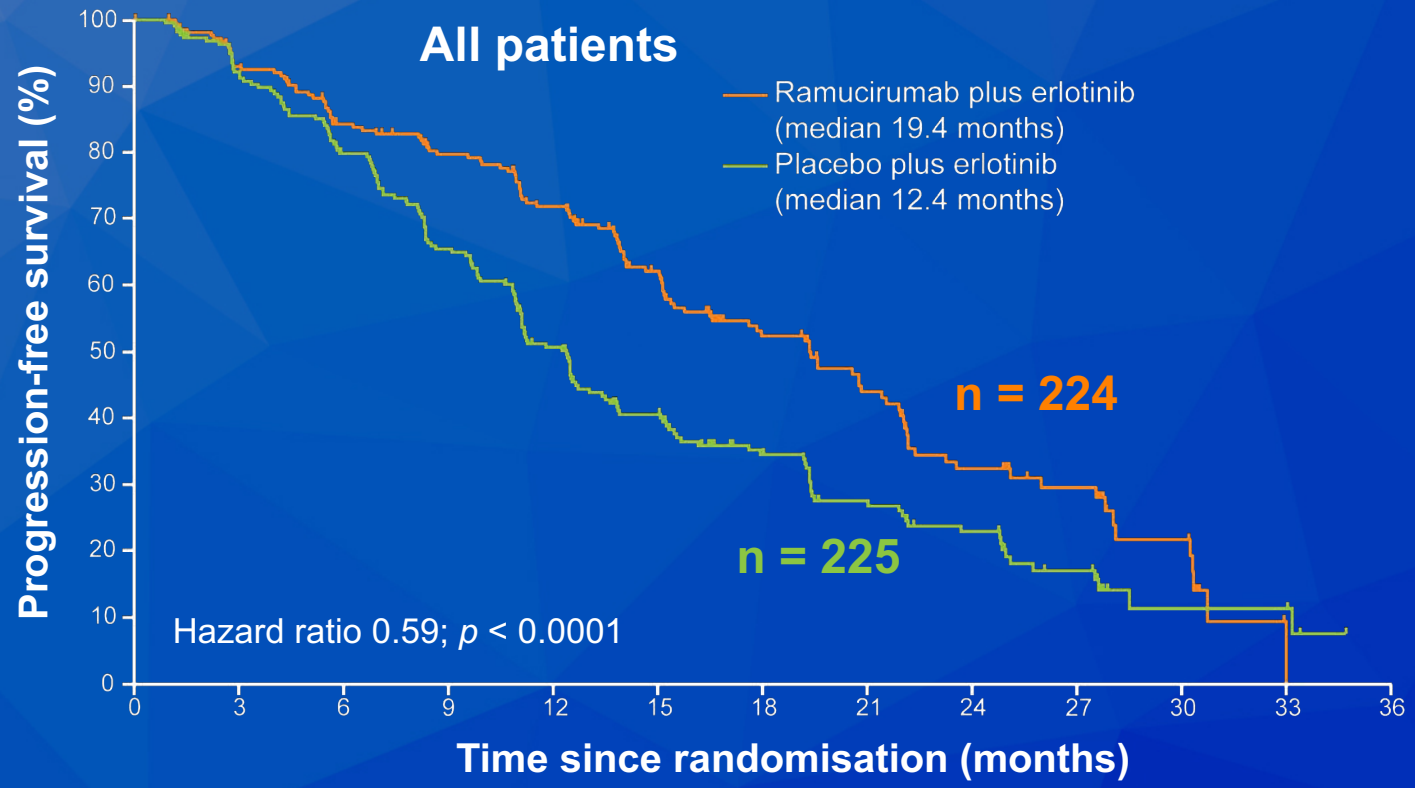
Editorial – Dr Riely

These patients came from other studies of osimertinib (AURA studies), and all were patients with EGFR T790M-positive advanced NSCLC and progression on prior EGFR-TKI. In this series, patients received osimertinib 80 mg daily. They saw a very similar response rate (55%) in patients with leptomeningeal disease. Of note, they did several comparisons with the BLOOM data (there are many authors who were involved in both studies) and suggest that osimertinib at 80 mg was largely similar to 160 mg. In pharmacokinetic analyses, they note that 80-mg concentration in LM is probably adequate for at least half the patients. Based on these data, I don't routinely use 160 mg of osimertinib for leptomeningeal disease. However, if osimertinib is not effective at 80 mg, then it would be reasonable to explore the higher dose.

Ramucirumab Plus Erlotinib in Patients with Untreated, EGFR-Mutated, Advanced Non-Small-Cell Lung Cancer (RELAY): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial

Nakagawa K et al.
Lancet Oncol 2019;20(12):1655-69.

RELAY: Investigator-Assessed PFS and Interim OS



- **Subgroup analysis of median PFS (RAM/ERL vs Placebo/ERL)**
  - Pts with baseline EGFR exon19 deletion mutation: 19.6 mo vs 12.5 mo (HR = 0.65; $p = 0.0098$)
  - Pts with baseline EGFR L858R mutation: 19.4 mo vs 11.2 mo (HR = 0.62; $p = 0.0060$)
- **Interim OS analysis (RAM/ERL vs Placebo/ERL)**
  - 2-year OS = 83% vs 79% (HR = 0.83; $p = 0.421$)
- **Overall response rate** = 76% (RAM/ERL) vs 75% (Placebo/ERL); $p = 0.741$

Nakagawa K et al. *Lancet Oncol* 2019;20(12):1655-69.

RELAY: Select Treatment-Emergent AEs

Select AE	RAM/ERL (n = 221)		Placebo/ERL (n = 225)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Dermatitis acneiform	52%	15%	59%	9%
Stomatitis	40%	2%	35%	1%
Pyrexia	21%	0	12%	<1%
AEs of special interest	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Bleeding or hemorrhage events	53%	1%	24%	2%
Proteinuria	32%	3%	8%	0
Hypertension	22%	24%	7%	5%
Congestive heart failure	1%	1%	<1%	0
ILD or pneumonitis	1%	<1%	2%	1%

- The most common serious AEs of any grade in the RAM/ERL group were pneumonia (7 [3%]) and cellulitis and pneumothorax (4 [2%], each).
- 1 on-study treatment-related death due to an AE occurred (hemothorax after a thoracic drainage procedure for a pleural empyema) in the RAM/ERL arm.

Nakagawa K et al. *Lancet Oncol* 2019;20(12):1655-69.

Editorial – Dr Riely

For several years, there have been trials reported from Japan that demonstrate the value of adding bevacizumab to 1st-generation EGFR TKI (e.g., Seto et al, *Lancet Onc* 2014; Saito et al, *JAMA Onc* 2019) in patients with EGFR-mutant NSCLC. In each of these trials, there have been clear improvements in PFS with the addition of bevacizumab and variable effects on overall survival. In this context, we have the recent report of a trial using a different approach to blocking VEGF signaling, ramucirumab. In this study patients were randomized to either single-agent erlotinib or the combination of erlotinib and ramucirumab. The group of patients who received the combination therapy had similar response rate to those who received erlotinib alone, but an increase in median PFS to 19 months. Notably, the trial excluded patients with CNS metastases. We have not seen a report of overall survival from this trial. In addition to the data combining erlotinib with bevacizumab, the other recent data to which we should compare these results is for first-line osimertinib.

Editorial – Dr Riely

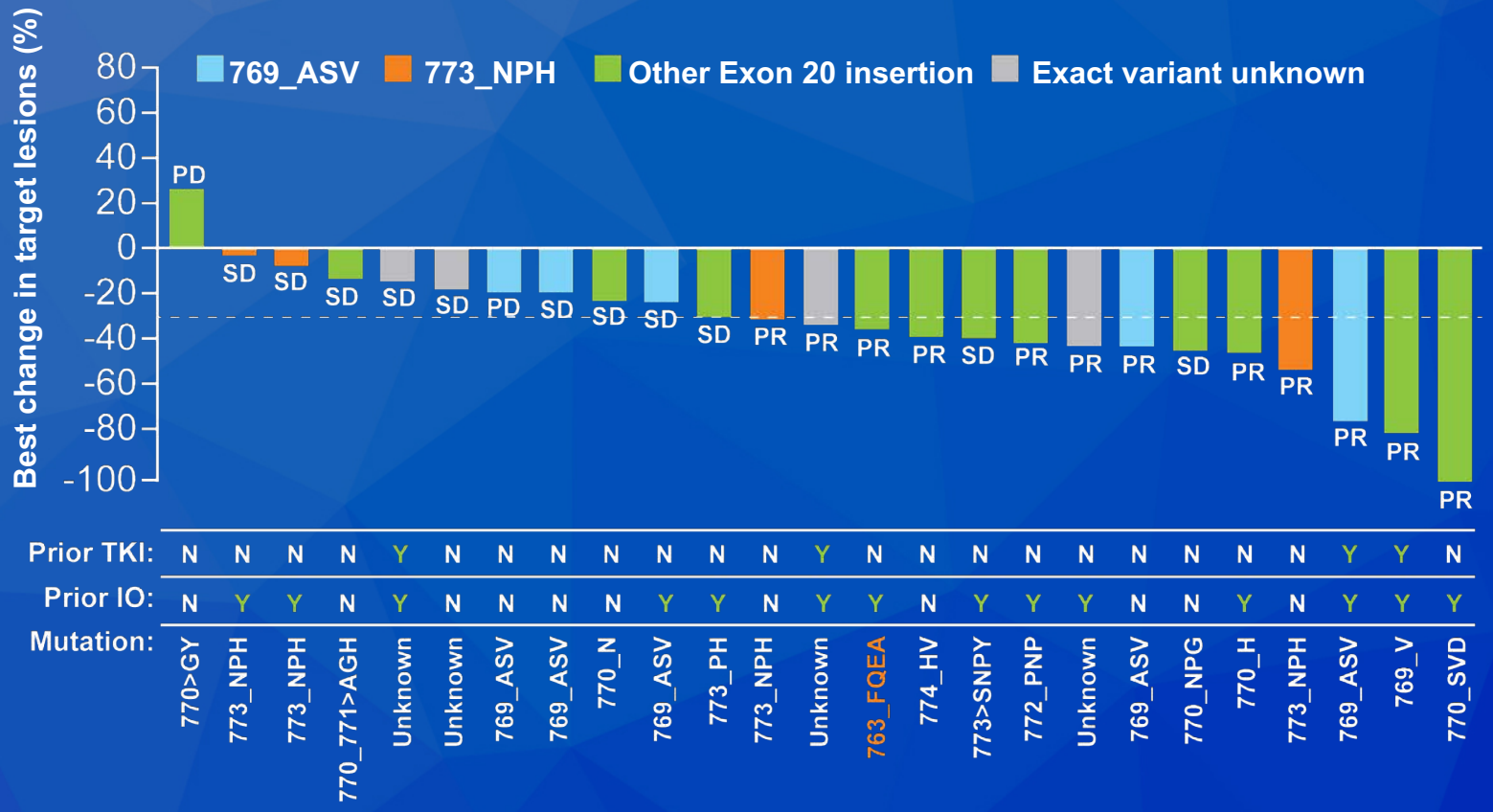
In the first-line osimertinib trial, the median progression-free survival is numerically superior (19 months), but patients with CNS metastases comprised approximately 20% of patients enrolled in the FLAURA trial. This trial suggests some opportunities to improve outcomes for patients by looking at osimertinib + bevacizumab or osimertinib + ramucirumab. Today, I think single-agent osimertinib remains the standard of care.

Antitumor Activity of TAK-788 in NSCLC with EGFR Exon 20 Insertions

Jänne PA et al.

Proc ASCO 2019;Abstract 9007.

TAK-788 for NSCLC with EGFR Exon 20 Insertions



Exon 20 insertion variant	No. of patients	No. of confirmed responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown	4	2	50%
Other	15	6	40%

- Median (range) best percentage change: -32.5% (-100%, 26.3%)
- Response to TAK-788 was observed in diverse EGFR exon 20 insertion variants

IO = immuno-oncology therapy; PD = progressive disease

Jänne PA et al. *Proc ASCO* 2019;Abstract 9007.

Editorial — Dr Neal

While most EGFR-mutant NSCLC tumors are sensitive to EGFR tyrosine kinase inhibitors, about 5% of EGFR mutations are EGFR exon 20 insertions. These are relatively insensitive to currently available TKIs. However, a number of drugs are emerging that appear more effective against this group of mutations. The pill inhibitor TAK-788, when given at the maximally tolerated dose, causes some tumor regression in most patients, with formal radiographic responses in over 40% of these patients. The time to progression is similar or a bit longer than expected from platinum chemotherapy, at over 7 months. Another EGFR exon 20 inhibitor TKI, poziotinib, causes tumors to shrink in over 50% of patients and works for a median time of more than 5 months. Both of these drugs predominantly cause side effects similar to those of first-generation EGFR inhibitors but perhaps somewhat more intense — acne-like rash and other skin effects, and GI effects including anorexia and diarrhea.

Editorial — Dr Neal (continued)

While patients with this type of lung cancer could still benefit from chemotherapy and sometimes immune therapy, drugs like these are exciting because they open up a new targeted option that can work in addition to other therapies.

Brigatinib (BRG) versus Crizotinib (CRZ) in the Phase III ALTA-1L Trial

Califano R et al.

Proc ELCC 2019;Abstract 106O.

Phase III ALTA-1L: Brigatinib (BRG) versus Crizotinib (CRZ)

BIRC-assessed endpoint, %	BRG (n = 137)	CRZ (n = 138)	*p*-value
All pts			
ORR[a]	76 (68-83[b])	73 (65-80[b])	0.0678
Confirmed ORR	71 (62-78[b])	60 (51-68[b])	
With any intracranial CNS metastases	**(n = 43)**	**(n = 47)**	
iORR[a]	79 (64-90[b])	23 (12-38[b])	<0.0001
Confirmed iORR	67 (51-81[b])	17 (8-31[b])	
Median iPFS, months	NR (11-NR[b])	6 (4-9[b])	
1-year iPFS	67 (47-80[b])	21 (6-42[b])	
HR	0.27 (0.13-0.54)		<0.0001[c]
With measurable intracranial CNS metastases	**(n = 18)**	**(n = 21)**	
iORR[a]	83 (59-96[b])	33 (15-57[b])	0.0028
Confirmed iORR	78 (52-94[b])	29 (11-52[b])	

[a] Response, ≥1 assessment; [b] 95% CI; [c] Log-rank

Califano R et al. *Proc ELCC* 2019;Abstract 106O.

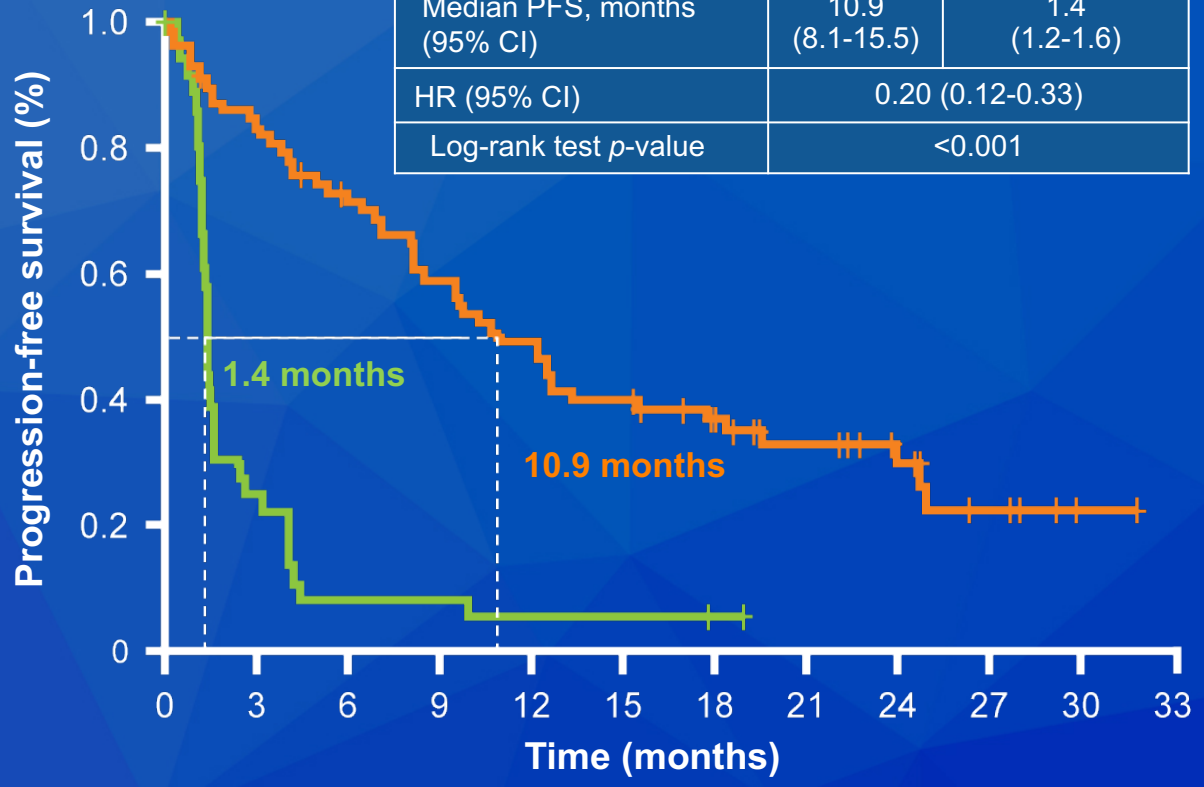
Phase 3 ALUR Study of Alectinib in Pretreated ALK+ NSCLC: Final Efficacy, Safety and Targeted Genomic Sequencing Analyses

Wolf J et al.
Proc IASLC 2019;Abstract OA02.07.

ALUR: Final Survival Analyses

PFS (investigator assessed)

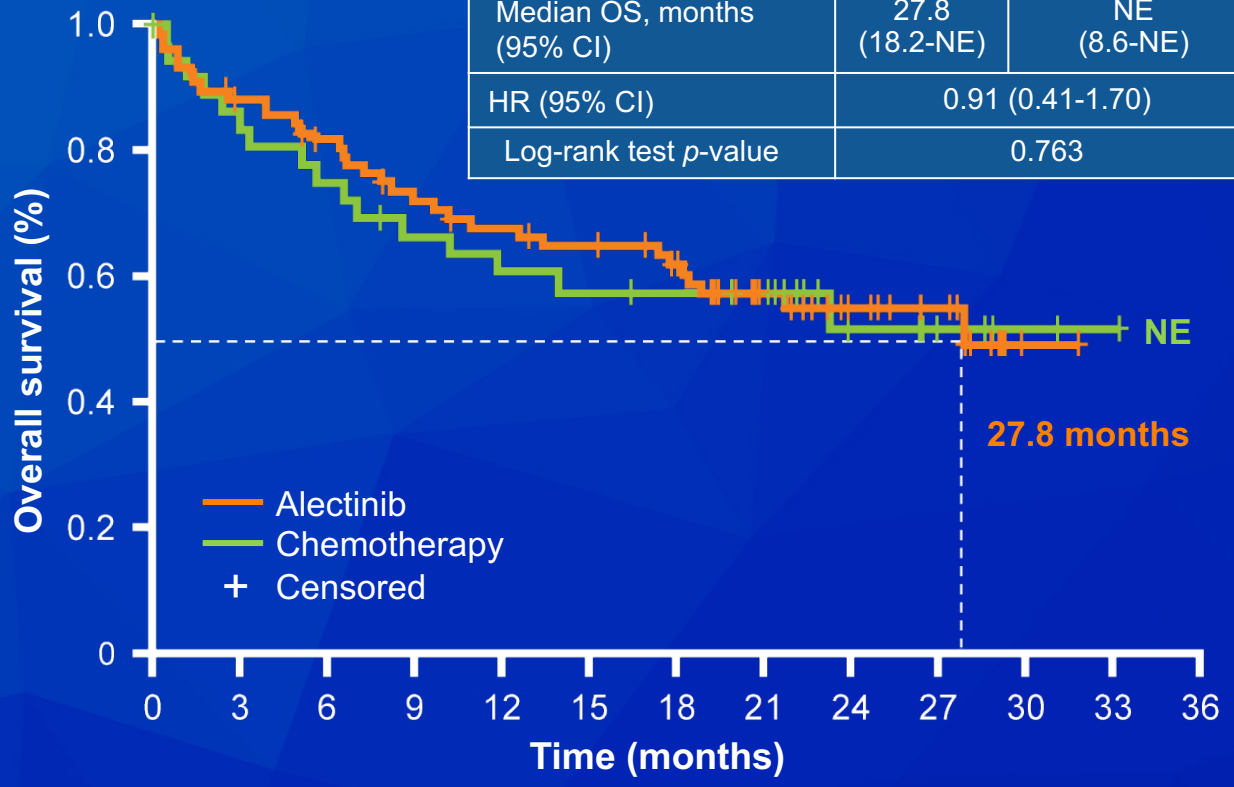
	Alectinib (n = 79)	Chemotherapy (n = 40)
Patients with event, n (%)	52 (65.8)	34 (85.0)
Median PFS, months (95% CI)	10.9 (8.1-15.5)	1.4 (1.2-1.6)
HR (95% CI)	0.20 (0.12-0.33)	
Log-rank test *p*-value	<0.001	



Data cut-off: 28 September 2018

Overall survival

	Alectinib (n = 79)	Chemotherapy (n = 40)
Patients with event, n (%)	33 (41.8)	16 (40.0)
Median OS, months (95% CI)	27.8 (18.2-NE)	NE (8.6-NE)
HR (95% CI)	0.91 (0.41-1.70)	
Log-rank test *p*-value	0.763	



- 17 (22.1%) patients received alectinib after disease progression
- 32 (86.5%) patients crossed over from chemotherapy to alectinib

Wolf J et al. *Proc IASLC* 2019;Abstract OA02.07.

Editorial — Dr Neal

ALK-positive NSCLC comprises about 4% of NSCLC overall, but is quite sensitive to ALK tyrosine kinase inhibitors (TKIs). For many years, the first-generation ALK TKI crizotinib was the standard of care, but multiple second-generation drugs have been developed that overcome resistance (which can be caused by either mutations in ALK or activation of other signaling pathways to bypass ALK). The currently approved second-generation ALK inhibitors are ceritinib, alectinib, brigatinib, and there is also a third-generation approved drug, lorlatinib. In the ALUR study, patients who had received prior crizotinib and then platinum-based chemotherapy were randomized to alectinib or single-agent chemotherapy. This study showed that alectinib has higher response rates than chemotherapy in both arms (>60% vs <10%) but also that alectinib was particularly effective when ALK secondary mutations were present, yet modestly less so when other new driver gene mutations emerged.

Editorial — Dr Neal (continued)

Following the phase III ALEX trial, alectinib has now displaced crizotinib as the preferred first-line agent for ALK-positive NSCLC. Brigatinib, another second-generation inhibitor, was tested head to head with crizotinib in the first-line ALTA-1L trial. Compared with crizotinib, brigatinib had a similar tumor response rate but was lower in the CNS for patients with untreated brain mets. At an interim analysis, the time to progression appears significantly longer for brigatinib and has not yet been reached. While not currently FDA approved in this setting, first-line brigatinib appears to be a compelling alternative to alectinib for patients with ALK-positive NSCLC.

FDA Approves Third Oncology Drug That Targets a Key Genetic Driver of Cancer Rather Than a Specific Type of Tumor

Press Release – August 15, 2019

"The US Food and Drug Administration today granted accelerated approval to entrectinib, a treatment for adult and adolescent patients whose cancers have the specific genetic defect, NTRK (neurotrophic tyrosine receptor kinase) gene fusion and for whom there are no effective treatments.

This is the third time the agency has approved a cancer treatment based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated. The approval marks a new paradigm in the development of cancer drugs that are 'tissue agnostic.' It follows the policies that the FDA developed in a guidance document released in 2018. The previous tissue agnostic indications approved by the FDA were pembrolizumab for tumors with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors in 2017 and larotrectinib for NTRK gene fusion tumors in 2018."

https://www.fda.gov/news-events/press-announcements/fda-approves-third-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor

Entrectinib in NTRK Fusion-Positive NSCLC: Integrated Analysis of Patients Enrolled in STARTRK-2, STARTRK-1 and ALKA-372-001

Doebele R et al.
Proc AACR 2019;Abstract CT131.

Paz-Ares L et al.
Proc ESMO 2019;Abstract 1130.

Entrectinib for NSCLC with NTRK Fusion: Integrated Analysis of Patients Enrolled in STARTRK-2, STARTRK-1 and ALKA-372-001

Outcome	Patients with advanced/metastatic solid tumors and NTRK fusion (n = 54)
Overall response rate (BICR)	57.4%, 4 CR (7.4%)
Median DoR (BICR)	10.4 months
Median PFS (BICR)	11.2 months
Median OS	20.9 months

- CNS disease at baseline: 22.2%
- Grade ≥3 treatment-related adverse events (TRAEs): 35.3%
- Conclusion: In this analysis, entrectinib was well tolerated and induced clinically meaningful, durable systemic and intracranial responses in patients with solid tumors and NTRK fusion, including those with NSCLC

BICR = blinded independent central review

Doebele R et al. *Proc AACR* 2019;Abstract CT131. Paz-Ares L et al. *Proc ESMO* 2019;Abstract 1130.

FDA Approves Entrectinib for Metastatic NSCLC with ROS1 Mutation

Press Release – August 15, 2019

“Entrectinib was also approved today for the treatment of adults with non-small cell lung cancer whose tumors are ROS1-positive (mutation of the ROS1 gene) and has spread to other parts of the body (metastatic). Clinical studies evaluated 51 adults with ROS1-positive lung cancer. The overall response rate was 78%, with 5.9% of patients having complete disappearance of their cancer. Among the 40 patients with tumor shrinkage, 55% had tumor shrinkage persist for 12 months or longer.

Entrectinib’s common side effects are fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, weight gain, cough, vomiting, fever, arthralgia and vision disorders.”

https://www.fda.gov/news-events/press-announcements/fda-approves-third-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor

Editorial — Dr Neal

In NSCLC, there are a variety of “driver” oncogene mutations that can be targeted by kinase inhibitors. The best described of these are EGFR and ALK, which occur at about 15% and 4% frequency. A recently described gene fusion, NTRK, occurs rarely, in significantly less than 1% of NSCLC, but can be potently inhibited by the TKIs larotrectinib and the more recently approved entrectinib. In a pooled analysis of multiple clinical trials, a total of 54 patients with different NTRK fusion-positive tumors, including 10 with NSCLC, were treated with entrectinib. Most patients had some decree of tumor regression, and the overall response rate was almost 60% with excellent CNS activity observed as well. The drug appears well tolerated, with mild TKI side effects such as fatigue, GI and taste alterations, plus peripheral edema, paresthesias, and arthralgias. In order to treat patients with these novel NTRK inhibitors, testing needs to be done.

Editorial — Dr Neal (continued)

Currently, the most reliable testing method to identify NTRK fusions is DNA NGS sequencing, or even potentially RNA fusion assays, which are even more sensitive for genetic alterations. Despite the low prevalence, sequencing will also identify other uncommon genetic rearrangements that may be targetable, such as ROS1 and RET, and is encouraged particularly in patients with NSCLC without a smoking history. Once identified, patients with NTRK-positive tumors should receive NTRK TKI therapy, since these agents appear effective enough that they would likely outperform even chemotherapy in the first-line setting of NSCLC.

Entrectinib in Locally Advanced or Metastatic ROS1 Fusion-Positive Non-Small Cell Lung Cancer (NSCLC): Integrated Analysis of ALKA-372-001, STARTRK-1 and STARTRK-2

Barlesi F et al.
Proc ELCC 2019;Abstract 109O.

ALKA-372-001, STARTRK-1, STARTRK-2: Integrated Analysis

Outcome	Patients with treatment-naïve NSCLC and ROS1 mutation (n = 53)
ORR (BICR)	77%, 3 CR 38 PR
Median DoR (BICR)	25 months
Median PFS (BICR) Without CNS disease (n = 30) With CNS disease (n = 20)	19 months 26 months 14 months
Intracranial ORR (n = 20)[a]	55%, 4 CR 7 PR
Median intracranial DoR (n = 11)[b]	13 months

[a] Patients with measurable CNS disease at baseline per BICR
[b] In patients with an intracranial response

Barlesi F et al. *Proc ELCC* 2019;Abstract 109O.

Editorial — Dr Neal

The ROS1 gene rearrangement is present in approximately 1%-2% of NSCLC and confers sensitivity to ROS1 tyrosine kinase inhibitors (TKIs). The current standard first-line TKI therapy is crizotinib, but the ROS1/NTRK inhibitor entrectinib was recently approved as well. In ROS1-positive NSCLC, entrectinib appears to have similar potency as crizotinib, with a response rate over 70% in a combined analysis of multiple clinical trials. Progression-free survival looks numerically better than most prior trials with crizotinib, but it is challenging to reliably compare between different studies. Interestingly, it appears to have better CNS penetration than expected from crizotinib, as the response rate in the CNS was over 50%. Based on these data, the approval of entrectinib has opened the door to its use in both ROS1- and NTRK-positive NSCLC. Future studies may elucidate whether it is a superior drug to crizotinib overall.

Editorial — Dr Neal (continued)

Despite these first-line options for treating ROS1-positive NSCLC, resistance to these drugs commonly occurs. One emerging option for this is repotrectinib, with much higher potency than crizotinib and better CNS penetration. Responses were observed in slightly less than half of patients that had progressed after prior TKI therapy, demonstrating its ability to overcome resistance to agents such as crizotinib. This appears to be a promising emerging option to combat resistance in patients with ROS1-positive NSCLC. Other potential options are moving forward to chemotherapy, or lorlatinib, which is approved in ALK-positive NSCLC but also has activity in crizotinib-refractory ROS1 patients.

FDA Breakthrough Therapy Designation for Two Selective RET Inhibitors

Press Release – July 10, 2019

"Two selective RET inhibitors have been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration: BLU-667 and LOXO-292 (selpercatinib).

BLU-667 is designed to inhibit *RET* alterations and resistance mutations. It is 90-fold more selective for *RET* than for *VEGFR2,* a common target of earlier multikinase inhibitors."

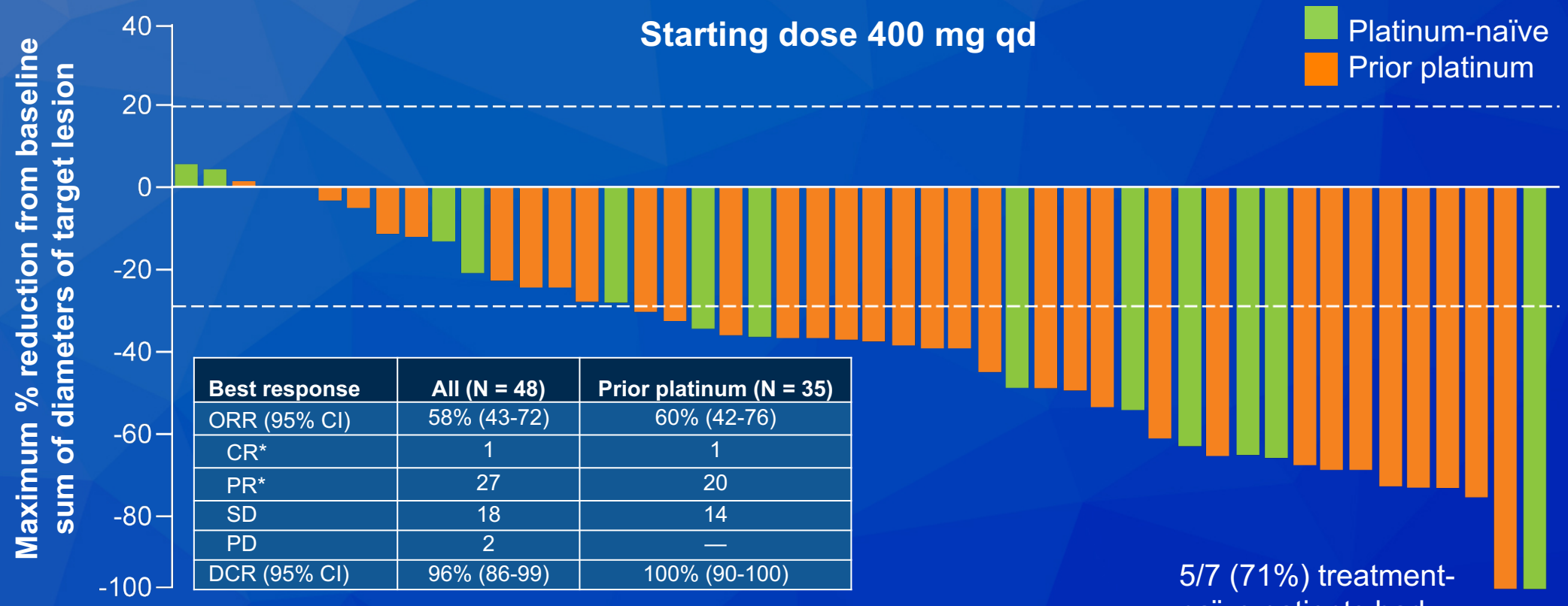
"Selpercatinib is an orally bioavailable selective inhibitor of wild-type, mutant and fusion products involving the proto-oncogene receptor tyrosine kinase rearranged during transfection (RET), with potential antineoplastic activity."

https://www.ascopost.com/issues/july-10-2019/advances-in-targeted-therapy-for-non-small-cell-lung-cancer/
https://www.cancer.gov/publications/dictionaries/cancer-drug/def/ret-inhibitor-loxo-292

Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients (pts) with Advanced RET-Fusion+ Non-Small Cell Lung Cancer (NSCLC)

Gainor JF et al.
Proc ASCO 2019;Abstract 9008.

BLU-667 (Pralsetinib) Demonstrates Substantial Antitumor Activity in Advanced NSCLC with RET Fusion



Best response	All (N = 48)	Prior platinum (N = 35)
ORR (95% CI)	58% (43-72)	60% (42-76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	—
DCR (95% CI)	96% (86-99)	100% (90-100)

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

5/7 (71%) treatment-naïve patients had confirmed PR

- Treatment-related toxicity is low grade and reversible
- 7% discontinued pralsetinib due to treatment-related toxicity: pneumonitis, respiratory distress/hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia
- TRAEs Grade ≥3 included neutropenia (13%), hypertension (10%), anemia (4%), fatigue (3%)

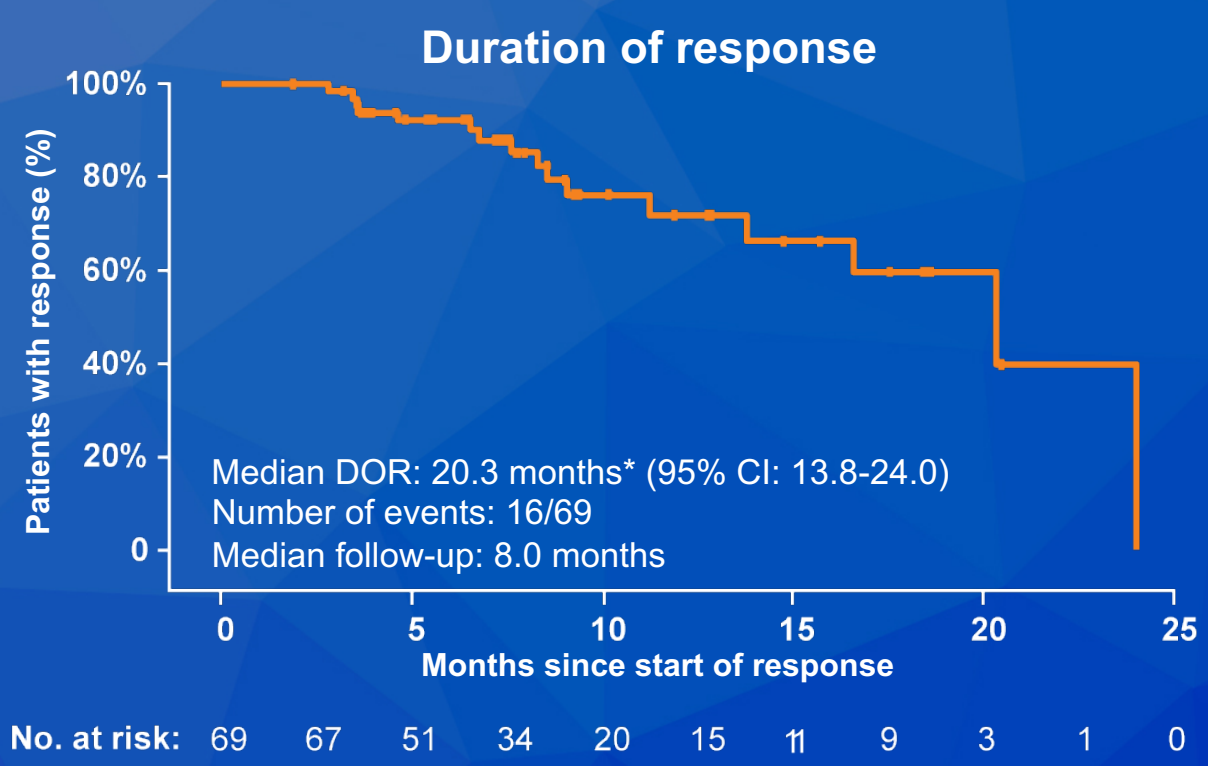
Gainor JF et al. *Proc ASCO* 2019;Abstract 9008.

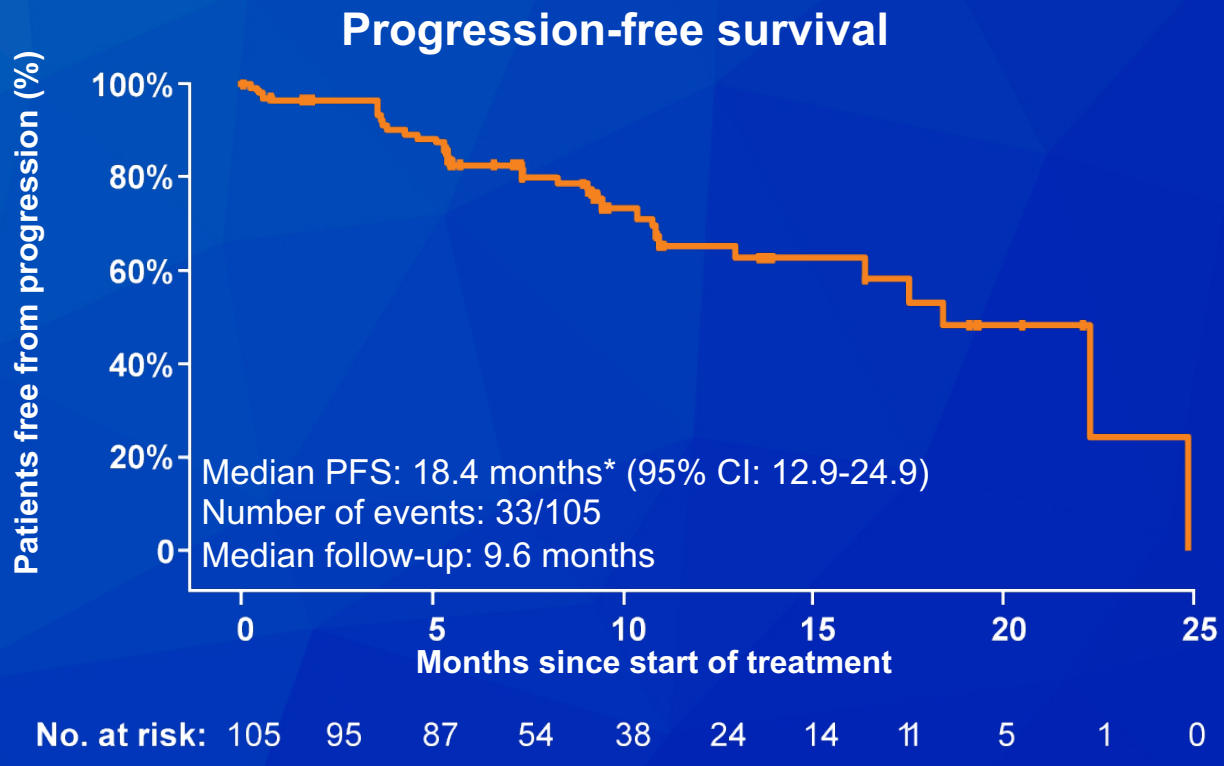
Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers

Drilon A et al.

Proc IASLC 2019;Abstract PL02.08.

LIBRETTO-001: Primary Analysis Set (PAS) with Selpercatinib (LOXO-292) for Lung Cancer with RET Fusion



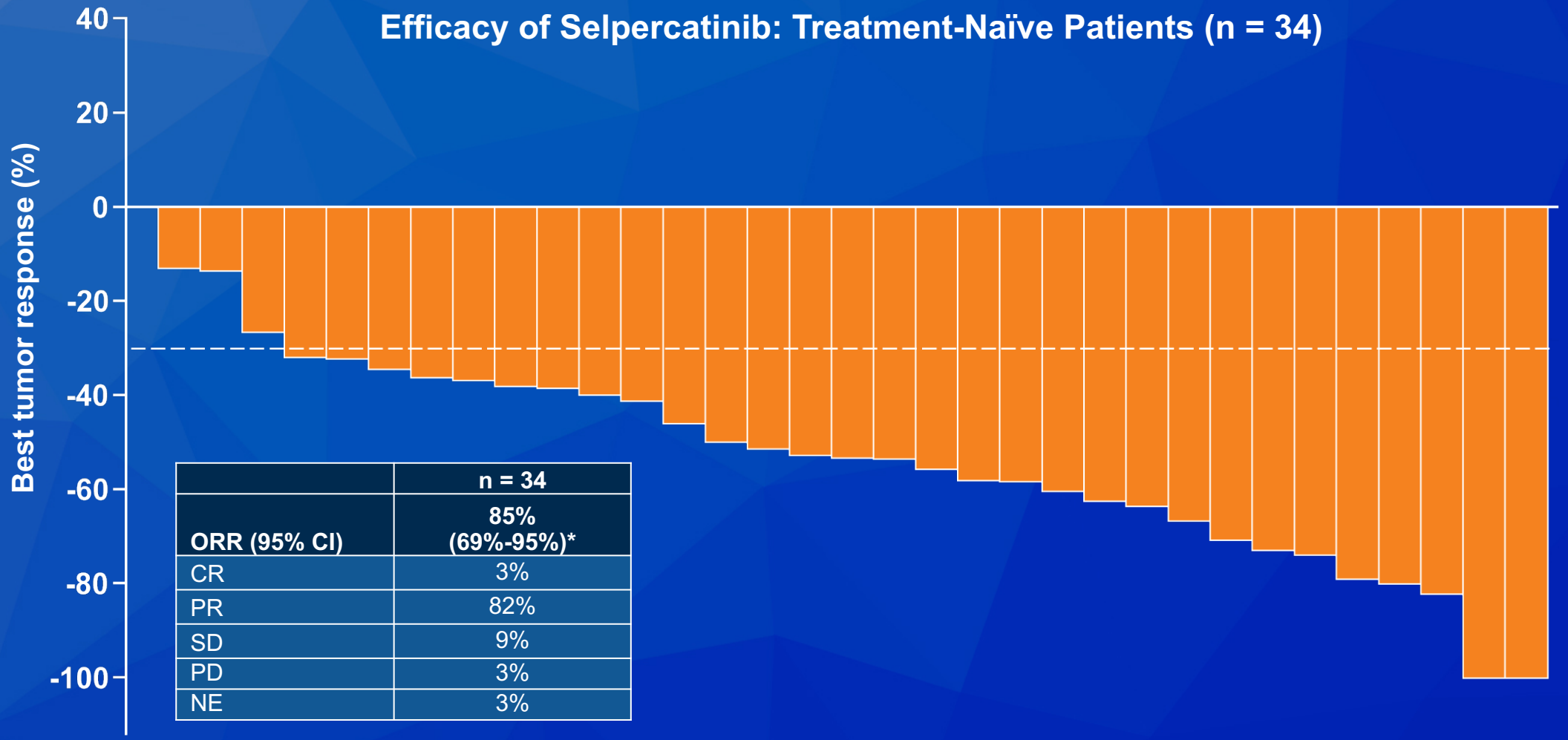


- ORR = 68%
- Intracranial ORR = 91%
- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2-16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (eg, anti-PD-1/PD-L1, MKIs)

Data cut-off: June 17th, 2019. Shading in PAS Kaplan-Meier curves indicates the 95% confidence band. * Medians are not statistically stable due to a low number of event

Drilon A et al. *Proc IASLC* 2019;Abstract PL02.08.

LIBRETTO-001: Primary Analysis Set (PAS) with Selpercatinib (LOXO-292) for Lung Cancer with RET Fusion



	n = 34
ORR (95% CI)	85% (69%-95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

Drilon A et al. *Proc IASLC* 2019;Abstract PL02.08.

Editorial — Dr Neal

In NSCLC, driver RET gene rearrangements are present in 1%-2% of tumors, but off-label treatment with currently available drugs such as cabozantinib, alectinib, and vandetanib has only modest activity. Newly developed potent and selective RET inhibitors are emerging, including LOXO-292 (selpercatinib) and BLU-667 (pralsetinib). In studies presented this year, both of these agents had high response rates in RET fusion-positive NSCLC. With LOXO-292, more than 250 patients have been treated, with a response rate of almost 70% and even higher in measurable CNS disease. While fewer than 80 patients have been treated with BLU-667, the response rate was similarly high and CNS activity was also seen. Side effects of both agents included hypertension, ALT/AST elevation, and fatigue. Both of these drugs are promising as emerging therapies and are poised to move to the first-line treatment setting for RET-positive NSCLC if approved. As with NTRK, the key to targeting RET is in identifying tumors harboring it, and either DNA NGS or RNA fusion assays are most sensitive for detection.

FDA Breakthrough Therapy Designation for Capmatinib (INC280) for Patients with MET-Mutated Advanced NSCLC

Press Release – September 6, 2019

"The US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to capmatinib (INC280) as a first-line treatment for patients with metastatic MET exon14 skipping-mutated non-small cell lung cancer (NSCLC)."

"Capmatinib (INC280) is an investigational, oral, highly potent and selective MET inhibitor. Recent research concludes that the cMET gene is an oncogenic driver, and the investigational lung cancer therapy capmatinib has been shown to be a highly potent and selective MET inhibitor. The MET mutation is seen in an estimated 3% - 4% of all patients with NSCLC. These patients are generally older and often have a poor prognosis that can limit lung cancer treatment options."

https://www.novartis.com/news/media-releases/novartis-investigational-lung-cancer-therapy-capmatinib-inc280-granted-fda-breakthrough-therapy-designation-patients-met-mutated-advanced-non-small-cell-lung

Capmatinib (INC280) in *METΔex14*-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC): Efficacy Data from the Phase II GEOMETRY mono-1 Study

Wolf J et al.
Proc ASCO 2019;Abstract 9004.

GEOMETRY mono-1: A Phase II Trial of Capmatinib for Patients with Advanced NSCLC Harboring MET Exon 14 Skipping Mutation

Eligibility

- Stage IIIB/IV NSCLC
- MET exon 14 skipping mutation irrespective of MET GCN by central RT-PCR
- EGFR wt (for L85R and delE19) and ALK-negative
- PS 0-1
- ≥1 measurable lesion
- Neurologically stable or asymptomatic brain metastases allowed

Cohort 4
(Pretreated, second/third line)
N = 69
Capmatinib 400 mg BID

Cohort 5b
(Treatment naïve)
N = 28
Capmatinib 400 mg BID

Primary endpoint: ORR (BIRC)
Secondary endpoints: DoR, PFS, OS, safety

- Cohort 4 overall response rate: 40.6%, median DoR: 9.72 months, median PFS: 5.42 months
- Cohort 5b overall response rate: 67.9%, median DoR: 11.14 months, median PFS: 9.69 months
- Deep responses observed in a majority of patients across both cohorts

Wolf J et al. *Proc ASCO* 2019;Abstract 9004.

FDA Breakthrough Therapy Designation for Tepotinib in Metastatic NSCLC with MET exon 14 Skipping Alterations

Press Release – September 11, 2019

"The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for the investigational targeted therapy tepotinib in patients with metastatic non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping alterations who progressed following platinum-based cancer therapy.

Tepotinib was associated with robust objective responses with durability that has not previously been seen in patients with metastatic NSCLC harboring MET exon 14 skipping alterations, selected by either tissue or liquid biopsy approaches."

"This breakthrough therapy designation further underscores the potential of tepotinib, and [the] aim [is] to advance this program and deliver this medicine as quickly as possible to patients with NSCLC who may benefit."

https://www.emdgroup.com/en/news/tepotinib-breakthrough-therapy-designation-11-09-2019.html

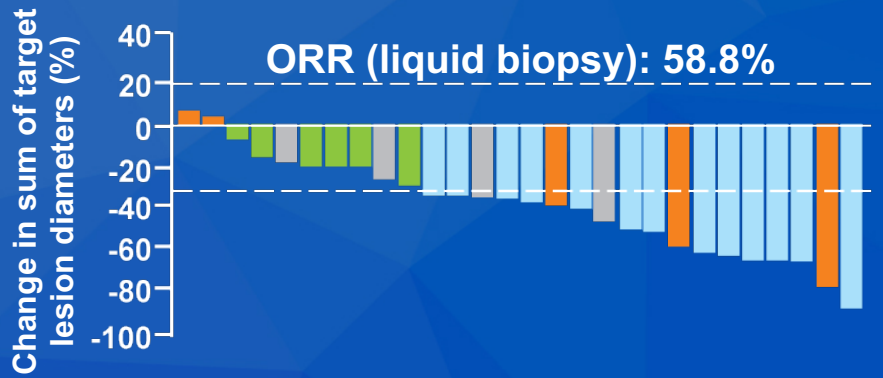
Phase II Study of Tepotinib in NSCLC Patients with METex14 Mutations

Paik PK et al.
Proc ASCO 2019;Abstract 9005.

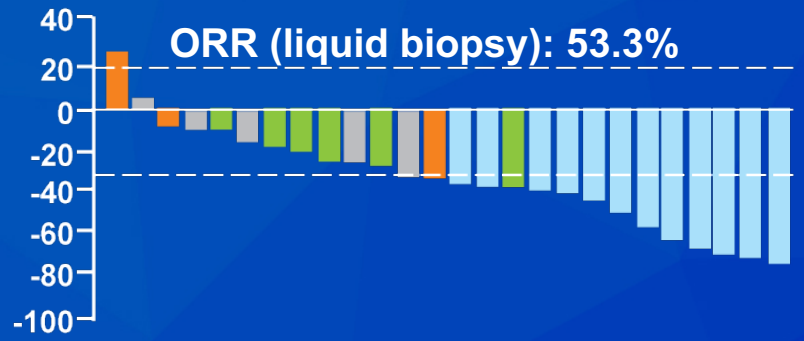
VISION Study: Tumor Shrinkage with Tepotinib by Line of Therapy (IRC)

First line

Evidence of tumor shrinkage in 92% of patients by both IRC and investigator read

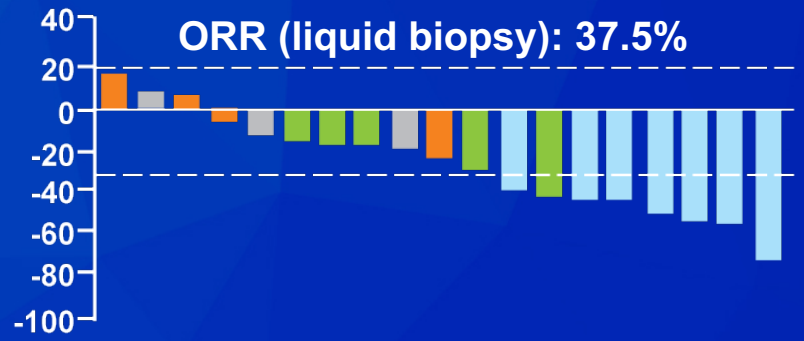


Second line



Thrid line

Evidence of tumor shrinkage in ≥75% of patients



Best overall response

PR SD PD NE

- Responses occurred early and were durable across treatment lines
- ORR (IRC): liquid biopsy 50%, tissue biopsy 45.1%
- Overall median duration of response: 14.3 months
- Patients with brain metastases at baseline benefitted equally from treatment
- TRAEs Grade ≥3 included peripheral edema (8%), increased ALT (2.3%), increased amylase (2.3%)

Paik PK et al. *Proc ASCO* 2019;Abstract 9005.

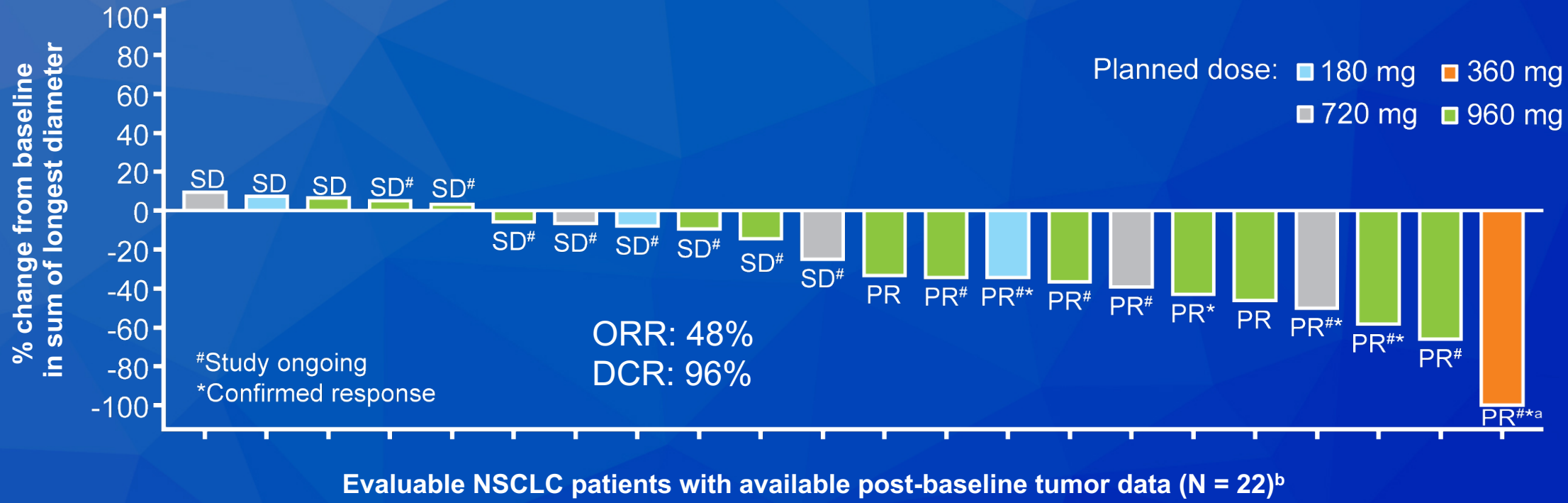
Editorial — Dr Neal

In NSCLC, another emerging driver mutation is the MET exon 14 splice site mutation. About as frequent as ALK-positive NSCLC (3%-4%), it is most reliably identified by DNA NGS or RNA fusion assays. The FDA-approved ALK and ROS1 inhibitor crizotinib is increasingly used off label for its MET-inhibitory activity for patients with METe14 NSCLC, but more potent and selective inhibitors are in development. At ASCO, a phase II study of tepotinib was presented including 85 patients and demonstrated response rates between 30% and 70%, depending on line of treatment and prior therapy. Peripheral edema was observed in addition to other common TKI side effects. Results on another potent MET inhibitor, capmatinib, were also presented at ASCO, again with response rates between 40% and 70%, depending on line of therapy. Adverse events appeared similar to those with tepotinib. Overall, these emerging MET inhibitors, along with others in development, are likely to displace the current off-label use of crizotinib if approved over the next year.

Phase 1 Study of AMG 510, a Novel KRAS^{G12C} Inhibitor, in Advanced Solid Tumors with *KRAS p.G12C* Mutation

Govindan R et al.
Proc ESMO 2019;Abstract 446PD.

AMG 510: Change in Tumor Burden from Baseline, Objective Response Rate and Safety in NSCLC



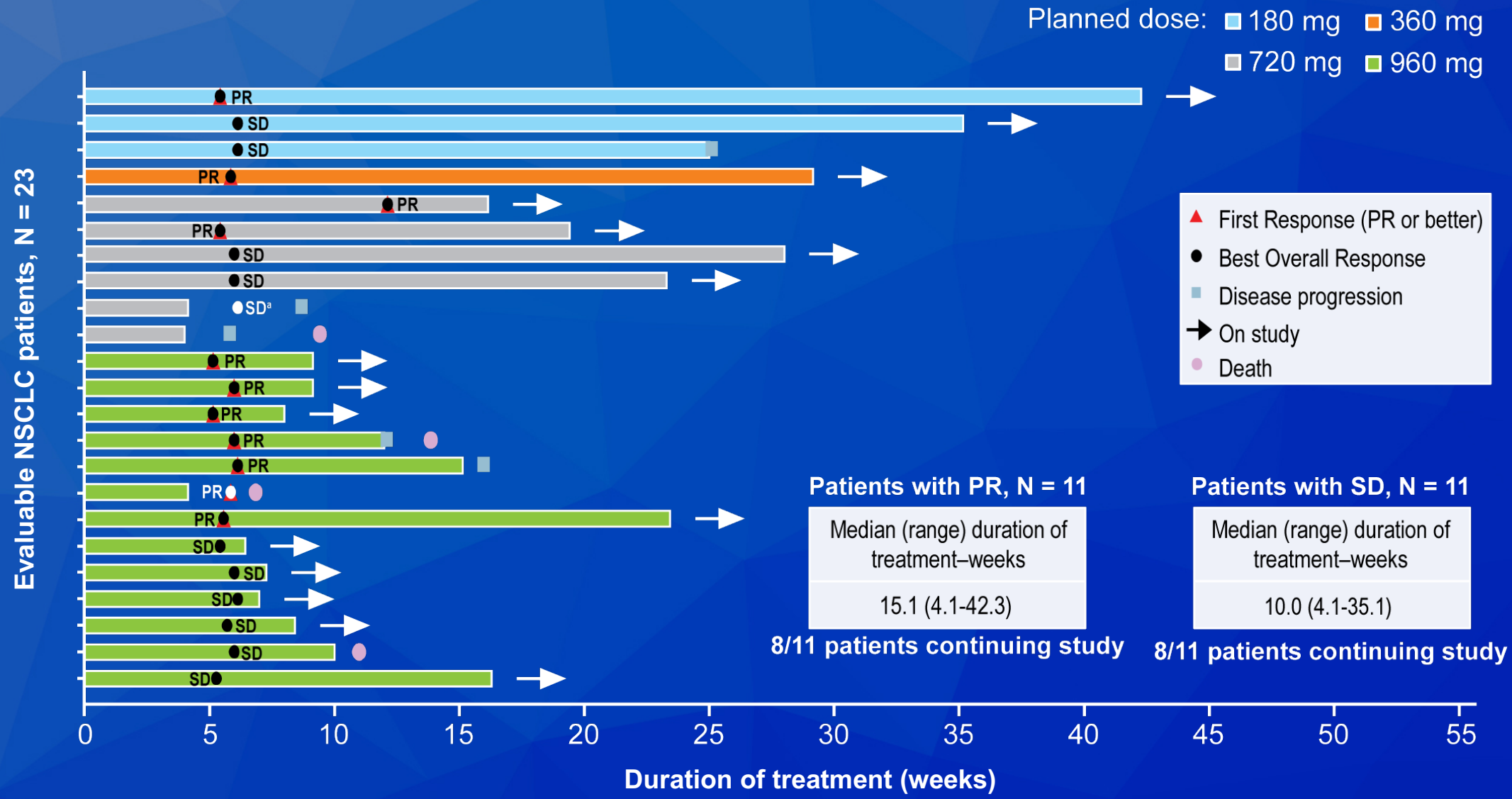
Evaluable NSCLC patients with available post-baseline tumor data (N = 22)[b]

[a] Patient had complete response to the target lesions, [b] 1 patient discontinued study due to PD prior to the 1st assessment without available post-baseline tumor burden data, and therefore is not shown on the graph.

- 26 of 76 patients (34.2%) reported treatment-related adverse events; most were Grade 1 or 2
- 6 of 76 patients (7.9%) reported 1 or more Grade 3 treatment-related adverse events: diarrhea and anemia
- No grade 4 or higher treatment-related adverse events were reported

Govindan R et al. *Proc ESMO* 2019;Abstract 446PD.

AMG 510: Time to Response and Duration of Treatment



Patients with PR, N = 11

Median (range) duration of treatment–weeks
15.1 (4.1-42.3)

8/11 patients continuing study

Patients with SD, N = 11

Median (range) duration of treatment–weeks
10.0 (4.1-35.1)

8/11 patients continuing study

Govindan R et al. *Proc ESMO* 2019;Abstract 446PD.

Lung Cancer — Drs Liu and Riely

Targeted Therapy in NSCLC

Immune Checkpoint Inhibitors (ICIs) in Patients with Locally Advanced NSCLC

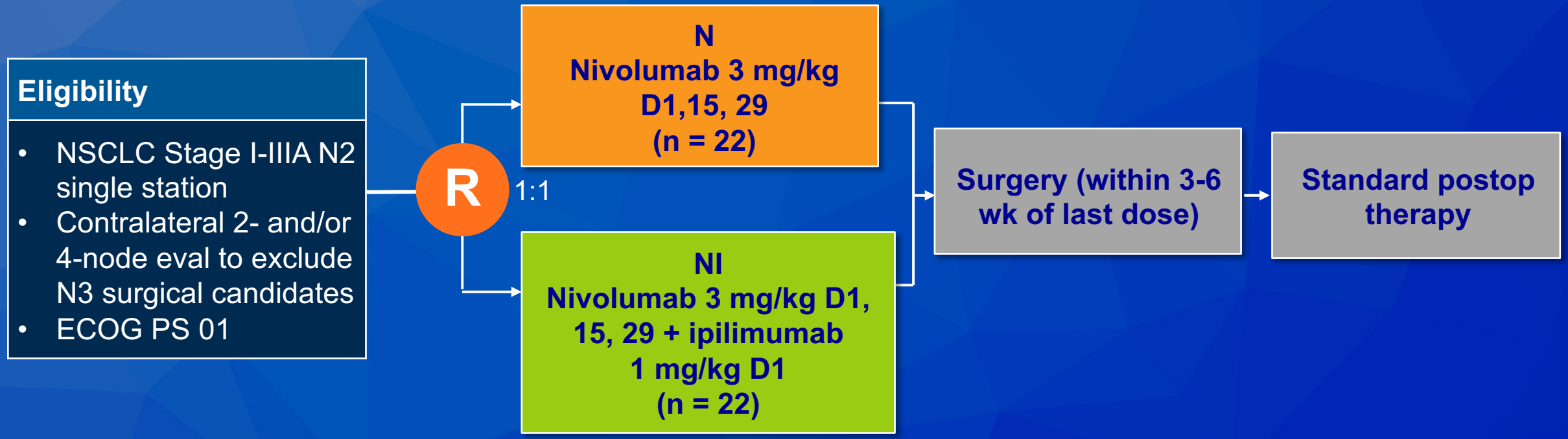
ICIs in Patients with SCLC

Integration of ICIs into Therapy for Metastatic NSCLC

Neoadjuvant Nivolumab (N) or Nivolumab plus Ipilimumab (NI) for Resectable Non-Small Cell Lung Cancer (NSCLC): Clinical and Correlative Results from the NEOSTAR Study

Cascone T et al.
Proc ASCO 2019;Abstract 8504.

NEOSTAR Study: Neoadjuvant Nivolumab or Nivolumab and Ipilimumab for Resectable NSCLC



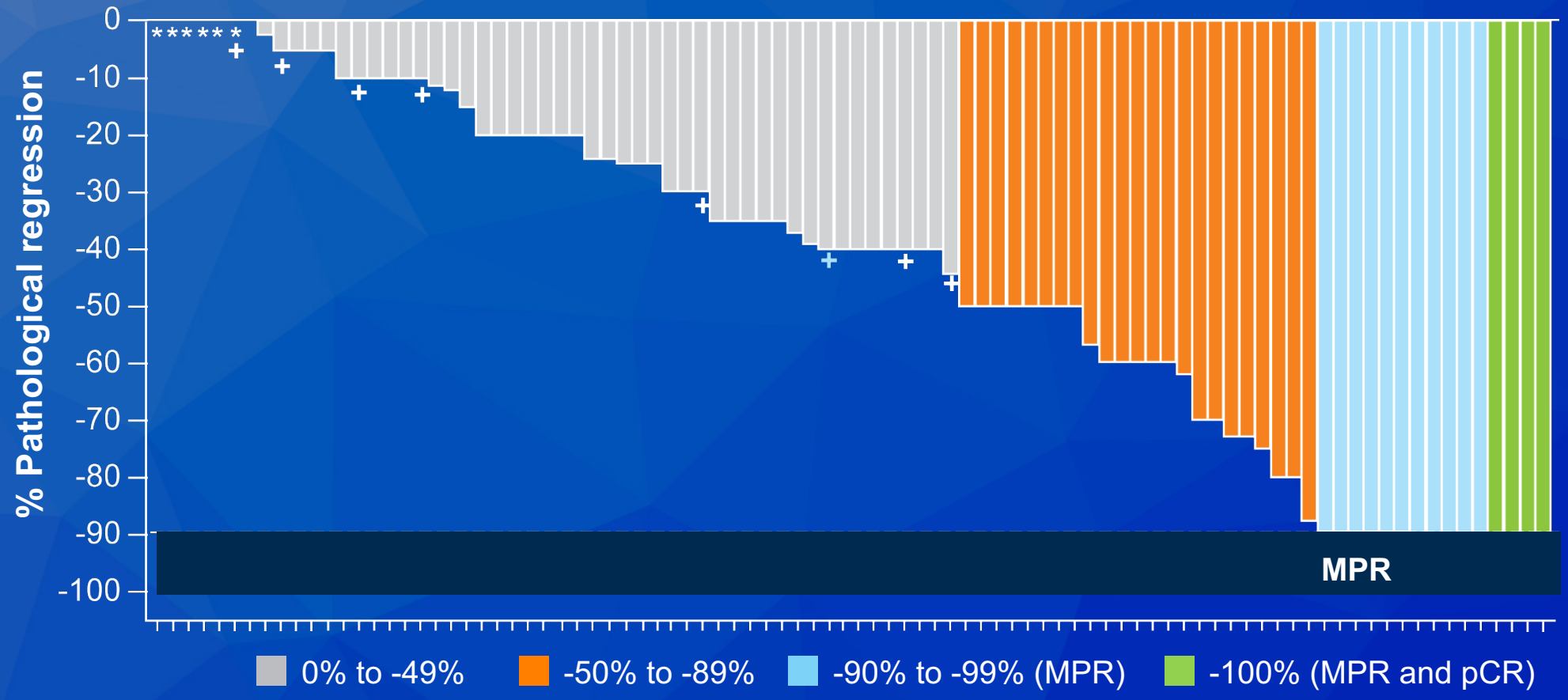
- Primary endpoint: MPR rate (≤10% viable tumor)
- MPR rate (ITT): N, 17%; NI, 33%

Cascone T et al. *Proc ASCO* 2019;Abstract 8504.

Neoadjuvant Atezolizumab in Resectable Non-Small Cell Lung Cancer (NSCLC): Interim Analysis and Biomarker Data from a Multicenter Study (LCMC3)

Kwiatkowski D et al.
Proc ASCO 2019;Abstract 8503.

LCMC3 Study: Neoadjuvant Atezolizumab for Resectable NSCLC



Pathological regression defined as % viable tumor cells – 100%. pCR = pathologic complete response.
[a] 1 EGFR+ patient had aborted surgery. * Pathologic response could not be assessed. + EGFR. + ALK+

Kwiatkowski D et al. *Proc ASCO* 2019;Abstract 8503.

Editorial — Dr Liu

While there are many efforts to optimize the use of immunotherapy in advanced lung cancer, one of the more compelling stories to emerge in 2019 is the potential impact of these agents in early stage disease. Unlike other solid tumors, early stage lung cancer is still characterized by high rates of relapse and an unacceptable mortality rate. With greater implementation of lung cancer screening, it is imperative that we improve outcomes for patients with resectable NSCLC, and there is considerable interest in the implementation of checkpoint inhibitors in the perioperative setting, particularly as neoadjuvant therapy.

There are several reasons neoadjuvant immunotherapy could offer an advantage over the traditional adjuvant approach. The primary tumor can serve as an antigen source to facilitate T-cell engagement – this may be more difficult when the tumor is removed. Practically, response (specifically, pathologic response) can be properly assessed, providing insight into sensitivity and efficacy.

Editorial — Dr Liu (continued)

And perhaps equally important, the use of surrogate endpoints such as major pathologic response can accelerate outcomes by years.

Early results have given us plenty of reason for optimism but also signals of caution. NEOSTAR and LCMC3 explored neoadjuvant checkpoint inhibitors alone and showed very high response rates with encouraging rates of both major pathologic response and pathologic complete response. Neoadjuvant chemoimmunotherapy has offered even higher response rates in the NADIM study. Important lessons learned from these early studies include observing “nodal flares,” which can be mistaken for progression, and immune related adverse events during therapy and after surgery. Close attention will be paid to the rate of patients who did not undergo surgery or who had significant delays, as this can compromise outcomes. As we look toward more results in 2020, it will be important to observe these trends in the setting of a comparator arm, but the early activity seen with these approaches has made this the approach to watch in early stage NSCLC.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

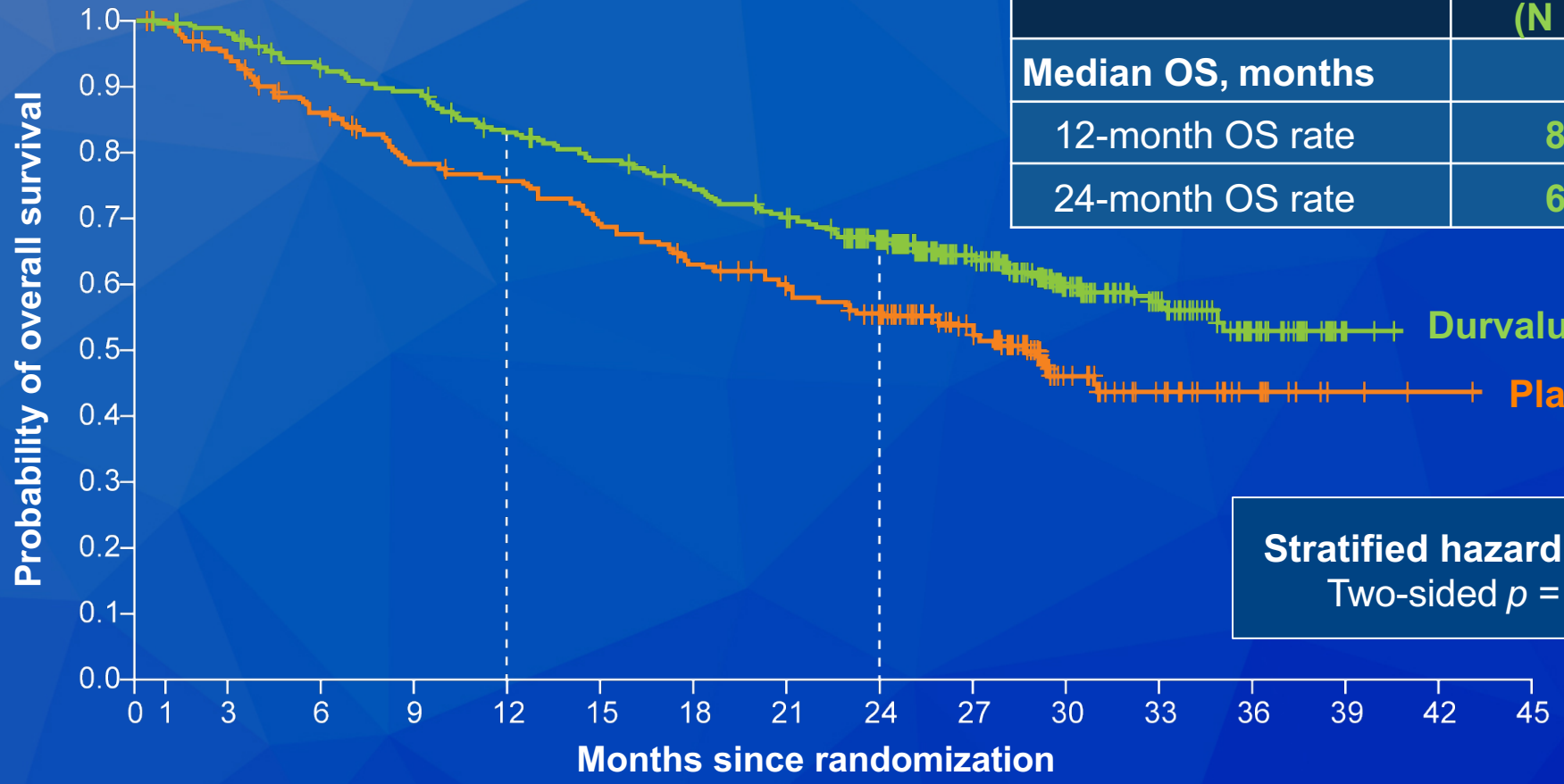
Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

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;379(24):2342-50.

PACIFIC Trial: 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;379(24):2342-50.

Editorial — Dr Liu

PACIFIC set a new standard of care for stage III unresectable NSCLC, with profound improvements in PFS. This year, the change in practice was solidified with the notable improvement in overall survival with this approach. The magnitude of PFS benefit in PACIFIC was fully expected to translate in a survival benefit, but this did not make the reveal any less exciting. With implementation of immunotherapy after chemoradiation, a significant proportion of our patients are living longer. There certainly remains room for improvement, and ongoing efforts will seek to optimize the approach. Is there a benefit to longer duration of therapy, beyond the 1 year employed in PACIFIC? Will there be further benefit if immunotherapy is given concurrently with radiation, an approach that could further leverage synergy between these modalities? We eagerly anticipate the results of these and other studies.

Lung Cancer — Drs Liu and Riely

Targeted Therapy in NSCLC

Immune Checkpoint Inhibitors (ICIs) in Patients with Locally Advanced NSCLC

ICIs in Patients with SCLC

Integration of ICIs into Therapy for Metastatic NSCLC

FDA Approves Atezolizumab for Extensive-Stage Small Cell Lung Cancer

Press Release – March 18, 2019

"On March 18, 2019, the Food and Drug Administration approved atezolizumab in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Approval was based on IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC who received no prior chemotherapy for extensive stage disease and had ECOG performance status 0 or 1. Patients were randomized to one of the following:

1. Atezolizumab 1200 mg and carboplatin AUC 5 mg/mL/min on day 1 and etoposide 100 mg/m^2 intravenously on days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by atezolizumab 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
2. Placebo and carboplatin AUC 5 mg/mL/min on day 1 and etoposide 100 mg/m^2 intravenously on days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles, followed by placebo once every 3 weeks until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-extensive-stage-small-cell-lung-cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

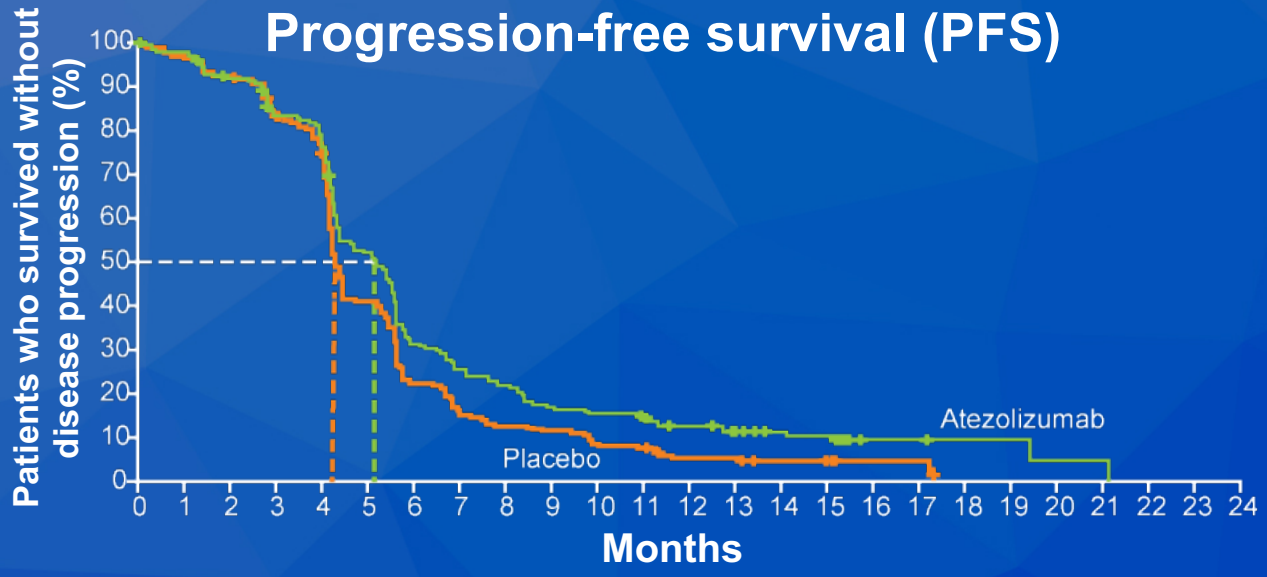
First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

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;379(23):2220-9.

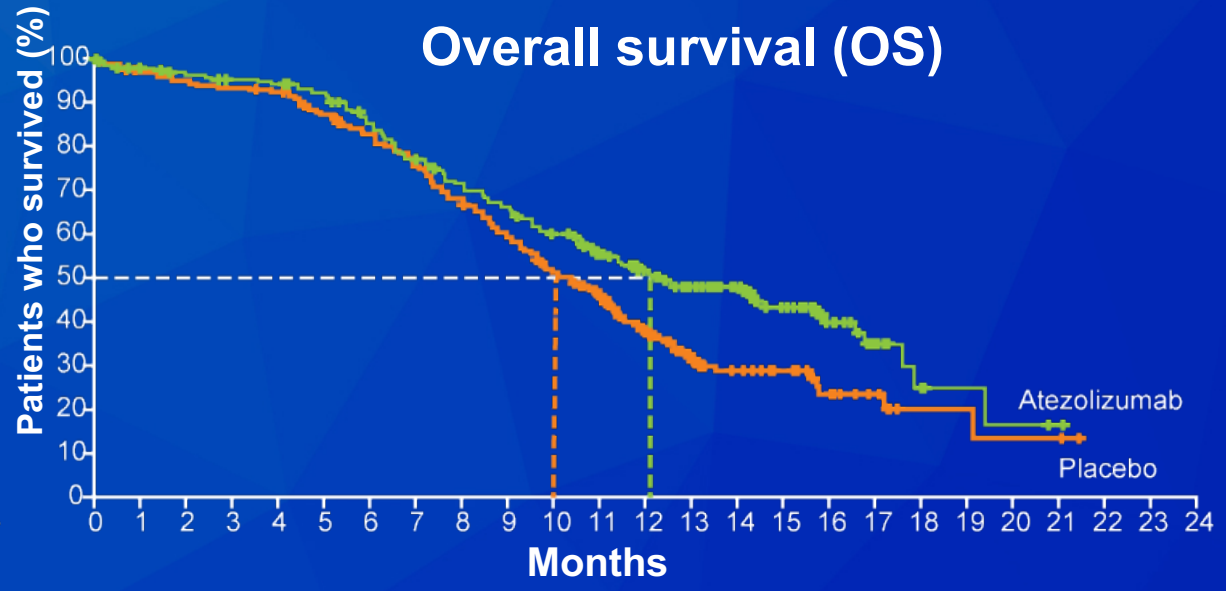
IMpower133: Survival Outcomes with First-Line Atezolizumab and Chemotherapy for Extensive-Stage SCLC

Progression-free survival (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 (OS)



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

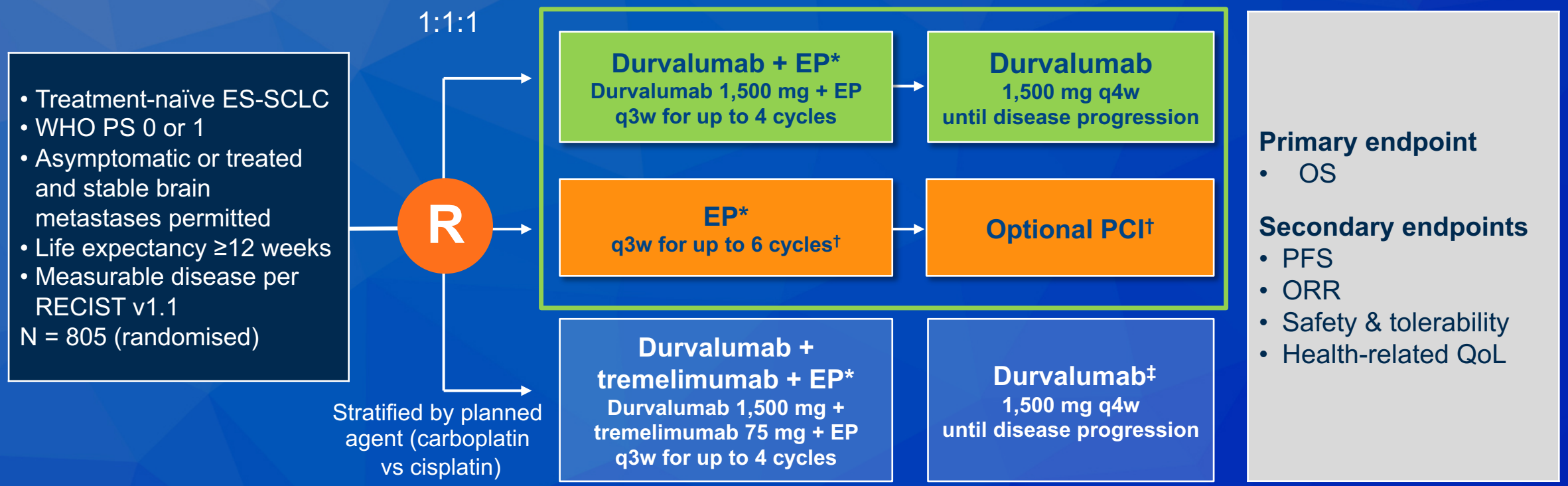
- The safety profile of atezolizumab + carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents; no new findings were observed.

Horn L et al. *N Engl J Med* 2018;379(23):2220-9.

Durvalumab Plus Platinum-Etoposide versus Platinum-Etoposide in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): A Randomised, Controlled, Open-Label, Phase 3 Trial

Paz-Ares L et al.
Lancet 2019;394(10212):1929-39.

CASPIAN: Phase III Trial Design



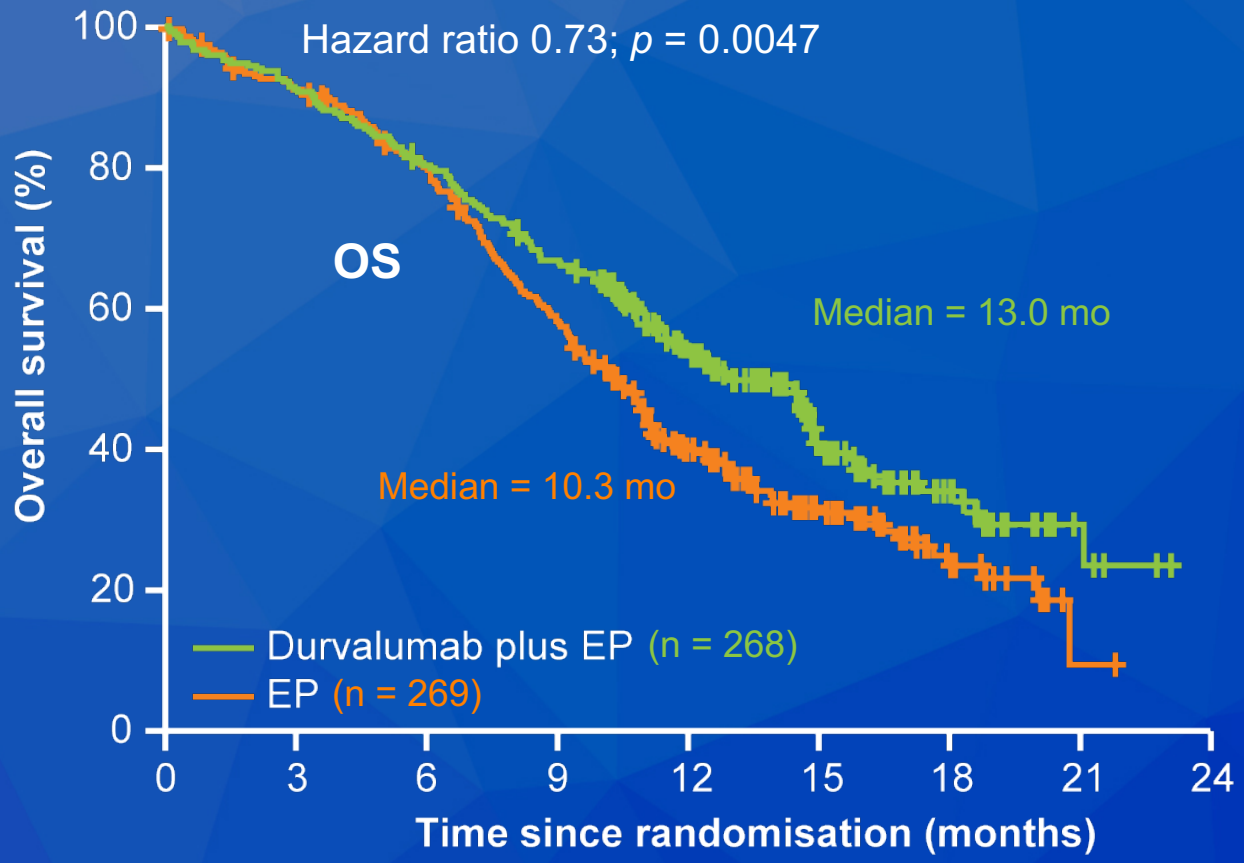
The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

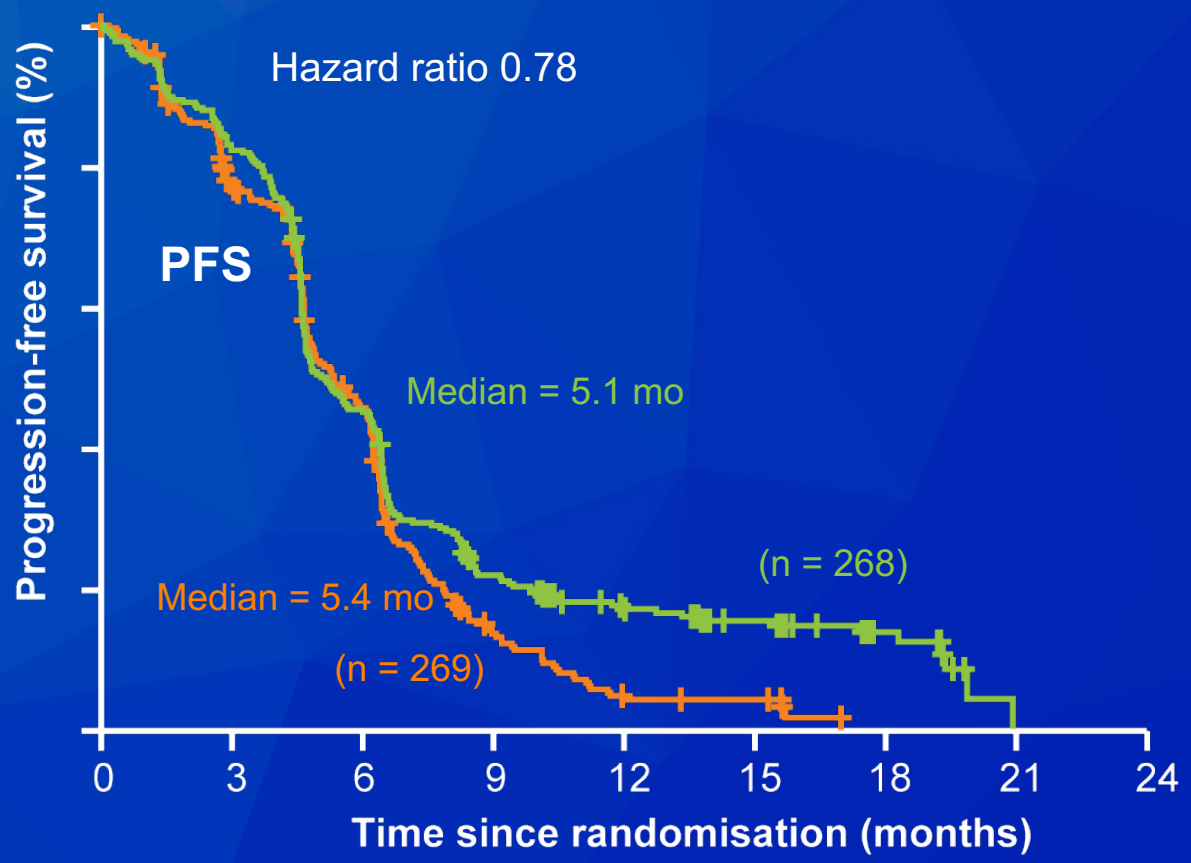
* EP consists of etoposide 80-100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75-80 mg/m^2
† Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡ Patients received an additional dose of tremelimumab post-EP

AUC = area under the curve; ORR = objective response rate; PCI = prophylactic cranial irradiation; PFS = progression-free survival; PS = performance status; q3w = every 3 weeks; q4w = every 4 weeks; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; WHO = World Health Organization

Paz-Ares L et al. *Proc IASLC* 2019;Abstract PL02.11.

CASPIAN: PFS, OS and Objective Response Rate in ITT Population





- **Confirmed ORR in ITT population:**
  - 68% (Durvalumab/EP) vs 58% (EP)
  - Odds ratio = 1.56

Paz-Ares L et al. *Lancet* 2019;394(10212):1929-39.

FDA Approves Pembrolizumab for Metastatic Small Cell Lung Cancer

Press Release – June 17, 2019

"On June 17, 2019, the Food and Drug Administration granted accelerated approval to pembrolizumab for patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Efficacy was investigated in 83 patients with SCLC who had disease progression on or after two or more prior lines of therapy enrolled in one of two multicenter, multi-cohort, non-randomized, open label trials: KEYNOTE-158 (NCT02628067) Cohort G or KEYNOTE-028 (NCT02054806) Cohort C1. Patients received either pembrolizumab 200 mg intravenously every 3 weeks (n = 64) or 10 mg/kg intravenously every 2 weeks (n = 19). Treatment continued until documented disease progression, unacceptable toxicity, or a maximum of 24 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-metastatic-small-cell-lung-cancer

Pembrolizumab After Two or More Lines of Prior Therapy in Patients with Advanced Small-Cell Lung Cancer (SCLC): Results from the KEYNOTE-028 and KEYNOTE-158 Studies

Chung HC et al.
Proc AACR 2019;Abstract CT073.

Pembrolizumab After 2 or More Lines of Prior Therapy in Patients with Advanced Small Cell Lung Cancer (SCLC): Results from the KEYNOTE-028 and KEYNOTE-158 Studies

Primary and secondary endpoints	Patients eligible for efficacy analyses (n = 83)
ORR	19.3%
Median PFS	2.0 mo
Median OS	7.7 mo
Median DoR	Not reached

- Pembrolizumab demonstrated promising antitumor activity in patients with advanced SCLC who had received ≥2 lines of prior therapy.
- No unexpected toxicities from pembrolizumab were observed.

Chung HC et al. *Proc AACR* 2019;Abstract CT073.

Editorial — Dr Liu

Based in part on its high rate of somatic mutations, there was great interest in immunotherapy in SCLC. Over the past few years, we have seen undeniable activity, though the benefit has been admittedly modest. Nivolumab was approved as monotherapy last year, and this year, in a pooled analysis of two single-arm studies, we saw comparable activity with pembrolizumab, leading to its approval as another third-line option. While response rates were fairly low, landmark survival and duration of response were both impressive. Second-line therapy, however, did not improve outcomes over standard chemotherapy, and disappointingly, use of maintenance nivolumab and ipilimumab in CheckMate 451 did not improve survival over placebo.

Fortunately, we have made long-overdue strides in the front-line setting, where two trials have now shown a survival advantage when PD-L1 inhibitors are added to platinum doublet chemotherapy.

Editorial — Dr Liu (continued)

IMpower133 showed an OS benefit (HR 0.70) when atezolizumab was added to carboplatin and etoposide, the first trial in over 30 years to improve OS as first-line therapy for SCLC. Less than a year later, we had another positive study, CASPIAN, which showed a strikingly similar OS benefit (HR 0.73) with the addition of durvalumab to platinum + etoposide. This validated the overall approach and confirmed our shift in standard of care. We must now build on these advances and deliver a meaningful survival benefit to a greater proportion of our patients with SCLC.

Lung Cancer — Drs Liu and Riely

Targeted Therapy in NSCLC

Immune Checkpoint Inhibitors (ICIs) in Patients with Locally Advanced NSCLC

ICIs in Patients with SCLC

Integration of ICIs into Therapy for Metastatic NSCLC

IMpower150: An Exploratory Analysis of Efficacy Outcomes in Patients with EGFR Mutations

Reck M et al.
Proc ELCC 2019;Abstract 104O.

IMpower150: An Exploratory Analysis of Efficacy Outcomes in Patients with EGFR Mutations

Median OS, mo	ABCP	BCP	ABCP vs BCP HR
EGFR mutation (n = 79)	NE	18.7	0.61
Sensitising EGFR mutation[a] (n = 58)	NE	17.5	0.31
Received prior TKI therapy (n = 50)	NE	17.5	0.39
Median PFS, mo	**ABCP**	**BCP**	**HR**
EGFR mutation (n = 78)	10.2	6.9	0.61
Sensitising EGFR mutation[a] (n = 58)	10.3	6.1	0.41
Received prior TKI therapy (n = 50)	9.7	6.1	0.42

[a] Defined as exon 19 deletions or L858R mutations.
A = atezolizumab; B = bevacizumab; C = carboplatin; P = paclitaxel; NE = not estimable

- IMpower150 is the first randomised Phase III trial of a checkpoint inhibitor to show a benefit for patients with pretreated disease with EGFR mutations.
- Overall survival was improved with ACP vs BCP in patients with EGFR mutations and sensitizing EGFR mutations.

Reck M et al. *Proc ELCC* 2019;Abstract 104O.

Positive Results from the Phase III IMpower110 Trial of Atezolizumab Monotherapy as First-Line Therapy for NSCLC

Press Release – September 12, 2019

"Positive data were announced from the Phase III IMpower110 study evaluating atezolizumab as a first-line (initial) monotherapy compared with cisplatin or carboplatin and pemetrexed or gemcitabine (chemotherapy) in advanced non-squamous and squamous non-small cell lung cancer (NSCLC) without ALK or EGFR mutations (Wild-Type or WT).

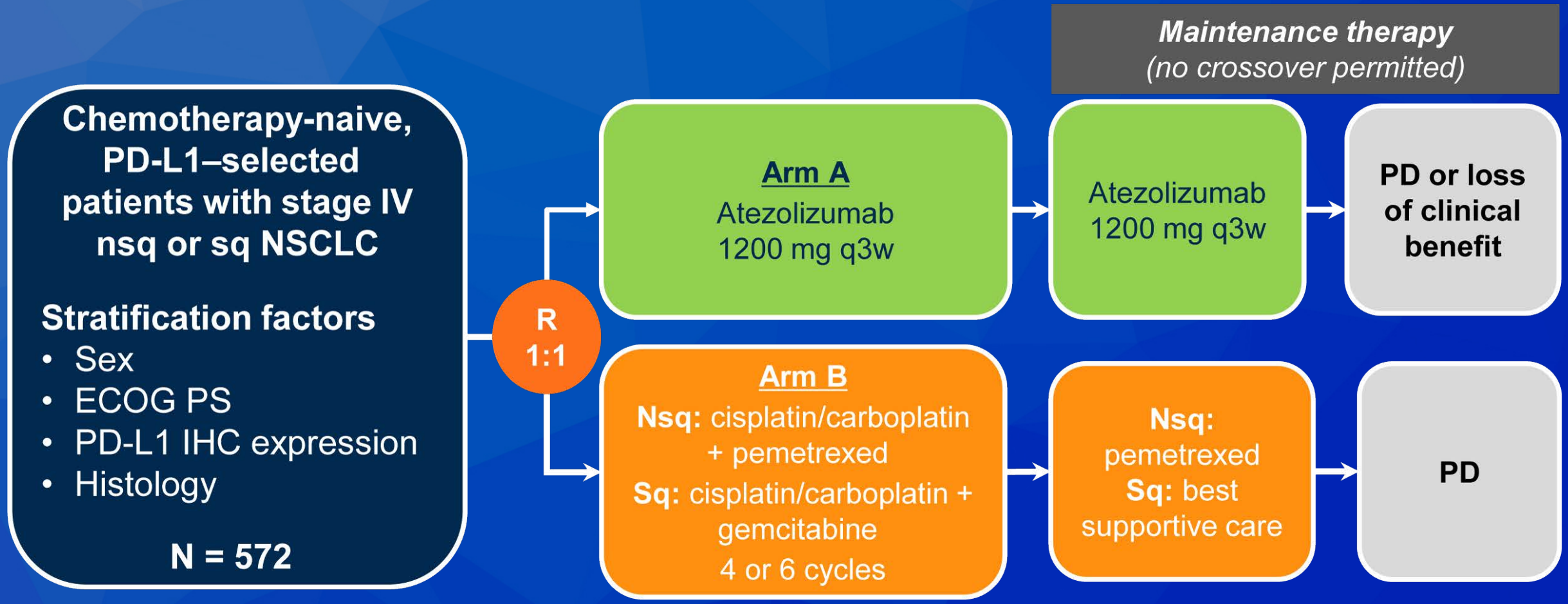
The study met its primary endpoint in an interim analysis showing that atezolizumab monotherapy demonstrated a statistically significant overall survival (OS) benefit in people with high PD-L1 expression (TC3/IC3-WT), compared with chemotherapy alone. Safety for atezolizumab appeared to be consistent with its known safety profile and no new safety signals were identified. The study will continue to final analysis for patients with lower levels of PD-L1 expression."

https://www.roche.com/investors/updates/inv-update-2019-09-12.htm

IMpower110: Interim OS Analysis of a Phase III Study of Atezolizumab (atezo) vs Platinum-Based Chemotherapy (chemo) as 1L Treatment (tx) in PD-L1–Selected NSCLC

Spigel DR et al.
Proc ESMO 2019;Abstract LBA-78.

IMpower110: Phase III Trial Design



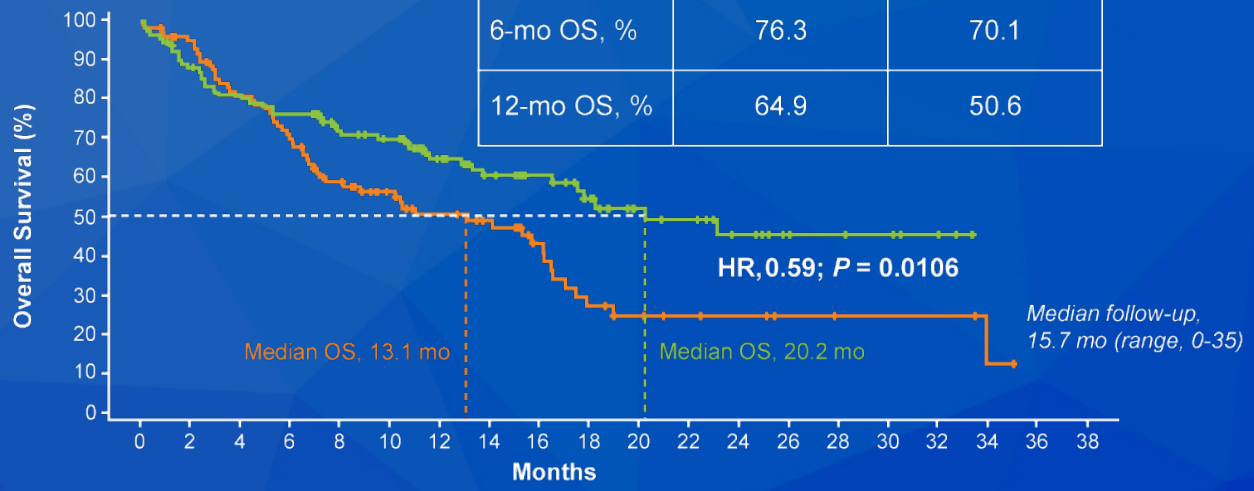
- **Primary endpoint: OS in WT population (excludes patients with EGFR+ and/or ALK+ NSCLC)**

Spigel DR et al. *Proc ESMO* 2019;Abstract LBA78.

IMpower110: OS Results

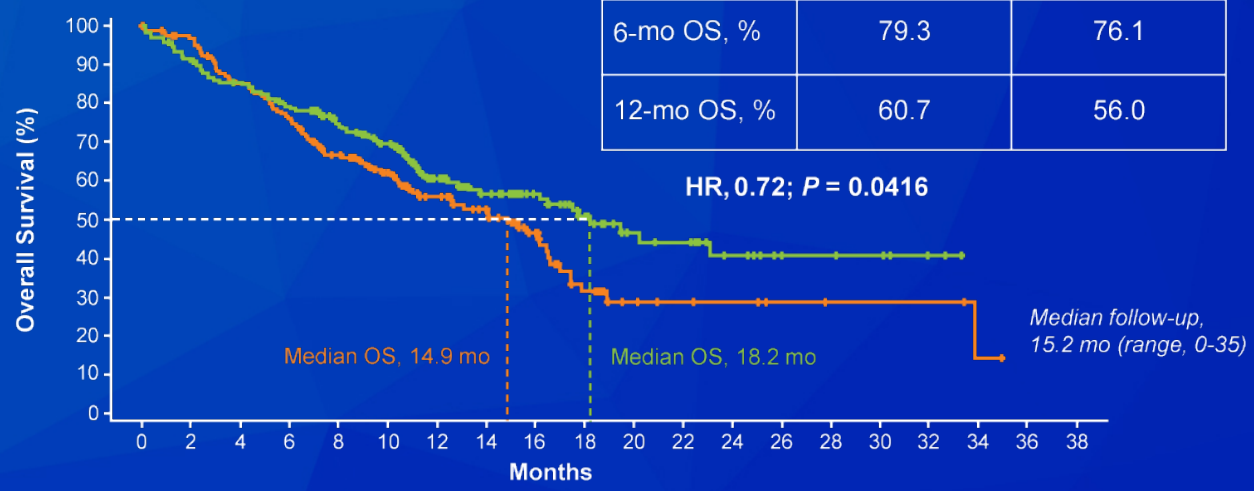
TC3 or IC3 WT Population

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS, %	76.3	70.1
12-mo OS, %	64.9	50.6



TC2/3 or IC2/3 WT Population

Landmark	Arm A (atezo) n = 166	Arm B (chemo) n = 162
6-mo OS, %	79.3	76.1
12-mo OS, %	60.7	56.0



NE = Not estimable. TC = tumor cell, IC = immune cell; TC1/2/3 and IC1/2/3 = PD-L1 expression on TC or IC by the SP142 IHC assay

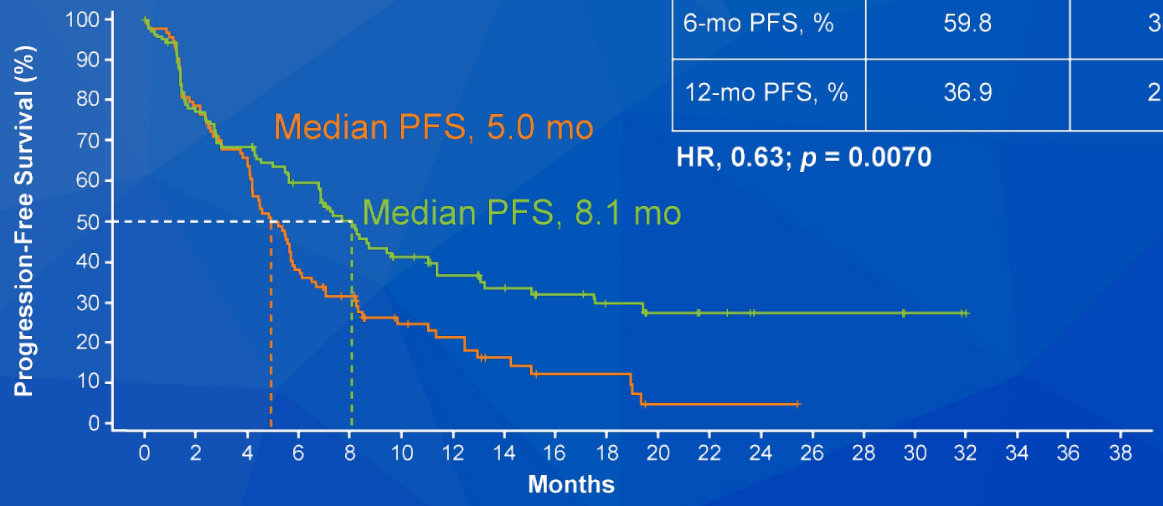
Spigel DR et al. *Proc ESMO* 2019;Abstract LBA78.

IMpower110: PFS and Response Rates

TC3 or IC3 WT Population

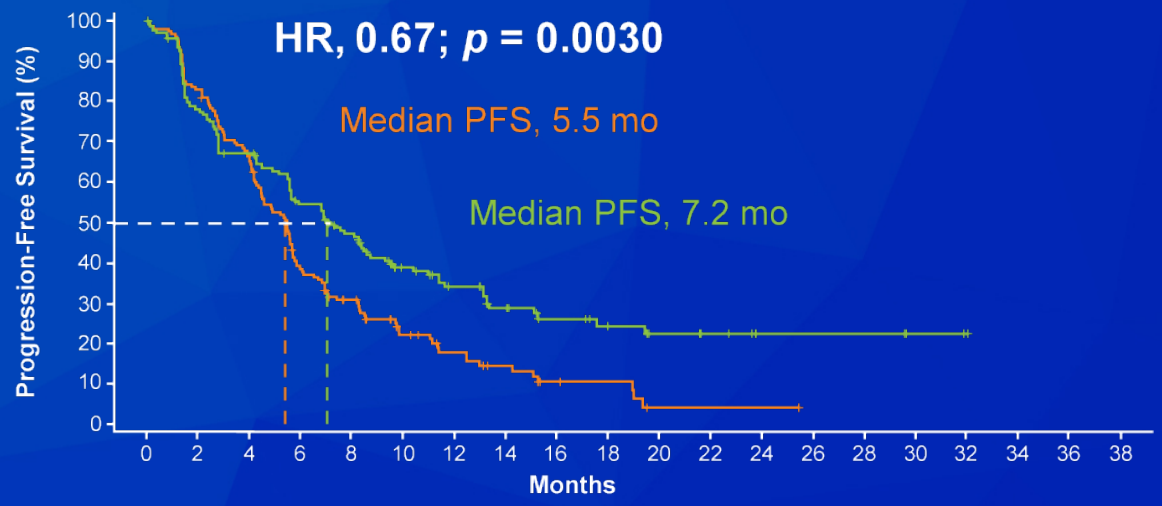
Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo PFS, %	59.8	38.3
12-mo PFS, %	36.9	21.6

HR, 0.63; $p = 0.0070$



- Median PFS in TC1/2/3 or IC1/2/3 WT population
  - 5.5 mo (atezo) vs 5.7 mo (chemo)
    - HR = 0.77; $p = 0.0104$

TC2/3 or IC2/3 WT Population



- ORR in TC3/IC3 WT population
  - 38.3% (atezo) vs 28.6% (chemo)
- ORR in TC1/2/3 or IC1/2/3 WT population
  - 29.2% (atezo) vs 31.8% (chemo)

Spigel DR et al. *Proc ESMO* 2019;Abstract LBA78.

Editorial — Dr Liu

Immunotherapy has radically improved outcomes for many patients with NSCLC, but one subset that has not derived much benefit is patients with EGFR+ NSCLC. Retrospective studies have shown low response rates to PD-1 inhibitor monotherapy and lack of clear benefit over chemotherapy. This is balanced by the observation that some of the long-term survivors on the phase I study of nivolumab were EGFR+. IMpower150 was one of the few trials combining chemotherapy and immunotherapy that included patients with EGFR mutations (after appropriate TKI therapy). While this was a relatively small cohort and statistically an exploratory subgroup, there was a compelling improvement in OS in this subset of patients when treated with the quadruplet of carboplatin, paclitaxel, bevacizumab and atezolizumab (over chemotherapy and bevacizumab alone).

Editorial — Dr Liu (continued)

Is the concurrent VEGF and PD-L1 inhibition the key to this approach? IMpower130, which added atezolizumab but not bevacizumab to chemotherapy, also included patients with EGFR mutation but did not see any impact on survival for this cohort.

While the data are far from perfect, they are the most impressive immunotherapy data we have seen thus far for this patient subgroup. Though use of the 4-drug regimen in EGFR+ NSCLC is not part of the FDA label, it is approved in this setting elsewhere in the world and has emerged as a promising option for patients with TKI-resistant EGFR+ NSCLC.

FDA Approval of Atezolizumab in Combination with *Nab*-Paclitaxel and Carboplatin for Metastatic NSCLC without EGFR/ALK Aberrations

Press Release – December 3, 2019

"The Food and Drug Administration approved atezolizumab in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

Efficacy was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with Stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor, if appropriate. The trial randomized 724 patients (ITT) to receive atezolizumab, paclitaxel protein-bound, and carboplatin, followed by single-agent atezolizumab or to receive paclitaxel protein-bound and carboplatin, followed by maintenance pemetrexed at the investigator's discretion (control)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-nab-paclitaxel-and-carboplatin-metastatic-nsclc-without-egfralk

Atezolizumab in Combination with Carboplatin Plus *Nab*-Paclitaxel Chemotherapy Compared with Chemotherapy Alone As First-Line Treatment for Metastatic Non-Squamous Non-Small-Cell Lung Cancer (IMpower130): A Multicentre, Randomised, Open-Label, Phase 3 Trial

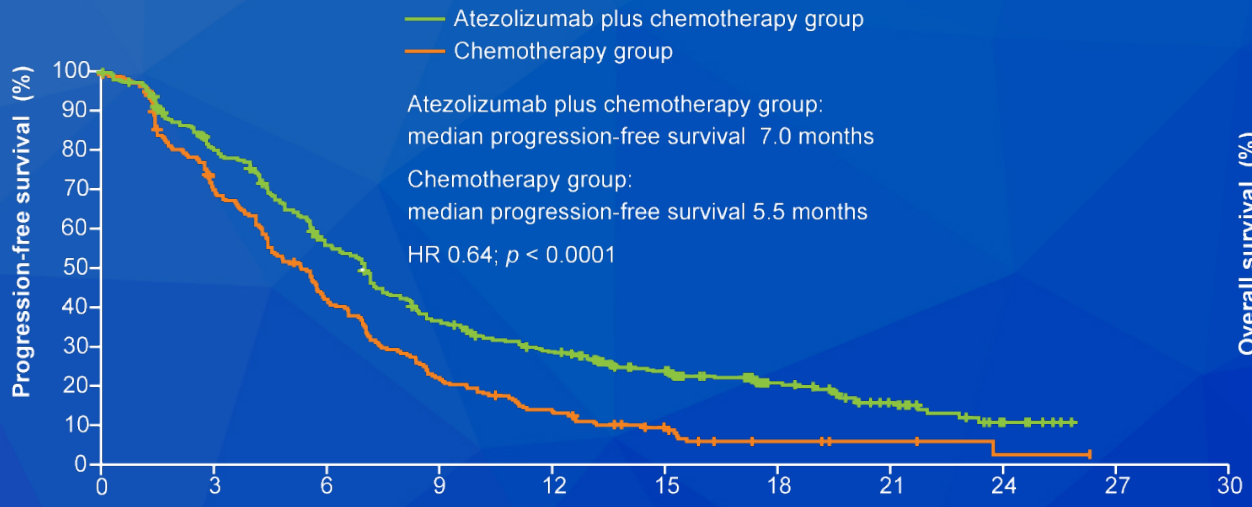
West H et al.

Lancet Oncol 2019;20(7):924-37.

IMpower130: PFS and OS Results

PFS in ITT-WT Population

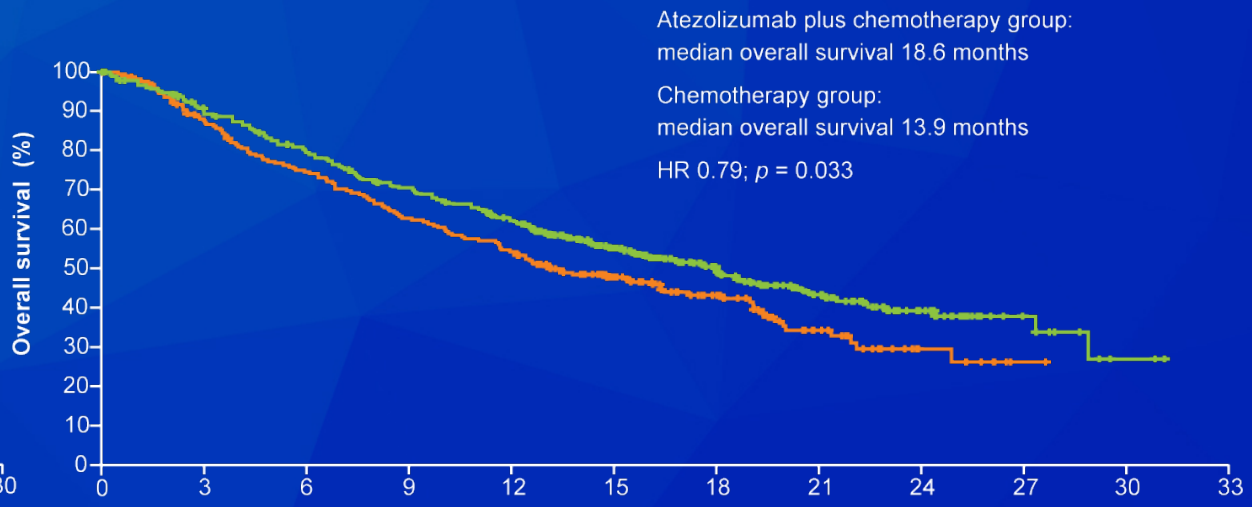
	Progression-free survival at 6 months	Progression-free survival at 12 months
Atezolizumab plus chemotherapy group	56.1%	29.1%
Chemotherapy group	42.5%	14.1%



- Median PFS in ITT population
  - 7.0 mo (atezo) vs 5.6 mo (chemo)
    - HR = 0.65; $p < 0.0001$

OS in ITT-WT Population

	Overall survival at 12 months	Overall survival at 24 months
Atezolizumab plus chemotherapy group	63.1%	39.6%
Chemotherapy group	55.5%	30.0%



- Median OS in ITT population
  - 18.1 mo (atezo) vs 13.9 mo (chemo)
    - HR = 0.80; $p = 0.039$

West H et al. *Lancet Oncol* 2019;20(7):924-37.

Editorial – Dr Riely

For patients with metastatic nonsquamous NSCLC, there has been a rapid transition in the standard of care first-line therapy. For patients whose PD-L1 is <50%, the standard is the combination of chemotherapy and an antibody that disrupts the PD-1/PD-L1 axis. The previously available options included pemetrexed, carboplatin, and pembrolizumab or carboplatin, paclitaxel, bevacizumab, and atezolizumab. This trial explores another combination, with carboplatin, *nab*-paclitaxel, and atezolizumab. In this study, the combination of chemotherapy and atezolizumab was superior to the chemotherapy alone option. When you compare the hazard ratios or the absolute numbers with regard to PFS/OS, you don't see a meaningful improvement upon the results seen with carboplatin, pemetrexed, and pembrolizumab. For example, the 12-month OS was 69% in a trial using carboplatin, pemetrexed, and pembrolizumab, while it's 63% in this study. Similarly, the mPFS was 7 months in this trial, while in the KEYNOTE-189 study, the mPFS was 8.8 months.

Editorial – Dr Riely

The primary reason for exploring the *nab*-paclitaxel backbone was that it required less steroid premedication than seen for patients who get solvent-bound paclitaxel. However, 80% of patients received steroids, primarily as an antiemetic. Ultimately, this trial shows that another chemotherapy combination with atezolizumab is superior to chemotherapy, but there is no real suggestion that it is superior to other available options.

FDA Expands Pembrolizumab Indication for First-Line Treatment of NSCLC (TPS ≥1%)

Press Release – April 11, 2019

"On April 11, 2019, the Food and Drug Administration approved pembrolizumab for the first-line treatment of patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients' tumors must have no *EGFR* or *ALK* genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] ≥1%) determined by an FDA-approved test.

Pembrolizumab was previously approved as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 TPS ≥50%.

Approval was based on KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III or IV NSCLC who had not received prior systemic treatment for metastatic NSCLC and whose tumors expressed PD-L1 (TPS ≥1%)."

https://www.fda.gov/drugs/fda-expands-pembrolizumab-indication-first-line-treatment-nsclc-tps-1

Pembrolizumab versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial

Mok TS et al.
Lancet 2019;393(10183):1819-30.

KEYNOTE-042: Pembrolizumab versus Chemotherapy for Previously Untreated, PD-L1-Expressing Locally Advanced or Metastatic NSCLC

Median OS	Pembrolizumab (n = 637)	Chemotherapy (n = 637)	Hazard ratio	*p*-value
PD-L1 TPS ≥50%	20.0 mo	12.2 mo	0.69	0.0003
PD-L1 TPS ≥20%	17.7 mo	13.0 mo	0.77	0.002
PD-L1 TPS ≥1%	16.7 mo	12.1 mo	0.81	0.0018

Mok TS et al. *Lancet* 2019;393(10183):1819-30.

Association of KRAS Mutation Status with Response to Pembrolizumab Monotherapy Given as First-Line Therapy for PD-L1-Positive Advanced Nonsquamous NSCLC in KEYNOTE-042

Herbst RS et al.
Proc ESMO Immuno-Oncology 2019;Abstract LBA4.

Pembrolizumab Monotherapy Response and Survival by KRAS Status

	With Any KRAS Mutation		With KRAS G12C Mutation		Without Any KRAS Mutation	
	Pembro Monotherapy (N = 30)	Chemo (N = 39)	Pembro Monotherapy (N = 12)	Chemo (N = 17)	Pembro Monotherapy (N = 127)	Chemo (N = 105)
ORR	56.7%	18.0%	66.7%	23.5%	29.1%	21.0%
Median PFS	12 mo	6 mo	15 mo	6 mo	6 mo	6 mo
	HR = 0.51		HR = 0.27		HR = 1.00	
Median OS	28 mo	11 mo	NR	8 mo	15 mo	12 mo
	HR = 0.42		HR = 0.28		HR = 0.86	

Herbst RS et al. *Proc ESMO Immuno-Oncology* 2019;Abstract LBA4.

Editorial — Dr Liu

Pembrolizumab has greatly improved outcomes in the initial treatment of NSCLC, both as monotherapy and in combination with chemotherapy. This year, several large studies expanded its reach and solidified current practice. KEYNOTE-407 showed that the strategy of adding pembrolizumab to chemotherapy also improved survival in squamous NSCLC, and consistent with efforts in non-squamous NSCLC, this benefit was seen across PD-L1 thresholds. This has now been established as our current standard for advanced squamous NSCLC. Monotherapy remains an important strategy after KEYNOTE-024 showed a clear survival advantage with pembrolizumab over chemotherapy for patients with a PD-L1 TPS of 50%. Can the threshold be lowered, to expand impact? KEYNOTE-042 used a 1% cutoff and did show a survival benefit, but this was largely driven by those with a PD-L1 TPS of 50%. For those with a low score (1%-49%), there was not a clear advantage over chemotherapy, though this was an exploratory subset.

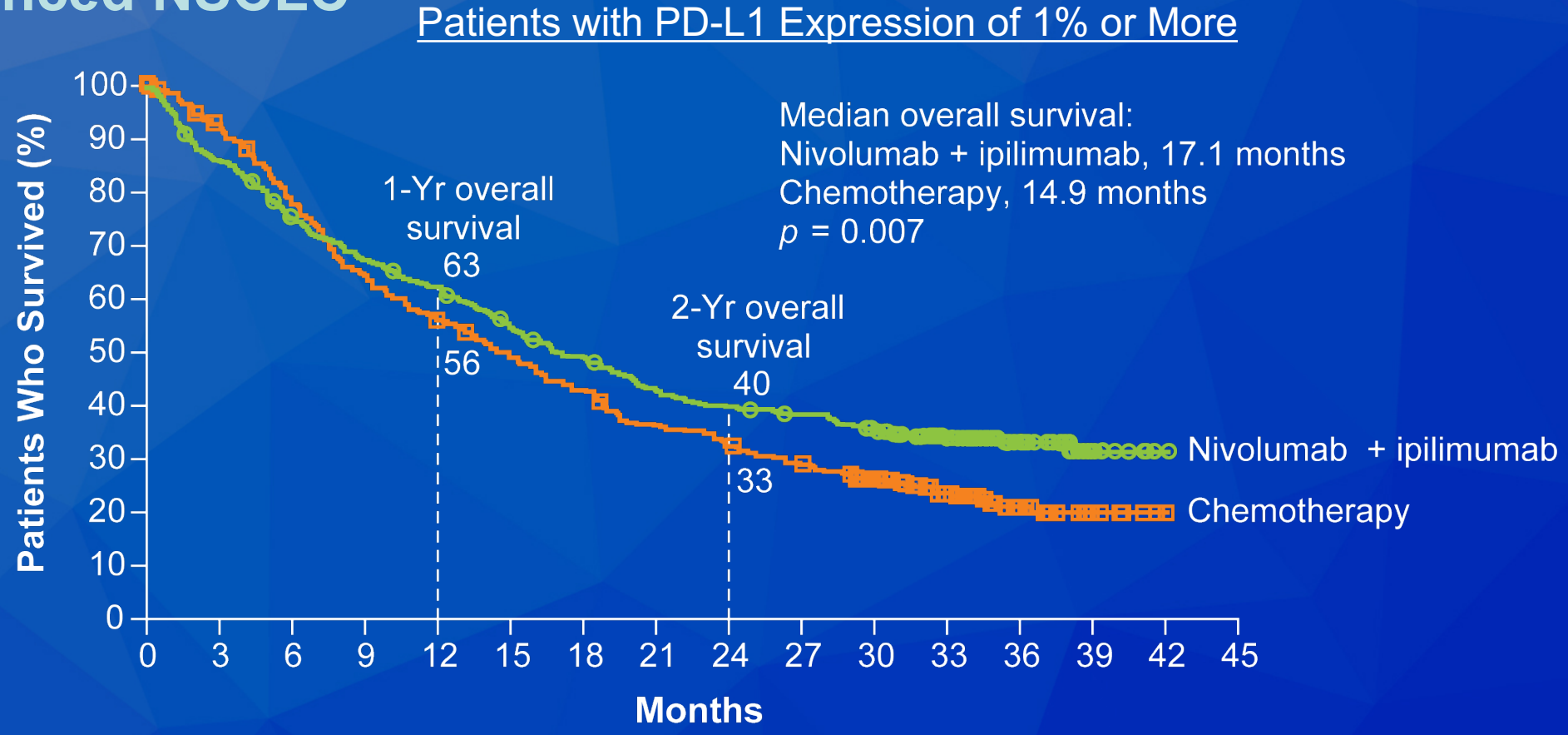
Editorial — Dr Liu (continued)

While we continue to refine our approach, long-term outcomes provide healthy reassurance. An update from the phase I study of pembrolizumab shows a 5-year OS rate of almost 30% with first-line therapy in patients with PD-L1-high NSCLC, confirming the need for early incorporation of immunotherapy for patients with advanced NSCLC. More importantly, we have validation that immunotherapy is now giving patients the hope for durable benefit and long-term survival.

Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer

Hellmann MD et al.
N Engl J Med 2019;381(21):2020-31.

CheckMate 227: OS Results with Nivolumab and Ipilimumab in Advanced NSCLC



- **OS benefit was also observed in patients with a PD-L1 expression level of <1% (n = 187, 186):**
  - Median OS = 17.2 mo (Nivo/Ipi) vs 12.2 mo (Chemo); HR = 0.62
- **Among all the patients in the trial (n = 583, 583):**
  - Median OS = 17.1 mo (Nivo/Ipi) vs 13.9 months (Chemo); HR = 0.73

Hellmann MD et al. *N Engl J Med* 2019;381(21):2020-31.

CheckMate 227: Treatment-Related AEs

Select AE	Nivo/Ipi (n = 576)		Chemo (n = 570)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhea	17.0%	1.7%	9.6%	0.7%
Rash	17.0%	1.6%	5.3%	0
Fatigue	14.4%	1.7%	18.9%	1.4%
Decreased appetite	13.2%	0.7%	19.6%	1.2%
Nausea	9.9%	0.5%	36.1%	2.1%
Anemia	3.8%	1.4%	33.0%	11.6%
Neutropenia	0.2%	0	17.2%	9.5%

- Treatment-related serious AEs (any grade): 24.5% (Nivo/Ipi) vs 13.9% (Chemo)
- Treatment-related AEs leading to discontinuation (any grade): 18.1% (Nivo/Ipi) vs 9.1% (Chemo)
- Treatment-related death (any grade): 1.4% (Nivo/Ipi) vs 1.1% (Chemo)

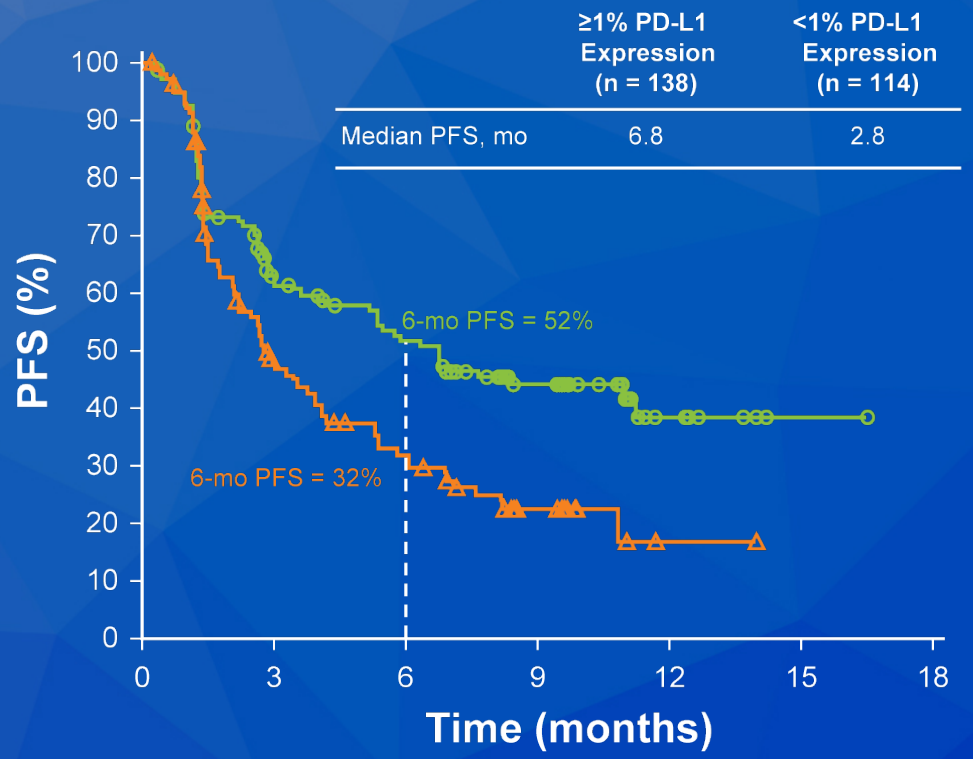
Hellmann MD et al. *N Engl J Med* 2019;381(21):2020-31.

First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers

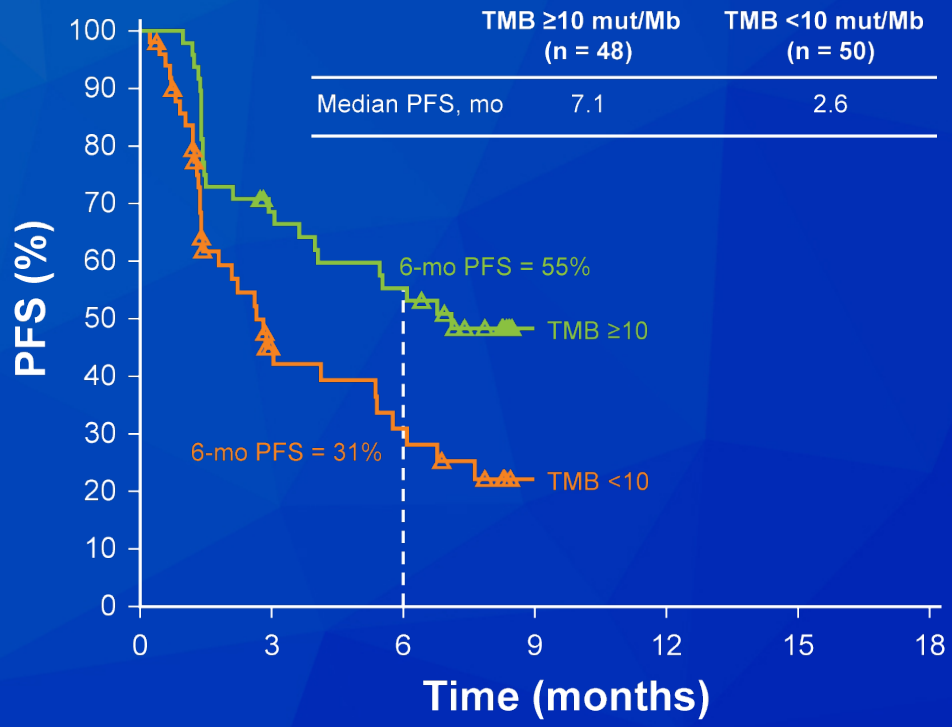
Ready N et al.
J Clin Oncol 2019;37(12):992-1000.

CheckMate 568: PFS and Objective Response Rates

By PD-L1 expression



By TMB



Best response	All (n = 288)	<1% PD-L1 (n = 114)	≥1% PD-L1 (n = 138)	≥50% PD-L1 (n = 68)	PD-L1 not quantifiable (n = 36)
Objective response	86 (29.9%)	17 (14.9%)	57 (41.3%)	34 (50%)	12 (33.3%)
CR	7 (2.4%)	3 (2.6%)	4 (2.9%)	3 (4.4%)	0

Ready N et al. *J Clin Oncol* 2019;37(12):992-1000.

Phase III CheckMate 9LA Trial of Nivolumab and Low-Dose Ipilimumab in Combination with Chemotherapy as First-Line Therapy for Metastatic NSCLC Meets Its Primary Endpoint

Press Release – October 22, 2019

"CheckMate -9LA, a pivotal Phase 3 trial evaluating nivolumab plus low-dose ipilimumab given concomitantly with two cycles of chemotherapy for the first-line treatment of advanced non-small cell lung cancer (NSCLC), met its primary endpoint of superior overall survival (OS) at a pre-specified interim analysis. The comparator in this study was chemotherapy alone for up to four cycles followed by optional maintenance therapy.

The safety profile of nivolumab plus low-dose ipilimumab and two cycles of chemotherapy in CheckMate -9LA was reflective of the known safety profiles of the immunotherapy and chemotherapy components in first-line NSCLC… The company will complete a full evaluation of the CheckMate -9LA data and present these results at an upcoming congress and share them with regulatory authorities."

https://finance.yahoo.com/news/checkmate-9la-phase-3-trial-105900417.html

Editorial — Dr Liu

CTLA-4 inhibition has yet to find a clear role in the treatment of NSCLC, with mixed results seen over the past few years. That may change soon with the long-awaited results of CheckMate 227. The combination of nivolumab and ipilimumab has improved overall survival compared to chemotherapy, providing a promising chemotherapy-free option for patients. Safety has been acceptable, even in patients with poorer performance status, though the approach is far from toxicity free. We will now need to determine where this regimen fits in our treatment approach. Patient selection will be challenging. TMB has consistently been shown to be a predictor of response and PFS but it was not a good predictive marker for survival. It potentially reserves doublet chemotherapy as a second-line option, but how to incorporate the regimen in the landscape of pembrolizumab monotherapy and the various chemo-immunotherapy regimens will be the next order of business.

Editorial — Dr Liu (continued)

Interestingly, combining nivolumab with chemotherapy did not improve outcomes, and in previously treated squamous NSCLC, the addition of ipilimumab to nivolumab did not improve efficacy. Whether these failed efforts were due to trial design, patient selection, or true differences in the drugs remains unclear.

Positive Results from the Phase III POSEIDON Trial of Durvalumab in Combination with Tremelimumab and Chemotherapy in Metastatic NSCLC

Press Release – October 28, 2019

"Positive progression-free survival (PFS) results announced for durvalumab and tremelimumab, an anti-CTLA4 antibody, when added to chemotherapy, from the Phase III POSEIDON trial in previously-untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC).

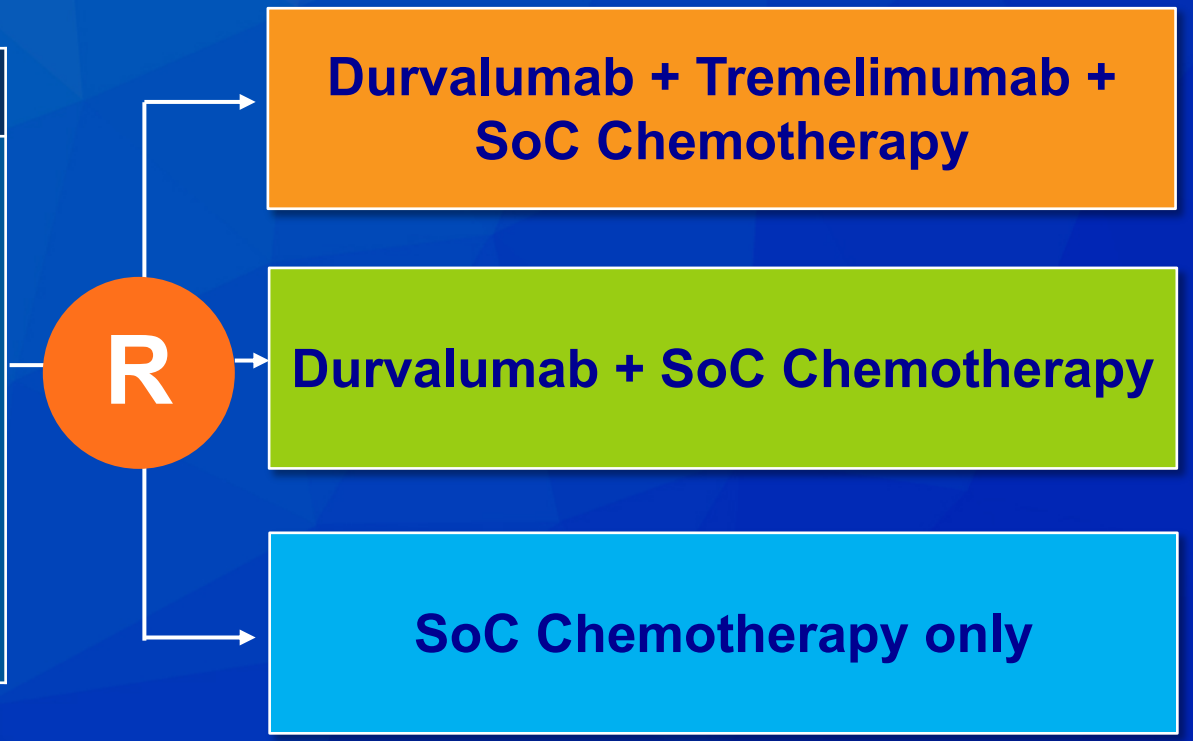
The trial met a primary endpoint by showing a statistically significant and clinically meaningful improvement in the final PFS analysis in patients treated with the combination of durvalumab and a broad choice of five standard-of-care platinum-based chemotherapy options vs. chemotherapy alone. The triple combination of durvalumab plus tremelimumab and chemotherapy also demonstrated a statistically significant and clinically meaningful PFS improvement vs. chemotherapy alone as a key secondary endpoint. The safety and tolerability of durvalumab were consistent with its known safety profile. The triple combination delivered a broadly similar safety profile to the durvalumab and chemotherapy combination and did not result in increased discontinuation of therapy."

https://www.astrazeneca.com/media-centre/press-releases/2019/imfinzi-and-imfinzi-plus-tremelimumab-delayed-disease-progression-in-phase-iii-poseidon-trial-for-1st-line-treatment-of-stage-iv-non-small-cell-lung-cancer.html

POSEIDON: Ongoing Phase III Trial Design

Target accrual (N = 1,000)

- Metastatic squamous or non-squamous NSCLC
- No prior therapy for metastatic disease
- Confirmed tumor PD-L1 status
- No activating EGFR mutations or ALK fusions



SoC chemotherapy includes: *nab*-paclitaxel/carboplatin (squamous/non-squamous), gemcitabine/cisplatin (squamous only), gemcitabine/carboplatin (squamous only), pemetrexed/carboplatin (non-squamous only), or pemetrexed/cisplatin (non-squamous only)

Coprimary endpoints: Progression-free survival and overall survival

www.clinicaltrials.gov (NCT03164616). Accessed January 2020.

Editorial – Dr Riely

This study explored the efficacy of a newer combination of CTLA-4/PD-L1 antibodies, durvalumab and tremelimumab, in patients with stage IV NSCLC, including both squamous and nonsquamous, but excluding those patients with ALK or EGFR. It's a three-arm trial with a control arm of platinum-doublet chemotherapy alone. The two experimental arms were durvalumab + chemotherapy or durvalumab/tremelimumab + chemotherapy. The co-primary endpoints of the trial were PFS and OS. We have only heard about the top-line results for PFS, so far, but what we have learned is that there was a "statistically significant and clinically meaningful improvement" in PFS for the combination of durvalumab + chemotherapy. The durvalumab/tremelimumab + chemotherapy arm also demonstrated a "statistically significant and clinically meaningful PFS" vs. chemotherapy alone. In the absence of seeing the numbers on PFS and exploring OS numbers, it's hard to make much of these preliminary results.

Editorial – Dr Riely

The treatment of people with NSCLC has changed dramatically over the last few years. The control arm used here (platinum-doublet chemotherapy alone) is no longer the standard of care, so seeing the magnitude of improvement upon chemotherapy alone will be critical. In addition, we've seen recent data exploring nivolumab + ipiliumumab without chemotherapy that were provocative. Moreover, analyses based on PD-L1 status will be important as well, since for patients with high PD-L1 we have seen excellent results with single-agent pembrolizumab