Year in Review

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

Saturday, February 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Mitchell R Smith, MD, PhD
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Moderator

Neil Love, MD

Research To Practice®

Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

Module 3 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Abramson, LaCasce and Smith*

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

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

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*

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Disclosures

Advisory Committee and Consulting Agreements	AbbVie Inc, Biodesix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, Lilly, Merck, Novartis, Pfizer Inc, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc, Takeda Oncology
Contracted Research	Advantage Pharmaceuticals, GlaxoSmithKline, Inovio Pharmaceuticals Inc, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Takeda Oncology
Data and Safety Monitoring Board/Committee	Amgen Inc, Incyte Corporation, Lilly, SWOG

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Disclosures

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

Lung Cancer — Drs Langer 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]

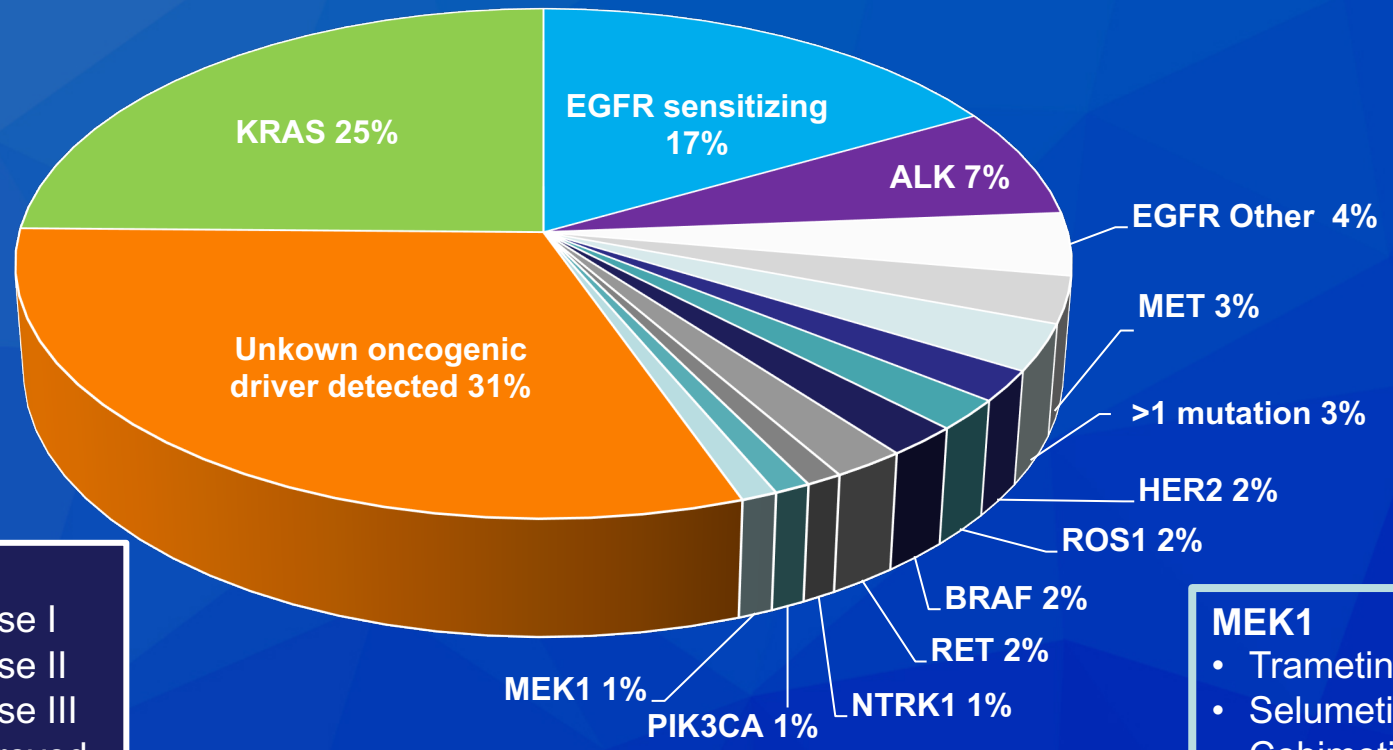
HER2
- Trastuzumab emtansine[2]
- Afatinib[2]
- Dacomitinib[2]

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]

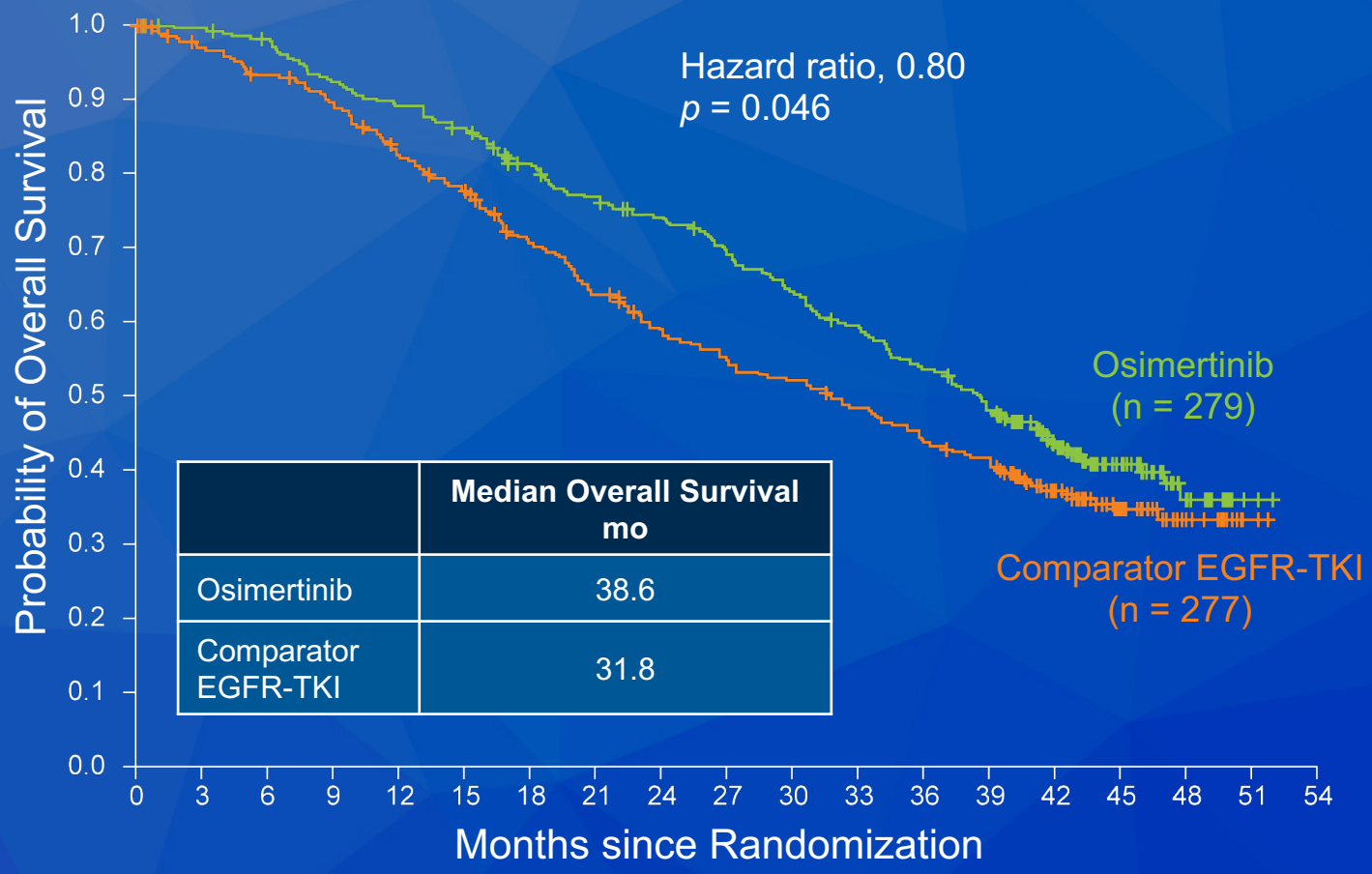
PIK3CA
- LY3023414[2]
- PQR 309[1]

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

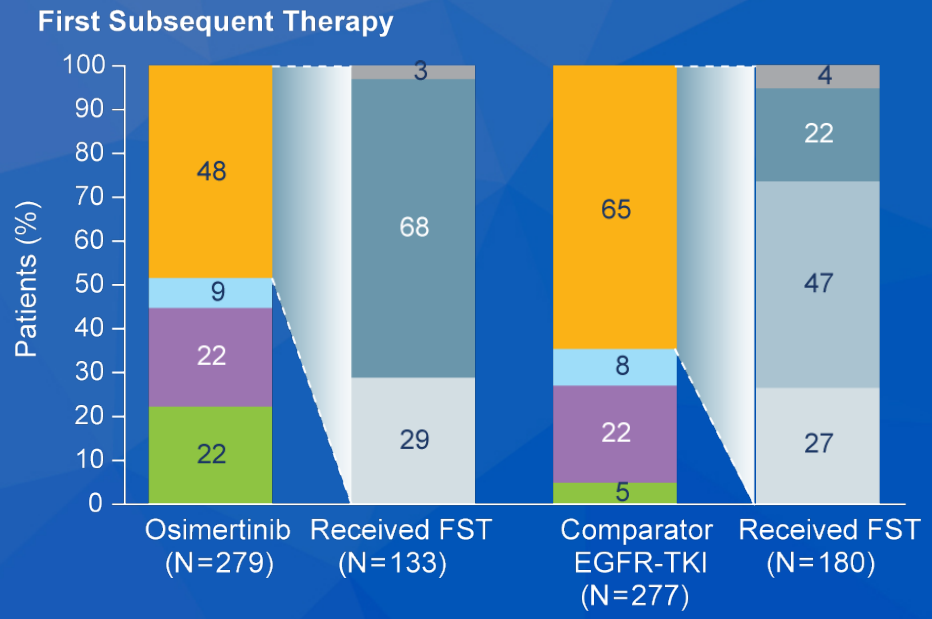
OS	Osimertinib (n = 279)	EGFR-TKI (n = 277)
12-mo OS	89%	83%
24-mo OS	74%	59%
36-mo OS	54%	44%
Pts continuing to receive first-line trial drug	**n = 279**	**n = 277**
At 12 mo	70%	47%
At 24 mo	42%	16%
At 36 mo	28%	9%

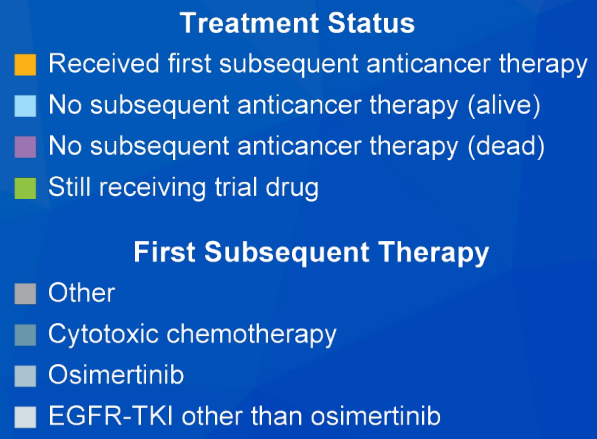
Comparator EGFR-TKI = erlotinib or gefitinib

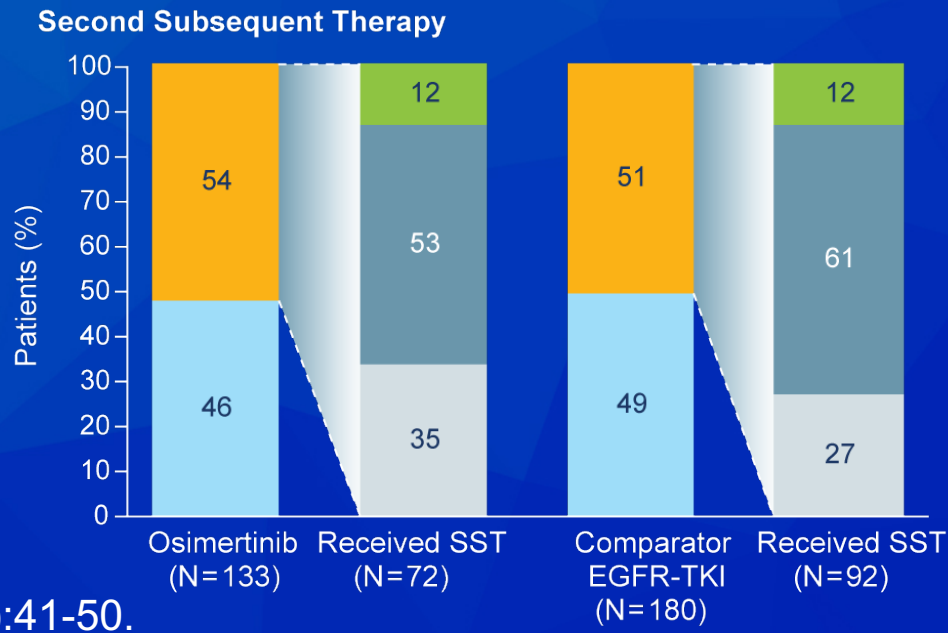
- The overall survival benefit with osimertinib as compared with the comparator EGFR-TKIs was consistent across most predefined subgroups, with varying magnitude of benefit.

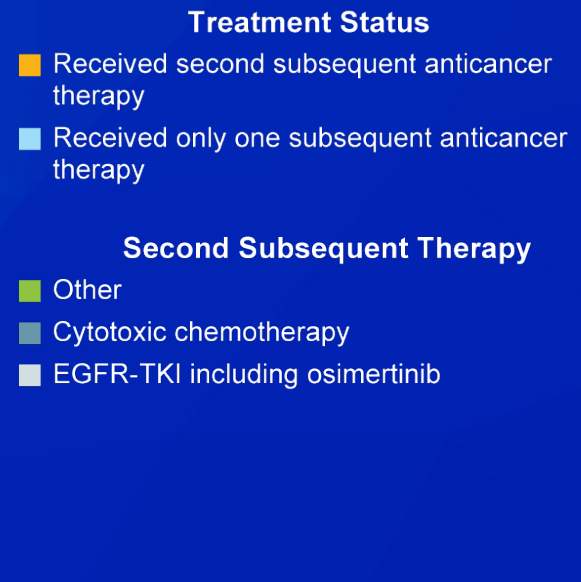
Ramalingam SS et al. *N Engl J Med* 2020;382(1):41-50.

FLAURA: Summary of First and Second Subsequent Therapies Received









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

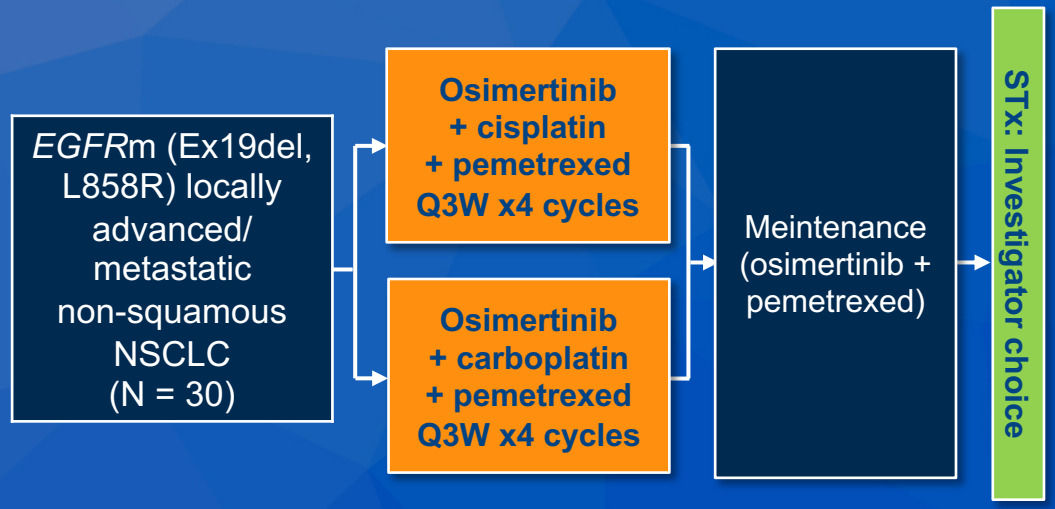
Osimertinib plus Platinum/Pemetrexed in Newly-Diagnosed Advanced EGFRm-Positive NSCLC; The Phase 3 FLAURA2 Study

Jänne PA et al.

Proc IASLC 2019;Abstract OA07.01.

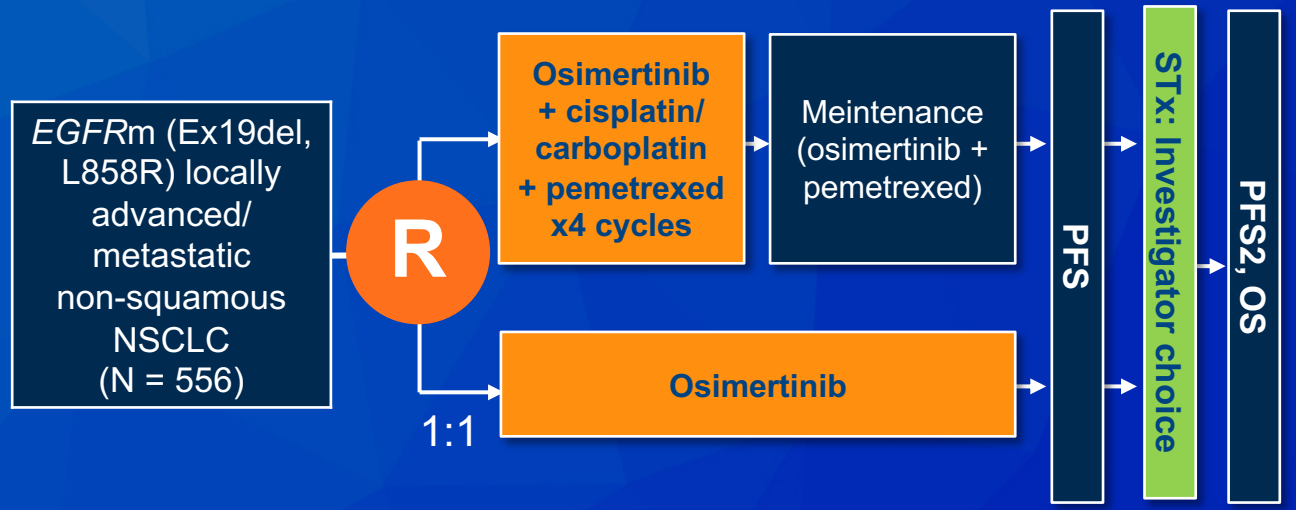
FLAURA2: Safety Run-In and Randomized Phase Designs

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 Langer

The FLAURA presentation by Ramalingam and colleagues at ESMO showed a statistically significant and clinically meaningful improvement in overall survival (OS) for osimertinib in treatment-naïve, EGFR mt (+) NSCLC compared with first-generation TKIs. This presentation cements the position of osimertinib as the “preferred” TKI in the management of EGFR mt (+) NSCLC, in light of its clear PFS and OS benefit, as well as its enhanced CNS penetrance and reduced toxicity. Truth be told, however, I was slightly disappointed by the results. In an earlier interim analysis at the time of the original FLAURA presentation at ESMO in 2017,[1] before “sufficient” events had occurred, there had been greater separation in the OS curves: with 556 patients enrolled and 141 deaths at that time, the HR was 0.63 with a *p*-value of 0.0068. Because that was an “early look,” it did not meet statistical significance, which was set at that point at a *p*-value of <0.0015.

Editorial — Dr Langer (continued)

Now, two years later, with mature f/u, the OS separation has met statistical significance, albeit with a higher HR (0.799) and higher *p*-value of 0.046, despite a near doubling in PFS from 10.2 to 18.9 mos. There are two potential explanations for the narrowing of this gap: (1) second- and third-line options worked better in patients on the control arm who received either erlotinib or gefitinib up front than they did in the investigational (osimertinib) arm; (2) fewer patients might have been exposed to second-line treatment in the osimertinib arm at the time of disease progression. An analysis reported at ESMO 2019 suggests it might be the former: 47% of those eligible for second-line therapy crossed over to osimertinib, while fewer than 5% in either arm failed to receive subsequent therapy. Of note, when tested, T790, because of continuous exposure to osimertinib, is virtually never a mechanism of resistance (MOR) in patients whose disease progresses on this agent.

Editorial — Dr Langer (continued)

On the other hand, as shown in recent trials comparing erlotinib alone to erlotinib and ramucirumab (RELAY)[2] or gefitinib alone to gefitinib and bevacizumab (JO25567),[3] T790 is still “operative.” We know, in this setting, that those who exhibit T790 as an MOR after first-generation TKI can “enjoy” an 8-10 month PFS when treated second line with osimertinib. On the other hand, there is no standard second-line treatment for those whose disease progresses on osimertinib; the default option, outside of an actionable marker or a clinical trial, is generally cytotoxic chemotherapy. Still, the 6.8-month OS improvement in the FLAURA trial from 31.8 months to 38.6 months is striking and sets a benchmark for future trials.

Given the marked PFS advantage seen in the RELAY trial and the JO25567 trial for TKI/angioinhibitor combinations vs TKIs alone, it is crucial that going forward we test osimertinib vs osimertinib combined with a monoclonal antibody targeting angiogenesis.

Editorial — Dr Langer (continued)

In addition, recent trials from Japan and India have demonstrated a striking PFS and OS advantage for the addition of chemotherapy (Carbo/Pem) to first-generation TKIs.[4, 5] Notably, in the NEJ009 trial, OS improved from 38.8 mos to 52.2 mos. The phase III FLAURA2 trial will determine whether an identical approach — grafting chemotherapy onto the TKI — can enhance PFS and OS compared with osimertinib alone.

Additional References

1. Soria J-C et al. *N Engl J Med* 2018;378:113-25.
2. Nakagawa K et al. (RELAY) *Proc Am Soc Clin Oncol* 2019.
3. Seto et al. (JO 25567) *Lancet Oncol* 2014;15(1);1235-44.
4. Noronha V et al. *Proc Am Soc Clin Oncol* 2019.
5. Nakamura et al. (NEJ009) *Proc Am Soc Clin Oncol* 2018.

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.

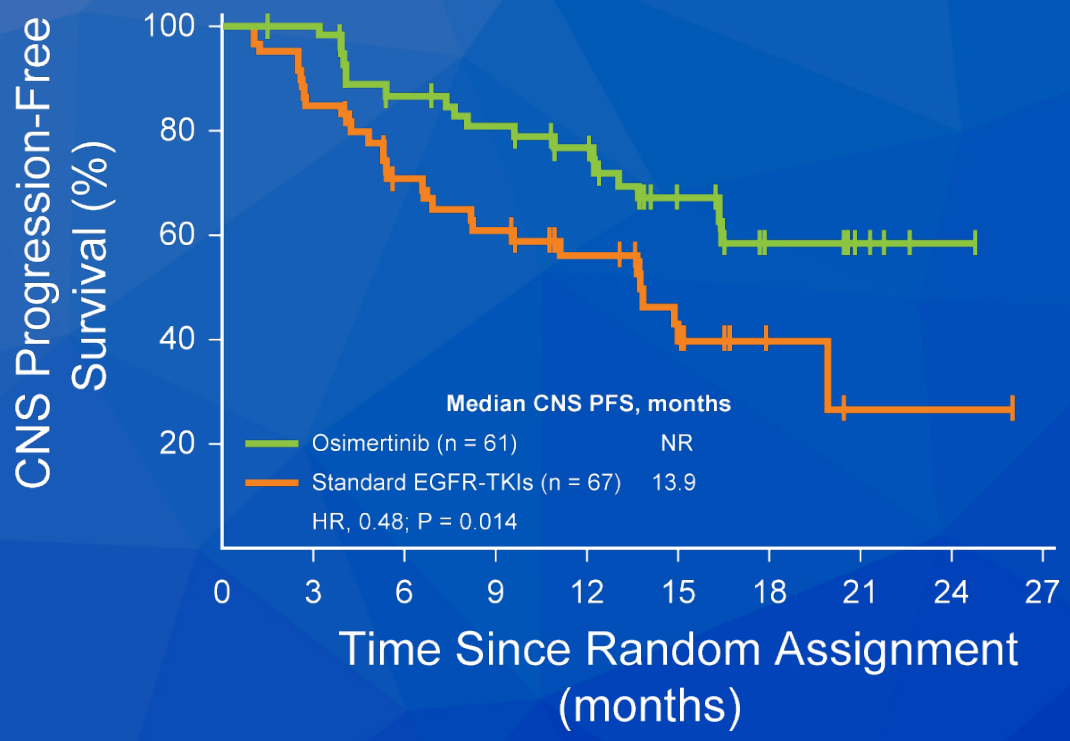
Ahn M et al. *Proc ELCC* 2019;Abstract 105O.

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

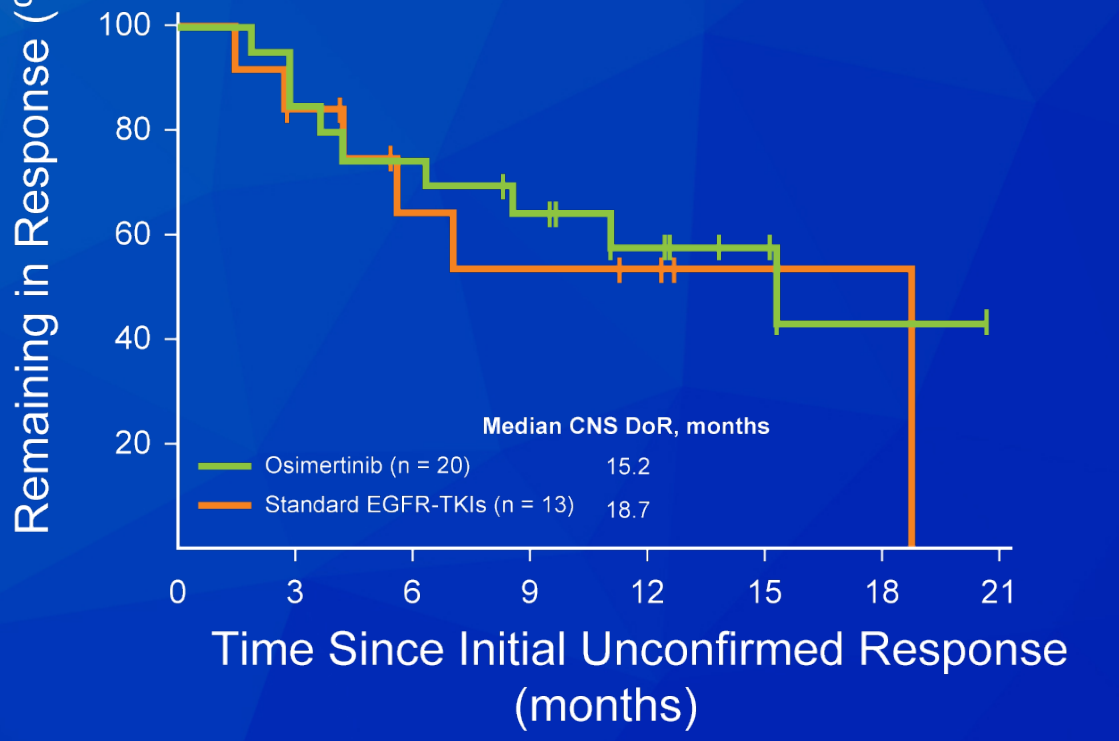
Reungwetwattana T et al.
J Clin Oncol 2018;[Epub ahead of print].

FLAURA: CNS PFS and Duration of CNS Response

CNS PFS (full analysis set)



CNS DoR (evaluable for response set)

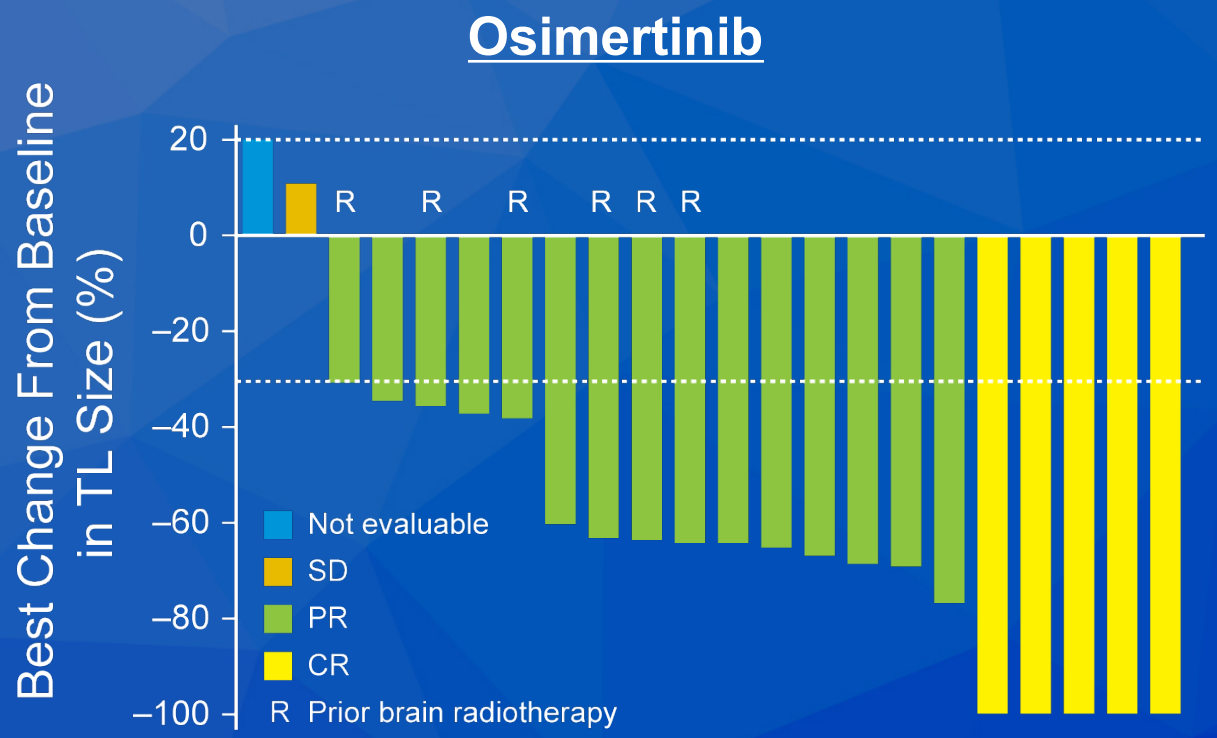


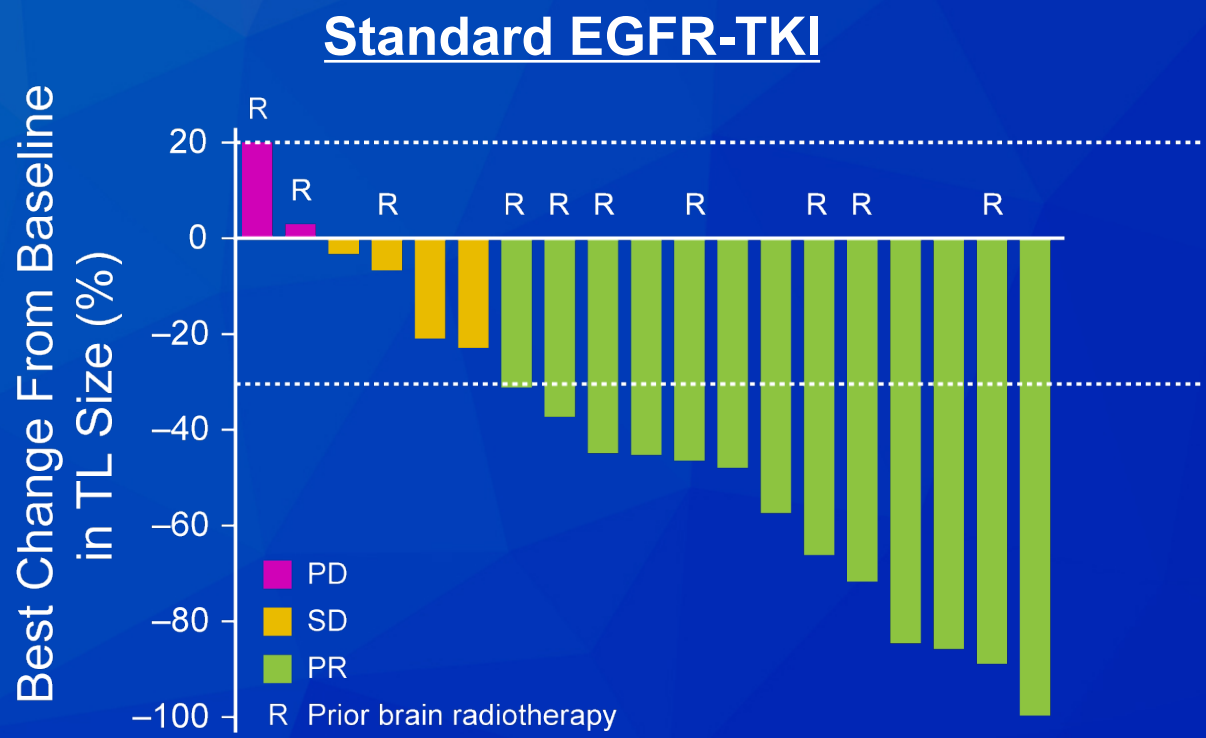
- CNS ORR (full analysis set)
  - Osimertinib = 40/61 (66%)
  - EGFR TKI = 29/67 (43%)

- 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 Langer

In contrast to first-generation TKIs, osimertinib has superior CNS penetrance. This was readily demonstrated during the initial presentation of the randomized phase III FLAURA trial, where the incidence of CNS progression was just 6% on the osimertinib arm compared to 15% on the control arm. PFS overall was not compromised in this population: 15.2 mos vs 9.8 mos, with HR of 0.47 and *p* value of 0.0009.[1, 2]

Reungwetwattana's paper[3] amplifies and details the original observations from the ESMO presentation. Of 200 patients with brain scans available at baseline, 128 (osimertinib, n = 61; standard EGFR-TKIs, n = 67) had measurable and/or nonmeasurable CNS lesions, including 41 patients (osimertinib, n = 22; standard EGFR-TKIs, n = 19) with at least one measurable CNS lesion. Median CNS PFS in patients with measurable and/or nonmeasurable CNS lesions was not reached with osimertinib (95% CI, 16.5 months to not calculable) and 13.9 months (95% CI, 8.3 months to not calculable) with standard EGFR-TKIs

Editorial — Dr Langer (continued)

(hazard ratio, 0.48; 95% CI, 0.26 to 0.86; *p* = .014). At one year, 77% of those with CNS metastases treated with osimertinib were free of intracranial progression compared to 56% on the control arm. CNS objective response rates were 91% and 68% in patients with at least one measurable CNS lesion (odds ratio, 4.6; 95% CI, 0.9 to 34.9 ; *p* = .066) and 66% and 43% in patients with measurable and/or nonmeasurable CNS lesions (odds ratio, 2.5; 95% CI, 1.2 to 5.2; *p* = .011) treated with osimertinib and standard EGFR-TKIs, respectively. At least five patients with measurable intracranial disease receiving osimertinib experienced a cCR in the CNS. Finally, the probability of experiencing CNS progression was consistently lower with osimertinib versus standard EGFR-TKIs.

Glenwood Goss, in a secondary analysis of the AURA extension and AURA2 trials, reported a slightly lower intracranial response rate of 54% in 50 patients with “measurable CNS lesions,” but a promising DCR rate of 92% and 12 mo

Editorial — Dr Langer (continued)

intracranial PFS of 56%.[4] The results cited by Goss and Reungwetwattana are unprecedented and have helped cement the superiority of osimertinib to first-generation TKIs in EGFR mt+ patients who present with CNS involvement. These studies have also helped reinforce the shift in our standard treatment paradigm to osimertinib front-line.

The activity of osimertinib in the CNS also has implications for leptomeningeal (LM) disease. Yang et al at ASCO in 2016 reported on the activity of double dose osimertinib (160 mg/d) in 21 patients with leptomeningeal disease.[5] Fifteen of 21 patients had stabilized or improved symptoms, 10 stayed asymptomatic and five improved. Seven were still on treatment after 9 mos or more. Irrespective of T790M status, osimertinib led to a change in MRI signal intensity, suggesting response. Osimertinib clearly crossed the blood-brain barrier; six of nine patients in whom it was tested had >50% decrease in CSF EGFR mutation level.

Editorial — Dr Langer (continued)

Ahn and colleagues reported activity with osimertinib 80 mg QD in pts with LM from studies across the AURA program (NCT01802632; NCT02094261; NCT02442349; NCT02151981).[6] Patients with EGFR T790M-positive advanced NSCLC and disease progression on first-line EGFR TKI received osimertinib 80 mg QD. Patients with LM and CNS metastases were eligible if asymptomatic and stable. Baseline brain scans were mandated in those with known or treated CNS metastases at study entry. Patients with evidence of LM by neuroradiological blinded independent review (BICR) were included for retrospective analysis. Follow-up brain scans were assessed for radiologic LM response by LM BICR per Response Assessment in Neuro-Oncology LM criteria. In total, 22 LM patients from the AURA studies were included in this analysis. Median treatment exposure was 7.3 mo (range 2.3–16.5). Baseline characteristics were broadly consistent with the overall AURA study population: median age 58 yrs; female 59%; Asian 82%; WHO PS 1 in 82%. LM ORR was

Editorial — Dr Langer (continued)

55% (95% CI 32, 76). Complete or partial LM responses were reported in 6 patients (27%) each. Median LM DoR was not reached (95% CI 2.8, not calculable [NC]). Median LM PFS was 11.1 mo (95% CI 4.6, NC). OS was 18.8 mo (95% CI 6.3, NC), a bit lower than one might expect in the EGFR mt+ population overall, but far better than we would typically expect in advanced NSCLC patients who present with LM disease. Consistent with the early efficacy observed in the BLOOM study (160 mg QD), osimertinib at 80 mg QD showed a clinically meaningful benefit in pts with T790M-positive NSCLC and radiographically detected LM. That we are seeing such activity in the LM is remarkable in itself. The observations of Ahn et al suggest that we do not need to automatically bump the osimertinib dose to 160 mg/d in those with LM disease but can start out with a standard dose.

Editorial — Dr Langer (continued)

Additional References

1. Ramalingam SS et al. **Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis.** *Proc ESMO* 2019;Abstract LBA5.
2. Soria J-C et al. *N Engl J Med* 2018; 378:113-25.
3. Reungwetwattana T et al. **CNS response to osimertinib versus standard EGFR tyrosine kinase inhibitors (TKIs) in patients with untreated EGFR-mutant advanced NSCLC.** *J Clin Oncol* 2018;36:3290-7.
4. Goss G et al. **CNS response to osimertinib in patients with T790Mpositive advanced NSCLC: Pooled data from two phase II trials.** *Ann Oncol* 2018;29:687-93.
5. Yang, JC et al. **Osimertinib activity in patients with leptomeningeal (LM) disease from NSCLC: Updated results from the BLOOM, a phase I study.** *Proc ASCO* 2016;Abstract 9002.
6. Ahn M et al. **Osimertinib for patients with leptomeningeal metastases (LM) associated with EGFR-mutant advanced NSCLC: The AURA LM study.** *Proc ELCC* 2019;Abstract 105O.

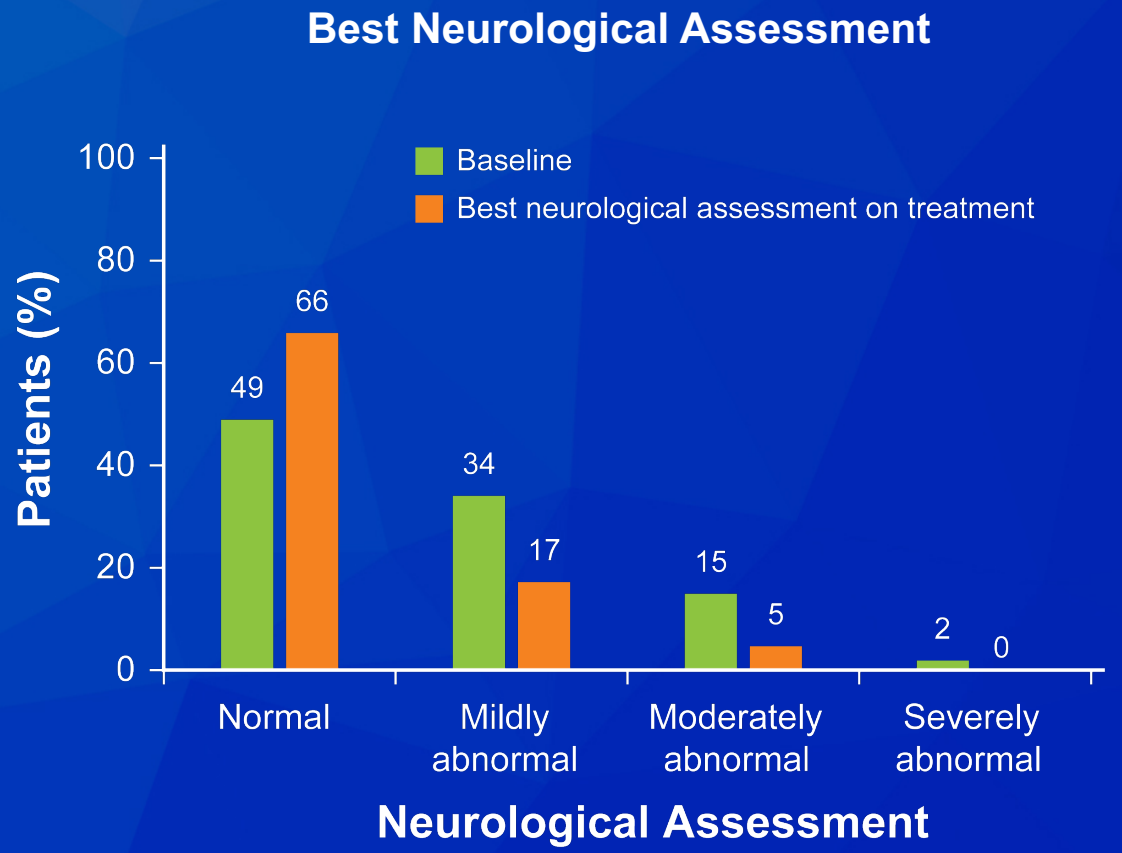
Osimertinib in Patients with Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

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).

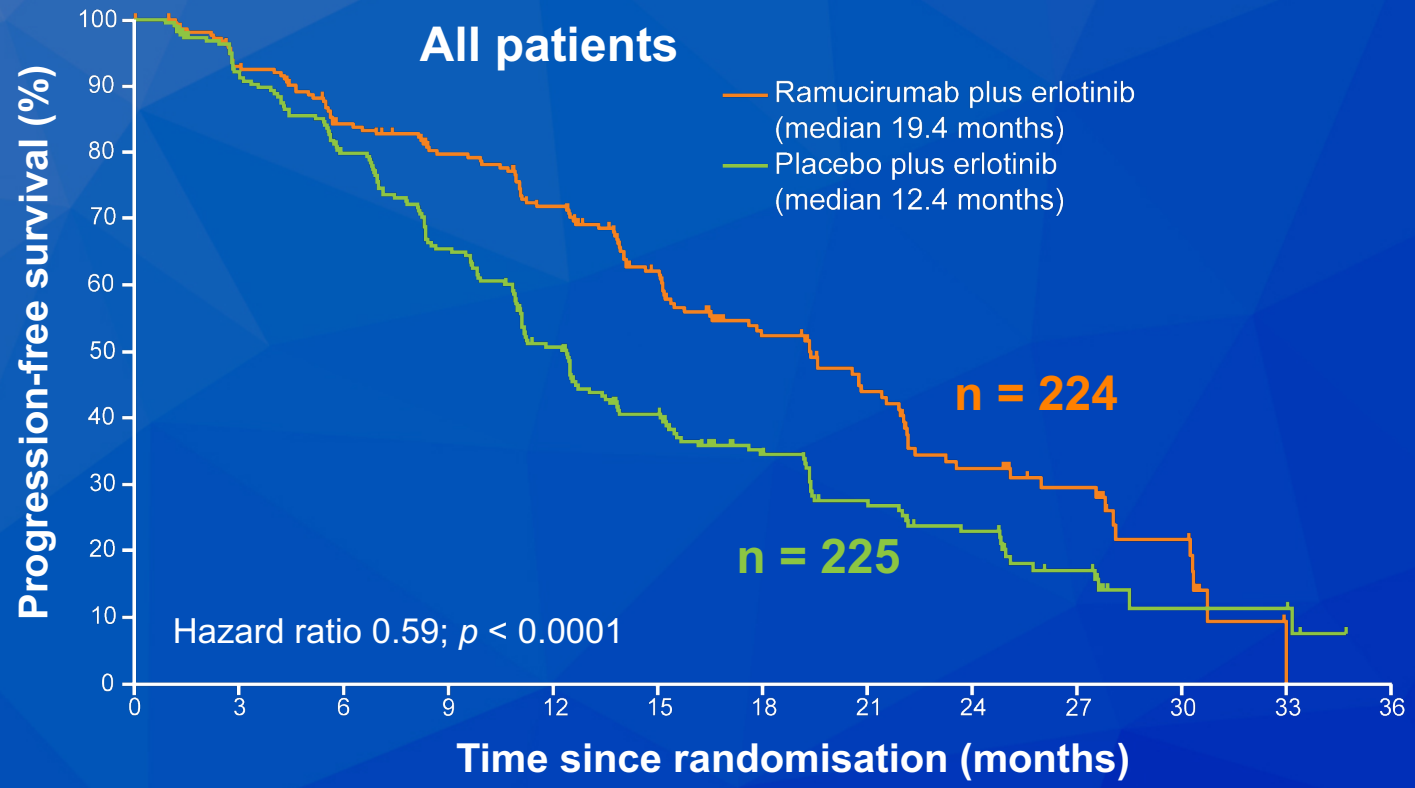
Editorial – Dr Riely

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

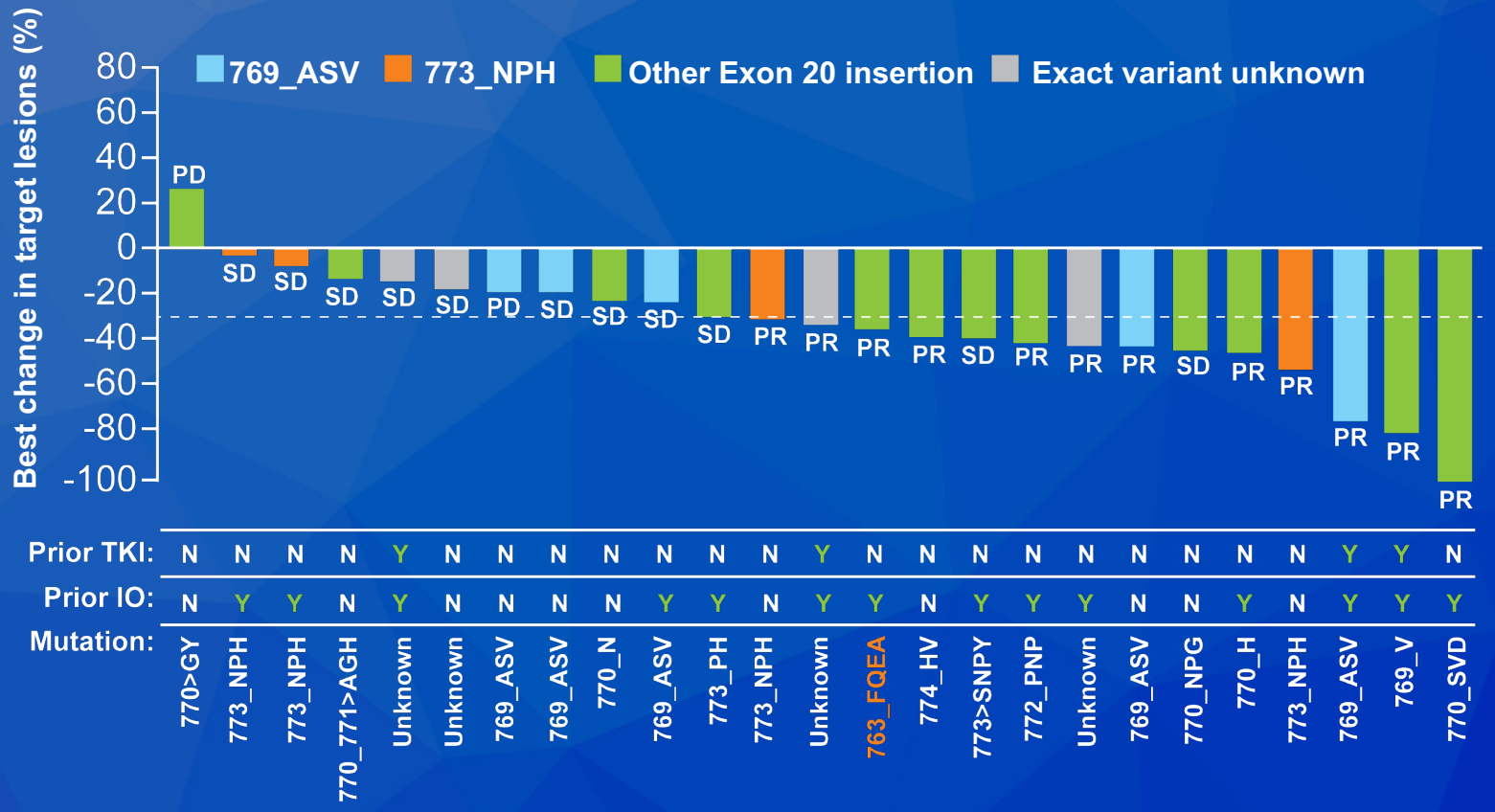
In the first-line osimertinib trial, the median progression-free survival is numerically superior (19 months), but patients with CNS metastases comprised approximately 20% of patients enrolled in the FLAURA trial. This trial suggests some opportunities to improve outcomes for patients by looking at osimertinib + 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 Langer

Exon 20 mutations, which constitute ~ 6% to 8% of all EGFR mutations, have been notoriously refractory to TKIs. Response rates with first- and second-generation TKIs have ranged from 10% to 25%, far below our expectations for TKIs targeting actionable mutations in exons 19 and 21. But we are starting to make headway with new agents, and I fully anticipate the formal approval of at least two agents in the next 6 to 12 months.

Poziotinib is one of the first TKIs to demonstrate “real” activity in both EGFR exon 20 mt (+) NSCLC and in HER2 exon 20 mutations. It is a potent and effective selective inhibitor in pre-clinical models. It overcomes steric hindrance caused by insertions by binding deep near the “back side” of the receptor pocket. In those with EGFR exon 20 mutations, the ORR was 55% with a median (m) PFS of 5.5 months. In patients with HER2 mutations, the results were similar: the ORR was 50% with a mPFS of 5.1 mos.

Editorial — Dr Langer (continued)

Of note, pyrotinib, an irreversible pan-ErbB inhibitor of HER1, HER2, and HER4, generated an ORR of 53% with mPFS of 6.3 mos in 15 patients with HER2 mutations. Finally, TAK-788 has demonstrated activity in NSCLC with exon 20 insertions. In 28 patients treated at the recommended phase 2 dose of 160 mg/d, the confirmed ORR was 43% with 7.3-month mPFS in all patients, including those with baseline CNS metastases. Responses were observed regardless of treatment history (prior chemo or CPI), specific exon 20 insertion variant, or CNS involvement. Three of 12 patients (25%) with brain mets had objective responses. 63% had grade ≥3 AEs. The most common AEs included diarrhea in 85% any grade (18% grade ≥3), nausea 43% (any grade), rash 36% (any grade) and vomiting 29% (any grade). However, with relatively brief PFS for most of these agents and some degree of toxicity, it is debatable whether these agents should be moved to the first-line setting or if they should be reserved for second-line treatment after standard chemotherapy.

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.

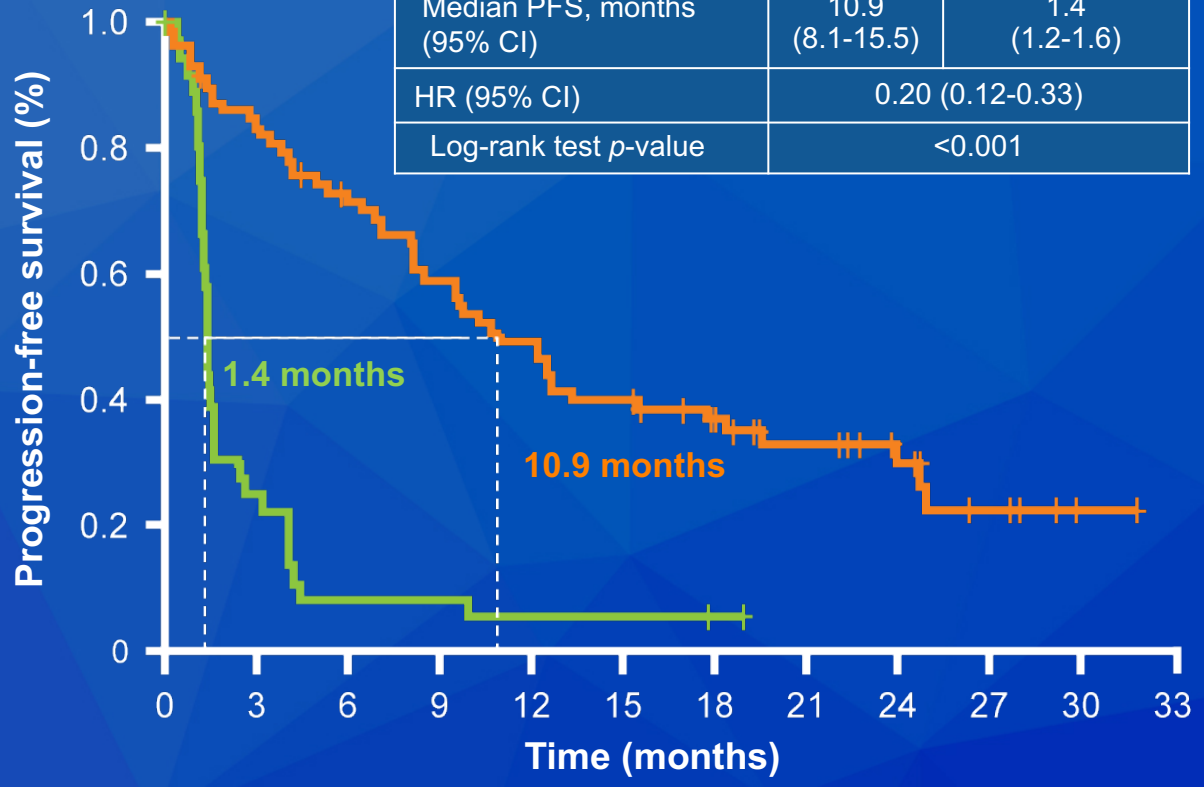
Phase 3 ALUR Study of Alectinib in Pretreated ALK+ NSCLC: Final Efficacy, Safety and Targeted Genomic Sequencing Analyses

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

ALUR: Final Survival Analyses

PFS (investigator assessed)

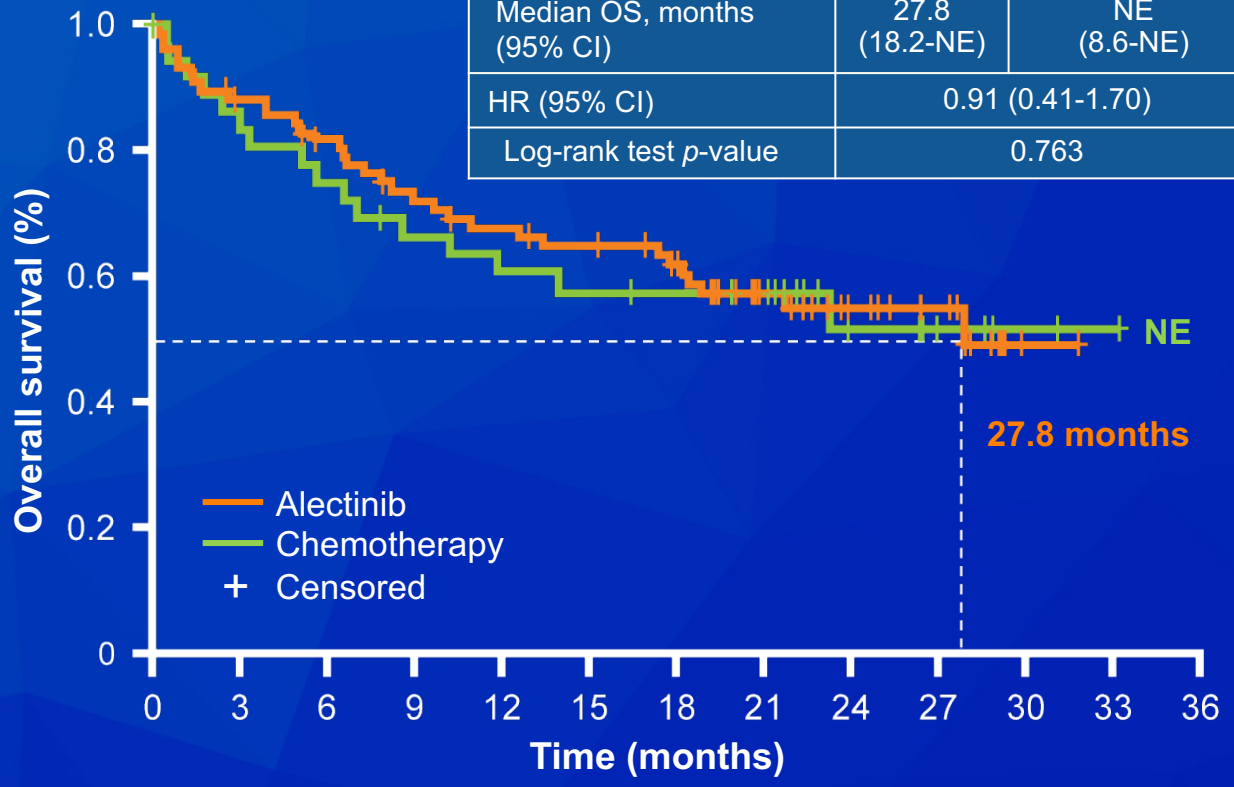
	Alectinib (n = 79)	Chemotherapy (n = 40)
Patients with event, n (%)	52 (65.8)	34 (85.0)
Median PFS, months (95% CI)	10.9 (8.1-15.5)	1.4 (1.2-1.6)
HR (95% CI)	0.20 (0.12-0.33)	
Log-rank test *p*-value	<0.001	



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 Langer

Both brigatinib and alectinib have shown stark superiority compared to crizotinib in TKI-naïve, ALK (+) NSCLC and, as a result, have displaced crizotinb as the standard of care in this setting. The Global ALEX trial and J ALEX trial in Japan demonstrated a nearly 3-fold increase in PFS for alectinib compared to crizotoinb, with mPFS exceeding 3 years. Likewise, the ALTA-1L phase III randomized trial comparing brigatinib to crizotinib in the same setting showed superior mPFS: NR on brigatinib vs 9.2 mos with crizotinib (HR 0.49 with $p = 0.0007$) with 1 year PFS rates of 67% and 43% respectively. Like alectinib, brigatinib exhibited superior CNS penetrance with confirmed CNS ORR% of 67% vs 17% with crizotinib ($p < 0.0001$) and intracranial mPFS NR vs 6 mos with an astounding HR of 0.27. Brigatinib was reasonably well tolerated; most dose reductions were predominantly protocol-mandated for asymptomatic lab abnormalities (CPK, amylase, lipase, AST). Early onset pneumonitis appears to be unique to brigatinib amongst ALK TKIs, but grade 3 events are rare (3%) and usually occur within 1-2 weeks of starting treatment.[1]

Editorial — Dr Langer

In this setting, the results of the Phase III ALUR trial comparing alectinib to salvage chemotherapy with either pemetrexed or docetaxel in platinum-exposed patients whose disease had progressed on or who proved intolerant to crizotinb is anticlimactic.[2] Patients were randomized 2:1 to alectinib or to chemotherapy with either docetaxel or pemetrexed. Results are summarized in the table below. Despite a major PFS advantage for alectinib (HR 0.20), survival was very similar (HR 0.91) because of cross over to alectinib in 86.5% of patients on the control arm

Arm	Alectinib	Chemotherapy	*p*-value
No	79	40	
mPFS (mo)	10.9	1.4	< 0.001
mOS (mo)	27.8	NE	0.763
ORR%	51	3	<0.001
Intracranial ORR%	67	0	<0.001

Editorial — Dr Langer

At this point, the jury is out on which agent is preferred in the first line setting. While brigatinib poses higher rates of pulmonary toxicity, alectinib likely features a bit more muscular toxicity and CPK elevations, though the latter can readily be managed with dose reductions and NSAIDs. When these agents cease to work in the front-line setting, options included lorlatinib as well as standard platinum-based chemotherapy (e.g pemetrexed/carboplatin +/- bevacizumab or IMPower 150 with paclitaxel/carboplatin/bevacizumab and atezolizumab).

1. Califano R et al. **Brigatinib vs Crizotinib in the phase III ALTA-1L trial**. *Proc ELCC* 2019; Abstract 106O
2. Wolf J et al. **Phase 3 ALUR Study of Alectinib in Pretreated ALK (+) NSCLC: Final Efficacy, Safety and Targeted Genomic Sequencing Analyses**. *Proc IASLC* 2019, Abstract OA 02.07

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 degree 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, 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 Langer

ROS1 is a human receptor tyrosine kinase (RTK), highly homologous to the ALK receptor family.[1] Despite the lack of clarity on the role of ROS1 in normal physiology, it has been well established as a driver oncogene in 1%-2% of NSCLC.[2] Typically, molecular alterations in ROS1 occur as rearrangements that produce fusion proteins, as opposed to true mutations. ROS1 alterations are found almost exclusively in adenocarcinomas.[2] Although ROS1 rearrangements are generally not seen alongside other driver alterations, rare cases of concurrent EGFR, MET, BRAF, and KRAS alterations have been reported.[3] Phenotypically, patients with ROS1 alterations are similar to those with EGFR- and ALK-positive NSCLC; they are often never smokers or remote past smokers, though the association is not as strong as that of EGFR and ALK.[4] As with ALK, the median age at diagnosis appears to be much younger in ROS1-positive patients, at 45 to 50 years, compared with 70 years in the overall NSCLC population.[3-5]

Editorial — Dr Langer (continued)

Of note, NSCLC with a ROS1 rearrangement confers a better prognosis compared with NSCLC without driver mutations.[6] A European study evaluating 19 patients with NSCLC harboring ROS1 rearrangements showed improved median overall survival (OS) regardless of whether patients received crizotinib (ROS1, 36.7 months; EGFR, 25.3 months; ALK, 23.9 months).[6] However, in a Taiwanese study, the OS difference among stage IV patients with ROS1 rearrangement, ALK rearrangement, KRAS mutation, or no ROS1, ALK, EGFR, or KRAS alteration was not significant.[5] Overall, the low incidence of ROS1 rearrangements in NSCLC and potential differences in its predictive and prognostic role in East Asian vs Caucasian populations makes it difficult to determine an effect on overall survival.

Due to the homology of ROS1 with ALK, several ALK inhibitors have been shown to inhibit ROS1.[6, 7] Crizotinib was initially approved for ALK-rearranged NSCLC in 2011 and subsequently approved for treatment of ROS1-rearranged

Editorial — Dr Langer (continued)

NSCLC in 2016.[7] Crizotinib, until recently, was the only targeted therapy licensed for this indication. In the pivotal study reported by Shaw and colleagues (N = 50; >80% with prior chemotherapy), the objective response rate (ORR) for crizotinib was 72%, with median duration of response (DOR) of 17.6 months and unprecedented mPFS of 19.2 months.[8] A retrospective study in Europe showed similar real-world results, with an ORR of 80% but a shorter median mPFS of 9.1 months (12-month PFS rate, 44%).[4]

As seen with many TKIs, resistance to crizotinib has been observed among some ROS1-positive patients over time, primarily via development of a G2032R mutation.[9, 10] Preliminary data suggest that cabozantinib, approved for the treatment of advanced renal cell carcinoma and metastatic medullary thyroid cancer, and the ALK/ROS1 inhibitors lorlatinib and brigatinib may be effective in ROS1-positive cancers that have become resistant to crizotinib.[11-13]

Editorial — Dr Langer (continued)

Ceritinib, approved for ALK-positive NSCLC, is also under investigation for ROS1-positive NSCLC. A phase 2 trial (N = 32) revealed an ORR of 62%, disease control rate (DCR) of 81%, mPFS of 9.3 months overall, and 19.3 months in crizotinib-naïve patients.[14]

Notably, the ALK inhibitor, alectinib, does not have activity against ROS1 at therapeutic concentrations and should ***not*** be considered for patients with ROS1-positive NSCLC.[15]

Two new agents, entrectinib and repotrectinib, have entered the realm of ROS1 inhibition. Entrectinib is a newly approved agent for the treatment of ROS1-positive NSCLC.[16, 17] A pivotal integrated analysis of results from ROS1-activating gene fusions from the phase 2 STARTRK-2, phase 1 STARTRK-1, and phase 1 ALKA trials (N = 53) showed an ORR of 77%, a median DOR of 24.6 months, and an intracranial response rate of 55%. mPFS was 19.0 months overall.[16] mPFS by blinded independent radiographic review (BICR) in

Editorial — Dr Langer (continued)

30 patients without CNS disease and in 23 with CNS disease were 26 months (95% CI 16–37) and 14 months (95% CI 5–NR) respectively. Intracranial ORR (n = 20) was 55% (95% CI 32–77), including 4 CR and 7 PR. Although the PFS proved virtually identical to the PFS seen with crizotinib, the enhanced CNS penetration observed with entrectinib, according to some thoracic oncology experts, makes this the “preferred agent.” In the ROS1 safety-evaluable population (n = 134), at least one treatment-related AE (TRAE) of any grade was seen in 93% of pts. TRAEs led to dose reduction or discontinuation in 34% and 5% of patients, respectively.

Repotrectinib is a next-generation ROS1/TRK/ALK TKI inhibiting ROS1 with >90-fold greater potency compared to crizotinib.[18] Preclinical studies showed robust kinase inhibitory activity of repotrectinib against all known ROS1 fusion-positive resistance mutations, including the most common ROS1 solvent-front mutation (SFM) G2032R, often a mechanism of resistance. In an ongoing phase 1

Editorial — Dr Langer (continued)

study (NCT03093116), TKI-naïve and TKI-refractory (≥1 TKI) patients with advanced ROS1/TRK/ALK+ solid tumors received repotrectinib. Endpoints include safety, PK, and confirmed overall response (cORR). A safety analysis for all patients (n = 75) and efficacy analysis for ROS1+ NSCLC patients (n = 28) enrolled on the study was conducted. As of 10/31/2018, 75 patients were treated with repotrectinib at dose levels from 40 mg QD to 200 mg BID. Most AEs were manageable and grade (Gr) 1-2. Common (>20%) TRAEs included dizziness (49%), dysgeusia (48%), paresthesia (28%), and constipation (20%). Four DLTs (Gr3 dyspnea/hypoxia [n = 1]; Gr2 [n = 1] and Gr3 [n = 1] dizziness at 160 mg BID, and Gr3 dizziness [n = 1] at 240 mg QD) occurred and were managed with dose modifications. The MTD has not been determined. Median number of prior TKI treatments was 1 (0-3), with all of TKI-naïve and 83% of TKI-pretreated patients having received prior chemotherapy. Among 10 evaluable TKI-naïve ROS1+ NSCLC patients, confirmed ORR by BICR was 90% (95% CI 56-100) with

Editorial — Dr Langer (continued)

median duration of response (DOR) not reached (range 5.5+–14.9+ months (mos). Among 18 TKI-pretreated pts, confirmed ORR by BCR was 28% (95% CI 10–54) with DOR of 10.2 mos. Subgroup analysis showed cORR 44% (95% CI 14-79) in 9 prior TKI patients treated at dose levels of 160 mg QD or above. In 7 patients with measurable target CNS lesions at baseline, the intracranial ORR was 3/3 (100%) with DOR (5.5+; 7.2+; 14.85+ mo) in TKI-naïve patients and 2/4 (50%) with DOR (5.5+; 14.8+ mo) in TKI-pretreated patients, respectively. Although the data are early and relatively sparse, repotrectinib is reasonably well tolerated and has demonstrated encouraging overall and intracranial clinical activity in patients with ROS1 fusion-positive NSCLC. How this stacks up against entrectinib is unclear. A global phase 2 study is planned.

Additional References

1. Lin JJ, Shaw AT. **Recent advances in targeting ROS1 in lung cancer.** *J Thorac Oncol* 2017;12:1611-25.

Editorial — Dr Langer (continued)

2. Bergethon K et al. **ROS1 rearrangements define a unique molecular class of lung cancers.** *J Clin Oncol* 2012;30:863-70.
3. Pal P, Khan Z. ROS1-1. *J Clin Pathol* 2017;70:1001-9.
4. Mazieres J et al. **Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: Results from the EUROS1 cohort.** *J Clin Oncol* 2015;33:992-9.
5. Chen YF et al. **Clinical and the prognostic characteristics of lung adenocarcinoma patients with ROS1 fusion in comparison with other driver mutations in East Asian populations.** *J Thorac Oncol* 2014;9:1171-9.
6. Thomas A et al. **Trends and characteristics of young non-small cell lung cancer patients in the United States.** *Front Oncol* 2015;5:113.
7. Scheffler M et al. **ROS1 rearrangements in lung adenocarcinoma: Prognostic impact, therapeutic options and genetic variability.** *Oncotarget* 2015;6:10577-85.

Editorial — Dr Langer (continued)

8. Shaw AT et al. **Crizotinib in ROS1-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;371:1963-71.
9. Gainor JF et al. **Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non–small-cell lung cancer.** *JCO Precis Oncol* 2017; doi: 10.1200/PO.17.00063.
10. Facchinetti F et al. **Crizotinib-resistant ROS1 mutations reveal a predictive kinase inhibitor sensitivity model for ROS1- and ALK-rearranged lung cancers.** *Clin Cancer Res* 2016;22:5983-91.
11. Zou HY et al. **PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations.** *Proc Natl Acad Sci U S A* 2015;112:3493-8.
12. Shaw AT et al. **Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: An international, multicentre, open-label, single-arm first-in-man phase 1 trial.** *Lancet Oncol* 2017;18:1590-9.

Editorial — Dr Langer (continued)

13. Katayama R et al. **Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer.** *Clin Cancer Res* 2015;21:166-74.
14. Lim SM et al. **Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement.** *J Clin Oncol* 2017;35:2613-8.
15. Kodama T et al. **Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer.** *Mol Cancer Ther* 2014;13:2910-8.
16. Doebele R et al. **OA02.01 Efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC).** *J Thorac Oncol* 2018;13:S321-S322.
17. Barlesi F et al. **Entrectinib in locally advanced or metastatic ROS1 fusion-positive (ROS1+) NSCLC: Integrated analysis of ALKA-372-001, STARTRK-1 and STARTRK-2.** *Proc ELCC* 2019;Abstract 109O.

Editorial — Dr Langer (continued)

18. Cho B et al. **Safety and preliminary clinical activity of repotrectinib in patients with advanced ROS1 fusion-positive non-small cell lung cancer (TRIDENT-1 study).** *Proc ASCO* 2019;Abstract 9011.

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."

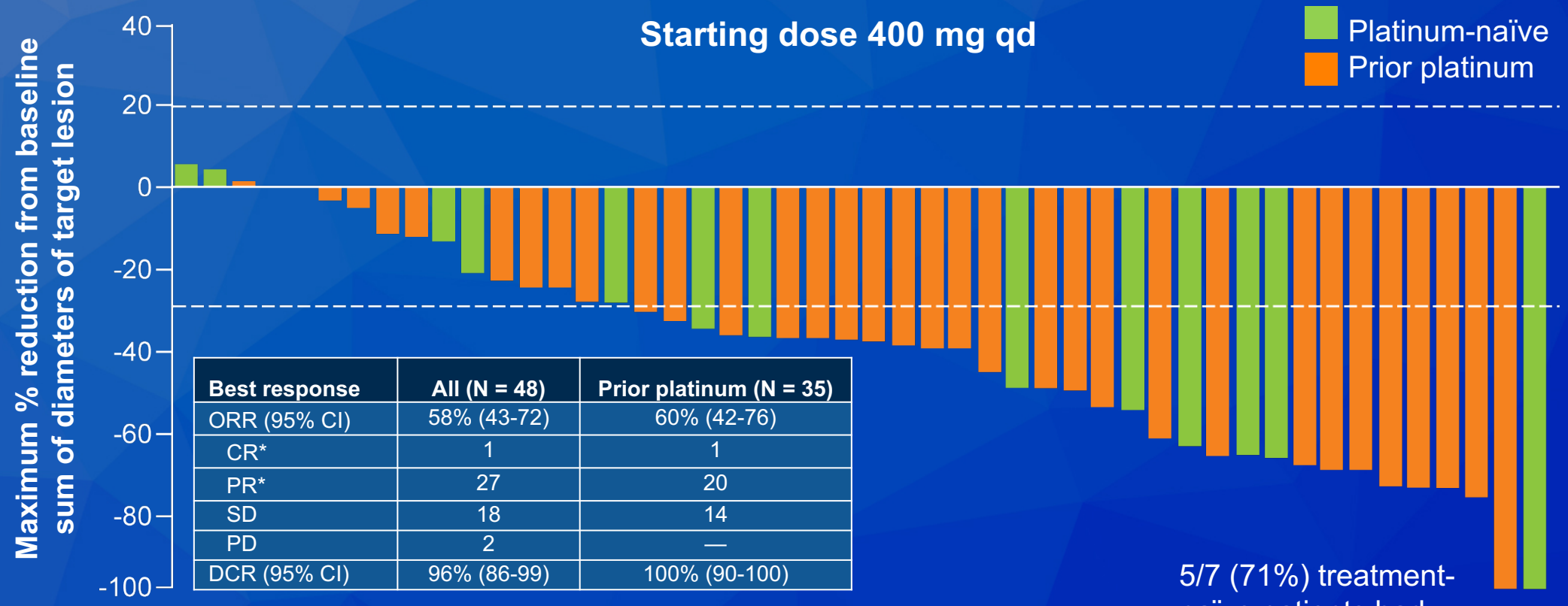
"Selpercatinib is an orally bioavailable selective inhibitor of wild-type, mutant and fusion products involving the proto-oncogene receptor tyrosine kinase rearranged during transfection (RET), with potential antineoplastic activity."

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%)

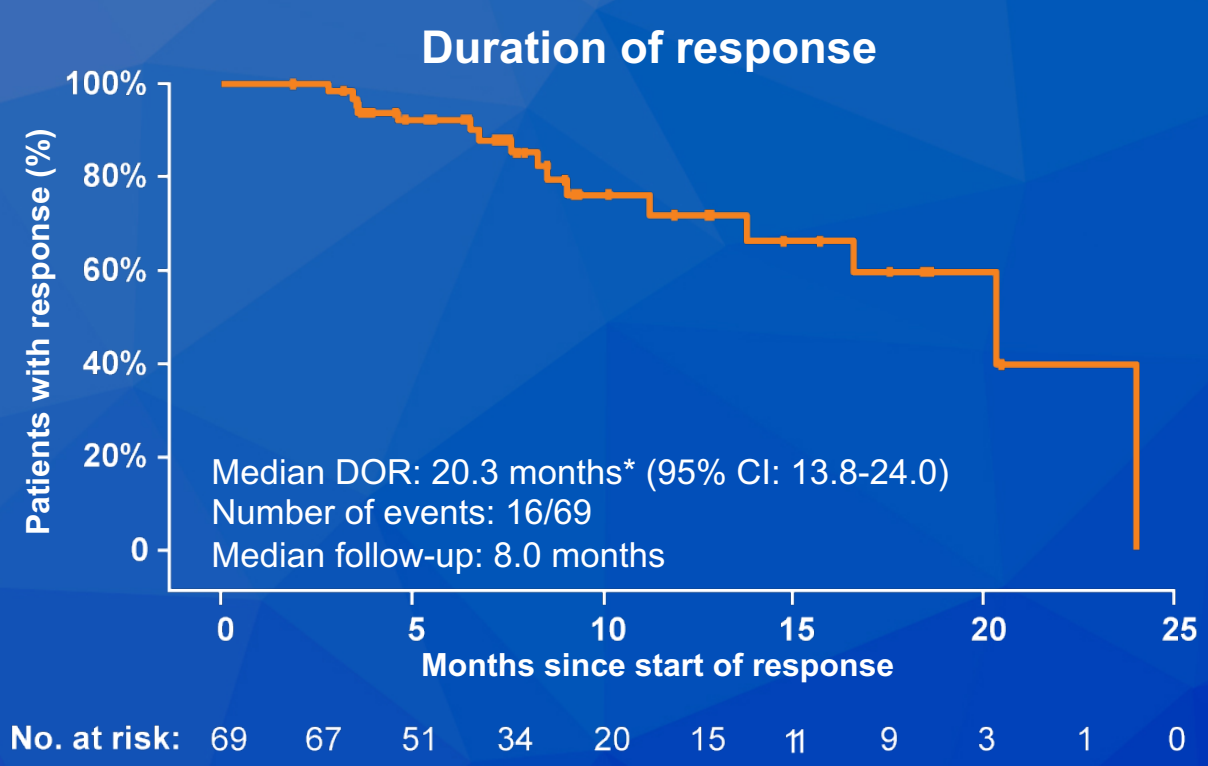
Gainor JF et al. *Proc ASCO* 2019;Abstract 9008.

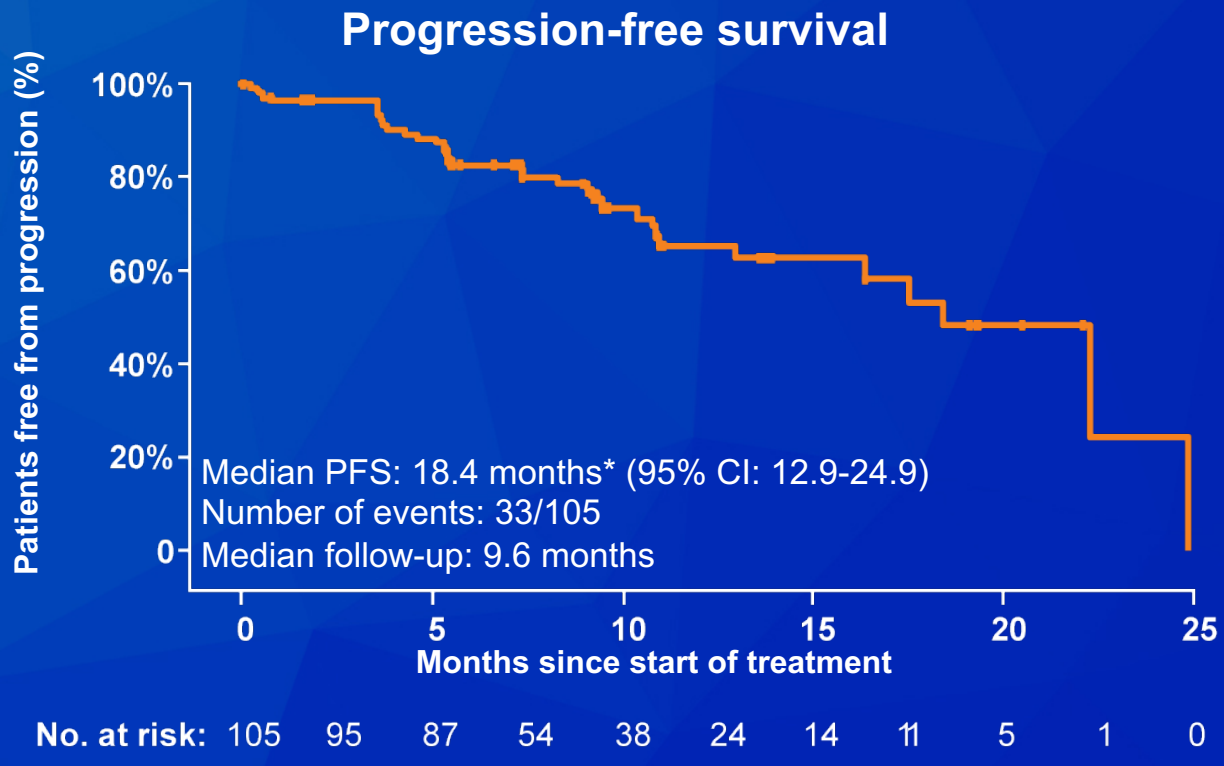
Registrational Results of LIBRETTO-001: A Phase 1/2 Trial of LOXO-292 in Patients with RET Fusion-Positive Lung Cancers

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



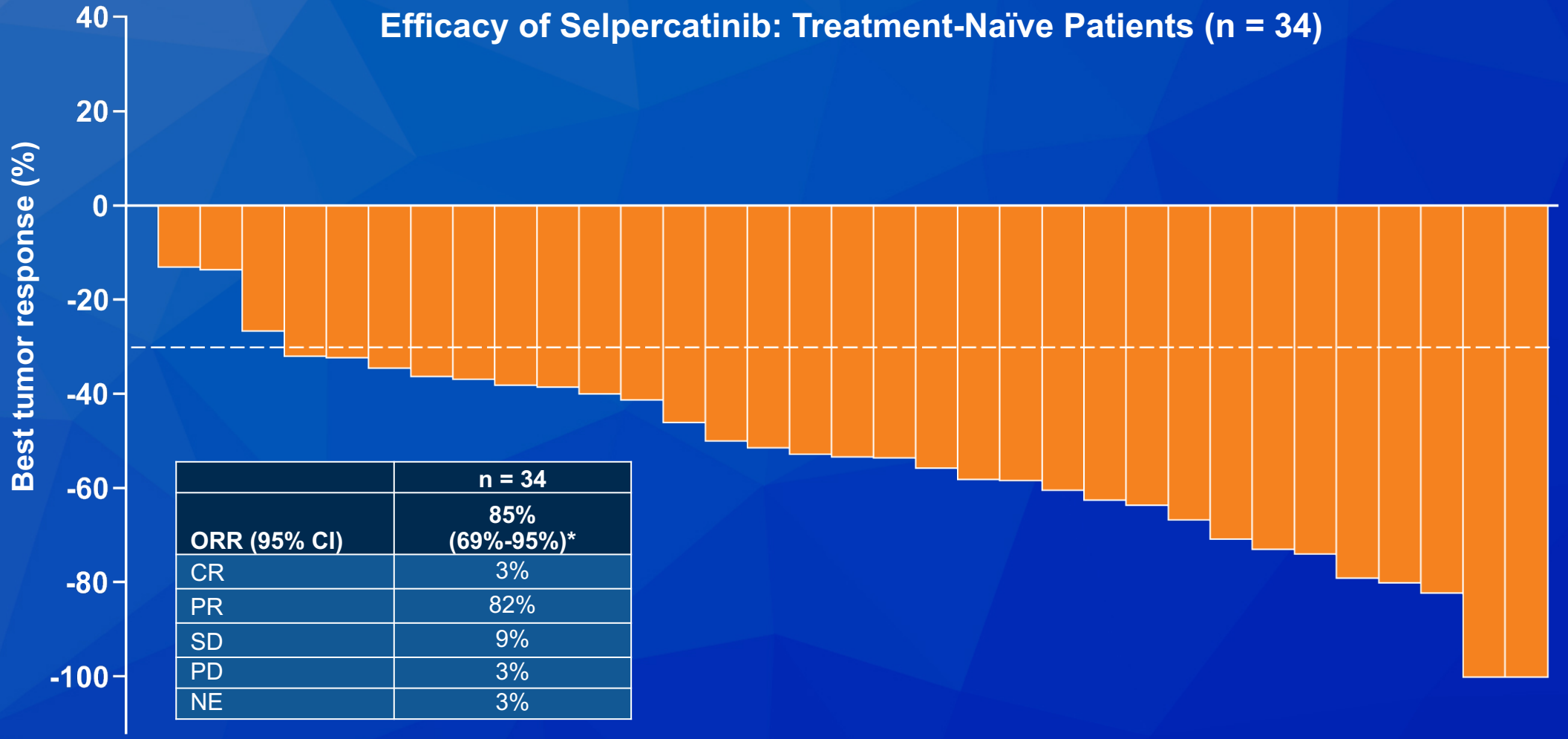


- ORR = 68%
- Intracranial ORR = 91%
- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2-16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (eg, anti-PD-1/PD-L1, MKIs)

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 Langer

The RTK RET (rearranged during transfection) is involved in the activation of cell-signaling pathways controlling proliferation, migration, and differentiation.[1] Chromosomal rearrangements of RET occur in 1.2% of unselected NSCLCs and are generally considered mutually exclusive of alterations in EGFR, KRAS, ALK, HER2, and BRAF.[2, 3] RET rearrangements are present in approximately 1.6% of patients with lung adenocarcinomas negative for EGFR, ALK, and KRAS.[4] Rarely, the coexistence of RET and other molecular alterations has been reported,[5] including patients with EGFR mutations who have developed resistance on EGFR TKIs.[6] RET rearrangements have not been reported in squamous cell carcinoma[7] or small-cell lung cancer. Currently, ≥12 fusion partners have been identified for RET in NSCLC, with KIF5B-RET being the most common and best characterized.[8]

A correlation exists between RET-positive NSCLC and adenocarcinoma histology,[9] poorly differentiated tumors, never-smoker status, younger age, and

Editorial — Dr Langer (continued)

smaller tumors (≤3 cm) with N2 disease.[10] Retrospective analyses have not shown a significant correlation between RET rearrangement and OS or recurrence-free survival (RFS) in patients with resected NSCLC.[10, 11]

As of October 2019, no targeted agent has yet been approved specifically for RET-positive NSCLC; however, several multikinase inhibitors with activity against RET have been evaluated, but results with these older agents have generally been disappointing. A recent retrospective analysis (GLORY) of 165 patients with RET-rearranged NSCLC assessed the clinical activity of several multikinase inhibitors, namely cabozantinib (n = 21), vandetanib (n = 11), sunitinib (n = 10), sorafenib (n = 2), alectinib (n = 2), lenvatinib (n = 2), nintedanib (n = 2), ponatinib (n = 2), and regorafenib (n = 1). The ORRs with cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively. The aggregate median PFS was disappointing at 2.3 months, with an OS in this heavily pretreated population of 6.8 months.[12] Vandetanib inhibits vascular

Editorial — Dr Langer (continued)

endothelial growth factor receptors 2 and 3 (VEGFR2 and VEGFR3), EGFR, and RET.[13] In the Japanese phase 2 LURET study (n = 19 with RET rearrangement), the ORR, DCR, median PFS, and 1-year OS in patients treated with vandetanib were 47%, 90%, 4.7 months, and 47%, respectively.[14] Treatment response and survival outcomes were better in patients with CCDC6-RET fusions vs those with the KIF5B-RET fusion. A high incidence of grade >3 AEs was observed: hypertension (58%), rash (16%), diarrhea (11%), and prolonged corrected QT interval (11%). In a Korean phase 2 study (n = 18 with RET-positive NSCLC), the ORR, DCR, median PFS, and OS were 18%, 65%, 4.5 months, and 11.6 months, respectively.[15] No patients with KIF5B-RET rearrangements had an objective response.

Cabozantinib inhibits VEGFR2, ROS1, MET, AXL, KIT, TIE2, and RET. Results from a single-arm, phase 2 study of cabozantinib in 26 patients with RET-positive lung adenocarcinomas showed a 28% ORR, a median PFS of 5.5

Editorial — Dr Langer (continued)

months, and a 9.9-month median OS.[16] The most common grade 3 TRAEs were lipase elevation (15%), increased alanine aminotransferase (8%), increased aspartate aminotransferase (8%), thrombocytopenia (8%), and hypophosphatemia (8%). No grade 4 toxicities or deaths related to treatment occurred. Of note, only 1 patient with a CCDC6-RET fusion was enrolled compared with 16 with the KEF5B-RET fusion. The ORR was lower in patients with KIF5B-RET rearrangements compared with patients with other fusions.

Far more promising are agents presented this past summer at ASCO and updated at WCLC. LOXO-292 (selpercatinib), a potent and selective RET inhibitor, is being evaluated in a phase 1/2 trial in patients with advanced solid tumors harboring a RET alteration (LIBRETTO-001; NCT03157128).[17] In the initial analysis of heavily pretreated NSCLC cohort (n = 30 evaluable for response), the ORR at 77% was far higher than we had observed with older agents, such as vandetinib and cabozantinib. LOXO-292 was well tolerated, with

Editorial — Dr Langer (continued)

only 2 grade ≥3 TRAEs reported (tumor lysis syndrome and increased alanine aminotransferase). The maximum tolerated dose had not been reached.

Results were updated this year at WCLC in Barcelona by Drilon et al during the plenary session.[18] The interim data included a primary analysis of the first 105 consecutive patients with NSCLC enrolled in LIBRETTO. Of these patients, all of whom had experienced disease progression on prior chemotherapy, checkpoint inhibitors, multikinase inhibitors or combination treatments, 68% realized an objective response. There were two complete responders at data cutoff and two more apparent complete responders awaiting confirmation. Among patients with brain metastases, 91% had an objective response. In a smaller group of 34 treatment-naïve patients, 85% achieved an objective response. Median duration of response to date in the primary analysis set was 20.3 months, and median PFS was 18.4 months. The durability of response is even murkier in the treatment-naïve population. Neither the median duration of response nor PFS

Editorial — Dr Langer (continued)

can be determined because there have been so few events, largely because the vast majority of patients enrolled to date have yet to experience disease progression. The most common treatment-emergent AEs (TEAEs) included dry mouth, reported in 32% of patients, followed by diarrhea (31%), hypertension (29%), and increased AST (28%) and ALT (26%) levels. There were relatively few serious adverse events, and only nine patients discontinued treatment due to TEAEs. Assuming this agent is approved in the near future, it will likely become the initial standard of care based on these robust and promising results.

The phase 1 ARROW trial is evaluating BLU-667 in patients with advanced, RET-altered solid tumors (NCT03037385).[19] In patients with NSCLC and RET fusions (n = 120 [n = 48 evaluable for response]), the ORR was 58% and the DCR was 96%. Antitumor activity was similar regardless of prior treatments, intracranial involvement, or RET fusion. Most TRAEs in patients treated with BLU-667 were low grade. The most common grade ≥3 TRAEs were neutropenia

Editorial — Dr Langer (continued)

(13%), hypertension (10%), and anemia (4%). Unfortunately, despite "Breakthrough Designation," neither agent has been FDA approved as of 10/19, so until that occurs, we are generally "stuck" with older, far less effective TKIs, in the second- or third-line setting, after conventional chemotherapy +/- checkpoint inhibitors. Finally, preclinical and preliminary clinical data suggest that the ALK inhibitor alectinib may also have activity in patients with RET-positive NSCLC.[20] Importantly, because alectinib does not target VEGFR2, it offers the potential of antitumor activity with an improved safety profile compared with other antiangiogenic multikinase TKIs. Whether alectinib will have any role once LOXO-292 and BLU-667 are approved is unclear.

Additional References

1. Kohno T et al. **KIF5B-RET fusions in lung adenocarcinoma.** *Nat Med* 2012;18:375-7.

Editorial — Dr Langer (continued)

2. Lipson D et al. **Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies.** *Nat Med* 2012;18:382-4.
3. Lee SE et al. **Comprehensive analysis of RET and ROS1 rearrangement in lung adenocarcinoma.** *Mod Pathol* 2015;28:468-79.
4. Song Z et al. **Clinicopathologic characteristics, genetic variability and therapeutic options of RET rearrangements patients in lung adenocarcinoma.** *Lung Cancer* 2016;101:16-21.
5. Klempner SJ et al. **Emergence of RET rearrangement co-existing with activated EGFR mutation in EGFR-mutated NSCLC patients who had progressed on first- or second-generation EGFR TKI.** *Lung Cancer* 2015;89:357-9.
6. Zhao W et al. **ALK, ROS1 and RET rearrangements in lung squamous cell carcinoma are very rare.** *Lung Cancer* 2016;94:22-27.

Editorial — Dr Langer (continued)

7. Kohno T et al. **Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer.** *Transl Lung Cancer Res* 2015;4:156-64.
8. Ferrara R et al. **Clinical and translational implications of RET rearrangements in non-small cell lung cancer.** *J Thorac Oncol* 2018;13:27-45.
9. Ju YS et al. **A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing.** *Genome Res* 2012;22:436-45.
10. Wang R et al. **RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer.** *J Clin Oncol* 2012;30:4352-9.
11. Tsuta K et al. **RET-rearranged non-small-cell lung carcinoma: A clinicopathological and molecular analysis.** *Br J Cancer* 2014;110:1571-8.

Editorial — Dr Langer (continued)

12. Gautschi O et al. **Targeting RET in patients with RET-rearranged lung cancers: Results from the global, multicenter RET registry.** *J Clin Oncol* 2017;35:1403-10.
13. Morabito A et al. **Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: current status and future directions.** *Oncologist* 2009;14:378-90.
14. Yoh K et al. **Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): An open-label, multicentre phase 2 trial.** *Lancet Respir Med* 2017;5:42-50.
15. Lee SH et al. **Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: A phase II clinical trial.** *Ann Oncol* 2017;28:292-7.

Editorial — Dr Langer (continued)

16. Drilon A et al. **Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: An open-label, single-centre, phase 2, single-arm trial.** *Lancet Oncol* 2016;17:1653-60.
17. Drilon AE et al. **A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers.** *J Clin Oncol* 2018;36:102.
18. Drilon A et al. **Registrational results of LIBRETTO-001: A phase 1/2 trial of LOXO-292 in patients with RET fusion-positive lung cancers.** *Proc IASLC* 2019;Abstract PL02.08.
19. Subbiah V et al. **Highly potent and selective RET inhibitor, BLU-667, achieves proof of concept in a phase I study of advanced, RET-altered solid tumors.** *Proc AACR* 2018;Abstract CT043.
20. Lin JJ et al. **Clinical activity of alectinib in advanced RET-rearranged non-small cell lung cancer.** *J Thorac Oncol* 2016;11:2027-32.

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

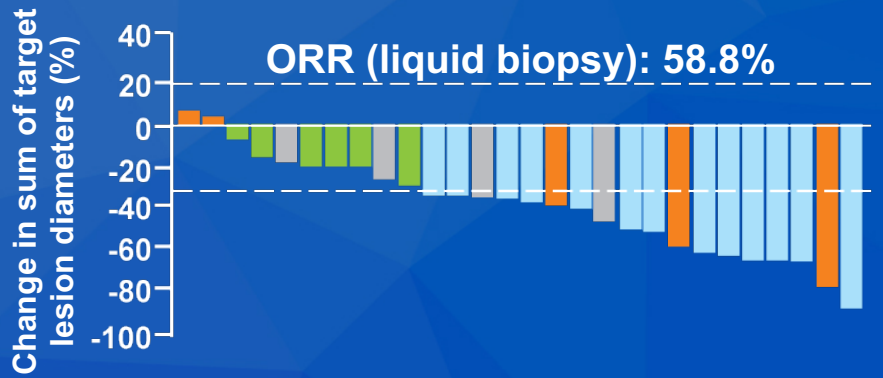
Phase II Study of Tepotinib in NSCLC Patients with METex14 Mutations

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

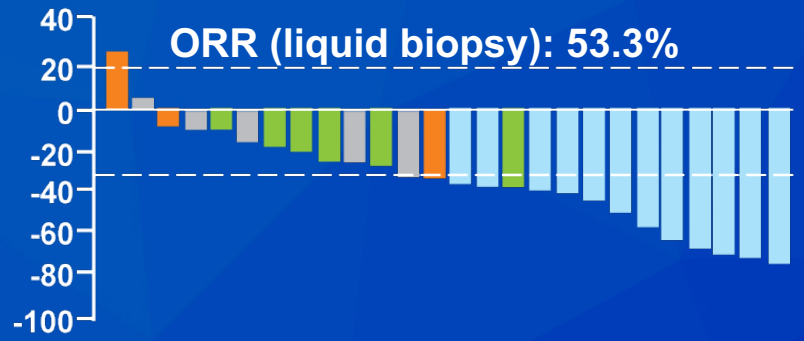
VISION Study: Tumor Shrinkage with Tepotinib by Line of Therapy (IRC)

First line

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

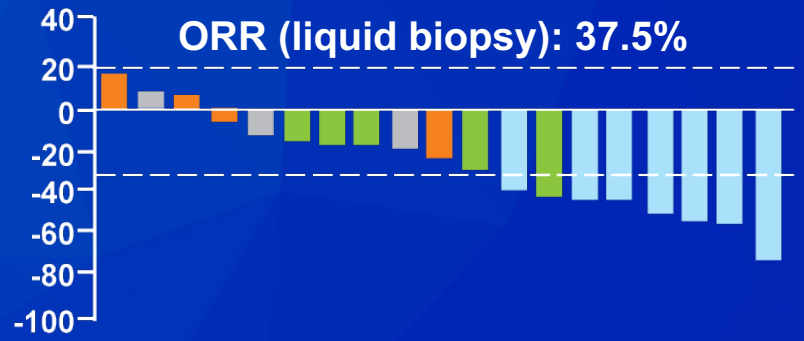


Second line



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 Langer

MET is a receptor tyrosine kinase for hepatocyte growth factor (HGF). Dysregulated MET signaling can occur via MET protein overexpression, gene amplification, rearrangements, and mutation. In NSCLC, MET amplification typically occurs in about 3%-5% of newly diagnosed patients.[1,2] MET mutation, predominantly exon 14 deletions, can occur in up to 3%-4% of NSCLC adenocarcinomas and 1%-2% of other NSCLC subsets,[3,4] though the “real” percentages may be quite a bit lower. MET overexpression has been reported in 20%-37% of tumor samples.[5,6] MET amplification is also implicated in acquired resistance to EGFR inhibitors in NSCLC.[7,8]

Data on clinical correlates are lacking overall. However, one study found that 22% of patients with pulmonary sarcomatoid carcinoma had a mutation in the MET exon-14 splice site, leading to exon 14 skipping.[9] Virtually all mechanisms of MET dysregulation have been associated with poor survival outcomes.[10]

Editorial — Dr Langer (continued)

Currently, no agents are formally approved for the treatment of MET-positive NSCLC, but several have been under investigation. The multikinase inhibitors crizotinib and cabozantinib are both in phase 2 development for patients with MET-positive NSCLC. Crizotinib has demonstrated antitumor activity in patients with either MET amplification or exon 14 alterations, and efficacy is supported by a series of case reports detailing clinical response in patients with MET-positive NSCLC.[11-15] In one such effort, the response rate was 33% with mPFS of 7.3 mos.

Data from a randomized phase 2 study demonstrated that PFS was significantly improved with cabozantinib or erlotinib plus cabozantinib vs erlotinib alone, although MET status was not considered a significant predictor of PFS.[16] The combination of cabozantinib and erlotinib was well tolerated. The most common grade 3/4 treatment-related AEs in the combination group were diarrhea (28%), fatigue (15%), anorexia (8%), acneiform rash (5%), and thromboembolic events (5%). One treatment-related death from pneumonitis occurred in the combination arm.

Editorial — Dr Langer (continued)

Several specific MET inhibitors are also undergoing clinical evaluation, including capmatinib and tepotinib. These appear to hold the greatest promise. The clinical activity of capmatinib was demonstrated in a phase 1 trial in patients with MET-dysregulated NSCLC. Although the ORR was 20% among all patients, MET gene copy number (GCN) ≥6 (ORR, 47%; median PFS, 7.4 months) and exon-14 skipping mutations (3 of 4 patients with a response) appeared to predict benefit.[17,18] A phase 2 trial (GEOMETRY mono-1; NCT02414139) evaluating capmatinib in patients with EGFR wild-type, MET-dysregulated NSCLC is ongoing. Preliminary results presented by Wolf and colleagues at ASCO 2019 were encouraging. In the second- and third-line setting (n = 69), in patients with the MET exon-14 skipping mutation, the ORR was 42% with mPFS of 5.42 mos. In a treatment-naïve cohort (n = 28), the ORR was 60.7% and the mPFS was 9.7 mos with nearly 50% of patients free from progression at one year.[19]

Editorial — Dr Langer (continued)

Preclinical data from an NSCLC xenograft model demonstrated favorable results for tepotinib in overcoming EGFR TKI resistance due to MET mutation. In an EGFR-mutated and MET-amplified cell line, EGFR TKIs were ineffective, while tepotinib alone induced complete tumor regression.[20] Tepotinib is currently under investigation in a phase 2 trial (NCT02864992) in patients with EGFR and ALK wild-type NSCLC. Preliminary results (n = 34) showed encouraging antitumor activity, with a confirmed ORR of 46% (9 of 15 patients). Grade ≥3 treatment-related AEs were reported in 2 of 22 evaluable patients.[21] An update at ASCO 2019 by Drilon showed continued promise.[22] In 89 patients with the MET exon-14 skipping mutation, diagnosed by liquid (L+) biopsy or tissue (T+) biopsy, the response rates were consistent with the L+ cohort demonstrating an ORR of 55.3% and mPFS of 9.5 mos, while the T + cohort exhibited an ORR of 54.95 and a mPFS of 12.2 mos. The demographics of this group were notable:

Editorial — Dr Langer (continued)

54% male, 38% treatment-naïve, 86% adenocarcinoma with only 1% sarcomatoid, and older median age of 74.

Toxicity, however, particularly fluid retention and peripheral edema, remains a challenge with both agents. The severity of these side effects in clinical practice may determine whether we consider these agents front line or after the failure of chemotherapy ± immunotherapy.

Additional References

1. Cappuzzo F et al. **Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients.** *J Clin Oncol* 2009;27:1667-74.
2. Kawakami H et al. **Targeting MET amplification as a new oncogenic driver.** *Cancers (Basel)* 2014;6:1540-52.

Editorial — Dr Langer (continued)

3. Frampton GM et al. **Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors.** *Cancer Discov* 2015;5:850-9.
4. Paik PK et al. **Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping.** *Cancer Discov* 2015;5:842-9.
5. Tsao MS et al. **Differential expression of MET/hepatocyte growth factor receptor in subtypes of non-small cell lung cancers.** *Lung Cancer* 1998;20:1-16.
6. Watermann I et al. **Improved diagnostics targeting c-MET in non-small cell lung cancer: Expression, amplification and activation?** *Diagn Pathol* 2015;10:130.

Editorial — Dr Langer (continued)

7. Bean J et al. **MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib.** *Proc Natl Acad Sci USA* 2007;104:20932-7.
8. Sadiq AA, Salgia R. **MET as a possible target for non-small-cell lung cancer.** *J Clin Oncol* 2013;31:1089-96.
9. Liu X et al. **Next-generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency of actionable MET gene mutations.** *J Clin Oncol* 2016;34:794-802.
10. Go H et al. **High MET gene copy number leads to shorter survival in patients with non-small cell lung cancer.** *J Thorac Oncol* 2010;5:305-13.
11. Camidge DR et al. **Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).** J *Clin Oncol* 2014;32:8001.

Editorial — Dr Langer (continued)

12. Drilon AE et al. **Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC).** *J Clin Oncol* 2016;34:108.
13. Waqar SN et al. **MET mutation associated with responsiveness to crizotinib.** *J Thorac Oncol* 2015;10:e29-31.
14. Jenkins RW et al. **Response to crizotinib in a patient with lung adenocarcinoma harboring a MET splice site mutation.** *Clin Lung Cancer* 2015;16:e101-4.
15. Mendenhall MA, Goldman JW. **MET-mutated NSCLC with major response to crizotinib.** *J Thorac Oncol* 2015;10:e33-4.

Editorial — Dr Langer (continued)

16. Neal JW et al. **Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): A randomized, controlled, open-label, multicentre, phase 2 trial.** *Lancet Oncol* 2016;17:1661-71.
17. Schuler MH et al. **Phase (Ph) I study of the safety and efficacy of the cMET inhibitor capmatinib (INC280) in patients (pts) with advanced cMET+ non-small cell lung cancer (NSCLC).** *J Clin Oncol* 2016;34:9067.
18. Wolf J et al. **Results of the GEOMETRY mono-1 phase II study for evaluation of the MET inhibitor capmatinib (INC280) in patients (pts) with METΔex14 mutated advanced non-small cell lung cancer (NSCLC).** *Proc ESMO* 2018;Abstract LBA52.

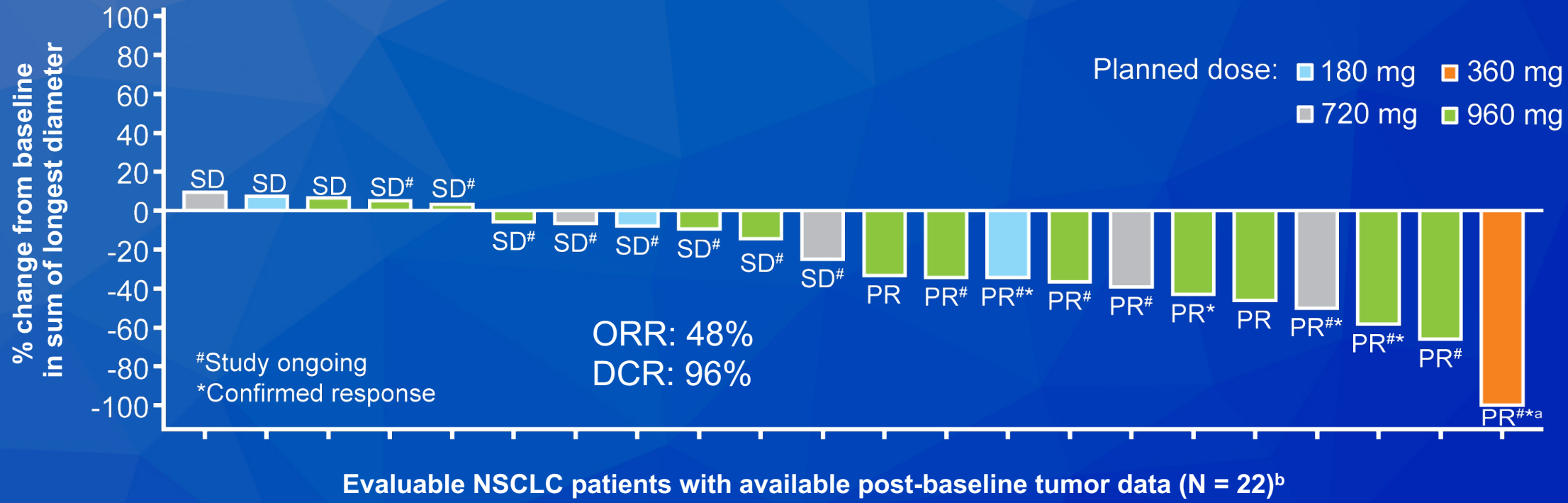
Editorial — Dr Langer (continued)

19. Wolf J et al. **Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study.** *Proc ASCO* 2019;Abstract 9004.
20. Friese-Hamim M et al. **The selective c-Met inhibitor tepotinib can overcome epidermal growth factor receptor inhibitor resistance mediated by aberrant c-Met activation in NSCLC models.** *Am J Cancer Res* 2017;7:962-72.
21. Felip E et al. **Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14-skipping mutations: Phase II trial.** *J Clin Oncol* 2018;36:9016.
22. Paik P et al. **Phase II study of tepotinib in NSCLC patients with METex14 mutations.** *Proc ASCO* 2019;Abstract 9005.

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



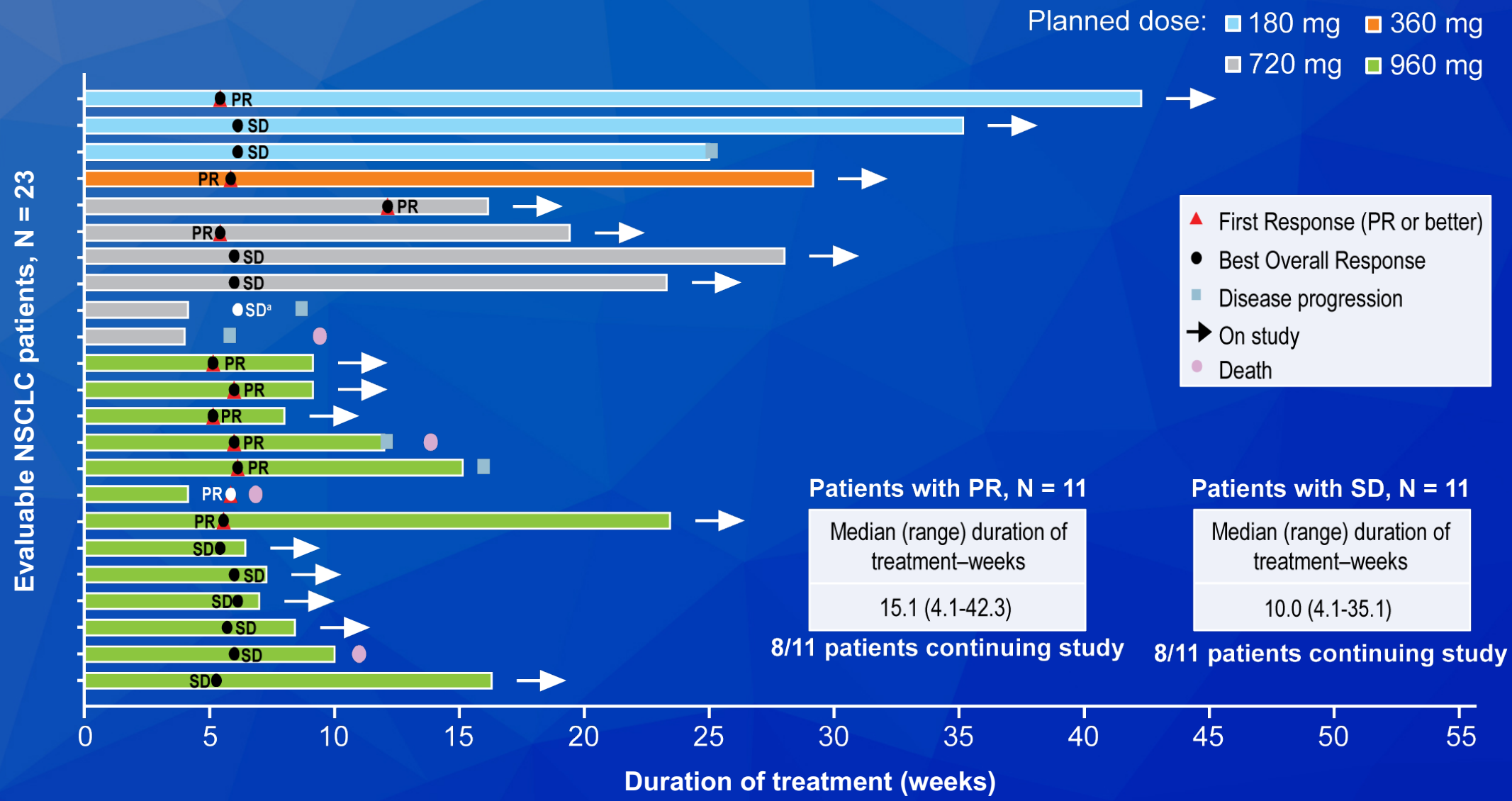
Evaluable NSCLC patients with available post-baseline tumor data (N = 22)[b]

[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 Langer and Riely

Targeted Therapy in NSCLC

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

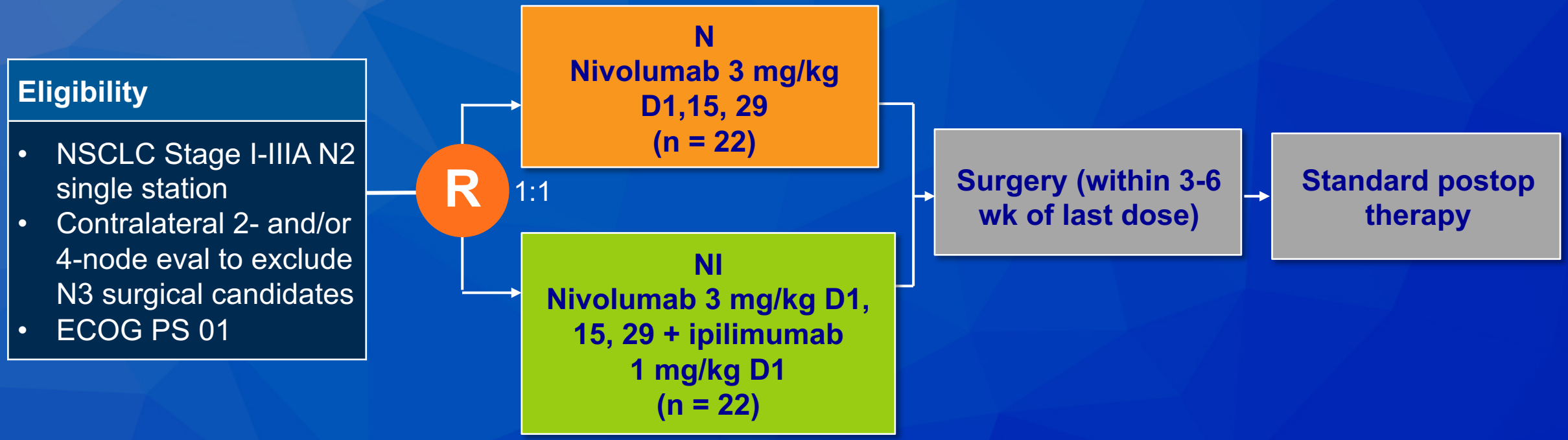
ICIs in Patients with SCLC

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



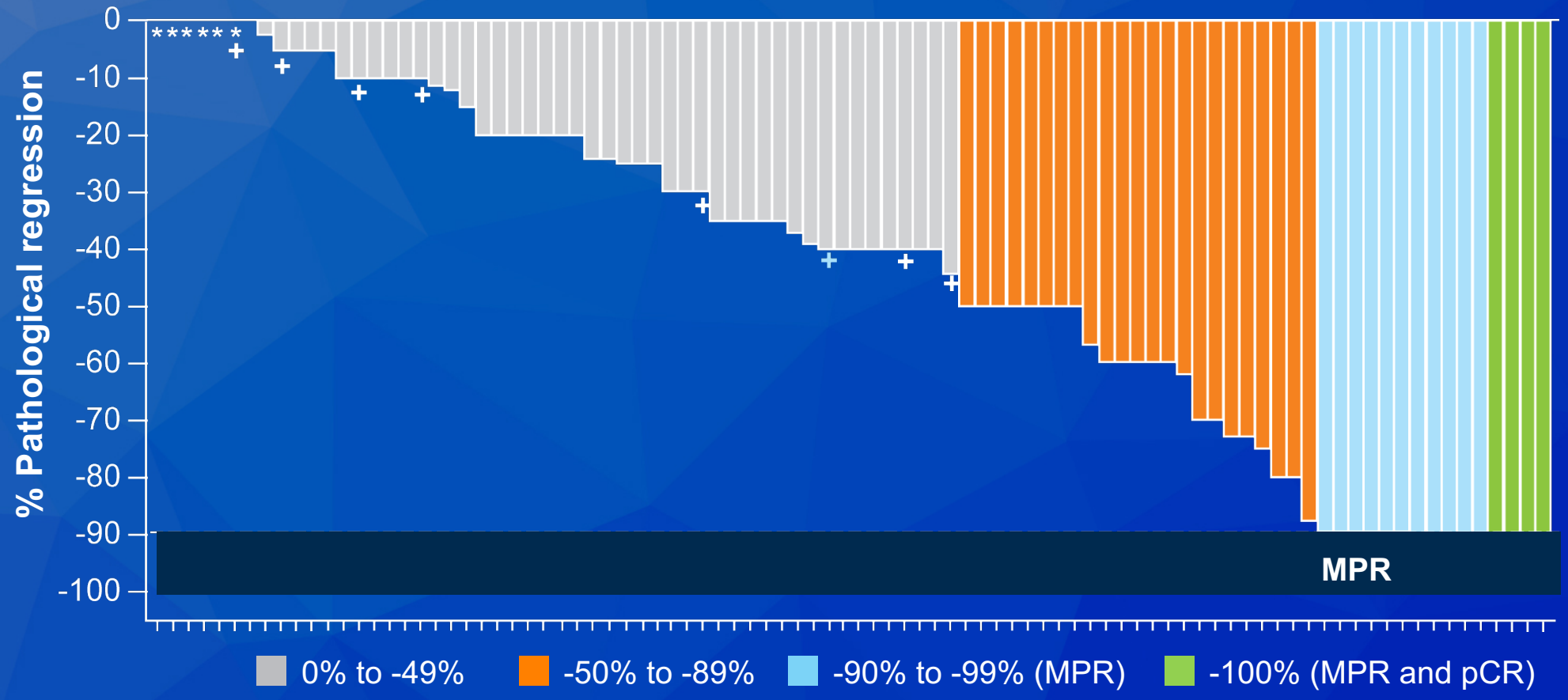
- Primary endpoint: MPR rate (≤10% viable tumor)
- MPR rate (ITT): N, 17%; NI, 33%

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

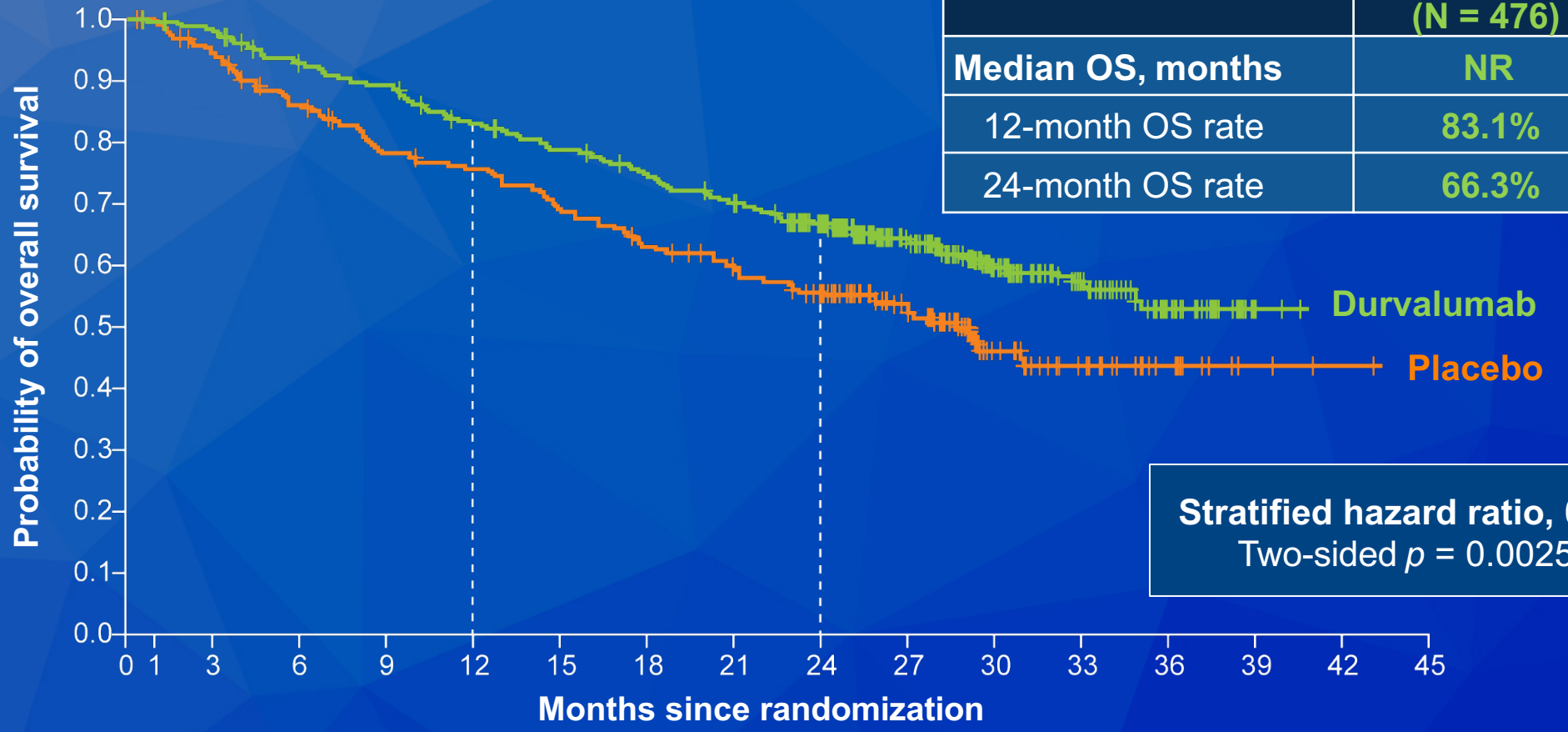
Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

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 Langer 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

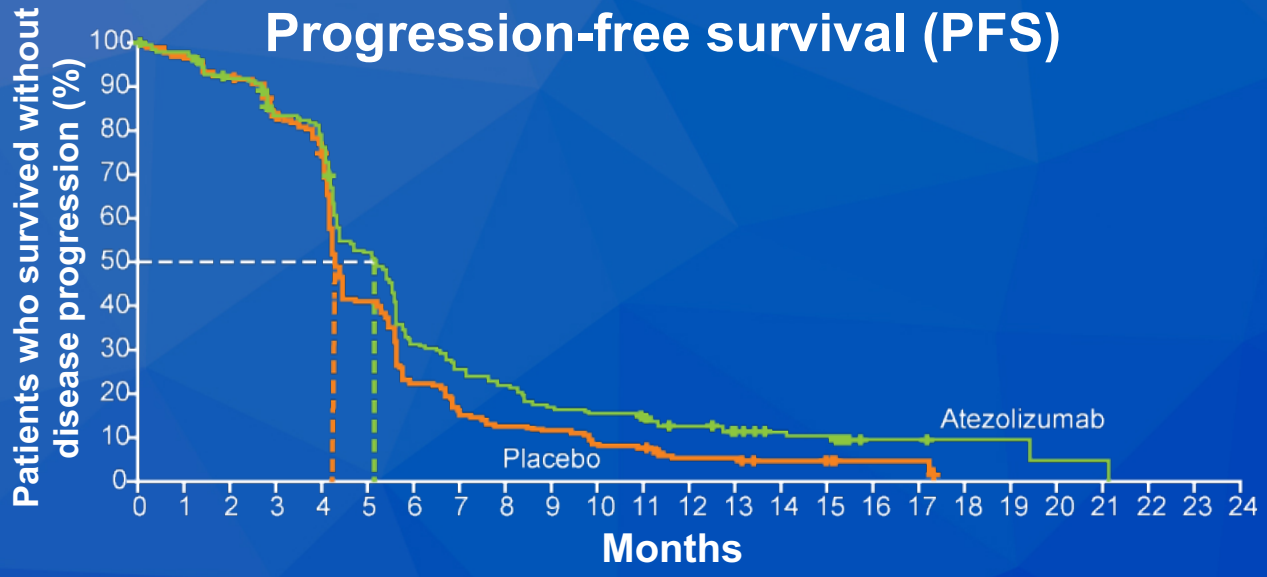
First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

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.

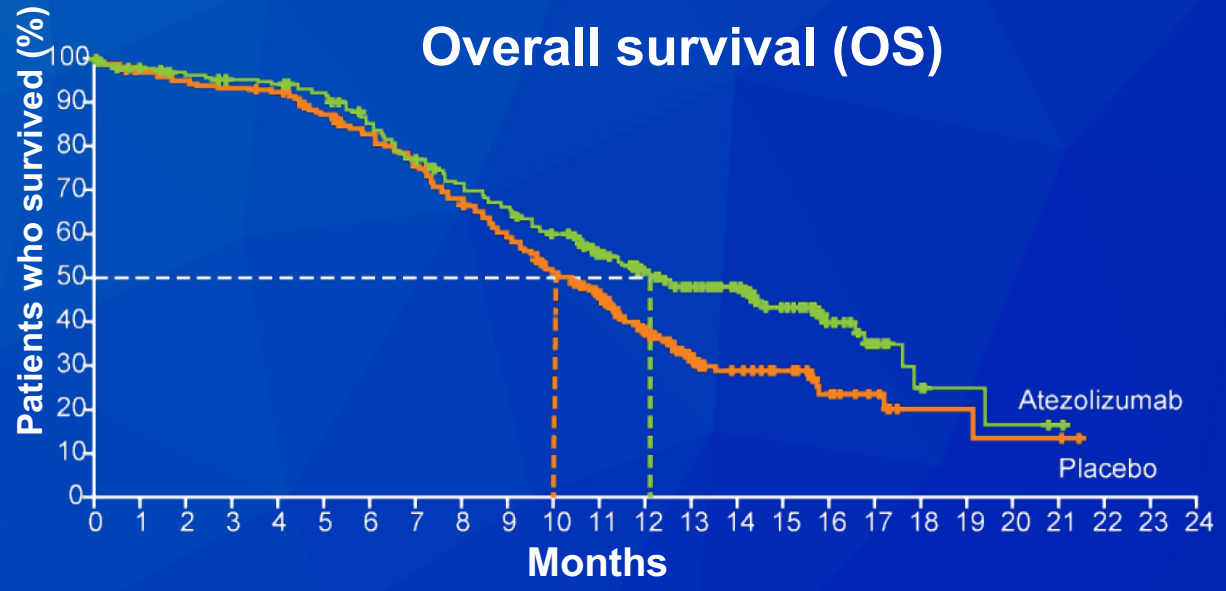
IMpower133: Survival Outcomes with First-Line Atezolizumab and Chemotherapy for Extensive-Stage SCLC

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%		

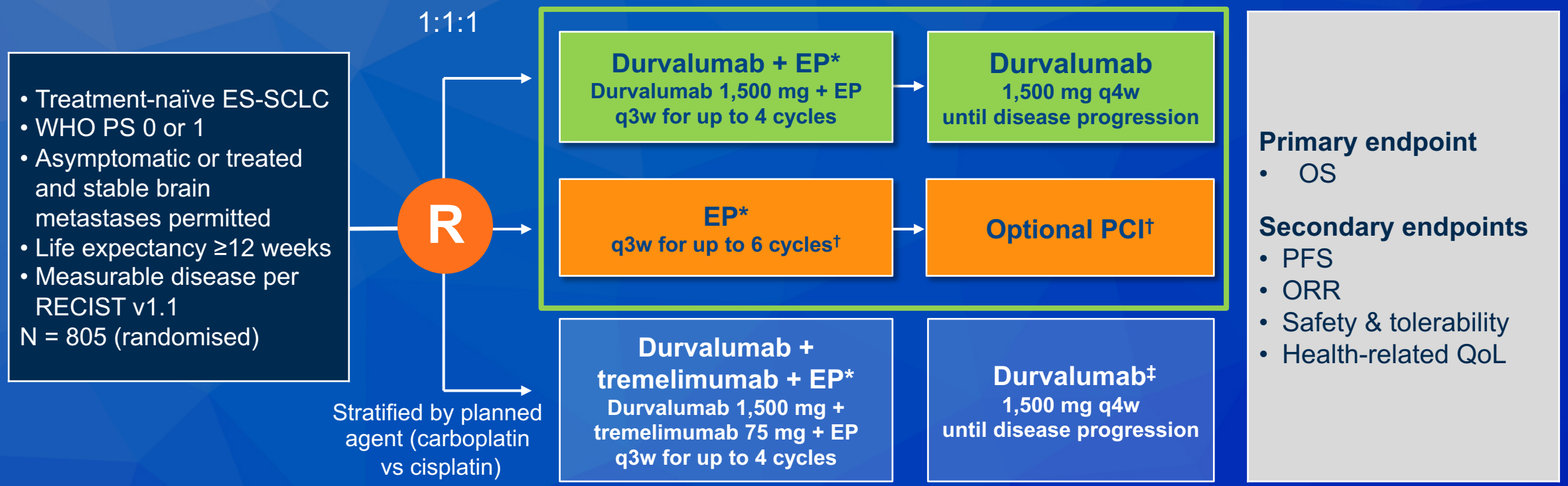
- The safety profile of atezolizumab + carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents; no new findings were observed.

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



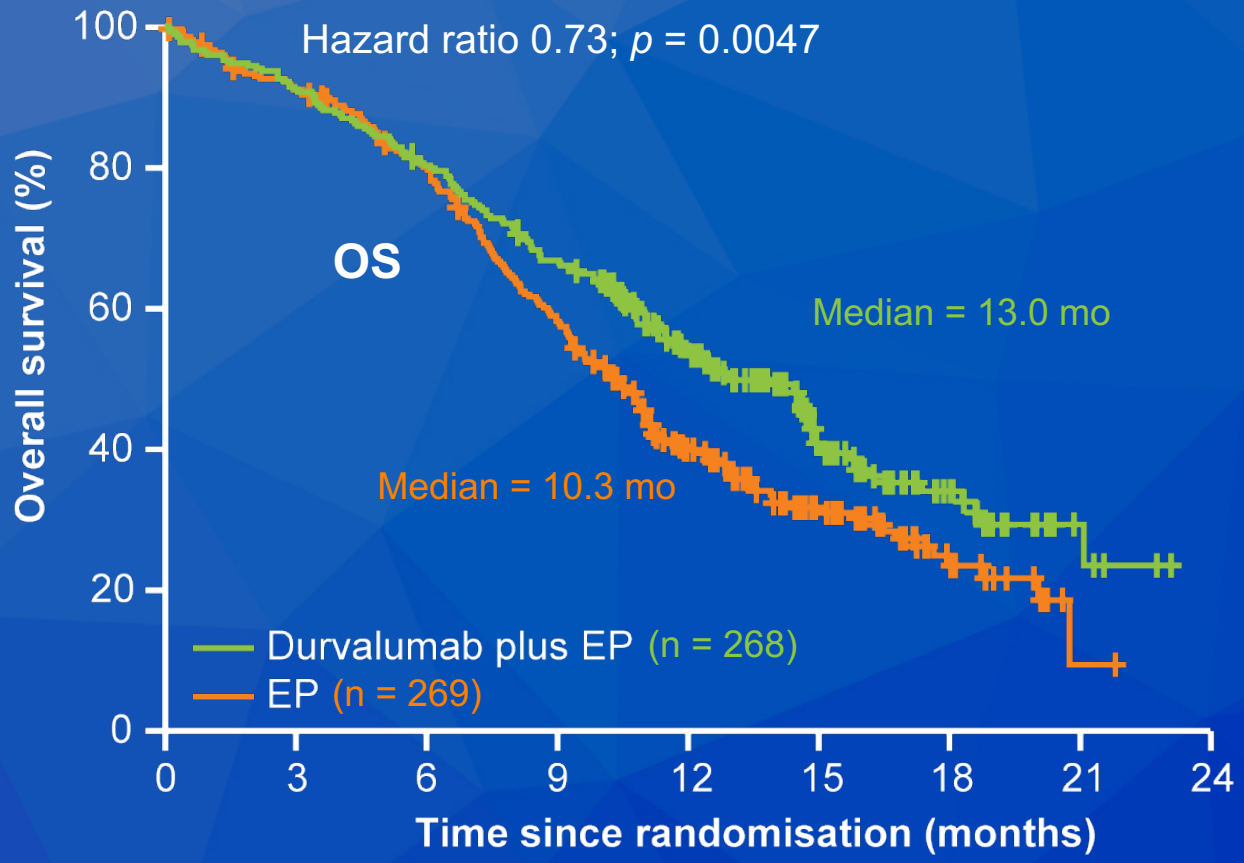
The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

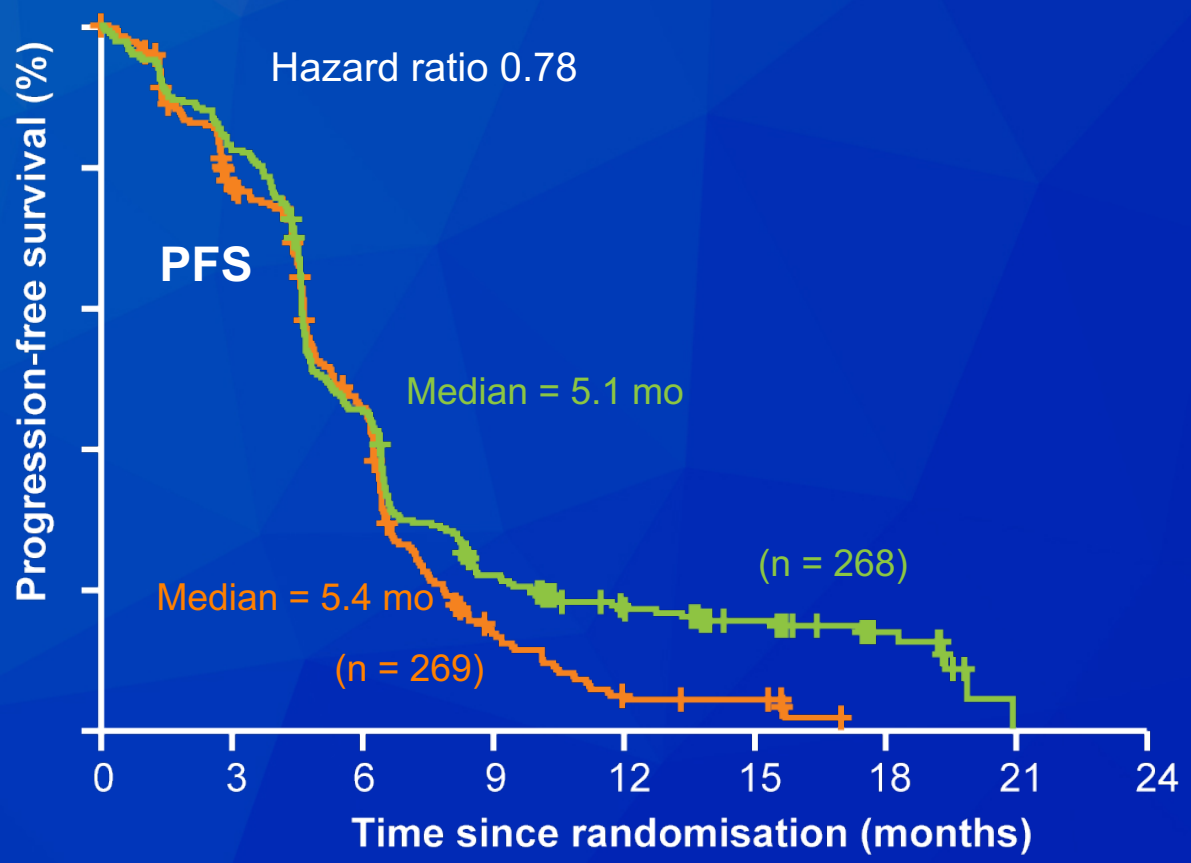
* EP consists of etoposide 80-100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75-80 mg/m^2
† Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡ Patients received an additional dose of tremelimumab post-EP

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 Langer 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

Therapy for Stage IV Non-Small-Cell Lung Cancer without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update

Hanna NH et al.
J Clin Oncol 2020;[Epub ahead of print].

ASCO/OH (CCO) Updated Recommendations for Stage IV NSCLC without Driver Alterations

- **Patients with high PD-L1 expression (TPS ≥50%) and nonsquamous cell carcinoma (non-SCC):**
  - **Single-agent pembrolizumab**
  - ***Additional treatment options*:** Pembrolizumab/carboplatin/pemetrexed, atezolizumab/carboplatin/paclitaxel/bevacizumab or atezolizumab/carboplatin/*nab* paclitaxel
- **For most patients with non-SCC and either negative (0%) or low-positive (1% to 49%) PD-L1:**
  - **Pembrolizumab/carboplatin/pemetrexed**
  - ***Additional treatment options*:** Atezolizumab/carboplatin/*nab* paclitaxel, atezolizumab/carboplatin/paclitaxel/bevacizumab, platinum-based 2-drug combination chemotherapy, or nonplatinum-based 2-drug therapy
  - Single-agent pembrolizumab is an option for low-positive PD-L1
- **Patients with high PD-L1 expression (TPS ≥50%) and SCC:**
  - **Single-agent pembrolizumab**
  - ***Additional treatment option*:** Pembrolizumab/carboplatin/(paclitaxel or *nab* paclitaxel)
- **For most patients with SCC and either negative (0%) or low-positive PD-L1 (TPS 1% to 49%):**
  - **Pembrolizumab/carboplatin/(paclitaxel or *nab* paclitaxel) or chemotherapy**
  - Single-agent pembrolizumab is an option in select cases of low-positive PD-L1
- *Recommendations are conditional on the basis of histology, PD-L1 status and/or the presence or absence of contraindications*

Hanna NH et al. *J Clin Oncol* 2020;[Epub ahead of print].

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).

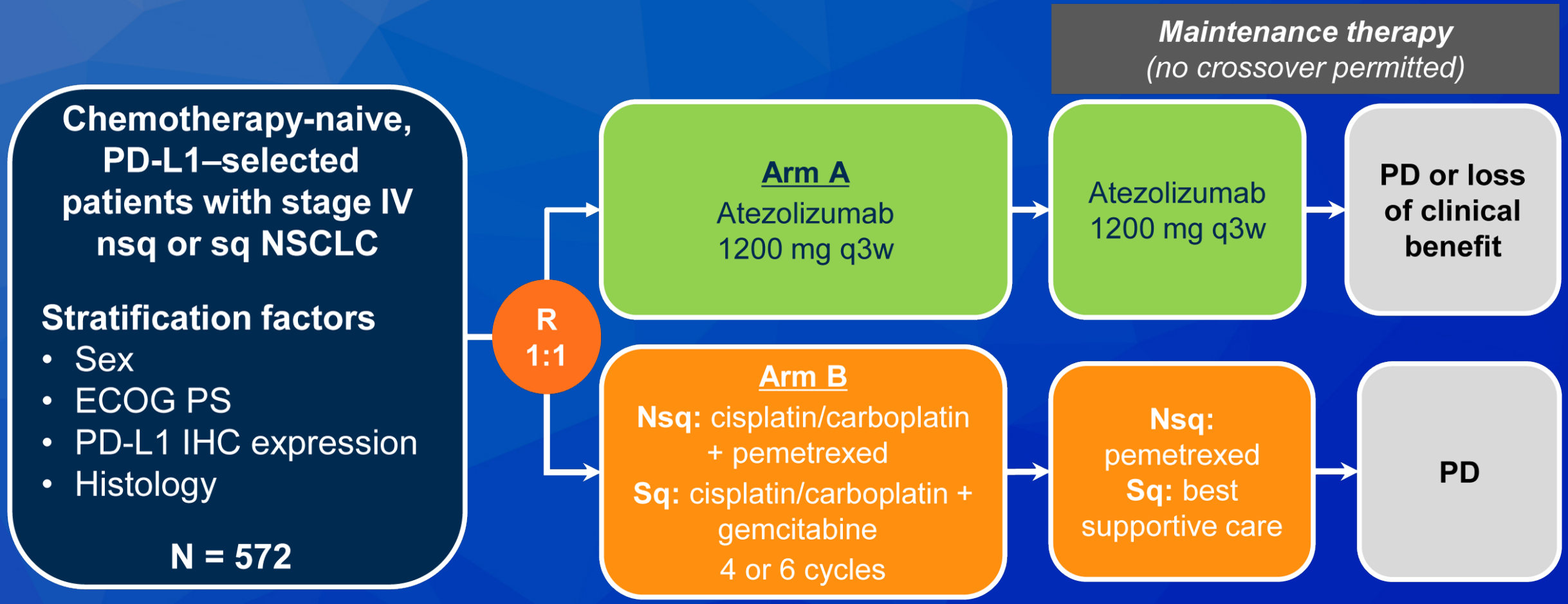
The study met its primary endpoint in an interim analysis showing that atezolizumab monotherapy demonstrated a statistically significant overall survival (OS) benefit in people with high PD-L1 expression (TC3/IC3-WT), compared with chemotherapy alone. Safety for atezolizumab appeared to be consistent 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



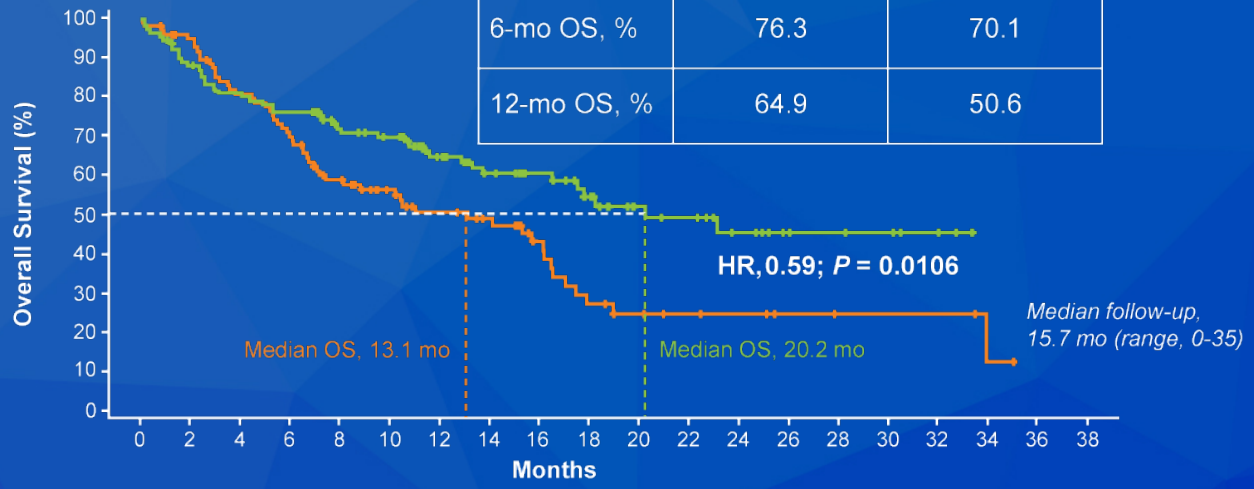
- **Primary endpoint: OS in WT population (excludes patients with EGFR+ and/or ALK+ NSCLC)**

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

IMpower110: OS Results

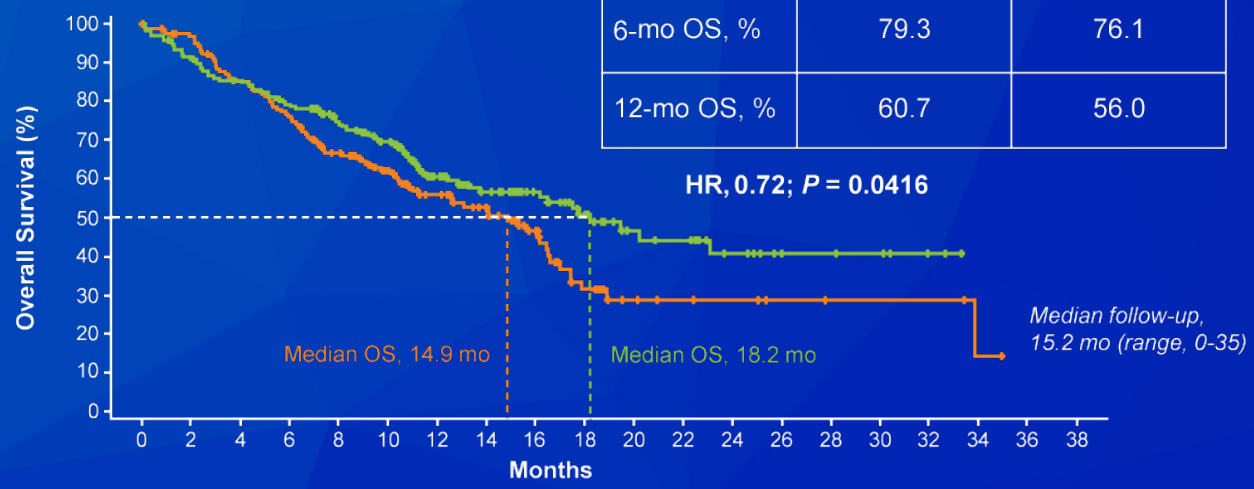
TC3 or IC3 WT Population

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

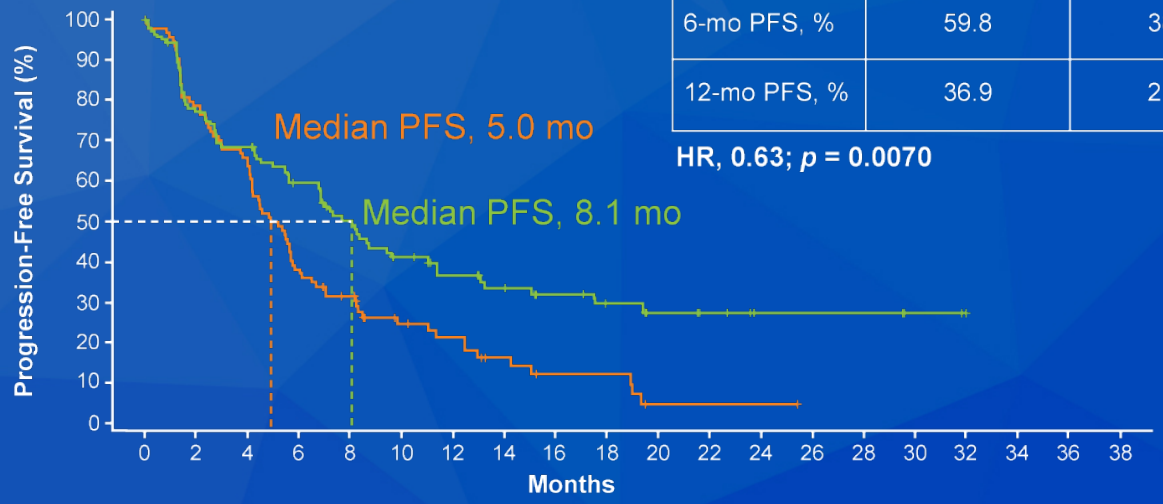
Spigel DR et al. *Proc ESMO* 2019;Abstract LBA78.

IMpower110: PFS and Response Rates

TC3 or IC3 WT Population

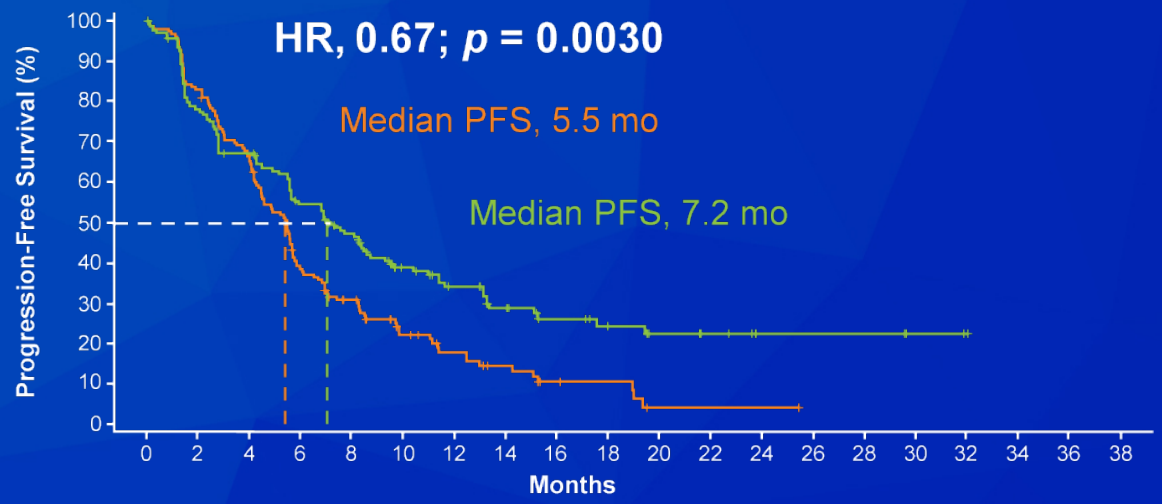
Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo PFS, %	59.8	38.3
12-mo PFS, %	36.9	21.6

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

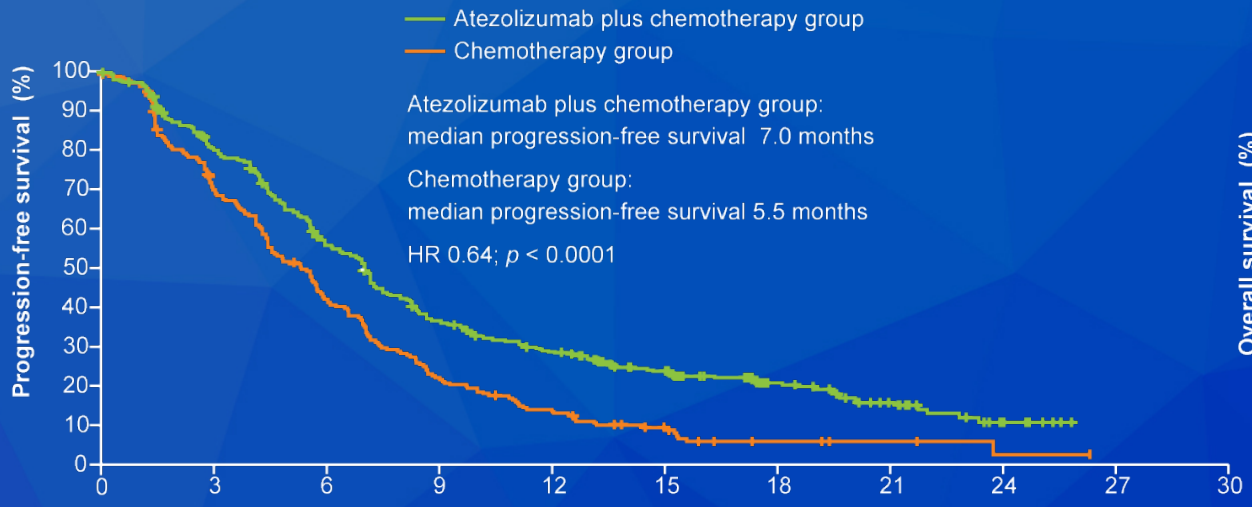
West H et al.

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

IMpower130: PFS and OS Results

PFS in ITT-WT Population

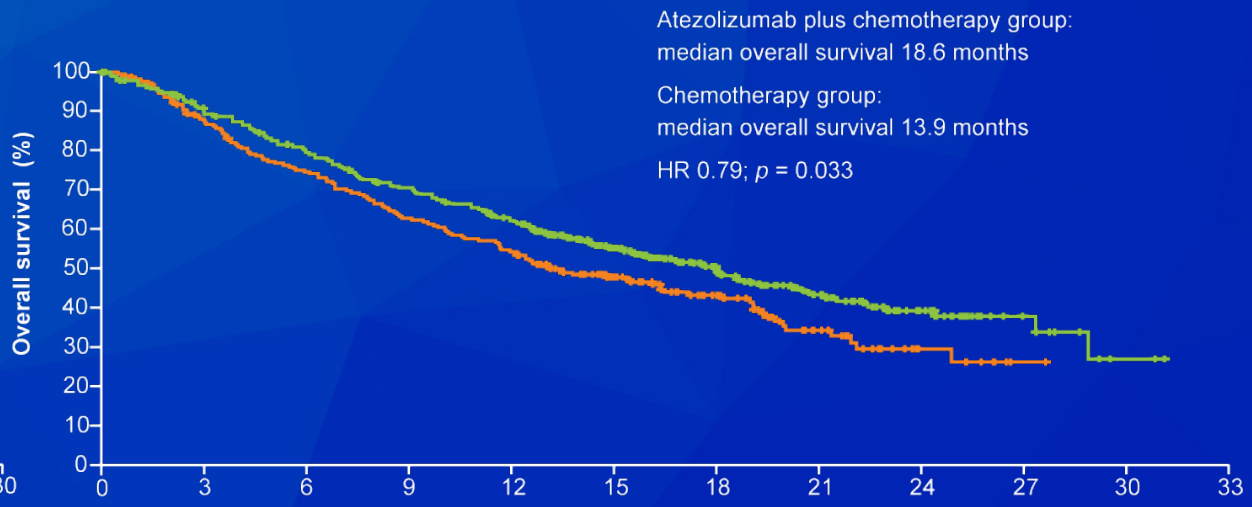
	Progression-free survival at 6 months	Progression-free survival at 12 months
Atezolizumab plus chemotherapy group	56.1%	29.1%
Chemotherapy group	42.5%	14.1%



- 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.

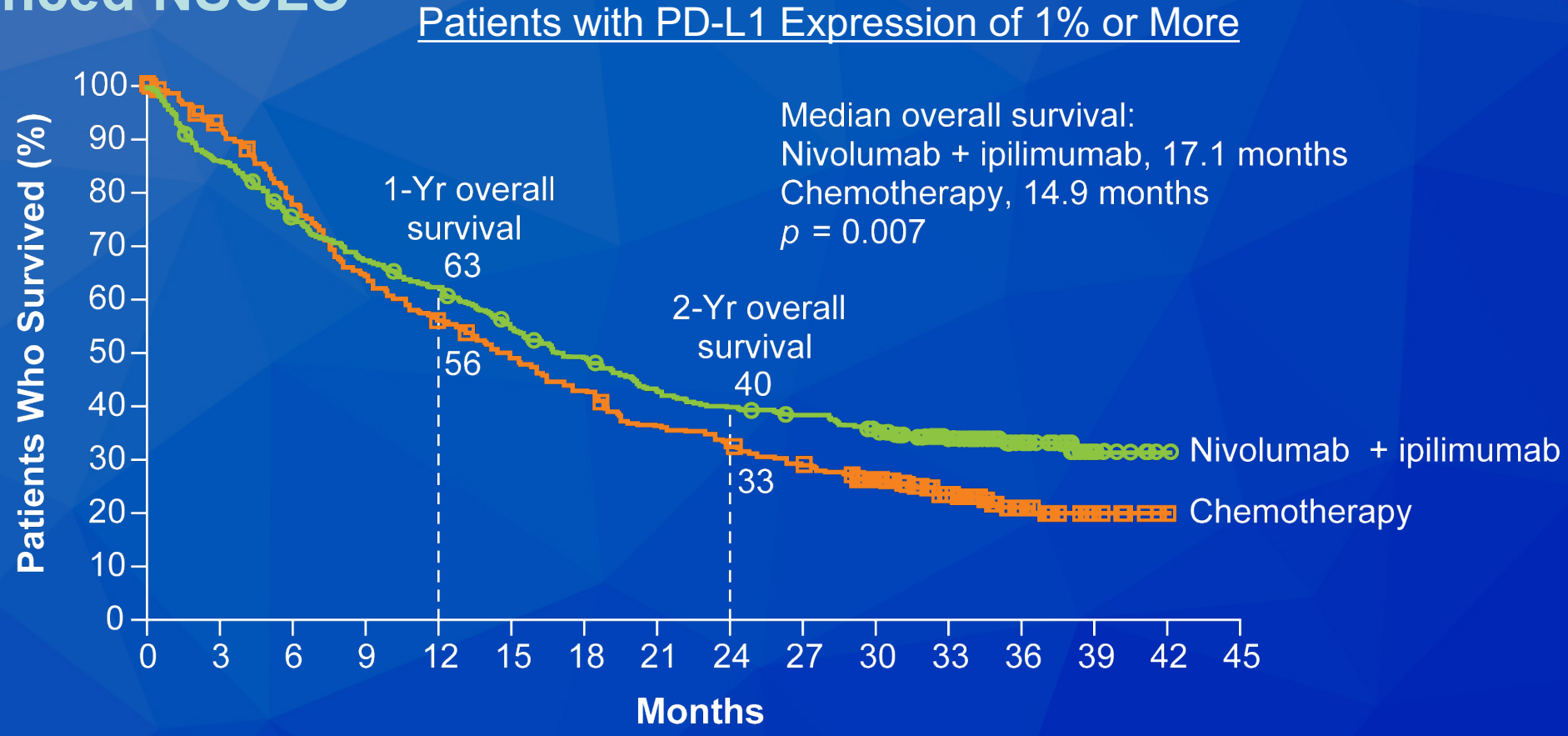
Editorial — Dr Liu (continued)

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)

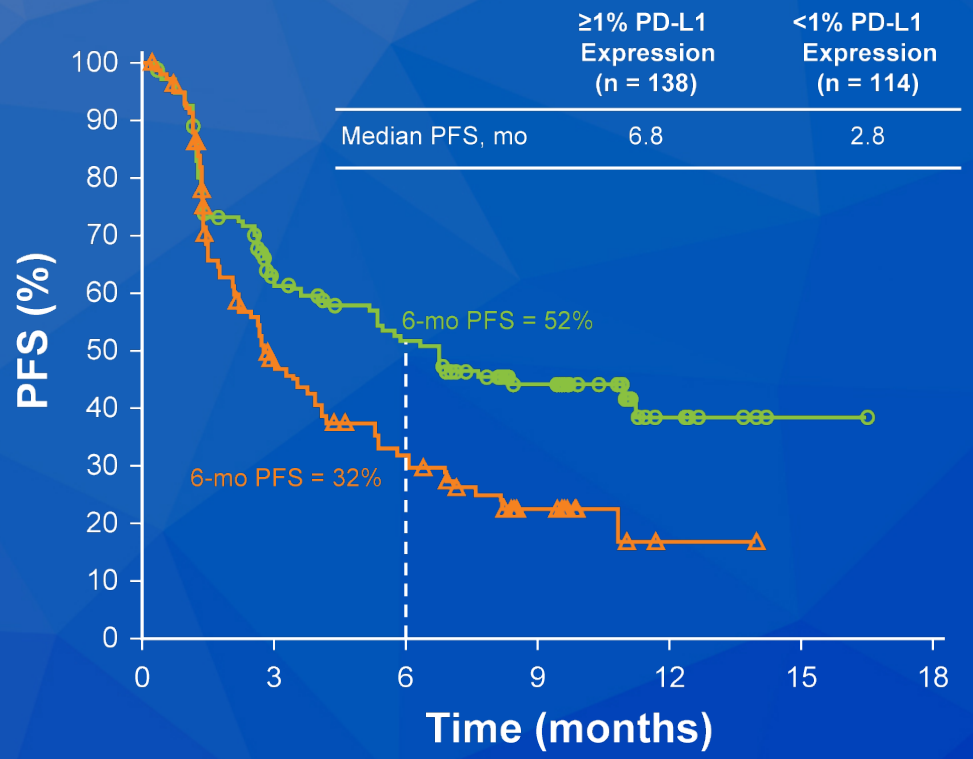
Hellmann MD et al. *N Engl J Med* 2019;381(21):2020-31.

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

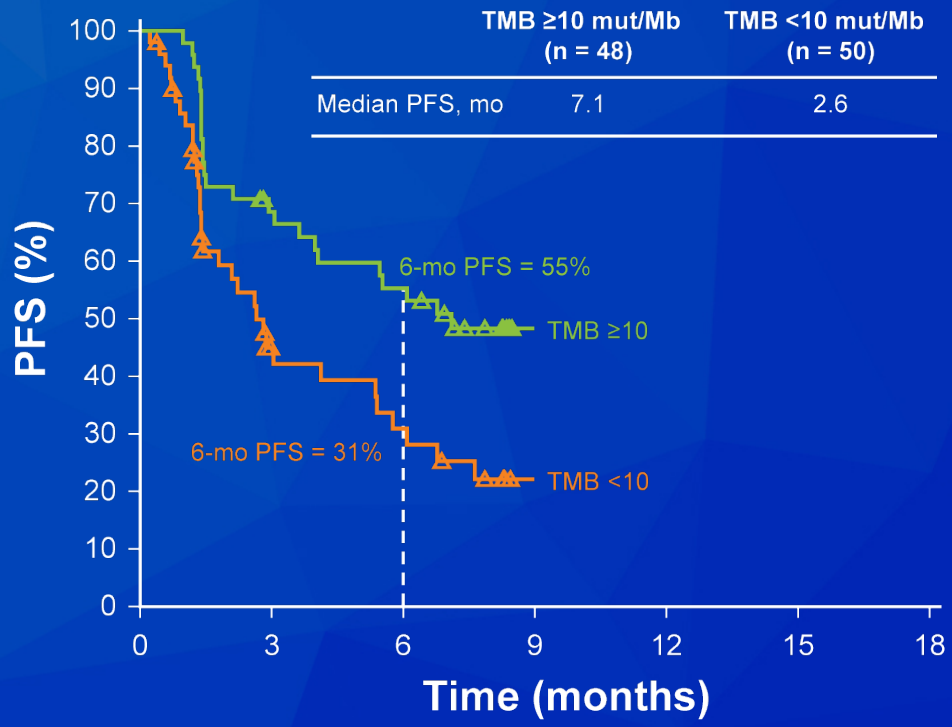
Ready N et al.
J Clin Oncol 2019;37(12):992-1000.

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).

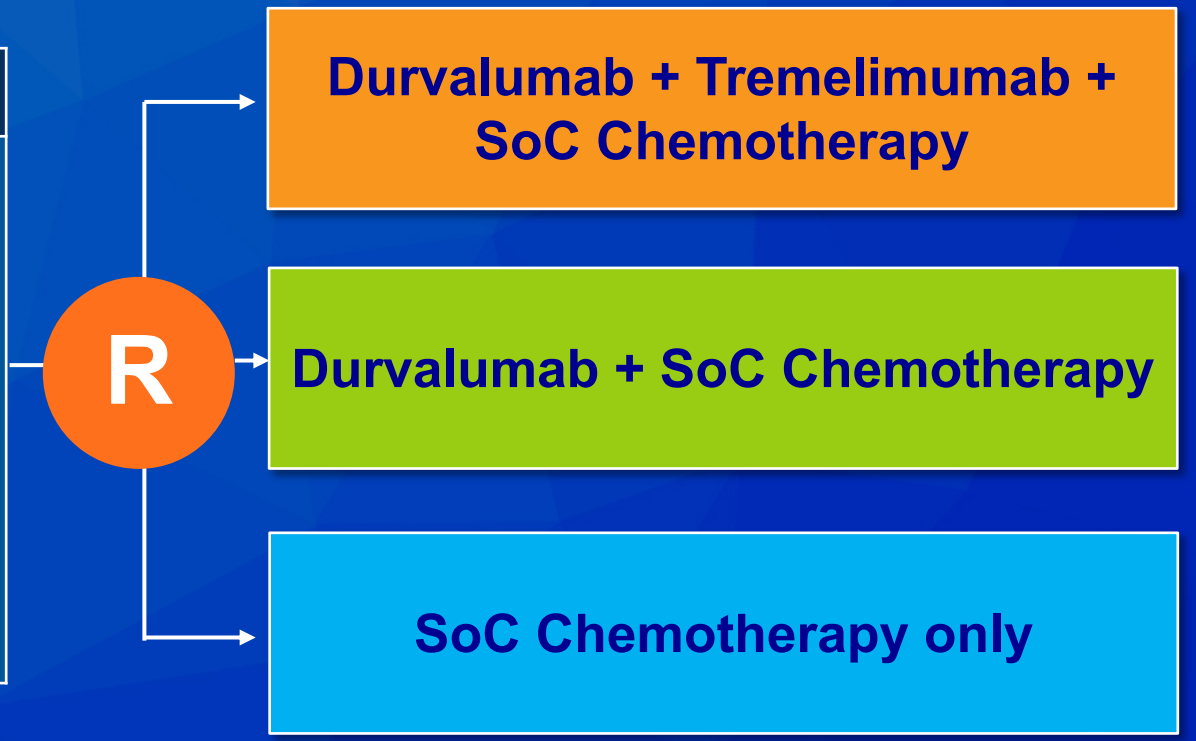
The trial met a primary endpoint by showing a statistically significant and clinically meaningful improvement in the final PFS analysis in patients treated with the combination of durvalumab and a broad choice of five standard-of-care platinum-based chemotherapy options vs. chemotherapy alone. The triple 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