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 24, 2018, 8:00 AM – 4:00 PM
Charlotte, North Carolina

Faculty

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Michael Birrer, MD, PhD
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Moderator

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Research To Practice®

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Regeneron Pharmaceuticals
Consulting Agreement	Lilly
Contracted Research	Merck

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Disclosures

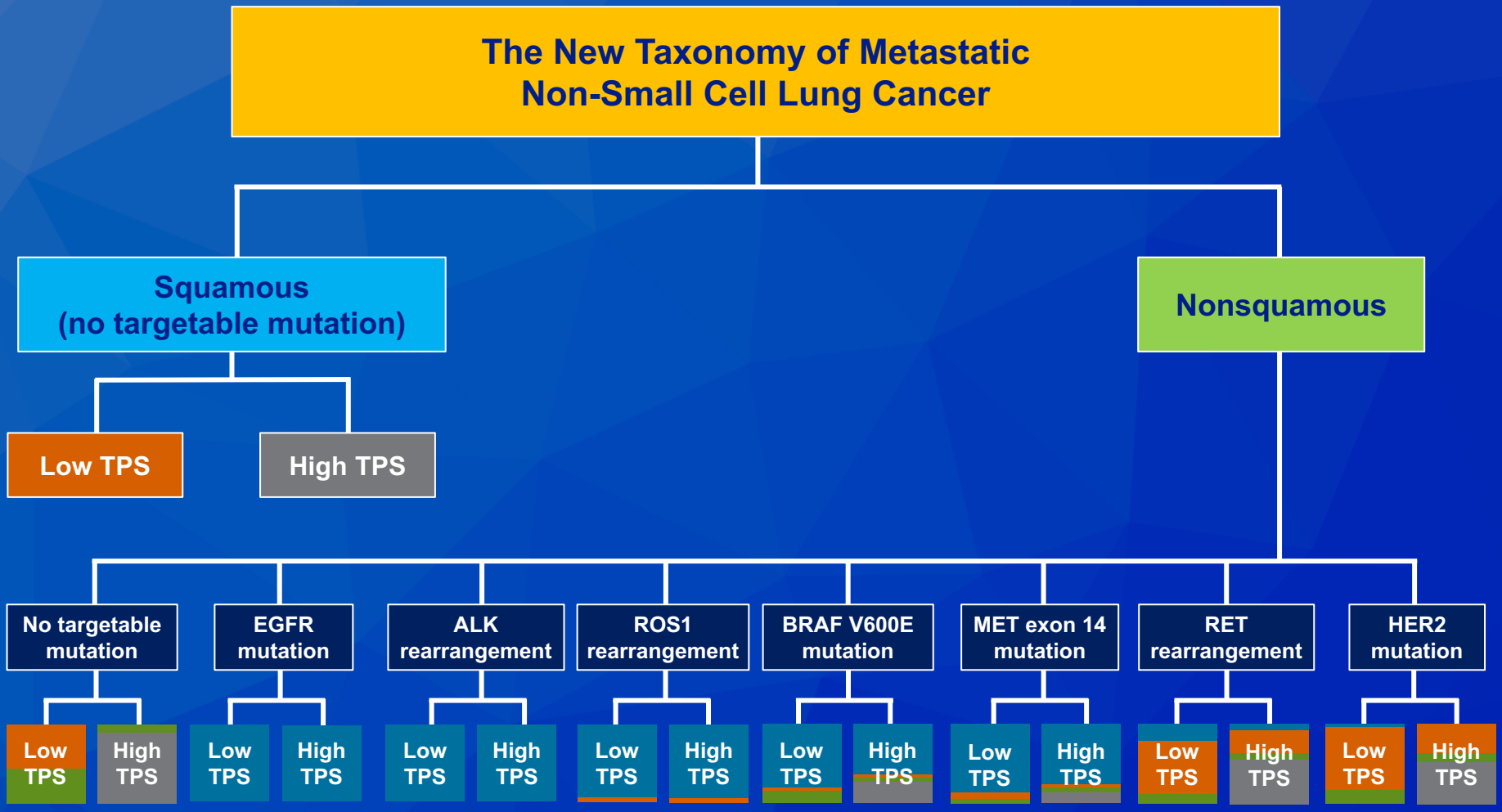
Advisory Committee	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Pfizer Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology
Speakers Bureau	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Lilly, Takeda Oncology

Select Recently Approved Targeted Agents in Lung Cancer

Agent	Approval date	Indication
Dabrafenib + trametinib	6/22/17	Metastatic NSCLC with a BRAF V600E mutation as detected by an FDA-approved test
Brigatinib	4/28/17	ALK-positive, metastatic NSCLC with disease progression or intolerance to crizotinib
Alectinib	12/11/15	ALK-positive, metastatic NSCLC with progression on or intolerance to crizotinib

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

The New Taxonomy of Metastatic Non-Small Cell Lung Cancer



TPS = PD-L1 tumor proportion score

Low TPS = 10%; high TPS = 60%

Targeted treatment

Chemotherapy ± biologic

Chemotherapy + checkpoint inhibitor

Checkpoint inhibitor

Love N et al. *Proc IASLC* 2017;Abstract 75.

Lung Cancer — Drs Pennell and Socinski

EGFR Tumor Mutations

ALK Rearrangements

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

Osimertinib granted breakthrough therapy designation for first-line treatment of EGFR mutation-positive NSCLC

Press Release — October 9, 2017

"… The US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation (BTD) for osimertinib for the 1st-line treatment of patients with metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC)…

The FDA granted the BTD based on data from the Phase III FLAURA trial of osimertinib versus standard-of-care EGFR tyrosine kinase inhibitor (TKI) therapy in previously-untreated patients with locally-advanced or metastatic EGFR mutation-positive NSCLC."

https://www.astrazeneca.com/media-centre/press-releases/2017/tagrisso-granted-breakthrough-therapy-designation-by-us-fda-for-the-1st-line-treatment-of-patients-with-egfr-mutation-positive-non-small-cell-lung-cancer-09102017.html

The NEW ENGLAND JOURNAL of MEDICINE

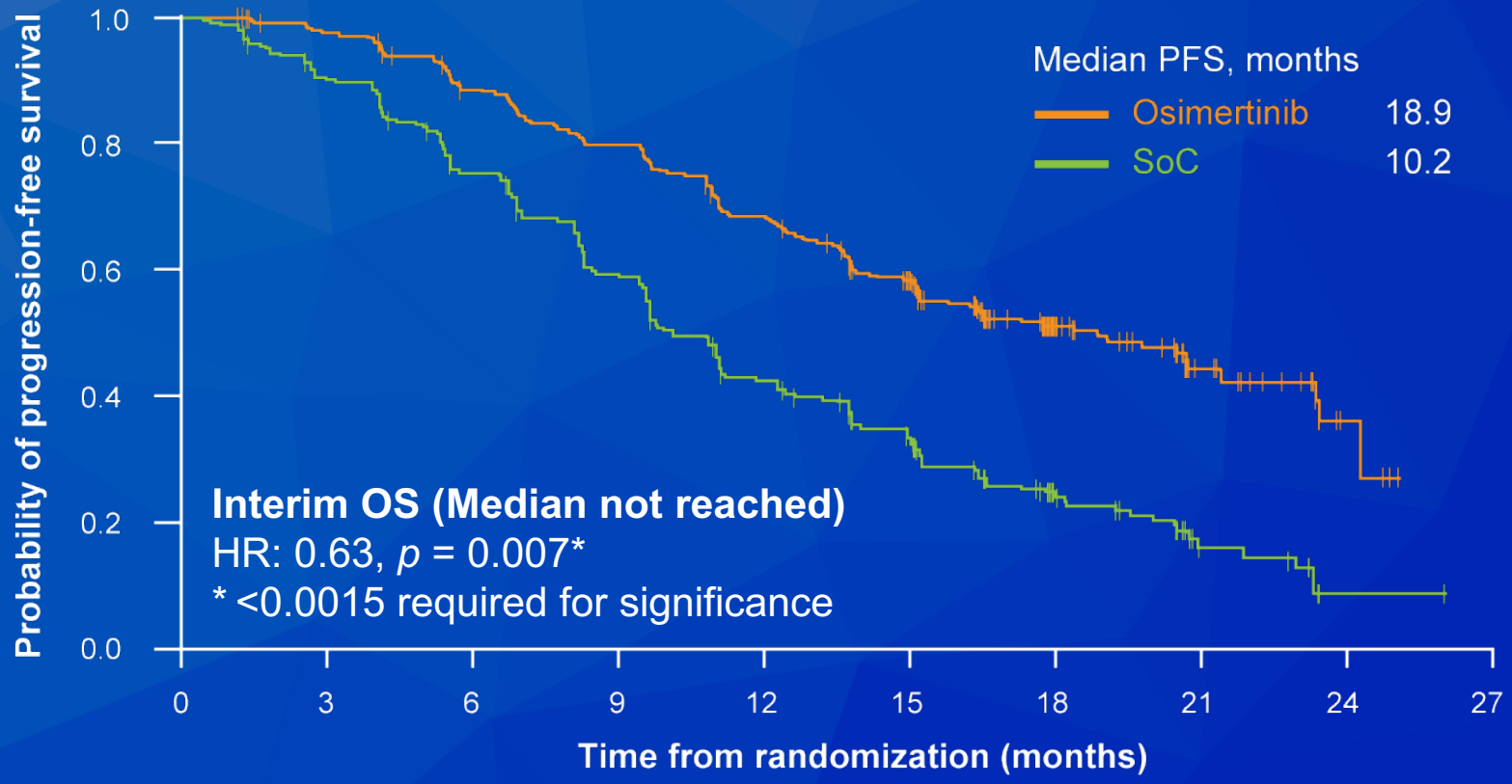
ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

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

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

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

FLAURA: PFS by Investigator Assessment and Interim OS Analysis



Median PFS	Osimertinib	SoC	HR	*p*
All (n = 279, 277)	18.9 mo	10.2 mo	0.46	<0.001
CNS mets (n = 53, 63)	15.2 mo	9.6 mo	0.47	<0.001
No CNS mets (n = 226, 214)	19.1 mo	10.9 mo	0.46	<0.001

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

Editorial — Dr Riely

The 3rd generation EGFR TKIs such as osimertinib were developed to target EGFR T790M, the most common cause of resistance to 1st/2nd generation EGFR TKIs. Osimertinib was previously proven to be superior to platinum-based doublet in patients with EGFR T790M after prior 1st/2nd generation EGFR TKI. In this trial, the investigators explored whether osimertinib would have greater value when given as a first line therapy, rather than at the time of resistance.

This FLAURA trial demonstrates a clear improvement in progression-free survival for the patients randomized to osimertinib. Patients reached a median progression-free survival of 18 months.

Editorial — Dr Riely (continued)

While the superiority of osimertinib with regard to PFS was expected by most observers, the surprising finding was the reporting of an immature overall survival analysis that, while not statistically significant due to a very high bar for statistical certainty, suggested that beginning with osimertinib allows improved overall survival. Some of the open questions remaining after this analysis include (1) whether this overall survival improvement will be present in the final analysis, and (2) what will be the most important mechanisms of resistance after use of first line osimertinib.

FDA broadens afatinib indication to previously untreated, metastatic NSCLC with other non-resistant EGFR mutations

Press Release — January 12, 2018

"On January 12, 2018, the Food and Drug Administration granted approval to afatinib for a broadened indication in first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test."

"FDA initially approved afatinib in 2013 for the treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test and in 2016 for metastatic, squamous NSCLC progressing after platinum-based chemotherapy."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm592558.htm

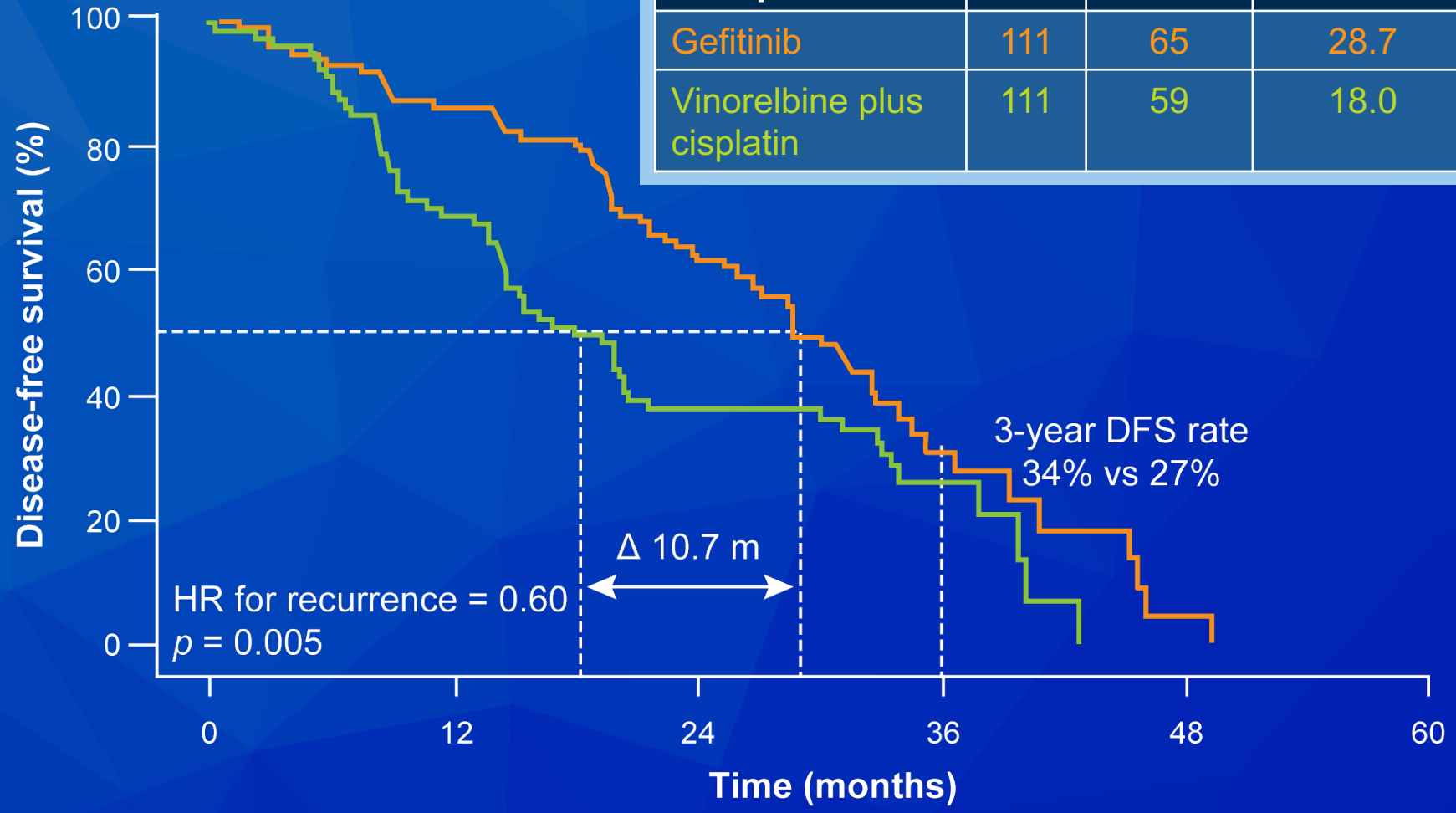
Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) *EGFR*-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study

*Wen-Zhao Zhong, Qun Wang, Wei-Min Mao, Song-Tao Xu, Lin Wu, Yi Shen, Yong-Yu Liu, Chun Chen, Ying Cheng, Lin Xu, Jun Wang, Ke Fei, Xiao-Fei Li, Jian Li, Cheng Huang, Zhi-Dong Liu, Shun Xu, Ke-Neng Chen, Shi-Dong Xu, Lun-Xu Liu, Ping Yu, Bu-Hai Wang, Hai-Tao Ma, Hong-Hong Yan, Xue-Ning Yang, Qing Zhou, Yi-Long Wu, on behalf of the ADJUVANT investigators**

Lancet Oncol 2018;19(1):139-48.

ADJUVANT Primary Endpoint: DFS (ITT Population)

Group	N	Events	Median, months
Gefitinib	111	65	28.7
Vinorelbine plus cisplatin	111	59	18.0



Zhong W-H et al. *Lancet Oncol* 2018;19(1):139-48; Wu YL et al. *Proc ASCO* 2017;Abstract 8500.

Editorial — Dr Riely

Given the clear benefit of EGFR TKI for patients with advanced EGFR-mutant NSCLC, there has been interest in moving these drugs into the adjuvant setting to improve the cure rate for patients with resected EGFR-mutant NSCLC. Despite their approval for use in advanced disease dating back to the early 2000s, this is the first trial reported that explored this specific question. Prior to this study, there was a randomized study of a broad population of patients with NSCLC that did not specifically evaluate patients with EGFR-mutant NSCLC (RADIANT). The ADJUVANT trial was conducted in China for patients with stage II-III NSCLC (N1-N2 disease) comparing adjuvant cisplatin/vinorelbine to adjuvant gefitinib for 2 years.

Editorial — Dr Riely (continued)

Importantly, unlike a number of trials, this study explored replacing chemotherapy with an EGFR TKI, rather than adding to the benefits of chemotherapy.

The primary endpoint was disease-free survival and the study met its primary endpoint, improving PFS at the median by 10 months. OS data were not presented. Evaluating the trial is complicated by a number of real-world problems. During the trial, more than 20% of patients randomized to chemotherapy chose not to receive the treatment. Approximately 65% of the patients randomized had N2 disease, which is a higher proportion than typically observed in North American trials.

Editorial — Dr Riely (continued)

The main conclusion of the authors was that adjuvant gefitinib was safe, which is well supported by the data. It is worth noting, though, that since gefitinib therapy was administered over 2 years, only 68% of patients were able to complete more than 18 months of therapy while 84% of the patients who started chemotherapy completed 4 cycles.

Given the absence of a plateau in the DFS curves and no report on OS, these data do not alter the available balance of data. Based on prior retrospective work, I still believe there is a role for adjuvant EGFR TKI and I look forward to the results of other trials, including the ALCHEMIST study sponsored by the NCI, which is exploring this question.

VOLUME 35 · NUMBER 10 · APRIL 1, 2017

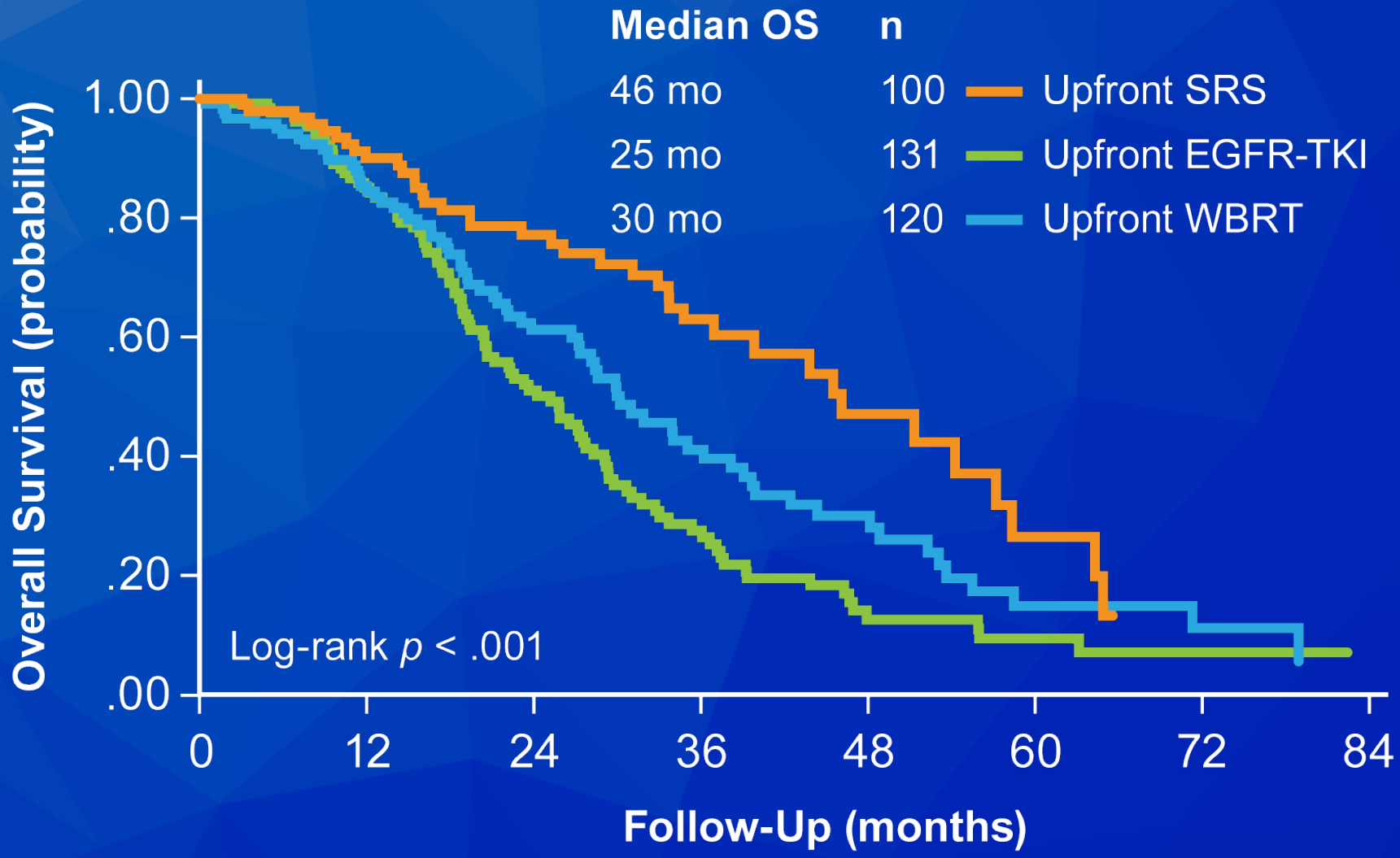
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

William J. Magnuson, Nataniel H. Lester-Coll, Abraham J. Wu, T. Jonathan Yang, Natalie A. Lockney, Naamit K. Gerber, Kathryn Beal, Arya Amini, Tejas Patil, Brian D. Kavanagh, D. Ross Camidge, Steven E. Braunstein, Lauren C. Boreta, Suresh K. Balasubramanian, Manmeet S. Ahluwalia, Niteshkumar G. Rana, Albert Attia, Scott N. Gettinger, Joseph N. Contessa, James B. Yu, and Veronica L. Chiang

Overall Survival by Treatment Approach



Magnuson WJ et al. *J Clin Oncol* 2017;35(10):1070-7.

Editorial — Dr Riely

Given the high frequency of CNS metastases in all types of lung cancer, but particularly EGFR-mutant NSCLC, the best choice of initial therapy for patients with CNS metastases is a frequent clinical challenge. In this retrospective analysis by a group of radiation oncologists and neurosurgeons, they assess the outcomes of patients with EGFR-mutant NSCLC who had brain metastases, exploring the effect of order of radiation and EGFR TKI. Clinically, many patients present with brain metastases and, particularly if those metastases are small and asymptomatic, most medical oncologists will begin with EGFR TKI given the competing risks associated with systemic disease and the broadly observed efficacy of EGFR TKI in the CNS.

Editorial — Dr Riely (continued)

In this analysis, the authors looked at a total of 351 patients with EGFR-mutant NSCLC. They conclude that "the use of up-front EGFR-TKI, and deferral of radiotherapy, is associated with inferior OS in patients with EGFR-mutant NSCLC who develop brain metastases." These results are surprising to most medical oncologists who treat such patients. To try to understand why these results differ from my clinical impression, I focus on the patient characteristics in the group studied. In the group studied, ~25% of patients had extra-CNS metastases at the time of CNS metastases.

Editorial — Dr Riely (continued)

This is not typically the group of patients that medical oncologists are making this decision for. We typically see CNS metastases at the time of diagnosis where patients have a broad range of sites of disease or during the course of EGFR TKI therapy. As such, the findings from this study are best applied to the type of patient studied here. Therefore, the recommendation for SRS (or whole brain radiation) for patients with CNS metastases is reasonable, but only in those patients who have no other sites of disease.

Lung Cancer — Drs Pennell and Socinski

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Small Cell Lung Cancer

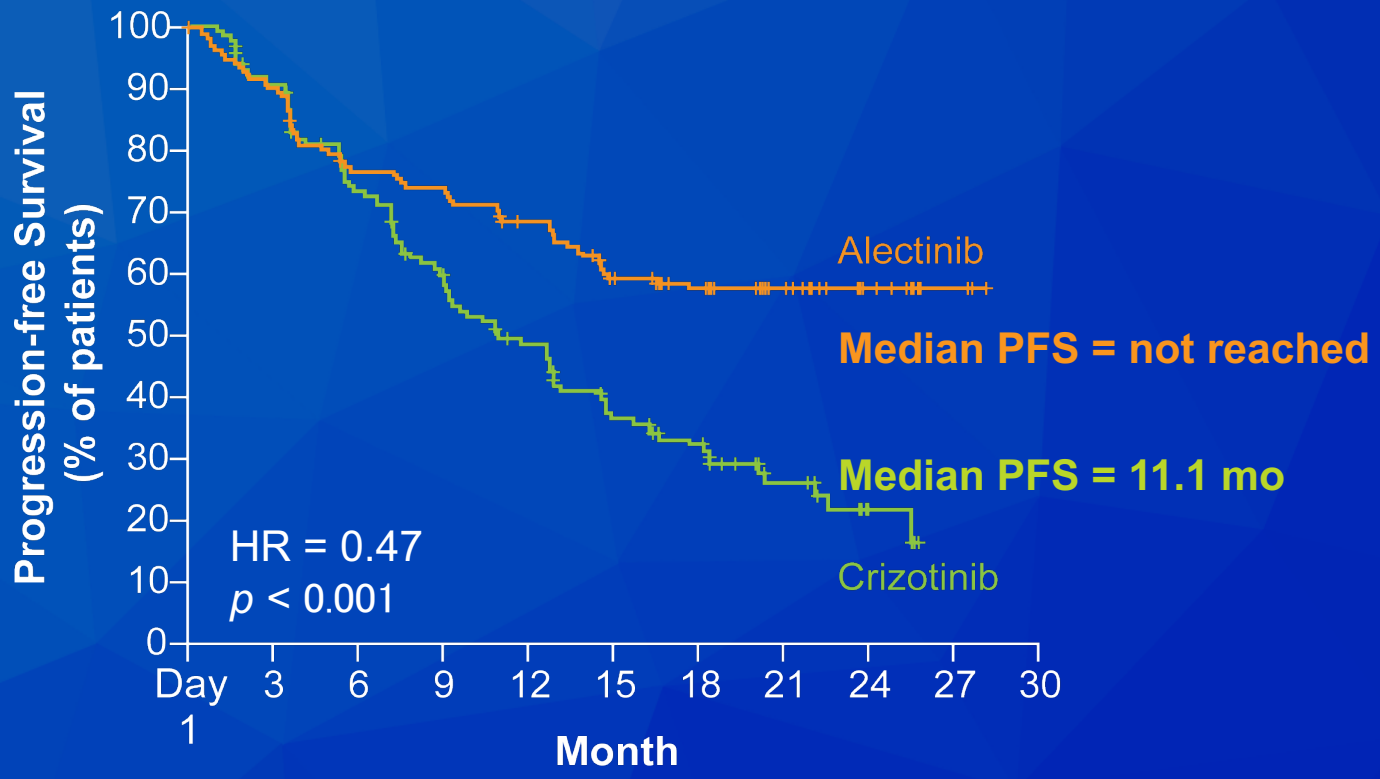
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2017;377:829-38

ORIGINAL ARTICLE

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

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D., Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D., for the ALEX Trial Investigators*

ALEX: Investigator-Assessed PFS and CNS Progression



	Alectinib (n = 152)	Crizotinib (n = 151)	HR	*p*
12-month event-free survival rate	68.4%	48.7%	0.47	<0.001
12-month cum. incidence of CNS progression	9.4%	41.4%	0.16	<0.0001

Peters S et al. *N Engl J Med* 2017;377:829-38; Shaw AT et al. *Proc ASCO* 2017;Abstract LBA9008.

FDA Approves Alectinib as First-Line Therapy in ALK-Positive Lung Cancer

Press Release — November 06, 2017

The US Food and Drug Administration (FDA) approved alectinib as first-line treatment for patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test. The approval is based on results from the Phase III ALEX study, which showed that alectinib significantly reduced the risk of disease worsening or death (PFS). The safety profile of alectinib was consistent with that observed in previous studies.

In addition, the FDA also converted alectinib's initial accelerated approval in December 2015 for the treatment of ALK-positive, metastatic NSCLC after progression on or intolerance to crizotinib (second-line) to a full approval.

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm584082.htm
https://www.roche.com/media/store/releases/med-cor-2017-11-07.htm

Editorial — Dr Riely

With the approval of crizotinib for the treatment of ALK-positive NSCLC, there was a dramatic change in the landscape of therapy for these patients. Perhaps even more impressive has been the development of a number of second-generation ALK inhibitors, including ceritinib, alectinib, and brigatinib. With all of these ALK inhibitors available, trying to understand the optimal sequence of them has been important. Alectinib is an ALK inhibitor with clear activity after patients have had progressive disease on crizotinib. In this trial, the two drugs were compared head to head as first-line therapy, the first TKI vs TKI trial in ALK-positive NSCLC.

Editorial — Dr Riely (continued)

The ALEX trial marked a clear step forward in therapy for ALK-positive NSCLC. In this trial, there was a clear improvement in progression free survival for those patients treated with alectinib as first line therapy. While the median PFS had not been reached, it appears to be longer than two years. As part of this trial, there was a clear plan for CNS evaluation with routine MRIs of the brain, and, importantly, patients with untreated CNS disease were allowed. While crizotinib has efficacy in CNS as well as systemic disease, alectinib has a superior response rate and duration of disease control in the CNS.

VOLUME 35 · NUMBER 22 · AUGUST 1, 2017

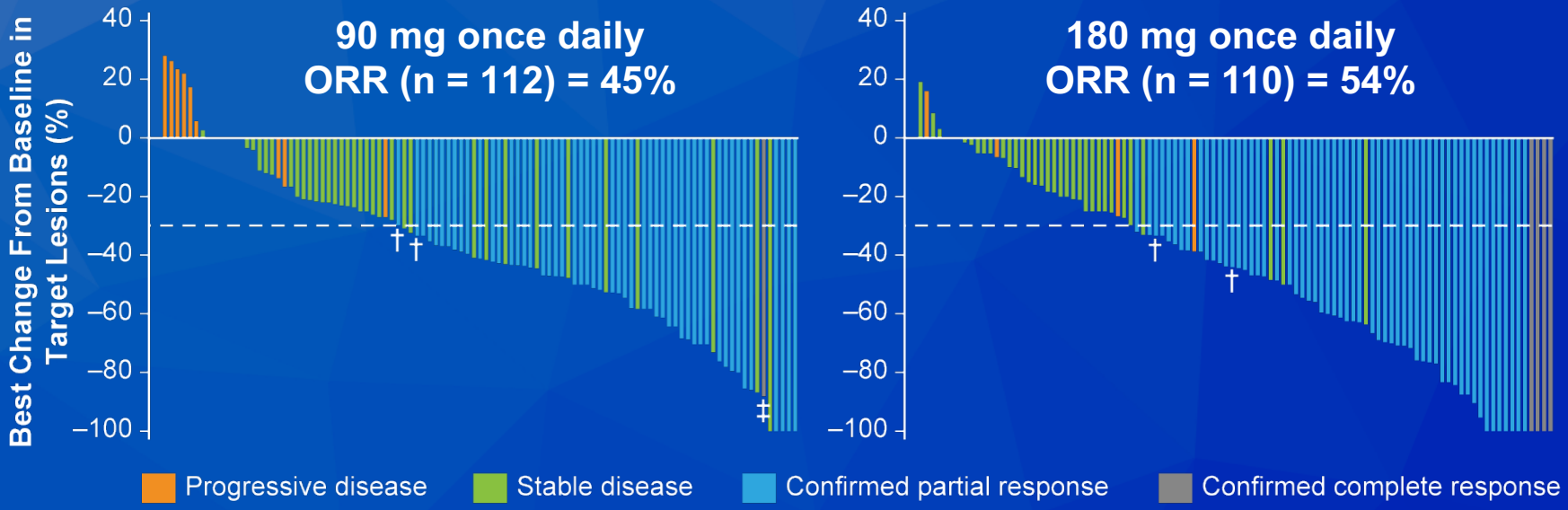
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial

Dong-Wan Kim, Marcello Tiseo, Myung-Ju Ahn, Karen L. Reckamp, Karin Holmskov Hansen, Sang-We Kim, Rudolf M. Huber, Howard L. West, Harry J.M. Groen, Maximilian J. Hochmair, Natasha B. Leighl, Scott N. Gettinger, Corey J. Langer, Luis G. Paz-Ares Rodríguez, Egbert F. Smit, Edward S. Kim, William Reichmann, Frank G. Haluska, David Kerstein, and D. Ross Camidge

Response with Brigatinib 90 mg and 180 mg Daily Dosing



Brigatinib-Associated Pulmonary Adverse Events

- A subset of pulmonary adverse events with early onset (median onset: day 2) occurred in 14 of 219 treated patients, including dyspnea, hypoxia, cough, pneumonia and pneumonitis
  - All grades: 6%; Grade ≥3: 3%
- Older age and shorter interval (<7 days) between the last crizotinib dose and the first brigatinib dose were associated with an increased event rate
- None occurred after escalation to 180 mg
- Pulmonary events were managed with dose interruption
- Seven of 14 patients were successfully re-treated with brigatinib

Kim DW et al. *J Clin Oncol* 2017;35(22):2490-8.

Editorial — Dr Riely

This paper describes an important element of the development program of brigatinib, a second generation ALK inhibitor with efficacy in patients with ALK-positive NSCLC previously treated with crizotinib. In the early clinical work with brigatinib, investigators noted a dose dependent difficulty with early onset pulmonary adverse events. These events occurred at higher dose levels of brigatinib. The etiology of this adverse event was not clear. In this trial, the investigators sought to investigate (a) the efficacy of 90 mg of brigatinib, and (b) the safety and efficacy of beginning with 90 mg of brigatinib for 7 days and, if tolerated, escalating to 180 mg. In prior trials, efficacy had been observed at 90 mg, but by increasing to 180 mg the investigators hoped to maximize efficacy both systemically as well as in the CNS.

Editorial — Dr Riely (continued)

In this study that randomized patients 1:1 to either dose/schedule, they found that 180 mg (after the 7-day 90 mg lead-in) was tolerable and associated with a median PFS of 13 months in patients previously treated with crizotinib. In the parallel arm at 90 mg, the median PFS was shorter at just 9 months. In addition, they noted a higher response rate in the CNS for the 180 mg dose as compared to the 90 mg dose.

These data support the currently approved dose of 180 mg and emphasize the importance of dose escalation if the patient tolerates the 90 mg lead-in.

Editorial — Dr Riely (continued)

In addition, while cross-trial comparisons are always challenging since they involve different patient populations, the efficacy of brigatinib in the study remains impressive. The 13-month median PFS in a group of patients previously resistant to crizotinib is numerically higher than what has been seen with other ALK inhibitors.

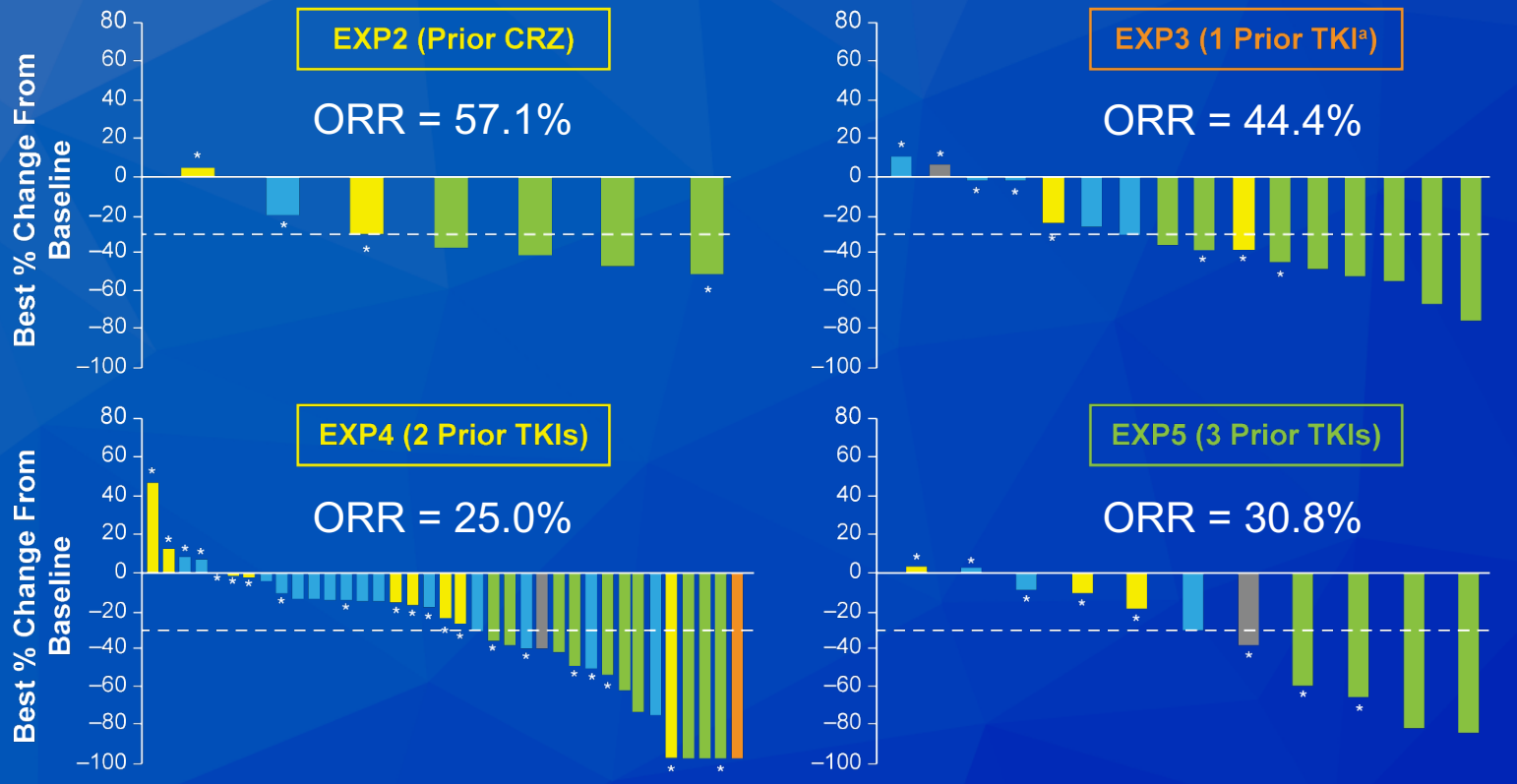
Articles

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

Alice T Shaw, Enriqueta Felip, Todd M Bauer, Benjamin Besse, Alejandro Navarro, Sophie Postel-Vinay, Justin F Gainor, Melissa Johnson, Jorg Dietrich, Leonard P James, Jill S Clancy, Joseph Chen, Jean-François Martini, Antonello Abbattista, Benjamin J Solomon

Lancet Oncol 2017;18(12):1590-9.

ORR and Best Response with Lorlatinib



[a] Prior CRZ + chemotherapy or 1 other ALK TKI ± chemotherapy
* Off treatment or disease progression

Most common treatment-related AEs

	All grade	Grade 3/4
Hypercholesterolemia	82%	12%
Hypertriglyceridemia	53%	12%

- **Dose interruptions due to TRAEs 29%**
- **Dose reductions due to TRAEs 20%**
- **Discontinuation due to TRAEs 4%**
- **Serious TRAEs 14%**

Shaw AT et al. *Lancet Oncol* 2017;18(12):1590-9; *Proc ASCO* 2017;Abstract 9006.

Editorial — Dr Riely

While multiple second-generation ALK inhibitors have been developed, all have been tested in the setting of patients previously treated with crizotinib. There is a relative absence of efficacy data for ALK inhibitors after more than one ALK inhibitor. As alectinib moves into the first line setting, knowing the efficacy of ALK inhibitors in that context is critical. Lorlatinib is the newest ALK/ROS1 inhibitor, with a structure very distinct from that of other ALK inhibitors.

In the data presented at this ASCO meeting, we saw reasonable efficacy in patients previously treated with two ALK inhibitors.

Editorial — Dr Riely (continued)

While detailed data are not available about specific prior ALK inhibitors, it does appear that lorlatinib has impressive efficacy after crizotinib, ceritinib, and alectinib, particularly since the only available alternative in this setting is conventional chemotherapy doublets. Learning more about the efficacy of lorlatinib with more patients and learning about its efficacy after first-line alectinib will be of significant value.

VOLUME 35 · NUMBER 23 · AUGUST 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

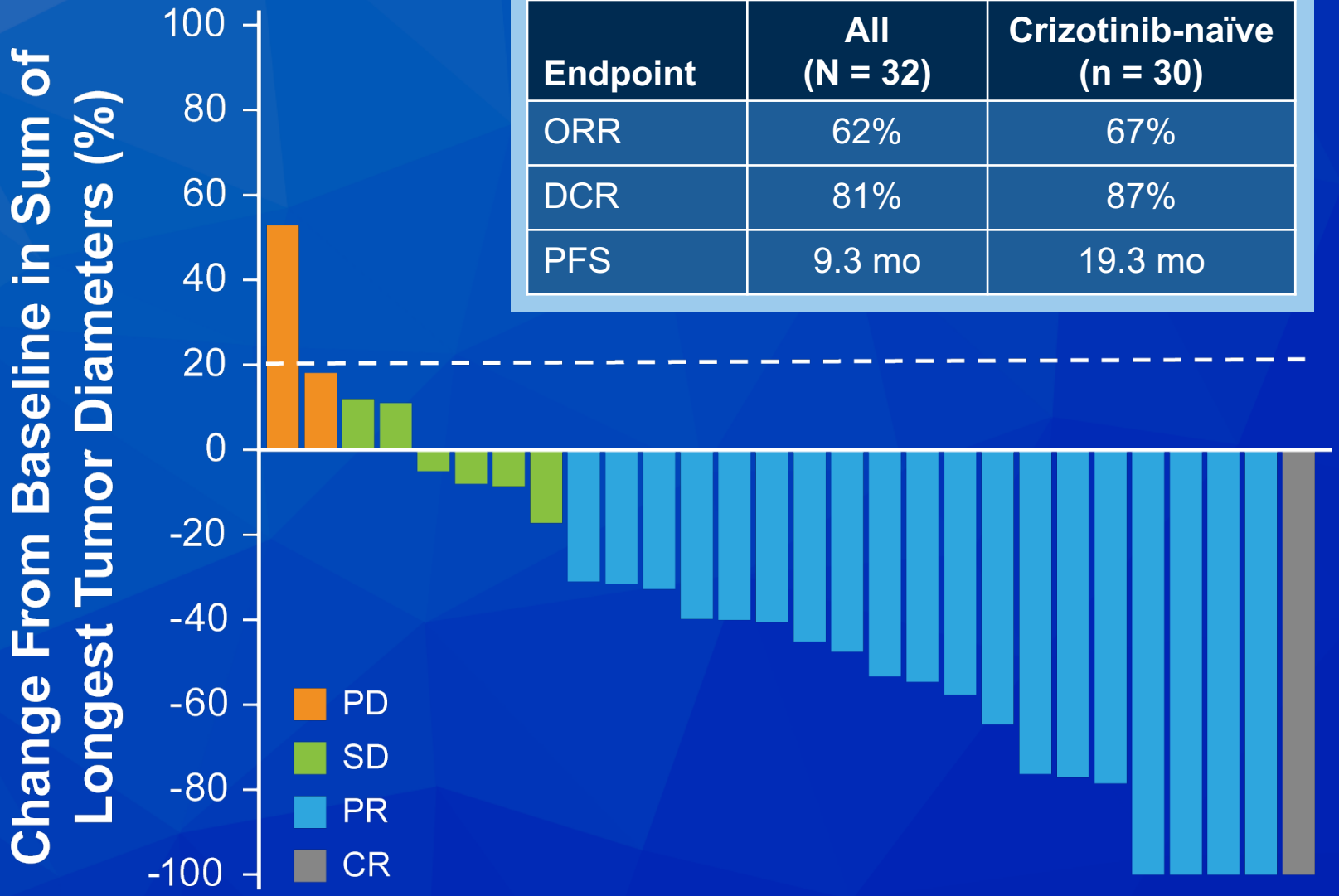
ORIGINAL REPORT

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring *ROS1* Rearrangement

Sun Min Lim, Hye Ryun Kim, Jong-Seok Lee, Ki Hyeong Lee, Yun-Gyoo Lee, Young Joo Min, Eun Kyung Cho, Sung Sook Lee, Bong-Seog Kim, Moon Young Choi, Hyo Sup Shim, Jin-Haeng Chung, Yoon La Choi, Min Jeong Lee, Maria Kim, Joo-Hang Kim, Siraj M. Ali, Myung-Ju Ahn, and Byoung Chul Cho

Efficacy of Ceritinib in ROS1-Rearranged NSCLC

Endpoint	All (N = 32)	Crizotinib-naïve (n = 30)
ORR	62%	67%
DCR	81%	87%
PFS	9.3 mo	19.3 mo



Lim SM et al. *J Clin Oncol* 2017;35(23):2613-8.

Editorial — Dr Riely

Shortly after the identification of the efficacy of crizotinib in the treatment of ALK-positive lung cancer, it was shown to have efficacy for the treatment of ROS1-positive NSCLC. In ROS1-positive NSCLC, crizotinib has a higher RR and PFS than crizotinib in ALK-positive NSCLC. In this trial, Dr Lim and colleagues explored the value of ceritinib in ROS1-positive NSCLC. Importantly, the patients enrolled in this trial had not had prior targeted therapy for ROS1-positive NSCLC (ie, these patients did not have resistance to crizotinib).

In this study, the authors found that ceritinib had similar efficacy to crizotinib in the first-line setting. Based on this, ceritinib is a reasonable first-line choice for ROS1-positive lung cancer.

Editorial — Dr Riely (continued)

There remains an important need for “second-line” ROS1 inhibitors for patients whose disease has progressed on crizotinib. It will also be valuable to explore the efficacy of ceritinib after crizotinib.

At the World Congress on Lung Cancer, we saw the preliminary report of the efficacy of lorlatinib in ROS1-positive lung cancer previously treated with crizotinib. There is modest but real efficacy of lorlatinib in this setting.

Lung Cancer — Drs Pennell and Socinski

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Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

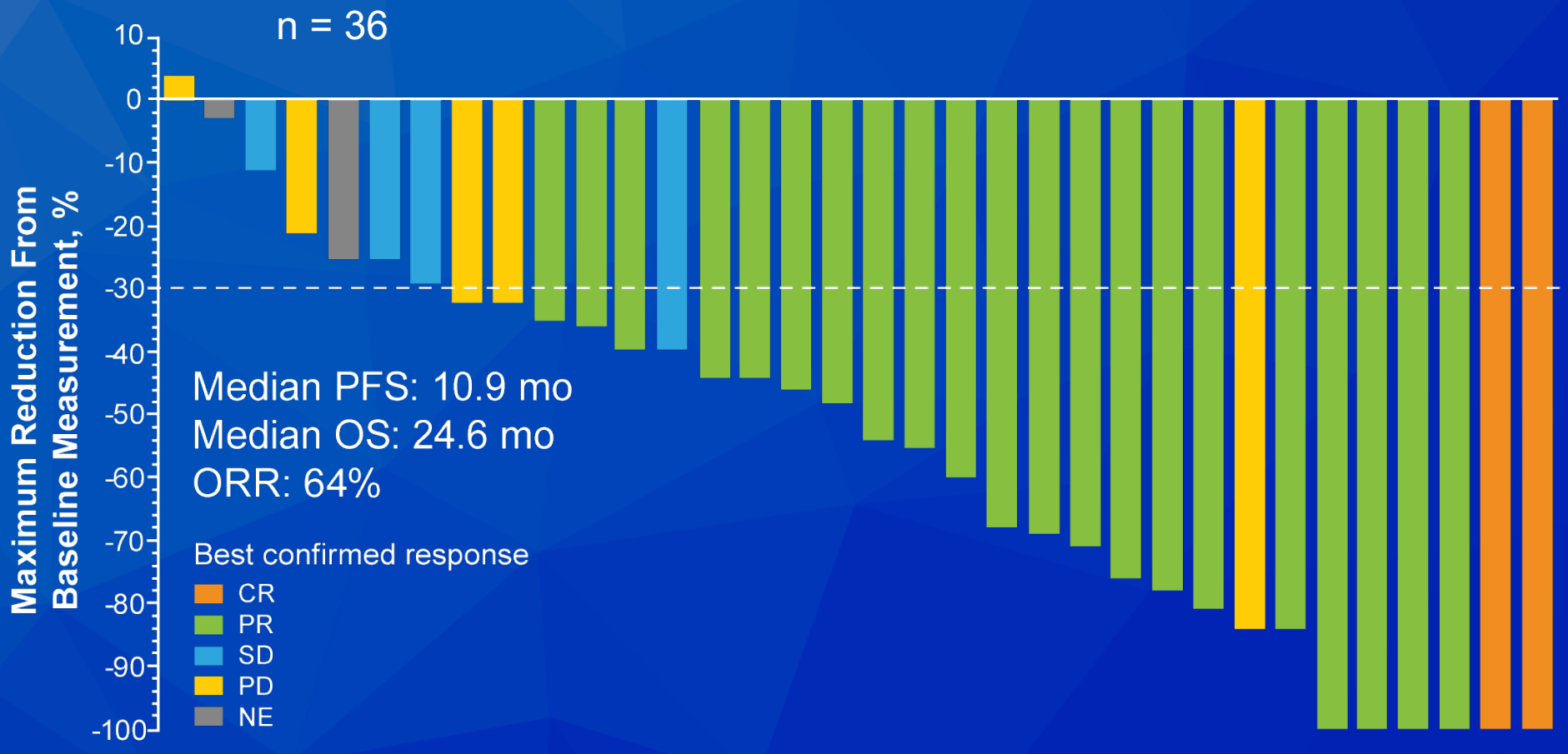
Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

Lancet Oncol 2017; 18: 1307–16

Planchard D et al. *Lancet Oncol* 2017 Oct; 18(10):1307-1316.

Investigator-Assessed Response and Survival with Dabrafenib and Trametinib



Planchard D et al. *Lancet Oncol* 2017;18(10):1307-1316.

Editorial — Dr Gubens

BRAF V600E is another of the rare but important target mutations in NSCLC, making up about 2% of the population (as compared to 50% in malignant melanoma). Planchard and his colleagues have steadily been updating their study with results from 3 cohorts, from which we first learned about single-agent dabrafenib activity in NSCLC BRAF V600E in 2014 (with a 33% ORR but a PFS of only 5.5 months), then the combination of dabrafenib and trametinib in previously treated patients in 2016 (ORR 67% with a PFS of 10.2 months).

This year the group published the findings of first-line dabrafenib and trametinib. 36 patients were evaluated, with an ORR of 64% and a DCR of 75%.

Editorial — Dr Gubens (continued)

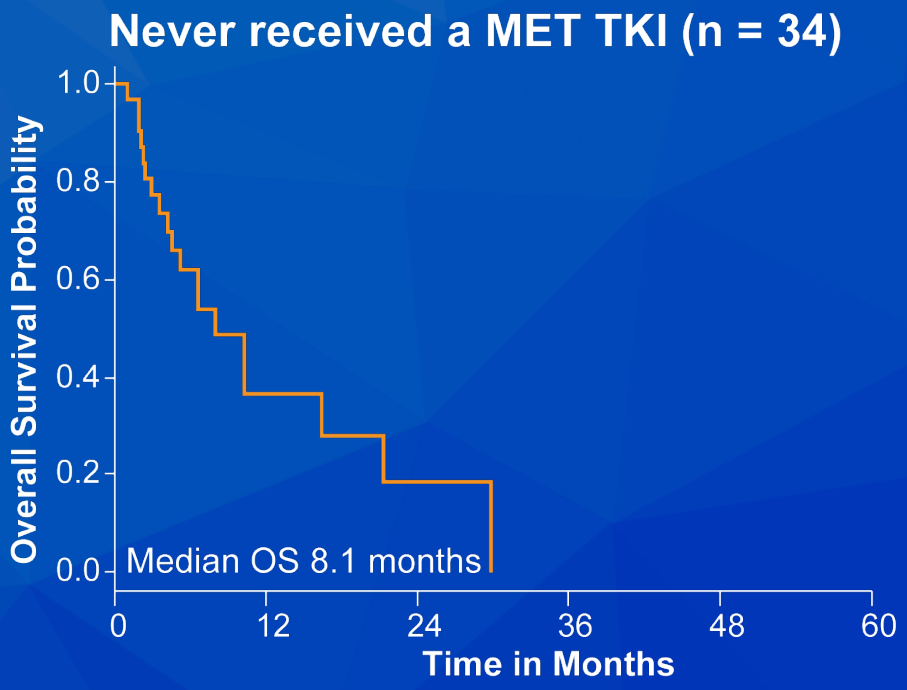
Median PFS was 10.9 months by investigator assessment, and 14.6 months by IRC. The tolerability profile was as expected from prior NSCLC experience, with perhaps somewhat more GI toxicity and pyrexia compared to the melanoma experience.

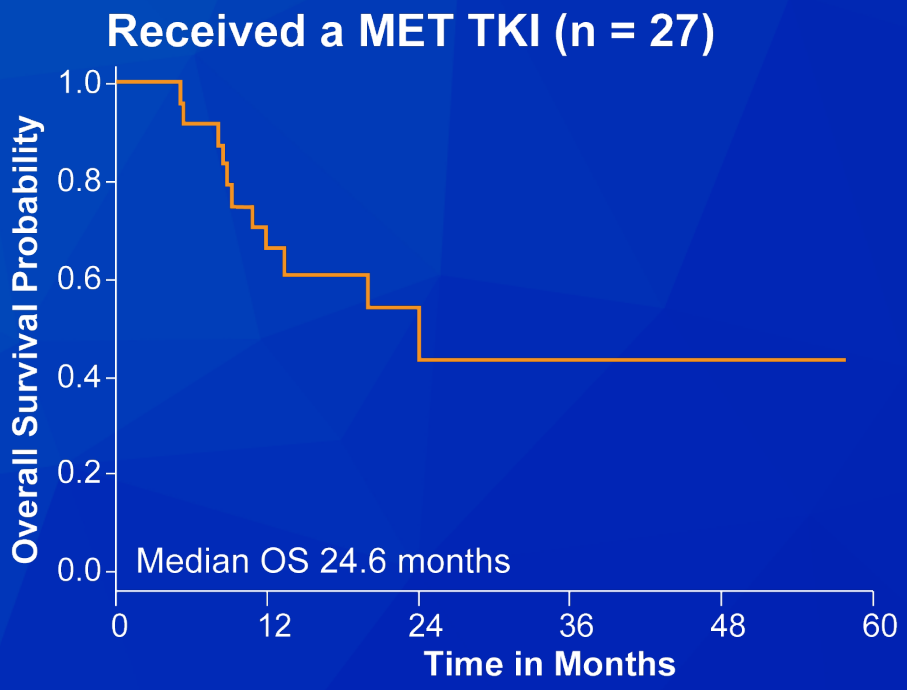
On the basis of these results, the US FDA has approved the combination treatment without reference to line of therapy, and this clearly underscores the need for BRAF to be included in mutational profiling. Especially in light of other ASCO data suggesting poorer immunotherapy responses than average in BRAF V600E patients, consideration of biopsy to ascertain resistance mechanisms and trial enrollment after failure of targeted therapy will be important for this cohort of patients.

Impact of MET Inhibitors on Survival Among Patients (pts) with MET Exon 14 Mutant (METdel14) Non-Small Cell Lung Cancer (NSCLC)

Awad MM et al.
Proc ASCO 2017;Abstract 8511.

Retrospective Survival Analysis from Date of Stage IV Diagnosis





Adjusted Survival
HR = 0.11, p = 0.04

Awad MM et al. *Proc ASCO* 2017;Abstract 8511.

Editorial — Dr Riely

The most recently identified driver oncogene in patients with NSCLC is a group of mutations that lead to skipping of MET exon 14. These have been shown to be oncogenic in animal models, and they are mutually exclusive with other driver oncogenes. Preliminary data presented at ASCO last year by Alex Drilon and colleagues showed that, in a prospective trial, crizotinib was shown to have activity in patients with MET exon 14 altered NSCLC. While crizotinib is primarily known as an ALK/ROS inhibitor, it was initially developed as a MET inhibitor. In this context Awad and colleagues presented an analysis of outcomes of patients with MET exon 14 alterations.

Editorial — Dr Riely (continued)

They again noted that patients with MET exon 14 alterations were typically older than other patients with lung cancer and most commonly had adenocarcinoma. However, one finding that has been noted by several groups is that among patients with sarcomatoid histology, MET exon 14 alterations are relatively common.

They note that these patients with MET exon 14 have a particularly poor overall survival of a median of 8 months in the absence of MET directed therapy. However, when patients are given MET inhibitors, they have a median overall survival that approaches 24 months. These data clearly support the further development of MET inhibitors for patients with MET exon 14 altered NSCLC.

Editorial — Dr Riely (continued)

This analysis provides an approach to understanding the effect of targeted therapies that may be more broadly applicable in other relatively rare populations.

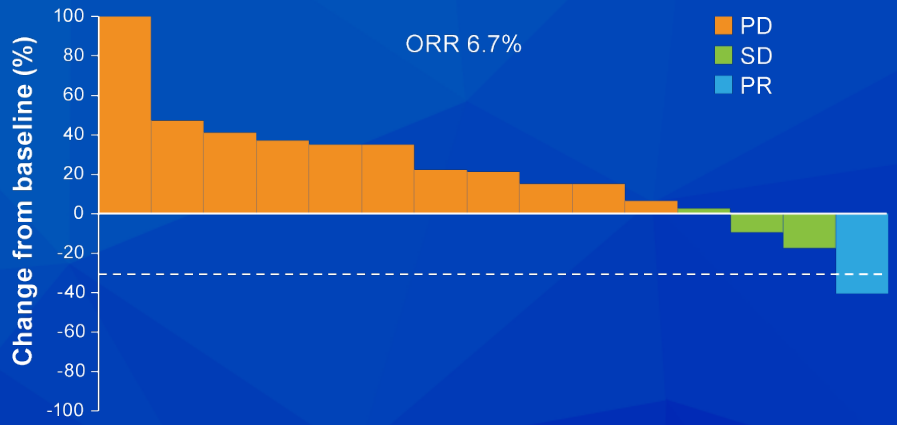
PD-L1 Expression and Response to Immunotherapy in Patients with MET Exon 14-Altered Non-Small Cell Lung Cancers (NSCLC)

Sabari JK et al.
Proc ASCO 2017;Abstract 8512.

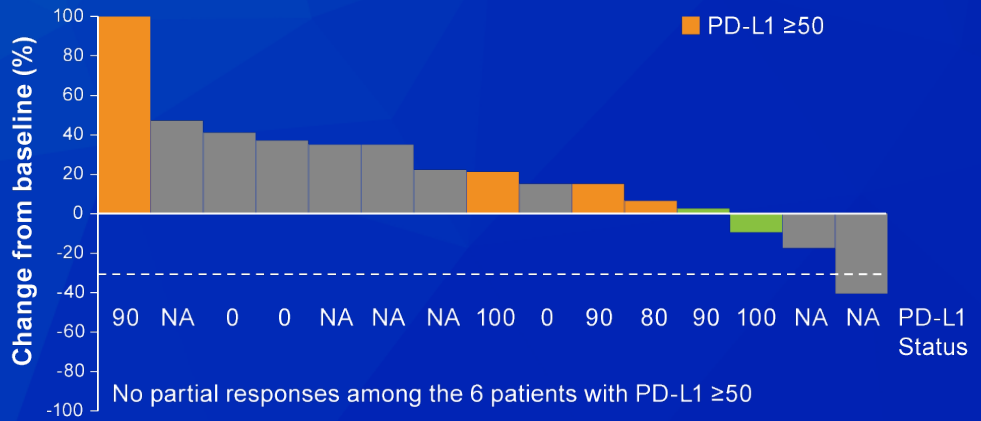
PD-L1 Expression in MET Exon 14-Altered NSCLC (N = 54) and Response to Immunotherapy (N = 15)

	PD-L1 expression (N = 54)		
PD-L1 expression	**0%**	**1%-49%**	**≥50%**
% pts expressing	19 (35%)	10 (19%)	24 (46%)

Response to immunotherapy by irRECIST criteria



PD-L1 and response to immunotherapy



Sabari JK et al. *Proc ASCO* 2017;Abstract 8512.

Editorial — Dr Gubens

The MET exon 14 skipping mutation has emerged as an actionable mutation with MET inhibitors such as crizotinib (with a reported 39% response rate and median DOR of 9.1 months). This target is of particular interest because it represents 3%-4% of nonsquamous NSCLC but 20%-30% of sarcomatoid lung cancers, with a higher proportion of smokers. This helps make even stronger the argument for broader availability of mutational screening in nonsquamous disease, well beyond the young, non-smoking phenotype we have historically considered for EGFR, ALK and ROS1.

This is a retrospective review of 81 patients with MET exon 14 altered NSCLC, and specifically the 20 of them who received immunotherapy, though only 15 were reportable.

Editorial — Dr Gubens (continued)

Among these, the response rate by irRECIST was only 6.7%, and specifically no response was seen among the 6 patients with PD-L1 expression ≥50%, nor among the 5 TMB high patients.

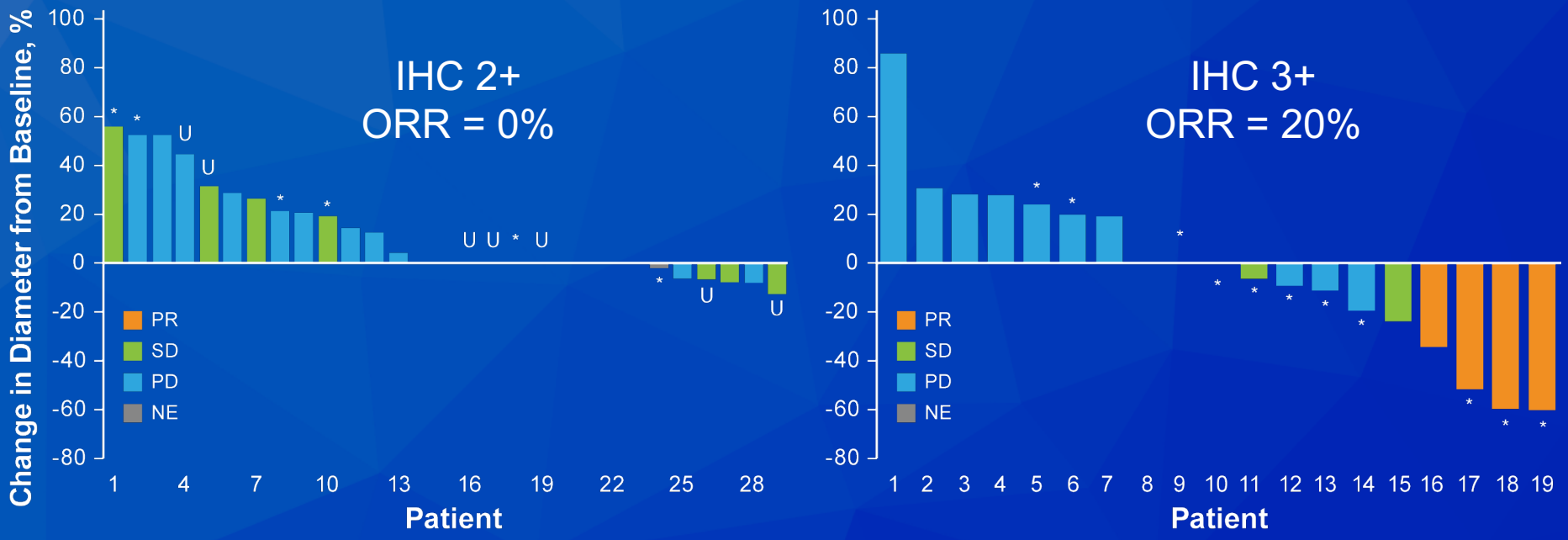
This is a small study, but it does add to the more general observation that NSCLC with actionable driver mutations tends to derive less benefit from single agent PD-1/PD-L1 inhibition than other NSCLC. In such a MET altered patient, I would be more inclined to employ both chemotherapy and MET-targeted therapy (on-trial or off-label but as supported by NCCN guidelines) before a line of single-agent immunotherapy, just as our practice should be for EGFR, ALK and BRAF.

Efficacy, Safety, and Biomarker Results of Trastuzumab Emtansine (T-DM1) in Patients (pts) with Previously Treated HER2-Overexpressing Locally Advanced or Metastatic Non-Small Cell Lung Cancer (mNSCLC)

Stinchcombe T et al.
Proc ASCO 2017;Abstract 8509.

Response and Survival to T-DM1 in HER2-Overexpressing NSCLC

Median duration of response: 7.3 months



* Indicates positive HER2 amplification; U indicates unknown HER2 amplification; all other patients' ISH status is negative

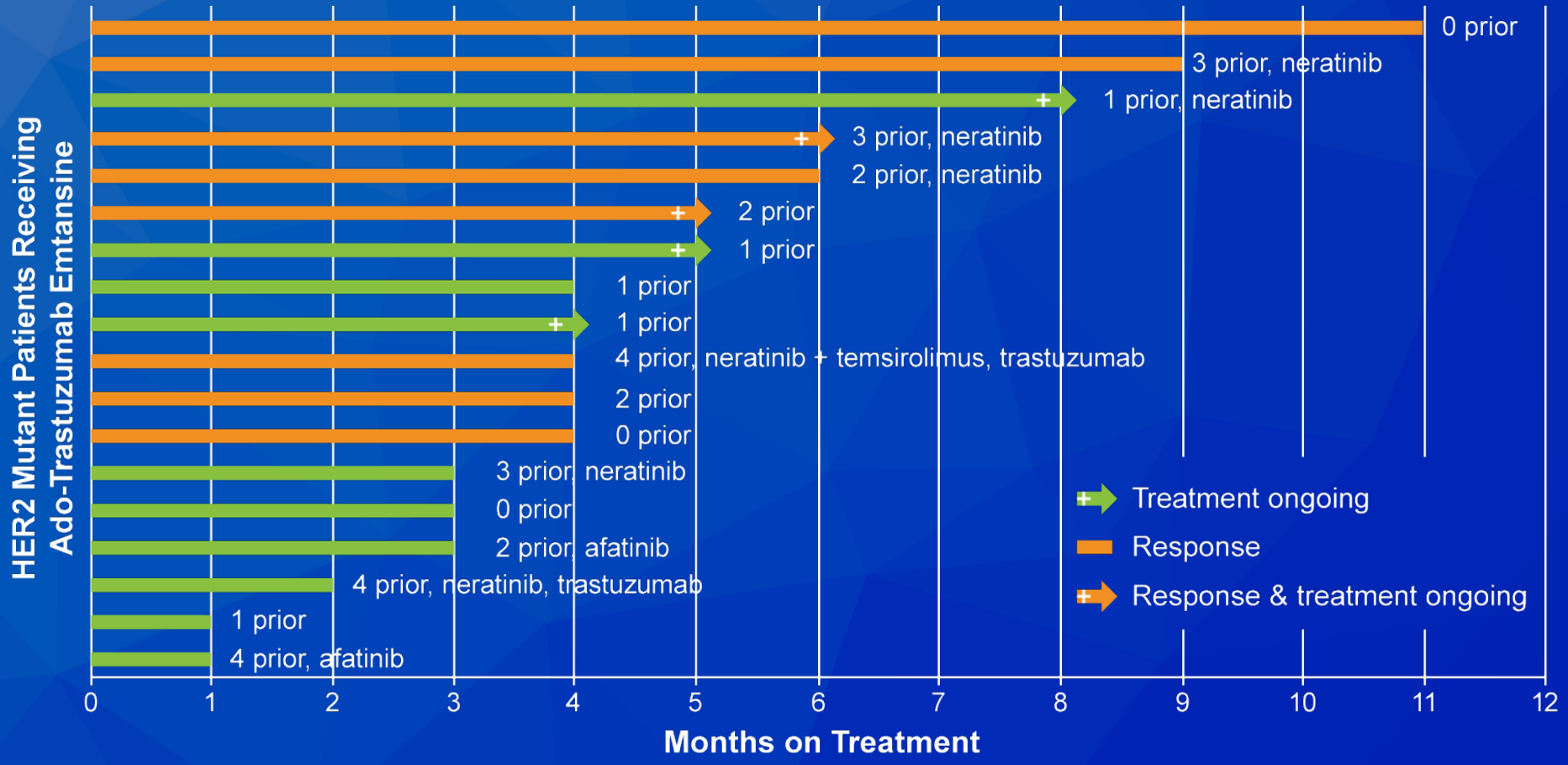
	IHC 2+ (n = 29)	IHC 3+ (n = 20)	All (N = 49)
Median PFS	2.6 mo	2.7 mo	2.6 mo
Median OS	12.2 mo	12.1 mo	12.2 mo

Stinchcombe T et al. *Proc ASCO* 2017;Abstract 8509.

Ado-Trastuzumab Emtansine in Patients with HER2 Mutant Lung Cancers: Results from a Phase II Basket Trial

Li BT et al.
Proc ASCO 2017;Abstract 8510.

Response to T-DM1 and Prior Therapies for HER2-Mutant NSCLC



ORR: 8/18 (44%)

6 of 8 responders were heavily pretreated, including prior HER2 targeted therapy

Median PFS: 4 months

Li BT et al. *Proc ASCO* 2017;Abstract 8510.

Editorial — Dr Gubens

Another emerging target in NSCLC is HER2, where the possibility of repurposing drugs developed for HER2+ breast cancer adds more promise. Approximately 2% of lung cancers are driven by a HER2 mutation, which is distinct from HER2 amplification by FISH or overexpression by IHC. Studies to date have been unimpressive for trastuzumab and pertuzumab, but there remains some question about which type of HER2 alteration may derive benefit from HER2-targeted agents. Both these studies evaluate T-DM1, a HER2-targeted antibody-drug conjugate.

The Stinchcombe study evaluated T-DM1 in patients with HER2 expression 2+ or 3+ by centrally assessed IHC.

Editorial — Dr Gubens (continued)

Among the 20 IHC 3+ patients, there was an overall response rate of 20% (4/20) and median duration of response of 7.3 months. 2 of these responders had HER2 mutation or gene rearrangement. No responses were seen in the 2+ cohort (n=26), regardless of HER2 amplification status.

Meanwhile, the Li study evaluated T-DM1 specifically in HER2-mutated patients in the cohort being reported. 18 patients were treated, half of whom had previously seen neratinib, afatinib or trastuzumab. Overall response rate was 44% with a PFS of 4 months and a median DOR of 5 months.

Editorial — Dr Gubens (continued)

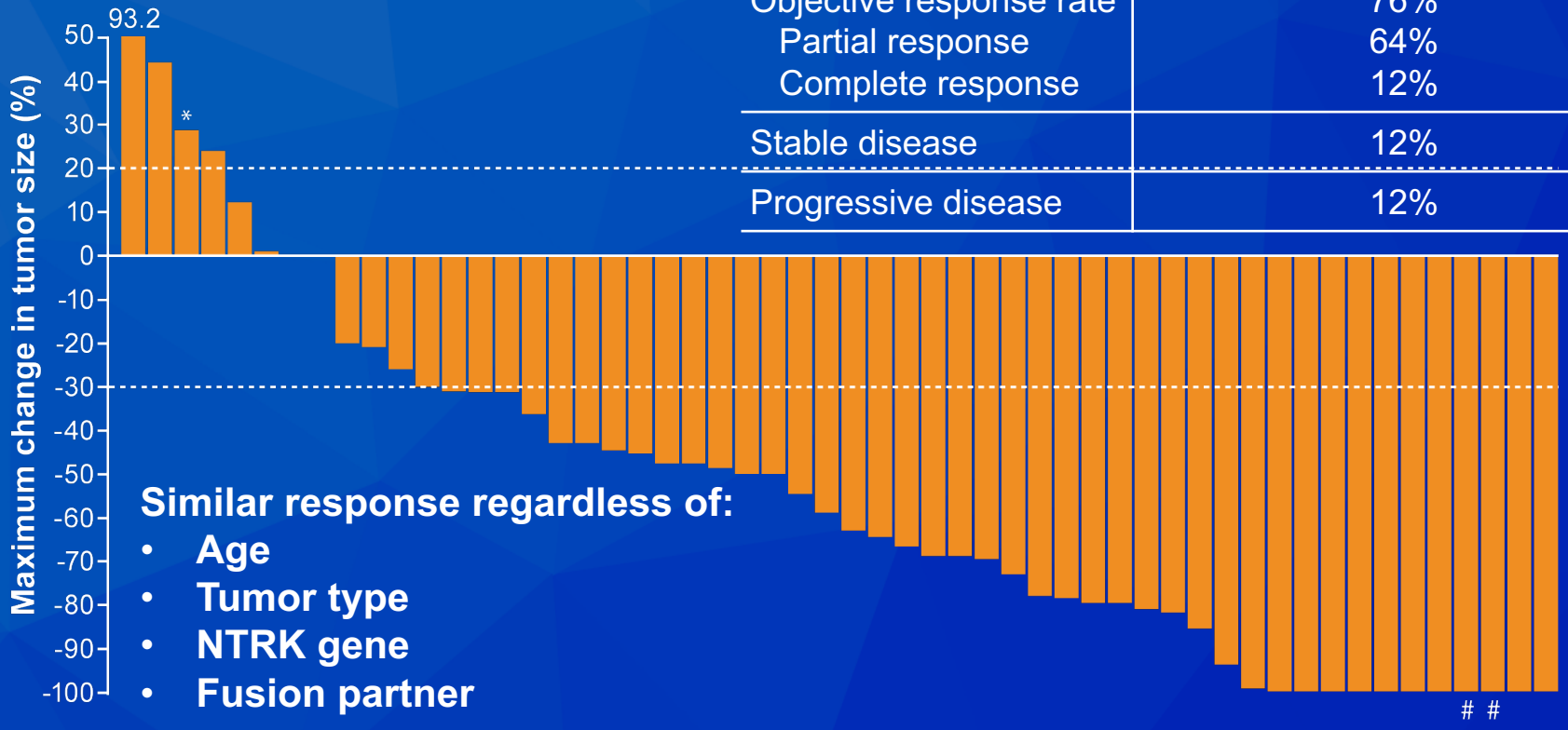
These two studies, though small, do shed more light on HER2 as an entity in NSCLC. Certainly HER2 mutation appears to be a more predictive biomarker for benefit than amplification or overexpression, just as our previous experience with EGFR and MET has shown. And T-DM1 appears more promising than initial attempts with HER2 inhibitors.

The Efficacy of Larotrectinib (LOXO-101), a Selective Tropomyosin Receptor Kinase (TRK) Inhibitor, in Adult and Pediatric TRK Fusion Cancers

Hyman DM et al.
Proc ASCO 2017;Abstract LBA2501.

Integrated Analysis of Response in 3 Studies of Larotrectinib in 17 Cancer Types with TRK Fusions

	Patients with confirmatory response data available (n = 50)
Objective response rate	76%
Partial response	64%
Complete response	12%
Stable disease	12%
Progressive disease	12%



* Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; # Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Hyman DM et al. *Proc ASCO* 2017;Abstract LBA2501.

Editorial — Dr Gubens

One of the newest targetable alterations is the family of TRK fusions, which are seen across a variety of tumor types (eg, high frequency in salivary tumors and secretory breast cancer) but also seen in a small number of lung cancers.

Hyman presented the results of a study of larotrectinib, the first pan-TRK inhibitor. 55 patients were enrolled, including 22 pediatric patients. 7% of these were lung cancer patients. The response rate was impressive, 76%, with a 12% complete response rate and a DCR of 88%. This benefit was seen across all ages, tumor types, NTRK gene involved (1, 2, or 3), and fusion partners.

Editorial — Dr Gubens (continued)

Duration of benefit data were immature, as 93% of responding patients remained on therapy, but some durable responses have been noted. The drug appears to be safe, with 13% requiring dose reductions, but no discontinuations required. Fatigue, dizziness, nausea/vomiting and anemia were most common, but most of these were grade 1.

This is a remarkable story of quick drug development for a target across many tumor types. As with our other targeted therapy results this past year for emerging targets, the availability of trials for this drug underscores the need for comprehensive genetic profiling in NSCLC, including NGS at the outset or at least if other methods don’t detect other driver mutations.

Lung Cancer — Drs Pennell and Socinski

EGFR Tumor Mutations

ALK Rearrangements

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

FDA approves durvalumab after chemoradiation therapy for unresectable Stage III NSCLC

Press Release — February 16, 2018

"The Food and Drug Administration approved durvalumab for patients with unresectable stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Approval was based on a planned interim analysis of progression-free survival from PACIFIC (NCT02125461), a randomized double-blind, placebo-controlled trial conducted in 713 patients with unresectable, stage III NSCLC."

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm597248.htm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

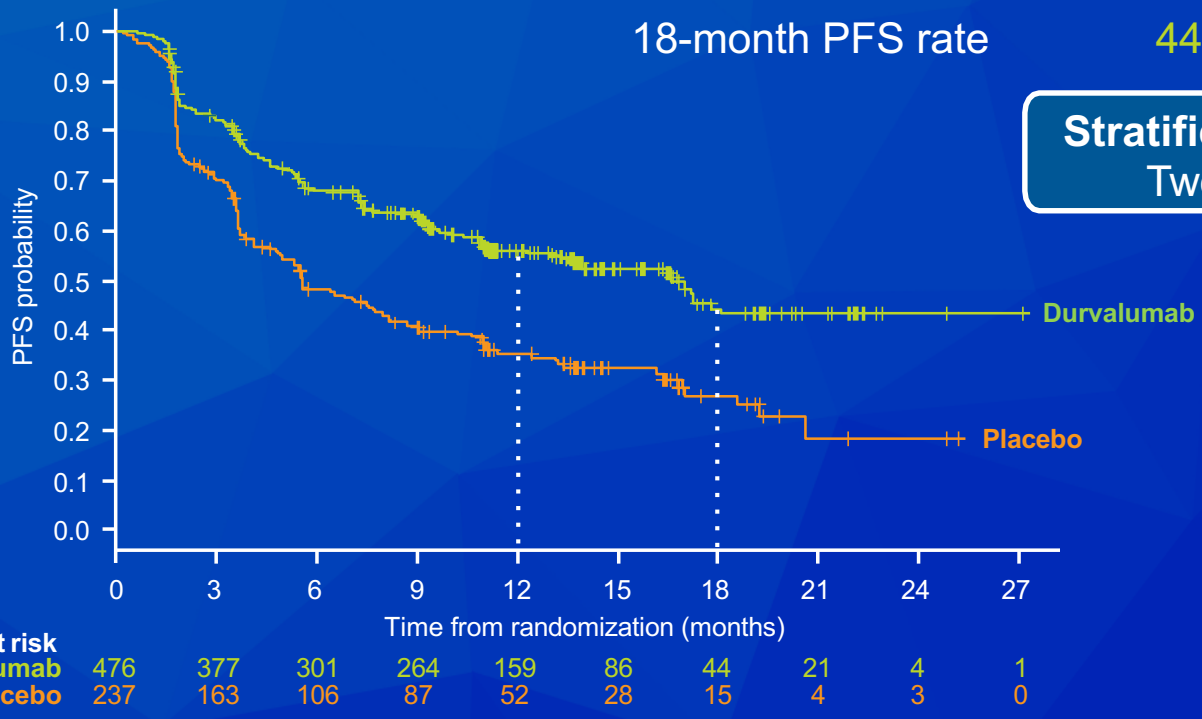
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

PFS by BICR (Primary Endpoint; ITT)

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

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



BICR = blinded independent central review; ITT = intention to treat

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

Editorial — Dr Gubens

We haven’t seen a significant advance in the treatment of stage III NSCLC beyond chemoradiation, and at best we can expect a 15% rate of 5-year survival.

Antonia et al presented initial results from the first large international phase 3 study investigating the addition of immunotherapy in stage III treatment. 713 patients who had completed definitive chemoradiation with at least stable disease after 2+ cycles of platinum-based chemotherapy were randomized on a 2:1 basis to durvalumab (a PD-L1 inhibitor) or placebo given q2 weeks for up to 1 year. Patients had to start within 42 days of completing chemoradiation. The study was designed to have co-primary endpoints, and at this point, OS is not yet mature.

Editorial — Dr Gubens (continued)

PFS, however, was significantly improved with durvalumab, median 16.8 vs 5.6 months (HR 0.52, $p<0.001$). Safety did not appear to be significantly different from our experience in the metastatic setting, and specifically the pneumonitis rate was 33.9% for durvalumab vs 24.8% for placebo (and grade 3/4 3.4% vs 2.6%).

This has the potential to be a practice changing study. Though OS is the gold standard in the curative setting (and fortunately OS is a co-primary endpoint we will learn about soon), the magnitude of this PFS benefit, with Kaplan-Meier curves that continue to diverge, convinces me to offer this approach to eligible patients today.

Editorial — Dr Gubens (continued)

Also, it was particularly reassuring to see a low pneumonitis rate, as we have been somewhat concerned about risk of PD-1/PD-L1 inhibition after full-dose radiation.

Press Release – Phase III KEYNOTE-189 Trial of First-Line Pembrolizumab plus Pemetrexed and Platinum January 16, 2018

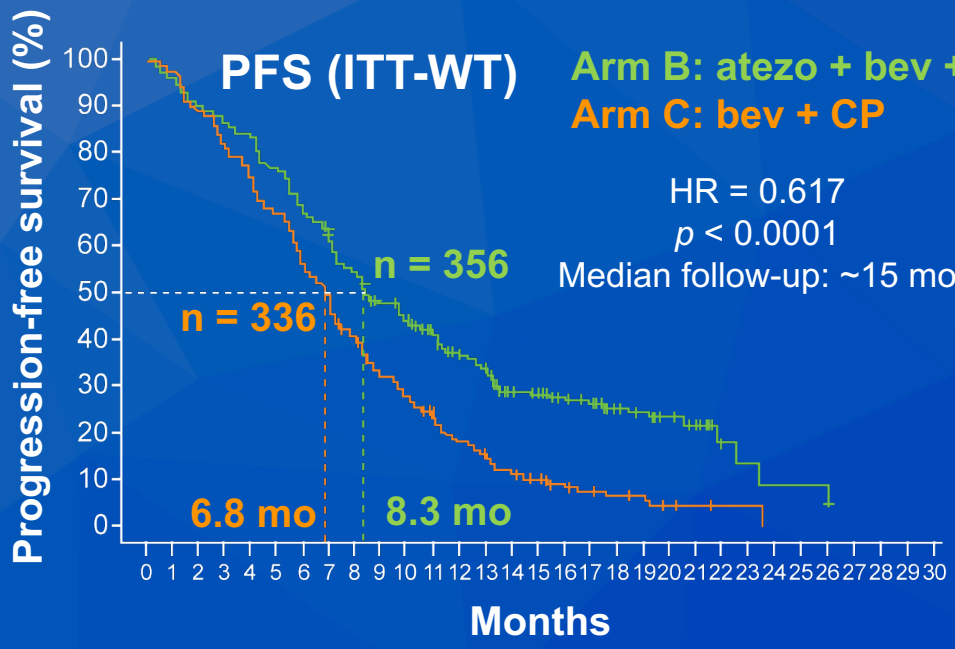
The pivotal Phase III KEYNOTE-189 trial investigating pembrolizumab, an anti-PD-1 antibody, in combination with pemetrexed and cisplatin or carboplatin, for the first-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC), met its dual primary endpoints of overall survival (OS) and progression-free survival (PFS). Based on an interim analysis conducted by the independent Data Monitoring Committee, pembrolizumab in combination with pemetrexed/platinum resulted in significantly longer OS and PFS versus pemetrexed and platinum chemotherapy alone. The safety profile of the pembrolizumab combination was consistent with that previously observed.

https://www.businesswire.com/news/home/20180116005680/en/Mercks-KEYTRUDA-pembrolizumab-Significantly-Improved-Survival-Progression-Free

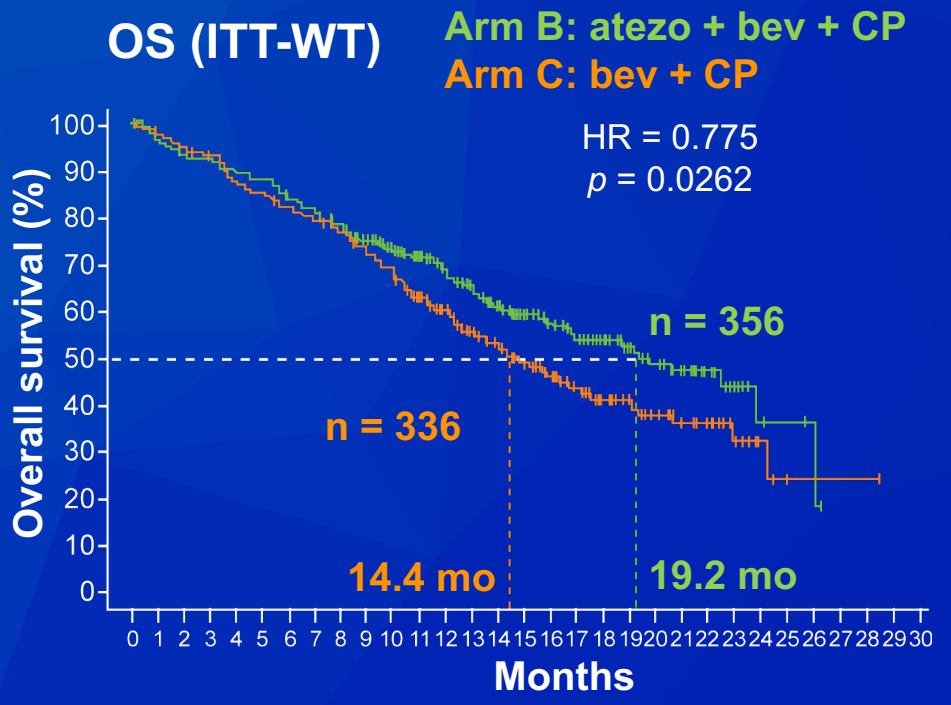
Primary PFS and Safety Analyses of a Randomized Phase III Study of Carboplatin + Paclitaxel +/– Bevacizumab, with or without Atezolizumab in 1L Non-Squamous Metastatic NSCLC (IMpower150)

Reck M et al.
Proc ESMO 2017;Abstract LBA1_PR.

IMpower150: Investigator (INV)-Assessed PFS and OS



WT = Patients without EGFR or ALK gene alterations



Teff-high* WT population	Arm B (n = 155)	Arm C (n = 129)
Median PFS	6.8 mo	11.3 mo
HR	0.505	
p-value	<0.0001	

* Teff-high = high T-effector gene signature expression

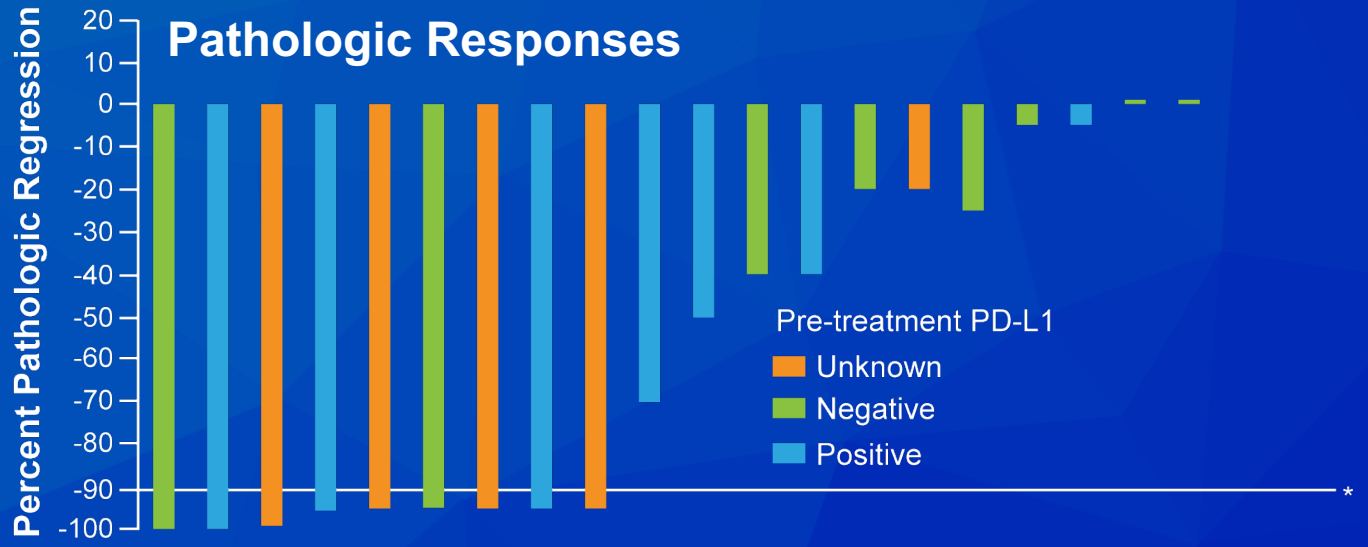
Reck M et al. *Proc ESMO* 2017;Abstract LBA1_PR.

Neoadjuvant Nivolumab in Early-Stage, Resectable Non-Small Cell Lung Cancers

Chaft JE et al.
Proc ASCO 2017;Abstract 8508.

Feasibility and Pathologic Response to 2 Doses of Neoadjuvant Nivolumab (N = 22)

- Neoadjuvant nivolumab did not delay surgery in any of the treated patients
- No unexpected safety signals observed
- 43% of tumors demonstrated a major pathologic response



- Associated mutation and mutation-associated neoantigen (MANA) burden with pathologic response
- Identified MANA-specific T-cell receptors (TCRs) in blood and tumor
- Observed temporal increases in MANA-specific TCRs in the peripheral blood after nivolumab treatment, a potential biomarker of response

Chaft JE et al. *Proc ASCO* 2017;Abstract 8508.

Editorial — Dr Hanna

Chaft et al report the first clinical trial data evaluating the role of neoadjuvant nivolumab prior to surgery in patients with stage I-III non-small cell lung cancer. The investigators enrolled 21 patients, 20 of whom eventually underwent surgical resection. All patients received nivolumab 3 mg/kg every 2 weeks x 2 followed by surgical resection. No unexpected toxicities were observed and there were no treatment-related postoperative deaths. Two achieved a PR per RECIST criteria and 18 had SD by RECIST criteria. However, 9 of 21 patients achieved a major pathological response (>90% necrosis in the surgical specimen). Multiplex immunofluorescence testing demonstrated an influx of CD8+ cells into the tumor microenvironment. Mutational burden and neoantigen density were associated with pathological response.

Editorial — Dr Hanna (continued)

These trial results are very promising. Of note, pathological responses were much higher than traditional clinical responses per RECIST. All surgically resectable patients were able to safely undergo surgery without delay. In addition, biomarker assessments for mechanisms of activity and resistance to checkpoint inhibitors can be ideally carried out in the neoadjuvant setting. Randomized prospective trials will ultimately determine the role of checkpoint inhibitors in the neoadjuvant or adjuvant setting, but this initial report is very promising.

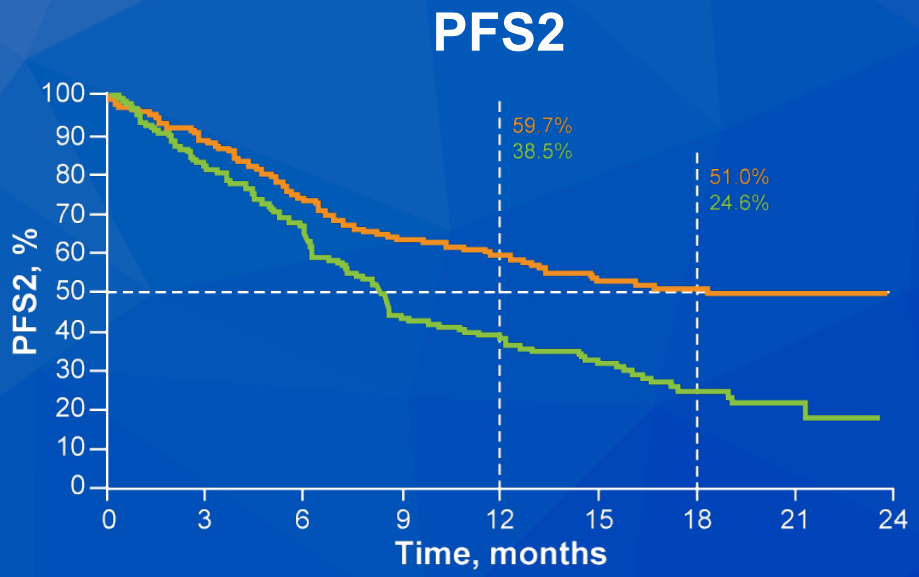
Pembrolizumab versus Chemotherapy for PD-L1-Positive Non–Small-Cell Lung Cancer

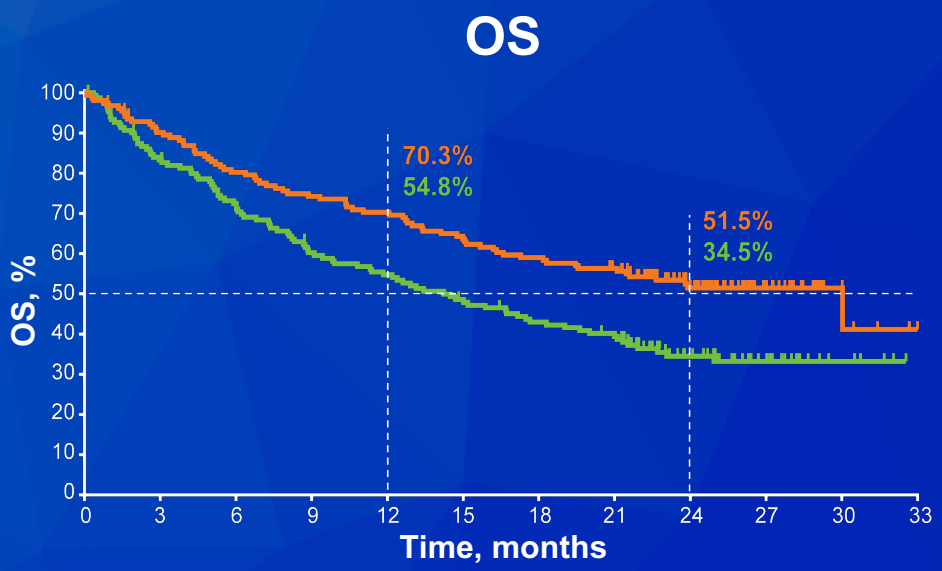
Updated Analysis of KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC with PD-L1 TPS ≥50%

Reck M et al.
N Engl J Med 2016;375(19):1823-33.

Brahmer JR et al.
Proc IASLC 2017;Abstract OA 17.06.

KEYNOTE-024: PFS, PFS2 and Updated Overall Survival





	Pembrolizumab (n = 154)	Chemotherapy (n = 151)	HR	*p*
Median PFS[1]	10.3 mo	6.0 mo	0.50	<0.001
Median PFS2[2]	18.3 mo	8.4 mo	0.54	<0.001
Median OS[3]	30.0 mo	14.2 mo	0.63	0.002

[1] Reck M et al. *N Engl J Med* 2016;375(19):1823-33; [2] Brahmer JR et al. Proc ASCO 2017;Abstract 9000; [3] Brahmer JR et al. *Proc IASLC* 2017;Abstract OA 17.06.

Editorial — Dr Gubens

ESMO 2016 had a truly remarkable session where we learned about two large, international, phase 3 trials of first-line PD-1 inhibitor versus chemotherapy. Pembrolizumab was superior to chemo in patients with PD-L1 expression ≥50% with respect to PFS and, strikingly, OS as well, despite allowed crossover for the patients starting on chemo. Nivolumab, meanwhile, did not beat chemo in patients with PD-L1 ≥5%. Testing for PD-L1 expression in the first line became the standard of care, as did single-agent pembrolizumab for that subset of patients.

Editorial — Dr Gubens (continued)

This year, Dr Brahmer updated the KEYNOTE-010 pembrolizumab results, and also presented PFS2 data, a metric of time from randomization to the end of the 2nd line of therapy, which can sometimes help assess the impact of crossover on OS assessment, and whether therapy affects the efficacy of the following line of therapy. Now with median 19 months of follow-up, OS continues to favor pembrolizumab, with HR 0.63 (p=.003), and with the median not reached vs 14.5 mo in the chemo arm. PFS2 also favors pembrolizumab, HR 0.54 (p<.001), median 18.3 vs 8.4 months.

Editorial — Dr Gubens (continued)

These data suggest that while patients with PD-L1 ≥50% derive benefit from pembrolizumab in the second-line, there is still PFS and OS advantage to starting with pembrolizumab in the first line. Sequence matters, and investigating the role of sequence as more immunotherapy data roll out will be important.

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

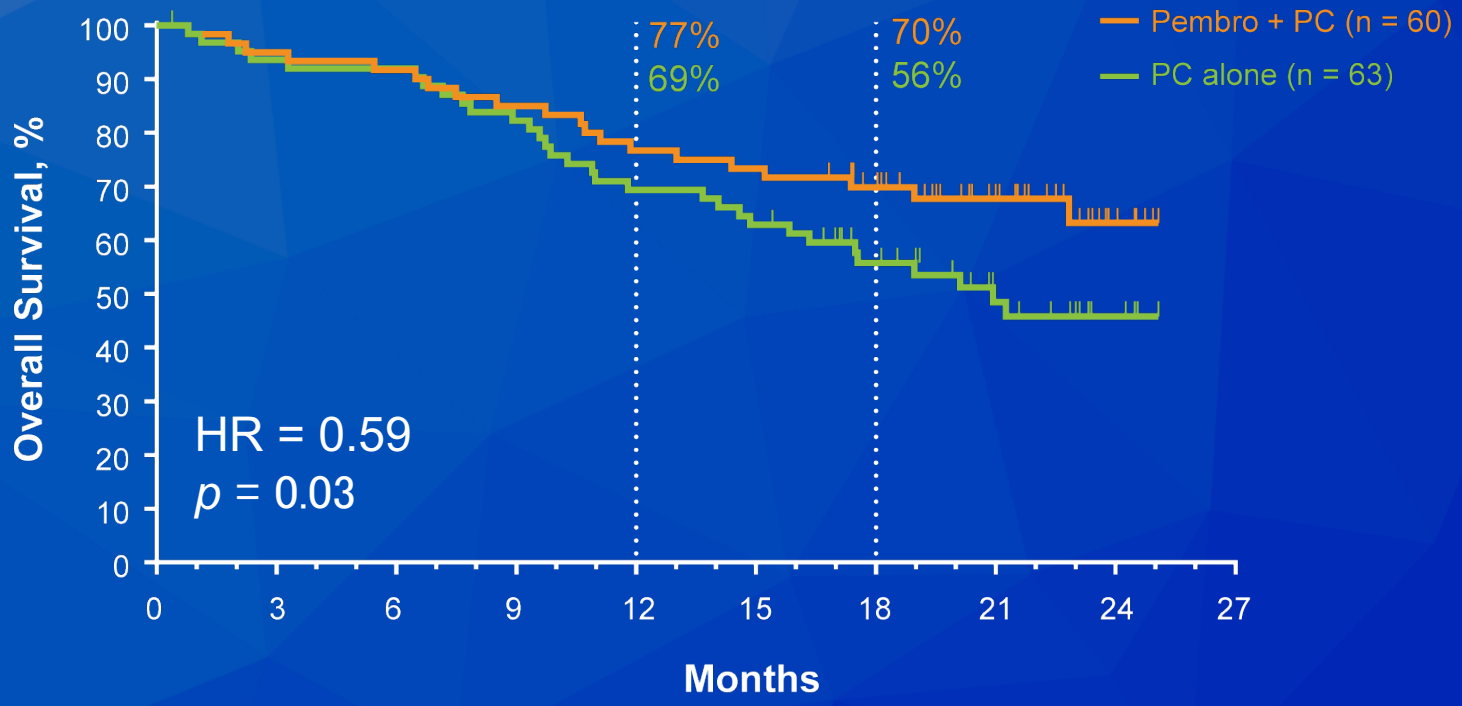
*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**

Lancet Oncol 2016;17(11):1497-508.

Updated Results from KEYNOTE-021 Cohort G: A Randomized, Phase 2 Study of Pemetrexed and Carboplatin (PC) with or without Pembrolizumab (pembro) as First-Line Therapy for Advanced Nonsquamous NSCLC

Borghaei H et al. *Proc ESMO* 2017;Abstract LBA49.

KEYNOTE-021 Cohort G: Response Rates and Updated Survival Analyses



Endpoint	Pembro + PC (n = 60)	PC alone (n = 63)	HR	*p*-value
ORR	56.7%	31.7%	—	0.0029
mPFS	19.0 mo	8.9 mo	0.54	0.0067
mOS	Not reached	20.9 mo	0.59	0.03

Borghaei H et al. *Proc ESMO* 2017;Abstract LBA49.

Editorial — Dr Gubens

Langer first presented phase 2 data of first-line carboplatin and pemetrexed with or without pembrolizumab at ESMO 2016, and strikingly, in 2017, the FDA granted accelerated approval for the combination in nonsquamous NSCLC regardless of PD-L1 expression.

Borghaei updated the data set at ESMO 2017. 123 patients without EGFR or ALK alterations were randomized 1:1 to carbo/pem with or without pembrolizumab for up to 2 years. There was 75% crossover to PD-1 therapy from the chemo alone arm. The primary endpoint was ORR, which was 56.7% vs 31.7% (p = .0029). PFS HR was 0.54 (p = .0067), median 19.0 vs 8.9 months. At this update, OS had improved with a HR of 0.59 (p = .03). Notably, the PFS and OS p-values were descriptive only.

Editorial — Dr Gubens (continued)

These are encouraging data, but as of November 2017, I remain reluctant to recommend this strategy to all comers. This was a small phase 2 study, not powered for survival (though the updated survival data are provocative). The data are somewhat unstable when looking at biomarker subsets (eg, response rate by PD-L1 status was 62%, 26%, and 80% for PD-L1 <1%, 1%-49%, and ≥50% in the pembrolizumab arm, with about 20 in each group). Fortunately, large phase 3 studies have fully accrued (including KEYNOTE-189) that will soon answer these questions more definitively. In the meantime, I discuss 21G data with patients, but tend to only recommend the triplet strongly in patients with high burden of symptomatic disease when I am concerned about them not making it to second-line therapy at all.

VOLUME 35 · NUMBER 7 · MARCH 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

Jarushka Naidoo, Xuan Wang, Kaitlin M. Woo, Tunc Iyriboz, Darragh Halpenny, Jane Cunningham, Jamie E. Chaft, Neil H. Segal, Margaret K. Callahan, Alexander M. Lesokhin, Jonathan Rosenberg, Martin H. Voss, Charles M. Rudin, Hira Rizvi, Xue Hou, Katherine Rodriguez, Melanie Albano, Ruth-Ann Gordon, Charles Leduc, Natasha Rekhtman, Bianca Harris, Alexander M. Menzies, Alexander D. Guminski, Matteo S. Carlino, Benjamin Y. Kong, Jedd D. Wolchok, Michael A. Postow, Georgina V. Long, and Matthew D. Hellmann

Incidence, Time to Onset and Severity of Anti-PD-1/PD-L1-Associated Pneumonitis

- 915 patients who received anti-PD-1/PD-L1 mAbs from Memorial Sloan Kettering Cancer Center or Melanoma Institute of Australia
- Pneumonitis incidence: 43/915 (5%)
  - Higher with combination immunotherapy (10%) than monotherapy (3%) $p < 0.01$
- Median time to onset of pneumonitis: 2.8 months (range: 9 days to 19.2 months)
  - Earlier onset with combination immunotherapy (2.7 mo) than monotherapy (4.6 mo)
- Pneumonitis severity was typically mild (72% Grade 1-2), but 5 patients worsened clinically and died during pneumonitis treatment
- Pneumonitis improved/resolved with drug holding/immunosuppression in most cases (86%)

Naidoo J et al. *J Clin Oncol* 2017;35(7):709-17.

Editorial — Dr Hanna

Naidoo et al reported the clinical, radiological, and pathological features of patients who developed pneumonitis related to checkpoint inhibition. Of 915 patients who received anti-PD-1 or PD-L1 monoclonal antibodies at Memorial Sloan Kettering or the Melanoma Institute of Australia, approximately 5% developed pneumonitis. The primary cancer type was predominately non-small cell lung cancer or melanoma. More than half of the patients were smokers. Most did not have underlying lung disease. Checkpoint inhibitors were given in any line, with 2/3 given as 2nd line or beyond. The time from the first dose of checkpoint inhibitor to the onset of pneumonitis ranged from just a few days to years later, although the majority occurred in the first 6 months.

Editorial — Dr Hanna (continued)

Twelve patients were rechallenged with immune therapy after an initial pneumonitis event. Three experienced a second episode of pneumonitis.

The radiological features were described in five categories: cryptogenic organizing pneumonia, ground glass opacities, interstitial, hypersensitivity, and pneumonitis not otherwise specified. Most cases were mild. Patients undergoing lung biopsy were discovered to have interstitial pneumonitis, diffuse alveolar damage, and organizing pneumonia.

As checkpoint inhibitors become more commonplace for use against a variety of cancers, treating oncologists will need to become expertise on the management of immune-mediated toxicities, some of which can be life threatening, such as pneumonitis.

Editorial — Dr Hanna (continued)

In my practice, I have managed immune-mediated toxicities of all organ systems, including dermatitis, arthritis, nephritis, adrenalitis, pancreatitis, encephalitis, hepatitis, colitis, thyroiditis, and pneumonitis. Most of these toxicities can be easily managed with supportive care and prednisone. However, I have encountered cases of severe pneumonitis that has resulted in mechanical intubation and prolonged pulmonary rehabilitation. While most of these events occur early on, some of these events can occur many months later, even off therapy. Oncologists will need to be vigilant in recognizing these toxicities and initiating prompt management. In addition, consultations with an infectious disease expert and pulmonologists are critical to optimally managing patients with severe pneumonitis.

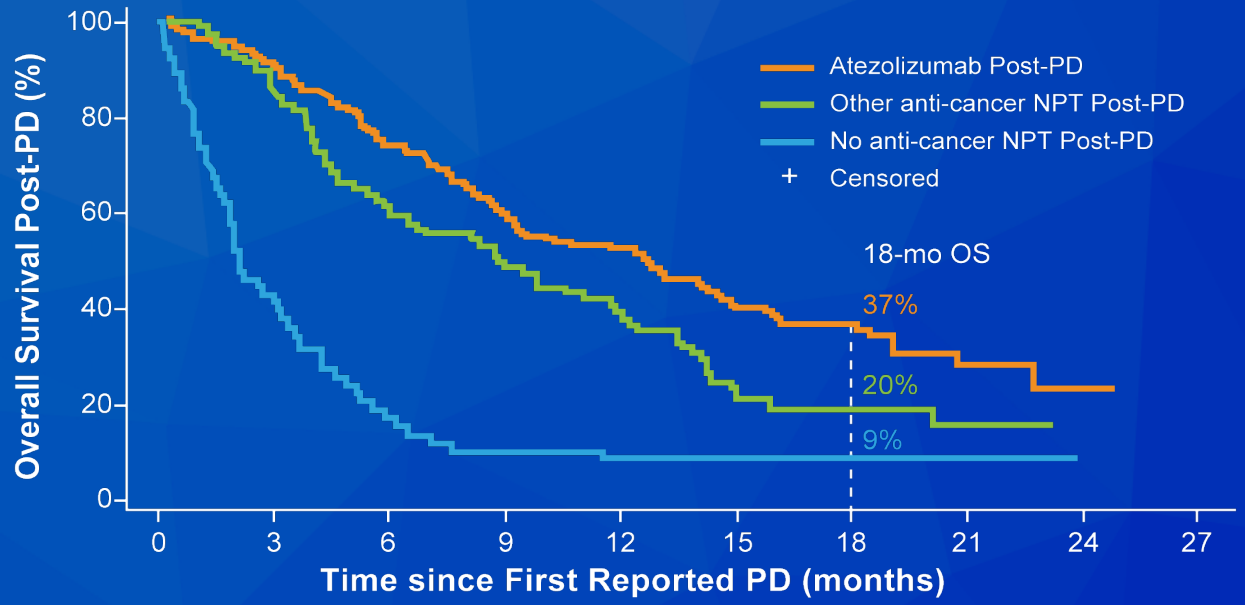
Impact of Atezolizumab (atezo) Treatment Beyond Disease Progression (TBP) in Advanced NSCLC: Results from the Randomized Phase III OAK Study

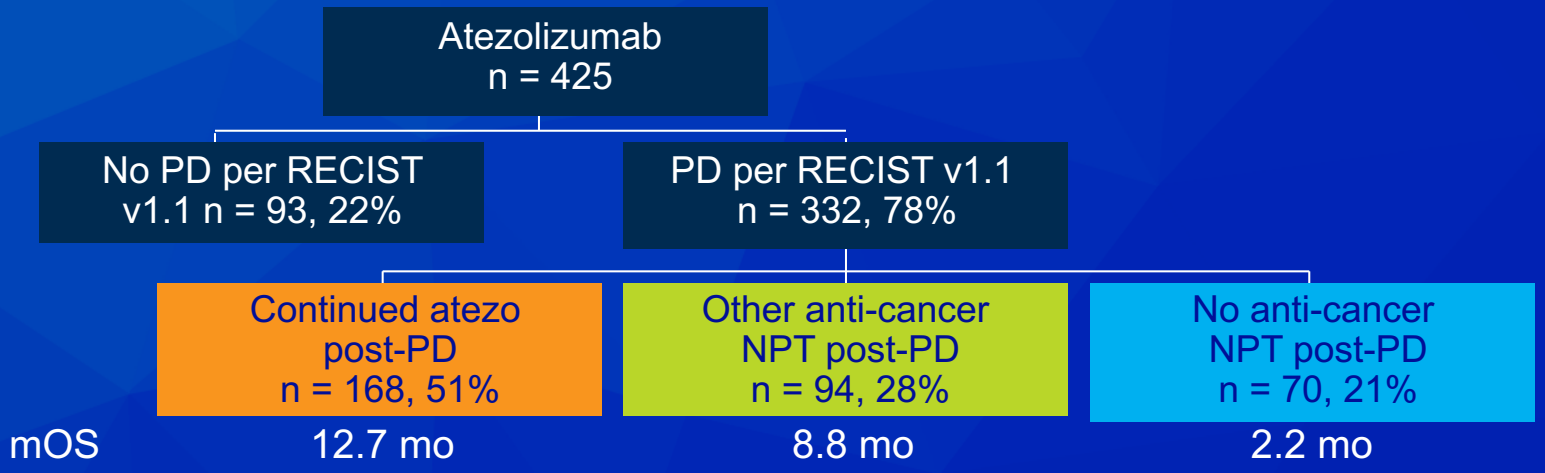
Randomized Results of Fixed-Duration (1-yr) vs Continuous Nivolumab in Patients (pts) with Advanced Non-Small Cell Lung Cancer (NSCLC)

Gandara DR et al.
Proc ASCO 2017;Abstract 9001.

Spigel D et al.
Proc ESMO 2017;Abstract 1297O.

OAK: OS Post-Progressive Disease (PD) in the Atezolizumab Arm: By Post-PD Treatment



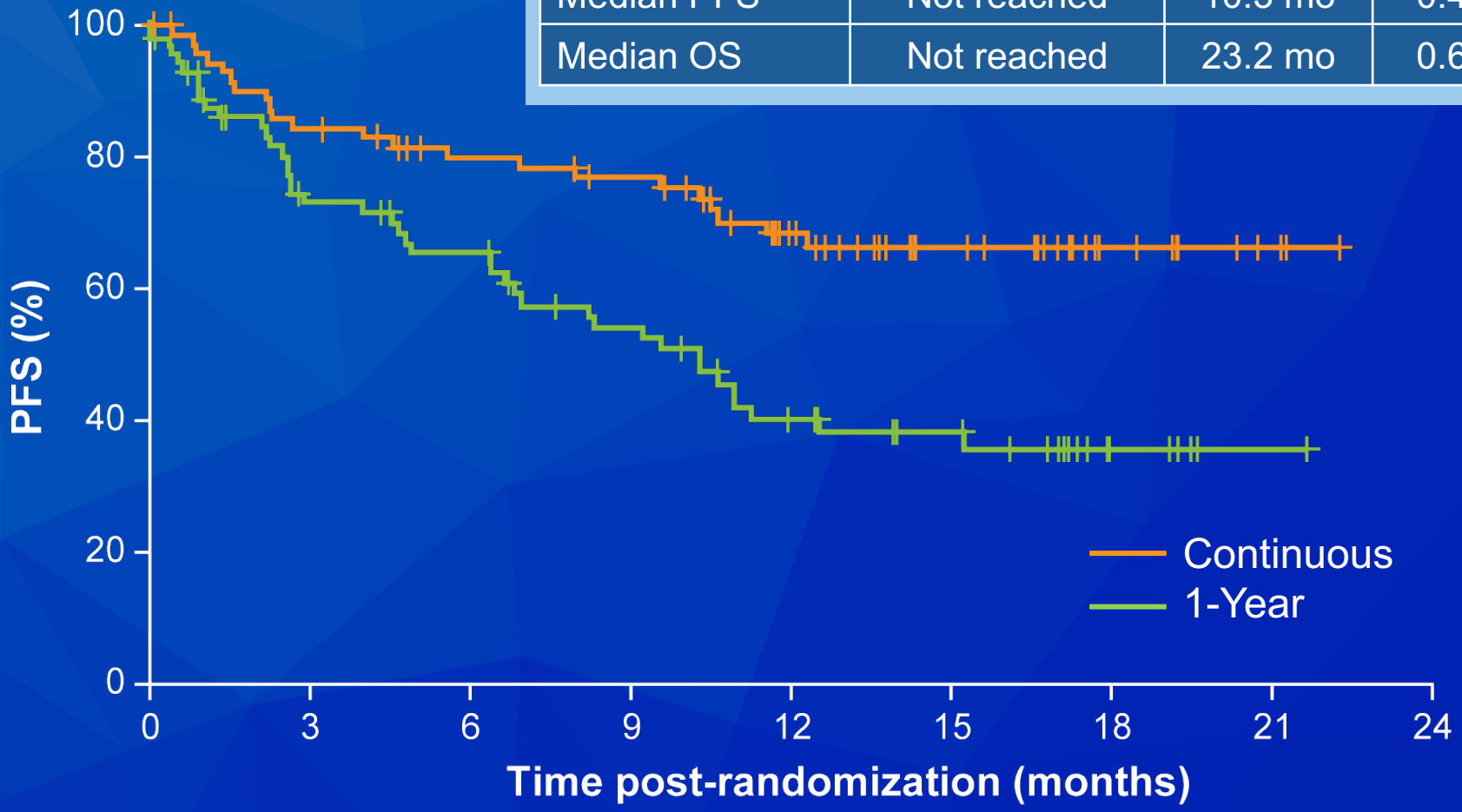


NPT = nonprotocol therapy

Gandara DR et al. *Proc ASCO* 2017;Abstract 9001.

CheckMate 153: Continuous vs 1-Year Nivolumab PFS from Randomization

	Continuous (n = 76)	1-Year (n = 87)	HR
Median PFS	Not reached	10.3 mo	0.42
Median OS	Not reached	23.2 mo	0.63



Spigel DR et al. *Proc ESMO* 2017;Abstract 12970.

Editorial — Dr Hanna

The optimal duration of checkpoint inhibition is undefined. Gandara and colleagues report the results of treatment beyond progression with atezolizumab from the randomized phase 3 OAK study. In the OAK study, patients received atezolizumab versus docetaxel in the second- or third-line setting. Patients achieved a longer overall survival with atezolizumab, although progression-free survival was not statistically different. The investigator has hypothesized those traditional endpoints such as progression-free survival may not be optimal in assessing the clinical benefits of immunotherapy agents. Patients on the OAK study were permitted to continue atezolizumab beyond progression. In fact, half the patients continued on atezolizumab after progression.

Editorial — Dr Hanna (continued)

Overall survival favored those who continued on treatment compared with those that did not. Some patients even achieved subsequent responses when treated beyond initial progression. On the docetaxel arm, those who received subsequent immunotherapy appeared to have better survival than those treated with subsequent non-immunotherapy agents.

The authors acknowledge the limitations of this analysis, namely that it was nonrandomized and criteria for continuation may have introduced biases in the survival results.

Editorial — Dr Hanna (continued)

Spigel and colleagues attempted to address the question of duration of therapy in a randomized cohort of patients initially treated on CheckMate 153 trial, in which all patients received nivolumab. Those without progression at the 1-year mark were randomized to continue nivolumab versus discontinuation. The investigators reported a prolonged progression-free survival, favoring continuation of nivolumab beyond 1 year (HR 0.42). This benefit held for those with an initial CR/PR as well as those with SD. An initial look at overall survival demonstrated a trend for longer survival in the continuation group.

Editorial — Dr Hanna (continued)

Both of these trials address a critical question in managing our patients with immunotherapy; namely, what is the optimal duration? While the data from CheckMate 153 is suggestive of prolonged benefits beyond 1 year, the sample size is small, and the results are not definitive. Is there an upper limit of duration of therapy that provides benefit? Perhaps 1 year is not enough. Is it 2 years? Is it indefinite treatment? Additional clinical trials will address these questions, including a trial from Europe that will randomize patients after 1 year of immunotherapy to continue the immunotherapy on their previous schedule versus prolonging the time in between immunotherapy agents. In my practice, I continue immunotherapy agents until progression of disease, undue toxicities, or the patients asks for a treatment break.

Cancer Therapy: Clinical

Clinical Cancer Research

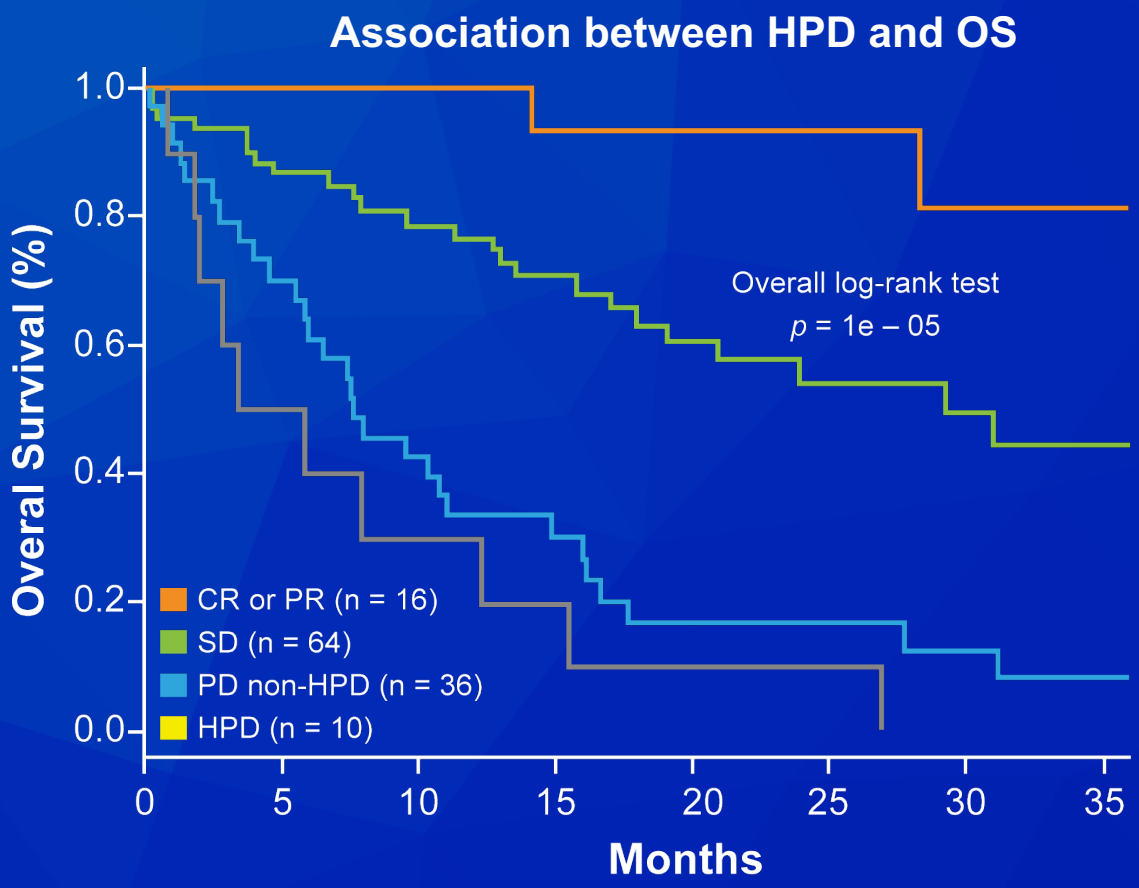
Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat[1,2], Laurent Dercle[3], Samy Ammari[4], Christophe Massard[1], Antoine Hollebecque[1], Sophie Postel-Vinay[1,2], Nathalie Chaput[5,6,7,8], Alexander Eggermont[9], Aurélien Marabelle[1,10], Jean-Charles Soria[1,2], and Charles Ferté[1,11,12]

Clin Cancer Res 2017;23(8):1920-8.

Incidence and Survival Outcomes of Patients with Hyperprogressive Disease (HPD)

- Analyzed medical records from all patients (N = 218) prospectively treated in Gustave Roussy by anti-PD-1/PD-L1 inhibitors within Phase I trials
- 12/131 evaluable (9%) demonstrated hyperprogressive disease (HPD)
- Patients with HPD had a lower rate of new lesions than those with disease progression without HPD
- HPD associated with higher age
- HPD associated with worse overall survival outcome



Champiat S et al. *Clin Cancer Res* 2017;23(8):1920-8.

Editorial — Dr Hanna

Checkpoint inhibitors have revolutionized our treatment of patients with advanced non-small cell lung cancer. However, reports have emerged that checkpoint inhibitors may exacerbate disease progression, so called “hyperprogression.” Champiat and colleagues reviewed the medical records of 218 patients treated in Gustave Roussy with anti-PD-1 or PD-L1 inhibitors on phase 1 clinical trials. They estimated the tumor growth rate prior to initiation of the checkpoint inhibitor and the tumor growth rate upon progression of disease after the checkpoint inhibitor. Data on 166 patients was available to assess the tumor growth rates before and after the checkpoint inhibitors were given.

Editorial — Dr Hanna (continued)

Overall, they identified 12 patients with hyperprogression. This was not associated with tumor mutational burden at baseline nor any specific tumor type. It was inversely related with response to anti-PD-1 or PD-L1 therapy. An editorial by Elad Sharon accompanied this study. Sharon identifies multiple limitations to the analysis, namely, the small sample size, the use of an unvalidated measure to assess tumor growth, and the lack of an identifiable method or predictive feature for identifying those at risk for this phenomenon.

In my practice, I have never appreciated a single case of hyperprogression. Pseudoprogression is a well-described phenomenon observed in some patients treated with checkpoint inhibitors.

Editorial — Dr Hanna (continued)

It is more commonly seen in patients with melanoma and less commonly seen in patients with lung cancer. My first patient I ever treated with nivolumab had pseudoprogression. She was clinically improving, although radiographically her masses were increasing in size. With continued treatment, her disease began to regress. She is now 4 years from her initial treatment with nivolumab and has achieved a near complete response. In contrast to this case of pseudoprogression, patients with hyperprogression are thought to have true tumor growth (not simply inflammatory changes that appear as tumor growth). If a patient has progression on imaging studies or exam with clinical deterioration, I discontinue the checkpoint inhibitor.

Editorial — Dr Hanna (continued)

If the patient is clinically stable but has slow radiographic progression, I will continue the checkpoint inhibitor at least another 2 cycles and will re-evaluate. If radiographic progression continues, I will then discontinue the checkpoint inhibitor.

Whole Body PD-1 and PD-L1 PET in Patients with NSCLC

Niemeijer A et al.
Proc ESMO 2017;Abstract 1305PD.

Whole Body PD-1 and PD-L1 PET

- Tumor PD-L1 IHC relates moderately with treatment outcome after anti-PD-1 therapy in pts with NSCLC, and single biopsies do not account for tumor heterogeneity
- PET-imaging with both ^{89}Zirconium-labeled nivolumab (^{89}Zr-nivo) and ^{18}F-labeled BMS-986192 (^{18}F-PD-L1) is safe and feasible, with good tumor-to-normal tissue contrast
- Tumor uptake showed heterogeneity among pts and among tumors within pts
- Pts with ≥50% tumor PD-L1 expression showed higher ^{18}F-PD-L1 uptake
- Pts with high PD-1 expression showed higher ^{89}Zr-nivo uptake, and pts with PR demonstrated higher ^{18}F-PD-L1 and ^{89}Zr-nivo tracer uptake than pts with PD/SD; these were not statistically significant

Niemeijer A et al. *Proc ESMO* 2017;Abstract 1305PD.

Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study

Matthew D Hellmann, Naiyer A Rizvi, Jonathan W Goldman, Scott N Gettinger, Hossein Borghaei, Julie R Brahmer, Neal E Ready, David E Gerber, Laura Q Chow, Rosalyn A Juergens, Frances A Shepherd, Scott A Laurie, William J Geese, Shruti Agrawal, Tina C Young, Xuemei Li, Scott J Antonia

Lancet Oncol **2017; 18: 31–41**

CheckMate 012: Efficacy and Summary of Adverse Events

	Nivo 3 mg/kg q2wk + ipi 1 mg/kg q12wk (n = 38)	Nivo 3 mg/kg q2wk + ipi 1 mg/kg q6wk (n = 39)
Confirmed ORR	18 (47%)	15 (38%)
Disease control rate	30 (79%)	22 (56%)
Median PFS	8.1 mo	3.9 mo
Adverse events		
Treatment-related serious AEs	12 (32%)	11 (28%)
Grade 3-4 AEs	14 (37%)	13 (33%)
AEs leading to treatment discontinuation	4 (11%)	5 (13%)
Skin-related AEs	15 (39%)	14 (36%)
GI-related AEs	9 (24%)	9 (23%)
Endocrine-related AEs	4 (11%)	8 (21%)

Hellmann MD et al. *Lancet Oncol* 2017;18(1):31-41.

Pivotal Phase III CheckMate-227 Study: Superior PFS with Nivolumab Plus Ipilimumab versus Chemotherapy as First-Line Therapy for Patients with Advanced NSCLC with High Tumor Mutation Burden

Press Release — February 5, 2018

"The ongoing Phase III CheckMate-227 study met its co-primary endpoint of PFS with the nivolumab plus ipilimumab combination versus chemotherapy in first-line advanced NSCLC patients whose tumors have high (≥10 mutations/megabase) tumor mutation burden (TMB), regardless of PD-L1 expression…

Additionally, based on an interim analysis for OS, the Data Monitoring Committee recommended that the study continue."

https://news.bms.com/press-release/bms/pivotal-phase-3-checkmate-227-study-demonstrates-superior-progression-free-surviva

Editorial — Dr Gubens

Even though pembrolizumab shows benefit over chemo in the first line for patients with high PD-L1 expression, the response rate is still only 45%, suggesting the need for other approaches, including combinations. Dual inhibition of PD-1/PD-L1 and CTLA4 has been synergistic in melanoma, so that has been an approach pursued by multiple groups in NSCLC as well.

Hellmann presented phase 1 data for nivolumab and ipilimumab in first-line NSCLC. Patients were randomized 1:1:1 to 3 dosing schedules of nivo and ipi until disease progression. They presented the 78 patients from the two nivo 3-mg cohorts.

Editorial — Dr Gubens (continued)

Response rates were 47% and 38%, and in patients with PD-L1 ≥1%, 57% in both cohorts. Median duration of benefit had not been reached after median follow-up of about 12 months. Grade 3 AEs were noted in 37% and 33% of patients, necessitating discontinuation in 11% and 13%.

In an unselected (or PD-L1 ≥1%) first-line population, these response rates compare favorably to chemotherapy, though tolerability is somewhat tougher with the nivo/ipi combination. The authors rightly point out that phase 3 studies are warranted, as well as more mature data on duration and OS, and indeed these are ongoing and we anticipate results soon.

Editorial — Dr Gubens (continued)

One warning flag, however, is a recent press release reporting that the MYSTIC trial of another PD-L1/CTLA4 combo (durvalumab and tremelimumab) did not improve PFS over chemotherapy in patients with PD-L1 ≥25%, though to date no specific data have been reported. OS was also an endpoint of the MYSTIC trial.

Phase III MYSTIC Trial Does Not Meet Its Primary Endpoint of Progression-Free Survival

Press Release — July 27, 2017

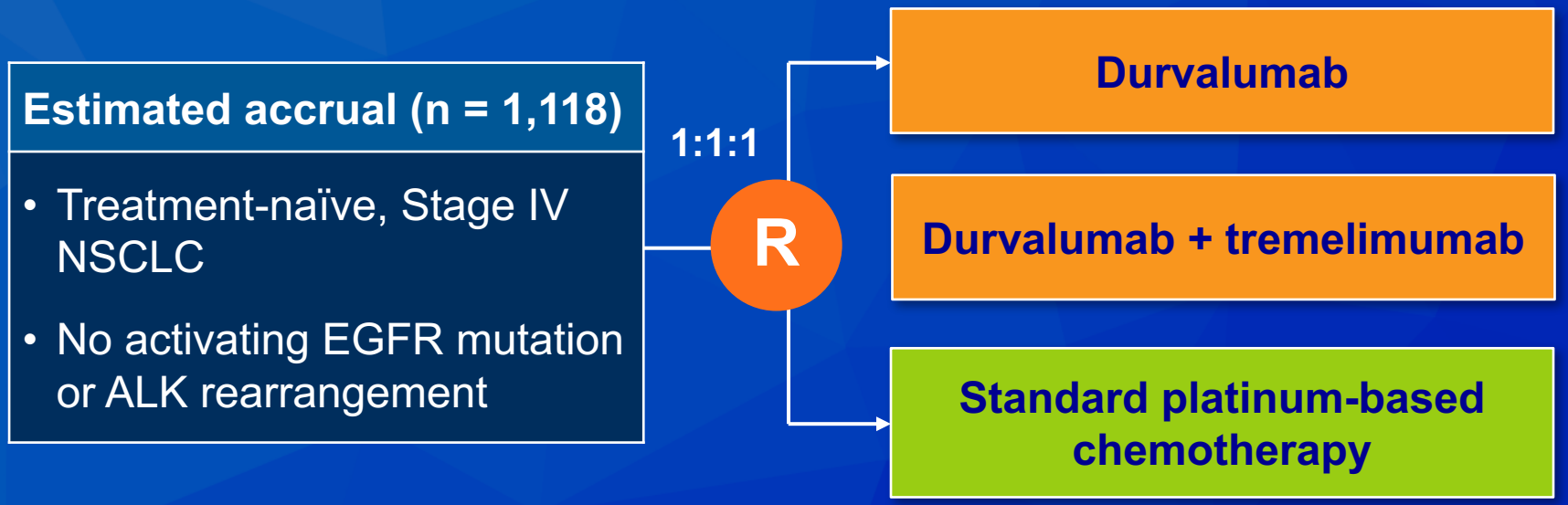
The combination of durvalumab and tremelimumab did not meet the primary endpoint of improving PFS compared to standard of care (SoC) in patients whose tumors express PD-L1 on 25% or more of their cancer cells (as determined by the VENTANA PD-L1 [SP263] assay).

As a secondary endpoint, although not formally tested, durvalumab monotherapy would not have met a prespecified threshold of PFS benefit over SoC in this disease setting.

The trial will continue to assess two additional primary endpoints of overall survival (OS) for durvalumab monotherapy and OS for the durvalumab plus tremelimumab combination. Final OS data from both primary endpoints are expected during the first half of 2018.

https://www.astrazeneca.com/media-centre/press-releases/2017/astrazeneca-reports-initial-results-from-the-ongoing-mystic-trial-in-stage-iv-lung-cancer-27072017.html

MYSTIC Phase III Trial Design



Primary Endpoints: PFS and OS of durvalumab + tremelimumab, OS of durvalumab monotherapy

www.clinicaltrials.gov; NCT02453282. Accessed October 2017.

ABOUND.70+: Safety and Efficacy of *Nab*-Paclitaxel/Carboplatin (*Nab*-P/C) in Elderly Patients (pts) with Advanced Non-Small Cell Lung Cancer (NSCLC)

Safety and Efficacy of *Nab*-Paclitaxel (*Nab*-P)–Based Therapy in Patients (pts) with Non-Small Cell Lung Cancer (NSCLC) and Performance Status (PS) 2: Results from ABOUND.PS2

Langer CJ et al.
Proc ASCO 2017;Abstract 9059.

Gajra A et al.
Proc ASCO 2017;Abstract 9058.

ABOUND.70+: Side Effects and Efficacy of *Nab* Paclitaxel/Carboplatin with a 1-Week Break

- Patients ≥70 y with treatment-naïve locally advanced/metastatic NSCLC randomized (1:1):
  - Arm A: *Nab*-P 100 mg/m d 1, 8, 15 + C AUC 6 d 1 q3wk
  - Arm B: Same *nab*-P/C dose q3wk followed by a 1-week break

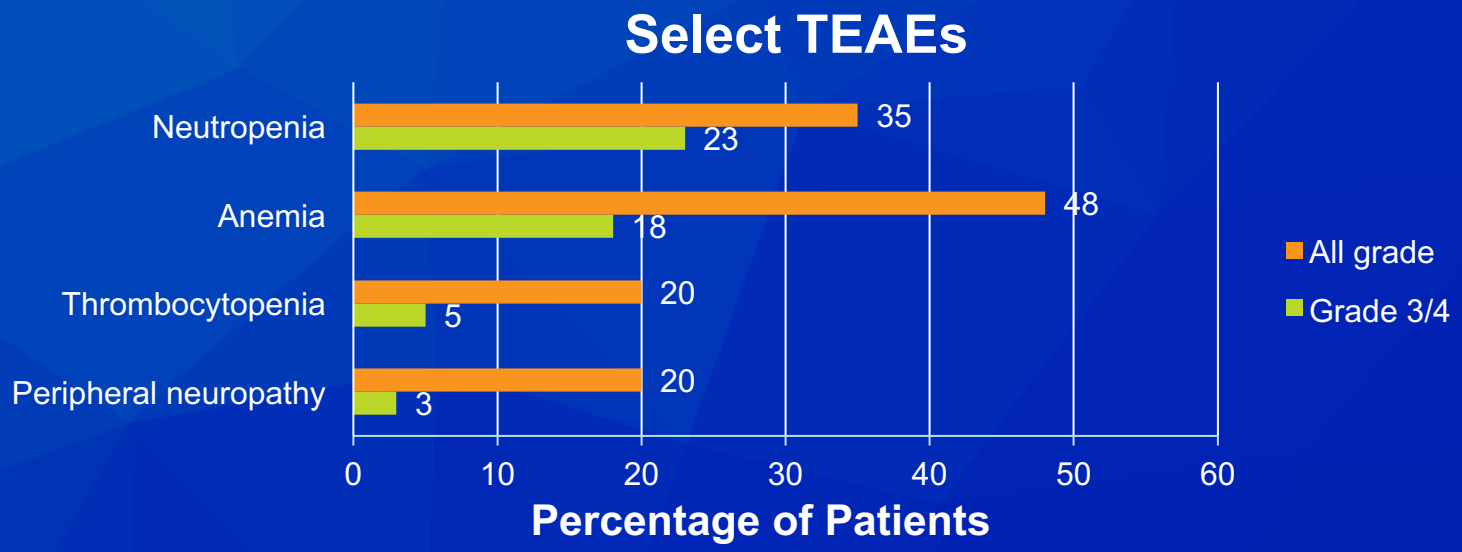
Adverse event	Arm A (n = 68)	Arm B (n = 70)
Grade ≥2 PN or Grade ≥3 myelosuppression	76%	77%
Grade ≥2 PN	37%	36%
Grade ≥3 myelosuppression	71%	64%
Neutropenia	57%	56%
Anemia	21%	24%
Thrombocytopenia	25%	17%

Endpoint	Arm A (n = 71)	Arm B (n = 72)	HR	*p*
ORR	24%	40%	—	—
Median PFS	3.58 mo	6.97 mo	0.48	0.0019
Median OS	15.18 mo	16.23 mo	0.72	0.1966

Langer CJ et al. *Proc ASCO* 2017;Abstract 9059.

ABOUND.PS2: Discontinuation of Treatment, Efficacy and Select Treatment-Emergent Adverse Events (TEAEs)

Endpoints	All treated patients (N = 40)
Discontinuation during induction	24 (60%)
Due to TEAE **(primary endpoint)**	11 (28%)
Discontinuation during monotherapy	16 (40%)
Median PFS	4.4 mo
Median OS	7.7 mo
ORR	12 (30%)



Gajra A et al. *Proc ASCO* 2017;Abstract 9058.

Editorial — Dr Hanna

The risk-benefit of chemotherapy in fit patients with metastatic non-small cell lung cancer generally favors treatment. However, those with diminished end organ function, such as elderly patients above the age of 70, or those at higher risk for side effects, namely those with performance status of 2, must be studied separately. Langer and colleagues evaluated the safety and efficacy of *nab* paclitaxel plus carboplatin in elderly patients with advanced non-small cell lung cancer. Treatment was as follows: carboplatin AUC 6 on day 1 and *nab* paclitaxel 100 mg/m^2 on days 1, 8, and 15 every 3 weeks or every 4 weeks. Approximately 70 patients were treated in each arm.

Editorial — Dr Hanna (continued)

The primary endpoint (grade 2 or higher neuropathy or grade 3 or higher myelosuppression) was similar on both arms. Patients receiving the every 4-week schedule were able to receive a median of 5.5 cycles compared with 4 cycles on the every 3-week regimen. Dose reductions and missing doses were more common on the every 3-week schedule. The median progression free survival favored the 4-week schedule (3.9 vs 7 months, HR 0.49, p=0.003). Median overall survival also favored the every 4-week arm (15.2 vs 16.2 months, HR 0.76, p=0.292). In a separate study, Gajra evaluated the safety and efficacy of carboplatin AUC 5 on day 1 plus *nab* paclitaxel 100 mg/m^2 on days 1 and 8 every 3 weeks in patients with an ECOG performance status of 2.

Editorial — Dr Hanna (continued)

The primary endpoint was the percentage of patients discontinuing treatment in the first 4 cycles. Forty patients were treated and 31 of 40 patients were able to complete at least 4 cycles of therapy. The regimen resulted in grade 3 or higher neutropenia in 9 of the 40 patients.

Taken together this data suggests that *nab* paclitaxel plus carboplatin is a reasonable option for elderly patients (given on the every 4-week schedule) and those with performance status of 2. I have used this regimen on clinical trials. One potential advantage of *nab* paclitaxel is the lack of need for dexamethasone to prevent hypersensitivity reactions. This may be especially important when combining chemotherapy with checkpoint inhibitors, where the use of steroids may be counterproductive to the efficacy of these agents.

Lung Cancer — Drs Pennell and Socinski

EGFR Tumor Mutations

ALK Rearrangements

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

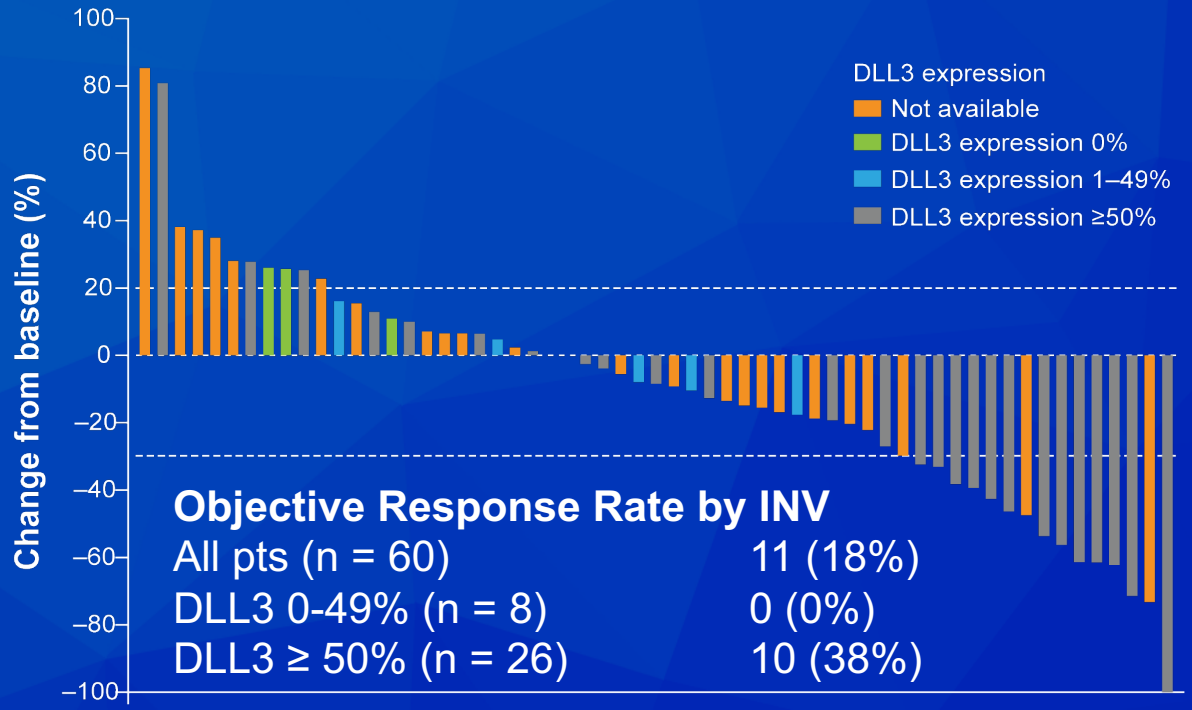
Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study

*Charles M Rudin, M Catherine Pietanza, Todd M Bauer, Neal Ready, Daniel Morgensztern, Bonnie S Glisson, Lauren A Byers, Melissa L Johnson, Howard A Burris III, Francisco Robert, Tae H Han, Sheila Bheddah, Noah Theiss, Sky Watson, Deepan Mathur, Bharathi Vennapusa, Hany Zayed, Satwant Lally, Donald K Strickland, Ramaswamy Govindan, Scott J Dylla, Stanford L Peng, David R Spigel, for the SCRX16-001 investigators**

Lancet Oncol 2017; 18: 42–51

Select Side Effects and Response to Rovalpituzumab Tesirine

Most frequent ≥ Gr 3 AEs	All patients (N = 74)
Thrombocytopenia	8 (11%)
Pleural effusion	6 (8%)
Increased lipase	5 (7%)



INV = investigator assessment

Rudin CM et al. *Lancet Oncol* 2017;18(1):42-51.

Editorial — Dr Hanna

The treatment of metastatic small cell lung cancer in the second- or third-line setting remains a vexing problem. Effective agents have been elusive in this setting. Rudin and colleagues report the results of a first-in-class agent, rovalpituzumab tesirine (Rova-T). This is an antibody-drug conjugate that binds an antibody to the delta-like protein (DLLR) expressed in more than 80% of small cell lung cancers. In this trial 74 patients with small cell lung and 8 patients with large cell neuroendocrine cancers were treated.

The dose-limiting side effects were grade 4 thrombocytopenia and grade 4 liver function tests. In addition, pleural effusions (non-malignant) were reported in 8% of patients.

Editorial — Dr Hanna (continued)

Confirmed objective responses were reported in 18% of assessable patients, including 38% of patients with high DLL3 expression (50% or more of tumor cells). Antonio Rossi provided an accompanying editorial to the study. Rossi notes that intriguing response rate in this group of patients, especially in the high DLL3 expressers. However, the progression-free and overall survival were modest. Rossi also emphasizes the novelty of the DLL3 biomarker and the potential to target other antibody-drug conjugates against it.

In my view, Rova-T is potentially a new therapeutic agent in the treatment of patients with metastatic small cell lung cancer. It is given once every 6 weeks for two treatments only.

Editorial — Dr Hanna (continued)

In addition to myelosuppression, Rova-T can also result in third spacing (pleural and pericardial effusions, ascites, and peripheral edema) that can persist despite repetitive drainage. In addition, some patients experience significant skin toxicity. Despite these challenges, the drug is clearly active in the chemo-resistant patient population. The Trinity trial is a single-arm trial of Rova-T in the second- and third-line setting. The results of this study may provide sufficient evidence for regulatory approval. If this occurs, incorporation of Rova-T into other settings should be explored, including concomitantly with chemotherapy, as maintenance therapy, in combination with immunotherapy, and in the limited stage setting.

Phase II Study of Maintenance Pembrolizumab (pembro) in Extensive Stage Small Cell Lung Cancer (ES-SCLC) Patients (pts)

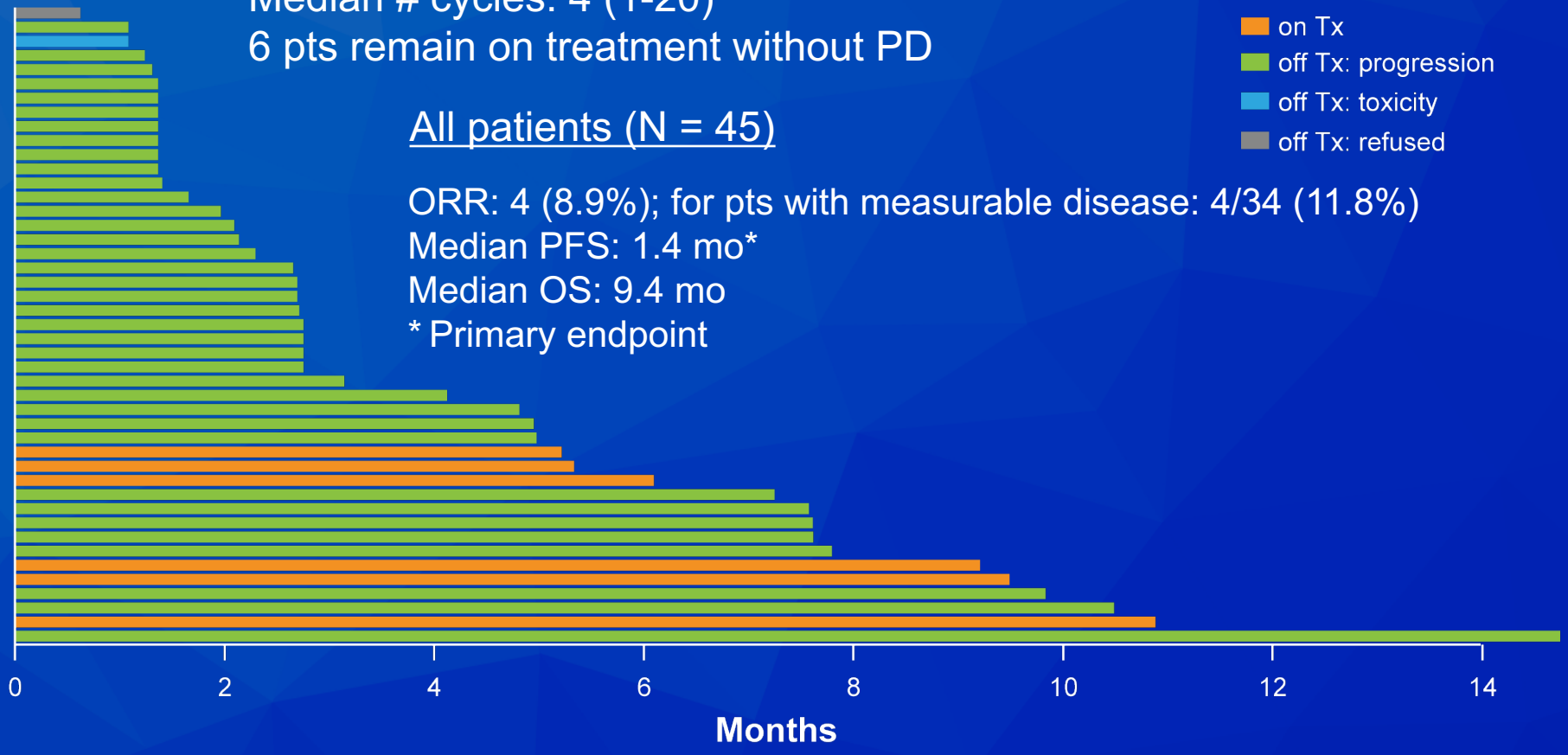
Gadgeel SM et al.
Proc ASCO 2017;Abstract 8504.

Survival, Response and Duration of Treatment with Maintenance Pembrolizumab

Duration of treatment

Median # cycles: 4 (1-20)

6 pts remain on treatment without PD



All patients (N = 45)

ORR: 4 (8.9%); for pts with measurable disease: 4/34 (11.8%)

Median PFS: 1.4 mo*

Median OS: 9.4 mo

* Primary endpoint

Gadgeel SM et al. *Proc ASCO* 2017;Abstract 8504.

Editorial — Dr Hanna

No substantial gains have been made in the treatment of patients with metastatic small cell lung cancer in 2 decades. Pembrolizumab, an antibody to PD-1, is active in patients with squamous and nonsquamous non-small cell lung cancer. Gadgeel and colleagues assessed the role of pembrolizumab as maintenance therapy in patients with extensive stage small cell lung cancer achieving a response to 4-6 cycles of initial chemotherapy. Forty-five patients were enrolled and treated with pembrolizumab every 3 weeks for up to 2 years. Progression-free survival was the primary endpoint.

The median progression-free survival was only 1.4 months and the 6-month progression-free survival was 21%. The median overall survival was 9.4 months.

Editorial — Dr Hanna (continued)

Six patients remain on therapy without disease progression (8-15 cycles). Three of 10 patients assessed had PD-L1 positivity in their tumor samples. The authors concluded that maintenance pembrolizumab did not improve median progression-free survival.

This is the first study to test a checkpoint inhibitor as maintenance therapy for patients with extensive stage small cell lung cancer. The trial did not prolong progression-free survival. Another study randomized patients with chemotherapy with or without ipilimumab, which did not result in improved survival. Taken together, the role of checkpoint inhibitors in the first-line treatment of small cell lung cancer has not proven effective thus far.

Editorial — Dr Hanna (continued)

Checkpoint inhibitors are active against small cell lung cancer, and some patients achieve durable responses. “Positive” trials for efficacy are likely to come only in an enhanced patient population selected for a predictive biomarker.

Nivolumab (nivo) ± Ipilimumab (ipi) in Advanced Small-Cell Lung Cancer (SCLC): First Report of a Randomized Expansion Cohort from CheckMate 032

Hellmann MD et al.
Proc ASCO 2017;Abstract 8503.

CheckMate 032: Response and Select AEs — Pooled Cohorts

Overall response	Nivolumab		Nivo + ipi	
Groups	**n**	**ORR**	**n**	**ORR**
Overall population	245	11%	156	22%
Line of therapy				
2nd line	137	12%	98	19%
≥3rd line	108	11%	58	26%
Platinum sensitivity				
Sensitive	133	13%	85	26%
Resistant	110	10%	65	15%
Treatment-related AEs	**Nivolumab (n = 245)**		**Nivo + ipi (n = 156)**	
	Any	**Gr 3-4**	**Any**	**Gr 3-4**
Skin	16%	<1%	36%	6%
Endocrine	8%	0%	21%	3%
Hepatic	6%	2%	12%	6%
Gastrointestinal	5%	0%	24%	8%

Hellmann MD et al. *Proc ASCO* 2017;Abstract 8503.

Editorial — Dr Hanna

Checkpoint inhibitors such as anti-PD-1 and PD-L1 antibodies have demonstrated substantial and durable activity in patients with metastatic non-small cell lung cancer. These agents appear more active in smokers, those with higher PD-L1 tumor proportion scores, and high tumor mutational burden. The vast majority of patients with small cell lung cancer are smokers. Some small cell lung cancers express PD-L1 and have high tumor mutational burdens. Therefore, checkpoint inhibition is rational to study in patients with metastatic small cell lung cancer.

Hellman and colleagues report the updated results of patients with small cell lung cancer treated with nivolumab or nivolumab plus ipilimumab.

Editorial — Dr Hanna (continued)

In the first cohort, 98 patients received nivolumab and 61 received nivolumab plus ipilumumab in a nonrandomized fashion. The second cohort of patients were randomized in a 3:2 fashion to either nivolumab or nivolumab plus ipilimumab. The overall response rate in the nonrandomized and randomized cohort treated with nivolumab was 11%-12%. Those treated with the combination in both cohorts had an overall response rate of 22%-23%. Responses were higher in those with PD-L1 expression. While response rate was higher with the combination in both cohorts, the 3-month progression-free survival was comparable. Grade 3 or 4 treatment-related adverse events were more common in the combination arms.

Editorial — Dr Hanna (continued)

Randomized trials are ongoing to define the role of checkpoint inhibitors in the treatment of small cell lung cancer. The combination of nivolumab plus ipilimumab appears more active than nivolumab alone, although progression-free survival may not be prolonged and toxicities are increased with the combination. Clearly, some patients with small cell lung cancer respond to immunotherapy and some of these responses are durable. Identifying predictive biomarkers in this population will be especially important as those that do not respond have a rapid progression of their disease. Tumor mutational burden may prove to be a better biomarker than PD-L1 status, but confirmatory trials are needed.