Year in Review

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

October 28, 2017, 8:00 AM – 4:00 PM
Orlando, Florida

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Research To Practice®

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Disclosures

Contracted Research	Genentech BioOncology, Pfizer Inc, Takeda Oncology
Paid Travel	Merck
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Disclosures

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Honoraria	ACEA Biosciences Inc, Helsinn Group, Peregrine Pharmaceuticals Inc

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

Lung Cancer — Drs Riely, Wakelee, and Spigel

EGFR-Mutated Disease

ALK-Rearranged Disease

BRAF and Other Targetable Mutations

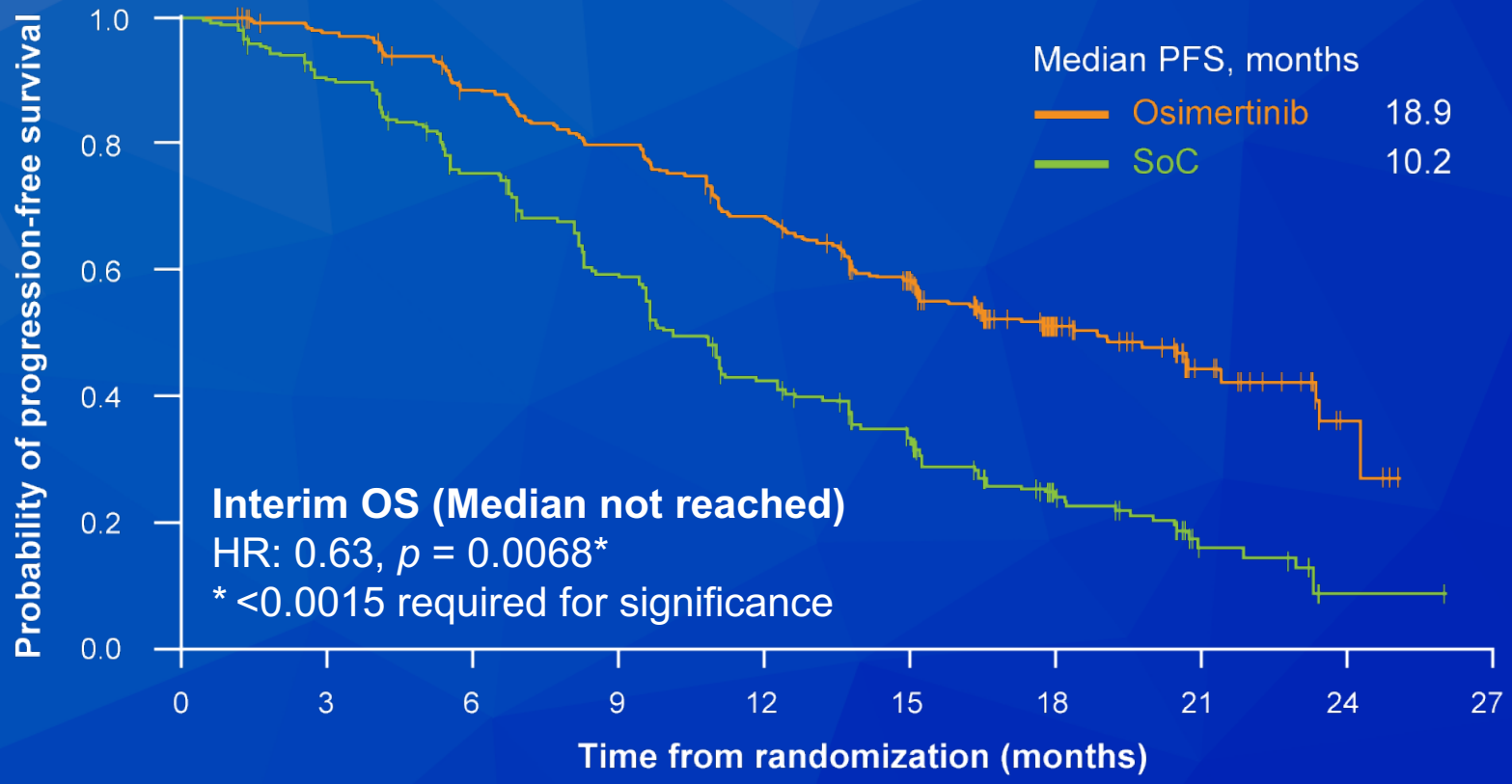
Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

Osimertinib vs Standard-of-Care EGFR-TKI as First-Line Treatment in Patients with EGFRm Advanced NSCLC: FLAURA

Ramalingam SS et al.
Proc ESMO 2017;Abstract LBA2_PR.

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	<0.0001
CNS mets (n = 53, 63)	15.2 mo	9.6 mo	0.47	0.0009
No CNS mets (n = 226, 214)	19.1 mo	10.9 mo	0.46	<0.0001

Ramalingam SS et al. *Proc ESMO* 2017;Abstract LBA2_PR.

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.

Cost and reimbursement issues aside, what adjuvant treatment would you recommend to a 60-year-old patient with Stage IIA NSCLC and an EGFR exon 19 deletion outside of a trial setting?

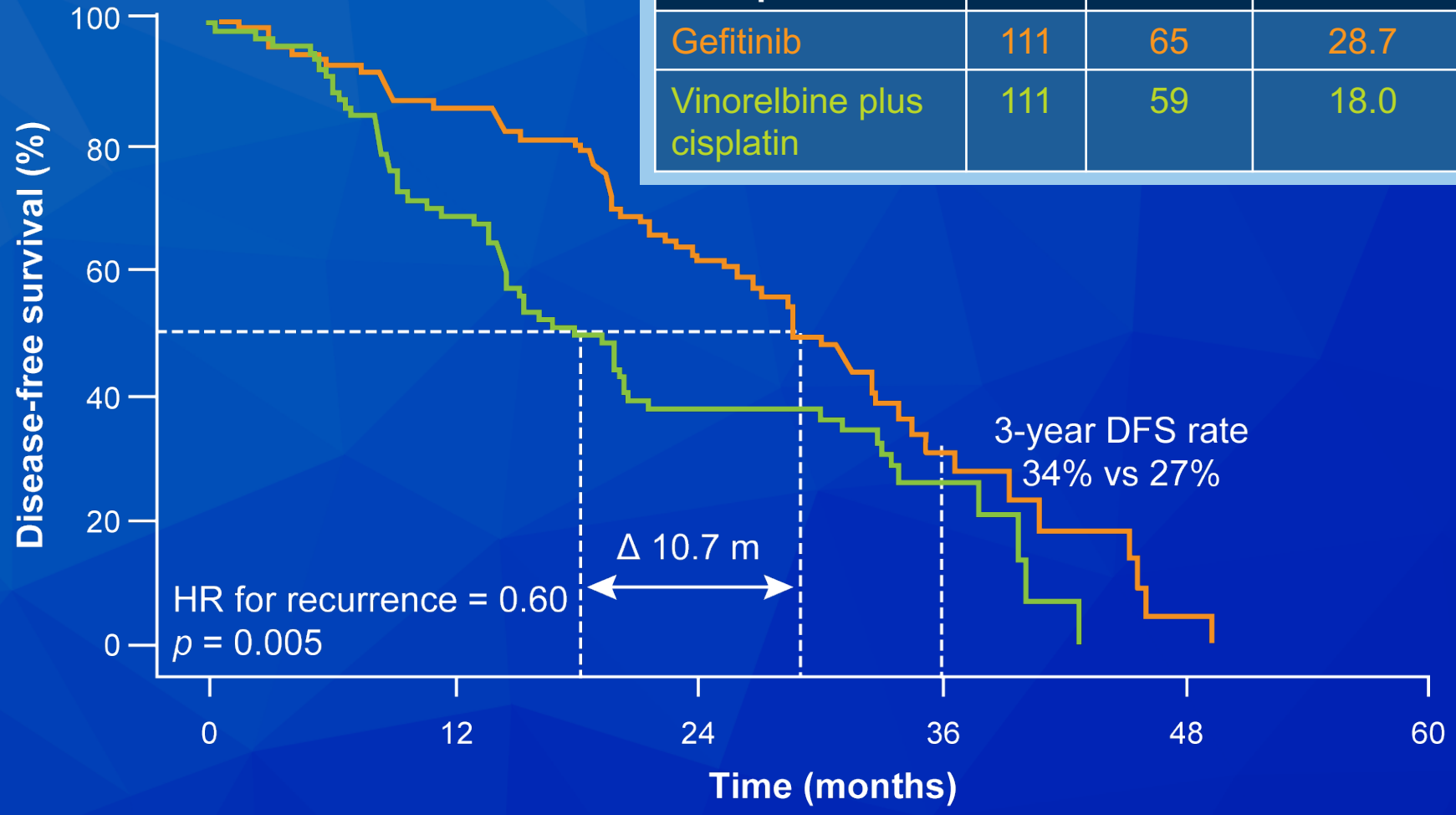
a. Chemotherapy
b. Afatinib
c. Erlotinib
d. Gefitinib
e. Osimertinib
f. Chemotherapy followed by an EGFR TKI
g. None
h. Other

Gefitinib (G) versus Vinorelbine + Cisplatin (VP) as Adjuvant Treatment in Stage II-IIIA (N1-N2) Non-Small-Cell Lung Cancer (NSCLC) with EGFR-Activating Mutation (ADJUVANT): A Randomized, Phase III Trial (CTONG 1104)

Wu YL et al.
Proc ASCO 2017;Abstract 8500.

ADJUVANT Primary Endpoint: DFS (ITT Population)

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



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

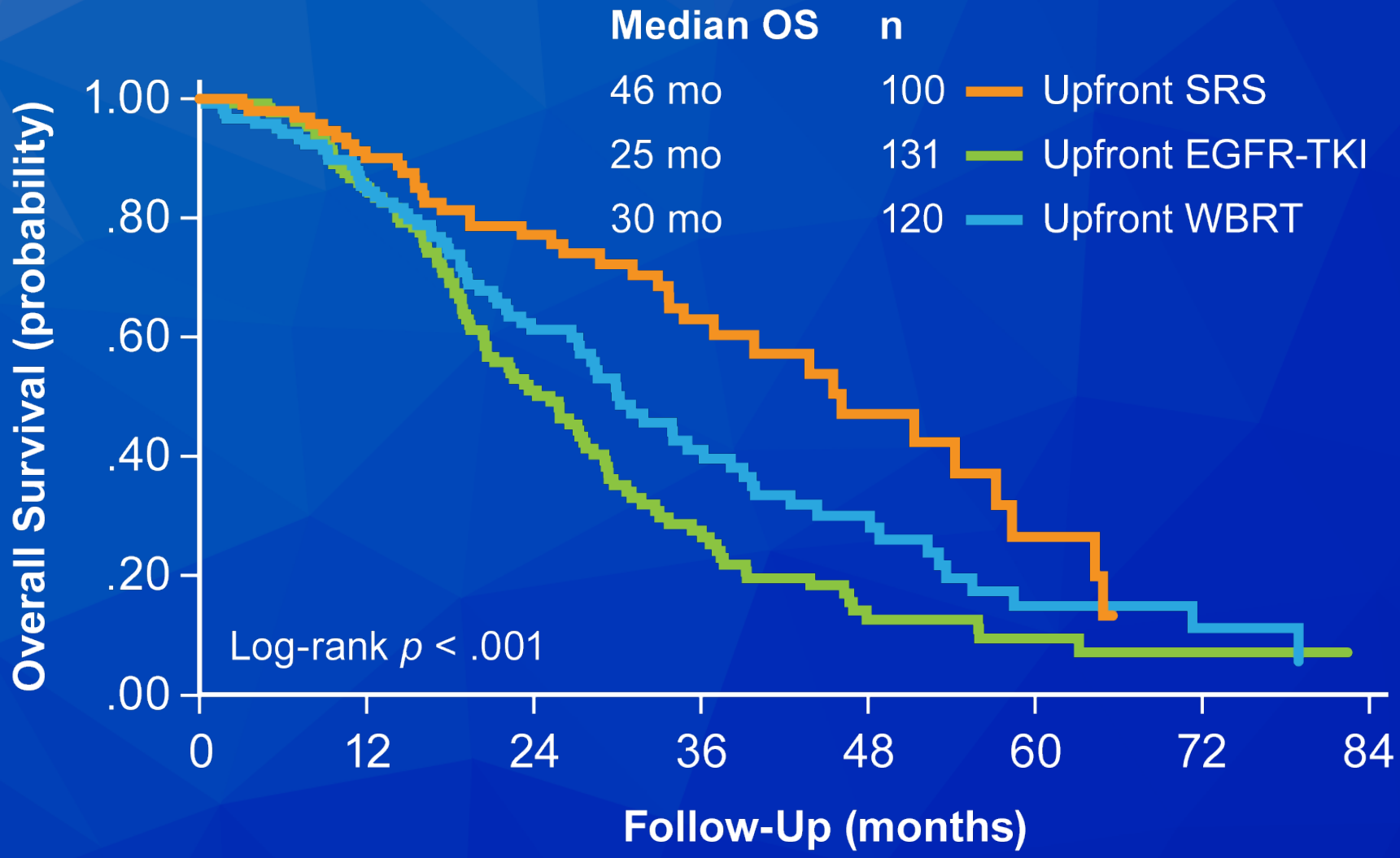
JOURNAL OF CLINICAL ONCOLOGY

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 Riely, Wakelee and Spigel

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Small Cell Lung Cancer

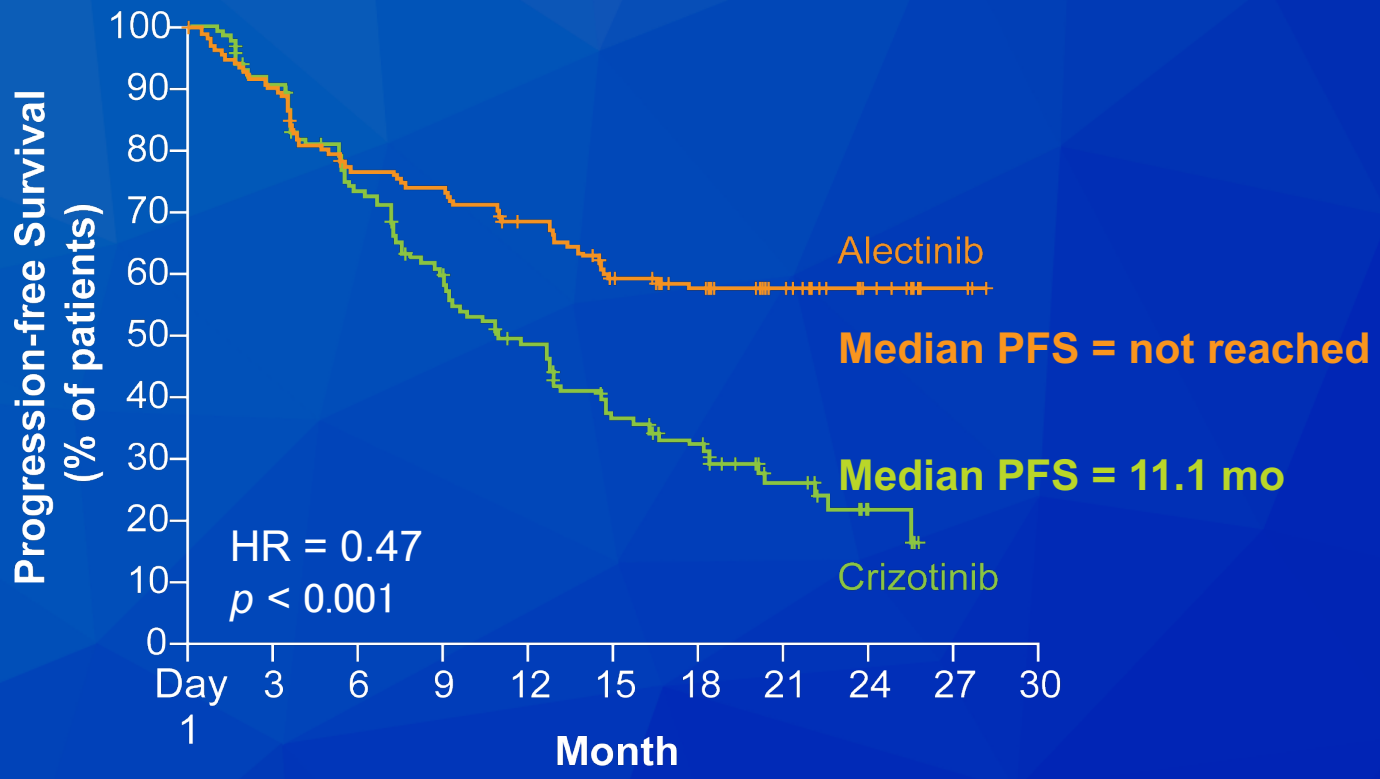
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2017;377:829-38

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.

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

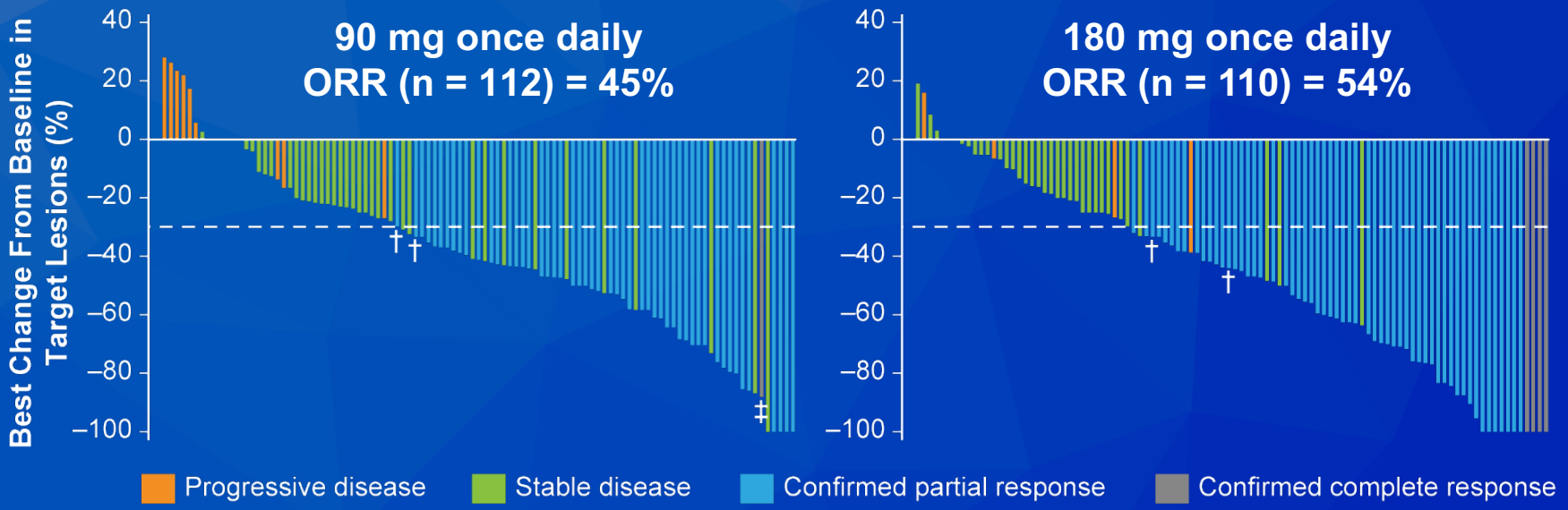
JOURNAL OF CLINICAL ONCOLOGY

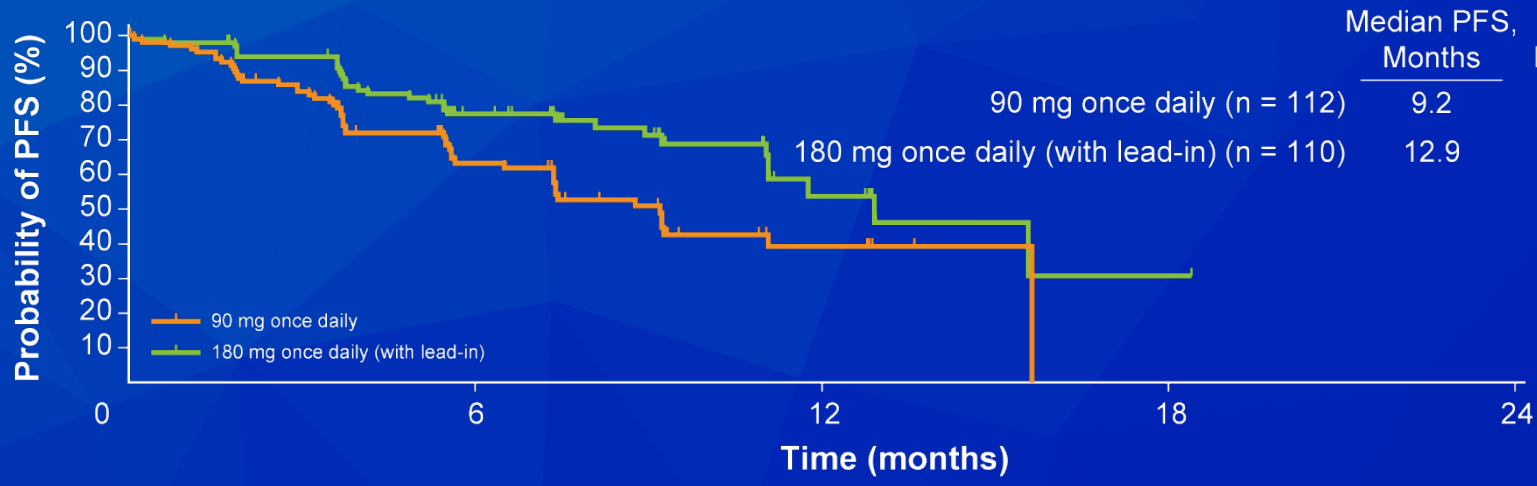
ORIGINAL REPORT

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 and PFS with Brigatinib 90 mg and 180 mg Daily Dosing





	Median PFS, Months	6-Month PFS Probability, %
90 mg once daily (n = 112)	9.2	63
180 mg once daily (with lead-in) (n = 110)	12.9	78

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.

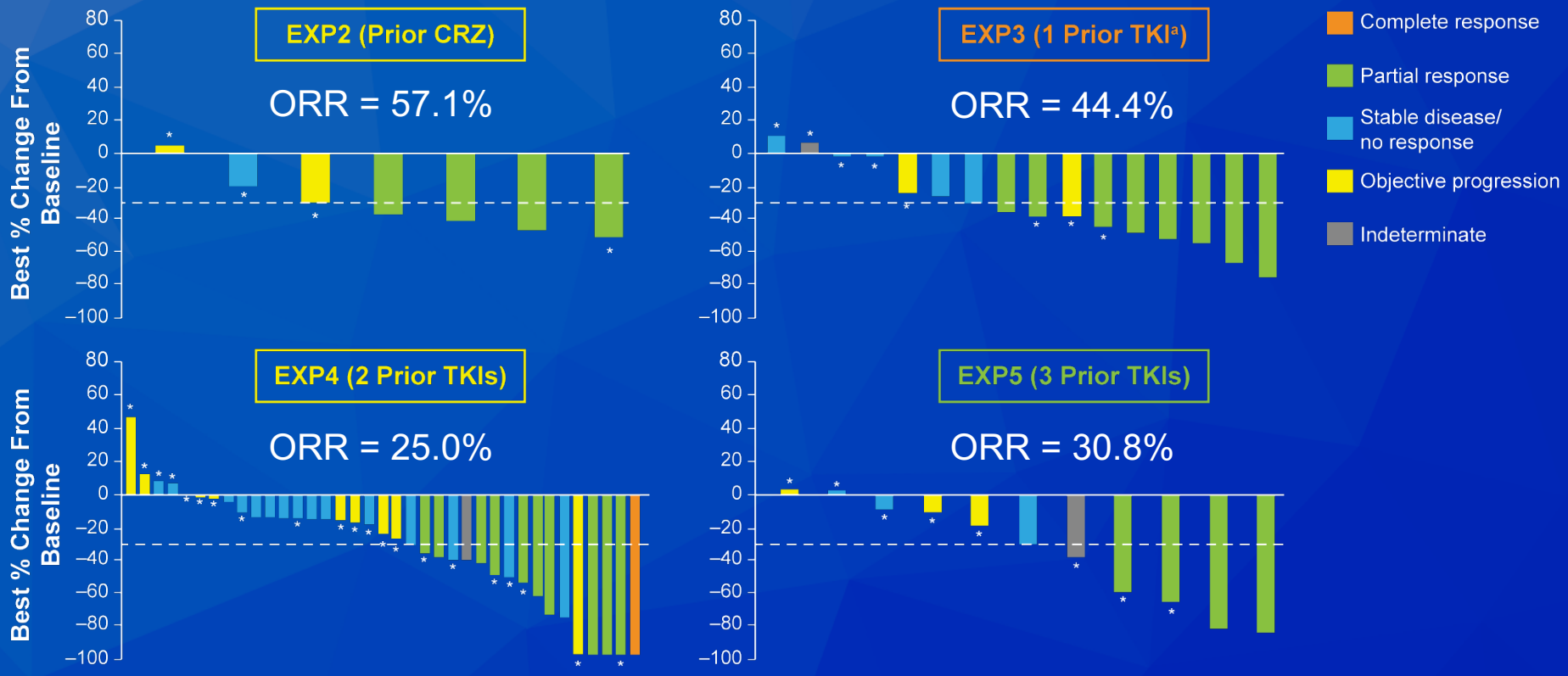
Editorial — Dr Riely (continued)

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.

Efficacy and Safety of Lorlatinib in ALK+ Non-Small Cell Lung Cancer (NSCLC) Patients (pts) with >1 Prior ALK Tyrosine Kinase Inhibitor (TKI): A Phase 1/2 Study

Shaw AT et al.
Proc ASCO 2017;Abstract 9006.

ORR, Best Response and Intracranial ORR with Lorlatinib



ALK = anaplastic lymphoma kinase; CRZ = crizotinib; TKI = tyrosine kinase inhibitor

[a] Prior CRZ + chemotherapy or 1 other ALK TKI ± chemotherapy

* Off treatment or disease progression

Intracranial ORR

Target + non-target lesions: 25/52 (48.1%); target lesions: 18/35 (51.4%)

Shaw AT et al. *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

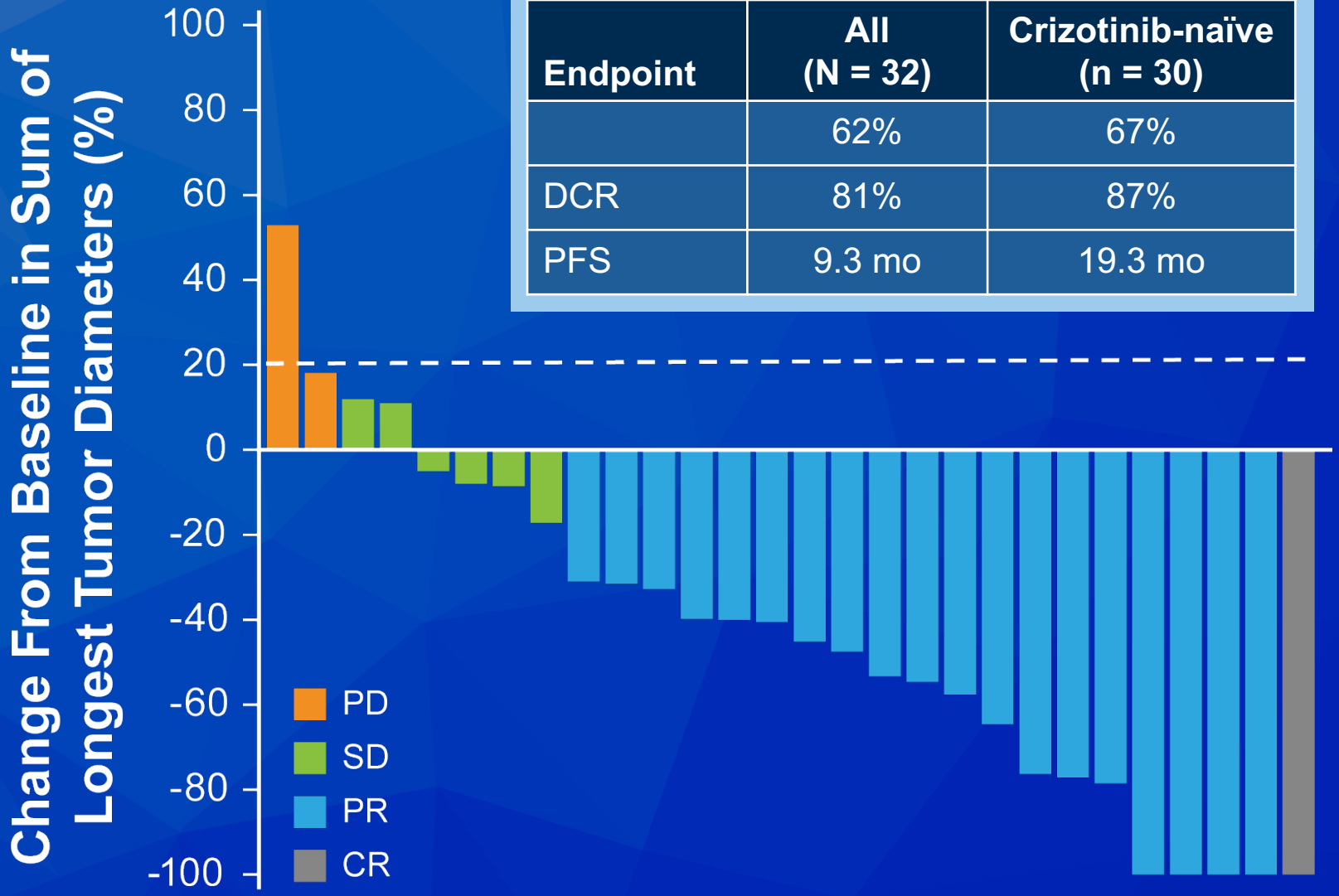
ORIGINAL REPORT

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)
	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 Riely, Wakelee and Spigel

EGFR-Mutated Disease

ALK-Rearranged Disease

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

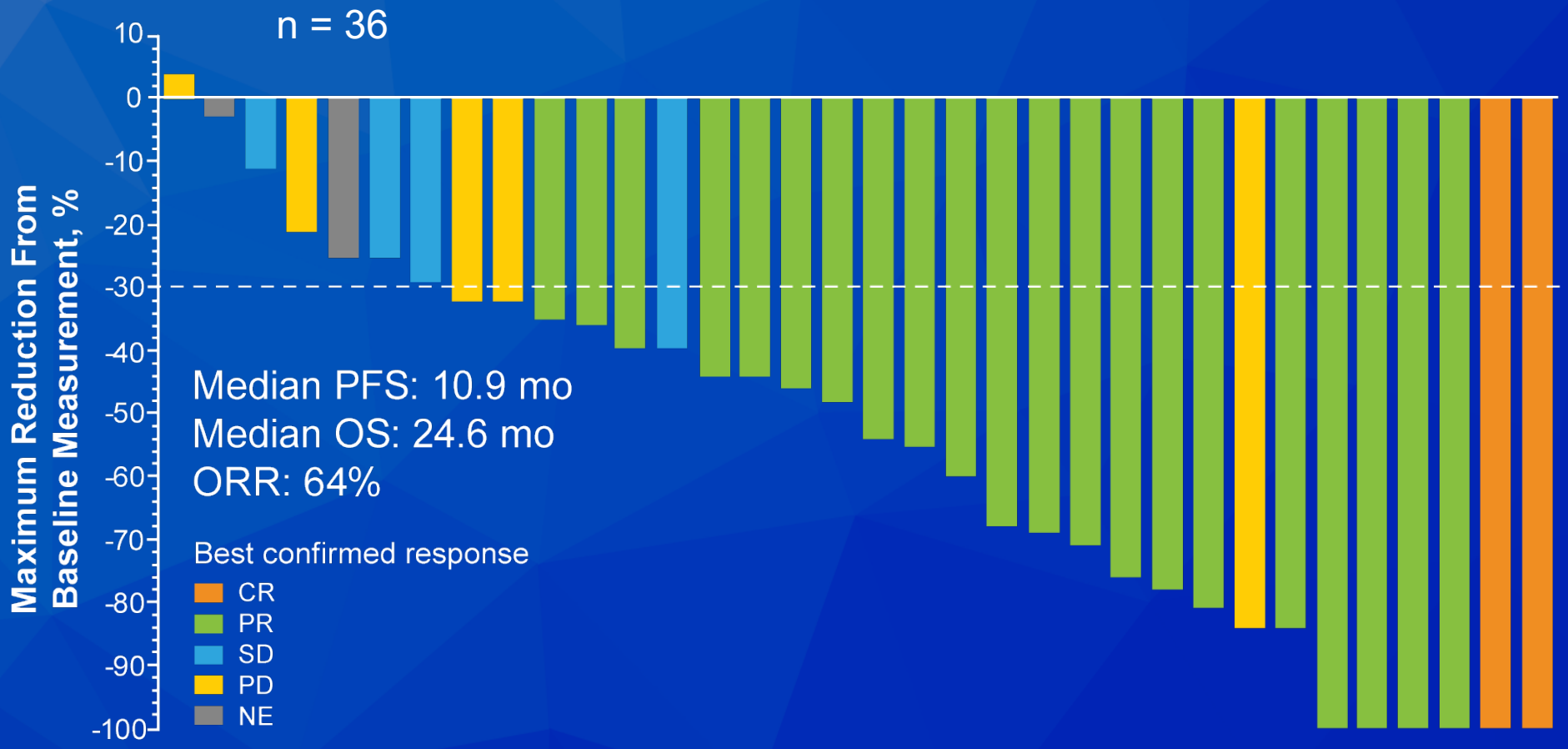
Which genomic alterations do you feel must be ruled out prior to initiation of first-line therapy for a patient with metastatic nonsquamous lung cancer in addition to EGFR, ALK and ROS1?

a. BRAF V600E mutation
b. MET exon 14 mutation
c. RET rearrangement
d. HER2 mutation/amplification
e. Other

Phase 2 Trial (BRF113928) of Dabrafenib (D) Plus Trametinib (T) in Patients (pts) with Previously Untreated BRAF V600E–Mutant Metastatic Non-Small Cell Lung Cancer (NSCLC)

Planchard D et al.
Proc ESMO 2017;Abstract LBA51.

Investigator-Assessed Response and Survival with Dabrafenib and Trametinib



Planchard D et al. *Proc ESMO* 2017;Abstract LBA51.

Editorial — Dr Wakelee

It is known that BRAF mutations represent 2% of driver mutations of lung adenocarcinoma, but not all are the V600E mutation that is most responsive to targeted therapy. Approximately 1.5% of adenocarcinoma of the lung harbor the BRAF V600E mutation. Planchard and colleagues have previously presented data on the efficacy of trametinib/dabrafenib in this patient population for previously treated patients. This study was focused on a cohort of previously untreated patients. We know from previous data that the ORR is 67% with the combination in previously treated patients, with a PFS of 10.2 months.

In total 36 patients were enrolled on the current study and treated with dabrafenib and trametinib with a median follow-up of 15.9 months for this presentation.

Editorial — Dr Wakelee (continued)

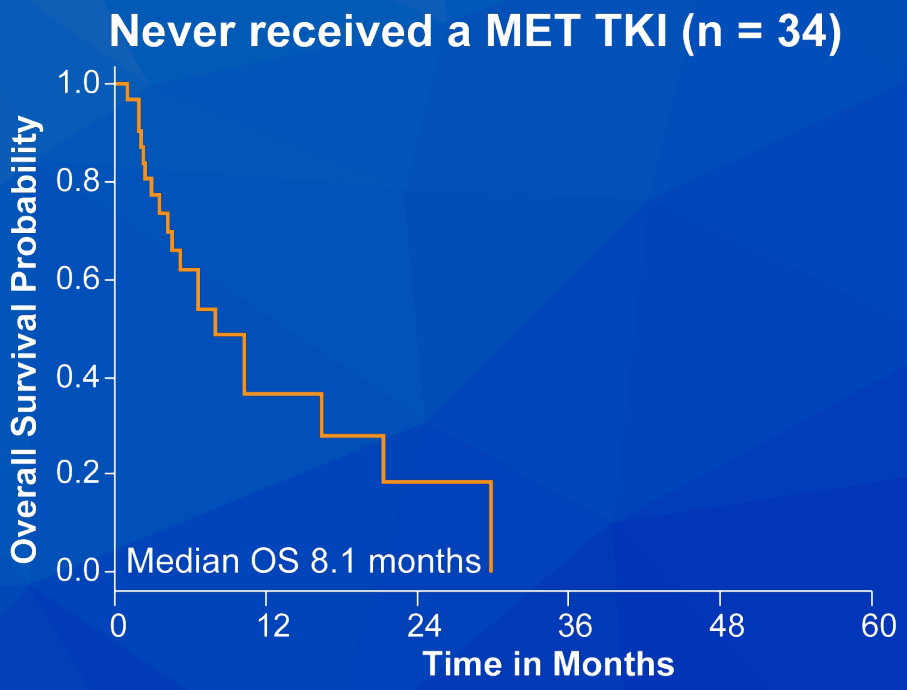
The overall response rate was 64% with a limited number (2) of complete responses. Median PFS was 10.9 months per investigator and 14.6 months by independent review. Overall survival is 24.6 months as of this report. No new safety signals were identified.

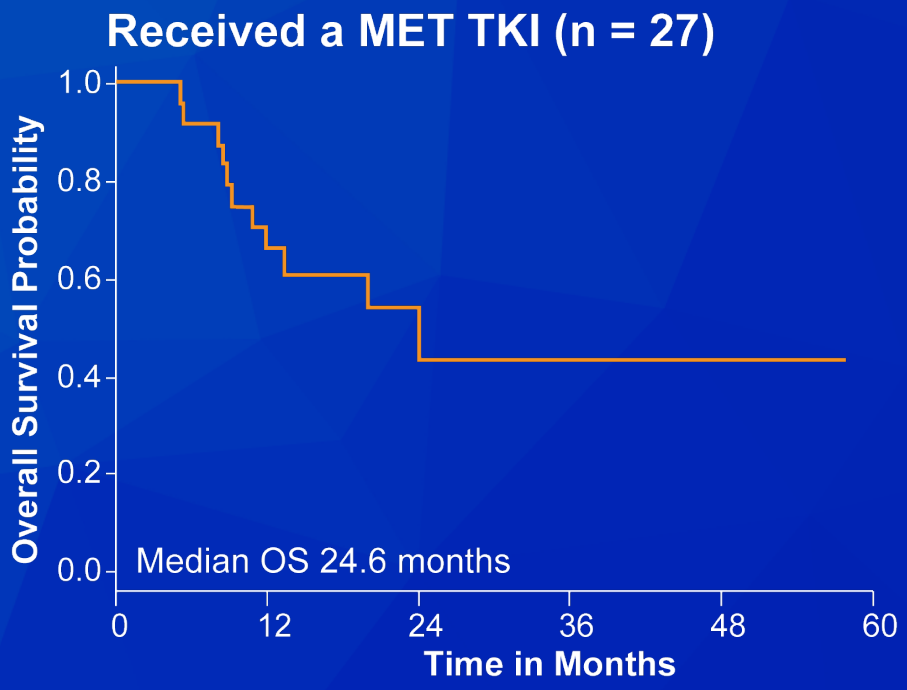
This study supports the current US FDA and European commission approvals of the combination of dabrafenib and trametinib for any metastatic NSCLC patient with BRAF V600E mutation regardless of prior treatment history.

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.

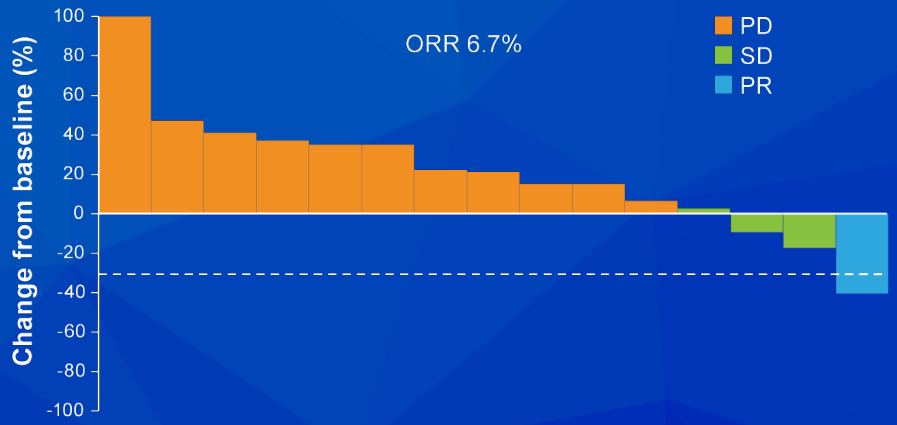
PD-L1 Expression and Response to Immunotherapy in Patients with MET Exon 14-Altered Non-Small Cell Lung Cancers (NSCLC)

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

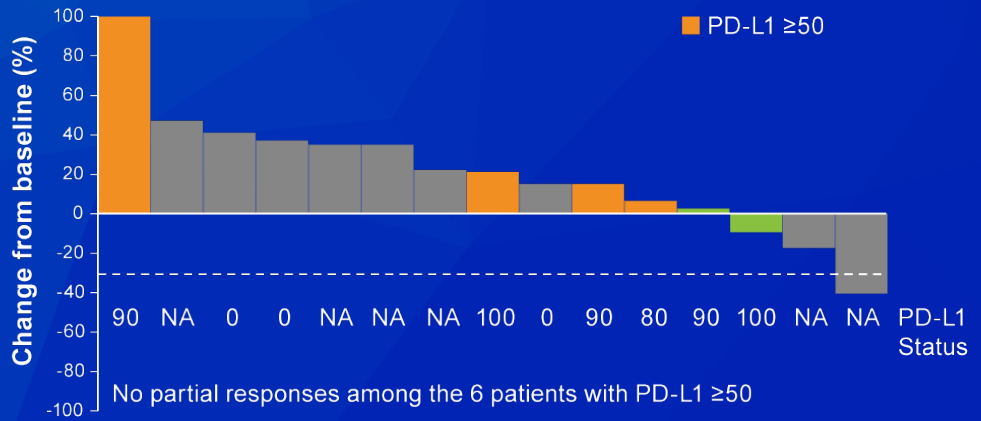
PD-L1 Expression in MET Exon 14-Altered NSCLC (N = 54) and Response to Immunotherapy (N = 15)

	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 Wakelee

MET exon 14 altered NSCLC represents 3%-4% of all non-squamous NSCLC and 20%-30% of sarcomatoid lung cancers and is recognized as a true driver mutation. High response rates have been noted with crizotinib especially and multiple other MET targeted TKIs additionally. In this analysis, a group from Memorial Sloan Kettering and Columbia University in New York looked at PD-L1 and response to immunotherapy in patients with MET exon 14 altered NSCLC. This was a retrospective review of 81 patients and they utilized PD-L1 staining with the E1L3N assay as well as looking at tumor mutational burden.

Editorial — Dr Wakelee (continued)

Only 20 of the 81 patients received immunotherapy, and 5 were on trials and thus not included in this analysis. Therefore this work only included 15 patients who were treated with IO. Of the 15, 6 of them did not have PD-L1 testing due to insufficient tissue, thus only 9 patients had IHC testing for PD-L1 and were also treated with IO. In this presentation the authors did describe the 81 MET altered NSCLC patients and identified that the median age was 73 years old, 58% were female, 42% had never smoked. Patients with pleomorphic histology were more likely to have high PD-L1 expression (7/11 versus 16/38 with adenocarcinoma). Tumor mutational burden (TMB) on average was lower in patients with MET exon 14 alterations compared to all NSCLC patients.

Editorial — Dr Wakelee (continued)

Only 1 patient of the 15 IO treated patients had a PR with immunotherapy, with SD noted in 3 others and PD in the majority. The responding patient did not have high PD-L1 expression and none of the 6 with high PD-L1 expression responded, nor did any of the 5 with high TMB. The take home from this presentation is that though PD-L1 expression can be high in some MET exon 14 alteration tumors, the TMB tends to be low in this group and response to PD-(L)1 checkpoint inhibitors is low.

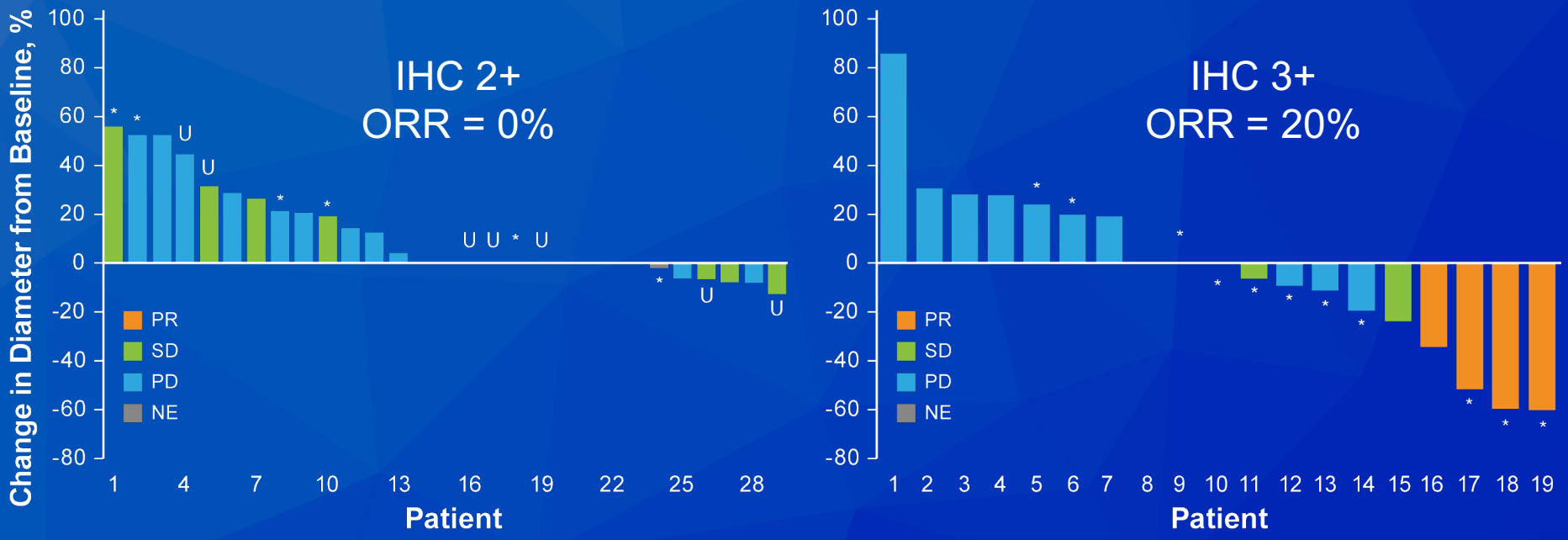
This adds to our growing understanding that patients with single driver mutations are not the best patients for single agent checkpoint inhibitor therapy, regardless of PD-L1 expression.

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

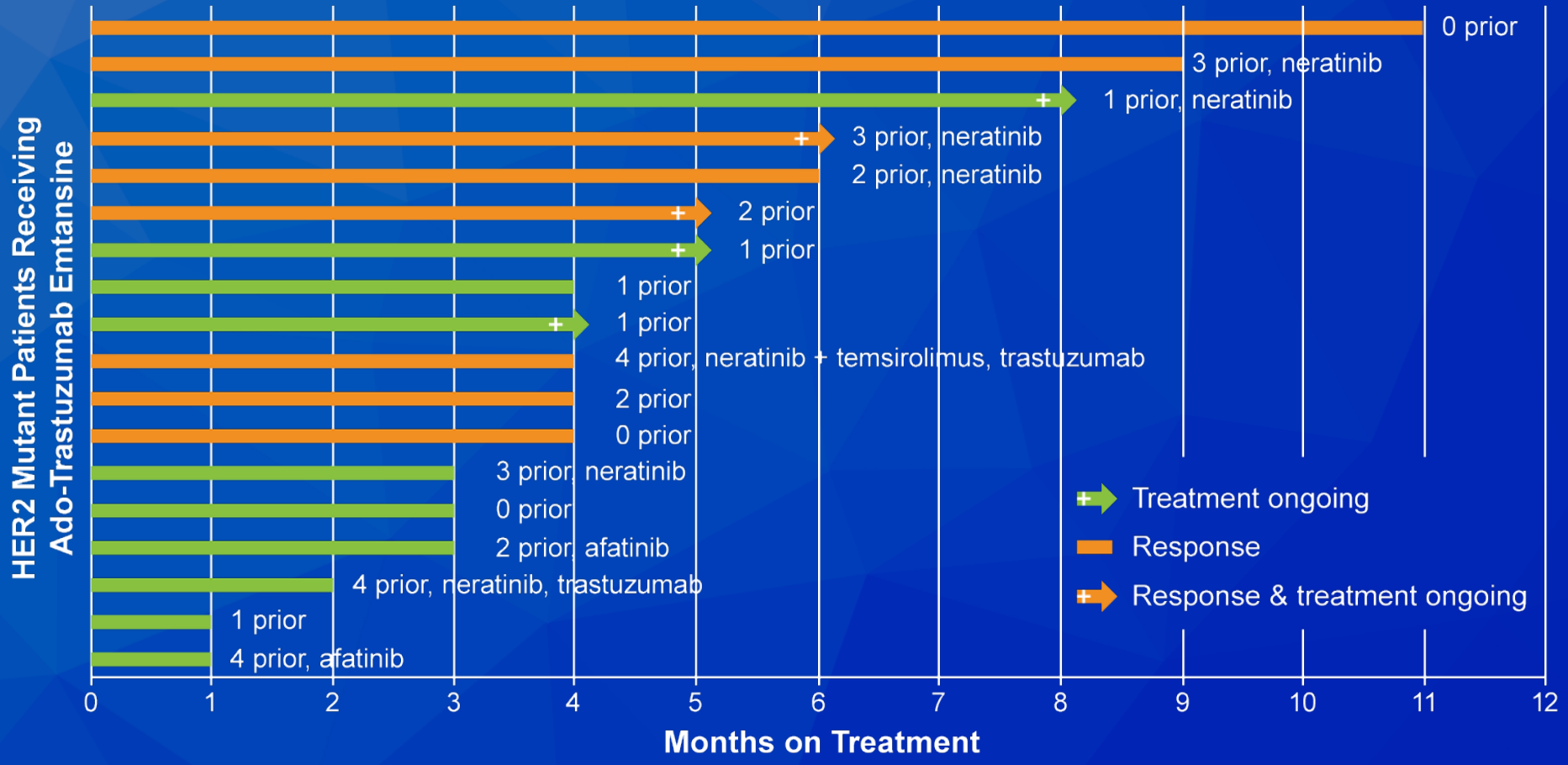
	IHC 2+ (n = 29)	IHC 3+ (n = 20)	All (N = 49)
Median PFS	2.6 mo	2.7 mo	2.6 mo
Median OS	12.2 mo	12.1 mo	12.2 mo

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 Wakelee

HER2 mutant lung cancer is a small but real proportion of patients with NSCLC and is a true driver mutation. At ASCO 2017 we had 2 trials looking at the use of trastuzumab emtansine (T-DM1) in HER2 advanced stage NSCLC patients either selected for overexpression of HER2 (Stinchcombe) or by HER2 mutation (Li). T-DM1 is a HER2 targeted antibody-drug conjugate used to treat HER2 positive breast cancer (defined by high HER2 expression). HER2 overexpression occurs in 15%-30% of NSCLC (IHC2+/3+ with 2%-6% IHC3+), with amplification seen in only 2%-6% and true driver mutations in 1%-5%.

Editorial — Dr Wakelee (continued)

The study presented by Stinchcombe et al enrolled previously treated NSCLC patients who had HER2 expression (IHC2+/3+) to standard dose T-DM1 of 3.6 mg/kg IV every 3 weeks. ORR was the primary endpoint. HER2 amplification was explored. Over a period of 18 months a total of 49 patients were enrolled of whom 20 were women, 10 were never-smokers and most had adenocarcinoma (N = 35). Most had no known driver mutation, but 4 had EGFR exon 20 insertion. No patients with IHC2+ responded, but the ORR was 20% for the IHC3+ group with 4 patients achieving a PR.

Editorial — Dr Wakelee (continued)

Of the 4 patients who responded, one had a HER2 mutation, another had a HER2 gene rearrangement and IHC3+ and amplification of HER2. Another had an EGFR exon 19 mutation. One responder only had IHC3+ and no other amplification or mutations noted.

The presentation by Li et al included patients who were included in a phase 2 basket study that identified patients by HER2 amplification or HER2 mutation and treated them with standard dose T-DM1. A total of 18 HER2 mutant NSCLC patients were identified with a median age of 63, and 13 (72%) were women. Only 7 (39%) were never smokers and 50% had received prior HER2 targeted therapy (neratinib, afatinib or trastuzumab [2 patients]).

Editorial — Dr Wakelee (continued)

The ORR in those with a HER2 mutation was 44% (8/18, CI 22%-69%). Median PFS was 4 months, but many responders had ongoing response at the time of publication. No patients had high IHC expression despite the HER2 mutation, but FISH was positive in 1 patient.

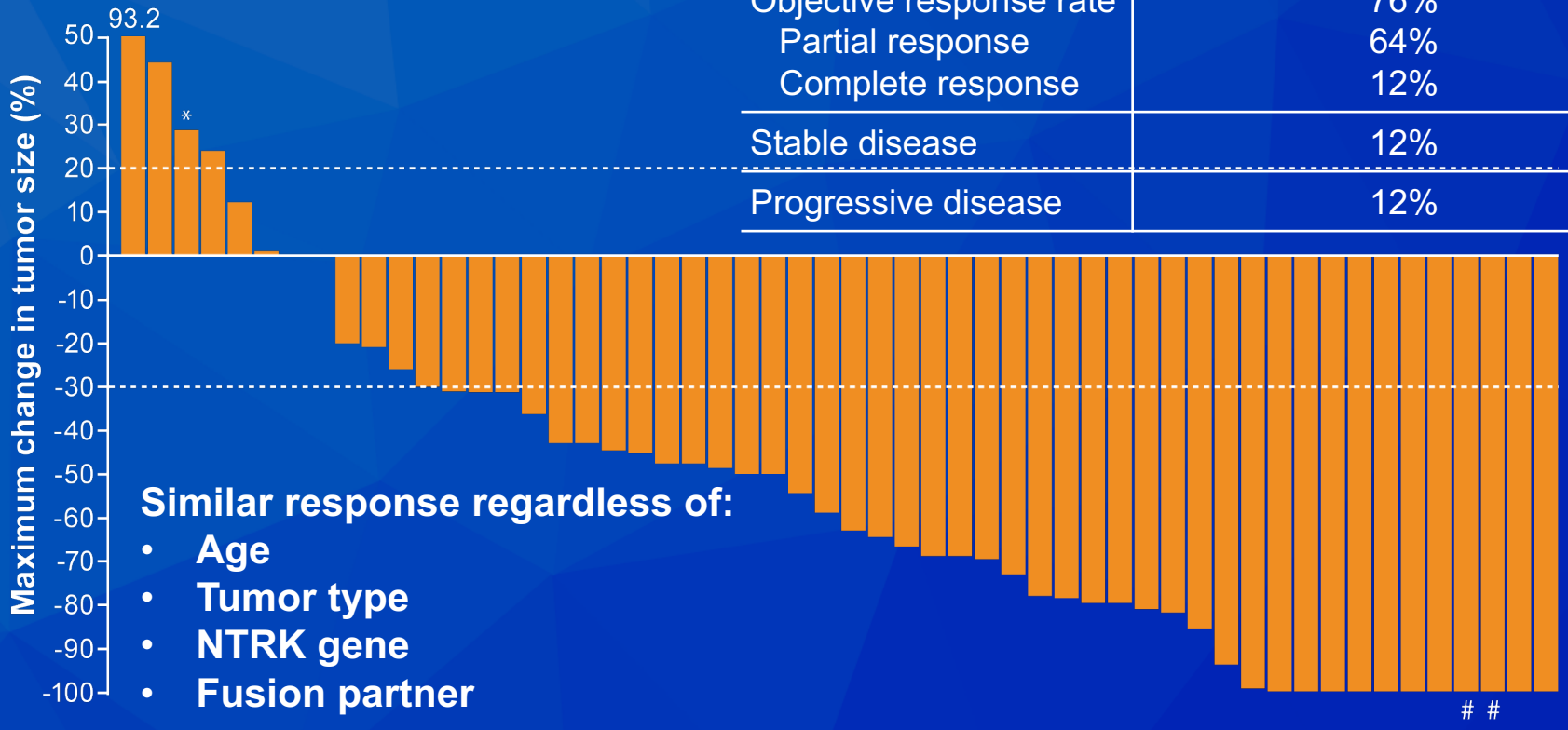
Taken together these 2 abstracts show that HER2 mutation and independently high expression (IHC3+) can be utilized to identify patients who may benefit from HER2 targeted therapy with T-DM1. The response rate (44%) was much higher in the cohort of patients identified by HER2 mutation versus those identified by 3+ IHC expression (20% ORR).

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 Wakelee

TRK fusion cancers are a rare subset of malignancies with an estimated 1,500-5,000 patients annually in the United States (both adult and pediatric). The neurotropin family of receptors have varied neurologic function and are rarely expressed in normal tissue but with fusions can be highly expressed. Larotrectinib is a selective pan-TRK inhibitor. This study was an update on 55 total patients with tumors with NTRK fusions, of whom 4 had lung cancer (7%).

The response rate was a remarkable 78% in the 55 patients with a 12% confirmed complete response rate and 64% confirmed partial response in the 50 patients with confirmatory response data. Of the 4 lung cancer patients 2 had a CR and 1 had a PR. Efficacy has been noted regardless of fusion partner.

Editorial — Dr Wakelee (continued)

Duration of treatment response is very long, and at the time of report 93% of the responding patients were still responding or had undergone a curative intent surgery. The 6 month landmark DOR is 91%. Toxicity overall was minimal with some grade 3 events of fatigue, anemia and transaminitis.

Screening for these TRK fusion proteins can be challenging and requires a focused effort, but given the remarkable responses seen with larotrectinib, with other TRK inhibitors in development, it is very appropriate to include TRK analysis as part of any lung cancer molecular analysis.

Lung Cancer — Drs Riely, Wakelee and Spigel

EGFR-Mutated Disease

ALK-Rearranged Disease

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

The NEW ENGLAND JOURNAL of MEDICINE

Sept 8, 2017;[Epub ahead of print].

ORIGINAL ARTICLE

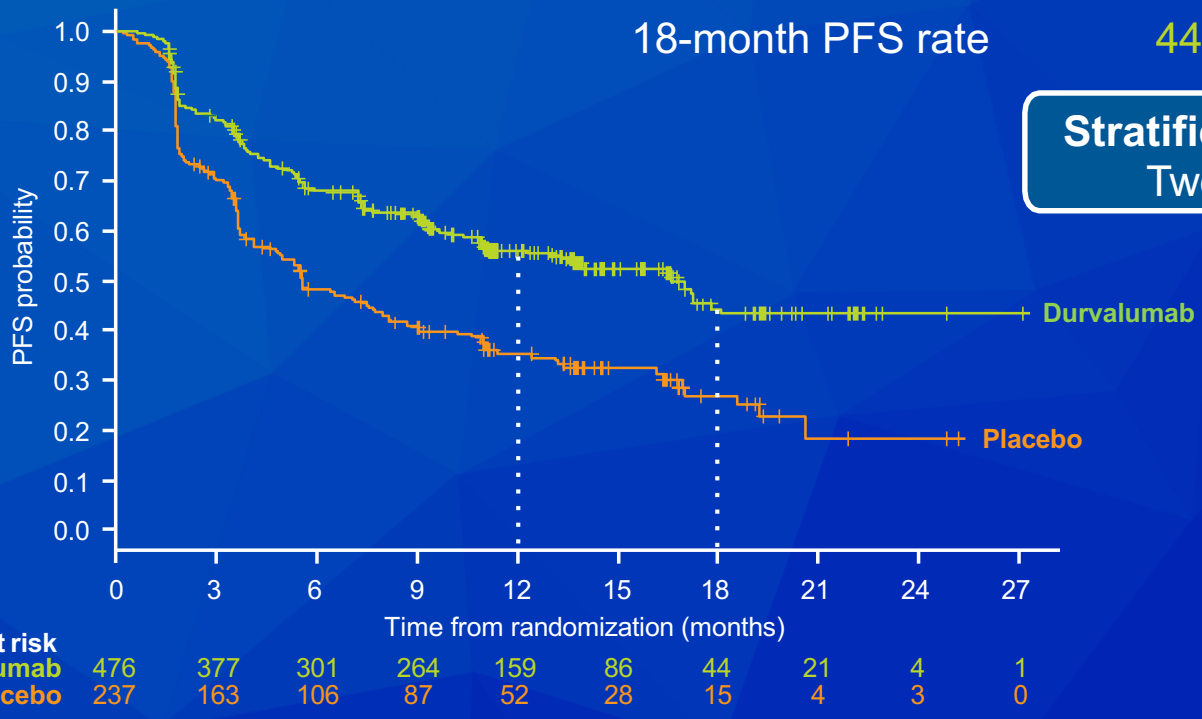
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

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;[Epub ahead of print].

Editorial — Dr Wakelee

PACIFIC, the first large trial utilizing a PD-(L)1 checkpoint inhibitor as adjuvant/consolidation therapy for NSCLC, was presented at ESMO 2017 and simultaneously published in the *NEJM*. The phase III trial randomized patients 2:1 to the PD-L1 inhibitor durvalumab (10 mg/kg IV every 2 weeks for up to 12 months) or placebo, to begin 1-42 days after completion of definitive chemoradiation for stage III NSCLC. Patients on trial had to have completed at least 2 cycles of platinum doublet chemotherapy and radiation to 54-66 Gy with limitations on V20 (volume of lung that had received 20 Gy or more) of less than 35%, and patients' disease could not have progressed. The co-primary endpoints are PFS and OS, but OS endpoints were not assessed yet and not presented.

Editorial — Dr Wakelee (continued)

The study randomized 713 patients, of whom 709 were treated (473 with durvalumab and 236 with placebo), and reported a median PFS from point of randomization of 16.8 months with durvalumab versus 5.6 months without durvalumab, with a stratified HR of 0.52 (95% CI 0.42-0.65, $p < 0.001$). This corresponded to 12 month PFS of 55.9% versus 35.3% and 18 month PFS of 44.2% vs 27.0%. Grade 3+ toxicity was reported in 29.9% of the durvalumab patients versus 26.1% of those on placebo, with pneumonia of grade 3/4 only reported in 4.4% versus 3.8% respectively. Durvalumab was discontinued in 15.4% of patients due to adverse events.

Editorial — Dr Wakelee (continued)

These results are striking and are likely to be practice changing. The only concern is trying to understand the results on the placebo arm, which seem to be worse than expected. Though doing cross-study comparisons is always a dangerous thing to do, the PFS on the placebo arm of PACIFIC does seem somewhat low compared to historical controls. The patients on PACIFIC were selected after completion of chemoradiation and thus were a different, and better, prognosis group than the patients on most stage III chemoradiation trials, given that the rapid progressors and those with significant toxicity were excluded from PACIFIC. Thus one would expect the PFS for the placebo group of PACIFIC to exceed that of historical comparison studies, which included all comers from the point of start of chemoradiation.

Editorial — Dr Wakelee (continued)

One also cannot do a strict comparison as the PFS on PACIFIC was calculated from the time period AFTER completion of chemoradiation therapy plus 1-42 days additional time before randomization. However, if we make a bold assumption that 2-4 months would have elapsed from start of standard chemoradiation to randomization on PACIFIC (to allow for 6-7 weeks of therapy plus 1-42 days after completion to randomization), we can assume that adding those 2-4 months to the median PFS of the placebo arm of PACIFIC (5.6 months) would bring us to 7.6-9.6 months estimated PFS if counting from the start of therapy (which is the start point of comparator trials such as RTOG-0617).

Editorial — Dr Wakelee (continued)

On RTOG-0617 (Bradley et al, *Lancet Oncol* 2015;16:187-99) the median PFS was 10.7 months when looking at the group who did not receive cetuximab (but had either 60 or 74 Gy), and median PFS for the 60 Gy group was 11.8 months (combining the with and without cetuximab patients). Both of these values exceed our rough calculation of the PFS for the placebo arm on PACIFIC counting from start of all therapy. This is despite the fact that the PACIFIC patients would be expected to be a better prognosis group as outlined earlier.

Editorial — Dr Wakelee (continued)

Questions about the poor performance of the placebo group will need to be addressed, and the overall survival data will be critical in determining the uptake of the use of checkpoint inhibitors after completion of chemoradiation in stage III NSCLC. However, it is very likely that this will become a standard approach in the near future.

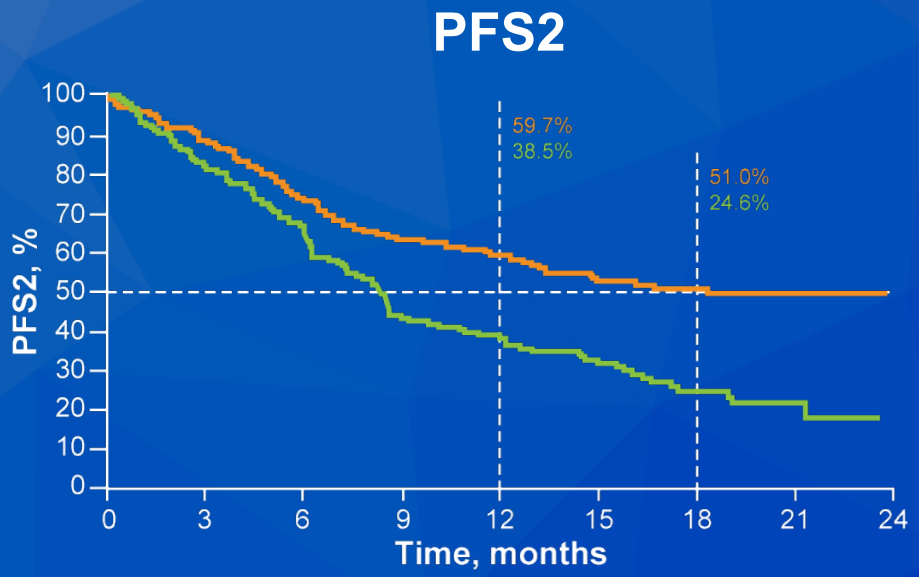
Pembrolizumab versus Chemotherapy for PD-L1-Positive Non–Small-Cell Lung Cancer

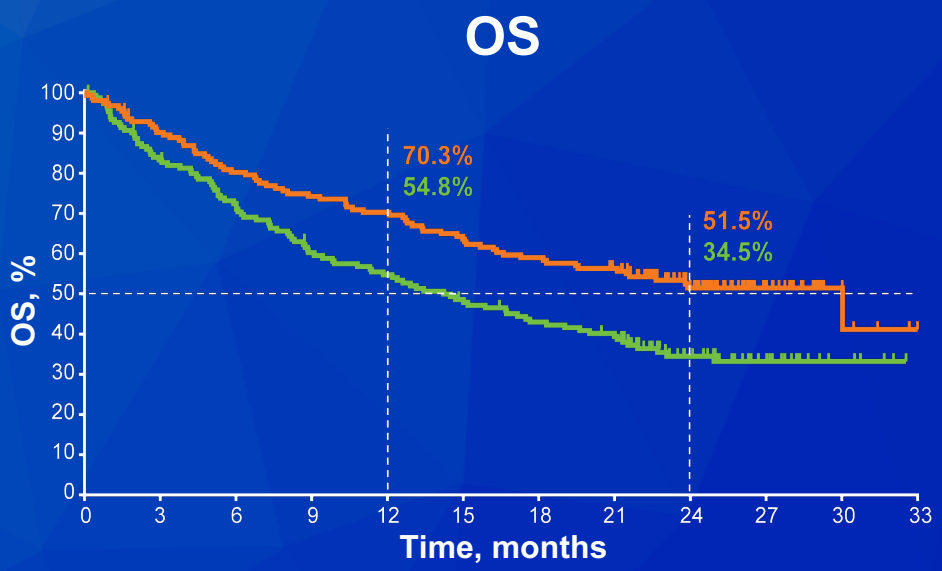
Updated Analysis of KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC with PD-L1 TPS ≥50%

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 Wakelee

When the phase III KEYNOTE-024 was presented at ESMO 2016 and simultaneously published in the *NEJM* it completely changed the treatment paradigm for newly diagnosed NSCLC patients. It became standard of care to test for PD-L1 expression with the 22C3 assay as part of initial evaluation of metastatic patients and to treat with pembrolizumab for patients with ≥50% TPS who did NOT have EGFR mutation or ALK or ROS1 translocations. Single agent pembrolizumab is the standard of care for such patients based on the KEYNOTE-024 data, which showed improved ORR (45% vs 28% $P = 0.0011$), improved PFS (HR 0.50, $P < 0.001$) and improved OS (HR 0.60, *P*.005) all favoring pembrolizumab over platinum based chemotherapy as first line therapy in this patient population with high PD-L1 expression.

Editorial — Dr Wakelee (continued)

At ASCO 2017 Julie Brahmer presented further follow-up data. This included progression-free survival in the second line (PFS2), which is defined as time from randomization (ie, at initial diagnosis) to objective tumor progression on the next line treatment (ie after 1st and 2nd line therapies) or death. This is helpful in evaluating the impact of crossover and the impact of 1st line therapy on outcomes of 2nd line therapy.

The ASCO 2017 presentation was based on a median follow-up of 19 months. At this time 46 patients on the 1st line pembrolizumab arm are ongoing compared to 1 on chemotherapy (though 29 completed therapy).

Editorial — Dr Wakelee (continued)

In total 91 of the 120 discontinued-chemotherapy patients have received checkpoint inhibitor therapy (60% effective crossover), and another 6 had some other 2nd line therapy. Of the 107 discontinued from pembrolizumab only 48 had any subsequent therapy (45%), of whom 42 had platinum doublet chemotherapy +/- bevacizumab. When one looks at the PFS2 for the 74 pembrolizumab-arm patients and 110 chemotherapy-arm patients eligible for this analysis, the HR is 0.54, p<.001. Bearing in mind this is an analysis from the point of initial randomization, when one looks at updated OS HR for all patients the HR is 0.63, P .003 at this time.

Editorial — Dr Wakelee (continued)

The key message from this subsequent analysis is that we cannot assume that the patients with high PD-L1 expression who start on chemotherapy will “catch up” with subsequent crossover to checkpoint inhibitor therapy at a later time.

This supports the original conclusions of the trial that first-line pembrolizumab therapy compared to platinum doublet chemotherapy leads to better survival outcomes in patients with PD-L1 TPS of ≥50% using the 22C3 assay.

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

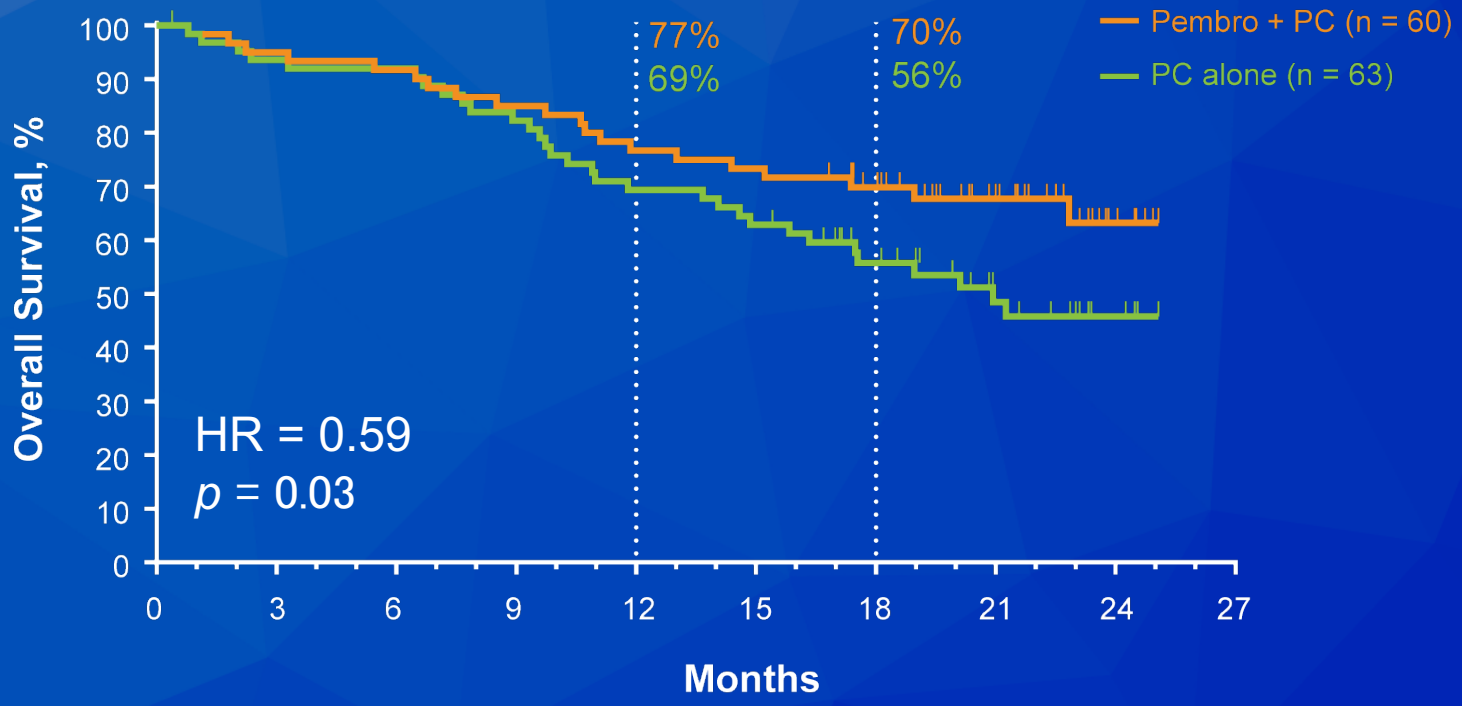
*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry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

The KEYNOTE-21G subset of 123 patients was published in 2016 and led to FDA approval of the combination of carboplatin/pemetrexed/pembrolizumab (CPP) as a first line option for patients regardless of PD-L1 status. The FDA approval has led to some use of this regimen, but there were concerns by many that the approval was premature as it was based on a randomized phase II study. Also, in looking at details, the response rates in those with high PD-L1 were exceedingly high with CPP compared to chemotherapy alone (80% versus 41%), but those with 1%-49% PD-L1 TPS have an opposite ORR pattern (26% for CPP versus 39% for chemotherapy alone).

Editorial — Dr Wakelee (continued)

Patients with PD-L1 <1% had ORR of 62% with CPP compared to 17% with chemotherapy alone, but all subsets are small and caution is critical in interpretation. It is also important to bear in mind that patients with known driver mutations such as EGFR or ALK are likely better treated with targeted therapy and were excluded from this trial.

At ESMO 2017 another update was presented, now with a median of 18.7 months of follow-up. At this time 75% of those eligible to cross over to checkpoint inhibitor therapy have done so (9 remain on therapy with chemotherapy alone). For the 3-arm combination 64% of those eligible to get subsequent treatment have done so to date. Approximately a third of patients on trial (37) had PD-L1 TPS of at least 50%.

Editorial — Dr Wakelee (continued)

The PFS HR is now 0.54, p = .0067. The overall survival HR is now 0.59, p = .03, bearing in mind that at 12 months this represented a difference of 3 deaths (46 alive versus 43 alive) and at 18 months the difference is 7 deaths (36 alive on the combination arm versus 29 alive on the chemotherapy arm). Thus, though the HR is impressive and now has reached statistical significance, one must look at that statistical difference carefully in light of the small total numbers of patients included on the trial.

Toxicity was minimally increased on CPP with 41% of patients developing grade 3-5 toxicity compared to 29% with chemotherapy alone (a difference of 6 patients). This regimen remains encouraging and the phase III data is eagerly anticipated.

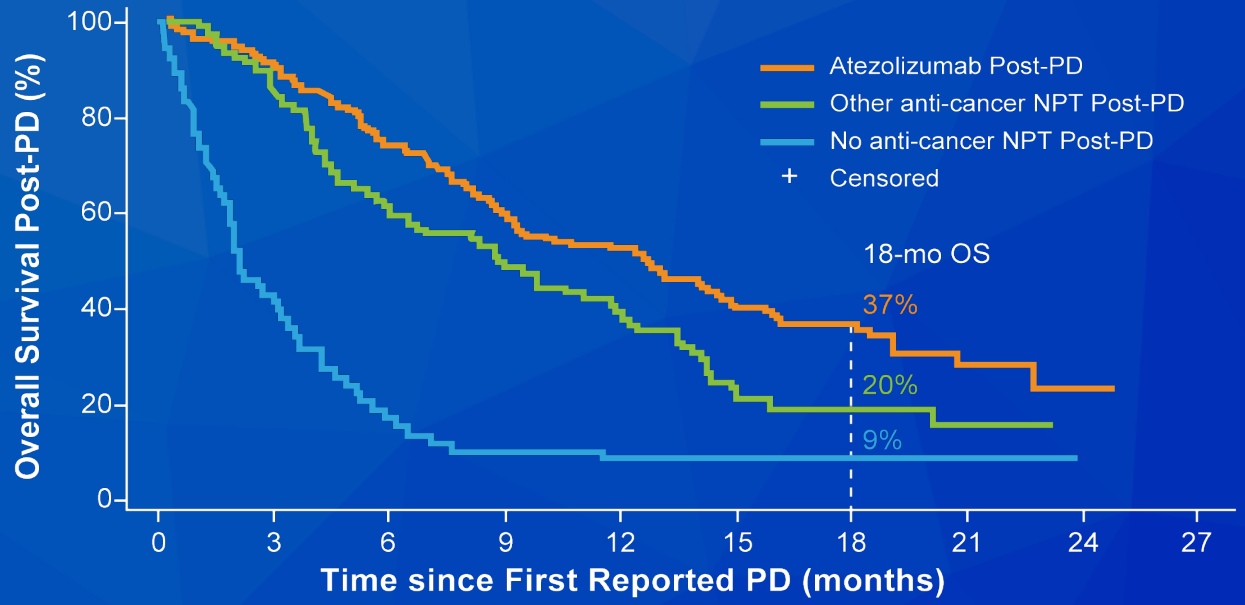
Impact of Atezolizumab (atezo) Treatment Beyond Disease Progression (TBP) in Advanced NSCLC: Results from the Randomized Phase III OAK Study

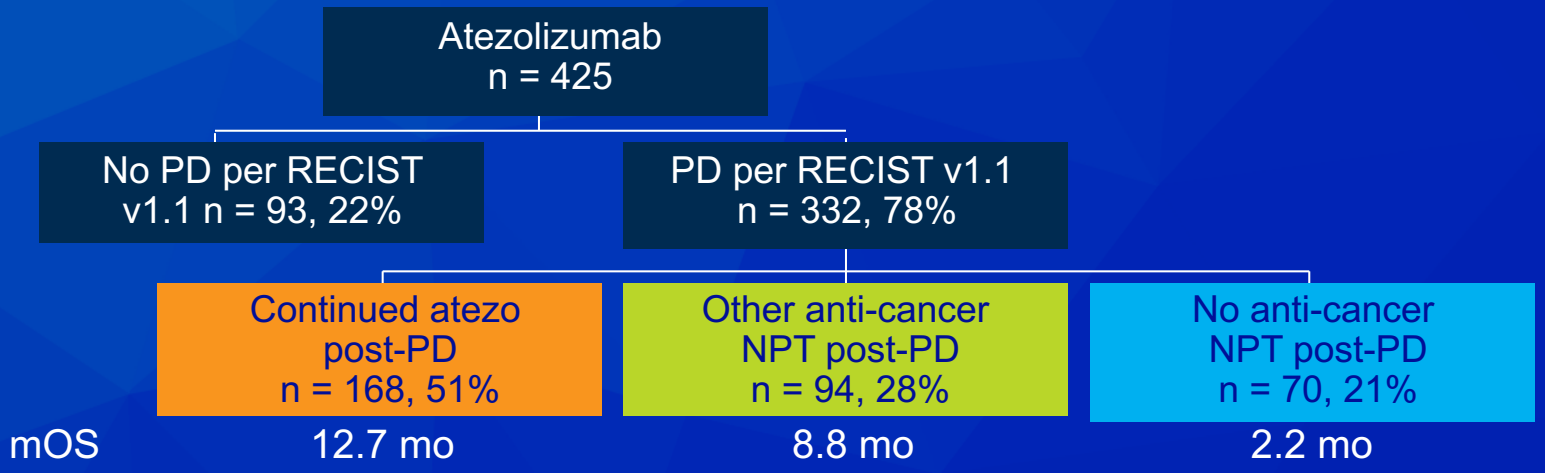
Randomized Results of Fixed-Duration (1-yr) vs Continuous Nivolumab in Patients (pts) with Advanced Non-Small Cell Lung Cancer (NSCLC)

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



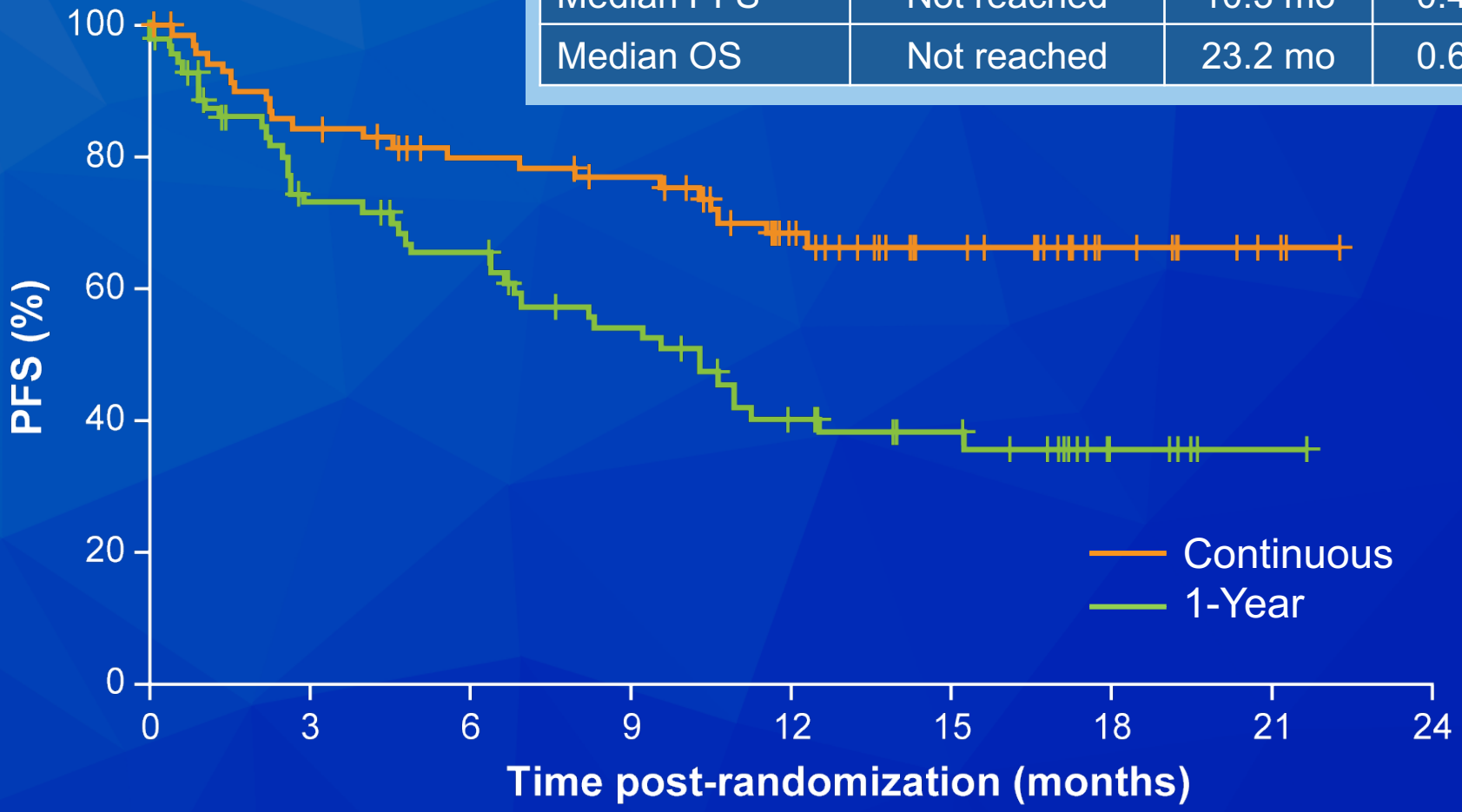


NPT = nonprotocol therapy

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 Spigel

The OAK study was the pivotal trial that proved atezolizumab was superior to docetaxel in patients with pretreated NSCLC, and was the basis for its FDA approval. In that study, patients with progressive disease (PD) who were otherwise stable and receiving clinical benefit were allowed to remain on atezolizumab — a likely common practice off-study. Gandara and colleagues examined this group of patients (n=168, 51% of patients with progressive disease per RECISTv1.1) for efficacy and safety.

Seven percent had a subsequent response in a target lesion, and 49% had stable target lesions — across all PD-L1 subgroups.

Editorial — Dr Spigel (continued)

The median survival ‘post-PD’ was 12.7 months, compared with 8.8 months in patients who received other ‘post-PD’ systemic therapy, and 2.2 months in patients who received no additional therapy.

This analysis is interesting, but limited. The survival analyses are difficult to interpret because there is potential selection bias. The patients who were deemed well enough to remain on atezolizumab by the treating physicians were potentially experiencing slower disease progression or fewer symptoms from disease than patients who went on to pursue other therapies or no therapy at all. However, it is notable that patients on the docetaxel arm who subsequently received immunotherapy after PD had a median overall survival of 17.3 months ‘post-PD.’

Editorial — Dr Spigel (continued)

Additionally, remaining on atezolizumab beyond progression did not result in increased toxicity. This analysis gives us a small view into what treatment beyond progression may look like, and seems to support what many are likely doing in practice. This is a difficult area to study, and a setting that is getting smaller as immunotherapy moves into the first-line setting. We may not get better data than these for our patients with NSCLC.

Editorial — Dr Spigel

How long we should treat patients with immunotherapy — for any cancer and in any setting — remains unknown. For now, physicians base treatment duration on the schedules followed in the pivotal trials for respective agents. CheckMate 153 was a large Phase IV trial designed to assess safety in patients with previously treated advanced NSCLC treated with nivolumab. The trial had several exploratory endpoints, including an analysis of patients who, after one year of nivolumab, were randomized to continue nivolumab or to stop treatment with the option of resuming nivolumab at the time of disease progression.

Editorial — Dr Spigel (continued)

The trial enrolled 1,245 patients, including patients with an ECOG PS of 2 and patients with previously treated brain metastases — patients excluded from the pivotal CheckMate 017 and 057 studies. Two hundred twenty patients completed 1 year of nivolumab and were eligible for randomization to continue nivolumab or stop. There were slightly more patients with squamous tumors in the ‘stop’ cohort, and slightly more patients who had achieved a response with initial nivolumab in the ‘continuous’ arm.

The progression-free survival (from randomization) was longer in the continuous arm vs the stop arm (HR 0.42, 0.25-0.71). This advantage seemed to hold true regardless of subset or in a multivariate analysis controlled for sex, histology, PD-L1 expression or best overall response.

Editorial — Dr Spigel (continued)

The survival was higher in the continuous group too, but this was not statistically significant (HR 0.63, 0.33-1.20). Importantly, there were no new safety signals in the patients who continued nivolumab.

This analysis suggests staying on immunotherapy is better than stopping, a conclusion that goes against what physicians want for their patients. However, it should be emphasized that this analysis was exploratory. The sample size is small, and the trial was not powered to fully assess survival. Nonetheless, this trial provides the only available randomized data from cohorts with different durations of treatment. Starting with over 1,200 patients and ending up with ~200 patients demonstrates the challenge of studying duration.

Editorial — Dr Spigel (continued)

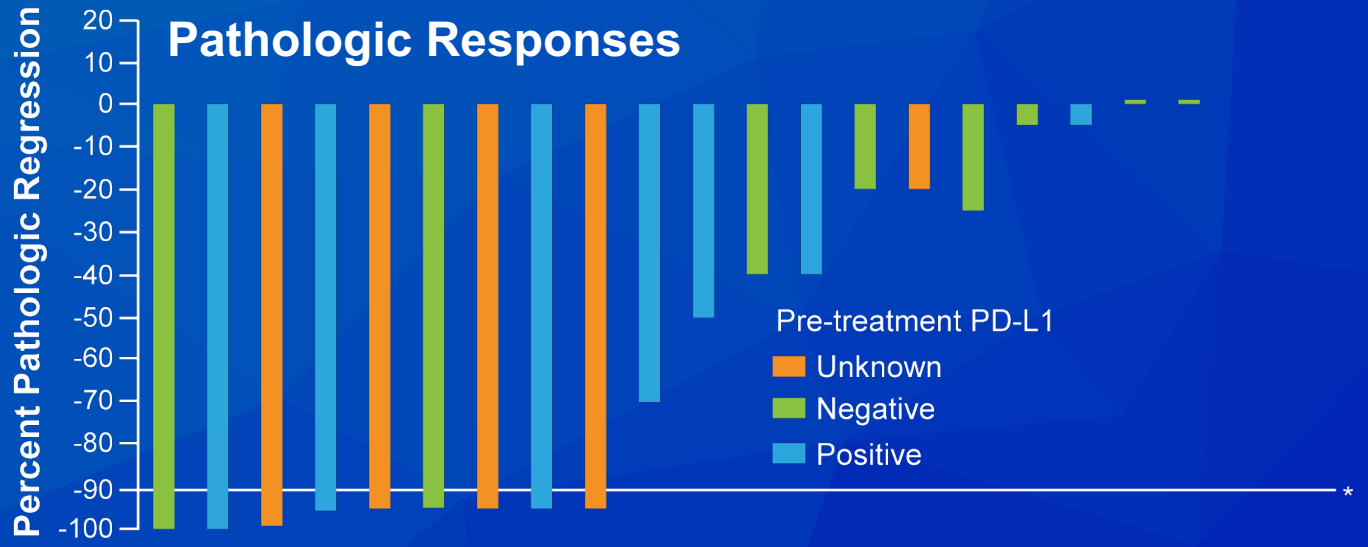
It seems unlikely that we will learn more about treatment duration in the near future, leaving us to base treatment duration on the original trial design and assessment of individual patient safety and efficacy.

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 Spigel

As immunotherapy development expands across tumor types in the advanced setting, an important goal is to move it into earlier stages of disease. Nivolumab is an established therapy in NSCLC in both squamous and nonsquamous patients following first-line chemotherapy. The Hopkins team has been interested in exploring nivolumab as a monotherapy in the neoadjuvant NSCLC setting. They reported more mature results from a small experience of patients with stage IB-IIIA NSCLC who received 2 doses of nivolumab 3 mg/kg IV over 4 weeks prior to surgery. The primary goal of this single center Phase II study was to assess safety.

Editorial — Dr Spigel (continued)

Results were initially reported in 2016, but updated data on 21 patients were presented at the ASCO 2017 Annual Meeting. In general, treatment was deemed safe and did not interfere with planned surgery. Radiographic partial responses were seen in 2 of 21 (10%) patients who underwent resection. However, 9 of 21 (43%) patients who underwent resection had a major pathologic response (<10% of viable tumor cells in the resection specimen). Pretreatment tumor mutation burden and neoantigen density correlated with response, but PD-L1 expression did not.

Editorial — Dr Spigel (continued)

These results are important, although in the end the sample size is too small to make any definitive conclusions. The first major takeaway from this analysis is that immunotherapy may be impacting tumors beyond what we can assess using traditional imaging. This is concerning, because CT imaging and RECIST measurements are the primary tools we use to know if treatment is working. These results suggest that imaging is underrepresenting immunotherapy efficacy. The other major point is that immunotherapy alone — and perhaps very little of it — may be all some patients need in addition to surgery for early stage NSCLC. More work is needed — and pivotal randomized trials are in progress.

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 Spigel

Pneumonitis is a rare but serious complication of immunotherapy. Naidoo et al performed a retrospective analysis of 915 patients with solid tumors from MSKCC and the Melanoma Institute of Australia treated with PD-1/PD-L1 inhibitors +/- CTLA4 antibodies. Five percent of patients developed pneumonitis, and this was more frequent with CTLA4 combinations than with monotherapy (10% vs 3%). The incidence was similar with monotherapy in melanoma and NSCLC. Pneumonitis was independent of line of therapy, smoking history, or prior RT. Interestingly, the ORR among patients with pneumonitis was 61% — and, specifically in melanoma, 73% with monotherapy and combination therapy.

Editorial — Dr Spigel (continued)

The onset of pneumonitis was variable — ranging from 9 days to 19 months. Most of the pneumonitis was low grade and reversible/manageable with suspension of treatment and use of steroids. One patient died from pneumonitis, and 3 from infection due to immunosuppression.

These findings are of interest as the use of immunotherapy expands across tumors and settings — and in the community. Pneumonitis is among the most feared toxicities, in part because it was associated with deaths in the early development of nivolumab, and it is also one of the more difficult toxicities to identify. Suspecting pneumonitis is easy, but proving that it is due to treatment is difficult because of the subtleties in presentation and confounding issues of comorbidities, particularly in patients with lung cancer.

Editorial — Dr Spigel (continued)

This paper is reassuring that pneumonitis is a problem for a minority and appears to be manageable. We will likely learn more about pneumonitis as experience broadens and combinations emerge.

Cancer Therapy: Clinical

Clinical Cancer Research

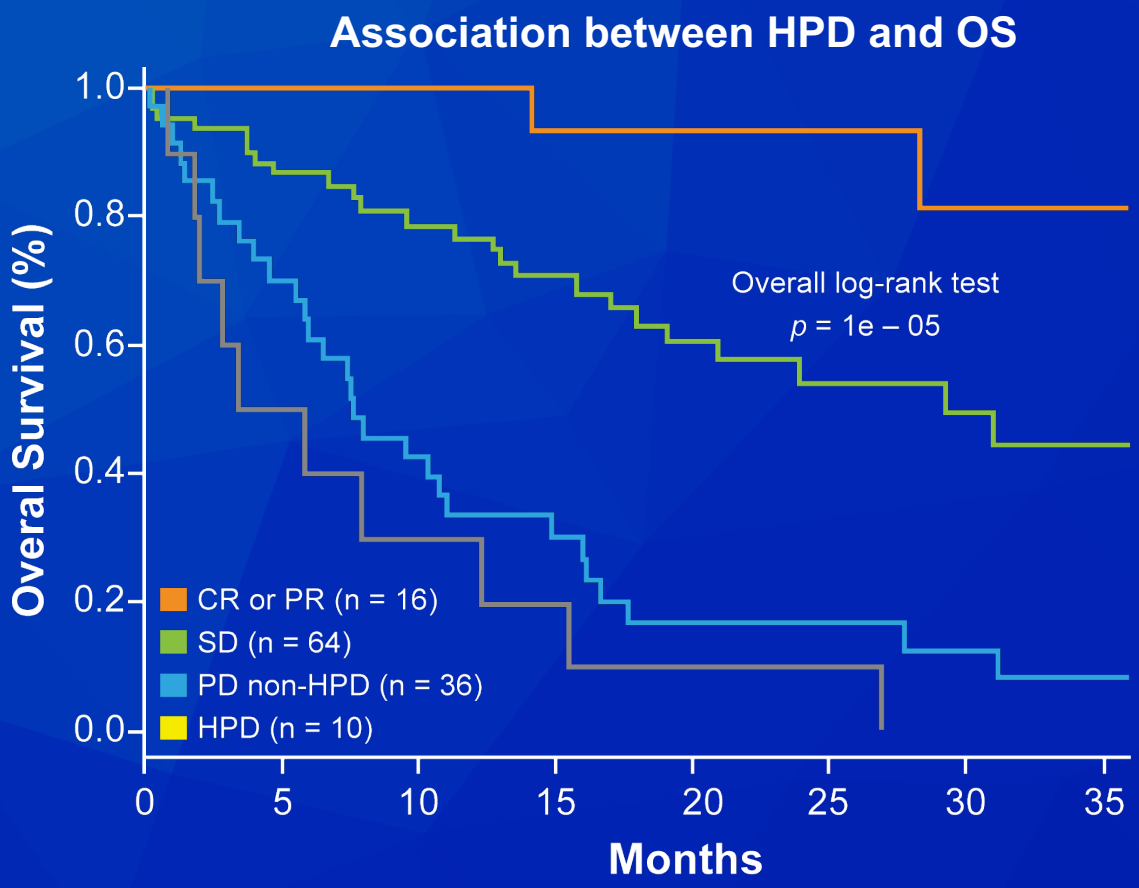
Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

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 Spigel

Hyperprogressive disease (HPD) has been proposed by some to be a pattern of progression in some patients treated with immune checkpoint inhibitors (CPIs). Champiat and colleagues reviewed records from 131 evaluable patients treated with CPIs at a single academic center. All patients were treated in Phase I trials. HPD was defined as patients with progressive disease at the first evaluation with at least a doubling of the tumor growth rate (by comparing the growth rate before and after CPI exposure).

Twelve (9%) patients were deemed to have HPD. These patients did not have one specific type of cancer or necessarily a higher tumor burden at baseline. HPD was associated with older patients and worse survival.

Editorial — Dr Spigel (continued)

This group also had a lower rate of new lesions than patients with disease progression without HPD. The authors conclude that these results suggest caution be exercised in treating patients older than 65.

The strength of this analysis was the comparison of the tumor growth rate before and after CPI treatment. However, defining a single type of progression using a variety of patients with refractory malignancies treated with a variety of therapies prior to, and enrollment on, Phase I studies is challenging. This may be a chance finding influenced by patient selection and simply reflect patients with aggressive disease that has nothing to do with CPI therapy. Case-control analyses would be needed before we can define a new subset of progression on CPI therapy.

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.

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

Press Release — July 27, 2017

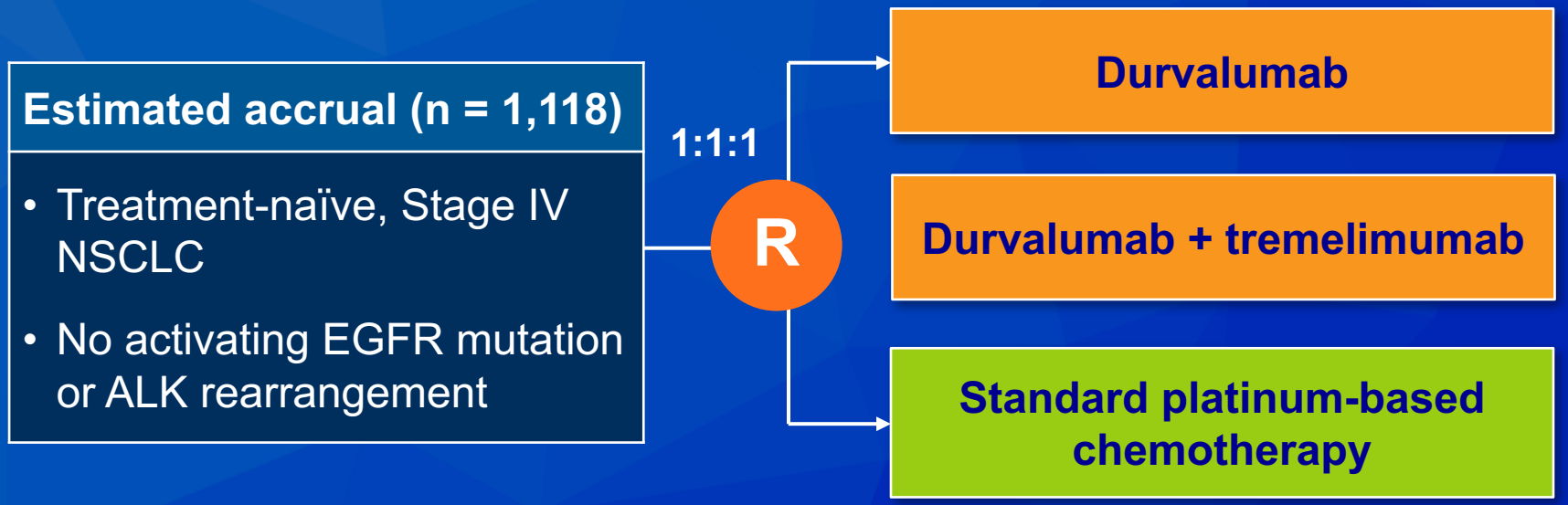
The combination of durvalumab and tremelimumab did not meet the primary endpoint of improving PFS compared to standard of care (SoC) in patients whose tumors express PD-L1 on 25% or more of their cancer cells (as determined by the VENTANA PD-L1 [SP263] assay).

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.

Editorial — Dr Wakelee

CheckMate 012 assessed the toxicity and efficacy of the combination of nivolumab plus ipilimumab as first line treatment in advanced NSCLC. This was an open-label phase I study and investigated different dosing regimens: Nivolumab (N) 1 mg/kg every 2 weeks plus ipilimumab (I) 1 mg/kg every 6 weeks versus N 3 mg/kg every 2 weeks plus I 1 mg/kg every 6 weeks or 12 weeks. The report focused only on the 2 cohorts of patients who received nivolumab at 3 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg either every 6 or 12 weeks (NI6 or NI12). The study randomized 78 patients to those 2 arms.

Editorial — Dr Wakelee (continued)

Grade 3-4 toxicity was reported in 37% on the NI12 arm and in 33% on the NI6 arm. There were no unexpected toxicities. Confirmed ORR was 47% (N = 18) on the 12-week cohort and 38% (N = 15) on the every 6 weeks cohort. For patients with PD-L1 of 1% or higher the ORR was the same in the 12 and 6 weeks cohorts (57%). Of note, the median duration of response was not yet reached with median follow-up times of 11.8 and 12.8 months in the 2 cohorts, thus indicating >1 year duration of response.

This is only a phase I study and not practice changing, but it does support the ongoing phase III CheckMate 227 study, which randomizes patients to first line nivolumab, nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy alone.

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

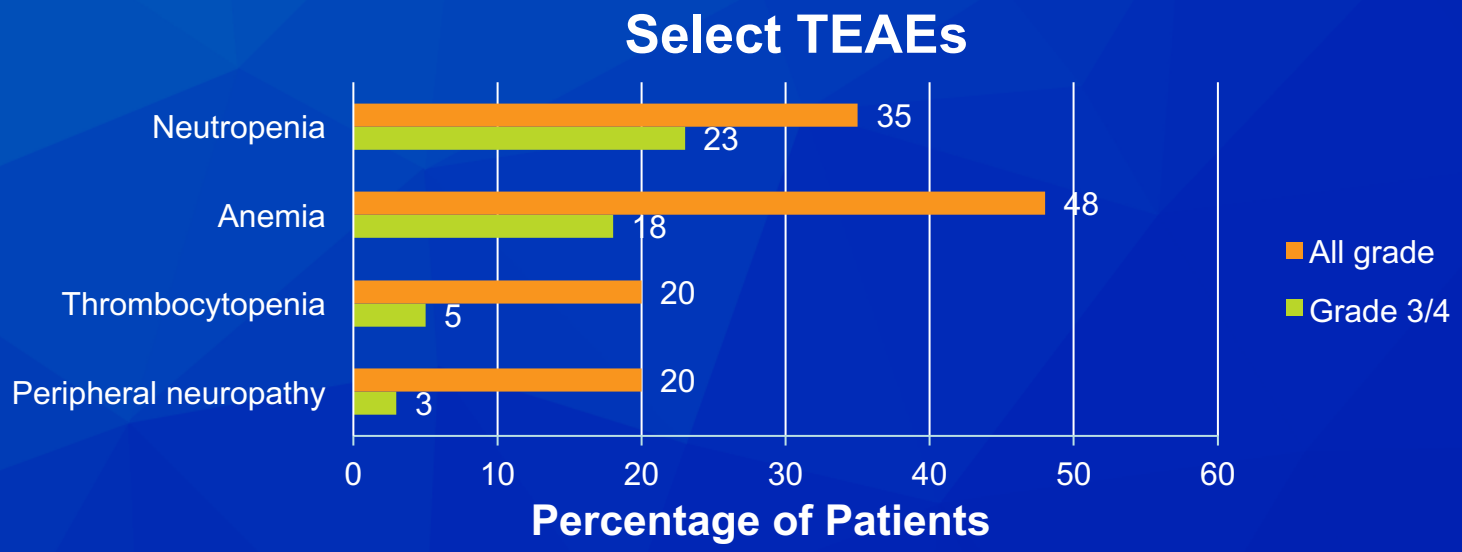
Adverse event	Arm A (n = 68)	Arm B (n = 70)
Grade ≥2 PN or Grade ≥3 myelosuppression	76%	77%
Grade ≥2 PN	37%	36%
Grade ≥3 myelosuppression	71%	64%
Neutropenia	57%	56%
Anemia	21%	24%
Thrombocytopenia	25%	17%

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 Spigel

Carboplatin/*nab*-paclitaxel is an FDA-approved regimen in the treatment of first-line advanced NSCLC. This approval was based on higher response rates (33% vs 25%, p=.005) compared with carboplatin/paclitaxel in a Phase III study (Socinski, *JCO* 2010). In this trial of 1,052 patients, there was evidence of improved survival (19.9 months vs 10.4 months, p=.009) with *nab*-paclitaxel in patients at least 70 years of age. ABOUND.70+ was a Phase II study designed to further assess this finding along with safety.

Langer et al reported interim results of 284 patients 70 years of age and older randomized to 2 different schedules of carboplatin/*nab*-paclitaxel (C: AUC=6; *nab*-P: 100 mg/m^2 D1, 8, 15 q3wk or q4wk).

Editorial — Dr Spigel (continued)

The trial was closed early after the incidence of G2+ peripheral neuropathy or G3+ myelosuppression (the primary endpoint) was similar between arms (76% 3wk vs 77% 4wk). The median PFS and OS were 3.6 and 15.2 months (3wk) and 7 and 16.2 months (4wk).

Gajra similarly explored this regimen in 50 patients with poor performance status (PS 2) using C: AUC=5; *nab*-P 100 mg/m^2 D1 and 8 q3wk x 4 cycles, with maintenance *nab*-P. The response rate was 30%, PFS 4.4 months, and toxicity was expected and manageable.

Editorial — Dr Spigel (continued)

Carboplatin/*nab*-paclitaxel is already an approved regimen in NSCLC, although its use tends to be limited to patients with squamous tumors based on other subset data from the pivotal randomized trial — where older (and less expensive) regimens are also commonly used. These additional analyses give us confidence that this regimen can be used safely in our older patients and those with poor PS.

Lung Cancer — Drs Riely, Wakelee and Spigel

EGFR-Mutated Disease

ALK-Rearranged Disease

BRAF and Other Targetable Mutations

Integration of Checkpoint Inhibitors into the Management of NSCLC

Small Cell Lung Cancer

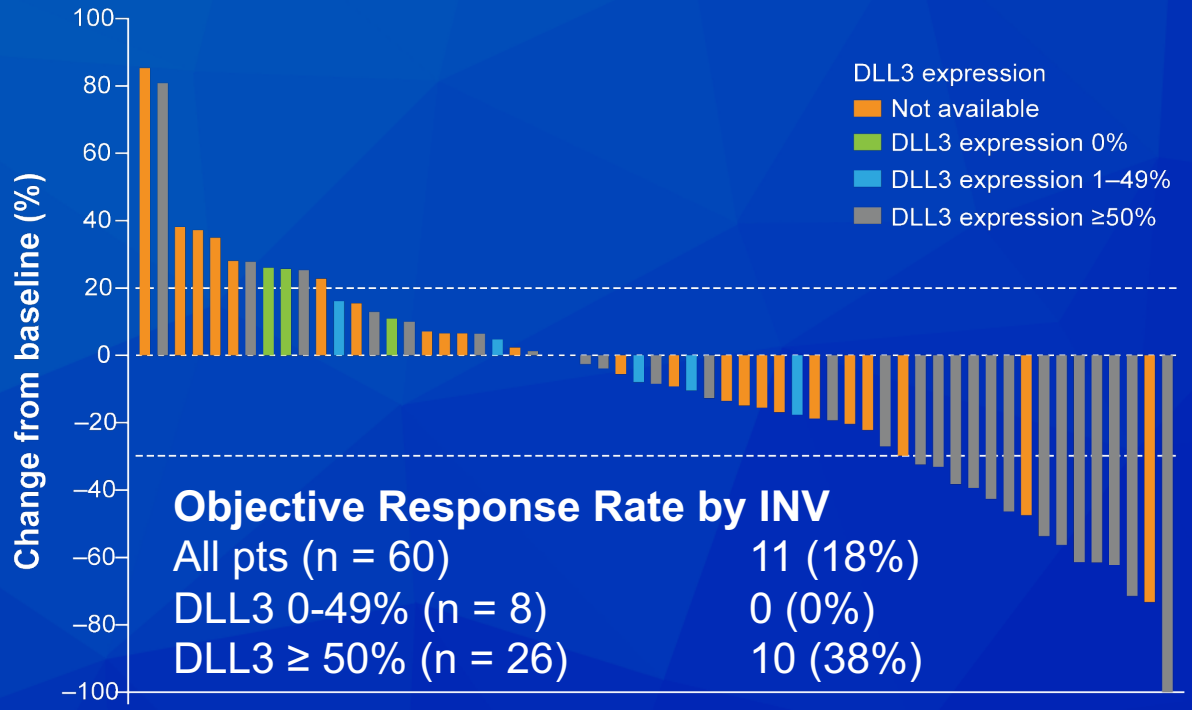
Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study

*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 Spigel

Little progress has been made in the treatment of relapsed SCLC in the last 18 years since topotecan was approved based on tolerability compared with cyclophosphamide, doxorubicin, and vincristine (von Pawel, *JCO* 1999). Rovalpituzumab tesirine (Rova-T) is a novel antibody-drug conjugate that targets DLL3, expressed in 80% of SCLC. Rudin and colleagues conducted a first-in-human Phase I study of Rova-T in patients with sensitive and refractory relapsed SCLC. Toxicity included thrombocytopenia, serosal effusions, and elevated hepatic transaminases. The recommended Phase II dose and schedule is 0.3 mg/kg every 6 weeks x 2. The objective response rate was 18% in a combined analysis and 38% in patients with high DLL3 expression.

Editorial — Dr Spigel (continued)

Rova-T looks promising in this early analysis of mixed types of patients with relapsed disease, and would be a welcome addition (and potential replacement of topotecan) in the relapsed setting. The every 6 week dosing x 2 is unique, but appears to be necessary to minimize the toxicities — namely the serosal effusions which can be troubling for some patients. Pivotal randomized trials in the maintenance first-line, relapsed, 3rd-line settings, and in combination with immunotherapy are in progress. The timing of this development with the emergence of immunotherapy is an exciting time for SCLC research.

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

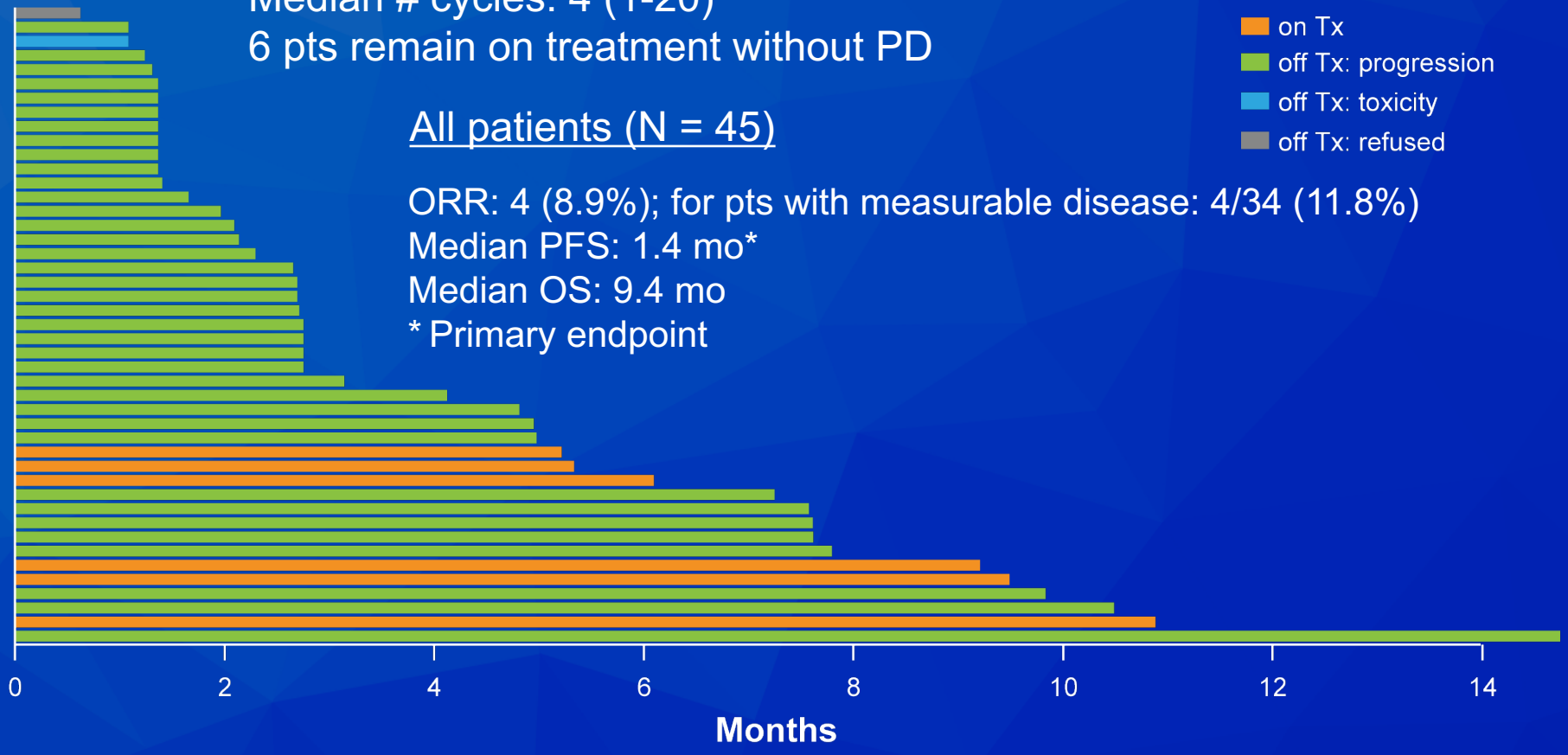
Gadgeel SM et al.
Proc ASCO 2017;Abstract 8504.

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 Spigel

Pembrolizumab has also been explored in relapsed SCLC. Early reports from the WCLC in 2016 suggested high response rates with monotherapy. Gadgeel and colleagues reported results from a small study of maintenance pembrolizumab in a single cohort Phase II study. All patients received pembrolizumab 200 mg IV q3wk following evidence of disease control following 4-6 cycles of platinum/etoposide therapy. The median PFS was 1.4 months, and median OS 9.4 months. The response rate was 9%. Safety was expected and manageable.

Editorial — Dr Spigel (continued)

These data are disappointing and do not suggest a role for pembrolizumab maintenance therapy in SCLC. A subset with PD-L1 expression suggests greater efficacy, but the sample is too small to draw any major conclusions. Pembrolizumab is being studied in combination with chemotherapy in a randomized Phase III first-line SCLC trial, and we await other SCLC trials with immunotherapy as well.

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 Spigel

CheckMate 032 was designed to explore nivolumab +/- ipilimumab in 4 cohorts: SCLC, Gastric/GE junction cancer, triple-negative breast cancer, and pancreatic cancer. The most promising signal of efficacy was in the relapsed SCLC cohort (n=216) (Antonia, *Lancet Oncol* 2016) where responses in non-randomized cohorts were: 10% with nivo 3 mg/kg q2wk; 23% with nivo 1 mg/kg and ipi 3 mg/kg q3wk; and 19% with nivo 3 mg/kg and ipi 1 mg/kg q3wk. The 2-year OS with nivo/ipi was 26%. Hellmann presented the initial report of an expanded randomized cohort of patients (n=242) with relapsed SCLC treated with either nivo or nivo 1 mg/kg and ipi 3 mg/kg q3wk.

Editorial — Dr Spigel (continued)

Responses were observed in 12% with nivo and 21% with nivo/ipi. The 3-month PFS was 18% with nivo and 30% with nivo/ipi. Grade 3 or 4 toxicity was seen in 12% with nivo and 37% with nivo/ipi, with 2% and 10% having severe toxicity leading to treatment discontinuation, respectively.

The Antonia data have led to the NCCN listing of nivo/ipi for SCLC treatment — a regimen that is currently widely used. The expanded randomized data replicate the early experience. The nivo/ipi schedule chosen for SCLC development is unfortunately different from the NSCLC regimen, where nivo is 3 mg/kg q2wk and ipi is 1 mg/kg q6wk. It is possible that this regimen would result in similar efficacy with similar (or better) toxicity.

Editorial — Dr Spigel (continued)

Pivotal randomized trials with nivo alone are in progress, as are several other trials using other PD-1/PD-L1 inhibitors in first-line and relapsed settings.