BRIEF REPORT

Modulation of Biomarker Expression by Osimertinib: Results of the Paired Tumor Biopsy Cohorts of the AURA Phase I Trial

Kenneth S. Thress, PhD,[a] Vivien Jacobs, BSc,[b] Helen K. Angell, PhD,[c] James Chih-Hsin Yang, MD, PhD,[d] Lecia V. Sequist, MD, MPH,[e,f] Fiona Blackhall, MD, PhD,[g,h] Wu-Chou Su, MD,[i] Martin Schuler, MD,[j] Jürgen Wolf, MD,[k] Kathryn A. Gold, MD,[l] Mireille Cantarini, MD,[m] J. Carl Barrett, PhD,[a] Pasi A. Jänne, MD, PhD[n,*]

[a]*IMED Oncology Translational Sciences, AstraZeneca, Gatehouse Park, Waltham, MA*
[b]*IMED Oncology Translational Sciences, AstraZeneca, Alderley Park, Macclesfield, United Kingdom*
[c]*IMED Oncology Translational Sciences, AstraZeneca, Cambridge, United Kingdom*
[d]*Department of Oncology, National Taiwan University Hospital, Taipei, Republic of China*
[e]*Department of Hematology, Massachusetts General Hospital, Boston, Massachusetts*
[f]*Department of Oncology, Massachusetts General Hospital, Boston, Massachusetts*
[g]*Division of Molecular and Clinical Cancer Sciences, University of Manchester, Manchester, United Kingdom*
[h]*Department of Medical Oncology, The Christie National Health Service Foundation Trust, Manchester, United Kingdom*
[i]*National Cheng Kung University Hospital, Tainan, Republic of China*
[j]*Clinic for Internal Medicine (Tumor Research), West German Cancer Center, University Duisburg-Essen and German Cancer Consortium, Partner Site University Hospital Essen, Essen, Germany*
[k]*Clinic for Internal Medicine, Uniklinik Köln, Köln, Germany*
[l]*Thoracic Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas*
[m]*AstraZeneca, Alderley Park, Macclesfield, United Kingdom*
[n]*Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Boston, Massachusetts*

Received 26 May 2017; revised 7 July 2017; accepted 12 July 2017
Available online - 24 July 2017

***Corresponding author.**

***Disclosure:** Drs. Angell, Barrett, and Thress are employees of AstraZeneca. Ms. Jacobs and Dr. Cantarini are former employees of AstraZeneca. Drs. Barrett, Cantarini, and Thress are shareholders in AstraZeneca. Dr. Blackhall declares honoraria for AstraZeneca, Pfizer, Boehringer Ingelheim, Medivation, Novartis, Merck Sharp and Dohme, and Bristol-Myers Squibb; consultancy fees from Medivation and Roche; research funding from AstraZeneca, Pfizer, Boehringer Ingelheim, Medivation, Novartis, Merck Sharp and Dohme, and Bristol-Myers Squibb; and reimbursement of expenses from Boehringer Ingelheim. Dr. Gold declares honoraria for Roche/Genentech; consultancy fees from ARIAD; research funding for Pharmacyclics, Bristol-Myers Squibb, AstraZeneca, ARIAD, Roche/Genentech, and Astellas Pharma; and reimbursement of expenses from AstraZeneca. Dr. Jänne declares consultancy fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Merrimack Pharmaceuticals, Roche/Genentech, Chugai, AceaBiosciences, Ariad Pharmaceuticals, Ignyta, and LOXO Oncology; stock ownership in Gatekeeper Pharmaceuticals; research funding from Astellas Pharmaceuticals and AstraZeneca; and intellectual property on EGFR mutations licensed to Lab Corp. Dr. Schuler declares consultancy fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Novartis, Roche, and the Institute for Quality and Efficiency in Health Care; honoraria for continuing medical education presentations from Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Merck Sharp and Dohme, and Novartis; research funding from Boehringer Ingelheim, Bristol Myers-Squibb, and Novartis; and intellectual property with Universität Duisburg-Essen. Dr. Sequist declares honoraria for AstraZeneca, consultancy fees from Clovis Oncology, Novartis, Merrimack, AstraZeneca, Ariad, Genentech/Roche and Bristol-Myers Squibb, research funding from Boehringer Ingelheim, Clovis Oncology, Genentech, Merrimack, Novartis, AstraZeneca, Johnson and Johnson, Merck, and Taiho Pharmaceutical. Dr. Wolf declares honoraria from AstraZeneca, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, and Roche; consultancy fees from AstraZeneca, Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis, Lilly, Merck Sharp and Dohme, Novartis, Pfizer, and Roche; research funding from Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, Pfizer, and Roche. Dr. Yang declares honoraria for Boehringer Ingelheim, Roche, Chugai Pharma, Merck Sharp and Dohme, AstraZeneca, and Novartis; consultancy fees from Boehringer Ingelheim, Novartis, AstraZeneca, Roche/Genentech, Clovis Oncology, Lilly, Merck Sharp and Dohme Oncology, Merck Serono, Celgene, Astellas Pharma, Bayer, Pfizer, Ono Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim, AstraZeneca, and Yuhan. The remaining author declares no conflicts of interest.*

Trial Registration: AZD9291 First Time In Patients Ascending Dose Study (AURA). NCT01802632.

Address for correspondence: Pasi A. Jänne, MD, PhD, Dana Farber Cancer Institute, Lowe Center for Thoracic Oncology, 450 Brookline Ave., LC4114, Boston, MA 02215. E-mail: Pasi_Janne@dfci.harvard.edu

© 2017 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2017.07.011

ABSTRACT

Introduction: Osimertinib is an oral, potent, irreversible EGFR tyrosine kinase inhibitor (TKI) selective for EGFR TKI and T790M resistance mutations. To enhance understanding of osimertinib's mechanism of action, we aimed to evaluate the modulation of key molecular biomarkers after osimertinib treatment in paired clinical samples from the phase I AURA trial.

Methods: Paired tumor biopsy samples were collected before the study and after 15 plus or minus 7 days of osimertinib treatment (80 or 160 mg daily). Clinical efficacy outcomes were assessed according to whether viable paired biopsy samples could be collected; safety was also assessed. Immunohistochemical analyses assessed key pathway and tumor/immune-relevant markers (phospho-EGFR, phospho-S6, phospho-AKT, programmed death ligand 1, and CD8), with samples scored by image analysis or a pathologist blinded to treatment allocation.

Results: Predose tumor biopsy samples were collected from 61 patients with *EGFR* T790M tumors; 29 patients had no viable postdose biopsy sample because of tumor regression or insufficient tumor sample. Evaluable predose and postdose tumor biopsy samples were collected from 24 patients. Objective response rate (ORR) and median progression-free survival (mPFS) were improved in patients from whom a postdose biopsy sample could not be collected (ORR 62% and mPFS 9.7 months [$p = 0.027$]) compared with those from whom paired samples were collected (ORR 29% and mPFS 6.6 months). Osimertinib modulated key EGFR signaling pathways and led to increased immune cell infiltration.

Conclusions: Collection of paired biopsy samples was challenging because of rapid tumor regression after osimertinib treatment, highlighting the difficulties of performing on-study biopsies in patients treated with highly active drugs.

© 2017 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

Keywords: Osimertinib; Biomarker; T790M; EGFR; NSCLC

Introduction

EGFR tyrosine kinase inhibitor (TKI)-sensitizing mutations occur in approximately 10% to 15% of Western and 30% to 40% of Asian patients with advanced NSCLC.[1–3] Current guidelines for this patient population recommend first-line treatment with the EGFR TKIs erlotinib, afatinib, and gefitinib.[4] Despite initial responses, acquired resistance and subsequent disease progression typically occur within 1 to 2 years of treatment initiation.[4–8] An additional mutation in exon 20 of the EGFR kinase domain, T790M, is responsible for resistance in approximately 60% of patients in whom acquired resistance develops.[9,10]

Osimertinib is an oral, potent, irreversible EGFR TKI selective for *EGFR* mutations and the T790M resistance mutation. In murine models, osimertinib induced durable tumor shrinkage consistent with inhibition of EGFR signaling and its downstream pathways.[11] Results from the phase III AURA3 trial confirmed that osimertinib is superior to chemotherapy in patients with T790M who had progressed during prior treatment with an EGFR TKI[12]; osimertinib is approved for this indication in multiple countries.[4]

We are reporting results from a planned paired biopsy analysis conducted in patients with advanced T790M NSCLC after prior treatment with an EGFR TKI who received osimertinib during the phase I AURA study (NCT01802632). This unique analysis aimed to assess the modulation of key components of the EGFR-signaling pathway, along with changes in the immune system, in paired patient tumor samples after exposure to osimertinib.

Patients and Methods

Study Design and Participants

Full details of the methodology for the AURA Phase I, open-label, multicenter study (NCT01802632) of osimertinib have been published.[13] Patients with tumor *EGFR* T790M status confirmed in a postprogression biopsy sample were enrolled to a preplanned paired biopsy sample cohort as part of the dose expansion cohorts of the study (see Supplementary Material for details). Eligibility criteria for this cohort included the presence of at least one nontarget lesion suitable for multiple biopsies during the study. Patients received 80 mg or 160 mg osimertinib, orally, once daily.

Osimertinib treatment was continued until disease progression (treatment beyond progression was permitted in patients with continued clinical benefit), the development of unacceptable adverse events (AEs), or withdrawal of consent. All participating sites received approval from the associated independent institutional review board or independent ethics committee. The study was performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on bioethics. All patients provided written informed consent before study inclusion.

Paired Tumor Tissue Sampling

Fresh tumor biopsy samples were collected at screening (before treatment with osimertinib), where possible. Alternatively, existing biopsy samples collected

after progression during the most recent line of therapy could be provided. In addition to the mandatory pre–osimertinib treatment biopsy sample, which was used as the baseline biopsy sample for all planned paired analyses and for central identification of T790M mutation status; an optional biopsy sample could be collected from a secondary lesion. On-study tumor biopsy samples were taken after 15 days (±7 days) of treatment with osimertinib.

Assessments

All patients had efficacy and safety assessments; patients received computed tomography or magnetic resonance imaging scans at baseline and every 6 weeks thereafter until disease progression. Tumor response was assessed by investigators according to the Response Evaluation Criteria in Solid Tumors (version 1.1) to determine objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS). AEs were graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.

Immunohistochemical Analyses

Immunohistochemical analyses were conducted using predose and postdose paired samples to profile relevant biomarkers from the EGFR signaling pathway (phospho-EGFR [pEGFR] [Y1173]/phospho-S6 [pS6] [Ser235/236]/phospho-AKT [Thr308]), the immunooncology biomarker programmed death ligand-1 (PD-L1) positivity, and the prevalence of cytotoxic T-cells (CD8) (see Supplementary Materials for further details). Only patients for whom evaluable tumor samples were collected both before and after a dose were included (Fig. 1).

Statistical Methods

Clinical data before the May 1, 2015, cutoff were analyzed. All patients with measurable disease at baseline according to the Response Evaluation Criteria in Solid Tumors (version 1.1) who had received at least one dose of osimertinib were considered evaluable for response and included in efficacy assessments. Definitions of ORR, DOR, and PFS have been presented previously[13] (see Supplementary Materials for further details).

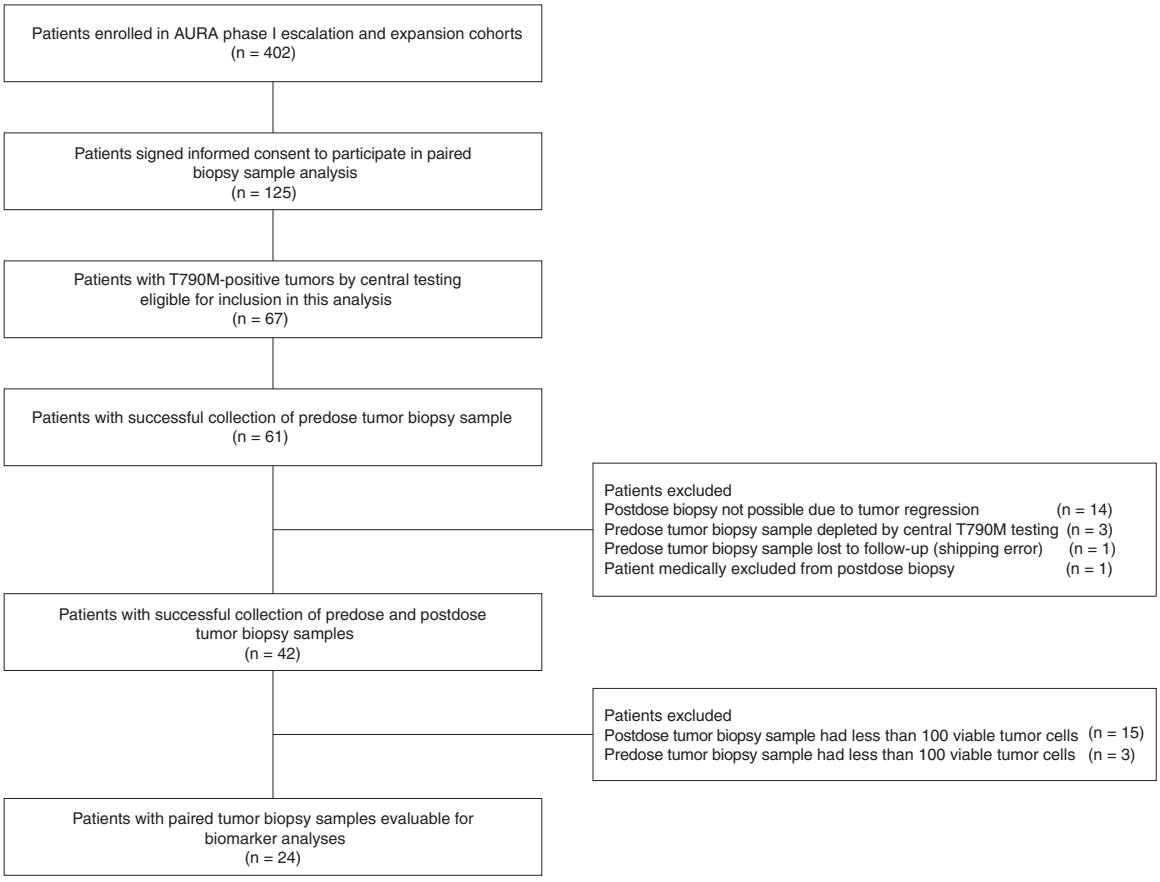

Figure 1. Flow diagram of the eligible study population. Of the 125 patients who provided signed informed consent to participate in the paired biopsy sample analyses, 67 had T790M-positive tumors by central testing. Predose tumor biopsy samples were successfully collected from 61 patients, and both predose and postdose biopsy samples were collected from 42 patients. Of these, 24 patients had viable predose and postdose samples and were eligible for biomarker analyses.

Results

Patients

Overall, 402 patients were enrolled across 35 centers globally onto the phase I component of AURA. Of these, 271 patients were included in the dose expansion cohorts, 190 received osimertinib at 80 mg or 160 mg once daily, and 125 provided signed informed consent to participate in the paired biopsy sample analysis. Of the 125 patients, 67 (54%) had T790M-positive tumors by central testing; predose tumor biopsy samples were successfully collected from 61 patients, and both predose and postdose biopsy samples were collected from 42 patients. Paired tumor biopsy samples evaluable for biomarker analyses were successfully collected from 24 patients (see Fig. 1), most of whom underwent their on-study biopsy within 7 to 10 days (range 7–20 days, median 9.5 days) of their first dose of osimertinib (16 of 24 [67%]). Eight of 24 patients (33%) received osimertinib 80 mg once daily; 16 patients (67%) received 160 mg once daily. Baseline demographics in these 24 patients were consistent with those reported for the overall study population (Supplementary Table 1). There were 29 patients for whom a postdose biopsy was not possible on account of tumor regression (n = 14) or because of the postdose biopsy sample having fewer than 100 viable tumor cells (n = 15).

Paired Biopsy Collections and Clinical Response

The confirmed ORR in the 24 patients evaluable for biomarker analyses was 29% (95% confidence interval [CI]: 13–51) (Table 1) with a median duration of follow-up of 2.8 months (interquartile range 1.4–5.5) at the time of data cutoff. Three patients were not evaluable for efficacy; the ORR in the 21 evaluable patients was 33% (95% CI: 15–57). Most patients (54%) achieved stable disease. Responses were higher in the 29 patients excluded from the biomarker analyses on account of lack of evaluable postdose biopsy tissue; the difference in response from that of the 24 patients evaluable for biomarker analyses ($p = 0.027$). Confirmed responses were reported in 62% (95% CI: 42-79) of the 29 patients lacking evaluable postdose biopsy tissue; the median duration of follow-up was 5.5 months (interquartile range 2.7–9.5). At the time of analysis, only one patient had progressive disease; this patient was included in the biomarker analyses group. In patients with an evaluable on-study biopsy sample (n = 24 [Fig. 2]), the median DOR was not calculable (NC) (95% CI: 2.8–NC) and the median PFS was 6.6 months (95% CI: 3.9–NC); the median time on treatment was 6.2 months. In the 29 patients in whom collection of a postdose biopsy sample was not possible, the median DOR and median PFS were 8.4 months (95% CI: 6.9–NC) and 9.7 months (95% CI: 7–NC), respectively (see Fig. 2); the median time on treatment was 7.9 months. The median PFS was not significantly different between those patients with and those without an evaluable on-study biopsy sample ($p = 0.101$).

Safety

All patients who received one or more doses of osimertinib and from whom a predose tumor biopsy sample was successfully collected (n = 61) were included in the safety analysis. AEs in this subgroup of patients were consistent with previous reports from the AURA study[13] (see Supplementary Material for details and Supplementary Table 2).

Table 1. Efficacy Outcomes in Evaluable Patients Included in the Paired Biopsy Sample Cohort

Endpoint	Predose and Postdose Biopsy Samples Evaluable for Biomarker Analysis (n = 24)	Predose Biopsy Sample but No Postdose Biopsy Sample (Tumor Regression/Lack of Viable Tissue) (n = 29)
Median follow-up (IQR), mo	2.8 (1.4-5.5)	5.5 (2.7-9.5)
Response, n (%)		
Complete response	0 (0)	1 (3)
Partial response	7 (29)	17 (59)
Stable disease	13 (54)	11 (38)
Progressive disease	1 (4)	0
NE	3 (13)	0
ORR (95% CI), n (%)	7 (29) (13-51)	18 (62) (42-79)
ORR in patients evaluable for response (95% CI)[a]	7 (33) (15-57)	—
Median DOR (95% CI), mo	NE (2.8-NE)	8.4 (6.9-NE)
Median PFS (95% CI), mo	6.6 (3.9-NE)	9.7 (7.0-NE)

[a]Of 24 patients, 21 were evaluable for response; two patients were not eligible, as they did not have measurable disease according to the blinded independent central review read, and one patient had no baseline scan.

CI, confidence interval; DOR, duration of response; IQR, interquartile range; NE, nonevaluable; ORR, objective response rate; PFS, progression-free survival.

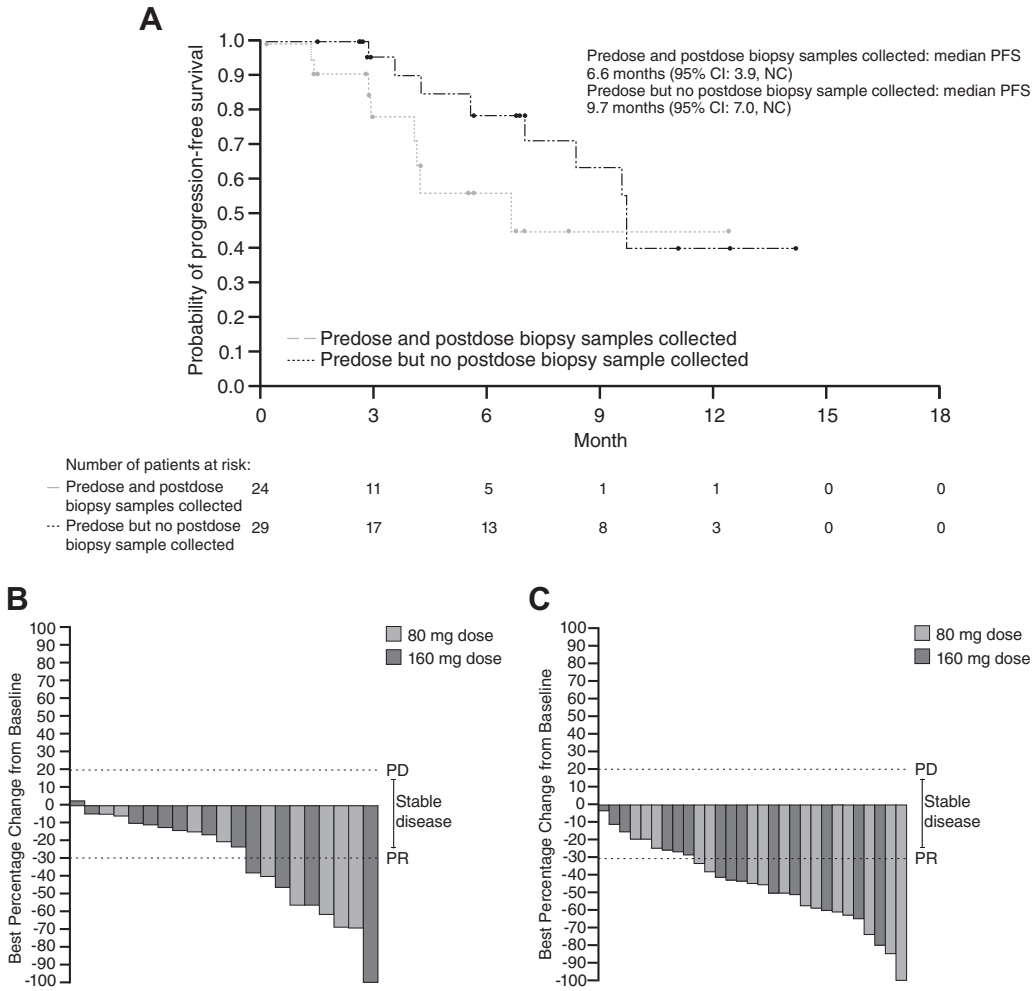

Figure 2. Kaplan-Meier curves of progression-free survival (PFS) (*A*) in patients from whom both a predose and postdose biopsy sample were successfully collected and those from whom a predose biopsy sample but no viable postdose tumor biopsy sample was collected. Waterfall plots showing best percentage change in target lesion diameter for evaluable patients from whom both predose and postdose biopsy samples were successfully collected (*B*) and those from whom a predose biopsy sample but no viable postdose tumor biopsy sample was collected (*C*). Abbreviations: CI, confidence interval; NC, not calculable; PD, progressive disease; PR, partial response.

Modulation of Key Molecular Biomarkers of Osimertinib Activity

pEGFR, pS6, and phospho-AKT levels were reduced from baseline in eight of nine (89%), 12 of 14 (86%), and seven of 13 (54%) evaluable paired samples, respectively. PD-L1 expression was consistently reduced from baseline, with a corresponding trend toward increased CD8-positive immune cell infiltration (Fig. 3) (for details, see Supplementary Material, Supplementary Table 3, and Supplementary Fig. 1).

Discussion

The collection of paired tumor samples for this unique analysis was challenging; viable postdose biopsy samples were available for only 24 of 61 patients with a predose biopsy sample. To overcome this limitation, collection of the postdose biopsy sample earlier in the predefined collection window was recommended to investigators. The difficulties in collecting viable post-treatment biopsy samples within 15 days (±7days) of treatment initiation indicated that significant tumor shrinkage may occur within the first 2 weeks of osimertinib treatment in some patients. Response at first scan (6 weeks after treatment initiation) has been reported in most responders in both AURA and the phase II AURA2 study[13,14]; this is consistent with other TKIs that target oncogenic driver mutations, which also show rapid times to first response.[15]

Patients eligible for the paired biopsy analyses achieved a lower ORR and median PFS (29% and 6.6 months, respectively) compared with patients for whom it was not possible to collect a viable postdose biopsy sample (62% and 9.7 months, respectively). These results suggest that patients eligible for the biomarker

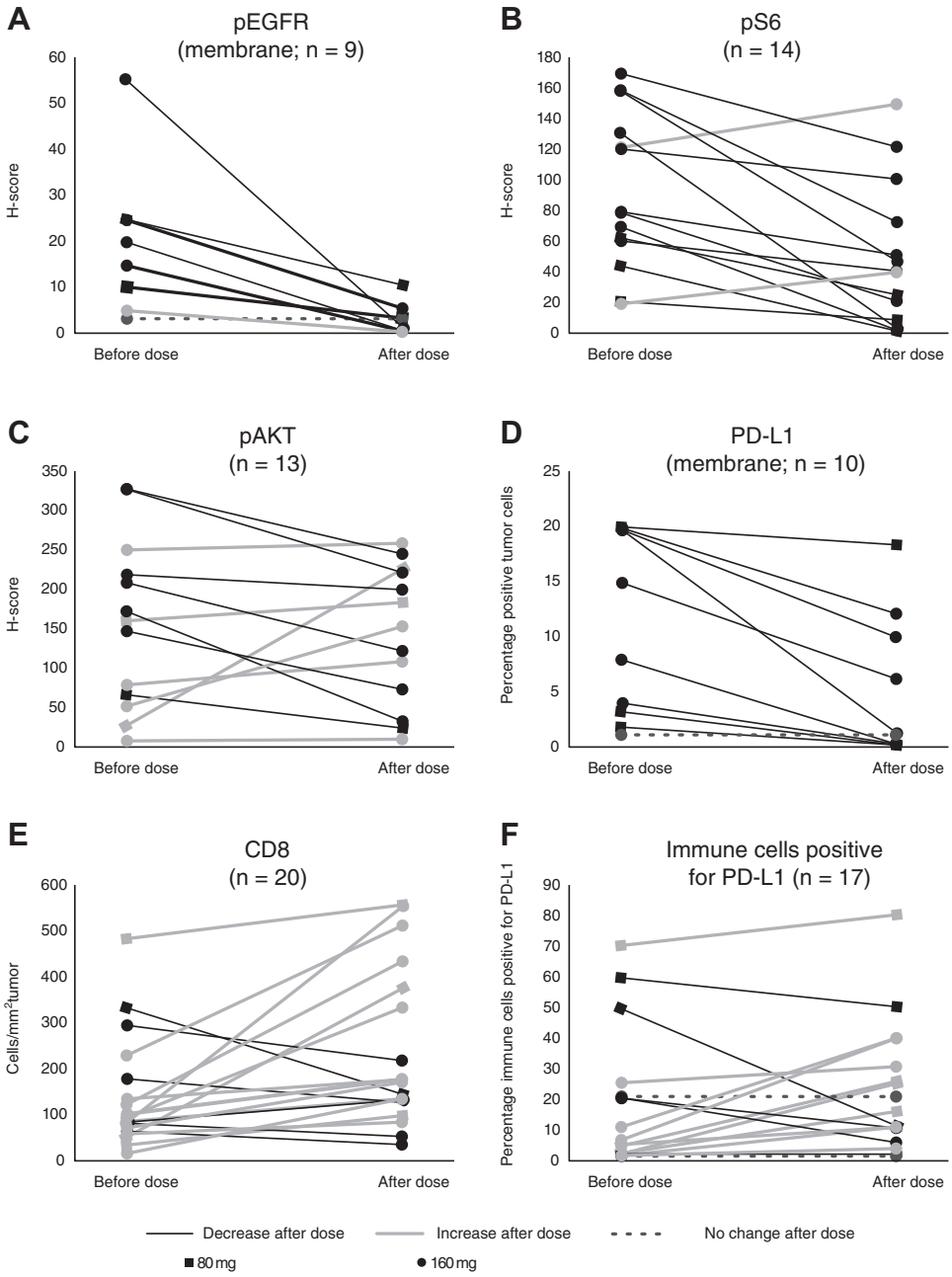

Figure 3. Line plots showing the predose and postdose H-score for matched samples for each individual patient stained for membrane phospho-EGFR (pEGFR) (*A*), phospho-S6 (S6) (*B*) and phospho-AKT (pAKT) (*C*). For tumor cells positive for membrane programmed death ligand 1 (PD-L1) (*D*), the percentage of positive tumor cells is shown. For CD8 (*E*) and immune cells positive for PD-L1 (*F*), cells per mm^2 and percentage of immune cells positive are shown, respectively. Change (decrease, increase, or no change) is indicated, as is the dose of osimertinib received (80 or 160 mg). Abbreviation: CD8, cytotoxic T-cell.

analyses—those with persistent disease after osimertinib treatment—may have less-responsive cancers compared with the overall population. However, although all patients had advanced disease, the analysis was not controlled for overall tumor burden at baseline, which may also be expected to influence response. The ORR for all patients with T790M NSCLC was 61% in the AURA phase I study (n = 138), and PFS was 9.6 months.[13] The relationship between persistent disease at time of rebiopsy and a poorer response requires further validation. In addition, biological studies are needed to understand the mechanisms that may underlie the observed differences in response.

Consistent with osimertinib's mechanism of action and preclinical data,[11] immunohistochemical analyses in a limited number of paired biopsy samples demonstrated trends toward pharmacodynamic inhibition of membrane pEGFR and cytoplasmic phospho-S6 levels.

Furthermore, membrane PD-L1 levels were consistently reduced after osimertinib treatment, with a corresponding increase in immune cell infiltration suggesting that inhibition of pEGFR by osimertinib may promote positive immune changes within the tumor microenvironment. However, because of the challenges of postdose biopsy sample collection, the number of paired samples was small and the analysis likely representative of a specific cohort of patients with limited response. Biopsy sample collection within a few days of treatment initiation may be required to accurately reflect biomarker modulation in a clinically relevant population. Analyses using plasma circulating tumor DNA offer an alternative technique that may overcome some of the challenges of obtaining tissue biopsy samples from patients with advanced disease.

Acknowledgments

The study (NCT01802632) was funded by AstraZeneca. The authors would like to thank all the patients included in this study and their families. In addition, the authors wish to thank the staff and investigators at each of the participating sites and acknowledge the contributions of Neil Smith, James Leeson, and Joseph Geradts. The authors would like to acknowledge Sarah Jane Rutherford, PhD, of iMed Comms, Macclesfield UK (an Ashfield Company and part of UDG Healthcare plc) for medical writing support that was funded by AstraZeneca in accordance with Good Publications Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2017.07.011.

References

1. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304:1497–1500.
2. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350:2129–2139.
3. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst*. 2005;97:339–346.
4. National Comprehensive Cancer Networks. NCCN clinical practice guidelines in oncology, non-small cell lung cancer (version 4.2017). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 14, February 2017.
5. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–957.
6. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362:2380–2388.
7. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
8. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
9. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med*. 2005;2:e73.
10. Huang L, Fu L. Mechanisms of resistance to EGFR tyrosine kinase inhibitors. *Acta Pharm Sin B*. 2015;5:390–401.
11. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4:1046–1061.
12. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–640.
13. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372:1689–1699.
14. Goss G, Tsai C-M, Shepherd FA, et al. Osimertinib for pretreated *EGFR* Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2016;17:1643–1652.
15. Kim DW, Mehra R, Tan DS, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2016;17:452–463.