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Patient-reported symptoms possibly related to treatment with osimertinib or chemotherapy for advanced non-small cell lung cancer

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ABSTRACT

Objectives: In the AURA3 trial, individuals received osimertinib 80 mg once daily or chemotherapy for advanced non-small cell lung cancer. Here, we explore patient-reported symptoms possibly related to treatment.

Materials and methods: AURA3 was an open-label, randomized phase III trial involving 419 patients. As part of the trial's exploratory objectives, individuals were asked to complete the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) electronically, first weekly for 18 weeks and then every 3 weeks for up to 57 weeks, subject to the availability of validated local-language versions (English, German, Japanese and Spanish versions were available).

Results: In total, 161 patients (38%; 102 receiving osimertinib, 59 receiving chemotherapy) provided data for PRO-CTCAE analyses (mean age: 64 years; 63% women). Diarrhea was reported more commonly with osimertinib than with chemotherapy, and was mostly graded as occurring rarely or occasionally. Decreased appetite was reported less commonly with osimertinib than with chemotherapy. The proportion of patients reporting nausea changed little from baseline with osimertinib and increased with chemotherapy. Few patients reported vomiting. Both nausea and vomiting were generally graded as mild in severity. Fatigue was reported less commonly with osimertinib than with chemotherapy, and was mostly graded as mild or moderate. Of patients reporting fatigue, the proportion grading it as interfering at least 'somewhat' with their usual or daily activities was lower with osimertinib than with chemotherapy.

Conclusion: Symptoms were generally mild and not frequent, with some differences in symptom patterns between the two treatment groups. The results support and complement the AURA3 trial data and give insight into patients' experience with treatment.

1. Introduction

Symptom reporting directly by patients using specific patient-reported outcome (PRO) instruments is a well-established means of measuring treatment effects in clinical trials and forms part of product development to support regulatory approvals [1]. Laboratory abnormalities and clinical observations that are potentially treatment-related are traditionally captured by the clinical investigators. For symptoms possibly related to treatment, the patient perspective captures information that may not be captured by clinicians, and provides details about frequency, intensity and impact on daily life [2,3]. Reports directly from patients tend to include more symptoms and to indicate a higher degree of symptom intensity than reports originating from the treating clinician [3,4].

The Common Terminology Criteria for Adverse Events (CTCAE) is a lexicon maintained by the US National Cancer Institute (NCI) for use in oncology trials to report adverse events. The CTCAE lexicon is organized by nied by descriptions of severity (grade) [5]. Approximately 10% of items listed in the CTCAE lexicon are symptoms, which, in clinical trials, are reported by the investigators [6]. Recently, the US NCI developed and validated a Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) to complement the standard CTCAE-based adverse event reporting in oncology trials [7,8]. A multidisciplinary group of

Abbreviations: CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; TKI, tyrosine kinase inhibitor

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investigators and patient representatives reviewed all CTCAE terms and identified 78 as being appropriate for self-reporting by adults with cancer in oncology clinical trials and thus for inclusion in the PRO-CTCAE [3]. In a multi-step process with patient input included at each step, plain-language terminology was developed for each symptom, and appropriate symptom attributes (frequency, severity, interference) were incorporated in the PRO-CTCAE to reflect those used in the corresponding CTCAE item. Translation of the PRO-CTCAE into various non-English language versions and validation of these versions are ongoing, and it is anticipated that the item library will continue to be refined as new possible treatment-related symptoms are identified and researchers gain experience in how these are best analyzed and interpreted [7]. Use of the PRO-CTCAE is supported by the US Food and Drug Administration, together with the Critical Path Institute, for the systematic assessment of possibly treatment-related patient-reported symptoms and their burden to patients, to complement existing clinical safety assessments [9].

PRO-CTCAE data were used in some of the exploratory analyses in the recently completed AURA3 trial, which assessed the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) osimertinib versus platinum-based chemotherapy as standard of care for patients with *EGFR* mutation-positive advanced non-small cell lung cancer (NSCLC) [10]. The PRO-CTCAE was included in AURA3 to increase understanding of patients' experience of symptoms potentially related to treatment. The CTCAE was the means to capture and report adverse events. To be included in AURA3, patients needed to have advanced NSCLC with confirmed presence of a p.Thr790Met point mutation (T790 M) in the gene encoding EGFR and to have acquired resistance to first-line EGFR-TKI therapy. Osimertinib is an oral, central nervous system (CNS)-active, third-generation EGFR-TKI selective for both EGFR-TKI sensitizing mutations and T790 M *EGFR* resistance mutations [11–13]. AURA3 met its primary endpoint of significantly improved progression-free survival with osimertinib relative to chemotherapy, and demonstrated improved patient-reported symptoms and health status with osimertinib compared with chemotherapy [10,14]. The most commonly reported adverse events in the early clinical development of osimertinib, captured using the CTCAE, were diarrhea, decreased appetite, nausea and rash [15]. In an interview sub-study that captured feedback on the treatment experience directly from patients, diarrhea, poor appetite, acne, rash, itching and fatigue/tiredness were identified as common symptoms/side effects in these patients [16].

Here, we report results from exploratory analyses conducted in a subset of patients as part of the AURA3 trial to capture patient-reported symptoms possibly related to treatment, using the PRO-CTCAE.

2. Materials and methods

2.1. Study design and patients

AURA3 (NCT02151981) was a multinational, open-label, randomized phase III trial. Patients were screened between August 2014 and September 2015, and 419 eligible patients were enrolled and randomized to treatment. To be eligible for inclusion, patients needed to have evidence both of locally advanced or metastatic NSCLC and of disease progression after first-line EGFR-TKI therapy [10]. An additional requirement was the documented presence of a T790 M *EGFR* mutation.

Patients were randomized in a 2:1 ratio to receive oral osimertinib 80 mg once daily or chemotherapy comprising intravenous pemetrexed 500 mg/m^2 of body surface area plus either carboplatin (at a dose aimed at providing an area under the plasma concentration–time curve of 5 mg/mL/min) or cisplatin 75 mg/m^2 every 3 weeks for up to six cycles, followed by optional pemetrexed maintenance therapy [10]. Treatment continued until disease progression, the development of unacceptable side effects, or a request by either the patient or the treating physician to discontinue treatment. The mean duration of treatment at the data cut-off date was 8.6 months in the osimertinib group and 4.8 months in the chemotherapy group.

Patients for whom validated local-language versions of the PRO-CTCAE were available (English, German, Japanese and Spanish [8]) were asked to complete the instrument electronically at baseline, every week for the first 18 weeks and then every 3 weeks thereafter for up to 57 weeks.

AURA3 was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation, applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, AstraZeneca. All patients provided written informed consent before being screened.

2.2. PRO-CTCAE

PRO-CTCAE is a validated PRO measurement system developed by the US NCI to assess symptoms possibly related to cancer treatments [3,6,8]. The PRO-CTCAE consists of 124 items, which are listed in a publicly available library and cover 78 symptoms [8]. Each item reflects specific symptom attributes included in the corresponding CTCAE. Depending on which PRO-CTCAE symptom is being assessed, up to three of the following item attributes are included: presence (yes; no); frequency (never; rarely; occasionally; frequently; almost constantly); severity (none; mild; moderate; severe; very severe); and/or interference with usual or daily activities (not at all; a little bit; somewhat; quite a bit; very much). Some PRO-CTCAE symptoms comprise just one item (e.g. yes/no for rash, frequency for diarrhea, severity for constipation), whereas others include two items (e.g. frequency and severity for nausea or vomiting, severity and interference with usual or daily activities for decreased appetite) and some include three items (e.g. frequency, severity and interference with usual or daily activities for pain in the abdomen).

The choice of PRO-CTCAE items for use in clinical trials depends on the symptoms anticipated to occur based on previous observations with the treatments that are being assessed. The standard PRO-CTCAE recall period is the past 7 days. For AURA3, 42 items relating to a total of 28 symptoms were selected as relevant from the PRO-CTCAE item bank and included in the trial. Item selection was consistent with that in the AURA2 study, based on documented EGFR-TKI class effects and the comparator effects, identified and potential risks of osimertinib, patient interviews and NCI core cancer symptoms, following NCI guidance [3,8]. Investigator interviews confirmed that the item selection for AURA3 was satisfactory to cover the symptoms that most commonly occurred in AURA3.

2.3. Data analyses

In accordance with the US NCI recommendations [8], PRO-CTCAE data were summarized descriptively as the number (%) of patients reporting each grade for individual items, and all available attribute items were included for each of the reported symptoms. The analyses were exploratory and descriptive, and no statistical comparisons were conducted. Results reported here are for the following 13 items representing eight symptoms, which were identified as common from patient interviews: diarrhea (frequency); fecal incontinence (frequency, interference); decreased appetite (severity, interference); nausea (frequency, severity); vomiting (frequency, severity); rash (presence); acne (severity); and fatigue (severity, interference).

3. Results

3.1. Patients

Data for PRO-CTCAE analyses were available for 161 (38%) of the 419 patients randomized in AURA3 (102 from the osimertinib group and 59 from the chemotherapy group) (Fig. 1). Patient demographics for the two treatment groups are presented in Table 1. The overall mean age of the patients was 64 years, and 63% were women. Most patients

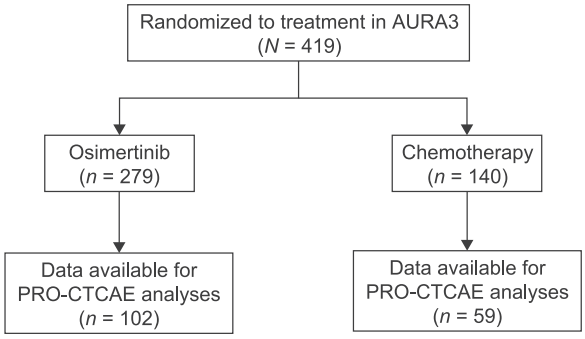

Fig. 1. CONSORT diagram showing patient flow in the AURA3 trial and for the subgroups with PRO-CTCAE data. CONSORT, Consolidated Standards of Reporting Trials; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

Table 1
Patient demographics.

	Osimertinib 80 mg (n = 102)	Chemotherapy (n = 59)
Age, years, mean (SD)	63.7 (12.3)	64.5 (11.0)
Women, n (%)	65 (63.7)	36 (61.0)
WHO performance status		
0	43 (42.2)	25 (42.4)
1	59 (57.8)	34 (57.6)
AJCC staging at diagnosis[a]		
IA	0 (0.0)	2 (3.4)
IB	6 (5.9)	5 (8.5)
IIA	3 (2.9)	0 (0.0)
IIB	1 (1.0)	0 (0.0)
IIIA	5 (4.9)	5 (8.5)
IIIB	4 (3.9)	3 (5.1)
IV	81 (79.4)	44 (74.6)
CNS metastases[b]	26 (25.5)	15 (25.4)
Study country, n (%)		
Japan	41 (40.2)	22 (37.3)
USA	10 (9.8)	11 (18.6)
Canada	10 (9.8)	5 (8.5)
Spain	7 (6.9)	7 (11.9)
UK	12 (11.8)	2 (3.4)
Germany	10 (9.8)	3 (5.1)
Australia	8 (7.8)	5 (8.5)
Mexico	3 (2.9)	2 (3.4)
South Korea	1 (1.0)	2 (3.4)

Abbreviation: AJCC, American Joint Committee on Cancer; CNS, central nervous system; SD, standard deviation; WHO, World Health Organization.

[a] Information missing for 2 patients in the osimertinib group.

[b] At baseline.

for whom PRO-CTCAE data were available were enrolled in Japan, the USA or Canada. PRO-CTCAE data were provided by 128 patients at baseline (80% response rate). At 24 weeks, 104 of the 114 patients who were still receiving study treatment at that time provided PRO-CTCAE data (91% response rate); and at 48 weeks, 40 of the 45 patients still receiving treatment provided data (89% response rate). In total, 73 of the patients providing PRO-CTCAE data experienced disease progression during the study period, and 67 discontinued treatment.

3.2. PRO-CTCAE symptoms

3.2.1. Gastrointestinal symptoms

At baseline, diarrhea was reported by 32% of patients in the osimertinib group and 36% in the chemotherapy group. Post-baseline, the proportion of patients reporting diarrhea was higher with osimertinib than with chemotherapy (Fig. 2a). Most patients reporting diarrhea graded it as occurring rarely or occasionally. Fecal incontinence was reported at baseline by 6% of patients in the osimertinib group and 15% in the chemotherapy group, and at 4 weeks post-baseline by 11% of patients in the osimertinib group and 9% in the chemotherapy group; most patients reporting this symptom graded it as interfering with their usual or daily activities at least 'a little bit' (data not shown).

Decreased appetite was reported by 54% of patients in the osimertinib group and by 53% of those in the chemotherapy group at baseline (Fig. 2b). Post-baseline, decreased appetite was reported less commonly in the osimertinib group than in the chemotherapy group. At 24 weeks, the proportion of patients reporting decreased appetite dropped in the chemotherapy group to a level similar to that in the osimertinib group. Among the patients who reported decreased appetite, the proportion who graded it as interfering with their usual or daily activities at least 'somewhat' was lower in the osimertinib group than in the chemotherapy group post-baseline (Fig. 2c).

For nausea, the reported frequency at baseline was 25% in the osimertinib group and 34% in the chemotherapy group (Fig. 2d). Post-baseline, the proportion of patients reporting nausea changed little in the osimertinib group and increased in the chemotherapy group. Among the patients who reported having nausea, most graded its severity as mild (Fig. 2e). Vomiting occurred in only a minority of patients (Fig. 2f). It was less frequent with osimertinib than with chemotherapy at baseline, and its frequency changed little post-baseline. Most patients who reported vomiting graded it as occurring rarely or occasionally. Among the patients who reported vomiting, most graded its severity as mild (Fig. 2g).

3.2.2. Cutaneous symptoms

At baseline, 37% of patients in the osimertinib group and 30% of those in the chemotherapy group reported the presence of acne. Post-baseline, rates of acne remained relatively constant over time in the osimertinib group and decreased in the chemotherapy group (Fig. 3a). The percentage of patients reporting the presence of rash was 36% in the osimertinib group and 19% in the chemotherapy group at baseline, and rates in each of the two groups remained relatively constant post-baseline (Fig. 3b).

3.2.3. Fatigue

Fatigue was reported at baseline by 64% of patients in the osimertinib group and 72% of those in the chemotherapy group. The proportion of patients reporting at least mild fatigue remained relatively constant in the osimertinib group and increased post-baseline in the chemotherapy group (Fig. 4a). Among those patients who reported fatigue, most graded it as mild or moderate in severity. The proportion who graded this symptom as interfering with their usual or daily activities at least 'somewhat' was lower in the osimertinib group than in the chemotherapy group (Fig. 4b).

4. Discussion

The PRO-CTCAE allows patients to self-report possible treatment-related symptoms while undergoing cancer treatment in oncology trials [7,8]. This paper presents results from exploratory analyses using PRO-CTCAE data, conducted as part of the recently completed AURA3 trial. To our knowledge, this is the first reporting of PRO-CTCAE data from a phase III clinical trial of oncology treatment. AURA3 assessed the efficacy and safety of osimertinib compared with platinum-based chemotherapy plus pemetrexed in patients with *EGFR* mutation-positive advanced NSCLC in whom disease had progressed during first-line therapy with an EGFR-TKI [10]. Osimertinib demonstrated improved efficacy compared with platinum-based chemotherapy (median duration of progression-free survival: 10.1 months vs 4.4 months, respectively; hazard ratio: 0.30; $p < 0.001$), including in patients whose disease had metastasized to the CNS [10]. Only those patients for whom validated local-language versions of the PRO-CTCAE were available (English, German, Japanese and Spanish [8]) were asked to complete the instrument, and PRO-CTCAE data were thus available only for a subset (38%) of the patients randomized in AURA3.

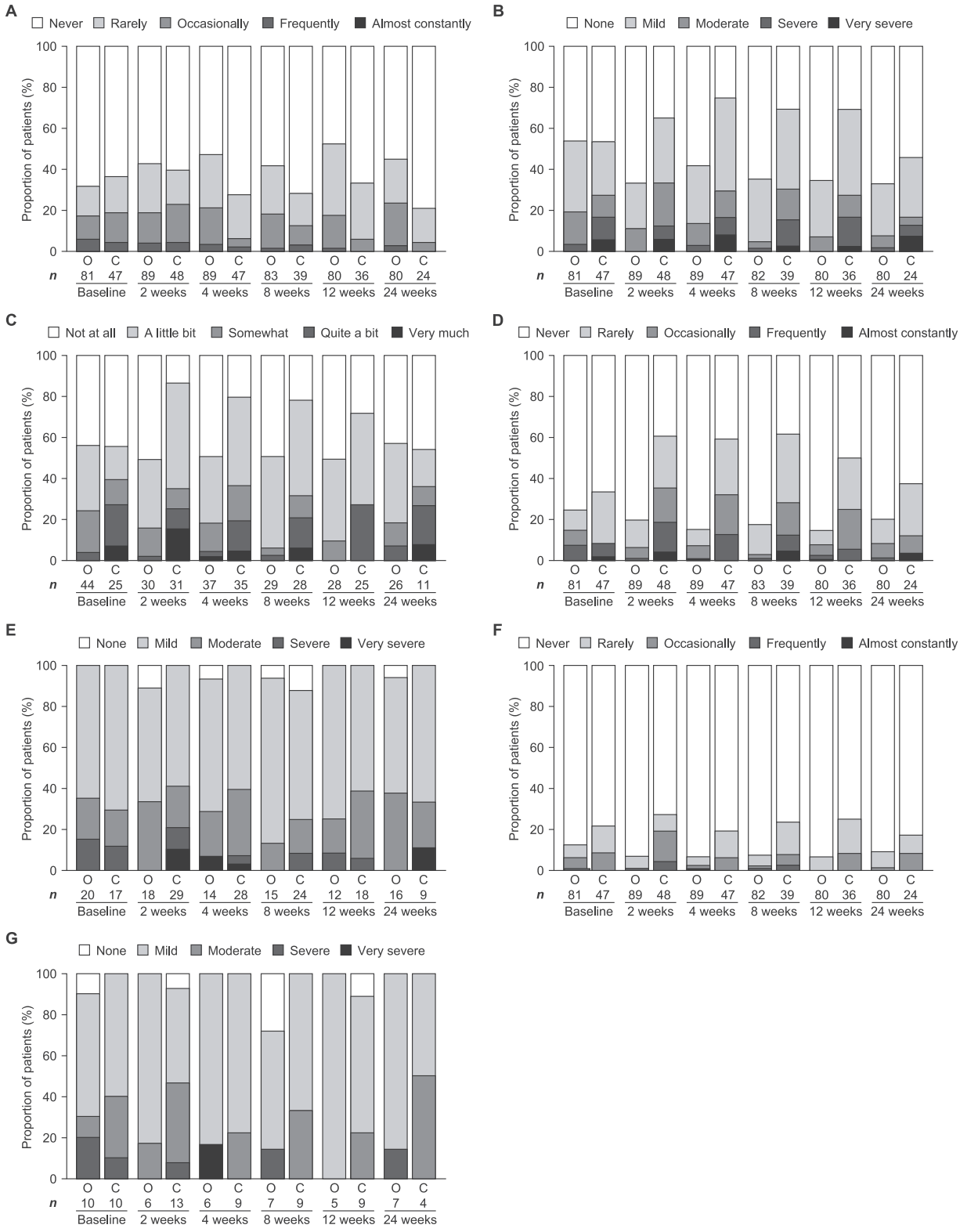

Fig. 2. Proportions of patients reporting attributes of gastrointestinal symptoms: (A) frequency of diarrhea; (B) severity of decreased appetite; (C) impact of decreased appetite among patients reporting at least mild symptom severity; (D) frequency of nausea; (E) severity of nausea among patients reporting at least rare symptom frequency; (F) frequency of vomiting; and (G) severity of vomiting among patients reporting at least rare symptom frequency. C, chemotherapy; O, osimertinib.

Results from the exploratory analyses reported here show that, overall, symptoms were generally mild and not frequent. There were some differences in symptom patterns between the group treated with osimertinib and the group receiving chemotherapy in AURA3. With regard to gastrointestinal symptoms, the proportion of patients reporting diarrhea was higher in the osimertinib group than in the chemotherapy group, whereas the proportions of patients reporting decreased appetite, nausea or vomiting were higher in the chemotherapy group than in the osimertinib group. Rates of acne and rash were already higher in the osimertinib group than in the chemotherapy

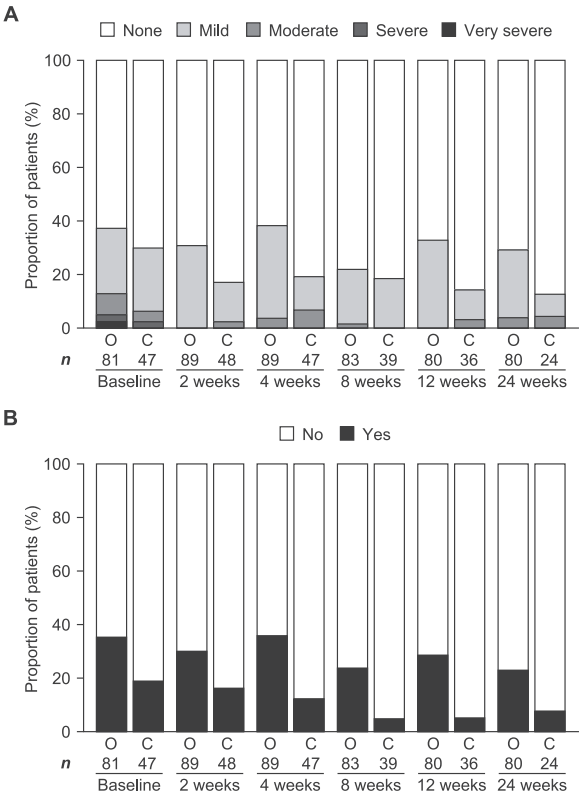

Fig. 3. Proportions of patients reporting attributes for cutaneous symptoms: (A) severity of acne; and (B) presence/absence of rash. C, chemotherapy; O, osimertinib.

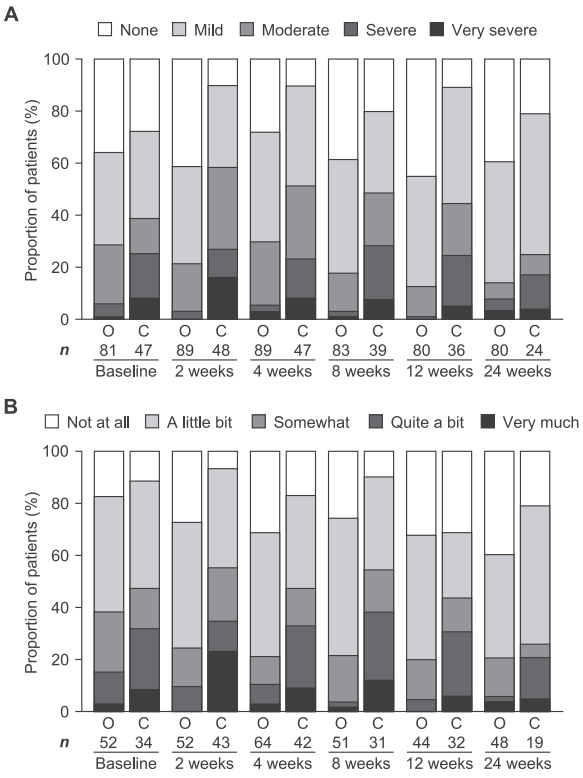

Fig. 4. Proportions of patients reporting (A) severity of fatigue; and (B) interference of fatigue with usual/daily activities among those patients reporting at least mild severity. C, chemotherapy; O, osimertinib.

group at baseline and changed little post-baseline in the two treatment groups, suggesting that the allocated treatments did not affect the prevalence of these symptom items. The PRO-CTCAE captures more detailed information about possible treatment-related symptoms than does the CTCAE, which for diarrhea captures only its frequency, grades nausea by its effect on food intake and includes loss of appetite only as a descriptor for nausea or anorexia events [17].

Fatigue was reported by more than two-thirds of patients included in the current analyses (67% at baseline and 78% at 4 weeks). The proportion of patients reporting this symptom was higher in the chemotherapy group than in the osimertinib group. Fatigue as a possible treatment-related symptom was reported by 17% of patients in a phase I/II study of osimertinib [15], and in AURA3 it was reported by 16% of patients receiving osimertinib and 28% receiving chemotherapy [10]. The CTCAE defines fatigue as a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities, and its grading depends on whether it is relieved by rest and the extent to which it limits activities of daily living [17]. The symptom can be difficult to describe, and agreement between patients and clinicians when reporting on patients' fatigue is lower than for those symptoms that can be observed directly, such as diarrhea and vomiting [18]. In a recently reported phase II trial that enrolled patients with head or neck cancer, participants completed the PRO-CTCAE, and their treating physicians submitted CTCAE reports [19]. Of 13 symptoms assessed, agreement between patient- and physician-reported scores was lowest for fatigue, indicating that this symptom is better described using the PRO-CTCAE: at 6 weeks post-baseline, fatigue was reported as being moderate, severe or very severe in 86% of patients when the symptom was patient-reported, compared with 14% of patients when the symptom was physician-reported [19].

Adverse events, captured in AURA3 using the CTCAE, tended to be less severe with osimertinib than with chemotherapy [10]. The observed differences between treatment groups in patient-reported items in the current analyses, assessed using the PRO-CTCAE, are in line with CTCAE-based adverse event reporting in AURA3, which showed higher rates of diarrhea and rash with osimertinib than with chemotherapy, and higher rates of decreased appetite, nausea, vomiting and fatigue with chemotherapy than with osimertinib [10]. The results of the current analyses are also in line with the good tolerability profile of osimertinib documented in the AURA interview sub-study. In the phase I/II study of osimertinib, diarrhea, decreased appetite, nausea and rash were the most commonly reported adverse events captured via the CTCAE [15], and patients participating in the interview sub-study reported diarrhea, poor appetite, acne, rash, itching and fatigue as common symptoms/side effects while receiving treatment, with mean scores generally in the low-to-moderate range [16]. Reduced quality of sleep and difficulty staying asleep, although rated by only one or two patients in the interview sub-study, received high bothersomeness and severity scores [16], and may contribute to patient-reported fatigue.

The current analyses support the use of the PRO-CTCAE in oncology trials to provide detailed, descriptive, patient-centered data on the frequency, intensity and impact on daily life of possible treatment-related symptoms; such data complement standard reporting using the CTCAE. Measuring the patient experience beyond survival outcomes can be particularly valuable when assessing potential new therapies in an advanced disease setting in which there are no curative options. Using PRO-CTCAE alongside other validated measures will ensure that symptoms possibly related to treatment and the impacts of these symptoms on functional health reported by patients are adequately captured. Guidelines published on behalf of the US Center for Medical Technology Policy recommend including validated PRO measures such as the PRO-CTCAE in all prospective comparative effectiveness oncology trials, with information collected using electronic data capture technologies whenever possible [20]. The 1-week recall period for the PRO-CTCAE used in AURA3 is as recommended by the US NCI and was shown recently to correspond better with daily reporting than longer recall periods of 2, 3 or 4 weeks in patients

receiving treatment for cancer [21]. In a feasibility study that enrolled patients receiving treatment for lung cancer, most participants (86%) were willing and able to self-report symptoms at expected time points during treatment using the PRO-CTCAE via tablet computer at clinic visits [22]. In the current analyses, the response rate was 80% at baseline and about 90% at 24 weeks and 48 weeks, indicating favorable adherence with no drop-off.

A novelty of the current analyses is that they represent one of only a handful of reported uses of the PRO-CTCAE and the first report of its use in a phase III clinical trial of oncology treatment. It provides 'proof of concept' for inclusion of this PRO measure in clinical trials as part of the reporting of possible treatment-related symptoms. Insights from the current analyses can help to guide discussion about potential further improvements of the PRO-CTCAE for future studies [7]. A limitation of the current analyses is that they included data from only a subset of patients enrolled in AURA3. Linguistic validations of different language versions of the PRO-CTCAE are ongoing. When the AURA3 trial was conducted, validated local-language versions of the PRO-CTCAE were available for only 38% of the study population. A large proportion (39%) of the patients with available PRO-CTCAE data were enrolled in a single country, Japan, which potentially affects the generalizability of the results. A limitation inherent to the PRO-CTCAE is that it does not measure the same attributes across all included symptoms. For some symptoms there is just one PRO-CTCAE item, whereas for others there are two or three. For example, there is only a binary question asking about the presence or absence of rash and only a single question asking about severity of acne, and yet other symptoms also have a question about interference with usual or daily activities. This inconsistent approach limits interpretation of PRO-CTCAE data.

In conclusion, results from the current exploratory analyses support and complement the AURA3 study results, and align with the good tolerability profile of osimertinib documented in the AURA interview sub-study. It is the first reported use of the PRO-CTCAE in a phase III clinical trial of oncology treatment to capture symptoms possibly related to treatment. The PRO-CTCAE has the potential to bring the patient voice to clinical trials, and to provide insights into patients' experiences of treatment.

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Conflict of interest statements

Martin Sebastian has received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme Ltd, Novartis, Pfizer, Pierre Fabre and Roche, and has acted as a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Merck Sharp & Dohme Ltd, Novartis, Pfizer and Roche. Anna Rydén and Andrew Walding are employees of AstraZeneca and hold AstraZeneca shares. Vassiliki Papadimitrakopoulou has received research support grants from ACEA, AstraZeneca, Bristol-Myers Squibb, Genentech, Janssen, Merck and Novartis, and has served on advisory boards for ARIAD, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Janssen Global Services, Merck and Novartis.

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