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RESEARCH ARTICLE

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Adverse events self-reported by patients with extensive-stage small-cell lung cancer in the phase III CASPIAN study

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ABSTRACT

Aim: In the phase III CASPIAN study, first-line durvalumab plus platinum-etoposide (EP) improved survival compared with EP in patients with extensive-stage small-cell lung cancer. We report an exploratory analysis of patient-reported adverse events (AEs).

Methods: Of 537 patients randomized to durvalumab + EP or EP arms, 164 were asked to complete the Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) for AEs at baseline, every 3 weeks (q3w) during EP, then q4w until disease progression, then post-progression on day 28, 2 months, and q8w until second progression/death. Presence/absence, frequency, or severity of 11 selected AEs were examined during the first 24 weeks of treatment, alongside interference with usual/daily activities for five AEs.

Results and conclusions: A minority of patients reported the examined AEs before starting treatment, from 3–5% who reported hand-foot syndrome, up to 34–41% for dry mouth. AE rates were generally comparable with baseline and the patterns of AEs reported by patients over time were similar in both treatment arms. Most patients indicated that reported AEs occurred rarely/occasionally and were mild/moderate in severity. These PRO-CTCAE data complement the clinician-reported AEs and give insight into patients' experience of treatment.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT03043872.

PLAIN LANGUAGE SUMMARY

What is this article about?

The CASPIAN clinical study, for patients with small-cell lung cancer (SCLC) that has spread beyond a single area (extensive-stage SCLC; ES-SCLC) who had not received any previous treatment, showed that patients treated with durvalumab plus chemotherapy had a better chance of living longer than patients treated with chemotherapy alone. Treatment for ES-SCLC causes side effects which add to the cancer-related symptoms that patients commonly experience and can impact quality of life. We investigated how a subset of patients in CASPIAN reported 11 side effects using a validated questionnaire developed by the US National Cancer Institute. Patients completed the questionnaire before starting treatment and at regular intervals during treatment.

What were the results?

We showed that patients treated with durvalumab plus chemotherapy reported a similar pattern of occurrence, frequency, and severity of side effects as patients treated with chemotherapy alone throughout the first 24 weeks of treatment. A comparable proportion of patients treated with durvalumab plus chemotherapy as of those treated with chemotherapy alone reported each side effect at any visit during this treatment period. Patients generally reported that side effects occurred only rarely or occasionally, or when present, as mild or moderately severe.

What do the results mean?

These findings give insight into patient experiences of treatment with durvalumab plus chemotherapy and support previously published results that this treatment prolongs the life of patients with ES-SCLC without adversely affecting patients' perspectives on side effects and quality of life when compared to treatment with chemotherapy alone.

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Article highlights

- In the phase III CASPIAN study, first-line durvalumab plus platinum-etoposide (EP) significantly improved overall survival (OS) compared with EP alone in patients with extensive-stage small-cell lung cancer (ES-SCLC), and OS benefit was sustained with a median follow-up of >3 years.
- While improvements in survival outcomes of patients with ES-SCLC are important and welcomed, it is important that the treatment provided to prevent disease progression does not in itself result in worsening of health-related QoL (HRQoL).
- Patient-reported outcomes (PROs) assessed using established HRQoL instruments have previously shown that patients who received durvalumab plus EP or EP alone in the CASPIAN study experience a numerical reduction in symptom burden over a 12 month-period for key disease-related symptoms including cough, dyspnea, chest pain, fatigue, and appetite loss.
- The present exploratory analysis assessed patient-reported adverse events (AEs) using the PRO version of the Common Terminology Criteria for AEs (PRO-CTCAE), developed by the US National Cancer Institute.
- We found that 11 selected AEs examined during the first 24 weeks of treatment in CASPIAN were generally reported by a minority of patients at each timepoint, mostly with rare or occasional frequency or mild-to-moderate severity. Reporting rates and patterns for all selected AEs were broadly similar in the durvalumab plus EP and EP arms.
- These results complement the clinician-assessed safety profile observed in the CASPIAN study and give insight into the patients' experience of treatment. Addition of durvalumab to EP appears to provide a meaningful benefit by significantly prolonging survival in patients with ES-SCLC without adversely impacting PROs on symptomatic AEs and HRQoL.

1. Introduction

In the phase III CASPIAN study (NCT03043872), first-line durvalumab in combination with etoposide plus either cisplatin or carboplatin (EP) significantly improved overall survival (OS) compared with EP alone in patients with extensive-stage small cell lung cancer (ES-SCLC), with a hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.59–0.91; $p = 0.0047$), establishing durvalumab plus EP as a global standard of care in this setting [1]. Notably, OS benefit was sustained with a median follow-up in censored patients of >3 years (HR = 0.71, 95% CI: 0.60–0.86; nominal $p = 0.0003$) [2]. Adverse events (AEs) reported in CASPIAN were consistent with the known safety profiles of durvalumab and EP [1,3].

While improvements in survival outcomes of patients with ES-SCLC are important and welcomed, longer survival ideally should not compromise patients' quality-of-life (QoL). Patients with SCLC commonly experience a broad range of disease-related symptoms that contribute considerably to worsening of health-related QoL (HRQoL); it has been suggested that the impact is greatest among treatment-naïve patients with ES-SCLC, as these patients are likely to experience rapid progression of disease if left untreated [4]. Nevertheless, it is important that the treatment provided to prevent disease progression does not in itself result in worsening of HRQoL. Results of the assessment of patient-reported outcomes (PROs) in CASPIAN using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3 and the Lung Cancer 13 (QLQ-LC13) module have been reported previously [5]. Briefly, the addition of durvalumab to first-line EP resulted in patients' HRQoL being maintained and delayed worsening of patient-reported symptoms, functioning, and global health status/QoL compared with EP alone [5].

Additionally, an exploratory study objective in CASPIAN was to assess patients' perspectives on key AEs of relevance. Standard AE reporting by physicians during the study incorporated classification of AEs according to Preferred Terms (PT) within the Medical Dictionary for Regulatory Activities (MedDRA) and grading of their severity per the Common Terminology Criteria for AEs (CTCAE) version 4.03, which include laboratory-based, observed or measurable, and symptomatic AEs. However, clinicians may under-report the incidence and severity of symptomatic AEs compared with what is reported directly by patients [6–8]; conversely, patients may underplay the severity of their symptoms to their physicians due to believing that treatment may be stopped if their clinical condition worsens [9]. Thus, to complement standard MedDRA- and CTCAE-based AE reporting by physicians, the US National Cancer Institute developed a PRO version of CTCAE (PRO-CTCAE®) [10,11] covering 78 common AEs that were identified by a multidisciplinary team including patients and clinicians, and validated with inputs from patients. The questionnaire was then tested and refined in academic and community-based cancer treatment sites [11]. Each of the AEs in the PRO-CTCAE is assessed using questions ('items') concerning 1–3 out of 4 attributes [10]: presence/absence, frequency, severity, and interference with usual/daily activities. The PRO-CTCAE thus captures symptomatic AEs systematically from patients and provides descriptive data to complement CTCAE-based reporting by clinicians [10,11]. The use of PRO-CTCAE as a means of systematic assessment of patient-reported AEs is supported by the US Food and Drug Administration (FDA) and the Critical Path Institute to provide complementary data to existing safety measures [12].

Here, we report the results of exploratory analyses using the PRO-CTCAE to assess select AEs from the perspective of patients treated with durvalumab plus EP or EP in the CASPIAN study. A plain language summary of this article can be found in the supplement.

2. Patients and methods

2.1. Study design and patients

CASPIAN was a randomized, open-label, sponsor-blind, multicenter, global phase III study. Efficacy and safety results have been reported previously [1–3], and the study methodology is described in detail in the primary report [1]. Briefly, eligible patients were aged ≥18 years (≥20 years in Japan) and had treatment-naïve histologically or cytologically documented ES-SCLC, World Health Organization performance status (WHO PS) score of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 [1].

As previously reported, the study was conducted in accordance with the International Conference on Harmonisation good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations with approval from an independent ethics committee or institutional review boards. The

protocol and all modifications were approved by relevant ethics committees and regulatory authorities [1–3,5].

2.2. Treatment

In brief and as previously summarized [5], patients were randomized to receive durvalumab plus EP, durvalumab plus tremelimumab plus EP, or EP in a 1:1:1 ratio. Randomization was stratified by planned platinum agent: either carboplatin or cisplatin. Administration of all drugs was by intravenous infusion (IV). In each arm, treatment with EP was composed of etoposide 80–100 mg/m^2, administered on days 1–3 of each 21-day cycle, and investigator's choice of either carboplatin area under the curve 5–6 mg/mL/min or cisplatin 75–80 mg/m^2, administered on day 1 of each cycle. In the immunotherapy arms, patients received EP plus durvalumab 1500 mg, either with or without tremelimumab 75 mg, every 3 weeks for 4 cycles; this was followed by maintenance durvalumab 1500 mg every 4 weeks. In the durvalumab plus tremelimumab plus EP group, patients received an additional dose of tremelimumab 75 mg after EP (i.e., up to five doses in total). Durvalumab and tremelimumab (where applicable) were administered on day 1 of each cycle. At the investigator's discretion, patients in the EP arm could receive 2 additional cycles of EP, up to 6 cycles in total; they could also receive prophylactic cranial irradiation after EP. Treatment continued until disease progression per investigator assessment, unacceptable toxicity, or other discontinuation criteria were met. Treatment with durvalumab could continue beyond disease progression if the investigator considered the patient to be deriving clinical benefit.

2.3. Endpoints and assessments

The primary endpoint of CASPIAN was OS; secondary endpoints included progression-free survival (PFS), objective response rate, safety and tolerability [1]. Assessment of AEs by patient self-reporting of specific CTCAE symptoms using the PRO-CTCAE was an exploratory objective.

The PRO-CTCAE consists of a library of 124 items representing 78 symptomatic AEs that are common in oncology clinical trials, derived from the CTCAE [10,11], with the questionnaire written in easily understandable language [10]. The 78 symptomatic AEs are divided into 14 categories: oral, gastrointestinal, respiratory, cardio/circulatory, cutaneous, neurological, visual/perceptual, attention/memory, pain, sleep/wake, mood, genitourinary, sexual, and miscellaneous. For this analysis, 11 AEs from the PRO-CTCAE item library were specifically selected before the start of the CASPIAN study as being the most relevant to patients with ES-SCLC and the treatment they received in CASPIAN. These 11 AEs were chosen as a result of internal discussion by the study sponsor that included members of different functions who considered the patient population of the study and the known safety profile of the treatment. Only items that were considered relevant for the study, site of cancer, and cancer treatment were selected. Fatigue and digestive issues were not included as they were reported in the previous PRO publication from the CASPIAN study by Goldman et al [5], which reported on PROs assessed with the EORTC QLQ-C30 and QLQ-LC13 modules; symptoms reported in the Goldman publication included appetite loss, constipation, diarrhea, fatigue, and nausea or vomiting.

For the 11 selected AEs from the PRO-CTCAE item library, 16 attributes were captured (Supplementary Table S1): pain and swelling at injection site (questionnaire language: "pain/swelling/redness at site of drug injection or IV;" attributes captured: presence/absence), rash ("rash;" presence/absence), swelling ("arm or leg swelling;" frequency and interference), abdominal pain ("pain in the abdomen;" frequency and interference), chills ("shivering or shaking chills;" frequency), dizziness ("dizziness;" severity and interference), dry mouth ("dry mouth;" severity), hand-foot syndrome ("hand-foot syndrome;" severity), itching ("itchy skin;" severity), mouth/throat sores ("mouth and throat sores;" severity and interference), and numbness and tingling ("numbness or tingling in hands or feet;" severity and interference).

The PRO-CTCAE was administered only in countries in which validated local-language versions were available (in English, German, Japanese, or Spanish) [10]. Patients were asked to complete the PRO-CTCAE by e-device, using conditional branching logic for data capture for symptomatic AEs for which more than one attribute was captured (in the sequence frequency, severity, interference [10]) to reduce respondent burden. Patients were asked to complete the PRO questionnaire during their clinic visit, before any other study procedures and before discussion of disease status to avoid introducing bias to the patient's responses to the questions. For swelling, abdominal pain and chills, for which frequency and severity are both attributes, we only analyzed frequency as this attribute is captured prior to severity, as per the FDA Project Patient Voice [13]. The recall period for the PRO-CTCAE (i.e., the period of time patients were asked to consider when responding to the questionnaire) was the past 7 days [10]. At the time of the study, there were no standardized scoring rules for how to combine attributes (frequency, severity, interference) into a single score, and no summation score exists for the PRO-CTCAE. As such, AEs and their corresponding attributes are presented separately.

Assessment of AEs by PRO-CTCAE was performed at baseline (defined as the last assessment on or prior to randomization, or before the first dose if assessment was only available after randomization), every 3 weeks during EP (in both arms), then every 4 weeks until disease progression (PD), followed by day 28 post-PD, 2 months post-PD, and every 8 weeks until second progression or death [10]. The present analysis includes data through to 24 weeks, per the focus of the AURA3 report in Project Patient Voice [14] and to focus on the time period of acceptable compliance with PRO-CTCAE completion.

Compliance rate for each visit was defined as the number of patients with an evaluable questionnaire within the analysis visit window, divided by the number of patients expected to complete the questionnaire (defined as the number of patients who were still enrolled in the study at the scheduled assessment but excluding patients in countries with no available translation). In the current study, a compliance rate equal to or higher than 60% was considered acceptable. Although there is no standard for acceptable response rates for PRO questionnaires in oncology trials, to the authors' knowledge,

Kennedy *et al.* [15] have used a rate of 60% as acceptable ("high compliance"). Furthermore, journals such as JAMA [16] require a minimum response rate of 60% for a manuscript reporting a survey study to be considered for submission and peer review. The analyses were exploratory and descriptive, and no statistical comparisons were conducted. While data were collected from patients in all three arms of CASPIAN, only data for durvalumab plus EP and EP are reported herein, as the regimen of durvalumab plus tremelimumab plus EP did not meet the primary efficacy endpoint and is not an established standard of care in ES-SCLC.

3. Results

3.1. Patients

Of the 537 patients randomized to the durvalumab plus EP and EP arms in CASPIAN, 164 patients (31%) who were enrolled in the US, Argentina, Austria, Germany, Japan, and Spain were asked to complete validated local-language versions of the PRO-CTCAE (durvalumab plus EP: $n = 83/268$; EP: $n = 81/269$) (Supplementary Figure S1). Among these patients, baseline demographics and disease characteristics were generally similar between the two arms (Table 1). Compared with the overall CASPIAN population [1], the population invited to complete the PRO-CTCAE questionnaire consisted of more female patients (durvalumab plus EP, 29% versus 37%; EP, 32% versus 42%) and more Asian patients (durvalumab plus EP, 13% versus 22%; EP, 16% versus 20%). In addition, there was an imbalance in the WHO PS 0 status between the overall CASPIAN population and the population asked to complete the PRO-CTCAE (durvalumab plus EP, 37% versus 36%; EP, 33% versus 44%).

Table 1. Baseline demographics and disease characteristics in patients asked to complete the PRO-CTCAE.

	Durvalumab + EP ($n = 83$)	EP ($n = 81$)
Median age, years (range)	65.0 (40–82)	63.0 (46–82)
Sex, n (%)		
Male	52 (62.7)	47 (58.0)
Female	31 (37.3)	34 (42.0)
Race, n (%)		
White	63 (75.9)	62 (76.5)
Asian	18 (21.7)	16 (19.8)
Other	2 (2.4)	3 (3.7)
WHO PS, n (%)		
0	30 (36.1)	36 (44.4)
1	51 (61.4)	44 (54.3)
Missing	2 (2.4)	1 (1.2)
AJCC disease stage at diagnosis, n (%)		
III	10 (12.0)	6 (7.4)
IV	73 (88.0)	75 (92.6)
Study country, n (%)		
Spain	20 (24.1)	25 (30.9)
United States	25 (30.1)	18 (22.2)
Japan	18 (21.7)	16 (19.8)
Germany	11 (13.3)	8 (9.9)
Austria	4 (4.8)	13 (16.0)
Argentina	5 (6.0)	1 (1.2)

AJCC, American Joint Committee on Cancer; EP, Platinum-etoposide; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; WHO PS, World Health Organization performance status.

3.2. Completion of PRO-CTCAE questionnaire

At baseline, the PRO-CTCAE was answered by 84% (70/83) of patients who were asked to complete the questionnaire in the durvalumab plus EP arm and by 81% (66/81) in the EP arm. Compliance with PRO-CTCAE completion is shown in Figure 1; compliance rates of ≥60% were achieved up to cycle 32 in the durvalumab plus EP arm and up to cycle 6 in the EP arm. Notably, the number of respondents at each timepoint were <10 from cycle 23 onwards for durvalumab + EP and cycle 16 onwards for EP.

3.3. Presence or absence, frequency, and severity of PRO-CTCAE symptomatic AEs at baseline and during the first 24 weeks of treatment

At baseline (i.e., before starting treatment), a minority of patients reported AEs ranging from 4–34% and 3–41% in patients who received durvalumab + EP and EP, respectively (Figure 2) [17].

At each timepoint during treatment, although some variability was observed, the proportions of patients reporting the AEs (expressed as percentages of the number of patients completing the PRO-CTCAE at the specific timepoints) were generally comparable with those at baseline in both arms up to cycle 8 or 24 weeks after starting treatment, although there were a few exceptions. The proportion of patients reporting "mild" or worse dizziness showed a numerical increase from 16% at baseline to a peak of 40% at cycle 5 in those who received durvalumab plus EP, while proportions were similar to baseline in those who received EP (Figure 2(f)). The proportion of patients reporting "mild" or worse itching showed a numerical increase from 13% at baseline to a peak of 34% at cycle 6 in those receiving durvalumab plus EP and from 12% at baseline to a peak of 42% at cycle 8 in those receiving EP (Figure 2(i)). Similarly, the proportion of patients reporting "mild" or worse numbness and tingling showed a numerical increase in both arms, from baseline values of 16% and 20% to peaks of 39% and 47% at cycle 8 in those who received durvalumab plus EP and EP, respectively (Figure 2(k)).

Among patients reporting any frequency of swelling, abdominal pain, or chills at baseline or at the on-treatment timepoints, the majority reported the frequency as "rarely" or "occasionally" (Figure 2(c–e)). Among patients reporting any severity of 6 AEs, the majority reported the severity as "mild" or "moderate" at baseline or at the on-treatment timepoints for dizziness, dry mouth, hand-foot syndrome, itching, mouth/throat sores, and numbness and tingling (Figure 2(f–k)). Thus, overall, the reported rates and patterns of the 11 examined AEs were generally similar in both arms up to 24 weeks of treatment.

In a similar analysis of AE reporting at the on-treatment timepoints among patients who did not report the respective AE at baseline, in general a minority of patients reported the presence of pain and swelling at injection site (durvalumab plus EP, 5–15%; EP, 6–14%) or rash (2–14%; 3–16%), a frequency of "rarely" or greater of swelling (8–20%; 3–31%), abdominal pain (10–31%; 13–28%), or chills (13–26%; 3–29%), and a severity of "mild" or worse of dizziness (6–32%; 0–35%),

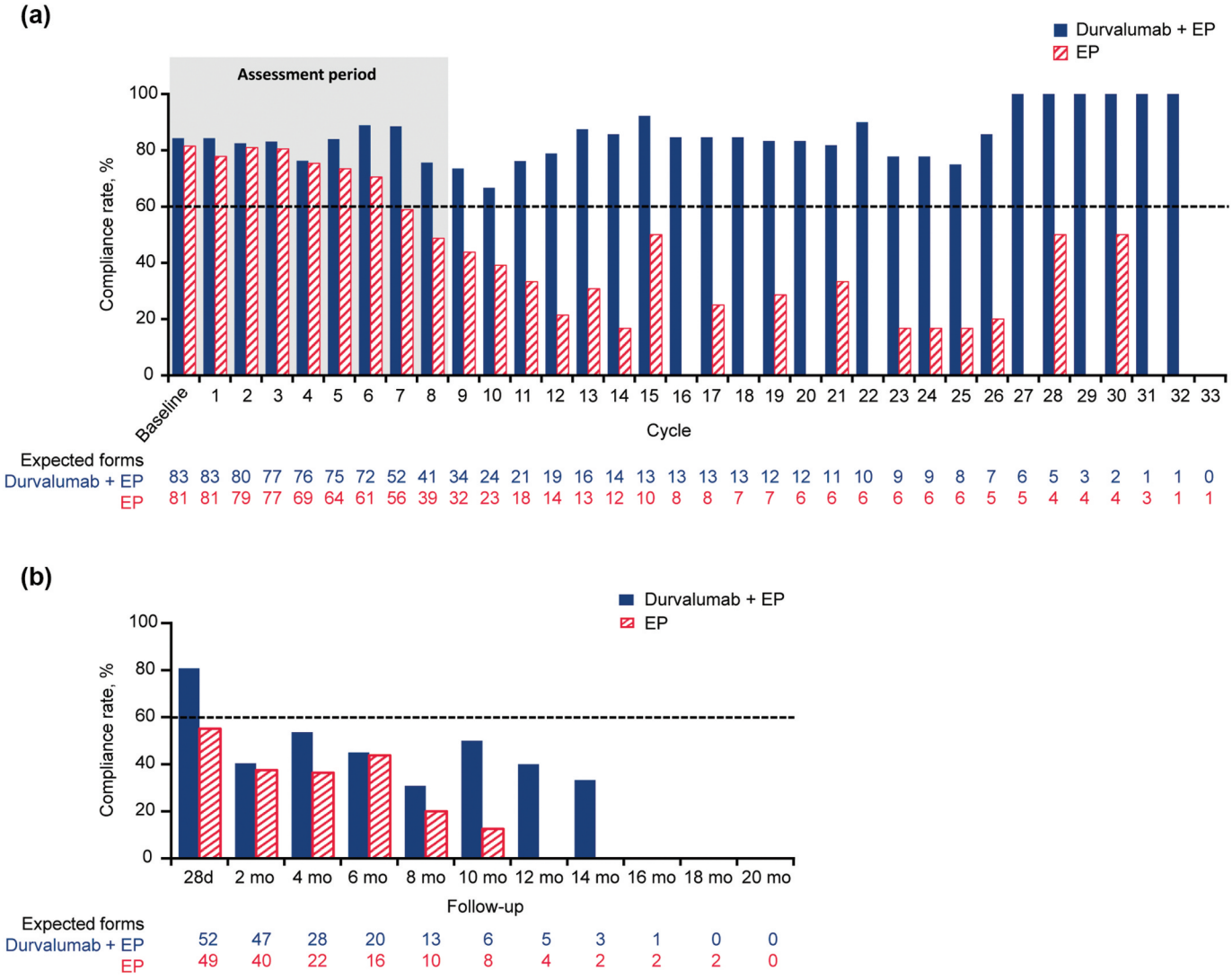

Figure 1. Compliance with completion of the PRO-CTCAE questionnaire (a) before progression, and (b) at follow-up post progression. Dashed line indicates threshold for acceptable to good compliance (≥60%). Cycle 8 corresponds to approximately 24 weeks.

d, Day; EP, Platinum-etoposide; mo, Months; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

dry mouth (14–36%; 5–56%), hand-foot syndrome (2–18%; 0–31%), itching (8–30%; 0–43%), mouth/throat sores (3–15%; 3–24%), or numbness and tingling (0–29%; 3–50%) on treatment (Supplementary Figure S2). In patients who experienced AEs at the on-treatment timepoints, the majority reported the frequency as "rarely" or "occasionally" for swelling, abdominal pain, and chills (Supplementary Figure S2c – S2e); or reported the severity as "mild" or "moderate" for dizziness, dry mouth, hand-foot syndrome, itching, mouth/throat sores, and numbness and tingling (Supplementary Figure S2f – S2k). Reported rates and patterns of AEs during the first 24 weeks of treatment were comparable between the two treatment arms for all examined AEs except for dry mouth of any severity, which was reported more commonly in the EP arm (up to 56% at cycle 8) than in the durvalumab plus EP arm (up to 36% at cycle 3) (Supplementary Figure S2g).

The proportion of patients reporting an AE of any frequency or severity at any timepoint during the first 24 weeks of treatment varied across the 11 examined AEs, with rash reported by the lowest proportion of patients (durvalumab plus EP, 30%; EP, 24%) and dry mouth reported by the highest proportion (76% in both groups) (Figure 3). Across the 11 examined AEs, overall reporting rates and patterns of worst responses for frequency or severity experienced during the first 24 weeks of treatment were similar between patients who received durvalumab plus EP and those who received EP.

Table 2 presents the proportion of patients reporting any worsening of each of the 11 AEs, as reported by PRO-CTCAE, during the first 24 weeks of treatment compared with baseline. The differences in the proportions of patients reporting any worsening between those who received durvalumab + EP and those who received EP were <5% for most AEs, with the largest differences observed in patients reporting a worsening in severity of dry mouth (durvalumab plus EP, 54%; EP, 61%), mouth/throat sores (29%; 34%), and numbness and tingling (36%; 45%). The proportions of patients whose scores worsened to 3 or 4 (i.e., to "frequently" or "almost constantly," or to "severe" or "very

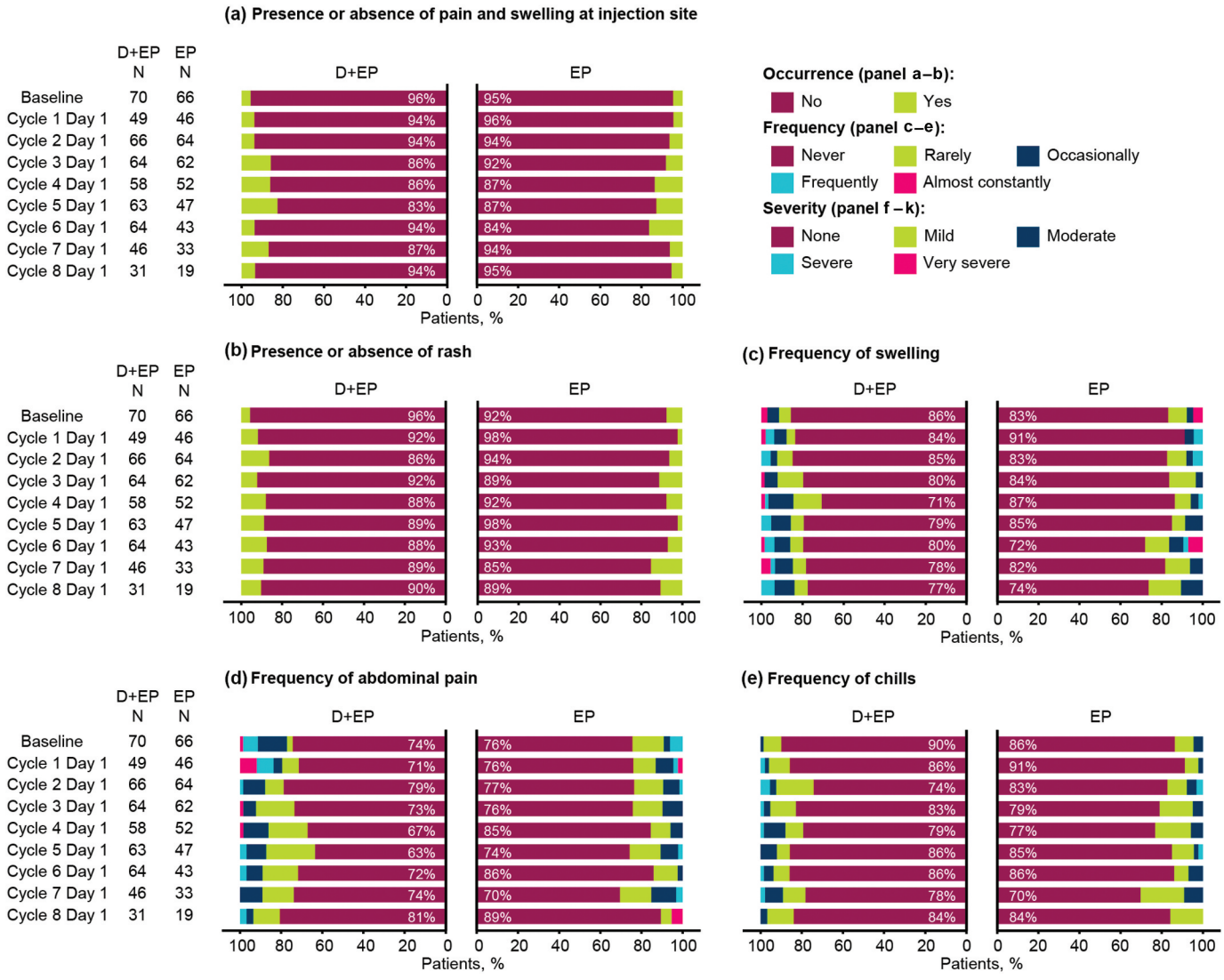

Figure 2. Proportion of patients reporting presence or absence, frequency, or severity of AEs in the durvalumab plus EP versus EP arms at each cycle. Reproduced from the poster presented by the authors at the 2022 ASCO annual meeting [17].

AE, Adverse event; D, Durvalumab; EP, Platinum-etoposide; N, Number.

severe") during treatment compared with baseline were the same or higher in patients who received durvalumab plus EP compared with those who received EP for most AEs except for the severity of dry mouth (durvalumab plus EP, 10%; EP, 21%) and hand-foot syndrome (1%; 3%).

3.4. Interference of AEs with usual or daily activities

Patients reporting any frequency or severity of swelling, abdominal pain, numbness and tingling, dizziness, and mouth/throat sores were asked about the extent to which the AEs interfered with their usual/daily activities (Figure 4). The numbers of patients who were asked about this attribute were small and varied between treatment groups and AEs because of the conditional branching logic used in the PRO-CTCAE (durvalumab plus EP, 2–25 patients; EP, 2–19 patients).

The proportions of patients reporting interference of "a little bit" or greater at the on-treatment timepoints were generally comparable with those at baseline in both treatment arms for numbness and tingling (durvalumab plus EP, 54% at baseline to 42–80%; EP, 54% at baseline to 50–70%) and dizziness (durvalumab plus EP, 67% at baseline to 50–88%; EP, 63% at baseline to 56–85%) (Figure 4(c, d)). Among patients who reported abdominal pain, the proportion who reported any level of interference with usual/daily activities showed a decreasing trend over the course of treatment compared with baseline values (durvalumab plus EP, 75% at baseline to 45% in cycle 7; EP, 73% at baseline to 50% in cycle 7; data for cycle 8 are not reported as there were ≤5 respondents in each arm) (Figure 4(b)). Interpretation is limited by the small numbers of respondents for the AEs of swelling and mouth/throat sores (Figure 4(a, e)).

Similar reporting rates and patterns for interference with usual/daily activities of the 5 AEs analyzed were observed up to 24 weeks of treatment in patients who received durvalumab plus EP and those who received EP. Among those who reported any interference of AEs with usual/daily activities, most patients at most timepoints reported the level of interference as "a little bit."

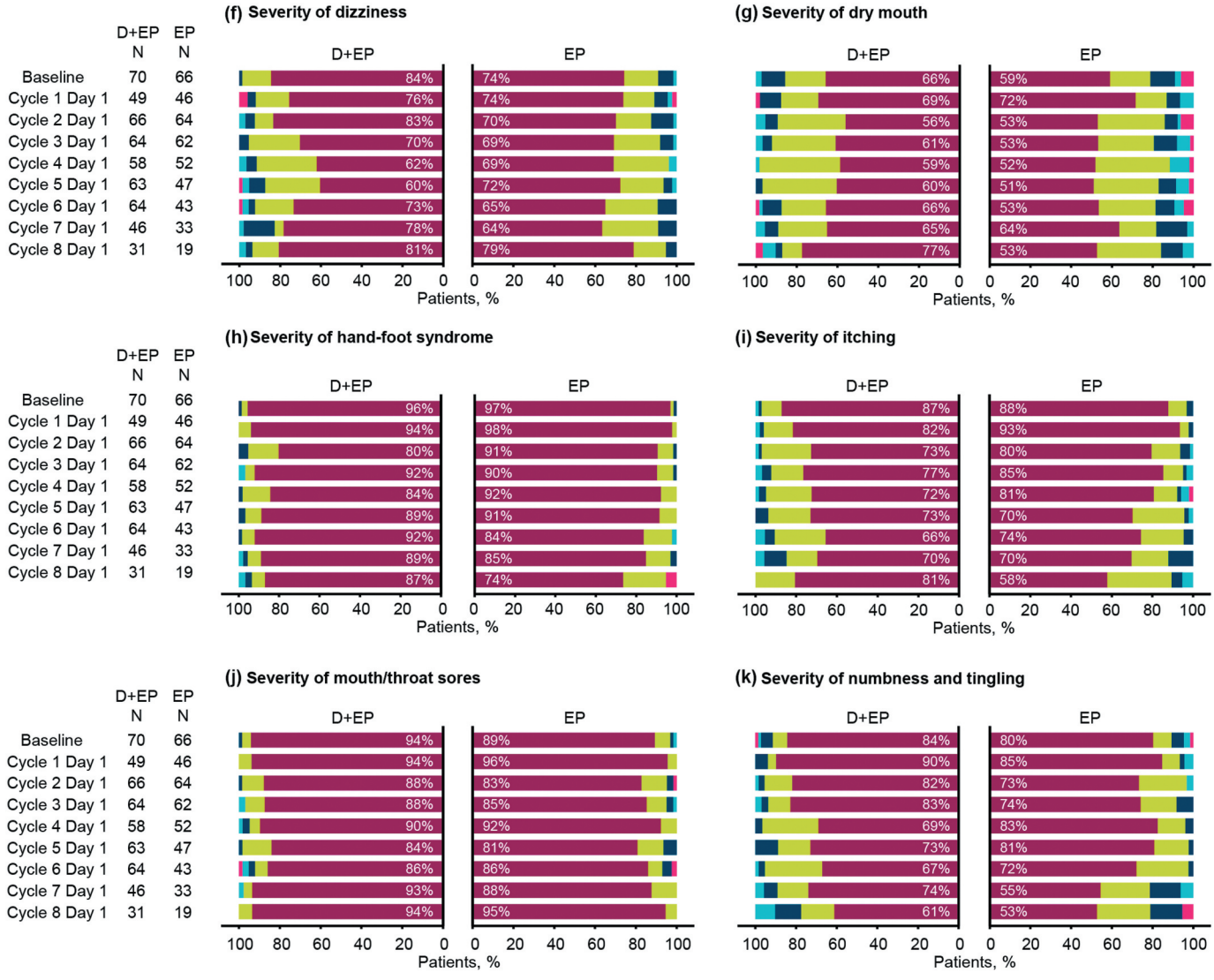

Figure 2. (Continued).

4. Discussion

The CASPIAN study demonstrated significantly improved OS with durvalumab plus EP compared with EP alone in first-line treatment of patients with ES-SCLC, which was sustained with a median follow-up of >3 years [1,2]. Clinician-reported safety findings in CASPIAN were consistent with the safety profiles observed previously for both durvalumab and EP [1,3]. Incidences of any AEs, grade 3 or 4 AEs, AEs leading to discontinuation, and AEs leading to death were similar across both treatment arms, and the most common AEs were hematological toxicities associated with chemotherapy [1,3]. In this manuscript, which to our knowledge is the first report of the use of the PRO-CTCAE tool in SCLC, we evaluated patient-reported AEs in CASPIAN to understand the impact of the disease and its treatment from the patients' perspective. The 11 selected AEs examined during the first 24 weeks of treatment were generally reported by a minority of patients at each timepoint, mostly with rare or occasional occurrence or mild-to-moderate severity, and the rates and the patterns for all examined AEs were broadly similar in patients who received durvalumab plus EP or those who received EP. Thus, these PRO safety data support the findings from physician assessment of limited differences between treatment arms with regard to specific AEs.

The PRO-CTCAE may be able to capture more detailed information about potential treatment-related symptomatic AEs than clinician-reported CTCAE data. For example, the PRO-CTCAE can examine the frequency or severity of a specific AE experienced by a patient in tandem with how it interferes with usual/daily activities, and can potentially provide insights into the relationship between the attributes. For the AEs examined in the current analysis, the PRO-CTCAE captured mostly similar attributes to those captured by CTCAE grading, such as the presence and severity of AEs, but also provided these additional details on frequency and interference with usual/daily activities. However, interpretation of the latter was limited by small numbers of respondents; the interference data presented in Figure 4 include findings from a small number of patients (2–25 patients for durvalumab plus EP; 2–19 patients for EP) that were variable for each cycle because of the conditional branching logic

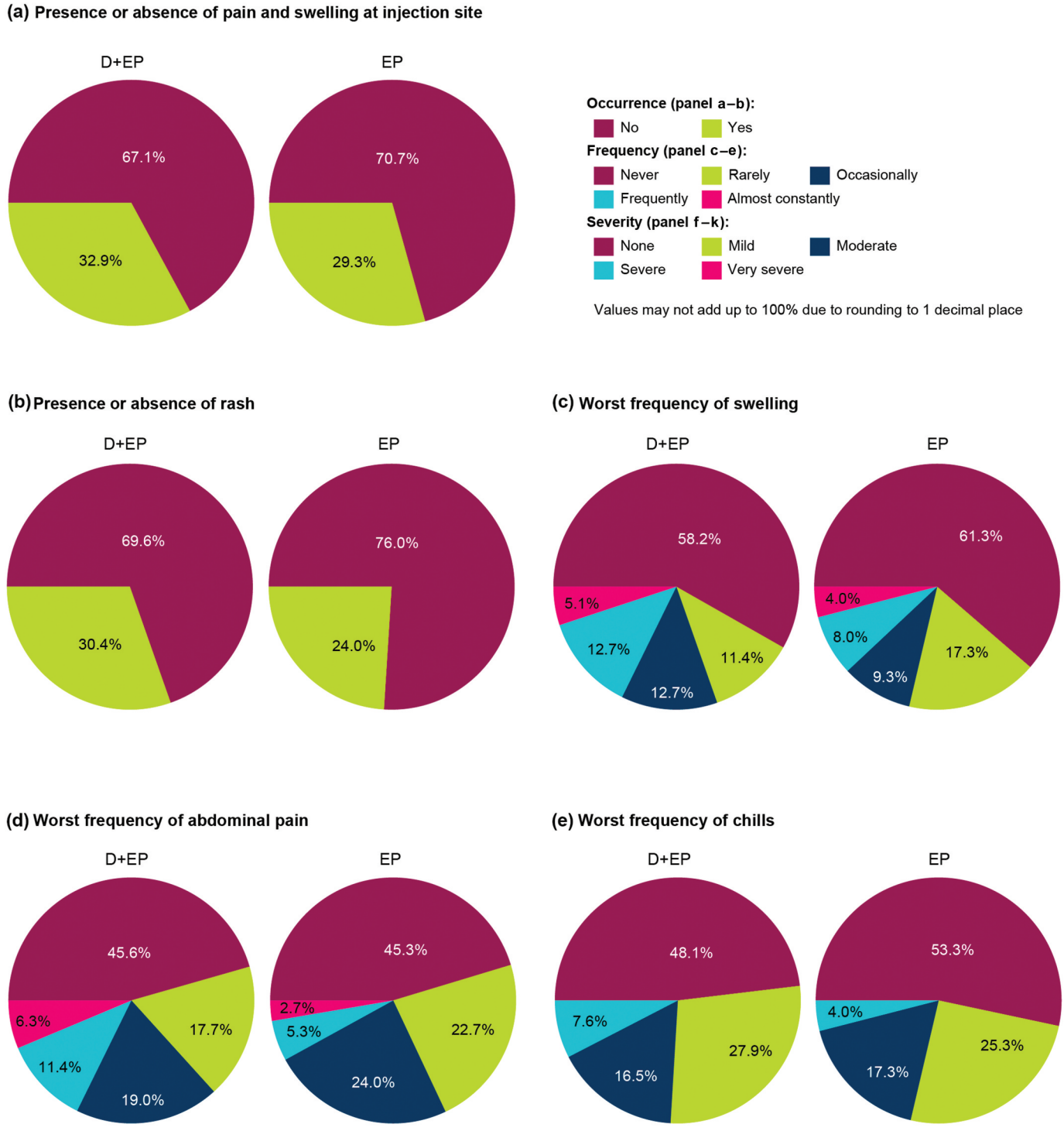

Figure 3. Proportion of patients reporting each AE at any visit during the first 24 weeks of treatment, by presence or absence, worst frequency, or worst severity, in the durvalumab plus EP ($n = 79$) versus EP ($n = 75$) arms.

Proportion is based on the number of patients with at least one post-baseline evaluation up to cycle 8 day 1.

AE, Adverse event; D, Durvalumab; EP, Platinum-etoposide.

used in the PRO-CTCAE instrument. In particular, interpretation was limited due to small numbers of respondents for swelling, for which <10 patients responded at 2 of the 9 on-treatment timepoints among those who received durvalumab plus EP and at 5 of 9 timepoints in those who received EP, and for mouth/throat sores, for which <10 patients responded at 8 of the 9 on-treatment timepoints among both treatment groups. Thus, based on the data presented herein, while the proportions of patients who reported "no interference" were broadly similar across timepoints between the two arms, we cannot extrapolate any apparent differential impact on health-related QoL based on degree of interference from symptomatic AEs to the overall study population, as the data are from only a very small fraction

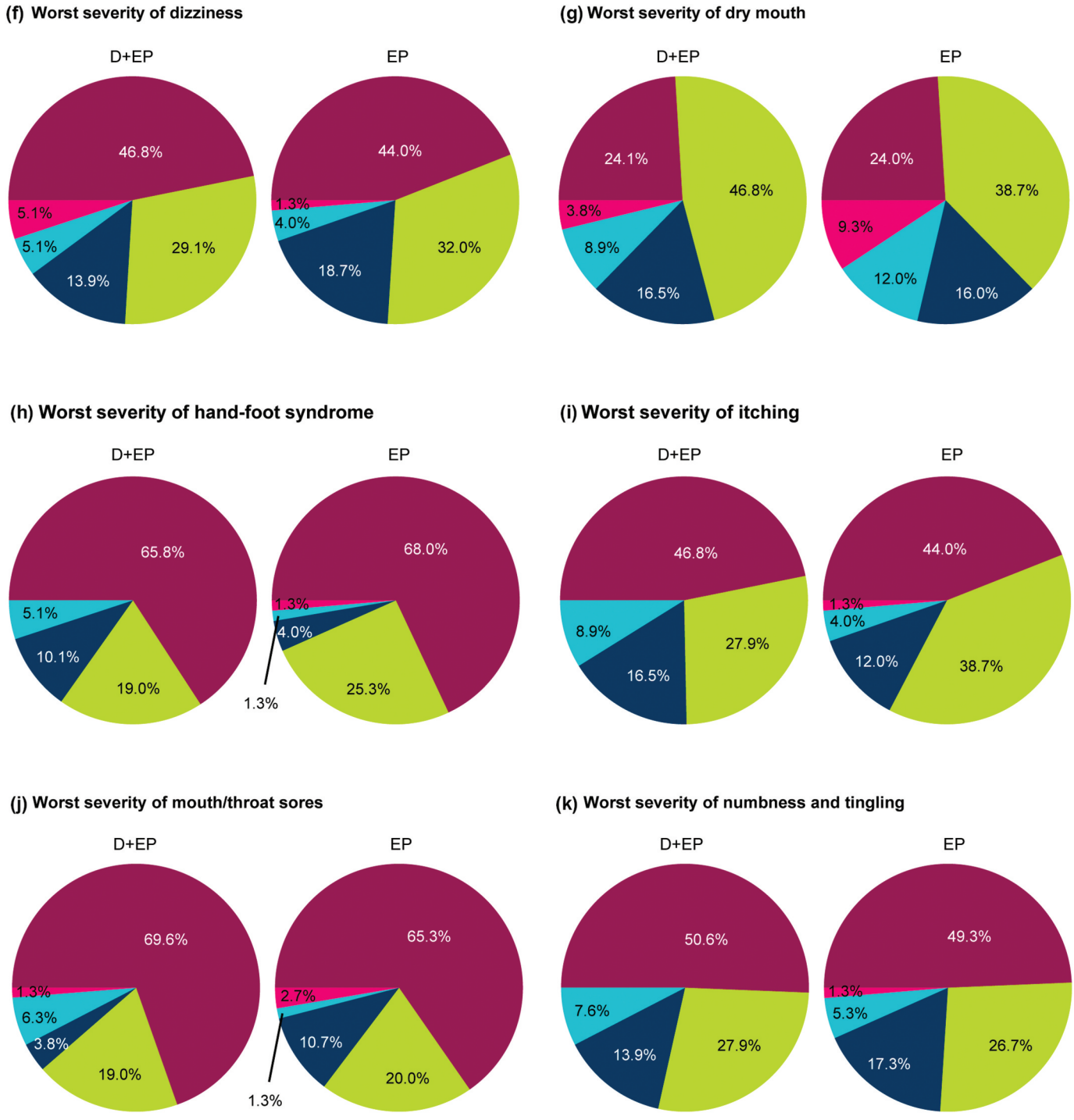

Figure 3. (Continued).

of the total CASPIAN population. Nevertheless, the findings do demonstrate that the PRO-CTCAE is able to provide more granular insights into the experience of treatment from the patient's perspective, data that are of considerable value, especially in settings in which AEs due to treatment and disease symptoms can have a substantial impact on overall HRQoL.

Further, the PRO-CTCAE data allowed for an assessment of changes in the rates of AEs reported over the time-course of treatment, and our findings indicated some slight differences between the arms for some AEs. For example, the timepoints of peak reporting rates for the various AEs differed between arms, such as we described for itching. These slight differences may be associated with the additional two cycles of chemotherapy that were allowed in the EP arm; overall, 57% of patients received 6 cycles of EP in that arm [1]. Longitudinal assessments using the PRO-CTCAE captured patients' perspectives on whether the specific AEs were worsening or improving over the course of treatment, with our findings showing generally similar rates of perceived worsening between the durvalumab plus EP and EP arms. In this context, telemonitoring of patients, especially during the

Table 2. Proportion of patients who reported worsening of 11 AEs by PRO-CTCAE compared with baseline during the first 24 weeks of treatment.

		Any Worsening of AE Score Compared with Baseline[b]		Worsening of AE Score to 3 or 4 Compared with Baseline[c]	
		Durvalumab + EP	EP	Durvalumab + EP	EP
Number of patients[a], n	Attribute	69	62	69	62
AE, (%)					
Pain and swelling at injection site	Occurrence	28	29	N/A	N/A
Rash	Occurrence	25	23	N/A	N/A
Swelling	Frequency	38	37	17	10
Abdominal pain	Frequency	43	40	13	5
Chills	Frequency	48	44	6	0
Dizziness	Severity	45	44	7	3
Dry mouth	Severity	54	61	10	21
Hand-foot syndrome	Severity	30	32	1	3
Itching	Severity	48	52	7	3
Mouth/throat sores	Severity	29	34	9	3
Numbness and tingling	Severity	36	45	6	6

[a]Number of patients who provided a score before treatment and at least one on-treatment score.
[b]The proportion of patients whose AE score increased during treatment, with respect to their score before treatment.
[c]The proportion of patients whose AE score increased to 3 or 4 (i.e., to "frequently" or "almost constantly," or to "severe" or "very severe") during treatment, with respect to their score before treatment; not applicable for AEs where occurrence was the measured attribute.
AE, Adverse event; EP, Platinum-etoposide; N/A, Not applicable; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

intervals between treatments when AEs may be more significant for the patient, may have been beneficial as it would have allowed for continuous monitoring of specific symptomatic AEs using PRO-CTCAE between site visits. Lee et al [18] reported improvement in cancer patients' participation in their symptom management during treatment when using a mobile application of PRO-CTCAE, compared with usual clinical practice. However, telemonitoring was not feasible for collection of PRO data at the time of protocol development in 2016.

Additionally, with regard to longitudinal monitoring, analysis of data on dose adjustments at each cycle may be useful when evaluating the progression of the symptomatic AEs reported using PRO-CTCAE during subsequent cycles. However, we report only on dose delays and interruptions (for durvalumab and chemotherapy) and dose reductions (for chemotherapy only) over the whole duration of the study, rather than per cycle, because such a complex analysis of our data would likely not provide meaningful insights for several reasons. Firstly, more than 82% of all patients had no dose reduction for chemotherapy and dose adjustments for durvalumab was not permitted according to the protocol. Secondly, such an analysis would be limited to those patients with longitudinal PRO-CTCAE data (i.e., patients who answered the questionnaire for a specific AE at each visit), and this would further reduce the already limited number of patients in the analysis. Finally, some of the AEs were reported only by a small number of patients (e.g., pain and swelling at injection site, and rash).

There are few published reports on the correlation between AEs captured by physicians using CTCAE and PRO-CTCAE in late-phase clinical trials. It is notable that the PRO-CTCAE reporting rates in this present analysis of CASPIAN do not align with clinician-led reporting of AEs per MedDRA PT and CTCAE. For example, while itching was reported by 53.2% and 56.0% of respondents on the PRO-CTCAE (Figure 3(i)), rates for the corresponding term in CTCAE v4.03 and v5.0 of "pruritus" (Supplementary Table S1) were markedly lower as reported by physicians, with low and similar rates of treatment-related pruritus in each arm of 4% with durvalumab plus EP and 2% with EP [3]. Although each symptomatic AE included in the PRO-CTCAE tool is mapped to a single CTCAE term (Supplementary Table S1), AEs as described by patients may cover multiple MedDRA PTs used by physicians. Therefore, direct comparisons between AEs described in the PRO-CTCAE and AEs reported by physicians using specific MedDRA PTs may be confounded. This may partly support the published observation that patients tend to grade their symptoms more severely than clinicians, and association between physician-reported AEs and patient-reported AEs is moderate at best [6–8,19–21]. This also provides further support to the complementary nature of these PRO-CTCAE data, as discussed in similar analyses from phase III trials in the settings of advanced non-small cell lung cancer [14] and metastatic prostate cancer [7].

The PRO-CTCAE analysis in CASPIAN was limited by the inclusion of data from only approximately 30% of patients, which may not be representative of the full study population (Supplementary Figure S1); within these patients, we believe selection bias was minimal as all eligible patients were asked to respond to the questionnaire. While validation of additional local-language versions of the PRO-CTCAE is ongoing, validated local-language versions were not available for all patients in CASPIAN at the start of the study.

Another limitation is that, although the PRO-CTCAE instrument allows flexibility in choosing items to include that are specific to the treatment used in the study, imAEs associated with the use of immune checkpoint inhibitors may not be adequately covered by individual PRO-CTCAE items, due to their complex and heterogenous nature. However, in this context, a recent publication has suggested a prioritized list of symptomatic imAEs that were selected by expert consensus [22,23]. Development of PRO-CTCAE items has focused on AEs associated with chemotherapy, targeted therapy and/or

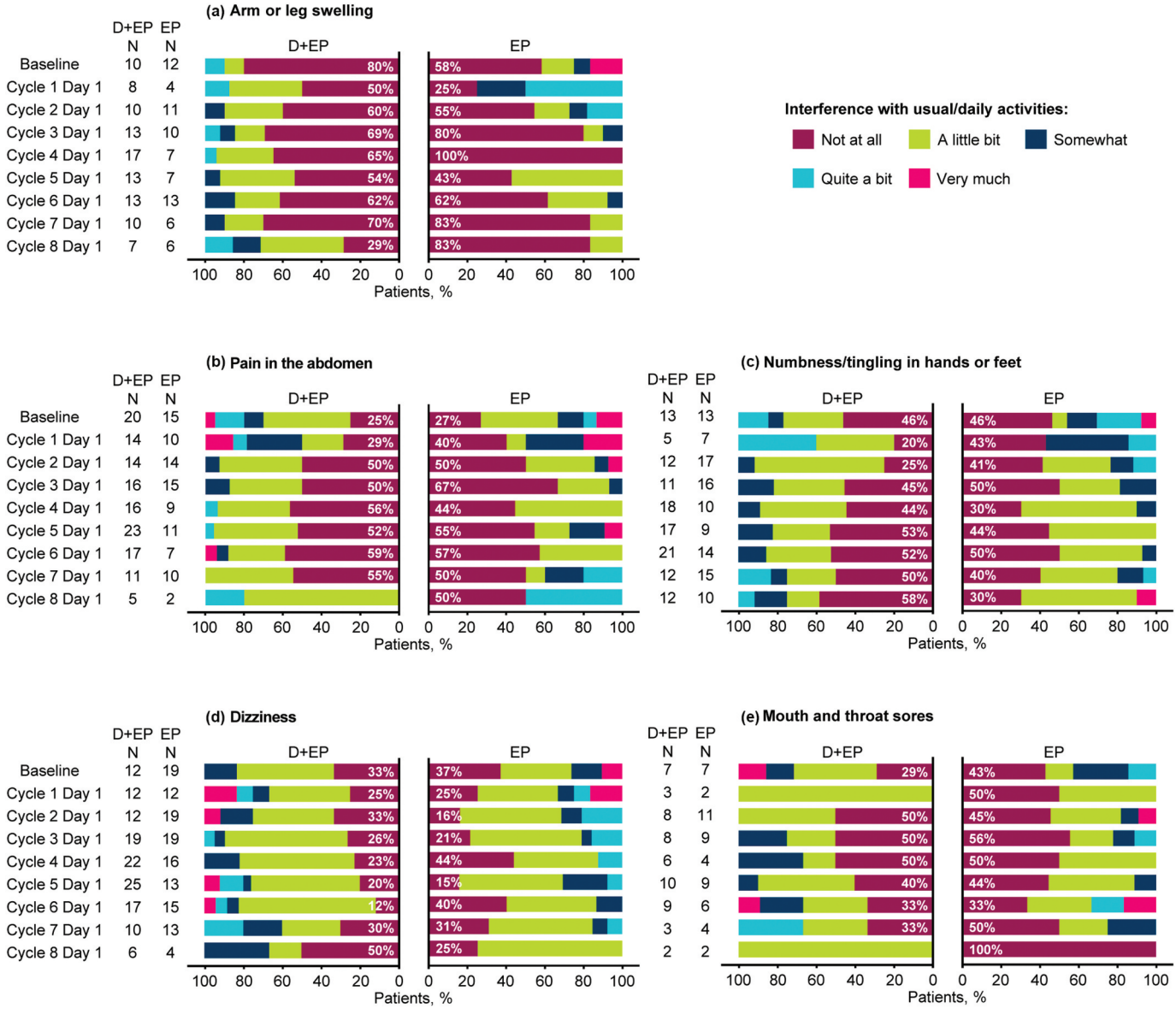

Figure 4. Interference of AEs with usual or daily activities at each cycle.

Interpretation is limited due to small numbers of respondents for swelling, where < 10 patients responded at 2 of the 9 on-treatment timepoints among those who received durvalumab plus EP and at 5 of the 9 timepoints in those who received EP, and mouth/throat sores, for which < 10 patients responded at 8 of the 9 on-treatment timepoints among both treatment groups.

AE, Adverse event; D, Durvalumab; EP, Platinum-etoposide; N, Number.

radiation, and therefore questions addressing imAEs are currently missing [24]. To address the need for patient-reported assessment of imAEs, an item library based on the Functional Assessment of Chronic Illness Therapy (FACIT) has been developed [25]. This may be an appropriate tool for future analyses of patient-reported AEs in those receiving immunotherapy-based regimens, either tailored to or added to the PRO-CTCAE for evaluation of regimens comprising immunotherapy and chemotherapy, especially if comparing a combined therapy regimen against a chemotherapy regimen as in CASPIAN.

A limitation that is inherent to the PRO-CTCAE instrument is its variability in the attributes captured for the various AEs; only one attribute is captured for some AEs, whereas for others there are two or three attributes that are captured. Although several statistical methods exist to assess the overall symptomatic AE burden, studies are ongoing and established guidelines are awaited [12]. Finally, it is worth noting that the CASPIAN trial was open label and, as such, neither the physicians nor patients were blinded to treatment, which could lead to reporting bias.

Our analysis highlights the feasibility of using the PRO-CTCAE instrument in large phase III clinical studies, giving additional insights into patients' experience of AEs while receiving treatment that complement physician-reported AEs. Using PRO-CTCAE in a clinical setting may allow physicians to measure the effect of treatment on the patient's daily life and better tailor treatment so the patient may be less inconvenienced by symptomatic AEs.

5. Conclusion

In conclusion, in this assessment of patient-reported AE data from patients in the CASPIAN study, the 11 selected AEs examined during the first 24 weeks of treatment were generally reported by a minority of patients at each timepoint, mostly with rare or occasional frequency or mild-to-moderate severity. Reporting rates and patterns for all selected AEs were broadly similar in the durvalumab plus EP and EP arms. These results complement the clinician-assessed safety profile observed in the CASPIAN study and give insight into the patients' experience of treatment. Addition of durvalumab to EP appears to provide a meaningful benefit by significantly prolonging survival in patients with ES-SCLC without adversely impacting PROs on symptomatic AEs and HRQoL.

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Author contributions

All authors have made a significant contribution to the work reported, whether in the conception of the analysis, execution, acquisition of data, analysis and interpretation. All authors have critically reviewed and edited the article. All authors have agreed on the journal to which the article was submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors have agreed to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Disclosure statement

Mustafa Özgüroğlu has been invited as a speaker by AstraZeneca, Regeneron; has consulted or had an advisory role with AstraZeneca, Bayer, MSD, Regeneron; was a principal investigator in trials sponsored by AstraZeneca, Bayer, Gilead, Janssen, MSD, Novartis, Regeneron, Roche, Sanofi; a member of steering committees for AstraZeneca, Bayer; and has received support for travel and accommodation from AstraZeneca.
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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical declaration

As previously reported (Paz-Ares L, et al. Lancet 2019;394:1929–1939; Paz-Ares L, et al. ESMO Open 2022;7:100408; Goldman JW, et al. Lancet Oncol. 2021;22:51–65; Goldman JW, et al. Lung Cancer 2020;149:46–52), the study was conducted in accordance with the International Conference on Harmonisation good clinical practice guidelines, the Declaration of Helsinki, and applicable local regulations with approval from an independent ethics committee or institutional review boards. The protocol and all modifications were approved by relevant ethics committees and regulatory authorities. Written informed consent was obtained from all patients enrolled in the CASPIAN Study.

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Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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