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Published in:
European Journal of Cancer

DOI:
10.1016/j.ejca.2022.10.030

Publication date:
2023

European Journal of Cancer 183 (2023) 98–108

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Patient-reported outcomes in capmatinib-treated patients with *MET*ex14-mutated advanced NSCLC: Results from the GEOMETRY mono-1 study

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Received 23 May 2022; received in revised form 26 October 2022; accepted 28 October 2022
Available online 10 December 2022

KEYWORDS
Patient-reported outcomes;
*MET*ex14-mutated;
Capmatinib;
Non-small cell lung cancer;
GEOMETRY mono-1

Abstract ***Introduction:*** Capmatinib, a MET inhibitor, showed substantial antitumour activity with manageable side effects in patients with *MET* exon 14 (*MET*ex14)-mutated advanced non-small cell lung cancer (aNSCLC) in the GEOMETRY mono-1 study. We report patient-reported outcomes (PROs) from this study.

Methods: Enrolled treatment-naïve (1L) or pre-treated ($2L^+$) patients with aNSCLC with a *MET*ex14-skipping mutation received 400 mg capmatinib twice daily during 21-day treatment cycles. PROs were collected at baseline and every six weeks thereafter using EORTC QLQ-C30 global health status/quality of life (GHS/QoL), QLQ-LC13 symptoms, and EQ-5D-5L visual analogue scale (VAS) questionnaires.

Results: As of 6 January 2020, 27/28 1L and 65/69 $2L^+$ patients had completed PROs at baseline; compliance rates remained >70%. Cough improved early, with meaningful improvements

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https://doi.org/10.1016/j.ejca.2022.10.030

(≥10-point change from baseline) observed throughout cycles (mean change from baseline [SD] by week 7: 1L −13.0 [39.9], $2L^+$ −8.2 [28.4]; week 43: 1L −28.2 [26.7], $2L^+$ −10.5 [27.3]). QoL, assessed by GHS/QoL and VAS, improved by week 7 in 1L and $2L^+$ patients, with improvements generally sustained over time. Median time to definitive deterioration (TTDD) in GHS/QoL was 16.6 months (95% CI: 9.7, not estimable [NE]) in 1L and 12.4 months (95% CI: 4.2, 19.4) in $2L^+$ patients. Median TTDD for dyspnoea was 19.4 months (95% CI: 12.4, NE) and 22.1 months (95% CI: 9.9, NE) for 1L and $2L^+$ patients, respectively, and NE for cough and chest pain.

Conclusions: Capmatinib was associated with clinically meaningful improvements in cough and preserved QoL, further supporting its use in patients with *MET*ex14-mutated aNSCLC.

Trial registration: ClinicalTrials.gov registry number: NCT02414139.

1. Introduction

Most patients diagnosed with non-small cell lung cancer (NSCLC) have advanced disease (stage III/IV) at diagnosis [1,2], often resulting in a significant symptom and emotional burden and, consequently, poor quality of life (QoL) [3–5]. Previous studies have demonstrated that the burden on QoL is greater in patients with lung cancer than in those with other types of cancer [6,7].

A *MET* exon 14 (*MET*ex14)-skipping mutation is an oncogenic alteration of the *MET* proto-oncogene detected in ~3% of patients with advanced NSCLC (aNSCLC) [8–13]. Recently, *MET*ex14-skipping mutations were shown to be oncogenic drivers associated with poor outcomes in patients with NSCLC [10,11,13]. Several highly specific MET kinase inhibitors show therapeutic activity in *MET*ex14-skipping aNSCLC, and two of them (capmatinib and tepotinib) have already been approved [14,15].

Capmatinib, a highly potent and selective inhibitor of MET, was first approved for adult patients with *MET*ex14-skipping metastatic NSCLC in May 2020 in the USA. Since then, capmatinib has received approval in nine countries for the treatment of patients with advanced and/or recurrent unresectable NSCLC with a *MET*ex14-skipping mutation [14,16,17]. Approval of capmatinib was based on findings from the phase 2, multi-cohort, non-randomised GEOMETRY mono-1 study (NCT02414139) that investigated the efficacy and safety of capmatinib in treatment-naïve (1L) and pre-treated ($2L^+$) patients with aNSCLC with dysregulated *MET* (*MET*ex14-mutated or *MET*-amplified) [18]. In patients with *MET*ex14-skipping NSCLC, capmatinib demonstrated antitumour activity, particularly pronounced in the treatment-naïve setting, with an overall response rate of 68% and 41% for 1L and $2L^+$ patients, respectively, and a median progression-free survival of 12.4 months [18]. Capmatinib was shown to be well tolerated, with most adverse events (AEs) being manageable with appropriate dose modifications and best supportive care [18]. The most common AEs of any grade related to capmatinib treatment were peripheral oedema (1L: 67.9% and $2L^+$: 44.9%), nausea (1L: 42.9% and $2L^+$: 37.7%), increased blood creatinine (1L: 25.0% and $2L^+$: 26.1%), and vomiting (1L: 17.9% and $2L^+$: 20.3%). The most common grade 3–4 AEs in treatment-naïve patients were peripheral oedema, increased alanine aminotransferase, increased amylase, and increased lipase (each 7.1%), whilst in pre-treated patients, it was peripheral oedema (14.5%) [18]. The safety profile of capmatinib appears to be similar to that reported for other MET small-molecule tyrosine kinase inhibitors (TKIs), including tepotinib, savolitinib, and crizotinib, with peripheral oedema and nausea being the most common AEs [19]. This knowledge base highlights MET TKIs as an effective and tolerable therapy option in patients with *MET*ex14-skipping NSCLC, particularly in elderly patients who may not respond to or not tolerate other types of treatment, including chemotherapeutic agents or immunotherapy.

In addition to increasing survival, maintaining health-related quality of life (HRQoL) and reducing the symptom burden are key treatment goals for patients with cancer and caregivers. Patient-reported outcome (PRO) data can help clinicians better understand symptoms and drug-related toxicity experienced by patients and facilitate shared and informed decision-making and assessment of overall risk–benefit profiles for possible treatment options. To date, there are no data available on the impact of capmatinib on QoL for patients with *MET*ex14-skipping aNSCLC. Here, we report PRO data for patients enrolled in the GEOMETRY mono-1 study.

2. Methods

2.1. Study design and patients

The GEOMETRY mono-1 study enrolled patients ≥18 years of age with advanced or metastatic (stage IIIb/IV),

dysregulated *MET*, *EGFR* wild-type, and *ALK* rearrangement-negative NSCLC and included both 1L and $2L^+$ patients. The study was composed of seven cohorts and included patients with *MET* amplification or a *MET*ex14-skipping mutation. The design of the GEOMETRY mono-1 study has been published previously [18]. Capmatinib was administered orally at the starting dose of 400 mg twice daily in 21-day treatment cycles. Patients with advanced/metastatic disease included in this PRO analysis were from cohort 4 (of which eligible patients had a *MET*ex14-skipping mutation and had been previously treated with 1 or 2 lines of therapy) and cohort 5b (of which eligible patients had a *MET*ex14-skipping mutation and had not received previous lines of therapy) [18].

2.2. Study assessments

PRO endpoints in this study were exploratory and measured through the following self-administered questionnaires validated in lung cancer studies: the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire – core 30 questionnaire (QLQ-C30), the EORTC QoL questionnaire – lung cancer module (QLQ-LC13), and the EuroQol 5 dimension, 5 level questionnaire (EQ-5D-5L) [20–23].

PRO data were collected at baseline, during treatment (day 1 of cycle 3, day 1 of cycle 5, and every 6 weeks until the end of treatment), and post-treatment until the end of efficacy follow-up.

The QLQ-C30 is made up of 30 questions with nine multi-item scales: five functional scales (physical, role, social, cognitive, and emotional), a global health status/QoL (GHS/QoL) scale, and three symptom scales (fatigue, pain, and nausea/vomiting). Several single-item symptom measures (dyspnoea, insomnia, appetite, constipation, diarrhoea, and the financial impact of the disease [20]) were also included. Patients assessed how true each statement in the questionnaire was for them on a four-point scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much), whereas GHS/QoL was assessed using a seven-point Likert scale (ranging from 'very poor' to 'excellent') for two items. All raw QLQ-C30 scores were transformed to scores ranging from 0 to 100, with higher scores indicating a high QoL for GHS/QoL, a high/healthy level of functioning for functional scales, and a high level of symptomatology for symptom scales.

The QLQ-LC13 complements the QLQ-C30 and measures disease symptoms and treatment-related AEs. The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis [21]. The multi-scale dyspnoea includes three items that assess resting, walking, and climbing of stairs. The multi-scale and single-item measures range in score from 0 to 100, with a high score for the scales and single items representing a high level of symptomatology or problems. An increase of $\geq$10 points in the absolute change from baseline for QLQ-C30 symptom scores was used to define a threshold for a deterioration event, and a decrease of $\geq$10 points in the absolute change from baseline for a QLQ-C30 GHS/QoL score was used to define PRO responders [22].

The EQ-5D-5L VAS is a widely used, generic self-administered questionnaire divided into two distinct sections for describing and valuing patients' health status [23]. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), which are rated as 'no problems', 'slight problems', 'moderate problems', 'severe problems', or 'unable to/extreme problems'. The second section of the questionnaire, the EQ-5D-5L VAS, measures self-rated global health where 100 represents the 'best imaginable health state' and 0 represents the 'worst imaginable health state' [24]. An increase of $\geq$7 points is considered a clinically meaningful improvement [25].

2.3. Statistical analysis

All analyses included data from the PRO-evaluable population, defined as all patients who received $\geq$1 dose of capmatinib and completed PRO questionnaires at baseline and $\geq$1 time point during treatment in cohorts 4 and 5b. Analyses were exploratory and were conducted without adjustment for multiple comparisons. All analyses were performed using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, 2011).

To assess the longitudinal experience of patients receiving capmatinib over the defined treatment period, mean and absolute change from baseline in QLQ-C30 GHS/QoL, QLQ-LC13 symptoms, and EQ-5D-5L VAS over 43 weeks were evaluated. QLQ-LC13 item-level responses ('not at all', 'a little', 'quite a bit', and 'very much') were further assessed over 25 weeks, with Sankey diagrams indicating the proportion of patients within each PRO response level and the proportional flow of patients between each PRO response level over time. Dyspnoea was assessed in three different conditions: resting, walking, and climbing of stairs.

Time to definitive deterioration (TTDD) in QLQ-C30 GHS/QoL and QLQ-LC13 symptoms were assessed by Kaplan–Meier analysis by cohort. For QLQ-LC13 symptom scores and a GHS/QoL score, TTDD was defined as time from treatment initiation to the first date of $\geq$10% increase or decrease, respectively, with no later improvement or death due to any cause.

Linear mixed models for longitudinal data were used to evaluate absolute changes from baseline in each QLQ-LC13 cough, dyspnoea, and chest pain scores over time by clinical response status as part of an exploratory

analysis. A blinded independent review committee (BIRC) was used to define patients with confirmed complete response (CR) or partial response (PR). Absolute change from baseline was modelled for each score, with categorical variables for best clinical response status and analysis visit, and baseline scores as continuous covariates and relevant interaction terms (clinical response status and baseline score by analysis visit).

3. Results

3.1. Patient selection

Between 11 June 2015 and 11 February 2020, 364 patients were enrolled in the GEOMETRY mono-1 study and treated with capmatinib orally at the starting dose of 400 mg twice daily. This PRO analysis included patients with a *MET*ex14-skipping mutation, the indication for which capmatinib is approved. These patients were from cohort 4 (69 pre-treated patients) and cohort 5b (28 treatment-naïve patients). Baseline demographics and disease characteristics of enrolled patients are shown in Table 1.

At 6 January 2020 cut-off for PRO analyses, median capmatinib exposure was 48.2 (4.0–117.4) weeks and 22.1 (0.4–136.0) weeks for 1L and $2L^+$ patients, respectively. The PRO-evaluable population included only those patients who received ≥1 dose of capmatinib and completed PRO questionnaires at baseline and ≥1 time point. For QLQ-C30, the PRO-evaluable population included 85 patients, with 26 in cohort 5b (1L) and 59 patients in cohort 4 ($2L^+$). The PRO-evaluable population for QLQ-LC13 and EQ-5D-5L VAS included 84 patients, with 26 in cohort 5b and 58 patients in cohort 4.

3.2. Questionnaire compliance rates

Twenty-seven of 28 (96.4%) 1L patients and 65 of 69 (94.2%) $2L^+$ patients completed all three PRO questionnaires at baseline. Compliance rates remained high (>70% of eligible patients) throughout the study (43 weeks) and were consistent across PRO measurements (Table S1). On week 43, 14 of 15 eligible 1L patients (93.3%) and 20 of 26 eligible $2L^+$ patients (76.9%) completed the QLQ-C30 questionnaire. Compliance rate was defined as the proportion of patients who completed a PRO instrument based on the patients eligible at the specified time point. Patients in the full analysis set who did not fill the study phase completion electronic case report form page at the specified time point were considered eligible.

Table 1
Demographics and baseline disease characteristics of enrolled patients.

	Treatment-naïve (1L) N = 28	Pre-treated ($2L^+$) N = 69
Median age, years (range)	71 (57–86)	71 (49–90)
Female, n (%)	18 (64)	40 (58)
Race, n (%)		
Asian	4 (14)	19 (28)
White	24 (86)	49 (71)
Native American	0 (0)	1 (1)
History of smoking (former/current), n (%)	10 (36)	29 (42)
ECOG PS, n (%)		
0	7 (25)	16 (23)
1+	21 (75)	53 (77)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

3.3. Change in lung cancer symptoms from baseline

Mean baseline QLQ-LC13, QLQ-C30 GHS/QoL, and EQ-5D-5L VAS scores are shown in Table 2. Mean QLQ-LC13 symptom scores were low to moderate at baseline in both 1L and $2L^+$ patients, with cough symptom scores at baseline greater in 1L patients than in $2L^+$ patients. Mean PRO scores for GHS/QoL and EQ-5D-5L VAS were both moderate to high at baseline for both 1L and $2L^+$ patients, although scores were greater in 1L patients (Table 2).

For QLQ-LC13 cough, the mean changes from baseline (standard deviation [SD]) at week 7 were −13.0 (39.9) in 1L and −8.2 (28.4) in $2L^+$, which decreased to −28.2 (26.7) in 1L and −10.5 (27.3) in $2L^+$ at week 43 (Fig. 1A). For QLQ-LC13 chest pain, the mean change from baseline (SD) at week 7 was −5.8 (19.2) for 1L and −3.8 (19.2) for $2L^+$. Mean change from baseline (SD) at week 43 was −12.8 (21.7) for 1L and −1.8 (17.5) for $2L^+$ (Fig. 1B). For QLQ-LC13 dyspnoea, the mean change from baseline (SD) decreased to −5.8 (18.0) for 1L and increased to +2.1 (19.4) for $2L^+$ at week 7. At week 43,

Table 2
Baseline PRO scores assessed by QLQ-LC13, QLQ-C30 GHS/QoL, and EQ-5D-5L VAS.

Baseline PRO scores	Treatment-naïve (1L)[a] Mean (SD)	Pre-treated ($2L^+$)[a] Mean (SD)
QLQ-LC13[b]	**N = 26**	**N = 58**
Cough	35.9 (32.6)	28.7 (28.2)
Chest pain	12.8 (23.2)	17.2 (22.7)
Dyspnoea	23.5 (23.4)	22.2 (20.8)
QLQ-C30 GHS/QoL[c]	**N = 26**	**N = 59**
Baseline score	64.7 (21.6)	58.8 (21.0)
EQ-5D-5L VAS[c]	**N = 26**	**N = 58**
Baseline score	67.7 (20.7)	61.9 (18.8)

Abbreviations: GHS, global health status; QoL, quality of life; SD, standard deviation; PRO, patient-reported outcome; VAS, visual analogue scale.

[a] Only patients with baseline and at least one post-baseline assessment were included in the calculation of mean baseline PRO scores.

[b] QLQ-LC13 was assessed on a 0- to 100-point scale, with 0 corresponding to the lowest and 100 to the highest symptom burden.

[c] QLQ-C30 GHS and EQ-5D-5L were assessed on a 0- to 100-point scale, with 0 corresponding to the worst and 100 to the best QoL.

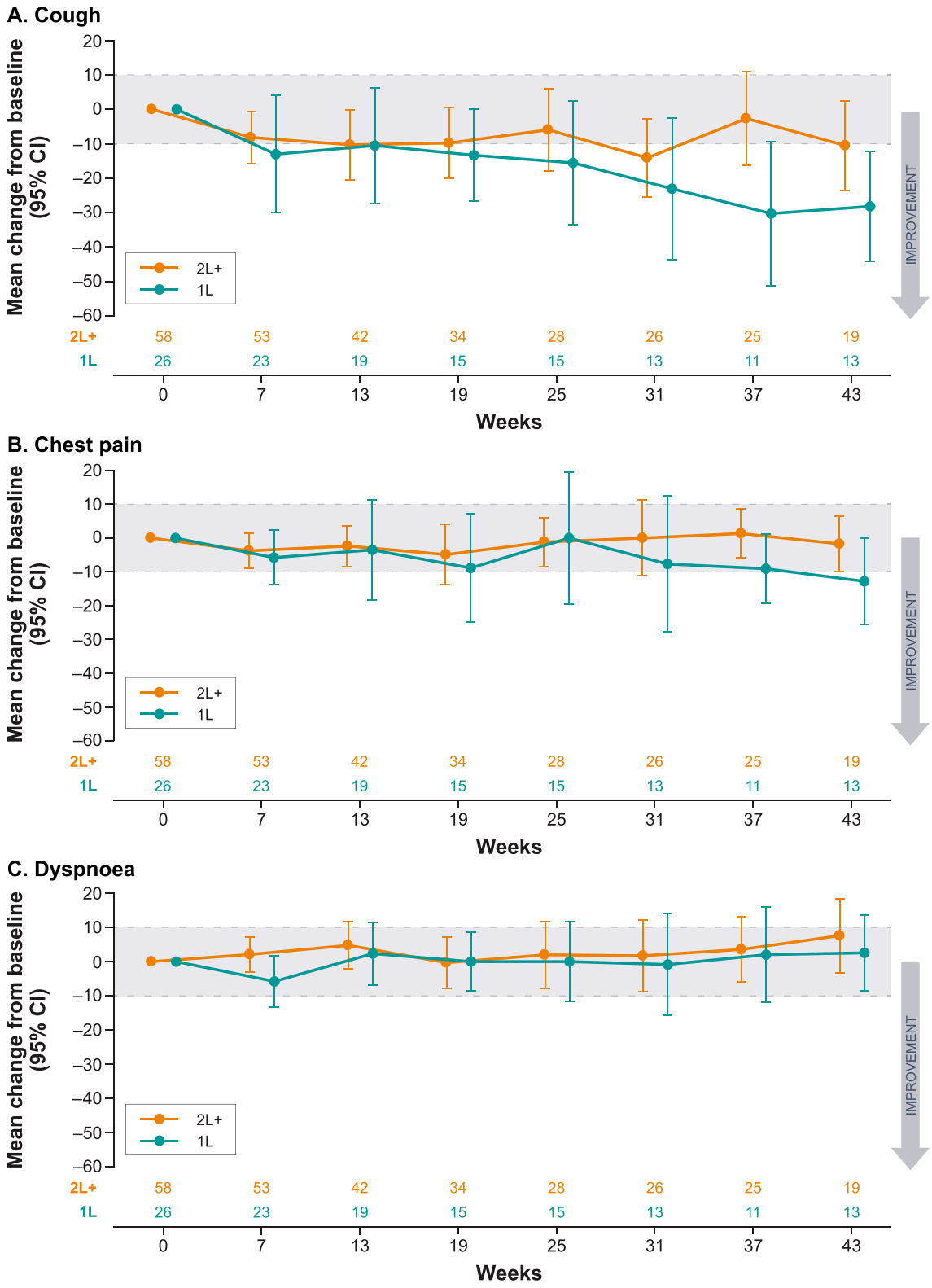

Fig. 1. Mean change from baseline in QLQ-LC13 symptom scores (cough, chest pain, and dyspnoea). Change from baseline <0 indicates reduction in symptom. An increase or decrease of ≥10 points is considered to be a clinically meaningful threshold (shaded area) for the QLQ-LC13 symptom score. Abbreviations: 1L, first-line; $2L^{+}$, second-line or more; CI, confidence interval.

mean changes from baseline (SD) were +2.6 (18.8) in 1L and +7.6 (22.9) in 2L$^+$ (Fig. 1C).

Mean changes from baseline in QLQ-LC13 symptoms (cough, chest pain, and dyspnoea) by clinical response (defined as CR/PR for best overall response by BIRC) up to week 25 are shown in Fig. S1.

Some clinically meaningful improvements in cough (decrease of ≥10 in least square [LS] mean from baseline) were observed for 1L and 2L$^+$ patients with CR/PR. At week 7, LS mean changes from baseline (standard error [SE]) were −17.6 (5.8) for 1L CR/PR (n = 15) and −12.7 (4.3) for 2L$^+$ CR/PR (n = 24). At week 13, LS mean change from baseline (SE) was −26.3 (6.3) for 1L CR/PR (n = 14) and −10.7 (4.2) for 2L$^+$ CR/PR (n = 23). At week 25, LS mean change from baseline (SE) was −17.0 (8.0) for 1L CR/PR (n = 13) (Fig. S1A). Some clinically meaningful improvements in chest pain (decrease of ≥10 in LS mean from baseline) were observed for 1L CR/PR patients at certain time points. LS mean change from baseline (SE) was −15.8 (2.7) and −14.7 (4.7) for 1L CR/PR at week 19 (n = 13) and week 25 (n = 13), respectively (Fig. 1SA). No clinically meaningful improvement in dyspnoea was evident at any time point, regardless of response status (Fig. S1C).

The distribution of QLQ-LC13 scores through week 25 is shown in Fig. S2. The proportion of patients reporting cough symptoms as 'very much' or 'quite a bit' was 11% at baseline (n = 27) and 0% at week 25 (n = 16), as well as 14% at baseline (n = 27) and 4% at week 25 (n = 16), respectively, for 1L (Fig. S2A). For 2L$^+$, proportions were 6% at baseline (n = 65) and 3% at week 25 (n = 28), as well as 19% at baseline (n = 65) and 1% at week 25 (n = 28) (Fig. S2B).

Fig. S2C–2J highlights decreases in the distribution of QLQ-LC13 symptom scores for shortness of breath and chest pain through week 25, for both 1L and 2L$^+$ patients.

3.4. Change in QLQ-C30 GHS/QoL

Mean changes from baseline in QLQ-C30 GHS/QoL score through week 43 are shown in Fig. 2. Mean changes from baseline (SD) increased to +4.8 (34.8) for 1L patients at week 13 and + 6.1 (26.6) for 2L$^+$ patients at week 7 (not pre-defined time points). Further increases were observed up to week 19 for 1L patients, with mean change from baseline +9.9 (17.8), after which the mean change from baseline (SD) decreased through week 43 to 0.0 (24.1). For 2L$^+$ patients, the mean change from baseline (SD) was 0.0 (19.0) at week 43.

3.5. Change in EQ-5D-5L VAS from baseline

Mean changes from baseline in EQ-5D-5L VAS score are shown in Fig. 3. The mean change from baseline (SD) at week 7 was +6.0 (19.9) for 1L and +3.8 (24.2) for 2L$^+$. Increases in mean change from baseline were observed up to week 31 for 1L patients, with the mean change from

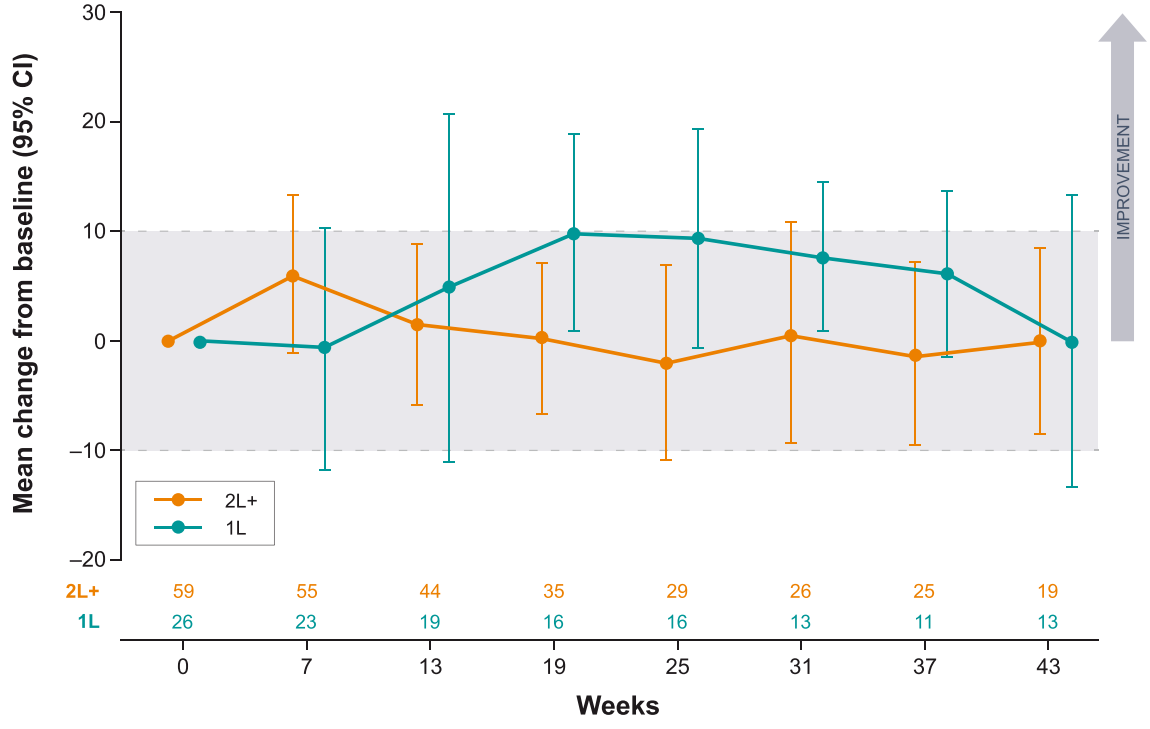

Fig. 2. Mean change from baseline in the QLQ-C30 GHS/QoL score. Change from baseline >0 indicates improvement in QoL. An increase or decrease of ≥10 points is considered to be a clinically meaningful threshold (shaded area) for the QLQ-LC13 GHS/QoL score. Abbreviations: 1L, first-line; 2L$^+$, second-line or more; CI, confidence interval; GHS, global health score; QoL, quality of life.

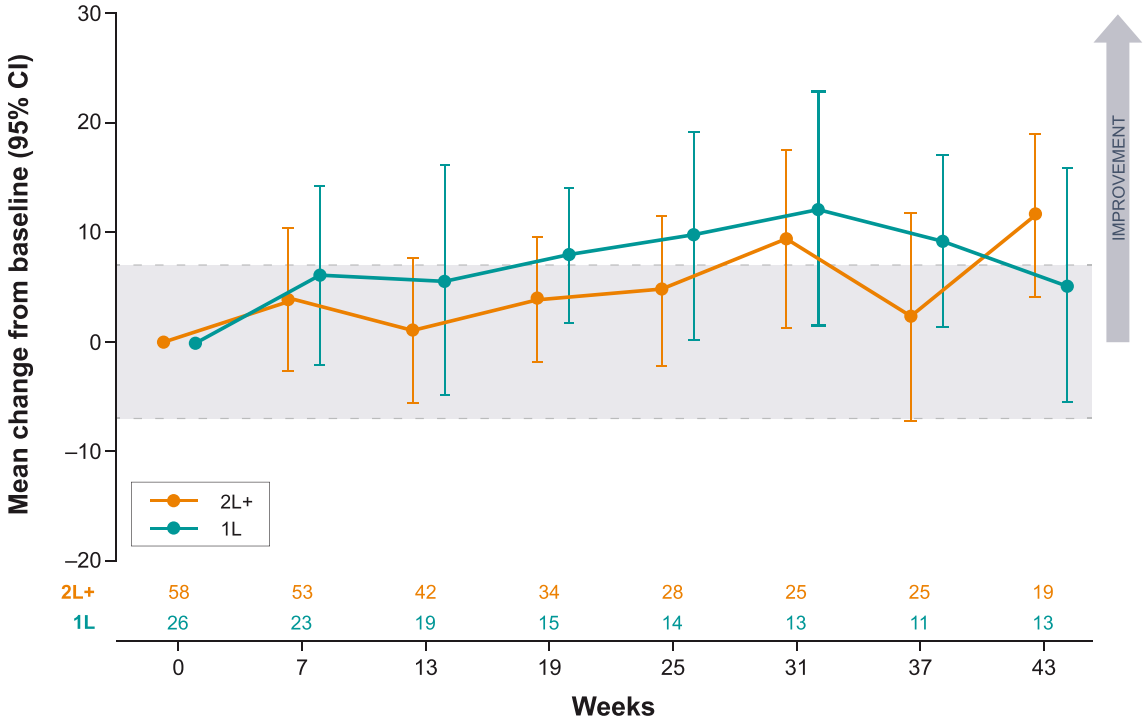

Fig. 3. Mean change from baseline in EQ-5D-5L VAS score. Change from baseline >0 indicates improvement in QoL. An increase or decrease of ≥7 points is considered to be a clinically meaningful threshold (shaded area) for the EQ-5D-5L VAS score. Abbreviations: 1L, first-line; 2L$^+$, second-line or more; CI, confidence interval; QoL, quality of life; VAS, visual analogue scale.

baseline (SD) reported as +12.1 (19.7). Mean change from baseline (SD) was +5.1 (19.6) at week 43. For 2L$^+$, mean change from baseline (SD) was +11.5 (16.5) at week 43.

3.6. TTDD in patient-reported GHS/QoL and lung cancer symptoms

Median TTDD in GHS/QoL was 16.6 months (95% CI: 9.7, not estimable [NE]) and 12.4 months (95% CI: 4.2, 19.4) in 1L and 2L$^+$ patients, respectively. The median TTDD for QLQ-LC13 symptoms (cough, chest pain, and dyspnoea) are shown in Fig. 4A–C. The median TTDD was not reached for cough or chest pain for both 1L and 2L$^+$ patients; the median (95% CI) TTDD for dyspnoea was 19.4 months (12.4–NE) for 1L patients and 22.1 months (9.9–NE) for 2L$^+$ patients.

4. Discussion

This is the first study to report on the impact of capmatinib on HRQoL in patients with NSCLC with a *MET*ex14-skipping mutation. In this PRO exploratory analysis of the GEOMETRY mono-1 study, capmatinib was associated with clinically meaningful improvements in cough and preserved QoL in 1L and 2L$^+$ patients with *MET*ex14-skipping NSCLC. Furthermore, patients treated with capmatinib experienced a long time to lung cancer symptom deterioration.

This analysis demonstrated the consistency of PRO results across cohorts by a BIRC-assessed clinical response. It is well known that the worsening of disease-related symptoms is often experienced by patients with lung cancer as their disease progresses, which can adversely affect their QoL [24]. Differences in PRO scores at baseline (although non-significant) observed in the 1L and 2L$^+$ cohorts justified the analysis conducted by cohort. The separation of patients to the 1L and 2L$^+$ cohorts in this study demonstrates that QoL and symptom control are maintained over time with capmatinib for both newly diagnosed treatment-naïve patients and pre-treated patients with more advanced disease. The phase 2 VISION study also assessed PROs in patients with *MET*ex14-mutated NSCLC treated with tepotinib [26]; however, pooled cohorts were used for the analysis. Tepotinib likewise reported clinically meaningful improvement in coughing symptoms whilst maintaining HRQoL in the same patient population. Owing to differences in reporting PROs, a direct comparison with this PRO analysis cannot be made.

In this study, clinically meaningful improvements (decrease of ≥10 points from baseline) in QLQ-LC13 cough symptom scores were sustained through week 43 for both 1L and 2L$^+$ patients. Improvements in QLQ-LC13 chest pain symptom scores were also observed in both 1L and 2L$^+$ patients, and clinically meaningful improvements in chest pain in 1L patients were sustained through week 43, whilst numerical improvements

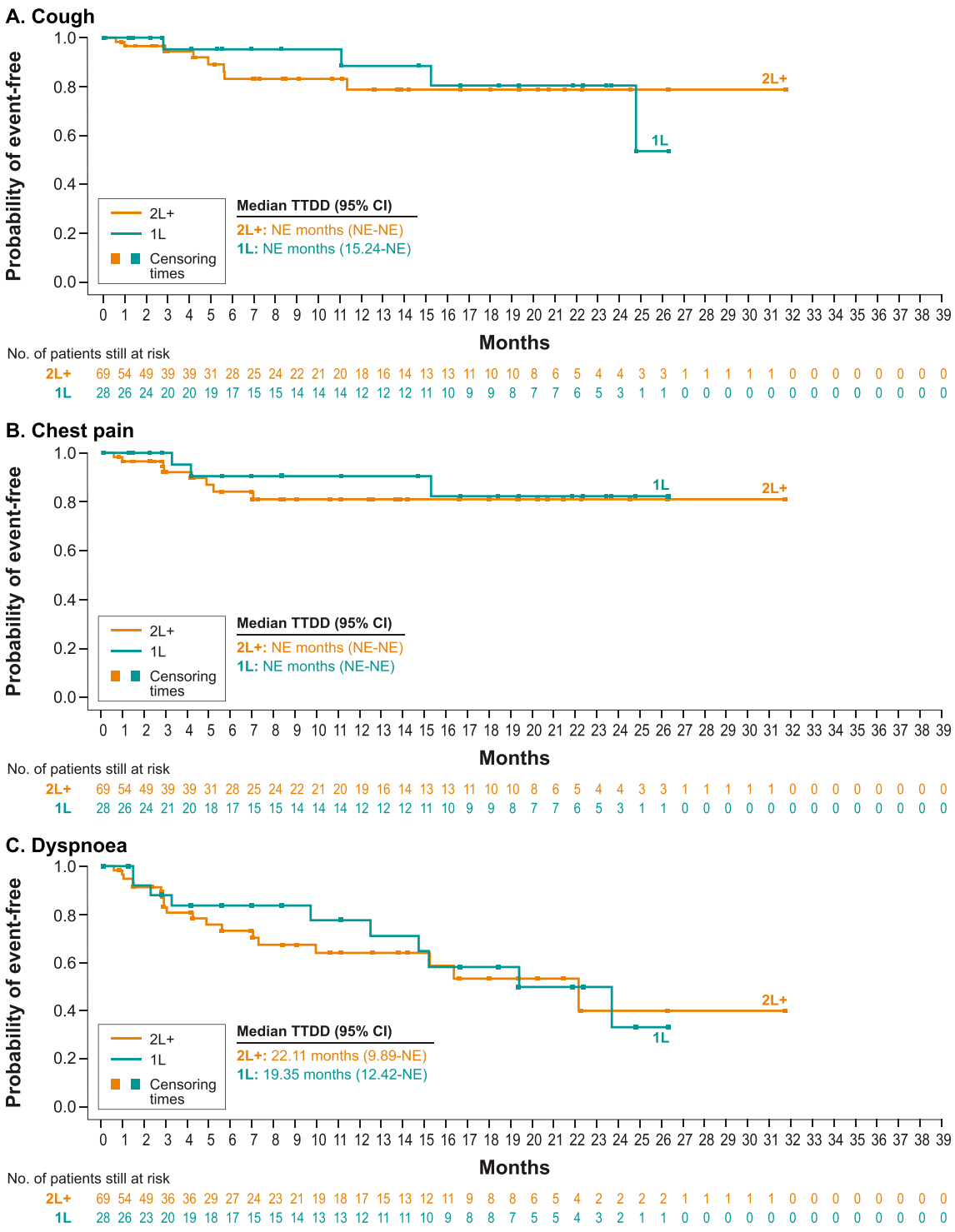

Fig. 4. TTDD in QLQ-LC13 symptom scores (cough, chest pain, and dyspnoea). TTDD in QLQ-LC13 symptom scores was defined as the time from treatment initiation to the first date of ≥10% absolute increase in symptom score from baseline with no later improvement. Abbreviations: 1L, first-line; $2L^{+}$, second-line or more; CI, confidence interval; NE, not estimable; TTDD, time to definitive deterioration.

were also observed in $2L^{+}$ patients over this time. The proportion of patients who experienced cough symptoms 'very much' or 'quite a bit' consistently decreased throughout treatment cycles over a 25-week period (≥10-point decrease from baseline to week 25) for both cohorts, indicating that pre-treatment does not affect symptom improvement with capmatinib. Decreases in the proportion of patients reporting 'very much' or 'quite a bit' were also observed for chest pain and shortness of breath when walking, resting, and climbing. Improvements in QoL, assessed by QLQ-C30 GHS/QoL and EQ-5D-5L VAS score, were observed as early as

week 7 for both 1L and $2L^+$ patients, as well as weeks 7 and 13 for $2L^+$ and 1L patients, respectively. Improvements in cough and chest pain symptoms, and QoL were consistently more pronounced for 1L patients versus $2L^+$ patients over the 43-week period, which may be expected due to a decline in health owing to the progression of disease for $2L^+$ patients or the observed improved clinical response versus $2L^+$. TTDD was not reached for cough and chest pain at the time of the analysis.

Post hoc analysis showed a possible association between symptom improvement and clinical response as measured by BIRC. The improvement in QLQ-LC13 symptom scores appeared to be more pronounced in 1L patients with CR/PR than in $2L^+$ responders, with a clinically meaningful improvement in both cough and chest pain versus a clinically meaningful improvement in cough only. A clinically meaningful improvement for dyspnoea was not achieved in both 1L and $2L^+$ patients who had CR/PR.

Overall, these PRO results showing improvements in symptoms and no deterioration of QoL should be interpreted in the context of a frail and old population, considering the median age in both cohorts (71 years). In addition, TTDD for symptoms was not estimable, and capmatinib has also demonstrated increased efficacy and an acceptable tolerability profile [18].

This study had limitations that should be considered. The small sample sizes and large standard deviations for PRO-evaluable populations, especially in cohort 5b, require additional patient experience data to complement the data described here. As a single-arm, non-randomised trial, a lack of causal interpretation and matched control group of patients with NSCLC warrant further gathering of patient experience data to validate initial findings. No approved treatment for this patient population was available before the initiation of GEOMETRY mono-1, which may have affected the study design. The efficacy and PRO improvements observed in this analysis warrant further exploration of PROs in future studies. To date, most PRO data with MET kinase inhibitors are available from single-arm, open-label studies [26]. Lastly, the measure of $\geq$10-point change from baseline for clinically meaningful interpretation of the PRO results may be considered as a limitation where other thresholds may be acceptable in the interpretation of the QLQ-C30 results [27,28].

5. Conclusions

Capmatinib treatment was associated with clinically meaningful improvements in cough and no deterioration of QoL over time in patients with *MET*ex14-mutated aNSCLC, with patients experiencing a substantial period between capmatinib initiation and definitive lung cancer symptom deterioration. These PRO data, together with the previously reported high efficacy and manageable capmatinib tolerability data [18], support its use as a treatment option for patients with *MET*ex14-skipping aNSCLC.

Funding

This study was supported by Novartis Pharmaceuticals.

Authors' contributions

Jürgen Wolf: conceptualisation, investigation, writing – original draft, writing – review and editing.

Edward B. Garon: conceptualisation, writing – original draft, writing – review and editing.

Harry J.M. Groen: conceptualisation, writing – original draft, writing – review and editing.

Daniel S.W. Tan: conceptualisation, writing – original draft, writing – review and editing.

Isabelle Gilloteau: conceptualisation, methodology, writing – original draft, writing – review and editing.

Sylvie Le Mouhaer: conceptualisation, data curation, formal analysis, methodology, software, validation, writing – original draft, writing – review and editing.

Marcio Hampe: conceptualisation, investigation, writing – original draft, writing – review and editing.

Can Cai: conceptualisation, methodology, writing – original draft, writing – review and editing.

Andrea Chassot-Agostinho: conceptualisation, writing – original draft, writing – review and editing.

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Bintu Sherif: conceptualisation, data curation, formal analysis, methodology, software, validation, visualisation, writing – original draft, writing – review and editing.

Rebecca S. Heist: conceptualisation, investigation, writing – original draft, writing – review and editing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jürgen Wolf reports consulting or advisory roles with Amgen, AstraZeneca, Bayer, Blueprint, Bristol Myers Squibb, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Ignyta, Janssen, Lilly, LOXO, MSD, Novartis, Pfizer, Roche, Seattle Genetics, and Takeda, and research funding from Bristol Myers Squibb, Janssen Pharmaceuticals, Novartis, and Pfizer.

Edward B. Garon reports consulting or advisory roles with ABL Bio, Boehringer Ingelheim, Bristol

Myers Squibb, Dracen Pharmaceuticals, Eisai, Eli Lilly, EMD Serono, Gilead, GSK, Merck, Natera, Novartis, Personalis, Regeneron, Sanofi, Shionogi, and Xilio Therapeutics, and research funding from ABL Bio, AstraZeneca, Bristol Myers Squibb, Dynavax Technologies, EMD Serono, Genentech, Iovance Biotherapeutics, Eli Lilly, Merck, Mirati Therapeutics, Neon Therapeutics, and Novartis.

Harry J.M. Groen reports consulting or advisory roles with Eli Lilly, Bristol Myers Squibb, Novartis, Roche, and AstraZeneca, and research funding from Roche and Boehringer-Ingelheim.

Daniel S.W. Tan reports consulting roles for AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, LOXO, Merck, and Novartis, research support from Amgen, AstraZeneca, Bayer, Novartis, and Pfizer, and honoraria from Boehringer Ingelheim, Merck, Novartis, Pfizer, Roche, and Takeda.

Isabelle Gilloteau, Sylvie Le Mouhaer and Marcio Hampe are full-time employees of Novartis. Can Cai and Andrea Chassot-Agostinho are full-time employees of Novartis and shareholders.

Maria Reynolds and Bintu Sherif are full-time employees of RTI Health Solutions.

Rebecca S. Heist reports consulting roles with Abbvie, EMD Serono, Daichii Sankyo, and Novartis, and institutional research funding from Abbvie, Agios, Exelixis, Daichii Sankyo, Novartis, Lilly, Mirati, Turning Point, Corvus, and Incyte.

Acknowledgements

Capmatinib was originally developed by Incyte and was in-licensed by Novartis as of 24 November 2009. Medical writing assistance was provided by Emma Richards-Sirianni, PhD, and Egle McDonald, PhD, of Novartis UK Ltd. and was funded by Novartis Pharmaceuticals in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). We are also grateful for the support of all those involved in the execution of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.10.030.

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