Correlation between clinical and health-related quality-of-life benefits in patients with *ALK*+ NSCLC in ALTA-1L

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Background

- The phase 3 ALTA-1L trial (NCT02737501) compared brigatinib versus crizotinib in patients with anaplastic lymphoma kinase (ALK) inhibitor–naive *ALK*+ non–small cell lung cancer (NSCLC)[1-3]
  - At final analysis, median progression-free survival (PFS) assessed by a blinded independent review committee (BIRC) was 24.0 months with brigatinib versus 11.1 months with crizotinib (hazard ratio [HR] 0.48; 95% confidence interval [CI]: 0.35–0.66; log-rank *P*<0.0001)[3]
- Brigatinib demonstrated significant improvement in health-related quality of life (HRQoL) compared with crizotinib in the ALTA-1L trial[3,4]
  - Median time to worsening (TTW) in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) global health status (GHS)/quality of life (QoL) score was 26.7 months with brigatinib versus 8.3 months with crizotinib (HR 0.69; 95% CI: 0.49–0.98; log-rank *P*=0.047) in the final analysis of ALTA-1L[3]
- Here, we compare HRQoL outcomes between patients with and without clinical responses (responders versus nonresponders) to brigatinib and crizotinib in ALTA-1L

Objective

- To compare TTW in GHS/QoL score and other domains of the EORTC QLQ-C30 between clinically responding and nonresponding patients treated with brigatinib or crizotinib in ALTA-1L

Methods

Study design

- ALTA-1L was an open-label, randomized, multicenter phase 3 trial in patients with locally advanced or metastatic *ALK*+ NSCLC and no prior ALK inhibitor treatment
- Patients were randomized to brigatinib 180 mg once daily (QD; following 7-day lead-in at 90 mg QD) or crizotinib 250 mg twice daily (BID)

Outcomes

- Clinical responders were defined as patients with best confirmed response of complete response (CR) or partial response (PR) by BIRC according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[5]
- HRQoL was measured by the EORTC QLQ-C30 v3.0, administered at baseline, Day 1 of every 4-week cycle, end of treatment, and 30 days after the last dose

Analysis

- The analysis population included patients in the intention-to-treat (ITT)–patient-reported outcomes (PRO) population (patients with baseline and ≥1 postbaseline GHS value) who had available data for clinical response or nonresponse
- Worsening in QoL was defined as ≥10-point decrease from baseline for EORTC QLQ-C30 GHS/QoL functioning, and summary scores, and as ≥10-point increase for EORTC QLQ-C30 symptom scores
- TTW analyses were performed for clinical responders and nonresponders by treatment group using Kaplan–Meier methods
- Differences between response groups by treatment and between treatments in the responder group were analyzed using a Cox proportional hazards model with study stratification factors as covariates
- Correlations between duration of response (DoR) and TTW in each EORTC QLQ-C30 domain were explored using Spearman and Pearson coefficient analyses
  - Thresholds for correlation are as follows: 1.00, perfect positive correlation; 0.70–0.90, very strong positive correlation; 0.40–0.60, strong positive correlation; 0.30–>0.40, moderate positive correlation; ≤0.20–>0.30, weak positive correlation; ≤0.10–>0.20, negligible positive correlation; 0, no correlation; −, negative correlation (strength based on number)[6]
- Data were from the final analysis of ALTA-1L (last patient, last contact: January 29, 2021)

Results

Patients

- Of 262 patients in the ITT-PRO population, 131 received brigatinib (101 responders; 30 nonresponders) and 131 received crizotinib (83 responders; 48 nonresponders)
- Demographics and baseline characteristics **(Table 1)** and baseline EORTC QLQ-C30 scores **(Table 2)** were similar in responders and nonresponders within and across treatment groups

Table 1: Demographics and baseline characteristics

Characteristic[a]		Brigatinib Responders n=101	Brigatinib Nonresponders n=30	Crizotinib Responders n=83	Crizotinib Nonresponders n=48
Median age, years		57.0	59.5	58.0	61.0
Sex, %	Female	51	43	64	48
Race, %	White, Asian, Black or African American, Other[a]	51, 47, 0, 2	60, 40, 0, 0	58, 41, 1, 0	73, 23, 2, 2
Geographical region, %	Asia Pacific, Europe, North America	46, 49, 6	40, 50, 10	42, 45, 13	23, 69, 8
ECOG performance status, %	0, 1, 2	43, 53, 4	33, 63, 3	49, 48, 2	21, 75, 4
Smoking history, %	Never, Former, Current	61, 38, 1	53, 40, 7	61, 34, 5	46, 48, 6
Stage of disease at study entry, n %	IIIB, IV	6, 94	3, 97	7, 93	13, 88[b]
ALK status assessed locally by FDA-approved test, %		88	93	82	77
CNS metastases at baseline, %		33	17	25	35
Prior chemotherapy for locally advanced or metastatic disease, %		26	33	24	31

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration
[a]Other includes race unknown; [b]Percentages sum to more than 100% due to rounding

Table 2: Mean (95% CI) EORTC QLQ-C30 scores at baseline

	Brigatinib Responders n=101	Brigatinib Nonresponders n=30	Crizotinib Responders n=83	Crizotinib Nonresponders n=48
GHS/QoL	59.6 (54.6–64.5)	63.3 (54.7–72.0)	61.6 (56.7–66.6)	54.9 (48.0–61.7)
Physical functioning	78.7 (74.8–82.7)	78.0 (71.9–84.1)	80.4 (75.9–84.9)	77.1 (71.7–82.4)
Role functioning	71.8 (66.0–77.6)	69.4 (59.6–79.3)	73.9 (68.0–79.8)	71.2 (61.9–80.5)
Emotional functioning	74.5 (70.6–78.5)	73.1 (64.4–81.7)	74.6 (70.1–79.1)	70.1 (63.1–77.1)
Cognitive functioning	86.6 (83.2–90.1)	83.9 (75.0–92.8)	88.0 (84.2–91.7)	86.5 (81.5–91.4)
Social functioning	74.3 (68.6–80.0)	73.3 (62.3–84.4)	77.7 (72.1–83.3)	68.8 (60.7–76.8)
Fatigue	34.0 (29.1–38.9)	37.0 (28.4–45.7)	30.8 (25.8–35.8)	37.5 (29.9–45.1)
Nausea and vomiting	6.6 (3.7–9.5)	11.1 (4.5–17.7)	7.8 (4.7–11.0)	7.3 (3.0–11.6)
Pain	26.9 (21.5–32.3)	31.7 (20.9–42.4)	25.5 (19.6–31.4)	29.5 (20.7–38.3)
Dyspnea	31.0 (24.9–37.1)	23.3 (12.9–33.7)	31.3 (25.0–37.7)	35.4 (25.8–45.1)
Insomnia	28.7 (23.1–34.3)	32.2 (21.6–42.8)	31.7 (25.0–38.4)	35.4 (26.4–44.4)
Appetite loss	21.1 (15.4–26.8)	22.2 (9.4–35.0)	18.9 (12.6–25.1)	23.6 (15.1–32.1)
Constipation	9.9 (6.1–13.7)	12.2 (5.3–19.1)	11.6 (7.2–16.1)	16.0 (8.5–23.4)
Diarrhea	4.9 (2.6–7.3)	7.8 (1.5–14.1)	5.2 (2.3–8.1)	4.9 (−0.4–10.1)
Financial difficulties	22.1 (16.2–28.0)	16.7 (7.6–25.8)	17.7 (12.2–23.2)	20.8 (11.8–29.9)
QLQ-C30 summary score	78.6 (75.4–81.8)	77.5 (72.4–82.6)	79.5 (76.0–82.9)	75.7 (70.5–80.9)

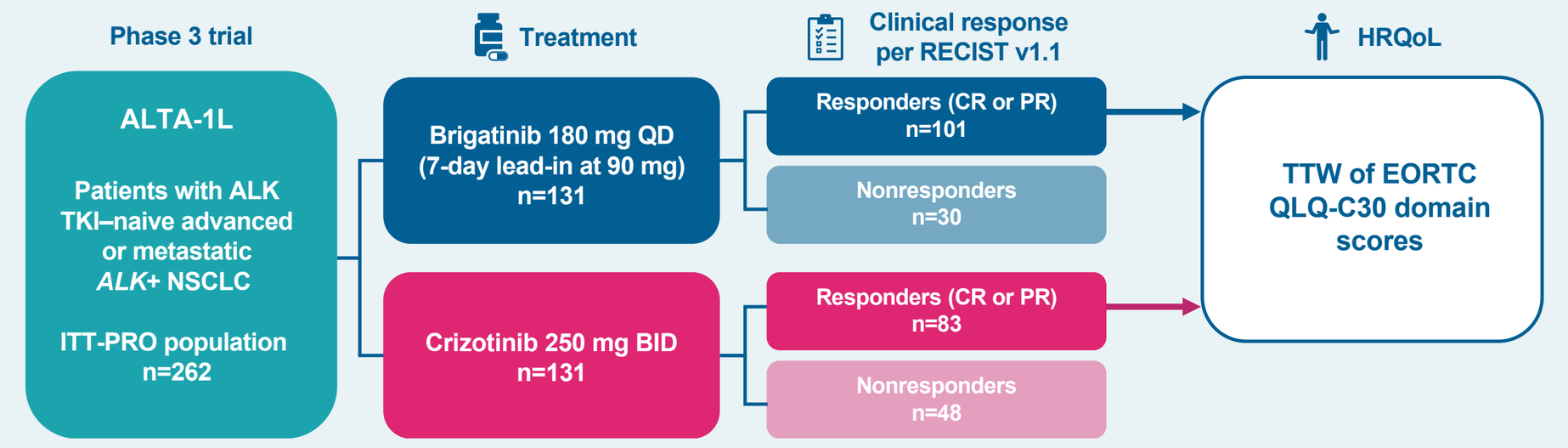
TTW in GHS/QoL

- Median TTW in GHS/QoL was significantly longer in responders than in nonresponders in the brigatinib and crizotinib arms **(Figure 1)**
  - Responders were ~50% (based on HR 0.51, as shown in **Figure 1**) as likely to have a worsening event than nonresponders with both treatments
- Median TTW in GHS/QoL was numerically longer for brigatinib responders (37.9 months) than crizotinib responders (13.0 months; HR 0.72; 95% CI: 0.47–1.09; *P*=0.1225; **Figure 2**)

Question

Does TTW in HRQoL differ between patients who have a clinical response to brigatinib versus crizotinib?

Study Design



Results

TTW in EORTC QLQ-C30 domains for brigatinib versus crizotinib responders

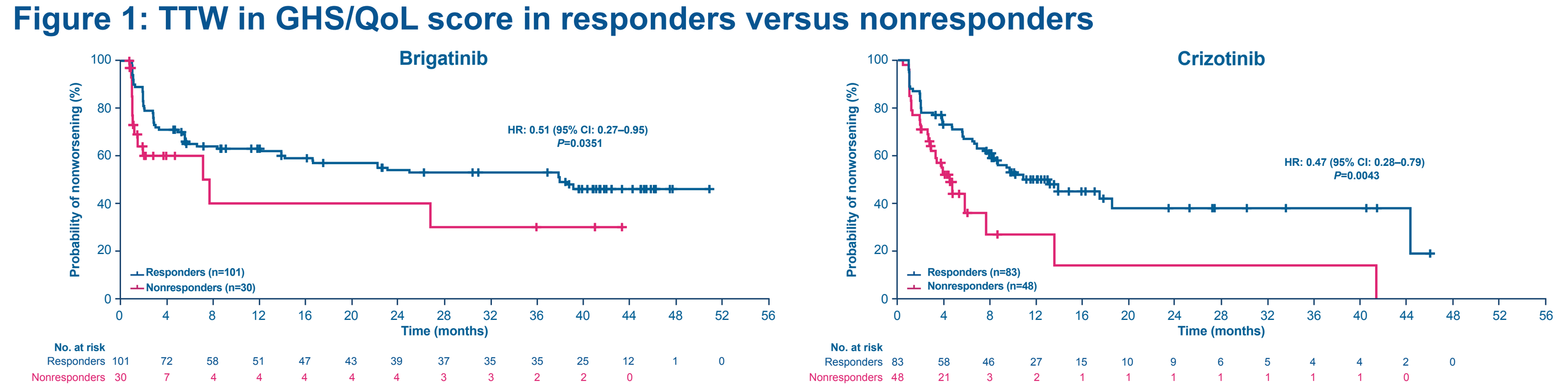
Domain	Median TTW, months (95% CI): Brigatinib responders (n=101)	Median TTW, months (95% CI): Crizotinib responders (n=83)	HR (95% CI)	*P* value
GHS/QoL	37.9 (13.9–NE)	13.0 (7.7–44.4)	0.72 (0.47–1.09)	0.1225
Functioning				
Physical	34.1 (22.1–NE)	17.5 (8.1–31.5)	0.65 (0.42–1.00)	0.0485
Role	12.1 (5.6–23.5)	7.5 (4.7–11.1)	0.85 (0.58–1.24)	0.3868
Emotional	NE (23.0–NE)	20.4 (10.1–NE)	0.67 (0.43–1.05)	0.0801
Cognitive	12.0 (4.7–16.9)	6.5 (3.8–10.3)	0.83 (0.58–1.21)	0.3370
Social	29.5 (14.9–NE)	4.8 (2.8–14.8)	0.52 (0.35–0.79)	0.0019
Symptoms				
Fatigue	15.9 (8.1–29.7)	8.3 (3.8–14.8)	0.72 (0.49–1.05)	0.0856
Nausea and vomiting	11.1 (3.8–23.0)	2.8 (1.9–6.6)	0.63 (0.44–0.91)	0.0126
Pain	12.2 (9.3–25.8)	10.2 (7.4–14.8)	0.89 (0.60–1.30)	0.5369
Dyspnea	NE (21.2–NE)	27.7 (11.1–37.1)	0.78 (0.50–1.22)	0.2710
Insomnia	42.4 (23.2–NE)	NE (14.0–NE)	0.91 (0.57–1.46)	0.7099
Appetite loss	NE (22.9–NE)	10.2 (4.8–27.2)	0.54 (0.35–0.82)	0.0041
Constipation	13.8 (7.3–30.3)	2.8 (1.9–4.6)	0.51 (0.35–0.75)	0.0005
Diarrhea	2.1 (1.9–3.6)	2.8 (1.9–3.8)	0.99 (0.71–1.38)	0.9662
Financial difficulties	NE (23.1–NE)	31.3 (19.4–NE)	1.01 (0.62–1.64)	0.9623
QLQ-C30 Summary Score	NE (28.6–NE)	17.5 (11.6–NE)	0.60 (0.38–0.96)	0.0320

Forest plot axis: 0.1 – 1 – 10; Brigatinib better / Crizotinib better

Key Takeaway

Brigatinib responders were ~35–50% less likely (HR 0.51–0.65) to have worsening in multiple EORTC QLQ-C30 domains of physical and social functioning, nausea and vomiting, appetite loss, constipation, and QLQ-C30 summary score compared with crizotinib responders

Figure 1: TTW in GHS/QoL score in responders versus nonresponders

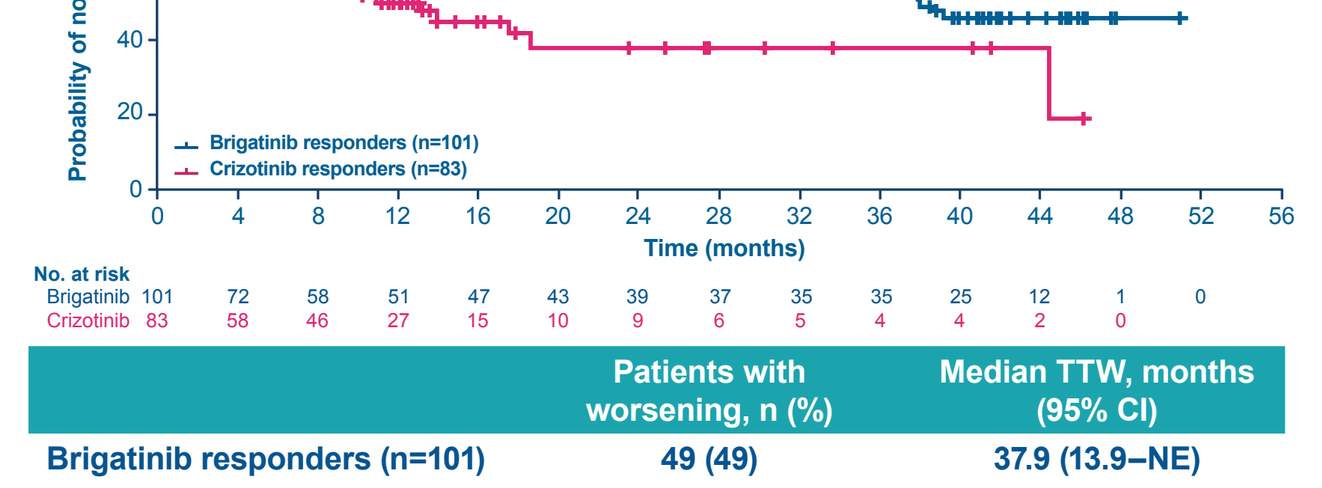


Brigatinib	Patients with worsening, n (%)	Median TTW, months (95% CI)
Responders (n=101)	49 (49)	37.9 (13.9–NE)
Nonresponders (n=30)	13 (43)	7.1 (1.2–NE)

Crizotinib	Patients with worsening, n (%)	Median TTW, months (95% CI)
Responders (n=83)	44 (53)	13.0 (7.7–44.4)
Nonresponders (n=48)	28 (58)	4.5 (2.8–7.6)

NE, not estimable

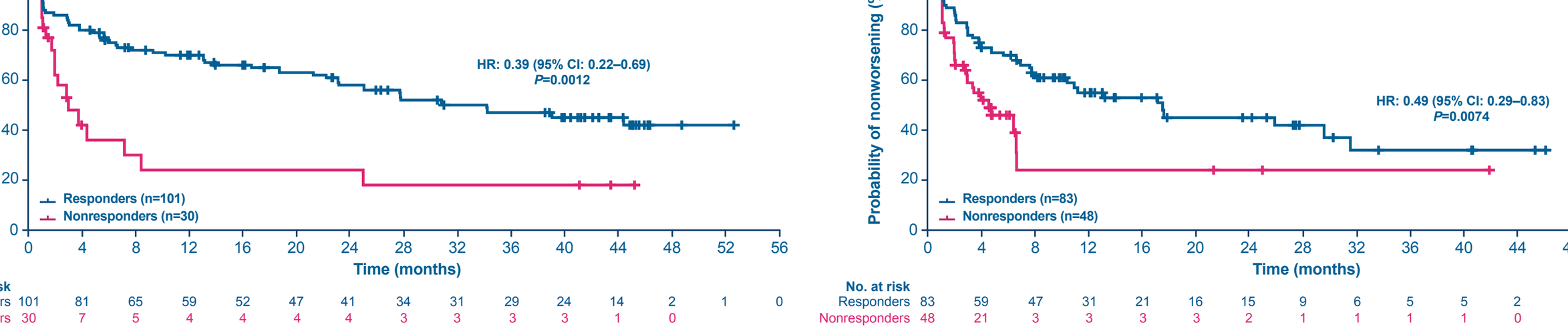
Figure 2: TTW in GHS/QoL score in responders to brigatinib versus crizotinib



	Patients with worsening, n (%)	Median TTW, months (95% CI)
Brigatinib responders (n=101)	49 (49)	37.9 (13.9–NE)
Crizotinib responders (n=83)	44 (53)	13.0 (7.7–44.4)

- Responders had significantly prolonged TTW in physical functioning versus nonresponders in both treatment arms **(Figure 3)**

Figure 3: TTW in physical functioning in responders versus nonresponders

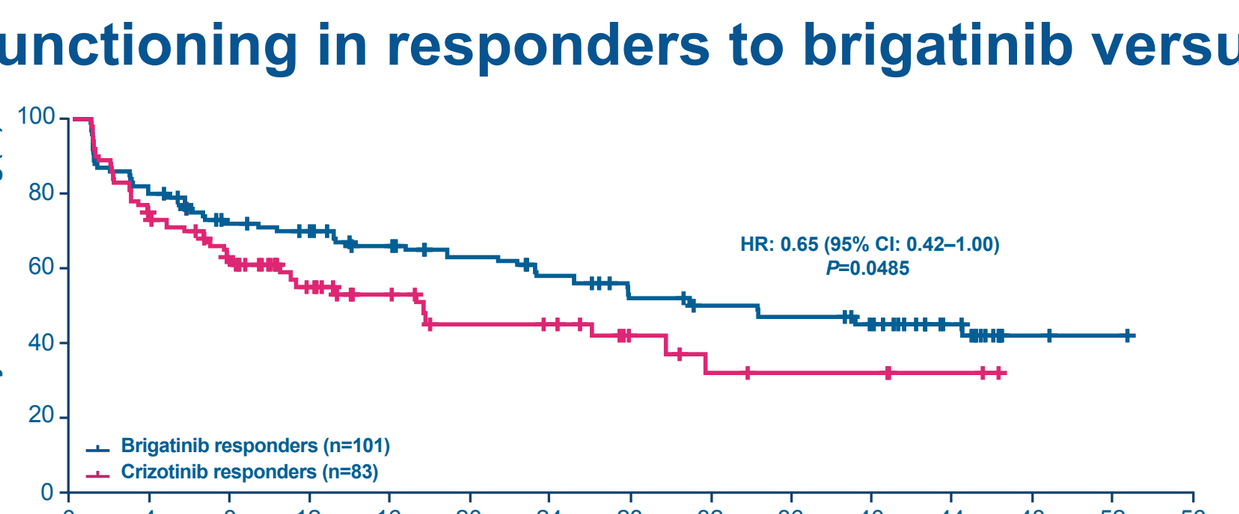


Brigatinib	Patients with worsening, n (%)	Median TTW, months (95% CI)
Responders (n=101)	48 (48)	34.1 (22.1–NE)
Nonresponders (n=30)	17 (57)	2.9 (1.7–8.3)

Crizotinib	Patients with worsening, n (%)	Median TTW, months (95% CI)
Responders (n=83)	42 (51)	17.5 (8.1–31.5)
Nonresponders (n=48)	27 (56)	4.5 (2.6–6.5)

- Median TTW in physical functioning was significantly longer in brigatinib responders versus crizotinib responders (34.1 vs 17.5 months; HR 0.65; 95% CI: 0.42–1.00; *P*=0.0485; **Figure 4**)

Figure 4: TTW in physical functioning in responders to brigatinib versus crizotinib



	Patients with worsening, n (%)	Median TTW, months (95% CI)
Brigatinib responders (n=101)	48 (48)	34.1 (22.1–NE)
Crizotinib responders (n=83)	42 (51)	17.5 (8.1–31.5)

- Brigatinib responders were ~50–65% less likely to have a worsening event than nonresponders in EORTC QLQ-C30 domains of physical functioning (median TTW: 34.1 vs 2.9 months; HR 0.39), dyspnea (NE vs 3.8 months; HR 0.34), insomnia (42.4 vs 9.3 months; HR 0.44), and appetite loss (NE vs 8.4 months; HR 0.52; **Figure 5**)
- Crizotinib responders were ~45–65% less likely than nonresponders to have a worsening event in the domains of physical functioning (median TTW: 17.5 vs 4.5 months; HR 0.49), emotional functioning (20.4 vs 3.9 months; HR 0.34), cognitive functioning (6.5 vs 2.9 months; HR 0.55), pain (10.2 vs 4.2 months; HR 0.56), dyspnea (27.7 vs 8.6 months; HR 0.54), and QLQ-C30 summary score (17.5 vs 8.6 months; HR 0.55; **Figure 5**)

Figure 5: HRs for TTW in EORTC QLQ-C30 domains for responders versus nonresponders

Brigatinib responders versus nonresponders

Domain	HR (95% CI)	*P* value
GHS/QoL	0.51 (0.27–0.95)	0.0351
Functioning		
Physical	0.39 (0.22–0.69)	0.0012
Role	0.70 (0.40–1.26)	0.2353
Emotional	0.62 (0.30–1.25)	0.1779
Cognitive	0.64 (0.35–1.16)	0.1375
Social	0.73 (0.38–1.44)	0.3666
Symptoms		
Fatigue	0.75 (0.41–1.39)	0.3673
Nausea and vomiting	1.39 (0.69–2.82)	0.3558
Pain	0.59 (0.32–1.11)	0.1048
Dyspnea	0.34 (0.18–0.61)	0.0004
Insomnia	0.44 (0.23–0.83)	0.0116
Appetite loss	0.52 (0.27–1.00)	0.0488
Constipation	0.60 (0.31–1.17)	0.1332
Diarrhea	0.85 (0.48–1.50)	0.5745
Financial difficulties	1.19 (0.49–2.85)	0.7018
QLQ-C30 summary score	0.74 (0.34–1.61)	0.4463

Crizotinib responders versus nonresponders

Domain	HR (95% CI)	*P* value
GHS/QoL	0.47 (0.28–0.79)	0.0043
Functioning		
Physical	0.49 (0.29–0.83)	0.0074
Role	0.67 (0.41–1.10)	0.1143
Emotional	0.34 (0.21–0.56)	<0.0001
Cognitive	0.55 (0.34–0.87)	0.0114
Social	0.99 (0.61–1.62)	0.9816
Symptoms		
Fatigue	0.69 (0.43–1.09)	0.1116
Nausea and vomiting	0.80 (0.51–1.25)	0.3277
Pain	0.56 (0.34–0.93)	0.0249
Dyspnea	0.54 (0.29–1.00)	0.0495
Insomnia	0.60 (0.31–1.13)	0.1149
Appetite loss	1.02 (0.59–1.78)	0.9348
Constipation	0.98 (0.61–1.56)	0.9213
Diarrhea	1.01 (0.64–1.61)	0.9648
Financial difficulties	0.96 (0.45–2.02)	0.9076
QLQ-C30 summary score	0.55 (0.32–0.97)	0.0377

Forest plot axis: 0.1 – 1 – 10; Responders better / Nonresponders better

Table 3: Correlation between DoR and TTW in EORTC-QLQ-C30

	Responders: Brigatinib (n=101)	Responders: Crizotinib (n=83)	Spearman coefficient[a]: Brigatinib	Spearman coefficient[a]: Crizotinib
Median DoR, months (95% CI)				
ITT-PRO population	(n=101); 33.1 (22.0–NE)	(n=83); 13.8 (10.4–22.8)		
Median TTW, months (95% CI)[b]				
GHS/QoL	(n=49); 37.9 (13.9–NE)	(n=44); 13.0 (7.7–44.4)	0.292**	0.065
Physical functioning	(n=48); 34.1 (22.1–NE)	(n=42); 17.5 (8.1–31.5)	0.291**	0.290*
Role functioning	(n=63); 12.1 (5.6–23.5)	(n=51); 7.5 (4.7–11.1)	0.304**	−0.036
Emotional functioning	(n=43); NE (23.0–NE)	(n=39); 20.4 (10.1–NE)	0.462***	0.183
Cognitive functioning	(n=66); 12.0 (4.7–16.9)	(n=52); 6.5 (3.8–10.3)	0.206*	0.029
Social functioning	(n=49); 29.5 (14.9–NE)	(n=51); 4.8 (2.8–14.8)	0.340***	−0.022
Fatigue	(n=60); 15.9 (8.1–29.7)	(n=52); 8.3 (3.8–14.8)	0.338***	−0.014
Nausea and vomiting	(n=66); 11.1 (3.8–23.0)	(n=60); 2.8 (1.9–6.6)	0.237*	0.027
Pain	(n=60); 12.2 (9.3–25.8)	(n=48); 10.2 (7.4–14.8)	0.233*	0.142
Dyspnea	(n=45); NE (21.2–NE)	(n=38); 27.7 (11.1–37.1)	0.215*	0.298*
Insomnia	(n=45); 42.4 (23.2–NE)	(n=31); NE (14.0–NE)	0.555***	0.490***
Appetite loss	(n=44); NE (22.9–NE)	(n=37); 10.2 (4.8–27.2)	0.412***	0.062
Constipation	(n=56); 13.8 (7.3–30.3)	(n=57); 2.8 (1.9–4.6)	0.206*	0.051
Diarrhea	(n=80); 2.1 (1.9–3.6)	(n=63); 2.8 (1.9–3.8)	0.087	−0.105
Financial difficulties	(n=41); NE (23.1–NE)	(n=29); 31.3 (19.4–NE)	0.404***	0.311*
QLQ-C30 summary score	(n=38); NE (28.6–NE)	(n=38); 17.5 (11.6–NE)	0.412***	0.338*

[a]Correlation coefficient of ≥0.3 represents a moderately positive correlation; [b]n=patients with worsening events; **P*<0.05; ***P*<0.01; ****P*<0.001

- Pearson correlation coefficients for DoR and TTW were generally similar

Conclusions

- Patients with *ALK*+ NSCLC who had a clinical response to first-line brigatinib or crizotinib in ALTA-1L had improved QoL outcomes compared with nonresponders
- In each treatment arm, responders had a lower likelihood of experiencing worsening events than nonresponders across multiple HRQoL domains (HRs <1)
- For patients who did have worsening events, TTW was significantly delayed in responders versus nonresponders for the following domains with each treatment:
  - Brigatinib responders versus nonresponders: GHS/QoL, physical functioning, dyspnea, insomnia, and appetite loss
  - Crizotinib responders versus nonresponders: GHS/QoL, physical/emotional/cognitive functioning, pain, dyspnea, and QLQ-C30 summary score
- Response to brigatinib was associated with QoL benefits compared with response to crizotinib, with reduced likelihood in experiencing an event and significant delays in TTW in physical functioning, social functioning, nausea and vomiting, appetite loss, constipation, and QLQ-C30 summary score
  - Median TTW in GHS/QoL was numerically, but not significantly, longer for brigatinib versus crizotinib responders, with the lack of significance likely due to the small number of patients remaining on crizotinib beyond 12 months
- Delayed TTW was correlated with longer DoR in brigatinib responders compared with crizotinib responders
  - Higher correlations in brigatinib responders versus crizotinib responders could be related to the large difference in median DoR (33.1 months vs 13.8 months)
- The observed QoL improvements in brigatinib versus crizotinib responders suggest a better quality of response with first-line brigatinib treatment for patients with *ALK*+ NSCLC

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