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Quality-adjusted survival with brigatinib versus crizotinib in *ALK*-positive (*ALK*+) non-small cell lung cancer (NSCLC): Results from the ALTA-1L trial

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Background

- Anaplastic lymphoma kinase (*ALK*) gene rearrangements occur in 3-8% of patients with NSCLC,[1-3] tumors harboring *ALK* rearrangements are sensitive to ALK tyrosine kinase inhibitors (TKI).
- Brigatinib is an ALK TKI approved by the United States Food and Drug Administration for treatment of *ALK*+ advanced NSCLC based on the open-label, phase 3 ALK in Lung Cancer Trial of brigAtinib in 1st Line (ALTA-1L):[4]
  - Brigatinib significantly improved blinded independent review committee (BIRC)-assessed progression-free survival (PFS) vs. crizotinib (median, 24.0 vs.11.1 months; hazard ratio [HR]=0.48, 95% confidence interval [CI] 0.35-0.66; P<0.0001) and investigator (INV)-assessed PFS vs. crizotinib (median, 30.8 vs. 9.2 months; HR=0.43, 95% CI [0.31-0.58]; P<0.0001).[4]
  - Grade 3-5 treatment emergent adverse events occurred in 73% vs. 61% of patients receiving brigatinib and crizotinib, respectively.
- The quality-adjusted time without symptoms and toxicity (Q-TWiST) method evaluates quality of life-time in a clinical trial setting by integrating benefits in quantity and quality of survival time into a single meaningful index.[5]

Objectives

- To compare the quality-adjusted survival time and quality-adjusted PFS of frontline brigatinib vs. crizotinib among patients with *ALK*+ NSCLC using Q-TWiST methodology.

Methods

- This is a post-hoc analysis of individual-level patient data from the ALTA-1L trial (NCT02737501). In the trial, ALK TKI treatment-naïve patients with locally advanced or metastatic *ALK*+ NSCLC were randomized (1:1) to receive brigatinib 180 mg once daily (with 7-day lead-in at 90 mg once daily) or crizotinib 250 mg twice daily. Patients treated in the crizotinib arm were allowed to cross over to brigatinib after BIRC-assessed progression. The efficacy endpoints measured in the trial include BIRC-assessed PFS, investigator-assessed PFS, objective response rate, intracranial response and overall survival. Details on the study design and methodology have been described previously.[4]
- The survival time for each treatment arm was partitioned into three mutually exclusive health states:
  - TOX: time spent with grade 3/4 toxicity, with any day with multiple adverse events counted once
  - TWiST: time before disease progression and without grade 3/4 toxicity
  - REL: time from disease progression until death or loss to follow-up
- Kaplan-Meier analysis was used to estimate mean duration in each health state.
- Mean Q-TWiST for each treatment arm was calculated as the sum of the utility-weighted mean duration for each health state:

$$\text{Q-TWiST} = (\mu_{TOX} \times \text{TOX}) + (\mu_{TWiST} \times \text{TWiST}) + (\mu_{REL} \times \text{REL})$$

where: U_{TOX}, U_{TWiST} and U_{REL} represented the average group utility values for each health state; TOX, TWiST and REL represented the mean duration of the health states; Q-TWiST for each treatment arm represented the quality-adjusted survival experienced by patients in ALTA-1L

- Quality-adjusted (QA) time spent in each state was calculated at 50 months of follow-up by applying health-state utilities: TOX, 0.756; TWiST, 0.793; REL, 0.55.[6]
- QA-PFS was calculated as the sum of the utility-weighted mean duration of each state prior to disease progression (REL utility=0 in the equation above).

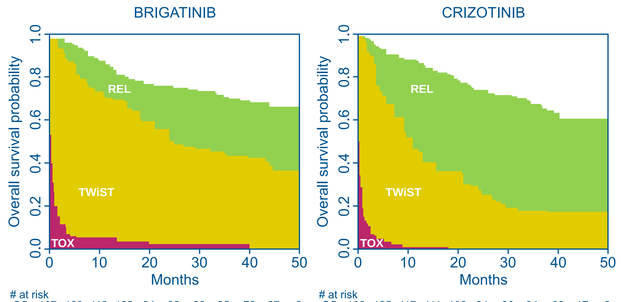
Methods

- Both BIRC- and INV-assessed progression were used for this post-hoc analysis.
- Relative Q-TWiST (% improvement) gains > 10% were considered clinically important.[7]
- A subgroup analysis was performed in patients without or with brain metastasis at baseline, respectively.
- All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

- Partitioned survival curves at 50 months of follow-up for are shown in **Figure 1**.

Figure 1. Partitioned Survival Curves at 50 Months of Follow-up (overall population)



The upper curve represents overall survival, the middle curve represents relapse-free survival, and the lower curve represents the time spent in toxicity.
BIRC, blinded independent review committee; OS, overall survival; PFS, progression-free survival; TOX, toxicity time for grade 3/4 adverse events; TWiST, time without toxicity or disease progression.

- Compared to patients receiving crizotinib, patients receiving brigatinib had a significantly longer duration of TWiST (P<0.001) and TOX, but shorter duration of REL (P<0.001) (**Table 1**).
- Patients receiving brigatinib spent a significantly longer time in TWiST (i.e., time without toxicity or disease symptoms) and experienced significantly greater overall Q-TWiST than patients receiving crizotinib (BIRC-assessed progression, diff: 3.1 months, P=0.045; INV-assessed progression, diff: 3.7 months, P=0.018). The relative gain in Q-TWiST was 10.4% and 12.3% for BIRC- and INV-assessed progression, respectively. These gains are considered clinically important improvements.

Results

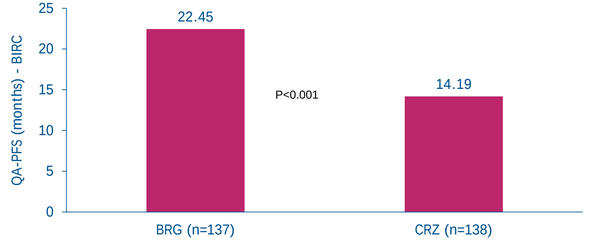
Table 1. Mean Duration in Health State and Q-TWiST at 50 Months of Follow-up (overall population)

Mean months, (SE)	BRG (n=137)	CRZ (n=138)	DIFF (BRG-CRZ)	P-value
BIRC-assessed progression				
TOX	2.32 (0.62)	1.08 (0.26)	1.24 (0.67)	0.064
TWiST	26.10 (1.75)	16.87 (1.60)	9.23 (2.37)	<0.001
REL	10.53 (1.53)	19.85 (1.73)	-9.32 (2.31)	<0.001
Q-TWiST	28.24 (1.15)	25.11 (1.07)	3.13 (1.57)	0.045

BIRC, blinded independent review committee; BRG, brigatinib; CRZ, crizotinib; DIFF, difference; Q-TWiST, quality-adjusted time without symptoms and toxicity; REL, post-disease progression; SE, standard error; TOX, toxicity time for grade 3/4 adverse events; TWiST, time without toxicity or disease progression.

- Compared to crizotinib, patients receiving brigatinib experienced a significantly longer QA-PFS (BIRC-assessed progression, diff: 8.3 months [95% CI 4.5–12.0, P<0.001]; INV-assessed progression, diff: 10.1 months [95% CI 6.5–13.8, P<0.001]) (**Figure 2**).
- Among patients with baseline brain metastases, the difference in QA-PFS and Q-TWiST between groups was 14.35 months and 10.01 months (both P<0.001) respectively, favouring brigatinib over crizotinib (**Table 2**).
- Among patients without baseline brain metastases, brigatinib patients had 6.05 months (P=0.011) of longer QA-PFS than crizotinib. No significant difference was found in Q-TWiST in this subgroup (**Table 3**). It is noted that the REL time was confounded by the crossover to brigatinib after disease progression in patients randomised to crizotinib (a total of 65 patients in crizotinib arm crossed over to brigatinib after progression).
- Data was consistent between BIRC- and INV-assessed results (INV assessed data not shown).

Figure 2. Mean Duration of QA-PFS (overall population)



BIRC, blinded independent review committee; BRG, brigatinib; CRZ, crizotinib; QA-PFS, quality-adjusted progression-free survival.

Table 2. Subgroup Analysis of Q-TWiST and QA-PFS Among Patients With Brain Metastasis at Baseline

Mean (SE) (months)	BRG (n=40)	CRZ (n=41)	DIFF	P-Value
BIRC-assessed progression				
QA-PFS	21.95 (2.26)	7.60 (1.50)	14.35	<0.001
Q-TWiST	28.96 (1.90)	18.95 (1.86)	10.01	<0.001

Table 3. Subgroup Analysis of Q-TWiST and QA-PFS Among Patients Without Brain Metastasis at Baseline

Mean (SE) (months)	BRG (n=97)	CRZ (n=97)	DIFF	P-Value
BIRC-assessed progression				
QA-PFS	22.65 (1.74)	16.60 (1.60)	6.05	0.011
Q-TWiST	27.93 (1.43)	27.42 (1.19)	0.51	0.78

BIRC, blinded independent review committee; BRG, brigatinib; CRZ, crizotinib; DIFF, difference; QA-PFS, quality-adjusted progression-free survival; Q-TWiST, quality-adjusted survival; SE, standard error.

Discussion

- There were significant benefits of brigatinib vs. crizotinib in quality-adjusted survival time measured by the Q-TWiST method in overall population.
- There were significant improvements in QA-PFS for brigatinib vs. crizotinib among all patients and those without and with brain metastases at baseline.
- This study was associated with a few limitations:
  - After progressive disease, a total of 65 patients from the crizotinib arm of the ALTA-1L trial crossed over to brigatinib per protocol.[1] As a result, REL time was confounded.
  - Only grade 3/4 adverse events were included, and the same utility value was assigned to the different adverse events; the current analysis was not designed to parse the length of grade 3/4 adverse events owing to limited data availability. This could lead to overestimation of time spent in TOX.[8]

Conclusion

- In patients with advanced *ALK*+ NSCLC, frontline treatment with brigatinib was associated with significant and clinically important gains in Q-TWiST and QA-PFS compared to crizotinib.
- The Q-TWiST assessment result is supportive of the study's primary endpoint PFS.
- These results further support brigatinib as first line treatment for *ALK*+ NSCLC.

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Disclosures

M.R. Garcia Campelo declares consulting/advisory roles with AstraZeneca, BMS, Novartis, Lilly, MSD, Janssen, Sanofi, Pfizer, Takeda, and Roche; participation in speakers' bureaus with AstraZeneca, BMS, Novartis, Lilly, MSD, Janssen, Sanofi, Pfizer, Takeda, and Roche; and receiving research funding from BMS. **Y. Wan, H.M. Lin, T. Chen, J. Shen, P. Zhang,** and **M. Humphries** are employees of Takeda and may own stock. **D.R. Camidge** declares ad hoc advisory roles with Abbvie, Achilles, Amgen, Anchiarno (SAB), Anheart, Apollomics (SRC), Archer, AstraZeneca (SRC/SC), BMS, Beigene (DSMC), BeyondSpring, Bio-Thera (DSMB), Blueprint, CBT Pharmaceuticals, Daiichi-Sankyo (ILD adjudication committee), EMD Serono, Eisai, Elevation (SRC), Eli Lilly (DSMB and NCCN), G1 Therapeutics (DSMB), GSK, Helsinn (DSMB), Hengrui (DSMC), Janssen, Kestrel (SAB, Medtronic, Mersana, Nuvalent (SAB), Onkure, Pfizer, Puma (NCCN), Qiliu, Ribon, Roche/Genentech, Sanofi, Seattle Genetics, Shares), Takeda, and Turning Point. **D.R. Camidge** also declares receiving research funding from Inivata and partaking in company sponsored trials (PI role) with Abbvie, AstraZeneca, Dizal, Inhibrx, Karyopharm, Pfizer, Phosplatin, Psioxus, Rain, Roche/Genentech, Seattle Genetics, Takeda, and Turning Point.

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