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Health-related quality of life of patients treated with repotrectinib for neurotrophic tyrosine receptor kinase (*NTRK*)-positive advanced solid tumors: results from TRIDENT-1

Bintu Sherif,[1] Benjamin Besse,[2] Benjamin Solomon,[3] Lyudmila Bazhenova,[4] Dong-Wan Kim,[5] Jessica J. Lin,[6] Juergen Wolf,[7] Sanjay Popat,[8] Koichi Goto,[9] Adrianus De Langen,[10] Christoph Springfeld,[11] Maria Reynolds,[1] Dawn Odom,[1] Yong Yuan,[12] Adam Lee,[13] Steven I. Blum,[12] Sanjay Thamake,[12] Felipe Ades,[12] Alexander Drilon[14]

[1] RTI Health Solutions, Research Triangle Park, NC, United States; [2] Paris-Saclay University, Gustave Roussy Cancer Center, Villejuif, France; [3] Peter MacCallum Cancer Centre, Melbourne, Australia; [4] UC San Diego Moores Cancer Center, La Jolla, CA, United States; [5] Seoul National University Hospital, Seoul, South Korea; [6] Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; [7] Centrum für Integrierte Onkologie–Uniklinik Köln, Köln, Germany; [8] The Royal Marsden NHS Foundation Trust, London, United Kingdom; [9] National Cancer Center Hospital East, Kashiwa, Japan; [10] Netherlands Cancer Institute, Amsterdam, Netherlands; [11] Heidelberg University Hospital, National Center for Tumor Diseases, Department of Medical Oncology, Heidelberg, Germany; [12] Bristol Myers Squibb, Princeton, NJ, United States; [13] Bristol Myers Squibb, Uxbridge, United Kingdom; [14] Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, United States

Introduction

- In TRIDENT-1 (NCT03093116), an ongoing pivotal multi-cohort phase 1/2 study, repotrectinib, a next-generation tyrosine kinase inhibitor (TKI), has shown durable clinical activity and manageable safety in *ROS1*+ advanced non-small cell lung cancer (NSCLC) and *NTRK*+ locally advanced/metastatic solid tumors
  - In the phase 2 expansion, enrolled patients in 6 distinct expansion cohorts received 160 mg QD oral repotrectinib for 14 days, then increased to 160 mg BID, if tolerated, until disease progression, unacceptable toxicity, or death
  - Updated results from TRIDENT-1 showed promising confirmed objective response rate, duration of response, progression-free survival, and manageable safety in patients with *NTRK*+ advanced solid tumors[1]
- Here, we present health-related quality-of-life (HRQOL) data for patients with *NTRK*+ solid tumors, summarized by TKI-naïve (i.e., with no prior TRK TKI) and TKI-pretreated (i.e., with prior TRK TKI) (data cutoff 19 December 2022)

Objective

- To examine the impact of repotrectinib treatment on HRQOL as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core Module (QLQ-C30) in patients with *NTRK*+ solid tumors

Methods

Health-related quality-of-life assessments

- EORTC QLQ-C30:
  - The EORTC QLQ-C30 contains 30 questions that incorporate 5 functional scales (Physical [PF], Role, Cognitive, Emotional, and Social), 3 symptom scales (Fatigue, Pain, and Nausea and Vomiting), a multi-item Global Health Status (GHS)/Quality-of-Life (QOL) scale, and 6 single-item symptoms (Dyspnea, Insomnia, Appetite, Constipation, Diarrhea, and Financial Impact)
  - The scales and items are linearly transformed to 0-to-100 scores according to the questionnaire scoring manual. For GHS/QOL and functional scales, higher scores represent better QOL or functioning; higher symptom scale scores represent more symptoms/worse status
- EORTC QLQ-C30 scores were assessed at baseline (last assessment predose), prior to the start (day 1) of each treatment cycle (i.e., every 4 weeks) until the end of treatment visit

Analysis methods

- Completion rates were summarized as the number of patients with at least 1 evaluable scale score at the timepoint divided by number of patients expected to complete the questionnaires
- Change from baseline score was summarized descriptively for subscale scores. For each scale, the percentage of patients reporting improved, worsened, or stable, using a minimal important difference (MID) of 10-point change from baseline[2] out of nonmissing responses was summarized using stacked bar charts
- Time to definitive deterioration (TDD, or time from first dose to first date of ≥ 10 points decrease/worsening change from baseline with no subsequent improvement or death if within 28 days of last assessment) in GHS/QOL and PF was assessed by Kaplan-Meier methods
- Time to first improvement (TFI, or time from first dose to first date of ≥ 10 points increase/improvement from baseline) in GHS/QOL and PF was assessed by Kaplan-Meier methods
- Data were analyzed as observed without imputation. No adjustments for multiple estimation were used; confidence intervals (CIs) should be considered nominal and descriptive in nature

Results

- A total of 79 patients with *NTRK*+ solid tumors who received the recommended phase 2 dose of repotrectinib with a baseline HRQOL and at least 1 postbaseline score were included in the analysis (TKI naïve, n = 35; TKI-pretreated, n = 44)
- The most frequent cancer types in the overall population (N = 79) were NSCLC (43%), salivary gland cancer (12.7%), and sarcoma (10.1%). The median duration of treatment (months) was 17.8 (range, 8.7-64.6) in the TKI-naïve cohort and 20.1 (8.7-69.4) in the TKI-pretreated cohort
- The EORTC QLQ-C30 completion rates were > 89% for TKI naïve and ≥ 87% for TKI-pretreated patients through cycle 12
  - At cycle 12, fewer than 20 patients in either the TKI-naïve or TKI-pretreated cohort remained on treatment, and > 89% completed the assessment
- Baseline values (mean [SD]) for GHS/QOL, PF, and pain were as follows: in the TKI-naïve cohort, 70.2 (22.53), 86.3 (15.08), and 15.2 (21.53), respectively; and in the TKI-pretreated cohort, 64.9 (21.33), 79.7 (23.05), and 29.8 (34.61), respectively (Table 1)
- Overall, mean changes over time remained stable in most of EORTC QLQ-C30 scale scores through the first year of treatment in both *NTRK*+ solid tumor cohorts. The mean change in GHS/QOL remained stable in both cohorts (Figure 1)
  - Improvements in change scores up to cycle 12 were observed in symptoms scales/items, particularly in Pain and Insomnia in both cohorts (data not shown)
  - Worsening was observed in the mean change score in Constipation in the TKI-naïve cohort (data not shown)
- The majority of patients in both TKI-naïve and TKI-pretreated cohorts had stable responses postbaseline in many EORTC QLQ-C30 scales/items
  - Among participants responding at cycle 12, 52.9% in the TKI-naïve group and 78.6% in the TKI-pretreated group had improved or stable responses in GHS/QOL (Figure 2)
  - Consistent worsening in Constipation was observed over time in the TKI-naïve group
- Less than half of patients with *NTRK*+ solid tumors experienced a deterioration event in GHS/QOL (45.7% for TKI-naïve and 36.4% for TKI-pretreated)
  - The median TDD for the GHS/QOL was 17.5 months for the TKI-naïve cohort and 13.1 months for the TKI-pretreated cohort (Figure 3)
  - The median TDD in PF was 17.5 months in the TKI-naïve cohort and 13.8 months in the TKI-pretreated cohort
- Less than 40% of patients reported improvement events in both *NTRK*+ solid tumor cohorts. The median TFI in GHS/QOL and PF was not reached in both cohorts

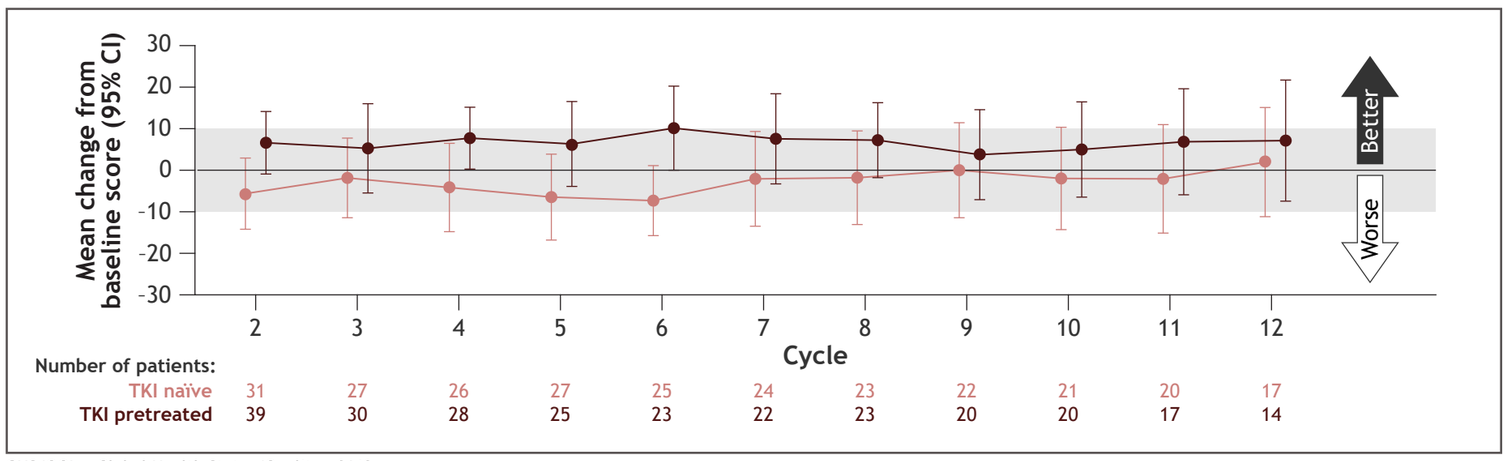
Table 1. EORTC QLQ-C30 scores at baseline (quality-of-life analysis set)

Scale	Mean (SD)	
	TKI-naïve (N = 35)	TKI-pretreated (N = 44)
GHS/QOL	70.2 (22.53)	64.9 (21.33)
Functional scales		
Physical	86.3 (15.08)	79.7 (23.05)
Role	88.6 (20.12)	70.9 (33.15)
Emotional	83.3 (18.74)	84.3 (15.77)
Cognitive	83.3 (26.20)	86.8 (17.65)
Social	86.7 (21.69)	83.3 (23.57)
Symptom scales		
Fatigue	22.9 (19.42)	29.7 (23.35)
Nausea and vomiting	4.3 (8.42)	3.9 (8.79)
Pain	15.2 (21.53)	29.8 (34.61)
Dyspnea	21.9 (21.30)	19.4 (26.46)
Insomnia	17.1 (24.75)	22.2 (28.20)
Appetite loss	8.6 (18.69)	14.0 (22.10)
Constipation	11.4 (19.71)	10.1 (21.25)
Diarrhea	4.8 (11.84)	6.2 (15.01)
Financial difficulties	15.2 (27.23)	12.4 (23.03)

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module; GHS/QOL = Global Health Status/Quality-of-Life

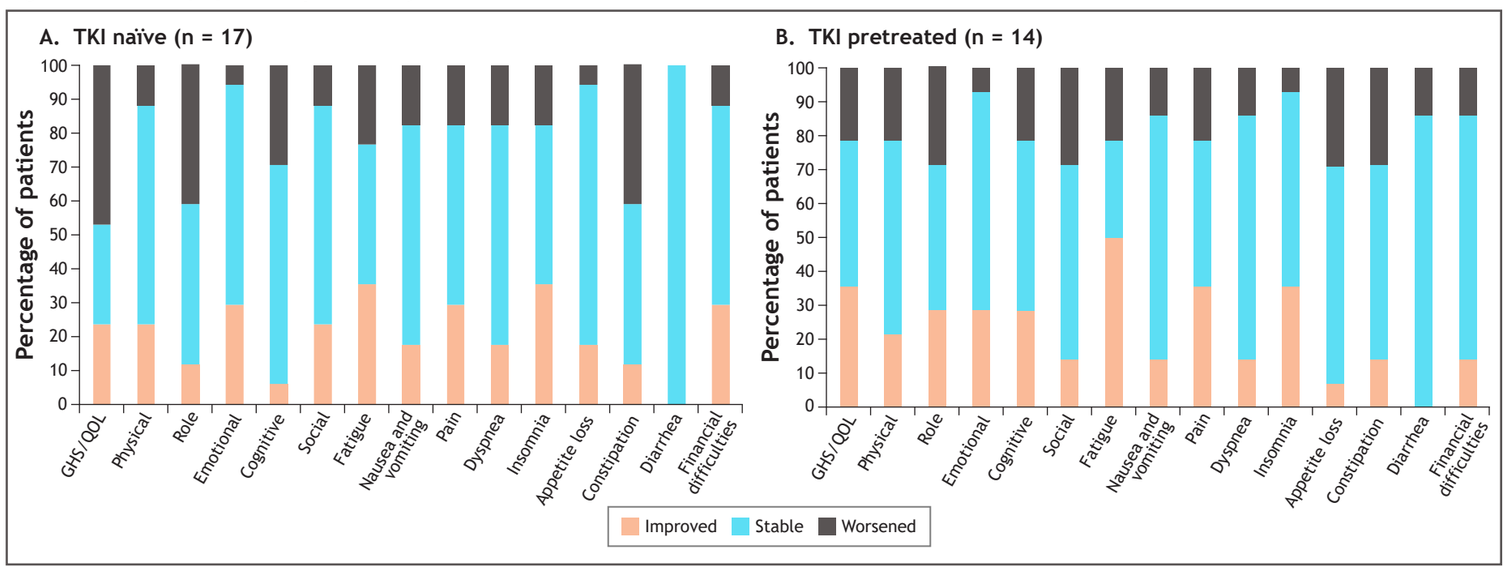
Note: The n for EORTC QLQ-C30 scores at baseline is 35 for TKI-naïve *NTRK*+ solid tumors and 42-43 for TKI-pretreated *NTRK*+ solid tumors

Figure 1. Mean change from baseline in GHS/QOL



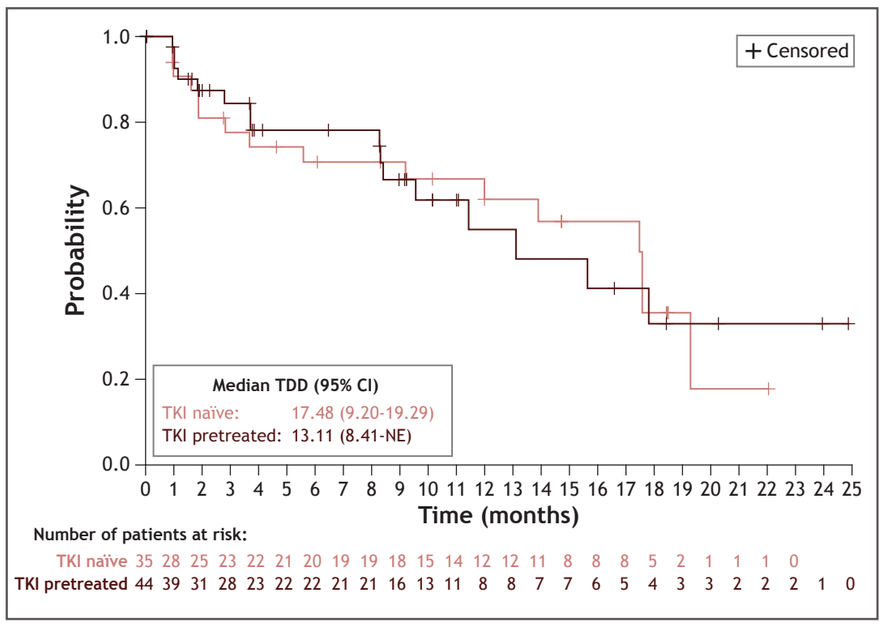
GHS/QOL = Global Health Status/Quality-of-Life

Figure 2. EORTC QLQ-C30 response at cycle 12



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module

Figure 3. TDD in GHS/QOL



GHS/QOL = Global Health Status/Quality-of-Life; NE = note estimable; TDD = time to definitive deterioration; TKI = tyrosine kinase inhibitor

Conclusions

- Patients with *NTRK*+ solid tumors who were treated with repotrectinib generally experienced stable or improved HRQOL as measured by the EORTC QLQ-C30 while on treatment
  - Mean changes from baseline were generally less than the MID through cycle 12
- Median time to deterioration was delayed by more than 12 months in both *NTRK*+ solid tumor cohorts
- The results presented here complement the efficacy and safety data of repotrectinib as a treatment option for patients with *NTRK*+ solid tumors

References

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Email: yong.yuan@bms.com