Evidence to Support the Use of the Functional Assessment of Cancer Therapy – General Item GP5 (FACT GP5) to Assess Comparative Tolerability Endpoint: Results From the LIBRETTO-531 Trial

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Background and Objectives

- Functional Assessment of Cancer Therapy-General (FACT) item GP5 is a validated and commonly used PRO measure of overall side-effect impact of cancer therapy[1-4]
- Increased bother from side effects is associated with lower quality of life (QoL) and a greater likelihood of treatment discontinuation[2,4]
- Understanding how patients interpret the term “bother” and how this is perceived by patients prior to starting systemic treatment is important
- LIBRETTO-531 (NCT04211337) is a phase 3 study comparing selpercatinib vs. comparator of physician’s choice (cabozantinib or vandetanib) in patients with progressive, advanced, tyrosine kinase inhibitors (TKI)-naïve, Rearranged during Transfection (RET)-mutation positive medullary thyroid cancer (MTC)[5]
- LIBRETTO-531included a key secondary PRO endpoint comparing the proportion of time on-treatment with high side-effect bother based on the GP5 rating of 3 or 4
- Additional evidence supporting the item GP5 as a fit-for-purpose measure of tolerability in LIBRETTO-531 is needed

Objectives

- To generate psychometric evidence supporting the use of GP5 to measure tolerability
- To evaluate the appropriateness of the categorization of “high side-effect bother” using GP5 rating of 3 or 4 using data from LIBRETTO-531

Methods

Study design and Data source

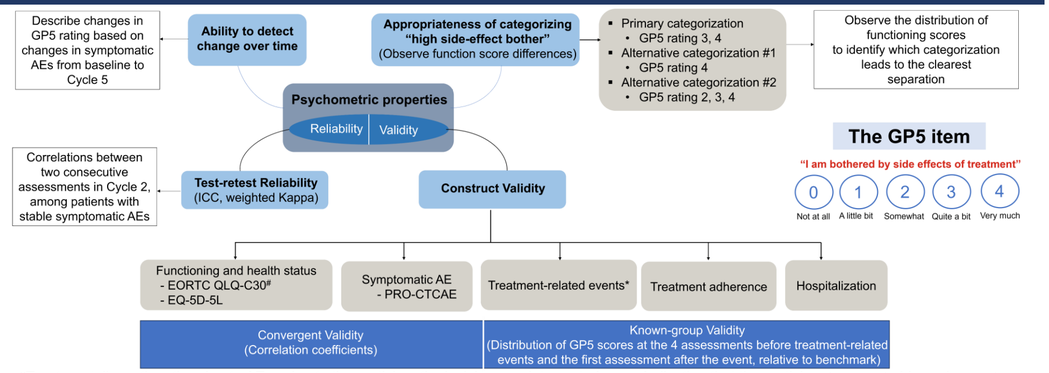
- Prespecified analysis on blinded patient data (N=290, data cutoff date May 22, 2023) from a randomized, open-label, LIBRETTO-531 phase 3 trial[5]

Patient Population

- Adult (age≥ 18 years) patients with locally advanced, TKI-naïve, *RET*- mutation-positive MTC

Assessment schedule

- **GP5 and PRO-CTCAE**
  - Data was collected at Cycle 1 Day 1 (baseline), then weekly post-baseline and at short-term follow-up
- **EORTC QLQ-C30 and EQ-5D-5L**
  - Data was collected at Cycle 1 Day 1 (baseline), then at D1 of each cycle (28-day) post-baseline and at short-term follow-up
- All PRO measures were captured electronically using either a device provided to the patient or a device at the clinic site



*Treatment discontinuation due to AE or due to the participant’s decision was interpreted as an indication that the participant was not able or does not desire to adhere to the treatment

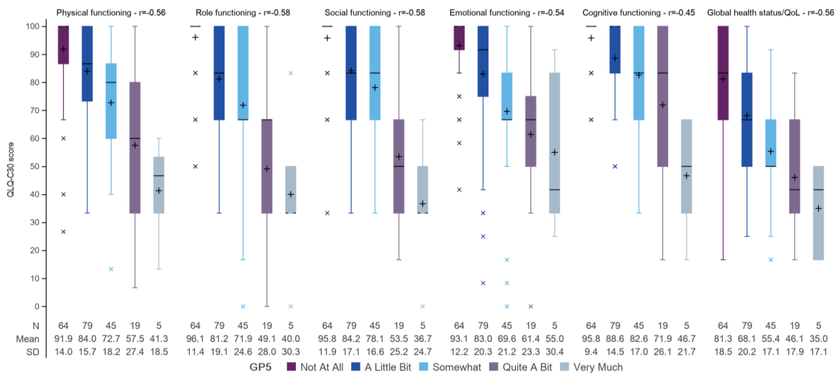
#EORTC QLQ-C30 included: Physical Functioning, Role Functioning, Social Functioning, Emotional functioning, and Cognitive Functioning domains

Results

Reliability of FACT GP5

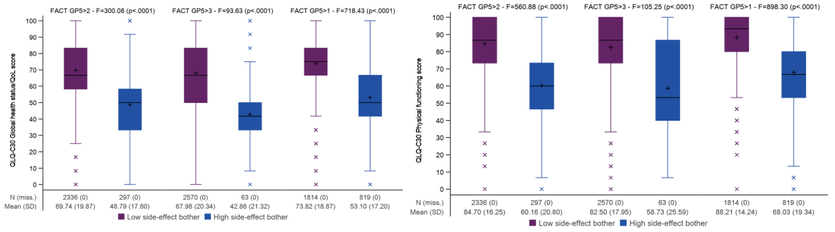
- During Cycle 2 (weeks 5-8) post-baseline:
  - -ICCs ranged between 0.80-0.85
  - -Kappa coefficients ranged between 0.68-0.75

Distribution of QLQ-C30 functioning and QoL scores according to GP5 ratings at cycle 3



- Patients with higher GP5 ratings showed association with
  - ➢ **lower QLQ-C30 scores** (lower functioning and QoL)
  - ➢ **lower EQ-5D-5L VAS ratings** (lower functioning)

Characterization of high side-effect bother using PRO scores of functioning

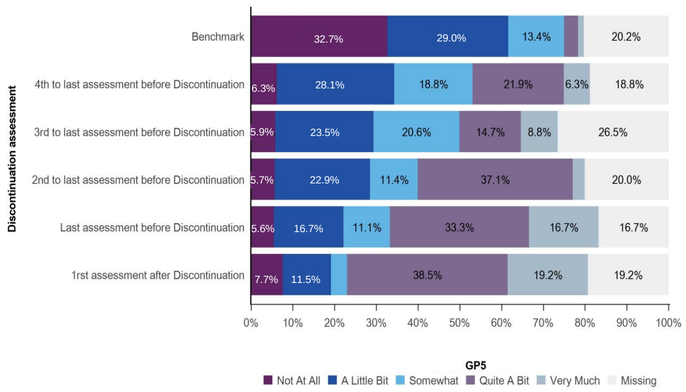


- All three GP5 categorizations showed good ability to separate the QLQ-C30 Global health status/QoL and physical functioning (PF) scores between patients identified as having high side-effect bother

GP5 categories	QLQ-C30 Global health status/QoL score	QLQ-C30 Physical functioning score
Primary categorization (score=3 or 4)	48.8±17.6 vs. 69.7±19.9	60.2±20.8 vs. 84.7±16.2
Alternative categorization #1 (score=4)	42.9±21.3 vs. 68.0±20.3	58.7±25.6 vs. 82.5±18.0
Alternative categorization #2 (score=2,3, or 4)	53.1±17.2 vs. 73.8±18.9	68.0±19.3 vs. 88.2±14.2

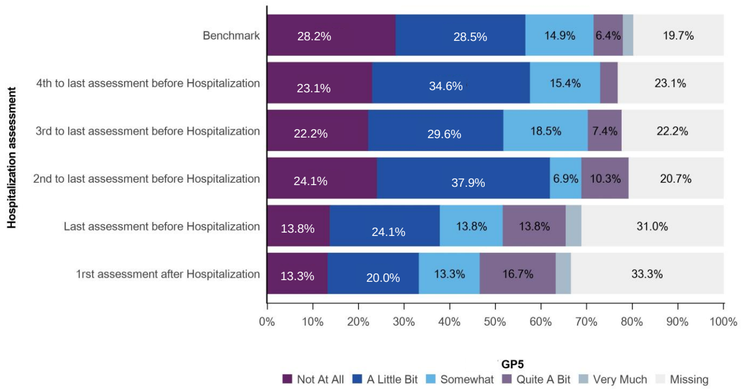
- Mean ± SD QLQ-C30 QoL and PF scores at the time of assessment when the patient was categorized as experiencing high side-effect bother vs. otherwise were significantly different (p<0.0001)

Known-group validity: Association between GP5 ratings and treatment discontinuation



- Level of bother (“Quite a bit” or “Very much”) with treatment side effects was higher at the assessment closer to treatment discontinuation ranging from **23.5%** to **57.7%** compared to only **4.7%** in the benchmark group*

Known-group validity: Association between GP5 ratings and hospitalization



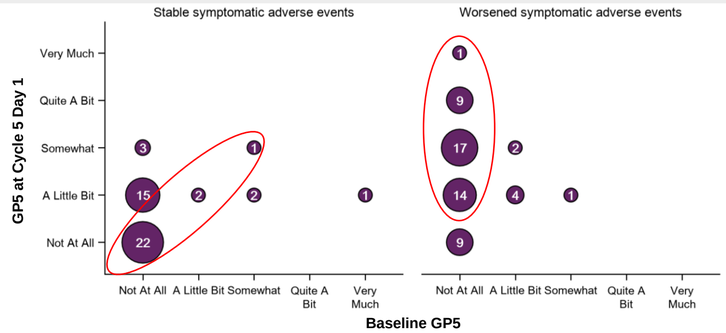
Increased proportion of patients reported “Quite a bit” or “Very much” bother on GP5 ratings among those hospitalized at assessment time points closer to hospitalization compared with the benchmark group*

*Benchmark group was created by pooling the rating of the first 5 cycles, excluding those from participants who discontinued treatment or had a dose modification or hospitalized over the first 2 cycles to aid interpretation in the analysis as the “normal” or “typical” GP5 response during the course of the study

Abbreviations: AE, Adverse event; ICC, Intra-class correlation coefficients; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EQ-5D-5L, 5-level-EuroQol; FACT GP5, Functional Assessment of Cancer Therapy Side Effects; PRO-CTCAE, Patient-Reported Outcome Common Terminology Criteria for Adverse Events; QOL, Quality of life

Ability of the GP5 to detect change over time

GP5 showed a good ability to detect change over time as participants with worsened symptomatic AEs had higher post-baseline GP5 rating as compared to their own baseline rating and those among stable participants



Note: Red circle indicates patients who reported stable symptomatic AE (no change from baseline) and patients who reported worsened symptomatic AEs from baseline

- Association between post-baseline GP5 ratings and worsening of symptomatic AEs were statistically significant (p<0.001)
- A greater proportion of the participants categorized as ‘worsened’ had scores no more than one point change on PRO-CTCAE ratings

Conclusions

- The quantitative evidence generated from the psychometric analysis demonstrates that the GP5 has sufficient reliability, validity, responsiveness, and interpretation standards
- The GP5 is a fit-for-purpose PRO measure for assessing patient-reported tolerability that is suitable for use in clinical trials among patients with RET-mutant MTC. Additional analysis may be required to assess fit-for-purpose of the GP5 in other cancer patient population
- The categorization of “high side-effect bother” using a GP5 score 3 or 4 is appropriate for use in evaluating comparative tolerability in LIBRETTO-531

Strengths

- Findings from this psychometric analysis are consistent with existing literature
- Availability of more granular data (i.e., GP5 weekly assessments) likely increased the accuracy of the test-retest reliability estimates

Limitations

- Association between treatment adherence and GP5 was not observed due to the clinical trial setting
- Interpretation of results based on hospitalization or focusing on consecutive high side-effect bother assessments, was limited due to low sample size

References: [1]United States Food and Drug Administration. Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry. Silver Spring, MD June 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomescancer-clinical-trials; [2]Pearman TP, et a. Cancer. 2018;124(5):991–997; [3]Wagner LI, et al. Breast Cancer Res Treat. 2018;169(3):537–548; [4]Griffiths P, et al. Support Care Cancer. 2022;30(4):3613–3623; [5]Wirth LJ, et al. Future Oncol. 2022;18(28):3143-3150

Disclosures : AMG, PM, YL, LMH and NP are employees and stockholders of Eli Lilly and Company. AR, LB and AL are employees of Modus outcomes, which was contracted by Eli Lilly and Company to conduct this study

Acknowledgements: Medical writing support was provided by Priyanka Bannikoppa and Vengal Rao Pachava Eli Lilly Services India Private Limited

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