Health-related quality of life in patients treated with ivosidenib for mutant-*IDH1* cholangiocarcinoma: Results from ClarIDHy

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BACKGROUND AND OBJECTIVES

- Advanced cholangiocarcinoma is a rare and aggressive cancer with treatment options primarily limited to chemotherapy[1]
- Ivosidenib is a first-in-class, oral, targeted, small-molecule inhibitor of the mutant isocitrate dehydrogenase 1 (mIDH1) protein,[2] which occurs in up to 20% of intrahepatic cholangiocarcinomas and ~1% of extrahepatic cholangiocarcinomas[1]
- Ivosidenib significantly improved progression-free survival (PFS) vs placebo (hazard ratio = 0.37; p < 0.001), and preliminary data showed improvement in overall survival in ClarIDHy (ClinicalTrials.gov NCT02989857), a phase 3, randomized, double-blind study of patients with m*IDH1* advanced cholangiocarcinomas[3]
  - 6- and 12-month PFS rates for ivosidenib were 32% (95% CI 23%, 42%) and 22% (13%, 32%), respectively, whereas no placebo-treated patients had PFS ≥ 6 months
  - Ivosidenib also showed a favorable safety and tolerability profile
- Here we describe the impact of ivosidenib vs placebo on health-related quality of life (HRQoL), including symptom burden

METHODS

ClarIDHy phase 3 trial

- A total of 185 patients were randomized to receive ivosidenib 500 mg daily (n = 124) or placebo (n = 61), with crossover to ivosidenib permitted at confirmed radiographic disease progression
  - As of the 31Jan2019 data cut, 35 placebo-treated patients (57.4%) crossed over to open-label ivosidenib upon radiographic disease progression and unblinding
- Additional details of the study design, and efficacy and safety analyses, are reported in a separate poster (see the poster by Macarulla et al) and have been published recently[3]

HRQoL assessments

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Cholangiocarcinoma and Gallbladder Cancer module (EORTC QLQ-BIL21) were administered before dosing on Cycle (C) 1, Day (D) 1, on the first day of subsequent cycles until the end-of-treatment visit, and every 12 weeks thereafter until the start of new anticancer therapy
- Patient Global Impression of Change (PGIC) and Severity (PGIS) data were collected as anchors for three prespecified subscales of interest (physical functioning [PF], pain, and appetite loss) at the same timepoints as for the EORTC instruments, except that C1D1 PGIC was not collected
- The EuroQol 5-Dimensions 5-Level version (EQ-5D-5L) was administered at C1D1, C3D1, and the end-of-treatment visit for use in future health economic modelling
- The original HRQoL assessment schedule was altered in a protocol amendment to increase the frequency of the EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L assessments, and to add the anchor questions

Statistical analyses

- HRQoL data were summarized for randomized patients who completed at least one baseline HRQoL assessment
- All analyses focused on data from patients randomized to the placebo arm in the period before crossover and the ivosidenib arm

EORTC QLQ-C30 and QLQ-BIL21

- Exploratory mixed-effect models with repeated measurements (MMRM) were conducted on EORTC QLQ-C30 and QLQ-BIL21 subscale score changes from baseline to C2D1, with baseline score, treatment, visit, and treatment-by-visit as fixed effects and patient as random effect. The focus was on C2D1 due to insufficient data at later timepoints. p-values were not adjusted for multiplicity
- Thresholds for clinically meaningful changes in the prespecified subscales were estimated by computing the C2D1 change scores for the EORTC QLQ-C30 and QLQ-BIL21 subscales of interest, and were associated with meaningful change using the respective 7-level PGIC ratings as anchors

EQ-5D-5L

- Descriptive analyses were conducted on data at baseline and the first postbaseline assessment (C3D1) due to insufficient data at later timepoints

RESULTS

Baseline characteristics

- A total of 113 patients in the ivosidenib arm and 52 in the placebo arm completed at least one baseline HRQoL assessment
- Baseline characteristics were generally similar in the ivosidenib and placebo arms (**Table 1**)
  - The distribution of clinical characteristics between arms was similar to the full intent-to-treat population in the primary efficacy analysis (see the poster by Macarulla et al for further details)

RESULTS (CONTINUED)

Table 1. Baseline characteristics among patients with at least one baseline HRQoL assessment

Characteristic, n (%)	Ivosidenib n = 113[a]	Placebo n = 52[b]
Randomization stratum		
One prior line of therapy	58 (51.3)	31 (59.6)
Two prior lines of therapy	55 (48.7)	21 (40.4)
***IDH1* mutation**		
R132C	76 (67.3)	39 (75.0)
R132L/G/S/H	19 (16.8); 16 (14.2); 2 (1.8); 0	6 (11.5); 4 (7.7); 1 (1.9); 2 (3.8)
ECOG PS score at baseline		
0	48 (42.5)	16 (30.8)
1	64 (56.6)	35 (67.3)
Cholangiocarcinoma type at diagnosis		
Intrahepatic	100 (88.5)	50 (96.2)
Extrahepatic/perihilar	5 (4.4)	1 (1.9)
Unknown	8 (7.1)	1 (1.9)
Extent of disease at screening		
Local/regional	8 (7.1)	5 (9.6)
Metastatic	105 (92.9)	47 (90.4)

[a]Six ivosidenib patients did not complete the EORTC QLQ-BIL21 and EQ-5D-5L baseline assessments
[b]One placebo patient did not complete the EORTC QLQ-BIL21 and EQ-5D-5L baseline assessments
ECOG PS = Eastern Cooperative Oncology Group performance status

EORTC QLQ-C30 and QLQ-BIL21

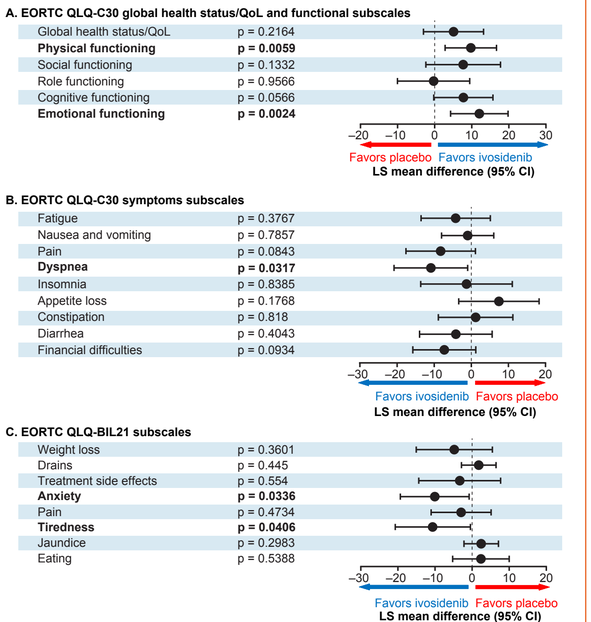
- Mean scores for almost all EORTC QLQ-C30 and QLQ-BIL21 subscales were similar between arms at baseline (**Table 2**)
  - The largest differences between arms were observed in the QLQ-C30 diarrhea and QLQ-BIL21 pain scores, which were each about 9 points higher (ie, more symptoms) in the placebo vs ivosidenib arm
- EORTC QLQ-C30 C2D1 change scores were available for 62 (54.9% of baseline QLQ-C30 completers) ivosidenib patients and 20 (38.5%) placebo patients; QLQ-BIL21 C2D1 change scores were available for 60 (56.1% of baseline QLQ-BIL21 completers) ivosidenib patients and 19 (37.3%) placebo patients

Table 2. Baseline mean (SD) EORTC QLQ-C30 and QLQ-BIL21 scores by treatment arm

Subscale/items	Ivosidenib	Placebo
EORTC QLQ-C30 global health status and functioning (higher scores represent better status/functioning)	**n = 113**	**n = 52**
Global health status/QoL	63.3 (22.8)	58.8 (19.5)
Physical functioning	74.6 (23.3)	74.2 (17.2)
Role functioning	64.7 (32.1)	66.0 (27.2)
Cognitive functioning	81.0 (20.4)	83.0 (18.2)
Emotional functioning	78.5 (20.8)	77.2 (18.7)
Social functioning	70.2 (26.0)	70.8 (28.0)
EORTC QLQ-C30 symptoms (higher scores represent worse symptoms)	**n = 113**	**n = 52**
Fatigue	40.4 (26.7)	44.2 (23.9)
Nausea and vomiting	11.8 (17.2)	16.0 (18.7)
Pain	27.9 (26.3)	33.3 (28.0)
Dyspnea	20.4 (24.6)	22.4 (26.2)
Insomnia	27.7 (28.8)	34.0 (26.8)
Appetite loss	27.1 (28.7)	30.8 (33.6)
Constipation	19.5 (26.6)	19.2 (25.9)
Diarrhea	7.7 (16.1)	16.7 (23.3)
Financial difficulties	22.1 (30.1)	17.3 (27.6)
EORTC QLQ-BIL21 symptoms (higher scores represent worse symptoms)	**n = 107**	**n = 51**
Eating	23.2 (20.7)	25.7 (26.0)
Jaundice	7.6 (13.3)	11.3 (16.0)
Tiredness	47.2 (30.0)	49.0 (28.1)
Anxiety	41.8 (24.6)	46.7 (25.7)
Pain	22.5 (19.7)	31.7 (23.9)
Treatment side effects	26.5 (27.8)	26.1 (30.8)
Drains	1.2 (7.8)	0.7 (4.7)
Weight loss	21.8 (28.6)	20.3 (29.9)

- Based on MMRM least squares (LS) mean changes, significant differences between arms were observed in subscales pertaining to physical and emotional functioning at C2D1 (**Figure 1**)
  - Among the prespecified subscales, only PF was significantly impacted by treatment
    - Placebo patients experienced a significantly larger decline at C2D1 on the EORTC QLQ-C30 PF subscale (LS mean [SE]: –13.1 [3.04]) vs ivosidenib patients (–3.4 [1.81])
  - Similarly, EORTC QLQ-BIL21 tiredness symptoms were significantly increased for placebo (12.2 [4.49]) vs ivosidenib (1.6 [2.58]) by C2D1
  - Significantly worsened emotional functioning for placebo vs ivosidenib was also observed on the EORTC QLQ-C30 emotional functioning (–12.4 [3.41] vs –0.4 [1.00]) and QLQ-BIL21 anxiety symptom (9.4 [4.10] vs –0.7 [2.36]) scores
- Significant differences were not observed in any other subscales or symptom items, except for EORTC QLQ-C30 dyspnea symptoms, which were significantly worsened for placebo vs ivosidenib (**Figure 1B**)

Figure 1. MMRM LS mean differences of ivosidenib versus placebo for EORTC QLQ-C30 and EORTC QLQ-BIL21 change scores between arms at C2D1



Clinically meaningful change in PF

- Anchor-based analyses indicated that a 12- to 13-point decrease in EORTC QLQ-C30 PF score represents clinically meaningful worsening (**Table 3**)
  - Patients who self-reported worsened PF at C2D1 via the PGIC also showed worsening on their mean EORTC QLQ-C30 PF subscale scores (–13.6), compared with patients reporting 'No Change' or improvement on the PGIC who had virtually no mean change in QLQ-C30 PF scores (–1.1)
  - Furthermore, the PGIC 'No Change' group had a median QLQ-C30 PF change score of 0, compared with –13.3 for the PGIC worsened group
- Thus, on average, a clinically meaningful decline in PF at C2D1 was only observed in the placebo arm based on LS mean changes in each arm
  - Furthermore, 21.2% (n = 11) of placebo patients met or exceeded the 13-point threshold of decline from baseline vs 12.4% (n = 14) of ivosidenib patients

Table 3. EORTC QLQ-C30 PF subscale change scores[a] at C2D1 stratified by PGIC for PF

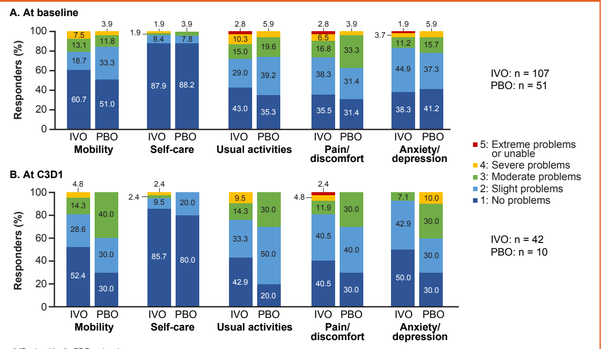
	Worsened PF n = 22	No change in PF n = 25	Improved PF n = 32
Mean (SD)	–13.6 (16.4)	–1.1 (12.1)	0.2 (17.8)
SE of measurement[b]	9.0	6.6	9.7
Median (minimum, maximum)	–13.3 (–53.3, 6.7)	0 (–26.7, 26.7)	0 (–40.0, 40.0)
Missing	1	3	1

[a]Higher score represents better level of functioning
[b]The SE of measurement is the SD of measurement errors. This statistic assesses the precision of the observed scores and is calculated by adjusting the SD by the score's reliability. For this analysis, all reliabilities were set to 0.7

EQ-5D-5L

- Visual analog scale (VAS) changes from baseline were only available for 38 (35.5%) and eight (15.7%) patients receiving ivosidenib and placebo, respectively
  - Mean (SD) VAS change score was –2.8 (8.3) in the placebo arm and 4.6 (14.4) in the ivosidenib arm, where a higher score represents better health status
- The descriptive distribution of responses by EQ-5D-5L dimension supports physical and emotional functioning findings from the EORTC instruments (**Figure 2**)
  - Mobility: the proportion of patients who had 'no problems' or 'slight problems' at baseline was similar between arms (ivosidenib 79.4%; placebo 84.3%), whereas at C3D1, 81.0% of ivosidenib patients had no/slight problems compared with 60.0% of placebo patients
  - Anxiety/depression: the proportion of patients who were 'not anxious or depressed' or 'slightly anxious or depressed' at baseline was also similar between arms (ivosidenib 83.2%; placebo 78.5%), whereas at C3D1, 92.9% of ivosidenib patients were not/slightly anxious or depressed, compared with 60.0% of placebo patients

Figure 2. Distribution of EQ-5D-5L responses by dimension



CONCLUSIONS

- **Subscale scores of the EORTC QLQ-C30 and QLQ-BIL21 demonstrated ivosidenib's preservation of physical and emotional functioning compared with placebo at C2D1, although analyses were limited by small sample sizes and the limited data beyond C2D1**
- **The available results from ClarIDHy suggest HRQoL benefits with ivosidenib early in the treatment of m*IDH1* advanced cholangiocarcinoma**
- **Future studies with robust sample sizes and longer follow-up are needed to confirm the impact of ivosidenib treatment on other HRQoL domains and over time**

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