Effects of Tislelizumab Monotherapy on Health-Related Quality of Life in Patients With Previously Treated Unresectable Hepatocellular Carcinoma

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Background

- Hepatocellular carcinoma (HCC) is a substantial global health challenge that accounts for approximately 75% of all reported cases of liver cancer[1]
  - Patients with unresectable HCC represent a population with great unmet medical needs, with a 5-year overall survival (OS) rate of 18%[2]
- The health-related quality of life (HRQoL) of patients with unresectable HCC is affected by multiple symptoms such as severe fatigue, muscle cramps, pain, sleep dysfunction, and nutritional problems[3]
  - Correlation of these symptoms with shorter OS[3-6] led to increased recognition of the need to assess HRQoL alongside traditional clinical outcomes in HCC trials[7]
- The immune-rich tumor microenvironment makes HCC an appealing target for immune-based therapies,[8] such as PD-1/L1 inhibitors targeting proteins of the PD-1/L1 axis; however, clinical responses observed with these checkpoint inhibitors are often limited due to primary and secondary resistance
- Tislelizumab, a monoclonal antibody against PD-1, was specifically engineered to minimize binding to Fcγ receptor on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential mechanism of resistance to anti-PD-1 therapy
- In a multinational phase 2 study (NCT03419897), single-agent tislelizumab demonstrated durable responses in patients with previously systemically treated unresectable HCC and was generally well tolerated; full clinical study design and methodology has been previously presented[9]
  - Objective response rate was 13.3%, median OS was 13.2 months, and median duration of response was not reached at 11.7 months (95% confidence interval: 8.5, 13.8) of median follow-up
  - Adverse events were consistent with the overall safety profile of tislelizumab observed in previous studies and were generally of low severity
  - The most common treatment-related adverse events were increased aspartate aminotransferase (n=32; 13%) and alanine aminotransferase (n=23; 9%)
- The objective of these analyses was to examine changes from baseline in the HRQoL scores in patients receiving single-agent tislelizumab in this phase 2 study

Methods

- The study population consisted of adult patients (aged ≥18 years) with histologically confirmed HCC that was not amenable to a curative treatment approach and who had received ≥1 line of systematic therapy for unresectable HCC. Patients received tislelizumab (200 mg) administered intravenously every 3 weeks until no further clinical benefit was observed
  - During enrollment, at least 100 patients were enrolled who had one line of prior systemic therapy; at least 100 patients were enrolled who had ≥2 lines of prior therapy
- HRQoL was a secondary endpoint and was assessed using patient-reported outcomes (PROs) via three validated PRO instruments:
  - The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (generic cancer module) and its HCC module, QLQ-HCC18
  - European Quality of Life 5 Dimensions-5 Level (EQ-5D-5L), measuring overall health

HRQoL Assessments and Endpoints

- The PRO measures were collected every two cycles from Cycles 2 through 12 (ie, Cycles 2, 4, 6, 8, 10, 12), and then every four cycles
- The key PRO endpoints included:
  - EORTC QLQ-C30 Global Health Score/Quality of Life (GHS/QoL), physical functioning, and fatigue scales
  - QLQ-HCC18 index score and fatigue scale
  - EQ-5D-5L Visual Analog Scale score (EQ-VAS)
- Higher scores in GHS/QoL, physical functioning, and VAS, and lower scores in fatigue scales and HCC-18 index score indicated better HRQoL outcomes
- Changes from baseline to Cycle 6 and Cycle 12 in the QLQ-C30 GHS/QoL, physical functioning and fatigue scales, and the QLQ-HCC18 index and fatigue scales were assessed
  - Worsening was defined as a ≥5-point decrease in the GHS/QoL, physical functioning, and a ≥5-point increase in the fatigue symptoms and HCC18 index scores at any time point after baseline

Statistical Analyses

- All analyses were conducted using the data cutoff of 27 February 2020
- Least-squares (LS) mean score change from baseline to Cycle 6 and Cycle 12 was assessed using a mixed model for repeated measurement with the change from baseline in PRO key endpoints score as the response variable and baseline PRO score, line of therapy, study visit, and line of therapy by study visit interaction as covariates, based on the missing at random assumption
- Mean change from baseline in the EQ-VAS was analyzed descriptively

Conclusions

- The results of this study show that overall HRQoL was maintained in HCC patients who were treated with tislelizumab
- In this patient population, which typically experiences significant fatigue independent of treatment modality,[10] the patients as a whole experienced stability
  - Patients who had already been on ≥2 prior lines of therapy experienced an improvement in fatigue between Cycles 6 and 12
  - However, differences between cycles should be interpreted with caution given participant dropout from Cycles 6 to 12
- HRQoL results reported in this study corroborate efficacy and safety data suggesting that tislelizumab is a promising treatment option in patients with pretreated HCC

Results

Patient Characteristics

- As of 27 February 2020, 249 patients were treated with tislelizumab, with a median duration of study follow-up of 12.4 months (range: 0.1, 21.4)
- Patient demographics and baseline disease characteristics are presented in Table 1

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Total (N=249)	Prior Therapy: 1 Prior Line (n=138)	Prior Therapy: ≥2 Prior Lines (n=111)
Age, median (range)	**62 (28, 90)**	**63.5 (28, 90)**	**60 (28, 82)**
Sex, n (%)			
Male	217 (87.1)	121 (87.7)	96 (86.5)
ECOG performance status at baseline, n (%)			
0	129 (51.8)	70 (50.7)	59 (53.2)
1	120 (48.2)	68 (49.3)	52 (46.8)
Child-Pugh classification at baseline, n (%)			
A	248 (99.6)	138 (100.0)	110 (99.1)
B	1 (0.4)	0 (0.0)	1 (0.9)
Alpha-fetoprotein at baseline (ng/ml), n (%)			
>400 ng/mL	112 (45.0)[a]	53 (38.4)[a]	59 (53.2)
Hepatitis virus infection, n (%)			
Uninfected	90 (36.1)	46 (33.3)	44 (39.6)
Hepatitis B only	123 (49.4)	71 (51.4)	52 (46.8)
Hepatitis C only	31 (12.4)	20 (14.5)	11 (9.9)
Coinfected	5 (2.0)	1 (0.7)	4 (3.6)

[a]Alpha-fetoprotein at baseline missing in one patient.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Completion Rates for HRQoL Assessments

- The adjusted completion rates, defined as the ratio of patients who completed the questionnaire and the number of patients expected to complete the PROs at each visit, were ≥90% at Cycles 6 and 12 for all three questionnaires (Table 2)

Table 2. Summary of EORTC QLQ-C30/EORTC QLQ-HCC18/EORTC EQ-5D-5L Completion Rate

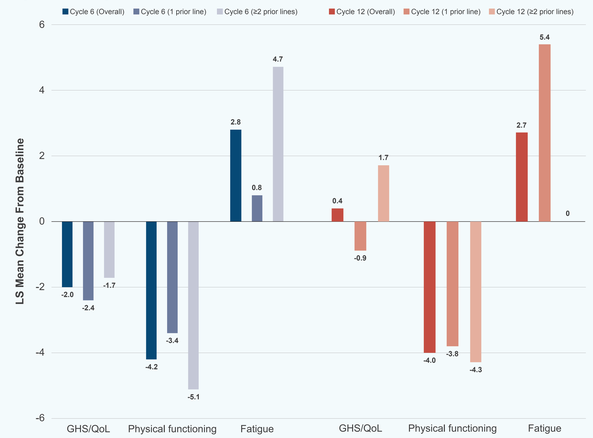
	Total (n=249)	1 Prior Line (n=138)	≥2 Prior Lines (n=111)
Cycle 6			
Patients ongoing at visit, n	134	75	59
Patients who completed questionnaire, n	129	75	54
Adjusted completion rate (%)	96.3	100.0	91.5
Cycle 12			
Patients ongoing at visit, n	57	35	22
Patients who completed questionnaire, n	54	33	21
Adjusted completion rate (%)	94.7	94.3	95.5

Abbreviations: EORTC EQ-5D-5L, European Quality of Life 5 Dimensions-5 Level; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-HCC18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire HCC module; HCC, hepatocellular carcinoma.

EORTC QLQ-C30: Change From Baseline

- LS mean changes from baseline in GHS/QoL remained stable with no observable worsening (Figure 1)
  - Though stable, there was a trend toward worsening at Cycle 6 but not Cycle 12 in patients with ≥2 prior lines of therapy
- For physical functioning, a similar pattern of stability was found except for patients with ≥2 prior lines of therapy at Cycle 6, which just reached the threshold for worsening
- Fatigue also remained relatively stable, with the exception of patients with one prior line of therapy at Cycle 12
  - Patients with ≥2 prior lines of therapy experienced an improvement in fatigue from Cycle 6 to Cycle 12

Figure 1. Changes From Baseline in EORTC QLQ-C30

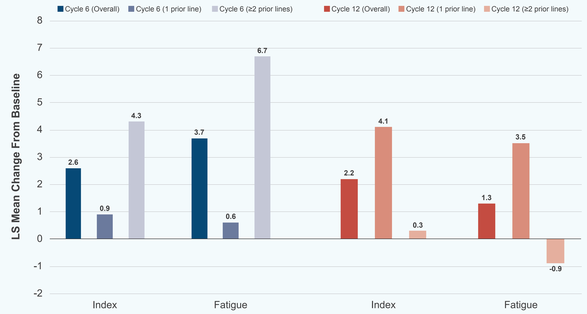


LS mean change from baseline: Scores ≤ −5 for GHS/QoL and physical functioning represent worsening. Scores ≥5 for fatigue represent worsening.
Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; GHS/QoL, global health score/quality of life; LS, least-squares.

EORTC QLQ-HCC18: Change From Baseline

- Mean changes from baseline in the index score remained stable with no observable worsening (Figure 2)
- For the whole sample, fatigue remained relatively stable across cycles
  - Similar to the QLQ-C30 fatigue score, patients with ≥2 prior lines of therapy experienced an improvement in fatigue from Cycles 6 to 12

Figure 2. Changes From Baseline in EORTC QLQ-HCC18

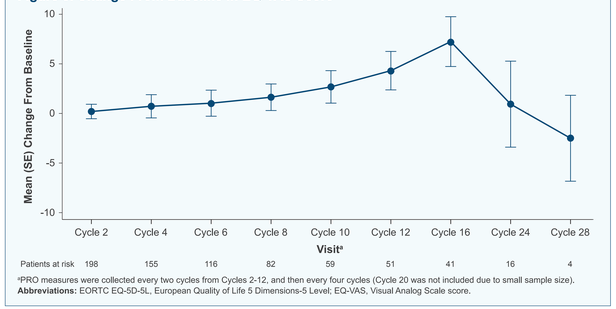


Scores ≥5 for index or fatigue represent worsening.
Abbreviations: EORTC QLQ-HCC18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire HCC module; GHS/QoL, global health score/quality of life; LS, least-squares.

EORTC EQ-5D-5L: Change From Baseline

- The VAS scores showed steady improvements in the key cycles of 6 and 12 (Figure 3)

Figure 3. Change From Baseline in EQ-VAS Score



[a]PRO measures were collected every two cycles from Cycles 2-12, and then every four cycles (Cycle 20 was not included due to small sample size).
Abbreviations: EORTC EQ-5D-5L, European Quality of Life 5 Dimensions-5 Level; EQ-VAS, Visual Analog Scale score.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424. **2.** Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Nat Cancer Inst.* 2017;109(9):djx030. **3.** Gandhi S, Khubchandani S, Iyer R. Quality of life and hepatocellular carcinoma. *J Gastrointest Oncol.* 2014;5(4):296-317. **4.** Bonnetain F, Paoletti X, Collette S, et al. Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials. *Qual Life Res.* 2008;17(6):831-843. **5.** Li L, Mo FK, Chan SL, et al. Prognostic values of EORTC QLQ-C30 and QLQ-HCC18 index-scores in patients with hepatocellular carcinoma - clinical application of health-related quality-of-life data. *BMC Cancer.* 2017;17(1):8. **6.** Diouf M, Filleron T, Barbare JC, et al. The added value of quality of life (QoL) for prognosis of overall survival in patients with palliative hepatocellular carcinoma. *J Hepatol.* 2013;58(3):509-521. **7.** Wible BC, Rilling WS, Drescher P, et al. Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. *J Vasc Interv Radiol.* 2010;21(7):1024-1030. **8.** Pinato DJ, Guerra N, Fessas P, et al. Immune-based therapies for hepatocellular carcinoma. *Oncogene.* 2020;39(18):3620-3637. **9.** Ducreux M, Abou-Alfa GK, Ren Z, et al. Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with previously treated advanced hepatocellular carcinoma. World Congress on Gastrointestinal Cancer; 2021. **10.** Swain MG, Jones DEJ. Fatigue in chronic liver disease: New insights and therapeutic approaches. *Liver Int.* 2019;39(1):6-19.

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