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Adding ipilimumab (IPI) to atezolizumab (ATEZO) plus bevacizumab (BEV) in patients (pts) with unresectable hepatocellular carcinoma (uHCC) in first-line systemic therapy (1L): PRODIGE 81/FFCD 2101 - TRIPLET HCC

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Background

Anti-PD-(L)1 plus anti-VEGF or anti-CTLA-4 are the validated 1L immunotherapies of uHCC based on the results of IMbrave150, HIMALAYA and CheckMate-9DW studies. Here we present the results of the phase-2 of the phase-2/3 TRIPLET-HCC trial comparing ATEZO/BEV/IPI vs ATEZO/BEV (NCT05665348).

Methods

This French, prospective, multicenter, open-label study randomized 1:1 pts to arm A [ATEZO 1200 mg + BEV 15 mg/kg + IPI 1 mg/kg Q3W (4 doses)] or arm B [ATEZO 1200 mg + BEV 15 mg/kg Q3W] for 2 years. Phase-2 was non comparative with a primary endpoint of objective response rate (ORR) ≥ 35% in arm A as assessed per investigator by Recist 1.1 within the first 24 weeks (one-sided α-risk 10%, power 81%, exact binomial method). If positive, the trial will move to phase-3 with overall survival (OS) between arms as primary endpoint. The main secondary endpoints of phase-2 were efficacy and tolerance (NCI CTC v4.0) in both arms.

Results

A total of 226 pts were randomized and analyzed in modified intention to treat (mITT) between arm A (n=113) and B (n=113) from March 2023 to September 2024 by 36 centers. With a power of 84%, ≥ 35 pts with objective response were needed in arm A to declare phase 2 as positive; only 34 pts showed objective response (30.1%, 80% CI: 24.4-36.3). In arm B, ORR was 27.4%, 80% CI: 22.0-33.5. With a median follow-up of 12.0 (Arm A) vs 12.5 months (mo) (Arm B), OS (median, 95% CI) was 22.6 mo (13.2-not estimable [NE]) vs NE (14.7-NE), progression-free survival 8.0 (5.8-10.7) vs 9.6 mo (7.6-10.2), time to progression 10.1 (7.9-12.1) vs 10.1 mo (8.9-20.1), time to response 3.5 (1.6-5.5) vs 3.5 mo (1.9-3.8), duration of response 15.2 mo (10.4-NE) vs NE (7.6-NE), Grade 3-4 treatment-related adverse events (TRAE) occurred in 44 vs 39%, leading to treatment withdrawal in 20 vs 11.5%, and 6 vs 0 pts had grade 5 TRAE.

Conclusions

This phase 2 did not meet its primary endpoint. Efficacy seemed to be similar between both arms whereas tolerance tended to be better in arm B. Finally, adding IPI at low dose (1 mg/kg) did not add benefit to ATEZO/BEV. A longer follow-up is needed to better assess the impact of IPI on OS, especially on the rate of long survivors.

Clinical trial identification

EU number: 2022-501217-31;NCT05665348.

Legal entity responsible for the study

Fédération Francophone de Cancérologie Digestive.

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Disclosure

All authors have declared no conflicts of interest.