Combining cabozantinib, nivolumab and ipilimumab in advanced hepatocellular carcinoma: does benefit outweigh toxicity?

Thiago A. Miranda[1]^, Daniel M. Girardi[1]^, Allan A. L. Pereira[2]^

[1]Department of Medical Oncology, Hospital Sírio-Libanês, Brasília, Brazil; [2]Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL, USA

Correspondence to: Daniel M. Girardi, MD. Department of Medical Oncology, Hospital Sírio-Libanês, SGAS 613/614 L2 Street, Conjunto E Lote 95-Asa Sul, Brasília 70200-730, Brazil. Email: daniel.mgirardi@hsl.org.br.

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Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor and the fourth leading cause of cancer deaths worldwide. Due to its poor prognosis, especially when diagnosed in later stages, HCC is a significant global health problem (1). Despite the lack of options besides using sorafenib as the only first-line treatment subsequent to the SHARP (2) and Asia-Pacific trials (3) for a decade, there have been notable advancements in the systemic management of HCC in recent years.

Soon after the proven non-inferiority of another tyrosine kinase inhibitor (TKI), lenvatinib (4), studies have demonstrated the clinical activity of immune checkpoint inhibitors (ICIs) in unresectable or metastatic disease (5). As our understanding of the molecular biology and actionable targets of cancer cells deepens, it becomes logical to question whether the combination of multiple therapies targeting different cancer hallmarks would yield higher response rates and more durable responses with manageable safety profiles. The results of the Imbrave-150 and HIMALAYA trials have shown that the combination of ICIs with antiangiogenics or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) agents can yield improved outcomes in terms of overall survival (OS) [median OS: 19.2 months; hazard ratio (HR): 0.66; P<0.001, for atezolizumab-bevacizumab versus sorafenib and median OS: 16.43 months; HR: 0.78; P=0.0035 for durvalumab and tremelimumab versus sorafenib] (5,6). Both treatment regimens have become standard first-line therapies for HCC. However, there is still room for further development.

The synergistic effect of combining ICIs with potential immunomodulatory agents, such as TKIs, represents a key point of interest in recent studies evaluating systemic treatments for HCC (7). Cabozantinib, a multi-receptor TKI, is being investigated for its immunomodulatory effects. This agent targets several molecular pathways involved in angiogenesis and the regulation of immune cells. Preclinical data have indicated that inhibiting the vascular endothelial growth factor receptor (VEGFR) and neoangiogenesis can alter the tumor microenvironment (TME), resulting in a decrease in the relative number of immunosuppressive T regulatory (Treg) cells and myeloid-derived suppressor cells and can lead to increased cytotoxic T-cell infiltration (7,8).

Analysis of the TME in patients with localized or locally advanced HCC, treated first with preoperative cabozantinib (40 mg daily for 2 weeks) followed by combined treatment with cabozantinib and nivolumab (240 mg IV every 2 weeks for 8 weeks), revealed potential immunostimulatory effects of this drug. The two-week treatment with isolated cabozantinib resulted in an increase in memory and effector

^ ORCID: Thiago A. Miranda, 0000-0002-0779-3803; Daniel M. Girardi, 0000-0002-7903-8217; Allan A. L. Pereira, 0000-0002-8573-7364.

T cell subtypes within the $CD4^+$ and $CD8^+$ populations compared to baseline samples. Interferon-γ, granzyme B, and Ki-67-positive cell subtypes were included among these populations and are signatures associated with antitumor activity. Cabozantinib treatment also led to reduced levels of CXCL1, a chemokine ligand associated with CXCR2 and mediated by VEGF signaling, linked to immunoresistance and the confinement of T-cells within the TME. A higher density of immune cells, such as lymphocytes, is associated with tumor response when treated with the combination of cabozantinib and nivolumab. On these studies, 5 out of 12 patients (42%) who underwent surgery had major or complete pathological responses. These findings indicate that cabozantinib promotes a favorable environment for an immune response through both systemic and localized effects (9,10).

Further investigation in patients with metastatic urothelial carcinoma who were refractory to ICIs therapy and were treated with a combination of cabozantinib (40 mg daily) and nivolumab (3 mg/kg every 2 weeks) demonstrated an increased number of anti-tumor nonclassical monocytes and a decrease in immunosuppressive monocytic myeloid-derived suppressor cells (M-MDSCs) and Tregs. These drug-induced changes in the immune landscape were associated with improved clinical outcomes for some patients [overall response rate (ORR) of 16%] with durable responses [median duration of response of 33.5 months; 95% confidence interval (CI): 3.7–33.5], suggesting a potential synergistic effect of the combination for some patients that experienced prolonged clinical benefit (11).

The drawback of combining drugs to enhance clinical outcomes is the potential for increased toxicity and the combination of cabozantinib, nivolumab, and ipilimumab is not without its challenges. The phase 1 trial that evaluated these combinations for genitourinary malignances and determined the recommended phase 2 dose showed that grade 3 or higher treatment-related adverse events (TRAEs) were common in the doublet (cabozantinib plus nivolumab) arm (75%) and higher in the triplet (cabozantinib plus nivolumab plus ipilimumab) arm (87%) (12). Dose holdings of cabozantinib due to side effects were also common (83% for doublet and 96% for triplet). Immune-related events requiring ≥40 mg of prednisone or equivalent occurred in 17% of patients in doublet combination and 29% of patients in the triplet combination. Despite this high prevalence of grade 3 and 4 TRAEs, there were no grade 5 TRAEs, and in general, the combinations were manageable and feasible. This trial showed interesting activity results in patients with advanced genitourinary tumors with an ORR of 39.1% for patients receiving doublet treatment and 23.1% for those receiving triplet combination (12). This numerical difference should be interpreted with caution as the populations of these two treatment regimens were different, and patients in the triplet group had, in general, more aggressive tumors (12).

Building on the findings of the phase 1 trial, these combinations were already tested in large phase 3 trials. The Checkmate 9ER evaluated this combination (nivolumab 240 mg once every two weeks and cabozantinib 40 mg once daily) versus sorafenib in patients with advanced renal-cell carcinoma (13). TRAEs occurred in 99.7% of patients, and 75.3% of patients had grade 3 or higher TRAEs. Immune-related adverse events requiring more than 40 mg of prednisone daily or equivalent occurred in 19.1% of patients. Despite the toxicity profile, the combination showed a statistically significant improvement in OS (HR: 0.60; P=0.001), progression-free survival (PFS) (HR: 0.51; P<0.001), and ORR (55.7% versus 27.1%; P<0.001), and is now approved for clinical use (13).

Additionally, the combination of nivolumab, ipilimumab, and cabozantinib was also evaluated in patients with advanced renal-cell carcinoma. The phase 3 COSMIC-313 evaluated the triplet therapy of nivolumab (3 mg per kilogram of body weight) and ipilimumab (1 mg per kilogram) intravenously every 3 weeks for four cycles, followed by nivolumab maintenance therapy (480 mg every 4 weeks) for up to 2 years in addition to cabozantinib at a dose of 40 mg orally once daily. The control arm received the doublet of nivolumab plus ipilimumab (at the same doses of the experimental arm) (14). The triplet combination showed grade 3 or higher TRAEs in 73% of patients, and 45% of patients discontinued treatment due to side effects, which was almost double the control arm—24%. The percentage of patients requiring more than 40 mg of prednisone daily or equivalent was also higher in the triplet arm (58%) than the doublet arm (35%). The median OS (95% CI) was 20.2 months (13.1 to 32.2) in the doublet arm and 22.1 (15.2 to not reached) in the triplet arm. The median PFS (95% CI) was 5.1 months (2.8 to 10.9) with the doublet therapy and 4.3 months (3.6 to 11.9) with the triplet combination. The higher toxicity of the triplet therapy in addition to a modest clinical benefit in PFS when compared to sorafenib (HR: 0.73; P=0.01), observed mainly in patients with intermediate risk, and

response rates (43% for triplet versus 36% for the doublet) caused triplet therapy not to be incorporated into clinical practice (14).

In patients with unresectable or metastatic HCC, Cohort 6 of the CheckMate 040 study examined the immunomodulatory effects of cabozantinib in combination with the programmed death-1 (PD-1) inhibitor nivolumab, with or without the anti-CTLA4 ipilimumab (15). This trial was designed as a multi-cohort, phase I/II open-label study that assessed nivolumab alone and its combination with other agents in patients with advanced HCC who were not suitable for surgery or locoregional therapy. Cohort 6 of the CheckMate 040 trial encompassed patients with a Child-Pugh score of A5 or A6, including those who were treatment-naive or had discontinued sorafenib due to toxicity or disease progression (15). The study enrolled 98 patients, of whom 71 were randomly assigned to the doublet arm (nivolumab 240 mg once every two weeks and cabozantinib 40 mg once daily) or to the triplet arm (nivolumab 3 mg/kg once every two weeks plus ipilimumab 1 mg/kg once every six weeks and cabozantinib 40 mg once daily). Of note, 25% of the study population was composed of Asian patients, 59% were previously exposed to sorafenib, and 50% had hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as the etiology for the HCC. The triplet arm tended to have patients with more severe disease, with slightly higher numbers of Barcelona Clinic Liver Cancer stage C; extrahepatic spread, alpha-fetoprotein ≥400 mg/L, and previously treated patients (15).

After 32 months of median follow-up, ORR was reported at 17% in the doublet arm and 29% in the triplet arm with three complete responses on both arms. Stable disease was achieved in most of the cases, with almost two times the number of partial responses on the triplet arm (26%) compared to the doublet arm (14%). Patients pretreated with sorafenib tended to have better response rates in both arms. The duration of response was 8.3 months on the doublet arm and was not reached on the triplet arm. The sample size was too small to draw any conclusion about the influence of the etiology on clinical outcomes. Similar to other studies evaluating ICIs, patients that showed some kind of response were able to sustain it for long periods of time (16). Of the 10 responders in the triplet arm, 90% maintained the response for ≥6 months, and 70% for ≥18 months (16).

Median PFS was slightly higher in the nivolumab plus cabozatinib population with 5.1 versus 4.3 months for the nivolumab plus ipilimumab and cabozatinib group, whereas the triplet arm had a 2-month higher median OS (20.2 and 22.1 months), considering that the study was not designed to make such a comparison. This demonstrated the potential of the combination. For comparison purposes, the Imbrave-150 trial (5) showed an ORR of 30% with the combination of antiangiogenic therapy plus ICIs, and the HIMALAYA study (6) reported an ORR of 20.1% with the combination of anti-PD-L1 and anti-CTLA4 drugs.

The TRAEs were reported in 89% of the doublet arm patients and 94% of the triplet arm patients, with 11% and 23% of those leading to treatment discontinuation. As expected, safety analysis showed a higher incidence of treatment-related serious adverse events (SAEs) on the triplet arm (11% versus 34%), most of which were hepatic events. The majority of these events involved elevations of serum transaminases, with one case of bilirubin elevation associated with cholangitis. The toxicity profile was comparable to previous trials investigating the same drugs, with the most common being diarrhea, hypertension, and aspartate aminotransferase (AST) increase (15).

Despite those findings, other studies combining TKIs and ICIs in patients with advanced HCC have reported conflicting results. The phase III trial LEAP-002 compared lenvatinib plus pembrolizumab versus lenvatinib alone and failed to significantly improve PFS (HR: 0.867; P=0.0466) and OS (HR: 0.840, P=0.0227) (17). Later, the COSMIC-312 trial (18) compared cabozantinib plus atezolizumab versus sorafenib and showed a higher ORR for the combination therapy (13% versus 6%), but also failed to improve OS (HR: 0.90, P=0.44). This data gives more context to the findings of the CheckMate-040 trial and shows that the combination of TKIs and ICIs in advanced HCC warrants further investigation, as these mixed results can be attributed to various factors, including study design or the choice of treatment arms.

In conclusion, the findings from Cohort 6 of the CheckMate 040 trial underscore the promise of combining TKIs and ICIs, as well as triplet therapies involving anti-CTLA4, anti-PD-L1, and TKIs for the treatment of metastatic HCC. However, the clinical benefits must be balanced against potential toxicity. To answer these and other questions, such as the influence of the etiology of HCC on response or the existence of predictive biomarker, we will require larger and randomized trials comparing the doublet and triplet combinations evaluated in Cohort 6 of CheckMate 040 with the current standard of care.

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Footnote

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