Clinical Trial Protocol

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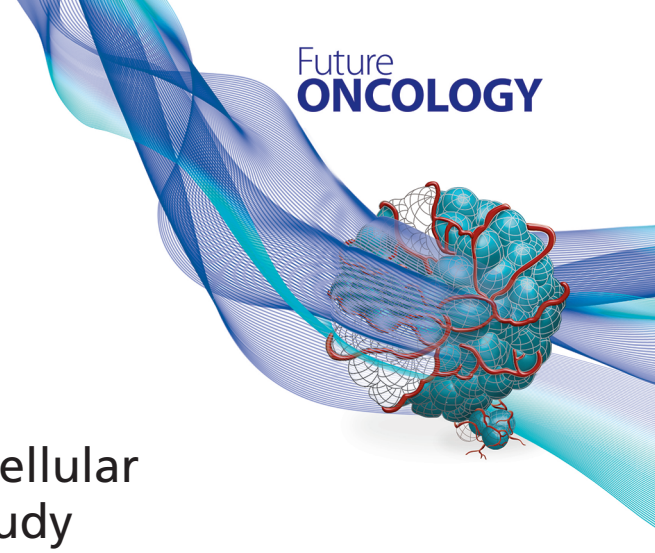

Cabozantinib in combination with atezolizumab versus sorafenib in treatment-naive advanced hepatocellular carcinoma: COSMIC-312 Phase III study design

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Cabozantinib is an oral tyrosine kinase inhibitor that targets VEGFR, MET and the TAM (TYRO3, AXL, MER) family of kinase receptors. In addition to their role in tumor growth and angiogenesis, cabozantinib targets promote an immune-suppressive microenvironment. Cabozantinib is approved as single-agent therapy for patients with advanced hepatocellular carcinoma who received prior sorafenib. Owing to its antitumor and immunomodulatory properties, cabozantinib is being developed in combination with immune checkpoint inhibitors. Early studies of these combinations have shown promising antitumor activity and tolerability in patients with solid tumors. Here, we describe the rationale and design of COSMIC-312, a Phase III study evaluating the safety and efficacy of cabozantinib in combination with atezolizumab (anti–PD-L1 monoclonal antibody) versus sorafenib for treatment-naive patients with advanced hepatocellular carcinoma. Clinical Trial Registration: NCT03755791

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The development of immune checkpoint inhibitors (ICIs) in hepatocellular carcinoma (HCC) and other solid tumors has prompted a growing interest in combination regimens to enhance efficacy with ICIs. HCC is characterized by immune tolerance, with a complex array of immune cells populating the tumor microenvironment that are inactivated by local immune-suppressive signals [1]. While single-agent ICIs have demonstrated improved overall survival (OS) across a number of tumor types in clinical trials, the benefit may be limited to a subset of patients who achieve durable immune responses. In HCC, ICI monotherapy has demonstrated clinically meaningful durable tumor responses in a subset of patients, with the objective response rate (ORR) ranging from 15 to 18% across studies, but has not shown a statistically significant OS benefit in either the first- or second-line setting [2,3]. Efforts have intensified to develop strategies to enhance the immune response and overall efficacy of ICIs, including combination regimens with agents that target pathways involved in tumor progression and possess immunomodulatory properties [4].

Single-agent treatment with tyrosine kinase inhibitors (TKIs) has been an effective strategy for the management of advanced HCC since 2007 with the approval of sorafenib [5], and the recent approvals of the newer TKIs,

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lenvatinib [6], regorafenib [7] and cabozantinib [8], as well as the VEGFR2 monoclonal antibody ramucirumab [9] have further expanded treatment options. Sorafenib and lenvatinib are approved for first-line treatment, while regorafenib, cabozantinib and ramucirumab are second-line options. There is a growing body of preclinical and clinical evidence in support of TKIs as well as bevacizumab, a monoclonal antibody-targeting VEGF, as suitable partners for ICIs in combination treatment strategies for solid tumors [4,10–13]. All of these agents inhibit angiogenesis and have immunomodulatory potential, but their other immunomodulatory targets likely differentiate the antitumor response of these TKIs in combination with ICIs.

Cabozantinib targets multiple receptor kinases involved in angiogenesis, tumor growth and metastasis, including VEGF receptors, MET and the TAM family of receptor kinases (TYRO3, AXL, MER) [14]. In early 2019, cabozantinib was approved for patients with advanced HCC who have received prior treatment with sorafenib based on outcomes from the Phase III CELESTIAL study [8]. In the CELESTIAL study, cabozantinib significantly improved OS, progression-free survival (PFS) and ORR compared with placebo in a population of patients with previously treated advanced HCC. In addition to its antitumor activity, cabozantinib has a unique immunomodulatory profile that has supported clinical studies of combination therapy with ICIs in solid tumors [15–17], including with atezolizumab, an anti-PD-L1 monoclonal antibody [18]. Early analysis of Phase I clinical data have shown promising safety and efficacy with eight of ten patients with RCC and a clear cell histology attaining a response [19]. These and other clinical data have supported the development of a Phase III trial program of cabozantinib in combination with atezolizumab in HCC.

Here we present the rationale and study design of COSMIC-312 (ClinicalTrials.gov: NCT03755791), a Phase III trial of cabozantinib in combination with atezolizumab as a first-line treatment for patients with advanced HCC. We discuss relevant data that informed the design of COSMIC-312 (NCT03755791), including results from pivotal studies of cabozantinib and atezolizumab in HCC as well as preclinical data describing the immunomodulatory activity of cabozantinib.

Rationale for combining cabozantinib with atezolizumab in patients with HCC

The pivotal Phase III CELESTIAL study randomized patients with previously treated advanced HCC to single-agent cabozantinib or placebo. CELESTIAL patients had received prior treatment with sorafenib, could have received up to two prior lines of systemic therapy, had Child–Pugh class A liver function, and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores of 0 or 1 [8]. Cabozantinib improved the primary end point of OS relative to placebo, with a median of 10.2 versus 8.0 months (hazard ratio [HR] 0.76; 95% CI 0.63–0.92; $p = 0.005$), and the secondary end point of PFS, with a median of 5.2 versus 1.9 months (HR: 0.44; 95% CI: 0.36–0.52; $p < 0.001$). The ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was 4% versus <1% ($p = 0.009$), all partial responses. Corresponding to the improved PFS, 64% of patients in the cabozantinib arm achieved disease control (best response of stable disease or better) compared with 33% in the placebo arm. The treatment refractory rate (i.e., progressive disease as best response) was 21 versus 55%. Safety results were consistent with previous studies of cabozantinib. The rate of grade 3 or 4 adverse events (AEs) was 68% in the cabozantinib arm and 36% in the placebo arm.

A number of ICI monotherapies have been developed in HCC, with mixed results. The anti–PD-1 monoclonal antibodies nivolumab and pembrolizumab both received accelerated approvals by the US FDA as second-line monotherapies for patients with advanced HCC based on clinically meaningful activity in single-arm Phase II trials [20,21]. However, in a confirmatory Phase III trial (KEYNOTE-240) in advanced HCC, second-line pembrolizumab versus placebo failed to improve OS (median 13.9 vs 10.6 months; $p = 0.024$ [did not reach prespecified level for significance]) or PFS (median 3.0 vs 2.8 months) despite an ORR of 18.3% for pembrolizumab versus 4.4% for placebo [3]. Similarly, first-line nivolumab in patients with advanced HCC failed to improve OS versus sorafenib (median 16.4 vs 14.7 months; $p = 0.08$) or PFS (3.7 vs 3.8 months) in the Phase III CheckMate 459 trial, despite an ORR of 15% for nivolumab versus 7% for sorafenib, and complete responses of 4% versus 1% [2]. Notably, the rate of progressive disease as best response with the ICI monotherapies was relatively high in these studies – 32.4% for pembrolizumab versus 42.4% for placebo in KEYNOTE-240 and 37% for nivolumab versus 28% for sorafenib in CheckMate 459, suggesting high rates of primary treatment-refractory disease to ICI monotherapy in advanced HCC.

Atezolizumab selectively inhibits the interaction between PD-L1 on tumor cells and PD-1 on cytotoxic T cells in the tumor microenvironment [22], allowing activation of the antitumor immune response that leads to tumor cell destruction [23]. The clinical development of atezolizumab in solid tumors has included combination therapy

with the anti-VEGF monoclonal antibody bevacizumab as well as with cabozantinib [18,24,25]. Recently, the Phase III IMbrave150 study demonstrated improved OS, PFS and ORR with first-line atezolizumab in combination with bevacizumab compared with single-agent sorafenib in patients with advanced HCC [4]. This study enrolled patients with Child–Pugh class A liver function and an ECOG PS score of 0 or 1. Atezolizumab plus bevacizumab improved the coprimary end points of PFS and OS versus sorafenib, with a median PFS of 6.8 versus 4.3 months (HR: 0.59; 95% CI: 0.47–0.76; $p < 0.0001$) and a median OS of not reached versus 13.2 months (HR 0.58; 95% CI 0.42–0.79; $p = 0.0006$). The investigator-assessed, confirmed ORR per RECIST 1.1 was 27 versus 12%, with 6 versus 0% achieving complete response. The treatment-refractory rate was relatively low in both treatment arms (20 vs 25%).

There are a number of proposed mechanisms for primary resistance to ICI monotherapy that highlight the complex interplay between immune tolerance and response within the tumor microenvironment [26]. Overexpression of immunosuppressive factors by tumor and non-tumor cells may maintain immune tolerance via 'alternative' pathways outside of current ICI targets. Immunosuppressive cytokines have been shown to be involved in the activation, migration and/or recruitment of T regulatory cells, tumor-associated macrophages and myeloid-derived suppressor cells (MDSCs) [27]. Therefore, inhibition of these alternative immunosuppressive pathways to promote an immune-permissive tumor microenvironment may enhance response to ICI treatment, leading to ongoing studies of ICI in combination with agents targeting these pathways [28].

Circulating VEGF and VEGF within the tumor microenvironment also have immunosuppressive effects [26,29]. Tumor cells release VEGF, which can increase the number and function of immunosuppressive cells, including T regulatory cells, MDSCs and tumor-associated macrophages. Inhibition of the VEGF pathway decreases the activity of T regulatory cells and MDSCs and promotes maturation of dendritic cells into antigen-promoting cells (APCs) and lymphocyte infiltration [30,31].

In addition to the VEGF pathway, preclinical studies have described the immunomodulatory activity of other cabozantinib targets, including MET and the TAM family of receptor kinases (Figure 1) [26,32,33]. Inhibition of these targets has been shown to promote an immune-permissive tumor microenvironment in preclinical models. Cancer-associated fibroblasts release HGF, which binds to MET receptors on tumor cells driving PD-L1 expression, and HGF in the tumor microenvironment promotes mobilization of immunosuppressive neutrophils [34–36]. Inhibition of MET downregulates expression of PD-L1 on tumor cells [34] and blocks the recruitment of immunosuppressive neutrophils following checkpoint blockade [35]. The TAM receptors and the ligand GAS6 have multiple immunosuppressive mechanisms. Tumor-associated macrophages release GAS6, which binds to AXL and TYRO3 receptors on APCs, suppressing APC maturation and thereby decreasing recruitment of tumor-infiltrating cytotoxic T cells [37–39]. Binding of GAS6 to MER receptors on macrophages promotes phenotype transition from M1 (immune-stimulating) to M2 (immune suppression) [40], and AXL activation on tumor cells can suppress MHC class I expression [37]. Targeting the TAM family of kinases can increase the number of circulating and tumor-infiltrating cytotoxic T cells and reprogram the phenotype of tumor-associated macrophages from M2 to M1 [32,39].

Preclinical studies have demonstrated the ability of cabozantinib to modulate both adaptive and innate immune cells and to exhibit synergistic activity when used in combination with ICIs. Cabozantinib has been shown to increase infiltration of cytotoxic T cells and decrease the number of MDSCs and tumor-associated macrophages [33]. In a chimeric murine model of metastatic castrate-resistant prostate cancer, an ICI regimen of anti-CTLA4 and anti-PD-1 could not generate an effective immune response. The addition of cabozantinib to the regimen elicited a robust synergistic antitumor response [41]. Cabozantinib was shown to decrease the number and activity of MDSCs and their suppression of cytotoxic T cells, and cabozantinib in combination with the ICI regimen reduced key cytokines involved in the recruitment and activity of MDSCs, including CCL5, CCL12, CD40 and HGF.

In clinical studies, single-agent cabozantinib leads to an increase in the number of circulating cytotoxic T cells and induces activation of the immune system in patients with triple-negative breast cancer [42]. In a study of patients with metastatic renal cell carcinoma (RCC), cabozantinib increased the number of activated cytotoxic T cells and produced a shift from an immunosuppressive to an antitumor phenotype in myeloid cells, with a priming of circulating cytotoxic natural killer and T cells [43]. Furthermore, cabozantinib decreased the number of regulatory T cells and increased the expression of PD-1 in patients with bladder cancer [16].

Clinical studies have evaluated cabozantinib in combination with ICIs in a number of solid tumors [12,17,18]. A Phase I trial investigated the combination of cabozantinib and nivolumab with or without ipilimumab in metastatic urothelial carcinoma and other genitourinary malignancies [12]. This trial demonstrated promising antitumor activity

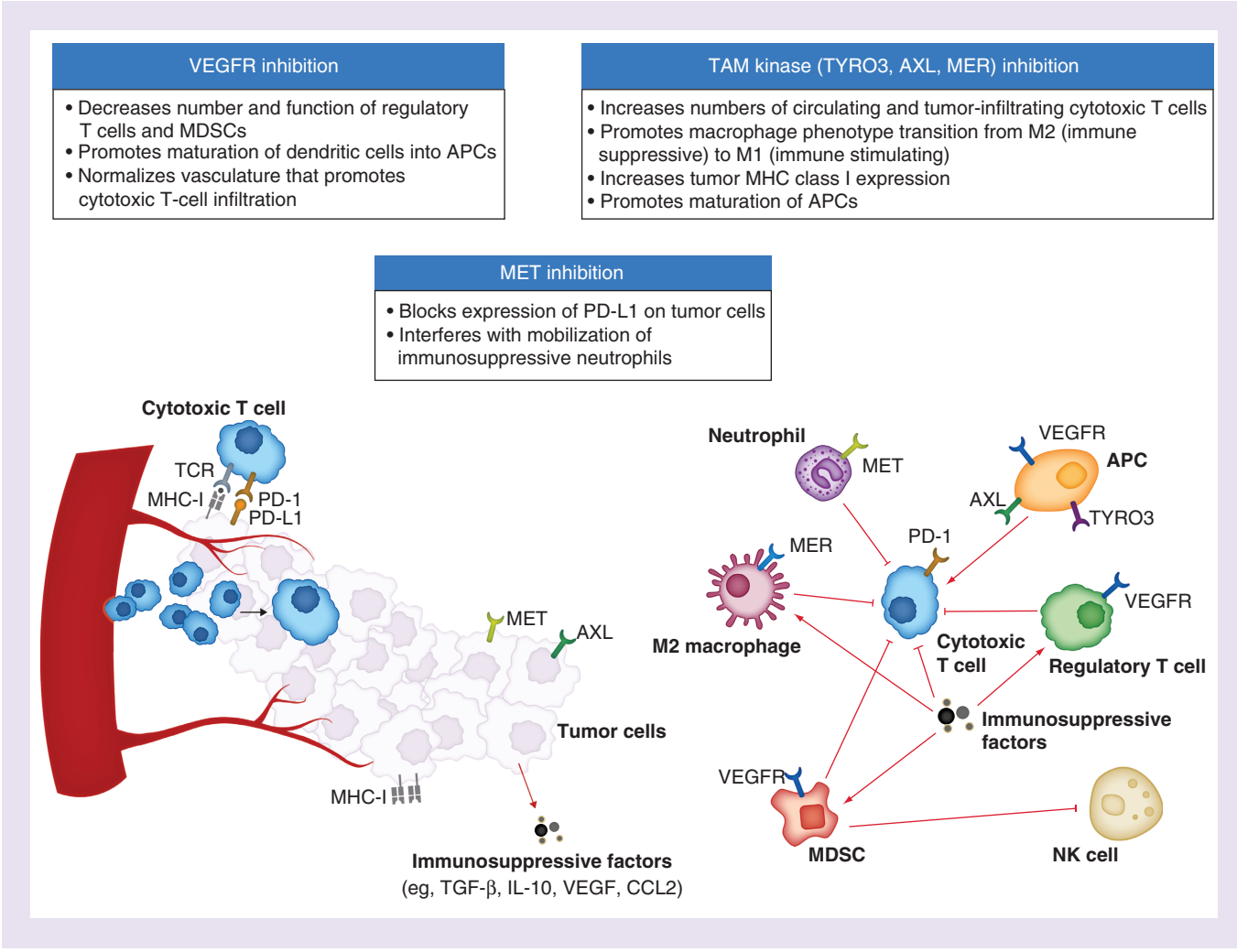

Figure 1. Cabozantinib targets pathways associated with tumor immune suppression.
APC: Antigen-presenting cell; MDSC: Myeloid-derived suppressor cells; NK cell: Natural killer cell; TCR: T-cell receptor.

with an ORR of 36% and a median duration of response of 24.1 months in 64 patients who had disease progression on at least one standard therapy. The Phase I/II CheckMate 040 study evaluated the combination of nivolumab and cabozantinib with or without ipilimumab in a small cohort of patients with advanced HCC [17]. The triplet combination (nivolumab, cabozantinib and ipilimumab) compared with the doublet combination (nivolumab and cabozantinib) resulted in higher ORR by investigator assessment (29 vs 19%), and longer PFS by investigator assessment (6.8 vs 5.4 months) and OS (not reached vs 21.5 months). Grade 3–4 AEs were more frequent in the triplet combination (71 vs 47%).

The ongoing Phase I COSMIC-021 study is assessing cabozantinib in combination with atezolizumab in multiple solid tumor types, including HCC, RCC, urothelial carcinoma and castration-resistant prostate cancer [18,19]. The dose-escalation stage of COSMIC-021 established the recommended dose of the combination (cabozantinib 40 mg daily plus atezolizumab 1200 mg every 3 weeks) and reported encouraging activity in patients with RCC, with eight of ten patients with clear cell histology achieving a response (one complete and seven partial responses). Most AEs were grade 1/2, including immune-related AEs, with no grade 4/5 AEs at the time of the analysis [19].

Taken together, preclinical and clinical data provide a strong rationale for cabozantinib in combination with ICI, including atezolizumab, and support the development of a definitive Phase III study to assess the efficacy and safety of the combination as a first-line treatment in patients with advanced HCC.

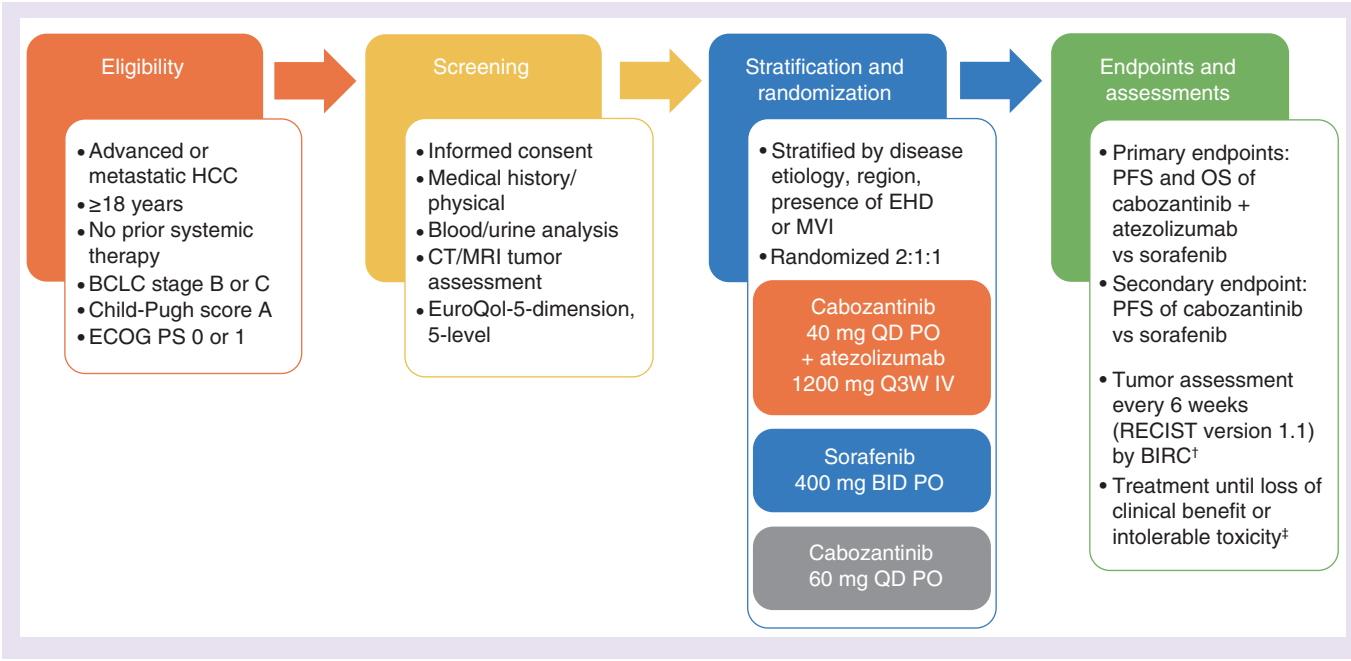

Figure 2. COSMIC-312 study design.
†Every 6 weeks for the first 48 weeks, then every 12 weeks thereafter.
‡Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator.
Clinical TrialRegistration: NCT03755791 (ClinicalTrials.gov).
BCLC: Barcelona Clinic Liver Cancer; BID: Twice daily; BIRC: Blinded independent radiology committee; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; EHD: Extrahepatic disease; HCC: Hepatocellular carcinoma; IV: Intravenous; MRI: Magnetic resonance imaging; MVI: Macrovascular invasion; OS: Overall survival; PFS: Progression-free survival; PO: Oral; PS: Performance Status; Q3W: Once every 3 weeks; QD: Once daily; RECIST: Response Evaluation Criteria in Solid Tumors.

COSMIC-312 study design

COSMIC-312 (NCT03755791) is a global, randomized, open-label Phase III trial evaluating the efficacy and safety of first-line therapy with cabozantinib in combination with atezolizumab versus sorafenib in patients with advanced HCC. COSMIC-312 (NCT03755791) includes a single-agent cabozantinib arm for comparison with single-agent sorafenib. The single-agent cabozantinib arm was included to better characterize the contribution of cabozantinib to the combination arm, given the lack of clinical data for single-agent cabozantinib as first-line therapy in HCC.

Approximately 740 eligible patients with advanced HCC are randomized in a 2:1:1 ratio to receive cabozantinib plus atezolizumab (~370 patients), sorafenib (~185 patients) or single-agent cabozantinib (~185 patients) (Figure 2). Randomization is stratified by disease etiology (hepatitis B virus [HBV] with or without hepatitis C virus [HCV], HCV [without HBV], other), region (Asia, other) and presence of extrahepatic disease and/or macrovascular invasion (yes, no).

For the combination, cabozantinib is administered orally at a dose of 40 mg once daily, and atezolizumab is administered intravenously at a dose of 1200 mg every 3 weeks. Single-agent sorafenib and cabozantinib are administered orally at their approved monotherapy doses – sorafenib 400 mg twice daily, and cabozantinib 60 mg once daily. Patients receive study treatment as long as they continue to experience clinical benefit or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment. Radiographic assessment by the investigator is used for treatment decisions. In the combination arm, dose reductions of cabozantinib are allowed to 20 mg daily and 20 mg every other day; dose reductions of atezolizumab are not allowed, but dose delays are permitted. Reescalation to the previous dose of cabozantinib is allowed provided that the AE has resolved to grade 1 (or baseline) and is deemed tolerable and easily managed. For patients who tolerate cabozantinib at 40 mg/day for 4 weeks, the dose may be increased to 60 mg/day upon sponsor approval. Patients on the combination arm are allowed to discontinue one component of the study treatment if clinically indicated. In the single-agent cabozantinib arm, dose reductions are allowed to 40 and 20 mg daily. Patients on the sorafenib arm are allowed dose interruptions

Table 1. COSMIC-312 study end points.

Primary efficacy end points	**Key additional end points**
Cabozantinib + atezolizumab vs sorafenib	ORR, TTP and DOR per RECIST version 1.1 by BIRC and by the investigator
PFS per RECIST version 1.1 by BIRC	Response per modified RECIST
OS	Safety, including evaluation of AEs and immune-related AEs
Secondary efficacy end point	Pharmacokinetics of cabozantinib
Cabozantinib vs sorafenib	Immunogenicity of atezolizumab
PFS per RECIST version 1.1 by BIRC	Biomarker analyses (e.g., AFP) and correlations with clinical outcomes
	Health-related quality of life and healthcare resource utilization

Clinical TrialRegistration: NCT03755791 (ClinicalTrials.gov).
AE: Adverse event; BIRC: Blinded independent radiology committee; DOR: Duration of response; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; TTP: Time to progression.

Table 2. Key inclusion/exclusion criteria.

Key inclusion criteria
Histological or cytological diagnosis of HCC or clinical diagnosis of HCC in cirrhotic patients by CT or MRI per AASLD or EASL guidelines[†]
Measurable disease per RECIST version 1.1 per the investigator
Disease that is not amenable to curative treatment or locoregional therapy
Child–Pugh class A liver function
BCLC Stage B (unsuitable for locoregional therapy) or C
Antiviral therapy if active HBV infection (HB surface antigen positive); HBV DNA <500 IU/ml
ECOG performance status of 0 or 1
Adequate organ and marrow function
Key exclusion criteria
Known fibrolamellar carcinoma, sarcomatoid HCC, or mixed hepatocellular cholangiocarcinoma
Prior systemic anticancer therapy for advanced HCC
Documented hepatic encephalopathy within 6 months before randomization
Clinically meaningful ascites within 6 months before randomization
Any local anticancer therapy including surgery, RFA or TACE within 28 days prior to randomization
Known brain metastases unless adequately treated and stable for at least 8 weeks prior to randomization
Uncontrolled, significant illnesses including active or history of autoimmune disease or immune deficiency
Patients with active, uncontrolled HCV are eligible if managed per local institutional practice; antiviral treatment allowed with sponsor approval
Previous solid organ transplant including liver or allogeneic stem cell transplant

[†]Sites must be accredited for imaging-based diagnosis of HCC. Patients who do not meet the AASLD or EASL guidelines for imaging diagnosis of HCC or who do not have cirrhosis must have histological or cytological diagnosis of HCC.
AASLD: American Association for the Study of Liver Diseases; BCLC: Barcelona Clinic Liver Cancer; CT: Computed tomography; EASL: European Association for the Study of the Liver; ECOG: Eastern Cooperative Oncology Group; HB: Hepatitis B; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; MRI: Magnetic resonance imaging; RECIST: Response Evaluation Criteria in Solid Tumors; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization.

and reductions as per local prescribing information. The study may transition to a crossover phase if the analysis of OS shows statistically significant and clinically meaningful evidence of improvement.

End points

The primary efficacy end points are PFS per RECIST version 1.1 [44] by blinded independent radiology committee (BIRC) and OS for cabozantinib plus atezolizumab versus sorafenib (Table 1). PFS is defined as time from randomization to the earlier of either progressive disease or death from any cause, and OS is the time from randomization to death due to any cause. The secondary efficacy end point is PFS per RECIST version 1.1 by BIRC for single-agent cabozantinib versus sorafenib.

Additional efficacy end points include the ORR, time to progression and duration of response per RECIST version 1.1 by BIRC and the investigator, and evaluation of radiographic response per modified RECIST [45]. Safety end points include AEs, immune-related AEs and other AEs of special interest. Other end points include the pharmacokinetics (PK) of cabozantinib, the immunogenicity of atezolizumab, biomarker analyses (e.g., α-fetoprotein) and correlations with clinical outcome, health-related quality of life (HRQoL) and healthcare resource utilization.

Eligibility criteria

Key inclusion/exclusion criteria are highlighted in Table 2. Patients with locally advanced or metastatic HCC are eligible for enrollment provided they are aged ≥18 years, have measurable disease (per RECIST v1.1 as determined by the investigator) that is Barcelona Clinic Liver Cancer Stage B (unsuitable for locoregional therapy) or C, have Child–Pugh class A liver function, and an ECOG PS of 0 or 1. Key exclusion criteria include

prior systemic anticancer therapy for advanced HCC, certain histopathological subtypes (fibrolamellar carcinoma, sarcomatoid HCC or mixed hepatocellular cholangiocarcinoma), active or a history of autoimmune disease or immune deficiency, and previous solid organ or allogeneic stem cell transplant. Patients with active HBV infection are required to receive antiviral therapy per local standard of care, and the patient must have HBV DNA <500 IU/ml. Patients with active, uncontrolled HCV are eligible provided liver function meets eligibility criteria and the disease is managed per local institutional practice.

Assessments

Patients are monitored for radiographic response and progression per RECIST version 1.1. Computed tomography (CT) of the chest/abdomen/pelvis or CT of the chest and magnetic resonance imaging (MRI) of the abdomen/pelvis are performed in all patients at screening, every 6 weeks through Week 49 and every 12 weeks thereafter. Any other known or suspected sites of disease, including in the brain or bone, are followed by CT or MRI at the same schedule.

Patients are followed for survival until death, withdrawal of consent for noninterventional study assessments, or sponsor decision to no longer collect survival data.

Safety is assessed every 3 weeks during study treatment and then at 30 and 100 days after treatment discontinuation. Routine safety evaluations include physical examination, vital signs, PS, electrocardiogram, hematology, serum chemistries, coagulation tests, urine tests and thyroid function tests. AE seriousness, severity grade, relationship to study treatment and relationship to immune effects are assessed by the investigator. Severity grade is defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.

Blood samples for PK and plasma, serum and cellular biomarkers are collected at screening, before first dose of study treatment, every 3 weeks for the first 12 weeks, and at the post-treatment follow-up visits. Blood samples for immunogenicity are collected before the first dose, after 12 and 24 weeks, and at post-treatment follow-up visits. Blood samples from all patients in the combination and the single-agent cabozantinib arms are used for cabozantinib PK assessment; samples from the combination arm are used for immunogenicity assessment and atezolizumab PK assessment. If available, tumor tissue (archival or recently biopsied) is collected at screening. An optional tumor biopsy may be collected approximately 6 weeks after the first dose of study treatment. Exploratory analyses may include: expression of PD-L1, MET, and other relevant biomarkers in tumor samples; immune cell infiltration; mutational load assessment; circulating immune cells; blood biomarkers (cytokines/chemokines); and cell or plasma pharmacogenomics (circulating tumor DNA).

HRQoL assessments are performed using the EuroQol Health questionnaire instrument EuroQol-5-Dimension, 5-Level [46] at baseline and every 6 weeks until the date of the last tumor assessment. Healthcare resource utilization parameters will be collected from randomization through the follow-up visits.

Statistical design

Analysis populations include the intention-to-treat (ITT) population that consists of all patients randomized to any of the three study treatment arms, the PFS ITT (PITT) population that consists of approximately the first 372 patients randomized to the combination and sorafenib arms evaluated for the PFS primary analysis, and the safety population that consists of all patients who receive any amount of study treatment.

The study is designed to provide adequate power for both primary end points and the secondary end point with a study population of approximately 740 patients. Two interim analyses of OS are planned at approximately 33 and 66% information fractions and will include all patients in the ITT population available at the time of each analysis. PFS and OS will be summarized by the Kaplan–Meier method. Inferential comparisons between treatment arms will use the stratified log–rank test. The HR will be estimated using a stratified Cox proportional hazards model, using the randomization stratification factors.

Study sites

Enrollment is planned at approximately 250 sites in 34 countries located in North and South America, Europe and the Asia-Pacific region. The first patient was enrolled in December 2018, and accrual is ongoing.

Summary & conclusions

Despite a number of advances in recent years, treatment of advanced HCC remains a clinical challenge. Cabozantinib is a standard-of-care treatment option for patients with advanced HCC previously treated with sorafenib. In addition

to its antitumor activity, cabozantinib has a unique immunomodulatory profile that supported its development in combination with ICIs. In patients with advanced HCC, ICI monotherapy has demonstrated clinically meaningful activity, but the recent negative results from Phase III studies of ICI monotherapy and the positive results of atezolizumab in combination with bevacizumab in IMbrave150 support a strategy of combination regimens to enhance the immune response. In addition to cabozantinib with atezolizumab discussed here, a variety of first-line ICI combination regimens are being assessed in Phase III trials for patients with advanced HCC, including durvalumab and tremelimumab in the HIMALAYA trial [47], and lenvatinib plus pembrolizumab in LEAP-002 [48]. As these studies mature, patients and clinicians await a potential shift in the therapeutic landscape of HCC.

Preclinical and clinical evidence provides a strong scientific rationale for the combination of cabozantinib with atezolizumab and suggests potential for a synergistic effect on tumor response. The Phase III COSMIC-312 (NCT03755791) study will assess the efficacy and safety of cabozantinib plus atezolizumab versus sorafenib for first-line treatment of patients with advanced HCC. Assessment of biomarkers and HRQoL outcomes will provide additional insights into the effects of the combination of cabozantinib and atezolizumab.

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Financial & competing interests disclosure/conflicts of interest

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Executive summary

Background

- Cabozantinib, a tyrosine kinase inhibitor whose targets include VEGFR, MET and the TAM (TYRO3, AXL, MER) family of kinase receptors, is approved as a second-line treatment for patients with advanced hepatocellular carcinoma (HCC).
- Cabozantinib has a unique immunomodulatory profile that has supported its development in combination with immune checkpoint inhibitors (ICIs).
- COSMIC-312 is a Phase III study of cabozantinib in combination with atezolizumab, an anti–PD-L1 antibody, as a first-line treatment for patients with advanced HCC.

Rationale for combining cabozantinib & atezolizumab in patients with HCC

- ICI monotherapies have had limited success in advanced HCC; however, the combination of the ICI atezolizumab with a VEGF inhibitor recently demonstrated positive results for the first-line treatment of advanced HCC in a pivotal Phase III trial.
- Cabozantinib targets pathways that have been shown to promote an immune-permissive environment through a number of mechanisms, including inhibition of the recruitment of neutrophils, decreased PD-L1 expression, promotion of an immune-stimulating macrophage phenotype, and increasing the number of cytotoxic T cells.
- Results from early clinical studies of cabozantinib in combination with atezolizumab for patients with solid tumors have demonstrated encouraging clinical activity with a manageable safety profile.

COSMIC-312 trial

- The Phase III COSMIC-312 trial (NCT03755791) will investigate the efficacy and safety of cabozantinib in combination with atezolizumab versus sorafenib in patients with advanced HCC who have not received previous systemic anticancer therapy. In addition, the trial will evaluate the activity of single-agent cabozantinib compared with sorafenib to characterize the contribution of cabozantinib to combination therapy.
- Patients will be randomized in a 2:1:1 ratio to receive the combination of cabozantinib and atezolizumab, sorafenib, or single-agent cabozantinib.

End points

- The primary efficacy end points of the study are progression-free survival (PFS) and overall survival (OS) for the combination of cabozantinib plus atezolizumab versus sorafenib.
- The secondary efficacy end point is PFS for single-agent cabozantinib versus sorafenib.
- Other efficacy end points include objective response rate (ORR), time to progression, duration of response, and radiographic response. Safety end points include adverse events (AEs) and immune-related AEs. Other end points include pharmacokinetics, immunogenicity, biomarker analyses and health-related quality of life.

Eligibility criteria

- Eligible patients have treatment-naive Barcelona Clinic Liver Cancer Stage B or C HCC, have Child–Pugh class A liver function, and an Eastern Cooperative Oncology Group Performance Status of 0 or 1.
- Exclusion criteria include certain histopathological subtypes, known brain metastasis, and previous solid organ transplant.

Assessments

- Patients will be monitored for radiographic response and progression per Response Evaluation Criteria in Solid Tumors version 1.1 at baseline and every 6 weeks.
- Safety will be evaluated every 3 weeks. AE seriousness, severity grade, relationship to study treatment and relationship to immune effects will be assessed by the investigator.
- Blood samples for pharmacokinetics, immunogenicity and plasma, serum and cellular biomarkers will be collected at screening, before the first dose of study treatment and every 3 weeks.

Statistics

- Approximately 740 patients are expected to enroll. The study is designed to provide adequate power for both primary end points and the secondary end point.
- The intention-to-treat population will include all randomized patients and will be used for analysis of the primary OS end point to compare the combination arm with the sorafenib arm.
- The PFS intention-to-treat population will consist of the first 372 patients randomized to the combination and sorafenib arms. The PFS intention-to-treat population will be used for analysis of the primary PFS end point.

Conclusion

- COSMIC-312 will provide efficacy and safety data on the combination of cabozantinib plus atezolizumab versus sorafenib, as well as PFS results for single-agent cabozantinib versus sorafenib.
- Results of this trial will define the role of cabozantinib as a partner with atezolizumab as a first-line treatment of patients with advanced HCC.

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