Clinical Trial Protocol

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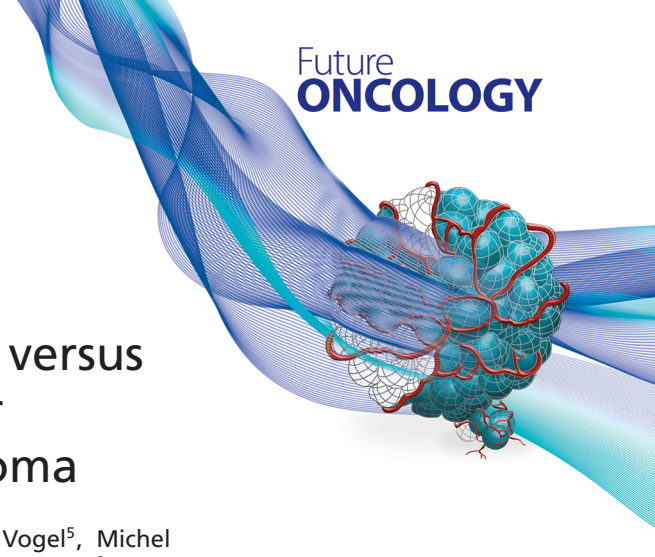

RATIONALE 301 study: tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma

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Advanced, unresectable hepatocellular carcinoma (HCC) has a poor prognosis with median life expectancy of approximately 1 year. Overexpression of PD-L1 in tumor cells and PD-1 on tumor-infiltrating T cells has been associated with poorer prognosis, more advanced disease and higher recurrence rates in HCC. Monoclonal antibodies against PD-1 have demonstrated antitumor activity in patients with solid tumors, including HCC. Tislelizumab, an investigational, humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1, has demonstrated preliminary antitumor activity in HCC. Here we describe a head-to-head Phase III study comparing the efficacy, safety and tolerability of tislelizumab with sorafenib as first-line treatment in unresectable HCC.

First draft submitted: 20 February 2019; Accepted for publication: 19 March 2019; Published online: 10 April 2019

Keywords: HCC • hepatocellular carcinoma • PD-1 • tislelizumab

Introduction to the trial

Here we describe an ongoing global, Phase III study of tislelizumab (BGB-A317) versus sorafenib as first-line treatment of unresectable hepatocellular carcinoma (HCC), assessing the safety and tolerability profile of tislelizumab as well as overall survival (OS; the primary end point), objective response rate (ORR), progression-free survival (PFS), duration of response (DoR) and time to progression (TTP) [1], all by a blinded independent review committee (BIRC) and investigator using RECIST v1.1 (ClinicalTrials.gov identifier NCT03412773).

Background & rationale

Current treatment for HCC

HCC is the sixth most common cancer worldwide, accounting for 782,000 new cases in 2012 and is a leading cause of cancer-related mortality [2]. Despite improvements in screening, surveillance rules and imaging, more than two-thirds of patients with HCC present with advanced disease at diagnosis [3], which makes them ineligible for curative treatments including resection, liver transplantation and ablation, or transcatheter arterial chemoembolization [4]. Patients with unresectable HCC have a poor prognosis, especially if the disease is complicated with cirrhosis [4]. Currently, multitargeted tyrosine kinase inhibitors (TKIs), such as sorafenib or lenvatinib, are approved first-line treatment for unresectable HCC [5,6]. Despite the recent approval of lenvatinib, only sorafenib is universally

Table 1. Results from clinical trials in advanced hepatocellular carcinoma.

Drug	Median OS	Median PFS	Median TTP	Responses	DoR	DCR	Ref.
Sorafenib	10.7 months		5.5 months†				SHARP [9]
Lenvatinib	13.6 months	7.4 months	8.9 months	ORR = 24.1%			REFLECT [11]
Regorafenib	10.6 months	3.1 months	3.2 months	ORR = 10.6%		65.2%	RESORCE [12]
Cabozantinib	10.2 months	5.2 months		ORR = 4%			CELESTIAL [13]
Ramucirumab	9.2 months (REACH) 8.5 months (baseline AFP ≥400 ng/ml, REACH-2)	2.8 months (baseline AFP ≥400 ng/ml, REACH-2)					REACH [14] REACH-2 [15]
Brivanib	9.5 months 9.4 months		4.2 months	ORR = 10%			BRISK-FL [16] BRISK-PS [17]
Sunitinib				ORR = 2.7%			[18]
Linifanib	9.1 months		5.4 months	Best response rate = 13.0%			[19]
Pembrolizumab				ORR = 17%			KEYNOTE-224 [20]
Nivolumab				ORR = 14.3%	17 months		CHECKMATE 040 [21,22]
Tislelizumab				ORR = 12%	15.7 months	51%	BGB-A317-001 [23]

†Radiological progression.
AFP: Alpha-Fetoprotein; DCR: Disease control rate; DoR: Duration of response; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression.

accessible from a reimbursement perspective and is considered the standard of care [7]. Regorafenib (approved for second-line treatment of HCC), cabozantinib and ramucirumab are positioned for second and third-line treatment [8]. To date, Phase III trials of other targeted therapies, such as brivanib, sunitinib and linifanib, have been disappointing, failing to provide survival benefit and/or causing substantial tolerability issues [4].

Sorafenib inhibits tumor angiogenesis and tumor cell proliferation by blocking multiple kinases involved in the VEGF, PDGF, c-Kit, B-Raf and p38 signaling pathways [4]. Its efficacy in unresectable HCC has been shown in two pivotal studies: the SHARP trial, conducted in Europe, North America, South America, Australia [9] and the Asia-Pacific trial [10]. In the SHARP study, 602 patients with unresectable HCC, well-preserved liver function and no history of prior systemic therapy, were randomized to receive oral sorafenib 400 mg twice-daily or placebo [9]. As described in Table 1, sorafenib significantly improved median OS (10.7 vs 7.9 months; hazard ratio [HR]: 0.69; 95% CI: 0.55–0.87; $p < 0.001$) and median time to radiographic progression (5.5 vs 2.8 months; HR: 0.58; 95% CI: 0.45–0.74; $p < 0.001$) compared with placebo. A second trial of similar design was conducted in a comparable group of 271 patients with unresectable HCC from China, Taiwan and South Korea [10]. Median OS was significantly improved with sorafenib compared with placebo (6.5 vs 4.2 months; HR: 0.68; 95% CI: 0.50–0.93; $p = 0.014$), as was median TTP (2.8 vs 1.4 months; HR: 0.57; 95% CI: 0.42−0.79; $p = 0.0005$).

Lenvatinib is a multikinase inhibitor targeting VEGFR, FGFR, PDGFR, RET and KIT pathways that was recently approved in the USA, European Union, Japan and China as a first-line treatment for unresectable HCC [24,25]. In the pivotal Phase III study, REFLECT, 954 patients with unresectable HCC were randomized 1:1 to treatment with sorafenib or lenvatinib. Lenvatinib was noninferior to sorafenib in OS (Table 1), with an HR of 0.92 (95% CI: 0.79–1.06) [26]. The median OS was 13.6 months (95% CI: 12.1–14.9) for lenvatinib-treated patients compared with 12.3 months (95% CI: 10.4–13.9) for sorafenib recipients.

Despite these results, the life expectancy of patients using tyrosine kinase inhibitor remains limited. Furthermore, the adverse event (AE) profile of sorafenib makes it difficult for some patients to tolerate [5], and as a result, they often require dose reductions or treatment interruptions. In an observational study in Italy, 54% of sorafenib-treated patients required dose reduction, primarily because of fatigue, hand-foot skin reaction and diarrhea; among patients who permanently discontinued, 40% were due to AEs, mainly fatigue [27]. The safety profile of lenvatinib partially overlaps with that of sorafenib; the most commonly reported AEs include: hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%) and fatigue (30%) [26].

PD-1 inhibition as a strategy for treating unresectable HCC

The PD-1/PD-L1 axis plays a central role in suppressing antitumor immunity [28]. Cancer cells can take advantage of this suppression by interfering with interactions between PD-L1 and PD-1 through numerous pathways.

Several studies have shown that PD-L1 is overexpressed in tumor cells in a variety of cancers, which results in ligation of PD-L1 to PD-1 on any antigen-specific T cells that infiltrate the tumor microenvironment, leading to functional anergy and/or apoptosis of effector T cells [29]. In addition, high levels of PD-1 expression on tumor-infiltrating T cells is associated with decreased cytokine production and impaired cytotoxic efficacy against tumor cells [30]. High expression of PD-L1 in tumors has been shown to be associated with a poorer prognosis in patients with resected HCC [31] and upregulation of PD-1 on T cells is associated with more advanced disease and higher recurrence rates in patients with HCC [32]. Signature genes that might be linked to immune suppression have been identified in subsets of infiltrating regulatory T cells and exhausted $CD8^+$ cells in patients with HCC [33]. The presence of tumor-infiltrating lymphocytes expressing PD-1 in HCC and their correlation with poor outcomes suggest that immunotherapeutic approaches might be useful in this setting [32].

Monoclonal antibodies (mAbs) against PD-1, such as nivolumab and pembrolizumab, have demonstrated antitumor activity across multiple malignancies [34], including in HCC [20,21]. Nivolumab has received accelerated approval in the USA for the treatment of patients with HCC who have previously been treated with sorafenib [22]. Approval was based on a subgroup of 154 patients enrolled in an ongoing, open-label, Phase Ib/II trial (CheckMate 040) who progressed on – or were intolerant to – sorafenib. ORR by RECIST 1.1 was 14.3% with a DoR of 3.2 to more than 38.2 months [22,35]. In the study's dose-expansion phase (n = 214 patients), ORR determined by investigator assessment using RECIST 1.1 ranged from 14 to 23%, with the lowest rates in patients infected with hepatitis B virus [21]. The safety profile of nivolumab was generally consistent with that reported in other tumor types [34]. Serious treatment-related AEs (TRAEs) associated with nivolumab included pemphigoid, adrenal insufficiency and liver disorder. Pembrolizumab has also shown promising clinical efficacy (17% ORR) and manageable safety in patients with unresectable HCC who had previously been treated with sorafenib in a Phase II study [20], and has just received accelerated approval in the USA for the treatment of patients with HCC who have previously been treated with sorafenib [36]. Recently, data from the Phase III KEYNOTE-240 trial evaluating pembrolizumab plus best supportive care versus placebo plus best supportive care in patients with advanced HCC previously treated with systemic therapy were released [37]. The study did not meet its co-primary end points of OS and PFS based on prespecified statistical criteria. However, both OS and PFS demonstrated improvement favoring patients treated with anti-PD-1 therapy further supporting the role of anti-PD-1 in the treatment of HCC patients [37]. Additional mAbs against PD-1 or PD-L1 are in clinical trials [38].

Tislelizumab: an anti-PD-1 antibody

Tislelizumab is differentiated from nivolumab and pembrolizumab in that it is designed to escape FcγR1-mediated effector function [39]. Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis [40], a potential mechanism of resistance to anti-PD-1 therapy (Figure 1) [28]. Tislelizumab has shown enhanced cellular functional activities in blocking PD-1-mediated reverse signal transduction and in activating human T cells and primary peripheral blood mononuclear cells (PBMCs) *in vitro* [40]. *In vitro* studies have shown that tislelizumab does not bind to FcγR1 expressed on HEK293 cells, whereas other checkpoint inhibitors such as nivolumab and pembrolizumab bind to FcγR1 with affinities close to human IgG4 antibody [41,42]. Preclinical models suggest that FcγR1 binding may compromise the activity of PD-1 antibodies [40] and tislelizumab has consistently diminished binding across all types of FcγRs [39]. Tislelizumab interacts with the IgV-like domain of PD-1 with an interface area of 1112 Å2 [43]. When compared with pembrolizumab and nivolumab, the dissociation rate of tislelizumab from wild-type PD-1 is about 100-fold and 50-fold slower, respectively. Gln75, Thr76, Asp77 and Arg86 on PD-1 are critical epitopes for tislelizumab, but their mutation showed little effect on the binding of PD-1 to pembrolizumab and nivolumab [43].

In the dose-finding phase of a first-in-human Phase Ia/Ib study (NCT02407990), the safety of tislelizumab was evaluated across a range of doses: 0.5 to 10 mg/kg every 2 weeks (Q2W) and 2 to 5 mg/kg every 3 weeks (Q3W) administered intravenously, without reaching the maximum tolerated dose [44]. Rates of TRAEs and serious AEs (SAEs) were similar, as were confirmed ORRs, in patients with a variety of solid tumors treated with tislelizumab 2 and 5 mg/kg Q2W and Q3W [45]. Based on the observations that clearance of tislelizumab is independent of bodyweight [45], a 200-mg dose Q3W was expected to lead to serum exposures between those observed after 2 and 5 mg/kg doses. This prediction was corroborated by data from population pharmacokinetic (PK) analyses, along

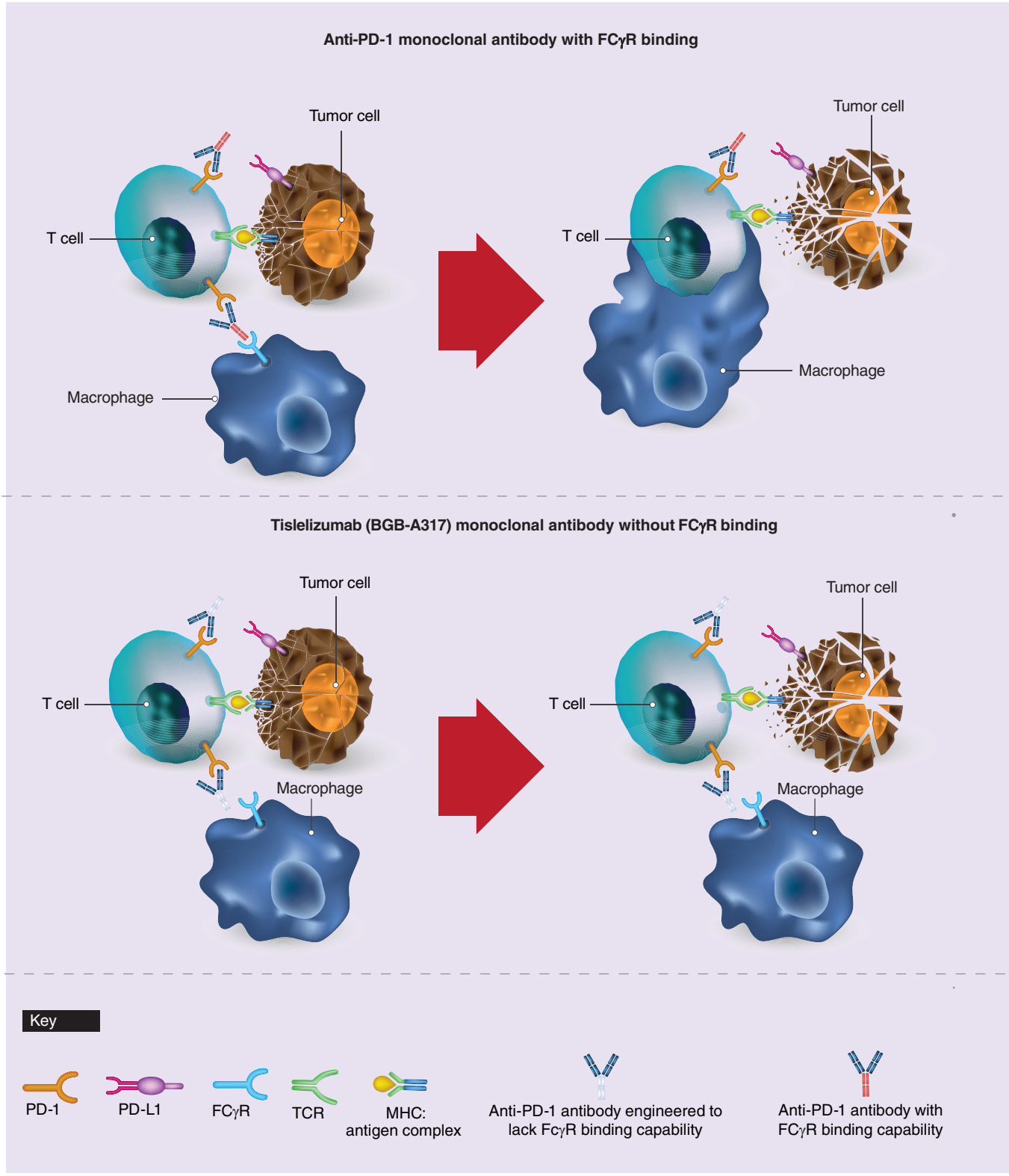

Figure 1. Lack of FcγR binding prevents macrophage-mediated T-cell clearance. PD-1 monoclonal antibody with FcγR binding. PD-1 monoclonal antibody without FcγR binding. Immune mechanisms are simplified in these illustrations. Tislelizumab (BGB-A317) is an investigational anti-PD-1 product that has not yet been approved by any regulatory agency as a safe and effective treatment for any disease.
MHC: Major histocompatibility complex; TCR: T-cell receptor.

with PK data from five patients who received 200 mg Q3W [44]. In addition, no unexpected TRAEs occurred in the 200-mg fixed dose cohort compared with bodyweight-based cohorts. The PK profile of tislelizumab was shown to be consistent between Asian (Chinese) and Caucasian patients. Given these data, tislelizumab 200 mg Q3W was chosen as the recommended dose for global Phase III testing [44].

A preliminary report of the HCC cohort consisted of 50 previously treated HCC patients with a median age of 55.5 years (range: 28–76) and a median of two prior therapies (range: 0–6) [46]. These patients were treated with tislelizumab 5 mg/kg every 3 weeks and were primarily Asian (n = 44), male (n = 41) and hepatitis B virus infected (n = 46). At the time of data cut-off (31 August 2018), median duration of follow-up was 10.8 months (range: 0.7–31.6) and five patients remained in the study. Forty-nine patients were evaluable for response; confirmed partial responses occurred in six patients and stable disease was observed in 19 patients. Confirmed ORR and disease control rates (DCRs) were 12.2% (95% CI: 4.6–24.8) and 51.0% (95% CI: 36.3–65.6), respectively; median DoR was 15.7 months [46]. The most common treatment-emergent AEs were decreased appetite (n = 14), rash (n = 12), decreased weight (n = 11) and cough (n = 10) [46]. One patient with HCC experienced a fatal TRAE of acute hepatitis, which was confounded by rapidly progressing disease; this was the only serious TRAE reported in the HCC cohort. Overall, the safety profile of tislelizumab is consistent with the overall Phase I study (n = 451) and included mostly mild-to-moderate AEs. This preliminary safety profile and antitumor activity support continued development of tislelizumab as a single agent or in combination with other agents in patients with unresectable HCC.

RATIONALE 301 study

Study design

RATIONALE 301 is a global, Phase III, randomized, open-label, multicenter study that will evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment in adult patients with unresectable HCC (Figure 2). The primary objective of the study is to compare OS between the two treatment groups. The key secondary objective is to compare ORR, as assessed by BIRC per RECIST v1.1. Other secondary objectives will include a comparison of tislelizumab and sorafenib in terms of various efficacy assessments (PFS, DoR, TTP, DCR and clinical benefit rate [CBR]), measures of health-related quality of life, and safety and tolerability. The study opened to accrual in December 2017 and is currently recruiting patients; approximately 640 patients will be recruited from approximately 100 sites globally.

Key eligibility criteria

Eligible patients must be aged ≥18 years and have histologically confirmed HCC, Barcelona Clinic Liver Cancer (BCLC) stage C disease or Barcelona Clinic Liver Cancer (BCLC) stage B disease that is not amenable to or has relapsed after locoregional therapy and is not amenable to a curative treatment approach, and no previous treatment with systemic therapy. Patients must also have an Eastern Cooperative Oncology Group (ECOG) score ≤1, a Child–Pugh A classification for liver function, one or more measurable lesions per RECIST v1.1 and adequate organ function.

Patients will be excluded if they have known fibrolamellar HCC, sarcomatoid HCC or mixed cholangiocarcinoma and HCC histology; tumor thrombus involving the main trunk of the portal vein or inferior vena cava; received locoregional therapy to the liver (TACE, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization or ablation) or any prior immunotherapy within 28 days prior to randomization, or any Chinese herbal medicine or patent medicine used to control cancer within 14 days of randomization; grade 2 or higher hepatic encephalopathy (at screening or prior history); or pericardial effusion, uncontrollable pleural effusion or clinically significant ascites at screening.

Study procedures

Patients will be randomized 1:1 to receive open-label treatment with tislelizumab 200 mg given i.v. Q3W (day 1 of each 21-day cycle) or sorafenib 400 mg (2 × 200 mg tablets) given orally twice-daily. Randomization will be stratified by the presence/absence of macrovascular invasion, the presence/absence of extrahepatic spread, ECOG performance status (0 vs 1), etiology (hepatitis C virus [HCV] vs other – including hepatitis B virus [HBV]) – and geography (Asia [excluding Japan] vs Japan vs the rest of the world). Treatment will be administered until loss of clinical benefit, intolerable toxicity or treatment discontinuation due to other reasons.

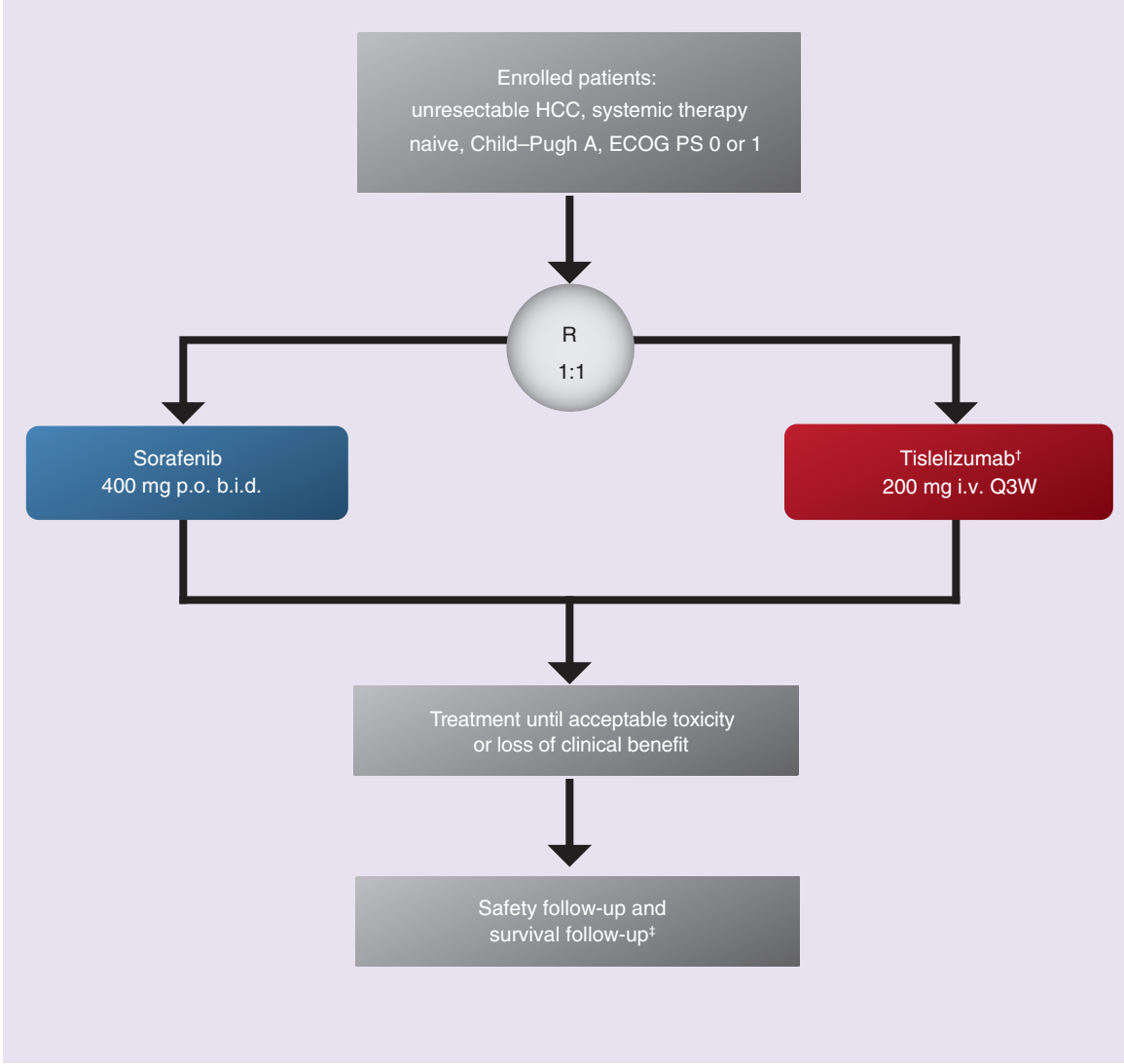

Figure 2. Study design. Randomization stratified by: macrovascular invasion (present vs absent); extrahepatic spread (present vs absent); ECOG PS (0 vs 1); etiology (HCV vs other [includes HBV]); geography (Asia vs Japan vs the rest of the world).
†The initial infusion (cycle 1, day 1) will be administered over 60 min; if well tolerated, subsequent infusions may be administered over 30 min. After tislelizumab infusion, patients will be monitored for 2 h during cycles 1 and 2, and for ≥30 min from cycle 3 onward.
‡Treatment beyond the initial investigator-assessed disease progression will be permitted in both treatment arms if pseudo progression is suspected or if there is a reasonable belief that the patient could derive benefit from the treatment.
b.i.d: Twice daily; ECOG PS: Eastern Cooperative Oncology Group performance status; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; i.v.: Intravenously; p.o.: Orally; Q3W: Every 3 weeks; R: Randomization.

Tislelizumab will be administered at a fixed dose with no dose reductions permitted. Dose delays or interruptions of less than 12 weeks are permitted. An Independent Data Monitoring Committee will evaluate and confirm the Phase III dose based on the safety and tolerability of tislelizumab.

Dose modifications for sorafenib are permitted in accordance with the investigator's clinical judgement and are consistent with the sorafenib prescribing information.

Outcome measures

The primary end point is OS for tislelizumab versus sorafenib, defined as the time from the date of randomization to the date of death due to any cause. Secondary efficacy end points include ORR, PFS, DoR and TTP, all assessed by the BIRC and investigator using RECIST v1.1; and DCR and clinical benefit rate, both assessed by BIRC and the investigator. Tumor response will be evaluated every 9 weeks during year 1 and every 12 weeks from year 2 onwards. Distribution of PD-L1 expression will be examined in the intent-to-treat (ITT) analysis set by central immunohistochemistry assay.

Safety and tolerability will also be evaluated as a secondary end point by monitoring AEs, including immune-related AEs (irAEs) and through physical examinations, vital signs and electrocardiograms. AEs and SAEs will be assessed up to 30 days after the last dose of the study drug or until initiation of new anticancer therapy (whichever comes first). In the tislelizumab arm, irAEs will be assessed up to 90 days after the last treatment dose irrespective of whether a new anticancer therapy is started.

Patients will complete questionnaires to assess health-related quality of life (secondary end point) during study visits; these include the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ-HCC18), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Quality of Life 5-Dimensions (EQ-5D-5 L).

Statistics

The trial is powered to demonstrate superiority of tislelizumab over sorafenib in the comparison of the primary end point, OS. A stratified log-rank test will be performed and 95% CI of the HR will be constructed in the primary analysis. The key secondary end point, ORR, will be compared using a Cochran–Mantel–Haenszel χ^2 test with stratification factors as strata. Other time to event variables, including PFS, DoR and TTP, will be estimated using the Kaplan–Meier method. Stratified log-rank tests will be used for the treatment comparisons. Health-related quality of life outcomes from EORTC QLQ-HCC18 and QLQ-C30 will be compared in a mixed model with baseline score, time since randomization and treatment arm in the model. The intent-to-treat population will be the analysis population for efficacy analysis with the per-protocol population used in the sensitivity analysis.

Safety analysis will be performed in the safety population and will include summary tables of study drug exposure, AE, SAE, TRAE, grade 3 or higher AE, AE leading to treatment discontinuation and death and irAEs. Clinical laboratory and vital sign data will also be summarized by treatment arm.

Conclusion

Immunotherapeutic approaches that target the PD-1/PD-L1 axis might be useful in unresectable HCC. PD-L1 is overexpressed in tumor cells and is associated with poorer prognosis in patients with HCC. PD-1 is highly expressed on tumor-infiltrating T cells, which is correlated with more advanced disease and higher recurrence rates in HCC. Furthermore, mAbs against PD-1, such as nivolumab and pembrolizumab, have demonstrated antitumor activity, including in patients with HCC who have previously been treated with sorafenib.

Tislelizumab is an investigational, humanized IgG4 mAb with high affinity and binding specificity for PD-1. Unlike other PD-1 inhibitors, tislelizumab has been specifically engineered to remove the Fc and hinge regions to minimize Fcγ receptor binding on macrophages, which may abate potentially negative interactions with other immune cells including macrophages and myeloid-derived suppressive cells (MDSC). Single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC, in a Phase Ia/Ib trial. Another open-label Phase II trial (NCT03419897) is investigating the efficacy and safety of tislelizumab in adult patients with previously treated HCC. The global, Phase III, randomized, open-label study reported here will evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment in adult patients with unresectable HCC. Positive results of the study may help to address the unmet need for a new systemic therapy in the first-line treatment of unresectable HCC.

Executive summary

Current treatment for hepatocellular carcinoma

- Patients with unresectable hepatocellular carcinoma (HCC) have a poor prognosis.
- Sorafenib and lenvatinib are the only approved first-line treatments for unresectable HCC. However, the median life expectancy remains approximately 1 year and sorafenib can be difficult for patients to tolerate.

PD-1 inhibition as a strategy for treating unresectable HCC

- Immunotherapeutic approaches that target the PD-1/PD-L1 axis might be useful in unresectable HCC.
- PD-L1 is overexpressed in tumor cells and PD-1 is highly expressed in tumor-infiltrating T cells; this overexpression is associated with poorer prognosis, more advanced disease and higher recurrence rates in patients with HCC.
- Monoclonal antibodies against PD-1 (nivolumab and pembrolizumab) have demonstrated antitumor activity, including in patients with HCC.

The PD-1 inhibitor, tislelizumab

- Tislelizumab (BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for PD-1.
- Tislelizumab has been specifically engineered to minimize Fcγ receptor binding to help abate potentially negative interactions with macrophages and myeloid-derived suppressive cells (MDSCs) that have high expression of Fcγ receptors.
- Single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC, in a Phase Ia/Ib trial.

Phase III trial

- This Phase III, randomized, open-label, global study will evaluate the efficacy and safety of tislelizumab versus sorafenib as a first-line treatment in adult patients with unresectable HCC.
- Enrolled patients must be aged ≥18 years and have histologically confirmed HCC; Barcelona Clinic Liver Cancer stage C disease classification, or Barcelona Clinic Liver Cancer stage B disease not amenable to, or relapsed after, locoregional therapy and not amenable to a curative treatment approach; no previous treatment with systemic therapy; Eastern Cooperative Oncology Group score ≤1; a Child–Pugh A classification and ≥1 measurable lesion per RECIST v1.1.
- Approximately 640 patients will be randomized 1:1 to tislelizumab 200 mg intravenously every 3 weeks or sorafenib 400 mg orally twice daily.
- Randomization will be stratified by the presence/absence of macrovascular invasion, the presence/absence of extrahepatic spread, Eastern Cooperative Oncology Group performance status (0 vs 1), etiology (hepatitis C virus vs other – including hepatitis B virus) – and geography (Asia [excluding Japan] vs Japan vs the rest of the world).

Objectives & end points

- The primary objective is to compare overall survival between the two treatment groups.
- The key secondary objective is to compare objective response rate, as assessed by blinded independent review committee per RECIST v1.1.
- Other secondary objectives will include a comparison of tislelizumab and sorafenib in terms of various other efficacy assessments, measures of health-related quality of life, and safety and tolerability.
- Secondary end points include: objective response rate, progression-free survival, duration of response and time to progression, all assessed by the blinded independent review committee and investigator using RECIST v1.1; quality of life; disease control rate and clinical benefit rate, both assessed by blinded independent review committee and the investigator; and safety and tolerability (including immune-related adverse events).
- Tumor response will be evaluated every 9 weeks during year 1 and every 12 weeks from year 2 onwards.
- Distribution of PD-L1 expression will be examined in the ITT analysis set. Any potential association between PD-L1 expression and superior tislelizumab treatment effect over sorafenib will be explored.

Statistics

- The primary efficacy end point of overall survival for tislelizumab versus sorafenib will be assessed in a stratified log-rank test.

Conclusion

- Tislelizumab is a humanized, IgG4 monoclonal anti-PD-1 antibody designed to minimize potentially negative interactions with macrophages and myeloid-derived suppressive cell.
- Positive results of the study may help to address the unmet need for new systemic therapy in the first-line treatment of unresectable HCC.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2019-0097

Authors' contributions

All the authors were involved in the design and/or conduct of the study. All authors have contributed to the preparation and writing of the manuscript and approved the final manuscript

Acknowledgments

The authors wish to acknowledge the investigative center study staff, the study patients and their families.

Financial & competing interests disclosure

RS Finn has served in a consulting or advisory role for Pfizer, Bayer, Novartis, Bristol-Myers Squibb and MSD. He has also received research funding from Pfizer. M Kudo has received honoraria from Bayer, Eisai, MSD and Ajinomoto, and research funding from Chugai Otuka, Takeda, Taiho, Sumitomo Daimippon, Daichi Sankyo, MSD, Eisai, Bayer and Abbvie. He has served in a consulting or advisory role for Kowa, MSD, Bristol-Myers Squibb, Bayer, Chugai and Taiho. T Meyer has served in a consulting or advisory role for Bayer, Eisai, MSD, Bristol-Myers Squibb and BeiGene, and has received research funding from BTG, Bayer and Ipsen. A Vogel has served in a consulting or advisory role for Novartis, Delcath Systems, Lilly, Roche, Amgen, Bayer and Baxalta. He has received honoraria from Novartis, Roche, Bayer, Sanofi, Amgen, Delcath Systems, Lilly, Bristol-Myers Squibb and MSD, travel, accommodations and expense support from Bayer, Roche and Ipsen, and research funding from Novartis. M Ducreux has served as an advisor for Roche, MSD, Amgen, Novartis, Sanofi, Bayer, Sirtex, Lilly, Servier and Ipsen, and as a speaker for Roche, MSD, Amgen, Novartis, Lilly and Ipsen. He has received research funding from Roche, MSD and Pfizer. AX Zhu has served in a consulting or advisory role for Eisai, Bristol-Myers Squibb, MSD, Novartis, Sanofi, AstraZeneca, Bayer, Exelixis and Lilly. He has received research funding from Lilly, Bayer, Bristol-Myers Squibb, Novartis and MSD. F Boisserie, J Hou, X Li and J Song are employees of BeiGene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

BeiGene, Ltd, provided financial support for this manuscript, including writing and editorial assistance by SuccinctChoice Medical Communications, Chicago, IL, USA.

Ethical conduct of research

The study is being conducted according to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, the principles of informed consent and the requirements of the public registration of clinical trials. Written informed consent was obtained from each patient prior to screening.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest.

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•• **Reports the co-crystal structure of the PD-1 extracellular domain and the Fab of tislelizumab and identifies unique epitopes of tislelizumab that correlate to the extremely slow dissociation rate of tislelizumab after binding to PD-1.**

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•• **Demonstrates that tislelizumab was generally well tolerated; adverse events were generally of mild or moderate severity and were consistent with prior reports for tislelizumab monotherapy.**

Article details

Title of article

A global Phase III study of tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma

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Article URL

www.futuremedicine.com/doi/10.2217/fon-2019-0097

Trial registration number

NCT03412773

Primary objectives/rationale

Primary objective

Compare OS of tislelizumab- and sorafenib-treated patients

Secondary objectives

Key secondary objective: compare ORR of tislelizumab and sorafenib, assessed by BIRC per RECIST v1.1
Other secondary objectives: compare tislelizumab and sorafenib in terms of other efficacy endpoints, HRQoL, and safety and tolerability

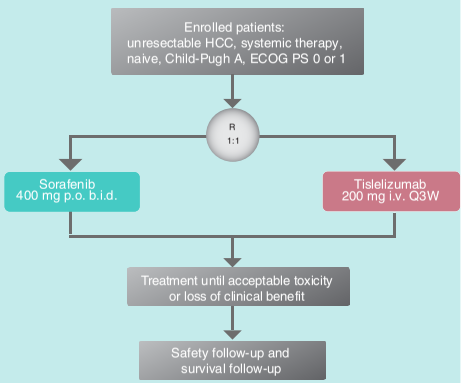
Study design and treatment including planned sample size, planned study period and study procedures

Patients will be randomized 1:1 to receive tislelizumab 200 mg intravenously every 3 weeks or sorafenib 400 mg orally twice daily

Tumor response will be evaluated every 9 weeks during Year 1 and every 12 weeks from Year 2 onwards

Study period: December 2017 to May 2022

Study design, treatment and study procedures



Key eligibility criteria

Age ≥18 years

Histological confirmed HCC

BCLC stage C disease classification, or BCLC stage B disease not amenable to, or relapsed after, locoregional therapy and not amenable to a curative treatment approach

No previous treatment with systemic therapy

ECOG score ≤1

Child-Pugh A classification

≥1 measurable lesion per RECIST v1.1

Outcome measures/end points

Primary end point:
OS

Secondary end points:
ORR, PFS, DoR, TTP, DCR, CBR, AEs, immune-related AEs, laboratory parameters

Glossary

AEs: Adverse events; BCLC: Barcelona clinic liver cancer-stage C; CBR: Clinical benefit rate; DCR: Disease control rate; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; HCC: Hepatocellular carcinoma; HRQoL: Health-related quality of life; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST v1.1: RECIST: Response Evaluation Criteria in Solid Tumors; TTP: Time to progression