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ORIGINAL ARTICLE

Phase 2 trial comparing sorafenib, pravastatin, their combination or supportive care in HCC with Child–Pugh B cirrhosis

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Abstract

Background and aims There is limited data regarding the role for systemic treatment in patients with Hepatocellular Carcinoma with Child–Pugh B cirrhosis.

Methods PRODIGE 21 was a multicentric prospective non-comparative randomized trial. Patients were randomized to receive sorafenib (Arm A), pravastatin (Arm B), sorafenib–pravastatin (Arm C) combination, or best supportive care (Arm D). Primary endpoint was time to progression (TTP), secondary endpoints included safety and overall survival (OS).

Results 160 patients were randomized and 157 patients were included in the final analysis. 86% of patients were BCLC C and 55% had macrovascular invasion. The safety profiles of the drugs were as expected. Median TTP was 3.5, 2.8, 2.0 and 2.2 months in arms A, B, C and D, respectively, but analysis was limited by the number of patients deceased without radiological progression (59%). Median OS was similar between the four arms: 3.8 [95% CI: 2.4–6.5], 3.1 [95% CI: 1.9–4.3], 4.0 [95% CI: 3.2–5.5] and 3.5 months [95% CI: 2.2–5.4] in arms A, B, C and D, respectively. Median OS was 4.0 months [95% CI: 3.3–5.5] for patients treated with sorafenib, vs 2.9 months [95% CI: 2.2–3.9] for patients not treated with sorafenib. In

Members of the PRODIGE 21 collaborators are listed in the Acknowledgement section.

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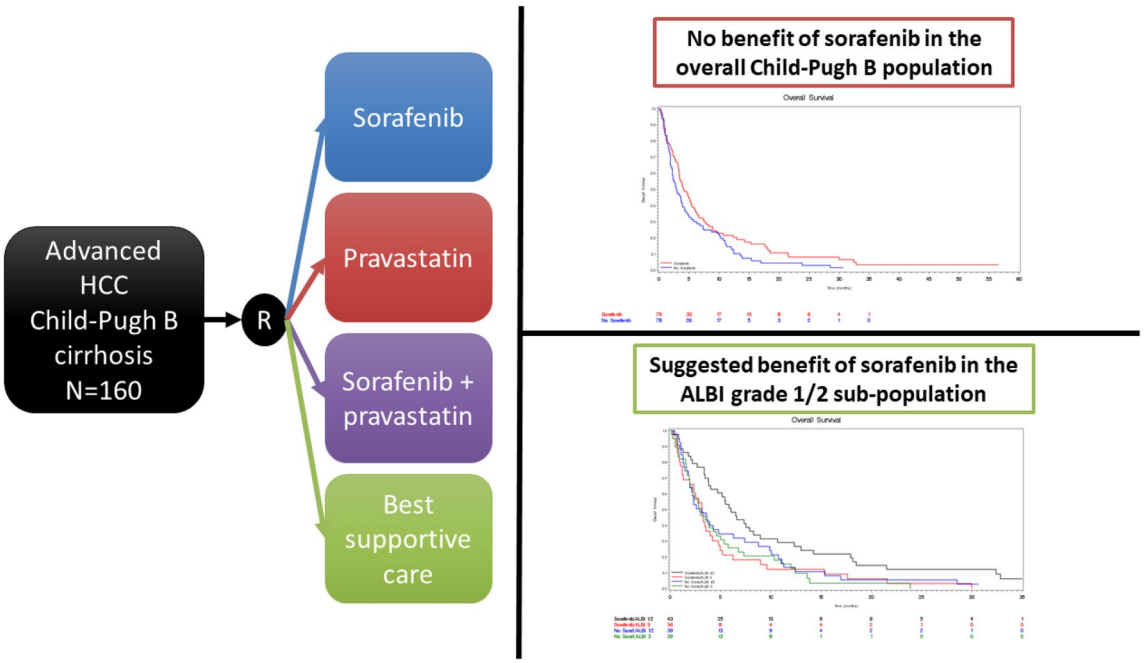
patients with ALBI grade 1/2, median OS was 6.1 months [95% CI: 3.8–8.3] in patients treated with sorafenib vs 3.1 months [95% CI: 1.9–4.8] for patients not treated with sorafenib.

Conclusion In the overall Child–Pugh B population, neither sorafenib nor pravastatin seemed to provide benefit. In the ALBI grade 1/2 sub-population, our trial suggests potential benefit of sorafenib.

Clinical trial registration The study was referenced in clinicaltrials.gov (NCT01357486).

Graphic abstract



Keywords HCC · Sorafenib · Liver functions · Randomized clinical trial · ALBI · Child–Pugh

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Introduction

Hepatocellular carcinoma (HCC) is the fourth cause of cancer death worldwide [1]. The mortality is rising in Western Countries [2]. Most HCC arise in patients with cirrhosis. In these patients, HCC and cirrhosis are both at risk of complications leading to death. Furthermore, HCC per se, due to the tumoral burden, could lead to worsening of liver functions.

Currently, there is no clear recommendation for systemic treatment of patients with Child–Pugh (CP) B cirrhosis [3–5]. CP A and B cirrhosis were generally together in the treatment algorithms presented, but details in the guidelines often state that CP B should be treated only if "highly selected", or clearly state that systemic therapies were not validated in CP B population [3–6]. The ALBI grade was recently described in HCC [7]. It allows for an objective evaluation of liver functions using only albumin and bilirubin values, and was demonstrated to provide adequate evaluation in sorafenib-treated patients [8–10].

Indeed, most phase 3 trials in HCC were either restricted to CP A population, or included very few selected CP B patients [11–15]. Sorafenib being the only drug approved for many years, an extensive literature exists as regards to the difference of activity of sorafenib in patients with CP A and B liver functions, but without randomized data. A recent meta-analysis including 1684 CP B patients from 30 studies reported a worse survival than the CP A population, with a median of only 4.6 months [16]. However, the large GIDEON cohort suggested better results in the Child–Pugh B7 population than in the B8 or B9 population [17]. Overall, the absence of adequately powered randomized trial do not allow to draw definitive conclusion on the potential interest of systemic treatment in this population. Results in the sorafenib population will still be important with the advent of new first-line treatments, as sorafenib will remain a second-line option.

Pravastatin was tested before the era of targeted therapy as a potential for prevention or treatment of HCC [18–20]. Statins are of particular interest because of their intrinsic action on HMG-CoA reductase, the concentration and the activity of which is increased in HCC cells. Inhibition of HMG-CoA reductase leads to depletion of mevalonate and, thus, of its products, farnesyl pyrophosphate and geranylgeranyl pyrophosphate used in the cell for post-translational modifications of many regulators of proliferation. Pravastatin has been shown to inhibit in vitro and in vivo HCC tumor growth, and has a pro-apoptotic action on tumoral liver cell lines. However, the existing literature was limited by mostly retrospective data and small randomized studies. Pravastatin was tested at the same time by our group in a phase 3 trial in the CP A population in combination with sorafenib [21]. Due to the predicted low toxicity of the drug, we felt that testing pravastatin in the CP B population might be interesting.

We thus decided to conduct a prospective trial evaluating the administration of sorafenib, pravastatin, their combination, or BSC alone, in patients treated for HCC with CP B liver functions.

Patients and methods

Study design and patients

The PRODIGE 21 trial was designed as a multicenter, open-label, randomized phase 2 trial. The study was conducted in 35 centers in France, within the PRODIGE (FFCD/UCGI/GERCOR) intergroup. The study was referenced in clinicaltrials.gov (NCT01357486). The protocol is provided as Acknowledgement.

The main inclusion criteria were: age older than 18 years, HCC diagnosed by biopsy or by radiological criteria according to AASLD guidelines, patient non eligible to curative or loco-regional therapy, Child–Pugh Score B7 to B9, Performance Status 0 to 2, stage B or C of BCLC classification, adequate biological parameters (Hb $\geq$ 8 g/dl, Platelets $\geq$ 50 G/L, creatinine $<$ 2 times the upper limit of normal, Neutrophils $\geq$ 1000/ mm^3). Patient with previous use of statin in the 6 months before the diagnosis of HCC or patients with previous exposure to sorafenib were excluded. Patients with myocardial infarction less than 6 months ago, uncontrolled arterial hypertension, congestive heart failure NYHA class $>$ 2, anti-arrhythmia treatment other than beta-blockers or digoxin were also excluded.

The criteria used for CP classification were those of the French recommendations (Supplementary Table 1). The ALBI score was calculated based on the published formula [7].

Eligible patients were randomly assigned in 4 arms according to 1:1 ratio: Arm A, sorafenib treatment, Arm B, pravastatin treatment, Arm C, sorafenib and pravastatin treatment, Arm D, BSC only. Randomization was done by minimization techniques and was stratified according to center and BCLC classification.

Procedures

Patients allocated to sorafenib started the drug at 400 mg twice a day, continuously. Subsequent dose reductions were done according to toxicities, as per local practice and label instructions. Pravastatin was given at the dose of 40 mg per day, continuously. BSC was given in every arm as per local practice, no specific guidelines were provided in the protocol. Treatment was continued until progression or intolerable toxicity.

Follow-up visits occurred on a monthly basis, consisting of clinical examination, chest abdomen and pelvis CT-scan and blood tests (including liver and renal function tests, alpha-fetoprotein (AFP) monitoring). In case of progression, further treatment was at the discretion of the investigator.

Outcomes

The primary endpoint was time to progression (TTP), defined as the time between randomization and first evidence of radiological progression as assessed by mRECIST [22]. Patients with no radiological progression were censored at the date of death or last follow-up.

Secondary endpoints included Overall Survival (OS), defined as the time between randomization and death, Progression-Free Survival (PFS), defined as the time between randomization and first radiological progression or death, time to treatment failure (TTF), defined as the time between randomization and discontinuation of the treatment, objective response rate at 4 months, safety, as assessed by NCI-CTCAE v4.03, and Quality of Life (QoL), as assessed by QLQ-C30 and FACT-Hep questionnaires.

Statistical analysis

The trial was designed as a non-comparative trial, with H0 hypothesis of median TTP of 10 weeks (2.3 months), and a goal to increase the median TTP to 18 weeks (H1, 4.1 months). This was based on the hypothesis that sorafenib efficacy in terms of control of the disease in the CP B population would be similar seen in the CP A population, but that OS might be lower due to competitive risk of cirrhosis complications. This hypothesis was tested in each of the 3 treatment arm separately, the Arm D serving at confirming the survival hypotheses in this understudied population. A non-comparative design was chosen due to the paucity of data in this population, and the difficulty to recruit sufficient number of patients in a comparative study. With a power of 90% and an alpha risk of 5%, 36 patients were required in each arm. With a 10% estimation of loss to follow-up, we planned to include 40 patients in each arm, for a total of 160 patients included in the study.

The analyses of the primary endpoints were done on the intention-to-treat population consisting of all randomized patients. A per protocol population was defined as the population respecting the 3 main inclusion criteria (CP B, BCLC

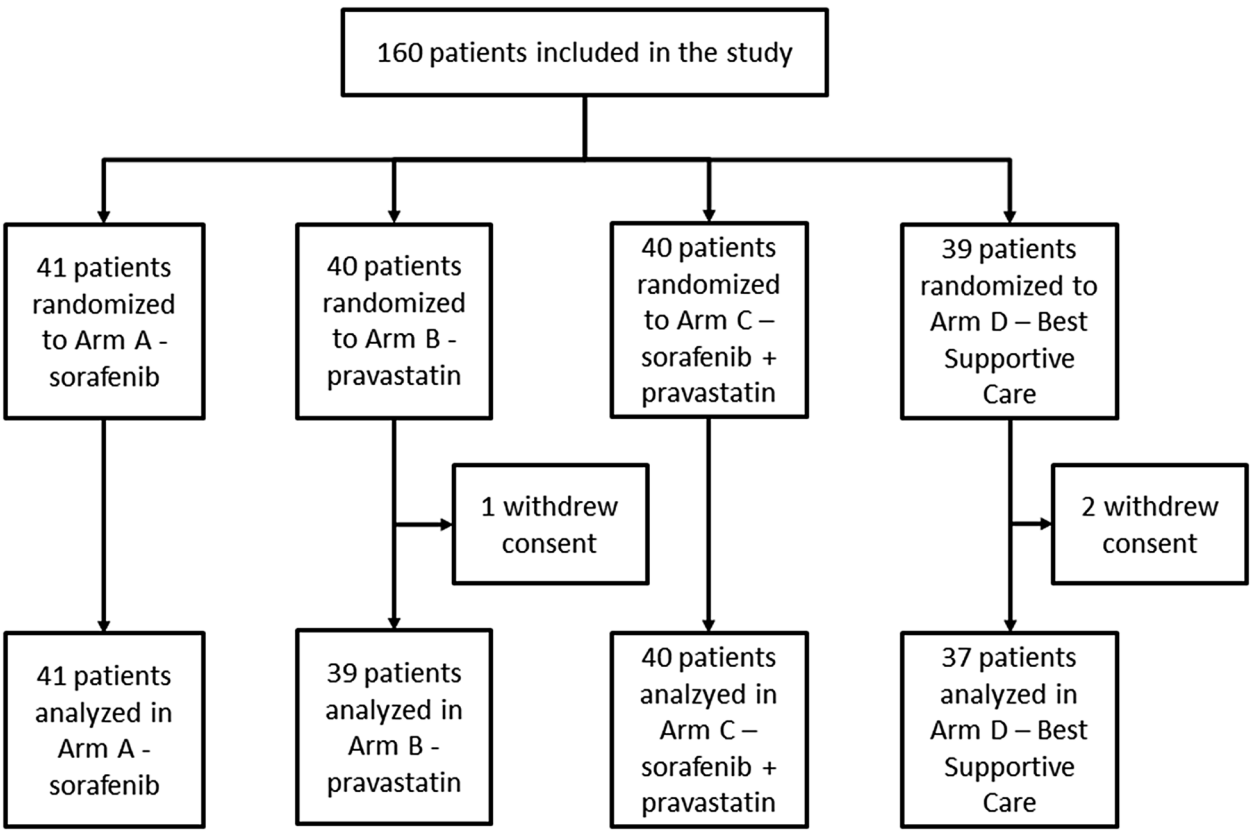

Fig. 1 Flowchart of the study. CONSORT diagram of inclusion of the patients in the trial

Table 1 Baseline characteristics

	Arm A Sorafenib ($n=41$)	Arm B Pravastatin ($n=39$)	Arm C Sorafenib + pravastatin ($n=40$)	Arm D BSC ($n=37$)	Total ($n=157$)
Age, median (range)	67 (51–84)	63 (43–77)	66 (44–82)	65 (47–84)	65 (43–84)
Gender: male	37 (90%)	34 (87%)	35 (88%)	35 (95%)	141 (90%)
Performance status: 0/1/2	5 (12%)/30 (73%)/6 (15%)	10 (26%)/20 (51%)/9 (23%)	6 (15%)/23 (58%)/11 (28%)	6 (16%)/22 (59%)/9 (24%)	27 (17%)/95 (61%)/35 (22%)
Etiology of cirrhosis: Alcohol only/alcohol + other/HBV/HCV/combined HBV and HCV/others	23 (56%)/10 (24%)/2 (5%)/1 (2%)/0 (0%)/5 (12%)	23 (59%)/9 (23%)/2 (5%)/4 (10%)/0 (0%)/1 (3%)	25 (63%)/5 (13%)/2 (5%)/2 (5%)/1 (3%)/5 (13%)	24 (65%)/7 (19%)/0 (0%)/1 (3%)/0 (0%)/5 (14%)	95 (61%)/31 (20%)/6 (4%)/8 (5%)/1 (1%)/16 (10%)
BCLC stage B/C/D	4 (10%)/36 (88%)/1 (2%)	6 (15%)/33 (85%)/0 (0%)	5 (13%)/35 (88%)/0 (0%)	4 (11%)/31 (84%)/2 (5%)	19 (12%)/135 (86%)/3 (2%)
Liver involvement ≥ 50%	5 (12%)	6 (15%)	8 (20%)	6 (16%)	25 (16%)
Size of the largest tumor (mm), median (IQR)	45 (23–72)	60 (40–90)	46 (36–80)	55 (43–75)	53 (37–79)
Macrovascular invasion	17 (41%)	22 (56%)	24 (60%)	23 (62%)	86 (55%)
Extra-hepatic disease	6 (15%)	7 (18%)	9 (23%)	4 (11%)	26 (17%)
CP class A/B/C	2 (5%)/38 (93%)/1 (2%)	0 (0%)/39 (100%)/0 (0%)	1 (3%)/39 (98%)/0 (0%)	0 (0%)/36 (97%)/1 (3%)	3 (2%)/152 (97%)/2 (1%)
CP score B7/B8/B9 in CP B patients ($n=152$)	15 (39%)/16 (42%)/7 (18%)	14 (37%)/18 (47%)/6 (16%)	16 (41%)/12 (31%)/11 (28%)	10 (28%)/16 (44%)/10 (28%)	55 (36%)/62 (41%)/34 (23%)
Ascites according to CP grade: 1/2/3	22 (54%)/14 (34%)/5 (12%)	24 (62%)/9 (23%)/6 (15%)	21 (53%)/11 (28%)/8 (20%)	13 (35%)/17 (46%)/7 (19%)	80 (51%)/51 (32%)/26 (17%)
Encephalopathy according to CP grade: 1/2/3	40 (98%)/1 (2%)/0 (0%)	37 (95%)/2 (5%)/0 (0%)	40 (100%)/0 (0%)/0 (0%)	36 (97%)/1 (3%)/0 (0%)	153 (97%)/4 (3%)/0 (0%)
Platelets (G/L), median (IQR)	132 (80–189)	127 (90–176)	116 (80–194)	160 (97–195)	132 (88–193)
Prothrombin ratio (%), median (IQR)	71 (61–82)	71 (62–80)	64 (58–74)	71 (58–77)	70 (58–80)
Albumin (g/L), median (IQR)	29 (26–33)	30 (28–32)	29 (26–31)	27 (25–31)	29 (26–32)
Total Bilirubin (mcmol/L), median (IQR)	34 (24–54)	47 (29–72)	38 (19–49)	32 (22–47)	35 (24–54)
AFP (mcg/L), median (IQR)	95 (6–1038)	1462 (48–15,510)	38 (8–148)	50 (14–7791)	85 (12–4588)

B or C, and Performance status 0 to 2) and receiving at least 4 weeks of treatment.

The survival curves were estimated using the Kaplan–Meier method.

Exploratory analyses, not initially planned in the statistical analysis plan, were also performed: analysis of patients treated with sorafenib (arms A and C) and patients not treated with sorafenib (arms B and D), and analysis according to the liver function evaluated by the CP scores and the ALBI grade.

All authors had access to the data and had reviewed and approved the final manuscript.

Table 2 Adverse events (related or not to study treatment)

	Arm A—Grade 1/2 (N = 40)	Arm A—Grade 3/4/5 (N = 40)	Arm B—Grade 1/2 (N = 38)	Arm B—Grade 3/4/5 (N = 38)	Arm C—Grade ½ (N = 39)	Arm C—Grade 3/4/5 (N = 39)	Arm D—Grade 1/2 (N = 37)	Arm D—Grade 3/4/5 (N = 37)
At least one toxicity of maximal grade	37 (92.5)	33 (82.5)	35 (92.1)	34 (89.5)	36 (92.3)	34 (87.2)	36 (97.3)	30 (81.1)
Liver function events	34 (85.0)	26 (65.0)	33 (86.8)	30 (78.9)	34 (87.2)	29 (74.4)	35 (94.6)	28 (75.7)
Liver dysfunction	5 (12.5)	8 (20.0)	0 (0)	7 (18.4)	2 (5.1)	13 (33.3)	3 (8.1)	5 (13.5)
Ascites	1 (2.5)	6 (15.0)	4 (10.5)	5 (13.2)	3 (7.7)	3 (7.7)	4 (10.8)	3 (8.1)
ALT increase	16 (40.0)	4 (10.0)	22 (57.9)	2 (5.3)	25 (64.1)	2 (5.1)	16 (43.2)	5 (13.5)
AST increase	24 (60.0)	7 (17.5)	21 (55.3)	12 (31.6)	26 (66.7)	7 (17.9)	23 (62.2)	10 (27.0)
BILIRUBIN increase	12 (30.0)	18 (45.0)	13 (34.2)	21 (55.3)	14 (35.9)	18 (46.2)	14 (37.8)	16 (43.2)
GGT increase	14 (35.0)	15 (37.5)	16 (42.1)	16 (42.1)	21 (53.8)	11 (28.2)	17 (45.9)	18 (48.6)
Alkaline Phosphatase increase	29 (72.5)	4 (10.0)	30 (78.9)	2 (5.3)	23 (59.0)	4 (10.3)	33 (89.2)	2 (5.4)
Limb swelling	12 (30.0)	0 (0)	12 (31.6)	1 (2.6)	6 (15.4)	0 (0)	7 (18.9)	2 (5.4)
Confusion	0 (0)	0 (0)	0 (0)	0 (0)	4 (10.3)	0 (0)	1 (2.7)	0 (0)
Vascular events	6 (15.0)	4 (10.0)	3 (7.9)	1 (2.6)	4 (10.3) (2.6)	5 (12.8)	5 (13.5)	2 (5.4)
Hypertension	3 (7.5)	2 (5.0)	0 (0)	0 (0)	2 (5.1)	1 (2.6)	2 (5.4)	0 (0)
Lower tract gastrointestinal bleeding	0 (0)	1 (2.5)	2 (5.3)	0 (0)	1 (2.6)	4 (10.3)	1 (2.7)	1 (2.7)
Upper tract gastrointestinal bleeding	2 (5.0)	1 (2.5)	0 (0)	0 (0)	0 (0)	2 (5.1)	1 (2.7)	0 (0)
Intracranial bleeding	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thromboembolic event	0 (0)	0 (0)	0 (0)	1 (2.6)	1 (2.6)	0 (0)	0 (0)	0 (0)
Epistaxis	2 (5.0)	0 (0)	1 (2.6)	0 (0)	0 (0)	0 (0)	1 (2.7)	0 (0)
Other events	34 (85.0)	27 (67.5)	35 (92.1)	21 (55.3)	36 (92.3)	23 (59.0)	35 (94.6)	21 (56.8)
Hand foot skin reaction	7 (17.5)	1 (2.5)	3 (7.9)	0 (0)	2 (5.1)	1 (2.6)	0 (0)	0 (0)
Diarrhea	9 (22.5)	4 (10.0)	9 (23.7)	0 (0)	9 (23.1)	1 (2.6)	6 (16.2)	0 (0)
Abdominal pain	5 (12.5)	0 (0)	4 (10.5)	3 (7.9)	7 (17.9)	1 (2.6)	8 (21.6)	2 (5.4)
Nausea	6 (15.0)	2 (5.0)	3 (7.9)	0 (0)	3 (7.7)	1 (2.6)	1 (2.7)	0 (0)
Vomiting	4 (10.0)	2 (5.0)	2 (5.3)	0 (0)	3 (7.7)	1 (2.6)	1 (2.7)	1 (2.7)
Anemia	23 (57.5)	1 (2.5)	30 (78.9)	2 (5.3)	24 (61.5)	4 (10.3)	26 (70.3)	4 (10.8)
Dyspnea	5 (12.5)	1 (2.5)	4 (10.5)	1 (2.6)	1 (2.6)	1 (2.6)	7 (18.9)	3 (8.1)

Table 2 (continued)

	Arm A—Grade 1/2 (N = 40)	Arm A—Grade 3/4/5 (N = 40)	Arm B—Grade 1/2 (N = 38)	Arm B—Grade 3/4/5 (N = 38)	Arm C—Grade ½ (N = 39)	Arm C—Grade 3/4/5 (N = 39)	Arm D—Grade 1/2 (N = 37)	Arm D—Grade 3/4/5 (N = 37)
CREATININE increase	10 (25.0)	0 (0)	13 (34.2)	2 (5.3)	9 (23.1)	0 (0)	16 (43.2)	1 (2.7)
White blood cells decrease	7 (17.5)	2 (5.0)	6 (15.8)	0 (0)	10 (25.6)	0 (0)	8 (21.6)	0 (0)
Neutrophil decrease	4 (10.0)	2 (5.0)	3 (7.9)	1 (2.6)	5 (12.8)	1 (2.6)	4 (10.8)	0 (0)
Weight loss	7 (17.5)	0 (0)	3 (7.9)	0 (0)	2 (5.1)	0 (0)	1 (2.7)	0 (0)
Platelets decrease	15 (37.5)	7 (17.5)	22 (57.9)	1 (2.6)	16 (41.0)	5 (12.8)	23 (62.2)	1 (2.7)
Anorexia	8 (20.0)	3 (7.5)	8 (21.1)	3 (7.9)	12 (30.8)	2 (5.1)	7 (18.9)	4 (10.8)
HYPERKALIEMIA	5 (12.5)	1 (2.5)	4 (10.5)	0 (0)	4 (10.3)	1 (2.6)	8 (21.6)	3 (8.1)
HYPOALBUMINEMIA	9 (22.5)	1 (2.5)	8 (21.1)	2 (5.3)	8 (20.5)	3 (7.7)	7 (18.9)	3 (8.1)
HYPOCALCEMIA	4 (10.0)	1 (2.5)	5 (13.2)	0 (0)	8 (20.5)	0 (0)	4 (10.8)	0 (0)
HYPONATREMIA	4 (10.0)	4 (10.0)	3 (7.9)	4 (10.5)	5 (12.8)	4 (10.3)	10 (27.0)	3 (8.1)
FATIGUE	10 (25.0)	16 (40.0)	13 (34.2)	13 (34.2)	15 (38.5)	10 (25.6)	11 (29.7)	10 (27.0)

Table 3 Efficacy results in the overall population

	Arm A Sorafenib ($n = 41$)	Arm B Pravastatin ($n = 39$)	Arm C Sorafenib + pravastatin ($n = 40$)	Arm D BSC ($n = 37$)
Intent-to-treat population				
Median TTP	3.5 months	2.8 months	2.0 months	2.2 months
Median PFS	3.3 months [95% CI: 1.9–4.8]	2.2 months [95% CI: 1.3–3.7]	3.4 months [95% CI: 2.0–4.4]	2.5 months [95% CI: 1.9–4.3]
Median OS	3.8 months [95% CI: 2.4–6.5]	3.1 months [95% CI: 1.9–4.3]	4.0 months [95% CI: 3.2–5.5]	3.5 months [95% CI: 2.2–5.4]
Median time to definitive deterioration of global quality of life	2.1 months	2.6 months	2.9 months	1.8 months
Per protocol population	Arm A Sorafenib ($n = 20$)	Arm B Pravastatin ($n = 29$)	Arm C Sorafenib + pravastatin ($n = 23$)	Arm D BSC ($n = 35$)
Median PFS	5.9 months [95% CI: 2.7–8.3]	3.6 months [95% CI: 1.9–3.9]	5.2 months [95% CI: 3.8–6.2]	2.5 months [95% CI: 1.9–4.3]
Median OS	6.5 months [95% CI: 3.4–9.6]	4.3 months [95% CI: 2.8–10.8]	5.5 months [95% CI: 4.0–9.0]	3.5 months [95% CI: 2.2–5.4]

TTP time to progression, *PFS* progression-free survival, *OS* overall survival

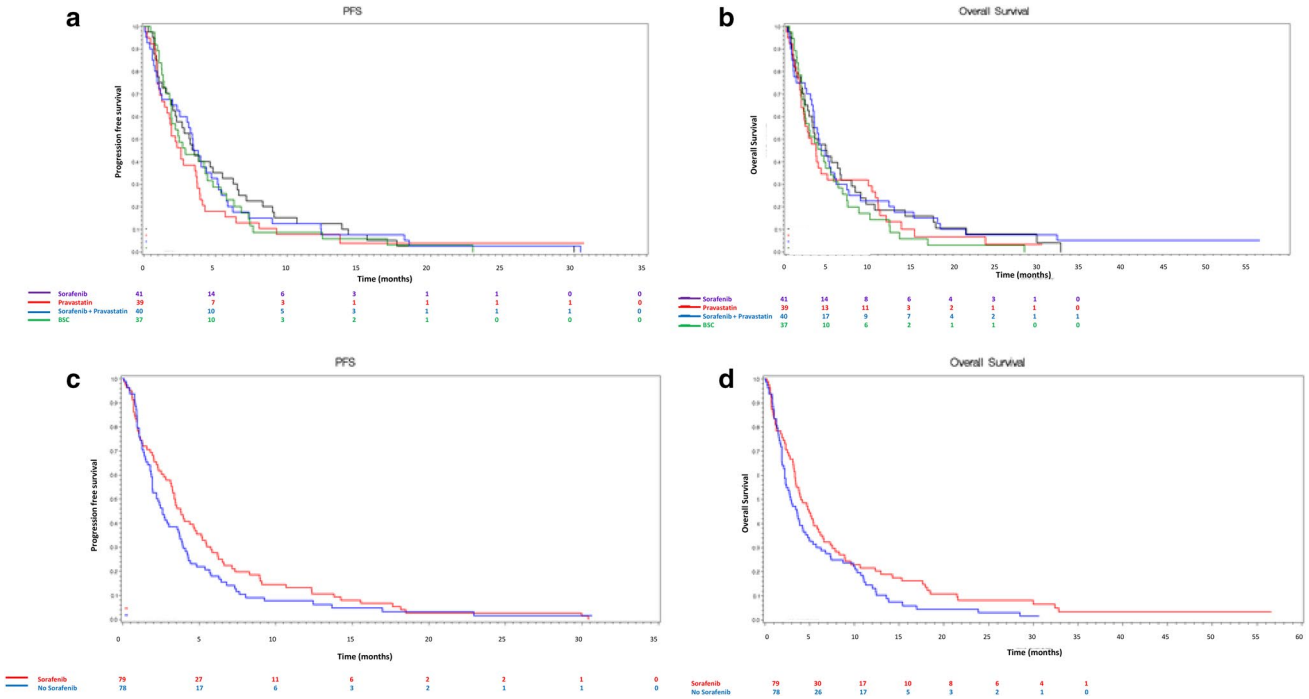

Fig. 2 Kaplan–Meier curves for **a** Progression-Free Survival (PFS) and **b** Overall Survival (OS) in the 4 arms; and Kaplan–Meier curves for **c** Progression-Free Survival (PFS) in patients treated or not by sorafenib and **d** Overall Survival (OS) in patients treated or not by sorafenib

Results

Characteristics of the population

160 patients were included between November 2011 and May 2016. 3 patients subsequently withdraw their consent, and 157 patients were included in the final analysis (Fig. 1).

Baseline characteristics of the patients are reported in (Table 1).

Safety

The median duration of treatment by sorafenib was 1.8 months in arm A and 0.8 month in arm C, the median duration of treatment by pravastatin was 2.1 months in arm B and 1.0 month in arm C. Interruption or dose reduction was applied for sorafenib in 70% in arm A and 59% in arm C, and for pravastatin in 50% in arm B and 56% in arm C.

Adverse events occurring in at least 10% of patients of any arm, related or not to study drug, as well as events of special interest (vascular adverse events and liver functions events) are presented in Table 2. Overall, the adverse events were as expected for sorafenib treatment, and many were also seen in the BSC arm.

Efficacy in the overall population

Median follow-up was 3.6, 2.8, 4.0 and 2.9 months in arms A, B, C and D, respectively. Patients experienced radiological progression and death without progression in 12 (29%) and 28 (68%); 19 (49%) and 18 (46%); 11 (28%) and 29 (73%); and 12 (32%) and 24 (65%) in arms A, B C and D, respectively. Causes of death were considered by investigators as at least in part related to cancer and cirrhosis in 24 (63%) and 13 (34%); 30 (83%) and 6 (17%); 27 (71%) and 11 (29%); and 26 (72%) and 11 (31%) in arms A, B, C and D, respectively. Only 1 death was considered related to treatment, in the sorafenib + pravastatin arm.

Due to the high number of patients with death without progression event, analysis of the primary endpoint TTP was limited by a low number of events in each arm. Results are presented in Table 3 and Fig. 2a, b. Median TTP of 2.2 months in arm D was in line with our H0 hypothesis (10 weeks), and none of the other arms reached the H1 hypothesis of 18 weeks (median TTP of 3.5, 3.0 and 2.0 in arms A, B and C, respectively). No trend was seen for difference in either TTP, PFS or OS in the intent-to-treat population; results in the per protocol populations were similar, however, a trend for different PFS was suggested.

130 patients completed baseline QLQ-C30 questionnaires and were evaluated for the time to definitive deterioration of global quality of life. There was no significant difference between arms (Table 3).

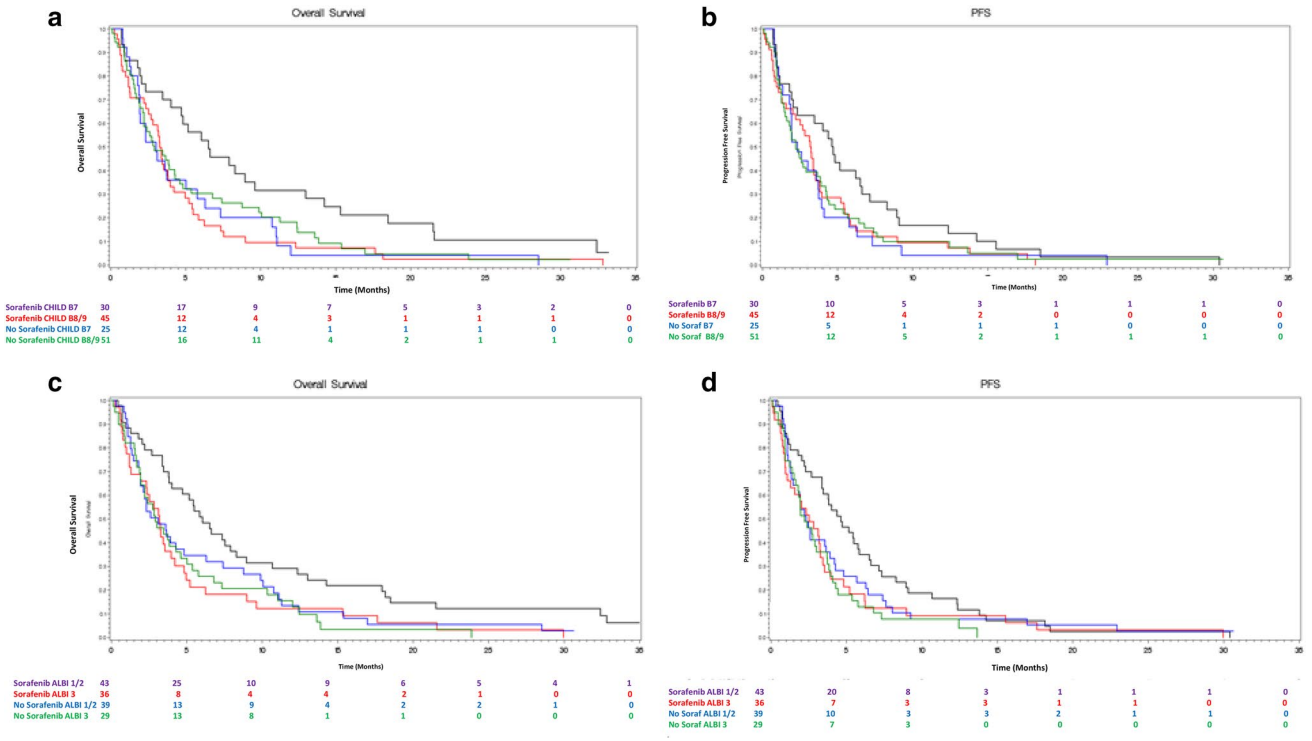

Fig. 3 Kaplan–Meier curves of **a** Overall Survival in patients treated or not with sorafenib, according to CP scores, **b** Progression-Free Survival in patients treated or not with sorafenib, according to CP scores, **c** Overall Survival in patients treated or not with sorafenib, according to ALBI grade and **d** Progression-Free Survival in patients treated or not with sorafenib, according to ALBI grade

A cox regression analysis of factors associated with OS was built. In univariate analysis, Performance Status less than 2, maximum tumor size 50 mm or less, ALBI grade 2 vs 3, absence of metastasis, bilirubin less than 50 mcmol/L, the absence of portal vein thrombosis, AFP level less than 85 µmol/L, Gamma Glutamyl Transferase level less than 3xULN were associated with better OS. In multivariate analysis, Performance status less than 2, maximum tumor size 50 mm or less, bilirubin level less than 35 µmol/L and the absence of portal vein thrombosis were associated with better OS.

Exploratory analysis of sorafenib-treated and non-sorafenib-treated patients in the overall population and across subgroups according to liver functions

As sorafenib is the most prescribed drug in the CP B population, we then pooled together arm A and C on the one hand, and arm B and D on the other hand, to perform exploratory analyses in patients treated with sorafenib ($n=79$) and patients not treated with sorafenib ($n=78$). No clear difference was suggested in either TTP, PFS or OS (Fig. 2c, d).

We then performed exploratory subgroup analysis in patients according to liver function (Supplementary Table 2). There were more patients classified as ALBI grade 1/2 than patients with CP B7. There was about a two-fold increase in median PFS and OS in favor of sorafenib in patients with better liver function (either CP B7 or ALBI grade 1/2), which was not the case in patients with worse liver functions (Fig. 3). For patients with CP B7 and ALBI grade 1/2, respectively, median OS was 6.5 months (95% CI: 4.0–9.6) and 6.1 months (95% CI: 3.8–8.3) for patients treated with sorafenib and 3.0 months (95% CI: 1.9–5.8) and 3.1 months (95% CI: 1.9–4.8) for patients not treated with sorafenib.

Discussion

The PRODIGE 21 is the first randomized trial completed in HCC specifically in the CP B population. Prospective studies are difficult to conduct in such population [23]. The first result of this study is the confirmation of the poor prognosis of patients with HCC and CP B cirrhosis, with median OS ranging from 3.1 to 4.0 months across the 4 arms of the trial. This also confirms that our trial population is representative of the CP B patients seen in routine care. The second important result is that overall in the CP B population, neither sorafenib nor pravastatin were associated with a trend for better OS. The third important observation is that

some trend toward benefit of sorafenib might appear when we select patients with better liver functions, namely CP B7 or ALBI grades 1/2, for whom median OS was numerically 3 months longer in patients treated with sorafenib. Even if the treatment field of HCC has clearly changed with the phase III Imbrave150 trial demonstrating superiority of the atezolizumab–bevacizumab combination over sorafenib, our results are still important to inform decision of systemic treatment, possibility with other therapies such as immunotherapy. Moreover, sorafenib will continue to play a role in patients progressing after atezolizumab–bevacizumab, a significant proportion of them having also their liver function deteriorated to CP B status. Finally, safety does not seem to be the major issue in this setting, with adverse events reported at similar frequencies as in the CP A population.

The results of the sorafenib arms are in line with previous reports in the CP B population [16, 17, 24, 25]. The previous studies indeed pointed at a worse prognosis in this population. However, the previous studies did not allow to estimate any potential benefit of sorafenib, as none was able to provide an adequate control group. Our study clearly indicates that when taken as a whole, the CP B population would not derive meaningful benefit from sorafenib treatment. However, the subgroup analysis does suggest that patients with better liver function might benefit. The non-comparative nature of this phase 2 trial does not allow to draw definitive conclusions, however suggests that sorafenib should only be considered in the patients with better liver function in the CP B population. Given the evolving nature of systemic treatment in HCC, and given that the BOOST trial (NCT 01405573) has been terminated due to low accrual, there is little chance that we will have better evidence as regards the potential benefit of sorafenib in this population. However, our trial might also inform on potential design for clinical studies with new treatment strategies involving immunotherapy.

Importantly, our trial was performed in a population with underlying liver disease of mainly alcoholic origin. This population could be more difficult to treat, in comparison to viral etiologies were successful antiviral therapies might improve liver functions. In our population, alcohol withdrawal could in some instance improve liver functions, but with less efficacy than with antiviral therapies. As such, our results might be difficult to generalize to other populations.

As regards to pravastatin, our trial did not show any benefit. This is in line with the PRODIGE 11 trial, which tested sorafenib ± pravastatin in the advanced HCC CP A population, with a negative result [21].

Results of nivolumab in a CP B cohort were released at the 2018 AASLD meeting [26]. Waiting for publication, limited results are available. However, the reported response rate of 10% and median OS of 7.6 months suggest a lower efficacy than in the CP A cohort. This would advocate for the need of a randomized study of immune checkpoint inhibitor or combinations in this context.

The most used system to evaluate liver function in cirrhosis is the CP system. However, many limitations were extensively discussed about this system, especially in the context of treatment of HCC [7, 27], and many different versions of the CP system are in frequent use [28]. Conversely, ALBI was created using an evidence-based approach, includes 2 variables easily available and objective, was developed also for patients without cirrhosis, and the score can be calculated using online-tool, the grade can be easily assigned with a heat map. All these arguments advocate for incorporation of ALBI in the evaluation of patients treated for HCC.

The primary endpoint of the PRODIGE 21 trial was TTP. It was chosen at a time when expert consensus recommended TTP as the primary endpoint for phase 2 trials [29]. However, in retrospect this endpoint did not appear to be adequate. Firstly, TTP was never demonstrated to be a surrogate for OS in HCC. Moreover, a high proportion of our patients did not have radiological progression documented, despite a planned intensive radiological follow-up every month, due to rapid clinical deterioration. Finally, the OS or PFS endpoints are of more relevance to demonstrate some clinically-meaningful benefit.

This study has some limitations. We already discussed the non-comparative design, as well as the choice of the primary endpoint. Moreover, the ALBI analyses were not preplanned, as the score was not described at the time of conception of the trial. The trial accrued slowly and across 35 sites; we did not record the number of patients assessed for screening. However, this also can be viewed as a force to be able to complete the planned accrual, and to the generalizability of the results. Some imbalances in baseline characteristics exist between the treatment arms; however, the baseline characteristics, with the majority of the population PS > 0, and a significant population with adverse prognostic factors (87% BCLC C) suggest that we are in a population representative of the daily practice CP B population. However, our population included mainly patients with cirrhosis from alcohol consumptions, and results might not be generalizable to other populations. We used standard dose of sorafenib, while a frequent practice would be to start at a lower dose. However, the type and rates of adverse events did not seem different from what is expected. The analysis of GIDEON suggested that despite equivalent starting doses between the CP A and B cohorts (72% and 70% starting at full dose, respectively), there was in fact more dose reduction in the CP A cohort (40% vs 29%), which does not support the necessity of lower starting dose in the CP B group [17]. Finally, our analyses based on liver functions are exploratory.

In conclusions, the PRODIGE 21 trial results suggest that in the overall CP B population, a BSC approach should be the standard treatment. However, more appropriate selection of patients could be made by restricting the population for systemic treatment to CP B7 or ALBI grade 1/2. This should be confirmed by future studies, especially in the context of the evolutions of systemic treatment of HCC towards multiple lines of antiangiogenic therapies and immunotherapy. Our trial might inform future research in this new context.

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Compliance with ethical standards

Conflict of interest Jean-Frédéric Blanc received honoraria from Bayer, Ipsen, Roche, outside the submitted work. Jean-Pierre Bronowicki received honoraria from Bayer outside the submitted work. Julien Edeline received honoraria from Roche, Bayer, Eisai, Ipsen, MSD, BMS, AstraZeneca, BTG, Amgen, Beigene, outside the submitted work.

Ethical approval This study was approved by an ethic committee and conducted under the principles of the declaration of Helsinki. The trial was approved by the Ethics Committee 'Comité de protection des personnes Sud Ouest et Outre Mer III' on the 23/02/2020.

Informed consent All patients provided written informed consent.

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