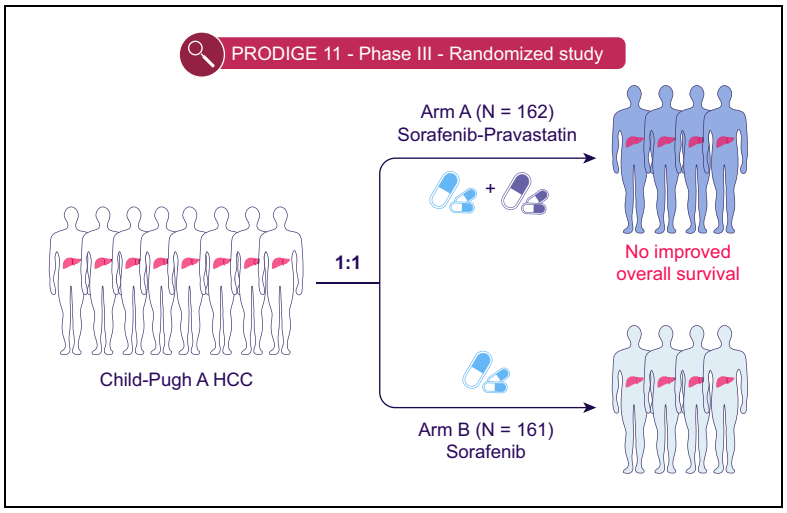
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma

Graphical abstract



Highlights

- Phase III, multicenter study, comparing sorafenib + pravastin to sorafenib alone in Child-Pugh A patients with HCC.
- The sorafenib-pravastatin combination did not improve overall survival in our study population.
- Significant prognostic factors for overall survival were CLIP score, performance status, and QoL scores.
- In multivariate analysis, only CLIP score was a prognostic factor for overall survival.
- The anticancer effect of statins may be more evident in the adjuvant setting, or in the early stages of carcinogenesis.

Authors

Jean-Louis Jouve, Thierry Lecomte, Olivier Bouché, ..., Jacques Denis, Sylvain Manfredi, Jean-Marc Phelip

Correspondence

jean-louis.jouve@chu-dijon.fr
(J.-L. Jouve)

Lay summary

Sorafenib has proven efficacy for the treatment of patients with advanced hepatocellular carcinoma. However, overall survival remains poor in these patients, so we were interested to see if the addition of a statin, pravastatin, improved outcomes in patients with advanced HCC. This randomized-controlled trial demonstrated that the sorafenib-pravastatin combination did not improve overall survival in this study population compared to sorafenib alone.

http://dx.doi.org/10.1016/j.jhep.2019.04.021

Research Article
Cancer

JOURNAL OF HEPATOLOGY

Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma

Jean-Louis Jouve[1,*], Thierry Lecomte[2], Olivier Bouché[3], Emilie Barbier[4], Faiza Khemissa Akouz[5], Ghassan Riachi[6], Eric Nguyen Khac[7], Isabelle Ollivier-Hourmand[8], Maryline Debette-Gratien[9], Roger Faroux[10], Anne-Laure Villing[11], Julien Vergniol[12], Jean-François Ramee[13], Jean-Pierre Bronowicki[14], Jean-François Seitz[15], Jean-Louis Legoux[16], Jacques Denis[17], Sylvain Manfredi[1,18], Jean-Marc Phelip[19], on behalf of PRODIGE-11 investigators/collaborators[†]

[1]*Department of Hepato-Gastroenterology, University Hospital F. Mitterrand, Dijon, France;* [2]*Department of Hepato-Gastroenterology, University Hospital Trousseau, Tours, France;* [3]*Department of Hepato-Gastroenterology, Robert Debré Hospital, Reims, France;* [4]*Fédération Française de Cancérologie Digestive (FFCD), Dijon, France;* [5]*Department of Hepato-Gastroenterology, Saint-Jean Hospital, Perpignan, France;* [6]*Department of Hepato-Gastroenterology, University Hospital Charles Nicolle, Rouen, France;* [7]*Department of Hepato-Gastroenterology, University Hospital Nord, Amiens, France;* [8]*Department of Hepato-Gastroenterology, University Hospital Côte de Nacre, Caen, France;* [9]*Department of Hepato-Gastroenterology, University Hospital Dupuytren, Limoges, France;* [10]*Department of Hepato-Gastroenterology, Les Oudairies Hospital, La Roche-sur-Yon, France;* [11]*Department of Medical Oncology, Auxerre Hospital, Auxerre, France;* [12]*Department of Hepato-Gastroenterology, University Hospital Haut-Lévêque, Pessac, France;* [13]*Department of Medical Oncology, Centre Catherine de Sienne, Nantes, France;* [14]*INSERM U954, University of Lorraine and University Hospital of Nancy, Vandoeuvre-les-Nancy, France;* [15]*Department of Oncology and Hepato-Gastroenterology, University Hospital La Timone, Marseille, France;* [16]*Department of Hepato-Gastroenterology, La Source Hospital, Orléans, France;* [17]*Department of Hepato-Gastroenterology, Louise Michel Hospital, Evry, France;* [18]*INSERM U1231, University of Bourgogne - Franche-Comté, Faculté de Médecine, Dijon, France;* [19]*Department of Hepato-Gastroenterology, University Hospital of Saint-Etienne – Hôpital Nord, Saint-Priest-en-Jarez, France*

Background & Aims: Sorafenib is the standard of care for advanced hepatocellular carcinoma (HCC). Combining sorafenib with another treatment, to improve overall survival (OS) within an acceptable safety profile, might be the next step forward in the management of patients with advanced HCC. We aimed to assess whether a combination of sorafenib and a statin improved survival in patients with HCC.

Methods: The objective of the PRODIGE-11 trial was to compare the respective clinical outcomes of the sorafenib-pravastatin combination (arm A) versus sorafenib alone (arm B) in patients with advanced HCC. Child-Pugh A patients with advanced HCC who were naive to systemic treatment (n = 323) were randomly assigned to sorafenib-pravastatin combination (n = 162) or sorafenib alone (n = 161). The primary endpoint was OS; secondary endpoints were progression-free survival, time to tumor progression, time to treatment failure, safety, and quality of life.

Results: After randomization, 312 patients received at least 1 dose of study treatment. After a median follow-up of 35 months, 269 patients died (arm A: 135; arm B: 134) with no difference in median OS between treatments arms (10.7 months *vs.* 10.5 months; hazard ratio = 1.00; $p = 0.975$); no difference was observed in secondary survival endpoints either. In the univariate analysis, the significant prognostic factors for OS were CLIP score, performance status, and quality of life scores. The multivariate analysis showed that the only prognostic factor for OS was the CLIP score. The main toxicity was diarrhea (which was severe in 11% of patients in arm A, and 8.9% in arm B), while severe nausea-vomiting was rare, and no toxicity-related deaths were reported.

Conclusion: Adding pravastatin to sorafenib did not improve survival in patients with advanced HCC.

Lay summary: Sorafenib has proven efficacy for the treatment of patients with advanced hepatocellular carcinoma. However, overall survival remains poor in these patients, so we were interested to see if the addition of a statin, pravastatin, improved outcomes in patients with advanced HCC. This randomized-controlled trial demonstrated that the sorafenib-pravastatin combination did not improve overall survival in this study population compared to sorafenib alone.

Clinical trial number: NCT01075555.

Introduction

Hepatocellular carcinoma (HCC) incidence is still growing in Western countries.[1,2] Tumor development is frequently related to liver damage, typically caused by cirrhosis. While curative treatments (transplantation, resection, percutaneous destruction) can be proposed for small tumors, about two-thirds of patients are not eligible for such treatments.[3]

Sorafenib, a tyrosine kinase inhibitor that targets signaling pathways involved in tumor cell proliferation (Ras-Raf-MAPK) and intracellular angiogenesis (VEGF-R, PDGF-R, *Ras*), demonstrated its efficacy as a treatment for advanced HCC. Two major randomized phase III trials showed that sorafenib significantly

Keywords: Tyrosine kinase inhibitors; Statins; Liver cancer; HCC; Systemic therapy; RCT.
Received 30 October 2018; received in revised form 23 April 2019; accepted 30 April 2019; available online 22 May 2019

* Corresponding author. Address: Service d'Hépato-Gastroentérologie, CHU F. Mitterrand, 14 rue Gaffarel, BP 77908, 21079 Dijon Cedex, France.
E-mail address: jean-louis.jouve@chu-dijon.fr (J.-L. Jouve).

† Please see the Supplementary Appendix for a list of the PRODIGE 11 investigators/collaborators.

improved overall survival (OS) and time to progression (TTP) compared to placebo, especially in patients with Child-Pugh A liver function.[4,5] Those results made sorafenib the standard of care for advanced HCC and led to its approval for this indication. However, median OS remains limited to about 11 months; therefore, the question of combining sorafenib to another treatment in order to improve OS with an acceptable safety profile is highly relevant.

Among potential substances that could be combined with sorafenib, 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.[6] 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. Moreover, the deregulation of cholesterol synthesis in HCC cells, particularly in mitochondria is implicated in their chemoresistance.[7] Indeed, statins demonstrated antitumoral properties both experimentally and clinically, especially in digestive cancers.[8–10] Pravastatin is one of the most widely studied statins. It has been shown that pravastatin inhibits *in vitro* and *in vivo* HCC tumor growth, and has a pro-apoptotic action on tumoral liver cell lines.[11,12] The antiproliferative activity is associated with a decrease in expression and activation of matrix metallopeptidase 2 and 9, which represents an original mechanism of action.[13] Thus, the combination of pravastatin and sorafenib appears to be promising for HCC: action on tumor cell proliferation by acting on 1 of the 2 main signaling pathways (Raf-Ras-MAPK) through 2 distinct mechanisms, and anti-invasive and anti-metastatic action of pravastatin as a complement to the anti-angiogenic action of sorafenib.

Beside biology, the potential HCC prevention effect of statin use was emphasized by a meta-analysis (adjusted odds ratio 0.63; 95% CI 0.52–0.76).[14]

In the field of HCC, there were only 2 clinical studies about the therapeutic interest of pravastatin. In a previous open-label trial published in 2001, 83 patients with advanced HCC, mostly Child-Pugh B, were treated by transarterial chemoembolization followed by fluoroacil for 2 months, then randomized to pravastatin or no added treatment. The median OS was significantly improved in patients with pravastatin (18 months *vs.* 9 months in the control arm; $p = 0.006$).[15] The second one, a randomized phase II trial conducted on 58 patients with advanced HCC, suggested that median OS was significantly longer for patients receiving pravastatin (7.2 months) than for patients receiving gemcitabine (3.5 months).[16]

In terms of safety, pravastatin has a good liver safety profile, including in cirrhotic patients, with 0.6% of cytolysis exceeding 2× the upper limit of normal (ULN).[17,18] Lastly, pravastatin metabolism is independent of CYP3A4, limiting drug interactions with sorafenib. Thus, the combination of sorafenib with pravastatin seemed promising in the treatment of HCC because of complementary mechanisms of action and limited risks of interactions.

The purpose of the PRODIGE-11 trial was to compare OS in Child-Pugh A HCC patients treated with a combination of sorafenib-pravastatin or sorafenib alone. The secondary objectives were progression-free survival (PFS), TTP, time to treatment failure (TTF), safety, and baseline quality of life (QoL).

Patients and methods

Study population

Patients of at least 18 with a histologically proven HCC. If an histological exam was not feasible (ascites, coagulation disorders), the diagnosis could be made in cases of cirrhosis by identification of 1 liver focal lesion larger than 10 mm, either on the basis of 2 dynamic imaging techniques for tumors <2 cm, or on the basis of 1 dynamic imaging technique for tumors ≥2 cm (according to the European Association for the Study of the Liver/American Association for the Study of Liver Diseases 2005 criteria). Patients had to be ineligible for curative treatment, chemoembolization, or have a progressing HCC after failure of a specific treatment. Other criteria: CLIP score[19] between 0–4, Child-Pugh score A, liver aminotransferases ≤5× ULN, blood creatinine ≤1.5× ULN, World Health Organization-performance status (WHO-PS) 0–2, life expectancy >12 weeks, and availability for regular follow-ups. Patients receiving a vitamin K antagonist were eligible if no major coagulation disorder was diagnosed before the onset of the oral anticoagulant.

The absence of consumption of any statin before inclusion in the study was carefully investigated by the practitioners.

Patients were not eligible if they had a recent or present life-threatening extrahepatic disease, another progressing tumoral disease (except *in situ* uterine cervix carcinoma, superficial bladder cancer, treated basal cell carcinoma, or other cancer treated for more than 3 years), a cardiac disease (heart failure New York Heart Association class ≥2, uncontrolled hypertension or arrhythmia, myocardial infarct <6 months), digestive bleeding <1 month; pregnant or breast-feeding women were also excluded.

Written informed consent was obtained before randomization. The protocol was reviewed and approved by the Ethics Committee/Institutional Review Board (CCPPRB Est-1) and the study was conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements. The study was registered under the number NCT01075555.

Treatment

The treatment was started within 15 days after randomization. Patients were assigned to receive oral sorafenib 400 mg twice daily combined with oral pravastatin (drug intake during the dinner) 40 mg per day (arm A), or oral sorafenib 400 mg twice daily (arm B). Patients received the treatment until death or treatment discontinuation due to serious adverse events, patient refusal, or WHO-PS ≥3. Isolated radiological progression, even with QoL improvement, was not considered a criterion for discontinuation. The final decision was left to patient and/or investigator's discretion. Patients had access to any useful symptomatic treatment.

Assessments

Clinical examinations had to be performed 2 weeks before enrollment, consisting of identification by an individual number, disease history, cirrhosis etiology, weight, physical exam, WHO-PS, and QoL questionnaires (European Organisation for Research and Treatment of Cancer core quality of life questionnaire [QLQ-C30] and functional assessment of cancer therapy-hepatobiliary [FACT-HEP]). Biological exams, performed 2 weeks before enrollment, consisted of: absolute blood count including platelets, prothrombin time, serum albumin, liver transaminases, alkaline phosphatase, blood creatinine,

alpha-fetoprotein, total cholesterol, triglycerides, and creatine phosphokinase. Hepatitis B virus antigens and hepatitis C virus antibodies had to be measured 3 months before enrollment, except in cases of a known previous infection. Morphological exams, performed 1 month before enrollment, included imaging by thoraco-abdominal CT-scan, or abdominal MRI and thoracic CT-scan. Tumor volume was defined according to Response Evaluation Criteria in Solid Tumors (or RECIST) criteria (version 1.1), and portal thrombosis (truncal or lobar) was explored.

During treatment, a consultation was performed every 4 weeks taking into account the biological exams and the regular intake of sorafenib and pravastatin, which was assessed by questioning and examination of pill packets. Every 12 weeks, an imaging identical to baseline was performed. Safety was evaluated with the NCI-CTC v2.0 grade.

Study design

This trial was phase III, multicenter, open-label, controlled, and randomized. The primary objective was to compare OS between patients receiving sorafenib-pravastatin versus sorafenib alone in Child-Pugh A patients with HCC. Secondary comparisons included PFS, TTP, TTF, QoL, and safety. Patients were randomized 1:1 using minimization technique, and stratified according to center, CLIP score (0 *vs.* 1 *vs.* 2–4), WHO-PS (0 *vs.* 1 *vs.* 2), and extrahepatic metastases.

Sample size determination and statistical analysis

The primary endpoint was OS defined as time from randomization until death from any cause. The trial was designed to detect an increase in median OS of 3.5 months (10 months with sorafenib alone; 13.5 months with sorafenib-pravastatin; hazard ratio [HR] = 0.74) with a power of 80% and a 2-sided type I error of 5%. Scheduled inclusion level was 15 patients per month for 32 months. The estimated rate of loss to follow-up was 5%. These hypotheses required 474 patients to be enrolled for 360 events. One interim analysis was prospectively planned when 180 deaths were registered to control combination safety and efficacy, using the alpha spending function and ranges defined in the O'Brien-Fleming method.[20] Interim analysis was performed in October 2013 after 53% of expected deaths had occurred (*i.e.* 190 deaths and 281 recruited patients), indicating the superiority of one treatment arm over the other was uncertain. Therefore, the recruitment was stopped in November 2013. The present report reflects the final analysis after recruitment interruption.

Secondary endpoints were PFS defined as time from randomization until first radiological and/or clinical progression or death (whatever the cause); TTP defined as time from randomization until first radiological and/or clinical progression according to physician assessment; and TTF defined as time from randomization until final treatment interruption.

The intention-to-treat (ITT) population was defined as all enrolled patients irrespective of eligibility criteria and treatment. The population assessable for safety was defined as patients who received 1 dose of study treatment. Qualitative data were presented as a percentage and compared using chi-square test or Fisher's exact test. Quantitative data were described using mean, standard deviation, median and range, and were compared with Student or Wilcoxon tests. Survival data were computed according to the Kaplan-Meier method, and survival curves were compared using the log-rank test. Univariate Cox models were used to calculate the HR with 95% CI. Proportional risks hypothesis was tested using the Schöenfeld residuals. Cox regression methods were used to determine prognostic factors, and those with a p value <0.15 in univariate analyses were kept for multivariate analyses. Median follow-up was calculated using the reverse Kaplan-Meier method.

Compliance to sorafenib and pravastatin was calculated as the ratio of real dose (sum of the dose of each delivered tablet)/theoretical dose (sum of the dose of each scheduled tablet).

For further details regarding the materials and methods used, please refer to the CTAT table and supplementary files.

Results

Demographics

From March 2010 to November 2013, 323 patients were randomized in 61 centers: 162 in the sorafenib-pravastatin arm (arm A) and 161 in the sorafenib arm (arm B). The study flow chart is presented in Fig. 1. The main baseline characteristics are presented in Table 1. Baseline characteristics were well-balanced between treatment arms, except for sex distribution with a higher rate of men in arm A ($p = 0.01$). Overall, 274 patients (86.2%) had an associated cirrhosis, related to alcohol alone in 55.6% of cases, viral infection alone in 13.3% of cases, hemochromatosis alone in 3%, other cause in 11.5%, or combined etiology in 16.7%.

Baseline quality of life

QoL was assessed before the onset of treatment (Table 2, Table 3). QoL items were well-balanced between treatment arms, except for diarrhea, which was more frequent in patients randomized in arm A ($p = 0.004$) and for hepatobiliary cancer subscale, which was higher in patients randomized in arm B ($p = 0.04$).

Treatment

After randomization, 312 patients received at least 1 dose of study treatment, 155 in arm A and 157 in arm B (Fig. 1). Median duration of treatment was 4.1 months (range: 0.03–50.9) in arm A and 3.6 months (range: 0.07–48.4) in arm B, with no

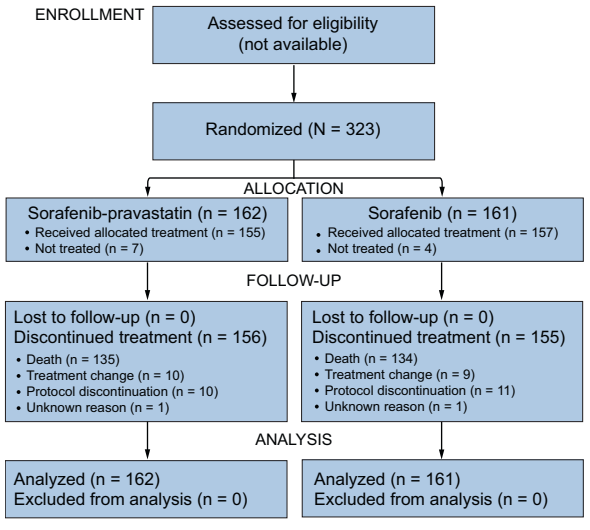


Fig. 1. Study flow chart (CONSORT diagram).

Table 1. Patient demographics.

Demographic	Sorafenib-pravastatin (n = 162)	Sorafenib (n = 161)
Age, years, median (range)	68 (37–86)	68 (39–85)
Male sex, n (%)	156 (96.3)	142 (88.2)
WHO-PS, n (%)		
0	80 (49.4)	89 (55.3)
1	75 (46.3)	64 (39.7)
2	7 (4.3)	8 (5.0)
CLIP score, n (%)		
0	7 (4.3)	11 (6.8)
1	66 (40.7)	64 (39.8)
2–4	89 (54.9)	86 (53.4)
Total cholesterol (mmol/L) mean(±SD)	4.50 (±1.19)	4.76 (±1.29)
Extrahepatic metastases, n (%)	47 (29.0)	49 (30.4)
Associated cirrhosis, n (%)	137 (85.6)	137 (86.7)
Missing	2	3
HCC diagnosis, n (%)		
Histological and/or cytological	78 (48.5)	76 (47.5)
EASL/AASLD 2005	83 (51.5)	84 (52.5)
Missing	1	1
Tumoral volume >50% of liver volume, n (%)	30 (19.1)	33 (21.0)
Missing	5	4
Type of extension, n (%)		
Uninodular	24 (14.8)	26 (16.2)
Multinodular	107 (66.1)	106 (66.2)
Diffuse	31 (19.1)	28 (17.5)
Missing	0	1
Portal thrombosis, n (%)	64 (39.7)	55 (34.6)
Missing	1	2
Esophageal varices, n (%)	51 (32.9)	60 (38.7)
Missing	7	6
Splenomegaly, n (%)	46 (28.9)	31 (19.6)
Missing	3	3

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; WHO-PS, World Health Organization – performance status.

Table 2. Quality of life assessment at baseline: QLQ-C30 questionnaire.

Items	Sorafenib-pravastatin (n = 162)	Sorafenib (n = 161)
Functional scales*, mean (±SD)		
Physical	78.0 (±21.3)	80.1 (±17.9)
Missing	36	34
Activity	79.1 (±29.0)	81.8 (±28.1)
Missing	35	32
Cognitive	84.9 (±19.5)	85.3 (±20.4)
Missing	34	32
Emotional	76.1 (±20.7)	75.8 (±24.8)
Missing	34	32
Social	87.6 (±21.1)	85.2 (±25.6)
Missing	36	35
Symptoms scales**, mean (±SD)		
Fatigue	34.9 (±24.7)	34.1 (±29.0)
Missing	34	32
Nausea-vomiting	4.3 (±13.4)	4.9 (±14.2)
Missing	34	32
Pain	26.0 (±28.2)	23.0 (±27.6)
Missing	35	32
Dyspnea	24.9 (±27.6)	25.5 (±27.0)
Missing	36	34
Insomnia	32.0 (±32.8)	31.8 (±35.2)
Missing	34	33
Appetite loss	22.9 (±30.9)	19.1 (±29.4)
Missing	34	32
Constipation	17.3 (±29.3)	17.3 (±29.3)
Missing	35	34
Diarrhea	15.3 (±24.5)	7.7 (±17.5)
Missing	36	35
Global health score*, n	126	127
Mean (±SD)	62.6 (±19.2)	60.2 (±25.0)
≤67, n (%)	87 (69.0)	86 (67.7)
>67, n (%)	39 (31.0)	41 (32.3)

*Scores range from 0 to 100, a higher score represents a higher (“better”) level of functioning.

**Scores range from 0 to 100, a higher score represents a higher (“worse”) level of symptoms. QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire.

difference between both treatment arms ($p = 0.38$). Median compliance to sorafenib was 91.5% in arm A, and 87.3% in arm B ($p = 0.79$). Median compliance to pravastatin was 98.7% in arm A. The main reason for treatment interruption was death.

Survival analysis

In November 2013, interim analysis showed that median OS was 9.5 months in arm A (95% CI 7.1–14.1) and 9.1 months in arm B (95% CI 6.4–11.8) ($p = 0.69$).

Final analysis showed median follow-up of 34.7 months (95% CI 32.4–37.5) in arm A, and 36.1 months (95% CI 28.1–47.3) in arm B.

The best tumor response was recorded in the ITT population, with at least 1 imaging assessment (n = 252; arm A = 127, arm B = 125; Table S1).

Overall, 269 patients died (n = 135 in arm A, and n = 134 in arm B). Deaths were related to disease progression, except for 3 patients who died from pulmonary infection (arm A), cholangiocarcinoma (arm A), and respiratory failure from choking (arm B); in 14 cases, the cause of death was unknown (arm A = 6: arm B = 8). There was no difference in OS between treatment arms (Table 4, Fig. 2A). In the univariate analysis, the significant prognostic factors for OS were CLIP score, WHO-PS, QLQ-C30 and FACT-HEP scores (Table 5). Only the CLIP score remained significant in multivariate analysis (Table 5).

Regarding secondary survival endpoints (PFS, TTP, and TTF), no statistically significant differences between treatment arms were observed (Table 4, Fig. 2B).

Safety

Toxicities occurring in more than 10% of patients, irrespective of severity, are presented in Table 6. Among digestive toxicities, severe (grade 3–4) nausea-vomiting were rare (arm A: 1.9%; arm B: 3.2%); the main digestive toxicity was diarrhea with severe events occurring in 11% of patients in arm A, and 8.9% in arm B. No toxic event was fatal.

Discussion

Based on a relevant rationale,[7–14] the PRODIGE-11 randomized, phase III trial was the first to investigate the contribution of pravastatin combined with sorafenib to improve the survival of Child-Pugh A patients with HCC. This study involved a representative medical community with university hospitals, regional hospitals, private hospitals, and anticancer centers. Unfortunately, this study failed to demonstrate any improvement in OS, compared to sorafenib alone, as well as in secondary survival endpoints (PFS, TTP, and TTF). Non-significant results of

Table 3. Quality of life assessment: FACT-HEP questionnaire.

Items	Sorafenib-pravastatin (n = 162)	Sorafenib (n = 161)
Wellbeing subscales*, mean (±standard deviation)		
Physical	23.0 (±4.6)	23.4 (±5.0)
Missing	40	35
Social/Family	19.5 (±5.9)	20.4 (±5.4)
Missing	43	38
Emotional	17.9 (±4.6)	17.2 (±4.7)
Missing	43	39
Functional	15.7 (±6.1)	15.9 (±6.3)
Missing	41	38
Hepatobiliary Cancer subscale*, mean (±SD)		
Cancer experience	56.2 (±8.4)	57.9 (±9.6)
Missing	41	38
Global scores*, mean (±SD)		
Trial outcome index**	93.6 (±18.7)	95.5 (±21.5)
Missing	39	35
FACT-G***	74.5 (±17.8)	75.5 (±17.1)
Missing	39	35
FACT-HEP global score, n	123	126
Mean (±SD)	129.8 (±26.5)	132.1 (±27.6)
≤135, n (%)	67 (54.5]	58 (46.0)
>135, n (%)	56 (45.5)	68 (54.0)

*Scores range from 0 to 100, a higher score represents a higher (“better”) level of well-being.
**Physical + functional + cancer experience index.
***Physical + social/family + emotional + functional index. FACT-G, functional assessment of cancer therapy-general; FACT-HEP, functional assessment of cancer therapy-hepatobiliary.

the interim analysis led to premature enrollment interruption. These results are strongly negative without any methodological bias. Negative results require us to review hypotheses that could explain our findings.

We can reasonably exclude a negative interaction between sorafenib and pravastatin, as sorafenib and the combination

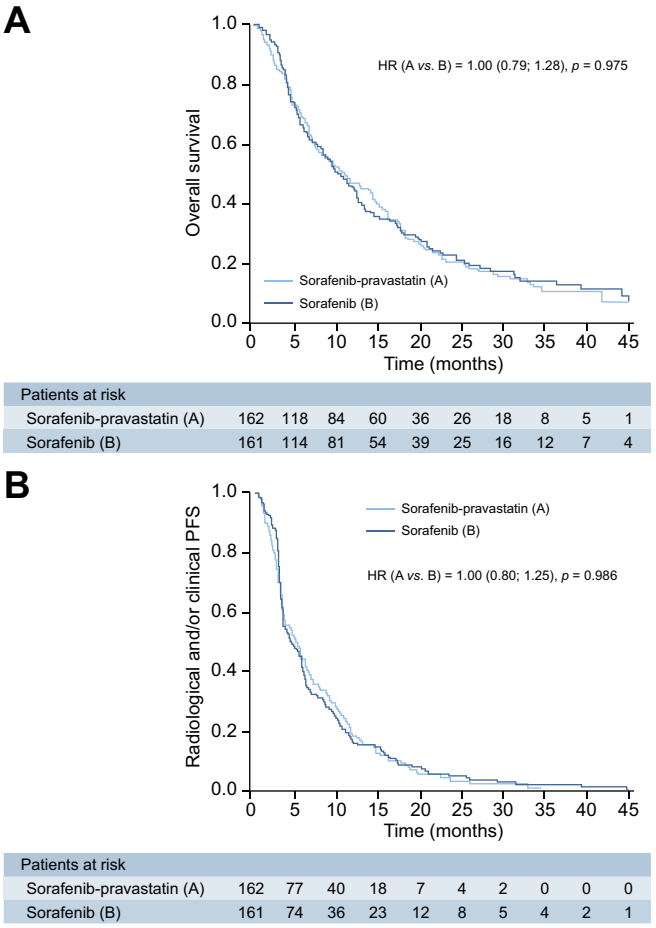


Fig. 2. Comparison of overall survival and progression-free survival in patients receiving sorafenib-pravastatin or sorafenib alone. (A) Overall survival and (B) progression-free survival curves; HR from Cox model and *p* value from log-rank test. HR, hazard ratio.

Table 4. Survival analysis.

Survival data	Sorafenib-pravastatin (n = 162)	Sorafenib (n = 161)	p*
OS			
Events, n	135	134	
Median OS, months (95% CI)	10.7 (7.7–14.3)	10.5 (8.2–12.4)	
1-year OS, % (95% CI)	47.2 (39.4–54.7)	44.9 (37.0–52.4)	
HR (95% CI)		1.00 (0.79–1.28)	0.975
PFS			
Events, n	147	153	
Median PFS, months (95% CI)	5.0 (3.4–6.0)	4.4 (3.3–5.6)	
1-year PFS, % (95% CI)	18.8 (13.0–25.4)	16.5 (11.1–22.8)	
HR (95% CI)		1.00 (0.80–1.25)	0.986
TTP			
Events, n	107	104	
Median TTP, months (95% CI)	6.1 (5.0–8.9)	6.0 (5.2–8.8)	
1-year TTP, % (95% CI)	26.9 (19.2–35.2)	28.3 (20.3–36.9)	
HR (95% CI)		1.06 (0.80–1.38)	0.698
TTF			
Events, n	144	146	
Median TTF, months (95% CI)	4.4 (3.4–6.5)	4.3 (3.3–5.7)	
1-year TTF, % (95% CI)	25.2 (18.6–32.3)	19.3 (13.5–25.1)	
HR (95% CI)		0.92 (0.73–1.16)	0.502

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTF, time to treatment failure.
*p: log-rank Test.

Table 5. Prognostic factors of overall survival.

	Univariate analysis			Multivariate analysis		
Prognostic factor	**HR**	**95% CI**	***p****	**HR**	**95% CI**	***p****
Sex (male *vs.* female)	1.33	0.83–2.13	0.230			
Age (≤70 *vs.* 70)	0.99	0.77–1.26	0.905			
Treatment (B *vs.* A)	0.96	0.76–1.23	0.763	0.94	0.71–1.25	0.688
CLIP score (2–4 *vs.* 0–1)	2.41	1.87–3.10	< 0.0001	2.54	1.88–3.44	< 0.0001
WHO-PS (2 *vs.* 0–1)	2.01	1.15–3.52	0.015	1.10	0.53–2.29	0.795
Extrahepatic metastases (no *vs.* yes)	1.23	0.64–1.61	0.134	1.30	0.95–1.77	0.098
QLQ-C30 (≤67 *vs.* >67)	1.44	1.06–1.94	0.019	1.38	0.96–1.99	0.080
FACT-HEP (≤135 *vs.* >135)	1.34	1.01–1.76	0.040	1.11	0.79–1.55	0.551

FACT-HEP, functional assessment of cancer therapy-hepatobiliary; HR, hazard ratio; QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire; WHO-PS, World Health Organization – performance status.
*Wald-test.

Table 6. Frequent toxicity according to NCI-CTC v2.0.

	Sorafenib-pravastatin (n = 155)		Sorafenib (n = 157)	
Toxicity, %	**Grade 1–2**	**Grade 3–4**	**Grade 1–2**	**Grade 3–4**
Hematologic toxicity				
Neutropenia	13.5	3.9	11.5	–
Anemia	60.0	5.2	53.5	6.4
Thrombocytopenia	58.7	7.1	53.5	5.1
Infections	10.3	8.4	11.5	3.2
Digestive toxicity	77.4	16.1	74.5	15.9
Anorexia	34.2	6.5	31.8	5.1
Asthenia	65.8	34.2	65.0	28.0
Hand-foot syndrome	43.2	14.8	35.0	9.6
Alopecia	11.6	–	12.1	–
Pruritis	16.1	–	10.8	–
Serum creatinine increase	20.0	1.3	19.1	0.6
Hepatobiliary disorders	94.2	67.1	97.5	52.9
Creatine kinase increase	18.7	0.6	19.1	–
Pain				
Abdominal	34.8	7.1	38.9	6.4
Muscular	15.5	1.9	12.1	–
Skeletal	16.8	3.9	17.8	3.2
Hemorrhage	9.7	3.9	10.2	5.7
Hypertension	8.4	1.9	11.5	4.5

provided similar results. Moreover, metabolic pathways of pravastatin do not interfere with those of sorafenib. The median OS and radiological PFS reported in the present study for sorafenib alone (10.5 months and 4.4 months, respectively) or sorafenib/pravastatin (10.7 months and 5.0 months, respectively) were close to those of the pivotal sorafenib trial (SHARP trial) with a median OS of 10.7 months and a median radiological PFS of 5.5 months.[5]

The PRODIGE-11 trial demonstrated that the sorafenib-pravastatin combination did not bring an OS improvement in our study population. Of course, it was not possible to evaluate the efficacy of pravastatin alone in those patients for ethical reasons.

Therefore, is there a proper effect of pravastatin itself? This will be analyzed in the PRODIGE 21 trial in Child-Pugh B patients with HCC, comparing the sorafenib-pravastatin combination to sorafenib alone, pravastatin alone and best supportive care. This study is closed for inclusion and analysis is ongoing.

An alternative hypothesis is that some patients could derive an advantage from pravastatin. Our study showed that classical prognostic factors predicted survival (CLIP score, WHO-PS, and QoL scales). Perhaps another statin would have been better? We chose pravastatin because it was the only statin investigated in clinical trials on HCC.

Perhaps the clinical anticancer effect of statins would be more evident in other situations; for example, in the adjuvant setting or the early stages of HCC carcinogenesis, as suggested by several retrospective studies after liver resection[21] or liver transplantation[22] for HCC with lower recurrence risk.

The preclinical studies have demonstrated molecular mechanisms by which statins promote anticancer effects. Many retrospective studies have suggested their potential benefits. Even if our study has clearly demonstrated no OS improvement with pravastatin in combination with sorafenib in advanced Child-Pugh A HCC, further prospective randomized studies are necessary to explore the potential oncologic interest of statins in clinical practice.

Financial support

The study was funded by the "Programme Hospitalier de Recherche Clinique" (PHRC) in 2009 (Institut National du Cancer [INCa]), and by "Ligue contre le cancer". Pravastatin was supplied by Sanofi, France.

Conflict of interest

Jean-Louis Legoux declared honoraria from Novartis. Jean-Marc Phelip declared honoraria from Bayer. Faiza Khemissa declared honoraria from Roche, Sanofi, Bayer. Isabelle Ollivier-Hourmand declared honoraria from Daichi, Bayer, Intercept Pharmaceuticals, Gilead Sciences, Abbvie, Boehringer Ingelheim. Jean-Pierre Bronowicki declared honoraria from Bayer. Jean-François Seitz declared honoraria from Bayer/Lilly/Novartis/Sanofi. All other authors declare no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Jean-Louis Jouve: conception and design; data acquisition, analysis and interpretation; writing; study supervision. Sylvain Manfredi: data collection, assembly, analysis and interpretation; writing and manuscript approval. Emilie Barbier: data analysis and interpretation, manuscript writing and approval. Faiza Khemissa Akouz, Thierry Lecomte, Olivier Bouche, Ghassan Riachi, Eric Nguyen Khac, Isabelle Ollivier-Hourmand, Maryline Debette-Gratien, Roger Faroux, Anne-Laure Villing, Julien Vergniol, Jean-François Ramee, Jean-Pierre Bronowicki,

Jean-François Seitz, Jean-Louis Legoux, Jacques Denis, Jean-Marc Phelip: collection and assembly of data, manuscript writing and approval.

Acknowledgements

We thank the FFCD operational team (statisticians, data managers and CRAs): Karine Le Malicot, Fadil Masskourri, Caroline Choine, Florence Guiliani, Nouredine Lasmi, Guillaume Arnould, Nathan Guiet, Morgane Maury-Nègre, Hicham Fattouh, Nicolas Le Provost, Jérémie Bez, and Cécile Girault; and Isabelle Chapelle-Marcillac for the editing support, and "Ligue contre le cancer".

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.04.021.

References

[1] La Vecchia C, Lucchini F, Franceschi S, Negri E, Levi F. Trends in mortality from primary liver cancer in Europe. Eur J Cancer 2000;36:909–915.
[2] El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004;127:S27–S34.
[3] Bruix J, Sherman M. Practice guidelines committee, American Association for the study of liver diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.
[4] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
[5] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[6] Kawata S, Takaishi K, Nagase T, Ito N, Matsuda Y, Tamura S, et al. Increase in the active form of 3-hydroxy-3-methylglutaryl coenzyme A reductase in human hepatocellular carcinoma: posible mechanism for alteration of colesterol biosynthesis. Cancer Res 1990;50:3270–3273.
[7] Montero J, Morales A, Llacuna L, Lluis JM, Terrones O, Basanez G, et al. Mitochondrial cholesterol contributes to chemotherapy resistance in Hepatocellular Carcinoma. Cancer Res 2008;68:5246–5256.
[8] Graaf MR, Richel DJ, van Noorden CJ, Guchelaar HJ. Effects of statins and farnesyltransferase inhibitors on the development and progression of cancer. Cancer Treat Rev 2004;30:609–641.
[9] Hindler K, Cleeland CS, Rivera E, Collard CD. The role of statins in cancer therapy. Oncologist 2006;11:306–315.
[10] Bhuket TP, Higgins PD. Drug insight: statins and gastrointestinal cancer. Nat Clin Pract Gastroenterol Hepatol 2006;3:552–562.
[11] Kawata S, Nagase T, Yamasaki E, Ishiguro H, Matsuzawa Y. Modulation of the mevalonate pathway and cell growth by pravastatin and d-limonene in a human hepatoma cell line (Hep G2). Br J Cancer 1994;69:1015–1020.
[12] Sutter AP, Maaser K, Höpfner M, Huether A, Schuppan D, Scherübl H. Cell cycle arrest and apoptosis induction in hepatocellular carcinoma cells by HMG-CoA reductase inhibitors. Synergistic antiproliferative action with ligands of the peripheral benzodiazepine receptor. J Hepatol 2005;43:808–816.
[13] Taras D, Blanc JF, Rullier A, Dugot-Senant N, Laurendeau I, Vidaud M, et al. Pravastatin reduces lung metastasis of rat hepatocellular carcinoma via a coordinated decrease of MMP expression and activity. J Hepatol 2007;46:69–76.
[14] Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of Hepatocellular Cancer: a systematic review and meta-analysis. Gastroenterology 2013;44:323–332.
[15] Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 2001;84:886–891.
[16] Lersch C, Schmelz R, Erdmann J, Hollweck R, Schulte-Frohlinde E, Eckel F, et al. Treatment of HCC with pravastatin, octreotide, or gemcitabine–a critical evaluation. Hepatogastroenterology 2004;51:1099–1103.
[17] Cohen DE, Anania FA, Chalasani N, National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. Am J Cardiol 2006;97:77C–81C.
[18] de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004;24:584–591.
[19] The Cancer of the Liver Italian Program (CLIP) Investigators. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000;31:840–845.
[20] DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–1352.
[21] Kawaguchi Y, Sakamoto Y, Ito D, Aita J, Akenaton N, Kancko J, et al. Statin use is associated with a reduced risk of hepatocellular carcinoma recurrence after initial liver resection. Biosci Trends 2017;11:574–580.
[22] Cho Y, Kim MS, Nam CM, Kang ES. Statin use is associated with decreased hepatocellular carcinoma recurrence in liver transplant patients. Sci Rep 2019;9:1467.