Undetectable HCV-RNA at treatment-week 8 results in high-sustained virological response in HCV G1 treatment-experienced patients with advanced liver disease: the International Italian/Spanish Boceprevir/Peginterferon/Ribavirin Name Patients Program

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SUMMARY. In many countries, first-generation protease inhibitors (PIs)/peginterferon/ribavirin (P/R) still represent the only treatment option for HCV-infected patients. Subjects with advanced disease and previous failure to P/R urgently need therapy, but they are under-represented in clinical trials. All treatment-experienced F3/4 Metavir patients who received boceprevir (BOC)+P/R in the Italian–Spanish Name Patient Program have been included in this study. Multivariate logistic regression analysis (MLR) was used to identify baseline and on-treatment predictors of SVR and adverse events (AEs). Four hundred and sixteen patients, mean age 57.7 (range 25–78 years), 70% males, 69.5% (289/416) F4, 14% (41/289) Child–Pugh class A6, 24% (70/289) with varices and 42% (173/416) prior null responders to P/R, were analysed. Overall, SVR rate (all 381 patients who received one dose of BOC) was 49%, (58% in F3, 45% in F4, 61% in relapsers, 51% in partial, 38% in null responders, and 72% in subjects with undetectable HCV-RNA at treatment-week (TW)8. Among patients with TW8 HCV-RNA ≥ 1000 IU/L, SVR was 8% (negative predictive value = 92%). Death occurred in 3 (0.8%) patients, while decompensation and infections were observed in 2.9% and 11%, respectively. At MLR, SVR predictors were TW4 HCV-RNA $\geq 1\log_{10}$-decline from baseline, undetectable TW8 HCV-RNA, prior relapse, albumin levels ≥ 3.5 g/dL and platelet counts $\geq 100\ 000/\mu$L. Metavir F4, Child-Pugh A6, albumin, platelets, age and female gender were associated with serious and haematological AEs. Among treatment-experienced patients with advanced liver disease eligible for IFN-based therapy, TW8 HCV-RNA characterised the subset with either high or poor likelihood of achieving SVR. Using TW8 HCV-RNA as a futility rule, BOC/P/R appears to have a favourable benefit–risk profile.

Keywords: boceprevir, cirrhosis, first-generation protease inhibitors, hepatitis C, IFN-based therapy.

INTRODUCTION

Hepatitis C virus -infected patients with advanced fibrosis and cirrhosis still represent a therapeutic challenge in the era of direct acting antiviral agents (DAAs) because of lower SVR rates and poorer tolerability of therapy [1–6]. Nevertheless, a clear benefit in treating cirrhotic patients exists. In many cases, the urgency to treat their disease before they reach the decompensated stage (i.e. when IFN-based antiviral therapies become contraindicated), is still an unmet clinical need. In this rapidly changing field, safer and more efficacious therapies are emerging, either with or without IFN [7–12]. Nevertheless, in a very large number of countries worldwide, first-generation protease inhibitors (PIs), combined with the IFN-based regimen, remain the only available option for these patients. To date, Boceprevir (BOC) has been approved and marketed in 67 countries (only 28 in 2013 and 1 in 2014) while it has been approved, but not marketed yet in 14 other countries. As a result, it is conceivable to speculate that, due to cost-containment policies or limited economic resources, new DAAs will not be affordable soon either. However, while waiting for new molecules, pivotal phase-3 clinical trials on BOC, which included a small sample size of patients with cirrhosis and only a few with both null response and advanced disease [3,6,13,14], resulted in insufficient data regarding maximum utilization of BOC. Therefore, useful information to guide clinicians in daily practice is needed.

Overall risk to benefit ratio of BOC/P/R treatment in cirrhotic patients was analysed using expanded data from 5 Phase-3 clinical trials [15]. Specifically, this study identified baseline and on-treatment variables (in particular week 8 response) that could help predict response and guide clinical decisions regarding BOC triple therapy for cirrhotic patients, including decisions about discontinuation for futility [15]. As a matter of fact, this *post hoc* analysis included a carefully selected population with well-compensated disease and, again, a small number of patients with prior null response. Consequently, the results obtained in this study are not fully representative of the real-life population. Some data have indeed been obtained by the CUPIC study [16,17], which evaluated triple combination regimens with either telaprevir or BOC in a wider range of treatment-experienced cirrhotic patients (many of whom would not have qualified for pivotal trials). However, this study included a very small number of prior null responders, as well [16,17]. In addition, the safety profile reported in the CUPIC study was restricted, mainly due to the considerable number of included patients described as being incompatible with IFN-based regimens [18,19].

Here, we report a detailed analysis on the International BOC Name Patient Program (NPP), which was independently carried out in Italian and Spanish qualified Centres. This was the largest cohort of patients with advanced fibrosis/cirrhosis and prior null response ever studied. The information provided enhances the quality of BOC treatment and, therefore, allows better management of these patients while filling the time gap until the arrival of new drugs. By a detailed assessment of efficacy and safety in all different categories of patients, including the week 8 response value, as a predictor of SVR [15], we were able to assess the number needed to treat (NNT) for each SVR achieved.

PATIENTS AND METHODS

From March 2011 to September 2012, all treatment-experienced patients with HCV genotype 1a or 1b, advanced fibrosis and compensated cirrhosis with or without portal hypertension were enroled for this analysis. The patients were treated in 74 centres in the context of the NPP and each centre included at least three patients.

Baseline recorded data were: gender, age, histology, liver stiffness by FS, oesophageal varices, quantitative HCV-RNA with the Roche COBAS® TaqMan® or Abbot assays with a lower limit of detection of 15 and 12 IU/mL [20,21], respectively, HCV genotype and IL28B polymorphism.

Clinical and virological assessments were performed every 4 weeks during therapy and at weeks 12 and 24 of the follow-up period. Futility rule was applied by label.

At the time of inclusion, patient disease stage was re-evaluated by liver stiffness measurement and by endoscopy. Cirrhosis was defined on the basis of any one of the following criteria: (i) liver biopsy performed prior to Day 1 of the study showing cirrhosis consistent with Metavir score F4 or Ishak F5/6, (ii) presence of oesophageal varices and (iii) fibroScan, performed within 12 calendar months of Day 1 of the study, showing cirrhosis (liver stiffness ≥12.5 kPa) [22,23]. The diagnosis of advanced liver fibrosis was performed on the basis of any one of the following criteria: (i) liver biopsy, performed within 24 months of Day 1 of the study, showing fibrosis with Metavir score F3 or Ishak F3/4 and (ii) fibroScan, performed within 12 months of Day 1 of the study, showing liver stiffness ≥9.5 and ≤12.5 kPa. In case of disagreement between previous histology (F3) and liver stiffness value, consistent with F4 at time of inclusion, the latter was considered the right one. Written informed consent was obtained from each patient before enrolment. The protocol was carried out in accordance with the Declaration of Helsinki and was approved by local Ethics Committees.

Safety assessment was carried out every 4 weeks with the recording of any AEs and serious AEs (SAEs; including deaths and hospitalizations), and AEs leading to study drug discontinuations. Laboratory assessments focused on anaemia, neutropenia and thrombocytopenia. EPO use and blood transfusions were also recorded. The following parameters were considered to potentially represent hepatic decompensation: onset of ascites, encephalopathy, bleeding

from oesophageal varices, jaundice, and sepsis (in the context of declining liver function).

Virological failures and futility rules at week 12 and 24 were used according to the label.

Breakthrough was defined as an HCV-RNA ≥ 1 log increase after an undetectable HCV-RNA. Relapse was defined as the onset of *de novo* detectable HCV-RNA after EoTR. SVR12 was defined as having undetectable HCV-RNA 12 weeks after completion or discontinuation of therapy.

Statistical analysis

The primary efficacy analysis was conducted on all patients who received at least 1 dose of BOC/P/R, while SVR12 rates (overall and according to fibrosis stage on all patients who received at least 1 dose of P/R during lead-in phase) were also provided. The relationship between baseline and on-treatment factors and SVR was explored using univariate and multivariate logistic regression analyses (MLR). We used a back-wise variable selection, and only variables for which the association remained statistically significant were included in the final multivariable logistic regression model. Stratified MLR analysis was also performed by fibrosis score. Analyses were performed with the SAS software (version 8.2; Cary, NC). All *P*-values were two-sided. $P < 0.05$ was considered statistically significant.

RESULTS

Patient accounting and baseline characteristics

Four hundred and sixteen treatment-experienced patients with HCV genotype 1a or 1b with advanced fibrosis or compensated cirrhosis were enroled from 74 centres, which enroled at least three patients in Italy and Spain. Baseline characteristics of the 416 enroled patients (overall and according to administration of BOC after the lead-in phase) are shown in Table 1. Briefly, 381 (92%) patients received at least one dose of BOC. In the remaining cases (8%), treatment was stopped before starting triple therapy due to poor tolerance to IFN and RBV. Mean age was 57.7 years (range 25–78). HCV genotype 1b (323/416, 77.6%) was the prevalent genotype. The majority of patients (289/416, 69.5%) had F4 cirrhosis. In this latter group, Child classes A5 and A6 accounted for 85.4% (240/416) and 14.6% (41/416) of patients, respectively; approximately, 25% (70/289) had oesophageal varices, 13.2% (55/416) had platelet counts $\leq 100\,000/\mu L$ and 8.7% (34/416) had serum albumin levels ≤ 3.5 g/dL. Seven patients (2.4%) in the F4 group had concurrent low albumin levels and low platelet counts. Regarding prior treatment history: 42% of patients (173/416) were null responders, 35% relapsers (145/416) and 23% partial responders (96/416). IL-28B genotype was available for

Table 1 Baseline characteristics of 416 patients at study entry

Patients characteristics*	All patients N (col. %)	Received boceprevir		P-value
		No	Yes (row %)	
Total patients	416	35	381 (91.6)	
Country				
Italy	280 (67.3)	13	267 (95.4)	**0.0002**
Spain	136 (32.7)	22	114 (83.8)	
Gender				
Male	291 (70.0)	21	270 (92.8)	0.18
Female	125 (30.0)	14	111 (88.8)	
Age				
<50 years	116 (28.4)	13	103 (88.8)	0.10
50–59 years	151 (37.0)	7	144 (95.4)	
≥60 years	141 (34.6)	14	127 (90.1)	
Metavir				
F3	127 (30.5)	6	121 (95.3)	0.08
F4	289 (69.5)	29	260 (90.0)	
Child class				
A5	240 (85.4)	20	220 (91.7)	**0.04**
A6	41 (14.6)	8	33 (80.5)	
Varices				
No	209 (74.9)	25	184 (88.0)	0.37
Yes	70 (25.1)	5	65 (92.9)	
FibroScan				
<12.5 kPa	131 (36.9)	8	123 (93.9)	0.24
≥12.5 kPa	224 (63.1)	23	201 (89.7)	
Albumin				
Low (≤3.5 g/dL)	34 (8.7)	6	28 (82.4)	0.10
>3.5 g/dL	357 (91.3)	28	329 (92.2)	
Platelets				
Low (≤100 000/μL)	55 (13.2)	10	45 (81.8)	**0.02**
>100 000/μL	361 (86.8)	25	336 (93.1)	
Genotype				
1b	323 (77.6)	27	296 (91.6)	1.00
1a	93 (22.4)	8	85 (91.4)	
Previous response				
Relapser	145 (35.0)	8	137 (94.5)	0.15
Partial responder	96 (23.2)	7	89 (92.7)	
Null responder	173 (41.8)	20	153 (88.4)	
IL28				
CC	28 (10.5)	2	26 (92.9)	0.51
CT	173 (64.5)	9	164 (94.8)	
TT	67 (25.0)	6	61 (91.0)	

*Some information is missing for few patients. Bold values are statistically significant.
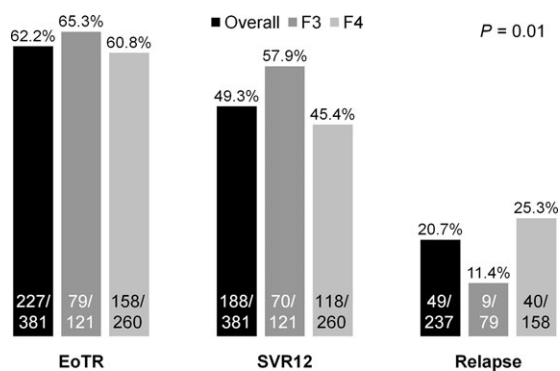
Fig. 1 EoTR, SVR12 and relapse rate overall and according to fibrosis stage. All patients who received at least one dose of BOC included in the study.

268 (64.4%) patients. The CT genotype was the most prevalent (64.5%) one. Table S1 shows the characteristics of the patients according to country of origin.

Efficacy

Overall, SVR12 rates on all enroled patients who received at least 1 dose of P/R during the lead-in phase were
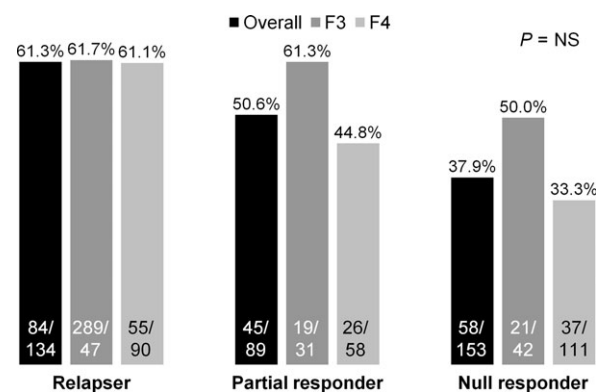

Fig. 2 SVR12 according to fibrosis stage and prior response. All patients who received at least one dose of BOC included in the study.

45.2%, (188/416), 55.1% in F3, (70/127) and 40.8% in F4, (118/289), respectively.

Figure S1 shows the rate of undetectable HCV-RNA at different week points during the full course of treatment and after its discontinuation. Figure 1 shows the overall EoTR, SVR12 and relapse rates, which were 62%, 49%

Table 2 Predictors of treatment failure among patients with undetectable HCV-RNA at TW8 and of treatment success among those with detectable HCV-RNA at TW8

	Overall		F3		F4	
	No SVR	SVR	No SVR	SVR	No SVR	SVR
TW8* (%)						
Detectable	132 (68.4)	61 (31.6)	35 (60.3)	23 (39.7)	97 (71.9)	38 (28.1)
Undetectable	44 (27.7)	115 (72.3)	11 (20.0)	44 (80.0)	33 (31.7)	71 (68.3)
PPV, %	72.3		80.0		68.3	
NPV, %	68.6		60.3		71.9	

	Overall		F3		F4	
	No SVR	SVR	No SVR	SVR	No SVR	SVR
TW8† (%)						
>1000	44 (91.7)	4 (8.3)	13 (100)	0 (0.0)	30 (90.9)	3 (9.1)
<1000	131 (43.4)	171 (56.6)	33 (33.0)	67 (67.0)	99 (48.3)	106 (51.7)
PPV, %	56.6		67.0		51.7	
NPV, %	91.7		100		90.9	

	Overall		F3		F4	
	No SVR	SVR	No SVR	SVR	No SVR	SVR
TW8‡ (%)						
<3 log-decline	26 (89.7)	3 (10.3)	12 (92.3)	1 (7.7)	14 (87.5)	2 (12.5)
≥3 log-decline	148 (46.5)	170 (53.5)	34 (34.0)	66 (66.0)	114 (52.3)	104 (47.7)
PPV, %	53.5		66.0		47.7	
NPV, %	89.7		92.3		87.5	

*HCV-RNA status is missing for 29 patients; †HCV-RNA evaluation is missing for 31 patients; ‡Log-decline.

Table 3 Univariate and Multivariate analysis for SVR12

Variable	Reference	Univariate RR (95% CI)	Multivariate* RR (95% CI)	P-value
TW8 < 1000 IU/mL	Undetectable	**3.97 (2.45–6.41)**	4.22 (2.49–7.16)	<0.0001
TW8 ≥ 1000 ≥ 3 log-decline	Undetectable	**47.0 (6.10–362.)**	**40.29 (10.7–152.)**	**<0.0001**
TW8 ≥ 1000 < 3 log-decline	Undetectable	**32.7 (7.42–143.)**		
TW4 < 1 log-decline	≥1 log-decline	**3.53 (2.04–6.11)**	2.75 (1.23–6.14)	0.01
TW4 1 log-decline	<1 log-decline	**0.47 (0.26–0.86)**		
TW4 2 log-decline	<1 log-decline	**0.24 (0.12–0.46)**		
TW4 3 log-decline	<1 log-decline	**0.18 (0.08–0.44)**		
TW4 4 log-decline	<1 log-decline	**0.06 (0.02–0.23)**		
TW4 5 log-decline	<1 log-decline	**0.05 (0.01–0.24)**		
TW4 log-decline (continuous)	Per log-decline	0.54 (0.44–0.65)		
Male	Female	**0.64 (0.41–0.99)**		
Age ≥60 years	<60 years	1.14 (0.73–1.77)		
Metavir F4	F3	**1.65 (1.07–2.55)**		
Metavir F4 Child A6	F4 – Child A5	**3.55 (1.48–8.52)**		
FibroScan (≥12.5 kPa)	<12.5 kPa	1.65 (1.05–2.60)		
FibroScan (continuous)	Per 1 kPa	**1.04 (1.02–1.07)**	**1.05 (1.02–1.09)**	0.003
Varices	F4 – No varices	1.03 (0.57–1.86)		
HCV genotype 1b	1a	0.89 (0.55–1.44)		
Prior null	Prior relapser	**2.60 (1.62–4.17)**	**2.06 (1.24–3.44)**	0.004
Prior partial	Prior relapser	1.55 (0.90–2.66)		
Albumin ≤3.5 g/dL	>3.5 g/dL	4.80 (1.78–12.9)	5.16 (1.67–16.0)	0.004
PLT ≤100 000/μL	>100 000/μL	**3.44 (1.69–7.02)**	**3.51 (1.50–8.21)**	0.004
Baseline viral load >800 000	≤800 000	1.04 (0.67–1.61)	–	

*Only variables for which the association remained statistically significant were included in the final multivariable logistic regression model (Back-wise variables selection). Bold values are statistically significant.

and 20%, respectively. No difference was observed in EoTR rate between F3 and F4 patients, while SVR12 was significantly lower in cirrhotic patients (*P* = 0.02) due to the higher relapse rate (*P* = 0.01) in this latter group of patients. SVR12 rates by historical response and by fibrosis stage are shown in Fig. 2. As expected, SVR12 rate was higher in relapsers (61.3%), compared to partial (50.6%) and null (37.9%) responders. None of the patients with concurrent low albumin levels and low platelet counts achieved SVR. Overall, a high proportion of patients (72.3%) with undetectable HCV-RNA levels at treatment-week (TW) 8 achieved SVR (PPV 72.3%, 68.3% in F4 and 80% in F3). On the contrary, very few patients (4/48, 8.3%) with detectable TW8 HCV-RNA ≥ 1000 IU/L achieved SVR (NPV = 91.7%, 90.9% in F4 and 100% in F3) (Table 2).

Of interest, among 98 patients without a 1-log-decline in HCV-RNA at TW4, 20 had undetectable HCV-RNA and 29 had HCV-RNA < 1000 IU/L at TW8, respectively.

Several factors predicting the achievement of SVR, overall and by F3/F4, were identified with MLR. The factors identified were historical response to P/R (relapser *vs* partial responder and null responder), fibroScan (1 kPa

increase, as a continuous variable), platelet counts (≤100 000/μL) and albumin levels (≤3.5 g/dL), HCV-RNA ≥ 1 $\log_{10}$-decline from baseline at TW4, and undetectable HCV-RNA at TW8, which were all independently associated with SVR (Tables 3 and 4).

In both F3 and F4 patients, HCV-RNA at TW8 ≥ 1000 IU/L (undetectable HCV-RNA as the standard reference) was associated with the lowest likelihood of attaining SVR (95% confidence interval (CI) 10.5–124; risk ratio (RR) 36.1, *P* < 0.0001, Table 3). SVR12, according to TW8 HCV-RNA is illustrated in Fig. 3. As mentioned, residual viremia >1000 IU/L was associated with high likelihood of not achieving SVR, regardless of whether or not HCV-RNA ≥ 3 log-decline was reached (Fig. 3). In particular, only 3 of 21 (14%) patients with TW8 HCV-RNA > 1000 IU/mL attained SVR, irrespective of having achieved HCV-RNA ≥ 3 log-decline.

At TW8, 45.2% (159/352) of patients had undetectable HCV-RNA. Baseline characteristics associated with a low likelihood to achieve this result were albumin levels and prior null response (Table S2). In addition, female gender, albumin levels and low platelet counts predicted treatment failure in this group of patients, while predictors of SVR in patients with HCV-RNA still detectable at TW8

Table 4 Univariate and Multivariate analysis for SVR12 in patients with F3 and F4 cirrhosis

Variable	Reference	Metavir-F3 Univariate RR (95% CI)	Metavir-F3 Multivariate* RR (95% CI)	P-value	Metavir-F4 Univariate RR (95% CI)	Metavir-F4 Multivariate* RR (95% CI)	P-value
TW8 < 1000 IU/mL	Undetectable	**3.83 (1.59–9.24)**	**3.76 (1.55–9.15)**	0.004	**4.06 (2.27–7.26)**	**4.49 (2.32–8.71)**	**<0.0001**
TW8 ≥ 1000 ≥ 3 log-decline	Undetectable	Na	TW8 > 1000		**34.4 (4.38–270.)**	TW8 > 1000	
TW8 ≥ 1000 < 3 log-decline	Undetectable	Na	Na†		**15.1 (3.24–70.1)**	**21.4 (5.11–89.4)**	**<0.0001**
TW4 < 1 log-decline	≥1 log-decline	**2.66 (1.01–7.05)**	1.33 (0.41–4.31)	0.64	**3.77 (1.91–7.42)**	**2.75 (1.23–6.14)**	0.01
Male	Female	**0.73 (0.34–1.59)**	–		0.57 (0.33–1.00)	–	
Age ≥60 years	<60 years	1.09 (0.51–2.34)	–		1.23 (0.71–1.48)	–	
Child A6	Child A5	–			**3.55 (1.48–8.52)**	–	
FibroScan (≥12.5 kPa)	<12.5 kPa	–			0.73 (0.25–2.07)		
FibroScan (continuous)	Per 1 kPa	0.97 (0.72–1.31)			1.04 (1.00–1.07)	1.07 (1.02–1.11)	0.003
Varices	F4 – No varices	–			1.03 (0.57–1.86)	–	
HCV genotype 1b	1a	0.99 (0.41–2.39)	–		0.85 (0.48–1.53)		
Prior null	Prior relapser	1.61 (0.69–3.75)	–		**3.14 (1.76–5.61)**	Prior null/partial	
Prior partial	Prior relapser	1.02 (0.40–2.58)	–		1.93 (0.99–3.78)	2.86 (1.50–5.48)	**0.001**
Albumin ≤3.5 g/dL	>3.5 g/dL	**0.74 (0.29–1.93)**	–		4.37 (1.60–11.9)	6.37 (1.96–20.7)	0.002
PLT ≤100 000/µL	>100 000/µL	–			**3.06 (1.48–6.36)**	**4.05 (1.65–9.90)**	0.002
Baseline viral load >800 000	≤800 000	1.04 (0.49–2.24)	–		1.00 (0.58–1.71)	–	

Na, Not available; *Only variables for which the association remained statistically significant were included in the final multivariable logistic regression model (Backwise variables selection); †No SVR in 11 patients. Bold values are statistically significant.
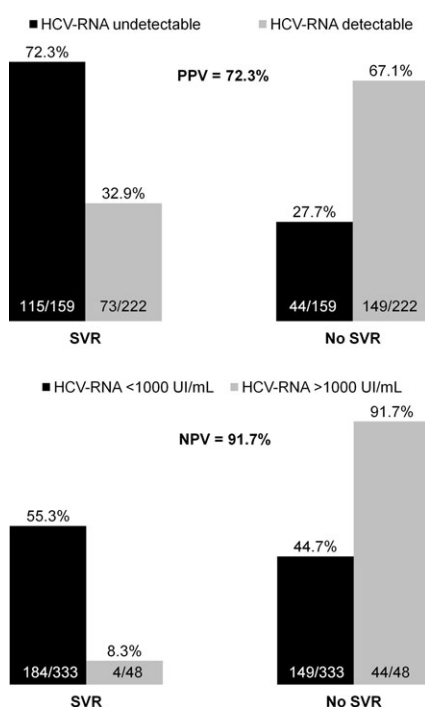
Fig. 3 SVR according to treatment-week 8 virological response. All patients who received at least one dose of BOC included in the study.

were Child class A5 *vs* A6, high albumin levels and high platelet counts, and favourable IL28B CC genotype (Table S3).

Table S4 shows the rate of SVR among the 159 patients with undetectable HCV-RNA at TW8 according to whether or not they had received a full course of treatment. Interestingly, 102 of 120 (85%) subjects who completed the full course of treatment achieved SVR. Detailed information describes the reasons for early discontinuation of treatment as shown in Table S5.

NNT calculation

SVR12 and NNT for single SVR stratified by patient characteristics at time of entry, TW8 response and F3/F4 stages are reported in Table 5.

Safety and tolerability

Overall, 92 patients (24.1%) withdrew from all treatments due to adverse events (Table 6). Serious adverse events (i.e. events that resulted in death were life threatening, resulted in persistent or clinically significant disability/incapacity or required hospitalization) occurred in 13.4% (51/381) of all patients. Overall, three patients died (0.8%; 0 in F3, 0 in F4/CP A5 and 3 (7.3%) in F4/CP A6) at weeks 6, 10 and 28. All deaths occurred in the F4 group of 289 patients (1%) compared to 0 deaths in the group of 127 F3 patients. The cause of death was attributable, in all cases, to multiple organ failure following the onset of severe infection and generalized sepsis (Table 6). Overall, 11 patients (2.9%) had hepatic decompensation, and all episodes were observed in cirrhotic patients (3.8%). The frequency of serious adverse events was higher in patients with more advanced disease and in the Spanish cohort (Table S6). At MLR, Metavir F4,

Table 5 SVR12 and NNT in patients receiving at least one BOC dose according to baseline characteristics, fibrosis stage, historical response and TW8 HCVRNA value

Variable	Total			Metavir F3			Metavir F4		
	Patients	SVR (%)	NNT	Patients	SVR (%)	NNT	Patients	SVR (%)	NNT
All	381	188 (49.3)	2.0	121	70 (57.9)	1.7	260	118 (45.4)	2.2
Italy	267	128 (47.9)	2.1	100	57 (57.0)	1.8	167	71 (42.5)	2.4
Spain	114	60 (52.6)	1.9	21	13 (61.9)	1.6	93	47 (50.5)	2.0
TW8 Undetectable	159	115 (72.3)	1.4	55	44 (80.0)	1.3	104	71 (68.3)	1.5
TW8 < 1000 IU/mL	143	56 (39.2)	2.6	43	22 (51.2)	2.0	100	34 (34.0)	2.9
TW8 ≥ 1000 IU/mL	48	4 (8.3)	12.0	15	1 (6.7)	15.0	33	3 (9.1)	11.0
Prior relapser	137	84 (61.3)	1.6	47	29 (61.7)	1.6	90	55 (61.1)	1.6
Prior partial	89	45 (50.6)	2.0	31	19 (61.3)	1.6	58	26 (44.8)	2.2
Prior null	153	58 (37.9)	2.6	42	21 (50.0)	2.0	111	37 (33.3)	3.0
FibroScan <12.5 kPa	123	71 (57.7)	1.7	107	65 (60.7)	1.6	16	6 (37.5)	2.7
FibroScan ≥12.5 kPa	201	91 (45.3)	2.2	–			201	91 (45.3)	2.2
Albumin >3.5 g/dL	329	168 (51.1)	2.0	99	56 (56.6)	1.8	230	112 (48.7)	2.1
Albumin ≤3.5 g/dL	28	5 (17.9)	5.6	–			28	5 (17.9)	5.6
PLT >100 000/μL	336	177 (52.7)	1.9	121	70 (57.9)	1.7	215	107 (49.8)	2.0
PLT ≤100 000/μL	45	11 (24.4)	4.1	–			45	11 (24.4)	4.1

NNT, number needed to treat; None of the seven patients with both low albumin and low platelet counts had SVR.

Table 6 Adverse events anytime during TW5-TW48 among 381 patients who received at least one dose of BOC

Adverse events during TW5-TW48	N (%)
Serious adverse events	51 (13.4)
Deaths	3 (0.8)
Sepsis, MOF	4 (1.1)
Infections	43 (11.3)
Hepatic decompensation	11 (2.9)
Haematological adverse events	265 (69.6)
Anaemia	
Grade 2–3 (8.5 < Hb < 10 g/dL)	198 (52.0)
Grade 4 (Hb < 8.5 g/dL)	57 (15.0)
Neutropaenia	
Grade 3 (500 < N < 750)	132 (34.7)
Grade 4 (N < 500)	46 (12.1)
Thrombocytopaenia	
Grade 3 (25 000 < PLT < 50 000)	67 (17.6)
Grade 4 (PLT < 25 000)	6 (1.6)
Other events	
Cutaneous adverse event	67 (17.6)
Cardiovascular adverse event	5 (1.3)
Cerebrovascular adverse event	11 (2.9)
Gastrointestinal adverse event	60 (15.8)
EPO	168 (44.1)
Transfusions	32 (8.4)

liver stiffness $\geq$12.5 kPa and Child class A6 were independently associated with the occurrence of SAEs (Table 7). Two other strong predictors of SAEs during treatment with BOC were also lower platelet counts and lower albumin levels at baseline with an OR of 2.39 (95% CI: 1.12–5.10) and of 3.42 (95% CI: 1.45–8.08), respectively (Table 7). Details on hospitalization are summarized in Table S7. Approximately 70% of patients had bone marrow toxicity (Table 6). Table S8 shows the proportion of patients who required reduction of IFN, RBV or both. RBV dose reduction was associated with higher SVR rates ($P < 0.003$), while IFN reduction had no effect on SVR. In multivariate analysis, female gender, older age (>60 years) and low platelet counts were associated with increased risk of haematological adverse events (Table 7).

Resistance-associated variants

NS3 genotype resistance testing by population sequencing was performed in 15 patients failing triple therapy with BOC (3 = GT-1a, 11 = GT-1b and 1 = GT-1 g) and in 4 patients with early treatment discontinuation for adverse events (1 = GT-1a and 3 = GT-1b) (Table S9). Population sequencing of the viral protease was performed after a median (IQR) of 5 (−5;34) days from the time of treatment discontinuation or virological failure. Upon sequencing, HCV-RNA had median (IQR) values of 5.1

(3.8–5.0) log IU/mL, ranging from 280 to 3 002 138 IU/mL. Overall, at least one resistance-associated variant (RAV) was found in 12 of 15 patients analysed at the time of virological failure. In particular, in all patients that showed viral breakthrough during treatment ($N = 3$) or relapse after reaching the end of treatment ($N = 4$), the increase of viremia after achieving undetectable HCV-RNA was associated with RAVs occurrence (Table S9). Conversely, among the eight patients who discontinued treatment in accordance with BOC stopping rules, the *de novo* development of RAVs was exclusively observed in the 2 patients in whom the interruption was delayed by investigator decision and in 1 GT-1a patient presenting at baseline with the NS3 mutation Q80K. The remaining 5 patients who discontinued treatment after 12 weeks for virological failure did not show *de novo* development of RAVs. One of them was however infected by GT-1 g [24]. The characteristics of *de novo* RAV mutations within the 10 patients experiencing virological failure is described in Table S9. Among the 4 patients who prematurely discontinued treatment due to adverse events, 1 who delayed the discontinuation of treatment despite the futility rule showed *de novo* development of RAVs (R155K).

DISCUSSION

Boceprevir, in combination with P/R, was launched in September 2010. However, in several countries, it is still not available. Since then, with the exception of the US and few European countries, all other nations permitted this treatment only for patients with more advanced liver disease, mainly due to cost-containment measures. This limitation is expected to be maintained for at least the next 2 years in the vast majority of the world. In addition, it is well known that achieving an SVR reduces the risk of HCC, decompensation, and all-cause mortality in patients with cirrhosis [25–27]. Therefore, deferring access to therapy in these patients while waiting for all oral IFN-free regimens might not be an option. However, the safety concern reported in the CUPIC study [17], especially for patients with severe portal hypertension and deteriorated liver function as well as lacking data in patients with previous null response to P/R, suggest that additional, reliable information to optimize BOC-based treatment in daily practice is needed. Here, we show that, 50% of all F4 patients treated with BOC/P/R can achieve an SVR. SVR rates were particularly high (69%) in patients with undetectable HCV-RNA at TW8, as previously reported in a smaller number of patients with such characteristics [18]; these patients accounted for almost half of all treated cirrhotic populations. Furthermore, F3 patients with undetectable viral load at TW8 achieved higher SVR rates (80%). The reason why the rate of SVR in patients with F4 is lower, when compared to F3 subjects, is easily explained by the higher

Table 7 Predictors of serious or haematological adverse events during treatment with BOC (week 5 to week 48)

	Serious events		Haematological events	
	Events/patients (%)	OR (95% CI)	Events/patients (%)	OR (95% CI)
Gender				
Male	33/270 (12.2)	1.00	176/270 (65.2)	1.00
Female	18/111 (16.2)	1.39 (0.75–2.59)	89/111 (80.2)	**2.16 (1.27–3.67)**
Age				
<50 years	10/103 (9.7)	1.00	60/103 (58.3)	1.00
50–59 years	21/144 (14.6)	1.59 (0.71–6.53)	98/144 (68.1)	1.53 (0.90–2.58)
≥60 years	19/127 (15.0)	1.64 (0.73–3.69)	101/127 (79.5)	**2.78 (1.56–4.98)**
Metavir				
F3	5/121 (4.1)	1.00	81/121 (66.9)	1.00
F4	46/260 (17.7)	**4.99 (1.93–12.9)**	184/260 (70.8)	1.20 (0.75–1.90)
Child class (F4)				
A5	35/220 (15.9)	1.00	155/220 (70.5)	1.00
A6	11/33 (33.3)	**2.74 (1.22–6.16)**	25/33 (75.8)	1.34 (0.57–3.11)
FibroScan				
<12.5 kPa	7/123 (5.7)	1.00	79/123 (64.2)	1.00
≥12.5 kPa	37/201 (18.4)	**3.74 (1.61–8.67)**	145/201 (72.1)	1.44 (0.89–2.33)
Per 1 kPa increase		1.03 (0.99–1.06)		1.03 (0.99–1.06)
Varices (F4)				
No	26/135 (19.3)	1.00	94/135 (69.6)	1.00
Yes	14/65 (21.5)	1.15 (0.56–2.39)	49/65 (75.4)	1.34 (0.68–2.62)
Genotype				
1b	40/296 (13.5)	1.00	209/296 (70.6)	1.00
1a	11/85 (12.9)	0.95 (0.47–1.95)	56/85 (65.9)	0.80 (0.48–1.34)
Albumin				
>3.5 g/dL	40/329 (12.2)	1.00	225/329 (68.4)	1.00
Low (≤3.5 g/dL)	11/52 (21.2)	**3.42 (1.45–8.08)**	40/52 (76.9)	1.39 (0.57–3.37)
Platelets				
>100 000/μL	41/340 (12.1)	1.00	228/340 (67.1)	1.00
Low (≤100 000/μL)	10/41 (24.4)	**2.39 (1.12–5.10)**	37/41 (90.2)	**5.13 (1.79–14.7)**
Previous response				
Relapser	22/137 (16.1)	1.00	105/137 (76.6)	1.00
Partial responder	12/89 (13.5)	0.82 (0.38–1.74)	66/89 (74.2)	0.88 (0.47–1.62)
Null responder	17/153 (11.1)	0.65 (0.33–1.29)	94/153 (61.4)	**0.49 (0.29–0.81)**

Bold values are statistically significant.

relapse rate observed in this latter group of patients. Additional information provided by this study is that in patients with undetectable HCV-RNA at TW8 who tolerated a full course of therapy, SVR was extremely high (86%) and this finding was observed in more than two-third of this group of patients. Moreover, as there was no discontinuation related to virological breakthrough in this group of subjects, we may assume that the emergence of escape mutants was absent or very low.

Previously, it was reported that SVR was more likely in patients with advanced fibrosis/cirrhosis who had an HCV-RNA decline ≥1.0 log at week 4 (end of the lead-in phase with P/R) [18]. However, although this result was confirmed in our analysis, we found that approximately 50% of patients with <1 log-decline at TW4 achieved undetect-

able HCV-RNA or <1000 IU/L at TW8. This data supports the decision to start BOC therapy after the lead-in phase, to avoid missing several SVRs in this poor IFN-sensitive population.

Irrespective of the fibrosis stage, HCV-RNA ≥ 1000 IU/L at TW8 was associated with a negligible rate of SVR (8%, NPV = 92%). In agreement with the FDA and the European Commission (EC), which approved a revision of the BOC Prescribing Information, (i.e. a futility rule to stop therapy with BOC/P/R in all patients if TW8 HCV-RNA levels are ≥1000 IU per mL was added), our results provide a solid validation in support of this decision.

Additional predictors of SVR for F4 patients in the MLR analysis included male gender, prior null response, low albumin levels and low platelet counts. Supplemen-

tary information emerging from the study was that liver stiffness, the value of which was found to be associated with disease outcome [28], paralleled some well-established surrogate markers of disease severity and portal hypertension (i.e. Child class, platelet counts, and oesophageal varices) in predicting SVR. Consequently, this variable may be proposed, as a useful tool to identify the subgroup of patients not eligible for therapy with first-generation PIs.

Although the clinical characteristics of F4 patients treated with BOC/P/R in the French Early Access Programme were similar to those of patients in our study (median age was 56.8 *vs* 57.7 years, proportion of male patients was 67.9% *vs* 69.5%), there were some differences between the two cohorts. First of all, null responders were originally excluded from the CUPIC study and, ultimately, 8% of these subjects were enroled. Moreover, both mean baseline platelet counts and serum albumin levels were lower in the BOC–CUPIC arm (144 000/μL *vs* 165 000/μL and 4.8 *vs* 4.0 g/dL, respectively) compared to patients enroled in our study, and NPP included 2.4% (*vs* 8.3% in CUPIC) of patients with concomitant low baseline albumin levels and platelet counts. Finally, the frequency of infection with HCV genotype 1a was different (41% *vs* 22.4%). The proportion of patients with oesophageal varices was also similar (37.6% *vs* 42%), but it should be noted that an upper gastrointestinal endoscopy was performed in only 51.4% of patients of the CUPIC population treated with BOC.

Despite these discrepancies, in agreement with the CUPIC study, we confirmed that the concurrent presence of low albumin levels and platelet counts at baseline was a strong predictor of poor response. Similarly, to the French study, our survey showed that poor TW8 response (i.e. HCV-RNA <3 log-decline compared to baseline) is associated with a low likelihood of SVR. Therefore, we may speculate that the two studies mutually validated themselves and may be considered complementary in enhancing the knowledge regarding this type of patients.

In summary, the present study provides the most detailed analysis ever carried out in the largest group of patients with advanced liver disease treated with BOC. The attained results enable clinicians to evaluate, in each single category of patients, predictors of both SVR (thus permitting the calculation of the NNT) and severe complications (both liver and haematological-related). The NNT in patients with undetectable HCV-RNA at TW8 is extremely favourable regardless of all negative baseline predictors. Moreover, using this new TW8 futility rule, which our

study strongly validates, EPO and blood transfusions may be spared, and the hospitalization rate may be reduced, thus lowering the total cost of therapy. Finally, this may be a way for clinicians to not deny BOC triple therapy '*a priori*' to all IFN-eligible patients, and thus safely prevent exposure to an ineffective treatment in patients with a potential high rate of adverse events.

In conclusion, this analysis assessed potential benefits and risks of BOC treatment in a wide range of patients with advanced liver disease. Using a simple combination of baseline and on-treatment predictors, clinicians may easily identify patients with a high likelihood of achieving SVR and those at risk for severe complications. To fill the time gap until all oral DAAs become available, an eight-week BOC-based treatment may be proposed as a right option to assess tolerability and likelihood of success of this therapy in cirrhotic patients whose characteristics make them eligible for IFN-based regimens.

AUTHOR CONTRIBUTIONS

All co-authors had full access to all pertinent data upon request. Each co-author has approved the final version of the manuscript. The corresponding authors had full access to all of the data and take full responsibility for the accuracy of the data and statistical analyses. The opinions expressed in this report represent the consensus of the authors and do not necessarily reflect the formal position of Merck or the authors' affiliated universities.

FINANCIAL SUPPORT AND POTENTIAL COMPETING INTERESTS

The provided results are independently assessed by all the investigators involved in the program, and no support was obtained by MSD, except for the compassionate use of drugs. The opinions expressed in this report represent the consensus of the authors. The corresponding authors had full access to all of the data and take full responsibility for the accuracy of the data and statistical analyses.

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APPENDIX 1

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1: Virological response during treatment and 12 weeks follow-up. All patients who received at least one dose of BOC included in the study. **Table S1:** Baseline patient characteristics at study entry, according to country of origin.

Table S2: Baseline predictors of HCV-RNA undetectable at TW8.

Table S3: Predictors of treatment failure (no SVR) in patients with undetectable HCV-RNA at TW8 or treatment success (SVR) in patients with detectable HCV-RNA at TW8.

Table S4: Details of patients with undetectable HCV-RNA at week 8.

Table S5: Treatment course and status of 381 patients who received at least one dose of BOC.

Table S6: Adverse events anytime during TW5-TW48 among 381 patients who received at least 1 dose of BOC.

Table S7: Hospitalization (41 in 36 patients).

Table S8: SVR according to Ribavirin and Peg/IFN reduction or interruption.

Table S9: NS3 genotypic resistance test in patients experiencing virological failure or early discontinuation of treatment administration.