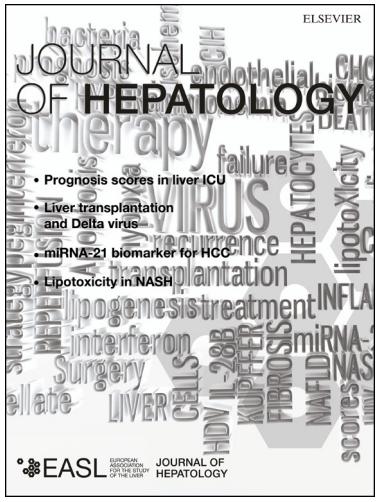

International Hepatology

HCV cirrhosis at the edge of decompensation: Will ABT-450/r, ombitasvir, dasabuvir and ribavirin solve the need for treatment?

Tarik Asselah, Savino Bruno, Antonio Craxi

PII: S0168-8278(14)00558-3
DOI: http://dx.doi.org/10.1016/j.jhep.2014.08.018
Reference: JHEPAT 5296

To appear in: *Journal of Hepatology*

Received Date: 13 June 2014
Revised Date: 6 August 2014
Accepted Date: 9 August 2014

Please cite this article as: Asselah, T., Bruno, S., Craxi, A., HCV cirrhosis at the edge of decompensation: Will ABT-450/r, ombitasvir, dasabuvir and ribavirin solve the need for treatment?, *Journal of Hepatology* (2014), doi: http://dx.doi.org/10.1016/j.jhep.2014.08.018

HCV cirrhosis at the edge of decompensation: Will ABT-450/r, ombitasvir, dasabuvir and ribavirin solve the need for treatment ?

Tarik Asselah[1,*], Savino Bruno[2], Antonio Craxi[3].

[1]Centre de Recherche sur l'Inflammation (CRI), UMR 1149 Inserm, Université Paris Diderot, Service d'Hépatologie, AP-HP Hôpital Beaujon, Clichy-France, [2]Department of Internal Medicine, A.O. Fatebenefratelli e Oftalmico, Milan, Italy; [3]Gastroenterologia & Epatologia, Di.Bi.M.I.S. ; University of Palermo, Italy.

Keywords: Portal hypertension, Advanced liver disease, Liver function, Direct-acting antivirals.

*Corresponding author. Address : Centre de Recherche sur l'Inflammation (CRI), UMR 1149 Inserm, Université Paris Diderot, Service d'Hépatologie, AP-HP Hôpital Beaujon, Clichy-France, 100 Bd du Général Leclerc, Clichy 92110, France. Tel: +33(0) 140875579; fax: +33(0) 147309440

E-mail address: tarik.asselah@bjn.aphp.fr (T. Asselah)

Abbreviations: DAAs, direct-acting antivirals; HCV, hepatitis C virus; NI, nucleoside inhibitors; PegIFN, pegylated-interferon; G, Genotype; QD, once daily; RBV, ribavirin; SVR, sustained virological response.

COMMENTARY ON:

Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. Feld JJ1, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. N Engl J Med. 2014 Apr 24;370(17):1594-603. doi: 10.1056/NEJMoa1315722. Copyright © 2014

http://www.ncbi.nlm.nih.gov/pubmed/24720703

Abstract

BACKGROUND: The interferon-free combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r) and the NS5A inhibitor ombitasvir (also known as ABT-267) plus the nonnucleoside polymerase inhibitor dasabuvir (also known as ABT-333) and ribavirin has shown efficacy against the hepatitis C virus (HCV) in patients with HCV genotype 1 infection. In this phase 3 trial, we evaluated this regimen in previously untreated patients with HCV genotype 1 infection and no cirrhosis.

METHODS: In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned previously untreated patients with HCV genotype 1 infection, in a 3:1 ratio, to an active regimen consisting of a single-tablet coformulation of ABT-450/r-ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir), and dasabuvir (250 mg twice daily) with ribavirin (in doses determined according to body weight) (group A) or matching placebos (group B). The patients received the study treatment during a 12-week double-blind period. The primary end point was sustained virologic response at 12 weeks after the end of treatment. The primary analysis compared the response rate in group A with the response rate (78%) in a historical control group of previously untreated patients without cirrhosis who received telaprevir with peginterferon and ribavirin. Adverse events occurring during the double-blind period were compared between group A and group B.

RESULTS: A total of 631 patients received at least one dose of the study drugs. The rate of sustained virologic response in group A was 96.2% (95% confidence interval, 94.5 to 97.9), which was superior to the historical control rate. Virologic failure during treatment and relapse

after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A. The response rates in group A were 95.3% among patients with HCV genotype 1a infection and 98.0% among those with HCV genotype 1b infection. The rate of discontinuation due to adverse events was 0.6% in each study group. Nausea, pruritus, insomnia, diarrhea, and asthenia occurred in significantly more patients in group A than in group B (P<0.05 for all comparisons). Reductions in the hemoglobin level were all of grade 1 or 2; reductions of grade 1 and 2 occurred in 47.5% and 5.8%, respectively, of the patients in group A, whereas grade 1 reductions occurred in 2.5% of the patients in group B.

CONCLUSIONS: In previously untreated patients with HCV genotype 1 infection and no cirrhosis, a 12-week multitargeted regimen of ABT-450/r-ombitasvir and dasabuvir with ribavirin was highly effective and was associated with a low rate of treatment discontinuation. (Funded by AbbVie; SAPPHIRE-I ClinicalTrials.gov number, NCT01716585.).

Patients with HCV cirrhosis are priority candidates for antiviral treatment, due to the high expected rate of progression to liver decompensation and eventually to death [1]. Interferon (IFN)-based dual or triple therapy with 1st generation protease inhibitors is poorly tolerated and has modest efficacy, especially in patients with marginally compensated or decompensated disease [2]. CUPIC, a large expanded access French program has shown in fact that low baseline albumin level (ie <35 g/L) combined with low platelet counts (ie <100,000/mm) predict an unfavourable on-treatment course, with a higher risk of decompensation, infections and death, together with a low chance of HCV clearance [3].

As the field moves rapidly to IFN-free regimen combining direct-acting antivirals (DAAs) which target multiple viral sites (NS3/4a protease, NS5B polymerase and NS5A replication complex), SVR rates beyond 90% are expected in non-cirrhotic patients, regardless of previous

response to IFN, with 8-12 weeks of therapy and with an excellent tolerability profile [4]. Notwithstanding the major clinical need of cirrhotics, most IFN-free trials up to now have excluded patients with cirrhosis or enrolled only a modest proportion (10 to 20%) of cirrhotics with well- compensated disease [5-7], thus negating the clinicians the information needed to treat those patients already bordering on the verge of decompensation.

Our comment deals with a recently published phase III trial (Turquoise-II) with ABT-450/r, ombitasvir, dasabuvir and ribavirin based regimen, performed exclusively in patients with GT1 HCV cirrhosis ranging from well to marginally compensated disease [8]. This phase III trial was performed as a global, multi-center, randomized, open-label study including 380 patients with cirrhosis in Child-Pugh class A5 to A6 randomly assigned to receive either 12 or 24 weeks of treatment with ABT-450/r-ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir), dasabuvir (250 mg twice daily), and ribavirin administered according to body weight (Figure 1A). Cirrhosis was documented by liver biopsy (Metavir score >3 or Ishak score >4) or FibroScan result (≥14.6 kPa within 6 months before screening or during screening). Interestingly, key eligibility criteria were a platelet count of 60,000 /mm or more, a serum albumin level of 2.8 g/dl or more, a total bilirubin level of less than 3 mg/dl, which makes us think that some patients actually belonged to Child-Pugh B7 class.

Patients achieved sustained virologic response rates 12 weeks post-treatment (SVR_{12}) of 91.8 percent and 95.9 percent in the 12-week and 24-week treatment arms, respectively (Figure 1B). Patients in the study were either naïves or treatment- experienced (failed previous treatment with pegylated (PEG)-IFN and RBV)(Figure 1C). A prior null response and infection with HCV subgenotype 1a were associated with a lower likelihood of a SVR. Genotype 1a with history of null response were the predictors of non SVR in multivariate analysis, and that for platelets and albumin there was a non significant trend, with indeed an excellent chance to cure in this population. Interestingly, for patients with low platelets (< 10^9/L) reflecting portal

hypertension and/or those with low albumin (< 35 g/l) reflecting decreased hepatic function, have a high chance to cure, even though their absolute number is limited (Figure 1D). We do not have the precise result in patients who met these criteria (but the number of patients is probably limited).

Discontinuation rates due to adverse events were 1.9 percent (four patients) and 2.3 percent (four patients) in the 12-week and 24-week arms, respectively. The most commonly reported adverse events (>10 percent in either arm) were fatigue, headache, nausea, pruritus, insomnia, diarrhea, asthenia, rash, cough, irritability, anemia and dyspnea. On-treatment virologic failure occurred in one patient (0.5 percent) in the 12-week arm and three patients (1.7 percent) in the 24-week arm. In addition, 12 patients (5.9 percent) in the 12-week arm and one patient (0.6 percent) in the 24-week arm experienced relapse within 12 weeks post-treatment.

So, what have we learned from Turquoise-II study ?

First, a regimen with high efficacy in a population previously defined as « difficult to cure »: a 12 or 24 weeks of treatment with coformulated ABT-450/r–ombitasvir and dasabuvir, administered with ribavirin, resulted in high rates of SVR in patients with HCV compensated cirrhosis. Notably, approximately 15% of the study population had platelet counts that were clinically suggestive of portal hypertension. The overall efficacy of 12-week and 24-week treatment did not differ significantly (91.8% and 95.9%, respectively). Patients with HCV genotype 1a infection and a null response to prior PegIFN–ribavirin treatment might benefit from a 24 weeks treatment duration. In the most severe patients, again those with low platelets (< 10^9/L) (SVR=88% for 12 weeks vs 97% for 24 weeks) and those with low albumin; the ideal duration of treatment remains unkown (12 vs 24 weeks).

Second, a regimen well-tolerated in this specific population. The majority of adverse events were mild or moderate in severity, with few events occurring more frequently in the 24-week group than in the 12-week group. Serious adverse events occurred in 5.5% of all patients, with similar rates in each group, and few patients discontinued the study treatment because of

adverse events (2.1% overall). Declines in the hemoglobin level of grade 2 or higher occurred in 7.2% of patients in the 12- week group and in 11.0% of patients in the 24-week group. Declines in the hemoglobin level were successfully managed with modifications in the ribavirin dose, without a negative effect on the rate of SVR. Elevations in indirect bilirubin with this regimen are probably related to ribavirin-associated hemolysis, along with inhibition of the bilirubin transporter OATP1B1 by ABT-450 (protease inhibitors). Elevated bilirubin levels did not lead to treatment discontinuation, were not associated with elevations in the alanine aminotransferase level, and resolved to baseline levels during the post-treatment period.

What are the gaps to fill ? what the ideal study should perform ?

(1) Eligibility criteria should be more precisely defined to include more patients with portal hypertension (oesophageal varices, low platelet count) liver insufficiency (low albumin), Child-Pugh A to B7, and/or compensated cirrhosis who presented previous decompensation (ascites or bleeding). A better definition and phenotyping of eligibility criteria should be outlined since significant proportion of patients with elasticity higher than 14.8 kPa might have bridging fibrosis (F3) without cirrhosis. To avoid unexpected issues with salvage therapy, well-designed studies in Child Pugh A to B7 and kidney dysfunction should be performed. In our opinion, patients with concurrent small hepato-cellular (HCC) and/or candidates to liver transplantation should be included.

(2) Long-term follow-up will be mandatory to demonstrate cirrhosis reversibility, portal hypertension reduction, HCC reduction and finally reduction of liver or not related mortality.

(3) These excellent results, however, should be confirmed in large number of patients with predictors of non response : in particular in patients with genotype 1a and previous non response and with more advanced cirrhosis. In European countries (specially southern and eastern europe) HCV genotype 1b is the most prevalent.

(4) Finally, do we need ribavirin in this difficult-to-treat population, given the excellent results of this combination and the adverse events related to ribavirin ? We will need to

investigate if ribavirin is necessary.

In conclusion, this large phase III study showed excellent results in term of efficacy and safety profile in GT1 HCV cirrhotic patients, in some cases bordering on decompensation. Several issues are still to be filled. We will need available IFN-free regimen for decompensated cirrhosis and a major issue will be access treatment. Phase III data in patients with cirrhosis and other HCV genotypes, such as Genotype 3 and 4, are clearly also an unfulfilled need [9]. While we have to congratulate this important addition to current knowldege, some caution and more importantly “real life” dataset are still needed, specially regarding safety and drug-drug interactions.

Conflict of interest

Tarik Asselah is a speaker and investigator for AbbVie, BMS, Tibotec, Janssen, Gilead, Roche and Merck.

Savino Bruno: advisory board MSD; speaker for AbbVIe, Roche and MSD.

Antonio Craxì is a speaker for AbbVIe, Gilead, Janssen, Roche and MSD.

References

[1] Bruno S, Shiffman ML, Roberts SK, Gane EJ, Messinger D, Hadziyannis SJ, et al. Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. Hepatology; 2010: 51:388–397.

[2] Boccaccio V, Bruno S. Management of HCV patients with cirrhosis with direct acting antivirals. Liver Int. 2014; 34 Suppl 1:38-45.

[3] Hezode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, et al. Effectiveness of Telaprevir or Boceprevir in Treatment-Experienced Patients With HCV Genotype 1 Infection and Cirrhosis. Gastroenterology. 2014; 147(1):132-142.

[4] Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents : the best interferon-free combinations. Liver Int. 2014; 34 Suppl 1:69-78.

[5] Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Müllhaupt B, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med 2013; 369: 630–9.

[6] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and

Sofosbuvir for Untreated HCV Genotype 1 Infection. N Engl J Med 2014 ; 370:1889

1898.

[7] Vierling JM, Zeuzem S, Poordad F, Bronowicki JP, Manns MP, Bacon BR, et al. Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: Meta-analysis of 5 trials.J Hepatol. 2014; 61(2):200-9.

[8] Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT 450/r Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med ; 2014 ; 370:1273–1982.

[9] Asselah T, De Muynck S, Broet P, Masliah-Planchon J, Blanluet M, Bieche I, et al. IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. J Hepatol 2011; 56: 527–532.

Fig. 1. Turquoise-II: trial design and results. (A) Trial Design. This is an open-label phase 3 trial involving previously untreated and previously treated adults with HCV genotype 1 infection and compensated cirrhosis. 380 patients with Child-Pugh class A cirrhosis were randomly assigned to receive either 12 or 24 weeks of treatment with ABT-450/r-ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir), dasabuvir (250 mg twice daily), and ribavirin administered according to body weight. (B) Main results. Patients achieved SVR_{12} of 91.8 percent and 95.9 percent in the 12-week and 24-week treatment arms, respectively (no statistical difference). (C) Results: SVR_{12} Rates by Prior Treatment Response in HCV Subtype 1a. Among patients with HCV genotype 1a infection and a prior null response, 39 of 42 patients in the 24-week group had a SVR12 (92.9% [95% CI, 85.1 to 100]), as compared with 40 of 50 patients in the 12-week group (80.0% [95% CI, 68.9 to 91.1]). (D) Results: ITT SVR12 rates by surrogates of portal hypertension and hepatic function.

Figure 1A

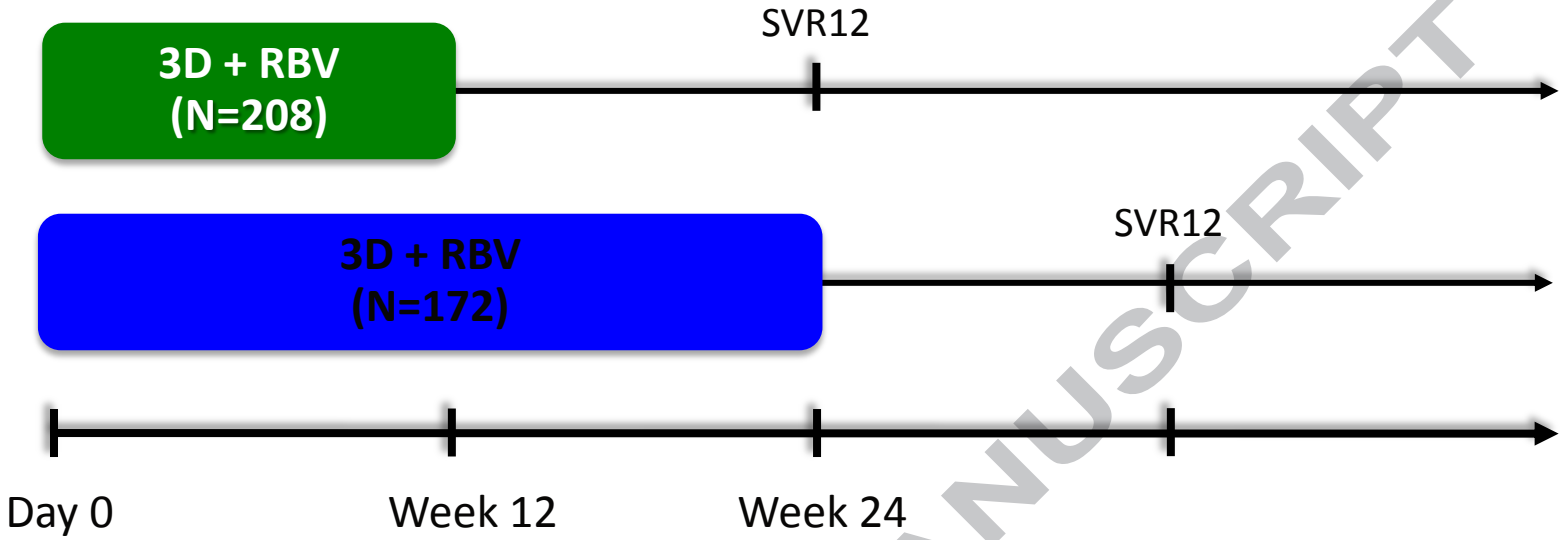

Figure 1B

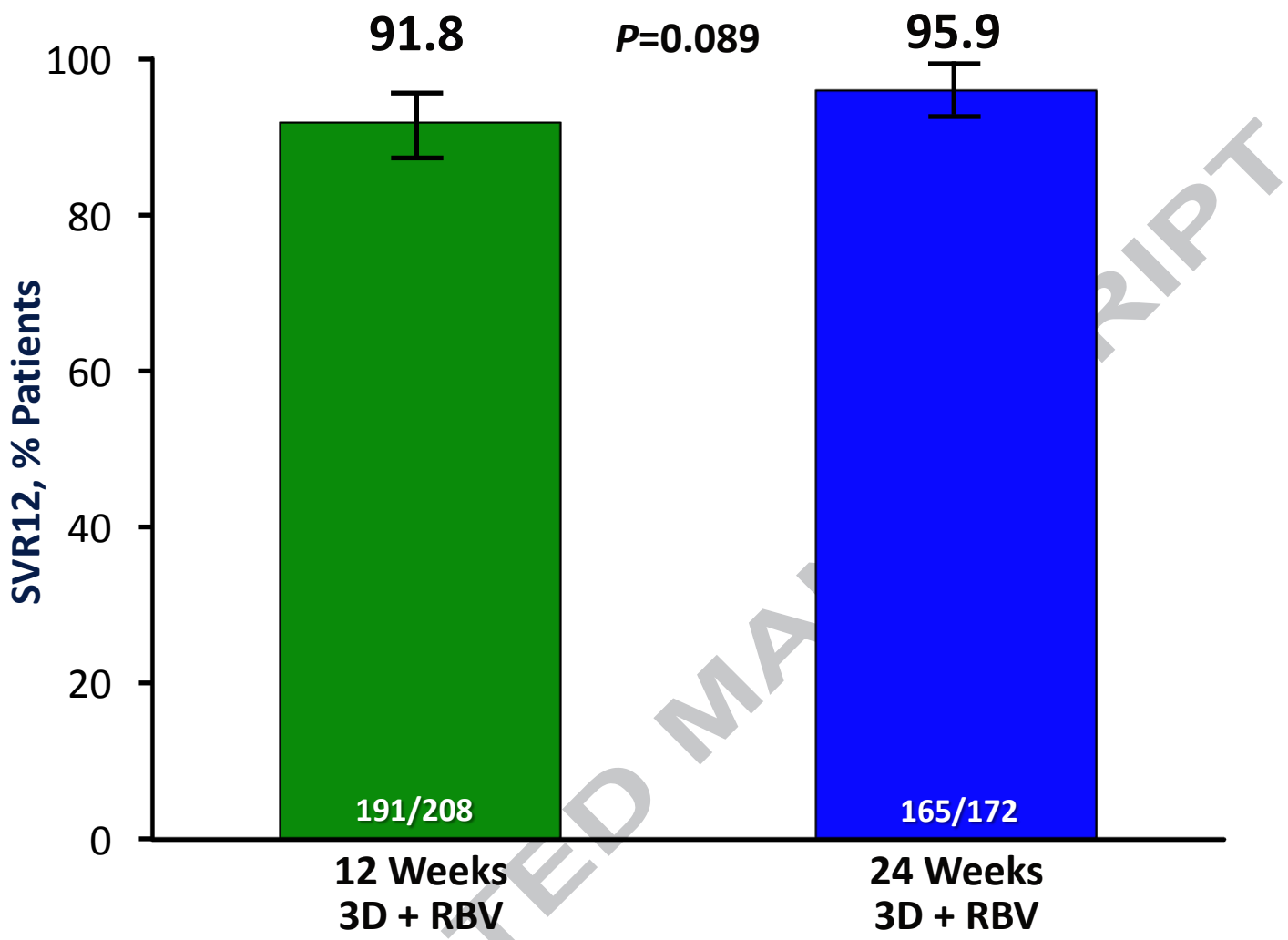

Figure 1C

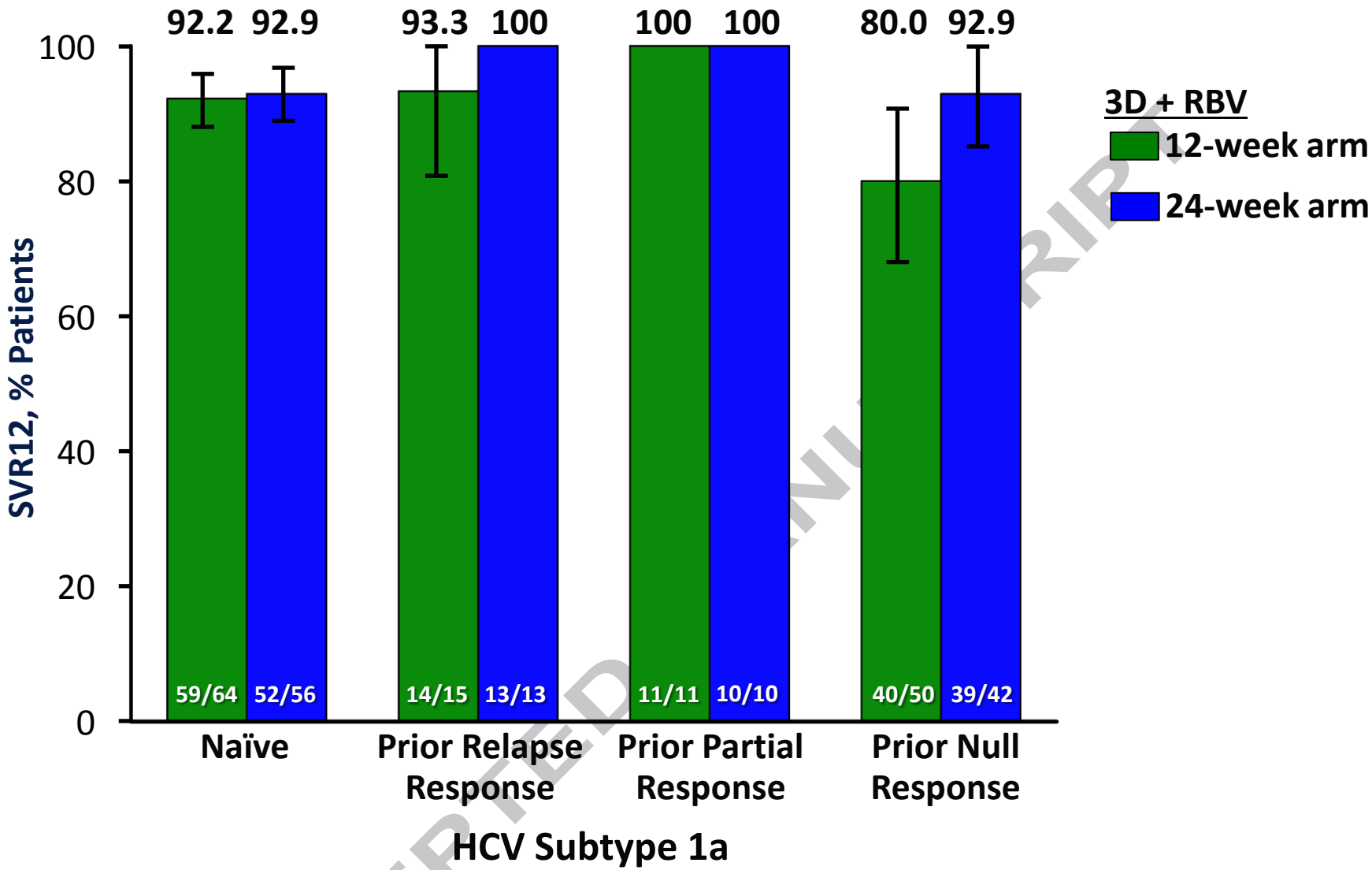

Figure 1D