Title:

JUMP-C: A Randomized Trial of Mericitabine Plus Peginterferon Alfa-2a/Ribavirin for 24 Weeks in Treatment-Naive HCV Genotype 1/4 Patients

Authors:

Paul J. Pockros,[1] Donald Jensen,[2] Naoky Tsai,[3] Ryan Taylor,[4] Alnoor Ramji,[5] Curtis Cooper,[6] Rolland Dickson,[7] Alan Tice,[8] Rohit Kulkarni,[9] John M. Vierling,[10] Marie Lou Munson,[9] Ya-Chi Chen,[11] Isabel Najera,[11] and James Thommes[9] on behalf of the JUMP-C Investigators*

1. Scripps Clinic and Scripps Translational Science Institute, La Jolla, CA; 2. Center for Liver Diseases, University of Chicago Hospitals, Chicago, IL; 3. University of Hawaii, Honolulu, HI; 4. The University of Kansas Hospital Medical Center, Kansas City, KS; 5. Division of Gastroenterology, University of British Columbia, Vancouver, BC, Canada; 6. University of Ottawa, The Ottawa Hospital, Ottawa, ON, Canada; 7. Dartmouth-Hitchcock Medical Center, Lebanon, NH; 8. Infections Limited Hawaii, Honolulu, HI; 9. Genentech, South San Francisco, CA; 10. Baylor College of Medicine, Houston, TX; 11. Roche, Nutley, NJ.

*Additional JUMP-C Investigators are listed in the Appendix.

Keywords

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FOOTNOTE PAGE

Corresponding author contact details:

Division of Gastroenterology/Hepatology and Liver Disease Center,

Scripps Clinic

10666 North Torrey Pines Road

La Jolla

CA 92037

USA

pockros.paul@scrippshealth.org

List of abbreviations:

CI, confidence interval;

eRVR, extended rapid virologic response;

HCV, hepatitis C virus;

RVR, rapid virologic response;

SVR, sustained virologic response.

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ABSTRACT

Mericitabine is a selective nucleoside analog inhibitor of the HCV NS5B RNA-dependent RNA polymerase, with activity across all HCV genotypes. Treatment-naive patients infected with HCV genotype 1 or 4 were randomized to 24 weeks of double-blind treatment with either mericitabine 1,000 mg (N = 81) or placebo (N = 85) twice daily in combination with peginterferon alfa-2a/ribavirin. Patients randomized to mericitabine with HCV RNA <15 IU/mL from week 4–22 (extended rapid virologic response RVR [eRVR]) stopped all treatment at week 24; all other patients continued peginterferon alfa-2a/ribavirin to complete 48 weeks of treatment. The primary efficacy endpoint was sustained virologic response (SVR, HCV RNA <15 IU/mL after 24 weeks of treatment-free follow-up). SVR was achieved in 56.8% (95% CI 45.9–67.0%) of mericitabine-treated patients and 36.5% (95% CI 27.0–47.1%) of placebo-treated patients (Δ = 20.3%, CI 5.5–35.2%). SVR rates were higher in mericitabine- than placebo-treated patients when subdivided by *IL28B* genotype (CC, 77.8% vs. 56.0%; non-CC, 44.1% vs. 16.2%) and hepatic fibrosis (noncirrhotic, 63.3% vs. 41.9%; cirrhotic, 38.1% vs. 21.7%). Overall relapse rates were 27.7% and 32.0% in mericitabine- and placebo-treated patients, respectively. No evidence of NS5B S282T-variant virus, or phenotypic resistance to mericitabine was observed in the one patient who experienced partial response. No S282T variants were detected in any baseline samples. The safety profile of mericitabine was similar to that of placebo and fewer patients in the mericitabine than in the placebo group discontinued treatment for safety reasons. ***Conclusion:*** A 24-week response-guided combination regimen of mericitabine 1,000 mg twice daily plus peginterferon alfa-2a/ribavirin is well tolerated and more effective than a standard 48-week course of peginterferon alfa-2a/ribavirin.

INTRODUCTION

Treatment for chronic hepatitis C virus (HCV) infection is evolving rapidly. The first direct-acting antiviral agents for HCV, protease inhibitors, were approved in 2011 and have changed the standard of care for patients with HCV genotype 1 infection.(1) A number of other agents from several different pharmacological classes are now in late-phase development. The HCV protease inhibitors boceprevir and telaprevir significantly increase sustained virologic response (SVR) rates for patients with genotype 1 infection, including previous non-responders to peginterferon/ribavirin.(2–6) However, boceprevir and telaprevir increase the safety burden on patients.(7,8) For example, real-life experience with telaprevir and boceprevir from an interim analysis of the French CUPIC (Compassionate Use of Protease Inhibitors in viral C Cirrhosis) study indicated that among patients with at least 16 weeks of treatment with boceprevir or telaprevir, patients with cirrhosis have higher rates of severe adverse events (38.4% and 48.6%, respectively) and higher rates of discontinuation due to severe adverse events (7.4% and 14.5%, respectively) than were experienced in phase 3 trials.(2–6, 9) Furthermore, boceprevir and telaprevir increase the dosing complexity and are metabolized by cytochrome P450 isoenzymes, which expose patients to a large number of potentially clinically significant pharmacokinetic drug–drug interactions.(10)

Thus, there is an ongoing need for new agents with different pharmacological properties to optimize treatment for chronic hepatitis C. Polymerase inhibitors are drugs that inhibit the NS5B RNA-dependent RNA polymerase of HCV. Polymerase inhibitors fall into two distinctive groups: nucleoside/nucleotide inhibitors and non-nucleoside inhibitors. Nucleoside/nucleotide inhibitors are analogs of natural substrates that bind to the active site of the viral polymerase and act as RNA chain terminators. The active site of the polymerase is highly conserved;(11) thus, viruses with mutations that disrupt the function of the active site tend to be replication impaired.(12,13) Nucleoside polymerase inhibitors are active across all HCV genotypes and for those with a

resistance profile that occurs through the S282T mutation have a high barrier to resistance.(13–17)

In contrast, non-nucleoside inhibitors bind to several allosteric sites and induce conformational changes in the polymerase. The antiviral activity of non-nucleoside inhibitors is influenced by HCV genotype and subtype and these drugs vary in the extent to which they select for resistant variants.(18,19)

Mericitabine is being evaluated in combination with peginterferon alfa-2a/ribavirin, with the HCV protease inhibitor danoprevir in a dual oral interferon-free regimen, and in a quadruple combination regimen with peginterferon alfa-2a/ribavirin and danoprevir.(20–24)

Treatment with mericitabine plus peginterferon alfa-2a/ribavirin for up to 12 weeks in a phase 2b clinical trial increased on-treatment virologic response rates and was safe and well tolerated, but did not increase SVR rates when compared with peginterferon alfa-2a/ribavirin.(25) The objective of the present trial (JUMP-C) was to evaluate the efficacy and safety of 24 weeks of response-guided therapy with mericitabine plus peginterferon alfa-2a/ribavirin in treatment-naive patients with HCV genotype 1 or 4 infection.

METHODS

Trial Design

JUMP-C was a phase 2b, randomized, double-blind, parallel-group study in treatment-naive patients with HCV genotype 1 or 4 infection (clinicaltrials.gov NCT01057667). The study was conducted at 25 sites in the United States and Canada. The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by an Institutional Review Board, and each patient provided informed consent.

Patients

Treatment-naive adults aged 18 to 70 years with chronic hepatitis C of at least 6 months' duration, a serum HCV RNA titer of at least 50,000 IU/mL (COBAS® Ampliprep/ COBAS® TaqMan® HCV Test; LLOD=15 IU/ml), and HCV genotype 1 or 4 infection were eligible for the study. Patients were required to have had a liver biopsy within the previous 24 months (36 months in patients with cirrhosis/bridging fibrosis). Patients with compensated cirrhosis (Child-Pugh Grade A) or transition to cirrhosis were required to have had an abdominal ultrasound, computerized tomography scan, or magnetic resonance imaging scan demonstrating the absence of evidence of hepatocellular carcinoma (within 2 months prior to randomization) and a serum alpha-fetoprotein level <100 ng/mL. Exclusion criteria are listed in the **Online Supplement**.

Treatment

Patients were randomized in a 1:1 ratio (Fig. 1) to receive either oral mericitabine (Genentech, San Francisco, CA) 1,000 mg or matching placebo twice daily in combination with peginterferon alfa-2a (40KD) (PEGASYS®, Roche, Basel, Switzerland) 180 µg subcutaneously once weekly and oral ribavirin (COPEGUS®, Roche) at a dosage of 1,000 mg/day (body weight <75 kg) or

1,200 mg/day (body weight ≥75 kg) in two divided doses. Mericitabine and ribavirin were taken together twice daily with food.

All patients in the mericitabine group received study treatment for 24 or 48 weeks, followed by a treatment-free period of 24 weeks. Patients with an eRVR, defined as undetectable HCV RNA from week 4 through 22, were assigned to complete 24 weeks of treatment with the three-drug regimen; patients without an eRVR were assigned to 48 weeks of treatment (24 weeks with the three-drug regimen followed by 24 weeks of treatment with peginterferon alfa-2a (40KD)/ribavirin). All patients in the placebo control group received study treatment for 48 weeks, with a treatment-free follow-up period of 24 weeks.

Patients were required to discontinue all study treatment if they did not experience a ≥2-$\log_{10}$ drop in HCV RNA by week 12 or had detectable HCV RNA (COBAS® Ampliprep/ COBAS® TaqMan® HCV Test; LLOD=15 IU/ml) at week 24.

Patients were randomized by an interactive voice response system (IVRS). Randomization was centralized and stratified by cirrhotic status (cirrhosis/transition to cirrhosis versus no cirrhosis/transition to cirrhosis) and creatinine clearance (no more than 20% of the patients enrolled were to have an estimated creatinine clearance >70 to ≤80 mL/min calculated by the Cockcroft-Gault formula). A computer-generated randomization list was maintained by the sponsor and neither study personnel nor investigators had access to the list. Double-blinding was achieved through the use of matching placebo tablets. Investigators were advised by IVRS at week 24 as to whether a patient was to stop treatment (mericitabine-treated patients with an eRVR) or continue to week 48 (mericitabine-treated patients without an eRVR and all placebo-treated patients).

Criteria for discontinuing or modifying the treatment regimen are listed in the **Online Supplement**.

The use of hematopoietic growth factors to manage hematologic adverse events or laboratory abnormalities was allowed, but not encouraged.

Outcomes

Serum HCV RNA concentration was determined at baseline and at weeks 1, 2, 4, 8, 16, 20, 22, 24, 36, 42, and 48 of treatment and at weeks 4, 12, and 24 of treatment-free follow-up using the Roche COBAS TaqMan® HCV Test (detection limit 15 IU/mL) (Roche Diagnostics, Indianapolis, IN). Investigators and patients were blinded to HCV RNA test results.

The primary efficacy endpoint was SVR defined as undetectable HCV RNA (<15 IU/mL) 24 weeks after the last dose of study medication. Other secondary efficacy endpoints included undetectable HCV RNA at weeks 4, 12, 24, 36, 48, and 60. Relapse was defined as detection of HCV RNA in a patient who had an end-of-treatment response (undetectable HCV RNA at end of treatment). Only patients with an end-of-treatment response were included in calculations of relapse.

Whole blood samples were taken from patients who consented to the optional sampling for the Roche Clinical Repository. *IL28B* rs12979860 genotype was determined by Real-time TaqMan PCR and results were reported as CC and non-CC (CT and TT combined).

Drug Resistance Monitoring

Blood samples were collected for resistance monitoring from all patients. Population and clonal sequencing was performed as well as phenotypic drug susceptibility evaluation for samples from patients meeting resistance monitoring criteria including those who experienced viral breakthrough, non-response, or partial response during treatment with mericitabine plus peginterferon alfa-2a/ribavirin. Viral breakthrough was defined as a sustained increase in HCV RNA level of >1 $\log_{10}$ from nadir before the end of treatment with mericitabine where nadir is ≥0.5 $\log_{10}$ decrease from baseline, *or* reversion of HCV RNA from undetectable (≥15 IU/mL) for ≥2 consecutive measurements to quantifiable (≥43 IU/mL) for ≥2 consecutive measurements.

Non-response was defined as a decline in serum HCV RNA level of <0.5 $\log_{10}$ by the end of mericitabine treatment of 2 weeks' duration. Partial response was defined as a serum HCV RNA level ≥1,000 IU/mL at the end of at least 4 weeks of mericitabine dosing or an initial decline in serum HCV RNA of >0.5 $\log_{10}$ from baseline followed by stabilization. Baseline samples from all patients were sequenced spanning the NS5B polymerase coding region.

Safety assessments included adverse events and laboratory tests. Because a renal safety signal was detected in preclinical studies in monkeys, the renal safety of mericitabine was a particular focus of the safety analysis.

Sample Size and Statistical Analysis

The study protocol did not specify any formal statistical hypothesis testing and the planned enrollment of 80 patients per treatment group was based on convenience. Also, for 80 patients per treatment group, the 95% confidence limits are approximately ±9% to ±11% around binomial proportions observed from 20% to 50%. The 95% confidence intervals (CI) for the individual patient virologic response rates were calculated by the Wilson score method without continuity correction. All patients who were randomized and who received at least one dose of study medication were included in the intention-to-treat population. All patients who received at least one dose of study medication and had at least one post-baseline safety assessment were included in the safety analysis.

Logistic regression analyses were used to explore associations between SVR and pretreatment variables and between relapse and pretreatment variables in patients with an eRVR (see **Online Supplement**).

RESULTS

Patient Disposition and Baseline Characteristics

The first patient was enrolled on January 26, 2010, and the last patient completed follow-up on October 10, 2011. A total of 228 patients were enrolled and 168 randomized at 25 study centers in the United States and Canada. Of those randomized, 166 patients (98.9%) received at least one dose of study medication and were included in the intention-to-treat population (Fig. 2).

A total of 59 patients (35.6%) were prematurely withdrawn during study treatment (Fig. 2). The majority of these (67.8%) were for non-safety reasons. Discontinuations due to lack of efficacy were more frequent in the placebo group than in the mericitabine group (26 vs. 7 patients, respectively).

Both groups were generally well balanced with regard to demographics and baseline disease characteristics (Table 1). The majority of patients were infected with HCV genotype 1a (62% in the mericitabine-treated group and 80% in the placebo group). Overall, approximately 25% of patients had transition to cirrhosis/cirrhosis at baseline (26% in the mericitabine-treated group versus 27% in the placebo group). From the subset of patients who had *IL28B* data available, a similar proportion of patients in each group had a non-CC *IL28B* genotype (65% and 60% in the mericitabine and placebo treatment groups, respectively).

Efficacy

Treatment with mericitabine plus peginterferon alfa-2a/ribavirin was associated with consistently higher virologic response rates compared with treatment with placebo plus peginterferon alfa-2a/ribavirin during treatment and follow-up (Fig. 3). A higher percentage of patients achieved the primary efficacy endpoint (SVR) after treatment with mericitabine than placebo (56.8%, CI 45.9–67.0%, vs. 36.5%, CI 27.0–47.1%, respectively, Δ = 20.3%, CI 5.5–35.2%).

Treatment with mericitabine was also associated with consistently higher on-treatment virologic response rates and SVR rates when patients were grouped according to cirrhosis status (Fig. 4A) and host *IL28B* genotype (CC or non-CC) (Fig. 4B).

In a logistic regression analysis HCV subtype (1a vs. 1b) was not associated with SVR in the overall population (P = 0.953) or in the sub-set of patients with known host *IL28B* genotype (P = 0.900).

An eRVR was achieved by 49 patients (60.5%) in the mericitabine group and 11 patients in the placebo group (12.9%). SVR rates among these individuals were 73.5% and 100.0%, respectively, and relapse rates were 21.3% (10/47) and 0% (0/11), respectively. Among non-eRVR patients SVR rates were 31.3% in the mericitabine group and 27.0% in the placebo group.

The overall relapse rate was 27.7% in mericitabine-treated patients and 32.0% in placebo-treated patients (Fig. 5). Among patients without cirrhosis the relapse rates were lower than in the overall study population (19.1% and 30.0% in patients treated with mericitabine and placebo, respectively), and among patients with transition to cirrhosis/cirrhosis relapse rates were higher than in the overall population (50.0% and 40.0% in patients treated with mericitabine and placebo, respectively). The greatest difference in relapse rates was observed in patients with a non-CC host *IL28B* genotype among whom the relapse rates were 38.5% in mericitabine-treated patients and 62.5% in placebo-treated patients (Fig. 5). In a logistic regression analysis, older age and higher weight were the two most important factors associated with relapse in patients with an eRVR who discontinued all therapy at week 24. Further analyses indicated that neither age nor weight was associated with trough concentrations of mericitabine (data not shown).

Resistance Monitoring

The *in vitro*-identified mericitabine NS5B resistance mutation S282T was not detected in baseline samples from any patient (samples from 160 of 161 genotype 1 patients and three of five genotype 4 patients were successfully amplified).

A total of 31 patients met the criteria for resistance monitoring: one patient (genotype 1b) had a partial response during mericitabine therapy; nine patients (five genotype 1a, four genotype 1b) experienced breakthrough during treatment with peginterferon alfa-2a/ribavirin; 16 patients (nine genotype 1a, six genotype 1b, one genotype 4) relapsed after completing 48 weeks of therapy; and five patients (four genotype 1a, one genotype 1b) discontinued treatment between weeks 4 and 12.

The NS5B region was successfully sequenced in samples obtained from 30 of these 31 patients. The S282T mutation was not detected in any sample from the 30 patients. Phenotypic characterization was performed in samples from 14 patients, including the patient with a partial response while on mericitabine, five patients who experienced breakthrough during treatment with peginterferon alfa-2a/ribavirin and eight patients who experienced relapse. Three common non-polymorphic amino acid changes (D61D/G, A112A/T, and D559D/N) were detected in samples obtained from these 30 patients but none of these mutations conferred resistance to mericitabine. In the one patient with a partial response during treatment with mericitabine, mixtures of wild-type and mutants at residues L159F, I262V, and L320F were identified in on-treatment and follow-up samples. For each patient, the EC_{50} values for mericitabine in on-treatment and follow-up samples remained within 2-fold of the respective baseline samples.

Safety

The safety profile of mericitabine did not differ greatly from that of placebo. The nature and incidence of adverse events and laboratory abnormalities were typical of those associated with

peginterferon alfa-2a/ribavirin. No new safety concerns were identified. The most frequent adverse events were fatigue, headache and nausea, with a similar incidence in both treatment groups (Table 2).

Fewer patients in the mericitabine plus peginterferon alfa-2a/ribavirin group discontinued treatment for safety reasons (n = 6 vs. n = 13 in the placebo plus peginterferon alfa-2a/ribavirin group, respectively).

The incidence of peginterferon alfa-2a and ribavirin dose adjustments for laboratory abnormalities occurred with similar frequency in the two treatment groups (Table 2).

In total, eight patients (4.8%) experienced serious adverse events: five patients in the mericitabine group (6.2%) and three patients in the placebo group (3.5%) (Table 2). One mericitabine-treated patient experienced a transient increase in serum creatinine to greater than 2 times the upper limit of normal 11 weeks after the last dose of mericitabine. The abnormality was not replicated in subsequent tests and was not considered to be clinically significant.

DISCUSSION

This study demonstrates that response-guided treatment with the combination of 24 weeks of treatment with mericitabine plus peginterferon alfa-2a/ribavirin for 24 or 48 weeks is safe and is associated with a 20% higher SVR rate than that achieved in patients randomized to placebo plus peginterferon alfa-2a/ribavirin (56.8% vs. 36.5%). Moreover, when compared with placebo, mericitabine produced higher SVR rates among patients irrespective of cirrhosis status and host *IL28B* genotype (i.e., CC or non-CC). SVR rates were higher and relapse rates similar in patients with an *IL28B* CC genotype treated with mericitabine, most of whom received only 24 weeks of treatment, compared to placebo-treated patients, all of whom received 48 weeks of treatment.

The virologic response rates at weeks 4 and 12 in the present study were similar to those reported in the PROPEL study,(25) in which mericitabine was administered for up to 12 weeks with peginterferon alfa-2a/ribavirin. However, SVR rates were not improved with the addition of 8 or 12 weeks of mericitabine treatment in the PROPEL study. In contrast, 24 weeks of mericitabine administered with peginterferon alfa-2a/ribavirin in a response-guided strategy increased SVR rates relative to the control group in the JUMP-C study. The difference in SVR rates can be explained by a comparative analysis of relapse rates. Among patients who received response-guided therapy with mericitabine in JUMP-C the overall relapse rate was 28%. In contrast, the relapse rate was 52% in patients who received response-guided therapy with mericitabine at a dosage of 1,000 mg twice daily for 12 weeks in the PROPEL study. When the analysis is restricted to patients who achieved an eRVR and stopped all therapy at week 24 in either study, the relapse rate was lower in the present study (22%) and higher in the PROPEL study (57%).(25)

Although the overall relapse rates were similar in both the mericitabine and placebo control groups in JUMP-C, relapse rates varied by patient subgroups. Among patients treated with

mericitabine relapse rates were lowest in non-cirrhotic patients (F0–2) and in those with a host *IL28B* CC genotype, and highest in patients with transition to cirrhosis/cirrhosis and in those with non-CC genotypes. Nonetheless, relapse rates in mericitabine-treated patients who achieved an eRVR and completed 24 weeks of treatment are higher than one might expect when compared with the results of studies of other direct-acting antiviral agents that employed a response-guided therapy strategy.(3–5) In an attempt to explain these comparatively high relapse rates in patients who achieved an eRVR, a regression analysis was used to explore predictors of relapse. In these analyses increased age (≥50 years) and body weight (≥85 kg) were associated with relapse in patients with an eRVR. Further analyses revealed no effect of age or weight on mericitabine exposure, suggesting that the comparatively high relapse rates in patients who achieved an eRVR are not driven by difference in exposure. However, both age and weight are known to influence the effectiveness of peginterferon/ribavirin therapy, suggesting that responsiveness to peginterferon strongly influences viral clearance during virologic suppression associated with mericitabine. Mericitabine-treated patients with an *IL28B* CC genotype had the highest end-of-treatment response rate (100%) but more than 20% of these individuals experienced virologic relapse. This phenomenon may be related to interferon responsiveness and overall treatment duration. Most of the genotype CC patients in the mericitabine-treatment group received 24 weeks of peginterferon alfa-2a/ribavirin therapy, whereas CC patients in the placebo group received a full 48-week course of peginterferon alfa-2a/ribavirin therapy, but had a similar relapse rate. This suggests that mericitabine acts primarily by inhibiting viral replication rather than by preventing relapse.

Mericitabine was well tolerated when administered for 24 weeks in combination with peginterferon alfa-2a/ribavirin. The spectrum and severity of adverse events was similar in the two treatment groups. No novel adverse effects were observed, and mericitabine treatment did not exacerbate any known adverse events of peginterferon alfa-2a/ribavirin. Indeed, fewer

patients discontinued treatment with mericitabine than placebo. There was also no evidence that mericitabine has an additive effect on laboratory abnormalities associated with peginterferon/ribavirin, such as neutropenia, thrombocytopenia, or anemia. Mericitabine treatment did not alter renal function as assessed by creatinine clearance. No patients experienced a virologic breakthrough or non-response while on treatment with mericitabine and no evidence of genotypic or phenotypic resistance to mericitabine was observed during the study. The variant that confers resistance to mericitabine (NS5B S282T) was not detected in any sample collected from any patient at baseline, during mericitabine treatment, during follow-on treatment with peginterferon alfa-2a/ribavirin or during untreated follow-up. This is consistent with observations in other studies of mericitabine resistance.(26,27)

Furthermore, in a study of all-oral regimens with mericitabine with danoprevir, with and without ribavirin, the most common resistant mutations accompanying treatment failure were associated with danoprevir (R155K, V36M/A, and D168T)(28). In that study, only one genotype 1a patient with treatment failure was shown to select a viral isolate with dual resistance to both mericitabine and danoprevir, containing mutations in NS5b (S282T) and NS3 (R155K).(28) Taken together, the low incidence of the S282T mutation in studies of mericitabine in all-oral regimens and in combination with peginterferon alfa-2a/ribavirin show that virus containing the S282T amino acid substitution has low fitness and that mericitabine has a high barrier to resistance. Preliminary data from an ongoing trial shows that the quadruple combination of mericitabine, ritonavir-boosted danoprevir, peginterferon alfa-2a and ribavirin produces higher SVR12 rates and lower relapse rates than the triple combination of ritonavir-boosted danoprevir plus peginterferon alfa-2a/ribavirin in patients with a prior partial response to peginterferon/ribavirin.(29)

In conclusion, when administered for 24 weeks at a dosage of 1,000 mg twice daily as part of a response-guided combination with peginterferon alfa-2a/ribavirin, mericitabine produced higher

SVR rates than a standard 48-week course of peginterferon alfa-2a/ribavirin and was extremely well tolerated, without any documented antiviral resistance. Despite these results, recent favorable results achieved with all-oral direct-acting antiviral combination regimens suggest that future development scenarios for mericitabine will need to include combinations with other direct-acting antiviral agents. The high barrier to resistance, and the good tolerability and safety profile, make mericitabine potentially useful in combination with other direct-acting antivirals that have a lower barrier to resistance and may be more potent. Ongoing studies will provide data on the efficacy and safety of mericitabine in various interferon-free combinations with protease inhibitors and non-nucleoside polymerase inhibitors, and in a quadruple combination regimen with a protease inhibitor and peginterferon/ribavirin in the most difficult-to-treat populations.

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APPENDIX

In addition to the authors, the JUMP-C Investigators include the following: F. Anderson, Liver and Intestinal Research Center, USA; S. Arora, University of New Mexico, USA; N. Bräu, James J. Peters Veterans Affair Medical Center, Bronx, NY, USA; B. Freilich, Kansas City Research Institute, USA; M. Galambos, Digestive Healthcare of Georgia, USA; E. Godofsky, Bach and Godofsky Infectious Diseases, USA; I. Jacobson, Cornell University, USA; K. Kaita, University of Manitoba, Canada; P.Y. Kwo, Indiana University Hospital, USA; S.S. Lee, University of Calgary, Canada; P. Marotta, London Health Sciences Centre, University of Western Ontario, Canada; A. Min, Beth Israel Medical Center, USA; M. Porayko, Vanderbilt University Medical Center, USA; K.R. Reddy, University of Pennsylvania, USA; R.A. Rubin, Digestive Healthcare of Georgia, Atlanta, GA, USA; J. Strohecker, Columbia Gastroenterology Associates, USA; E. Tam, Liver and Intestinal Research Center, Canada.

Figure 1. Study design

Figure 2. Patient disposition

Figure 3. Virologic response over time

Figure 4. Virologic response (HCV RNA <15 IU/mL) stratified by cirrhosis status or *IL28B* genotype

Figure 5. Relapse rates overall and stratified by cirrhosis status or host *IL28B* genotype

Table 1: Baseline patient demographics and disease characteristic

ONLINE SUPPLEMENTARY APPENDIX

Exclusion criteria

Exclusion criteria included: infection with hepatitis A or B viruses or HIV; previous treatment with interferon-based therapy or any investigational anti-HCV agent; systemic antiviral therapy within the previous 3 months; history or evidence of medical condition associated with chronic liver disease other than HCV; absolute neutrophil count <1.5 x 10^9 cells/L; platelet count <90 x 10^9 cells/L; hemoglobin concentration <12 g/dL in females (<13 g/dL in males); history of renal disease, serum creatinine >1.5 times the upper limit of normal, an estimated creatinine clearance ≤70 mL/min or microproteinuria.

Pregnant or breastfeeding females and male partners of pregnant females were not eligible for the study.

Criteria for discontinuing or modifying the treatment regimen

Treatment with mericitabine or placebo was to be discontinued if any of the following occurred and were considered to be related to study treatment: any serious adverse event; ≥35% decrease in creatinine clearance; urine protein/creatinine ratio ≥0.5; hematuria of Grade 2 or higher severity; sustained hypertension (systolic/diastolic blood pressure >170/110 mm Hg); progressive rash of Grade 2 or higher severity; any clinically significant Grade 4 laboratory abnormality.

The dose of peginterferon alfa-2a could be reduced in a step-wise manner from 180 µg/week to 135 and 90 µg/week, and the dose of ribavirin could be reduced in 200 mg decrements in the event of adverse events or laboratory abnormalities. Patients who discontinued mericitabine

could continue with peginterferon alfa-2a/ribavirin, but patients who discontinued peginterferon alfa-2a were required to discontinue the entire treatment regimen.

Exploratory analyses

Logistic regression analyses were used to explore associations between 1) SVR and pretreatment variables among patients who received mericitabine and had genotype 1a or 1b infection (n = 74) including the subset of patients with a known host *IL28B* genotype (n = 47); and 2) differences between patients who achieved an SVR and those who relapsed after achieving an eRVR and stopping therapy at week 24 (n = 46; 36 with an SVR and 10 who relapsed). Independent variables included in these analyses were genotype (1a vs. 1b in the SVR analysis), age (≥50 vs. <50 years), weight (≥85 vs. <85 kg), sex (male vs. female), race (white vs. non-white), fibrosis stage (F3/4 vs. F0–2), baseline HCV RNA level (≥800,000 IU/mL vs. <800,000 IU/mL) and *IL28B* genotype (CC vs. non-CC, only in the subset of patients with known *IL28B* genotype).

CONFLICTS OF INTEREST

Paul J. Pockros – Consulting: Roche/Genentech, Vertex; Advisory arrangements: Roche/Genetech, Vertex, Merck; Speakers' bureau: Roche/Genetech, Vertex, Merck; Grants/contracts: research: Roche/Genetech, Vertex; Grants/contracts: unrestricted: Roche/Genetech, Vertex, Merck.

Donald Jensen – Consulting: Abbott, BMS, Boehringer-Ingelheim, Genentech/Roche; Tibotec/J&J, Astex, Biotica, Vertex, Gilead/Pharmasset, Inhibitex, Merck; Grants/contracts: research: Abbott, BMS, Boehringer-Ingelheim, Genentech/Roche; Tibotec/J&J; Other interests: Consensus Medical Communications, Clinical Care Options.

Naoky Tsai – Consulting: Roche/Genentech; Advisory arrangements: Roche/Genentech; Speakers' bureau: Roche/Genentech; Grants/contracts: research: Roche/Genentech; Beckman.

Ryan Taylor – Speakers' bureau: Roche; Grants/contracts: research: Roche.

Alnoor Ramji – Consulting: Gilead, Merck & Co., Hoffman La Roche, Vertex, Janssen; Advisory arrangements: Gilead, Merck & Co., Hoffman La Roche, Vertex, Janssen; Speakers' bureau: Gilead, Merck & Co., Hoffman La Roche, Vertex, Janssen; Grants/contracts: unrestricted: Gilead, Merck & Co., Hoffman La Roche, Vertex; Travel grants: Merck & Co., Hoffman La Roche, Vertex.

Curtis Cooper – Advisory arrangements: Roche, Merck; Speakers' bureau: Roche, Merck, Vertex; Travel grants: Roche, Merck, Vertex

Rolland Dickson – No conflicts.

Alan Tice – No conflicts.

Rohit Kulkarni – Employment, office, directorship, or personal compensation: Employee of Genentech.

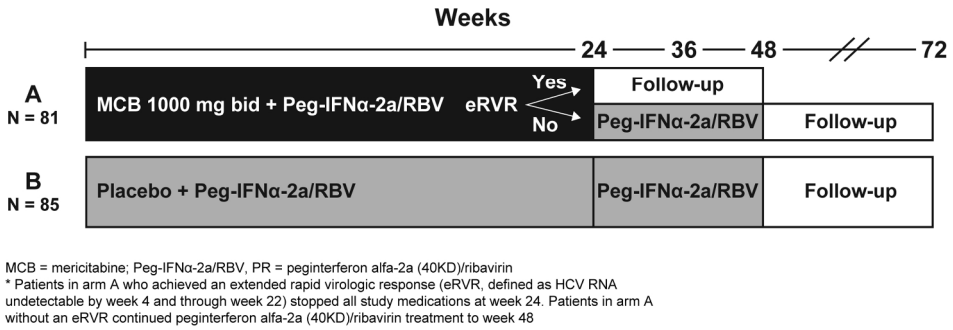
John M. Vierling – Advisory arrangements: Abbott, Bristol-Myers Squibb, Excalenz, Gilead, Globeimmune, HepQuant, Hyperion, Immuron, Janssen, Novartis, Roche, Schering (now Merck), Salix, Sundise, Vertex, HepaLife Technologies, Herbalife, Ocera; Speakers' bureau: Chronic Liver Diseases Foundation; Grants/contracts: research: Abbott, Bristol-Myers Squibb, Conatus, Excalenz, Gilead, Globeimmune, Hyperion, Idenix-Novartis, Ikaria, Intercept, Merck (formerly Schering), Mochida, Novartis, Ocera, Pfizer, Pharmasset, Roche, Sundise, Vertex, Zymogenetics

Marie Lou Munson – Employment, office, directorship, or personal compensation: Employee of Genentech.

Ya-Chi Chen – Employment, office, directorship, or personal compensation: Employee of Roche.

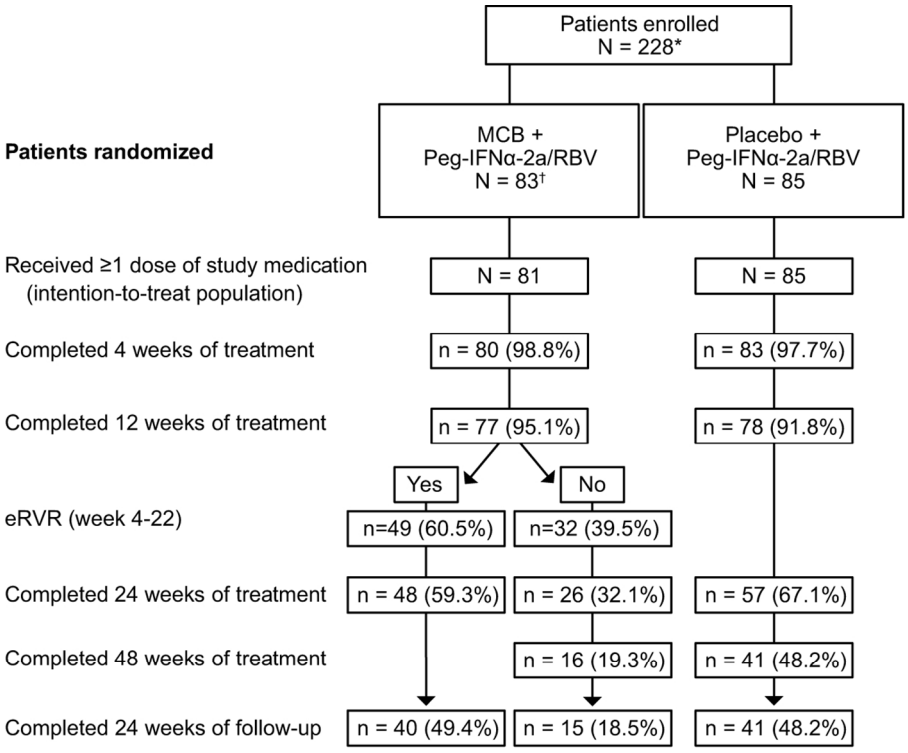
Isabel Najera – Stock ownership or equity: Roche; Employment, office, directorship, or personal compensation: Employee of Roche.

James Thommes – Employment, office, directorship, or personal compensation: Medical Director at Genentech.



MCB = mericitabine; Peg-IFNα-2a/RBV, PR = peginterferon alfa-2a (40KD)/ribavirin
* Patients in arm A who achieved an extended rapid virologic response (eRVR, defined as HCV RNA undetectable by week 4 and through week 22) stopped all study medications at week 24. Patients in arm A without an eRVR continued peginterferon alfa-2a (40KD)/ribavirin treatment to week 48

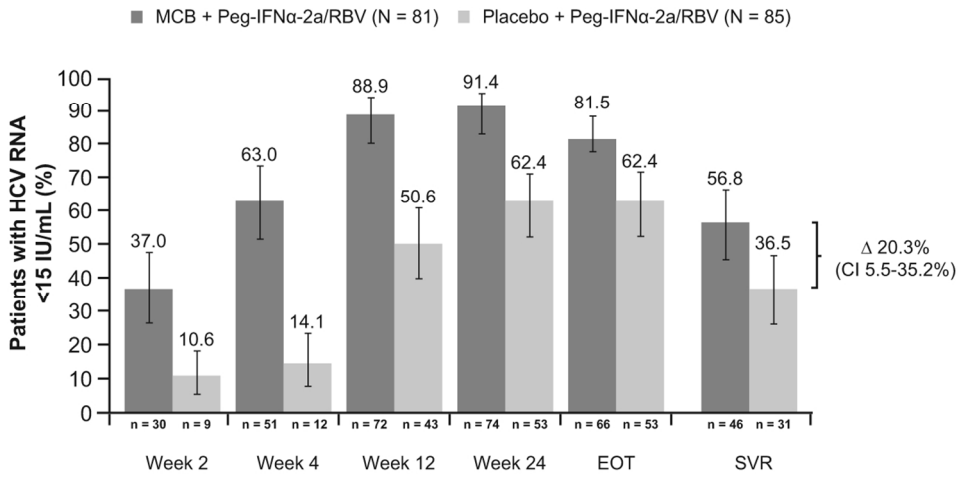
Figure 1. Study design
180x59mm (300 x 300 DPI)



Premature withdrawal (weeks 0-48), n (%):	17 (21)	42 (49)
Adverse events	6 (7)	13 (15)
Insufficient therapeutic response	7 (9)	26 (31)
Violated entry criteria	1 (1)	0 (0)
Refused treatment	1 (1)	0 (0)
Failure to return	0 (0)	1 (1)
Administrative/other	0 (0)	2 (2)
Withdrew consent	2 (3)	0 (0)

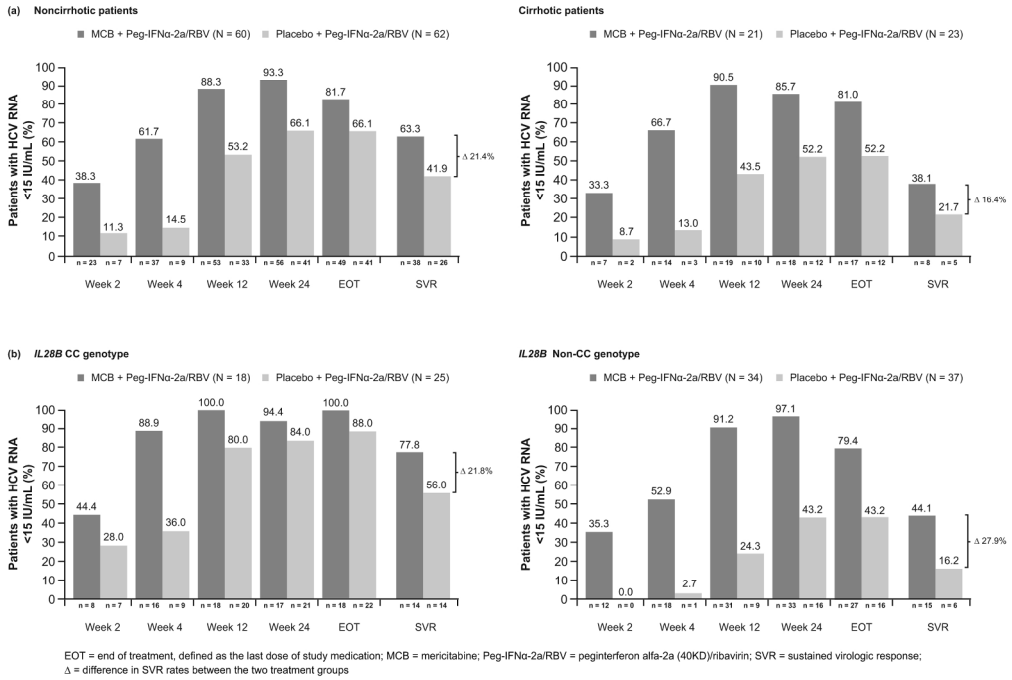
MCB = mericitabine; Peg-IFNα-2a/RBV = peginterferon alfa-2a (40KD)/ribavirin
* Sixty patients were enrolled but not randomized because of violation of entry criteria (n=51), withdrawal of consent (n=5) and other reasons (n=4); † Two patients were randomized but did not receive study medication because they violated entry criteria

Figure 2. Patient disposition
103x137mm (300 x 300 DPI)



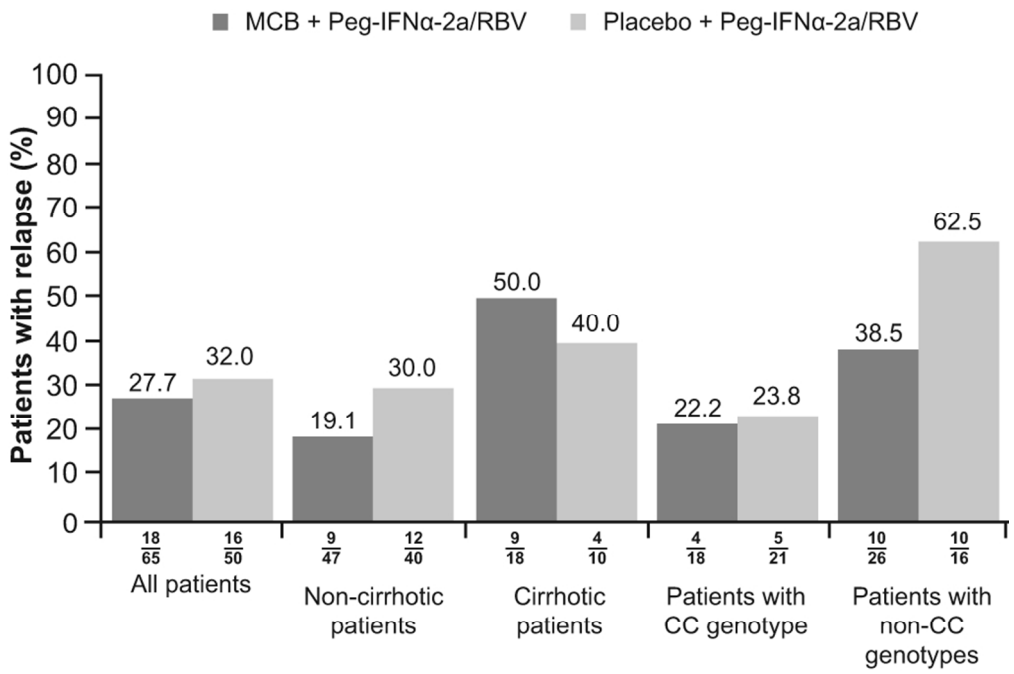
EOT = end of treatment, defined as the last dose of study medication;
MCB = mericitabine; Peg-IFNα-2a/RBV = peginterferon alfa-2a (40KD)/ribavirin;
SVR = sustained virologic response; Δ = difference in SVR rates between the two treatment groups;
Error bars correspond to 95% confidence interval (CI) of the difference in SVR rates between the two treatment groups

Figure 3. Virologic response over time
114x66mm (300 x 300 DPI)



EOT = end of treatment, defined as the last dose of study medication; MCB = mericitabine; Peg-IFNα-2a/RBV = peginterferon alfa-2a (40KD)/ribavirin; SVR = sustained virologic response; Δ = difference in SVR rates between the two treatment groups

Figure 4. Virologic response (HCV RNA <15 IU/mL) stratified by cirrhosis status or IL28B genotype
204x136mm (300 x 300 DPI)



MCB = mericitabine; Peg-IFNα-2a/RBV = peginterferon alfa-2a (40KD)/ribavirin

Figure 5. Relapse rates overall and stratified by cirrhosis status or host IL28B genotype
86x61mm (300 x 300 DPI)

Table 1: Baseline patient demographics and disease characteristics

	Mericitabine plus peginterferon alfa-2a /ribavirin N=81	**Placebo plus peginterferon alfa-2a /ribavirin N=85**
Male, n (%)	51 (63.0)	67 (78.8)
Race, n (%)		
White	63 (77.8)	69 (81.2)
Black	10 (12.4)	8 (9.4)
Other	8 (9.9)	8 (9.4)
Hispanic, n (%)	10 (12.4)	9 (10.6)
Mean age (± SD), years	49.7 (10.4)	48.2 (9.8)
Mean weight (± SD), kg	82.3 (14.8)	84.8 (16.0)
Mean BMI (± SD), kg/m^2	27.6 (4.2)	27.7 (4.0)
Mean creatinine clearance (± SD), mL/min	116.6 (30.7)	120.3 (31.7)
HCV genotype, n (%)		
1a	50 (61.7)	68 (80.0)
1b	24 (29.6)	17 (20)
1 (indeterminate)	2 (2.5)	0
4	5 (6.2)	0
Mean HCV RNA, log_{10} IU/mL (± SD),	6.6 ± 0.7	6.5 ± 0.6
Mean HCV RNA level, IU/mL, n (%)		
<400,000	9 (11.1)	6 (7.1)
400,000 – <800,000	2 (2.5)	8 (9.4)
≥ 800,000	70 (86.4)	71 (83.5)
Fibrosis status, n (%)		
No-cirrhosis	60 (74.1)	62 (72.9)

Cirrhosis/transition to cirrhosis	21 (25.9)	23 (27.1)
Host *IL28B* genotype	N=52	N=62
CC, n (%)	18 (34.6)	25 (40.3)
Non-CC, n (%)	34 (65.4)	37 (59.7)

Table 2: Summary of adverse events and laboratory abnormalities

	Mericitabine plus peginterferon alfa-2a/ribavirin N=81	Placebo plus peginterferon alfa-2a/ribavirin N=85
Patients with serious adverse events, n (%)	5 (6.2)	3 (3.5%)
Serious adverse events, n	6	4
Incidence of individual adverse events[a], n (%)		
Fatigue	58 (72)	58 (68)
Headache	42 (52)	38 (45)
Nausea	33 (41)	34 (40)
Chills	31 (38)	33 (39)
Insomnia	31 (38)	28 (33)
Decreased appetite	25 (31)	22 (26)
Myalgia	24 (30)	24 (28)
Pyrexia	20 (25)	27 (32)
Irritability	21 (26)	25 (29)
Rash	17 (21)	28 (33)
Pruritus	15 (19)	28 (33)
Cough	17 (21)	22 (26)
Arthralgia	18 (22)	21 (25)
Dizziness	19 (23)	20 (24)
Diarrhea	18 (22)	20 (24)
Alopecia	14 (17)	17 (20)
Laboratory abnormalities, n (%)		
Neutrophils <0.5 x 10^9 cells/L	1 (1)	5 (6)

Hemoglobin <8.5 g/dL	1 (1)	1 (1)
Platelets <20 x 10^9 cells/L	0	0
Lymphocytes <0.35 x 10^9 cells/L	4 (5)	4 (5)
Decreased creatinine clearance[b]	2 (2)	1 (1)
Serum creatinine >2 x ULN	1 (1)	0
BUN >2 x ULN	0	0
Urine protein/creatinine ratio ≥0.5	2 (2)	0
Marked increase in urine protein/creatinine ratio	0	0
Dose modifications for AEs, n (%)		
Mericitabine	4 (5)	0
Peginterferon alfa-2a	7 (9)	4 (5)
Ribavirin	15 (19)	13 (15)
Dose modifications for lab abnormalities, n (%)		
Mericitabine	0	0
Peginterferon alfa-2a		
Anemia	1 (1)	0
Neutropenia	8 (10)	9 (11)
Thrombocytopenia	2 (2)	3 (4)
Ribavirin		
Anemia	11 (14)	13 (15)
Other lab abnormality	0	2 (2)

BUN = blood urea nitrogen; ULN = upper limit of normal

a. Adverse events that were reported in ≥20% of patients in at least one treatment group.

b. Defined as <60 mL/min or ≥35% decrease from baseline

c. Marked increase in urine protein/creatinine ratio was defined as >1 and >200% increase from baseline; last or replicated value