A CONTINUING MEDICAL EDUCATION ACTIVITY

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Online Expert Poster Review and Discussion

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

First SVR data with the nucleoside analogue polymerase inhibitor mericitabine (RG7128) combined with peginterferon/ribavirin in treatment-naive HCV G1/4 patients: interim analysis from the JUMP-C trial

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Abstract 1359

Background

- Mericitabine (RG7128, MCB) is a potent, selective nucleoside inhibitor of the HCV NS5B RNA-dependent RNA polymerase
  - Active against the most common HCV genotypes: 1, 2, 3 and 4[1–4]
  - Demonstrates a high barrier to resistance with no RAVs seen in any completed or ongoing clinical trials[5,6]
  - Renally excreted and not hepatically metabolised, thus reducing the potential for drug–drug interactions

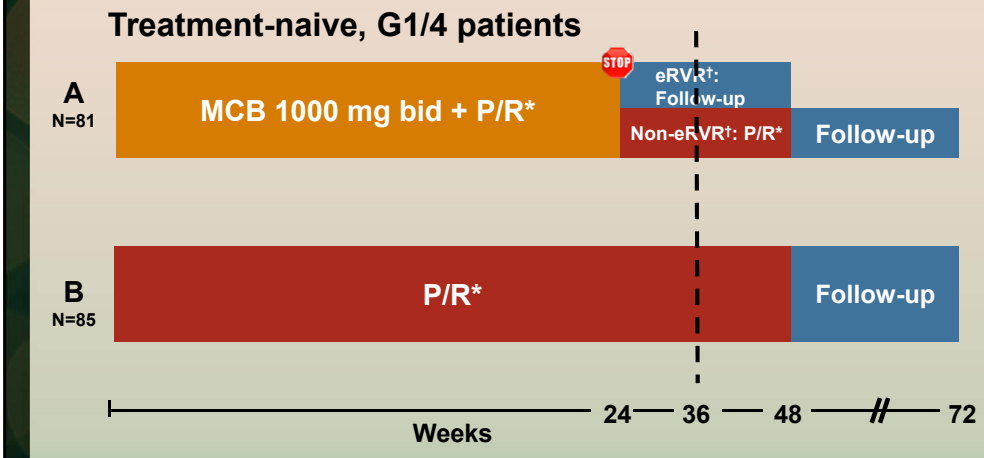
RAV = resistance-associated variant

1. Reddy R, et al. Hepatology 2007; 46 (Suppl): 862A (Abstract LB9)
2. Gane EJ, et al. Hepatology 2008; 48 (Suppl): 1024A (Abstract LB10)
3. Rodriguez-Torres M, et al. Hepatology 2008; 48 (Suppl): 1160A (Abstract 1899)
4. Jensen DM, et al. Hepatology 2010; 52 (Suppl): 360A (Abstract 81)
5. Le Pogam S, et al. J Hepatol 2009; 50 (Suppl): S348 (Abstract 958)
6. Le Pogam S, et al. Hepatology 2010; 52 (Suppl): 701A (Abstract 799)

JUMP-C study objectives and design

- Objectives
  - To compare a response-guided therapy regimen of MCB in combination with peginterferon alfa-2a (40KD) plus ribavirin (P/R) with P/R alone
  - To assess resistance development after 24 week therapy
- Design
  - Randomised, double-blind, placebo-controlled phase IIb trial
  - Treatment-naive patients infected with HCV G1/4
  - Trial is ongoing

JUMP-C: study design



*P/R = Peginterferon alfa-2a (40KD) 180 µg/week plus ribavirin 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg)
† eRVR = extended rapid virological response, defined as undetectable (<15 IU/mL) HCV RNA from wk 4 to wk 22 of treatment

Baseline characteristics

	ARM A (N=81) MCB 24 wks P/R 24/48 wks RVR-guided	ARM B (N=85) P/R 48 wks
Male, n (%)	51 (63)	67 (79)
Race, n (%)		
Caucasian	63 (78)	69 (81)
African-American	10 (12)	8 (9)
Hispanic ethnicity	8 (10)	8 (9)
Mean age, years (SD)	50 (10)	48 (10)
Mean weight, kg (SD)	82 (15)	85 (16)
Mean BMI, kg/m^2 (SD)	28 (4)	28 (4)
Genotype, n (%)		
1a	50 (62)	68 (80)
1b	24 (30)	17 (20)
1 (indeterminate)	2 (2)	0
4	5 (6)	0
Mean baseline HCV RNA, $\log_{10}$ IU/mL (SD)	6.6 (0.7)	6.5 (0.6)
METAVIR F3, n (%)	7 (9)	17 (20)
METAVIR F4, n (%)	12 (15)	5 (6)

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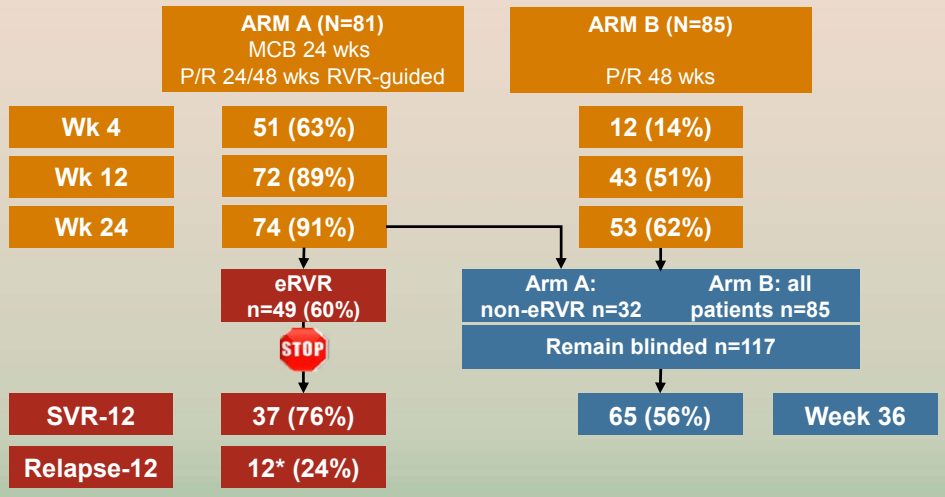
Week 36 planned interim analysis

High SVR-12 achieved with 24 wks MCB + P/R in patients with eRVR



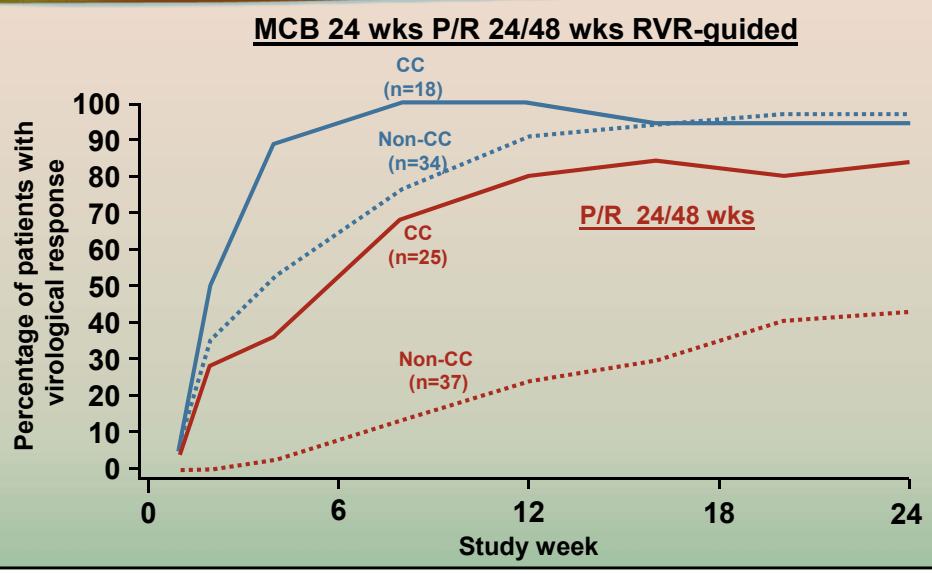
eRVR = extended RVR (HCV RNA <15 IU/mL from weeks 4 to 22)
* Includes 2 patients who failed to return for SVR-12 assessment

Rates of SVR-12 similar in patients with an eRVR irrespective of *IL28B* genotype

Endpoint	ARM A (N=81) MCB 24 wks P/R 24/48 wks RVR-guided		
RCR consented	52		
eRVR (wk 4–22)	YES 33 (63%)		NO 19 (37%)
eRVR by IL28B genotype	CC 15	Non-CC 18	N/A
SVR-12	12 (80%)	13 (72%)	N/A

RCR = Roche Clinical Repository

MCB overcomes the *IL28B* polymorphism effect



No difference in safety and tolerability between MCB + P/R vs P/R alone through week 36

	ARM A (N=81) MCB 24 wks P/R 24/48 wks RVR-guided	ARM B (N=85) P/R 48 wks
SAEs, n (%)	5 (6)	2 (2)
Discontinuation due to safety	5 (6)	11 (13)
AEs (>20% of patients)		
Fatigue	70%	67%
Headache	49%	42%
Chills	38%	39%
Nausea	40%	39%
Insomnia	37%	32%
Decreased appetite	31%	26%
Pyrexia	25%	31%
Irritability	26%	29%
Myalgia	26%	28%
Pruritus	19%	33%
Rash	21%	29%
Diarrhoea	21%	22%
Dizziness	23%	21%
Arthralgia	21%	21%

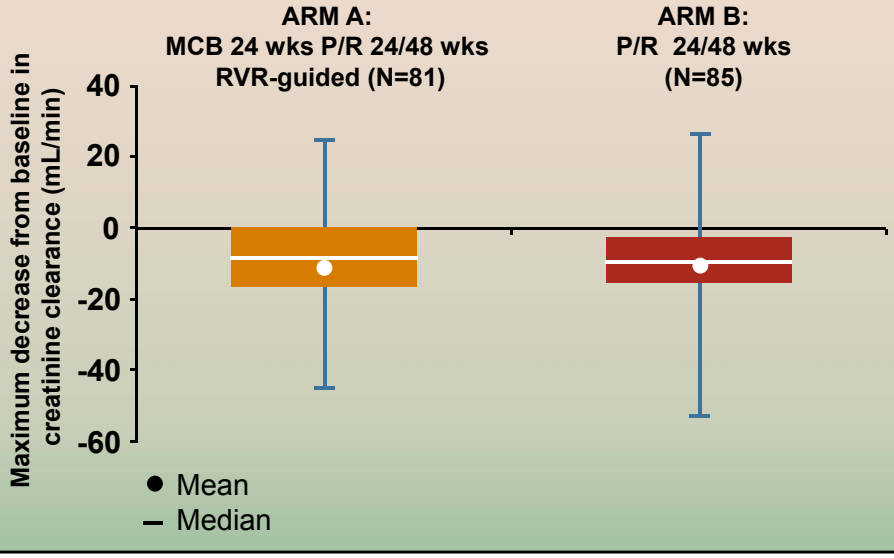
All safety data are based on patients in the safety population with at least 36 weeks on study

No difference in frequency of haematological and renal labs between MCB + P/R vs. P/R alone

n (%)	ARM A (N=81) MCB 24 wks P/R 24/48 wks RVR-guided	ARM B (N=85) P/R 48 wks
Neutrophils <0.5 x 10^9/L	1 (1)	5 (6)
Hgb <8.5 g/dL	1 (1)	1 (1)
Platelets <20 x 10^9/L	0 (0)	0 (0)
Lymphocytes <0.35 x 10^9/L	3 (4)	3 (4)
Creatinine clearance ≥35% drop from BL or <60 (mL/min)	1 (1)	1 (1)
Serum creatinine >2 x ULN	1 (1)	0 (0)
Blood urea nitrogen >2 x ULN	0 (0)	0 (0)
Urine protein/creatinine ratio ≥0.5	0 (0)	0 (0)

All safety data are based on patients in the safety population with at least 36 weeks on study

MCB demonstrates no impact on creatinine clearance



No evidence of RAVs associated with NS5B polymerase inhibitor MCB

Analysis	Number of patients	Observation	
Baseline sequence analysis (all patients)	163	GT 1a = 119 GT1b = 41 GT 4 = 3	No RAVs No RAVs No RAVs
Virologic responses in MCB arm until wk 24	80	HCV RNA <15 IU/mL	No breakthrough
	1	HCV RNA = 2000 IU/mL	No RAVs
Virologic responses in eRVR at wk 36	37	SVR-12	
	10	Confirmed relapse	No RAVs*
	2	Failure to return	-

* Amplification failed in 1 patient

Conclusion

- At 24 weeks of MCB plus P/R, 91% of patients achieved virological suppression
- 60% of patients had an eRVR
  - Of these, 76% of patients achieved an SVR-12
- MCB triple combination was well tolerated up to 24 weeks
- This potent nucleoside analogue appears to overcome IL28B polymorphism effect
- No breakthroughs observed during 24 weeks of treatment and no RAVs were observed
- A good safety and tolerability profile, strong antiviral potency and no evidence of resistance-related breakthrough makes MCB highly desirable for further study, including combinations with other DAAs