DANOPREVIR PLUS LOW DOSE RITONAVIR ACHIEVED ROBUST VIROLOGICAL RESPONSE IN TREATMENT NAIVE AND IN GT 1b PRIOR NULL RESPONDER PATIENTS AFTER UP TO 12 WEEKS TREATMENT


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Introduction

- Danoprevir (DNV; RG7227; ITMN-191) is a potent, highly selective macrocyclic oral inhibitor of the HCV NS3/4A serine protease.

- Current development strategy utilizes the combination of low doses of DNV with low dose of ritonavir (RTV; 100 mg) to maximize the safety and efficacy.

- Low dose RTV is used successfully to ‘boost’ exposure to HIV protease inhibitors that are CYP3A substrates \(^1\).
  - Simplifies regimens – fewer pills and less frequent dosing.
  - Improves antiviral efficacy.


DNV resistance

- Resistance to DNV is largely restricted to the single amino acid substitution R155K in the NS3 protease sequence.

- Low rate of resistance to DNV has been observed only in GT 1a, after up to 12 weeks of treatment with unboosted DNV in combination with PEG-IFN and RBV (ATLAS study)¹.

- When administered for 2 weeks in combination with mericitabine (RG7128), DNV resistance was not detected in any patient, suggesting a role for mericitabine in preventing resistance to danoprevir².

¹ Le Pogam S et al, AASLD 2010; ² Le Pogam S et al, AASLD 2009
Ritonavir boosting of low-dose danoprevir

Cohorts GT 1 treatment-naive patients

1. **15 days**
   - DNV/r: 100/100 mg BID + P/R, or
   - PBO/r: PBO/100 mg BID + P/R

2. DNV/r: 200/100 mg QD + P/R, or
   - PBO/r: PBO/100 mg QD + P/R

3. DNV/r: 200/100 mg BID + P/R, or
   - PBO/r: PBO/100 mg BID + P/R

Cohort GT 1 prior null responders

4. **12 weeks**
   - Open label DNV/r 100/100 mg BID + P/R

*Not part of study protocol; continuation of P/R at the discretion of the investigator

DNV = danoprevir; PBO = placebo; P/R = peginterferon alfa-2a/ribavirin


Study objective

- Monitor for development of resistance to DNV after 2 to 12 weeks of treatment in GT 1 treatment-naive and prior null responders.
- Resistance monitoring was performed on patients while on DNV/r therapy.
- Baseline sequencing for all patients.
- On-Treatment samples: sequencing and phenotypic assay.
- Follow up time points for patients with DNV resistance.
DNV/r + P/R provides robust virological response with no selection of resistance after 2 weeks¹

- All treatment-naïve patients experienced a viral load decline (22 GT 1a, 9 GT 1b).
- No pre-existing Danoprevir resistance identified by population sequencing (n=34).

Potent Viral Load Decline of DNV/r 100 mg/100 mg BID With Peg/RBV in GT 1b Prior Null Responders

- 12 weeks of DNV/r/P/R followed by 36 weeks of SOC (16 GT 1b patients).

- Only 1/16 GT 1b patients experienced a viral breakthrough at week 8.
High breakthrough rate in GT 1a Prior Null Responders

- 12 weeks of DNV/r/P/R followed by 36 weeks of SOC (8 GT 1a patients).
- 4 out of the 8 GT 1a patients experienced a viral breakthrough before week 8:
  - 2 @ week 2, 1 @ week 4, 1 @ week 8
- Enrollment of GT 1a patients was stopped due to high breakthrough rate.

Resistance Analysis of 5 breakthrough Prior Null responder patients

- No pre-existing Danoprevir resistance identified by population sequencing (n=24).
- Treatment-emergent resistance mutation R155K was observed in the protease coding region of the 5 patients.
- Clonal analysis (80 clones/sample) did not detect R155K at baseline.
- High EC$_{50}$ fold shift for on-treatment R155K-containing protease isolates.

- R155K persisted in 4/5 patients during the FU period of the treatment (3-8 mo)
- R155K replaced by WT (by population sequencing) in 1 GT 1a patient (~ 8 mo post-trt)

- clonal analysis on going

Conclusions

- **DNV/r 100/100 mg BID + P/R for 12 weeks** provides robust virological response in GT 1b HCV infected prior null responders with a low rate of virological breakthrough (1/16).

- Higher genetic barrier to resistance in GT 1b (2 nt changes for 155K) may account for the low frequency of resistance observed in this genotype.

- In contrast, high rate of virological breakthrough was observed with GT 1a null responders (4/8).

- **MATTERHORN study** will look at DNV/r + mericitabine (RG7128) + ribavirin +/- peginterferon alfa in this null-responder population.
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