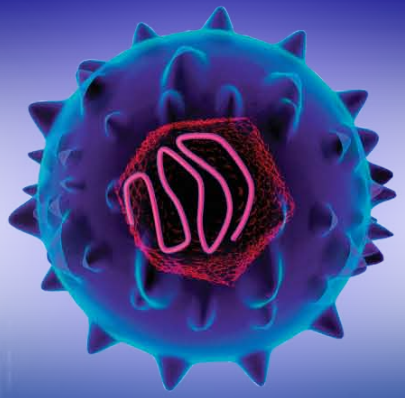
HEPATITIS C MANAGEMENT
STATE OF THE ART



Update: Treatment Pipeline 2016

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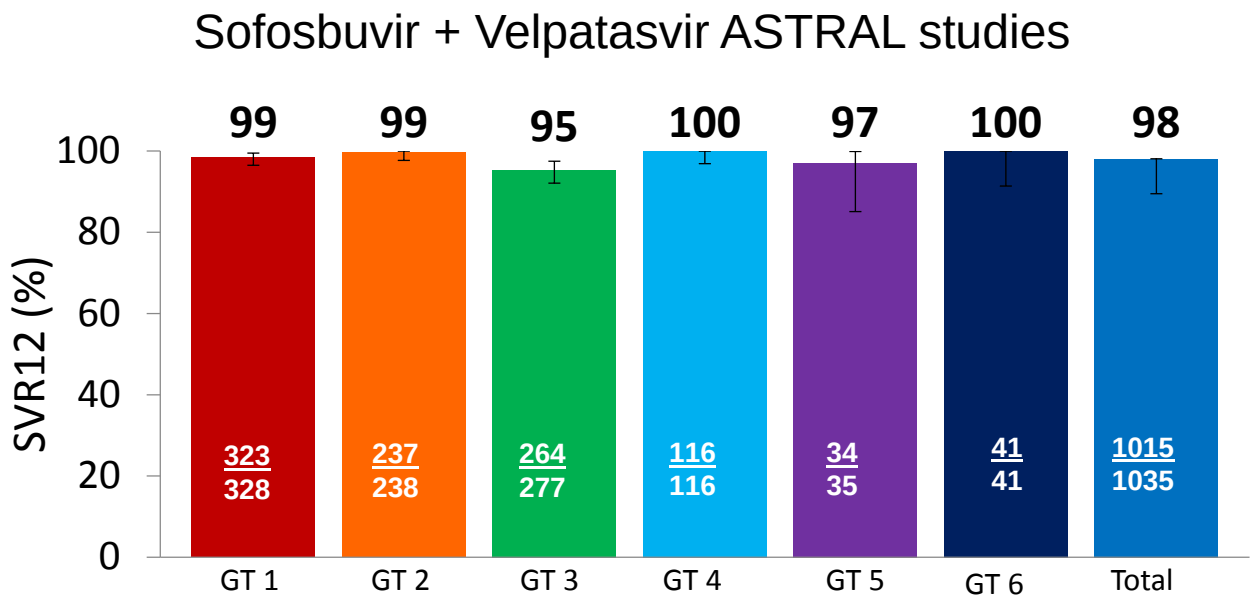
Department of Medicine
Director, Gastroenterology Research
Duke Clinical Research Institute
Duke University School of Medicine

Disclosures

- Research grants & advisory boards:
  - AbbVie, BMS, Gilead, Janssen, Merck

HCV pipeline

- What will the pipeline address?

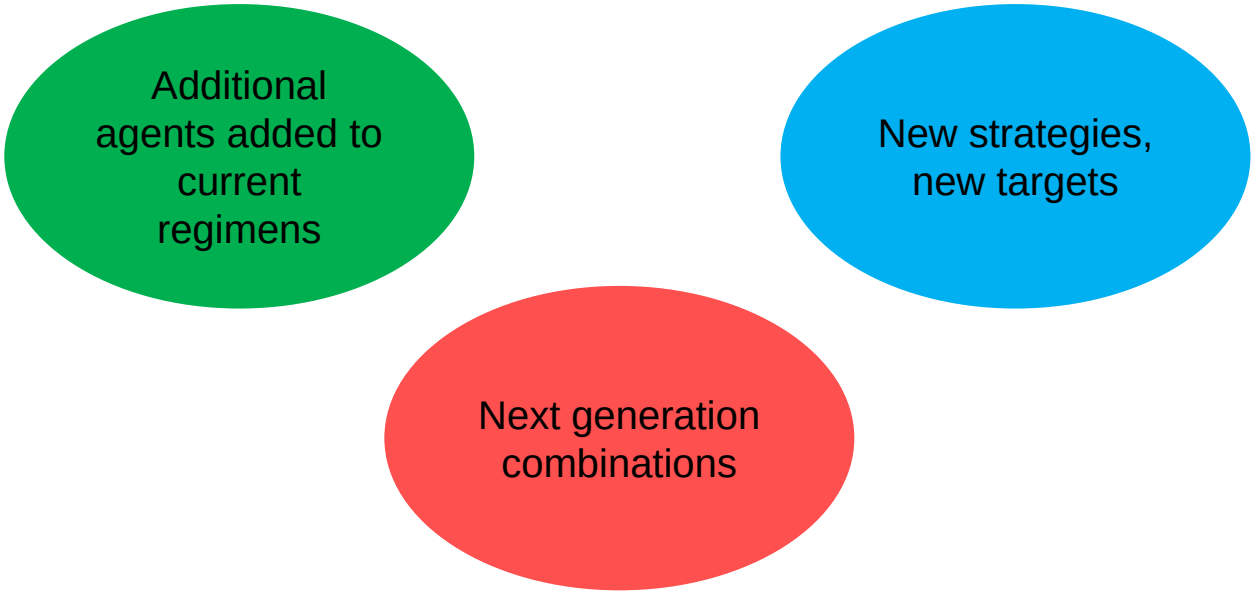


Feld JJ. NEJM. 2015; Foster GR. NEJM. 2015

HCV pipeline

- What will the pipeline address?
  - Genotype 3
  - Ribavirin-free
  - Resistance
  - Duration for < 12 weeks

HCV pipeline strategies



GS-9857

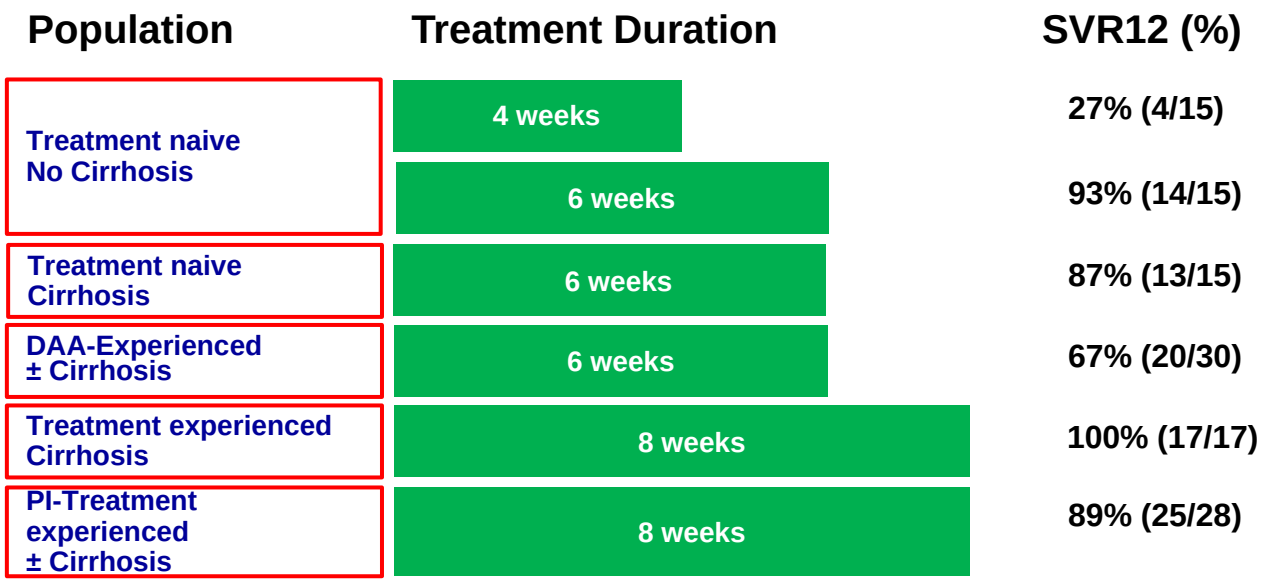
- HCV NS3/4A protease inhibitor
- Potent pangenotypic antiviral activity
- Study design: 3 day monotherapy
  - Patients: NS3/4A naïve, no cirrhosis
  - Dose range: 50, 100, 300 mg or placebo

Maximal reduction in HCV RNA

Genotype	1a	1b	2	3	4
N	8	6	6	6	4
Median ↓	-4.38	-3..90	-3.60	-3.24	-4.11

Rodriguez-Torres M. EASL 2015.

SOF/VEL/9857 phase 2 Genotype 1



Gane EJ. EASL 2015; Gane EJ. AASLD 2015

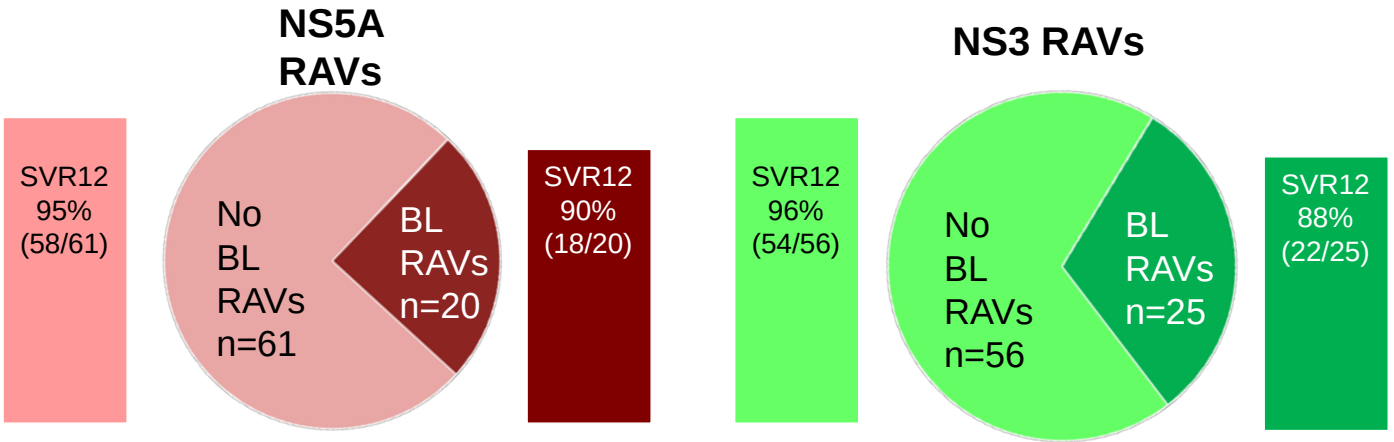
SOF/VEL/9857 phase 2
Genotype 3

Population	Treatment Duration	SVR12 (%)
Treatment naive Cirrhosis	6 weeks	83% (15/18)
Treatment experienced Cirrhosis	8 weeks	100% (19/19)

Gane EJ. EASL 2015; Gane EJ. AASLD 2015

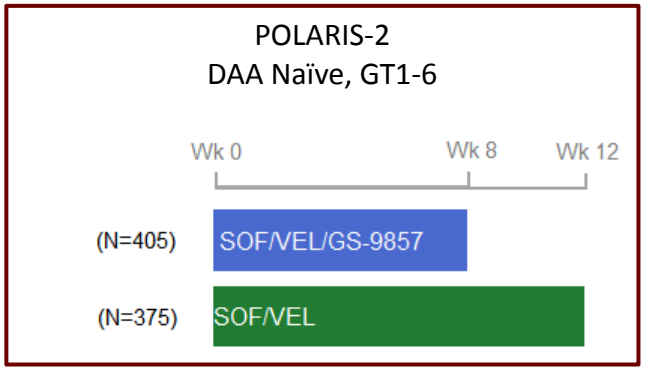
SOF/VEL/9857 phase 2
Impact of baseline resistance

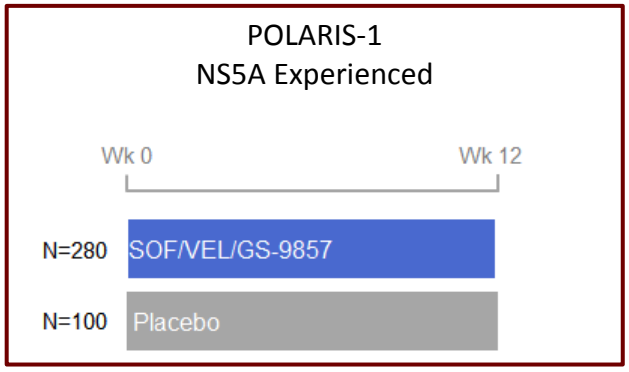
- Baseline Resistance Associated Variants (RAVs)
  - Deep sequencing with 1% cut-off

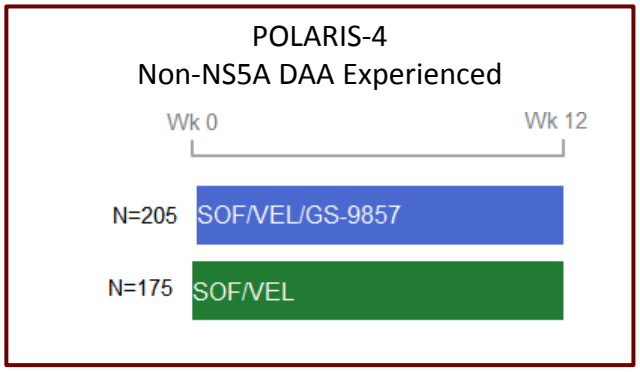


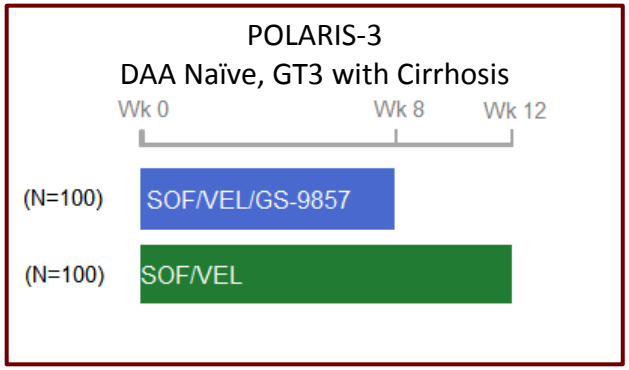
Gane EJ. AASLD 2015

SOF/VEL/9857 phase 3 program

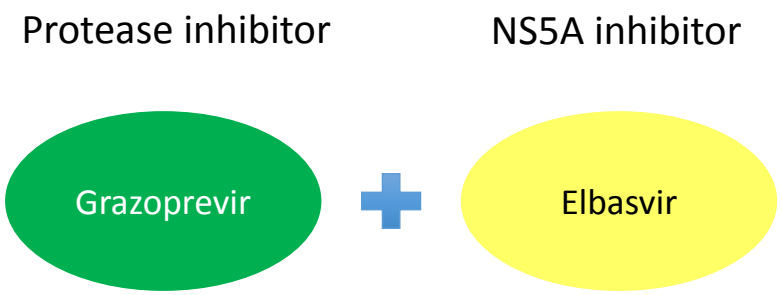






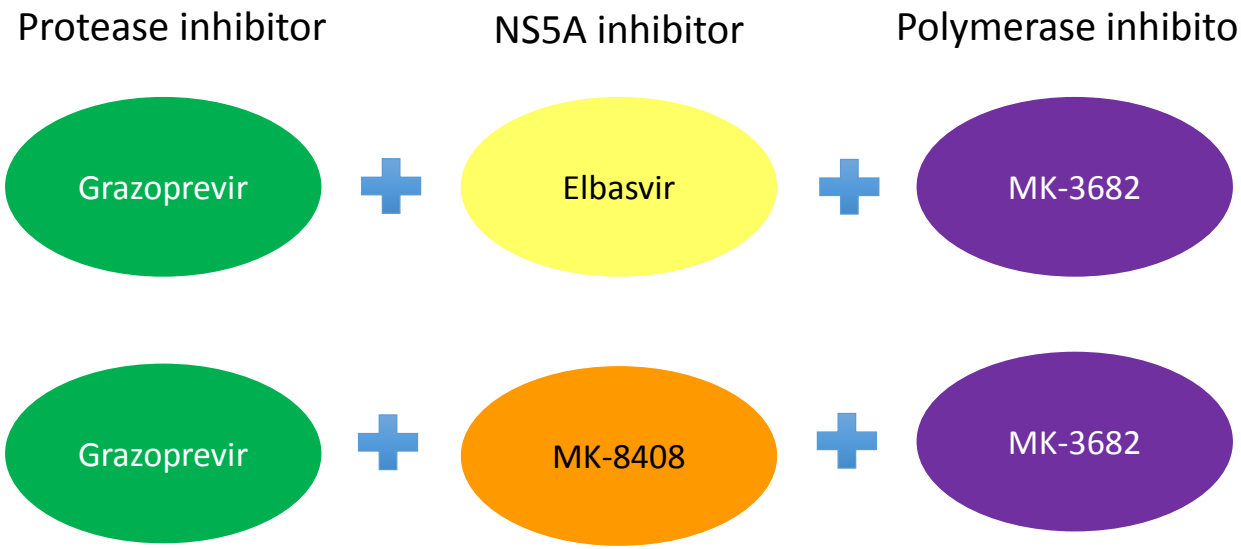


Grazoprevir/elbasvir



- FDA approved regimen genotypes 1, 4

Grazoprevir/elbasvir PLUS



New agents

- MK-8408
  - 2nd generation NS5A inhibitor
  - 60 mg once daily
  - GT 1-3 with >3-log ↓ HCV RNA day 5
- MK-3682
  - Nucleotide NS5B polymerase inhibitor
  - 300/450 mg once daily
  - GT 1-2 with >4-log ↓ HCV RNA day 7

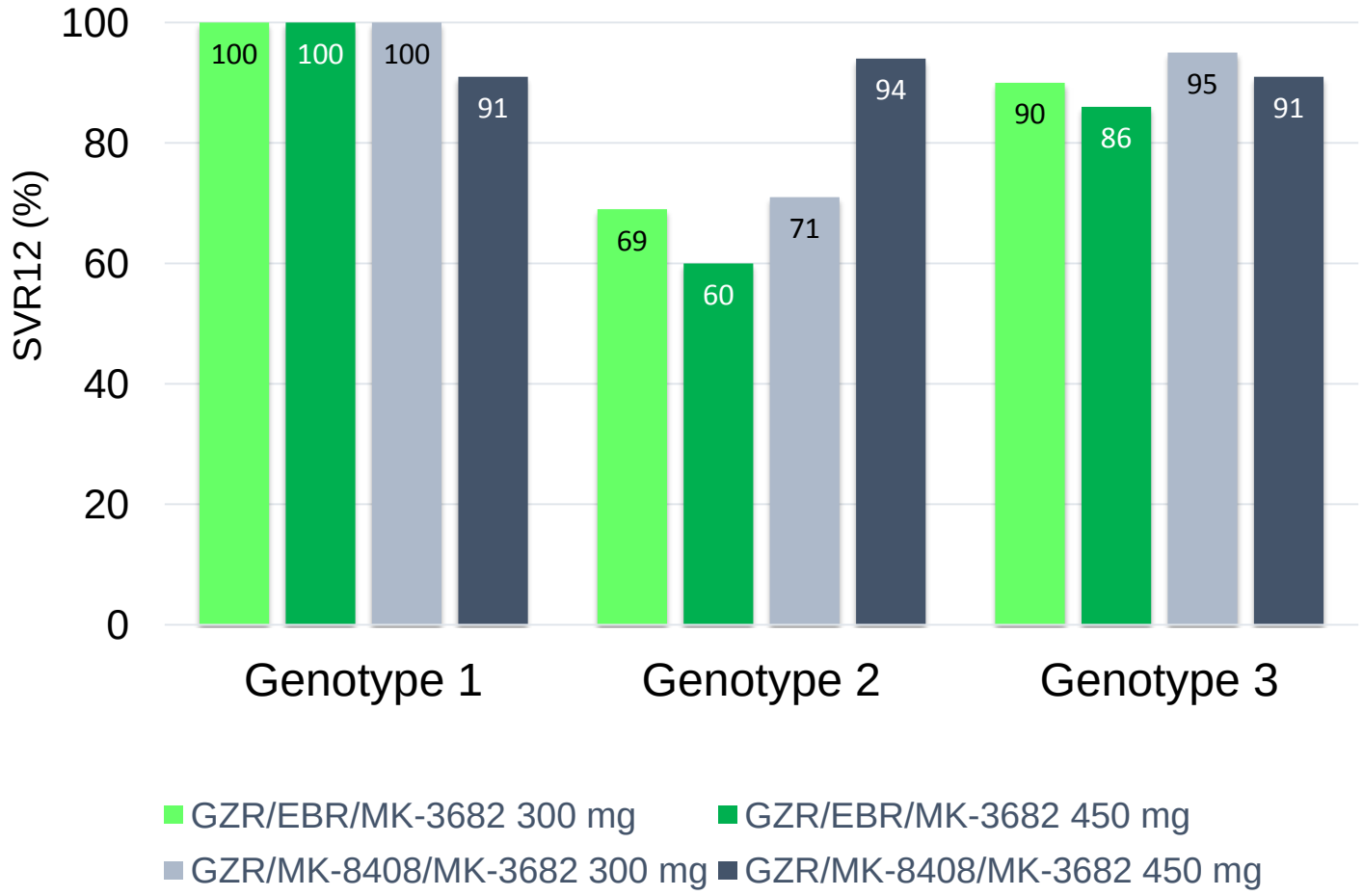
Lahser et al. AASLD 2014; Assante-Appiah et al. AASLD 2014; Zhou et al. EASL 2015.

MK-8408 & MK-3682

- C-CREST 1 and 2
  - Genotype 1-3
  - Treatment naïve
  - No cirrhosis
  - RCT
- Part A to select Part B regimen

Gane EJ. HEPDART 2015

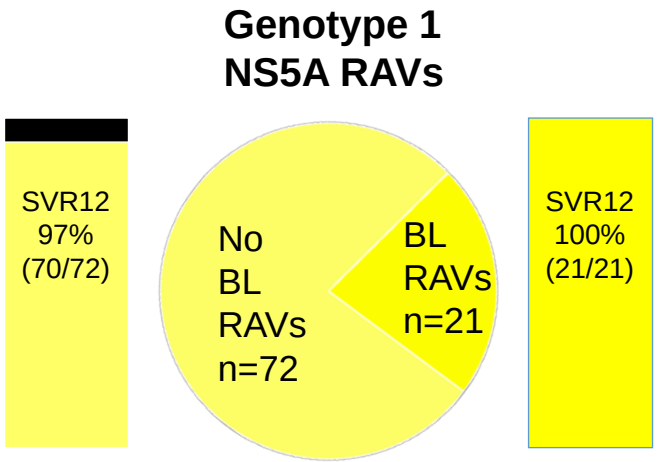
MK-8408 & MK-3682



Gane EJ. HEPDART 2015

MK-8408 & MK-3682
Impact of baseline resistance

- Baseline Resistance Associated Variants (RAVs)
  - Any changes from wild-type at 9 positions (24, 28, 30, 31, 32, 38, 58, 92, 93)
  - Population sequencing (20-25% threshold)



Gane EJ. HEPDART 2015

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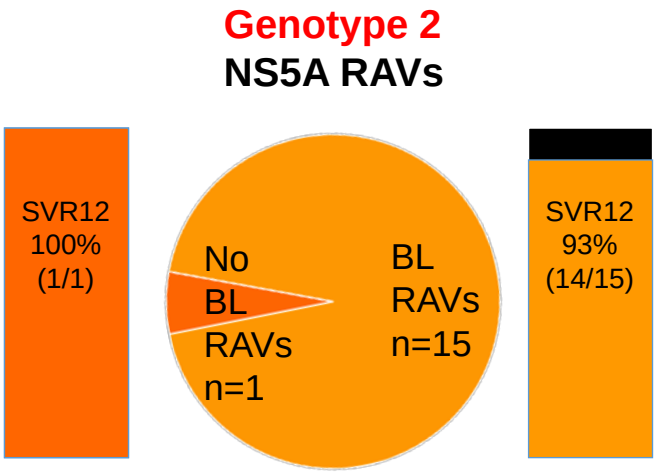
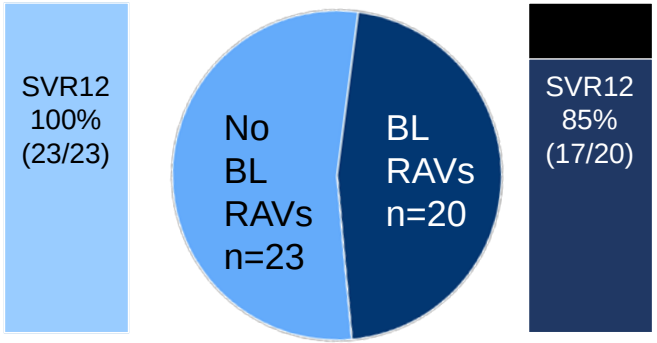


Gane EJ. HEPDART 2015

MK-8408 & MK-3682
Impact of baseline resistance

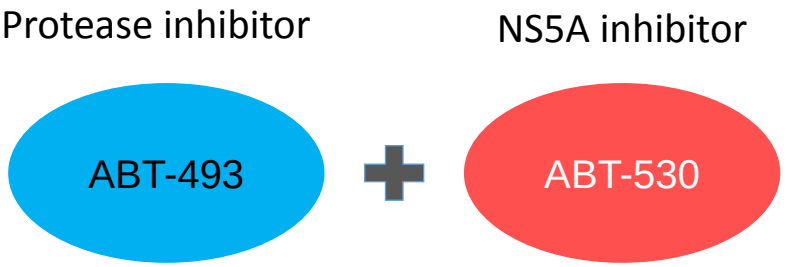
- Baseline Resistance Associated Variants (RAVs)
  - Any changes from wild-type at 9 positions (24, 28, 30, 31, 32, 38, 58, 92, 93)
  - Population sequencing (20-25% threshold)

Genotype 3
NS5A RAVs



Gane EJ. HEPDART 2015

ABT-493 and ABT-530

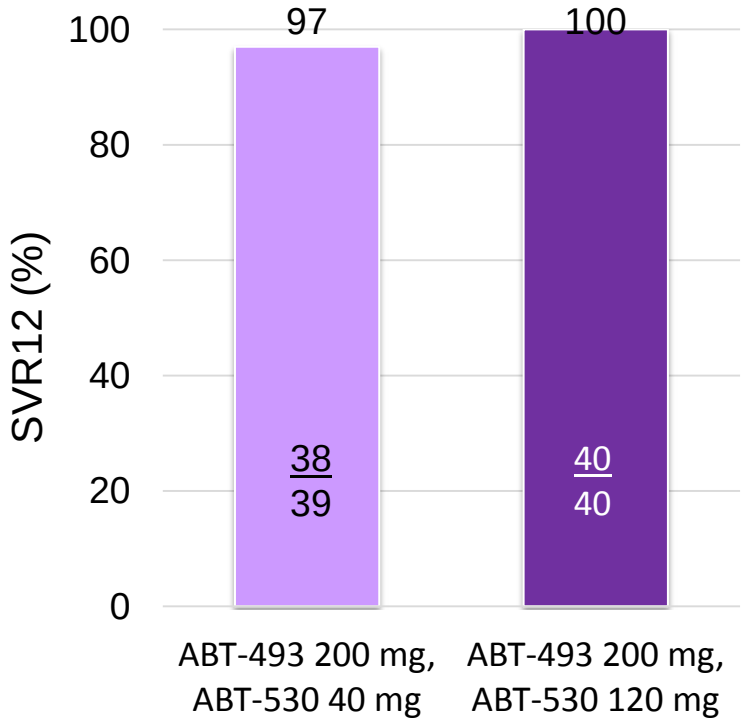


- ABT-493
  - Pangenotypic NS3/4A protease inhibitor
- ABT-530
  - Pangenotypic NS5A inhibitor
- Combination
  - 3-day monotherapy study
  - ~4-log ↓ HCV RNA
  - <1% renal excretion

Lawitz EJ. AASLD 2014

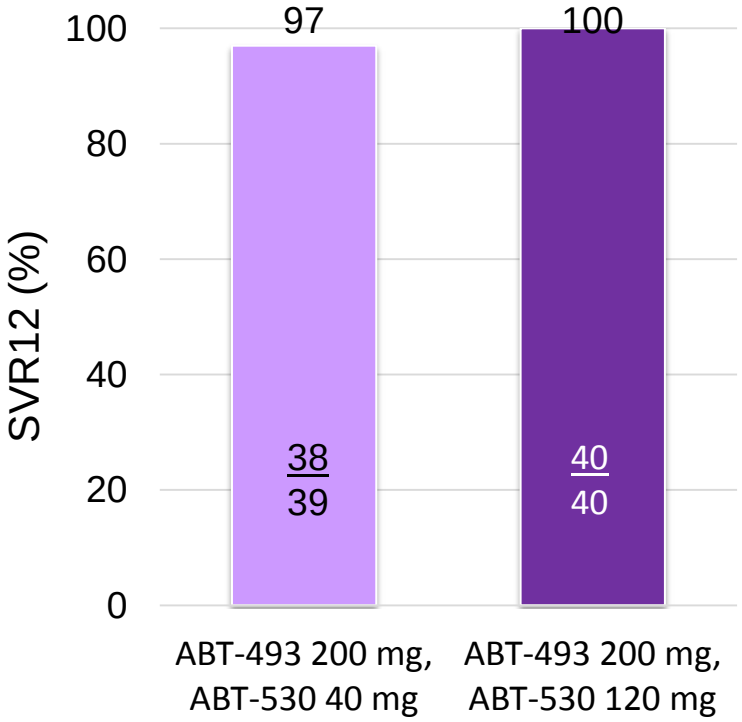
ABT-493 and ABT-530 SURVEYOR-I

- Part 1
- Genotype 1, noncirrhotic
- Treatment naïve (50) and experienced (29)
- Randomized to ABT-530 40 mg or 120 mg
- Duration: 12 weeks



Poordad F. AASLD 2015

ABT-493 and ABT-530 SURVEYOR-I

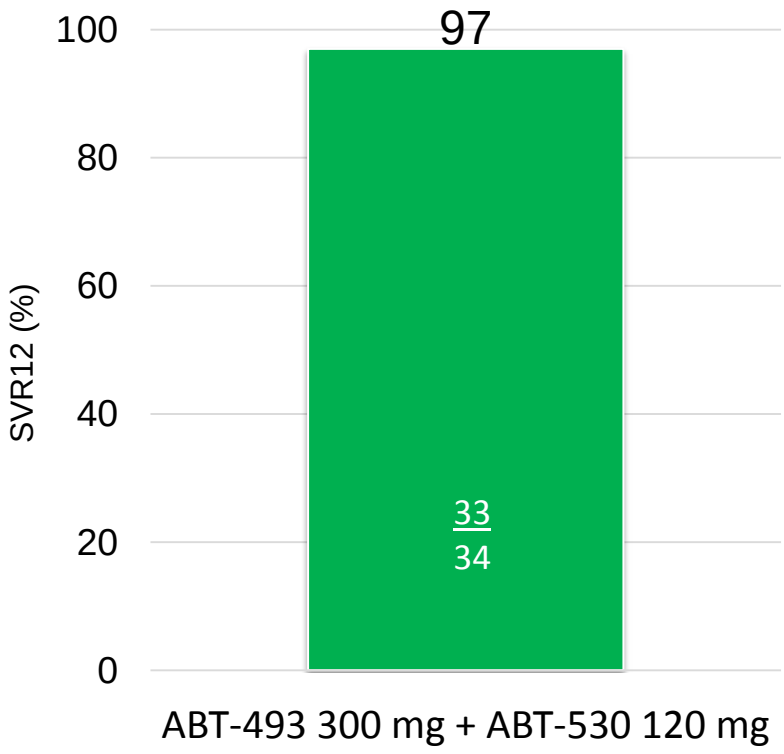


- Part 1
- 1 treatment failure
  - Relapse in treatment naïve genotype 1a
- Baseline RAVs
  - NS3 only: 47%
  - NS5A only: 8%
  - NS3+NS5A: 4%

Poordad F. AASLD 2015

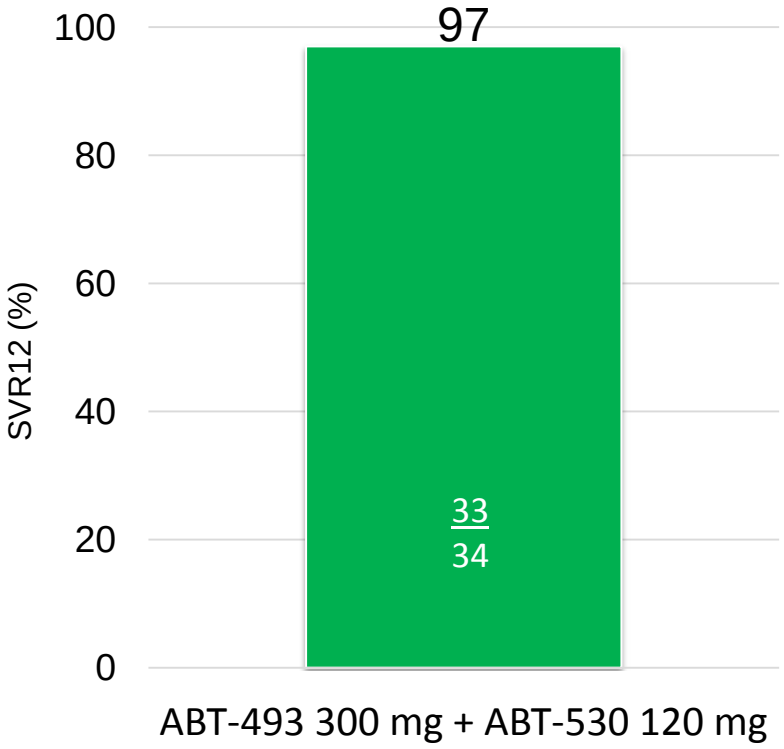
ABT-493 and ABT-530 SURVEYOR-I

- Part 2
- Genotype 1, noncirrhotic
- Treatment naïve (29) and experienced (5)
- Single arm ABT-493 300 mg + ABT-530 120 mg
- Duration: 8 weeks



Poordad F. HEPDART 2015

ABT-493 and ABT-530 SURVEYOR-I

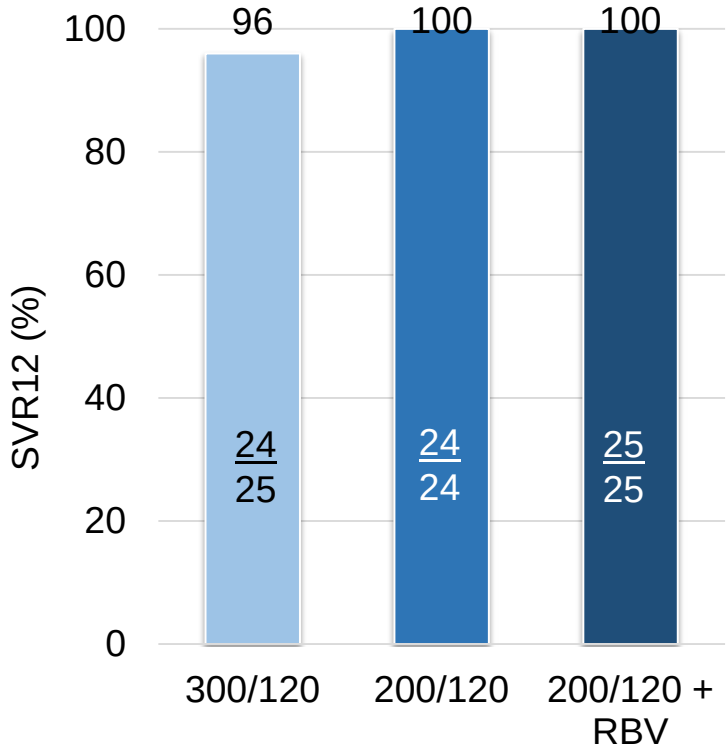


- Part 2
- 1 treatment failure
  - Relapse in patient with 4-week duration after diagnosis of cancer
- Baseline RAVs
  - NS3 only: 16%
  - NS5A only: 3%
  - NS3+NS5A: 4%

Poordad F. AASLD 2015

ABT-493 and ABT-530 SURVEYOR-II

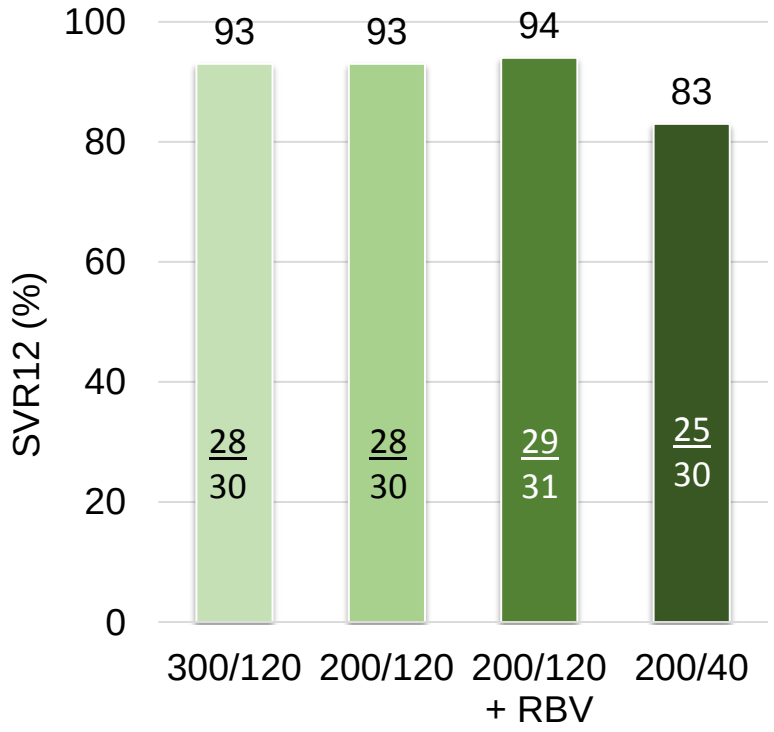
- Genotype 2, noncirrhotic
- Treatment naïve and experienced
- Randomized
  - ABT-493 300 mg + ABT-530 120 mg
  - ABT-493 200 mg + ABT-530 120 mg
  - ABT-493 200 mg + ABT-530 120 mg + RBV
- Duration: 12 weeks



Wyles D. AASLD 2015

ABT-493 and ABT-530 SURVEYOR-II

- Genotype 3, noncirrhotic
- Treatment naïve and experienced
- Randomized
  - ABT-493 300 mg + ABT-530 120 mg
  - ABT-493 200 mg + ABT-530 120 mg
  - ABT-493 200 mg + ABT-530 120 mg + RBV
  - ABT-493 200 mg + ABT-530 40 mg
- Duration: 12 weeks



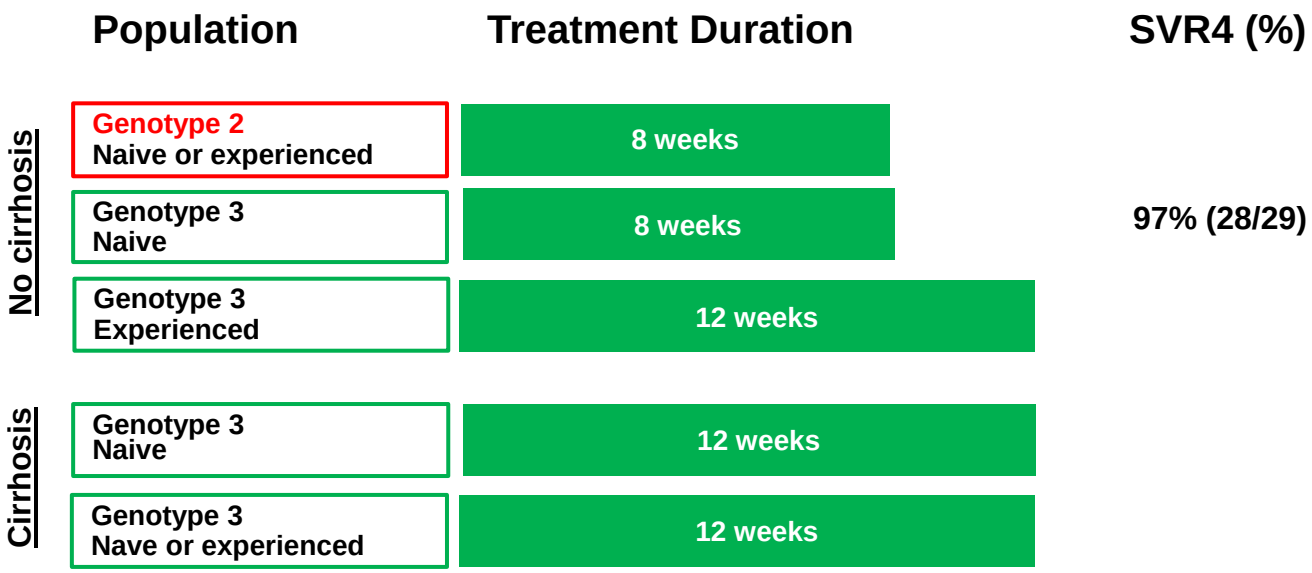
Kwo P. AASLD 2015

ABT-493 and ABT-530 SURVEYOR-II, genotype 3

	ABT-493 300 mg + ABT-530 120 mg (n=30)	ABT-493 200 mg + ABT-530 120 mg (n=30)	ABT-493 200 mg + ABT-530 120 mg + RBV (n=30)	ABT-493 200 mg + ABT-530 40 mg (n=30)
SVR12	28/30 (93%)	28/30 (93%)	29/31 (94%)	25/30 (83%)
Non-SVR				
Virologic failure	1	2	1	3
On-treatment breakthrough	0	0	1	1
Relapse	1	2	0	2
Non-virologic failure				
Early study drug d/c	0	0	1	1
Missing SVR12 data	1	0	0	1

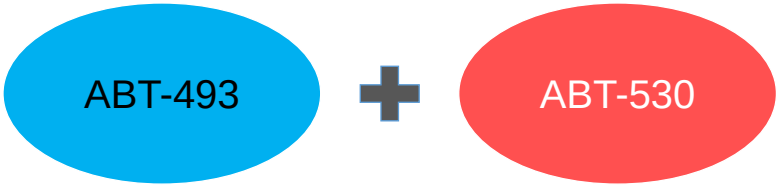
Kwo P. AASLD 2015

ABT-493 and ABT-530 SURVEYOR-II



Kwo PY EASL 2016; Muir AJ. EASL 2016

ABT-493 and ABT-530

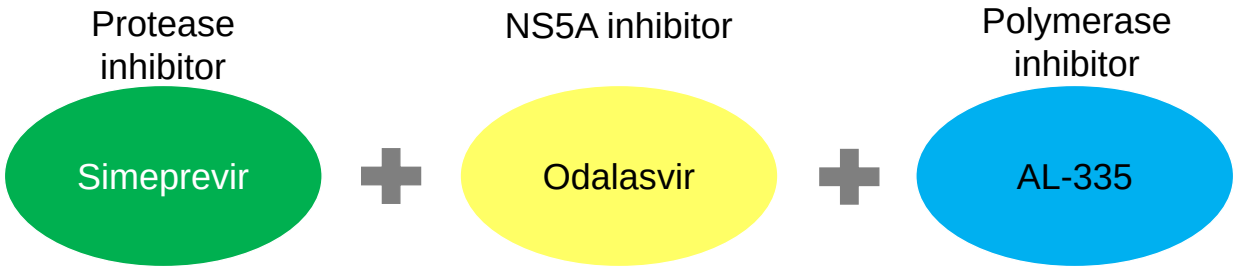


- Doses
  - ABT-493 300 mg
  - ABT-530 120 mg
- Development program
    - Genotypes 1-6
    - Noncirrhotic 8 weeks
    - Compensated cirrhosis 12 weeks
    - HIV co-infection
    - Chronic kidney disease
    - DAA failures

Simeprevir

- NS3/4A protease inhibitor
  - Antiviral activity against genotypes 1, 2, 4, 5, 6
  - FDA approved combinations
    - Peginterferon + ribavirin
    - Sofosbuvir

Simeprevir PLUS

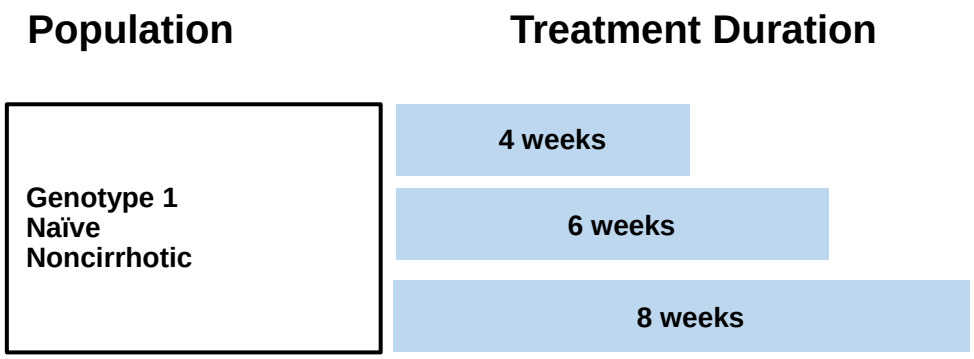


- Also ACH-3102
- Combo with sofosbuvir x 6 weeks SVR12 in 12/12 genotype 1

- Uridine-based nucleotide analog

Gane EJ. EASL 2015

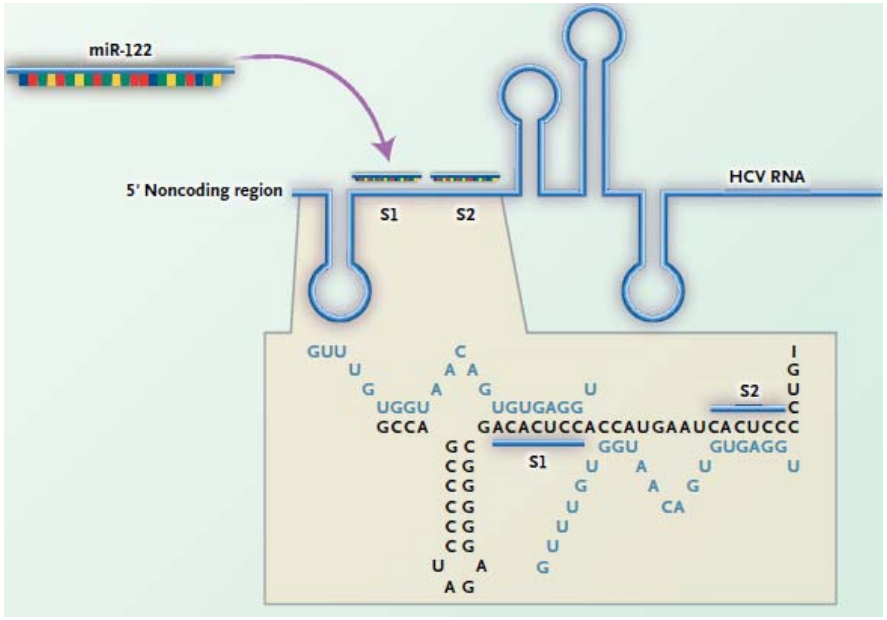
Simeprevir + Odalasvir + AL-335
Phase 2a



clinicaltrials.gov

miR-122

- miRNAs: noncoding RNAs that direct post-transcriptional regulation of gene expression by binding to complementary sites
- miR-122
  - Most abundant miRNA in liver
  - Binds to HCV genome in 5’ untranslated region
  - Promotes HCV RNA stability
  - Protects from degradation



Janssen H. NEJM 2013

Miravirsen

- Sequesters miR-122 in a heteroduplex and inhibits function
- Phase 2a study
  - 36 patients
  - Genotype 1, noncirrhotic
  - Miravirsen weekly subcu injection
  - Doses
    - Placebo
    - 3 mg/kg
    - 5 mg/kg
    - 7 mg/kg
  - Duration: 5 injections
  - Follow-up: 14 weeks

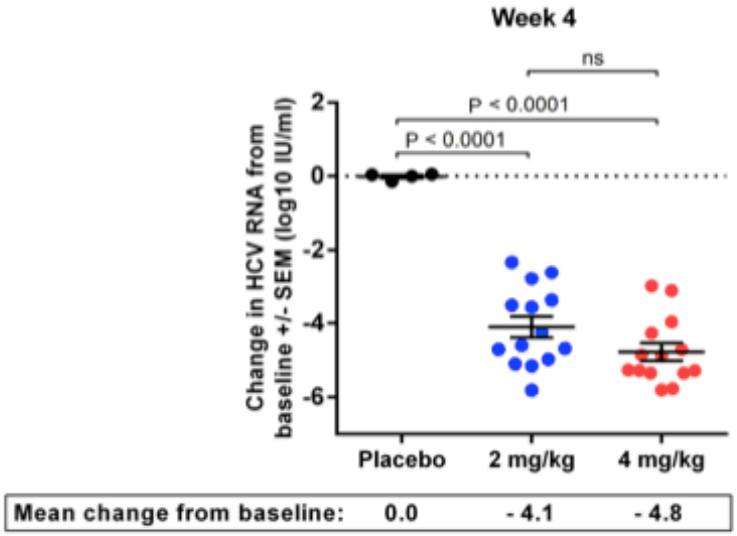
Dose	N	Mean maximum ↓ HCV RNA (log)
Placebo	9	0.4
3 mg/kg	9	1.2
5 mg/kg	9	2.9
7 mg/kg	9	3.0

- 14 week follow-up
- HCV RNA not detected
  - 5 mg/kg - 1 patient
  - 7 mg/kg - 4 patients

Janssen H. NEJM 2013

RG-101

- Oligonucleotide inhibitor of miR-122
- Patients
  - N=32
  - Genotype 1, 3, 4
  - Treatment naïve or prior relapsers
  - Placebo, 2 mg/kg, 4 mg/kg
- Single dose
- Follow-up: 8 weeks and extended to 28 weeks



Week 28

HCV RNA target not detected

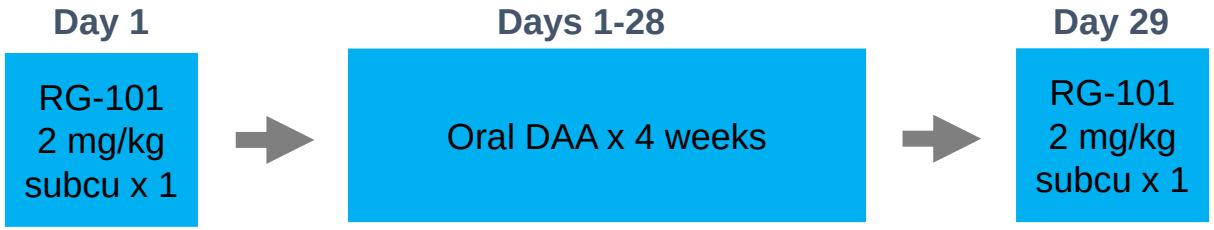
6 patients

- Genotype 1 (n=1)
- Genotype 3 (n=2)
- Genotype 4 (n=3)

Van de Ree M H. AASLD 2015

RG-101

- Phase 2
  - Treatment naïve, genotype 1 or 4

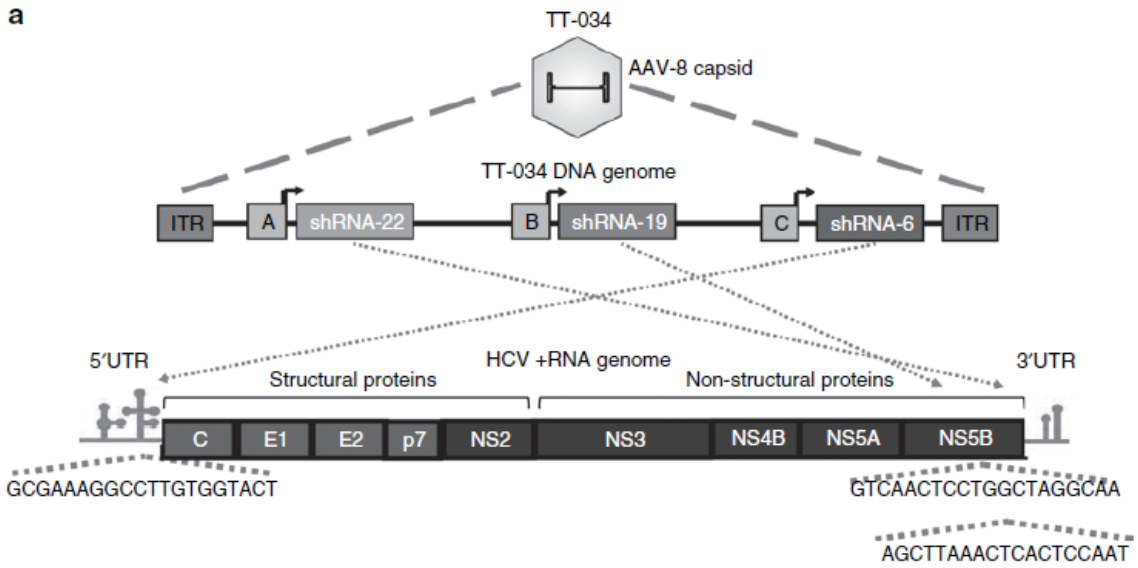


3 DAA groups
- Ledipasvir/sofosbuvir (n=27)
- Simeprevir (n=27)
- Daclatasvir (n=25)

Interim results
- F/U week 8: < LOQ 37/38
- F/U week 12: < LOQ 14/14

TT-034

- TT-034
  - recombinant adeno-associated virus serotype 8 (AAV8) agent expressing 3 short hairpin RNA (shRNA) pro-drugs that target the HCV genome
  - cytosolic enzyme Dicer cleaves each shRNA into multiple, potentially active small interfering RNA (siRNA) drugs



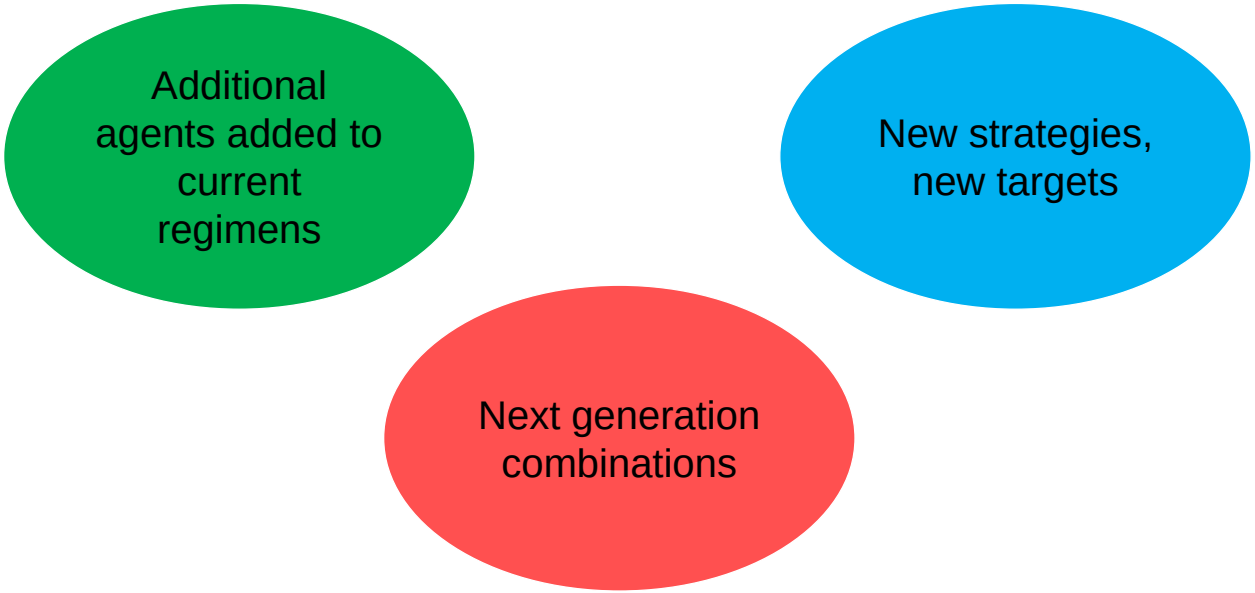
Denise H. Mol Ther Nucleic Acids 2014

TT-034

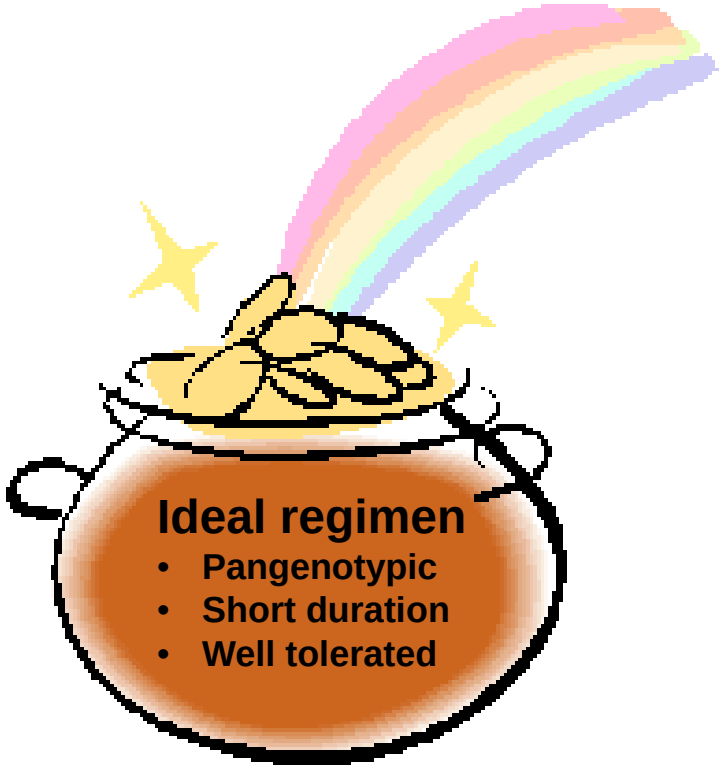
- Ongoing study
- Phase I/II
- Single IV infusion
- Patients
  - Genotype 1, non-cirrhotic
  - Prior treatment failure
- Results expected late 2016

www.clinicaltrials.gov

HCV pipeline strategies



HCV pipeline



Thank you

HEPATITIS C MANAGEMENT
STATE OF THE ART