New Therapeutic Strategies: Polymerase Inhibitors

6th Paris Hepatitis Conference
14th - 15th January, 2013

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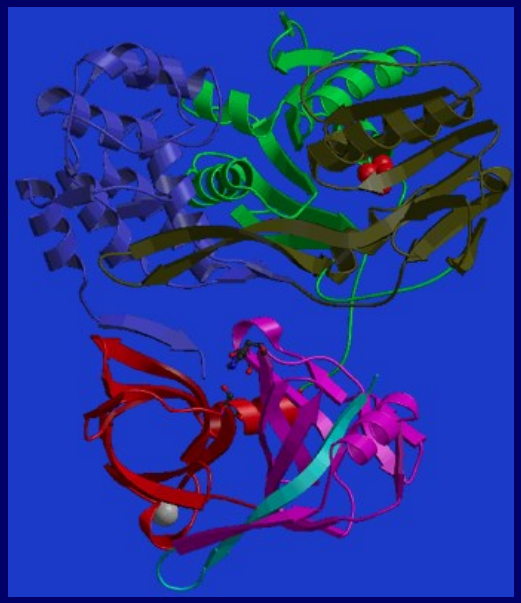
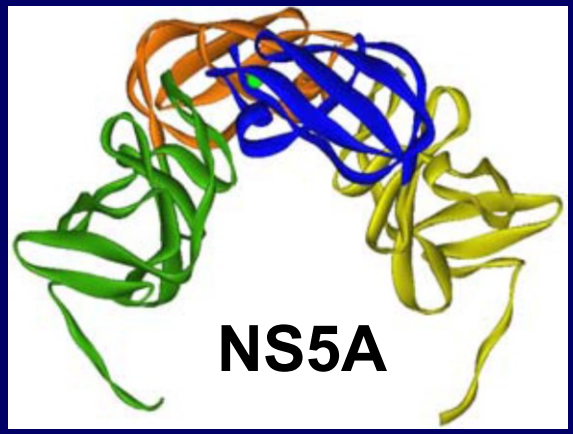
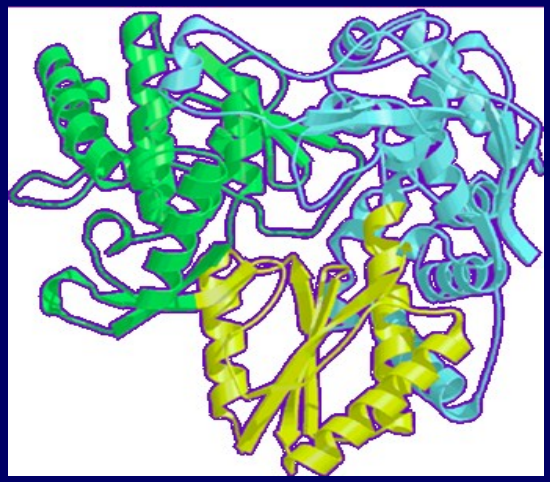
MEDIZINISCHE KLINIK 1

Direct antiviral targets

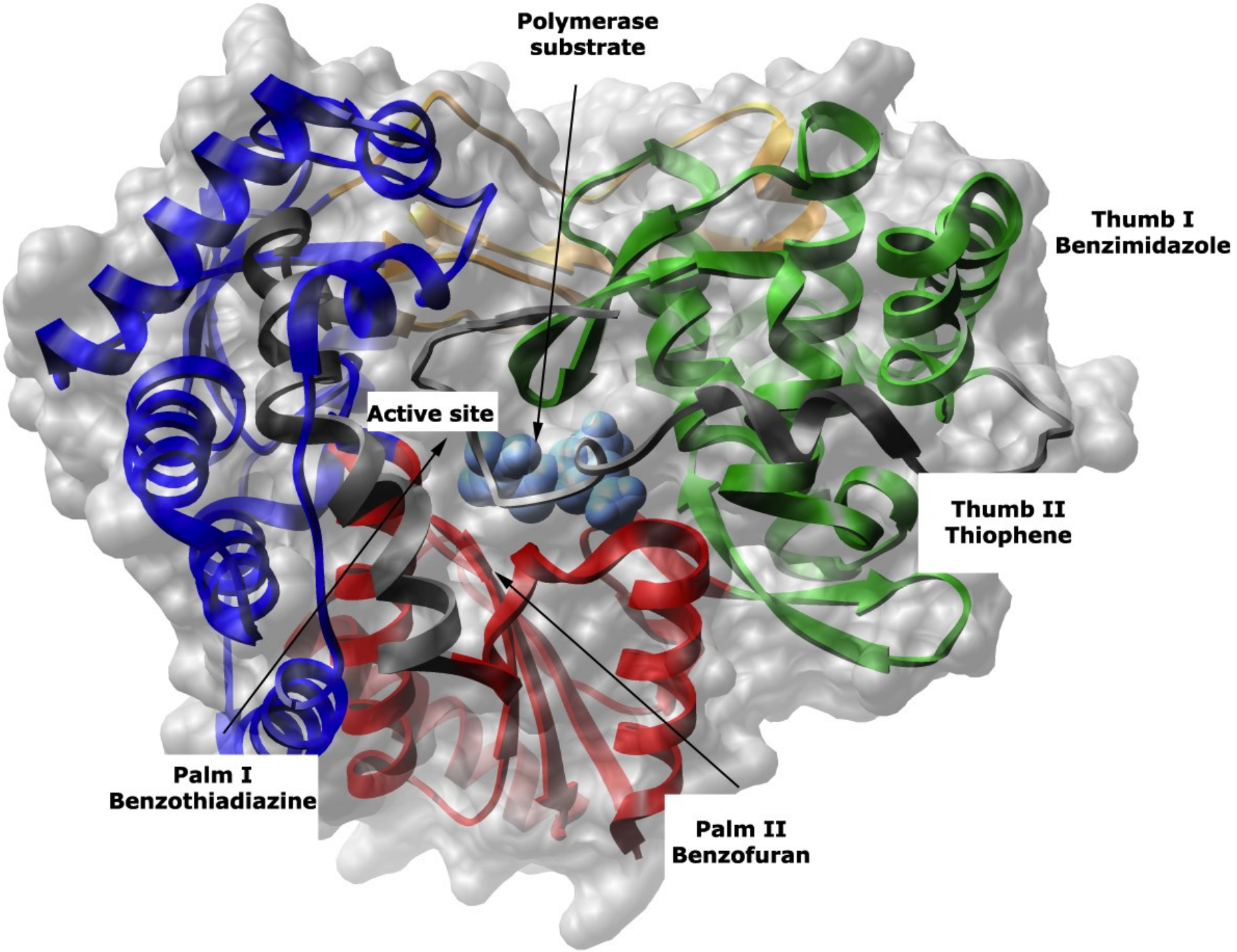


NS3 Bifunctional protease / helicase

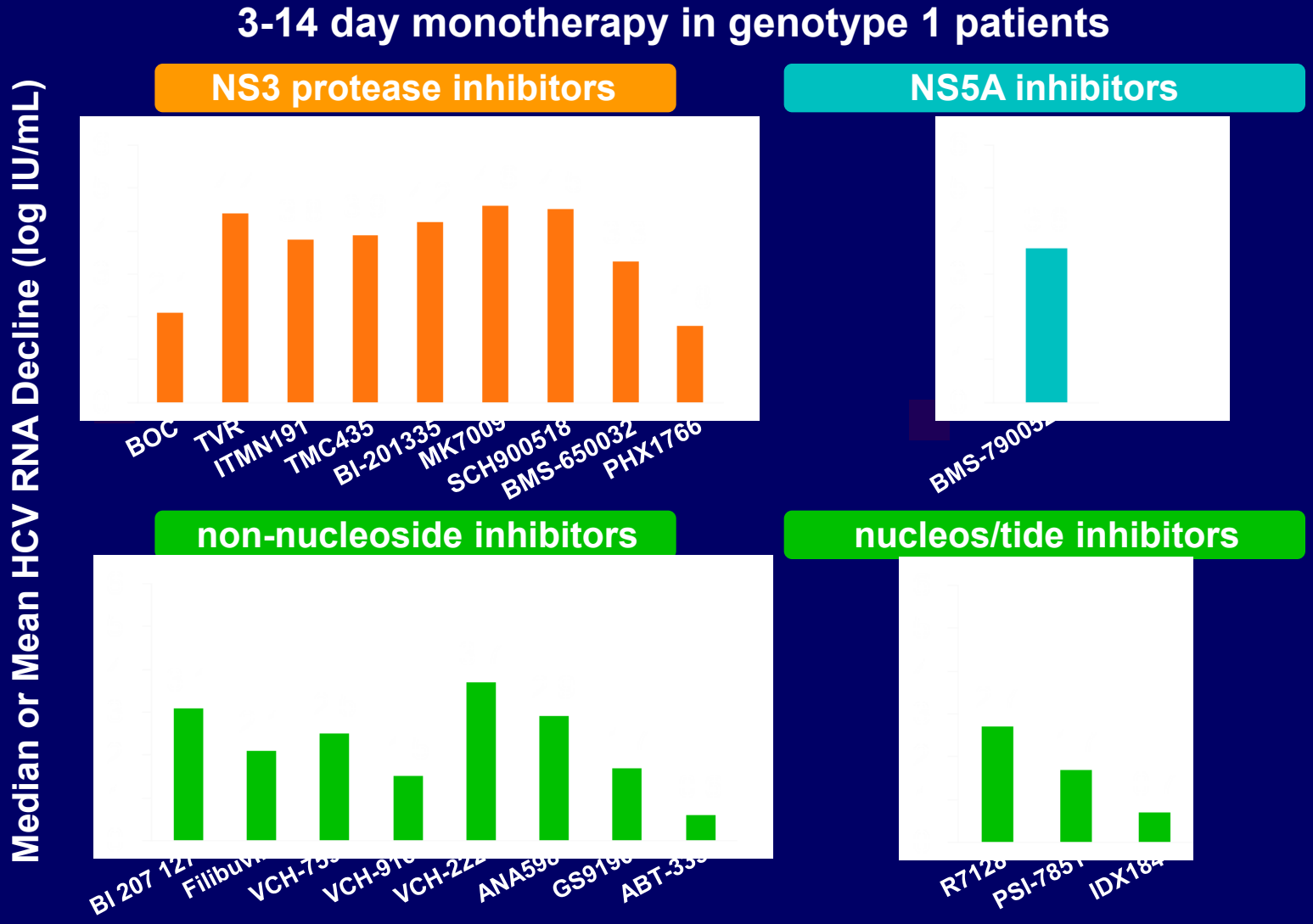




NS5B RNA-dependent RNA polymerase


Polymerase
substrate
Thumb I
Benzimidazole
Active site
Thumb II
Thiophene
Palm I
Benzothiadiazine
Palm II
Benzofuran

Antiviral Activity of DAAs Vary Among and Within Classes



BCP, boceprevir; TVP, telaprevir. Sarrazin C, Zeuzem S. *Gastroenterology.* 2010;138:447-62.

Characteristics of DAAs and HTAs

	Efficacy	Genotype independency	Barrier to resistance
NS3/4A (protease inhibitors)	**+++**	**++**	**+ - ++**
NS5A	**+++**	**+ - ++**	**+ - ++**
NS5B (nucleosides)	**+ - +++**	**+++**	**+++**
NS5B (non-nucleosides)	**+ - ++**	**+**	**+**
Cyclophilin Inhibitors	**++**	**+++**	**+++**

Nucleosidic polymerase inhibitors

- RG-7128 (Mericitabine): moderate efficacy, safe
- GS-7977 (Sofosbuvir): high efficacy, safe
- Alios-2200 = VX135: high efficacy, early phase 2
- NM-283 (Valopicitabine): low efficacy, GI toxicity >
- R-1626: moderate efficacy, lymphopenia >
- INX-189 = BMS-986094: high efficacy, cardiac tox. >
- IDX-184: moderate efficacy, on hold
- PSI-938: high efficacy, hepatotoxicity >

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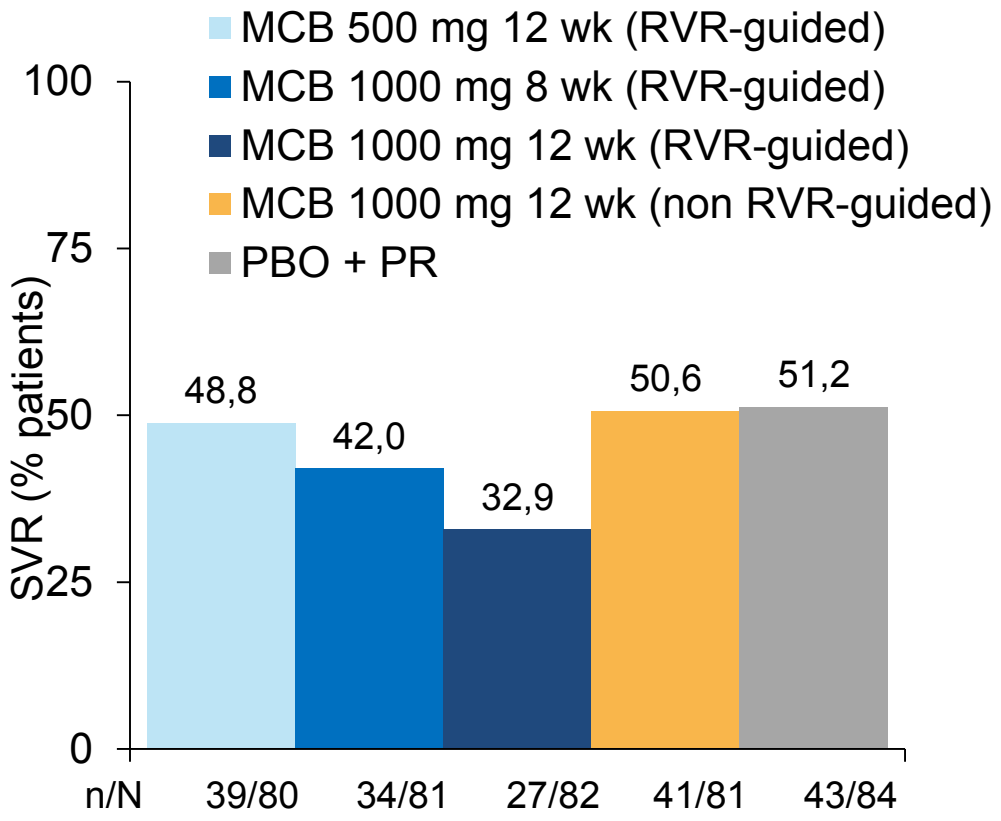
PROPEL study: Efficacy and safety of MCB + PR in G1/4 treatment-naive patients

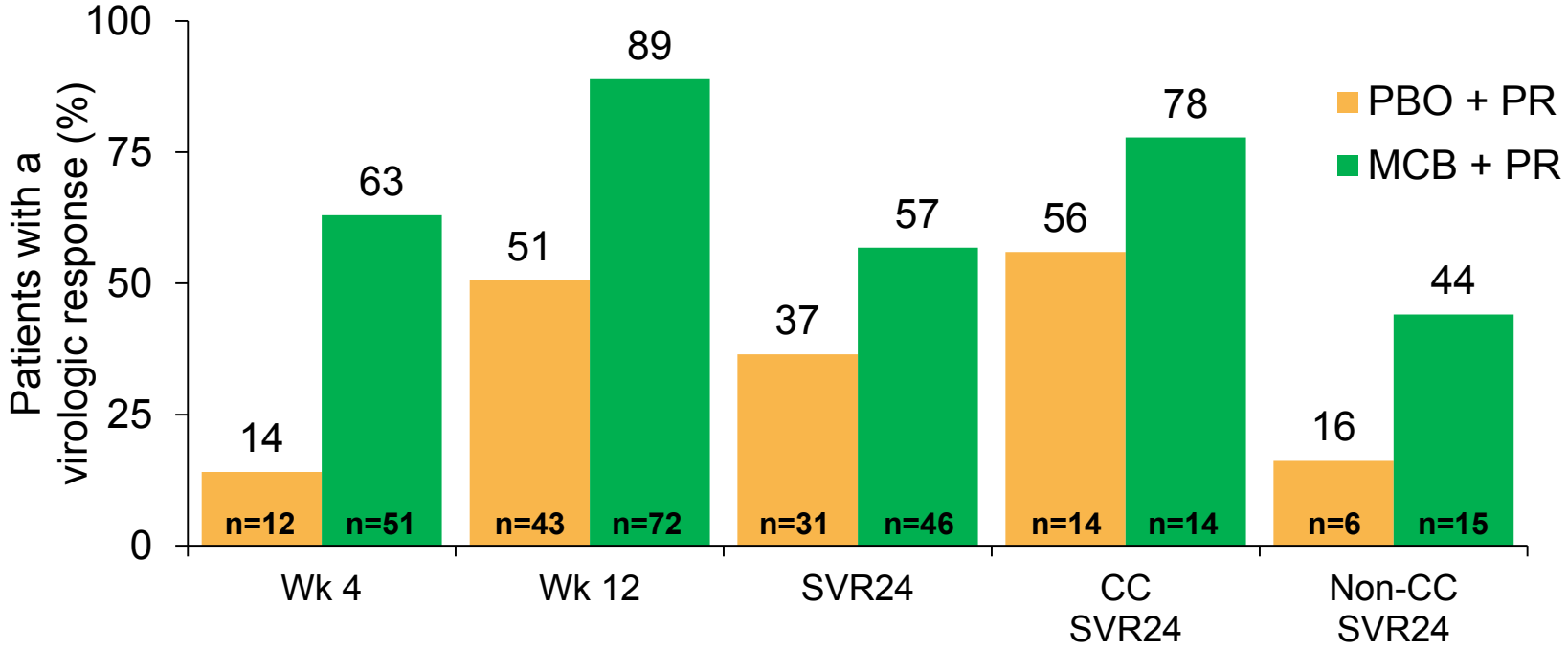
- Mericitabine nucleoside analog polymerase inhibitor
- 5–10% G4
- 9–11% Stage 4 fibrosis
- On-treatment responses enhanced by MCB
- SVR unaffected by MCB
- No new toxicities or resistance



- SVR not better with MCB, despite better on-treatment responses
- May reflect inadequate duration of therapy, contrasting to JUMP-C study where SVR was increased

Wedemeyer H, et al. EASL 2012, Barcelona, #1213

JUMP-C: PR + mericitabine: Virologic responses



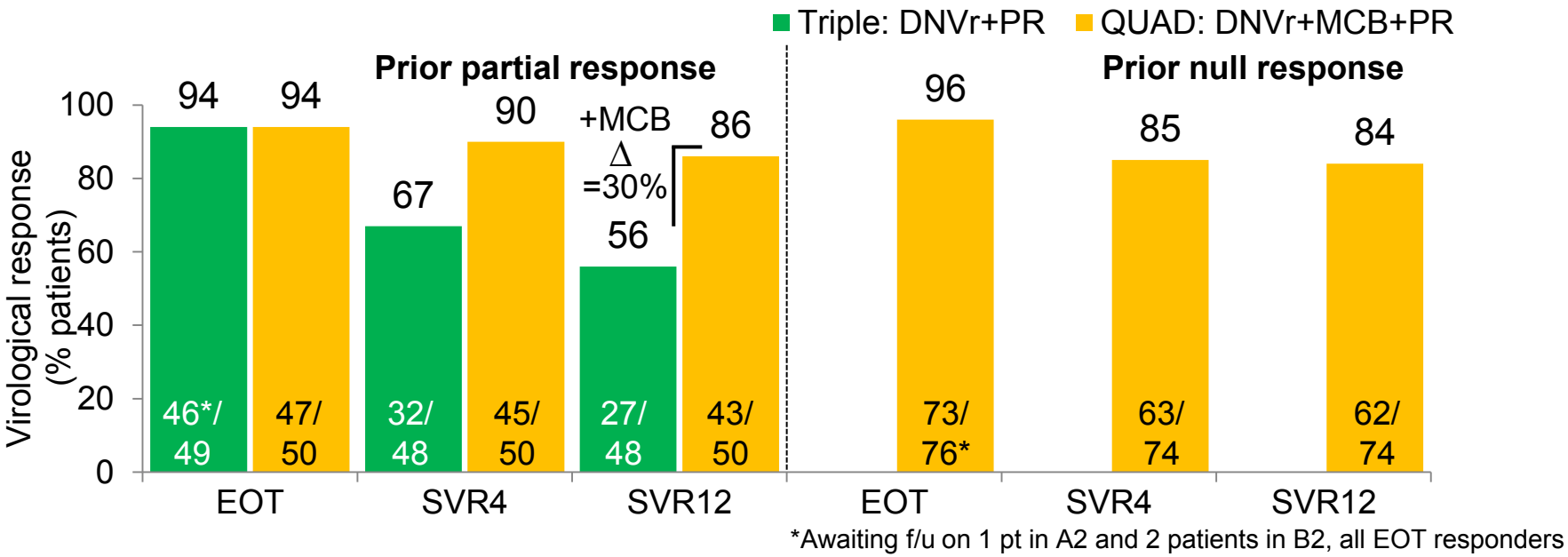
- Relapse rates: MCB 28%; PR 32%
  - Non-cirrhotics MCB 19% vs PR 30%; Cirrhotics MCB 50% vs PR 40%

- High relapse rates led to suboptimal SVR rates despite increment above control
- With no emergent S282T, high barrier to resistance affirmed
- Results illustrate importance of optimizing potency even if a nucleotide has high resistance barrier

Pockros P, et al. EASL 2012, Barcelona, #1205

DNVr, MCB, RBV + PEG-IFN in G1-infected partial and null responders: Results from the MATTERHORN study

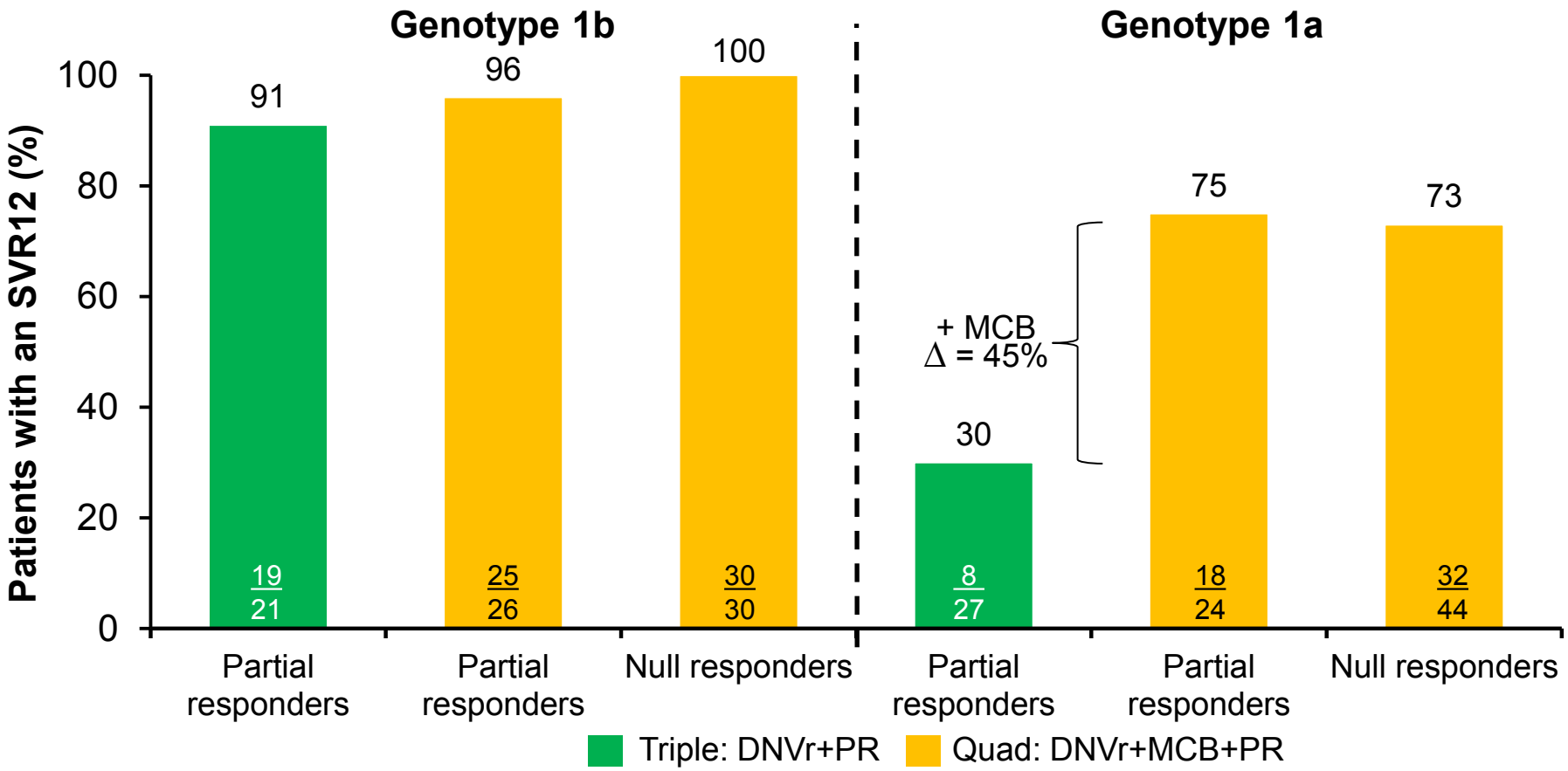
Efficacy of DNVr +PR and QUAD for 24 weeks



*Awaiting f/u on 1 pt in A2 and 2 patients in B2, all EOT responders

Feld JJ, et al. AASLD 2012, Boston. #81

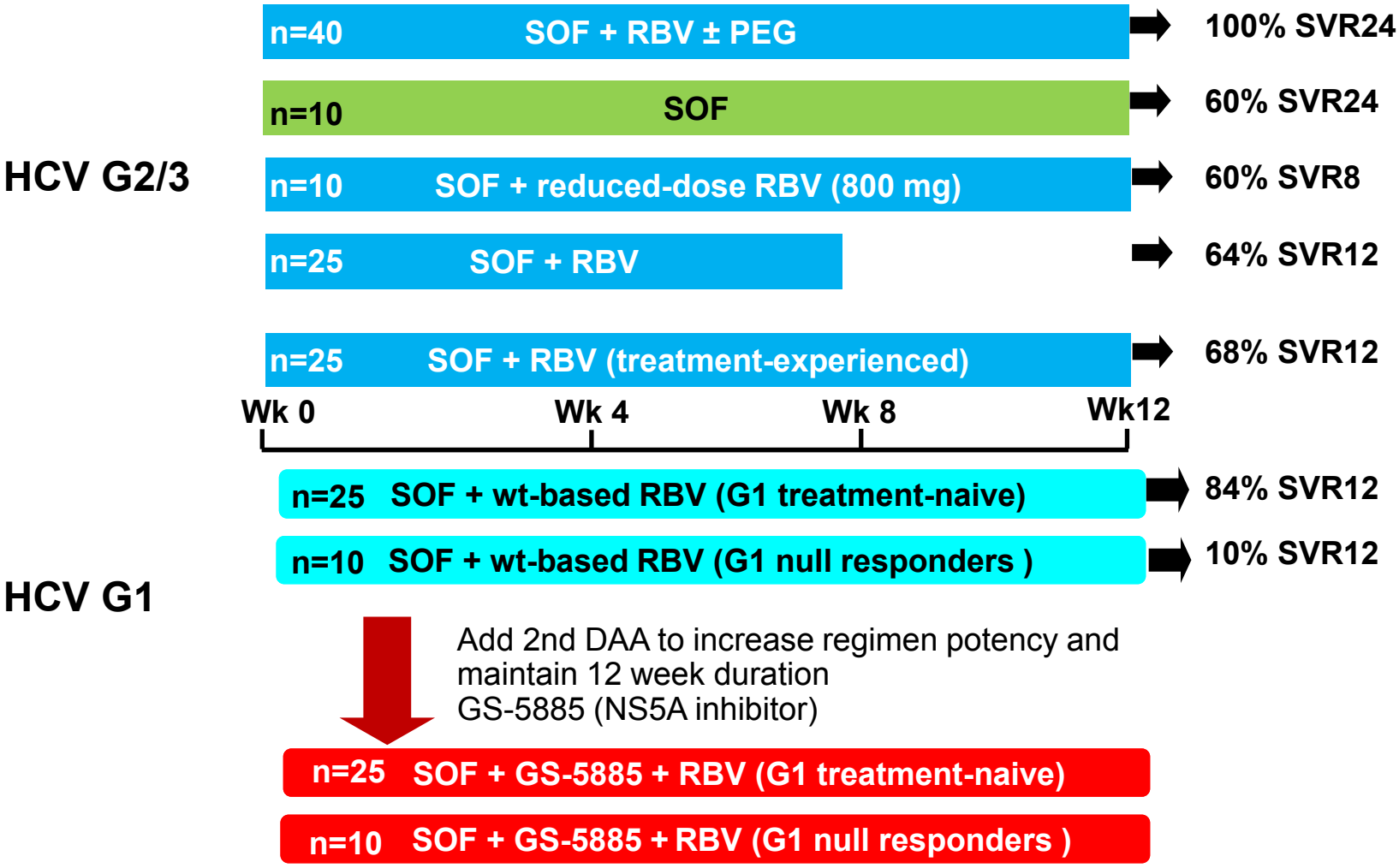
SVR12 by subtype: Addition of MCB improves SVR12 in G1a by 45%



- Triple therapy effective in G1b partials, much less so in G1a
- Mericitabine helps to prevent relapse
- Very high SVR rates to QUAD in nulls, higher in G1b

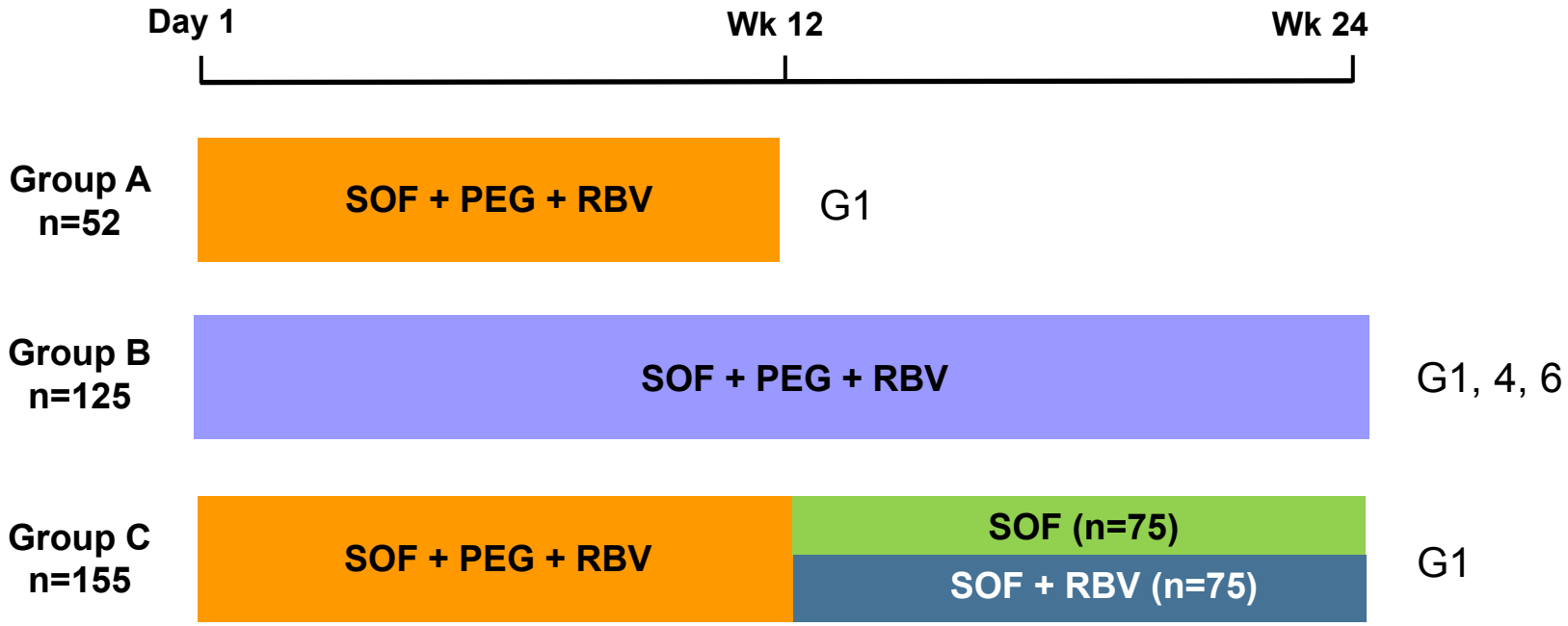
Feld JJ, et al. AASLD 2012, Boston. #81

Once daily Sofosbuvir (GS-7977) plus RBV in patients with HCV G1, 2, and 3: ELECTRON trial



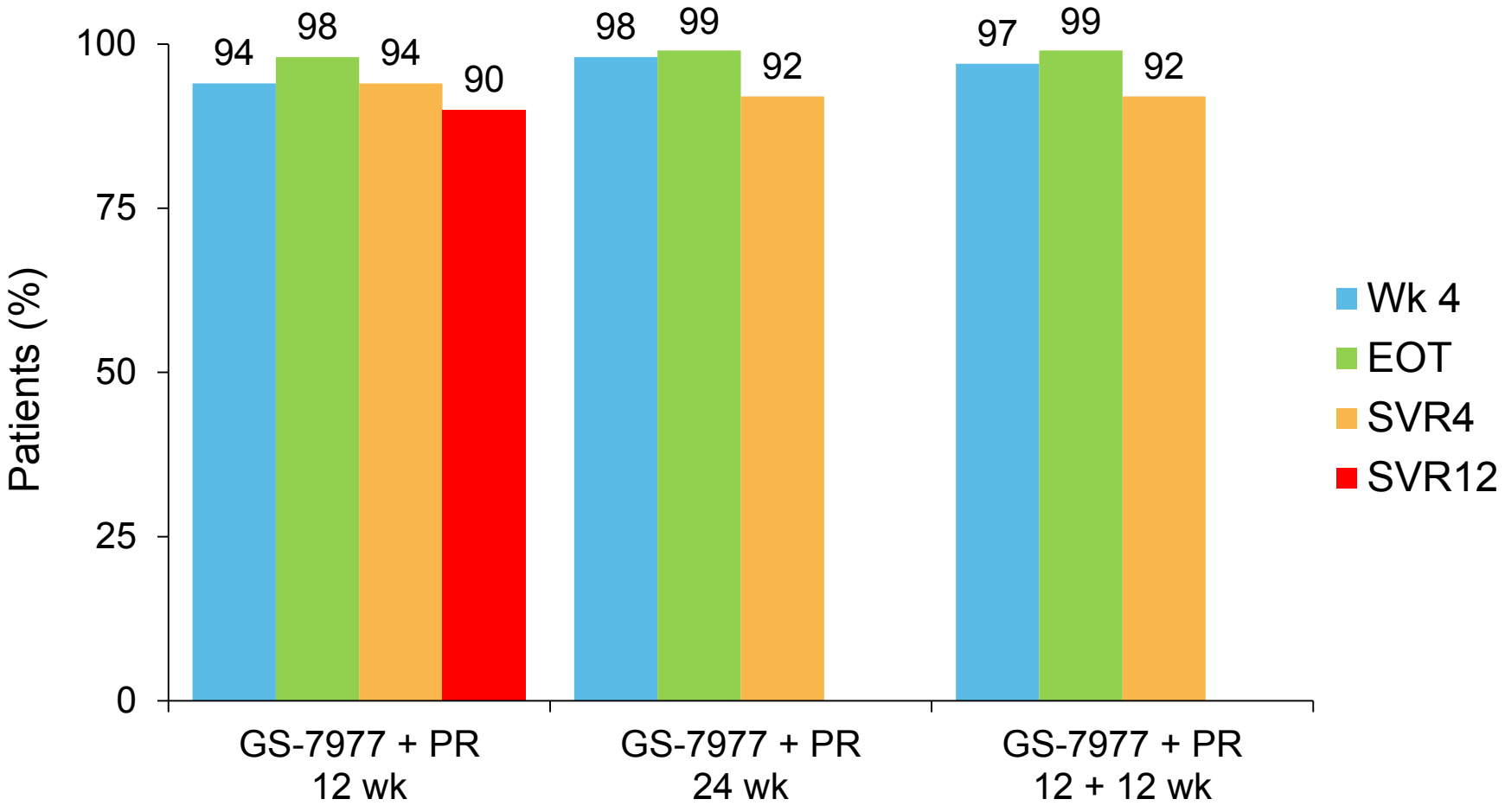
Gane EJ, et al. AASLD 2012, Boston #229

ATOMIC: Sofosbuvir QD + PR



- N=332, treatment naive, non-cirrhotic
- G1a= 68–78%
- IL28B CC= 25–29%

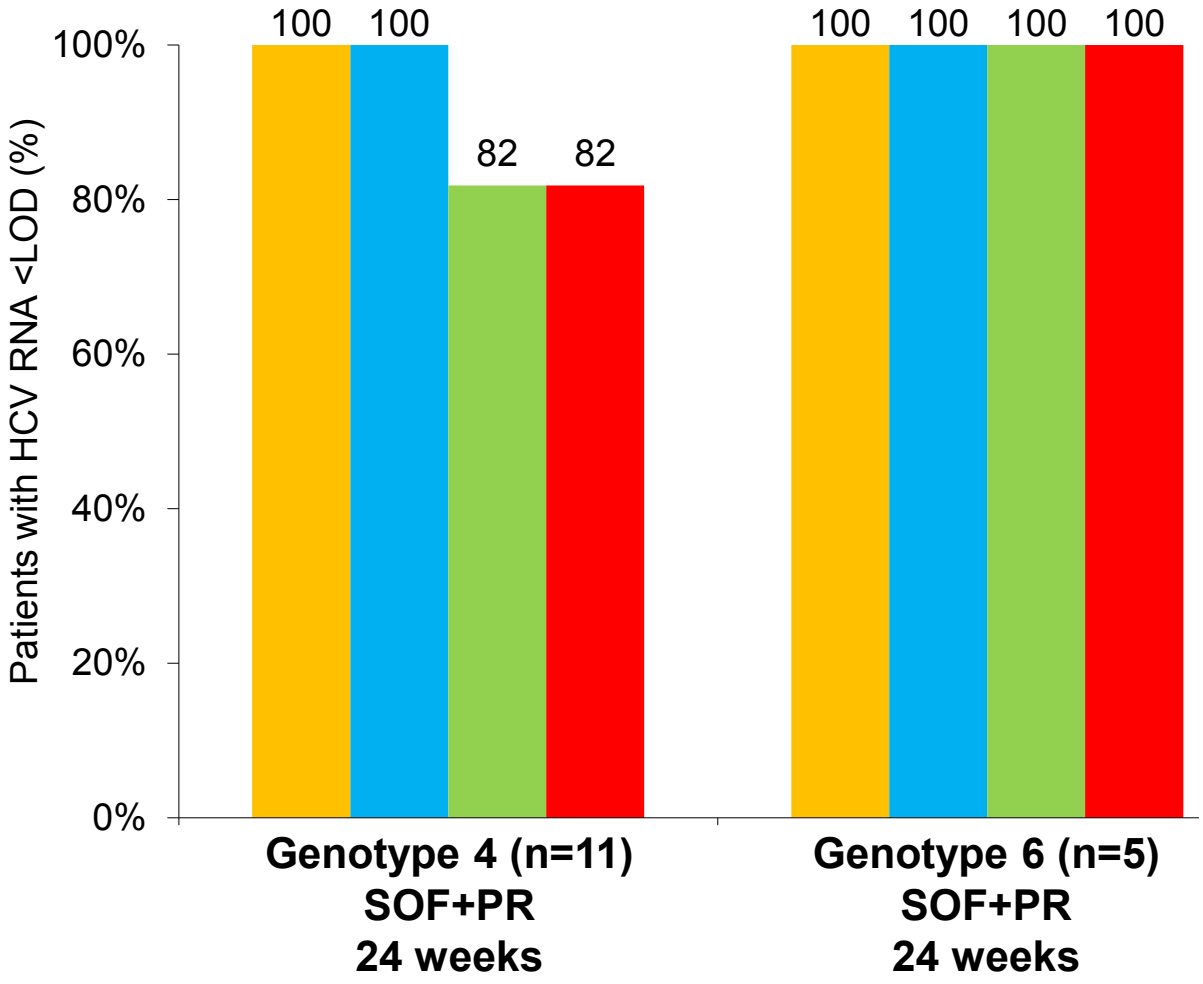
ATOMIC study: A new plateau for IFN-based therapy



- SVR12 not yet reported for the 24 week groups

Kowdley KV, et al. EASL 2012, Barcelona, #1

ATOMIC: Genotype 4 and 6 results



Week 4 EOT
SVR4 SVR12

- Safety
  - No new safety signals
- Resistance
  - No S282T variants identified

Hassanein T, et al. AASLD 2012, Boston #230

Resistance testing in relapsers after treatment with sofosbuvir-containing regimens in Phase 2 studies

- 661 patients in P7977-0221, PROTON, ELECTRON and ATOMIC
  - ⇨No breakthroughs, 53 relapses
- All had WT S282 at baseline
- 52/53 treatment failures underwent population and deep sequencing

G	Number of patients with relapse samples sequenced		
	Population	Deep	NS5B 282 Variants >1%
1a	n=27	n=25	All WT S282
1b	n=13	n=13	All WT S282
2	n=2	n=2	n=1 S282T
3	n=10	n=10	All WT S282

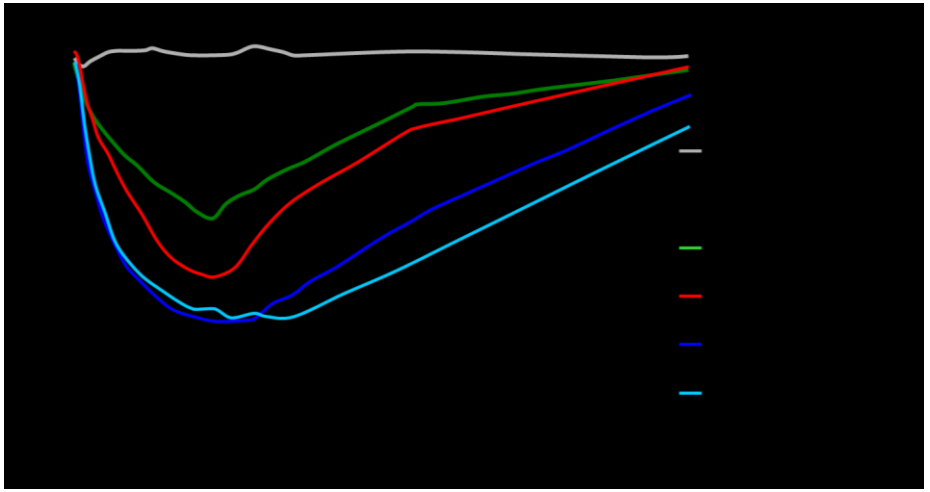
- Single patient with confirmed S282T mutation

Visit	Population sequence change from BL: NS5B	Deep sequencing: S282T ≥1%
Follow-up Week 4	S79N V/I147I S282T I/T309T T/A/I/V312T	>99% S282T
Follow-up Week 8	S79N V/I147I S282S/T I/T309T T/A/I/V312T	27.6% S282T
Follow-up Week 12	S79N V/I147I I/T309T T/A/I/V312T	>99% WT S282

Svarovskaia ES, et al. AASLD 2012, Boston. #753

ALS-2200 demonstrates potent antiviral activity over 7 days in treatment-naive G1 patients

- Novel uridine base nucleotide analog
  - Potent, specific inhibition of HCV NS5B
  - No cross-resistance to other DAAs
  - Pan-genotypic activity in replicon
  - Long intracellular T1/2 of triphosphate
  - Multiple ascending dose for 7 days in treatment-naive, non-cirrhotic G1



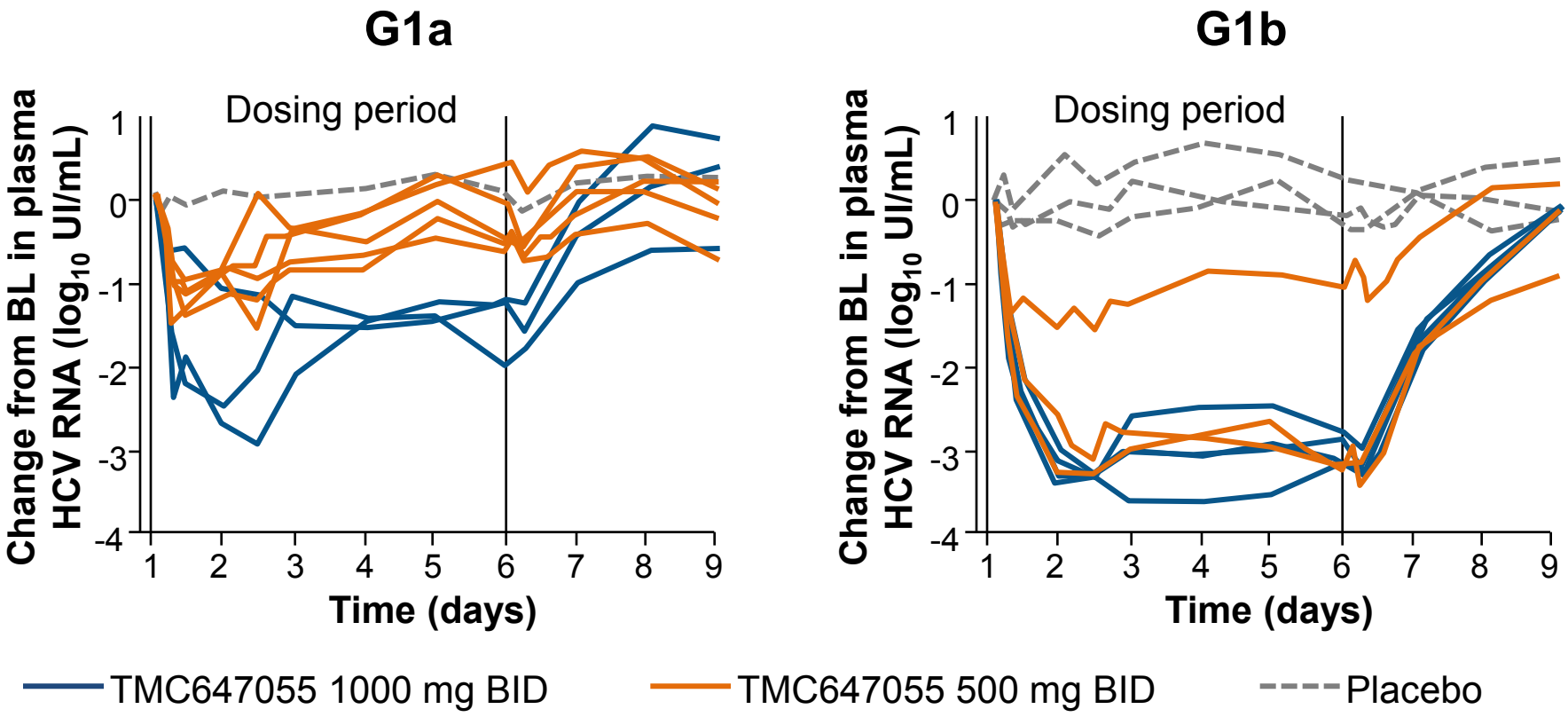
HCV RNA after 7 days treatment	PBO (n=8)	15 mg (n=8)	50 mg (n=8)	100 mg (n=8)	200 mg (n=8)	200mg + RBV (n=8)
<LLOQ, n (%)	0 (0)	0 (0)	0 (0)	1 (13)	4 (50)	5 (63)
<LOD, n (%)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	2 (25)
Median HCV RNA reduction (min, max)	0.11 (-0.28,0.66)	-0.97 (-0.17,-1.59)	-3.02 (-2,21, -3.57)	-3.95 (-3.39,-4.51)	-4.54 (-3.81,-5.08)	-4.18 (-3.6, -5.2)

Marcellin P, et al. AASLD 2012, Boston #86

Non-Nucleosidic polymerase inhibitors

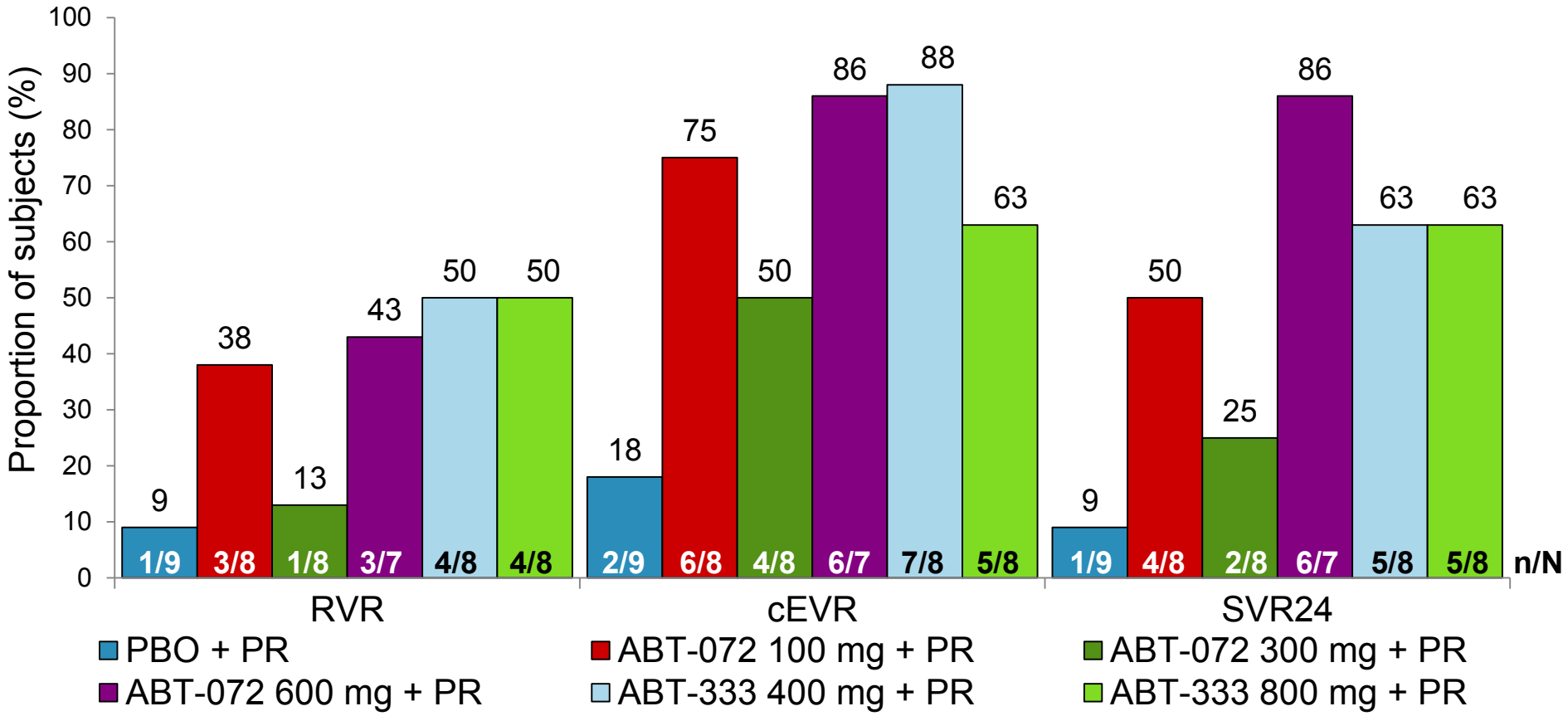
- Thumb I inhibitors (benzimidazole site)
  - TMC-647055
  - BI-207127
- Thumb II inhibitors (thiophene site)
  - PF-868554 (Filibuvir)
  - VX-222
- Palm I inhibitors (benzothiadiazine site)
  - ABT-072, ABT-333
  - ANA-598 (Setrobuvir)
- Palm II inhibitors (benzofuran site)
  - HCV-796 (Nesbuvir)
  - IDX-375

HCV non-nucleoside inhibitor TMC647055: Change in HCV RNA from BL in individual G1a/1b pts



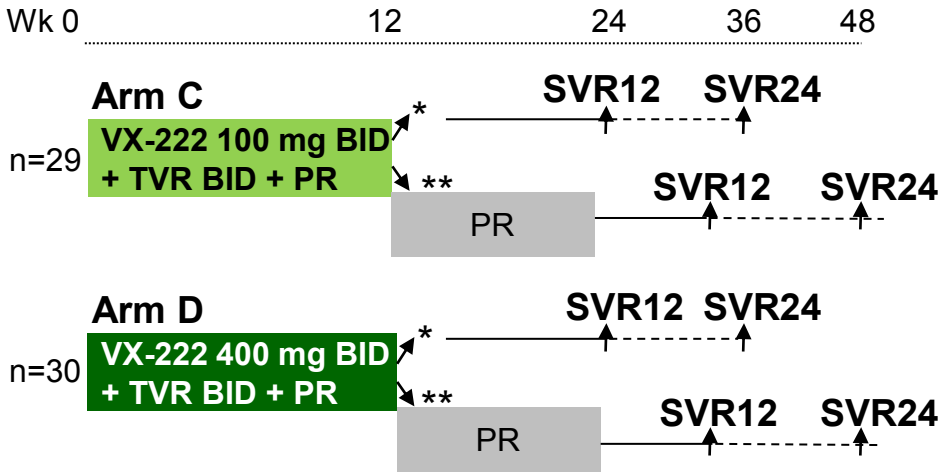
Leempoels J, et al. AASLD 2011, San Francisco, #350

ABT-072 or ABT-333 combined with PR



Poordad F, et al. EASL 2012, Barcelona, #1206

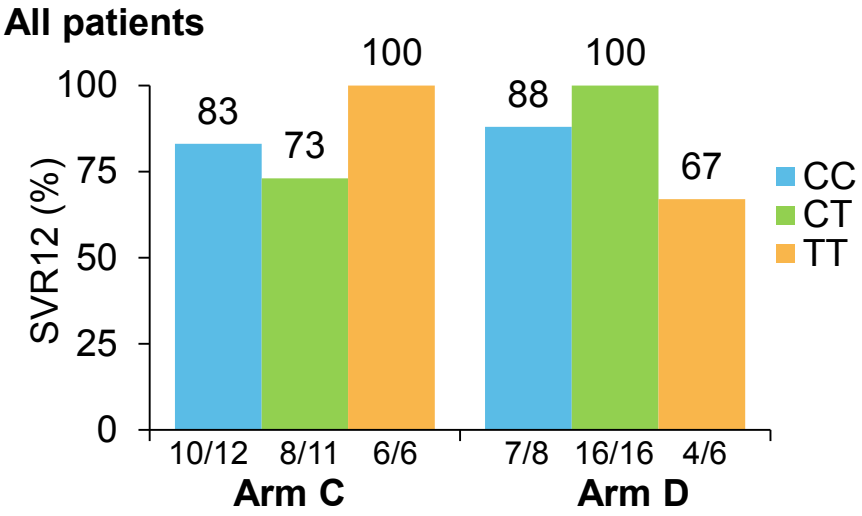
ZENITH study quad arms: SVR12 by IL28B genotype

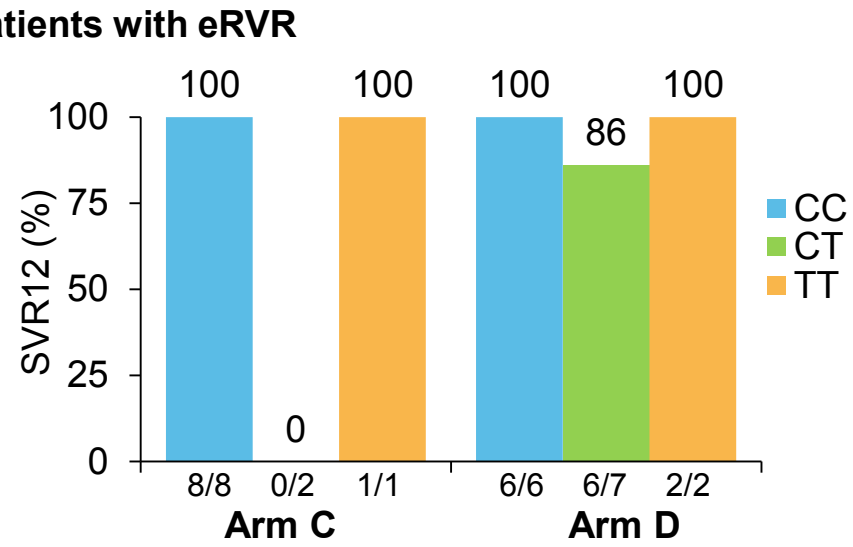


*HCV RNA undetectable at Wk 2 and 8
**HCV RNA undetectable at Wk 2 and/or 8

- 34% CC; 20% TT; 46% CT
- Overall SVR rate 83% Arm C, 90% Arm D

- Quad therapy may still be an option for difficult-to-cure patients





Penney MS, et al. EASL 2012, Barcelona, #1203

Conclusions

- HCV polymerase is an attractive target with two drug classes: nucleosidic (NI) and non-nucleosidic polymerase inhibitors (NNI)
- Potent NIs in combination with P/R achieve high SVR rates; no clinically relevant selection of RAVs
- Less potent NIs show some promising results in quadruple therapies
- NNIs of little importance in the combination with P/R, some interesting data in quadruple therapies; risk of RAVs
- Both, NIs and NNIs play a pivital role in the clinical development of IFN-free regimen