

R1626 Demonstrates Synergistic Antiviral Effect in Combination with Peginterferon Alfa-2a [40KD], with or without Ribavirin, and High Barrier to Resistance

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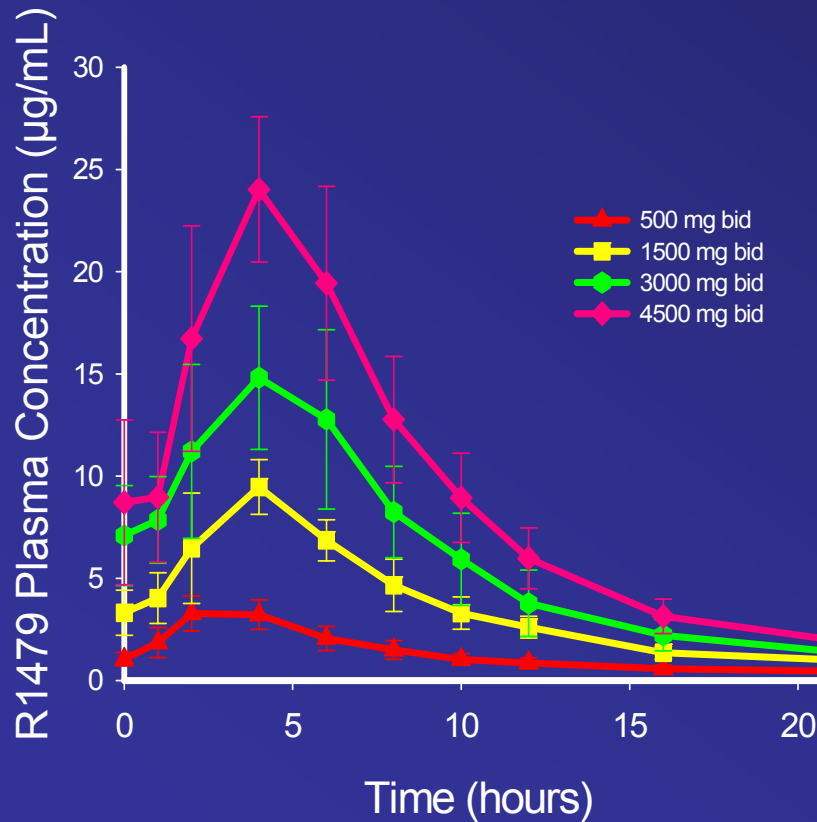
HEPDART Meeting 2007

R1626: Characteristics

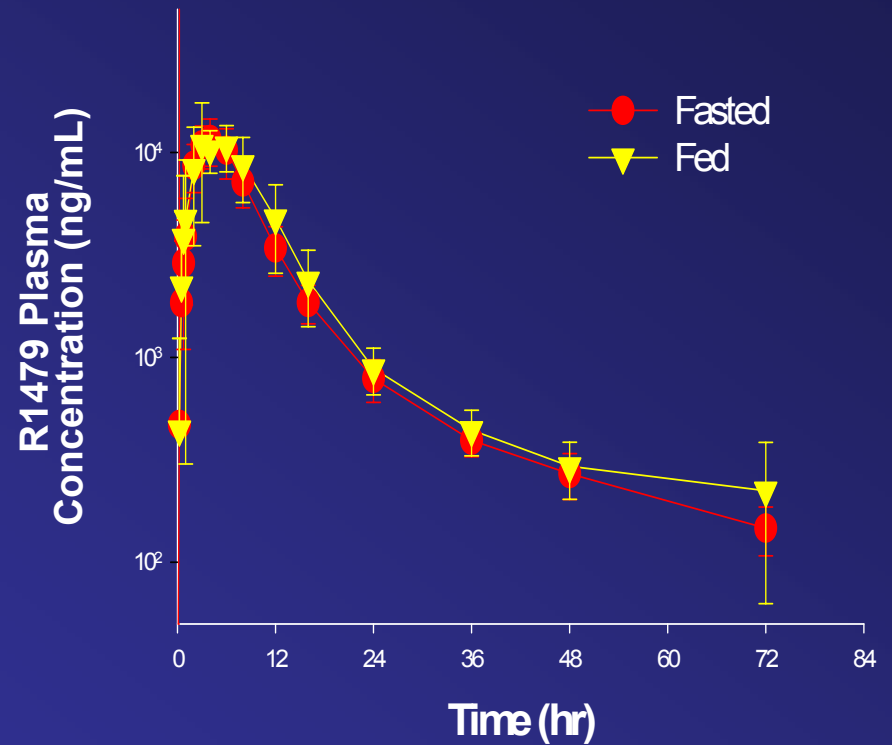
- ▶ **R1626 is a pro-drug of the nucleoside analog, R1479, a potent and selective inhibitor of the HCV polymerase enzyme**
 - Rapid conversion in intestinal mucosa to R1479
- ▶ **The mode of action of R1626 as a chain terminator may offer an advantage vs. non-nucleoside analog inhibitors (NNIs) of the polymerase and protease inhibitors (PIs)**
 - Similar potency against all genotypes and subtypes
 - Potential high barrier to resistance selection

PK of R1479 following MAD oral administration of R1626

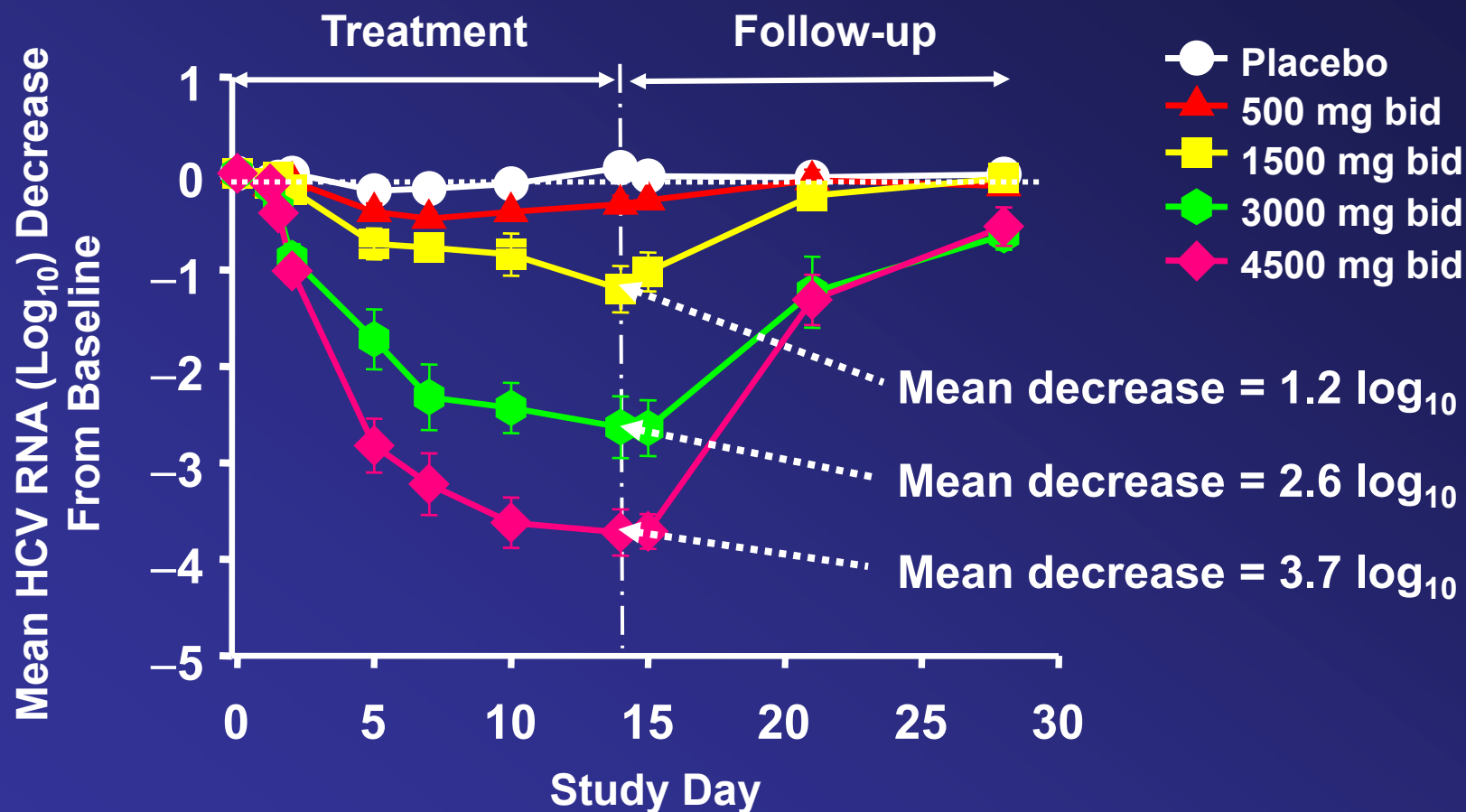
Dose proportional PK



No effect of food



R1626 showed a potent antiviral effect in Phase 1b MAD study



* 8/9 BQL (< 600 IU/mL) and 5/9 HCV RNA undetectable (< 50 IU/mL) at 4500 mg bid dose

Phase 2a study objectives and design

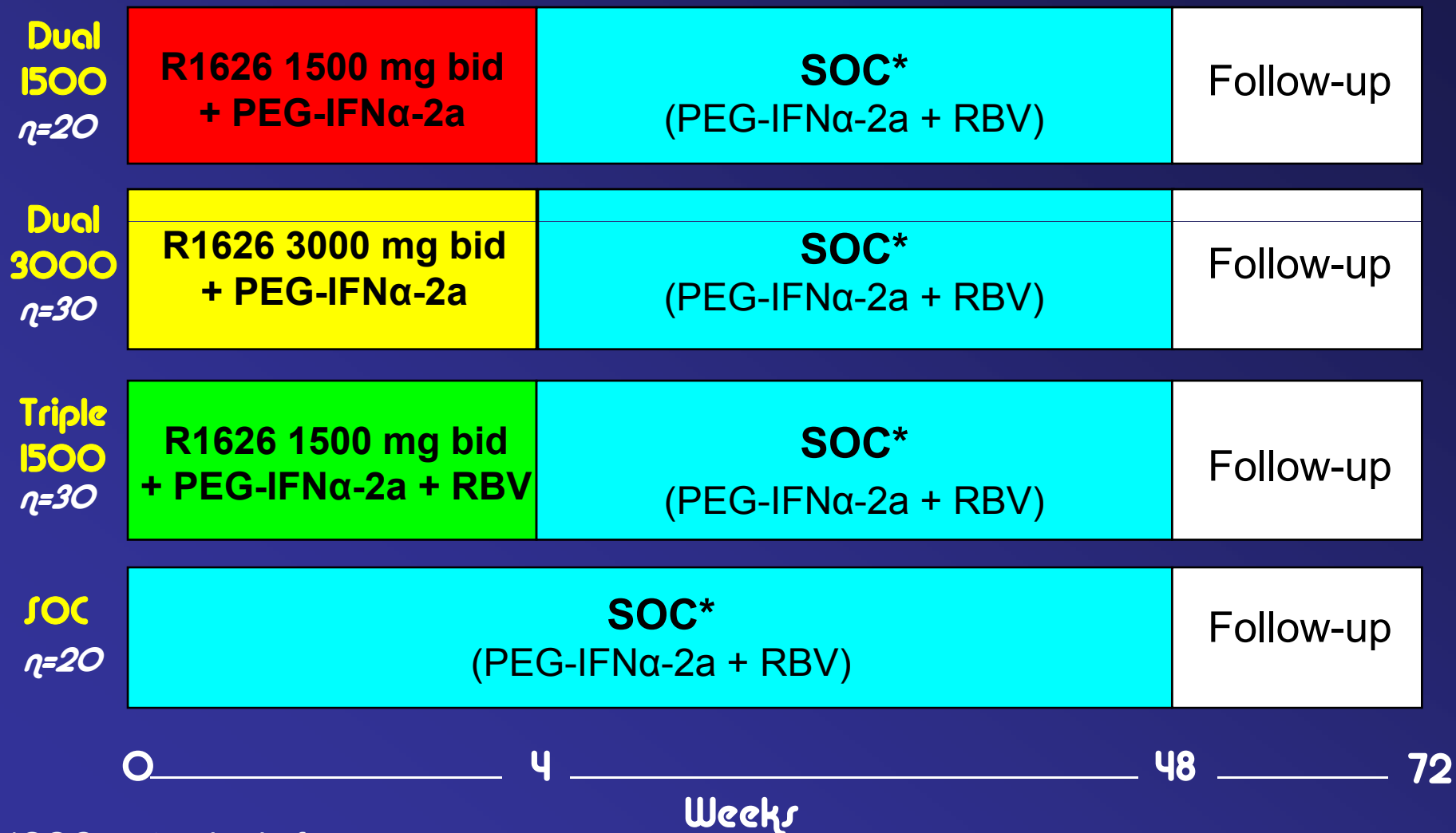
▶ Objective

- Evaluate antiviral activity, drug resistance, and define safety/tolerability profile

▶ Design

- Multi-center, randomized, double-blind (R1626 and RBV), active-controlled
- 4-week combination with peginterferon alfa-2a (40KD] (PEGASYS) ± RBV (COPEGUS) with follow-up safety data on SOC to week 48
- Patient population
 - Treatment-naïve, genotype 1
 - Non cirrhotic (Metavir ≤ 2, Knodell ≤ 1, Ishak ≤ 4)

Phase 2a study design

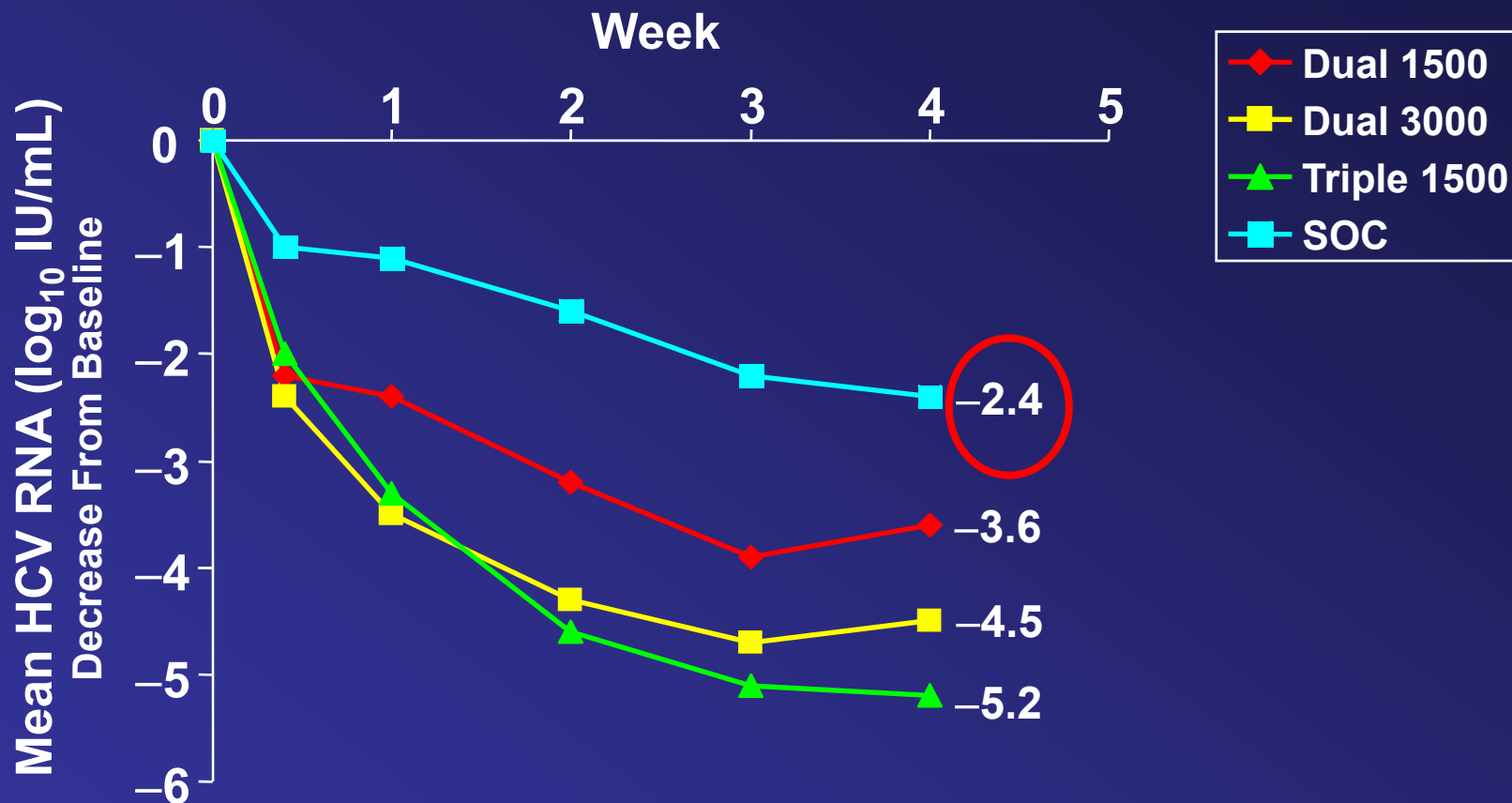


*SOC = standard of care

Baseline characteristics

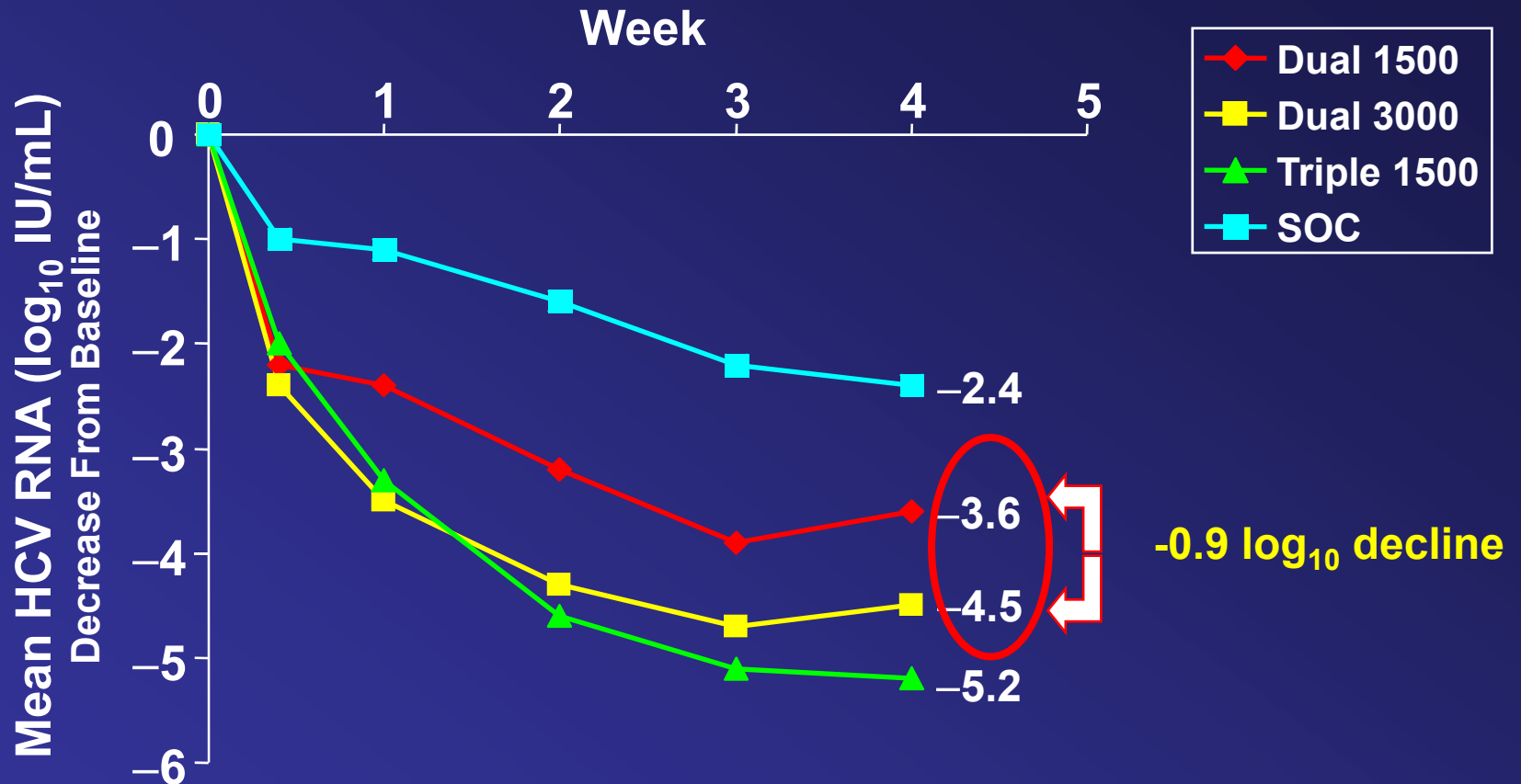
	Dual 1500 (n=21)	Dual 3000 (n=32)	Triple 1500 (n=31)	SOC (n=20)
Gender				
(M / F)	81% / 19%	59% / 41%	61% / 39%	60% / 40%
Age (y)				
Mean	48	47	48	45
Weight (kg)				
Mean	87	80	80	85
ALT (U/L)				
Mean	45	59	57	53
HCV RNA (log₁₀)				
Mean	6.7	6.5	6.7	6.7
Fibrosis Score				
F0 – F1	52%	53%	68%	65%
F2	48%	47%	32%	35%

Reduction in HCV RNA over time



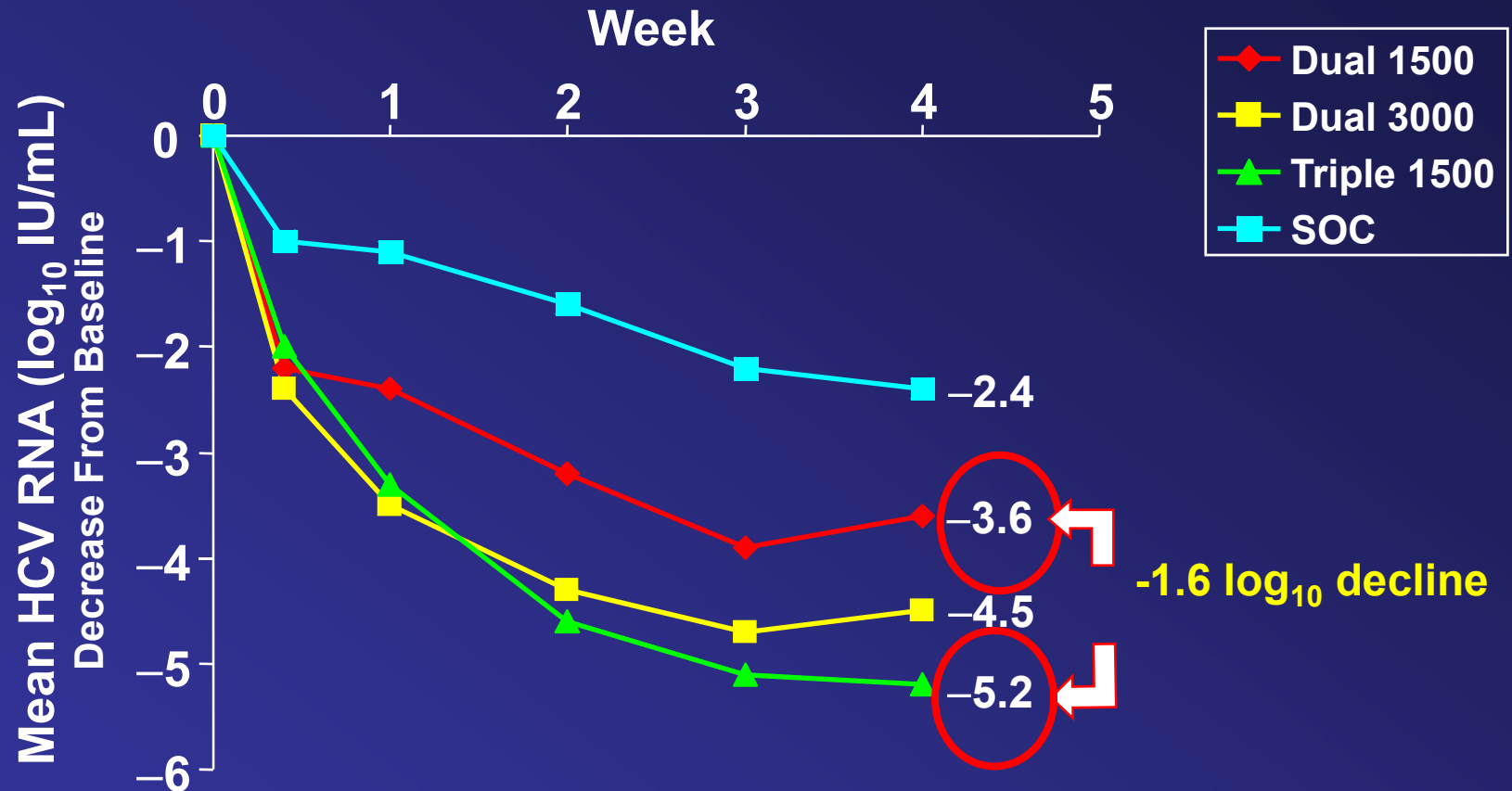
SOC had expected -2.4 log₁₀ decline by week 4

Dose-dependent antiviral effect of R1626 with peginterferon alfa-2a



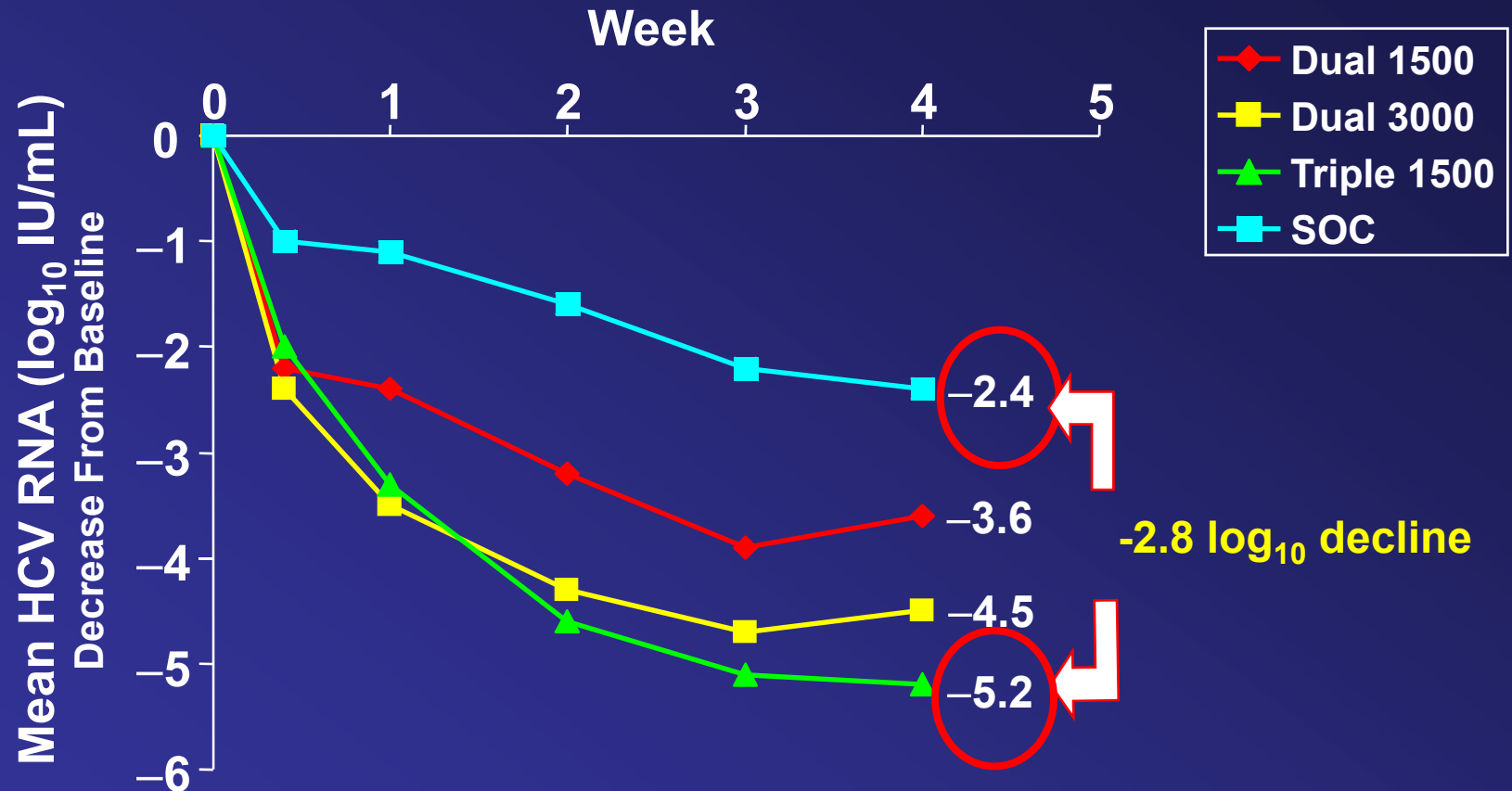
R1626 dose response: Additional $-0.9 \log_{10}$ decline
for 3000 mg versus 1500 mg dose

Synergistic antiviral effect of R1626 with RBV



Synergy between R1626 and RBV: Additional $-1.6 \log_{10}$ decline
RBV mono-therapy known to have $\sim 0.5 \log_{10}$ reduction in viral load

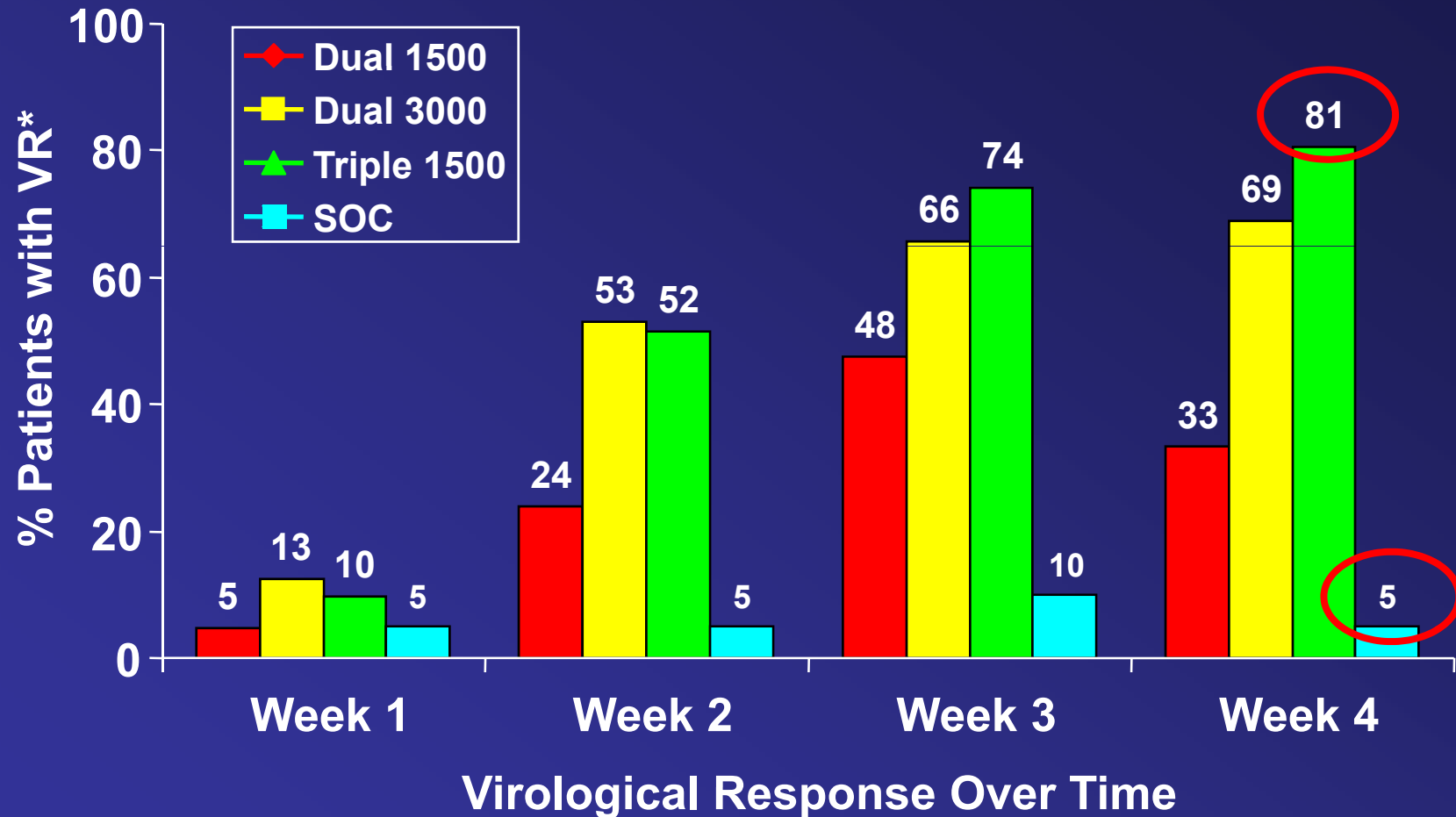
Synergistic antiviral effect of R1626 with peginterferon alfa-2a and RBV



Synergy between R1626 and SOC: Additional $-2.8 \log_{10}$ decline

R1626 monotherapy at 1500 mg showed $1.2 \log_{10}$ decline after 2 weeks

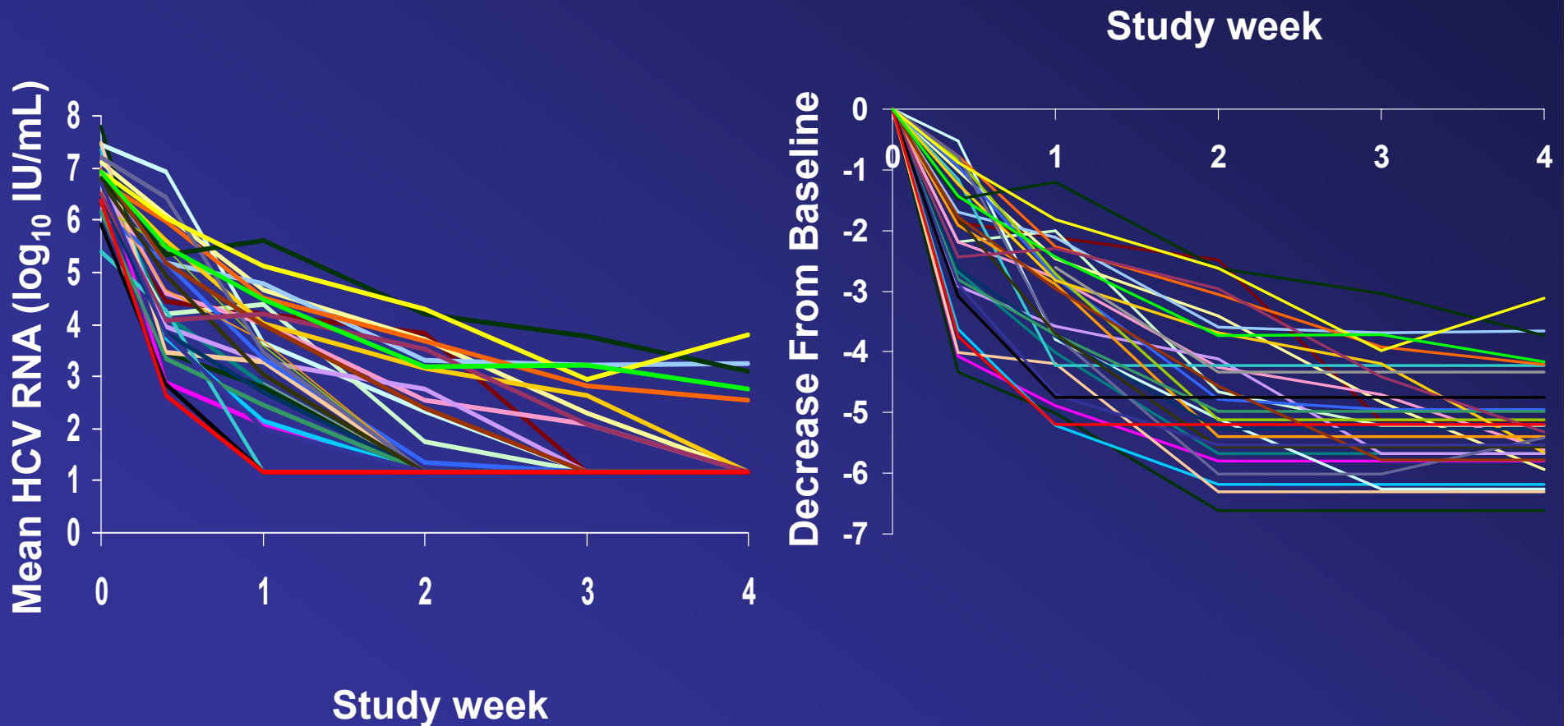
% of patients with virological response (undetectable HCV RNA) over time



* Virological Response = HCV RNA undetectable (< 15 IU/mL), Roche COBAS TaqMan HCV Test

Individual observed HCV RNA level and reduction from baseline

Triple 1500 arm

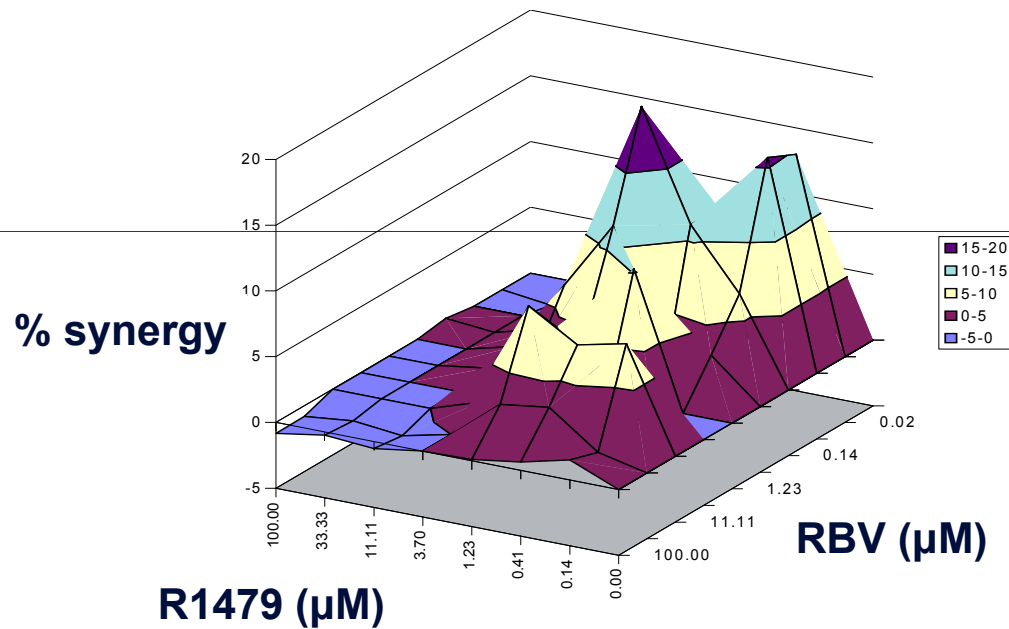


**How can we explain this
apparent synergy?**

R1479 is synergistic with IFN α -2a and RBV in replicon cells

Jiang et al. AASLD 2006, Abs 928

R1479/RBV efficacy synergy plot (95% confidence)

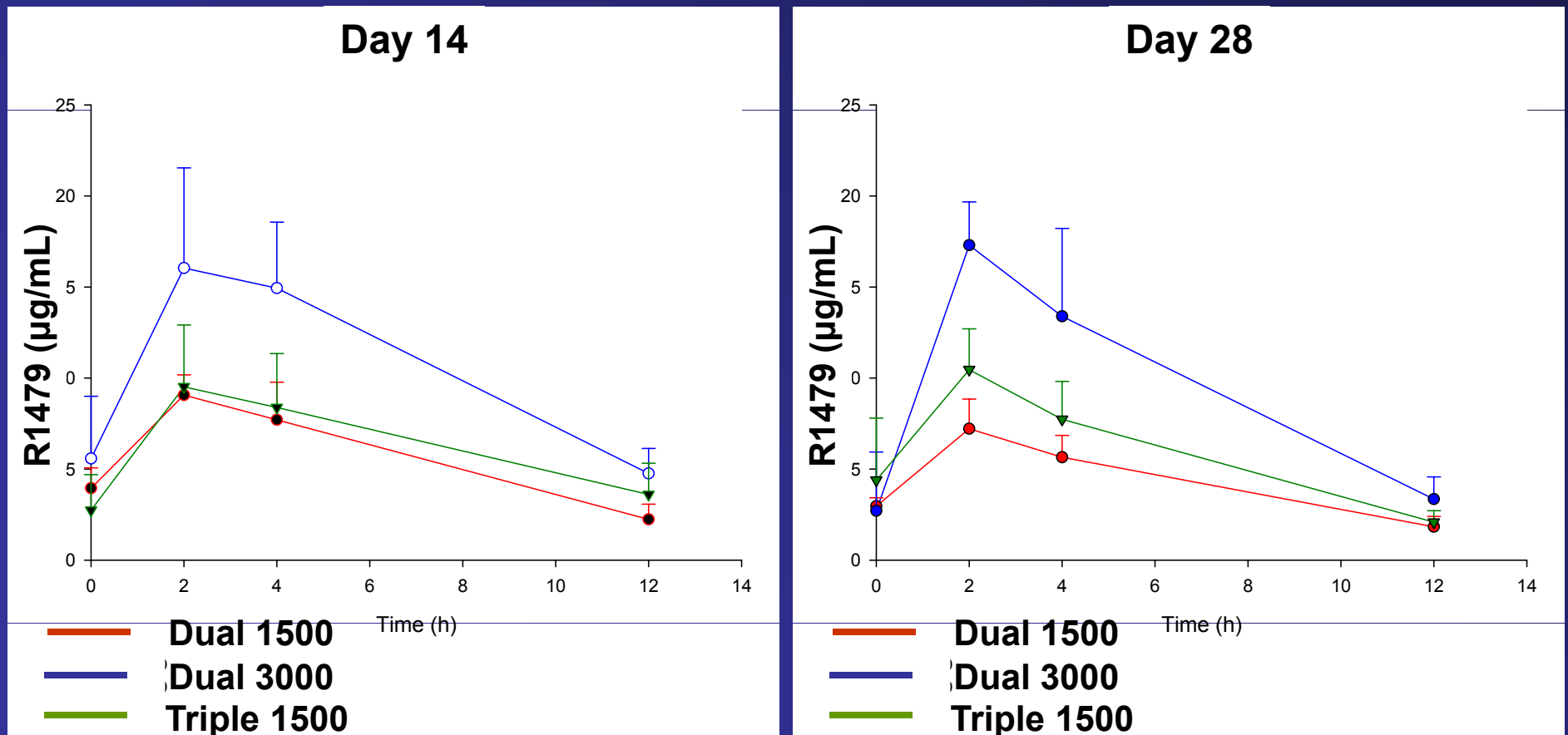


*Synergy defined as volume of > 50 $\mu\text{M}^2\%$

Combination		Synergy Volume	Assessment*
Drug 1	Drug 2	$\mu\text{M}^2 \%$	
R1479	RBV	182	Synergy
RBV	IFN α -2a	116	Synergy
R1479	IFN α -2a	73	Moderate Synergy

Antiviral synergy is not due to changes in R1479 PK

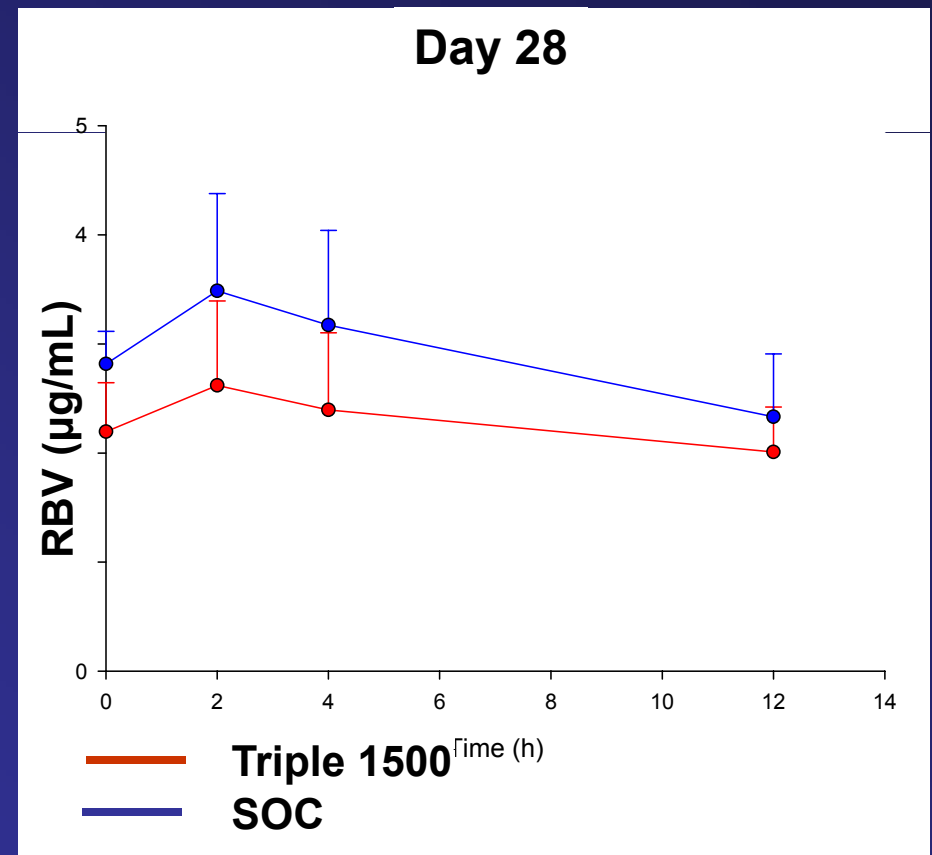
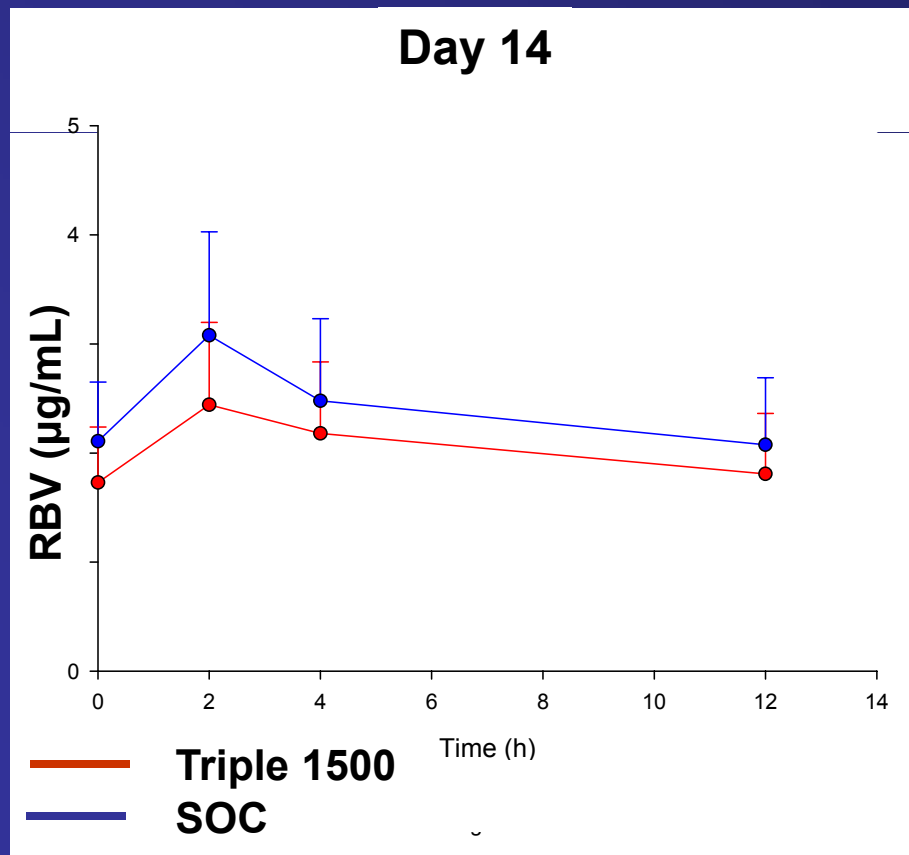
Preliminary **R1479** mean concentration versus time profiles across treatments on Day 14 and 28



Includes patients who were dose reduced

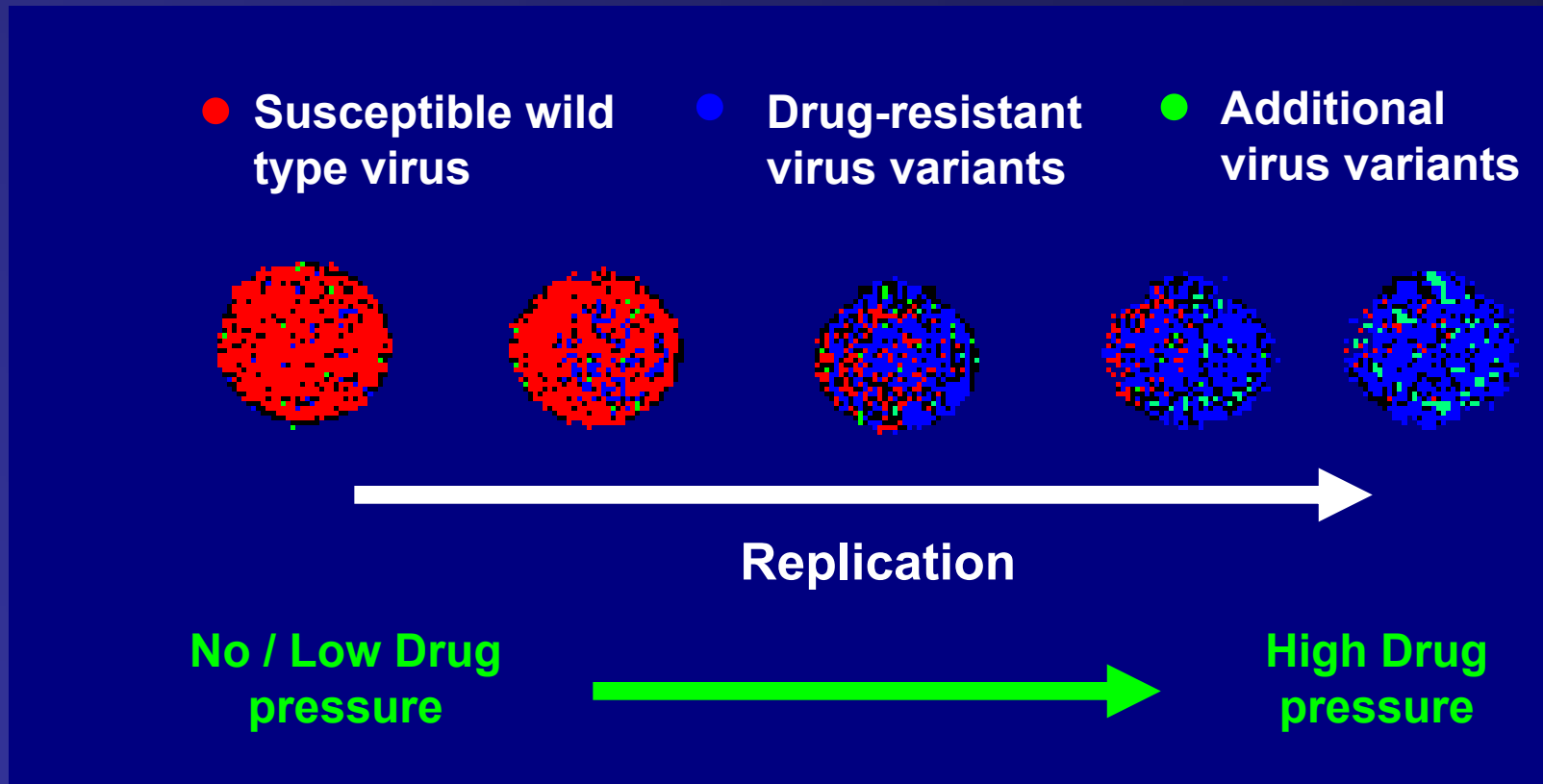
Antiviral synergy is not due to changes in RBV PK

Preliminary **RBV** mean concentration versus time profiles across treatments on Day 14 and 28



Analysis of potential resistance

Pre-existence of resistant virus variants in the baseline quasispecies affects barrier to resistance



- ▶ **Pre-existence of minority resistant virus in baseline quasispecies**
 - Will result in rebound of resistant virus, unless suppressed by non-cross-resistant antiviral agents in combination therapy

No baseline minority virus resistant to inhibition by R1479* observed to date

- ▶ All baseline virus samples from the phase 1 and phase 2A studies were similarly sensitive to inhibition by R1479
- ▶ No pre-existing R1479 resistance mutations (S96T or N142T) detected by sequencing (n=150)
 - Including clonal sequencing of >1000 clones
- ▶ In contrast, pre-existing Non-Nucleoside Inhibitor resistance mutations found in ~ 10 % of baseline samples

*R1626 is the prodrug
of active compound R1479

No resistance selection following treatment with R1626 in Ph 1 and Ph 2a studies



*viral load reduction $\geq 0.5 \log_{10}$ IU/mL followed by viral load increase $\geq 0.5 \log_{10}$ above nadir or detectable viral load after viral response while on treatment in 2 consecutive measurements

- No pre-existing mutations at baseline
- No \downarrow in drug sensitivity vs baseline samples (phenotype assay)
- No S96T or N142T mutations (known to confer resistance in vitro) and no other common amino acid substitutions (sequence analysis)
- **No evidence for resistant virus variants after up to 4 weeks of treatment**

**Patients who showed viral rebound:
had lowest (ineffective) 500 mg dose (n=3) or had discontinued R1626 prior to rebound (n=8)**

R1626 Resistance – Summary

- ▶ Potential resistance to R1626 (prodrug of active compound R1479) was studied extensively
- ▶ Sequence analysis showed no known resistance mutations at baseline for all patients (n=150)
- ▶ No evidence for phenotypic and genotypic changes in patients with viral rebound
 - Rebound associated with inadequate drug levels
- ▶ No selection of viral resistance to R1626, neither at a population level nor at low level in the quasispecies

R1626 exhibits a high barrier to resistance

Safety: Most AEs were mild or moderate

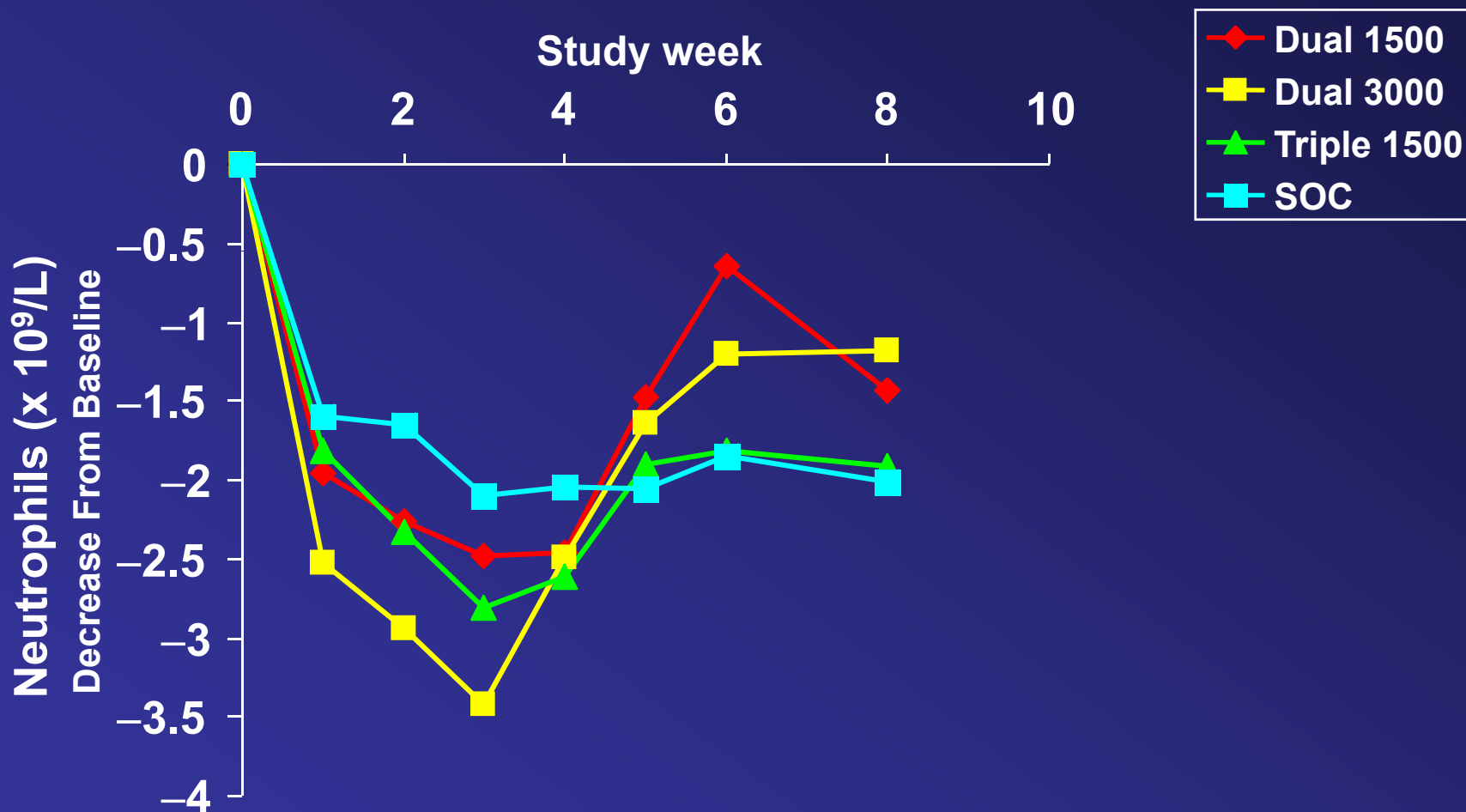
AE (%)	Dual 1500 (n=21)	Dual 3000 (n=32)	Triple 1500 (n=31)	SOC (n=20)
Nausea	38	69	61	50
Diarrhea	38	75	32	25
Vomiting	10	50	26	10
Headache	62	50	58	55
Fatigue	43	50	65	50
Chills	67	47	32	45
Pyrexia	38	31	35	40
Myalgia	14	31	32	55
Insomnia	29	25	42	30
Arthralgia	29	31	16	25
Pain	38	22	23	10
Rash	14	16	39	10
Irritability	24	16	32	5
Cough	10	25	16	20
Dizziness	24	13	19	15
Pruritis	10	13	16	30
Injection Site Erythema	14	13	10	25
Patients with Serious AEs (n)	-	4	1	1

Incidence of laboratory abnormalities

	Dual 1500 (n=21)	Dual 3000 (n=32)	Triple 1500 (n=31)	SOC (n=20)
ANC				
0.5 – < 1.0 x 10 ⁹ /L	8 (38%)	5 (16%)	16 (52%)	6 (30%)
< 0.5 x 10 ⁹ /L	10 (48%)	25 (78%)	12 (39%)	2 (10%)
Platelet				
< 50,000 x 10 ⁹ /L	2 (10%)	15 (47%)	4 (13%)	–
Hemoglobin				
< 10 g/dL	–	3 (9%)	10 (32%)	1 (5%)
< 8.5 g/dL	–	–	3 (10%)	–

Degree of neutropenia not associated with incidence of infection

Neutrophil counts up to week 8



Neutrophil decrease was reversible in all patients

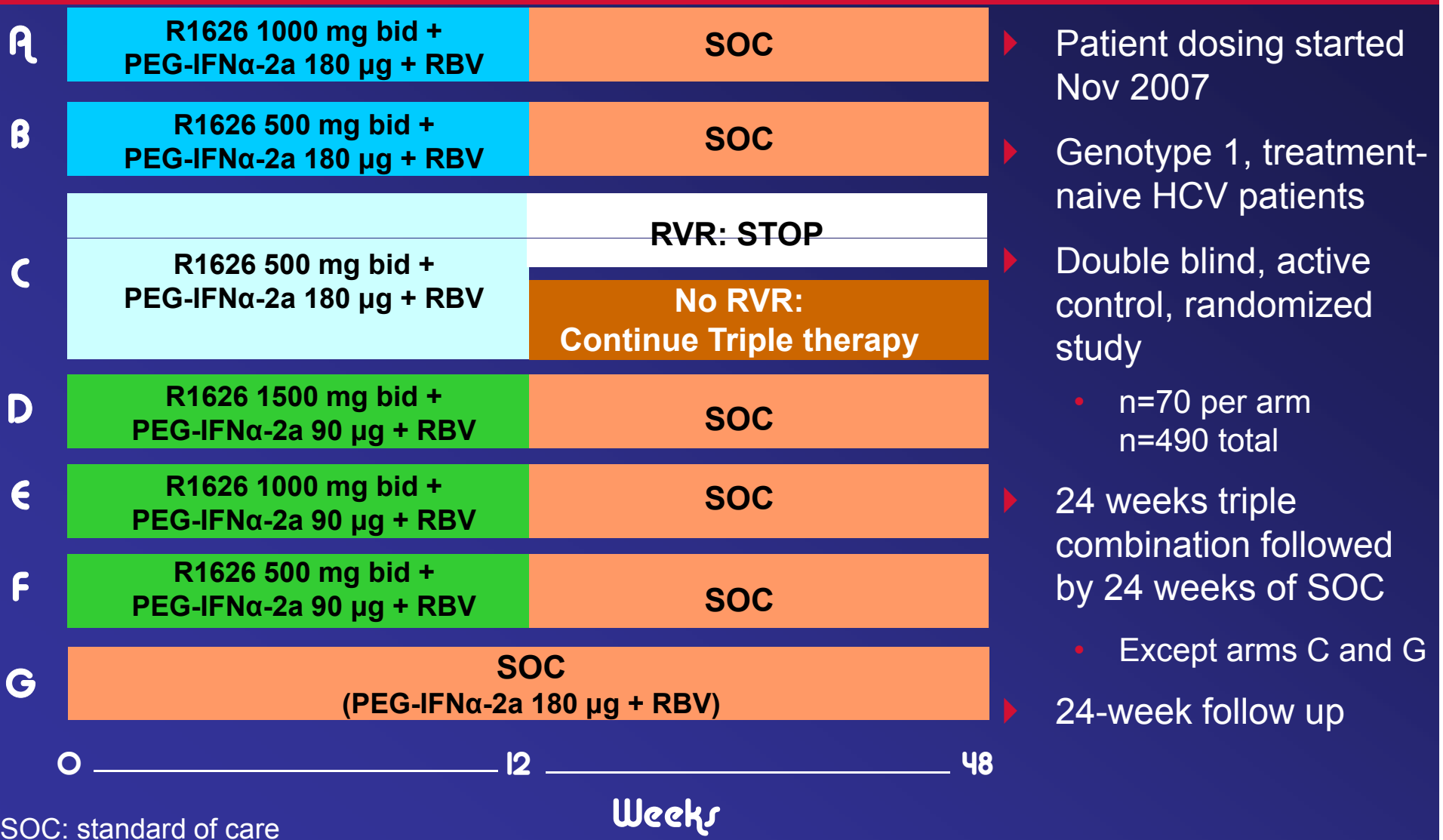
R1626 – Overall summary

- ▶ **Robust synergistic antiviral effect of R1626 in combination with PEGASYS and RBV**
 - 81% patients with undetectable HCV RNA by week 4 (R1626 1500 mg bid + PEG-IFN α -2a + RBV)
- ▶ **Lack of viral resistance**
 - Observed viral load rebound was not due to viral resistance selection
- ▶ **Dosing of R1626 was limited by neutropenia**
 - Degree of neutropenia not associated with incidence of infection

Next step for R1626...

- ▶ **R1626, appears to be a promising agent for treatment of patients chronically infected with HCV genotype 1**
- ▶ **A global phase 2b study (490 patients) is underway to evaluate R1626 in triple combination for up to 48 weeks**
 - **R1626 at doses of 500, 1000 and 1500 mg bid**
 - **PEG-IFN α -2a at 90 μ g and 180 μ g**
 - **Standard dose of RBV**

R1626 phase 2b study: Design



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