

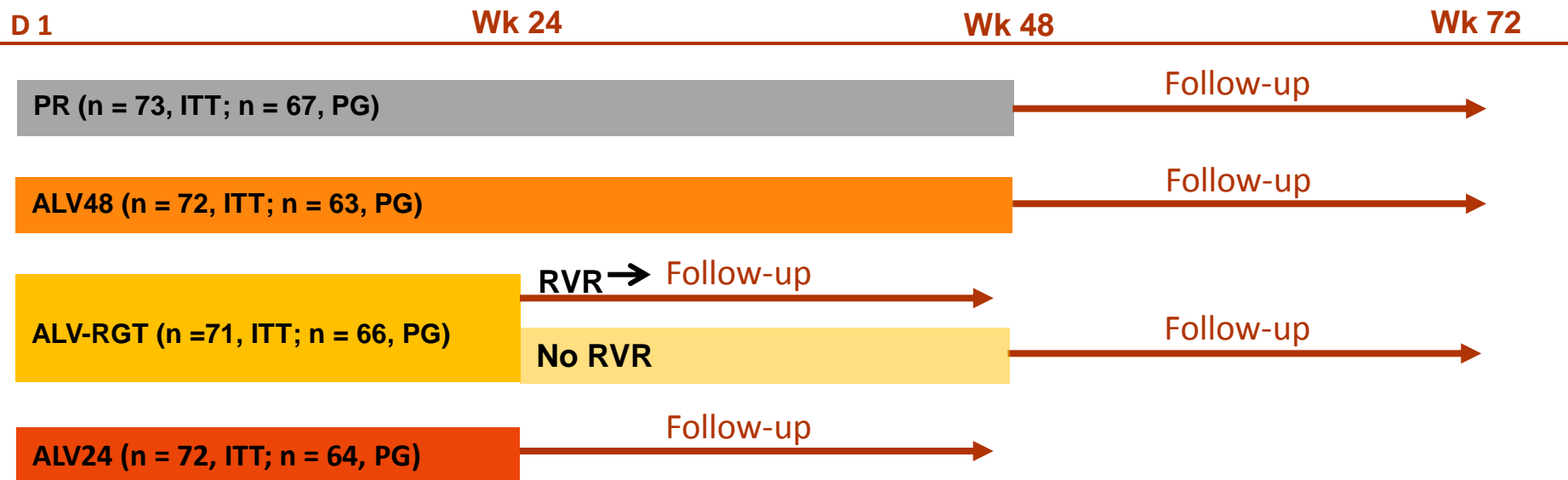
Alisporivir Plus Peg-IFN α -2a/Ribavirin Treatment for Chronic Hepatitis C Genotype 1 Treatment-Naïve Patients Shows Superior Sustained Virologic Response Irrespective of *IL28B* Genotype and High Barrier to Resistance

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ESSENTIAL study design

- ALV (Debio 025) → cyclophilin inhibitor → Host Targeting Antiviral (HTT).
- 288 treatment-naïve CHC genotype 1 infected patients without cirrhosis randomized to 4 treatment arms (ITT).



Primary endpoint: SVR at 24 wk post-treatment with ALV48 vs PR48
Pharmacogenomic (PG) population: patients with known *IL28B* Gt

ALV48, alisporivir (ALV) + peginterferon alfa-2a (Peg-IFN)/ribavirin (RBV) for 48 wk; ; ALV24, ALV + PegIFN/RBV for 24 wk; ALV-RGT, ALV + PegIFN/RBV response-guided treatment for 24/48 wk with/without rapid virologic response (RVR); Gt, genotype; HCV, hepatitis C virus; *IL28B*, interleukin-28B; ITT, intention-to-treat population; PR48, PegIFN/RBV for 48 wk. RVR, rapid virologic response; SVR, sustained virologic response.

Baseline characteristics

no randomisation according to pharmacogenomic profile

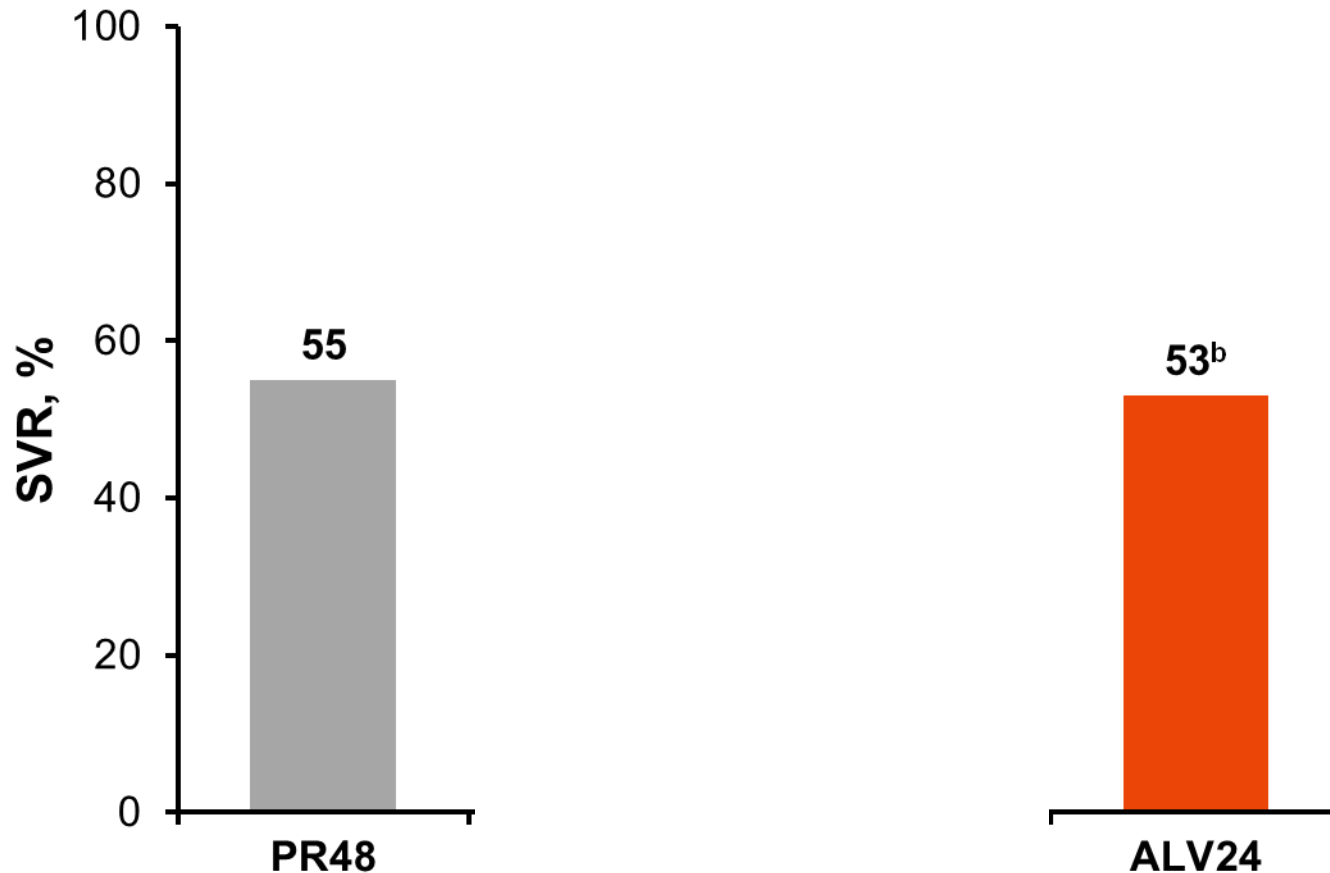
	PR48	ALV48	ALV-RGT	ALV24
ITT (N = 288)	n = 73	n = 72	n = 71	n = 72
Men, %	52	51	44	60
Caucasian, %	97	97	96	97
Mean age, y	41.6	41.1	42.2	39.1
Mean BMI, kg/m ² ,	25.4	24.3	24.8	24.2
≥25 kg/m ² , %	56.2	36.1†	40.9	40.3
Mean HCV-RNA, Log ₁₀ IU/mL	6.2	6.2	6.2	6.2
>600,000 IU/ml, %	78.1	79.2	78.9	77.8
Mean ALT, U/L	67.7	67.2	63.1	86.4
Mean total bilirubin, mg/dL	0.7	0.6	0.6	0.6
Mean platelet, x 10 ⁹ /L	239	244	247	252
Mean ANC, x 10 ⁹ /L	3.7	3.6	3.7	3.7
PG (n = 259)	n = 67	n = 67	n = 67	n = 67
<i>IL28B</i> (rs12979860) CC Gt, %	32.8	19.7	22.7	23.8

^aP < .05.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; BMI, body mass index.

Superior SVR24 with ALV triple therapy vs PegIFN/RBV alone

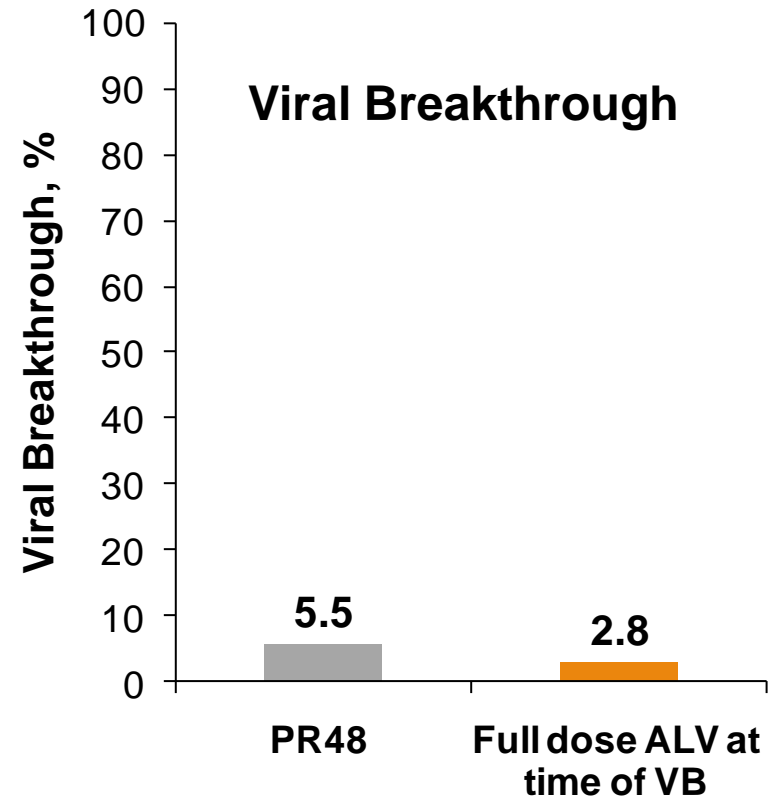
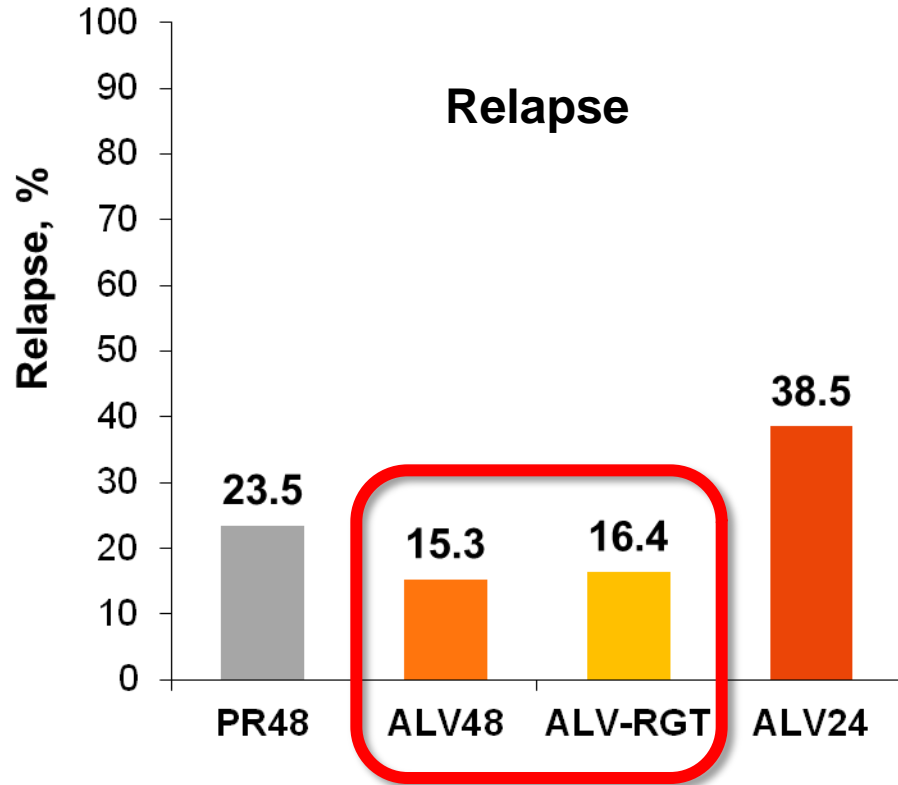
Primary Endpoint, ITT Population



^a*P* = .08 vs PR48; ^b*P* = .06 vs ALV-RGT.

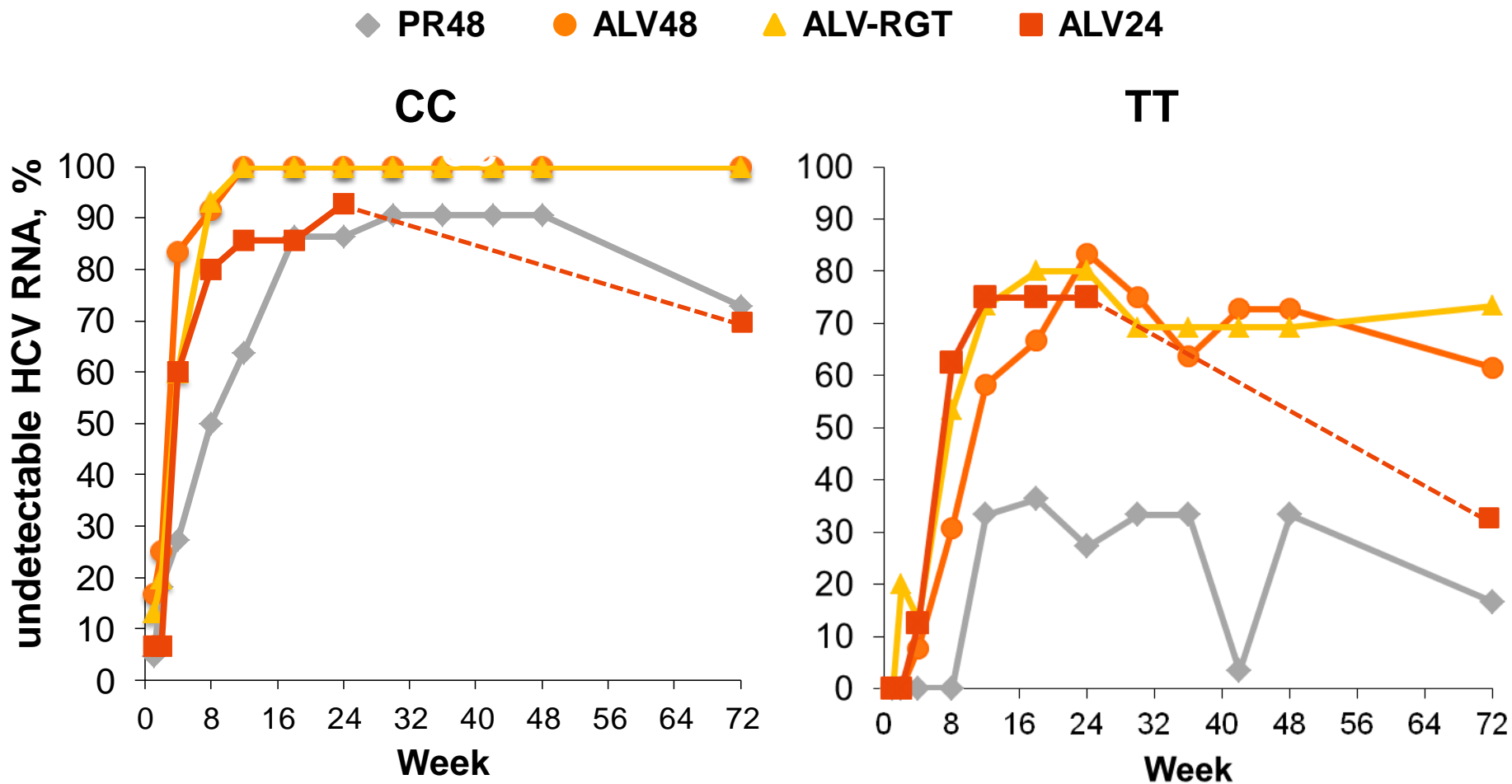
7% difference between ALV-RGT and ALV48 due to study discontinuations in 48-wk treatment of RGT.

Low relapse rate with ALV48 or ALV+RGT and low Viral Breakthrough rates with full ALV dose



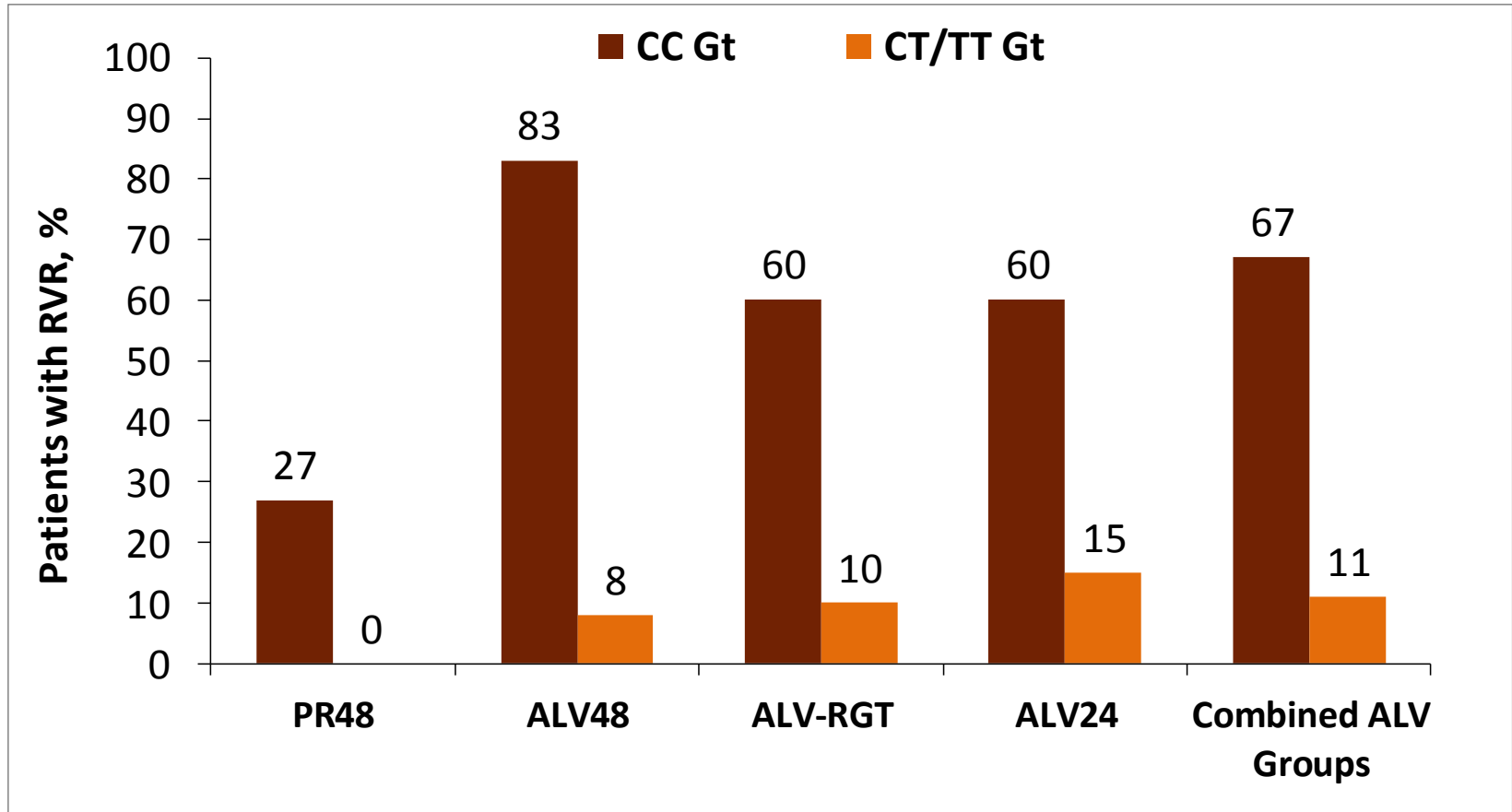
- 7/10 VB in ALV arms preceded by dose reductions in ≥ 1 drug
- No resistance mutations consistently associated with VB
- Unlike DAA, VB in ALV triple therapy is not driven by genotypic resistance
- D320E mutation (NS5A) emerged in only 1 patient at time of VB

ALV for 48 weeks or as RGT improved SVR rates irrespective of *IL28B* genotype



Significant difference ($P=0.02$) in SVR rates for TT Gt between combined ALV48 and ALV-RGT arms (67.8%) and PR48 arm (16.7%)

RVR achieved in more ALV-treated patients regardless of *IL28B* genotype



Achieving RVR was 100% predictive of SVR with ALV48 and ALV-RGT

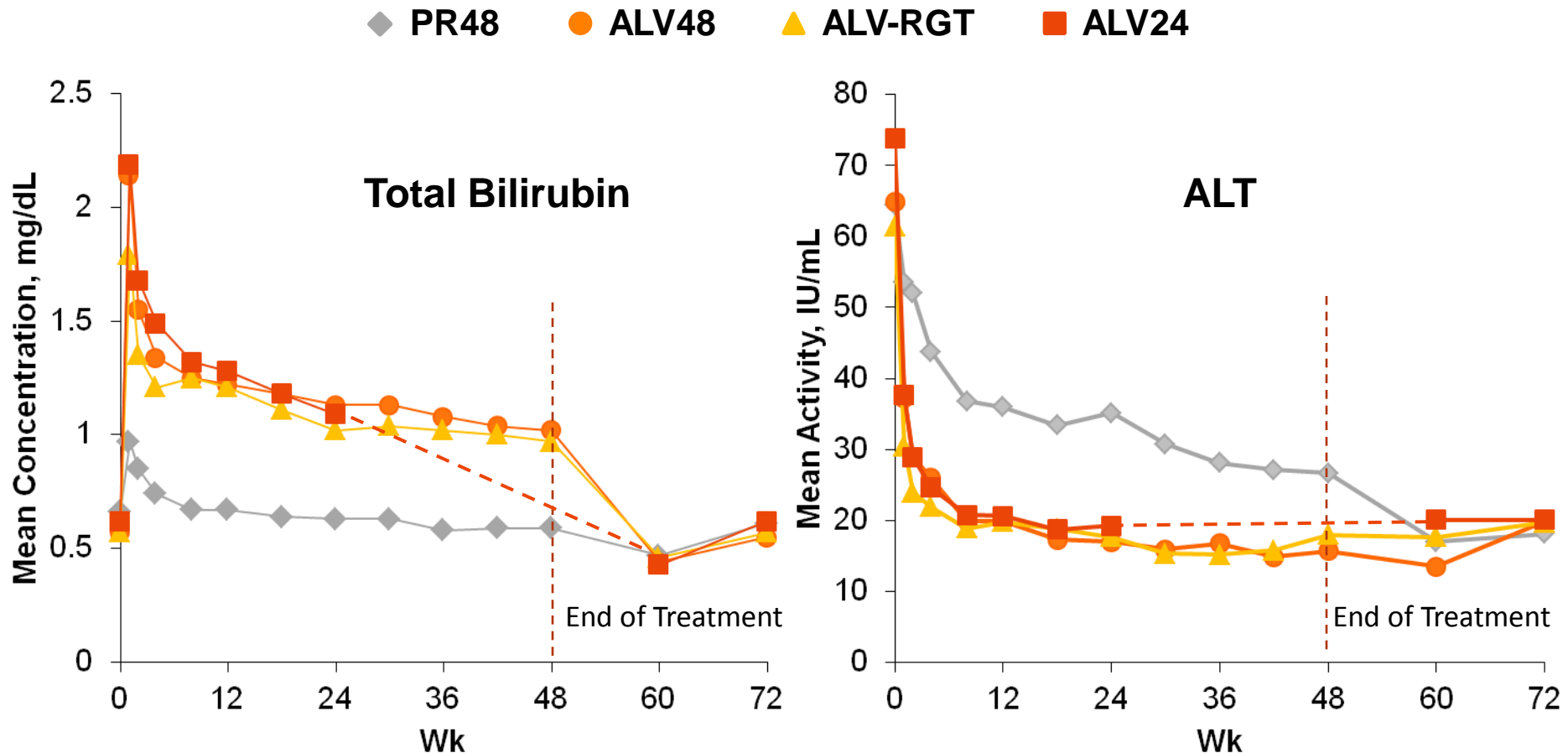
Multivariate logistic-regression analysis

Effect/Predictor for SVR24	Odds Ratio	95% Wald CI	P Value
ALV48 vs PR48	3.01	1.42, 6.38	0.0071
HCV RNA \geq vs $<$ 800,000 IU/mL	0.31	0.16, 0.59	0.0003
Age \geq vs $<$ 40 y	0.53	0.30, 0.95	0.0338
RVR LOD, yes vs no	28.41	6.36, 126.91	$<$ 0.0001
EVR LOD, yes vs no	41.98	17.99, 97.93	$<$ 0.0001

Lower baseline viral load, younger age, RVR and EVR were significant predictors of achieving SVR

EVR, early virologic response; LOD, limit of detection; Wald CI, confidence intervals based on asymptotic normality of parameter estimators.

Safety hyperbilirubinemia



- **Transient and reversible hyperbilirubinemia during ALV loading dosage**
- **No association with increase in ALT or GGT**
- **In 4.2% patients bilirubin above 5xULN → resolved by wk 4**

Conclusions

1. In the ESSENTIAL Study, ALV in combination with Peg-IFN/RBV demonstrated superior efficacy to Peg-IFN/RBV alone in treatment-naïve patients infected with genotype 1 HCV, regardless of *IL28B* genotype.
(the largest improvement in SVR rate in patients with TT genotype)
2. Achievement of RVR with ALV containing triple therapy was highly predictive of SVR.
3. ALV-associated hyperbilirubinemia was transient, reversible, and not associated with hepatocytes injury or cholestasis.

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