The Science of HBV Cure Meeting – June 8, 2019

Update on Inarigivir: a novel RIG-I agonist to stimulate Innate Immunity and promote functional cure in chronic HBV

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Forward Looking Statements

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All forward-looking statements speak only as of June 8, 2019 and should not be relied upon as representing our views as of any other date. We specifically disclaim any obligation to update any forward-looking statement, except as required by applicable law. All trademarks, service marks, trade names, logos and brand names identified in this presentation are the properties of their respective owners.

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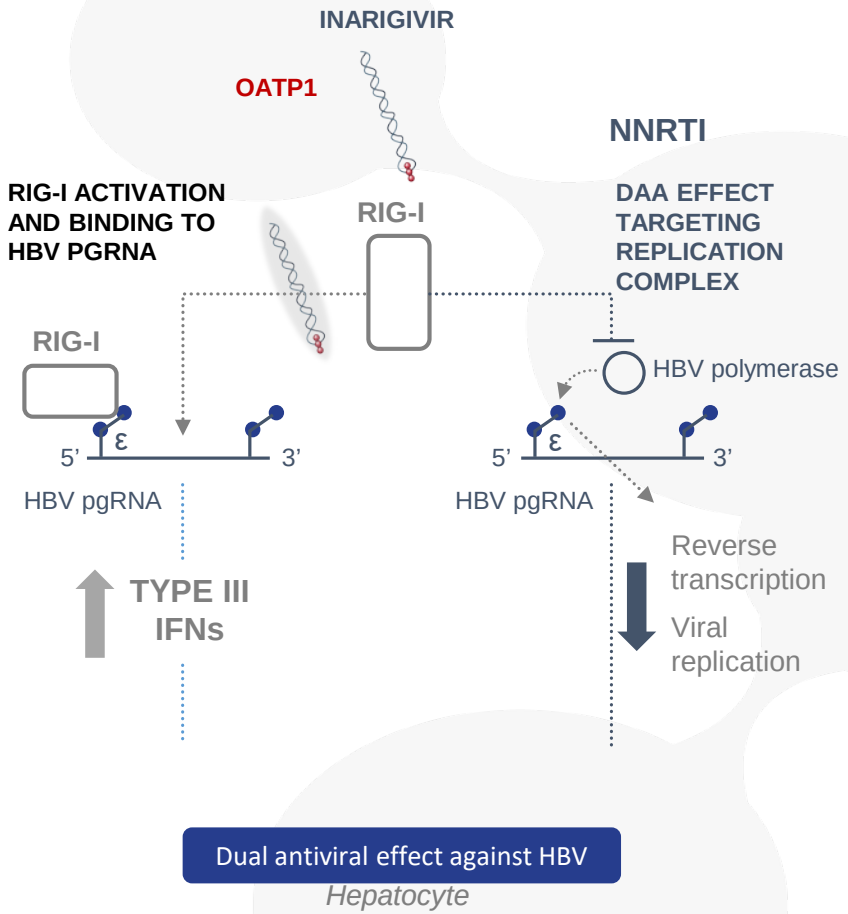
Inarigivir – Hepatic-Selective Immunomodulator with a Dual Mechanism of Action

Inarigivir is a RIG–I Agonist designed to:

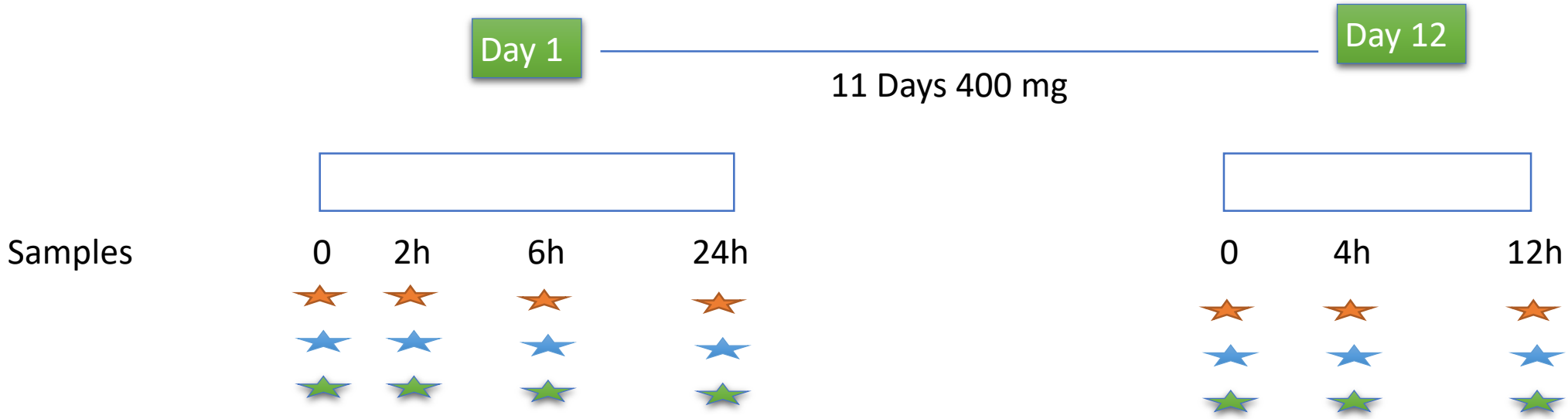
- **Restore hepatic-selective innate and adaptive immune response**[1] stimulating the production of type I and III IFNs without systemic toxicity
- Inhibit the HBV replication complex via a direct acting antiviral effect as a non-nucleoside reverse transcript inhibitor (NNRTI)
- Target cccDNA and is only oral agent to demonstrate reduction in HBV DNA, HBV RNA and HBsAg
- Potential backbone immunomodulator for combinatorial treatments of HBV



1 Sato et al. Immunity. 2015;42:123-132.

HEALTHY VOLUNTEERS TRIAL DESIGN

14 healthy volunteers
Inarigivir 400 mg /Daily



Cytokines in sera (IFN-a, IP-10, TNF-a, IFN-g, IL-6, IL-12p70)
PBMC for flow cytometry analysis (T, NK, myeloid cells activation)
PBMC for Nanostring analysis

Results summary

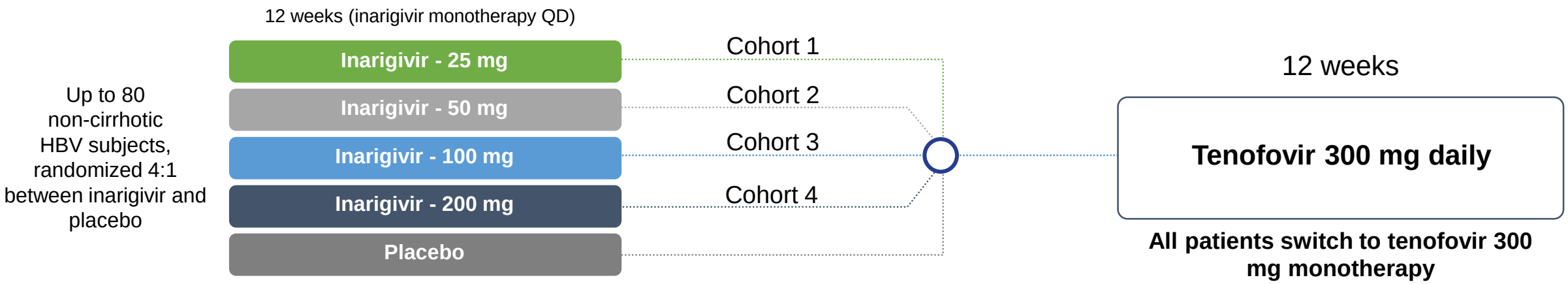
- Serum cytokine levels of IFN-a, IFN-g, TNF-a, IL-6 and IL-12p70 were undetectable while IP-10 levels declined after inarigivir treatment.
- As early as 2h post treatment, phenotypic analysis showed uniform up-regulation of activation markers on monocytes (CCR2, CD16, CD86) and dendritic cells (CD86).
- The frequency of peripheral NK and CD8+ T cells declined and was associated with reduction of activating receptor NKG2D (NK cells) and increase of activation markers CD39 and HLA-DR (T cells).
- Measurements of immune cell activation before and after the first and final dose demonstrated a similar response with no evidence of tolerance.

Conclusion

- Inarigivir transiently modifies expression of activation markers on circulating immune cells in a uniform and non-tolerance inducing manner, without an associated increase of serum cytokines.
- These findings validate inarigivir’s ability to activate intracellular innate immune pathways with a safety profile that demonstrates minimal serum cytokine activation and toxicity.

ACHIEVE Phase 2 Dose Escalation Study

Inarigivir monotherapy 12 weeks followed by switch to Tenofovir 300 mg for 12 weeks



PRIMARY ENDPOINT

Safety and HBV DNA reduction at 12 weeks

SECONDARY ENDPOINTS

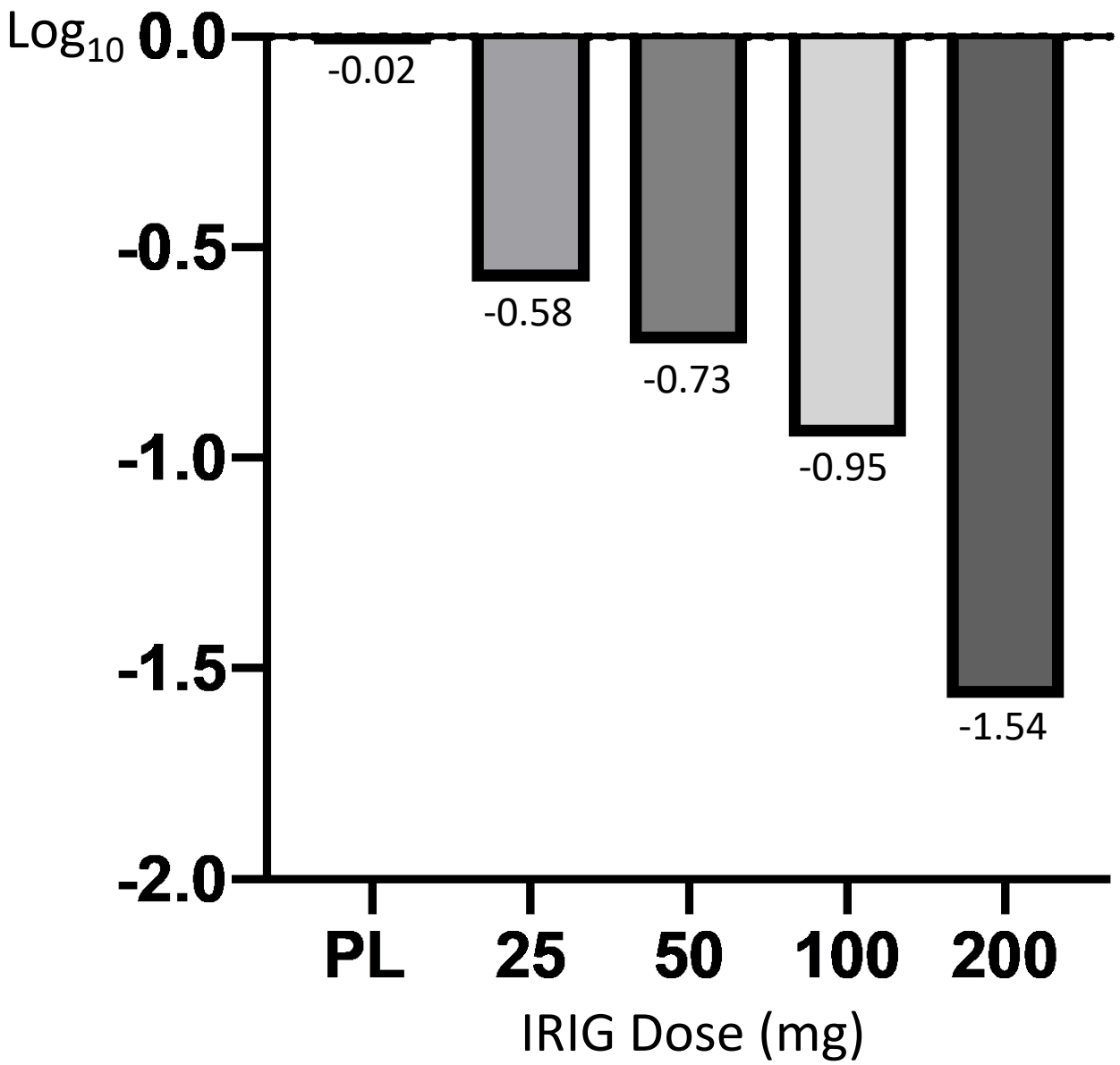
PK, change in serum HBV DNA, HBsAg, HBV RNA, HBcrAg and HBeAg from baseline to weeks 12 and 24

Mean Baseline Demographics by IRIG Dosing Cohort and HBeAg status

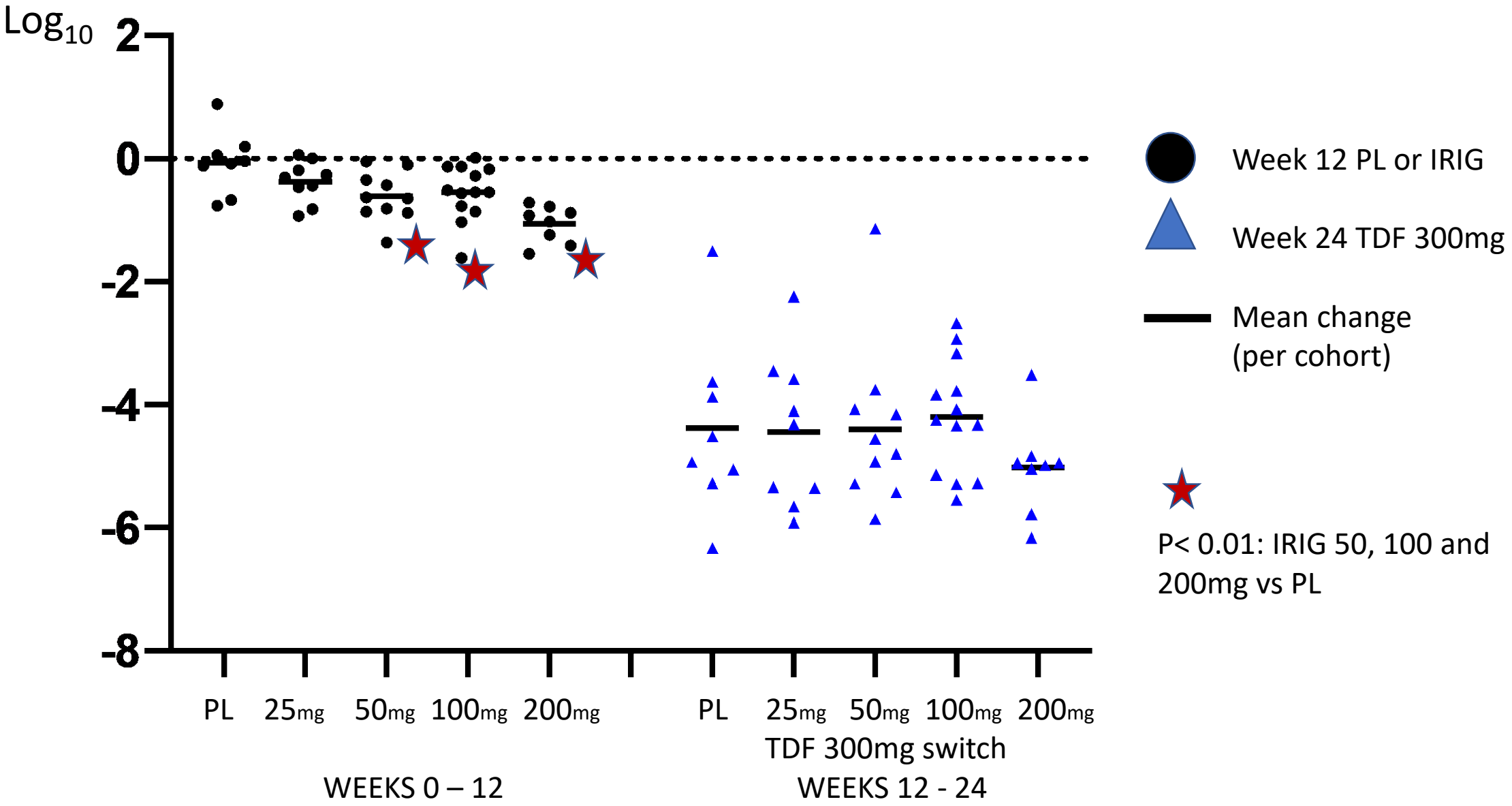
	Pbo Epos	Pbo Eneg	E+ve 25mg	E-ve 25mg	E+ve 50mg	E-ve 50mg	E+ve 100 mg	E-ve 100 mg	E+ve 200 mg	E-ve 200 mg
n	8	8	9	7	11	5	13	4	8	7
Age	35	48	37	43	36	47	34	46	42	52
M:F	7:1	5:3	5:5	3:3	9:2	5:0	7:6	3:1	4:4	2:5
ALT	85	53	82	75	75	65	75	90	54	73
HBV DNA	7.64	4.75	7.86	5.69	7.79	4.55	8.20	5.95	7.88	4.95
HBV RNA	6.44	2.23	6.36	4.2	6.58	1.54	7.23	2.77	6.68	2.86
HBsAg	4.17	2.79	4.32	3.17	4.13	2.96	4.38	2.68	4.15	2.72
GT A		1		1						
GT B	2	6	4	3	3	4	4	3	2	5
GT C	6	1	5	1	7	1	8	1	6	2
GT D				2	1		1			

* 9 HBeAg negative patients had undetectable HBV RNA at baseline

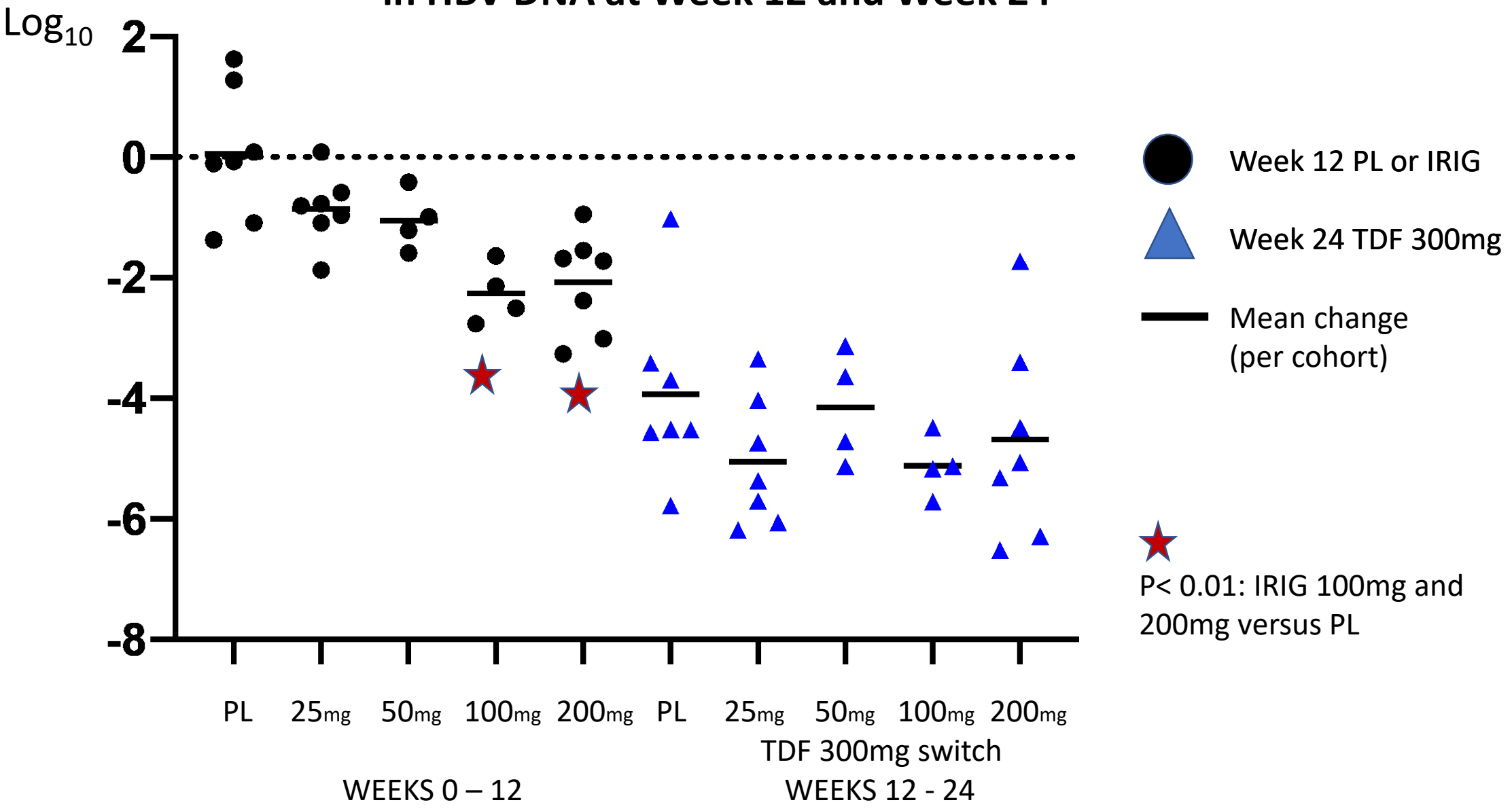
Primary Endpoint: Mean Change from Baseline in HBV DNA to Week 12 in Placebo (PL) and IRIG cohorts



HBeAg positive patients: Change from Baseline in HBV DNA at Week 12 and Week 24

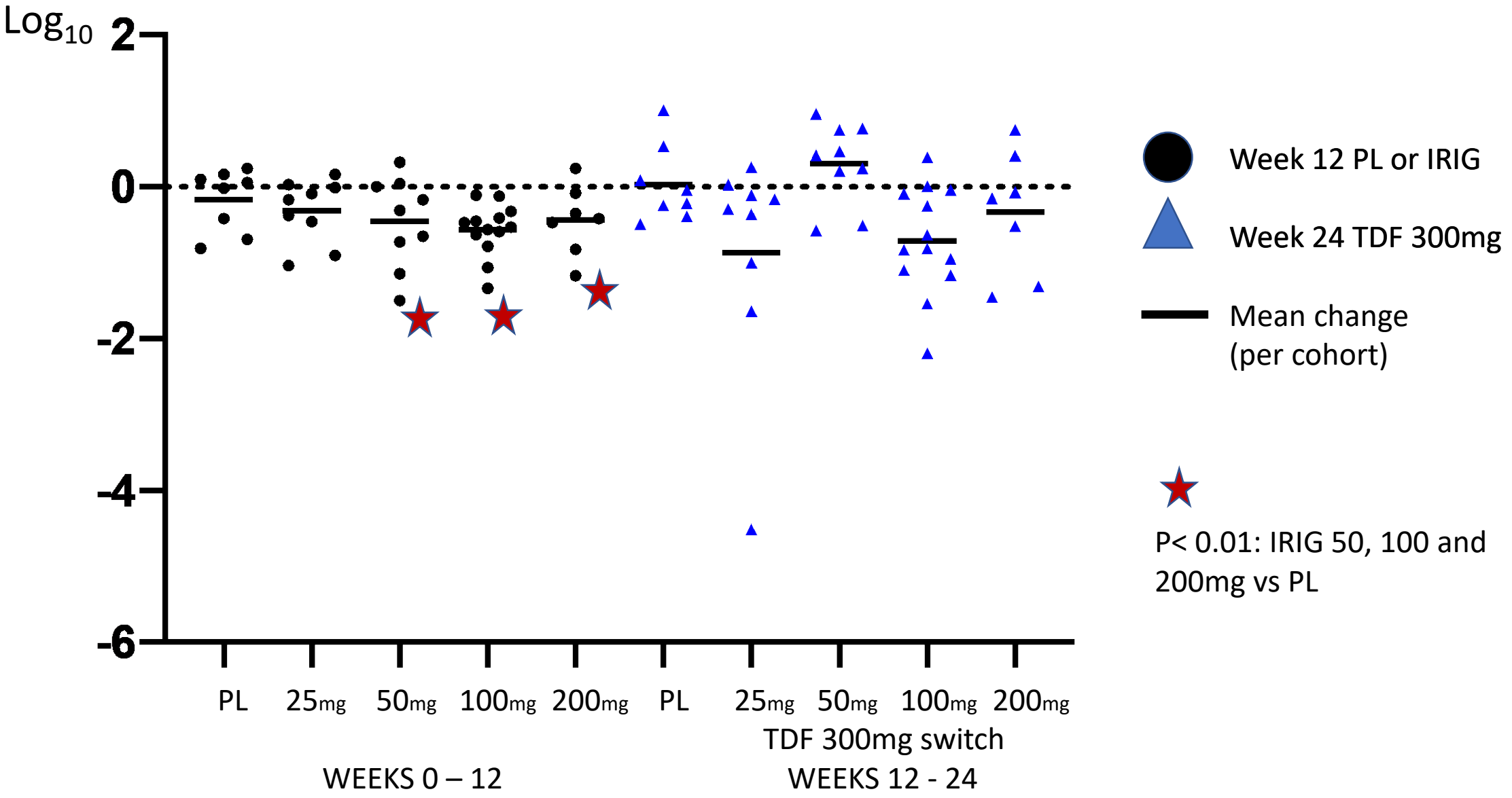


HBeAg negative patients: Change from Baseline in HBV DNA at Week 12 and Week 24

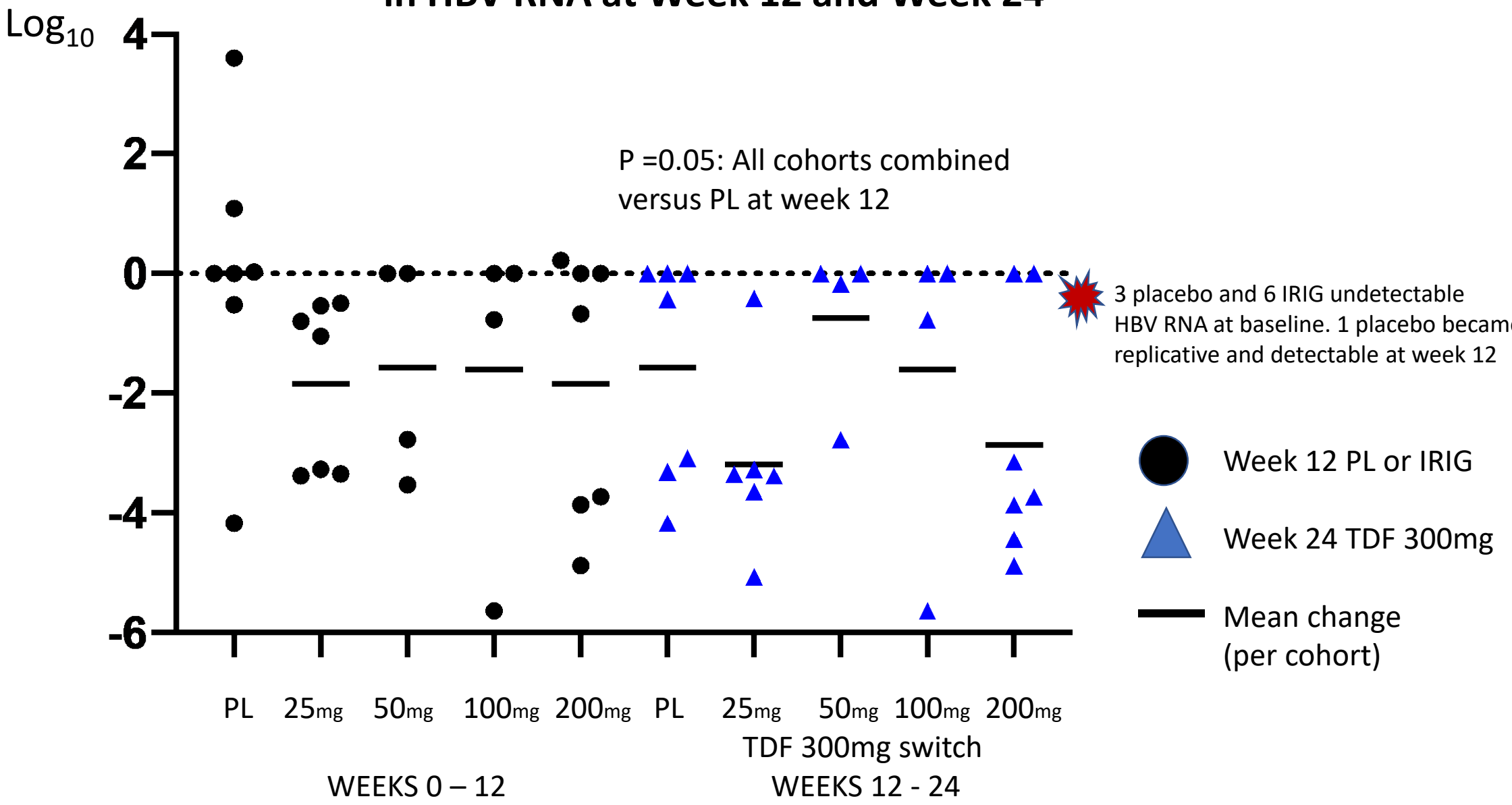


18 of 22 (82%) patients undetectable at week 24

HBeAg positive patients: Change from Baseline in HBV RNA at Week 12 and Week 24



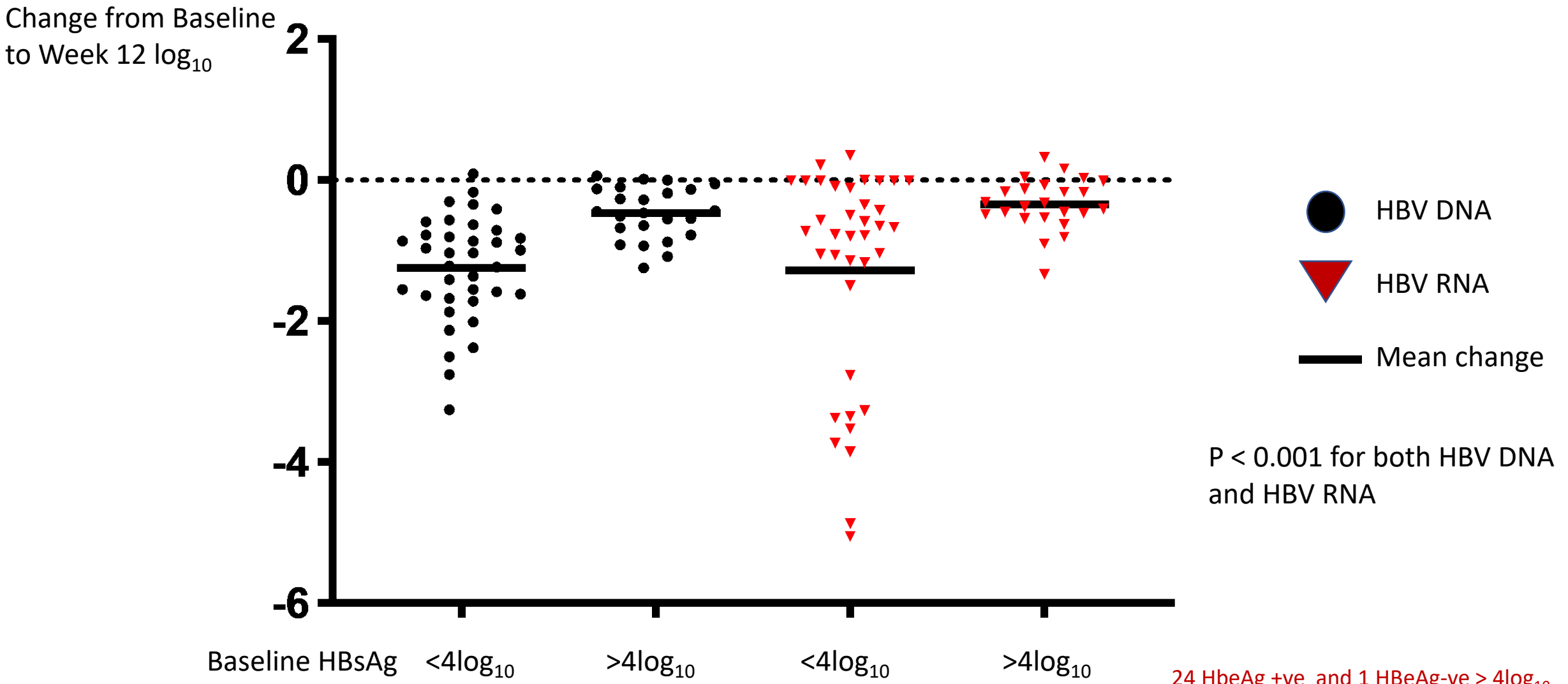
HBeAg negative patients: Change from Baseline in HBV RNA at Week 12 and Week 24



Positive Predictors of Response to IRIG

- *HBV DNA and HBV RNA*
  - HBeAg negative – pre-core mutations > core promoter mutations alone
  - Baseline HBsAg < $4\log_{10}$
  - Baseline IP-10 > 310ng/L
  - Reduction in IP-10 > 110ng/L between baseline and week 12
- *HBsAg*
  - Genotype B > C
  - Good responses genotype A / D but numbers small

Baseline HBsAg cutoff of $4\log_{10}$ Predictor of HBV DNA and HBV RNA Response to IRIG at Week 12

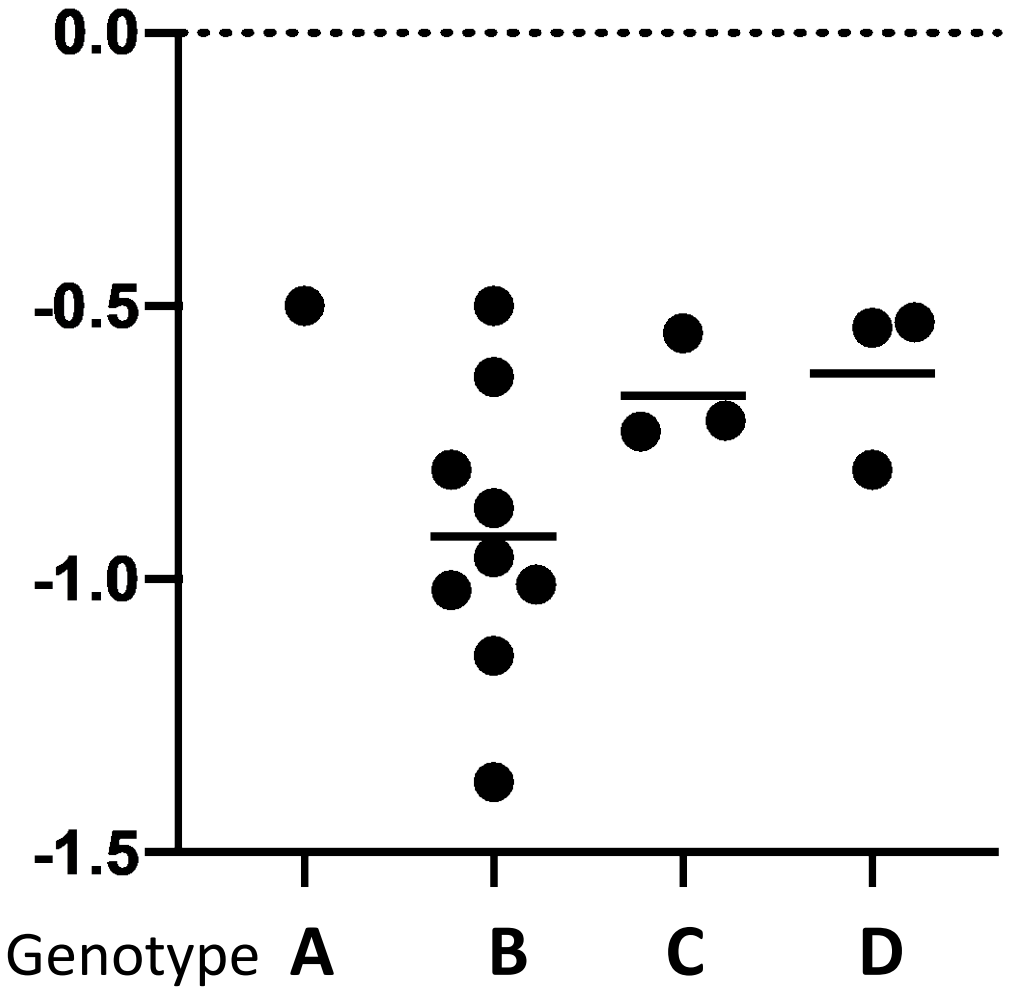


P < 0.001 for both HBV DNA and HBV RNA

24 HbeAg +ve and 1 HBeAg-ve > $4\log_{10}$
16 HBeAg +ve and 21 HBeAg -ve < $4\log_{10}$

HBsAg Response ($\geq$ 0.5log$_{10}$) by Genotype

HBsAg change in log$_{10}$



Percentage of responders within each Genotype

GT A 100%
GT B 33%
GT C 10%
GT D 75%

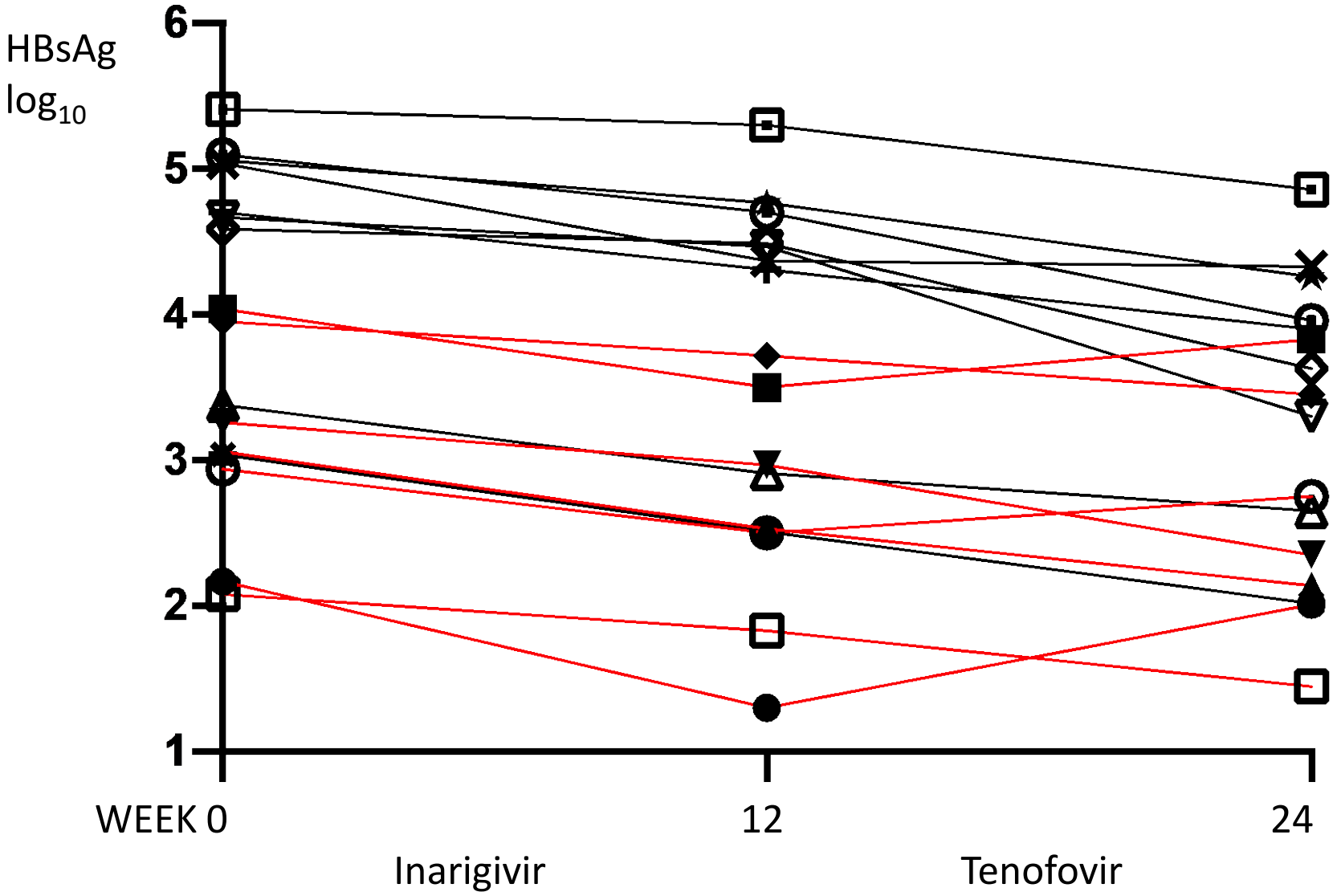
Genotype response data consistent with that seen with IFN therapy

Secondary Endpoint: Predefined Responders with HBsAg Reduction of $\geq 0.5\log_{10}$

	Week 12 $>0.5\log_{10}$	Week 24 $>0.5\log_{10}$	Total Responders	
Placebo /TDF	1*	2*	2	*ALT flare > 400 IU/ml
IRIG 25mg/TDF	4#	6	8	# 2 non sustained of which 1 dose reduced
IRIG 50mg/TDF	1$	2	2	$ 1 non sustained and dose reduced
IRIG 100mg/TDF	1	2	2	1 non-sustained with a flare
IRIG 200mg/TDF	1	3	3	2 GT C patients

- 16 IRIG patients (26%) met predefined HBsAg loss criteria for response at week 12 or 24
- Response in 7 HBeAg negative (mean $0.7\log_{10}$) and 9 HBeAg positive (mean $0.9\log_{10}$)
- Overall mean responder reduction of $0.8\log_{10}$ (range 0.5 – $1.4\log_{10}$)

Quantitative HBsAg in Responder Patients ≥ 0.5log$_{10}$ Reduction at Week 12 or Week 24 from Baseline



Mean Change in HbsAg

Week 12: 0.4log$_{10}$

Range 0.1 – 0.9log$_{10}$

Week 24: 0.72log$_{10}$

Range 0.15 - 1.4log$_{10}$

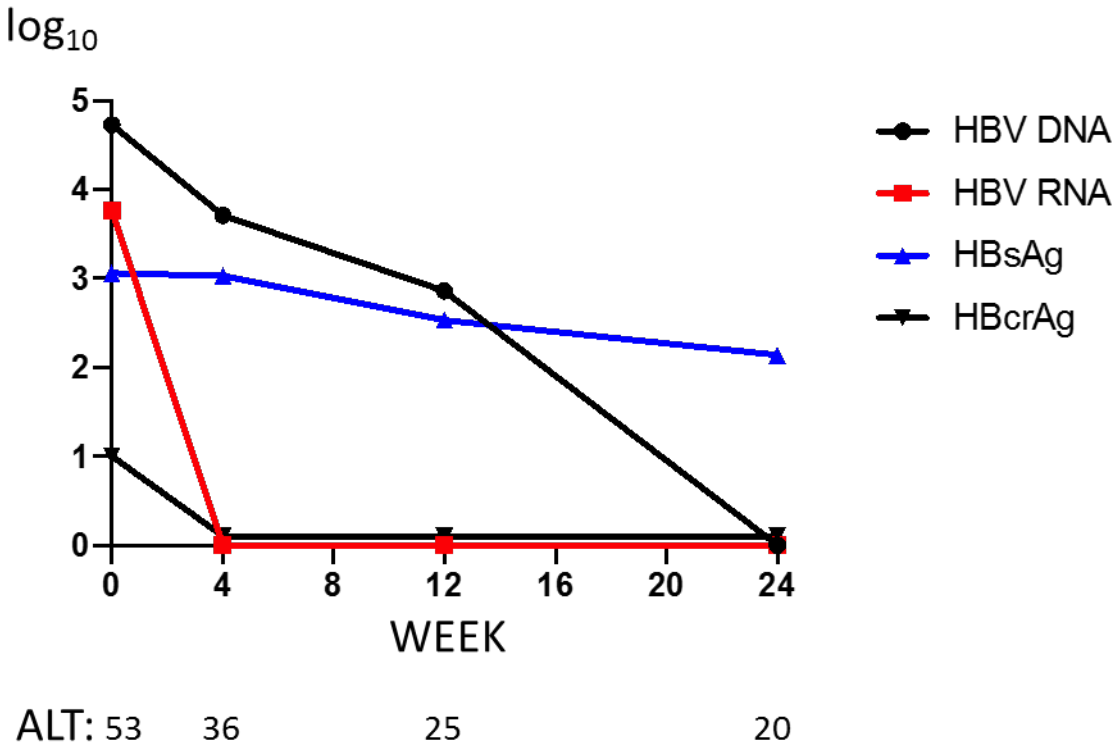
HBeAg +

HBeAg -

11 of 16 patients had evidence of HBsAg reduction in weeks 0 – 12 on IRIG

Rapid Transcription Termination – IRIG 25mg

56 year old Caucasian male, GT D,
HBeAg negative, IL28b TT

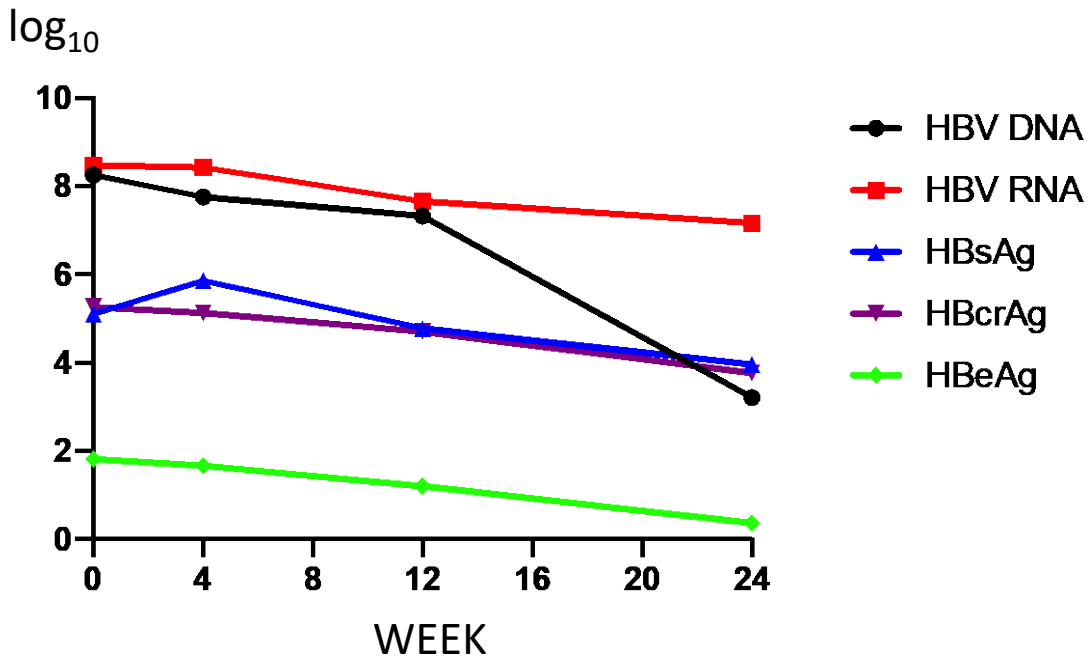


ALT: 53 36 25 20

- Rapid reduction to undetected for HBV RNA and HBcrAg with associated slower declines in HbsAg and HBV DNA

IRIG 200mg Responder – Transcription Inhibition Continued on TDF Switch

19 year old Asian male, GT B,
HBeAg positive, IL28b CC



- Responder at week 12 all parameters 0.5 – 1 log_{10} mini ALT flare to 150 IU/ml on switch to TDF with further reduction

Two distinct populations of HBeAg-ve patients for HBsAg response

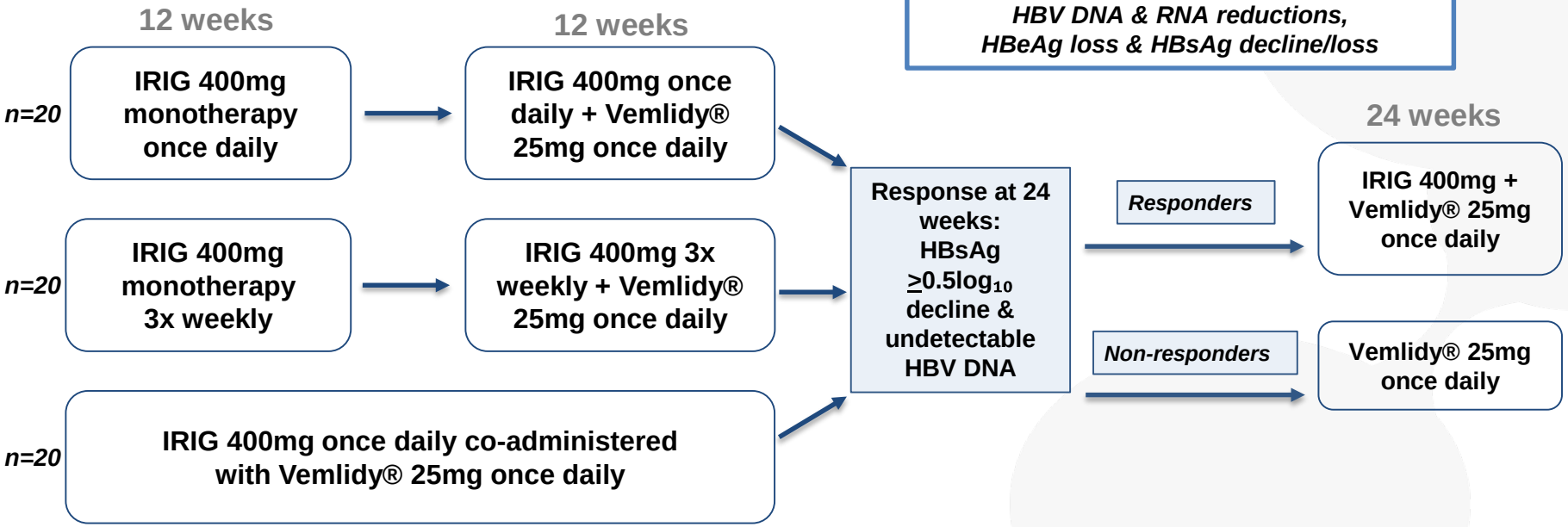
- 7 responders (HbsAg >0.5log reduction) and 12 non-responders (< 0.1 log reduction) to IRIG
- Non-responders are a clear subset of non-transcriptionally active patients (low / undetectable HBV RNA and HBcrAg) despite elevated ALT and HBV DNA
- Non-replicative subset less likely to have early HBsAg response and should be accounted for in novel treatment trials
- Rapid cessation of viral production in all IRIG patients – Will duration have an impact for HBsAg loss?
- Non-replicative subset represents a target population for prolonged HBV DNA suppression after stopping treatment

CATALYST 1 - Global Inarigivir HBV Phase 2b Trial

Inarigivir 400mg monotherapy & co-administration with Vemlidy® (tenofovir alafenamide) 25mg HBeAg –ve and +ve non-cirrhotic treatment naïve HBV patients

Response-Guided Trial Design

Capability to observe functional cure
Key endpoints:
HBV DNA & RNA reductions,
HBeAg loss & HBsAg decline/loss



Together with data from Gilead's trial of inarigivir + Vemlidy®, will inform Phase 3 treatment-naïve strategy for SB 9225 (IRIG + tenofovir disoproxil fumarate) fixed-dose combination

CATALYST 2 - Global Inarigivir HBV Phase 2b Trial

Inarigivir 400mg in virally suppressed –ve, non-cirrhotic chronic HBV patients

Cohort 1 – "Stop & Shock"

n=20

Stop NUC therapy

"Shock" with inarigivir

24 weeks

IRIG 400mg monotherapy once daily

Up to week 96

No treatment – follow to observe sustained HBsAg loss

Key endpoints:
ALT Flare
HBsAg loss
fine needle aspirase (FNA)

Capability to observe functional cure

Cohort 2 – "Suppress & Shock"

n=40

Continue NUC therapy

24 – 48 weeks

IRIG 400mg monotherapy once daily added to NUC therapy

Up to week 96

No treatment – follow to observe sustained HBsAg loss

Key endpoint:
HBsAg loss/reduction
+
Intra-hepatic virology & Immunology with Liver FNA

Will inform Phase 3 program in virally-suppressed patients in 2020

Conclusion

- IRIG continuing to be developed as a backbone immunomodulator in combination studies with agents having different MOAs
- IRIG + NUC studies for up to 1 year in progress with focus on biomarkers for patient heterogeneity and anti-viral response
- CATALYST trials will evaluate sustained response in naive and suppressed patients
- Triple therapy combinations under development

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