

Investigational treatment combining TG1050, an HBV-specific immunotherapeutic, with direct acting antivirals or immunomodulators, improves sustained antiviral effects and immune responses in HBV-persistent mice.

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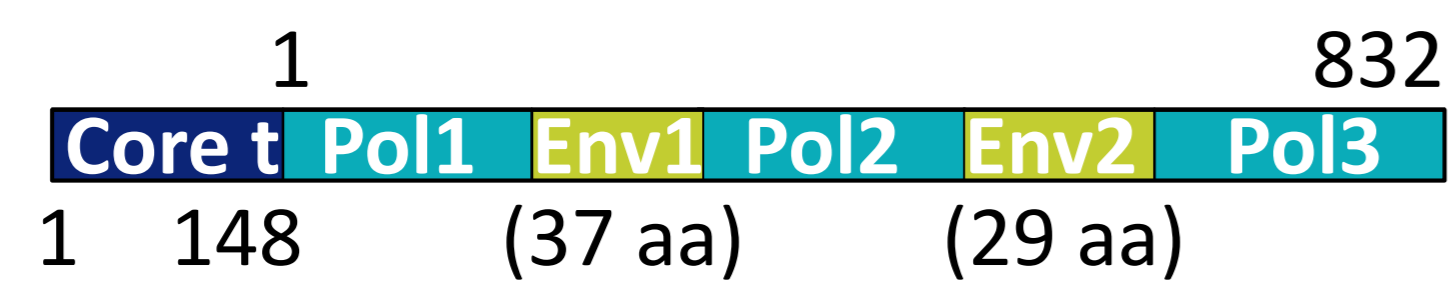
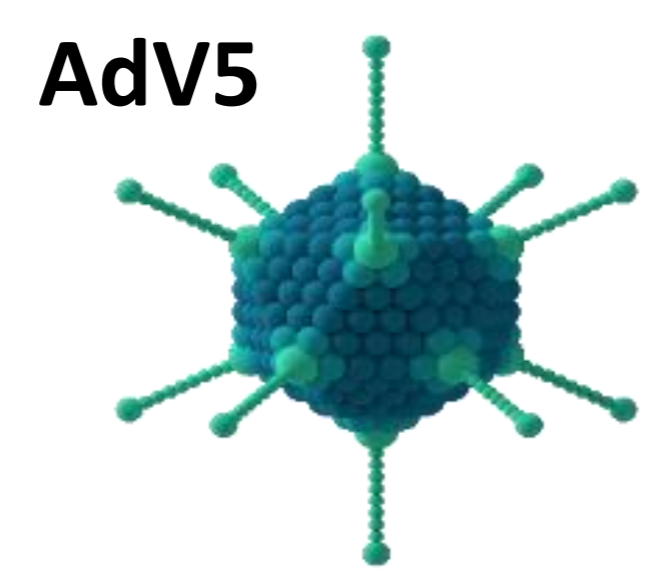
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OBJECTIVE AND PRODUCT DESCRIPTIONS

Evaluation of the potentiation of TG1050 activity by combining with immunomodulators or direct acting antivirals

IMMUNOTHERAPEUTIC

TG1050 (Transgene SA) is based on a recombinant non-replicative adenovirus 5 vector encoding for truncated Core, an almost full-length Polymerase and domains of Envelope^a. It is in clinical development (Ph.I)^b. In preclinical models TG1050 demonstrated the induction of functional HBV-specific T cells and an antiviral effect by decreasing both HBV viremia and circulating HBsAg^{a,c}.



IMMUNOMODULATORS

CpG-28 (Oligovax) is a class B CpG ODN^d. TLR9 agonists are well described as adjuvant of vaccination and have been shown to favor intrahepatic T cell proliferation^e.

Sildenafil is a PDE5 inhibitor, interfering with the inhibitory functions of MDSCs. MDSCs have been detected in the liver of CHB patients in high frequency^f.

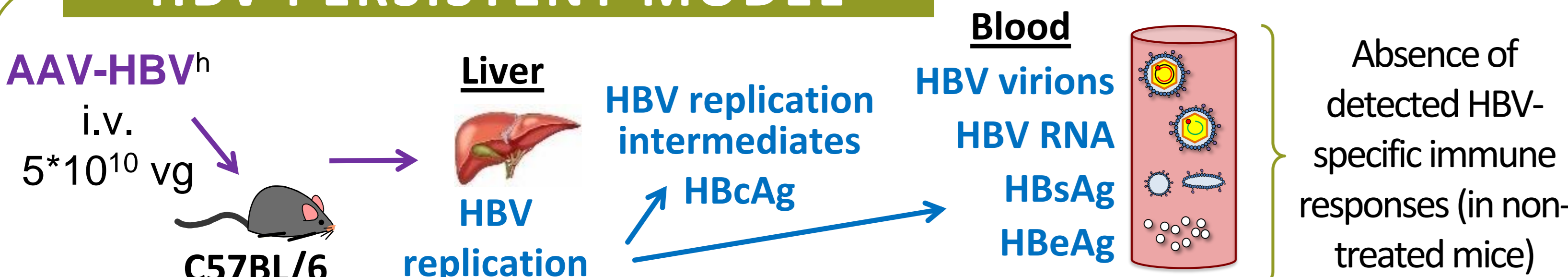
DIRECT ACTING ANTIVIRALS

siRNA-HBV (Alnylam Pharmaceuticals, licensed to Vir Biotechnology) is a GalNAc conjugated siRNA targeting one highly conserved sequence (silencing all viral products).

HEC73045 (HEC Pharma) is a 2nd generation capsid inhibitor (CpAM). CpAM treatment inhibits HBV encapsidation^g and decreases HBV viremia and HBV-RNA secretion.

Entecavir (ETV) is a standard of care HBV polymerase inhibitor.

HBV PERSISTENT MODEL



CONCLUSION

► Combination of TG1050 with 3 different types of drugs led to encouraging improvements of antiviral effects:

TLR9 agonist, MDSC inhibitor, siRNA

► To be further evaluated in clinical trials

ACKNOWLEDGEMENTS

Selected experiments have been done in collaboration. CpG-28, siRNA-HBV and HEC73045 have been kindly provided by Oligovax, Alnylam Pharmaceuticals and HEC Pharma Group, respectively.

All authors are or were employed by Transgene SA, Oligovax, Alnylam Pharmaceuticals or HEC Pharma Group, companies developing TG1050, CpG-28, siRNA-HBV or HEC73045, respectively.

TG1050 + IMMUNOMODULATORS

TG1050 + CpG-28

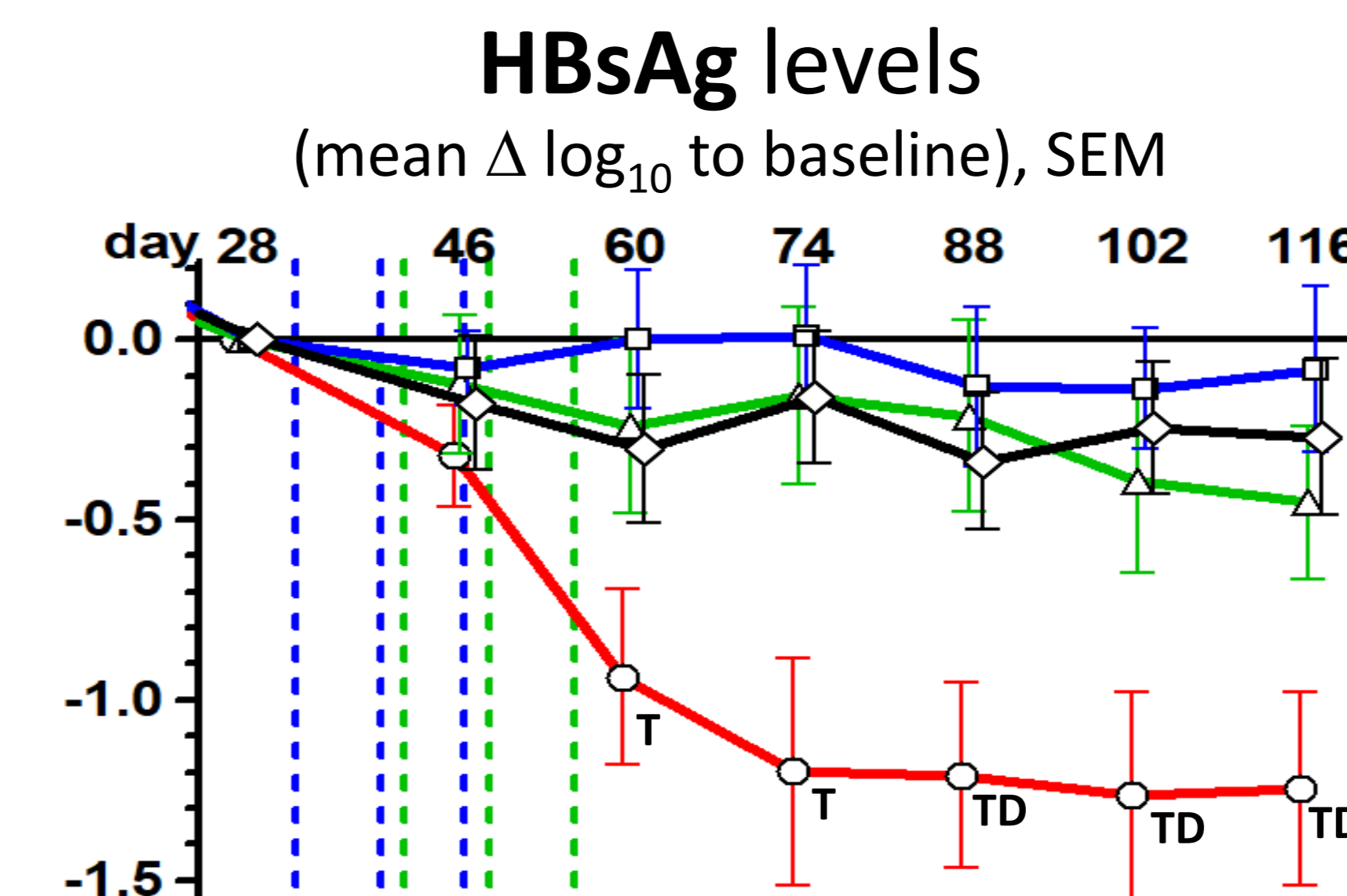
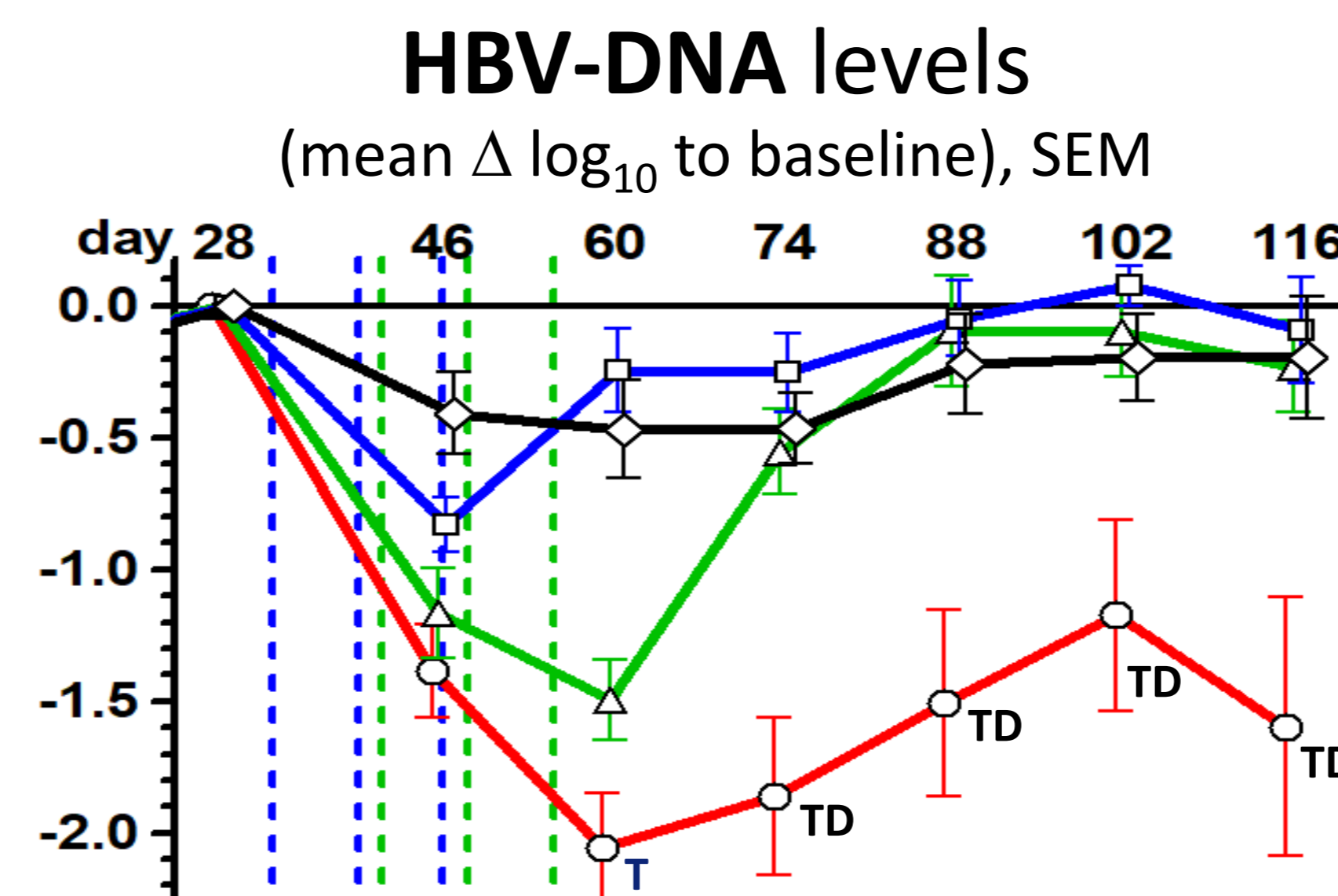
8 mice/group

% responder*

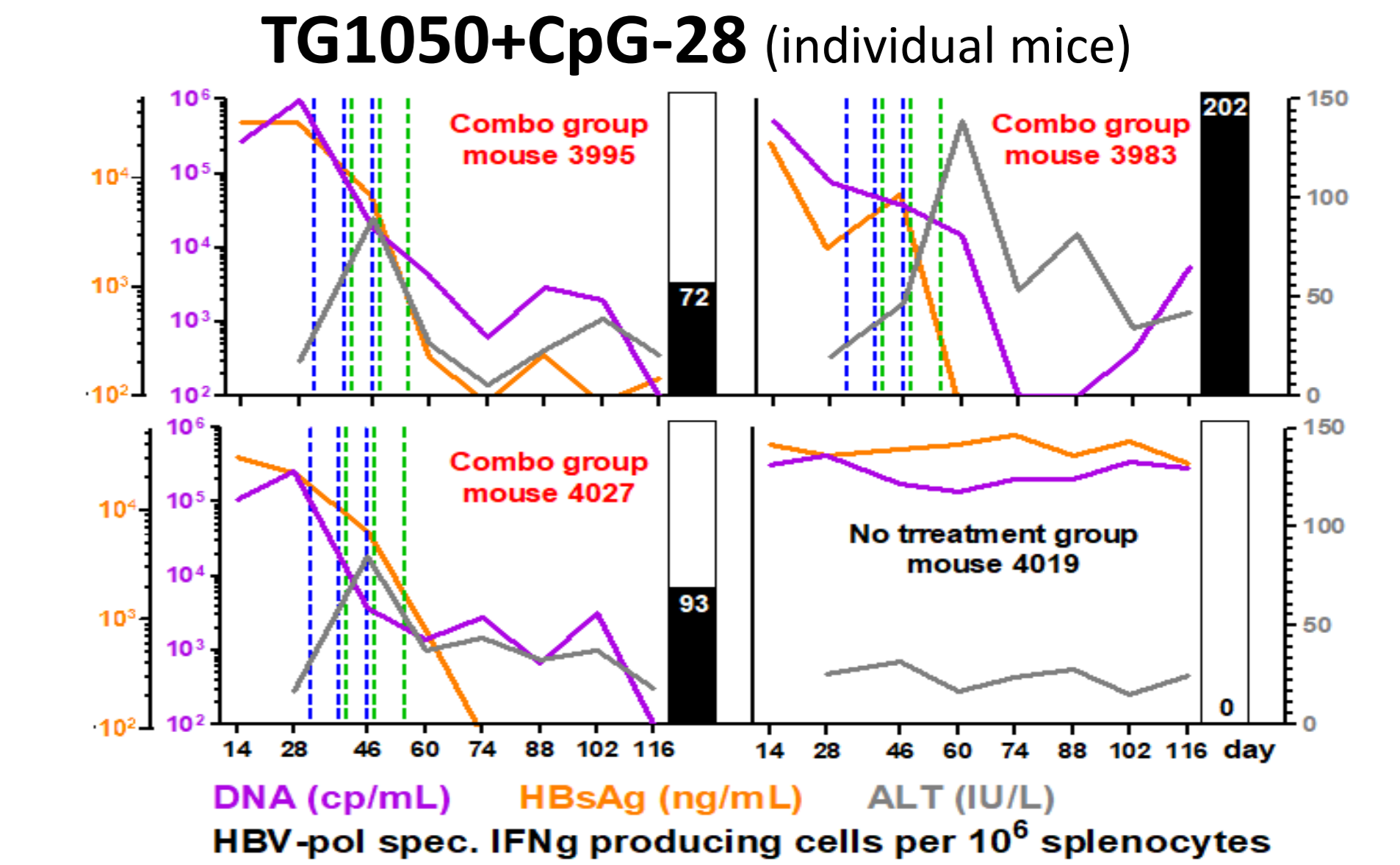
DNA HBsAg

No treatment	25	38
TG1050 (3x 2E+09vp, SC)	25	38
CpG-28 (3x 20µg, IP#)	88	50
Combination therapy	100	88

comparable results when injected SC



Correlation in combination therapy group



► TG1050 + TLR9 agonist combo therapy led to strong sustained antiviral effects : up to 2.1 log decrease for viremia, 1.3 log for HBsAg
Combo therapy group: the 3 mice with lowest HBsAg values showed the highest immune response (IFNg-ELISpot)

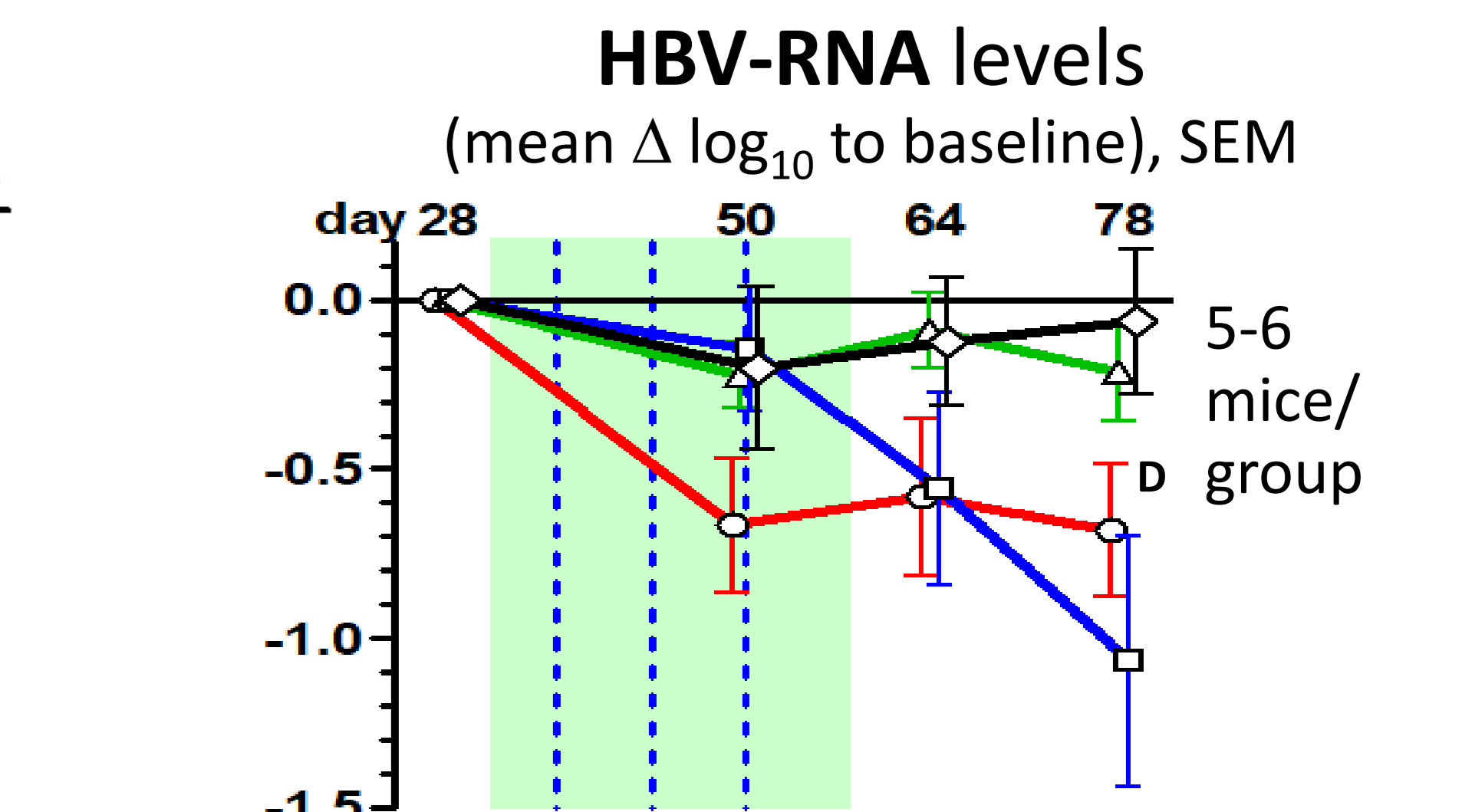
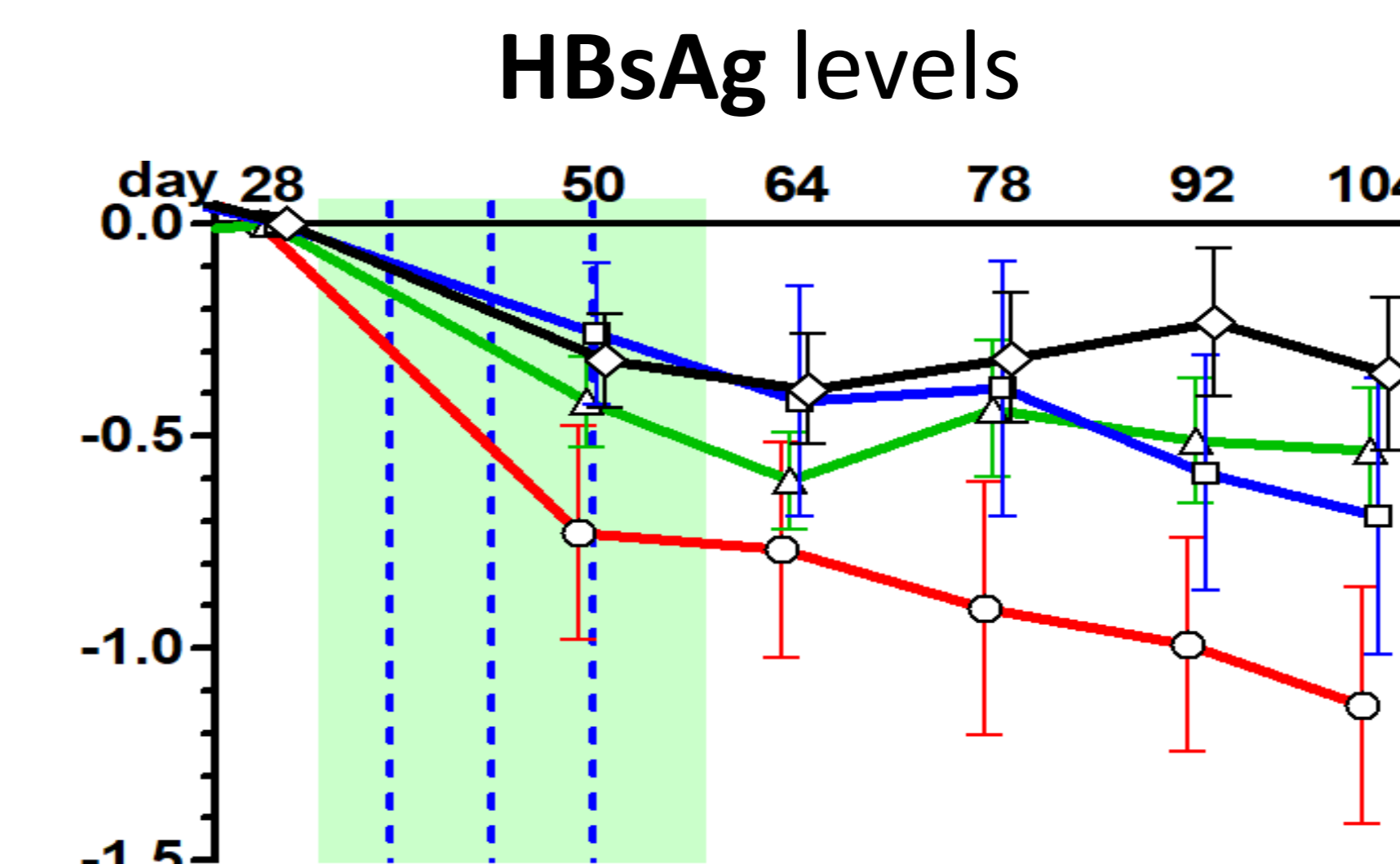
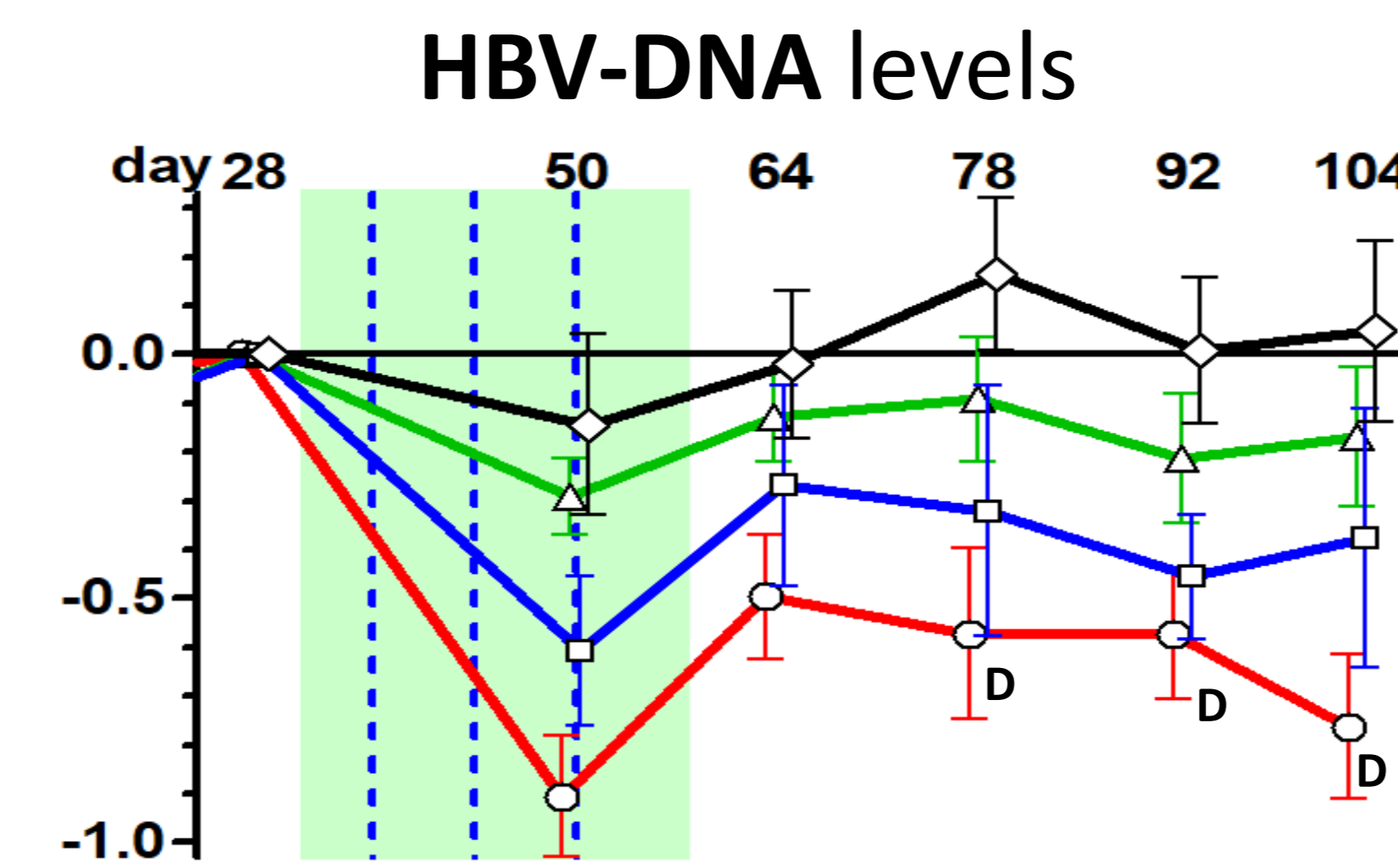
TG1050 + Sildenafil

10 mice/group

% responder*

DNA HBsAg

No treatment	10	40
TG1050 (3x 2E+09vp, SC)	50	50
Sildenafil (5mg/kg/d, per os)	10	50
Combination therapy	90	80



► TG1050 + MDSC inhibitor combo therapy led to strong sustained antiviral effects : up to 0.9 log decrease for viremia, 1.1 log for HBsAg
TG1050 monotreatment led to the strongest decrease in HBV-RNA levels: 1.1 log

TG1050 + DIRECT ACTING ANTIVIRALS

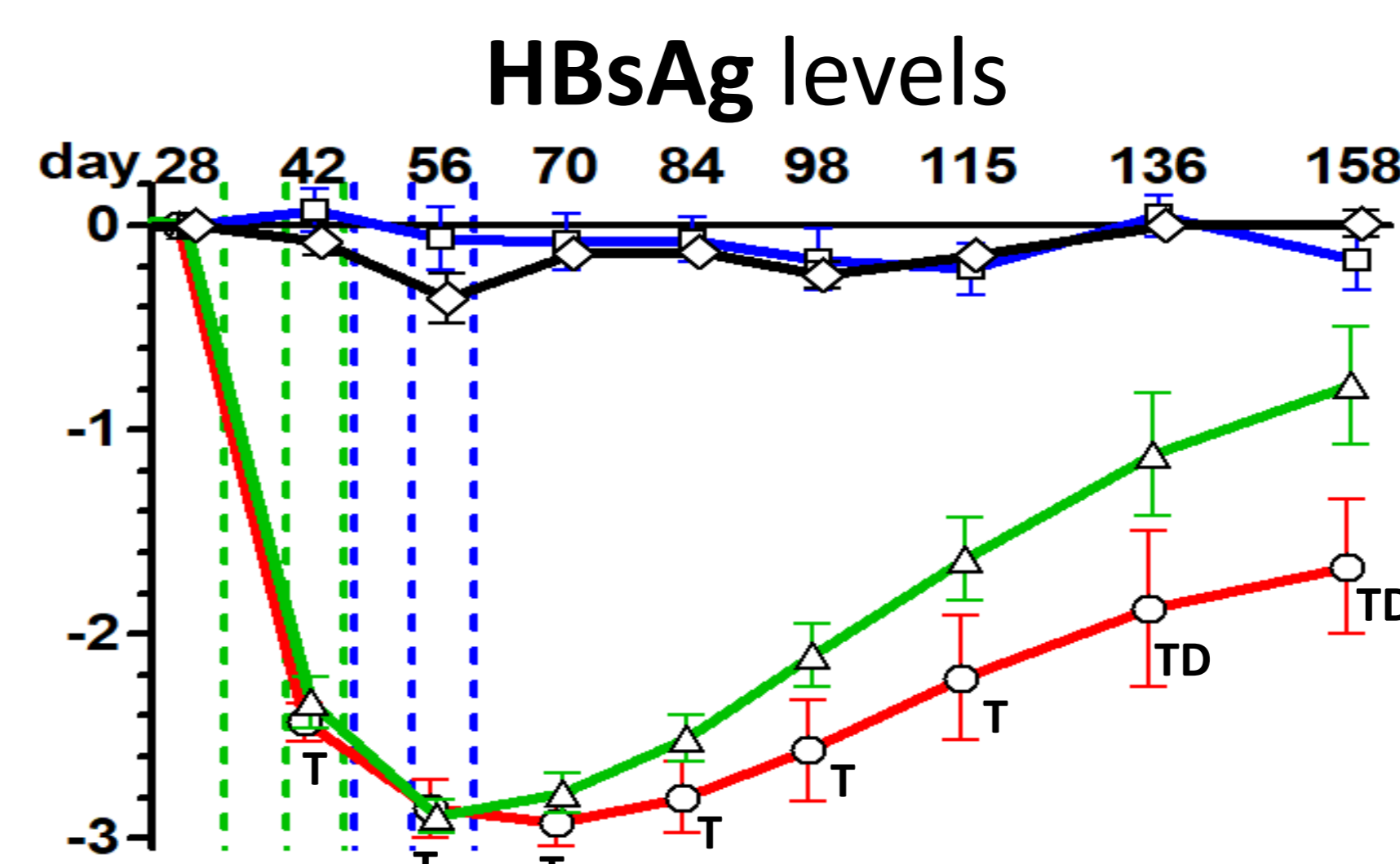
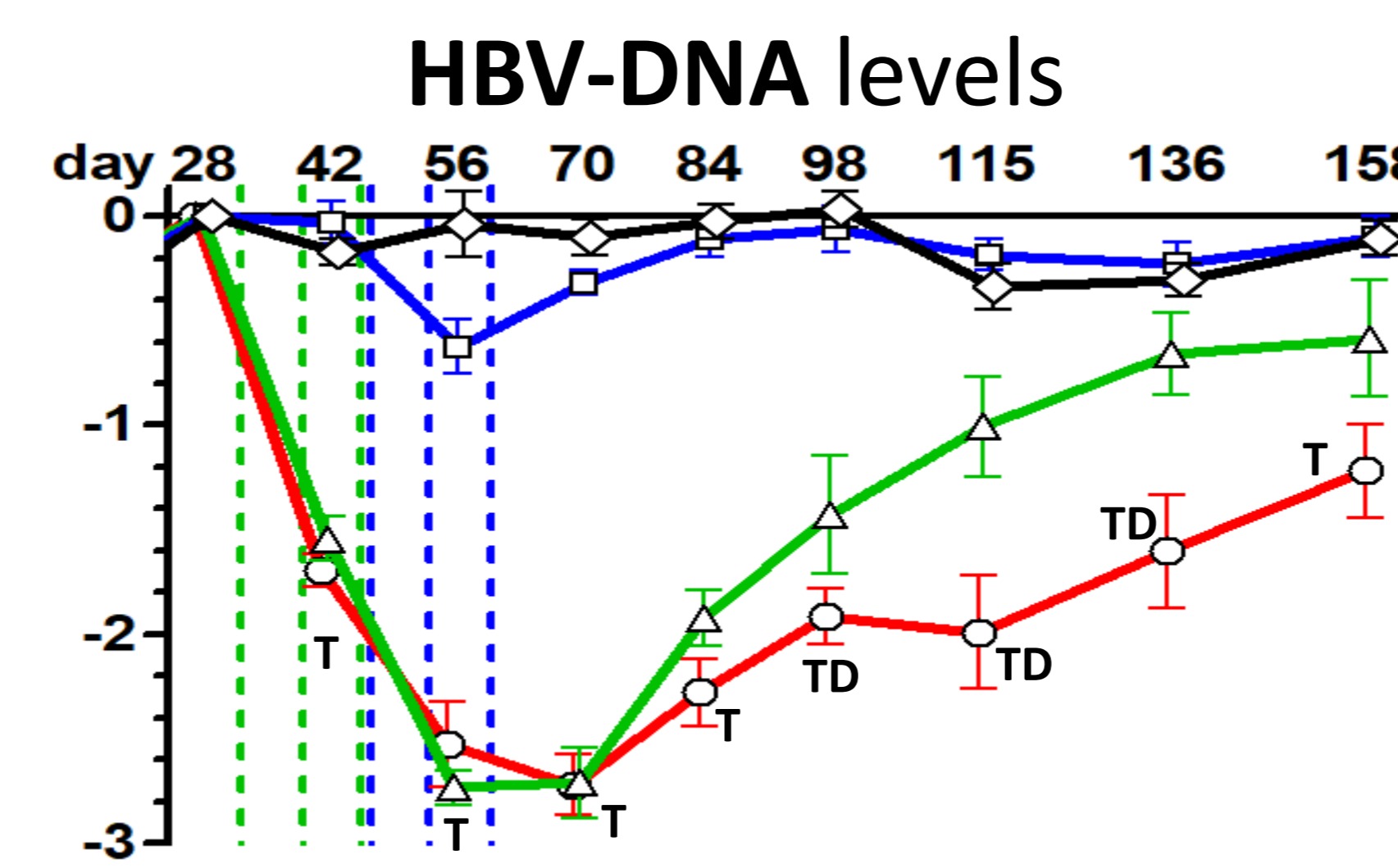
TG1050 + siRNA-HBV

10 mice/group

% responder*

DNA HBsAg

No treatment	30	10
TG1050 (3x 2E+09vp, SC) + siRNA-ctrl	40	30
siRNA-HBV (3x 3mg/kg, SC) + AdEmpty	100	100
Combination therapy	100	100



► TG1050 + siRNA combination therapy led to a delayed rebound of viremia and HBsAg levels

TG1050 + HEC73045

► No additive effect of combination therapy on viral parameters but significant increase of anti-HBc antibodies (data not shown)

HBsAg: max Δ log ₁₀ to baseline (% of mice below LLOQ ^h)	TG1050 alone:	0.8 (10)	HEC73045:	1.1 (11)	Combo:	1.0 (-)
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TG1050 + ETV

► Impact of TG1050 alone but no additive effect of combination therapy on viral parameters (data not shown)

HBsAg: max Δ log ₁₀ to baseline (% of mice below LLOQ ^h)	TG1050 alone:	0.7 (-)	ETV:	0.4 (-)	Combo:	0.6 (-)
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* % responder mice: >0.5 log₁₀ decrease for at least 2 time points

T, D : Significant difference of combo group versus monotreatment groups TG1050 (T), 2nd combination drug (D) or both (TD); mixed model analysis, post-hoc tests adjusted for multiplicity (p<0.05)

φ LLOQ: 88 -103 ng/mL post treatment (depending on exp.)

REFERENCES

- ^a Martin et al., Gut, Dec 2015; 64(12)
- ^b ClinicalTrials.gov: NCT02428400
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- ^d Ursu et al., Eur J Cancer, Mar 2017; 73
- ^e Huang et al., Nat Immunol, Jun 2013; 14(6)
- ^f Pallett et al., Nat Med, Jun 2015; 21(6)
- ^g Ren et al., Bioorg Med Chem, Feb 2017; 25(3)
- ^h Dion et al., J Virol, May 2013; 87(10)

AAV – Adeno-associated virus
GalNAc – N-Acetylgalactosamine
LLOQ – Lower limit of quantification
MDSC – Myeloid-derived suppressor cell
ODN – Oligodeoxynucleotide
PDE5 – Phosphodiesterase 5
TLR – Toll-like receptor

