Vaccins thérapeutiques et VHC

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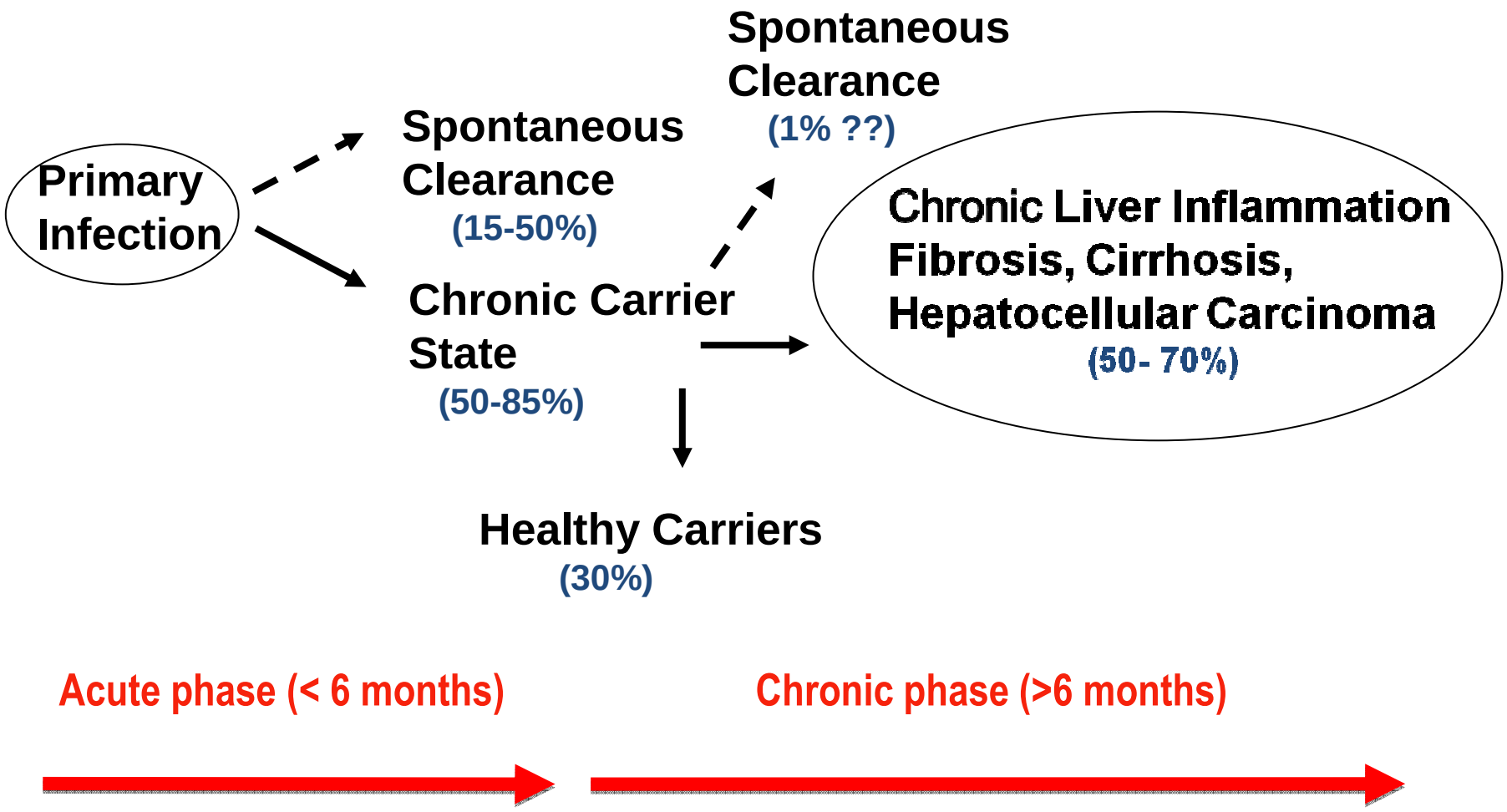
HCV: natural course of infection



Components of the adaptative anti-hepatitis C virus immune responses

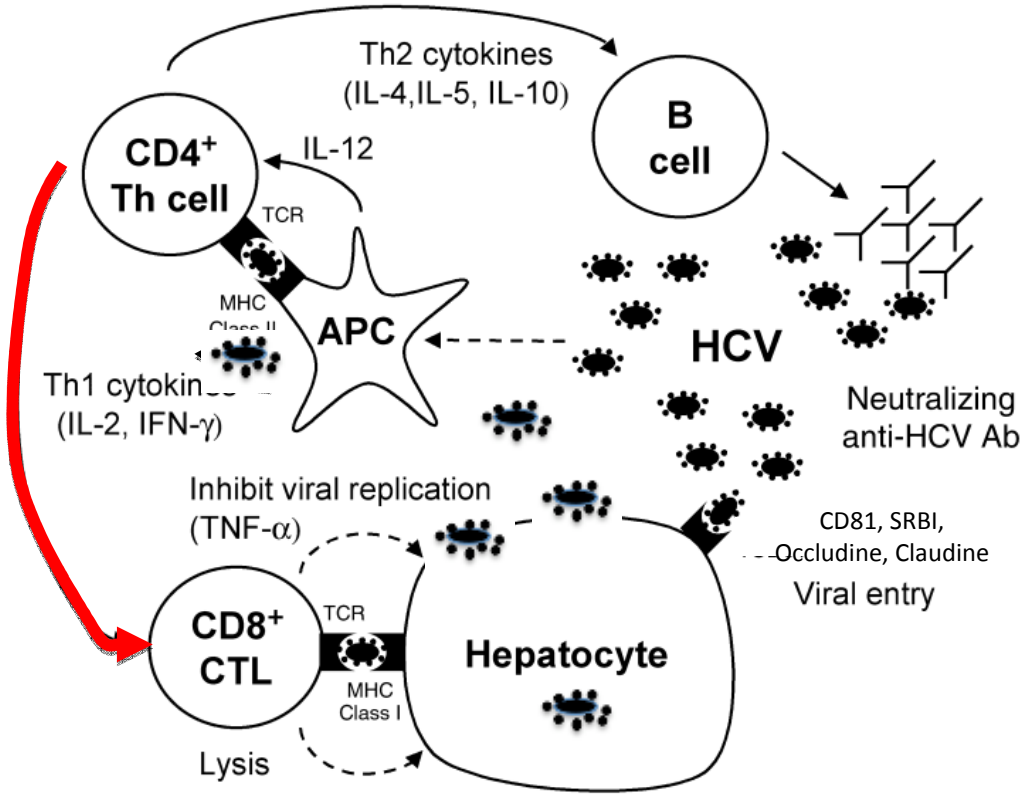
Spontaneous Clearance of HCV infection requires :

•Early and multispecific class 1 restricted CD8+ T cell and class II restricted CD4+ T cell responses directed to S and NS HCV proteins

• The quality of HCV clearance and protection from reinfection is determined by the functional potency and cytotoxic potential of HCV-specific CD8+cells

•NS3 is a key viral protein for HCV elimination

NAb responses to epitopes in E1 and E2 are associated with resolution of infection and protection against reinfection

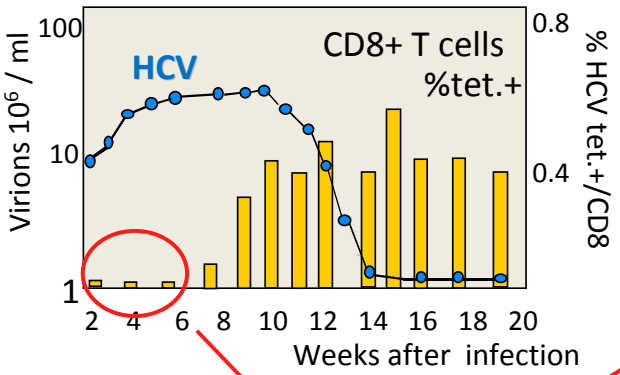


Adapted from Freeman AJ et al. Immunology and Cell Biology 2001: 79: 515-536.
Rehermann et al. JCI, 2009

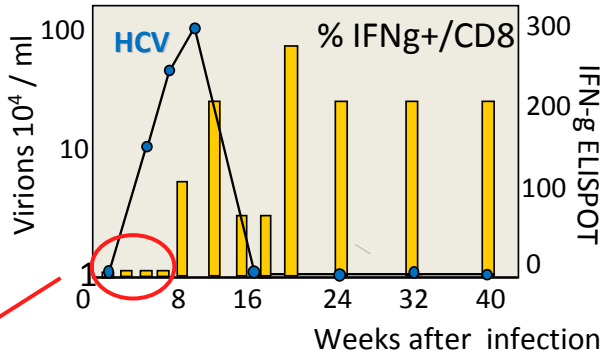
Importance of HCV-Specific Intra-Hepatic CD8+ T Cell Immune Responses (IFN-γ) in Control of HCV Replication

HUMAN INFECTION

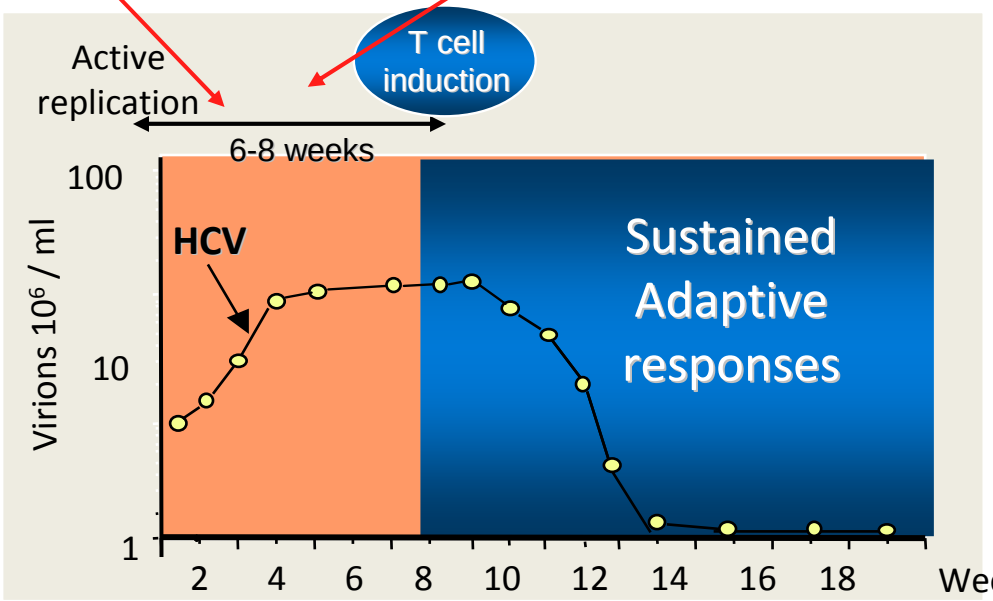
Thimme, R. et al, J Exp Med 2001



Shoukry, N. et al, J Exp Med 2003



CHIMPANZEE INFECTION



NS3 is a key target

Mechanism of HCV Clearance and Persistance

Spontaneous Clearance of HCV infection	Persistance of HCV infection
Strong and wide CD8+ and CD4+ T –cell responses to HCV epitopes	Limited T-cell responses and limited reactivity to HCV epitopes; Viral CD4+ and CD8+ escape mutants Lack of memory T-cell maturation Persistence of dysfunctional T-cells
Strong cytotoxic T cell responses	Negative costimulators of T cells : PD-1/PDL1 receptors-ligand; Immunoregulatory cytokines IL10
Neutralising Ab to E1/E2	Escape Mutants
IL28B gene polymorphisms C/C genotype	IL28B gene polymorphisms T/T genotype
	Impairment of DC maturation

Ferrari C. Gastroenterology 2008; 134: 1601-1604; Rehermann B et al. Nat Rev Immunol 2005; 5: 215-229;
Thomas DL et al. Nature 2009; 461: 798-801; Wherry EJ et al. J Virol 2004; 78: 5535-5545

Need to develop vaccine strategies

For Preventing HCV infection: need of strong cross-reactive neutralising (Ab) responses

To reconstitute efficient immune control in chronically infected patients : by restoring functional T-cell responses similar to those patients who resolve the HCV infection spontaneously : le vaccin thérapeutique

Therapeutic Vaccines for chronic hepatitis C

- **Different strategies for immunization**

✓ Peptides
✓ Proteins
✓ DNA-immunization
✓ Virus-like particules
✓ Tarmogens
✓ Life attenatued carriers : recombinant viruses and bacteria

Recombinant viruses are an efficient way to deliver heterologous DNA that can mediate a large amount of HCV antigens potentially increasing the immunogenicity of the vaccine in comparison with peptides and proteins

HCV Treatment: TG4040 Therapeutic Vaccine

- Based on **non-replicative, poxvirus MVA** (Modified Viral Ankara strain) was choice because he was successfully administered to immunize high risk patients against smoll pox without any significant side effects in the primary vaccination of over 150 000 humans

- **T cell-based therapeutic vaccine**: expressing 3 of the major non-structural HCV proteins (NS3, NS4, NS5B) that are prominant targets of host induced immune responses during clearance / control of infection

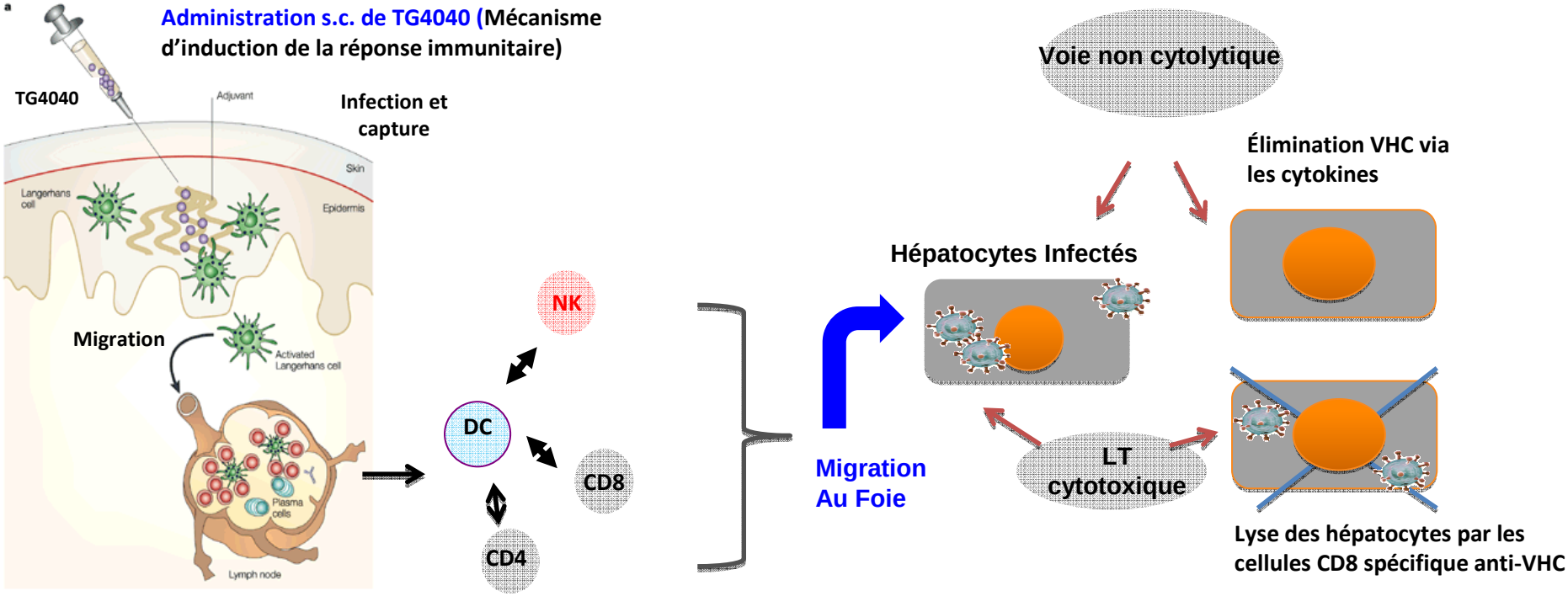
- **First viral-based vaccine in the field of HCV** therapies having entered clinical development

- **Objective:** to prime **HCV specific functional CD4+ and CD8+ T lymphocytes** capable to produce **IFN-γ** and **lyse infected cells**

Mécanisme d'action supposé de TG4040

Induction d'une réponse immunitaire cellulaire après injection de TG4040

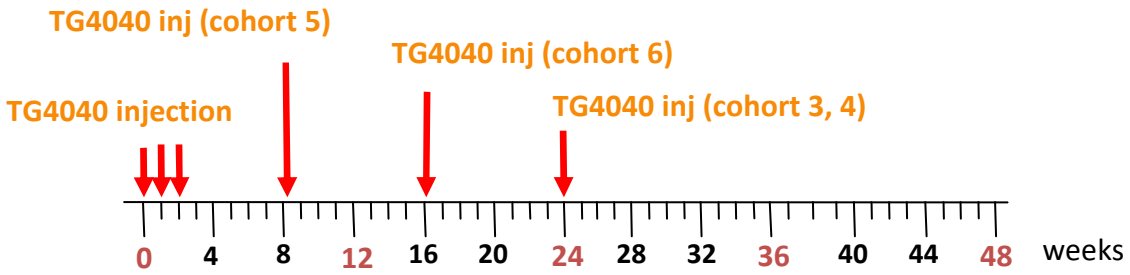
Destruction des hépatocytes infectées par la réponse cellulaire induite par TG4040 et/ou inhibition de la replication virale via un mécanisme non- cytopathique



Etude de phase 1 - TG4040.01 - d'escalade de dose chez des patients ayant une hépatite chronique C minime

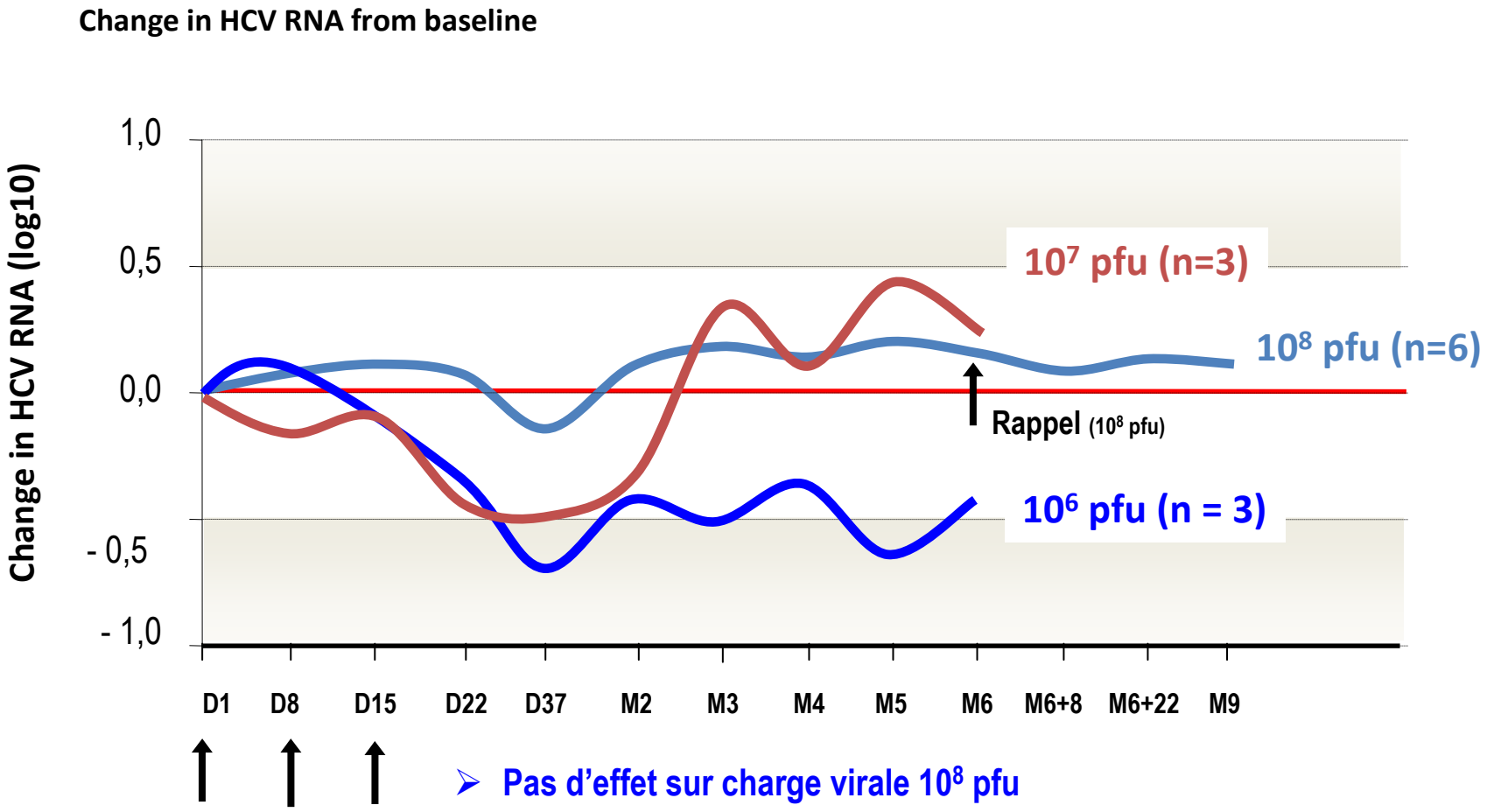
- **Dose escalating study**
  - Cohort 1: 10^6 pfu, 3 patients
  - Cohort 2: 10^7 pfu, 3 patients
  - Cohort 3: 10^8 pfu, 9 patients + boost at month 6

All patients: **Prime injection** (3 weekly injections)



Habersetzer F et coll. Gastroenterology, 2011.

Étude de phase 1 d'escalade de dose: Evolution de la virémie

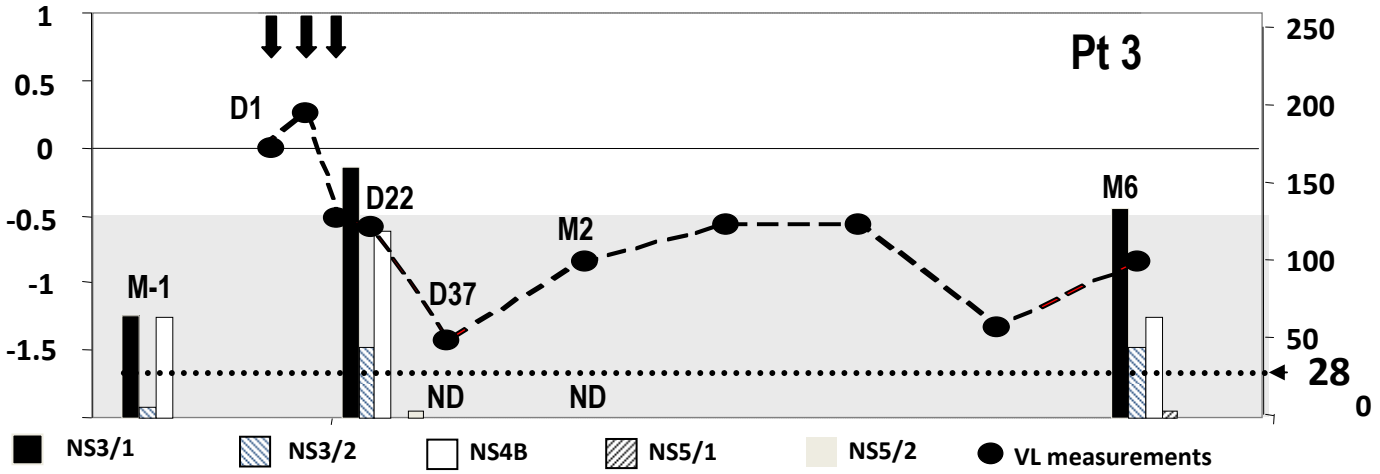


- Pas d'effet sur charge virale 10^8 pfu
- Nadir après 37 j
- Diminution prolongée de la virémie de 37 à 6 mois 10^6 pfu

Habersetzer F et coll. Gastroenterology, 2011.

Patient 3 Corrélation réponse T et virémie C

ELISpot : Réponse augmentée contre NS3/1 et NS4B (> moy pré-thérapeutique + 2SD) et induction de réponse contre NS3/2



Corrélation entre la diminution de la virémie et la réponse immunitaire spécifique au TG4040

Habersetzer F et coll. Gastroenterology, 2011.

Résultats étude de phase 1 : preuve de concept

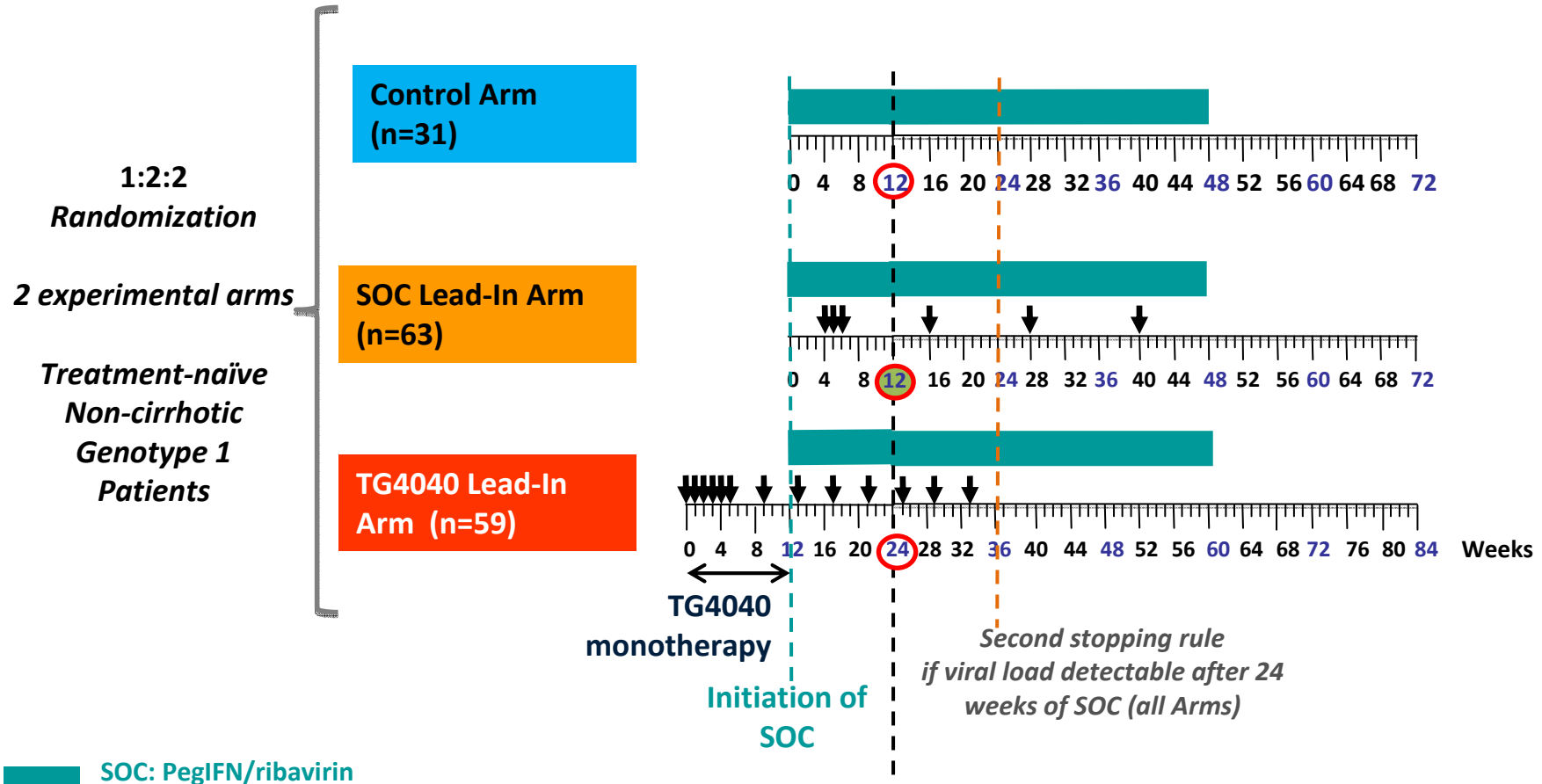
Chez des patients ayant une hépatite C chronique

- ✓ Vaccin thérapeutique TG4040 bien toléré
- ✓ Baisse transitoire de la virémie chez 50% des patients
- ✓ Permet d'induire une réponse immunitaire chez 33% des patients

Nécessité d'envisager des combinaisons pour permettre une élimination virale

Habersetzer F et coll. Gastroenterology, 2011.

Résultats étude de phase 1 : preuve de concept



Wedemeyer H et al. EASL 2013

Demographic and baseline characteristics

- Stratification by age (>vs≤50 years) and baseline viral load (>vs≤400 000 IU/mL)

	Control (n=31)	SOC Lead-In (n=63)	TG4040 Lead-In (n=59)
Mean Age in years	41	44	43.6
Gender, n females / n males	15/16	27/36	27/32
Caucasian, n (%)	30 (96.8)	60 (95.2)	59 (100)
Mean Baseline HCV RNA in log10 IU/mL (SD)	5.96 (0.68)	5.74 (0.81)	5.71 (0.81)
HCV genotype, n (%)			
1a	6 (19.4)	12 (19)	15 (25.4)
1b	25 (80.6)	50 (79.4)	44 (74.6)
1a/b	0	1 (1.6)	0
IL28B n C-C / n non C-C *(All data are not yet available)*	7/17	14/33	16/32
F3 Fibrosis, n (%) (Biopsy or FibroScan®)	1 (3.2)	6 (9.5)	7 (11.8)
High Baseline ALT (≥ 2 ULN), n (%)	5 (16.1)	15 (23.8)	16 (27.1)

- Good balance between arms, including IL28B polymorphism and genotype 1a/1b distribution

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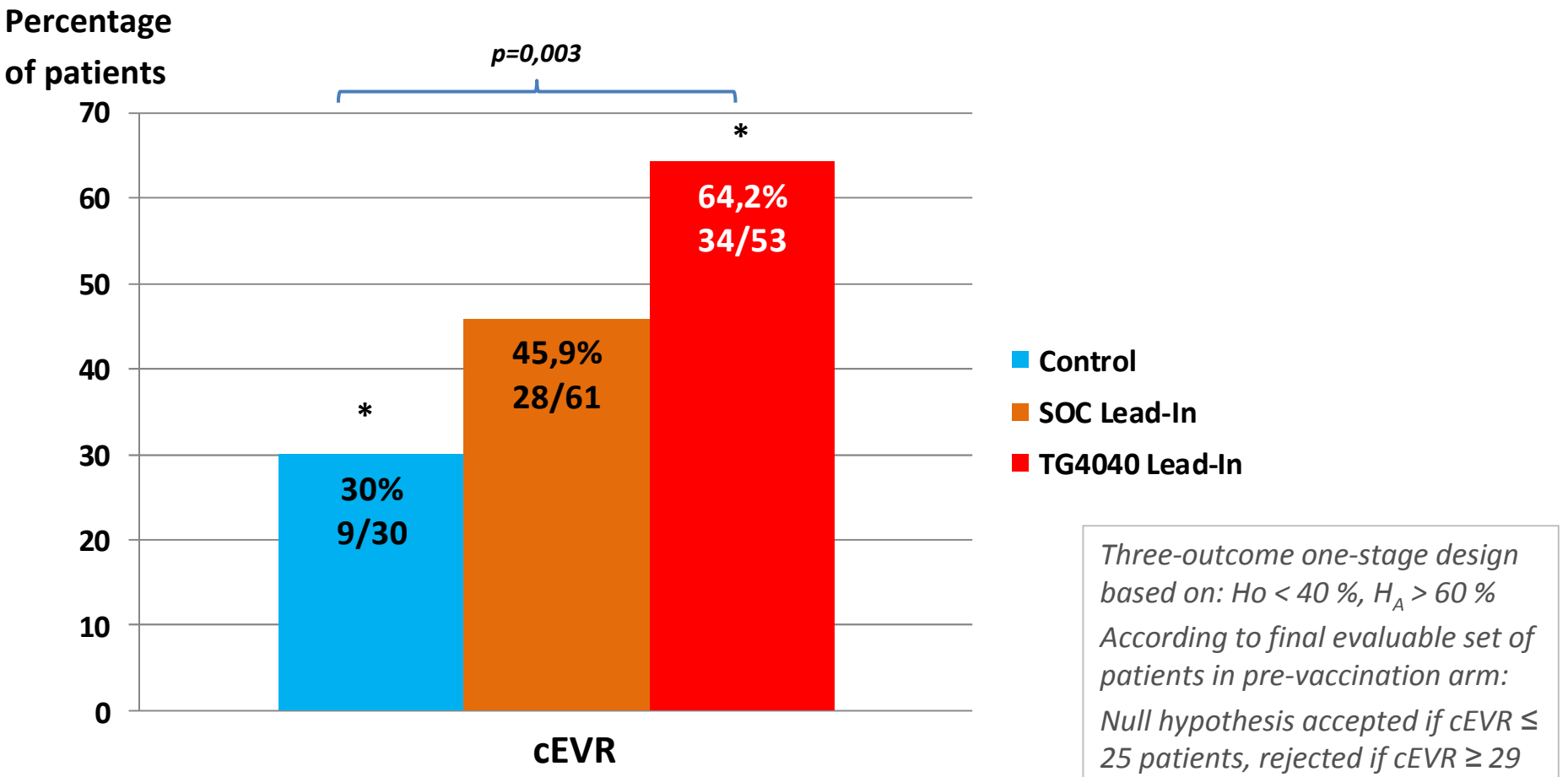
TG4040 Pre-Vaccination Improves cEVR Rates



Three-outcome one-stage design based on: Ho < 40 %, H_A > 60 %

According to final evaluable set of patients in pre-vaccination arm:

Null hypothesis accepted if cEVR ≤ 25 patients, rejected if cEVR ≥ 29

- Primary objective of the study reached: significant improvement of cEVR rates in TG4040 lead-in arm (64.2 %)

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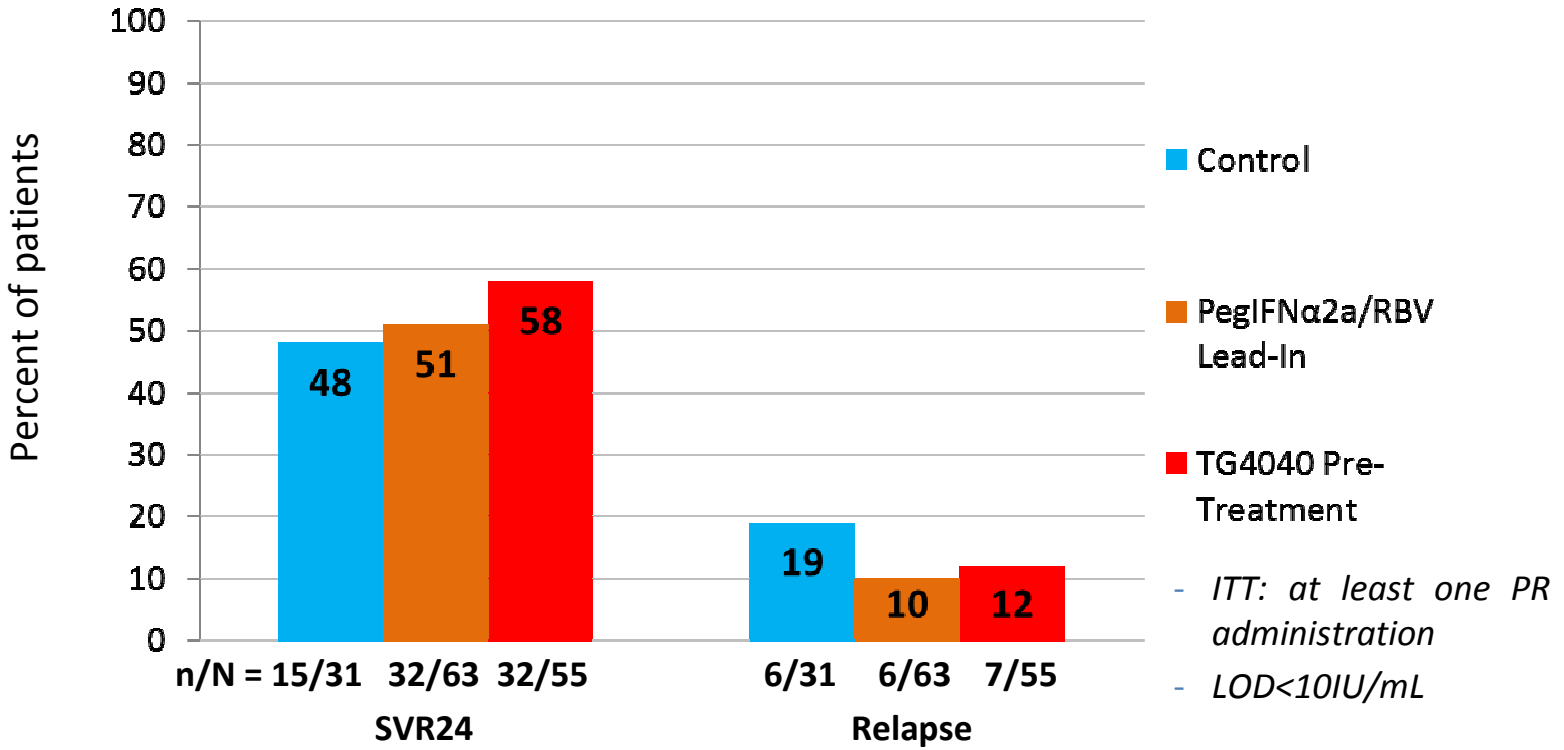
SVR24 Response Relapse and Viral Breakthrough



- Viral breakthrough (defined as greater than or equal 100IU/mL increase in HCV RNA after drop to BLOD) occurred in 5% (3/63) and 2% (1/55) in PR lead-in and TG4040 pre-treatment arms vs 0% in control arm

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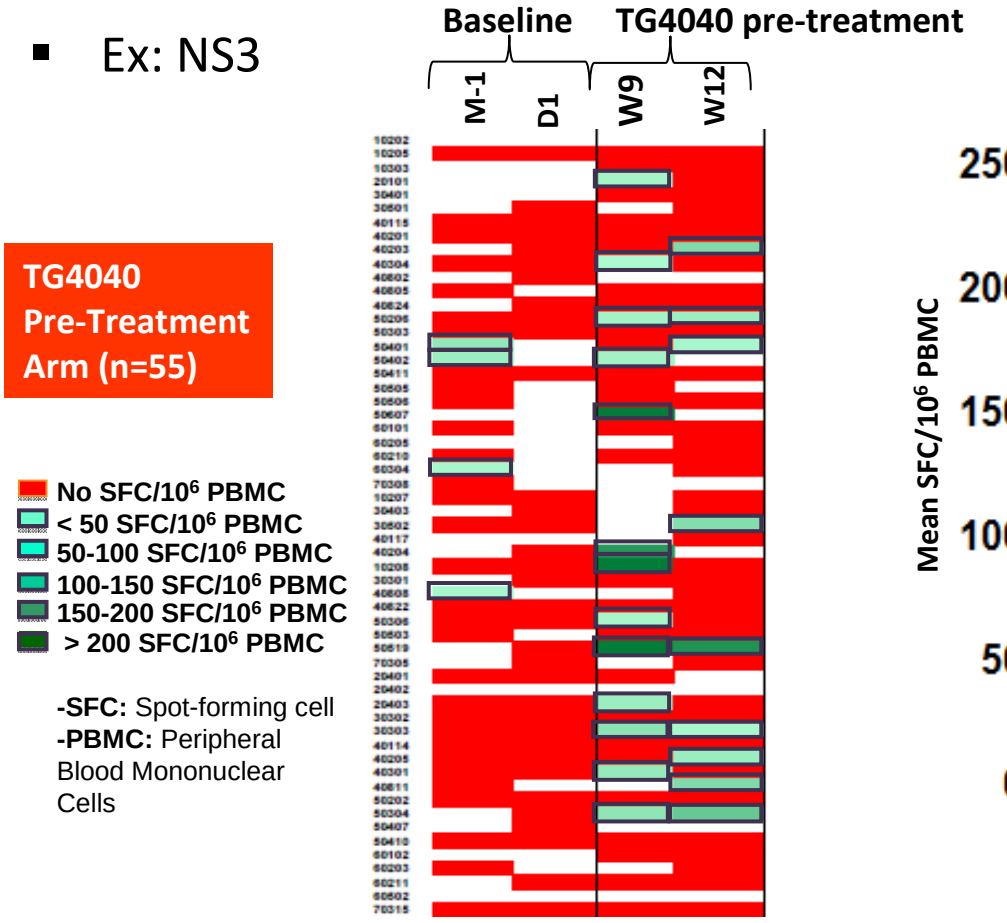
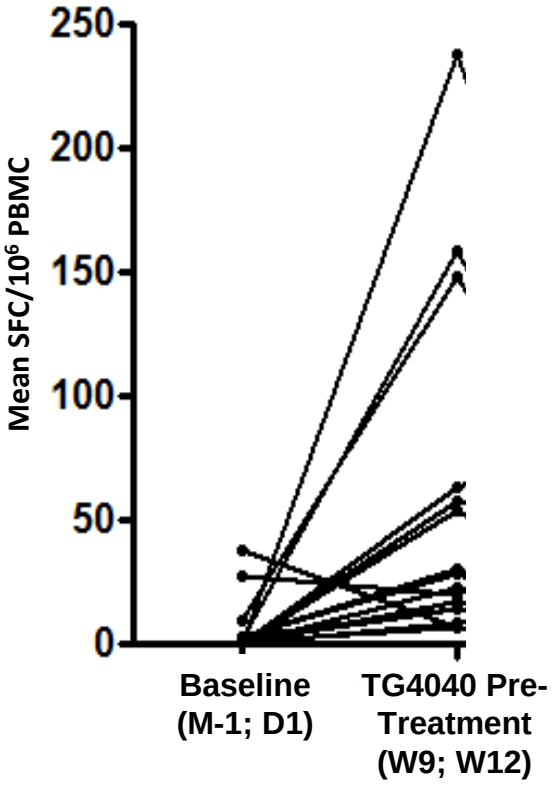
TG4040 Induces HCV Specific T-Cell Responses

- Ex: NS3

TG4040 Pre-Treatment Arm (n=55)





- NS3 specific ELISpot IFN-γ responses: 46% of patients
- **Overall, 71% of patients had TG4040 specific T-cell responses**

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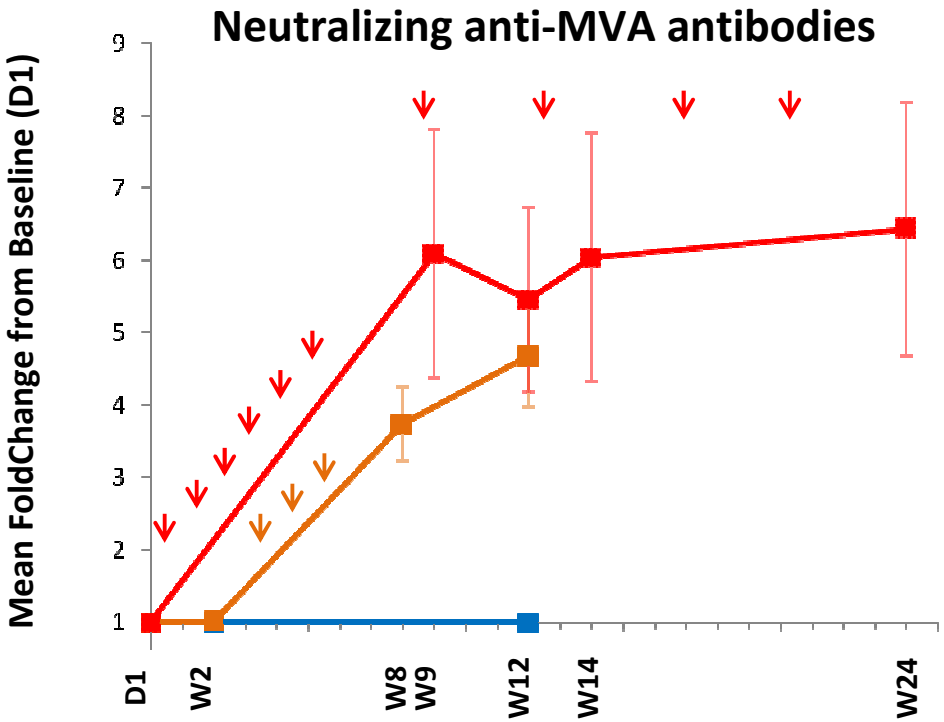
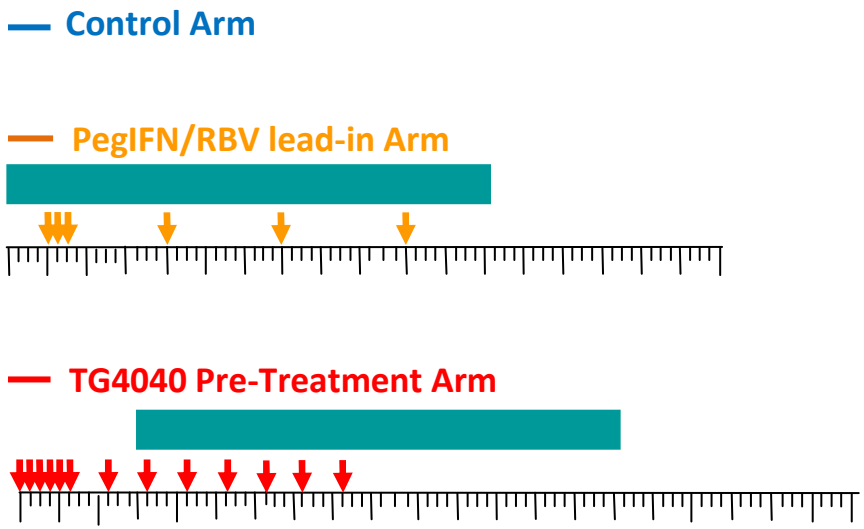
Induction of Anti-MVA Humoral Immune Responses





- All TG4040 treated patients developed detectable anti-MVA humoral responses
- No significant correlation between neither total nor neutralizing antibodies and virological response (cEVR and/or SVR24)

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Safety

Cut-off: 24 weeks of PegIFN/riba. in each arm	Control (n=31)	SOC Lead-In (n=63)	TG4040 Lead-In (n=59)
Any adverse events *n (%)*	27 (**87.1%**)	58 (**92.1%**)	57 (**96.6%**)
Adverse events related to PegIFN & ribavirin	25 (**80.6%**)	56 (**88.9%**)	51 (**86.4%**)
Adverse events related to TG4040	NA	21 (**33.3%**)	35 (**59.3%**)
Most common adverse events (more than 15%) (*; significant difference; p ≤ 0,05)			
Fatigue	18 (**58.1%**)	33 (**52.4%**)	30 (**50.8%**)
Pyrexia	6 (**19.4%**)	15 (**23.8%**)	21 (**35.6%**)
Injection site erythema*	1 (**3.2%**) *	11 (**17.5%**)	18 (**30.5%**) *
Influenza like illness	8 (**25.8%**)	11 (**17.5%**)	8 (**13.6%**)
Injection site induration	0	4 (**6.3%**)	9 (**15.3%**)
Injection site pruritus	0	4 (**6.3%**)	9 (**15.3%**)
Neutropenia	9 (**29%**)	18 (**28.6%**)	15 (**25.4%**)
Anaemia	8 (**25.8%**)	8 (**12.7%**)	16 (**27.1%**)
Leukopenia	5 (**16.1%**)	4 (**6.3%**)	7 (**11.9%**)
Headache	7 (**22.6%**)	13 (**20.6%**)	17 (**28.8%**)
Insomnia	7 (**22.6%**)	8 (**12.7%**)	5 (**8.5%**)
Pruritus	6 (**19.4%**)	9 (**14.3%**)	9 (**15.3%**)
Alopecia	2 (**6.5%**)	4 (**6.3%**)	12 (**20.3%**)
Nausea	5 (**16.1%**)	5 (**7.9%**)	7 (**11.9%**)
Decreased appetite	5 (**16.1%**)	5 (**7.9%**)	12 (**20.3%**)
Myalgia	4 (**12.9%**)	12 (**19%**)	9 (**15.3%**)
Grade 3/4 adverse events	7 (**22.6%**)	15 (**23.8%**)	13 (**23.7%**)

Safety

- As of today, 19 SAEs reported in 13 patients, none related to TG4040 alone

	Control	SOC Lead-In	TG4040 Lead-In	Total
Total SAEs (events)	**4**	**11**	**4**	**19**
Related to PegIFN/ribavirin only	**2**	**5**	**0**	**7**
Related to TG4040 only	**0**	**0**	**0**	**0**
Related to TG4040 & PegIFN/ribavirin	**-**	**2**	**3**	**5**
SAEs unrelated to treatments	**2**	**4**	**1**	**7**

- SAEs related to PegIFN/ribavirin & TG4040 in 4 patients
  - Three patients with severe peripheral thrombocytopenia (2 in SOC lead-in arm, 1 in vaccine lead-in arm) and one patient with aplastic anemia in vaccine lead-in arm
  - Recovery of blood parameters in 1 to 4 months, one recent case ongoing
  - Common feature between the 3 patients with thrombocytopenia: HLA-DRB1*04 allele (statistical association p=0.001)

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Summary and Conclusions

- Pre-treatment with immunotherapeutic TG4040 followed by PegIFNα2a/RBV significantly increased cEVR as compared to PegIFNα2a/RBV alone, in treatment-naive patients with genotype 1 HCV: **64% compared to 30%**

- In pre-treatment arm, higher SVR24 rate as compared to the control arm: **58% vs 48%**
  - And lower relapse rate: **12% vs 19%**

- TG4040 alone was generally well tolerated.

  However, TG4040 treatment may be associated with exacerbation of IFNa-related immune side effects in distinct HLA-backgrounds

Summary and Conclusions

- TG4040 induced HCV-specific T cell responses:

  46% NS3-specific ELISpot IFN-gamma responses, 71% overall
- T cell and/or B cell responses against MVA were induced in all patients

In Conclusion:

This study in chronic hepatitis C illustrates the **potential value of viral vector-based immunotherapy for the treatment of chronic infections** including viral hepatitis which warrants further evaluation

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