

**Erasmus MC**

Universitair Medisch Centrum Rotterdam



## **Engineered T Cell Therapy Trials in Rotterdam**

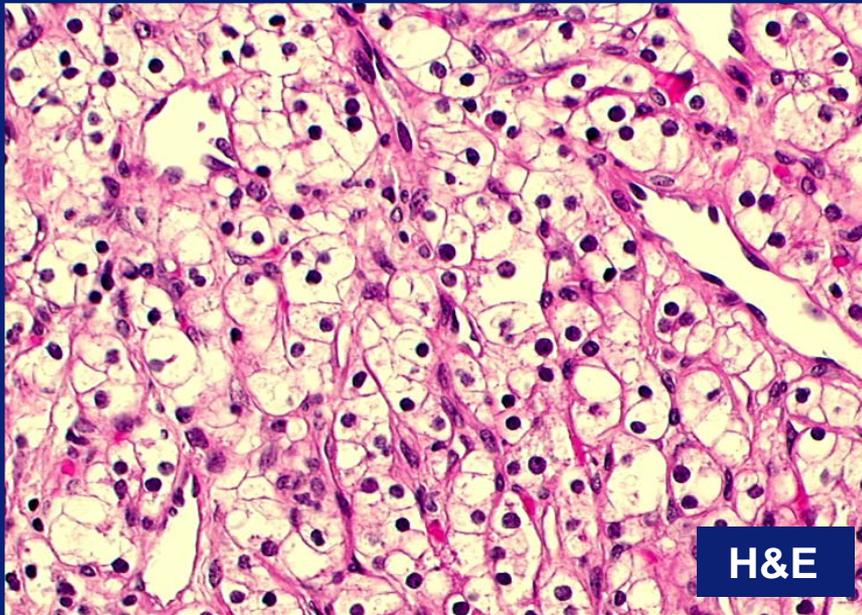
**Toxicity profile of the therapy of renal cell cancer  
using a chimeric antibody receptor directed  
towards carboxy anhydrase IX**

**Cor Lamers**

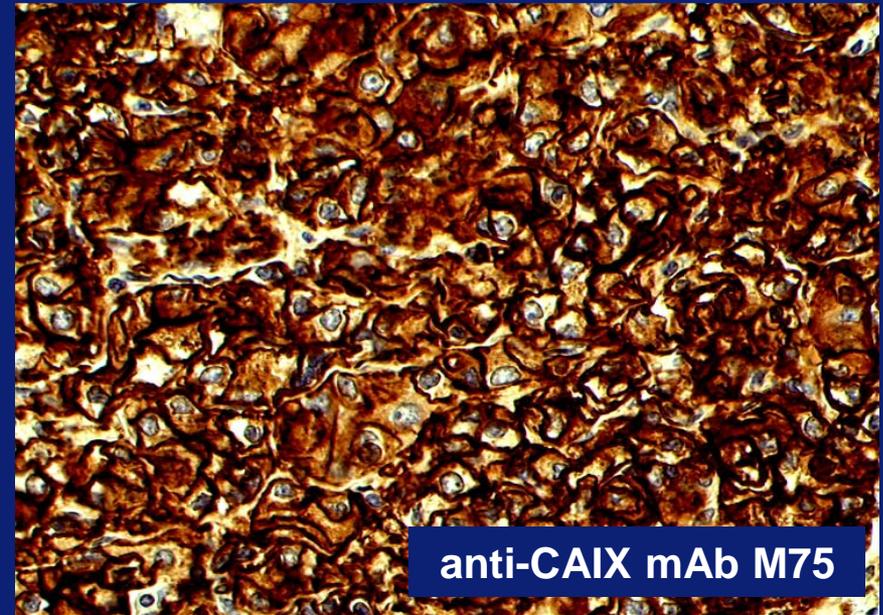
**Department of Medical Oncology  
Erasmus MC – Daniel en Hoed Cancer Centre  
Rotterdam, The Netherlands**

# Renal Cell Carcinoma

## Histology and immunohistochemistry



H&E



anti-CAIX mAb M75

Clear cell renal cell carcinoma

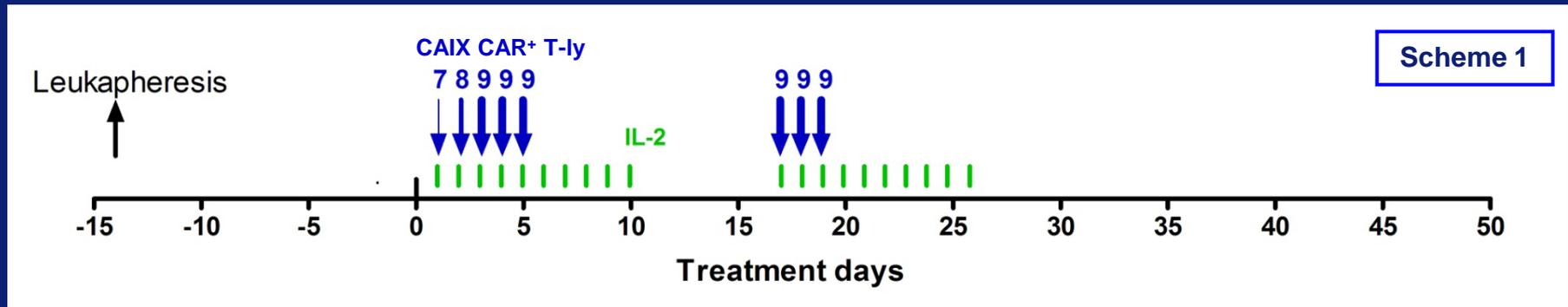
Grawitz tumor

**CAIX: Membrane antigen:** 90% primary RCC  
80% RCC metastases

**Weak expression on:** epithelium of larger bile ducts  
gastric mucosal cells

In immunogene therapy: anti-CAIX mAb G250

## Patient Treatment Scheme



In-patient dose escalation: intravenous infusion of  $2 \times 10^7$ ,  $2 \times 10^8$ ,  $2 \times 10^9$  G250 CIR<sup>+</sup> T cells  
IL-2: patients receive sc  $5 \times 10^5$  IU IL-2/m<sup>2</sup>/12h through days 1-10 and days 17-26

*CAIX CAR = scFv(G250)-CD4 $\gamma$  Chimeric Antibody Receptor*

Primary study objective:

Determine safety of escalating dose of intravenous infusions of CAIX CAR<sup>+</sup> T cells

# Rotterdam RCC Gene Therapy Trial (P00.0040C)

## Treatment Characteristics and Toxicity

Cohort	Patient	Total cells in fused (x 10 <sup>-9</sup> )	CAIX CAR (%)	CAIX CAR+ cells infused (x10 <sup>9</sup> )	CD4/CD8	IL-2 doses	Toxicity Liver enzymes (max grade)	
							Cycle 1	Cycle 2
1	1	4.0	53	2.1	36/64	9	<b>4</b>	-
	2*	1.4	61	0.85	39/61	36	1	1
	3*	0.6	63	0.38	60/42	9	<b>3</b>	-

IL-2 dose: 5x10<sup>5</sup> IU/m<sup>2</sup>/12 h at days 1-10 and days 17-26

\* max cell dose reduced to 2x10<sup>8</sup> cells per infusion

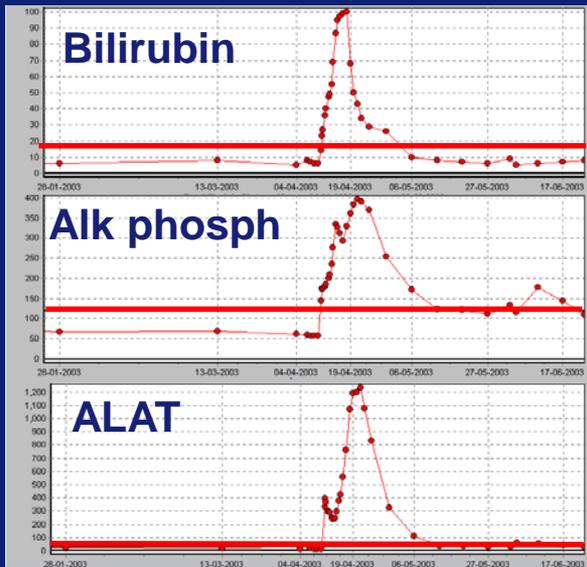
Lamers et al, JCO, 2006

- ▶ Toxicity is highly probably induced by the specific interaction of CAIX CAR<sup>+</sup> T cells with CAIX expressed on bile duct epithelium
- ▶ Adapt treatment scheme and include a blocking strategy of the CAIX-sites in the liver

# Clinical observations first 3 patients: liver enzyme abnormalities

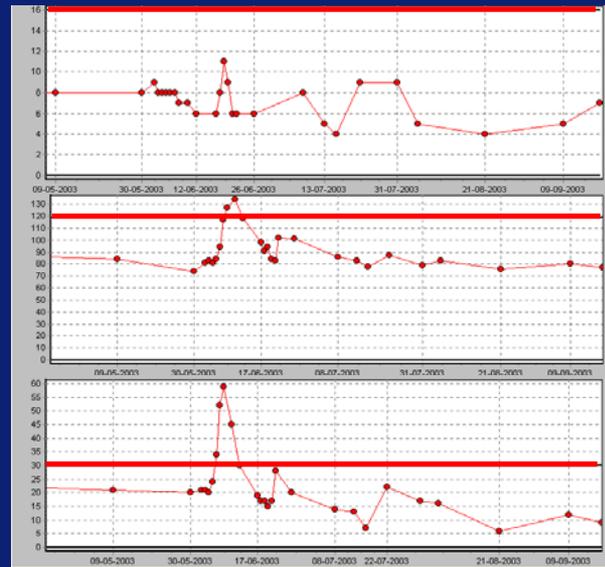
## Patient 1

Treatment stopped at day 5, max  $2 \times 10^9$



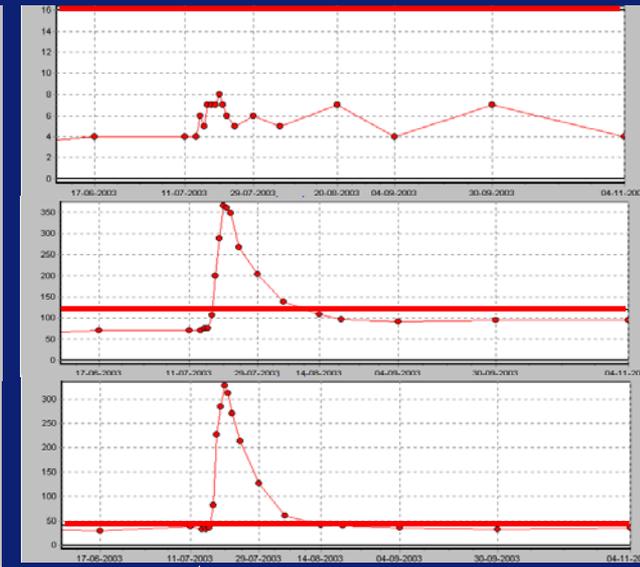
## Patient 2

Treatment completed at max  $2 \times 10^8$



## Patient 3

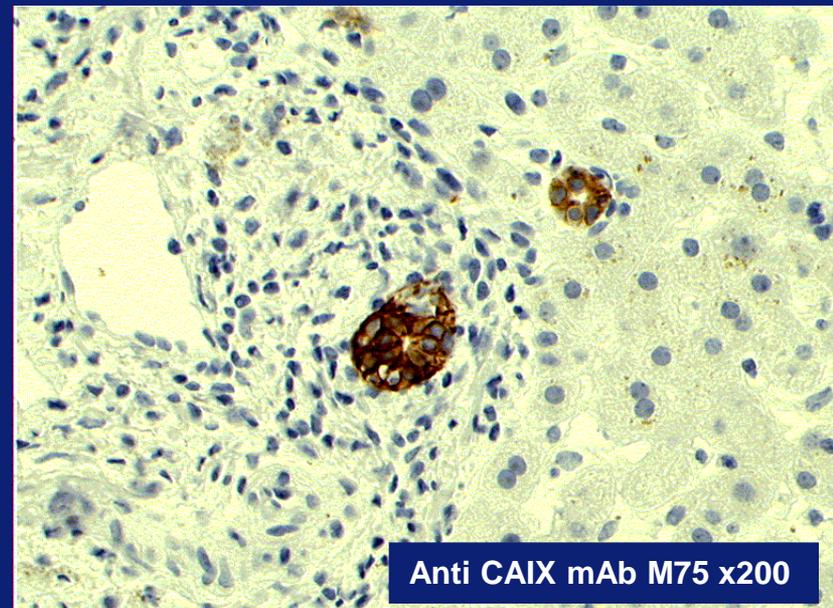
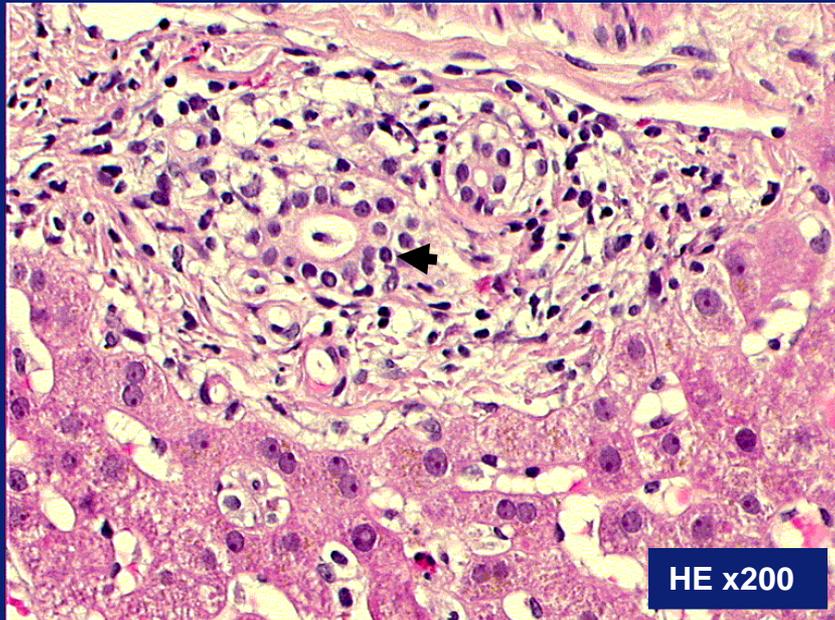
Treatment stopped at day 5, max  $2 \times 10^8$



-  Upper limit normal
-  Start T cell infusion
-  Start Solumedrol

# Follow-up studies liver toxicities

## Pathology liver biopsy patient 1



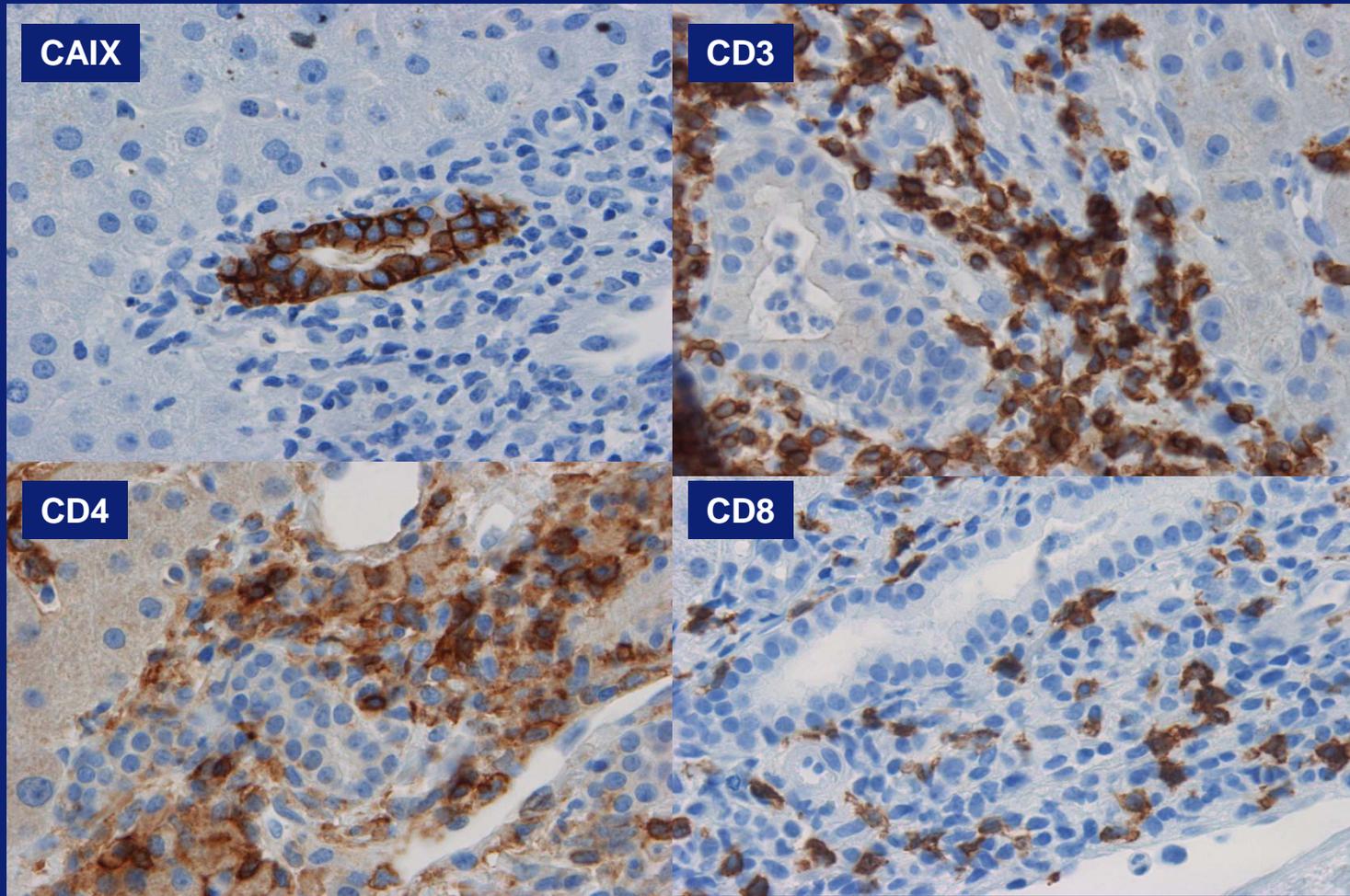
- Intact liver architecture
- In portal triangles increased infiltrate of lymphocytes and eosinophils
- Some bile ducts infiltrated by T lymphocytes
- Clear expression of CAIX on bile duct epithelium

**Conclusion:** discrete cholangitis, limited inflammation and damage of bile duct epithelium might be therapy related effects

**Are CAIX CAR+ T lymphocytes involved in the liver pathogenesis?**

# Follow-up studies liver toxicities

## Pathology liver biopsy patient 8



Conclusion: discrete cholangitis, inflammed portal triangles, T-cell infiltrates  
Are G250 CIR+ T lymphocytes involved in the liver pathogenesis?

## Change study design

### Cohort 2

- Increase time interval between doses
- Switch from intra-patient to inter-patient dose-escalation

### Cohort 3

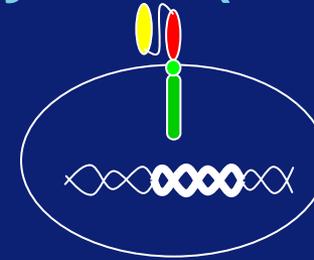
- Add blocking antibody (cG250)
  - single dose of 5 mg cG250, blocks liver CAIX but RCC metastases not saturated
  - cG250 mAb does not enhance, but blocks function of CAR+ T cells

## Hypothesis

An infusion with 5 mg of cG250 mAb shields the CAIX sites in the liver from recognition by CAIX CAR+ T cells reactivity, while CAIX sites in RCC metastasis are still accessible

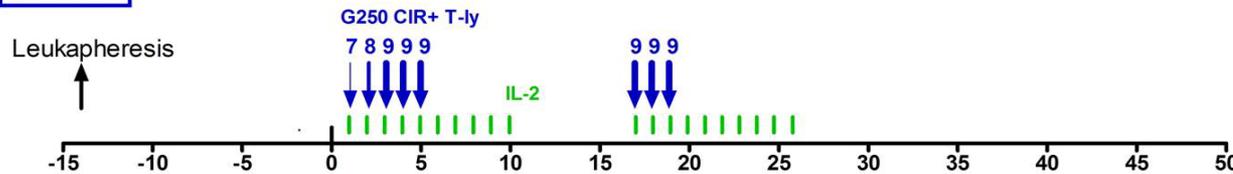
# Rotterdam RCC Gene Therapy Trial (P00.0040C)

CAIX CAR: scFv(G250)-CD4/γ

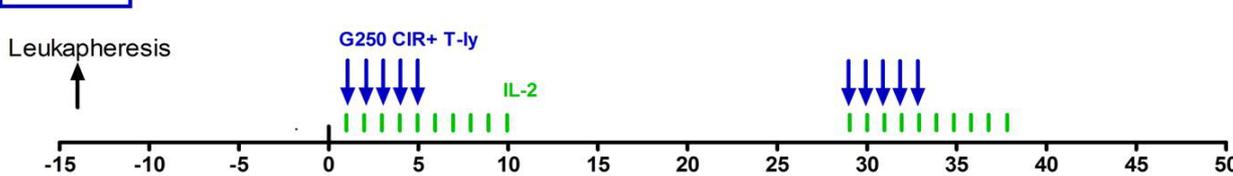


anti-CAIX reactivity

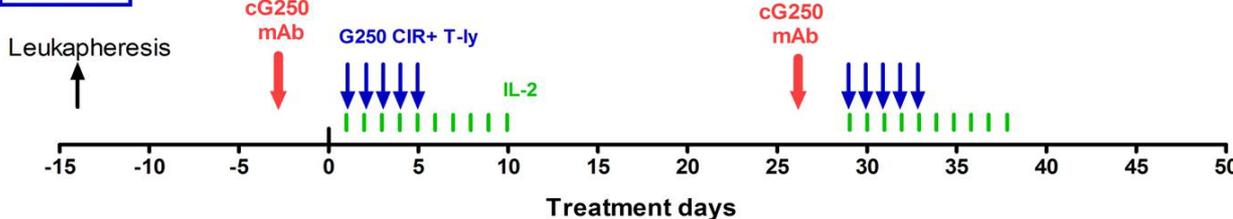
**Scheme 1**



**Scheme 2**



**Scheme 3**



## Renal Cell Cancer patient numbers and clinical observations

**Scheme 1:** patient 1-3

SAE/DLT in 2 patients  
liver enzyme disturbances  
(grade 3, 4)

**Scheme 2:**

Dose:  $1 \times 10^8$  CAR+ T-ly: patient 4-8  
SAE/DLT in 2 patients  
liver enzyme disturbances  
(grade 3)

**Scheme 3:**

Dose:  $1 \times 10^8$  CAR+ T-ly: patient 9-11  
 $2 \times 10^8$  CAR+ T-ly: patient 12  
ongoing

so far no SAE  
liver enzymes  $\leq$  grade 1

CAIX CAR+ T-ly: Scheme 2 + 3: 1, 2, 4, 8, 16, 20, and 25  $\times 10^8$  per infusion; 3 patients per dose level

IL-2: sc  $5 \times 10^5$  IU IL-2/m<sup>2</sup>/12h through days 1-10 and days 17-26 / 29 – 38

cG250 mAb: 5mg cG250 mAb per infusion

# Rotterdam RCC Gene Therapy Trial (P00.0040C)

## Summary liver enzyme toxicity

P00.0040C: toxicity score

Liver enzymes, pre-treatment and max score per treatment cycle

Treatment cycle	Liver enzymes					
	Bili	AP	gGT	ASAT (GOT)	ALAT (GPT)	LDH
<b>Cohort 1</b>						
#01 BBE	pre TX	0	0	0	0	0
	I	3	2	2	3	4
	II	-	-	-	-	-
#02 CGR	pre TX	0	0	0	0	0
	I	0	1	1	1	0
	II	0	0	1	0	0
#03 MWE	pre TX	0	0	0	0	1
	I	0	2	3	3	3
	II	-	-	-	-	-

<b>Cohort 2</b>						
#04 AEK	pre TX	0	1	0	0	0
	I	0	1	1	0	0
	II	0	1	1	0	0
#05 GGA	pre TX	0	0	1	0	0
	I	0	1	1	0	1
	II	0	1	1	0	0
#06 MGE	pre TX	0	0	0	0	1
	I	0	0	0	1	2
	II	0	0	1	2	3
#07 CBR	pre TX	0	0	0	0	0
	I	0	0	0	0	1
	II	0	0	0	0	0
#08AKR	pre TX	0	1	2	1	1
	I	1	2	3	3	3
	II	-	-	-	-	-

Treatment cycle	Liver enzymes					
	Bili	AP	gGT	ASAT (GOT)	ALAT (GPT)	LDH
<b>Cohort 3</b>						
#09 ADI	pre TX	0	0	1	0	0
	I	0	0	1	0	0
	II	0	0	1	0	0
#10 JBA	pre TX	0	0	0	0	0
	I	0	1	0	0	0
	II	0	1	0	0	0
#11 CVE	pre TX	0	1	1	0	0
	I	0	1	0	0	1
	II	0	1	1	0	0
#12 WBA	pre TX	0	0	0	0	0
	I	0	0	0	0	0
	II	0	0	0	0	0

# Rotterdam RCC Gene Therapy Trial (P00.0040C)

---

## Conclusions (clinic)

- ◆ Establish toxicity profile CAIX CAR<sup>+</sup> T cells + IL2
  - => Liver toxicity  $\geq$  grade 3 in 4/8 patients at dose  $1 \times 10^8$  CAIX CAR<sup>+</sup> T cells (scheme 1+2).
  - => Low numbers of CAIX CAR<sup>+</sup> T cells + IL2 may cause
  - => Likely on-target toxicity against CAIX expressed on bile duct epithelium
  
- ◆ Establish safety, toxicity and MTD of CAIX CAR<sup>+</sup> T cells + IL2 and cG250 pre-Tx
  - => To be determined: patients treatment according this scheme is ongoing
  - preliminary: cG250 blocking improves toxicity profile (4 patients)
  
- ◆ Assess anti-tumor response: WHO criteria
  - => no objective responses yet (0 out of 12)