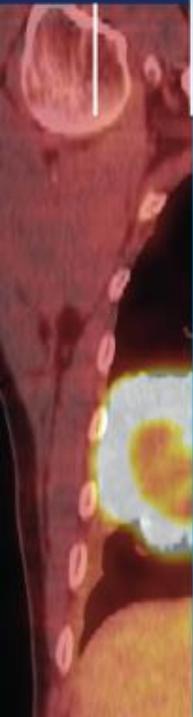




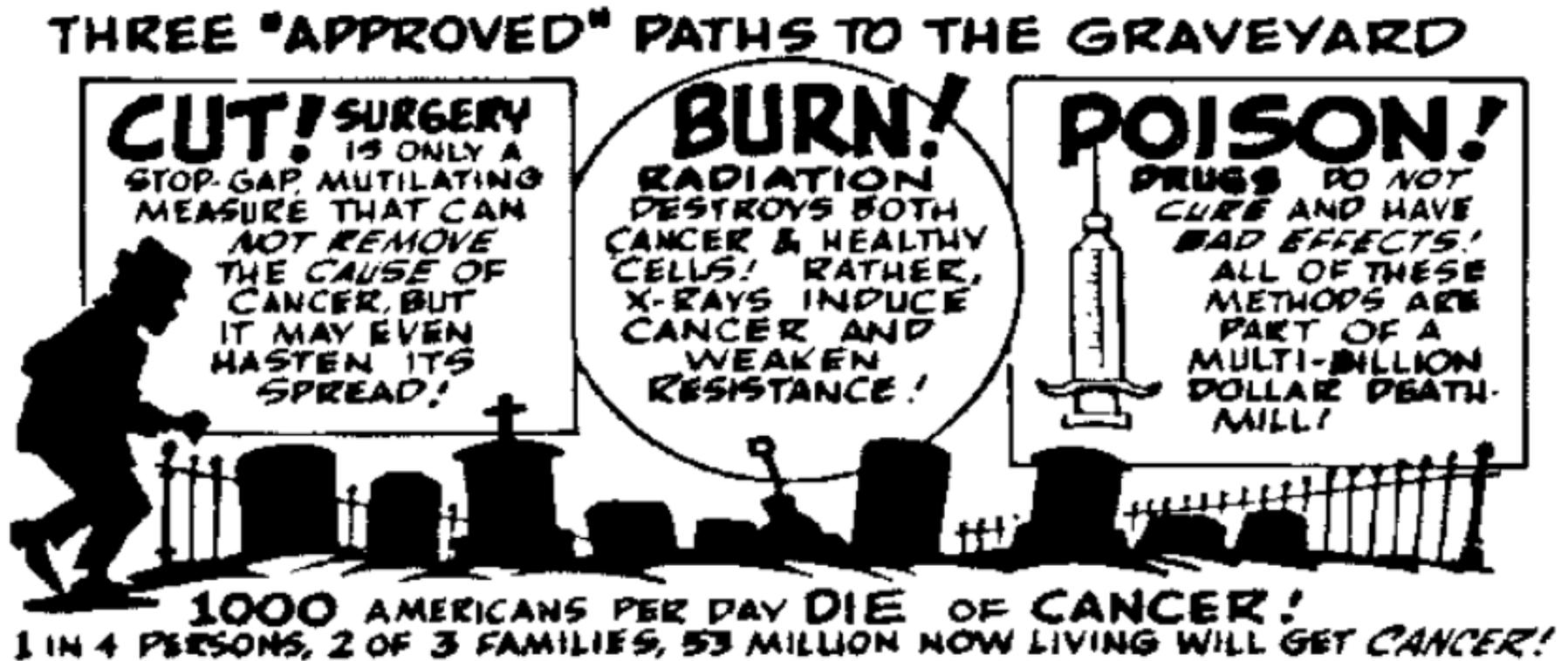
# Radiotherapy and immunotherapy: partners in crime?

*Ludwig Dubois, PhD*

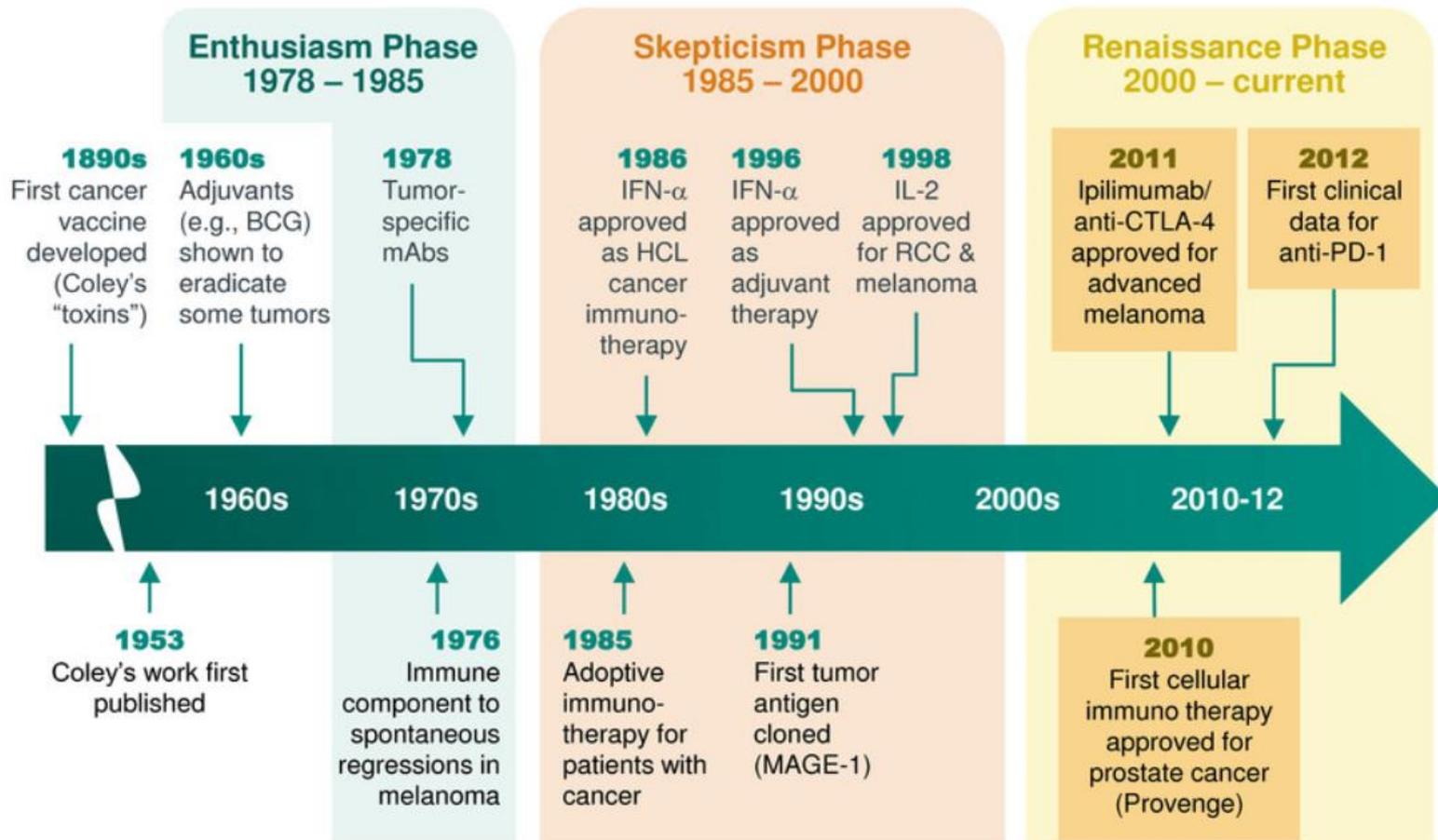


Department of Radiation Oncology (MAASTRO)  
GROW, Maastricht University,  
Maastricht, The Netherlands  
[ludwig.dubois@maastrichtuniversity.nl](mailto:ludwig.dubois@maastrichtuniversity.nl)

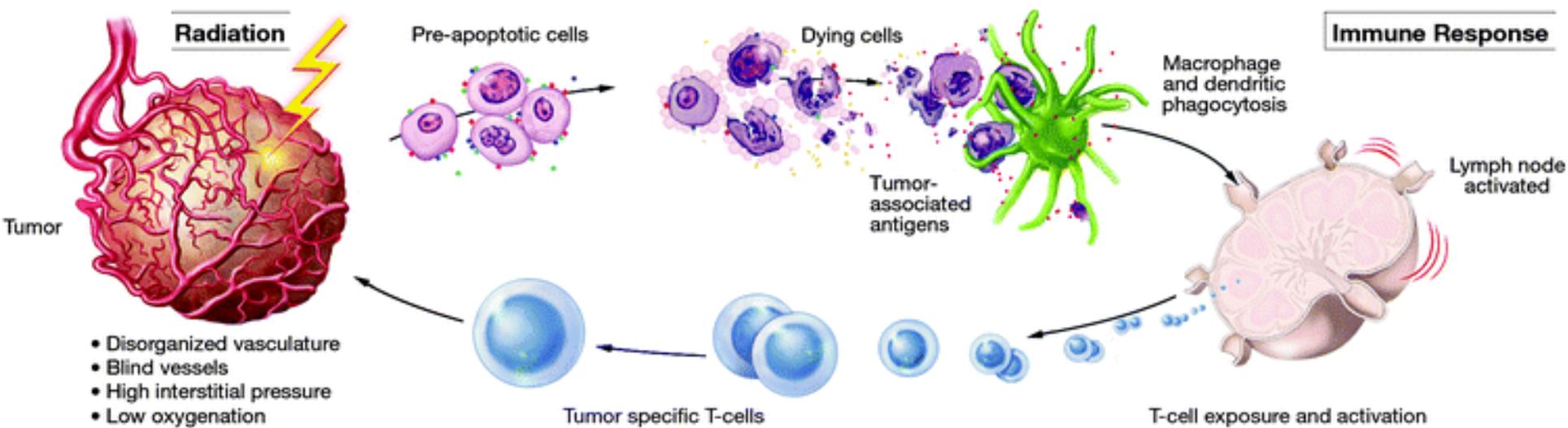
# Current treatment possibilities: a problem for oncologists



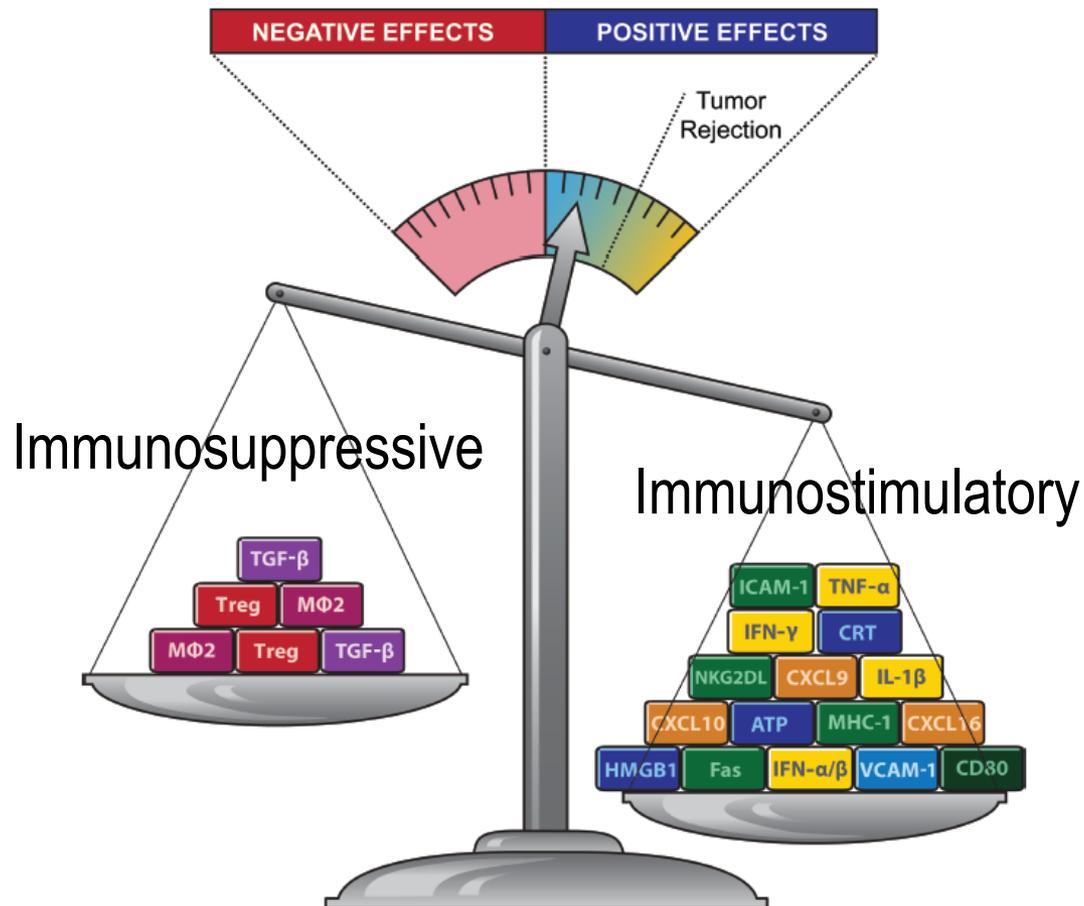
# Milestones within immunotherapy



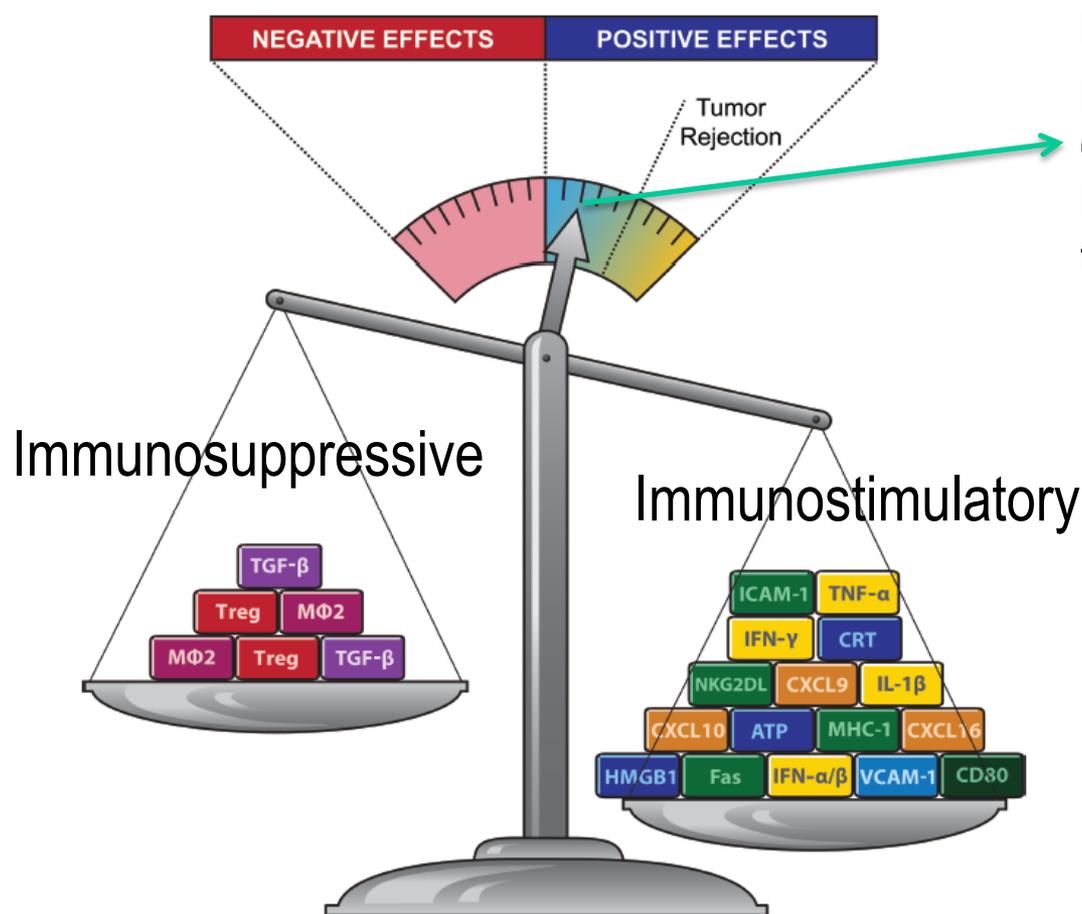
# Radiotherapy and immunogenicity



# Radiotherapy and immunogenicity



# Radiotherapy and immunogenicity



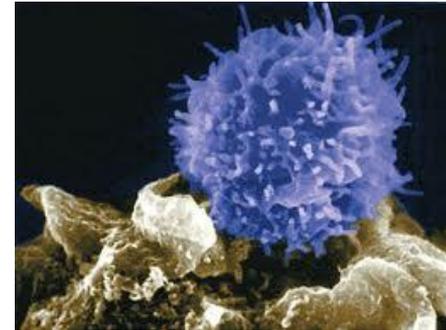
Positive effects predominate, but are often insufficient to shift balance to achieve tumor regression

# How to improve RT response?

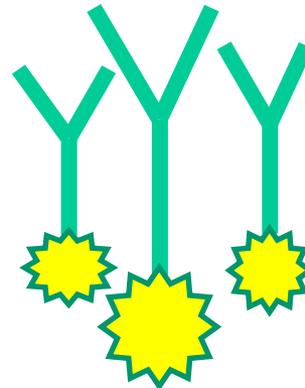
## Vaccine-based strategies



## Adoptive T/NK cell therapies



## Cytokines and immune-targeted agents

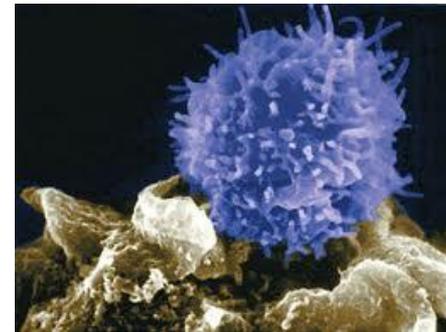


# How to improve RT response?

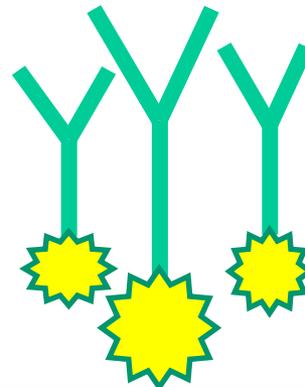
## Vaccine-based strategies



## Adoptive T/NK cell therapies



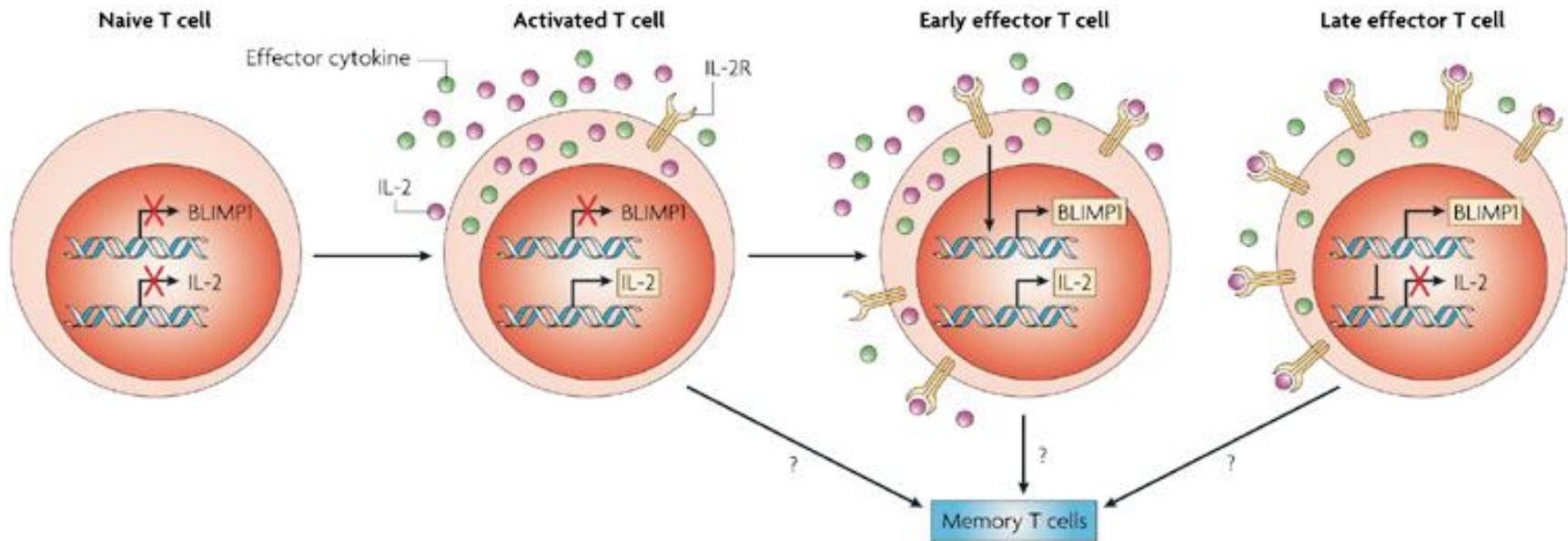
## Cytokines and immune-targeted agents



# Cytokines

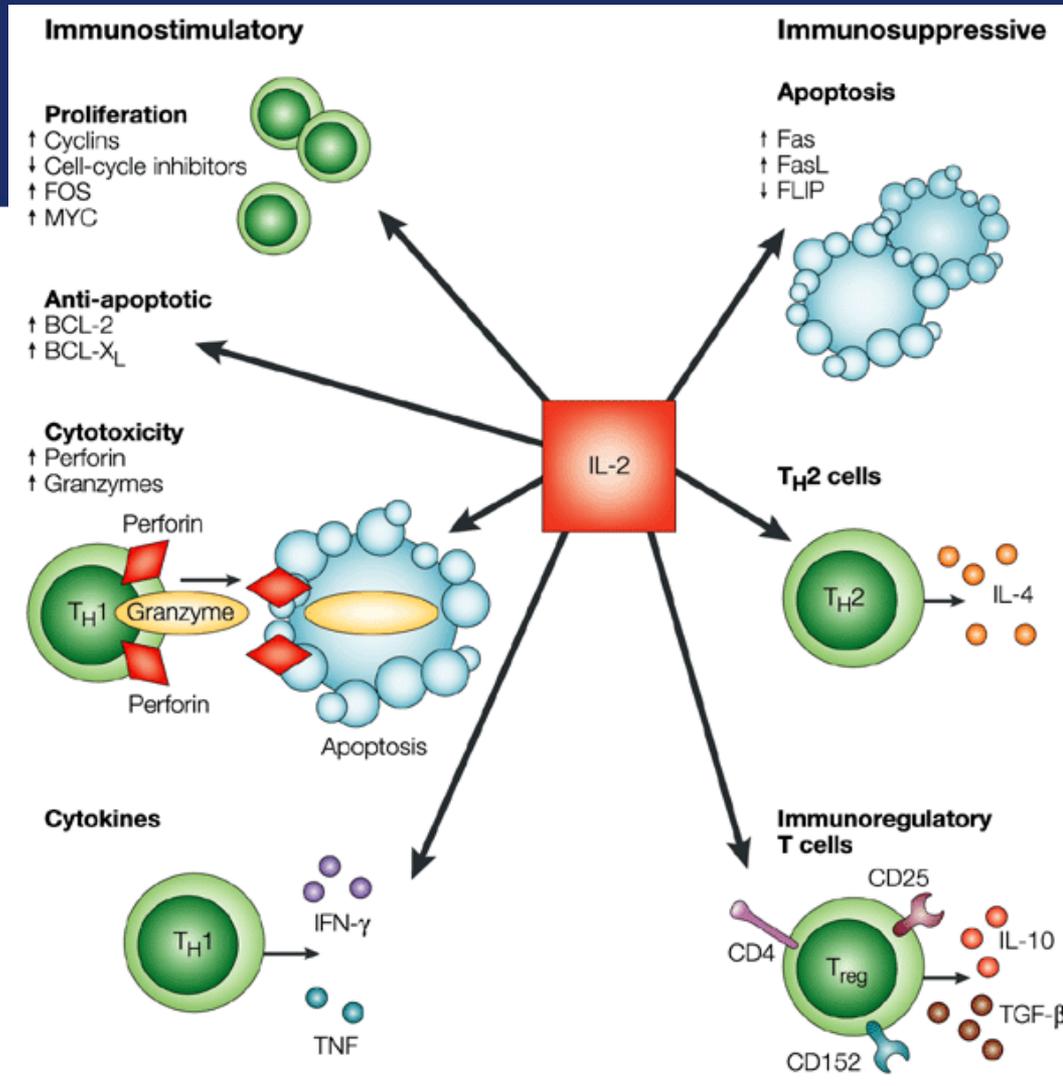
- substances secreted by immune cells
- function locally or at a distance to enhance or suppress immunity
- regulate NK cells, macrophages and neutrophils (innate immune system) + T cells and B cells (adaptive immune system)
- important for cancer:
  - IL1 $\beta$  (ineffective, but mediates toxicity of others)
  - TNF (promising but severe hypotension)
  - IL4 (minimal anti-cancer activity and toxic)
  - IL6 (some activity, but was a growth factor for meyloma cells)
  - GM-CSF (used primarily in SC transplants)
  - INF $\alpha$  (activity against RCC, melanoma, lymphoma, leukemia, Kaposi's sarcoma)
  - IL2 (activity against RCC, melanoma, lymphoma, leukemia)
  - IL12 (minimal anti-tumor activity as stand alone, but good as adjuvant)

# Interleukin 2



Nature Reviews | Immunology

# Interleukin 2

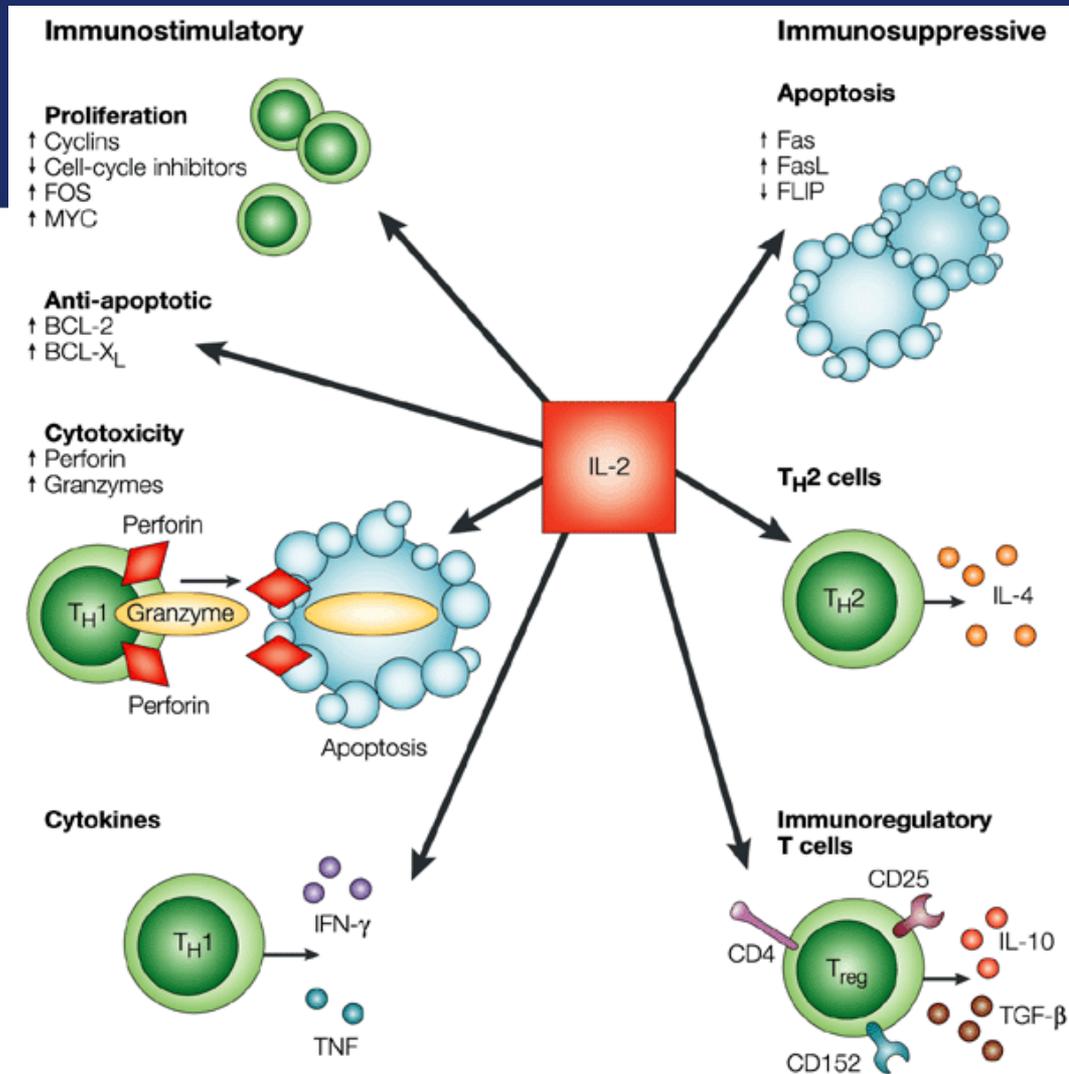


# Systemic interleukin 2

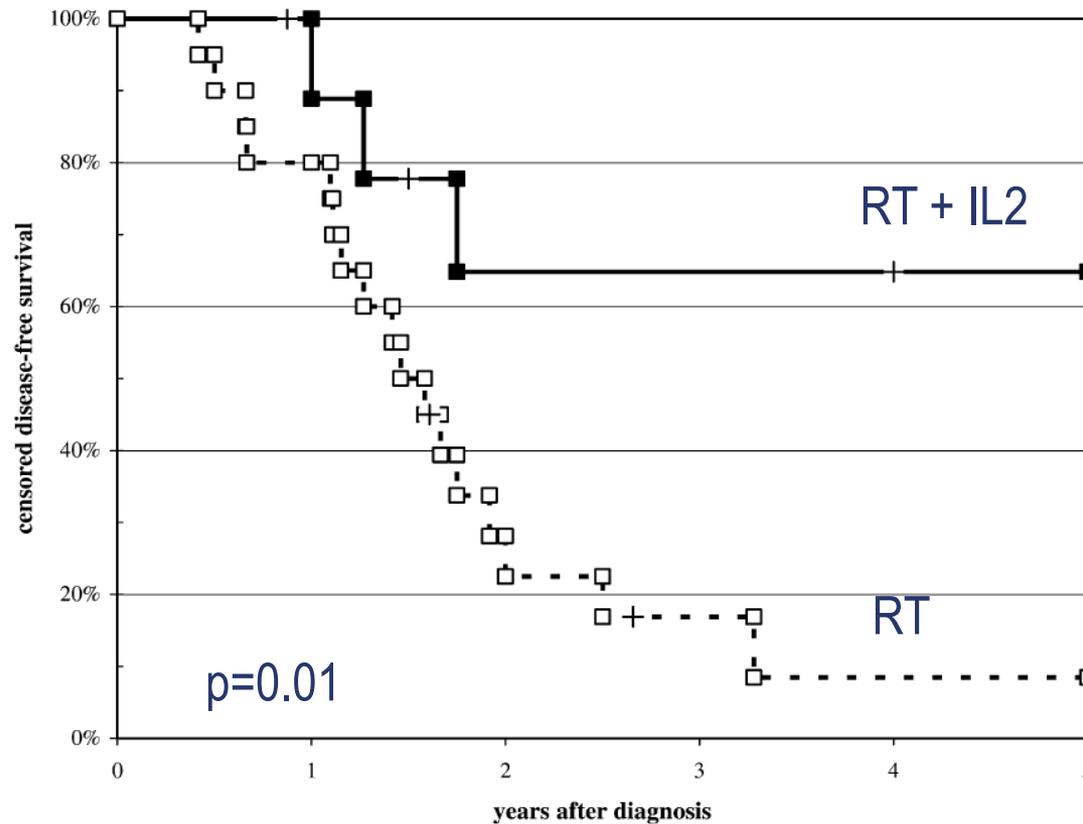
## Toxicity:

- Capillary leakage syndrom
- Severe flue-like symptoms
- Coma

Not used for systemic treatment in Europe

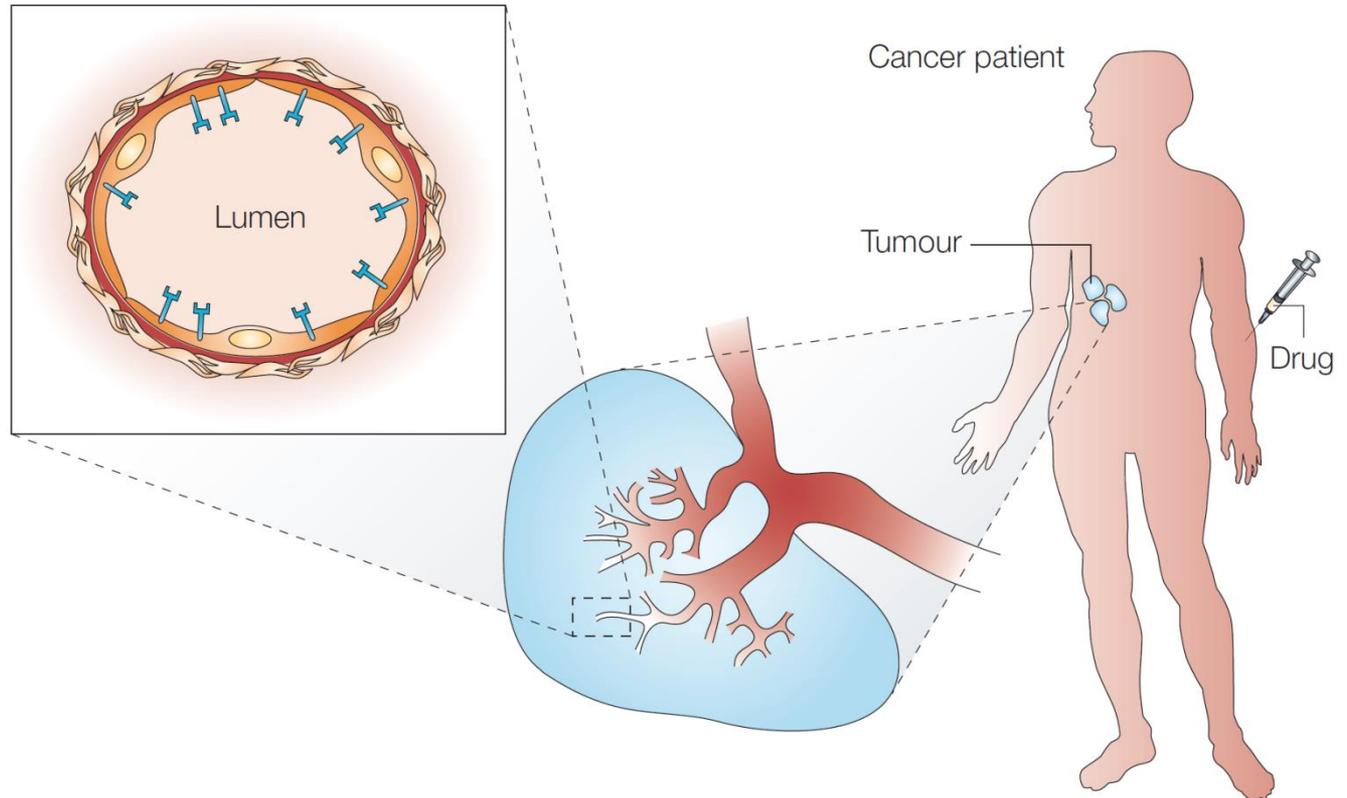


# Interleukin 2 intratumoral (nasopharyngeal carcinoma)

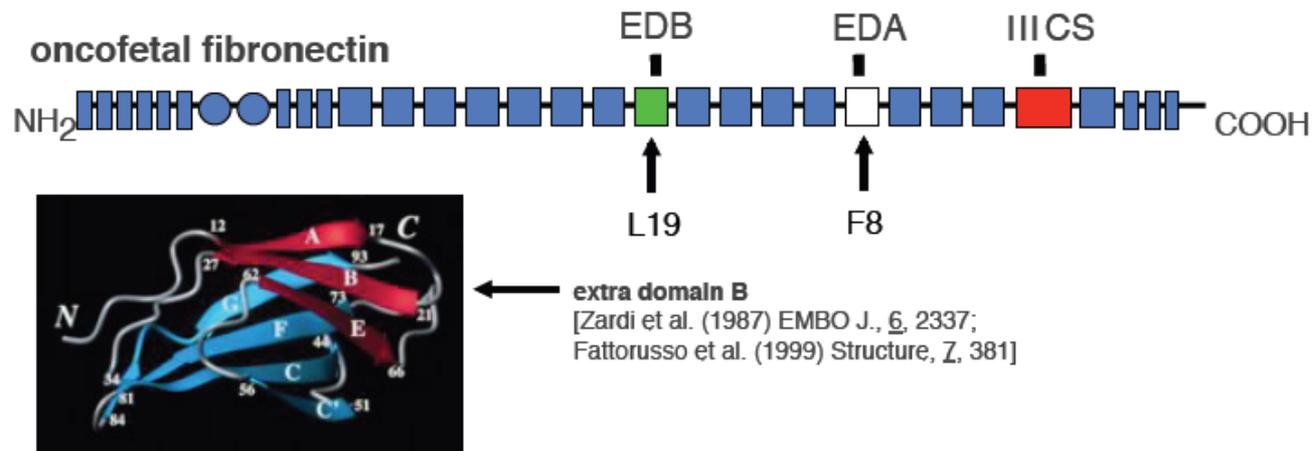


# Vascular targeting – L19

EDB

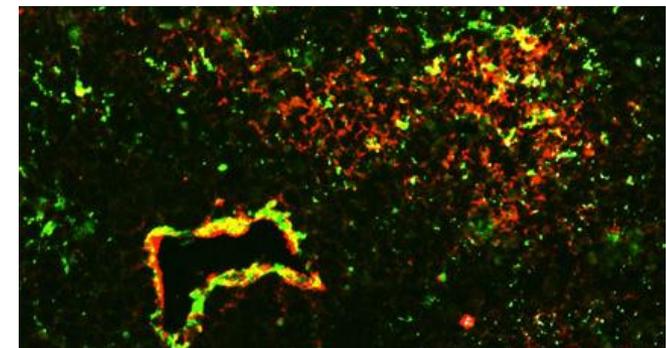


# Vascular targeting – L19

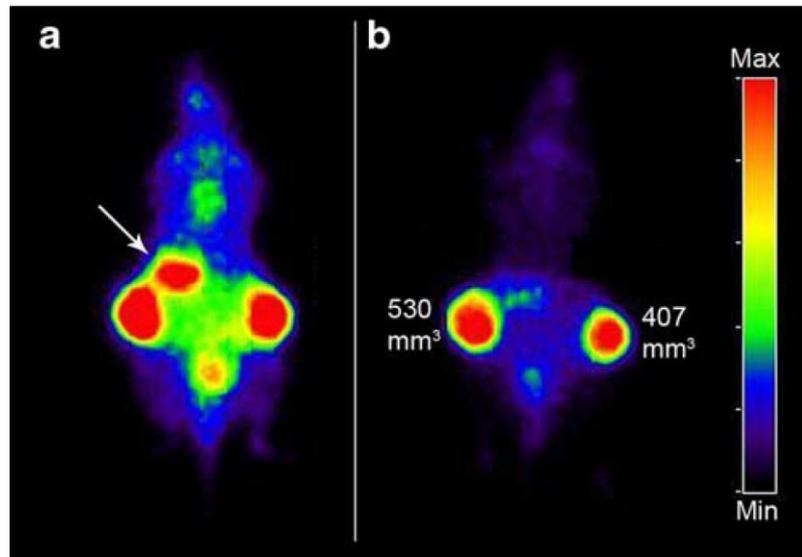


## Human single chain Fv mAb fragment L19

- Binding affinity ED-B (fibronectin)
- Specific for neovasculature
- Identical sequence in mouse and human

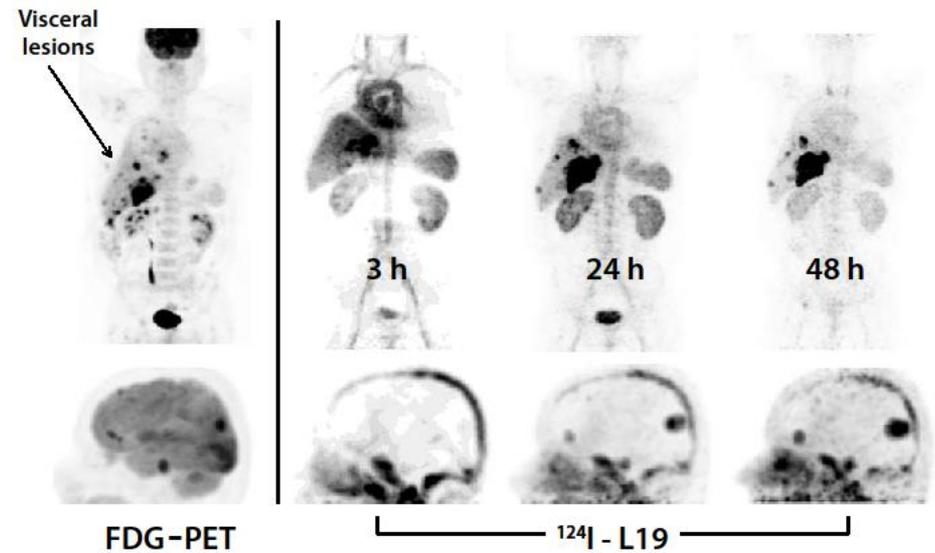


# $^{124}\text{I}$ -L19-SIP: PET imaging

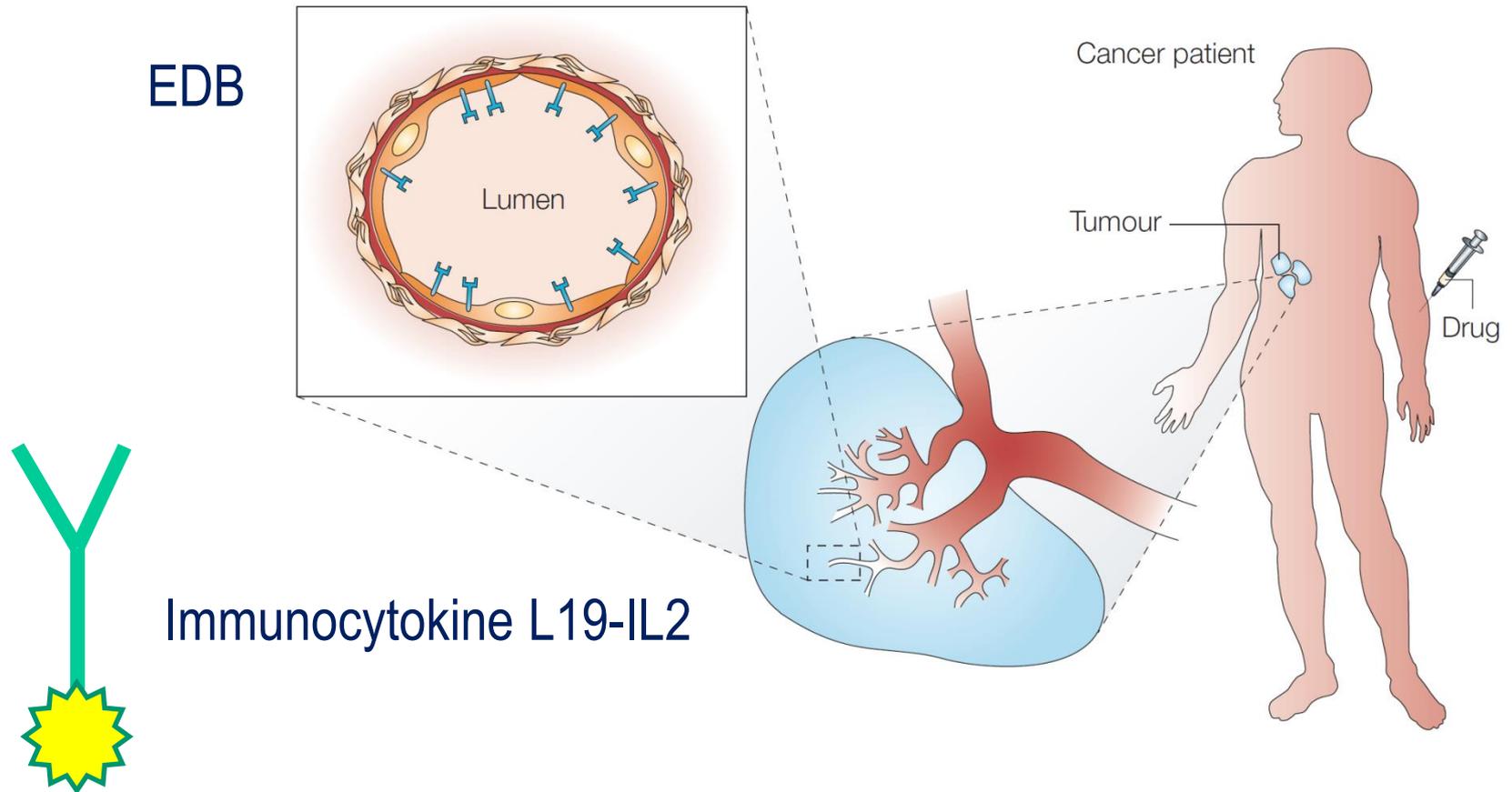


24 h

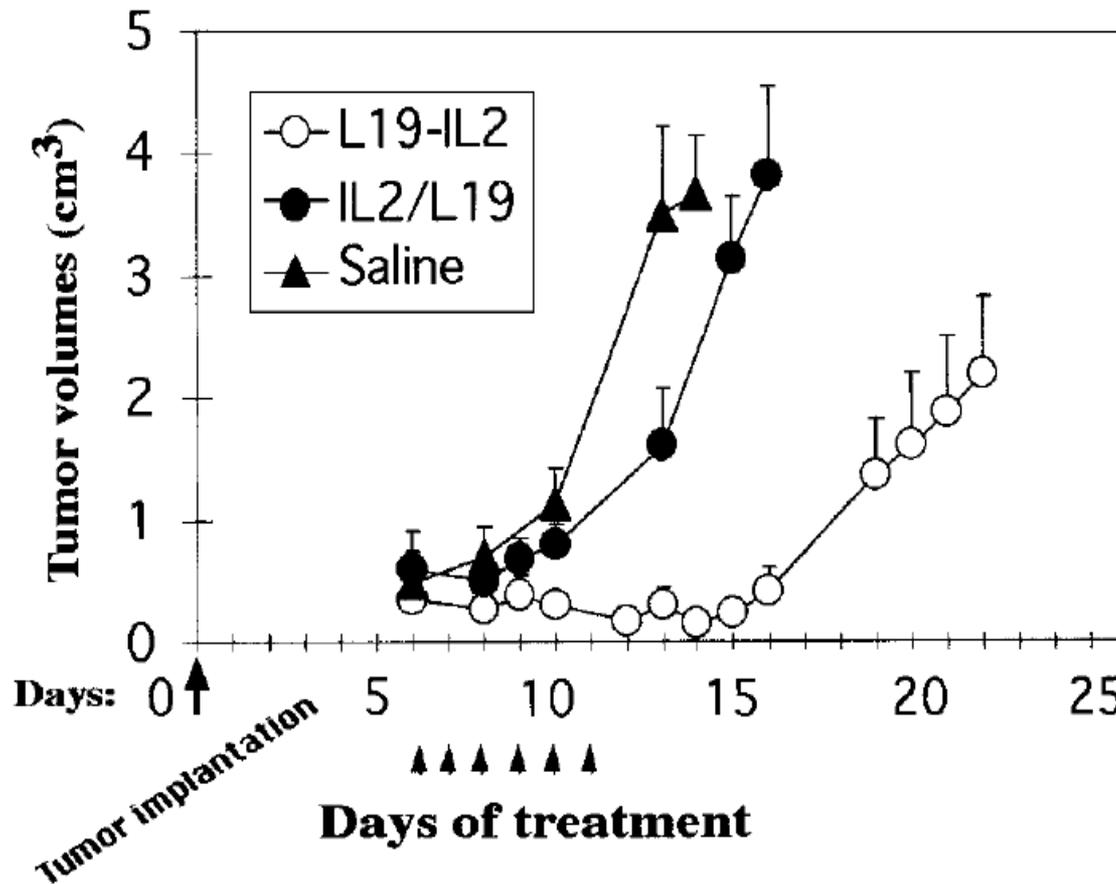
48 h



# L19 as “targeting vehicle” for selective tumoral delivery of IL2



# L19-IL2 enhanced therapeutic efficacy



# L19-IL2: combination with RT?!?!

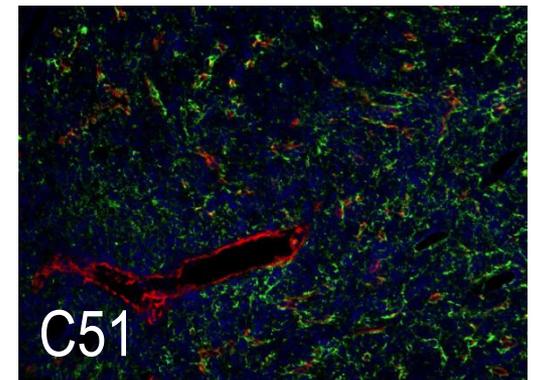
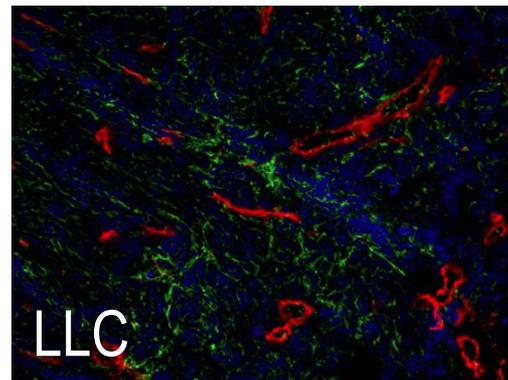
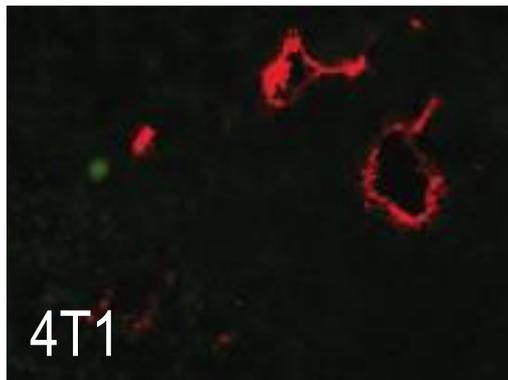
# L19-IL2: combination with RT?!?!

## Hypothesis

Radiotherapy combined with L19-IL2 induces a cytotoxic T-cell mediated anti-tumour immune response

# The models

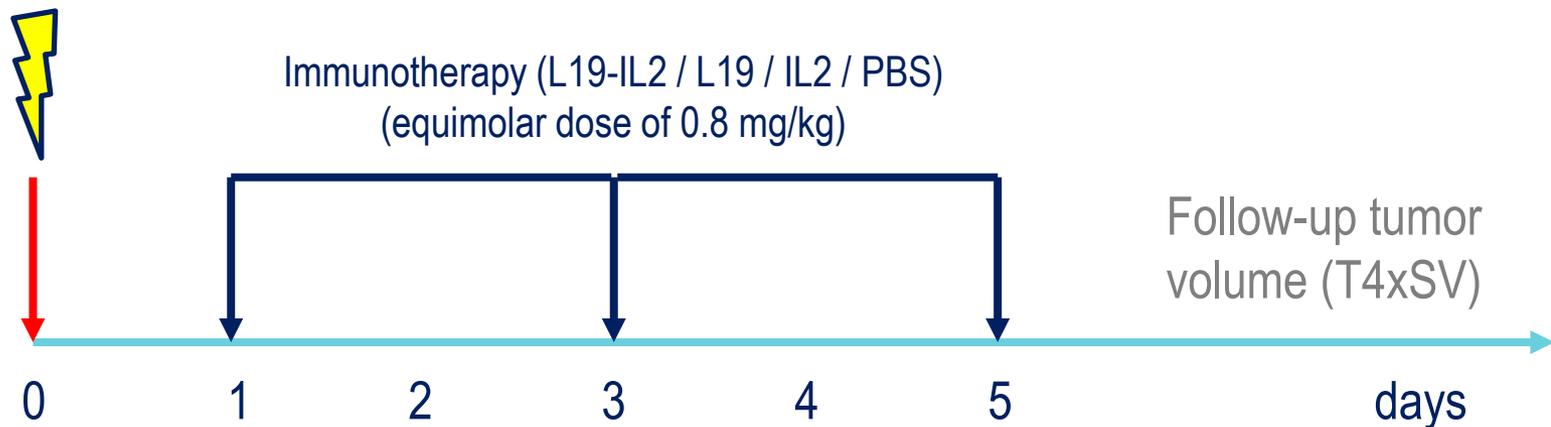
- C51 colon carcinoma in Balb/c immuno-competent mice
- Lewis Lung Carcinoma in C57Bl/6J immuno-competent mice
- 4T1 breast Carcinoma in Balb/c immuno-competent mice



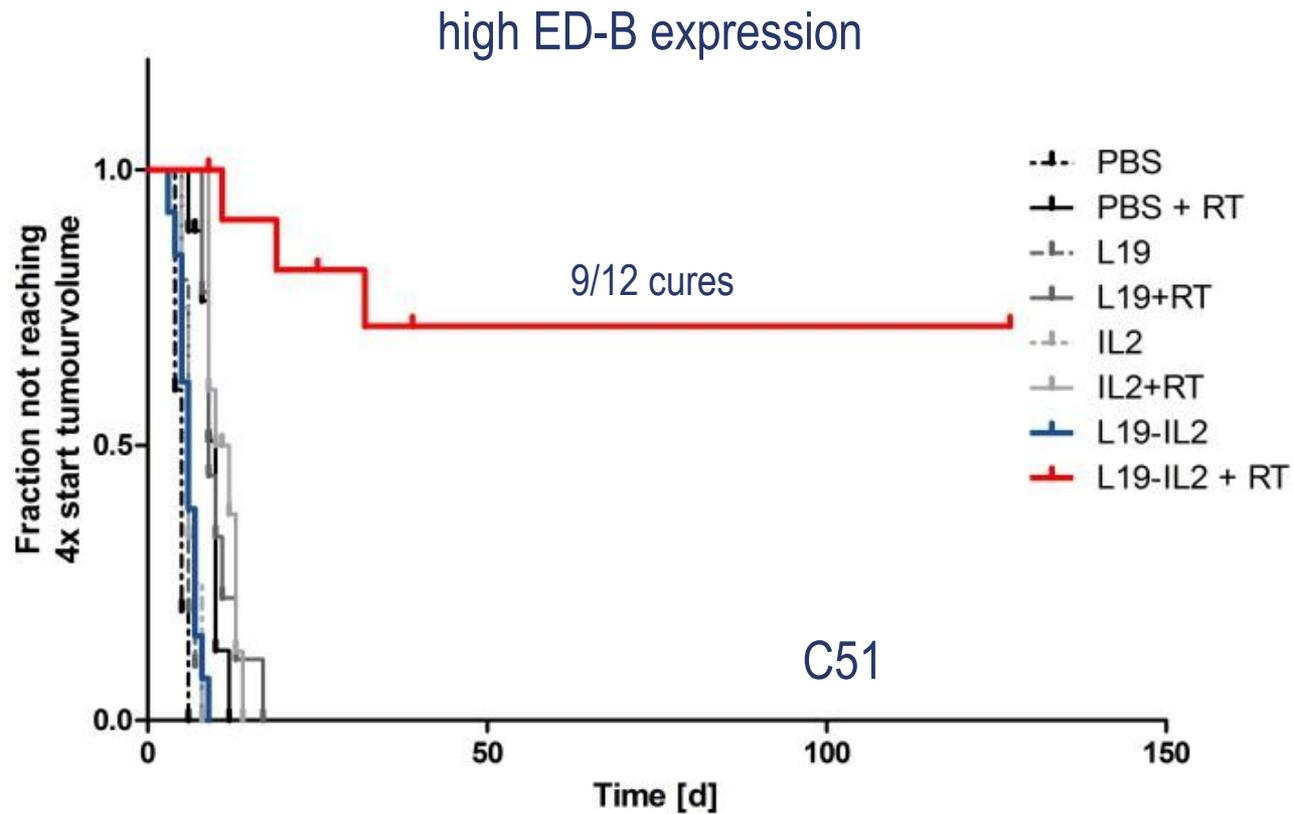
Green-EDB  
Red- CD31

# Bi-modal treatment: experimental design

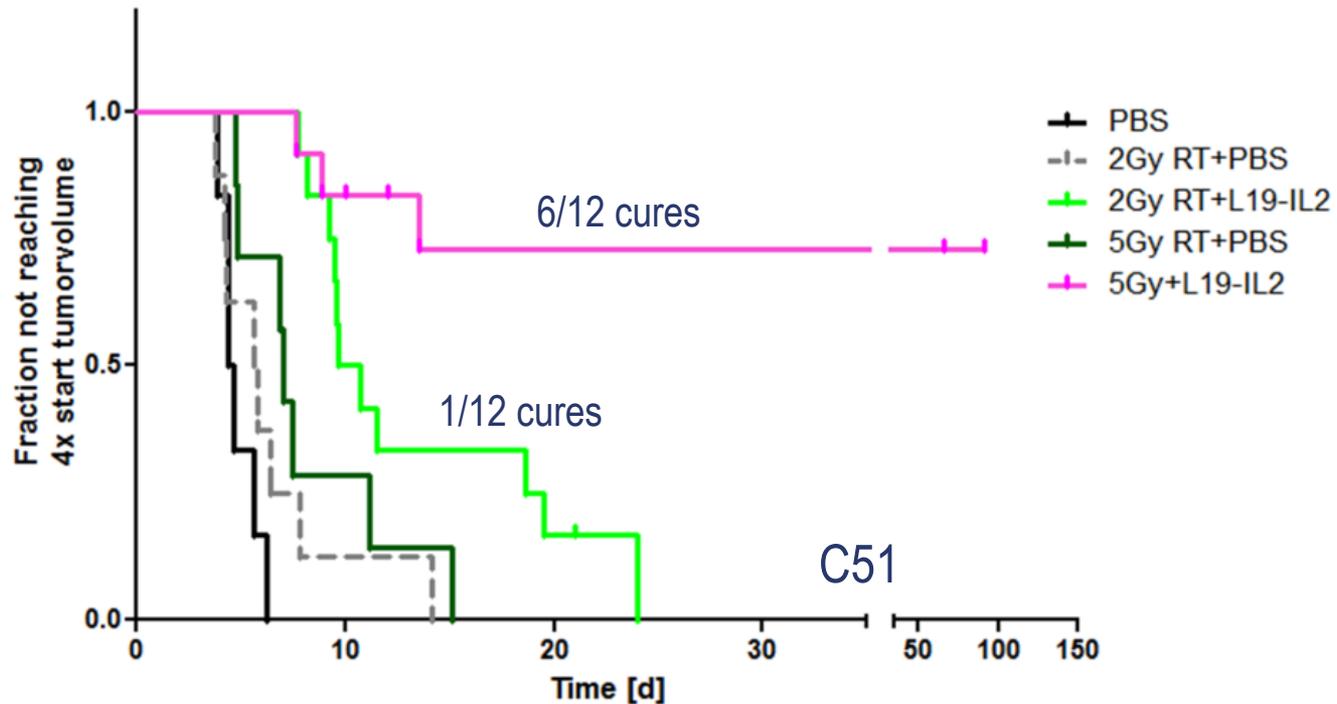
Start experiment – day 0: tumour starting volume of approximately 250mm<sup>3</sup>



# Bi-modal treatment results in convincing tumor response

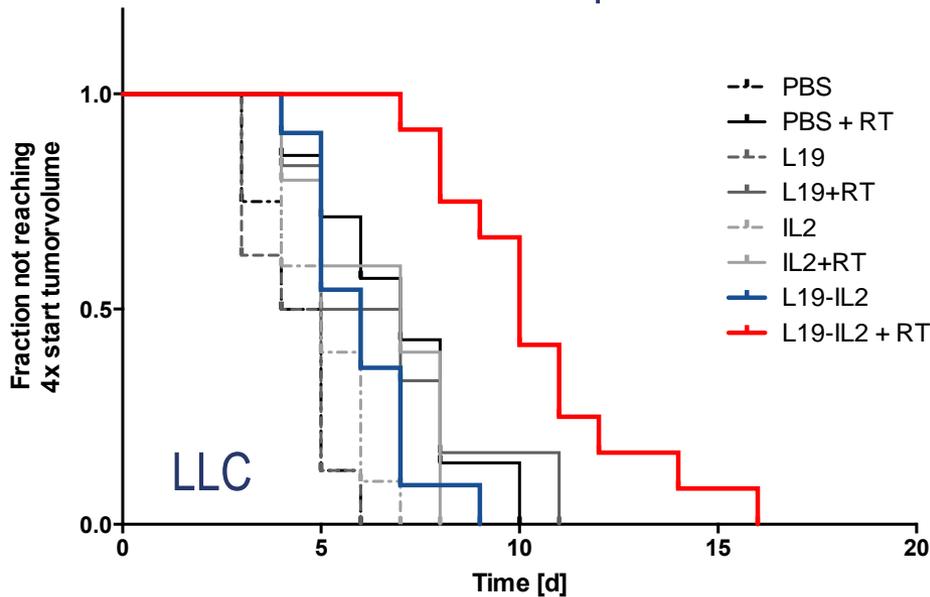


# Number of cures depends on trigger dose

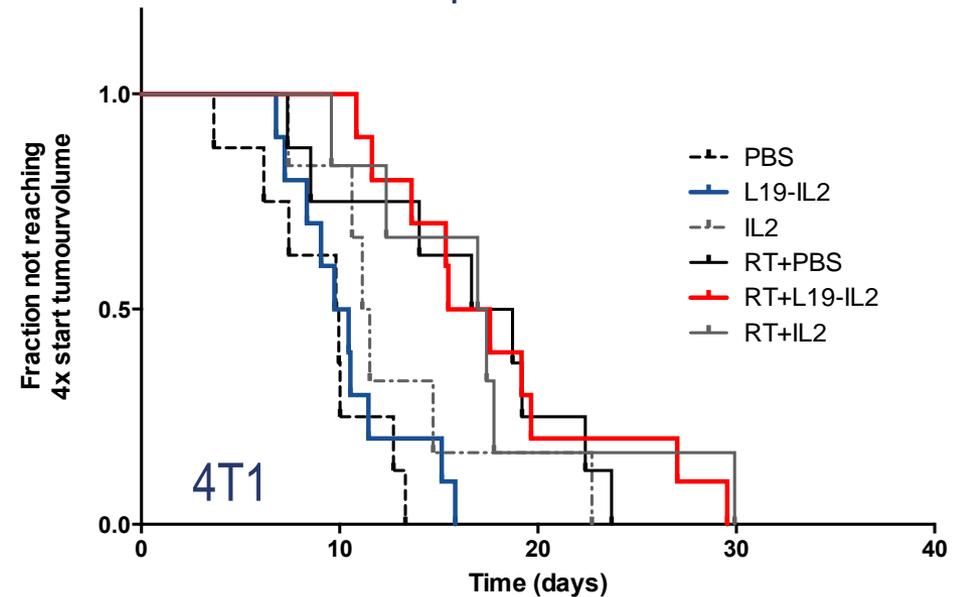


# Tumor response dependent on ED-B presence

intermediate ED-B expression



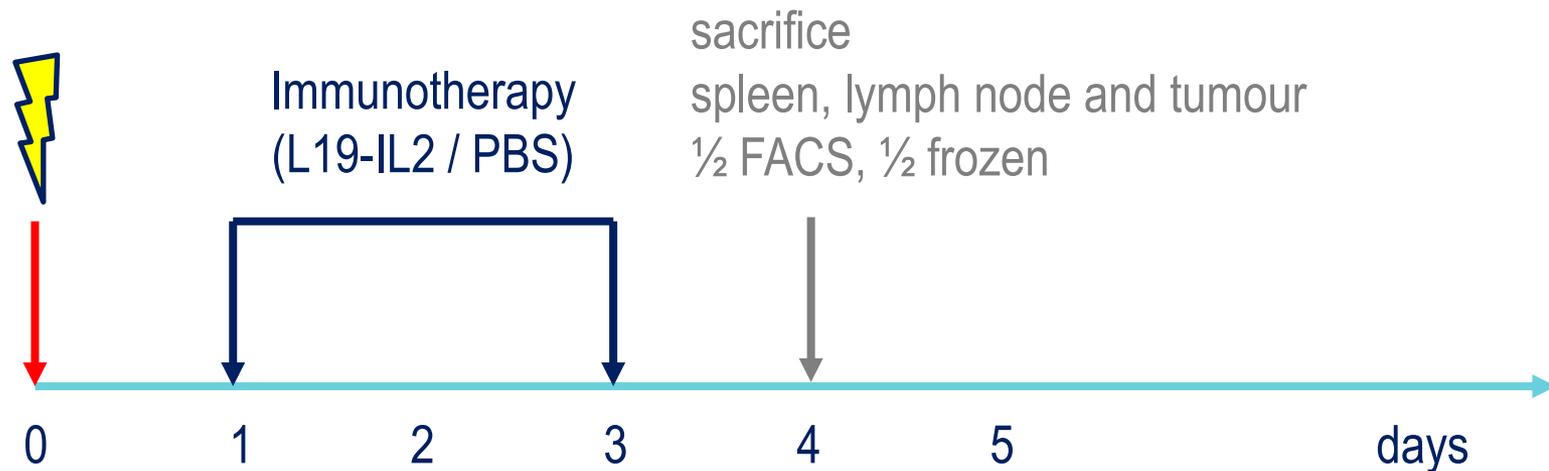
ED-B expression absent



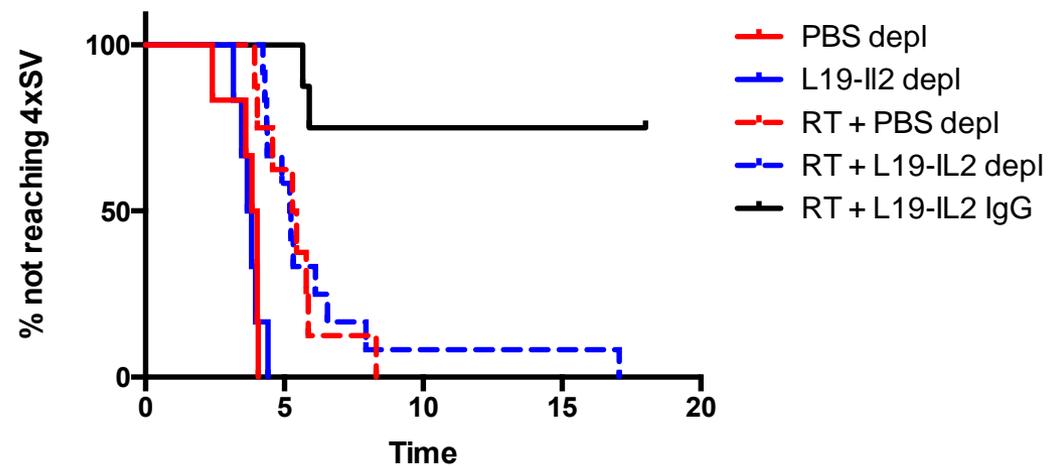
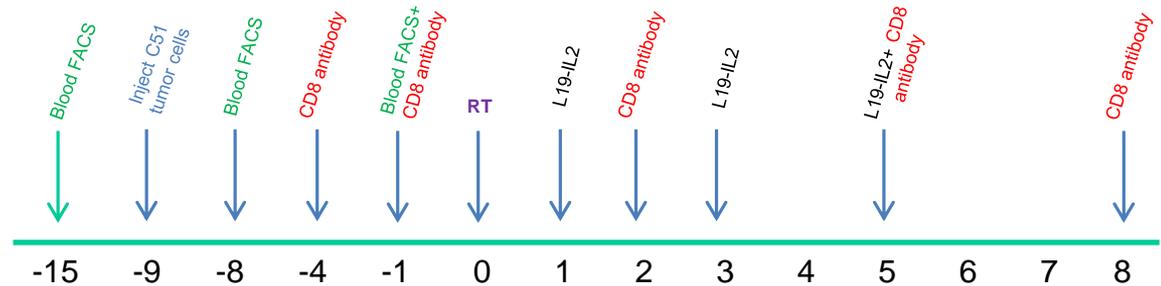
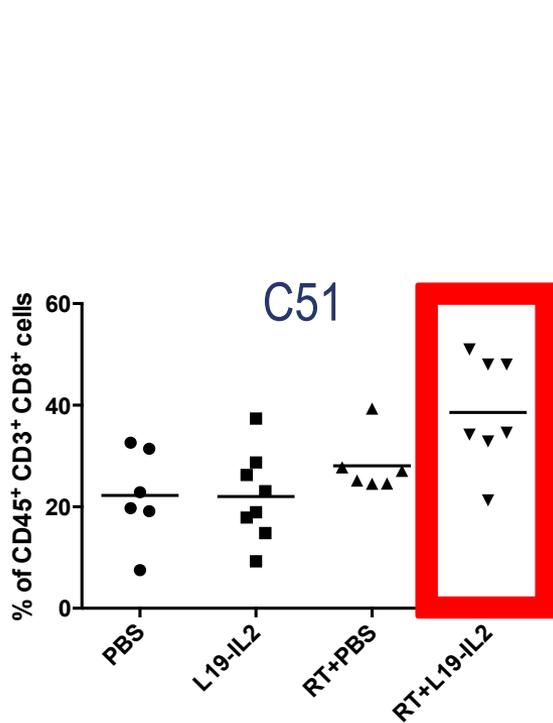
# Mechanisms



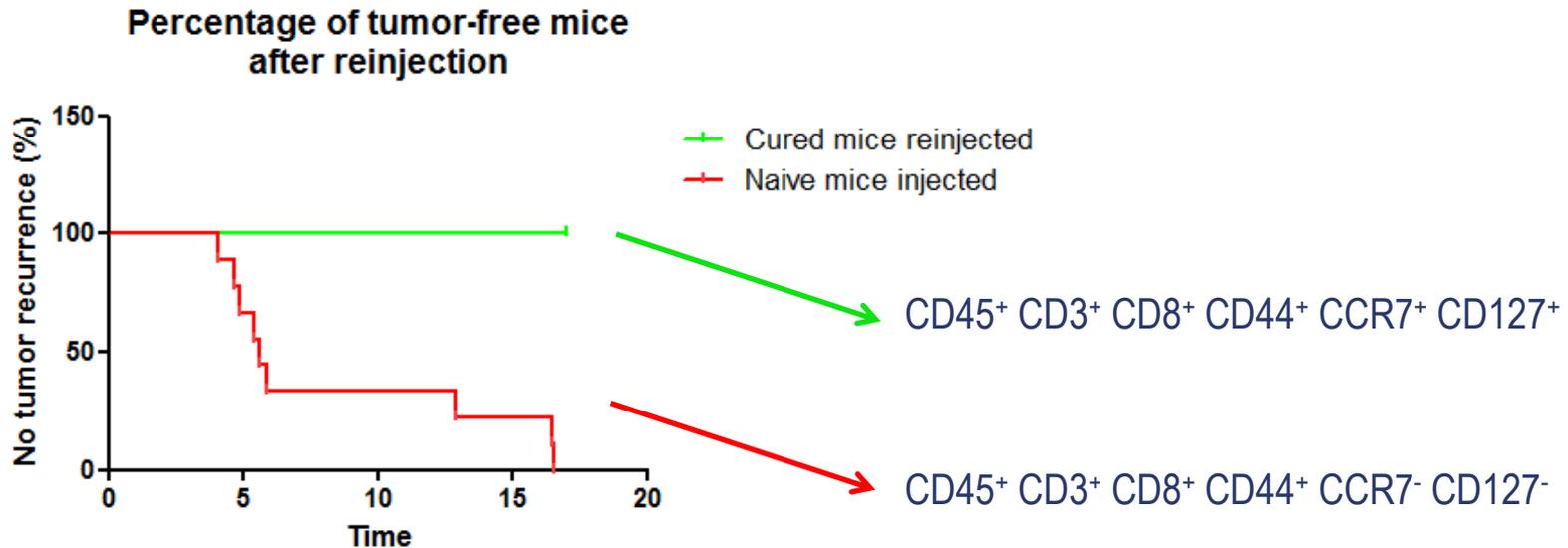
# Bi-modal treatment: experimental design



# Tumor response causally related to cytotoxic T cells presence

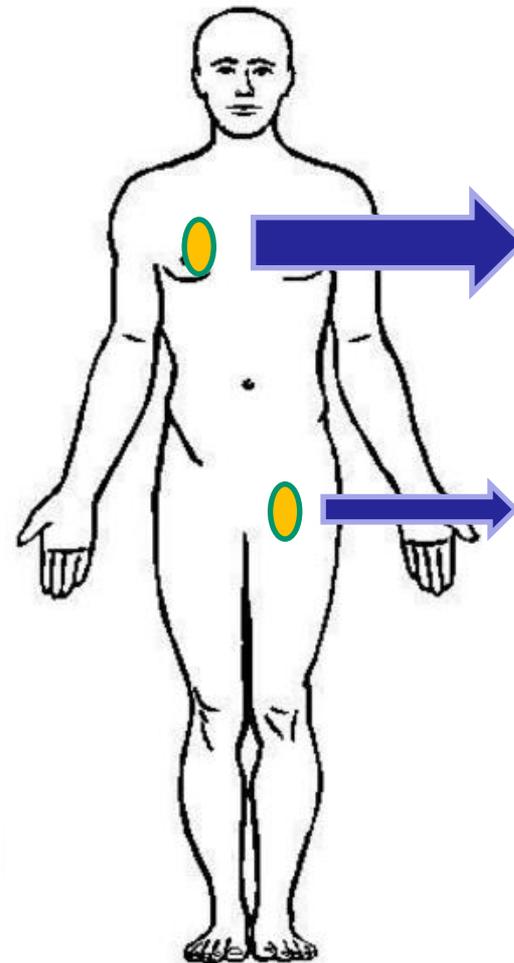
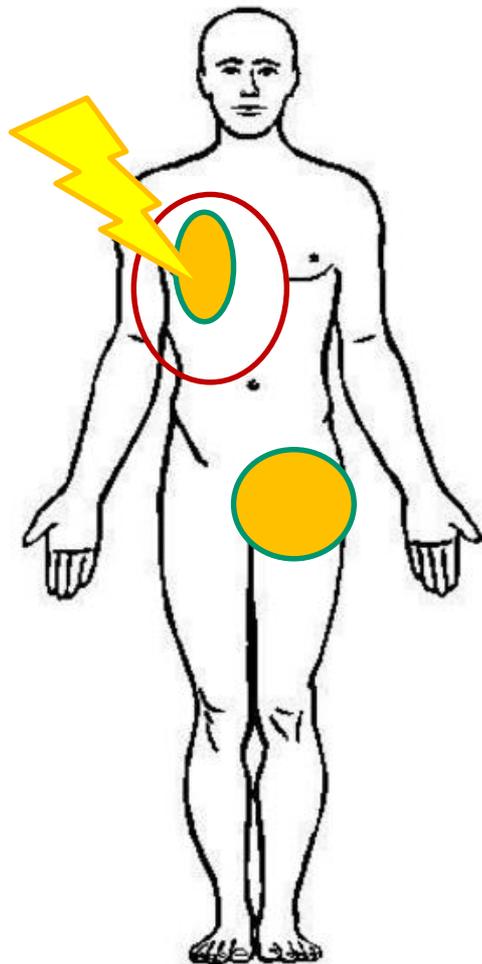


# Central memory effect upon cure (re-challenge after 150 days)



Tn	TcM	TeM	Teff
CCR7+	CCR7+	CCR7-	CCR7-
CD127+	CD127+	CD127+	CD127-
CD44-	CD44+	CD44+	CD44+

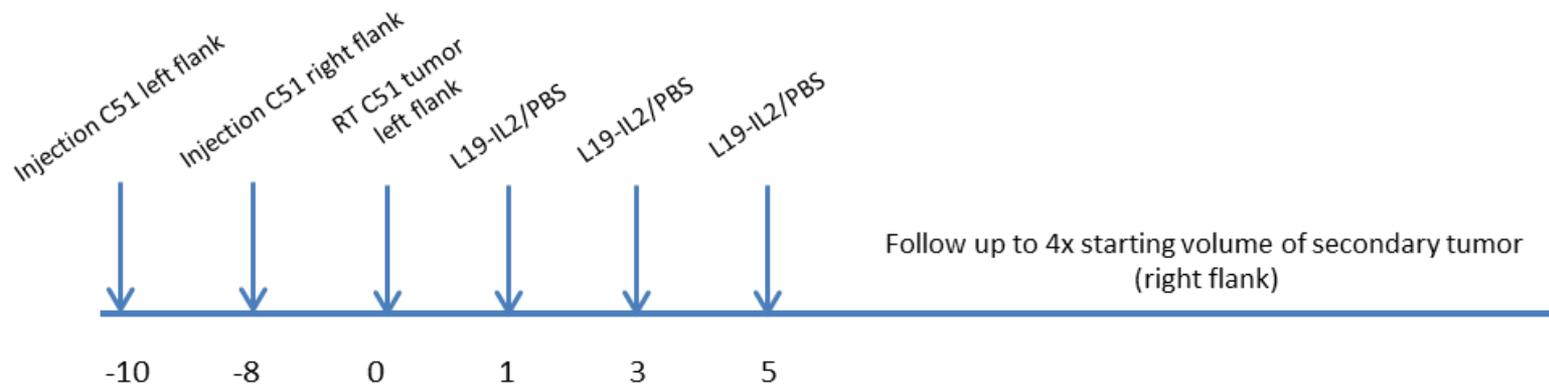
# Abscopal effect



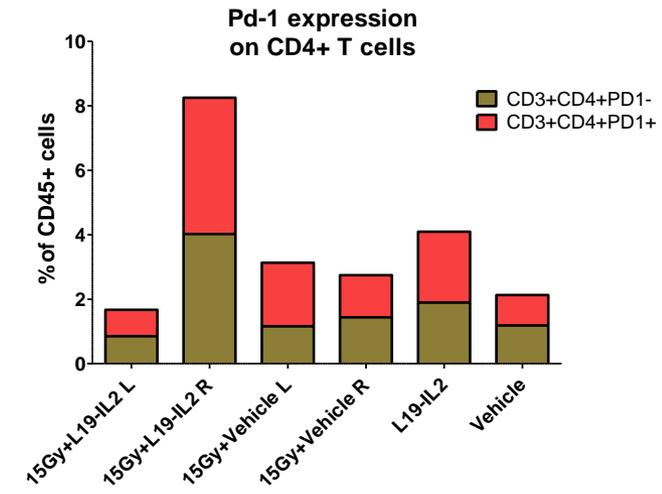
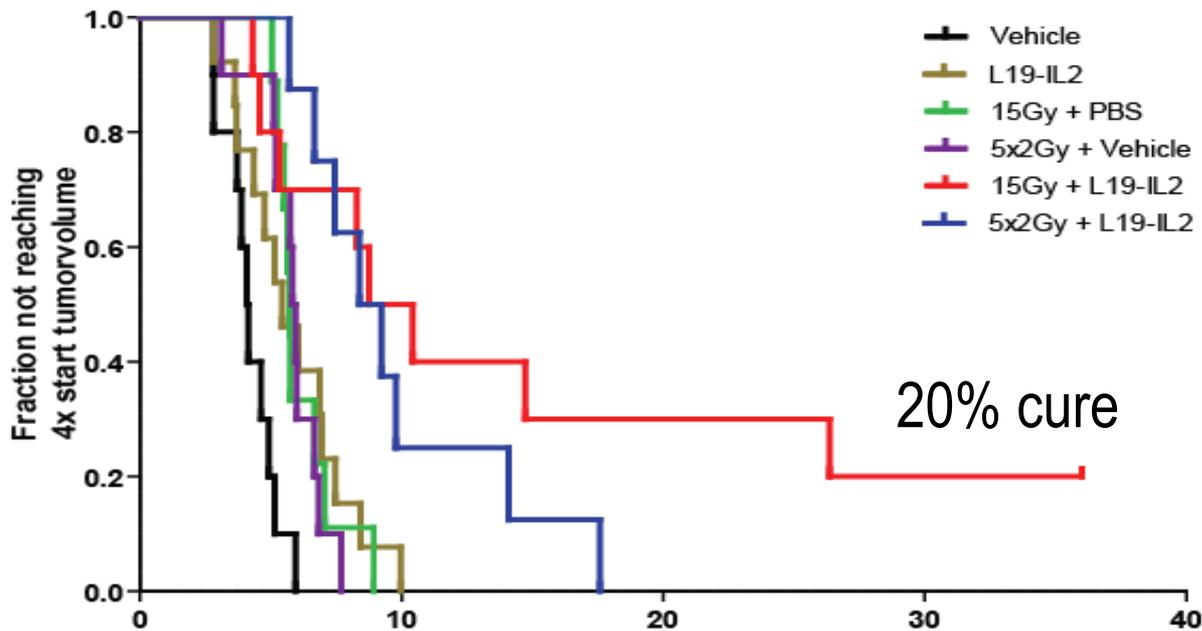
Radiotherapy  
response

“Abscopal”  
response

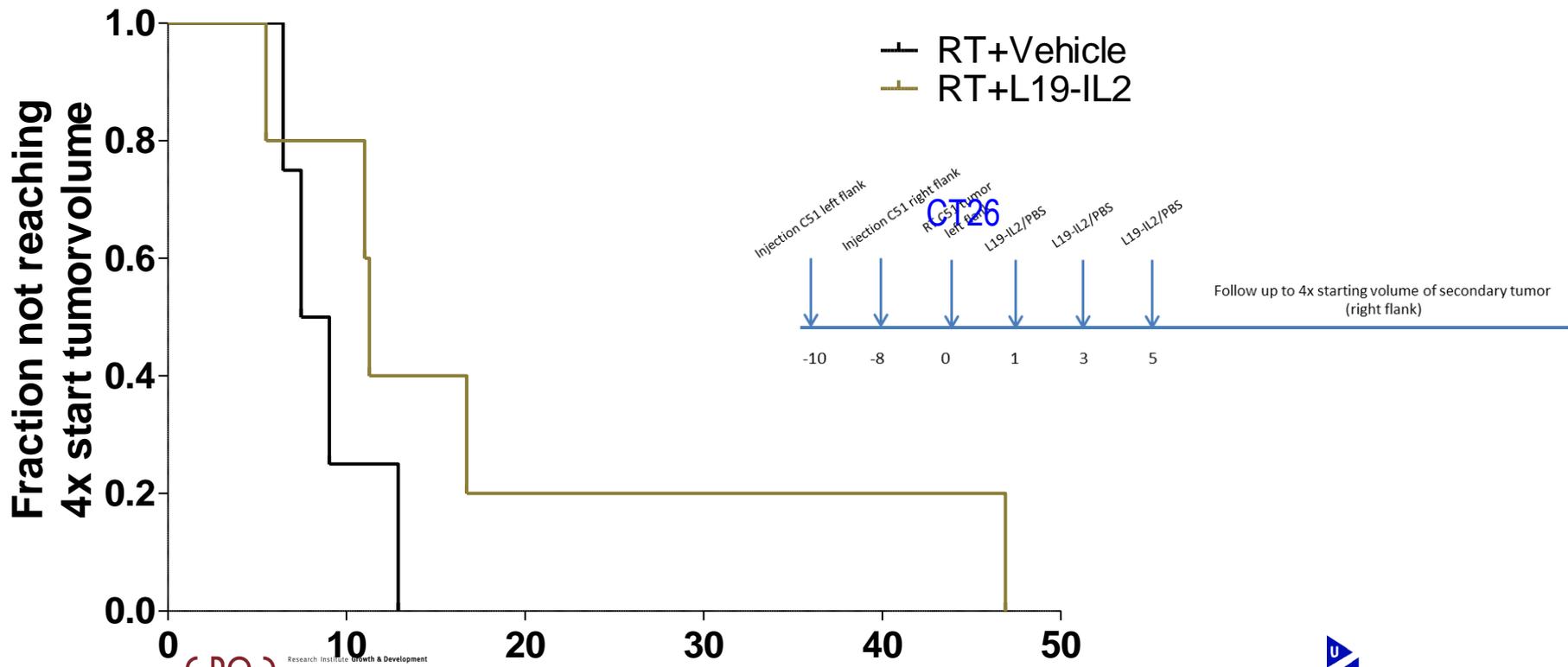
# Abscopal effect



# Abscopal effect: an effect of CD4<sup>+</sup> T-cells?



# Abscopal effect: a general phenomenon?



# Abscopal effect: human evidence?

van den Heuvel *et al.* *Journal of Translational Medicine* (2015) 13:32  
DOI 10.1186/s12967-015-0397-0



JOURNAL OF  
TRANSLATIONAL MEDICINE

RESEARCH

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## NHS-IL2 combined with radiotherapy: preclinical rationale and phase Ib trial results in metastatic non-small cell lung cancer following first-line chemotherapy

Michel M van den Heuvel<sup>1\*</sup>, Marcel Verheij<sup>2</sup>, Rogier Boshuizen<sup>1</sup>, José Belderbos<sup>2</sup>, Anne-Marie C Dingemans<sup>3</sup>, Dirk De Ruyscher<sup>4</sup>, Julien Laurent<sup>5</sup>, Robert Tighe<sup>6</sup>, John Haanen<sup>1</sup> and Sonia Quarantino<sup>5,7</sup>

### Clinical outcome

No objective responses were observed during the trial, based on RECIST v1.0 criteria for tumor response, PFS, and OS. Median PFS was 2.9 months (95% confidence interval [CI] 1.5; 3.1) and median OS was 8.6 months (95% CI 4.9; not evaluable). As of the day of reporting there are 2 long-term survivors (both in good performance status 4 years after start of first-line chemotherapy). One patient discontinued treatment with NHS-IL2 in November 2013 and there were still no signs of disease activity in August 2014. Of note, both long-term survivors developed thyroiditis during treatment.

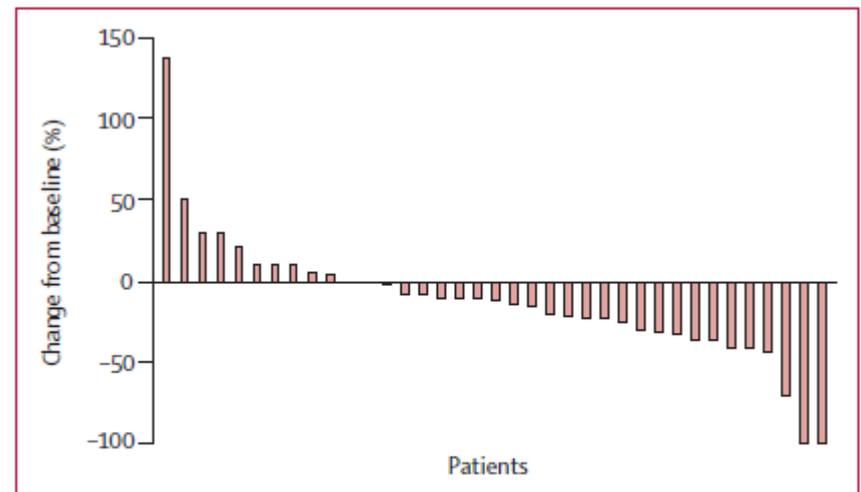
# Abscopal effect: human evidence?

## Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial



*Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponso, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti*

- Abscopal responses in 11/41 patients



**Figure 2: Waterfall plot of best abscopal responses**  
The plot shows the percent change from baseline in the best responding abscopal lesions. Each bar represents the best abscopal response for one patient.

# **Future perspectives**

*Clinical phase I trial*

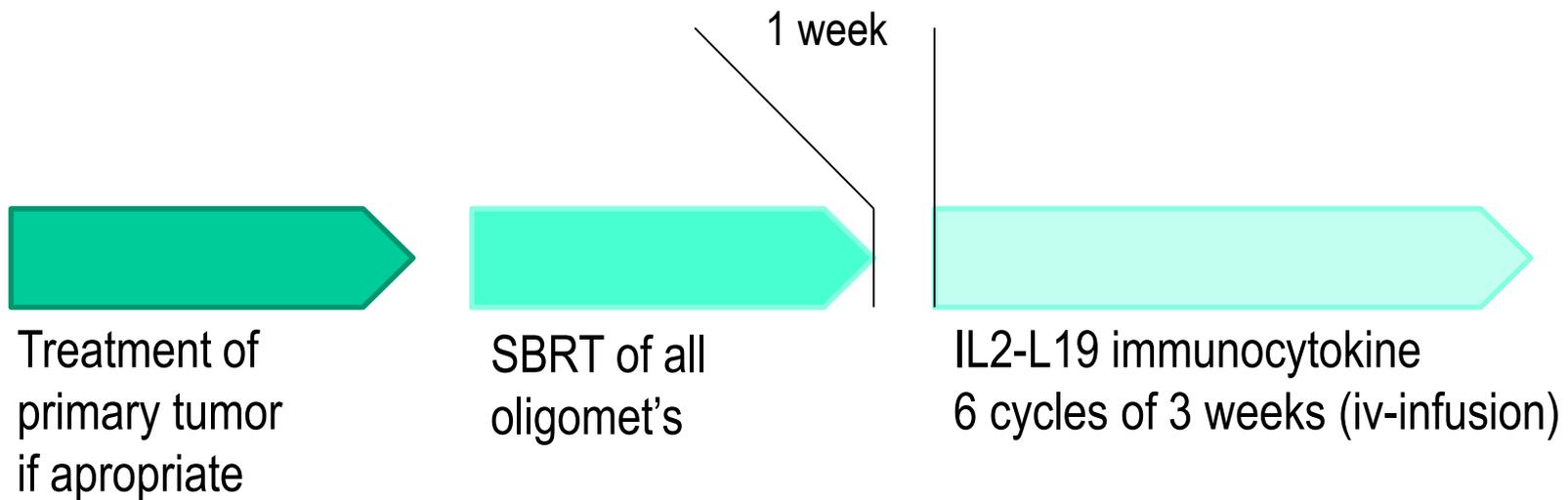
# Inclusion/exclusion criteria

## Patient profile:

- Synchronous or metachronous **oligometastatic** solid tumor (NSCLC, RCC, HNSCC, CRC, melanoma)
- **Referred for SABR**
- **$\geq 2$  and  $\geq 5$  metastatic sites**
- Adequate bone marrow, hepatic and renal function
- Life-expectancy > 3 months
- Capable of complying with study procedures

# General overview

## Phase I « 3 + 3 » design



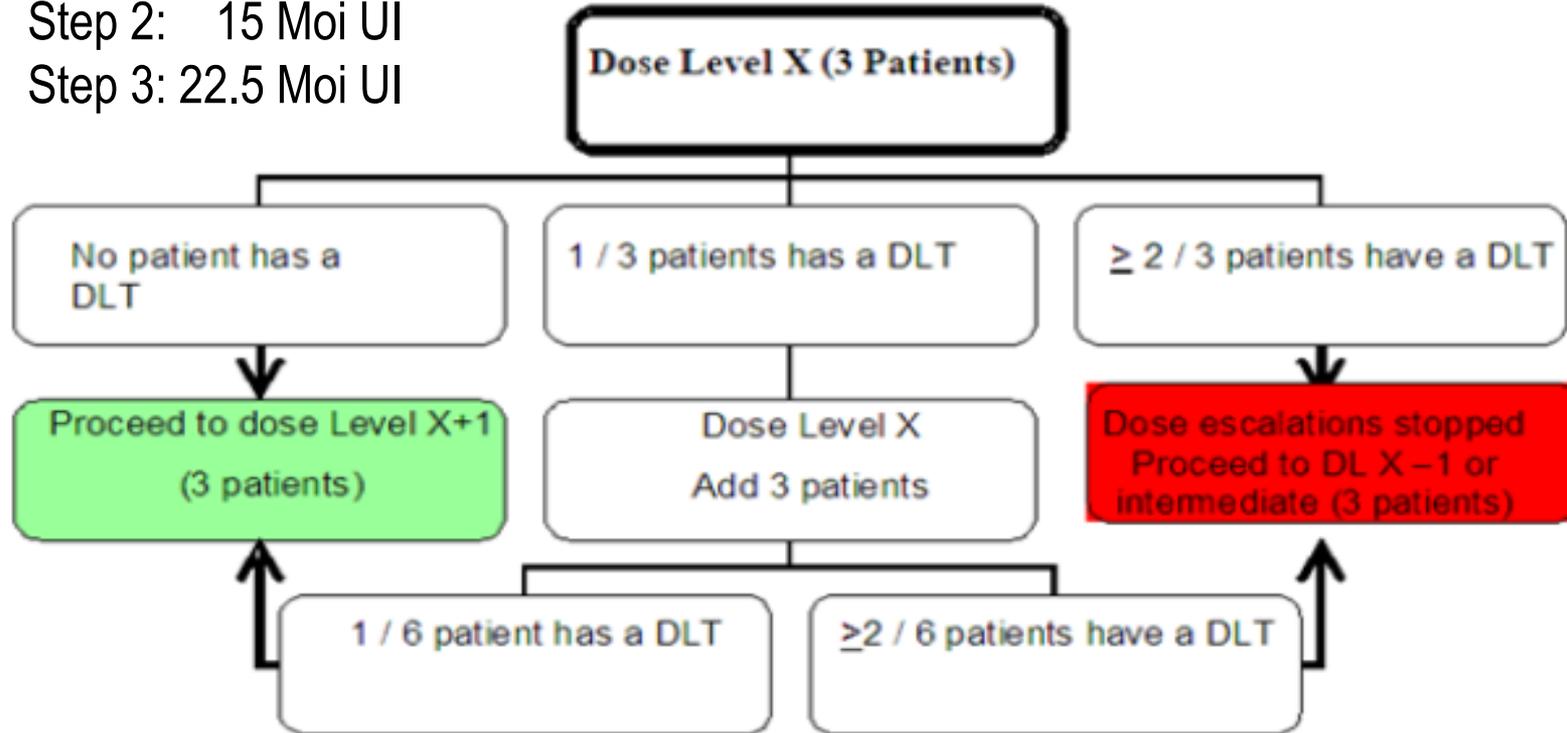
# Dose and dose escalation

Phase I: « 3 + 3 design »

Step 1: 10 Moi UI

Step 2: 15 Moi UI

Step 3: 22.5 Moi UI



## Conclusions – L19-IL2

- IR + L19-IL2 significantly enhances cytotoxic T-cell differentiation resulting in a long-lasting anti-tumor immunity
- Tumor response is dependent on levels of ED-B expression and is causally related to cytotoxic T-cell presence
- RT + L19-IL2 results in tumor-specific CD4+ T-cell dependent abscopal effect
- RT + L19-IL2 phase 1 trial is open for inclusion: NCT02086721

# Acknowledgements

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(MAASTRO), Maastricht, The Netherlands

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Biosciences, Zurich, Switzerland

- Dario Neri
- Francesca Pretto

**Philogen**  
innovating targeting

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- Gerard Bos