<Carmen Scheibenbogen>

The following relationships exist related to this presentation:

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Cancer vaccines 2007

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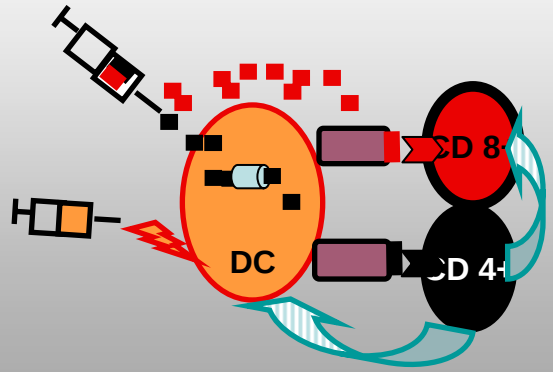
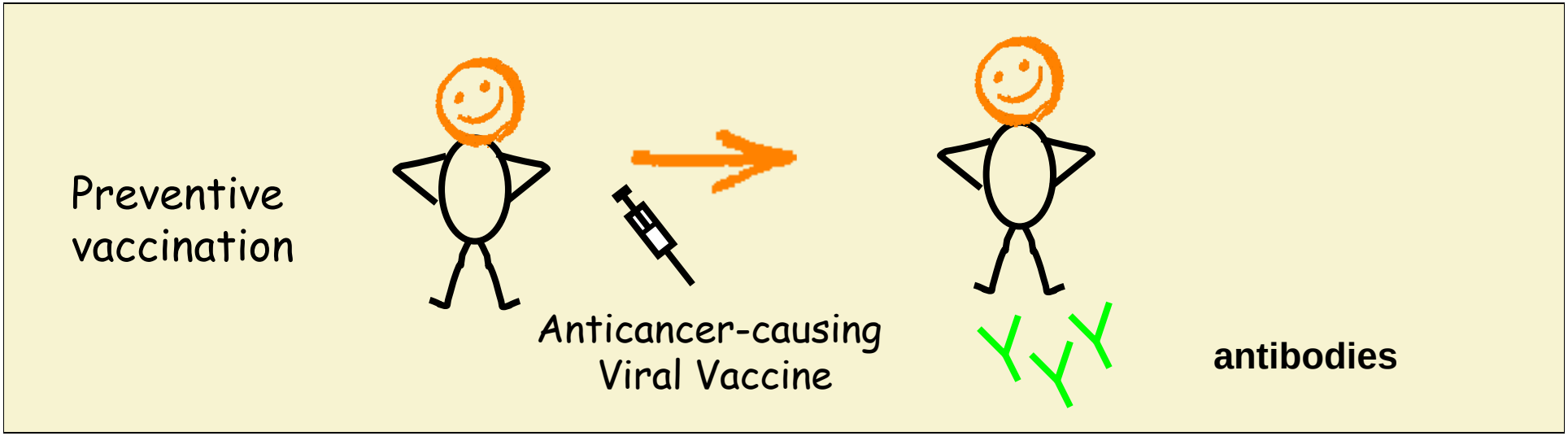
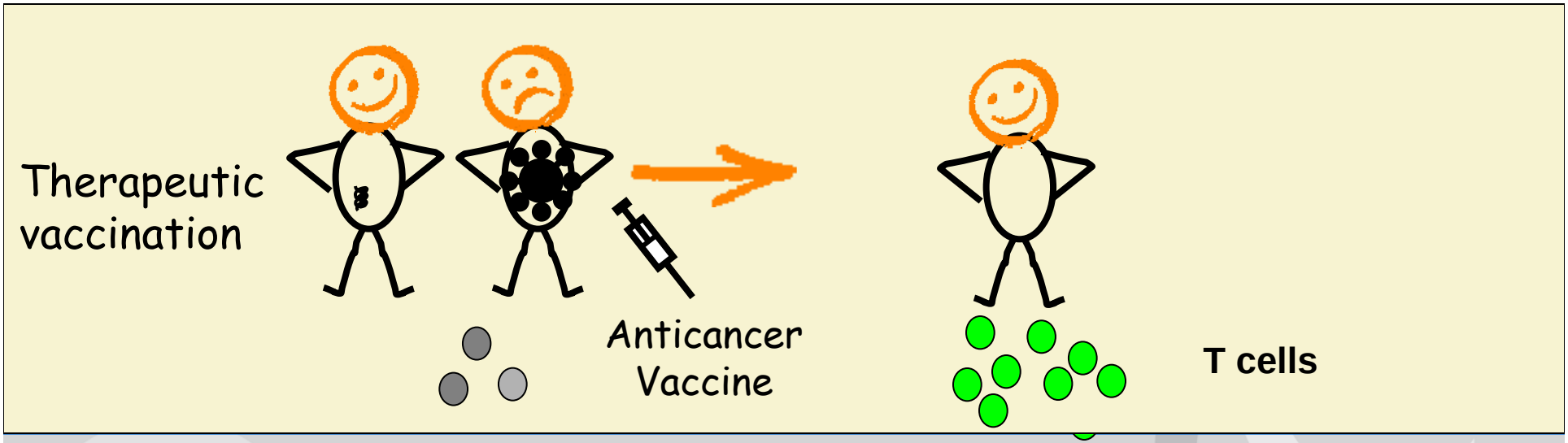
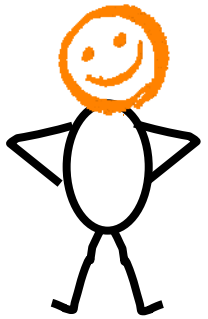


Anti-cancer vaccines





Preventive cancer vaccines

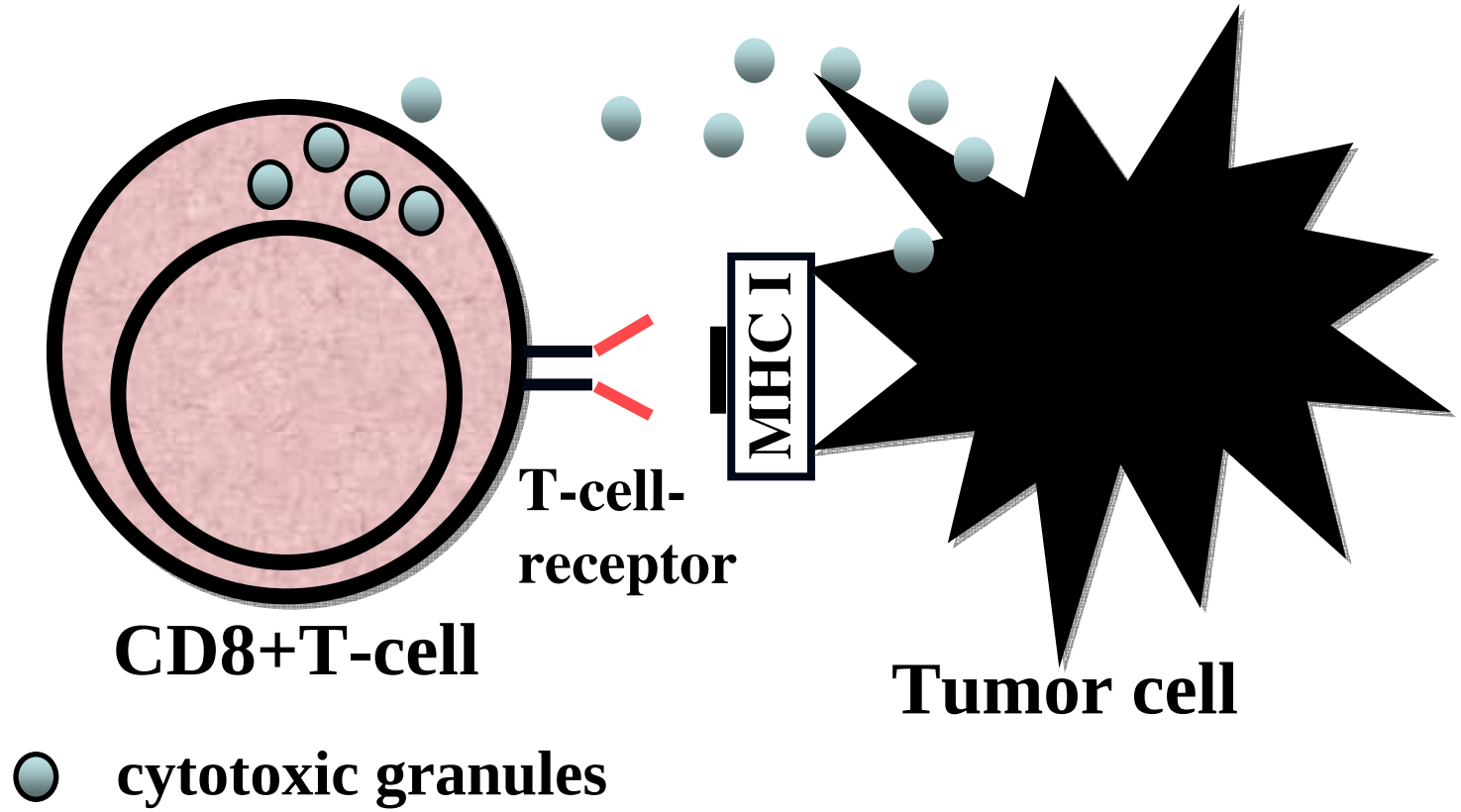


- Prevention of hepatocellular carcinoma by hepatitis B vaccination (Chang MH, NEJM, 1997)
- Prevention of cervical cancer by HPV16/18 vaccine (Ault KA, Lancet, 2007)

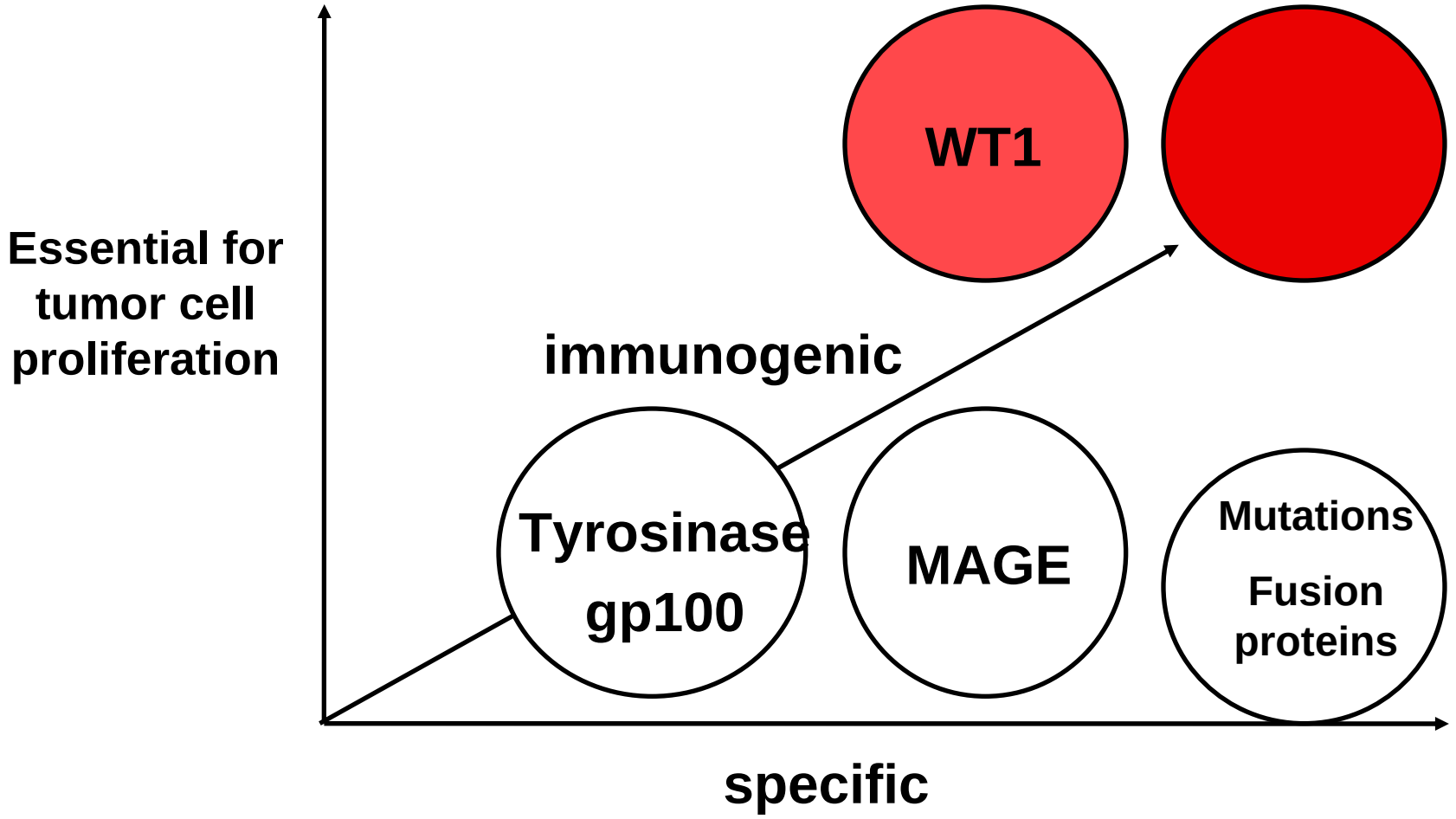
Therapeutic cancer vaccines

1. Principles
2. Clinical trials - current status
3. Future directions

Tumor cells can be recognized and destroyed by CD8+ T cells,
thus a therapeutic vaccine needs to activate T cells recognizing tumor antigens



Hierarchy of tumor antigens as suitable treatment targets



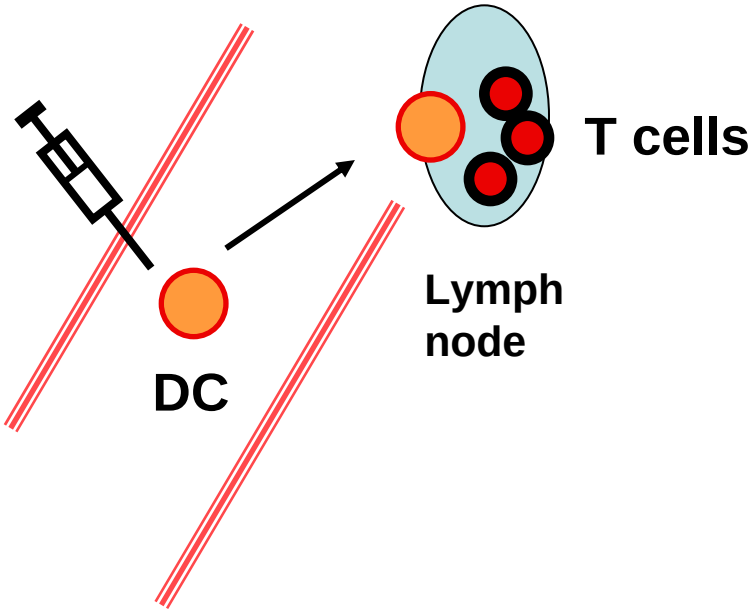
Cancer vaccine- Composition

1. Tumor antigen
- whole cell
- synthetic +/- dendritic cells

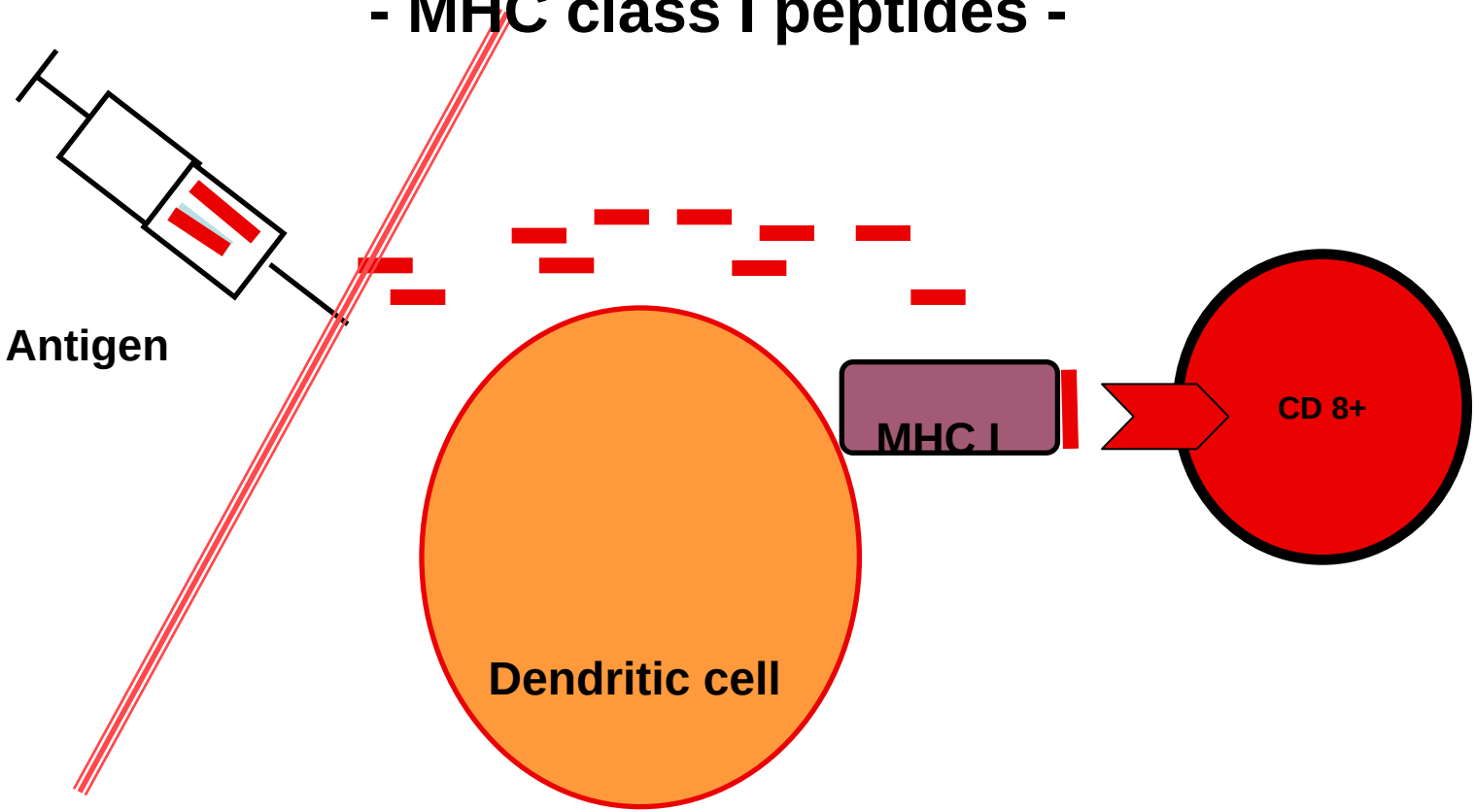
2. Adjuvants
3. Antigen delivery

A

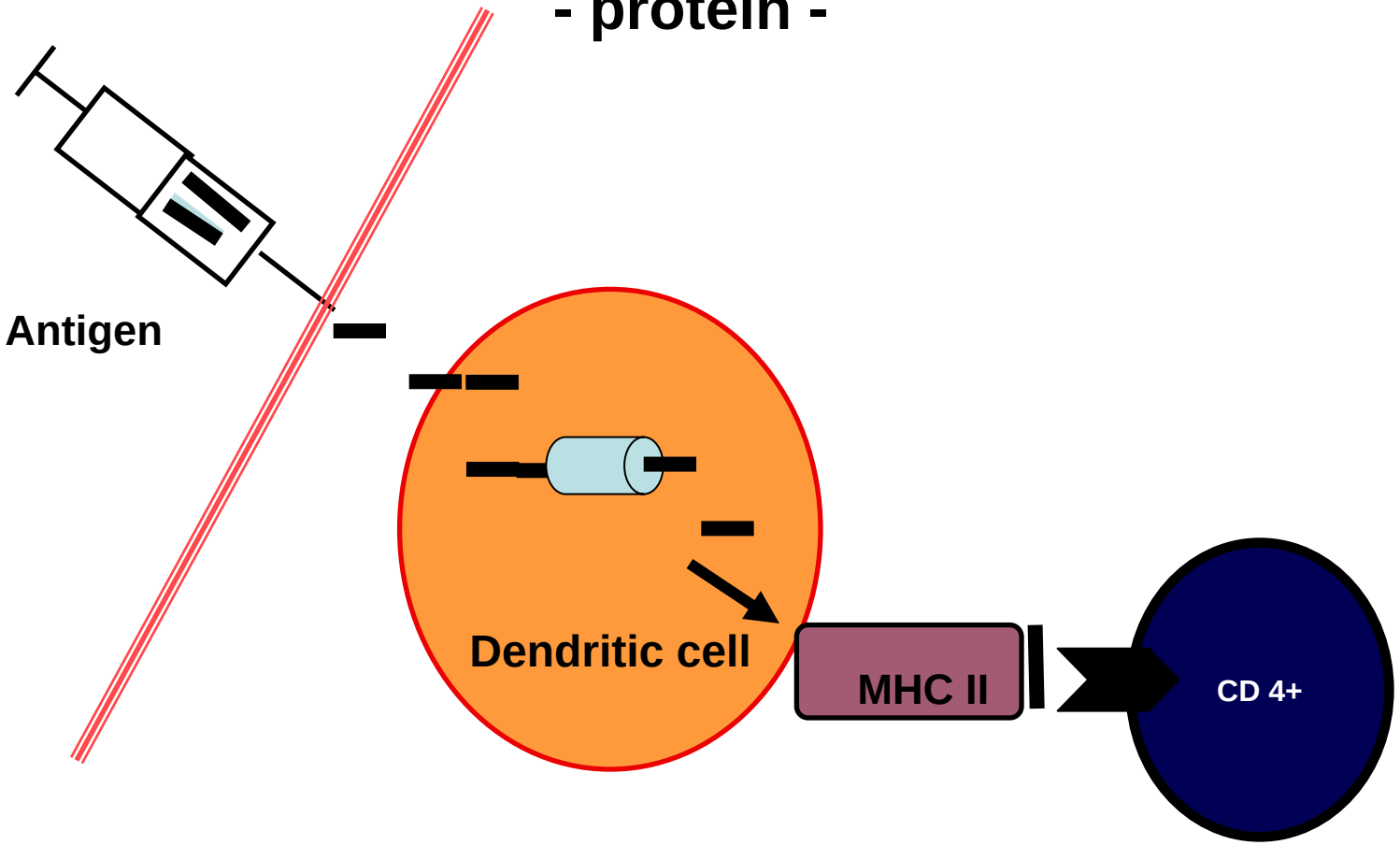
B



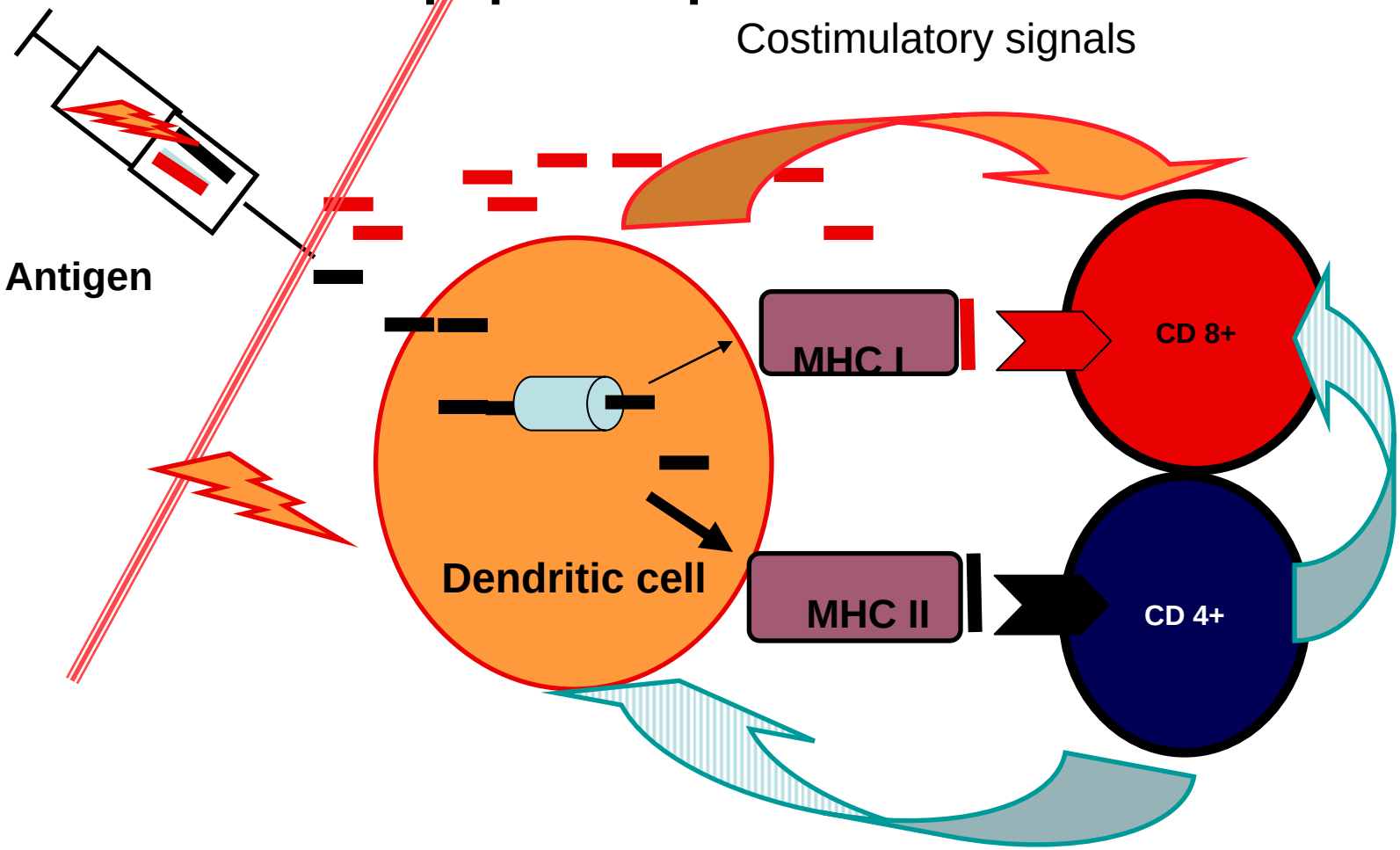
Strategies to induce tumor-specific T cell responses
- MHC class I peptides -



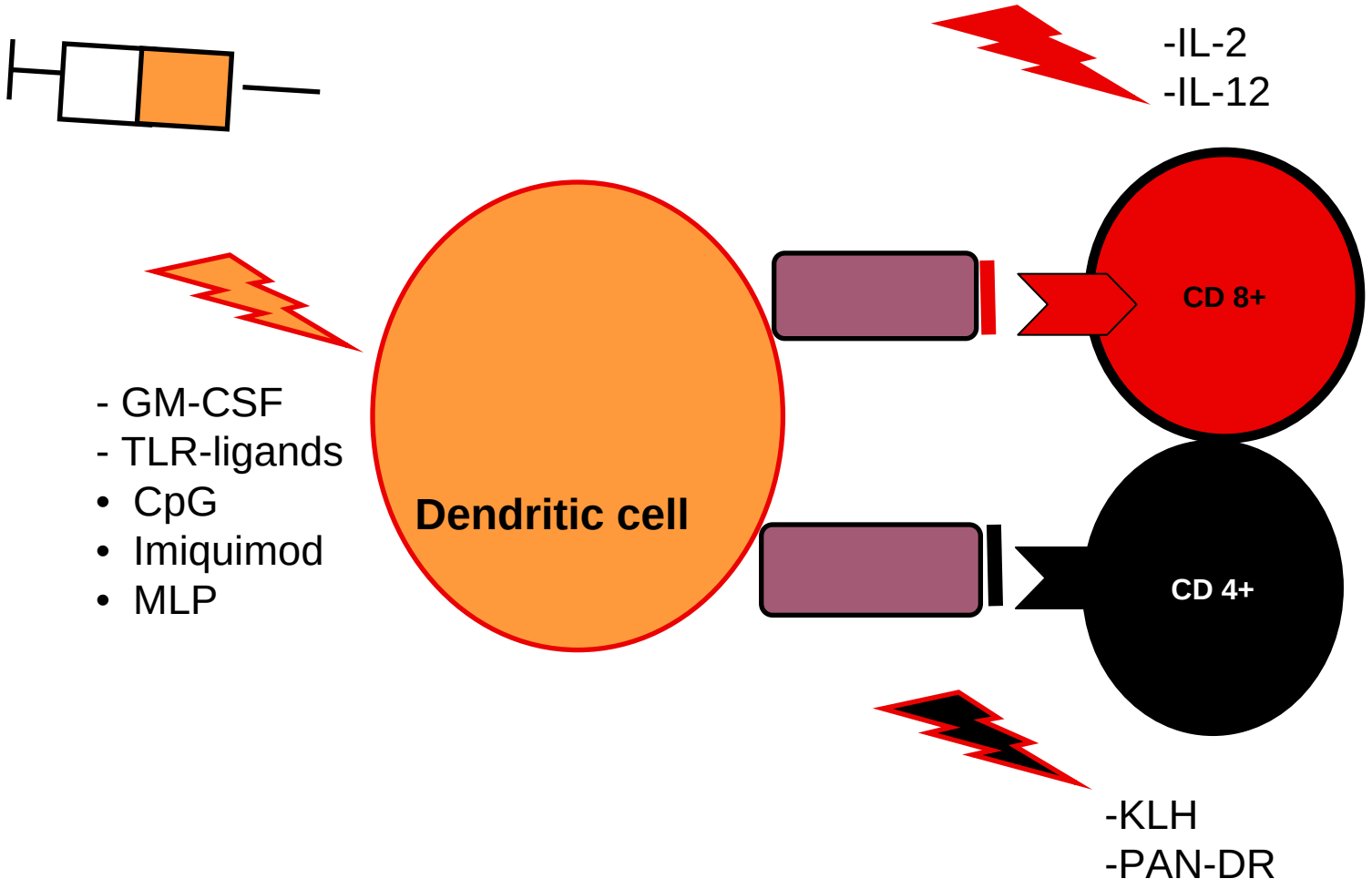
Strategies to induce tumor-specific T cell responses
- protein -



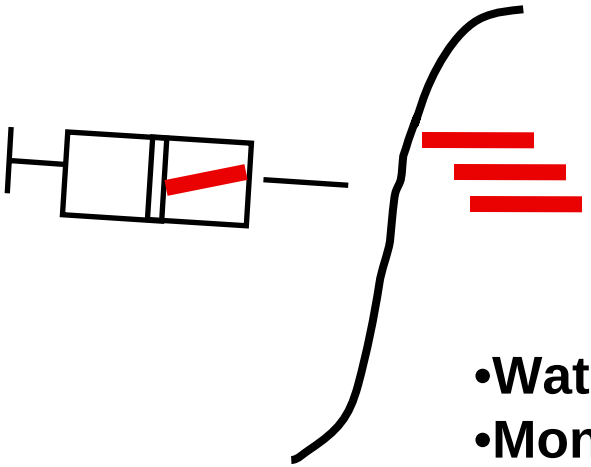
Strategies to induce tumor-specific T cell responses
- peptide + protein -



Cancer vaccines- Adjuvants



Cancer vaccines- Antigen delivery



- Water/DMSO
- Montanide (IFA)
- Liposomes

Therapeutic cancer vaccines

1. Principles
2. Clinical trials - current status
3. Future directions

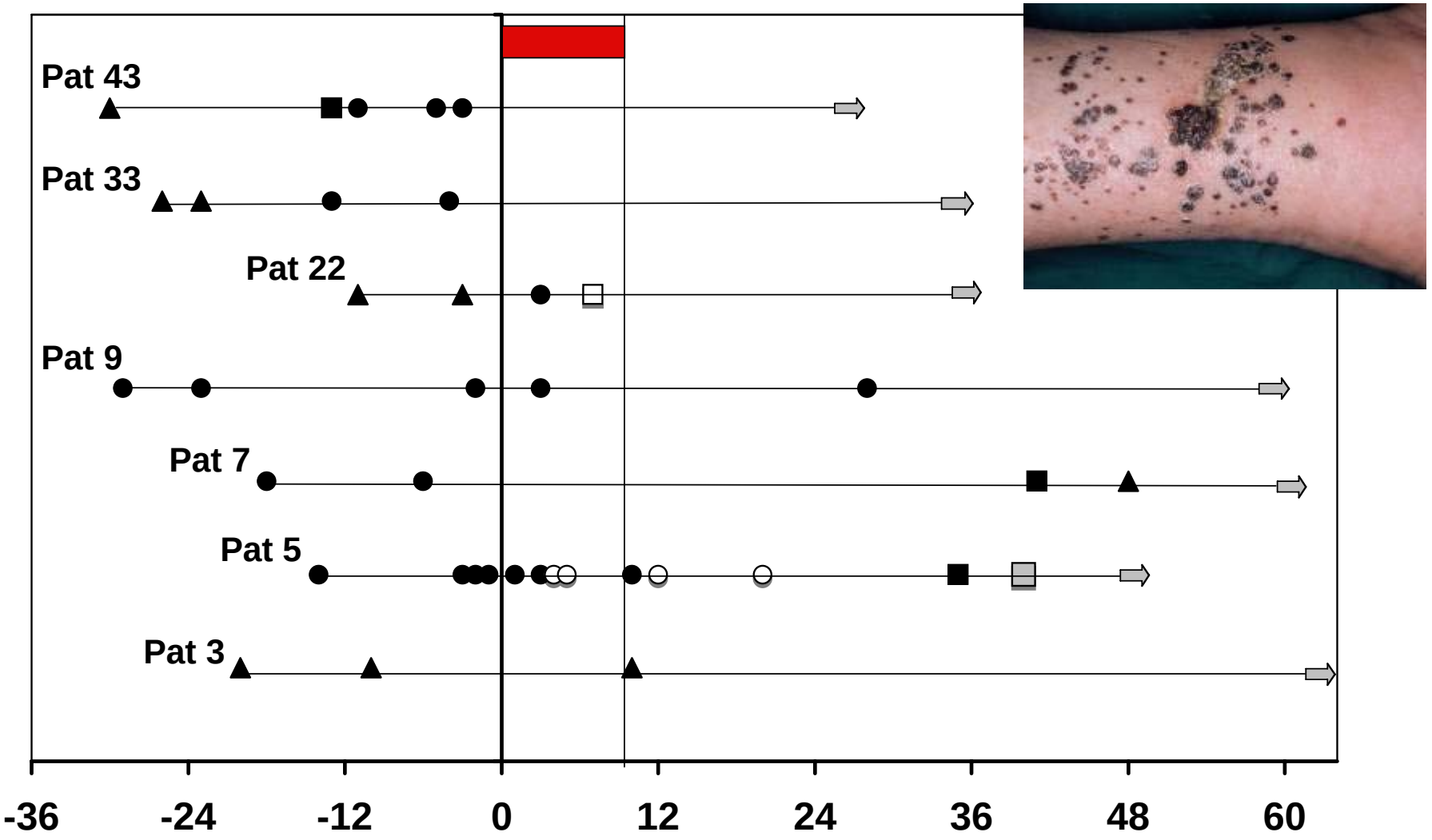
Cancer vaccines
A decade of vaccination trials in metastatic melanoma

Vaccination is:
- **immunogenic - induction of T cells**
- **can induce tumor regression**

however:
- **Objective response rates „RECIST“ < 10%**
- **Weak association between quantitative T cell responses and tumor responses**

Cancer vaccines- Current trials
- High risk melanoma -

Tyrosinase vaccination of patients with relapsing melanoma - cessation of relapses in a subset of patients

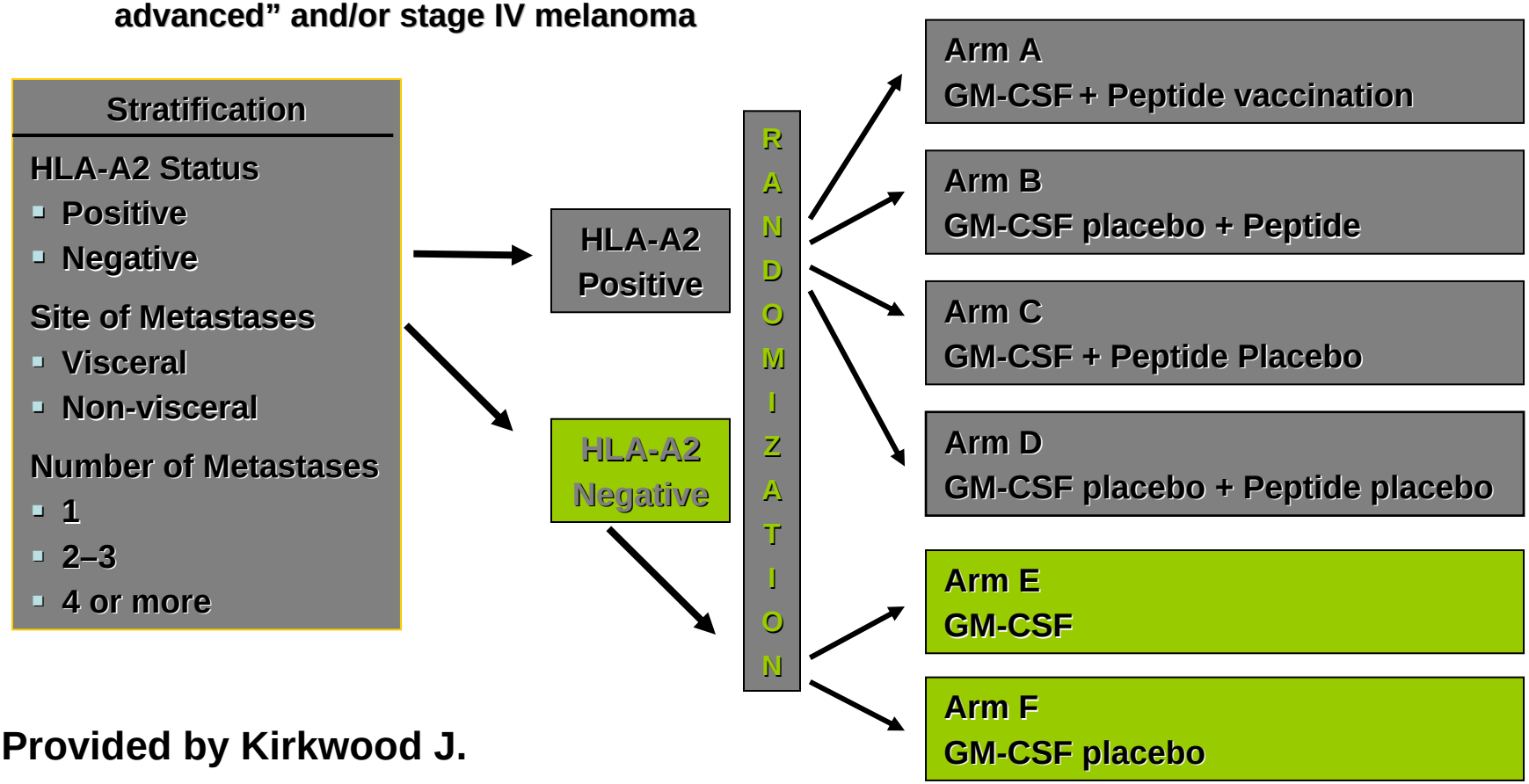


Letsch et al, unpublished

E4697- Adjuvant trial for high risk resected stage III-IV melanoma

Hypothesis: GM-CSF and/or multi-epitope peptide vaccine will be of therapeutic benefit, acting upon T-cells or through dendritic cells in resected stage III-IV melanoma

E4697 Intergroup Trial: A randomized, placebo-controlled phase III trial of yeast derived GM-CSF vs peptide vaccination vs GM-CSF plus peptide vaccination vs placebo in patients with "no evidence of disease" after complete surgical resection of "locally advanced" and/or stage IV melanoma



Provided by Kirkwood J.

Cancer vaccines- Current trials

ASCO 2007:

51 abstracts related to vaccination

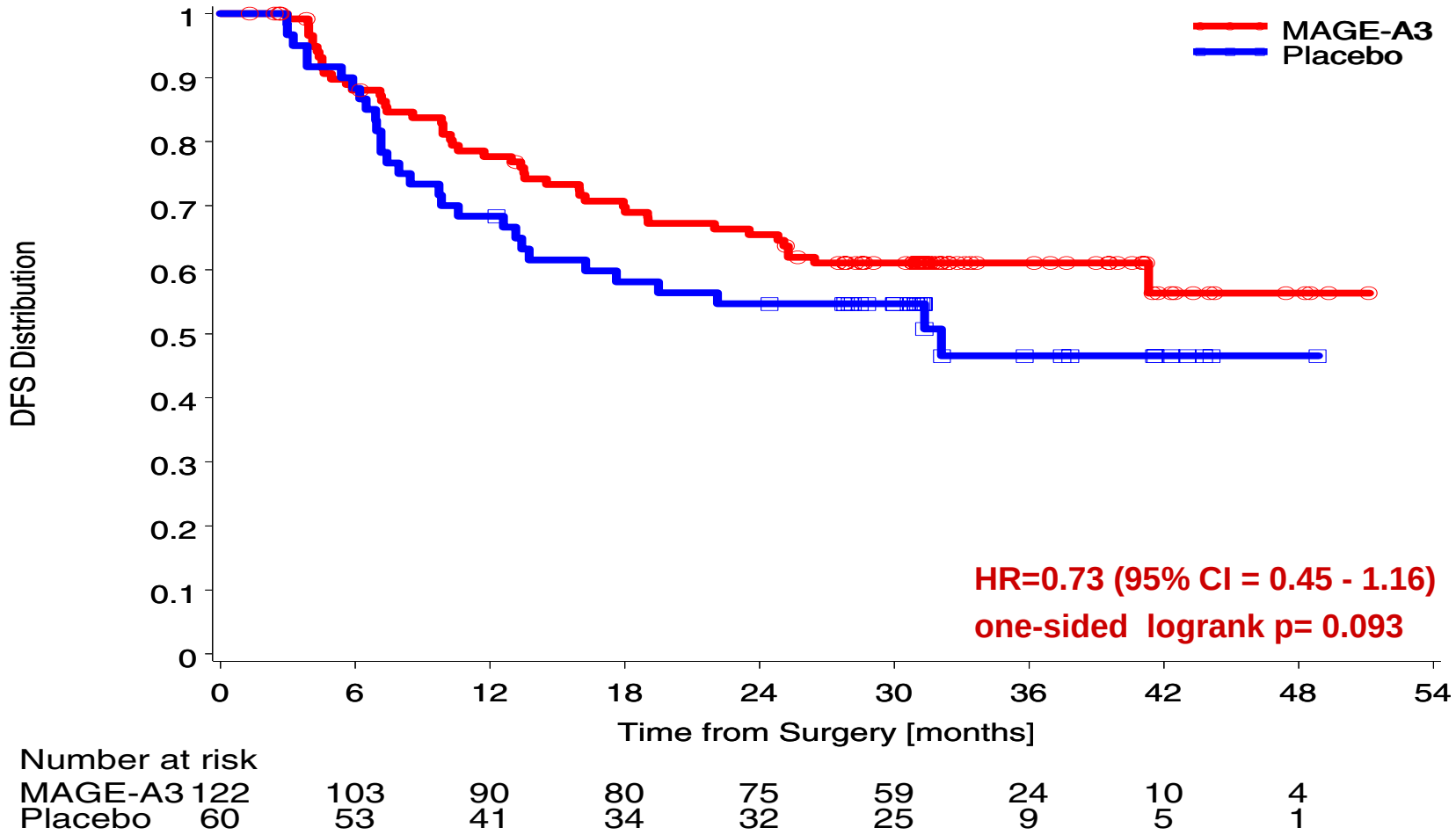
Cancer vaccines- Current trials
- ASCO: NSCLC -

Vansteenkiste J. et al. Final results of a multi-center, double-blind, randomized, placebo-controlled phase II study to assess efficacy of MAGE-A3 as adjuvant therapy in stage IB/II NSCLC

D. Soulieres et al. A multicentre open-label study to assess safety of Stimuvax (BLP25 liposome vaccine or L-BLP25) in NSCLC with unresectable stage III disease.

Vansteenkiste J. et al., MAGE-3 in resected NSCLC, ASCO 2007

Kaplan-Meier curve for Disease-Free Survival

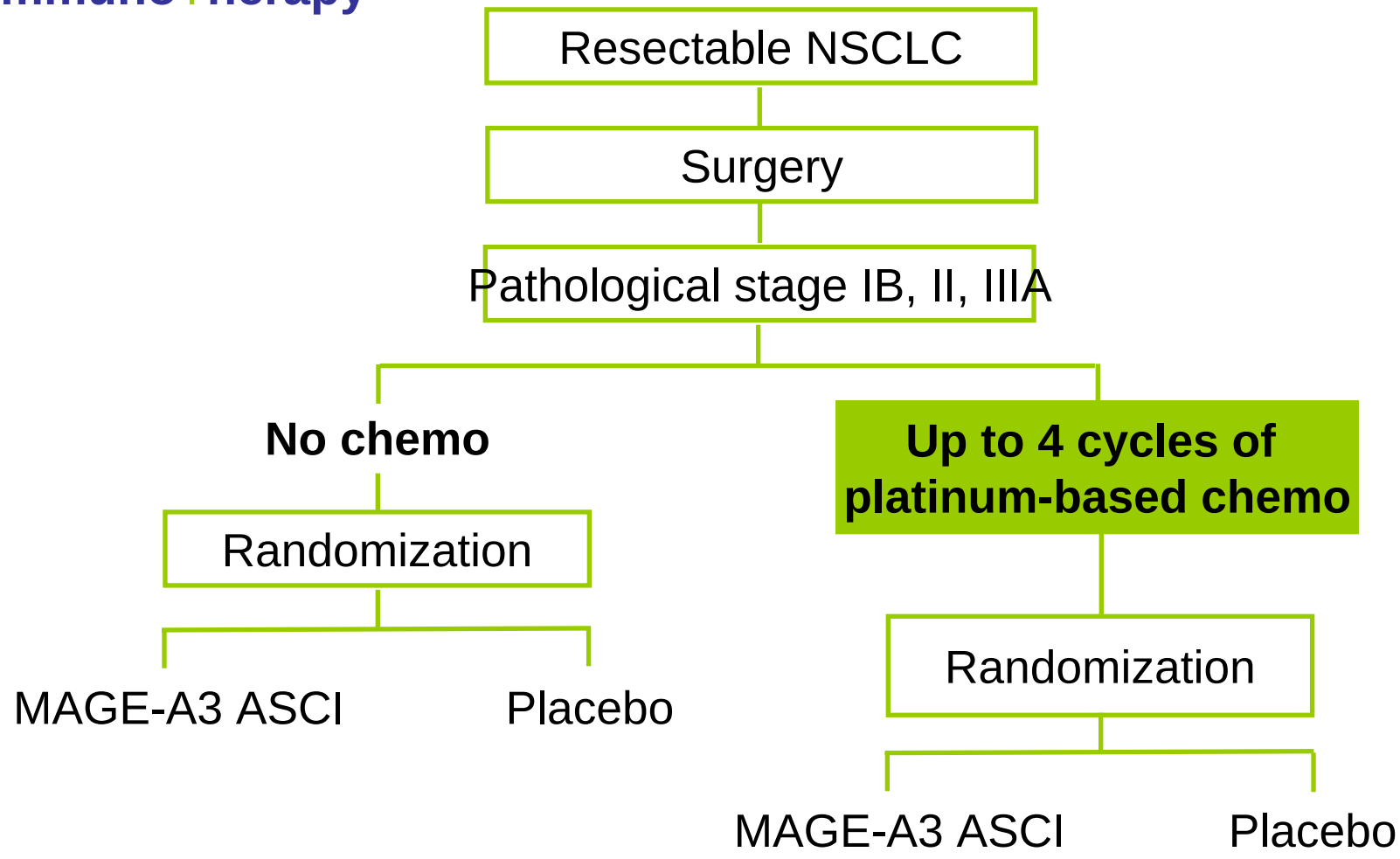


DFS: Interval from the date of surgical resection to the date of recurrence OR death, irrespective of cause of death

HR: Hazard ratio calculated by Cox analysis

Phase III study – MAGRIT (Vansteenkiste J. et al. ASCO 2007)

MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy



2,270 patients – double-blind, randomized trial

Cancer vaccines- Current trials
- ASCO: NSCLC -

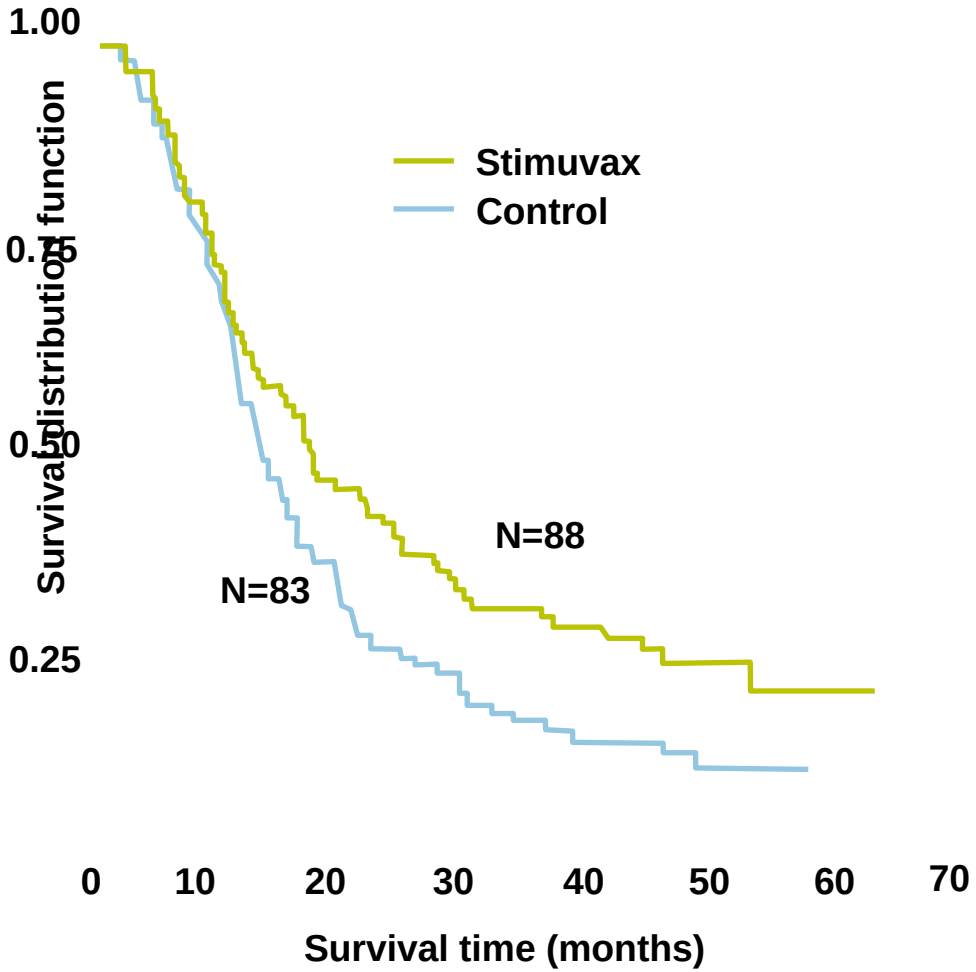
Vansteenkiste J. et al. Final results of a multi-center, double-blind, randomized, placebo-controlled phase II study to assess efficacy of MAGE-A3 as adjuvant therapy in stage IB/II NSCLC

D. Soulieres et al. A multicentre open-label study to assess safety of Stimuvax (L-BLP25 vaccine*) in NSCLC with unresectable stage III disease.

***L-BLP25 = synthetic MUC1 lipopeptide liposome vaccine**

Multi-center phase IIB randomized controlled study of L-BLP25 liposome vaccine for vaccination of stage IIIb/IV NSCLC (D. Soulieres et al, ASCO 07)

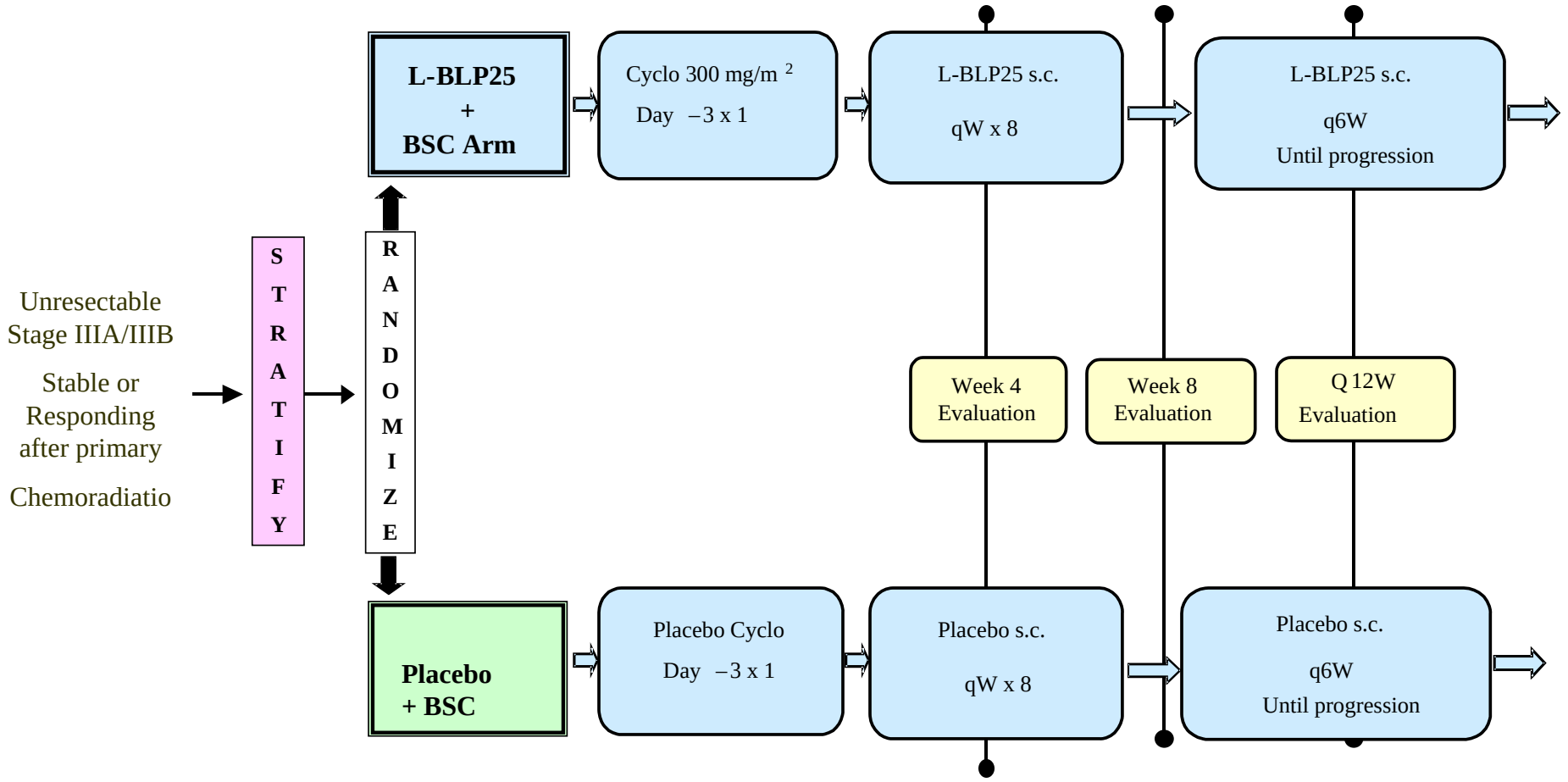
Overall Kaplan–Meier Survival: ITT



	BSC	Stimuvax + BSC
Median follow-up	56 mo	51 mo
Median survival [95% CI]	13.0 mo [11.2–16.2]	17.2 mo [12.9–24.2]
Hazard ratio [95% CI]; p value	0.745 [0.533–1.042] p=0.085	
1-year survival rate	55%	63%
2-year survival rate	27%	41%
3-year survival rate	17%	31%

Butts C, et al. JCO 27, Sept. 05 , data updated in March 2006

Randomised phase III trial of L-BLP25 versus placebo in patients with stage III non-small cell lung cancer after response to primary chemoradiotherapy (D. Soulieres et al, ASCO 07)



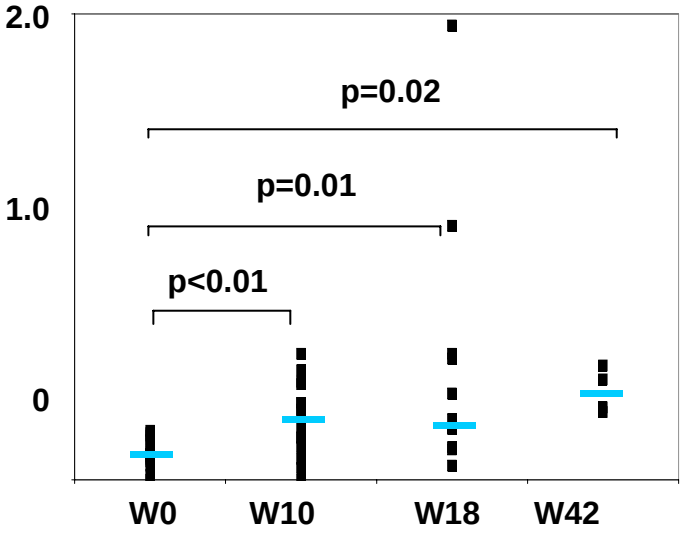
Cancer vaccines- Current trials
- ASCO: AML -

Letsch A et al. Phase II trial of vaccination with WT1 peptide, GM-CSF, and KLH in patients with acute myeloid leukemia and myelodysplasia: Final immunological, molecular, and clinical results

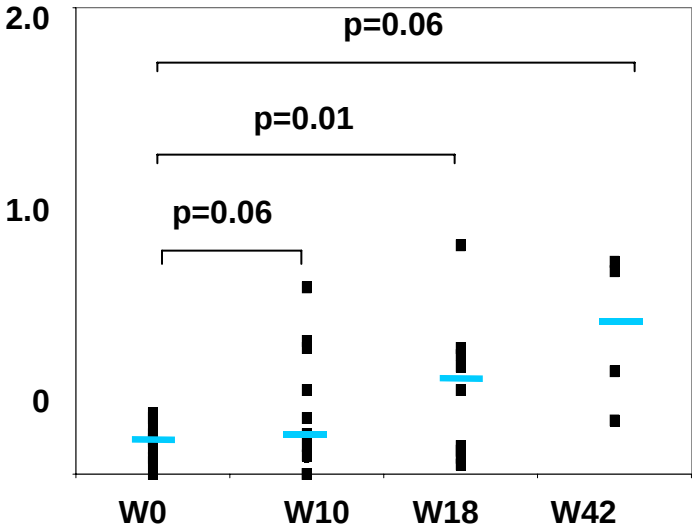
Qazilbash MH et al. PR1 peptide vaccination for patients with myeloid leukemias

WT1 vaccination in AML: WT1-Tetr+ T cells in PB and BM
(Letsch et al. ASCO 2007)

Peripheral blood
(without preexisting response)



Bone marrow
(without preexisting response



WT1 vaccination -Clinical efficacy (Letsch et al. ASCO 2007)

Status at study onset	n	outcome
Untreated AML or sAML BM blasts med 70%, range 40 - 85%	8	SD 2, 3, 3, 4, 4, 5, 7, 15+ months (4 pts. ≥ 50% blast reduction, 1 reduction of peripheral blasts, 1 erythoid response)
RAEB I/II	2	2 pts. with major neutrophil response (1 with 50% blast reduction, initial PD)
No CR following chemo:		
- PR	4	1 CR at week 10 for 12 mo (initial PD) 1 SD 4 mo 2 PD
- no response	1	SD 4+ mo with 50% blast reduction
- PD, relapse	3	1 SD for 2 mo, 2 PD
	18	**1 CR, 12 SD > 2 months**
High - risk CR	**8**	**TTF 2, 2, 4, 5, 10, 14+, 16+, 38**

Cancer vaccines- Current trials
- ASCO: AML -

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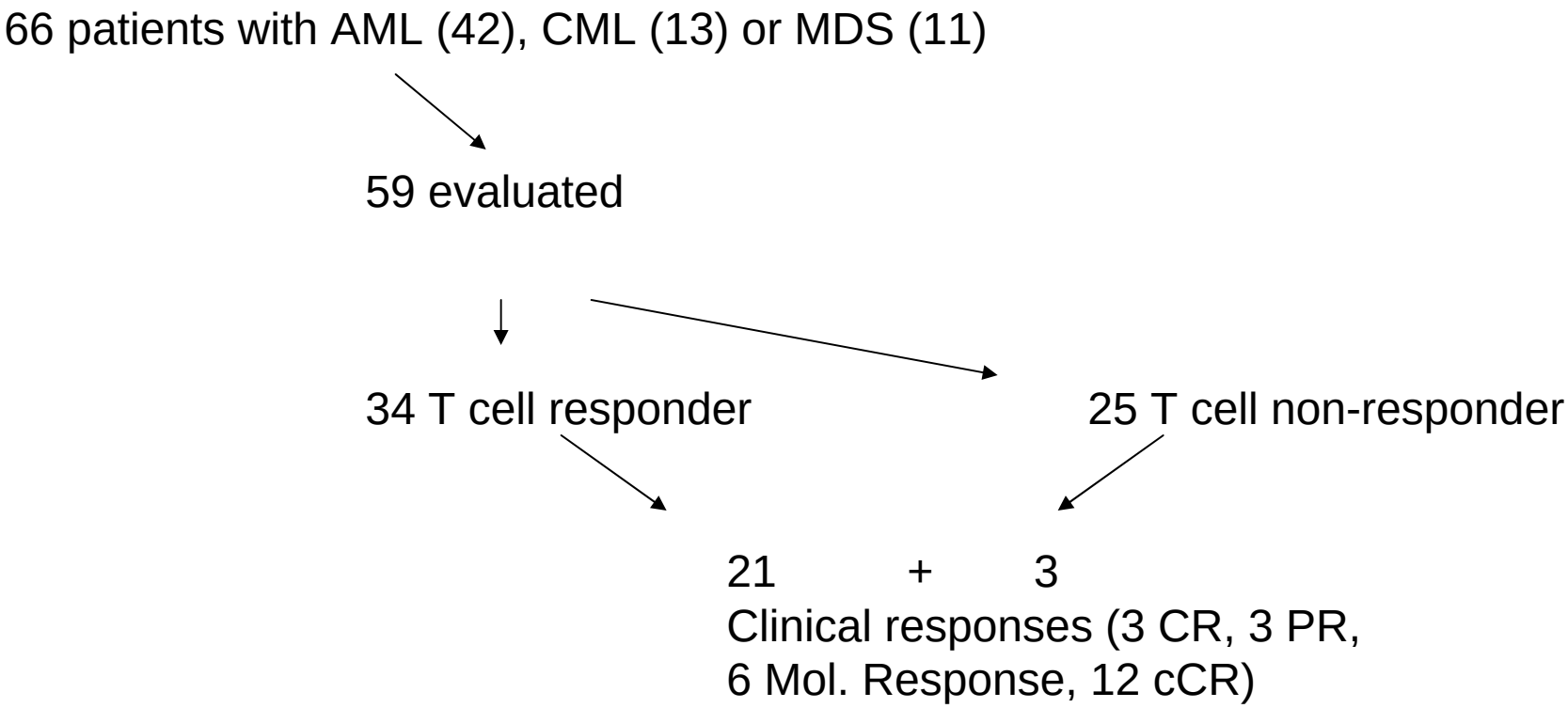
Qazilbash MH et al. PR1 peptide vaccination for patients with myeloid leukemias

PR1 peptide vaccination for patients with myeloid leukemias

Qazilbash MH et al., ASCO 2007



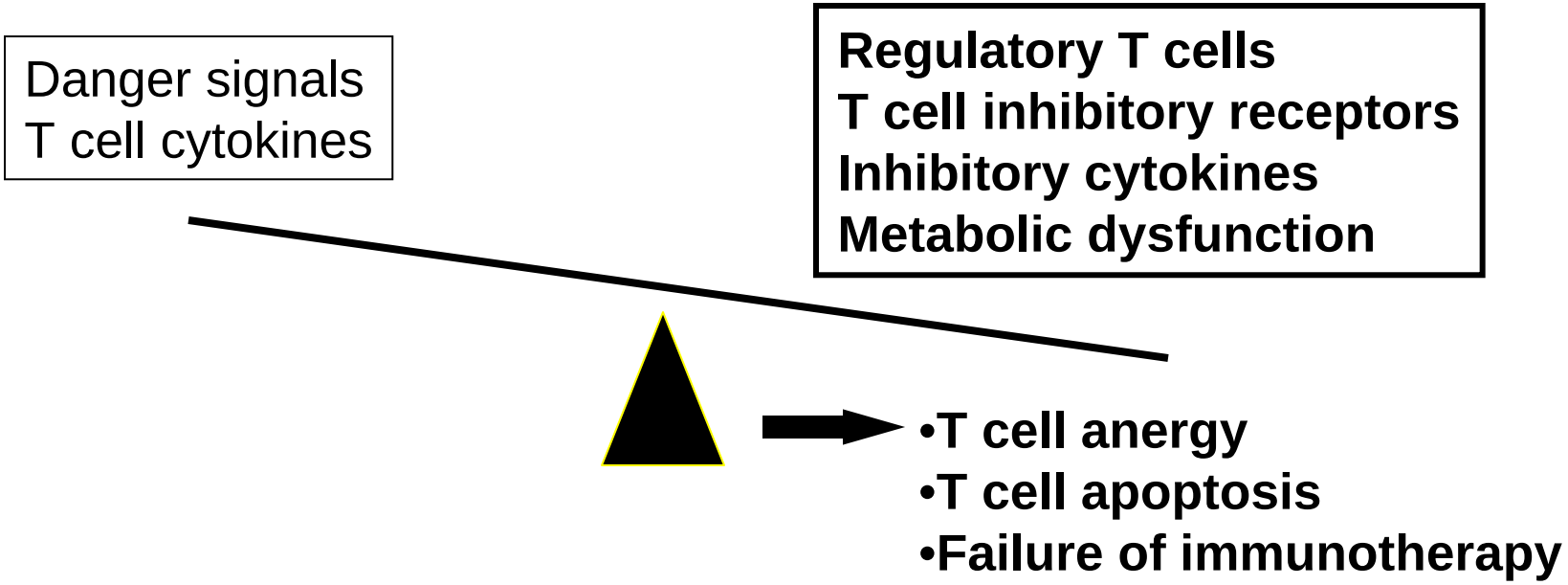
Therapeutic cancer vaccines

1. Principles
2. Clinical trials - current status
3. Future directions

How to improve cancer vaccines?

Tumor Dysbalance

Immune stimulation - Immunosuppression

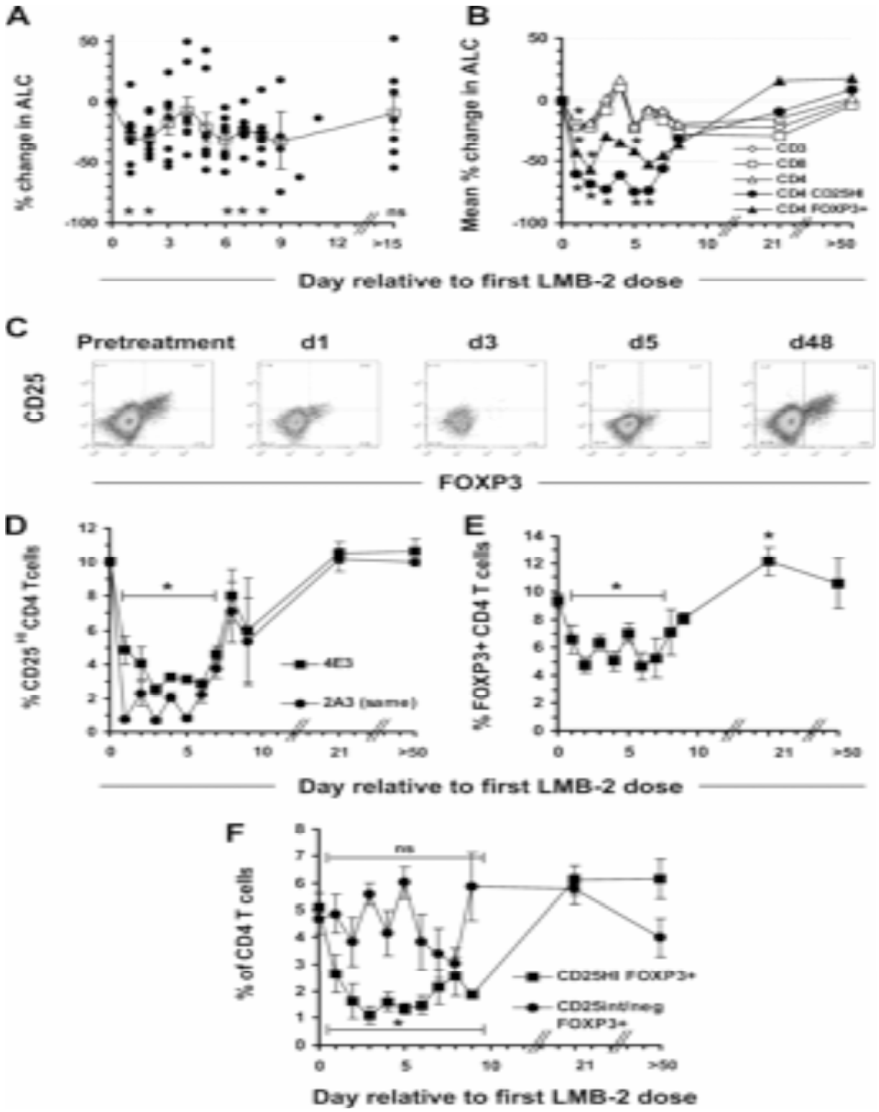


Cancer vaccines
- New developments -

Target	Interventions (clinical trials ongoing or to be activated soon*)
Immunostimulation	
- Dendritic cell activation	TLR-Ligand: MLP (TLR4) Resiquimod (TLR 7), CpG (TLR9), Poly I:C (TLR3)
- T cell proliferation, inhibition of AICD, reversal of anergy, memory	(IL-15), IL-7, IL-21
Immunosuppression	
- blockade of T cell receptors for negative regulation	Anti-CTLA-4 , Anti-PD-1*
- Depletion of regulatory T cells	Anti-CD25, anti-GITR*
- Restoration of metabolic dysregulation (IDO)	1-Methyltryptophan*

LMB-2, a CD25-directed immunotoxin, causes a selective, transient elimination of circulating CD25+ Treg cells in vivo

Powell DJ Jr, et al.
J Immunol. 2007 Oct 1;179:4919-28.



Antibody blockade of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4): Association of tumor response with autoimmunity

- 137 melanoma, 61 renal cell pts treated
- 21% rate of GI toxicity (90% colitis); 5% mortality
- Response rates in patients
  with colitis: 36% / 35%,
  without colitis: 11% / 2%

Beck KE et al *J Clin Oncol* 24, 2006

CTLA-4 antibody with multipeptide vaccine for resected stages III/IV melanoma

- Total of 44 patients treated with CTLA-4 antibody with a multi-peptide vaccine
- 20 IBEs (grades II/III)
- 4/20 patients with IBEs had a relapse, versus 13/24 without an IBE, $p<0.03$ (Fisher's exact)
- 3 deaths in 20 patients with IBE versus 9/24 without an IBE

Ongoing randomized study of CTLA-4ab and gp100 peptide

Jeffrey Weber, unpublished, 2007

Cancer vaccines
- New developments -

Biomarker/Immunomonitoring:

• Multifunctional Th1 cells define a correlate of vaccine-mediated protection against Leishmania (Darrah, Nat Med, 2007)

IFNγ/TNFα/IL-2+

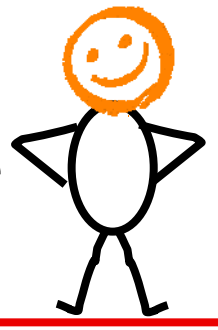
• HIV controllers exhibit ... a peculiar CD8 T cell activation phenotype (Saez-Cirion A, PNAS, 2007)

HLA-DR high CD38 low

Cancer vaccines 2007 - Conclusion

- Proof of immunogenicity
- Proof of clinical efficacy
  - therapeutic:

    frequent tumor stabilization, rare tumor regression
  - adjuvant: ongoing phase III trials
- Promising new strategies to enhance immunostimulation and revert tumor-induced immunosuppression
- Refined T-cell monitoring (quality) to define correlates of clinical efficacy



Thank you - Questions ??

Strategies to induce tumor-specific T cell responses
- genetic approaches -