New developments in clinical vaccinations

Ulrich Keilholz
Acting Director
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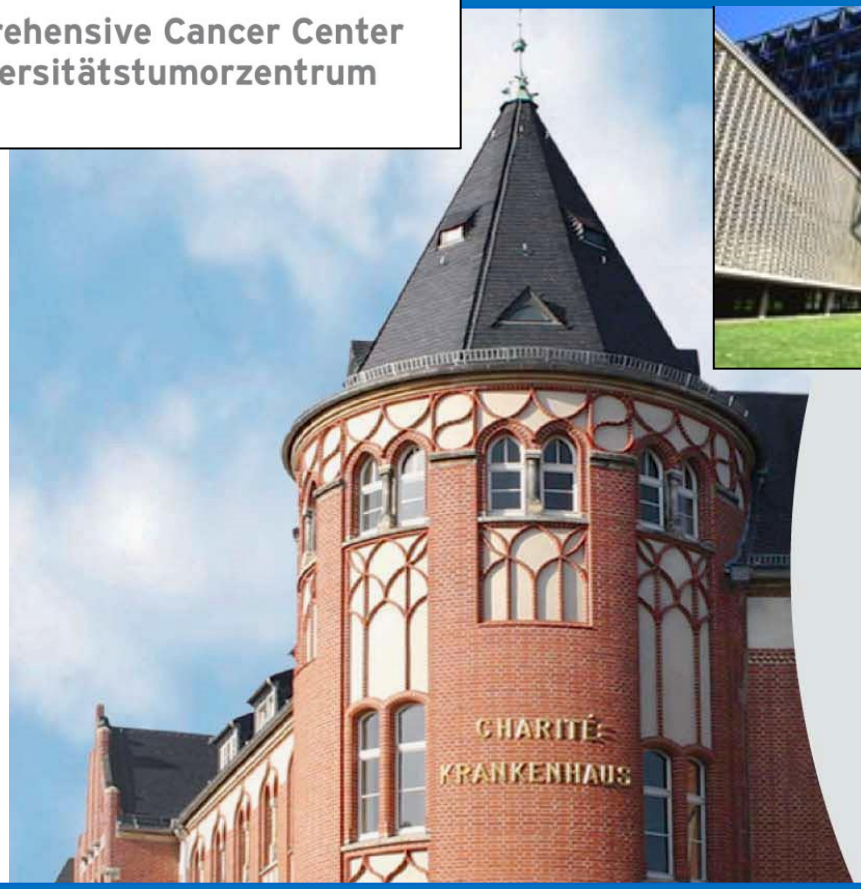
Berlin, Germany

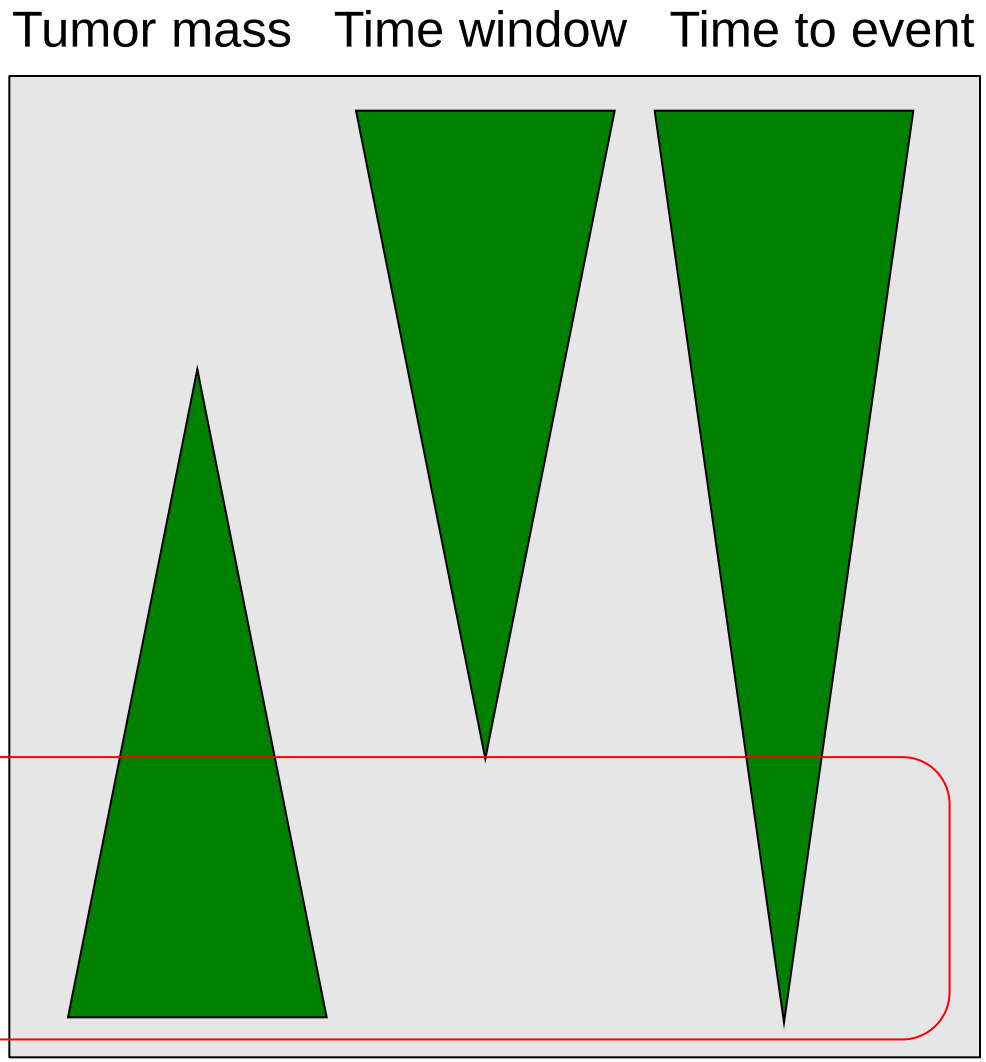
CHARITÉ

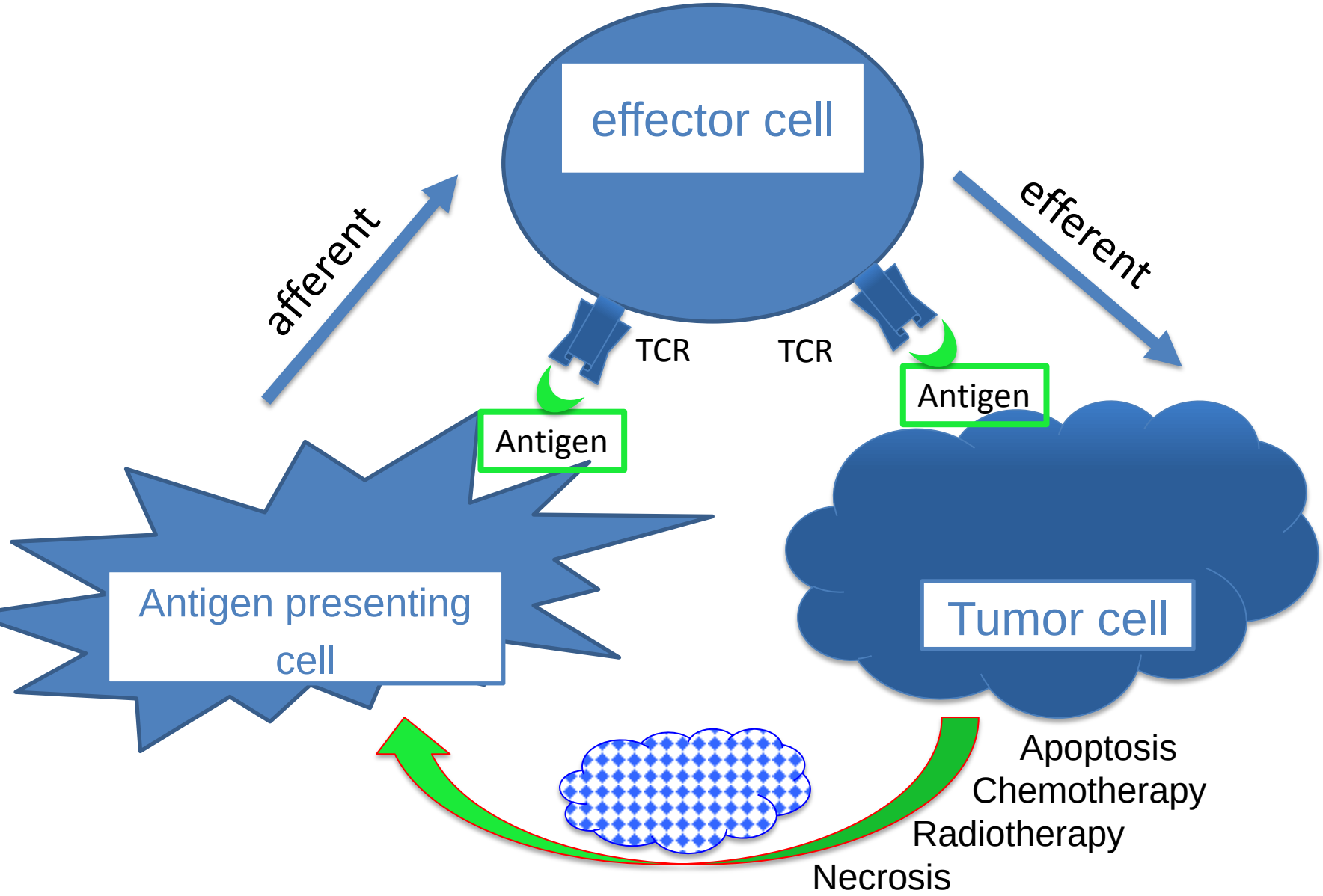
Comprehensive Cancer Center
Universitätstumorzentrum



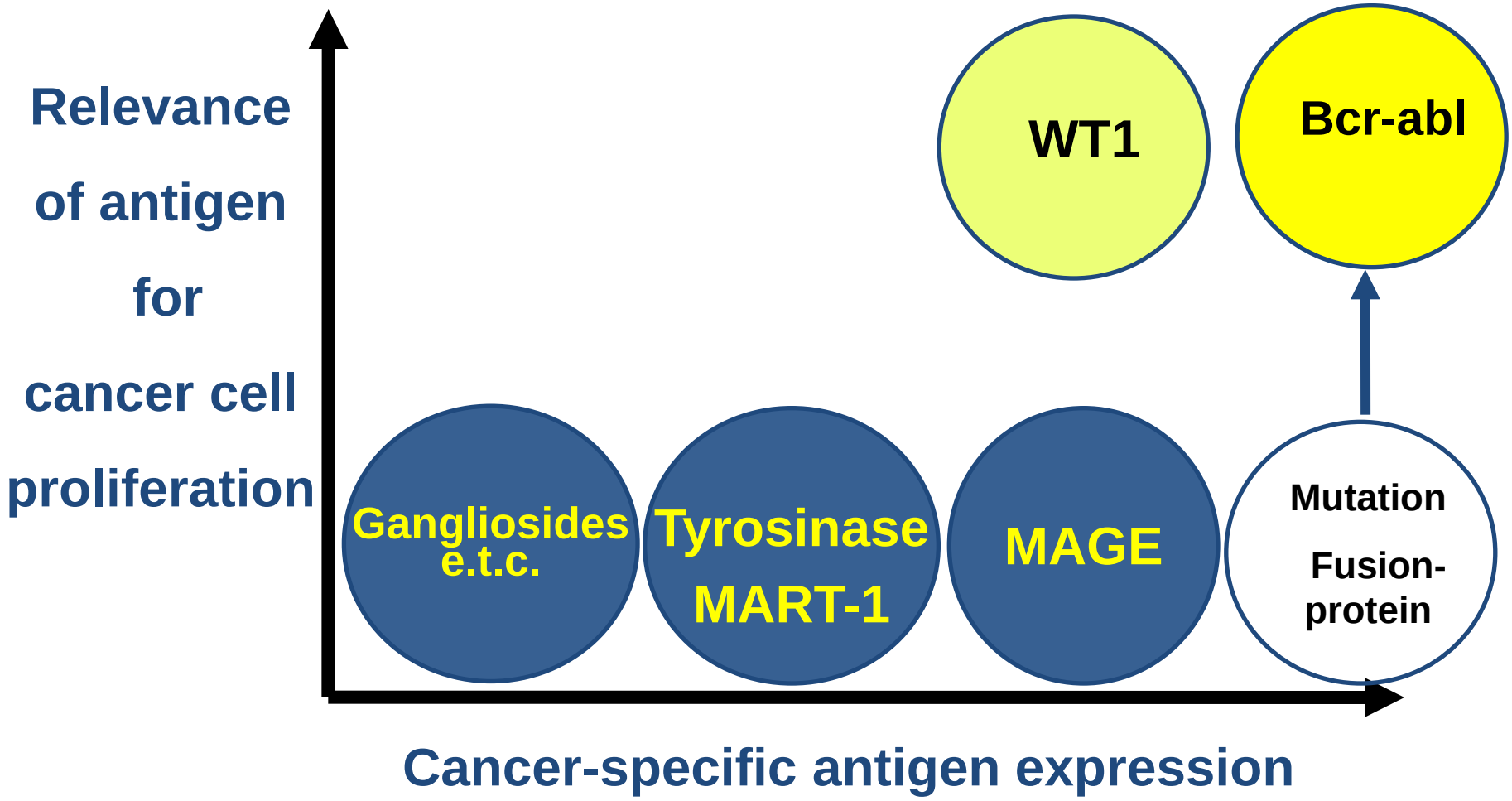
Cancer vaccine development – clinical opportunities

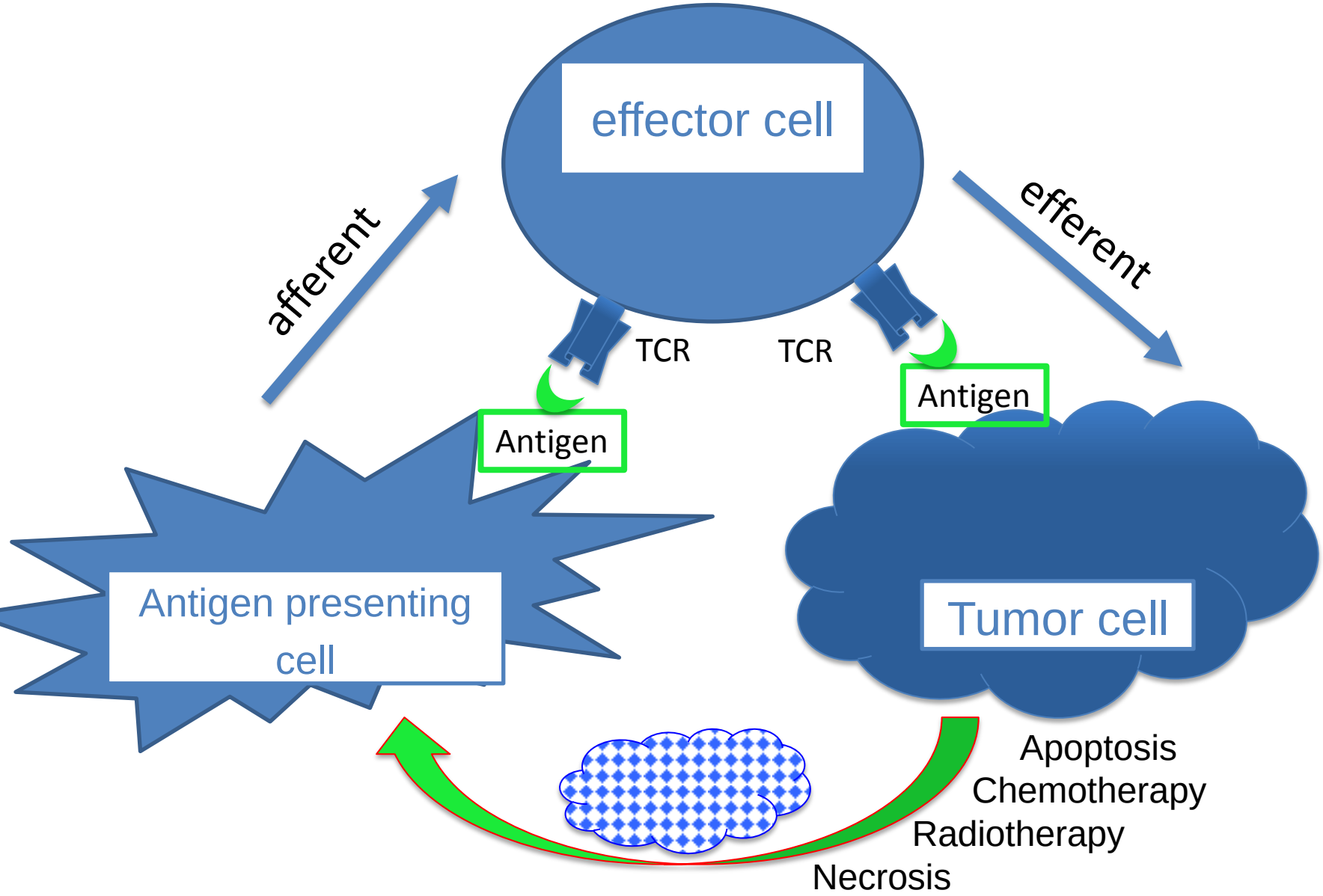
- High-risk populations
  (BRCA, FAP)
- Carcinogenic infections
  (Hepatitis, HPV)
- Premalignant lesions
  (leukoplakia, MDS)
- Adjuvant treatment
- Metastatic disease

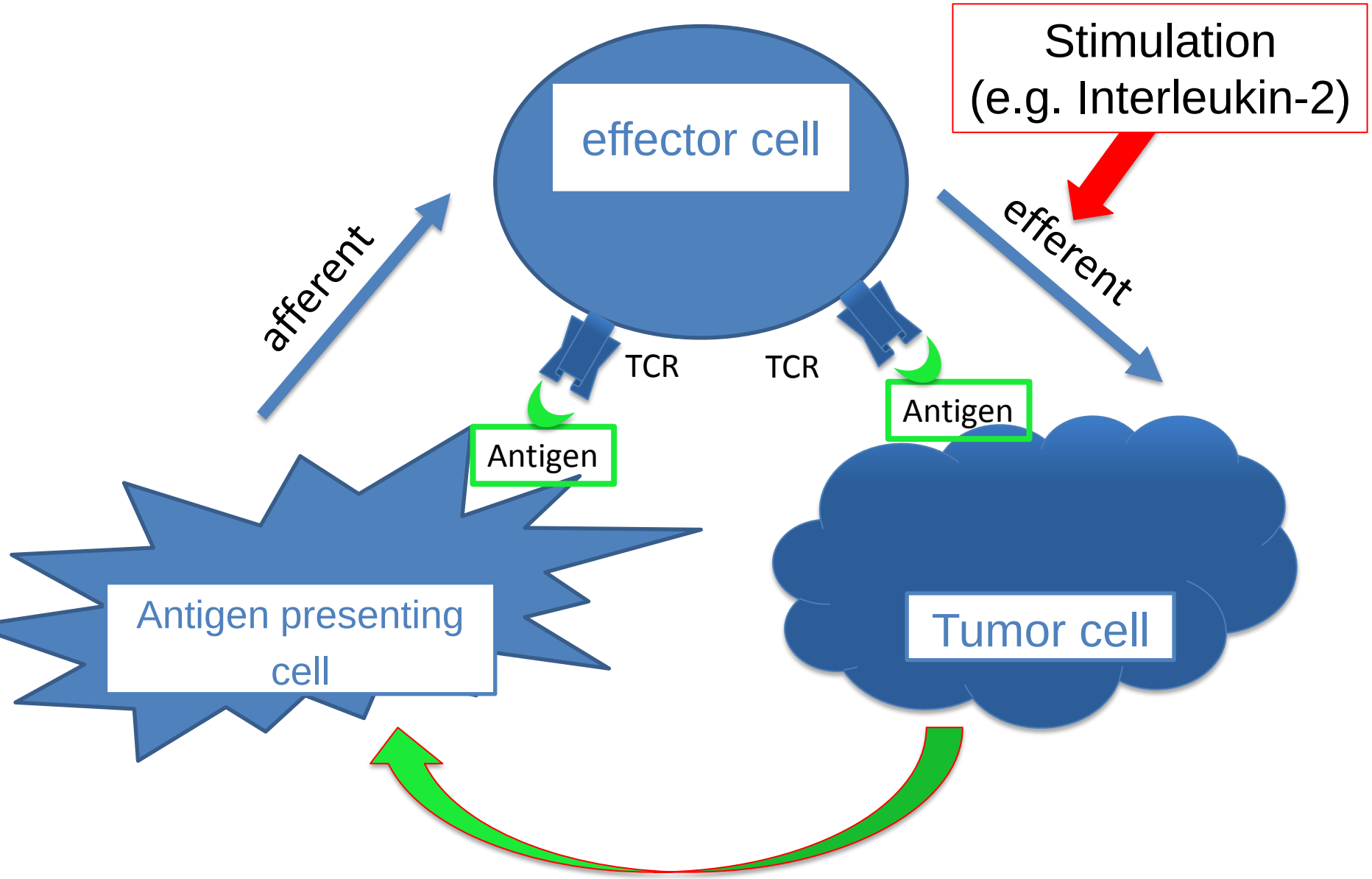


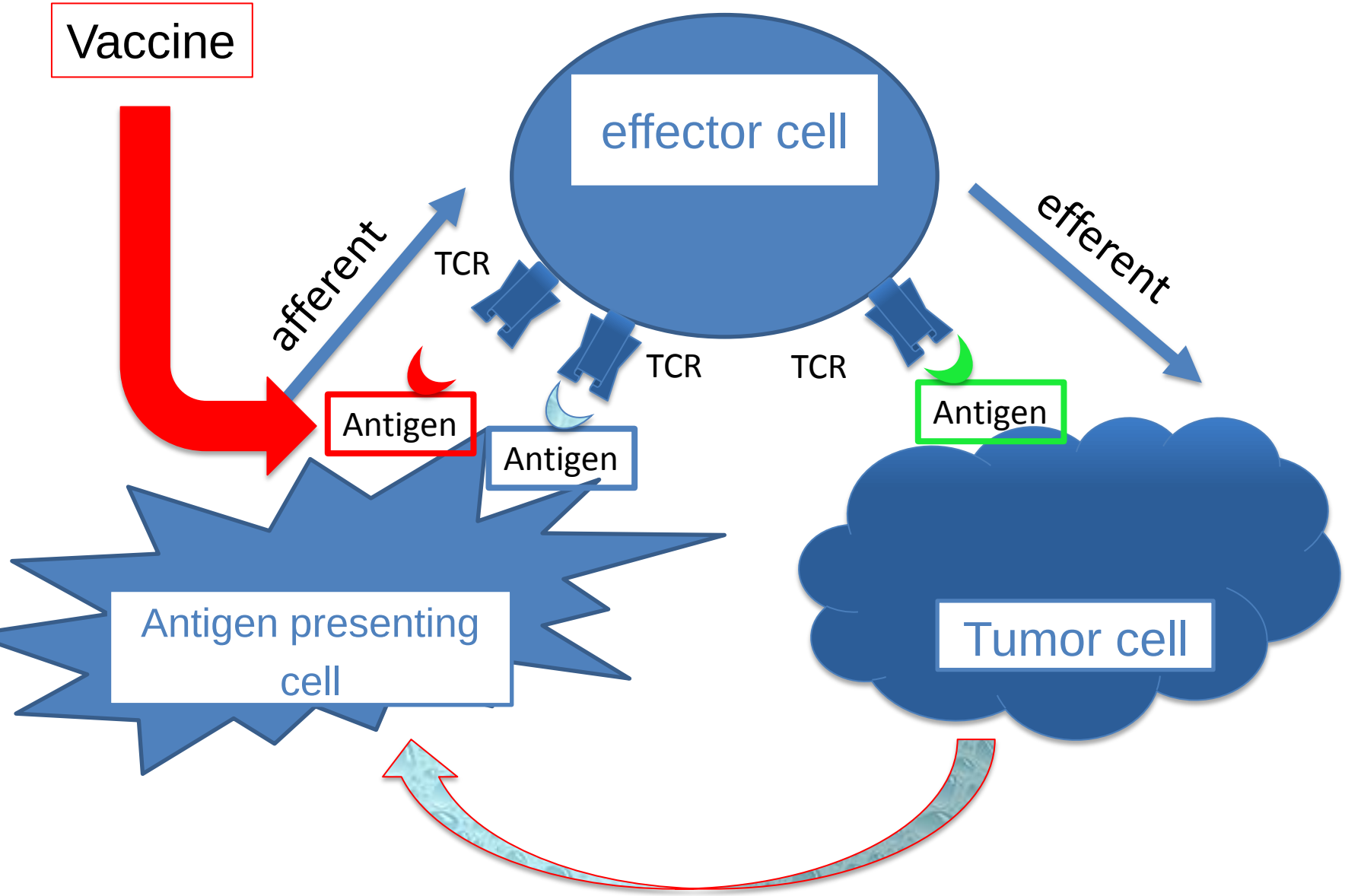

effector cell
afferent
efferent
TCR
TCR
Antigen
Antigen
Antigen presenting cell
Tumor cell
Apoptosis
Chemotherapy
Radiotherapy
Necrosis

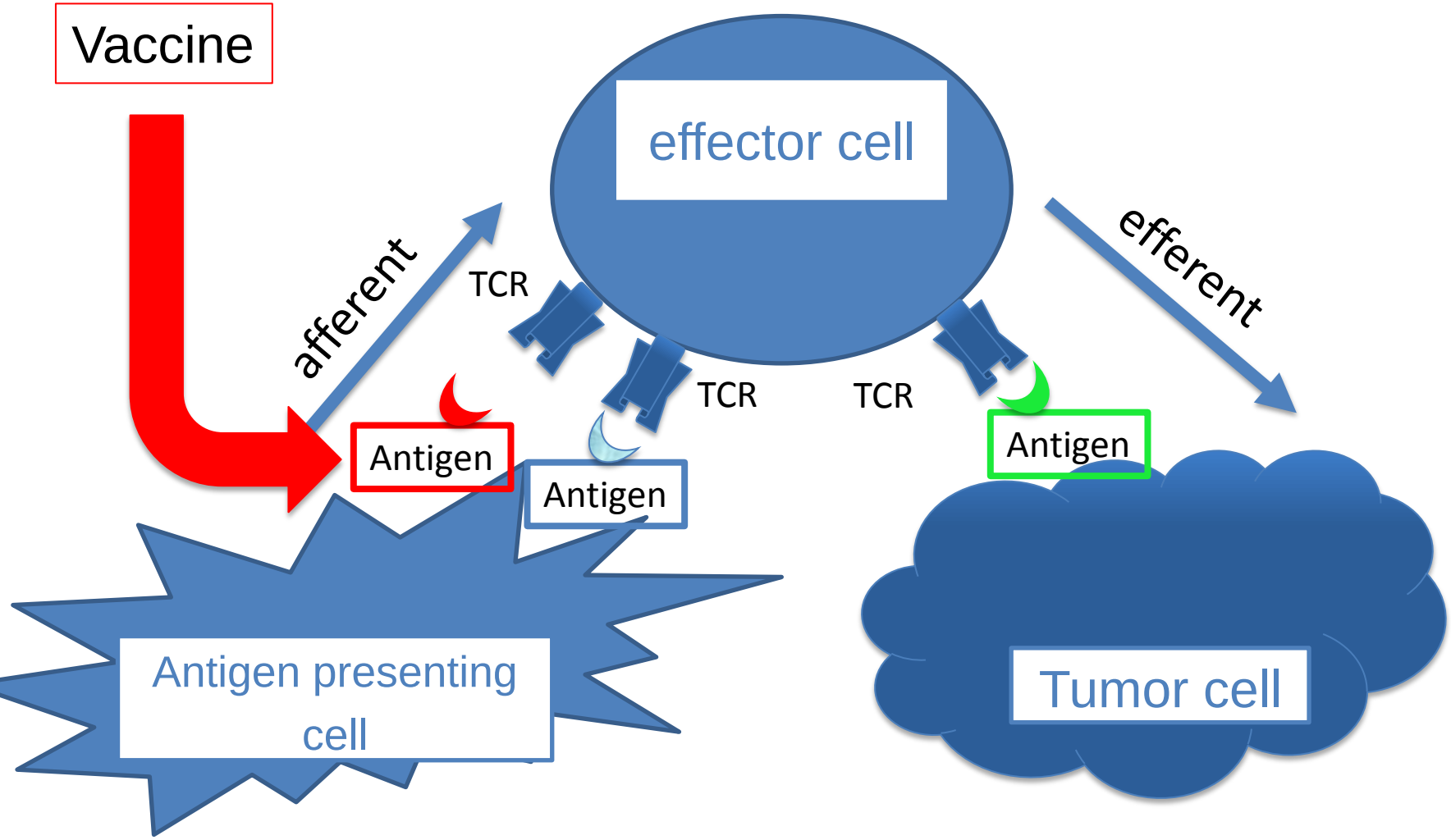
Hierarchy of tumor antigens




effector cell
afferent
efferent
TCR
TCR
Antigen
Antigen
Antigen presenting cell
Tumor cell
Apoptosis
Chemotherapy
Radiotherapy
Necrosis


Stimulation
(e.g. Interleukin-2)
effector cell
afferent
efferent
TCR
TCR
Antigen
Antigen
Antigen presenting cell
Tumor cell


Vaccine
effector cell
afferent
efferent
TCR
TCR
TCR
Antigen
Antigen
Antigen
Antigen presenting cell
Tumor cell



Early clinical vaccine trials

VOLUME 23 · NUMBER 35 · DECEMBER 10 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumoral and Immunologic Response After Vaccination of Melanoma Patients With an ALVAC Virus Encoding MAGE Antigens Recognized by T Cells

Nicolas van Baren, Marie-Claude Bonnet, Brigitte Dréno, Amir Khammari, Thierry Dorval, Sophie Piperno-Neumann, Danielle Liénard, Daniel Speiser, Marie Marchand, Vincent G. Brichard, Bernard Escudier, Sylvie Négrier, Pierre-Yves Dietrich, Dominique Maraninchi, Susanne Osanto, Ralf G. Meyer, Gerd Ritter, Philippe Moingeon, Jim Tartaglia, Pierre van der Bruggen, Pierre G. Coulie, and Thierry Boon

VOLUME 23 · NUMBER 35 · DECEMBER 10 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumoral and Immunologic Response After Vaccination of Melanoma Patients With an ALVAC Virus Encoding

Results

Forty patients with advanced cancer were treated, including 37 melanoma patients. The vaccines were generally well tolerated with moderate adverse events, consisting mainly of transient inflammatory reactions at the virus injection sites. Among the 30 melanoma patients assessable for tumor response, a partial response was observed in one patient, and disease stabilization in two others. The remaining patients had progressive disease. Among the patients with stable or progressive disease, five showed evidence of tumor regression. A CTL response against the MAGE-3 vaccine antigen was detected in three of four patients with tumor regression, and in only one of 11 patients without regression.

Conclusion

Repeated vaccination with ALVAC miniMAGE-1/3 is associated with tumor regression and with a detectable CTL response in a minority of melanoma patients. There is a significant correlation between tumor regression and CTL response. The contribution of vaccine-induced CTL in the tumor regression process is discussed in view of the immunologic events that could be analyzed in detail in one patient.

Active immunization towards the MAGE-A3 antigen in patients with metastatic melanoma: four-year follow-up results from a randomized Phase II study (EORTC16032-18031)

WHJ Kruit, S Suciu, B Dreno, V Chiarion-Sileni , L Mortier, C Robert, M Maio, F Lehmann, V Brichard, A Spatz, A Eggermont and U Keilholz

Wim HJ Kruit, ASCO 2011, JCO 2013
On behalf of the study Investigators
Department of Internal Oncology,
Erasmus Medical Center (Daniel den Hoed Cancer Center)
Rotterdam, Netherlands

Melanoma Phase II Trial- Study Design

- **Open, randomized, Phase II study NCT00086866 (EORTC study 16032-18031 – GSK 249553/008)**

Metastatic Melanoma
- Unresectable stage III and stage IV M1a
- 1st line metastatic treatment
- Progressive disease
- MAGE-A3 (+) tumor

R

N = 34 — **MAGE-A3 + $AS02_B$**

- Cycle 1: q2w x 6
- Cycle 2: q3w x 6
- Cycle 3: q6w x 4
- Cycle 4: q3m x 4 - q6m x 4
- Total: 4 years

N = 34 — **MAGE-A3 + AS15**

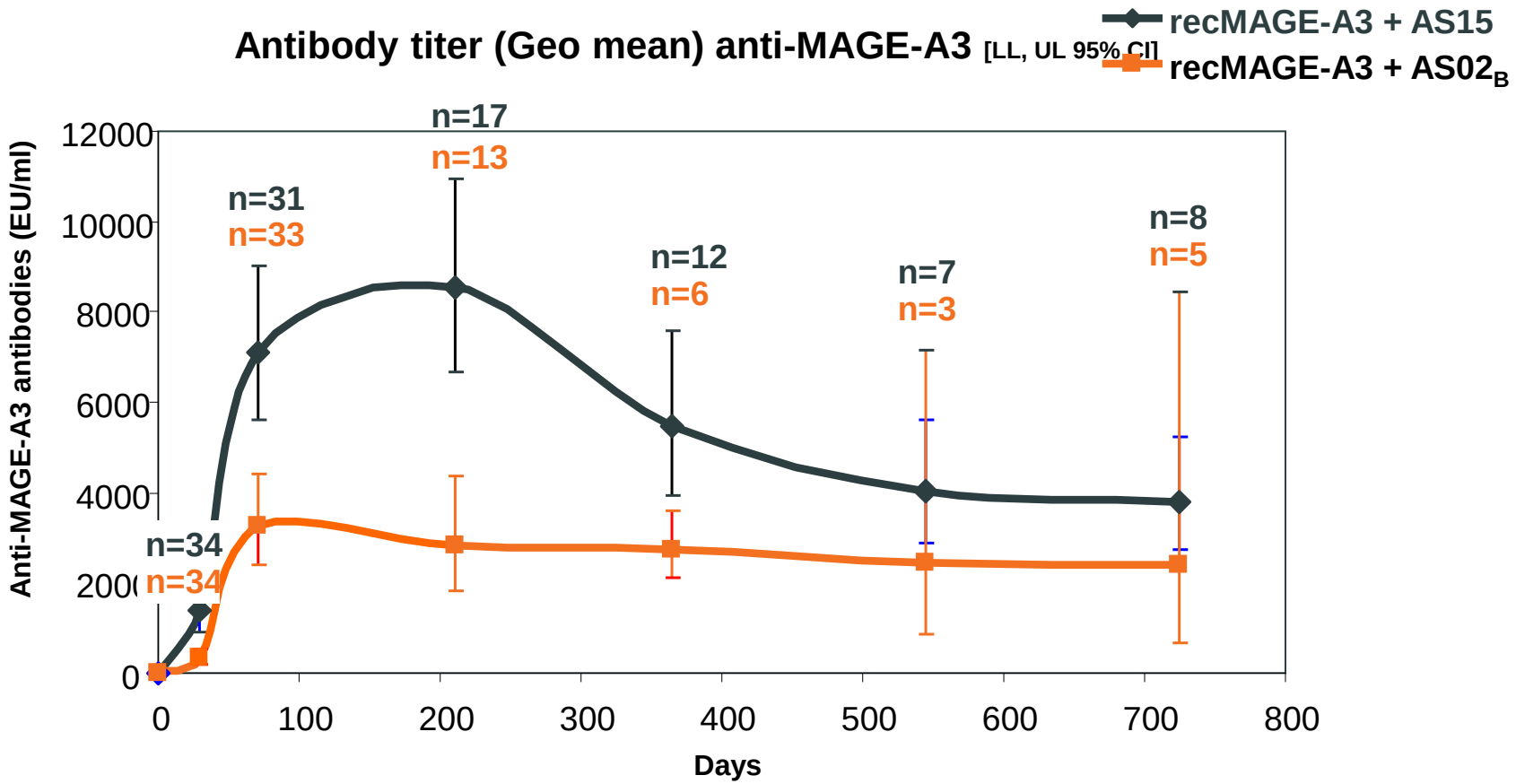
MAGE A3 rec. protein 300 ug i.m.

AS15 (MPL, QS21**, CpG, liposome-based** Adjuvant)

$AS02_B$ (MPL, QS21, o/w emulsion based Adjuvant)

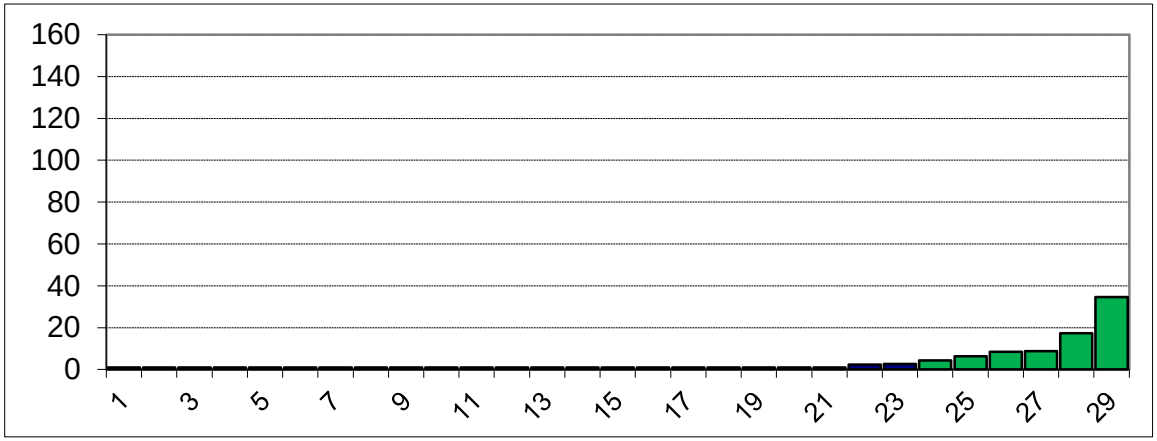
Induction of anti-MAGE-A3 antibody response

- Immunological Adjuvant Systems are not equivalent

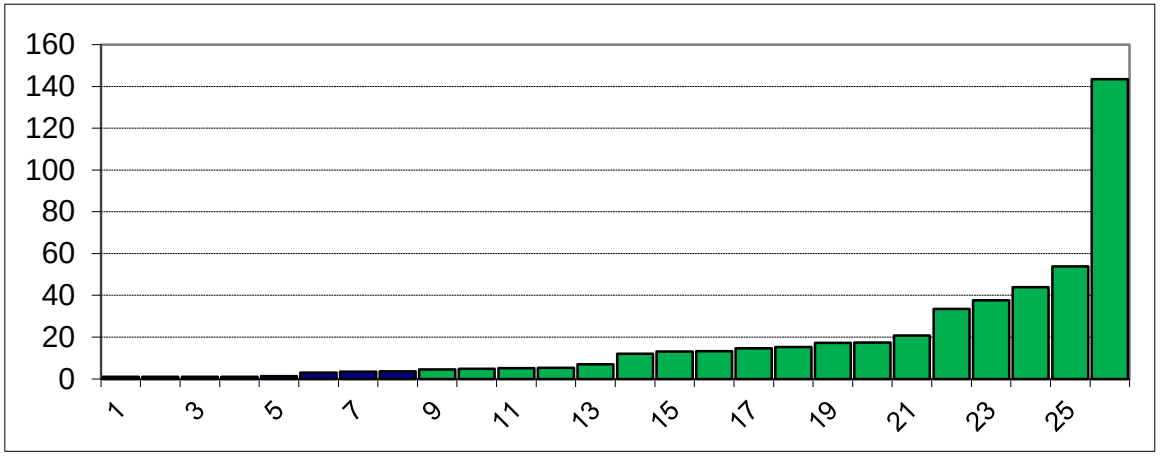


Induction of anti-MAGE-A3 CD4+ T-cells

RecMAGE-A3 + AS02$_B$



RecMAGE-A3 + AS15



Max Ratio baseline/any timepoint

Individual Patients

CD4 + T cell Responders*

6/29

21%

18/26

69%

***CD4 + T cell Responders are defined as when ratio any time point CD4 activity/ baseline CD4 activity is >4**

Melanoma Trial - Clinical Results (1)

EORTC European Organization for Research and Treatment of Cancer

- **Immunological Adjuvants Systems are not equivalent**

- **Median follow-up = 4-Years**
  N patients who have received > 16 doses:
  - recMAGE-A3 + AS15 Arm: 8 patients
  - recMAGE-A3 + $AS02_B$ Arm: 5 patients

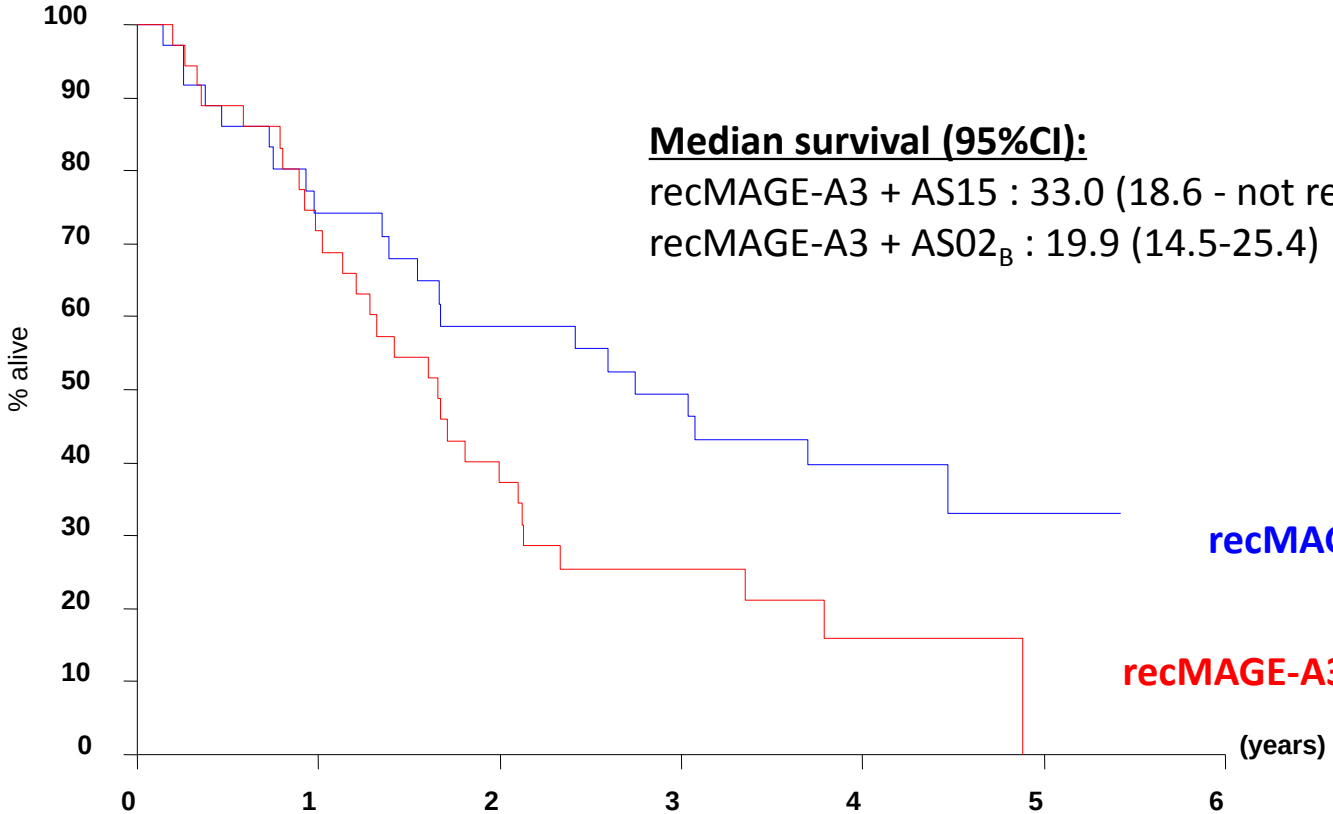
- **5 clinically objective responses were observed**

	recMAGE-A3 + $AS02_B$		recMAGE-A3 + AS15	
	N	Duration	N	Duration
CR	**0**		**3**	**11 months** **28+ months** **55+ months**
PR	**1**	**7 months**	**1**	**6 months**
SD > 16 wk	5		5	
PD*	30		26	
NE	0		1	

- * MixR in 3 ($AS02_B$) and 4 (AS15) patients, respectively
- CR: Complete Response, PR: Partial Response, SD: Stable disease, PD: Progressive Disease, NE: Non evaluable

Melanoma Trial - Clinical Results (2)

Overall Survival



Median survival (95%CI):

recMAGE-A3 + AS15 : 33.0 (18.6 - not reached) months

recMAGE-A3 + $AS02_B$: 19.9 (14.5-25.4) months

recMAGE-A3 + AS15

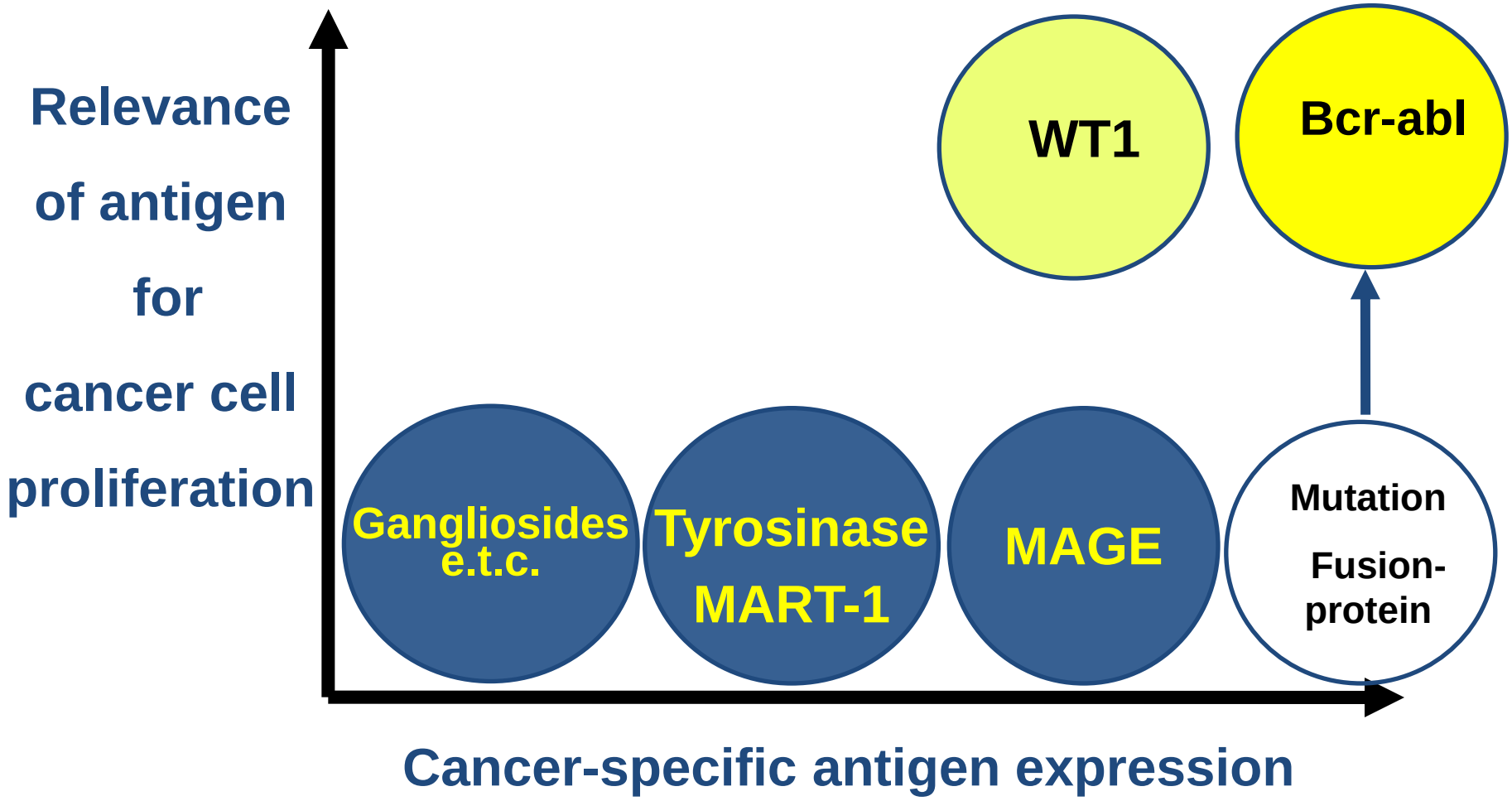
recMAGE-A3 + $AS02_B$

O	N	Number of patients at risk :					Treatment
21	36	24	19	16	8	2	AS15
29	36	25	13	8	3	0	$AS02_B$

Melanoma Trial - Conclusions

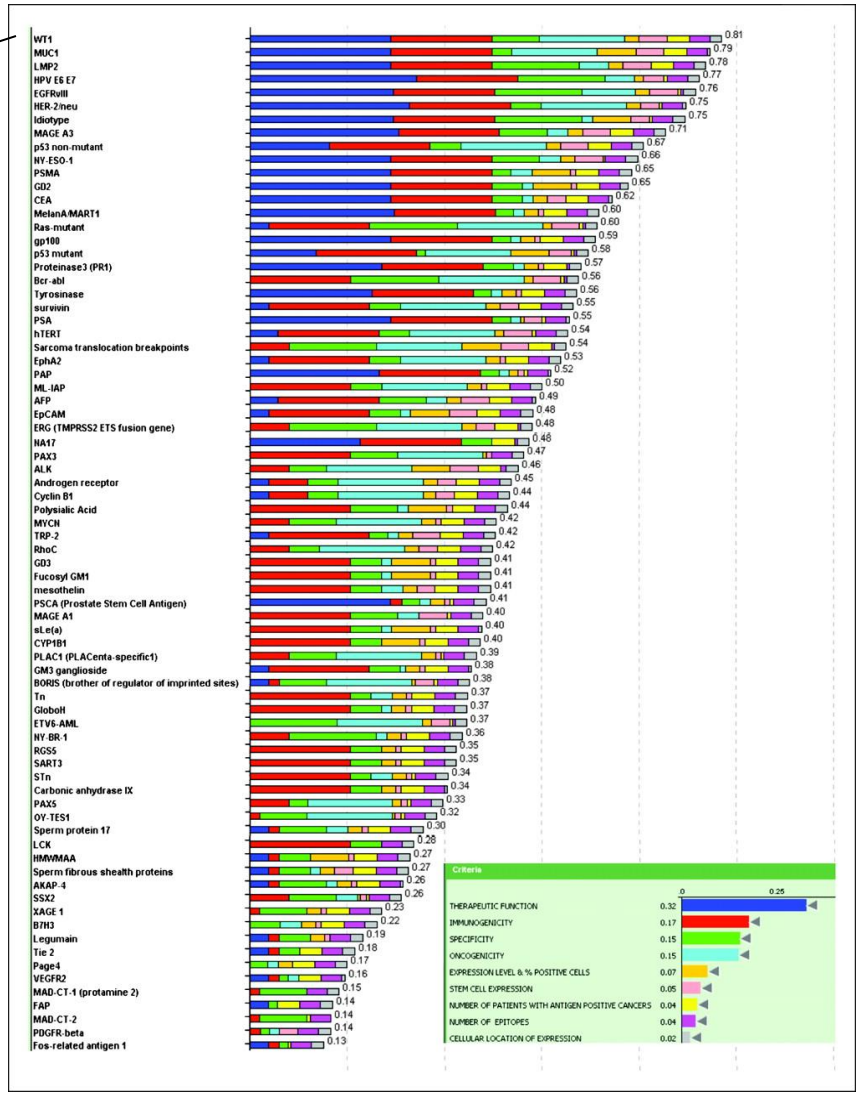
- Both MAGE-A3 ASCI formulations were well tolerated
- recMAGE-A3 + AS15 showed clinical activity in metastatic melanoma
  - 25% tumor control rate (CR+PR+SD)
  - 11% objective response rate (CR+PR)
  - Long-lasting responses and SD
  - A median survival of 33 months
- recMAGE-A3 + AS15 yielded high MAGE-A3-specific antibody titers and T-cell induction
- AS15 was selected for multiple Phase III developments

Hierarchy of tumor antigens



Cancer antigen pilot prioritization: representation of ranking based on predefined and preweighted criteria and subcriteria.

WT1
MUC1
LMP2
HPV E6 E7
EGFRvIII
HER-2-neu
Idiotype
MAGE A3
p53 (non-mut.)
NY-ESO-1
….



Criteria:
specificity
expression level
patients with positive cancers
stem cell expression
oncogenicity
cellular location of expression
number of epitopes
immunogenicity
therapeutic function

Cheever *et al.* Clin Cancer Res 2009

Clinical efficacy of WT1 vaccine in active AML/MDS (modified IWG-assessment)

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, 36+ 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), 6, 22 months
No CR following chemo:		
- PR	4	1 CR at week 10 for 12 months 2 SD 4 2 PD
- no response	1	SD 7 mo with 50% blast reduction
- PD, relapse	3	1 SD for 2 mo, 2 PD
	18	1 CR, 12 SD > 2 months **(6 patients > 6 months)**

Keilholz et al, BLOOD 2009

Clinical efficacy of WT1 vaccine in various carcinomas (RECIST 1.0)

Tumor entity	**n**	**Clinical response**	**WT1+T cells**
Ovarian cancer (chemo-refractory x 2)	7	4 SD (6 - 27 months) 3 PD	**3 / 4** 2 / 3
Mesothelioma (chemo-refractory x 2)	4	2 SD (15 - 54+ months) 2 PD	n.r.
Thyroid cancer (Iodine-refractory)	2	1 PR (10 months) 1 PD	**1 / 1** 0 / 1
Breast cancer (chemo-refractory x 2)	1	1 SPD (12 months)	**1 / 1**
Larynx cancer (chemo-refractory x 1)	1	1 PD	n.r.
Astrocytoma PD on RCT	1	1 SD (15 months)	n.r.
Gastric cancer (chemo-refractory x 1)	1	1 PD	n.r.

Keilholz, Letsch et al, WT1 conference Kyoto, 2010

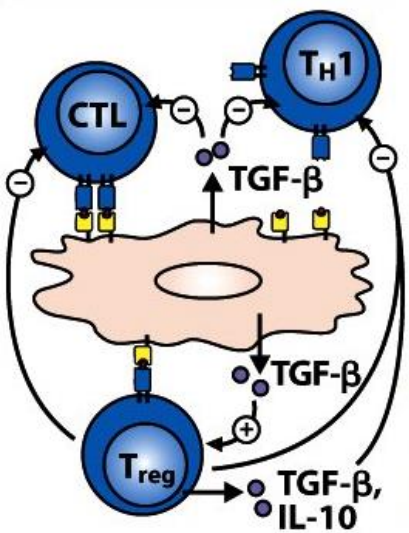
Immune-Resistance?

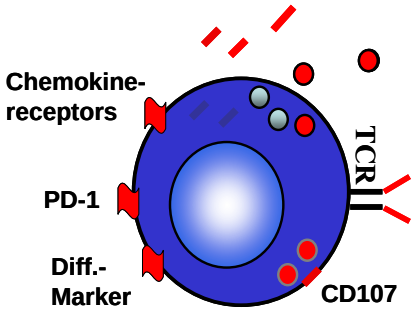
Blasts

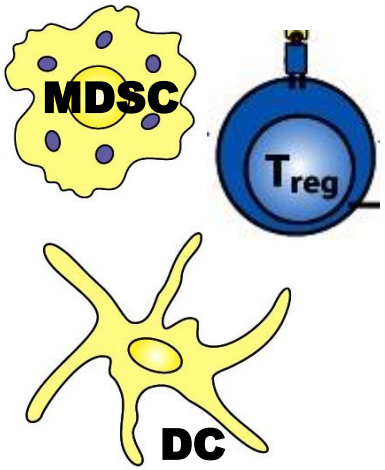
Immune system

Effectors

Modulators







Mechanism of resistance during WT1 vaccination

20 factors reported to correlate with primary or secondary resistance in cancer vaccine trials

Leukemic blasts	
HLA-loss/downregulation *	**- / 2**
WT1-downregulation*	**3/10**
WT1-mutation *	**-**
TGF beta	**-**
IL-10	**-**
PD-L1	**-**
IDO	**-**
PI-9	**-**
HMOX	**-**

T cells	
tetramer	**-**
cytokines	**-**
CD137	**-**
CD107a	**-**
memory decrease	**+**
PD-1	**+**
no BM homing#	**+**

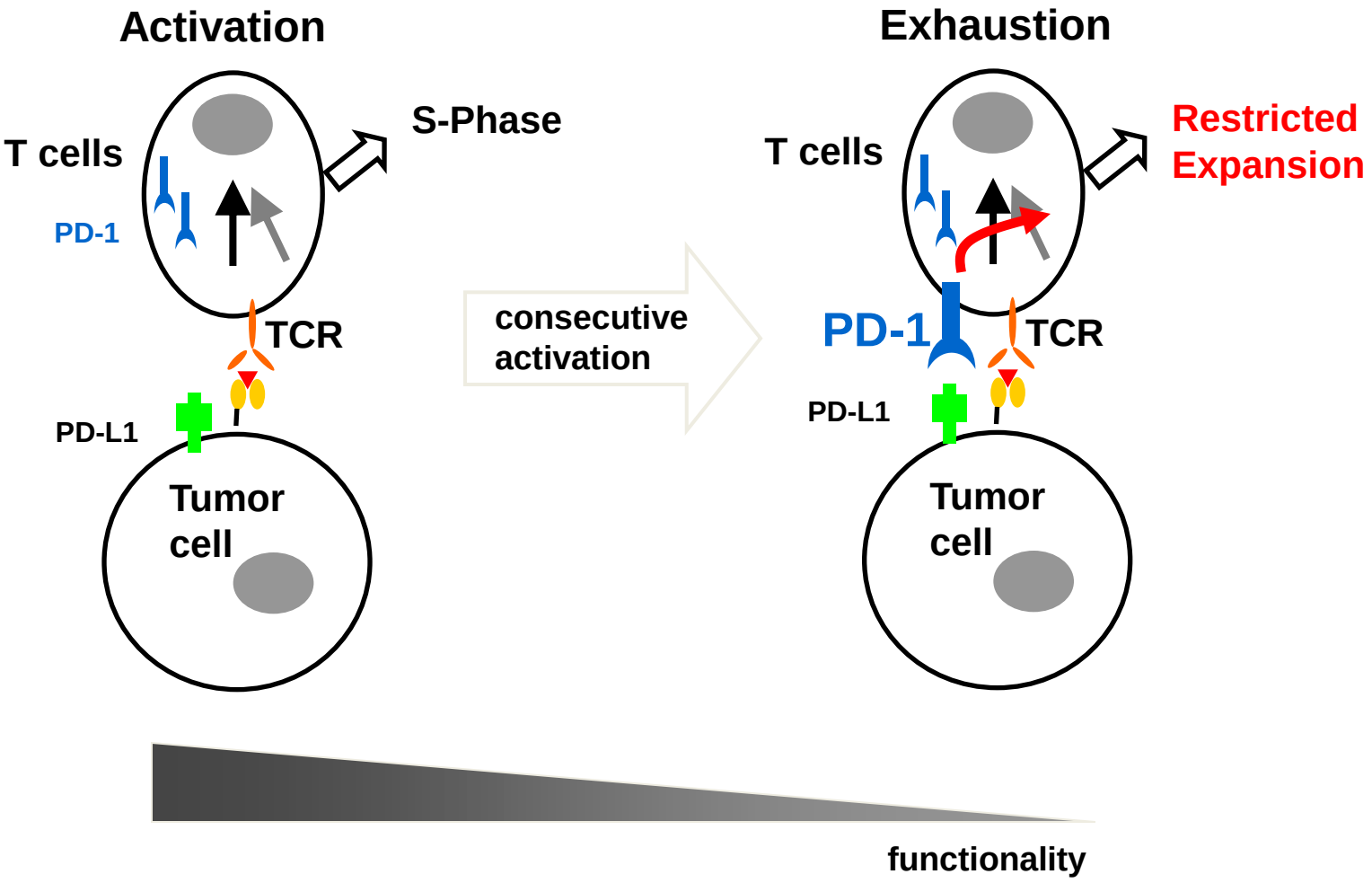
Regulatory cells	
regulatory T cells	**-**
Myeloid derived suppressor cells	**-**

B cells	
Ig G	**-**
Ig M	**(+)**

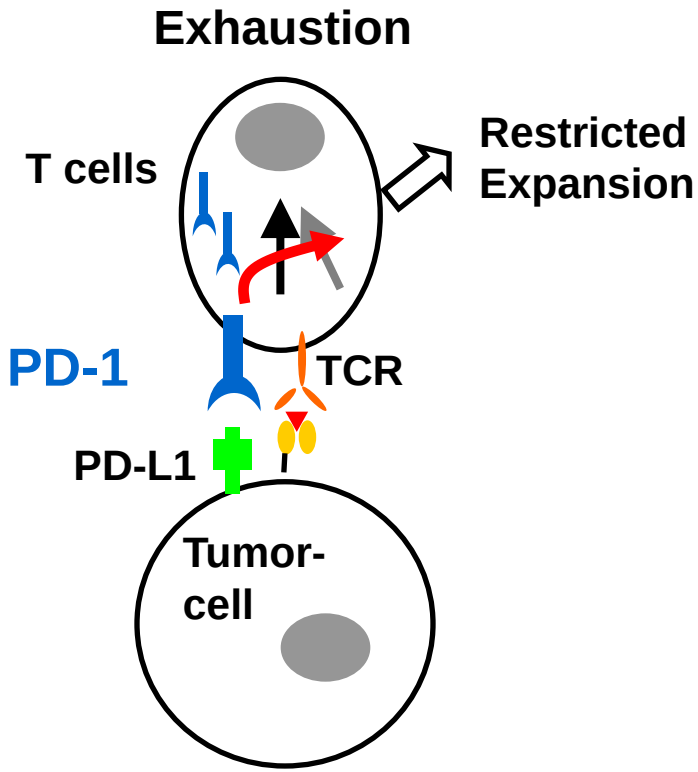
* Busse, J Transl Med 2010

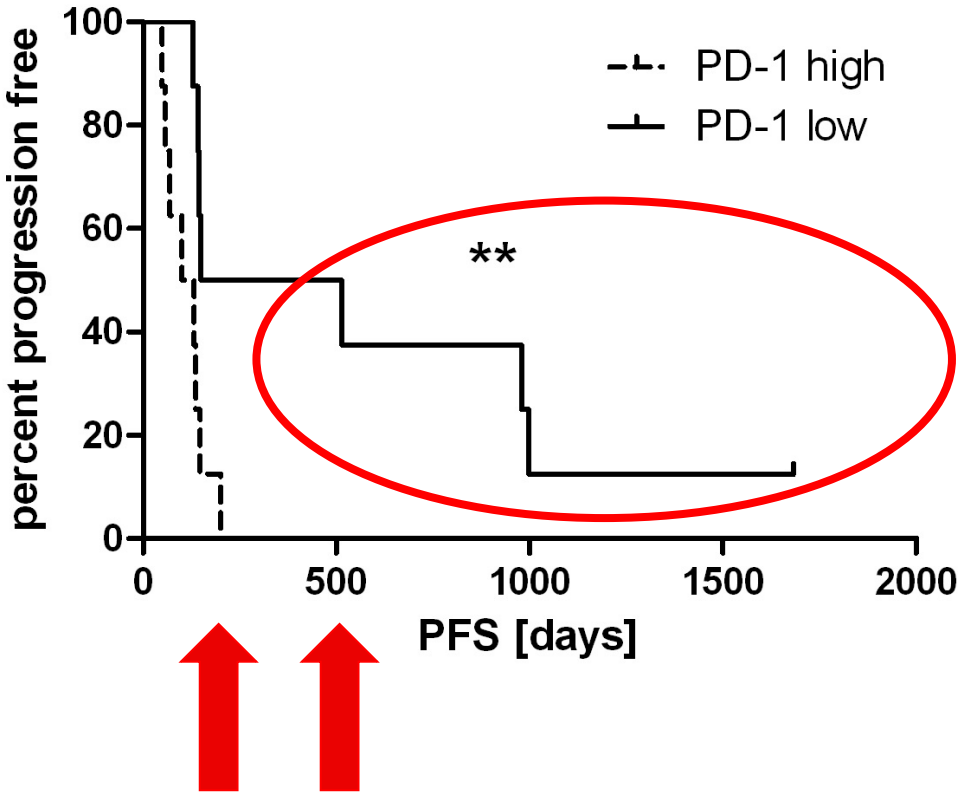
\# Ochsenreither, J Immunother 2011

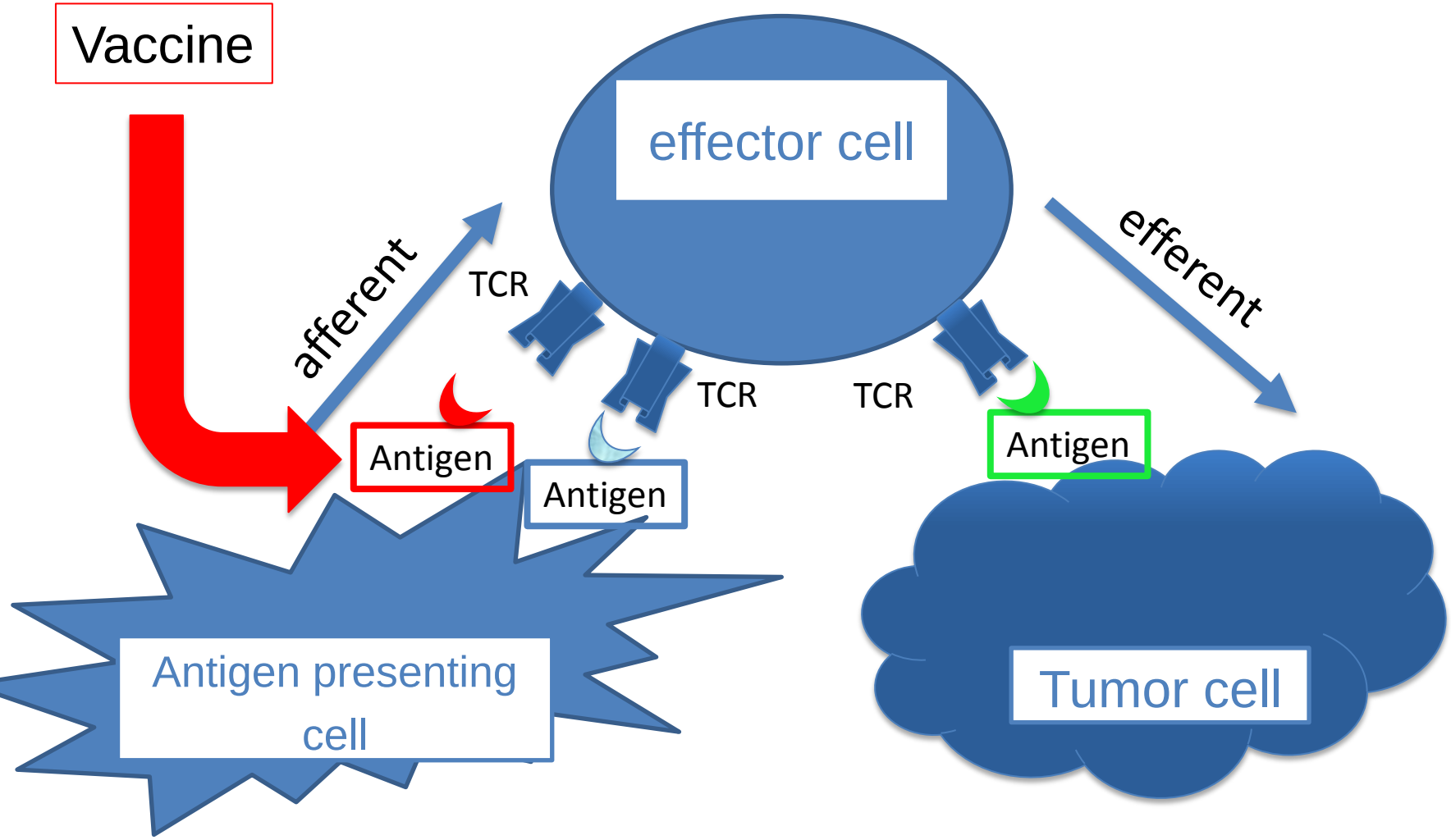
Programmed Death 1 receptor (PD-1)



High levels of PD-1 on CD8+ T cells at baseline associated with unfavorable clinical outcome

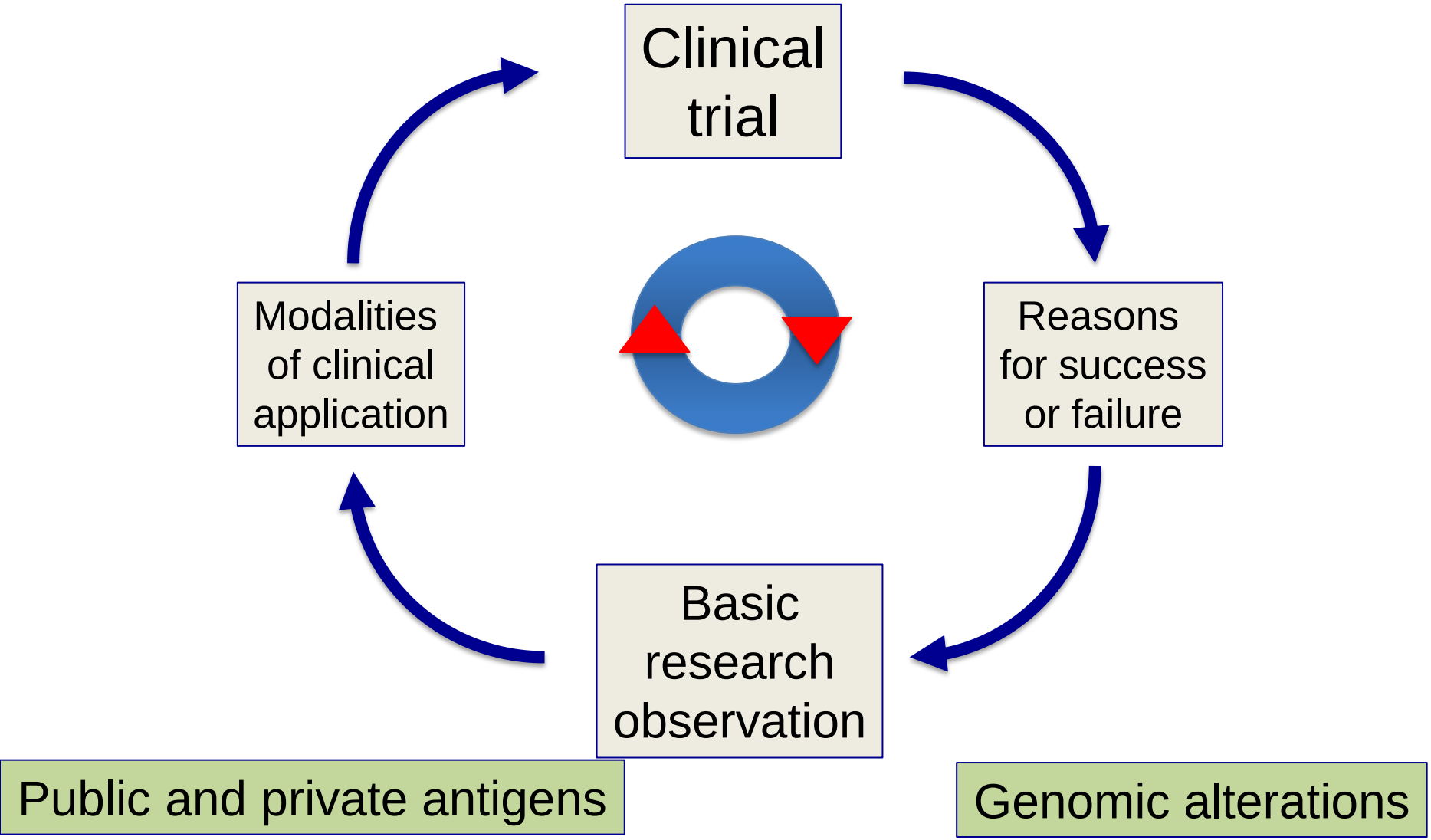






Late clinical vaccine trials

The translational research cycle



VOLUME 24 · NUMBER 19 · JULY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer

Eric J. Small, Paul F. Schellhammer, Celestia S. Higano, Charles H. Redfern, John J. Nemunaitis, Frank H. Valone, Suleman S. Verjee, Lori A. Jones, and Robert M. Hershberg

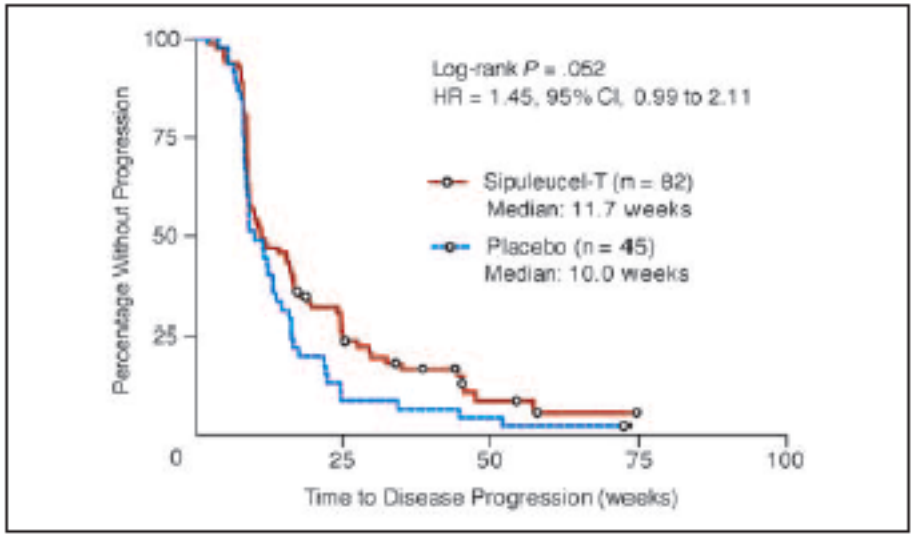


Fig 2. Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

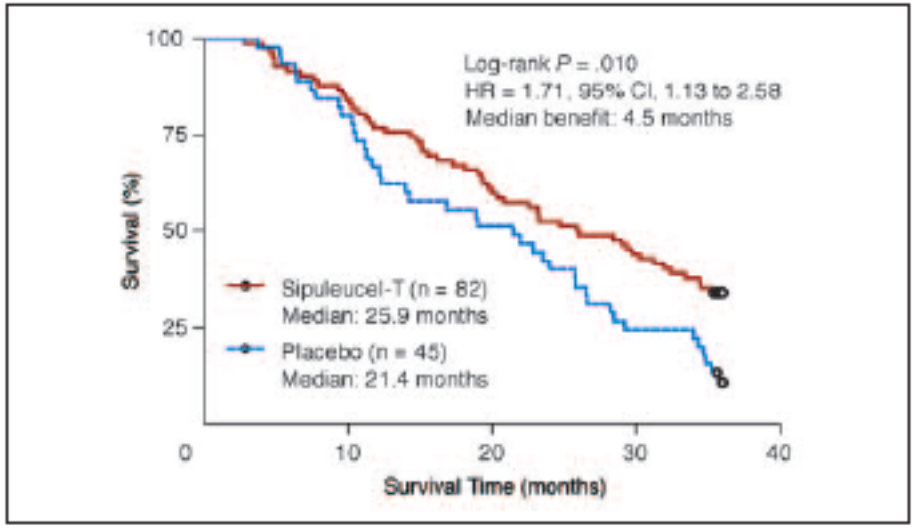


Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

Listen

FDA OKs Provenge for Prostate Cancer Therapy

'Vaccine' Is an Immune Therapy That Treats Advanced Prostate Cancer

By Daniel J. DeNoon
WebMD Health News
Reviewed by Laura J. Martin, MD

WebMD News Archive

April 29, 2010 -- The FDA today approved Provenge, Dendreon Corp.'s individualized "vaccine" for the treatment of advanced prostate cancer.

The action comes more than three years after an FDA advisory panel recommended approval, declaring the immune therapy safe and effective. But FDA concerns over efficacy led the FDA to delay a decision until more data became available.

VOLUME 31 · NUMBER 30 · OCTOBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Ganglioside GM2-KLH/QS-21 Vaccination Versus Observation After Resection of Primary Tumor > 1.5 mm in Patients With Stage II Melanoma: Results of the EORTC 18961 Randomized Phase III Trial

Alexander M.M. Eggermont, Stefan Suciu, Piotr Rutkowski, Jeremy Marsden, Mario Santinami, Philippa Corrie, Steinar Aamdal, Paolo A. Ascierto, Poulam M. Patel, Wim H. Kruit, Lars Bastholt, Lorenzo Borgognoni, Maria Grazia Bernengo, Neville Davidson, Larissa Polders, Michel Praet, and Alan Spatz

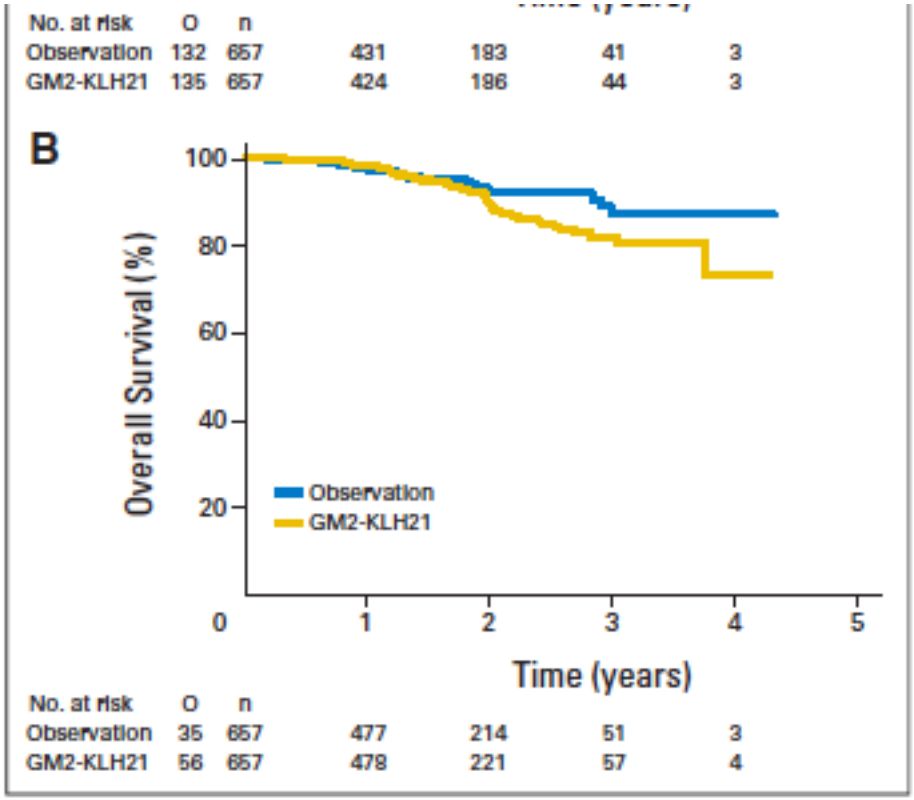


Fig 2. Results of second interim analysis. Kaplan-Meier curves of (A) relapse-free (hazard ratio [HR], 1.00; 98% CI, 0.75 to 1.34; two-sided Wald test $P = .99$) and (B) overall survival (HR, 1.66; 99.99% CI, 0.69 to 3.99; two-sided Wald test $P = .02$) from random assignment by treatment group. Cox models stratified by Breslow thickness, lymph node dissection, ulceration, and sex.

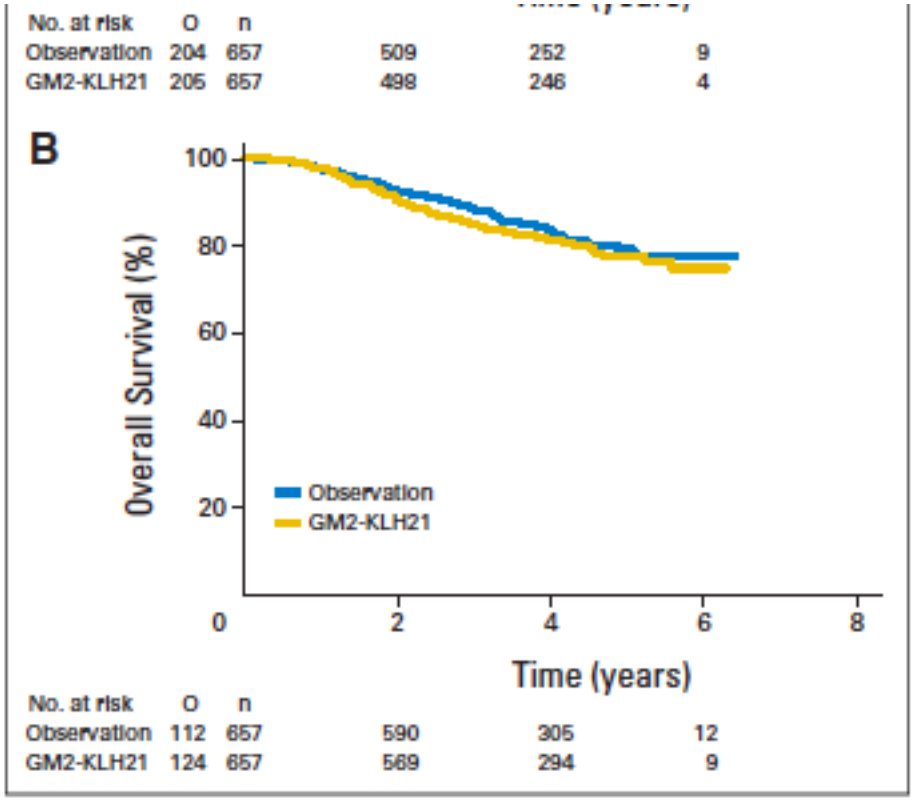


Fig 3. Results of final analysis. Kaplan-Meier curves of (A) relapse-free (hazard ratio [HR], 1.03; 95% CI, 0.84 to 1.25; two-sided Wald test $P = .81$) and (B) overall survival (HR, 1.16; 95% CI, 0.90 to 1.51; two-sided Wald test $P = .25$) from random assignment by treatment group. Cox models stratified by Breslow thickness, lymph node dissection, ulceration, and sex.

Merck KGaA ends lung cancer vaccine trials

FRANKFURT, Sept 12 Fri Sep 12, 2014 8:04am EDT

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(Reuters) - German drugmaker Merck KGaA drug stopped all remaining clinical studies of the experimental lung cancer vaccine tecemotide, formerly known as Stimuvax, after renewed attempts to show its effectiveness failed.

Press release Sept. 12, 2014

GSK cancer vaccine fails in lung cancer trial

WORLD NEWS | MARCH 20, 2014

KEVIN GROGAN

Tweet 0 0 Share 3

GlaxoSmithKline has suffered a setback after announcing more disappointing late-stage data from a non-small cell lung trial of its cancer vaccine MAGE-A3.

The UK major says that its MAGE-A3 antigen-specific cancer immunotherapeutic did not meet its first or second co-primary endpoint in a Phase III NSCLC trial. The study did not significantly extend disease-free survival when compared to placebo in the overall MAGE-A3 positive patients or patients who did not receive chemotherapy.

The MAGRIT trial enrolled 2,312 MAGE-A3-positive patients across more than 400 sites in 34 countries. Patients were given up to 13 intramuscular injections of either the immunotherapeutic or placebo over a period of 27 months.

Presidential session ESMO 2014

Abstr. 11730

GSK cancer vaccine fails first part of melanoma trial

WORLD NEWS | SEPTEMBER 05, 2013 Tweet 1 0 Share

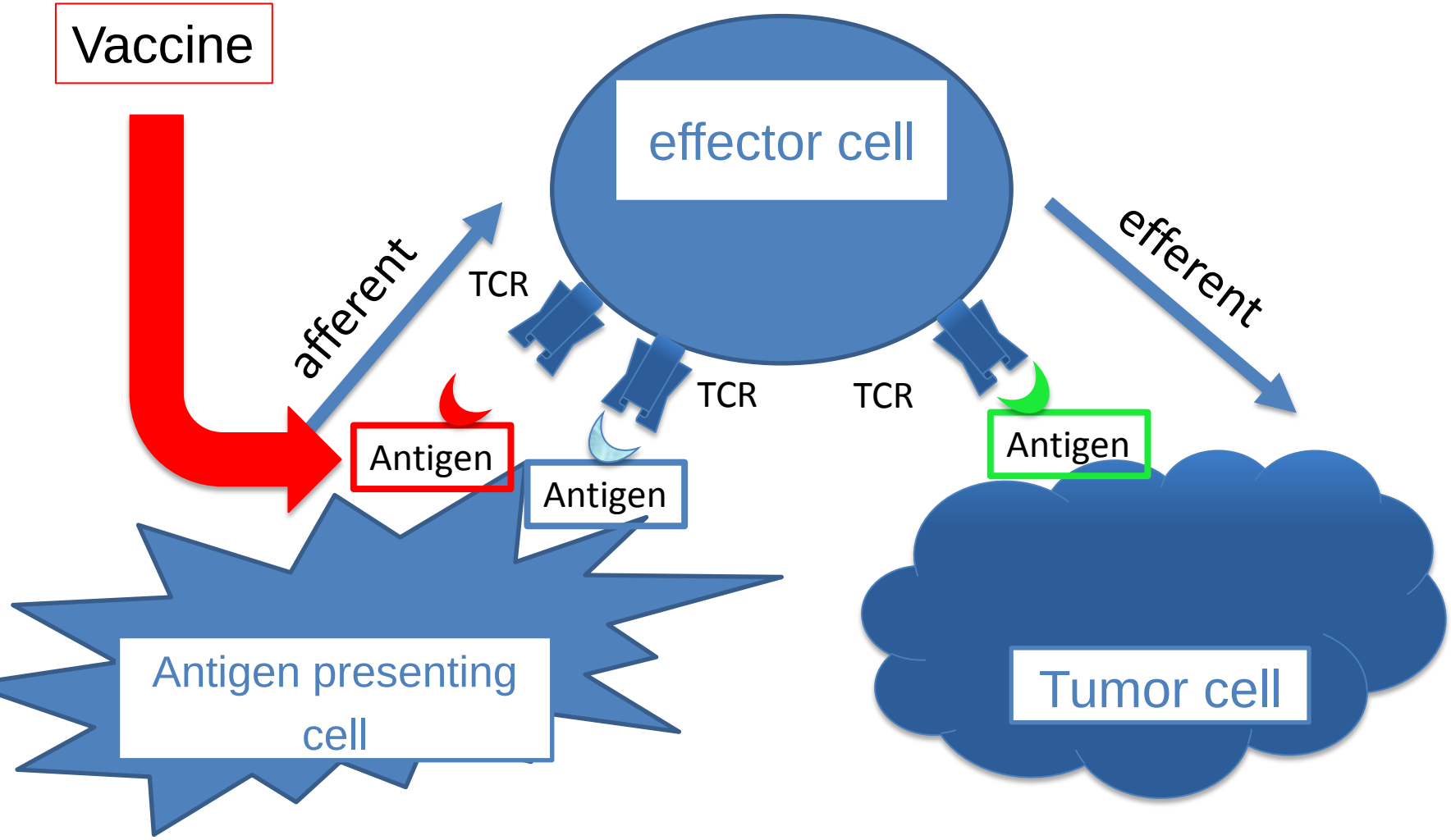
KEVIN GROGAN

GlaxoSmithKline's cancer vaccine has failed to meet its first co-primary endpoint in a Phase III melanoma clinical trial.

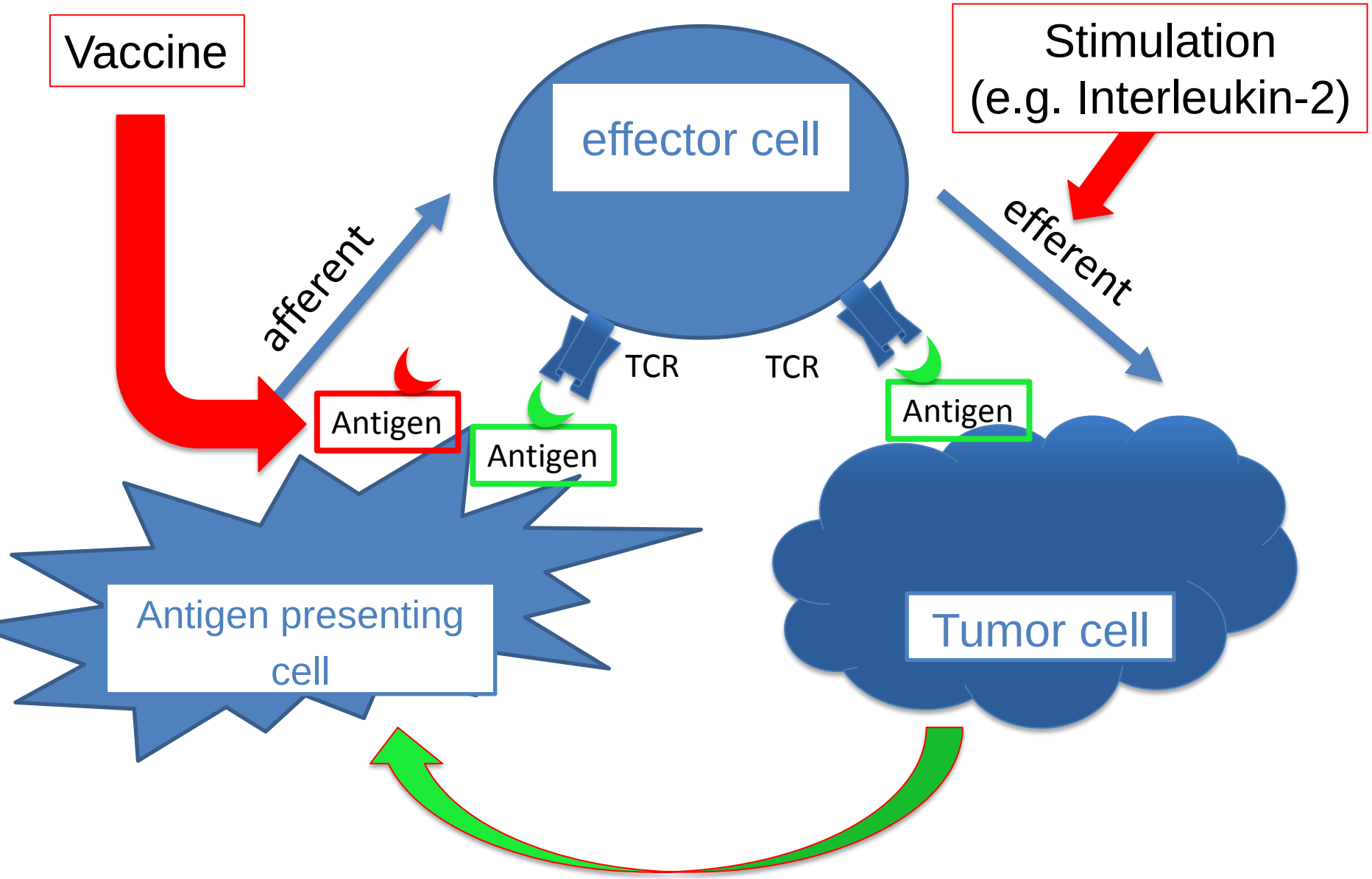
The drugs giant notes that an independent analysis of the DERMA study of its MAGE-A3 cancer immunotherapeutic showed that it did not significantly extend disease-free survival in stage IIIB/C melanoma patients with macroscopic nodal disease, whose tumours expressed the MAGE-A3 gene when compared to placebo. The aforementioned gene is expressed in about 65% of stage III melanomas.

Press release Sept. 5, 2013

Subgroup analysis still maturing



How to overcome low efficacy

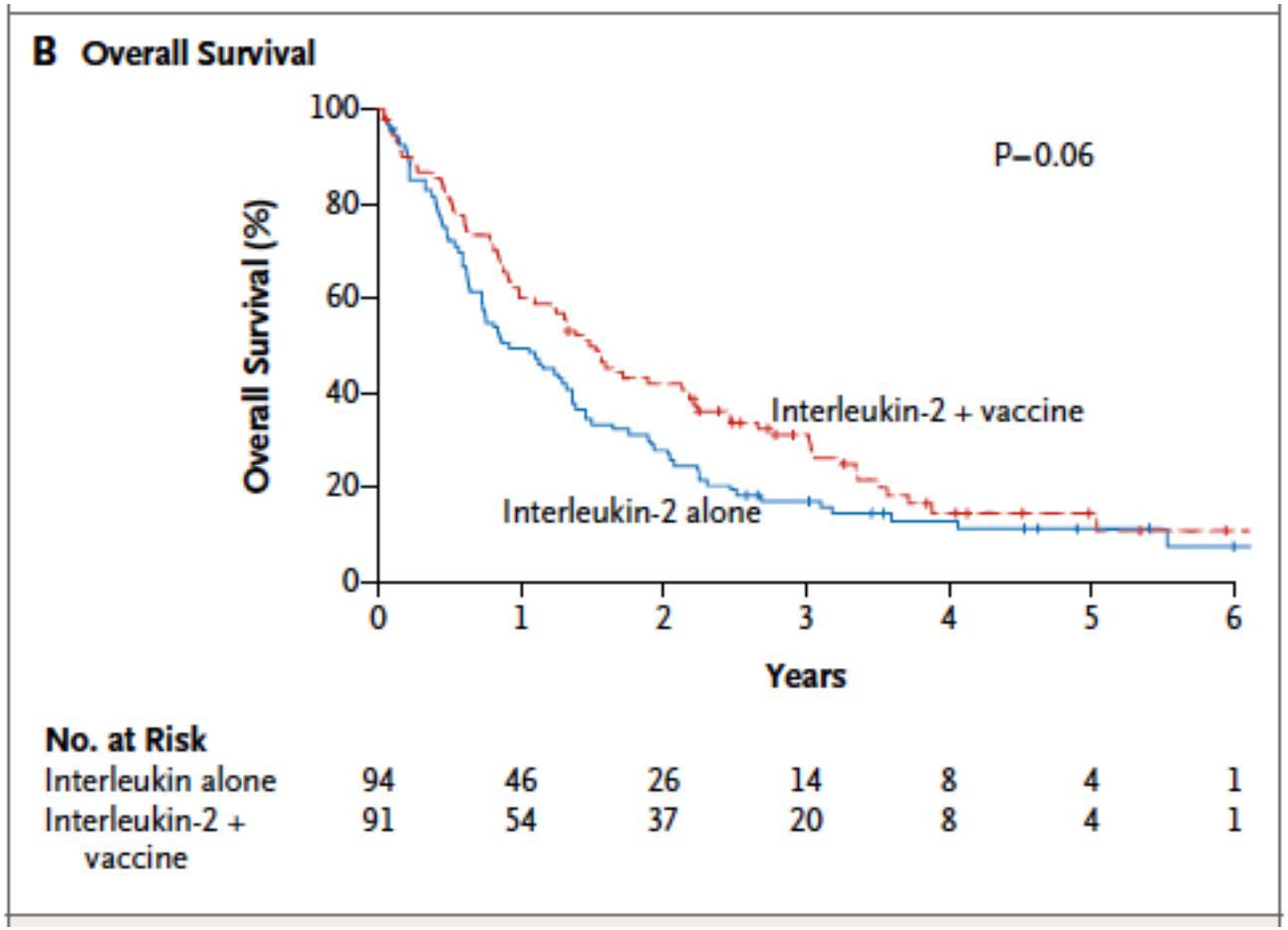

Vaccine
Stimulation
(e.g. Interleukin-2)
effector cell
afferent
efferent
TCR
TCR
Antigen
Antigen
Antigen
Antigen presenting
cell
Tumor cell

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

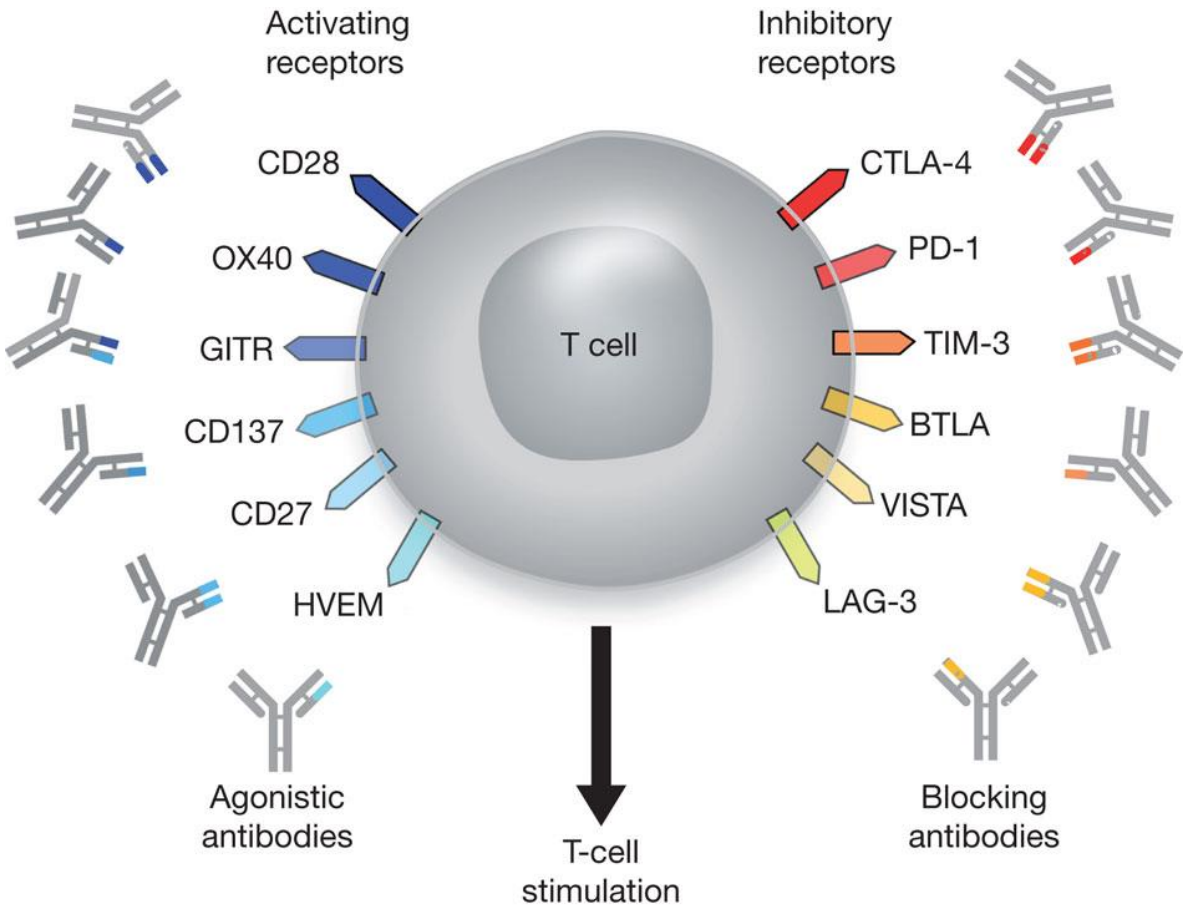
gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.

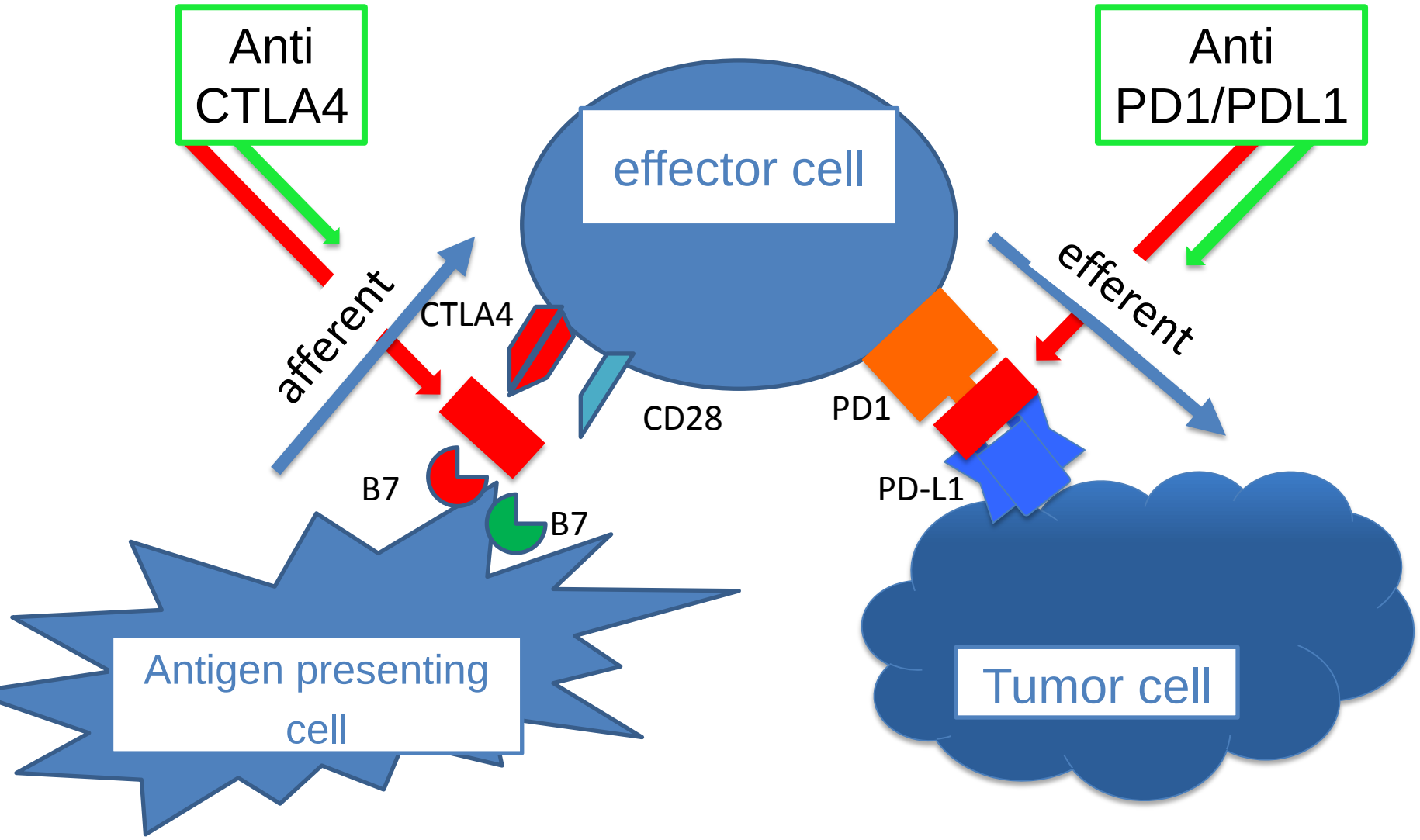


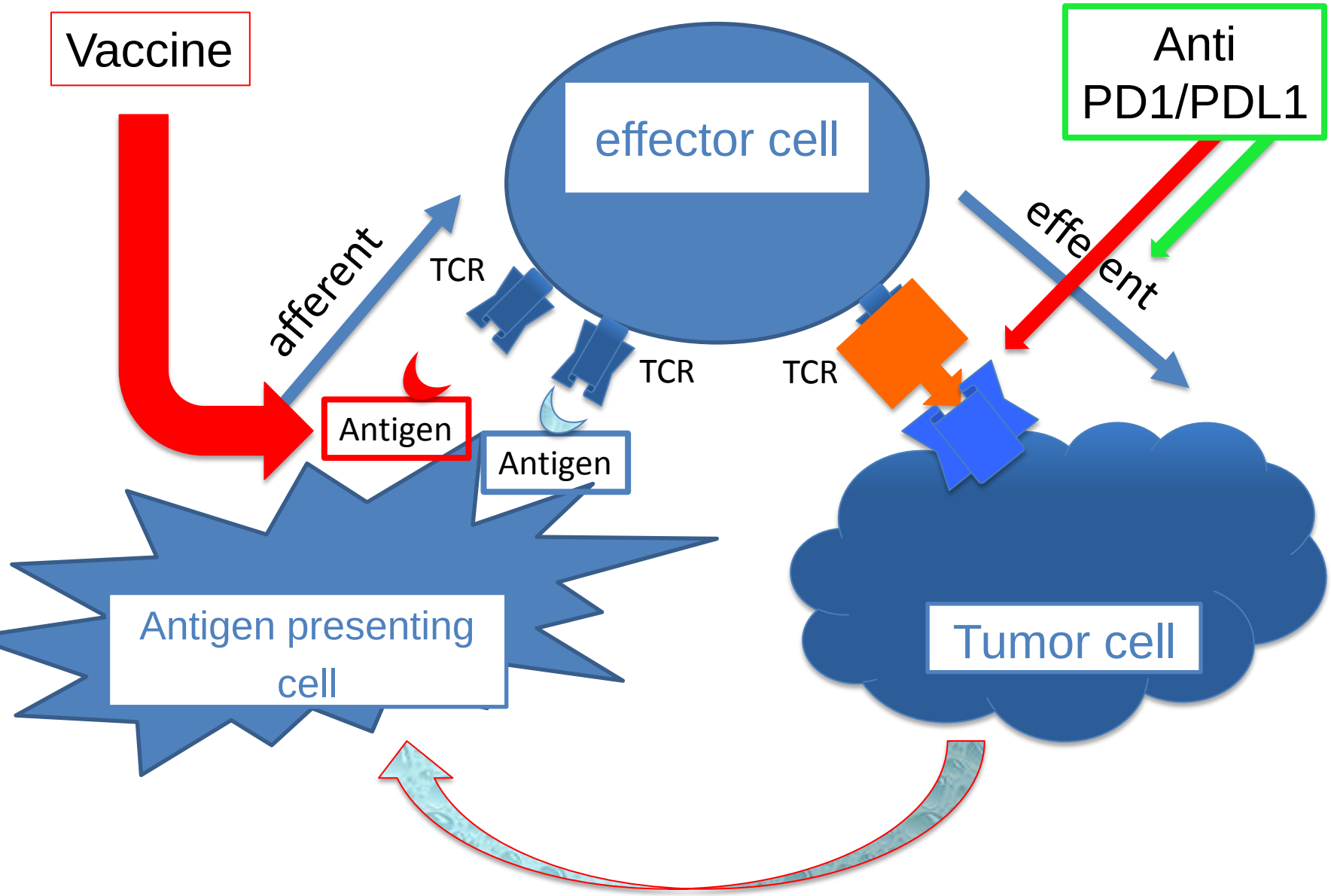
Schwartzentruber et al., NEJM 2011

T-cell-Targets for immunoregulatory antibodies



I Mellman *et al. Nature* 480, 480-489 (2011)


Anti
CTLA4
Anti
PD1/PDL1
effector cell
afferent
efferent
CTLA4
CD28
PD1
B7
B7
PD-L1
Antigen presenting
cell
Tumor cell


Vaccine
effector cell
Anti
PD1/PDL1
afferent
TCR
TCR
TCR
effe ent
Antigen
Antigen
Antigen presenting
cell
Tumor cell

Future direction
... leading into the presentation by Ignacio Melero

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ORIGINAL REPORT

Safety, Efficacy, and Biomarkers of Nivolumab With Vaccine in Ipilimumab-Refractory or -Naive Melanoma

Jeffrey S. Weber, Ragini Reiney Kudchadkar, Bin Yu, Donna Gallenstein, Christine E. Horak, H. David Inzunza, Xiuhua Zhao, Alberto J. Martinez, Wenshi Wang, Geoffrey Gibney, Jodi Kroeger, Cabell Eysmans, Amod A. Sarnaik, and Y. Ann Chen