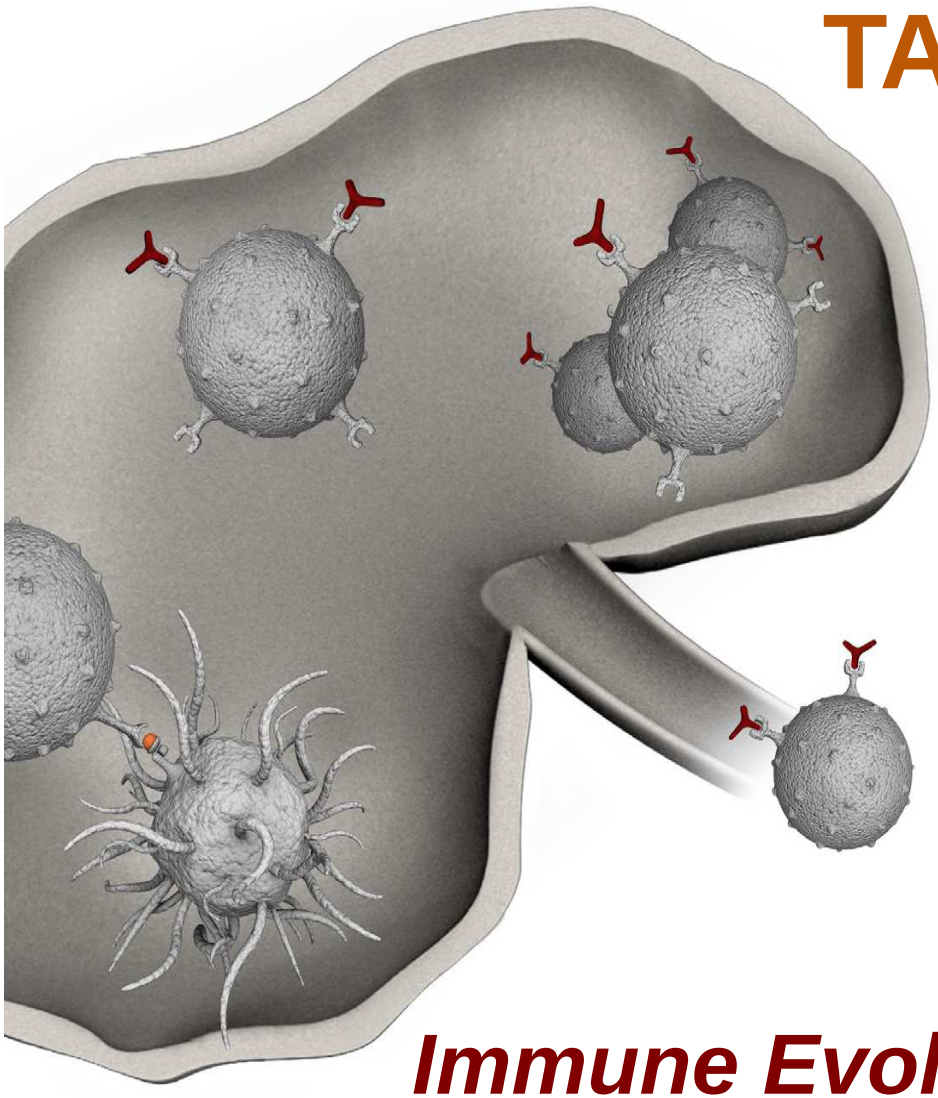
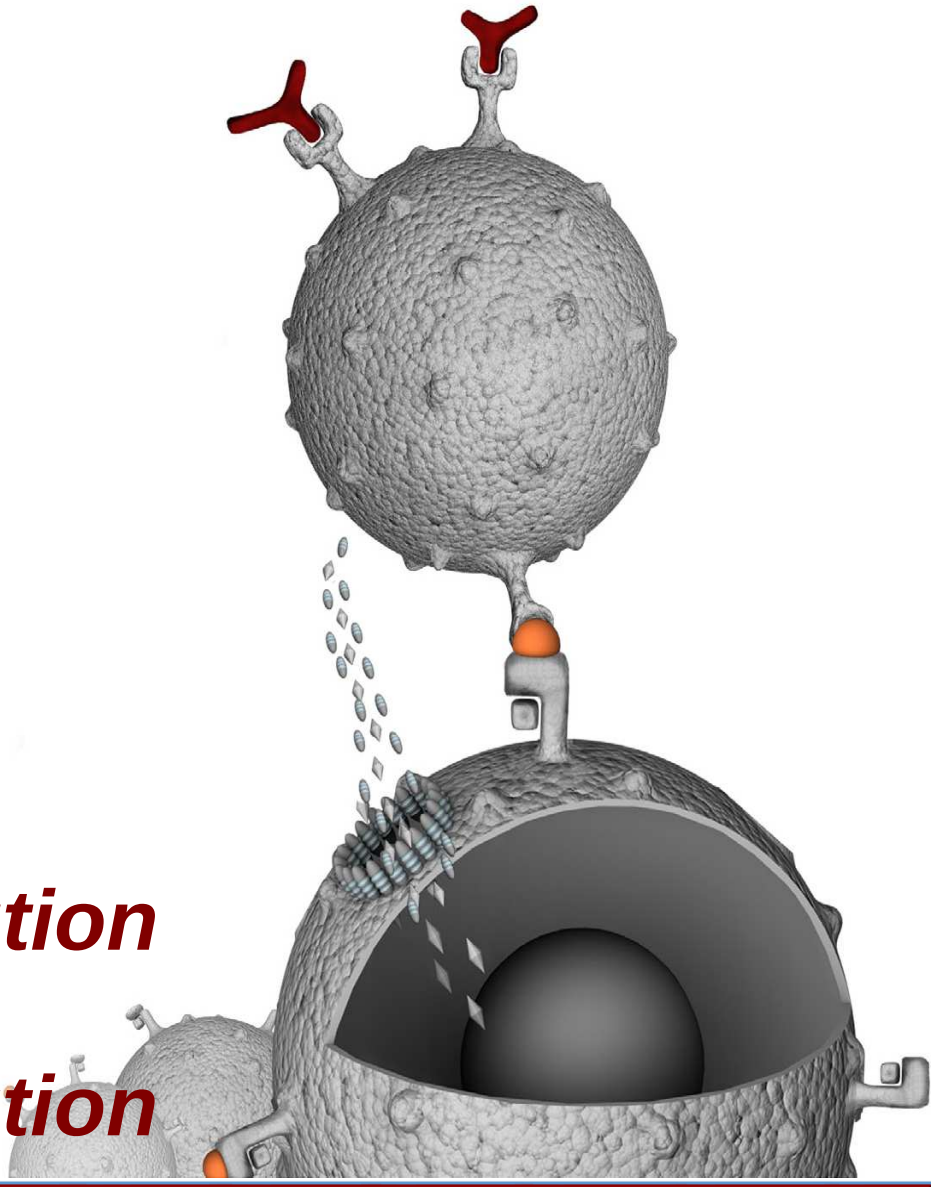
TARGETING 4-1bb



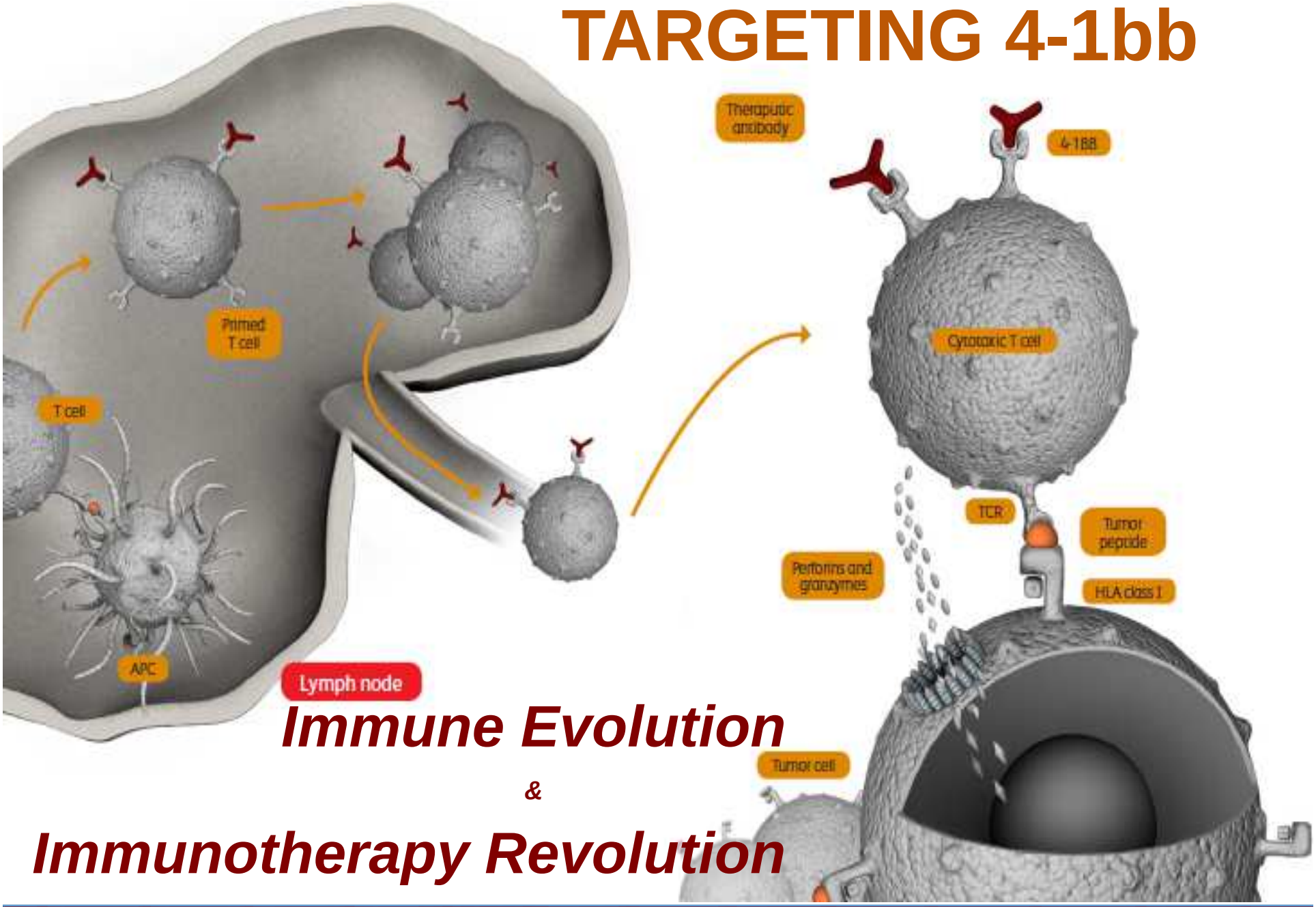


Immune Evolution

&

Immunotherapy Revolution

TARGETING 4-1bb



Immune Evolution

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Immunotherapy has changed the game

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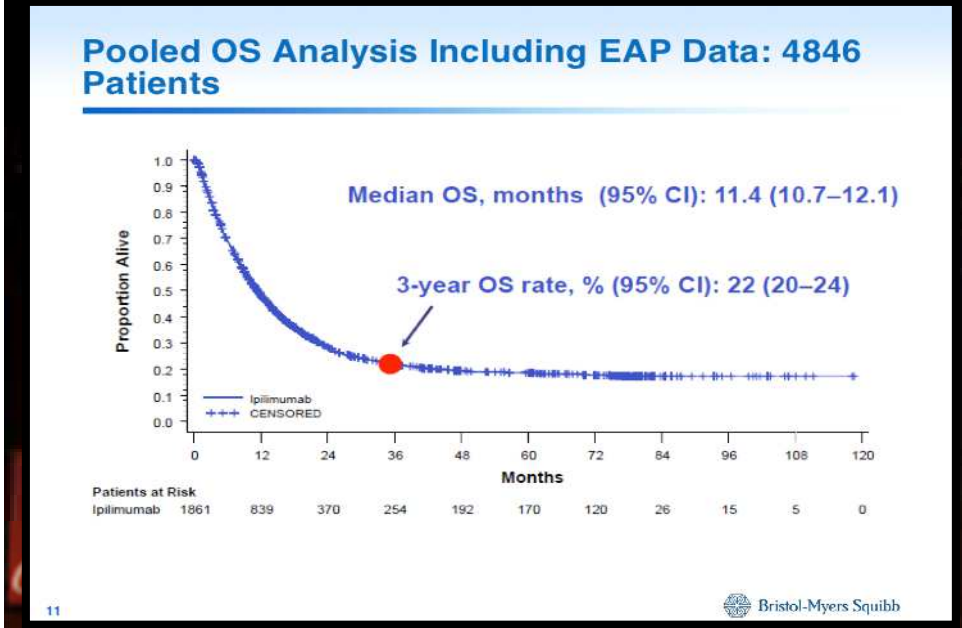
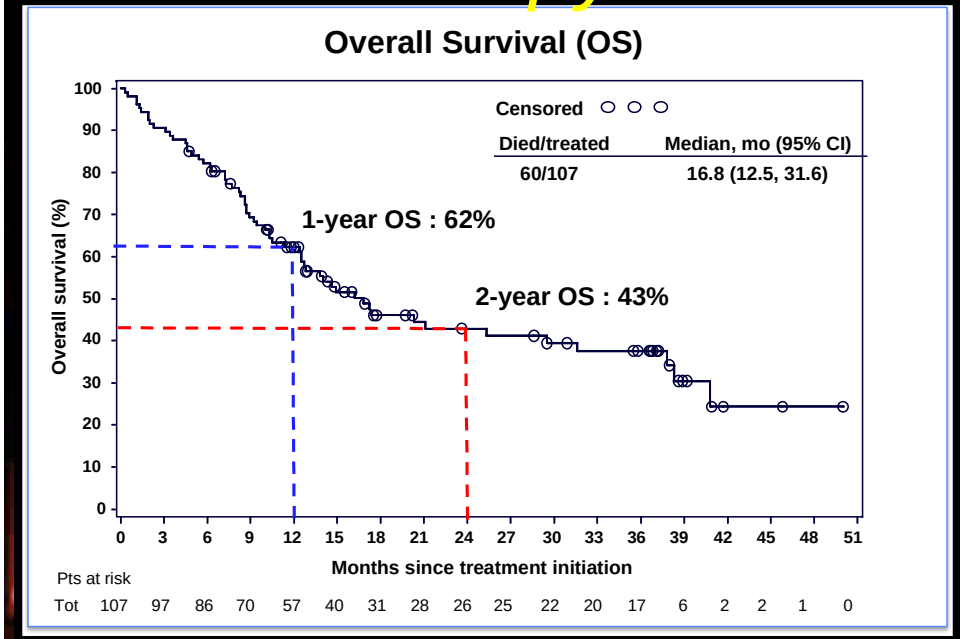


Immunotherapy has changed the game



Immunotherapy has changed the game

… A new roster of players

Immunotherapy has changed the game

… A new roster of players

LINE-UP CARD

Team: Immunotherapy
vs Cancer

Date: November 2014

#	POS.	BATTING ORDER		SUBSTITUTES	INNING	POS.	UNI #
1	2011	CTLA-4	BMS	MedImmune			
2	2014	PD-1	Merck	BMS, Tesaro/Anaptys, CoStim/Novartis, MedImmune/Amplimmune, CureTech			
3	?	PD-L1	?	Genentech/Roche, MedImmune, EMD Serono			
4	?	LAG-3	?	BMS, GSK			
5	?	KIR	?	BMS			
6	?	CD27	?	Celldex			
7	?	OX-40	?	MedImmune			
8	?	GITR	?	GITR Inc., Merck			
9	?	CD137, 4-1bb	?	BMS, Pfizer			

USED	POS.	PINCH HITTERS AVAILABLE	BATS R	BATS L
		CD47		
		CD40		
		B7-H3		
		IL-15		
		IL-21		
		CCR2		
		CXCR4		
		CCR4		
		IDO		
		VEGF		

Next at bat

USED	PITCHERS AVAILABLE	AVAIL. INNINGS	THROWS R	THROWS L
	ICOS			
	TIGIT			
	TIM-3			
	VISTA			
	STING			

In the bullpen

Immunotherapy has changed the game

… A new roster of players

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In the bullpen

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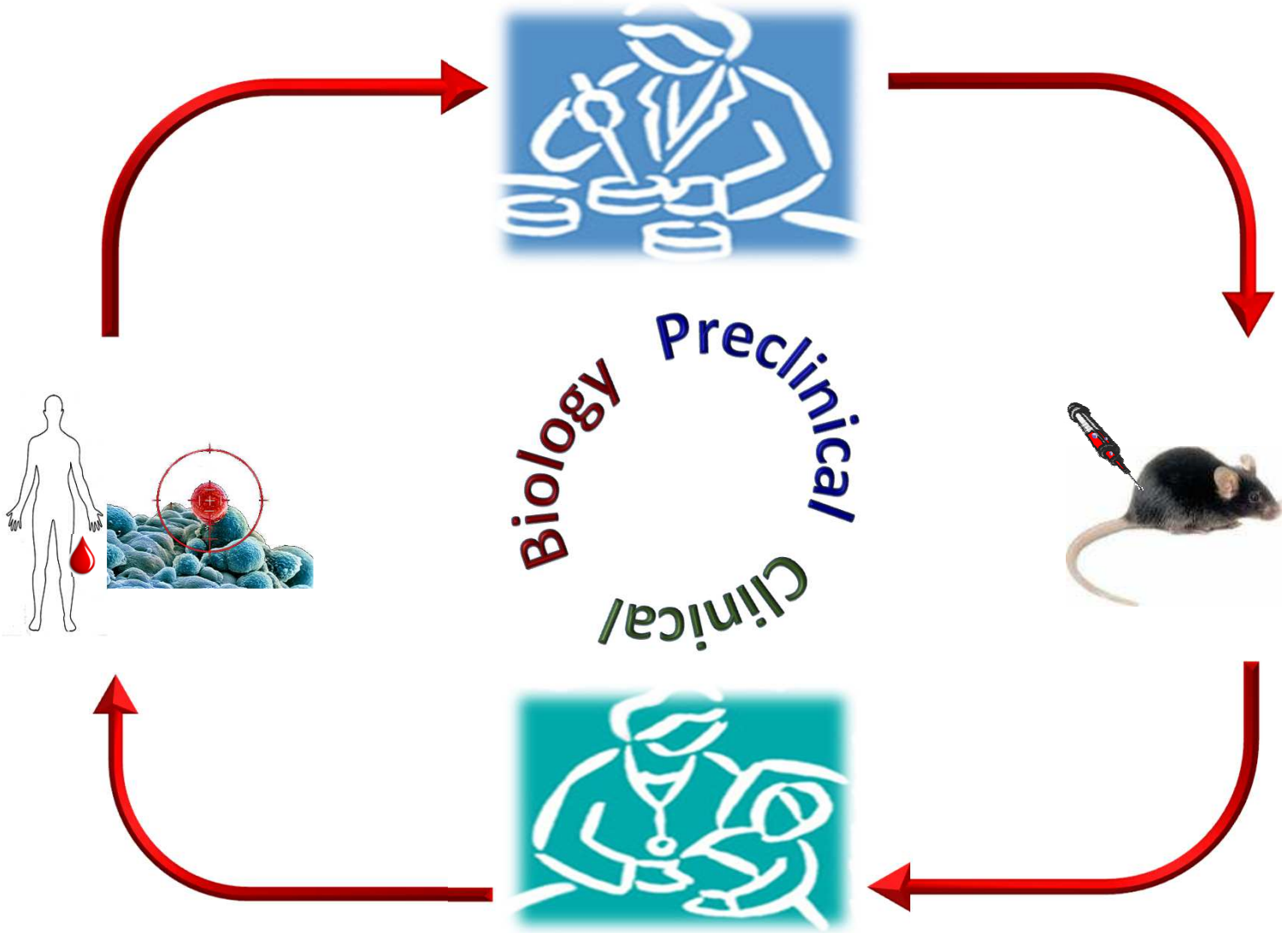
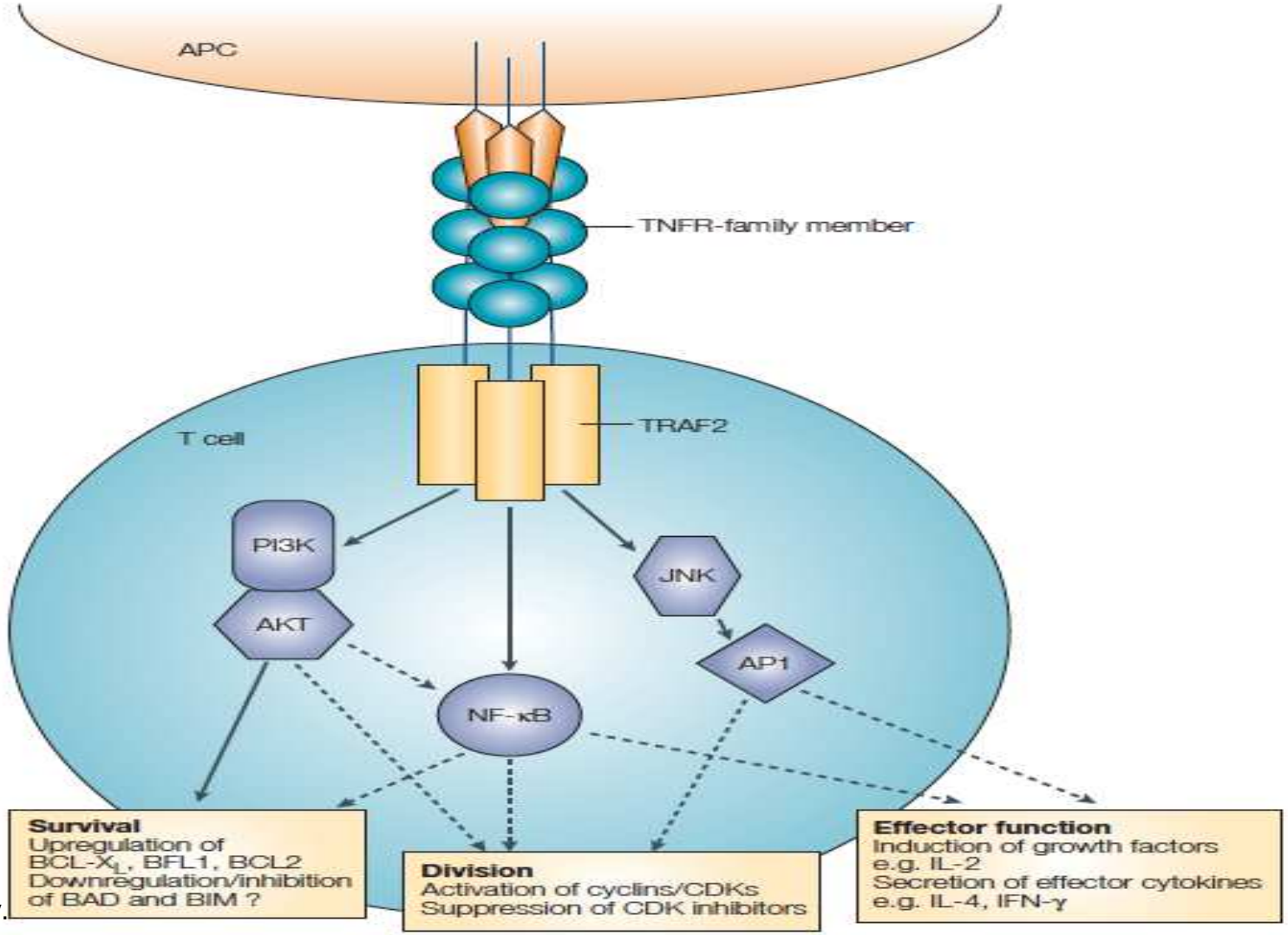


MOLECULAR BIOLOGY



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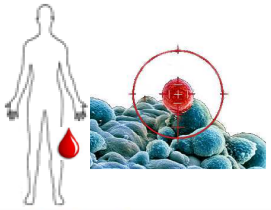
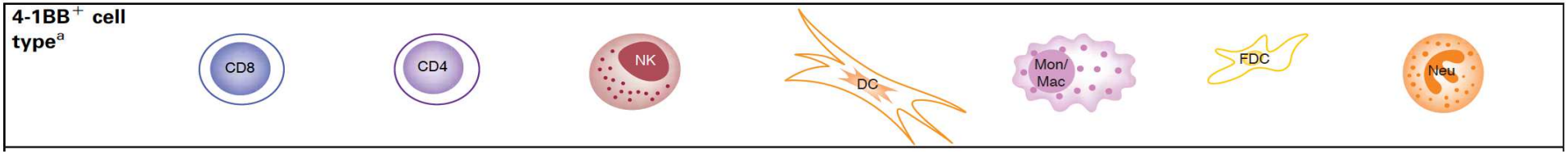


CELLULAR BIOLOGY



Inhibition/activation
In vivo paradox

Antigen-independent activation

-Resistance to apoptosis
-Proliferation
-Gain effector functions
-Differentiation to memory cells

Activated CD4+ T cell

Memory CD8+ T cell

Activated CTL

Cytokine Secretion IL-13 and IFN-γ

NKT cell

T regs ?

Anti-CD137 mAb

Activated NK cell

Early Cytokine production

Controversial effects on regulatory function

Tumor endothelium

Dendritic cell

IKDC?

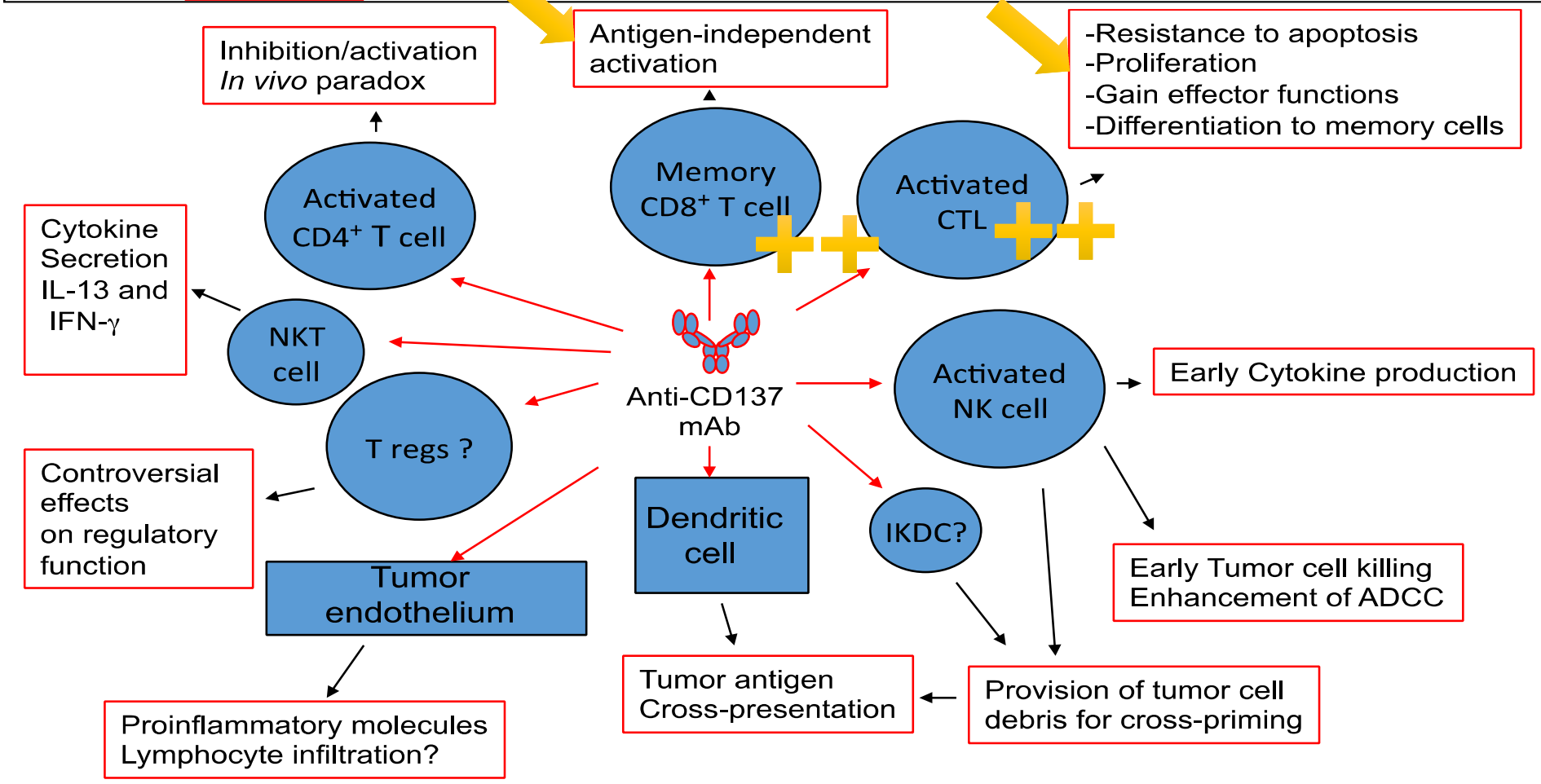
Early Tumor cell killing
Enhancement of ADCC

Proinflammatory molecules
Lymphocyte infiltration?

Tumor antigen Cross-presentation

Provision of tumor cell debris for cross-priming

4-1BB$^+$ cell type[a]	CD8 + CD4	NK	DC	Mon/Mac	FDC	Neu
Effects of acute induction[b]	Increased survival and IFN-γ and IL-2 production, also cytotoxicity	Increased survival and IL-2 and IL-4 production	CD8 T-cell 'help', IFN-γ production, proliferation, IL-2Rα expression	Increased IL-6 and IL-12 production and CD80 and CD86 expression	Decreased IL-10 and increased IL-8 production, TNF production	Unknown	Abrogation of GM-CSF production
Outcome[c]	Antiviral and tumoricidal activity and regulation	Inhibition of B-cell help (anergy) and effects on Treg cells	Enhances tumoricidal activity	Enhances T-cell activation	Contact-dependent B-cell apoptosis	Potential to stimulate B-cell activation	Potential to inhibit tissue damage



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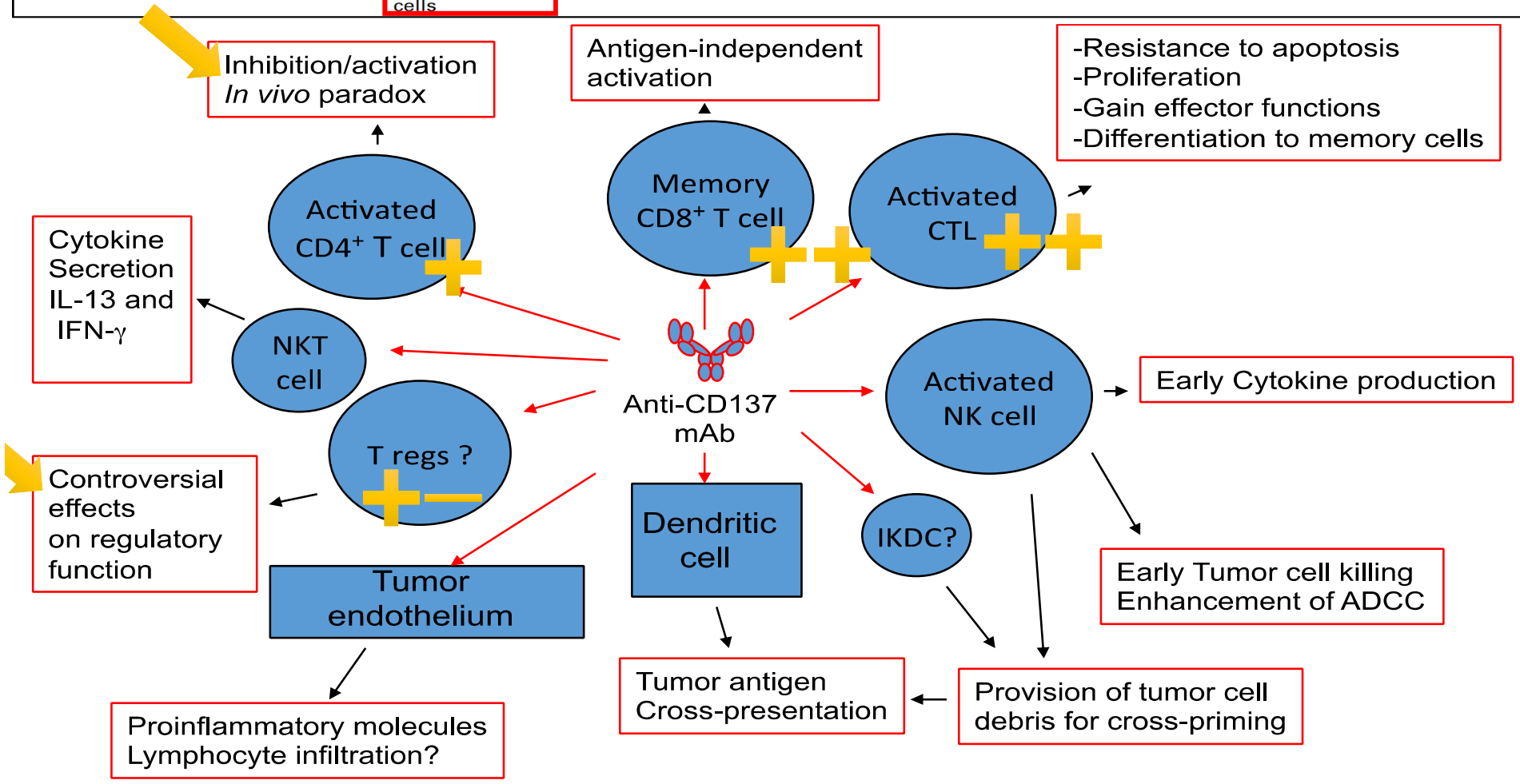

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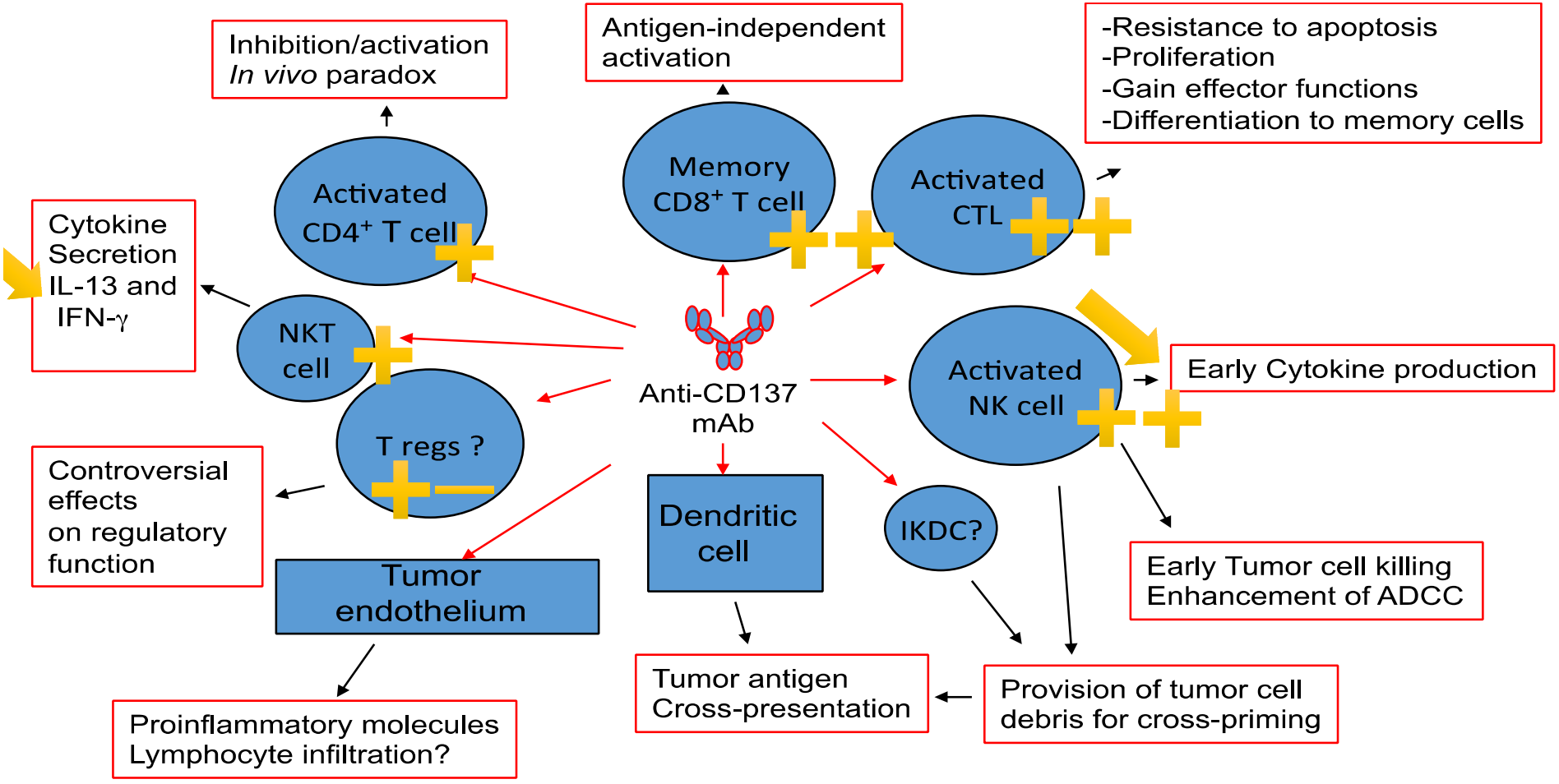

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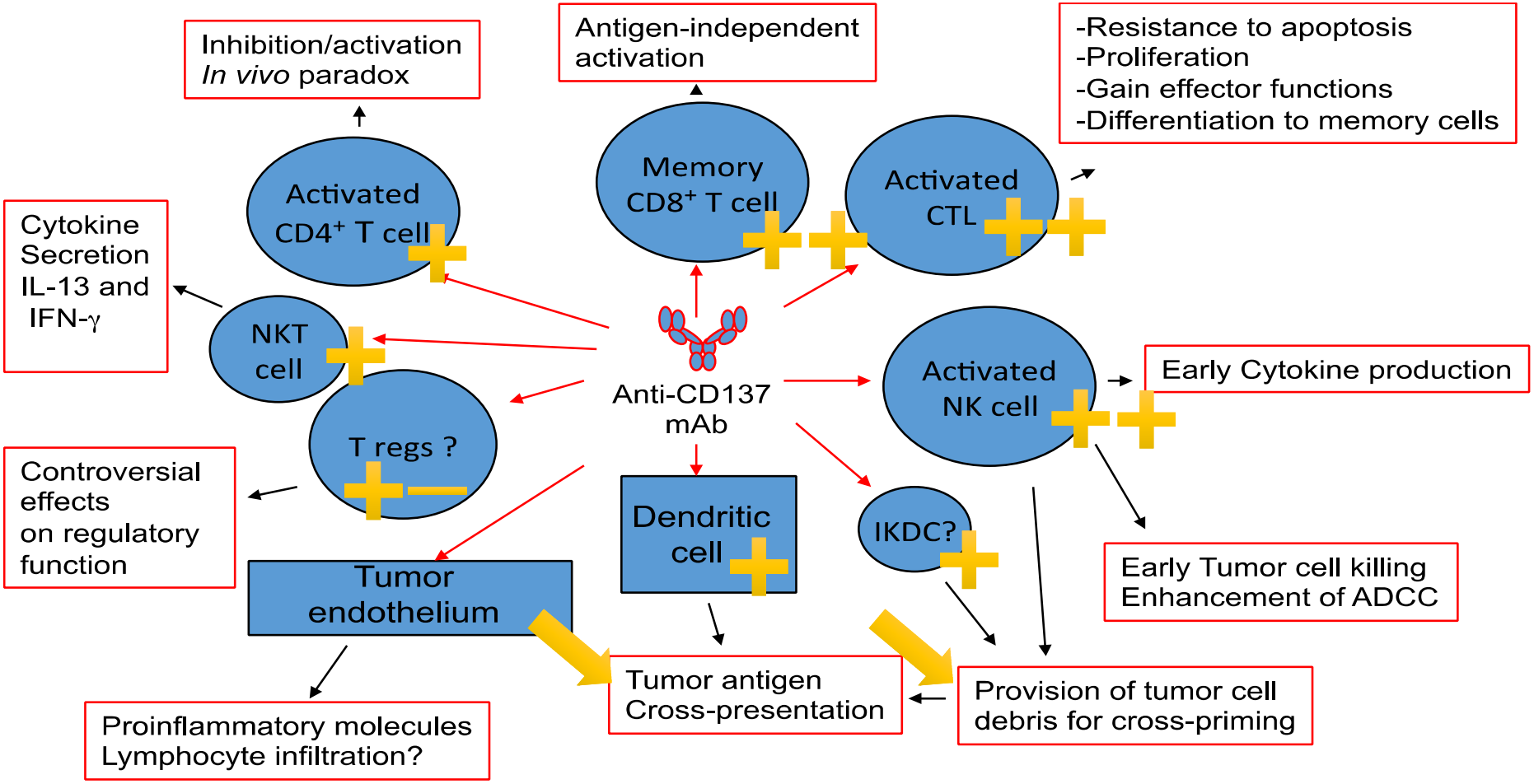

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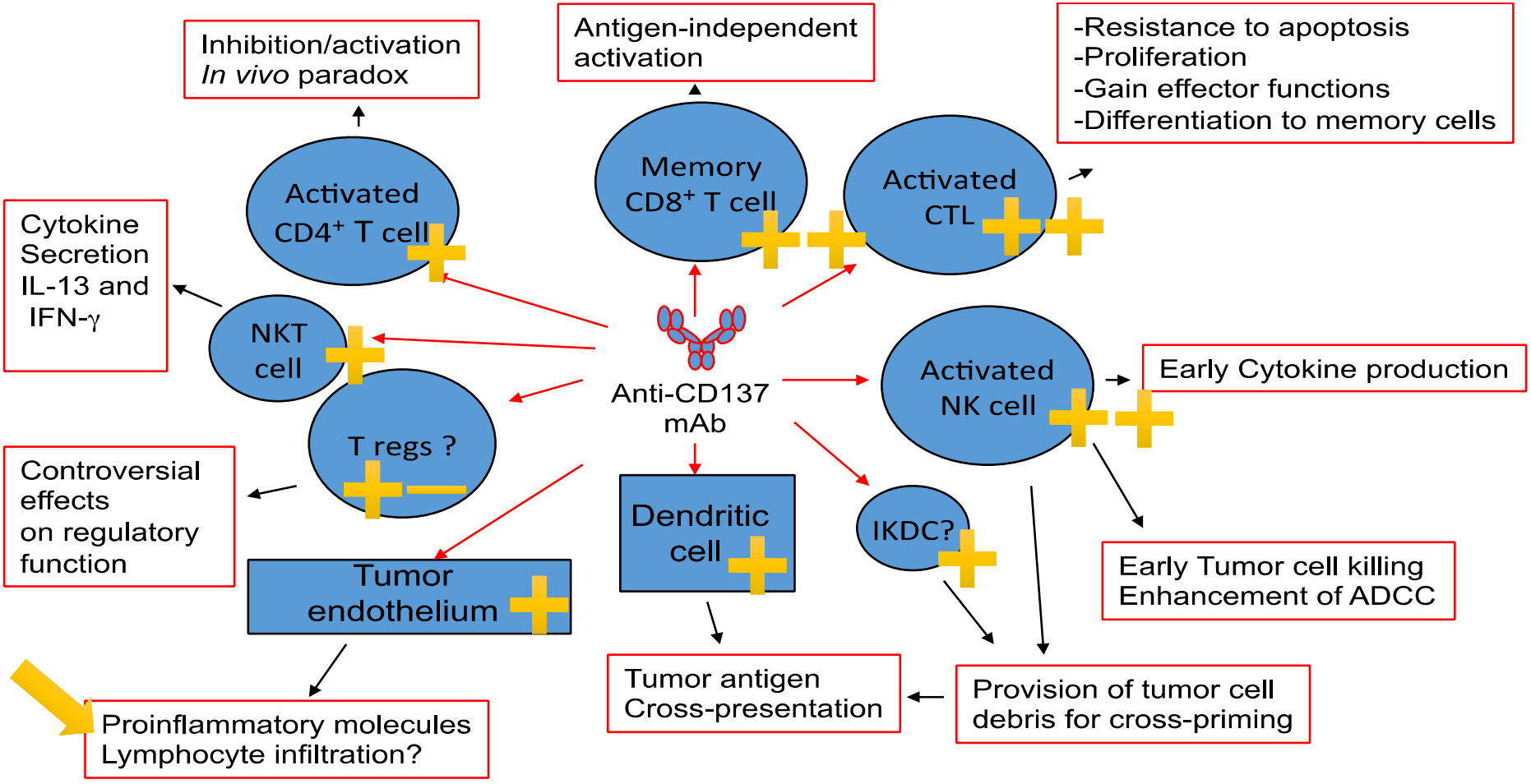
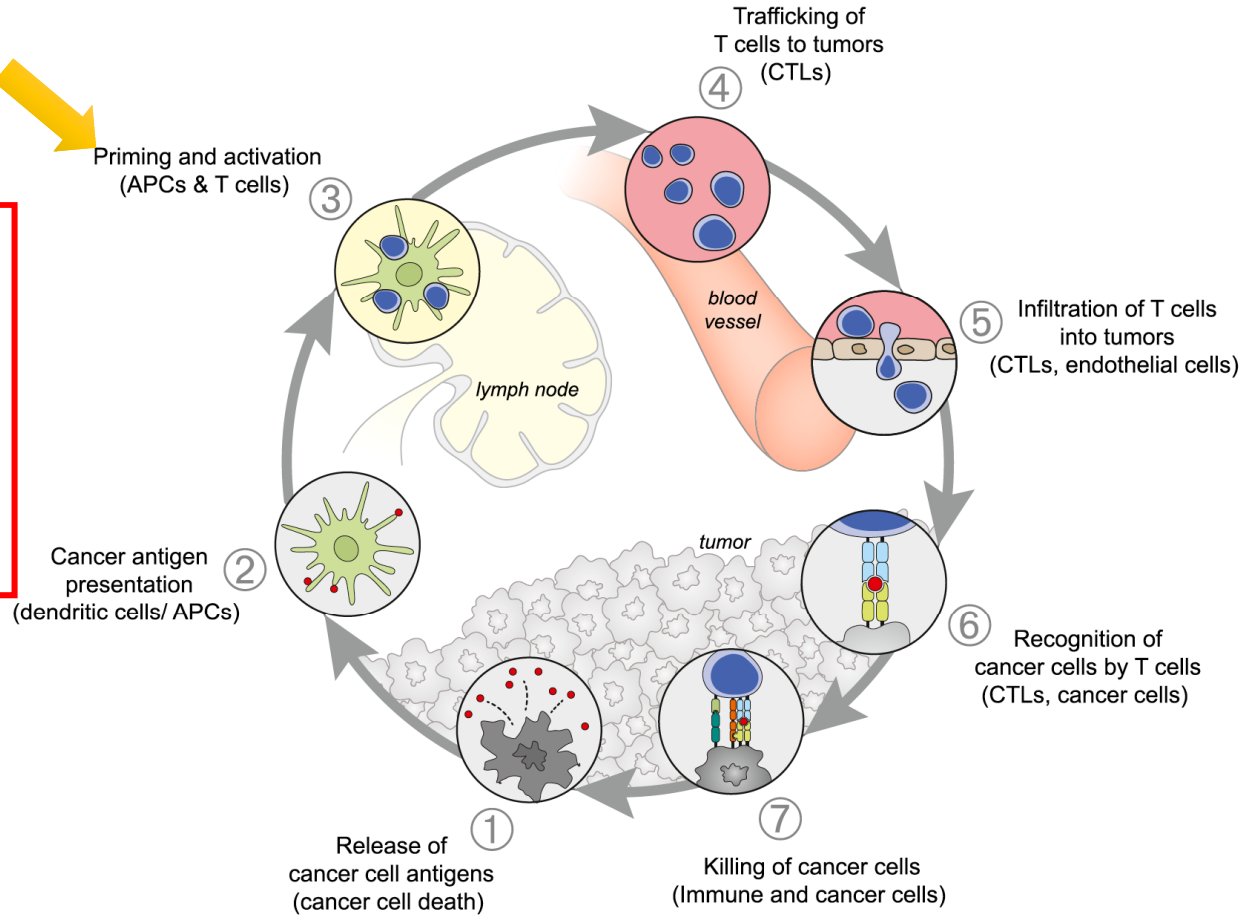


IMMUNE RESPONSE BIOLOGY

- CD137 (ILA) is an inducible co-stimulatory molecule on CD4 and CD8 T cells, T_{regs}, NK cells, NK-T cells, monocytes, neutrophils, and DCs
- On T cells, CD137 is induced upon TCR activation and leads to:
  - increased T-cell proliferation
  - cytokine production
  - functional maturation
  - prolonged CD8 T-cell survival
- CD137 stimulation has a role in priming / activation phase AND maturation AND survival AND effector function / cytokine production.



Immunity 39, July 25, 2013

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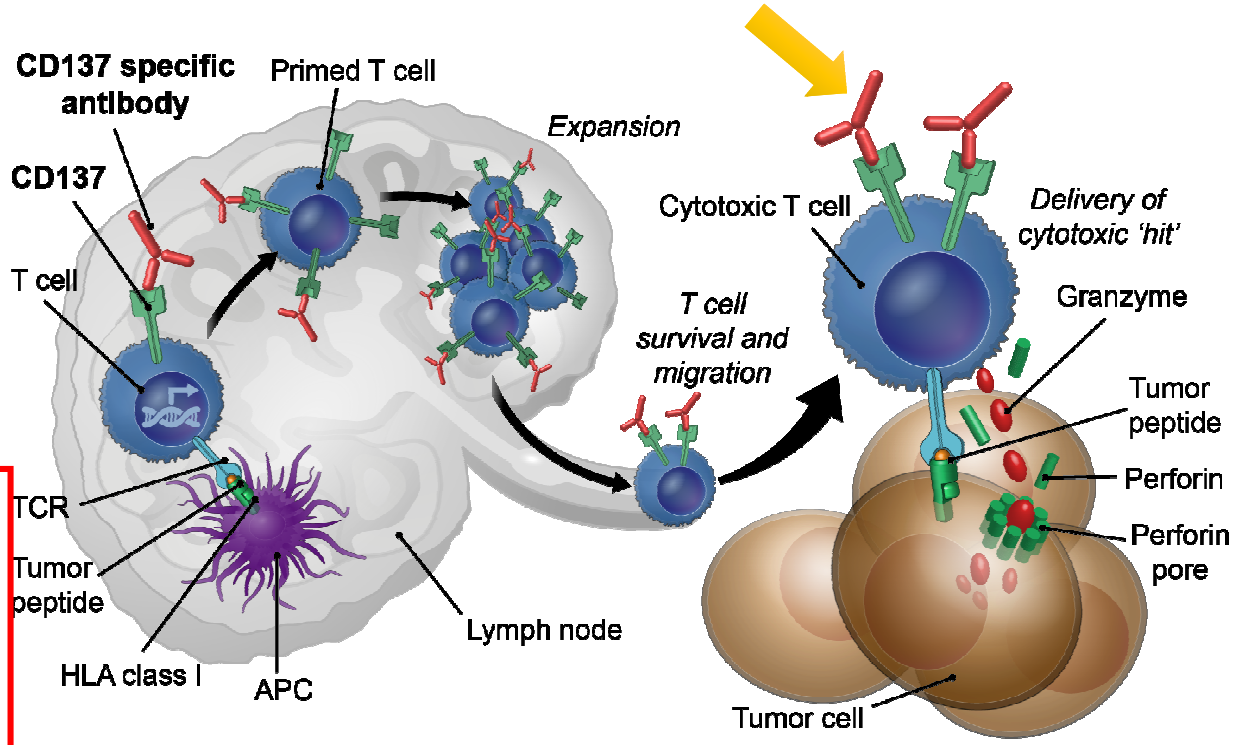

PRECLINICAL PROMISE OF 4-1BB

- JUNE 1997

PRECLINICAL PROMISE OF 4-1BB

Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors

IGNACIO MELERO, WALTER W. SHUFORD, STEPHANIE ASHE NEWBY, ALEJANDRO ARUFFO, JEFFREY A. LEDBETTER, KARL ERIK HELLSTRÖM, ROBERT S. MITTLER & LIEPING CHEN

NATURE MEDICINE • VOLUME 3 • NUMBER 6 • JUNE 1997

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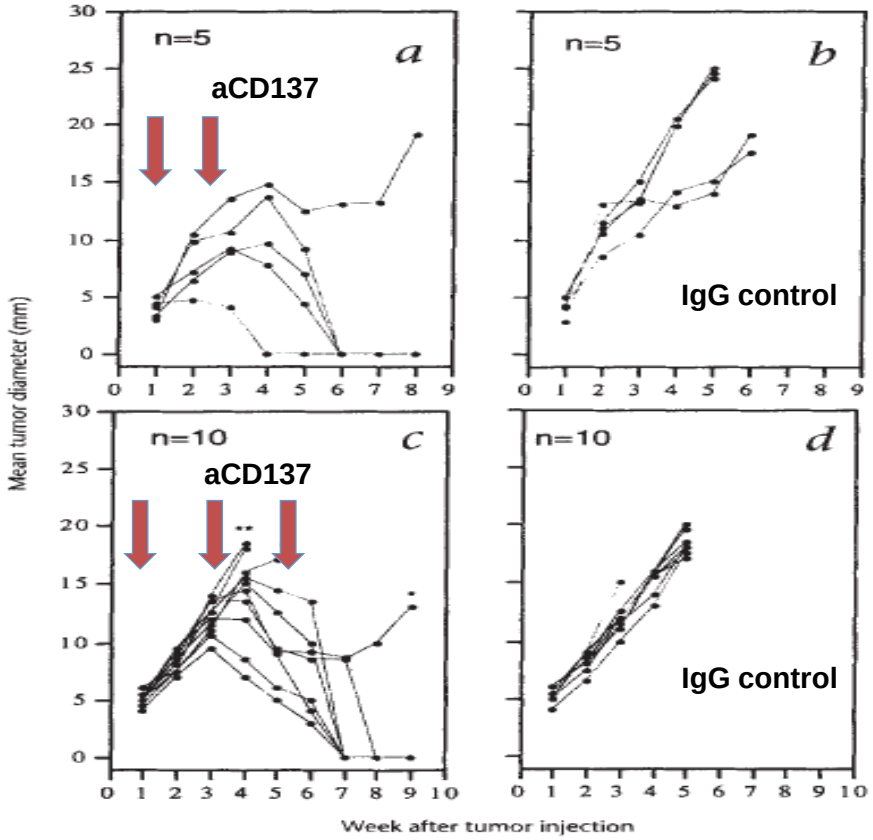
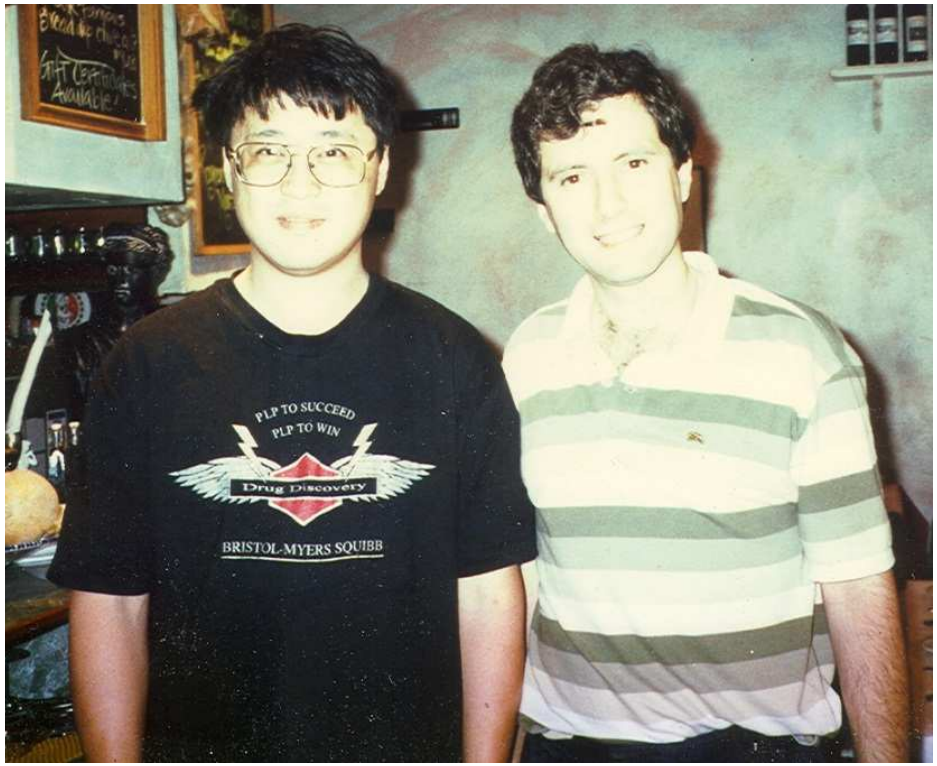
Ag104A poorly immunogenic sarcoma model





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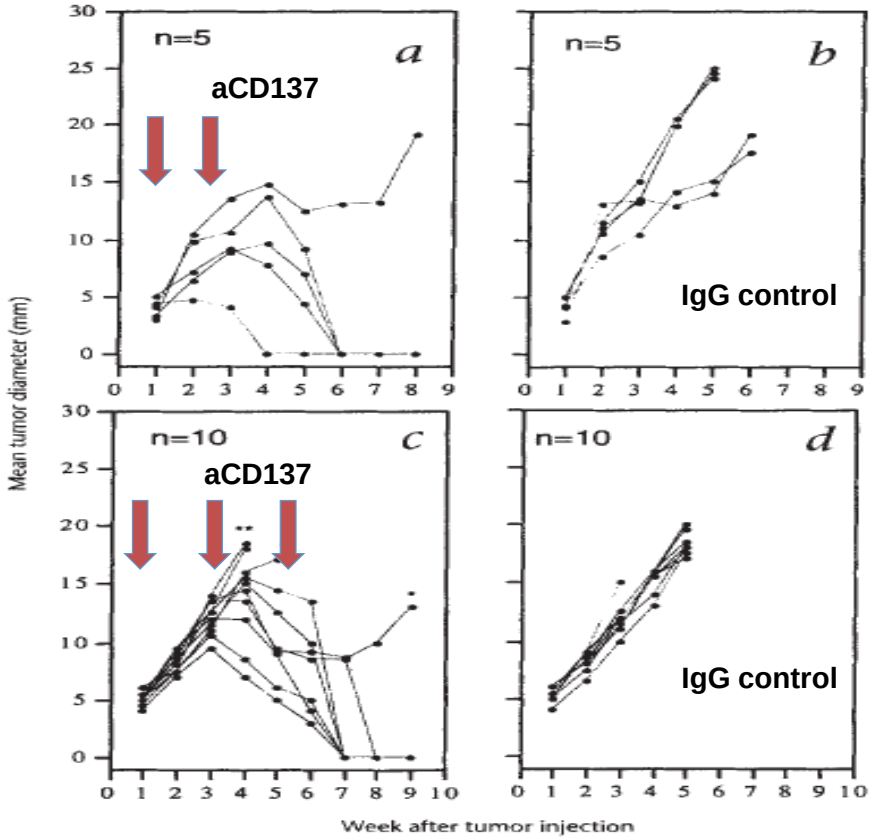

P815 Mastocytoma model

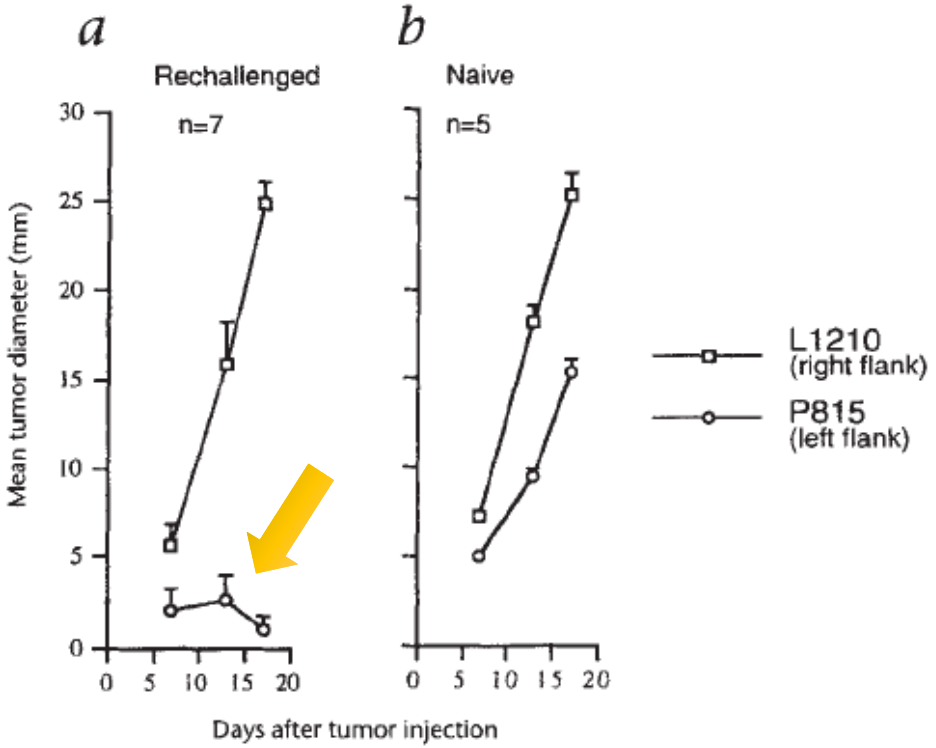

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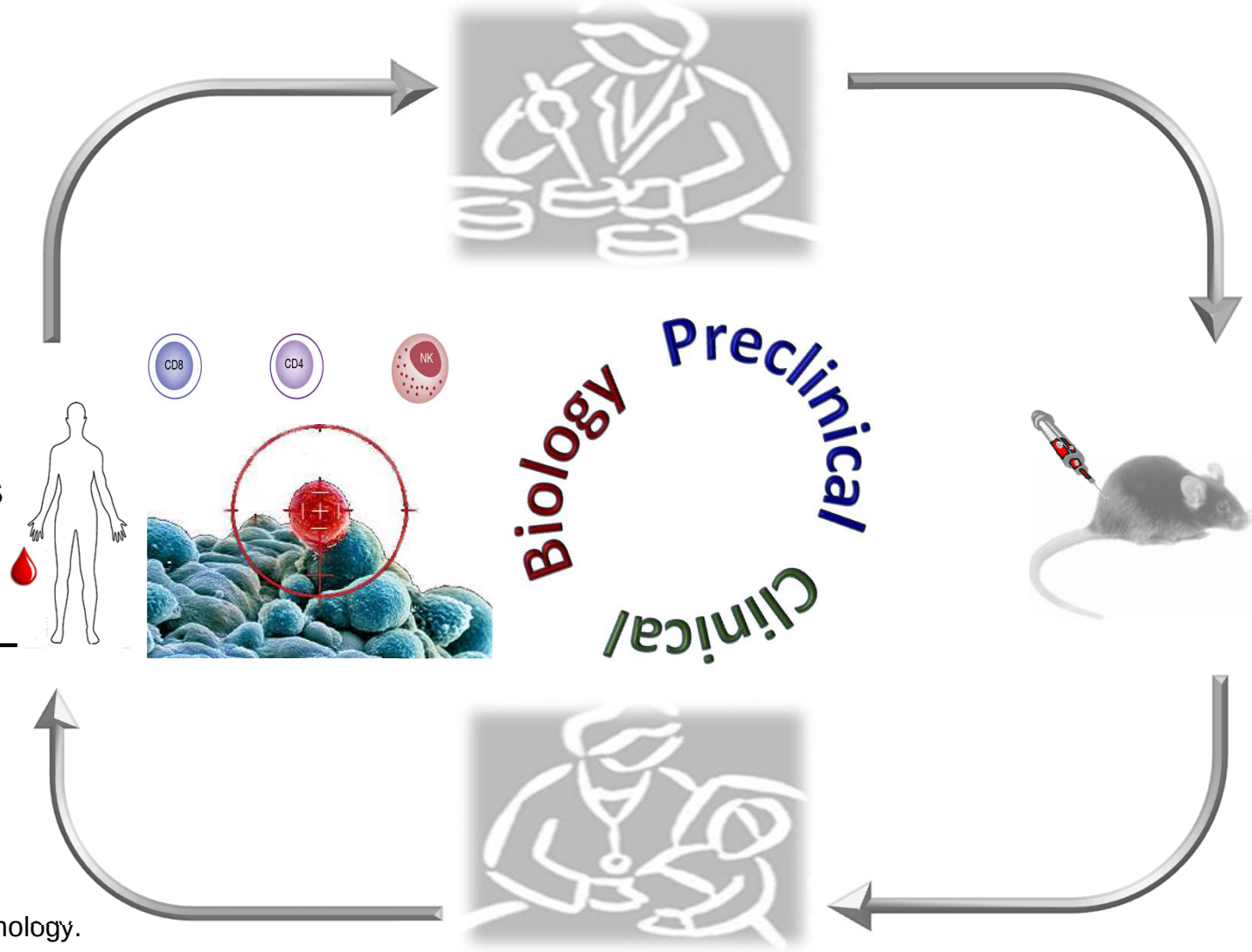
Table 1 Anti 4-1BB mAb 1D8 induces the regression of established P815 and Ag104A tumors

Tumor	Form of tumor growth[b]	Days of mAb treatment[c]	Surviving mice (%) 10 weeks after treatment with[a]: 1D8	Control mAb
P815 mastocytoma	Solid s.c. tumor	3*, 6*	23/25 (92)[d]	3/25 (12)
		12[†], 15[†]	11/15 (73)[d]	2/15 (13)
Ag104A sarcoma	Solid s.c. tumor	3*, 6[†]	8/10 (80)[d]	0/10 (0)
		12*, 15*	6/10 (60)[d]	0/10 (0)
	Disseminated metastases	3*, 6*	10/20 (50)[d]	2/20 (10)

- **Both CD4 and CD8 T cells** required for anti-tumor activity
- **In vitro cytotoxicity** increased following treatment with anti-CD137 mAb

PRECLINICAL PROMISE OF 4-1BB

- **Activity of anti-CD137 mAb is dependent on location and level of expression of CD137**
- Function requires expression – CD137 referred initially to as ILA – *gene induced by lymphocyte activation*



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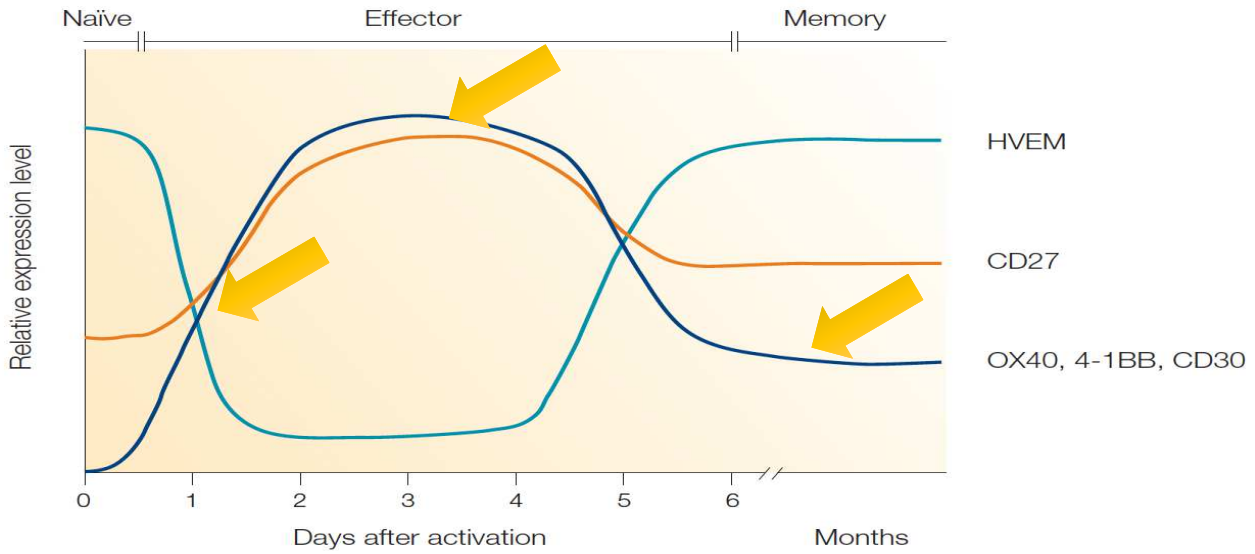

Expression characteristics of TNFR and TNF molecules by T cells and APCs

Molecule	T cells			APCs	
	Naïve	*Effector*	*Memory*	*Resting*	*Activated*
CD27	++	+++	++/–	–	B*
CD70	–	+++*	–	–	B, DC, MØ
HVEM	+++	+	+++	B, DC*	B, MØ*
LIGHT	–	+++	–	DC	–
OX40	–	+++	+/–	–	B, DC*
OX40L	–	+++*	–	–	B, DC, MØ
4-1BB	–	+++	+/–	–	B, DC*
4-1BBL	–	+++*	–	–	B, DC, MØ

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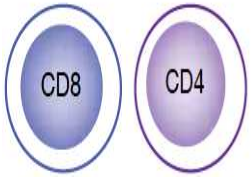
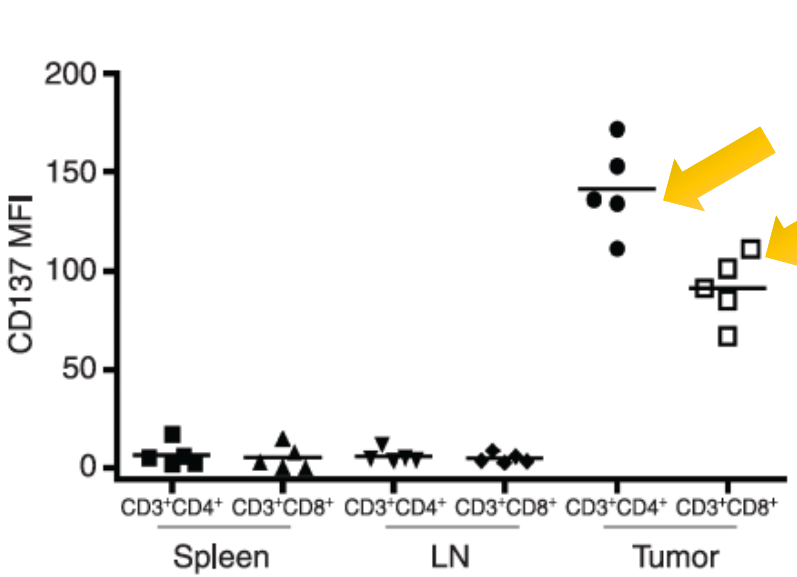
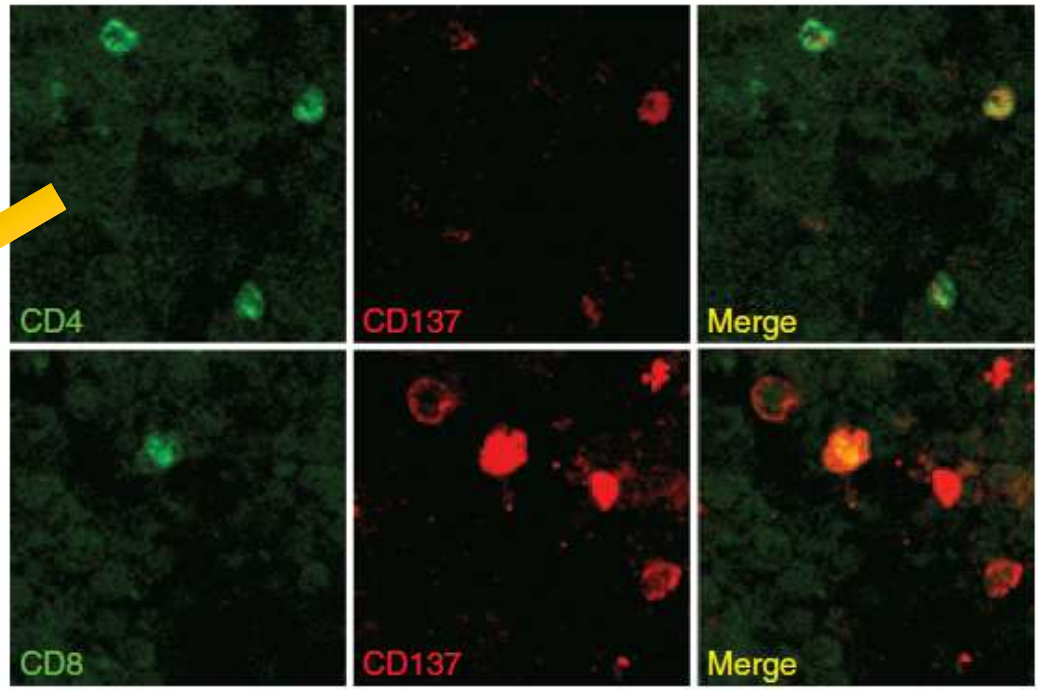


PRECLINICAL PROMISE OF 4-1BB

CT26, analysis d12-d14



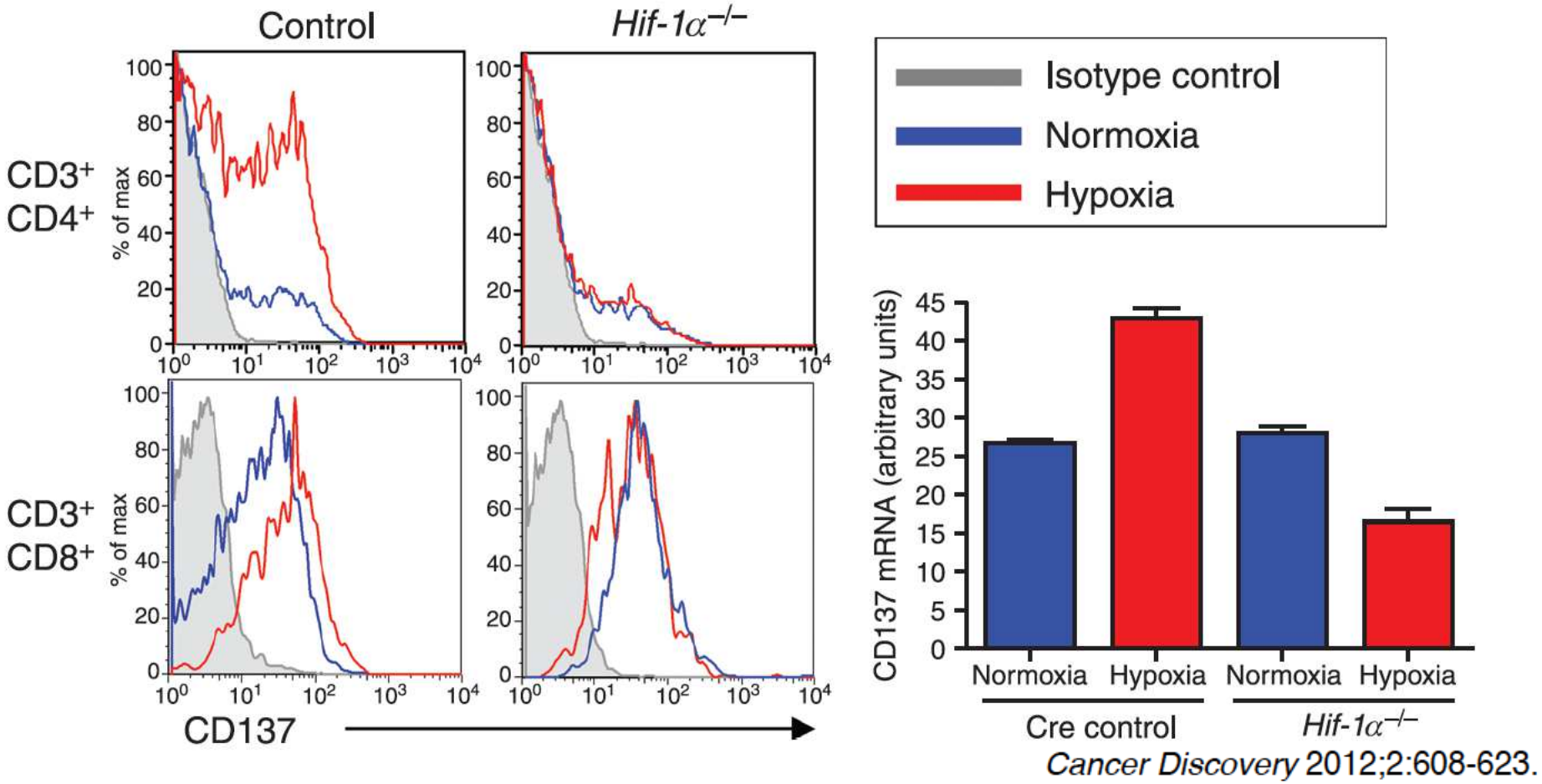


Cancer Discovery 2012;2:608-623.

- **In tumor models, high levels of CD137 on intratumoral CD4 and CD8 T cells.**

PRECLINICAL PROMISE OF 4-1BB

CT26, analysis d12-d14



- **Mechanism of induction of intratumoral CD137 expression includes tumor-specific factors associated with hypoxia mediated by HIF-1a.**

PRECLINICAL PROMISE OF 4-1BB

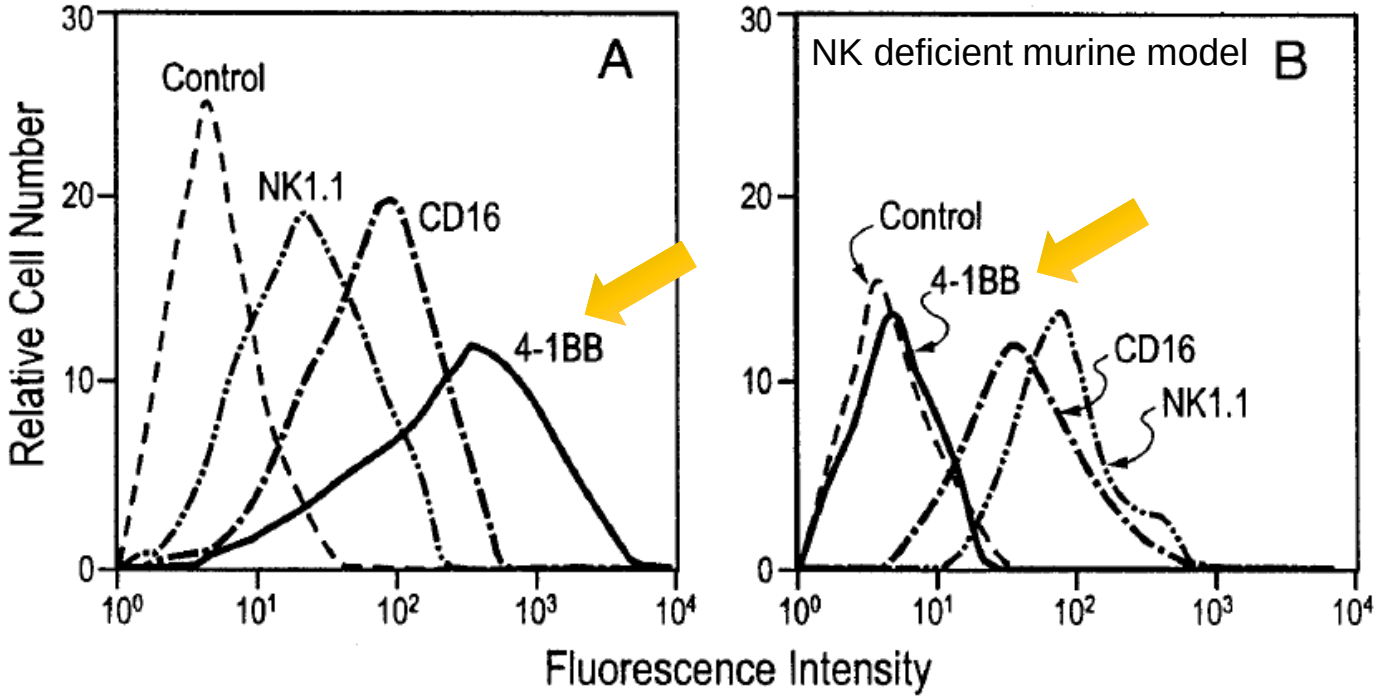
CELLULAR IMMUNOLOGY **190**, 167–172 (1998)
ARTICLE NO. CI981396

NK1.1 Cells Express 4-1BB (CDw137) Costimulatory Molecule and Are Required for Tumor Immunity Elicited by Anti-4-1BB Monoclonal Antibodies

Ignacio Melero,* Janet V. Johnston,* Walter W. Shufford,* Robert S. Mittler,* and Lieping Chen*,†,[1]

Activated NK cells (A) prepared with 7 days of culture with IL-2, and compared to resting (B) NK cells.

- **Activated NK cells in addition to CD8 T cells** express CD137.



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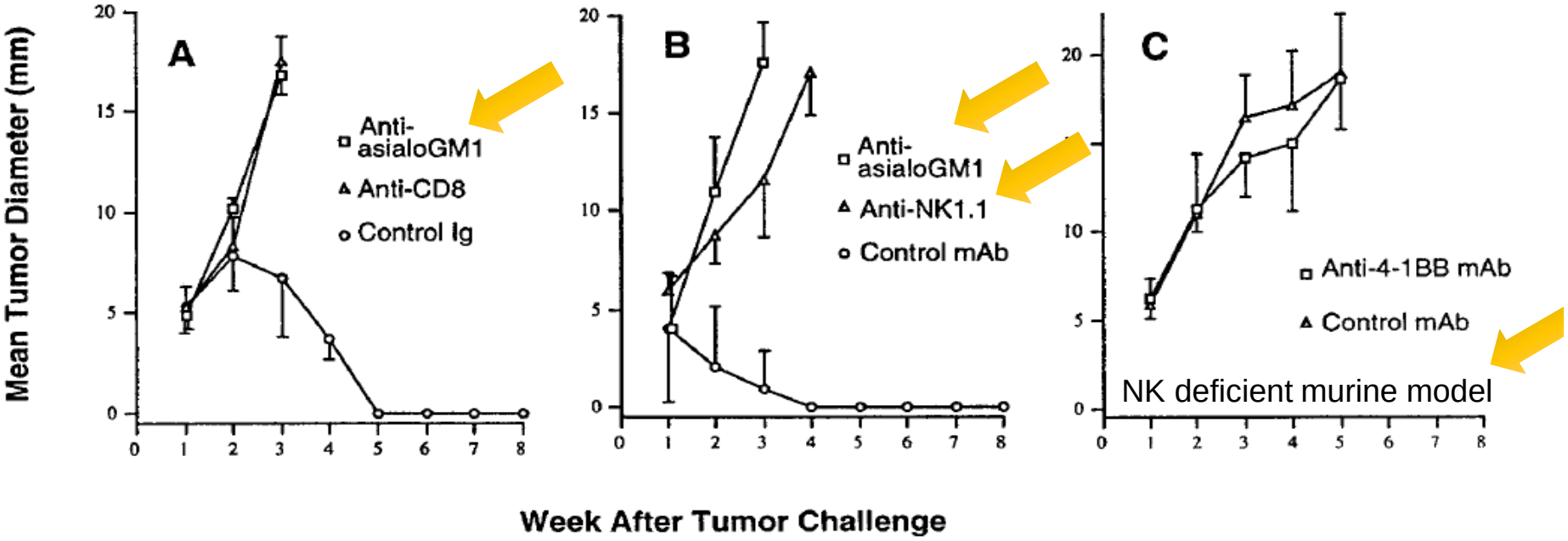
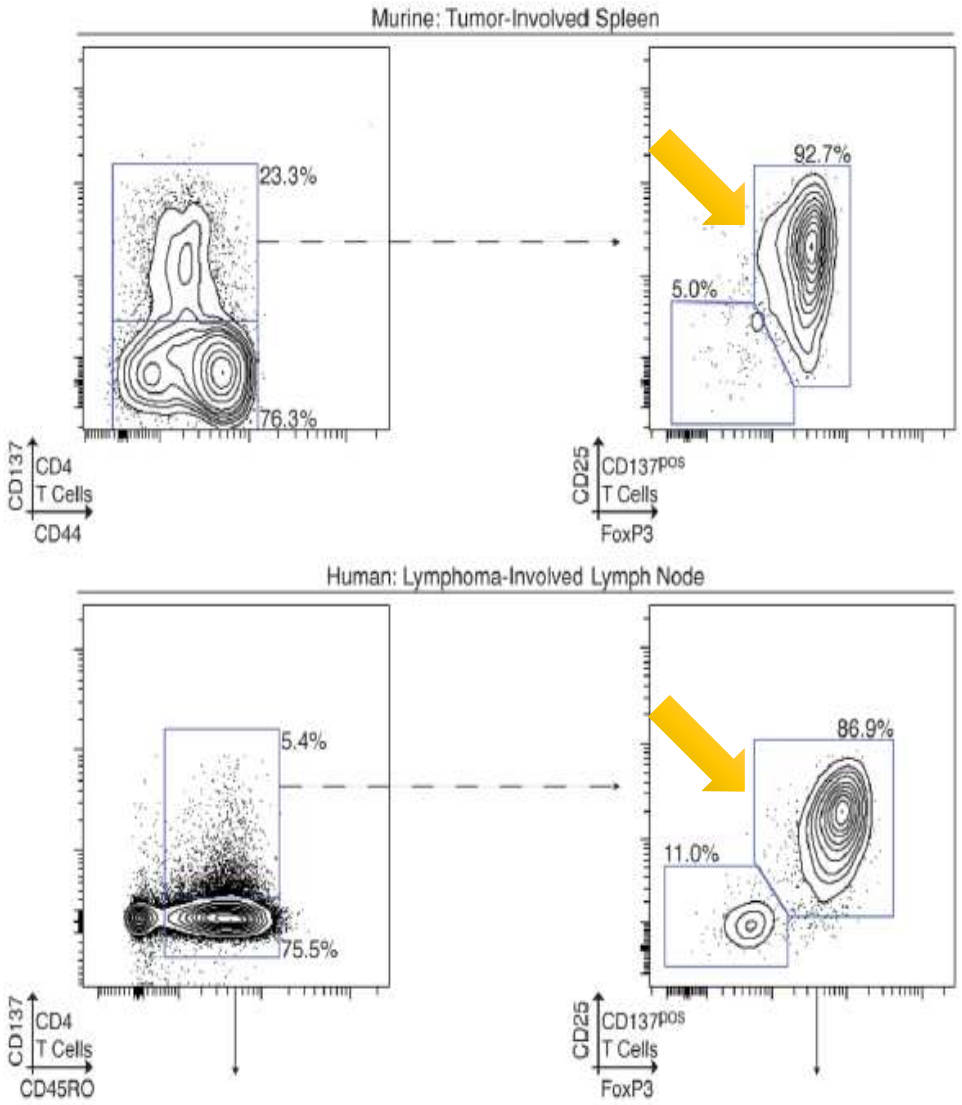


- Intratumoral NK cells express CD137 in addition to CD8 T cells required for anti-tumor activity

CD4 Treg

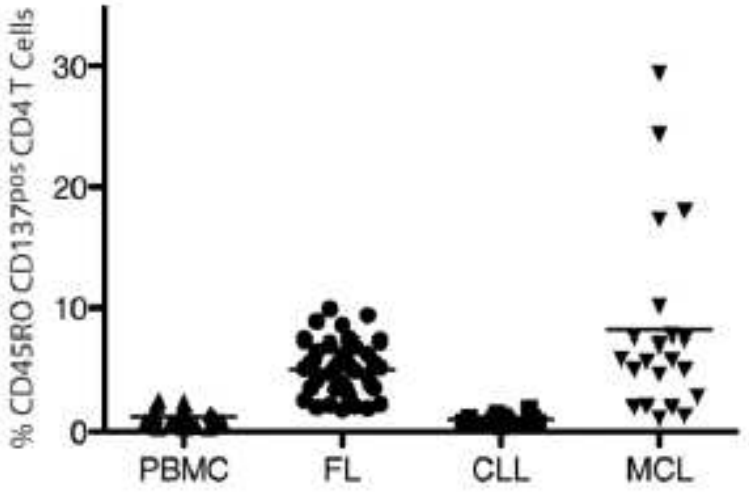
PRECLINICAL PROMISE OF 4-1BB



Adoptive Cell Therapy for Lymphoma with CD4 T Cells Depleted of CD137 Expressing Regulatory T Cells

Matthew J Goldstein, **Holbrook E Kohrt**, **Roch Houot**, **Bindu Varghese**, **Jack T Lin**, **Erica Swanson**, and **Ronald Levy**
Department of Medicine, Stanford University School of Medicine, Stanford CA

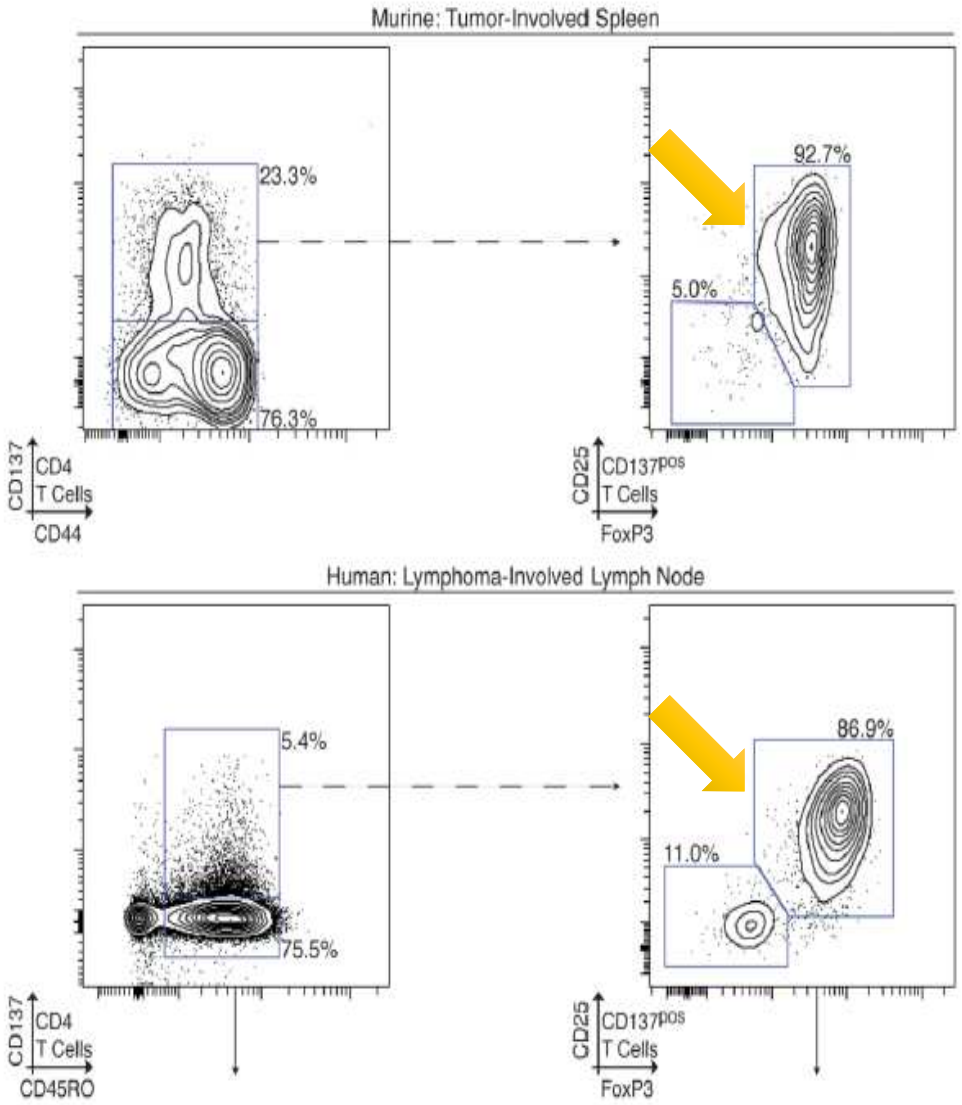
***Regulatory T cells* in murine lymphoma models and patients with lymphoma express high levels of CD137.**



Cancer Res. 2012 March 1; 72(5): 1239–1247

CD4 Treg

PRECLINICAL PROMISE OF 4-1BB



Adoptive Cell Therapy for Lymphoma with CD4 T Cells Depleted of CD137 Expressing Regulatory T Cells

Matthew J Goldstein, **Holbrook E Kohrt**, **Roch Houot**, **Bindu Varghese**, **Jack T Lin**, **Erica Swanson**, and **Ronald Levy**
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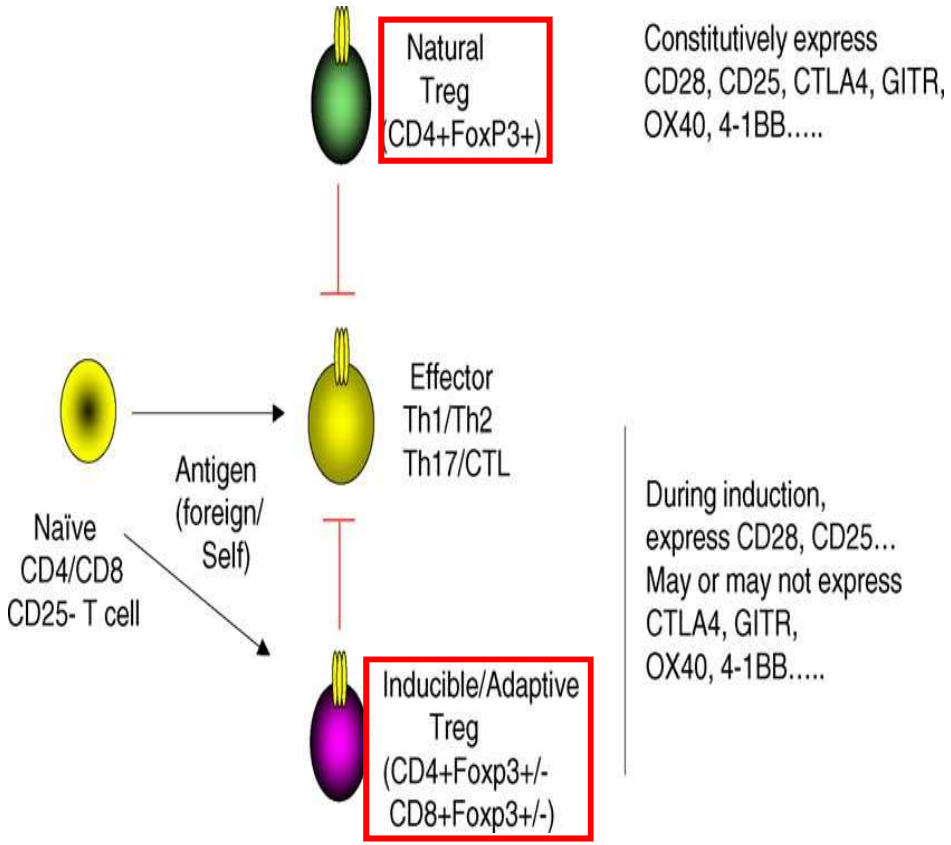
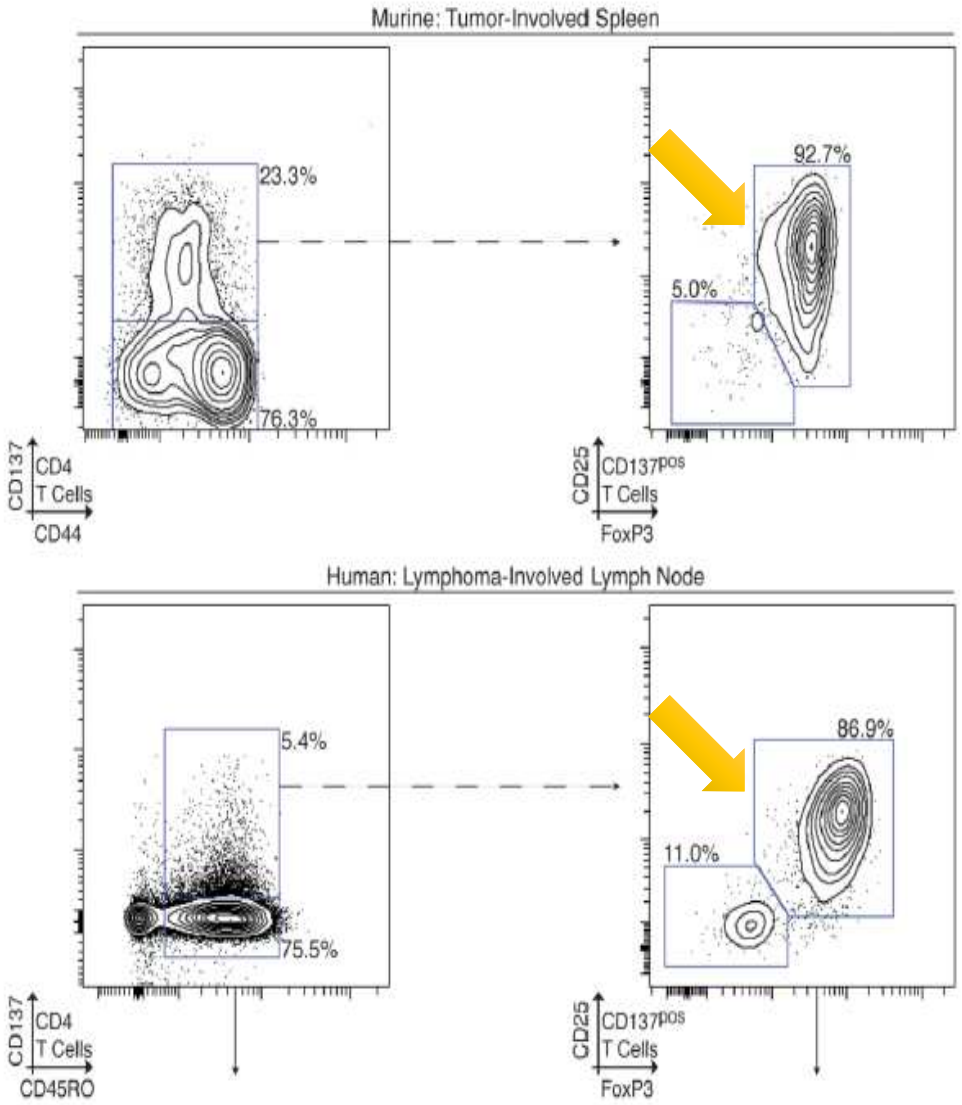


Cytokine & Growth Factor Reviews 19 (2008) 253–262

CD4 Treg

PRECLINICAL PROMISE OF 4-1BB



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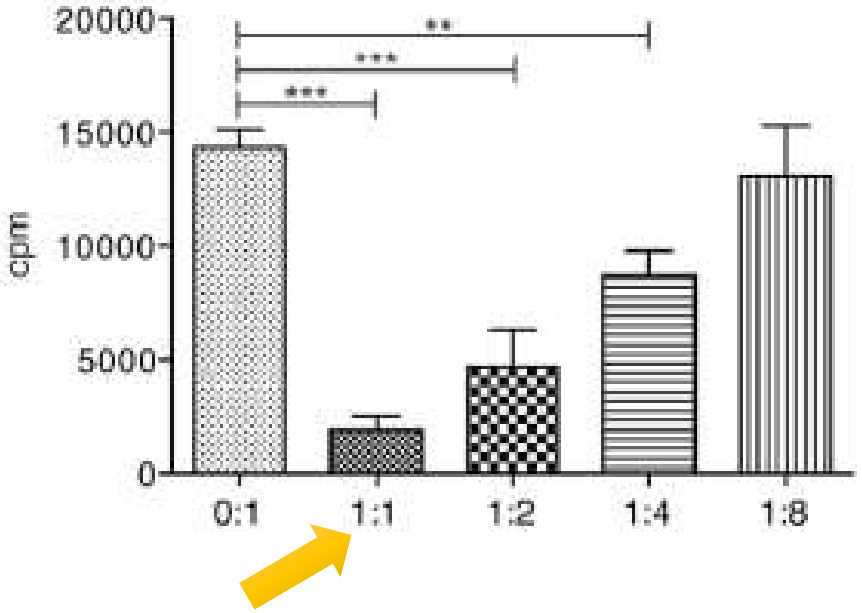
CD137⁺ Tregs suppress In Vitro



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CD4 Treg

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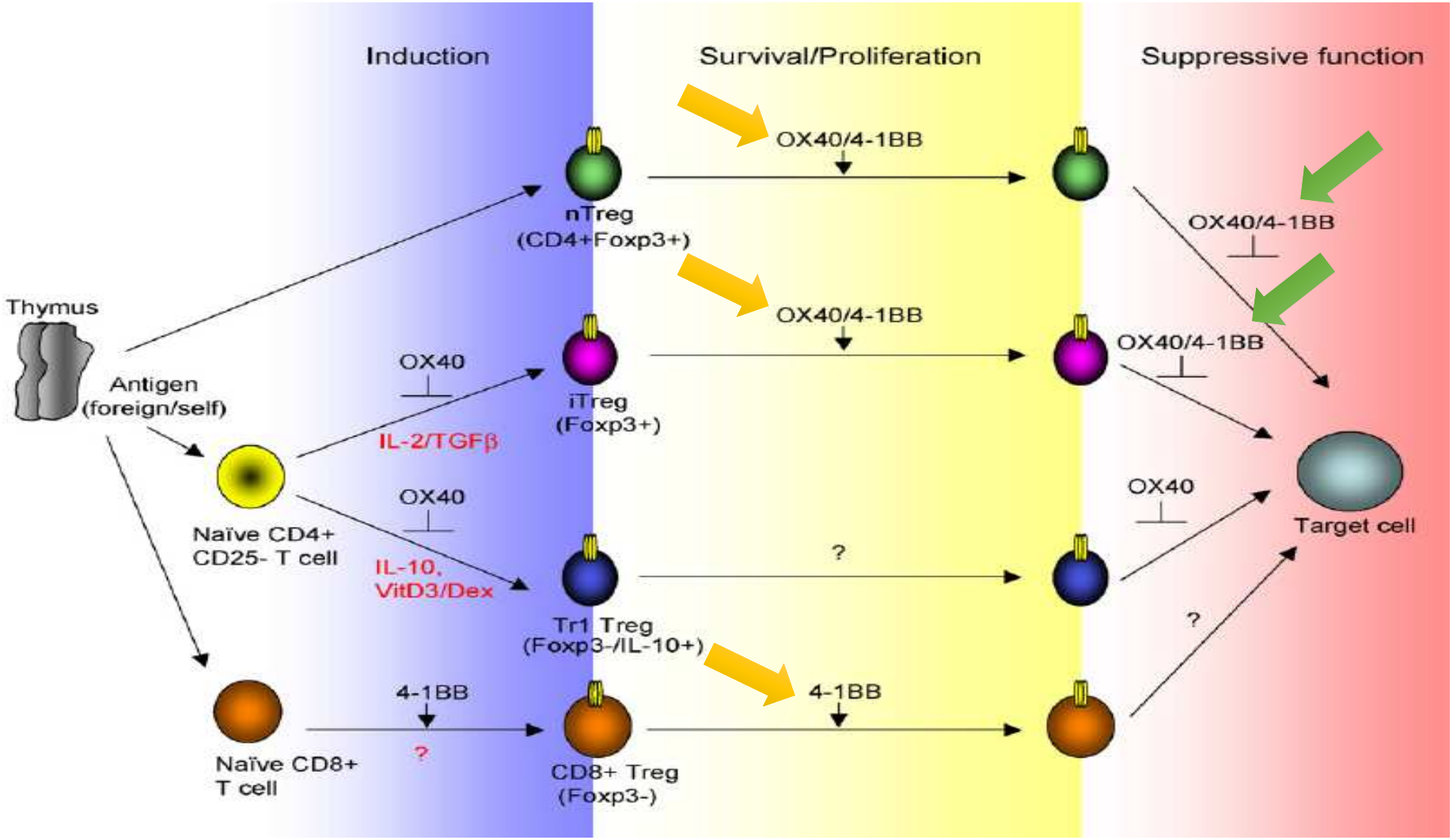

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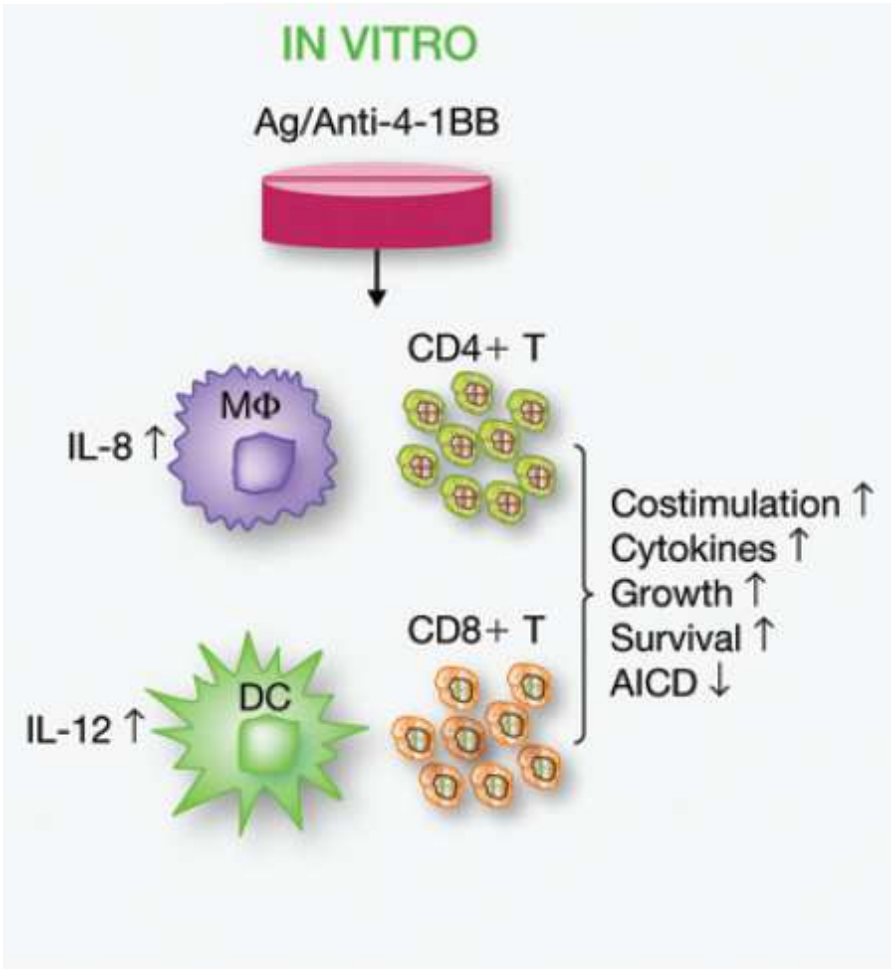
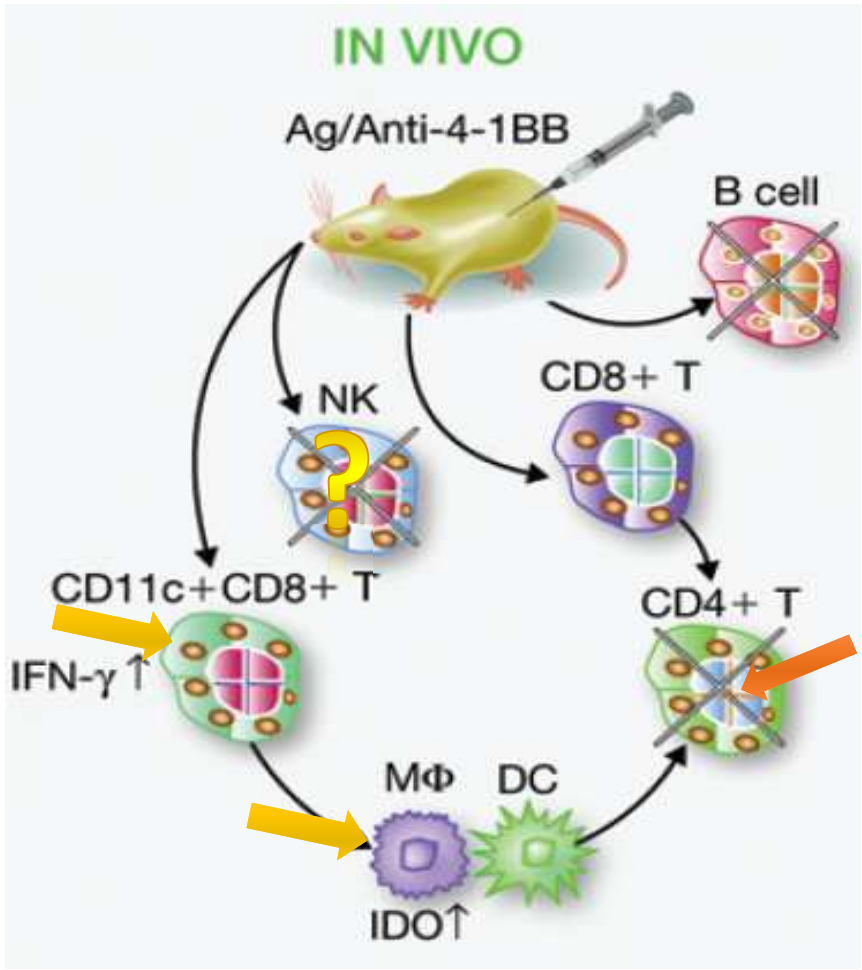
SUMMARY PRECLINICAL MOA

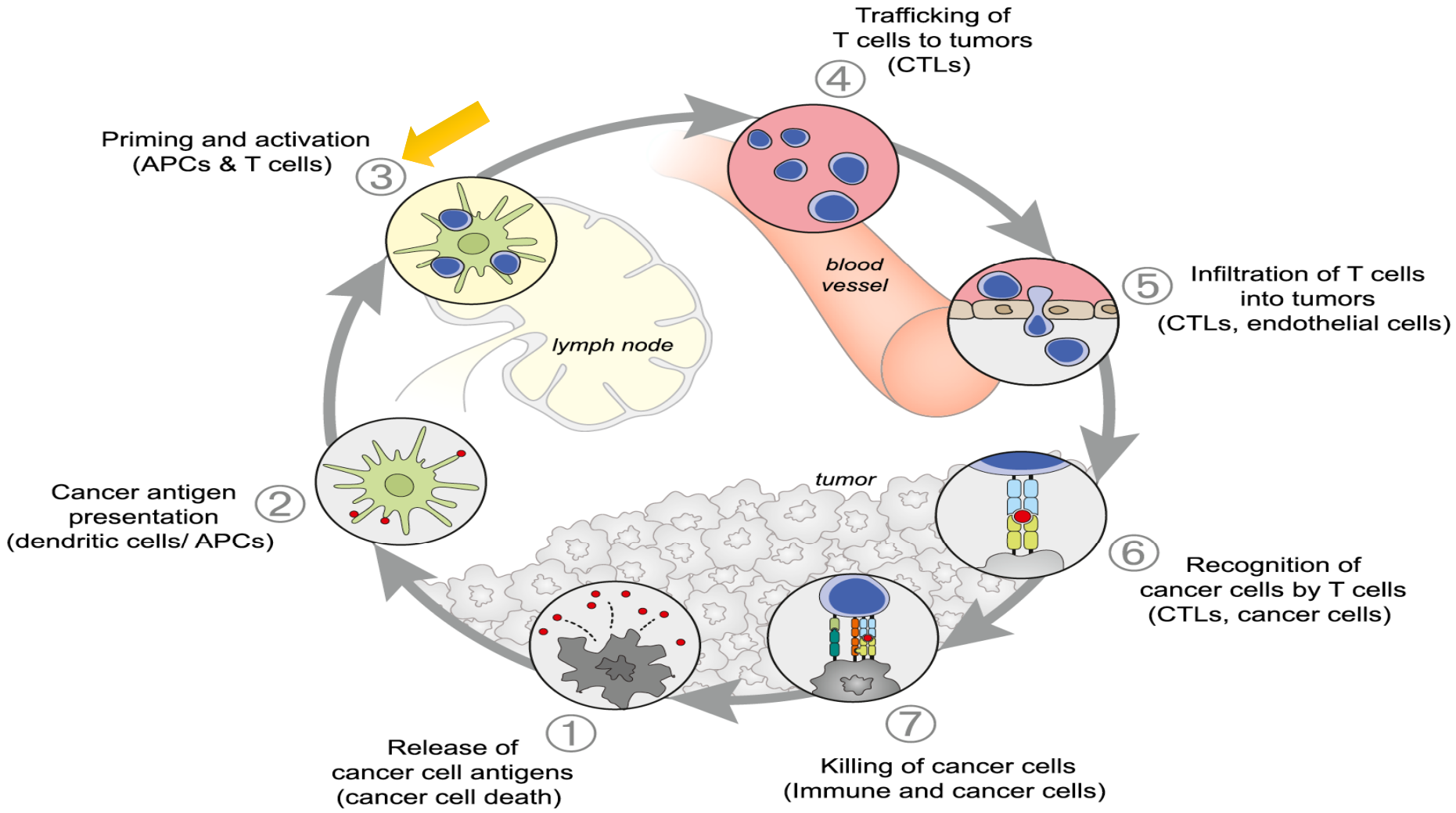




Nature Reviews Immunology. 3:609-620. 2013.

Kwon **Mol Ca Ther** 11(5):1-9 2012.

MONOTHERAPY PROMISE OF 4-1BB



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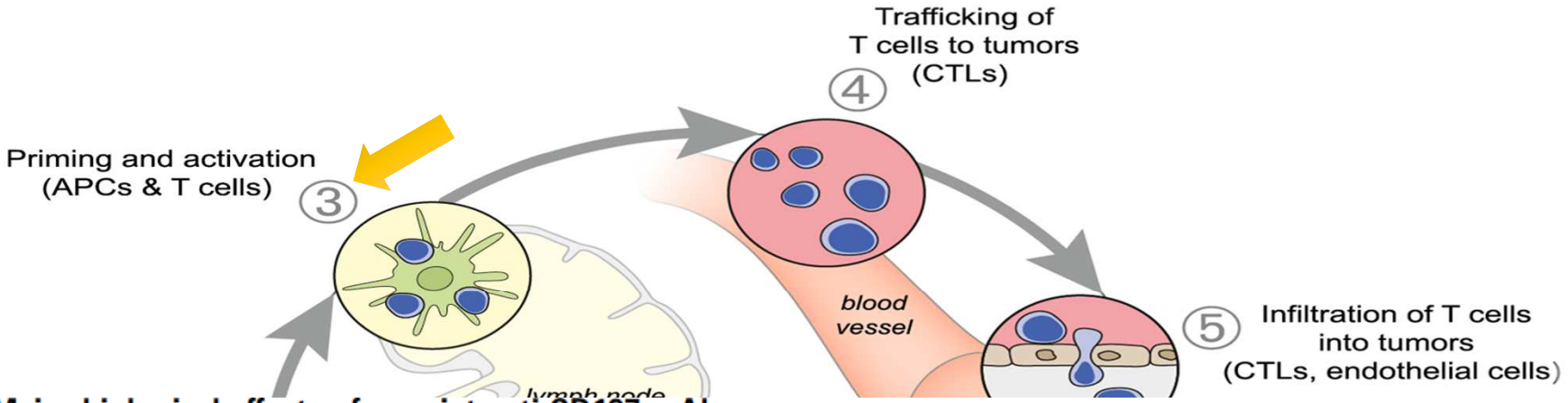
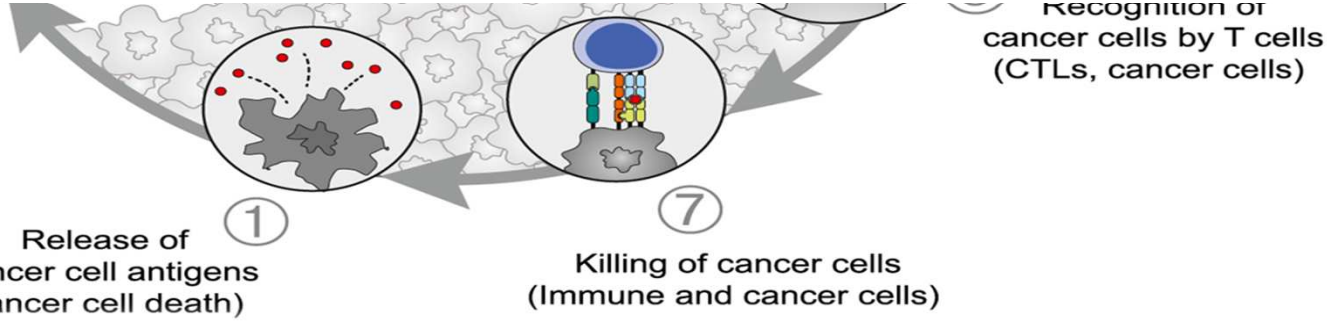
MONOTHERAPY PROMISE OF 4-1BB



Major biological effects of agonist anti-CD137 mAb

Model	Physiological outcome
P815/Ag104A	Clears established tumors, with roles for CD8, CD4 and NK cells
C3 tumor, TC-1 lung carcinoma, and B16-F10 melanoma	Significantly eradicates large and established tumors (or metastasis) in mice, with dependence on signal 1 and NK cells but no dependence on CD4



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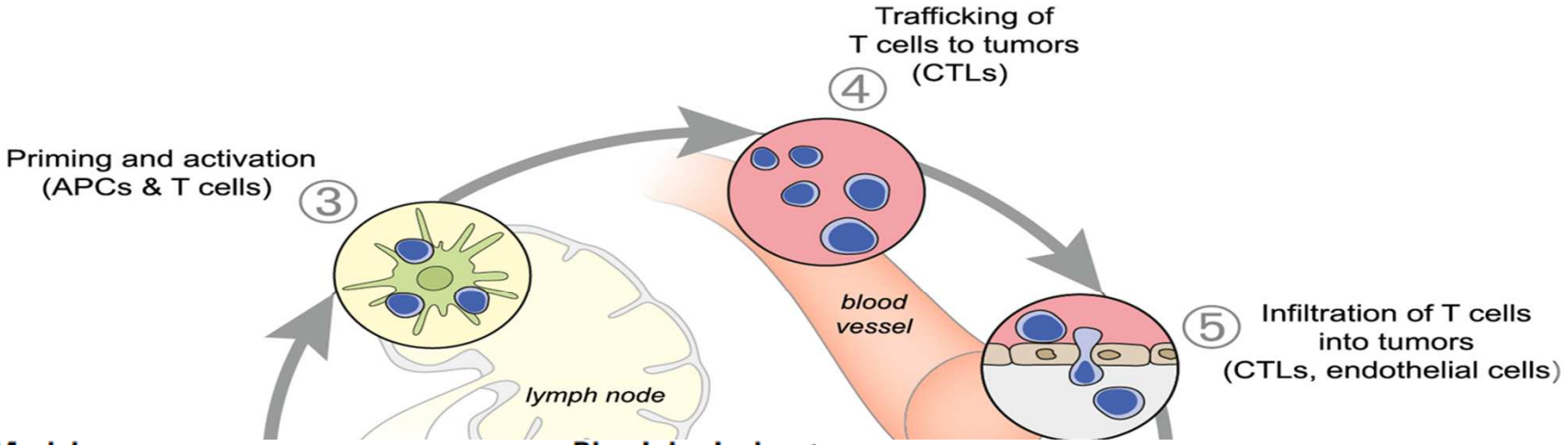
MONOTHERAPY PROMISE OF 4-1BB



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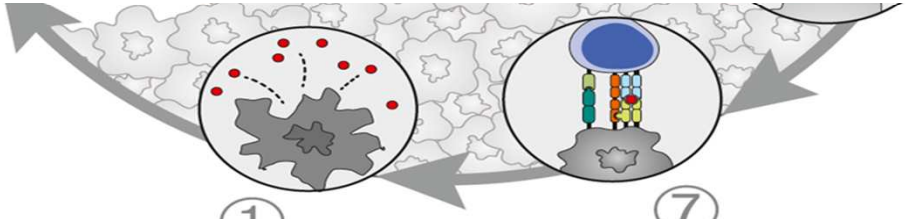


Recognition of
cancer cells by T cells
(CTLs, cancer cells)

1
Release of
cancer cell antigens
(cancer cell death)

7
Killing of cancer cells
(Immune and cancer cells)

MCA205 sarcoma/
GL261 glioma (30)

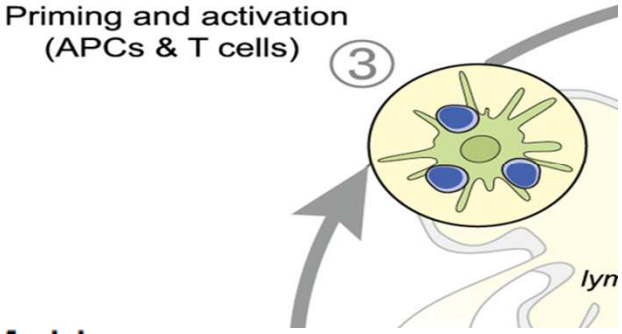
K1735 melanoma (46)

EMT6 (53)

Adapted from I Mellman **Immunity** 39: 2013.

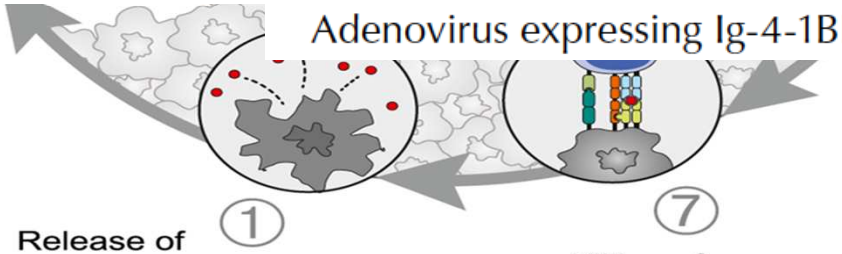
Kwon **Mol Ca Ther** 11(5):1-9 2012.

MONOTHERAPY PROMISE OF 4-1BB



Model
P815/Ag104A
C3 tumor, TC-1 lung carcinoma, and B16-F10 melanoma

Method	Tumor Type
Agonist 4-1BB-specific antibody	Sarcoma, mastocytoma
Tumor transfected with 4-1BBL	Sarcoma, mastocytoma
Tumor transfected with 4-1BBL	Lymphoma
Agonist 4-1BB-specific antibody	Fibrosarcoma
Agonist 4-1BB-specific antibody	Lung carcinoma, melanoma
Tumor transfection with Fv of 4-1BB-specific antibody	Melanoma
Agonist 4-1BB-specific antibody with adenovirus expressing IL-12	Colon carcinoma
Agonist 4-1BB-specific antibody with dendritic cell vaccine	Fibrosarcoma
Adenovirus expressing Ig-4-1BBL	Hepatic colon carcinoma (CTLs, cancer cells)



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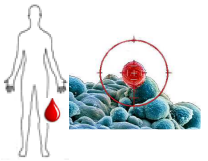
Adapted from I Mellman **Immunity** 39: 2013. Grewal **Ther Target of TNF** 2009

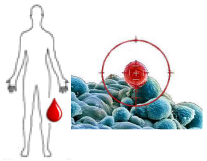
MONOTHERAPY PROMISE OF 4-1BB



- **Urelumab,** BMS, Anti-CD137
  - Fully human
  - Non-ligand blocking
  - IgG4
  - Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

MONOTHERAPY PROMISE OF 4-1BB



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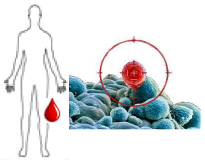
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

NCT00309023

- Study of BMS-663513 in patients with advanced cancer
- Open-label, ascending, multi-dose phase I-II study conducted in subjects with locally advanced or metastatic solid tumors
- Six dose-cohorts (0.3, 1, 3, 6, 10, or 15 mg/kg), 60-minute IV every 3 weeks
- Expansion cohorts in melanoma, renal cell carcinoma, or ovarian carcinoma randomized to receive one of three doses (1, 3, or 10 mg/kg)

MONOTHERAPY PROMISE OF 4-1BB



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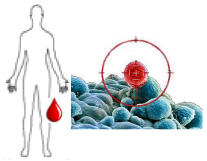
  - Expansion cohorts in melanoma, renal cell carcinoma, or ovarian carcinoma randomized to receive one of three doses (1, 3, or 10 mg/kg)
- **Results**
  - ASCO 2008: 83 patients (54 melanoma, 15 RCC, 13 ovarian, 1 prostate)
  - DLTs: 0.3 mg/kg (Gr 3 neutropenia) and 15 mg/kg (Gr 4 neutropenia) cohorts
  - AEs:
    - Fatigue (All, 26%, Gr 3–4, 3%), reversible Gr 3–4 transaminitis (11%) and Gr 3–4 neutropenia (5%)
    - 106 of the total 115 patients enrolled, the most frequent grade 2 laboratory abnormalities were increases in ALT (15%) and AST (12%), leukopenia (8%), neutropenia (6%), thrombocytopenia (4%), and hyperbilirubinemia (1%)

MONOTHERAPY PROMISE OF 4-1BB

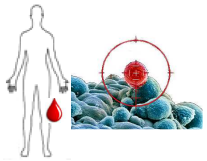


- **Urelumab,** BMS, Anti-CD137, Fully human, Non-ligand blocking, IgG4, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

- **NCT00309023**
- **Results**
  - 3 PRs (18+ m, 3+ m, 1.5+ m, all melanoma (6% of evaluable melanoma)
  - 4 SD (10 m, 6 m, 6 m, 4+ m)
  - SD of > 6m = 17% of melanoma pts and 14% of RCC pts
  - Responses at all three doses tested in expansion cohorts.
- **Preliminary biomarker analysis**
  - increased expression of IFN-inducible genes in peripheral blood,
  - percentage of circulating activated (HLA-DR+, CD69+) CD8 and CD4 T-cells following a single treatment
  - Increased expression of CD8a and IFN-gamma were detected in post-treatment biopsies

MONOTHERAPY PROMISE OF 4-1BB



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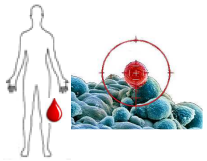
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

NCT00309023

NCT00309023

- Phase II
- Randomized, multi-dose, open-label, phase II study of BMS 663513 as second-line monotherapy in metastatic melanoma.
- 4 arms
  - arm 1, 0.1 mg/kg every 3 weeks;
  - arm 2, 1 mg/kg every 3 weeks;
  - arm 3, 1 mg/kg every 6 weeks;
  - arm 4, 5 mg/kg every 3 weeks.
- The study was terminated in May 2009 due to unusually high incidence of grade 4 hepatitis

MONOTHERAPY PROMISE OF 4-1BB



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NCT00309023

NCT00309023

NCT00351325

- **Phase I, A study of BMS-663513 administered in combination with chemotherapy to subjects with advanced solid malignancies**
- **TERMINATED**

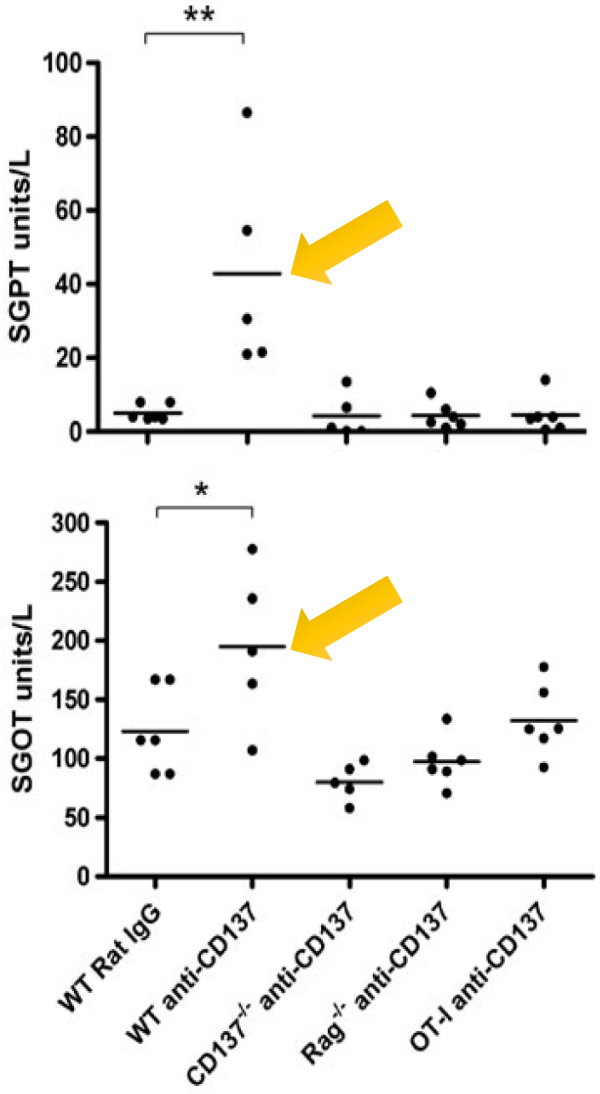
NCT00461110

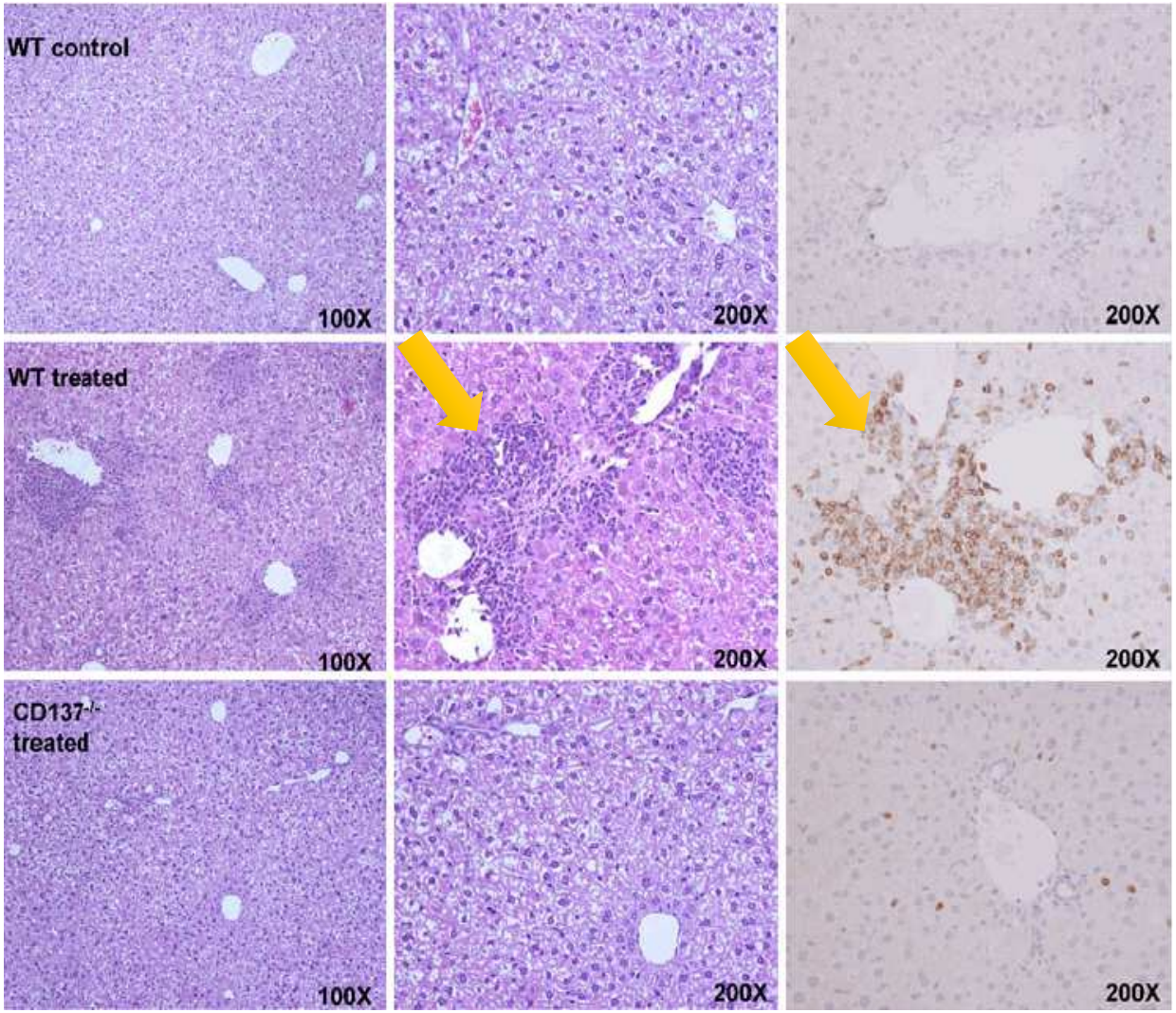
- **Phase I/II, A study of BMS-663513 in combination with chemoradiation in subjects with non small cell lung carcinoma (NSCLC)**
- **TERMINATED**

NCT00803374

- **Phase I, Combination of anti-CD137 and ipilimumab in patients with melanoma**
- **WITHDRAWN**

PRECLINICAL TOXICITY MODELING





Dubrot **Cancer Immunology Immunotherapy** 2010

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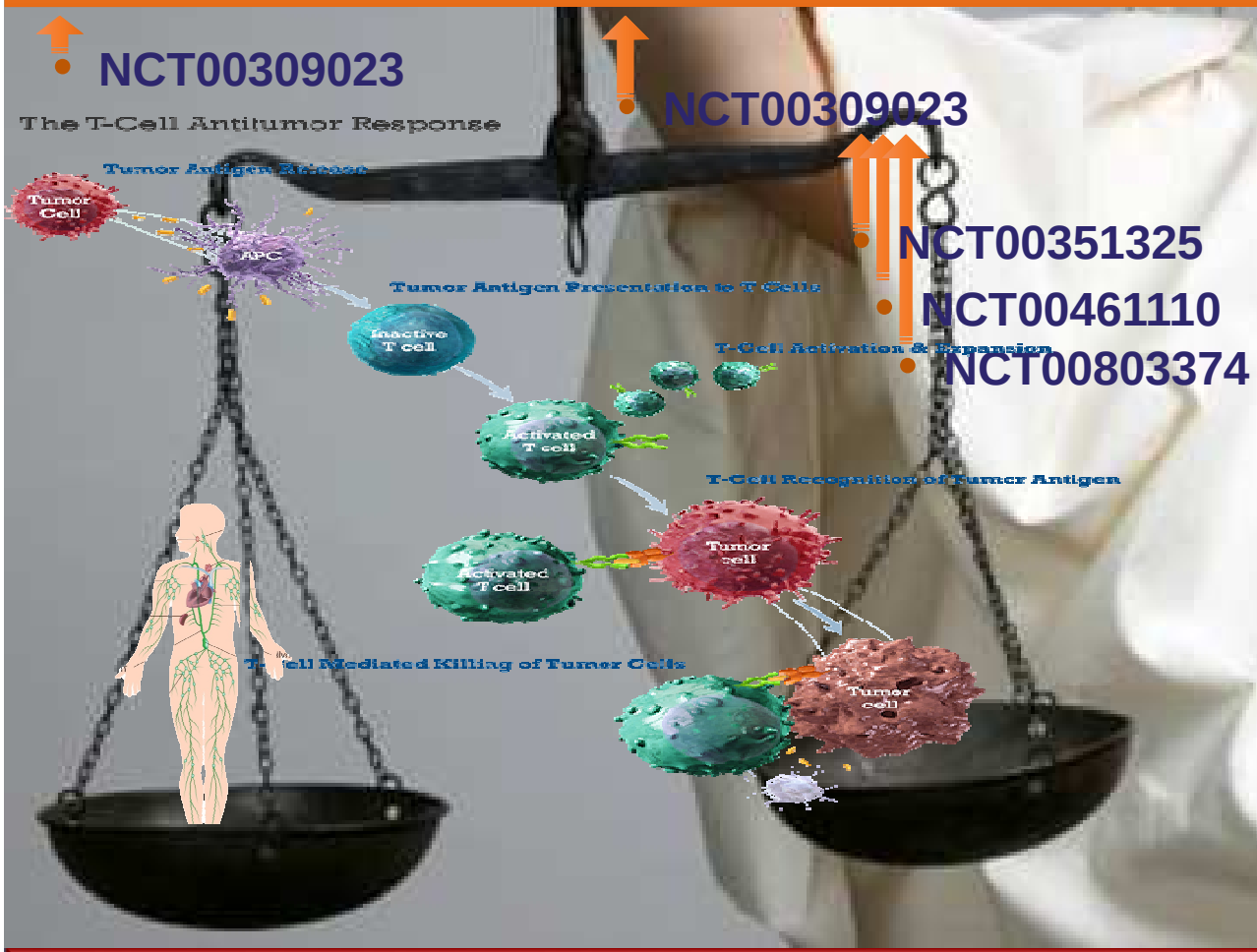

- **Can 1 + 1 =**
  - **– toxicity of 1**
  - **– efficacy of 10**

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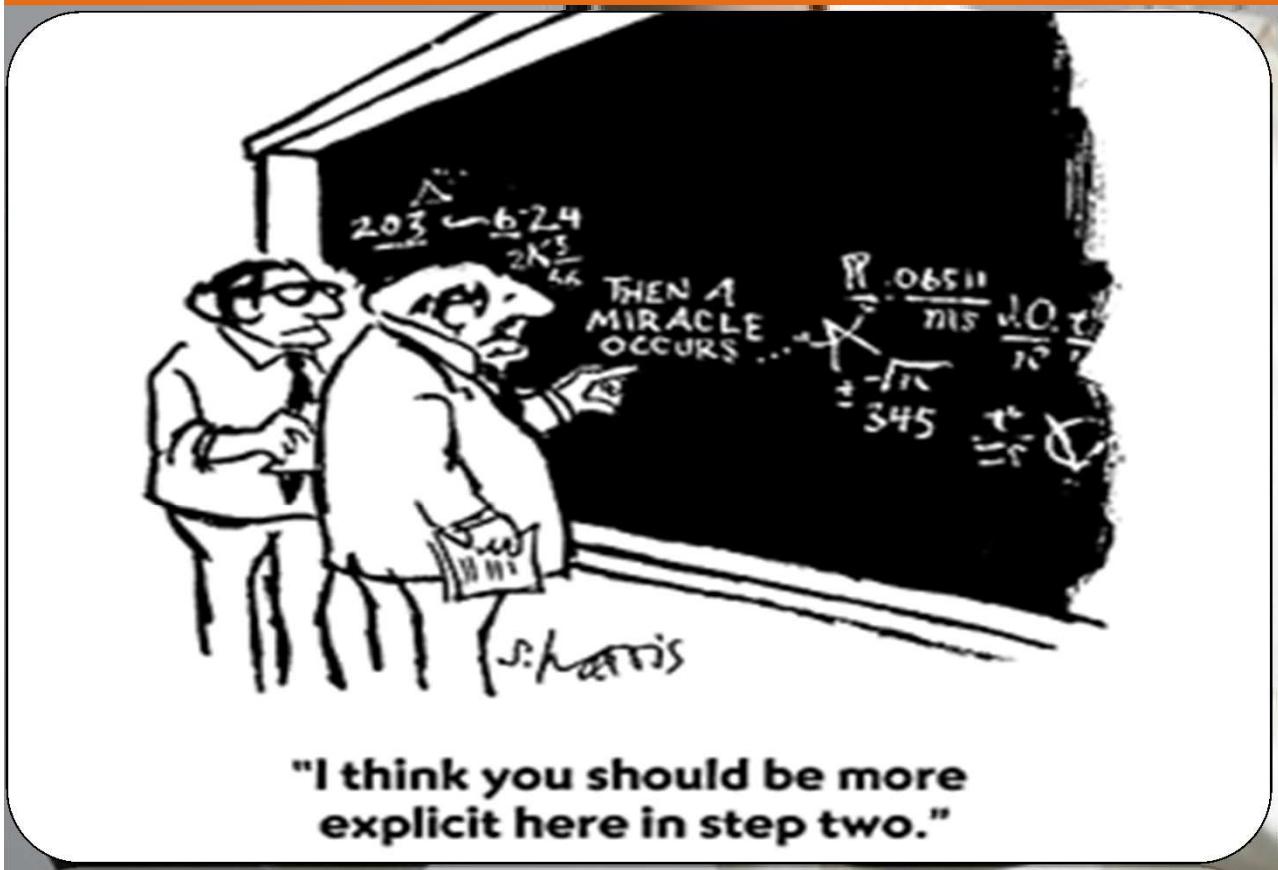

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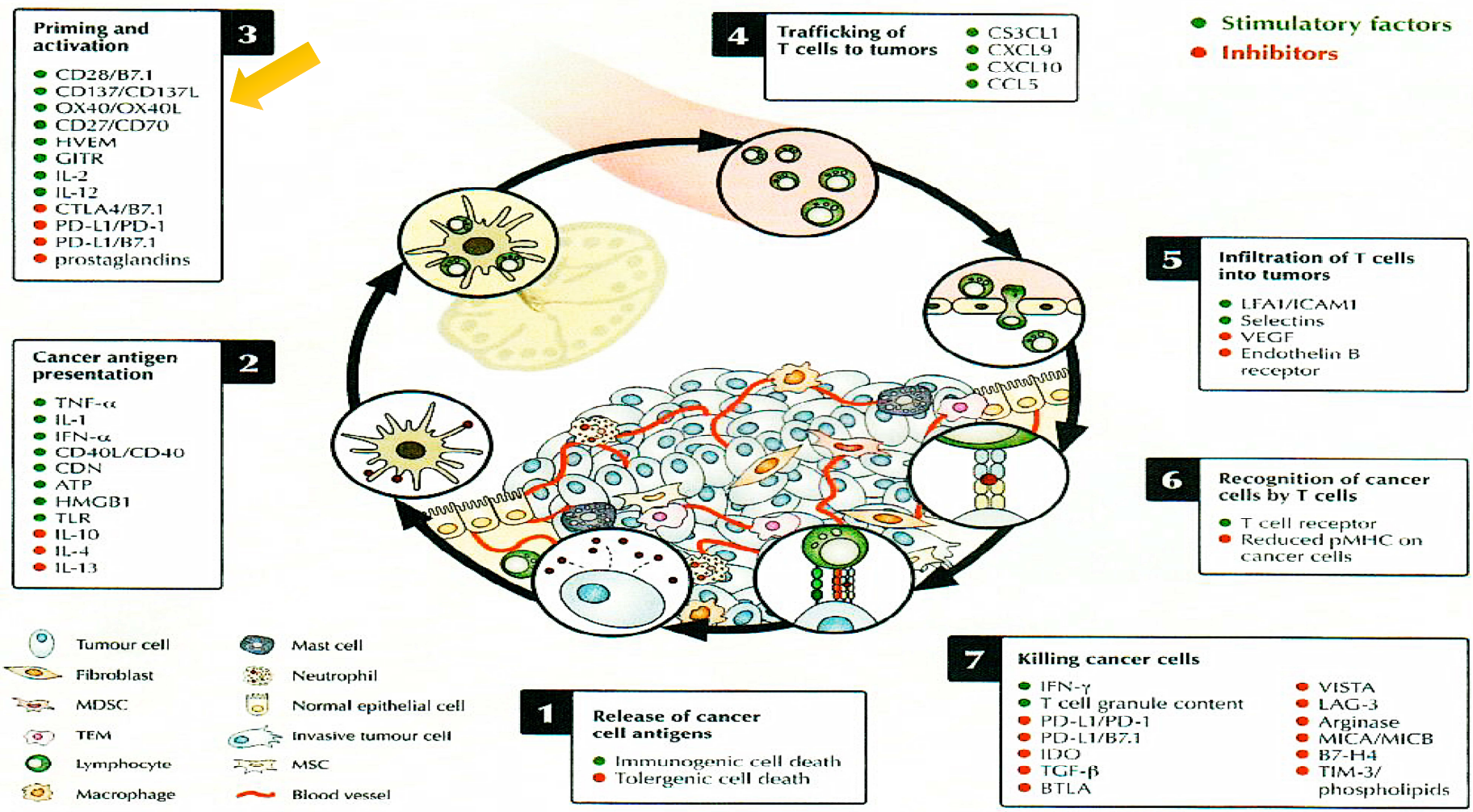
DOUBLET COMBINATION 4-1BB TX



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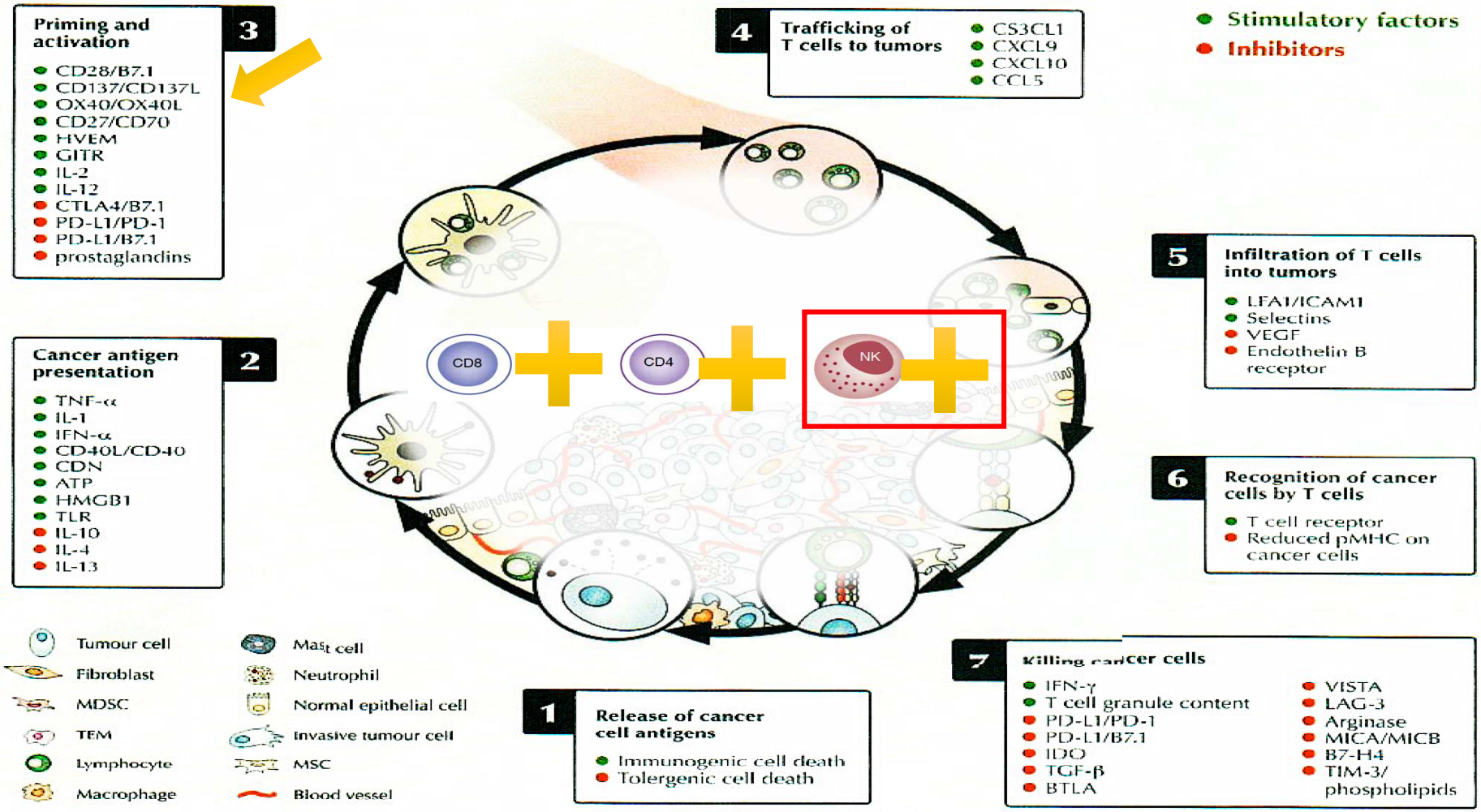
DOUBLET COMBINATION 4-1BB TX



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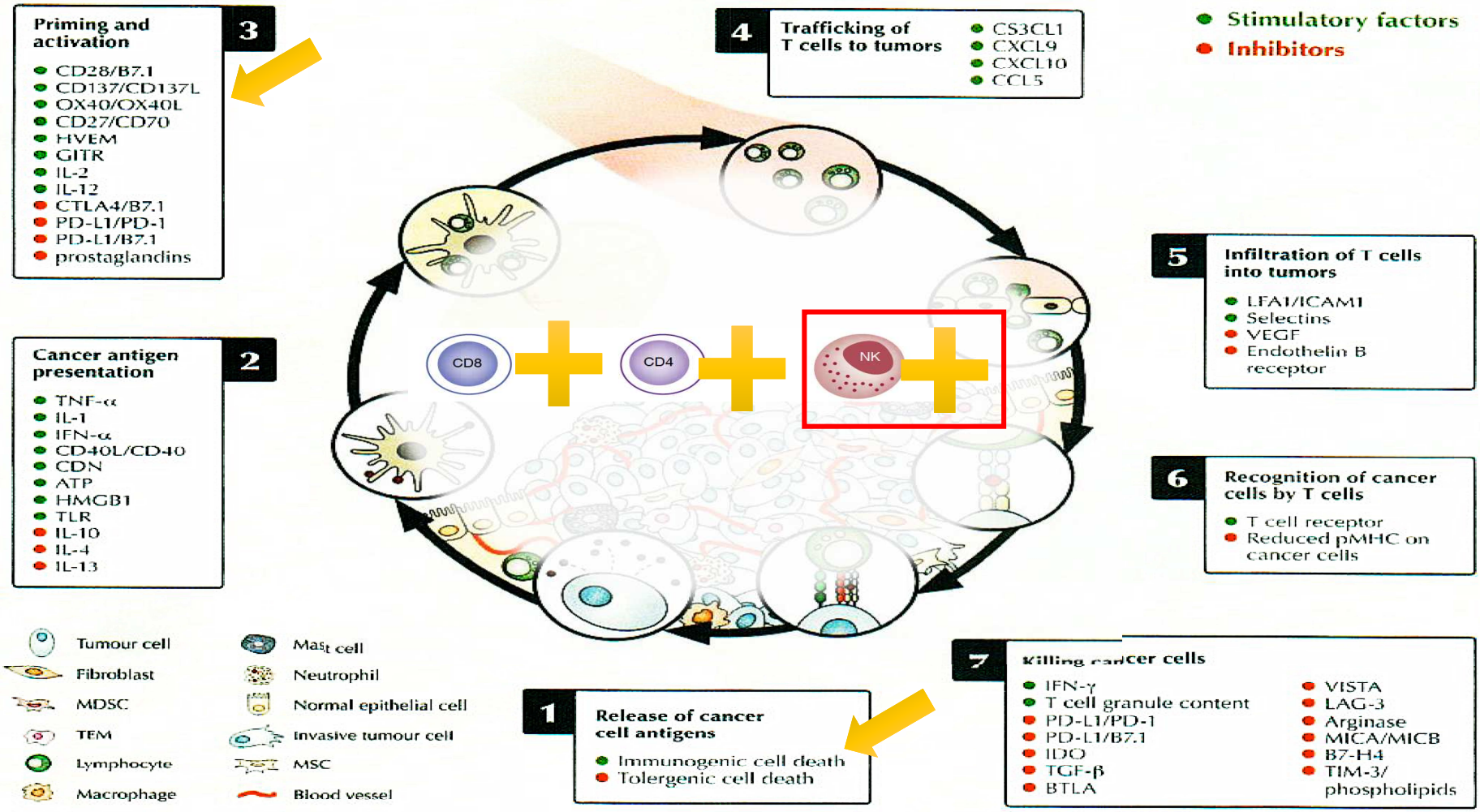

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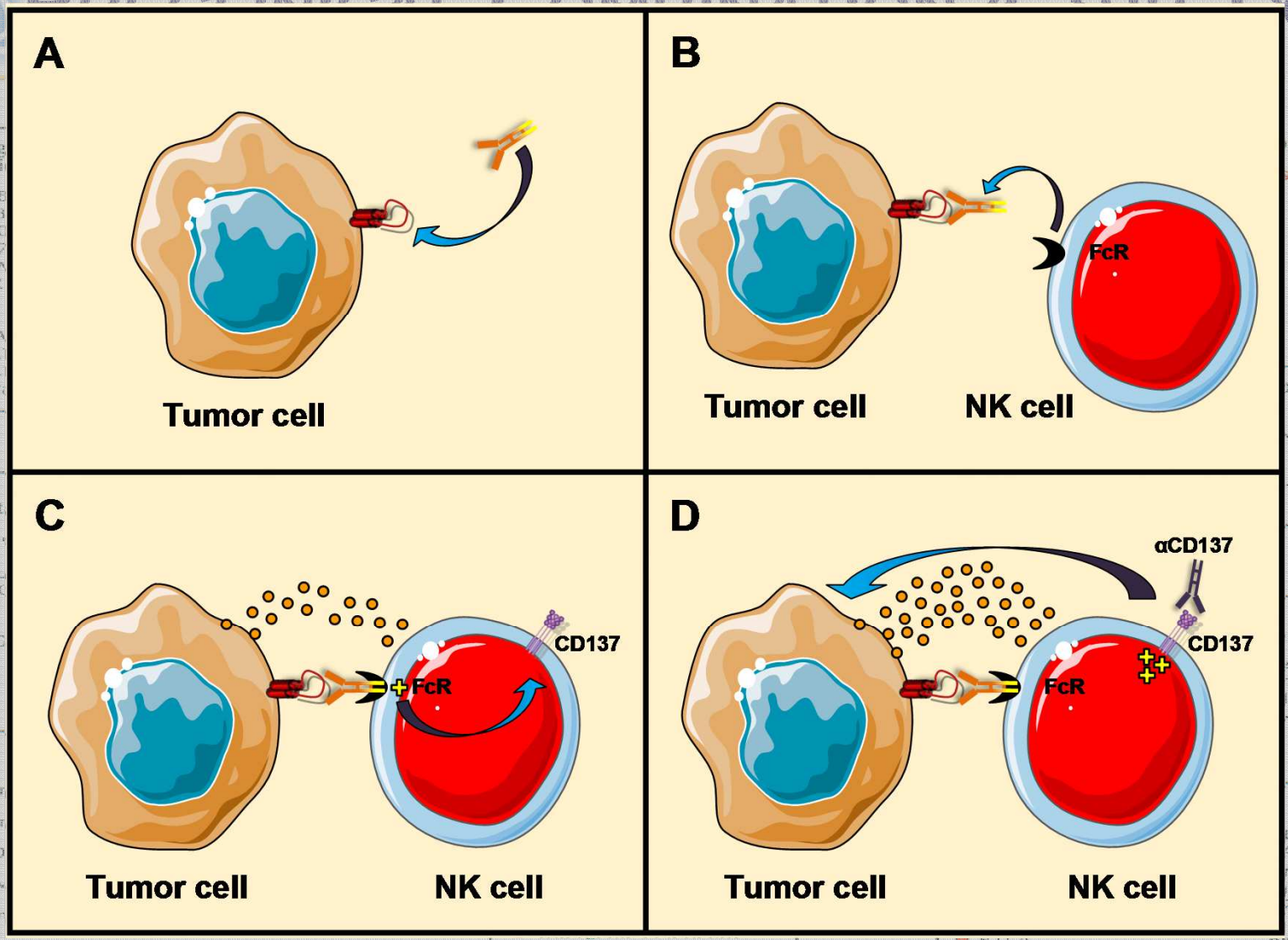

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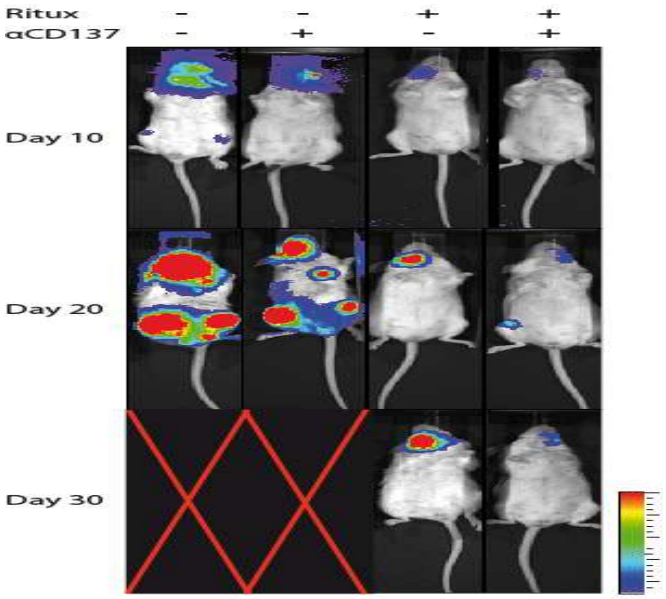
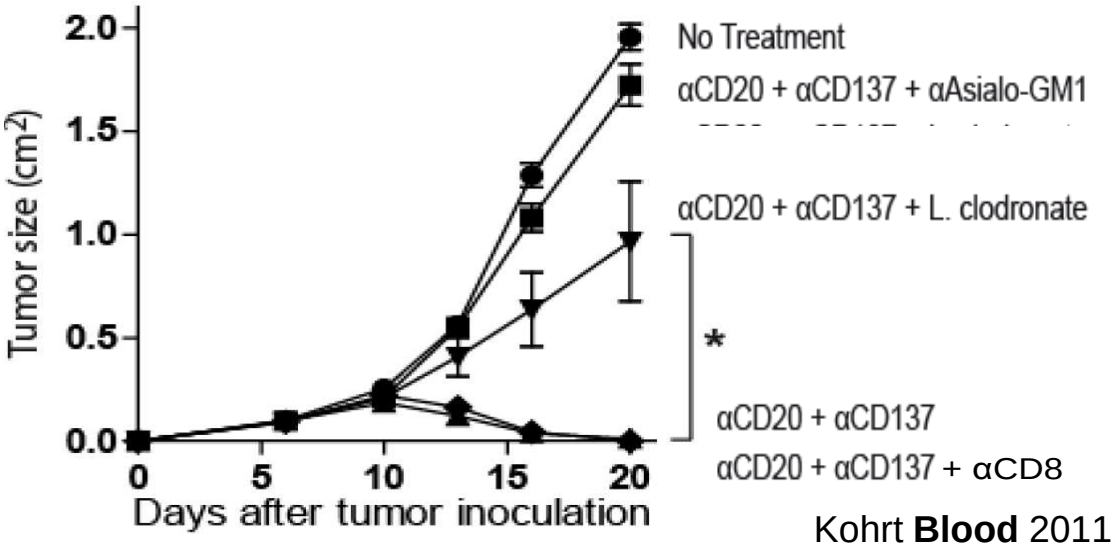
Rituximab + anti-CD137

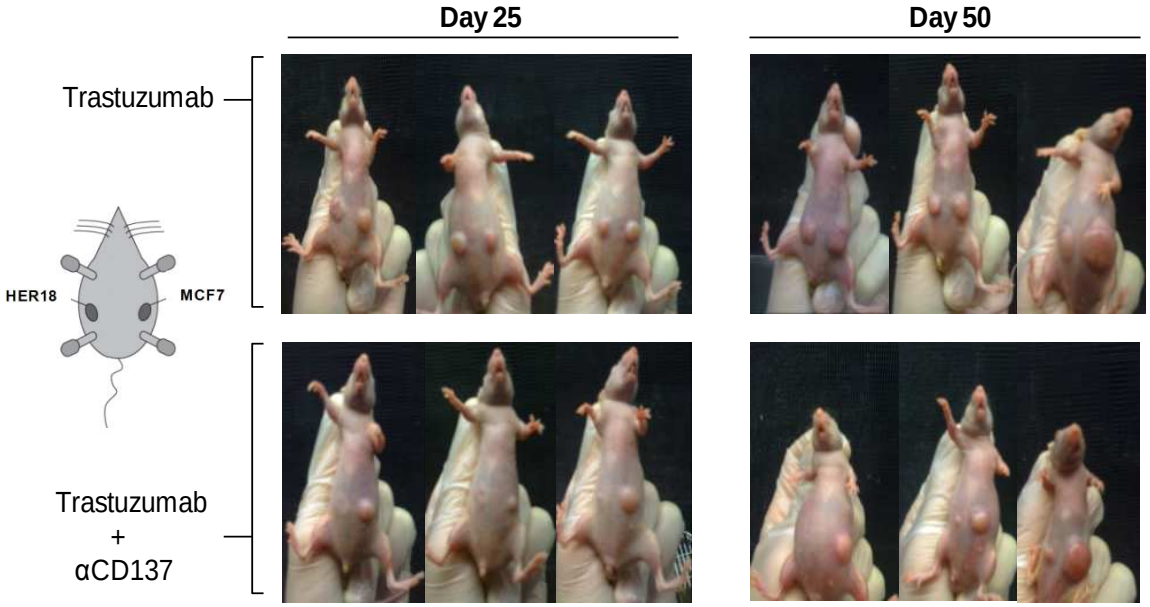


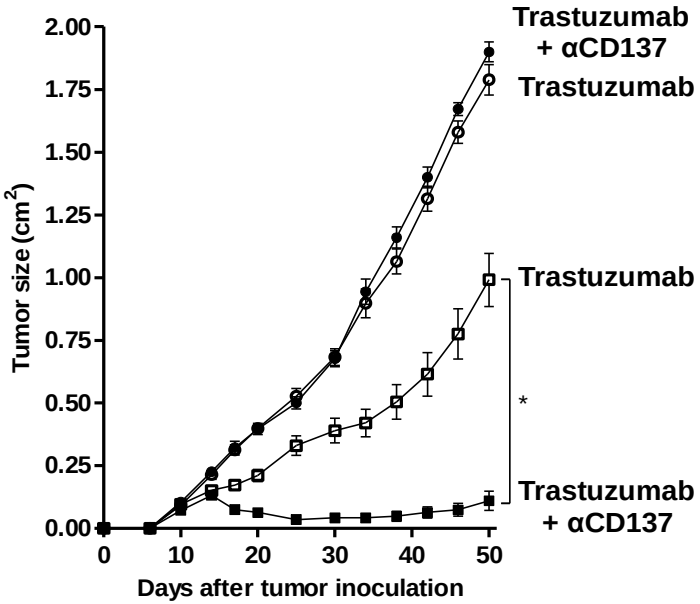


Kohrt **Blood** 2011.

Trastuzumab + anti-CD137

Kohrt **JCI** 2013.





COMBINATION PROMISE OF 4-1BB

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2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

NCT00309023

NCT00309023

NCT00351325

NCT00461110

NCT00803374

NCT01471210

- Phase I
- Safety, Tolerability, Pharmacokinetics, and Immunoregulatory Study of Urelumab (BMS-663513) in Subjects With Advanced and/or Metastatic Solid Tumors and Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma

Part 1	Part 2	Part 3	Part 4
Dose escalation	**Cohort Expansion**	**Tumor-Specific Cohort Expansion**	**Lymphoma expansion**:
0.1 mg/kg q 3 weeks and 0.3 mg/kg q 3 weeks	Additional 20 subjects at expansion dose 0.3 mg/kg	B-cell NHL, CRC and SCCHN	1:1 randomization q 3 weeks, and q 6 weeks

SITC 2013

CANCER CENTER
Stanford Hospital & Clinics

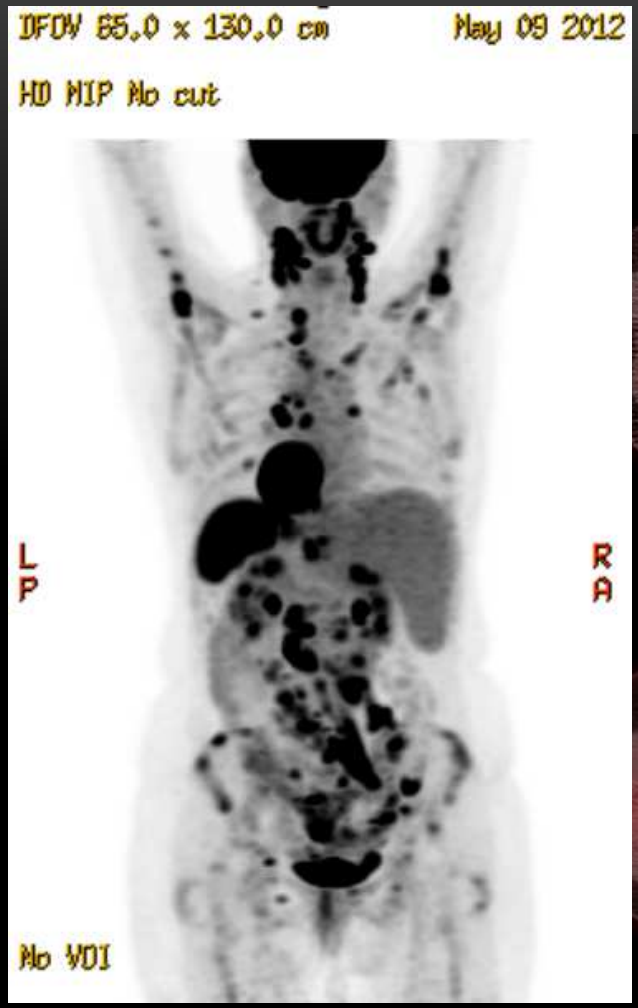
Society for Immunotherapy of Cancer

NATIONAL HARBOR, MD • NOVEMBER 7-10, 2013

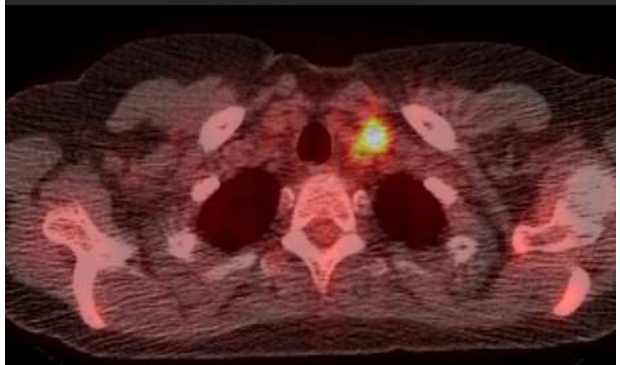
Annual Meeting • Workshop • Primer

*Presented by Levy, Ronald Stanford

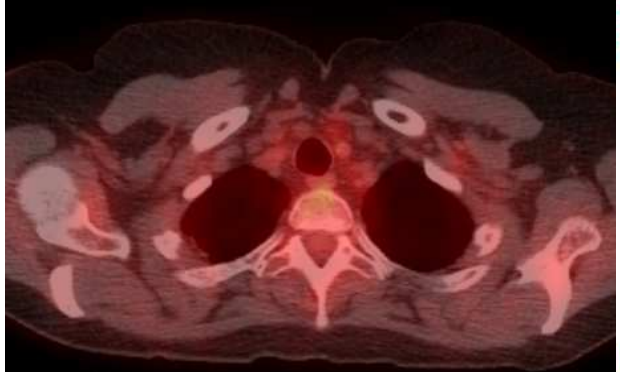
May 9, 2012



May 9, 2012



Nov 28, 2012



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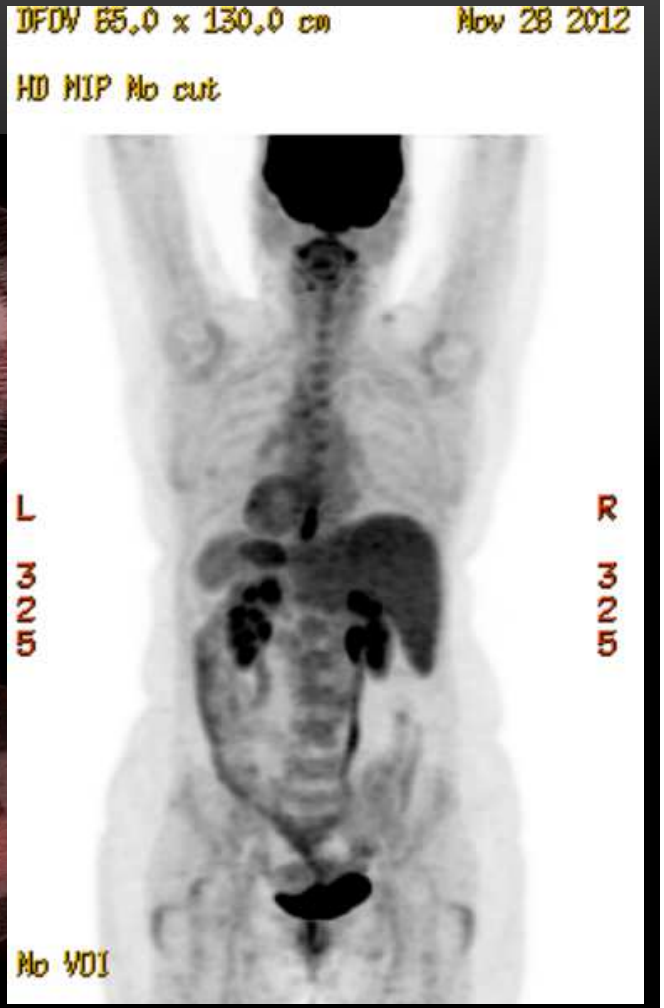

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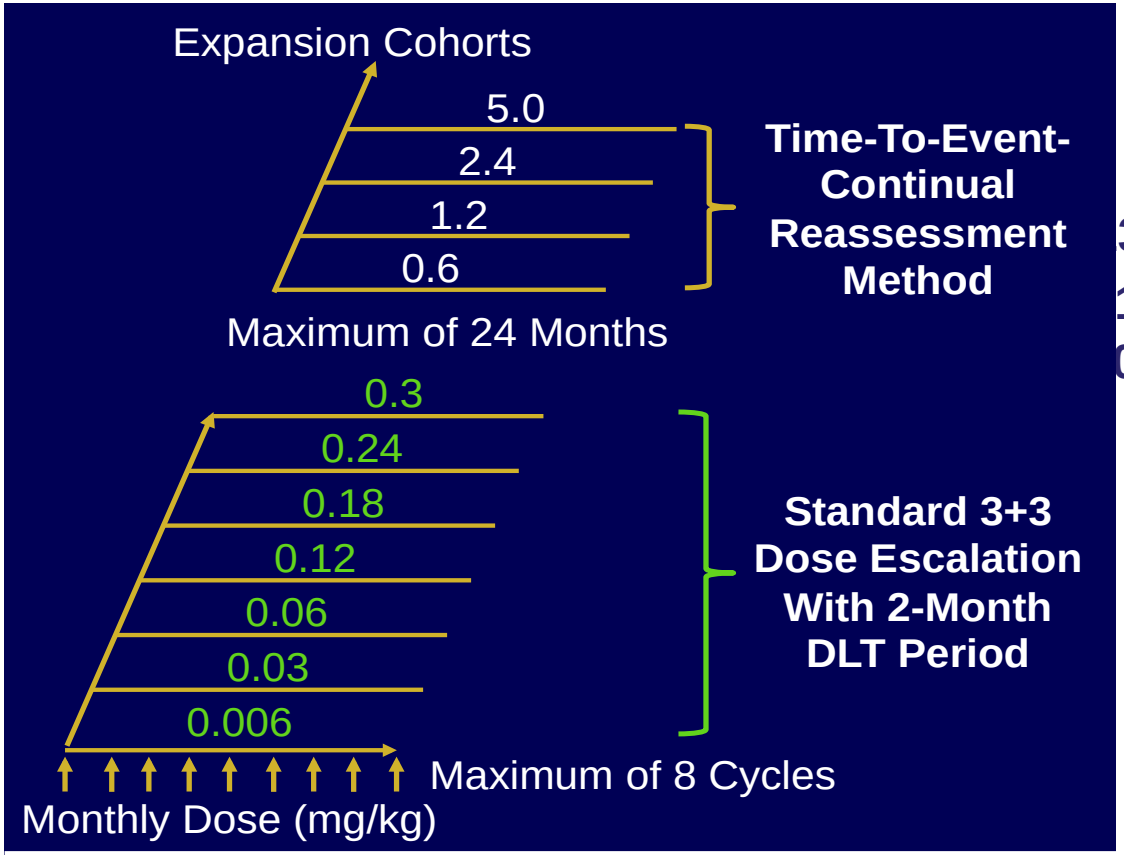
- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

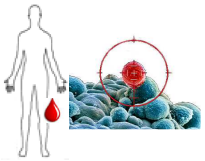


325
1110
03374

- NCT01471210
- NCT01307267

– Phase I, reported by N Segal at *ASCO 2014*
– A Study Of PF-05082566 As A Single Agent And In Combination With Rituximab

COMBINATION PROMISE OF 4-1BB



- **Urelumab,** BMS, Anti-CD137, Fully human, IgG4, Agonist
- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

	n (%)
Total Patients Treated	34 24 Male (71) 10 Female (29)
Prior Therapies (mean)	3.6
Primary Cancer	
Colorectal cancer	12 (35)
Merkel Cell carcinoma	11 (32)
Pancreatic carcinoma	2 (6)
Non-Hodgkin's lymphoma	2 (6)
Squamous cell lung	1 (3)
Nasopharyngeal	1 (3)
Melanoma	1 (3)
Breast	1 (3)
Unknown primary	3 (9)

325

1110

03374

- **NCT01471210**
- **NCT01307267**

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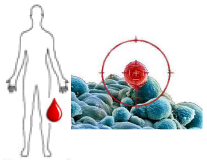
COMBINATION PROMISE OF 4-1BB



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- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Adverse Events – Related

- No Grade 2 or higher treatment related adverse events were observed up to the current dose level of 2.4 mg/kg
- Grade 1 related adverse events occurred at all doses, except at 1.2 mg/kg

Adverse event	N (%)
Rash	3 (9)
Fever	2 (6)
Nausea/ vomiting	2 (6)
Weight loss	1 (3)
Headache	1 (3)
Fatigue	1 (3)
Thrombocytopenia	1 (3)

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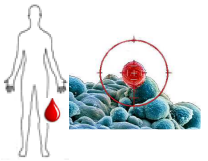
COMBINATION PROMISE OF 4-1BB



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- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Preliminary Assessment of Best Overall Response

- 34 treated
- 24 evaluable for response
- 1 patient – PR (0.6 mg/kg)
- 1 patient – Mixed response (0.06 mg/kg)
- 7 patients – Stable disease across multiple doses

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COMBINATION PROMISE OF 4-1BB

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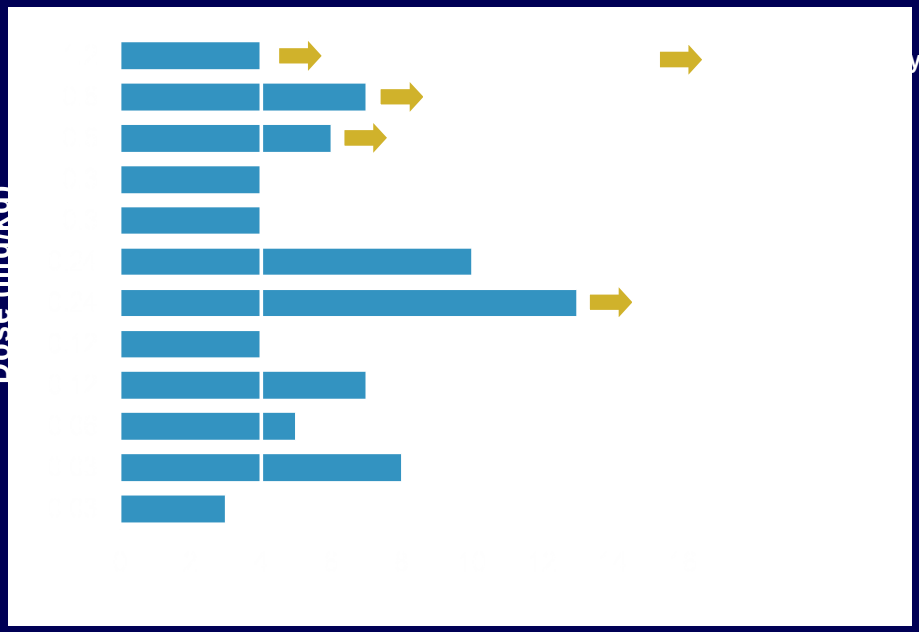
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Duration of Treatment in Patients with Measurable Disease



None of these patients discontinued due to adverse events attributed to the study drug.
Data as of May 19, 2014

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- NCT01471210
- NCT01307267

– Phase I, reported by N Segal at *ASCO 2014*
– A Study Of PF-05082566 As A Single Agent And In Combination With Rituximab

COMBINATION PROMISE OF 4-1BB

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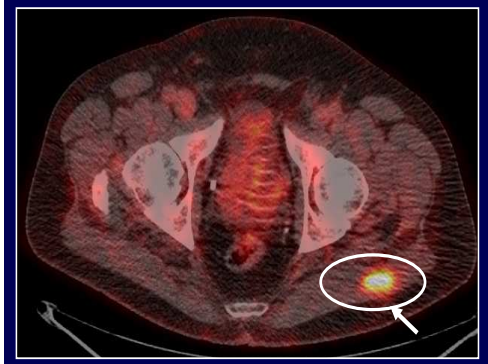
- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

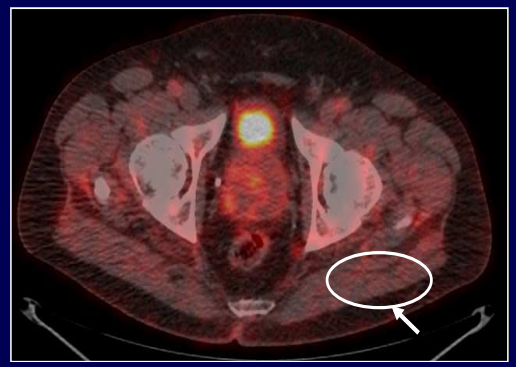
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

Tumor Response in Merkel Cell Carcinoma Patient Treated At 0.6 mg/kg

Baseline PET Scan



Week 16 PET Scan



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– *Awaiting combination results*

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- NCT00309023
- NCT00309023
- NCT00351325
- NCT00461110
- NCT00803374
- NCT01471210
- NCT01307267
- NCT01775631

– Phase I
– Combination Study of Urelumab and Rituximab in Patients With B-cell Non-Hodgkins Lymphoma

COMBINATION PROMISE OF 4-1BB

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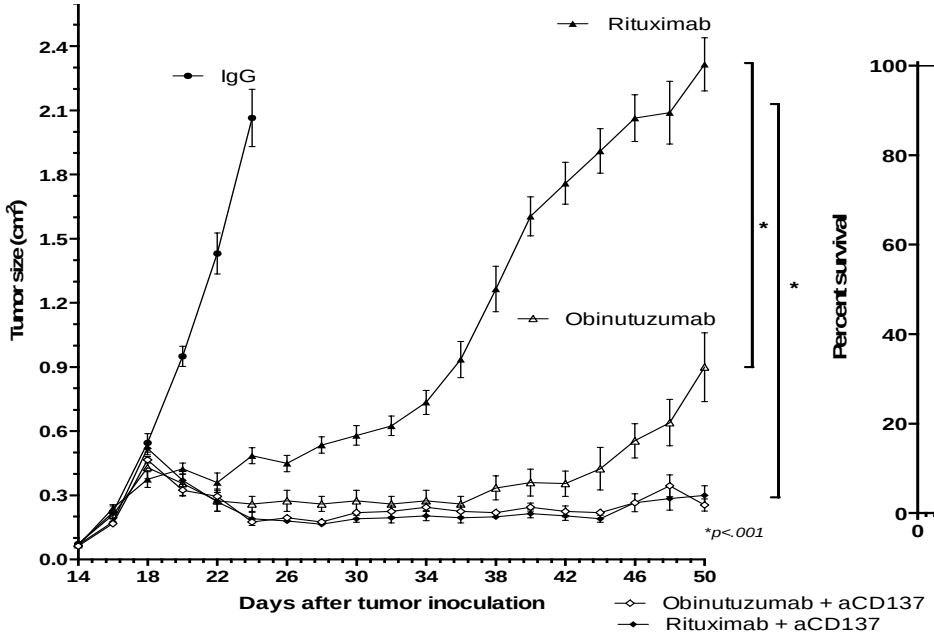
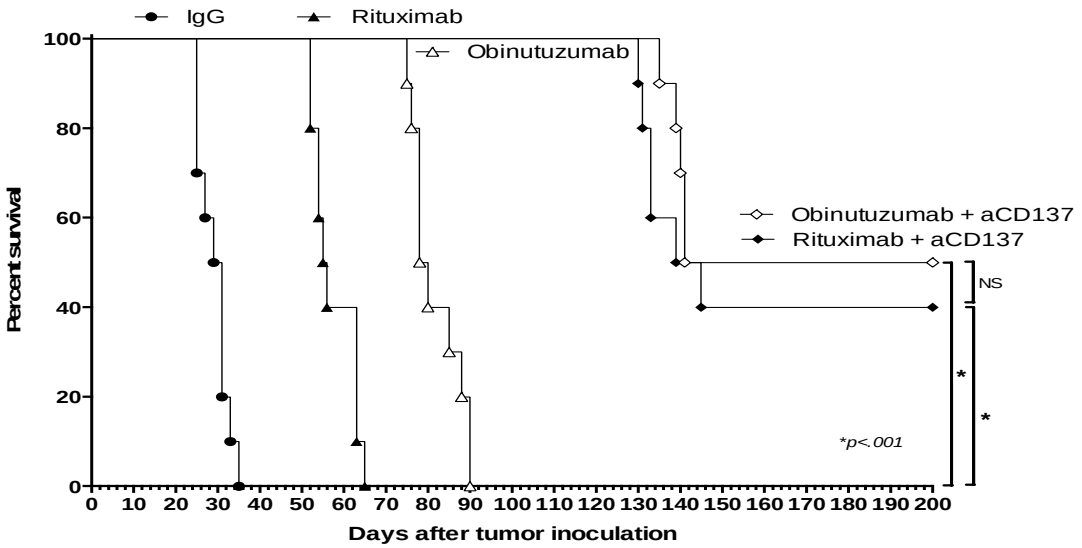
- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

- **Can 1 + 1 =**
  - **– toxicity of 1**
  - **– efficacy of 1000**

Rituximab vs Obinutuzumab + anti-CD137

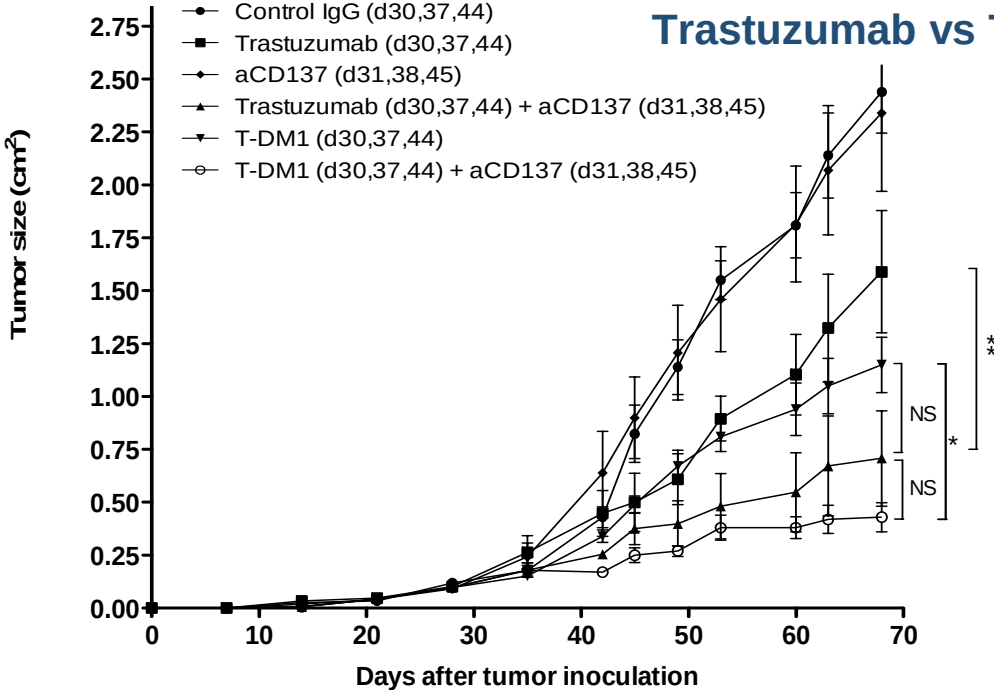


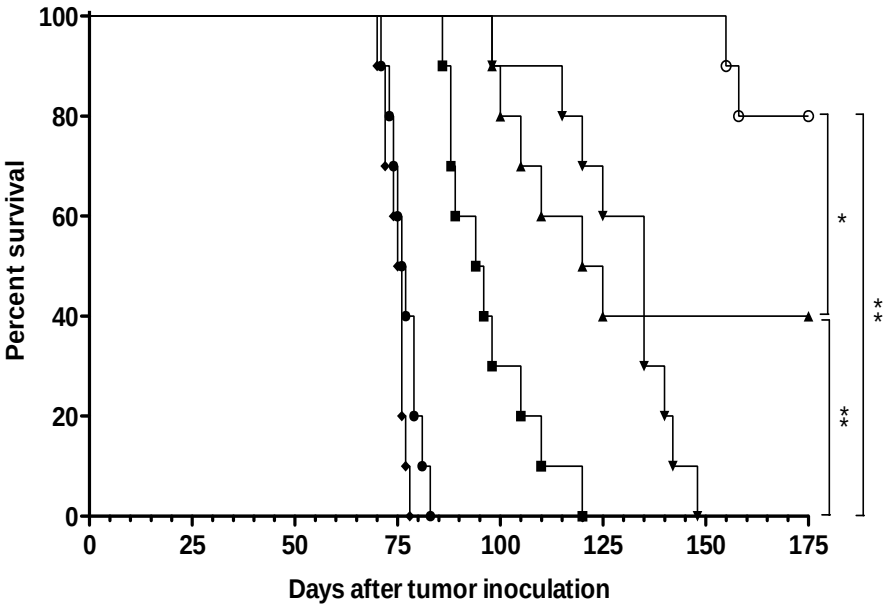


Kohrt *unpublished*.

Trastuzumab vs T-DM1 + anti-CD137

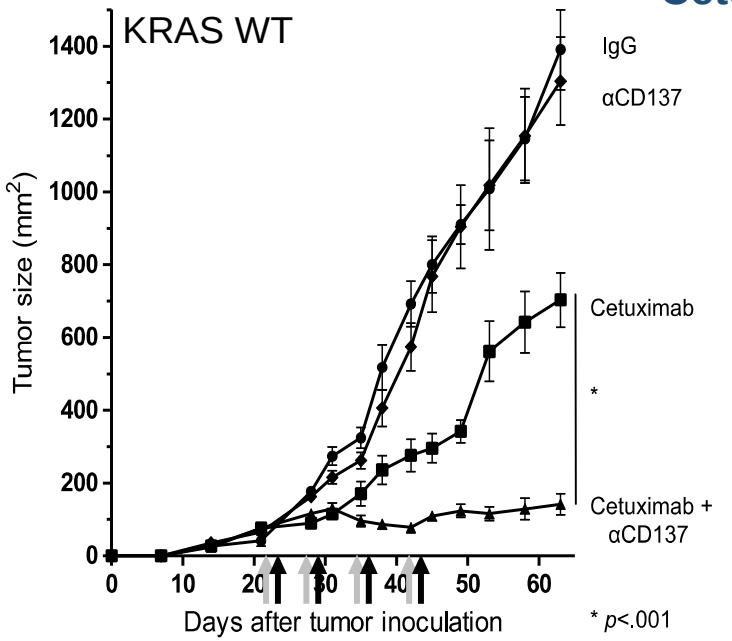
Kohrt *unpublished*.

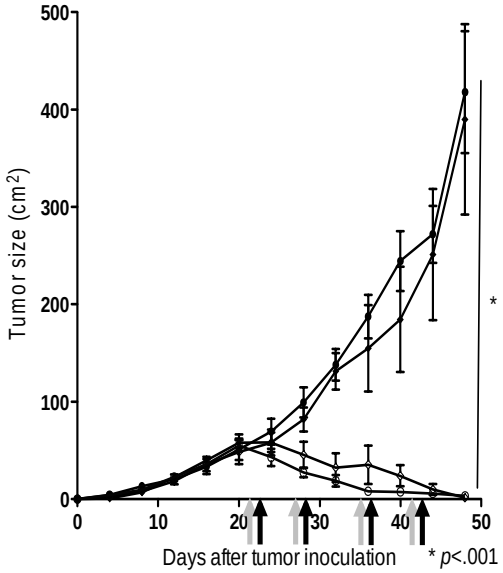


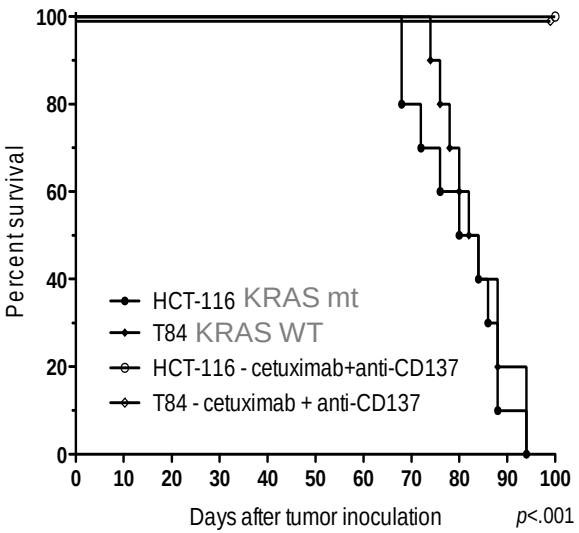


Cetuximab + anti-CD137 in KRAS WT & Mutant CRC

Kohrt **JCI** 2014.

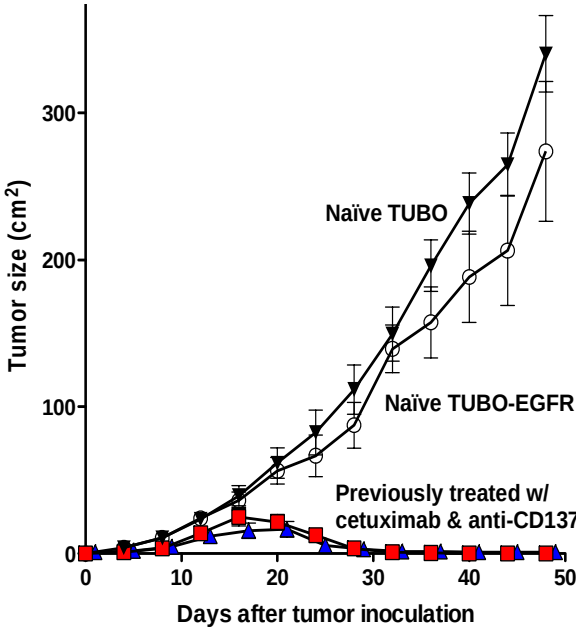


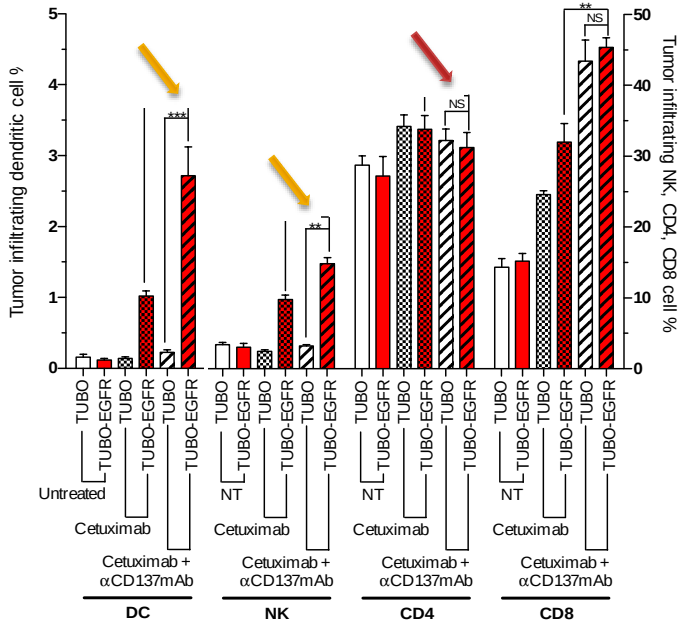


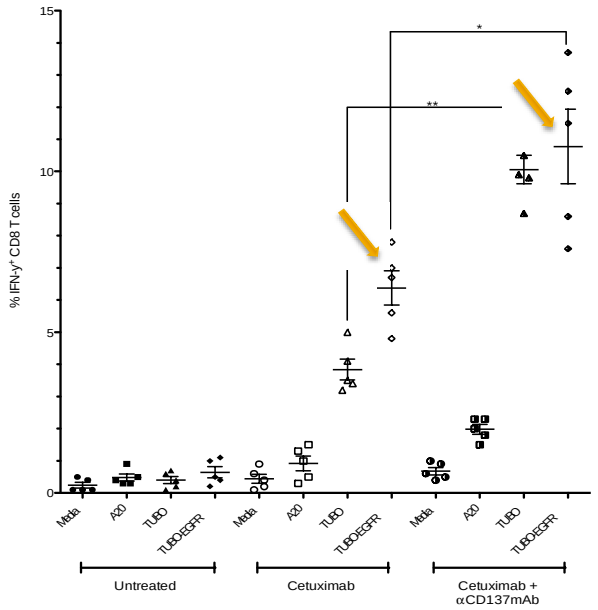


Cetuximab + anti-CD137 in Head & Neck

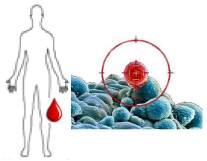
Kohrt **JCI** 2014.







COMBINATION PROMISE OF 4-1BB



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2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

- NCT00309023
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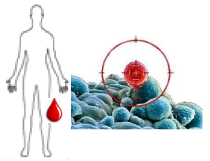
- NCT00461110
- NCT00803374
- NCT01471210
- NCT01307267
- NCT01775631
- NCT01775631

– Phase I

– Combination Study of Urelumab and Cetuximab in Patients With Advanced/Metastatic Colorectal Cancer or Advanced/Metastatic Head and Neck Cancer

COMBINATION PROMISE OF 4-1BB



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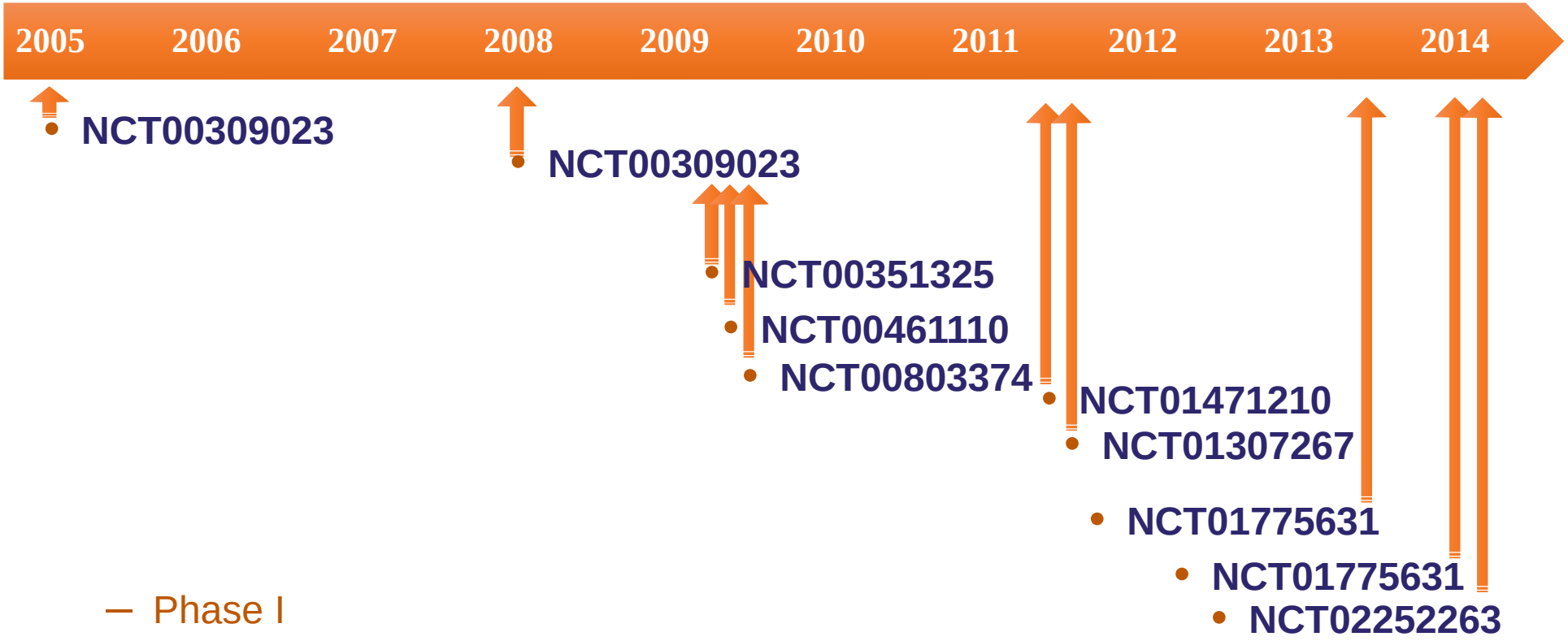
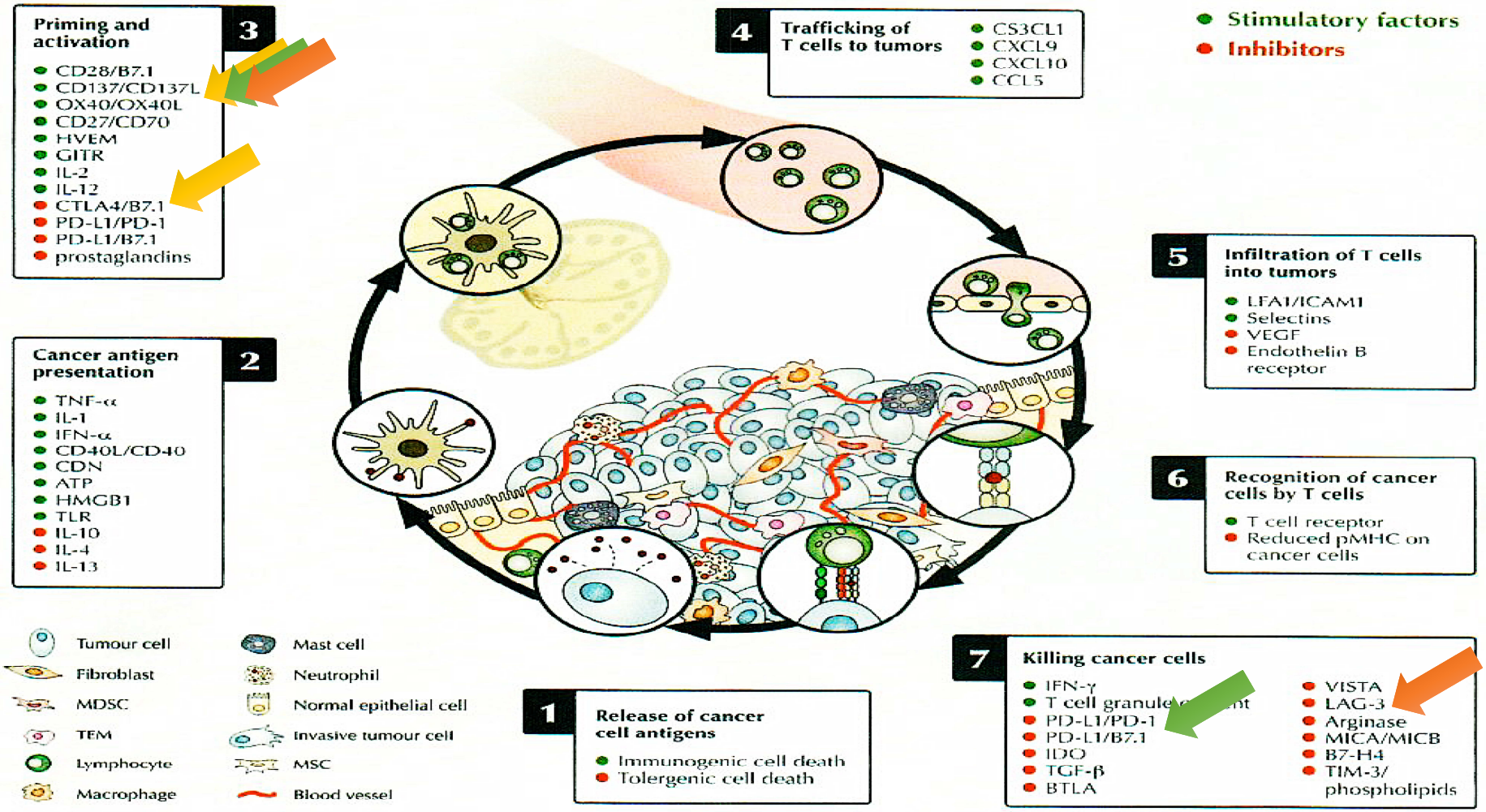
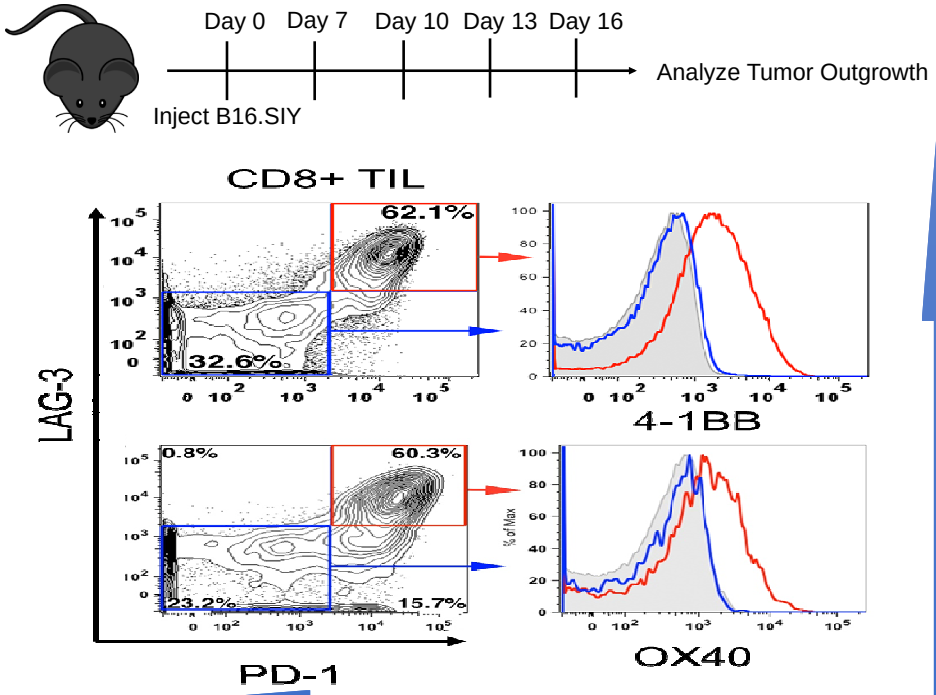


- Phase I
- A Phase I Open Label Study of the Safety and Tolerability of Elotuzumab (BMS-901608) Administered in Combination With Either Lirilumab (BMS-986015) or Urelumab (BMS-663513) in Subjects With Multiple Myeloma

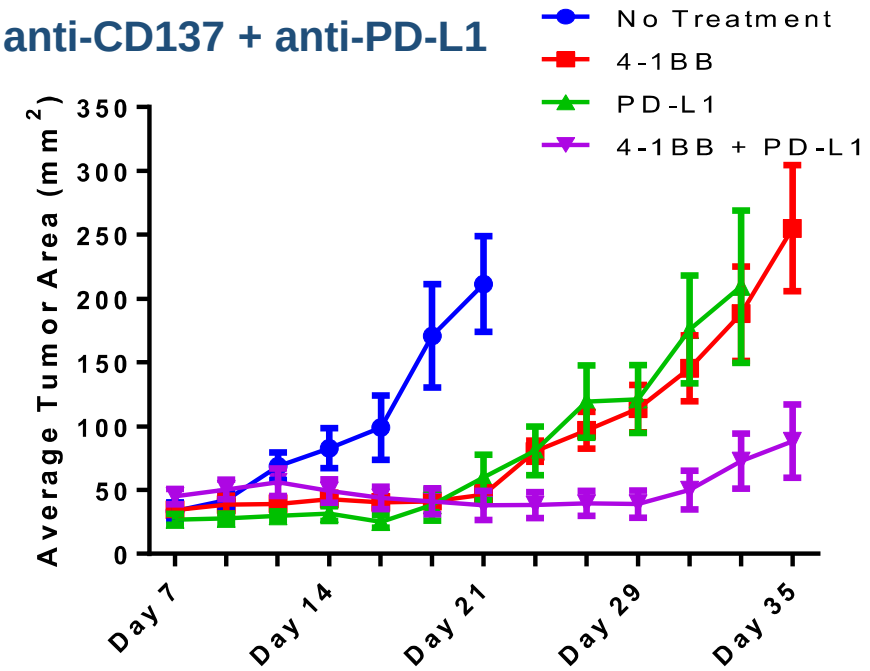
DOUBLET COMBINATION 4-1BB TX



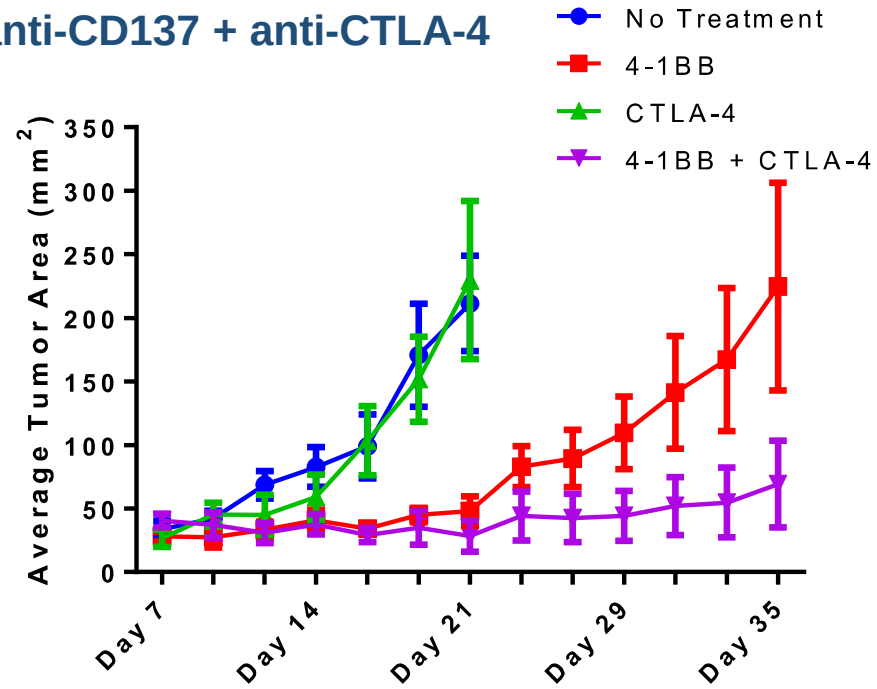
Adapted from I Mellman **Immunity** 39: 2013.



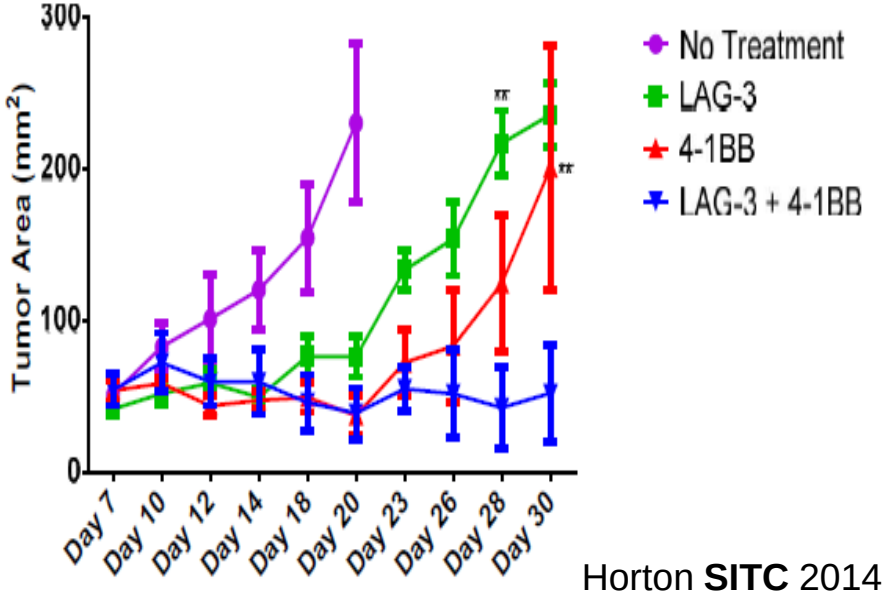
anti-CD137 + anti-PD-L1



anti-CD137 + anti-CTLA-4

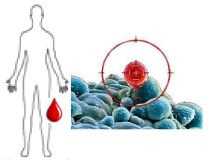


anti-CD137 + anti-LAG3



Horton **SITC** 2014.

COMBINATION PROMISE OF 4-1BB



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2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

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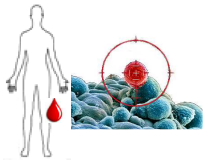
- NCT00803374
- NCT01471210
- NCT01307267
- NCT01775631
- NCT01775631
- NCT02252263
- NCT02253992

– Phase I/II

– Study of the Safety and Tolerability of Urelumab Administered in Combination With Nivolumab in Solid Tumors and B-cell Non-Hodgkins Lymphoma

COMBINATION PROMISE OF 4-1BB



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- NCT01471210
- NCT01307267
- NCT01775631
- NCT01775631
- NCT02252263
- NCT02253992
- NCT02179918

– Phase I

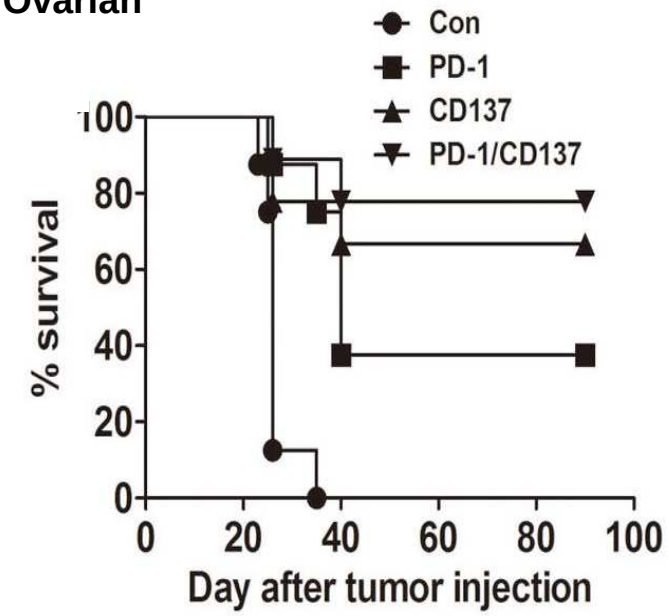
– A Study Of 4-1BB Agonist PF-05082566 Plus PD-1 Inhibitor MK-3475 In Patients With Solid Tumors (B1641003/KEYNOTE-0036)

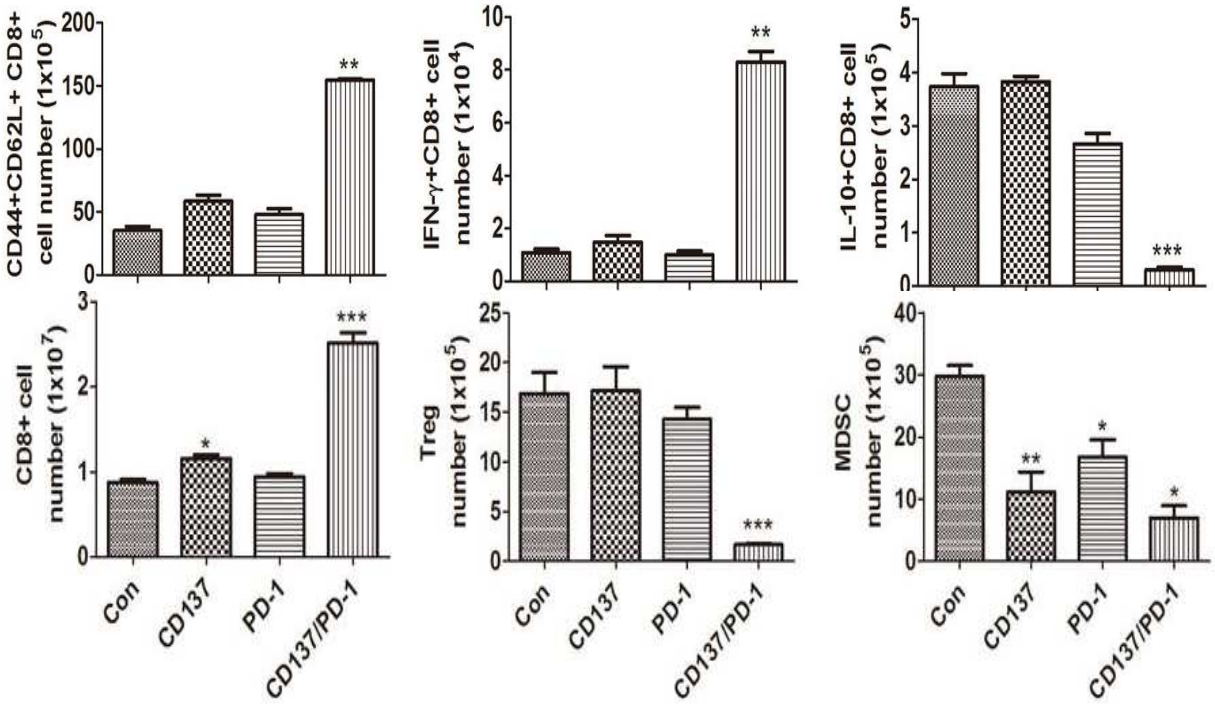
TRIPLET COMBINATION 4-1BB TX

Adapted from I Mellman **Immunity** 39: 2013.

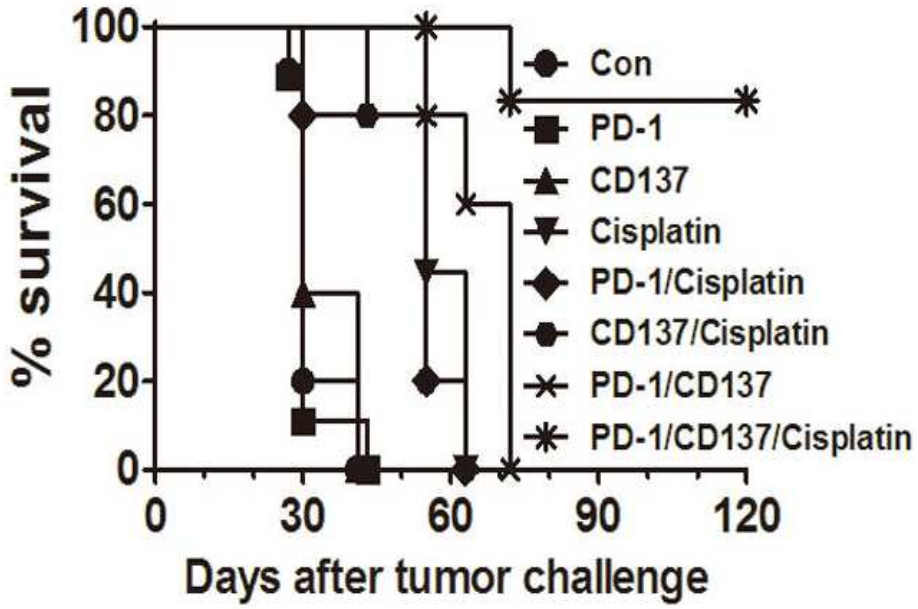
ID8 Ovarian

anti-CD137 + anti-PD-1

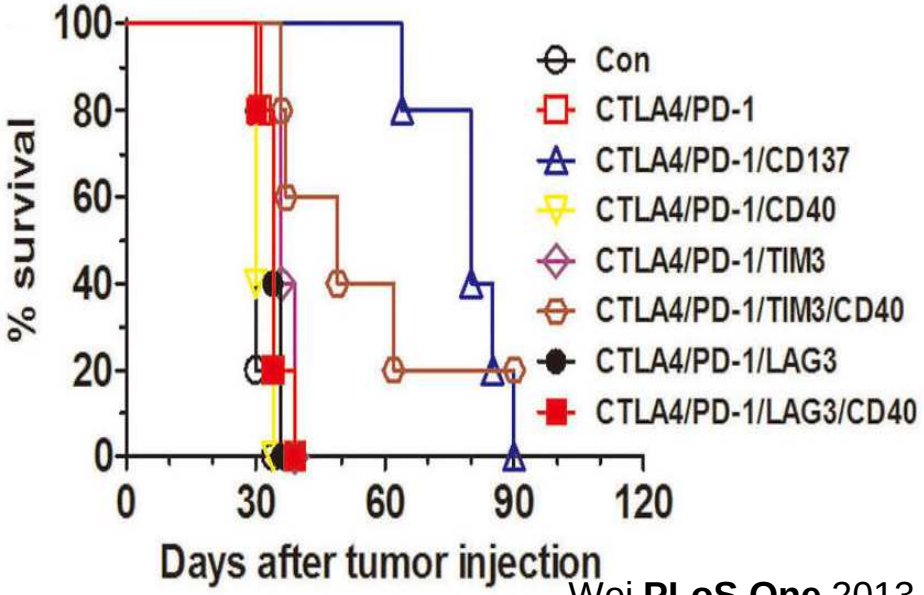




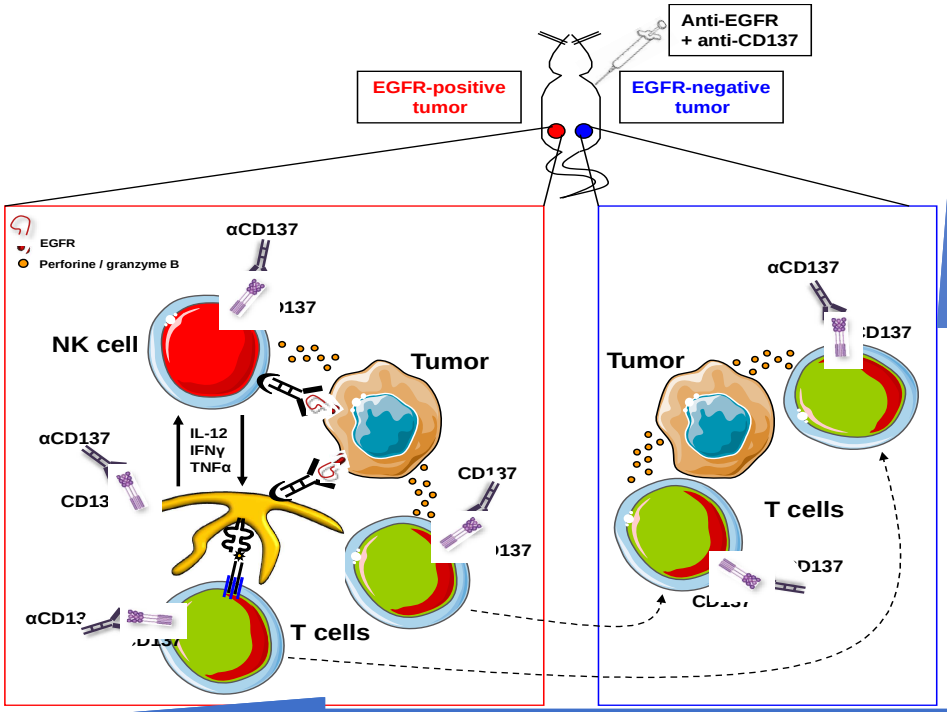
anti-CD137 + anti-PD1 + Cisplatin



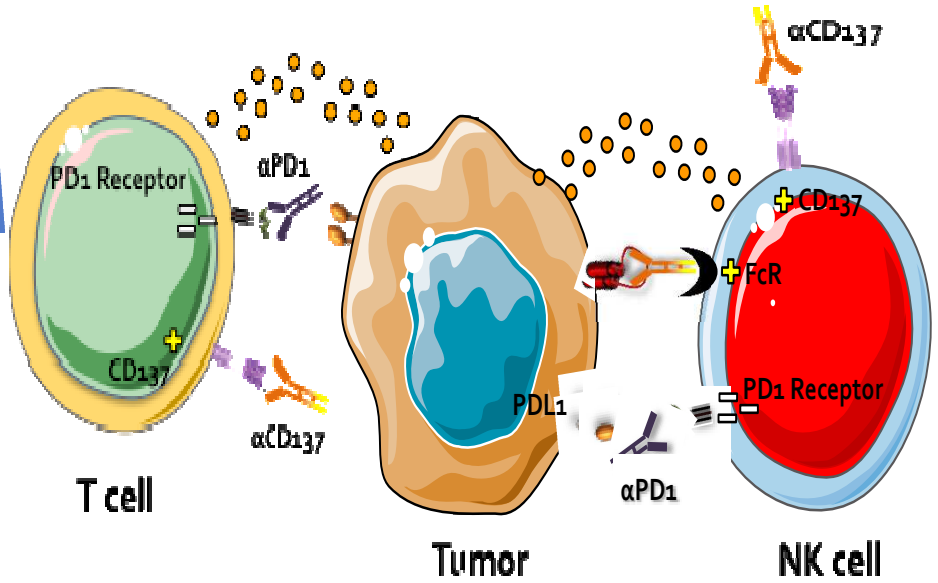
anti-CD137 + anti-PD-L1 + anti-CTLA-4



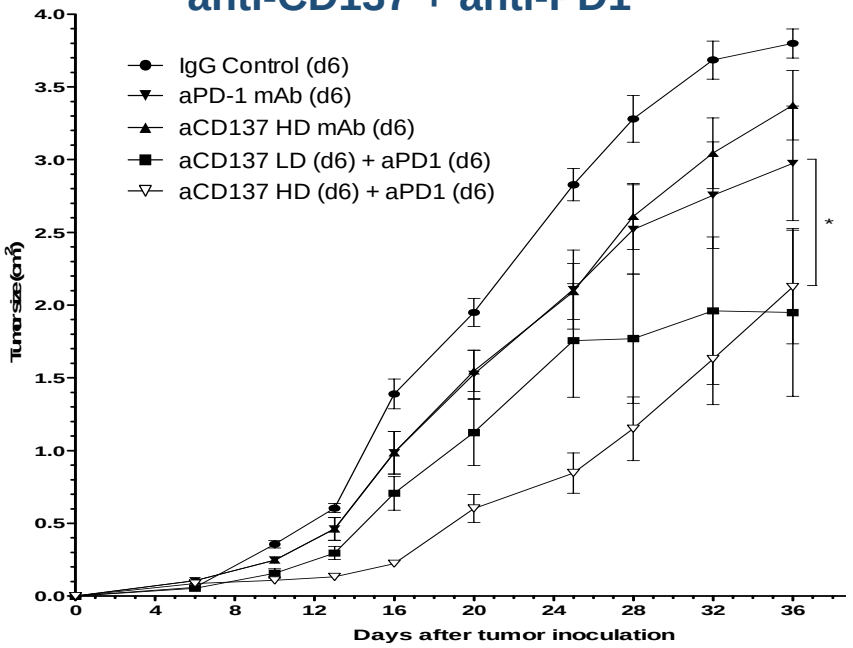
Wei **PLoS One** 2013.



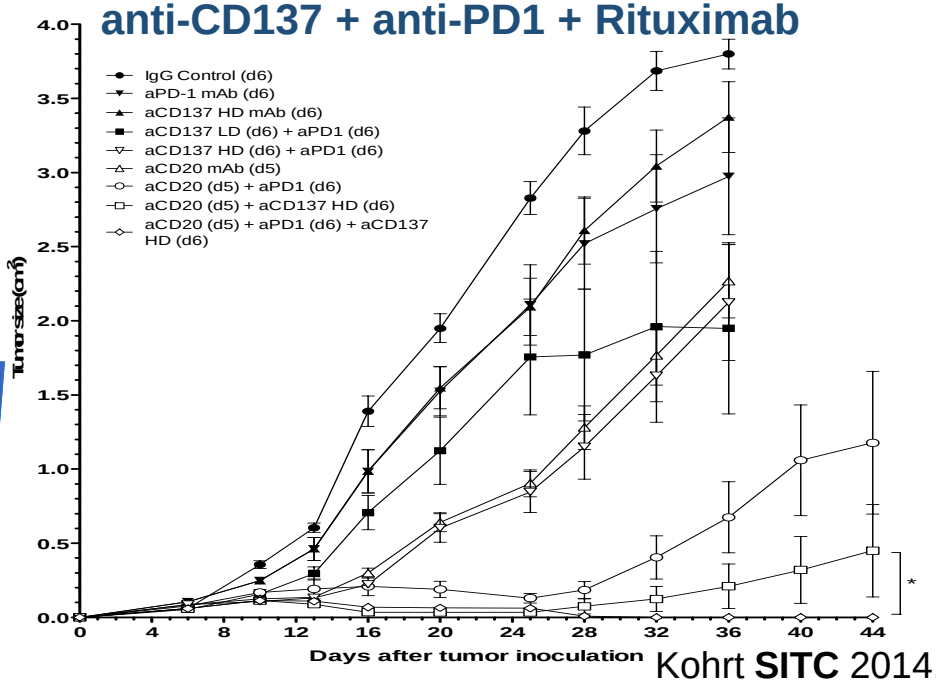
anti-CD137 + anti-PD-L1 +/- Rituximab



anti-CD137 + anti-PD1



anti-CD137 + anti-PD1 + Rituximab

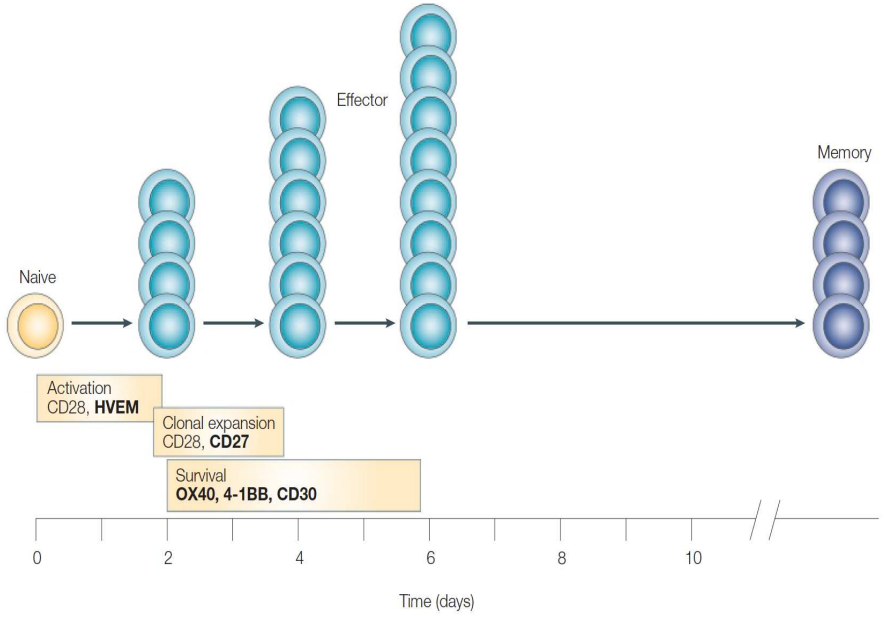


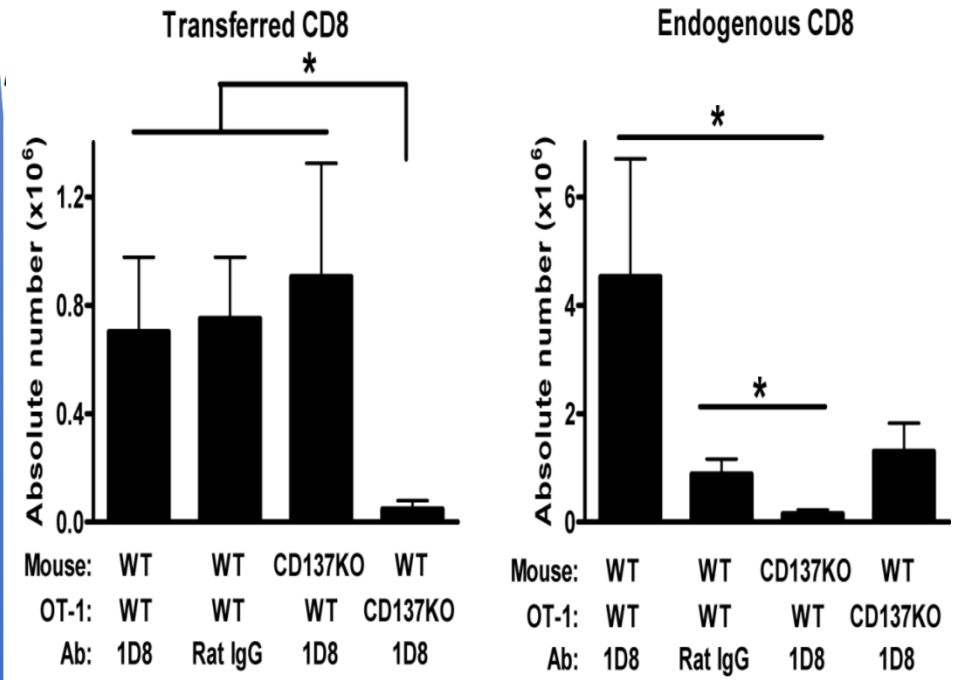
Kohrt **SITC** 2014.

CELL-BASED COMBINATION 4-1BB TX

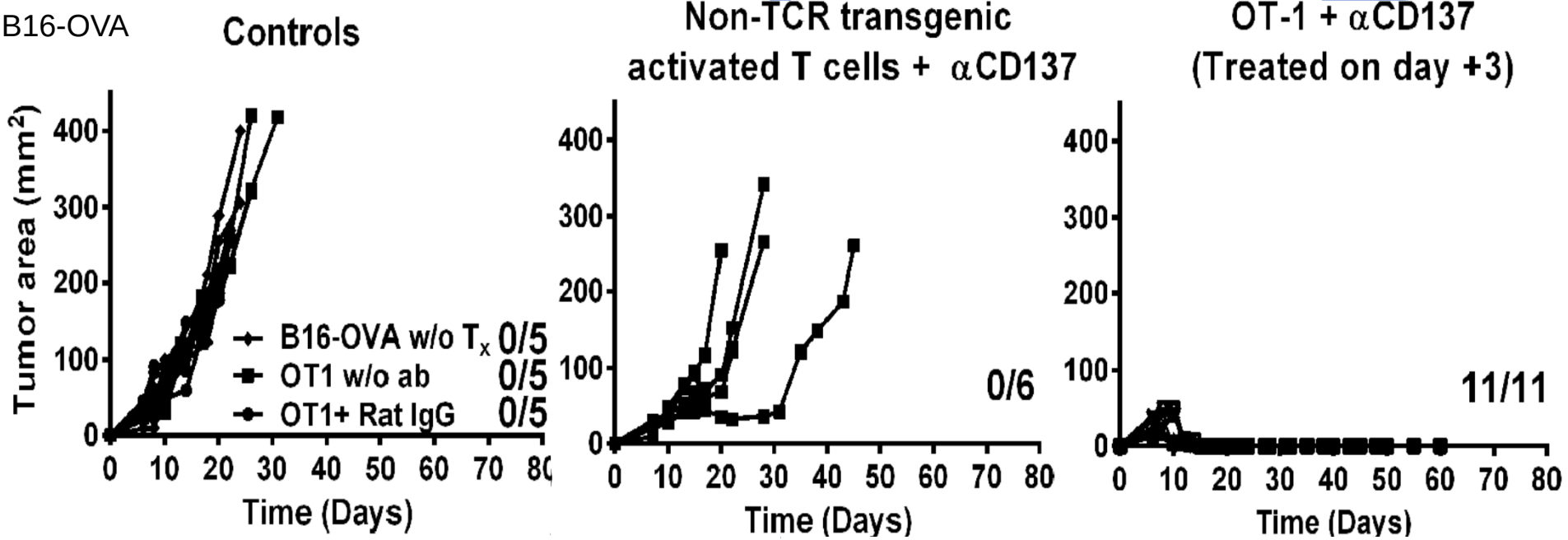
Adapted from I Mellman **Immunity** 39: 2013.

anti-CD137 and Adoptive Cell Therapy





B16-OVA



Bolanos-Mateo **SITC** 2014.

COMBINATION PROMISE OF 4-1BB

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- NCT01307267
- NCT01775631
- NCT01775631
- NCT02252263
- NCT02253992
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COMBINATION PROMISE OF 4-1BB

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- NCT01307267
- NCT01775631
- NCT01775631
- NCT02252263
- NCT02253992
- NCT02179918

THE PROMISE OF 4-1BB

- **Urelumab,** BMS, Anti-CD137, Fully human, IgG4, Agonist
- **PF-05082566,** Pfizer, Anti-CD137, Fully human, IgG2, Agonist

2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

- NCT00309023
- NCT00309023

- NCT01471210
- NCT01307267
- NCT01775631
- NCT01775631
- NCT02252263
- NCT02253992
- NCT02179918