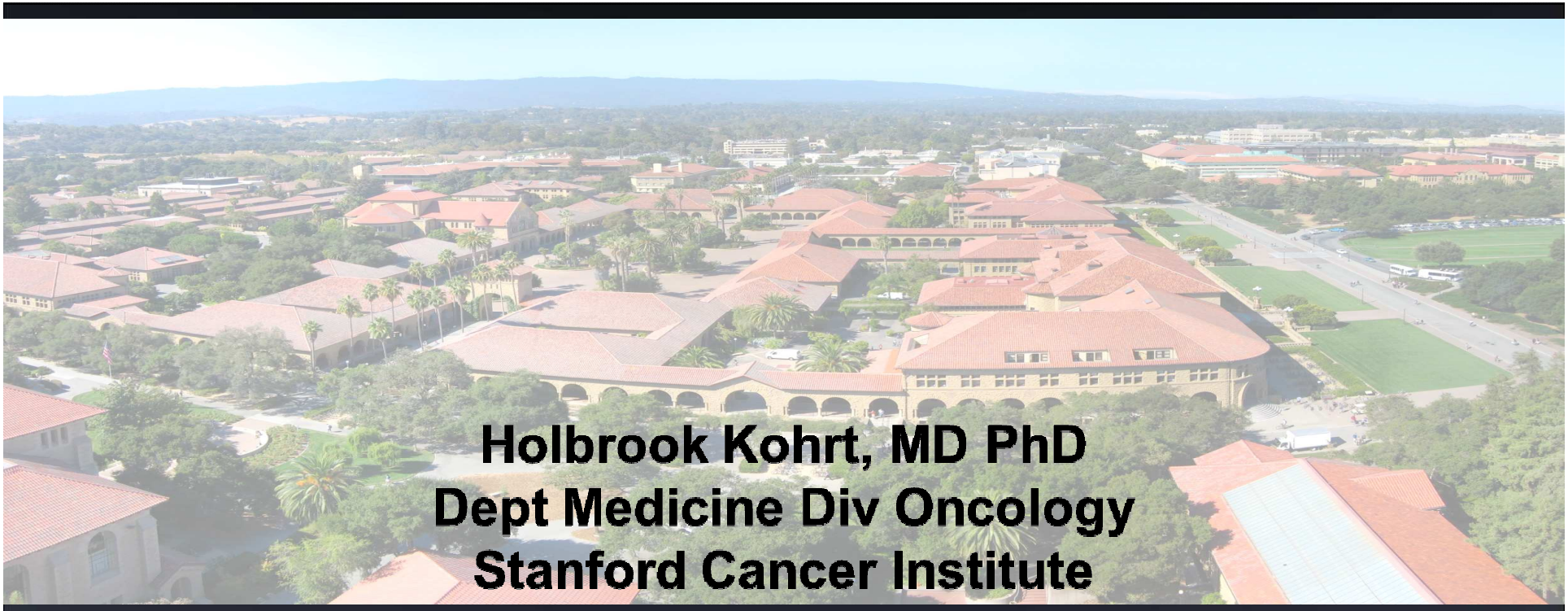
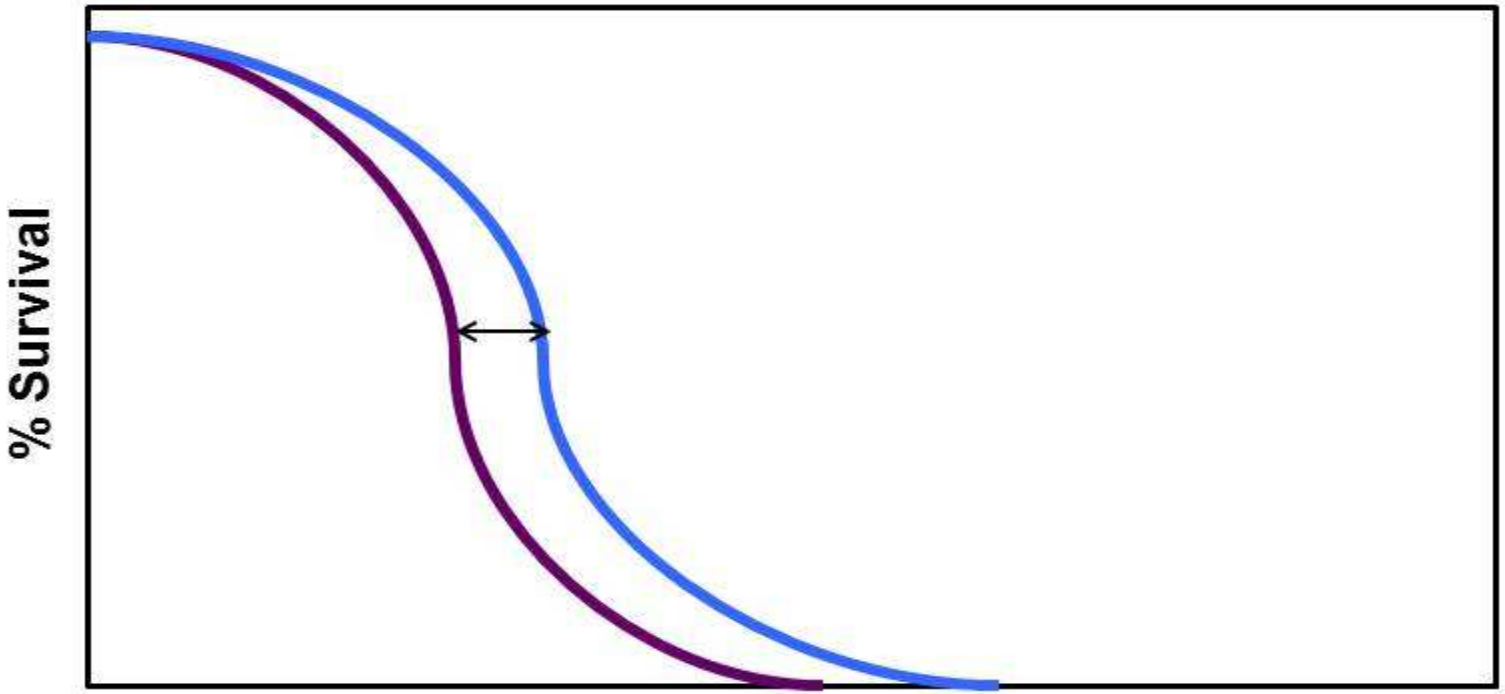
The Emerging Role of Combination Tumor Immunotherapy



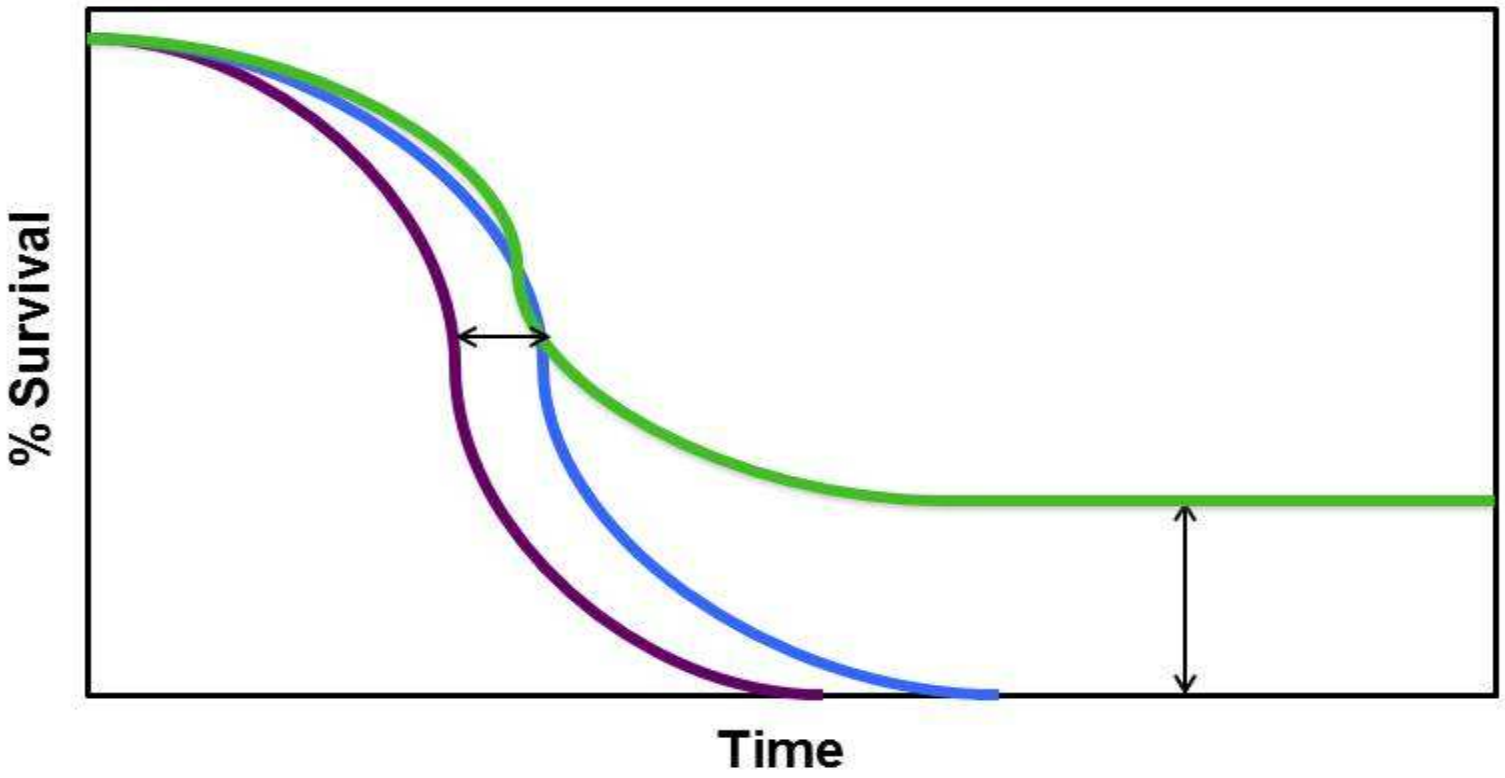
Holbrook Kohrt, MD PhD
Dept Medicine Div Oncology
Stanford Cancer Institute

STANFORD SCHOOL OF MEDICINE
CANCER CENTER
Stanford Hospital & Clinics

Improving Survival with Combination Therapy

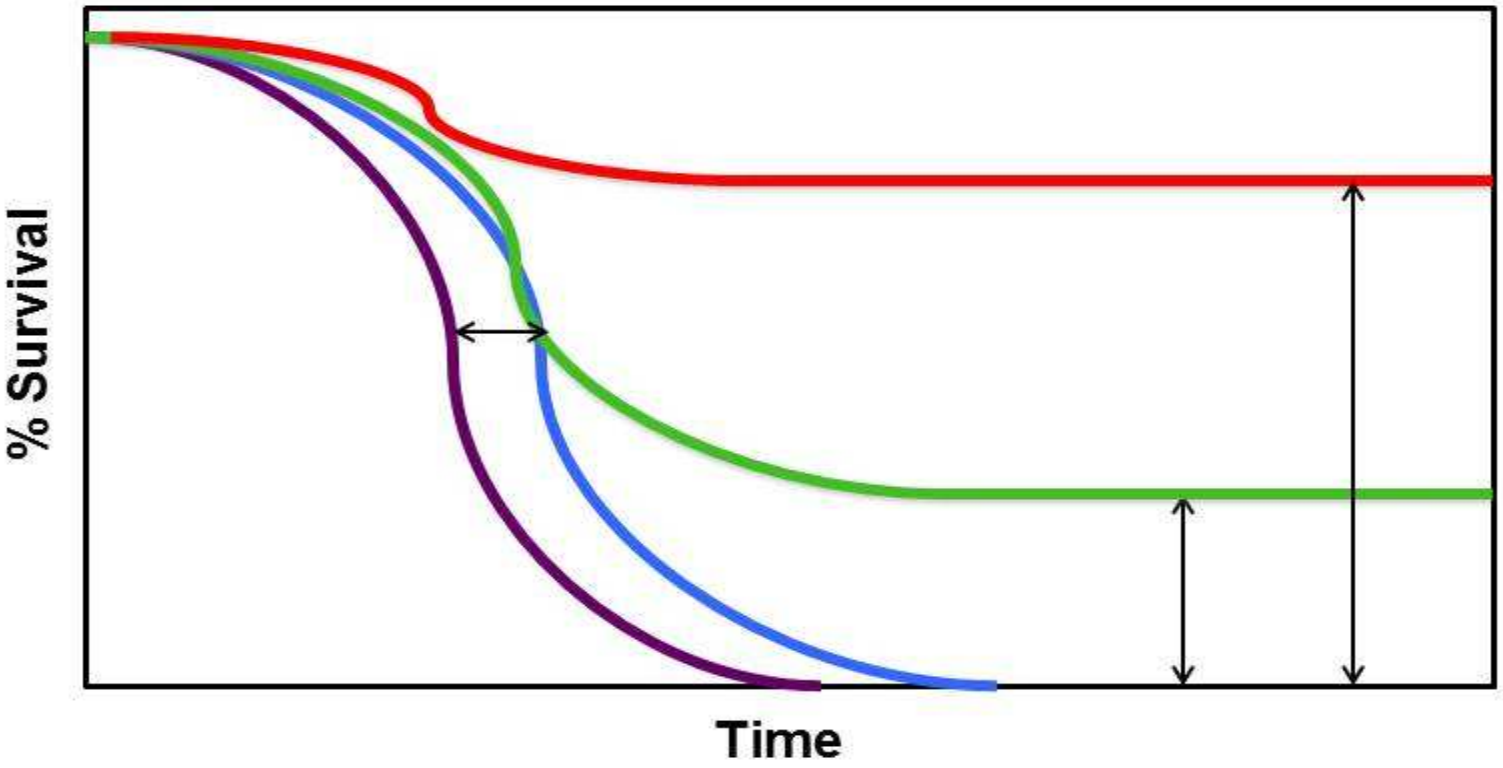


Improving Survival with Combination Therapy



Control
Standard or Other Therapy
Anti-CTLA-4/Anti-PD-1/Anti-PD-L1

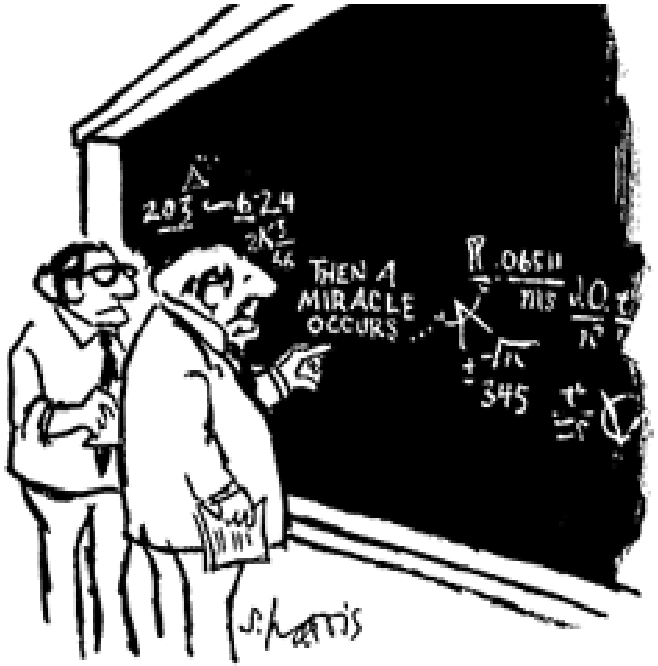
Improving Survival with Combination Therapy



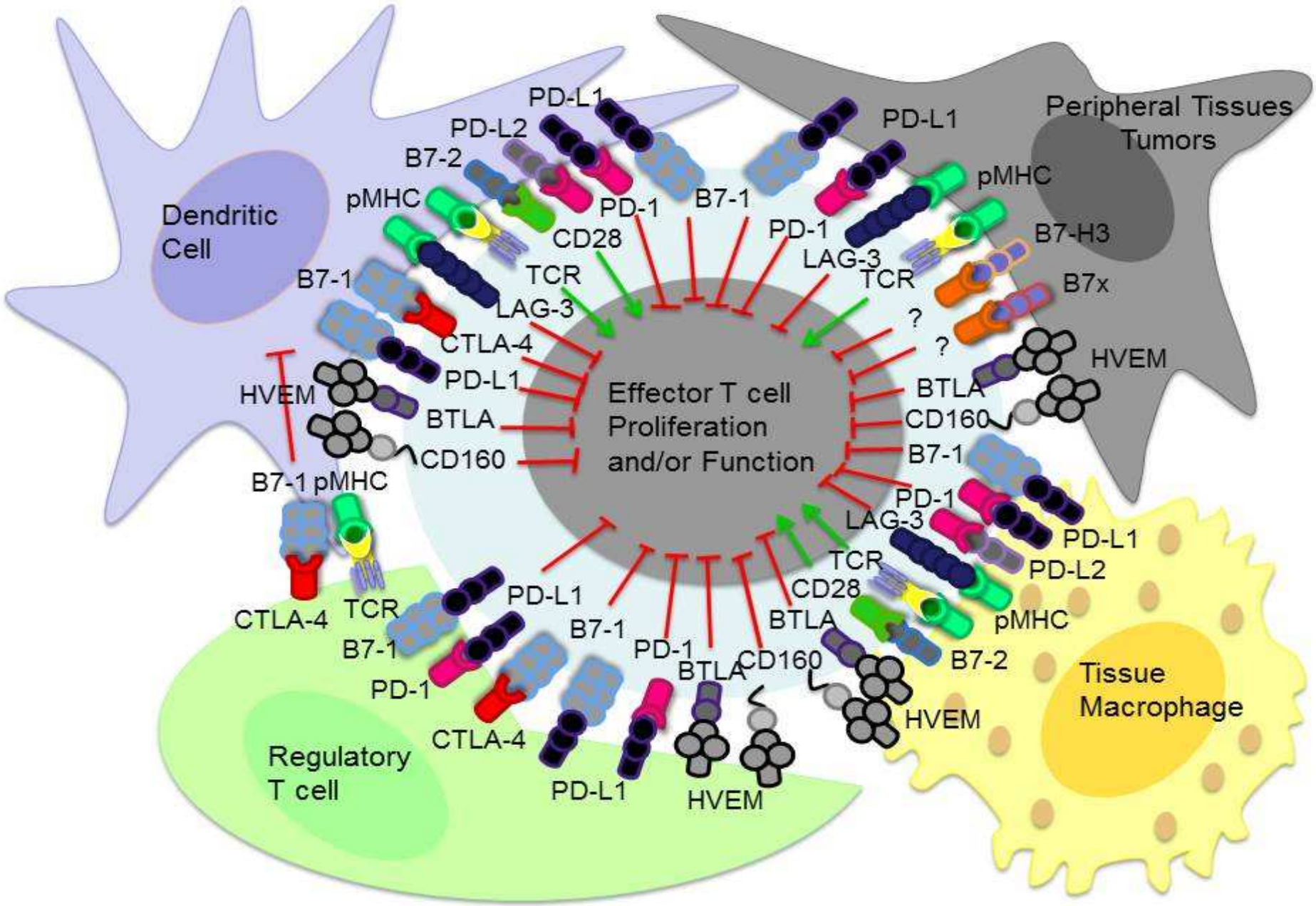
Control
Standard or Targeted Therapy
Anti-CTLA-4/Anti-PD-1/Anti-PD-L1
Combination Therapies

Combination strategies:
A ‘four-strike’ approach to cancer therapy

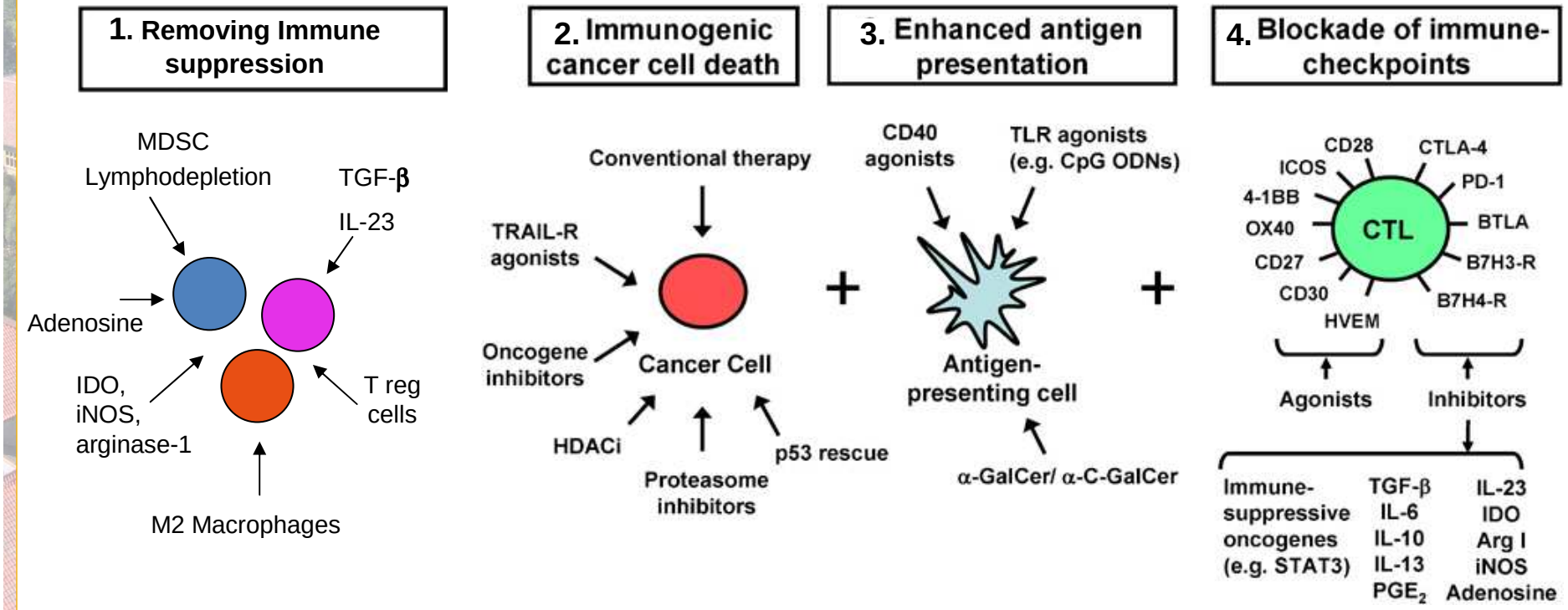
“We’ve found a mass. The good news is we have weapons of mass destruction.”



"I think you should be more explicit here in step two."


Dendritic Cell
PD-L1
PD-L2
B7-2
pMHC
PD-1
CD28
TCR
LAG-3
B7-1
CTLA-4
PD-L1
BTLA
CD160
HVEM
B7-1 pMHC
Peripheral Tissues Tumors
PD-L1
pMHC
B7-H3
B7x
HVEM
BTLA
CD160
B7-1
PD-1
LAG-3
PD-L1
PD-L2
pMHC
B7-2
Tissue Macrophage
Effector T cell Proliferation and/or Function
Regulatory T cell
CTLA-4
TCR
B7-1
PD-1
PD-L1
HVEM
BTLA
CD160
CD28
?
?

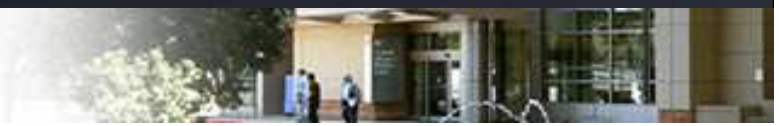
Combination strategies:
A ‘four-strike’ approach to cancer therapy



The Emerging Role of Combination Tumor Immunotherapy

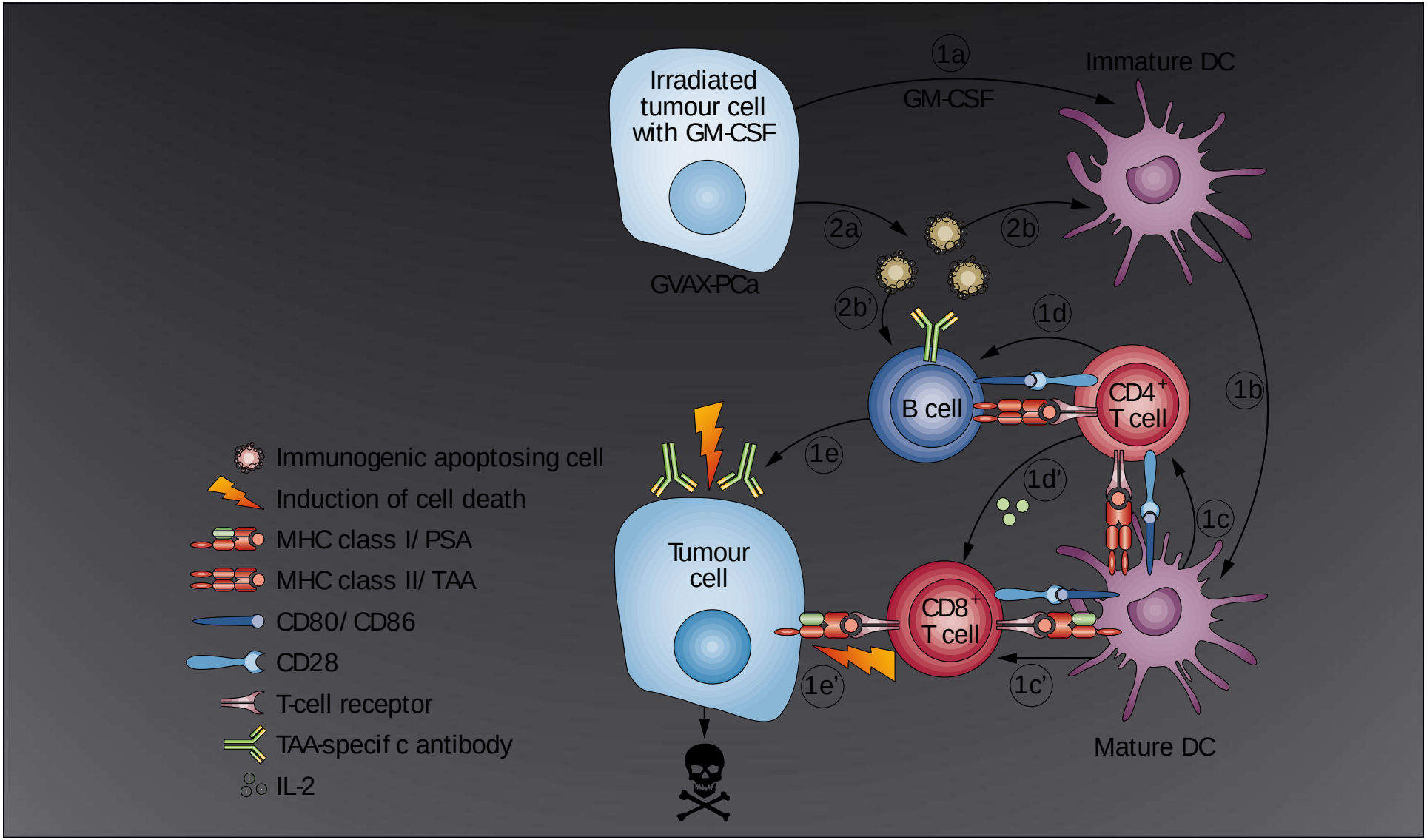
Combination Immunotherapy To Improve Cancer Vaccines:

GVAX



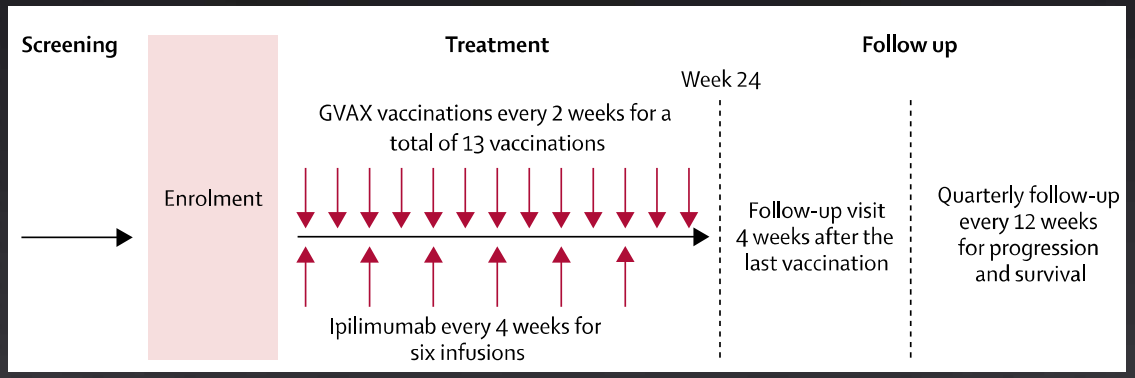
IMPROVING CANCER VACCINES

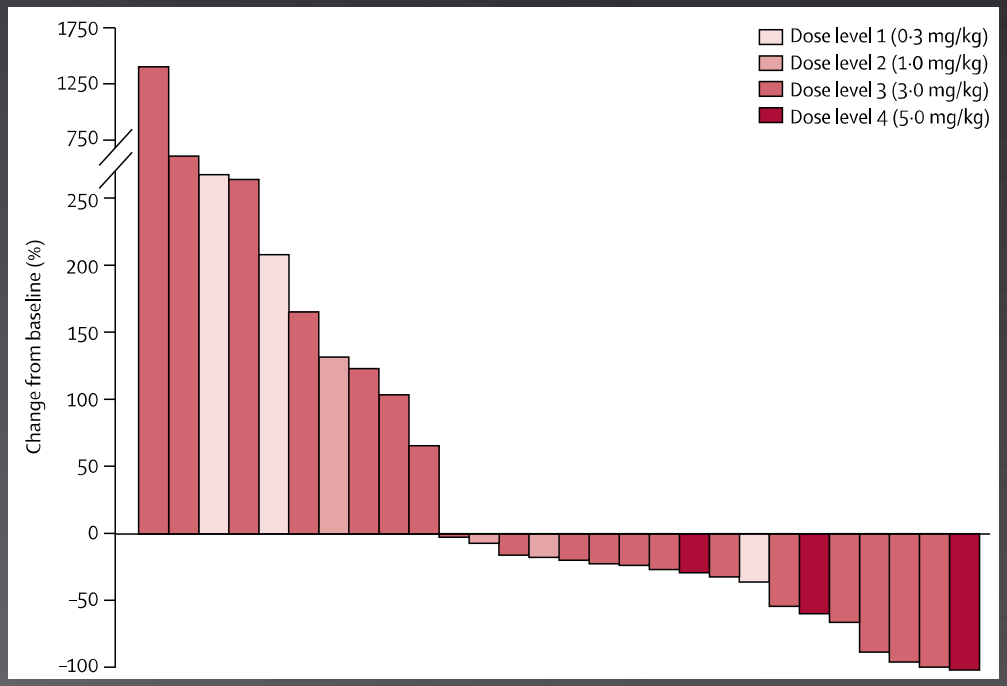
COMBINING GVAX WITH IPILIMUMAB

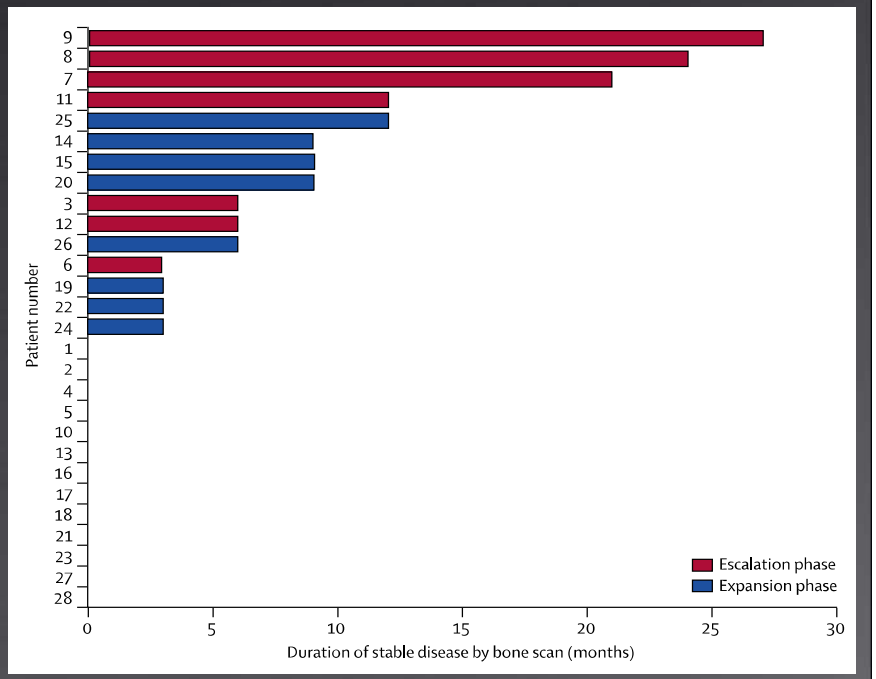


Improving Cancer Vaccines

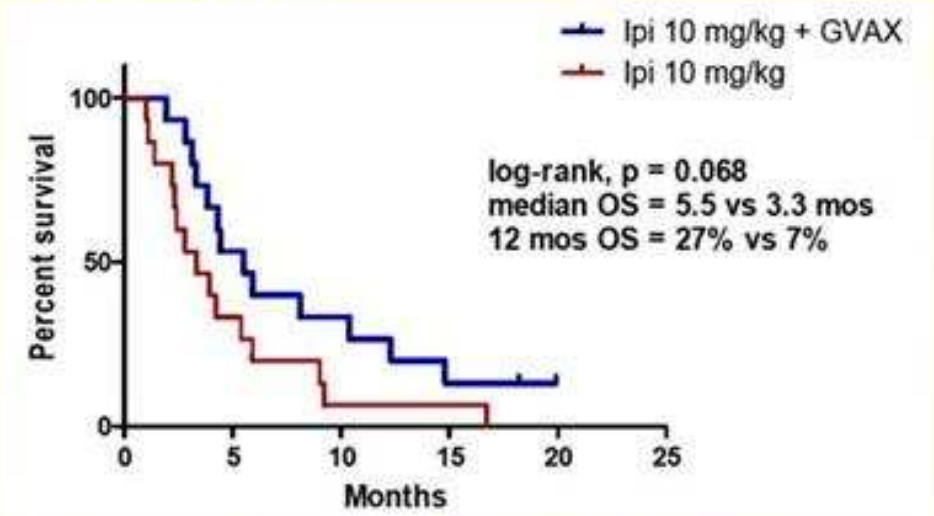
Combining GVAX with Ipilimumab







GVAX Pancreas + Ipilimumab (BMS:Yervoy) Clinical Results*



- 30 patients with previously treated, locally advanced or metastatic pancreatic adenocarcinoma

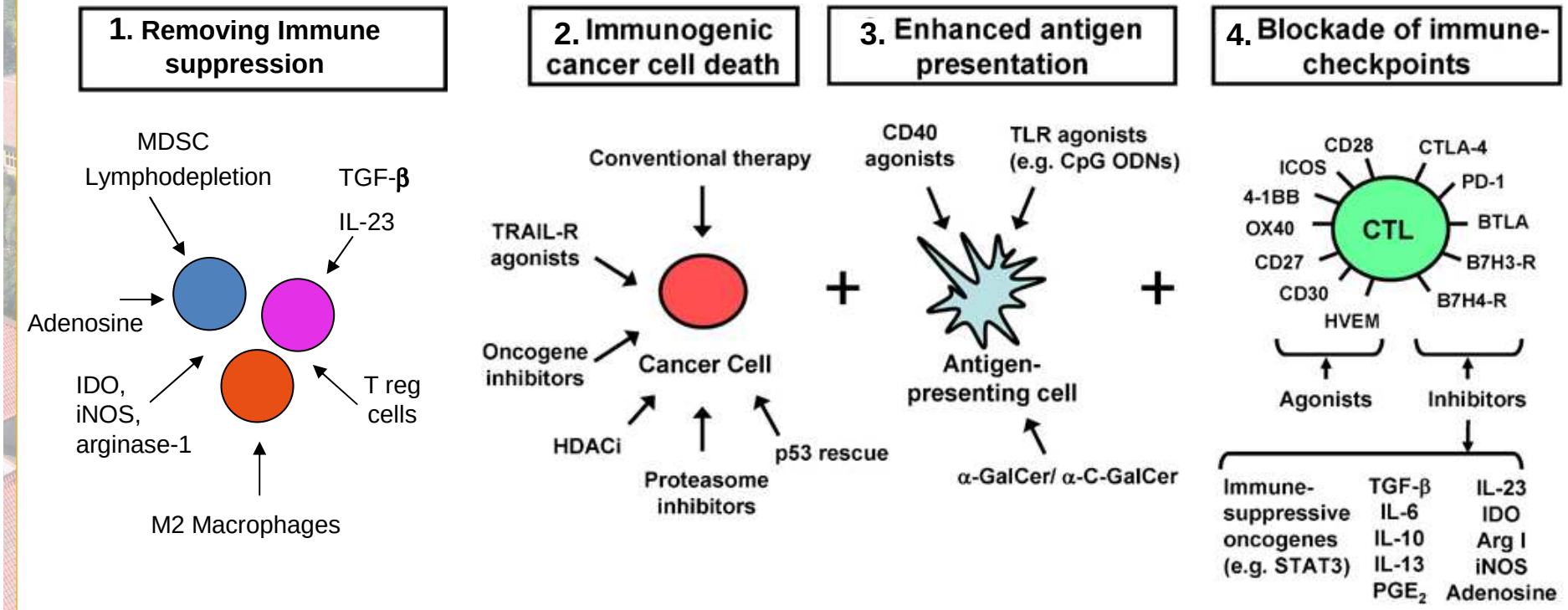
	Ipi + GVAX Pancreas	Ipi Alone
Median monthly overall survival	5.5 months	3.3 months
12 month overall survival	27%	7%

- Conclusion
  - Over 60% improvement in Overall Survival

*Dung T. Le, et al

BioSante Pharmaceuticals

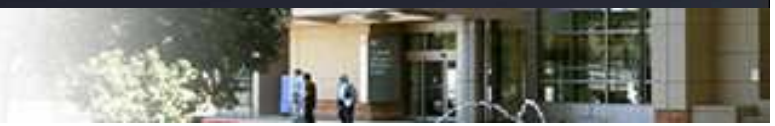
Combination strategies:
A ‘four-strike’ approach to cancer therapy



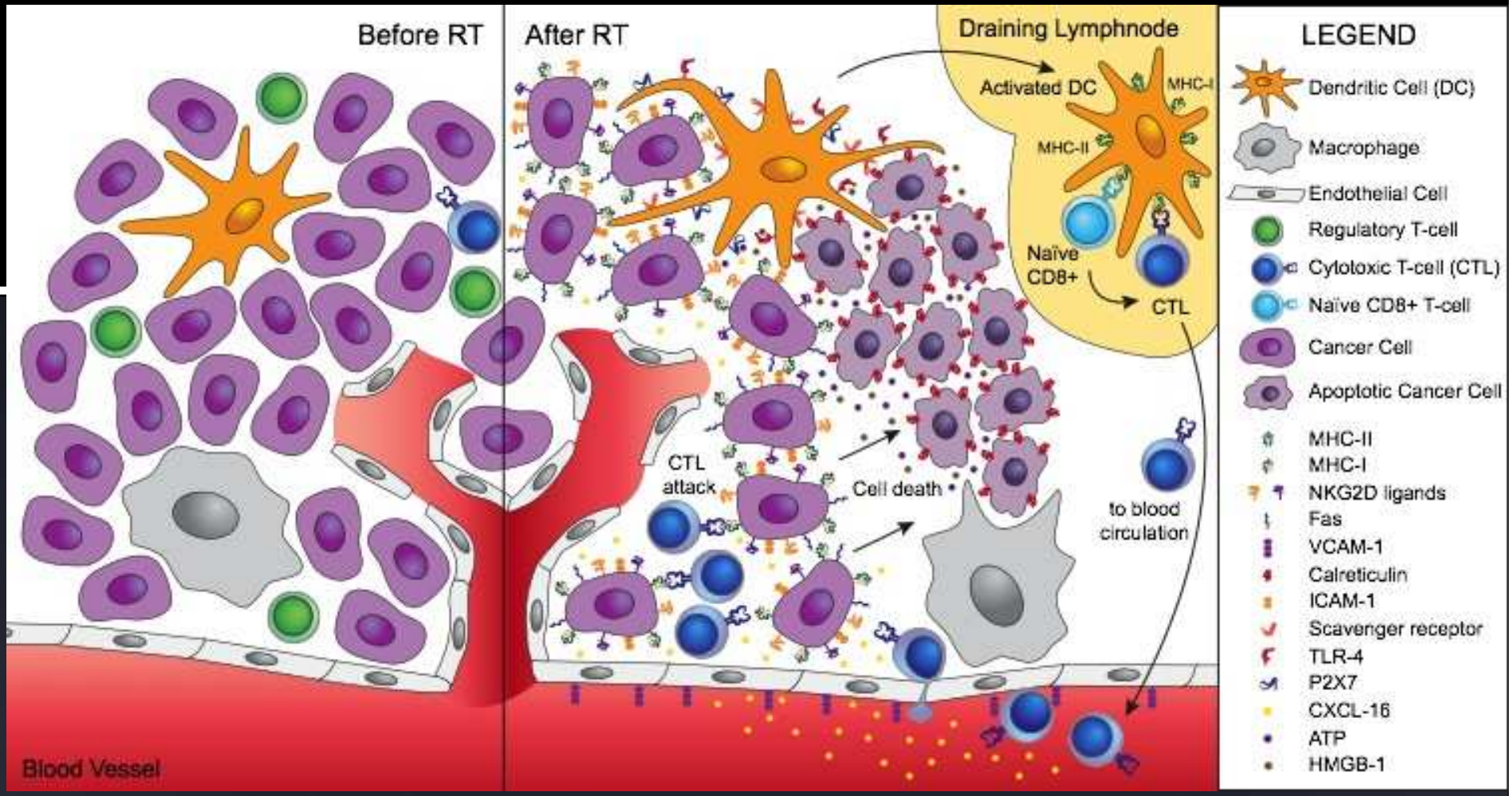
The Emerging Role of Combination Tumor Immunotherapy

Combination Immunotherapy To Improve Today's Current Therapy:

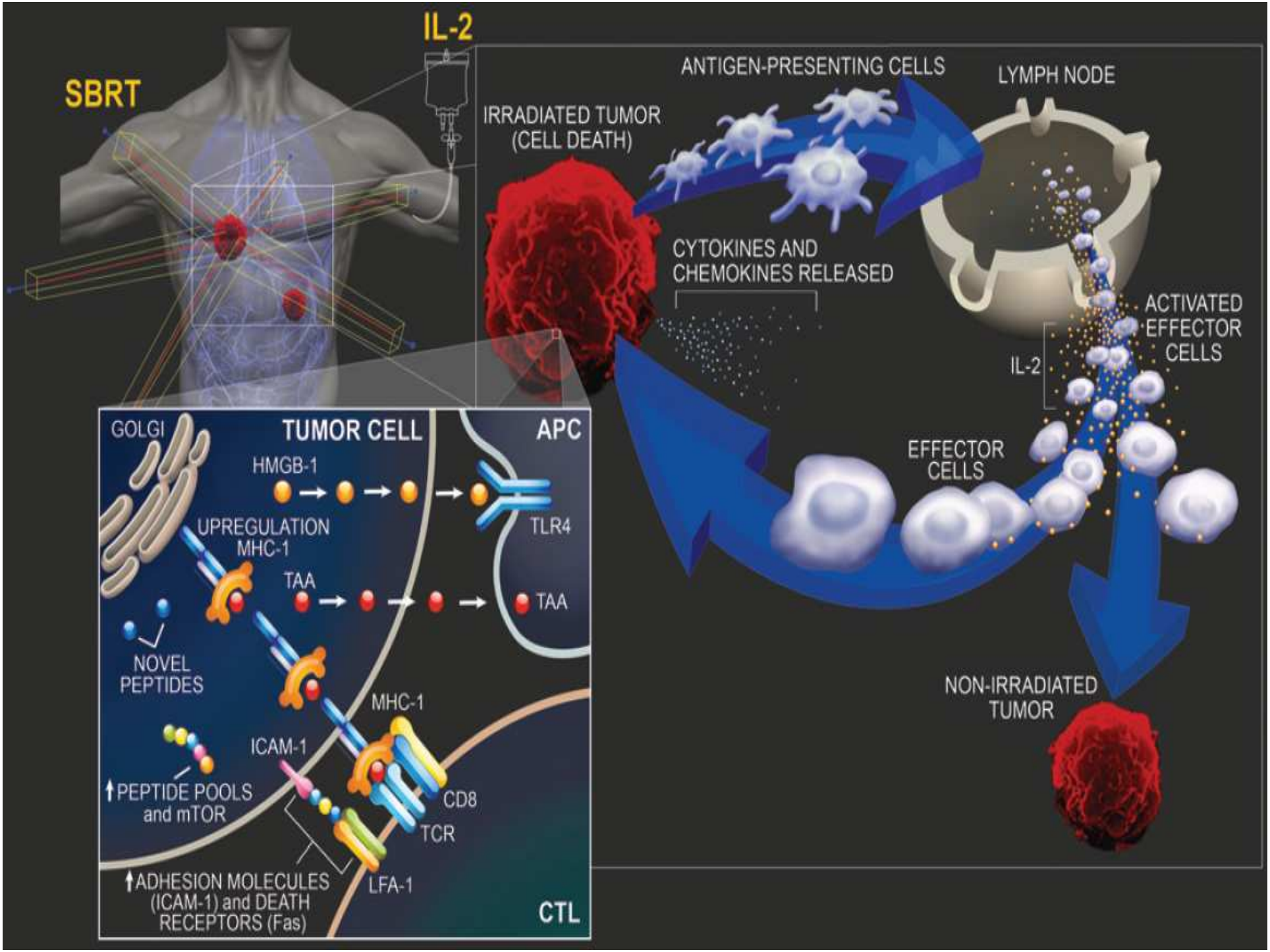
RADIATION



Pro-Immunogenic Effects Of Radiation At Irradiated Site

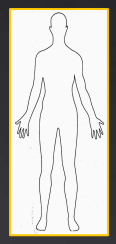


Demaria & Formenti, Front Oncol 2012

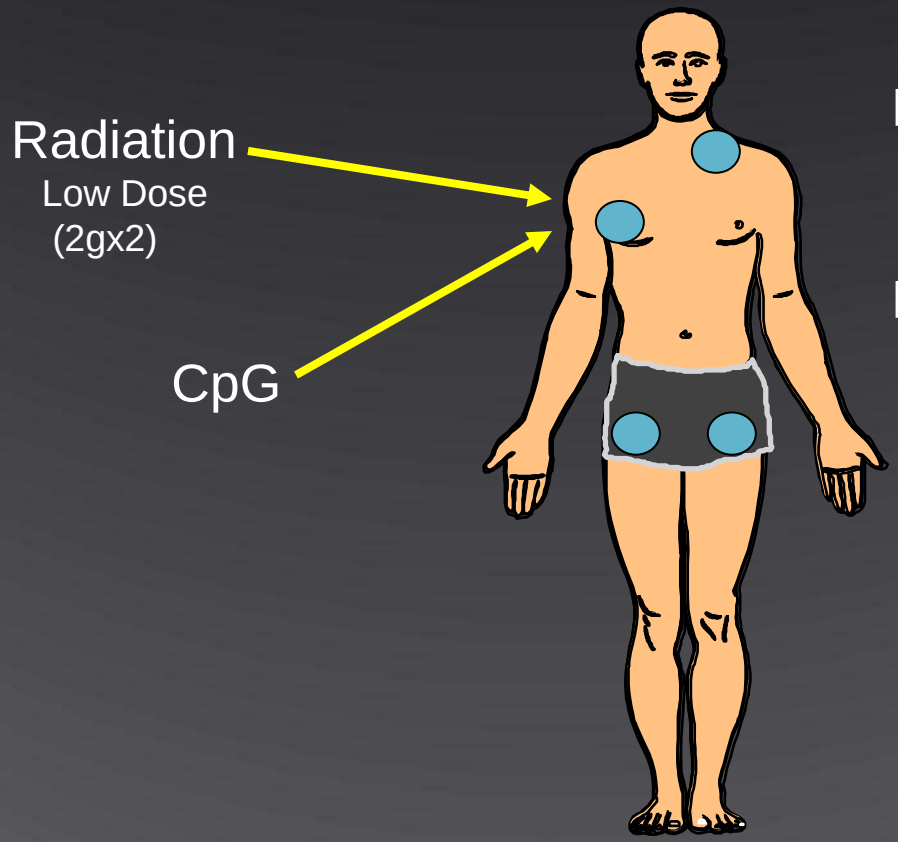

SBRT
IL-2
IRRADIATED TUMOR
(CELL DEATH)
ANTIGEN-PRESENTING CELLS
LYMPH NODE
CYTOKINES AND
CHEMOKINES RELEASED
ACTIVATED
EFFECTOR
CELLS
IL-2
EFFECTOR
CELLS
NON-IRRADIATED
TUMOR
GOLGI
TUMOR CELL
APC
HMGB-1
TLR4
UPREGULATION
MHC-1
TAA
TAA
NOVEL
PEPTIDES
MHC-1
ICAM-1
PEPTIDE POOLS
and mTOR
CD8
TCR
LFA-1
ADHESION MOLECULES
(ICAM-1) and DEATH
RECEPTORS (Fas)
CTL

IN-SITU VACCINATION: BACKGROUND

PROOF OF CONCEPT – LOCAL CPG & RADIATION



A Phase I/II Trial of Intratumoral Injection of CpG Oligonucleotides and Local Low Dose Radiation Therapy in Non-Hodgkin Lymphoma



POPULATION
Low grade NHL

ENDPOINTS
Safety/feasibility
Clinical response
T cell immune response

IN-SITU VACCINATION: BACKGROUND

CPG

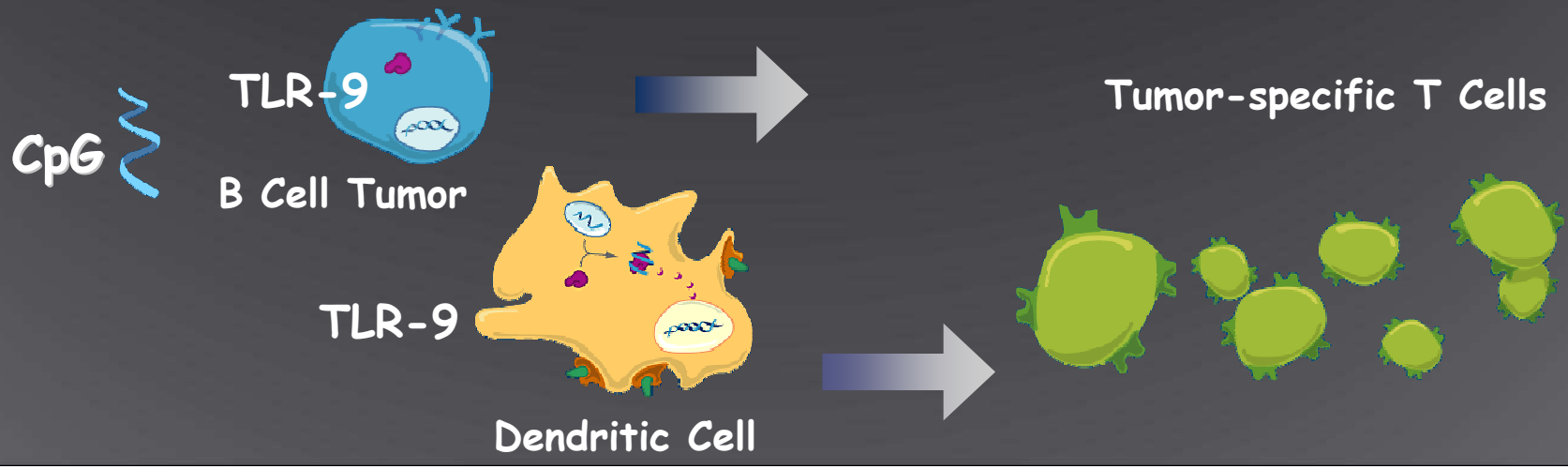
- Bacterial DNA

  ACGTTGAGTTCGTACGCATACGA

- Vertebrate DNA

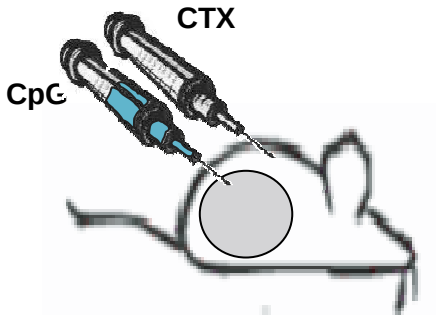
  AGCTTGAGTC^{m}CGGATGGGTAAGA

- Immune system recognizes CpG through TLR-9 and activates DC and B cells



IN-SITU VACCINATION: BACKGROUND

CPG + CYCLOPHOSPHAMIDE



Lymphoma Immunotherapy with CpG Oligodeoxynucleotides Requires TLR9 Either in the Host or in the Tumor Itself[1]

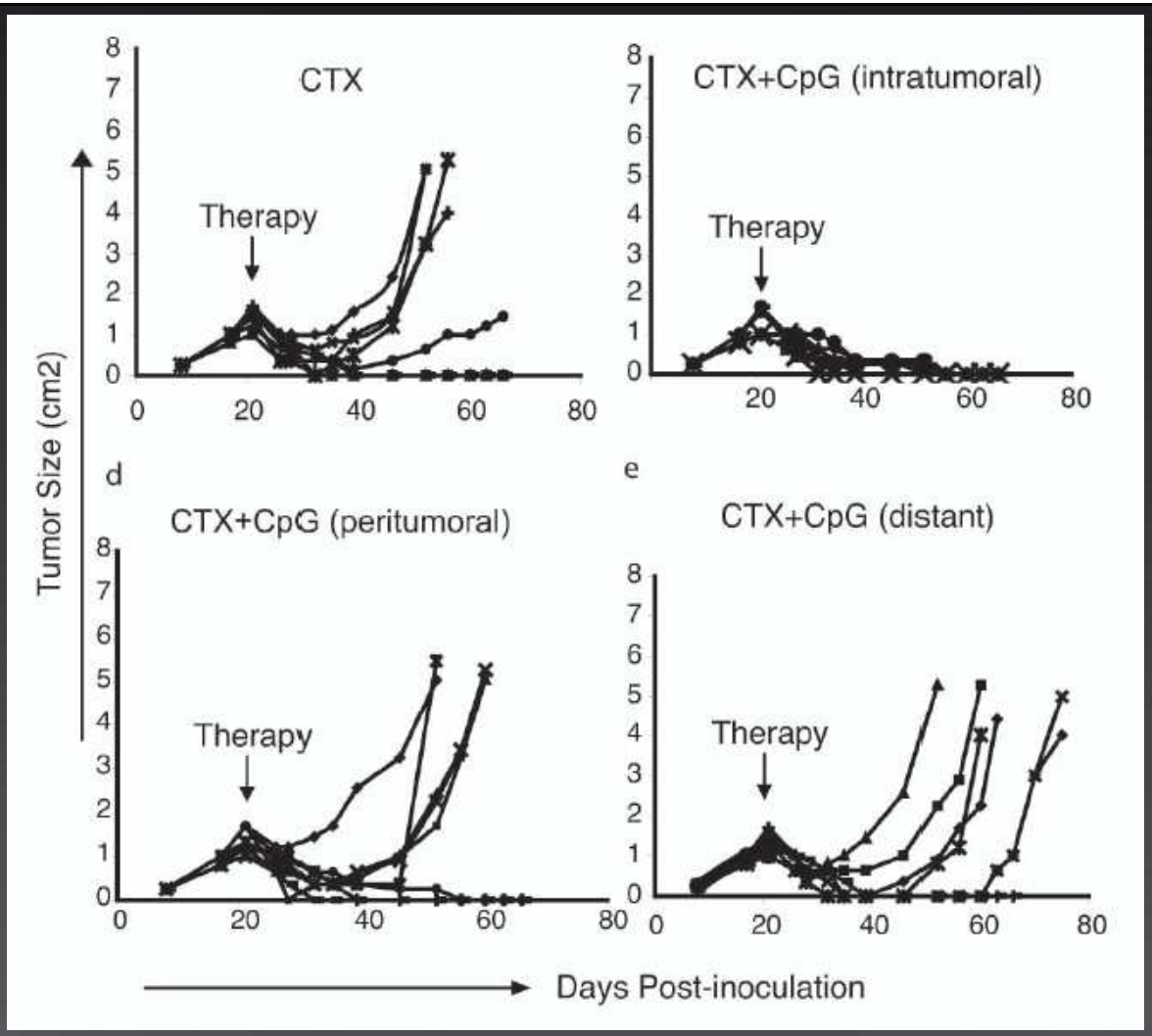
The Journal of Immunology, 2007, 179: 2493–2500.

Jiali Li,* Wenru Song,* Debra K. Czerwinski,* Bindu Varghese,* Satoshi Uematsu,† Shizuo Akira,† Arthur M. Krieg,‡ and Ronald Levy[2]*

Li J, et al., J Immunol. 2007

IN-SITU VACCINATION: BACKGROUND

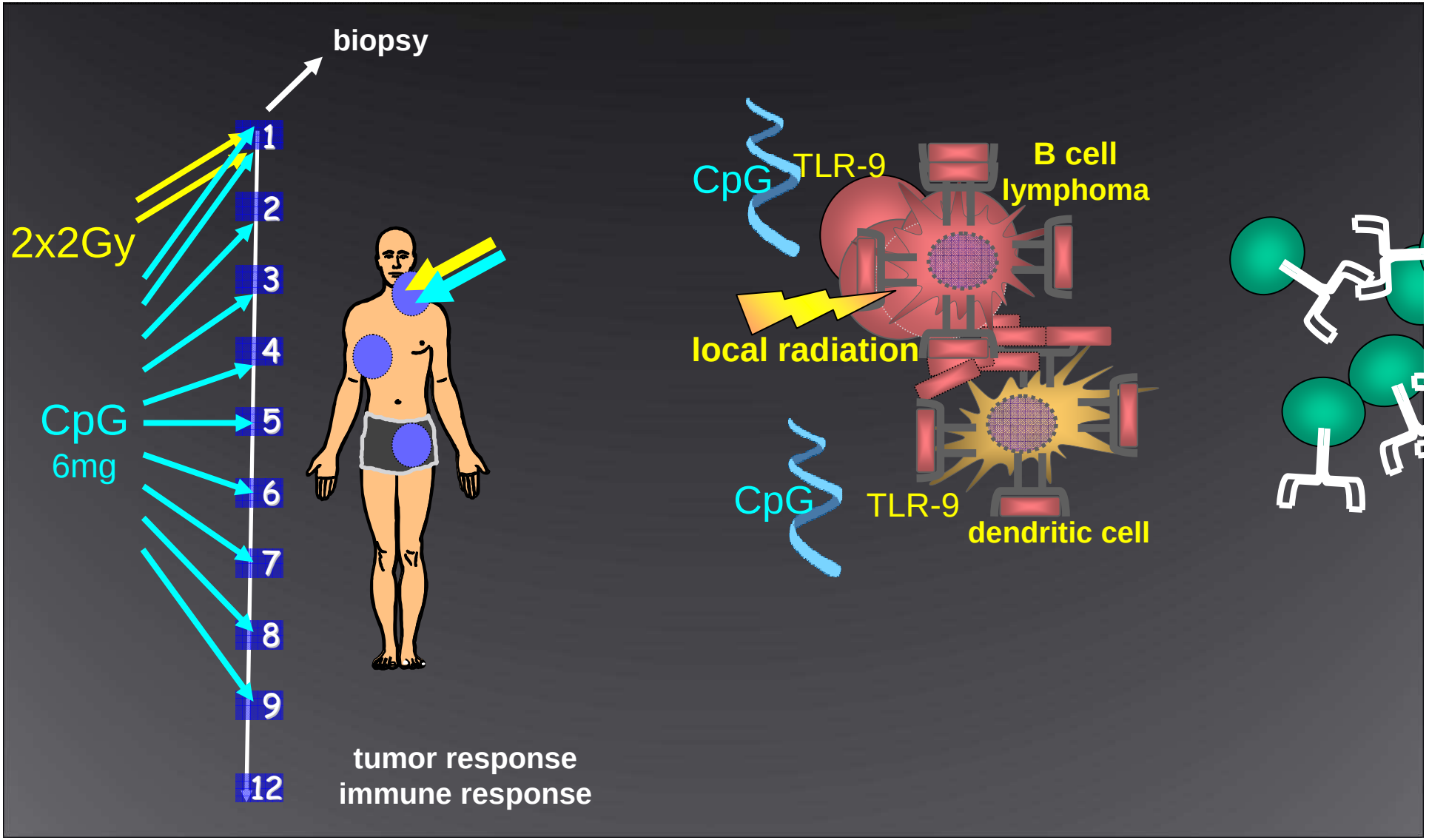
CPG + CYCLOPHOSPHAMIDE



Li J, et al., J Immunol. 2007

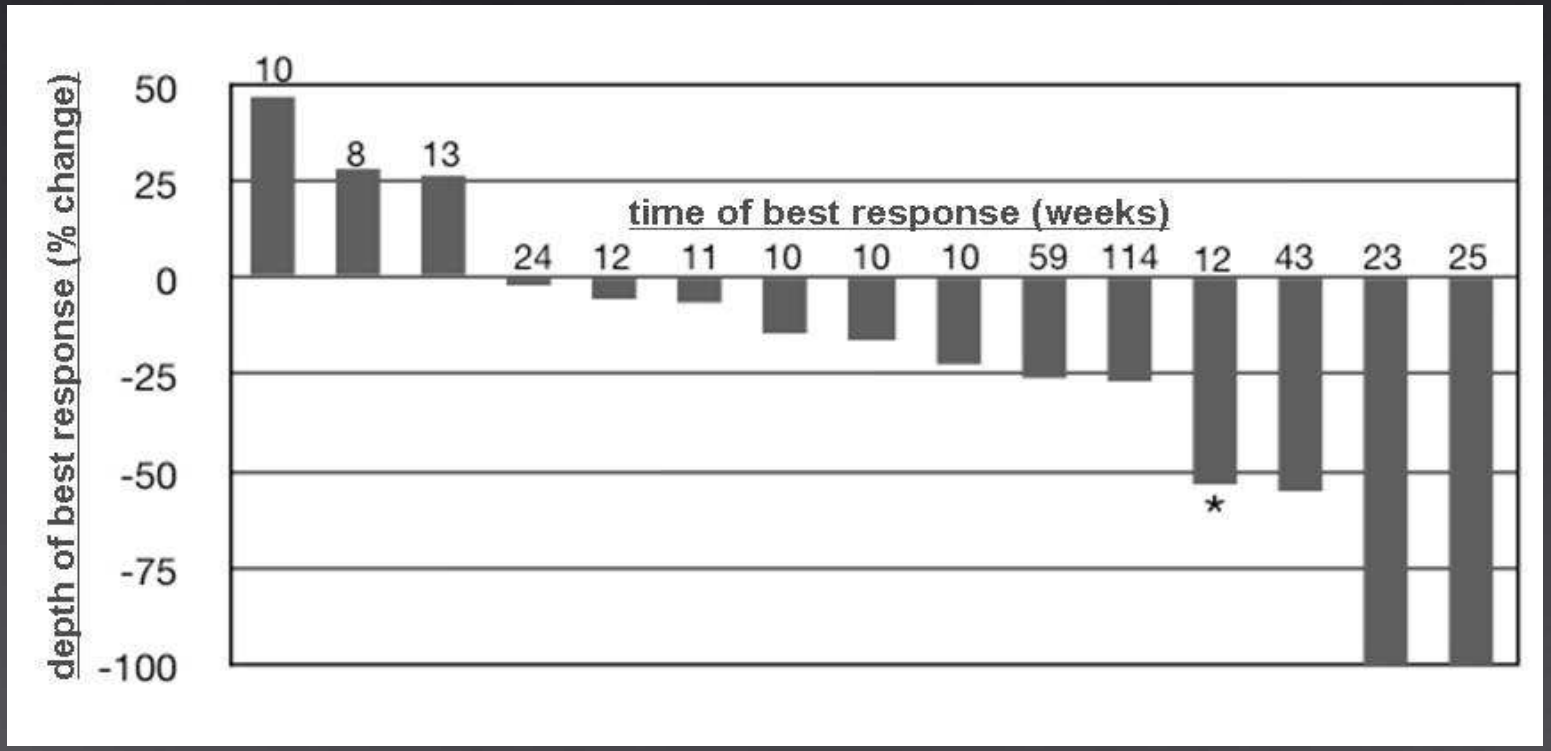
IN-SITU VACCINATION

CLINICAL TRIAL SCHEMA



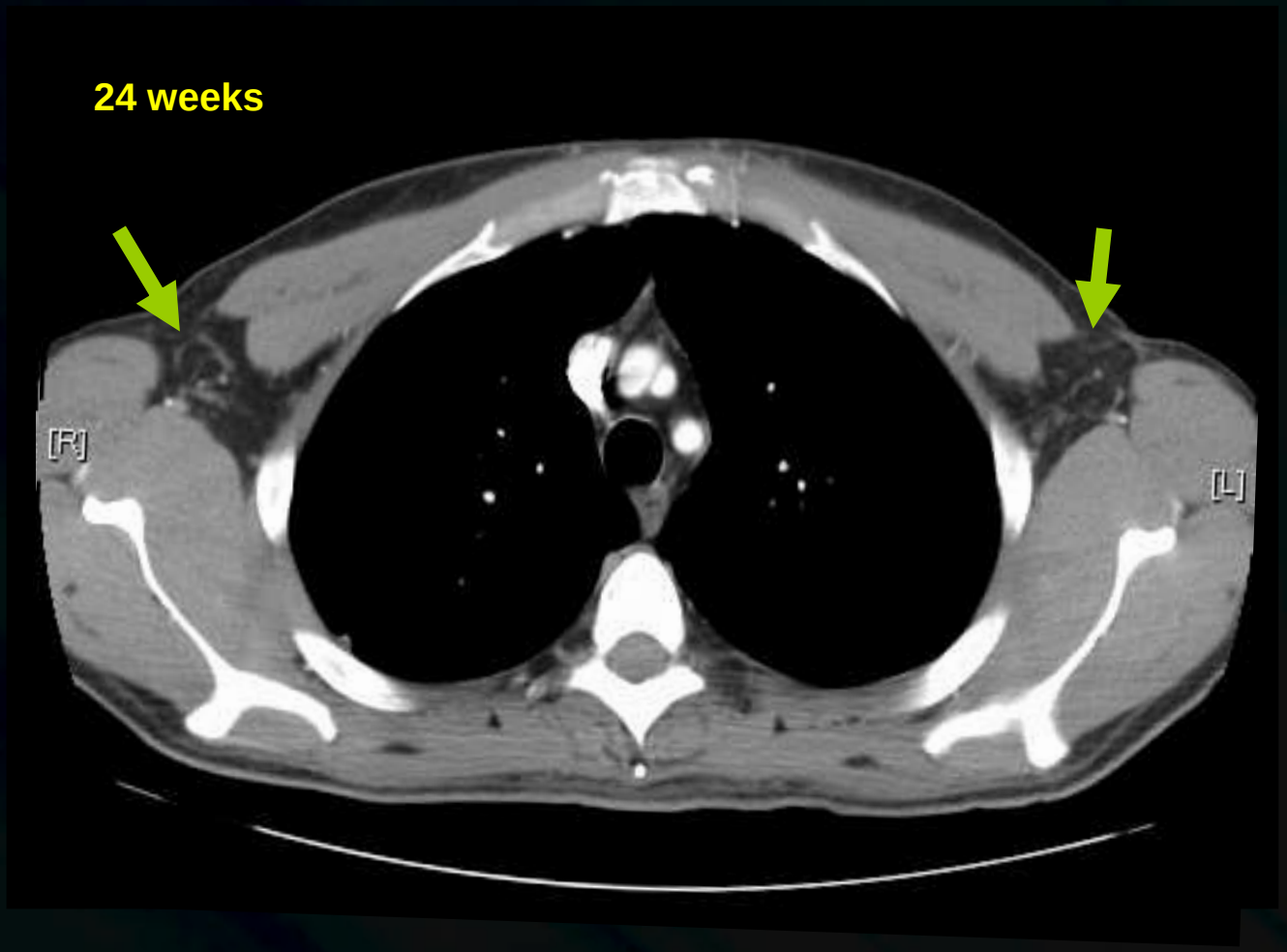
IN-SITU VACCINATION

CLINICAL RESPONSE



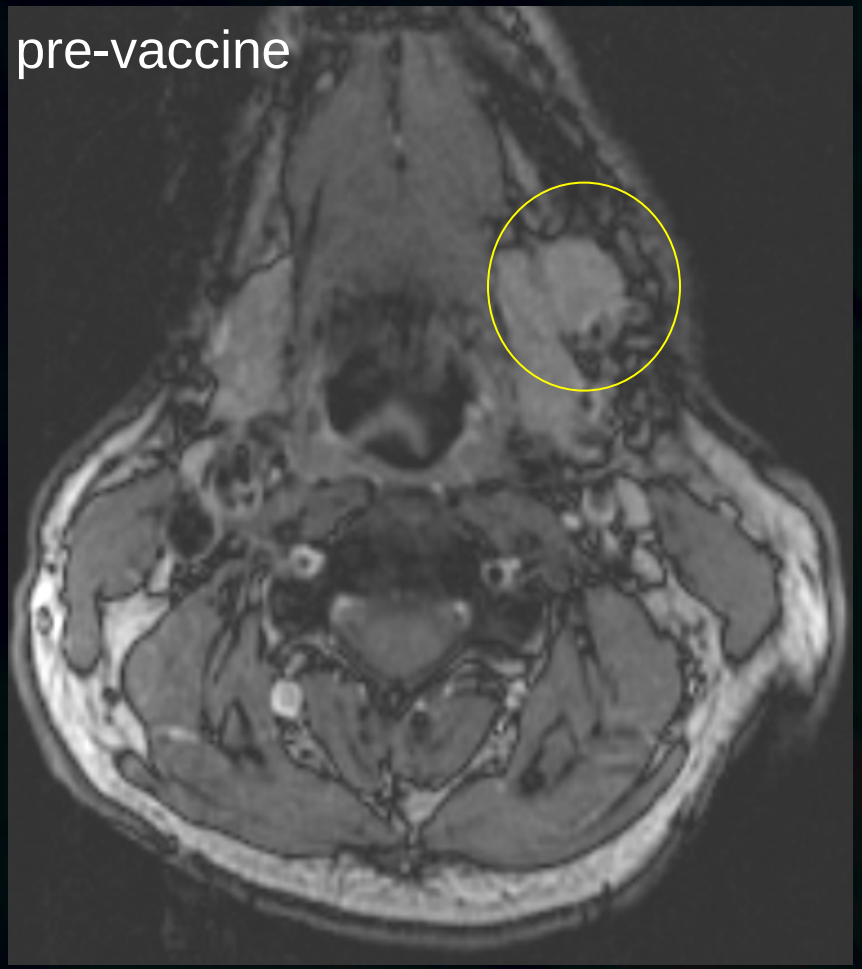
Brody JD et al., *J Clin Oncol*. 2010 Oct 1;28(28).

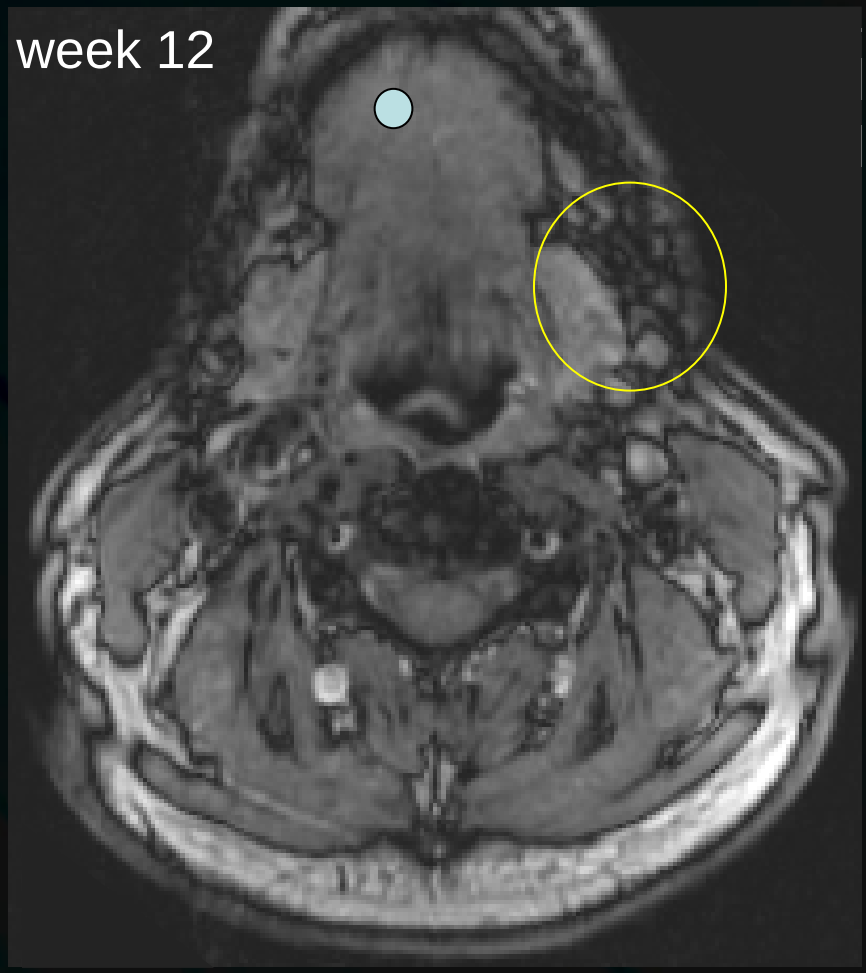
Clinical Response



38 year old male with recurrent follicular lymphoma:
Complete Response

Clinical Response



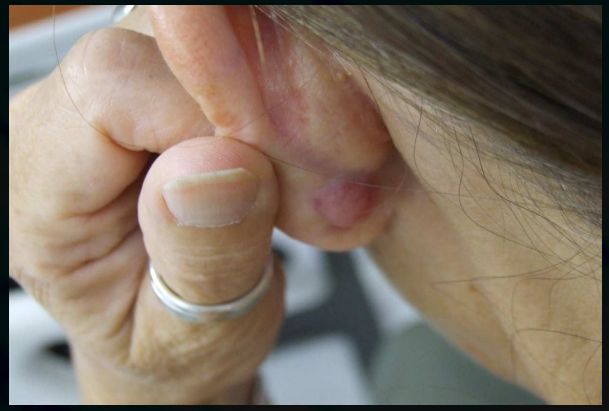


63 year old male with recurrent follicular lymphoma:
Partial Response

Clinical Response

pre-vaccine

week 4



week 12

56 year old female with recurrent follicular lymphoma:
Mixed Response (Stable Disease)

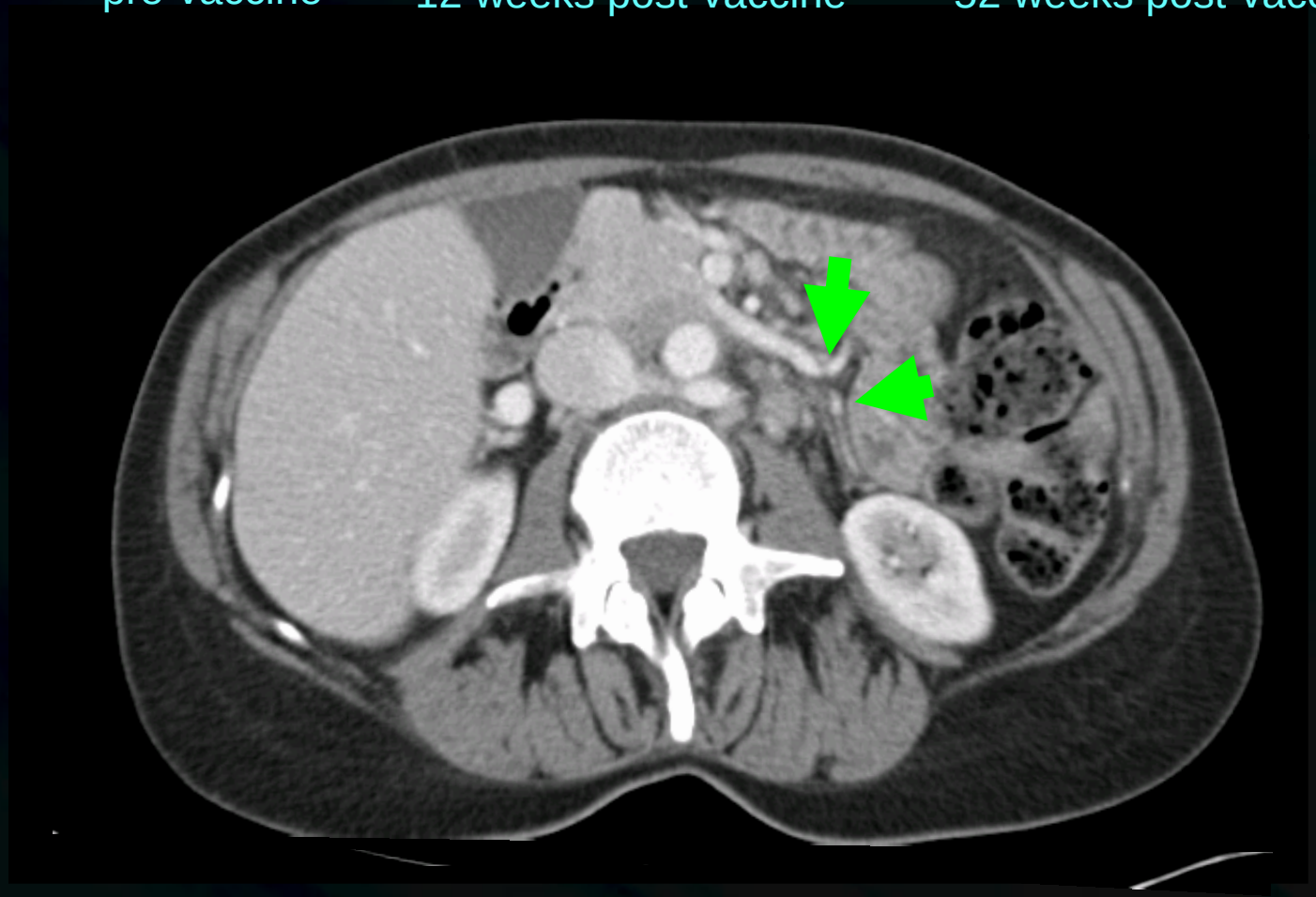
Clinical Response

pre-vaccine | Week 7 | Week 39

66 year old female with recurrent marginal zone lymphoma:
Partial Response

Clinical Response

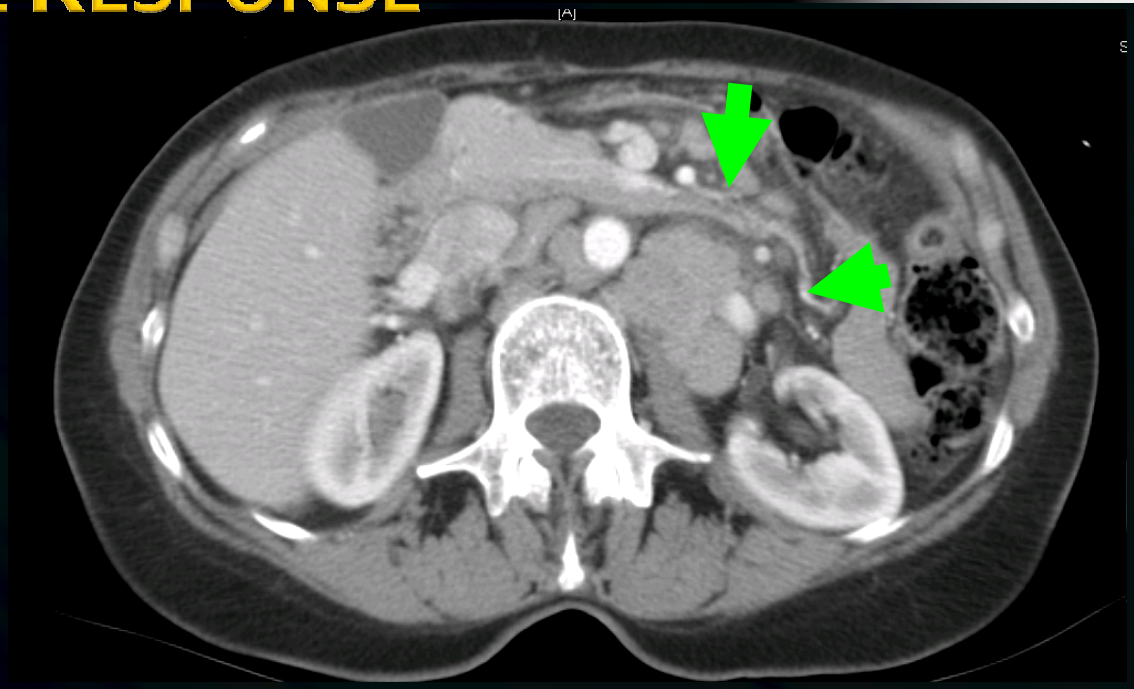
pre-vaccine 12 weeks post-vaccine 52 weeks post-vaccine



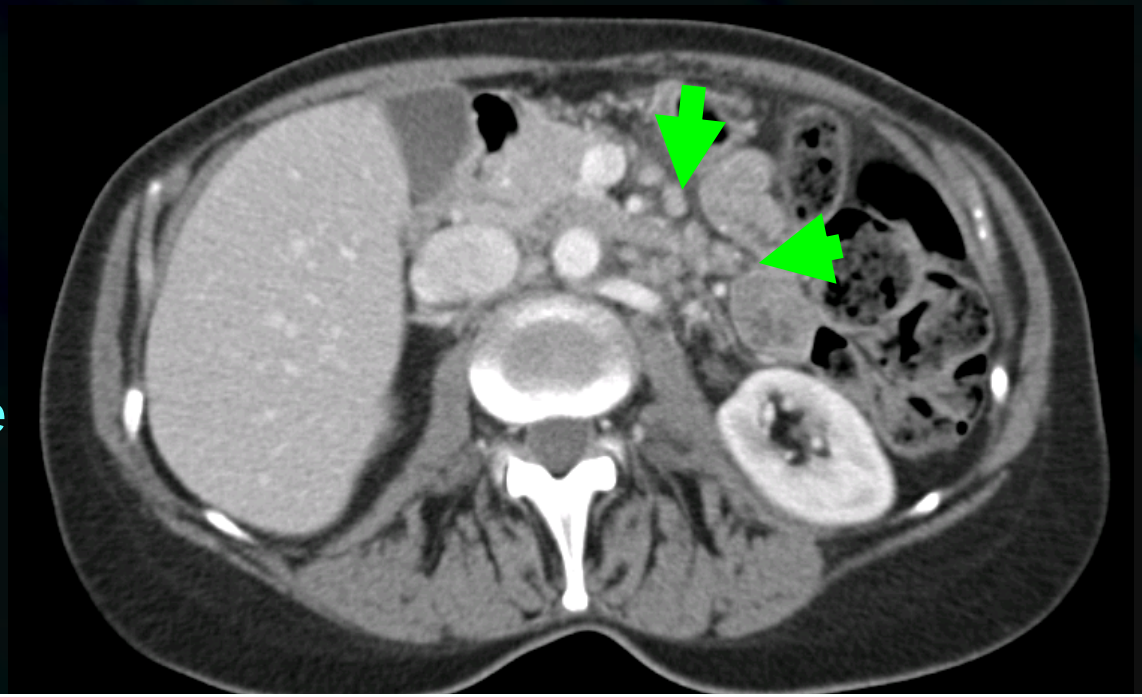
62 year old female with recurrent follicular lymphoma:
Stable Disease (with late improvement)

Clinical Response

pre-vaccine



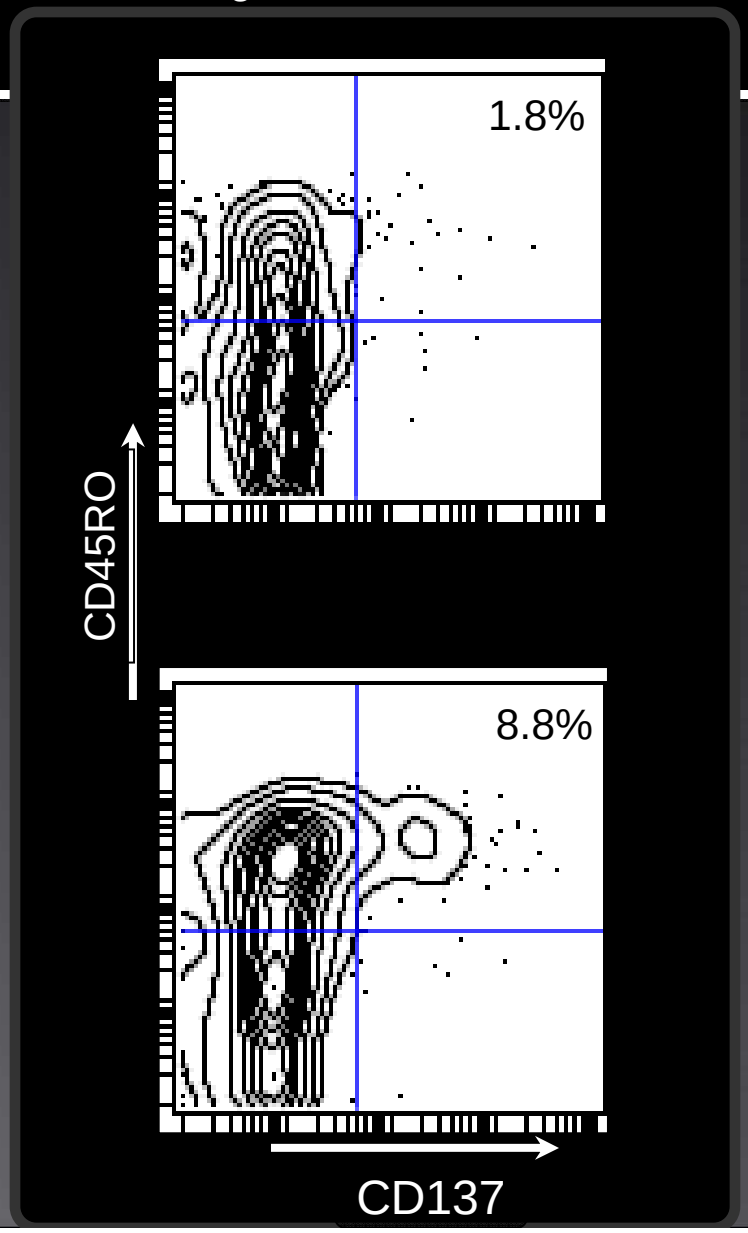
52 weeks post-vaccine



IMMUNE RESPONSE

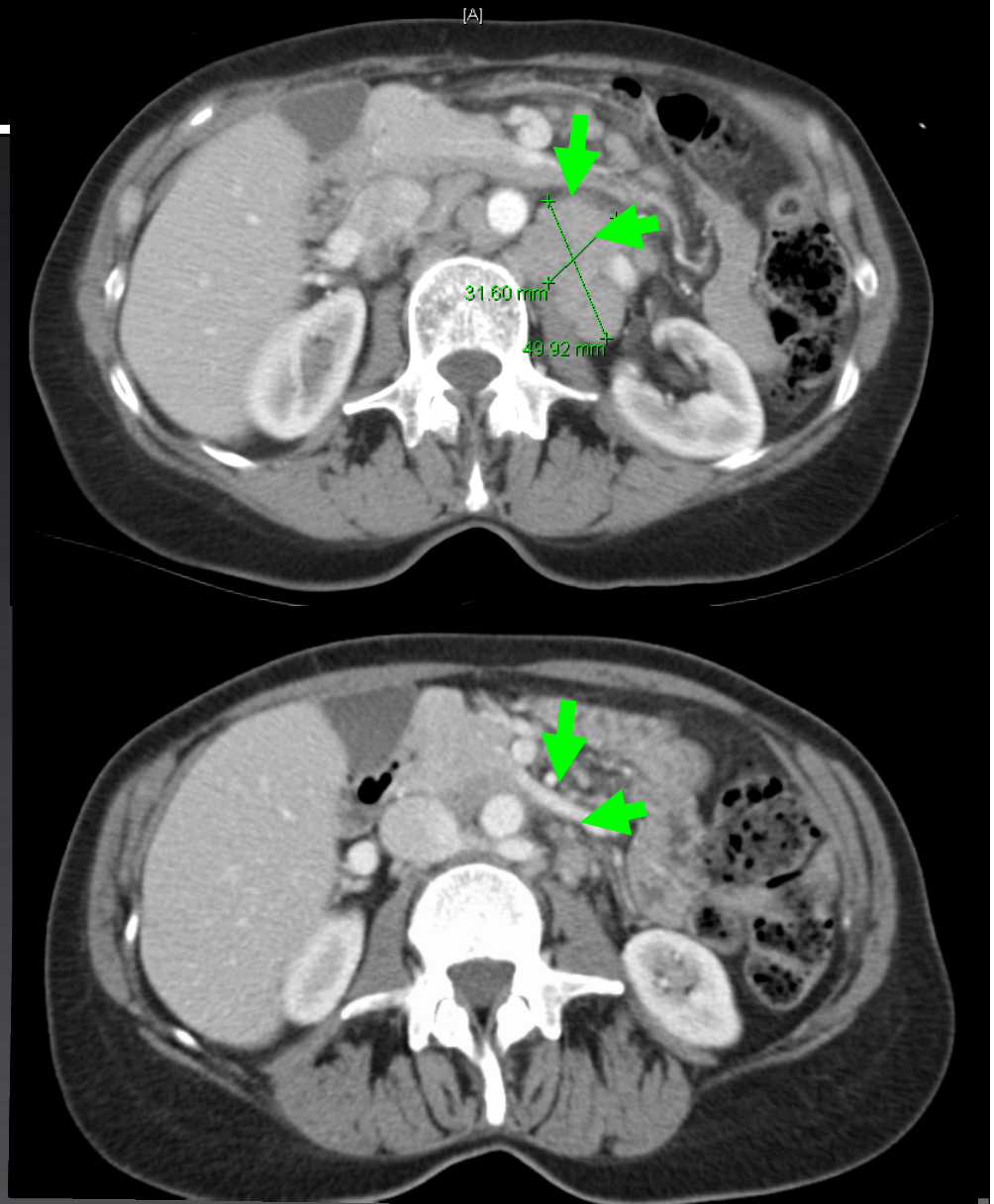
CANCER CENTER
Stanford Hospital & Clinics

gated on CD8 T cells



pre

post



Brody JD et al. *J Clin Oncol* 2010 Oct 1;28(28).

Brody et al, JCO 2010

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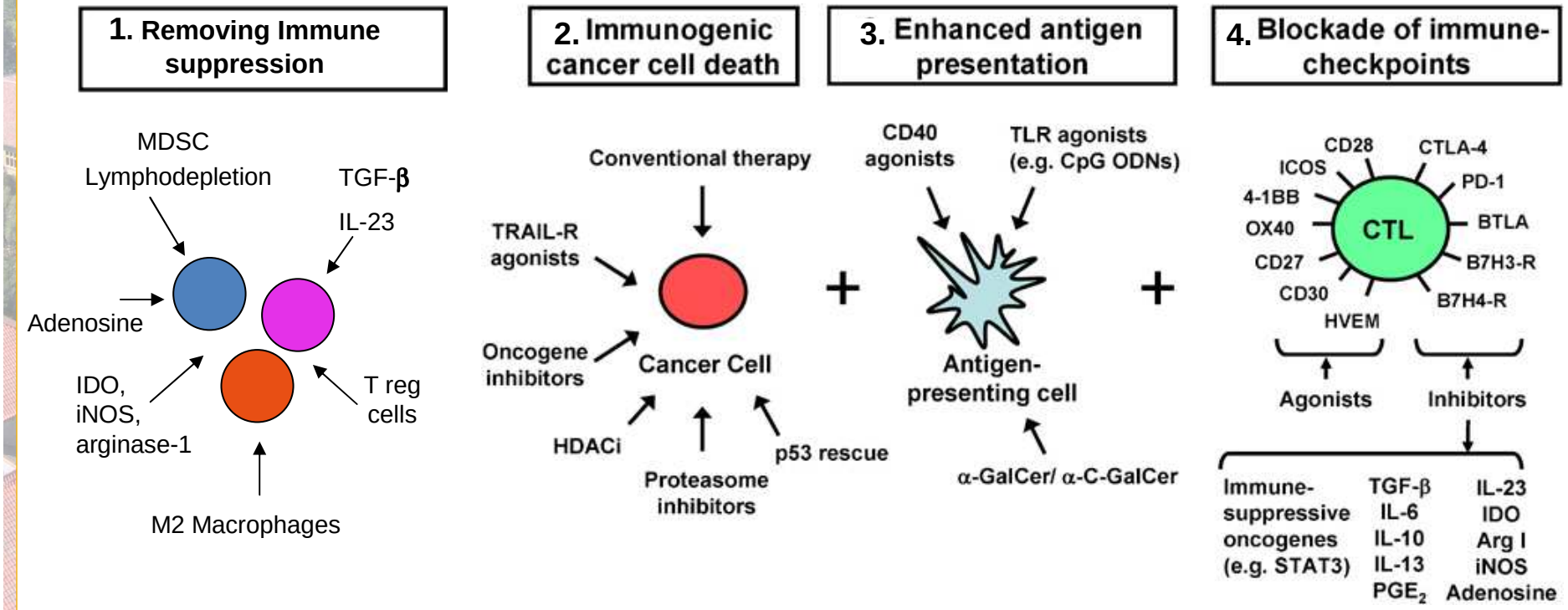
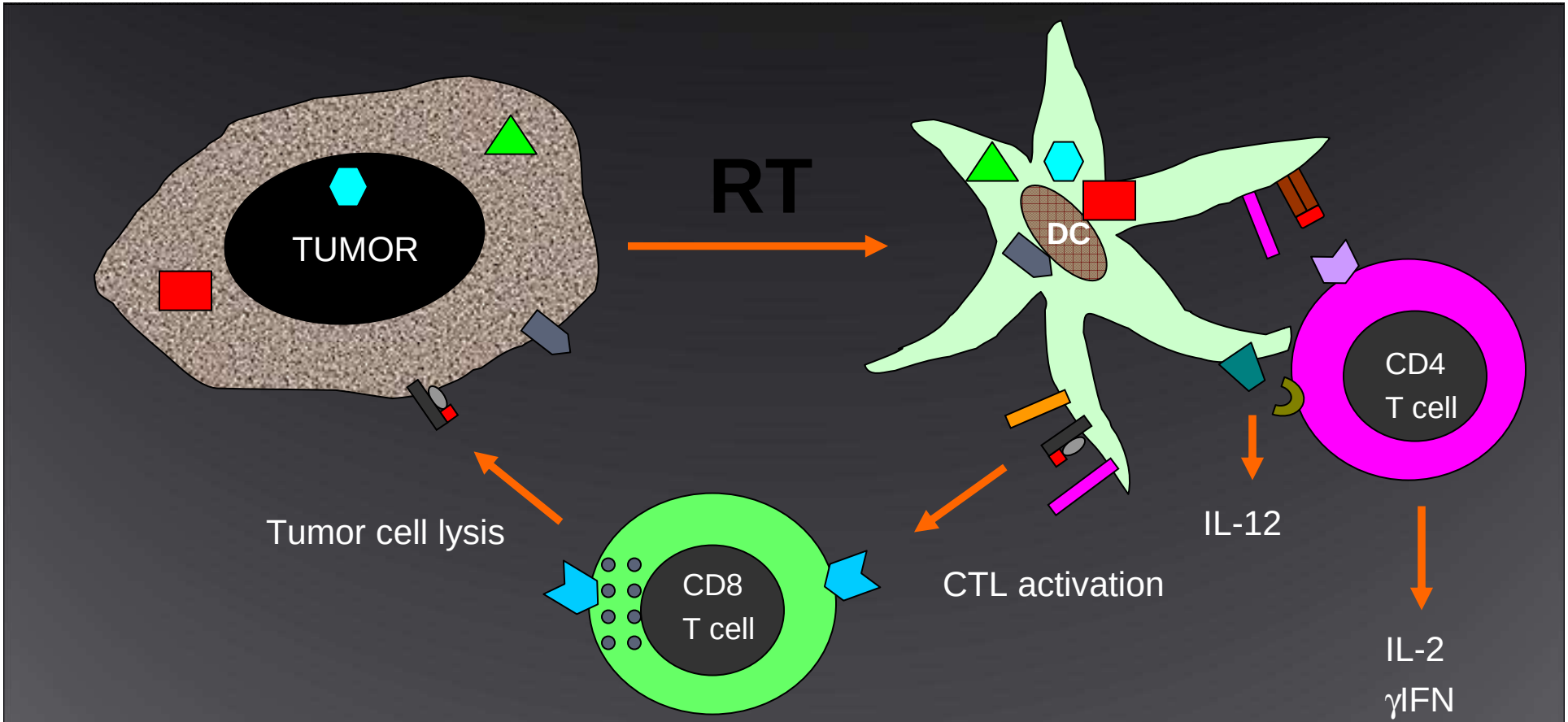
A ‘four-strike’ approach to cancer therapy



In situ vaccination by radiation



Demaria et al., IJROBP 2005
Formenti & Demaria, Lancet Oncol 2009
Formenti & Demaria, IJROBP 2012, 84(4):879-80.

Pre-clinical testing of combinations of RT

Flt3L (Demaria et al., *Int J Radiat Oncol Biol Phys*, 2004). (one trial closed)

anti-CTLA-4 (Demaria et al., *Clin Cancer Res* 2005; Matsumura et al., J Immunol 2008; Pilones et al., *Clin Cancer Res* 2009; Dewan et al., *Clin Cancer Res* 2009; Ruocco et al., J Clin Invest 2012) (two trials opening)

GVAX (Newcomb et al., Clin Cancer Res 2006)

anti-CD137 (Newcomb et al., Rad Res 2010)

TLR7-agonist (Dewan et al. Clin Cancer Res 2012, Epub Oct 9) (open trial NCT01421017)

anti-TGFβ (manuscript in preparation) (open trial NCT01401062)

IMMUNOTHERAPY & RADIATION

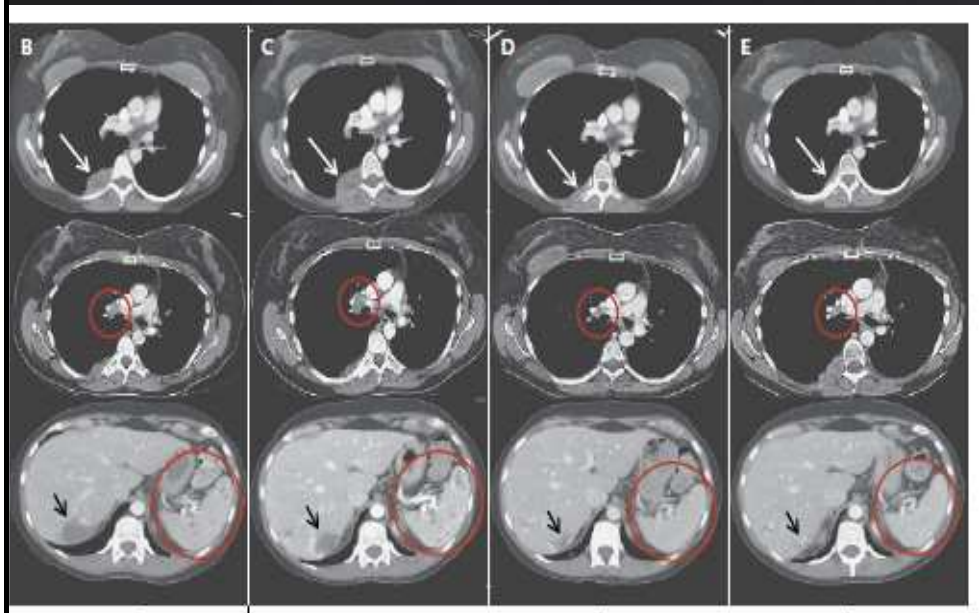
BRIEF REPORT

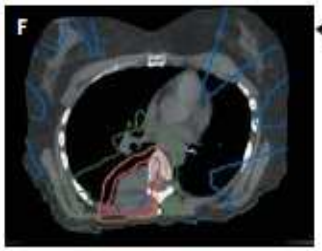
Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

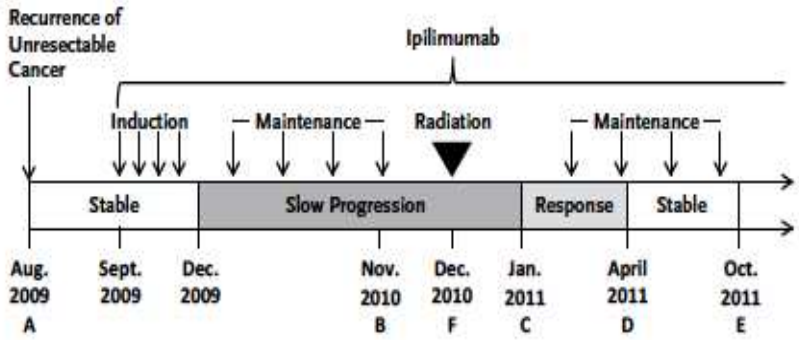
SUMMARY

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. The abscopal effect may be mediated by activation of the immune system. Ipilimumab is a monoclonal antibody that inhibits an immunologic checkpoint on T cells, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). We report a case of the abscopal effect in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer–testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy. (Funded by the National Institutes of Health and others.)



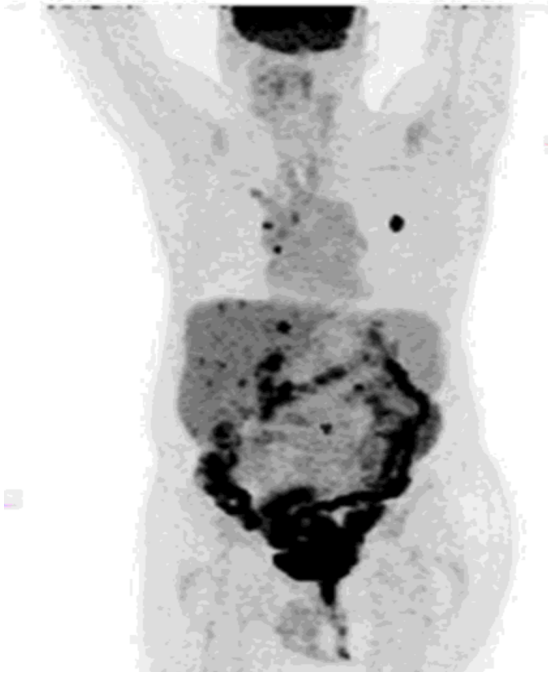


December 2010

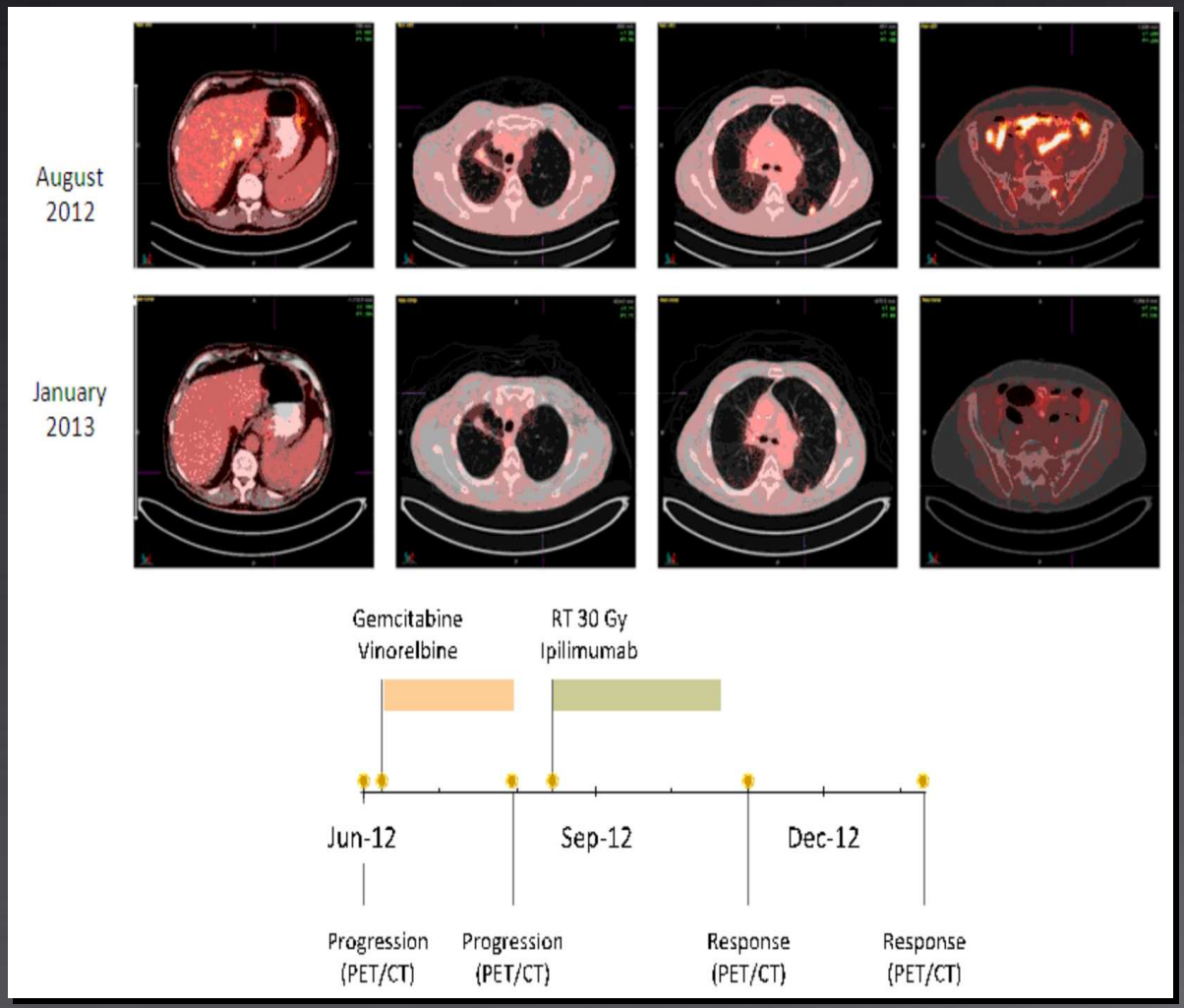


COMBINATION IMMUNOTHERAPY & RADIATION

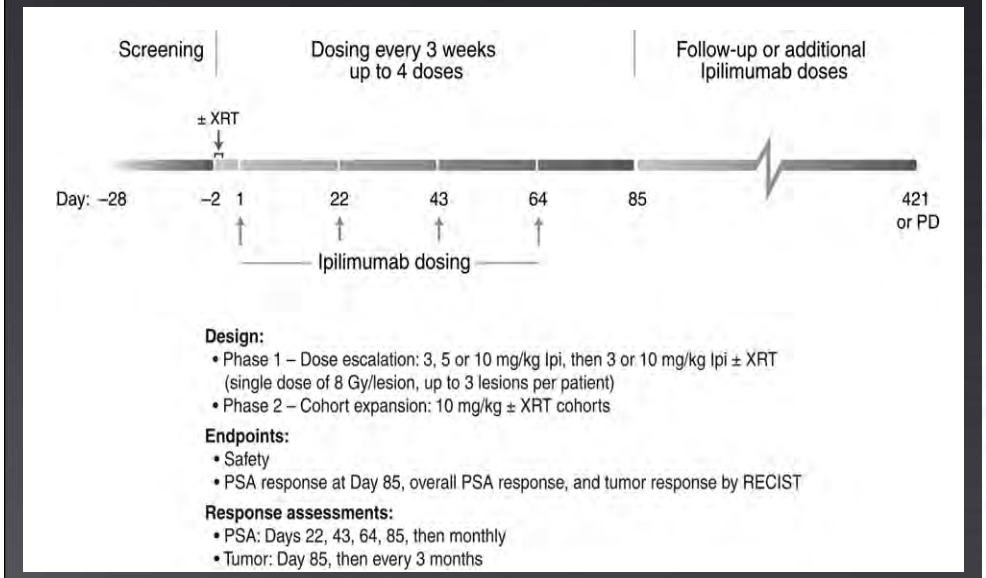
Dx: stage IV (pT1bN3M1a) NSCLC



concurrent ipilimumab (3mg/kg q 3wks x4c)
+ RT (30Gy delivered in 5 fractions QOD)



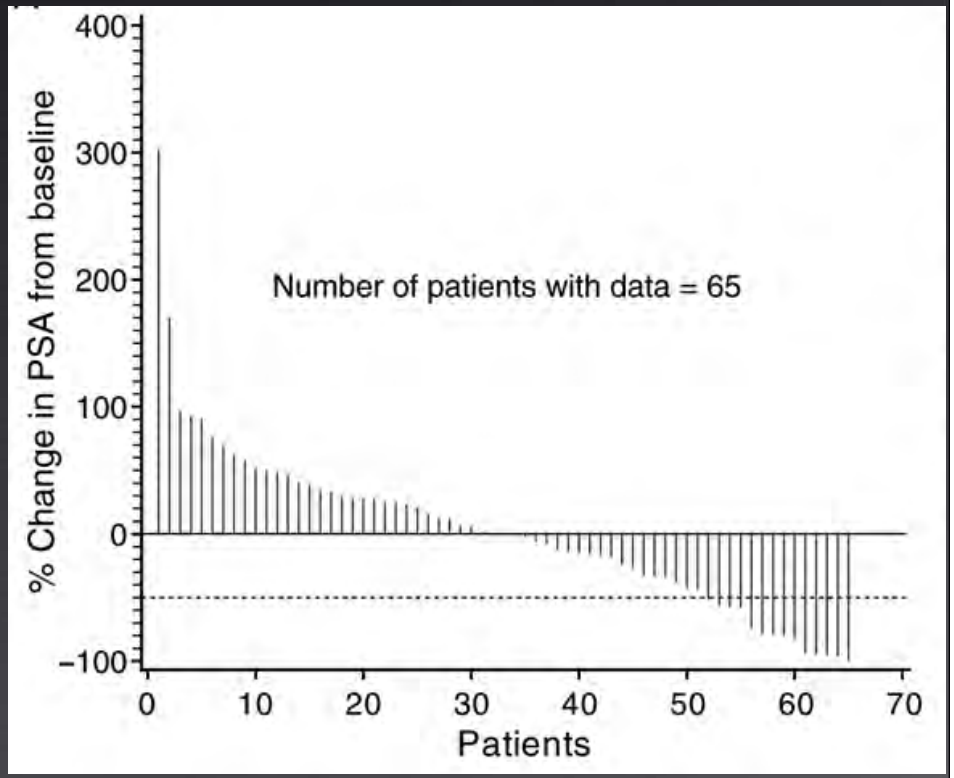
Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study



Design:
- Phase 1 – Dose escalation: 3, 5 or 10 mg/kg Ipi, then 3 or 10 mg/kg Ipi ± XRT (single dose of 8 Gy/lesion, up to 3 lesions per patient)
- Phase 2 – Cohort expansion: 10 mg/kg ± XRT cohorts

Endpoints:
- Safety
- PSA response at Day 85, overall PSA response, and tumor response by RECIST

Response assessments:
- PSA: Days 22, 43, 64, 85, then monthly
- Tumor: Day 85, then every 3 months



Slovin et al. Annals of Oncology 24: 1813–1821, 2013

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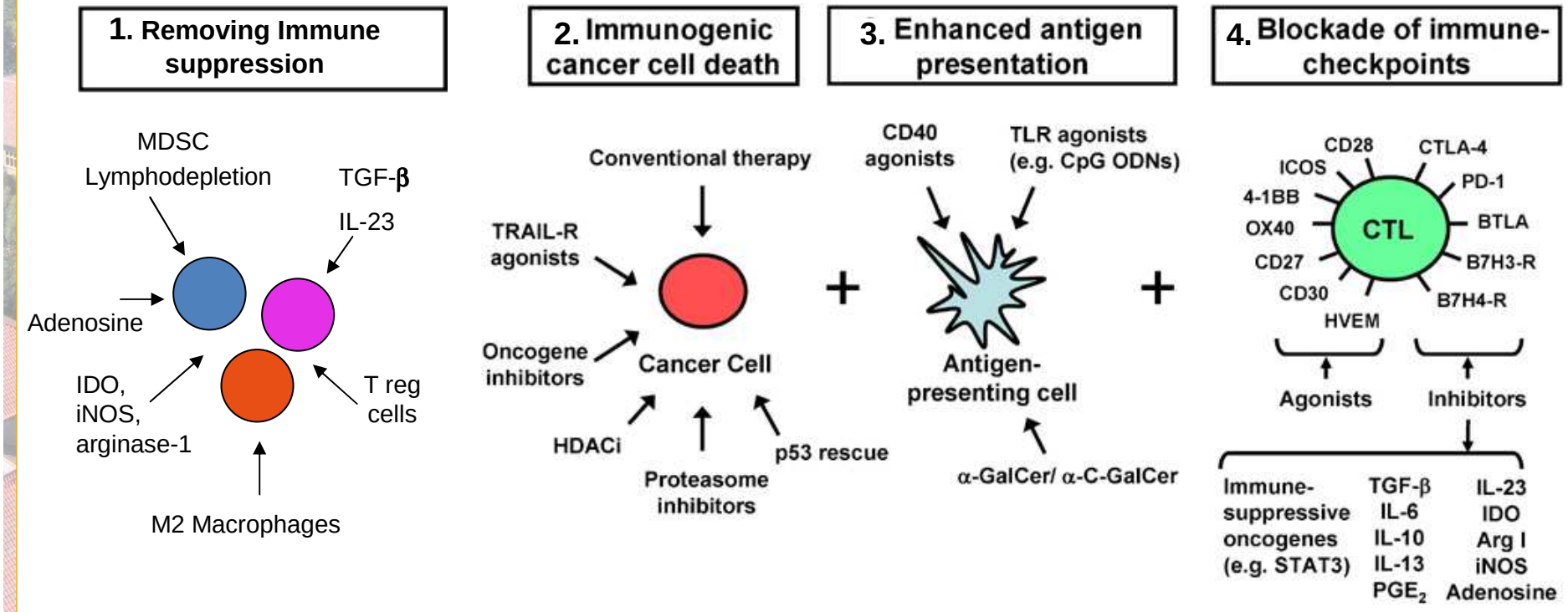
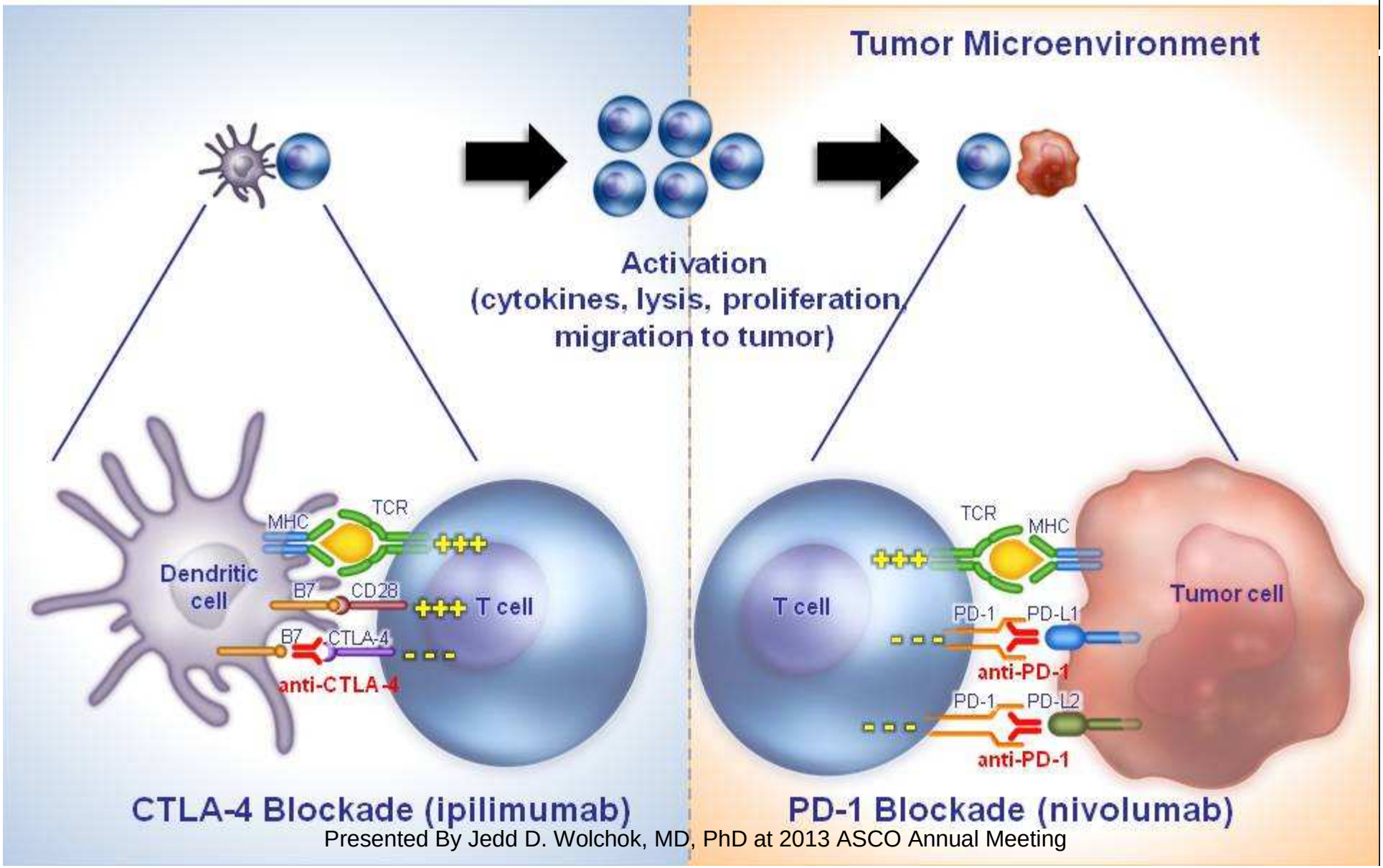


Blocking CTLA-4 and PD-1



Presented By Jedd D. Wolchok, MD, PhD at 2013 ASCO Annual Meeting

Clinical activity and safety of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients with advanced melanoma

Jedd D. Wolchok,[1] Harriet Kluger,[2] Margaret K. Callahan,[1] Michael A. Postow,[1] RuthAnn Gordon,[1] Neil H. Segal,[1] Naiyer A. Rizvi,[1] Alexander M. Lesokhin,[1] Kathleen Reed,[2] Matthew M. Burke,[2] Anne Caldwell,[2] Stephanie A. Kronenberg,[1] Blessing U. Agunwamba,[1] William Feely,[3] Quan Hong,[3] Christine E. Horak,[3] Alan J. Korman,[4] Jon M. Wigginton,[3] Ashok Gupta,[3] and Mario Sznol[2]

[1]Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Yale University School of Medicine and Yale Cancer Center, New Haven, CT; Bristol-Myers Squibb, [3]Princeton, NJ and [4]Redwood City, CA

Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

- **Ipilimumab:** 3 mg/kg every 3 wk, 4 doses (Phase 3)
  - ORR: 11%; 2 patients with CR[1]
  - Median OS: 10.1 mo;[1] 4-year survival rate (Phase 2 studies): 18%[2]
  - Grade 3-4 related AEs: 23%; included diarrhea (5%) and colitis (5%)[1]

- **Nivolumab**: 0.1 mg/kg to 10 mg/kg every 2 wk, ≤48 doses (Phase 1b)
  - ORR: 41%; 1 patient with CR (3 mg/kg)[3]
  - Median OS: 16.8 mo;[4] 2-year survival rate: 43%[4]
  - Grade 3-4 related AEs: 14%; included diarrhea (1%), pneumonitis (1%), and hypophosphatemia (1%)[3]

[1]Hodi et al. NEngl J Med. 2010;363:711-23. [2]Wolchok et al. Ann Oncol 2013 May10 [Epub ahead of print].
[3]Topalian et al. N Engl J Med 2012;2443-54. [4]Sznol et al. ASCO 2013, oral presentation, abs CRA9006.

Treatment-Related Adverse Events (≥10% of all patients)

Treatment-Related Adverse Event Number of Patients (%)	Concurrent All Cohorts (n=53)		Sequenced All Cohorts (n=33)	
	All Gr	Gr 3-4	Al Gr	Gr 3-4
Any adverse event	49 (93)	28 (53)	24 (73)	6 (18)
Rash	29 (55)	2 (4)	3 (9)	0
Pruritus	25 (47)	0	6 (18)	0
Fatigue	20 (38)	0	3 (9)	0
Diarrhea	18 (34)	3 (6)	3 (9)	0
Nausea	11 (21)	0	1 (3)	0
Pyrexia	11 (21)	0	1 (3)	0
↑ AST	11 (21)	7 (13)	0	0
↑ ALT	11 (21)	6 (11)	1 (3)	0
↑ Lipase	10 (19)	7 (13)	4 (12)	2 (6)
↑ Amylase	8 (15)	3 (6)	1 (3)	1 (3)
Cough	7 (13)	0	2 (6)	0
Vomiting	6 (11)	1 (2)	0	0
Vitiligo	6 (11)	0	0	0
Headache	6 (11)	0	0	0

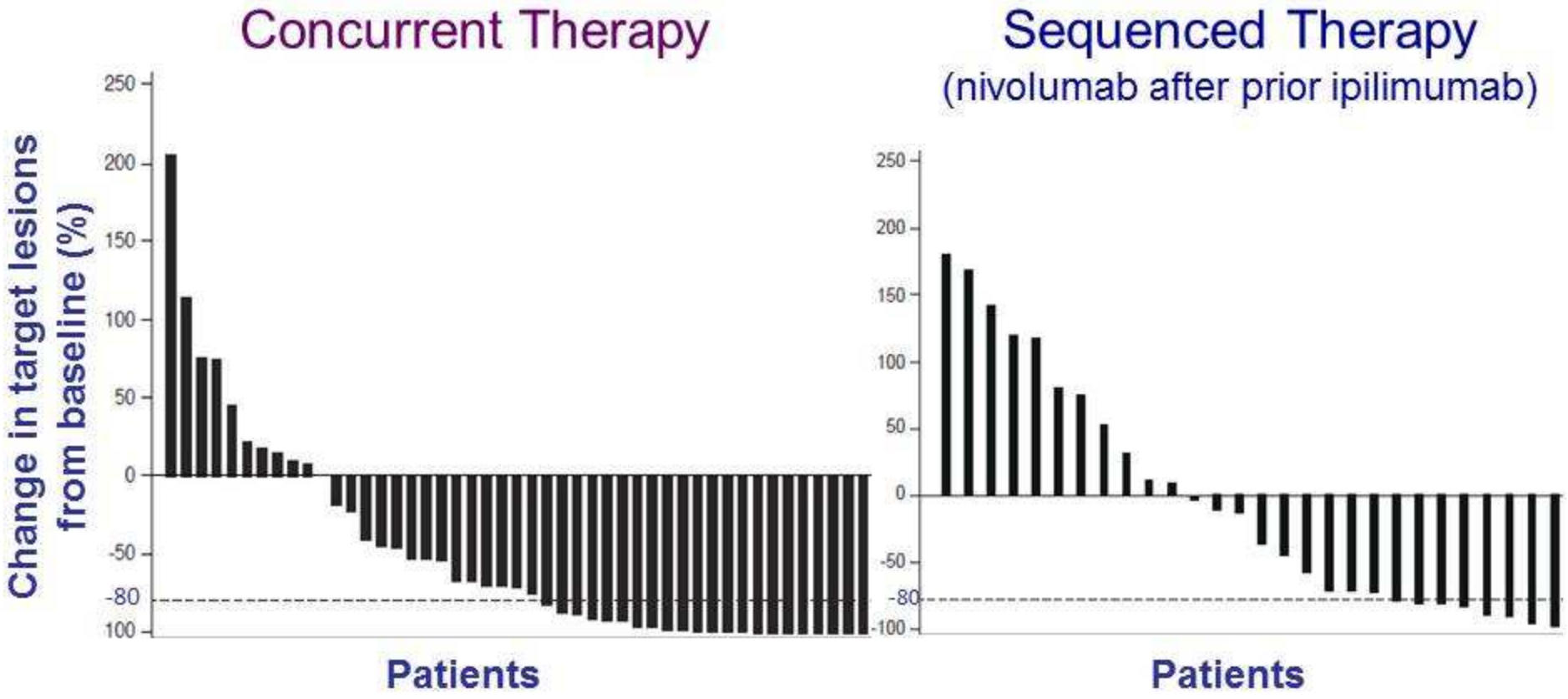
Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

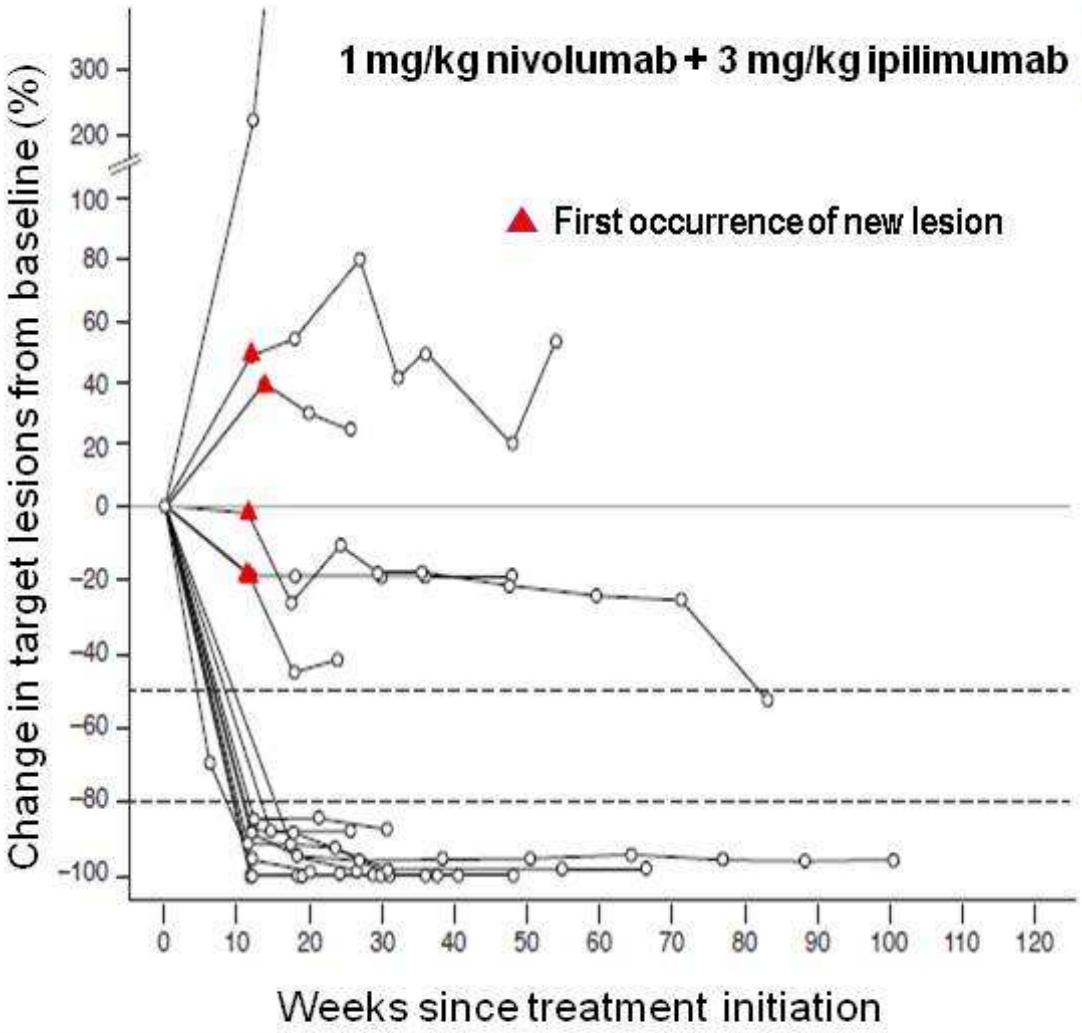
Clinical activity: combination of nivolumab and ipilimumab therapy

Best responses in all evaluable patients



Wolchok et al. ASCO 2013, abs 9012, oral presentation, Clinical Science Symposium, June 2.

Rapid and Durable Changes in Target Lesions



Pre-treatment

12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Evaluating PD-L1 status as a putative biomarker

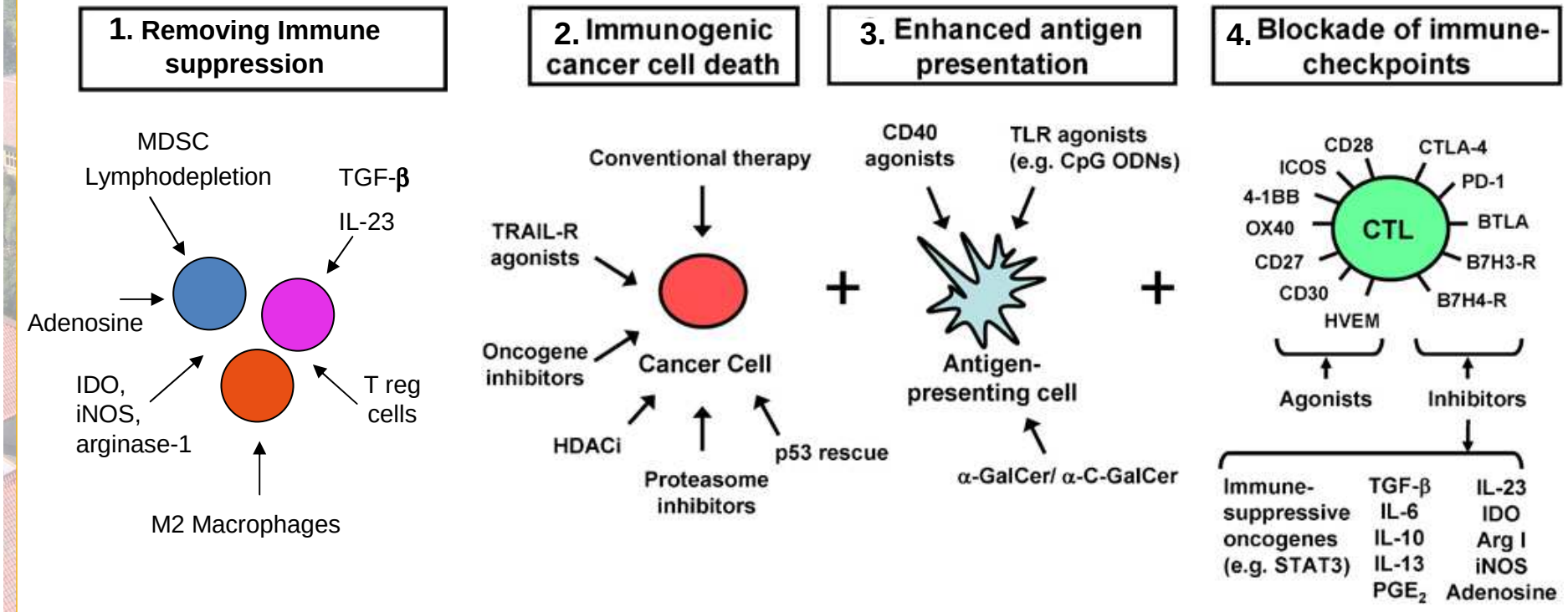
Therapy	PD-L1 Status	ORR
Nivolumab monotherapy (melanoma) (0.1-10 mg/kg) Grosso et al. ASCO 2013	+	**41%** (7/17)
	-	**14%** (3/21)
Concurrent ipilimumab + nivolumab	+	**46%** (6/13)
	-	**41%** (9/22)
Sequenced nivolumab (after ipilimumab)	+	**50%** (4/8)
	-	**8%** (1/13)

PD-L1 Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)

Therapeutic Opportunities: Combinations with PD-1 Pathway Blockade

- PD-1 pathway blockade + other immunoinhibitors
  - —e.g., CTLA-4, TIM-3, LAG-3
- PD-1 pathway blockade + immunostimulators
  - —e.g., anti-OX40, anti-4-1BB, IL-2, TLR ligands
- PD-1 pathway blockade + kinase inhibitors like Braf
- PD-1 pathway blockade + standards of cancer therapy
  - —Synergy with chemotherapy or radiation
- PD-1 pathway blockade + cancer vaccine
  - − Synergy between PD-1 blockade and therapeutic vaccination in chronic viral infection

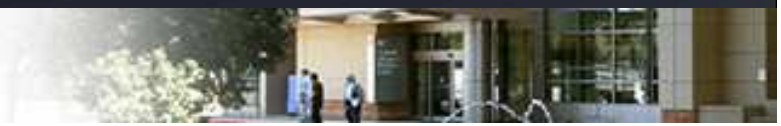
Combination strategies:
A ‘four-strike’ approach to cancer therapy



The Emerging Role of Combination Tumor Immunotherapy

Combination Immunotherapy To Improve Today's Current Therapy:

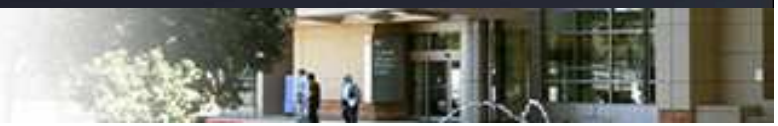
Monoclonal Antibodies



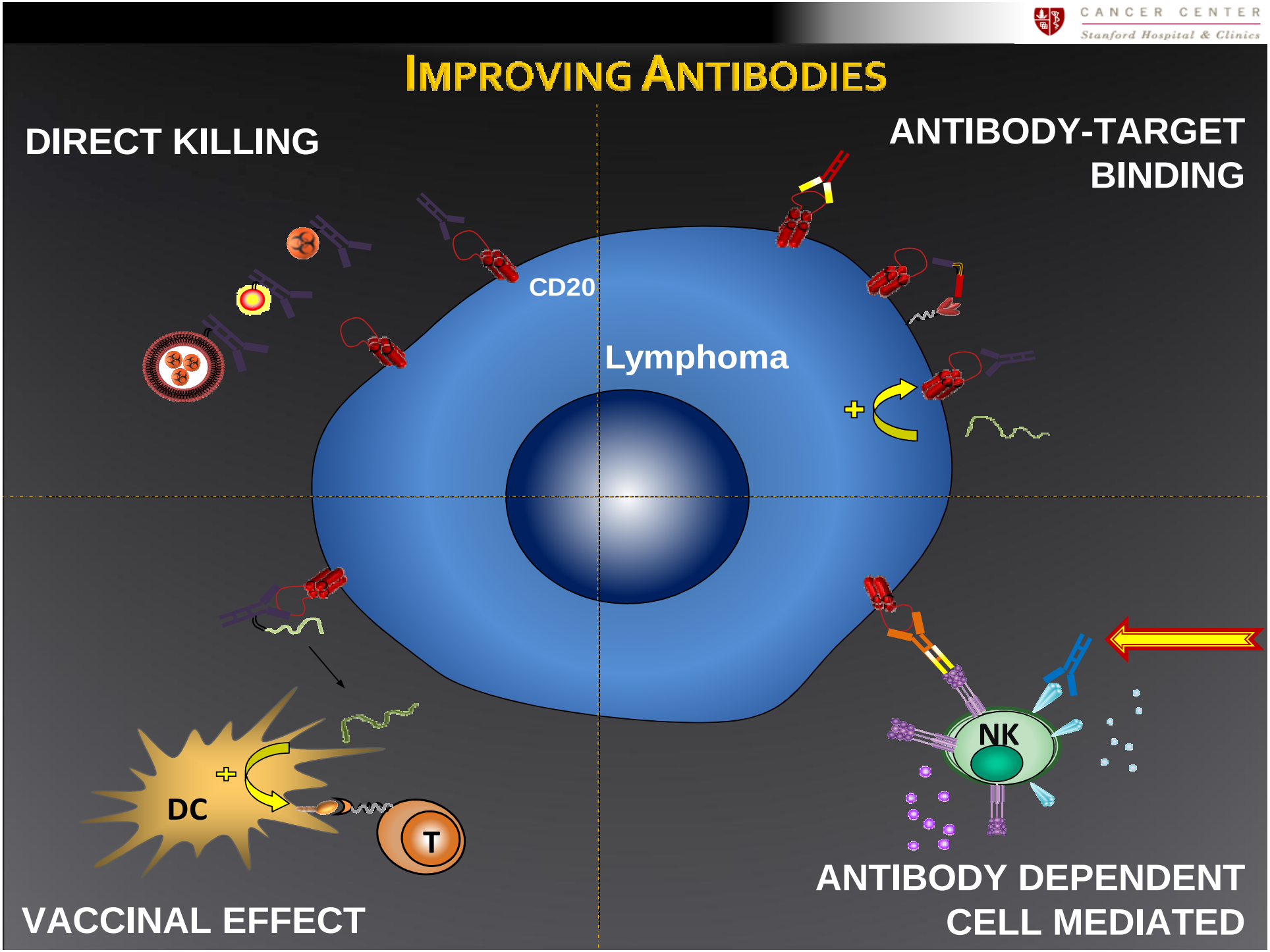
The Emerging Role of Combination Tumor Immunotherapy

Stimulation of Natural Killer Cells with an Anti-CD137 Antibody Enhances the Efficacy of Trastuzumab, Cetuximab & Rituximab

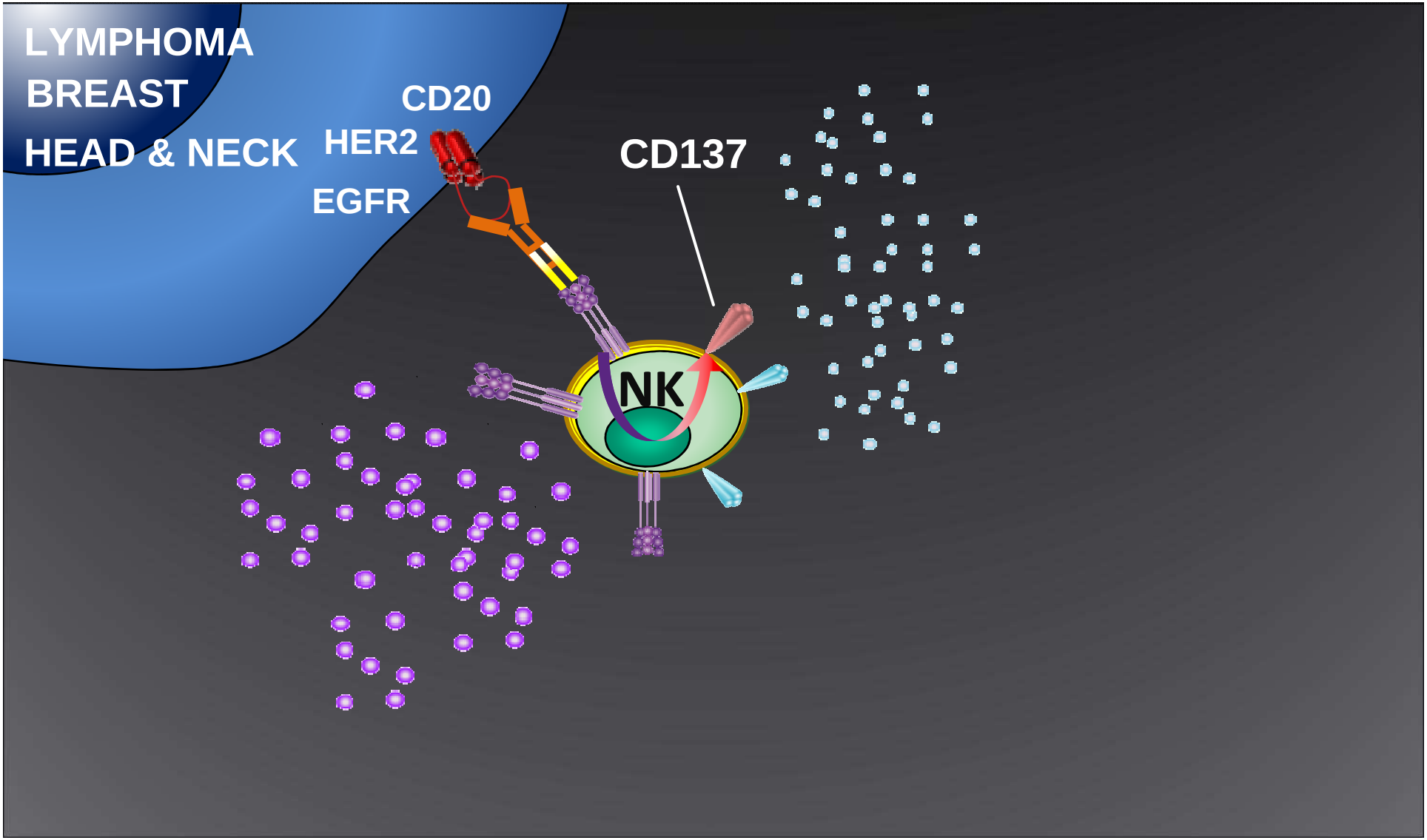
STANFORD SCHOOL OF MEDICINE
CANCER CENTER
Stanford Hospital & Clinics



IMPROVING ANTIBODIES

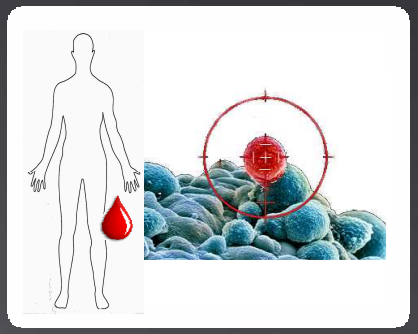


4-1BB (CD137)
Inducible Costimulatory Target On NK Cells

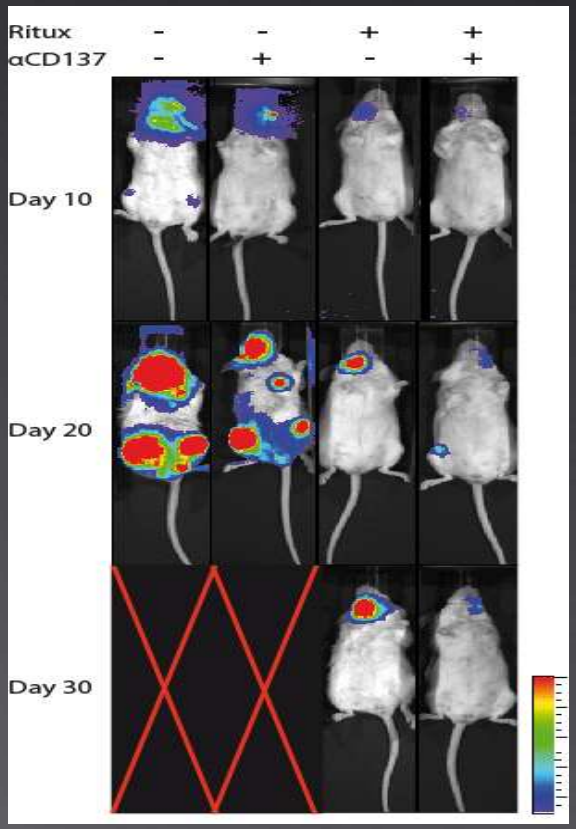


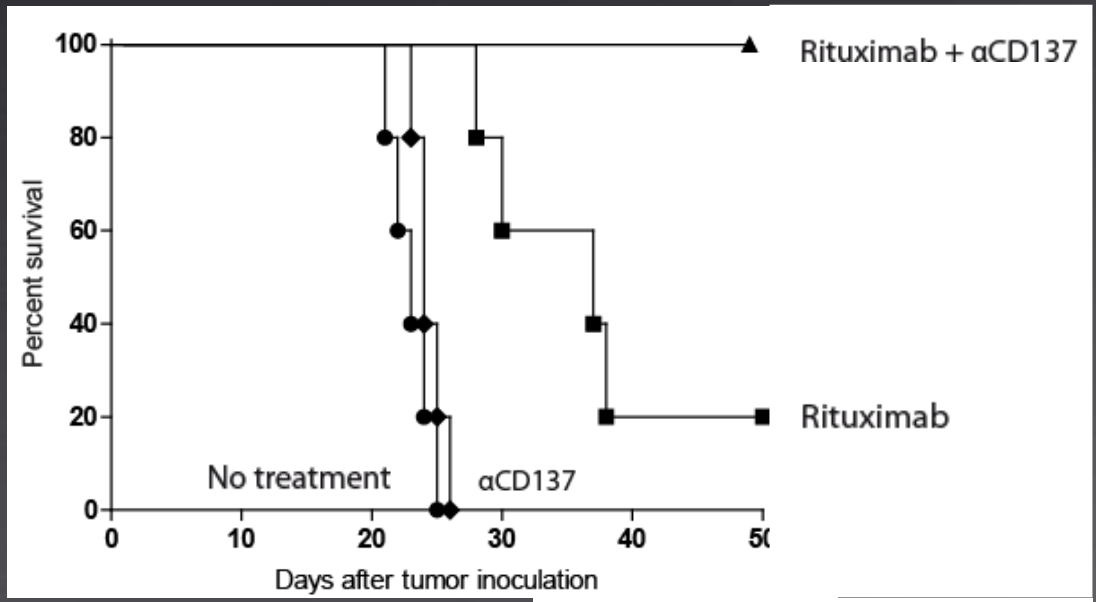
NOVEL THERAPEUTIC TARGET

IN VIVO VALIDATION OF ANTI-CD137 THERAPY



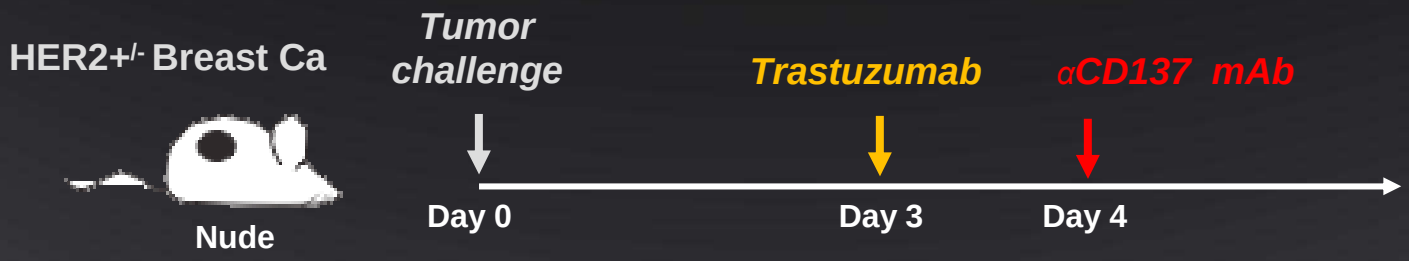
In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb

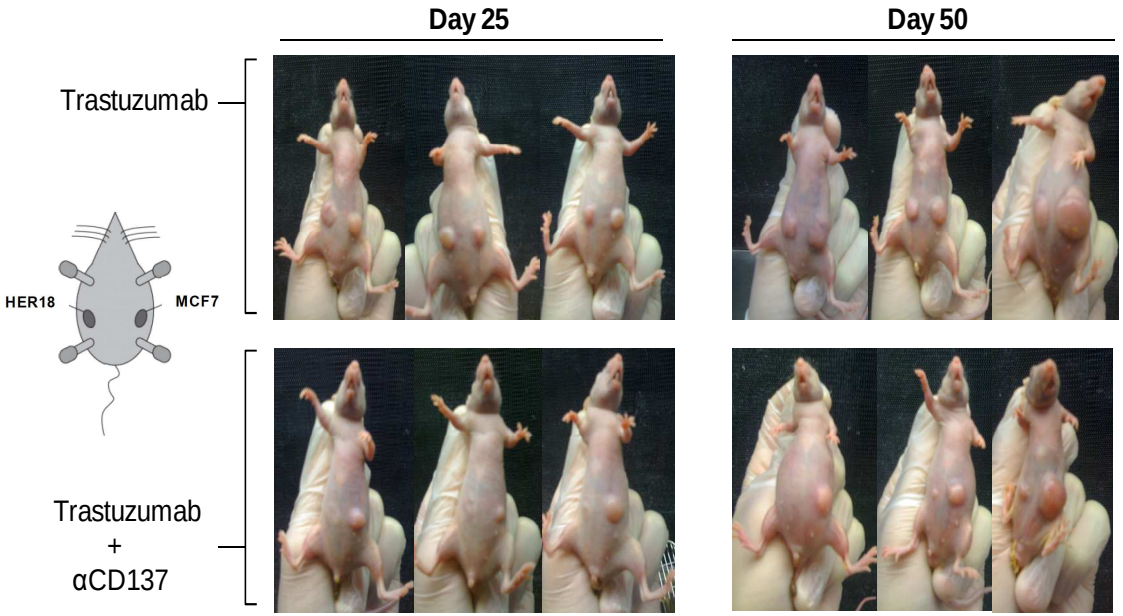


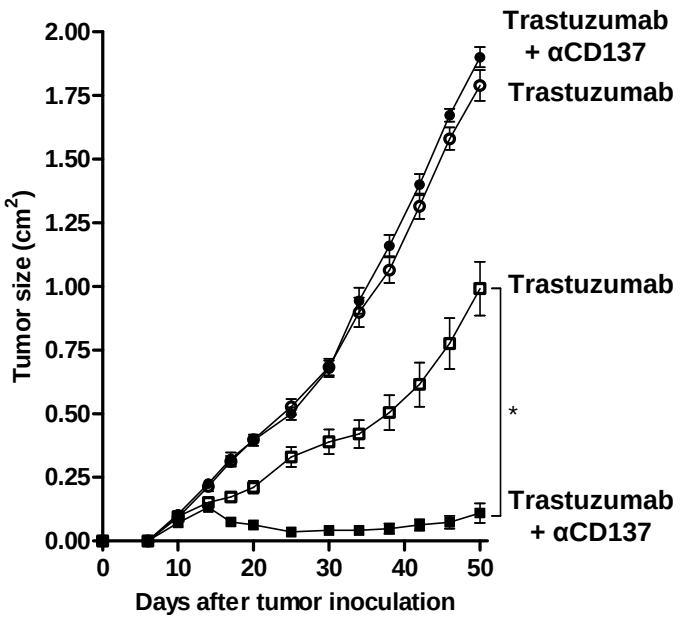


KOHRT et al blood Prepublished online Dec 30, 2010; doi:10.1182/blood-2010-08-301945

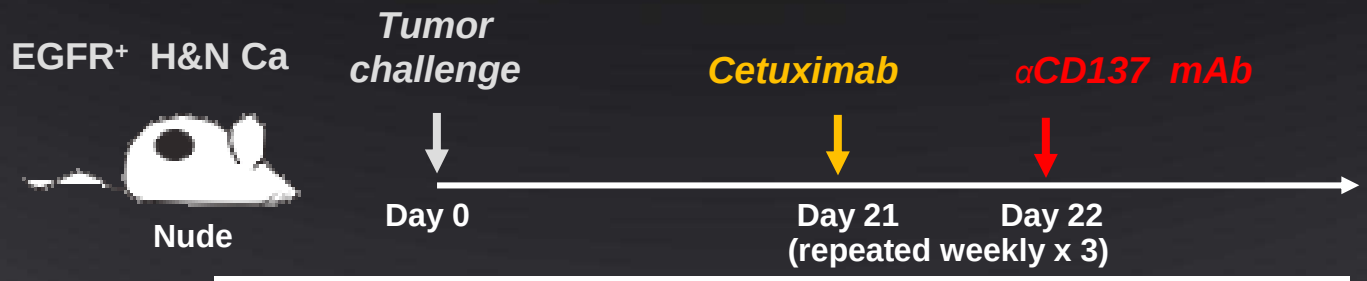
In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb

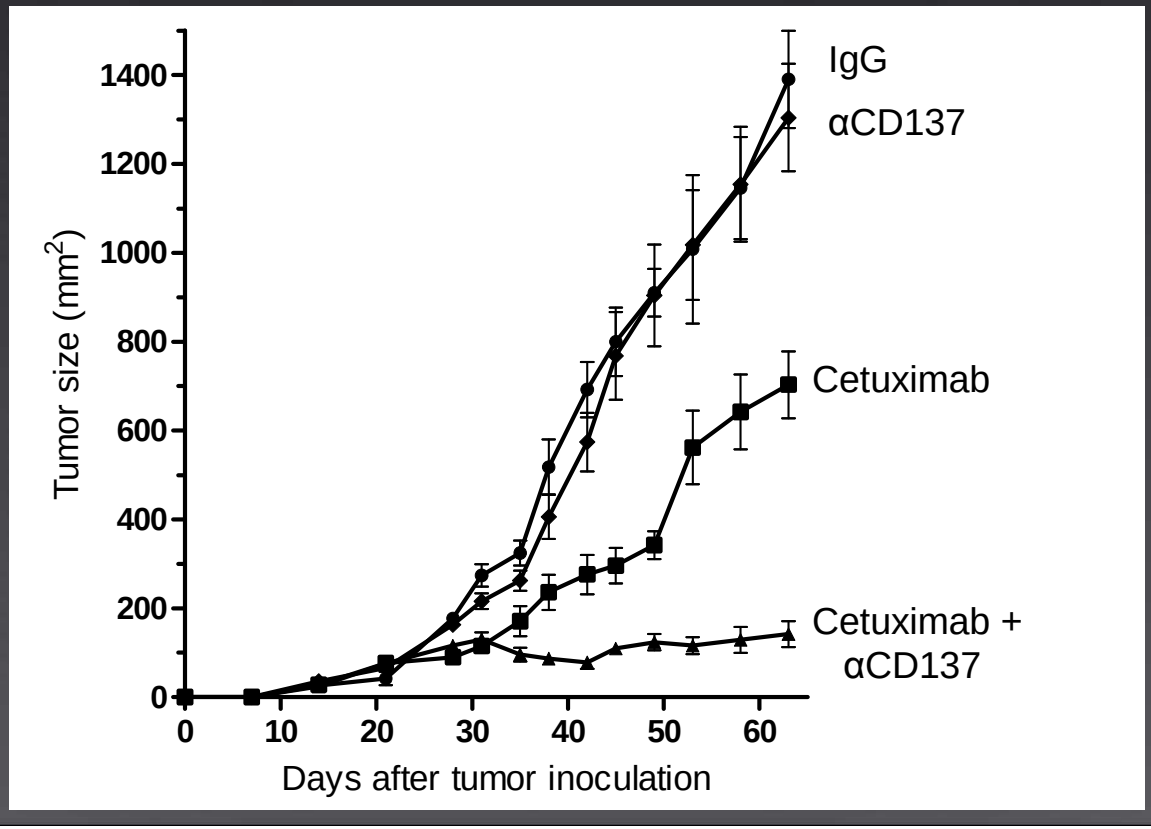






In vivo Enhancement of Anti-Cancer Activity with αCD137 mAb





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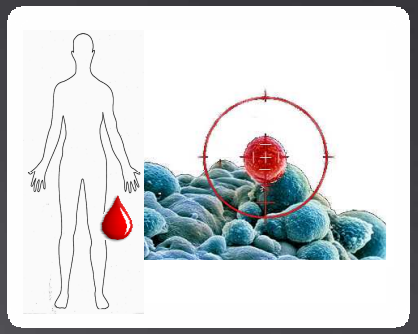
Novel Therapeutic Target & Potential Biomarker

Phase 0 Study of CD137



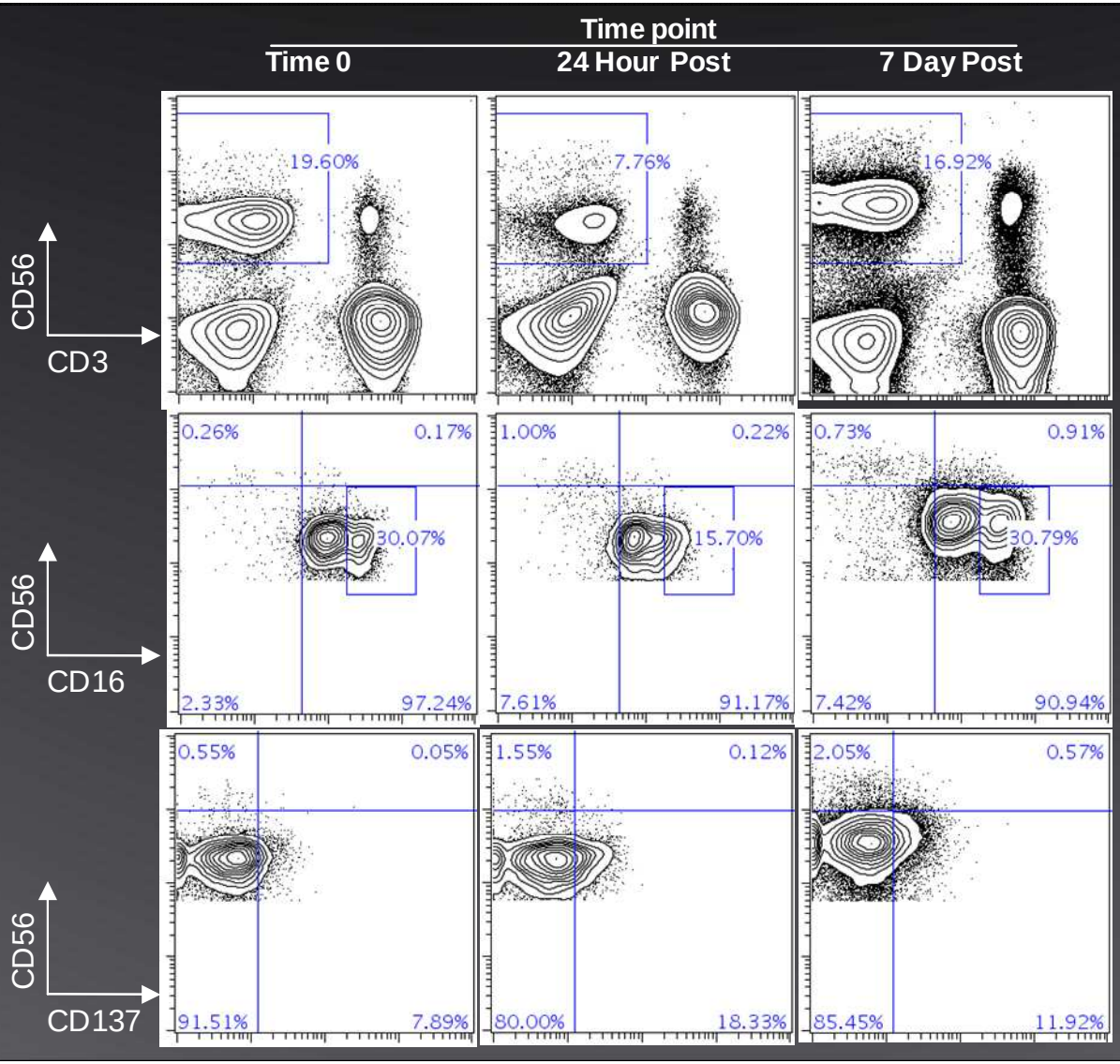
NCT01114256

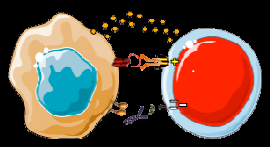
Bedside to Bench Lessons Critical to Clinical Translation – Time Post Trastuzumab

HER2+ Breast Cancer

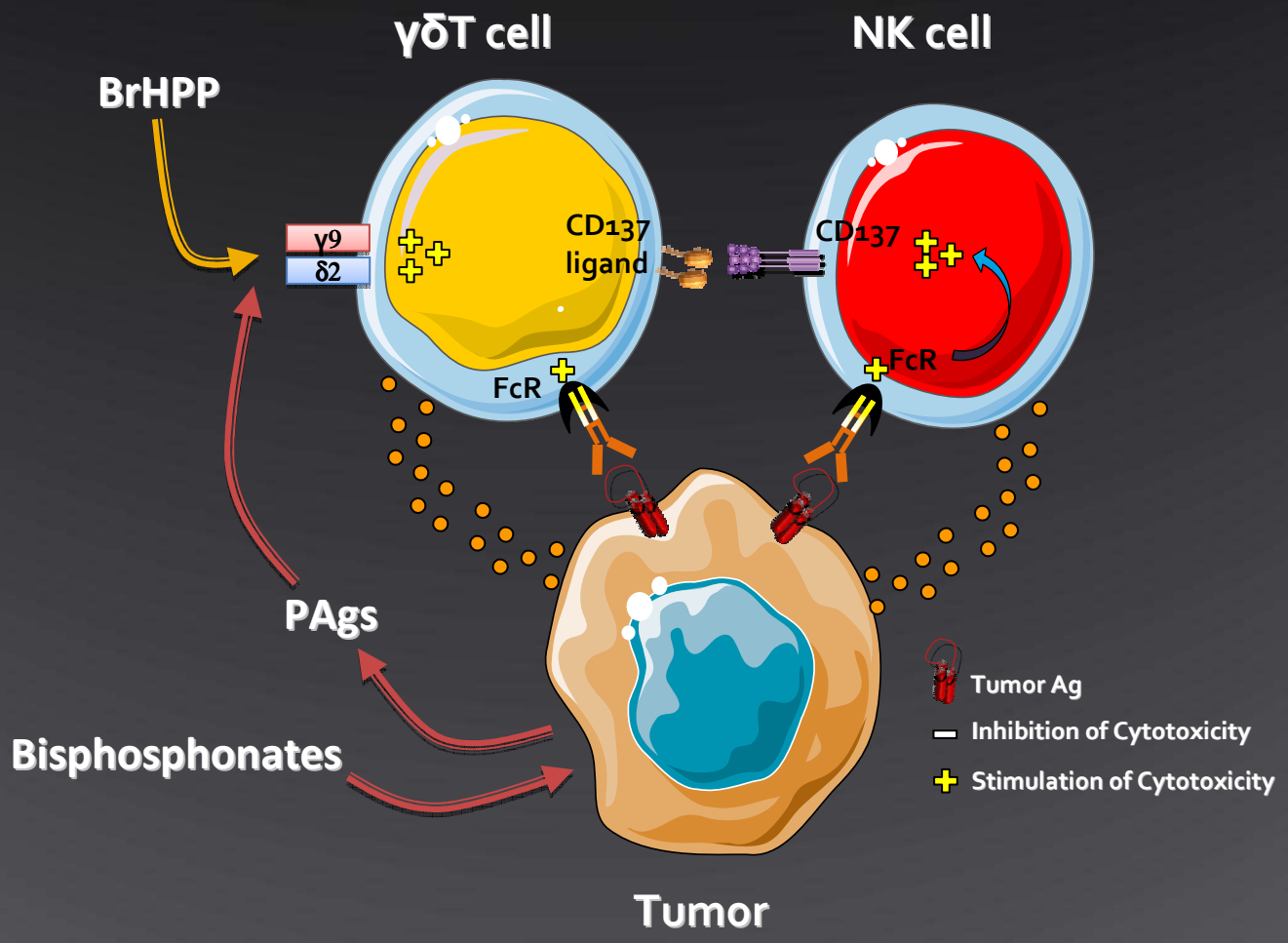
Trastuzumab

NK cell CD137 expression



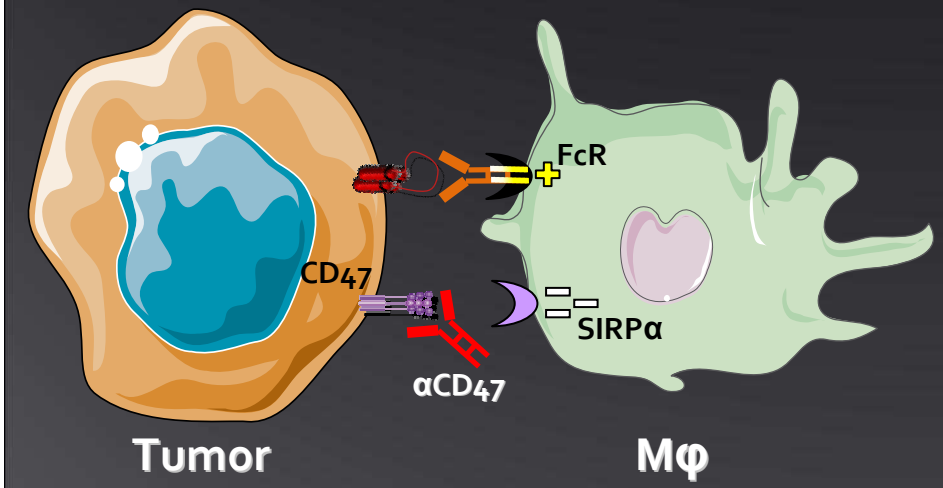


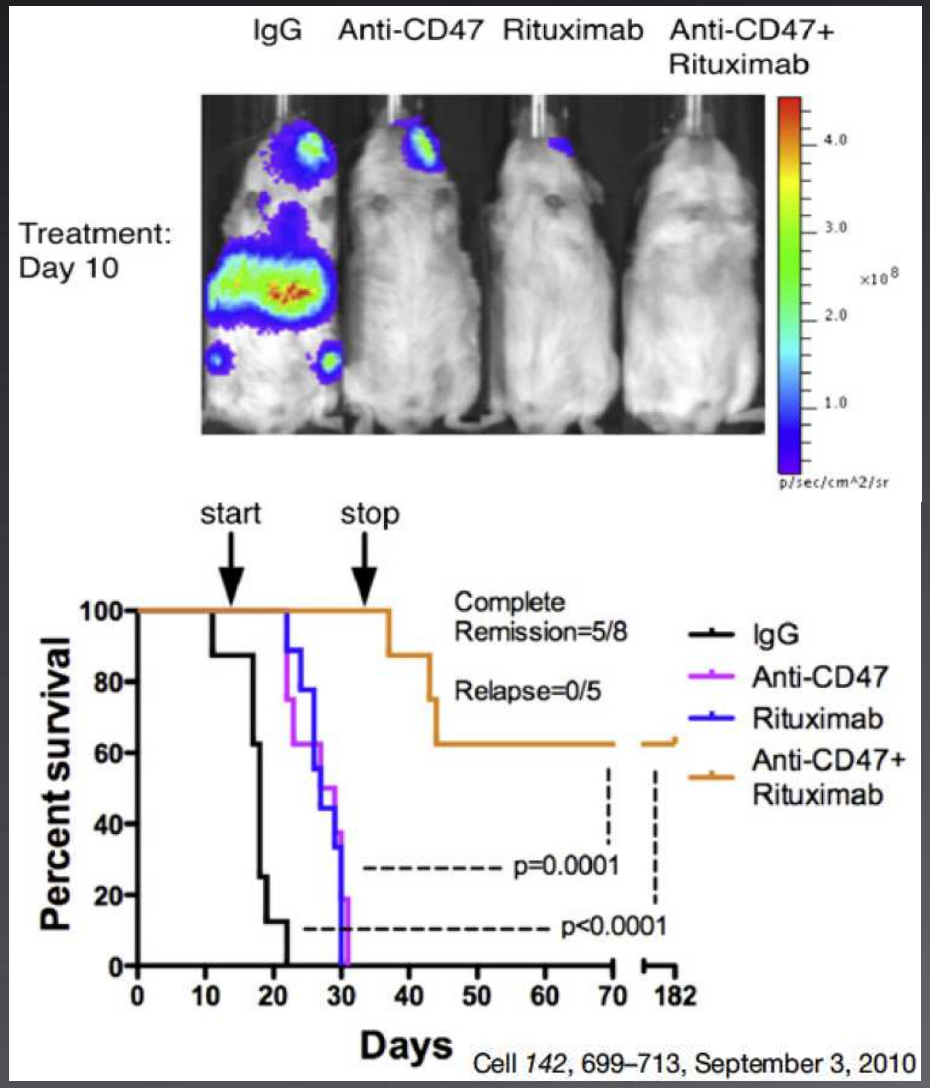
Enhancing ADCC through *Gamma-Delta* T Cell Stimulation – Applying Approved Therapies

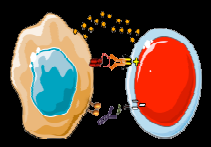


Increased ADCC

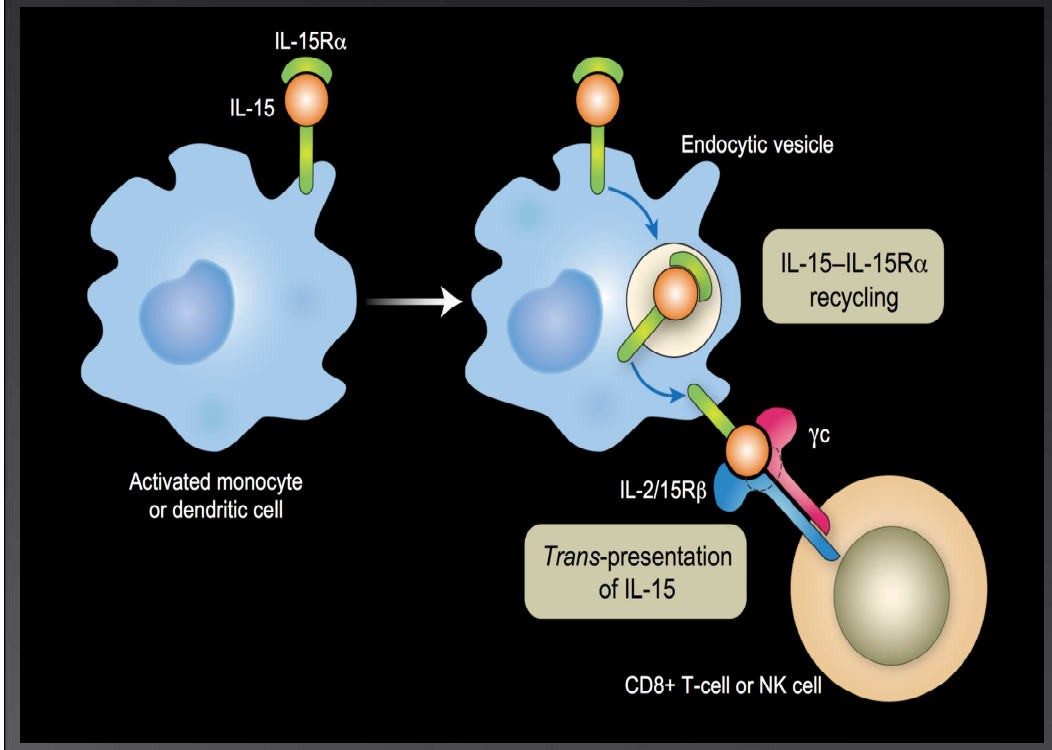
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

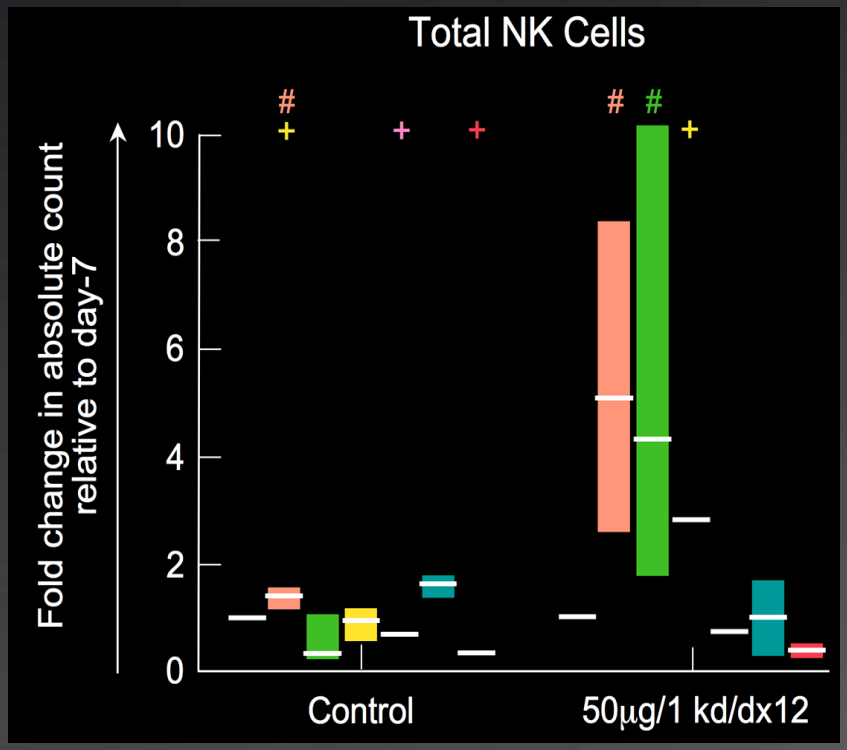


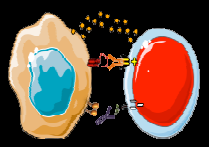




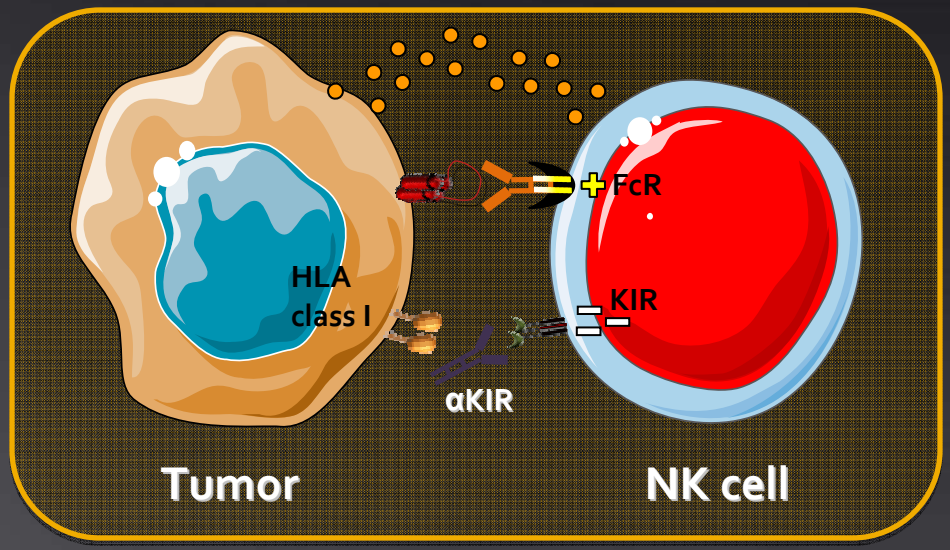
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

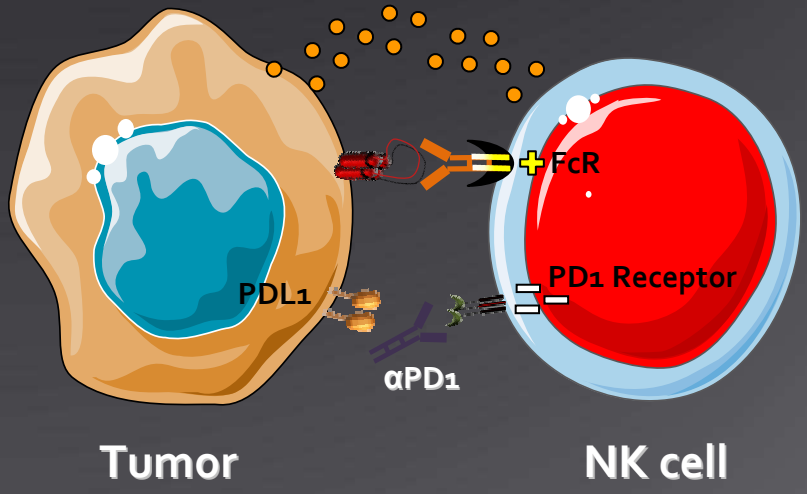


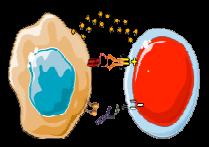




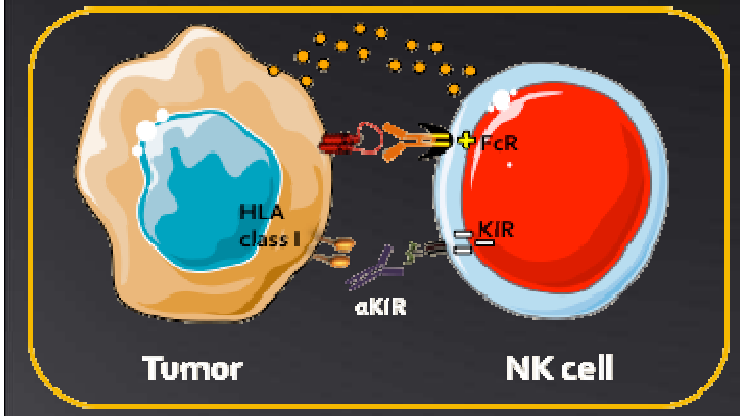
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

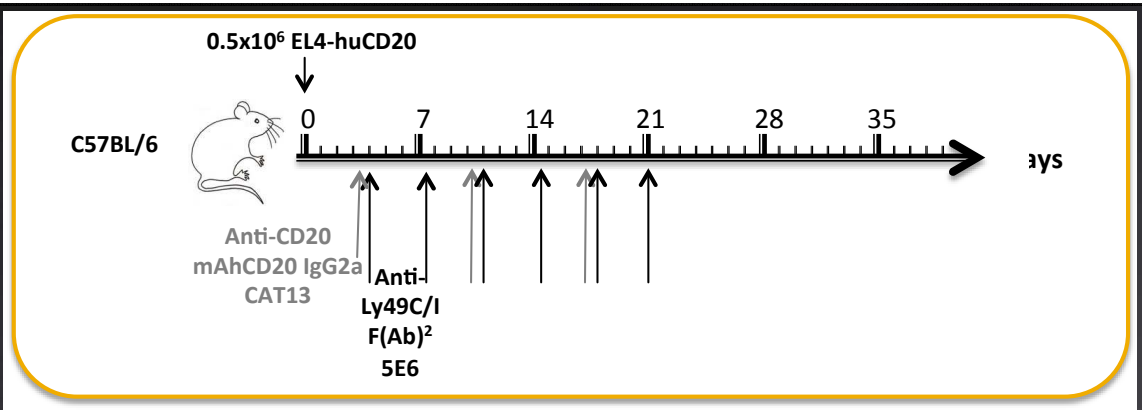


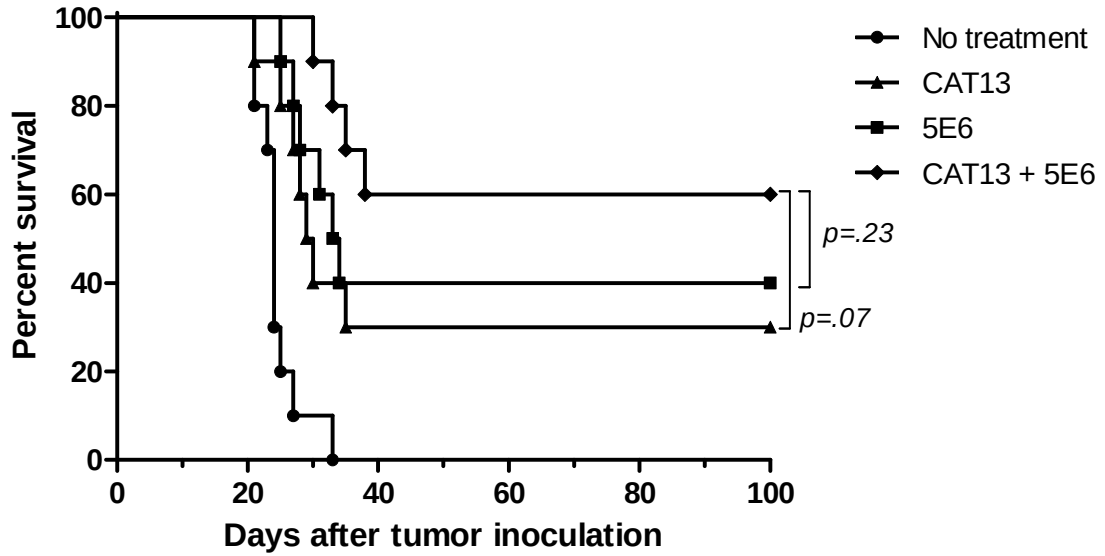




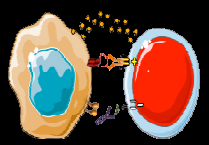
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations



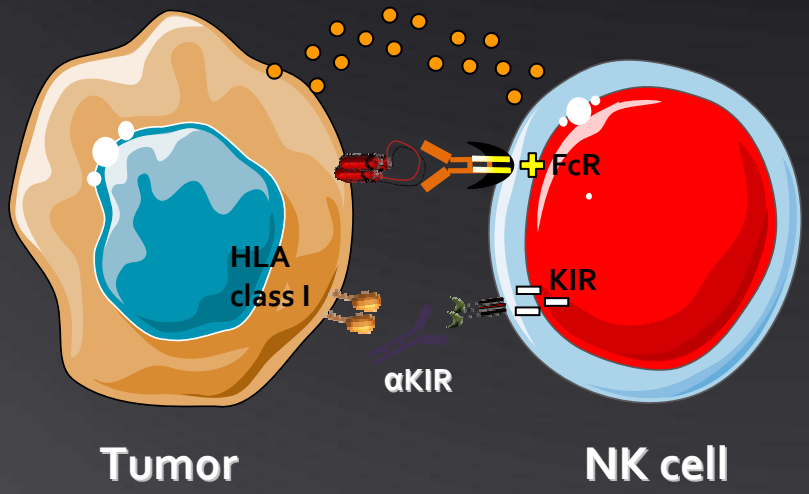


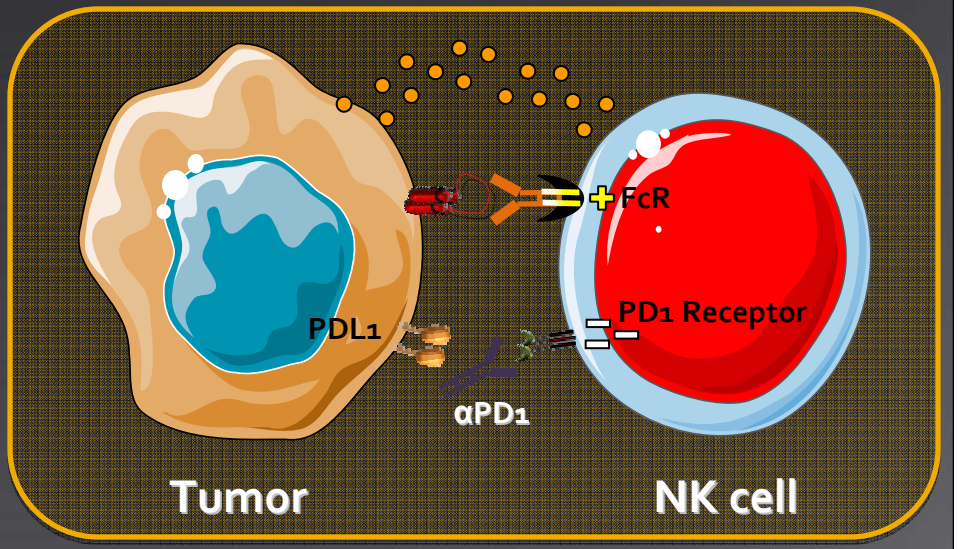


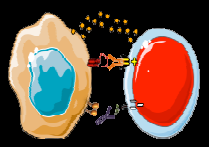
- αLy49C/I increases anti-tumor activity of anti-CD20 mAb in-vivo



Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations



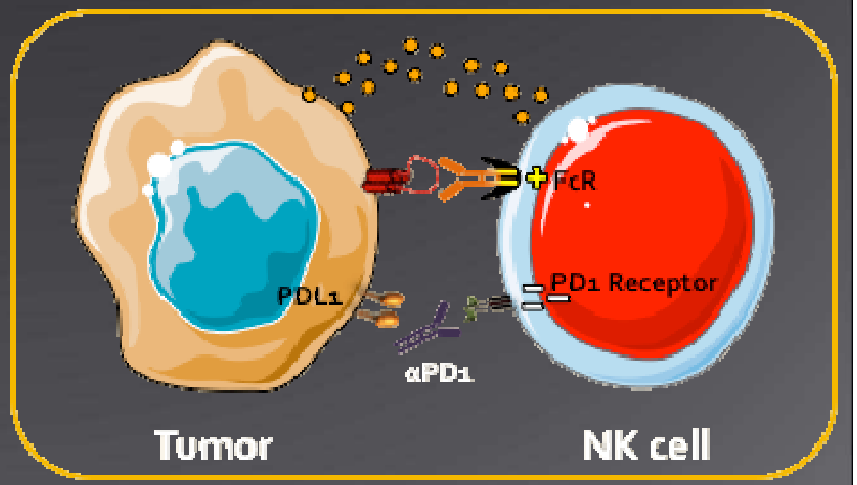




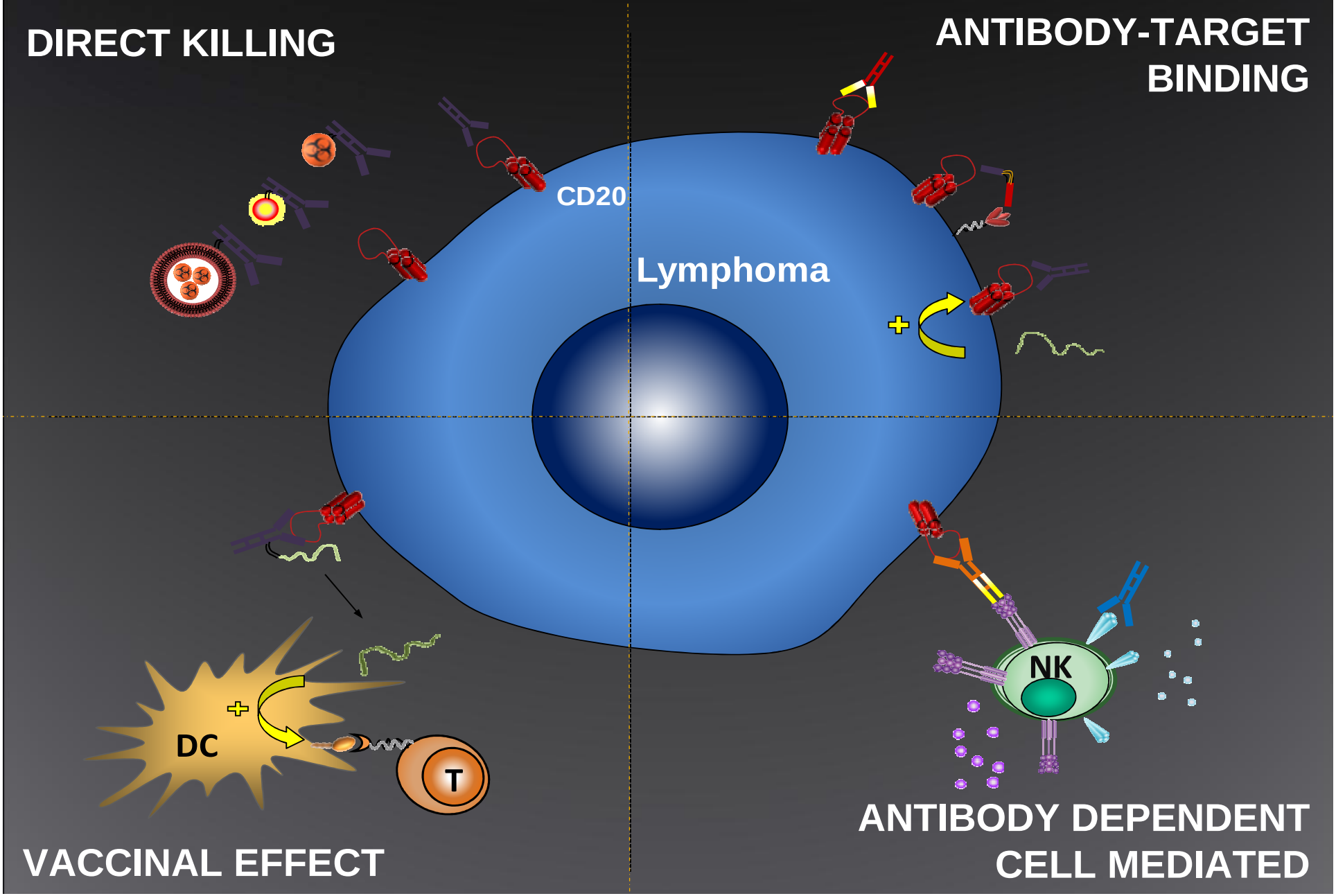
Enhancing ADCC through blockade of inhibitory signals – Novel Therapy Combinations

Phase II Safety and Efficacy Study of CT-011, a Humanized Anti-PD-1 Monoclonal Antibody, in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma (NCT00904722)

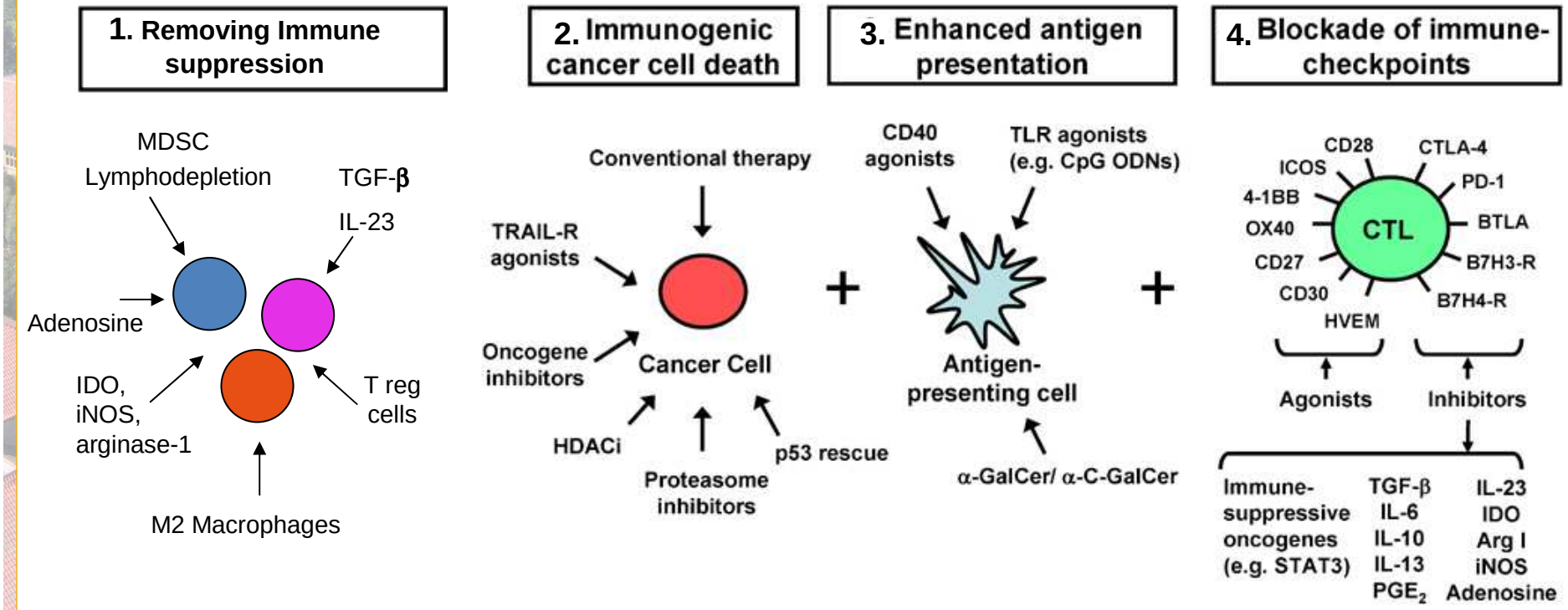
- Single arm phase II trial to determine the safety and efficacy of CT-011 and rituximab in patients (pts) with relapsed FL
- CT-011 was dosed at 3 mg/kg IV every 4 weeks (wks) for 4 infusions and rituximab was dosed at 375 mg/m2 IV weekly for 4 wks starting 2 wks after the first infusion of CT-011. was 88 days.
- Of 29 pts eligible for efficacy analysis, 19 pts had an objective response for an ORR of 66%. CR was observed in 15 (52%) and PR in 4 (14%). Altogether, 25 (86%) pts had measurable tumor regression. Median time to response was 88 days.



EXCITING FUTURE OF ANTIBODY THERAPIES

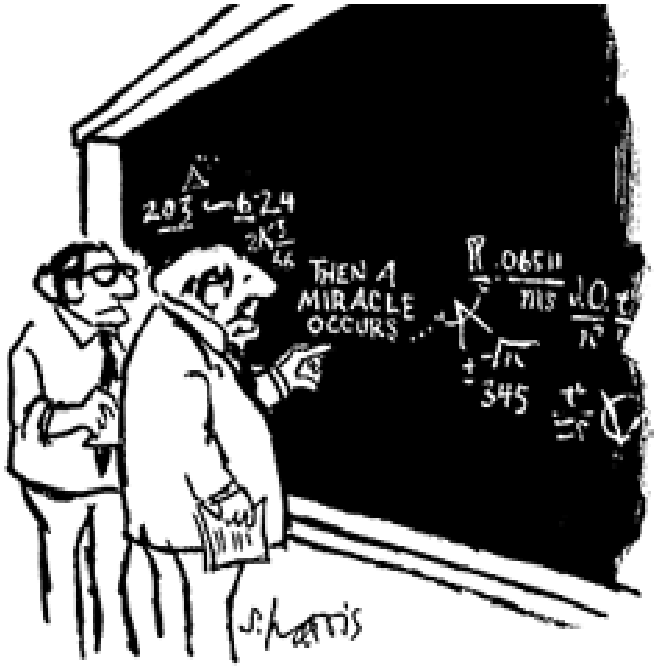


Combination strategies:
A ‘four-strike’ approach to cancer therapy



The Emerging Role of Combination Tumor Immunotherapy

"We've found a mass. The good news is we have weapons of mass destruction."



"I think you should be more explicit here in step two."

The Emerging Role of Combination Tumor Immunotherapy

Promising combinations with immunotherapy include:

(a) Combination radiation and anti-CTLA4 antibody

(b) Combination cancer vaccine and anti-CTLA4 antibody

(c) Combination anti-CTLA4 antibody and anti-PD1 antibody

(d) All of the above

The Emerging Role of Combination Tumor Immunotherapy

Limitations to combinations of immunotherapy include:

(a) Low toxicity

(b) Low efficacy

(c) High cost

(d) High efficacy

(e) a and b

The Emerging Role of Combination Tumor Immunotherapy

The combination of anti-CTLA4 antibody and anti-PD1 antibody is promising for patients with:

(a) Melanoma

(b) Lymphoma

(c) Colorectal carcinoma

(d) Mycosis fungoides

(e) Prostate cancer

The Emerging Role of Combination Tumor Immunotherapy

Tumor responses at distant systemic sites following local radiation is known as the _____ effect.

(a) Warburg

(b) Heisenberg

(c) Abscopal

(d) Adaptive immune

(e) Innate immune

The Emerging Role of Combination Tumor Immunotherapy

The combinations of anti-CD137 antibody and monoclonal antibodies are promising for patients with:

(a) HER2+ breast cancer

(b) CD20+ lymphoma

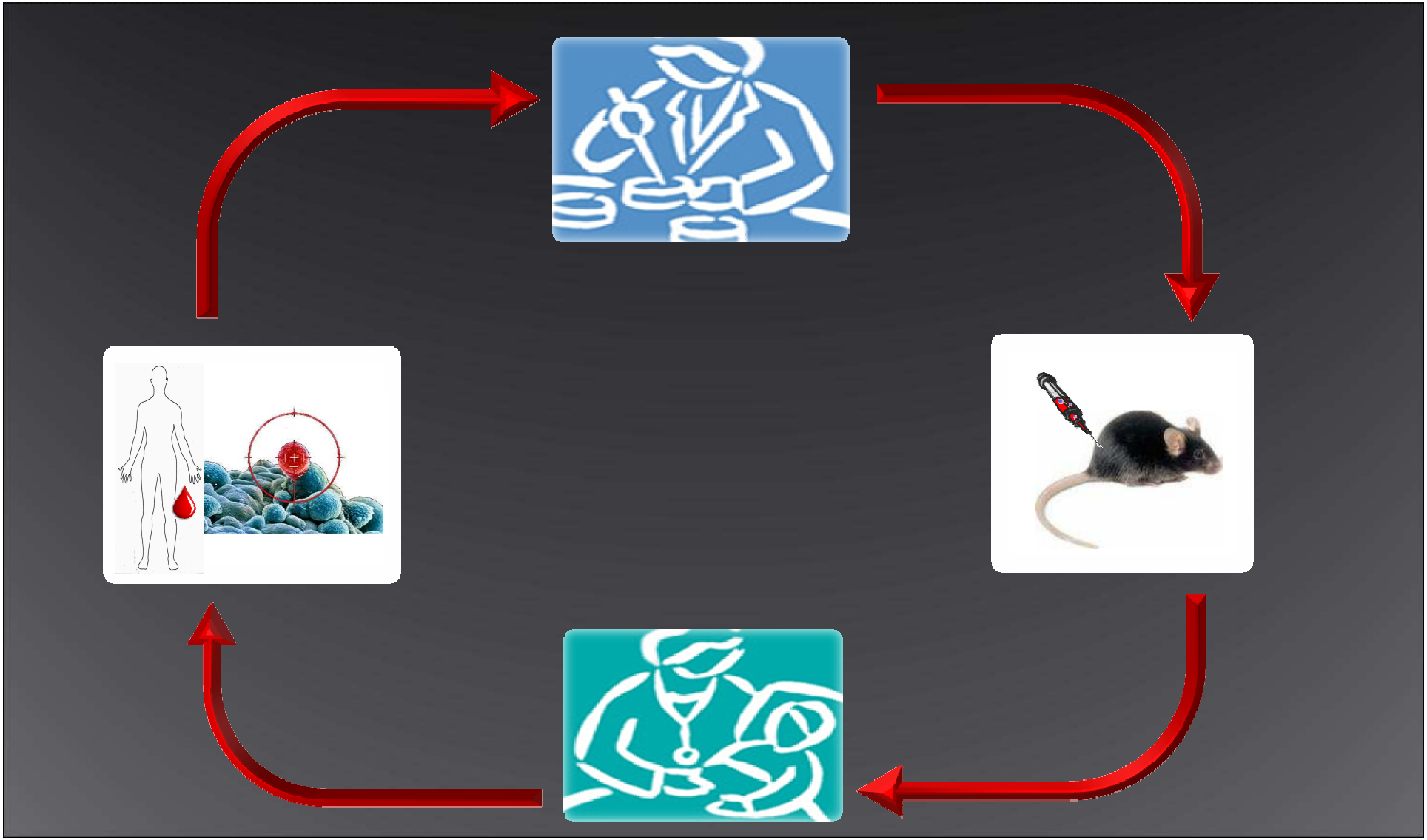
(c) EGFR+ colorectal carcinoma

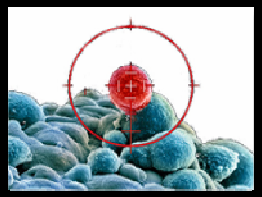
(d) EGFR+ head and neck cancer

(e) All of the above

NOVEL TARGET

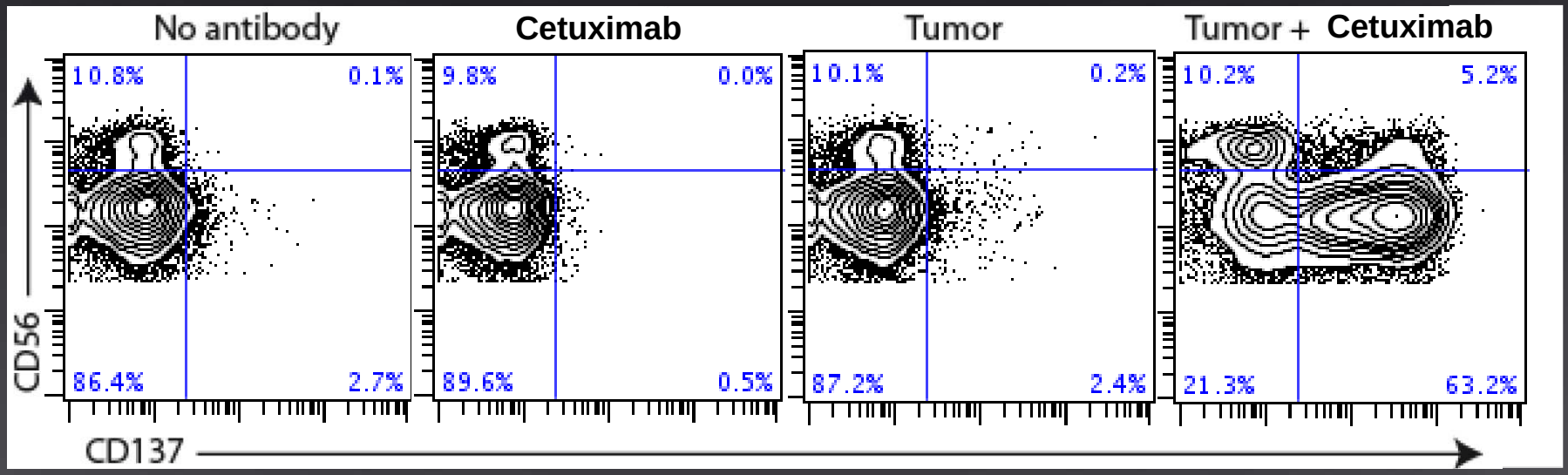
IDENTIFICATION OF CD137





Induction of CD137 on NK Cells

NK Cells and EGFR+ lymphoblastoid cell line against cancer

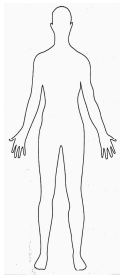


- Rituximab induces CD137 expression on NK cells in the presence of CD20+ tumor
- Trastuzumab induces CD137 expression on NK cells in the presence of HER+ tumor
- Cetuximab induces CD137 expression on NK cells in the presence of EGFR+ tumor

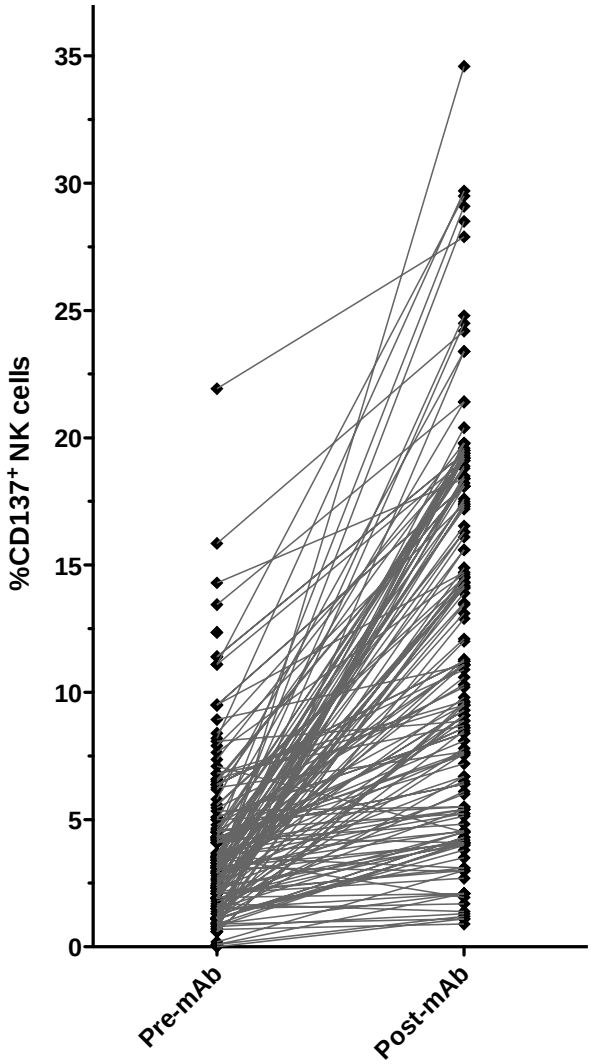
KOHRT et al blood Prepublished online Dec 30, 2010; doi:10.1182/blood-2010-08-301945

Bedside to Bench Lessons Critical to Clinical Translation

EGFR+
Head & Neck
HER2+ Breast
CD20+ NHL
(n=165)

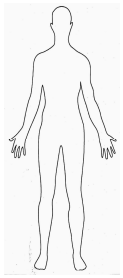


NK cell
CD137
expression

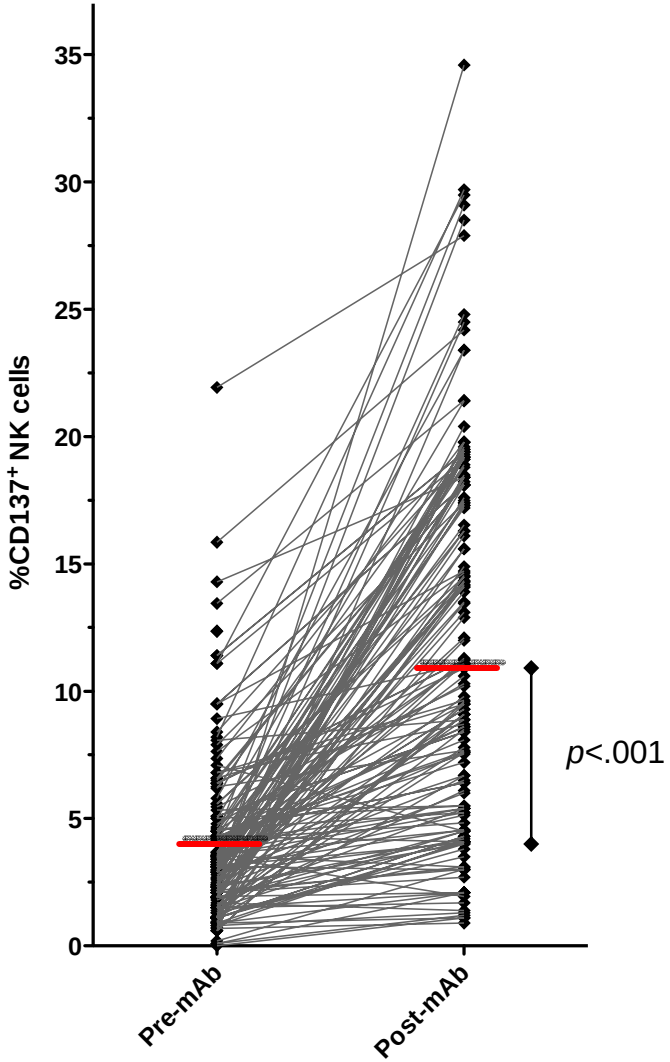


Bedside to Bench Lessons Critical to Clinical Translation

EGFR⁺
Head & Neck
HER2⁺ Breast
CD20⁺ NHL
(n=165)

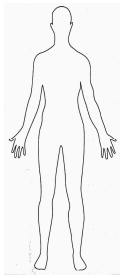


NK cell CD137 expression

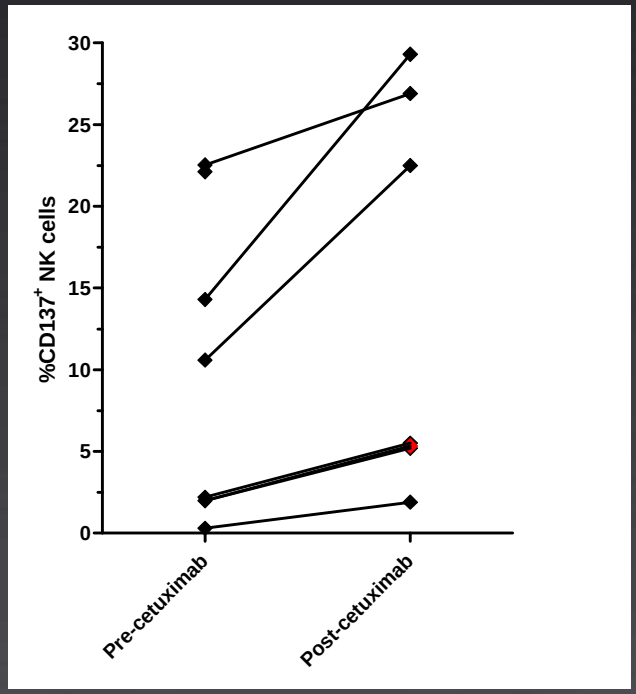


Bedside to Bench Lessons Critical to Clinical Translation

EGFR$^+$
Head & Neck
HER2$^+$ Breast
CD20$^+$ NHL
(n=7)
FNA



NK cell CD137 expression

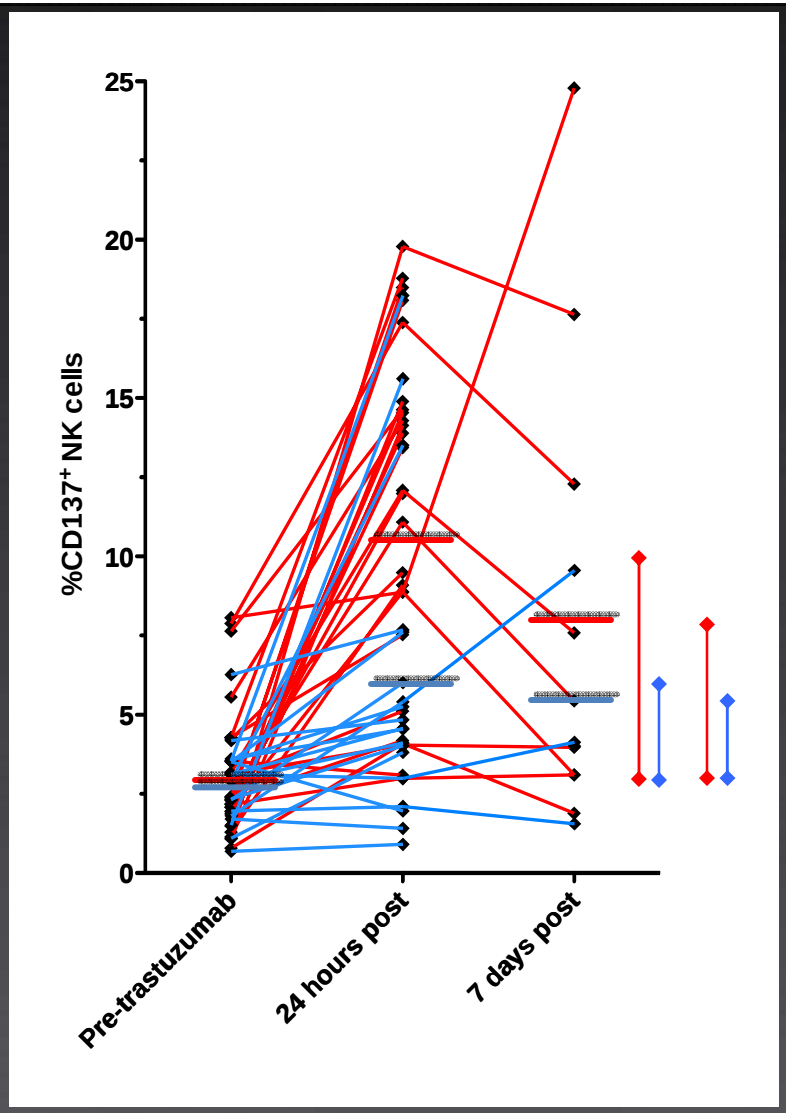


Bedside to Bench Lessons Critical to Clinical Translation – Prior Trastuzumab Tx

HER2+ Breast Cancer

Trastuzumab

NK cell CD137 expression



Minimally Previously Treated
(<5 cycles of trastuzumab)

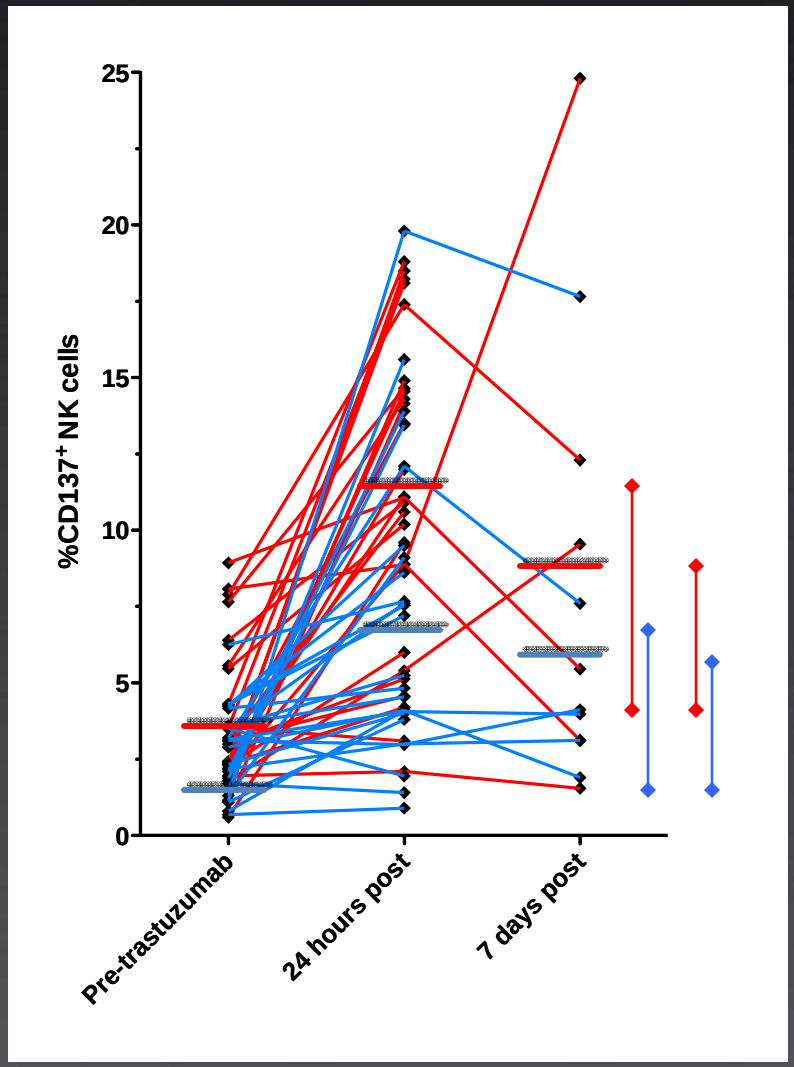
Heavily Previously Treated
(>25 cycles of trastuzumab)

Bedside to Bench Lessons Critical to Clinical Translation – HER2 level

HER2+ Breast Cancer

Trastuzumab

NK cell CD137 expression

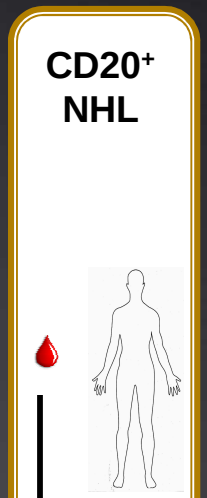


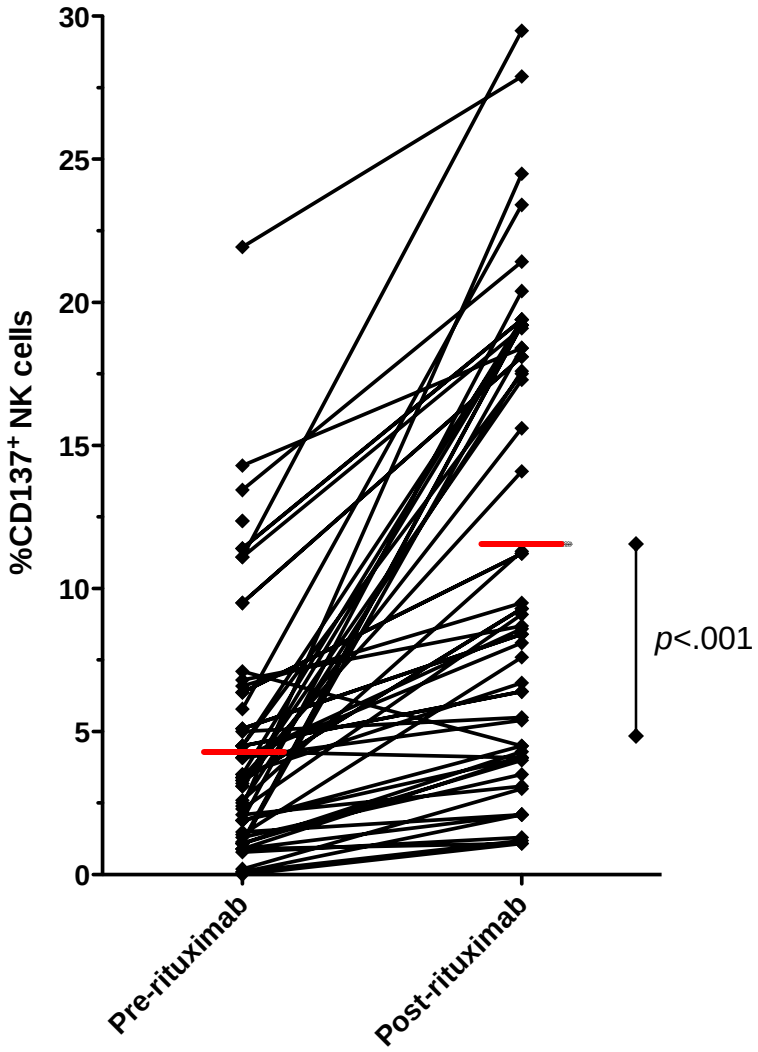
HER2 Level High

HER2 Level Low

BEDSIDE TO BENCH LESSONS – LYMPHOMA IN VIVO

CD20+ Non Hodgkin Lymphoma

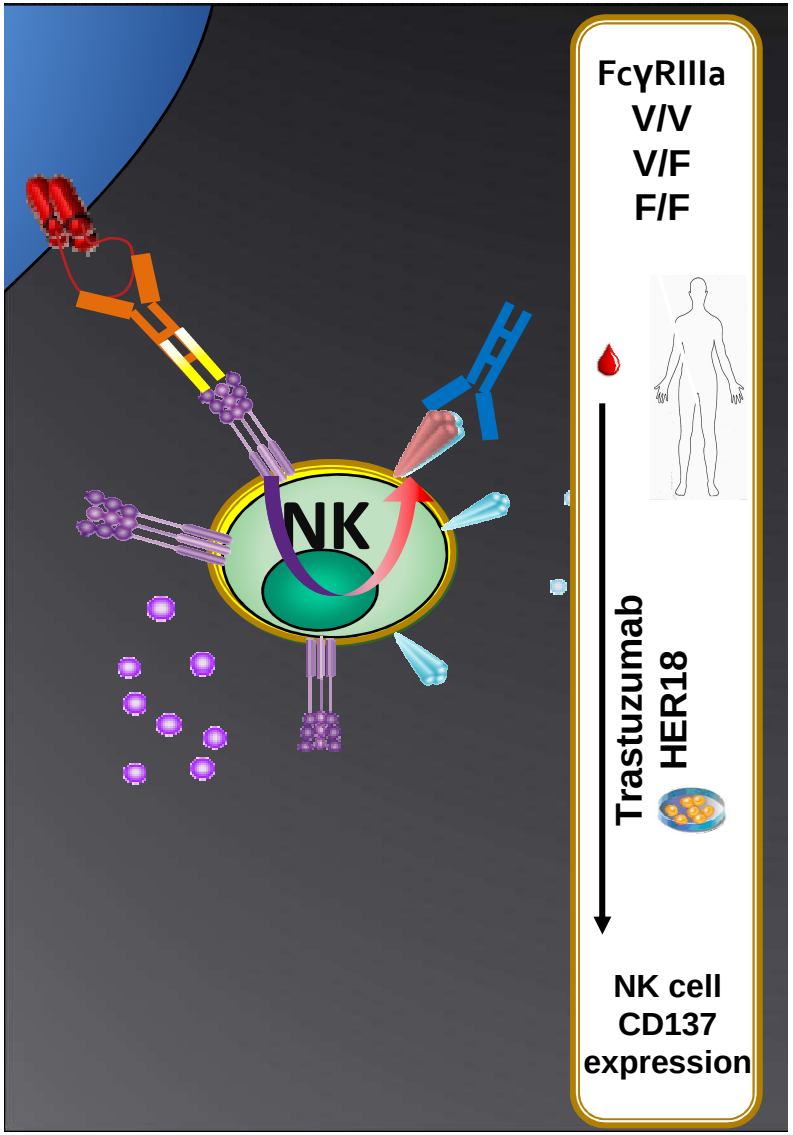


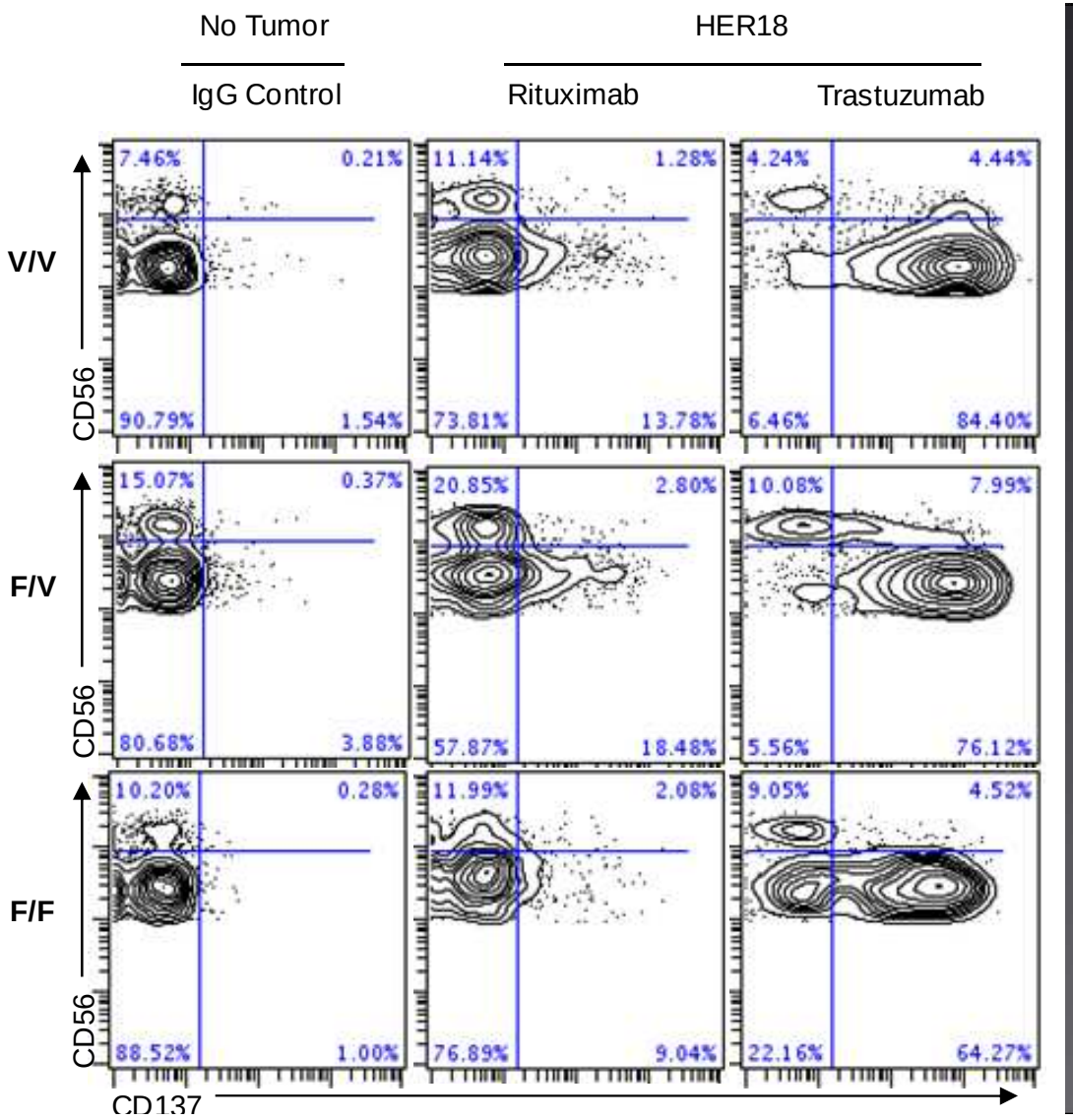


≥10% Circulating Tumor Cells

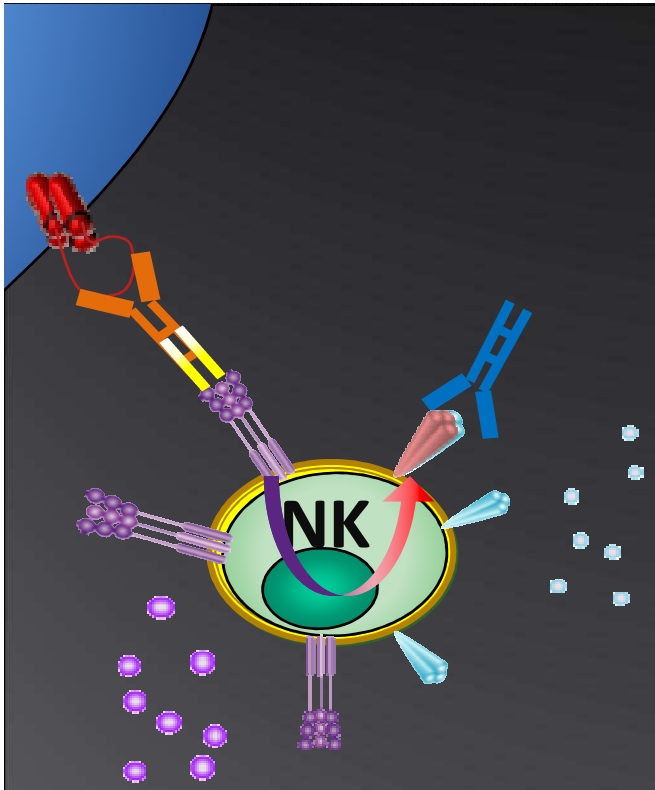
<10% Circulating Tumor Cells

Bedside to Bench Lessons Critical to Clinical Translation – FcγRIIIa Polymorphism

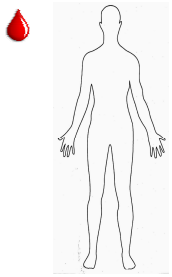




Bedside to Bench Lessons Critical to Clinical Translation – FcγRIIIa Polymorphism



EGFR+
Head & Neck
HER2+ Breast
CD20+ NHL
(n=165)



Cetuximab
Trastuzumab
Rituximab

NK cell
CD137
expression