University of Wisconsin
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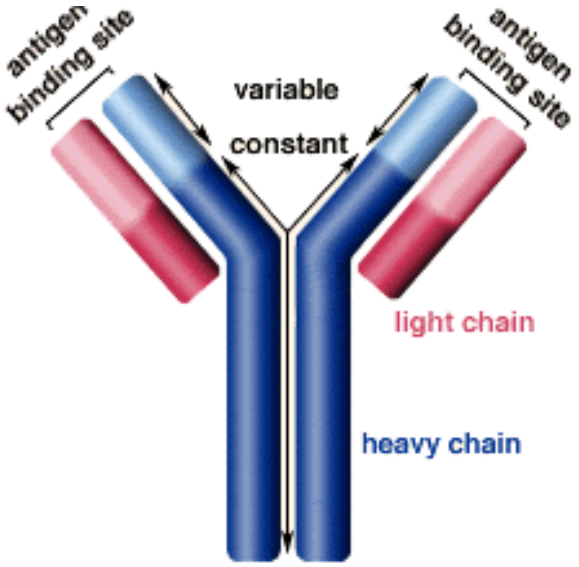
Comprehensive Cancer Center

UW Health
American Family
Children's Hospital

Tumor Immunology on the Horizon

Nov. 12, 2016
SITC Meeting
National Harbor, MD



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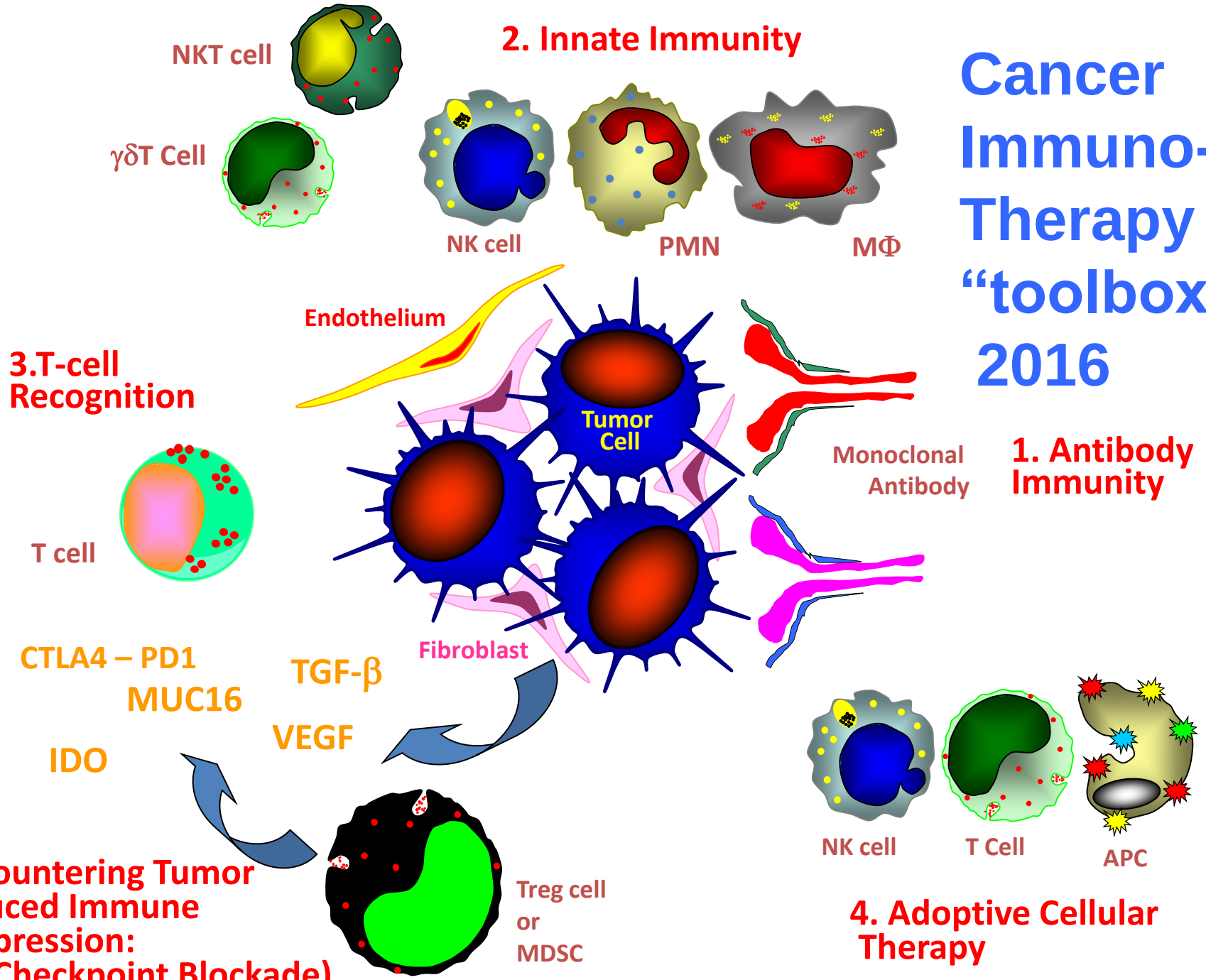
Disclosure:

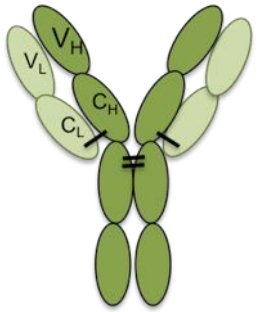
Neither I nor any member of my family has a financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this presentation

Cancer Immuno-Therapy "toolbox" 2016

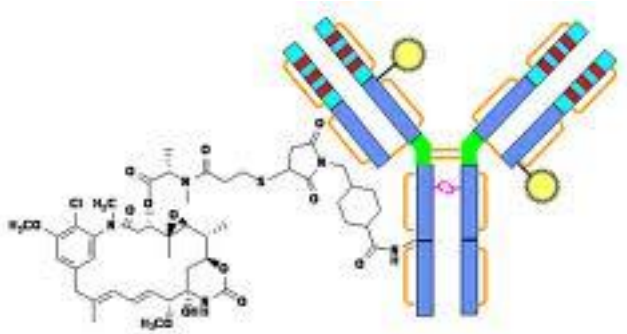


Examples of monoclonal antibody (mAb) -based anti-cancer therap

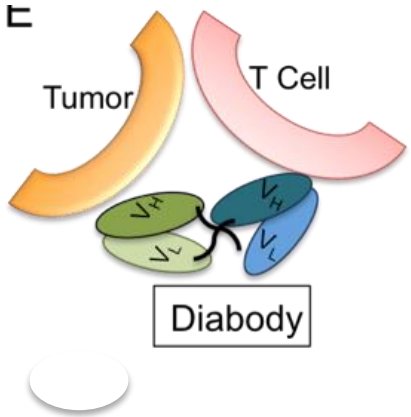
scFv



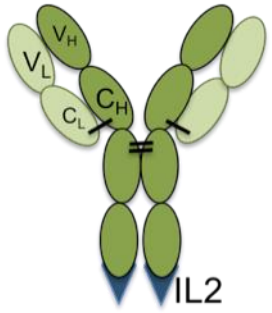
Monoclonal Antibody



mAb linked to drug, toxin, or radionuclide



Diabody



Immunocytokine

Targets for anti-cancer mAbs:

Molecules selectively expressed on tumor cells or Tumor stroma or vessels : Cancer Antigens
(ie: Rituximab, Dinutuximab, etc.)

Or

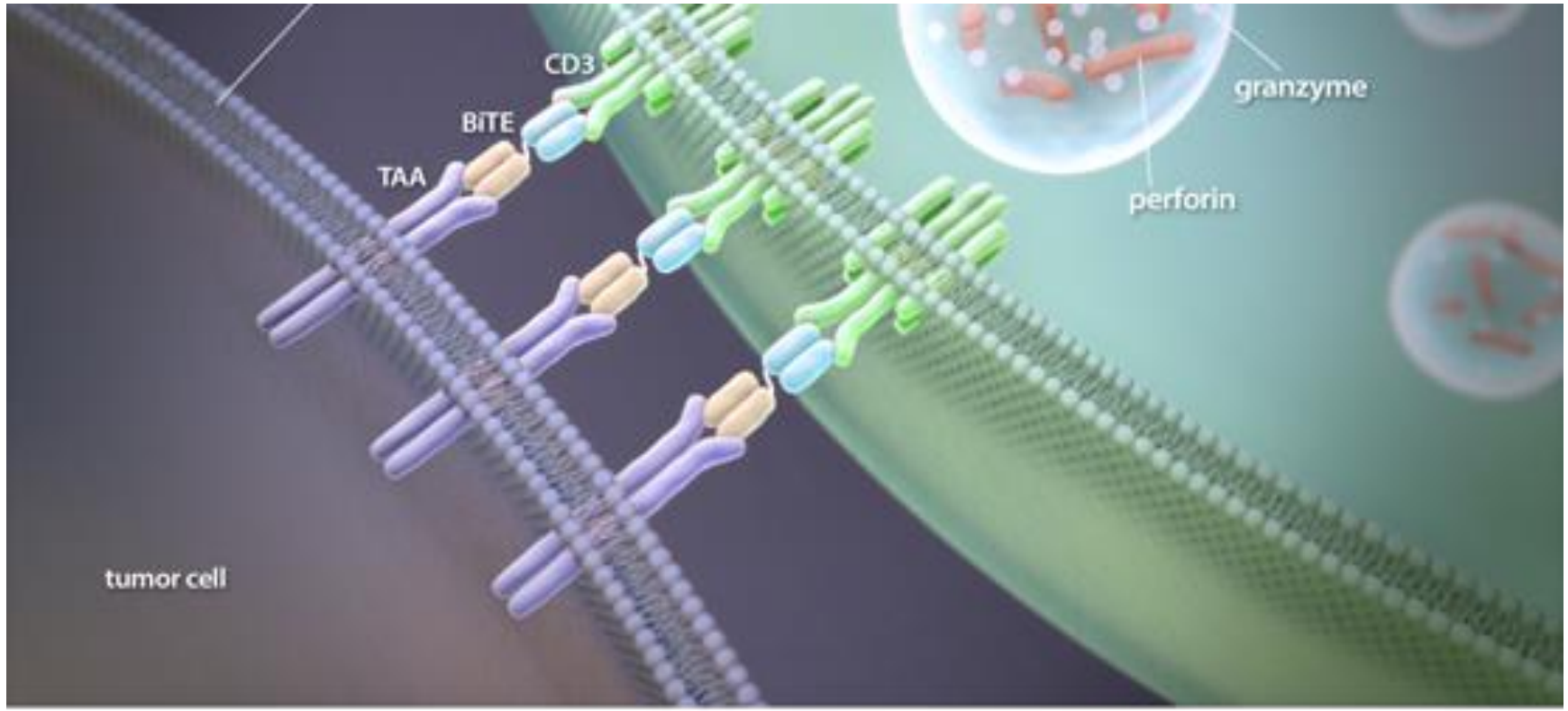
Molecules expressed on immune cells that regulate Immune function: Immunoregulatory targets
"Checkpoint Blockade"
(ie: Ipilimumab, Nivolumab, etc.)

BLINATUMOMAB

Bi-specific T-cell Engager Technology (BiTE*)

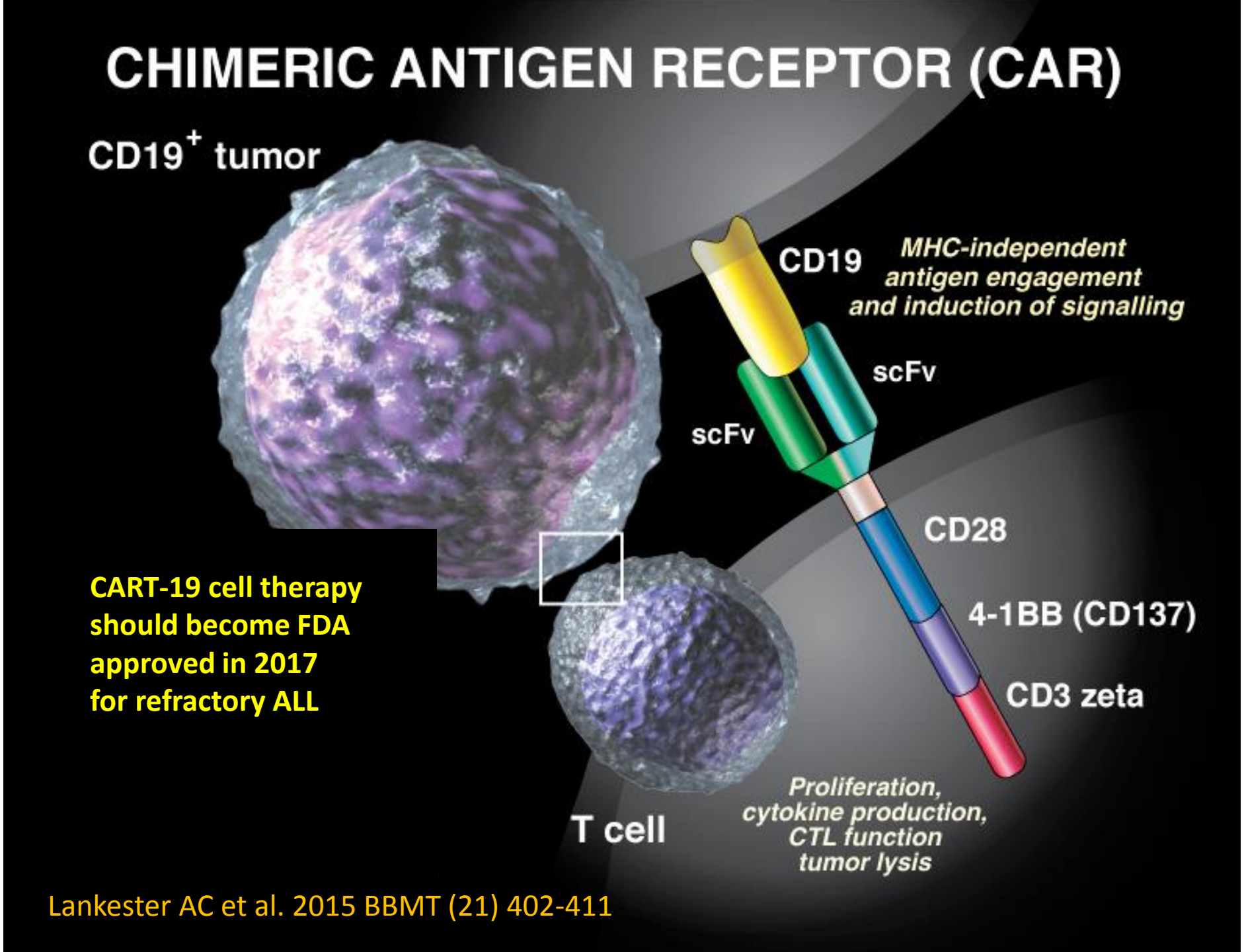
Micromet (Baeuerle, P. et al) – [Purchased by Amgen]:

FDA Approved as “breakthrough therapy” for ALL 2015

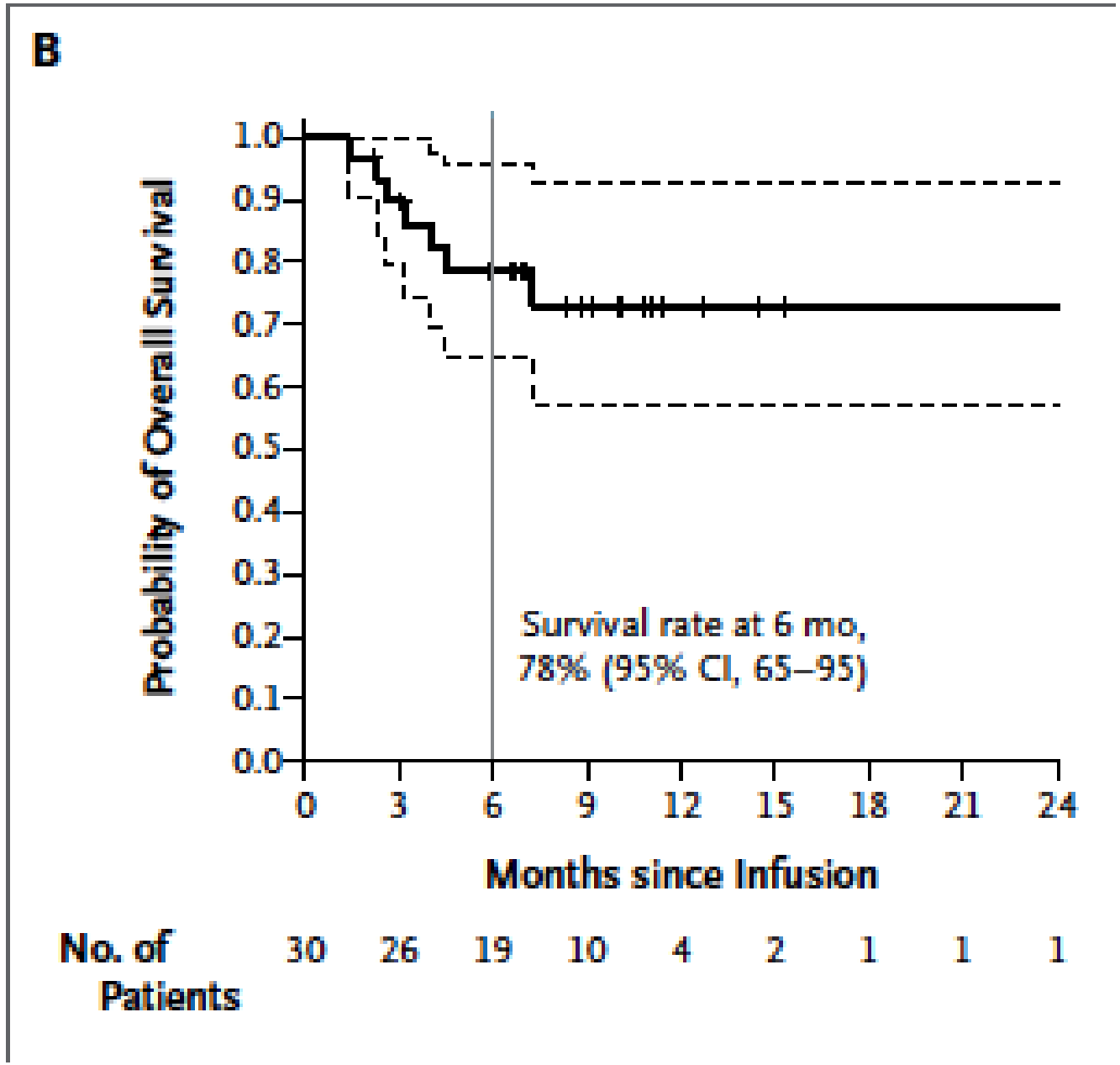


Tumor cells develop a way to escape notice by T cells.

BiTE molecules act as bridges that allow the T cells (right) to detect the tumor cells (left).



Lankester AC et al. 2015 BBMT (21) 402-411

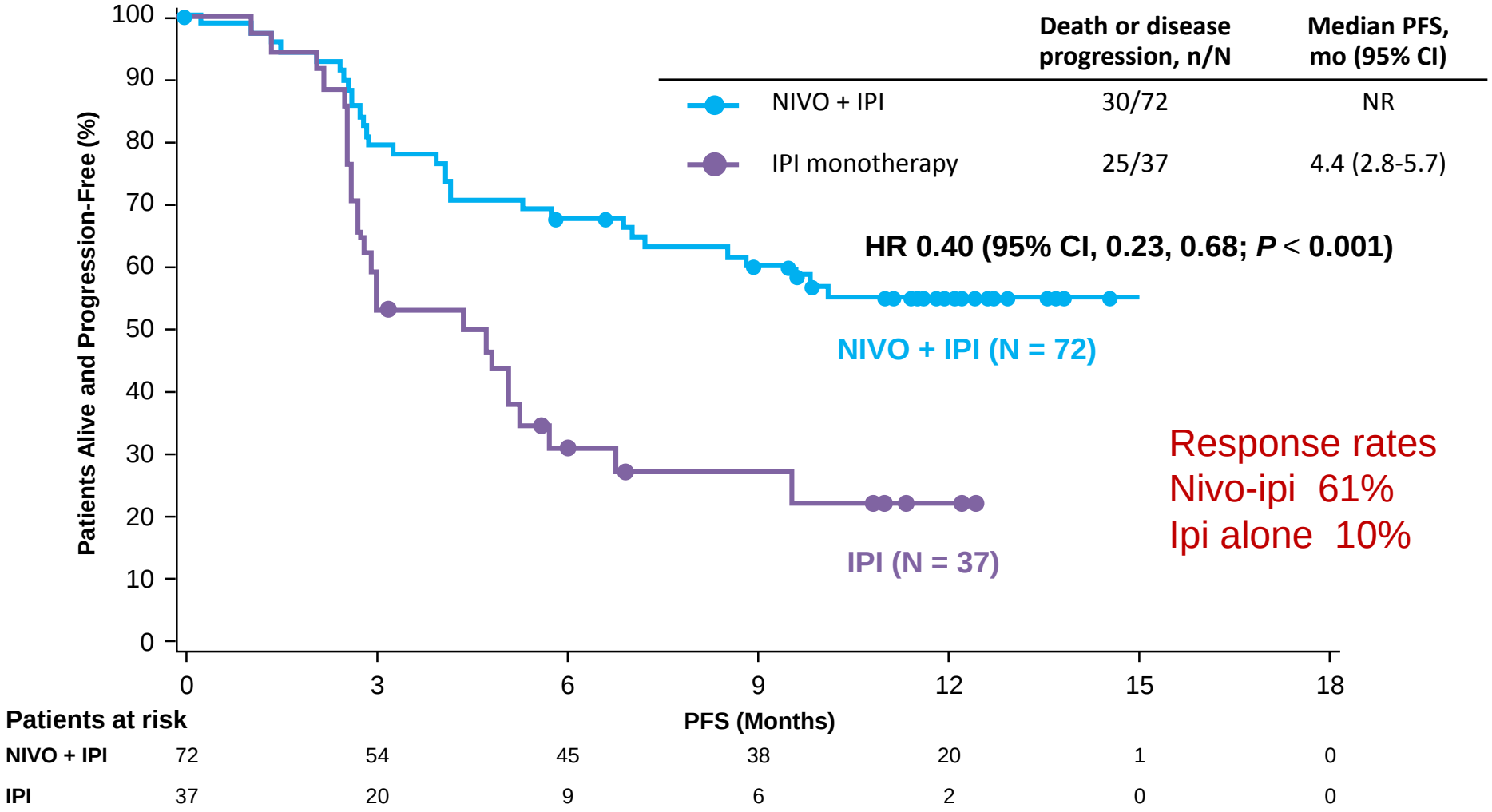


Clinical effects of anti CD19 CART therapy for relapsed ALL

Maude et al. 2014 NEJM

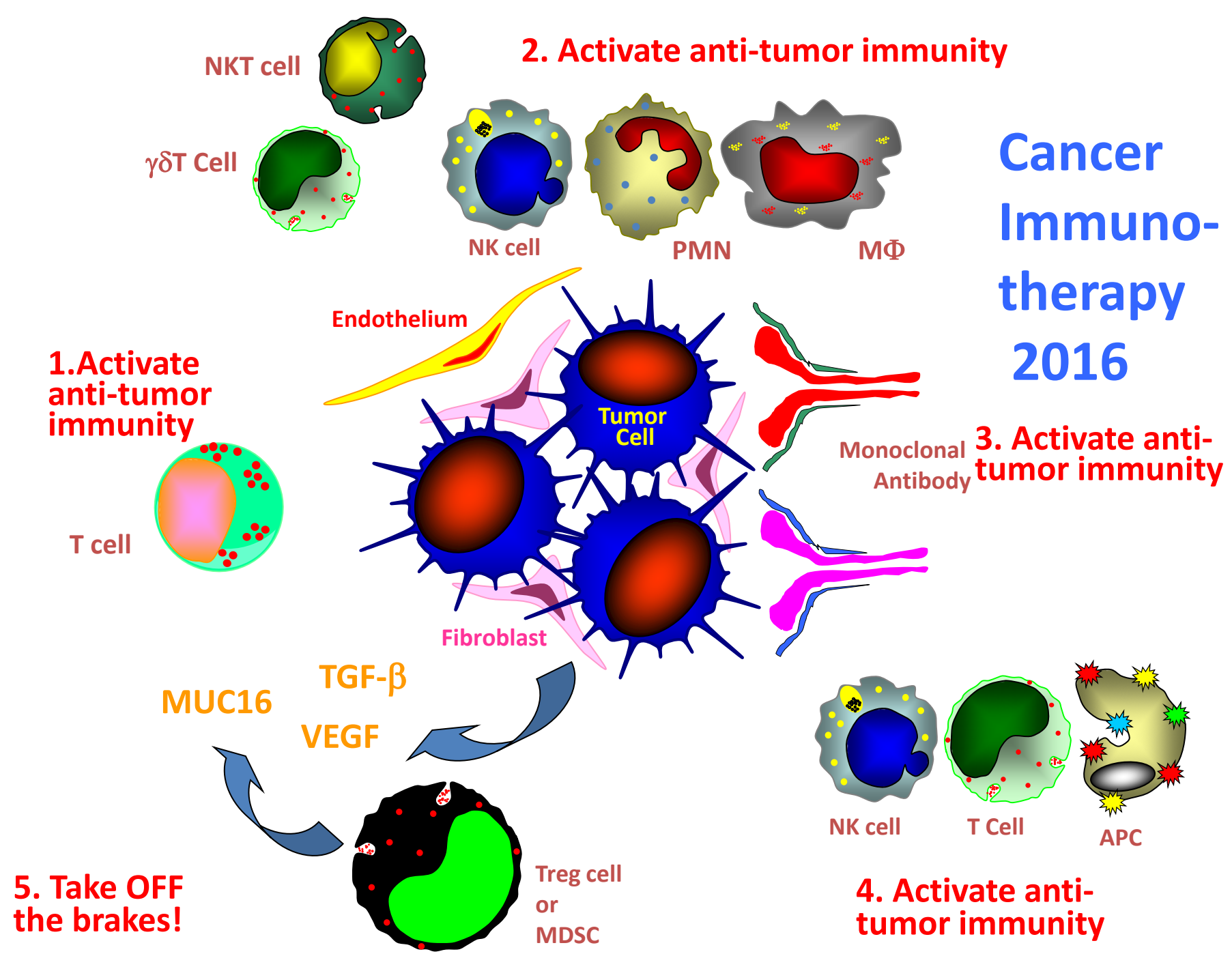
Combination Therapy (2 forms of "checkpoint blockade)

Nivolumab +Ipilimumab vs Ipilimumab alone



Response rates
Nivo-ipi 61%
Ipi alone 10%

Postow et al NEJM, 2015



Cancer Immuno-therapy 2016

On The Horizon:

Combining:

1. Different forms of Immunotherapy

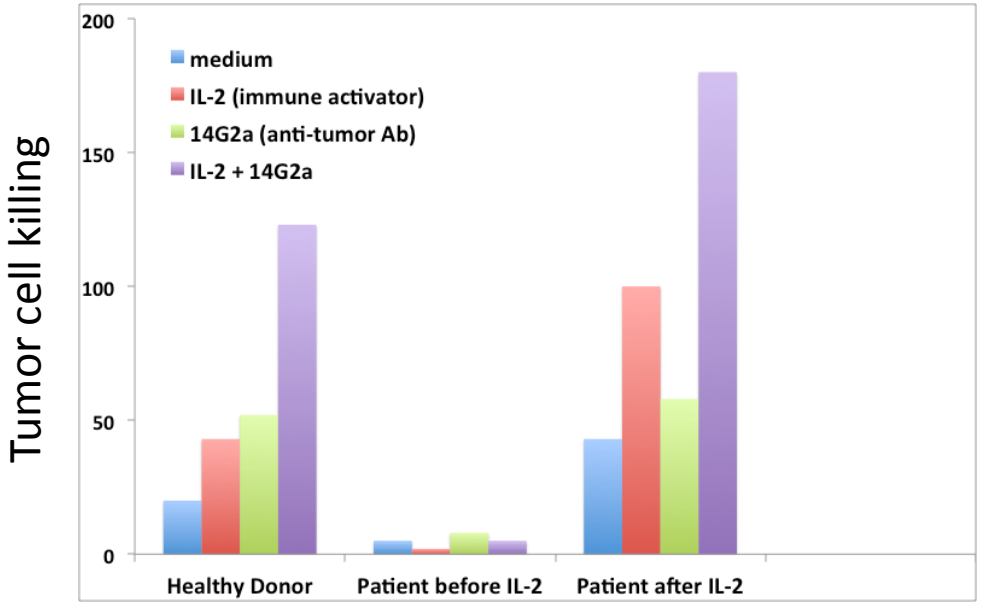
and

2. Immunotherapies with "conventional" treatments:

2 "off the shelf" examples

Interleukin-2 (IL2) activates NK cells to kill neuroblastoma cells coated with an anti-GD2 mAb

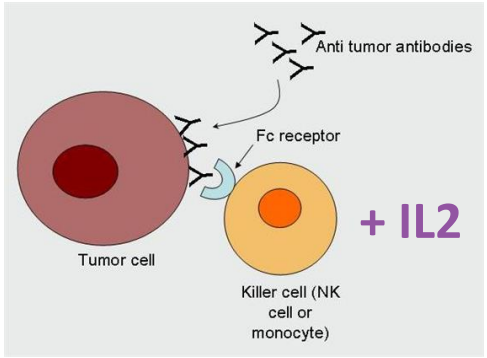
(14.18 mAb, sees GD2 on neuroblastoma, melanoma, sarcomas and some other tumors)



Jackie
Hank PhD

Hank JA, Robinson RR, Surfus J, Mueller BM, Reisfeld RA, Cheung NK, Sondel PM. , Cancer Res. 50:5234, 1990

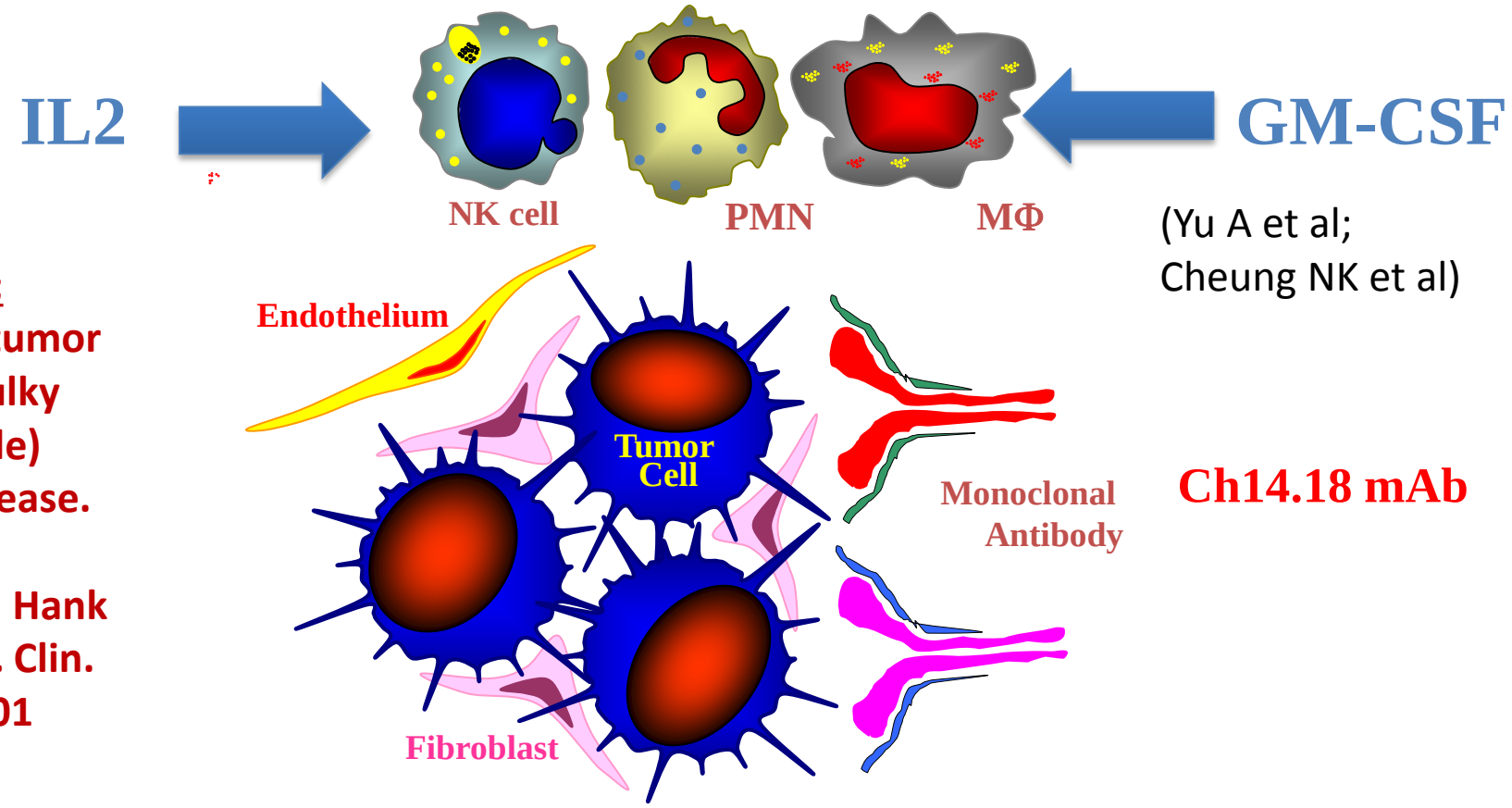
1. NK cells from healthy donors kill best with IL2 AND anti-GD2 mAb
2. NK cells from cancer patients receiving **IL2,** kill best with anti-tumor antibody AND IL2



These in vitro studies showed that adding IL2 + mAb augments NK-mediated *Antibody Dependent Cell-mediated Cytotoxicity (ADCC)*

How to move this into effective clinical treatment? *(Phase I/II studies at UWCCC and COG)*

COG's approach to Innate Immunity and ADCC for NBL (ANBL0032)



(Yu A et al;
Cheung NK et al)

1993-2003;
Little anti-tumor effect in Bulky (measurable) Clinical Disease.

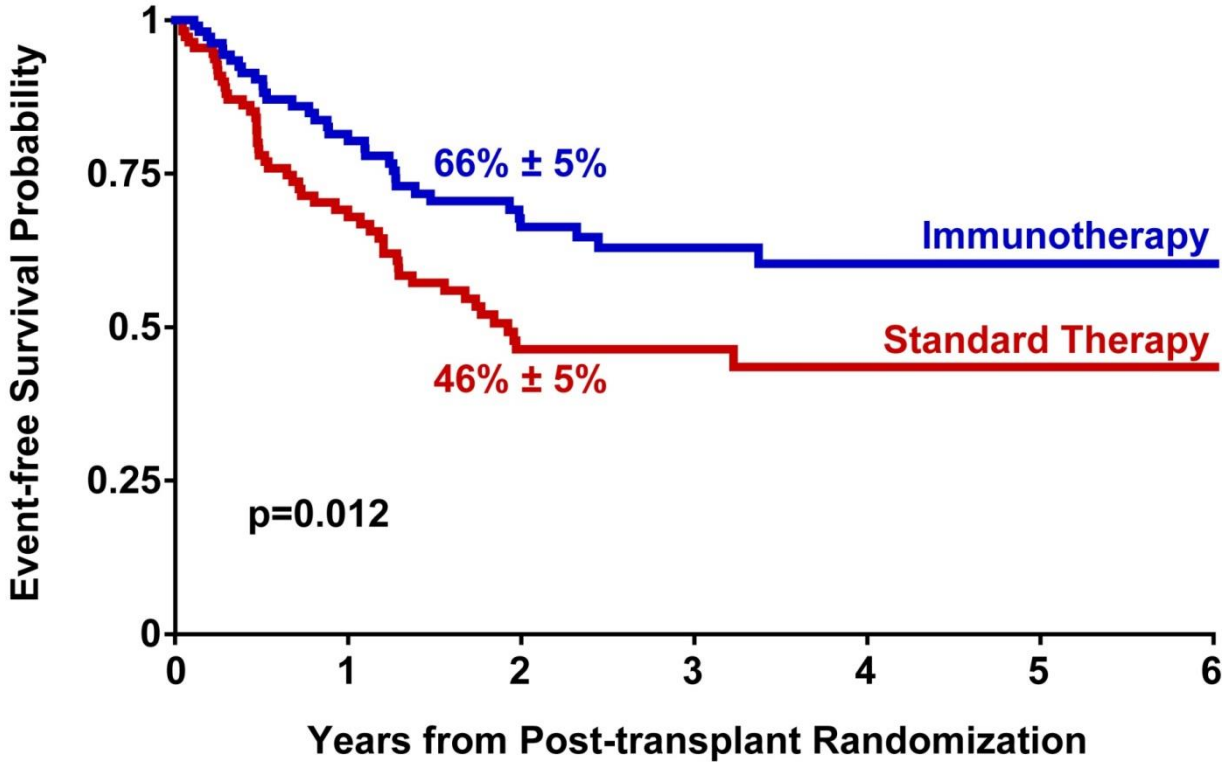
Sondel and Hank Heme-Onc. Clin. N. Am, 2001

Ch14.18 mAb

1. Activate Multiple Pathways of ADCC (ie: stimulate and engage several different populations of ADCC effector Cells)
2. Administer Immunotherapy in Minimal Residual Disease

[ie: patients in remission, at risk of relapse, *to circumvent poor penetration, Tregs, myeloid derived suppressor cells (MDSCs)]*

EFS for 226 Children: Immunotherapy vs No Immunotherapy

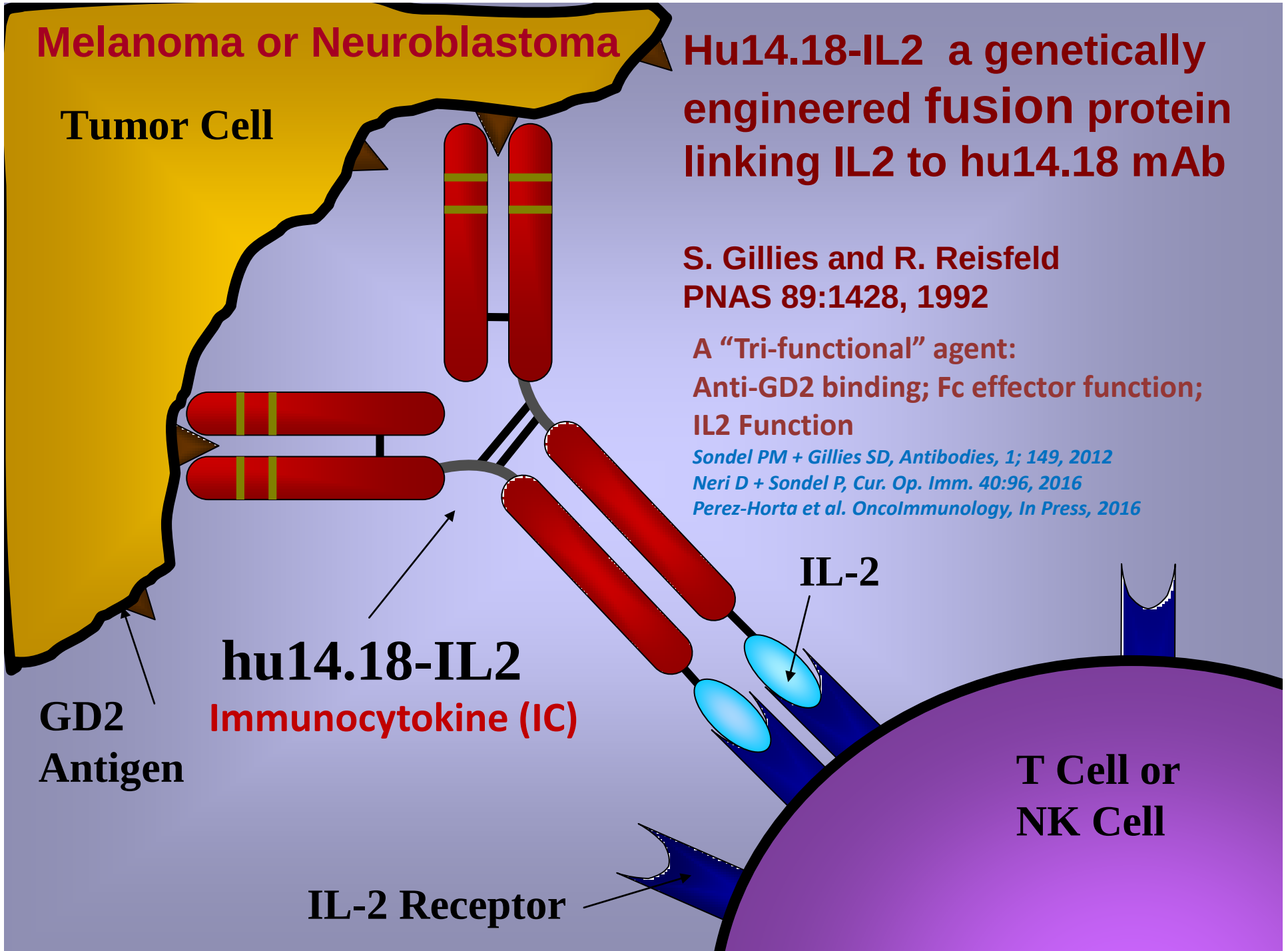


The NEW ENGLAND JOURNAL of MEDICINE

Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman S, Chen H, Smith M, Anderson B, Villablanca J, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM.

New Eng. J. Med.
335: 1324, 9/30/10

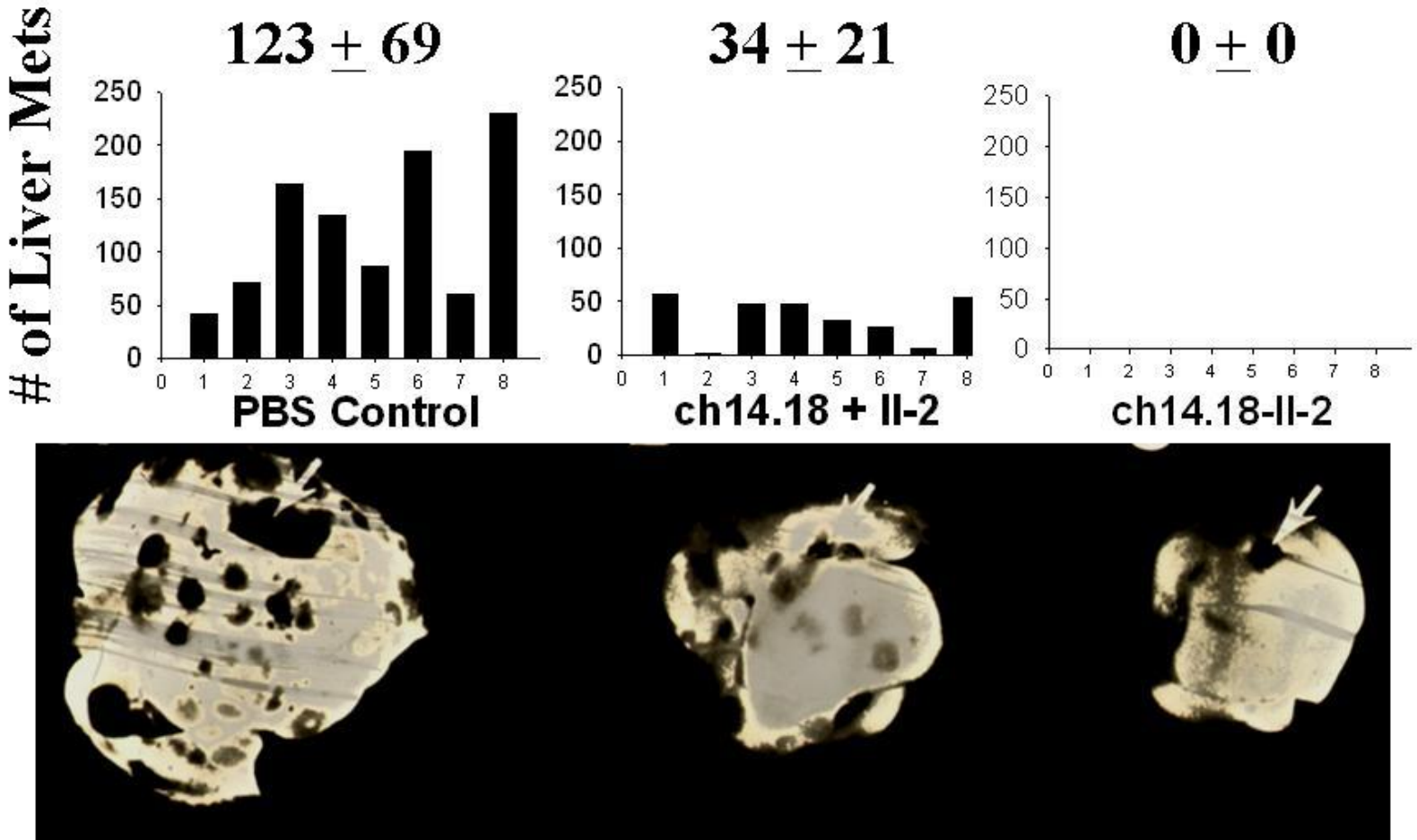
- **New Standard (Dinutuximab-FDA approved 2015) post-consolidation for Neuroblastoma**
- **Event-free survival (for patients that enter remission) still only 50-60%**
- **30-40% of patients don't achieve remission (are not eligible)**
- ***More improvements needed (for patients in remision, and those that don't achieve remission) !***


Melanoma or Neuroblastoma
Tumor Cell
Hu14.18-IL2 a genetically engineered fusion protein linking IL2 to hu14.18 mAb
S. Gillies and R. Reisfeld
PNAS 89:1428, 1992
A "Tri-functional" agent:
Anti-GD2 binding; Fc effector function;
IL2 Function
Sondel PM + Gillies SD, Antibodies, 1; 149, 2012
Neri D + Sondel P, Cur. Op. Imm. 40:96, 2016
Perez-Horta et al. OncoImmunology, In Press, 2016
IL-2
hu14.18-IL2
Immunocytokine (IC)
GD2
Antigen
T Cell or
NK Cell
IL-2 Receptor

Improving outcome in the setting of minimal residual disease (MRD; remission):

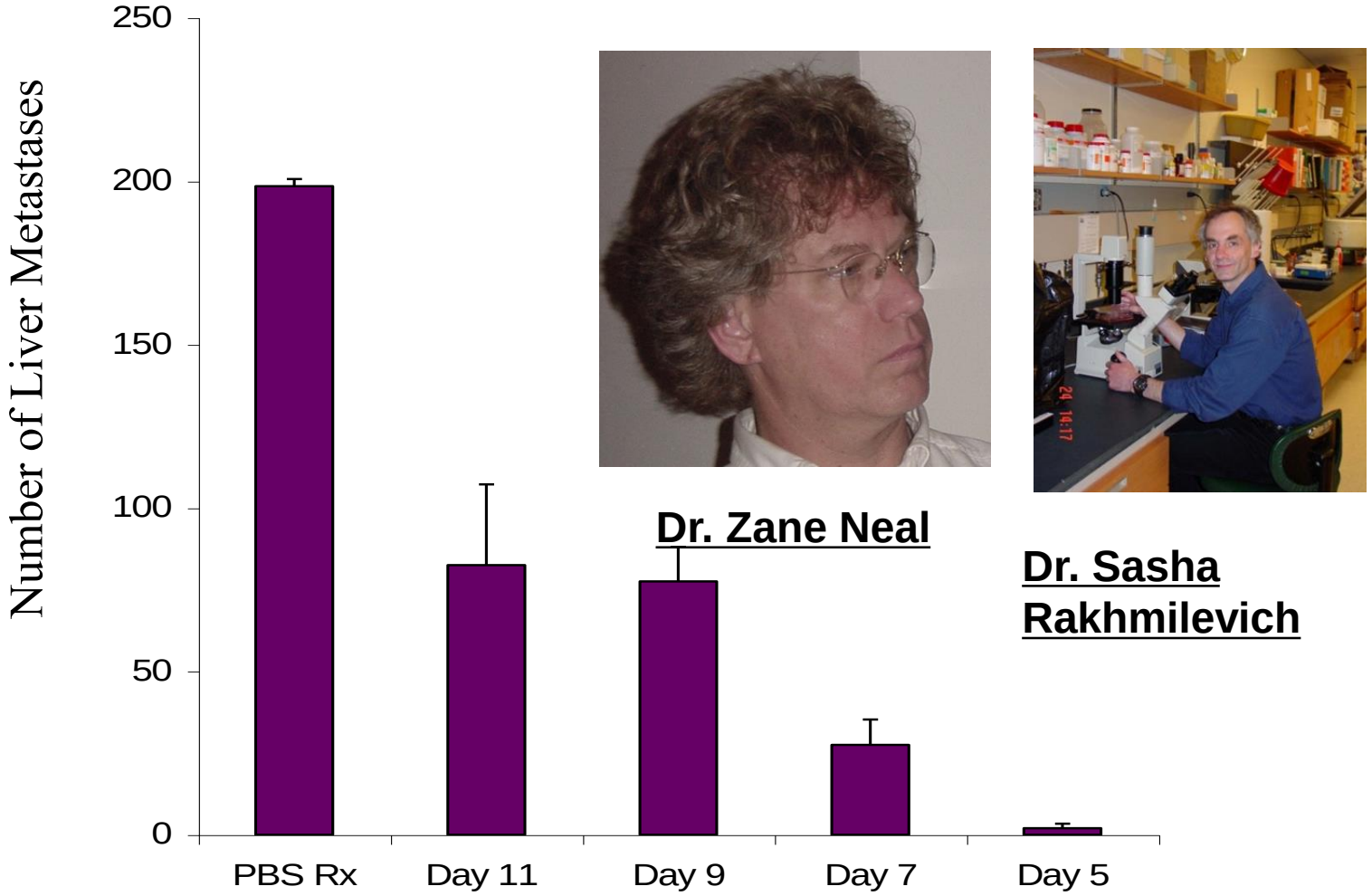
Efficacy of ch14.18-IL2 Immunocytokine against Murine Neuroblastoma Liver Metastases

Lode et al: *J. Natl. Cancer Inst.* 89:1586, 1997



Effective anti-GD2 Immunotherapy: Dependence on Minimal Tumor Status

(IV admin). Neal ZC,et al Clinical Cancer Research, 10:4839, 2004



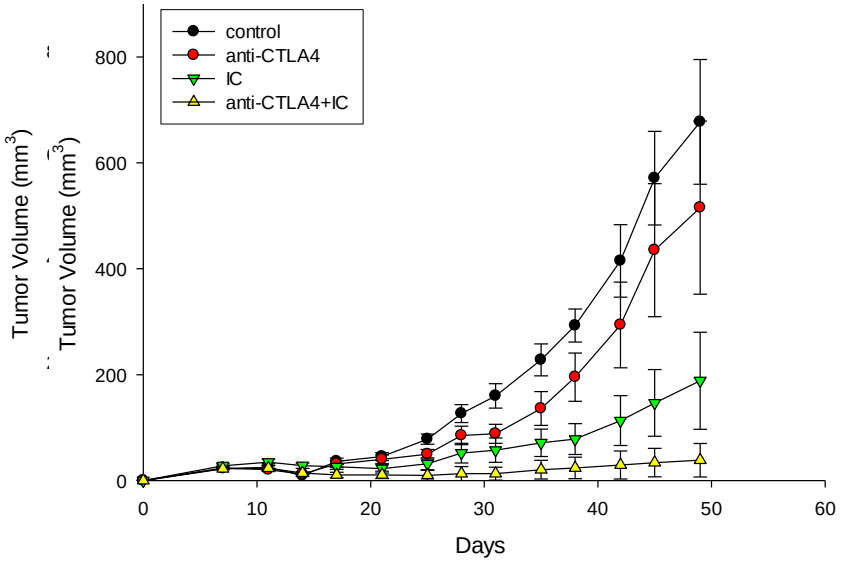
hu14.18-IL2 (10ug/d) for 5 days starting on day 5, 7, 9, or 11 following 5 X 10^5 NXS2 cells injected on day 0, and harvested on day 28.

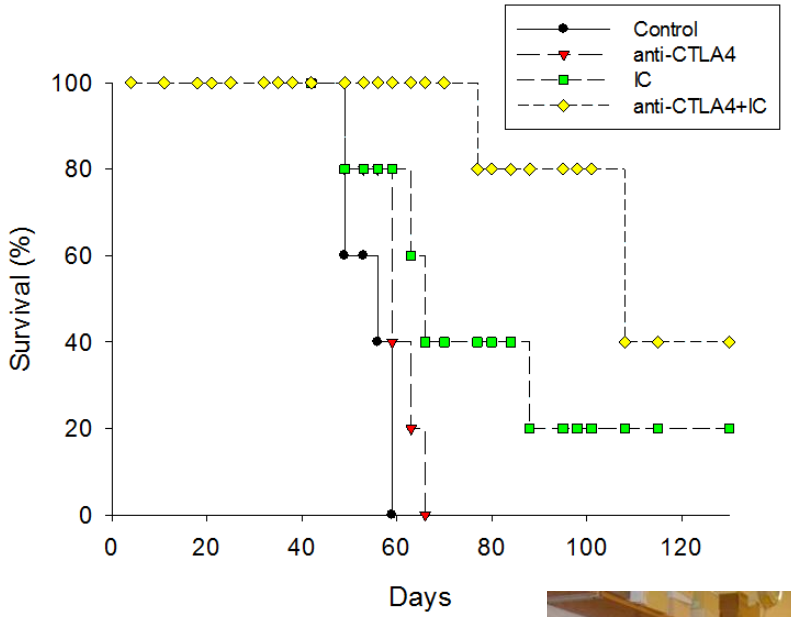
Anti-tumor activity seen clinically in "non-bulky" Neuroblastoma (2 COG Phase-2 Trials): Shusterman S et al. J.Clin. Oncol. 28:4969, 2010, and ASCO abstract 2015 (not shown)

Can Intratumoral Injection (IT) + Checkpoint Blockade enhance this Immunocytokine (IC) response?

[ALL SUBSEQUENT SLIDES WITH B78 (GD2+B16) MEL (weakly immunogenic)]

Effect of anti-CTLA-4 mAb and IT-IC are synergistic on d-7 B78 (<50mm^3) tumors





Day 0: B78 s.c. (2x10^6/mouse)

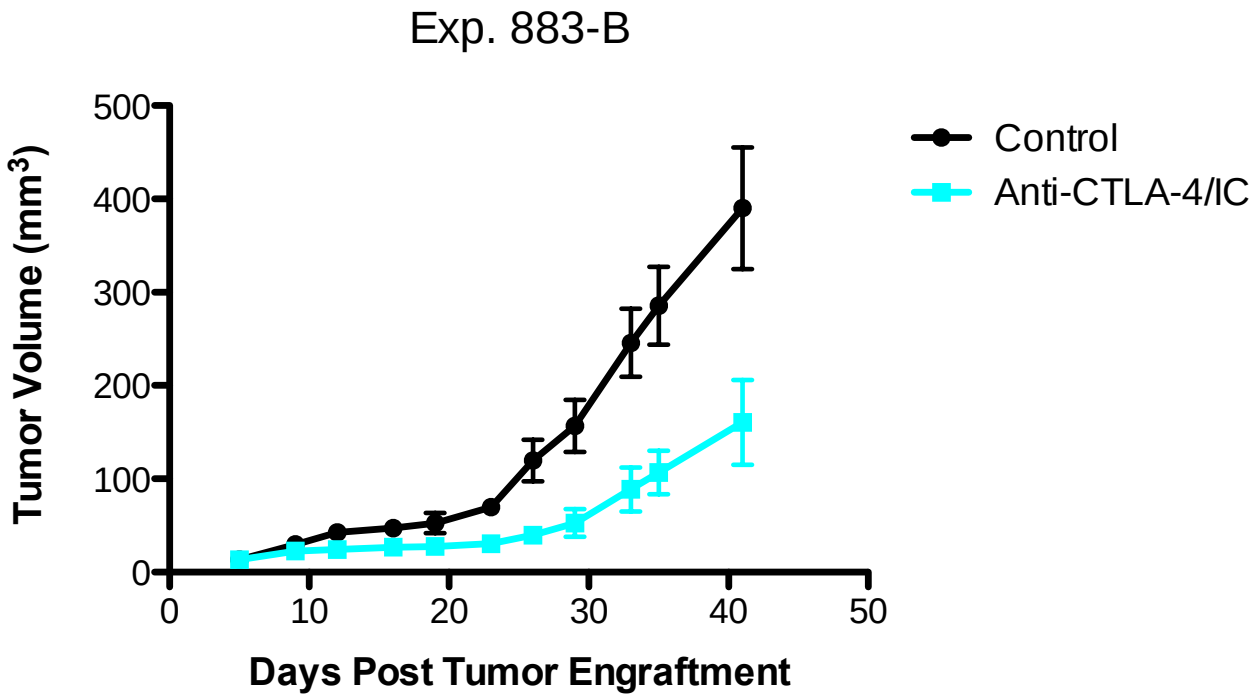
Day 7-11: 14.18-IL2 i.t. (5 mcg/mouse)

Day 7,9,11,14,16,18: anti-CTLA4 i.p. (200 mcg/mouse)

Alexander Rakhmilevich MD PhD et al, in revision, 2016;

Beneficial effect of IT-IC + anti-CTLA-4 is LESS EVIDENT on more advanced (d12) B78 tumors

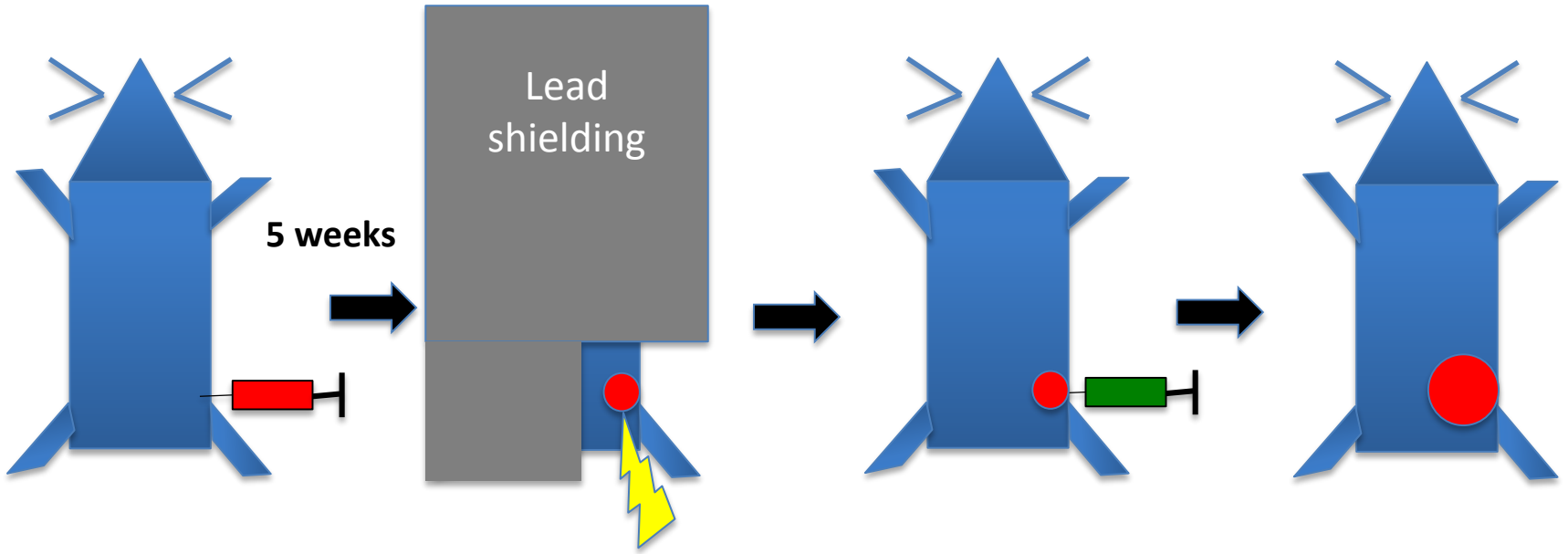
Larger (d-12) tumors grow more slowly (but still grow)



Day 0: B78 s.c. ($2x10^6$/mouse)
IC i.t. (5 mcg), **d.12-16**;
anti-CTLA-4 i.p., d. 12,14,16,19,26,33

Alexander Rakhmilevich MD PhD et al, in revision, 2016

Can augmented activity to **macroscopic disease** be obtained by combination with immunomodulatory radiation therapy (RT)?



Tumor cells injected in syngeneic mice

DAY 1. Macroscopic tumors radiated to 12 Gy

DAY 6-10. Daily intra-tumor injections of IC

Tumor growth and animal survival monitored

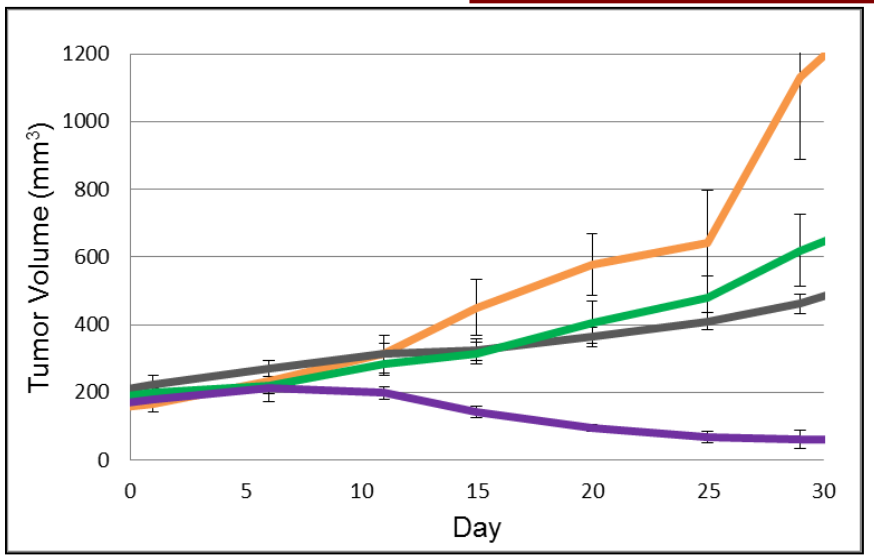
Tumor cells

B78 melanoma – poorly immunogenic B16 melanoma that expresses GD2

(transfected with β-1,4-N-acetylgalactosaminyltransferase)

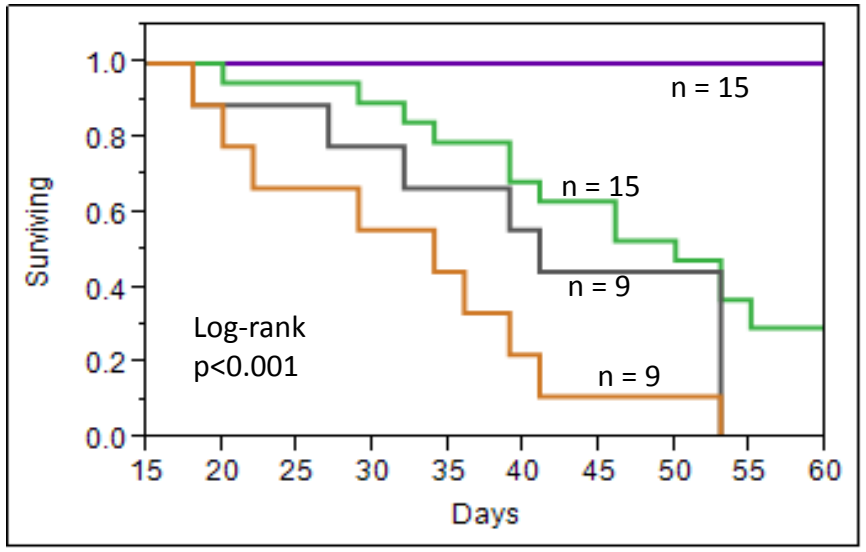
Zach Morris MD PhD et al
Can. Res. May, 2016

Radiation and IT hu14.18-IL2 results in cure of most ***5-week (200mm³)*** B78 tumors



Day 30 mean tumor volume (mm^3) +- SE
1161 +/- 233
619 +/-106
462 +/- 29
61 +/- 26**

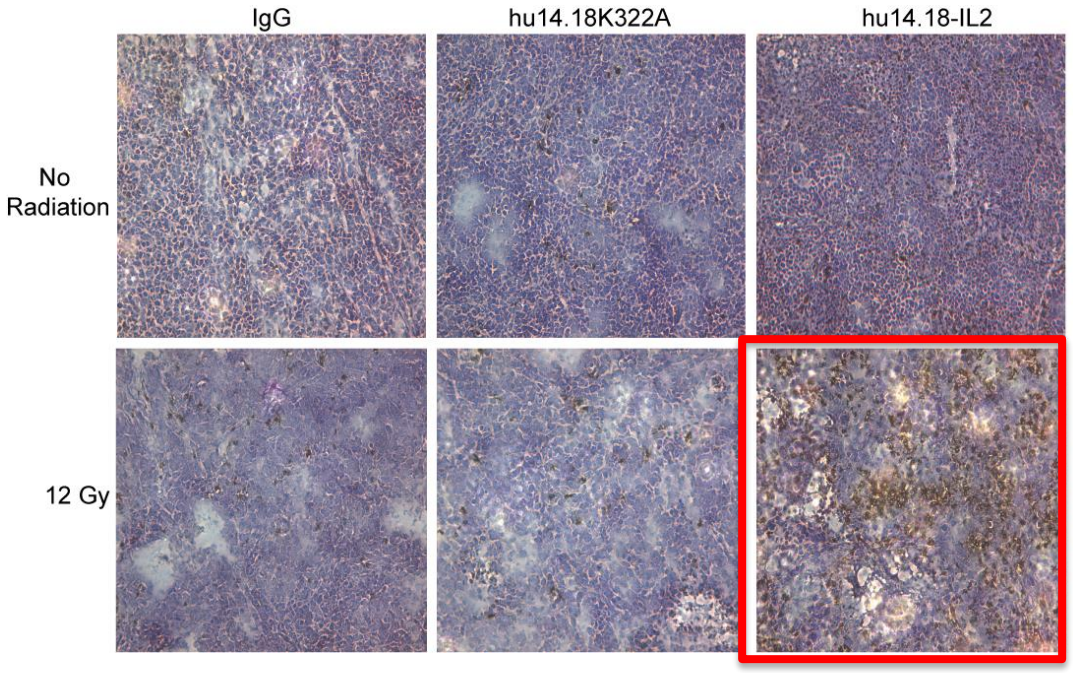
12 Gy + hu14.18-IL2
12 Gy + IgG
hu14.18-IL2
IgG

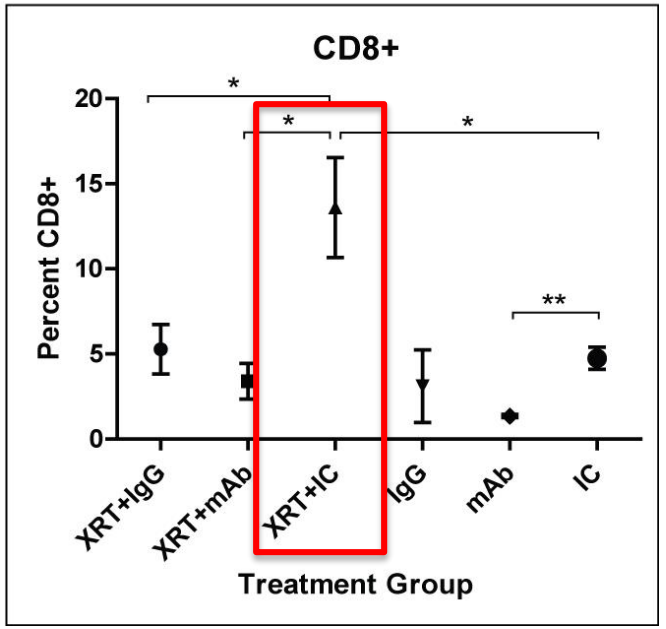


* $p < 0.05$

**** 73% (11/15)** of mice had durable complete tumor regression vs. none of the control mice

RT + IT-IC increases tumor infiltration by CD8+ T cells



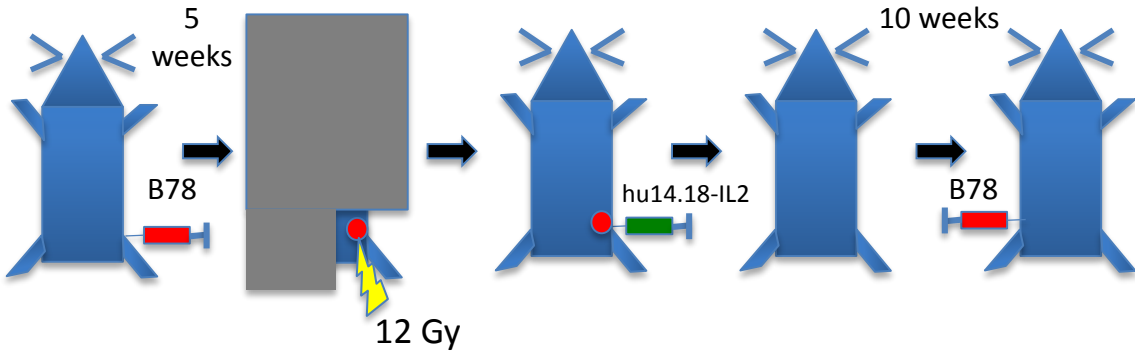


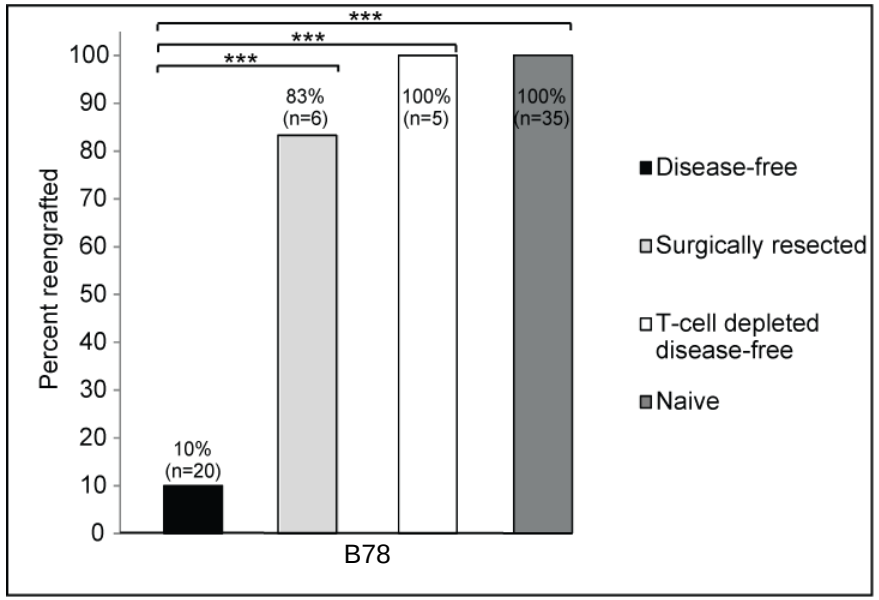
Day 12 post radiation
B78 melanoma tumors

* $p < 0.05$

RT + IT-IC induces a tumor-specific memory T cell response

(In Situ Vaccine Effect)

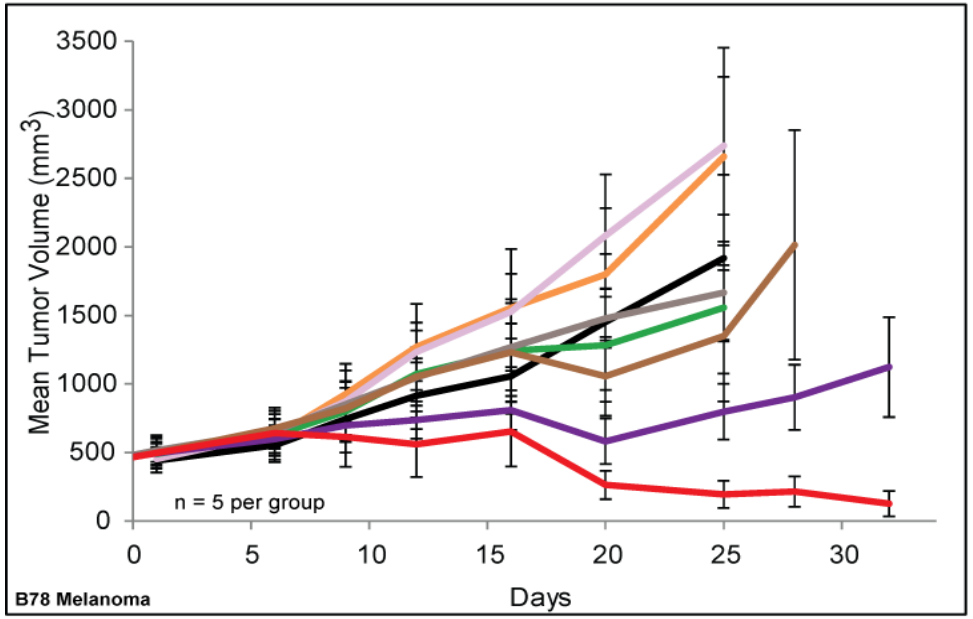


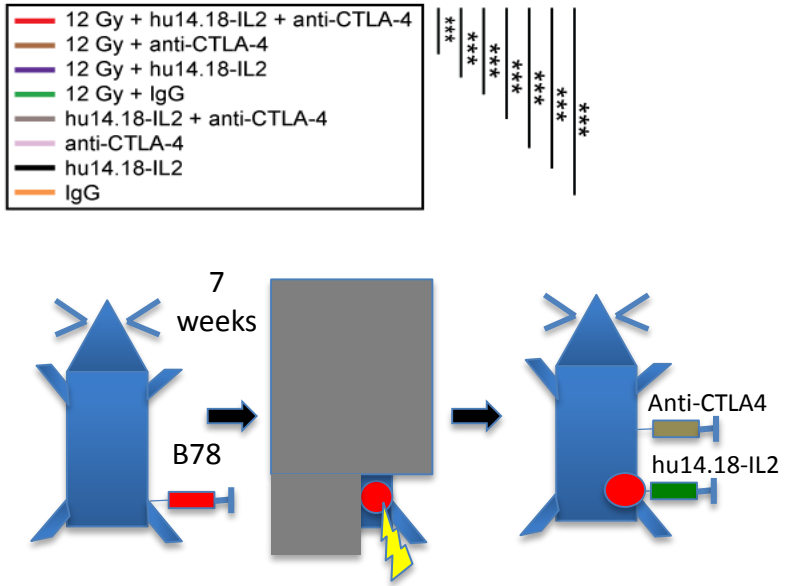


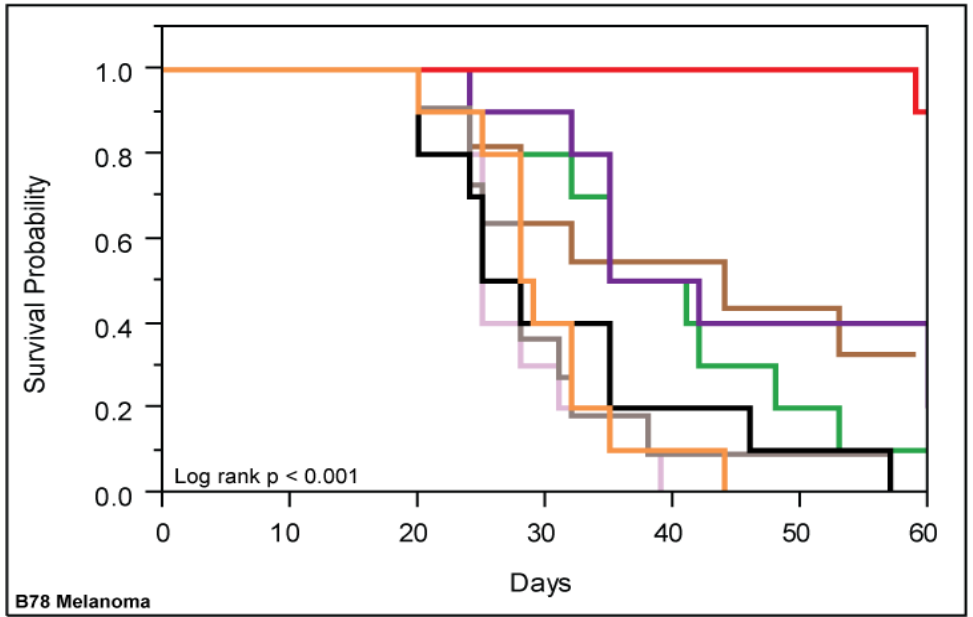
*** $p < 0.001$

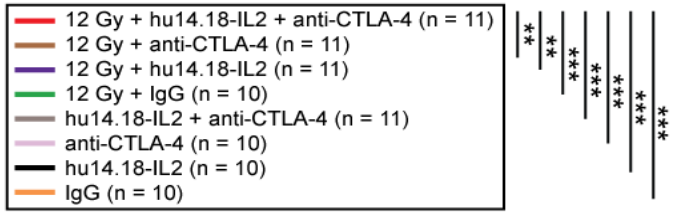
B16 is parent to B78, but is GD2-
(9 of 12 mice that resist B78 now resist B16-"epitope spread")
Panc02 is syngeneic to but a distinct tumor from B16/B78

For very large (**7-week, 500 mm^3**) tumors combining radiation, hu14.18-IL2 and anti-CTLA4 checkpoint blockade improves tumor response and animal survival









B78 Melanoma ~ 7 weeks prior to treatment
Radiation: 12 Gy x 1 – Day 1
IC : 50 µg /mouse IT - daily Days 6-10
anti-CTLA4 IgG2A: 200 µg /mouse IP – Days 3, 6, 9

First clinical testing of the combination of:

1. Radiation;

2. Anti-tumor Antibody/IL2 Immunotherapy &

3. Taking off the brakes (checkpoint blockade)

In development:

A. In childhood cancer (neuroblastoma)

B. In Melanoma

Lessons and Take Home Messages

- Key points
  - Multiple different types (mechanisms) of immunotherapy, already showing antitumor benefit
  - Side effects of immunotherapy are distinct from those with prior standard care (immune mediated, more akin to auto-immunity)

- Potential impact on the field
  - Virtually all tumors that are not curable by surgery alone are (or soon will be) targets for immunotherapy
  - This will change the nature of oncology care (and training)

- Lessons learned
  - Immunotherapy in combination has synergistic anti-tumor effects

Collaborators in our Immunotherapy Research: 2016

- **UWCCC (partial list)**
  - **J Hank**
  - **A Rakhmilevich**
  - **A Erbe**
  - **Z Morris**
  - **KM Kim**
  - **M Albertini**
  - **E Ranheim**
  - **M Patankar**
  - **K DeSantes**
  - **C Capitini**
  - **M Otto**
  - **R Yang**
  - **P Harari**
  - **K McDowell**
  - **W Wang**
  - **Z Perez-Horta**
  - **A Hofges**
  - **M Merdler**
  - **J Weiland**
  - **Jacob Goldberg**
  - **Tyler Van Der Voort**
  - **Patrick Reville**
  - **Several Energetic Undergrads**

INBRACED Consortium

J. Gray
M. Gaze
H. Lode

- **C.O.G. (Many Pediatric Oncologists)**
  - **S Shusterman**
  - **A Yu**
  - **J Maris**
  - **J Park**
  - **W London**
  - **R Seeger**
- **St. Jude**
  - **F Navid**
  - **V Santana**
  - **W Furman**
- **Provenance**
  - **S Gillies**
- **BMS**
  - **Alan Korman**
- **Apeiron**
  - **H Loibner**
- **Scripps**
  - **R Reisfeld**

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- NCI grant R35-CA 197078
- Stand Up 2 Cancer
- Solving Kid's Cancer (SKC)
- Hyundai Hope on Wheels
- St. Baldrick's Foundation
- Alex's Lemonade Stand
- MACC Fund
- University of Wisconsin ICTR Grant
- UWCCC-pilot grant

University of Wisconsin's Childhood Cancer Reunion

KIDS WITH COURAGE V

September 29, 2013
Kalahari Resort and Convention Center
Wisconsin Dells, WI

PROOF THAT CANCER RESEARCH MAKES A DIFFERENCE!

Our Goal: Use Improved Therapy (like Immunotherapy) to help cure cancer for many more children (and adults)!

UW Health
American Family Children's Hospital

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH