Immunotherapy: Revolutionizing the Way We Treat Cancer

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Disclosures

- Honoraria
  - Celgene
- More important I am a transplanter

Immunotherapy: Revolutionizing the Way We Treat Cancer

- Rationale for immunotherapy in cancer
- Immunotherapy
  - Cytokines and Adoptive Immunotherapy
  - Vaccines
  - Monoclonal antibodies
  - Immune Checkpoint Blockade
  - Allogeneic cellular therapy
  - Chimeric antigen receptors

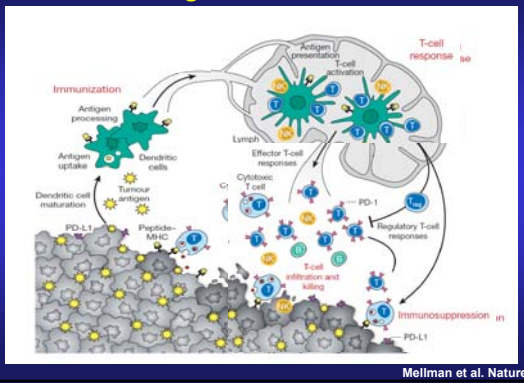
Cancer Immunotherapy Comes of Age

Cancer immunotherapy comes of age
Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]
Nature 2011

Cancer immunotherapy comes of age
Suzanne L. Topalian, George J. Weinner, and Drew J. Pardoll
2011

Cancer immunotherapy comes of age
Steven A Rosenberg
nature CLINICAL PRACTICE ONCOLOGY
2009

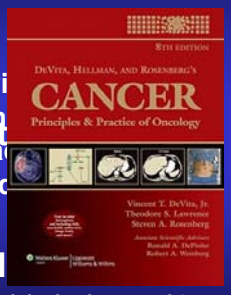
Generation and Regulation of Antitumor Immunity



Mellman et al. Nature 2011

Immunotherapy for Cancer Has a Long History

Cancer Immunotherapy



Steven A. Rosenberg – *Biologic Therapy of Cancer*

Cytokines and Adoptive Immunotherapy

Rosenberg and Adoptive Immunotherapy

- Biologic activity of interleukin-2 (IL-2)

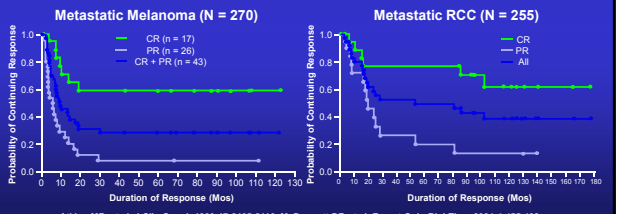
  Rosenberg SA, et al. Science 1984; 223:1412–5.
- Lymphocyte Activated Lymphocytes (LAK):
  - Lytic cell population generated by incubation with IL-2

  Rosenberg SA, et al. N Engl J Med 1985;313:1485-92.
- Tumor-Infiltrating Lymphocytes (TIL)
  - Isolated from tumors and incubated with IL-2

  Rosenberg SA, et al. Science 1986;233:1318-21.

HD IL-2 Therapy: Durable Responses

- HD IL-2 produces durable responses in 6% to 10% of patients with advanced melanoma or RCC
- Few relapses in patients responding for over 2.5 years (likely cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)

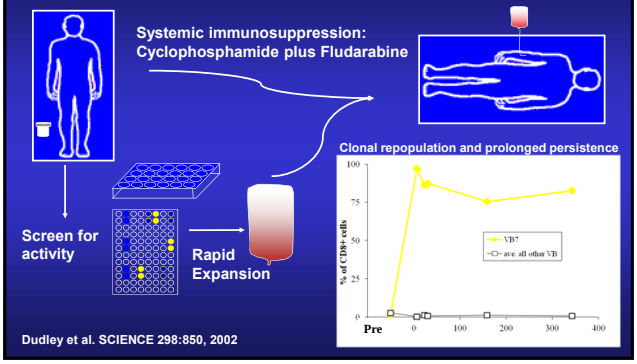


Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116. McDermott DF, et al. Expert Opin Biol Ther. 2004;4:455-468.

HD IL-2 Therapy in Melanoma and RCC

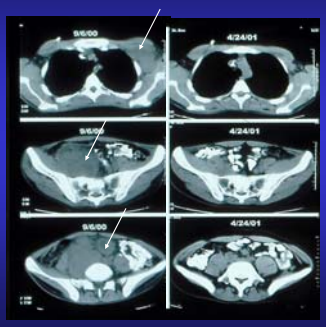
- High-dose IL-2 appears to benefit patients:
  - Toxic
  - Impractical: must be delivered as an inpatient procedure
- Use remains limited to selected patients treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select patients who might benefit from HD IL-2 therapy have produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in patients with cancer, but newer immunotherapies are needed

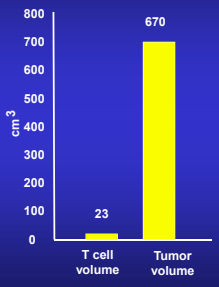
Selected Autolgous T Cell Therapy In Metastatic Melanoma



Dudley et al. SCIENCE 298:850, 2002

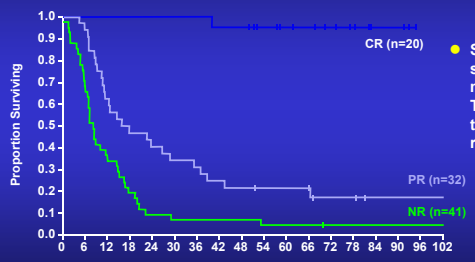
PATIENT 1: BULKY NODAL DISEASE





Dudley et al. SCIENCE 298:850, 2002

Tumor-Infiltrating Lymphocytes + IL-2 in Metastatic Melanoma: OS

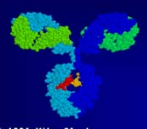


- Strong data suggest that mutation-reactive T cells contribute to these responses

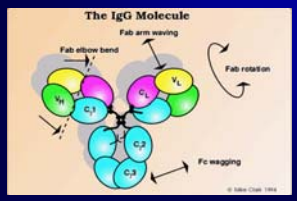
Robbins PF, et al. Nat Med. 2013;19:747-752

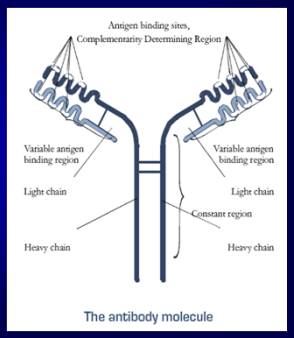
Monoclonal Antibodies

The Structure of Antibodies

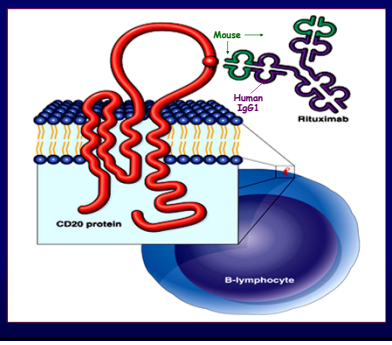


© 1996 Mike Clark





Rituximab Targets CD20 Specifically Expressed on The Surface of B Cells

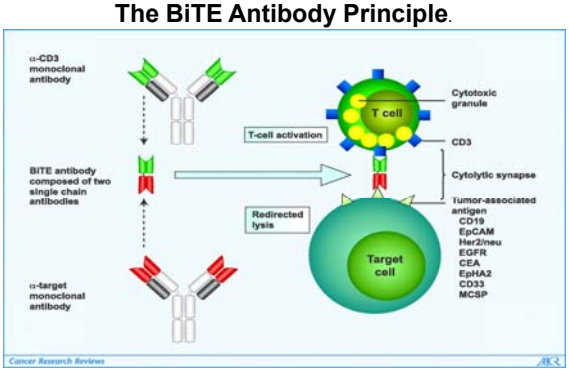


Monoclonal Antibody Therapy for Cancer

FDA approved:

Rituximab	anti-CD20	lymphoma
Herceptin	anti-her2/neu	breast cancer
Myelotarg	anti-CD33	AML
Campath	anti-CD52	CLL
Zevalin	^{90}Y anti-CD20	lymphoma
Bexxar	^{131}I anti-CD20	lymphoma

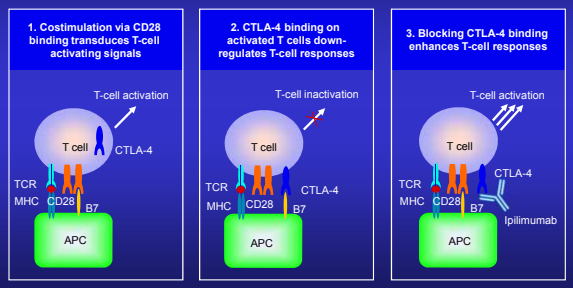
The BiTE Antibody Principle



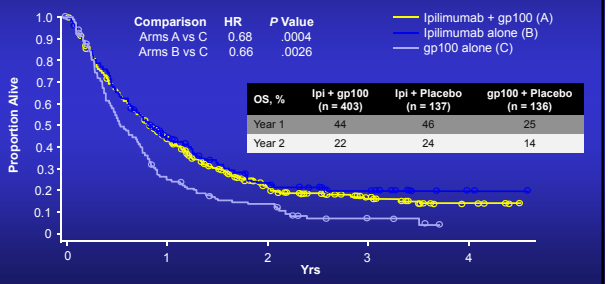
Baeuerle P A , and Reinhardt C Cancer Res 2009;69:4941-4944

American Association for Cancer Research

Ipilimumab a Member of Novel Class of Immunotherapeutic Abs: Anti–CTLA-4



Ipilimumab, gp100 Vaccine, or Both in Advanced Melanoma (MDX010-20): Survival



OS, %	Ipi + gp100 (n = 403)	Ipi + Placebo (n = 137)	gp100 + Placebo (n = 136)
Year 1	44	46	25
Year 2	22	24	14

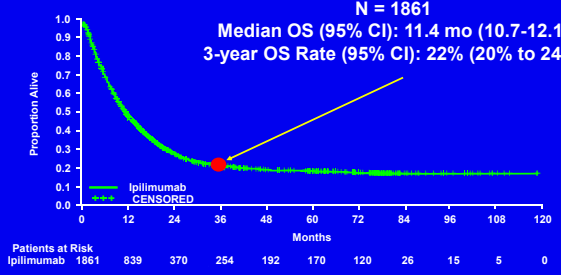
Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Anti-CTLA4 Antibodies: Disease Can Get Worse Before It Gets Better

- 4 distinct response patterns associated with favorable OS:
  - Response in baseline lesions (typical RECIST response)
  - Stable disease with slow decline in tumor volume
  - Response following an initial increase in tumor volume
  - Response following the appearance of new lesions
- Infiltration of patient immune cells can cause an initial increase in tumor volume or appearance of new lesions on imaging scans (pseudoprogression)

Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420.

Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.

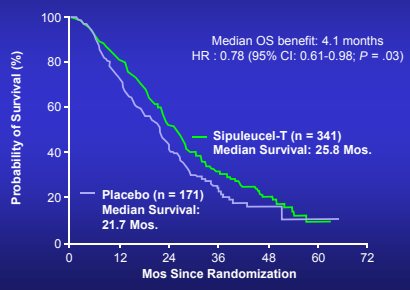
Tumor Vaccines

Cancer Vaccines: Current Status

- Many promising phase II studies compared to historical controls:
  - Whole-cell vaccines: allogeneic melanoma cells/cell lysates
  - Tumor antigen directed: MAGEA3, MUC1
  - Manipulated oncolytic virus: T-VEC
- Failure to show survival benefit in Phase III trials
- Only approved cancer vaccine: Sipuleucel-T in prostate cancer[1]
- Encouraging results with T-Vec in melanoma[2]

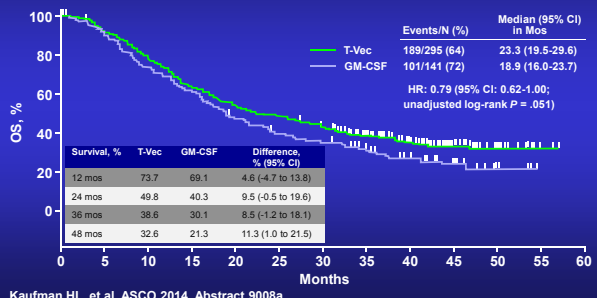
1. Di Lorenzo G, et al. BJU Int. 2012;110:E99-104. 2. Kaufman HL, et al. ASCO 2014. Abstract 9008a.

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): Overall Survival



Kantoff PW, et al. N Engl J Med. 2010;363:411-422.

OPTiM Study of T-Vec in Stage IIIB-IV Melanoma: Overall Survival



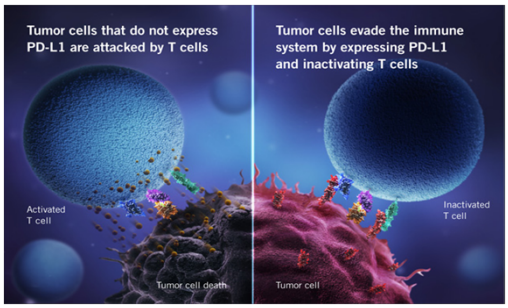
Kaufman HL, et al. ASCO 2014. Abstract 9008a.

Immune Checkpoint Blockade

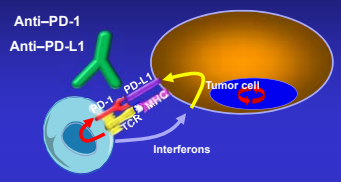
Tumor-Derived Immune Suppression

- Tumors go to great lengths to evade the immune response
- Systematic studies have identified multiple mechanisms cancers employ to defeat the immune response
  - Immunosuppressive cytokines: TGF-β, IL-4, -6, -10
  - Immunosuppressive immune cells: T-regs, macrophage
  - Disruption of immune activation signaling: loss of MHC receptor, IDO production
- Goal: therapy strategies that "*liberate*" underlying anticancer immune responses
- Immune checkpoints not even in the picture in 2008

Weiner LM. N Engl J Med. 2008;358:2664-2665.



PD-1 Adaptive Resistance to Immunotherapy



- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)[1,2]
  - PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, death)
- In RCC, melanoma, and other tumors, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features[3]

1. Topalian SL, et al. Curr Opin Immunol. 2012;24:207-212. 2. Taube JM, et al. Sci Transl Med. 2012;4:127ra37. 3. Thompson RH, et al. Proc Natl Acad Sci USA. 2004;101:17174-17179.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Development stage
PD-1	Nivolumab (BMS-936558)	Fully human IgG4	Phase III multiple tumors (melanoma, RCC, NSCLCa, HNSCC)
	Pembrolizumab (MK-3475)	Humanized IgG4	Phase I-II multiple tumors Phase III NSCLC/melanoma
	Pidilizumab (CT-011)	Humanized IgG1	Phase II multiple tumors
PD-L1	MEDI-4736	Engineered human IgG1	Phase I-II multiple tumors
	MPDL-3280A	Engineered human IgG1	Phase I-II multiple tumors Phase III NSCLC
	MSB0010718C	Fully human IgG1	Phase I solid tumors

Nivolumab: Clinical Activity

Tumor Type	Dose, mg/kg	ORR (CR/PR), n (%)	SD ≥ 24 Wks, n (%)	Median PFS, Mos	Median OS, Mos	1 yr, %	2 yr, %
MEL (n = 107)	0.1-10	32 (34)	7 (7)	3.7	17.3	68	48
NSCLC (n = 129)	1-10	22 (17)	13 (10)	2.3	9.9	42	24
RCC (n = 34)	1 or 10	10 (29)	9 (27)	7.3	> 22	70	50

- 28 responses (16 MEL, 6 RCC, and 6 NSCLC) lasted ≥ 1 yr among 54 patients with treatment initiation ≥ 1 yr before data analysis
- 13 patients (4 MEL, 6 NSCLC, 3 RCC) demonstrated nonconventional patterns of response but were not included as responders

Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. Hodi FS, et al. ASCO 2014. Abstract 9002. Brahmer JR, et al. ASCO 2014. Abstract 8112.

Pembrolizumab: NSCLC Clinical Activity

	First-line[1]	Previously treated[2]	
	PD-L1+ (n = 42)	PD-L1+ (n = 159)	PD-L1 – (n = 35)
ORR*, %	26	23	9
DCR*, %	64	42	31
Median duration of response, wks	NR	31	NR

*RECIST v1.1

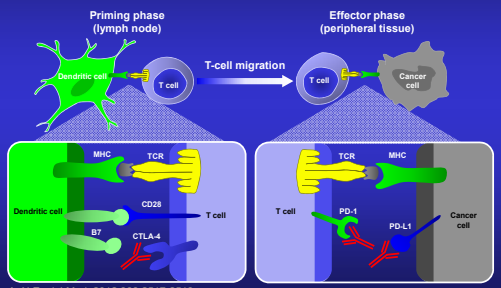
- ~ 80% of screened patients in each study were PD-L1+
- Among previously treated patients with NSCLC, ORR was 26% in current/former smokers and 9% in never smokers

1. Rizvi N, et al. ASCO 2014. Abstract 8007. 2. Garon E, et al. ASCO 2014. Abstract 8020.

Tumors Shown to Respond to Anti-PD1 or Anti-PD-L1 Therapy

- Melanoma
  - Pembrolizumab approved by FDA in September 2014
- RCC
- NSCLC
- Bladder
- Head and Neck cancer
- Lymphomas
- ???

CTLA-4 and PD-1/L1 Checkpoint Blockade for Cancer Treatment



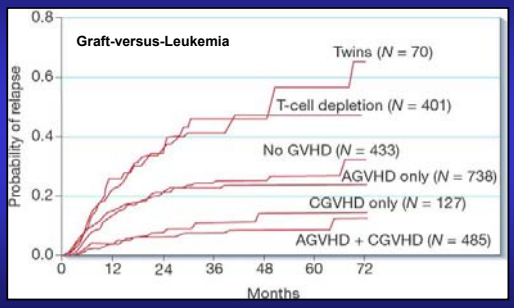
Ribas A. N Engl J Med. 2012;366:2517-2519.

Other Combinations with PD-1 Checkpoint Inhibitors

- Other coinhibitory pathways
  - TIM-3, LAG-3, IDO
- Co- or immunostimulatory pathways
  - OX40, 4-1BB, GITR, IL-2, IFN, IL-21
- Standard of care
  - Chemotherapy, TKI, VEGF inhibitor, XRT
- Cancer vaccines
- Cellular therapies
- Epigenetic therapy

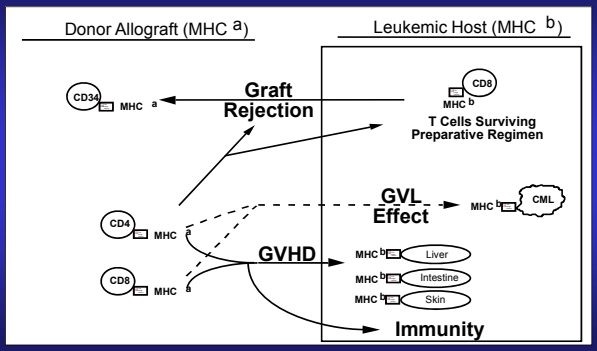
Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic Hematopoietic Stem Cell Transplantation



Horowitz, M. M. *et al. Blood* 75:555-62, 1990

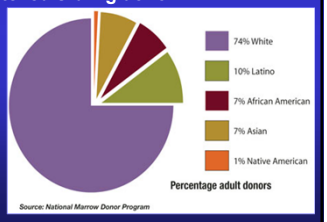
Role Of Donor T Cells In Allogeneic HSCT



Courtesy of D. Fowler, NCI

Allogeneic Hematopoietic Stem Cell Transplantation

- Only curative treatment for high-risk and recurrent hematologic malignancies
- Matched related donor (MRD) is preferred (8/8 match at HLA-A, -B, -C, and –DR)
- Only 25-30% have an HLA-matched sibling donor
- Matched unrelated donor (MUD) is next preferred
  - White = 60%
  - Black = 20%
  - Other minorities = 20-45%
- Approximately 5,000 per year require an alternative donor

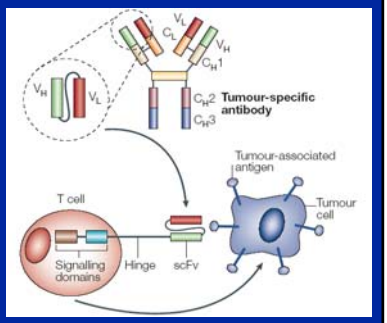


Ballen et al; Bone Marrow Transplant 2007

T Cell Engineering with Chimeric Receptor Antigens

Chimeric Antigen Receptors

- Tumor-specific cells
- Majority use Ab-derived ag binding motif
- Non- MHC restricted
- Dual or triple signaling domains include signaling molecules (CD3-zeta and CD28):
  - Proliferation
  - Survival



M.H. Kershaw et al. Nature Reviews Immunology 5:928-940, 2005

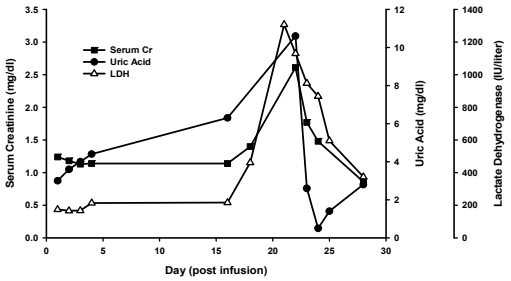
Chimeric Antigen Receptor (CAR)-modified T Cells in Chronic Lymphoid Leukemia

Study Design and Considerations

- Single center pilot trial
- Primary objective: evaluate safety, feasibility and immunogenicity of CD19-BBz CAR in patients with CD19+ leukemia and lymphoma
- Eligibility: CD19+ B cell malignancies with no available curative options who have limited prognosis (several months to <2 year survival) with currently available therapies
- Cell dose: $1.5x10^7$ – $5 x10^9$ CART-19 cells

Porter DL et al. N Engl J Med 2011

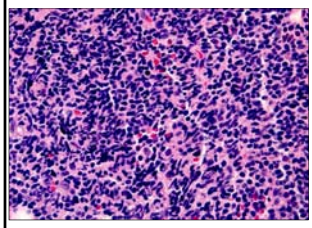
Delayed onset Tumor Lysis Syndrome after infusion of CART-19 cells: Pt #3



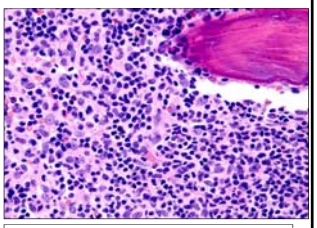
Penn

Courtesy of D. Porter U Penn

Patient #3 Marrow Response by Day 31



Pre-infusions marrow: >50% involved by CLL (40x)



Day 31
No evidence CLL and negative by flow cytometry, cytogenetics and FISH

Penn

Porter et al, NEJM Aug 2011

Courtesy of D. Porter, U Penn

CART-19 Dose Response Observations

1. Dose-Response relationship was not observed with the first 3 CART-19 patients.
2. Complete Response (CR) observed in patients administered with two log fold difference in dose.

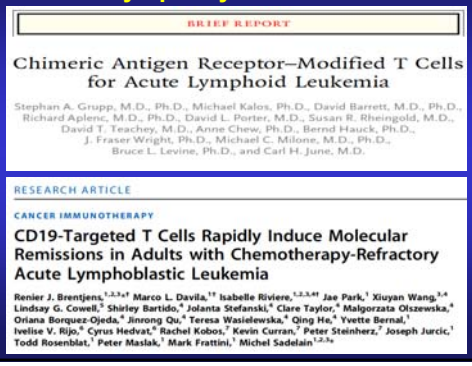
	Baseline Tumor Burden	Tumor Mass in Kg (pounds)	CART19+ Cells Infused	Response
UPN 01	2.5×10^{12}	2.5 (5.5)	1.13×10^9	CR (+19 months)
UPN 02	3.5×10^{12}	3.5 (7.7)	5.8×10^8	PR (+9 months)
UPN 03	1.3×10^{12}	1.3 (2.9)	1.42×10^7	CR (+17 months)

1 kg = ~10^{12} tumor cells

Penn

Porter et al, NEJM Aug 2011; Kalos et al, Science Translation Med Aug 2011

Anti-CD19 CAR T-cells for B-cell Acute Lymphocytic Leukemia



BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

RESEARCH ARTICLE

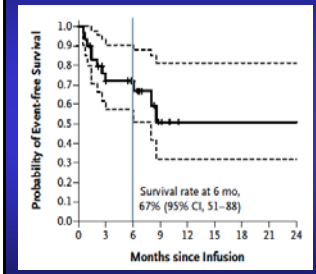
CANCER IMMUNOTHERAPY

CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia

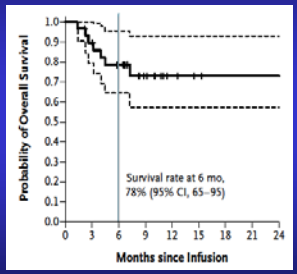
Renier J. Brentjens, Marco L. Davila, Isabelle Riviere, Jae Park, Xiuyan Wang, Lindsay G. Cowell, Shirley Bartido, Jolanta Stefanski, Clare Taylor, Malgorzata Olszewska, Oriana Borquez-Ojeda, Jinrong Qu, Teresa Wasielewska, Qing He, Yvette Bernal, Ivelise V. Rijo, Cyrus Hedvat, Rachel Kobos, Kevin Curran, Peter Steinherz, Joseph Jurcic, Todd Rosenblat, Peter Maslak, Mark Frattini, Michel Sadelain

Anti-CD19 CAR T-cells for B-cell Acute Lymphocytic Leukemia

Event-free Survival



Overall Survival



Maude et al. N Engl J Med 371:1507, 2014

Conclusions and Future Directions

- Various form of immunotherapy can produce durable antitumor responses in some patients with cancer
- Treatment of patients with immune checkpoint inhibitors can be different than with conventional therapies
- Chimeric antigen receptors T cells are highly effective in hematologic malignancies.
- Multiple Immune Inhibitory And Co-stimulatory Pathways In The Tumor Microenvironment Are Targets Of Therapeutic Manipulation By Antibodies Or Drugs
- Rationale For Combining Targeted Therapies With Adoptive Cell Transfer-based Immunotherapy