THE UNIVERSITY OF CHICAGO MEDICINE

Immunotherapy in Hematologic Malignancies

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Disclosures

- I have served as consultant in Advisory Board meetings for MedImmune/AstraZeneca Pharmaceuticals and Pfizer
- I will discuss non-FDA approved treatments, and ongoing clinical trials sponsored by Pharmaceuticals

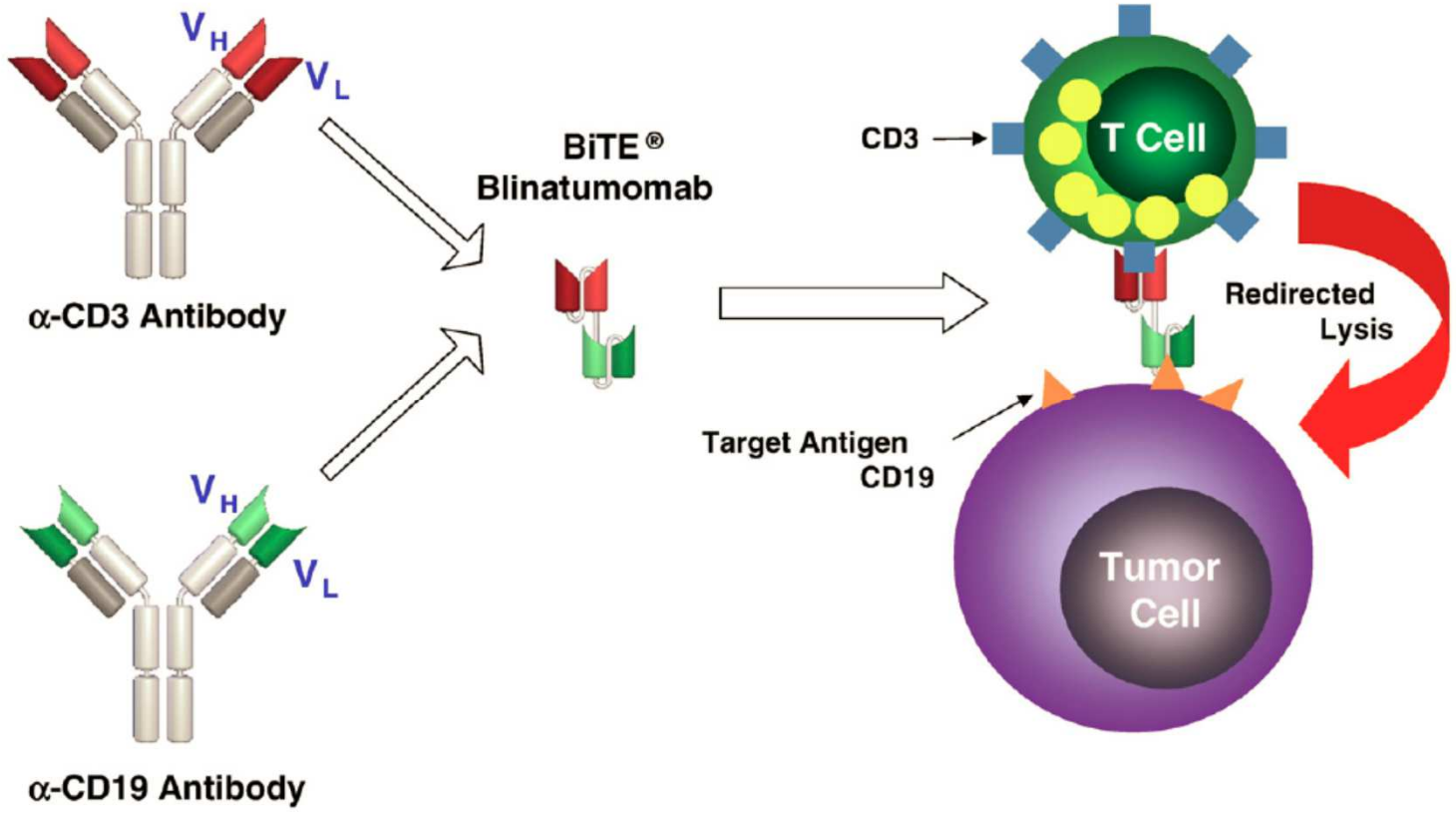
Established immunotherapy strategies under continued investigation

- **Cytokine-based therapies**
  - Interferon alpha, Interleukin-2, etc
- **Monoclonal antibody therapies:**
  - Rituximab (CD20); Ofatumumab (CD20), Alemtuzumab (CD52)
  - Conjugated Abs: Brentuximab vedotin (CD30); Inotuzumab ozogamicin (CD22)
- **Vaccines:**
  - Peptide vaccines
  - DNA Vaccines (plasmid or viral vector)
  - Dendritic cell vaccines (DC loaded with antigen)
  - Autologous tumor cell vaccines
- **Adoptive immunotherapy with tumor/leukemia-specific CTLs**
  - TIL, WT1-specific CTLs for AML, EBV-specific CTLs for PTLD, etc

New immunotherapy strategies

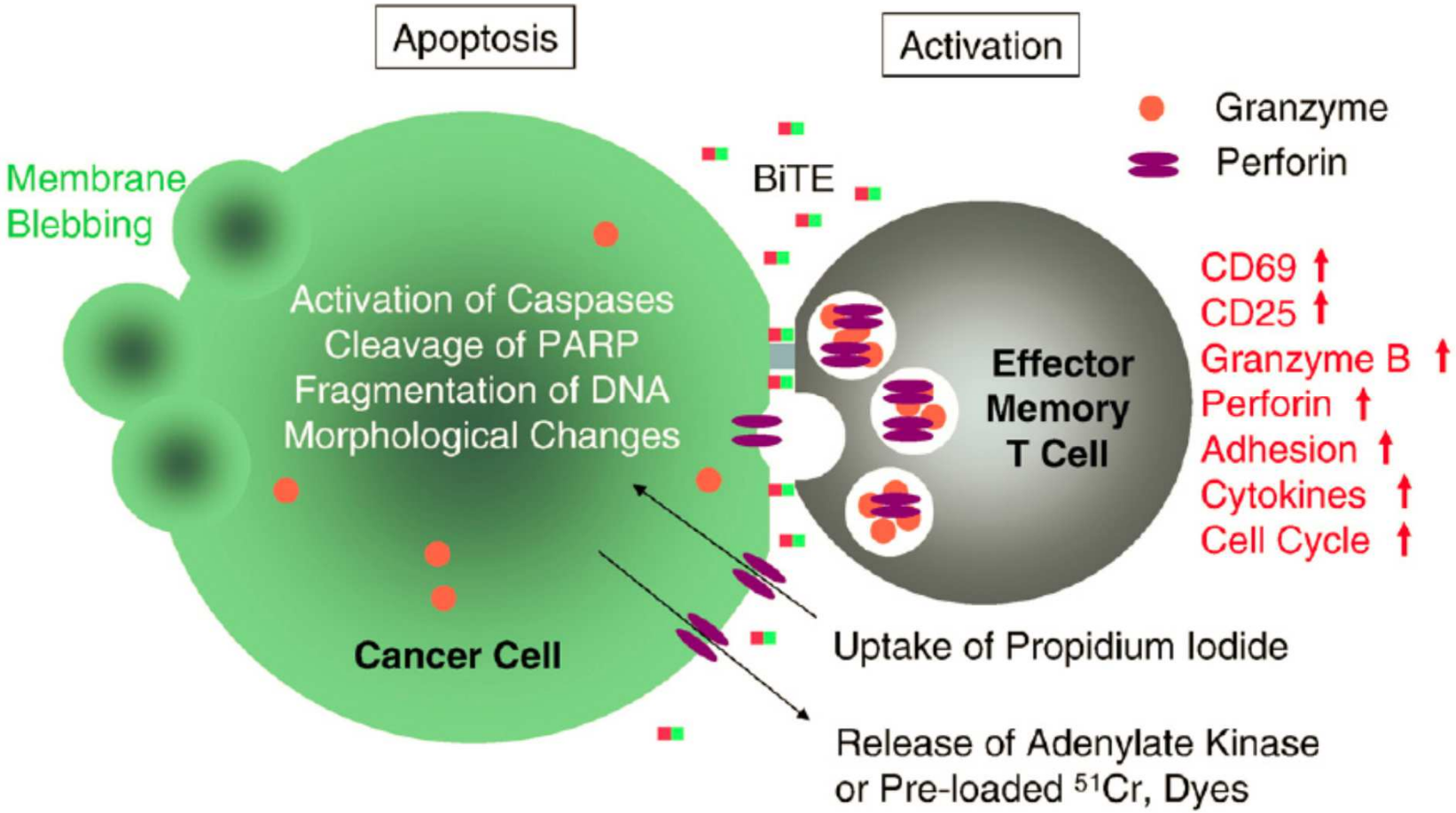
- **BiTEs: (Bi-specific T-cell engagers)**
  - Blinatumomab, a bi-Specific Anti-CD19/CD3 BiTE Antibody (Approved by FDA in December, 2014 for ALL)
- **CARs (Chimeric antigen receptors):** Targeting CD19 in lymphoid leukemia. CTL019 (U Penn). CD19-CAR (NCI), 19-28z CAR (MSK)
- **Immune Checkpoint Blockers:**
  - Anti-CTLA4: Ipilimumab
  - Anti-PD1: Nivolumab; Pembrolizumab
  - Anti-PDL1: MPDL3280A, MEDI4736
  - T reg depletion and Indoeamine-2,3-dioxygenase (IDO) inhibitors
- **Immune activators:** T cells (4-1BB agonist), APCs (TLRs agonist) , etc
- **Adoptive transfer of haplo-identical NK-T cells**
- **Oncolytic Viruses:** Genetically engineered viruses to selectively kill tumor cells, while initiating robust immune response against the tumor. JX-594 (Poxvirus), MG1 (Maraba virus), etc.

Blinatumomab, a bispecific single-chain antibody construct with dual specificity for CD19 and CD3



Nagorsen D, Baeuerle PA. Experimental Cell Research, 317 (9):1255-1260

Blinatumomab transiently induces a synapse between a T cell and the cancer target cell



Nagorsen D, Baeuerle PA. Experimental Cell Research, 317 (9):1255-1260

Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study

Max S Topp, Nicola Gökbuget*, Anthony S Stein, Gerhard Zugmaier, Susan O'Brien, Ralf C Bargou, Hervé Dombret, Adele K Fielding, Leonard Heffner, Richard A Larson, Svenja Neumann, Robin Foà, Mark Litzow, Josep-Maria Ribera, Alessandro Rambaldi, Gary Schiller, Monika Brüggemann, Heinz A Horst, Chris Holland, Catherine Jia, Tapan Maniar, Birgit Huber, Dirk Nagorsen, Stephen J Forman, Hagop M Kantarjian*

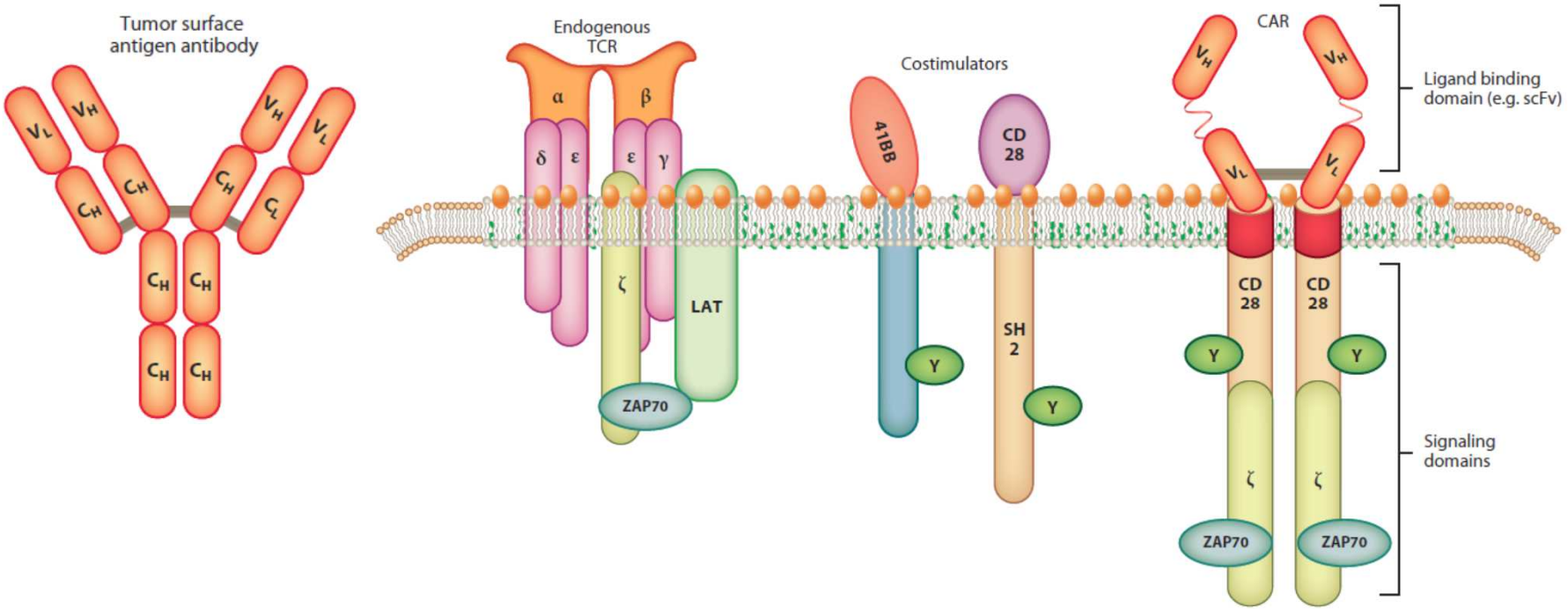
Lancet Oncol 2015; 16: 57–66

	Patients	Proportion (95% CI)
CR or CRh during the first two cycles	81/189	43% (36–50)
Best response during the first two cycles*		
CR	63/189	33% (27–41)
CRh	18/189	10% (6–15)
No response to therapy†	90/189	48%
Not evaluable‡	18/189	10%
Allogeneic HSCT after CR or CRh	32/81	40%
Allogeneic HSCT after CR	28/63	44%
Allogeneic HSCT after CRh	4/18	22%
MRD response during first two cycles in patients with CR or CRh§	60/73	82% (72–90)
100-day mortality from day of HSCT	32	11% (0–23)

Challenges with Blinatumomab

- Ideal patient population needs to be defined:
  - ALL with MRD vs relapse/refractory ALL
- Severe life-threatening reactions can occur:
  - Neurologic toxicities, reversible
  - CRS (cytokine release syndrome)
- B-cell depletion by Blinatumomab increases the risk of infections
- Blinatumomab has a fairly short half-life requiring continuous infusion over 4-week cycles through a portable mini-pump
- The best use of blinatumomab is not known:
  - Single agent or in combination with chemotherapy.
  - A Phase III Randomized Trial of chemo+/- Blinatumomab for Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia in Adults is recruiting. (ECOG/NCI)

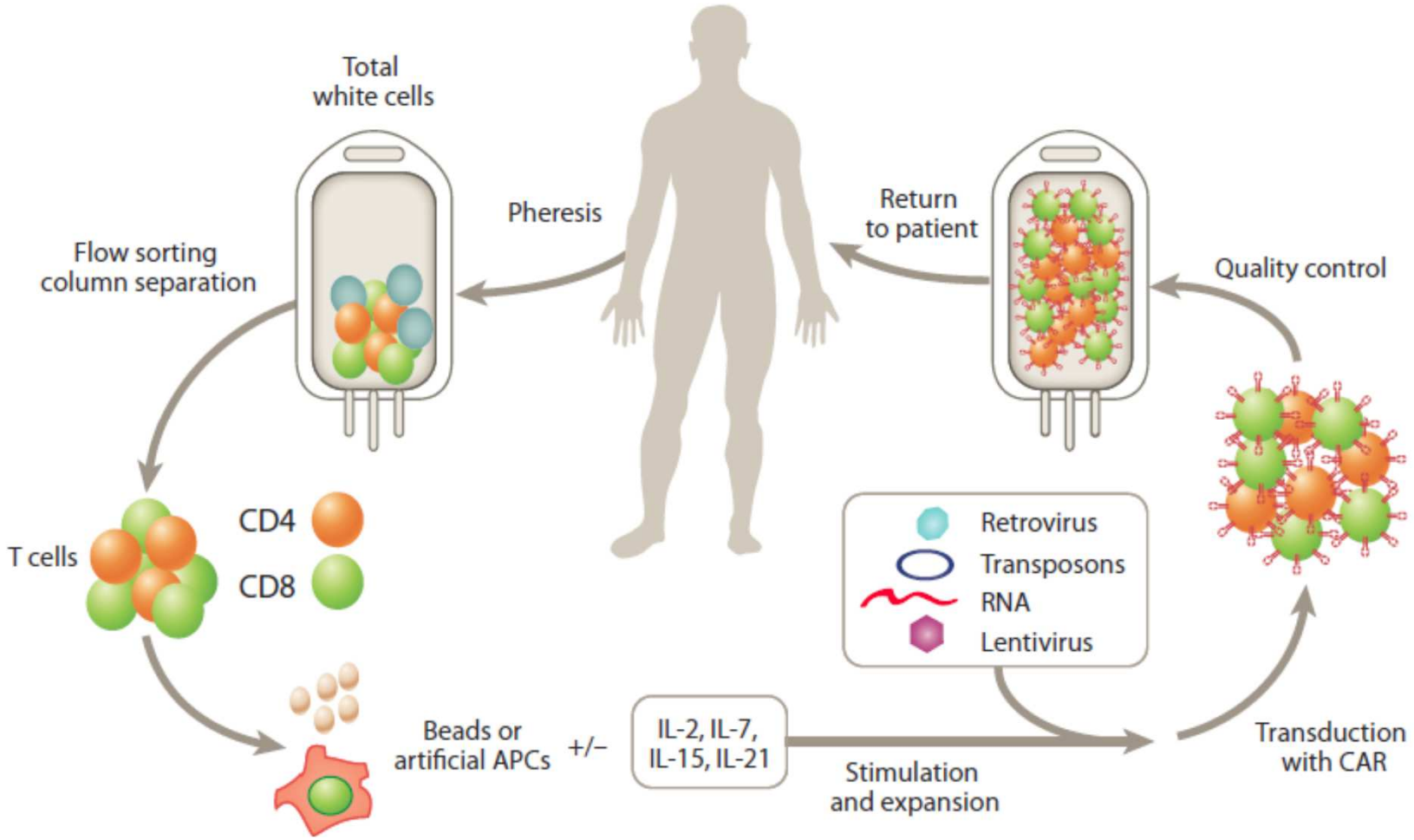
Schematic structure of CARs



Chimeric antigen receptors (CARs) have a single-chain antibody fragment (scFv), expressed in tandem with signaling elements derived from the T cell receptor (TCR) and costimulatory domains such as 4-1BB and CD28.

Barrett DM et al. Annu. Rev. Med. 2014. 65:333–47

Procedure to generate CAR T cells



Barrett DM et al. Annu. Rev. Med. 2014. 65:333–47

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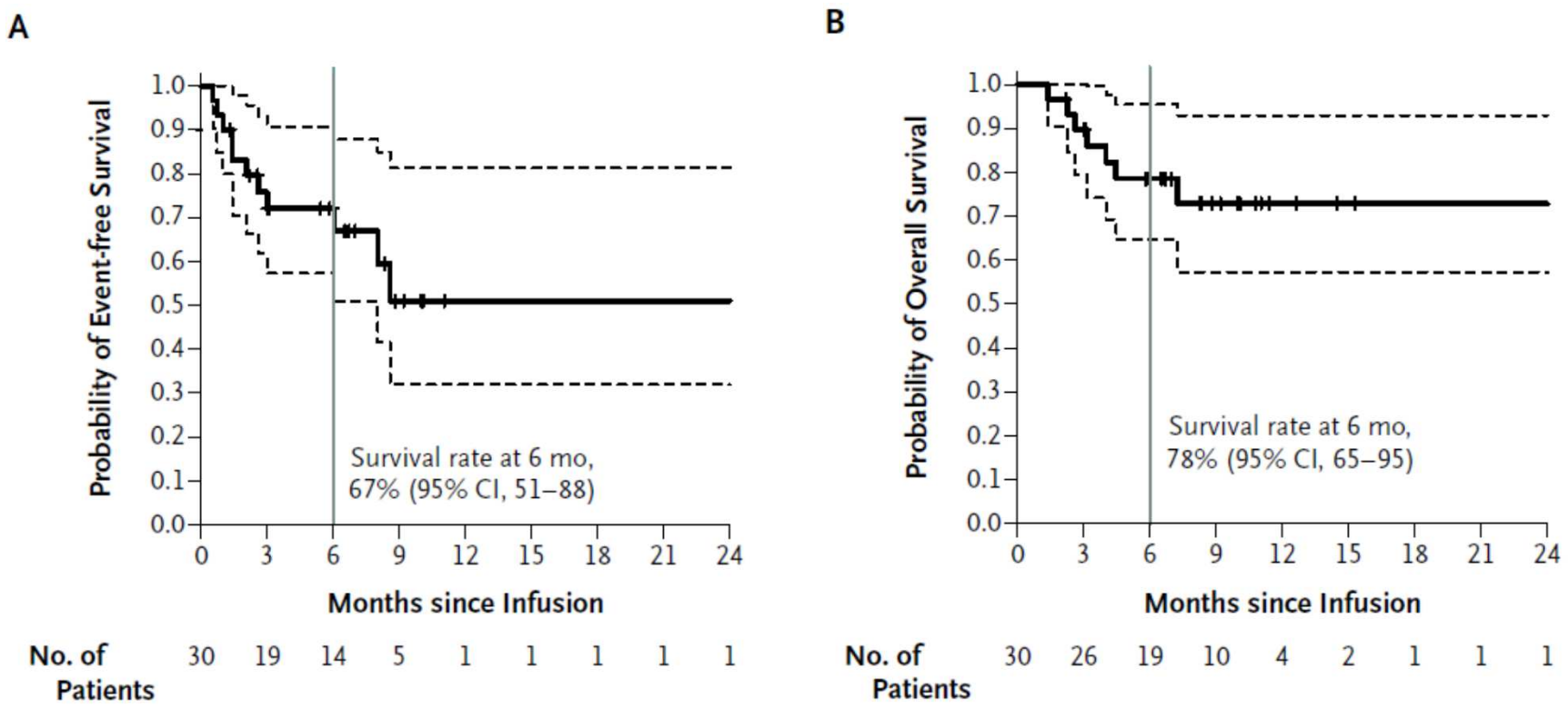
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia



Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation.

Maude SL, et al N Engl J Med 2014;371:1507-17.

Promises and challenges with CAR T cells

- Unprecedented response rates of 60–80% in patients with relapsed or refractory ALL

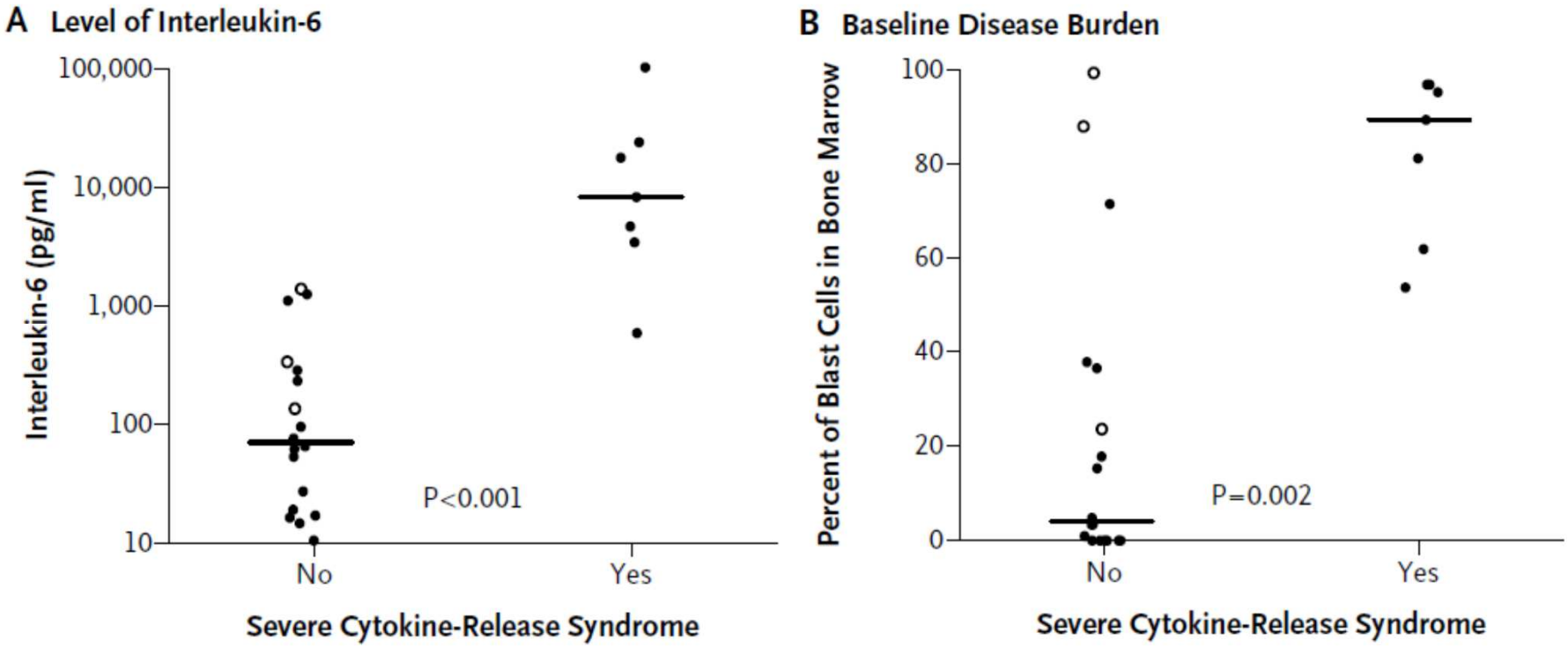
- Factors that are probably crucial for effectiveness:
  - Lympho-depleting chemotherapy before CAR T-cell (Cytoxan/Fludarabine)
  - Second-generation CAR incorporating a co-stimulatory domain
  - T cells were expanded in short-term culture
  - CAR T-cell expansion *in vivo* correlates with both response and toxicity.

- Response rates in ALL significantly higher than non-Hodgkin's lymphoma and chronic lymphocytic leukemia.
  - Might be due to tumor microenvironment and T cell homing

- The major toxicities:
  - Cytokine release syndrome. Disease burden-related; IL-6R blocking antibody tocilizumab.effectiveness
  - Unexplained transient neurotoxicity
  - On-target, off -tumor depletion of normal B cells

Amrolia PJ, Pulewww M. Lancet. 2015, 385: 488-489

Bone marrow disease burden and inflammatory cytokines elevation correlate with the Cytokine Release Syndrome after CAR T cell infusion



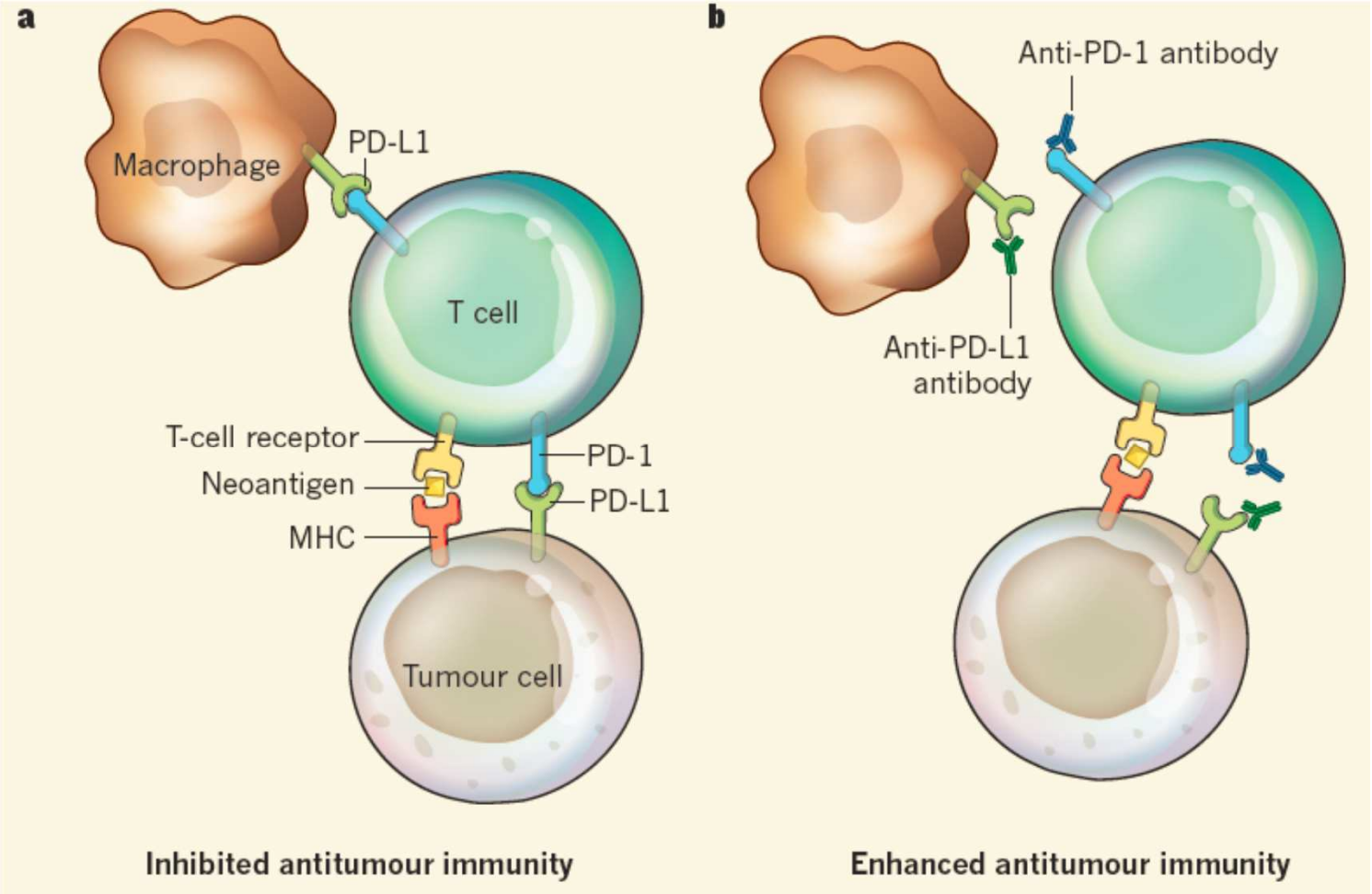
Maude SL, et al N Engl J Med 2014;371:1507-17.

Comparison of antigen-specific immunotherapy approaches for B cell malignancies

Technology	CART	ADC	BiTE
Example	CART19 (Penn) CTL019 (Novartis) (autologous *ex vivo* expanded T cells transduced with an anti-CD19 scFv)	Inotuzumab (anti-CD22 Mab linked to calicheamycin)	Blinatumumab (anti-CD3 anti-CD19 bispecific antibody)
Dosing	One infusion	Once every 3 weeks; or weekly	Continuous infusion 28 days on, 14 days off
Complete responses (relapsed/refractory B-ALL)	90% (173)	19% (174)	66% (175)
Survival	78% 6 months OS	5–6 months median	9 months median
Major toxicity	Cytokine release syndrome, encephalopathy	Fever, hepatotoxicity	Cytokine release syndrome, encephalopathy
Antigen-loss relapses noted?	Yes	No	Yes
Major challenges	Complex process to manufacture an individualized product	Relatively lower response rates	Burdensome infusion regimen

Gill S, June CH. Immunological Reviews 2015 Vol. 263: 68–89

Checkpoint blockade activates anti-tumor immunity



Wolchok JD, Chan TA. Nature. 2014; 515: 496-497

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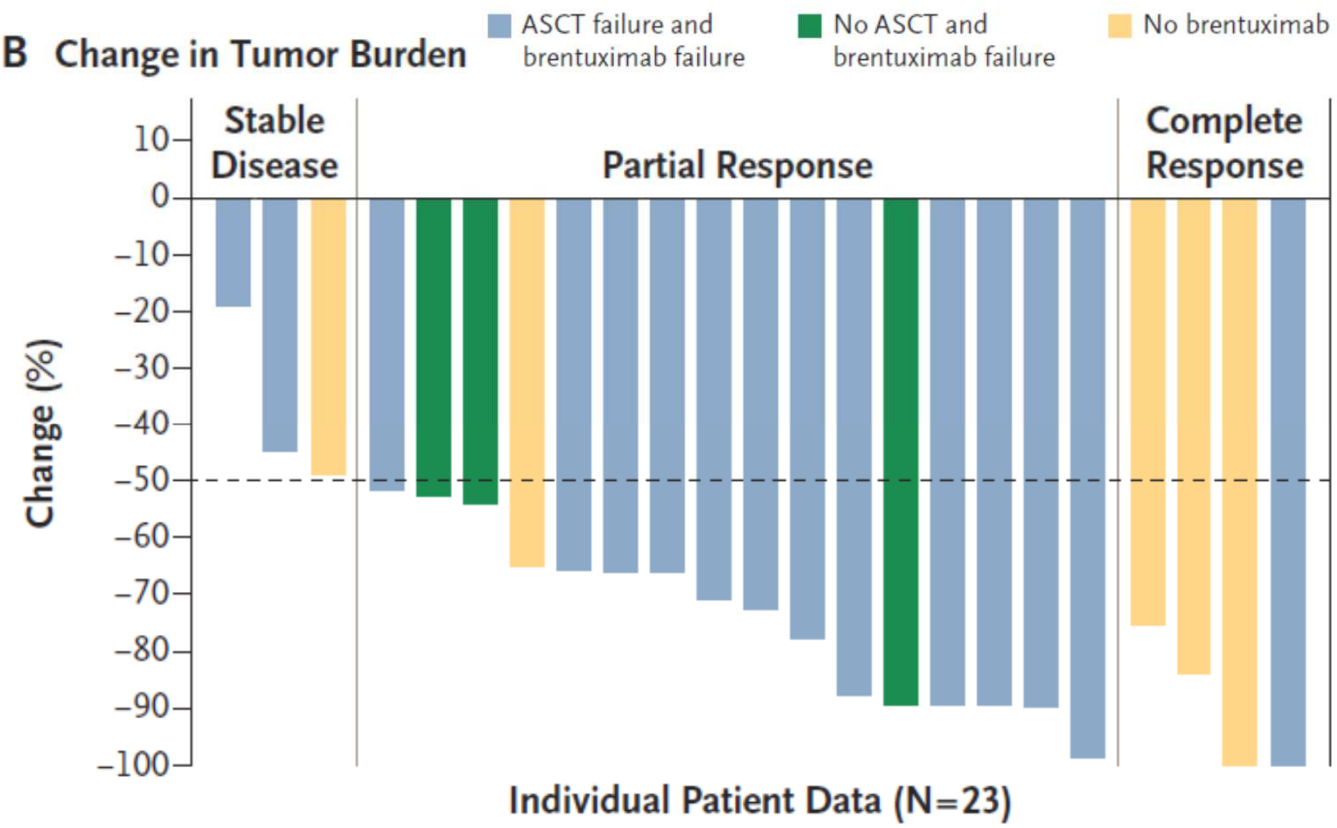
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Table 3. Clinical Activity in Nivolumab-Treated Patients.*

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

N Engl J Med. 2015 Jan 22;372(4):311-9.

Changes in tumor burden in patients with Hodgkin's Lymphoma receiving nivolumab



N Engl J Med. 2015 Jan 22;372(4):311-9.

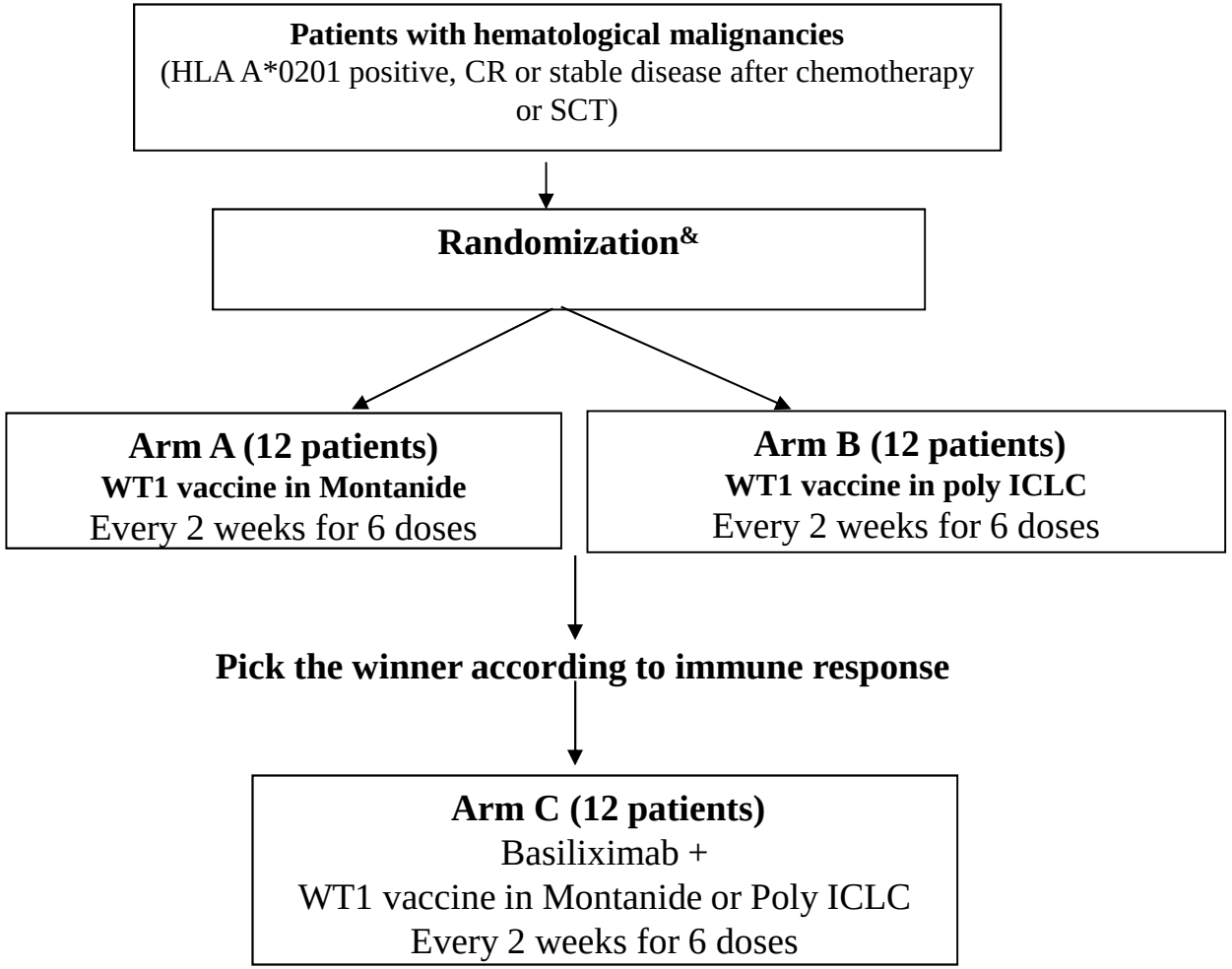
Immunotherapy trials for leukemia at UCMC

- WT1 peptide vaccination to eliminate MRD in AML
  - TLR3 agonist, Poly: ICLC as vaccination adjuvant
  - T regulatory cell depletion prior to WT1 vaccination
- Anti-PD1 antibody (Nivolumab) as maintenance therapy for AML in CR1 after induction/consolidation
- Cellular therapy with CAR CTL019 for ALL, CLL by Novartis; NK-T cells for AML collaborating with U of Minnesota. (Local PI: Dr. Michael Bishop)

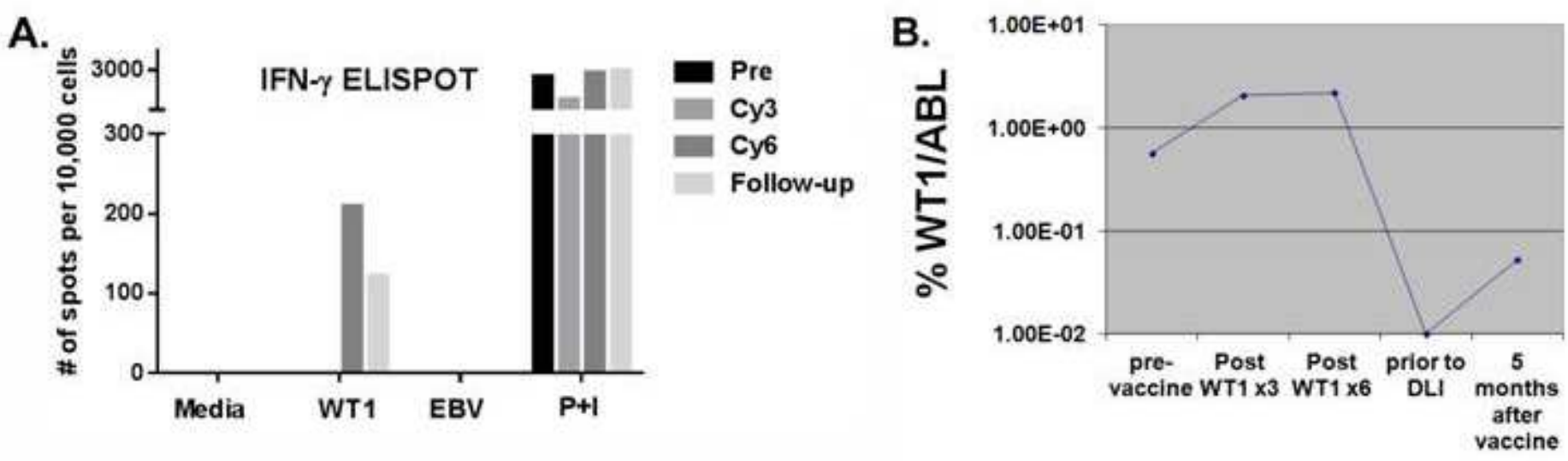
Randomized phase I study combining suppression of T regulatory cells with WT1 vaccine therapy for patients with hematologic malignancies

- 36 patients with hematologic malignancies with stable disease after chemotherapy and stem cell transplant
- Patient must express HLA-A*0201
- Antigen: WT1 126-134 peptide (RMFPNAPYL) in Montanide or poly ICLC (TLR3 agonist)
- TLR3 activation by poly ICLC, 1mg in 1ml aqueous solution administered intradermally/subcutaneously
- Suppression of Tregs by Basiliximab 20mg IV 1mg/kg 7 days prior to peptide vaccination

Protocol schema



WT1 vaccination can induce functional T cell responses which correlate with a decrease in minimal residual disease



Other ongoing vaccine trials

- IRB #:12-1959: Initial Phase 1 Study of WT2725 Dosing Emulsion in Patients with Advanced Malignancies (Sunovion); AML/GBM patients

- IRB14-1076: Phase I Study of an Oncofetal Antigen ("OFA") Multi-Peptide Immunotherapy ("BB-MPI-03") in Subjects with Hematologic Cancer (Benovus Bio Inc): AML/MDS/MM

  - Patients with HLA A0201/A0206 (about 30-50% Caucasian)
  - Could be post-chemotherapy or post-SCT off immuno-suppression
  - Best AML candidates will be patients in morphologic CR, but with MRD by WT1 qRT-PCR

ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

Randomized phase II study to assess the role of Nivolumab as single agent to eliminate minimal residual disease and maintain remission in acute myelogenous leukemia (AML) patients after chemotherapy

(Approved by NCI CTEP; FDA IND, UCCCC CTRC, and CIRB of NCI)

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

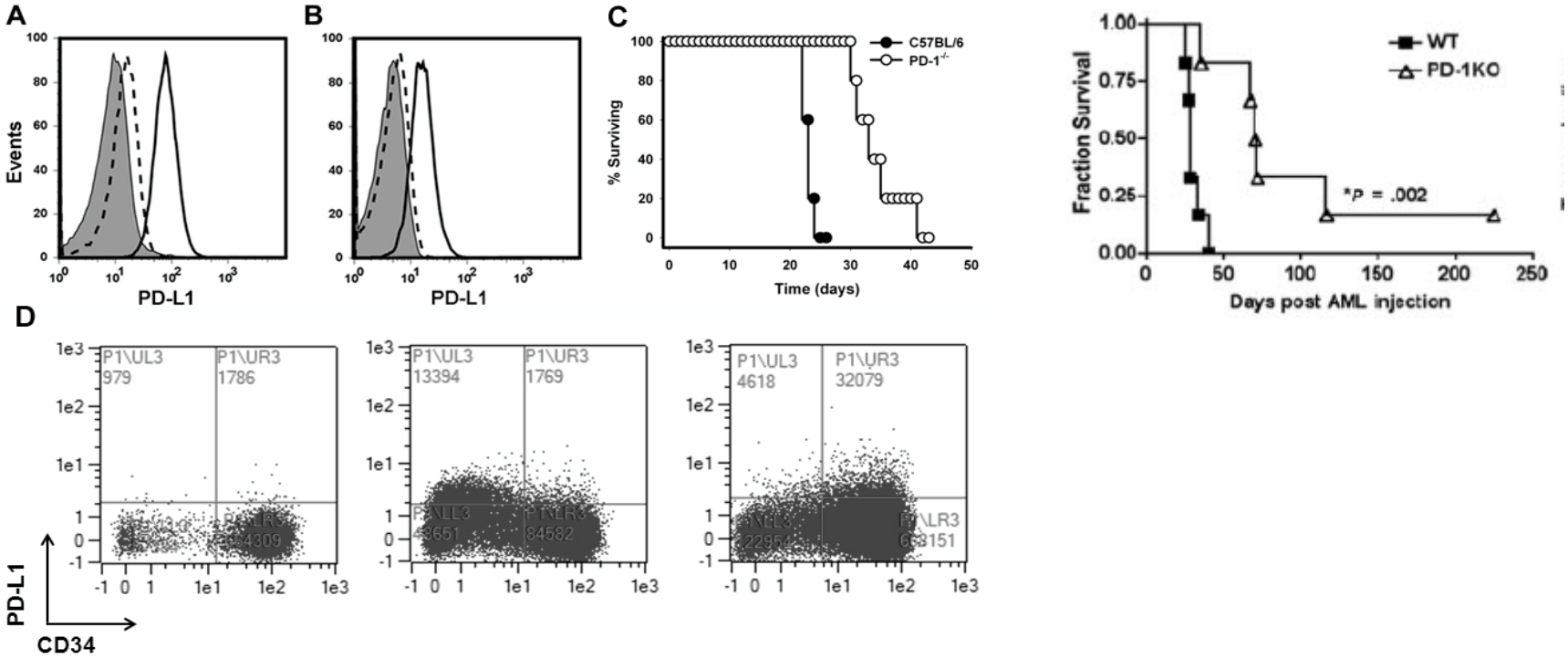
NIH

NATIONAL CANCER INSTITUTE

Background and rationale

- Relapse remains as the main failure of treatment in AML patients after chemotherapy, with 2 years PFS around 25% after induction/consolidation chemotherapy excluding young favorable patients.
- Immunotherapy could play an important role in preventing relapse, in the state of minimal residual disease
- Available data suggested that PD-1/PD-L1 pathway contributes to the immune evasion in AML
- Inhibition of PD-1/PD-L1 might activate immune response to eliminate MRD in AML patients, thus preventing disease relapse

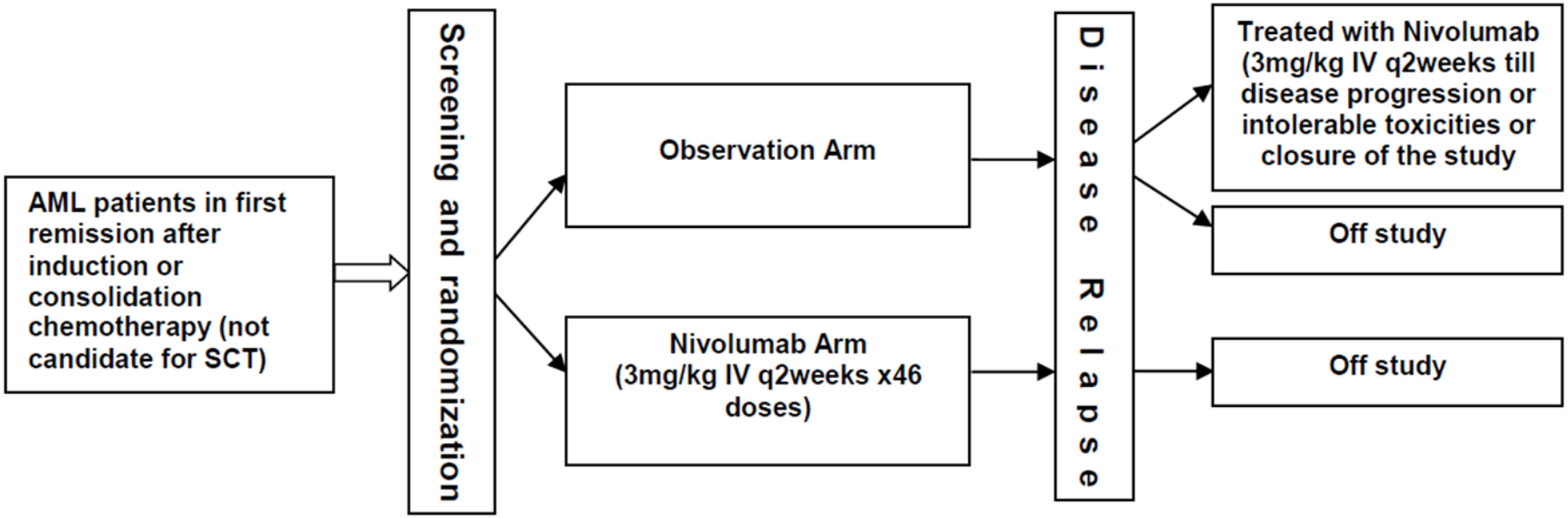
PD-L1 is expressed on murine and human AML cells and promotes immune evasion in a pre-clinical AML model



A) PD-L1 expression on C1498 AML cells after in vitro exposure to IFN-gamma for 48 hours.
B) PD-L1 expression on C1498 AML cells following IV inoculation into C57BL/6 mice.
C) C1498 AML cells were inoculated into syngeneic control or PD-1-/- mice.
D) Three patterns of PD-L1 expression on bone marrow samples from AML patients.

Zhang, L., Gajewski, T.F., and Kline, J. 2009. Blood 114:1545-1552.
Zhou, Q et al. Blood, 2010 116: 2484-2493

Treatment Plan/Schema



Conclusions

- Advances in immunotherapy are changing the landscape of leukemia treatment, providing promising outcomes with limited toxicities.
- Leukemia is an ideal setting for immunotherapy due to easy interaction between lymphocyte and leukemia cell, except the bone marrow environment.
- Immunotherapy might provide the best outcomes in the setting of MRD, which has been continuously defined in multiple type of leukemia: CML/ALL, APL, AML, etc.
- Combination of multiple immunotherapy modalities with chemotherapy/targeted therapy may help to achieve the maximal efficacy, leading to cure of leukemia.
- Adoptive transfer of leukemia-specific CTLs will prevent disease relapse and infection after curative allogeneic stem cell transplant is an attractive approach under development.