Immunotherapy in Hematologic Malignancies: Past, Present, and Future

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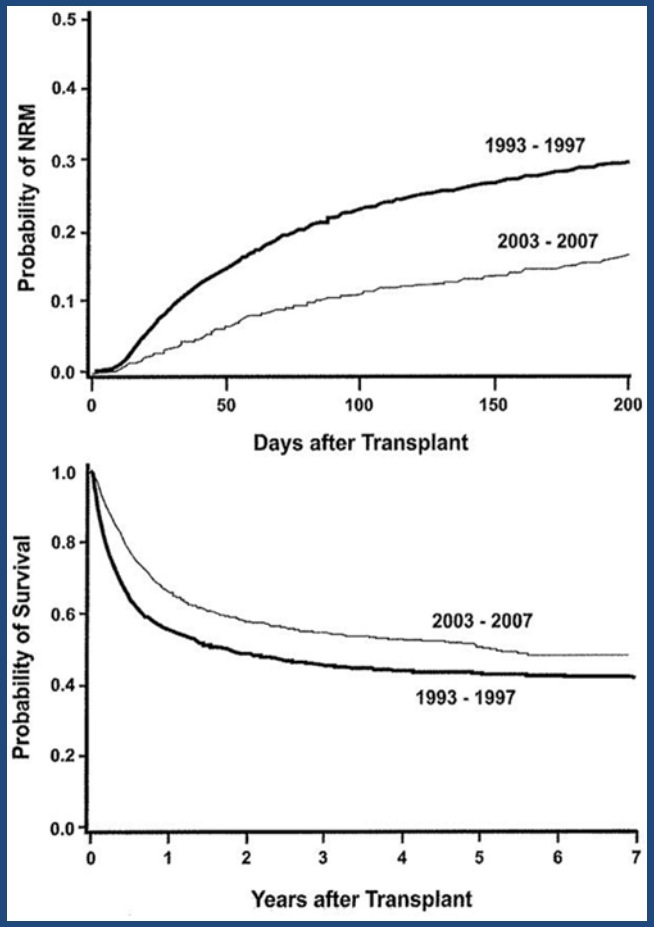
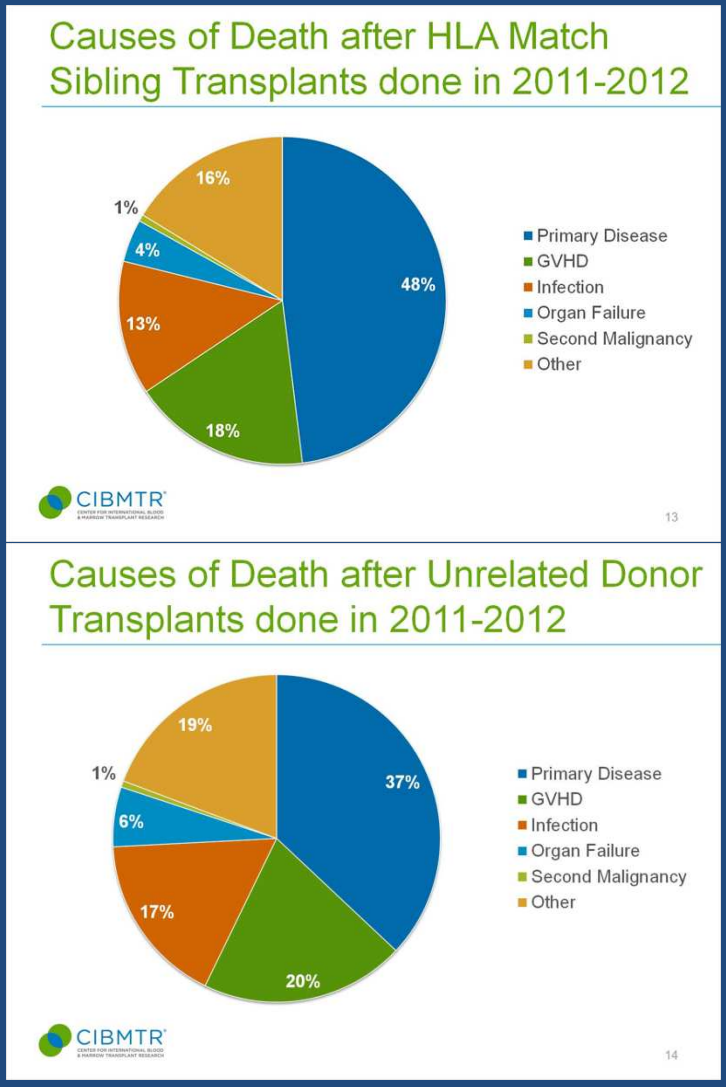
Immunotherapy in hematologic malignancies: Past (and Present)

Allogeneic hematopoietic stem cell transplantation (SCT):

- One of oldest forms of immunotherapy
- Proof of sensitivity of hematologic malignancies to immunotherapy, i.e. “graft-versus-leukemia” effect
  - Efficacy in chemo-refractory disease
  - Use of donor lymphocyte infusion (DLI) to treat relapse after SCT
  - Development of reduced-intensity conditioning SCT for older or unfit patients

Immunotherapy in hematologic malignancies: Past (and Present)





Gooley *et al.,* N Engl J Med 2012
www.cibmtr.org

Unique features of immunotherapy in hematologic malignancies

Advantages:

- Immune responsiveness (as demonstrated by SCT and DLI)
- Close and constant apposition of malignancy to sites of immune monitoring
- Cellular origins of malignancy are related to immunity → same origin
- Feasibility of isolating and manipulating malignant cells, i.e. pre and post immunotherapy

Challenges:

- Malignant cells can be stimulated by inflammation and thrive off of same stimulatory signals as immune system
- By nature, the malignant cells are corruptions of normal hematopoiesis and thus the immune system
- Exceptional ability of malignant cells to suppress and evade the immune system

Immunotherapy in hematologic malignancies: Present (and Future)

Novel strategies in immunotherapies:

1) Direct targeting of tumor antigens
   - Monoclonal antibodies and antibody-drug conjugates
   - Bispecific T-cell engagers (BiTE)
   - CAR T-cells

2) Augmentation of immune effectors
   - CAR T-cells
   - NK cell therapy

3) Activation of tumor antigen-specific immunity
   - Vaccines

4) Overcoming tumor-derived immune inhibition
   - Immune checkpoint inhibitors

Direct targeting of tumor antigens:

Monoclonal antibodies
Antibody-drug conjugates
Bispecific T-cell engagers

Monoclonal antibodies

Mechanisms of action: antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), complement-dependent cytotoxicity (CDC), direct cytotoxicity

FDA approved agents:

- Rituximab: the prototype for anti-CD20 monoclonal antibodies and a backbone of B-cell lymphoma regimens
- Ofatumumab (anti-CD20): single agent efficacy in relapsed/refractory CLL, or combined with chlorambucil in newly diagnosed CLL
- Obinutuzumab (anti-CD20): combined with chlorambucil in newly diagnosed CLL

Monoclonal antibodies

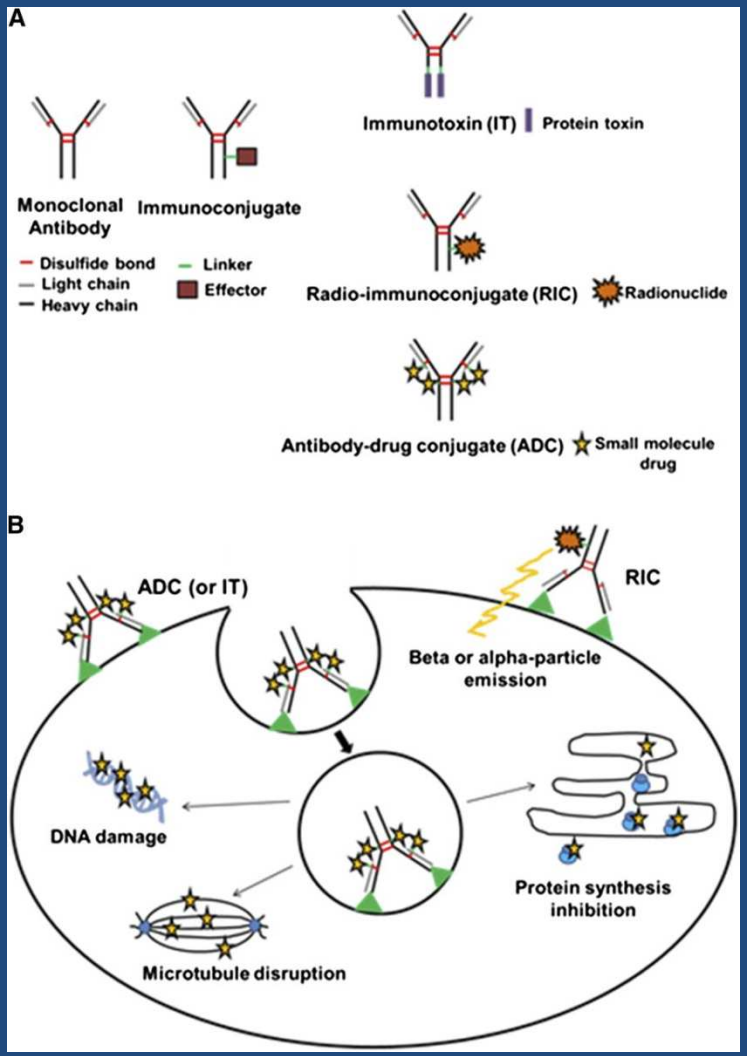
In development: Multiple myeloma

- Daratumumab (anti-CD38)
  - Preliminary results of Phase 1/2 study showed ORR 42% in heavily pretreated population
  - Combined with lenalidomide/dexamethasone showed ORR 75%
  - Main toxicities are infusion-related
  - FDA breakthrough-therapy designation in 2013
- Elotuzumab (anti-SLAMF7 or CS1)
  - Single agent use showed no objective response and stable disease in 26%
  - Combined with lenalidomide/dexamethasone showed ORR 79% and median PFS 14.9 months in randomized Phase 3 study in heavily pretreated population
  - FDA breakthrough-therapy designation in 2014
- Others in development: mAbs against CD38, CD138, CD56, CD40, Bcell activating factor (BAFF)

Plesner *et al.*, ASH 2014
Lonial *et al.*, N Engl J Med 2015

Antibody-drug conjugates

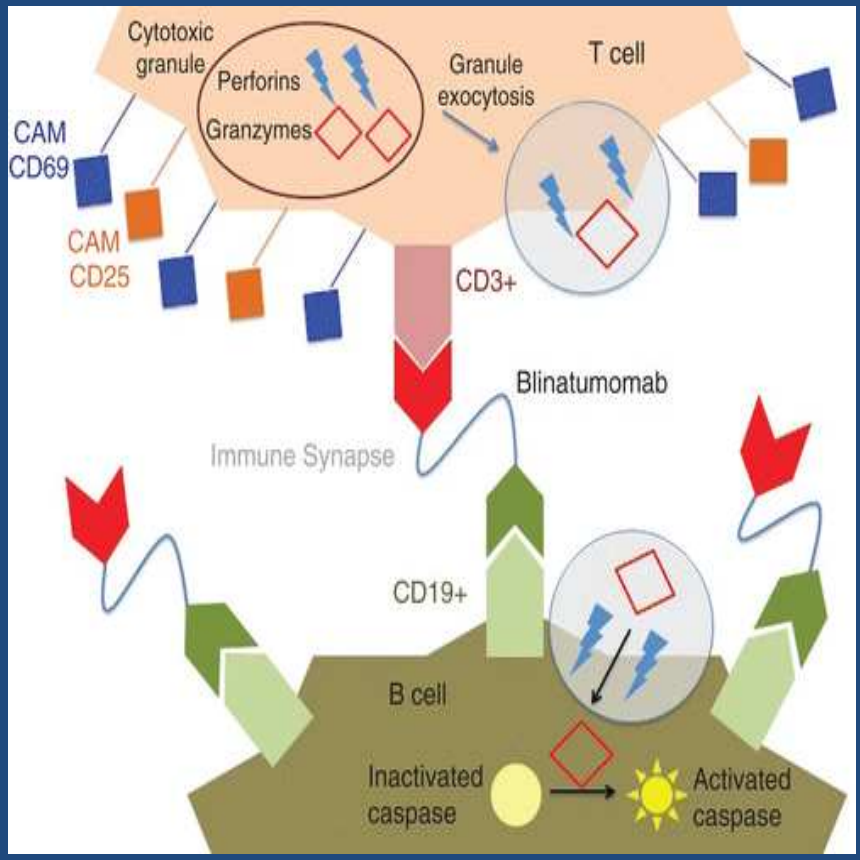
- Immunoconjugate – a targeting antibody linked to an effector molecule (cytotoxic agent), providing direct delivery to malignant cell
- Brentuximab vedotin (anti-CD30 and a microtubule inhibitor): FDA approved for relapsed/ refractory Hodgkins lymphoma and anaplastic large cell lymphoma FDA
- In development: ADCs targeting CD138, CD19, CD33, and others



Palanca-Wessels and Press, Blood 2014

Bispecific T-cell engagers (BiTE)

- Dual specificity for CD3 (T cells) and tumor surface antigen → passive recruitment of cytotoxic T cells to catalyze formation of the immunologic synapse
- Polyclonal T cell response and independent of MHC expression, thus overcoming a common mechanism of tumor immune escape



Rogala *et al.*, Expert Opin Biol Ther 2015

Bispecific T-cell engagers (BiTE)

Blinatumomab (CD19/CD3)

- Anti-CD19 and anti-CD3 variable fragments joined by a linker
- Phase 2 study of blinatumomab in 189 patients with relapsed/refractory Ph-negative acute lymphoblastic leukemia (ALL) – CR/CRi rate 43%, half of whom went on to allogeneic SCT
- FDA approved for relapsed/refractory Ph-negative ALL in December 2014
- Toxicities:
  - Cytokine release syndrome
  - Neurotoxicity
  - Guidelines have been developed for management of toxicities and dose reduction
- Administration is continuous infusion (inpatient or outpatient)

Topp *et al.*, Lancet Oncol 2015

Bispecific T-cell engagers (BiTE)

In development

- Evaluating blinatumomab for other B-cell malignancies
- CD3-CD33 BiTEs for AML
- Bispecific NK cell engagers (BiKE)

Augmentation of immune effectors AND
Direct targeting of tumor antigens:

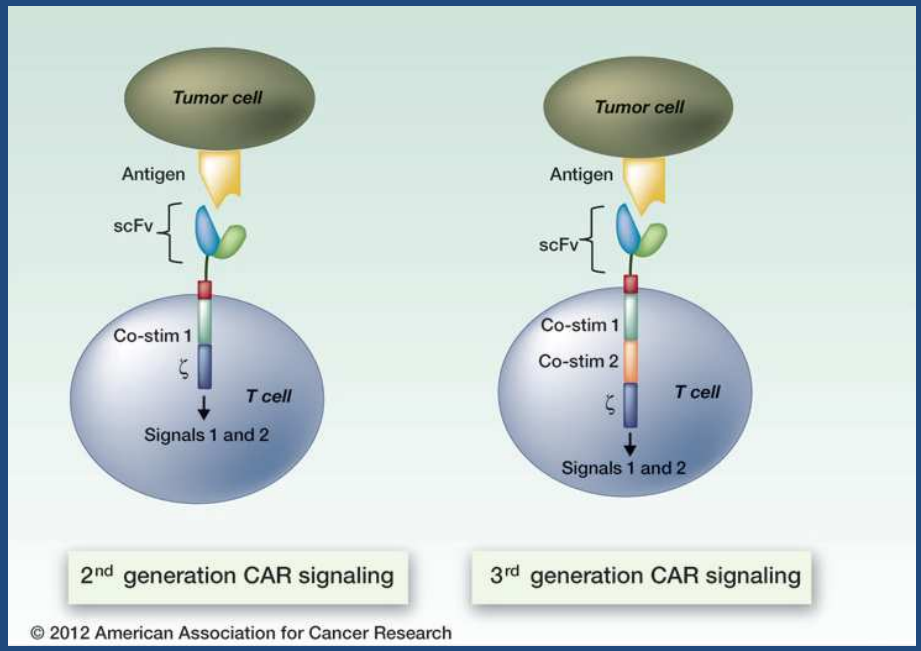
CAR T-cells

CAR T-cells

- Autologous T-cells engineered to express synthetic chimeric antigen receptor (CAR) against tumor surface antigen – antigen specific, HLA independent

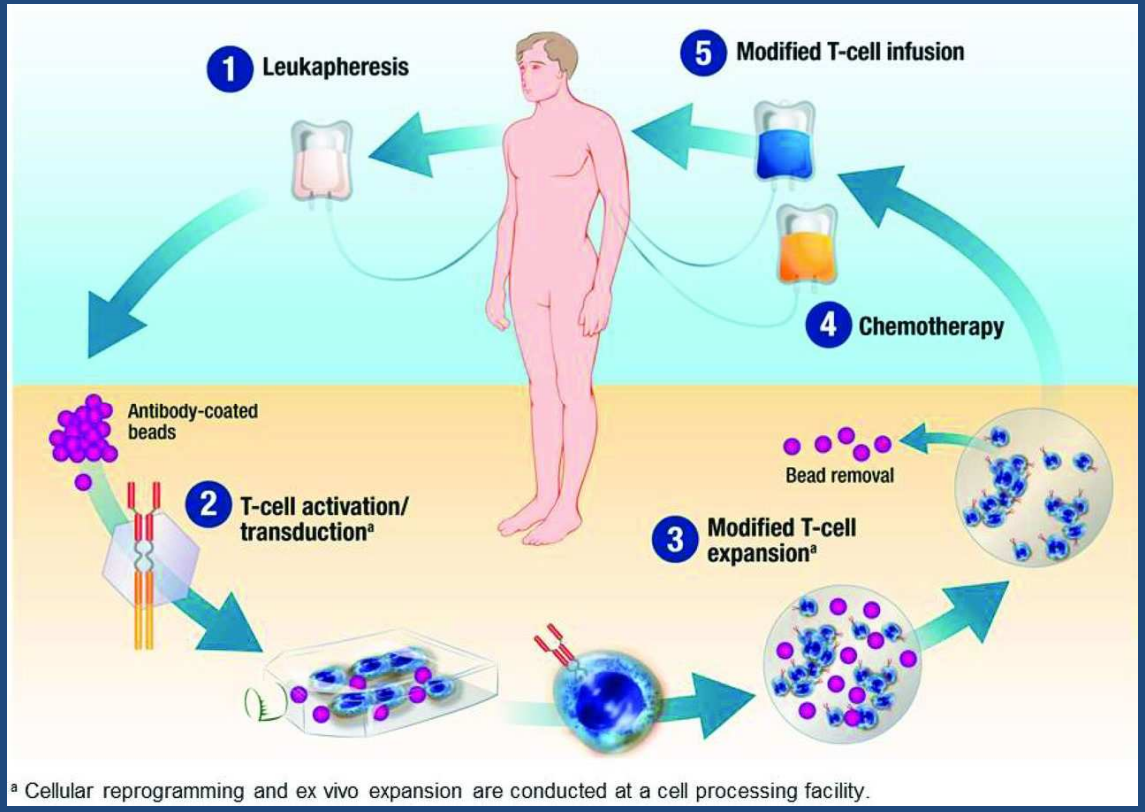
Advantages in hematologic malignancies:

- Known cell surface antigens (i.e. CD19)
- Easy sampling of tumor
- Natural T-cell homing to hematologic organs – blood, bone marrow, lymph nodes



Lee *et al.*, Clin Cancer Research 2012

CAR T-cells



- Lymphodepletion with chemotherapy enhances homeostatic expansion of infused T-cells
- Engagement of tumor antigen by CAR to T-cells leads to cytotoxicity and massive T-cell proliferation independent of MHC

Maude *et al.*, Blood 2014

Clinical trials for CD19 CAR T-cells (1)

Author	Center	No. patients	Disease (all relapse/refr-actory)	Outcomes	Duration of CARs	Best duration of response	Comments
Jensen *et al* (2010)	City of Hope	4	NHL	No responses (2 with CR after autoSCT)	1 week	-	1st generation CAR
Kochenderfer *et al* (2010, 2012)	NIH	8	NHL (4) and CLL (4)	80% RR (1 CR, 5 PRs)	Up to 6 months	>18 months	5/8 CRS 4/8 Bcell aplasia
Savoldo *et al* (2011)	Baylor	6	NHL	2 SD	2nd generation – up to 6 months	-	Infusion of 1st and 2nd generation T cells in same patient
Brentjens *et al* (2011)	MSKCC	10	CLL (8) and ALL (2)	CLL – 1 PR, 2 SD ALL – 1 durable Bcell aplasia	Up to 6 weeks (correlated with burden of disease)	8 months	Most with CRS
Porter *et al* and Kalos *et al* (2011)	U Penn	3	CLL	2 CR, 1PR	Up to 6 months (↑ expansion)	>11 months	All with CRS

NHL: Non Hodgkins Lymphoma, CLL: Chronic Lymphocytic Leukemia, ALL: Acute Lymphoblastic Leukemia, SCT: Stem Cell Transplant, CR: Complete Response, PR: Partial Response, SD: Stable Disease, RR: Response Rate, CRS: Cytokine Release Syndrome

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Kochenderfer *et al* (2013)	NIH	10	CLL (4) and NHL (6) post-alloSCT	1 PR, 1 CR, 6 SD	Up to 30 days (used donor T cells)	9 months	No GVHD
Kochenderfer *et al* (2014)	NIH	15	NHL (DLBCL and indolent lymphomas)	8 CR, 4 PR, 1 SD	Up to 11 weeks	22 months	6/7 DLBCL with response
Lee *et al* (2014)	NIH	21	ALL (20), NHL (1), 8 post-alloSCT	14 CR (13 MRD-), correlated with CAR expansion	Up to 8 weeks (most went on to alloSCT)	19 months	3 severe CRS CRP, IL6, and CAR expansion correlated with CRS
Grupp *et al* and Maude *et al* (2013, 2014)	U Penn	30	ALL, 18 post-alloSCT	90% (15 post-alloSCT, 2 post-blinatumomab)	Up to 2 years	24 months	All with CRS

DLBCL: Diffuse Large Bcell Lymphoma, MRD: Minimal Residual Disease, GVHD: Graft Versus Host Disease

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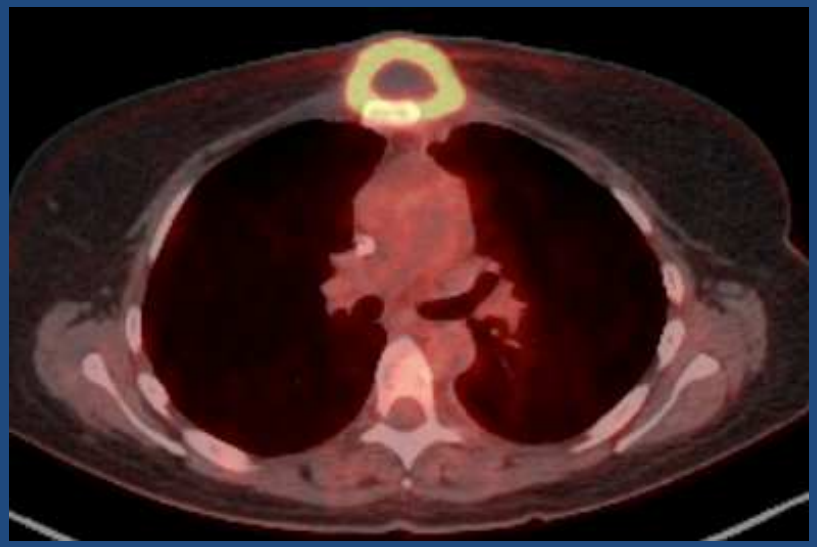
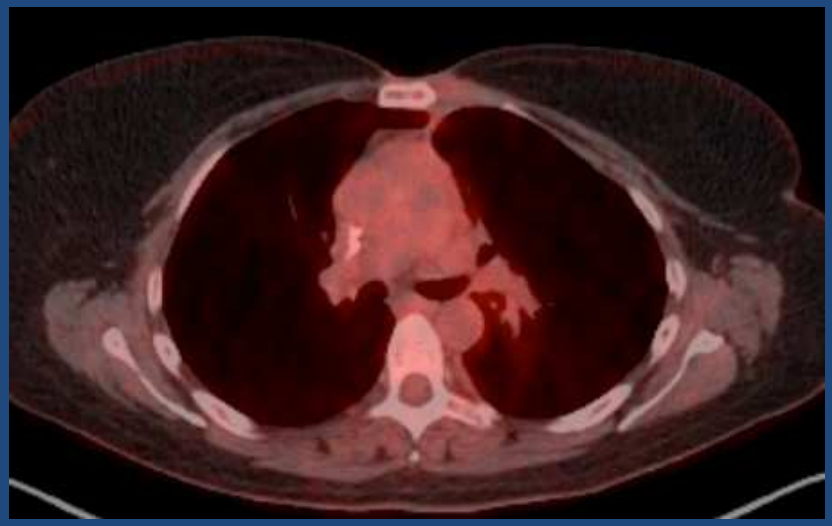
DLBCL: Diffuse Large Bcell Lymphoma, MRD: Minimal Residual Disease, GVHD: Graft Versus Host Disease

Complete remission of chemo-refractory primary mediastinal B-cell lymphoma ongoing after 35 months in Large Cell Lymphoma Patient 1

Before treatment



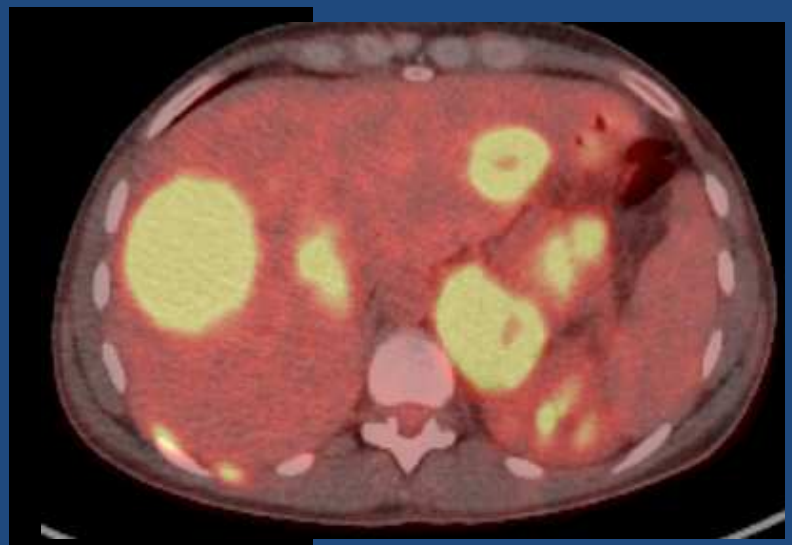
23 months after treatment



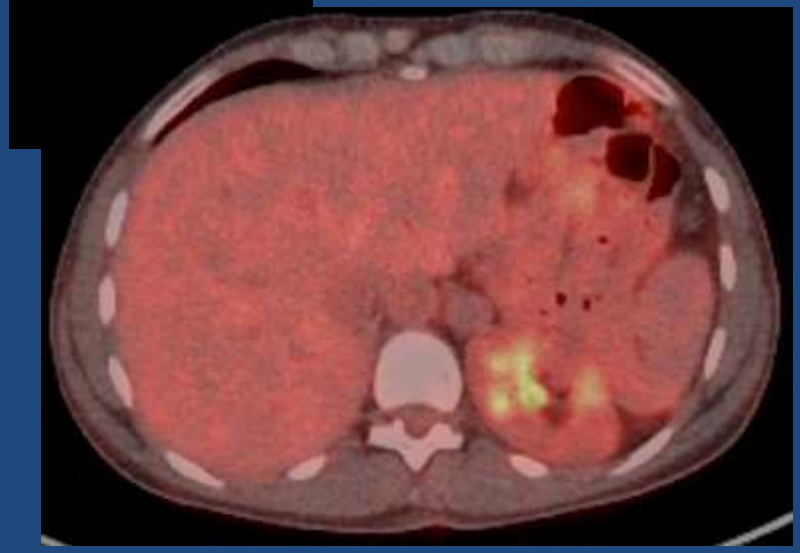
Courtesy of James Kochenderfer, MD

Complete remission of chemo-refractory primary mediastinal B-cell lymphoma occurred despite 10 prior treatments and is ongoing after 21 months in Large Cell Lymphoma Patient 4

Before treatment



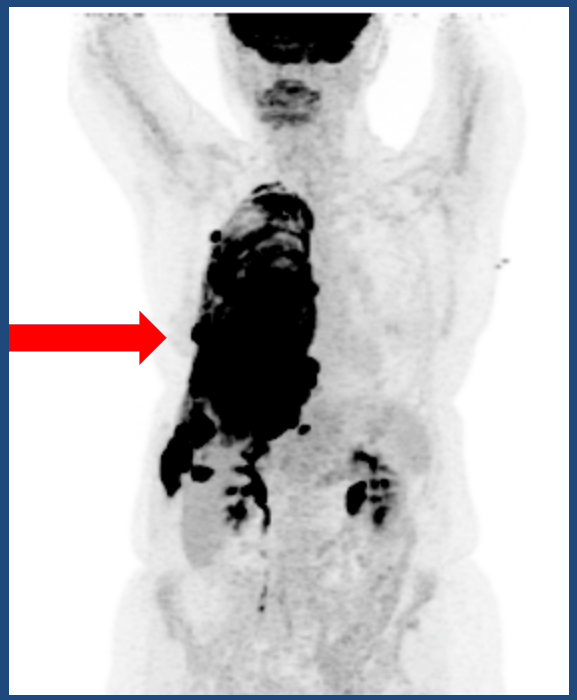
9 months after treatment



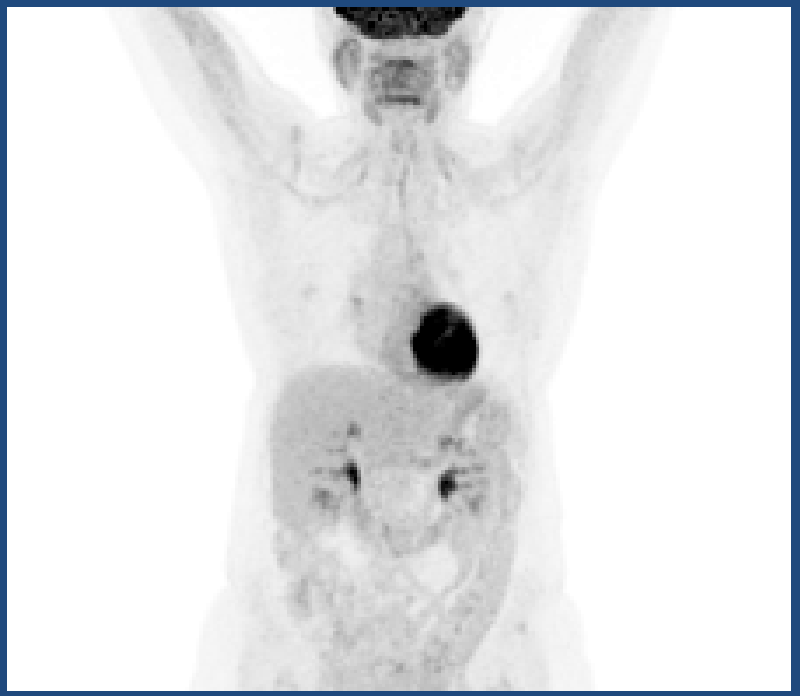
Courtesy of James Kochenderfer, MD

Patient 2 had a PR of chemotherapy-refractory triple-hit DLBCL after infusion of anti-CD19 CAR T cells

Before treatment



6 months after treatment



Resolution of a large malignant pleural effusion and lymphoma masses

CAR T-cells: Lessons learned

- Durable remissions have been seen in ALL, CLL, NHL - persistence of circulating CAR T-cells has been seen >3 years after infusion in CLL
- In ALL, CR rates of 90% in a relapsed/refractory population are remarkable, especially compared to historical controls
- CAR T-cells have been effective pre- and post-transplant (relapse after allogeneic SCT) and in chemo-refractory disease
- Responses are correlated with expansion of CAR T-cells (not cell dose at infusion) and presence of cytokine release syndrome (CRS)

CAR T-cells: Lessons learned

- CNS disease has been cleared with CAR T-cell therapy
- B-cell aplasia is a surrogate for persistence of CAR T-cells
- Antigen-positive relapses occur after CAR T-cells are no longer circulating; antigen-negative relapses occur in the presence of CAR T-cells
- It is not clear which costimulatory domain is best (CD28 vs 4-1BB)

CAR T-cells

- CTL019 – FDA breakthrough therapy designation in July 2014 in relapsed/refractory ALL
- Antigen discovery is leading to development of CAR T-cells for other malignancies (i.e. anti-BCMA in multiple myeloma)
- 41 trials actively enrolling for CAR T-cells in hematologic malignancies

CAR-T cells: Cytokine release syndrome (CRS)

- Inflammatory process related to exponential T cell proliferation associated with cytokine elevation
- Occurrence of CRS correlates with response, but severity of CRS does not
- Mild: high fevers, myalgias, flu-like symptoms
- Severe: Vascular leak, hypotension, multi-organ failure
- Only predictor of CRS – high disease burden at time of treatment (IL6, CRP?)
- Management guidelines exist – steroids, tocilizumab (anti-IL6)

Lee DW *et al.*, Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

- Tocilizumab does not appear to impact anti-tumor response

CAR-T cells: Other toxicities

Acute:

- Neurotoxicity
  - Global encephalopathy, seizures, mostly self-limited and without long term sequelae
  - Not related to CRS and not prevented by tocilizumab

Long term:

- B-cell depletion
  - Useful surrogate for CAR-T cells
  - Can be managed with IVIg infusions
- TBD?

CAR T-cells: Challenges and future directions

- Optimizing CAR and graft engineering: intracellular signaling domain, CD4:CD8 ratio, presence of Tregs
- Identification of targets – antigen discovery
- Ideal duration of engraftment
- Impact of tumor microenvironment (combine with PD1/PDL1 inhibition)
- Strategies to approach antigen-negative relapse
- Technical, regulatory, and financial obstacles – manufacturing on a wide scale

Augmentation of immune effectors and Activation of tumor antigen-specific immunity

Other strategies:

- NK cell alloreactivity
  - UPCI 12-151 (PI: Michael Boyiadzis): Phase I study of adoptive immunotherapy using the natural killer cell line, Neukoplast (NK-92) for the treatment of refractory or relapsed AML

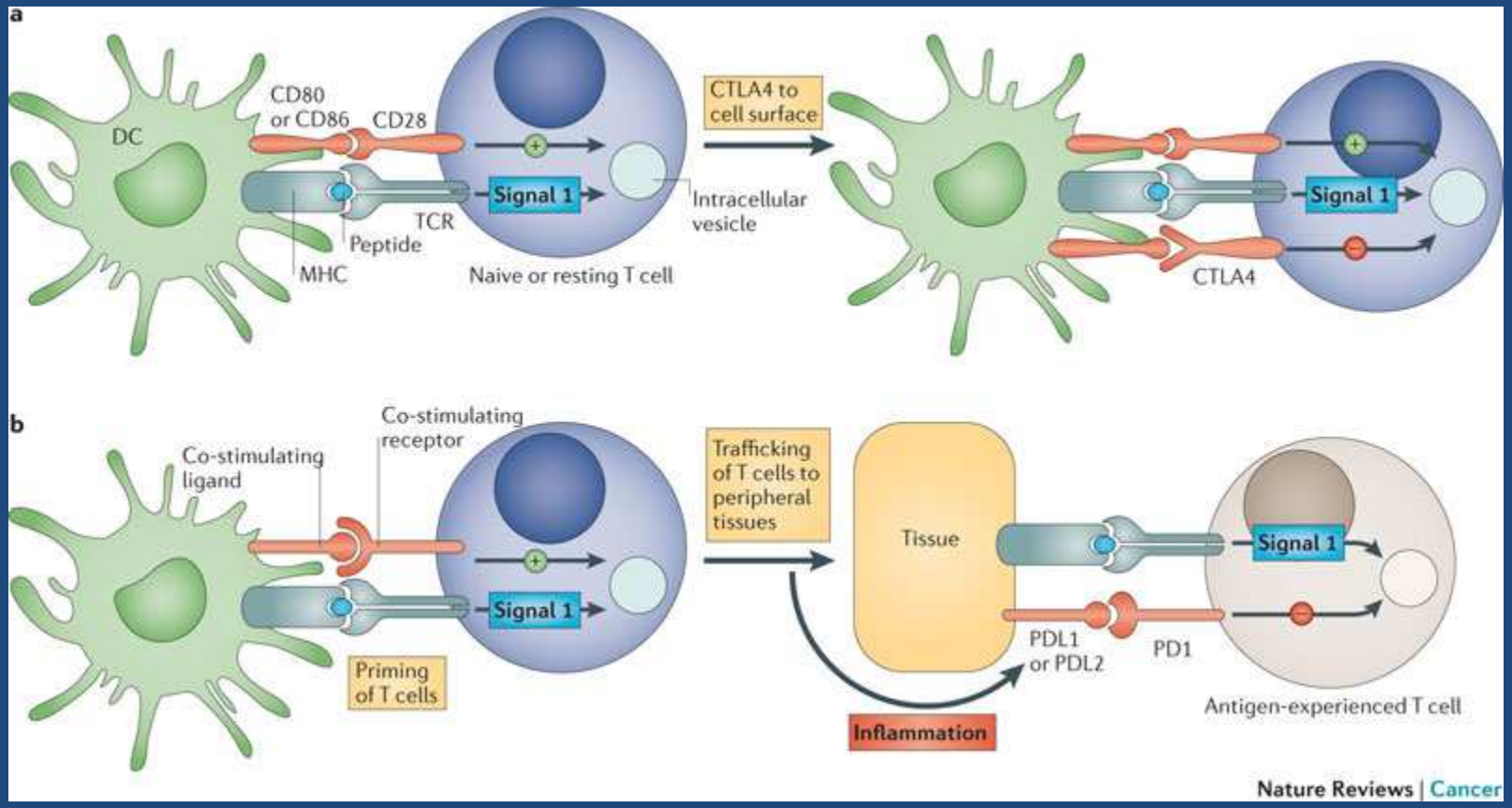
- Vaccines: AML in CR or PR
  - Known intracellular tumor-associated antigens exist in AML (i.e. WT1, PRTN3, MAGE, etc)
  - Vaccines trials have not been successful in patients with high tumor burden
  - WT1 and hTERT dendritic cell vaccines have induced cellular immune responses and were associated with durable remissions

van Tendeloo *et al.*, Proc Natl Acad Sci 2010
Khoury *et al.*, ASCO Annual Meeting 2015

Overcoming tumor-derived immune inhibition:

Immune checkpoint blockade

Immune checkpoint blockade



Pardoll, Nat Rev 2012

Immune checkpoint blockade

1) Hodgkins lymphoma (HL): observations suggest that it is uniquely vulnerable…

- Reed-Sternberg cells typically surrounded by extensive (but ineffective) immune infiltrate
- HL characterized by genetic alteration in 9p24.1, which results in *PDL1* and *PDL2* copy gain and overexpression
- Epstein-Barr virus (EBV) infection, common in HL, also leads to PDL1 overexpression (mechanism to allow viral persistence in the host)
- Increased surface expression of PDL1 in HL tumors has been observed

Armand, Blood 2015

Immune checkpoint blockade

Nivolumab (anti-PD1)

- Phase I study in relapsed/ refractory MM, NHL, HL; expansion cohort for HL
- 23 patients with median 5 lines of prior therapy
- ORR 87% (CR 17%)
- PDL1 and PDL2 expression observed in all tumor samples tested
- FDA breakthrough therapy designation in 2014

Pembrolizumab (anti-PD1)

- Phase 1 study in relapsed/ refractory MDS, MM, NHL, HL; expansion cohort for HL
- 15 patients with median 4 lines of prior therapy
- ORR 65% (CR 21%)
- Responses for both agents appear durable, though longer follow up is needed

Ansell *et al.*, N Engl J Med 2015
Moskowitz *et al.*, ASH 2014

Immune checkpoint blockade

2) After stem cell transplant (SCT): pros and cons…

- Minimal residual disease state
- Immune reconstitution leads to increased lymphocyte subsets that are targets of PD1 inhibition
- Augmentation of graft-versus-tumor effect in allogeneic setting

but

- Impact on risk of graft-versus-host disease in allogeneic setting

Immune checkpoint blockade

Pidilizumab (anti-PD1)

- Phase 2 study in 72 patients with diffuse large B-cell lymphoma (DLBCL) after autologous SCT
- 18-month PFS 72% (51% RR in patients with measurable disease *after* SCT)

Ipilimumab (anti-CTLA4)

- CTLA4 blockade not as well studied in hematologic malignancies, but may have a role in post-SCT setting
- Phase 1 study in 29 patients with relapse after allogeneic SCT
- No severe GVHD or DLTs
- Some evidence of anti-tumor activity (2 CRs and 1 PR)

Armand *et al.*, J Clin Oncol 2013
Davids *et al.*, Blood 2014

Immunotherapy in hematologic malignancies: The Future!

Future Directions:

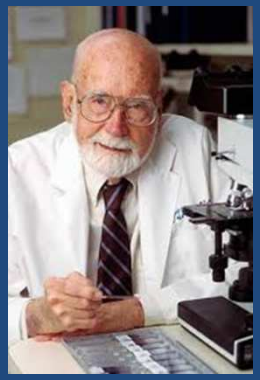
- Ongoing development and refinement of antigen discovery and novel immunotherapies
- Broadening the availability of novel immunotherapies beyond highly specialized centers
- Developing experience in the management of complications of immunotherapies
- Developing appropriate clinical endpoints and response assessments
- *Combining immune therapies*

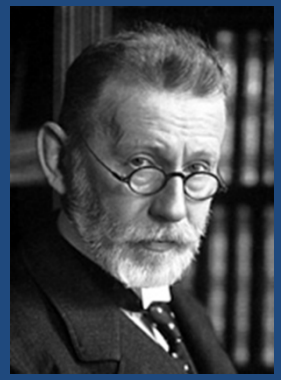
Immunotherapy in hematologic malignancies: The Future!

Best role for novel immunotherapies?

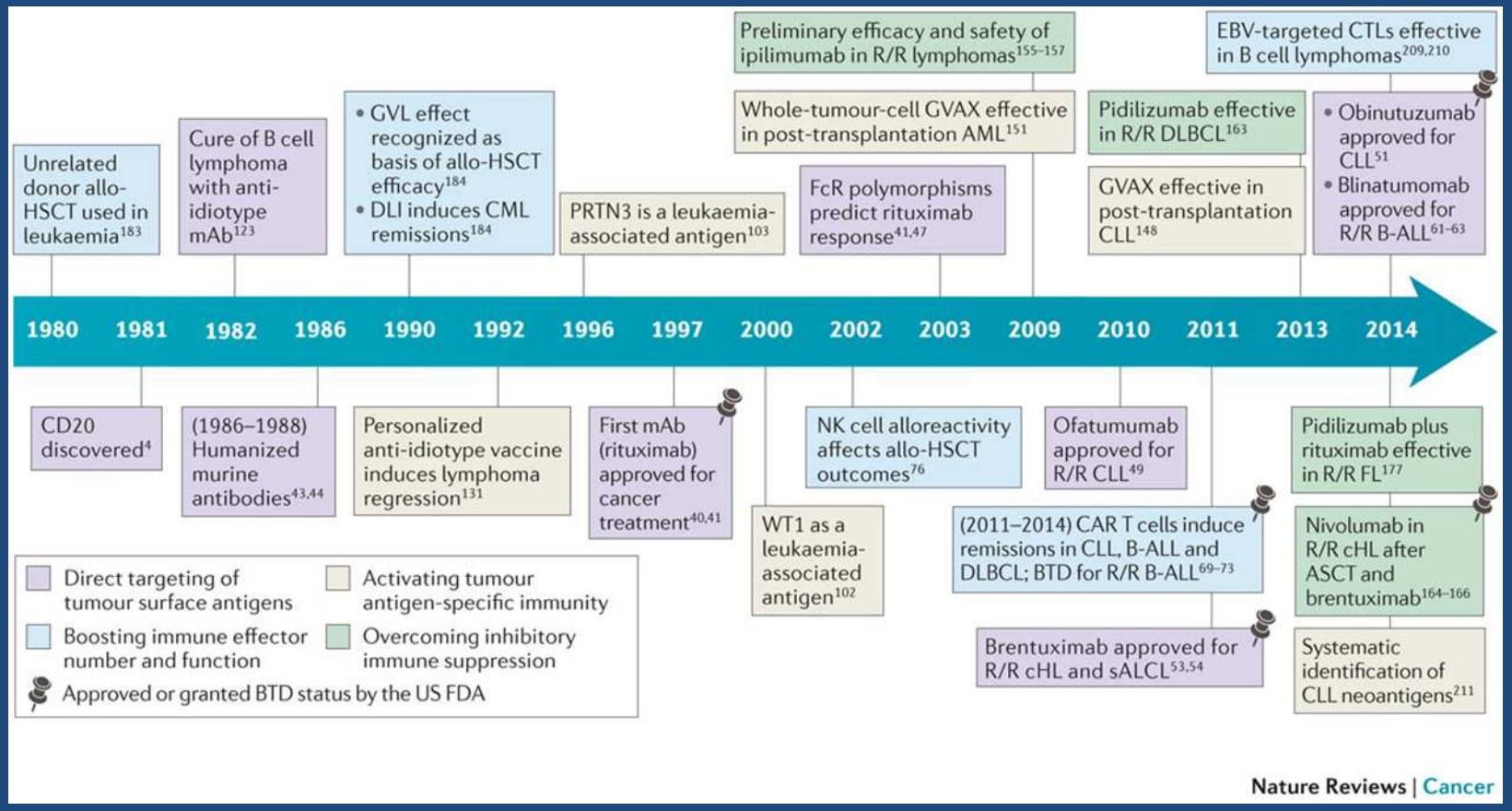
- As a bridge to SCT
- To treat post-SCT relapse
- Treatment for transplant-ineligible or lack of donor
- *As a complement to SCT (enhancement of graft-versus-leukemia effect)*
- In place of SCT…? (durability of response)

Chemotherapist's bluntest weapon → magic bullet





Timeline of major immunotherapeutic advances in hematologic malignancies



Bachireddy *et al.,* Nat Rev 2015