CUTANEOUS T-CELL LYMPHOMA: SYSTEMIC THERAPY

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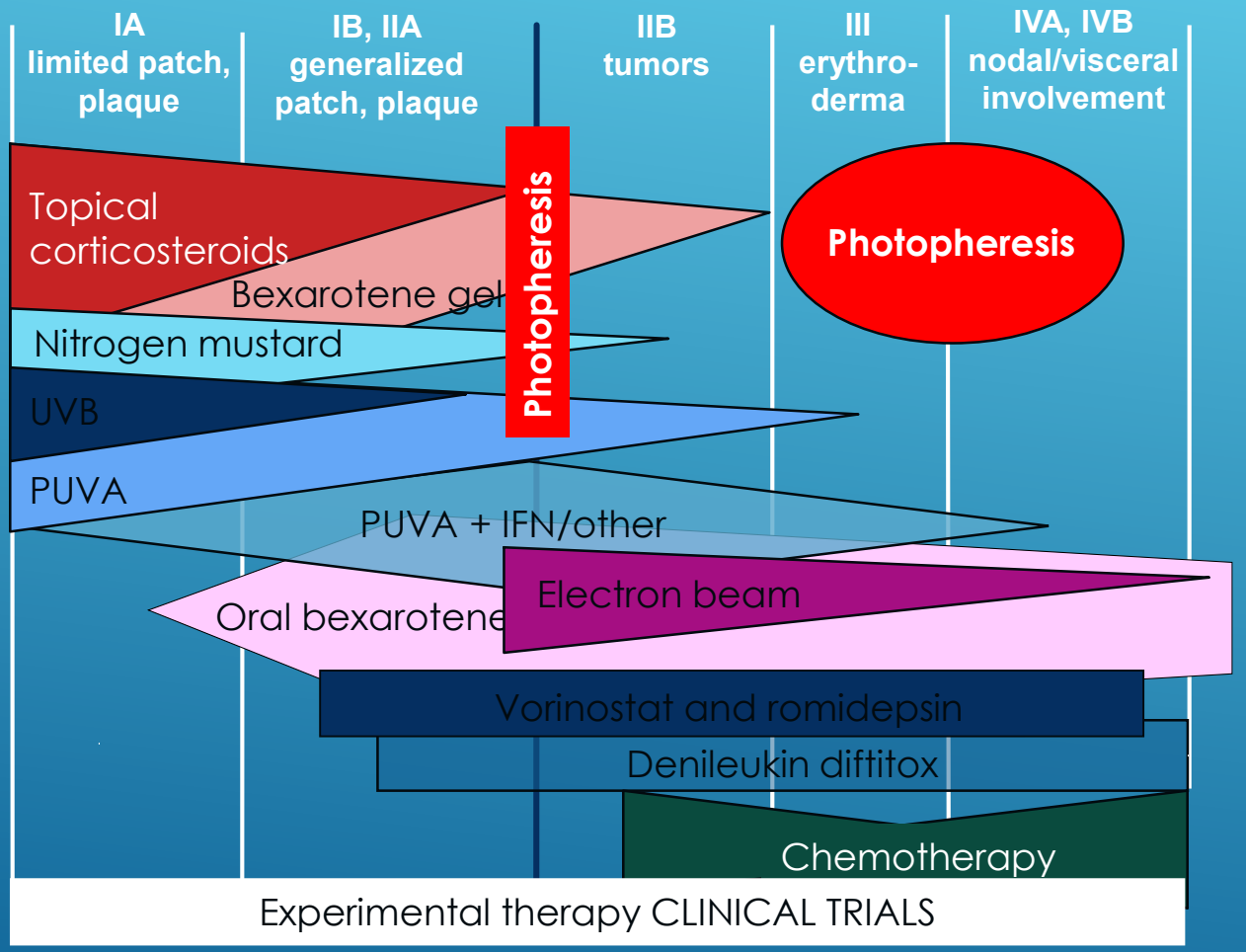
CTCL	Extranodal	Nodal	Leukemia
Mycosis fungoides	Extranodal NK/T cell lymphoma, nasal type	Peripheral T-cell lymphoma, NOS	Adult T-cell leukemia/lymphoma
Sezary Syndrome	Enteropathy-associated T-cell lymphoma	Angioimmunoblastic T-cell lymphoma	T-cell prolymphocytic leukemia
Subcutaneous panniculitis-like TCL	Hepatosplenic T-cell lymphoma	*Follicular T-cell lymphoma**	T-cell large granular lymphocytic leukemia
CD30+ T-cell LPDs (LyP, pcALCL)	Monomorphic epitheliotropic intestinal TCL*	*Nodal T-cell lymphoma with TFH phenotype**	Aggressive NK-cell leukemia
PC γδ T-cell lymphoma	Indolent T-cell LPD of the GI tract*	Anaplastic large-cell lymphoma, ALK-pos	*Chronic LPD of NK cells*
PC CD8+ epidermotropic cytotoxic TCL	*Breast implant-associated ALCL**	Anaplastic large-cell lymphoma, ALK-neg *	
*PC acral CD8+ TCL**	Systemic EBV+ TCL of childhood*		
*PC CD4+ small/medium T-cell LPD**	Hydroa Vacciniforme-like LPD*		

2016 WHO Classification
Swerdlow, et al. Blood. 2016; 127(20):2375-2390.

CTCL PRIMARY TREATMENT MAP



Pozadzides J, et al. T Cell Lymphomas. In: Kantarjian HM, et al. The M. D. Anderson Manual of Medical Oncology, 2nd Edition. 2011

Slide by Madeline Duvic,

GENERAL MANAGEMENT OF MF/SS

- Mycosis Fungoides and Sezary Syndrome are chronic illnesses
- Long term treatment required
  - Combination of approaches w/ topical and systemic and radiation therapy
  - Treatments sometimes re-used over the years
  - Chemotherapy only used in advanced stage disease – usually monotherapy
  - Multidisciplinary approach: Dermatology, oncology, radiation oncology, pathologists, wound care
- Complete remission unlikely
  - Minor or partial response not considered failure
  - Aim for durability and low toxicity
- Supportive care – consider antibiotics for prophylaxis of skin infections

GOALS OF THERAPY IN CTCL

"The aim of treatment in relapsed/refractory CTCL is to safely induce prolonged remission without compromising a patient's immunity or adversely affecting their quality of life."

Zinzani et al. Critical Reviews in Oncology/Hematology 99:228-240, 2016.

WHEN DO WE USE SYSTEMIC THERAPIES IN MF?

- Early stage MF (I/IIA), refractory to skin-directed therapies
- Significant folliculotropic disease, large cell transformation
- Advanced stage MF/SS, IIB-IV – systemic therapy used upfront

→ Systemic therapy +/- skin directed therapy

Used with permission from Alison Moskowitz, MD

WHAT ARE THE SYSTEMIC THERAPIES?

CLASSIC CHEMOTHERAPY DRUGS

- **Gemcitabine**
- Schedule: IV weekly for 3 of every 4 weeks
- Response (based on skin response):
  - Overall response rate of 68%
  - Complete response 12%
- Most frequent side effects:
  - A decrease in blood counts, especially platelets
  - Abnormal liver results on blood tests
  - Fatigue

- **Liposomal doxorubicin**
- Schedule: IV every other week for up to 6 months
- Response(based on skin response):
  - Overall response rate of 41-84%
  - Complete response rate of 6-42%
- Notable side effects:
  - Rash
  - Cardiac (heart) toxicity

Dummer et al. JCO 30:4091-4097, 2012.
Duvic et al. Clin Lymph & Myeloma 7;51-58, 2006.

HISTONE DEACETYLASE INHIBITORS

FDA APPROVED FOR CTCL

	ORR, %	CR Rate, %	Median TTFR, mo	Median DOR, mo	Median TTP, mo	Toxicities
Vorinostat Study 1 (N=74)[8]	30	1	2	5.6	5	Thromboembolism, thrombocytopenia, anemia, nausea, vomiting, diarrhea (may require electrolyte replacement), fatigue
Vorinostat Study 2 (N=33)[13]	24	0	3	3.5	7	
Romidepsin Study 1 (N=96)[10,11]	34	6	2	15	Not reported	Neutropenia, thrombocytopenia, anemia, nausea, fatigue, T-wave changes, QT prolongation requiring electrolyte monitoring
Romidepsin Study 2 (N=71)[12]	35	6	2	13.7	15.1	

ORR: Overall response rate
CR: Complete response rate
TTFR: Time to First Response
DOR: Duration of response

Lansigan and Foss, Clinical Oncology 2010

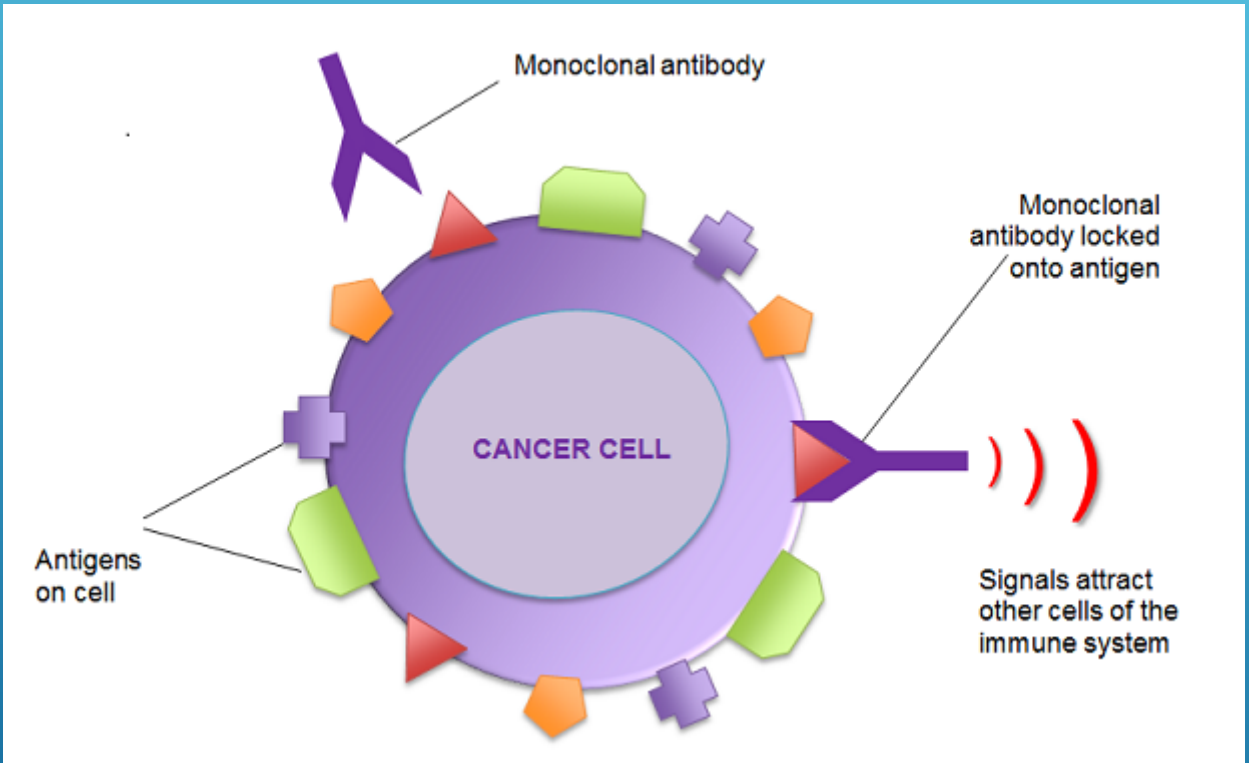
PRALATREXATE

ANTINEOPLASTIC FOLATE THAT PREVENTS DNA SYNTHESIS AND CAUSES CELL DEATH

- Patients (n=54):
  - Median of 4 prior systemic therapies
  - ≥ stage Ib
- Schedule: IV weekly for three of every 4 weeks
- Response:
  - Overall response rate: 41% (mostly partial responses)
  - Median time to best response 57 days
- Most frequent side effects:
  - Sores in mouth 56% (severe 17%)
    - All patients will get vitamin B12 and folic acid supplements to decrease risk
  - Fatigue 41%
  - Mild nausea 39%

Horwitz et al. Blood 2012;119:4115-4122.

IMMUNOTHERAPY FOR CTCL



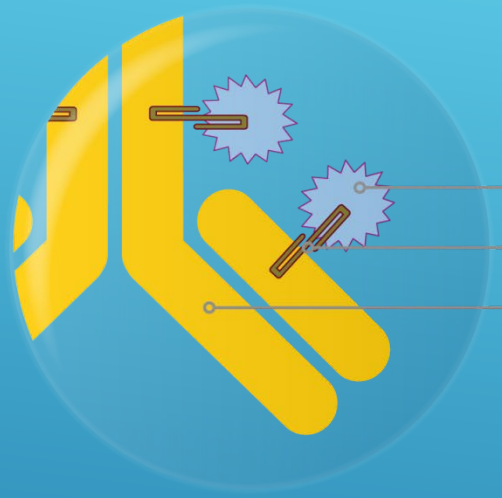
Picture from https://myepqlog.wordpress.com/2017/01/20/what-is-immunotherapy/ accessed on 10/3/18

ALEMTUZUMAB

- Monoclonal Antibody against CD52
  - CD52 is expressed on B and T cells
- Schedule:
  - Monday, Wednesday and Friday for up to 3 months
  - IV or as a shot
- Outcomes:
  - Overall response rates of 38-100% - most reports are around 80%
  - Complete response rates 21-100%
  - Duration of response:6-12 months – some long term responders
- Mostly used in sezary syndrome
- Adverse Events: infections so patients maintained on anti-infectious medications

Alinari et al. Leuk res 32:1299-1303, 2008.
Kenndey et al. Eur J haem 2003:71:250-6.
Querfeld et al. Leuk lymphoma 2009:50:1969-1976.
Benengo et al Haematologica 2007;92:784094.

Brentuximab Vedotin

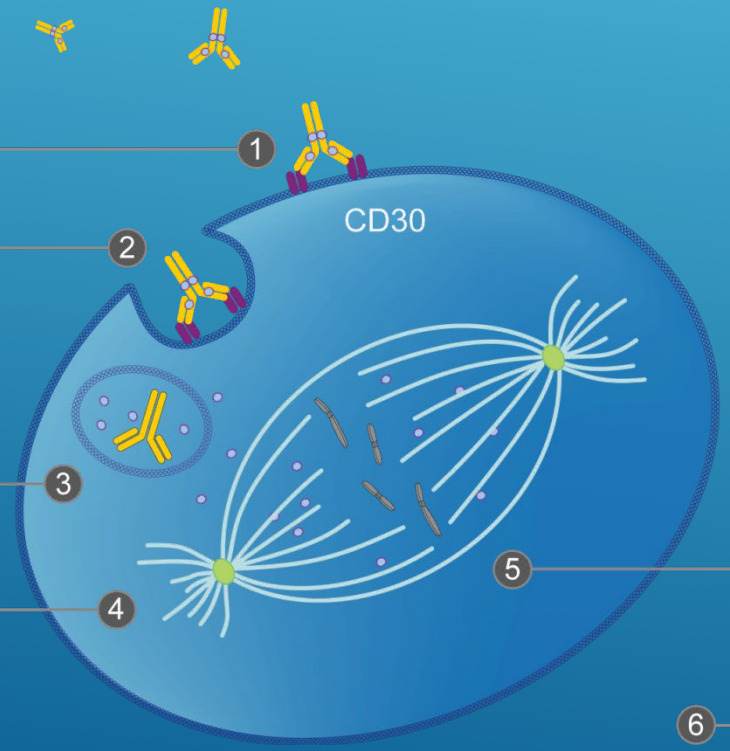


Brentuximab vedotin (SGN-35) ADC

Monomethyl auristatin E (MMAE), potent antimicrotubule agent

Protease-cleavable linker

Anti-CD30 MoAb



ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

MMAE disrupts microtubule network

G2/M cell cycle arrest

Apoptosis

Used with permission from Frederick Lansigan, MD

ALCANZA Phase III study

Brentuximab vedotin: 1.8 mg/kg IV, every 3 weeks

vs

Methotrexate: 5–50 mg
Or
Bexarotene: 300 mg/m²

- **Eligibility**
  - **CD30⁺ cutaneous lymphoma**
  - **MF made up 75% of patients**
  - **131 patients were enrolled**

- **Primary endpoint**
  - **ORR4 = rate of objective response lasting ≥4 months**
  - **Global response of all compartments using consensus criteria (mSWAT for skin evaluation, radiographic assessment, and circulating Sézary cell assessment as appropriate)**

Kim YH, et al. ASH 2016
Prince HM and Kim YH, et al. Lancet. June 2017.
Used with permission from Alison Moskowitz, MD

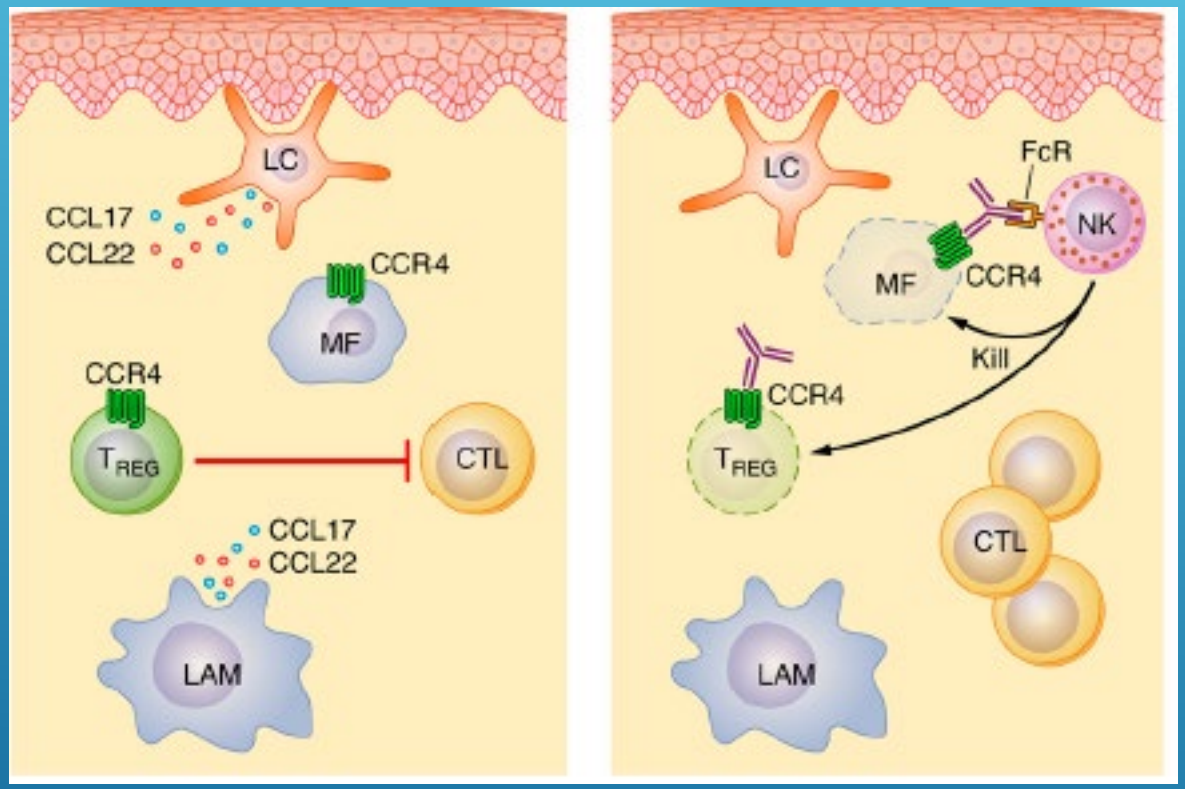
ALCANZA PHASE III STUDY RESULTS

	Brentuximab Vedotin	MTX or Bexarotene
Overall Response Rate	67%	20%
Response lasting ≥4 months all patients	56%	12%
Complete Response Rate	16%	2%
Median Duration of Response	15 months	18 months
Peripheral neuropathy	67%	6%

Prince HM and Kim YH, et al. Lancet. June 2017.

MOGAMULIZUMAB:

MONOCLONAL ANTIBODY TARGETING THE CHEMOKINE RECEPTOR CCR4
CCR4 IS EXPRESSED ON MYCOSIS FUNGOIDES CELLS AND T REGULATORY CELLS



Mogamulizumab allows your immune system to better attack the cancer cells

Ryan A. Wilcox Blood 2015;125:1847-1848

Phase III Mavoric study

Mogamulizumab 1mg/kg IV, q14 days

VS

Vorinostat 400mg po daily

- **372 patients with CTCL randomized**
  - ***Stage Ib-IVb***
  - ***Median age 64 years***
  - ***Median of 3 prior therapies***

- **Excluded**
  - **Large cell transformation**
  - ***Patients with active autoimmune disease***

Kim et al. Lancet Oncology 2018;19:1192-1204

PHASE III MAVORIC STUDY RESULTS

	Mogamulizumab	Vorinostat
Global Response Rate • Skin response • Lymph node response • Blood response	28% • 42% • 15% • 67%	5% • 16% • 4% • 18%
Median Duration of Response • Skin • Lymph node • Blood	 • 20 months • 15 months • 25 months	 • 10.7 months • NE • NE
Median Time to Response	3.3 months	5.1 months
NE=Not evaluable		

Kim et al. Lancet Oncology 2018;19:1192-1204

MOGAMULIZUMAB SIDE EFFECTS

- Rash:
  - 25% of patients
  - Severe rash in 3.6%
- Infusion reaction while receiving drug:
  - Chills, nausea, fever, fast heart rate, headache, vomiting
  - 1/3 of patients; severe in 8%
  - Usually 1st cycle
- Autoimmune complications to thyroid, lungs, liver etc.
  - Severe in <5%

Kim et al. Lancet Oncology 2018;19:1192-1204

CHECKPOINT INHIBITORS IN CTCL

PEMBROLIZUMAB

Patients:

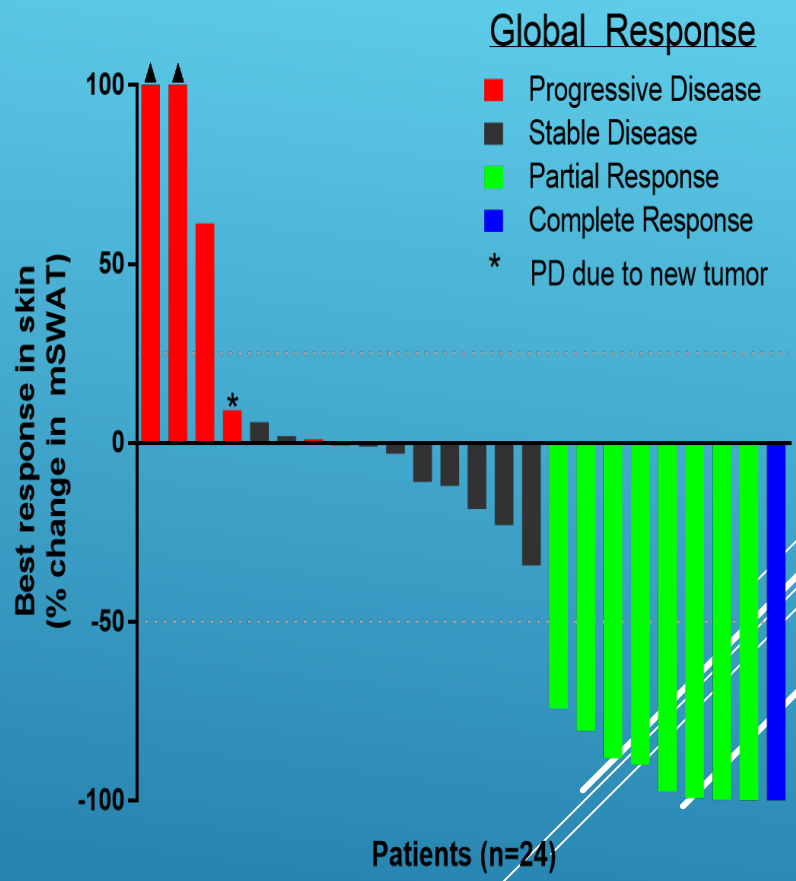
- 24 patients with relapsed/refractory CTCL
- 63% had received ≥ 4 prior therapies

Results:

- ORR 38% (CR 4%)
- 6 of 9 responders had a 90% decrease in skin disease
- Sustained response in 8 of 9 responders

Side effects:

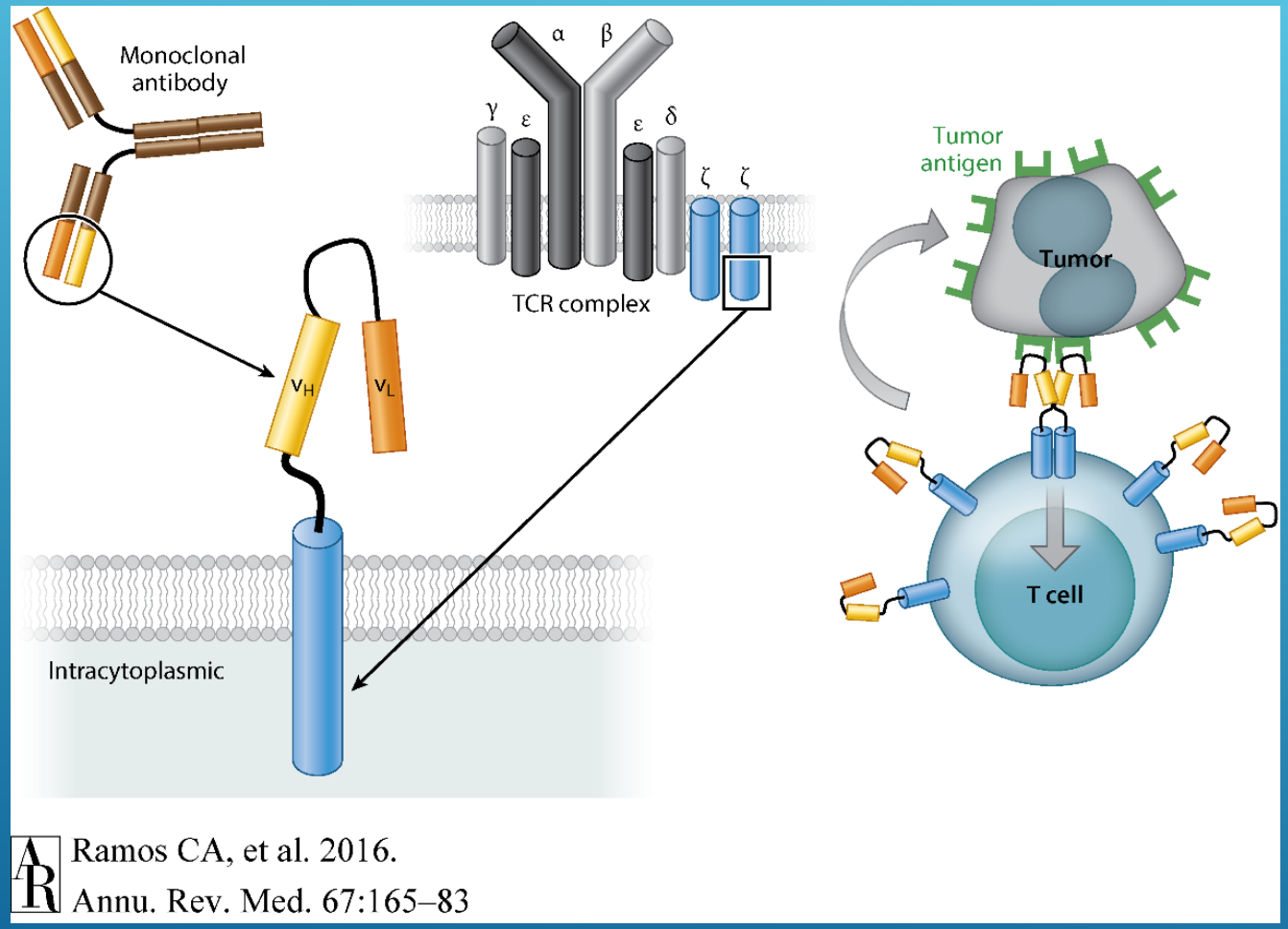
- Flare up of the skin disease
- Autoimmne issues (diarrhea, pneumonitis)



Khodadoust et al. Blood 2016 128:181.

CLINICAL TRIAL AT UNC

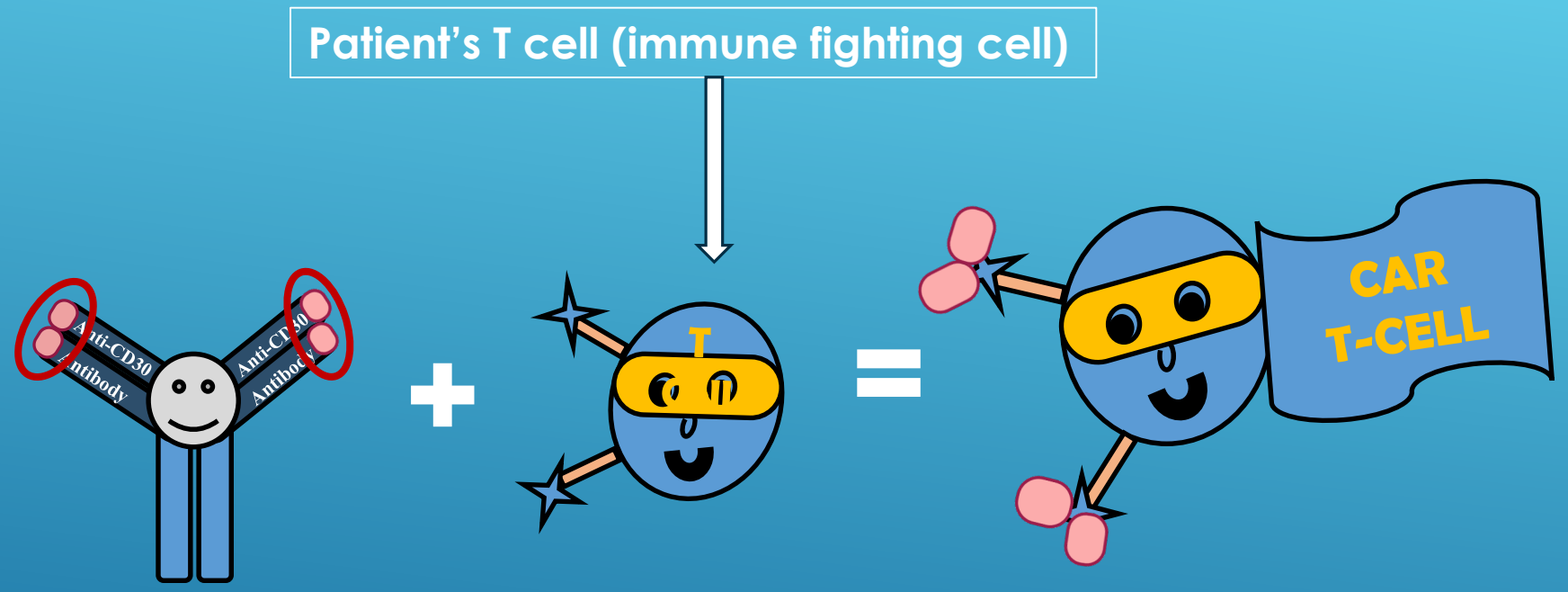
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS



- Hybrid molecule:
  - Extracellular antigen-recognition site from an antibody
  - Intracellular signaling domain of T-cell receptor
- CAR binds antigen on surface of tumor cells -> T cell activation and killing of tumor cells

Slide courtesy of Natalie Grover, MD

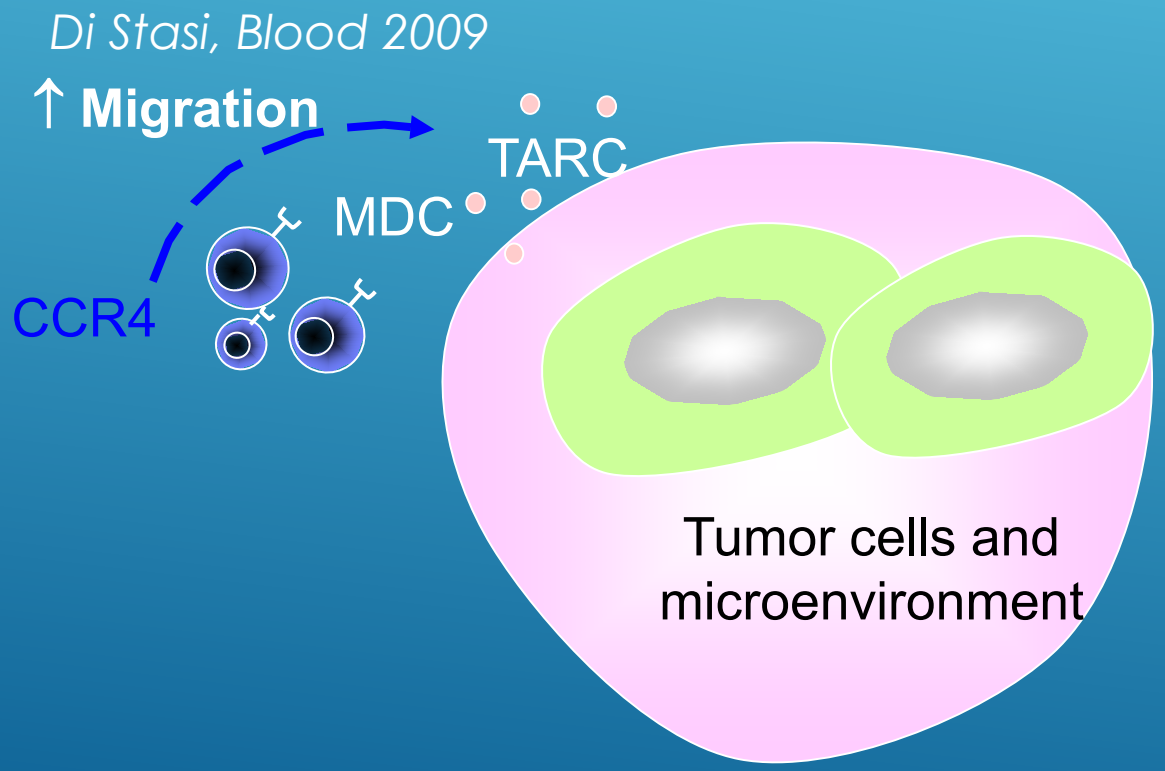
Patient's T cell (immune fighting cell)



Protein targeting CD30 marker
(CD30 is what brentuximab vedotin targets)

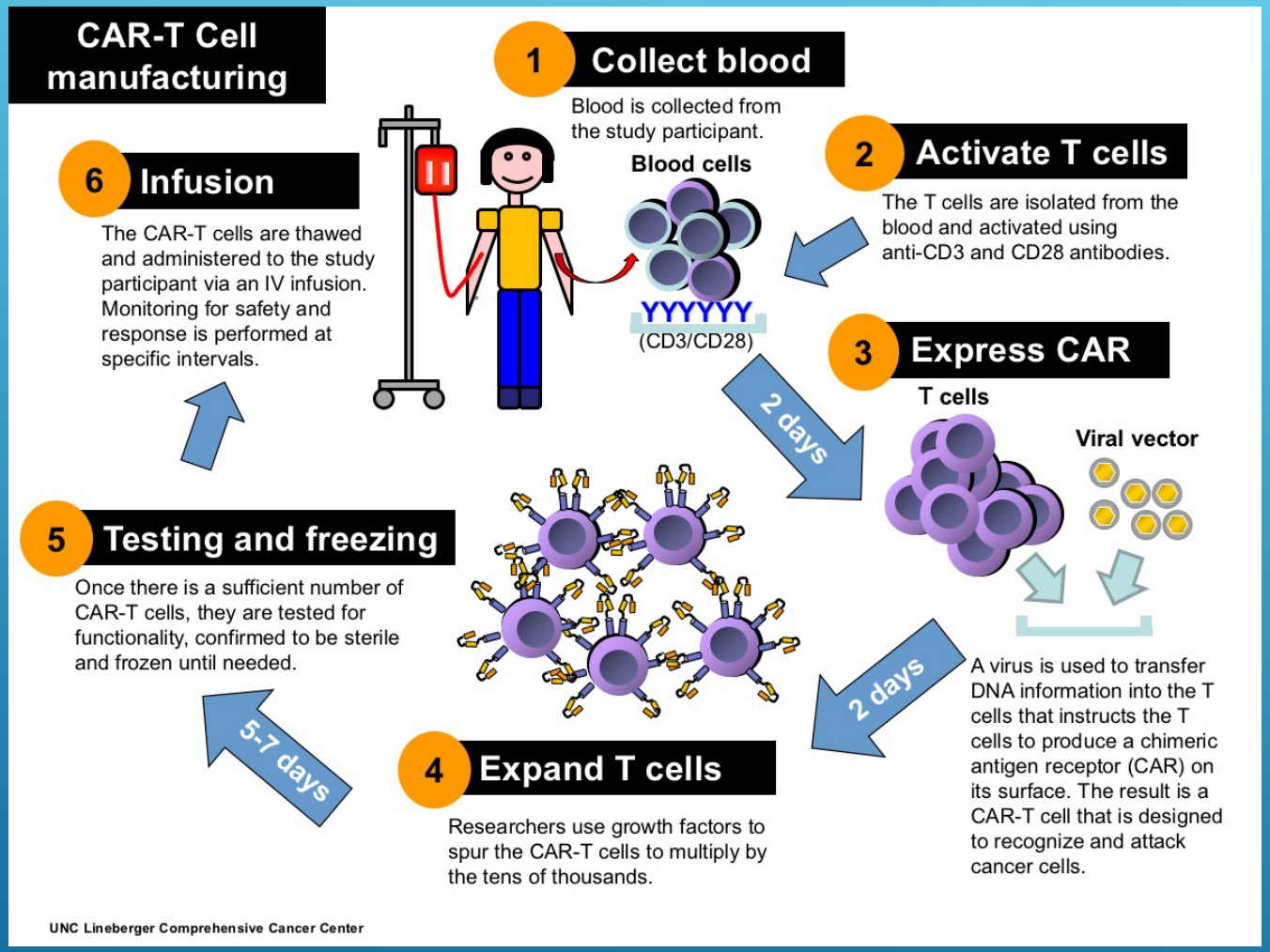
Slide courtesy of Natalie Grover, MD

LCCC 1606: HOW TO OPTIMIZE BENEFIT OF CAR-T CELLS FOR CD30+ LYMPHOMA?



- CD30.CART enhanced with expression of CCR4 (same target as mogamulizumab)
- Hypothesis: Improved targeting of CAR-CD30 modified T cells to tumor site, leading to increased anti-lymphoma activity

Slide courtesy of Natalie Grover, MD


CAR-T Cell manufacturing
1 Collect blood
Blood is collected from the study participant.
Blood cells
2 Activate T cells
The T cells are isolated from the blood and activated using anti-CD3 and CD28 antibodies.
YYYYYY
(CD3/CD28)
3 Express CAR
T cells
Viral vector
2 days
A virus is used to transfer DNA information into the T cells that instructs the T cells to produce a chimeric antigen receptor (CAR) on its surface. The result is a CAR-T cell that is designed to recognize and attack cancer cells.
2 days
4 Expand T cells
Researchers use growth factors to spur the CAR-T cells to multiply by the tens of thousands.
5-7 days
5 Testing and freezing
Once there is a sufficient number of CAR-T cells, they are tested for functionality, confirmed to be sterile and frozen until needed.
6 Infusion
The CAR-T cells are thawed and administered to the study participant via an IV infusion. Monitoring for safety and response is performed at specific intervals.
UNC Lineberger Comprehensive Cancer Center

PROSPECTIVE DATA IN CTCL

	ORR	CR	Median DOR. months	Pruritus Improved	FDA approved for CTCL
Gemcitabine	64%	9%	NR	NR	No
HDAC-I (romidepsin, vorinostat)	14-34%	0-10%	1.4-15	Y	Yes
Alemtuzumab*	38-84%	0-47%	2.2-6	Y	No
Brentuximab vedotin**	67-73%	16-35%	7.4-15	NR	No
Liposomal Doxorubicin	41%	6%	6	NR	No
Pralatrexate	41%	6%	NR	NR	No
Mogamulizumab	28%	NR	14	NR	Yes

NR=Not reported; CR=complete response; ORR=overall response rate; DOR=duration of response
*Most benefit seen in sezary syndrome/erythroderma
** Responses seen even with very low level of CD30 expression
HDAC-I- Histone deacetylase inhibitor

Modified from Zinzani et al. Critical Reviews in Oncology/Hematology 99:228-240, 2016.
Dummer et al. JCO 30:4091-4097, 2012.
Kim et al. Blood 2017 130:817.

CTCL - Take home messages

- **Most commonly: indolent, chronic disease**
- **Focus of treatment:**
  - **Improve symptoms**
  - **Minimize toxicity**
  - **Improve and maintain quality of life**
- **Management is very individualized and involves input from dermatology and oncology and radiation oncology**

THANK YOU FOR YOUR ATTENTION