Cutaneous Lymphomas

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Paris 1806: the beginning…

Alibert JLM. Déscriptions des maladies de peau observes à l'Hospital St. Louis, et exposition des meilleurs methodes suivies pour leur traitment. L'Aine Fils, Paris 1806:157–158.

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Treatment Regimens in CTCL 2019

SYSTEMIC THERAPIES			
	Preferred regimens[g] (alphabetical order)	Other recommended regimens	Useful under certain circumstances
SYST-CAT A	• Brentuximab vedotin[h,i,j] • Bexarotene[f] • Extracorporeal photopheresis (ECP)[k] • Interferons (IFN-alpha, IFN-gamma) • Methotrexate (≤50 mg q week) • Mogamulizumab[l] • Romidepsin[f] • Vorinostat[f]	• Acitretin[f] • All-trans retinoic acid[f] • Isotretinoin [13-cis-retinoic acid][f]	
SYST-CAT B	• Brentuximab vedotin[h,i,j] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose)		• Relapsed/refractory disease requiring systemic therapy; alphabetical order by category) ‣ Alemtuzumab[j,n] ‣ Chlorambucil ‣ Cyclophosphamide ‣ Etoposide ‣ Pentostatin ‣ Temozolomide for CNS involvement ‣ Bortezomib (category 2B) ‣ Pembrolizumab (category 2B)[o,p] ‣ See TCEL-B 2 of 5 for regimens listed for PTCL-NOS[m]
Large-Cell Transformation (LCT)	• Brentuximab vedotin[h,i,j] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose) • Romidepsin • See TCEL-B 2 of 5 for regimens listed for PTCL-NOS[m]		

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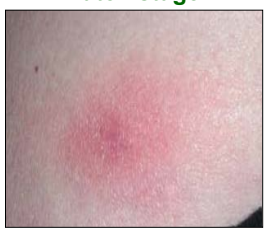
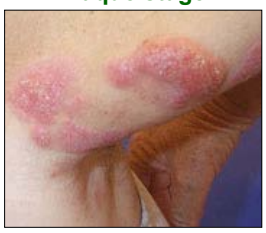
Mycosis fungoides – can progress

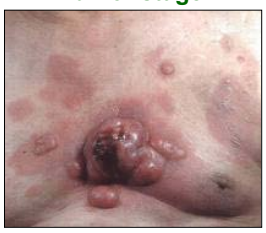
Patch stage



Plaque stage



Tumor stage



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Staging of cutaneous T-cell lymphomas - T category-

Table 1. Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS[1]

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area

Olsen E et al. *Blood* 2007; Olsen E at al. *J Clin Oncol* 2011

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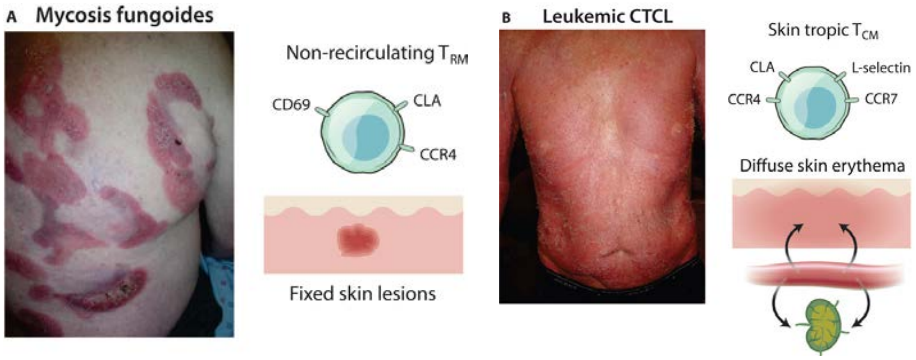
Skin-resident memory and central memory T-cells give rise to distinct forms of lymphoma



Clark RA. *Sci Transl Med.* 2015

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CD30⁺ Lymphoproliferative Disorders (CD30⁺ LPD)

- Second most common group of CTCL after MF/SS
- 25% of CTCL
- Spectrum of diseases including:
  -- Lymphomatoid papulosis (LyP)
  -- Primary cutaneous anaplastic large cell lymphoma (ALCL)
  -- "borderline cases"

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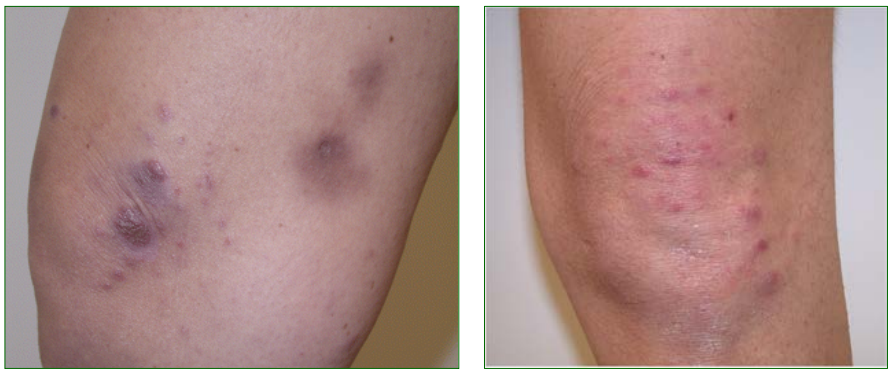

Kempf W et al. *Blood* 2011

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Lymphomatoid papulosis (LyP)

- Chronic, recurrent, self-healing papulonecrotic skin eruption (=multiple lesions)
- Typical: spontaneous regression after weeks-months
- Persists/recurrent disease for years or decades
- No effect on mortality
- Up to 25% risk to develop “second” lymphoma (Hodgkin lymphoma, mycosis fungoides, cutaneous or nodal anaplastic large cell lymphoma)
- Histological subtypes, A-F (G), with the same benign clinical course despite sometimes “aggressive” histology/cytology

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LYP types

LYP type	Histological pattern	Phenotype	Major differential diagnoses
A	Mixed cellular	Mostly CD4+	Hodgkin's lymphoma, transformed mycosis fungoides
B	Epidermotropic	CD4+ Note: CD30 can be negative	Mycosis fungoides
C	Cohesive infiltrate	CD4+ > CD8+	Anaplastic large cell lymphoma, HTLV1-associated lymphoma
D	Epidermotropism (pagetoid pattern)	CD8+ (100 %) Note: CD30+ (in 90 % cases)	Aggressive epidermotropic CD8(+) cytotoxic T-cell lymphoma
E	Angiocentric and angiodestructive	CD8+ (70 %)	NK/T-cell and gamma/delta lymphoma

Additional patterns described in the literature:
- Folliculotropic growth pattern
- Granulomatous and syringotropic/eccrinotropic growth pattern
- Intralymphatic growth pattern

Note: Types A to E are included in the revised 2016 WHO classification of hematopoietic and lymphoid tumors.

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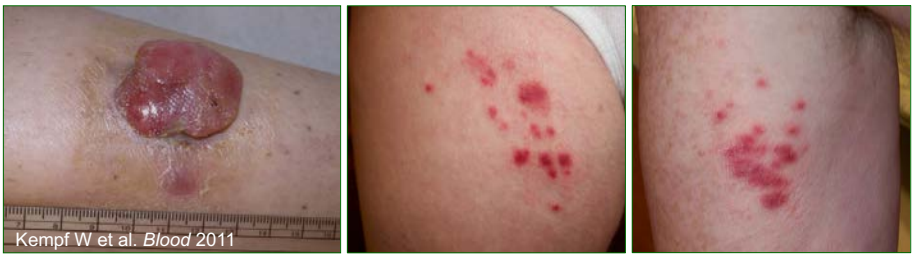
Cutaneous anaplastic large cell lymphoma (ALCL)



- Solitary or grouped, rapidly growing nodules or tumors
- Often multifocal
- Overall favorable prognosis with 5-year survival rates of 76-96%
- pcALCL arising on legs has worse prognosis (76%)

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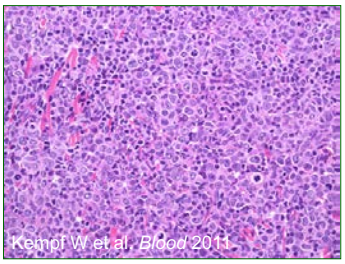
Cutaneous anaplastic large cell lymphoma (ALCL)



- Histology: nodular, cohesive infiltrates (sheets) of large pleomorphic, anaplastic tumor cells
- > 75% of tumor cells $CD30^+$
- Primary cutaneous ALCL usually negative for ALK and t(2;5)
- Systemic ALCL → ALK^+ > ALK^-

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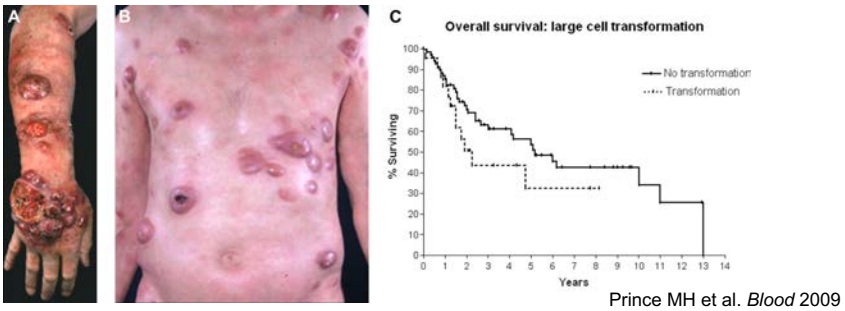
Large Cell Transformation (LCT)



Prince MH et al. *Blood* 2009

- Progression from low-grade to high-grade lymphoma
- LCT after 12.8 yrs of MF
- Clinical: rapid development of tumors (T3)
- Histology: at least 25% of large cells (arbitrary!!!)
- **NEW DATA:** subgroup of LCT patients with more indolent clinical course
- $CD30^+$ associated with longer survival than $CD30^-$

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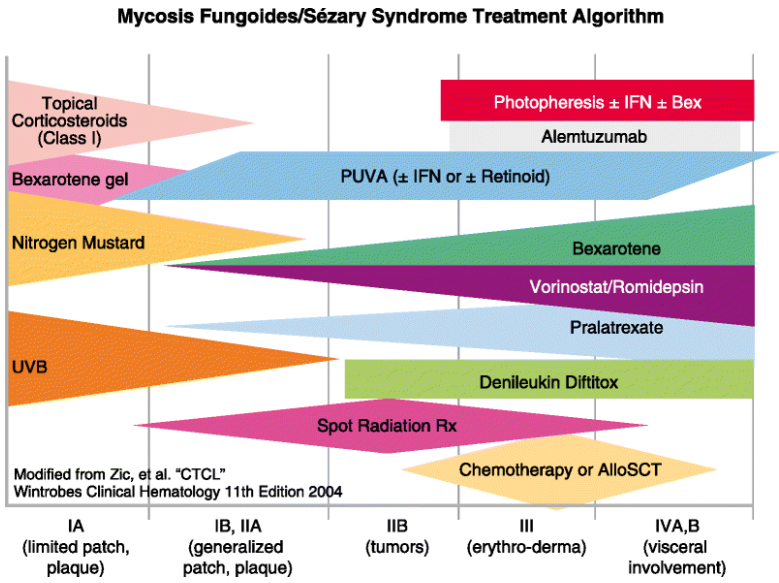

Bloom T et al. *Curr Treat Options Oncol* 2012

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Treatment Regimens in CTCL

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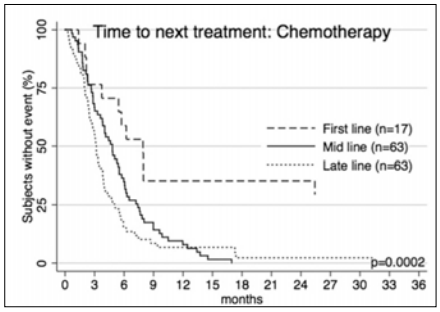
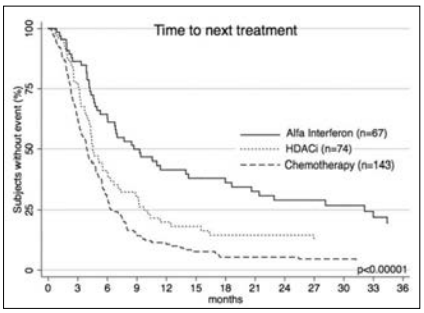
Limited durability of disease control with chemotherapy

Efficacy decreases in pretreated disease



Lack of durable disease control



Hughes CFM et al. *Blood* 2015

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Limited durability of disease control with chemotherapy

Table 1. Major clinical studies of systemic chemotherapy in MF/SS

Therapy	Study type	Efficacy	Durability
EPOCH	NR[14]	ORR stage IIB-IV: 80%	PFS: 8 mo
CHOP-based	NR[15]	ORR stage IIB: 66%	
Fludarabine plus α-interferon	NR[16]	ORR stage IIA-IVA: 58% ORR stage IVB: 40%	PFS: 5.9 mo
Fludarabine plus cyclophosphamide	NR[17]	ORR stage IIB-III: 55%	DOR: 10 mo
Gemcitabine	NR[18]	CR: 22%	Duration of CR: 10 mo
	NR[19]	CR: 11.5%	Duration of CR: 15 mo
	NR[20]	ORR: 51%	DFI: 15-120 mo
Pegylated liposomal doxorubicin	RA[21]	ORR stage IA-IV: 88%	DFS: 13.3 mo
	NR[25]	ORR: 41%	DOR: 6 mo
Low-dose methotrexate	RA[22]	ORR T2 disease: 33%	TTF: 15 mo
	RA[23]	ORR T4 disease: 58%	TTF: 31 mo
Pralatrexate	NR[24]	ORR transformed disease: 25%	PFS: 1.7 mo

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete response; DFI, disease-free interval; DFS, disease-free survival; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisolone; NR, nonrandomized; RA, retrospective analysis; TTF, time-to-treatment failure.

Hughes CFM et al. *Blood* 2015

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METHOTREXATE

- Low dose weekly
- Generally well tolerated and convenient (oral weekly)
- Dose- response effect is common and usually start at 20-30 mg/wk (up to 60-70 mg/ wk)
- Some responses can be very durable
- Most common side effects are cytopenias and long-term risk of liver disease
- Very effective in patients with coexistent lymphomatoid papulosis (LyP)
- Can be used in conjunction with other therapies such as steroids, ECP, PUVA, IFN-a

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SYSTEMIC BEXAROTENE

- FDA approval for refractory cutaneous T-cell lymphoma
- Third generation retinoid with antineoplastic (anti-cancer) effects
- often used in combination with other treatments (e.g. ECP, IFN, phototherapy)
- Elevated triglycerides, depressed thyroid function, decreased blood counts (platelets!)
- Usually requires treatment for hypertriglyceridemia, hypothyroidism
- **Administration orally using low-dose regimen in the US**

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INTERFERON

- Major difficulty is tolerance and compliance
- Somewhat inconvenient (daily sc injection)
- Most common side effect is fatigue, anorexia, and mood changes particularly in older patients
- Monitoring for cytopenias and thyroid disturbance is recommended
- Requires moderately high doses aiming for 3-5+ MU 3x/wk
- Monitor FBC and thyroid function
- IFN-a can also be combined with ECP, PUVA, bexarotene

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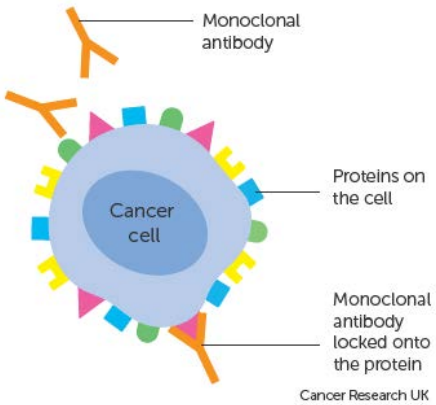
Monoclonal antibodies

TARGETED SYSTEMIC THERAPIES



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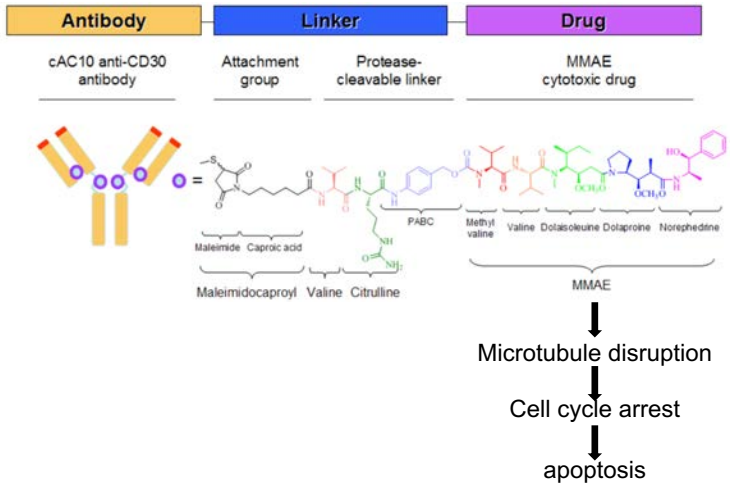
BRENTUXIMAB VEDOTIN (ADCETRIS®)



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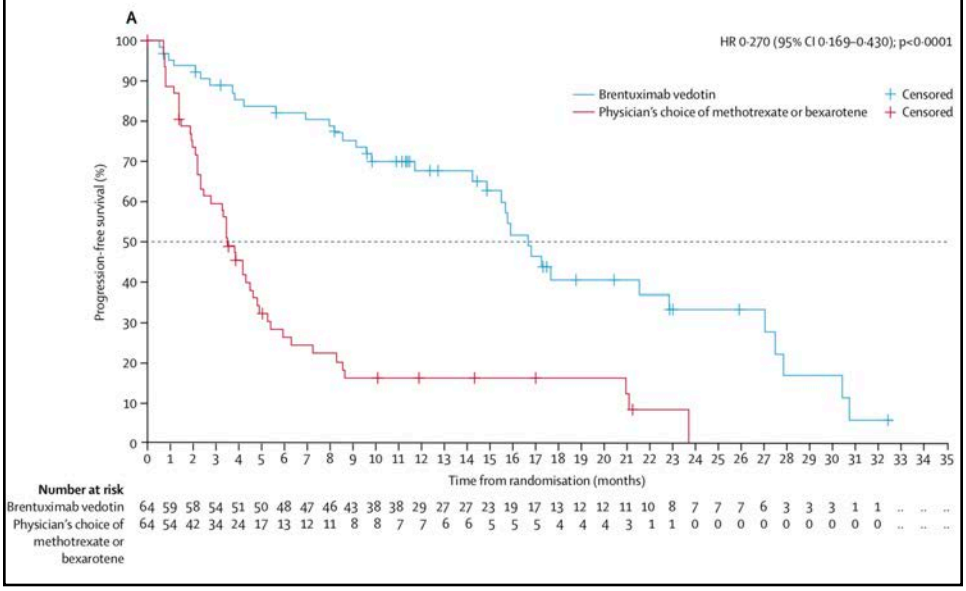
The "ALCANZA" trial – Brentuximab vedotin in Mycosis fungoides (CD30+) and pc Anaplastic Large-Cell Lymphoma



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BRENTUXIMAB VEDOTIN (SGN35)

- FDA approval for Hodgkin's lymphoma, ALCL and **CTCL (Nov 2017)**
- CTCL: primary cutaneous anaplastic large cell lymphoma (pcALCL) and CD30-expressing mycosis fungoides (≥10% of infiltrate by central review)
- Responses lasting at least 4 months in 60.9% of patients versus 7.8% in patients receiving physician's choice of standard therapies (ALCANZA trial)
- Peripheral neuropathy: 67% (vs. 6% in control arm)
- **Administration by infusions at infusion center (day 1 of 21-day cycle, up to 16 cycles)**

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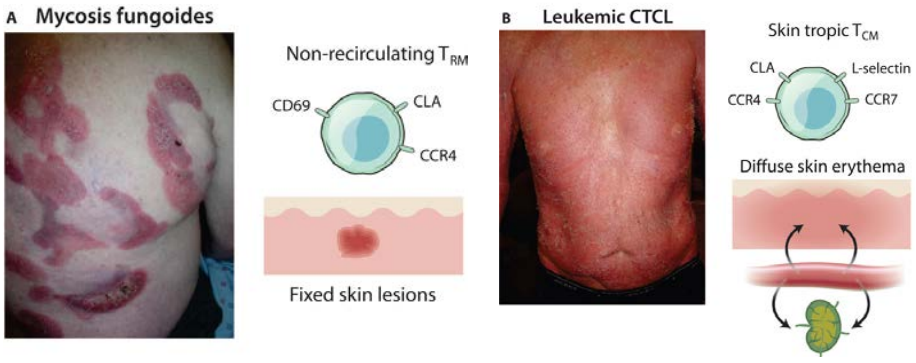
Circulating and skin-resident T-cells give rise to distinct forms of lymphoma



Clark RA. *Sci Transl Med.* 2015

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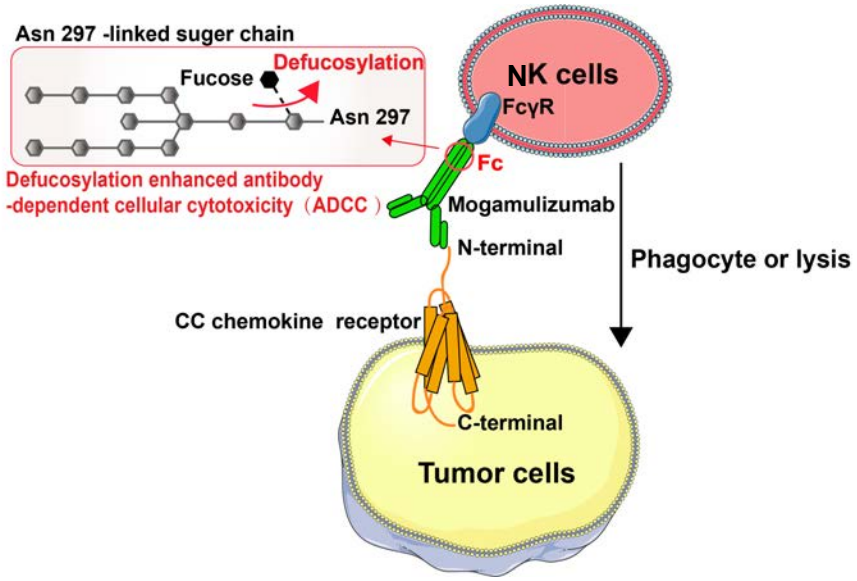
MOGAMULIZUMAB-KDKC (POTELIGEO®)



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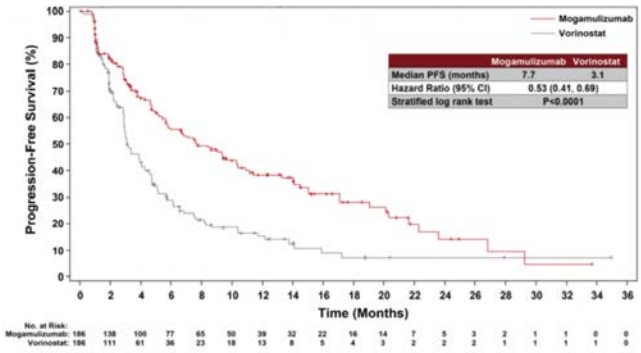
The "MAVORIC" trial – Mogamulizumab in Mycosis fungoides and Sézary syndrome

Figure 1. Primary Endpoint: Progression-free Survival



Source: Kim YH et al. Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): Results from the Phase III MAVORIC Study. Presented at the ASH Annual Meeting; December 2017. Abstract 817.

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MOGAMULIZUMAB-KPKC

- FDA approval for Mycosis fungoides and Sézary syndrome (Aug 2018)
- *Median PFS 7.7 months versus 3.1 months in patients receiving vorinostat (MAVORIC trial)*
- *Infusion reaction*
- *Rash*
- **Administration by infusions at infusion center (days 1, 15 of 28-day cycle, start days 1, 8, 15, 22 of 28-day cycle)**

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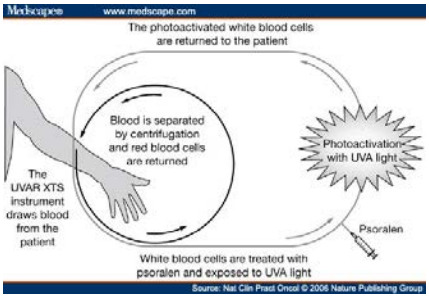
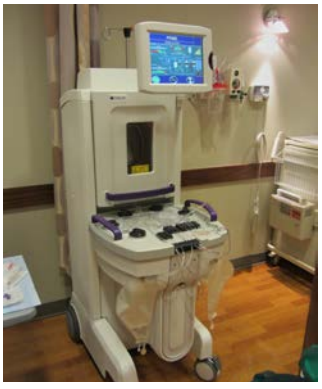
Extracorporeal Photopheresis (ECP)





- FDA-approved for CTCL in 1988
- Sézary syndrome, erythrodermic CTCL
- 2 consecutive days every 2-4 weeks

Side effects
- Dizziness, hypotension
- Headache
- Fever, chills, nausea

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Stem Cell Transplantation

Basic concept
- Complete elimination of disease with aggressive treatment and subsequent transplantation of healthy immune system from patient (autologous) or matched donor (allogeneic)

Steps
- "Conditioning treatment" with destruction of ideally all lymphoma cells
- "Transplantation" of donor stem cells giving rise to a healthy immune system

Problems
- Toxicity, infections related to conditioning
- "Graft-versus-host disease"
- Recurrent disease (autologous > allogeneic)

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Clinical trials: new and better treatment options ?

Concept
- New treatments are tested in controlled environment
- Every single step is highly regulated and overseen by the institutional review boards (IRB)

Pros
- Possible effective therapy after several treatment failures
- Results may help to find new treatments for many patients to follow

Cons
- Varying levels of side effects
- Varying levels of research testing

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