Choice of systemic treatment and radiation therapy for CTCL

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Disclosures

Employers:

- Rigshospitalet, Dept. of Oncology, Capital Region, Denmark
- University of Copenhagen, Faculty of Health and Medical Sciences, Denmark

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Primary extranodal lymphomas

- Lymphomas that present primarily with lesions wholly or predominantly confined outside lymph node areas, with or without involvement of adjacent or draining lymph nodes
- Approximately one third of non Hodgkin lymphomas present as extranodal lymphomas
- The most common site is the gastro-intestinal tract, and the second most common is the skin

Primary cutaneous lymphomas (PCL)

- estimated annual incidence 1 /100,000 in Western countries
- differ significantly from nodal lymphomas and from primary extranodal lymphomas in other locations
- remain localized to the skin for a long time
- have a much more indolent course and a much better prognosis than that of lymphomas of similar histological subtype in other locations
- In recent lymphoma classifications PCL are therefore classified as separate entities

The histopathological subtypes of PCL

- Occur in a distinct pattern
- T-cell lymphomas constitute 75-80 %
- Distinct geographic variations
- In the Western world most cutaneous T-cell lymphomas (CTCL) are mycosis fungoides
- In Southeast Asia other types of CTCL predominate
- In the Western world primary cutaneous B-cell lymphomas (CBCL) constitute around 20 % of all PCL
- They are much less common in Asia

Primary Cutaneous T-Cell Lymphomas (PCTCL)

Cutaneous T cell lymphoma

Mycosis fungoides (MF)

Variants of MF

- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin

Sézary syndrome

- Most common cutaneous T-cell lymphoma
- 4 % of all lymphomas, 50 % of all cutaneous lymphomas

Primary cutaneous $CD30^+$ lymphoproliferative disorders

- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

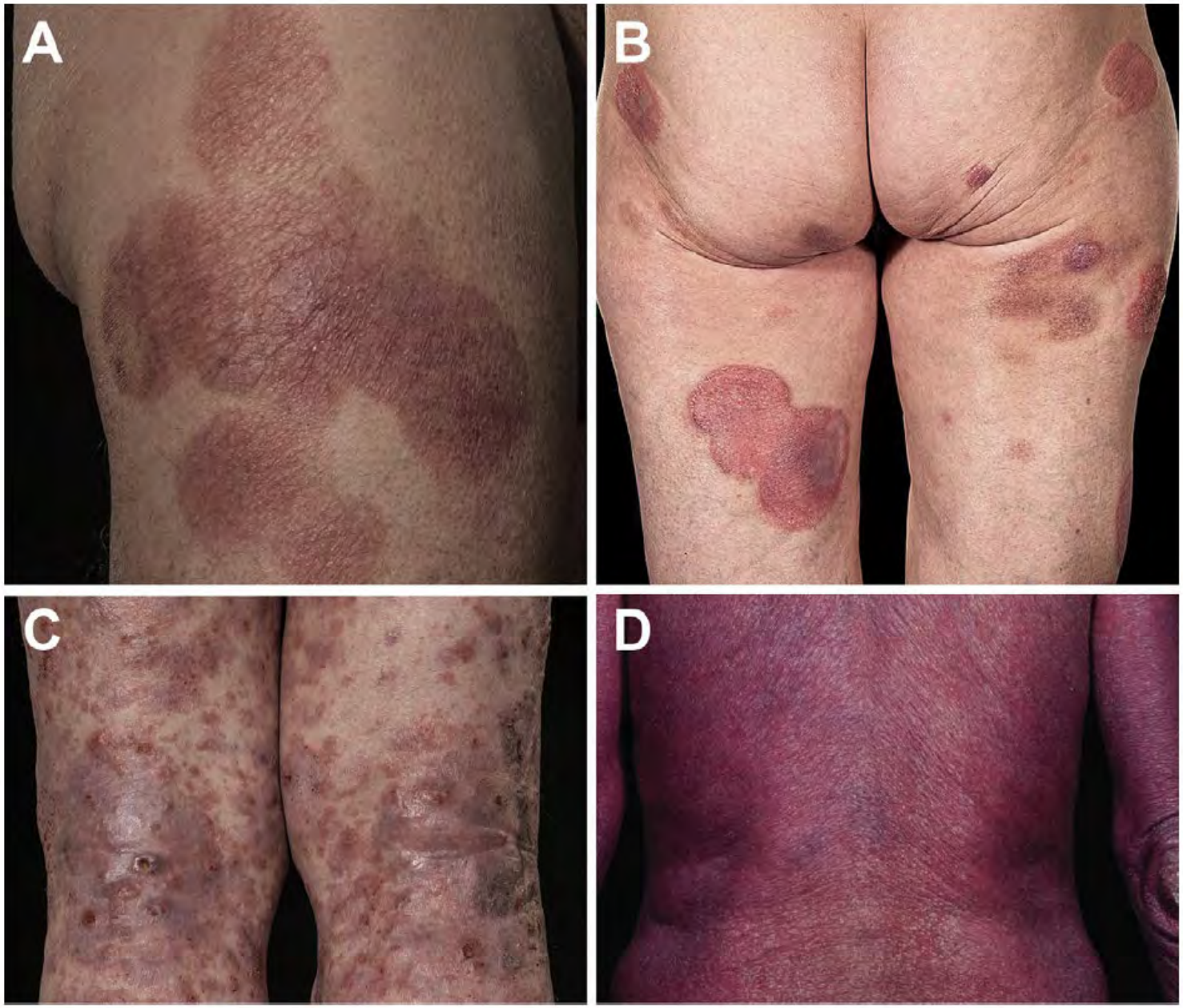
Subcutaneous panniculitis-like T cell lymphoma

Extranodal NK/T cell lymphoma, nasal-type

Primary cutaneous peripheral T cell lymphoma-not otherwise specified

- Primary cutaneous γ/δ T cell lymphoma
- Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T cell lymphoma[a]
- Primary cutaneous acral $CD8^+$ T cell lymphoma[b]
- Primary cutaneous $CD4^+$ small/medium T cell lymphoproliferative disorder[a]

WHO-EORTC classification. Willemze et al, Blood 2019; 133: 1703-14.


A
B
C
D

Clinical behaviour

- Indolent behaviour in most cases, course over many years
- Remains confined to the skin in most cases for a very long time, often for the rest of the patient's lifetime
- Even when the disease has spread to lymph nodes and viscera, the skin is often the major symptomatic disease burden
- Incurable except for patients with localized disease (CS IA, especially if unilesional)
- Early aggressive systemic therapy is not associated with improved survival (but with considerable side effects)

Treatment

Skin directed therapies, either alone (early stages IA-IIA) or in combination with some systemic therapy

- topical steroids
- psoralens plus ultraviolet A (PUVA)
- narrow-band ultraviolet B (nb-UVB)
- topical cytostatic agents, such as mechlorethamine (nitrogen mustard)
- local radiation therapy

For patients with more extensive infiltrated plaques and tumours (stage IIB) or erythroderma (stage III), or patients refractory to skin-directed therapies, additional systemic therapy

- interferon alpha (IFNa)
- retinoids (including bexarotene)
- Low-dose Methotrexate
- or total skin electron beam therapy (TSEBT)

Interferons

- Only pegylated interferon-α-2a available, s.c. og i.m.
- Immune modulator
- Achieves remission in > 50% of patients
- Used either alone or in combination with other standard treatments, e.g., PUVA, retinoids, and extracorporeal photopheresis
- Side effects:
  - Flue-like symptoms
  - Myelosuppression
  - Liver toxicity
  - Depression

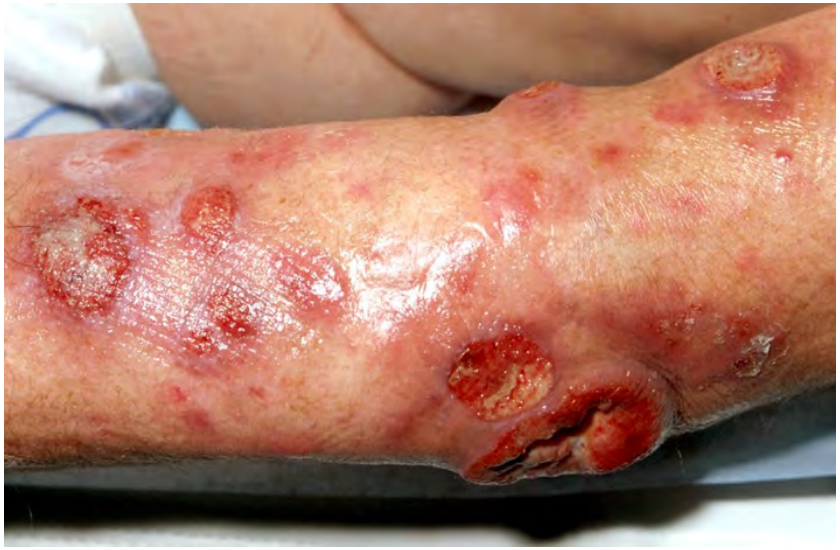
Retinoids

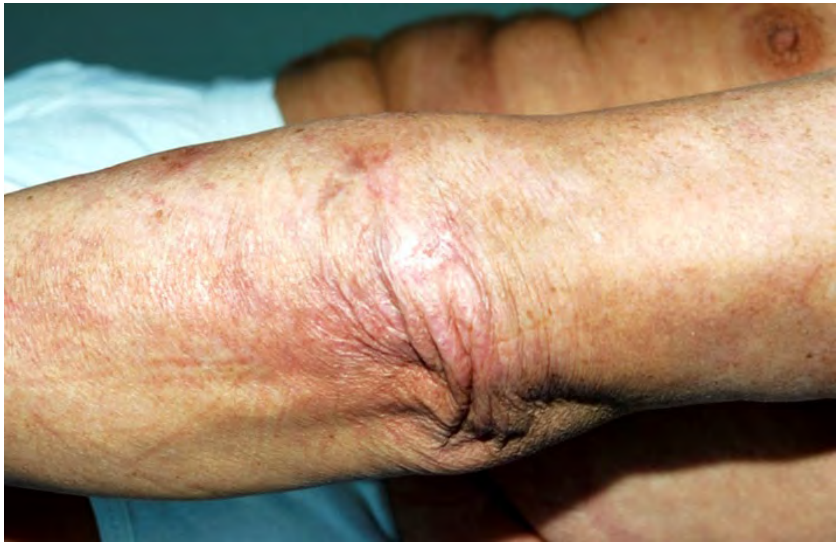
- Vitamin A analogues, oral
- Bind to the retinoic acid receptor
- Regulate gene transcription and modulate the immune system
- Used in several dermatologic diseases
- Achieve PR in about 50% of CTCL patients
- Bexarotene approved by FDA and EMA for mycosis fungoides
- Often combined with other modalities, e.g. phototherapy, interferons, extracorporeal photopheresis and chemotherapy
- Side effects:
  - Hypertriglyceridemia
  - Central hypothyroidism
  - Leukopenia
  - Headache

Low-dose Methotrexate

- Folic acid antagonist, oral or s.c.
- Used for many years with few studies of efficacy
- Used for mycosis fungoides and primary cutaneous CD30-positive lymphoproliferative disorders, in particular lymphomatoid papulosis
- Response rates 30-70%
- Often combined with skin directed therapies, can also be combined with interferons or bexarotene
- Side effects:
  - Myelosuppression
  - Mucositis
  - Nausea/vomiting
  - Liver toxicity

Treatment





Radiation therapy remains the most effective powerful agent for achieving local lymphoma control

– true also for PCTCL

Treatment

For patients refractory to previous treatments, have visceral or blood involvement, or have reached the limit for more radiation therapy, additional systemic therapy:

- Gemcitabine
- Liposomal doxorubicin
- Combination chemotherapy
- Alemtuzumab (low dose)
- Histone deacetylase inhibitors
- Brentuximab vedotin
- Mogamulizumab
- Non-myeloablative allogeneic stem cell transplantation

Gemcitabine

- Pyrimidine anti-metabolite, i.v.
- Response rates up to 70%
- Side effects:
  - Dyspnoea
  - GI toxicity

Doxorubicin

- Topoisomerase II inhibitor, i.v.
- Used in its pegylated form
- Response up to 80% in rel/ref mycosis fungoides
- Side effects:
  - Myelosuppression
  - Cardiac toxicity, congestive heart failure, cardiomyopathy

Other cytotoxic agents, usually in low-dose regimens

Depending on patient's comorbidities and physician preference:

- Chlorambucil, alkylating agent, oral
- Cyclophosphamide, alkylating agent, oral
- Etoposide, topoisomerase II inhibitor, oral or i.v.
- Pralatrexate, folic acid antagonist, oral or i.v.
- Fludarabin and pentostatin, purine analogues, i.v.
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)

Remissions usually short

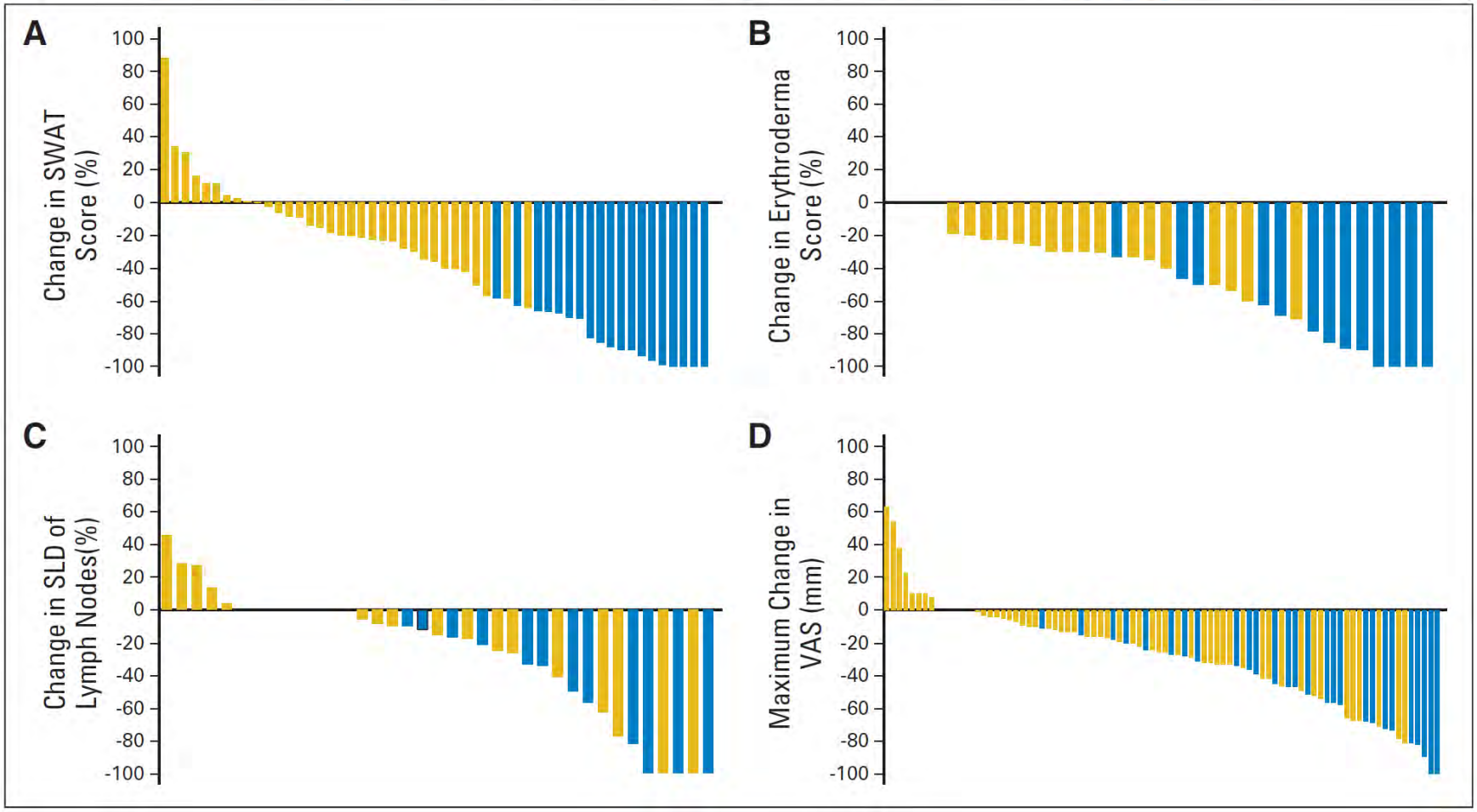
Alemtuzumab (low dose)

- Humanized monoclonal antibody against CD52 (found on the surface of nearly all peripheral lymphocites
- Induces antibody-dependent cell-mediated cytotoxicity
- Administered s.c., 1-3 times per week
- Side effects:
  - Immune suppression, antibiotic prophylaxis needed
  - GI-toxicity
  - Cardiac toxicity
  - Requires close observation

HDAC inhibitors

- Inhibits histone deacetylase
- Romidepsin given i.v., vorinostat given orally
- Response rates ~ 30 %
- Side effects:
  - Myelosuppression
  - GI-toxicity
  - Fatigue

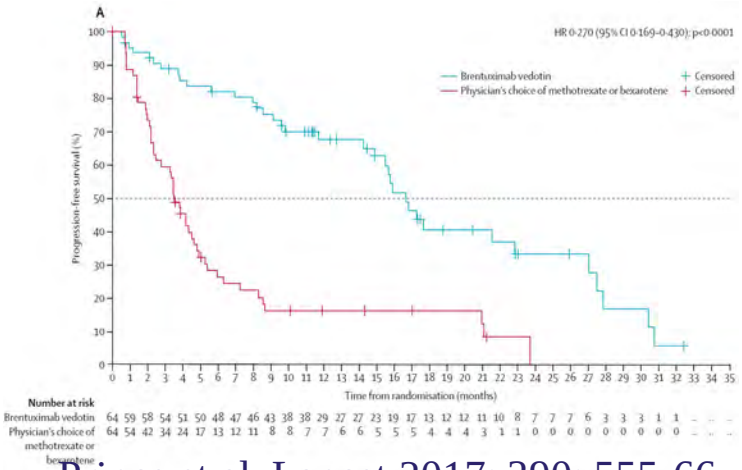
Final Results From a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma



Whittaker et al, JCO 2010; 28: 4485-91

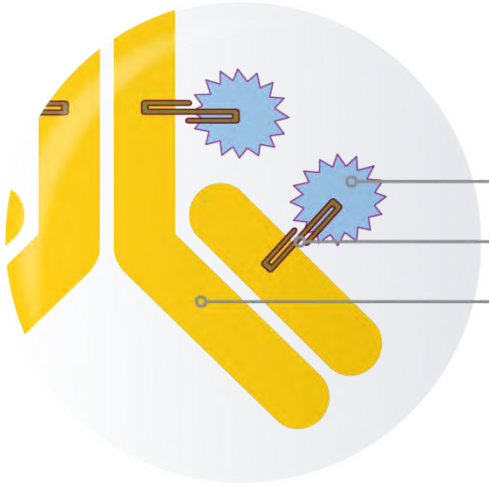
Brentuximab vedotin

- Chimeric antibody against CD30 coupled with monomethylauristatin, an anti-microtubuli drug. When bound to cell surface the drug is internalized by endocytosis
- CD30 on cell membranes in variable percentages of tumour cells in mycosis fungoides (and in virtually all cases of primary cutaneous anaplastic large cell lymphoma)
- Response rate over 50% in mycosis fungoides, higher with high CD30 expression, but responses are seen in patients with low (< 5%)
- In a randomized trial it was superior to vorinostat
- Side effects:
  - Myelosuppression
  - Neuropathy



Prince et al, Lancet 2017; 390: 555-66

Brentuximab Vedotin Mechanism of Action

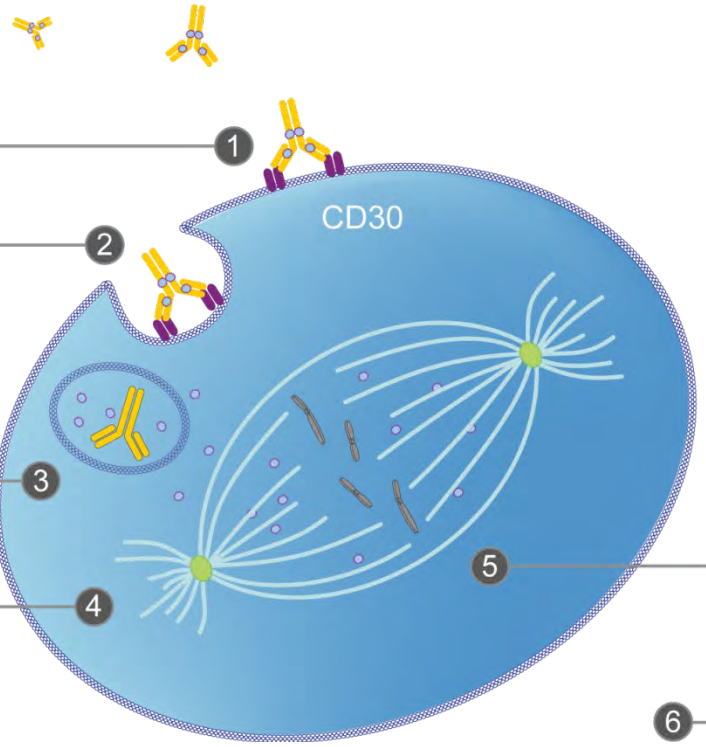


Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



1 ADC binds to CD30

2 ADC-CD30 complex traffics to lysosome

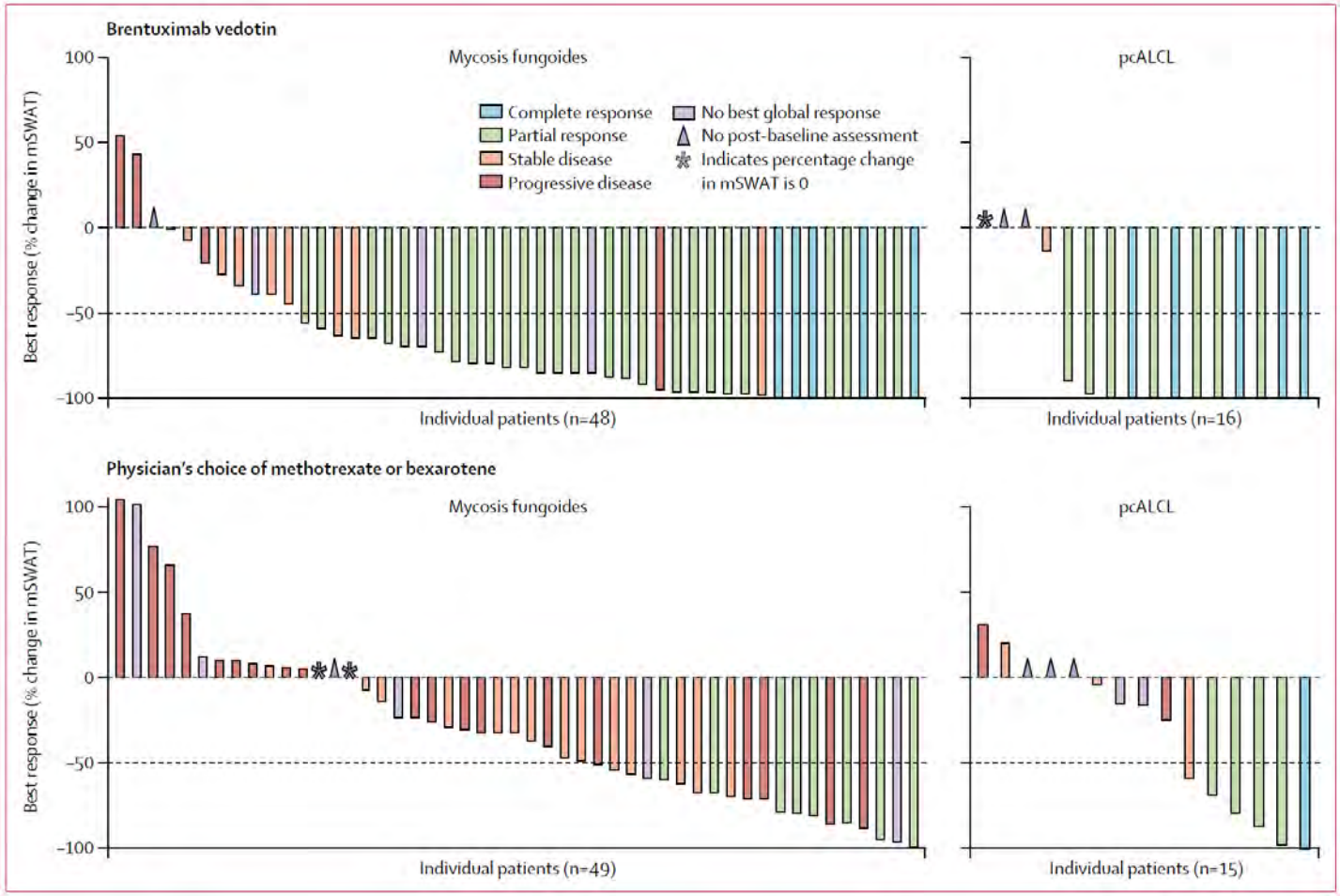
3 MMAE is released

4 MMAE disrupts microtubule network

5 G2/M cell cycle arrest

6 Apoptosis

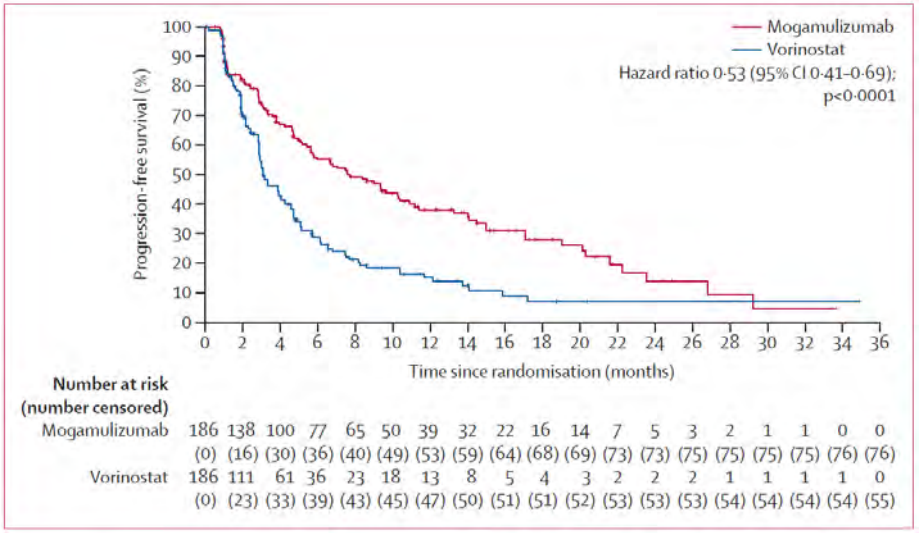
Brentuximab vs. Physician's choice



Prince et al, Lancet 2017; 390: 555-66

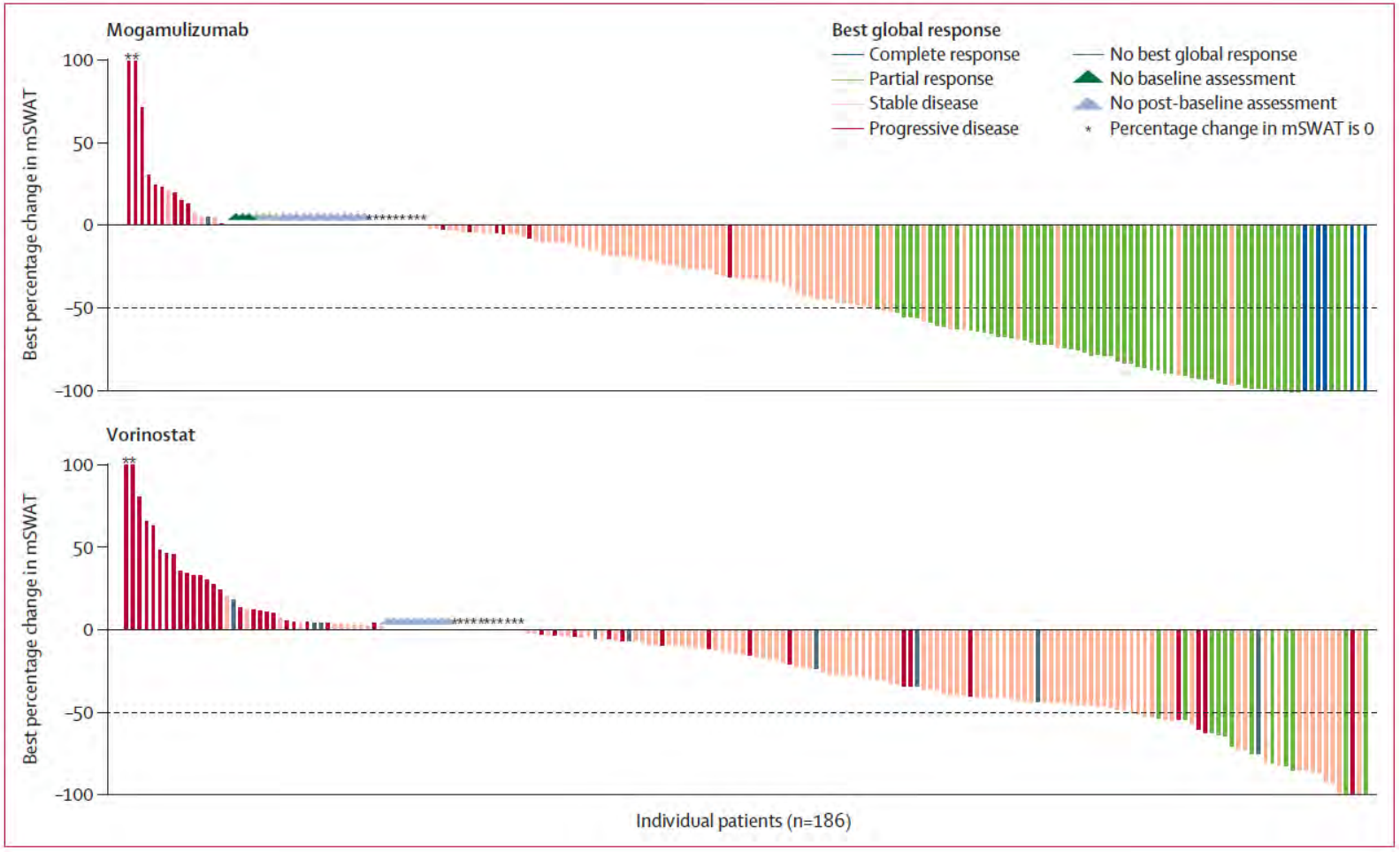
Mogamulizumab

- Humanized monoclonal antibody targeting the CC chemokine receptor 4 (CD194) which is overexpressed on malignant T-cells
- In a randomized trial it was superior to vorinostat
- Overall response rate of about 30 %
- Median duration of 8 months
- Even better for Sézary syndrome (40%, 17 months)
- Side effects generally mild, most often drug-related skin rash



MAVORIC trial
Kim et al, Lancet Oncol 2018; 19: 1192-204

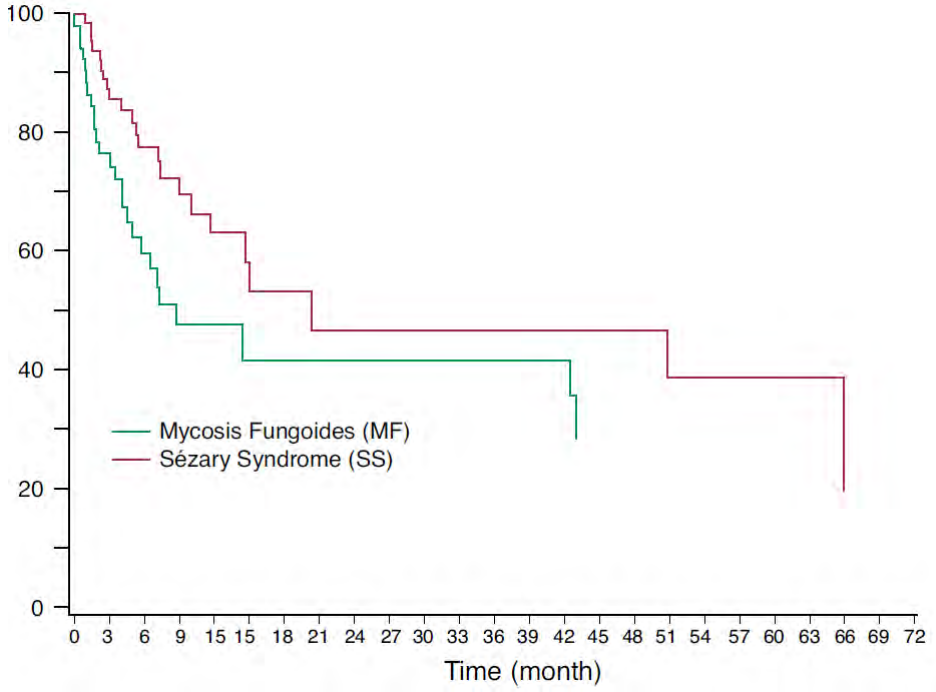
Mogamulizumab vs. vorinostat



MAVORIC trial
Kim et al, Lancet Oncol 2018; 19: 1192-204

Mogamulizumab

- 109 pts, 78% advanced disease (IIB-IVB), median 3 previous systemic treatments
- ORR
  - 70% for SS
  - 46% for MF
- Response duration
  - 20 months in SS
  - 9 months for MF
- Better response in patients with blood involvement
- Adverse reactions mostly rash and infusion related reactions



OMEGA real-world French study
Beylot-Barry et al. J Eur Acad Dermatol Venerol 2023

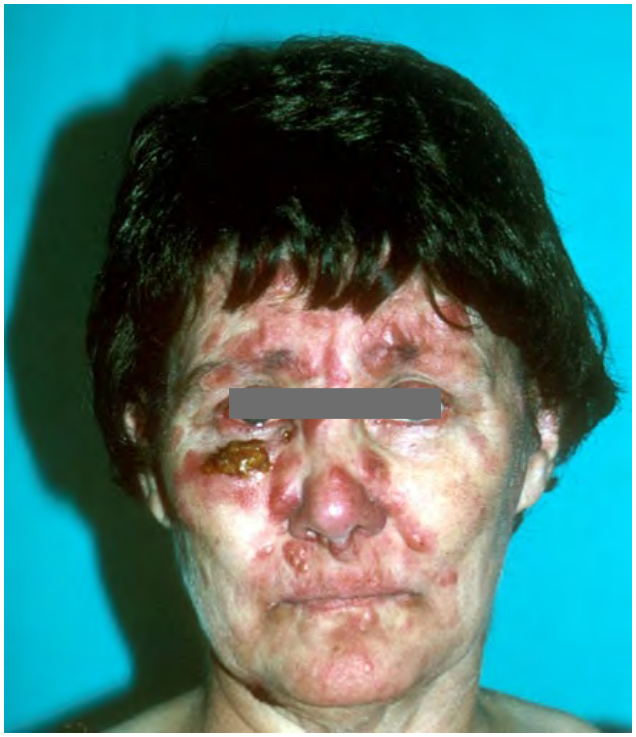
General treatment principles for late stage disease

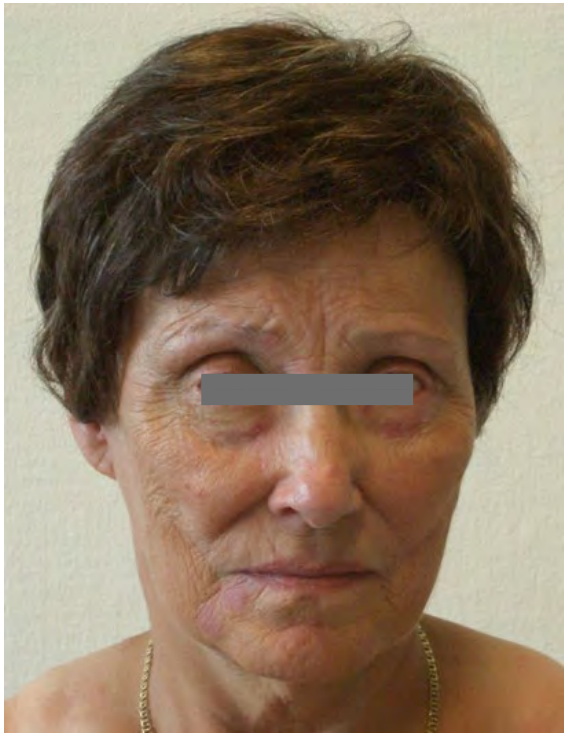
- Decided by a multidisciplinary team of dermatologists, radiation oncologists, and medical oncologists/hematologists
- Few randomized trials – limited evidence supporting one treatment over another
- Patients often cycle through different treatments and combinations of treatment
- Patients are often elderly and have comorbidities
- Even in late stage disease, the major tumour burden and major cause of symptoms is often the skin, so skin directed therapies also needed
- Very rarely cured by present treatment modalities – an important goal is to use treatments that are:
  - well tolerated
  - can achieve long-term control of symptoms
  - can postpone disease progression

Non-myeloablative allogeneic stem cell transplantation – possibly curative

- Autologous stem cell transplantation has been tested in primary CTCL, responses have generally been short
- Allogeneic transplantation results have been better
- Most of the allogeneic transplants have been nonmyeloablative
- Evidence of an allogeneic graft versus lymphoma effect
- Long-term relapse-free survival is only about 30 %, but may perhaps be improved with some form of maintenance treatment
- Outcome is better the lower the tumour burden before transplant
- TSEBT is often needed to achieve remission in the skin

Radiation therapy is very effective



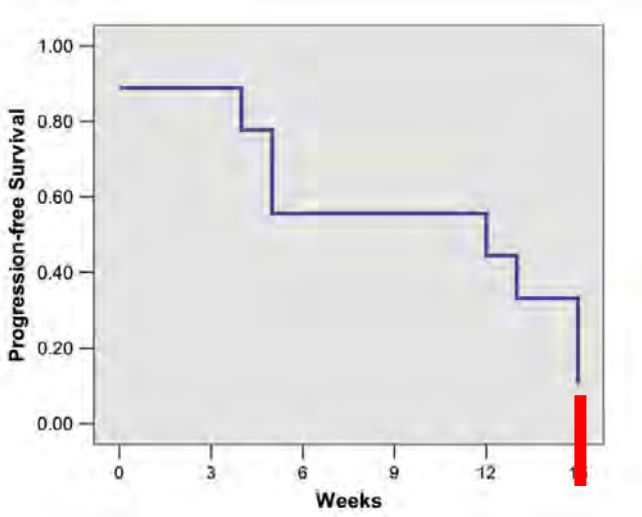


- but there is a limit to the cumulative dose to the skin

Maintenance of response is crucial

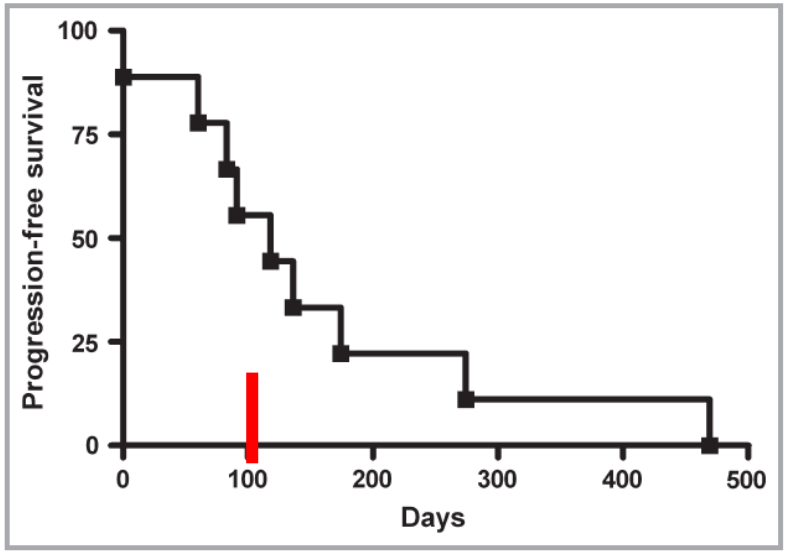
TSEBT: Lower radiation doses – treatment could be repeated more times

4 Gy too little, response rate 80%, median duration 2.7 months (range 1-3.5)



Kamstrup et al. IJROBP 2008; 71: 1204-7

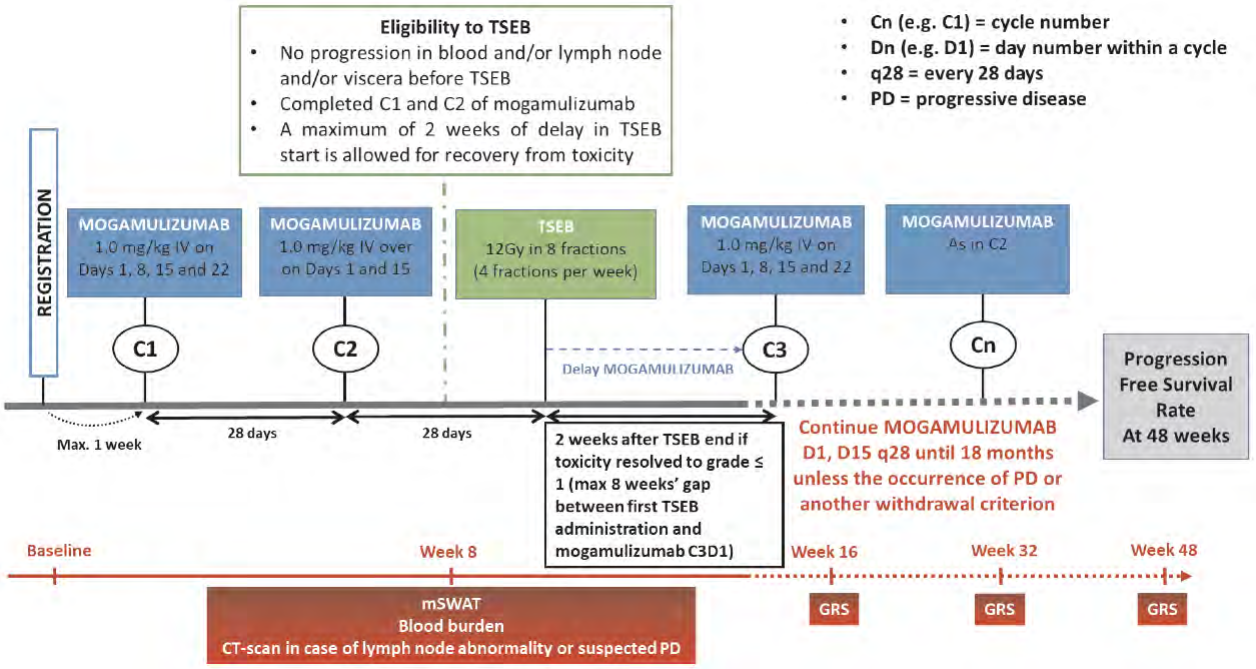
10 Gy better, response rate 90%, median duration 4.2 months (range 2-15.6)



Kamstrup et al. BJD 2012; 166: 399-404

TSEBT: Maintenance treatment needed to prolong duration of remission

- Psoralens plus ultraviolet A (PUVA)
- Topical cytostatic agents, such as mechlorethamine (nitrogen mustard)
- Interferon alpha (IFNa)
- Retinoids (including bexarotene)
- Low-dose Methotrexate
- Mogamulizumab? EORTC MOGAT trial:



Guidelines

GUIDELINES

BJD
British Journal of Dermatology

British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018

D. Gilson,[1] S.J. Whittaker,[2] F.J. Child,[2] J.J. Scarisbrick,[3] T.M. Illidge,[4] E.J. Parry,[5] M.F. Mohd Mustapa,[6] L.S.Exton,[6] E. Kanfer,[7] K. Rezvani,[8] C.E. Dearden[9] and S.L. Morris[10]

S2k-Guidelines – Cutaneous lymphomas (ICD10 C82 - C86): Update 2021

Edgar Dippel[1], Chalid Assaf[2], Jürgen C. Becker[3], Michael von Bergwelt-Baildon[4], Sophie Bernreiter[1], Antonio Cozzio[5], Hans T. Eich[6], Khaled Elsayad[6], Markus Follmann[7], Stephan Grabbe[8], Uwe Hillen[9], Wolfram Klapper[10], Claus-Detlev Klemke[11], Carmen Loquai[8], Frank Meiss[12], Christina Mitteldorf[13], Ulrike Wehkamp[14], Dorothee Nashan[15], Jan P. Nicolay[16], Ilske Oschlies[10], Max Schlaak[17], René Stranzenbach[18], Rose Moritz[19], Christoph Stoll[20], Tibor Vag[21], Michael Weichenthal[14], Marion Wobser[22], Rudolf Stadler[23]

J Dtsch Dermatol Ges 2022

Primary Cutaneous Lymphomas, Version 2.2020

Featured Updates to the NCCN Guidelines

Neha Mehta-Shah, MD[1,*]; Steven M. Horwitz, MD[2,*]; Stephen Ansell, MD, PhD[3]; Weiyun Z. Ai, MD, PhD[4]; Jeffrey Barnes, MD, PhD[5]; Stefan K. Barta, MD, MRCP, MS[6]; Mark W. Clemens, MD[7]; Ahmet Dogan, MD, PhD[2]; Kristopher Fisher, MD[8,*]; Aaron M. Goodman, MD[9,*]; Gaurav Goyal, MD[10,*]; Joan Guitart, MD[11,*]; Ahmad Halwani, MD[12]; Bradley M. Haverkos, MD, MPH, MS[13,*]; Richard T. Hoppe, MD[14,*]; Eric Jacobsen, MD[15]; Deepa Jagadeesh, MD, MP[16,*]; Matthew A. Lunning, DO[17]; Amitkumar Mehta, MD[10]; Elise A. Olsen, MD[18,*]; Barbara Pro, MD[11]; Saurabh A. Rajguru, MD[19]; Satish Shanbhag, MBBS, MPH[20]; Aaron Shaver, MD, PhD[21]; Andrei Shustov, MD[22,*]; Lubomir Sokol, MD, PhD[23]; Pallawi Torka, MD[24]; Carlos Torres-Cabala, MD[7]; Ryan Wilcox, MD, PhD[25]; Basem M. William, MD[26,*]; Jasmine Zain, MD[27]; Mary A. Dwyer, MS, CGC[28,*]; Hema Sundar, PhD[28,*]; and Youn H. Kim, MD[14,*]

European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017

Franz Trautinger [a,b,*], Johanna Eder [a,b], Chalid Assaf [c], Martine Bagot [d], Antonio Cozzio [e], Reinhard Dummer [f], Robert Gniadecki [g,h], Claus-Detlev Klemke [i], Pablo L. Ortiz-Romero [j], Evangelia Papadavid [k], Nicola Pimpinelli [l], Pietro Quaglino [m], Annamari Ranki [n], Julia Scarisbrick [o], Rudolf Stadler [p], Liisa Väkevä [n], Maarten H. Vermeer [q], Sean Whittaker [r], Rein Willemze [q], Robert Knobler [s]

Eur J Cancer 2017

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

Annals of Oncology 2018

Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Lena Specht, MD, PhD,* Bouthaina Dabaja, MD,† Tim Illidge, MD, PhD,‡ Lynn D. Wilson, MD,§ and Richard T. Hoppe, MD||, on behalf of the International Lymphoma Radiation Oncology Group

Int J Radiat Oncol Biol Phys 2015

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