Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Therapeutic developments in CTCL

Part I & II

Prof. Julia Scarisbrick MD MBChBhons FRCP

Consultant Dermatologist
Centre of Rare Diseases
University Hospital Birmingham
Institute of Immunology and Immunotherapy
University of Birmingham

Birmingham, England 14.12.2020

Co-funded by the Health Programme of the European Union

Centre for Rare Diseases

UNIVERSITY OF BIRMINGHAM

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Consultancy and/or principle investigator for Takeda, 4SC, Kyowa Kirin, Helsinn, Mallinckrodt, Recordati, Miragen

Therapeutic developments in CTCL

Part I

Treatment of mycosis fungoides (MF) and Sezary syndrome (SS) is stage related

1. Staging in MF
   - Early stages IA-IIA
   - Advanced stages MF IIB-IVA2
2. Guidelines
3. Stage related treatments

Treatment CD30+ CTCL

1. Lymphomatoid Papulosis
2. Large Cell Anaplastic Lymphoma

Part II

Newly approved drugs for CTCL

- Ledaga™ ▼ (chlormethine gel) – EU approval CTCL 2017
- Adcetris™ ▼ (brentuximab vedotin) – EU approval CTCL 2017
- Poteligeo™ ▼ (mogamulizumab) – EU approval CTCL 2018

ISCL/EORTC/USCLC Staging in MF/SS- TNMB classification

Early Stages IA - IIA

Advanced Stages IIB - IVB

Stage	Tumour (T)	Lymph Node (N)	Metastasis (M)	Blood (B)
IA	**T1:** Patches/plaques over < 10% of body surface **T1a** patches only **T1b** plaques only	**N0:** No palpable nodes or histological evidence of MF **N1a** clone negative **N1b** clone positive	**M0**: No visceral involvement	**B0**: <5% peripheral blood lymphocytes atypical **B0a** clone negative **B0b** clone positive **B1**: ≥5% of lymphocytes atypical but <1000/ul **B1a** clone negative **B1b** clone positive
IB	**T2:** Patches/plaques over > 10% of body surface **T2a** patches only **T2b** plaques only	**N0**	**M0**	**B0-1**
IIA	**T1 or T2**	**N1:** no histological evidence **of MF** (dermatopathic) **N1a** clone negative **N1b** clone positive **N2:** early involvement with MF, aggregates of atypical cells with preservation of nodal architecture **N2a** clone negative **N2b** clone positive	**M0**	**B0-1**
IIB	**T3:** Tumours, lesions >1cm diameter with deep infiltration	**N0-2**	**M0**	**B0-1**
IIIA	**T4:** Erythroderma >80% BSA involved	**N0-2**	**M0**	**B0**
IIIB	**T4:** Erythroderma	**N0-2**	**M0**	**B1**>5% of lymphocytes atypical but <1000/ul
IVA1	**T1 - T4**	**N0-2**	**M0**	**B2:** >1000/ul circulating atypical lymphocytes (Sézary cells)
IVA2	**T1 - T4**	**N3:** Lymph nodes involved with effacement of normal architecture	**M0**	**B0-2**
IVB	**T1 - T4**	**N0 - N3**	**M1**: Metastasis	**B0-2**

Olsen. Blood. 2007;110:1713.

GUIDELINES

British Associa
Lymphoma Gro
cutaneous lym

D. Gilson,[1] S.J. Whittaker
L.S.Exton,[6] E. Kanfer,[7] K.

[1]Leeds Cancer Centre, St James's Universit
[2]St John's Institute of Dermatology, Guy's
[3]Queen Elizabeth Hospital, University Hos
[4]Institute of Cancer Sciences, University o
[5]Tameside Hospital Integrated Care NHS
[6]British Associ
[7]Haematology
[8]The Universit
[9]Chronic Lymp
[10]Guy's and St

European
Cancer cor
mycosis fu

Franz Trautin
Antonio Cozzio [a], Reinhard Dummer [b], Robert Gniadecki [c],
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]

European Journal of Cancer 77 (2017) 57–74

NCCN National Comprehensive Cancer Network®

UK CLG UK Cutaneous Lymphoma Group

BAD British Association of Dermatologists Established 1920 Healthy Skin for All

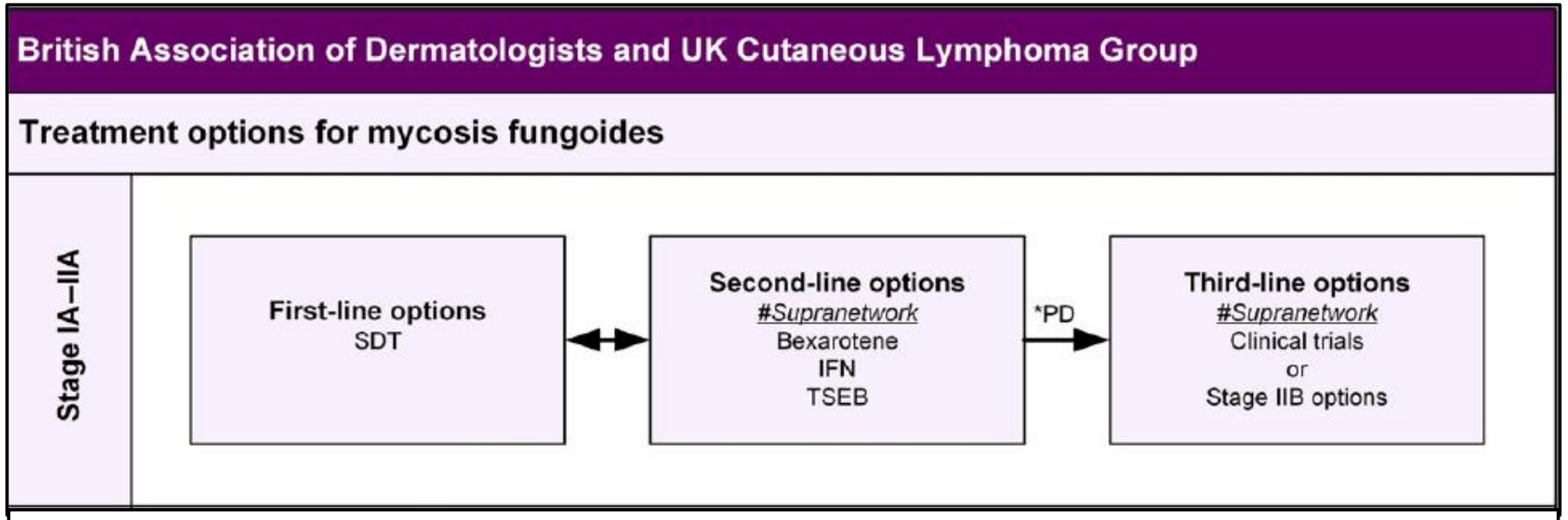
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Primary Cutaneous Lymphomas

Version 2.2020 — April 10, 2020

NCCN.org

RTC The future of cancer therapy



SDT: skin-directed therapy (topical steroids, ultraviolet B, psoralen–ultraviolet A, skin radiotherapy, topical nitrogen mustard); **IFN:** interferon; **RIC-allo-SCT**, reduced intensity allogeneic stem cell transplantation; **TSEB:** total skin electron beam radiotherapy. #Supranetwork: refers to the supranetwork multidisciplinary team (MDT) meeting for treatment decision. **PD**=progressive disease

*PD and exhausted first- and second-line options. **Chemotherapy only as recommended by the supranetwork MDT.
***Consider only if the patient has durable complete response. ↔ indicates that after treatment, patients may respond to treatments included in earlier 'line' options. Patients can move between first- and second-line options.

Early stage MF should be treated first line with skin directed therapy (SDT) or expectant therapy

Localised treatments

Potent or very potent topical corticosteroids

Topical chlormethine gel

Superficial Radiotherapy; 8Gy in 2# plaques,

Whole body treatments

UV-B (290nm-320nm)

Psoralen plus ultraviolet A (320-400nm) (PUVA)

Total Skin Electron Beam Therapy (TSEBT)
Doses: 30Gy in 20#
Or 12Gy in 8# (low dose)

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars Cutaneous Lymphoma
EuroBloodNet Topic on Focus

CHLORMETHINE, 160 mg/g GEL (LEDAGA®):

Therapeutic indication
Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients

Date of issue of marketing authorisation valid throughout the European Union by European Medical Association 03/03/2017

Proven efficacy in Lessin Trial 201

Low Dose Total Skin Electron Beam Therapy (TSEBT)

- 2 week
- lower dose
- 12Gy in 8# vs 5 week (30Gy in 20#)
- Less travel time
- Less skin reactions
- May be repeated
- Duration of response is less

RESULTS
103 patients UK,
18% CR 69%PR
Median response duration 11.8 months

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group

Stephen Morris, MBBS, MRCP, FRCR,* Julia Scarisbrick, MBChB, FRCP, MD,† John Frew, MBChB, MRCP, FRCR,‡ Clive Irwin,† Robert Grieve, FRCP, FRCR,† Caroline Humber, MRCP, FRCR,† Aleksandra Kuciejewska, MRCP,* Sally Bayne, DCR (T),* Sophie Weatherhead, MBBS, BSc, MRCP, PhD,‡ Fiona Child, MD, MRCP,* Mary Wain, MD, MRCP,* and Sean Whittaker, MD, FRCP*

**Guy's and St Thomas' NHS Foundation Trust, London, UK; †University Hospital Birmingham, Birmingham, UK; and ‡Freeman Hospital, Newcastle upon Tyne, UK*

Received Mar 22, 2017, and in revised form May 7, 2017. Accepted for publication May 31, 2017.

Int J Radiation Oncol Biol Phys, Vol. 99, No. 3, pp. 627–633, 2017

Morris. Int J Radiat Oncol Biol Phys. 2017;99:627.

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Cutaneous Lymphoma
EuroBloodNet Topic on Focus

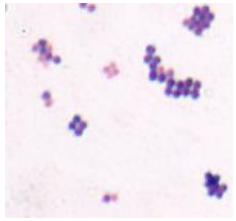
Expectant Therapy: No specific anti-CTCL therapy

Doesn't mean do nothing! Symptomatic relief & palliation through supportive care

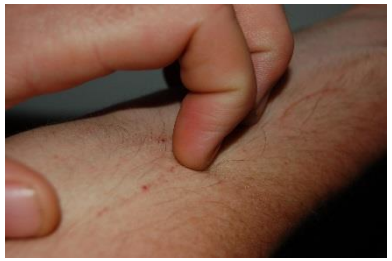
Supportive care

- Pruritus treatment
  - Moisturisers
  - Antihistamines, doxepin
  - Gabapentin
  - Apreptitant
  - Mirtrazapine
  - Selective serotonin reuptake inhibitors (SSRI's)
  - Naltrexone
- Infections
  - Anti-bacterial agents
  - Anti-viral agents
  - Bleach baths
- Pain relief
  - Paracetamol / Codeine
  - Morphine
- Psychological support
  - Cancer psychologist
  - Patient help groups
  - Anti depressants

Depression



Skin infections – Staph aureus



Pruritus

Social isolation

Loss of body heat, shivering

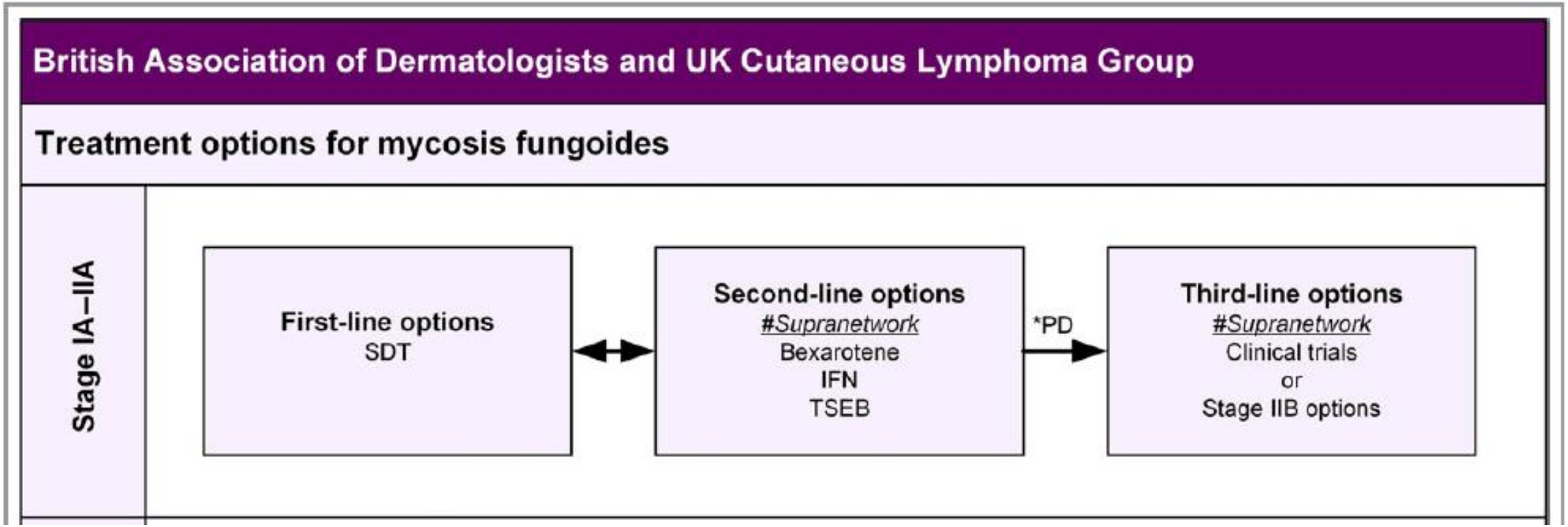
Living with a cancer diagnosis

Pain

Painful hands

Failure of SDT
What next?

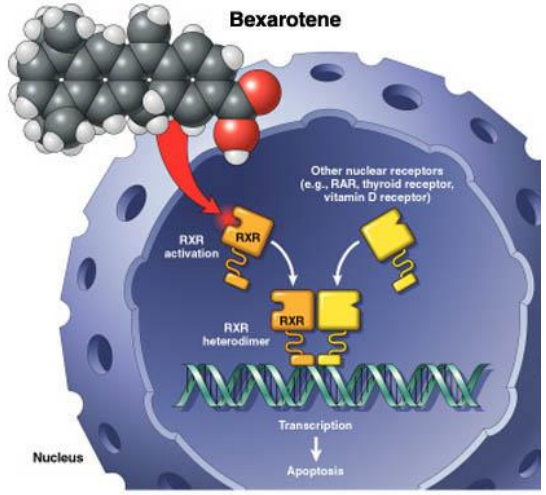
UKCLG Guidelines recommendations for second-line options stages IA-IIA MF



Clinical trials in early stages

Bexarotene

- Selectively binds & activates nuclear retinoid X receptor
- Approved in Europe for stage IIB - IVB CTCL since 1999
- Bexarotene - 300mg/m^2 once daily oral medication
- RR 40-67%, higher in early stage
- High response rate by 4 weeks
- Maximal response reached in 16 weeks
- Response duration ~9 months
- Side effects - hyperlipidaemia ~75%, central hypothyroidism, leucopaenia

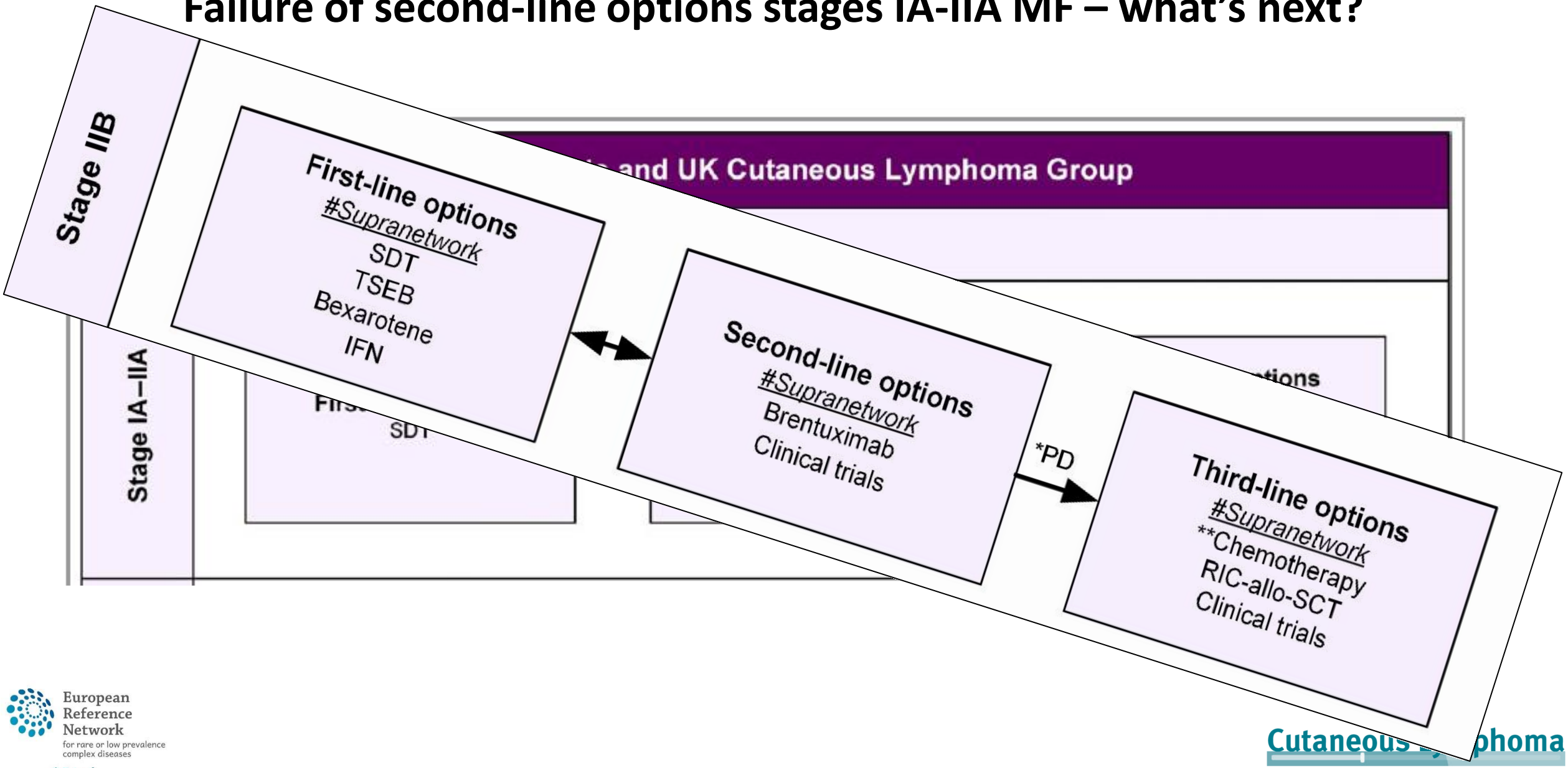


Scarisbrick JJ et al. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. ***Br J Dermatol***. 2013; 168:192-200.

Interferon - alpha

- Enhance anti-tumour host immune responses by promoting cytotoxic T-cells & Th1 response
- IFN-α-2 (3-36MU 3 x week), RR 88% in IB/IIA, 63% in III/IV
- Combined treatment with PUVA & IFN-2 α may allow lower cumulative doses
- Combined therapy ECP & IFN-2 α +/- bexarotene beneficial in erythrodermic disease
- Roferon™ (Roche) and Intron-A ™ (Schering-Plough) both now discontinued (3 x week dose)
- **Pegylated IFN alpha-2a : longer half life & once per week dose 180mcg s/c**

Failure of second-line options stages IA-IIA MF – what's next?



European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Cutaneous Lymphoma
EuroBloodNet Topic on Focus

Principles of Management of Early Stage MF

1. **Improve symptoms and QoL**
2. **Reduce tumour burden**
3. **Delay progression**

Long survival in early MF with high symptom burden but occasional disease mortality requires tailored therapeutic strategies

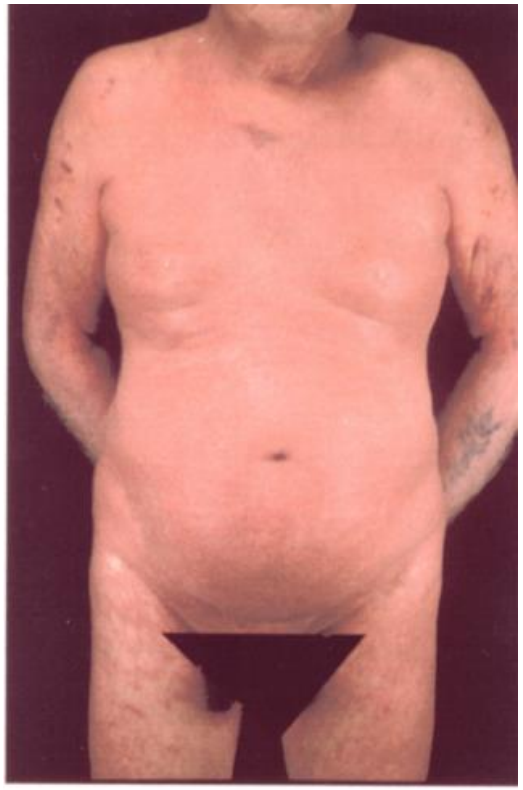
Improving quality of life with symptom control and supportive care should be ongoing

SDTs should be considered before systemic therapies

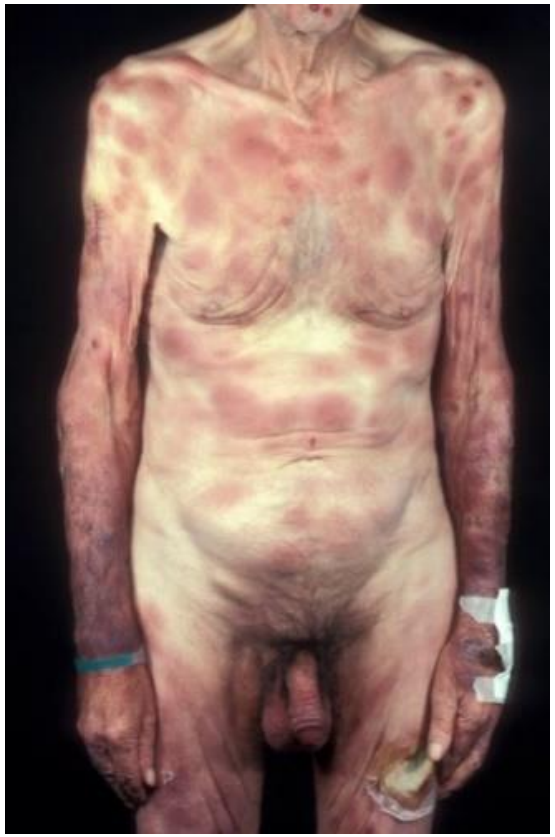
QoL, quality of life; SDT, skin-directed therapy

Advanced Stage MF; IIB-IVB

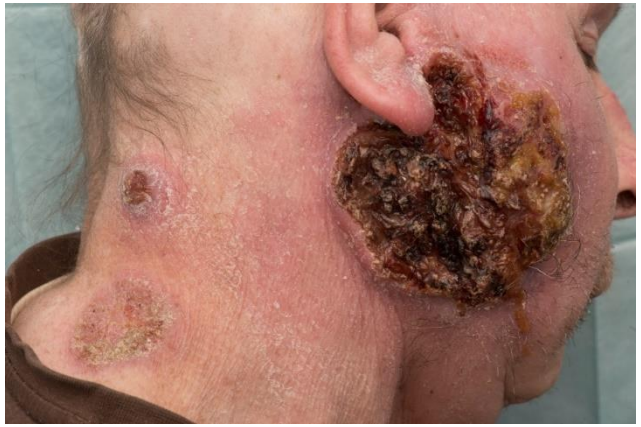
- Around 30% MF patients present with the advanced stages
- IIB, IIIA, IIIB, IVA2 or IVB
- With tumours or erythroderma, extensive lymph node, leukaemic blood or visceral involvement



Erythroderma stages IIIA-IVA1
Stage depends on blood class

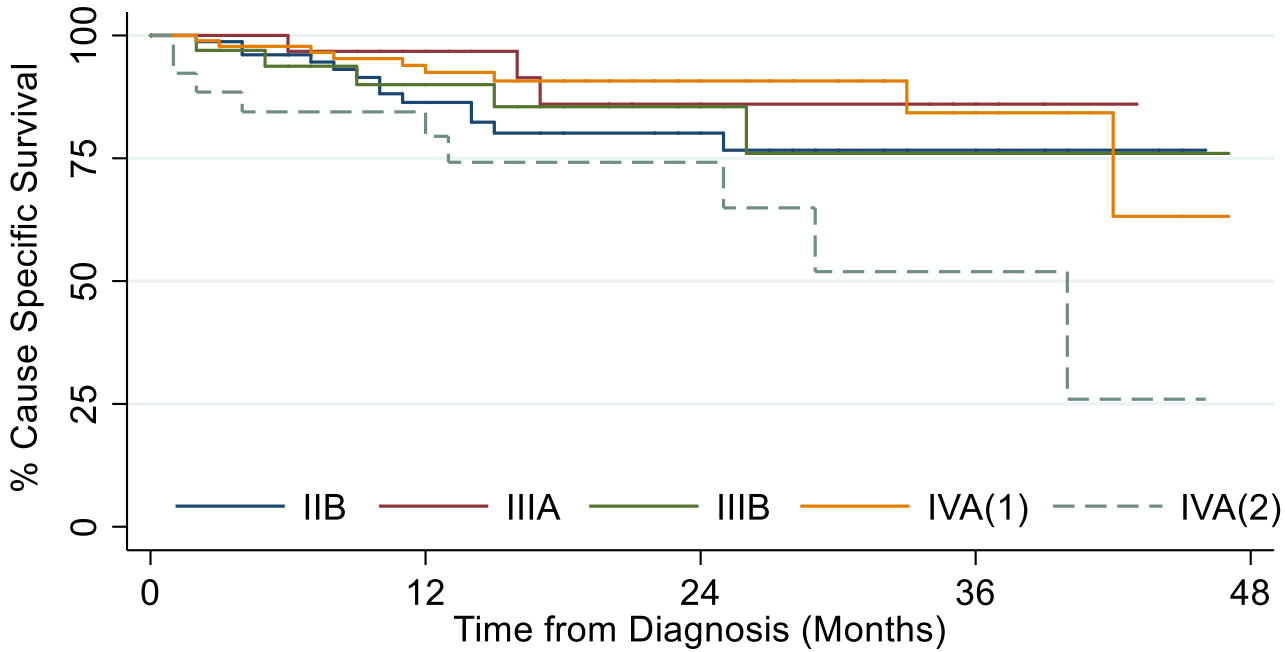


Stage IVA2
(lymphomatous nodes)



Stage IIB (tumours)

Overall (Disease Specific survival) – Advanced Stage from PROCLIPI



Number at risk

IIB	92	46	25	11	0
IIIA	34	21	11	4	0
IIIB	37	21	11	5	0
IVA(1)	97	66	27	8	0
IVA(2)	26	17	8	3	0

IVA2 vs not IVA2
(Excluding IVB) p=0.0021

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
EuroBloodNet Topic on Focus

GENERAL DERMATOLOGY

BJD
British Journal of Dermatology

Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study*

K. Molloy,[1] C. Jonak,[2] F.J.S.H. Woei-A-Jin,[3] E. Guenova,[4] A.M. Busschots,[3] A. Bervoets,[3] E. Hauben,[3] R. Knobler,[2] S. Porkert,[2] C. Fassnacht,[4] R. Cowan,[5] E. Papadavid,[6] M. Beylot-Barry,[7] E. Berti,[8] S. Alberti Violetti,[8] T. Estrach,[9] R. Matin,[10] O. Akilov,[11] L. Vakeva,[12] M. Prince,[13] A. Bates,[14] M. Bayne,[15] R. Wachsmuch,[16] U. Wehkamp,[17] M. Marschalko,[18] O. Servitje,[19] D. Turner,[20] S. Weatherhead,[21] M. Wobser,[22] J.A. Sanches,[23] P. McKay,[24] D. Klemke,[25] C. Peng,[1] A. Howles,[1] J. Yoo,[1] F. Evison[1] and J. Scarisbrick[1]

Conclusions HRQoL is significantly more impaired in advanced stages MF/SS, women with MF/SS, and in those with alopecia.

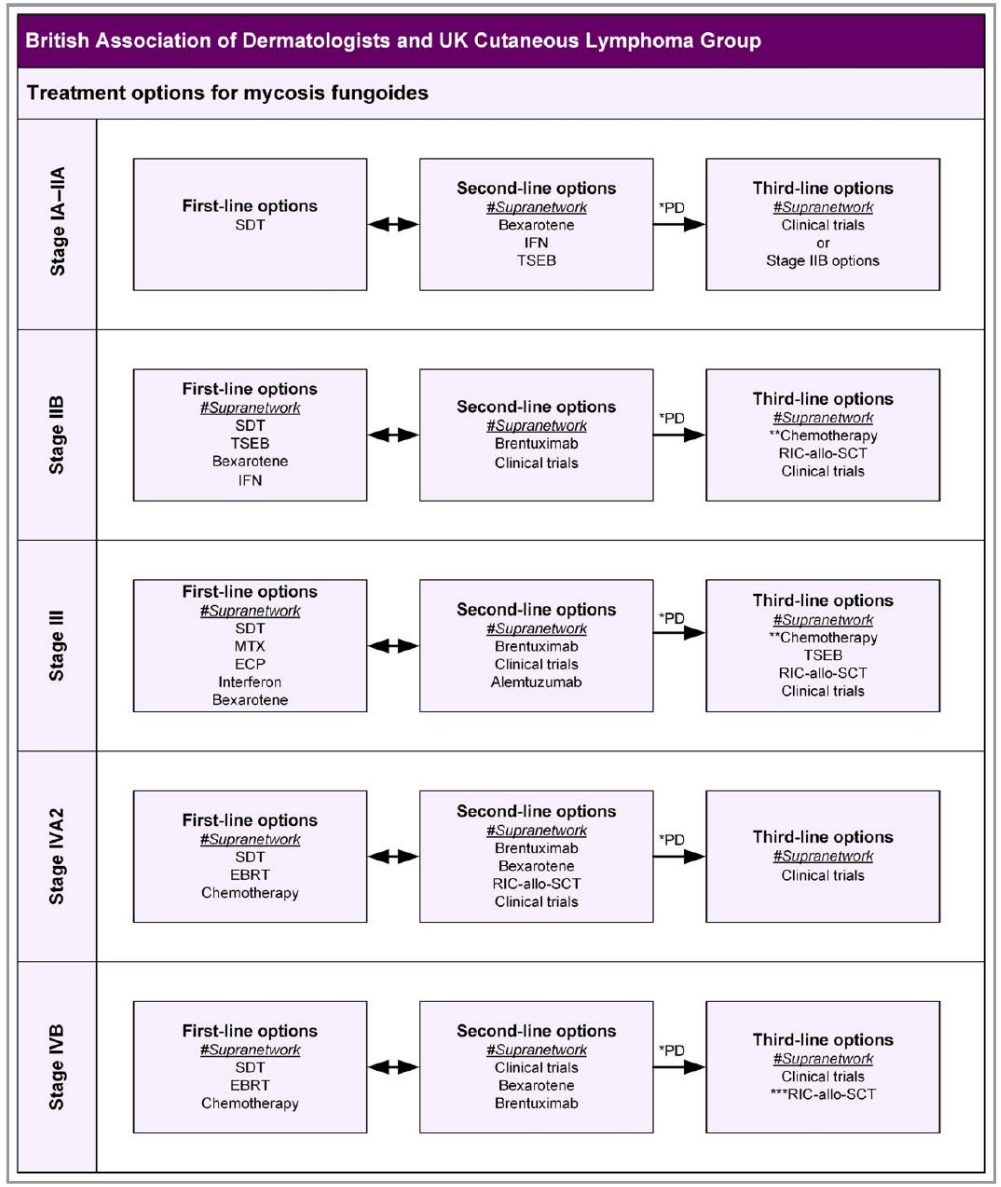


Fig 1. Treatment guidelines for mycosis fungoides. EBRT, external beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma; ECP, extracorporeal photopheresis; IFN, interferon; MTX, methotrexate; PD, progressive disease; RIC-allo-SCT, reduced-intensity allogeneic stem cell transplantation; SDT, skin-directed therapy (topical steroids, ultraviolet B, psoralen–ultraviolet A, skin radiotherapy, topical nitrogen mustard); TSEB, total skin electron beam radiotherapy. Skin radiotherapy indicates superficial radiotherapy or EBRT to skin patches, plaques and tumours. #Supranetwork: refers to the supranetwork multidisciplinary team (MDT) meeting for treatment decision. *PD and exhausted first- and second-line options. **Chemotherapy as recommended by the supranetwork MDT. ***Consider only if the patient has durable complete response. ↔ indicates that after treatment, patients may respond to treatments included in earlier 'line' options. Patients can move between first- and second-line options.

EBRT: external beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma; **ECP:** extracorporeal photopheresis; **IFN:** interferon; **MTX:** methotrexate;
PD: progressive disease; **RIC-allo-SCT**, reduced intensity allogeneic stem cell transplantation;
*PD and exhausted first- and second-line options. **Chemotherapy only as recommended by the supranetwork MDT.
***Consider only if the patient has durable complete response.
↔ indicates that after treatment, patients may respond to treatments included in earlier 'line' options. Patients can move between first- and second-line options.

SUGGESTED TREATMENT REGIMENS[a,b]

SYSTEMIC THERAPIES

SYST-CAT A	*SYST-CAT B*	*Large-Cell Transformation (LCT)*	*Relapsed/Refractory Disease Requiring Systemic Therapy*
Preferred Regimens (alphabetical order) • Bexarotene[h] • Brentuximab vedotin[i,j,k] • Extracorporeal photopheresis (ECP)[l] • Interferons (IFN alfa-2b[m] or IFN gamma-1b) • Methotrexate (≤50 mg q week) • Mogamulizumab[n] • Romidepsin[h] • Vorinostat[h] **Other Recommended Regimens** • Acitretin[h] • All-trans retinoic acid[h] • Isotretinoin (13-cis-retinoic acid)[h]	**Preferred Regimens** • Brentuximab vedotin[i,j,k] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose)	**Preferred Regimens** • Brentuximab vedotin[i,j,k] • Gemcitabine • Liposomal doxorubicin • Pralatrexate (low-dose or standard dose) • Romidepsin • See TCEL-B 2 of 5 for regimens listed for PTCL-NOS[o]	**Useful Under Certain Circumstances** (alphabetical order by category) • Alemtuzumab[p] • Chlorambucil • Cyclophosphamide • Etoposide • Pembrolizumab[q,r] • Pentostatin • Temozolomide for CNS involvement • Bortezomib (category 2B) • Pembrolizumab[q,r] • See TCEL-B 2 of 5 for regimens listed for PTCL-NOS[o]

[a] See references for regimens MFSS-A 4 of 6, MFSS-A 5 of 6, and MFSS-A 6 of 6.

[b] The optimal treatment for any patient at any given time is often individualized based on symptoms of disease, route of administration, toxicities, and overall goals of therapy. Laboratory studies for triglycerides, and thyroid function tests (with free thyroxine T4) are recommended for patients receiving bexarotene.

[h] Safety of combining TSEBT with systemic retinoids, HDAC inhibitors (such as vorinostat or romidepsin), or mogamulizumab, or combining phototherapy with vorinostat, romidepsin, or mogamullzumab is unknown.

[i] In the ALCANZA trial (Prince HM, et al. Lancet 2017;390:555-566) brentuximab vedotin (BV) was associated with superior clinical outcome in patients with CD30+ MF and pcALCL. CD30 positivity was defined as CD30 expression ≥10% of total lymphoid cells. However, in other clinical studies, clinical responses with BV have been reported across all CD30 expression levels including negligible CD30 expression.

[j] Patients with Sézary syndrome were excluded from the ALCANZA trial.

[k] See Supportive Care for Patients with Cutaneous Lymphomas (PCLYMP-C).

[l] ECP may be more appropriate as systemic therapy in patients with some blood involvement (B1 or B2).

[m] Peginterferon alfa-2a may be substituted for other interferon preparations. Schiller M, et al. J Eur Acad Dermatol Venerol 2017;31:1841-1847.

[n] Patients with LCT were excluded from the MAVORIC trial.

[o] Multiagent chemotherapy regimens are generally reserved for patients with relapsed/refractory or extracutaneous disease. Most patients are treated with multiple SYST-CAT A/B before receiving multiagent chemotherapy.

[p] Lower doses of alemtuzumab administered subcutaneously have shown lower incidence of infectious complications. While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Recommend CMV monitoring or prophylaxis. (See PCLYM-C).

[q] Preliminary phase II data in patients with MF and SS. Disease flare is seen in some patients (especially in erythrodermic skin/Sézary patients) and should be distinguished from disease progression. Khodadoust MS, et al. J Clin Oncol 2020:38:20-28.

[r] Rapid progression has been reported in HTLV positive patients receiving pembrolizumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Stage IIB – localised tumours

- In IIB with localised tumours superficial radiotherapy is the treatment of choice
- 8Gy in 2# (12Gy in 3-4#)
- Excellent responses
- Occasional radio-resistance
- Response takes up to 8 weeks
- Side effects include skin atrophy, telangiectasia, dyspigmentation

IIB failure radiotherapy or extensive disease

Systemic therapy

- Brentuximab vedotin:
  - 1.8 mg/kg IV, every 3 weeks, 16 cycles
- Single agent chemotherapy:
  - gemcitabine or liposomal doxorubicin
- Clinical Trials:
  - PORT – pembroluzimab + RT
  - PARCT - atezolizumab

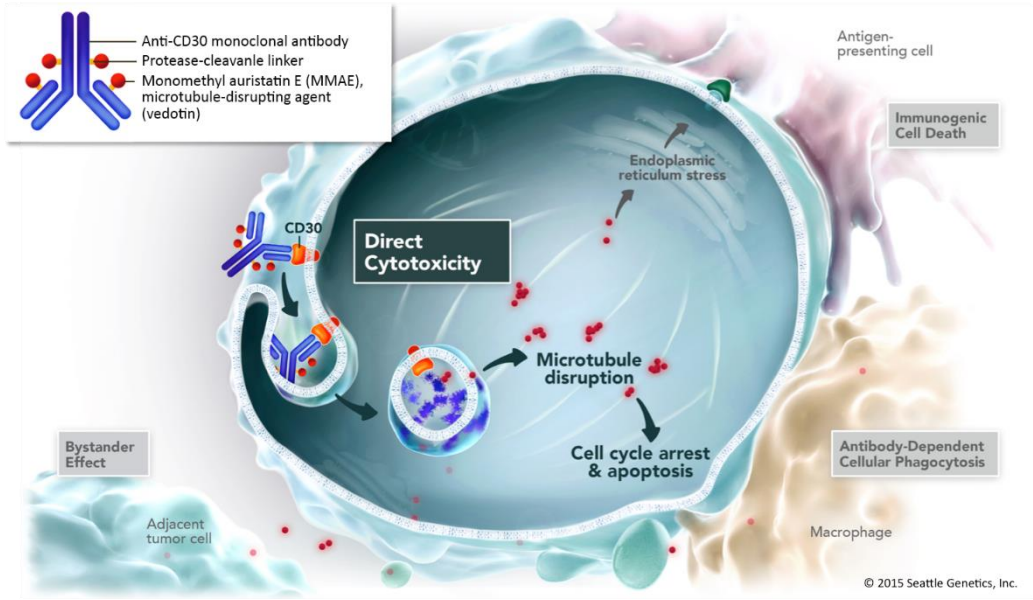
Brentuximab Vedotin (ADCETRIS)

ADCETRIS was granted approval by FDA November 2017 for:

- The treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy

ADCETRIS was approved in EC in December 2017 for:

- The treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy to received up to 16 cycles

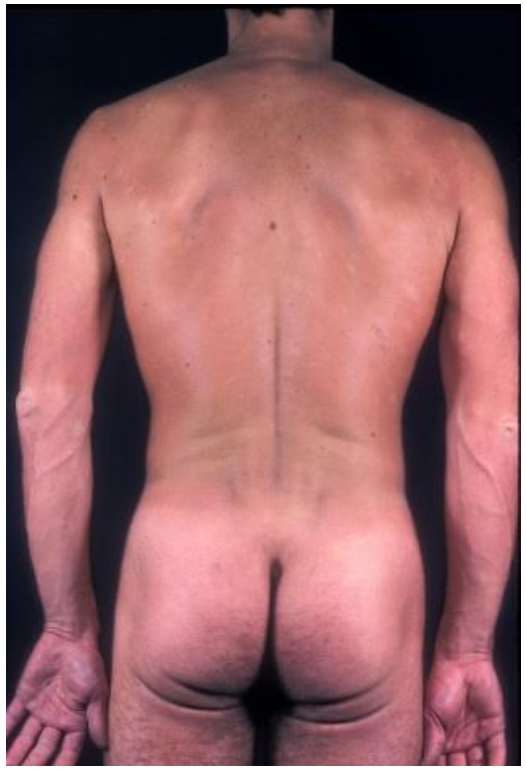


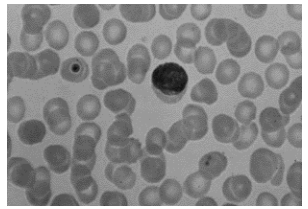
Brentuximab Vedotin is a 'CD30 antibody drug conjugate ADC

Treatment options Stage IIIA (refractory SDT) & IIIB

FIRST LINE

- Total skin electron beam (low dose 12Gy in 8# over 2 weeks)
- Methotrexate, 10-25mg per week
- Extracorporeal photopheresis (2 treatments, 2-4 weekly)
- Interferon alpha (3MU 3 x week), Pegylated 1x week sc
- Bexarotene 150-300mg/m^2





SECOND / THIRD LINE

- Gemcitabine
- Mogamuzilumab
- Alemtuzumab, low dose subcut. 3 mg on day 1, then 10 mg on alternating days
- Brentuximab if CD30+ve
- Clinical trials
- Allo HSCT if remission

Treatment options Sezary syndrome IVA1 ($T_4N_{0-2}M_0B_2$)

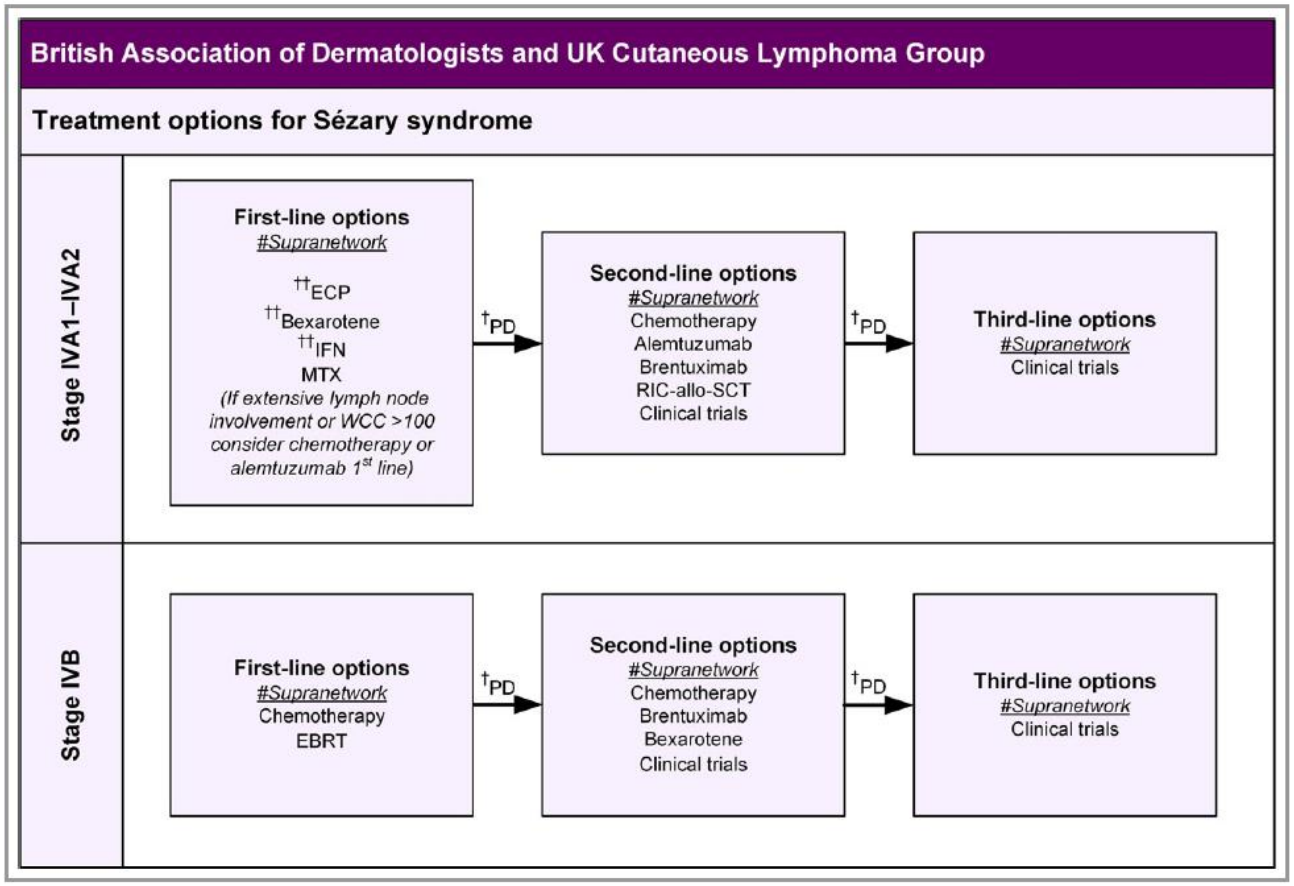


Fig 2. Treatment guidelines for Sézary syndrome. Palliative skin-directed therapy can be used for symptom control if required. Chemotherapy is as directed by the supranetwork multidisciplinary team (MDT). EBRT, external beam radiotherapy; ECP, extracorporeal photopheresis; IFN, interferon; MTX, methotrexate; PD, progressive disease; RIC-allo-SCT, reduced-intensity allogeneic stem cell transplantation; WCC, white cell count, $\times 10^9$. #Supranetwork: refer to the supranetwork MDT meeting for treatment decision. †PD and exhausted first- and second-line options. ††May be used in combination.

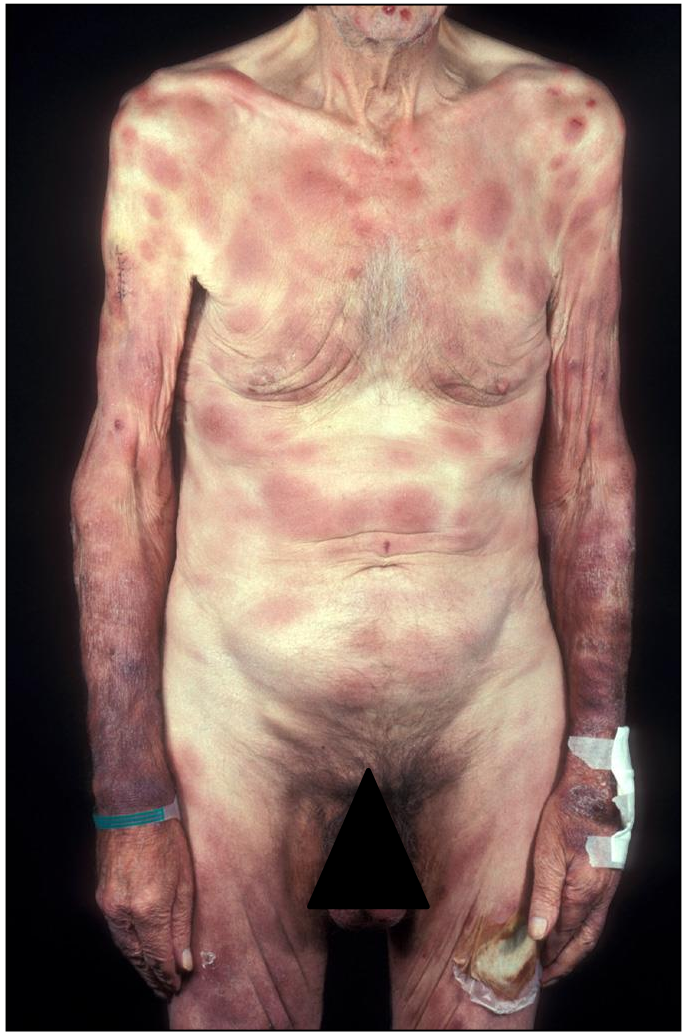
THIRD LINE

- Mogamuzilumab (anti CCR4)– available compassionate use program UK
- anti-KIR3DL2 (anti CD158) available in TELLOMAK trial: Phase 2 study of ‘IPH4102’ in relapsed or refractory CTCL

Stage IVA2 / IVB

‘FIRST’ LINE

- Single agent chemotherapy - gemcitabine
- Multiagent chemotherapy – CHOP, CHOEP
- Brentuximab if CD30+
- Clinical Trials



‘SECOND’ LINE

- Multiagent chemotherapy – CHOP, CHOEP
- Allo HSCT if remission
- Palliation

Stanford Protocol: Non-myeloablative Allogeneic Transplantation Using Total Lymphoid Irradiation (TLI) and Antithymocyte Globulin (ATG) In Patients with Cutaneous T Cell Lymphoma

TLI/ATG CONDITIONING AND ALLOGENEIC TRANSPLANTATION

Day-35 to Day-2	TSEBT 100 cGy (4X/week) for extensive Skin involvement
Day-11 to Day-7	TLI 80 cGy ATG 1.5 mg/kg & solumedrol 1 mg/kg
Day-4 to Day -2	TLI 80 cGy
Day-3	Start oral cyclosporine
Day -1	TLI 80 cGy x 2
Day 0	Infusion of mobilized peripheral blood cells from donor, Start oral MMF
Day +28	ECP weekly X4, then every two week x4, then monthly X4 in patients with persistent Sezary cells

BJD British Journal of Dermatology

RESEARCH LETTER

Evaluation of haematopoietic stem cell transplantation in patients diagnosed with cutaneous T cell lymphoma at a tertiary care centre: Should we avoid chemotherapy in conditioning regimes?

S. Ritchie, I. Qureshi, K. Molloy, J. Yoo, F. Shah, A. Stevens, C. Irwin, S. Chaganti, J.J. Scarisbrick

First published: 19 September 2019 | https://doi.org/10.1111/bjd.18541

- 17 patients (MF n=11, SS n=4, ALCL n=2) transplanted with TSE/ATG/TNI
- Relapse frequent 47%, majority managed with decreased immunosuppression, DLI or SDT, terminal in 2 patients (11.7%)
- Transplant related mortality was 6.7% at 1-year, 7.1% at 2-years
- The 1-year overall survival (OS) was 86.7%, 2-year 78.6%

Principles of Management of Advanced Stage MF

1. **Improve symptoms and QoL**
2. **Delay progression**
3. **Aim for allo HSCT in first remission for suitable patients**

Longer survival in IIB-IIIB disease allows treatments to be less aggressive

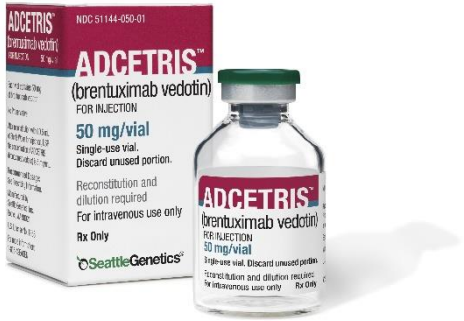
Survival in patients with IVA2 disease is short & if eligible allo HSCT should not be delayed

Consider immunotherapies before chemotherapy

QoL, quality of life; SDT, skin-directed therapy

Summary treatment CTCL

- Treatment is stage related
- Early stage should be treated with skin directed therapy
- Advanced stages and refractory early stages may require systemic therapy
- Select the therapy which best fits the individual patients needs
- Most patients require multiple treatment modalities during their course of disease
- Aim to reduce tumour burden, prolong survival and improve quality of life



RECENTLY APPROVED TREATMENTS FOR CTCL

Ledaga™ (chlormethine gel) – EU approval CTCL 2017

Adcetris™▼ (brentuximab vedotin) – EU approval CTCL 2017

Poteligeo™▼ (mogamulizumab) – EU approval CTCL 2018

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
University Hospitals Birmingham NHS Foundation Trust

CHLORMETHINE, 160 mg/g GEL (LEDAGA®): A TOPICAL TREATMENT FOR MF-CTCL

Therapeutic indication
Ledaga is indicated for the topical treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-type CTCL) in adult patients

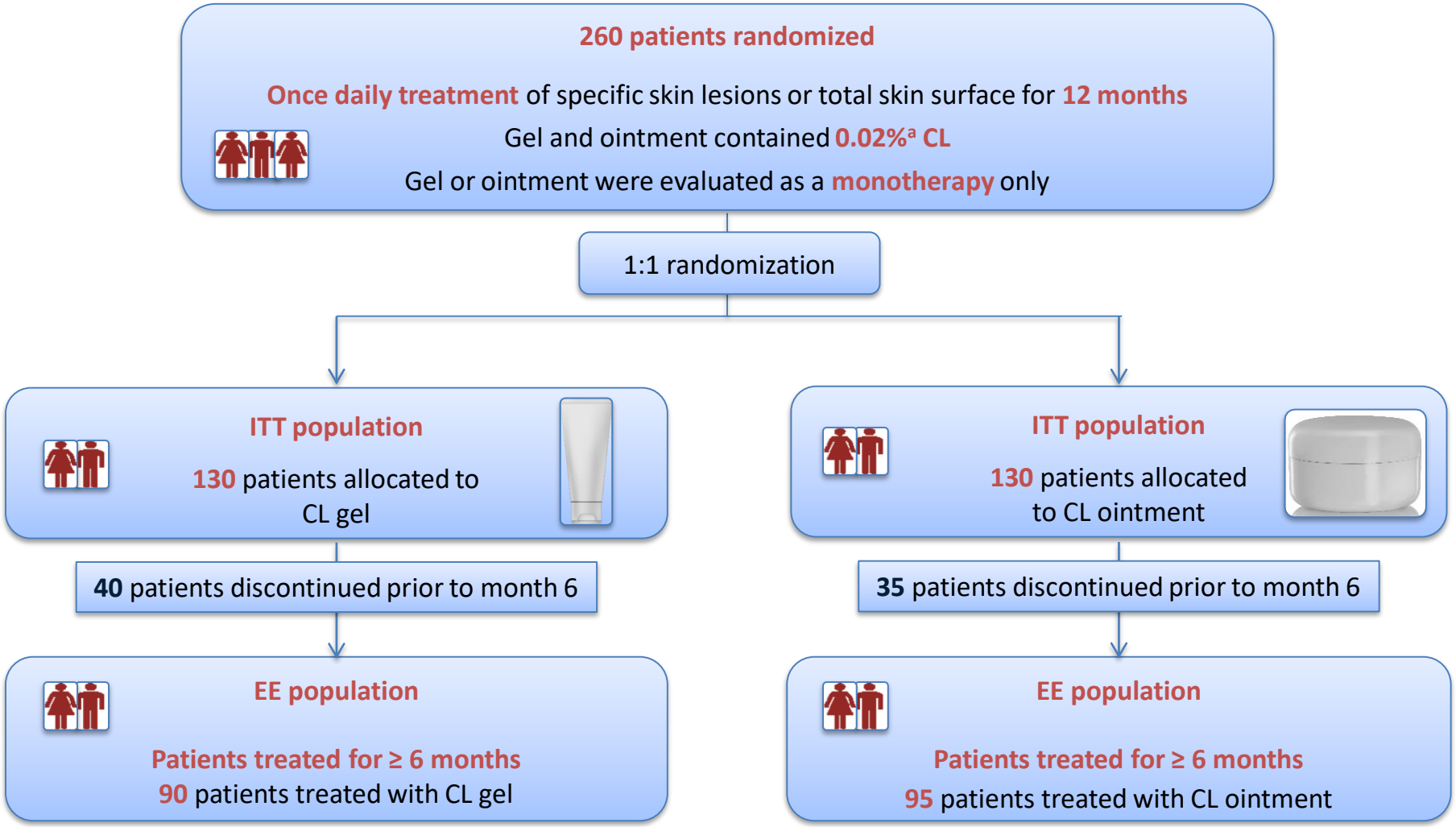
Date of issue of marketing authorisation Ledaga® valid throughout the European Union by European Medical Association 03/03/2017
NB FDA approved as Valchlor® 23/8/2013

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
University Hospitals Birmingham NHS Foundation Trust

Pivotal study for chlormethine gel (CL gel) was the 201 Study by Lessin et al.

Phase 2, multicentre, randomized, observer-blinded, non-inferiority trial with chlormethine ointment in 260 MF patients; stage I–IIA



Lessin SR, et al. JAMA Dermatol. 2013;149:25-32.

[a] Equivalent to 160 µg/g CL.

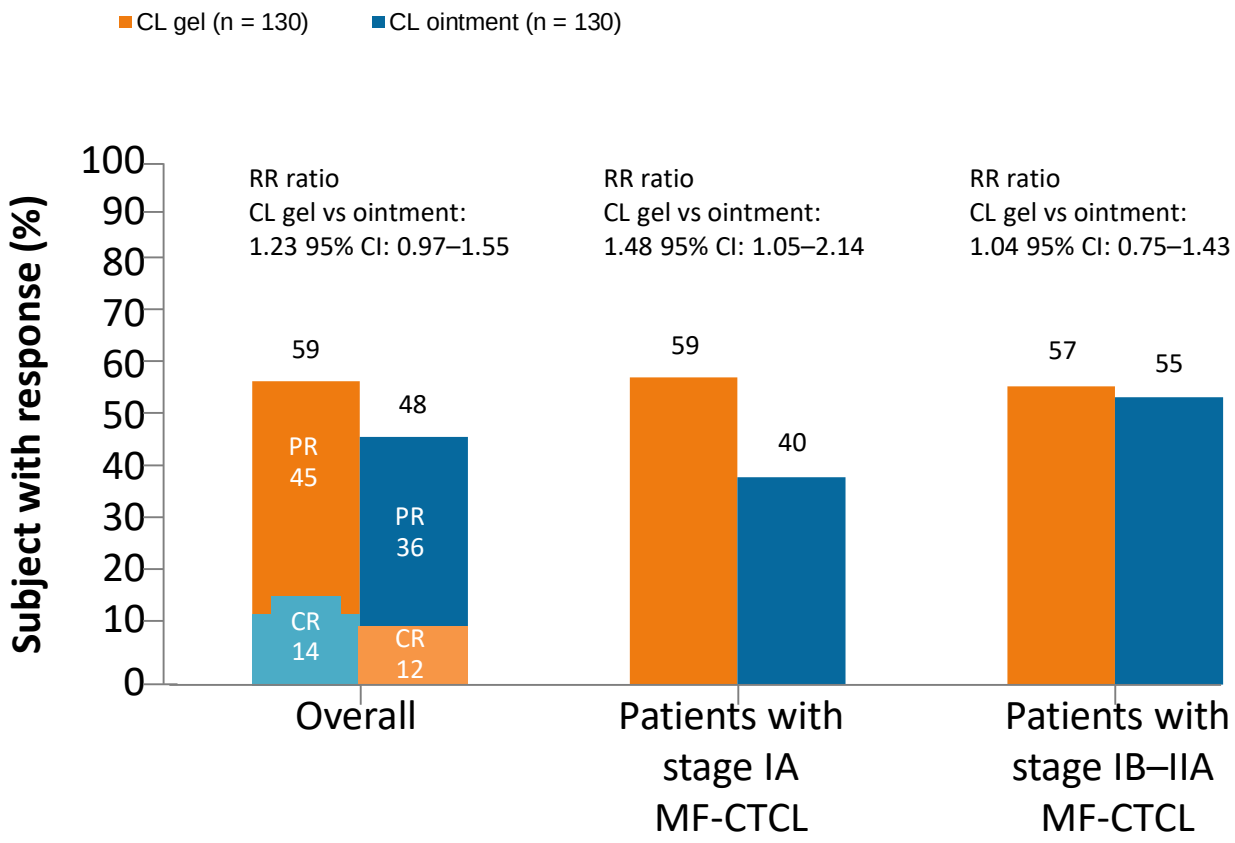
EE, efficacy evaluable; ITT, intent-to-treat.

Primary efficacy endpoint

Lessin SR, et al. JAMA Dermatol. 2013;149:25-32.

CAILS response: ITT population

CAILS, composite assessment of index lesion severity.



~ 59% of patients treated with **gel** showed ≥ 50% improvement in skin lesion severity

~ 48% of patients treated with **ointment** showed ≥ 50% improvement in skin lesion severity

CL gel was non-inferior to CL ointment

Conclusions from Lessin study 201

CL gel was shown to be non-inferior to CL ointment

Longer duration of treatment with CL gel increased response rate

The main side effect was skin irritation (dermatitis)

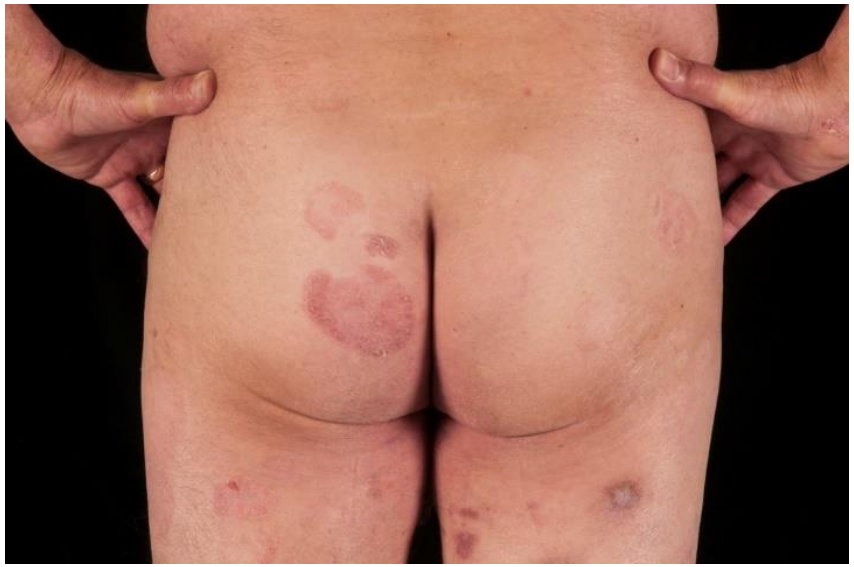
No serious AEs were associated with the use of CL gel

No detectable levels of CL were observed in the blood

Development of non-melanoma skin cancers was considered unrelated to the use of CL gel

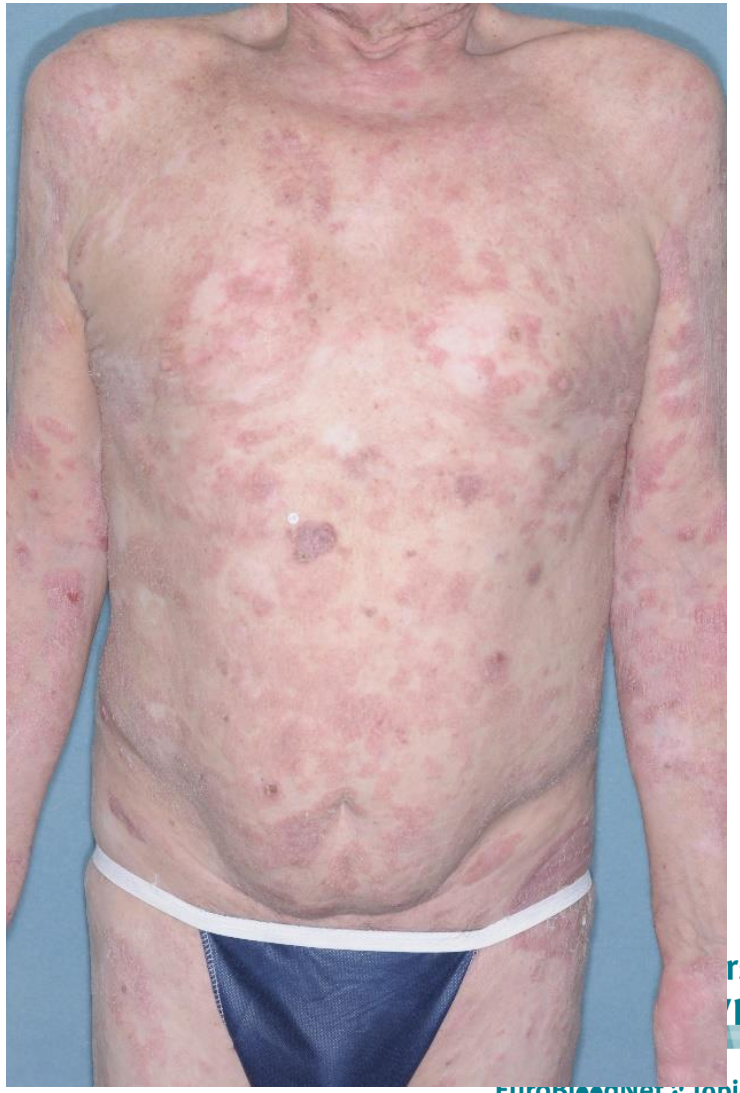
Chlormethine gel (Ledaga®) in stage IA MF

- Application to patches and plaques
- Once daily
- 60 g tube, expiry of 2 months
  - If 4% body surface area involved
  - 1 fingertip, about 0.5 g, covers 2%
  - Therefore, 2 × 0.5 g (a fingertip) per day for 2 months = 60 g
- Must be stored in fridge in a child tamper-proof bag



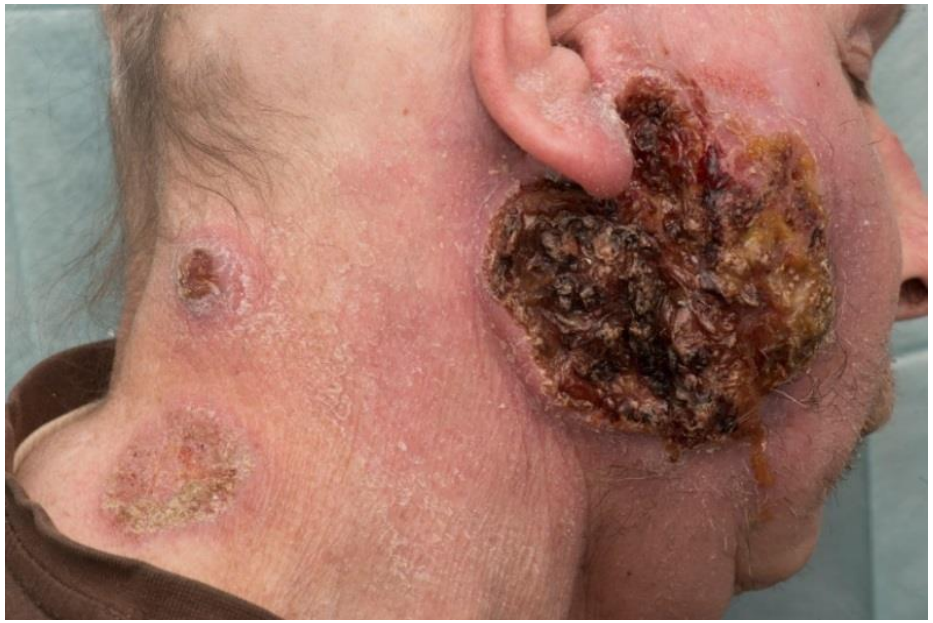
Chlormethine gel (Ledaga®) in stage IB/IIA MF

- Application to patches and plaques, or all over the affected areas
- Once daily
- Continued for 12 months or complete response
- ~2 x 60 g tubes per month



Chlormethine gel (Ledaga®) in advanced stages of MF

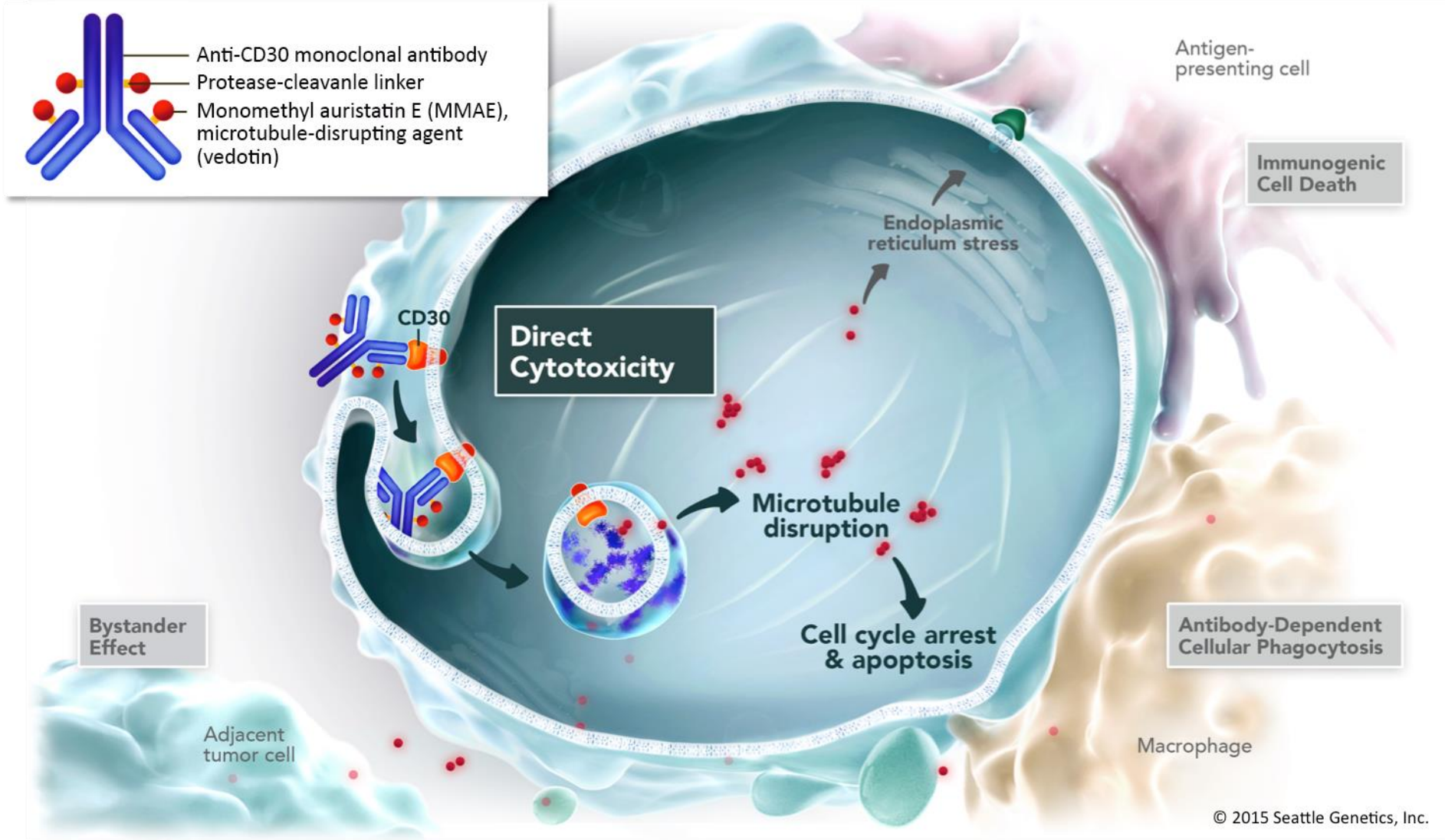
- CL gel may be safely applied to patch/plaque disease in patients receiving systemic treatments for advanced MF
- CL gel may be safely applied to patch/plaque disease in patients receiving radiotherapy for tumours but avoid application on irradiated areas
- CL gel may be useful in treating low grade skin lesions (patches and plaques) which may be resistant to chemotherapy (better for high grade lesions such as tumours)



Brentuximab Vedotin (ADCETRIS™)

Brentuximab vedotin – a drug antibody conjugate

Anti CD30 monoclonal antibody with a protease cleavable linker to a microtubule disrupting agent; vedotin



Seattle Genetics Announces FDA Approval of Adcetris (Brentuximab Vedotin) for Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) and CD30-Expressing Mycosis Fungoides (MF)

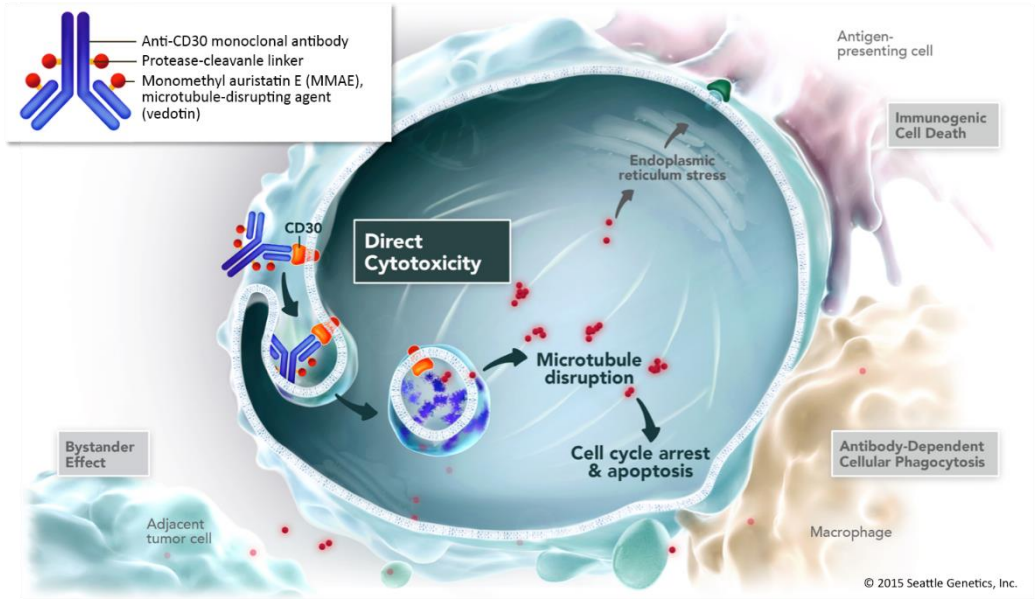
Brentuximab Vedotin (ADCETRIS™)

ADCETRIS was granted approval by FDA November 2017 for:

- The treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy

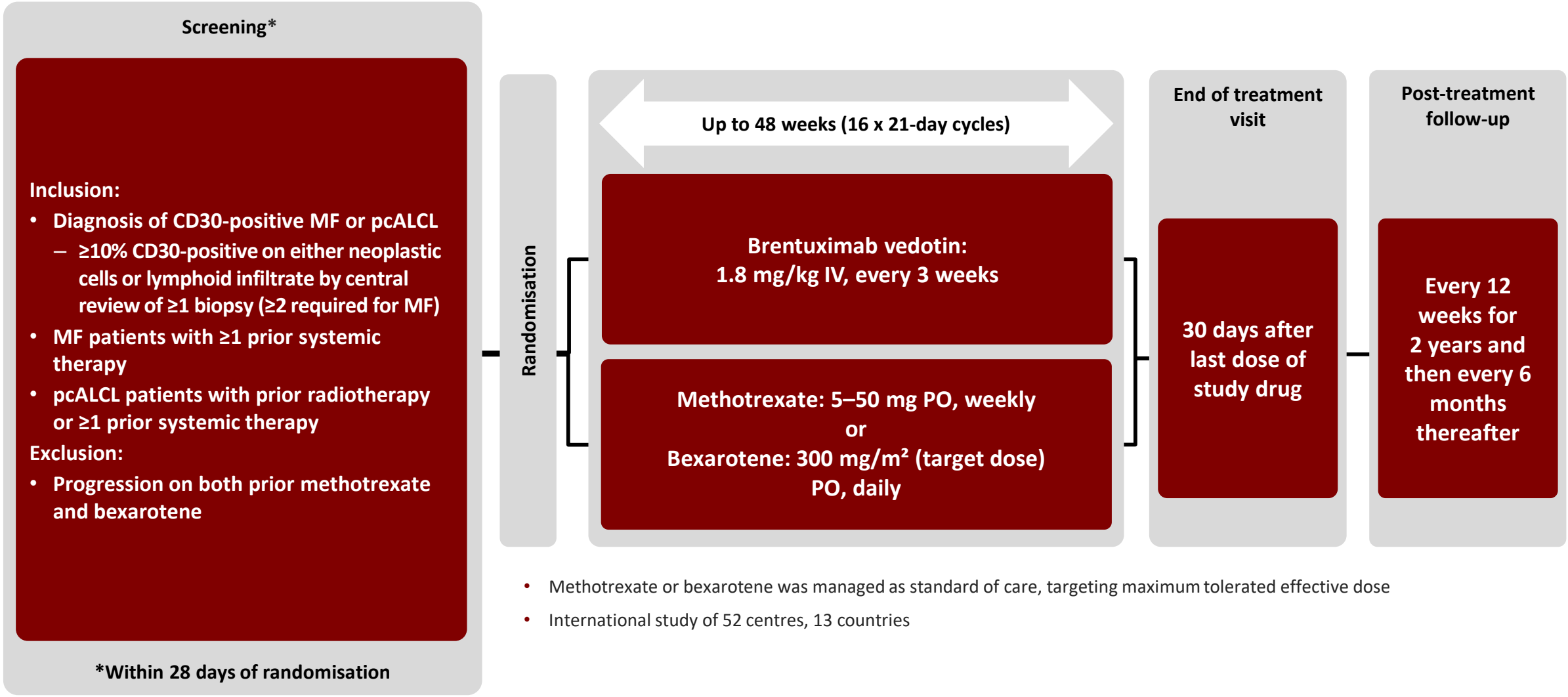
ADCETRIS was approved in EC in December 2017 for:

- The treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy to received up to 16 cycles



Brentuximab vedotin – a drug antibody conjugate
Anti CD30 monoclonal antibody with a protease cleavable linker to a microtubule disrupting agent; vedotin

ALCANZA: A phase 3, randomised study comparing the efficacy and safety of brentuximab vedotin versus physician's choice in CD30-positive MF or pcALCL



- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- International study of 52 centres, 13 countries

IV, intravenously; PO, orally

Prince HM, et al. Lancet 2017;390:555–66

ALCANZA: Patient baseline characteristics: ITT population, N=128

	Brentuximab vedotin (n=64)	Methotrexate or bexarotene (n=64)
Median age, years (range)	62 (22–83)	59 (22–83)
Male gender, n (%)	33 (52)	37 (58)
ECOG performance status 0–1, n (%)	61 (95)	62 (97)
Median of average CD30 expression from multiple biopsies at baseline, % (range)	33 (3–100)	31 (5–100)
MF*, n (%)	48 (75)	49 (77)
Early (IA-IIA)	15 (31)	18 (37)
Advanced (IIB-IVB)**	32 (67)	30 (61)
pcALCL, n (%)	16 (25)	15 (23)
Skin only	9 (56)	11 (73)
Extracutaneous disease	7 (44)	4 (27)
Total number of prior therapies, median (range)	4.0 (0–13)	3.5 (1–15)
Number of prior systemic therapies, median (range)	2.0 (0–11)	2.0 (1–8)

*One patient in each arm had incomplete staging data and are not included
** stage IVB MF, n=7 in brentuximab arm vs. n=0 in methotrexate/bexarotene arm

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; MF, mycosis fungoides; pcALCL, primary cutaneous anaplastic large cell lymphoma.

Kim et al. ASH 2016; Abstract #182
Prince et al. Lancet Oncology 2017. 6736(17)31266-7

ALCANZA demonstrated superior clinical activity for brentuximab vedotin

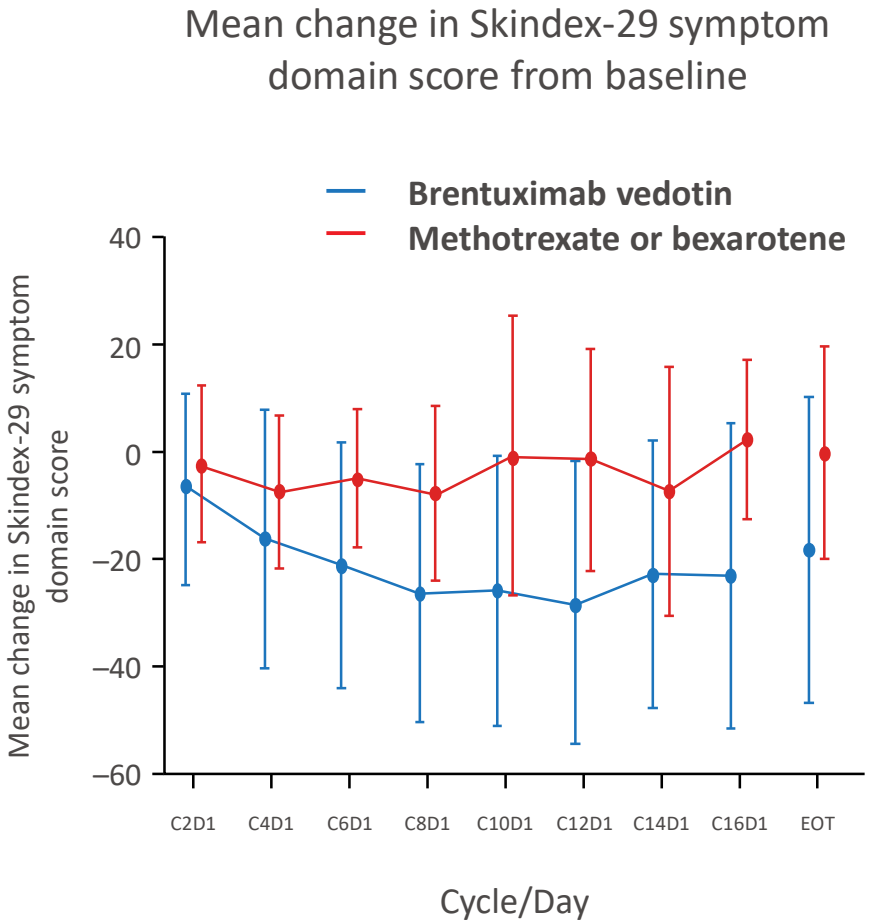
- The primary endpoint for the ALCANZA study was the proportion of patients achieving an objective global response lasting (from first to last recorded response) at least 4 months (ORR4)
- Brentuximab vedotin was superior to physician's choice at a median follow-up of 22.9 months in terms of:
  - ORR4 (56% vs 13%; p<0.0001)
  - CR rate (16% vs 2%; adjusted p=0.0046) including 6/16 (38%) with PC-LCAL
  - PFS (16.7 vs 3.5 months; HR=0.270, 95% CI: 0.169–0.430; adjusted p<0.0001)
  - Reduction in patient-reported symptoms per Skindex-29 symptom domain (–27.96 vs –8.62; adjusted p<0.0001)
- Safety data were consistent with the established tolerability profile

CI, confidence interval; CR, complete response; HR, hazard ratio; ORR4, overall rate of responses lasting ≥4 months; PFS, progression-free survival

Ref. Prince HM, et al. Lancet 2017;390:555–66

ALCANZA: Patient-reported burden of life quality symptoms

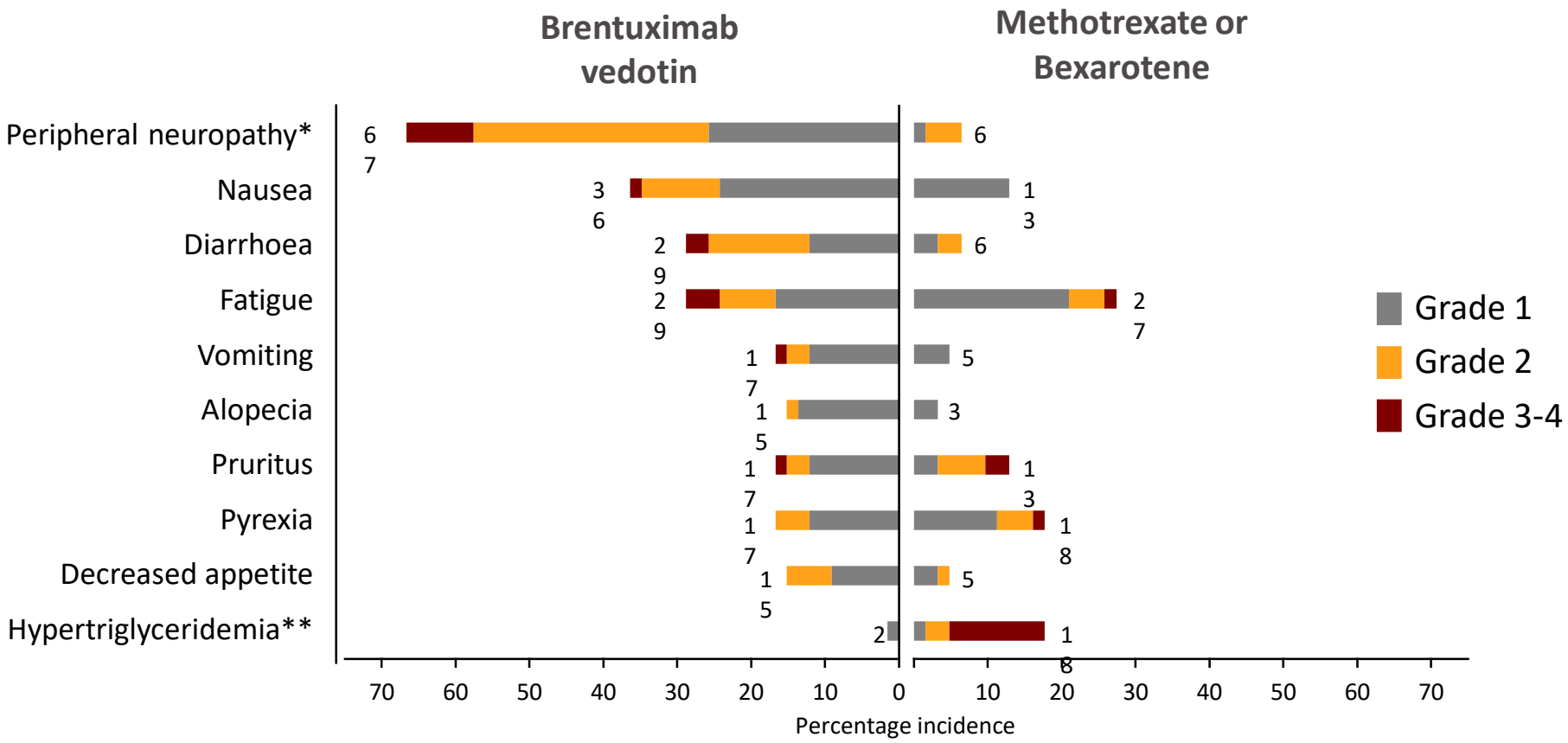
- Patients with CTCL suffer altered QoL, symptoms not captured by objective response measures.[1]
- The 29-item Skindex is an established and validated tool for the assessment of QoL in dermatologic diseases.
- Mean of the maximum reduction of patient-reported burden of symptoms, measured by the Skindex-29 symptom domain,[2] of
  - -27.96 for brentuximab vedotin
  - -8.62 for physician's choice (adjusted p<0.0001)



EOT, end of treatment

1. Wright A, et al. J Pain Symptom Manage 2013;45(1):114–9
2. Chren MM, et al. Arch Dermatol 1997;133:1433-40

ALCANZA: Commonly reported (≥15% of patients) treatment-emergent AEs



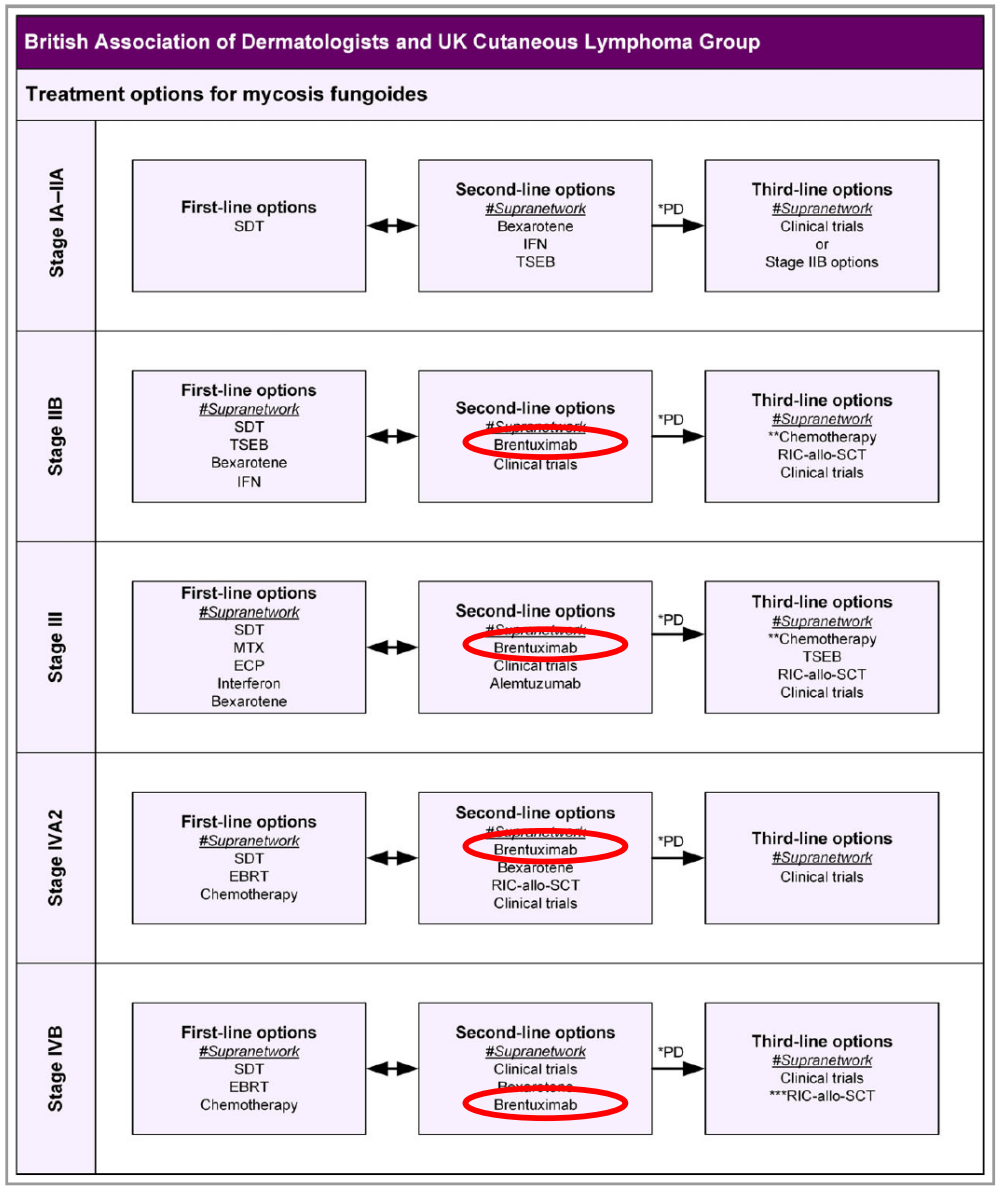
*No Gr 4 peripheral neuropathy was reported in the brentuximab vedotin (26% Gr 1, 32% Gr 2, 9% Gr 3) or physician's choice arms (2% Gr 1, 5% Gr 2). At last follow-up (median 22.9 months), 36/44 (82%) patients in the brentuximab vedotin arm had improvement or resolution of peripheral neuropathy.

**Elevated triglycerides, were reported in 2% of patients receiving brentuximab vedotin versus 30% of patients receiving bexarotene (14% Gr 3, 8% Gr 4)

Length of drug exposure: median 12 cycles (36 weeks) of BV vs. 17 weeks of bexarotene or 9 weeks of methotrexate

Kim et al. ASH 2016; Abstract #182
Prince HM et al. Lancet 2017;390:555-566.

Where should brentuximab be placed in management CTCL?



EBRT: external beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma; **ECP:** extracorporeal photopheresis; **IFN:** interferon; **MTX:** methotrexate;
PD: progressive disease; **RIC-allo-SCT**, reduced intensity allogeneic stem cell transplantation;
*PD and exhausted first- and second-line options. **Chemotherapy only as recommended by the supranetwork MDT.
***Consider only if the patient has durable complete response.
↔ indicates that after treatment, patients may respond to treatments included in earlier ‘line’ options. Patients can move between first- and second-line options.

Mogamulizumab (POTELIGEO™)

Mogamulizumab is a humanized, afucosylated monoclonal antibody targeting C-C chemokine receptor 4 (CCR4) also designated CD194.

2012 Japan approved mogamulizumab for

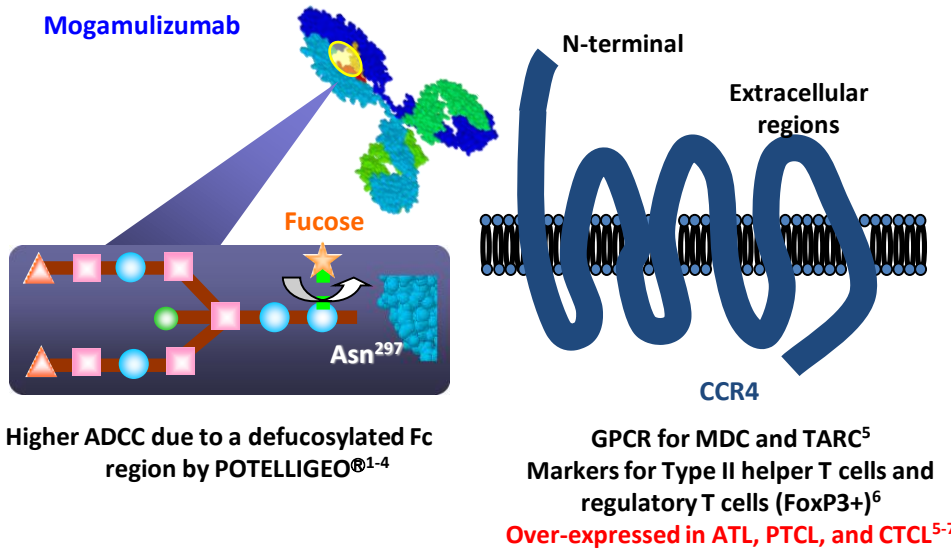
- Treatment of relapsed or refractory CCR4+ adult T-cell leukemia/lymphoma (ATCLL)
- 2014 for relapsed or refractory CCR4+ cutaneous T cell lymphoma (CTCL).

August 2018 FDA granted approval for

- Treatment of adult patients with relapsed or refractory MF/SS after at least one prior systemic therapy

September 2018, the EMA granted the use of POTELIGEO ™ for

- Treatment of adult patients with MF/SS having received at least one prior systemic therapy

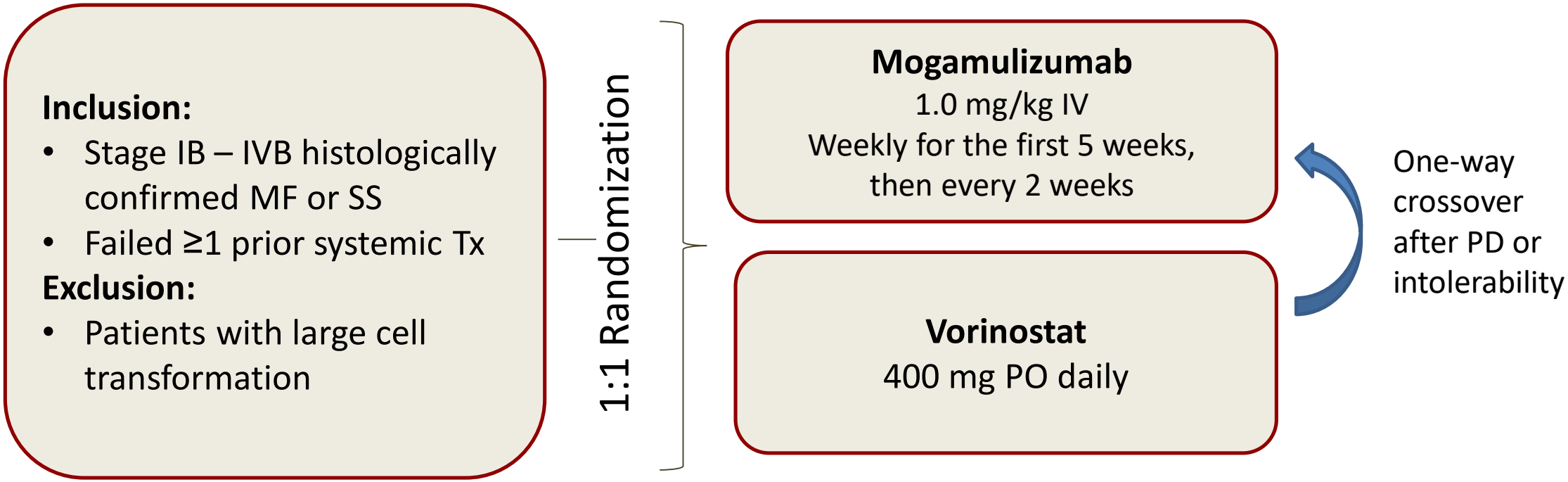


Higher ADCC due to a defucosylated Fc region by POTELLIGEO®[1-4]

GPCR for MDC and TARC[5]
Markers for Type II helper T cells and regulatory T cells (FoxP3+)[6]
Over-expressed in ATL, PTCL, and CTCL[5-7]

MAVORIC Trial: International, open-label, randomised, controlled phase 3 trialof mogamulizumab versus vorinostat in previously treated CTCL

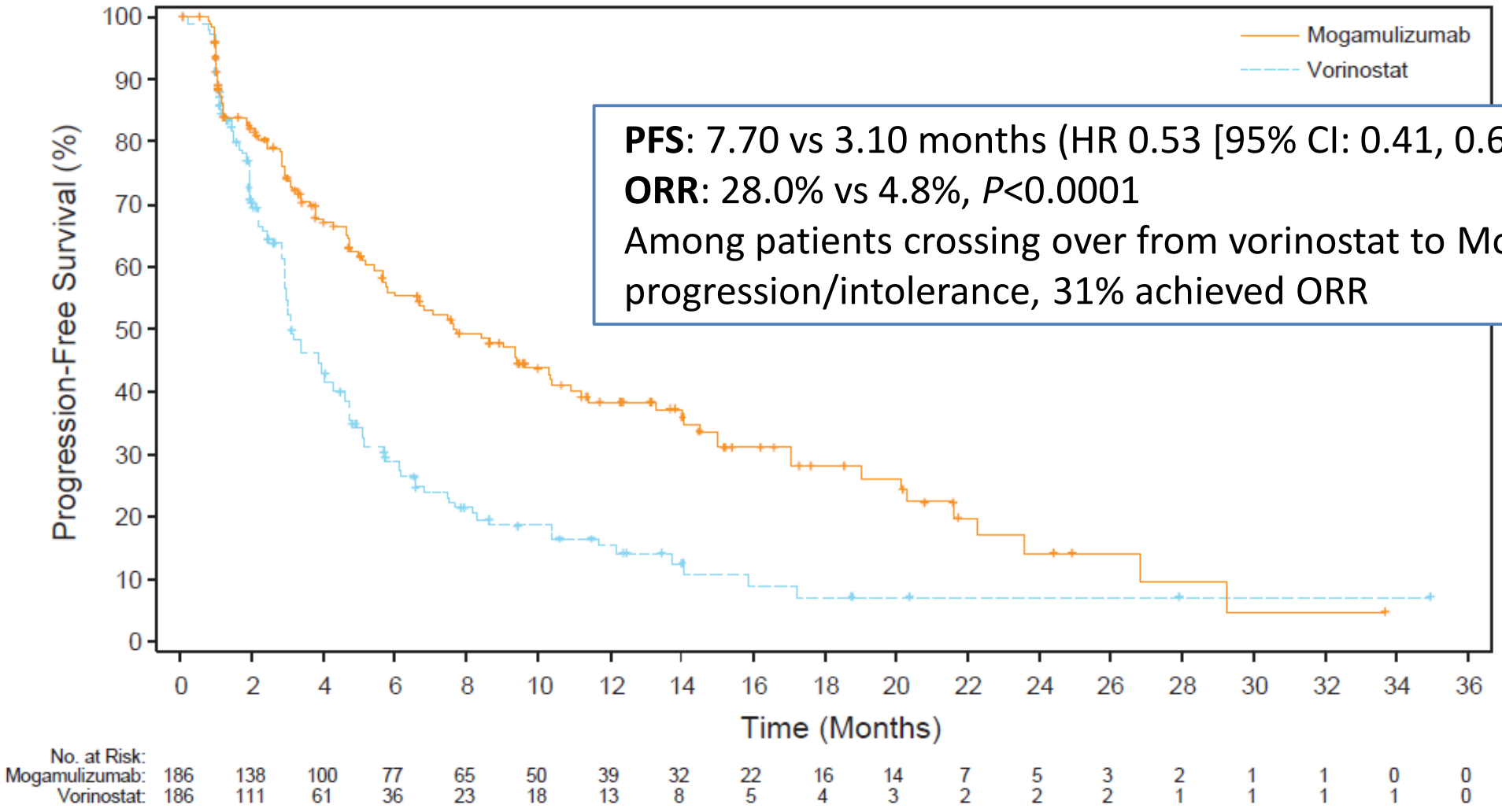
Study Design:



- 372 patients were randomized at 59 centers across 11 countries
- Tx was administered on an outpatient basis
- Vorinostat was administered in accordance with US prescribing information
- Patients could remain in the Tx phase up until progression or intolerable toxicity

IV, intravenously; PD, disease progression; PO, orally; Tx, treatment.

PRIMARY ENDPOINT
PROGRESSION FREE SURVIVAL



PFS: 7.70 vs 3.10 months (HR 0.53 [95% CI: 0.41, 0.69], *P*<0.0001)
ORR: 28.0% vs 4.8%, *P*<0.0001
Among patients crossing over from vorinostat to Moga, n=133, due to progression/intolerance, 31% achieved ORR

CI, confidence interval; HR, hazard ratio; Moga, mogamulizumab; ORR, overall response rate; PFS, progression free survival.

Kim YH, et al. Lancet Oncol. 2018;19(9):1192-1204.

Summary MAVORIC trial

- First report of a randomized phase 3 study evaluating PFS as a primary endpoint in CTCL
- Largest randomized controlled trial in CTCL of 364 patients
- Mogamulizumab, a CCR4-targeting antibody therapy, demonstrated significantly superior efficacy outcomes compared to vorinostat in patients with previously treated CTCL with high response rates in blood
  - **PFS**: 7.70 vs 3.10 months (HR 0.53 [95% CI: 0.41, 0.69], P<0.0001)
  - **ORR**: 28.0% vs 4.8%, P<0.0001
- The most common side effects are drug eruption (including skin rash), infections (including upper respiratory tract infection and skin infections), infusion related reaction, headache, fatigue, peripheral oedema, pyrexia and gastrointestinal disorders (such as constipation, diarrhoea, nausea, stomatitis).
- Patient-reported quality-of-life, measured by Skindex-29, showed better symptom reduction & improved functional status in favor of mogamulizumab vs vorinostat (P<0.05)
- This study supports mogamulizumab as a valuable additional therapeutic option in CTCL patients

Recent Treatments For CTCL

- Chlormethine Gel – approved in EU CTCL 2017

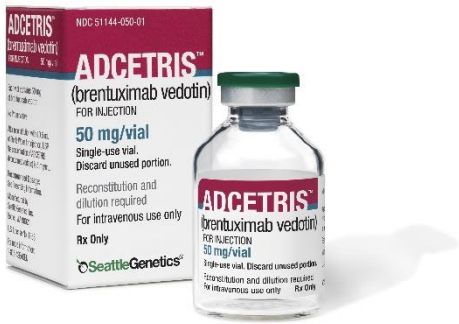
Monotherapy in patch / plaque MF in early stage or adjuvant therapy in advanced stage disease

- Brentuximab vedotin – approved in EU CTCL 2017, NICE approved

Relapsed refractory CD30+ CTCL (MF/SS and LCAL)

- Mogamulizumab - approved in EU CTCL 2018

Second line Sezary syndrome or 3rd line in relapsed refractory CTCL



Euro Refe Netw
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Webinars
Cutaneous Lymphoma
EuroBloodNet Topic on Focus