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

Disclosures

Galderma Research funds

Takeda Advisory board

Actelion Advisory board
Sex and Age Distribution 2009-13

NCIN audit data 2016

Total new cases: 1659

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of cases</th>
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<tbody>
<tr>
<td>MF</td>
<td>920</td>
</tr>
<tr>
<td>SS</td>
<td>42</td>
</tr>
<tr>
<td>SPTCL</td>
<td>9</td>
</tr>
<tr>
<td>CTCL</td>
<td>466</td>
</tr>
<tr>
<td>CD30+ CTCL</td>
<td>160</td>
</tr>
<tr>
<td>Rare variants</td>
<td>62</td>
</tr>
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</table>
Age Standardised Incidence Rates per 100,000 UK Population CTCL 2009-13
Distribution of CTCL for Strategic Clinical Networks 2009-13

“Cutaneous T-cell lymphoma nos”
Stage recording 7% 2009 – 20% 2013
## WHO 2016

### Cutaneous B-cell lymphoma
- Indolent clinical behaviour
  - Primary cutaneous marginal zone B-cell lymphoma**
  - Primary cutaneous follicle centre lymphoma
- Intermediate behaviour
  - Primary cutaneous diffuse large B-cell lymphoma, leg type

### Cutaneous T-cell lymphoma
- Indolent clinical behaviour
  - Mycosis fungoides (and variants)
  - Primary cutaneous CD30+ lymphoproliferative disorder: anaplastic large cell lymphoma
  - Primary cutaneous CD30+ lymphoproliferative disorder: lymphomatoid papulosis
  - Subcutaneous panniculitis-like T-cell lymphoma
    - Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder*
    - Primary cutaneous acral CD8+ T-cell lymphoma*
    - Hydroa vacciniforme-like lymphoproliferative disorder*
- Aggressive clinical behaviour
  - Sézary syndrome
  - Extranodal NK/T-cell lymphoma, nasal-type
  - Primary cutaneous aggressive epidermotropic cytotoxic CD8+ T-cell lymphoma
  - Primary cutaneous γ/δ T-cell lymphoma
  - Primary cutaneous peripheral T-cell lymphoma (PTCL), unspecified
The diagnosis of mycosis fungoides (MF) and Sézary syndrome (SS) is based on a combination of clinical and pathologic criteria and requires close multidisciplinary team (MDT) collaboration between different specialities.

<table>
<thead>
<tr>
<th>Category</th>
<th>33 Specialist MDTs</th>
<th>7 Supra-network MDTs</th>
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<tbody>
<tr>
<td>MF stage IA-IIA</td>
<td>Required</td>
<td>Optional</td>
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<tr>
<td>MF stage IA-IIA refractory to SDT</td>
<td>Required</td>
<td>Essential</td>
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<tr>
<td>MF stage IIB-IVB</td>
<td>Required</td>
<td>Essential</td>
</tr>
<tr>
<td>SS stage IVA1-IVB</td>
<td>Required</td>
<td>Essential</td>
</tr>
<tr>
<td>CD30+ lymphoproliferative disorders</td>
<td>Required</td>
<td>Preferred</td>
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<tr>
<td>CTCL variants</td>
<td>Required</td>
<td>Essential</td>
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<tr>
<td>CBCL</td>
<td>Required</td>
<td>Preferred</td>
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</table>

All patients with early-stage MF *refractory to SDT* and *late-stage MF/SS* should be reviewed by supra-network MDTs to agree a management plan and provide the opportunity for consideration in appropriate clinical trials.

[https://www.nice.org.uk/guidance](https://www.nice.org.uk/guidance)
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<th>Supra-network MDTs</th>
<th>TSEB</th>
<th>ECP</th>
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<td>Birmingham (Queen Elizabeth Hospital)</td>
<td>Yes (Coventry and Warwickshire University Hospital)</td>
<td>Yes</td>
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<tr>
<td>Leeds (St James's University Hospital)</td>
<td>Yes</td>
<td>No, referred to Rotherham Hospital</td>
</tr>
<tr>
<td>Liverpool (Royal Liverpool Hospital)</td>
<td>Yes (Clatterbridge Hospital, Wirral)</td>
<td>Yes</td>
</tr>
<tr>
<td>London (Guy's &amp; St Thomas's Hospital)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Manchester (The Christie Hospital)</td>
<td>Yes</td>
<td>Yes, Central Manchester University Hospital</td>
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<tr>
<td>Newcastle (Freeman Hospital)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nottingham (City Hospital)</td>
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<td>Yes</td>
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<td><strong>Other network skin lymphoma service</strong></td>
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<td>Belfast</td>
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<td>No</td>
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<tr>
<td>Cardiff</td>
<td>No, referred to Guy's and St Thomas's</td>
<td>No, referred to Bristol University Hospitals</td>
</tr>
<tr>
<td>Glasgow</td>
<td>No, referred to Newcastle</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Elise A. Olsen, Sean Whittaker, Youn H. Kim, Madeleine Duvic, H. Miles Prince, Stuart R. Lessin, Gary S. Wood, Rein Willemze, Marie-France Demierre, Nicola Pomponi, Maria Grazia Bernengo, Pablo L. Ortiz-Romero, Martine Bagot, Teresa Estrach, Joan Guaita, Robert Knobler, José Antonio Sanches, Keiji Iwatsuki, Makoto Sugaya, Reinhard Dummer, Mark Pittelkow, Richard Hoppe, Sareeta Parker, Larisa Gerskin, Lauren Pinter-Brown, Michael Girardi, Günter Burg, Amsamari Ranki, Maarten Vermeer, Steven Horwitz, Peter Heald, Steve Rosen, Lorenzo Cerroni, Brigette Dreno, and Eric C. Vonderheid

Free Cutaneous Lymphoma App

Courtesy of Stephen Morris
### Skin
- T1a-patches <10%
- T1b-patches/plaques <10%
- T2a-patches >10%
- T2b-patches/plaques >10%
- T3-tumours
- T4-erythroderma

### Nodes
- N0-no palpable nodes
- N1-dermatopathic nodes (LN 0-2)
- N2-early involvement (LN 3)
- N3-effaced nodes (LN 4)
- Nx-palpable nodes/no biopsy

### Visceral
- M0 - no visceral disease
- M1 - visceral disease
- B0 - no blood disease (B0a/b)
- B1 – Sezary cells >5% PBL
- B2 – Sezary cells >1000/ul

*Olsen et al Blood 2007: 110; 1722-1722*
Stage Dependent Treatment

Stage IA-IIA
- Early stage disease (SDT)
- Excellent prognosis (T1a/T2a>T1b/T2b)

Stage IB-III
- Resistance to SDT
- Intermediate prognosis

Stage IIB/IV
- Advanced stage IV disease
- Poor prognosis (chemo-resistance)

UKCLG draft NICE accredited guidelines 2018
EORTC guidelines Trautinger et al EJC 2017
US National Comprehensive Cancer Network guidelines www.nccn.org
MF/SS Treatment Recommendations (I)

- Skin-directed therapies (SDT), including phototherapy and local radiotherapy, are the standard of care for patients with early-stage IA-IIA MF.

- Patients with stage IA-IIA MF who are refractory to SDT often require TSEB and systemic biologic therapies. There is no evidence to support use of maintenance phototherapy.

- All patients with early-stage MF refractory to SDT should be offered the opportunity to participate in well-designed clinical trials.
Stage IA-IIA Mycosis Fungoides

Skin directed therapy
- topical (mechlorethamine)
- phototherapy (PUVA/UVB)
- radiotherapy (local and TSEB)

PUVA response data:
- Stage IA – IB (OR 75% & CR 25%)
- Sanctuary sites resistant
- Relapse rates – 50% within 18 months
MF/SS Treatment Recommendations (II)

• Stage IIB MF patients can have an unpredictable clinical course: some patients only develop small and infrequent skin tumours and often obtain durable responses to localised radiotherapy and other SDT options for persistent patches and plaques; other patients develop extensive bulky skin tumours and rapidly progressive disease requiring TSEB and systemic chemotherapy.

• Following treatment, patients with advanced disease may develop recurrent, low-grade disease which can be responsive to SDT.

• Patients with erythrodermic MF (stage III) and SS (stage IVA1) often require single or combination biologic therapies such as methotrexate, photopheresis, bexarotene and interferon-alpha as first-line treatment.

• Options for SS (stage IVA1-2) also include clinical trials and alemtuzumab.
Superficial Radiotherapy

- Palliative low dose/energy
- 8-12 Gy in 2-3 fractions with 80-120Kv
- CR > 90%
- Overlapping fields
• 103 patients 12Gy in 8 fractions

• Median follow up 20.6 months (3.3-53)

• Global response: ORR 87% (CR 18% PR 69% PD 5%)
Low dose TSEB in MF: Clinical outcomes by stage and time Morris et al 2017

- Median response duration 11.8 months
- Median time to relapse 7.3 months
- Median duration of clinical benefit 18.9 months
- Median PFS 13.2 months (26.5 months for stage IB compared to 11.3-10.2 months for stage IIB-III)
# Treatment options for mycosis fungoides

## Stage IA-IIB
- **First-line options**
  - SDT
  - Expectart
- **Second-line options**
  - Bexarotene
  - IFN
  - TSEB
- **Third-line options**
  - Clinical trials
  - Stage IIB options

## Stage IIB
- **First-line options**
  - SDT
  - TSEB
  - Bexarotene
  - IFN
- **Second-line options**
  - Brentuximab
  - Clinical trials
- **Third-line options**
  - Chemotherapy
  - RIC-allo-SCT
  - Clinical trials

## Stage III
- **First-line options**
  - SDT
  - MTX
  - ECP
  - Interferon
  - Bexarotene
- **Second-line options**
  - Brentuximab
  - Clinical trials
  - Alemtuzumab
- **Third-line options**
  - Chemotherapy
  - TSEB
  - RIC- allo-SCT
  - Clinical trials

*PD indicates progression disease.*
**MF/SS Treatment Recommendations (III)**

- For stage IVA2-B radiotherapy (including TSEB for selected stage IV patients) and single-agent chemotherapy regimens are the preferred option, but response duration is often short

- Brentuximab offers an excellent option for refractory stage IB and advanced stages of MF/SS with tumour CD30 expression

- Autologous HSCT should **not** be considered for advanced stages of MF/SS

- Reduced-intensity allogeneic HSCT should be considered for selected groups of patients with advanced disease to consolidate treatment responses

- The conditioning regimens and outcomes of RIC-allo-SCT should be collected through data registries such as the EBMT registry
Prospective International Multicenter Phase II Trial of Intravenous Pegylated Liposomal Doxorubicin Monochemotherapy in Patients With Stage IIB, IVA, or IVB Advanced Mycosis Fungoides: Final Results From EORTC 21012

Reinhard Dummer, Pietro Quaglino, Jürgen C. Becker, Baktiar Hasan, Matthias Karrasch, Sean Whittaker, Stephen Morris, Michael Weichenthal, Rudolf Stadler, Martine Bagot, Antonio Cozzio, Maria G. Bernengo, and Robert Knobler

J Clin Oncol 30:4091-4097

Wollina et al Cancer 2003
Di Lorenzo et al BJD 2005
Pulini et al Haematologic 2007
Quereux et al Arch Dermatol 2008

<table>
<thead>
<tr>
<th>Best Overall Response to treatment</th>
<th>Treatment (N=49) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (34.7)</td>
</tr>
<tr>
<td>SD</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (10.2)</td>
</tr>
<tr>
<td>Early death-toxicity</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Early death-other</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>8 (16.3)</td>
</tr>
</tbody>
</table>

The best overall response (CCR/PR) rate is 40.8%.

Exact one-sided 90% Confidence Interval is: (31.2%, 100%).

Median duration of response 6 months
Time to progression 7.4 months
Brentuximab vedotin or physician’s choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial

H Miles Prince*, Youn H Kim*, Steven M Horwitz, Reinhard Dummer, Julia Scarisbrick, Pietro Quaglini, Pier Luigi Zinzani, Pascal Wolter, Jose A Sanchez, Pablo L Ortiz-Romero, Oleg E Akilov, Larisa Geskin, Judith Trotman, Kerry Taylor, Stephane Dalle, Michael Weichenthal, Jan Walewski, David Fisher, Brigitte Dréno, Rudolf Stadler, Tatyana Feldman, Timothy M Kuzel, Yinghui Wang, Maria Corinna Palanca-Wessels, Erin Zagaidailov, William L Trepicchio, Wenwen Zhang, Hui-Min Lin, Yi Liu, Dirk Huebner, Meredith Little, Sean Whittaker†, Madeleine Duvic†, on behalf of the ALCANZA study group†

www.thelancet.com Published online June 6, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31266-7

<table>
<thead>
<tr>
<th>Screening*</th>
<th>Treatment (N=131)</th>
<th>Follow-up¹</th>
</tr>
</thead>
</table>
| • Age ≥18 years  
• Diagnosis of ≥10% CD30+ MF or pcALCL* (N=131)  
  - MF patients (N=100) with ≥1 prior systemic therapy  
  - pcALCL patients (N=31) with prior radiotherapy or ≥1 prior systemic therapy | • Up to 48 weeks  
  (16 x 21-day cycles)  
  • Brentuximab vedotin: 1.8mg/kg IV, every 3 weeks  
  VS  
  • Methotrexate: 5–50 mg PO, weekly or  
  • Bexarotene: 300 mg/m² (target dose) PO, daily | • Every 12 weeks for 2 years and then every 6 months thereafter |
ALCANZA study endpoints

- **Primary endpoint** to assess **durable responses**: ORR4
  
  ORR4 = Rate of **objective responses lasting 4 months or more**

  Measured by Global Response Score (GRS): Independent review of global response of all compartments using consensus guidelines, as assessed by mSWAT (skin evaluation), radiographic assessment (lymph nodes and viscera), and circulating Sézary cell assessment (blood)\(^1\)\(^-\)\(^3\)

- **Key secondary endpoints** to assess other **clinically meaningful** measures:
  - Rate of complete response (CR)
  - Progression-free survival (PFS)
  - Symptom burden/quality of life (measured by Skindex-29 questionnaire\(^4\))
Phase III ALCANZA Study: Brentuximab Vedotin approved for adult patients with CD30+ cutaneous T-cell lymphoma after at least one prior systemic therapy (EMA 2017)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Brentuximab vedotin (n=64)</th>
<th>Methotrexate or bexarotene (n=64)</th>
<th>Difference between arms (95%CI)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR4 n(%)</td>
<td>36 (56.3)</td>
<td>8 (12.5%)</td>
<td>43.8% (29.1, 58.4)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CR n(%)</td>
<td>10 (15.6)</td>
<td>1 (1.6)</td>
<td>14.1% (-4.0, 31.5)</td>
<td>p=0.0046&lt;sup&gt;adj&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median PFS months</td>
<td>16.7</td>
<td>3.5</td>
<td></td>
<td>p&lt;0.0001&lt;sup&gt;adj&lt;/sup&gt; HR=0.270 (95%CI: 0.169,0.430)</td>
</tr>
<tr>
<td>Mean maximum reduction in Skindex-29 symptom domain</td>
<td>-27.96</td>
<td>-8.62</td>
<td>-18.9 (-26.6, -11.2)</td>
<td>p&lt;0.0001&lt;sup&gt;adj&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Adj, adjusted p-value calculated from a weighted Holm’s procedure; HR, hazard ratio; IRF, independent review facility

mSWAT response >50% in 77% of MF patients on Brentuximab

Best global response

CI, confidence interval; MF, mycosis fungoides; PFS, progression-free survival.
Brentuximab vedotin significantly extended PFS (median 16.7 vs 3.5m)\(^1\)

Log-rank test p-value: \(<0.0001\)
Hazard ratio (95% CI): 0.270 (0.169, 0.430)
Median (months):
  - Brentuximab vedotin (BV): 16.7
  - Methotrexate or bexarotene (MTX or Bex): 3.5
Number of events:
  - Brentuximab vedotin (BV): 36
  - Methotrexate or bexarotene (MTX or Bex): 50

HR, hazard ratio; IRF, independent review facility.
Transplantation in MF/SS

**Autologous**
- Short term remissions

**Allogeneic**
- Durable complete remissions
- Meta-analysis confirms worse outcomes for myeloablative transplants and unrelated donors (EBMT)

**Myeloablative**
- EBMT: OS 46% and PFS 32% at 5 years
- Relapse/progression 45% median of 3.8mos (DLI beneficial)
- Non-relapse mortality 22%

**Non-Myeloablative**

Overall Survival
Stanford regimen (TSEB/TNLI/ATG) compared to chemotherapy conditioned allografts

St Johns and Hammersmith
29 patients 2003-15
# Reduced Intensity Allogeneic Stem Cell Transplantation in late stage MF/SS: Long term responses

<table>
<thead>
<tr>
<th>Sex</th>
<th>MF or SS</th>
<th>OS post RISCT (yr)</th>
<th>Current Status</th>
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<tbody>
<tr>
<td>Male</td>
<td>SS (IVA1)</td>
<td>2.42</td>
<td>CR</td>
</tr>
<tr>
<td>Male</td>
<td>SS (IVA2)</td>
<td>3.1</td>
<td>PR</td>
</tr>
<tr>
<td>Male</td>
<td>SS (IVA2)</td>
<td>4.36</td>
<td>CR</td>
</tr>
<tr>
<td>Male</td>
<td>SS (IVA1)</td>
<td>5.21</td>
<td>CR</td>
</tr>
<tr>
<td>Male</td>
<td>SS (IVA1)</td>
<td>5.92</td>
<td>CR</td>
</tr>
<tr>
<td>Female</td>
<td>MF (IIB)</td>
<td>7.6</td>
<td>CR</td>
</tr>
<tr>
<td>Male</td>
<td>SS (IVA2)</td>
<td>9.3</td>
<td>CR (GvHD)</td>
</tr>
</tbody>
</table>

St Johns and Hammersmith
29 patients 2003-15
Stanford conditioning: Updated data 2018

- 10% Non relapse mortality
- 30% Lymphoma relapse
- 60% Complete remission
## Treatment options for mycosis fungoides

### Stage IV A2

<table>
<thead>
<tr>
<th>First-line options</th>
<th>Second-line options</th>
<th>Third-line options</th>
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<td>#Supra-network</td>
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<tr>
<td>SDT</td>
<td>Brentuximab</td>
<td>Clinical trials</td>
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<td>EBRT</td>
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<tr>
<td>Chemotherapy</td>
<td>RIC-ALlo-SCT</td>
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### Stage IVB

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<td>SDT</td>
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<td>Bexarotene</td>
<td>RIC-allo-SCT</td>
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<tr>
<td>Chemotherapy</td>
<td>Brentuximab</td>
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</tbody>
</table>

*PD* denotes progressive disease.
Recommendations: Primary cutaneous CD30+ lymphoproliferative disorders

- Primary cutaneous CD30+ lymphoproliferative disorders are diagnosed on the basis of careful clinico-pathologic correlation. Staging investigations are not appropriate for LyP but are essential for ALCL or borderline cases.

- Treatment for LyP ranges from an expectant policy for patients with limited disease to phototherapy, radiotherapy, low-dose methotrexate or interferon-alpha for patients with extensive disease.

- Treatment for pcCD30+ ALCL consists of surgical excision and/or radiotherapy for localized disease.

- Combination chemotherapy or brentuximab may be appropriate for pcCD30+ ALCL patients with extensive cutaneous disease or those with systemic progression.


**Recommendations: Rare CTCL Variants**

- Treatment of rare CTCL variants depends on the subtype as some (SPTCL; CD4+ small/medium pleomorphic; CD8+ acral T-cell lymphoma) are indolent with an excellent prognosis, whilst others are aggressive and may require chemotherapy and consideration for stem cell transplant in line with recommendations for systemic PTCL (NOS)

- Primary cutaneous PTCL(NOS) are rare and heterogenous in behaviour. Some present with limited skin disease which can be managed with skin directed options such as radiotherapy, whilst others present with extensive or bulky skin disease and will require treatment options as for systemic PTCL(NOS)
**Recommendations: Primary cutaneous low grade B-cell lymphomas**

- Small individual skin lesions can be completely excised and monitored but treatment with radiotherapy (tumour/scar with a 2 cm margin of skin to define CTV) is preferred to reduce the risk of local relapse.

- Following a diagnostic biopsy, the first-line treatment for individual skin lesions should be radiotherapy. The radiotherapy target volume (CTV) should be the tumour plus a 2 cm margin of normal skin around the tumour.

- Active monitoring is an option for patients with limited asymptomatic disease.

- Systemic chemotherapy should be reserved for patients with widespread extensive lesions or high tumour burden (stage T2c-T3), or patients with nodal or visceral progression. Treatment is palliative and for disease confined to the skin consideration should be given to single-agent rituximab, or chlorambucil as this is well tolerated and effective. Further choice of chemotherapy should be in line with local guidelines for the management of indolent lymphomas.

- Patients who relapse with nodal or visceral lymphoma should be treated according to local and national management guidelines for systemic lymphoma.
Recommendations: Primary cutaneous diffuse large B-cell lymphoma

- PCLBCL leg type should be treated with CHOP-R chemotherapy followed by local radiotherapy as per local guidelines for systemic DLBCL. Current protocols recommend three to six cycles of CHOP-R chemotherapy followed by 30 to 36 Gy in 2 Gy fractions of local radiotherapy.

- Palliative radiotherapy alone can be considered for patients unfit for chemotherapy.

- Future trials should concentrate on improving clinical outcomes for PCLBCL.

- PCLBCL-other should be treated as per local guidelines for systemic DLBCL.