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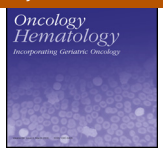

Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: Cutaneous T-cell lymphomas

Pier Luigi Zinzani[a,*], Vijayveer Bonthapally[b], Dirk Huebner[c], Richard Lutes[c], Andy Chi[d], Stefano Pileri[e,f]

[a] Institute of Hematology 'L. e A. Seràgnoli', Policlinico Sant'Orsola-Malpighi, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy
[b] Global Outcomes and Epidemiology Research (GOER), Millennium Pharmaceuticals Inc., 40 Lansdowne Street, Cambridge, MA 02139, USA[1]
[c] Oncology Clinical Research, Millennium Pharmaceuticals Inc., 35 Lansdowne Street, Cambridge, MA 02139, USA[1]
[d] Department of Biostatistics, Millennium Pharmaceuticals Inc., 40 Lansdowne Street, Cambridge, MA 02139, USA[1]
[e] Department of Experimental, Diagnostic, and Specialty Medicine, Bologna University School of Medicine, Via Massarenti 8, 40138 Bologna, Italy
[f] Unit of Hematopathology, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy

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ABSTRACT

Primary cutaneous T-cell lymphomas (CTCLs), such as mycosis fungoides and Sézary syndrome, are a rare group of non-Hodgkin lymphomas, usually treated using a multimodal approach. Unfortunately, many patients go on to develop relapsed/refractory disease. Systemic treatment for relapsed/refractory CTCL has historically relied on chemotherapies and interferons, and while active, responses are often short-lived. Three drugs are now approved in the US to treat relapsed/refractory CTCL including the oral retinoid, bexarotene, and histone deacetylase inhibitors, romidepsin and vorinostat. Although response rates are typically <35%, romidepsin and vorinostat can induce some durable responses in heavily pretreated patients and alleviate bothersome symptoms, such as pruritus. New studies indicate that the anti-CD30 antibody-drug conjugate brentuximab vedotin, anti-CCR4 antibody mogamulizumab, and fusion protein immunotoxin A-dmDT390-bisFv(UCHT1) may be particularly active in this setting. In this paper, we present an exhaustive review of the clinical data on current and possible future drug treatment options for relapsed/refractory CTCL.

1. Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are a rare group of non-Hodgkin lymphomas (NHLs) derived from malignant transformation of mature skin-homing/resident T cells (Guenova et al., 2014). They represent a disparate group of lymphoid T-cell

* Corresponding author. Fax: +39 516364037.
E-mail address: pierluigi.zinzani@unibo.it (P.L. Zinzani).
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malignancies with heterogeneous clinical, immunologic, histologic, cytogenetic, and molecular characteristics. CTCLs are less common than peripheral T-cell lymphomas (PTCLs) and only account for about 4% of all NHLs (Criscione and Weinstock, 2007). The annual age-adjusted incidence of CTCLs in the United States is about 6–10 per million persons (Criscione and Weinstock, 2007; Imam et al., 2013; Korgavkar et al., 2013). While the incidence of CTCLs has remained stable since 1998 in the United States, it is increasing in some Asian countries, such as Japan (Korgavkar et al., 2013; Chihara et al., 2014); this is believed to be due to the adoption of a more westernized lifestyle (Chihara et al., 2014). CTCLs are approximately twice as common in men than in women, with black men particularly affected (Criscione and Weinstock, 2007; Imam et al., 2013; Bradford et al., 2009; Wilson et al., 2012). Usually diagnosed in patients aged 50–70 years, the prevalence of CTCL (all subtypes and stages combined) peaks between the ages of 70 and 84 years (Criscione and Weinstock, 2007; Korgavkar et al., 2013; van Doorn et al., 2000; Kim et al., 2003).

The most common CTCL subtype is mycosis fungoides (MF) (Criscione and Weinstock, 2007), which together with its more aggressive leukemic and erythrodermic variant, Sézary syndrome (SS), accounts for about 65% of all CTCLs (Guenova et al., 2014; Trautinger et al., 2006). Other CTCL subtypes include primary cutaneous CD30+ TCL (primary cutaneous ALCL [pcALCL] and lymphomatoid papulosis [LyP], which represent at least 25% of all CTCLs (Willemze et al., 2005)) and rarer entities, such as primary cutaneous gamma/delta type TCL, primary cutaneous CD8+ aggressive epidermotropic TCL, and primary cutaneous CD4+ small/medium TCL (Fig. 1). The aggressiveness of CTCL depends on the diagnosis: MF, primary cutaneous CD30+ TCL (pcALCL/LyP), and primary cutaneous CD4+ small/medium TCL tend to run a rather indolent course, whereas SS and other rare primary cutaneous TCL entities are often associated with rapid progression and low survival rates (Swerdlow et al., 2008; Li et al., 2012). Five-year survival rates vary from 25 to 40% in SS to 73–100% in MF or primary cutaneous CD30+ TCL (MF 88–91%, LyP 73–100%, and pcALCL 95–96%) (Bradford et al., 2009; Willemze et al., 2005; Bekkenk et al., 2000).

CTCLs are generally treated using a multimodal approach, although there is no single common management plan (especially for the rarer variants) due to the diversity of diagnoses and clinical presentations. Frontline treatment for limited disease is usually directed at the lesion, and involves using a combination of surgery, radio- and phototherapy, and specific skin-directed treatments (topical corticosteroids, chemotherapies, retinoids, or imiquimod) (National Cancer Institute, 2015; Akilov and Geskin, 2011). Systemic therapies and autologous or allogeneic stem cell transplantation tend to be reserved as options for more generalized or advanced disease (e.g., for patients with folliculotropic or large-cell transformation, or blood/organ involvement) (National Cancer Institute, 2015; Akilov and Geskin, 2011). The most indolent variants of CTCL, including pcALCL, LyP, and primary cutaneous CD4+ small/medium TCL, which are associated with excellent prognoses, often require less aggressive treatment, although treatment is not curative (National Cancer Institute, 2015; James et al., 2015; Kempf et al., 2011). Localized or solitary pcALCL, for instance, can be treated with surgical excision and/or radiotherapy if spontaneous remission does not occur, with systemic therapies reserved for the small minority of patients with multifocal lesions/extracutaneous dissemination (National Cancer Institute, 2015; Kempf et al., 2011). Primary cutaneous CD4+ small/medium TCL is often treated in a similar manner despite the lack of a standardized treatment approach (James et al., 2015). For LyP, which is characterized by chronic, recurrent, spontaneously regressing, papulonodular skin lesions, observation alone (in asymptomatic patients with few lesions and minimal scarring), topical treatments, or phototherapy may be sufficient for most patients (National Cancer Institute, 2015; Kempf et al., 2011). Regrettably, however, many patients with CTCL who receive frontline therapy, particularly those with the more aggressive subtypes, will relapse and/or develop treatment-refractory disease (Dreyling et al., 2013).

Until recently, treatment for relapsed/refractory CTCL had been very challenging due to the limited options available; however, the introduction of new treatments is beginning to have a positive impact on clinical outcomes. In this article, we present an exhaustive review of the clinical data on current and possible future drug treatment options for relapsed/refractory CTCL, looking at both approved and investigational agents and regimens.

2. Review methodology

A literature search was conducted to identify studies reporting clinical outcomes following drug therapy in patients with relapsed and/or refractory CTCL (defined according to the 2008 World Health Organization classification) (Fig. 1) (Swerdlow et al., 2008). MEDLINE (PubMed) was searched for studies published up to February 6, 2015, and reference lists of recent reviews and meta-analyses (2011–14) were investigated manually. Congress abstracts from the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society for Medical Oncology (ESMO), and European Hematology Association (EHA) annual meetings (2013–14) were also evaluated. Search terms included 'cutaneous T-cell lymphoma', 'mycosis fungoides', 'Sézary syndrome', 'primary cutaneous CD30-positive T-cell lymphoma', 'primary cutaneous anaplastic large cell lymphoma', and 'lymphomatoid papulosis'. Results were screened by title and abstract to identify clinical studies of pharmacologic therapies in relapsed and/or refractory CTCLs. Prospective trials were selected as the primary data sources; studies of previously untreated patients were excluded. After identifying relevant publications, data were collected on study type, patients, diagnosis, treatment history, and efficacy.

3. Treatment of relapsed/refractory CTCL

Treatments for relapsed/refractory CTCLs generally consist of additional or alternative skin-directed therapies with or without systemic biologic agents or chemotherapy (National Cancer Institute, 2015; Willemze et al., 2013). Phototherapy, local radiotherapy, total skin electron beam therapy, and extracorporeal photopheresis are also sometimes used as adjunct options as part of a multimodal treatment approach (National Cancer Institute, 2015). For the more indolent CTCLs, options for relapsed/refractory disease are similar to frontline treatment (e.g., methotrexate, chemotherapy, and radiotherapy) with participation in a clinical trial as an additional option (Bekkenk et al., 2000; National Cancer Institute, 2015; Kempf et al., 2011). The aim of treatment in relapsed/refractory CTCL is to safely induce prolonged remission without compromising a patient's immunity or adversely affecting their quality of life (Akilov and Geskin, 2011). As stated in Section 2 (Review Methodology), the following review focuses only on systemic drug therapies that have been investigated specifically in relapsed/refractory CTCL, with an emphasis on novel therapies. It is beyond the scope of this paper to discuss other treatment approaches in CTCL.

As most recent trials in relapsed/refractory CTCL have recruited patients with MF or SS, the term 'CTCL' is often used synonymously with these two conditions in many published articles. It is also important to note that cross-trial comparisons are problematic in this setting because of differences in: (1) the tools used to measure objective responses, which may not always consider nodal, blood, and visceral involvement, in addition to the ubiquitous assessment of cutaneous manifestations; (2) the criteria used

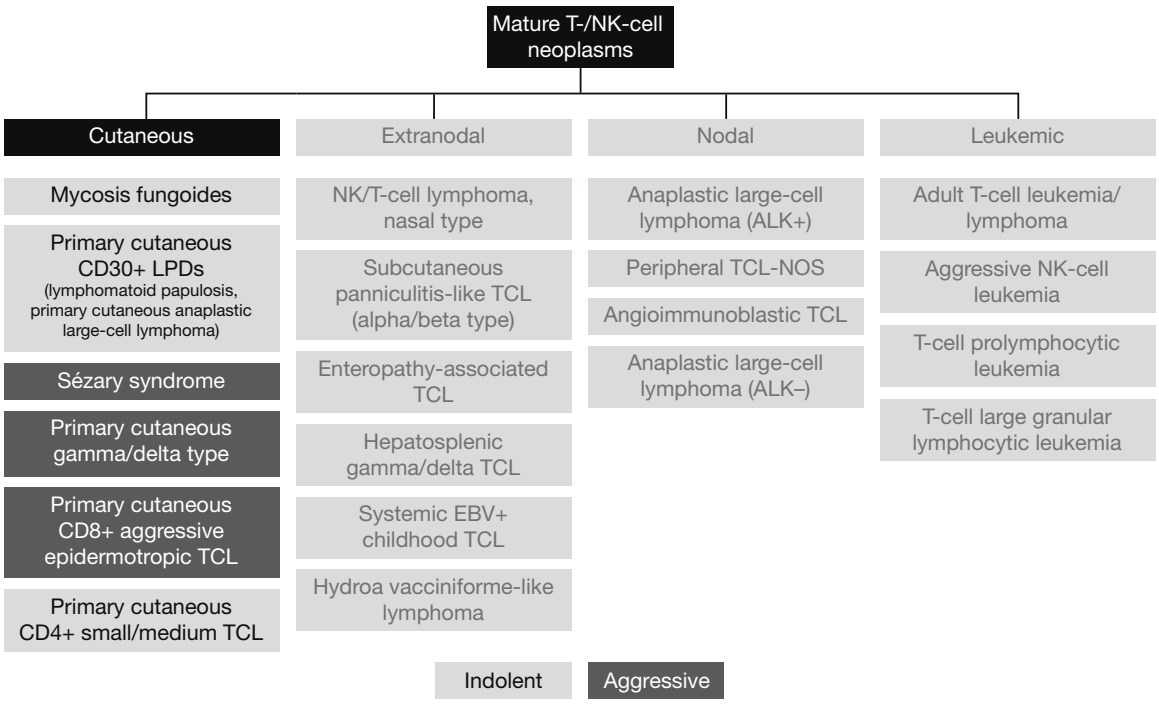

Fig. 1. World Health Organization 2008 classification of mature T-cell lymphomas: cutaneous T-cell lymphomas (Swerdlow et al., 2008) +, positive; –, negative; ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorders; TCL, T-cell lymphoma; NK, natural killer; NOS, not otherwise specified.

to diagnose and classify patients; and (3) definitions of clinical endpoints and follow-up times. All of these factors, in addition to the expected variations in study populations, need to be considered when comparing trial results.

3.1. Conventional therapies in relapsed/refractory CTCL

A number of systemic chemotherapies have traditionally been used to treat patients with relapsed/refractory CTCL. As in PTCL, the evidence for using such therapies is largely derived from retrospective cohort studies and case series, and only a small minority of patients achieve durable responses.

In general, chemotherapy in relapsed/refractory CTCL is administered as monotherapy (National Cancer Institute, 2015), as multi-agent treatment can result in increased immunosuppression (resulting in an increased risk of serious infection) and poor tolerance (Akilov and Geskin, 2011). Examples of single-agent chemotherapies that are used in relapsed/refractory CTCL include gemcitabine, pentostatin, temozolomide, methotrexate, fludarabine, etoposide, cyclophosphamide, and chlorambucil (National Cancer Institute, 2015; Quereux et al., 2008). Of these therapies, gemcitabine, temozolomide, and pentostatin have been investigated in prospective clinical trials (Duvic et al., 2006a; Tani et al., 2005; Querfeld et al., 2011; Cummings et al., 1991; Monfardini et al., 1996; Kurzrock et al., 1999; Ho et al., 2000; Tsimberidou et al., 2004), as well as in observational studies (Zinzani et al., 2000; Zinzani et al., 2010; Pellegrini et al., 2014; Jidar et al., 2009; Mercieca et al., 1994; Greiner et al., 1997; Foss, 2000; Dearden et al., 2000). As shown in Table 1, these three cytotoxic agents can induce clinical responses in a substantial proportion of patients. Gemcitabine appears to be one of the most effective single-agent chemotherapies with overall response rates (ORRs) of 48–68%, complete response (CR) rates of 9–20%, and reports of some prolonged responses (albeit uncommon) (Duvic et al., 2006a; Zinzani et al., 2000; Zinzani et al., 2010; Pellegrini et al., 2014; Jidar et al., 2009). The purine analog, pentostatin is also active (ORR 14–71%, CR rate 0–25%), and there is a suggestion that this agent may achieve particularly high response rates (up to 71%) in patients with SS (Cummings et al., 1991; Monfardini et al., 1996; Kurzrock et al., 1999; Ho et al., 2000; Tsimberidou et al., 2004; Mercieca et al., 1994; Greiner et al., 1997). Although prospective studies are lacking, methotrexate appears to be similarly active in previously treated CTCL (Zackheim et al., 1996; Zackheim et al., 2003).

More recently, pegylated liposomal doxorubicin (PLD) – a formulation of doxorubicin in polyethylene glycol-coated liposomes that has a prolonged circulation time, higher target specificity, and improved safety profile compared with the parent drug (Gabizon, 2001) – has achieved impressive response rates (ORR 41–84%) in relapsed/refractory CTCL patients, including those with advanced MF or SS (Quereux et al., 2008; Wollina et al., 2003; Pulini et al., 2007; Dummer et al., 2012; Straus et al., 2014). These results imply that PLD is at least as active as other single-agent chemotherapies in this setting. Treatment with PLD also appears to be generally well tolerated, with a low rate of grade 3/4 adverse events (AEs) (Quereux et al., 2008; Dummer et al., 2012; Wollina et al., 2000). Toxicities associated with PLD reflect those seen with doxorubicin (albeit at a lower severity), and include asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand-foot syndrome, rash, neutropenia, thrombocytopenia, and anemia (DOXIL®, 2015).

Interferons (α and γ) also still have a role in the treatment of relapsed/refractory CTCL (National Cancer Institute, 2015), but as they have been used for many decades, it is beyond the scope of this paper to report the clinical data on these agents. The effectiveness and safety of interferons in CTCL is reviewed in detailed by Olsen (Olsen, 2003).

3.2. Approved therapies in relapsed/refractory CTCL

Over the past 15 years, novel targeted agents have been introduced into therapy for relapsed/refractory CTCL. Four of these agents are currently approved for use in the United States for the treatment of relapsed/refractory CTCL (Table 1). The first of these drugs is bexarotene, an orally administered retinoid that

Table 1
Summary of prospective clinical trials for approved (bexarotene, denileukin diftitox, romidepsin, and vorinostat) and investigational/off-label agents and regimens in relapsed/refractory cutaneous T-cell lymphoma.

Agent/regimen and reference	Phase	N	CTCL diagnoses	Median prior treatments (range)	ORR (%)[a]	CR/CCR rate (%)[a]	Median DoR, months (range/95% CI)	Median PFS, months	Median OS, months	Pruritus improvement
Bexarotene										
Duvic et al. (2001a)	2/3	94	CTCL *n* = 94	5 (1–11) Sys: 2 (1–6)	45–55	2–13	9.8–12.7[b]	NR	NR	Y
Duvic et al. (2001b)	2/3	58	CTCL *n* = 58	3 (2–8)	54–67	7–27	NR–14.9	6.9–16.9[c]	NR	Y
Bexarotene + denileukin diftitox										
Foss et al. (2005)	1	12	CTCL *n* = 14	NR (1–12)	67	33	NR	NR	NR	NR
Bexarotene + gemcitabine										
Illdge et al. (2013)	2	36	CTCL *n* = 35 Erythro *n* = 17	NR	31 Erythro: 18 non-Erythro: 42	0	NR	5.3 Erythro: 5.3 non-Erythro: 4.6	21.2	Y
Bexarotene + IFNα										
Straus et al. (2007)	2	18	CTCL *n* = 18	NR	39[d]	6[d]	2.7 (1.1–7.6)[d]	NR	NR	NR
Bexarotene + pralatrexate										
Talpur et al. (2014)	1/2	14	MF *n* = 14	NR	50	0	NR	NR	NR	NR
Denileukin diftitox										
LeMaistre et al. (1998)	1	35	CTCL *n* = 35	3 (0–15)	37	14	10 (2.4–39+)[e]	NR	NR	NR
Saleh et al. (1998)	1	35	IL-2R+: MF *n* = 30 pcALCL *n* = 4 Other CTCL *n* = 1	3 (0–6)[d]	37[d]	14[d]	NR	NR	NR	Y
Olsen et al. (2001)	3	71	MF or SS *n* = 71	5 (1–12)	30	10	6.9 (2.7–46.1+)	NR	NR	Y
Prince et al. (2010)	3	144	All CD25+: MF *n* = 123 SS n = 9 Other *n* = 12	NR (0–3+)	44[f] (central)	10[f]	7.8+	26.1+	NR	Y
Prince et al. (2013)	4	36	ALL CD25–: MF or SS n = 36	NR	31 (central)	8	11.2 (4.6, not reached)	16.0+	NR	Y
Duvic et al. (2013a)[g]	3	20	MF *n* = 20	NR	40	10	9.0	6.7	NR	Y
Duvic et al. (2013b) *Pooled phase 3*	3	263	CTCL *n* = 263	NR	38 9 μg/kg: 3118 μg/kg: 47 Retreated: 28 CD25–: 31	9	9.1 (1.4–43.5) 9 μg/kg: 9.1 18 μg/kg: 8.8 Retreated: 9.0 CD25–: 11.2	NR	NR	NR
Talpur and Duvic (2012)	Pilot	8	CD30+ cALCL = 5 Other pcPTCL *n* = 3	NR (1–2)	62.5	25	2.8 (1.8–95.7)	NR	NR	NR
Romidepsin										
Piekarz et al. (2009)	2	71	MF or SS *n* = 71	4 (0–14)	34	7	13.7	NR responders: 15.1[c]	NR	NR
Whittaker et al. (2010) and Duvic et al. (2014a)	2	96	CTCL *n* = 96	4 (1–11) Sys: 3 (1–8)	34 Prior CT: 34	6 Prior CT: 8	15.0 (0+–19.8+) prior CT: 15	8[c]	NR	Y
Vorinostat										
Olsen et al. (2007)	2b	74	MF *n* = 44 SS *n* = 30	Sys: 3 (1–12)	30 SS: 33	1	≥6.1 (1.1 + –14.5 +)	≥4.9[c]	NR	Y
Duvic et al. (2007)	2	33	MF *n* = 22 SS *n* = 11	Sys: 5 (1–15)	24 SS: 36	0	3.5 (2.2–4.5)	2.8[c]	NR	Y
Wada et al. (2012)	1	6	MF *n* = 6	Sys: 2.5 (1–5)	0	0	NR	NR	NR	Y
Alemtuzumab										
Kennedy et al. (2003)	2	8	MF *n* = 5 SS *n* = 2 tMF *n* = 1	NR (1–17)	38	0	NR (1.8–3.2)	2.2[c]	4	Y

Table 1 (*Continued*)

Agent/regimen and reference	Phase	N	CTCL diagnoses	Median prior treatments (range)	ORR (%)[a]	CR/CCR rate (%)[a]	Median DoR, months (range/95% CI)	Median PFS, months	Median OS, months	Pruritus improvement
Lundin et al. (2003)	2	22	CD52+ MF or SS *n* = 22	3 (1–5)	55	32	NR	NR	NR	Y
Zinzani et al. (2005)	2	4	MF *n* = 4	3 (2–4)[h]	75	0	7 (2–10)[h]	NR	NR	NR
Bernengo et al. (2007)	NR	11	SS *n* = 11		86[i]	21[i]	Not reached	NR	35[i]	Y
Querfeld et al. (2009)	2	19	Erythro MF *n* = 2 SS *n* = 17	5 (2–10) Sys: 3 (1–7) Skin: 1 (1–5)	84	47	6 (2–39+)	6	41	NR
Belinostat										
Foss et al. (2015)	2	29	MF *n* = 17 SS *n* = 7 pcALCL *n* = 2 other CTCL *n* = 2 SPTCL *n* = 1	NR (1–12) Sys: 4 (1–9) Skin: 1 (0–4)	14	10	2.7 (1.8, 4.2)	1.4[c]	NR	Y
Bortezomib										
Zinzani et al. (2007)	2	12	MF *n* = 10 pcPTCL *n* = 2	NR (2–5)	67 MF: 70	17 MF: 10	NR	NR	NR	NR
Brentuximab vedotin										
Duvic et al. (2015a)	2	48	CD30+: MF *n* = 28 LyP *n* = 9 pcALCL *n* = 2 LyP/MF *n* = 7 pcALCL/LyP/MF *n* = 2	5 (1–13)	73 MF: 54 LyP: 100 pcALCL: 100 LyP/MF: 100 pcALCL/LyP/MF: 100	35 MF: 7 LyP: 56 pcALCL: 100 LyP/MF: 86 pcALCL/LyP/MF: 100	NR MF: 7.4 (0.7–21.5) LyP/pcALCL: 6.0 (1.4–10.2)	13.2	Not reached	NR
Kim et al. (2015)	2	32	CD30, 0–100% (median 13%): MF stage IB/IIB *n* = 22 MF stage IV/SS *n* = 10	3 (1–13)	70 MF stage IB/IIB: 77 MF stage IV/SS: 50 CD30 <10%: 54 CD30 10–50%: 79 CD30 >50%: 100	3	NR (1-yr: 79%)	NR (1-yr: 54%)	NR	NR
Duvelisib (IPI-145)										
Horwitz et al. (2014)	1	17	CTCL *n* = 17	4 (1–11)[j]	38	0	NR	NR	Not reached	NR
E7777										
Duvic et al. (2014b)	3	17	MF *n* = 13 SS *n* = 4	NR (≥4: 82%)	29	6	NR	NR	NR	NR
Forodesine										
Duvic et al. (2006b)	1/2	37	CTCL *n* = 37	NR	54	7	NR	NR	NR	NR
Duvic et al. (2009a)	NR	64	CTCL *n* = 64	NR	27	NR	NR	NR	NR	NR
Dummer et al. (2014)	2	144	MF *n* = 125 SS *n* = 19	4 (3–15)	11	0	6.3	6.3[c]	NR	NR
Gemcitabine										
Duvic et al. (2006a)	2	33	CD30+ cALCL *n* = 2 MF or SS *n* = 31	5 (1–13)	64 MF: 54 SS: 73	9	NR	NR	20.4 (3 yr: 24%)	NR
Lenalidomide										
Querfeld et al. (2014)	2	32	MF *n* = 18 Erythro MF *n* = 3 SS *n* = 11	6 (1–14) Sys: 4 (0–12) Skin: 2 (0–6)	28 Erythro MF/SS: 38	0	10 (1.1, 11.0)	8	43 (1 yr: 83%, 2 yr: 62%, 5 yr: 48%)	NR
Mogamulizumab										
Ogura et al. (2014)	2	8	CCR4+: MF *n* = 7 cALCL *n* = 1	3 (1–6)	38 MF: 29 cALCL: 100	0	NR	NR	NR	NR
Duvic et al. (2015b)	1/2	41	MF *n* = 22 SS *n* = 19	Sys: 3 (1–17)	37 MF: 47 SS: 29	8 MF: 5 SS: 12	10.4 (IQR 6.9–33.2)	11.4	NR	NR

Table 1 (*Continued*)

Agent/regimen and reference	Phase	N	CTCL diagnoses	Median prior treatments (range)	ORR (%)[a]	CR/CCR rate (%)[a]	Median DoR, months (range/95% CI)	Median PFS, months	Median OS, months	Pruritus improvement
Panobinostat										
Ellis et al. (2008)	1	10	MF *n* = 7 SS n = 3	NR	60	20	NR	5.9[c]	NR	NR
Duvic et al. (2013c)	2	139	MF *n* = 105 SS *n* = 33 Other n = 1	4 (1–15)	17 Bexarotene exp: 15 Bexarotene naïve: 20	2 Bexarotene exp: 1 Bexarotene naïve: 1	Bexarotene exp: 5.6 Bexarotene naïve: not reached	Bexarotene exp: 4.2 Bexarotene naïve: 3.7	NR	Y
Pentostatin										
Cummings et al. (1991)	2	8	CTCL *n* = 8	NR	50	NR	NR	NR	NR	NR
Monfardini et al. (1996)	2	7	MF *n* = 5 SS *n* = 1 other *n* = 1	NR	14	0	NR	NR	NR	NR
Kurzrock et al. (1999)	NR	24	*SS n* = 14 MF *n* = 6 tMF *n* = 1 pcPTCL *n* = 3	3 (1–12)	71 SS: 71 MF: 66 pcPTCL: 100	25	NR MF: 2 (1–2) SS: 3.5	NR	NR	NR
Ho et al. (2000)	2	43	MF *n* = 22 SS *n* = 21	NR	SS: 33 MF: 23	SS: 5 MF: 0	NR	NR	SS: 8 MF: 12.5	NR
Tsimberidou et al. (2004)	2	32	MF or SS *n* = 32	2 (1–12)[k]	56	13	NR	NR	418[k](2 year: 42%)[k]	NR
PLD										
Wollina et al. (2003)	Pilot	10	MF *n* = 6	NR	83	67	NR	NR	NR	NR
Quereux et al. (2008)	NR	25	MF *n* = 15 SS *n* = 10	NR (1–6)	56 SS: 60	20 SS: 10	NR	NR responders: 5	43.7	NR
Pulini et al. (2007)	2	19	MF *n* = 10 tMF *n* = 3 SS *n* = 3 pcPTCL *n* = 3	NR (1–5)	84	42	NR	19 (46 mo: 37%)	34 (46 mo: 44%)	NR
Dummer et al. (2012)	2	49	MF *n* = 49	NR	41	6	6 (5.0, 10.4)	7.4[c]	NR	NR
Straus et al. (2014)	2	34	MF *n* = 27 SS *n* = 8 Other n = 2	2 (1–11)	41 SS: 50	6	NR	NR	NR	Y
Pralatrexate										
Horwitz et al. (2012)	1/2	54	MF *n* = 38 SS *n* = 15 pcALCL *n* = 1	6.5 (1–25) Sys: 4 (1–11)	41 At OD: 45 MF: 47 SS: 20	6 At OD: 3 MF: 3 SS: 7	At OD: not reached (0.03–12.2)	At OD: not reached	NR	NR
Resimmune										
Frankel et al. (2013)	1	17	CTCL *n* = 17	NR (0–4)[l]	35[l]	24[l]	NR	NR	NR	NR
Temozolomide										
Tani et al. (2005)	2	9	MF *n* = 9	3 (2–5)	33	11	NR	NR	NR	NR
Querfeld et al. (2011)	2	26	MF or SS *n* = 26	NR	27	8	NR	4	24 (1 yr: 86%, 2 yr: 50%, 5 yr: 25%)	NR

[a] Responses were measured using various assessment criteria.
[b] Median time to relapse.
[c] Time to progression.
[d] Includes data on 1 treatment-naïve patient.
[e] Data presented for CTCL (*n* = 13) and NHL (*n* = 3) patients.
[f] Includes data on 20 treatment-naïve patients.
[g] All patients had relapsed after responding to denileukin diftitox.
[h] Data presented for 10 patients: 4 with MF and 6 with PTCL.
[i] Data presented for 14 SS patients: 11 relapsed/refractory and 3 newly diagnosed.
[j] Data presented for 33 patients: 17 with CTCL and 16 with PTCL.
[k] Data presented for 42 patients: 32 with MF/SS and 10 with PTCL.
[l] Includes data on 2 previously untreated patients. CCR, clinical complete response; central, central response review; CT, chemotherapy; CTCL, cutaneous T-cell lymphoma; CR, complete response; DoR, duration of response; Erythro, erythrodermic; IFN, interferon; IQR, inter-quartile range; LyP, lymphomatoid papilosis; MF, mycosis fungoides; NOS, not otherwise specified; NR, not reported; OD, optimal dose; ORR, overall response rate; OS, overall survival; pcALCL, primary cutaneous anaplastic large cell lymphoma; pcPTCL, primary cutaneous peripheral T-cell lymphoma; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PTCL, peripheral T-cell lymphoma; PUVA, psoralen plus ultraviolet A; SPTCL, subcutaneous, panniculitis-like T-cell lymphoma; SS, Sézary syndrome; Sys, systemic treatments; TCL, T-cell lymphoma; tMF, transformed MF; Y, yes.

selectively activates retinoid × receptors, which then act as transcription factors to regulate the expression of genes that control cellular proliferation and differentiation (Targretin®, 2015). In the United States, bexarotene is approved for the treatment of cutaneous manifestations of CTCL in patients who are refractory to at least one prior systemic therapy (Targretin®, 2015). The second approved agent is romidepsin, an intravenously (IV) administered, epigenetic-modifying, class 1 histone deacetylase (HDAC) inhibitor that alters gene transcription by catalyzing the removal of acetyl groups from lysine residues in histones (Akilov and Geskin, 2011; Khot et al., 2013; ISTODAX®, 2014). HDAC treatment also leads to de-acetylation of non-histone proteins, such as transcription factors (ISTODAX®, 2014). Romidepsin is indicated for the treatment of CTCL in patients who have received at least one prior systemic therapy (ISTODAX®, 2014). Another HDAC inhibitor, vorinostat, is also approved for use in previously treated CTCL. Vorinostat is an orally bioavailable, pan-HDAC inhibitor licensed to treat cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies (ZOLINZA®, 2013). The final approved therapy is the CD25-directed, IV interleukin-2 (IL-2)—diphtheria toxin fusion protein, denileukin diftitox, which is approved to treat patients with persistent or recurrent CTCL whose malignant cells express the CD25 component of the IL-2 receptor (ONTAK®, 2011). Of these agents, only bexarotene is approved by the European Medicines Agency to treat skin manifestations of advanced stage CTCL in adult patients refractory to at least one systemic treatment (Targretin®, 2014).

Oral bexarotene was shown to be effective in refractory/persistent CTCL in two phase 2/3 trials, both published in 2001, which enrolled patients (diagnoses not specified) with early-stage ($N = 58$) and advanced ($N = 94$) CTCL, respectively (Duvic et al., 2001a; Duvic et al., 2001b). Forty-five percent of patients with advanced CTCL who received the currently recommended starting dose of 300 mg/m^2/day (Targretin®, 2015) achieved an objective response (median duration 9.8 months; clinical CR rate 2%); this compared with an ORR of 55% (median duration 12.6 months; clinical CR rate 13%) in patients who received doses >300 mg/m^2/day (Duvic et al., 2001a). These responses were accompanied by improvements in skin appearance, pruritus, and quality of life. In early-stage patients, ORRs at bexarotene doses of 300 and >300 mg/m^2/day were 54% (clinical CR rate 7%; median time to progression [TTP] 6.9 months) and 67% (clinical CR rate 27%; median TTP 16.9 months), respectively (Duvic et al., 2001b). As these responses are higher than in advanced disease, it appears that bexarotene may be more active if given earlier on in the disease course, a premise that is supported by observational data (Sokolowska-Wojdylo et al., 2014; Väkevä et al., 2012). Significant side effects reported during bexarotene therapy include hypothyroidism, altered lipid metabolism, and glucose and liver enzyme abnormalities (Scarisbrick et al., 2013); in the main, these AEs can be managed with careful monitoring and supportive treatments. Other common bexarotene-associated toxicities include headache, asthenia, skin rash, leukopenia, anemia, nausea/vomiting, infection, peripheral edema, abdominal/back pain, diarrhea, pruritus, and dry skin (Targretin®, 2015; Sokołowska-Wojdyło et al., 2013).

New data reporting on long-term experience with single-agent bexarotene suggests that durable responses are possible in pretreated CTCL patients (lasting for a median duration of 8–21 months depending on the disease stage) providing that side effects are managed proactively (Sokolowska-Wojdylo et al., 2014; Väkevä et al., 2012; Abbott et al., 2009). Bexarotene has also recently demonstrated anti-lymphoma activity in rarer variants of CTCL, as well as the more common diagnoses, in a large retrospective cohort study of 200 patients with CTCL and ≥1 prior treatment failure (Weichenthal et al., 2013). ORRs in the different CTCL subtypes were as follows: MF 37%, CD30+ pcALCL 50%, LyP 60%, SS 33%, and other rare CTCL forms 33%. Overall, these data indicate that oral bexarotene should be considered as a key option for all subtypes of relapsed/refractory CTCL, including rare variants. Interestingly, combining or sequencing bexarotene with other treatments, such as denileukin diftitox, gemcitabine, interferon-α2b, or pralatrexate, in relapsed/refractory CTCL appears to offer no major advantage, in terms of response, over monotherapy with either agent (although controlled trials are not available) (Foss et al., 2005; Illidge et al., 2013; Straus et al., 2007; Talpur et al., 2014); the reasons for this are not clear. Though not indicated, other oral retinoids (tretinoin [all-trans-retinoic acid], isotretinoin, acitretin, and alitretinoin) are also sometimes used to treat CTCL (National Cancer Institute, 2015; Sokołowska-Wojdyło et al., 2013). These agents appear to have some clinical activity, but evidence supporting their use is patchy and prospective clinical trials are lacking (Sokołowska-Wojdyło et al., 2013; Kapser et al., 2015; Cheeley et al., 2013).

The approval of romidepsin in CTCL was based on the results of two single-arm phase 2 trials, involving a total of 167 patients with refractory CTCL, mainly MF or SS (Piekarz et al., 2009; Whittaker et al., 2010). Across the two studies, both of which included highly pretreated patients, romidepsin was associated with ORRs of 34% (in both studies; measured using stringent response criteria) and CR rates of 6–7%; median duration of response was 14–15 months, with some patients maintaining their response for >3 years. In the larger of the two trials, romidepsin was associated with an anti-pruritic effect, in which 43% of evaluable patients achieved a clinically meaningful improvement in pruritus, including those who did not achieve an objective response (Whittaker et al., 2010). As also shown in PTCL (Khot et al., 2013; ISTODAX®, 2014), the most frequently reported side effects with romidepsin are infections, fatigue/asthenia, nausea, vomiting, and transient thrombocytopenia, neutropenia, and anemia (Foss et al., 2014); most of these AEs tend to be of mild or moderate intensity. Infection represents the most common serious AE and the most frequent cause of hospitalization (Foss et al., 2014).

The oral HDAC inhibitor, vorinostat, was associated with ORRs of 24–30% in patients with refractory MF or SS who were treated in two key phase 2 trials ($N = 33$ and 74, respectively) (Olsen et al., 2007; Duvic et al., 2007). CRs were rare (only one patient had a CR) and median TTP was <6 months in both studies, an observation that may be explained, at least in part, by the fact that many patients had advanced disease and had received multiple lines of prior therapy (Olsen et al., 2007; Duvic et al., 2007). More recent data suggest that vorinostat can induce durable responses lasting for ≥2 years in some patients (Duvic et al., 2009b; Kogge et al., 2015). AEs associated with vorinostat tend to be mild to moderate in intensity, and treatment is usually well tolerated (Olsen et al., 2007; Duvic et al., 2007). The most common drug-related AEs reported in the largest of the two phase 2 trials were diarrhea, fatigue, nausea, anorexia, dysgeusia, and thrombocytopenia (Olsen et al., 2007). Grade ≥3 AEs were uncommon (≤5% incidence), although there was an increased risk of thromboembolism (Olsen et al., 2007), which necessitates monitoring during treatment (ZOLINZA®, 2013). While results are not remarkable, the vorinostat and romidepsin data both support HDAC inhibition as an important therapeutic strategy in CTCL, not only for lymphoma control but also to alleviate bothersome symptoms, such as pruritus, without increasing morbidity through toxicity (Olsen et al., 2007; Duvic et al., 2007). Current combination trials have been disappointing, but it is still likely that increased benefit will be achieved through combining HDAC inhibitors with other interventions or treatment modalities.

A large number of clinical trials have explored the utility of denileukin diftitox for the treatment of CD25+ relapsed/refractory CTCL (LeMaistre et al., 1998; Saleh et al., 1998; Olsen et al., 2001; Prince et al., 2010; Prince et al., 2013; Duvic et al., 2013a; Duvic et al., 2013b). In a recently published pooled analysis of data from three

phase 3 studies ($N = 263$), the ORR with denileukin diftitox was 38% (CR rate 9%) and median duration of response was 9.1 months, with some CTCL patients maintaining a response for >3.5 years (Duvic et al., 2013b). Patients who have been retreated following prior exposure to denileukin diftitox also appear to benefit, and can achieve similar response rates (28–40%) to those obtained on first use (Duvic et al., 2013a; Duvic et al., 2013b). In addition, denileukin diftitox treatment is associated with improvements in patient quality of life, skin appearance, and pruritus severity (Duvic et al., 2002), and there is emerging evidence that even patients with CD25−CTCL may derive some benefit from treatment (Duvic et al., 2013b). Across the three phase 3 trials, the most common AEs associated with denileukin diftitox were nausea, pyrexia, fatigue, capillary leak syndrome, and rigors (Duvic et al., 2013b). Unfortunately, because denileukin diftitox is linked with a number of serious side effects, including capillary leak syndrome, infusion reactions, and loss of visual acuity (ONTAK, 2011), production of the current formulation was discontinued by the manufacturer in January 2014. A phase 3 trial of E7777 – a formulation of denileukin diftitox with improved purity and a higher percentage of active protein monomer species – is, however, now ongoing in patients with persistent/recurrent CD25+ CTCL (MF or SS) (NCT01871727) (Duvic et al., 2014b). For this trial to be successful, efficacy will have to be maintained with a much reduced risk of serious adverse reactions. Early results from the dose-finding, lead-in phase for this study indicate that the toxicity profile of E7777 is acceptable and, to date, no new safety signals relative to the parent compound have been identified (although two patients have developed capillary leak syndrome) (Duvic et al., 2014b). Five of the 17 patients (13 with MF and 4 with SS) treated so far have achieved an objective response and dose-finding is continuing.

3.3. *Investigational and off-label therapies in relapsed/refractory CTCL*

As in PTCL, various novel therapeutic agents and regimens are currently under investigation in relapsed/refractory CTCL (usually MF or SS). These treatments include novel chemotherapies (pralatrexate and forodesine), immunomodulatory drugs (lenalidomide), next-generation HDAC inhibitors (belinostat and panobinostat), other targeted agents (bortezomib and duvelisib), and biologics (brentuximab vedotin, alemtuzumab, mogamulizumab, and A-dmDT390-bisFv(UCHT1)). Available data on the efficacy of these experimental drugs are presented in Table 1.

Novel chemotherapeutic agents that are in clinical trials in previously treated CTCL include pralatrexate (a potent IV antifolate, 10-deazaaminopterin analog of methotrexate, currently indicated in relapsed or refractory PTCL, which acts to disrupt DNA/RNA synthesis through inhibition of dihydrofolate reductase and thymidylate synthase (Wang et al., 2003; Sirotnak et al., 1998; Shimanovsky and Dasanu, 2013; FOLOTYN®, 2012) and forodesine (a potent, transition-state, purine nucleoside phophorylase inhibitor that works to disrupt DNA synthesis through accumulation of plasma 2′-deoxyguanosine and intracellular dGuo triphosphate, and consequent inhibition of ribonucleotide reductase [Gandhi and Balakrishnan, 2007; Korycka et al., 2007]). Following demonstration of activity in PTCL (O'Connor et al., 2011), pralatrexate has exhibited favorable single-agent anti-lymphoma effects (ORR of 41% [45% at the recommended dose] and a CR rate of 6%, including some long-lasting responses) in a small phase 1/2 trial of patients with heavily pretreated, relapsed/refractory CTCL, mainly MF or SS (Horwitz et al., 2012). Tolerability was generally acceptable and severe AEs, with the exception of grade 3 oral mucositis (15%), were uncommon. As in PTCL (O'Connor et al., 2011), the most frequently reported AEs were mucositis, fatigue, nausea/vomiting, and skin toxicity (Horwitz et al., 2012). Hematologic toxicities were also observed.

Promising results (ORRs of 27–54%) were reported for forodesine in early studies in CTCL (Duvic et al., 2006b; Duvic et al., 2009a), but final results from a large multicenter, phase 2 trial suggest that forodesine may only have partial activity in relapsed or refractory MF or SS (ORR of 11% with no CRs, and a median TTP of 6.3 months) (Dummer et al., 2014). It should be noted, though, that some patients did achieve durable responses and, as all patients in this phase 2 study had failed ≥3 prior systemic therapies, it could be that forodesine may be more effective in less treatment-experienced patients. The study investigators also suggested that the patients had been under-dosed (Dummer et al., 2014). AEs reported with forodesine included peripheral edema, fatigue, insomnia, pruritus, diarrhea, headache, and nausea (Dummer et al., 2014). Of concern, some patients treated with forodesine developed serious infections leading to death (Dummer et al., 2014), and therefore close monitoring for infectious episodes will be required in any future investigations of this drug.

The oral thalidomide analog, lenalidomide – an immunomodulatory drug with antiangiogenic and antineoplastic properties that is currently used in multiple myeloma and mantle cell lymphoma (REVLIMID®, 2014; National Cancer Institute, 2016) – achieved an ORR of 28%, a median progression-free survival (PFS) of 8 months, and a median overall survival of 43 months when given as monotherapy to 32 patients with heavily pretreated, advanced MF or SS (Querfeld et al., 2014). However, high toxicity (e.g., anemia, fatigue/malaise, skin pain/burning, pruritus, diarrhea, infection, and lower leg edema) resulted in two-fifths of patients (41%) discontinuing the study (Querfeld et al., 2014). These results suggest that a lower dose of lenalidomide or schedule modification is likely to be required, along with supportive measures, if the drug is to be investigated further in refractory CTCL.

Based on experience with romidepsin and vorinostat, the hydroxamic acid-type IV pan-HDAC inhibitor, belinostat (O'Connor et al., 2011; BELEODAQ®, 2014), which is approved for the treatment of patients with relapsed or refractory PTCL (BELEODAQ®, 2014), and the oral pan-HDAC inhibitor, panobinostat, which is approved for use in previously treated multiple myeloma (National Cancer Institute, 2016), have both been investigated in phase 2 trials of patients with relapsed/refractory CTCL (predominantly MF or SS) (Foss et al., 2015; Duvic et al., 2013c). While belinostat and panobinostat have predictable and manageable safety profiles typical of HDAC inhibitors (predominantly mild or moderate gastrointestinal, constitutional, and hematologic [panobinostat only] AEs, and altered laboratory parameters), response rates have been modest (<20%) and CRs relatively rare (Foss et al., 2015; Duvic et al., 2013c). Nonetheless, some patients did achieve prolonged responses and the ORRs were not dissimilar to those seen with vorinostat (Olsen et al., 2007; Duvic et al., 2007); the observed lack of activity may simply reflect the extensive treatment histories of patients included in the trials. It would now be interesting to see how these two drugs compare with vorinostat and romidepsin but, at present, no studies are planned.

The first-generation 20S proteosome inhibitor, bortezomib, an IV drug indicated for use in multiple myeloma and pretreated mantle cell lymphoma (National Cancer Institute, 2015; National Cancer Institute, 2015), has been investigated in a small phase 2 trial of 12 assessable patients with relapsed/refractory CTCL, predominantly MF (Zinzani et al., 2007). Treatment with single-agent bortezomib was associated with an ORR of 67% and a CR rate of 17%, with all patients remaining in remission for 7–14+ months. Bortezomib was also generally well tolerated and no grade 4 toxicities were observed. In spite of these promising initial results, no further development of bortezomib specifically in CTCL has been reported, although the combination of bortezomib and romidepsin is under

investigation in a phase 1 trial of patients with various forms of relapsed/refractory NHL, including one patient with CTCL (Holkova et al., 2014). In this trial, the single CTCL patient achieved a best response of stable disease to bortezomib/romidepsin.

Another drug to be investigated in relapsed/refractory CTCL is the anti-CD30 antibody-drug conjugate, brentuximab vedotin, which comprises an anti-CD30 antibody (cAC10) linked to the potent microtubule-disrupting agent, monomethyl auristatin E (MMAE) (Chen et al., 2013). Brentuximab vedotin targets CD30+ malignant T cells by binding to CD30, becoming internalized, and then releasing MMAE to provoke cell cycle arrest and programmed cell death (Chen et al., 2013). Brentuximab vedotin has shown high activity (ORR of 73%, CR rate of 35%, and median PFS of 1.1 year) in a phase 2 trial of 48 patients with CD30+ relapsed/refractory CTCLs and LyP (Duvic et al., 2015a). The drug was active in MF (ORR 54%) irrespective of the degree of CD30 expression, and achieved an ORR of 100% in the small number of patients with CD30+ pcALCL and/or LyP ($n = 12$) (Duvic et al., 2015a). Significantly, responses were observed in patients with multifocal lesions and in those with regional lymph node involvement. Toxicities, which included peripheral neuropathy, drug rashes, diarrhea, nausea, fatigue, myalgias, localized skin infections, and neutropenia, were as expected from experience in other indications (Duvic et al., 2015a; Chen et al., 2013; Pro et al., 2012; ADCETRIS®, 2015a; ADCETRIS®, 2015b). A separate investigator-initiated phase 2 trial of 32 patients with previously treated MF or SS (91% with large-cell transformation or folliculotropism) across all CD30 expression levels reported an ORR of 70% (including one global CR) (Kim et al., 2015). Responses were seen across all levels of CD30 expression, but the probability of achieving a response was lower in patients with CD30 levels of <5% ($p < 0.005$). At 12 months, 79% of responses were still ongoing and 54% of responders were progression-free. Additionally, eight patients had a >90% reduction in their Modified Severity Weighted Assessment Tool (mSWAT) score. These exciting results have led to the initiation of a phase 3 trial investigating the efficacy and safety of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in previously treated patients with CD30+ primary CTCL (MF or pcALCL) (NCT01578499). First results are expected to be reported in the near future.

The humanized, anti-CD52 monoclonal antibody, alemtuzumab – a drug currently indicated for use in B-cell chronic lymphocytic leukemia that targets the CD52 antigen expressed on malignant T cells (and other immune cells) to enable antibody-dependent cellular-mediated lysis (Campath®, 2014) – has also been investigated in pretreated cutaneous T-cell malignancies. Alemtuzumab has been shown to be active in relapsed/refractory CTCL (with ORRs ranging from 38 to 86%), including advanced erythrodermic MF/SS (ORR 84%, CR rate 47%) (Kennedy et al., 2003; Lundin et al., 2003; Zinzani et al., 2005; Bernengo et al., 2007; Querfeld et al., 2009), and there is some evidence to suggest that alemtuzumab may be more effective in SS than MF (Bernengo et al., 2007; Querfeld et al., 2009). Additionally, long-lasting responses have been reported in a minority of patients (Kennedy et al., 2003; Lundin et al., 2003; Zinzani et al., 2005; Bernengo et al., 2007; Querfeld et al., 2009). However, treatment with alemtuzumab can result in serious opportunistic infections as a consequence of immunosuppression (Kennedy et al., 2003; Lundin et al., 2003; Campath®, 2014; Zinzani et al., 2012) and, as such, the drug must be used carefully along with antimicrobials and at lower doses to reduce the likelihood of infections. Unfortunately, this elevated risk of infection, combined with the increased risk of infusion reactions and cytopenias (Campath®, 2014), has resulted in the commercial withdrawal of alemtuzumab in the United States, and the drug is now only available through the Campath Distribution Program or via clinical trials. Further dedicated clinical development of alemtuzumab in CTCL is unlikely.

Another antibody to be investigated in CTCL is the defucosylated, humanized anti-CC chemokine receptor 4 (CCR4) monoclonal antibody, mogamulizumab (KY-0761), which targets the CCR4 antigen expressed on type 2 helper T cells or regulatory T (Treg) cells (Ogura et al., 2014). As the CCR4 antigen is variably expressed on neoplastic CTCL cells (Ni et al., 2015; Yagi et al., 2006; Yamaguchi et al., 2006), there is a rationale for clinical study in this setting. Anti-lymphoma activity has been observed with mogamulizumab in patients with relapsed CCR4+ CTCL (ORR 38%, CR rate 14%), and in patients with previously treated MF or SS (ORR 37% [47% in SS patients and 29% in MF patients]) (Ogura et al., 2014; Duvic et al., 2015b). Significantly, mogamulizumab appears to lack many of the serious autoimmune-associated side effects associated with alemtuzumab; the most common AEs, which are largely low grade, reversible and manageable, include hematologic toxicities, pyrexia, skin disorders, nausea, chills, headache, and infusion-related reactions (Ogura et al., 2014). Based on these data and the promising results in PTCL (Ogura et al., 2014; Duvic et al., 2015b; Ishida et al., 2012; Yamamoto et al., 2010), mogamulizumab is currently being investigated versus vorinostat in a pivotal phase 3 trial in relapsed/refractory CTCL (NCT01728805) (Kim et al., 2014). The primary data from this study are expected to be released in mid-2016.

A-dmDT390-bisFv(UCHT1) is a high potency, experimental fusion protein immunotoxin (comprising catalytic and translocation domains of diphtheria toxin fused to two anti-human CD3 Fv fragments) that is targeted against the CD3 receptor, commonly expressed on skin-tropic T cells (Frankel et al., 2013; Woo et al., 2008). Data from the phase 1 portion of a phase 1/2 trial revealed an ORR of 35% among 17 evaluable patients with CTCL (most of whom had failed 1–4 prior therapies), including four CRs, three of which were >4 years' duration (Frankel et al., 2013). A subanalysis showed an ORR of 86% and CR rate of 56% in patients with stage IB/IIB disease and a skin coverage mSWAT score of <50%. As the CRs in this patient subset were long-lasting, these results suggest the potential for clinical cure in these selected patients (Frankel et al., 2013). The phase 2 portion of this trial is now enrolling patients who have characteristics associated with the high treatment response rate (NCT00611208). Side effects reported so far, most of which were mild or moderate and transient (following implementation of supportive therapies), include fevers, chills, nausea, transaminasemia, hypoalbuminemia, lymphopenia, viral reactivation, and hypophosphatemia (Frankel et al., 2013).

Lastly, the oral phosphoinositide-3-kinase-δ,γ inhibitor, duvelisib (IPI-145), has entered clinical trials in TCL (Horwitz et al., 2014). Phosphoinositide-3-kinase-δ and γ are intracellular signaling molecules believed to play important roles in facilitating the growth and survival of T-cell malignancies, including CTCL (Horwitz et al., 2014; Curran and Smith, 2014; Winkler et al., 2013). Data from a disease-specific cohort of patients with relapsed or refractory CTCL or PTCL in an ongoing phase 1 study showed that duvelisib could achieve an ORR of 38% (all partial responses) in 16 evaluable CTCL patients (Horwitz et al., 2014). The most common grade ≥3 AEs among all patients combined were elevated liver transaminases, rash, and neutropenia, and approximately one-third of patients discontinued due to AEs. Based on these preliminary results, further evaluation of this novel oral agent in relapsed/refractory CTCL is warranted.

4. Concluding remarks

This paper presents a comprehensive report on the current and future potential treatment options for relapsed and/or refractory CTCLs, particularly MF and SS. The initial treatment strategies for CTCLs differ considerably from those used for PTCLs (National

Cancer Institute, 2015; Dreyling et al., 2013; Willemze et al., 2013), yet there is a large overlap in the systemic options used to manage relapsed/refractory disease. Targeted agents, such as the HDAC inhibitors, are becoming important options for relapsed/refractory CTCL patients when other approaches have failed, and add to the available treatment armamentarium, which includes the oral retinoid, bexarotene, and conventional chemotherapies. Novel investigational therapies, particularly biologic agents, are also showing great promise. With their differential activity in different subsets of patients, biologic agents may offer the potential for personalized therapy. It is hoped that over the next 2–3 years, ongoing phase 3 trials (e.g., mogamulizumab in CTCL, E777 in CD25+ MF/SS, and brentuximab vedotin in CD30+ MF or pcALCL) will yield positive results, and thereby boost the range of options available to treat this diverse range of refractory malignancies.

Conflict of interest

Employment: V.B. (Takeda), D.H. (Takeda), R.L. (Takeda), A.C. (Takeda).

Stock ownership: A.C. (Takeda).

Conflicts of interest: PLZ, SP advisory board membership (Takeda).

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Biography

Pier Luigi Zinzani is an Associate Professor of Hematology at the Institute of Hematology 'L. e A. Seràgnoli' at the University of Bologna in Italy. He is a member of the Italian Society of Hematology, Italian Society of Experimental Hematology, American Society of Hematology, and American Society of Clinical Oncology, and is currently serving as President of the Fondazione Italiana Linfomi. Professor Zinzani has presented his research at more than 220 national and international congresses, has written more than 400 peer-reviewed articles in high-profile hematology and oncology journals, and has held the position of Associate Editor of Annals of Oncology since January 2014. His current research projects focus on clinical trial methodology, new drug development, non-Hodgkin lymphoma (including exploration of prognostic factors), Hodgkin's disease, chronic lymphocytic leukemia, and hairy cell leukemia.