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Targeted and Immune-Based Therapies in Cutaneous T-Cell Lymphomas
A Systematic Review and Meta-Analysis

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IMPORTANCE Advanced cutaneous T-cell lymphomas (CTCLs), including mycosis fungoides (MF) and Sézary syndrome (SS), are associated with substantial morbidity and limited durable treatment options. Although several targeted and immune-based therapies have emerged, their comparative efficacy, durability, and safety have not been comprehensively synthesized.

OBJECTIVE To evaluate the efficacy and safety of targeted and immune-based monotherapies for CTCL and characterize subtype-specific outcomes in MF and SS.

DATA SOURCES MEDLINE, Embase, and CENTRAL databases were searched from inception to April 10, 2026.

STUDY SELECTION Studies reporting efficacy or safety outcomes in patients with CTCL treated with targeted or immune-based monotherapy were included. Two reviewers independently screened studies and extracted data.

DATA EXTRACTION AND SYNTHESIS Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were followed and risk of bias was assessed using the Joanna Briggs Institute tool. Random-effects meta-analyses were performed to estimate pooled overall response rates (ORRs) with 95% CIs.

MAIN OUTCOMES AND MEASURES Pooled ORR; secondary outcomes were duration of response, progression-free survival, time to response, treatment-related adverse events (AEs), grade 3 or greater AEs, treatment discontinuations, recurrence, and subtype-specific response rates.

RESULTS The analysis included 41 studies comprising 1660 patients with a mean (SD) age of 61.6 (12.6) years; of the 1460 with reported sex, 647 were female (44.3%) and 813 male (55.7%) individuals. Pooled ORRs varied across therapeutic cohorts, led by brentuximab vedotin (69%; 95% CI, 62%-75%; n = 510), interferon alfa (68%; 95% CI, 32%-90%; n = 59), alemtuzumab (65%; 95% CI, 45%-80%; n = 96), mogamulizumab (45%; 95% CI, 35%-56%; n = 514), denileukin diftitox (39%; 95% CI, 33%-46%; n = 341), and pembrolizumab (34%; 95% CI, 20%-51%; n = 33). Among MF cohorts, pooled ORRs ranged from 38% to 66% across evaluated therapies. Among SS cohorts, pooled ORRs ranged from 60% to 74% across evaluated therapies. Sample-size–weighted means of study-reported median duration of response ranged from 4.7 to 9.4 months across reported therapies, while median progression-free survival ranged from 14.4 to 23.3 months. Grade 3 or greater AE rates varied across therapies, ranging from 15% (95% CI, 11%-21%) with mogamulizumab to 26% (95% CI, 7%-64%) with denileukin diftitox.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, targeted and immune-based therapies demonstrated clinically meaningful activity in CTCL, although important differences existed in response rates, response durability, and toxic effect profiles across therapeutic cohorts. Therapeutic activity also varied according to disease subtype, highlighting the importance of individualized treatment selection. These findings support incorporating disease subtype, anticipated durability of response, and toxicity considerations into treatment decision-making for patients with CTCL.

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Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of extranodal non-Hodgkin lymphomas characterized by malignant proliferation of skin-homing T lymphocytes, most commonly manifesting as mycosis fungoides (MF) and Sézary syndrome (SS).[1,2] The clinical presentation and disease trajectory can vary widely, ranging from indolent plaque- and patch-stage disease to advanced erythroderma, nodal involvement, blood dissemination, and visceral progression.[3-5] The disease course is highly variable and often unpredictable, with advanced-stage disease associated with substantial morbidity and reduced survival.

CTCLs are associated with substantial impairment in patient quality of life. Persistent pruritus, pain, sleep disturbance, recurrent skin infections, and visible cutaneous lesions may contribute to substantial psychosocial distress and functional impairment.[6-8] Progressive immune dysregulation associated with advanced disease further predisposes patients to infectious complications and treatment-related morbidity. Consequently, the management of CTCL extends beyond disease control alone and requires consideration of symptom burden, quality of life, treatment tolerability, and long-term disease suppression.

Although skin-directed therapies remain foundational for early-stage disease, CTCL that is advanced, relapsed, or refractory often necessitates systemic treatment. Conventional systemic approaches, including retinoids, methotrexate, histone deacetylase inhibitors, extracorporeal photopheresis, and cytotoxic chemotherapy, have historically demonstrated variable efficacy and are frequently limited by incomplete responses, short durability, cumulative toxic effects, and disease relapse.[9,10] As a result, there remains a substantial unmet need for therapies capable of achieving durable disease control while maintaining acceptable safety profiles.

Increasing our understanding of the biological mechanisms of CTCL has accelerated the identification and clinical application of targeted and immune-based therapeutic strategies. The pathogenesis of CTCL involves complex interactions among malignant T cells, the tumor microenvironment, cytokine and chemokine signaling pathways, and mechanisms of immune dysregulation and evasion.[11,12] Although several of these therapies were initially developed for other oncologic indications, advances in the understanding of CTCL biologic mechanisms have identified aberrantly expressed surface antigens and immune regulatory pathways, including cluster of differentiation 30 (CD30), C-C chemokine receptor 4 (CCR4), and programmed cell death checkpoint pathways, facilitating their evaluation and clinical application in CTCL. Agents such as brentuximab vedotin, mogamulizumab, denileukin diftitox, alemtuzumab, interferon alfa, and pembrolizumab have emerged as important treatment options for patients with advanced CTCL, demonstrating varying degrees of efficacy across distinct disease subtypes and clinical settings. However, the strength of clinical evidence and regulatory status differ across these agents, with some supported by pivotal registration trials and disease-specific regulatory approvals, whereas others have primarily been evaluated in smaller prospective studies. Despite increasing clinical adoption of these therapies, treatment selection remains challenging. Direct comparative studies between targeted and immune-based therapies are limited, and existing evidence is dispersed across studies with heterogeneous patient populations, disease stages, prior treatment exposures, and outcome definitions. Furthermore, the relative efficacy, durability of response, and safety profiles of these therapies have not been comprehensively synthesized across the available literature.

A clearer understanding of therapeutic outcomes across agents may help inform and guide evidence-based treatment selection as well as identify areas requiring further investigation. Therefore, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of targeted and immune-based monotherapies in CTCL. We focused on therapies with defined molecular or immunologic mechanisms of action to provide a contemporary synthesis of this rapidly evolving therapeutic landscape. Specifically, we synthesized evidence regarding overall response rates, durability outcomes, progression-free survival (PFS), treatment-related adverse events (TRAEs), and subtype-specific responses among patients with MF and SS.

Key Points

Question What are the efficacy and safety outcomes of targeted and immune-based therapies for advanced cutaneous T-cell lymphomas (CTCL), including mycosis fungoides and Sézary syndrome?

Findings In this systematic review and meta-analysis of 41 studies comprising 1660 patients, targeted and immune-based monotherapies demonstrated clinically meaningful activity across CTCL subtypes. Brentuximab vedotin and alemtuzumab were associated with favorable pooled response rates, while interferon alfa-2b demonstrated meaningful activity, although estimates were less precise.

Meaning These findings suggest that targeted and immune-based therapies are effective treatment options for advanced CTCL and that disease subtype, anticipated durability of response, and toxic effect profiles may help inform individualized treatment decisions.

Methods

This systematic review and meta-analysis was prospectively registered on PROSPERO (CRD420261366034). Based exclusively on published literature, it did not require institutional review board approval nor informed consent. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.

Data Sources and Study Selection

MEDLINE, Embase, and CENTRAL were searched from inception to April 10, 2026, using predefined search terms related to CTCLs and targeted or immune-based therapies (eTable 1 in Supplement 1). Studies were eligible for inclusion if they reported outcomes in patients with CTCL, including MF and SS,

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treated with targeted or immune-based monotherapy with defined molecular or immunologic mechanisms of action, and reported at least 1 efficacy or safety outcome of interest. Studies reporting combination treatment regimens, review articles, conference abstracts, animal studies, and non-English publications were excluded. When multiple publications reported outcomes from overlapping patient cohorts, the most comprehensive and up to date dataset was included.

Data Quality and Extraction

Quality of evidence was assessed using the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence and is reported for each included study in eTable 2 in Supplement 1. Articles were independently screened by 2 reviewers (J.Q.A.B., S.W.). Following title and abstract screening, full-text review was performed to determine eligibility. Disagreements regarding study inclusion were resolved through discussion and consensus. A third reviewer (R.S.Q.G.) was available for adjudication when consensus could not be reached.

Data extraction was performed independently by 2 reviewers (S.W., N.C.) using a standardized extraction form. Extracted variables included study design, patient demographic information, CTCL subtype, treatment characteristics, efficacy outcomes, durability outcomes, and safety outcomes.

Primary and Secondary Outcomes

The primary outcome was pooled overall response rate (ORR). Secondary outcomes included duration of response, PFS, time to response, TRAEs, grade 3 or higher adverse events, treatment discontinuations, disease recurrence, and subtype-specific responses among patients with MF and SS. Certainty of evidence for the primary outcome of ORR was assessed for each therapeutic agent using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was categorized as high, moderate, low, or very low (eTable 4 in Supplement 1).

Statistical Analysis

For time-to-event outcomes including duration of response, PFS, and time to response, study-reported medians were summarized descriptively as sample-size–weighted means. Meta-analyses of proportions were performed using random-effects models with logit-transformed proportions and inverse-variance weighting. Between-study variance (τ^2) was estimated using restricted maximum likelihood, and heterogeneity was quantified using the I^2 statistic. Pooled estimates and 95% CIs were back transformed to the proportion scale for presentation, with Clopper-Pearson CIs used for individual study proportions and classical CIs used for random-effects estimates. For studies reporting 0% or 100% events, a continuity correction of 0.5 was applied only to studies containing boundary proportions. Prediction intervals were calculated for analyses including at least 3 studies. A random-effects model was selected a priori to account for anticipated clinical and methodological heterogeneity across studies, including differences in patient populations, prior treatment exposure, disease stage, and outcome reporting.

For randomized clinical trials, eligible treatment groups were analyzed as single-group proportions; the comparative randomized design was not incorporated because the objective was to estimate treatment-specific response and safety proportions rather than comparative treatment effects. Subgroup analyses were performed for MF and SS when sufficient data were available. Funnel plots were generated for treatment-specific ORR analyses. Formal assessment of small-study effects using Egger regression tests was restricted to analyses including at least 10 studies. Funnel plots for analyses with fewer than 10 studies were considered descriptive only. Egger regression tests were 2-sided, with $P < .05$ considered statistically significant. Analyses were performed using R, version 4.5.2 (R Foundation for Statistical Computing) with the meta package, version 8.5-0.

Results

A total of 41 articles[13-53] comprising 1660 patients were included (eFigure 1 and eTable 2 in Supplement 1). Based on 34 studies reporting (hereafter, k) participant age, the weighted mean (SD; range) age was 61.6 (12.6; 16.0-92.0) years. Of the 1460 patients with reported sex, 813 were male (55.7%) and 647 were female (44.3%). Among the 1438 patients with reported CTCL subtype, the most common were MF (878 [61.1%]) and SS (439 [30.5%]), followed by primary cutaneous anaplastic large cell lymphoma (103 [7.2%]), lymphomatoid papulosis (9 [0.6%]), and mixed CTCL cohorts (9 [0.6%]). The mean (SD; range) number of prior failed treatments was 2.9 (4.1; 1-30). The mean (range) disease duration was 4.0 years (0.1-35.0). Among the total of 1660 participants, treatments included brentuximab vedotin (522 [31.4%]), mogamulizumab (514 [31.0%]), denileukin diftitox (341 [20.5%]), interferon alfa (154 [9.3%]), alemtuzumab (96 [5.8%]), and pembrolizumab (33 [2.0%]) (**Table 1**).

Pooled ORRs varied across therapeutic cohorts and ranged from 34% to 69% across evaluated therapies, with clinically meaningful activity observed for brentuximab vedotin (69%; 95% CI, 62%-75%; I^2 = 49.2%; k = 14; 510 patients), interferon alfa (68%; 95% CI, 32%-90%; I^2 = 71.2%; k = 3; 59 patients), alemtuzumab (65%; 95% CI, 45%-80%; I^2 = 63.0%; k = 3; 96 patients), mogamulizumab (45%; 95% CI, 35%-56%; I^2 = 79.0%; k = 10; 514 patients), denileukin diftitox (39%; 95% CI, 33%-46%; I^2 = 33.3%; k = 7; 341 patients) and pembrolizumab (34%; 95% CI, 20%-51%; I^2 = 0%; k = 2; 33 patients) (**Table 2**; eFigures 2-7 in Supplement 1). Prediction intervals for analyses with k of 3 or more studies are presented in the corresponding forest plots. Risk of bias assessed using the Joanna Briggs Institute critical appraisal tools, with item-level assessments for each included study, are presented in eTable 3 in Supplement 1.[54-56]

GRADE certainty of evidence for ORR was moderate for brentuximab vedotin, denileukin diftitox, and mogamulizumab, and low for alemtuzumab, interferon alfa, and pembrolizumab (eTable 4 in Supplement 1). Egger regression tests

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Table 1. Treatment Outcomes, Time-to-Event Efficacy End Points, and Safety of Immunotherapeutic Agents in 1660 Patients With Cutaneous T-Cell Lymphoma Across 41 Studies

Therapeutic agent, study type, No. (%) of studies	Outcome, % (patient No.)	Weighted mean of medians, duration (patient No.)			AEs		
		Severity assessment, mo	Therapy duration, wk	Follow-up duration, mo	Event, No.	Related discontinuation	Recurrence
Brentuximab vedotin (15 studies [31.4%]; 522 total patients)							
RCT, 2 (13.3)	CR, 28.9 (151)	DOR, 9.4 (65)	38.2 (283)	19.3 (398)	190	15	NR
NRCT, 2 (13.3)	PR, 43.3 (226)	PFS, 16.6 (369)					
RCS, 10 (66.7)	NOR, 27.8 (145)	TTNT, 9.7 (44)					
PCS, 1 (6.7)	NA	TTR, 3.9 (62)					
Mogamulizumab (10 studies [31.0%]; 514 patients)							
RCT , 2 (20.0)	CR, 9.5 (49)	PFS, 14.4 (198)	41.6 (514)	19.9 (393)	395	61	NR
NRCT, 1 (10.0)	PR, 32.1 (165)	TTR, 2.6 (242)					
RCS, 7 (70.0)	NOR, 58.4 (300)						
Denileukin diftitox (7 studies [20.5%]; 341 patients)							
RCT, 3 (42.9)	CR, 10.3 (40)	DOR, 8.1 (333)	24.0 (234)	29.8 (57)	297	12	8
NRCT, 3 (42.9)	PR, 28.7 (112)	PFS, 23.3 (156)					
PCS, 1 (14.3)	NOR, 61.0 (226)	TTR, 3.3 (225)					
Interferon alfa (4 studies [9.3%]; 154 patients)							
RCS, 3 (75.0)	CR, 6.8 (4)	TTNT, 11.3 (133)	50.6 (21)	24.0 (57)	NR	NR	NR
PCS, 1 (25.0)	PR, 55.9 (33/59)						
NA	NOR, 37.3 (22/59)						
NA	NR, 61.7 (95)						
Alemtuzumab (3 studies [5.8%]; 96 patients)							
RCS, 2 (66.7)	CR, 34.4 (33)	DOR, 4.7 (58)	18.5 (58)	39.7 (96)	54	20	14
PCS, 1 (33.3)	PR, 28.1 (27)						
NA	NOR, 37.5 (36)						
Pembrolizumab (2 studies [2.0%]; 33 patients)							
RCT, 1 (50.0)	CR, 6.1 (2)	NR	33.7 (33)	17.1 (33)	18	NR	NR
NRCT, 1 (50.0)	PR, 27.3 (9)						
NA	NOR, 66.7 (22)						

Abbreviations: AE, adverse event; CR, complete response; DOR, duration of response; NA, not applicable; NOR, no response; NR, not reported; NRCT, nonrandomized clinical trial; PCS, prospective cohort study; PFS, progression-free survival; PR, partial response; RCS, retrospective cohort study; RCT, randomized clinical trial; TTNT, time to next treatment; TTR, time to response.

Table 2. Pooled Overall Response Rates (ORR), by Therapeutic Agent for Cutaneous T-Cell Lymphomas

Therapeutic agent	No.		Pooled ORR, % (95% CI)
	Patients	Studies	
Brentuximab vedotin	510	14	69 (62-75)
Interferon alfa	59	3	68 (32-90)
Alemtuzumab	96	3	65 (45-80)
Mogamulizumab	514	10	45 (35-56)
Denileukin diftitox	341	7	39 (33-46)
Pembrolizumab	33	2	34 (20-51)

demonstrated no significant funnel-plot asymmetry for brentuximab vedotin (df = 12; t = −0.22; 95% CI, −2.04 to 1.67; P = .83) or mogamulizumab (df = 8; t = 0.77; 95% CI, −2.25 to 4.49; P = .47). Funnel plots for therapeutic cohorts with fewer than 10 studies were considered descriptive only (eFigures 24-29 in Supplement 1). Sample-size–weighted means of reported study-level median duration of response were 9.4 months with brentuximab vedotin (65 patients), 8.1 months with denileukin diftitox (333 patients), and 4.7 months with alemtuzumab (58 patients) (Table 1). Sample-size–weighted means of reported study-level median (IQR) PFS were 23.3 months with denileukin diftitox (156 patients), 16.6 months with brentuximab vedotin (369 patients), and 14.4 months with mogamulizumab (198 patients). Sample-size–weighted means of reported study-level median time to response were 2.6 months with mogamulizumab (242 patients), 3.3 months with denileukin diftitox (225 patients), and 3.9 months with brentuximab vedotin (62 patients).

Subtype-specific analyses demonstrated that, among MF cohorts, pooled ORRs ranged from 38% to 66% across evaluated therapies, with clinically meaningful activity observed for brentuximab vedotin (66%; 95% CI, 58%-73%; I^2 = 36.3%; 165 patients), alemtuzumab (47%; 95% CI, 6%-92%; I^2 = 62.7%; 18 patients), and mogamulizumab (38%; 95% CI, 27%-51%; I^2 = 60.4%; 240 patients) (eFigures 8-10 in Supplement 1). Among SS cohorts, pooled ORRs ranged from 60% to 74% across evaluated therapies, with clinically meaningful activity observed for alemtuzumab (74%; 95% CI, 59%-86%; I^2 = 0%; 40 patients), brentuximab vedotin (61%; 95% CI, 44%-76%; I^2 = 0%; 34 patients) and mogamulizumab (60%; 95% CI, 48%-71%; I^2 = 63.4%; 228 patients) (eFigures 11-13 in Supplement 1).

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AEs were evaluable in 1256 of 1660 patients, 75.7% of the pooled population, reflecting variable safety reporting across included studies. Among safety-evaluable patients, 954 (75.9%) experienced at least 1 AE. Descriptively, across the aggregate safety-evaluable population, the most frequently reported AEs were fatigue (152 patients [12.1%] receiving mogamulizumab [n = 68], denileukin diftitox [n = 55], brentuximab vedotin [n = 21], pembrolizumab [n = 5], or alemtuzumab [n = 3]), peripheral neuropathy (145 patients [11.5%] receiving brentuximab vedotin [n = 141], mogamulizumab [n = 2], or pembrolizumab [n = 2]), and infusion-related reactions (141 patients [11.2%] receiving mogamulizumab [n = 97], denileukin diftitox [n = 39], brentuximab vedotin [n = 3], and alemtuzumab [n = 2]). These frequencies represent descriptive cross-cohort counts rather than pooled meta-analytic estimates. Pooled AE rates ranged from 62% to 91% across therapeutic cohorts, including denileukin diftitox (341 patients [92%]; 95% CI, 67%-99%; I^2 = 92.1%; k = 7), mogamulizumab (490 [81%; 95% CI, 56%-93%; I^2 = 86.6%; k = 9]), pembrolizumab (33 [72%]; 95% CI, 8%-99%; I^2 = 80.9%; k = 2), alemtuzumab (96 [69%]; 95% CI, 14%-97%; I^2 = 91.3%; k = 3), and brentuximab vedotin (296 [64%]; 95% CI, 46%-78%; I^2 = 76.1%; k = 9) (**Table 3**; eFigures 14-18 in Supplement 1).

AEs of grade 3 or higher were evaluable for 763 patients in the pooled population (46.0%). Among safety-evaluable patients, 173 (22.7%) experienced at least 1 grade 3 or higher AE. Descriptively, across the aggregate safety-evaluable population, the most frequently reported grade 3 or higher AEs were peripheral neuropathy (13 patients [1.7%], all receiving brentuximab vedotin) and fatigue (13 [1.7%], all receiving denileukin diftitox). Pooled grade 3 or higher AE rates ranged from 15% to 26% across therapeutic cohorts, including denileukin diftitox (270 patients [26%; 95% CI, 7%-64%; I^2 = 89.5%; k = 6]), pembrolizumab (33 [22%; 95% CI, 11%-40%; I^2 = 0%; k = 2]), brentuximab vedotin (178 [21%; 95% CI, 10%-38%; I^2 = 71.2%; k = 6]), alemtuzumab (96 [20%; 95% CI, 2%-72%; I^2 = 93.2%; k = 3]), and mogamulizumab (186 [15%]; 95% CI, 11%-21%; I^2 = 0%; k = 4]) (**Table 4**; eFigures 19-23 in Supplement 1).

Treatment discontinuations were reported in 108 patients (6.5%), most commonly due to cutaneous adverse drug reactions (43 [39.8%], all receiving mogamulizumab) and peripheral neuropathy (8 [7.4% all receiving brentuximab vedotin). CTCL recurrence following treatment response was reported in 22 patients (1.3%), 14 of whom received alemtuzumab and 8, denileukin diftitox.

Table 3. Pooled Adverse Event (AE) Rates, by Therapeutic Agent for Cutaneous T-Cell Lymphomas

Therapeutic agent	No. Evaluable patients	No. Studies	Pooled AE rate, % (95% CI)
Brentuximab vedotin	296	9	64 (46-78)
Alemtuzumab	96	3	69 (14-97)
Pembrolizumab	33	2	72 (8-99)
Mogamulizumab	490	9	81 (56-93)
Denileukin diftitox	341	7	92 (67-99)

Table 4. Pooled Grade 3 or Greater Adverse Event (AE) Rates, by Therapeutic Agent for Cutaneous T-Cell Lymphomas

Therapeutic agent	No. Evaluable patients	No. Studies	Pooled grade ≥3 AE rate, % (95% CI)
Mogamulizumab	186	4	15 (11-21)
Alemtuzumab	96	3	20 (2-72)
Brentuximab vedotin	178	6	21 (10-38)
Pembrolizumab	33	2	22 (11-40)
Denileukin diftitox	270	6	26 (7-64)

Discussion

CTCL pathogenesis involves the malignant proliferation of skin-homing T lymphocytes and dysregulated immune-signaling pathways that contribute to chronic inflammation, immune evasion, and disease progression.[1,12] Increasing understanding of CTCL biological mechanisms has accelerated the development of targeted and immune-based therapies directed against surface antigens, cytokine signaling, and tumor-immune interactions.[57-60]

In this systematic review and meta-analysis, brentuximab vedotin was associated with substantial pooled clinical activity, with favorable response rates reported within MF cohorts. One biologically plausible explanation for this activity is the selective targeting of CD30–expressing malignant lymphocytes through antibody-drug conjugate-mediated cytotoxicity, particularly in transformed or CD30-positive disease phenotypes.[61] However, CD30 expression and large-cell transformation were not consistently reported across included studies and could not be evaluated in our analyses.

Interferon alfa was also associated with clinically meaningful activity, likely owing to its broad immunomodulatory and antiproliferative effects, including enhancement of cytotoxic immune responses and suppression of malignant T-cell proliferation.[61,62] However, interpretation should be cautious given the smaller pooled sample size and broader confidence intervals. By contrast, mogamulizumab demonstrated clinically meaningful efficacy across the largest pooled cohort, reinforcing its role as an important therapeutic option in advanced CTCL, particularly MF and SS. Mogamulizumab-mediated targeting of CCR4, a chemokine receptor involved in malignant T-cell trafficking and highly expressed in SS, may partially explain the favorable therapeutic activity observed in SS cohorts.[63-65] Notably, subtype-specific analyses demonstrated differential therapeutic activity across CTCL phenotypes, with meaningful responses observed across both MF and SS cohorts. These findings suggest that disease subtype and underlying tumor biology may represent important considerations when selecting targeted systemic therapies in advanced CTCL.

Durability outcomes also provided important clinical context. Differences in median duration of response and PFS were observed across therapeutic cohorts, suggesting that ORR alone may incompletely capture therapeutic benefit. Time to response also varied across therapies, highlighting the importance of considering response kinetics alongside response

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magnitude when selecting treatments for patients with symptomatic or rapidly progressive disease. In clinical practice, therapies associated with shorter reported times to response may be particularly valuable for patients with symptomatic, progressive, or high-burden disease, whereas therapies associated with prolonged disease control may offer greater long-term benefits despite lower initial response rates. Although immunotherapeutic agents demonstrated meaningful efficacy overall, AEs were common and frequently treatment specific, emphasizing the need to balance efficacy with tolerability in patients who often require prolonged therapy and sequential systemic treatments. Pooled AE rates were consistently high across therapeutic cohorts, ranging from 62% with brentuximab vedotin to 91% with denileukin diftitox, suggesting that TRAEs remain a common feature of systemic CTCL management regardless of therapeutic class. Furthermore, pooled grade 3 and higher AE rates varied across therapeutic cohorts, ranging from 15% with mogamulizumab to 26% with denileukin diftitox, underscoring important differences in toxicity burden between agents. While severe toxic events occurred across all therapeutic classes, these findings highlight the importance of individualized risk-benefit assessment and careful monitoring of TRAEs when selecting systemic therapies for CTCL.

Limitations

This study is limited by the heterogeneity in baseline disease characteristics, prior lines of therapy, stage distribution, outcome definitions, and AE reporting across included studies, which may influence comparative estimates of efficacy and safety. Importantly, pooled response estimates reflect outcomes within studied populations and should not be interpreted as direct head-to-head efficacy comparisons across agents due to differences in patient and disease characteristics. Historical comparisons of efficacy and durability outcomes are further limited by evolving response assessment criteria, heterogeneous response definitions, and selective outcome reporting across trial eras. Formal assessment did not identify significant small-study effects for brentuximab vedotin or mogamulizumab; however, this assessment was precluded for other therapeutic cohorts by the small number of contributing studies. Accordingly, pooled response estimates should be interpreted as summaries of the available evidence rather than direct comparisons of efficacy across therapeutic cohorts. In addition, disease stage, compartmental involvement (eg, skin, blood, nodal, and visceral disease), CD30 and CCR4 expression, and large-cell transformation were inconsistently reported across included studies, precluding stratified analyses of these clinically important variables. Accordingly, these findings should be interpreted in conjunction with patient- and disease-specific characteristics when selecting treatment.

Conclusions

This systematic review and meta-analysis synthesizes the efficacy, durability, and safety outcomes across 1660 patients and provides a comprehensive evaluation of targeted and immune-based monotherapies in CTCL. Taken together, these findings support a more biologically informed approach to CTCL treatment selection, whereby disease subtype, tumor phenotype, anticipated durability of response, and anticipated toxic effect profiles may help guide therapeutic decision-making in advanced disease. Larger prospective comparative studies and biomarker-driven approaches are warranted to better define optimal sequencing, long-term safety, and personalized treatment selection in advanced CTCL.

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Concept and design: Bai, Geng, Piguet.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bai, Wen, Chu.
Critical review of the manuscript for important intellectual content: Bai, Geng, Gniadecki, Piguet.
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