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Clinical trial

Phase II trial of atezolizumab (Anti-PD-L1) in the treatment of relapsed/refractory IIB/IVB mycosis fungoides/Sézary syndrome patients after previous systemic treatment. EORTC-1652-CLTG "PARCT"

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ABSTRACT

Introduction: Treatment of advanced mycosis fungoides (MF) and Sézary syndrome (SS) is a challenge. In this international, multicenter, open-label phase II trial, we assessed the efficacy and safety of anti-PD-L1 atezolizumab in stage IIB-IV refractory/relapsed MF and SS.

Materials and methods: Patients received atezolizumab 1200 mg IV Q3w for up to 1 year unless progression or withdrawal. The main study endpoints were overall response rate (ORR), progression-free survival (PFS), time to next systemic treatment (TTNT), and overall survival (OS).

Results: A total of 26 patients were enrolled from seven countries. Seventeen patients met the inclusion criteria. At a median follow-up of 36.6 months, the ORR was 15.4 % in the intention to treat (ITT) and 17.6 % in the per protocol (PP) population, respectively. In the PP group, 58.8 % of patients, and in the ITT group, 53.9 % of patients achieved partial response or stable disease as their best outcome. One complete response was observed after 1 year. Median PFS was 3 months (95 % CI 1.4–4.9) in PP and 3.1 months (95 % CI 2.4–4.0) in ITT. Median OS was not reached for PP and was 22.3 months (20.0-NE) for ITT. Median TTNT was 5.9 months (2.8-NE) in PP and 6.2 months (3.1–14.8) in ITT. The most common grade ≥ 3 adverse events were fatigue (23.1 %) and infections (15.4 %), with two sepsis-related deaths. Atezolizumab was primarily discontinued due to disease progression (50 %).

Conclusions: Atezolizumab shows moderate activity in pretreated refractory/relapsed MF and SS. Further studies are needed to identify reliable predictors of safety and treatment response.

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1. Introduction

Treatment of Mycosis fungoides (MF) and Sézary syndrome (SS) represents a challenge, with diversity of treatment approaches encompassing over twenty modalities, despite no significant improvement in survival outcomes [1]. In advanced cases, patients have a 5-year survival rate of 28 %, alongside impaired quality of life and recurrent infections [2]. Despite new immunotherapies showing superiority over traditional regimens in terms of progression-free survival [3,4], there remains a need for novel treatments based on the molecular and immunological features underlying cutaneous-T-cell lymphomas (CTCLs) [5–8]. In this scenario, the role of the tumor microenvironment (TME) and related immune exhaustion has been subject of recent investigations [9,10]. In particular, PD-1 (programmed death-1) functions together with its ligands (PD-L1 and PD-L2) as a checkpoint in regulating immune responses, minimizing activity within inflammatory responses and promoting cancer cell proliferation [11–13]. PD-1 checkpoint inhibitors have been effective in treating melanoma and Hodgkin lymphoma and are now being studied in relapsed/refractory MF-SS [14,15]. The interaction between tumor cells, tumor-infiltrating lymphocytes (TIL), and tissue-resident antigen-presenting cells (APC) Langerhans cells (LC) has been explored in MF, with LC appearing to decrease with increasing disease stages [16,17]. Moreover, Murray *et al.* have shown that TILs display an exhausted phenotype characterized by the expression of PD-1 and TIGIT, whilst retaining cytotoxic activity and production of interferon-γ and interleukin-17 [18]. As for tumor cells, they are characterized by high heterogeneity, with three different phenotypes based on the expression of HLA-DR: “cold” (DR−), “exhausted” (DR+ PD-1 +), and “evasive” (DR++ PD-L1 +). Hence, the relative expression of PD-1/PD-L1 on TILs and tumor cells may be useful in predicting response to anti-PD1/PD-L1 therapies [18]. In addition, PD-L1 expression on the T-cell surface positively correlates with disease stage and lymphoma progression [19]. Atezolizumab, a human immunoglobulin (Ig) G1 monoclonal antibody targeting human PD-L1, inhibits the interaction with its receptors, PD-1 and B7.1 (CD80, B7–1). Both interactions are reported to provide inhibitory signals to T-cells and other immune cells. Currently, atezolizumab is considered as a first-line treatment in PD-L1 + metastatic lung carcinoma [20]. Considering this evidence, blocking the PD-1-L1 pathway may represent a promising option in CTCLs. This study aimed to prove the therapeutic potential of atezolizumab in advanced CTCLs.

2. Patients and methods

2.1. 2.1 Trial design

In this international, multi-center, phase II, single-arm trial, patients received intravenous atezolizumab 1200 mg for one year unless clinically relevant disease progression or other protocol withdrawal criteria occurred. The study was approved by the competent Authorities and Ethical Committees. All patients gave written informed consent prior to enrollment. Inclusion criteria were: patients aged ≥ 18 years, stage IIB-IVB MF/SS, relapsed/refractory disease after standard systemic therapy, and WHO performance status ≤ 1. Patients with documented clinical benefit after one year could continue treatment for two additional years. Adverse events (AEs) of grade ≥ IV resulted in treatment discontinuation. Standard disease assessment was performed every 2 cycles (skin-blood) and every 4 cycles (lymph nodes-visceral organs) by local investigators, according to the EORTC-ISCL-USCLC criteria, allowing a global response call every 4 cycles [21]. If progression was not deemed clinically relevant, patients proceeded with 2 additional cycles of atezolizumab. If progression was confirmed, atezolizumab was discontinued permanently.

2.2. 2.2 Statistical analysis

This study used an A′Hern design to detect a 15 % improvement in the overall response rate (ORR). It aimed to reject the null hypothesis (H0: ORR=40 %) with 90 % power under the alternative hypothesis (H1: ORR=65 %) using an exact binary test at 10 % significance level 1–sided. 29 eligible patients were required, with the drug considered for further investigation if 16 or more were responders. Exact type I error and power were 7.1 % and 90.2 %, respectively. The ORR for encapsulated doxorubicin reported in EORTC-21012 trial served as reference. This reference was based on older response criteria (excluding blood, tumor burden), yet no major outcome migration was expected. All registered patients represent the ITT population. The PP population includes all eligible patients receiving atezolizumab. Safety population considered all registered patients receiving treatment. The primary endpoint was ORR defined as proportion of patients achieving complete response (CR) or partial response (PR) up to a maximum of 1 year after registration [21]. Secondary endpoints included time to response, measured from treatment start to CR/PR, with non-CR/PR patients censored at their last disease assessment; response duration, measured from initial determination of CR/PR until first documentation of progressive disease (PD); clinical benefit rate, measured as the proportion of CR, PR, or stable disease (SD) achieved; time to next systemic treatment (TTNT), measured from initiation of atezolizumab to record of subsequent systemic treatment; progression-free survival (PFS), measured from treatment initiation to first documentation of PD or death from any cause; overall survival (OS), measured from treatment initiation and date of death from any cause. Main analyses of the efficacy endpoints were performed in the PP population and descriptively reported in the ITT population. Safety data were analyzed in the safety population. Time to event endpoints, duration of response, TTNT, PFS and OS are displayed using Kaplan-Meier (KM) curves with median time estimates and 95 % CIs. For time to response, a competing risk analysis was performed, treating death before response or immediate progression on treatment as competing risks.

2.3. 2.3 Immunohistochemical and mass cytometry analysis

Standard immunohistochemical analysis was conducted on biopsies to evaluate PD-L1 expression. Assessments included baseline (n = 22), 6-month (n = 8), and 1-year (n = 9) reviews, categorizing PD-L1 status as ’low’ (score 0–1) or ’high’ (score 2–3) after peer review. Mass cytometry analysis [13,18] utilized fresh skin and blood samples from 11 patients across three time points, analyzing cell populations and markers descriptively [18,22] (Supplementary Appendix 1).

3. Results

3.1. 3.1 Statistical reconsideration

The power calculation was revised due to 3 deaths, including 1 toxic death, leading to premature stopping of accrual. There were 26 enrolled patients at closure, amongst whom 17 were eligible (Fig. 1, Supplement Table 2). Recruited patients continued treatment if the investigator considered it beneficial. Assuming the same design parameters (Null hypothesis (H0): ORR= 40 %, alternative hypothesis (H1): ORR= 65 %, and alpha= 0.1), at least 10 responders out of 17 were needed to justify further investigation of the drug, achieving a power of 78 %. The exact type I error and power was 9.2 % and 78.7 %, respectively. All 26 patients were registered by 7 institutions in 7 countries (Spain, France, Germany, Italy, Poland, Austria, Switzerland and Greece) between October, 23rd 2018 and September, 16th 2019. This analysis includes all available data up to the database lock on August 18, 2022, with a median follow-up of 36.6 months (IQR: 35.2–37.3 months) for all enrolled patients.

3.2. 3.2 Patients’ characteristics

Baseline characteristics of the PP and ITT populations are shown in Table 1. Median age among the 17 eligible patients was 66 years (range

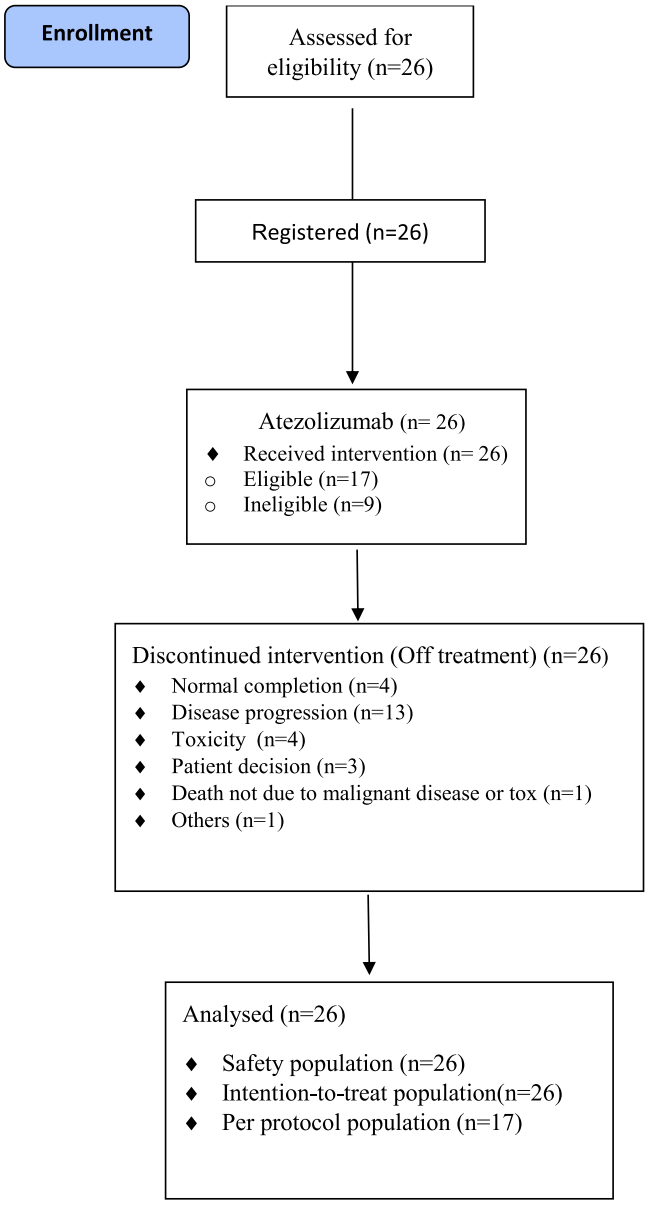

Fig. 1. Patient disposition for the single-arm phase II EORTC-1652-CLTG PARCT trial.

52–82), all with other medical conditions at entry. Most patients had MF (70.6 %), stage IIB disease (41.2 %) and no nodal involvement (58.8 %). The median mSWAT score was 79 (range 1–190). All patients were off-treatment at the time of the lock, with 57.7 % receiving at least 4 cycles (median number of 5 cycles, range 1–51), with 9 (34.6 %) experiencing a delayed treatment partly due to adverse events (55.6 %). The median treatment duration was 15 weeks (range 3–160). Twelve patients (46.2 %) had a relative dose intensity (RDI) of 80–100 %, and 14 patients (53.8 %) had a RDI $\geq$ 100 %. The median RDI was 100 % (Table 2). The main reason for treatment discontinuation was PD (50 %). Four patients (15.4 %) stopped protocol treatment due to toxicity (Table 2). After recruitment closure, 8 patients continued atezolizumab due to perceived benefit, amongst whom 4 completed as per protocol, 3 stopped due to PD, and 1 for patient's decision. Fifteen patients had stopped treatment before the closure mainly due to PD (66.7 % [10/15]). Four out of 26 ITT (15.4 %) had a PR within 1 year. Most patients had skin improvement, with a median change mSWAT scores of −52.6 % from baseline (Fig. 2. E/F) (Table 3).

-*Clinical benefit rate*: The clinical benefit rate within 1 year since registration was 58.8 % in the PP patients and 53.9 % in the ITT. Seven (41.2 %) PP patients and ten (38.5 %) ITT patients had a SD.

-*Best overall response throughout follow-up*: There were 5 responders (1 CR, 4 PRs) in the ITT population (median follow-up of 36.6 months), specifically 1 CR and 1 PR in SS patients and 3 PRs in MF patients. The highest response rates occurred in patients under 65 years, with 5 responses (1 CR, 4 PRs), in stage IVA disease (19 %) with 2 PRs and in stage IIIB (15 %) with 1 CR (Table 1). Two of the 5 responders progressed or relapsed after 4.3 and 21 months of response duration, respectively.

-*Time-to event endpoints:* The median PFS was 3 months (95 % CI 1.4–4.9) in the PP patients and 3.1 months (95 % CI 2.4–4.0) in the ITT population. The 1-year PFS rate was 11.8 % (2.0–31.2 %) and 15.4 % (4.8–31.5 %) in the PP and ITT populations, respectively. The median OS was 22.3 months (20.0-NE) in the ITT population. The 1-year OS rate was 87.8 % (59.5–96.8 %) and 76.7 % (55.3–88.8 %) in the PP and ITT populations respectively (Fig. 2). The median TTNT was 5.9 months (2.8-NE) in the PP and 6.2 months (3.1–14.8) in the ITT population (Supplementary Figure 1).

3.3. 3.4 Safety

Among the ITT patients, 21 (80.8 %) experienced at least a grade 1 AE, with 14 (53.8 %) possibly related to atezolizumab (Table 4). The most common AEs, occurring in $\geq$ 10 % of patients, were fatigue (23.1 %) and infection (15.4 %). Five out of 6 fatigue cases and two out of 4 infectious events were possibly treatment-related. Two deaths due to sepsis were recorded. All severe AEs occurred at treatment initiation. Four patients experienced immune AEs: grade 3 pancreatitis, drug induced liver injury, myositis, and maculo-papular rash. Four patients had grade 1 pruritus, with two treatment-related cases. There were three deaths (two sepsis and one disease progression), one of which was possibly related to atezolizumab (sepsis). Biochemical and hematological toxicities are summarized in Supplementary Table 3.

3.4. 3.5 Immunohistochemical and mass cytometry analyses

As for of PD-L1 expression at baseline, higher levels were detected in the dermal region compared to the epidermis (Supplementary Table 4). In the dermal region, patients were similarly distributed between high or low in PD-L1 positive cells scores, with no significant differences in terms of clinical outcomes (Table 5), serum chemistry, hematology, and AEs (results not shown). The cell population demographics detected by mass cytometry is depicted in Fig. 3A. At baseline, dominant skin cell populations included tumoral cells (35 %), along with CD4 + T-cells (17 %), myeloid APCs (LC and dendritic cells, DC (12 %)) and CD8 + T-cells (5 %). Early after treatment, the cutaneous LC subset briefly expanded yet returned to near baseline by cycle 2 (Fig. 3B). CD8 + and NK cells showed a smaller, more sustained increase in the TME, while tumor cells decreased from baseline. Unlike the TME, CD4 + T-cells were the predominant peripheral blood population (44 %) and remained stable during treatment. PD-L1 showed the highest expression on APCs (LC and DC) within the TME (2.2 median intensity (MI) at baseline), followed by a minority (<1 %) of T-cell double negative (DNEG) (Fig. 3C). The MI of PD-L1 expression on LCs decreased substantially with treatment, whereas PD-L2 expression did not. The highest PD-L1 and PD-L2 expressions in the peripheral blood at baseline were observed on monocytoid (0.21 MI) and B cells (0.25MI), respectively. PD-L1 was predominantly expressed on LCs in the TME, which also showed high PD-L2 levels. Peripherally, PD-L2 expression was highest on B cells. Baseline LCs were notably high in a patient who died early, decreasing over time (Fig. 4A). Patients with grade 3 treatment-related AEs showed higher PD-L1/PD-L2 expression on cell subsets, as those with immune-related AEs (Fig. 4B). Overall, no significant differences in the PD-L1 expression or in the magnitude of expression decrease were observed between responders and non-responders.

Table 1
Baseline characteristics and clinical response.

	Population		Overall response achieved within 1 year since registration (ITT)	[a]Best overall response achieved throughout follow-up evaluations.(in the ITT population, n = 26)			
	Per-protocol (N = 17)	Intention-to-treat (N = 26)	CR/PR(N = 4)	CR (n = 1)	PR (n = 4)	SD (n = 9)	PD (n = 6)
Age (randomization)							
> =65 years	10 (58.8)	16 (61.5)	0	0	0	8	4
< 65 years	7 (41.2)	10 (38.5)	4	1	4	1	2
Mean (SD)	67.88 (8.12)	66.77 (11.14)					
Median	66.0	65.5					
Range	52.0–82.0	41.0–84.0					
Sex							
Female	10 (58.8)	14 (53.8)	3	1	2	5	5
Male	7 (41.2)	12 (46.2)	1	0	2	4	1
Current WHO performance status							
0	9 (52.9)	15 (57.7)	1	0	1	9	4
1	8 (47.1)	11 (42.3)	3	1	3	0	2
Stage							
IB	1 (5.9)	1 (3.8)	0	0	0	0	1
IIB	7 (41.2)	9 (34.6)	1	0	1	4	3
IIIA	1 (5.9)	3 (11.5)	1	0	1	0	1
IIIB	3 (17.6)	4 (15.4)	1	1	0	2	1
IVA	4 (23.5)	5 (19.2)	1	0	2	3	0
IVB	1 (5.9)	4 (15.4)	0	0	0	0	0
Diagnosis of CTCL							
Mycosis fungoides (MF)	12 (70.6)	20 (76.9)	2	0	3	6	5
Sézary Syndrome (SS)	5 (29.4)	6 (23.1)	2	1	1	3	1
Skin							
T1	1 (5.9)	1 (3.8)	1	0	1	0	0
T2	3 (17.6)	6 (23.1)	1	0	1	2	1
T3	7 (41.2)	9 (34.6)	0	0	0	4	3
T4	6 (35.3)	10 (38.5)	2	1	2	3	2
Node							
N0	10 (58.8)	14 (53.8)	3	0	3	6	4
N1	0 (0)	2 (7.7)	0	0	0	0	1
N2	0 (0)	1 (3.8	0	0	0	1	0
N3	5 (29.4)	7 (26.9)	1	1	0	2	0
Nx	2 (11.8)	2 (7.7)	0	0	1	0	1
Visceral							
M0	16 (94.1)	22 (84.6)	4	1	4	9	6
M1	1 (5.9)	4 (15.4)	0	0	0	0	0
Blood							
B0	8 (47.1)	13 (50.0)	1	0	1	5	5
B1	5 (29.4)	7 (26.9)	2	1	1	3	1
B2	4 (23.5)	6 (23.1)	1	0	2	1	0
mSWAT score							
1–50	3 (17.6)	6 (23.1)	1	0	1	1	1
51–100	9 (52.9)	14(53.8)	2	0	2	7	4
101–150 `	2 (11.8)	3 (11.5)	0	0	1	0	1
> 150	3 (17.6)	3 (11.5)	1	1	0	1	0
Mean (SD)	87.95 (55.49)	79.98 (48.53)					
Median	79.0	77.0					
Range	1.0–190.0	1.0–190.0					
PD-L1 positive cells in epidermal region: tumor cells							
Low	14 (82.4)	20 (76.9)	4	1	4	6	3
High	0 (0)	1 (3.8)	0	0	0	0	1
Unknown	3 (17.6)	5 (19.2)	0	0	0	3	2
PD-L1 positive cells in epidermal region: reactive cells (or dendritic cells)							
Low	14 (82.4)	20 (76.9)	4	1	4	5	4
High	0 (0)	1 (3.8)	0	0	0	1	0
Unknown	3 (17.6)	5 (19.2)	0	0	0	3	2
PD-L1 positive cells in dermal region: tumor cells or reactive cells							
Low	9 (52.9)	11 (42.3)	2	1	1	4	3
High	6 (35.3)	11 (42.3)	2	0	3	2	2
Unknown	2 (11.8)	4 (15.4)	0	0	0	3	1

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease
[a] Results from 6 patient (3 early death and 3 unevaluable) are not included

Table 2
Exposure to study treatment, schedule modifications and treatment discontinuation.

	Treatment Atezolizumab (N = 26)
Exposure to study treatment	
Total dose (mg)	
Median	6000.0
Range	1200.0–62400.0
Relative Dose Intensity (%)	
Median	100.0
Range	84.4–102.4
80–100 %	12 (46.2)
> =100 %	14 (53.8)
Number of treatment cycles	
Median	5.0
Range	1.0–52.0
Treatment schedule modified > 48 h, n (%)	
No	17 (65.4)
Treatment delayed	9 (34.6)
Major reason for protocol treatment discontinuation, n (%)	
Normal completion	4 (15.4)
Progressive disease	13 (50.0)
Toxicity	4 (15.4)
Patient's decision	3 (11.5)
Death not due to malignant disease or toxicity	1 (3.8)
Other	1 (3.8)

Table 3
Summary of the main clinical activity endpoints.

	per protocol population(n = 17) n (%)	Intention-to-treat population(n = 26) n (%)
Overall response rate within 1 year since registration		
Responders (CR + PR)	3 (17.6)	4 (15.4)
ORR (1-sided 90 % CI)	0.176 (0.066 – 1)	0.154 (0.068 – 1)
ORR (95 % CI)	0.176 (0.038 – 0.434)	0. 154 (0.043 – 0.348)
Best overall response within 1 year from registration		
Partial response	3 (17.6)	4 (15.4)
Stable disease	7 (41.2)	10 (38.5)
Progression	5 (29.4)	6 (23.1)
Not evaluable	1 (5.9)	3 (11.5)
Early death	1 (5.9)	3 (11.5)
Best overall response achieved throughout follow-up evaluations		
Best overall response		
Complete Response	1 (5.9)	1 (3.8)
Partial response	3 (17.6)	4 (15.4)
Stable disease	6 (35.3)	9 (34.6)
Progression	5 (29.4)	6 (23.1)
Not evaluable	1 (5.9)	3 (11.5)
Early death	1 (5.9)	3 (11.5)
Time to event endpoints		
Median PFS (95 % CI)	3.0 mo (1.4–4.9 mo)	3.1 mo (2.4–4.0 mo)
Median time to next systemic treatment (95 % CI)	5.9 mo (2.8–33.4)	6.2 mo (3.1–14.8 mo)
Median OS (95 % CI)	NE	33.6 (16.5-NE)
1-year PFS rate	11.8 % (2.0–31.2 %)	15.4 % (4.8–31.5 %)
1-year OS rate	88.2 (60.6–96.9 %)	76.9 (55.7–88.9 %)
Time to response: Status		
CR or PR	4 (23.5)	5 (19.2)
Competing event	13 (76.5)	21 (80.8)

mo; month, NE; No estimate, OS; overall survival, PFS; progression free survival

4. Discussion

Key challenges in treating CTCL include the distinct nature of the tumor, which arises from CD4 + T-cells rather than other types of skin cells, and the heterogeneity of its TME [9,23,24]. This trial did not reach the minimum responders needed to recommend atezolizumab for advanced CTCL, with only 3 of 17 PP patients achieving PR, likely due to underpowering (78.7 %) from early closure. Notably, one patient achieved a rare CR in this advanced-refractory group. The ORR was 17.6 % in PP and 15.4 % in ITT, with a total of 4 PRs. One patient had a CR during follow-up, suggesting that checkpoint inhibition may be of significant therapeutic value in individual cases. Responding patients received more than 60.000 mg of atezolizumab. Fatigue and infections were the most common AEs, with two deaths due to sepsis. To date, data on anti-PD1/PD-L1 agents in CTCL remain limited. A phase I study on nivolumab included 13 pre-treated MF patients, showing a 15 % ORR with a median PFS of 10 months [25]. A phase II trial of pembrolizumab including 3 patients with transformed MF reported 1 CR and 2 PD and was halted early following a preplanned interim analysis [26]. More recently, a larger phase II trial on 24 patients with advanced MF/SS explored pembrolizumab every 3 weeks for up to 24 months, achieving an ORR of 38 % [13]. Transient worsening of erythroderma occurred in 53 % of SS patients, linked to high PD-1 expression on Sezary cells, yet responses were not associated with PD-L1 expression. In 2023, a phase II study on anti-PD1 tislelizumab reported an ORR of 45 % in 11 MF/SS patients, with 2 patients discontinuing therapy early [27]. 90.9 % had treatment-emergent adverse events, with 72.7 % experiencing grade $\geq$ 3. Preliminary reports from a phase II trial comparing durvalumab to durvalumab + lenalidomide showed an ORR of 58 % for the combination *vs* 36 % for durvalumab alone in 23 relapsed/advanced MF/SS patients [28]. A grade IV neutropenia event and one death after discontinuation due to PD were reported. Ongoing combination studies are expected to release further results [29]. Overall, the activity of single agent anti-PD-1/PD-L1 appears limited and requires further translational investigation [30]. Responses may be influenced by varying PD-1/PD-L1 expression levels across disease subtypes, PD-1 loss, PD-L2 levels, monocyte/LC/T-cell exhaustion in tumor cells, and PD-L1 structural variants in large cell transformation [11,24,31,32]. In this trial, PD-L1 expression did not serve as an effective predictive marker of response to therapy. LCs expressed the highest levels of PD-L1/PD-L2 within the TME and PD-L1 expression decreased with treatment, possibly due to antigen-antibody binding or genuine PD-L1 down-regulation across cell populations. Further studies on PD-L2 levels and their maintenance or increase in immune cell populations could elucidate the immune biology and treatment outcomes. As for safety, Saulite *et al.* reported that PD-1 blockade can elicit a remarkable proliferation of CD4 + malignant T cells [32]. This observation was confirmed in another case and linked to oncogenic activation of the T-cell receptor signaling pathway [33]. Recently, Philipps *et al.* found no differences in the frequencies of immune or tumor cells between responders and non-responders to pembrolizumab, yet identified a spatial biomarker derived from differences in the functional immune state correlated with immunotherapy response [34]. In this trial, progression was more common in stage IIb patients, regardless of PD-L1 expression, possibly due to a more immunosuppressive environment associated with ulcerated tumors with high bacterial loads. In conclusion, significant challenges remain, particularly the lack of reliable predictors for immunotherapy response and toxicity. Atezolizumab showed moderate activity in pretreated-advanced CTCLs (PR 4/26, CR 1/26). Refining clinical trial inclusion criteria and further investigating new biomarker profiles may help identifying the most suitable population for an effective and safe use of checkpoint-inhibitors in CTCL.

CRediT authorship contribution statement

Moss Paul: Writing – review & editing, Methodology, Investigation,

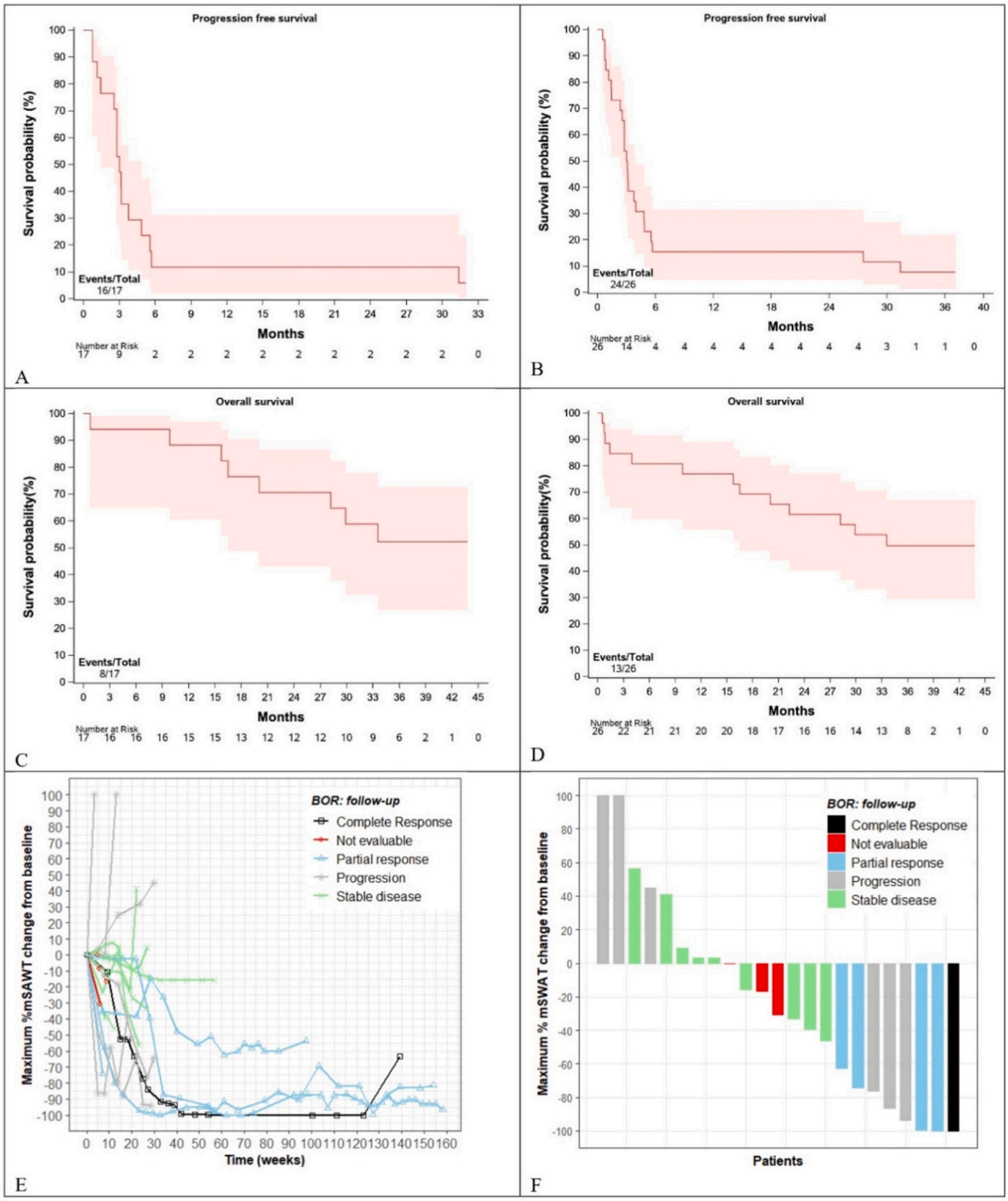

Fig. 2. (A) PFS KM curves in the per-protocol, (B) PFS KM curves in the ITT (C) OS KM curves in the per-protocol, (D) OS KM curves in the ITT, (E) Longitudinal change of skin modified Severity Weighted Assessment Tool (mSWAT) score from baseline. (F) Maximum % change in mSWAT score from baseline. Note: E and F does not include patients with early death as BOR since patient had only baseline data. Three patients with a partial skin response were classified as having progressive disease due to lymph node progression. *Abbreviations:* BOR; Best Overall response achieved throughout follow-up evaluations, OS; Overall survival, PFS; progression free survival, KM; Kaplan–Meier.

Table 4
Adverse events (AEs) occurring in ≥ 10 % of patients for all grades and immune related AEs.

	Safety population (N = 26)						
	Grade1N (%)	Grade2N (%)	Grade3N (%)	Grade4N (%)	Grade5N (%)	Grade≥ 3 N (%)	Grade≥ 1 N (%)
All AEs	3 (11.5)	8 (30.8)	6 (23.1)	1 (3.8)	3 (11.5)	10 (38.5)	21 (80.8)
AEs occurring in ≥ 10 % of patients							
Fatigue	5 (19.2)	1 (3.8)					6 (23.1)
Sepsis			1 (3.8)	1 (3.8)	2 (7.7)	4 (15.4)	4 (15.4)
Alanine Aminotransferase Increased		3 (11.5)	1 (3.8)			1 (3.8)	4 (15.4)
Aspartate Aminotransferase Increased	3 (11.5)		1 (3.8)			1 (3.8)	4 (15.4)
Myalgia		3 (11.5)					3 (11.5)
Alopecia	3 (11.5)						3 (11.5)
Headache	1 (3.8)	2 (7.7)					3 (11.5)
Immune related AEs							
Pancreatitis			1 (3.8)			1 (3.8)	1 (3.8)
Drug-induced liver injury			1 (3.8)			1 (3.8)	1 (3.8)
Pruritus	4 (15.4)						4 (15.4)
Myositis			1 (3.8)			1 (3.8)	1 (3.8)
Rash Maculo-Papular			1 (3.8)			1 (3.8)	1 (3.8)

Table 5
Baseline PD-L1 positive cells in dermal region: tumor cells or reactive cells versus clinical data.

	PD-L1 positive cells in dermal region: tumor cells or reactive cells	
	Low(N = 11)	High(N = 11)
	N (%)	N (%)
Survival status		
Death	6 (54.5)	6 (54.5)
Alive	5 (45.5)	5 (45.5)
Best Overall response		
Stable disease	4 (36.4)	2 (18.2)
Progression	3 (27.3)	2 (18.2)
Partial response	1 (9.1)	3 (27.3)
Not evaluable	1 (9.1)	2 (18.2)
Early death	1 (9.1)	2 (18.2)
Complete Response	1 (9.1)	0 (0.0)
Progression status (PFS)		
Event	10 (90.9)	10 (90.9)
Censored	1 (9.1)	1 (9.1)
Time to next systemic treatment: Status		
Event	7 (63.6)	6 (54.5)
Censored	4 (36.4)	5 (45.5)
Best overall response within 1 year from registration		
Stable disease	4 (36.4)	3 (27.3)
Progression	3 (27.3)	2 (18.2)
Partial response	2 (18.2)	2 (18.2)
Not evaluable	1 (9.1)	2 (18.2)
Early death	1 (9.1)	2 (18.2)
Overall Response status within 1 year since registration		
Failure	9 (81.8)	9 (81.8)
Success	2 (18.2)	2 (18.2)
Sepsis status		
No sepsis	10 (90.9)	8 (72.7)
Non-fatal sepsis	1 (9.1)	1 (9.1)
Fatal sepsis	0 (0.0)	2 (18.2)

Formal analysis. **Quaglino Pietro:** Writing – review & editing, Methodology, Investigation. **Sartori Delphine:** Writing – review & editing, Methodology, Formal analysis. **Guenova Emmanuella:** Writing – review & editing, Methodology, Investigation. **Drennan Samantha:** Writing – review & editing, Formal analysis. **Ortiz-Romero Pablo:** Writing – review & editing, Methodology, Investigation. **Van Hear Jimmy:** Writing – review & editing, Formal analysis. **Bagot Martine:** Writing – review & editing, Methodology, Investigation. **Jonak Constanze:** Writing – review & editing, Methodology, Investigation. **Papadavid Evangelia:** Writing – review & editing, Methodology, Investigation. **Willemze Rein:** Writing – review & editing, Methodology, Investigation. **Stranzenbach René:** Writing – review & editing, Methodology, Investigation. **Scarisbrick Julia:** Writing – review & editing, Supervision, Methodology, Investigation. **Battistella Maxime:** Writing – review & editing, Methodology, Investigation. **Casas-Martin Jose:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Stadler Rudolf:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Murray Duncan:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Roccuzzo Gabriele:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Data curation. **Marreaud Sandrine:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Knobler Robert:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Musoro Jammbe:** Writing – review & editing, Supervision, Methodology, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial

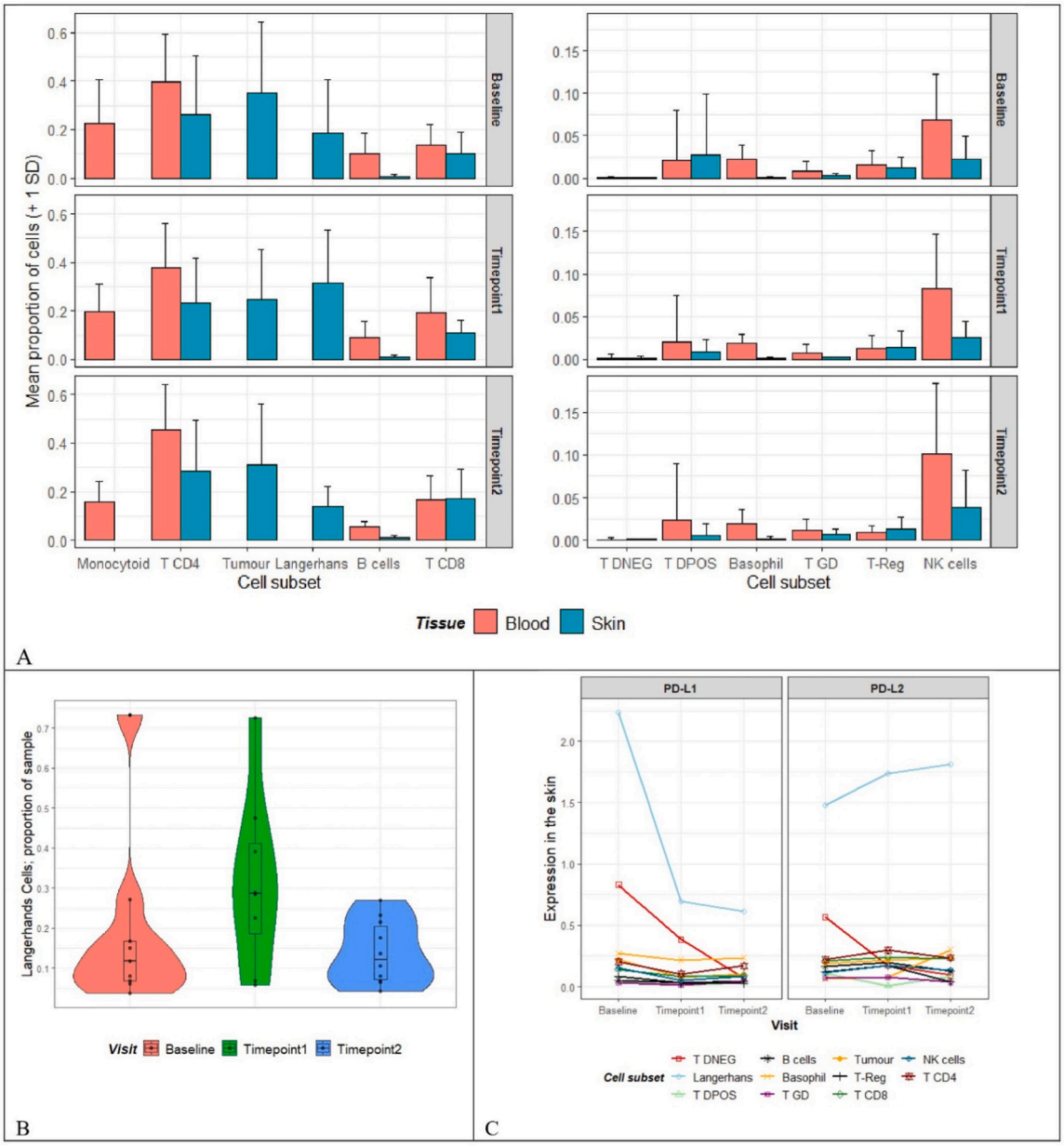

Fig. 3. (A): Mean proportions of the different cell subsets in blood and skin at the different assessment timepoints. (B): Expansions of Langerhans cell (LC) subset in skin occurs briefly following treatment. (C): PD-L1 detectable expression (median) decrease substantially with treatment, whereas PD-L2 expression did not. *Baseline; pre-treatment, Timepoint 1; day 5 (+/-1) of treatment cycle 1, Timepoint 2; day 1 (+/-1) of treatment cycle 2.

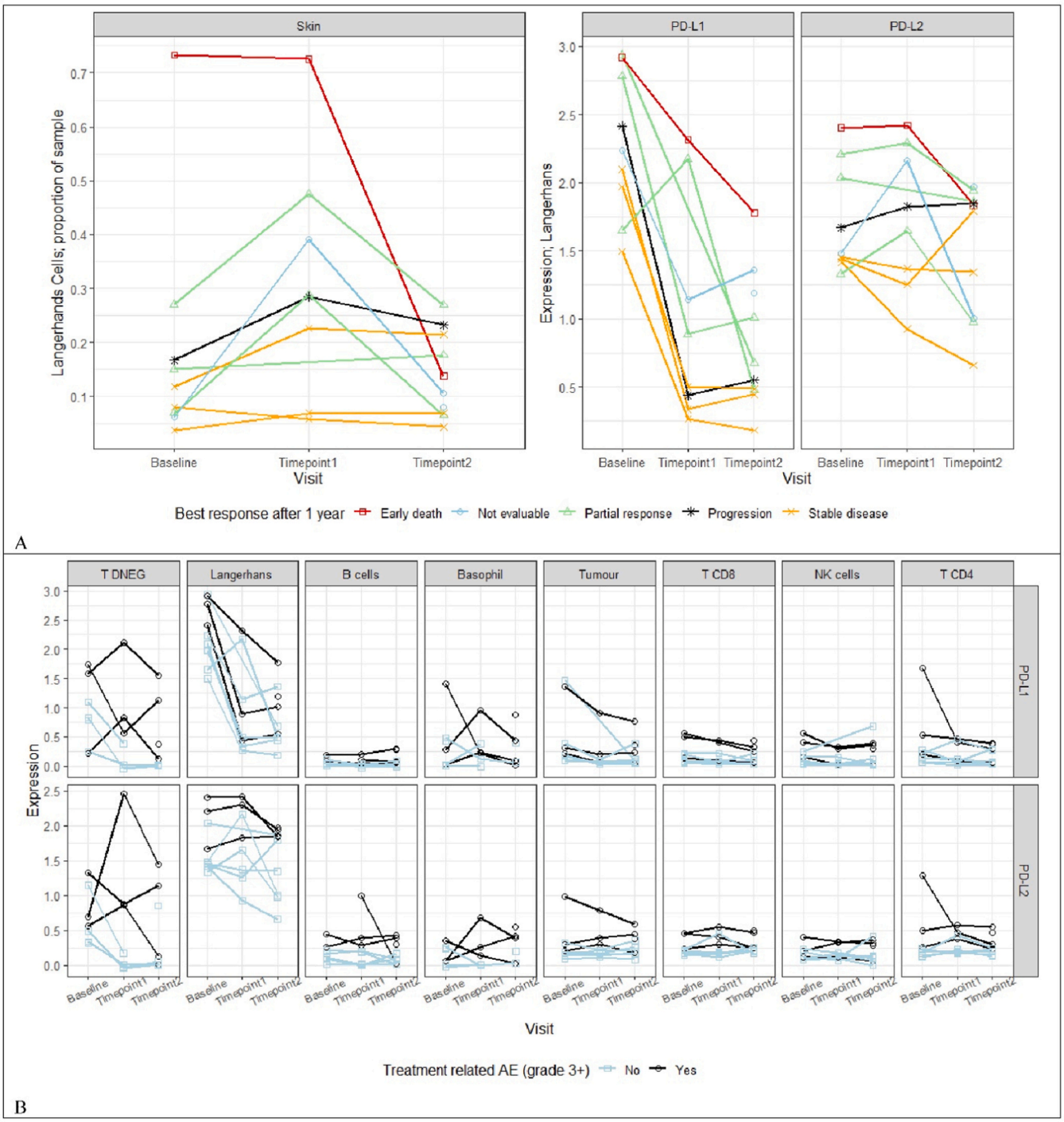

Fig. 4. (A): Proportion of Langerhans cell in the skin and PD-L1 and PD-L2 expression on Langerhans cell in the skin. (B): PD-L1 and PD-L2 expression by cell subset in skin by treatment related adverse event (AE) status (at least a grade 3 AE). *Baseline; pre-treatment, Timepoint 1; day 5 (+/-1) of treatment cycle 1, Timepoint 2; day 1 (+/-1) of treatment cycle 2.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115484.

References

[1] Quaglino P, et al. Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the cutaneous lymphoma international consortium. Ann Oncol 2019;30:494.

[2] Scarisbrick JJ, et al. Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and sézary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol 2015;33:3766–73.
[3] Prince HM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 2017;390:555–66.
[4] Kim YH, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 2018;19:1192–204.
[5] Hanel W, et al. A retrospective comparative outcome analysis following systemic therapy in mycosis fungoides and Sezary syndrome. Am J Hematol 2016;91.
[6] Quaglino P, et al. Phenotypical markers, molecular mutations, and immune microenvironment as targets for new treatments in patients with mycosis fungoides and/or sézary syndrome. J Invest Dermatol 2021;141:484–95.
[7] Stadler R, Hain C. New insights into the pathogenesis and molecular understanding of cutaneous T-cell lymphomas. Dermatology 2022;73:765–71.
[8] Dummer R, et al. Cutaneous T cell lymphoma. Nat Rev Dis Prim 2021;7.
[9] Roccuzzo G, et al. Immune check point inhibitors in primary cutaneous T-cell lymphomas: biologic rationale, clinical results and future perspectives. Front Oncol 2021;11:733770.
[10] Chang Y-T, et al. MHC-I upregulation safeguards neoplastic T cells in the skin against NK cell-mediated eradication in mycosis fungoides. Nat Commun 2024;15:752.
[11] Park J, et al. Integrated genomic analyses of cutaneous T-cell lymphomas reveal the molecular bases for disease heterogeneity. Blood 2021;138:1225–36.
[12] Ansell SM. Checkpoint Blockade in Lymphoma. J Clin Oncol 2021;39:525–33.
[13] Khodadoust MS, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and sézary syndrome: a multicenter phase II study. J Clin Oncol 2020;38:20–8.
[14] Sahni S, Valecha G, Sahni A. Role of anti-PD-1 antibodies in advanced melanoma: the era of immunotherapy. Cureus 2018;10:e3700.
[15] Sun C, Chen H, Wang Y, Zheng C. Safety and efficacy of PD-1 and PD-L1 inhibitors in relapsed and refractory Hodgkin's lymphoma: a systematic review and meta-analysis of 20 prospective studies. Hematology 2023;28:2181749.
[16] Caorsi I, Figueroa CD, Rodriguez EM. Morphologic and morphometric study of the two main cell lineages involved in mycosis fungoides: the lymphoid cells and the langerhans cells. Ultrastruct Pathol 1982;3:119–36.
[17] Pileri A, et al. Langerhans, plasmacytoid dendritic and myeloid-derived suppressor cell levels in mycosis fungoides vary according to the stage of the disease. Virchows Arch 2017;470:575–82.
[18] Murray D, et al. Progression of mycosis fungoides occurs through divergence of tumor immunophenotype by differential expression of HLA-DR. Blood Adv 2019;3:519–30.
[19] Kantekure K, et al. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. Am J Dermatopathol 2012;34:126–8.
[20] Herbst RS, et al. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. N Engl J Med 2020;383:1328–39.
[21] Olsen EA, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the international society for cutaneous lymphomas, the United States cutaneous lymphoma consortium, and the cutaneous lymphoma task force of the European organisation for research and treatment of cancer. J Clin Oncol 2011;29:2598–607.
[22] Iyer A, Hamers AAJ, Pillai AB. CyTOF(®) for the masses. Front Immunol 2022;13.815828–815828.
[23] Querfeld C, et al. Primary T cells from cutaneous T-cell lymphoma skin explants display an exhausted immune checkpoint profile. Cancer Immunol Res 2018;6:900–9.
[24] Cetinözman F, Jansen PM, Vermeer MH, Willemze R. Differential expression of programmed death-1 (PD-1) in Sézary syndrome and mycosis fungoides. Arch Dermatol 2012;148:1379–85.
[25] Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol 2016;34:2698–704.
[26] Barta SK, et al. Phase II study of the PD-1 inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma. Clin Lymphoma Myeloma Leuk 2019;19:356–364.e3.
[27] Bachy E, et al. Treating relapsed/refractory mature T- and NK-cell neoplasms with tislelizumab: a multicenter open-label phase 2 study. Blood Adv 2023;7:4435–47.
[28] Querfeld C, et al. Preliminary analysis demonstrates durvalumab (Anti-PD-L1) & lenalidomide is superior to single-agent durvalumab (anti-PD-L1) in refractory/advanced cutaneous T cell lymphoma in a randomized phase 2 trial. 3077–3077 Blood 2023;142. 3077–3077.
[29] Marchi E, et al. The Integration of PD1 blockade with epigenetic therapy is highly active and safe in heavily treated patients with T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). J Clin Oncol 2020;38. 8049–8049.
[30] van Gulijk M, et al. PD-L1 checkpoint blockade promotes regulatory T cell activity that underlies therapy resistance. Sci Immunol 2023;8.
[31] Beygi S, et al. Pembrolizumab in mycosis fungoides with PD-L1 structural variants. Blood Adv 2021;5:771–4.
[32] Saulite I, et al. Blockade of programmed cell death protein 1 (PD-1) in Sézary syndrome reduces Th2 phenotype of non-tumoral T lymphocytes but may enhance tumor proliferation. Oncoimmunology 2020;9:1738797. –1738797.
[33] Gao Y, et al. Hyperprogression of cutaneous T cell lymphoma after anti–PD-1 treatment. JCI Insight 2023;8.
[34] Phillips D, et al. Immune cell topography predicts response to PD-1 blockade in cutaneous T cell lymphoma. Nat Commun 2021;12:6726.