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Phenotypical Markers, Molecular Mutations, and Immune Microenvironment as Targets for New Treatments in Patients with Mycosis Fungoides and/or Sézary Syndrome

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Primary cutaneous lymphomas encompass a wide spectrum of rare lymphoproliferative disorders originating in the skin, among which, mycosis fungoides (MF) is the most common subtype. The treatment of this disease is based on skin-directed therapies eventually in association with biologic response modifiers in the early phases, whereas in patients with the advanced stages, several therapeutic strategies can be used including mono and/or polychemotherapy and bone marrow transplantation. In recent years, the identification of specific markers (phenotypical, immunological, and molecular) has led to the development of several studies (including two randomized phase III trials). The results of these studies are modifying our therapeutic strategy toward a personalized treatment approach in which the clinical characteristics of the patients and tumor-node-metastasis-blood stage are considered together with the expression of specific markers (i.e., a CD30-positive expression for the use of brentuximab vedotin). This review will provide a comprehensive scenario of the main phenotypical, molecular, and immunological markers related to MF pathogenesis and disease evolution, which could represent the target for the development of innovative effective treatments in this disease.

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Introduction

Primary cutaneous T-cell lymphomas (CTCLs) encompass a wide spectrum of rare lymphoproliferative disorders originating in the skin. Among them, mycosis fungoides (MF), the most common subtype (Campbell et al., 2010; Quaglino et al., 2012; Scarisbrick et al., 2019; Willemze et al., 2019), is an indolent CTCL clinically characterized by long-standing, scaly, patch lesions preferentially involving the buttocks and body areas infrequently exposed to sunlight (bathing trunk) and by a slow evolution over years from patches to plaques (early stage) and eventually tumors or erythroderma (advanced stage). Lymph node and visceral involvement, as well as large cell transformation, usually occur in the late stages (Pimpinelli et al., 2005; Willemze et al., 2019) (Figure 1). Sézary syndrome (SS) is the erythrodermic and leukemic variant in the CTCL spectrum. In recent years, specific phenotypical features and molecular mutations, which characterize each tumor type related to the growth and spreading, have been identified. Moreover, it has become clear that immunological host response plays a major role in modulating disease evolution and that immune mechanisms develop through definite immunological synapses able to upregulate or downregulate the response. This review will provide an update of the main phenotypical, molecular, and immunological markers identified in the literature as involved in the pathogenesis and disease evolution of MF and/or SS, focusing on those representing the target of innovative drugs.

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Abbreviations: Akt, protein kinase B; CR, complete response; CTCL, cutaneous T-cell lymphoma; DC, dendritic cell; EMA, European Medicines Agency; FDA, Food and Drug Administration; HDAC, histone deacetylase; MAVORIC, mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma; MDSC, myeloid-derived suppressor cell; MF, mycosis fungoides; miRNA, micro RNA; NFAT, nuclear factor of activated T cell; ORR, overall RR; ORR4, ORR of at least 4 months; PI3K, phosphoinositide 3-kinase; RR, response rate; SC, Sézary cell; SS, Sézary syndrome; STAT, signal transducer and activator of transcription; Th, T helper; Treg, regulatory T cell

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Phenotypical diagnostic markers

Neoplastic T cells present a characteristic post-thymic phenotype, helper cells (CD4+ and CD8-), with features of memory cells (CD4+, CD45RO+, CD45RA-; CD4+, CD29+, CD45RA-) (Bernengo et al., 1998; Bogen et al., 1996; Harmon et al., 1996; Rappl et al., 2001; Sterry and Mielke, 1989; Vonderheid et al., 1994; Worner et al., 1990) (Figure 2). Aberrant phenotypes are described in the literature as well as the loss of T-cell markers (especially CD2), usually associated with a worse prognosis (Bernengo et al., 1998; Bogen et al., 1996; Harmon et al., 1996; Rappl et al., 2001; Sterry and Mielke, 1989; Van der Putte et al., 1988; Vonderheid et al., 1994; Worner et al., 1990). The loss of CD7 has been described as a specific feature (Bernengo et al., 1998; Harmon et al., 1996; Haynes et al., 1981; Vonderheid et al., 1994; Wood et al., 1990), even if accumulating evidence supports the view that 10–40% of cases present with CD7+ circulating Sézary cells (SCs) (Bernengo et al., 2001, 1998; Laetsch et al., 2000; Novelli et al., 2015; Vonderheid and Hou, 2018; Yagi et al., 1996). A relevant immune-phenotypical feature is the constant loss of CD26, first described by the Turin group in both the skin and peripheral blood (Bernengo et al., 2001, 1998; Novelli et al., 2015, 2003; Yagi et al., 1996) and later confirmed by several authors (Hristov et al., 2011; Jones et al., 2001; Nagler et al., 2012; Narducci et al., 2006; Sokolowska-Wojdylo et al., 2005) and recently also confirmed in a multicenter European study (Boonk et al., 2016).

CD30. CD30 is a cell membrane protein of the TNF receptor family; it is expressed by activated, but not by resting, T and B cells. As to CTCL, it can be expressed in a percentage

of MF (10–15%), especially in the presence of large cell transformation. Moreover, it is constitutively expressed in the group of CD30+ lymphoproliferative disorders (Kempf et al., 2011). The ALCANZA trial (Prince et al., 2017) was a randomized, phase III, multicenter trial enrolling adult patients with CD30-positive MF or primary cutaneous anaplastic large-cell lymphoma who had been previously treated. Patients were randomly assigned (1:1) to receive brentuximab vedotin or physician's choice (methotrexate or bexarotene). This study had a new primary endpoint defined as the proportion of patients achieving a global response lasting at least 4 months (overall response rate [ORR] of at least 4 months [ORR4]). Among a total of 128 patients, ORR4 was significantly higher in the brentuximab group (56.3%) than in the physician's choice (12.5%). According to the subtypes of patients, the drug showed higher activity in patients with CD30+ anaplastic large-cell lymphoma and, among patients with MF, in those at tumor stage.

CD47. CD47 belongs to the immunoglobulin superfamily as a heavily glycosylated protein and was found overexpressed in hematological and solid tumors. CD47 is a protective signal for tumor cells (do-not-eat), inhibiting the phagocytosis of tumor cells by macrophages and other myeloid cells. A novel promising agent targeting CD47 is the fusion protein SIRPαFc (TTI-621), which activates macrophages, neutralizing the inhibitory effect of CD47. CD47 has been shown to be highly expressed on SCs in the peripheral blood and skin; the expression levels of this marker would correlate with a poor outcome (Johnson et al., 2019). A phase I clinical trial is evaluating the safety and tolerability of intralesional different dosages of anti-CD47 antibody

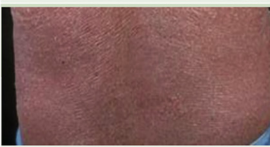
	Clinics	Stage	T	N	M	B	Definition	Median Sur (y)	10-y OS (%)
EARLY-STAGE		IA	T1	N0	M0	B0-1	Patches (T1a) or plaques (T1b) < 10% body surface area	35.5	80–100
		IB	T2	N0	M0	B0-1	Patches (T2a) or plaques (T2b) > 10% body surface area	21.5	58–75
		IIA	T1-T2	N1-N2	M0	B0-1	Nodal enlargement without histological involvement	15.8	45–52
ADVANCED-STAGE		IIB	T3	N0-2	M0	B0-1	Skin tumours	4.7	20–39
		IIIA	T4	N0-2	M0	B0	Erythroderma with no blood involvement	4.7	20–40
		IIIB	T4	N0-2	M0	B1	Erythroderma with low tumor burden in the blood	3.4	25
	EXTRACUTANEOUS INVOLVEMENT	IVA1	T1-4	N0-2	M0	B2	Blood involvement	3.8	18
		IVA2	T1-4	N3	M0	B0-2	Nodal involvement	2.1	15
		IVB	T1-4	N0-3	M1	B0-2	Visceral involvement	1.4	NR

Figure 1. Staging classification of MF with survival median (y) and 10-y OS. B, blood; M, visceral metastasis; MF, mycosis fungoides; N, nodes; NR, not reached; OS, overall survival; T, skin; y, year.

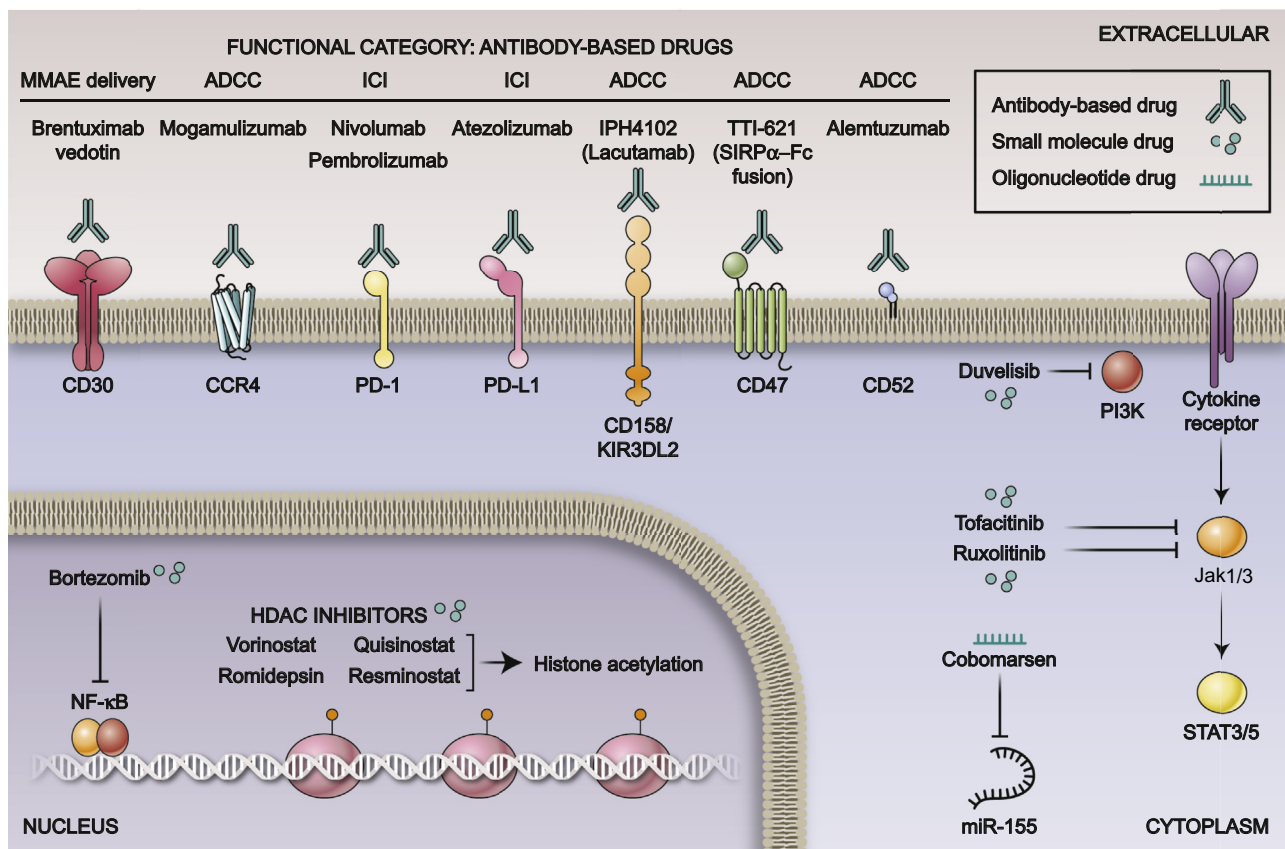


Figure 2. Molecular targets of the main drugs. ADCC, antibody-dependent, cell-mediated cytotoxicity; HDAC, histone deacetylase; ICI, immune checkpoint inhibitor; MMAE, Monomethyl Auristatin E; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

(TTI-621) in patients with refractory and/or relapsing CTCL (NCT02890368), showing in first reports a favorable safety profile and an interesting clinical activity (Querfeld et al., 2017).

CD52. CD52 is a low molecular weight phosphatidylinositol-linked glycoprotein that is expressed by most mature lymphocytes and monocytes. CD52 is recognized by alemtuzumab (Campath-1H), a humanized IgG1 antibody. Alemtuzumab induces apoptosis and cytotoxicity through the activation of complement and antibody-dependent cellular cytotoxicity (Jiang et al., 2009). Previous studies supported the clinical activity of alemtuzumab, which appeared to also be maintained when reduced dosages were used to lower the high risk of infectious complications (Bernengo et al., 2007). In a systematic review, alemtuzumab was shown to be an effective agent for SS, showing 81% ORR and 38% complete response (CR) but is less effective for MF. The authors, despite some concerns regarding the severe toxicity with high infection rate and hematological effects, suggest the use of low-dose alemtuzumab as a third-line treatment for SS (Stewart et al., 2018).

CCR4. CCR4 is a marker of skin-homing T cells. Ferenczi et al. (2002) found significantly increased percentages of T cells displaying the skin-homing phenotype (CLA+CCR4+) compared with those in healthy individuals in the blood of patients with CTCL. The T cells expressing CLA and CCR4 were also found at high levels in CTCL lesions along with an

abundant expression of the CCR4 ligands CCL17 (TARC) and CCL22 (MDC). The overexpression of skin-homing T-cell markers offers a potential explanation for the preferential accumulation of these T cells in the skin. CCR4 is predominantly expressed by T helper (Th) 2 cells, thus confirming the relationship within the Th2 pattern and CTCL cells (Ferenczi et al., 2002).

The mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC) trial (Kim et al., 2018) was a phase III randomized trial comparing the anti-CCR4 antibody mogamulizumab with vorinostat. Patients enrolled were patients with MF and/or SS stage Ib/IV already treated with at least one systemic therapy. The study met its objective, demonstrating a significantly higher progression-free survival in the mogamulizumab arm than in vorinostat arm (median 7.7 vs. 3.1; $P < 0.0001$). In addition, the response rate (RR) was significantly higher (28% vs. 5%). The highest RR was achieved in patients with SS (37%) and in the blood (68%). The median duration of responses was 25.5 months in the blood and 20.6 months in the skin.

CD158k. This molecule (Poszepczynska-Guigné et al., 2004) belongs to the family of immunoglobulin-like receptors and is normally present in a proportion of circulating NK cells and CD8+. In SS and transformed MF, CD158k (also known as KIR3DL2) is preferentially expressed on neoplastic T cells where it can be used as a diagnostic marker (Bahler et al., 2008; Ortonne et al., 2012; Roelens et al., 2020).

CD158k has an inhibitory function on neoplastic T cells, where it downregulates CD3-dependent signaling and is implicated in the maintenance of a high circulating malignant-cell burden by preventing activation-induced cell death (Bagot, 2017).

IPH4102 is a humanized mAb that blocks the CD158k receptor and induces antibody-dependent cell cytotoxicity and phagocytosis (Marie-Cardine et al., 2014). Recently, the results of an international, open-label, phase I, multicenter study evaluating IPH4102 in relapsed and/or refractory CTCL were reported (Bagot et al., 2019). This study showed the favorable safety profile of the drug (primary endpoint of this phase I trial), coupled with a potentially relevant clinical activity. Indeed, the most common adverse events were grades 1–2 peripheral edema (27%) and asthenia and fatigue (20%). As to clinical activity, the treatment-induced significant RRs in SS, that is, global and blood response, were 42.9% and 55.9%, respectively, and the median response duration was 13.8 months.

Aberrant molecular findings and driver mutations

A series of studies have identified multiple molecular changes in CTCL (Abraham et al., 2011; Horwitz et al., 2018; Krejsgaard et al., 2006); the majority of the studies were directed at advanced stages of MF, including SS, but some of them were also directed at early stages. Taken together, these studies showed a heterogeneous landscape with a large number of genetic alterations summarized in Table 1. Molecular mutations could be found more frequently in the pathways of epigenetic and/or chromatin regulation, TCR and T-cell/ cytokine signaling, Jak/signal transducer and activator of transcription (STAT), and phosphoinositide 3-kinases (PI3K)/protein kinase B (Akt) and NF- κ B pathway. Nearly all the studies reported alterations in *TP53*. Less frequently affected pathways are represented by the MAPK and NOTCH pathway.

Park et al. (2017) performed in 2017 a meta-analysis search identifying nine studies with a total of 220 CTCLs mutational data, finding 55 putative driver genes, 17 of which were not previously implicated in CTCL. Importantly, 43% of CTCL harbor potentially targetable point mutations. Among the group of chromatin modification genes, the most frequently found are *DNMT3A*, *NCOR1*, *ARID1A*, and *SETDB2* as tumor suppressor genes. Among putative oncogenes, the most frequently mutated belong to the T-cell activation/NF- κ B pathway and Jak/STAT pathway (STAT3 60% and STAT5B 60%).

Recent massive parallel sequencing data have shown that patients with SS are characterized by *TP53* alterations as a prevalent genetic abnormality. Gros et al. (2017) recently confirmed these data showing *TP53* mutations and/or deletions in 83% of patients with SS studied. Aberrant gene expression in SS samples was analyzed in a European multicenter study by Boonk et al. (2016). With respect to patients with erythrodermic inflammatory dermatosis and healthy control samples, patients with SS were characterized by copy number alterations in *MYC* (gain) and/or *MNT* (loss); increased expression of *DNM3*, *TWIST1*, *EPHA4*, and *PLS3*; and increased expression of *STAT4*. In a whole-exome sequencing analysis comparing SS with other CTCLs,

patients with SS showed a distinctive pattern of somatic copy number alterations, including highly prevalent chromosomal deletions (*TP53*, *RB1*, *PTEN*, *DNMT3A*, and *CDKN1B* tumor suppressors), and a broad spectrum of somatic mutations in key genes involved in epigenetic regulation and signaling, including *MAPK1*, *BRAF*, *CARD11*, and *PRKG1* mutations driving increased MAPK, NF- κ B, and nuclear factor of activated T cell (NFAT) activity (da Silva Almeida et al., 2015).

Gene expression profile studies have also been used to identify molecular markers related to a higher risk of disease progression from early to MF advanced phases. Lefrançois et al. (2018) identified TOX, FYB, CCR4, and CD52 as disease progression and decreased survival biomarkers in CTCL. Pérez et al. (2020), using immunohistochemistry and genomics, demonstrated that STAT3 is activated in advanced cases of MF. They also found that STAT3 is associated with large-cell transformation, whereas NFAT and NF- κ B alterations are maintained throughout the disease (Pérez et al., 2020).

Jak/STAT signaling pathway is implicated in CTCL pathogenesis (Netchiporouk et al., 2014), with overexpression of STAT4 in early-stage MF (Litvinov et al., 2014). STAT4 is activated by IL-12 through Jak2 and tyrosine kinase 2 and regulates Th1 differentiation. In the late MF and/or SS stage, when the disease develops a predominantly Th2 phenotype, STAT4 is downregulated (Showe et al., 1999). In the advanced stage of the disease, STAT3 is overexpressed. STAT3 can be activated by cytokines such as IL-2, IL-6, IL-7, IL-9, IL-10, IL-15, and in particular IL-21, which has an autocrine stimulation (Van der Fits et al., 2012a). The constitutive expression of STAT3 in MF advanced stages leads to increased survival of T cells that become resistant to apoptosis (Nielsen et al., 1999). It also promotes the Th2, induces the expression of cytokines involved in eosinophilia and erythroderma (Abraham et al., 2011), and upregulates VEGF and IL-10. The role of the Jak/STAT signaling pathway in the pathogenesis of CTCL is also confirmed by whole-genome sequencing.

To date, any of the drugs targeting molecular markers have been approved for therapeutic use in MF. However, trials with a small number of patients have suggested the potential clinical activity of some of these targeted drugs. A phase II trial reported the results for duvelisib, a PI3K- δ and/or PI3K- γ inhibitor, in a cohort of 19 patients with CTCL with 31.6% RR (Horwitz et al., 2018). Bortezomib (NF- κ B inhibitor) was analyzed in a small group of 12 patients with CTCL; the RR was 67%, all responses were reported as durable, and the drug was well-tolerated (Zinzani et al., 2007). Another phase II trial reported the activity of alisertib, an oral inhibitor of the aurora A kinase, a mitotic serine/threonine kinase whose expression is upregulated in highly proliferating lymphomas. The trial enrolled 37 patients with peripheral T-cell lymphoma, including seven with transformed MF; the ORR was 30%, but no responses were achieved in MF (Barr et al., 2015).

Among the group of therapies against molecular targets, histone deacetylase (HDAC) inhibitors have received Food and Drug Administration (FDA) approval but not European Medicines Agency (EMA) approval. Two drugs have been mainly investigated, vorinostat and romidepsin. In two phase II trials (Duvic et al., 2007; Olsen et al., 2007), vorinostat induced responses in <30% of patients, with only one

Table 1. Summary of Main Somatic Mutations Reported by Genomic Studies in CTCLs, Divided According to their Functional Role and Pathway Belongings

Somatic Mutations								
Epigenetic regulation	<i>DNMT3A</i> , <i>ASXL3</i> , <i>TET1-3</i> (Woollard et al., 2016)	<i>MLL2</i> , <i>SETD1A</i> , <i>RNF20</i> (McGirt et al., 2015)	<i>BCOR</i> , <i>KDM6A</i> , <i>SMARCB1</i> , <i>TRRAP</i> (Park et al., 2017)	<i>TET2</i> , <i>CREBBP</i> , <i>KMT2D</i> (<i>MLL2</i>), <i>KMT2C</i> (<i>MLL3</i>), <i>BRD9</i> , <i>SMARCA4</i> , <i>DNMT3A</i> , <i>CHD3</i> (da Silva Almeida et al., 2015)	<i>ARID1A</i> (Kiel et al., 2015)	<i>ARID1A</i> , <i>CTCF</i> , <i>DNMT3A</i> (Choi et al., 2015)	<i>DOT1L</i> , <i>KDM6A</i> , <i>LIFR</i> (Bastidas Torres et al., 2018)	<i>ARID1A</i> <i>RP56KA1</i> (Wang et al., 2015)
Chromatin regulation	<i>TOX</i> (Lefrançois et al., 2018)	<i>POT1/ATM</i> (chromosome instability) (Woollard et al., 2016)	<i>RAD51C</i> , <i>BRCA2</i> , <i>POLD1</i> (DNA repair) (Woollard et al., 2016)	<i>ATM</i> (Choi et al., 2015)	<i>MYC</i> , <i>MNC</i> , <i>TWIST1</i> (Boonk et al., 2016)			
Receptor-mediated tyrosine kinase mediators	<i>PLCG1</i> (Choi et al., 2015; Kiel et al., 2015; Pérez et al.,2020; Ungewickell et al., 2015; Vaqué et al., 2014; Wang et al., 2015; Woollard et al., 2016)	<i>ITPR1</i> , <i>ITPR2</i> , <i>RIPK2</i> (Prasad et al., 2016)	<i>EPHA4</i> (Boonk et al., 2016)					
T-cell and/or cytokine and/or immune suppression	<i>CCR4</i> , <i>CARD11</i> , <i>ZEB1</i> (Wang et al., 2015)	<i>FYB</i> , <i>CCR4</i> , <i>CD52</i> (Lefrançois et al., 2018)	<i>ZEB1</i> (Caprini et al., 2018; Choi et al., 2015; McGirt et al., 2015; Prasad et al., 2016)	<i>CD58</i> , <i>RFXAP</i> (Park et al., 2017)				
TCR signaling	<i>NFAT</i> (da Silva Almeida et al., 2015; Pérez et al., 2020)	<i>PTPRN2</i> , <i>RLTPR</i> , <i>RARA</i> (Park et al., 2017)	<i>TCR</i> clonotypes (Iyer et al., 2019a)	<i>CTLA4/CD28</i> (Ungewickell et al., 2015)	<i>CBLB</i> , <i>RASA2</i> , <i>BCL7C</i> , <i>RAMP3</i> , <i>TBRG4</i> , <i>DAD1</i> , <i>RAG2</i> (Prasad et al., 2016)	<i>PRKCQ</i> (Woollard et al., 2016)	<i>CD28</i> (Choi et al., 2015)	
Jak/STAT pathway	<i>Jak3</i> (McGirt et al., 2015)	<i>Jak/STAT3</i> (Pérez et al., 2020)	<i>SOCS1</i> (Bastidas Torres et al., 2018)	<i>Jak1</i> , <i>Jak3</i> , <i>STAT3</i> , <i>STAT5B</i> (Kiel et al., 2015)	<i>STAT5B</i> (Choi et al., 2015)	<i>STAT4</i> (Boonk et al., 2016)	<i>HNRNPK</i> , <i>SOCS1</i> (Bastidas Torres et al., 2018)	
MAPK	<i>KRAS/NRAS</i> (Kiessling et al., 2011)	<i>KRAS</i> (Yanagi et al., 2017)	<i>MAP2K1</i> , <i>NF1</i> (Park et al., 2017)	<i>MAPK1</i> , <i>BRAF</i> , <i>CARD11</i> , <i>PRKG1</i> (da Silva Almeida et al., 2015)	<i>BRAF</i> (Choi et al., 2015)			
PI3K/Akt pathway	<i>PTEN</i> , <i>RB1</i> (Caprini et al., 2018)	<i>PI3KR6</i> , <i>PI3KCD</i> , <i>VAV1</i> (Ungewickell et al., 2015)	<i>CDKN2A</i> (Bastidas Torres et al., 2018)	<i>PIK3R1</i> , <i>VAV1</i> (Park et al., 2017)	<i>RB1</i> , <i>PTEN</i> , <i>CDKN1B</i> (da Silva Almeida et al., 2015)	<i>CDKN2A</i> (Wang et al., 2015)	<i>CDKN2A</i> , <i>CDKN2B</i> , <i>VAV1</i> (Bastidas Torres et al., 2018)	
NF-κB pathway	(da Silva Almeida et al., 2015; Pérez et al., 2020)	<i>PRKCB</i> , <i>CSNK1A1</i> (Park et al., 2017)	<i>NFKB2</i> , <i>TNFRSF1B</i> , <i>TNFR2</i> (Ungewickell et al., 2015)	<i>NFKB2</i> (Prasad et al., 2016)	<i>NFKB2</i> , <i>TNFAIP3</i> , <i>PRKCQ</i> , <i>IRF4</i> (Choi et al., 2015)			
NOTCH pathway	<i>NOTCH1</i> (Gallardo et al., 2015)	<i>NOTCH2</i> (McGirt et al., 2015)	<i>NOTCH1</i> , <i>NOTCH2</i> , <i>JAGGED</i> (Van der Fits et al., 2012b)					
Cytoskeleton regulation	<i>RHOA</i> (Choi et al., 2015; Park et al., 2017;)	<i>DNM3</i> , <i>PLS3</i> (Boonk et al., 2016)						

Abbreviations: Akt, protein kinase B; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

complete remission but with a marked improvement in pruritus in more than half of the patients. However, the clinical activity of vorinostat in the MAVORIC trial (Kim et al., 2018), as evaluated in a phase III trial with strict modern response criteria, was lower (7%). Two phase II trials have evaluated romidepsin in advanced-stage MF (Duvic et al., 2018; Whittaker et al., 2010), with an RR of 36% and a promising median duration of response of 15 months. An ongoing trial is evaluating the maintenance activity of another HDAC inhibitor (resminostat): resminostat for T-cell lymphoma of the skin is a phase III multicenter, double-blind, randomized trial versus placebo enrolling patients with MF and/or SS stage IIb–IV in response or stable disease after a previous therapy (NCT02953301).

MicroRNAs

MicroRNAs (miRNAs) are noncoding RNAs (20–25 nucleotides long, typically) that regulate post-transcriptional gene expression—through homologous base pairing with the 3' untranslated regions—of specific mRNA targets. This binding blocks mRNAs' translation into proteins. MiRNA–mRNA interactions can promote mRNA degradation and inhibit the translation of many genes; miRNAs can interact approximately with more than one third of human genes, enabling them to regulate the entire pathways (Lewis et al., 2005).

In recent years, it has been reported that miRNAs participate in CTCL pathogenesis and progression, serving also as biomarkers (Querfeld, 2019; Sandoval et al., 2015; Seto et al., 2018; Shen et al., 2018). The upregulation of miR-21, miR-486, and miR-214, for example, are recurrent findings in patients with SS. MF tumors, instead, are typified by increased expression of miR-146a, miR-142-3p and/or -5p, miR-21, miR-181a and/or b, and miR-15573,74. Moreover, miR-155 appears to be highly expressed also in patients with SS, compared with the expression in healthy patients and in patients with MF (Fava et al., 2017).

MiR-155 is one of the most studied miRNAs in oncology (Fava et al., 2017; Querfeld, 2019; Rodríguez et al., 2007; Sandoval et al., 2015; Seto et al., 2018; Shen et al., 2018; Tensen and Vermeer, 2017).

MiR-155 is transcribed from the *MIR155HG* gene, located on chromosome 21. This specific miRNA regulates pathways linked to immune cell function and cell proliferation and survival pathways; some groups reported that an upregulation of miR-155 expression can lead to a constitutive activation of Jak/STAT, NF-κB, and PI3K-Akt pathways. The miR-155 mechanism could be attributed to caspase-3 activity blockage. Overexpression of miR-155 decreases TP53INP, which is a nuclear protein for cell cycle arrest and revolution through caspase-3 activation. The pharmacological inhibition of the c-Jun N-terminal kinase pathway shows a perspective in miR-155 levels, suggesting that the sequence is involved in this signaling pathway, along with that of MAPK.

As to treatment approaches, positive updated data have been reported from a phase I trial assessing the safety, tolerability, and efficacy of cobomarsen (MRG-106, an oligonucleotide inhibitor of miR-155) for the treatment of CTCL and adult T-cell leukemia and/or lymphoma. Cobomarsen is currently being evaluated in a phase II study of patients with MF to characterize the safety profile, pharmacokinetics, and

initial efficacy of this miR-155 inhibitor (the so-called SOLAR trial [NCT03713320]) (Seto et al., 2018).

Immune microenvironment

Th subsets, cytokines, and dendritic cells in MF and/or SS. The interaction between tumor cells and microenvironment is one of the mechanisms involved in the progression from early to advanced MF stages. In the early phases, the neoplastic cells are few and intermingled in a dense reactive infiltrate consisting of Th1 and CD8+ antitumor cells (Chen et al., 2015; DeSimone et al., 2015; Krejsgaard et al., 2017; Miyagaki and Sugaya, 2014). Neoplastic cells however acquire the ability to orchestrate a change in the microenvironment cellular composition, shifting from an antitumor (Th1) to a tumorigenic (Th2) response (Krejsgaard et al., 2017). Such changes lead to (i) increase in immunosuppressive cytokine release (IL-4, IL-10, IL-13) by tumor-associated and neoplastic cells, sustaining tumor growth and spread; (ii) accumulation of immature and depletion of mature dendritic cells (DCs), leading to tolerance and immune suppression; (iii) increase in (lymph) angiogenic factors cells (Chen et al., 2015; DeSimone et al., 2015; Karpova et al., 2011; Krejsgaard et al., 2017). A decrease in STAT4 coupled with STAT5 overexpression (Kopp et al., 2013) may lead to an increase in immunosuppressive cytokine release (IL-4, IL-10, IL-13) and decrease in Th1 cytokine release (IFN-γ) with an accumulation of immature DCs. DCs are antigen-presenting cells with a double-sided function (Banchereau and Steinman, 1998; Fujii, 2018), prompting immune response at mature state while inducing tolerance at an immature state. Different authors (Der-Petrossian et al., 2011; Lüftl et al., 2002; Pileri et al., 2017; Schlapbach et al., 2010; Schwingshackl et al., 2012; Zhang et al., 2014) investigated the role of DCs in MF, observing an increase in different immature DC subsets with respect to inflammatory and/or healthy donor skin. Furthermore, two distinct groups correlated different DC changes with disease progression (Pileri et al., 2017; Zhang et al., 2014). Consequently, an increase in immunosuppressive cytokine release may occur, leading to an increase in the recruitment of immunosuppressive cells from blood vessels, such as myeloid-derived suppressor cells (MDSCs). MDSCs' physiologic function is to suppress autoreactive T cells (Bronte and Zanovello, 2005; Gabrilovich and Nagaraj, 2009; Rodríguez and Ochoa, 2008). A recent study suggested their potential role in MF progression, with an increased number in tumors compared with that in early lesions (Pileri et al., 2017).

PD-1/PD-L1 axis and other immune markers in MF and/or SS.

In patients with MF and/or SS, immune checkpoint molecules are interesting diagnostic and prognostic markers for several reasons: (i) in both, the presence of local and systemic immunosuppression is well-characterized during disease progression (Krejsgaard et al., 2012); (ii) high numbers of tumor-infiltrating CD8+ T cells are associated with improved survival (Hoppe et al., 1995; Vermeer et al., 2001; Vonderheid et al., 2014); and (iii) finally, immune checkpoint-related genes are often altered in tumors of patients with MF and SS, supporting the development of immune evasion strategies (Ungewickell et al., 2015). PD-1 and

its ligands (PD-L1 and PD-L2) are currently the best-characterized and exploited immune checkpoint molecules. PD-1 mediates the inhibitory signals that block T-cell activation and proliferation (Zou et al., 2016). In different cancers, tumor-infiltrating T cells express high levels of PD-1 and are functionally impaired (Zou et al., 2016). Antibodies blocking PD-1 can partially restore PD-1+ T-cell function and are clinically effective in different malignancies (Topalian et al., 2015; Wong et al., 2007).

In patients with MF and SS, circulating and skin-infiltrating T cells express high levels of PD-1 (Cetinözman et al., 2012; Samimi et al., 2010). This high PD-1 expression can be used to differentiate patients with SS from patients affected by other erythrodermic inflammatory dermatoses (Klemke et al., 2015). Higher levels of the ligand PD-L1 have also been detected in MF lesions, where the expression seems to increase with lymphoma progression and correlate with an enhanced immunosuppressive microenvironment (Kantekure et al., 2012).

PD-1 and/or PD-L1 expression can however also be found in other T-cell subsets. Indeed, PD-1 can be expressed on regulatory T cells (Tregs), playing a role of a negative Treg cell mediator. PD-1 blockade could therefore enhance the suppressive functions of Treg cells, thus hindering immune surveillance against the cutaneous lymphoma rather than stimulating (Togashi et al., 2019). The scenario is even more complicated if considering that tumor cells in MF and/or SS have been reported to present in some cases a Treg phenotype (Clark, 2009) and have been shown to be able to suppress T-cell proliferation *in vitro*. PD-1 expression is also associated with the so-called exhausted phenotype characterized by an impaired T-cell response behavior, upregulation of inhibitory molecules, and decreased production of effector cytokines and cytotoxic activity (Davoodzadeh Gholami et al., 2017). Indeed, both tumor-infiltrating lymphocytes and tumor cells from patients with MF and/or SS were found to potentially present an exhausted PD-1-positive phenotypes, thus implying a reduction in immune surveillance and adoption of escape phenotypical profiles (Murray et al., 2019). The high PD-1 expression found in CTCLs led to clinical studies exploring the use of anti-PD-1 antibodies in patients with MF and/or SS. In a phase I, open-label, dose-escalation, cohort-expansion basket trial enrolling 81 patients, 13 heavily pretreated patients with MF received nivolumab. The RR was 15%, lower than that achieved in the other diseases (from 36% to 40%). Drug-related adverse events occurred in 63% of the patients, most of them were grade 1 or 2; the duration of responses ranged up to 81 weeks (Lesokhin et al., 2016). In a phase II clinical trial, anti-PD1 was performed in 24 patients with MF and/or SS (Khodadoust et al., 2020) with advanced-stage disease (23 of 24 with stage IIb–IV) and heavily pretreated (median of four prior systemic therapies). Nine out of 24 patients (38%) responded (two CRs and eight partial responses), and eight had durable responses. Immune-related adverse events led to treatment discontinuation in four patients. A transient worsening of erythroderma and pruritus occurred in 53% of the patients with SS, however not resulting in treatment discontinuation. A European Organisation for Research and Treatment of Cancer phase II trial of atezolizumab (anti-PD-L1)

(PARCT: trial of atezolizumab in relapsed and/or refractory CTCL) in the treatment of patients with relapsed and/or refractory stage IIb–IV MF and/or SS (NCT03357224) is ongoing as well as another PD-L1 inhibitor (durvalumab) currently being evaluated in a clinical phase I and/or II trial in patients with advanced CTCL (NCT03011814). The results are encouraging, especially in terms of response duration, even if anti-PD1 blockade seems to give less favorable results in CTCL than in other solid tumors or hematological malignancies.

The therapy of MF and/or SS from the bench to the bedside

The treatment of MF and/or SS is stage based: the early-stage disease is mainly treated by skin-directed therapies, whereas the advanced-stage disease is treated with systemic therapies, including chemotherapy and allogeneic bone marrow transplantation (Quaglino et al., 2017; Trautinger et al., 2017). In the past years, the main recent achievements in terms of molecular alteration and immune pathogenesis were translated from the laboratory to the bed in terms of new therapeutic approaches able to improve the disease outcome (Table 2), and a relevant number of trials have been conducted to ascertain their clinical activity.

The majority of them were phase I or II with a small number of patients, but two were phase III randomized and led to the approval of two new drugs (Kim et al., 2018; Prince et al., 2017). Brentuximab vedotin, an anti-CD30 antibody-drug conjugate, received extended approval by the US FDA in 2017 to include primary cutaneous anaplastic large-cell lymphoma and CD30-expressing MF (Prince et al., 2017). Mogamulizumab, an anti-CCR4 antibody, received FDA approval in 2018 for relapsed or refractory MF and SS. Both drugs also received EMA approval (Kim et al., 2018). Besides these compounds, a series of phase I and II trials supported the potential role of other drugs targeting either immunomodulating pathways (i.e., anti-PD1 axis) or phenotypical and/or molecular targets. None of these drugs is still available for clinical use outside clinical trials.

However, the molecular pathogenesis of MF and/or SS on the basis of the recent data implies an integrated and comprehensive approach in terms of precision medicine. Indeed, MF and SS are characterized by an extensive intra-tumor heterogeneity, which increases in progressive disease with the divergent evolution of cancer subclones. This pathogenetic model implies a high variability in the pattern of clonal driver mutations in different patients as well as in the same patients in different phases of the disease (Iyer et al., 2020). Moreover, it has been suggested that cutaneous MF lesions could be repeatedly replenished by circulating neoplastic T-cell clones, which would determine a continuous modulation of the mutation patterns, thus increasing the molecular heterogeneity using a mechanism similar to the consecutive tumor seeding (Iyer et al., 2019b). From a clinical point of view, there should be a need for repeated molecular analyses in different disease sites and at different time point to characterize the disease evolution from a molecular point of view and thus be able to identify the adequate targeted treatment.

Therefore, we need to identify molecular markers associated with disease course as well as new therapies able to

Table 2. Summary of the Results from the Main Studies with New Drugs in CTCL

Target	Drug	Phase	No. of Pts	Inclusion	ORR	Disease Outcome	Drug Approval
CD30	Brentuximab vedotin	III randomized vs. best clinical choice (Bexarotene or methotrexate) (Prince et al., 2017)	128	CD30-positive MF or primary cutaneous anaplastic large-cell lymphoma	56.3% vs. 12.5% (ORR4); MF IIb: 63%; CD30+ anaplastic: 75%	Median PFS:16.7 vs. 3.5 mo	FDA and/or EMA
CCR4	Mogamulizumab	III randomized vs. vorinostat (Kim et al., 2018)	372	MF and/or SS stage Ib–IV with at least one systemic therapy.	28% vs. 5%; RR in SS is 37%; 68% in the blood	PFS median 7.7 vs. 3.1; $P < 0.0001$	FDA and/or EMA
CD158k	IPH4102	I open-label dose-escalation and cohort expansion (Bagot et al., 2019)	44	Dose escalation: relapsed and/or refractory CTCL stage $\geq$ Ib, at least 5% skin-infiltrating or phenotypically abnormal circulating T cells expressing KIR3DL2; cohort expansion: pts with SS and/or MF with large cell transformation, independently from KIR3DL2	36.4% in SS, 42.9% global, and 55.9% in the blood	Median DOR: 13.8 mo	—
PI3K- δ,γ	Duvelisib	I (Horwitz et al., 2018)	19	CTCL	31.6%	—	—
NF-kB	Bortezomib	II (Zinzani et al., 2007)	12	CTCL	67%	DOR from 7 to >14 mo	—
HDAC	Vorinostat	Open-label phase IIb trial (Olsen et al., 2007)	74	Ib–IVa MF and/or SS, at least two prior systemic therapies, at least one of which was bexarotene	29.7% (32% pruritus relief)	Median DOR NR (>185 d). Median TTP 4.9 mo, 9.8 mo stage IIb or higher responders	FDA
HDAC	Vorinostat	II (Duvic et al., 2007)	33	Refractory CTCL	RR 24%; 14/31 ps had pruritus relief (45%)	Median DOR: 15.1 wk; median TTP: 30.2 wk	FDA
HDAC	Romidepsin	II (Duvic et al., 2018)	84	Relapsed or refractory CTCL stage IA–IVB and ECOG 0–2	RR 35% and 31% for Pts with and without prior chemotherapy, respectively	Median DOR 23 mo	FDA
HDAC	Romidepsin	pivotal, single-arm, open-label, phase II (Whittaker et al., 2010)	96	Stage Ib–IVA CTCL at least one prior systemic therapy	RR 34%, 38% IIb–IV; pruritus relief 43%	Median DOR 15 mo	FDA
HDAC	Resminostat	III maintenance randomized vs. placebo	190	MF and/or SS stage IIb–IV in response or SD after previous therapy.	—	—	Trial ongoing
HDAC	Quisinostat	II (Child et al., 2016)	26	MF stage Ib–IVa with at least one systemic therapy	RR 24%, pruritus relief in responders	DOR in skin ranged from 2.8 to 6.9 mo; median PFS was 5.1 mo	—
MiR-155	MRG-106, cobomarsen	II randomized vs. vorinostat	126	CTCL and ATLL	—	—	Trial ongoing
PD-1	Nivolumab	I open-label, dose-escalation, cohort- expansion basket (Lesokhin et al., 2016)	13	MF heavily pretreated	15%	DOR of up to 81 wk	—
PD-1	Pembrolizumab	II (Khodadoust et al., 2020)	24	Pts with MF and/or SS (23 of 24 with stage IIb–IV) and heavily pretreated	38	8 durable responses (median DOR not reached at >58 wks)	—
PD-1	Atezolizumab	II	25	Stage IIb–IV Pts with MF and/or SS relapsed and/or refractory	—	—	Trial ongoing

Abbreviations: ATLL, adult T-cell leukemia and/or lymphoma; CTCL, cutaneous T-cell lymphoma; d, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; HDAC, histone deacetylase inhibitor; MF, mycosis fungoides; No., number; NR, not reached; ORR, overall response rate; ORR4, ORR for at least 4 mos; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; Pt, patient; RR, response rate; SD, stable disease; SS, Sézary syndrome; TTP, time to progression.

target these selected markers. A series of potentially relevant new targets for treatment have been indeed identified in preclinical studies. A genome organizer protein, SATB1, has been found to be downregulated by STAT5 through the induction of miR-155; decreased SATB1 enhances the expression of cytokines such as IL-5 and IL-9 linked with MF disease progression (Fredholm et al., 2018). Poly-ADP-ribose polymerase 1, which is implicated in the regulation of several DNA repair pathways by modulating chromatin structure and interacting with different DNA repair factors, showed higher expression in aggressive disease and was found to be overexpressed in patients with early-stage MF who developed progressive disease (Lemchak et al., 2018). Somatic mutations in *PLCG1* increased downstream signaling toward NFAT activation and thus proliferative mechanisms in CTCL. The kinase TGF- β -activated kinase 1, firstly described as essential in B-cell lymphoma, is constitutively activated in CTCL cells and was associated with the presence of lymphoma in a primary human sample correlating with NF- κ B and β -catenin activation (Gallardo et al., 2018). CD31 is an angiogenic marker whose expression was found to correlate with the severity of cutaneous extent and extracutaneous spreading in MF (Jankowska-Konsur et al., 2016).

Future trials could be developed to identify the potential activity of new-targeted therapies; in this context, Jak and/or STAT inhibitors represent a promising class of inhibitors given the frequency of the alterations of this pathway in CTCL and the disposability of different inhibitors already experimented in other dermatological diseases (Damsky and King, 2017). Future studies should also explore the potential of checkpoint inhibitors and clarify how to improve their activity (Sivanand et al., 2019). Finally, the knowledge of the molecular and immunological mechanisms could also help us in identifying patients with different disease outcomes and pave the way to the evaluation of combination-targeted therapies to improve the course of the disease.

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CONFLICT OF INTEREST

JJS acted as a consultant and/or advisory and/or honoraria for Takeda, Helsinn, 4SC, Recordati, Mallinckrodt, Miragen, Codiak BioSciences, Kyowa, and Innate Pharma. PQ acted as a consultant and/or advisory and/or honoraria for Therakos, 4SC, Millennium/Takeda, Actelion, Kiowa-Kirin, Innate Pharma, and Helsinn-Recordati. MV acted as a consultant and/or advisory for Kiowa and Innate. SAV, NP, and EB acted as an advisory for Kiowa-Kirin and Helsinn-Recordati. The remaining authors state no conflicts of interest.

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PQ, JJS, MV, and NP participated in ALCANZA clinical trial. PQ, JJS, MV, and NP participated in the mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma clinical trial. MV and JJS participated in IPH41092 clinical trial. PQ, JJS, MV, NP, EB, SAV, and AP participated in resminostat for T-cell lymphoma of the skin clinical trial. PQ, JJS, and MV participated in the European Organisation for Research and Treatment of Cancer -1652 (Atezolizumab) clinical trial. JJS, PQ, and MV participated in SOLAR MiR-155 clinical trial.

AUTHOR CONTRIBUTIONS

Conceptualization: PQ, SR; Data Curation: PQ; Project administration: PQ; Validation: PQ, PF, AP, VG, MS, VP, AG, SAV, MN, CA, MR, LT, EB, NP, SOA, MTF, MV, JJS, SR; Writing - Original Draft Preparation: PQ, SR, PF, AP, VG, MS, VP, AG, SAV, SOA, MN, CA, MR, LT, EB, NP; Writing - Review and Editing: MTF, JJS, MV

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