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Research Article

Molecularly targeted therapies for relapsed and refractory peripheral T-cell lymphomas

Zachary D. Epstein-Peterson, Steven M. Horwitz*

Lymphoma Service, Division of Hematologic Malignancies, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

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ABSTRACT

The advent of molecularly targeted agents for patients with peripheral T-cell lymphomas (PTCL) has begun to change the therapeutic landscape in these diseases, especially for patients with relapsed or refractory disease. These agents, grounded in targeting numerous pathways or alterations related to disease pathogenesis, have shown promise across many PTCL subhistologies. Aided by significant advances in experimental techniques related to molecular biology, epigenetics, and immunology, more recent studies have begun elucidating mediators of resistance, both intrinsic and acquired, to inform future therapeutic advances. Defining and targeting these escape mechanisms through rational combination approaches will likely be important to continue to build on these promising advances and further improve clinical outcomes for patients facing PTCL.

Introduction

Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous collection of malignancies arising from the malignant transformation of mature T cells and include nearly 30 histologic subtypes with distinct clinical behavior and disease pathogenesis. Patients with aggressive PTCL subtypes are frequently treated with upfront combination chemotherapy with consideration of stem cell transplantation if remission is achieved depending on the specific disease subtype and patient suitability [1]. Other patients ineligible for this intensive approach or with more indolent disease behavior are typically treated with ongoing, sequential, maintenance-type treatments attempting to maximize clinical benefit with acceptable long-term toxicities. Broadly, however, compared to those for patients with B-cell lymphomas, the outcomes for patients with PTCL are poor, especially for those patients with relapsed or refractory (R/R) disease [2,3]. This disparity has stimulated significant recent progress in defining the disease pathobiology of PTCL subtypes and the development of novel therapeutic approaches to ultimately improve patient outcomes.

The advent of high-throughput genomic sequencing and advances in molecular biology has generated deep insights into the genomic landscape and molecular pathogenesis of PTCL subtypes. Indeed, nearly all PTCL subhistologies have multiple published manuscripts detailing the landscape of molecular alterations present [4-8]. For example, Watatani et al used whole-exome sequencing on PTCL tumor samples to reveal a new molecular subtype of PTCL-NOS characterized by alterations in *TP53* and *CDKN2A*. Paralleling these discoveries into the genetic lesions underlying PTCL has been other lines of investigation into the cellular signaling pathways that PTCLs are dependent on for growth and proliferation [9,10] that may be susceptible to therapeutic targeting. Among these that are most advanced therapeutically are the phosphatidyl inositol-3-kinase pathway (PI3K), the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, and the spleen tyrosine kinase (SYK) pathway.

An additional line of background research in PTCL pathogenesis concerns epigenetic alterations in PTCL. Many PTCL subtypes contain epigenetic changes and/or mutations in epigenetic-related genes, which have prompted the use of epigenetic-directed therapies such as histone deacetylase (HDAC) inhibitors [11]. Besides implications for pathogenesis, such markers may carry prognostic importance [12,13]. Epigenetic alterations are especially well defined in the PTCL-T_{FH}/AITL subtypes with frequent mutations in epigenetic regulators such as *TET2* and *DNMT3A* [7], and emerging evidence suggests superior efficacy with HDAC inhibition in these diseases compared to other PTCL subtypes [14]. Newer targeted approaches are seeking to explore other epigenetic-targeted therapies such as the enhancer of zeste homolog 1/2 (EZH1/2) [15] or non-enzyme inhibition-based approaches [16,17] to disrupting perturbed epigenetic networks and pathways for therapeutic gain.

In the present review, we discuss therapeutic targets and compounds under investigation for use in treating R/R PTCL-NOS, focusing on those farthest along in clinical development or showing

* Corresponding author. Steven M. Horwitz, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, 530 E 74th St., New York, NY, 10021
E-mail address: horwitzs@mskcc.org (S.M. Horwitz).

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particular promise in earlier-phase investigations. Where possible, we will seek to highlight translational efforts seeking to understand mediators of response to these agents.

Kinase-targeted therapies

PI3K

Cellular signaling through the PI3K-Akt-molecular target of rapamycin (mTOR) pathway has been shown to be critical for growth and differentiation of lymphocytes [9,18,19], and therefore targeting this pathway with small molecule PI3K inhibitors has emerged as a promising approach in many malignancies, especially lymphoid cancers. Available PI3K inhibitors include idelalisib, copanlisib, zandelisib, tenalisib, and duvelisib; the last two agents are most investigated for patients with R/R PTCL [20,21]. A completed phase I study of duvelisib, a, oral δ/γ isoform-specific inhibitor, showed promising responses among 16 patients with R/R PTCL (study also included patients with R/R cutaneous T-cell lymphomas, not discussed here) following a median of >2 lines of therapy. In this population (largest histologic subtype PTCL-NOS, N = 6), the overall response rate was 50%, including 3 complete responses and 5 partial responses. Analysis of toxicities observed among all patients showed side effects common in this class of agents: elevations in AST/ALT (31% grade >2), rash (14% grade >2), and grades 1/2 pyrexia (37%) and cough (34%). Biologically, increases in CCL1, IL-17a, and sCD40L and diminution in p40 and CXCL13 correlated with responses. This has prompted the ongoing phase II dose optimization/expansion study (NCT03372057) seeking to further explore and potentially register the use of this agent in patients with R/R PTCL [22]. In preliminary results among 25 response assessed patients, 13 had responses, including 9 complete responses, with a median duration of response of 4.1 months. The toxicity profile was notable for cytopenias (24%) and elevated ALT (56%).

More recently, phase I data concerning another dual PI3K δ/γ inhibitor tenalisib were published including 28 patients with R/R PTCL (histologic subtypes not reported), over 20% of whom had received >4 prior lines of therapy [21]. Among these 28 patients, 15 completed at least 2 cycles of therapy, 3 of whom achieved CR and 4 achieved PR. The median duration of response was 6.5 months. Toxicities were generally comparable to those observed with duvelisib, with the most common grade >2 toxicity being elevated AST/ALT (19% each across all patients). Based on these promising results, two ongoing studies are investigating each of these agents in combination with the HDAC inhibitor romidepsin (NCT02783625 and NCT03770000) for patients with R/R PTCL. Other ongoing or planned studies with PI3K inhibitors in patients with R/R PTCL include combination with immune checkpoint blockade (copanlisib plus pembrolizumab, NCT02535247) and with chemotherapy (copanlisib plus gemcitabine, NCT03052933). For upfront treatment, a planned intergroup study (A051902) will randomize patients with CD30-negative PTCL to CHO(E)P versus CHO(E)P plus duvelisib versus CHO(E)P plus azacitidine to advance these promising agents earlier in the care of patients.

JAK

The Janus kinase family proteins (JAK1, JAK2, JAK3, and TYK2) contribute to critical pathways mediating immune responses and inflammation in normal physiology. Downstream of the JAK proteins are the STAT family of transcription factors, most importantly STAT3 and STAT5B, which mediate effects of JAK signaling through transcriptional regulation. Cancer-associated *JAK* family gene mutations were initially discovered in the myeloproliferative neoplasms, but recent work has begun elucidating their prevalence and significance across nearly all TCL histologies and potential for therapeutic targeting [23-28]. Besides activating mutations, there are also gene fusions involving JAK family genes [29] leading to activated JAK-STAT pathway signaling. Recent data have emerged regarding efficacy of JAK pathway inhibition as a therapeutic approach in PTCL: Moskowitz et al reported results from a phase II study of ruxolitinib in 53 patients with R/R PTCL, with 48 evaluable patients. The largest subgroup by histology was PTCL-NOS (N = 11) followed by PTCL-T_{FH} and angioimmunoblastic T-cell lymphoma (AITL, N = 9). Patients were analyzed according to JAK/STAT pathway status: activating mutation present, pathway activation evident by immunohistochemistry, or neither. The overall response rate (including patients with cutaneous T-cell lymphomas) was 23%; the response rate plus rate of maintaining stable disease for >6 months reached 35%. Three patients achieved complete responses, and 8 (17%) partial responses. In terms of subtypes, particularly high rates of clinical benefit were seen in patients with PTCL-T_{FH}/AITL (44%), large granular lymphocytic leukemia (75%), and T-cell prolymphocytic leukemia (50%). When analyzed according to JAK/STAT pathway status, the overall response rate was 29% in those with an activating mutation present or elevated pSTAT3 by immunohistochemistry compared to only 11% in those with neither. The most frequent drug-related grade 3/4 adverse events were cytopenias, with neutropenia being the most common (N = 13). An ongoing study (NCT01712659) is testing ruxolitinib specifically in patients with adult T-cell leukemia/lymphoma harboring JAK/STAT pathway activation [28,30].

SYK

SYK encodes a protein tyrosine kinase with pleiotropic downstream signaling partners, including PI3K and PLC-gamma [31], and is normally expressed on B cells but absent on T cells [32]. Aberrant expression of SYK is observed in the majority (94%) of T-cell lymphoma (TCL) cases [33]. Cerdulatinib is a pan-JAK/SYK pathway inhibitor that has been investigated for treating patients with R/R hematologic malignancies, including PTCL [34]. Among 60 evaluable patients with PTCL who received cerdulatinib, the overall response rate was 35%; the response rate specifically in patients with PTCL-T_{FH}/AITL was 55% (12/22). The main treatment-emergent adverse event grade >2 included lipase elevation (21%) with diarrhea, neutropenia, anemia, and fatigue all between 5% and 10%. Another SYK inhibitor, TAK-659, which also targets fms-like tyrosine kinase 3, is in development and is undergoing evaluation for patients with B-cell non-Hodgkin lymphomas (NCT03357627, NCT02000934, and NCT03742258).

ITK

The interleukin-2-inducible kinase (ITK) is a member of the Tec family nonreceptor tyrosine kinase and mediates T-cell activation and differentiation [35]. ITK is specific to T cells and is required for signaling through the T-cell receptor: when TCR is activated, ITK is recruited, phosphorylated, and activated, thus activating secondary downstream messengers including members of the NF-κB, mTOR, and ERK pathways [36]. Certain PTCL subtypes have been shown to harbor activating ITK fusions [37] and pre-clinical evidence suggests ITK-mediating signaling may underlie chemoresistance [38]. This has spurred the development of small molecule inhibitors of ITK for use in PTCL, including CPI-818. Interim results for this agent [39] included 16 patients in dose escalation with a variety of PTCL and cutaneous T-cell lymphoma sub-histologies (including 4 patients with PTCL-NOS). Evidence of activity with no grade 3/4 adverse events has been noted particularly in patients

with Sezary Syndrome, a form of cutaneous T-cell lymphoma, and the study remains ongoing (NCT03952078).

Aurora A kinase

Aurora kinase A is a serine/threonine protein kinase that mediates spindle formation during mitosis and is overexpressed in a wide range of malignancies, including PTCL [40], and targeting this pathway was shown to have preclinical activity [41]. Alisertib is an oral Aurora kinase A inhibitor, and data for this agent came from a randomized, phase III study of alisertib versus investigator's choice in R/R PTCL [42]. The study was terminated early due to evidence of lack of benefit for progression-free survival for alisertib, with an overall response rate of 33% compared to 45% for the comparison arm. Based on these results, further single-agent development has been halted for patients with PTCL.

ALK

Anaplastic large cell lymphoma (ALCL) is a common subtype of PTCL and is subdivided based on the presence or absence of the t(2;5)(p23;q35) translocation that fuses the anaplastic lymphoma kinase (ALK) gene to NPM. As ALK is a readily targetable tyrosine kinase receptor, this has led to use of ALK inhibitors for patients with R/R ALK$^+$ ALCL [43,44]. Crizotinib, the first ALK inhibitor developed, was used in 9 patients with R/R ALK+ ALCL, and all 9 patients experienced complete responses to therapy, many of which were durable [43]. Three of these 9 patients had prior stem cell transplantation (2 autologous, 1 allogeneic). Richly, et al. investigated the second-generation ALK-inhibitor ceritinib in 3 patients with R/R ALK$^+$ ALCL, 2 of whom achieved CR, 1 PR, all of which were ongoing at time of publication [44].

Epigenetic-targeted therapies

HDAC

Protein acetylation is governed by histone acetyltransferases that catalyze the addition of acetyl groups and HDAC enzymes, which remove them. Among HDAC inhibitors, belinostat [45] and romidepsin [46] are the most thoroughly studied for patients with PTCL histologies and HDAC inhibition is an established treatment for patients with R/R PTCL in current practice. Coiffier et al reported updated results for romidepsin in patients with R/R PTCL [46] in 2014, involving 130 patients with PTCL-NOS, AITL, and ALK-negative anaplastic large cell lymphoma. The overall response rate was 25%, including 29% in the 69 patients with PTCL-NOS. The median time to response was 1.8 months and median duration of response was 28 months, highlighting its potential role as a chronic, maintenance-type therapy in this setting. The most common side effects included gastrointestinal toxicities (nausea, vomiting), cytopenias (especially anemia, thrombocytopenia), and fatigue/asthenia. Belinostat, among 129 patients with R/R PTCL, garnered a response rate of 26%; median progression-free survival and overall survival were 1.6 and 7.9 months, respectively. A similar toxicity profile to romidepsin was observed with this agent. Reported combination studies using romidepsin in R/R PTCL are summarized in Table 1.

Further studies are underway or planned to investigate other therapies in combination with HDAC inhibitors, including PI3K inhibitors (duvelisib, NCT02783625; tenalisib, NCT03770000), proteasome inhibitors (ixazomib, NCT03547700), aurora kinase inhibitors (alisertib, NCT01897012 [56]), other epigenetic therapies (azacitidine + lenalidomide NCT04447027), immunotherapy (durvalumab + pralatrexate or azacitidine, NCT03161223).

Table 1
Reported combination studies with romidepsin in R/R PTCL

Combination agent(s)	N evaluable	ORR	CR	Citation
Duvelisib	14	36%	21%	[47]
Pembrolizumab	15	44%	20%	[48]
Pralatrexate	14	71%	29%	[49]
Liposomal doxorubicin	12	25%	25%	[50]
Gemcitabine	20	30%	15%	[51]
ICE	18	93%	80%	[52]
Azacitidine	6	83%	50%	[53]
Gemcitabine, cisplatin	20	50%	0%	[54]
Lenalidomide, carfilzomib	11	46%	36%	[55]

ICE, ifosfamide, carboplatin, and etoposide.

EZH1/2

The EZH1/2 enzymes are histone methyltransferases and serve as the active SET domain-containing catalytic subunits of the polycomb repressive complex 2, which regulates chromatin topology (reviewed in [57]). Mutations in *EZH2* were observed in 10% (7/68) patients with hepatosplenic T-cell lymphoma [4], a rare and aggressive subtype of PTCL, and preclinical data suggest efficacy for EZH2 inhibition in this disease [58]. In follicular lymphoma, an indolent subtype of B-cell non-Hodgkin lymphoma, the EZH2 inhibitor tazemetostat has received accelerated FDA approval for patients with R/R disease, irrespective of *EZH2* mutation status [59]. Fewer preclinical data exist concerning the role for EZH1/2 in PTCL. Dhiran et al showed EZH2 IHC staining to be a distinguishing factor between malignant and normal T cells [60] and it was also shown that EZH2 overexpression is present in many TCL subtypes [61], mediated by the TCR/CD28 pathway. Emerging data suggest efficacy of EZH1/2 inhibition in R/R PTCL subtypes [15] with the dual EZH1/2 inhibitor valemetostat: among 9 patients with ATLL, there was 1 unconfirmed complete remission, 3 partial responses, and 3 patients with stable disease. Frequent adverse events included cytopenias (most commonly thrombocytopenia, 78%), dysgeusia, alopecia, and dry skin. An ongoing study (NCT02732275) will report further data for this promising agent more broadly in patients with PTCL.

DNMT

DNA methylation is a critical process to regulating gene expression and governed by tightly regulated enzymes that add or remove methyl groups at particular sequences. The DNA methyltransferase (DNMT) enzymes specifically catalyze the addition of methyl groups, and oncogenic lesions in these enzymes are principally found in PTCL-TFH and AITL subtypes within PTCL [6,7]. This has spurred investigations into the use of DNMT inhibitors, also known as hypomethylating agents, for therapeutic gain in these diseases [53,62-65], although most such reports are confined to single case reports or small case series. Falchi et al reported data from a prospective study of 14 patients with R/R PTCL (65% with AITL) using the DNMT inhibitor 5-azacitidine plus romidepsin [53]. Among 13 response evaluable patients (completing $\geq$2 cycles of treatment), 7 (54%) experienced response, including 5 complete response and 2 partial responses. Among all patients, grade $\geq$3 treatment-emergent toxicities were primarily hematologic in nature. An ongoing upfront study [64] (NCT03542266) is evaluating oral azacitidine with combination chemotherapy for patients with PTCL, enriching for those with PTCL-TFH/AITL subtypes. Finally, an ongoing randomized study (NCT03593018) is evaluating oral azacitidine versus investigator's choice in patients with R/R AITL.

Table 2
Ongoing studies of targeted therapies for R/R PTCL

Drug category	Agent(s)	NCT	Recruitment status	Eligible diagnoses
Kinase	Duvelisib	NCT03372057	Recruiting	PTCL-NOS, AITL, ALCL, NKTL
	Duvelisib + romidepsin	NCT02783625	Recruiting	PTCL, CTCL
	Tenalisib	NCT03770000	Active, not recruiting	TCL
	Copanlisib + pembrolizumab	NCT02535247	Active, not recruiting	PTCL, transformed CTCL
	Copanlisib + gemcitabine	NCT03052933	Active, not recruiting	PTCL, NKTL
	Ruxolitinib	NCT01712659	Recruiting	ATL
	TAK-659 + venetoclax	NCT03357627	Active, not recruiting	NHL
	TAK-659	NCT02000934	Active, not recruiting	Lymphoma
	CPI-818	NCT03952078	Recruiting	TCL
	Tenalisib + romidepsin	NCT03770000	Active, not recruiting	TCL
Epigenetic	Romidepsin + ixazomib	NCT03547700	Active, not recruiting	PTCL
		NCT04447027	Recruiting	TCL
	Romidepsin + azacitidine + lenalidomide			
	Romidepsin +/- pralatrexate +/- durvalumab +/- azacitidine	NCT03161223	Recruiting	PTCL
	Valemetostat	NCT02732275	Recruiting	NHL
	Azacitidine	NCT03593018	Recruiting	AITL
Other	PRT1419	NCT04543305	Recruiting	NHL
	AMG 397	NCT03465540	Recruiting	NHL
	AZD5991	NCT03218683	Recruiting	NHL
	Venetoclax	NCT03534180	Recruiting	PTCL, transformed MF
	Lenalidomide + brentuximab	NCT03302728	Recruiting	CD30$^+$ PTCL
	Lenalidomide + durvalumab	NCT03011814	Recruiting	PTCL

NKTL, NK/T-cell lymphoma; CTCL, cutaneous T-cell lymphoma; FTCL, follicular T-cell lymphoma; ATL, adult T-cell leukemia/lymphoma.

Non–cell signaling kinase/nonepigenetic targets

Antiapoptotic therapies

The advent of apoptosis-targeting therapies for patients with non-Hodgkin lymphoma has shown particular promise for patients with chronic lymphocytic leukemia and mantle cell lymphoma, with high rates of remission seen in each histology with the BCL2 inhibitor venetoclax [66,67]. Emerging evidence suggests a role for such agents for treating patients with PTCL [68-70]. Apoptosis is governed by the BCL2 family of proteins with counterbalancing pro- and antiapoptotic members, including MCL1 and BCL2. Spinner et al revealed high levels of MCL1 expression across PTCL subtypes and that targeting this pathway delayed PTCL development and reduced survival in vivo [68]. Building off this work, Koch et al identified an MCL1-dependent PTCL patient-derived tumor xenograft model wherein MCL1 inhibition improved survival and was synergistic with standard multiagent chemotherapy [70]. These data have spurred development of agents for patients with R/R PTCL in ongoing trials targeting MCL1 (PRT1419 – NCT04543305; AMG 397 – NCT03465540; AZD5991 – NCT03218683) and BCL2 (venetoclax – NCT03534180).

Stapled peptide therapies

Stapled peptides represent a novel class of anticancer agents that disrupt protein-protein interactions for therapeutic benefit, in contrast to enzymatic inhibition characteristic of most targeted agents. Preliminary data have been reported [71] in 26 patients with R/R PTCL by Shustov et al using ALRN-6924. This agent mimics the inhibitor binding region of p53, thus binding endogenous inhibitors of p53 and restoring its normal induction of cell cycle arrest and apoptosis. In 15 evaluable patients, the overall response rate was 27% and disease control rate (ORR + SD) 47%, with an acceptable profile (most common treatment-related adverse event fatigue, 50% followed by nausea, 43%). Further development of this agent for patients with R/R PTCL is not currently planned.

Immunomodulatory agents

The immunomodulatory agent lenalidomide has broad activity across numerous hematologic malignancies, including multiple myeloma, deletion 5q myelodysplastic syndrome, mantle cell lymphoma, and follicular lymphoma. Lenalidomide binds to cereblon, the substrate adapter of the CRL4-cereblon E3 ubiquitin ligase complex, thus modulating its substrate specificity and inducing degradation of selected protein targets. As many of these protein targets mediate immune responses such as interleukin production and T/NK-cell proliferation/activation, these effects are believed to mediate the antitumor properties of this agent (reviewed in [72]). Furthermore, lenalidomide has been shown to strengthen immune synapses as another means to promote anti-tumor immunity [73]. Lenalidomide has been investigated for use in patients with R/R PTCL [74,75] and is the subject of ongoing trials. Morschhauser et al reported [74] an overall response rate of 22% in 54 patients with PTCL (median prior therapies 3); the median progression-free survival was 2.5 months. Frequent adverse events included thrombocytopenia (20%) and neutropenia (15%). Further data [75] were reported in 40 patients with a range of PTCL histologies, including 14 with PTCL-NOS. The overall response rate was similar, 26%. Ongoing investigations of lenalidomide in patients with R/R PTCL include in combination with the antibody-drug conjugate targeting CD30 brentuximab vedotin (NCT03302728, also including patients with Hodgkin lymphoma) and the anti-PD1 monoclonal antibody durvalumab (NCT03011814, also including patients with cutaneous T-cell lymphomas).

Farnesyltransferase inhibitors

Tipifarnib is a farnesyltransferase/CXCR4 inhibitor that has recently been investigated specifically for biomarker-driven use in patients with R/R PTCL, especially AITL or CXCL12$^+$ PTCL-NOS [76]. CXCL12 expression has been suggested to be prognostic in patients with PTCL and tipifarnib was shown to downregulate CXCL12 secretion in stromal cultures, hence its selected use for treating patients with CXCL12$^+$ PTCL [77,78]. Within this trial, in the PTCL-NOS subcategory, patients were stratified according to the vari-

Table 3
Development status for targeted therapies in R/R PTCL by mechanism of action

Class	Agent	Phase of study/status
Kinase	Cerdulatinib	Phase I ongoing
	TAK-659	
	CPI-818	
	Crizotinib	
	Ceritinib	
	Copanlisib	
	Duvelisib	Phase II ongoing
	Tenalisib	
	Ruxolitinib	
	Alisertib	Phase III completed
Epigenetic	Valemetostat	Phase I ongoing
	Romidepsin + other (multiple)	Phase II ongoing
	Azacitidine	Phase III ongoing
	Romidepsin alone	Approved
	Belinostat	
Other	ALRN-6924	Phase I completed
	MCL1 inhibitors	Phase I ongoing
	Lenalidomide	Phase II completed
	Tipifarnib	Phase II ongoing
	Venetoclax	

ant status of the 3' UTR of the *CXCL12* gene; among 9 evaluable patients with wildtype 3' UTR, the clinical benefit rate was 82%, whereas all 6 patients with variant 3' UTR had progressive disease [76]. The primary toxicities were cytopenias, especially thrombocytopenia (39%) and neutropenia (31%).

Incorporating molecularly targeted therapies into clinical practice

The care of patients with R/R PTCL is complex and a full discussion of this clinical scenario is beyond the scope of this review. However, in our practice, our approach relies principally on the patient's goals/wishes for treatment and age/comorbidities, prior therapies received and tolerability therein, the tempo and extent of disease, and in some instances, availability of a suitable donor for allogeneic stem cell transplantation. Whenever feasible, we seek to molecularly characterize a patient's tumor (preferably using a specimen confirming R/R disease) through targeted next-generation sequencing. Emerging evidence suggests that such results may carry implications for prognosis [79] or therapeutic selection [80]. In practice, we decide between non-cross-resistant combination therapies and targeted agents (potentially in the context of a clinical trial) primarily based on the tempo/extent of disease and the patient's preferences for treatment, balancing what may be more quickly achieving a response versus a greater potential for lasting responses with chronic, maintenance-type treatments. Ongoing clinical trials mentioned in this article are summarized in Tables 2 and 3 (current as of January, 2021).

Finally, the decision regarding consolidating deep responses to targeted therapies with allogeneic stem cell transplantation is complex and should be individualized to each patient's situation.

Conclusions

In this review, we have attempted to outline areas of progress in defining the disease biology and therapeutic targeting needed to advance the care of patients with R/R PTCL forward. Clearly, there are promising agents with tangible benefits in this patient population, yet further work is needed to: (1) refine patient selection for these therapies based on genomic, epigenomic, or immunologic tumor markers, (2) more precisely define mediators of response to these agents, and (3) understand patterns of treatment failure from multiple perspectives towards ultimately targeting these bypass mechanisms. Furthermore, future therapeutic approaches may not take the form of small molecule kinase inhibitors, but instead as stapled peptides, micro RNA-targeted therapies, enzyme degraders, enzyme agonism, or other emerging strategies. Finally, irrespective of therapeutic interventions, further work remains to gain deeper understanding into fundamental disease mechanisms to identify other rational targets for therapeutic gain.

Author statement

Zachary D. Epstein-Peterson: Writing - Original Draft; Steven M. Horwitz: Writing - Review & Editing

Conflicts of interest

Dr. Epstein-Peterson declares no conflicts of interest. He is the recipient of an AACR-AstraZeneca Lymphoma Research Fellowship and a Lacher Fellowship at MSKCC.

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