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Novel Aurora Kinase Inhibitor-Based Combination Therapies for PTCL

Pavan Tenneti, Lisa E. Davis and Daruka Mahadevan

Abstract

Peripheral T-cell lymphomas (PTCLs) are a rare, heterogeneous group of T-cell non-Hodgkin's lymphomas (T-NHL) that display distinct clinical and biological features. Despite a detailed understanding of PTCL transformation, there is no current accepted standard of care for newly diagnosed or relapsed/refractory (r/r) patients. PTCL are highly proliferative neoplasms with an immunosuppressive microenvironment that elaborates drug resistance to current therapies with poor outcomes. Aurora kinases (AKs) are a family of mitotic oncogenic serine/threonine kinases (A, B/C) that are aberrantly expressed in PTCL, providing a growth advantage. Alisertib, an AK-A inhibitor, blocks the mitotic phase of the cell cycle resulting in apoptosis. Preclinical and clinical trials in PTCL demonstrated an ~30% response rate in r/r PTCL similar to other investigational agents. In order to improve response rates, alisertib-based combination therapies were tested with HDAC inhibitors, romidepsin and vorinostat, in phase Ib trials. To improve response rates to alisertib, we evaluated alisertib-induced polyploidy as a drug resistance mechanism by targeting microtubules with vincristine. In addition, we also targeted immunosuppression-induced proliferation with an anti-PD-L1 antibody and PI3K inhibition in PTCL. Targeting aberrant proliferation and immunosuppression is a novel strategy that warrants evaluation in clinical trials for PTCL, an unmet clinical need.

Keywords: peripheral T-cell lymphoma, aurora kinases, aurora kinase inhibitors, immune therapy, targeted therapy

1. Introduction

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of lymphoproliferative disorders that comprise ~10% of non-Hodgkin's lymphomas (NHL) [1]. PTCL is classified into at least 19 different subtypes affecting precursor T cells or mature post-thymic T cells with the cell of origin, an activated memory CD44+ T cell [2]. Approximately 60% of PTCL diagnoses fall into one of the four subtypes [e.g., peripheral T-cell lymphoma not otherwise specified (PTCL-NOS, 26%), anaplastic large-cell lymphoma (ALCL, ALK+ 7%, ALK- 6%), angioimmunoblastic T-cell lymphoma (AITL, 19%), and enteropathy T-cell lymphoma (<5%)] [3]. Frontline anthracycline-based therapies (e.g., CHOP-like) utilized in diffuse large B-cell lymphoma (DLBCL) provide inferior outcomes to PTCL (NOS) and ALCL-ALK- versus ALCL-ALK+ disease [4]. Further, for CD30+ PTCL (19/26

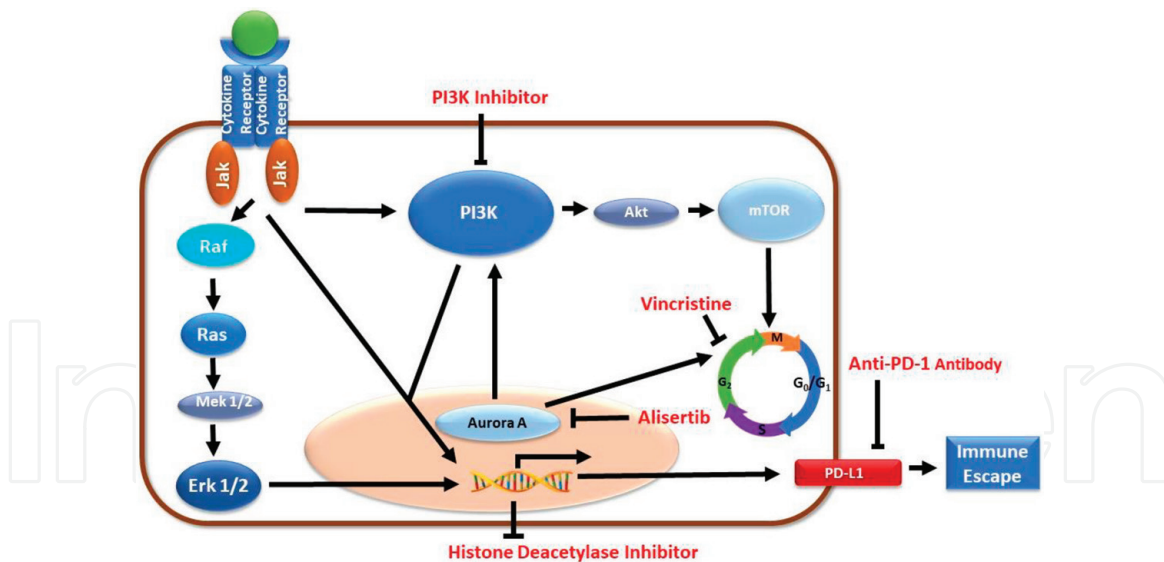


Figure 1.

Aurora kinase-based combination therapy for PTCL (modified from Mahadevan et al. [63]). Inhibition of aurora A kinase (e.g., alisertib) activates PI3K signaling in PTCL which in turn enhances the induction of PD-L1. Cytokine signaling through the MAPK pathway also induces PD-L1 expression leading to profound immune suppression in PTCL. Targeting mitosis with alisertib and immune suppression with an anti-PD-L1 antibody leads to a highly synergistic combination in a syngeneic mouse model of PTCL [52]. Targeting mitosis with alisertib plus vincristine is synergistic causing mitotic catastrophe. This combination is synthetic lethal when combined with anti-PD-L1 plus PI3K inhibition [52]. Further, Aurora A kinase inhibition combined with histone deacetylase inhibitors is also synergistic implicating epigenetic modulation.

ALCL), frontline brentuximab vedotin + CHP had a 92% complete response rate with an estimated 5-year PFS and OS rates of 52 and 80%, respectively, suggestive of an treatment option that is curative for some patients with CD30+ PTCL [5]. In addition, for young fit chemosensitive patients in the relapse setting, HD therapy followed by auto-SCT may be curative in a small proportion of patients [6].

PTCL patients with refractory or relapsed disease should be encouraged to participate in clinical trials with novel investigational agents [7]. USFDA has approved four drugs as single agents: pralatrexate (an antifolate), romidepsin and belinostat (histone deacetylase [HDAC] inhibitors), and brentuximab vedotin (anti-CD30 Mab-ADC). Several agents have demonstrated antitumor activity with response rates of 10–30% (e.g., gemcitabine, bendamustine, duvelisib, copanlisib, alisertib, mogamulizumab) [8]. Preclinical studies with novel agents support combinations that target cell proliferation and immune suppression which are expected to enhance degree, depth, and duration of responses in PTCL. Here, we review novel aurora kinase inhibitor-based combination therapies for PTCL (**Figure 1**).

2. Aurora kinases

The aurora kinases (Aks) are a family of serine/threonine kinases that regulates multiple aspects of cell division and proliferation through the mitotic (M) phase of the cell cycle. They play an essential role in progression through the cell cycle during mitosis and meiosis in ensuring error-free chromosome arrangement around assembly of the mitosis spindle, centrosome alignment and separation, and cytokinesis [9–12]. AKs are composed of three highly conserved isoforms, aurora A, B, and C, which share substantial similarity in sequence and structure in their catalytic domain but are diverse in N-terminal domain sequence, subcellular localization, and functions [13, 14]. AKs A and B are ubiquitously expressed in normal tissues, whereas AK C is specifically expressed in the testis, where it functions primarily in

spermatogenesis [13, 15]. AK A localizes primarily at centrosomes, spindle poles, and later on the spindle midzone, where it recruits the cyclin B1-CDK1 complex and promotes the cell to mitotic entry and exit, centrosome separation and maturation, and bipolar spindle assembly [9, 11, 16–18]. Inhibition of AK A causes defects in chromosome segregation and maturation, mitotic spindle aberrations, non-diploidy, cell cycle arrest, and apoptosis [15, 19, 20].

AK B is referred to as a chromosomal passenger protein and, along with other regulatory proteins, constitutes the chromosome passenger complex [13, 15, 16]. This complex concentrates at centrosomes and the central spindle, then relocates to the midzone to ensure proper chromosome alignment and segregation and spindle assembly, and regulates cytokinesis [12, 13, 15, 16]. Inhibition of AK B interferes with normal chromosomal alignment during mitosis and leads to inhibition of histone H3 phosphorylation, cytokinesis failure, and polyploidization [15, 21].

AK C concentrates in the centrosomes and shares interacting proteins and functional overlap with AK B during mitosis, although its primary role is in meiosis, where it is necessary for efficient spermatogenesis [22]. With similar structural and localization properties, its functions may be redundant or cooperative to those of AK B [22].

2.1 Role of aurora kinases in tumorigenesis

AKs A and B are frequently amplified in many epithelial tumors, cancers of solid organs, and hematological malignancies, with elevated levels of mRNA and protein present in tumors [11, 19]. Amplification of the chromosomal region that encodes *AURKA* has been linked to high levels of expression of AK A in a wide range of tumor types, and strong expression of the *AURKB* gene is observed in many tumor types [20]. AK A overexpression is sufficient to transform NIH/3T3 cells in vitro, which then induced tumors when transplanted into nude mice [12]. In addition, increased risk of breast, non-small cell lung, esophageal, and ovarian cancer is associated with the *AURKA* Phe3Ile polymorphism [18]. Furthermore, aberrant AK A expression may contribute to cancer cell survival through activities that enhance NF- κ B, mTOR, Raf1, Myc, Wnt, or AKT signaling pathways [23]. Because AK A interacts with p53 at multiple levels, cancer cells with a deficient p53-p21^{Waf1/Cip1} postmitotic checkpoint function may be more susceptible to AK inhibition [18, 24].

AK overexpression is also associated with a mitogenic phenotype and genetic instability [25, 26]. Resulting tumor cell non-diploidy contributes to uncontrolled cell cycle progression and promotes cell survival. These effects are synergistic with histone deacetylases in regulating cell proliferation and survival through activation of AKT/mTOR signaling in lymphomas [27]. AK C is overexpressed in several cancers and cancer cell lines, but its role in carcinogenesis and effect on tumor cell proliferation is unclear [28, 29]. Similar to AK B, overexpressed AK C binds to and localizes with the IAP protein survivin in mitotic cells [15, 27]. However, a clear role for AK C in tumorigenesis has not been identified.

2.2 Role of aurora kinases in drug resistance

Drug resistance remains a major challenge in oncology, regardless of whether cancer resistance to drug therapy is de novo and/or acquired. Elevated AK A and B expression is associated with chemoresistance in multiple tumor types and to different classes of anticancer drugs [30–39]. AK A has been implicated in the development of resistance and reduced sensitivity to microtubule-targeted chemotherapy [11, 31, 40–42]. Elevated levels override the spindle assembly checkpoint (SAC) responsible for monitoring defective mitotic spindle formation, thus conferring

resistance to paclitaxel-induced apoptosis [42]. Similarly, there was a dose-dependent association between AK B expression in cell lines and resistance to paclitaxel [43]. AK activity also contributes to resistance to platinum-containing agents, and sensitivity to these drugs in vitro can be restored by AK inhibition [30, 38, 44]. These mechanisms present a potential opportunity to inhibit AK to restore or enhance drug sensitivity, which has been demonstrated preclinically [23]. This strategy holds implications for combination therapies with AK inhibitors and their potential role for relapsed/refractory malignancies including PTCL.

3. Aurora kinase inhibition in PTCL

Given the poor clinical outcomes associated with PTCL, more effective treatments informed by a better understanding of PTCL biology are needed. Several subtypes of PTCL have shown to overexpress AK A and B [45–47], making them an attractive therapeutic target. CD8⁺ T cells expressing STAT5B N642H, the most frequent STAT5B mutation found in patients with leukemias and lymphomas, were exquisitely sensitive to AK inhibition in a transgenic mouse model [48]. Given their role in multiple oncogenic processes, inhibition of AKs has a potential of halting malignant progression in PTCL.

Multiple preclinical and clinical studies have been conducted to explore the role of AK inhibitors in the treatment of advanced PTCL. Small molecules designed to bind competitively and reversibly to the ATP-binding pocket have been developed for all three AKs, including isoform-specific and pan-AK inhibitors [15, 21, 49]. AK isoform selectivity and inhibitory activity differ among individual agents. However, it is unclear whether a strategy of selective or pan-AK inhibition will provide superior efficacy [15, 19] without compromising safety.

3.1 Preclinical studies involving aurora kinase inhibitors

AK inhibitors were first studied in solid organ tumors and in hematologic tumor cell lines other than PTCL. Agents that have undergone preclinical evaluation in lymphomas are listed in **Table 1**. Much focus has been on AK A inhibition, as the mechanism of AK B in cancer is less clear.

Alisertib is a potent inhibitor of AK A, with a half maximal inhibitory concentration (IC₅₀) value of 1.2 nmol/L [50]. It has less activity against AK B, with an IC₅₀ value of 396.5 nmol/L. Alisertib was studied in colorectal cancer and non-Hodgkin's lymphoma tumor cell lines in vivo and in vitro. In vitro, alisertib showed inhibition of proliferation in tumor cell lines, more so for lymphoma cell lines. In vivo, alisertib caused tumor growth inhibition (TGI) of 43.3, 84.2, and 94.7% when given at doses of 3, 10, and 30 mg/kg, respectively, in nude mice with subcutaneous colorectal HCT-116 cell. In a non-Hodgkin's lymphoma model ONI-LY19, there was tumor regression (TR) when alisertib was given at doses of 20 and 30 mg/kg [50]. Based on preliminary data from this study and similar preclinical studies of solid organ and hematological malignancies, phase I clinical trials involving alisertib in r/r PTCL were conducted.

The first preclinical study of alisertib involving PTCL cell lines was conducted by Qi et al. [47]. In this in vitro study, alisertib was tested on two mouse PTCL cell lines, TIB-48 and CRL-2396. AK A contributes to autophosphorylation on Thr288 in the activation loop. Alisertib at 0.1 μM completely inhibited AK A autophosphorylation on Thr288. Analysis of DNA content with flow cytometry showed that treatment of both PTCL cell lines with alisertib at 0.5, 1, and 1.5 μM resulted in cell cycle arrest in G2/M phase and there was evidence of endoreduplication resulting in

Name	Target (IC ₅₀ <i>in vitro</i>)	Sponsor	Comments
AT9283	Aurora A (3 nM) Aurora B (3 nM)	Astex	Multikinase inhibitor, including JAK2, JAK3, Abl T3151, Flt3
AZD1152 (barasertib)	Aurora A (1369) Aurora B (0.37 nM)	AstraZeneca	
Chiauranib	Aurora B (0.37 nM)	Chipscreen Biosciences	Multikinase inhibitor, including VEGFRs, c-KIT, and PDGFRs
MLN8237 (alisertib)	Aurora A (1.2 nM) Aurora B (396.5 nM)	Takeda/millennium Pharmaceuticals	Aurora A
TAK-901	Aurora A (21 nM) Aurora B (15 nM)	Takeda	Pan-Aurora

Table 1.
 Aurora kinase inhibitors studied for lymphomas (from: Refs. [15, 20, 49, 60]).

polyploidy. These changes led to dose-dependent apoptosis of both cell lines when alisertib was used at 100 nM or higher.

Zullo et al. studied the cytotoxic effects of alisertib *in vivo* [51]. In addition, the effects of various combination drug regimens involving alisertib *in vitro* and *in vivo* on cell lines of r/r TCL were also studied. Alisertib alone showed concentration and strong time-dependent cytotoxicity with the lowest IC₅₀ value achieved at 72 hours noted to be 60–1000 nm/L. Alisertib (IC₁₀–IC₃₀) given along with romidepsin (IC₁₀–IC₂₀) had a synergistic interaction *in vitro* in eight different TCL cell lines following 72 hours of drug exposure [51]. The greatest interaction was seen in C5MJ, an alisertib-resistant ATLL HTLV-1 Tax⁺ cell line. This combination induced polyploidy in all TCL cell lines after 48 hours of treatment. There was also evidence of increased apoptosis with approximately 13 and 52% of cells showing apoptosis with increasing concentrations of alisertib (50 nmol/L and 100 nmol/L) used. In this same trial, *in vivo* analysis with this combination regimen was conducted on a xenograft model using HH cell lines of TCL. The combination drug regimen was statistically superior compared to single agent alone and control group cohort (dimethyl sulfoxide) in decreasing the mean tumor burden over time ($p < 0.05$) and in prolonging the survival in mice ($p < 0.05$) by day 58. Drug concentration analysis in the animals inside the tumors showed that concentration of alisertib in the combination tumor samples increased at 1 (400 vs. 100 nmol/L) and 6 hours (300 vs. 150 nmol/L) compared to tumor samples in mice where drug was given alone. These data support synergistic cytotoxicity of a combination drug regimen of alisertib plus romidepsin [51]. In the same study, alisertib was also evaluated in combination with other drugs including pralatrexate or ixazomib, but there were no synergetic interactions *in vitro* in TCL cell lines.

Immunohistochemistry (IHC) analysis of tumor samples from patients treated with alisertib for r/r PTCL (SWOG 1108) showed a high Ki-67 and programmed death ligand (PD-L1): PD-1 staining ratio of 8.9-fold [52]. Increased levels of PD-L1 are associated with immune suppression. In view of this, Islam et al. conducted a study where alisertib was given along with PD-L1 antibody (BE0101,

Bio X Cell, NH) in mice with r/r PTCL xenografts (CRL-2396 cells) [52]. Since the pan-PI3K inhibitor (PF-04691502) inhibits expression of the PD-L1 along with vincristine, these were also added to the former drug combination, and the results were compared between the two groups. Alisertib given alone resulted in tumor growth regression of ~30%, whereas PD-L1 antibody given alone had no anti-PTCL activity. Alisertib plus PD-L1 antibody resulted in ~90% TGI, but 20% of mice had a relapse at 2 weeks and 50% mice relapsed at 4 weeks. The combination of alisertib plus PD-L1 antibody plus pan-PI3K inhibitor and vincristine showed a 100% TGI. Only 25% of mice had recurrence at 4 weeks after discontinuation of treatment. It was noted that the OS with the four-drug regimen ($p < 0.0001$) was statistically superior to the two-drug combination.

3.2 Clinical trials involving aurora kinase inhibitors

AK A inhibitors have been studied in clinical trials after antitumor activity was shown in multiple in vitro and in vivo studies (**Table 2**). In two phase I trials by Cervantes et al. ($n = 59$) and Dees et al. ($n = 87$) in patients with advanced solid organ malignancies, the maximum tolerated dose of alisertib was 50 mg twice a day for 7 days in a 21-day cycle [53, 54]. Similarly, in another phase I study by Kelly et al. ($n = 58$), alisertib was evaluated in patients with multiple relapsed/refractory hematologic malignancies (multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia) [55]. In this study there were two patients with advanced PTCL. Just as with the other phase I studies, this study also determined that the MTD for alisertib was 50 mg twice a day for 7 days. The drug pharmacokinetics was also studied, with the terminal elimination half-life noted to be 19.5 hours. The safety analysis showed that most frequent grade 3 or greater adverse effects were hematological in nature including neutropenia (45%), thrombocytopenia (28%), anemia (19%), and leukopenia (19%). One patient with PTCL experienced a PR.

Given the promising outcomes of alisertib in preclinical studies and previous phase I clinical trials, phase II trials were conducted for PTCL patients [56, 57]. In one such study by Friedberg et al. ($n = 48$), alisertib was given to patients with multiple hematological malignancies (diffuse large B-cell lymphoma, mantle cell lymphoma, transformed follicular lymphoma, Burkitt's lymphoma, non-cutaneous T-cell lymphoma) at a dose of 50 mg twice a day for 7 days in 21-day cycles. This study included eight patients with advanced PTCL. Four of eight patients (ORR = 50%) with advanced PTCL showed a clinical response (CR/PR). Three patients that showed response continued to be in remission and had received alisertib for greater than 1 year at the time of publication of the study [57]. In the phase II study by Barr et al. ($n = 37$) patients with various subtypes of r/r PTCL (PTAL, NOS ($n = 13$), AITL ($n = 9$), adult T-cell leukemia/lymphoma ($n = 4$), anaplastic large-cell lymphoma ($n = 2$), extra nodal natural killer/T-cell lymphoma ($n = 2$), and transformed mycosis fungoides ($n = 7$)) received alisertib at the RP2D. In patients with PTCL, the ORR was 30% (CR = 7%, PR = 23%). The long-term outcomes were reported for the whole group and not reported for PTCL subtypes. The median PFS time was noted to be 3 months with a 1-year PFS rate of 8%. The median OS was determined to be 8 months, with OS at 1 year estimated to be 30% for the entire group. The long-term outcomes in this study could have been negatively biased because none of patients with transformed mycosis fungoides showed any clinical response with alisertib. As seen in the phase I studies, the most common grade 3 or higher adverse effects were due to myelosuppression (neutropenia 32%, anemia 30%, thrombocytopenia 24%). Common non-hematologic adverse effects included fatigue (50%), alopecia (24%), and mucositis (20%) [56].

Author	Phase	No. of patients	MTD	Response	EFS/PFS	OS	SE (>grade 3)
Kelly et al. [55]	I	2	50 mg bid for 7 days	PR = 50%	NL	NL	Neutropenia = 9% Gi side affects Alopecia
Friedberg et al. [57]	II	8	NR	ORR = 50%	1 yr. = 75%	1 yr. = 75%	Neutropenia = 63% Leukemia = 54% Anemia = 35% Thrombocytopenia = 33% Stomatitis = 15% Fatigue = 6%
Barr et al. [56]	II	30	NR	ORR = 30% CR = 7% PR = 23%	NLS	NLS	Neutropenia = 32% Anemia = 30% Thrombocytopenia = 24%
O'Connor et al. [58]	III	A = 120 C = 118	NR	ORR A = 33% ORR C = 43%	mPFS A = 3.7 m mPFS M = 3.4 m	mOS A = 9.9 m mOS M = 12.2 m	Grade 3 A ≥ 85% Grade 3 M ≥ 81%

Abbreviations: No., number; MTD, maximum tolerated dose; NR, not reached; PR, partial remission; ORR, overall response rate; CR, complete remission; EFS, event free survival; PFS, progression-free survival; SE, side effects; NL, not listed; NLS, not listed separately for alisertib; mPFS, median progression-free survival; mOS, median overall survival; A, alisertib; M, monotherapy; SE(>grade 3), greater than grade 3 side effects; yr. = year.

Table 2.
 Clinical trials of alisertib in treatment of relapsed/refractory PTCL.

Based on good tolerance and positive response/survival seen in patients with advanced PTCL in multiple phase I and II studies with alisertib, an international phase III randomized controlled study was conducted [58]. In this study, patients with r/r PTCL received either enteric-coated alisertib (n = 120) at a dose of 50 mg twice a day for 7 days in a 21-day cycle or investigator's choice of monotherapy treatment (n = 118) using pralatrexate, romidepsin, or gemcitabine. The treatment was intended to be continued until disease progression, unacceptable toxicity, or for 2 years. An interim analysis showed that ORR, median PFS, and median OS were 33%, 3.7 months, and 9.9 months versus 43%, 3.3 months, and 12.2 months, respectively, with alisertib and investigator's choice of treatment. The rate of grade 3 or higher side effects was 85% for alisertib and 81% for the investigator's treatment choice. Since the interim analysis of this phase III study failed to show superior outcomes of alisertib compared to investigator's preferred choice of drugs, a decision was made by the investigators to discontinue the study.

Given the promise of combination regimen with alisertib given along with another drug that is generally used for patients with r/r PTCL in preclinical studies, phase I clinical studies with some of these regimens are in progress. In one such phase I study by Strati et al., alisertib plus romidepsin in patients with PTCL (n = 3) or aggressive B-cell lymphoma (n = 16) [59] showed that the drug combination was well tolerated with most common grade 3–4 side effects due to myelosuppression. One patient with PTCL showed a CR and other two patients showed stable disease. The enrollment for the highest dose for these regimens is ongoing. Similarly, in another phase I study, vorinostat plus alisertib is being evaluated for patients with r/r PTCL (NCT01567709).

4. Conclusion and future directions

PTCLs are highly aggressive clinically challenging diseases, with high rates of relapse, and poor overall survival with traditional cell cycle directed anti-lymphoma therapies. Effective treatment options are limited for patients with newly diagnosed and r/r PTCL. AKs are aberrantly expressed and active in PTCL, leading to uncontrolled cell division, immune suppression, and oncogenesis. AK inhibition leads to catastrophic errors of mitosis, such as defective cytokinesis, misaligned centrosomes, and mitotic spindle malformation, culminating in apoptosis [60, 61]. However, drug-resistant non-diploid cells can enter the cell cycle by reductive divisions during intermittent therapy [62]. Several AK inhibitors have been studied preclinically and clinically in trials for patients with r/r PTCL. Despite showing benefit in phase II studies, an interim analysis of a phase III trial of alisertib, a selective AK inhibitor, failed to show improved response or survival rates compared to standard of care single-agent monotherapy for patients with r/r PTCL. However, targeting cell proliferation plus immune suppression in preclinical studies of novel combinations of alisertib plus a PD-L1 inhibitor plus a pan-PI3K inhibitor plus vincristine as well as combined HDAC inhibition plus alisertib shows synergistic activity and prolonged survival in mouse models of PTCL. Furthermore, AK inhibition may improve or restore tumor sensitivity to anticancer agents, particularly microtubule-targeted and platinum-containing drugs in the context of pathogenic *TP53* mutant status. Continued clinical studies of novel drug combinations with AK inhibitors are warranted to target not only malignant T cells but also their immune suppressive T cells residing in the tumor microenvironment.

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Conflict of interest

There is no conflict of interest for all three authors.

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