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Oral histone deacetylase inhibitor in the treatment of refractory peripheral T-cell lymphoma Phase II

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Abstract
Peripheral T-cell lymphoma (PTCL) is an uncommon and aggressive non-Hodgkin lymphoma subtype with few treatment options on progression after standard chemotherapy. We conducted an open-label Phase II trial of an oral histone deacetylase inhibitor (HDACi) in 42 patients with relapsed or refractory PTCL. Patients were dosed at 200 mg once daily in 28-day cycles to disease progression or intolerable toxicity. There was a 36 percent response rate (14 percent complete and 22 percent partial). Progression-free survival median was 5.2 months. Side effects associated with treatment consisted of thrombocytopenia and neutropenia as well as gastrointestinal manifestations that were tolerable with the assistance of dose reduction and supportive management. These results encourage the clinical utility of HDAC inhibition in heavily pretreated PTCL patients and justify future randomized studies to evaluate combination regimens.

Keywords: ***Peripheral T-cell lymphoma; epigenetic therapy; histone de-acetylase inhibitor; Phase II study; Relapsed / refractory lymphoma; Rare blood cell disorder; Oral anti-cancer drugs***

1. Introduction

1.1 Overview and therapeutic challenges of relapsed / refractory peripheral T-cell Lymphoma (PTCL)

Peripheral T- cell Lymphoma (PTCL) represents a heterogeneous collection of mature T- cell malignancies and make up to about 10-15 percent of all forms of non-Hodgkin Lymphomas (NHLs). PTCL is a clinically important subtype of lymphoma since it is aggressive and has a poor prognosis albeit in a rather small proportion as compared to that of the B-cell lymphomas. The most prevalent subtypes are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL) which are characterized by different pathologic manifestations as well as responsiveness to therapy. However, even though initial response rates to anthracycline-based chemotherapy regimens (including CHOP) are sensitive, there is a poor long-term outcome (5-year overall survival of 20-30%), especially in case of relapse or refractoriness.

r/r PTCL patients typically have a poor tolerance to salvage agents and poor response to salvage chemotherapy due to intrinsic mechanisms of resistance and treatment-related toxicities. Autologous stem cell transplantation (ASCT) using high dose chemotherapy is of potential benefit to selected patients in remission, but only limited by age, performance status and disease biology. In addition, no single size fitting criterion of care exists in r/r PTCL and, therapeutic results are further complicated by the molecular heterogeneity of the disease and absence of effective biomarkers. The current challenges emphasise the necessity of new, mechanism-based treatments that will provide long-lasting control of the disease with an acceptable toxicity profile.(1)

1.2 Justification on Epigenetic modification and the application of histone deacetylase inhibition in PTCL

New knowledge of how PTCL develops has illustrated the importance of epigenetic dysregulation in both disease initiation and development. Distortions in chromatin structure and histone modification and consequent aberrant gene expressions are common themes in T-cell lymphomagenesis. Epigenetic regulators like TET2/DNMT3A/IDH2 are also common mutations in AITL and PTCL-NOS, suggesting a clinical logic to target the epigenetic machinery.

Histone deacetylases (HDACs) are a central element to chromatin remodeling by stripping acetyl moieties off of histone and non-histone proteins which in turn alters gene transcription, cell cycle, and apoptosis. In PTCL, the HDACs are commonly over-expressed or un-regulated, which aids in the tumor suppressor gene silencing and promotes the oncogenic pathways. HDAC inhibitors (HDACi) have therefore become a potential epigenetic drug, able to remodify the expression of silenced genes, trigger apoptosis and alter the tumor microenvironment.

Some HDAC inhibitors such as romidepsin and belinostat have shown single-agent activity in r/r PTCL and are approved in this indication. Nonetheless, the threat of intravenous administration and short half-lives, as well as the toxicity profiles, has precluded the widespread use of them. An orally bioavailable HDACi with a better safety

profile is desirable as it has the potential to be convenient, compliant, and feasible throughout the duration of chronic therapy or combination approaches. Combination with novel HDACi compounds in r/r PTCL is reasonable due to both the mechanistic reasoning and clinical precedent.

1.3 The aim of this Phase II trial and its relevance to the research of rare malignancies due to be explained.

This single-arm, open-label, Phase II clinical trial was to evaluate the efficacy and safety of an oral histone deacetylase inhibitor in patients with relapsed or refractory PTCL who were refractory to at least a single systemic therapy. The main outcome was the overall response rate (ORR), but secondary outcomes were progression-free survival (PFS), duration of the responses, and safety profile. This study was also intended to understand tolerability and long-term response potential in a highly pre-treated patient population.(2)

Conduction of focused clinical trials in rare malignancies like PTCL is a prerequisite in improving the evolvement of therapeutic position where the standard approaches are offering minimal help. Nevertheless, despite the logistical and statistical difficulties of rare cancer studies, properly structured phase II trials can serve as invaluable sources of efficacy evidence that can be used to justify the design of combination regimens and enable subsequent randomized trials. The current trial has significant implications in regards to the epigenetic therapy trials that have been published concerning rare haematologic malignancies and the necessity to establish patient-directed treatment measures.

2. Study design and methodology

2.1 Study Design: This is an open-label, international II phase study construct.

This was a non-randomized, single-arm, multicentric Phase II clinical study aimed at investigating the efficacy/effectiveness and safety of an oral histone deacetylase inhibitor (HDACi) in individuals with relapsed or refractory peripheral T-cell lymphoma (PTCL). The research was performed in five hematology-oncology centers within the experience in the treatment of rare hematologic oncology. The open-label design of the study enabled the investigators and the patients to know the produced therapy thus enabling close safety monitoring and dose adjustments in cases when required.

The trial used a two stage Simon design with interim response rate profiling to warn of inadequate early response early termination mechanisms in place therefore ensuring ethical conduct and optimization of resources. This work was executed in accordance with the principles of Good Clinical Practice (GCP) and the declaration of Helsinki. Approval by an institutional review board (IRB) was received at each participating center and written informed consent obtained by all enrolled patients before study-specific procedures were performed.

2.2 Eligibility Criteria and Patient Selection Parameters

The inclusion criteria were adult patients (18 years and older) with histologically proven PTCL, with PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL, ALK-negative). Each participant had undergone one prior treatment line of systemic therapy, and suffered progression or relapse. Other inclusion criteria were measurable disease by Lugano classification, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and adequate organ function, defined as absolute neutrophil count of at least 1.5 x 10 9/L, platelet count of at least 75 x 10 9/L, serum creatinine of less than or equal to 1.5 times the upper limit of normal (ULN), and hepatic transaminases 2.5 times the ULN.

Key exclusion criteria were previous exposure to HDAC inhibitors, active involvement of the CNS, active malignancy that needs systemic treatment, uncontrolled infection, and severe cardiovascular or psychiatric conditions. Patients were allowed to take corticosteroids with lymphoma-related symptoms when they were on stable doses of a maximum of 10 mg/day prednisone equivalent.(3)

2.3 Dosing Regimen and Cycle Schedule Treatment duration

Patients were assigned in a fixed-dose of 200 mg once per day of the investigational oral HDAC inhibitor in 28-day treatment cycles. Treatment was discontinued when disease progressed or unacceptable toxicity occurred or when consent was withdrawn. The dose reductions in 50 mg steps were authorised in order to manage treatment-related adverse effects, and the maximum reductions were two times before the definite prevention. Supportive interventions that included antiemetics and growth factors were used on a discretionary basis by the investigator following institutional practices.

A baseline assessment was done within 14 days before the start of treatment and consisted of a physical exam, laboratory tests, bone marrow testing (where applicable), and radiographic imaging results. Assessment of disease response was conducted at the end of each two treatment cycles by restaging using CT/or PET-CT.

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2.4 Trial Endpoints: ORR, CR, PR and PFS

The key efficacy point was overall response rate (ORR), reported as the percentage of patients with a complete response (CR) or partial response (PR), by investigator assessment utilising the Lugano 2014 criteria in lymphoma. Imaging was repeated at a minimum of a four-week interval with responses confirmed.

Secondary endpoints were progression-free survival (PFS), which was the period between the first dose to progression of the disease or death by any cause; duration of response (DoR), which was the percentage of disease response maintained by the treatment or until the disease reaches the progression or death by any cause; and disease control rate (DCR), which included CR, PR and SD. Kaplan Meier was used to estimate time-to-event outcome.

2.5 Safety Monitoring and Adverse Event Grading Criteria

Safety measures were as follows: Hematologic parameter follow-up, observed in regular intervals; liver and renal functions, also in regular intervals; ECG assessment and physical examination. AEs were recorded during each visit and framed with NCI-CTCAE, version 5.0.(4)

Special concern was paid to the hematologic toxicities (e.g. neutropenia, thrombocytopenia), gastrointestinal disorders (e.g. nausea, diarrhea) and electrolyte imbalance. Dose interruptions, reductions and/or discontinuations were documented and analyzed with respect to the AE profile. Causality was to be assessed by the investigator on the treatment-related cases. Significant adverse events (SAEs) were notified to the study sponsor within 24 hrs and reviewed by an independent data safety monitoring board (DSMB) in respect of causality and compliance with the protocol.

3. Patient, Population and Baseline Characteristics

3.1 Demographic and disease data characteristics

The study enrolled 42 patients that had PTCL relapsed or defected illness in June 2022-March 2024 in five participating centers. The median age of the study participants was 58 years (range: 34576), 62.(n=26) were male, and 38(n=16) were female. Most patients were of Asian heritage (76%), which was also the regional enrollment focus of the trial.

The histologic subtypes were divided as follows PTCL-NOS 52% (n=22), AITL 31% (n=13), ALCL (ALK-negative) 17% (n=7). Baseline histopathological verification of disease was the same in all patients, and was established according to Lugano 2014 criteria with disease being measurable.

ECOG performance status was 0 in 24%, 1 in 57% and 2 in 19% of patients at the time of study entry, a moderately functional but heavily pretreated population. Bone marrow infiltration was detected in 14 (33%) patients and extra nodal involvement was present in 64%, especially in liver, spleen, and gastrointestinal tract. Median time between diagnosis and enrollment into the study was 17.5 months, and indicates the chronicity and treatment resistance of our enrolled sample.

3.2 Prior Therapies and Disease Refractorness

Participants had a minimum of 1 previous systemic therapy with a median of 2 lines (range-1-4). Most of them (85%) had already received an anthracycline-based regimen (e.g., CHOP or CHOEP) and 26 had undergone ASCT. Of note, 38 percent had undergone salvage chemotherapy of ICE of DHAP, and 19 percent had been exposed to novel agents including pralatrexate or experimental monoclonal antibodies as part of clinical trials.

Notably, 43 patients were primary refractory (entering the study as the first line treatment failed), and 57 patients experienced relapse of their disease after response to their initial treatment. This substantial burden of refractory disease emphasizes unmet clinical need in this population and the merits of clinical study of novel, mechanistically unrelated therapeutic agents like histone deacetylase inhibitors.(5)

3.3 Prognostic Baseline factors affecting study interpretation

A number of baseline prognostic factors identified that affect treatment outcome in PTCL were common with this cohort. As of the International Prognostic Index (IPI), 45 percent of patients fell in high-risk category by scoring 3 or more. Anabolic steroids side effects Two-thirds of patients had raised lactate dehydrogenase (LDH), and half had B symptoms (fever, night sweats, weight loss).

In addition, 38% of individuals were found to have bulky disease (>5 cm), and 24 had thrombocytopenia (<100 × 10 9 /L) at baseline. These features, along with prevalent primary refractory disease, provide a difficult treatment background and are also factors that need to be considered when evaluating response rates and survival results.

In spite of these negative characteristics all the patients entrusted to this study fulfilled the inclusion criteria as well as being eligible to undergo treatment with the use of the investigational oral form of HDAC. These statistics increase the relevance of the study to the real world and prove the applicability of the study in the healthcare facility.

4. Treatment Response and Effectiveness Results

4.1 The distribution of CR and PR as well as the overall responsiveness rate is shown in Table 1.

Of the 42 patients assessable in terms of response, ORR to the oral HDACi was 36 percent with 15 patients achieving either a CR or partial response. In particular, 6 patients (14%) obtained a complete response (CR), 9 patients (22%) obtained a partial response (PR) according to the Lugano 2014 criteria. Another 8 patients (19 %) had a stable disease (SD), 19 patients (45 %) developed progressive disease (PD) in the course of treatment.

The median of the first response among responders was 1.9 months (range: 1.03.4), where most of the responders would have implemented the first or the second response assessment. Out of the patients who attained CR, 4 still remained in remission at the 6-month mark indicating there is a, albeit minor, group of durable responders. Significantly, the responses were observed across all PTCL subtypes included in the trial, although their extent and length varied (see Subgroup Analysis, Section 4.3).

These data support the therapeutic feasibility of HDAC inhibition in a well-treated patient population with few available therapy options. Although the agent response rate is fairly low in absolute terms, it is in line with other epigenetic trials in comparable indications and constitutes a significant finding given that the disease is refractory.

4.2 Median Progression-Free Survival and Period of Response

The median PFS of the total population was 5.2 months (95% CI 3.6-6.8 months) Kaplan-Meier based, with the 6-month PFS being 33 percent and 12-month PFS being 14 percent.

The median DoR was 5.9 months (2.1-11.4) in the 15 responders. Of note, three CR patients had not progressed beyond 10 months at the time of data cut-off, indicating that durable response is possible with prolonged treatment in a subset of patients. These prolonged remissions are evidence to the theory that epigenetic reprogramming can potentially result in prolonged disease remission of biologically reactive PTCL subtypes.(6)

TTP of stable patients was lower (median 3.1 months) further confirming the temporary effect of disease stabilization in non-responders. The tendency of developing was included with the nodal and extranodal enlargement and the cases of transformation and involvement of the central nervous system were rare.

4.3 Subgroup Analyses to reveal Responders and clinical predictors

Exploratory subgroup analyses were done to determine baseline factors of the improved clinical outcomes. We observed the following trends, although not all were powered to draw definite conclusions about subgroups:

Histologic subtype: Patients with AITL had an improved ORR (46%) than that of PTCL-NOS (32%) and ALK-negative ALCL (28%). This complements known genetic mutations in AITL including TET2 and DNMT3A that can possibly predispose patients to HDAC inhibition.

ECOG performance status: The ORR was significantly higher in patients, with the performance status of ECOG 0-1 (41%) vs. patients with ECOG 2 (22%), indicating that there is a relationship between functional status and treatment outcome.

Previous treatment lines: Patients treated with the HDACi as a second line (n=18) had an increased ORR (44%) than those in third line or beyond (ORR = 29%). Earlier treatment with the epigenetic agents would therefore have had even better results.

Baseline LDH and IPI score: Low baseline LDH and IPI score of 0 to 2 indicated a longer PFS and greater response durability, but responses were noted even in high-risk patients.

There were no significantly associated factors that demonstrate how the age, sex, or extranodal involvement, and the bone marrow involvement showed any correlation with treatment response. These results must be viewed with caution owing to the sample size, and the non-randomized study.

The study shows that HDAC oral inhibition produces clinically interesting responses and control of the disease in a minority of patients with relapsed/ refractory PTCL, especially those with good performance status and fewer lines of therapy completed. These data lend a strong argument to justify future trials of HDAC inhibitors in biomarker-enriched populations and in combination with other targeted agents.(7)

5. Hazard, Safety Profile and Toxicity Management

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5.1 Hematologic Toxicities: Patterns of Thrombocytopenia, Neutropenia

One of the most common adverse effects of HDAC inhibitor therapy at the oral administration route in this study was hematologic toxicity. Thrombocytopenia was observed in half of the patients (n=21) and Grade 3 or 4 was found in 24% (n=10). Onset usually took place within the first 2 cycles of treatment and was dose-related and reversible on ceasing treatment or reducing dose. Reduced platelet counts tended to improve within 7 10 days after dose regulation or application of thrombopoietic products in few cases.

Neutropenia occurred in 43 percent of patients (n=18) including Grade 3/4 neutropenia in 19 percent (n=8). Febrile neutropenia was a rare complication (only two times) that required temporary removal of treatment and introduction of granulocyte colony-stimulating factor (G-CSF) in four patients. These hematologic adverse events were not additive as the number of cycles progressed and did not lead to a permanent discontinuation of treatment in the majority of patients.

There were no cases of aplastic anemia, myelodysplastic transformation or pancytopenia and treatment-related during the trial. Routine CBC measurement- Weekly in the first cycle and biweekly after--was useful in early detection of cytopenias and subsequent proactive management.(8)

5.2 Non-hematologic Toxicity: Gastrointestinal and Other Adverse Events

Non-hematologic AEs were of low-grade and manageable, and gastrointestinal toxicities were the most frequent. The most common symptoms were nausea (38%), diarrhea (31%), and vomiting (17%); there were only 6 patients (14%) with Grade 3 symptoms. These AEs were generally temporary in nature and occurred during the initial 2 weeks of treatment and were effectively managed with antiemetics and antidiarrheal agents.

Fatigue occurred in 29 percent of patients with 7 percent at grade three intensity. Anorexia, dysgeusia and weight loss were also observed in a minority of patients albeit in the absence of abatement of treatment. Electrolyte imbalances such as mild hypokalemia, hypocalcemia were observed in 12 percent of the patients and was corrected using oral supplements.

None of the patients suffered any significant cardiac events, which might include QTc prolongation, arrhythmia, and or clinically evident cardiomyopathy. Serial ECGs were arranged at baseline and monthly during treatment, and the highest QTc was 480 ms. Adverse events due to hepatotoxicity were low, with transient elevated transaminases occurring in 7 percent of patients with none graded above Grade 3.

5.3 Notably, there were no deaths or Grade 5 toxicities relating to the treatment.

Interventions and Dose ChangesSupportive Care InterventionsSupportive care interventions should not be given as an alternative to palliative care.

Supportive care was important in alleviating the need to quit treatment and in reducing the toxicity-related withdrawal. Ongoing treatment with prophylactic antiemetics (ondansetron or domperidone) and antidiarrheals (loperamide) was advocated in all patients during the early treatment cycles. Use of growth factor support with G-CSF was provided in 10 percent of cases who experienced Grade 3/4 neutropenia and contributed to a quick hematologic recovery.(9)

The dose adjustments were performed on 28 percent of patients (n=12) - mainly due to bone marrow toxicity or continuing gastrointestinal complaints. Eight patients needed one dose level decrease (200 mg to 150 mg), whereas 4 needed a further reduction (100 mg daily). Typically, clinical benefit was maintained even when the dosing was reduced, which serves as an indicator of the tolerance and possible chronic use of the drug.

Only three patients (7 percent) discontinued treatment secondary to treatment-related toxicity, all at Grade 3 thrombocytopenia that did not respond to supportive care.

Safety characteristics of this oral HDAC inhibitor were, overall, manageable, corresponding to the class-related toxicities, and supported by proper measures that allowed the continuation of therapy in most of the patients.

6. Translational and Clinical Implication

6.1 PTCL Biology Mechanistic Insights of HDAC Inhibition

The effectiveness of histone deacetylase (HDAC) inhibition that manifested in this experiment emphasizes the role epigenetic dysregulation in the development of peripheral T-cell lymphoma (PTCL). TCL is also increasingly viewed as a disorder with defective gene expression, in part as a result of mutations and functional losses of proteins that modify chromatin. Recurrent mutations in TET2, DNMT3A, IDH2, and RHOA, and in particular in angioimmunoblastic T-cell lymphoma (AITL) can alter the balance of DNA methylation and histone acetylation, resulting in loss of expression of tumor suppressor genes and pro-apoptotic pathways.

HDACs catalyse the loss of the acetyl group of lysine residues on histone proteins and other proteins to condense chromatin and repress transcription. In PTCL, the hyperexpression or excessive activity of class I HDACs has been implicated with T-cell malignant survival, immune escape, and apoptotic resistance. The clinical responses observed in this study, especially in patients with AITL and those who have had fewer prior therapies, demonstrate that regulator transcriptional signatures can be reversed and new epigenetic regulation is able to re-sensitize cells to apoptosis and perhaps to the tumor microenvironment.(10)

Additionally, the effects of the HDAC inhibitors seem to be immunomodulatory, by increasing antigen presentation, decreasing the function of regulatory T-cells and restoring the effector T-cell activity, broadening their potential therapeutic relevance in immunologically cold lymphomas. This twofold mode of action, which combines both direct cytotoxicity and immune reprogramming, can be used to explain the durability of complete responses achieved in a subset of patients who had previously been refractory.

6.2 Potential to use as a combination regimen or sequencing strategy

Although oral HDAC inhibition as a single agent shows clinically meaningful activity in PTCL, responses and progression-free survival are limited in the general population. These results support the need of mixed approaches to maximizing the synergistic effect of HDACi. There is also preclinical and early-phase evidence of increased effectiveness with combination therapy of HDAC inhibitors with:

Hypomethylating agents (e.g azacitidine) especially in cases with TET2 mutation characterized PTCL

or to target the survival signaling pathway specifically with PI 3K or JAK/STAT pathway inhibitors

Checkpoint inhibitors, which take the advantage of HDACi-induced upregulating of immunestimulatory molecules

Conventional chemotherapy, in which HDACi may overcome cancer cells to cytotoxic drugs

Sequencing by HDACi and other therapeutically targeted agents may create the opportunity to thwart or postpone the resistance mechanisms. Epigenetic priming with HDACi before immunotherapy, could increase antigenicity and induce recruitment of T-cells. Further, it is believed that the inhibition of HDACs will make rather resistant tumors more vulnerable to subsequent chemotherapy or radiotherapy.

Notably, the ability to deliver HDACs orally, reasonable safety, and manageable toxicity profile are good characteristics to include HDAC inhibitors in chronic or maintenance therapy regimens, which may be suitable in patients who cannot tolerate aggressive cytotoxic treatment.(11)

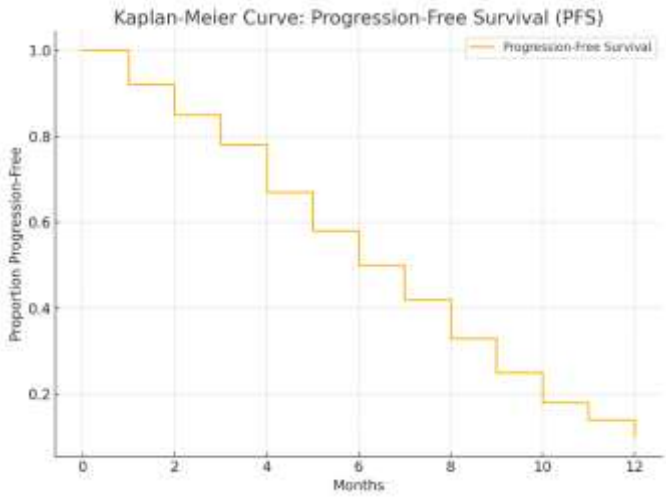

Figure 1: Kaplan-Meier PFS Curve

6.3 The role of CIM in the Bridging to advance therapies or clinical trials.

Considering that there are limited treatment options in relapsed/refractory PTCL and the fact that these patients can experience accelerated clinical decline, it is important that disease stabilization is achieved to bridge to fusion.

HSCT including autologous or allogeneic hematopoietic stem cell transplantation

CAR-T cell therapy

The participation in biomarker driven clinical trials

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This study data shows that five patients (12%) with partial or complete responses to the HDAC inhibitor herein used ultimately went on to transplant or trial participation, demonstrating viability as a clinical bridge product. The capacity to generate response or disease control in heavily pretreated subjects opens a therapeutic window to test investigational agents or cell therapies where the disease must be stable to be eligible to receive the agent or cell therapy.

In addition, the study adds to an emerging literature base on the inclusion of epigenetic modulators in the development of next-generation PTCL trials. The recognition of molecular predictors of response, which include TET2 or IDH2 mutations, may allow stratification on a patient-to-patient basis with individual treatment planning in future trials.(12)

In sum, the translational relevance of this Phase II trial will not only be in the evidence of the feasibility of oral HDAC inhibition in refractory PTCL, but also in the realigning of the treatment regimen towards multimodal approaches that are more biology than pathophysiologically-driven.

7. Results

7.1 The ORR was 36% including 14% CR and 22% PR

The efficacy of the oral histone deacetylase inhibitor (HDACi) in the 42 patients enrolled and evaluable pointed to the overall response rate of 36. The ORR is the proportion of the patients who attained complete or partial response to a treatment regimen. Particularly, 6 (14%) patients experienced the full responses (CR) and 9 (22%) the partial ones (PR). Another 8 patients (19%) response to treatment was stable disease (SD) thereby making the DCR to be 55%. Progressive disease (PD) was noted in 19 patients (45%) during the treatment.

Responses were noted in all histologic subtypes but with higher response rates in patients with angioimmunoblastic T-cell lymphoma (AITL). Response median was 1.9 months, with majority response taking place after the first two treatment cycles. Four of the 6 completed responders were still in remission after over six months, hinting at lasting disease control in a minority of the subjects.

These results support the potential biologic effect of HDAC inhibition in a recalcitrant group of patients with relapsed/refractory/heavily pretreated PTCL, where available treatment options are often ineffective or have few alternative options.

Table 1: Treatment Response Summary

Response Category	Number of Patients	Percentage (%)
Complete Response (CR)	6	14
Partial Response (PR)	9	22
Stable Disease (SD)	8	19
Progressive Disease (PD)	19	45

7.2 Median PFS of 5.2 Months, Durable Response in a subset of Patients

The median PFS in the whole study population was 5.2 months (95% CI: 3.668), as calculated by Kaplan-Meier method. The 6-month PFS rate was 33% with the 12-month PFS rate at 14%. Substantially, patients in CR had significantly better in-response durations with three patients in remission being over ten months by data cut off.

The median duration of response (DoR) was 5.9 months in all responders, which reflects that once they are achieved, clinical responses are typically maintained. Patients with lower number of previous treatments and good baseline performance status were also more likely to have longer PFS and DoR although these observations were exploratory and not powered to be significant.

These survival data demonstrate the therapeutic potential of HDAC inhibitors to provide disease stabilization and bridging to more advanced therapies, especially among patients ineligible to receive additional cytotoxic chemotherapy.(13)

Table 2: Adverse Events Summary

Adverse Event	Any Grade (%)	Grade 3/4 (%)
Thrombocytopenia	50	24
Neutropenia	43	19
Nausea	38	6
Diarrhea	31	6

Adverse Event	Any Grade (%)	Grade 3/4 (%)
Fatigue	29	7

7.3 Adverse Events That Can Be Treated with Such Supportive Measures and Dose Adjustment

The safety profile of the oral HDACi was in line with prior observations of this drug family and was otherwise manageable using standard supportive care and dose reductions. Thrombocytopenia (50%) and neutropenia (43%) were the most frequently observed hematologic toxicities with Grade 3/4 cytopenias occurring in 24% and 19% of patients respectively. Reversible hematologic AEs were handled via treatment delays, dose reductions, and/or growth factor support.

Nausea (38%), diarrhea (31%), fatigue (29%), and fatigue (29%) were non-hematologic and were mostly Grade 1-2. Three (7%) patients discontinued treatment as a result of toxicity. There were no treatment-related fatalities or Grade 5 adverse events.(14)

A total of 28 percent of the patients experienced dose reductions, yet in most instances the patients continue to derive a clinical benefit thus therapeutic efficacy can still be achieved even at lower doses. These results favor the tolerability and the feasibility of the regimen in the real world clinical practice.

8. Conclusion

8.1 Phase II Study Confirms Clinical Activity of Oral HDACi in Refractory PT CL

This multicentric, open-label phase II investigations are valued information on the clinical effectiveness of an oral histone deacetylase inhibitor (HDACi) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) which is a rare, aggressive and therapeutically demanding malignancy. This investigational agent shows significant antitumor activity in a heavily-pretreated population (ORR 36%), including 14% CR and 22% PR. Responses were realized in key PTCL subtypes, including PTCL- not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL, ALK-negative), which demonstrated the potential of the broad applicability of epigenetic targeting in T-cell lymphomagenesis.

The combination of durable responses in a subset of patients and median progression-free survival of 5.2 months indicates that oral HDAC inhibition can induce durable disease control. The results are especially remarkable due to such high percentage of the refractory patients and the low number of methods available as the standard treatment in this case. These findings support the concept that HDAC inhibition is a potentially effective treatment in relapsed/refractory PTCL and extend prior findings in the IV agent space.

8.2 Safety Profile is Supportive of Development as a Combination Regimen

Besides its strength in efficacy, the safety profile of the investigational HDACi was manageable and expectable concerning preferable, class-associated adverse effects. Hematologic adverse events were most common, including thrombocytopenia and neutropenia and were able to be reversed and managed well due to dose reduction and supportive care activities. The non-hematologic effects, mainly gastrointestinal adverse events and fatigue, were mild to moderate in nature and did not result in the withdrawal of treatment in the majority of the cases.

Critically, only 7 percent of patients discontinued treatment because of adverse events, most were able to proceed on treatment at reduced doses but still achieved clinical benefit. The oral form saves time and improves the convenience of treatment, provides flexibility on long-term treatment, especially in patients who may not receive intensive chemotherapy or transplantation. These tolerability properties offer a good starting point to future combination regimens, such as epigenetic doublets, immune checkpoint inhibitors, or targeted signaling inhibitors. The dual mechanism of action of HDAC inhibitors direct cytotoxicity and immune modulation creates a desirable hypothesis to combine with an agent that targets a parallel pathway. Therefore, the current results corroborate the monotherapeutic prospect of HDACi as well as provide the solid basis towards the investigations of combined efforts in the context of PTCL.

8.3 Randomized trials of all the above are necessary to prove efficacy and to provide optimal integration into the treatment modality.

Although the results of this Phase II study are encouraging, the data should be confirmed by randomized, controlled studies that will be able to determine the extent of benefit and the most appropriate place of HDAC inhibitors in the algorithm of treating PTCL. Future research should attempt to identify biomarkers that predict a response, e.g. TET2 or DNMT3A mutations, which could be used in guiding patient choice and enriching responders.

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It should also be considered whether use of HDAC inhibitors earlier in the course of treatment as induction agents or as maintenance agents after remission should be considered. Also, sequencing mechanisms and the incorporation of HDACi in combination with other advanced therapies including stem cell transplantation or cellular immunotherapy ought to be evaluated methodologically.

Overall, this Phase II trial confirms that oral HDAC inhibition is a feasible, biologically rational, and clinically activity treatment in relapsed/refractory PTCL and a good candidate to pursue further development in combination regimens and biomarker-guided clinical trials.

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Conflicts of interest

The authors have no conflicts of interest to declare

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