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Panobinostat in combination with bortezomib in patients with relapsed or refractory peripheral T-cell lymphoma: an open-label, multicentre phase 2 trial

Daryl Tan, Colin Phipps, William Y K Hwang, Soo Yong Tan, Chun Hsien Yeap, Yiong Huak Chan, Kevin Tay, Soon Thye Lim, Yuh Shan Lee, Sathish Gopalakrishnan Kumar, Soo Chin Ng, S Fadilah, Won Seog Kim, Yeow Tee Goh, for the SGH652 investigators

Summary

Background Patients with relapsed or refractory peripheral T-cell lymphoma have a poor prognosis after conventional chemotherapy. Approved novel agents have only modest single-agent activity in most subtypes of peripheral T-cell lymphoma. Panobinostat is a potent oral pan-deacetylase inhibitor. Findings of many preclinical studies have shown synergistic antilymphoma activity when panobinostat is combined with the proteasome inhibitor bortezomib. We aimed to study the effect of panobinostat and bortezomib in patients with relapsed or refractory peripheral T-cell lymphoma.

Methods In this open-label, multicentre phase 2 trial, we recruited patients aged 21 years or older with relapsed or refractory peripheral T-cell lymphoma who had received at least one previous line of systemic therapy from five tertiary hospitals in Singapore, Malaysia, and South Korea. Patients received 20 mg oral panobinostat three times a week and 1·3 mg/m² intravenous bortezomib two times a week, both for 2 of 3 weeks for up to eight cycles. The primary endpoint was the proportion of patients who achieved an objective response in accordance with the International Working Group revised response criteria; analyses were by intention to treat. The study is completed and is registered with ClinicalTrials.gov, number NCT00901147.

Findings Between Nov 9, 2009, and Nov 26, 2013, we enrolled 25 patients with various histological subtypes of peripheral T-cell lymphoma. Of 23 patients assessable for responses, ten (43%), 95% CI 23–63) patients had an objective response, of which five were complete responses. Serious adverse events were reported in ten (40%) of 25 patients. Common treatment-related grade 3–4 adverse events included thrombocytopenia (17 [68%]), neutropenia (ten [40%]), diarrhoea (five [20%]), and asthenia or fatigue (two [8%]). We recorded peripheral neuropathy of any grade in ten (40%) patients.

Interpretation Combined proteasome and histone deacetylase inhibition is safe and feasible and shows encouraging activity for patients with peripheral T-cell lymphoma. Our findings validate those of preclinical studies showing synergism in the combination and represent a rational way forward in harnessing the full potential of novel agents in peripheral T-cell lymphoma.

Funding Novartis Pharmaceuticals, Janssen Pharmaceuticals, and Singhealth Foundation.

Introduction Peripheral T-cell lymphomas constitute a biologically heterogeneous group of aggressive cancers derived from mature (post-thymic) T cells and natural killer cells. These lymphomas are uncommon and account for 10–15% of all non-Hodgkin lymphomas worldwide.¹ However, a geographical variation in the incidence of peripheral T-cell lymphomas is well documented and in some parts of Asia, incidences as high as 20–25% have been reported.² This disparity might be caused by a higher geographical susceptibility to specific pathogenic viruses in Asian countries, such as Epstein-Barr virus and human T-cell leukaemia virus-1 (HTLV-I). With the exception of ALK-positive anaplastic large-cell lymphoma, peripheral T-cell lymphomas are associated with a poor prognosis with estimated 5-year overall survival of 10–20%.³ In the absence of a consensus on the optimum standard first-line treatment for peripheral T-cell lymphoma, most newly diagnosed patients are treated like diffuse large B-cell lymphoma with CHOP-like chemotherapy (cyclophosphamide, vincristine, doxorubicin, and prednisolone), with younger patients having the option of consolidation with upfront high-dose therapy with autologous stem-cell transplantation. Despite 50–60% of patients responding to this treatment, relapses are common and outcomes of patients with relapsed or refractory disease after failing such conventional chemotherapies have been poor.⁴

Of late, several novel agents have been approved by the US Food and Drug Administration (FDA) for patients with relapsed or refractory peripheral T-cell lymphomas. Although the objective response rate of 86% shown with brentuximab vedotin in systemic anaplastic large-cell lymphoma is remarkable, the efficacy of pralatrexate, romidepsin, and belinostat with objective response rates ranging between 25% and 29% is modest for other forms of treatment.
leads to increased cell stress and apoptosis. The combination of the two drugs is highly synergistic.

T-cell lymphoma, preclinical data suggest that the inhibition of the nuclear factor NFκB, which

Regulation, and apoptosis.

of peripheral T-cell lymphoma. Therefore, more effective treatments are needed to improve on these single agents in this setting.

Panobinostat is a pan-deacetylase inhibitor with potent activity against class I, II, and IV deacetylases. Inhibition of deacetylases induces the acetylation of both histone and other non-histone proteins, resulting in antitumour activity via increased tumour suppressor gene transcription, growth inhibition, cell cycle regulation, and apoptosis. Proteasome inhibitors such as bortezomib are clinically effective in multiple myeloma and mantle cell lymphoma. Potential mechanisms of action include inhibition of tumour growth by cell cycle arrest and induction of cell death. This process involves the inhibition of the nuclear factor kB (NFκB), which could be upregulated in some types of peripheral T-cell lymphoma and confer resistance to apoptosis. Although both panobinostat and bortezomib have only modest single-agent activities in patients with peripheral T-cell lymphoma, preclinical data suggest that the combination of the two drugs is highly synergistic. One hypothesis for synergy is through the accumulation of polyubiquitinated proteins by concurrent targeting of the proteasome with bortezomib and the aggresome pathway via histone deacetylase 6 inhibition, and this leads to increased cell stress and apoptosis. Collectively, these data and the unmet need for more novel approaches in patients with relapsed or refractory peripheral T-cell lymphomas provide a strong rationale for the clinical testing of this combination. In our multi-institutional phase 2 trial, we aimed to study the activity of this novel combination in patients with peripheral T-cell lymphoma.

Methods

Study objectives, design, and patients

In this open label, single-arm, phase 2 study done at five tertiary hospitals in Singapore, Malaysia, and South Korea, we recruited patients with relapsed or refractory peripheral T-cell lymphoma who had received at least one previous line of systemic therapy. The following histological subtypes of peripheral T-cell lymphoma as defined by WHO and confirmed by local pathologists were included for enrolment: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, extranodal natural killer (NK) T-cell lymphoma, nasal type, enteropathy-type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, cutaneous gamma or delta T-cell lymphoma, transformed mycosis fungoides, hepatosplenic T-cell lymphoma, ALK-negative anaplastic large-cell lymphoma, and ALK-positive anaplastic large-cell lymphoma that had relapsed after autologous stem-cell transplant.

Other eligibility criteria included age of 21 years or older, measurable disease according to International

B (NFκB), which

implication of all the available evidence

Because peripheral T-cell lymphoma is clinically heterogeneous and associated with a very poor prognosis, the identification of synergistic novel combinations preclinically and the translation to clinical studies represents the most rational way forward in harnessing the full potential of novel agents in peripheral T-cell lymphoma. This approach will certainly fill the emergent need for improved treatment strategies in these patients.

Evidence before this study

Relapsed or refractory peripheral T-cell lymphoma after conventional chemotherapy is associated with a very poor prognosis and there is currently no recommendation on the standard approach to helping these patients. Between January, 2010, and January, 2015, we searched PubMed and abstracts from all major oncology and haematology congresses including the annual meetings of the American Society of Clinical Oncology, the American Society of Haematology, the European Haematology Association, and the International Conference on Malignant Lymphoma, to identify publications in English on novel targeted treatments for relapsed or refractory peripheral T-cell lymphoma. We used the search terms “T-cell lymphoma”, “novel agents”, “histone deacetylase inhibitor”, “proteasome inhibitor”, and “anti-folate”, and restricted our search to novel compounds that are in more advanced stages of clinical testing (phase 2 or 3 studies). We identified several full publications and congress abstracts describing the results of phase 2 studies on romidepsin, pralatrexate, belinostat, brentuximab vedotin, denileukin diftitox, bendamustine, bortezomib, and lenalidomide in relapsed or refractory peripheral T-cell lymphoma. No clinical study reported on the use of novel combination of targeted agents. The respective studies on romidepsin, pralatrexate, belinostat, and brentuximab vedotin led to their approvals by the US Food and Drug Administration (FDA). With the exception of the remarkable efficacy of brentuximab vedotin in systemic anaplastic large cell lymphoma (86% of patients responding to treatment), the efficacy of romidepsin, pralatrexate, and belinostat in relapsed or refractory peripheral T-cell lymphoma is only modest with objective response rates between 25% and 29%.
Workshop Criteria (IWC), and measurable cutaneous disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate bone marrow and organ function: absolute neutrophil count of 1.0 × 10^9 cells per L or higher, platelet count of 50 × 10^9 platelets per L or higher, or 30 × 10^9 platelets per L or higher if bone marrow involvement was recorded; total bilirubin, aspartate aminotransferase and alanine aminotransferase two times or lower than the upper limit of normal; and serum creatinine two times or lower than the upper limit of normal. Major exclusion criteria included the concomitant use of any other anticancer treatment, therapeutic warfarin, and drugs that could prolong the corrected QT (QTc) interval or inhibitors of CYP3A4.

Additionally, patients were ineligible if they had received previous treatment with a deacetylase inhibitor or bortezomib, or had treatment with chemotherapy or immunotherapy within 3 weeks before the start of study. Patients were not eligible if they had any known cardiac abnormalities such as congenital long QT syndrome, QTcF interval less than 480 ms, a myocardial infarction within 12 months of study entry, substantial electrocardiogram abnormalities, congestive heart failure, left ventricular ejection fraction below normal, known history of sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes, hypertrophic cardiomyopathy or restrictive cardiomyopathy, or any cardiac arrhythmia requiring anti-arrhythmic drugs. We also excluded any patients with coexisting peripheral neuropathy or neuropathic pain of grade 2 or worse severity or any clinically significant active infection such as HIV or clinically active hepatitis B and C.

Written informed consent was obtained from all patients and the protocol was approved by the institutional review boards of all participating institutions. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures
Patients received 20 mg oral panobinostat three times per week and 1.3 mg/m² intravenous bortezomib twice per week (on days 1, 4, 8, and 11), both for 2 of 3 weeks for up to six to eight 21-day cycles or until the onset of unacceptable toxic effects or disease progression. Per protocol, extension of therapy beyond eight cycles was not allowed, even for responding patients. The dosages of the study drugs were based on the maximum tolerated dose of both drugs derived from the phase I component of the panobinostat or placebo with bortezomib and dexamethasone in patients with relapsed multiple myeloma (PANORAMA [NCT01023308]) study that assessed the same combination in patients with relapsed or refractory multiple myeloma.9

Dose delays and reductions were allowed for grade 3 or worse non-haematological toxic effects, absolute neutrophil count 0.5 × 10^9 cells per L or lower, or platelet count 25 × 10^9 platelets per L or lower. Panobinostat doses were reduced from 20 mg to 15 mg (one dose level reduction), or 15 mg to 10 mg (two dose levels reduction). Bortezomib doses were reduced from 1.3 mg/m² to 1.0 mg/m² (one dose level reduction) and 1.0 mg/m² to 0.7 mg/m² (two dose levels reduction). Patients who could not tolerate both panobinostat and bortezomib were required to permanently discontinue treatment, but were still followed up for disease assessment and survival. We used the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Patients had electrocardiogram monitoring done in triplicate on days 1 and 5 of cycle one and on day 8 of cycles two to eight. Data were reviewed locally and centrally. Efficacy and safety data were reviewed by an independent data monitoring committee.

Outcomes
The primary endpoint was the proportion of patients with an objective response according to the Revised Response Criteria in eligible patients given the combination of bortezomib and panobinostat. Secondary endpoints were progression-free survival, overall survival, time to response, duration of response, and safety and tolerability of the treatment combination.

We assessed responses for activity with CT or 18F-fluorodeoxyglucose–PET (FDG-PET) scans after every two cycles at weeks 6, 12, 18, and 24 in accordance with the lymphoma subtype. Table 1: Patient characteristics at study baseline

<table>
<thead>
<tr>
<th>Patients (n=25)</th>
<th>Age (years)</th>
<th>59 (35–79)</th>
<th>Sex</th>
<th>Men 16 (64%)</th>
<th>Women 9 (36%)</th>
<th>ECOG performance status</th>
<th>0 9 (36%)</th>
<th>1 15 (60%)</th>
<th>2 1 (4%)</th>
<th>Time from diagnosis (months)</th>
<th>12 (4–85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage at enrolment</td>
<td>II 4 (16%)</td>
<td>III 11 (44%)</td>
<td>IV 10 (40%)</td>
<td>Previous lines of treatment</td>
<td>2 (1–4)</td>
<td>Previous high-dose therapy</td>
<td>7 (28%)</td>
<td>Lymphoma subtype</td>
<td>Peripheral T-cell lymphoma, not otherwise specified 9 (36%)</td>
<td>Angioimmunoblastic T-cell lymphoma 8 (32%)</td>
<td>ALK-positive anaplastic large cell lymphoma 1 (4%)</td>
</tr>
</tbody>
</table>

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.
Clinical response was established both by investigators and by an independent central review committee. Complete response required clearing of known sites of disease and partial response required recorded response in affected areas. The key secondary endpoint was progression-free survival, which was defined as the time from the date of start of treatment to the date of event defined as the first documented progression or death due to any cause. Other secondary endpoints included the overall survival, defined as the time from date of treatment to the date of death due to any cause, the time to response, defined as the time from the date of start of treatment to the date of first documented response (complete response or partial response) and the duration of response, defined as the time from the date of first documented response (complete response or partial response) to the date of event as defined for the progression-free survival. The data cutoff for this report was Nov 1, 2014.

**Statistical analysis**

To establish the sample size needed, we assumed that 20–50% of patients would respond to the combination. The Gehan’s two stage optimum design required a response in one of 11 patients in stage 1 of the study to accrue the full cohort of 25 patients to target a response rate of 25% or better with a power of 95%, and to rule out a lower than 25% response rate, with 10% probabilities of accepting a poor study regimen and of rejecting a good one. We used the Kaplan-Meier method to determine duration of response, progression-free survival, and overall survival. Response durations were censored at the time of first disease recurrence. The interim analysis was planned after the last patient enrolled in stage one had undergone the first response evaluation. All descriptive statistical analyses were done with SPSS software (version 21.0). The study is registered with ClinicalTrials.gov, number NCT00901147.

**Role of the funding source**

The funders of the study collaborated with the study steering committee (DT, YTG, YHC, SCN, and WSK) in the study design and data collection. They were not involved in data analysis, data interpretation, and preparation of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

**Results**

We enrolled 25 patients between Nov 9, 2009, and Nov 26, 2013. Table 1 shows patient demographic and baseline characteristics. Several different histological subtypes were accrued, with the most common being peripheral T-cell lymphoma not otherwise specified (36%), followed by angioimmunoblastic T-cell lymphoma (32%). Most patients (88%) had stage III or IV disease at study entry. The median time from peripheral T-cell lymphoma diagnosis to study entry was 12 months, and the median number of previous systemic therapies was two (range one to four) with seven (28%) patients having undergone previous autologous stem-cell transplantation.

<table>
<thead>
<tr>
<th>Best clinical response</th>
<th>Assessable patients (n)</th>
<th>Objective response rate (%)</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients 25</td>
<td>10 (43%)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, not otherwise specified</td>
<td>7</td>
<td>2 (22%)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>8</td>
<td>4 (50%)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ALK-positive anaplastic large cell lymphoma</td>
<td>1</td>
<td>1 (100%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALK-negative anaplastic large cell lymphoma</td>
<td>4</td>
<td>1 (25%)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma, nasal type</td>
<td>2</td>
<td>1 (50%)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>1</td>
<td>1 (100%)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n or n (%).

Table 2: Responses by peripheral T-cell lymphoma subtype
At the time of data cutoff, all patients had discontinued treatment. As a standard in most participating centres, most patients were assessed by FDG-PET. Six of 11 patients (55%) enrolled in stage one of the study showed a response by central review and this allowed the full recruitment of 25 patients for the study. Two patients enrolled in stage two of the study withdrew consent during cycle 1 of treatment before completion of the treatment cycle and before any efficacy assessment could be made and were therefore excluded from overall response assessment. Otherwise, all enrolled patients were included for all other analyses. Median follow-up duration was 15·3 months (range 0·3–40·0, IQR 5·3–33·4). Objective responses were noted in ten (43%, 95% CI 23–63) of 23 assessable patients, of whom five (22%) had complete responses. Five (22%) patients had stable disease whereas eight (35%) developed progressive disease during the study. Figure 1 shows details of individual responses. The study regimen showed activity across different peripheral T-cell lymphoma subtypes (table 2). Patients with angioimmunoblastic T-cell lymphoma had the greatest response with four (50%) of eight patients responding. The median time to response was 39·5 days (range 33–127, IQR 42–84) and the median duration of response was 5·6 months (range 2–33, IQR 1·25–27·5). The median duration of treatment was 54 days (range 10–208, IQR 28–116). Ten (40%) patients were treated for at least four cycles, and six (24%) patients received six to eight cycles of treatment. All seven patients who had progressive disease had rapid disease progression soon after study enrolment and none received more than two cycles of treatment. Five patients had a subsequent stem-cell transplant. Median progression-free survival was 2·59 months (95% CI 0·01–5·42; figure 2A) whereas median overall survival was 9·90 months (3·52–16·26; figure 2B) after a median follow-up duration of 15·3 months (IQR 5·3–33·4). Eight of the enrolled 25 patients remained alive at the time of data lock. Five patients who completed all treatment cycles successfully went on to receive sequential allogeneic stem-cell transplantation. The primary reasons for discontinuing treatment were progressive disease (ten [40%]), adverse events (four [16%]), withdrawal of consent (four [16%]), and death (one [4%]).

Table 3 shows toxic effect data. Common non-haematological adverse events of any grade included diarrhoea, peripheral neuropathy, fatigue or asthenia, and vomiting. The most common haematological adverse events of any grade were thrombocytopenia, neutropenia, and anaemia. The most common grade 3 and 4 adverse events recorded were thrombocytopenia, neutropenia, and diarrhoea. However, febrile neutropenia occurred in only three (12%) patients and platelet concentrations typically returned to baseline levels at the beginning of the subsequent cycle. Grade 1 and 2 adverse events occurring in 10% or more of patients were diarrhoea, peripheral neuropathy, fatigue, vomiting, and decreased appetite.

We noted a higher incidence of grade 3 to 4 thrombocytopenia and neutropenia in patients who had received previous autologous stem-cell transplantation (seven [100%] of seven patients with previous autologous stem-cell transplantation vs six [32%] of 18 without previous autologous stem-cell transplantation), suggesting that previous treatment might be an important contributing cause. Both thrombocytopenia and neutropenia were managed with dose interruptions and modifications. No patients discontinued the study due to haematological toxic effects and we recorded no major haemorrhagic complication. We noted no significant study drug-related cardiac abnormalities. Although ten (40%) patients had treatment-emergent peripheral neuropathy, events were generally mild, with only two (8%) grade 3 or 4 events in which patients had to discontinue study even after dose...
interruptions and dose modifications. A patient who had a previous cardiac history developed acute coronary syndrome that led to cardiogenic shock and had to be taken off the study. This event was deemed to be non-study drugs related. One patient died while on study during treatment cycle two and the reported cause of death was progressive disease. Overall, the major adverse events leading to study treatment discontinuation were peripheral neuropathy (two), diarrhoea (one), and acute coronary syndrome (one). There were ten reported serious adverse events judged to be possibly related to the study . This event was deemed to be non-study drugs related. One patient who had a previous cardiac history developed acute coronary syndrome that led to cardiogenic shock and had to be taken off the study. This event was deemed to be non-study drugs related. One patient died while on study during treatment cycle two and the reported cause of death was progressive disease. Overall, the major adverse events leading to study treatment discontinuation were peripheral neuropathy (two), diarrhoea (one), and acute coronary syndrome (one). There were ten reported serious adverse events judged to be possibly related to treatment: the events were infection (two), thrombocytopenia (three), peripheral neuropathy (two), diarrhoea (one), constipation (one), and rash (one).

The median relative dose intensity was 80·8% for bortezomib and 89·2% for panobinostat. Dose reductions were needed for 21 patients (84%) because of adverse events. Eight patients (32%) had dose reductions for both bortezomib and panobinostat. 22 (88%) patients required dose interruptions of both or either drugs due to adverse events. Seven (28%) patients had their treatment cycles delayed more than 7 days, six (24%) because of adverse events, and one (4%) because of other reasons.

Discussion
In this phase 2 study, we recorded encouraging objective responses, including complete responses in a fifth of patients with the combination of panobinostat with bortezomib in patients with relapsed or refractory peripheral T-cell lymphoma, many of whom had been heavily pre-treated. Although a validation study might be essential to confirm our findings, the proportion of patients who responded compares favourably with the modest activity of novel single-agents that were recently approved by the FDA for use in this same setting.\(^\text{6, 8}\) However, the median duration of response of 5-6 months is short compared with the duration of responses of 17 months recorded with romidepsin and 13·6 months with belinostat.\(^\text{6, 8}\) This finding might be attributable to the limitation of treatment cycles to eight rather than the allowance for extended treatment until disease progression even in responding patients. As a result, some patients with no alternative sequential treatment like stem-cell transplantation developed progressive disease shortly after completion of treatment. Notwithstanding the duration of response, our study combination could serve as an important bridge to allogeneic stem-cell transplantation in which disease control is a prerequisite. To our knowledge, this study is the first to show that epigenetic modulation via pan-deacetylase-inhibitor-based treatment in combination with proteasome inhibition is feasible and potentially synergistic in peripheral T-cell lymphoma. A combination of bortezomib with either romidepsin or belinostat would have been regarded as a more logical sequential study approach after the phase 2 studies of both drugs. However, when we initiated this study, there was no access to belinostat in Asia and we excluded romidepsin because it is a selective class I deacetylase inhibitor and does not inhibit the aggresome pathway, which is dependent on histone deacetylation 6 activity. Additionally, the FDA had also recently issued guidance in support of the co-development of two or more investigational drugs in combination if the disease or disorder studied was serious and there was a strong biological rationale for use of the combination.

Although peripheral T-cell lymphoma is clinically heterogeneous, we recorded activity of the combination across the different subtypes. Because the numbers are small, no meaningful statistical correlation can be made. An objective response rate of close to 50% has been reported with belinostat, another pan-deacetylase inhibitor in angioimmunoblastic T-cell lymphoma.\(^\text{6}\) This finding was not shown with the use of romidepsin.\(^\text{3, 8}\) Whether the effect of deacetylase inhibitors on angioimmunoblastic T-cell lymphoma is class dependent deserves further exploration. The complete response reported in the patient with subcutaneous panniculitis-like T-cell lymphoma corroborates similar findings of complete response with the use of romidepsin in this rare entity.\(^\text{3, 8}\) A patient with nasal type NK/T-cell lymphoma responded very well whereas another had disease stabilisation. In view of the highly aggressive nature of this entity in the relapsed or refractory setting and the reliance of Epstein-Barr virus on the NFκB and other anti-apoptotic pathways in lymphomagenesis, further exploration of this combination is warranted in patients with nasal type NK/T-cell lymphoma. Because distinct oncogenic pathways might be associated with the different peripheral T-cell lymphoma entities, the study regimen might have different mechanisms of action.

### Table 3: Incidences of non-haematological and haematological toxic effects

<table>
<thead>
<tr>
<th>Non-haematological toxic effects</th>
<th>All grades (%)</th>
<th>Grades 1-2 (%)</th>
<th>Grades 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>12 (48%)</td>
<td>7 (28%)</td>
<td>5 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>10 (40%)</td>
<td>8 (32%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>9 (36%)</td>
<td>7 (28%)</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (28%)</td>
<td>5 (20%)</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (12%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (16%)</td>
<td>4 (16%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological toxic effects</th>
<th>All grades (%)</th>
<th>Grades 1-2 (%)</th>
<th>Grades 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>17 (68%)</td>
<td>6 (24%)</td>
<td>11 (44%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (44%)</td>
<td>4 (16%)</td>
<td>7 (28%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (24%)</td>
<td>4 (16%)</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
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in the various entities. Hence, our continuing biomarker correlative studies are designed to establish whether the study regimen is more active in entities with upregulation of NFκB activity or transcription factors or co-regulators modified by acetylation, and hopefully this will help further elucidate the best way forward in the treatment of each subtype.

Common grade 3–4 adverse events and haematological toxic effects with incidence of 20% or more included thrombocytopenia, neutropenia, anaemia, and diarrhoea. These data partly reflect the overlapping toxic effect profiles of panobinostat and bortezomib. Although more than two-thirds of patients in the panobinostat group had grade 3–4 thrombocytopenia, no patient discontinued study because of thrombocytopenia. In addition to the effects of the drugs on platelet concentrations, the high incidence is also attributable to the lower platelet entry criterion of 50 × 10^3 platelets per L or more for study enrolment. This study was designed to allow better recruitment of patients with peripheral T-cell lymphoma who frequently have disease involvement in marrow and had previous myelosuppressive chemotherapeutic treatments and hence, tend to have lower baseline platelet concentrations. Generally, thrombocytopenia was manageable and reversible, with platelet concentrations typically recovering to baseline at the end of each treatment cycle. This is consistent with the understanding that bortezomib and histone deacetylase inhibitors cause thrombocytopenia by reversibly inhibiting the function and maturation of megakaryocytes and the related release of pro-platelets rather than a direct cytotoxic effect on the megakaryocytes or their progenitors. Hence, the resultant thrombocytopenia is non-cumulative and would rapidly resolve upon treatment interruption.30–32

Diarrhoea could be managed supportively and with dose interruptions and modifications. Treatment-emergent peripheral neuropathy and fatigue or asthenia were two other adverse events with an incidence of 30% or higher. Most events were grade 1 or 2. Peripheral neuropathy is a common toxic effect associated with the use of bortezomib. Because the standard of care for administration of bortezomib at the time of study inception was via the intravenous route, the high incidence of peripheral neuropathy was anticipated. With the shift in clinical practice toward subcutaneous bortezomib, on the basis of a more favourable safety profile, a switch to subcutaneous bortezomib in combination with panobinostat could lead to improved tolerability and a longer treatment duration with the combination and perhaps, improved outcomes.33 The incidences of toxic effects recorded in this phase 2 study were similar to those reported in the major phase 3 PANORAMA1 study.34 The on-treatment deaths and drop-outs due to progressive disease were within the range of what can be anticipated for patients with relapsed or relapsed peripheral T-cell lymphoma.

In summary, our study is the first to show that combined proteasome and histone deacetylase inhibition is safe, feasible, and promising in patients with peripheral T-cell lymphoma. Our findings validate abundant preclinical studies suggesting that a combination approach is synergistic and represents a rational way forward that harnesses the full potential of novel agents in peripheral T-cell lymphoma.

Contributors
DT, YTG, CP, and CHY researched the scientific literature. DT, YTG, and CHY contributed to study design. DT, CP, WYKH, SYT, CHY, KT, STL, YSL, SGK, SCN, SF, WSK, and YTG collected data. DT, CP, CHY, YHC, and YTG analysed and interpreted data. All authors participated in drafting or reviewing of the report and all authors approved the submitted version.

Declaration of interests
DT reports grants from Janssen and Novartis during the conduct of the study; personal fees from Janssen and Celgene. YTG reports grants from Novartis and Janssen during the conduct of the study; personal fees from Janssen, BMS, Novartis, Sanofi, Roche, Celgene, and Gilead Sciences. CP, WYKH, SYT, CHY, YHC, KT, STL, YSL, SGK, SCN, SF, and WSK declare no competing interests.

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