346 POSITIVE CORRELATION BETWEEN CIRCULATING NK CELLS AFTER INFECTION RESPONSE IN MANTLE CELL LYMPHOMA (MCL) TREATED WITH LENALIDOMIDE: FIRST IN VIVO DATA SUPPORTING NK-MEDIATED CYTOTOXICITY AS A MECHANISM OF ACTION

H. Eve1, S. Carey1, S.RULE1
1Hematology Department, Denford Hospital, Plymouth, United Kingdom

Introduction: In vitro work shows that lenalidomide enhances NK-mediated cytotoxicity against MCL but the significance of this in vivo is unknown. Lenalidomide has also been shown in vitro to inhibit regulatory T cells (Tregs) which are over-represented in some lymphomas and may suppress anti-tumour immunity. Tregs and their response to lenalidomide in MCL have however never been studied.

Methods: As part of a phase 2 trial investigating lenalidomide in relapsed MCL, peripheral blood T/NK cells and Tregs (CD4+ FOXP3+ CD25hi) were measured before and during treatment to detect trends correlating with response. All patients received lenalidomide 25mg/day (days 1-21 of a 28 day cycle) for up to 6 cycles, and responding patients (complete/partial remission (CR/PR) or stable disease (SD)) continued maintenance lenalidomide 15mg/day (days 1-21 of a 28 day cycle) until progression or toxicity.

Results: 26 patients were enrolled. 13 had adequate T/NK data to analyse alongside response. Patients were defined as "responders" (CR/PR, n=8) or "non-responders" (median change of -16.7% after 9 cycles. This was preceded by an initial dip (-19.7%) within the first cycle -16.7% after 9 cycles. This was preceded by an initial dip (-19.7%) within the first cycle). Firstly, CD3 cells demonstrated an early rise in responders compared to non-responders (median change +34.2% vs -9.3% after 1 cycle) which was maintained throughout treatment with equal contributions from CD4 and CD8 cells. Secondly, NK cells demonstrated a steady and sustained rise in responders compared to non-responders with a median change of +45.5% vs -8.0% after 6 cycles and +45.7% vs -16.7% after 9 cycles. This was preceded by an initial dip (-19.7%) within the first cycle which may reflect tumour infiltration. MCL patients (n=17) had higher baseline Tregs than healthy volunteers (n=20) (median 5.77% vs 3.92%, p=0.012). Tregs were monitored in 13 patients during lenalidomide therapy and demonstrated an early and sustained rise (median fold increases of 1.8, 2.0 and 1.5 after 1, 3 and 6 cycles respectively) in all, regardless of response.

Conclusions: The immunomodulatory properties of lenalidomide correlate well with response in MCL. Our unique in vivo findings suggest that lenalidomide acts by stimulating NK-mediated cytotoxicity against MCL, possibly via initial co-stimulation of CD4 and CD8 cells. Although Tregs are increased in MCL and expand further with lenalidomide exposure, this has no correlation with response and is thus unlikely to play a role in drug efficacy.

347 ENHANCED CORD BLOOD (CB) NATURAL KILLER (NK) CELL EXPANSION, EXPANSION, AND CYTOLYTIC ACTIVITY IN-VITRO AND IN-VIVO AGAINST B-NHL FOLLOWING STIMULATION WITH GENETICALLY REENGINEERED K562MBIL15-41BBL (MODK562): POTENTIAL FOR ADOPTIVE CELLULAR IMMUNOTHERAPY IN B-NHL

M. Cairo1, J. Ayello1, M. Levin2, J. Hochberg1, F. Zhao3, Y. Chui4, C. Vandeven2
1Pediatrics, Medicine, Pathology and Cell Biology, Columbia University, New York, United States, 2Pediatrics, Columbia University, New York, United States, 3Pediatrics, New York Medical College, Maria Fareri Children’s Hospital, Valhalla, United States

Background: NK cells appear to play a significant role in reducing relapse in patients with hematological malignancies following AlloSCT (Dunbar et al. Haematologica 2008). Limitations of NK B-NHL therapy include lack of B-NHL recognition and limited NK cell numbers (Shereck/Cairo et al. Ped Bld Can 2007). We evaluated in-vitro and in-vivo B-NHL cytolytic activity of CBMNC expanded (E) with MODK562, a glycoengineered and humanized anti-CD20 mAb, which appears to be more potent than rituximab in inducing cell death via induction of apoptosis (Dalle et al. Molecular Cancer Therapeutics, 2010). It also exhibits superior activity of direct and cellular immune mediated cytotoxicity against CD20+ nonlymphomatous NHL (BL/DLBCL); but, eventually release or refractoriness may occur (Coiffier et al. NEJM 2002; Cairo et al ASCO 2010). GA101 is a type-II glycoengineered and humanized anti-CD20 ab, which appears to be more potent than rituximab in inducing cell death via induction of apoptosis (Dalle et al. Molecular Cancer Therapeutics, 2010). It also exhibits superior activity of direct and cellular immune mediated cytotoxicity against CD20+ nonlymphomatous NHL (BL and DLBCL) in-vitro and in human B-NHL xenograft models (Monscher et al. Blood 2010). The majority of lymphoblastic lymphoma in children and adolescents is T-cell in origin; however, about 10% are B-cell and express CD20 (PBLL). This study was to determine the optimal GA101 dose and incubation time for induction of in-vitro cell death in PBLL.

Material and Methods: Pre-B-ALL (Tanour) and PBLL (U98M; DMSZ) tumor targets (TT) were cultured in RPMI+10% FBS. The T-ALL cell line Loucy, CD20-, (ATCC), served as a negative control; whereas, T-cell leukemia line Jurkat (ATCC) with camptothecin, served as a positive cell death control. TT were stained with fluorescein-conjugated anti-CD20 mAb to assess CD20 expression by flow cytometry. TT (3x10^5) were incubated with 1, 10 or 100 ug/ml of GA101 (generously supplied by Roche) or IgG isotype control at 37°, 5% CO2 for 24, 36, 48, or 72h. Cells were stained with annexin V/propidum iodide and cell death assessed within 1hr by flow cytometry (Ayllo/Cairo et al Exp Heme 2009).

Results: CD20 expression on PBALL and PBLL cell line was 8.2±2.1 and 33±2.5%, respectively. At 56h the PBALL line demonstrated no significant change in cell death; while in PBLL cell death was significantly increased at 100ug/ml of GA101 compared to 1 and 1.0 (16.3 ± 7.3±0.4±5.2±0.2±0.2% respectively, p<0.001) and compared to isotype and Loucy (16.3±0.3 vs 1.1±2.6 vs 0±8.2%, respectively, p<0.001). Following 72h incubation, GA101 induced a significant increase in cell death in PBLL (55% CD20+) vs PBALL (8% CD20+) vs isotype vs neg control (Loucy CD20+) [59±6.3 vs 39±2.3 vs 0±2±0.0±1.3% vs 2.8±6.1±0.1% respectively, p<0.001].

Conclusion: GA101 induced significant cell death in CD20+ Pre-B-Lymphoblastic Lymphoma and appears to be dependent in part on degree on CD20 expression. Based on these results, GA101 has potential to be an active agent in CD20+ lymphoblastic disease.

348 GA101, A TYPE II GLYCOENGINEERED ANTIBODY AGAINST CD20 INDUCES SIGNIFICANT IN-VITRO CELL DEATH OF CD20+ AND PREB LYMPHOMBlastic LYMPHOMA (PBLL)

M. Cairo1, C. Cho2, J. Ayello1, M. Levin2
1Pediatrics, Medicine, Pathology and Cell Biology, Columbia University, New York, United States, 2Pediatrics, Columbia University, New York, United States

Background: CD20 is an excellent tumor target and rituximab, a chimeric type I antibody (IgG1), directed at CD20, has shown enhanced activity in adult and pediatric B-cell nonlymphomatous NHL (BL/DLBCL); but, eventually release or refractoriness may occur (Coiffier et al NEJM 2002; Cairo et al ASCO 2010). GA101 is a type-II glycoengineered and humanized anti-CD20 ab, which appears to be more potent than rituximab in inducing cell death via induction of apoptosis (Dalle et al. Molecular Cancer Therapeutics, 2010). It also exhibits superior activity of direct and cellular immune mediated cytotoxicity against CD20+ nonlymphomatous NHL (BL and DLBCL) in-vitro and in human B-NHL xenograft models (Monscher et al. Blood 2010). The majority of lymphoblastic lymphoma in children and adolescents is T-cell in origin; however, about 10% are B-cell and express CD20 (PBLL). This study was to determine the optimal GA101 dose and incubation time for induction of in-vitro cell death in PBLL.

Material and Methods: Pre-B-ALL (Tanour) and PBLL (U98M; DMSZ) tumor targets (TT) were cultured in RPMI+10% FBS. The T-ALL cell line Loucy, CD20-, (ATCC), served as a negative control; whereas, T-cell leukemia line Jurkat (ATCC) with camptothecin, served as a positive cell death control. TT were stained with fluorescein-conjugated anti-CD20 mAb to assess CD20 expression by flow cytometry. TT (3x10^5) well were incubated with 1, 10 or 100 ug/ml of GA101 (generously supplied by Roche) or IgG isotype control at 37°, 5% CO2 for 24, 36, 48, or 72h. Cells were stained with annexin V/propidium iodide and cell death assessed within 1hr by flow cytometry (Ayllo/Cairo et al Exp Heme 2009).

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Conclusion: GA101 induced significant cell death in CD20+ Pre-B-Lymphoblastic Lymphoma and appears to be dependent in part on degree on CD20 expression. Based on these results, GA101 has potential to be an active agent in CD20+ lymphoblastic disease.
In clinical practice the combination of rituximab with chemotherapy results in a substantial clinical benefit.

To assess the potential of chemotherapy combination, GA101 and rituximab monotherapy at sub-optimal doses (1 mg/kg once weekly) were compared to the corresponding combination with i) bendamustine (5 mg/kg days 19, 20, 21, 22); ii) fludarabine (40 mg/kg days 22, 23, 24) or iii) chlorambucil (4 mg/kg day 27, 28, 29) in subcutaneous Z138 (MCL) xenografts in Scid beige mice.

GA101 in combination with bendamustine mediated statistically superior efficacy compared with rituximab plus bendamustine: Tumor growth inhibition (TGI) values on day 33 were 29% for rituximab, 42% for rituximab + bendamustine, 47% for GA101 and 72% for GA101 + bendamustine. Treatment with bendamustine did not show significant antitumor activity. Statistical evaluation based on aSUC showed a more than additive effect on tumor growth for the combination of GA101 with bendamustine compared with the corresponding monotherapy arms.

GA101 in combination with fludarabine demonstrated statistically superior efficacy and a significant difference compared with GA101 monotherapy or rituximab with fludarabine. TGI values on day 36 were 50% for fludarabine, 66% for rituximab, 85% for rituximab + fludarabine, 86% for GA101 and >100% for GA101 + fludarabine. Furthermore, the superiority of the GA101-fludarabine combination was demonstrated by the observation of 3 tumor-free animals at the end of the study versus none in the other treatment groups.

GA101 in combination with chlorambucil resulted in statistically superior efficacy and a significant difference compared with GA101 monotherapy or the combination of rituximab and chlorambucil. TGI values on day 41 were 29% for chlorambucil, 44% for rituximab 88% for rituximab + chlorambucil, 74% for GA101 and >100% for GA101 chlorambucil.

These data strongly support the clinical investigation of GA101 in combination with fludarabine, bendamustine or chlorambucil.

350 SIGNIFICANT CLINICAL ACTIVITY OF CAL-101, AN ISOFORM-SELECTIVE INHIBITOR OF PHOSPHATIDYLINOSITOL 3 KINASE (PI3K) D1102, IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT AND MANTLE CELL LYMPHOMA

B. Kahl1, J. Byrd2, I. Finn3, N. Wagner-Johnston4, S. Spurgeon5, D. Benson6, P. Fairman7, J. Brown8, S. Coutre9, A. Yu81

1Medicine, U. of Wisconsin, Madison, United States, 2Medicine, The Ohio State U., Columbus, United States, 3Bone Marrow Transplant Unit, Sarah Cannon Research Institute and Tennessee Oncology, Nashville, United States, 4Medical Oncology, Washington U., St. Louis, United States, 5Medicine, Onyx Health Sciences U., Portland, United States, 6Medicine, Well Cornwall Medical College, New York, United States, 7Medical Oncology, Dana Farber Cancer Inst., Boston, United States, 8Medicine, Stanford U., Stanford, United States, 9Clinical Affairs, Calistoga Pharmaceuticals, Seattle, United States

Background: The class I phosphatidylinositol 3-kinases (PI3Ks) regulate cellular functions relevant to oncogenesis. Expression of the PI3K p110 d isomomorph (PI3Kd) is restricted to cells of hematopoietic origin. CAL-101 is a selective inhibitor of PI3Kd that induces apoptosis of non-Hodgkin lymphoma (NHL) cell lines in vitro.

Methods: This Phase I study evaluated CAL-101 in patients with relapsed or refractory hematologic cancers. CAL-101 was administered orally 1 or 2 times per day (QD or BID) continuously in 28-day cycles as long as patients were benefiting. Efficacy was assessed using standard criteria.

Results: A total of 20 patients were enrolled. 30% of patients achieved a partial response (PR) or better.

Conclusions: CAL-101 has significant antitumor activity in patients with relapsed or refractory indolent non-Hodgkin lymphomas (iNHL) and chronic lymphocytic leukemia (CLL). CAL-101 is an oral PI3Kd-specific inhibitor which has shown preclinical and clinical activity in relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) and chronic lymphocytic leukemia (CLL).

Background: Deregulation of the phosphatidylinositol 3-kinase (PI3K) pathway due to constitutive activation or through the influence of microenvironmental factors is thought to play an important role in the maintenance and expansion of B cell malignancies. PI3K signaling is mediated by four Class I isozymes (α, β, δ, and γ) that have distinct biological functions and tissue distributions. CAL-101 is an oral PI3Kδ-specific inhibitor which has shown preclinical and clinical activity in relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) and chronic lymphocytic leukemia (CLL).

Methods: To evaluate constitutive PI3K pathway activation, tumor cells from treatment-naïve patients were screened for levels of pAkt by measuring the phosphorylation of Akt at both the Thr308 and Ser473 by flow cytometry. In most cases primary malignant cells (4/5) displayed constitutive levels of pAkt which was significantly reduced in the presence of CAL-101 with an EC50 of 0.1-1.0 μM. In contrast, phosphorylation of Akt at Thr388 was low or undetectable above background in all patient samples. Since signals from the microenvironment can be important in the expansion, survival, and chemo-resistance of malignant B cells, we studied invovled stimulation of malignant cells with sCD40L, or BCR crosslinking in the presence or absence of CAL-101. Stimulation with sCD40L, or BCR crosslinking caused rapid induction of both pAktT388 and pAktS473 which was PI3Kδ-dependent as shown by its complete inhibition with CAL-101 at 0.1-1.0 μM.

Conclusions: Our findings demonstrate that CAL-101 blocked both constitutive and invovled PI3K signaling in treatment-naïve follicular patients samples resulting in decreased phosphorylation of Akt suggest that PI3Kδ may play an important role in regulating signals between malignant B cells and their microenvironment thus providing support for a planned front-line clinical evaluation in iNHL.

353 THE JAK INHIBITOR AZD1440 REGULATES PROLIFERATION AND IMMUNITY IN HODGKIN LYMPHOMA

E. Derenzini1, H. Katayama2, R. E. Davis3, J. P.4, D. Buglio,5 S. Sen6, A. Younes7

1Lymphoma/Mylotia, MD Anderson Cancer Center, Houston, United States, 2Molecular Pathology, Division of Pathology and Laboratory Medicine, MD
Background: Aberrant activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway has been reported to promoteproliferation, survival and mechanisms of immune escape in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma (HL). We investigated the activity of the JAK inhibitor AZD1480 in HL and determined its mechanisms of action.

Material and Methods: HRS-derived cell lines HD-LM2, L-428, KM-H2, and L-540 were obtained from the German Collection of Microorganisms and Cell Cultures (Braunschweig, Germany). The JAK2 inhibitor AZD1480 was obtained from AstraZeneca, (Waltham, MA) and the MEK inhibitors U0126 and PD98059 were purchased from Cell Signaling Technology (Beverly, MA). Intracellular protein levels were evaluated by western immunoblotting. PD-L1 and PD-L2 expression levels, apoptosis and cell cycle fractions were evaluated by flow cytometry. Concentrations of cytokines and chemokines in the supernatants were measured by ELISA.

Results: AZD1480 at low doses (0.1-1 µM) potently inhibited STAT5, STAT6, and STAT7 phosphorylation in all the cell lines with constitutive JAK/STAT activation (HDLM-2, L-428, L-540). Cytotoxicity was evaluated by MTS assay: the L-540 cell line showed the highest sensitivity, with a decrease in cell viability close to 30% after 72 hours in the resistant cell lines treatment with AZD1480 did not result in antiproliferative effects as it activated a negative feed-back loop causing hyperphosphorylation of JAK2, activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), and increased IP-10, RANTES and IL-8 concentrations in the supernatants. Inhibition of ERK activity by MEK inhibitors [UO126 and PD98059 (10-100 nM for 72 hours)] enhanced the cytotoxic activity of AZD1480. Interestingly submicromolar concentrations of AZD1480 demonstrated significant immunoregulatory effects by downregulating T helper 2 (Th2) cytokines and chemokines, including IL-4, IL-5, IL-13, thymus and activation-regulated chemokine TARC, and immunoregulatory effects by downregulating T helper 2 (Th2) cytokines and chemokines, including IL-4, IL-5, IL-13, thymus and activation-regulated chemokine TARC, and upregulated chemokines, including IP-10 and MIP-1α.

Conclusions: Our study demonstrates that AZD1480 regulates proliferation and immunoregulation in HL cell lines, and provides mechanistic rationale for evaluating AZD1480 alone or in combination with MEK inhibitors in HL.

354 LONG-TERM FOLLOW-UP IN PX-171-003-A1, AN OPEN-LABEL, SINGLE-ARM PHASE (PH) 2 STUDY OF CARFILZOMIB (CFZ) IN PATIENTS (PTS) WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (R/R MM): ANALYSIS BY SUBGROUPS OF INTEREST IN PATIENTS (PTS) ENROLLED IN PX-171-003-A1, AN OPEN-LABEL, SINGLE-ARM PHASE (PH) 2 STUDY OF CARFILZOMIB (CFZ), IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA (MM)


Introduction: CFZ is a novel, highly selective epoxysketone proteasome inhibitor in development for treatment of MM. Single-agent CFZ has demonstrated durable activity in pts with R/R MM in ph 1 and 2 studies. Here we report on clinical experience with single-agent CFZ in the open-label, single-arm ph 2 PX-171-003-A1 trial in pts with multiply-relapsed and refractory MM, including those pts with Grade (G) 1/2 peripheral neuropathy (PN) at study entry.

Methods: Pts must have received ≥2 prior therapies including bortezomib, either thalidomide or lenalidomide, and an alkylating agent. Pts received CFZ on Days 1, 2, 8, 9, 15, and 16 of every 28-day cycle, for up to ≥12 Cycles (C). Both cohorts received 20 mg/m2 CFZ during C1. Pts in Cohort 2 were escalated to 27 mg/m2 beginning at C2. Dexamethasone (4 mg) prophylaxis was administered in C1. The primary endpoint was overall response rate (ORR). Secondary endpoints included clinical benefit response (CBR), duration of response (DOR), overall survival (OS), and safety. PN history, ISS/Durie-Salmon staging, and prior treatment history were collected for all pts for subset analyses. Responses were assessed according to International Myeloma Working Group criteria and confirmed by Independent Review Committee. New incidental PN or worsening PN were monitored by prospective neurologic exams every 2 C.

Results: Of 266 pts enrolled, 257 were response-evaluable as detailed below.

Baseline characteristic

<table>
<thead>
<tr>
<th>Total n</th>
<th>ORR (≥PR)</th>
<th>CBR (≥MR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>257</td>
<td>71 (28%)</td>
</tr>
<tr>
<td>&lt;5 mo</td>
<td>110</td>
<td>27 (25%)</td>
</tr>
<tr>
<td>≥5 mo</td>
<td>147</td>
<td>35 (24%)</td>
</tr>
<tr>
<td>Baseline PN, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>55</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>I</td>
<td>76</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>II</td>
<td>96</td>
<td>24 (25%)</td>
</tr>
<tr>
<td>III</td>
<td>78</td>
<td>14 (18%)</td>
</tr>
</tbody>
</table>

The ORR was 24% with a median DOR of 7.4 mo (range 6.2–10.3). 202 of 257 pts (79%) had G1/2 PN at baseline and achieved an ORR of 24%, with a median DOR of 7.4 mo (95% CI 5.6–9.2). The OS for all pts was 15.5 mo (95% CI 12.7–19.0). The most common treatment-emergent adverse events ≥G3 regardless of relationship to study drug were predominantly hematologic and included thrombocytopenia (22%), anaemia (20%), lymphopenia (10%), pneumonia (8%), neutropenia (8%), fatigue (7%), hyponatraemia (5%), and hypercalcemia (5%). New-onset PN and PN G3 or ≥G4 were infrequent. 27 pts completed 12C and continued on extension protocol PX-171-010. Based on the data presented thus far, PX-171-004 is an ongoing Phase II study of single-agent CFZ in pts with relapsed MM following 1–3 prior regimens. Here we present an update on BTZ-naïve pts treated on this study.

Methods: Pts, enrolled into 2 sequential cohorts, received IV CFZ on Days 1, 2, 8, 9, 15, and 16 of every 28-day cycle, for up to 12 Cycles (C). Both cohorts received 20 mg/m2 CFZ during C1. Pts in Cohort 2 were escalated to 27 mg/m2 beginning at C2. Common treatment-emergent adverse events ≥G3 were predominantly hematologic and included thrombocytopenia (22%), anaemia (20%), lymphopenia (10%), pneumonia (8%), neutropenia (8%), fatigue (7%), hyponatraemia (5%), and hypercalcemia (5%). New-onset PN and PN G3 or ≥G4 were infrequent. 27 pts completed 12C and continued on extension protocol PX-171-010.

Conclusions: Single-agent CFZ achieved significant durable responses in pts with R/R MM, including those with active G1/2 PN at study entry. CFZ was well tolerated and AEs were clinically manageable with new, unexpected, or cumulative toxicities. Importantly, exacerbation of pre-existing PN was uncommon. Cumulative side effects were not observed, allowing prolonged single-agent dosing for disease control. The authors wish to acknowledge the support of the Multiple Myeloma Research Consortium (MMRC).
Conclusions: In this BTZ-naïve pt population, the ORR, DOR, and TTP are neuropathy (PN) was infrequent (18%) and mild. Only 1 case of G3 PN was observed. Treatment-emergent peripheral anemia (13%), lymphopenia (13%), pneumonia (13%), neutropenia (12%), and thrombocytopenia (11%) were the most common grade 3/4 AEs regardless of relationship to study drug in >5% of all included pts. Only 11% of AEs were severe. There were 2 deaths, 1 pt died as a result of AEs. No treatment-related deaths were observed. The incidence of AEs was similar in pts receiving ≥20mg/m² and <20mg/m² of CFZ.

Class V: 39% and 15% of all included pts developed ≥1 grade 3/4 AEs. The most common grade 3/4 AEs in the ≥20mg/m² and <20mg/m² of CFZ cohorts, respectively, were neutropenia (10% vs. 8%), anemia (20% vs. 23%), and thrombocytopenia (11% vs. 12%).

Toxicities observed in ≥5% of all included pts included anemia (13%), lymphopenia (13%), pneumonia (13%), neutropenia (12%), anorexia (10%), and thrombocytopenia (11%), and fatigue (6%). Treatment-emergent peripheral neuropathy (PN) was infrequent (18%) and mild. Only 1 case of G3 PN was observed. There were no treatment discontinuations due to PN. As of 28 January 2011, 49 (39%) pts completed the full 12C protocol. No cumulative dose-limiting toxicities were observed in pts continuing on extended carfilzomib dosing protocol PX-171-010.

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360 PRALATREXATE, AN EFFECTIVE SINGLE-AGENT SECOND-LINE TREATMENT FOLLOWING FAILURE OF CYCLOPHOSPHAMIDE/DOXORUBICIN/VINCRISTINE/PREDNISONE (CHOP) IN PATIENTS WITH RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA (PTCL)

C. Gisselbrecht, B. Pro, A. Koutsoukos, A. R. Shustov, O. O’Connor

Institute of Hematology, Hôpital Saint-Louis, Paris, France, 2Dept of Medical Oncology, Fox Chase Cancer Ctr, Philadelphia, United States, 3Biometrics, Allos Therapeutics, Westminster, United States, 4Div of Hematology, University of Washington, Seattle, United States, 5Div of Medical Oncology, NYU Cancer Institute, New York, United States

Background: The most common 1st-line treatment for PTCL is multagent CHOP; but, despite high response rates, most patients (pts) progress within 6-12 months. Pralatrexate (PDX, Folotyn®), a rationally designed antifolate, was approved in the United States for treatment of relapsed/refractory PTCL based on results of pivotal PROPEL study. This agent targets dihydrofolate reductase, has high affinity for reduced folate carrier-1 protein leading to increased cellular entry, and is an efficient substrate for polyglutamylation by polyglutamyl synthetase, resulting in increased cellular retention and tumor cell death. This analysis was conducted to assess efficacy of single-agent PDX as 2nd-line treatment post-CHOP.

Methods: Of the 109 efficacy evaluable pts treated with PDX in Propell, a subset of 15 pts received PDX as 2nd-line treatment post-CHOP. The demographics and disease characteristics of 15 pts treated 2nd-line with PDX post-CHOP were reflective of overall Propell population. Nine pts (60%) were male; median age was 60 years. Eleven pts (73%) had responded previously to CHOP per investigator review (7 complete response [CR]; 4 partial response [PR]). Response rate to 2nd-line PDX in these pts was 40% (CR=33%; PR=7%) per investigator review; median duration of response (DoR) was 12.5 months. These pts received median of 16 doses of PDX for median of 134 days. One pt had Grade 4 adverse event (AE), sepsis. Grade 3 AEs in >1 pt were thrombocytopenia (n=4) and mucositis (n=3). Two pts discontinued treatment due to AEs (mucositis and pneumonitis). At data cutoff, 2 of 15 pts remained on treatment (time on treatment = 13 and 18.5 months) and in remission. For the 13 pts who discontinued treatment, their DoR data were used. Two pts proceeded to stem-cell transplant (SCT) after response to PDX, thereby censored for DoR (at 2.3 and 3.3 months). These pts remain in CR and their current disease-free period (DoR: PDX + SCT) is 20 and 21.7 months.

Conclusions: Pralatrexate administered 2nd-line post-CHOP to pts with PTCL demonstrated high activity with durable responses, including CRs leading to SCT. These data suggest that PDX is an effective single-agent 2nd-line option for pts with relapsed/refractory PTCL, including those receiving 1st-line CHOP as well as those who are candidates for SCT.

361 PRALATREXATE REVERSES THE TREND TO PROGRESSIVE RESISTANCE IN PATIENTS WITH RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMA (PTCL)

B. Coffiey, P. Zinzani, A. Koutsoukos, O. O’Connor

1Hematology Dept, Centre Hospitalier Lyon-Sud, Pierre-Benite, France, 2Eimatologia, Istituto di Eimatologia di Bologna, Bologna, Italy, 3Biometrics, Allos Therapeutics, Westminster, United States, 4Div Medical Oncology, NYU Cancer Institute, New York, United States

Background: In several malignancies objective response rate (ORR) and progression free survival (PFS) are known to decrease with each subsequent chemotherapy regimen. In PTCL, the most common 1st line treatment is cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP); however, despite high response rates, most patients progress within 6 to 12 months and require further salvage systemic therapy. Pralatrexate (Folotyn®) was approved in the United States for treatment of relapsed/refractory PTCL. This retrospective analysis from the pivotal Propel study was conducted to evaluate whether progressive resistance is observed in relapsed/refractory PTCL and to assess activity of pralatrexate compared with patients’ previous treatments.

Methods: Using investigator assessments of response, PFS and ORR for pralatrexate were compared with PPS and ORR for the most recent therapy prior to pralatrexate (-1); PPS and ORR of the most recent therapy prior to pralatrexate was compared with those of the second prior therapy (-2); PPS and ORR of second prior therapy (-2) were compared with those of the most recent therapy prior to pralatrexate. For the 109 evaluable pts in the Propel study, all had ≥1 prior therapy. For the 57 pts who had ≥3 prior therapies, in the -3 vs -2 analyses, hazard ratio (HR) was 0.660, median PFS was 213.5 days and ORR was 56% for -3 therapy compared with 140 days PFS and 33% ORR for -2 therapy. These same pts had a further decrease in median PFS and ORR (95 days, 30%) with their -1 therapy but the trend was reversed with pralatrexate. Pralatrexate demonstrated higher ORR and longer PFS than earlier lines of therapy.

Results: Results indicated a trend of reduced PFS and ORR with successive therapies; this trend was reversed by pralatrexate. Of 109 evaluable patients in the Propel study, all had ≥1 prior therapy. For the 57 pts who had ≥3 prior therapies, in the -3 vs -2 analyses, hazard ratio (HR) was 0.660; median PFS was 213.5 days and ORR was 56% for -3 therapy compared with 140 days PFS and 33% ORR for -2 therapy. These same pts had a further decrease in median PFS and ORR (95 days, 30%) with their -1 therapy but the trend was reversed with pralatrexate with which they experienced median PFS of 134 days and ORR of 40%. For the 86 pts who had ≥2 prior therapies, in the -2 vs -1 analysis the HR was 0.785 and median PFS was 144 days and ORR was 38%. In the full 109 patient population who had ≥1 prior therapy, the HR further increased to 1.051 for the -1 prior therapy when compared with pralatrexate; median PFS was 114 days and ORR was 38% with the immediately previous line of therapy as compared with median PFS of 121 days and ORR of 39% for pralatrexate.

Conclusions: This analysis demonstrated that patients with PTCL exhibit progressive resistance to treatment in which outcomes worsened with successive therapy. This trend was reversed with pralatrexate. Pralatrexate demonstrated higher ORR and longer PFS than earlier lines of therapy.