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

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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" (SD, n=5) after lenalidomide. Baseline CD4 cells were lower in responders than non-responders (median 163 vs 461/µl, p=0.02) whilst other cell types (CD3, CD8, NK) were similar. Changes were observed in T/NK subsets during lenalidomide therapy according to response. 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 3.29%, p=0.02). 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, ACTIVATION, 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

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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 (generously supplied by D. Campana MD, PhD).

Materials and Methods: After 100GY irradiation, CBMNC + MODK562 or wildtype (WT) K562 were cultured in RPMI+IL-2 for 7d. NK activation marker, LAMP-1, and cytolytic mechanism markers, perforin, and granzyme B, expression was examined by flow cytometry. Cytotoxicity was assessed by europium release assay at 20:1 E:T ratio against Ramos (BL), K562 (NK-sensitive) and SUDHL-6 (DLBCL). NK cytotoxicity was performed invivo, using NODSCID mice xenografted with human BL that was transfected with mammalian construct luciferase (ffLUCZeo-pcDNA, generously supplied by L. Cooper, MD, PhD). 6wk old NODSCID (NOD.Cg-Prkdc^{scid}IL2rg^{tm1Wjl}/SzJ) mice received 5x10^6 BL cells IP, and treated 5 wks IP with: PBS, BL only, 5x10^6 WTK562E CBMNC, 5x10^6 MODK562E CBMNC or 5x10^7 MODK562E CBMNC. B-NHL growth was monitored by tumor volume, bioluminescent imaging and survival for 10 wks.

Results: In-vitro, MODK562E CBMNC showed increased NK activation ($p<0.05$) and increased granzyme B and perforin expression compared to WTK562 (22±.5 vs 11±.3%, $p<0.001$; 42±1.5 vs 15±.5, $p<0.001$, respectively). MODK562E CBMNC cytotoxicity was increased compared to WTK562E BL ($p<0.01$) and DLBCL ($p<0.01$). At 5 wks, B-NHL volume in mice receiving either dose of MODK562E CBMNC was decreased compared to WTK562E (2±0.6 and 0.4±.05vs 3± 0.25/mm^3, p=0.0086 and p=.0001, respectively), as was B-NHL luminescence ($p<0.01$). At 10 wks, xenografted mice treated with 5x10^7 MODK562E CBMNC showed increased survival compared to WTK562E ($p<0.001$).

Conclusion: CBMNC stimulation with MODK562 was associated with a significant increase in expression of NK activation marker, LAMP-1, and proteases, perforin and granzyme B, enhanced B-NHL in-vitro cytotoxicity and increased B-NHL in-vivo survival. Future directions include CAR CD20 (MSCV-anti-CD20-41BB-CD3ε) transduction into MODK562E CBMNC to enhance B-NHL targeting.

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

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Background: CD20 is an excellent tumor target and rituximab, a chimeric type I antibody (ab)directed at CD20, has shown enhanced activity in adult and pediatric B-cell nonlymphoblastic NHL (BL/DLBCL); but, eventually relapse 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 Can Therapeutics*, 2010). It also exhibits superior activity of direct and cellular immune mediated cytotoxicity against CD20$^+$ nonlymphoblastic NHL (BL and DLBCL) in-vitro and in human B-NHL xenograft models (Mössner 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 (Tanoue) and PBLL (U698M; DSMZ) 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) orIgG isotype control at 37^o, 5% CO_2 for 24, 36, 48, or 72h. Cells were stained with annexin V/propidium iodide and cell death assessed within 1hr by flow cytometry (Ayello/Cairo et al *Exp Heme* 2009).

Results: CD20 expression on PBALL and PBLL cell line was 8.2±2.1 and 53±2.5%, respectively. At 36h the PBALL line demonstrated no significant change in cell death; while in PBLL cell death was significantly increased at 100µg/ml ofGA101 compared to 10 and 1.0 (16±.3 vs 7.3±.04vs 5±0.42%, respectively, p<.001) and compared to isotype and Loucy (16± 0.3 vs 1.1±.26 vs 0.8±.2%, respectively, p<.001). Following 72h incubation, GA101 induced a significant increase in cell death in PBLL (53% CD20$^+$) vs PBALL (8% CD20$^+$) vs isotype vs neg control (Loucy CD20$^-$) [59±0.3 vs 39±2.3 vs 0.02±0.01 vs 2.86±0.13%, 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.

349 ENHANCED ACTIVITY OF THE TYPE II, GLYCOENGINEERED CD20 ANTIBODY GA101 IN COMBINATION WITH BENDAMUSTINE, FLUDARABINE, AND CHLORAMBUCIL

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GA101 is type II, glycoengineered anti-CD20 antibody currently in PhII/III clinical trials. GA101 mediates enhanced direct cell death compared with Type I mAbs and enhanced ADCC induction due to increased affinity for FcgRIIIa. We have shown that compared with rituximab, GA101 mediates superior efficacy in NHL xenograft models.

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 (3 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 sAUC 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 yielded a significant difference compared with GA101 monotherapy or rituximab with fludarabine. TGI values on day 36 were 50% for fludarabine, 60% 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 P110D, IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT AND MANTLE CELL LYMPHOMA

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Background: The class I phosphatidylinositol 3-kinases (PI3Ks) regulate cellular functions relevant to oncogenesis. Expression of the PI3K p110 d isoform (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 1 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: At data cutoff, patient enrollment was 30 for indolent NHL (iNHL) and 21 for mantle cell lymphoma (MCL). Patient characteristics included: median age [range] of 68 [32-85] years; 76% males; 45% refractory disease; and a median [range] of prior therapies of 4 [1-12]. CAL-101 dose levels were 50, 100, 150, 200, and 350 mg BID; and 300 mg QD. The median [range] number of CAL-101 treatment cycles was 5 [1-19]. Grade ≥3 adverse events included ALT/AST increase (27%), anorexia (10%), pneumonia (10%), diarrhea (8%), neutropenia (8%) and fatigue (6%). ALT/AST increases occurred 2-8 weeks after CAL-101 initiation and resolved after drug interruption; most patients resumed CAL-101 at a reduced dose without recurrence. Intention-to-treat overall response rates were 63% for iNHL and 48% for MCL. Respective medians for duration of response and progression-free survival were 9 and >12 months in iNHL and 3 and 4 months in MCL. High plasma levels of CCL17, CCL22, CXCL13, and TNF-a at baseline were decreased with 1 cycle of CAL-101. PK analyses showed minimal plasma C_{max} and AUC increases at doses >150 mg BID.

Conclusions: CAL-101, an oral PI3Kd isoform-selective inhibitor, shows acceptable safety and promising clinical activity in patients with indolent NHL and MCL. Dose-response assessments support the 150 mg BID dose for future single-agent and combination studies.

351 CAL-101, A SPECIFIC INHIBITOR OF PHOSPHATIDYLINOSITOL-3-KINASE-DELTA (PI3KD), ATTENUATES PATHWAY SIGNALING, INDUCES APOPTOSIS, AND ENHANCES THE ANTITUMOR ACTIVITY OF THE MTOR INHIBITOR, EVEROLIMUS (RAD001), IN MANTLE CELL LYMPHOMA (MCL)

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Background: The PI3K-Akt-mammalian target of rapamycin (mTOR) pathway plays a pivotal role in cell proliferation and survival, transducing signals from cell-surface receptors to proteins involved in cell cycling (eg, cyclin D1) and mRNA translation (eg, ribosomal protein S6 and translation initiation factor 4E-binding protein 1 [4E-BP1]). Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma. Overexpression of cyclin D1 in MCL has prompted clinical evaluation of mTOR inhibitors (everolimus, temsirolimus). While efficacy has been observed, the extent and duration of tumor control has been modest, encouraging assessment of additional methods of intervention. Among the several PI3K isoforms (p110a, b, g, d), we have previously shown a unique role for PI3K-delta in maintaining the survival of hematological cancers and have also shown that CAL-101, a highly selective oral PI3K delta-isoform-specific inhibitor with no activity against mTOR, shows promising activity in patients with hematological cancers. These considerations prompted us to assess the specific role of PI3Kd in MCL and to determine if dual PI3Kd-mTOR inhibition might enhance antitumor effects.

Methods and Results: In all evaluated MCL cell lines (Jeko, Mino, Granta, and NCEB), PI3Kd levels were high while expression of PI3Ka, b, and g were variable. PI3K delta was functionally active, inducing phosphorylation of Akt (pAkt) in all tested cell lines and also in 4 of 4 primary MCL variants. Single-agent CAL-101 decreased pAkt in cell lines and primary samples. The pAkt decrease was associated with growth suppression and apoptosis in all MCL cell lines. Consistent with these effects, immunoblotting showed that CAL-101 decreased cyclin D1 levels in all tested MCL cell lines. Treatment with CAL-101 also decreased S6 phosphorylation, but levels of phospho-4E-BP1 remained high, suggesting that mTOR signaling was not completely inhibited. However, the combination of CAL-101 and everolimus suppressed phosphorylation of both S6 and 4E-BP1, inhibiting MCL viability and enhancing apoptosis relative to treatment with either CAL-101 or everolimus alone.

Conclusion: Our findings indicate that excessive PI3K delta activity is characteristic in MCL and CAL-101-mediated PI3Kd inhibition reduces MCL growth and survival. Combination therapy to address the molecular complexity associated with the diverging and converging PI3Kd-Akt and mTOR pathways may provide a novel treatment approach for MCL.

352 CAL-101, AN ISOFORM-SELECTIVE INHIBITOR OF PHOSPHATIDYLINOSITOL 3-KINASE-DELTA (PI3Kδ), INHIBITS PATHWAY SIGNALING IN PRIMARY FOLLICULAR PATIENT SAMPLES

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Background: Deregulation of thephosphatidylinositol 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 isoforms (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). Prior *in vitro* iNHL studies revealed that CAL-101 induces caspase-dependent apoptosis, and inhibits CD40L-, BAFF-, CXCL12- and CXCL13-derived survival signals in cellular models (Lannutti BJ, et al., Blood 2010). A Phase I CAL-101 clinical experience detailed the significant activity of this agent in heavily pre-treated relapsed or refractory iNHL & MCL (Kahl BS, et al., Blood 2010). In support of a planned trial for treatment-naive patients with iNHL, we sought to investigate the potential role of PI3Kδ in primary follicular lymphoma patient samples *in vitro*.

Methods and Results: To evaluate constitutive PI3K pathway activation, tumor cells from treatment-naive patients were screened for levels of pAkt by measuring the phosporylation of Akt at both the Thr308 and Ser473 by flow cytometry. In most cases primary malignant cells (4/5) displayed constitutive levels of $pAkt^{S473}$ 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 Thr308 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 invoked 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 $pAkt^{S473}$ and $pAkt^{Thr308}$ that was PI3Kδ-dependent as shown by its complete inhibition by CAL-101 at 0.1-1.0 μM.

Conclusion: Our findings demonstrate that CAL-101 blocked both constitutive and invoked 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 frontline clinical evaluation in iNHL.

353 THE JAK INHIBITOR AZD1480 REGULATES PROLIFERATION AND IMMUNITY IN HODGKIN LYMPHOMA

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Background: Aberrant activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway has been reported to promote proliferation, 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-derived cell lines 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, Inc. (Waltham, MA) and the MEK inhibitors UO126 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 STAT3, STAT5, and STAT6 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 50% 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 mM 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-13, thymus and activation-regulated chemokine TARC, and the surface expression of PD-L1 and PD-L2. On the other hand higher concentrations of AZD1480 (5μM) induced G2/M arrest and cell death in all the cell lines by inhibiting aurora kinases.

Conclusions: Our study demonstrates that AZD1480 regulates proliferation and immunity 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

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Introduction: CFZ is a novel, highly selective epoxyketone 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 28-day cycles (C), at 20 mg/m2 in C1, escalating to 27 mg/m2 in C2–12. 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. Newly incident 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	Total n	ORR (≥PR)	CBR (≥MR)
Overall	257	61 (24)	93 (36)
Number of prior therapies, n (%)			
<5	110	27 (25)	36 (33)
≥5	147	35 (24)	53 (36)
Baseline PN, n (%)			
None	55	14 (26)	20 (36)
G1/2	202	48 (24)	68 (34)
ISS disease stage, n (%)			
I	76	24 (32)	35 (46)
II	96	24 (25)	34 (35)
III	78	14 (18)	19 (24)

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%), anemia (20%), lymphopenia (10%), pneumonia (8%), neutropenia (8%), fatigue (7%), hyponatremia (5%), and hypercalcemia (5%). New-onset PN and PN ≥G3 were infrequent. 27 pts completed 12C and continued on extension protocol PX-171-010. Updated long-term follow-up data will be presented.

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 no 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).

355 UPDATED RESULTS FOR BORTEZOMIB (BTZ)-NAÏVE PATIENTS (PTS) ENROLLED IN PX-171-004, AN ONGOING OPEN-LABEL, PHASE (PH) 2 STUDY OF CARFILZOMIB (CFZ), IN RELAPSED MULTIPLE MYELOMA (MM)

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Introduction: CFZ, a selective, epoxyketone proteasome inhibitor, produces potent, sustained proteasome inhibition and lacks many off-target activities associated with BTZ. Durable activity has been observed in pts with advanced-stage relapsed/refractory MM, including those with significant comorbidities. PX-171-004 is an ongoing ph 2 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. Dexamethasone (4 mg) prophylaxis was administered in C1. The primary endpoint was overall response rate (ORR) per International Myeloma Working Group criteria. Secondary endpoints were clinical benefit response rate (CBR), duration of response (DOR), time to progression (TTP), and safety.

Results: 123/125 pts (59 in Cohort 1; 64 in Cohort 2) were response-evaluable. Prior therapies included thalidomide (58%), lenalidomide (59%), alkylating agents (82%), and stem cell transplant (73%). Forty-four (35%) patients had disease refractory to the most recent therapy. In general, responses occurred rapidly, in a median of 0.75 mo (range 0.5–2.3) in Cohort 1 and 1.9 mo (range 0.5–4.9) in Cohort 2. A median TTP of 8.3 mo and a median DOR of 13.1 mo were observed for Cohort 1. The median TTP and DOR for Cohort 2 have not been reached.

Best response	Cohort 120 mg/m^2(N=59)	Cohort 2, 20/27 mg/m^2(N=64)
CR	2 (3)	1 (2)
VGPR	8 (14)	17 (27)
PR	15 (25)	16 (25)
MR	10 (17)	6 (9)
SD	13 (22)	12 (19)
PD	7 (12)	9 (14)
ORR (CR+VGPR+PR)	25 (42)	34 (53)
CBR (ORR+MR)	35 (59)	40 (63)

Grade (G) 3/4 AEs regardless of relationship to study drug in >5% of all included: anemia (13%), lymphopenia (13%), pneumonia (13%), neutropenia (12%), 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.

Conclusions: In this BTZ-naïve pt population, the ORR, DOR, and TTP are particularly noteworthy for a single-agent, steroid-sparing regimen. This suggests that CFZ can be safely administered for prolonged periods to pts with R/R MM with minimal potential for clinically significant, therapy-limiting AEs. The authors wish to acknowledge the support of the Multiple Myeloma Research Consortium (MMRC).

356 PROTEASOME INHIBITION LEADS TO DEPHOSPHORYLATION AND DOWNREGULATION OF PROTEIN EXPRESSION OF MEMBERS OF THE AKT/MTOR PATHWAY IN MCL

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Background: Mantle cell Lymphoma (MCL) is a distinct B-cell subtype characterized by the chromosomal translocation t(11;14)(q13;q32), an especially poor clinical outcome and low response to chemotherapy. The proteasome inhibitor, bortezomib, is approved for treatment of relapsed and refractory MCL and achieves a response rate of 30-40%. However, little is known which molecules represent the critical targets of proteasome inhibition and how different regulators of cell cycle and apoptosis are affected. Bortezomib has been shown to inactivate the NFkB pathway in MCL, but recent findings indicate Bortezomib is also active in a proteasome –dependent manner suggesting Bortezomib must target also other pathways.

Methods: Four MCL cell lines (HBL2, Granta 519, Jeko-1, NCEB-1), two CLL cell lines (Mec1, Mec2) and two hematological control cell lines (Jurkat, Karpas 422) were exposed to Bortezomib at a previously defined cytotoxic concentration (25nmol). Western blot and mRNA analysis were performed for various members of the PI3K/Akt/mTOR and the MEK/ERK pathway after 24h Bortezomib exposure. Results were compared to cell proliferation (WST1, trypanblue staining), induction of apoptosis (Annexin V PE/7-AAD staining) and cell cycle data (FACS).

Results: Western blot analysis revealed reduced phosphorylation of Akt at Ser473 in all cell lines while autophosphorylation of mTOR at Ser2481 was completely downregulated only in the susceptible cell lines. In addition further members of the mTOR pathway were affected by bortezomib treatment. Dephosphorylation of the 4E-BP1, downregulation of p70S6 protein expression was detected in all cell lines whereas eIF4Edephosphorylation was only in the susceptible MCL cell lines. Interestingly Bortezomib did not affect members of the MEK/ERK pathway (MEK1/2, p42/44MAPK). In on of the cell lines there was an antagonism detectable between the mRNA and proteinexpression profile of CCND1 suggesting an involvement of bortezomib in the regulation of translation initiation. This data were supported by microarray analysis. Analysis of patient samples underlined the influence of bortezomib on the Akt/mTOR pathway.

Conclusions: In this study we could show that Bortezomib treatment targets the Akt/mTOR pathway especially by dephosphorylation of the translation initiation factor eIF4E and other molecules of this signal pathway. The influence of bortezomib on translation initiation has to be further elucidated.

357 SEROLOGICAL IDENTIFICATION OF HSP105 AS A NOVEL NON-HODGKIN LYMPHOMA ASSOCIATED ANTIGEN

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Background: We reported that vaccination with dendritic cells pulsed with autologous killed tumor cells achieved clinical responses that correlated with antitumor immune-activation in relapsed indolent non-Hodgkin lymphoma (NHL) patients. Thus, we set out to determine whether vaccine-induced humoral response was directed against common NHL-specific antigens (Ags), which might represent novel targets for therapy.

Methods: Immunoglobulins (Igs) were purified from pre- and post-vaccine patients' serum samples, biotin-conjugated, and tested by immunohistochemistry (IHC), flow cytometry (FC) and western blot (WB) on allogeneic tumor biopsies or primary tumor cells and cell lines. Ag discovery was performed by a serological proteomic-based approach (SERPA) followed by mass spectrometry (MS). The specific targeting of identified Ags was studied in vitro, by 3-(4,5- dimethylthiazol- 2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays, and in human lymphoma-xenotransplanted SCID mice.

Results: IHC and FC showed an increased tumor-specific alloreactivity with post-vaccine Igs of responders (R) compared to matched pre-vaccine samples or non-R (NR) Igs. Rs' post-vaccine sera significantly impaired the growth of follicular NHL cell line DOHH-2 in MTT assays (p=0.001). WB analysis of DOHH2 protein fractions obtained by isoelettrofocusing probed with patients' Igs revealed one differential band migrating at about 100 kDa only using post-vaccine samples of R. MS identified heat shock protein (HSP) 105 in the differentially reacting band. FC revealed HSP105 both on the cell membrane and in the cytoplasm of a panel of B-NHL cell lines and normal B cells, with a significantly higher surface-expression in aggressive tumor cell lines. IHC analyses on 97 diagnostic NHL specimens (54 low- and 43 high-grade NHL) showed a significant positive correlation between NHL aggressiveness and HSP105 expression (r=0.8484), with high-grade NHL displaying more frequently a specific cell-surface staining. In-vitro treatment with anti-HSP105 Ab significantly impaired the growth of aggressive NHL cell lines, NAMALWA and SU-DHL-4, compared to isotype Igs (p=0.02, p=0.04). In-vivo administration of anti-HSP105 Ab provided, respectively, 70% and 60% growth delay of NAMALWA and SU-DHL-4 xenografts compared to isotype Igs (p<0.01, p<0.001) as evaluated by nuclear magnetic resonance. These effects were associated with a significant recruitment of gramzyme positive cells, extended necrosis and reduction of tumor endothelial area.

Conclusions: Our results point to HSP105 as a novel potential biotarget for improving B-NHL therapy.

358 WITHDRAWN

359 COMPLETE RESPONSES (CR/CRU) ON A PHASE 2 STUDY OF ROMIDEPSIN IN RELAPSED OR REFRACTORY PERIPHERAL T-CELL LYMPHOMA (R/R PTCL)

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Background: Potent histone deacetylase inhibitor romidepsin has shown durable clinical benefit and tolerability in patients (pts) with R/R PTCL with objective response rates of 38% (17/45, NCI1312) and 26% (34/130, GPI-06-0002) reported in phase 2, single-arm, open-label trials. This abstract provides a subset analysis of pts who achieved CR/CRu on the GPI-06-0002 trial.

Methods: Pts with R/R PTCL received romidepsin 14 mg/m^2 as a 4-h IV infusion on days 1, 8, and 15 every 28 days. An Independent Review Committee made blinded efficacy assessments in a 2-step process: initial radiographic review followed by an overall clinical assessment based on radiology and relevant clinical parameters.

Results: The CR/CRu rate was 13% (17/130); median time to CR/CRu was 4 mo (range 2-9 mo). At the data cut-off (March 31, 2010), median duration of response (DOR) was not reached with longest DOR of 26+ mo. With a median follow-up of 8.2 mo, 16/17 (94%) pts had not progressed and 9 continued on romidepsin. Pts who achieved CR/CRu were representative of the overall pt population (Table). The majority of pts who achieved CR/CRu were > 60 years of age (10/17, 59%); receiving > 2 prior systemic therapies or being refractory to last prior therapy did not impact CR/CRu rate. Most common grade 3/4 adverse events (AEs) were thrombocytopenia (24%), neutropenia (20%) and anemia (10%). Rates of grade 3/4 AEs were similar for pts who did or did

not achieve CR/CRu. Long-term follow-up data for the pts who achieved CR/CRu will be presented.

Conclusions: Durable CR/CRu were observed with single-agent romidepsin in pts with R/R PTCL, including those with advanced and heavily pretreated disease.

Baseline Characteristics	CR/CRu (n = 17)	Other (n = 113)
Age in years, median (range)	62 (37-78)	61 (20-83)
Stage III/IV disease, n (%)	13 (77)	78 (69)
PTCL subtype, n (%)		
PTCL NOS	9 (53)	60 (53)
AITL	4 (24)	23 (20)
ALK1-negative ALCL	4 (24)	17 (15)
Bone marrow disease, n (%)	6 (35)	30 (27)
International prognostic index, n (%)		
< 2	2 (12)	29 (26)
≥ 2	15 (88)	84 (74)
Number of prior systemic therapies, n (%)		
≤ 2	10 (59)	72 (64)
> 2	7 (41)	41 (36)
Refractory to last prior systemic therapy, n (%)	7 (41)	42 (37)
Prior stem cell transplant, n (%)	2 (12)	19 (17)

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)

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Background: The most common 1st-line treatment for PTCL is multiagent 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 folylpolyglutamyl 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 Propel, a subset of 15 pts received PDX as 2nd-line treatment post-CHOP.

Results: The demographics and disease characteristics of 15 pts treated 2nd-line with PDX post-CHOP were reflective of overall Propel 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 response, and their DoR data were censored. 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)

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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 to12 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 PFS and ORR for the most recent therapy prior to pralatrexate (-1); PFS and ORR of the most recent prior therapy (-1) were compared with those of the second prior therapy (-2); PFS and ORR of second prior therapy (-2) were compared to the third therapy prior to pralatrexate (-3).

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 patients 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 patients 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 patients 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.