245 IMMUNE TARGETING OF THE PHOSPHOPROTEOME IN HEMATOLYMPHOID MALIGNANCY

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Introduction: $CD8^+$ T cells have been identified as potent effectors of the adaptive anti-tumor immune response. So far, only a small number of tumor antigens have been objectively linked to the oncogenic processes. Alteration in phosphorylation status of cellular proteins is a hallmark of malignant transformation and a proven important therapeutic target. Phosphorylated antigens thus represent attractive immunotherapeutic targets.

Methods: Using a mass spectrometry approach phosphopeptide display was analyzed in CLL, AML, ALL, HCL and MCL samples. X-ray crystalography studies were perfomed on 6 of the phosphopeptides identified. Phosphopeptide-specific T cells were generated from lab donors using DCs and tested for activity in xenogeneic models of lymphoma.

Results: 88 phosphopeptides have been characterized many derived from phosphoproteins known to function in signaling cascades implicated in neoplastic transformation including c-Myc, NFAT and Bcl-11 with many representing novel phosphorylation sites. Six HLA-phosphopeptide structures were resolved and demonstrate upward facing phosphate moiety with potential for direct recognition by the TCR. Phosphopeptide-specific primary T cell lines were also generated *ex-vivo* from healthy lab donors which bound HLA-phosphopeptide tetramers and recognized HLA-matched primary tumor samples. Xenogeneic studies revealed activity of adoptively transfered T cells into tumor-bearing NOD/SCID mice.

Conclusion: This work characterizes phosphopeptides that are differentially presented on primary leukemia and lymphoma samples by class I MHC molecules. These post-translationally modified peptide antigens represent distinct antigenic determinants which may overcome barriers of immune tolerance and autoimmunity inherent with other tumor antigens. These phosphopeptides therefore represent attractive novel candidates for future cancer immunotherapy.

246 CLINICAL AND IMMUNOLOGIC RESPONSES TO A NOVEL *IN SITU* LYMPHOMA VACCINE MANEUVER: RESULTS OF A PHASE II TRIAL OF INTRA-TUMORAL CPG - [PF-3512676]

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Background: Therapeutic lymphoma vaccines are an appealing concept, but their development has been slowed by the difficulty of individualized ex vivo production. An "off-the-shelf" vaccine would greatly facilitate clinical development. Historically, assays of T cell mediated, tumor-specific immune responses have been difficult to reproduce and clinically validate. A more rigorous approach in which patient peripheral blood lymphocytes are simultaneously analyzed per multiple parameters at a single cell level, could allow for intra-assay correlation of specificity and anti-tumor responsiveness.

Methods: Patients with recurrent, low-grade lymphoma, received a vaccine maneuver consisting of 2x2Gy irradiation to a single site of lymphoma and 10 weekly intra-tumoral injections of CpG-[PF-3512676] at the same site. Peripheral blood samples from these patients were used to design a method for multi-color flow cytometric detection of three independent markers of tumor-specific CD8 T-cell immunity: intracellular IFN-Y, CD137, and CD107.

Results: As of January 2008, all of the planned 15 patients have been enrolled, 14 of whom are clinically evaluable. There were no significant adverse events. Tumor at the treated site almost always responded to the local therapy. Evaluation of uninjected sites showed 1 CR, 2 PR, 1 MR, 5 SD, and 4 PD. We have been able to use a panel of B cell lymphoma lines and primary tumor specimens as allo-stimulators to establish our T cell response assays. There is excellent correlation between the different measures of CD8 T cell responsiveness. These assays will be used in an attempt to correlate clinical outcome with T cell response.

Conclusions: This is the first report of an intra-tumoral CpG based vaccine for lymphoma. We demonstrated feasibility and safety. Objective clinical responses have been documented. Correlation of immunologic findings and clinical responses in this cohort will guide the development of subsequent iterations of this trial.

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247 THE IN VIVO IMMUNOGENICITY OF HUMAN IDIOTYPE-KLH VACCINES IS MARKEDLY ENHANCED BY MALEIMIDE CONJUGATION

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Tumor-specific immunoglobulin (idiotype, Id) can serve as a target for therapeutic vaccination against B cell malignancies. While Id chemically-coupled to the immunogenic foreign carrier protein keyhole limpet hemocyanin (Id-KLH) has shown promising results in phase I/II clinical trials, many immunized patients fail to mount anti-Id immune responses, and one phase III trial recently failed in its primary efficacy endpoint. Id is traditionally coupled to KLH using glutaraldehyde (glut). We developed an alternative Id-KLH conjugation method employing maleimide (mal) chemistry, that markedly improved anti-tumor efficacy in 3 different murine lymphoma models (A20, 38C13, and BCL-1) owing to increased induction of tumor-specific CD8+ T cells and antibodies. To move towards clinical application, we conjugated human monoclonal Igs (IgG1 or IgG3) to KLH using mal or glut and tested their immunogenicity in vivo. The immunoreactivity of polyclonal anti-human IgG towards various conjugates was measured by ELISA. Surprisingly, glut conjugates of IgG1 and IgG3 showed only 1-16.5% of the reactivity of free IgG, while that of mal conjugates was highly preserved (91.7-99.7%), indicating a substantial reduction in antigenic content after glut conjugation. Mice were vaccinated with various conjugates plus GM-CSF and sera tested for binding to each immunogen. In all four cases, mal Ig-KLH resulted in higher (2.1 to 14.2-fold) anti-Id antibody titers than glut Ig-KLH (Table below). In conclusion, like murine lymphoma Id proteins, human mal Ig-KLH conjugates are more immunogenic than glut conjugates. The observed destruction of human IgG antibody epitopes by glut may help explain the unfavorable results seen in some Id-KLH trials. Thus, maleimide Id-KLH therapeutic vaccines deserve testing in human lymphoma trials.

	Anti-Id antibody levels in vaccinated mice (mcg/ml)			
	IgG1 (Rituximab)	IgG1 (Trastuzumab)	IgG3 (Kappa)	IgG3 (Lambda)
Maleimide Id-KLH	136	1950	454	420
Glutaraldehyde Id-KLH	40	137	214	140

248 ANTITUMORAL EFFECT OF VACCINATION WITH CD40L-GENETICALLY MODIFIED DENDRITIC AND TUMOR CELLS FUSIONS IN MYELOMA

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Introduction: Fusions of dendritic cells (DCs) and tumor cells represent a novel approach that combines the expression of molecules needed for immune stimulation with the presentation of a repertoire of tumor antigens. Several studies have shown the importance of triggering CD40 molecules to enhance the efficiency of DC as antigen presenting cells. Fusions of dendritic and tumor cells stimulated through the CD40 pathway could enhance their capacity to stimulate specific antitumor T cells. We have studied the antitumoral effect of the administration of cell fusions transduced with a recombinant adenovirus encoding the CD40L gene (AdvCD40L) in a murine model of myeloma.

Material and Methods: DCs obtained from bone marrow of Balb/c mice were fused with tumor cells, a syngenic murine myeloma cell line (4TOO). Fusion cells (FC) were generated in polyethylene glycol and selected after culturing in HAT medium plus GM-CSF for 7 days. FC were quantified by determining the percentage of cells that coexpress specific DCs (CD11c) and tumor (CD138) markers. FC were transduced with AdvCD40L (FC-CD40L) or a recombinant adenovirus encoding green fluorescent protein (FC-GFP) as control. For vaccination, mice (n= 10 per group) were injected i.v. with $2.5x10^5$ tumor cells and treated with irradiated FC, FC-GFP or FC-CD40L ($1x10^6$ cells each, i.v) on days 2, 6 and 10 after tumor challenge.

Results: Mean fusion efficiency was 30% (range, 20-40%). FC expressed moderate levels of CD80, CD86, CD54, CD40 and MHC class II. In contrast, FC-CD40L showed a significant increase of expression of costimulatory molecules (CD80, CD86, CD54, and MHC class II) compared to FC-GFP (p= 0.011). 40% of mice treated with FC-CD40L had long-term survival (>120 days). In contrast, all mice treated with FC or FC-GFP died between days 25 and 35 (p= 0.012). In parallel, mice treated with mixed cells (DC+tumor cells without fusing), mix transduced with GFP or mix transduced with CD40L did not provide a significant antitumor effect.

Conclusions: Dendritic-tumor cells fusions transduced with recombinant viruses encoding CD40L gene stimulates antitumor immune responses in vivo and may provide a strategy for treating patients with myeloma or lymphoma.

249 ADOPTIVE TRANSFER OF AUTOLOGOUS CD25-DEPLETED, CD3/CD28-COSTIMULATED T-CELLS (ACTC) AFTER CYCLOPHOSPHAMIDE - FLUDARABINE CHEMOTHERAPY (CF) ENHANCES LYMPHOCYTE RECOVERY AND REDUCES T REGULATORY CELLS IN PATIENTS (PTS) WITH LOW-GRADE FOLLICULAR LYMPHOMA (FL)

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Introduction: CF is effective therapy for pts with FL but causes immunosuppression, possibly limiting immunologic control of residual disease. CD4+CD25+FOXP3+ T regulatory cells (Tregs) can suppress cellular immune responses. Adoptive transfer of ACTC may improve disease control after CF by accelerating T-cell recovery and reducing Tregs.

Methods: We initiated a phase I study in pts with relapsed FL (grade 1 or 2). After leukapheresis, pts receive 4 cycles of CF. Four weeks after last CF, responding pts (CR, PR) receive escalating doses of ACTC prepared from autologous T-cells collected before CF.

Results: 14 pts have been enrolled: median age 49 (32–68); median prior therapies 2 (1–3). For 10 evaluable pts completing CF and ACTC, 8 pts achieved CR and 2 pts achieved PR to CF. 5 pts received 1–5 $x10^9$ and 5 pts 5–10 $x10^9$ CD3+ ACTC. There have been no adverse events due to ACTC. Following CF, median CD4 and CD8 counts were 91 (15–169) and 64 (19–273); four weeks after ACTC, median CD4 and CD8 counts were 502 (156-1053) and 509 (158-1860). Median %CD4+FOXP3+ blood cells before CF was 15.8% (n=8; 5.07-37.1); after CF/before ACTC 21.4% (n=7; 6.15-56.3); on day 60 after ACTC 3.3% (n=8; 1.5-20.4) (p=.01 for both pre ACTC and post ACTC comparisons). All 10 pts receiving ACTC were anergic to candida antigen by DTH skin testing before CF. 5 pts developed a positive DTH response to candida antigen 60 days after ACTC (p=.03). From start of therapy, median follow-up is 26 months (8–49) with median progression-free survival not yet reached. This is significantly longer than the progression-free survival for preceding therapy (median 11 months) (p=.01).

Conclusions: ACTC after CF chemotherapy: (1) accelerates recovery of CD4+ and CD8+ lymphocyte numbers compared to historical controls; (2) enhances recovery of lymphocyte function; (3) results in reduction of peripheral blood FOXP3+ Tregs; (4) can result in a longer progression-free survival compared to prior therapy.

250 IDIOTYPE VACCINATION OF UNTREATED B-CELL LYMPHOMA IS ASSOCIATED WITHDURABLE FREEDOM FROM CYTOREDUCTIVE THERAPYAND CELLULAR IMMUNE RESPONSES

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Tumor-specific immune responses induced by idiotype immunization of B-NHL patients correlate with prolonged remission and survival rates after cytoreductive therapy. Conventional idiotype vaccines are coupled to the carrier KLH and are administered subcutaneously with adjuvant. Intradermal administration of recombinant idiotype Fab fragment with lipid-based adjuvant and subcutaneous coadministration of GM-CSF has excellent immunogenicity in advanced B-NHL patients (Bertinetti et al., 2006). In a subsequent trial, 19 patients with untreated indolent B-NHL (13 follicular [FL], 3 nodal marginal zone [nMZL], 3 mantle cell [MCL]) and without immediate need for cytoreduction received at least 6 monthly idiotype vaccinations. After a median follow-up of 32 months, 9 patients (47%) are in progression-free survival (PFS), and 11 (53%) had no requirement of cytoreductive therapy (TFS). 5 patients (26%; only FL or nMZL) achieved an objective partial remission. Of these, 4 cases are in continuing remission after 18-37 months. IFNgamma ELISpot indicated a cellular immune response to the idiotype in 10/13 analyzed patients (77%). These responses were associated with superior PFS ($p<0.05$), and all 3 nonresponders eventually required cytoreductive therapy. 6/15 analyzed patients (40%) developed anti-idiotype IgG or IgM antibodies as assessed by ELISA. These responses were not correlated to PFS. The combined immune response rate was 85%. In a parallel cohort of 19 indolent lymphoma patients vaccinated in remission after cytoreductive therapy, 6 relapses/progressions (32%) occurred during a median follow-up of 20 months, including 4/6 MCL. Cellular and humoral immune response rates in this group were 78% and 83%, respectively, but not associated with PFS. In conclusion, intradermal idiotype vaccination has an excellent cellular immune response rate. Since durable responses and long-term freedom of requirement for conventional therapy were observed after this active immunotherapy in otherwise untreated FL and nMZL, this vaccine warrants comparison to no treatment or passive immunotherapy with anti-B cell antibodies. Given the possible importance of cellular immune responses, combined active and passive immunotherapy may be envisioned to act synergistically.

251 SYNERGISTIC EFFECT OF T-CELL ADOPTIVE IMMUNOTHERAPY WITH ANTI-CD19 OR ANTI-CD38 CHIMERIC RECEPTOR ON B-CELL LYMPHOMA IN CONJUNCTION WITH RITUXIMAB

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Introduction: Using artificial receptors it is possible to redirect the specificity of immune cells to tumor-associated antigens, a strategy that holds great potential as a cancer therapy. Since B-cell non-Hodgkin's lymphoma (B-NHL) cells invariably express CD19 and CD38, these antigens are suitable molecular candidates for immunotherapy.

Material and methods: We transduced human peripheral T cells or T cell lines with an anti-CD19-chimeric receptor (CR) or anti-CD38-CR containing 4-1BB as well as anti-CD19 or anti-CD38 antibody-derived single-chain variable domain respectively.

Results: Retroviral transduction led to anti-CD19-CR or anti-CD38-CR expression in T cells with high efficiency. T cell line Hut78 retrovirally transduced with anti-CD19-CR or anti-CD38-CR exerted powerful cytotoxicity against the B-NHL cell lines RL, and HT in vitro individually. To determine the synergy of two chimeric receptors, we incubated Hut78-anti-CD19-CR and/or -anti-CD38-CR in the presence of HT cells. Interestingly, we found that two sets of chimeric receptors made an additive cytotoxic effect on HT cells in vitro. To confirm the mutual effect of T cells with these chimeric receptors on lymphoma cells in vivo, human peripheral T cells expressing either anti-CD19-CR or anti-CD38-CR were synergistically effective in NOD-SCID mice inoculated subcutaneously with HT cells. Intriguingly, we found that T cells with either anti-CD19-CR or anti-CD38-CR enhanced cytotoxicity against HT cells in xenografted mice in conjunction with rituximab.

Conclusion: We demonstrated that simultaneous immunotherapy against different antigens augmented cytotoxicity to lymphoma cells in vitro and in vivo. These results may provide a rationale for clinical testing of autologous T cells with anti-CD19-CR or anti-CD38-CR in the presence of rituximab in patients with aggressive or relapsed B-NHLs refractory to conventional therapy.

252 FILTERING OUT REGULATORY T CELLS AND CURE OF LARGE LYMPHOMA TUMORS USING SYNGENEIC IMMUNOTRANSPLANTATION

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Background: We previously described a vaccination maneuver against murine B-cell lymphoma combining chemotherapy (CTX) and intra-tumor injection of an immunostimulant - CpG, which induced T-cell immunity and eradicated established tumors. An ongoing clinical trial of this maneuver has demonstrated complete and partial responses in lymphoma patients, though immune-regulatory factors such as regulatory T cells (T_{regs}) and limiting amounts of "homeostatic" cytokines might prevent even more powerful anti-tumor immunity. Transfer of tumor-specific lymphocytes into lymphodepleted recipients may eliminate these immune-regulatory obstacles.The clinical potency of this approach has been seen with *ex vivo* activated tumor-infiltrating lymphocytes, though, the use of *in vivo* vaccine-primed anti-tumor lymphocytes could make it sufficiently feasible for broad clinical application.

Methods: Donor mice were immunized with the CTX/CpG vaccination and recipient mice were conditioned with lethal irradiation followed by transfer of syngeneic bone marrow and immunized donor splenocytes, i.e. 'immunotransplant'. Peripheral blood tumor-specific T cell responses were measured by flow cytometric assay of intra-cellular IFNY up-regulation on exposure to irradiated tumor. Transplanted animals were tested for tumor resistance.

Results: We show that transfer of T cells into the lymphodepleted recipient selectively filters against T_{regs} and doubles the transferred $T_{effector}$:T_{reg} ratio. Transferred tumor-specific CD8 T cells preferentially expand in the lymphodepleted recipient. Immunotransplant cures large subcutaneous (> $100mm^2$) and metastatic tumors in 100% of recipients and enhances tumor-specific T cell memory. The addition of a vaccine "boost" to the immunotransplant maneuver, results in an additional 3-fold increase in tumor-specific immunity.

Conclusions: As hematopoietic stem cell transplantation is a standard therapy for lymphoma patients, pre-transplant vaccination followed by post-transplant transfer of tumor-specific T cells could be tested in clinical trials. Our model suggests that this immunotransplant approach would allow the benefit of cancer vaccines to be revealed and might lead to cure of otherwise resistant malignancies.

253 T CELL MODULATION COMBINED WITH INTRATUMORAL INJECTIONS OF CPG OLIGODEOXYNUCLEOTIDES CURES LARGE AND SYSTEMIC LYMPHOMA TUMORS IN MICE

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Introduction/Background: In a murine B cell lymphoma model, we have previously shown that the combination of intratumoral CpG and chemotherapy can cure metastatic tumors (Li *et al.*, J Immunol 2007). Although CpG induces an anti-tumor T cell response through the activation of antigen presenting cells, it requires the combination with chemotherapy to be effective. We now asked whether those immune responses can be enhanced by using T cell-specific antibodies, thereby eliminating the need for chemotherapy.

Material and Methods: Mice were challenged with A20 tumors at 2 different sites (right and left abdomen). Only one site was injected with CpG allowing us to evaluate the systemic anti-tumor response at the distant site. Treatment started when tumors became palpable. CpG was administered intratumorally and all monoclonal antibodies used to modulate the T cell responses were administered i.p. : - Regulatory T cells were depleted using anti-Folate Receptor 4 (FR4) antibodies or functionally blocked using anti-GITR antibodies, - Effector T cells were triggered through their co-stimulatory molecules using anti-OX40 or anti-4-1BB antibodies, while inhibitory signals were blocked using anti-CTLA4 or anti-PD-L1 antibodies.

Results: Treatment with CpG alone cured no mice as expected, while the combination of CpG with each antibody alone only partially increased the cure rate (range: 0-40%). Selected antibodies (anti-OX40, anti-CTLA4, anti-FR4, and anti-GITR) were then used in various combinations, in conjunction with CpG. Three antibody combos showed strong efficacy, curing between 80 to 100% of the mice (anti-OX40+anti-CTLA4, anti-OX-40+anti-FR4, and anti-CTLA4+anti-GITR), whereas other combinations did not provide any significant improvement (anti-OX40+anti-GITR, anti-CTLA4+anti-FR4, anti-FR4+anti-GITR).

Conclusions: Our results show that the addition of specific antibodies against different functional T cell targets greatly enhances the therapeutic potency of intratumoral vaccination with CpG. Antibodies against these human targets are becoming available for clinical trials.

254 ANTI-CD19 BITE ANTIBODY MT103 (MEDI-538) INDUCES DURABLE OBJECTIVE RESPONSES IN PATIENTS WITH RELAPSED NON-HODGKIN'S LYMPHOMA (NHL). UPDATE FROM ONGOING PHASE I STUDY MT103-104

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Introduction: MT103/MEDI-538, a BiTE antibody targeting the CD19 antigen, is a member of a novel class of molecules that direct T cells to target cells. A Phase 1 dose escalation study is conducted in patients with advanced NHL.

Methods: Relapsed incurable NHL patients requiring treatment were included. Most patients were heavily pre-treated with a median of 4 previous chemo/immuno therapy regimens. A classical 3+3 dose escalation was employed. To date, 6 dose levels ranging from 0.5 to 60 $\mu g/m^2$ per day have been tested. MT103 was continuously infused as single agent over a period of 4-8 weeks. Objective responses assessed by Cheson criteria were centrally reviewed. Anti-tumor activity in bone marrow and liver was assessed by histochemical analysis of biopsies obtained before and after treatment with MT103.

Results: To date 37 patients have been treated. Most common AEs included lymphopenia, leucopenia and pyrexia. The majority of the AEs improved or resolved during treatment. Few patients experienced fully reversible CNS events in terms of confusion and cerebellar symptoms. Dose-dependent responses in mantle cell lymphoma; follicular lymphoma and CLL were observed in 9 out of 25 patients starting at the dose level of 15 $\mu g/m^2$/24hr.Four patients had complete and 5 had partial responses. Histochemical analysis of biopsies showed removal of target cells from in bone marrow and liver. All responders had been pre-treated with rituximab-based combination regimens. At the highest dose level of 60 $\mu g/m^2$/24hr administered to date, 5 out of 5 patients have shown objective responses. The first response observed in mantle cell lymphoma has been ongoing for 11 months and none of the responders at the two highest dose levels of 30 µg and 60 $\mu g/m^2$/24hr has experienced treatment failure to date.

Conclusions: MT103/MEDI-538 as single agent induces durable responses in pre-treated NHL patients and is well tolerated. Dose escalation is ongoing.

255 PHASE I STUDY OF KW-0761, A HUMANIZED ANTI-CCR4 ANTIBODY, IN PATIENTS WITH RELAPSED ADULT T-CELL LEUKEMIA-LYMPHOMA (ATL) AND PERIPHERAL T-CELL LYMPHOMA (PTCL)

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Introduction: KW-0761 is a defucosylated humanized IgG1 monoclonal Ab against CC chemokine receptor 4 (CCR4) with enhanced ADCC activity. Previous studies revealed that CCR4 was overexpressed on tumor cells from 88% of pts with ATL and 38% of pts with PTCL, and was associated with poor prognosis. These results suggest that CCR4 could be a reasonable molecular therapeutic target.

Methods: A multicenter P-I study of KW-0761 is being conducted for relapsed pts with CCR4-positive ATL and PTCL to evaluate its safety, pharmacokinetics, immunogenicity and efficacy. Pts were planned to receive 4 weekly IV infusions of KW-0761 at 0.01, 0.1, 0.5, and 1.0 mg/kg.

Results: As of Jan 8 2008, 8 pts (7 ATL and 1 PTCL) were treated with KW-0761 at 0.01 (N=3), 0.1 (N=4), and 0.5 mg/kg (N=1). It was well tolerated without dose-limiting toxicities. Major toxicities included; *hematologic*: lymphopenia (G4: N=1, G3: N=2, G2: N=3), neutropenia (G3: N=1, G2: N=2), eosinophilia and thrombocytopenia (G2: N=1 each), *non-hematologic*: herpes zoster (3 months after the 4th dosing, G3: N=1), acute infusion reaction/cytokine release syndrome (G3: N=1, G2: N=3), constipation, rash, QTc prolongation and ALT elevation (G2: N=1 each). One pt was withdrawn due to early disease progression. PK analysis showed that Cmax at 0.01 and 0.1 mg/kg after the 4th dosing were 324±57 and 1835±438 ng/ml, respectively. $T_{1/2}$ of each pt was between 60 and 380 h. No anti-KW-0761 Ab has been detected. Preliminary investigator-assessed responses for 8 enrolled pts included 1 CR (0.1 mg/kg; PB & skin), 2 PRs (0.01 mg/kg; CR in PB & PR in LN, 0.1 mg/kg; CR in PB & PR in skin) and 3 SDs.

Conclusions: KW-0761 is a promising new Ab therapy for CCR4-positive ATL and PTCL. Pt accrual is ongoing and the updated results will be presented.

256 CLINICAL ACTIVITY OF LUMILIXIMAB AND FCR DOES NOT CORRELATE WITH BASELINE LEVELS OR MODULATION OF SERUM CD23, BETA-2 MICROGLOBULIN, AND CLL CELL LEVELS IN CLL PATIENTS

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Background: Lumiliximab, a monoclonal antibody specific for the human CD23 glycoprotein expressed on a majority of CLL cells, is under investigation for the treatment of patients (pts) with relapsed chronic lymphocytic leukemia (CLL). In a Phase I/II single arm study evaluating lumiliximab in combination with fludarabine, cyclophosphamide, and Rituxan (L+FCR) in relapsed CLL, a high CR rate of 52% was observed. High baseline levels of sCD23, b2 microglobulin and CLL cell counts have all previously been shown to correlate with poor prognosis. In order to assess if L+FCR clinical activity is related to any of these prognostic markers, levels of sCD23, b2 microglobulin and CLL cell counts were evaluated in this study.

Methods: 31 pts with relapsed CLL received up to 6 cycles of L+ FCR. sCD23 levels were measured in 22 pts using an enzyme-linked immunosorbant assay. b2 microglobulin levels were measured in 31 pts using the Immulite system with follow-up levels available for 25 pts.Peripheral blood samples for CLL cell analysis were measured for 31 pts by flow cytometry; CLL cells were identified as CD45+/CD5+/CD19+ lymphocytes.

Results and Conclusions: Our analyses show that baseline levels of sCD23, b2 microglobulin, and CLL cell counts did not correlate with L+FCR activity, thus, suggesting that L+FCR may also provide clinical benefit to pts with unfavorable clinical outcomes. Furthermore, modulation of sCD23, b2 microglobulin levels, and of CLL cell counts following L+FCR treatment was observed. All pts assessed (22/22) showed increase of sCD23 levels, 21/25 pts showed modest decreases in b2 microglobulin levels and 31/31 pts had decreases in CLL cell counts after treatment, although intensity of change did not appear to correlate with clinical response with any factor. These findings will be further evaluated in future clinical trials.

257 PROMISING RESULTS OF EPRATUZUMAB AND RITUXIMAB IN COMBINATION WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISONE CHEMOTHERAPY (ER-CHOP) IN PATIENTS WITH PREVIOUSLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA

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Background: A prior pilot study of epratuzumab (Immunomedics) and rituximab in combination with CHOP chemotherapy (ER-CHOP) in untreated patients with DLBCL demonstrated feasibility and safety. This multicenter phase II study was carried out to assess efficacy.

Methods: Patients received immunochemotherapy on the following schedule: epratuzumab 360 mg/m^2, rituximab 375 mg/m^2, and standard dose CHOP every 3 weeks for 6 cycles. Primary endpoint was 12 month event free survival (EFS12). Secondary endpoints were complete response rate (CR), overall response rate (ORR). An interim analysis was planned when the first 34 eligible patients were evaluable for EFS12.

Results: This study has met full accrual, with 107 patients (pts) entered between Feb 2006 and Aug 2007. The median age was 62 (range 21-82), the performance score was 0-1 in 94 pts and 2-3 in 13 pts, and 59 were male. Most (82%) had advanced stage disease; IPI was 0-1 in 22 pts (21%), 2 in 27 pts (25%), 3 in 40 pts (37%) and 4-5 in 18 pts (17%). Seventy-two pts (67%) had an elevated LDH. Overall, 104 patients were evaluable for toxicity, of which 71 patients (68%) developed grade 4 neutropenia, grade 3 or 4 anemia (9%) and thrombocytopenia (13%). Non-hematological adverse events included neuro-sensory (45%), fatigue (36%), and vomiting (28%). The most common grade 3 or 4 treatment related event was febrile neutropenia (17%). Response rates of the 34 patients at the time of the planned interim analysis were 16 CR, 3 CRu (56% CR + CRu), 13 PR (38%), and 2 SD with an ORR of 94%. Data on the primary endpoint (EFS12) is still maturing and will be reported at the meeting.

Conclusions: ER-CHOP every 21 days is safe. The ORR is encouraging; further analysis will determine if this regimen should be evaluated in a phase III randomized study.

258 RESULTS OF A PHASE IB STUDY OF RECOMBINANT HUMAN APO2L/TRAIL WITH RITUXIMAB IN PATIENTS WITH RELAPSED, LOW-GRADE NHL

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Background: Low-grade non-Hodgkin lymphoma (NHL) is not usually curable, and thus a crucial need exists to improve therapies and outcomes for these patients (pts). Recombinant human Apo2L/TRAIL (rhApo2L/TRAIL), a derivative of the naturally occurring Apo2 Ligand/TNF-Related, Apoptosis Inducing Ligand, is a pro-apoptotic receptor agonist that can engage both death receptors DR4 and DR5 on tumor cells. It exhibits additive or synergistic activity in combination with Rituximab (R) in SCID mice bearing tumors derived from multiple NHL cell lines.

Methods: Pts ≥18 yrs with relapsed, low-grade NHL who received prior R-containing therapy were eligible for this dose comparison study of the safety and compatibility of R and rhApo2L/TRAIL. All pts received R, 375mg/m^2 wkly x 8, and rhApo2L/TRAIL, 4mg or 8mg/kg/d x 5 every 21d (1 cycle) for 4 cycles. Adverse events (AEs), laboratory and pharmacokinetic assessments were collected; efficacy (ORR, PFS) was assessed by IWG criteria (Cheson B et al, 1999).

Results: Twelve pts (6 in each rhApo2L/TRAIL dose group) aged 39-82 yrs were treated on study after a median of 2 prior therapies (range: 1-8). Ten pts completed all protocol-specified study treatment; 1 pt in each dose group discontinued study treatment after 2 cycles of rhApo2L/TRAIL (1 for PD; 1 for an AE). The most common AEs were fatigue, rash, anorexia, chills, nausea and diarrhea; all except 1 episode of Grade 4 diarrhea were Grade 1 or 2. A total of 26 Grade 3/4 AEs in 5 pts were reported; 22 occurred in a single pt in conjunction with a serious AE (pseudomonas sepsis) while the remaining 4 events were not dose limiting. Two serious AEs were reported. Six pts (4 in the 4mg/kg/d and 2 in the 8mg/kg/d dose groups) had objective responses (3 CRs, 3 PRs).

Conclusions: The combination of R and rhApo2L/TRAIL at 4mg and 8mg/kg/d appears to be safe and well-tolerated. Further investigation of this combination is warranted. A randomized, Phase II comparison study is underway.

259 VORINOSTAT PROVIDES PROLONGED SAFETY AND CLINICAL BENEFIT TO PATIENTS WITH ADVANCED CTCL

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Background: Vorinostat (Zolinza™), a histone deacetylase inhibitor, was approved in 2006 by the FDA for the treatment of the cutaneous manifestations of CTCL in patients (pts) with progressive, persistent or recurrent disease on or following 2 prior systemic therapies.

Methods: Pts with stage ≥ IB CTCL who had received ≥ 2 prior therapies received oral vorinostat 400 mg daily, until intolerable toxicity or progressive disease (PD), in an open-label, Phase IIb trial. The primary endpoint was objective response rate. This post hoc subset analysis reports results from patients who received vorinostat for ≥ 2 years.

Results: As of November 1 2007, 6 of 74 pts had received vorinostat for ≥ 2 years: median age 65 years (range 57-74), median number of prior therapies 2.5, median time from diagnosis to enrollment 1.8 years (range 0.7-5.9). 1 pt had a complete response, 4 a partial response and 1 stable disease. Diarrhea (100%), nausea (83%), fatigue (67%) and alopecia (50%) were common drug-related AEs. 1 pt had a serious AE of pulmonary embolism, resolving in 7 days. This pt is continuing therapy as of Day 955. 1 pt who experienced serious AEs of increased creatinine phosphokinase (CPK) [Day 490] and rash (Day 645) remained on therapy until Day 948. The only other grade ≥ 3 AEs were anorexia (n=1) and thrombocytopenia (n=1). 1 pt discontinued due to PD, 1 discontinued due to PD, rash and increased CPK, and 4 are continuing therapy. Updated data will be presented.

Conclusions: Vorinostat has demonstrated prolonged safety and clinical benefit in these pts with advanced CTCL.

260 PCI-24781, A NOVEL HISTONE DEACETYLASE INHIBITOR (HDACI), INDUCES CASPASE–DEPENDENT APOPTOSIS IN HODGKIN LYMPHOMA (HL) AND NON-HODGKIN LYMPHOMA (NHL) CELL LINES AND IS SYNERGISTIC IN COMBINATION WITH BORTEZOMIB

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Background: PCI-24781 (PCI) is a new HDACi with pan-HDAC inhibitory activity. We investigated the cytotoxicity and cell death mechanisms of PCI with/without the NFκB inhibitor bortezomib in lymphoma cell lines.

Methods: HL (L428) and NHL (HF1, Ramos, SUDHL4) cells were incubated with PCI (0.25-2.0μM) and bortezomib (2.5-20nM) for 24-72 hours. Apoptosis was determined by fluorescence-activated cell sorting (FACS) using annexinV/propidium iodide staining without/with the pan-caspase inhibitor Q-VD-OPh. Loss of mitochondrial membrane potential (MMP) was measured by FACS, while PARP, cleaved caspases, and histone acetylation were measured by immunoblot. Reactive oxygen species (ROS) were measured by oxidation of 2'7'dichlorofluorescein diacetate to dichlorofluorescein and detected by FACS. Downstream targets of NFκB (NFκB1, c-Myc, IL-8) were measured by RT-PCR.

Results: Dose-dependent apoptosis was seen with PCI in all cell lines. IC50 of PCI was <1μM for Ramos, HF1, and SUDHL4 and <1.5μM in L428. With bortezomib, the IC50 was 10nM in all NHL lines and 20nM in L428. Of note, the combination of PCI/bortezomib resulted in highly synergistic apoptosis in all 3 NHL lines (combination index (CI) <0.2) and to a lesser extent L428 (CI <0.6). 40-50% loss of MMP was seen with PCI (0.25μM) or bortezomib (5nM) alone in Ramos and L428, while the combination resulted in >75% MMP loss. Following PCI (0.25μM)/ bortezomib (5nM) combination in Ramos and L428, highly enhanced cleavage of caspases 3, 8, 9, and PARP were seen compared with either agent alone; while Q-VD-OPh blocked apoptosis in both cell lines, suggesting that synergy was in part caspase-dependent. All cell lines showed 2-4 fold increase in ROS following PCI and/or bortezomib treatment. Furthermore, apoptosis of PCI and/or bortezomib was abrogated with the anti-oxidant, catalase. In Ramos and L428, hyperacetylation of histone-3 and -4 was significantly increased with PCI/bortezomib compared to PCI alone. Finally, in Ramos cells, down-regulation of NFκB1, c-Myc and IL-8 was seen with PCI alone, effects which were enhanced with bortezomib.

Conclusion: The HDACi, PCI, induces dose-dependent apoptosis in HL and NHL cells as a single agent and results in synergistic apoptosis combined with bortezomib. Furthermore, cell death is NFκB-related and caspase- and ROS-dependent.

261 LOW DOSE PRALATREXATE (PDX) IS ACTIVE IN CUTANEOUS T-CELL LYMPHOMA: PRELIMINARY RESULTS OF A MULTI-CENTER DOSE FINDING TRIAL

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Background: PDX is a novel antifolate with activity at a range of doses in rel/ref T-cell lymphoma (TCL). The maximum tolerated dose (MTD) from our phase I study was 30 mg/m^2 weekly for 6/7 weeks. In that study, responses were seen in patients (pts) with cutaneous T-cell lymphoma (CTCL). To explore this activity, we designed a trial of PDX in pt with CTCL. CTCL is more indolent than peripheral TCL and treatment paradigms use maintenance approaches. We sought a best tolerated, yet active dose and schedule for these unique pts by designing a dose reduction scheme. PDX-010 is a multi-center, open : label, Phase 1 study of PDX with vitamin B_{12} and folic acid in pts with rel/ref CTCL.

Methods: Eligibility includes CTCL types: mycosis fungoides (MF), Sezary syndrome (SS), cutaneous anaplastic large cell lymphoma (ALCL) and progression of disease after ≥1 systemic therapy. The dosing scheme uses 2 schedules: 3/4 weekly and 2/3 weekly. Doses are reduced in sequential cohorts based on toxicity. Optimal dose and schedule is defined as activity without Grade (Gr) 4 heme tox, Gr 3-4 infection, or febrile neutropenia.

Results: From 8/07-1/08, 12 pts have enrolled. 11 with MF and/or SS, 1 with ALCL. Med prior therapies 4 (range 3-7). Med systemic therapies 3 (range 1-6). Cohorts are: 30 mg/m^2 3/4 weeks (n=2), 20 mg/m^2 3/4 weeks (n=3), 20 mg/m^2 2/3 weeks (n=7). Drug related DLT are: Gr 3 infection (2), tumor lysis syndrome (1), Gr 2-3 mucositis (3), Gr 3 myalgias (1), Gr 3 LFT (1). 11 pts are evaluable. Responses are investigator-assessed using an mSWAT. Best response to date: stable disease 3, partial response (PR) 3, complete response (CR) 2, ORR of 45%. 1 pt with PR and 1 pt with CR progressed soon off therapy. 7/12 pts remain on treatment.

Conclusion: PDX shows promising early activity in the treatment of CTCL at much lower doses than used for aggressive lymphomas. This study is ongoing to see if low doses of PDX can result in maintained responses with minimal toxicity and will be updated.

262 ORAL MTOR INHIBITION WITH EVEROLIMUS IN RELAPSED T CELL AND HODGKIN LYMPHOMA

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Introduction: mTOR inhibition has demonstrated promising activity in phase II trials for aggressive B-cell non-Hodgkin lymphomas, including mantle cell and diffuse large cell types (*Blood 110 (11) 2007 Abst 121 and J Clin Oncol 23 (23):5347, 2005)*). This study tested oral everolimus in a phase II trial for patients with T cell lymphoma (TCL) or Hodgkin lymphoma (HL) to learn the toxicity and overall response rate (ORR) in these two disease types.

Materials and Methods: Patients received everolimus 10 mg po daily for each 28 day cycle and were restaged after 2, 6, and 12 cycles. The primary endpoint was the ORR, including CR, CRu and PR.

Results: Twenty-five patients were enrolled - 17 patients with HL and 8 patients with TCL The T cell lymphoma cohort included MF (4), peripheral T cell (3) and ALCL (1). The median age was 47.3 years. The patients were heavily pre-treated with a median of 6 prior therapies. Sixty percent of all patients (87.5% of HL) had undergone prior stem cell transplant. The ORR was 56% (14/25) with all responses being PR; 9 additional pts had stable disease. The ORR was 63% (5/8) for TCL and 53% (9/17) for HL.The patients have completed a median of 6 cycles of therapy (range, 1 – 14+) with 10 patients (9 with HL) still on active therapy. Everolimus was well-tolerated with the main toxicity being reversible myelosuppression.

Conclusions: Oral everolimus has activity in a spectrum of lymphomas including T cell lymphomas and Hodgkin lymphoma. The drug had limited toxicity even in this heavily pretreated population. This study provides the rationale for integrating mTOR inhibitors in salvage or upfront treatment regimens for aggressive lymphomas.

263 TREATMENT OF RELAPSED OR REFRACTORY NON-HODGKIN LYMPHOMA WITH THE ORAL ISOTYPE-SELECTIVE HISTONE DEACETYLASE INHIBITOR MGCD0103: INTERIM RESULTS FROM A PHASE II STUDY

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Background: MGCD0103 is an orally available selective inhibitor of histone deacetylases (HDACs) with significant biological activity in preclinical models of both solid tumors and hematopoietic cancers.

Methods: Open-label, Phase II trial (Trial 008) in adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL). Eligibility required measurable disease (≥ 2.0 cm), ECOG 0 or 1. MGCD0103 given 3x/week starting at 110 mg; after 32 patients (pts) an 85 mg starting dose was evaluated. Tumor responses were determined every 2 cycles. PK was evaluated on Day 1, Cycle 1.

Results: 50 pts received treatment; 33 DLBCL & 17 FL; median age [range], 61.5 years [32-80]; male, n=27; prior rituximab therapy: 96%; prior stem cell transplant: 33%. Response rate in the DLBCL cohort met criteria for expansion and complete enrollment of 41 pts has been achieved. Among 34 pts who had tumor reassessed, most exhibited tumor reductions including a CR and 3 PRs in DLBCL pts; with progression free survival (PFS) for responders ranging from 168 to >336 days. Five DLBCL pts with stable disease had PFS ranging 112 to >336 days. One of 10 FL pts with tumor reassessment had a PR. Comparison of the 85 and 110 mg cohorts revealed 16% & 53% of patients, respectively, with ≥ grade 3 toxicity. PK evaluation revealed Tmax = 1 hr, with biphasically elimination & plasma t ½ ~8 hrs. Similar Cmax & AUC were observed at 85 (n=8) and 110 (n=17) mg, suggesting a trend towards saturable absorption. Inhibition of HDAC activity in PBMCs was seen in 13/18 pts and was similar between the 85 & 110 mg groups.

Conclusions: MGCD0103 demonstrated significant anti-cancer activity in relapsed or refractory NHL (DLCBL and FL subtypes) and had a manageable side effect profile.

264 SAFETY AND TOLERABILITY OF VORINOSTAT – EXPERIENCE FROM THE VORINOSTAT CLINICAL TRIAL PROGRAM

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Background: We present the safety and tolerability data from patients (pts) who received vorinostat, a HDAC inhibitor with anticancer properties, alone or with other systemic therapies for solid and hematologic malignancies.

Methods: Safety data from all pts in the Vorinostat Clinical Trial Program were collated (cut-off Dec 2007).

Results: 476 pts with CTCL, solid or hematologic malignancies received vorinostat as monotherapy (n=341) or in combination therapy (n=135). As monotherapy, the most common AEs were fatigue (68.3%), nausea (60.1%), diarrhea (55.4%), and anorexia (49.9%). Grade 3-4 AEs included thrombocytopenia (15.2%), fatigue (13.5%), dehydration (8.5%), and anemia (7.9%). There were 3 drug-related deaths (ischemic stroke, tumor hemorrhage, unspecified). Of 156 pts who received monotherapy at 400 mg q.d. (the dose approved by the FDA for advanced CTCL treatment), 13 (8.3%) discontinued due to AEs (anorexia [1.3%], pulmonary embolism [0.6%], and weight decrease [0.6%]), and 24 (15.4%) required dose modifications (commonly due to thrombocytopenia [5.8%], diarrhea [1.9%], and nausea [1.9%]). In combination therapy, the most common AEs were nausea (52.6%), diarrhea (43.0%) and fatigue (41.5%). Grade 3-4 events included fatigue (16.3%), diarrhea (5.9%), dehydration (5.2%), and nausea (5.2%). 1 drug-related death occurred (hemoptysis, NSCLC pt). 25 (18.5%) pts discontinued due to AEs (fatigue [3.0%] dehydration and nausea [both 2.2%]), and 23 (17%) required dose modifications (commonly due to fatigue [5.9%], diarrhea [1.5%] and hypertriglyceridemia [1.5%]).

Conclusion: Vorinostat has an acceptable safety and tolerability profile as monotherapy or in combination with other systemic therapies in cancer pts; dose modifications are usually not required in the majority of pts.

265 A PHASE I-II TRIAL OF THE KINESIN SPINDLE PROTEIN (KSP) INHIBITOR SB-743921 ONDAYS 1 AND 15 EVERY 28 DAYS IN NON-HODGKIN OR HODGKIN LYMPHOMA

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Background: KSP is a mitotic kinesin essential for cell cycle progression. SB-743921 (SB-921), a selective KSP inhibitor, blocks mitotic spindle assembly with cell cycle arrest in mitosis and cell death. In the first-in-humans (FIH) trial, the maximum tolerated dose (MTD) was 4 mg/m^2 q21 days (d), i.e., 0.2 mg/m^2/d. Neutropenia was the major dose-limiting toxicity (DLT).

Methods: Phase I of this trial determines the MTD of SB-921 without prophylactic GCSF (pGCSF) in patients (pts) with Non-Hodgkin (NHL) or Hodgkin Lymphoma (HL). Eligible pts with relapsed or refractory lymphoma had at least 1 prior chemotherapy regimen, and had relapsed after or were not candidates for autologous stem cell transplant. SB-921 is given to cohorts of 3 on d1/d15 q28d, starting at 2 mg/m^2 and escalating by 1 mg/m^2. Cohorts expand to 6 if 1/3 pts have a DLT.

Results: To date, 32 pts have received ≤ 7 mg/m^2 of SB-921; 14 had HL; 18 had NHL (9 indolent, 9 aggressive). Thirty-one pts had ≥ 2 prior chemotherapy regimens (14 had ≥ 5). Cycle 1 neutropenia ≥ grade 3 occurred in 7 pts. Two DLTs at 6 mg/m^2 occurred with ≥ grade 3 neutropenia; one was noted after escalation to 7 mg/m^2, a dose tolerated through cycle 1 without DLT by 3 pts. Cycle 1 drug-related non-hematologic toxicities ≥ grade 3 were infection (1), dehydration (1) and dyspnea (1). A HL pt had a partial response (PR) for 4 cycles at 6 mg/m^2; a NHL pt begun at 3 mg/m^2 and escalated to 5 mg/m^2 had stable disease for 13 cycles.

Conclusions: SB-921 is well tolerated without pGCSF at < 6 mg/m^2 and possibly at ≥ 7 mg/m^2 given d1/d15 q28d, an increase from the MTD of 4 mg/m^2 q21d in the FIH trial (possibly ≥ 0.5 vs. 0.2 mg/m^2/d). The 6 mg/m^2 cohort was expanded and may allow re-escalation to > 7 mg/m^2. A HL pt had a PR at 6 mg/m^2. If the DLT without pGCSF is neutropenia, the MTD will next be determined with pGCSF.