19. New Agents

095

FINAL RESULTS OF A PHASE II TRIAL OF SINGLE-AGENT TEMSIROLIMUS (CCI-779) FOR RELAPSED MATURE CELL LYMPHOMA

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Purpose: Relapsed mature cell lymphoma (MCL) is characterized by a (11;14) resulting in overexpression of cyclin D1 messenger RNA. This study tested whether temsirolimus (previously known as CCI-779), an inhibitor of the mammalian target of rapamycin (mTOR) kinase that regulates cyclin D1 translation, could produce tumor responses in patients with MCL.

Patients and methods: Patients with biopsy-proven, cyclin D1 positive MCL that had relapsed or were refractory to therapy were eligible to receive temsirolimus 250 mg IV every week as a single agent. Patients with a tumor response after 6 cycles were eligible to continue drug for a total of 12 cycles or 2 cycles after complete remission (CR) and then were observed without maintenance.

Results: Thirty-five patients were enrolled and are evaluable for toxicity; 1 patient had MCL by histology but was cyclin D1 negative and was ineligi-
ble for efficacy. The median age was 70 years (range 38–89), 91% were stage 4, and 66% had 2 or more extranodal sites. Patients had received a median of 3 prior therapies (range 1–11) and 54% were refractory to the last treat-
ment. The overall response rate was 38% (13/34; 90% CI: 24–54%) with 1 CR (3%) and 12 partial responses (35%). The median response duration was 1 month (range 1–8). The median time-to-progression in all patients was 6.5 months (95% CI 2.9–8.3 months) and the duration of response for the 13 responders was 6.9 months (95% CI 5.2–12.4 months). Hematologic toxicities were the most common, with 71% (25/35) grade 3 and 11% (4/35) grade 4 toxicities observed. Thrombocyto-
penia was the most frequent cause of dose-reductions but was of short duration, typically recovering within one week.

Conclusions: Single-agent temsirolimus has substantial anti-tumor activity in relapsed MCL. Further studies of this agent in MCL and other lymph-
omalignancies are warranted.

096

FLAVOPIRIDOL GIVEN AS A 30-MIN INTRAVENOUS (IV) BOLUS FOLLOWED BY 4-HR CONTINUOUS IV INFUSION (CIVI) RESULTS IN CLINICAL ACTIVITY AND TUMOR LYSIS IN REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background: Flavopiridol induces p53-independent apoptosis in CLL cells, but phase II studies using 24–72 hr CIVI schedues showed mini-
mal activity. Pharmacokinetic modeling indicated that a 30-min IV bolus (IVB) followed by 4-hr CIVI would achieve plasma drug concentrations necessary to induce apoptosis in CLL cells in vitro.

Methods: An ongoing phase I study has administered flavopiridol by 30-

min IVB followed by 4-hr CIVI weekly for 4 doses, every 6 weeks for up to 6 cycles, to patients (pts) with relapsed and refractory CLL.

Results: To date, 26 pts with previously treated CLL have been enrolled on two dose levels (30 mg/m² IVB + 30 mg/m² CIVI and 40 mg/m² IVB + 40 mg/m² CIVI). Dose limiting toxicity was acute tumor lysis in 2 pts treated at dose level 2, including 1 pt who died of hyperkalemia. Aggres-
sive measures to prevent and manage tumor lysis, including hospitaliza-
tion, alkaline hydration, allopurinol, rasburicase and vigorous manage-
ment of hyperkalemia, have made this drug safe to administer at dose level 1. To date, 17 additional pts have been treated at dose level 1. Two pts developed tumor lysis and hyperkalemia adequately controlled by hemodialysis. One pt died of documented gram negative sepsis following treatment. Other manageable toxicities include neutropenia, anemia, thrombocytopenia, infection, fatigue, and diarrhea. Ten of 23 evaluable pts achieved a partial response (43%), and 8 remain in remission (5–14+ months). Nine responders had high-risk genetic features predicting poor response to therapy. Three of 8 pts with del (17p13) responded to treatment.

Conclusions: Single agent flavopiridol given weekly by 30-min IVB fol-
lowed by 4-hr CIVI is active in refractory CLL, resulting in clinical responses and tumor lysis. This study is ongoing, and results will be updated at the meeting. In addition, we are using our experience with flavo-
piridol in CLL, in particular the prophylaxis and management of tumor lysis, to study the safety and efficacy of this promising schedule in other lymphoid malignancies.

097

BORTEZOMIB (VELCADE®) IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOMA: POTENTIAL CORRELATION OF TNFα RESPONSE AND IN VITRO SENSITIVITY WITH CLINICAL ACTIVITY

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Introduction: The proteasome regulates proteins involved in cell survival, in part by transcription of anti-apoptotic proteins by NF-kB, activated by tumor necrosis factor (TNFα) signaling. Bortezomib (VELCADE®) is a proteasome inhibitor with clinical activity in myeloma. A phase II clinical study was undertaken to examine the efficacy, toxicity and biological activity of bortezomib in pts with relapsed, refractory lymphoma.

Methods: 1.3 mg/m² bortezomib was given twice weekly for 2 of 3 weeks to pts who fulfilled eligibility criteria. Where possible treatment patient biopsy specimens were cultured using a CD40 feeder system to assess in vitro sensitivity. Plasma samples were taken to examine possible cytokine correlates.

Results: 42 pts with a median age of 57 yrs (35–75) received a median of 4 cycles (range 1–8) of treatment. The most common grade III/IV toxicities were thrombocytopenia in 18 pts (40%) and fatigue in 5 pts (11%). Seven of 22 evaluable pts with MCL initially responded to treatment, 6 PR, 1 CR/CRu, (ORR of 32%); 1 pt progressed towards the end of 8 cycles. None of 12 patients with FL had an objective response at the out-
come assessment (4 cycles); however, 2 achieved a ‘late’ partial response 3 mos later. Two of 5 pts with WM achieved a PR. None of 4 pts with HD responded to treatment. Pre-treatment plasma TNFαs, measured in 10 patients with MCL to date, were raised in 5 responders (R) and 5 non-
responders (NR), mean 20.5 vs 24.4 pg/ml respectively, P=0.53. After 4 cycles of treatment there was a mean reduction in TNFαs of 97 ± 3% in R (to < 1.0–9.0 pg/ml in 4/5) vs 42 ± 24% in NR (9–350 pg/ml in 3/5, P=0.04). Two of 5 NR completed only 1 and 2 cycles of therapy, with changes in TNFαs of +132% and -28% respectively. One responder pro-
gressed between cycles 6 and 8 with a corresponding rise in TNFαs from 0.5 pg/ml to 14.9 pg/ml. Pre-treatment IL-6 and MCP-1 were also raised, but did not show consistent changes between R and NR. Sensitivity to bortezomib in vitro in 7 pts correlated with clinical response. In a larger group of patients the median EC50 was 377 nM in MCL (n=10), and 1311 nM in FL (n=8, P<0.05).

Conclusions: The first European study of bortezomib in pts with relapse-

drefractory lymphoma demonstrates encouraging efficacy in MCL. Clin-
ical activity correlated with reduction in plasma TNFαs and In vitro sensitivity to bortezomib in small numbers of pts.

098

PHASE II STUDY OF BORTEZOMIB IN RELAPSED/REFRACTORY WALDENSTROM’S MACROGLOBULINEMIA: INTERIM RESULTS OF WMCTG 03-248

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TARGETING THE PROTEASOME PATHWAY WITH BORTEZOMIB IN PATIENTS WITH MANTLE CELL (MCL) AND FOLLICULAR LYMPHOMA (FL) PRODUCES PROLONGED PROGRESSION FREE SURVIVAL AMONG 1-4, EIGHTH AND 7 PATIENTS: RESULTS OF A MULTICENTER PHASE II EXPERIENCE


Targeting of the ubiquitin proteasome pathway has proven to be a valid and efficacious approach for the treatment of several hematologic malignancies. To date, we have registered 65 patients, including 35 with MCL, 19 with FL, 6 with marginal zone lymphoma and 5 with small lymphocytic lymphoma/CLL. The population demographics include a median age of 66 (43 to 84), 42 males and 23 females, and a median KPS of 90%. The median number of prior conventional chemotherapies for the population is 3. Patients were treated at a dose of 1.5 mg/m^2 twice weekly for two consecutive weeks with a one week rest period. The only Grade 3 or greater toxicities seen were lymphopenia (~40% of patients) and one patient that developed a grade 3 sensory and motor neuropathy. The overall response rate was 52%. Of the evaluable patients, the ORR in FL and MCL was 60% (1 CR/1 CRu) and 54% (3 CR/2 Crn) respectively. Interestingly, 34% of patients with MCL had stable disease on study despite progression of disease at study entry. The time to response (TTR) was also different between these two populations, with a median TTR of 5 weeks and 11 weeks in patients with MCL and FL, respectively. The PFS among all patients with MCL versus all other NHL was 7 months and 5 months respectively. However, among all responding patients on study the PFS was 18 months. When broken down by subtype, the PFS among responding patients with MCL and FL was one year (range 6 months to 19 months) respectively. Comparison to the PFS obtained from the line of treatment prior to study drug administration was uniformly better for patients receiving bortezomib. This study continues to accrue patients with different sub-types of NHL, and continues its follow-up of all patients treated on study. We will present an update on the emerging role this promising new class of drugs is beginning to play in the management of NHL.

100

GEMCITABINE AS FRONT-LINE TREATMENT FOR CUTANEOUS T-CELL LYMPHOMAS: PHASE II STUDY ON 32 PATIENTS

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Introduction: On the basis of gemcitabine activity in heavily pretreated cutaneous T-cell lymphoma (CTCL) patients the objective of this study was to determine the role of Gemcitabine in advanced untreated CTCL.

Methods: Between June 2002 and February 2004, 32 untreated patients with mycosis fungoides (MF) (26 patients), peripheral T-cell lymphoma unspecified (PTCLU) with exclusive skin involvement (5 patients) and Sezary Syndrome (SS) (1 patient) were enrolled in a 2-institution, phase II trial and treated with gemcitabine. This drug was given on days 1, 8, 15 of a 28-day schedule at a dose of 1200 mg/m^2 intravenously over 30 minutes for a total of six cycles. Results: Of the 32 patients, 7 (22%) achieved complete response (CR), 17 (53%) partial response (PR), while the remaining 8 showed no benefit to the treatment. Five of the 8 patients were among the 5 patients with PTCL who were enrolled. The CR and PR rates were used for the MF and PTCLU patients, respectively. The median duration of CR patients was 10 months (range 4 to 22 months). Treatment was well tolerated; hematologic toxicity was mild and no nausea/vomiting or organ toxicity was recorded. Conclusions: The results of the present phase II study show activity of gemcitabine as a single agent in untreated CTCL patients. Further studies using gemcitabine in combination, or potentially in sequential, with other drugs in advanced stage untreated CTCL patients are needed.

NEW DRUGS FOR LYMPHOMAS

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Despite recent advances in the treatment of the lymphomas, novel therapeutic agents are still needed to improve prognosis. Renewed interest in bendamustine is based on impressive results in CLL and NHL. Recent data suggest response rates of 90% in relapsed and refractory NHL when combined with rituximab. New drugs with activity in mantle cell lymphoma include bortezomib (Velcade) with responses in 30–50% of patients, and activity in other histologies as well. CCI-779, a rapamycin analog, blocks mTOR in the PI3K pathway, inhibiting cyclin D1, preventing cells from going from G1 to S phase. Responses to this agent in MCL have been around 40%, although myelosuppression has led to additional studies to optimize the dose. Activity has also been reported with olinibensin (genasense) alone and in combination with chemotherapy. This agent is also being studied in various combinations for other NHL. Histone deacetylase inhibitors in clinical trials include suberoylanilide hydroxamic acid (SAHA), a small molecule that inhibits tumor growth in animal leukemias and lymphoma models. SAHA has excellent oral bioavailability. Responses observed in pilot trials in lymphoma led to an ongoing phase II trial in aggressive NHL. Interest in thalidomide for NHL was stimulated by its activity in multiple myeloma and Waldenstrom’s macroglobulinemia. Unfortunately, activity in NHL is minimal. Newer “IMiDs” (immunomodulatory derivatives) are in development, notably lenalidomide. New monoclonal antibodies include galiximab, an anti-CD20 antibody with activity in refractory NHL. Based on preclinical data suggesting synergy, a phase III study of the combination with rituximab has been completed. A phase II study will be activated in the CALGB of rituximab and galiximab in previously untreated follicular NHL. For patients with CLL/SL, humiliximab, a primatized, anti-CD23 monoclonal antibody, is under evaluation alone and in combination with fludarabine and rituximab. CD30 on Reed-Sternberg cells in HL and the malignant cells of anaplastic large cell NHL provides an excellent. Anti-CD30 antibodies in clinical trials have been well tolerated, but dose and schedule need to be optimized for greater activity. Therapies are moving away from nonspecific cytotoxic agents and towards more targeted approaches. Genomics and proteomics, provide the opportunity to develop disease-specific and even patient specific therapies. Combining targeted therapies in a manner that will optimize their activity,
and identifying patients most likely to respond to those therapies will improve our ability to cure patients with lymphomas.


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Foodful discussion among the scientific advisors of the Lugano conference in the late 1980s about the most relevant open issues in the management of non-Hodgkin lymphomas resulted in the decision of organizing a sort of brainstorming on the development of reproducible and effective prognostic systems to guide therapeutic decisions in diffuse large cell lymphoma. Indeed, a workshop of a relatively small group of experts convened to discuss the “Prognostic Factors in diffuse large cell lymphomas”. This meeting is believed having had a likely relevant role in the constitution of “The International Non-Hodgkin’s Lymphoma Prognostic Factors Project”, which later produced the International Prognostic Index (N Engl J Med. 1993; 329:987–94).

On the basis of the successful first one, a second workshop was organized during the fifth Conference in 1993 to discuss the controversial pathological and staging classifications of gastrointestinal tract lymphoma. It generated the modified Blackledge staging system that is presently widely known as the “Lugano staging system for GI lymphoma” (Ann Oncol. 1994;5:397–400).

A third workshop in 1996 put the attention on the clinical validation of the REAL classification, which at that time was not yet widely accepted, especially by American clinicians. The effort of the “Non-Hodgkin’s Lymphoma Classification Project” to carry out a clinical evaluation of the REAL classification (Blood. 1997; 89:3909–3918) has been a cornerstone for the later development of the, nowadays universally used, WHO classification of lymphomas, which directly derives from the REAL classification.

The seventh Lugano conference 1999 was preceded by a workshop on the molecular identification of the relevant biological prognostic features of diffuse large cell lymphoma. The aim was to help the successful outcome of the large international groups that later confirmed the utility of gene expression profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma (N Engl J Med. 2002; 346:1937–47 and Nat Med. 2002; 8:68–74).

The 2002 workshop was aimed to create an international, interdisciplinary research collaboration around primary central nervous system lymphoma (J Clin Oncol. 2003; 21:2407–14). Subsequent to that workshop, the International PCNSL Collaborative Group was created.

The 2005 workshop during the Ninth International Conference on Malignant Lymphomas will deal with the still inadequately understood peripheral T-cell lymphomas. Hopefully it will be successful as the former ones.
20. New Treatment Modalities

A PHASE II TRIAL OF OBLIMERSEN SODIUM (G3139) PLUS RITUXIMAB FOR TREATMENT OF PATIENTS WITH RECURRENT B-CELL NON-HODGKIN’S LYMPHOMA

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Introduction: Olimersen sodium (Genasense; GNS) produces downregulation of bel-2 expression and enhances the antitumor activity of rituximab (RIT).

Methods: We are conducting a phase II study to determine the efficacy and toxicity of GNS + RIT in patients (pts) with recurrent B-cell NHL. GNS (3 mg/kg/d) is administered as continuous IV infusion for seven days in weeks 1, 3, and 5. RIT (375 mg/m²) is given weekly for 6 doses.

Results: To date 35 pts have been entered. Twenty-four pts were previously treated with rituximab, and 7 were refractory. Eighty-two of 22 (36%) evaluable patients achieved an objective response. Two patients achieved CR (1 MALT, 1 FL); 1 pt achieved an unconfirmed CR, and 3 pts achieved a PR (1 MCL, 2 FLCL, 1 SLL, 1PL). Two pts had minor response and 6 pts SD. One CR occurred in a rituximab-refractory patient. The most common grade 3–4 adverse events included: neutropenia in 7 pts (25%), thrombocytopenia in 3 pts (10%), non-neutropenic fever in 4 pts (14%).

Conclusions: GNS can be safely combined with RIT. This preliminary analysis shows clinical activity of this combination and warrants ongoing study.

RITUXIMAB PLUS GM-CSF (LEUKINE®) FOR INDOLENT LYMPHOMA

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Introduction: GM-CSF may enhance cell-mediated immunity and thereby improve the efficacy of rituximab.

Methods: 39 evaluable indolent lymphoma patients (pts) received rituximab x 4 wks and GM-CSF x 8 wks. All but one had follicular lymphoma. 14 were previously untreated; 25 had prior therapy. Antitumor dependent cellular cytotoxicity (ADCC) and natural killer cell (NKC) activity were evaluated in 14 pts (Liu N et al. Blood 2003; 102 (Suppl): 411a).

Results: The overall and complete (CR) response rates were 79% and 36%, respectively. Tolerance was comparable to rituximab alone. Both CR and PR/ NR pts had significant increases in ADCC activity following therapy. By contrast, there was not a significant change in the NKC activity of both groups post-therapy. Median incremental ADCC activity post-therapy was greater among CR pts (16%) compared with PR/NR pts (6%), approaching statistical significance (P = 0.056).

Conclusion: In this small trial, the response rate, especially CR, was encouragingly high. These data suggest that the combination of GM-CSF with rituximab enhances ADCC activity, and that the increase in ADCC correlates with response in patients with indolent lymphoma.

PHASE I STUDY OF INTRAVENTRICULAR ADMINISTRATION OF RITUXIMAB IN PATIENTS WITH RECURRENT INTRACULAR AND CNS LYMPHOMA

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Introduction: Ten patients with recurrent, or refractory CD20+ CNS NHL were treated at UCSF and at Memorial Sloan-Kettering Cancer Center in this first phase I dose escalation protocol of intrathecal rituximab monotherapy.

Methods: The protocol design incorporated nine planned injections of Rituximab at 10 mg, 25 mg and 50 mg dose levels through an Omaya reservoir over a five week period. CSF and serum levels of Rituximab were measured at baseline, one, two, four, eight, twenty-four and ninety-six hours. To define transcriptional events associated with Rituximab exposure, gene expression profile analysis was conducted on B-lymphoma cells purified from the CSF at baseline, one, two, and four hours post-Rituximab administration.

Results: We defined the safety profile of intrathecal rituximab and demonstrated that the maximum tolerated dose is 25 mg by intraventricular administration. We did not detect serious adverse toxicity in eight consecutive subjects treated at the 10 mg (three patients) and 25 mg (five patients) dose levels. Dose-limiting toxicity was grade three hypertension at the 50 mg dose level. High peak drug levels were obtained within the venicles with evidence for rapid craniospinal axis distribution; Rituximab was reproducibly detectable in the lumbar sac at four hours. Administration of Rituximab by LP in three patients resulted in a five-fold increase in intraventricular concentration at ninety minutes. Cytologic responses were immediately detected in six patients; four patients exhibited complete response during restaging at six weeks. One patient had complete resolution of parenchymal NHL. Two patients exhibited significant improvement in intraventricular NHL as determined by complete ophtalmologic examination. Gene expression profile analysis of lymphomatous meningitis specimens at baseline revealed high relative expression of a number of anti-apoptotic mediators in tumors refractory to intrathecal Rituximab.

Conclusions: Intraventricular Rituximab administration may represent a novel means of treatment of ocular and CNS complications of NHL. Early safety and efficacy data are promising. A follow-up study of combination intrathecal rituximab plus MTX is in development based upon these results.

CLINICAL UPDATE ON FRACTIONATED RADIOMMUNEOTHERAPY IN PATIENTS WITH NHL USING HUMANIZED 90Y-LABELLED ANTI-CD22 EPRATUZUMAB


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Introduction: The advantages of increased efficacy of RAIT compared to the naked antibody are at expense of temporary reversible bone marrow suppression. An ongoing, phase II/II multi-center, dose-escalation trial in patients with NHL is assessing safety and efficacy of 90Y-epratuzumab administered weekly for 2 or 3 consecutive weeks.

Methods: Patients with indolent and aggressive NHL who failed prior therapy were eligible for this study.

Results: Twenty-one patients have been treated without achieving MTD (total 90Y dose, 30 mCi/m²). Of the 21 patients, 13 (62%) had an objective response (OR) by IWG criteria, including patients with indolent and aggressive disease (7/10 (70%) and 6/11 (55%), respectively, across histologies [follicular NHL, 7/10 (70%); DLBCL, 3/4 (75%); mantle cell, 3/4 (75%)], and in patients failing rituximab (10/16, 63%). Most OR s were complete responses (CR/Cru, 11/13), and with follow-up now available in 8 CR/Cru responders, all had responses ≥ mo, including 2 patients continuing ≥1 yr. Dose escalation continues after 5/6 patients (83%) in the last cohort receiving 10 mC/m² × 3 weekly infusions had an objective response, including 4 patients with CR/Cru.
Conclusions: This fractionated schedule of 90Y-labeled humanized anti-CD22 antibody appears safe and efficacious in patients with recurrent NHL. Dose escalation continues after achieving 66% complete responses at a 30 mCi/m² cumulative 90Y-dose.

RAPID INFUSION RITUXIMAB CAN BE SAFELY ADMINISTERED AND HAS A POSITIVE IMPACT ON RESOURCE UTILIZATION

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Background: Administration of rituximab, a chimeric anti-CD20 monoclonal antibody, can be associated with substantial infusion-related toxicity. Guidelines for administration require lengthy infusion times (5–6 h for first infusion, 3–4 h for remaining infusions). Lengthy infusion may be unnecessary when rituximab is administered in combination with steroid containing chemotherapy.

Methods: In March 2004, we began a pilot study investigating the safety of a rapid infusion rituximab schedule for all patients with NHL receiving rituximab with steroid containing chemotherapy. The schedule of administration for cycle 1 of therapy was unaltered and delivered according to the product monograph. All further cycles were administered the same day of chemotherapy, over a total infusion time of 90 minutes (20% of the dose in the first 30 min then the remaining 80% over 60 min; total dose delivered in 250 mL). Patients took their daily prednisone dose prior to receiving rituximab. Safety information was monitored prospectively using an infusion monitoring record.

Results: 130 patients have now been treated for a total of 342 infusions (median infusions per patient: 2). Patient characteristics are as follows: median age, 61 y (range 19–92); 62% male; 63% stage III/IV; 26% PS=1; 36% IP score high/intermediate. Histology: 61 DLBCL, 32 follicular, 14 transformed, 7 mantle cell, 16 other. No patients had increased numbers of circulating lymphocytes. Chemotherapy regimen: 106 CHOP, 18 CVP, 6 other. The 90-minute rituximab infusion schedule was extremely well tolerated. The overall rate of grade 3/4 infusion related reactions was 0% (95% CI 0.0–0.23), which is as low as the expected rate following the standard infusion schedule. No increased incidence in minor reactions was noted. The rapid infusion schedule has enabled us to administer rituximab in less than half the standard infusion time, allowing for more patients to be conveniently treated.

Conclusion: A rapid (90-minute) rituximab infusion schedule in combination with a steroid containing chemotherapy regimen is well tolerated and safe when administered from the second infusion onward. This shortened infusion schedule substantially reduces resource utilization and has become the standard administration schedule in the province of British Columbia.

DOSE-ADJUSTED EPOCH-RITUXIMAB: A NOVEL PHARMACODYNAMIC REGIME WITH HIGH EFFICACY IN ALL CLINICAL RISK GROUPS, AND GCB AND ABC SUBTYPES OF UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA

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Diffuse large B-cell lymphoma (DLBCL) prognosis is dependent on IPI risk group and on the cell of origin as defined by germline center B-cell (GCB) and activated B-cell (ABC) subtypes. These subtypes have 5-year survivals of 54% and 31%, respectively, using CHOP. A molecular predictor showed high tumor proliferation and the ABC subtype are associated with a poor outcome. We showed DA-EPOCH overcomes the adverse effects of high tumor proliferation (Blood 99:2683, 2002) and rituximab overcomes the adverse effects of BCL-2, which is associated with ABC (Proc Am Soc Hem 102:abstr 356, 2003). We assessed DA-EPOCH-R with G-CSF and NO radiation in these risk groups. GCB and ABC subtypes were identified using a validated IHC algorithm (Blood 103:275, 2004). GCB was defined as CD10+ or BCL-6+ and MUM1−. ABC was defined as CD10− and BCL-6− or CD10−, BCL-6+ and MUM1+. Eligibility includes de novo DLBCL, no prior chemotherapy, any PS, HIV− and stage I/II thymic DLBCL, >5 cm and all stage II/IIV. Characteristics of 83 enrolled pts include median (range) age 48 (12–85); stage III/IV 62%; and LDH>15% all 55% and; H/Hi IPI 36%. Overall CR/CRu is 94%. At the median (range) follow-up of 32 (8–68) mos, PFS and OS are 82%, with no progression beyond 18 mos, PFS at 32 mos according to IPI L/I=1−94% and H/I=57%. Using IHC, 42 pts were subdivided in GCB (32) and ABC (10) subtypes. The proportion of the ABC subtype vs. GCS is low and likely due to incomplete IHC for the ABC subtype. Specifically, 16 cases that were CD10− did not have IHC for BCL-6 and/or MUM1 IHC for categorization. PFS at 32 mos for the GCB and ABC subgroups were 83% and 69%, respectively. DA-EPOCH-R employs a pharmacodynamic design where doses of doxorubicin, etoposide and cyclophosphamide are adjusted i.e. (normalized) to achieve neutrophil nadirs <5000/μL. PK analysis showed that clearance of rituximab and etoposide varies by up to 1 log and that dose-adjustment compensates for these differences. This approach increases dose intensity in pts with high drug clearance while limiting toxicity. Based on 451 cycles, the target nadir ANC < 500/μL was achieved on 61% of cycles but with 15% febrile neutropenia. DA-EPOCH-R is highly effective in all clinical risk groups and biological subtypes of de novo DLBCL. A phase III study comparing R-CHOP and DA-EPOCH-R with microarray analysis of tumor biopsies is under development.

THE LUNENBURG LYMPHOMA BIOMARKER CONSORTIUM (LLBC): DEVELOPING BIOMARKERS FOR CLINICAL USAGE

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Biological prognostic markers have been shown to be predictive of outcome in patients with non-Hodgkin’s lymphoma but have not gained acceptance in clinical practice. Clinical prognostic markers, such as the IPI and the FLIPI, have gained widespread use as clinically relevant prognostic markers, in part following their validation using large cohorts of patients from international trials. Clinical factors, however, represent surrogates for the underlying biology and do not directly identify potential targets for novel therapies. Important biomarkers have been described in both diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL), but require validation and systematic study in a large cohort of patients.

The LLBC is an international effort with a mission to move risk stratification beyond clinical factors to biologically based markers. The ultimate goals of this consortium are to standardize the methodology for routine measurement of biomarkers in a validation study using tissue microarray (TMA) techniques and immunohistochemistry and to determine their independent contribution to predict patient outcome. Standardization of the reagents and methodology will establish the thresholds for determining positivity. Initially biomarkers and clinical data will be evaluated among a large number of patients with DLBCL treated with CHOP or CHOP+Rituximab (R) on clinical trials from both North America and Europe with at least 3 years of follow-up. The importance of the biomarkers alone or in combination in predicting outcome will be compared between patients with DLBCL receiving CHOP and CHOP+R. Similar validation and prognostic relevance studies of FL will be performed. The LLBC hopes to achieve results from these studies that will firmly establish the role of biomarkers beyond the IPI, providing further justification for risk stratification by biomarkers and IPI in future clinical trials of non-Hodgkin’s lymphoma.
TRIGGERING OF TRAIL-R1 AND TRAIL-R2 DEATH RECEPTORS BY THEIR SELECTIVE FULLY HUMAN AGONISTIC ANTIBODIES INDUCES APOPTOSIS IN PRIMARY AND CULTURED LYMPHOMA CELLS

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Background: Tumor necrosis factor (TNF) related apoptosis inducing ligand (TRAIL/Apo2L) is a member of TNF superfamily that preferentially induces apoptosis in cancer cells, while sparing normal cells. Because of the potential therapeutic application of this pathway, further study of mechanisms of resistance have been proposed for TRAIL, similar mechanisms have not been identified for these selective agonistic antibodies.

Methods: We evaluated the in vitro activity of two selective fully human agonistic monoclonal antibodies to the TRAIL death receptors TRAIL-R1 (HGS-ETR1) and TRAIL-R2 (HGS-ETR2) in 9 lymphoma cell lines and 27 primary lymphoma tumor samples. Cell proliferation and apoptosis were determined by the MTS and Annexin-V binding assays. Cell surface receptor expression was determined by Western blot, flow cytometry, and immunohistochemistry.

Results: HGS-ETR1 and HGS-ETR2 antibodies demonstrated antiproliferative activity in 5 of 9 cell lines which was associated with caspase 8 activation and induction of apoptosis. Both antibodies induced cell death in two-thirds of the primary lymphoma samples, irrespective of prior exposure to chemotherapy. Sensitivity to these antibodies could not be predicted by the level of surface TRAIL-R1 or TRAIL-R2 receptor expression, or by the intracellular levels of cFLIP, caspase-8, or Bax. Moreover, the absence of Bid expression in the lymphoma cell lines correlated with resistance to both antibodies (P = 0.0159).

Conclusions: Our data demonstrate that HGS-ETR1 and HGS-ETR2 monoclonal antibodies to the TRAIL death receptors TRAIL-R1 and TRAIL-R2 can induce cell death in a variety of cultured and primary lymphoma cells, and therefore may have therapeutic value in lymphoma. Phase II study of HGS-ETR1 (TRM-1) antibody is currently enrolling patient to evaluate the activity of this antibody in vivo.

GCS-100 A NOVEL GALECTIN-3 ANTAGONIST AND CASPASE9 ACTIVATING THERAPY FOR INDOLENT B-CELL MALIGNANCIES

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Introduction: GCS-100 is a novel polysaccharide agent with anti-cancer activity thought to work through Galactosin-3. The pharmacological effects include pro-apoptotic and anti-angiogenic properties. In a Phase I cancer study a good non myelosuppressive safety profile was seen. This study investigated GCS-100 as a therapy for indolent B-cell lymphomas, CLL and myeloma.

Methods: GCS-100 was tested in varying doses with B-cell cultures including the DoHH2 (14:18), Ramos (high and low Bcl-2 expression), BV173 (19:22), K562 cell lines, various myeloma cell lines, primary patient CD19 selected CLL cells, indolent primary lymphoma cells, and normal B-cells. Apoptosis was assessed by parameters including mitochondrial transmembrane potential (MTPP) by DiOC6, caspase-8 and -9 activity membrane blebbing by MC540, Galactosin-3 (Gal-3) expression was measured together with Bcl-2, Mcl-1, AKTI, Stat 5 and NFkB by western and SELDI ProteinChip analysis.

Results: GCS-100 induced significant apoptosis in both malignant cell lines and primary patient CLL cells with a minimum effect against normal B-cells and myeloma cells. The apoptotic pathway activated was caspase-9 pathway and GCS-100 also enhanced chemotherapy, particularly in the presence of high Bcl-2. Bcl-2 co precipitates with Galactosin-3 (Gal-3)

is decreased by GCS-100. AKTI and NFkB changes suggest an additional down regulation of signal transduction by GCS-100 and may provide further pro-apoptotic stimulus.

Conclusion: Gal-3 is a member of the beta-galactoside-binding protein family that play significant roles in cellular interactions, cell growth and differentiation. GCS-100 blocks its action. Gal-3 shares the highly conserved BH1 functional receptor domain (NHGR) of the Bcl-2 gene family within its carbohydrate binding domain, the binding site of GCS-100. Thus GCS-100 delivers its pro-apoptotic mechanism in B-cell malignancies. Normal B-cells with lower Gal-3 expression do not show significant apoptosis indicating GCS-100 is a selective anti-lymphoma agent. The possibility of using GCS-100 as a non myelosuppressive anti B-cell malignancy agent is suggested. A Phase I study is underway.

THE USE OF AUTOLOGOUS LMP2-SPECIFIC CYTOTOXIC T LYMPHOCYTES FOR THE TREATMENT OF RELAPSED EBV + VE HODGKIN DISEASE AND NON-HODGKIN LYMPHOMA

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EBV-associated HD and some NHL show type II latency expressing the subdominant EBV antigens EBNA1, LMP1 and LMP2, which may serve as targets for immunotherapy approaches. In previous studies, we used polyclonal EBV-specific CTL in patients with relapsed EBV +ve HD and saw 2 CR and 1 PR in 11 patients. Analyses of EBV-CTL lines showed that small populations of T cells reactive against the tumor-associated antigen LMP2 were present in the majority of the infused lines, with some expansion in the peripheral blood following infusion. We therefore hypothesized that CTL specifically targeting LMP2 might have greater efficacy in these patients. LMP2-CTL were generated using DC and LCL genetically modified to overexpress LMP2 (GM-LMP2). Polyclonal LMP2-CTL lines recognized 2–6 (median 4) LMP2 epitopes, as determined using overlapping LMP2 peptide pools in ELISPOT assays. A mean of 22.8% (5–42%) of CD8+ T cells bound HLA-restricted LMP2 tetramers, compared to 0.11% (0.01–0.24%) of LMP2-tetramer positive CD8+ T cells found in CTL generated with genetically unmodified LCL from the same patients. So far, 10 patients have been treated on this dose escalation study. 6 patients have been treated on dose level 1 (4 x 10^6/m^2) and 4 patients on dose level 2 (1.2 x 10^6/m^2). No immediate toxicity was observed. In patients with identified LMP2-epitopes, measurement of IFNγ secretion by CD8+ T cells after stimulation with LMP2-pedptides in ELISPOT assays showed a 4–25-fold increase in SP after infusions. In contrast, frequencies of CMV and superantigen-specific T cells did not increase. 4 of 5 patients who received LMP2-CTL as adjuvant therapy post SCT or chemotherapy remain in remission up to 12 months post LMP2-CTL. One patient presented with progressive disease following SCT and had detectable disease at the time of CTL therapy. 5 patient had a very good PR. Two patients are too early to assess. The other 2 patients had stable disease 8 wks post LMP2-CTL & received 2 further doses. One patient continues with stable disease and the other had a complete radio.

HUMAX-CD4 A FULLY HUMAN ANTI-CD4 MONOCLONAL ANTIBODY: PHASE II TRIAL IN CUTANEOUS T-CELL LYMPHOMA

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Introduction: HuMax-CD4 is a cytotoxic and anti-proliferative human monoclonal IgG1 antibody that targets the CD4 molecule on T-cells.
**Methods:** 47 patients with CD4<sup>+</sup> refractory Mycosis Fungoides (MF) or Sézary syndrome were enrolled. The chemotherapy was infused i.v. at doses of 280 mg, 560 mg or 980 mg once weekly for 17 weeks.

**Results:** Here we report efficacy data on the 38 MF patients and safety data on all patients. Significant difference in response was seen between low dose (280 mg), where 15% RR (3/20) was obtained, and high doses (560 mg, where 50% RR (7/14) were obtained or (980 mg), where 75% RR (3/4) were obtained, P = 0.016. Fisher's Exact Test. Increasing doses resulted in an increased maximal serum concentration; measured as trough values. Furthermore, patients with similar maximal serum concentrations >10 mg/ml, clinical response was seen in 12/22 (55%) compared to only 1/16 (6%) in patients not reaching this serum level, P = 0.002. Projected median response duration was 45 weeks. In 8 of 47 patients, 8 grade 3 and two grade 4 adverse events were considered related to HuMax-CD4 treatment; hypersensitivity reaction, dermatitis, two cases of aggravated pruritus, influenza like illness, CMV infection (grade 4), disease progression (grade 4), peri-oral infection, muscle fiber rupture and pyrexia.

**Conclusions:** HuMax-CD4 induced long-lasting responses in MF, with a 55% RR in patients reaching ≥10 mg/ml serum concentration. The treatment was well tolerated.

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**RESULTS FROM A PHASE I/II STUDY OF GALIXIMAB (ANTICD80) IN COMBINATION WITH RITUXIMAB (ANTICD20) FOR RELAPSED OR REFRACTORY, FOLLICULAR NHL**

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**Introduction:** Galiximab, a chimeric anti-CD80 monoclonal antibody, has clinical activity in the treatment of follicular NHL. In a recently reported 37-patient multicenter trial, a brief course of single agent galiximab produced tumor burden reductions in 49% of patients with relapsed or refractory, follicular NHL, including 2 CRs and 2 PRs (ORR 11%). Pretreatment data demonstrated that galiximab in combination with rituximab may be more effective than either antibody alone. Here we report on a Phase I/II multicenter clinical trial evaluating galiximab in combination with rituximab for the treatment of relapsed or refractory, follicular NHL.

**Methods:** Patients with progressive follicular NHL who failed and/or were intolerant to previously administered escalating doses of galiximab (125, 250, 375, or 500 mg/m<sup>2</sup> qwk x 4) concurrently with a standard course of rituximab (375 mg/m<sup>2</sup> qwk x 4). Rituximab refractory patients (no response or response with TTP <6 months) were excluded. Study objectives were to evaluate safety, PK, and efficacy. Seventy three patients received study treatment, 64 in the 500 mg/m<sup>2</sup> galiximab group. **Results:** The mean age at study entry was 61 years. The majority of patients (88%) were Stage III or IV at presentation and 43% had at least one tumor ≥5 cm in maximum diameter. FLIPI risk groups were distributed as good (23% of patients), intermediate (41%), or poor (36%). All patients had received at least 1 prior course of lymphoma therapy (range 1 to 9); 40% were rituximab naive. Galiximab infusions were delivered over 1 hr in an outpatient setting and were well tolerated. No DLTs were reported. The most common related AE's (possible, probable, or unknown relationship to treatment) were fatigue (33% of patients), rigors (27%), pyrexia (21%) and nausea (18%); the majority were Grade 1 or 2 (89%). No Grade 3 related AE was experienced by >1 patient. One patient in the 500 mg/m<sup>2</sup> galiximab group developed Grade 4 neutropenia that was considered possibly related to treatment; the event resolved with medication. The ORR in the 500 mg/m<sup>2</sup> galiximab group was 54% (16 CRs, 4 CRs, 10 PRs and 14 RRs). At 12 months median follow-up, 58% of this group remains on study. The median TTR for galiximab was 22 days for the 500 mg/m<sup>2</sup> galiximab group and the median TTR for rituximab was 24 days.

**Conclusions:** These results suggest that galiximab can be safely and conveniently combined with a standard course of rituximab, and the combination may enhance clinical benefit for patients with relapsed or refractory, follicular NHL. Future work will further evaluate galiximab in combination with standard therapies for follicular NHL and other hematologic malignancies.

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**PHASE I/II STUDY OF THE ANTI-CD30 ANTIBODY MDX-060 IN PATIENTS WITH RELAPSED/REFRACTORY CD30 POSITIVE LYMPHOID**

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**Introduction:** MDX-060 is the first fully human anti-CD30 IgG1 monoclonal antibody. It has shown promising results in preclinical studies. The purpose of this study was to determine the safety and tolerability profile of the drug, and to preliminarily evaluate any clinical efficacy.

**Methods:** In the Phase I portion of the study, MDX-060 was administered intravenously at dose levels of 0.1, 1, 5, or 10 mg/kg weekly for 4 weeks to cohorts of 3–6 patients. In the Phase II portion of the study additional patients were included at 10 (n=10) or 15 (n=17) mg/kg. Responses were assessed at month 2.
Results: MDX-060 has been administered to 48 patients; 40 with Hodgkin’s lymphoma (HL), 6 with anaplastic large cell lymphoma (ALCL) and 2 with other CD30-positive lymphomas. A maximum tolerated dose has not been identified due to a lack of severe toxicities. Objective clinical responses have been observed in 5 patients. Two patients had complete responses; 1 patient with ALCL (1 mg/kg lasting 100 days) and 1 patient with HL (15 mg/kg). Retreatment of the ALCL patient with MDX-060 resulted in a second complete response. Three patients (2 HL, 1 ALCL) had partial responses. Stable disease was observed in 17 patients.

Conclusions: MDX-060 is well tolerated in heavily pre-treated patients with CD30+ lymphomas. In addition, clinical activity was observed at 1 mg/kg, 5 mg/kg and 15 mg/kg with complete remissions in chemotherapy-refractory patients. The study is ongoing. Updated results will be presented.

ROLE OF MICROENVIRONMENT IN INHIBITION OF APOPTOSIS IN B-CELLS: REGULATION BY PI3-K INHIBITORS AND SIRNA

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Introduction: The expansion of the malignant clone in B-cell chronic lymphocytic leukemia (B-CLL) appears to be due to inhibition of apoptosis and activation of survival signals provided by the lymphoid microenvironment. Here we study the role of microenvironment in activation of antiapoptotic PI3-K/Akt signal transduction pathway.

Methods and Results: Co-cultivation of B-CLL cells with human bone marrow fibroblasts (BMFs) under serum free conditions inhibited apoptosis and significantly enhanced viability of the leukemic cells in comparison to suspension cultures (P<0.01). Trans-well culture experiments indicated that cell-cell interaction and soluble mediators are essential for this supportive effect. PI3-K inhibitors (wortmannin and Ly294002) or siRNAs against PI3-K (p110 θ subunit) and Akt1 significantly abolished the supportive effect of BMFs and induced apoptosis in B-CLL cells. The leukemic cells were far more sensitive to PI3-K inhibitors than T cells, monocytes and BMFs. Induction of apoptosis was associated with a significant decrease in the intracellular PP3, PI3-K, PDK1 and Akt1 and downregulation of NF-kappa B, IKK, and de-phosphorylation/activation of tumour suppressor protein PTEN.

Conclusion: The results indicate that PI3-K/Akt pathway is selectively involved in inhibition of apoptosis of the leukemic cells and suggest that targeting this pathway represent a new therapeutic approach in B-CLL.

CLINICAL REMISSEIS IN PREVIOUSLY UNTREATED PATIENTS WITH FOLLICULAR LYMPHOMA AFTER INTRADERMAL IMMUNIZATION WITH A RECOMBINANT IDIOTYPE VACCINE

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Introduction: Immunization of B-NHL patients against the individual immunoglobulin expressed by the lymphoma (idiotype; Id) may induce tumor-specific immune responses. A phase I trial testing recombinant Fab fragments expressed in E.coli mixed with the adjuvant MF59 as intradermal injection plus GM-CSF s.c. has demonstrated induction of immune responses to the vaccine in 65% of patients with advanced B-NHL (Blood 102:898a, 2003).

Methods: An ongoing phase II trial evaluates this vaccine in patients with low-grade, stage III/IV B-NHL in untreated “watch and wait” (W&W) situation or in remission after systemic therapy. Patients receive 6 vaccinations, each consisting of 250 μg GM-CSF s.c. on the same day at the site and intradermal injection of 0.5 mg Id/MF59 immediately above the GM-CSF site, in monthly intervals.

Results: As of January, 2005, 13 patients have commenced treatment, and 6 have completed 6 cycles. No patient had any evidence for spontaneous lymphoma regression prior to vaccination. One patient required dose reduction of GM-CSF due to cutaneous side effects; no other symptomatic toxicity was noted. No disease progression occurred under treatment. Of 4 follicular lymphoma (FL) W&W patients, 3 achieved a partial remission (PR) after 6 vaccinations, and 1 had a mixed response with regression of lymph nodes (LN) but persistence of subcutaneous nodules. Immune monitoring has been performed on the 1st PR patient and demonstrated induction of Id-specific cellular and humoral immunity. One W&W patient with mantle cell lymphoma had stable disease after completing treatment. Of 2 patients vaccinated in PR after systemic chemotherapy, both had gradual further shrinking of residual enlarged LN after 2 and 6 vaccinations, respectively. One additional FL patient who had experienced complete clearance of residual masses which lasted for 2 years during the phase I trial was revaccinated according to the phase II schedule on a compassionate basis. He achieved a PR after 3 vaccinations and is continuing treatment.

Conclusions: Intradermal vaccination with recombinant idiotypic in conjunction with GM-CSF may induce clinical remissions in untreated NHL patients at a substantially higher rate than expected spontaneously.