Session 6: targeting the lymphoma cell surface

065 INTRODUCTORY LECTURE

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The surface architecture of lymphocytes is among the best-characterised of human cells, thanks to their availability for study in the blood, their key role in immunity and the variety of malignancies to which they give rise. One of the success stories of cancer medicine is the use of monoclonal antibodies (mAb) to target molecules on the cell surface for therapy, and we continue to uncover novel aspects of biology in refining this approach. The molecules to which mAb have been targeted were identified several decades ago, and few new ones have emerged in the last 10 years. The earliest target identified as tumour-specific was the B-cell idiotype, whose clonality is a defining feature of malignancy and which was successfully, if laboriously, targeted with patient-specific Ab. It was not clear at the time whether the dominant mechanism of action was the induction of signaling through the B-cell receptor or recruitment of effectors to the cell surface, and to some extent this uncertainty persists for mAb therapy generally, but with several important discoveries in the interim. Although few new antigens have been discovered recently, there is increasing interest in effector mechanisms, the role of different Fc receptors, the selective delivery of radionuclides or toxins, and the use of bispecific molecules to attract T- or NK- cells. The results of anti-idiotype mAb encouraged exploration of selective rather than specific targets, and from this a variety of molecules were identified. A lack of knowledge regarding normal cellular function has surprisingly not impeded their exploitation for therapy, and by far the most successful target has been CD20, about whose function relatively little was known until recently. Although perceived as a comparatively inert component of the cell membrane, we have learned that CD20 is a highly dynamic molecule. It can undergo rapid redistribution, and different mAb evoke different patterns of behaviour: those like Rituximab (''type I'') cause redistribution into lipid-rich rafts, mediate complement fixation and antibody-directed cell-mediated cytotoxicity (ADCC). In contrast, those like the first anti-B-cell mAb characterised, B1 (''type II'') do not cause redistribution into rafts but mediate homotypic cell adhesion and stimulate programmed cell death. These differences have important therapeutic results, and we have found that on some lymphomas type I mAb mediate rapid internalization of CD20 with lysosomal consumption, while type II do not. Our understanding of mAb action at the lymphoma cell surface continues to evolve, and the complex interactions of Ab half-life, isotype and Fc effector cell biology are increasingly recognized as critical to therapy. We are also returning to discarded approaches such as immunotoxins, which now benefit from advances in chemistry to improve their therapeutic ratio.

066 RESULTS FROM A PHASE I/II STUDY (BO20999) OF RO5072759 (GA101) MONOTHERAPY IN RELAPSED/REFRACTORY NON-HODGKIN'S LYMPHOMA

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Background: GA101 is a type II, glycoengineered, humanized monoclonal anti-CD20 antibody currently in clinical trials. Phase (P) I and II results are reported.

Methods: PI: GA101 (Cycle 1D1,C1D8 and D1 C2-8) was given as monotherapy (50-2000mg) to patients (pts) with CD20+ indolent NHL (iNHL) with a primary endpoint to determine the safety and pharmacokinetics (PK) of GA101. PII: patients with CD20+ iNHL were randomised to receive GA101 at 2 dose levels: GA101 at 400mg for all infusions (LD) or 1600mg on D1, D8 then 800mg for 7 infusions q3wks (HD). The primary endpoint in PII was end of treatment response (EOR), assessed 4 weeks after last infusion. Secondary endpoints were safety, PK and progression-free survival (PFS).

Results: In PI (n=21), GA101 showed an EOR of 33% (7/21 pts). In pts with fNHL only, EOR was 54% (7/13 pts). Phase I PK data showed accumulation of GA101 levels in plasma consistent with target saturation. Taking into account inter-patient variability (e.g., various patient histologies, tumour burden, PK) and responses observed across all dose levels, no clear dose-response relationship was established leading to the exploration of two dose levels in PII. In PII, (n=40) EOR was 17% for patients receiving LD (n=18) GA101 and 55% in the HD cohort (n=22). Median PFS was 6 months (1.1–16.9+ months) and 11.3 months (1.8–14.2+ months) for the LD and HD cohorts, respectively. Of note, 6/22 rituximab-refractory pts (5 HD, 1 LD) responded (HD only, 5/10 responses). In PII GA101 was well tolerated in both dose cohorts, the most common AEs being infusion related reactions (LD 72%, HD 73% of patients), mostly of G1-2. During treatment, related G3-4 hematological AEs were transient neutropenia, febrile neutropenia, thrombocytopenia, and infection. Nine patients had 12 SAEs during treatment, with 4 related to GA101 (HD n=4; herpes zoster, febrile neutropenia, pancreatitis, neutropenia).

Conclusions: GA101 monotherapy is well tolerated with promising efficacy in heavily pre-treated indolent NHL patients. Trials are ongoing with GA101 in combination with chemotherapy, with a further two 1st line phase III trials scheduled to commence enrollment in 2011.

067 ANTI-CD40 MONOCLONAL ANTIBODY LUCATUMUMAB EXHIBITS ANTI-TUMOR ACTIVITY IN FOLLICULAR LYMPHOMA AND OTHER LYMPHOMA SUBTYPES: PHASE I/II PRELIMINARY FINDINGS

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Background: Lucatumumab (HCD122) is a fully human IgG1 exclusively antagonistic anti-CD40 mAb being investigated in patients with Hodgkin's lymphoma (HL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), or mucosal associated lymphoid tissue (MALT), who have progressed after at least two prior therapies.

Methods: Lucatumumab was administered IV once weekly for 4 weeks. Patients with stable disease or better were eligible for additional treatment. Primary objective: determine maximum tolerated dose (MTD). Secondary objectives: assess clinical response rate at MTD and to characterize safety and tolerability.

Results: Preliminary efficacy and safety data is available on 98 patients with median age of 57 years (range 19 - 84); 80% with stage III/IV disease and median of 4 prior regimens (range 1 - 14). In phase I, patients were treated with 3, 4 (MTD; phase II dose), or 6 mg/kg. Of the subtypes in which more than 10 patients were enrolled, FL patients exhibited the highest overall response rate (ORR).

	Phase I (n = 32)				Phase II (n= 66)			
Disease classification	n	PR n (%)	CR n (%)	ORR n (%)	n	PR n (%)	CR n (%)	ORR n (%)
HL	10	1 (10)	0 (0)	1 (10)	24	3 (13)	0 (0)	3 (13)
FL	10	3 (30)	0 (0)	3 (30)	16	3 (19)	1 (6)	4 (25)
DLBCL	7	0 (0)	1 (14)	1 (14)	17	0 (0)	1 (6)	1 (6)
MCL	5	0 (0)	0 (0)	0 (0)	5	0 (0)	0 (0)	0 (0)
MALT	0	0 (0)	0 (0)	0 (0)	4	2 (50)	1 (25)	3 (75)

Median duration of response for all subtypes and FL is 16 weeks (range 6 – 33) and 16 weeks (range 8 - 21), respectively. No correlation is observed between rituximab levels at baseline and clinical response.

DLTs were reversible asymptomatic grade 3/4 amylase, lipase, ALT, or AST elevations. Grade 3/4 adverse events (>5%) were lipase elevation and neutropenia. The most commonly reported adverse events (>20%) were chills, pyrexia, lipase elevation, nausea and fatigue. At 4 mg/kg, >90% of the peripheral blood B-cell CD40 receptors were saturated for at least 4 weeks after the last dose. The $t_{1/2}$ at 4 mg/kg after the 4th infusion was 13 days. No immunogenicity to lucatumumab was observed in this study.

Conclusions: Lucatumumab was generally well tolerated up to 4 mg/kg and demonstrated preliminary clinical activity in FL. A phase Ib study evaluating lucatumumab and bendamustine in rituximab-refractory FL patients is currently ongoing.

HCD122, subject to agreement between Xoma and Novartis.

068 BLINATUMOMAB (CD3/CD19 BITE® ANTIBODY) RESULTS IN A HIGH RESPONSE RATE IN PATIENTS WITH RELAPSED NON-HODGKIN LYMPHOMA (NHL) INCLUDING MCL AND DLBCL

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Blinatumomab (MT103) is a single-chain bispecific antibody construct designed to use a patient's own cytotoxic T cells to attack CD19-positive tumor cells, and belongs to a new class of agents called bispecific T cell engager (BiTE) antibodies. Blinatumomab leads to peripheral B cell depletion, proliferation of T effector cells, and induces objective clinical responses. Here, we update the results of an ongoing phase 1 trial in patients with relapsed NHL. Seven dose levels, ranging from 0.5 to 90 μg/m^2/d, have been tested in 62 patients. Blinatumomab is delivered by continuous intravenous infusion over 4-8 weeks as single agent. Most AEs were early-onset, transient, reversible, easily managed, and did not require treatment discontinuations. The most common clinical AEs include fever, chills, headache, fatigue, and weight increase. The clinically most relevant AEs were fully reversible CNS events (*e.g.*, seizures, disorientation, confusion, cerebellar symptoms) seen primarily at the onset of treatment. A low peripheral blood B:T cell ratio as a biomarker for patients with a higher frequency of reversible neurological adverse events is now prospectively used to stratify patients and to further optimize treatment. A dose-related effect was seen with first responses at 15 μg/m^2/d and a much higher response rate at 60 μg/m^2/d. Initial infusion with 90 μg/m^2/d exceeded the maximal tolerable dose. Among evaluable patients who received 60 μg/m^2/d, 82% (18 of 22) achieved an objective response. Response duration is currently up to 32 months with 11 of 18 responses still ongoing. In DLBCL, three out of five patients receiving 60 μg/m^2/d blinatumomab achieved at least a CRu (median follow-up of 48 d; range 1-58 d). Four of five evaluable MCL patients treated with the target dose had an objective response including three patients with at least a CRu. Response duration is currently up to 24+ months. These data confirm high single-agent activity of 60 μg/m^2/d blinatumomab continuously infused for 4-8 weeks with long-lasting remissions and a favorable risk/benefit profile. First efficacy signals in patients with DLBCL have been observed.

069 INOTUZUMAB OZOGAMICIN (INO, CMC-544) IN PTS WITH INDOLENT B-CELL NHL REFRACTORY TO RITUXIMAB (R), R PLUS CHEMOTHERAPY, OR RADIOIMMUNOTHERAPY (RIT)

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Background: INO is a humanized anti-CD22 antibody conjugated to calicheamicin, a potent antitumor antibiotic. CD22 is expressed on the majority of B-cell NHL. Safety and efficacy of INO were evaluated in indolent B-cell NHL refractory to R, R + chemotherapy, or RIT.

Patients: Pts had CD22+ indolent B-cell NHL (follicular not transformed [FL], marginal zone [MZL], and small lymphocytic lymphoma [SLL]) with progression after 2+ systemic therapies and no response/progression within 6 mo of completion of R-containing therapy or within 12 mo of RIT completion. Pts received INO 1.8 mg/m^2 every 28 d for 4-8 cycles, with dose and/or frequency adjusted based on toxicities.

Results: 59 pts have been enrolled and dosed with INO: 50 with FL, 5 with MZL, 3 with SLL and 1 with indolent NHL unspecified. Median age was 62 y (range 29-84 y); 44% were male; pts were heavily pretreated: median of 3 prior anticancer regimens, 5% had 1 prior regimen, 35% had 2, 22% had 3 and 38% had 4+. Based on FLIPI, 20%, 26% and 54% of FL pts, respectively, were low, intermediate and high risk. Common TEAEs (>30%, all grades) were thrombocytopenia (67%), neutropenia (52%), elevated AST (47%), nausea (47%), fatigue (43%), leukopenia (34%) and lymphopenia (34%). Grade 3/4 TEAEs (≥5%) were thrombocytopenia (50%), neutropenia (31%), lymphopenia (16%), leukopenia (7%), increased GGT (7%), nausea (5%) and elevated AST (5%). 21 serious AEs were reported for 10 pts. 18 (31%) pts discontinued treatment due to AEs, most due to persistent grade 2 toxicity that failed to recover to grade 1/0 within the 28-day dose delay period allowed per protocol. AEs leading to treatment discontinuation were thrombocytopenia (n = 13), neutropenia (n = 4), increased GGT (n = 2), and hepatic dysfunction, hyperbilirubinemia, leukopenia and pneumonia (n = 1 each). Of 53 evaluable pts, ORR was 55% (62% in FL); 10 FL pts had complete response. PFS rate at 12 mo was 50%. 9 deaths (disease progression [n = 7], aspiration pneumonia [n = 1], sepsis [n = 1]) were reported, all >30 d from the last INO dose.

Conclusions: In pts with relapsed/refractory indolent B-cell NHL, INO demonstrated definitive clinical activity and had a similar safety profile to that previously reported, with hematologic, GI and hepatic lab abnormalities being the most common.

070 PHASE I/II STUDY OF THE ANTI-CD19 MAYTANSINOID IMMUNOCONJUGATE SAR3419 ADMINISTERED WEEKLY TO PATIENTS (PTS) WITH RELAPSED / REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA (NHL)

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SAR3419 (huB4-DM4) is an antibody–drug conjugate composed of a humanized IgG1 monoclonal antibody, huB4, which specifically targets the CD19 antigen, conjugated through a disulfide link to the maytansinoid derivative DM4, a potent tubulin inhibitor. After binding to the CD19 antigen, SAR3419 undergoes internalization and intracellular release of DM4. In this phase I/II study SAR3419 was administered by intravenous infusion, weekly for 8 to 12 doses, to pts with relapsed / refractory B-cell NHL expressing CD19. Forty-four pts were enrolled at 7 dose levels from 10 to 70 mg/m^2. Main histologies were follicular (18; 41%) and diffuse large B-cell (17; 39%). Median number of prior regimens was 3 [1-8] and 19 pts had received prior transplantation. Twenty-eight pts were enrolled in the dose escalation part. Of 6 pts at 70 mg/m^2, 1 pt had a protocol defined dose limiting toxicity of neutropenia and 2 pts had grade 2 significant toxicities with late onset: blurred vision associated with corneal deposits and left bundle branch block. The maximum tolerated dose (MTD) was defined at 55 mg/m^2. Of 22 pts at the MTD, 4 pts had related reversible grade 3-4 toxicities after 6-8 doses: optic neuropathy, paraesthesia, neutropenia and thrombocytopenia. Of 38 pts at doses of 20 mg/m^2 or higher, 12 (32%) pts achieved an objective response including 6 CR/CRu, with no obvious dose effect. Of 22 pts at the MTD (55 mg/m^2), 8 (36%) had a response, including 3 CR/CRu. Of 9 pts evaluable for response duration (RD), 4 pts had a RD ranging from 6 to at least 12 months. These results demonstrate evidence of clinical activity and manageable safety, without significant myelosuppression. A modified schedule (4 weekly doses of 55 mg/m^2 followed by every 2 weeks dosing) is under evaluation. Updated clinical and pharmacokinetic data will be presented.