‘‘focus on…’’ session: new treatments modalities

098 GA101, A NOVEL THERAPEUTIC TYPE II CD20 ANTIBODY WITH OUTSTANDING ANTI-TUMOR EFFICACY IN NON-HODGKIN LYMPHOMA XENOGRAFT MODELS AND SUPERIOR B CELL DEPLETION

P. Umana[1], E. Moessner[1], R. Grau[1], C. Gerdes[1], A. Nopora[1], C. Schmidt[1], P. Strein[2], S. Bauer[2], T. Friess[2], K. Dabbagh[3], J. DalPorto[3], C. Klein[2]
[1]Discovery Oncology, GlycArt Biotechnology AG, Schlieren, Switzerland, [2]Discovery Oncology, Roche Diagnostics GmbH, Penzberg, Germany, [3]Inflammation Discovery, Roche Palo Alto, Palo Alto, United States

GA101 is the first humanized, glycoengineered type II CD20 antibody. It is currently in Ph I clinical trials. GA101 was derived by humanization of the murine B-Ly1 antibody and is characterized by high binding affinity, type II mode of CD20 binding with reduced CDC and strong direct cell death induction compared to classical type I CD20 antibodies. The glycoengineered Fc region binds with enhanced affinity to FcgRIIIa on immune effector cells leading to enhanced ADCC relative to rituximab. We studied the effects of GA101 on the growth of s.c. NHL xenografts in SCID beige mice; a model primarily indicative of non-effector cell mediated mechanisms. In different NHL models GA101 demonstrated outstanding anti-tumor efficacy. Specifically, complete tumor remission was induced in SU-DHL4 DLBCL xenografts at 30 mg/kg weekly dose. By contrast, rituximab at higher doses was only able to slow down tumor progression. In addition, treatment with GA101 increased the median and overall survival in an orthotopic disseminated Z138 MCL model compared to rituximab. In hCD20 transgenic mice, GA101 demonstrated superior depth of B cell depletion. The increased B cell depletion extended into the peripheral lymphoid compartments and to the range of B cell subsets targeted. Analogous findings were observed in cynomolgus monkeys where the efficacy of GA101 in depleting B cells in lymphoid tissues was compared with that of rituximab. Although ADCC plays an integral role, the enhanced depth of depletion observed with GA101 treatment is influenced by its unique binding mode and the induction of CD20-dependent cell death. In summary, the data demonstrate that GA101 represents a novel class of CD20 antibodies with outstanding efficacy compared to classical CD20 antibodies. It is anticipated that the combination of the type II epitope recognition with improved ADCC potency exclusive to GA101 will translate into superior clinical efficacy establishing GA101 as best in class anti-CD20 therapy.

099 SGN-40 SHOWS EVIDENCE OF ACTIVITY IN PATIENTS WITH RELAPSED NON-HODGKIN LYMPHOMA: FINAL RESULTS OF A PHASE I DOSE-ESCALATION STUDY

R. Advani[1], A. Forero-Torres[2], R.R. Furman[3], J.D. Rosenblatt[4], A. Younes[5], K. Harrop[6], N.C. Whiting[6], J.G. Drachman[6]
[1]Oncology, Stanford Univ, Stanford, United States, [2]Hematology-Oncology, UAB, Birmingham, United States, [3]Hematology & Medical Oncology, Weill Cornell MC, New York, United States, [4]Hematology-Oncology, Univ of Miami, Miami, United States, [5]Lymphoma and Myeloma, MD Anderson CC, Houston, United States, [6]Seattle Genetics, Inc, Clinical, Bothell, United States

Background: SGN-40 is a humanized monoclonal antibody that binds to CD40, triggers pro-apoptotic signal transduction and mediates effector cell function (ADCC/ADCP).

Methods: A multicenter, phase I, open-label, dose escalation study was conducted to assess the safety, MTD, PK profile, and preliminary antitumor activity of SGN-40 in patients with relapsed NHL. Cohorts of 3-6 patients received 6 IV infusions of SGN-40 (2-8 mg/kg) over 5 wks (Cycle 1). Patients with SD or better were eligible to receive a 2nd cycle. The dose escalation phase included 35 patients; 15 patients were added at the highest dose cohort to further evaluate SGN-40 safety and efficacy.

Results: Fifty patients (33 M, 17 F) with a median age of 62 yrs (range 24-86) participated at 5 sites. All patients who received at least 1 dose of SGN-40 were included in the analysis. Patients with multiple histologic subtypes of NHL were enrolled, including DLBCL (21), FL (12), MCL (10), MZL (3), SLL (1) and other (3). Patients were heavily pre-treated, with a median of 3 prior therapies (range 1-8). Treatment with SGN-40 was well tolerated and MTD was not reached. Two patients experienced dose limiting toxicity; conjunctivitis and transient loss of visual acuity (N=1) and Gr 3 ALT elevation (N=1). No dose related trends in adverse events were observed. PK demonstrated dose related increases in serum exposures. Six patients (12%) achieved an objective response (5 PRs and 1 CR) and 13 patients (26%) achieved SD. Three responses were ongoing at final clinical evaluation, up to 2 years after completing treatment. Two additional patients who discontinued SGN-40 due to toxicity achieved durable CRs after withdrawal from the study and without subsequent treatment. The median overall survival was 10.5 months (range 0.1-16.9).

Conclusions: Single-agent treatment with SGN-40 is well tolerated and shows promising antitumor activity in a heavily pre-treated patient population.

100 IDENTIFICATION OF CD20 MUTATION ASSOCIATED WITH MODIFICATION OF CD20 EXPRESSION AND POOR PROGNOSIS AFTER RITUXIMAB IN NON-HODGKIN’S LYMPHOMA

Y. Terui[1], Y. Mishima[1], M. Yokoyama[1], M. Kodaira[1], K. Takeuchi[2], K. Hatake[1]
[1]Clinical Chemotherapy, Japanese Foundation for Cancer Research, Tokyo, Japan, [2]Pathology, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Resistance to rituximab is one of the important issues to be clarified in the increasing number of monoclonal antibody therapy, and we experienced the case whose lymphoma cells never expressed CD20 at the relapsed phase during rithuximab therapy. We examined whether CD20 mutation is related to expression level of CD20, relapse or resistance to rituximab therapy, and prognosis.

Methods: We analyzed 50 patients with fresh or relapsed/resistant non-Hodgkin’s B cell lymphomas and direct DNA sequencing analysis of CD20 products from RT-PCR and genomic DNAs was performed. CD20 mutants were subcloned into the mammalian expression vector, and tested CD20 expression after transfection to K562 cells, and then CD20 expression was examined by a laser scanning confocal microscopy. Response and Time to progression after rituximab treatment were analyzed by SPSS statistical software.

Results: Four types of CD20 mutations were found in 11 of 50 NHL patients (22.0%), including the mutations of C-terminal deletion (8.0%), extracellular domain (2.0%), transmembrane domain (2.0%), and early termination (10.0%). In clinical samples, the group with C-terminal deletion mutations significantly showed lower CD20 expression (mean fluorescent intensity (MFI) = 3.26, 95%CI = 0.09 to 6.89) than that with non-mutation (MFI = 30.8, 95%CI = 22.4 to 39.2) ($p<0.05$). In transfection experiment, C-terminal deletion mutant of CD20 showed lower CD20 expression than non-mutant on the transfected K562 cells under the confocal microscopy. Western blot analysis revealed that C-terminal deletion mutant was detectable as well as non-mutant, suggesting that C-terminal deletion mutant could not come up onto the plasma membrane in spite of its production in the cells. In clinical response and prognosis, there was no significant difference between the groups with non-mutation and C-terminal deletion mutation in complete response rate (49% versus 25%, respectively, Fisher’s exact test; $p = 0.6137$), and time to progression after rituximab therapy in C-terminal deletion mutation (7 months, 95%CI = 0 to 18 months) was significantly shorter than that in non-mutation (31 months, 95%CI = 18 to 44 months) by log-rank test ($p = 0.0481$). Non-mutation and early termination groups did not show any significant differences in TTP and CD20 expression.

Conclusion: The critical mutations of CD20 gene related to shortened time to progression disease after rituximab therapy were discovered.

101 A PHASE 1 STUDY EVALUATING THE SAFETY, PK & EFFICACY OF ABT-263 IN SUBJECTS WITH REFRACTORY OR RELAPSED LYMPHOID MALIGNANCIES

O. O’Connor[1], M. S. Czuczman[2], A. LaCasce[3], J. Gerecitano[4], J.P. Leonard[5], K. Dunleavy[6], A. Krivoshik[7], M. Shovlin[6], A. Narwal[1], H. Xiong[7], Y. Chiu[7], W. Wilson[6]
[1]Irving Cancer Research Cntr, Columbia Univ, NY, United States, [2]Lymphoma/Myeloma Serv, Roswell Park Cancer Inst., Buffalo, United States, [3]Lymphoma Program, Dana Farber Cancer Inst, Boston, United States, [4]Lymphoma Serv, Memorial Sloan-Kettering Cancer Cntr, NY, United States, [5]Weill Cornell Med College, Cornell Univ, NY, United States, [6]NCI, NIH, Bethesda, United States, [7]Oncology, Abbott Labs, Abbott Park, United States

Background: ABT-263 is a novel BH3 mimetic that binds with high affinity ($K_i \leq 1$ nM) & inhibits antiapoptotic Bcl-2 family proteins. ABT-263 displays potent mechanism-based toxicity ($EC_{50} \leq 1\mu M$) against human lymphoid & small cell lung cancer cell lines. Anticipated ABT-263 toxicities are mechanism based, Bcl-X_L-dependent decrease in circulating platelets, Bcl-w-dependent testicular toxicity, & Bcl-2-dependent lymphopenia.

Methods: Safety & PK profiles of ABT-263 were studied in patients with relapsed or refractory lymphoid malignancies. In 21-d cycles, subjects received ABT-263 orally QD for 14 d followed by 7 d off drug. The dose was doubled in each cohort until a grade 3 toxicity occurred, after which escalations were in 40% increments.

Results: 30 patients enrolled in the lymphoma study in the 10, 20, 40, 80, 160, 225 & 315 mg cohorts. One grade 3 dose limiting toxicity occurred during cycle 1 in each of the 160 (URI) & 315 (ALT) mg cohorts resulting in cohort expansion. Responses include: 2 patients with bulky CLL in the 40 mg cohort had 99% & 36% tumor reductions after cycles 8 & 7, respectively, 1 patient with bulky CLL/SLL in the 160 mg cohort had 75% reduction at cycle 4, 1 patient with follicular lymphoma in the 80 mg cohort had 20% reduction after cycle 7 & 1 patient with NK/T cell lymphoma at 315 mg had 75% reduction at cycle 2. These subjects remain on study with intrapatient dose

escalation of the 40 mg patients. The PK profile of ABT-263 was linear & the terminal half-life was 14-20 h. ABT-263 dose-dependently reduced platelet levels. Grade 3 thrombocytopenia was seen in 5 patients during cycle 1 without bleeding.

Conclusions: ABT-263 is a novel, orally bioavailable & active small molecule Bcl-2 family protein inhibitor that shows early evidence of activity in lymphoid malignancies.

102 TAMATINIB FOSDIUM (TAMF), AN ORAL SYK INHIBITOR, HAS SIGNIFICANT CLINICAL ACTIVITY IN B-CELL NON-HODGKIN'S LYMPHOMA (NHL)

J. Friedberg[1], J. Sharman[1], J. Schaefer-Cutillo[1], P. Johnston[1], S. de Vos[1], A. LaCasce[1], J. Leonard[1], R. Sinha[1], L. Cripe[1], S. Gregory[1], J. Sweetenham[1], J. Vose[1], A. Lowe[1], M. Shipp[1], R. Levy[1]

[1]Heme/Onc, U of Rochester, Rochester, United States, On Behalf of R788 Clinical Investigators

Certain normal and malignant B-cells rely upon B-cell receptor (BCR)-mediated survival signals. Spleen tyrosine kinase (SYK) initiates signaling from the BCR, and amplifies the original BCR signal. Pharmacologic inhibition of SYK arrests NHL growth *in vitro*. Moreover, gene expression profiling has identified a subgroup of diffuse large B-cell NHL (DLBCL) with a proliferation cluster that includes SYK. We therefore evaluated TamF, the first clinically available oral SYK inhibitor with demonstrated activity against NHL *in vitro*, in patients (pts) with a variety of B-cell NHLs. First, we enrolled 13 pts in Phase I, exploring two dose levels of TamF administered BID. Pts were heavily pretreated with relapsed/refractory NHL (Follicular [FL], 5; CLL, 2; mantle [MCL] 3; DLBCL 3). Upon response evaluation at Day 57, 1 pt with FL had PR, and 3 pts had PD. DLT in Phase I was neutropenia; 200 mg BID was chosen for Phase II. We then enrolled 59 pts with relapsed/ refractory disease in 3 cohorts: DLBCL, 17; FL, 20 and other NHL, 22, including MCL, 8; marginal zone/ MALT, 3; lymphoplasmacytic, 1; and SLL/CLL, 10. Median age was 62 (range 43-87); pts received a median of 5 prior therapies. Possibly related SAEs included cytopenias (2), infection (4), diarrhea (1), and abdominal pain (1). Day 57 response evaluation revealed: FL, (18 evaluable): 1 PR, 11 SD and 6 PD; other NHL, (21 evaluable): 7 PR (6 SLL/CLL, 1 MCL), 5 SD, and 9 PD; DLBCL, (14 evaluable): 3PR, 2 SD, 9 PD. 6 pts withdrew before Day 57 (AE, 5; noncompliance, 1). Overall, as of 01/15/08: 44% of total pts remain on trial for up to 224 days, without PD. Therefore, TamF appears to be a safe and well-tolerated oral agent in patients with relapsed/refractory NHL. After 2 months of therapy, 11 PRs have been observed, including 6 of 10 pts with SLL/CLL. We conclude that disrupting BCR-induced signaling by inhibiting SYK kinase represents a novel therapeutic approach to NHL. TamF should be developed further, as a single agent and in rational combinations, for the NHL treatment.

103 INTERNATIONAL TRIAL CONFIRMS ROMIDPESIN EFFICACY IN REFRACTORY CTCL PATIENTS

A. Prentice[1], S. Whittaker[2], Y. Kim[3], E. Kim[4], A. Lerner[5], M. Duvic[6], T. Robak[7], E. Baran[8], J. Becker[9], W. McCulloch[10]

[1]Haematology, Royal Free Hospital, London, United Kingdom, [2]Dermatology, Guys and St Thomas Hospital, London, United Kingdom, [3]Dermatology, Stanford Univ Med Center, Stanford, United States, [4]Dermatology, Univ of Pennsylvania, Philadelphia, United States, [5]Dermatology, Boston Medical Center, Boston, United States, [6]Dermatology, MD Anderson Cancer Ctr, Houston, United States, [7]Haematology, Medical Univ, Lodz, Poland, [8]Dermatologii, Katedra i Klinika, Wroclaw, Poland, [9]Dermatology, Univeritätsklinikum und Poliklinik für, Wurzburg, Germany, [10]Medical, Gloucester Pharmaceuticals, Cambridge, United States

Background: Romidepsin, a bicyclic peptide that inhibits Class I and II HDACs, has reported activity in CTCL. To confirm this, a single arm, open-label Phase II study enrolled CTCL (Stages 1B-1VA) patients (pts) from 36 international sites.

Material and Methods: Pts with CTCL who failed ≥1 prior systemic therapy received romidepsin at 14 mg/m^2 on Days 1, 8, and 15 q 28 days. Exclusions included significant CV abnormality or treatment with QTc-prolonging or CYP3A4-inhibiting drugs. The primary endpoint was response rate measured by a composite endpoint that included a combination of imaging, circulating malignant T-cell counts and a skin scoring instrument. 96 pts were eligible with 73 evaluable for efficacy per protocol.

Results: Responses in evaluable pts are 4 CCRs, 21 PRs, 42 SD and 6 PD for an ORR of 34%. The median time to response is 6 wks and the median duration of response is 5 months (range 2+- 21 months). Responses by disease stage at entry in evaluable pts are: Stage IB-IIA 7/24 (29%) and Stage IIB-IVA 20/49 (41%). In pts with pruritus, relief was seen in 23/61 pts (38%) and in 13/35 (37%) pts with severe pruritus (VAS score ≥70 mm). The most frequent AEs were nausea (51%), fatigue (27%), vomiting (22%), anorexia (11%), aguesia (11%) and headache (11%). Serious AEs considered possibly, probably or likely related to treatment were reported in 14 pts but there were no deaths attributed to romidepsin, although 4 pts died of progressive disease and 1 from right ventricular failure. Asymptomatic ECG abnormalities were noted in 6% of the pts.

Conclusions: This study confirms the clinical efficacy of romidepsin in refractory CTCL, including relief of pruritus, and a manageable safety profile.