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

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Background: SGN-40 is a humanized monoclonal antibody that binds to CD20, 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 25 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 (35 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 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.

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

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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)

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We conclude that disrupting BCR-induced signaling by inhibiting SYK kinase with 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. A total of 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); 96 pts were eligible with 73 evaluable for efficacy per protocol. 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. DLBCL in Phase I was neutropenia; 200 mg BID was chosen for Phase II. We then enrolled 39 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 (All 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 ROMIDESPIN EFFICACY IN REFRACTORY CTCL PATIENTS

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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 IB-IVA) patients (pts) from 36 international sites. Material and Methods: Pts with CTCL who failed 2-3 prior systemic therapy received romidepsin at 14 mg/m2 on Days 1, 8, and 15 q28 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-IVA 7/24 (29%) and Stage IIB-IVB 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.