3904 Navitoclax (ABT-263) Plus Fludarabine/Cyclophosphamide/Rituximab (FCR) or Bendamustine/Rituximab (BR): A Phase 1 Study in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

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Background: Navitoclax (ABT-263), a novel, orally bioavailable, small molecule, binds with high affinity (Ki ≤1nM) to Bcl-2, Bcl-xL, and Bcl-w, promoting apoptosis. *In vitro*, navitoclax shows potent targeted cytotoxicity (EC_{50}≤1 μM) against T and B lymphoid malignancies that overexpress Bcl-2. In preclinical models of B-cell lymphoma, navitoclax enhanced efficacy of rituximab (R) when used alone or in combination with chemotherapy. Based on phase 1 trial data, oral navitoclax monotherapy was well-tolerated and had anti-tumor activity in patients (pts) with chronic lymphocytic leukemia (CLL). Thrombocytopenia was the dose-limiting toxicity (DLT). We examined whether navitoclax could be used safely in combination with fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR) for treatment of pts with CLL.

Methods: This ongoing, phase 1 dose-escalation study is evaluating the safety and pharmacokinetics (PK) of oral navitoclax used in combination with FCR (Arm A) or BR (Arm B) for treatment of pts with relapsed/refractory CLL. Secondary objectives are efficacy endpoints (PFS, ORR, TTP, OS, duration of response). Eligible pts had measurable disease, ECOG performance score ≤1, ANC ≥1000/μL, platelets ≥100,000/mm^3, and hemoglobin ≥9.0 g/dL. Preliminary results are reported. Enrolled pts (6 pts/cohort) were assigned to Arm A or Arm B based on physician preference. In both arms, R was 375 mg/m^2 on Day 1 of Cycle 1; and 500 mg/m^2 on Day 2 of Cycle 2 and on Day 1 of subsequent 28-day cycles. In Arm A, F 25 mg/m^2 and C 175 mg/m^2 were dosed on Days 2-4 in Cycles 1 and 2, and on Days 1-3 in subsequent cycles. In Arm B, B was dosed at 70 mg/m^2 on Days 2 and 3 of Cycles 1 and 2, and on Days 1 and 2 in subsequent cycles. Oral navitoclax was administered once daily (starting dose of 110 mg) pre-chemotherapy on Days 3-5 of Cycle 1 and Days 1-3 of subsequent cycles. Dose escalation decisions were made independently in each arm via a continuous reassessment method, and the objective was to identify a dose of navitoclax in combination with chemotherapy in which <33% of subjects experienced DLTs. Tumor responses were evaluated using NCI-WG 1996 criteria. Adverse events

(AE) were graded by NCI CTCAE V3. Pts continued on navitoclax monotherapy up to the recommended phase 2 dose of 250 mg daily for 1 year or until progressive disease or intolerable toxicity.

Results: As of July 2011, 28 pts (median age 59 yr [39-80]) have enrolled; 5 in Arm A (FCR+navitoclax; 110 mg) and 23 in Arm B (BR+navitoclax; 110-250 mg). The median number of prior therapies was 2 (range 1–13). In Arm A, 1 pt had a DLT of febrile neutropenia (110 mg). In Arm B, 5 pts had DLT; 1 had elevated ALT and AST (110 mg), 1 had grade 4 febrile neutropenia (200 mg), and 3 had grade 4 thrombocytopenia (250 mg). Overall, the most common (>20%) navitoclax-related AEs of any grade were nausea (73%), fatigue (50%), neutropenia (50%), cough (39%), vomiting (35%), chills (31%), diarrhea (31%), constipation (27%), headache (27%), anemia (23%), and thrombocytopenia (23%). The most common (>19%) grade 3/4 navitoclax-related AE was neutropenia (35%) and thrombocytopenia (19%); but only 2 of the latter pts had hemorrhagic events (Grade 1 epistaxis) unlikely related to navitoclax. Of the 28 pts evaluated for safety, 6 remain active and 22 discontinued (DC); 1 due to AE, 1 due to AE and progressive disease (PD), 3 due to PD, 6 withdrew consent, 3 due to physician discretion, 4 completed therapy, 2 proceeded to transplant, and 2 due to toxicity.
Preliminary best anti-tumor responses were assessed in 20 pts. Of the 16 pts assessed in Arm B (BR), 6 achieved complete responses (CR), 7 partial responses (PR), 2 stable disease (SD) and 1 with PD. The ORR was 81% (13/16). In this arm, 3/5 pts with 17p deletion achieved PR. Of the 4 pts assessed in Arm A (FCR), 2 achieved PR, 1 SD and 1 with PD. Preliminary PK results suggest that there is no apparent PK interaction between navitoclax and bendamustine.

Conclusions: The combination of navitoclax with BR appears well-tolerated and to have anti-tumor activity. The maximum tolerated dose of navitoclax has been reached at 250 mg for Arm B, but not for Arm A where escalation continues. To date, we have not observed unacceptable myelotoxicity when this bcl-2 antagonist was used in combination with standard cytotoxic chemo-immunotherapy regimens for treatment of pts with CLL.

Disclosures: Kipps: *Igenica:* Equity Ownership, Membership on an entity's Board of Directors or advisory committees; *Celgene:* Consultancy, Research Funding; *Abbott Industries:* Research Funding; *Pharmacyclics:*Membership on an entity's Board of Directors or advisory committees; *Genentech:* Research Funding; *GSK:* Research Funding; *Gilead Sciences:* Consultancy, Research Funding; *Amgen:* Research Funding. **Off Label Use:** R05429083 is a novel humanized antibody direct against the standard region of CD44. R05429083 is currently intensive pre-clinical studies and fist dosing of cancer patients has started in Europe in 2011. **Swinnen:** *Abbott Laboratories:* Research Funding. **Yang:** *Abbott Laboratories:* Employment. **Cui:** *Abbott Laboratories:* Employment, Stock Holder at Abbott Laboratories. **Busman:** *Abbott Laboratories:* Employment, Owns Abbott Laboratories Stock. **Enschede:** *Abbott Laboratories:* Employment, Owns Abbott Laboratories Stock. **Humerickhouse:** *Abbott Laboratories:* Employment, Owns Abbott Laboratories Stock.

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