Title

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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PHASE I STUDY OF THE CYCLIN-DEPENDENT KINASE (CDK) INHIBITOR DINACICLIB (SCH 727965) IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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Background. Dinaciclib (MK-7965/SCH 727965) is a novel, potent, small molecule inhibitor of CDKs 1, 2, 5, and 9 (IC_{50} values between 1-4 nM) with anti-leukemic activity against CLL. **Aims.** A Phase 1 trial was initiated to characterize the dose-limiting toxicity (DLT) and determine the recommended phase 2 dose (RPTD) of dinaciclib administered as a 2-hour IV infusion to patients with relapsed or refractory CLL. **Methods.** Patients received treatment on days 1, 8 and 15 of a 28-day cycle. Based on preclinical data, 5 mg/m^2 was selected as the initial starting dose. Once the RPTD was determined, additional patients were accrued utilizing an intrapatient dose escalation schedule to mitigate tumor lysis toxicity (7, 10 and 14 mg/m^2 on days 1, 8, and 15 during cycle 1 and 14 mg/m^2/dose for each cycle thereafter). Response was assessed according to 1996 NCI Working Group (NCI-WG) criteria for CLL. Patients were followed until disease progression, death, or dropout. **Results.** To date 39 pts have been treated in 5 dose-escalation cohorts (5, 7, 10, 14 and 17 mg/m^2). Median age is 62 (range 43-79) years, with 40% ≥65 years, 71% Rai stage 3 or 4, 63% with bulky disease, and 43% with del 17p. The median number of prior therapies is 3 (range 1-12) with 89% having received prior fludarabine. In the dose determination phase, the RPTD was established as 14 mg/m^2. Dose limiting toxicities (DLT) of bacterial pneumonia and tumor lysis syndrome were observed at the maximum administered dose of 17 mg/m^2. TLS was observed in 7 of the first 39 subjects with CLL, 2 of the 7 TLS events resulted in temporary hemodialysis. Both subjects recovered rapidly and continued dinaciclib after dose reduction. Other common treatment related adverse events included leukopenia, neutropenia, anemia, thrombocytopenia, hyperglycemia, and diarrhea. Clinical response as assessed by the 1996 NCI-WG CLL criteria indicated an overall partial response rate of 54%. Response rates in patients withdel 17p was 53% (9/17), and 58% (7/12) withdel 11. Overall clinical response rates on the RPTD were 69% (11/16), with 6 responders out of 8 patients with del 17. An additional 13 patients have been enrolled in the intrapatient dose escalation expansion cohort, of which 7 are currently evaluable for response. Five patients have achieved a PR, 1 stable disease and 1 with progressive disease. **Conclusions.** Dinaciclib demonstrates single-agent activity in heavily pre-treated CLL patients, including those with deletion 17p and other high-risk genomic features. Compared to first-generation CDK inhibitors, the drug demonstrates a broader therapeutic index, but investigation of alternative dosing schemes to further mitigate risk for tumor lysis are warranted and ongoing. This study supports further study of dinaciclib in CLL, both alone and in combination.

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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. Orally bioavailable navitoclax binds with high affinity (Ki ≤1nM) to Bcl-2, Bcl-xL, and Bcl-w, promoting apoptosis. Preclinically, N enhances rituximab (R) efficacy in B-cell lymphoma, alone or combined with chemotherapy. Phase 1 data showed that N monotherapy was well-tolerated and had anti-tumor activity in CLL patients. **Methods.** We treated relapsed/refractory CLL patients in a phase 1 study to evaluate the safety and pharmacokinetics (PK) of escalating doses of navitoclax combined with standard-dose bendamustine (B)-rituximab (R) or a fixed dose of navitoclax (110 mg) with standard-dose fludarabine (F)-cyclophosphamide (C)-R. Secondary objectives were to assess efficacy endpoints (PFS, ORR, TTP, OS, duration of response). Patients required therapy as per iwCLL criteria and had ECOG ≤1. For patients treated with navitoclax-BR, navitoclax was administered once daily (starting dose, 110 mg) on D3-5 of C1 and D1-3 of subsequent cycles, with 6 patients per dose cohort. Dose escalations were via continuous reassessment to identify a dose combined with chemotherapy in which <33% of patients experienced dose-limiting toxicity (DLTs). We assessed tumor response (NCI-WG 1996 criteria; updated 2008) and adverse events (AE; NCI CTCAE V4). Patients received navitoclax for 1 year or until progressive disease (PD) or intolerable toxicity. **Results.** 26 patients (median age 58 yr [39-80]) enrolled in the BR navitoclax-dose escalation study and 5 patients in the fixed-dose navitoclax-FCR cohort. Median number of prior therapies was 2 (range 1-13). For patients treated with navitoclax-BR 5 had DLTs; 1 elevated liver enzymes (110 mg), 1 grade 4 febrile neutropenia (200 mg), and 3 grade 4 thrombocytopenia (250 mg). 1 patient had a DLT of febrile neutropenia in the navitoclax-FCR cohort. Frequent (>20%; any grade) AEs were nausea (77%), neutropenia (46%), fatigue (42%), vomiting (31%), pyrexia (31%), headache (31%) and diarrhea (27%). For patients treated with N-FCR, 2 had partial responses (PR) (including 1 with del[11q] CLL), 2 had stable disease (SD) and 1 had incomplete data. Among patients treated with navitoclax-BR, there were 6 complete responses (1 confirmed; 2 with del[17p] and del [11q] CLL), 7 PR (2 confirmed; 2 with del[17p] and del [11q] CLL and 1 with del[17p] CLL), 4 SD, 1 PD, and 8 with incomplete data.The overall response rate of patients treated with navitoclax-BR was 72% (13/18). Preliminary PK results suggest no apparent PK interaction between navitoclax and bendamustine. **Conclusions.** Navitoclax combined with BR appears well-tolerated and shows anti-tumor activity. The maximum tolerated dose (MTD) and recommended phase 2 dose of navitoclax is 250 mg. Navitoclax at 110 mg dose also appears well tolerated when combined with FCR. To date, unacceptable myelotoxicity has not been observed when navitoclax was combined with standard chemo-immunotherapy regimens for treatment of patients with CLL.

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SELECTIVE INHIBITION OF BCL-2 IS ACTIVE AGAINST CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): FIRST CLINICAL EXPERIENCE WITH THE BH3-MIMETIC ABT-199

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Background. New treatments are needed for patients with relapsed CLL, especially fludarabine-refractory disease. Targeted therapy with the BH3-mimetic navitoclax inhibits BCL-2, induces apoptosis and achieves partial remissions (PRs) in patients with CLL (Seymour EHA 2011). However, concomitant inhibition of BCL-x_L by navitoclax results in dose-limiting thrombocytopenia, highlighting the need for a more BCL-2-selective inhibitor. ABT-199 is a potent, orally bioavailable BCL-2 inhibitor (K_i<0.10 nM) with 500-fold less activity against BCL-x_L (K_i=48 nM). ABT-199 induces apoptosis of primary CLL cells *in vitro*. **Methods.** This first-in-human study of ABT-199 is a phase-I dose-escalation trial using a modified Fibonacci design in patients with relapsed/refractory CLL or non-Hodgkin lymphoma (NHL) with the objectives: evaluate safety, pharmacokinetics (PK), maximum tolerated dose, efficacy, and recommend a phase-2 dose. Patients with measurable disease, ECOG ≤1, and adequate marrow function were enrolled to Arm-A (CLL/SLL) or Arm-B (NHL). Data from Arm-A are reported. Patients received a single dose of ABT-199 on Week1 Day -7 (W1D-7), followed by continuous once-daily dosing from W1D1, until progressive disease (PD) or unacceptable toxicity. Evaluations included: adverse events (AE; NCI CTCAE V4), tumor response (NCI-WG 1996 criteria; updated 2008), and mechanism-of-action studies (Annexin-V and caspase-3 activation assays). **Results.** To date, 15 patients (median age 65 yr [36-84]) have enrolled. They had received a median of 3 (range 1-8) prior therapies; 8 had bulky adenopathy (≥5 cm), 8 were fludarabine-refractory, and 5 had del(17p) on FISH. The first three patients (cohort 1) experienced dose-limiting, clinically significant Gr3 tumour-lysis syndrome (TLS) following the W1D-7 single dose (200mg, 200