Bendamustine HCl (TREANDA™) Treatment Results in High Rates of Objective Response in Patients with Rituximab-Refractory and Alkylator-Refractory Indolent B-Cell Non-Hodgkin's Lymphoma (NHL): Results from a Phase II Multicenter Single-Agent Study (SDX-105-01).

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Background: Bendamustine HCl (Treanda™) is a multifunctional, alkylating agent with novel mechanisms of action. Unlike other commonly used chemotherapeutic agents, bendamustine in vitro induces durable cell damage resulting in rapid cell death in apoptosis-resistant cancer cell lines through the apoptosis independent pathway of mitotic catastrophe. European studies have reported single-agent activity in patients with relapsed/refractory NHL, chronic lymphocytic leukemia, multiple myeloma, and breast cancer. Aim: This study evaluated the efficacy and toxicity of bendamustine in patients with NHL who have relapsed or are refractory to previous chemotherapy regimens. Patients refractory to Rituximab had disease progression within 6 months of treatment. Methods: This Phase II multicenter trial enrolled patients with relapsed indolent or transformed rituximab-refractory B-cell NHL from 17 sites in the US and Canada. Indolent histologic phenotype was seen in 84% of patients, while 16% had transformed disease. Median age of patients was 63 years (range: 38-84) and 88% had Stage III/IV disease. Patients received bendamustine 120 mg/m² IV over 30-60 minutes, days 1 and 2, every 21 days for up to 6 cycles. Response was measured using the International Working Group criteria. Results: The intent-to-treat (ITT) population consisted of 75 heavily pretreated patients with a median of 2 prior chemotherapies. The overall objective response rate (ORR) in the ITT population was 74%; 25% had a complete response, 49% had a partial response, 12% had stable disease, and 14% had disease progression. Of 15 patients who were refractory to prior alkylator treatment (patients who progressed after at least one prior alkylator-containing therapy), 10 (67%) experienced an objective response to bendamustine. The median duration of response was 6.6 months for all patients, 9.3 months for indolent patients, and 2.4 months for transformed patients. The most frequent nonhematologic adverse events were nausea (63%), fatigue (39%), vomiting (38%), fever (25%), and diarrhea (22%). Most of these events were grade 1 or 2; alopecia and hemorrhagic cystitis were not observed. Grade 3 or 4 reversible hematologic toxicities seen included neutropenia (47%), thrombocytopenia (24%), and anemia (11%). Conclusions: Single-agent bendamustine produced durable objective responses with acceptable toxicity, despite unfavorable prognostic features, in heavily pretreated rituximab-refractory indolent and transformed NHL patients. Durable response has been seen in alkylator-resistant patients. A Phase III trial with bendamustine as a single agent in patients with rituximab-refractory indolent NHL is ongoing.

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Bendamustine HCl (TREANDA™) Treatment in Combination with Rituximab Results in Objective Responses in Patients with Refractory/Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma: Results from Phase II Multicenter Study (SDX-105-02).

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Background: Bendamustine hydrochloride (SDX-105; Treanda™) is a multifunctional, alkylating agent with a purine-like ring system and novel mechanisms of action that exhibits impressive single-agent activity in multiple hematologic and solid tumors. In vitro data indicate that bendamustine induces cell death as a result of both apoptosis and mitotic catastrophe, resulting in potent cell-killing activity in cancer cells that are resistant to traditional chemotherapy (alkylating and fludarabine-containing regimens). In vitro data have also demonstrated a synergistic effect with rituximab for the treatment of non-Hodgkin's lymphomas (NHL). A Phase II multicenter study (SDX-105-02) was conducted to determine the efficacy and toxicity of the combination of bendamustine with rituximab in relapsed NHL patients. Methods: The intent-to-treat (ITT) population consists of 54 patients with relapsed indolent CD20-positive B-cell or mantle cell NHL, enrolled from 22 sites in the US and Canada. Median age of the patients was 60 years (range 40-84); 59% had follicular NHL, 6% had small lymphocytic lymphoma, 4% had lymphoplasmacytoid lymphoma, 4% had marginal zone lymphoma, and 17% had mantle cell lymphoma; and 72% of all patients had Stage III/IV disease. Patients relapsed from a median of 1 prior therapy. Patients received rituximab, 375 mg/m^2 IV on day 1, and bendamustine, 90 mg/m^2 on days 2 and 3, every 28 days for 4-6 cycles. All patients received an additional dose of rituximab 1 week prior to the first cycle of bendamustine and 4 weeks after the last cycle. Results: Of the 54 ITT patients, 37% had prior treatment with rituximab. Forty-three patients are currently evaluable for response, as defined by the International Working Group. The overall response rate was 84%, with complete response in 21% and partial response in 63% of patients. The median duration of response has not yet been reached after a median follow up of 3.6 months. Minimal toxicity was observed. The most common nonhematologic toxicities included grade 1/2 gastrointestinal complications. The primary grade 3/4 hematologic toxicity was neutropenia (with no neutropenic fever), observed in 22% of patients. Grade 3/4 anemia and thrombocytopenia were observed in only 1 patient. No alopecia was observed. Conclusions: Bendamustine, administered in combination with rituximab, produced high objective response rates with minimal toxicity in patients with refractory indolent and mantle cell NHL, including patients that previously failed alkylating and fludarabine-containing regimens. A Phase III trial with bendamustine as a single agent in patients with rituximab-refractory indolent NHL is ongoing.