

A First in Human Phase I Trial (LS1681) of Abraxane®/Rituximab 160 nm nanoparticle (AR160) in Relapsed Refractory B-Cell Lymphomas Including Transformed Follicular Lymphoma: A Final Report

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Introduction: Nanotechnology for cancer therapy aims to increase drug delivery to tumor sites while lowering toxicity. AR160 is a novel 160 nm nano-immunoconjugate consisting of commercial grade nab-paclitaxel (NP) nanoparticles non-covalently coated with rituximab (R) for targeted delivery into tissues expressing CD20. The drug delivery system and clinical grade product was developed in the laboratory of Svetomir N. Markovic, M.D., Ph.D. Single agent rituximab at a dose of 375 mg/m² in relapsed patients with aggressive lymphomas is not utilized and has limited activity in patients with multiple relapses. Taxanes (Younes 1995, Wilson 1995) have modest clinical activity as a single agent with overall response rates of 23% and 17%, respectively, when administered at doses of 200 mg/m² and 140 mg/m² in previously treated patients with non-Hodgkin lymphoma (NHL). We hypothesized that utilizing the targeted ability of rituximab that the AR160 taxane nanoparticle would have activity in relapsed B-cell NHL and offer a new class of agents for relapsed B-cell NHL.

Methods: A 3+3 phase I clinical trial was conducted in patients with relapsed refractory non-Hodgkin lymphoma to determine the maximum tolerated dose of AR160 administered intravenously on days 1, 8, and 15 of a 28-day cycle. Patients were required to have had prior systemic treatment with no other therapy with clinical benefit. Patients with aggressive lymphoma were required to have a stem cell transplant if transplant eligible. AR160 was prepared on-site in the Mayo Clinic Cancer Center Research Pharmacy, and the product was reconstituted by mixing the two agents delivering as one combined infusion at a specific concentration. The starting dose level (DL1) was NP at 100mg/m² with R at 40 mg/m². These doses were significantly lower than standard doses. Disease evaluations were conducted after every 2 treatment cycles using CT based criteria from the revised 2014 Lugano Classification or PET

scans. Patients were treated until disease progression or intolerability. Samples were collected for pharmacokinetic (PK) studies.

Results: Nine (7 males and 2 females) patients with a median age of 61 (range 55-84 years) were enrolled (2 follicular lymphoma (FL), 1 previously transformed from FL to diffuse large B-cell lymphoma (DLBCL) followed by FL relapse, 1 high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements transformed from FL, 1 transformed FL to DLBCL, 2 high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements, 1 high-grade B-cell lymphoma NOS and 1 mantle cell lymphoma. The median number of prior treatments was 4 (range 3-16). At dose level 1, all 3 of the first 3 patients experienced grade 3 or 4 neutropenia (C1D15, C4D1, and C1D15) with the C4D1 a grade 4 and unlikely related. After the first three patients, de-escalation to dose level -1 was implemented per protocol with NP at 75 mg/m² and rituximab at 30 mg/m². There was one patient with a grade 3 non-hematological adverse event all possibly related to treatment (anorexia, diarrhea, and enterocolitis). There were 6 partial responses (71%), 1 complete response (14%) with high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement, 1 stable disease with mantle cell lymphoma and 1 patient had progressive disease. Six of the 9 patients were alive with subsequent therapies. PK evaluation is pending.

Conclusion: AR160 therapy is a novel drug delivery system incorporating significantly lower doses of paclitaxel and rituximab that is safe and demonstrates promising clinical activity in patients with low-grade and high-grade previously treated B-cell lymphomas. This principle of treatment is applicable to other disorders. Further clinical testing is warranted in these patient populations.