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CHOP in Combination with Pralatrexate, a Novel Folate Analogue Metabolic Inhibitor in Patients with Previously Untreated Peripheral T-Cell Lymphoma (PTCL): Interim Results of the Phase 1 Trial

Andrei R. Shustov, MD,[1] Yasuhiro Oki, MD,[2] Stefan Klaus Barta, MD MRCP, MS,[3] Patrick B. Johnston, MD PhD,[*,4] Pankaj Sharma,[*,5] Tao Song,[*,5] Sanjay Mourya[*,5]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA

[2]Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

[3]Fox Chase Cancer Center, Philadelphia, PA

[4]Division of Hematology, Mayo Clinic, Rochester, MN

[5]Spectrum Pharmaceuticals, Irvine, CA

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Abstract

Background: Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of mature T-cell and natural-killer-cell aggressive non-Hodgkin lymphomas associated with poor prognosis with current therapies. Numerous studies have reported poor survival for PTCL patients with a median Overall Survival (OS) shorter than 2 years and 5-year survival rates of <30%. Traditionally, patients with PTCL have been treated with a cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-like first-line chemotherapeutic regimen. Unfortunately, the prognosis remains poor with most patients relapsing within 2 years. Thus, improved front line treatment strategies are needed.

Pralatrexate (Folotyn) is a folate analogue metabolic inhibitor that was the first drug approved in the US for the treatment of patients with relapsed or refractory PTCL (R/R PTCL). Approval was based on results from the pivotal Phase 2 PROPEL study (O'Connor et al, JCO, 2011) of pralatrexate in R/R PTCL, in which pralatrexate monotherapy demonstrated a durable clinical benefit (objective response rate of 29%). Pralatrexate is administered intravenously (IV) at a dose of 30 mg/m^2 weekly for 6 weeks of a 7-week treatment cycle. Since pralatrexate and each of the components of the CHOP regimen target different

aspects of tumor cell growth and proliferation, there is a potential for synergistic anti-tumor effect, and limited additive toxicities.

Objectives: The primary endpoint of the study is the determination of the MTD of pralatrexate in combination with CHOP (Fol-CHOP) in previously untreated PTCL patients. Secondary endpoints included safety, tolerability and ORR (complete response [CR] + partial response [PR]) and pharmacokinetics.

Methods: In this study, patients with PTCL received CHOP in combination with pralatrexate, repeated every 3-weeks for up to 6 cycles. Part 1 of the study was to determine the Maximum Tolerated Dose (MTD) of the Fol-CHOP combination. Once the MTD was determined, an additional 10 patients were treated in the Expansion Phase (Part 2). The cohort schema followed a traditional "3+3" design. Pralatrexate was to be administered as 10, 15, 20, 25, or 30 mg/m^2 IV push over 3 to 5 minutes on Days 1 and 8 of each cycle. The starting cohort was CHOP + 10 mg/m^2 of pralatrexate.

Patients received prophylaxis with acyclovir and sulfamethoxazole/trimethoprim during the study and primary prophylaxis with growth factor (filgrastim or pegfilgrastim) support. Dose-limiting toxicities (DLT) were considered during the 1st cycle and included: Severe infections, study treatment-related non-hematological toxicity Grade 3-4, platelet count < 25 X 10^9/L at any time or ANC < 0.5 X 10^9/L lasting more than 7 days despite G-CSF administration.

Results: A total of 12 patients have been enrolled in Part 1 of the study at the time of abstract submission. Nine patients have completed Cycle 1 and no DLT was reported. Among these nine patients, three patients each were treated at CHOP + 10 mg/m^2, 15 mg/m^2 and 20 mg/m^2 of pralatrexate. One patient (11%) treated with CHOP + 10 mg/m^2 had one serious adverse event (SAE) of febrile neutropenia that was deemed unrelated to any study drug. Only four Grade 3 AEs (anemia, constipation, mucosal inflammation, and nausea) were reported, in one patient (11%). The enrollment into the study continues.

Conclusions: These interim results demonstrate that the combination of pralatrexate with CHOP (Fol-CHOP) is well tolerated, with all components of CHOP as well as pralatrexate being given at close to or at standard doses. The rates of AEs are comparable to those typically reported with CHOP alone. The study is ongoing to confirm the MTD and to assess preliminary efficacy of the Fol-CHOP combination. Updated results will be presented at the meeting.

Disclosures

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Author notes

*Asterisk with author names denotes non-ASH members.