697 Temsirolimus in Combination with Bendamustine and Rituximab for the Treatment of Relapsed Mantle Cell and Follicular Lymphoma: Report on An Ongoing Phase I/II Trial

Program: Oral and Poster Abstracts
Type: Poster
Session: 623. Lymphoma - Chemotherapy, excluding Pre-Clinical Models: Poster II
Sunday, December 11, 2011, 6:00 PM-8:00 PM
Hall GH (San Diego Convention Center)

Georg Hess, MD[1*], *Ulrich Keller, MD*[2*], *Johannes Atta*[3*], *Christian Buske*[4], *Peter Borchmann, MD*[5], *Christoph Medler*[6*], *Mathias Witzens-Harig*[7*] *and Martin H. Dreyling, PhD*[8]

[1]*Department of Hematology, Oncology and Pneumology, Universitaetsmedizin Mainz, Mainz, Germany*
[2]*III. Department of Internal Medicine, Hematology/Oncology, Technical University of Munich, Munich, Germany*
[3]*Haematology / Oncology, University Hospital Frankfurt*
[4]*Institute of Experimental Cancer Research, University of Ulm, Ulm, Germany*
[5]*Department of Internal Medicine I, University Hospital Cologne, Cologne, Germany*
[6]*IZKS, Universitätsmedizin Mainz, Mainz*
[7]*Med. Dep. V, University of Heidelberg, Heidelberg*
[8]*Department of Internal Medicine III, University Hospital Munich, Munich, Germany*

Background: mTOR inhibition has been shown to be effective in various subtypes of malignant lymphomas. Based on a phase III trial in relapsed MCL which proved superiority of temsirolimus to standard options, the drug is approved for this indication in the EU. Additionally, promising response rates could be observed in patients with follicular and diffuse large B-cell lymphoma (Smith et al, JCO 2010). Whereas combination to single agent rituximab seems feasible and with improved efficacy (Ansell et al, Lancet Oncology 2011), there is limited information on the feasibility and efficacy in combination with chemotherapy. Bendamustine has been shown to be effective in indolent lymphoma and has a beneficial side effect profile (Rummel et al, JCO, 2005). To evaluate the potential of the combination of temsirolimus with bendamustine and rituximab an ongoing phase I/II trial was initiated.

Methods: This is a multicenter, national, prospective trial, approved by the centralized EC. Patients were eligible if they had histologically proven follicular (FL) or mantle cell lymphoma (MCL), the latter with Cyclin D1 positivity or detectable t(11;14), 1-3 prior treatment lines, no curative option available, no refractoriness to bendamustine, measurable disease, ECOG < 3, sufficient bone marrow reserve, no severe concomitant diseases and given informed consent. Treatment consisted of bendamustine 90mg/m² day 1-2, rituximab 375mg/m² day 1 and temsirolimus day 2, 8, 15 of a 28d cycle. A total of 4 cycles was planned with interim staging after 2 cycles. In the ongoing phase I part (3+3 design) the following dose cohorts for temsirolimus were planed: A 25mg, B 50mg, C 75mg. Currently cohort C is ongoing. Toxicity was evaluated throughout the treatment and analysis for DLT was performed after 2 cycles. An independent data safety monitoring board decided on the escalation to the next dose level.

Results: Overall 9 patients have been included until now (6 pts cohort A, 3 patients cohort B) and 4 patients are in the prescreening period (cohort C). Median age 64; Histology: 8MCL / 1FL; sex 2F/ 7M, median number of pretreatments 2 (1-3). Adverse events: overall the treatment was well tolerated. Toxicity was predominant hematologic with mostly leukopenia and thrombocytopenia . In 29 evaluable cycles of chemotherapy the following grade 3 / 4 toxicities were noted: Thrombocytopenia in 3 (all grade 3);

leukopenia in 11 (9 grade 3; 2 grade 4), and increase in triglycerides, hyperglycemia and hypertension in one patient each (all grade 3). Importantly, one case of pneumonitis occurred, which resolved after steroid treatment and study treatment could be resumed w/o further problems. In addition, one reaction to contrast agent, an allergic reaction to berries and a transient parasthesia during the study phase were noted, leading to hospitalization. All of these events occurred several days after the last application of study drug and were considered not to be associated to the study treatment. As the episode of hypertension led to hospital admission, it was considered to be potentially a DLT, and cohort A was escalated to 6 patients w/o further DLT. In cohort B no DLT were observed in 3 patients and cohort C has been opened for inclusion. 5 patients have completed the entire treatment, in one patient treatment was stopped after cycle 3 due to delayed recovery of platelets, and treatment is ongoing in 3 patients. At interim staging all 9 patients evaluable achieved a partial remission (ORR 100%). After completion of the entire treatment ORR was 100% with 1 CR and 5 PR in 6 evaluable patients.

Summary: In this ongoing phase I/II trial the combination of temsirolimus with bendamustine and Rituximab was feasible applying 3 weekly doses of up to 50mg temsirolimus in a 4 week cycle. Until now promising response rates have been noticed. Cohort C is currently recruiting patients (Temsirolimus 75mg), updated results of the phase I part of the trial will be presented at the meeting. If no dose limiting toxicities are observed, the extended phase II part of the trial will be initiated with patients stratified according to lymphoma subtype (30 patients each with FL and MCL).

Disclosures: Hess: *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Honoraria. **Keller:** *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Roche:* Membership on an entity's Board of Directors or advisory committees. **Witzens-Harig:** *Pfizer:*Membership on an entity's Board of Directors or advisory committees, Research Funding; *Roche:* Consultancy.**Dreyling:** *Pfizer:* Research Funding, Speakers Bureau, scientific advisory.