COSMOS: MOR208 plus idelalisib or venetoclax in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) previously treated with a Bruton’s tyrosine kinase inhibitor (BTKi) – a two-cohort phase II study

Clemens-Martin Wendtner,1 John Byrd,2 Robin Foà,3 Richard Greil,4 Peter Hillmen,5 Ulrich Jäger,6 Wojciech Jurczak,7 Peter Kelemen,8 Kamel Laribi,9 Talha Munir,10 Johannes Schetelig,10 Philipp B. Staber,10 Stephan Stilgenbauer,11 Jennifer Woyach2

1Klinikum Schwabing, Department I of Medicine, Academic Teaching Hospital of University of Munich, Munich, Germany; 2Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA; 3Division of Hematology, Sapienza University of Rome, Rome, Italy; 4Department of Internal Medicine III with Hematology, Medical Oncology, Hemostaseology, Infectious Diseases, Rheumatology, Oncologer, Paracelsus Medical University Salzburg, Salzburg, Austria; 5St James’s University Hospital, Leeds, United Kingdom; 6Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital - Medical University of Vienna, Vienna, Vienna, Austria; 7Department of Hematology, Jagiellonian University, Kraków, Poland; 8MorphoSys AG, Planegg, Germany; 9Department of Hematology - Centre Hospitalier du Mans, 72037 Le Mans, France; 10Medizinische Klinik und Poliklinik I, TU Dresden, Dresden, Germany; 11Department of Internal Medicine III, Ulm University, Ulm, Germany

Background

• The BTKi, ibrutinib, is an important treatment option for patients with CLL/SLL.1,2
• Patients who discontinue treatment with ibrutinib due to progression, transformation or intolerance have a particularly dismal prognosis, as alternative therapeutic options are limited.1-6
• Phosphoinositide-3-kinase δ (PI3K-δ) is hyperactivated in B-cell malignancies and plays a pivotal role in the B-cell receptor pathway.6,7
• Idelalisib is a first-in-class, orally administered, potent, reversible, small-molecule inhibitor of PI3K-δ and is approved in combination with rituximab for the treatment of patients with relapsed CLL and as mono-therapy for patients with relapsed follicular lymphoma or SLL.6
• Venetoclax, an orally administered, small-molecule inhibitor of BCL-2, is currently approved for the treatment of patients with CLL who have a tumor chromosomal 17p deletion and who have received at least one prior therapy.8
• CD19 expression is highly conserved at normal to high levels in most B-cell tumors during the course of disease, including in CLL and B-cell lymphoma.9
• MOR208, an Fc-enhanced monoclonal antibody, binds to CD19 (Figure 1), demonstrating significantly increased tumor cytotoxicity compared with the parental, non-engineered antibody.10,11
• A phase I study showed MOR208 to be generally safe and well tolerated, with encouraging single-agent activity in patients with CLL/SLL.12

Methods

• This is a phase II, two-cohort, open-label, multicenter study to evaluate the efficacy and safety of MOR208 combined with idelalisib or venetoclax in patients with R/R CLL/SLL previously treated with a BTKi (NCT026359910; Figure 2).

Outcome measures

Primary endpoint

• Overall response rate (based on independent review), defined for Cohort A as the percentage of patients achieving a complete response (CR), a partial response (PR) or a PR with lymphocytosis, and for Cohort B as the percentage of patients achieving a CR or a PR.

Secondary endpoints

• Progression-free survival; overall survival; time to progression; time to treatment failure; time to response; lymph node response.
• Incidence and severity of adverse events.
• Detection of anti-MOR208 antibodies (immunogenicity).
• MOR208 pharmacokinetics.
• Patient-reported quality of life outcomes.

Exploratory endpoints

• Proportion of patients with minimal residual disease negativity. Changes from baseline in B-, T- and natural killer (NK) cell populations. Analysis of exploratory and diagnostic biomarkers from blood (e.g., CD19 expression, BTK and phospholipase C (PLC)γ2 mutational status, CD16 expression on NK cells, antibody-dependent cell-mediated cytotoxicity capacity, cytogenetics and further mutational analysis).

Patients

Key inclusion criteria

• Diagnosis of CLL or SLL with an indication for treatment, as defined by the International Workshop on CLL guidelines.
• R/R disease while on BTKi therapy given as a single-agent or as combination therapy for at least one month, or intolerant to such therapy:
  – Relapsed disease is defined as progressive disease in patients who have previously achieved a PR or CR to their most recent BTKi therapy
  – Refractory disease is defined as progressive disease in patients who have never previously achieved a PR or CR to their most recent BTKi therapy, or stable disease as the best response after 12 months of receiving their most recent BTKi therapy.
• ECOG performance status of 0–2, adequate bone marrow, hepatic and renal function.

Key exclusion criteria

• Non-Hodgkin’s lymphomas other than CLL/SLL; transformed CLL/SLL or Richter’s syndrome.
• Active and uncontrolled autoimmune cytopenia; ongoing systemic viral, bacterial or fungal infection.
• Treatment with a BTKi within 5 days prior to day 1 dosing.
• Prior treatment with a CD19-targeted agent, a PI3K inhibitor (Cohort A) or a BCL-2 inhibitor (Cohort B).

Current status

• Recruitment start date: November 2016.
• To date 4 patients have been enrolled.
• The study will include a safety run-in phase and there will be an interim analysis to determine the preliminary safety and efficacy of each combination. The evaluation will be done by an independent data monitoring committee.

References


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Correspondence

Clemens-Martin Wendtner@klinikum-muenchen.de

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