Ibrutinib, a Bruton’s tyrosine kinase inhibitor (BTKi), is an important treatment option for patients with CLL/SLL.\(^1\)\(^2\)

Patients who received ibrutinib and had to discontinue treatment due to progression, transformation or intolerance have a particularly dismal prognosis, as their therapeutic options are very limited.\(^3\)\(^5\)

Phosphoinositide-3-kinase δ (PI3K-δ) is constitutively activated in B-cell malignancies and plays a pivotal role in the B-cell receptor (BCR) pathway.\(^6\)\(^7\) Idelalisib is a first-in-class, orally administered, potent reversible small-molecule inhibitor of PI3K-δ approved in combination with rituximab for the treatment of relapsed CLL and as monotherapy for relapsed follicular lymphoma and SLL.\(^8\)

CD19 expression is highly preserved on most B-cell tumors, thus CD19 is expressed in CLL and B-cell lymphomas at normal to high levels during the course of the disease.\(^8\)

MOR208, an Fc-engineered monoclonal antibody, binds to CD19 (Figure 1), demonstrating significantly increased tumor cytotoxicity compared with the parental, non-engineered antibody.\(^8\)

A phase I study showed MOR208 to be generally safe and well-tolerated, with encouraging single-agent activity in patients with CLL/SLL – at a recommended dose of 12 mg/kg, IV weekly.\(^9\)

### Figure 1. MOR208 mode of action

**Figure 2. Study design and treatment**

![Study design and treatment](image)

<table>
<thead>
<tr>
<th>R/R CLL or SLL pretreated with BTKi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
</tbody>
</table>
| **Cycles 1-3**
  | Idelalisib 150 mg orally twice a day Days 1–28 |
| **MOR208**
  | 12 mg/kg IV Days 1, 8, 15, 22 |
| **Cycles 4-24**
  | Idelalisib 150 mg orally twice a day Days 1–28 |
| **MOR208**
  | 12 mg/kg IV Days 1 and 15 |
| **EOT** |

*Patients who are discontinued from treatment due to PD will undergo follow-up for survival every 3 months for up to 3 years after EOT. Patients who discontinue from treatment for reasons other than PD, death or withdrawal of consent will undergo tumor assessment until PD occurs, then they will enter follow-up for survival every 3 months for up to 3 years after the EOT. BTKi, Bruton’s tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EOT, end of treatment; PD, progressive disease; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma.

### Secondary endpoints

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

### Exploratory endpoints

- Change from baseline in B-, T- and NK cell populations. Blood biomarkers (e.g. CD19 expression; BTK and phospholipase C [PLCγ2] mutational status; CD16 expression on NK cells; ADCC capacity; cytogenetics/additional mutational analysis).

### Patients

#### Key inclusion criteria
- Diagnosis of CLL or SLL requiring treatment (according to IWCLL guidelines).
- Relapsed or refractory disease while on BTKi therapy given as single-agent or 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 most recent BTKi therapy
  - Refractory disease is defined as progressive disease in patients who have previously not achieved a PR or CR to most recent BTKi therapy, or stable disease as best response after 12 months of receiving the most recent BTKi therapy.
- Eastern Cooperative Oncology Group 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; uncontrolled active viral, bacterial, or systemic fungal infection.
- Treatment with a BTKi within 5 days prior to day 1 dosing.
- Prior treatment with CD19-targeted or PI3Ki therapy.

### Treatment start date: January 2016.

### Current status

- Study start date: January 2016.
- Up to 120 patients planned.
- The study will include a safety run-in phase and there will be an interim analysis to determine preliminary safety and efficacy. The evaluation will be done by an independent data monitoring committee (IDMC).

### References


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### Disclosures

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### Correspondence

Clemens-Martin.Wendtner@klinikum-muenchen.de

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**A phase II study of MOR208 plus idelalisib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) previously treated with a Bruton’s tyrosine kinase inhibitor**

Clemens-Martin Wendtner,\(^1\) John Byrd,\(^2\) Barbara Eichhorst,\(^3\) Robin Foà,\(^4\) Michael Hallek,\(^5\) Peter Hillmen,\(^5\) Ulrich Jäger,\(^6\) Wojciech Jurczak,\(^7\) Peter Kelemen,\(^8\) Kamel Laribi,\(^9\) Talha Munir,\(^5\) Philipp B. Staber,\(^6\) Stephan Stilgenbauer,\(^10\) Jennifer Woyach\(^7\)

**Klinikum Schwabing, Department I of Medicine, Academic Teaching Hospital of University of Munich, Munich, Germany;**

**Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA;**

**Klinik I für Innere Medizin, Uniklinik Köln, Köln, Germany;**

**Division of Hematology, “Sapienza” University of Rome, Rome, Italy;**

**St James’s University Hospital, Leeds, United Kingdom;**

**Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital –Medical University of Vienna, Vienna, Austria;**

**Department of Hematology, Jagiellonian University, Kraków, Poland;**

**MorphoSys AG, Martinsried, Germany;**

**Department of Hematology, Centre Hospitalier Le Mans, Le Mans, France;**

**Department of Internal Medicine III, Ulm University, Ulm, Germany**

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