# 7. Trial conduct

## 7.1. Trial design

This trial is a phase-III study and – according to the definitions of the ICH Harmonized Tripartite Guideline E8 – a therapeutic study, which is designed as a prospective, multicenter, randomized, open-label, four-arm trial. The study aims to investigate the efficacy of standard chemoimmunotherapy (BR/FCR) versus rituximab plus venetoclax (RVe) versus obinutuzumab plus venetoclax (GVe) versus obinutuzumab plus ibrutinib plus venetoclax (GIVe) in previously untreated, fit CLL patients without del(17p) or TP53 mutation.

### 7.1.1. Standard chemoimmunotherapy (SCIT)

All patients may be treated with up to a total of six cycles of standard chemoimmunotherapy depending on response and toxicity. Restart every cycle 28 days after start of the previous cycle.

Dosing of chemotherapy will be calculated with help of the Body Surface Area (BSA) using the Mosteller Formula: $BSA(m^2) = ([Height\ (cm)\ \times Weight\ (kg)]/3600)^{½}$

#### 7.1.1.1. Fludarabine, cyclophosphamide plus rituximab (FCR)

Rituximab (MabThera®) will be provided as study medication and will be administered as an intravenous infusion before the application of FC. No subcutaneous application or biosimilars are allowed in the trial.

| | |
|---|---|
| Cycle 1: | 375 mg/ m² i.v. |
| Cycles 2-6: | 500 mg/ m² i.v |

For the first administration, an initial infusion rate of 50 mg/h is recommended. If this is well tolerated it can be increased by 50 mg/h every 30 minutes up to a maximum infusion rate of 400 mg/h. If the first administration of rituximab was well tolerated all subsequent administrations can be started at a rate of 100 mg/h which is then increased by 100 mg/h every 30 minutes up to 400 mg/h.

In patients with high lymphocyte counts (> 100 x10^9/l) who thus have an increased risk of occurrence of a cytokine release syndrome the infusion rate of 50 mg/h can remain for the entire infusion. Moreover, in case of a high lymphocyte count at treatment course one or if the dose splitting is according to the standard practice in the participating site the rituximab dose might be split and given on two days.

If any of the following side effects occur, the rituximab infusion should be interrupted and only continued after clinical improvement:

- Fever > 38.5°C
- Shaking chills
- Bronchoconstriction
- Hypotension by more than 30 mmHg

Fludarabine will be administered in a dosage of 25 mg/m² over 15-30 minutes i.v. on days 1, 2 and 3 of each cycle.

Cyclophosphamide will be administered in a dosage of 250 mg/m² over 15-30 minutes i.v. on days 1, 2 and 3 of each cycle.

Fludarabine and cyclophosphamide can be administered immediately one after the other. The dose of fludarabine and/or cyclophosphamide may be capped for patients with a BSA above a certain level (2.0 or higher) according to local practice and the investigator's clinical judgement. The dose of rituximab should not be capped.

After Cycle 3, evaluate patients for response before proceeding to cycle 4. If a patient has stable disease or appears to be responding to therapy and toxicity is acceptable, the patient should continue therapy.

#### 7.1.1.2. Bendamustine plus rituximab (BR)

Rituximab (MabThera®) will be provided as study medication and will be administered as an intravenous infusion before the application of bendamustine. No subcutaneous application or biosimilars are allowed in the trial.
Please refer to chapter 7.1.1.1 for further information on infusion rates and interruptions.

| | |
|---|---|
| Cycle 1: | 375 mg/ m² i.v. |
| Cycle 2-6: | 500 mg/ m² i.v. |

Bendamustine will be administered in a dosage of 90 mg/m² over 30 minutes i.v. on days 1 and 2 of each cycle.

### 7.1.2. Rituximab plus venetoclax (RVe)

The RVe treatment consists of 12 cycles, each with a duration of exactly 28 days.

Rituximab (MabThera®) will be administered intravenously on day one; at a dosage of 375 mg/m² in the first cycle and at a dose of 500 mg/m² in cycles 2-6. Please refer to chapter 7.1.1.1 for further information on infusion rates and interruptions.
The continuous daily administration with a slow dose escalation of venetoclax starts on cycle 1 day 22.

Venetoclax p.o.:

| | | |
|---|---|---|
| Cycle 1: | Days 22-28: | venetoclax 20 mg (2 tabl. at 10 mg) |
| Cycle 2 | Days 1-7: | venetoclax 50 mg (1 tabl. at 50 mg) |
| | Days 8-14: | venetoclax 100 mg (1 tabl. at 100 mg) |
| | Days 15-21: | venetoclax 200 mg (2 tabl. at 100 mg) |
| | Days 22-28: | venetoclax 400 mg (4 tabl. at 100 mg) |
| Cycles 3-12: | Days 1-28: | venetoclax 400 mg (4 tabl. at 100 mg) |

Due to the risk of adverse events, especially tumor-lysis-syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400 mg is reached (ramp-up). In order to diagnose a TLS at an early stage certain safety measures must be followed (see 8.4.2 *Safety precautions with venetoclax*).
Please refer to chapter 8.4.1 *Adminsitration of venetoclax* for further information.

### 7.1.3. Obinutuzumab plus venetoclax (GVe)

The GVe treatment consists of 12 cycles, each with a duration of exactly 28 days. During the first cycle obinutuzumab is administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of cycles 2-6.

Obinutuzumab i.v. infusion:

| | | |
|---|---|---|
| Cycle 1: | Day 1: | obinutuzumab 100 mg |
| | Day 1 (or 2): | obinutuzumab 900 mg |
| | Day 8: | obinutuzumab 1000 mg |
| | Day 15: | obinutuzumab 1000 mg |
| Cycles 2-6: | Day 1: | obinutuzumab 1000 mg |

The first infusion of obinutuzumab may be administered at the full dose (1000 mg) on day 1 of the first cycle if the infusion of a test-dosage of 100 mg is well tolerated by the patient. Alternatively, if the first 100 mg infusion on day 1 is not tolerated well, the remaining 900 mg of the first dose should be administered on day 2.
Please refer to chapter 8.2*3 Obinutuzumab (GA101)* for further information.

The continuous daily administration with a slow dose escalation of venetoclax starts on day 22 in cycle one.

Venetoclax p.o.:

| | | |
|---|---|---|
| Cycle 1: | Days 22-28: | venetoclax 20 mg (2 tabl. at 10 mg) |
| Cycle 2 | Days 1-7: | venetoclax 50 mg (1 tabl. at 50 mg) |
| | Days 8-14: | venetoclax 100 mg (1 tabl. at 100 mg) |
| | Days: 15-21: | venetoclax 200 mg (2 tabl. at 100 mg) |
| | Days 22-28: | venetoclax 400 mg (4 tabl. at 100 mg) |
| Cycles 3-12: | Days 1-28: | venetoclax 400 mg (4 tabl. at 100 mg) |

Due to the risk of adverse events, especially tumor-lysis-syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400 mg is reached (ramp-up). In order to diagnose a TLS at an early stage certain safety measures must be followed (see 8.4.2 *Safety precautions with venetoclax*).
Please refer to chapter 8.4.1 *Administration of venetoclax* for further information.

### 7.1.4. Obinutuzumab, ibrutinib plus venetoclax (GIVe)

The GIVe treatment consists of 12 cycles (ibrutinib up to 36 cycles), each with a duration of exactly 28 days; during the first cycle obinutuzumab is administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of cycles 2-6.
Obinutuzumab i.v. infusion:

| | | |
|---|---|---|
| Cycles 1: | Day 1: | obinutuzumab 100 mg |
| | Day 1 (or 2): | obinutuzumab 900 mg |
| | Day 8: | obinutuzumab 1000 mg |
| | Day 15: | obinutuzumab 1000 mg |
| Cycles 2-6: | Day 1: | obinutuzumab 1000 mg |

The first infusion of obinutuzumab may be administered at the full dose (1000 mg) on day 1 of cycle 1, if the infusion of a test-dosage of 100 mg is well tolerated by the patient. Alternatively, if the first 100

mg infusion on day 1 is not well tolerated, the remaining 900 mg of the first dose should be administered on day 2.
Please refer to chapter 8.2 *Obinutuzumab (GA101)* for further information.

Ibrutinib will be administered as a daily oral dosage of 420 mg (3 x 140 mg) starting on day 1 of cycle 1 until:

1.) MRD negativity (i.e. < $10^{-4}$) in peripheral blood and confirmed by a bone marrow aspirate 2 months later or by two consecutive peripheral blood samples (MRD-staging 1 and 2 [MO 9/13] or MRD-stagings 2 and 3 [MO 12/15]; all other patients will continue treatment) or
2.) until 36 months of treatment are finished
3.) start of new anti-CLL therapy or
4.) progression of CLL or
5.) unacceptable toxicity, whatever occurs first.

Ibrutinib po:

| | | |
|---|---|---|
| Cycles 1-12: | Days 1-28 | ibrutinib 420 mg daily |
| Cycles 13-36: | Days 1-28 | ibrutinib 420 mg daily |

Please refer to chapter 8.5.1 *Administration of ibrutinib* for further information.

The continuous daily administration with a slow dose escalation of venetoclax starts on cycle 1 day 22.

Venetoclax p.o.:

| | | |
|---|---|---|
| Cycle 1: | Days 22-28: | venetoclax 20 mg (2 tabl. at 10 mg) |
| Cycle 2 | Days 1-7: | venetoclax 50 mg (1 tabl. at 50 mg) |
| | Days 8-14: | venetoclax 100 mg (1 tabl. at 100 mg) |
| | Days: 15-21: | venetoclax 200 mg (2 tabl. at 100 mg) |
| | Days 22-28: | venetoclax 400 mg (4 tabl. at 100 mg) |
| Cycles 3-12: | Days 1-28: | venetoclax 400 mg (4 tabl. at 100 mg) |

Due to the risk of adverse events, especially tumor-lysis-syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400mg is reached (ramp-up). In order to diagnose a TLS at an early stage certain safety measures must be followed (see 8.4.2 *Safety precautions with venetoclax*).
Please refer to chapter 8.4.1 *Administration of venetoclax* for further information.

#### 7.1.4.1. Follow up

After the end of therapy and the appropriate staging procedures of initial response assessment and final restaging there will be a regularly follow up until the end of the study as defined in section *7.4.1.3 End of study* .

Visits will take place every three months until disease progression; afterwards annually visits will be performed for documentation of survival and start of new CLL treatment.