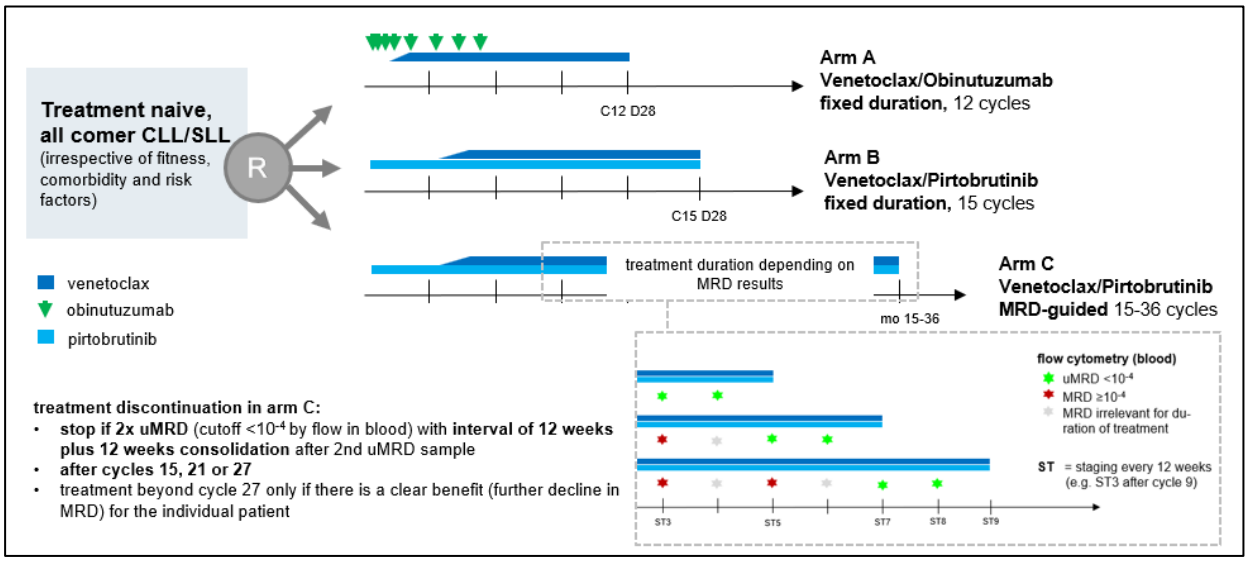
CLL18 / MOIRAI TRIAL

A phase 3 multicenter, randomised, prospective, open-label trial of **fixed-duration** (12 cycles) **venetoclax/ obinutuzumab** vs. **fixed-duration** (15 cycles) **venetoclax/ pirtobrutinib** vs. **MRD-guided venetoclax/ pirtobrutinib** in patients with previously untreated chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) aiming to establish **m**easurement **o**f **i**ndividual **r**esidual disease for **a**djustment of treatment duration to **i**mprove outcomes

DESIGNED AND CONDUCTED BY THE GERMAN CLL STUDY GROUP (GCLLSG) IN COOPERATION WITH

Cancer Trials Ireland, CSG CLL, GELLC, GIMEMA, HOVON, LYSA, Nordic CLL Study Group, PALG, SAKK, ICLLA and ICLLSG

Trial Schema



Study synopsis

Trial objective	The primary objective of the study is to compare the efficacy of MRD-guided Venetoclax/Pirtobrutinib vs fixed-duration (15 cycles) Venetoclax/Pirtobrutinib and MRD-guided Venetoclax/Pirtobrutinib vs. fixed-duration (12 cycles) Venetoclax/Obinutuzumab by measuring progression-free survival (PFS) in patients with previously untreated chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).
Investigational medicinal products (IMPs)	• Venetoclax (Ven, Venclyxto®) • Obinutuzumab (Obi, Gazyvaro®) • Pirtobrutinib (Pirto, Jaypirca®)
Study arms	• Ven-Obi fixed duration over 12 cycles (arm A, standard arm) • Ven-Pirto fixed duration over 15 cycles (arm B) • Ven-Pirto MRD-guided duration of 15 to 36 cycles (arm C)
Primary endpoint	Progression-free survival (PFS)

Secondary endpoints	• Measurable residual disease (MRD) levels by the following different types of measurement from the following materials: - flow cytometry from peripheral blood (PB) and bone marrow (BM) - next-generation sequencing (NGS) from PB performed at - final restaging (performed 3 months after end of treatment in all patients - except for patients that show progression of CLL disease or Richter transformation before this point of time - which differs depending on the duration of treatment) and - selected other time points during and after treatment • Overall response rate (ORR) and complete response (CR) rate at the final restaging and selected other time points • Best response assessed until 1 year after end of treatment • Duration of response (DOR) • Time to next treatment (TTNT) • Treatment-free survival (TFS) • Overall survival (OS) • Safety parameters: Type, frequency and severity of - adverse events (AEs) - adverse events of particular interest (AEPI)
Trial design	• prospective • 3 arms • randomised (1:1:1) and stratified • parallel-group • open-label • phase-III-trial
Population	Adult patients with previously untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).
Sites	approximately 165 sites in the following 16 countries: • Austria • Belgium • Czech Republic • Denmark • Finland • France • Germany • Ireland • Israel • Italy • Netherlands • Norway • Poland • Spain • Sweden • Switzerland
Number of patients	813 eligible patients, i.e. 271 patients per arm.

IMP dosage and method of administration, duration of treatment	**Arm A (Venetoclax/Obinutuzumab, Ven-Obi):** Treatment in the standard arm will be the approved combination of venetoclax/obinutuzumab (Ven-Obi). According to the established treatment schema, Ven-Obi treatment consists of 12 cycles, each with a duration of 28 days resulting in a treatment duration of approximately 11 months. Obinutuzumab is administered intravenously on days 1 (and 2), 8 and 15 of cycle 1, and day 1 of cycles 2-6. The continuous daily administration of venetoclax starts on day 22 of the first cycle with a weekly dose ramp-up from 20mg to 400mg over five weeks with the necessary safety measures needed for mitigation and early detection of a tumour lysis syndrome. Obinutuzumab intravenous (i.v.) infusion: Cycle 1: Day 1: obinutuzumab 100mg i.v. Day 1 (or 2): obinutuzumab 900mg i.v. Day 8: obinutuzumab 1000mg i.v. Day 15: obinutuzumab 1000mg i.v. Cycles 2-6: Day 1: obinutuzumab 1000mg i.v. Venetoclax p.o.: Cycle 1: Days 22-28: venetoclax 20mg (2 tabl. at 10mg) Cycle 2: Days 1-7: venetoclax 50mg (1 tabl. at 50mg) Days 8-14: venetoclax 100mg (1 tabl. at 100mg) Days 15-21: venetoclax 200mg (2 tabl. at 100mg) Days: 22-28: venetoclax 400mg (4 tabl. at 100mg) Cycles 3-12: Days 1-28: venetoclax 400mg (4 tabl. at 100mg) The first dose of obinutuzumab has to be split into a 100mg and a 900mg infusion, which may be administered both after another on the same day (1000mg) if the infusion of a test-dose of 100mg is well tolerated by the patient. If the 100mg test dose infusion on day 1 is not tolerated well, the remaining 900mg have to be administered on day 2. The first dose of venetoclax will be administered on day 22 of the first cycle in hospital/outpatient clinic/private practice. Certain safety precautions depending on the patient´s risk for a tumour lysis syndrome are necessary (see below). Weekly dose ramp-up will be performed on days 1, 8, 15 and 22 of cycle 2 (also with safety precautions). On the days between the dose escalations, patients take the respective dose of venetoclax at home (preferably during or within 30 minutes after breakfast). This slow increase of the dose over five weeks (ramp-up) is necessary due to the risk of tumour lysis syndromes (TLS). In order to diagnose a TLS at an early stage, patients must have a laboratory monitoring before and after the intake of the first dose and the dose escalations (pre-dose before the intake of the first dose at each dose level, i.e. 20mg, 50mg, 100mg, 200mg and 400mg venetoclax and afterwards at least at the first two dose levels. Additionally, patients should have an adequate hydration of ≥2 liters per day orally and potentially also intravenously e.g. in case of an increased TLS risk, should receive a uric acid reducer, e.g. allopurinol and potentially also rasburicase. Some patients have to be hospitalised in case of a significantly increased risk of a TLS. **Arm B and C (Pirtobrutinib/Venetoclax, Ven-Pirto):** The two experimental arms evaluate the combination of pirtobrutinib and venetoclax (Ven-Pirto), arm B in a fixed duration schema over 15 cycles and arm

C with an individualised, MRD-guided treatment duration of 15 to a maximum of 36 cycles. The duration of each cycle is 28 days. In both arms, treatment starts with pirtobrutinib on day 1 of the first cycle and will be continued daily. The daily administration of venetoclax starts on day 1 of the fourth cycle with a weekly dose ramp-up from 20mg to 400mg over five weeks with the necessary safety measures needed for mitigation and early detection of a tumour lysis syndrome.

Pirtobrutinib p.o.:

Cycles 1-15+:	Days 1-28:	pirtobrutinib 200mg (2 tabl. at 100mg)

Venetoclax p.o.:

Cycle 4:	Days 1-7:	venetoclax 20mg (2 tabl. at 10mg)
	Days 8-14:	venetoclax 50mg (1 tabl. at 50mg)
	Days 15-21:	venetoclax 100mg (1 tabl. at 100mg)
	Days 22-28:	venetoclax 200mg (2 tabl. at 100mg)
Cycles 5-15+	Days: 1-28:	venetoclax 400mg (4 tabl. at 100mg)

The first dose of pirtobrutinib will be administered on the first day cycle one under medical supervision (in hospital/outpatient clinic/private practice). From the second dose onwards, patients take the study medication at home (preferably 30 minutes before breakfast).

The first dose of venetoclax will be administered on day 1 of the fourth cycle under medical supervision (in hospital/outpatient clinic/private practice). Certain safety precautions depending on the patient´s risk for tumour lysis syndrome are necessary (see below). Weekly dose ramp-up will be performed on days 8, 15 and 22 of cycle 4 as well as day 1 of cycle 5 (also with safety precautions). On the days between the dose escalations, patients take the respective dose of venetoclax at home (preferably during or within 30 minutes after breakfast).

This slow increase of the dose over five weeks (ramp-up) is necessary due to the risk of tumour lysis syndromes (TLS). In order to diagnose a TLS at an early stage, patients must have a laboratory monitoring at the first dose at each dose level (i.e. 20mg, 50mg, 100mg, 200mg and 400mg venetoclax. Additionally, patients should have an adequate hydration of ≥2 liters per day orally and potentially also intravenously e.g. in case of an increased TLS risk, should receive a uric acid reducer, e.g. allopurinol and potentially also rasburicase. Some patients have to be hospitalised in case of a significantly increased risk of a TLS.

While the treatment in arm B has a predefined “fixed” duration of 15 cycles (with a duration of 28 days), the treatment duration in arm C is MRD-guided and ranges from 15 cycles (as in arm B) to up to 36 cycles. Patients will stop treatment after 15 cycles only if they achieved undetectable MRD in peripheral blood by standardised flow cytometry with the well-established cutoff of 10^{-4} at the end of cycle 9 and 12. In case the patient had still detectable MRD at one of these time points, the combination of Ven-Pirto will be continued until patients achieve undetectable MRD at two stagings with an interval of 12 weeks (e.g. cycles 15 and 18) and thus fulfil the criteria for treatment discontinuation. Treatment should be continued for another 12 weeks after the second uMRD result (as a consolidation). This prolonged treatment can be continued until cycle 27 (i.e. 24 cycles of combination treatment). In case a patient has not yet achieved the goal of two uMRD in two assessments with an interval of 12 weeks plus the consolidation of another 12 weeks by cycle 27, a further continuation of treatment is permitted only if there is a clear benefit with a decreasing MRD level

	(defined as one log reduction between the last two MRD assessments). However, the maximum duration of treatment is 36 cycles (33 cycles of combination treatment).
Trial duration	approximately 6 years
Duration of follow-up	arms A and B: approximately 3 to 5 years (depending on timepoint of recruitment) arm C: approximately 1.5 to 4.5 years (depending on timepoint of recruitment and duration of MRD-guided treatment)
Re-treatment option	At this time point no general recommendation for a re-treatment can be made. However, the investigators may wish to include an optional re-treatment with venetoclax and pirtobrutinib in this trial at a later time point.
Long-term follow up following the end of the study	To be able to collect long term follow up data after the end of the CLL18 study, it is strongly recommended to include the patients in a registry, patients from countries where no country-specific registry is available, a follow-up in the registry of the European research initiative on CLL (ERIC) is encouraged.