### Table 10.2.1 Required investigations at entry, during treatment and during follow up

| | At entry[1] | After each induction cycle | Extra at end of cycle 2 | Cycle 3 day 8 and 15 Cycle 4 day1 | Extra at end of cycle 3 and 6 | Extra at end of cycle 9 | Extra at end of cycle 12 | Extra at day 15 of cycle 15[9] | After cycle 15: Every 3 months for 2 years, every 4 months for 3rd year (= until 51 months) | Extra at month 27 | After month 51[2] | Progressive disease |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Informed consent** | X | | | | | | | | | | | |
| **Medical history** | X | | | | | | | | | | | |
| **Adverse events** | X | X | | | | | | | X | | X | |
| **Physical examination** | X | X | | | | | | | X | | X | X |
| **CIRS / CCI** | X | | | | | | | | | | | |
| **Rapid Report Form** | | | | | X | X | X | | | | | |
| **Binet stage** | X | | | | | | | | | | | |
| **TLS risk category (appendix G)** | X | | X[4] | | | | | | | | | |
| **Lab tests** | | | | | | | | | | | | |
| Hematology | X | X | | | | | | | X | | X | X |
| Blood chemistry | X | X | | | | | | | X | | X | |
| Additional chemistry | X | | | | | | | | | | | |
| **Virology** | X | | | | | | | | | | | |
| **Bone marrow** | | | | | | | | | | | | |
| Bone marrow biopsy | | | | | | | | X | | X | | X |
| **(PET)-CT scan[5]** | X | | X[6] | | | | | X | | X | | X |
| **(Clinical) response evaluation** | | | | | X[7] | X | X | | X | X | X | X |
| **Quality of Life[7]** | X | | | | | | | | X[8] | | X[8] | |
| **Pregnancy test** | X | | | | | | | | | | | |

1. Laboratory tests should be performed within 2 weeks prior to registration flow and CT can be maximally 42 days old
2. Every 6 months until 7 years after registration or until progression, whatever comes first.
3. The form needs to be filled out every 3 months for as long as the patient is on ibrutinib treatment
4. In patients with high risk for TLS or CrCL 30-50 ml/min
5. PET only in case of suspected transformation.

6 CT scan after cycle 2 in patients with high risk for TLS or CrCL 30-50 ml/min

7 Only at end of cycle 3

8. Quality of life at entry, after induction cycle 15 and at 6 months, 1, 2 and 3 years after start maintenance/observation.

9. MRD and CT should be done at day 15 cycle 15 to have results available to assess SD, PR, CR, MRD negativity at end of cycle 15.

### Table 10.2.2 .Collection for central lab.

| | At entry | After each induction cycle | Extra at end of cycle 2 | Cycle 3 day 8 and 15 Cycle 4 day1 | Extra at end of cycle 3 and 6 | Extra at end of cycle 9 | Extra at end of cycle 12 | Extra at day 15 of cycle 15[4] | After cycle 15: Every 3 months for 2 years, every 4 months for 3rd year (= until 51 months) | Extra at month 27 | After month 51 | Progressive disease |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mutational status**[1] PB | X | | | | | | | | | | | |
| Serum parameters | X | | | | | | | | | | | |
| **FISH/CGH and NGS** PB | X | | | | | | | | | | | X |
| **MRD (flowcytometry)** | | | | | | | | | | | | |
| PB | X | | X | | | X | X | X | X[2] | X[2] | | X |
| BM aspirate | | | | | | | | X | | X | | X |
| **Side studies** | | | | | | | | | | | | |
| PB | X | | X | X | | X | X | X | X | X | | X |
| BM aspirate | | | | | | | | X | | X | | X |
| Lymph node biopsy | | | | | | | | | | | | X[3] |

1 If not performed earlier

2 Patients becoming MRD pos. retest 1 month later (only during observation)

3 If accessible lymph node is present

4. MRD and CT should be done at day 15 cycle 15 to have results available to assess SD, PR, CR, MRD neg at end of cycle 15.

### Table 10.2.3 Required investigations during/after reinitiation treatment[1]

| | Before start of reinduction treatment | Extra at end of cycle 3 | Extra at end of cycle 12 | After cycle 12: Every 3 months for 2 years, every 4 months for 3rd year | Extra at 1 year after cycle 12 | After month 51[2] | Progressive disease |
|---|---|---|---|---|---|---|---|
| **Medical history** | X | | | X | | X | |
| **Adverse events** | X | | | X | | X | |
| **Physical examination** | X | | | X | | X | X |
| **TLS risk category (appendix G)** | X | | | | | | |
| **Lab tests** | | | | | | | |
| Hematology | X | | | X | | X | X |
| Blood chemistry | X | | | X | | X | |
| Additional chemistry | X | | | | | | |
| **Bone marrow** | | | | | | | |
| Bone marrow biopsy | | | X | | X | | |
| **(PET)-CT scan** | X | | X | | X | | X |
| **(Clinical) response evaluation** | | X | X | | X | X | X |
| **Quality of Life**[2] | X | | | | | | |
| | | | | | | | |
| **CENTRAL LAB** | | | | | | | |
| **Flowcytometry** PB (or BM if PB not done) | | | | | | | X |
| **FISH/CGH and NGS** PB | | | | | | | X |
| **MRD (flowcytometry)** | | | | | | | |
| PB | | | X | X | X | | X |
| BM aspirate | | | X | | X | | X |
| **Side studies** | | | | | | | |
| PB | | | X | | X | | X |
| BM aspirate | | | X | | X | | X |
| Lymph node biopsy | | | | | | | X[3] |

1 Note that the required investigations from month 27 as mentioned in table 10.2.1 are required for all patients

2. Follow the original schedule: quality of life at 1, 2 and 3 years after start maintenance/observation
3. If accessible lymph node is present

**Medical history**

Standard medical history, including:
- B symptoms
- Concomitant diseases
- Concomitant medications
- Adverse events

At entry
- Proven CLL or SLL by minimal required markers (CD19/CD20/CD5/CD23/Kappa/Lambda)
- Cumulative Illness Rating Score (see appendix F)
- Binet classification (see appendix A)
- Charlson comorbidity index (CCI)

**Physical examination**

Standard physical examination including body weight and height, with special attention for:
- Vital signs (Blood pressure, body temperature, pulse)
- WHO performance status (see appendix C)
- Palpable lymph nodes, spleen and liver sizes

**Hematology**

- Hemoglobin
- Leukocyte count
- Differential count
- Platelets count

At entry and on indication:
- DAT (direct antiglobulin test/Coombs test)
- PT
- PTT

**Blood chemistry**

- Creatinine clearance (calculated see appendix E)
- Bicarbonate
- Haptoglobin
- AST or ALT
- Bilirubine
- LDH

Special attention to tumor lysis lab according to appendix G. Please see appendix G for full details.

**Additional blood chemistry at entry**
- Glucose
- Total protein
- Albumin
- IgG
- IgM
- IgA
- Monoclonal protein
- β-2 microglobulin

**Virology**
- Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).
- Hepatitis C virus (HCV), if positive: HCV- (RNA)
- Human immunodeficiency virus (HIV) positive patients;

**Bone marrow examination** . Bone marrow pathology will be performed locally. Side studies will be performed centrally by bone marrow aspirate.

**(PET-)CT scan**

A (high resolution PET-)CT scan of neck, thorax, abdomen and pelvis and reported according to Cheson criteria. CT scan to determine lymphnode size(s) is obligatory to evaluate CR.

## 10.3 Storage for future studies

In addition to these investigations, all patients will be asked for informed consent to store biological material for future studies. Material for future investigations will be shipped to the central laboratory of the Academic Medical Center Amsterdam and/or Copenhagen University Hospital. More details can be found in the study lab manual. All materials are anonymized and stored for a maximum of 15 years after end of study, after which the samples will be destroyed.

## 10.4 Response evaluation

Response will be evaluated without CT (clinical response) at cycle 3, 9, and 12, after cycle 15 every 3 months for 2 years, and every 4 months for the 3rd year(until 51 months), and month 51 Response will be evaluated with CT at cycle 15 and month 27, and in case of suspected progressive disease. Response will be determined according to the definitions of response in the IWCLL updated NCI-WG guidelines [Hallek et al., 2008] For a tabular summary of all criteria of response definition in CLL patients see Appendix B.

## 10.5 Quality of Life assessment

Health related outcome parameters will be collected in this study, i.e. quality of life (QoL).
QoL will be assessed at entry, after 15 induction cycles and at 6 months, 1, 2 and 3 years after start maintenance/ observation.
The quality of life measurements will be continued after the patient is off protocol treatment, but discontinue when progression has been observed.

- EORTC QLQ-C30 questionnaire
- EORTC QLQ-CLL16