SAMENVATTING HOVON 141

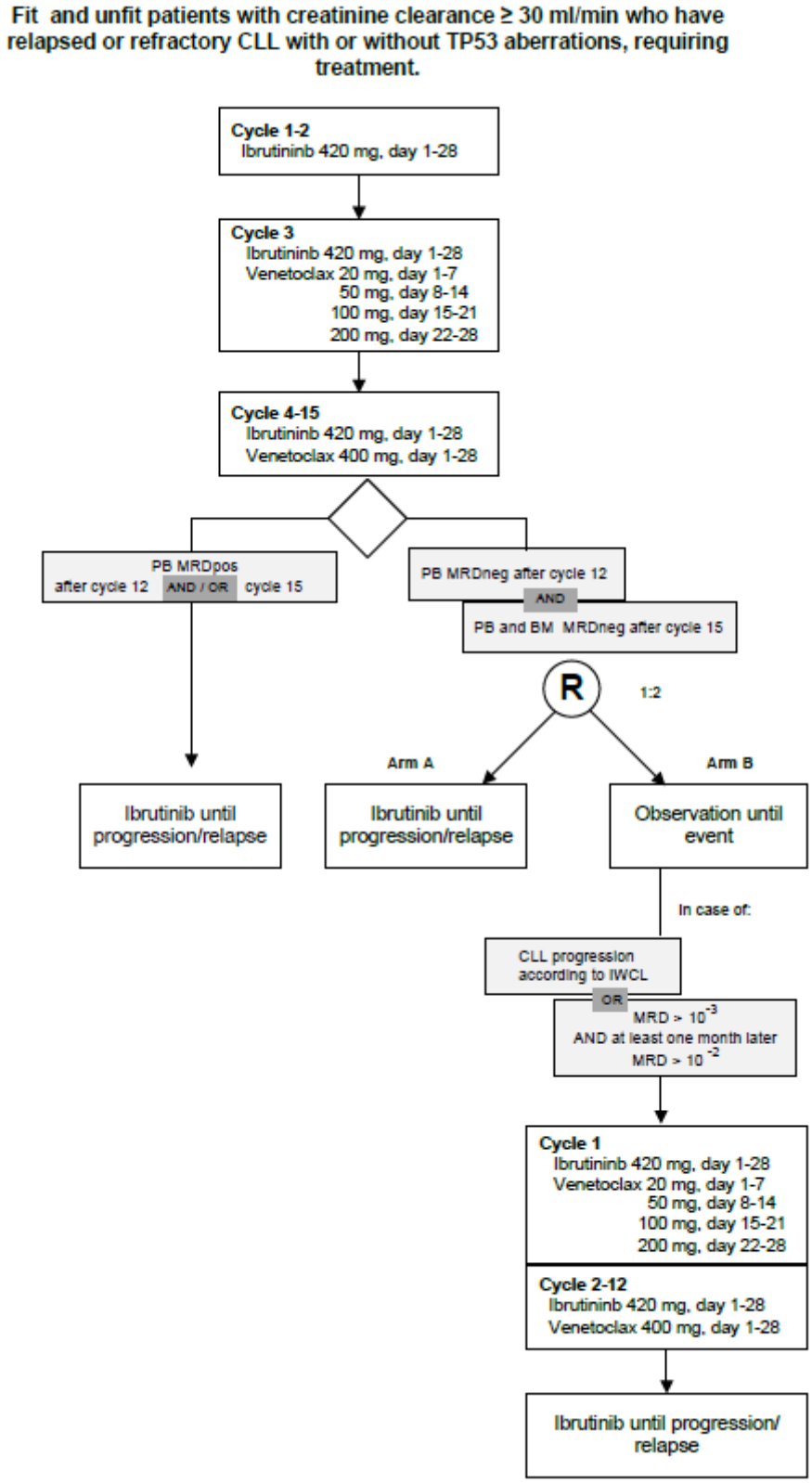
TITEL

A prospective, multicenter, phase-II trial of ibrutinib plus venetoclax in patients with creatinine clearance ≥ 30 ml/min who have relapsed or refractory chronic lymphocytic leukemia (RR-CLL) with or without TP53 aberrations

INDICATIE

Fit (CIRS ≤ 6) and unfit (CIRS >6) patients with a creatinine clearance ≥ 30 ml/min with previously treated CLL with or without TP53 aberrations requiring treatment.

SCHEMA


Fit and unfit patients with creatinine clearance ≥ 30 ml/min who have relapsed or refractory CLL with or without TP53 aberrations, requiring treatment.
Cycle 1-2
Ibrutininb 420 mg, day 1-28
Cycle 3
Ibrutininb 420 mg, day 1-28
Venetoclax 20 mg, day 1-7
50 mg, day 8-14
100 mg, day 15-21
200 mg, day 22-28
Cycle 4-15
Ibrutininb 420 mg, day 1-28
Venetoclax 400 mg, day 1-28
PB MRDpos
after cycle 12 AND / OR cycle 15
PB MRDneg after cycle 12
AND
PB and BM MRDneg after cycle 15
R
1:2
Arm A
Arm B
Ibrutinib until progression/relapse
Ibrutinib until progression/relapse
Observation until event
In case of:
CLL progression according to IWCL
OR
MRD > 10-3
AND at least one month later
MRD > 10-2
Cycle 1
Ibrutininb 420 mg, day 1-28
Venetoclax 20 mg, day 1-7
50 mg, day 8-14
100 mg, day 15-21
200 mg, day 22-28
Cycle 2-12
Ibrutininb 420 mg, day 1-28
Venetoclax 400 mg, day 1-28
Ibrutinib until progression/ relapse

INCLUSIE CRITERIA

♦ Documented CLL or SLL requiring treatment according to IWCLL criteria after either being refractory to first line therapy or relapse after initial therapy.
♦ Age at least 18 years.
♦ Adequate bone marrow function defined as:
- Absolute neutrophil count (ANC) >0.75 x 109/L
- Platelet count >30,000 /μL 30 x 109/L.
- Hemoglobin >8.0 g/dL (5 mmol/L)
Unless directly attributable to CLL infiltration of the bone marrow, proven by bone marrow biopsy
♦ Creatinine clearance (CrCL) ≥ 30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24hr urine collection.
♦ Adequate liver function as indicated
- Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN)
- Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of nonhepatic origin)
- Prothrombin time (PT)/International normal ratio (INR) <1.5 x ULN and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are related to coagulopathy or bleeding disorder).
♦ Negative serological testing for hepatitis B (HBsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every month until 12 months after last dose), negative testing for hepatitis C RNA within 42 days prior to registration.
♦ WHO/ECOG performance status 0-3 (appendix C), stage 3 only if attributable to CLL.
♦ Negative pregnancy test at study entry (for women of childbearing potential).
♦ Male and female subjects of reproductive potential must agree to use both a highly effective method of birth control (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence , or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug.
♦ Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements.
♦ Written informed consent.

Exclusion criteria

- Any prior therapy with ibrutinib and/or venetoclax.
- Transformation of CLL (Richter's transformation).
- Patients with a history of confirmed PML.
- Malignancies other than CLL currently requiring systemic therapies or not being treated in curative intention before or showing signs of progression after curative treatment.
- Known allergy to xanthine oxidase inhibitors and/or rasburicase.
- Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
- Uncontrolled or active infection.
- Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix X).
or anticoagulant therapy with warfarin or phenoprocoumon or other vitamin K antagonists.
Please note: Patients being treated with NOACs can be included, but must be properly informed about the potential risk of bleeding under treatment with ibrutinib.
- History of stroke or intracranial hemorrhage within 6 months prior to randomization.
- Major surgery within 4 weeks of first dose of study drug.
- Use of investigational agents which might interfere with the study drug within 28 days prior to registration.
- Vaccination with live vaccines within 28 days prior to registration
- Pregnant women and nursing mothers.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.