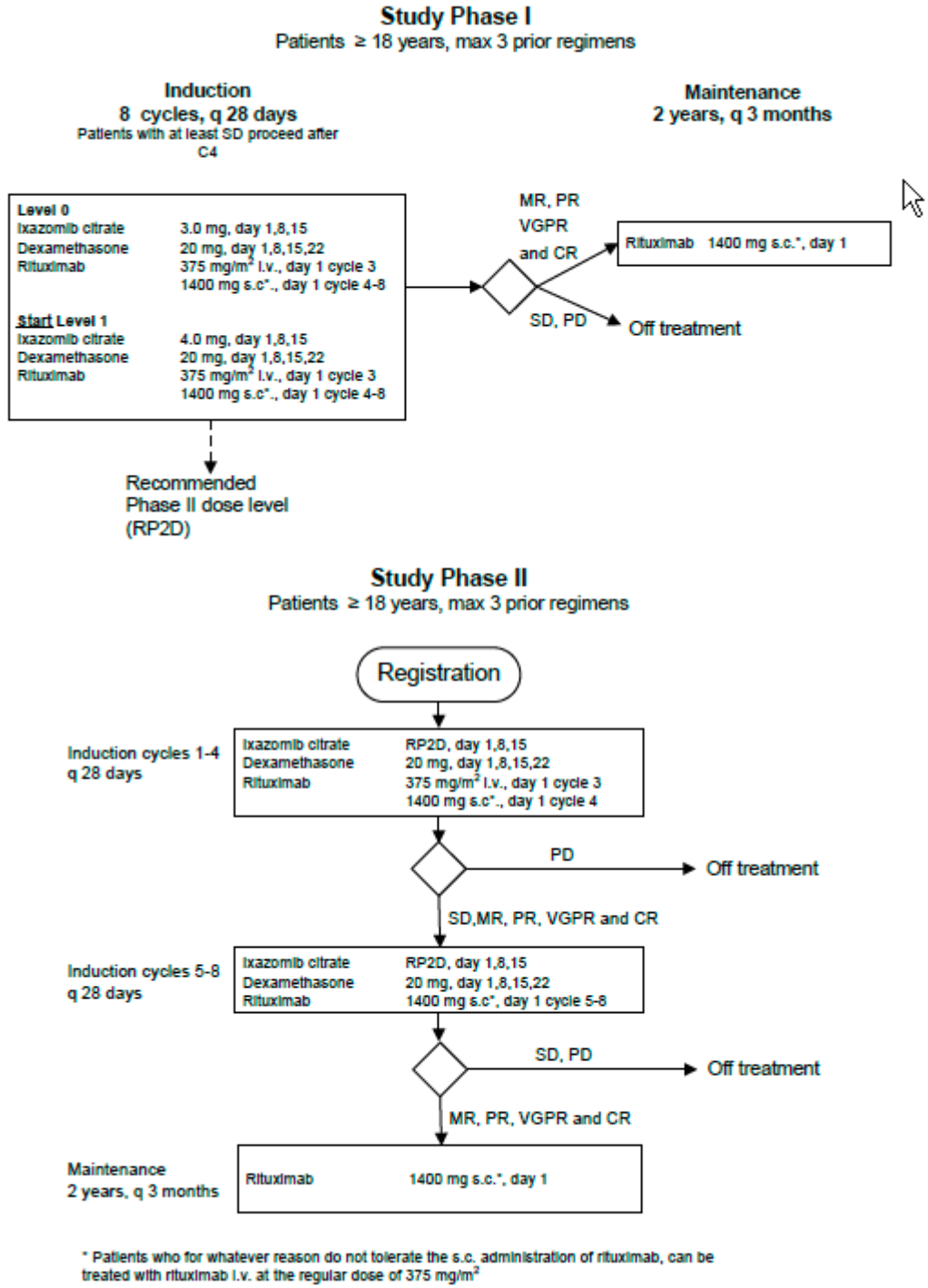
SAMENVATTING HOVON 124/ ECWM-R2

INDICATION

Patients aged 18 years or older with relapsed WM, with ≥1 lines of prior systemic treatment.

STUDY DESIGN



INCLUSION CRITERIA

A diagnosis of relapsed or progressive WM (lymphoplasmacytoid lymphoma in the bone marrow with an IgM M-protein)
♦ Age ≥ 18 years
♦ WHO 0-2
♦ Presence of an IgM M-protein in the serum (as demonstrated by SPEP and IF)
♦ Measurable disease (IgM M-protein > 10 g/l (1 g/dl))or, in case the M-protein is present but unquantifiable, total serum IgM level > 10 g/l (1 g/dl))
♦ Symptomatic disease (see appendix C)
♦ ≥ 1 prior(s) lines of treatment
♦ Patients showing progressive disease under treatment with chemotherapy only (e.g. chlorambucil, CVP, fludarabine or fludarabine/cyclophosphamide) are allowed on study
♦ Platelets > 75x109/l. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
♦ ANC >1.0 x109/l
♦ Negative pregnancy test at study entry for women of childbearing potential
♦ A female patient is either post-menopausal for at least 1 year before the screening visit, or surgically sterile, or, if of childbearing potential, agrees to practice 2 effective methods of contraception at the same time, from the time of signing the informed consent until 12 months after the last dose of rituximab, or agrees to completely abstain from heterosexual intercourse. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
♦ Male patients, even if surgically sterilized, (i.e., status post vasectomy) must agree to practice effective barrier contraception during the entire study period and through 90 days after the last dose of ixazomib and/or rituximab, or agree to completely abstain from heterosexual intercourse. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
♦ Written informed consent
♦ Prior plasmapheresis in case of symptomatic hyperviscosity is allowed

EXCLUSION CRITERIA

♦ Bortezomib refractory (no PR/CR after treatment with bortezomib, and/or progression within 6 months of treatment with bortezomib)
♦ Rituximab refractory (progressive disease during treatment or within 6 months after last administration of rituximab)
♦ Amyloidosis
♦ Peripheral neuropathy, grade 3 or higher, or grade 2 with pain on clinical examination during the screening period. For assessment of the peripheral neuropathy the neuropathy questionnaire tool must be used (see 10.4.2)
♦ Creatinine clearance <30 ml/min according to the Cockroft&Gault formula (see appendix I)
♦ Known HIV seropositivity
♦ Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or history of HBV infection (patients with serological evidence of current or past HBV exposure are excluded unless the serological findings are clearly due to vaccination)
♦ History of organ transplantation including allogeneic stem cell transplantation
♦ Known intolerance of rituximab and/or boron
♦ Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
♦ Bing Neel syndrome, or other forms of central nervous system involvement, or severe neurological disorders

♦ Severe cardiac dysfunction (NYHA classification III-IV; see appendix H)
♦ Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months
♦ Severe pulmonary dysfunction (CTCAE grade III-IV)
♦ Significant hepatic dysfunction (defined as total bilirubin >1.5 ULN (unless caused by Gilbert syndrome) and/or transaminases ≥3 times upper limit of normal, unless caused by WM
♦ Active, uncontrolled infections requiring systemic antibiotic therapy or other serious infections within 14 days before study enrollment
♦ Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, hypertension)
♦ Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and having any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection
♦ Major surgery within 14 days of enrollment
♦ Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administrations of the ixazomib citrate
♦ Systemic treatment, within 14 days before the first dose of ixazomib citrate, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort
♦ Breastfeeding
♦ Current participation in another therapeutic clinical trial (other study medication should have been stopped at least 4 weeks before registration in this trial) and throughout the duration of this trial.
♦ Failure to have fully recovered (i.e., ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
♦ Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib citrate including difficulty swallowing.
♦ Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule