A prospective multicenter Phase 2 Study of the Chemotherapy-free Combination of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib) in Combination with Obinutuzumab (GA 101) in Patients with Previously Untreated Follicular Lymphoma (FL) and a High Tumor Burden

Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class, potent, orally-administered covalently-binding small molecule inhibitor of Bruton's tyrosine kinase currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics, Inc for the treatment of B-cell malignancies.

Obinutuzumab (GA 101) is a first-in-class, potent, intravenously administered type II anti-CD 20 antibody that is developed by Roche AG for the treatment of B-cell malignancies.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

The primary objective of this study is to evaluate the efficacy of the chemotherapy-free combination of ibrutinib and obinutuzumab (GA 101) in patients with previously untreated follicular lymphoma (FL) and a high tumor burden. Primary endpoint to be observed for this is the rate of progression free survival one year after start of therapy.

Hypothesis

The hypothesis of the study is that ibrutinib in combination with obinutuzumab will achieve response rates (CR and PR), rates of MRD negativity and PFS which are comparable to currently used standard rituximab-chemotherapy combinations such as R-CHOP or R-bendamustine in subjects with previously untreated FL and a high tumor burden.

OVERVIEW OF STUDY DESIGN

This is a prospective, multicenter phase 2 study in up to 98 subjects with previously untreated FL and a high tumor burden in advanced stages and in need of therapy. The study will include a central monitoring of MRD by PCR, a central pathologic review and complimentary research projects including monitoring of immune response.

The study therapy comprises an initial 6 cycles of ibrutinib plus obinutuzumab followed by an additional 24 months of ibrutinib plus obinutuzumab maintenance.

In patients being MRD negative at 30 months, i.e. at the end of ibrutinib plus obinutuzumab maintenance, and without clinical progression no further treatment is given while MRD monitoring is continued.

MRD monitoring will be regularly performed on peripheral blood samples collected before the start of therapy and at months 3, 6, 9, 12, 18, 24 and 30 respectively. Subsequently, MRD analyses will be performed every 6 months until clinical progression of the disease or for a maximum of 4 years (until the end of the study).

If MRD assessment on peripheral blood samples turns from positive to negative within the first 30 months, confirmatory blood and bone marrow samples should be taken 6 months thereafter.

In patients remaining MRD positive at 30 months without clinical progression, single agent ibrutinib therapy is continued for another 12 months.

An independent Data Monitoring Committee (DMC) will be formed and constituted. The independent DMC will review the safety of the treatment and make recommendations as to the further conduct of the study.

The data generated by this phase II study should serve as the basis for a subsequent randomized phase III study comparing the chemotherapy-free combination of ibrutinib plus obinutuzumab with standard immune-chemotherapy.

SUBJECT POPULATION

- **Key Eligibility Criteria include:**
  Histologically confirmed follicular lymphoma grade 1, 2 or 3A with a biopsy performed within 12 months before study entry and with material available for central review and complementary scientific analyses
- Ann Arbor stage III/IV, or stage II not suitable for radiotherapy, or stage II bulky disease
- Age ≥ 18 years
- No prior lymphoma therapy
- Need for start of therapy as defined by:
    - bulky disease at study entry according to the GELF criteria (nodal or extranodal mass >7 cm in its greater diameter)
    - and/or B symptoms (fever, drenching night sweats, or unintentional weight loss of >10% of normal body weight over a period of 6 months or less)
    - and/or hematopoietic insufficiency (granulocytopenia < 1.500/µl, Hb < 10 g/dl, thrombocytopenia < 100.000/µl)
    - compressive syndrome or high risk for compression syndrome
    - and/or pleural/peritoneal effusion
    - and/or symptomatic extranodal manifestations
- At least one bi-dimensionally measurable lesion (> 2 cm in its largest dimension by CT scan or MRI)
- Performance status ≤ 2 on the ECOG scale
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows:
    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count ≥ 1500 /µl
    - Platelet count ≥ 75000 /µl
- Women are not breast feeding, are using highly effective contraception, are not pregnant, and agree not to become pregnant during participation in the trial and during the 18 months thereafter (pregnancy testing is mandatory for premenopausal women).
- Men agree not to father a child during participation in the trial and during the 18 months thereafter.
- Written informed consent

Key Exclusion Criteria are:
- Transformation to high-grade lymphoma (secondary to “low grade” FL)
- Grade 3B follicular lymphoma
- Presence or history of CNS disease (either CNS lymphoma or leptomeningeal lymphoma).
- Known hypersensitivity to any of the study drugs

- Known sensitivity to murine products
- Regular use of corticosteroids during the last 4 weeks, unless administered at a dose equivalent to < 20 mg/day prednisone.
- Concomitant use of strong CYP3A4 inhibitors and / or oral anticoagulants (warfarin and/or phenprocoumon)
- Prior or concomitant malignancies except:
    - non-melanoma skin cancer or adequately treated in carcinoma in situ of the cervix
    - Other malignant diseases not specified above which have been curatively treated by surgery alone and from which subject is disease-free for ≥5 years without further treatment
- Serious disease interfering with a regular therapy according to the study protocol:
    - Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification
    - pulmonary (e.g. chronic lung disease with hypoxemia)
    - endocrine (e.g. severe, not sufficiently controlled diabetes mellitus)
    - renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min)
    - impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2,0 mg/dl (unless caused by known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome])
- Positive test results for chronic HBV infection (defined as positive HBsAg serology) Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Known history of HIV seropositive status.
- Patients with a history of confirmed PML
- Vaccination with a live vaccine within 28 days prior to registration
- Recent major surgery (within 4 weeks prior to the start of Cycle 1)
- History of stroke or intracranial hemorrhage within 6 months prior to registration
- Serious underlying medical conditions, which could impair the ability of the patient to undergo the treatment offered in the study (e.g. ongoing infection, gastric ulcers, active autoimmune disease)
- Treatment within a clinical trial within 30 days prior to trial entry.
- Prior organ, bone marrow or peripheral blood stem cell transplantation
- Known or persistent abuse of medication, drugs or alcohol
- Any other co-existing medical or psychological condition that will preclude participation in the study or compromise ability to give informed consent.

DOSAGE AND ADMINISTRATION

Initial therapy will comprise 6 cycles of ibrutinib plus obinutuzumab:

Ibrutinib will be administered orally at a dose of 560 mg once daily every day until the start of maintenance for a total of 24 weeks.

Obinutuzumab will be applied at a dose of 1000 mg by intravenous infusion on days d 1, 8, 15 of cycle 1 and on day 1 of cycles 2-6 to be given every 21 days.

Maintenance therapy will comprise another 24 months of ibrutinib plus obinutuzumab in patients with clinical remission 21 days after the last induction cycle:

Ibrutinib will be administered orally at a dose of 560 mg once daily every day for another 24 months.

Obinutuzumab will be applied at a dose of 1000 mg by intravenous infusion every 2 months for a total of 24 months.

The total duration of ibrutinib plus obinutuzumab therapy will therefore be 30 months

Extended maintenance

In patients remaining MRD positive at 30 months ibrutinib is continued for another 12 months. In this case the total duration of ibrutinib therapy will be 42 months.

EFFICACY EVALUATIONS

Assessment of tumor response and progression will be conducted in accordance with the 2007 Revised Response Criteria for Malignant Lymphoma. Efficacy evaluations include physical examination including lymphoma B symptoms computed tomography scans, magnetic resonance imaging, if applicable, bone marrow aspirate and biopsy, or other procedures as necessary. Efficacy evaluations will be performed after 6 cycles of induction treatment, and every 6 months after induction until clinical progression. Subjects who discontinue treatment prior to disease progression will have regularly scheduled disease evaluations until disease progression, death, or study end, whichever occurs first. For all subjects, survival and subsequent antineoplastic therapy data will be collected until lost to follow-up, withdrawal of consent, or study end.

In addition MRD is assessed by PCR on peripheral blood samples collected before the start of therapy and at months 3, 6, 9, 12, 18, 24 and 30 respectively. Subsequently, MRD analyses will be performed every 6 months until clinical progression of the disease or for a maximum of 4 years (until the end of the study).

If MRD assessment on peripheral blood samples turns from positive to negative, confirmatory blood and bone marrow samples should be taken 6 months thereafter (during the study duration).

SAFETY EVALUATIONS

Safety evaluations include: adverse event monitoring, physical examinations, evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, coagulation, serum chemistry, serum immunoglobulin [IgG, IgM, IgA], and $beta_2$-microglobulin). All adverse events that occur between the subject registration until completion of the subject's last study-related procedure (which may include contact for follow-up of safety) will be collected. Infections and secondary malignancies will be reported

during the whole duration of the trial. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. Intracranial hemorrhage, major hemorrhage, tumor lysis syndrome, serious infusion related reactions and serious infections have been identified as adverse events of special interest and will require enhanced reporting and data collection. Serious adverse events will be reported according to the GCP regulations.

STATISTICAL METHODS

The study will enroll a maximum of 98 subjects based on the following considerations:

In advanced stage follicular lymphoma (FL) long lasting periods of progression-free survival of about 10 years are currently achieved by standard immuno-chemotherapy including two years of maintenance. Still, FL remains an incurable disease, and relapses constantly occur. New therapies must therefore not only aim at a further enhancement of anti-lymphoma activity but also at a reduction of treatment associated side effects and long term toxicities such as secondary malignancies. Ibrutinib plus obinutuzumab may provide a highly attractive chemotherapy-free alternative to standard immuno-chemotherapy by combining a high anti-lymphoma activity with a convenient form of application and by avoiding the objective and subjective disadvantages of standard cytotoxic chemotherapy.

These prerequisites provide the basis for the statistical rationale of the proposed study. It comprises the evaluation of the efficacy and tolerability of the new ibrutinib/obinutuzumab combination in comparison with the estimates from the preceding R-CHOP trial of the GLSG. In addition to progression-free survival as primary endpoint serial measurements of MRD will be performed by PCR during induction and maintenance to not only evaluate the anti-lymphoma efficacy of the new chemotherapy-free ibrutinib/obinutuzumab combination but also to generate information on the duration and effect of maintenance therapy.

Primary Endpoint:

The rate of patients archiving a progression free survival of more than one year after registration (one-year PFS) will serve as early readout for efficacy and will be the primary endpoint of this trial. Chemotherapy without antibody-therapy but with post remission therapy (IFN or high dose therapy with stem cell support) did archive a one-year PFS of 84.5% in the GLSG study comparing CHOP with R-CHOP. For the R-CHOP therapy the one-year PFS was 92.6%, while progression free survival after three years was 73.6%. Using obinutuzumab in combination with chemotherapy and maintenance, at least a progression free survival of 77.4% after three years is expected (hazard ratio 0.74). Using the proportional hazard assumption, the one-year PFS for an obinutuzumab combination with chemotherapy should be about 94.4%. According to the data for chemotherapy without antibodies, the one-year PFS must be better than 85% and the probability to accept a chemotherapy free combination with a real one-year PFS rate ≤ 85% should be safely controlled and smaller than 5%. If a combination has a one year PFS of about 95%, it will be a good candidate for challenging immuno-chemotherapy and the probability for accepting this combination for further evaluation should be about 95%.

So the decision about the new combination will be based on a binomial test of the form

HA: { one-year PFS > 85%} vs. H0: { one-year PFS ≤ 85%}

with a working significance level α=0.05 and a power of 95% for a reference improvement of 10% to 95%. For these parameters the observation of 93 full evaluable patients will be necessary. For a smaller improvement of 9% (8%) the test will then still provide a power of about 90% (80%).

The primary parameter PFS will be evaluated in a full intention to treat way, so that only patients without observed progression or death during the first year but with missing staging result one year after registration will be excluded for the evaluation of the primary endpoint. It is expected, that the rate of non-evaluable patients is smaller than 5%. As secondary sensitivity analysis, we will evaluate the 1-year PFS rate counting patients non-evaluable for the primary endpoint as PFS failures. According to these specifications, the study will enroll a maximum of 98 subjects. PFS will be monitored during the study and if more than 8 failures for PFS are observed during the first year after registration, recruitment will be stopped for futility.

Progression-free survival (PFS) is chosen as primary endpoint since it represents beside overall survival the most relevant parameter for patients. PFS is defined as the time from registration to lymphoma progression or death from any cause.

Secondary Endpoints:

- Progression free survival after start of therapy (continuous observation)
- three-year-PFS
- CR, PR and SD rates at end of induction, CR, PR rates one year after start of therapy and after end of maintenance therapy (at 30 months after start of therapy: CR30)
- Duration of Response
- Percentage of progression during induction and maintenance therapy
- Time to treatment failure after start of therapy (failure defined by failure to achieve a CR/PR after 6 months or progression after CR or PR or death in remission)
- Time to next anti-lymphoma therapy and time to next chemotherapy based treatment
- Treatment associated adverse events
- Percentage of MRD negative patients during induction therapy (midterm), after induction therapy and after maintenance therapy
- Duration of molecular remission for MRD negative patients after the end of induction and maintenance
- Percentage of secondary transformation to aggressive lymphoma
- Percentage of secondary malignancies
- Time to first secondary malignancy
- Overall survival
- percentage of patients with compliance to therapy after 1, 2 and 3 years
- patient-reported lymphoma symptoms and concerns (FACT-Lym)

All secondary endpoints will be evaluated in a descriptive way with 95% confidence intervals provided for numeric estimates. For time event data Kaplan-Meier-Estimates will be provided with 95%-CI for one and three years.

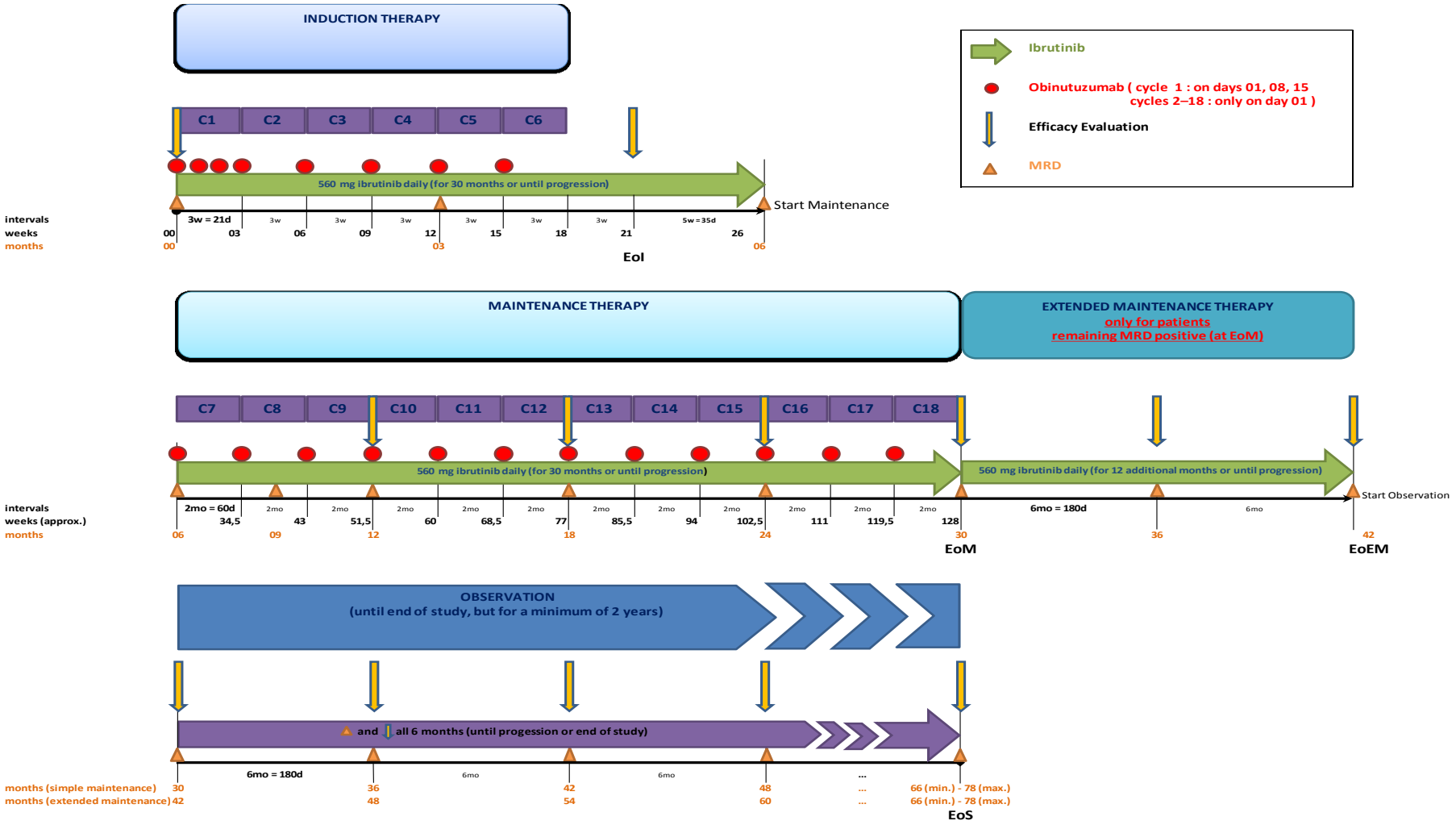
Duration of the Study:

With an expected recruitment of about 100 patients per year, recruitment for the ibrutinib/obinutuzumab combination should be finished within one year. After the end of induction which should be finished after six months, a maintenance phase of two years

follows. In the event of MRD positivity after 30 months without clinical progression single agent ibrutinib therapy is continued for another 12 months (extended maintenance) After the end of maintenance or extended maintenance every patient should be followed without therapy for a minimum of two years. So the study is expected to be closed 6 ½ years after start of recruitment.

Reports:

No interim report for efficacy will be provided before decision of the statistical test. The evaluation of the primary endpoint will be done one year after the end of recruitment, when complete data for all patients for the first year are evaluable. After this evaluation, yearly follow-up reports are provided until the study is closed and the final report is created.


INDUCTION THERAPY
C1
C2
C3
C4
C5
C6
560 mg ibrutinib daily (for 30 months or until progression)
Start Maintenance
intervals
weeks
months
3w = 21d
5w = 35d
00
03
06
09
12
15
18
21
26
EoI
Ibrutinib
Obinutuzumab (cycle 1 : on days 01, 08, 15
cycles 2–18 : only on day 01)
Efficacy Evaluation
MRD
MAINTENANCE THERAPY
EXTENDED MAINTENANCE THERAPY
only for patients
remaining MRD positive (at EoM)
C7
C8
C9
C10
C11
C12
C13
C14
C15
C16
C17
C18
560 mg ibrutinib daily (for 30 months or until progression)
560 mg ibrutinib daily (for 12 additional months or until progression)
Start Observation
2mo = 60d
6mo = 180d
34,5
43
51,5
60
68,5
77
85,5
94
102,5
111
119,5
128
09
12
18
24
30
36
42
EoM
EoEM
OBSERVATION
(until end of study, but for a minimum of 2 years)
and all 6 months (until progession or end of study)
months (simple maintenance)
months (extended maintenance)
30
42
36
48
42
54
48
60
66 (min.) - 78 (max.)
66 (min.) - 78 (max.)
EoS