SUPPLEMENTARY APPENDIX

Feasibility and efficacy of addition of individualized-dose lenalidomide to chlorambucil and rituximab as first-line treatment in elderly and FCR-unfit patients with advanced chronic lymphocytic leukemia

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ONLINE APPENDIX

Title

Feasibility and efficacy of addition of individualized dose lenalidomide to chlorambucil and rituximab as first-line treatment in elderly and FCR-unfit patients with advanced chronic lymphocytic leukemia

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Supplemental tables

Supplemental Table 1. Patient selection criteria

Inclusion criteria
Diagnosis of CLL without prior treatment;
Patients with symptomatic Binet stage A / Rai stage 0 or Binet stage B or C / Rai I, II, III or IV;
Age 65 – 80 years, inclusive, at the time of signing the informed consent form, or age 18 – 64, inclusive, and CIRS ≥ 7;
Able to adhere to the study visit schedule and other protocol requirements;
WHO performance status of ≤ 2;
Laboratory test results within these ranges: absolute neutrophil count ≥ 1.0 x 10^9/l, platelet count ≥ 30 x 10^9/l, creatinine clearance ≥ 60 ml/min, total bilirubin ≤ 25 µmol/l, AST & ALT ≤ 2 x ULN; in case the estimated creatinine clearance is too low (≥40, <60 ml/min) one may determine the Glomular Filtration Ratio (GFR) from creatinine by 24 hours urine collection. This should be ≥ 60 ml/min;
Females of childbearing potential must have a negative serum or urine pregnancy test within 10 – 14 days prior to and again within 24 hours of starting lenalidomide
Patients who are willing and capable to use adequate contraception during the therapy (all men, all women of childbearing potential). Patients must be able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;
Written informed consent.
Exclusion criteria
Patients that are unable or unwilling to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;
Intolerance of exogenous protein administration;
Hepatitis B Ag positive, Hepatitis C positive and/or HIV positive patients;
Patients with uncontrolled Autoimmune Hemolytic Anemia (AIHA) or autoimmune thrombocytopenia (ITP);
Active fungal, bacterial, and/or viral infection;
Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking lenalidomide);

Use of any other experimental drug of therapy within 28 days of baseline;
Known hypersensitivity and/or serious adverse reactions to lenalidomide or similar drugs;
Any prior use of lenalidomide;
Concurrent use of other anti-cancer agents or treatments;
Uncontrolled hyperthyroidism or hypothyroidism;
Patients with history of idiopathic deep venous thrombus and/or pulmonary embolism within last three years;
Neuropathy ≥ grade 2;
History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin; squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, prostate cancer (TNM stage of T1a or T1b);
Current inclusion in other clinical trials;
Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Supplemental Table 2. Lenalidomide management

Reasons to interrupt (and discontinue) treatment with lenalidomide
Neutropenic fever
Neutropenia associated with other toxicity
Thrombocytopenia defined as platelet count <30x10^9/L
Non-blistering rash grade 3 – If ≥ grade 4 lenalidomide therapy was discontinued – Note: lenalidomide therapy was discontinued in case of any grade desquamating (blistering) rash
Sinus bradycardia/other cardiac arrhythmia grade 2 – If ≥ grade 3 lenalidomide therapy was discontinued
Allergic reaction or hypersensitivity grade 2 – If ≥ grade 3 lenalidomide therapy was discontinued
Venous thrombosis/embolism ≥ grade 3
Other non-hematologic toxicity assessed as lenalidomide-related ≥ grade 3
Laboratory tumor lysis syndrome
Hyperthyroidism or hypothyroidism

Supplemental Table 3. Restarting treatment with lenalidomide

Criteria for restarting treatment with lenalidomide*
Absolute neutrophil count ≥ $0.5x10^9$/L
Platelet count ≥ $30x10^9$/L (unless thrombocytopenia due to marrow infiltration)
Any lenalidomide-related allergic reaction/hypersensitivity/rash or sinus bradycardia/other cardiac arrhythmia adverse event that may have been occurred has resolved to ≤ grade 2 severity
Pregnancy test is confirmed negative for women of child bearing potential (test max. 28 days old)
Treatment is not held for more than 28 days (if treatment is held for more than 2 weeks clinically appropriate biochemical monitoring for TLS should be employed). If treatment is required to be held for toxicity > 28 days the subject will go off protocol treatment

*All criteria should be met to enable restarting treatment with lenalidomide. If these conditions are not met, the patients will be followed weekly and lenalidomide will not be initiated until the toxicity has resolved as described above. Lenalidomide dose will be reduced in the new cycle if treatment was held in the previous cycle or in the new cycle on day one. Lenalidomide dose will maintained if dose was reduced in the previous cycle and did not require further delay. If no toxicity occurs, dose can be increased in the following cycle.

Patients who did not tolerate the lowest dose of Len (2.5 mg) due to non-hematological toxicity, discontinued treatment with Len. As for hematological toxicity, patients were able to continue Len following recovery, if the investigators felt that the subject was otherwise benefiting from therapy.

Supplemental Table 4. Prophylactic treatment

Type of prophylaxis	Treatment	Subgroup
Pregnancy prevention	Contraceptive measures	All males and females with child-bearing potential
TLS prophylaxis	Oral hydration Allopurinol 300 mg p.o. daily cycle I, day 1-21 Prednisone 25 mg i.v., clemastine 2 mg i.v. or p.o. and acetaminophen 100 mg p.o. before each rituximab dose	All patients
Tromboembolic prophylaxis	100 mg/day aspirin, cycle I-VI	All patients
Febrile neutropenic profylaxis and prevention of dose reduction/postponement	G-CSG Antibiotics	Patients with neutrophils levels $<1.0x10^9$/L, aiming at 0.5 $x10^9$/L
TFR prophylaxis	Prednison (day 1-3 25 mg, day 4-6 20 mg, day 7-10 10mg, day 11-14 5 mg, then stop) in case of TFR grade >2 NSAIDs in case TFR grade <2	Patients with TFR

Supplemental Table 5. Definition of dose limiting toxicities (DLTs)

Definitions of DLT
Cairo-Bishop grade III or IV tumor lysis syndrome (TLS) defined as
– Presence of laboratory tumor lysis syndrome (LTLS) – Creatinine > 3 x ULN and at least one of the following: – Cardiac arrhythmia: symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator), or life threatening – Seizure in which consciousness is altered, seizure of any kind which are prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)
Tumor flare reaction (TFR) grade IV, defined as Painful enlargement of lymph nodes and/or spleen with associated low-grade fever and rash, resulting is disabling disease
Neutropenic sepsis defined as grade IV sepsis (life-threatening consequences; urgent intervention indicated) Notation: Grade III infections (infections which require intravenous antibiotics) do not count as DLT
Death not due to CLL occurring between start cycle I and 28 days after start of cycle II

Supplemental Table 6. Endpoints as defined in the protocol

Phase I	
Primary endpoints	• Dose-limiting toxicity (DLT) (Supplemental Table 2) • Maximum tolerated dose (MTD) defined as the maximum dose at which only 0/1 of 6 patients exhibit DLT • Recommended part II dose (RDL) defined as the dose of chlorambucil remmended for further study in part II of the study
Secondary endpoints	• Toxicity, especially tumor lysis syndrome (TLS), tumor flare reaction (TFR) and neutropenic sepsis
Phase II	
Primary endpoint	• Response rate on induction I (i.e. treatment cycle 1-6). A patient is considered a responder in case the best response to cycle 1-6 is at least a PR*
Secondary endpoints	• Overall Survival (OS), defined as the time from registration to death from any cause; • Progression-Free Survival (PFS), defined as the time from registration to progression or death from any cause (whichever occurs first) • Induction failure, defined as not achieving at least PR during the 12 cycles of induction treatment (i.e. on protocol treatment) • Event-Free Survival (EFS), defined as the time from registration to induction failure, progression or death (whichever occurs first). EFS for patients with induction failure is set at 1 day • Duration of response, defined as time between date of first response (at least PR) until progression or death from any cause • Improvement of response during induction II, defined as improvement of response after induction II compared to the response of induction I, with the following categories: SD → PR, SD → CR, PR → CR (all improved response), PR → PR, CR → CR (no improvement of response Note: improvement of response is only defined for patients receiving (at least) the first cycle of induction II (i.e. treatment cycle 7); and with response data available. • Overall Survival from start of induction II (OS2), defined as the time from start of treatment cycle 7 to death from any cause. OS2 is only defined for patients receiving (at least) the first cycle of induction II (i.e. treatment cycle 7) • Progression-Free Survival from start of induction II (PFS2), defined as the time from start of treatment cycle 7 to progression or death from any cause (whichever occurs first). PFS2 is only defined for patients receiving (at least) the first cycle of induction II (i.e. treatment cycle 7)

*

Supplemental Table 7. Number of patients included in the phase 2 part of the study that received G-CSF support indicated per cycle

G-CSF per cycle	N patients no G-CSF	N patients yes G-CSF	N Total patients per cycle
Induction-I Cycle 1	51	2	53
Induction-I Cycle 2	46	5	51
Induction-I Cycle 3	39	9	48
Induction-I Cycle 4	32	15	47
Induction-I Cycle 5	28	19	47
Induction-I Cycle 6	26	21	47
Induction-II Cycle 1	34	8	42
Induction-II Cycle 2	32	9	41
Induction-II Cycle 3	31	7	38
Induction-II Cycle 4	28	9	37
Induction-II Cycle 5	29	7	36
Induction-II Cycle 6	28	8	36