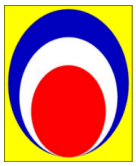

Venetoclax, lenalidomide and rituximab in patients with relapsed/refractory mantle cell lymphoma (VALERIA)

NORDIC LYMPHOMA GROUP

NLG-MCL7 (VALERIA)

EudraCT number: 2017-001060-38

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SYNOPSIS

Total number of patients:

9-24 in phase I portion, +44-47

In total: 56-68 pts (3 or 6 patients in phase 1 will be part of the phase 2 cohort)

Expected accrual time:

Jan 2018 – Nov 2021

Study design

A phase I-II, open-label multicenter trial

Primary endpoint

The primary efficacy variable is the evaluation of overall response rate (ORR) at 6 months with lenalidomide-venetoclax and rituximab, in patients with relapsed or refractory mantle cell lymphoma (MCL), using an MRD driven strategy

Secondary endpoints (evaluated at 24 months)

1. ORR in patients previously treated with ibrutinib
2. ORR in patients with *TP53*-mutation and/or 17p deletion
3. Progression-free survival (median)
4. Response duration (median)
5. Molecular remission rate by PCR according to EURO-MRD guidelines
6. Overall survival (median)

7. Health-related quality of life
8. Safety (Grade 3-4 AE according to CTCAE v 4.03)
9. Evaluation of biomarkers for efficacy, by mutational profile and immunohistochemistry

Key criteria for patient selection:

1. Age >18 years
2. Histologically confirmed (according to the WHO classification) MCL stage I-IV
3. Who have received at least 1 prior rituximab-containing chemotherapy regimen, with documented relapse or disease progression following the last anti-MCL treatment

Treatment plan:

Phase 1

The phase 1 will consist of 3 groups with escalating doses of venetoclax and lenalidomide, using an MRD driven strategy.

Definition of dose limiting toxicity

Dose-limiting toxicity (DLT) is defined as a grade 3 or greater non-hematologic toxicity within the first 8 weeks of therapy (exceptions below).

Exceptions

1. Non-hematologic toxicity attributed to rituximab is not counted as DLT.
2. For nausea, vomiting, or diarrhoea, subjects must have a Grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT.
3. Grade 3 transaminitis (serum transaminase >5 x and ≤20 x ULN) must be present for ≥ 7 days to be considered a DLT.
4. If symptoms indicating DLT is attributed to progressive disease, it will not be counted as a DLT.

Dose finding schedule in phase I

The phase I part of the study will follow a sequential dose escalation, '3 + 3' design. Initially, three subjects are started on treatment with dose regimen A. After the third subject completed 8 weeks of treatment, if no DLT occurred, the next group of three subjects is treated at the next dose level (B). If one of the three initial subjects experienced a DLT, the cohort of subjects will be expanded to six subjects. If less than two out of the six subjects experienced a DLT, then the next higher dose group will be initiated. If two or more (of a cohort of up to six) subjects experienced a DLT, no higher dose levels will be tested and the MTD has been exceeded. Intra-patient dose escalation is not permitted. If two or more subjects, out of 6, in Group A experience a DLT, the next group of 3 patients will be treated in the de-escalation Group X.

The MTD is defined as the highest dose studied for which the incidence of DLT is less than two out of the six subjects during the first 8 weeks of treatment.

Amendment v 1.6

After evaluating 3 patients each in Groups A, B and C, after 8 weeks of treatment, no DLT were encountered in Groups A and B. In Group C, 2 out of 3 patients were hospitalized for grade 3 and 4 infection, and the MTD was considered to have been exceeded. To investigate further dose levels, NLG-MCL Working Group decided to include patients at one more dose level, Group Y (below), before settling on a recommended phase 2 dose.

Amendment v 1.8

The phase 1 was completed in December 2019 and dose group Y selected as the recommended phase 2 dose.

Dose Escalation Schema

COHORT	Target Venetoclax Dose	Lenalidomide Dose[c]	Rituximab Dose[d]
Group A	400[a]	15	375/1400
Group B	400[a]	20	375/1400
Group Y	600[b]	15	375/1400
Group C	800[b]	20	375/1400

Group X[e]	400[a]	10	375/1400

a. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, for one week each

b. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, 400 mg for one week each

c. With corresponding dose-reduction, as necessary, for those with impaired renal function

d. 375 mg/m2 IV cycle 1, day 1; 1400 mg sc days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11

e. De-escalation cohort.

Phase 2

Treatment will be given according to dosing below, with an MRD driven strategy.

- Venetoclax, p o. RP2D 600 mg, with ramp up as above, starting at 20 mg QD days 1-7.
- Lenalidomide: RP2D 15 mg p o, days 1-21
- Rituximab 375 mg/m2 i v Day 1, cycle 1. 1400 mg sc,days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11.

Evaluations during treatment

- Minimal residual disease (MRD) (RQ-PCR of blood according to EURO-MRD guidelines) and computed tomography (CT) is performed every 3 months
- A [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET-CT) is performed after 6 months (for evaluation of primary endpoint)
- When MRD-negative in blood according to EURO-MRD guidelines for deescalating treatment, treatment will continue for another 3 months, when a new evaluation of MRD in blood and bone marrow will be performed. If MRD-negativity is confirmed, treatment is stopped and the patient will be followed with MRD and CT every 3 months for up to 24 months.
- Patients without bone marrow/blood involvement by RQ-PCR at baseline or where a probe for MRD cannot be constructed, are followed by PET-CT every 3 months. When PET-CT is negative (Deauville score 1-2), treatment will continue for another 3 months,

when a new PET-CT is performed. If PET-negativity is confirmed, treatment is stopped and the patient will be followed with PET-CT every 3 months for up to 24 months.

- When MRD-positivity occurs, according to EURO-MRD guidelines for escalating treatment, without a clinical relapse: the treatment will be restarted, after CT, bone marrow and clinical evaluation. If low risk for tumor lysis syndrome, the treatment will be started at full dose, at RP2D. In case of higher tumor burden, Venetoclax (VEN) will be ramped up as above.
- If MRD – negativity is not attained, treatment will continue until clinical progression, for up to 24 months.