1. SUMMARY

<table>
<tr><td rowspan="2">Name of Sponsor:
International Extranodal Lymphoma Study Group – IELSG</td><td colspan="2">Investigational Medical Product:
RAD001 (Everolimus)</td></tr>
<tr><td>Study number:
IELSG 34</td><td>EudraCT mumber:
2009-011725-14
ClinicalTrials.gov ID:
NCT01164267</td></tr>
<tr><td colspan="3">Title of the study:
A Multicentre Phase II study to evaluate the clinical activity and the safety profile of everolimus (RAD001) in marginal zone B-cell lymphomas (MZL)</td></tr>
<tr><td colspan="3">Study Centres and Principal Investigators:
Emanuele Zucca (Chairperson and Principal Investigator), IOSI, Bellinzona, Switzerland
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Luca Arcaini, Policlinico San Matteo, Pavia, Italy
Giovanni Martinelli, European Institute of Oncology, Milan, Italy
Umberto Vitolo, Ospedale San Giovanni Battista, Torino, Italy
Liliana Devizzi, Istituto Nazionale Tumori, Milan, Italy
Monica Balzarotti, Humanitas Cancer Centre, Rozzano, Italy</td></tr>
<tr><td colspan="2">Study period
First subject enrolled: 28 August 2010
Last subject completed: 11 December 2012
Last follow-up: 13 March 2013</td><td>Phase of development
II</td></tr>
<tr><td colspan="3">Objectives
<u>Primary objective</u>: Overall response rate of everolimus in MZL patients, including primary extranodal, splenic and nodal entity.
<u>Secondary objectives</u>: progression-free survival, duration of response, safety profile of RAD001 in this population.</td></tr>
<tr><td colspan="3">Study design and Methodology
Multicenter open-label uncontrolled phase II study according to the Simon’s optimal two-stage design. In the first stage, 15 patients were to be treated; if >1 objective response was observed, patient accrual was to be continued and 10 further patients were to be evaluated up to 25 patients in total. If >5 out of 25 patients showed partial or complete response, the study treatment was to be considered worth of further development.
Oral Everolimus was given daily at a dose of 10 mg/day up to 6 cycles (1 cycle=28 days) or until disease progression, whichever occurred earlier. Patients with complete or partial response were allowed to continue the study treatment beyond cycle 6 until disease progression if well tolerated.
Screening assessments to be performed in the 3 weeks preceding treatment start included clinical assessments (physical examination, vital signs, performance status), laboratory tests (hematology, blood chemistry, serology for hepatitis B and C and HIV) and tumor assessment (total body CT-scan, esophagogastroduodenoscopy or colonscopy where indicated, bone marrow biopsy and aspiration, and pregnancy test, if applicable). Clinical visits and routine hematology and blood chemistry were to be repeated on day 1 and 15 of each treatment cycle, while tumor assessment was to be repeated at cycle 3 and 6 and after treatment discontinuation in patients with no tumor progression every 3 months during the first year and every 6 months thereafter.</td></tr>
<tr><td colspan="3">Number of subjects (planned and analyzed)
Planned: 25
Actual: 30
Analyzed:
<u>Safety population:</u> (all patients receiving at least one IMP dose): 30
<u>Efficacy population:</u> (all patients included in the primary endpoint analysis, i.e., overall response rate): 24</td></tr>
</table>

Eligibility Criteria

Inclusion criteria:

- Histologically proven diagnosis of marginal zone B-cell lymphoma relapsing/refractory following at least one prior systemic treatment (chemotherapy and/or monoclonal antibodies)
- Any stage (Ann Arbor I-IV)
- No evidence of histological transformation to aggressive lymphoma
- Measurable or evaluable disease
- Age ≥18 years
- Life expectancy of at least 3 months
- ECOG performance status
- No prior diagnosis of neoplasm within 5 years, except cervical type 1 intraepithelial neoplasia or localized non-melanomatous skin cancer
- In case of prior diagnosis of solid organ tumors, no treatment over the last 5 years and no current evidence of disease
- No prior chemo- or radiotherapy in the last 6 weeks, no prior immunotherapy in the last 8 weeks, no corticosteroids during the last 4 weeks unless low-dose prednisone chronically administered for indications other than lymphoma or lymphoma-related symptoms
- No major impairment of bone marrow, renal or liver function, unless due to lymphoma
- No evidence of opportunistic infections, no HIV infection. Patients with chronic active hepatitis and chronic persistent hepatitis B and C as well as other active viral infections were allowed to participate and were to undergo specific monitoring and prophylactic treatment
- Women of childbearing potential had to use effective contraception, and had not to be breast-feeding or pregnant and had to agree not to become pregnant during trial participation and during 12 months thereafter. Male participants had to agree not to father a child during study participation and during 12 months thereafter
- No serious cardiac, neurological or psychiatric disorders potentially hampering compliance with the study protocol and follow-up schedule
- Fasting serum cholesterol ≤200 mg/dL or ≤5 mmol/L and fasting triglycerides ≤200 mg/dL. In case one or both thresholds were exceeded, the patient could be included after initiation of proper lipid lowering medication
- Written informed consent

Exclusion criteria:

- Patients with newly diagnosed marginal MZL
- Patients with concomitant or past haematological malignancies
- Presence or history of central nervous system lymphoma localization (either parenchymal or leptomeningeal disease)
- Cardiovascular disease (congestive heart failure; NYHA III or IV), unstable angina pectoris, significant arrhythmias requiring chronic treatment, or prior history of myocardial infarction in the last 3 months
- Serious underlying medical condition which could impair the ability of the patient to participate in the trial (e.g., uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease, ongoing infection such as HIV or hepatitis, liver disease such as cirrhosis or decompensated liver disease)
- Concurrent anticancer drugs/treatments and experimental drugs. Previous radiation is allowed, uless the indicator lesion(s) are in the irradiated field
- Previous organ transplantation
- Participation in another clinical trial within 30 days prior to trial entry
- Pregnant or lactating women

Test product, dose and mode of administration

RAD001 (everolimus) was to be taken orally by the patients in an outpatient setting at a dose of 10 mg/day, once daily from day 1 to day 28 of each cycle. The study drug was to be taken at the same time every day in fasting conditions or after a light fat-free meal.

RAD001 5 mg tablets were supplied free of charge by the manufacturing company Novartis.

Specific treatment modification criteria (temporary dosing interruption, dose reduction, treatment withdrawal) were to be applied for severe/intolerable adverse reactions.

Duration of treatment
RAD001 dosing was to be continued for 6 cycles (1 cycle=28 days) or disease progression, whichever occurred earlier. Patients with partial or complete response were allowed to continue the study treatment beyond cycle 6 if well tolerated.

Criteria for evaluation
Primary end-point:
Tumor response assessed according to the "*Revised response criteria for malignant lymphoma*" (Cheson BD et al, 2007) or – for primary gastric localizations - the endoscopic and histological criteria of the *Groupe d'Etude des Lymphomes de l'Adulte* (GELA) .

Secondary end-points
1) Progression-free survival: for all patients, time from study entry to disease relapse/progression or death from any cause
2) Duration of response: for patients achieving partial or complete response, time from first assessment of response to disease relapse/progression
3) Incidence and severity of adverse events classified according to the NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events, version 3.0) scale

Statistical methods
The Simon's optimal two-stage design with a significance level of 5% and a power of 80% was applied.

The treatment was to be considered ineffective if the response rate was <20%.

In the first stage, 15 patients were to be treated; if >1 objective response was observed, patient accrual was to be continued and 10 further patients were to be evaluated up to 25 patients in total. If >5 out of 25 patients showed partial or complete response, the study treatment was to be considered worth of further development.
The final response rate was to be calculated with its 95% confidence interval.

Progression-free survival and duration of response were to be analyzed applying the Kaplan-Meier method.

Summary:
Efficacy Results
Six out of 30 enrolled patients were not evaluable for the primary efficacy endpoint due to early treatment discontinuation and were excluded from the overall response rate evaluation.
In total 6 objective responses were observed in 24 evaluable patients (25%; 95%CI: 10%-47%): one complete response and 5 partial responses. Disease stabilization was reported in 11 patients (46%; 95%CI: 26%-67%), while 7 patients (29%; 95%CI: 13%-51%) had disease progression as best response to treatment.
The median progression-free survival calculated on all 30 patients receiving at least one RAD001 dose was 14 months, with a projected progression-free survival of 29% (95%CI: 9%-52%), while the median duration of response (complete and partial responses) was 6.8 months.

Safety Results

Adverse events were analysed in 30 patients receiving at least one RAD001 dose, and 140 cycles. The most frequent adverse event was thrombocytopenia, which was reported in 28 patients overall (93.3%), of Grade 3 in 5 (16.7%), followed by stomatitis, observed in 23 patients (76.7%), of Grade 3 in 3 (10.0%) and of Grade 4 in 1 (3.3%). Other common adverse events were neutropenia (15 patients, 50.0%), cutaneous rash (12 patients, 40.0%), leukopenia, infection, asthenia, hypercholesterolemia (8 patients each, 26.7%).

Three Grade 4 adverse events were reported: neutropenia, stomatitis and infectious pneumonia. This last event had a fatal outcome and was considered related to the study treatment.

In addition to this fatal event, six non-fatal serious adverse events were reported, of which 4 had a suspected relationship to the study treatment: Grade 3 stomatitis, Grade 2 acute renal failure, Grade 2 pleural effusion, and Grade 3 pneumonia.

RAD001 dose reduction was required because of adverse events in 9 of patients (30.0%) and 10 patients (33.3%) discontinued the study treatment for safety reasons.

Conclusions
In this multicenter phase II trial of single agent oral RAD001, 30 patients in total were enrolled and 24 were evaluable for the primary endpoint, i.e., overall response rate.
RAD001 displayed clinical activity, with an overall response rate of 25% and 46% of patients showed

disease stabilization as best tumour response. The median progression-free survival was 14 months.
These results may suggest a pathogenic relevance of the mTOR pathway in MZL and appears in keeping with the results reported in mantel cell lymphoma and other histologic subtypes. RAD001, however, does not appear to be a valuable treatment option considering that the observed level of activity was relatively modest, and that significant treatment-related, difficult to manage adverse events were reported, namely stomatitis in over 2/3 of patients, and severe pulmonary diseases such as interstitial pneumonitis (3 patients), dyspnoea (2 patients), and bronco-pulmonary infections (4 patients, one with fatal outcome).
RAD001 may therefore not be considered an acceptable treatment option, also in light of the fact that MZLs are often an indolent type of disease, for which more active and tolerable therapies are required. Alternative strategies, perhaps combination regimens, could be investigated to potentiate activity and overcome the otherwise limited applicability of RAD001 in this setting.

Date of report: 09/01/2016