Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication(s)

Non-Hodgkin's lymphoma

Protocol Number

CRAD001C1104

Protocol Title

A phase I dose escalation study of RAD001 administered in Japanese patients with relapsed or refractory non-Hodgkin's lymphoma

Clinical Trial Phase

I

Phase of Drug Development

III

Study Start/End Dates

12-Mar-2008 to 28-May-2014 (Database lock)

Study Design/Methodology

This was an open label, non-randomized, sequential dose escalation phase I study of RAD001 administered in adult Japanese patients with relapsed or refractory non-Hodgkin's lymphoma. Safety, tolerability, and pharmacokinetics at 5 mg/day and 10 mg/day were evaluated as the primary endpoints with a treatment cycle of 28 days.

Note: As of the cut-off date (17-Dec-2008) for the core clinical study report (CSR), five patients were still on-study. Additional data for these five patients were reported in a final close-out clinical study report.

Centers

8 centers in one country: Japan

Publication

Tobinai K, Ogura M, Maruyama D, et al. (2010) Phase I study of the oral mammalian target of rapamycin inhibitor everolimus (RAD001) in Japanese patients with relapsed or refractory non-Hodgkin lymphoma. Int J Hematol; 92:563-70.

Objectives:

Primary objectives:

- To assess the safety and tolerability of RAD001 in Japanese patients with relapsed or refractory non-Hodgkin's lymphoma
- To assess pharmacokinetics in Japanese patients

Secondary objective:

- To seek preliminary evidence of efficacy in this population

Test Product (s), Dose(s), and Mode(s) of Administration

The dose of RAD001 was 5 mg/day or 10 mg/day. Patients were instructed to take one 5 mg tablet or two 5 mg tablets oral once-daily.

Statistical Methods

The recommended dose (5 or 10 mg daily dose) would be the highest safe and tolerable dose, and was investigated based on incidence of dose limiting toxicity (DLT) and clinical safety assessment. A Bayesian logistic model estimation approach for probability of incidence of DLT might be used for dose escalation / recommendation with clinical assessment of toxicity and safety profiles.

Six patients would be continuously recruited in the initial cohort (5 mg). If DLT was observed in $\leq$ 2/6 patients at 5 mg, dose escalation to 10 mg would be discussed based on the Bayesian estimates and clinical assessment. Otherwise ($\geq$ 3/6), this study would be stopped. In case of the dose escalation to 10 mg, 6 patients would be continuously recruited in the cohort. If DLT was observed in $\leq$ 2/6 patients at 10 mg, then the recommended phase II dose would be discussed and determined based on the Bayesian estimates and clinical assessments. If DLT was observed in $\geq$ 3/6 patients at 10 mg, then 5 mg would be declared as the recommended dose.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients must have histopathologically confirmed diagnosis of non-Hodgkin's lymphoma
- Patients must have disease that is either relapsed or refractory after at least one prior treatment regimen and must not be eligible for any standard treatments

- Patients must not have received autologous stem cell transplant at least within 12 weeks prior to study treatment. If patients received autologous stem cell transplant more than 12 weeks ago, they must be fully recovered from the side effects of such treatment
- Patients who have not received autologous stem cell transplant must be either ineligible for the treatment or, if eligible, patients must have chosen not to receive stem cell transplant
- Patients must have at least one measurable lesion
- Age above 20 years old
- Performance Status 0, 1, or 2 on Eastern Cooperative Oncology Group (ECOG) scale
- Patients with a life expectancy of at least 12 weeks
- Patients must be willing to provide portion of bone marrow aspirate and biopsy during study

Exclusion criteria:

- Patients with history of another primary malignancy that is currently clinically significant or currently requires active intervention
- Patients with prior allogeneic stem cell transplant
- Patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study
- Patients who have received radiation therapy for ≤ 28 days prior to first study treatment or who have not recovered from side effects of such therapy.
- Patients who have received any other investigational agents ≤28 days prior to the first study treatment
- Patients who have received anti-neoplastic therapy within 28 days (60 days for monoclonal antibody or radioimmunotherapy) prior to the first study treatment or who have not recovered from side effects of such therapy
- Patients who have received treatment with oral or intravenous steroids or any immunosuppressive agents ≤ 28 days prior to the first study treatment
- Patients who have received prior therapy with RAD001 or other mTOR inhibitors
- Patient with prior therapy of > 450 U bleomycin
- Patients with an active, bleeding diathesis.
- Treatment with any hematopoietic colony-stimulating growth factors (e.g., G-CSF) ≤ 14 days prior to the first study treatment
- Patients who have an impairment of gastrointestinal function or who have gastrointestinal disease that may significantly alter the absorption of study treatment

(e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)

- Patients with active respiratory (excluding interstitial lung disease), skin, mucosal, renal, neurological, or ocular disorder of grade > 1
- Patients with a history of interstitial lung disease of grade ≥ 1
- Patients with a known history of human immunodeficiency virus seropositivity, hepatitis B or C seropositivity

Other protocol-defined inclusion/exclusion criteria may apply

Results

Data in all tables were based on the cut-off date on 17-Dec-2008; the tables were not rerun at the time of the final database lock (28-May-2014), therefore, these tables do not include data for the 5 ongoing patients.

Participant Flow Table

Disposition Reason	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
Ongoing (at the time of data cutoff date)	2(28.6)	3(50.0)	5(38.5)
Discontinued study treatment	5(71.4)	3(50.0)	8(61.5)
Disease progression	4(57.1)	1(16.7)	5(38.5)
Adverse event(s)	1(14.3)	2(33.3)	3(23.1)

The data for the 5 patients still on-study were reported in the final close-out CSR as follows: Primary reason for end treatment for the 5 patients on treatment: 3 patients discontinued due to adverse events, 2 patients disease progression.

Baseline Characteristics

Demographic and baseline characteristics

Demographic Variable	RAD001 5 mg/day N=7	RAD001 10 mg/day N=6	All Patients N=13
Sex			
Female	3(42.9%)	2(33.3%)	5(38.5%)
Male	4(57.1%)	4(66.7%)	8(61.5%)
Age			
< 65	3(42.9%)	4(66.7%)	7(53.8%)
≥ 65	4(57.1%)	2(33.3%)	6(46.2%)

Demographic Variable	RAD001 5 mg/day N=7	RAD001 10 mg/day N=6	All Patients N=13
Age (Years)			
Mean	63.3	61.0	62.2
SD	14.64	10.00	12.26
Median	65.0	59.0	60.0
Min	47.0	47.0	47.0
Max	82.0	74.0	82.0
Race			
Oriental	7(100.0%)	6(100.0%)	13(100.0%)
Height (cm)			
Mean	158.8	164.2	161.3
SD	13.51	9.70	11.76
Median	160.5	163.3	161.0
Min	137.0	149.7	137.0
Max	173.0	177.0	177.0
Weight (kg)			
Mean	56.5	64.5	60.2
SD	20.13	12.49	16.88
Median	48.6	58.8	57.5
Min	34.4	53.7	34.4
Max	92.4	84.1	92.4
Body surface area (m^2) [a)]			
Mean	1.6	1.7	1.6
SD	0.32	0.20	0.27
Median	1.5	1.6	1.6
Min	1.1	1.5	1.1
Max	2.0	2.0	2.0
ECOG PS			
0	4(57.1%)	6(100.0%)	10(76.9%)
1	3(42.9%)	0	3(23.1%)

a) Body surface area : BSA= $(Weight^{0.425} \times Height^{0.725}) \times 0.007184$

Disease history and baseline characteristics

	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
Primary site of cancer			
Lymphoma: Non-Hodgkin's disease	7 (100.0)	6 (100.0)	13 (100.0)
Stage at initial diagnosis			

	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
Stage I	1 (14.3)	0	1 (7.7)
Stage II a	1 (14.3)	1 (16.7)	2 (15.4)
Stage II b	1 (14.3)	0	1 (7.7)
Stage III a	1 (14.3)	1 (16.7)	2 (15.4)
Stage IV	1 (14.3)	2 (33.3)	3 (23.1)
Stage IV a	2 (28.6)	1 (16.7)	3 (23.1)
Stage IV b	0	1 (16.7)	1 (7.7)
Time since initial diagnosis			
≤ 12 months	1 (14.3)	0	1 (7.7)
> 12 - ≤ 24 months	1 (14.3)	1 (16.7)	2 (15.4)
> 24 - ≤ 36 months	1 (14.3)	1 (16.7)	2 (15.4)
> 36 months	4 (57.1)	4 (66.7)	8 (61.5)
Time since first recurrence/relapse			
≤ 1 months	1 (14.3)	0	1 (7.7)
> 1 - ≤ 6 months	0	1 (16.7)	1 (7.7)
> 6 - ≤ 12 months	0	1 (16.7)	1 (7.7)
> 12 - ≤ 18 months	3 (42.9)	1 (16.7)	4 (30.8)
> 18 months	2 (28.6)	2 (33.3)	4 (30.8)
Time since most recent recurrence/relapse			
≤ 1 months	2 (28.6)	1 (16.7)	3 (23.1)
> 1 - ≤ 6 months	2 (28.6)	4 (66.7)	6 (46.2)
> 6 - ≤ 12 months	2 (28.6)	0	2 (15.4)
> 12 months	1 (14.3)	1 (16.7)	2 (15.4)
Types of lesions			
Target only	4 (57.1)	1 (16.7)	5 (38.5)
Target and Non-target	3 (42.9)	5 (83.3)	8 (61.5)
Ann Arbor Stage			
Stage I	0	1 (16.7)	1 (7.7)
Stage II	1 (14.3)	2 (33.3)	3 (23.1)
Stage III	3 (42.9)	1 (16.7)	4 (30.8)
Stage IV	3 (42.9)	2 (33.3)	5 (38.5)

	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
Histology (WHO classification, 2001)			
B cell neoplasms	4 (57.1)	5 (83.3)	9 (69.2)
Follicular lymphoma (FL)	1 (14.3)	4 (66.7)	5 (38.5)
B-cell - mantle cell lymphoma (MCL)	1 (14.3)	1 (16.7)	2 (15.4)
Diffuse large B-cell lymphoma (DLBCL)	2 (28.6)	0	2 (15.4)
T cell neoplasms	3 (42.9)	1 (16.7)	4 (30.8)
Anaplastic large cell lymphoma (ALCL), T-/null - cell, primary cutaneous type	1 (14.3)	0	1 (7.7)
Anaplastic large cell lymphoma (ALCL), T-/null - cell, primary systemic type	0	1 (16.7)	1 (7.7)
T-cell - mycosis fungoides	1 (14.3)	0	1 (7.7)
T-cell - peripheral T-cell lymphoma (PTCL), unspecified	1 (14.3)	0	1 (7.7)
Bulk > 10 cm (Yes)	1 (14.3)	1 (16.7)	2 (15.4)
Extranodal extension or single extranodal site of disease (Yes)	3 (42.9)	2 (33.3)	5 (38.5)
Bulk symptoms weight loss > 10%, fever, drenching night sweat (Yes)	2 (28.6)	0	2 (15.4)

Prior antineoplastic therapy

	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
Any prior antineoplastic therapy [1]	7 (100.0)	6 (100.0)	13 (100.0)
Any prior radiotherapy	5 (71.4)	0	5 (38.5)
Any prior surgery	1 (14.3)	0	1 (7.7)
Any prior medication [2]	7 (100.0)	6 (100.0)	13 (100.0)
Chemotherapy	6 (85.7)	6 (100.0)	12 (92.3)
Immunotherapy	1 (14.3)	0	1 (7.7)
Targeted therapy	4 (57.1)	5 (83.3)	9 (69.2)

[1]Any prior antineoplastic therapy includes patients who have had medication, radiotherapy or surgery.
[2]A patient with multiple therapy types is only counted once within 'Any prior medications'

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Best overall response [a)]	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)
Complete response (CR)	1 (14.3)	1 (16.7)
Complete response/unconfirmed (CRu)	0	0
Partial response (PR)	1 (14.3)	1 (16.7)
Stable disease (SD)	1 (14.3)	4 (66.7)
Progression (PD)	4 (57.1)	0
Unknown (UNK)	0	0

a) The best overall response is the best response assessed by the investigator from the start of the treatment until progression of disease or the discontinuation of the study or the time of the data cutoff date (17-Dec-2008).

Summary of Safety

Safety Results

DLT

No DLT was observed during the study.

Summary of posterior distribution of DLT rates

Dose (mg/day)	Posterior probabilities in percent (%)								
	Probabilities that Pr (DLT) was in interval:				Mean	SD	Quantile		
	0-20%	20-35%	35-60%	60-100%			2.5%	50%	97.5%
5	99.9	0.1	0	0	2.7	2.6	0.1	2.0	9.8
10	99.1	0.9	0	0	4.9	4.0	0.7	3.8	15.8

Safety

Adverse events regardless of the study drug relationship, by SOC and dose cohorts (Safety population)

SOC	RAD001 5 mg/day N=7 n (%)	RAD001 10 mg/day N=6 n (%)	All Patients N=13 n (%)
-Any SOC	7(100.0)	6(100.0)	13(100.0)
Blood and lymphatic system disorders	6(85.7)	6(100.0)	12(92.3)
Metabolism and nutrition disorders	5(71.4)	6(100.0)	11(84.6)
Investigations	6(85.7)	4(66.7)	10(76.9)
Gastrointestinal disorders	4(57.1)	4(66.7)	8(61.5)
Infections and infestations	4(57.1)	3(50.0)	7(53.8)

SOC	RAD001 5 mg/day N=7 n (%)	RAD001 10 mg/day N=6 n (%)	All Patients N=13 n (%)
General disorders and administration site conditions	2(28.6)	2(33.3)	4(30.8)
Musculoskeletal and connective tissue disorders	2(28.6)	1(16.7)	3(23.1)
Nervous system disorders	0(0.0)	3(50.0)	3(23.1)
Respiratory, thoracic and mediastinal disorders	1(14.3)	2(33.3)	3(23.1)
Skin and subcutaneous tissue disorders	1(14.3)	2(33.3)	3(23.1)
Eye disorders	1(14.3)	1(16.7)	2(15.4)
Renal and urinary disorders	1(14.3)	1(16.7)	2(15.4)
Cardiac disorders	0(0.0)	1(16.7)	1(7.7)
Ear and labyrinth disorders	1(14.3)	0(0.0)	1(7.7)
Hepatobiliary disorders	0(0.0)	1(16.7)	1(7.7)
Neoplasms benign, malignant and unspecified(incl cysts and polyps)	1(14.3)	0(0.0)	1(7.7)

SOCs are sorted by descending frequency in All patients.

A patient with multiple adverse events within a SOC is counted only once.

Frequent adverse events (33% or more in either treatment arm), regardless of the study drug relationship, by PT and dose cohorts (Safety population)

PT	RAD001 5 mg/day N=7 n (%)	RAD001 10 mg/day N=6 n (%)	All Patients N=13 n (%)
-Any PT	7(100.0)	6(100.0)	13(100.0)
Aspartate aminotransferase increased	5(71.4)	4(66.7)	9(69.2)
Leukopenia	4(57.1)	4(66.7)	8(61.5)
Thrombocytopenia	3(42.9)	5(83.3)	8(61.5)
Stomatitis	3(42.9)	4(66.7)	7(53.8)
Alanine aminotransferase increased	3(42.9)	3(50.0)	6(46.2)
Anaemia	6(85.7)	0(0.0)	6(46.2)
Nasopharyngitis	3(42.9)	3(50.0)	6(46.2)
Blood lactate dehydrogenase increased	2(28.6)	3(50.0)	5(38.5)
Diarrhoea	1(14.3)	4(66.7)	5(38.5)
Lymphopenia	2(28.6)	3(50.0)	5(38.5)
Neutropenia	2(28.6)	3(50.0)	5(38.5)
Anorexia	1(14.3)	3(50.0)	4(30.8)
Blood alkaline phosphatase increased	1(14.3)	3(50.0)	4(30.8)
Hypercholesterolaemia	1(14.3)	3(50.0)	4(30.8)
Hyperglycaemia	2(28.6)	2(33.3)	4(30.8)
Blood cholesterol increased	1(14.3)	2(33.3)	3(23.1)
Hyperlipidaemia	1(14.3)	2(33.3)	3(23.1)

PT	RAD001 5 mg/day N=7 n (%)	RAD001 10 mg/day N=6 n (%)	All Patients N=13 n (%)
Abdominal pain upper	0(0.0)	2(33.3)	2(15.4)
Blood creatinine increased	0(0.0)	2(33.3)	2(15.4)
Fatigue	0(0.0)	2(33.3)	2(15.4)
Pyrexia	0(0.0)	2(33.3)	2(15.4)

PTs are sorted by descending frequency in All patients.

A patient with multiple adverse events within a PT is counted only once.

Adverse events with an overall incidence rate of 33% or more in either treatment arm, regardless of the study drug relationship, are shown.

Number (%) of patients who died, had a SAE, discontinued because of an AE, had a grade 3-4 AE, or had a clinically notable AE by dose cohorts (Safety population)

	RAD001 5 mg/day N= 7 n (%)	RAD001 10 mg/day N= 6 n (%)	All Patients N= 13 n (%)
All deaths	0	1 (16.7)	1 (7.7)
On-treatment death [1]	0	1 (16.7)	1 (7.7)
Serious adverse event (SAE)	2 (28.6)	2 (33.3)	4 (30.8)
Adverse event of grade 3-4	5 (71.4)	3 (50.0)	8 (61.5)
Adverse event leading to discontinuation	1 (14.3)	2 (33.3)	3 (23.1)
Clinically notable adverse event	7 (100.0)	6 (100.0)	13 (100.0)

Categories are not mutually exclusive

[1] Deaths occurring after study evaluation completion are not summarized

Adverse events occurring after study evaluation completion are not summarized

Clinically notable adverse events are the events for which there is a specific clinical interest in connection with RAD001 or adverse events which are similar in nature

Other Relevant Findings

Pharmacokinetic parameters of RAD001 on Day 1 and at steady state (PK population)

PK parameter	5 mg/day (N=7)		10 mg/day (N=6)	
	Day 1	Day 15 (steady state)	Day 1	Day 15 (steady state)
Tmax (h)	2.00 (1.00, 4.00)	2.02 (1.93, 4.00)	1.06 (1.00, 4.00)	1.03 (1.00, 2.07)
Cmax (ng/mL)	23.7 ± 7.76	30.4 ± 13.8	42.6 ± 11.5	68.5 ± 18.3
AUCtau (ng·h/mL)	168 ± 108	333 ± 232	273 ± 89.5	611 ± 320
CL/F (L/h)	NA [a)]	18.9 ± 7.05	NA	19.1 ± 6.61
Accumulation ratio by Cmax	NA	1.28 ± 0.254	NA	1.66 ± 0.524
Accumulation ratio by AUCtau	NA	1.96 ± 0.253	NA	2.19 ± 0.557

Each value represents mean ± SD except for Tmax of median (range)

a: Not applicable

RAD001 trough concentrations by time point (PK population)

Cycle	Day	5 mg/day (N=7)	10 mg/day (N=6)
1	Day 2	2.91 ± 1.99	5.04 ± 2.13
1	Day 8	7.77 ± 4.50	14.0 ± 5.10
1	Day 15	7.73 ± 4.76	15.8 ± 9.23
1	Day 16	7.99 ± 6.29	15.9 ± 9.74
1	Day 22	8.46 ± 3.68	11.8 ± 3.43 [a)]
2	Day 1	7.83 ± 4.64 [a)]	19.4 ± 18.8 [a)]
2	Day 15	5.34 ± 1.29 [b)]	12.7 ± 1.91 [a)]
3	Day 1	4.63 ± 2.27 [b)]	8.46 ± 1.47 [c)]
3	Day 15	4.47 ± 1.81 [d)]	9.21 [e)]

Each value represents mean ± SD

a, N=5; b, N=4; c, N=3; d, N=2; e, N=1

Conclusion:

After the last cut-off date (17-Dec-2008), one patient who had achieved SD by the time of previous data cut-off, achieved PR.

No death was observed during the study after the last cut-off date. Two patients had at least one SAE and three patients had at least one AE leading to the study drug discontinuation after the last cut-off date.

The data gathered from the last five patients since the data cut-off use for the core CSR (17-Dec-2008), regarding efficacy and safety, does not affect conclusions drawn from the core CSR.

Date of Clinical Trial Report

11 September 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

9 November, 2014

Date of Latest Update

Reason for Update