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Full Novartis CTRD Results Template

Sponsor

Novartis Pharma GmbH, Germany

Generic Drug Name

RAD001 (everolimus)

Therapeutic Area of Trial

pancreatic cancer

Approved Indication for Germany

- Indicated for the treatment of advanced renal cell carcinoma after disease progression during or after a VEGF-targeted therapy
- Indicated for the treatment of non-resectable or metastatic pancreatic neuroendocrine tumors in case of progressive disease
- Indicated for the treatment of patients ≥ 3 years with subependymal cell astrocytoma from tuberous sclerosis

Protocol Number

CRAD001C2491

Title

Combination of antiangiogenic therapy using the mTOR-inhibitor RAD001 and low dose chemotherapy for locally advanced and/or metastatic pancreatic cancer – a dose finding study

Phase of Development

Phase I/II

Study Start/End Dates

31 Oct 2007 to 03 Jan2011.

Study Design/Methodology

This was an open-label, multicenter two-arm combined phase I/II study of continuous doses of RAD001 every 2nd day (cohorts 1, 2 and 3) or every day (cohorts 4 and 5)[1] in combination with escalating low dose gemcitabine in patients with locally advanced and/or metastatic pancreatic cancer[2]. The study consisted of a dose finding (dose escalation phase [phase I])

[1]Protocol amendment no. 3 added these 2 cohorts

[2] Protocol amendment no. 1 introduced clarifications concerning study design.

Dose escalation for gemcitabine followed the strict traditional escalation rule (STER). Dose levels x were escalated step by step from x_i to x_{i+1} with $i = 1,2\ldots$ Each cohort (3 patients pro cohort up to 6 patients) consisted of newly enrolled patients. Intra-patient dose escalation was not permitted. Dose levels were escalated in successive cohorts of three patients as long as no DLT occurred. Toxicity was assessed using the NCI/NIH Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 grading scale. At least 6 patients needed to be treated at the MTD level and a minimum of 12 patients overall needed to be treated. The final recommended dose combination agent was based on considerations of the MTDs and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose levels tested. A treatment cycle was defined as RAD001 and gemcitabine administered for 28 days for the purpose of scheduling evaluations. All patients were followed for a minimum of 8 weeks following start of study treatment before escalating to the next level.

Centres

4 centers in German

Publication

N.a. so far.

Outcome measures

Primary outcome measures(s)

Maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of escalating doses of RAD001(everolimus) in combination with gemcitabine.

Secondary outcome measures(s)

- Safety and tolerability of RAD001(everolimus) in combination with gemcitabine including acute and chronic toxicities in these patient populations.
- Pharmacokinetic assessments of RAD001 and gemcitabine combination therapy in these patient populations[3].
- At MTD dose level expansion: To evaluate preliminary efficacy (objective response rates [ORR], duration of response, progression-free survival [PFS] at 36 weeks and overall survival [OS])[4].

The specific key measure(s) or observation(s) that will be used to determine the effect of the interventions).

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

Gemcitabine was provided as an infusion prepared by a local pharmacist according to current practice at the center using commercially available gemcitabine. Gemcitabine was given by the oncologist as intravenous infusion over 30 minutes application time.

[3] Protocol amendment no.3 cancelled the measurement of ribosomal protein S6 kinase 1 and protocol amendment no. 4 cancelled the analysis of RAD001 serum trough levels at Week 1 Visit 2 of phase I and II.
[4] The original protocol also had evaluation of quality of life in phase II as an objective. This was removed by protocol amendment no. 4.

Oral RAD001 was to be taken every 2nd day as a single dose of 5 mg (or 2.5 mg twice) for the cohorts 1, 2 and 3[5]. For the cohorts 4 and 5 RAD001 has to be taken every day as a single dose of 5 mg. After a light meal, study medication of RAD001 was to be taken with a large glass of water. Patients were to wait at least two hours before any subsequent meal.

The starting dose of RAD001 were 5 mg every 2nd day in combination with 400 mg/m^2 gemcitabine once weekly. The gemcitabine dose was escalated to 500 and 600 mg/m^2 weekly in the cohorts 2 and 3. The dose of RAD001 was not escalated. Two further dose escalation cohorts (cohorts 4 and 5) were included in the phase I. In both cohorts, 5 mg RAD001 were given on a daily basis. The weekly doses for gemcitabine in the cohorts 4 and 5 were 400 and 500 mg/m^2 over 30 min i.v., respectively.

Statistical Methods

According to the protocol, a safety population and a MTD-determining population were defined. Additionally, an intent-to-treat population (ITT) and a per-protocol (PP) population were defined for the efficacy analyses and a pharmacokinetic population was defined for the pharmacokinetic analyses of Phase II data. As the study was stopped before Phase II, these populations were not used in the analysis. Instead of this, data for phase I were analyzed using summary tables, explorative analysis, and single data listings.

Data from all participating centers were combined, so that an adequate number of patients were available for analysis. Data were summarized with respect to demographic and baseline characteristics (including disease characteristics), efficacy observations and measurements as well as safety observations and measurements. Frequency distributions were provided for categorical variables. Descriptive statistics of mean, standard deviation, minimum, median and maximum were presented for continuous variables. Time-to-event data including rates of affected patients were to be assessed by Kaplan-Meier statistics according to the protocol. However, no such analyses were done, as the study was stopped before phase II.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients aged ≥ 18 years with histologically confirmed locally advanced, irresectable pancreatic adenocarcinoma (head, corpus, tail) with or without distant metastases were included in this study. Further key inclusion criteria were: adequate bone marrow, liver and renal function on RAD001 treatment; at least one measurable lesion (longest diameter ≥ 20 mm on conventional CT or MRI scan; ≥ 10 mm on spiral CT) according to RECIST criteria that has not been previously irradiated (if the patient had had previous radiation to the marker lesion(s), there had to be evidence of progression since the radiation. The scans were to be approximately 2 weeks old to be used as baseline scan); at least 4 weeks time since prior major surgery and recovered, at least 2 weeks and recovered since prior minor surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy); ECOG Performance Status 0-2.

Key exclusion criteria were documented intolerance or history of allergy to RAD001 or gemcitabine; history of another malignancy within 5 years prior to study entry (except curatively treated non-melanotic skin cancer or in-situ cervical cancer); use of other investigational cancer therapies within 28 days prior to enrollment or which are currently being or planned to be received during the course of the study; known or symptomatic central nervous system metastases or leptomeningeal involvement; chronic treatment with systemic steroids or another immunosuppressive agent; impairment of gastrointestinal function or gastrointestinal disease that may significantly alter RAD001 absorption; active, bleeding diathesis or on oral anti-vitamin K

[5] Before protocol amendment 2 took effect, the dose of RAD001 was to be adjusted to reach a serum level of 4 – 7 ng/ml.

medication (except low dose coumarin). Quick-value < 50 % or PTT more than 1.5 fold higher; prior treatment with an mTor inhibitor or with gemcitabine (only adjuvant gemcitabine treatment allowed).

Participant Flow

Patient disposition for each treatment group:

	Screened	Treated	Discontinued	Completed
Number (%) of patients				
All cohorts (N=27)	27	27	6	21
Cohort 1 (N= 3)	3	3	0	3
Cohort 2 (N= 4)	4	4	1	3
Cohort 3 (N= 6)	6	6	0	6
Cohort 4 (N= 7)	7	7	3	4
Cohort 5 (N= 7)	7	7	2	5
Main reason for discontinuation			n (%)	
Adverse event(s)			3 (11.11)	
Subject withdrew consent			1 (3.70)	
Lost to follow-up			1 (3.70)	
Death			1 (3.70)	

Cohort 1: 400mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 2: 500mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 3: 600mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 4: 400mg/m2/week gemcitabine & 5mg/d RAD001; Cohort 5: 500mg/m2/week gemcitabine & 5mg/d RAD001

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Baseline Characteristics

		Total (N=27)	Cohort 1 (N=3)	Cohort 2 (N=4)	Cohort 3 (N=6)	Cohort 4 (N=7)	Cohort 5 (N=7)
Age (years)	n	27	3	4	6	7	7
	Mean	66.2	61.0	65.8	69.2	67.0	65.4
	SD	8.6	13.1	10.0	3.2	10.6	8.4
	Min	46.0	46.0	53.0	64.0	55.0	57.0
	Median	67.0	67.0	67.0	70.0	67.0	63.0
	Max	83.0	70.0	76.0	73.0	83.0	80.0
Age group – n (%)	Total	27 (100.00%)	3 (100.00%)	4 (100.00%)	6 (100.00%)	7 (100.00%)	7 (100.00%)
	≤55	2 (7.41%)	1 (33.33%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	>55 to ≤65	10 (37.04%)	0 (0.00%)	1 (25.00%)	1 (16.67%)	3 (42.86%)	5 (71.43%)
	>65 to ≤75	11 (40.74%)	2 (66.67%)	1 (25.00%)	5 (83.33%)	2 (28.57%)	1 (14.29%)
	75 or older	4 (14.81%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (28.57%)	1 (14.29%)
Gender – n(%)	Total	27 (100.00%)	3 (100.00%)	4 (100.00%)	6 (100.00%)	7 (100.00%)	7 (100.00%)
	Male	17 (62.96%)	3 (100.00%)	2 (50.00%)	3 (50.00%)	7 (100.00%)	2 (28.57%)
	Female	10 (37.04%)	0 (0.00%)	2 (50.00%)	3 (50.00%)	0 (0.00%)	5 (71.43%)
Race – n(%)	Total	27 (100.00%)	3 (100.00%)	4 (100.00%)	6 (100.00%)	7 (100.00%)	7 (100.00%)
	Caucasian	27 (100.00%)	3 (100.00%)	4 (100.00%)	6 (100.00%)	7 (100.00%)	7 (100.00%)

Cohort 1: 400mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 2: 500mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 3: 600mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 4: 400mg/m2/week gemcitabine & 5mg/d RAD001; Cohort 5: 500mg/m2/week gemcitabine & 5mg/d RAD001

Outcome measures

All should match the corresponding section of the NLM ClinicalTrials.gov results record as much as applicable.

Primary Outcome Result(s)

A total of 3 patients experienced DLTs. For 2 of these, hepatic toxicity was reported with the DLT criterion being CTCAE grade 3 aspartate aminotransferase/glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/glutamic pyruvic transaminase (ALT/SGPT) lasting for > 7 days. For the remaining DLT, the DLT was added as a worst case assumption.

One of these DLTs was seen in cohort 4 and 2 were seen in cohort 5.

The dose escalation for gemcitabine used for the determination of the MTD in this study followed the STER. Dose levels were escalated in successive cohorts of 3 patients as long as no DLT occurred. If exactly 1 out of the 3 patients treated at x_i exhibited DLT, the next cohort of 3 patients was treated at x_i. If 2 or more patients out of the 6 exhibited DLT, MTD was supposed to be surpassed and dose escalation stops at that level. In cohort 5, 2 out of the 6 patients experienced DLTs. Thus, MTD was determined to be 400mg/m^2/week gemcitabine & 5mg/d RAD001.

Secondary Outcome Result(s)

Safety and tolerability

Overall, 25 of 27 patients (92.59%) reported at least one AE. This percentage was lower in cohort 1 (66.67%) and cohort 2 (75.00%) than in cohorts 3, 4 and 5, in which each patient reported at least one AE. At the preferred term (PT) level, thrombocytopenia was the most frequent AE overall, followed by leukopenia and nausea. In the individual dose groups, thrombocytopenia was the most common AE in cohorts 1, 2 and 5. In cohort 3, leukopenia was the most frequent AE and in cohort 4 nausea was the most frequent AE. The majority of patients experienced AEs with suspected relation to study drug (81.48%), AEs leading to dose adjustments or temporary interruption (77.78%) or required concomitant medication (66.67%).

A total of 11 patients (40.74%) experienced at least 1 SAEs. Two patients died during the study (Not related to study drug). An additional patient died after study termination. AEs leading to permanent discontinuation were reported for 4 patients. For 2 of these, the event was an SAE.

Pharmacokinetic assessments

Overall, the median serum trough level the entire study population was 4.41 ng/ml. Median serum trough levels were higher in cohort 4 (6.84 ng/ml) and cohort 5 (5.23 ng/ml) than in cohort 1 (3.08 ng/ml), cohort 2 (2.43 ng/ml) and cohort 3 (4.10 ng/ml).

Preliminary efficacy at MTD dose level expansion

N.a. since dose level expansion was not initiated.

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Safety Results

Adverse Events by System Organ Class

	Total (N=27)		Cohort 1 (N=3)		Cohort 2 (N=4)		Cohort 3 (N=6)		Cohort 4 (N=7)		Cohort 5 (N=7)	
	n	%	n	%	n	%	n	%	n	%	n	%
No. (%) of patients studied	27	100.00	3	100.00	4	100.00	6	100.00	7	100.00	7	100.00
No. (%) of patients with AE(s)	25	92.59	2	66.67	3	75.00	6	100.00	7	100.00	7	100.00
System organ class affected												
Blood and lymphatic system disorders	21	77.78	2	66.67	3	75.00	4	66.67	6	85.71	6	85.71
Cardiac disorders	1	3.70	1	33.33	0	0.00	0	0.00	0	0.00	0	0.00
Gastrointestinal disorders	16	59.26	0	0.00	2	50.00	3	50.00	6	85.71	5	71.43
General disorders and administration site conditions	13	48.15	0	0.00	0	0.00	5	83.33	5	71.43	3	42.86
Hepatobiliary disorders	3	11.11	0	0.00	0	0.00	0	0.00	0	0.00	3	42.86
Infections and infestations	14	51.85	2	66.67	0	0.00	5	83.33	2	28.57	5	71.43
Investigations	10	37.04	0	0.00	1	25.00	0	0.00	4	57.14	5	71.43
Metabolism and nutrition disorders	4	14.81	0	0.00	1	25.00	0	0.00	3	42.86	0	0.00
Musculoskeletal and connective tissue disorders	2	7.41	1	33.33	0	0.00	0	0.00	1	14.29	0	0.00
Neoplasms benign, malignant and unspecified	1	3.70	0	0.00	0	0.00	0	0.00	0	0.00	1	14.29
Nervous system disorders	4	14.81	0	0.00	0	0.00	0	0.00	1	14.29	3	42.86
Psychiatric disorders	1	3.70	0	0.00	0	0.00	0	0.00	1	14.29	0	0.00
Renal and urinary disorders	1	3.70	0	0.00	0	0.00	0	0.00	0	0.00	1	14.29
Respiratory, thoracic and mediastinal disorders	4	14.81	1	33.33	0	0.00	0	0.00	2	28.57	1	14.29

Skin and subcutaneous tissue disorders	6	22.22	0	0.00	0	0.00	0	0.00	3	42.86	3	42.86
Surgical and medical procedures	1	3.70	0	0.00	0	0.00	0	0.00	0	0.00	1	14.29
Vascular disorders	1	3.70	1	33.33	0	0.00	0	0.00	0	0.00	0	0.00

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SOCs are presented in alphabetical order.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Number (%) of patients with most frequent AEs (AEs in more than a third of patients in any cohort):

	Total (N=27)		Cohort 1 (N=3)		Cohort 2 (N=4)		Cohort 3 (N=6)		Cohort 4 (N=7)		Cohort 5 (N=7)	
	n	%	n	%	n	%	n	%	n	%	n	%
No. (%) of patients studied	27	100.00	3	100.00	4	100.00	6	100.00	7	100.00	7	100.00
No. (%) of patients with AE(s)	25	92.59	2	66.67	3	75.00	6	100.00	7	100.00	7	100.00
AE preferred term												
Thrombocytopenia	17	62.96	2	66.67	3	75.00	3	50.00	3	42.86	6	85.71
Leukopenia	9	33.33	1	33.33	1	25.00	4	66.67	3	42.86	0	0.00
Nausea	9	33.33	0	0.00	0	0.00	2	33.33	4	57.14	3	42.86
Urinary tract infection	6	22.22	0	0.00	0	0.00	2	33.33	0	0.00	4	57.14
Abdominal pain	5	18.52	0	0.00	1	25.00	1	16.67	3	42.86	0	0.00
Blood potassium decreased	3	11.11	0	0.00	0	0.00	0	0.00	0	0.00	3	42.86
Dizziness	3	11.11	0	0.00	0	0.00	0	0.00	0	0.00	3	42.86
Neutropenia	3	11.11	0	0.00	0	0.00	0	0.00	3	42.86	0	0.00
Oedema	3	11.11	0	0.00	0	0.00	3	50.00	0	0.00	0	0.00

Preferred terms are listed by frequency in the total of cohorts
Cohort 1: 400mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 2: 500mg/m2/week gemcitabine & 5mg/2nd day RAD001;

Cohort 3: 600mg/m2/week gemcitabine & 5mg/2nd day RAD001; Cohort 4: 400mg/m2/week gemcitabine & 5mg/d RAD001; Cohort 5: 500mg/m2/week gemcitabine & 5mg/d RAD001

Serious Adverse Events and Deaths A total of two patients (both in cohort 4) died during this study. Neither of the 2 deaths was suspected to be related to study medication. A total of 11 patients (1 each in cohorts 1 and 3 and 3 each in cohorts 2, 4, and 5) experienced 18 SAEs. The majority of the SAEs were mild or moderate in intensity. Only 4 SAEs were of severe intensity (PTs: death, sepsis, renal failure, and cholangitis). SAEs with suspected causal relationship and SAEs without suspected causal relationship were equally frequent.
Other Relevant Findings N.A.
Date of Clinical Trial Report 12 Dec 2011
Date Inclusion on Novartis Clinical Trial Results Database 7-Feb-2012
Date of Latest Update