SYNOPSIS OF RESEARCH REPORT NO21884

COMPANY: Hoffmann-La Roche Ltd/Inc/AG/Roche Global Development NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A multiple ascending dose study to evaluate the safety, tolerability and effect on tumor response of the mTOR inhibitor (RAD001) in combination with the IGF-1R antagonist (R1507) in patients with advanced solid tumors / Report No. NO21884 / August 2010 Synopsis format report due to discontinuation of compound development (non-safety reasons).		
INVESTIGATORS / CENTERS AND COUNTRIES	[redacted] Texas, USA [redacted] New York, USA [redacted] Milano, Italy		
PUBLICATION (REFERENCE)	Not applicable.		
PERIOD OF TRIAL	First patient, first dose: Oct 30, 2009 Last patient, last dose: NA Data cut-off for analysis: Mar 5, 2010	CLINICAL PHASE	Ib/II
COMPLIANCE WITH GOOD CLINICAL PRACTICE (GCP)	This study was conducted in accordance with GCP guidelines		

OBJECTIVES

Primary Objectives

Phase Ib:

- To characterize the safety and tolerability of R1507 administered intravenously (IV) every 3 weeks in combination with daily RAD001 administered orally (PO).
- To determine the maximum-tolerated dose (MTD) of RAD001 administered PO daily, in combination with R1507 administered IV every 3 weeks in patients with advanced solid malignancies, and to determine the recommended dose of RAD001 for the phase II study of the combined regimen.

Phase II:

- To assess the clinical activity of combination R1507 and RAD001 in 2 cohorts of patients, defined by:
  - Progression free survival (PFS) rate at 24 weeks, in a cohort of patients with advanced stage renal cell carcinoma [RCC cohort].
  - PFS rate at 24 weeks, in a cohort of patients with advanced low- to intermediate grade metastatic or unresectable locoregional pancreatic neuroendocrine tumors (pNET) and carcinoid tumors, [NET cohort].

    NOTE: the NET cohort was to be comprised of equal numbers of patients of 2 tumor subgroups, (pancreatic islet cell tumors and carcinoid tumors)

Secondary Objectives

Phase Ib:

- To describe the tolerability and adverse event profile of the combination of R1507 and RAD001 in patients with advanced solid tumors.

	• To describe pharmacokinetics (PK) of the combination of RAD001 and R1507 using a population PK approach. • To evaluate preliminary anti-tumor activity of the combination. Phase II: • To determine the overall objective response rate, response duration, PFS and overall survival in 2 cohorts of patients 1) patients with advanced stage renal cell carcinoma (RCC cohort), and 2) patients with advanced low- to intermediate grade metastatic or unresectable locoregional pNETs, and carcinoid tumors (NET cohort). • To determine the tolerability and adverse event profile of combination R1507 and RAD001 in patients with advanced solid tumors. • To describe PK of the combination of RAD001 and R1507 using a population PK approach. **Exploratory Objectives** Phase Ib and phase II: • To evaluate phospho-akt murine thymoma viral oncogene homolog (pAKT) level change as a pharmacodynamic (PD) marker in paired skin biopsies before and after the combination of R1507 and RAD001 in a subset of patients. • To evaluate biomarkers in the serum and archival tumor biopsy samples that may be predictive of activity of the combination of R1507 and RAD001. • To evaluate dynamic biomarkers in tumor tissue samples that may be predictive of activity of the combination of R1507 and RAD001, and potentially further delineate mechanism of action of the combination. **Roche Clinical Repository Exploratory Objectives** • To identify dynamic biomarkers that are predictive of response to R1507 and RAD001 treatment (in terms of dose, safety and tolerability). • To identify gene expression profiles of genes known to be involved in cancer pathogenesis, or genes differentially expressed relative to response or dose response. • To identify genetic and pharmacogenomic analysis aimed at identifying genes associated with treatment response, toxicity or disease risk.
STUDY DESIGN	This was a single-arm phase Ib/II (dose escalation phase/efficacy phase) trial of R1507 in combination with RAD001. Patients were to be treated until disease progression, unacceptable adverse event, withdrawal or death.
NUMBER OF SUBJECTS	**Phase 1b**: Planned recruitment was a minimum of 15 and a maximum of 24 patients. **Phase II**: 50 RCC and 60 NET patients were planned.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult (≥ 18 years of age) male or female patients must have had: **Phase Ib**: Histologically confirmed recurrent or refractory advanced solid malignancy with no known standard of care according to the judgment of the Investigator (including Hodgkin's and non-Hodgkin's lymphoma) **Phase II**: Histologically confirmed advanced metastatic renal cell carcinoma (RCC) (with evidence of progressive disease despite prior VEGFr-TKI therapy) or advanced low- to intermediate grade metastatic or unresectable locoregional pancreatic neuroendocrine tumors (pNET) and carcinoid tumors who have failed standard therapy and have evidence of progressive disease.

TRIAL DRUG / STROKE (BATCH) No.	R1507: [redacted] (US), [redacted] (Italy) RAD001: [redacted] (US), [redacted] (Italy)
DOSE / ROUTE / REGIMEN / DURATION	In phase Ib, patients were to receive RAD001 (5 or 10 mg PO) daily and R1507 (16 mg/kg IV) every 3 weeks (q3w). The initial infusion of R1507 was to occur over 90 minutes; in the absence of an infusion reaction, subsequent infusions were to occur over 60 minutes. In phase II, patients were to receive the recommended dose of RAD001 (as determined in phase Ib) and R1507 (16 mg/kg IV) q3w.
CRITERIA FOR EVALUATION	
EFFICACY:	Efficacy was to be evaluated by assessment of tumor response (based on RECIST criteria). Patients enrolled in phase 1b with a diagnosis of lymphoma were to have their tumor response measured based on Cheson Response Criteria. See page 160.
PHARMACOKINETICS:	Blood samples were to be obtained at Cycles 1, 2, 3, and 4 for a population PK analysis in patients receiving R1507 and RAD001 page 166.
PHARMACODYNAMICS:	Pharmacodynamic assessments were to include analysis of serum and archival tumor biopsy samples for biomarkers potentially related to IGF signaling page 168.
SAFETY:	Safety assessments were to include physical examination, vital signs (temperature, resting blood pressure, pulse, respiratory rate), routine laboratory determinations (blood counts and differential, serum chemistries, and urinalysis), 12-lead electrocardiogram (ECG), serum troponin, pulmonary function tests, adverse events (AEs), and serious adverse events (SAEs). Additional safety assessments were to include determination of fasting glucose and hemoglobin A1C and human anti-human antibody (HAHA) measurement. All AEs were to be assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading system (5-point scale, with 1 being mild and 5 being death). Safety assessments were to be performed at protocol-specified intervals throughout the study. See page 156, page 163, page 164, and page 165 for further detail regarding timing and procedures.
OTHER:	The level of a patient's activity was to be assessed using the Eastern Cooperative Oncology Group Performance Status Scale (page 162).
STATISTICAL METHODS (SAFETY)	Patients who received at least one dose of R1507 and RAD001 and had at least one post-baseline safety follow-up were to be included in the safety population. All safety analyses were to use the safety population. Descriptive statistics were to be used to analyze all safety data. See page 195 for further detail regarding the safety analyses.

METHODOLOGY:

Complete details of the study methodology are presented in page 141 .

The study schedule consisted of a screening visit (between 14 and 0 days prior to the first day of treatment), 21-day treatment cycles (Days 1-21), a final study visit, a follow-up study visit (28 days after the last dose), and a follow-up phase (12 weeks post final visit and every 12 weeks thereafter). All patients were to be observed for dose limiting toxicity (DLT) (page 145) during the first 21 days (Cycle 1) of treatment.

Overview

In the phase Ib stage, patients with advanced solid tumors were to be enrolled sequentially to escalating dose cohorts of RAD001. All patients were to receive R1507 16 mg/kg IV every 3 weeks. In phase II, patients were to be enrolled into 2 cohorts: 1) patients with advanced RCC (RCC cohort), and 2) patients with advanced low- to intermediate grade metastatic or unresectable locoregional pNET and carcinoid tumors (NET cohort). Evaluation of extent of disease (using CT/MRI) was to occur at baseline for patients in both cohorts (RCC and NET) and thereafter at 6-week (RCC cohort) or 12-week (NET cohort) intervals, until patients reached the time-point of the primary analysis after which all CT/MRI evaluations were to be on a 12-week schedule. Enrollment into the study was discontinued before enrollment into phase II commenced.

Enrolled patients were to receive R1507 and RAD001 until progressive disease, intolerable toxicity, or withdrawal of consent.

Phase Ib: Dose Escalation Phase

The phase Ib portion of the study was designed as a sequential dose-defining study to assess the feasibility (safety and tolerability) of the RAD001 and R1507 combination treatment based on the rate of DLTs occurring during the first cycle (21 days) of treatment.

While the dose of R1507 was fixed (16 mg/kg IV q3w) throughout the dose-escalation phase, RAD001 was to be administered daily, first as a 5 mg PO dose (3 patients) then, in the absence of DLT, as a 10 mg PO dose (6 patients).

Dose escalation was to proceed based on the following scheme:

Dose Level 1 (RAD001 5 mg daily and R1507 16 mg/kg q3w)	
Number of patients with DLT at a given dose level	**Escalation Decision Rule**
0 out 3	Enter 6 patients at the next dose level (10 mg)
1 out of 3	Enter 3 more patients at this dose level: If 0 of these 3 patients experience DLT (total 1/6), proceed to the next dose level (10 mg). If 1 or more patients experience DLT (total ≥ 2/6), then dose escalation and the trial is stopped.
≥ 2 out of 3	Dose escalation and the trial will be stopped.
Dose Level 2 (RAD001 10 mg daily and R1507 16 mg/kg q3w)	
Number of patients with DLT at a given dose level	**Escalation Decision Rule**
0 to 1 out of 6	This is declared the maximally administered dose and the recommended dose for phase II*.
2 out of 6	Enter at least 6 more patients at this dose level: If 0-1 of these 6 patients (total 2 or 3 of 12 patients) experience DLT, this dose is declared the MTD** and the recommended phase II dose. If 2 or more patients in this group (total of ≥ 4/12) experience DLT, this dose is declared the maximally administered dose and 5 mg PO daily is the MTD** and recommended Phase II dose*
≥ 3 out of 6	No further enrollment at this dose level. This dose level will be declared the maximally administered dose and 5 mg PO daily is the MTD** and recommended phase II dose*
* At least 12 patients must be treated at recommended phase II dose prior to initiating the phase II component of the study ** MTD is defined as dose with 33% DLT	

Phase II: Efficacy Phase

All patients were to receive R1507 (16 mg/kg IV) q3w in combination with RAD001 (PO) daily at the dose determined by the preceding phase Ib portion of the study. Enrollment into the study was discontinued before enrollment into phase II commenced.

End of Study

Patients were to remain on study treatment until disease progression, intercurrent illness preventing treatment, intolerable AEs, withdrawal of consent, or deemed unacceptable for further treatment by the treating physician. Patients who were withdrawn from study treatment for reasons other than progressive disease were to be followed for progressive disease and survival at 12 week intervals. Patients who were withdrawn from study treatment for any reason (except for death) were to be followed for survival at 12 week intervals.

REASON FOR STUDY TERMINATION:

The decision to discontinue development of R1507 was made by Hoffmann-La Roche based on available clinical data and was not due to safety reasons. Enrollment into the study was discontinued before enrollment into phase II commenced. This synopsis report presents all the safety data collected during the study as of the data cut-off date (March 5, 2010).

RESULTS

STUDY POPULATION:

Disposition of patients

A total of 11 patients were enrolled from 3 centers; 2 centers in the US and 1 in Italy. Four patients were enrolled into the RAD001 5 mg group and 7 patients into the RAD001 10 mg group. Names and addresses of the centers are provided in page 315 and IRB information is on page 316 . At the time of the clinical cut-off, 6 patients were still on active treatment.

Premature withdrawal

Overall 6 patients withdrew from study treatment, four of these due to progression of disease, one due to an AE/intercurrent illness (patient [redacted]) and one for an unspecified reason (patient [redacted] – see narratives) (page 43). Note that patient [redacted] withdrew after the cut-off date for the study analysis (March 5, 2010) and is not recorded as having withdrawn in the AE listing (page 71). Further details for this patient are provided in the study narratives.

Analysis populations

All 11 patients were included in the safety population. No efficacy population was defined and no efficacy data were analyzed due to early termination of the study.

Demographic data and baseline characteristics

Ten [redacted] patients, age range 37 to 77 years, and one [redacted] patient, age [redacted] years, were enrolled. Demographic data and baseline characteristics are listed on page 39 and page 41 respectively.

SAFETY RESULTS:

Extent of Exposure to Study Treatment

Details of R1507 administration are listed on page 45 . At the time of clinical cut-off, the 4 patients in dose level 1 received 1, 5, 6 and 9 cycles of R1507 16 mg/kg q3w combined with RAD001 5 mg po daily. The 7 patients in dose level 2 received 1, 2 [3 patients], 4, 6 and 7 cycles of R1507 16 mg/kg q3w in combination with RAD001 10 mg po daily. (page 14). Details of RAD001 administration are listed on page 49 . Mean total cumulative dose of RAD001 was 435.00 mg (standard deviation [SD] 308.03 mg) in the RAD001 5 mg group and 547.14 mg (SD 400.95 mg) in the RAD001 10 mg group (page 15).

Adverse Events

An overview of AEs is summarized on page 16 . A total of 102 AEs were reported by the 11 study patients. The most commonly reported events were gastrointestinal disorders (10/11, 91%) including diarrhea (4 patients); abdominal pain, constipation, gastritis, nausea, vomiting (each reported by 3 patients); and dry mouth and stomatitis (each reported by 2 patients). Hyperkalemia and hyperglycemia were each reported by 4 patients. Other AEs reported by more than one patient were fatigue (3 patients), pruritus (2), mucosal inflammation (5), infection (3), urinary tract infection (2), headache (3), dysgeusia (2), weight decreased (2), peripheral neuropathy (2) (page 17). There were no AEs that started during or within 24 hours of an infusion of R1507 and no AEs that led to discontinuation of study drug (see note above for patient [redacted]).

All AEs are listed by patient on page 71 . A glossary of AE preferred terms is provided on page 319 .

At the time of the clinical cut-off, some AEs were still ongoing and had not yet had the most severe intensity recorded. Where CTC grades were assigned, the majority of AEs were of CTC grade 1 or 2 and

there were no CTC grade 4 events. Grade 3 events considered to be related to one or both of the study drugs were hyperglycemia (2 events) and one event each of neutropenia, infection, and increased alanine aminotransferase. Grade 3 events unrelated to study drugs were single reports of tumor pain, bone pain, hyponatremia, hypokalemia, anemia, and encephalopathy.

There were no deaths during the study. Four patients reported 7 SAEs and 3 of these events in 2 patients were considered by the investigators to have a relationship to the study drugs (page 78). Patient [redacted] (5 mg RAD001) had an episode of hyperglycemia of CTC grade 3 which was probably related to both study drugs. RAD001 treatment was interrupted. Patient [redacted] (10 mg RAD001) reported events of diarrhea and infection, both CTC grade 3 and both possibly related to the study drugs. Narratives for these events are appended to this report.

Laboratory Safety Parameters

Laboratory test results are summarized on page 22 . Shift tables of highest post-baseline fasting glucose are presented on page 32 and post-baseline platelet levels are presented on page 33 . There were no troponin values above the investigator reference ranges page 53 . No data listing was produced for HAHA values because there were no patients with a positive HAHA value at any time, either pre-dose or on-study,

Electrocardiogram

No subject had a post-baseline QTcF interval >500 ms (page 35) and there were no post-baseline changes in QTcF >30 ms (page 36).

CONCLUSIONS:

- No AEs occurred during or within 24 hours following an infusion of R1507.
- No AEs resulted in withdrawal of study drug prior to the clinical cut-off for analysis.
- Three SAEs were related to study drug administration (diarrhea, infection, hyperglycemia).
- R1507 in combination with RAD001 5 mg or 10 mg was tolerated.
- The safety profile was similar to that seen in previous studies and no new safety signals were identified.

PATIENT NARRATIVES

[redacted]