Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Advanced non-small cell lung carcinoma (NSCLC).

Approved Indication

Everolimus is originally approved in several countries for use as prophylaxis (in combination with cyclosporine A and glucocorticoids) to prevent solid organ transplant rejection.

It has also been approved last year for the treatment of patients with advanced renal cell carcinoma after failure of treatment with Sunitinib or Sorafenib.

Study Number

CRAD001C2235

Title

Open label, non-randomized, phase II study investigating the effect of everolimus monotherapy in patients with advanced non-small cell lung carcinoma (NSCLC) previously treated with either chemotherapy only or with chemotherapy and EGFR inhibitor(s).

Phase of Development

Phase II

Study Start/End Dates

26-Jul-2005 to 24-Oct-2007

Study Design/Methodology

This was an open-label, non-randomized, phase II study evaluating the efficacy and safety of everolimus 10 mg once daily (q.d.). Patients were enrolled into two separate arms, both of which received the same treatment with everolimus:

- Arm 1 - patients previously treated with up to 2 chemotherapeutic regimens only (Prior Chemo arm)
- Arm 2 - patients previously treated with up to two chemotherapeutic regi mens and with a small molecule EGFR inhibitor (Prior Chemo+EGFRI arm).

Patients were administered everolimus continuously from Day 1 until disease progression or unacceptable toxicity.

Centers

9 centers in 6 countries: Canada (1), USA (2), France (2), Germany (1), Italy (2), The Netherlands (1).

Objectives

Primary objective(s)

- To assess the efficacy of everolimus monotherapy in patients with advanced non-small cell lung cancer (NSCLC), measured by the objective tumor response rate (ORR)

Secondary objective(s)

- To assess the safety of everolimus monotherapy
- To assess the rate of patients with early disease progression (EPR)
- To assess steady state levels of everolimus in blood
- To assess potential molecular markers predictive of clinical effect

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

Patients self-administered everolimus at a daily oral dose of 10 mg. Novartis supplied everolimus 5 mg tablets in aluminum blister packs in units of 10 tablets, which were to be opened only at the time of administration as the drug is both hygroscopic and light-sensitive.

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

Not applicable.

Criteria for Evaluation

Primary variables

- The objective tumor response rate was the primary efficacy endpoint of the study. The objective tumor response rate was calculated from the best overall response, based on RECIST criteria.

Secondary variables

- The secondary efficacy endpoints were: early disease progression rate (EPR), i.e. fraction of patients who progress within the first 8 weeks of treatment, progression-free survival (PFS) and time to progression (TTP). All of these endpoints were calculated based on RECIST via tumor response assessments.

Safety and tolerability

- Safety assessments consisted of monitoring and recording all AEs and serious AEs (SAEs), pregnancies, laboratory and urinalysis evaluations, vital signs, electrocardiogram (ECG) evaluations, WHO performance status, and physical examinations. A retrospective review of pneumonitis was conducted.

Pharmacology

- Everolimus trough concentrations in whole blood were determined by a validated liquid chromatography method with mass spectrometry following liquid/liquid extraction.
- FDG-PET was evaluated as the tool for the evaluation of early pharmacodynamic effect of mTOR inhibition.

Other

- None

Statistical Methods

The study applied a Simon two-stage design to investigate the efficacy of everolimus independently in each of the two arms based on the primary endpoint of ORR. Recruitment in the two arms proceeded in parallel. No formal interim analysis was planned. However, at the end of stage 1 in each arm separately the number of patients with a best overall response of partial response or better was tabulated and compared to the efficacy requirements needed to proceed into stage 2. Inferential statements were based on the Simon design set-up.

Secondary endpoints of progression-free survival and time to progression, to investigate efficacy based on disease stabilization, were evaluated descriptively via Kaplan-Meier estimates. All other statistical analyses conducted were descriptive in nature.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males or females = 18 years of age with advanced (unresectable or metastatic) NSCLC and a World Health Organization (WHO) performance status = 2.
- At least one measurable site of disease according to RECIST that had not been previously irradiated. If the patient had received previous radiation to the marker lesion(s), there must have been evidence of progression since the radiation.
- Receipt of no more than two previous chemotherapy regimens, one of which must have included cisplatin or carboplatin, with documented evidence of tumor progression (Prior Chemo arm). For patients who had received previous chemotherapy and small molecule EGFR inhibitor therapy (as separate regimens), there must be documented tumor progression despite at least 4 weeks of therapy with either gefitinib or erlotinib (Prior Chemo+EGFRI arm).
- Serial CT scans demonstrating progressive disease according to RECIST and pathologic confirmation of NSCLC with a tissue sample of the metastatic or primary tumor.
- Minimum of 2 weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy).
- Adequate bone marrow function as shown by: absolute neutrophil count (ANC) = 1.5 x 109/L, platelets = 100 x 109/L, hemoglobin > 9 g/dL.
- Adequate liver function as shown by: serum bilirubin = 1.5 x upper limit of normal (ULN) and serum transaminase activity = 3 x ULN. Patients with liver metastases with serum transaminases < 5 x ULN were also eligible.
- Provided signed informed consent.

Exclusion criteria

- Concurrent therapy with any chemotherapeutic agents other than study drug, even if used to treat non-cancer indications (e.g. methotrexate for rheumatoid arthritis).
- Receipt of any investigational drug, other than EGFRI (Arm 2), within the 4 weeks preceding study entry.
- Chronic treatment with steroids or other immunosuppressive agents.
- Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.
- Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinoma of the skin.
- Other concurrent severe or uncontrolled medical disease that could compromise participation in the study (i.e. uncontrolled diabetes or hypertension, severe infection, severe malnutrition, unstable angina, New York Heart Association Class III or IV congestive heart failure, ventricular arrhythmias, active ischemic heart disease, myocardial infarction within six months preceding study entry, chronic liver or renal disease, active upper gastrointestinal tract ulceration).
- A known history of HIV seropositivity.
- Impairment of gastrointestinal function or presence of gastrointestinal disease that may signif-

icantly alter the absorption of everolimus (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

- Active bleeding diathesis or taking oral anti-vitamin K medication (except low dose warfarin). Women who are pregnant or breast feeding, or women able to conceive and unwilling to practice an effective method of birth control. Women of childbearing potential must have had a negative urine or serum pregnancy test within 7 days prior to administration of everolimus.
- History of noncompliance to medical regimens.
- Patients unwilling to or unable to comply with the protocol.

Number of Subjects

Patient disposition - (ITT population)

	Prior Chemo N = 42 n (%)	Prior Chemo + EGFRI N = 43 n (%)	All patients N = 85 n (%)
Discontinued	42 (100)	43 (100.0)	85 (100)
Reason for discontinuation			
Adverse event(s)	3 (7.1)	4 (9.3)	7 (8.2)
Abnormal laboratory value(s)	1 (2.4)	1 (2.3)	2 (2.4)
Abnormal test procedure result(s)	0	0	0
Protocol violation	1 (2.4)	1 (2.3)	2 (2.4)
Subject withdrew consent	2 (4.8)	2 (4.7)	4 (4.7)
Lost to follow-up	0	0	0
Administrative problems	0	1 (2.3)	1 (1.2)
Death	2 (4.8)	0	2 (2.4)
Disease progression	33 (78.6)	34 (79.1)	67 (78.8)
Discontinuation reason missing	0	0	0

Demographic and Background Characteristics

Demographic summary by treatment arm (ITT population)

	Prior Chemo N = 42 n (%)	Prior Chemo + EGFRI N = 43 n (%)	All patients N = 85 n (%)
Age (years)			
N	42	43	85
Mean	59.0	58.1	58.5
SD	8.50	10.84	9.71
Gender – n (%)			
Male	26 (61.9)	21 (48.8)	47 (55.3)
Female	16 (38.1)	22 (51.2)	38 (44.7)
Race – n (%)			
Caucasian	35 (83.3)	33 (76.7)	68 (80.0)
Asian	4 (9.5)	8 (18.6)	12 (14.1)
Black	1 (2.4)	2 (4.7)	3 (3.5)
Pacific Islander	1 (2.4)	0	1 (1.2)
Other	1 (2.4)	0	1 (1.2)

Primary Objective Result(s)

Calculated best overall response by arm (ITT population)

Best overall response	Prior Chemo N = 42 n (%)	Prior Chemo + EGFRI N = 43 n (%)	All patients N = 85 n (%)

Disease control rate (CR or PR or SD)	22 (52.4)	18 (41.9)	40 (47.1)
Overall Response (CR or PR)	3 (7.1)	1 (2.3)	4 (4.7)
Complete Response (CR)	0	0	0
Partial Response (PR)	3 (7.1)	1 (2.3)	4 (4.7)
Stable Disease (SD)	19 (45.2)	17 (39.5)	36 (42.4)
Progressive Disease (PD)	18 (42.9)	17 (39.5)	35 (41.2)
Unknown (UNK)	2 (4.8)	8 (18.6)	10 (11.8)
Patients with early progression	14 (33.3)	15 (34.9)	29 (34.1)

Calculated best overall response by arm (efficacy-determining population)

	Prior Chemo	**Prior Chemo + EGFRI**	**All patients**
	N = 36	**N = 34**	**N = 70**
Best overall response	**n (%)**	**n (%)**	**n (%)**
Disease control rate (CR or PR or SD)	18 (50.0)	17 (50.0)	35 (50.0)
Overall Response (CR or PR)	2 (5.6)	1 (2.9)	3 (4.3)
Complete Response (CR)	0	0	0
Partial Response (PR)	2 (5.6)	1 (2.9)	3 (4.3)
Stable Disease (SD)	16 (44.4)	16 (47.1)	32 (45.7)
Progressive Disease (PD)	17 (47.2)	16 (47.1)	33 (47.1)
Unknown (UNK)	1 (2.8)	1 (2.9)	2 (2.9)
Patients with early progression	14 (38.9)	14 (41.2)	28 (40.0)

Secondary Objective Result(s)

For disease control and early disease progression (within the first 8 weeks of treatment) in both ITT and ED patient populations please refer the primary results above.

Calculated time to progression (weeks) by time point and arm (ITT population)

	Prior Chemo N=42			Prior Chemo + EGFRI N=43		
	Cumulative information			Cumulative information		
Time point	Subjects at risk	n	KM% est. without event % (95% CI)	Subjects at risk	n	KM% est. without event % (95% CI)
Baseline	42	0	100.0 (100.0, 100.0)	43	0	100.0 (100.0, 100.0)
Week 4	42	4	90.2 (81.2, 99.3)	43	5	87.2 (76.7, 97.7)
Week 8	37	14	65.7 (51.1, 80.3)	33	14	62.1 (46.4, 77.9)
Week 12	25	23	41.4 (25.8, 57.0)	22	19	48.0 (31.7, 64.3)
Week 16	14	30	20.7 (7.3, 34.0)	17	23	36.7 (20.9, 52.5)
Week 20	7	30	20.7 (7.3, 34.0)	12	29	18.4 (5.3, 31.4)
Week 24	6	31	17.2 (4.5, 30.0)	6	29	18.4 (5.3, 31.4)
Week 32	5	32	13.8 (2.0, 25.6)	5	32	7.3 (0.0, 16.8)
Week 48	4	34	6.9 (0.0, 15.9)	2	34	0.0 (0.0, 0.0)
Week 64	2	35	3.4 (0.0, 10.0)	0	34	0.0 (0.0, 0.0)
Week 80	1	35	3.4 (0.0, 10.0)	0	34	0.0 (0.0, 0.0)
Week 96	1	36	0.0 (0.0, 0.0)	0	34	0.0 (0.0, 0.0)

- Subjects at risk immediately prior to (i.e. not including) the time point

- Kaplan-Meier estimates are displayed. Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals

- n = number of subjects with event (i.e. progression/death due to underlying disease)

Progression free survival (weeks) by time point and arm (ITT population)

	Prior Chemo N=42			Prior Chemo + EGFRI N=43		
	Cumulative information			Cumulative information		
Time point	Subjects at risk	n	KM% est. without event % (95% CI)	Subjects at risk	n	KM% est. without event % (95% CI)
Baseline	42	0	100.0 (100.0, 100.0)	43	0	100.0 (100.0, 100.0)
Week 4	42	4	90.2 (81.2, 99.3)	43	5	87.2 (76.7, 97.7)
Week 8	37	14	65.7 (51.1, 80.3)	33	14	62.1 (46.4, 77.9)
Week 12	25	23	41.4 (25.8, 57.0)	22	19	48.0 (31.7, 64.3)
Week 16	15	31	19.3 (6.6, 32.0)	17	23	36.7 (20.9, 52.5)
Week 20	7	31	19.3 (6.6, 32.0)	12	29	18.4 (5.3, 31.4)
Week 24	6	32	16.1 (4.0, 28.2)	6	29	18.4 (5.3, 31.4)
Week 32	5	33	12.9 (1.7, 24.1)	5	32	7.3 (0.0, 16.8)

Week 48	4	35	6.4 (0.0, 14.9)	2	34	0.0 (0.0, 0.0)
Week 64	2	36	3.2 (0.0, 9.4)	0	34	0.0 (0.0, 0.0)
Week 80	1	36	3.2 (0.0, 9.4)	0	34	0.0 (0.0, 0.0)
Week 96	1	37	0.0 (0.0, 0.0)	0	34	0.0 (0.0, 0.0)

- Subjects at risk immediately prior to (i.e. not including) the time point

- Kaplan-Meier estimates are displayed. Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals

- n = number of subjects with event (i.e. progression/death due to any cause)

Summary statistics of pre-dose everolimus concentrations in blood (PK population)

	Day 8	Day 16	Day 22	Week 5	Month 2	Month 3
N	**62**	**61**	**58**	**14**	**37**	**29**
Mean ±SD (ng/ml)	33.9 ±30.29	33.3 ±27.51	27.0 ±27.68	32.7 ±17.80	22.2 ±11.10	27.3 ±20.52
Range (ng/ml)	5.0 - 144.0	0 - 137.0	1.0 - 166.0	7.0 - 69.0	4.0 - 47.0	4.0 - 100.0

Biomarker analysis

Tissue from the primary tumor resection (in one instance from a cerebral metastasis) was available for analysis of one or more IHC markers from 40 patients (19 adenocarcinoma, 16 squamous cell carcinoma, 3 bronchioloalveolar carcinoma and 2 undetermined). Univariate Cox-models with H-scores predictive of PFS found that only pAKT473 and

pAKT308 was independently significant at an un-adjusted alpha-level of at most 5%. The independent estimate of hazard ratio (high vs. low) was pAKT473 (3.31), pAKT308 (2.24). Only 11 cases were evaluable for mutation, 2 of which harbored Kras mutations at G12V, while no EGFR mutations were detected.

FDG-PET

An exploratory evaluation of FDG-PET showed reduction of $sSUV_{max}$ on Day 8. This suggests a potential use of FDG-PET as a tool for the early pharmacodynamic evaluation of mTOR inhibition in NSCLC patients.

Safety Results

Adverse Events by System Organ Class

	Prior Chemo	Prior Chemo + EGFRI	All patients	Prior Chemo	Prior Chemo + EGFRI	All patients
	N = 42	N = 43	N = 85	N = 42	N = 43	N = 85
System organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred term	All CTCAE grades			CTCAE grades 3/4		
Any primary system organ class	41 (97.6)	41 (95.3)	82 (96.5)	21 (50.0)	24 (55.8)	45 (52.9)
Gastrointestinal disorders	33 (78.6)	29 (67.4)	62 (72.9)	3 (7.1)	4 (9.3)	7 (8.2)
Respiratory, thoracic and mediastinal disorders	31 (73.8)	29 (67.4)	60 (70.6)	7 (16.7)	5 (11.6)	12 (14.1)
General disorders and administration site conditions	29 (69.0)	28 (65.1)	57 (67.1)	7 (16.7)	8 (18.6)	15 (17.6)
Metabolism and nutrition disorders	22 (52.4)	24 (55.8)	46 (54.1)	3 (7.1)	7 (16.3)	10 (11.8)
Skin and subcutaneous tissue disorders	23 (54.8)	14 (32.6)	37 (43.5)	0	0	0
Investigations	20 (47.6)	16 (37.2)	36 (42.4)	1 (2.4)	6 (14.0)	7 (8.2)
Blood and lymphatic system disorders	16 (38.1)	16 (37.2)	32 (37.6)	4 (9.5)	3 (7.0)	7 (8.2)
Infections and infestations	16 (38.1)	14 (32.6)	30 (35.3)	3 (7.1)	3 (7.0)	6 (7.1)
Musculoskeletal and connective tissue disorders	19 (45.2)	10 (23.3)	29 (34.1)	0	2 (4.7)	2 (2.4)
Nervous system disorders	11 (26.2)	9 (20.9)	20 (23.5)	0	0	0
Cardiac disorders	4 (9.5)	4 (9.3)	8 (9.4)	3 (7.1)	1 (2.3)	4 (4.7)
Psychiatric disorders	5 (11.9)	7 (16.3)	12 (14.1)	0	1 (2.3)	1 (1.2)
Eye disorders	4 (9.5)	1 (2.3)	5 (5.9)	1 (2.4)	0	1 (1.2)
Hepatobiliary disorders	3 (7.1)	2 (4.7)	5 (5.9)	1 (2.4)	0	1 (1.2)
Injury, poisoning and procedural complications	0	3 (7.0)	3 (3.5)	0	0	0
Renal and urinary disorders	0	3 (7.0)	3 (3.5)	0	1 (2.3)	1 (1.2)
Reproductive system and breast disorders	1 (2.4)	2 (4.7)	3 (3.5)	0	1 (2.3)	1 (1.2)
Ear and labyrinth disorders	2 (4.8)	0	2 (2.4)	0	0	0
Vascular disorders	1 (2.4)	1 (2.3)	2 (2.4)	1 (2.4)	1 (2.3)	1 (1.2)
Endocrine disorders	0	1 (2.3)	1 (1.2)	0	1 (2.3)	1 (1.2)
Neoplasms benign, malignant and unspecified	1 (2.4)	0	1 (1.2)	0	0	0

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

The most commonly reported AEs included of dyspnea, stomatitis, fatigue, anorexia, cough, nausea, anemia, diarrhea, rash and epistaxis.

The most common AEs suspected by the investigator to be treatment related were stomatitis, rash, fatigue, thrombocytopenia, epistaxis, anemia and leukopenia. The majority of events were CTC grade 1/2.

Serious Adverse Events and Deaths

Deaths, SAEs, other grade 3/4 AEs, or AEs resulting in discontinuation or dose adjustment/interruption (safety population)

	Prior Chemo	Prior Chemo + EGFRI	All patients
	N = 42	N = 43	N = 85
	n (%)	n (%)	n (%)
Patients with AEs	41 (97.6)	41 (95.3)	82 (96.5)
Death during study	4 (9.5)	5 (11.6)	9 (10.6)
Primary reason for discontinuation	2 (4.8)	0 (0.0)	2 (2.4)
Not primary reason for discontinuation	2 (4.8)	5 (11.6)	7 (8.2)
SAEs	13 (31.0)	18 (41.9)	31 (36.5)
Grade 3 or 4 AEs	21 (50.0)	24 (55.8)	45 (52.9)
Discontinuation due to AEs	7 (16.7)	8 (18.6)	15 (17.6)
AEs resulting in dose adjustment/interruption	9 (21.4)	10 (23.3)	19 (22.4)

The most common SAEs affected the SOC of Respiratory, thoracic and mediastinal disorders, particularly dyspnea.

Other Relevant Findings

Laboratory evaluation

Hematology: Main newly occurring or worsening CTCAE grade 3 hematological abnormalities were: lymphopenia (15.4%) and anemia (6.1%). Only one patient experienced a newly occurring CTCAE grade 4 hematological abnormality (thrombocytopenia).

Clinical biochemistry: Hyponatremia and, hypokalemia were the most frequent newly occurring or worsening CTCAE grade 3 or 4 biochemistry abnormalities.

Review of CT scans for Interstitial Lung changes/ Pneumonitis

CT scans from 64 patients were available for radiological review, of these only three relevant pulmonary events were reported as AEs during the study (with corresponding reported terms “pneumopathy” “pneumonitis” and “infiltrative abnormalities”). A total of 27 of the 64 patients subset had radiographic lung findings at some time-point (baseline or during study treatment), of these 25% (16/64) were suspected to be related to everolimus. The other suspected causes included infection, cancer, radiation and fluid overload, as well as toxicity from prior medications.

Date of Clinical Trial Report

04 Jun 2008

Date Inclusion on Novartis Clinical Trial Results Database

11 May 2010

Date of Latest Update