Sponsor

Novartis

Generic Drug Name

Everolimus/RAD001

Therapeutic Area of Trial

Metastatic Breast Cancer

Approved Indication

- Postmenopausal women with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, after prior endocrine therapy (Argentina).
- Advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Advanced renal cell carcinoma.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS)
- For the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, everolimus should be used in combination with ciclosporin for microemulsion and corticosteroids.
- For the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids

Protocol Number

CRAD001J2102

Title

A phase Ib study investigating the combination of RAD001 with trastuzumab and vinorelbine in patients with Human epidermal growth factor receptor 2 (HER2)-overexpressing metastatic breast cancer

Phase of Development

Phase Ib

Study Start/End Dates

12-Feb-2007 to 15-Jun-2010

Study Design/Methodology

Open-label, multi-center, dose-escalation Phase Ib study of everolimus in combination with trastuzumab and vinorelbine (HV) in patients with HER2-overexpressing metastatic breast cancer whose disease progressed on/after trastuzumab mono and/or combination therapy. The study consisted of a Core treatment phase during which patients received vinorelbine in combination with everolimus and trastuzumab for up to six cycles followed by an Extension phase. At the investigator's discretion treatment with vinorelbine could continue beyond 6 cycles, i.e. during the Extension phase.

Centres

Belgium (2), France (1), Italy (1), Poland (1) and Sweden (1)

Publication

None

Outcome measures

Primary outcome measure

The primary variable used in the time to event model was time-to-Dose-Limiting Toxicity (DLT).

Secondary outcome measures

- Relative dose intensity (RDI) of vinorelbine
- Discontinuation rate of trastuzumab
- PK parameters derived from the PK profile of treatment drugs when administered alone and in combination
- Best overall response
- Safety assessments consisted in collecting all adverse events (AEs) and serious adverse events (SAEs)

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

2.5, 5, 10 mg everolimus oral tablets + commercially available trastuzumab 2 mg/kg i.v. + commercially available vinorelbine 25 mg/m^2 i.v.

Statistical Methods

The primary endpoint was expressed in terms of the probability of End-of-Cycle 1 DLT rate falling within pre-specified intervals, estimated via the Bayesian time-to-event model, fitted by using all data during the core phase. This model assumes that, given a fixed dose, the time-to-DLT follows a Weibull distribution. The optimal dose needs to have an acceptable toxicity profile and also maximize the probability of End of Cycle 1 DLT rate within the targeted toxicity interval.

Best overall response rates and corresponding 95% confidence intervals (CIs) by Clopper-Pearson method were calculated. Kaplan-Meier estimates of median progression free survival (PFS) as well as the 95% CIs were provided at the end of the study as exploratory analyses on the FAS.

Unless otherwise stated, continuous data were summarized using descriptive statistics such as mean, standard deviation, median and range; categorical data were summarized using contingency tables with frequency and percentages.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Female or male patients (≥ 18 years)
2. World Health Organization (WHO) performance status ≤ 1
3. Histologically confirmed diagnosis of metastatic breast cancer demonstrating HER2-overexpression (immunohistochemistry (IHC) 3+ or Fluorescence in situ hybridization (FISH) positive)
4. Progressive disease on prior trastuzumab alone or in combination with other anticancer agents, or relapse any time after completion of this therapy. Patients could have been treated with trastuzumab ≤ 4 weeks of study treatment start.
5. Women using an acceptable form of contraception or women who met the protocol definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous or induced amenorrhea with serum follicle stimulating hormone levels > 40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy
6. Patients who gave a written informed consent obtained according to local guidelines

Exclusion Criteria

1. Patients receiving endocrine therapy for breast cancer ≤ 2 weeks prior to study treatment start (endocrine therapy had to have either failed in patients with hormone receptor positive disease or to be considered unsuitable for endocrine therapy)
2. Patients currently receiving chemotherapy, immunotherapy, or radio-therapy or who received these ≤ 4 weeks prior to study treatment start or who received lapatinib ≤ 2 weeks prior to study treatment start

3. Patients who previously received vinorelbine
4. Patients who previously received mTOR inhibitors
5. Patients with a known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients
6. Patients receiving chronic treatment with steroids or another immunosuppressive agent
7. Patients using other investigational agents or who received investigational drugs ≤ 4 weeks prior to study treatment start
8. Patients treated with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A
9. Persistent ≥ grade 2 neuropathy or history of grade 3/4 neuropathy of any etiology
10. Female patients who were pregnant or breast feeding, or adults of reproductive potential who were not using effective birth control methods. Unless demonstrated to be post-menopausal, pregnancy was to be excluded by serum pregnancy test ≤ 48 hours prior to administration of the first study treatment.
11. History of noncompliance to medical regimens
12. Patients unwilling to or unable to comply with the protocol

Participant Flow

Patient disposition – n (%) of patients by regimen and dose level (Core treatment phase) (Full Analysis Set)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=30 n (%)	**All QD patients N=30 n (%)**	**Everolimus 20 mg + HV N=6 n (%)**	**Everolimus 30 mg + HV N=14 n (%)**	**All QW patients N=20 n (%)**
Enrolled	30 (100.0)	30 (100.0)	6 (100.0)	14 (100.0)	20 (100.0)
Completed 6 cycles	22 (73.3)	22 (73.3)	4 (66.7)	11 (78.6)	15 (75.0)
Entered extension phase [a]	21 (95.5)	21 (95.5)	4 (100.0)	10 (90.9)	14 (93.3)
Discontinued	8 (26.7)	8 (26.7)	2 (33.3)	3 (21.4)	5 (25.0)
AEs	3 (10.0)	3 (10.0)	0	0	0
Abnormal laboratory value(s)	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0
Patient withdrew consent	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Administrative problem	0	0	0	1 (7.1)	1 (5.0)
Death	0	0	0	0	0
New cancer therapy	5 (16.7)	5 (16.7)	2 (33.3)	2 (14.3)	4 (20.0)
Disease progression	0	0	0	0	0
Entered extension phase [b]	0	0	0	0	0

a: Percentage of patients entering Extension who completed 6 cycles in Core treatment phase
b: Percentage of patients who entered Extension having discontinued Core treatment phase

Patient disposition – n (%) of patients by regimen, schedule and dose level (Extension phase) (Full Analysis Set)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=21 n (%)	**All QD patients N=21 n (%)**	**Everolimus 20 mg + HV N=4 n (%)**	**Everolimus 30 mg + HV N=10 n (%)**	**All QW patients N=14 n (%)**
Entered extension phase	21 (100.0)	21 (100.0)	4 (100.0)	10 (100.0)	14 (100.0)
Discontinued	21 (100.0)	21 (100.0)	4 (100.0)	10 (100.0)	14 (100.0)
AEs	2 (9.5)	2 (9.5)	0	1 (10.0)	1 (7.1)
Abnormal laboratory value(s)	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0
Patient withdrew consent	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Administrative problem	0	0	0	0	0

Death	0	0	0	0	0
New cancer therapy	0	0	0	1 (10.0)	1 (7.1)
Disease progression	19 (90.5)	19 (90.5)	4 (100.0)	8 (80.0)	12 (85.7)

Baseline Characteristics

Demographic summary by regimen, schedule and dose level (Full Analysis Set)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=30 n (%)	All QD patients N=30 n (%)	Everolimus 20 mg + HV N=6 n (%)	Everolimus 30 mg + HV N=14 n (%)	All QW patients N=20 n (%)
Sex					
Female	29 (96.7)	29 (96.7)	6 (100.0)	14 (100.0)	20 (100.0)
Male	1 (3.3)	1 (3.3)	0	0	0
Baseline Age (years)					
< 65	24 (80.0)	24 (80.0)	6 (100.0)	13 (92.9)	19 (95.0)
≥ 65	6 (20.0)	6 (20.0)	0	1 (7.1)	1 (5.0)
N	30	30	6	14	20
Mean	51.9	51.9	53.0	48.5	49.9
SD	10.67	10.67	7.38	8.65	8.37
Median	52.5	52.5	51.5	47.5	48.5
Range	30-72	30-72	44-63	38-68	38-68
WHO performance status [a]					
0	22 (73.3)	22 (73.3)	5 (83.3)	6 (42.9)	11 (55.0)
1	8 (26.7)	8 (26.7)	1 (16.7)	8 (57.1)	9 (45.0)

a: Key: 0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work, 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, 4=Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair

Disease history and baseline characteristics by regimen, schedule and dose level (Full Analysis Set)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=30 n (%)	All QD patients N=30 n (%)	Everolimus 20 mg + HV N=6 n (%)	Everolimus 30 mg + HV N=14 n (%)	All QW patients N=20 n (%)
Histology/Cytology					
Invasive ductal carcinoma	22 (73.3)	22 (73.3)	5 (83.3)	11 (78.6)	16 (80.0)
Invasive lobular carcinoma	3 (10.0)	3 (10.0)	1 (16.7)	0	1 (5.0)
Other	4 (13.3)	4 (13.3)	0	3 (21.4)	3 (15.0)
Missing	1 (3.3)	1 (3.3)	0	0	0
Histologic grade					
Well differentiated	0	0	0	0	0
Moderately differentiated	7 (23.3)	7 (23.3)	0	4 (28.6)	4 (20.0)

Poorly differentiated	17 (56.7)	17 (56.7)	4 (66.7)	6 (42.9)	10 (50.0)
Undifferentiated	1 (3.3)	1 (3.3)	0	0	0
Unknown	5 (16.7)	5 (16.7)	2 (33.3)	4 (28.6)	6 (30.0)
Current stage of cancer					
Stage IV	27 (90.0)	27 (90.0)	6 (100.0)	11 (78.6)	17 (85.0)
Stage IVa	3 (10.0)	3 (10.0)	0	3 (21.4)	3 (15.0)
HER2 status					
IHC 3+	10 (33.3)	10 (33.3)	4 (66.7)	4 (28.6)	8 (40.0)
FISH positive	20 (66.7)	20 (66.7)	2 (33.3)	10 (71.4)	12 (60.0)
Other	0	0	0	0	0
Target lesions					
Yes	26 (86.7)	26 (86.7)	4 (66.7)	9 (64.3)	13 (65.0)
No	4 (13.3)	4 (13.3)	2 (33.3)	5 (35.7)	7 (35.0)
Non-target lesions					
Yes	20 (66.7)	20 (66.7)	5 (83.3)	11 (78.6)	16 (80.0)
No	10 (33.3)	10 (33.3)	1 (16.7)	3 (21.4)	4 (20.0)
Disease free interval (weeks) [1]					
N	19	19	5	10	15
Median	127.71	127.71	76.71	149.71	97.86
Min – Max	0.1-364.7	0.1-364.7	32.4-759.9	2.9-722.3	2.9-759.9

[1] Disease free interval was calculated as the interval between date of first surgery with no residual disease and date of first recurrence of disease.

Outcome measures

Primary Outcome Result(s)

Summary of DLTs by cycle, regimen, schedule and dose level (Dose determining population)

Regimen: Continuous

		Daily		Weekly		
Cycle		**Everolimus 5 mg + HV** **N=26** **n (%)**	**All QD patients** **N=26** **n (%)**	**Everolimus 20 mg + HV** **N=3** **n (%)**	**Everolimus 30 mg + HV** **N=11** **n (%)**	**All QW patients** **N=14** **n (%)**
	Total of patients with DLTs	20 (76.9)	20 (76.9)	0	6 (54.5)	6 (42.9)
	Total number of DLTs	27	27	0	12	12
1	No. of patients exposed	26	26	3	11	14
	No. of patients with DLT	15 (57.7)	15 (57.7)	0	4 (36.4)	4 (28.6)
	No. of DLTs	16	16	0	4	4
2	No. of patients exposed	25	25	3	11	14
	No. of patients with DLT	2 (8.0)	2 (8.0)	0	0	0
	No. of DLTs	2	2	0	0	0
3	No. of patients exposed	24	24	3	10	13

	No. of patients with DLT	6 (25.0)	6 (25.0)	0	3 (30.0)	3 (23.1)
	No. of DLTs	6	6	0	3	3
4	No. of patients exposed	22	22	3	10	13
	No. of patients with DLT	1 (4.5)	1 (4.5)	0	1 (10.0)	1 (7.7)
	No. of DLTs	1	1	0	1	1
5	No. of patients exposed	21	21	3	10	13
	No. of patients with DLT	1 (4.8)	1 (4.8)	0	1 (10.0)	1 (7.7)
	No. of DLTs	1	1	0	1	1
6	No. of patients exposed	21	21	3	10	13
	No. of patients with DLT	1 (4.8)	1 (4.8)	0	2 (20.0)	2 (15.4)
	No. of DLTs	1	1	0	3	3

End of Cycle 1 DLT rate (Dose determining population)

Everolimus dose (mg)	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**	**[0%,20%) [1]**	**[20%,35%) [2]**	**[35%,60%) [3]**	**[60%,100%] [4]**
5.0 mg (N= 26)	0.307	0.065	0.191	0.304	0.441	0.037	0.716	0.248	0.000
20.0 mg (N= 3)	0.078	0.043	0.014	0.072	0.178	0.991	0.009	0.000	0.000
30.0 mg (N= 11)	0.139	0.056	0.054	0.131	0.264	0.858	0.141	0.002	0.000

Based on posterior distribution
[1] Probability of DLT rate being within [0%,20%]; [2] Probability of DLT rate being within [20%,35%]; [3] Probability of DLT rate being within [35%,60%]; [4] Probability of DLT rate being within [60%,100%]

The model estimated that in the daily group, 5 mg daily maximized the probability of End-of-Cycle 1 DLT rate falling within the targeted toxicity interval (71.6%) and also controlled the rate within the excessive (24.8%) and unacceptable toxicity intervals (0%). In the weekly group, the probability of End-of-Cycle 1 DLT rate being within the excessive toxic interval was almost 0 for both 20 mg and 30 mg weekly treatment schedules, but the 30 mg weekly (14.1%) had a higher probability of being within the targeted toxicity interval than 20 mg weekly (<1%). Therefore, 5 mg daily had an acceptable toxicity profile and also maximized the probability of End of Cycle 1 DLT rate within the targeted toxicity interval among three dose groups.

Secondary Outcome Result(s)

Cumulative dose, dose intensity and relative dose intensity of study treatment, by regimen, schedule and dose level (Safety population)

Regimen: Continuous

	Daily		Weekly			
	Everolimus 5 mg + HV		Everolimus 20 mg + HV		Everolimus 30 mg + HV	
	Everolimus N=30 (mg)	Vinorelbine N=30 (mg/m^2)	Everolimus N=6 (mg)	Vinorelbine N=6 (mg/m^2)	Everolimus N=14 (mg)	Vinorelbine N=14 (mg/m^2)
Cumulative dose [1]						
n	30	30	6	6	14	14
Mean	365.7	202.6	250.0	217.5	370.7	221.4
SD	160.57	81.71	81.73	92.80	155.39	82.24
Median	330.0	219.6	280.0	262.7	405.0	259.2
Range	75 - 660	25 - 307	100 - 320	76 - 300	0 - 540	25 - 300
Dose intensity (x/day) [2]						
n	30	30	6	6	14	14
Mean	3.24	1.75	2.25	1.90	3.11	2.01
SD	0.922	0.375	0.302	0.415	1.080	0.277
Median	3.18	1.75	2.35	2.02	3.29	2.06
Range	1.7 - 5.0	0.6 - 2.4	1.7 - 2.6	1.3 - 2.3	0.0 - 4.2	1.5 - 2.4
Relative dose intensity [3]						
n	30	30	6	6	14	14
Mean	0.656	0.736	0.788	0.798	0.725	0.844
SD	0.1868	0.1574	0.1057	0.1743	0.2521	0.1165
Median	0.642	0.737	0.824	0.850	0.768	0.865
Range	0.34-1.00	0.25-0.99	0.61-0.91	0.56-0.99	0.00-0.98	0.61-1.00
Relative dose intensity - n (%) [3]						
0.00 to <0.50	8 (26.7)	2 (6.7)	0	0	1 (7.1)	0
0.50 to <0.70	8 (26.7)	8 (26.7)	1 (16.7)	2 (33.3)	5 (35.7)	2 (14.3)
0.70 to <0.90	11 (36.7)	16 (53.3)	4 (66.7)	1 (16.7)	4 (28.6)	8 (57.1)
0.90 to <1.10	3 (10.0)	4 (13.3)	1 (16.7)	3 (50.0)	4 (28.6)	4 (28.6)
≥ 1.10	0	0	0	0	0	0

[1] Cumulative dose = total dose received.

[2] Dose intensity = cumulative dose/duration of exposure.

[3] Relative dose intensity = dose intensity/planned dose intensity.

The relative dose intensity for vinorelbine is around 0.8 for all groups and the mean relative dose intensity for everolimus/vinorelbine is slightly smaller for the 5 mg daily group than for the two weekly dose groups. Most patients had relative dose intensity >0.50.

Discontinuation of trastuzumab

There is no discontinuation from trastuzumab in patients who were still on everolimus/vinorelbine in 5 mg daily and 20 mg weekly groups. There are overall 3 patients (21.4%) in the 30 mg weekly group who discontinued trastuzumab, while still on everolimus/vinorelbine.

Cumulative relative dose intensity

In the 5 mg daily and 30 mg weekly treatment groups, the mean cumulative RDI for both everolimus and vinorelbine were relatively constant through the six cycles of treatment.

In the 20 mg weekly group, patients showed a constant mean cumulative RDI for everolimus over cycles. For vinorelbine, a slight increasing of the mean cumulative RDI over cycles was observed.

PK Parameters

Summary statistics of everolimus pharmacokinetic parameters at Cycle 1 Day 8 and at Cycle 1 Day 15

			Daily	Weekly	
Everolimus PK parameter (units)	**Profile day/ cycle***	**Summary stats**	**Everolimus 5 mg + HV**	**Everolimus 20 mg + HV**	**Everolimus 30 mg + HV**
$AUC_{0\text{-last}}$ (ng.h/mL)	C1D8	n	20	2	3
		Mean ± SD	313.80 ± 99.107	1741.32 ± 20.908	2452.76 ± 736.879
		CV%	31.6	1.2	30
	C1D15	n	8	1	3
		Mean ± SD	347.26 ± 131.776	1818.86	2849.6 ± 1891.804
		CV%	37.9		66.4
C_{max} (ng/mL)	C1D8	n	23	5	9
		Mean ± SD	41.33 ± 14.94	93.22 ± 14.421	107.43 ± 31.817
		CV%	36.1	15.5	29.6
	C1D15	n	9	3	8
		Mean ± SD	42.1 ± 19.847	89.53 ± 19.795	120.78 ± 45.05
		CV%	47.1	22.1	37.3
C_{min} (ng/mL)	C1D8	n	26	4	10
		Mean ± SD	6.85 ± 3.11	0.48 ± 0.103	1.04 ± 0.894
		CV%	45.4	21.2	85.6
	C1D15	n	17	2	4
		Mean ± SD	6.67 ± 3.833	0.43 ± 0.008	0.5 ± 0.085
		CV%	57.5	1.9	17
CL/F (L/h)	C1D8	n	20	2	3
		Mean ± SD	17.664 ± 6.0913	11.486 ± 0.1379	12.955 ± 3.658
		CV%	34.48	1.2	28.24

	C1D15	n	8	1	3
		Mean ± SD	17.057 ± 9.1819	10.996	13.598 ± 7.1614
		CV%	53.83		52.67
CL/Fnb ($L/h/m^2$)	C1D8	n	20	2	3
		Mean ± SD	10.451 ± 3.8981	7.176 ± 0.9965	6.806 ± 2.1202
		CV%	37.3	13.89	31.15
	C1D15	n	8	1	3
		Mean	10.555 ± 5.9478	7.48	7.903 ± 4.7344
		CV%	56.35		59.91
T_{max} (h)	C1D8	n	23	5	9
		Median	0.98	1	0.5
		Range	0.4 - 1.3	0.5 - 2.0	0.5 - 1.0
	C1D15	n	9	3	8
		Median	1	0.5	0.55
		Range	0.5 - 4.0	0.5 - 1.0	0.5 - 2.0

* D8 C1 Everolimus + HV in combination; D15 C1 Everolimus (no vinorelbine)

Summary statistics of vinorelbine pharmacokinetic parameters at Cycle 1 Day 1 and at Cycle 1 Day 8

PK parameter (units)	Profile day/cycle*	Summary stats	Daily Everolimus 5 mg + HV	Weekly Everolimus 20 mg + HV	Weekly Everolimus 30 mg + HV
$AUC_{0\text{-last}}$ (ng.h/mL)	C1D1	n	22	6	9
		Mean ± SD	531.87 ± 409.517	1619.77 ± 595.874	325.73 ± 204.23
		CV%	77	36.8	62.7
	C1D8	n	19	3	9
		Mean ± SD	588.83 ± 425.995	1480.1 ± 415.079	482.4 ± 367.74
		CV%	72.3	28	76.2
C_{max} (ng/mL)	C1D1	n	23	6	9
		Mean ± SD	116.4 ± 110.926	226.5 ± 22.323	62.62 ± 39.052
		CV%	95.3	9.9	62.4
	C1D8	n	21	3	9
		Mean ± SD	127.31 ± 113.402	238.67 ± 50.362	69.86 ± 39.078
		CV%	89.1	21.1	55.9
T_{max} (h)	C1D1	n	23	6	9
		Median	0.67	0.71	0.75
		Range	0.5 - 1.7	0.7 - 0.8	0.7 - 1.4
	C1D8	n	21	3	9
		Median	0.67	0.68	0.67
		Range	0.5 - 1.4	0.7 - 0.8	0.7 - 24.4

*: C1D1 Vinorelbine alone; C1D8 Everolimus + HV in combination

Trastuzumab pharmacokinetics:

Trastuzumab concentrations were in the range of 23.77 – 35.7 µg/mL at Cycle 1 Day 8, and all subsequent cycles. Everolimus dose levels and cycle numbers did not seem to have any influence on trastuzumab concentrations in this study. Trastuzumab concentration at Cycle 1 Day 1 was 69.1 ± 34.949 µg/mL at the everolimus 5 mg dose level and 39.40 ± 11.879 µg/mL at the 30 mg weekly everolimus dose regimen. These levels are higher than concentrations noted in subsequent cycles, and could be attributed to the treatment by trastuzumab prior to the start of the study on Cycle 1 Day 1.

Statistical analysis of the drug interaction for everolimus, by everolimus PK parameter, regimen, schedule and actual everolimus dose level at sample time (Safety population)

Regimen: Continuous – Schedule: Daily (N=30)							
PK parameter (units) [a]	**Everolimus Dose (mg)**	**Profile Day/Cycle**	**n**	**Geometric mean [b]**	**Ratio of geometric means [c]**		**Intra-patients**
					Ratio	**90% CI**	**CV% [d]**
$AUC_{0\text{-}tlast}$ (ng.h/mL)	5	A: C1D15 (ref)	8	292.19			
		B: C1D8 (test)	20	296.12	1.01	(0.83, 1.24)	14.9
C_{max} (ng/mL)	5	A: C1D15 (ref)	9	37.05			
		B: C1D8 (test)	23	38.68	1.04	(0.77, 1.41)	42.8
Regimen: Continuous – Schedule: Weekly (N=20)							
PK parameter (units) [a]	**Everolimus Dose (mg)**	**Profile Day/Cycle**	**n**	**Geometric mean [b]**	**Ratio of geometric means [c]**		**Intra-patients**
					Ratio	**90% CI**	**CV% [d]**
$AUC_{0\text{-}tlast}$ (ng.h/mL)	20	A: C1D15 (ref)	1	1834.33			
		B: C1D8 (test)	2	1741.22	0.95	(0.95, 0.95)	
	30	A: C1D15 (ref)	3	2362.13			
		B: C1D8 (test)	3	2621.40	1.11	(1.11, 1.11)	
C_{max} (ng/mL)	20	A: C1D15 (ref)	3	89.50			
		B: C1D8 (test)	5	94.01	1.05	(0.74, 1.50)	
	30	A: C1D15 (ref)	8	112.21			
		B: C1D8 (test)	9	105.97	0.94	(0.75, 1.19)	23.8

a: The log-transformed PK parameter was modeled by means of a linear model including terms for treatment (i.e. combination or alone), actual dose level at sample time and treatment*actual dose at sample time interaction, and patient as a random effect.
b: The geometric mean was obtained by back-transforming on the original scale the mean of the log-transformed PK parameters.
c: Comparison of interest: B/A (test/ref).
d: Intra-patient CV: calculated from the variance of the residual error of the model, by means of the formula: CV = SQRT(EXP(variance)-1)×100.

Statistical analysis of the drug interaction for vinorelbine, by vinorelbine PK parameter, regimen, schedule and actual everolimus dose level at sample time (safety population)

Regimen: Continuous – Schedule: Daily (N=30)							
PK parameter (units) [a]	**Everolimus Dose (mg)**	**Profile Day/Cycle**	**n**	**Geometric mean [b]**	**Ratio of geometric means [c]**		**Intra-patients**
					Ratio	**90% CI**	**CV% [d]**
$AUC_{0\text{-}tlast}$							

(ng.h/mL)	5	A: C1D1 (ref)	22	420.44			
		B: C1D8 (test)	19	493.63	1.17	(1.04, 1.32)	20.1
C_{max} (ng/mL)	0	A: C1D1 (ref)	5	66.44			
	5	A: C1D1 (ref)	23	84.16			
		B: C1D8 (test)	21	96.00	1.14	(0.91, 1.42)	42.9

Regimen: Continuous – Schedule: Weekly (N=20)

PK parameter (units) [a]	Everolimus Dose (mg)	Profile Day/Cycle	n	Geometric mean [b]	Ratio of geometric means [c]		Intra-patients
					Ratio	90% CI	CV% [d]
$AUC_{0\text{-}tlast}$ (ng.h/mL)	20	A: C1D1 (ref)	6	1550.10			
		B: C1D8 (test)	3	1609.44	1.04	(0.69, 1.56)	
	30	A: C1D1 (ref)	9	280.85			
		B: C1D8 (test)	9	382.93	1.36	(1.07, 1.73)	28.4
C_{max} (ng/mL)	0	A: C1D1 (ref)	5	120.15			
	20	A: C1D1 (ref)	6	225.56			
		B: C1D8 (test)	3	249.89	1.11	(0.84, 1.45)	
	30	A: C1D1 (ref)	9	54.04			
		B: C1D8 (test)	9	61.12	1.13	(0.97, 1.32)	18.6

a: The log-transformed PK parameter was modeled by means of a linear model including terms for treatment (i.e. combination or alone), actual dose level at sample time and treatment*actual dose at sample time interaction, and patient as a random effect.
b: The geometric mean was obtained by back-transforming on the original scale the mean of the log-transformed PK parameters.
c: Comparison of interest: B/A (test/ref).
d: Intra-patient CV: calculated from the variance of the residual error of the model, by means of the formula: CV = SQRT(EXP(variance)-1)×100.

Best overall response by regimen, schedule and dose level (Full Analysis Set)

Regimen: Continuous

	Daily		Weekly		
Best overall response	**Everolimus 5 mg + HV**	**All QD patients**	**Everolimus 20 mg + HV**	**Everolimus 30 mg + HV**	**All QW patients**
	N=30	**N=30**	**N=6**	**N=14**	**N=20**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Complete response (CR)	1 (3.3)	1 (3.3)	0	0	0
Partial response (PR)	5 (16.7)	5 (16.7)	1 (16.7)	2 (14.3)	3 (15.0)
Stable disease (SD)	18 (60.0)	18 (60.0)	3 (50.0)	9 (64.3)	12 (60.0)
Progressive disease (PD)	4 (13.3)	4 (13.3)	2 (33.3)	2 (14.3)	4 (20.0)
Unknown (UNK)	2 (6.7)	2 (6.7)	0	1 (7.1)	1 (5.0)
Objective response rate (CR or PR)	6 (20.0)	6 (20.0)	1 (16.7)	2 (14.3)	3 (15.0)
95% CI of response rate	[7.7, 38.6]	[7.7, 38.6]	[0.4, 64.1]	[1.8, 42.8]	[3.2, 37.9]
Disease control rate (CR or PR or SD)	24 (80.0)	24 (80.0)	4 (66.7)	11 (78.6)	15 (75.0)
95% CI of disease control rate	[61.4, 92.3]	[61.4, 92.3]	[22.3, 95.7]	[49.2, 95.3]	[50.9, 91.3]
CR or PR or SD ≥ 24 weeks	16 (53.3)	16 (53.3)	4 (66.7)	8 (57.1)	12 (60.0)
95% CI of clinical benefit rate	[34.3, 71.7]	[34.3, 71.7]	[22.3, 95.7]	[28.9, 82.3]	[36.1, 80.9]

The best overall response was determined based on investigator assessments of overall lesion response as recorded in the eCRF.
The Clopper-Pearson method was used to determine the confidence intervals.

Safety Results

Adverse Events by System Organ Class (Safety Population)

Number of patients with most frequent (at least 30% of all patients) AEs regardless of study treatment relationship by primary system organ class and preferred term (Safety population)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=30 n (%)	**All QD patients N=30 n (%)**	**Everolimus 20 mg + HV N=6 n (%)**	**Everolimus 30 mg + HV N=14 n (%)**	**All QW patients N=20 n (%)**
Any primary system organ class (SOC)					
Total	30 (100.0)	30 (100.0)	6 (100.0)	14 (100.0)	20 (100.0)
Blood and lymphatic system disorders					
Total	29 (96.7)	29 (96.7)	6 (100.0)	12 (85.7)	18 (90.0)
Neutropenia	29 (96.7)	29 (96.7)	6 (100.0)	12 (85.7)	18 (90.0)
Leukopenia	15 (50.0)	15 (50.0)	5 (83.3)	3 (21.4)	8 (40.0)
General disorders and administration site conditions					
Total	29 (96.7)	29 (96.7)	5 (83.3)	13 (92.9)	18 (90.0)
Asthenia	20 (66.7)	20 (66.7)	4 (66.7)	4 (28.6)	8 (40.0)
Pyrexia	14 (46.7)	14 (46.7)	4 (66.7)	6 (42.9)	10 (50.0)
Gastrointestinal disorders					
Total	29 (96.7)	29 (96.7)	6 (100.0)	11 (78.6)	17 (85.0)
Stomatitis	24 (80.0)	24 (80.0)	5 (83.3)	6 (42.9)	11 (55.0)
Nausea	15 (50.0)	15 (50.0)	2 (33.3)	8 (57.1)	10 (50.0)
Diarrhoea	10 (33.3)	10 (33.3)	1 (16.7)	6 (42.9)	7 (35.0)
Musculoskeletal and connective tissue disorders					
Total	24 (80.0)	24 (80.0)	6 (100.0)	13 (92.9)	19 (95.0)
Myalgia	8 (26.7)	8 (26.7)	4 (66.7)	4 (28.6)	8 (40.0)
Nervous system disorders					
Total	19 (63.3)	19 (63.3)	4 (66.7)	12 (85.7)	16 (80.0)
Headache	11 (36.7)	11 (36.7)	3 (50.0)	10 (71.4)	13 (65.0)
Respiratory, thoracic and mediastinal disorders					
Total	23 (76.7)	23 (76.7)	2 (33.3)	10 (71.4)	12 (60.0)
Cough	11 (36.7)	11 (36.7)	2 (33.3)	4 (28.6)	6 (30.0)
Epistaxis	12 (40.0)	12 (40.0)	0	3 (21.4)	3 (15.0)
Metabolism and nutrition disorders					
Total	12 (40.0)	12 (40.0)	2 (33.3)	6 (42.9)	8 (40.0)
Decreased appetite	9 (30.0)	9 (30.0)	1 (16.7)	5 (35.7)	6 (30.0)

Primary SOCs were presented by descending frequency in the everolimus group; preferred terms were sorted within primary SOC by descending frequency in the everolimus group.
A subject with multiple occurrences of an AE was counted only once in the AE category.
A subject with multiple AEs within a primary SOC was counted only once in the total row.

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

CTC grade 3 or 4 adverse events (experienced by at least 5% of all patients) regardless of study treatment relationship by primary system organ class and preferred term (Safety population)

Regimen: Continuous

	Daily		Weekly		
Primary SOC Preferred term	**Everolimus 5 mg + HV N=30 n (%)**	**All QD patients N=30 n (%)**	**Everolimus 20 mg + HV N=6 n (%)**	**Everolimus 30 mg + HV N=14 n (%)**	**All QW patients N=20 n (%)**
Neutropenia	26 (86.7)	26 (86.7)	6 (100.0)	12 (85.7)	18 (90.0)
Leukopenia	15 (50.0)	15 (50.0)	5 (83.3)	3 (21.4)	8 (40.0)
Lymphopenia	4 (13.3)	4 (13.3)	3 (50.0)	0	3 (15.0)
Anaemia	2 (6.7)	2 (6.7)	0	1 (7.1)	1 (5.0)
Febrile neutropenia	2 (6.7)	2 (6.7)	0	1 (7.1)	1 (5.0)
Stomatitis	5 (16.7)	5 (16.7)	0	1 (7.1)	1 (5.0)
Diarrhoea	2 (6.7)	2 (6.7)	0	1 (7.1)	1 (5.0)
Fatigue	1 (3.3)	1 (3.3)	0	2 (14.3)	2 (10.0)
Decreased appetite	2 (6.7)	2 (6.7)	0	1 (7.1)	1 (5.0)

A subject with multiple occurrences of an AE was counted only once in the AE category.

Serious Adverse Events and Deaths

Number (%) of patients who died, had SAEs, discontinued because of an AE or had a grade 3-4 AE (Safety population)

Regimen: Continuous

	Daily		Weekly		
	Everolimus 5 mg + HV N=30 n (%)	**All QD patients N=30 n (%)**	**Everolimus 20 mg + HV N=6 n (%)**	**Everolimus 30 mg + HV N=14 n (%)**	**All QW patients N=20 n (%)**
All deaths [1]	1 (3.3)	1 (3.3)	0	1 (7.1)	1 (5.0)
On treatment deaths [2]	1 (3.3)	1 (3.3)	0	1 (7.1)	1 (5.0)
SAEs	8 (26.7)	8 (26.7)	1 (16.7)	4 (28.6)	5 (25.0)
AEs leading to any study treatment discontinuation	9 (30.0)	9 (30.0)	1 (16.7)	2 (14.3)	3 (15.0)
AEs of grade 3-4	30 (100.0)	30 (100.0)	6 (100.0)	14 (100.0)	20 (100.0)
Clinically notable AEs	30 (100.0)	30 (100.0)	6 (100.0)	14 (100.0)	20 (100.0)

[1] Included all deaths regardless of whether they were within 28 days of last treatment.
[2] Death occurring not more than 28 days after end of study treatment.

Categories were not mutually exclusive.
AEs occurring more than 28 days after EOT were not summarized. Clinically notable AEs were the events for which there was a specific clinical interest in connection with everolimus or events which were similar in nature.

Other Relevant Findings

None

Date of Clinical Trial Report

06-Mar-2012

Date Inclusion on Novartis Clinical Trial Results Database

29-Mar-2012

Date of Latest Update