Developmental Therapeutics Poster Discussion

Sylvie Rottey, MD, PhD

Medical Oncologist

Clinical Pharmacologist

Ghent University Hospital, Belgium

Disclosure slide

- Consultancy

Bayer	Pfizer	Novartis
Merck	J&J	Sanofi-Aventis
GSK	Roche	

Abstracts

- I. PHASE I STUDY OF AFATINIB (BIBW 2992), AN ERBB FAMILY BLOCKER PLUS NINTEDANIB (BIBF 1120), A TRIPLE ANGIOKINASE INHIBITOR, IN PATIENTS (PTS) WITH ADVANCED SOLID TUMOURS
  J. Soria et al. - Villejuif, France

- II. PRECLINICAL AND CLINICAL EVALUATION OF THE COMBINATION OF SORAFENIB AND EVEROLIMUS IN PATIENTS WITH ADVANCED SOLID TUMORS W.W. Ma et al. – Buffalo, USA

- III. A PHASE I STUDY OF THE COMBINATION OF RO4929097 AND CEDIRANIB IN PATIENTS WITH ADVANCED SOLID TUMORS. S. Sahebjam et al. – Toronto, Canada

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
Administration	2 x oral	2 x oral	2 x oral
Mode of action	Irrev. ErbB family blocker + Triple angiokinase inhibitor VEGFR 1–3 FGFR 1–3 PDGFR-α and -β	VEGFR PDGFR RAF kinases + mTOR	selective inhibitor of gamma secretase (NOTCH) + VEGFR-1, VEGFR-2, VEGFR-3, and c-Kit

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
Primary Objectives	-MTD	/	-Assess safety -Tolerability -Recommended phase II dose
Secondary Objectives	-Safety -Efficacy -PK -CTC	/	-Efficacy -PK -PD

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
Number of patients included	45	22	20
Main diagnoses	-Colon (9) -NSCLC (6) -Ovary (6)	Adenocarcinoma pancreas (12)	-Colorectal cancers (6) -Uterine sarcoma (4) -RCC (3)
Number of cohorts	9	2	3

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
Evaluable patients	41/45	10/22	19/20
Cycle	28 days	28 days 1 week run-in 1 drug	42 days C1 – 21 days from C2 on
3 + 3 design	+	+	+

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
AE grade 3	Diarrhoea 43% Dehydration 11% Anorexie 9% Asthenia 7% AST rise 7% ALT rise 11% Hypokalemia 9% Cytolytic hepatitis 5%	Diarrhea (1) Hand foot skin (1) GI fistula (1) Rash (2) Hypophosphatemia (4)	Hypertension (3) Hypophosphatemia (1) AST rise (1) ALT rise (1)
DLT	*After 1 cycle* Diarrhoea Rise AST/ALT Rise Screa Dehydration	*After 1 cycle* Diarrhea Hand foot skin GI fistula Rash Hypophosphatemia	*After 42 days* Grade 4 AST elevation Grade 4 hypertension

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
PK	No interaction both drugs	No interaction both drugs	PK analysis of RO: no evidence of CYP3A4 auto-induction
Prognostic Predictive	CTC	/	Serum angiogenic biomarkers and expression of Notch pathway biomarkers : not associated with TTP
Best response	PR (1 H&H, 1 Breast)	SD (1 uterine carcinosarcoma, 6 C)	SD in 12 patients
Median time on R/	60 days	1,5 cycles (42 days)	3 cycles (84 days)

	I. Afatinib + Nintedanib	II. Sorafenib + Everolimus	III. RO4929097 + Cediranib
Phase I monotherapy	50 mg a day A 250 mg BID N	400 mg BID S 10 mg a day E	20-135 mg (3 d a wk) RO 45 mg a day C
Dose first cohort	10 mg C + 200 mg BID	400 mg BID + 5 mg	10 mg (3 days a week) + 20 mg daily
MTD	40 mg I + 150 mg BID + 30 mg C + 150 mg BID	Not determined : DLTs in both studied dose levels	Recommended phase II dose : 20 mg RO 30 mg C

Cohorts and DLTs – Soria et al.

Cohort	Afatinib (mg q.d.)	Nintedanib (mg b.i.d.)	Patients entered/ evaluable	Patients with DLT	DLT/CTCAE Grade
1	10 C	200	3/3	0	
2	20 C	200	3/3	0	
3	30 C	200	8/7	3	• G3 diarrhoea (2 patients) • G3 transaminase elevation/diarrhoea
4	40 C	200	3/3	3	• G3 diarrhoea • G3 transaminase elevation • G2 creatinine increase/G3 transaminase elevation
5	30 I	200	6/5	2	• G3 diarrhoea/G2 creatinine increase • G3 transaminase elevation
6	40 I	200	6/5	2	• G3 dehydration • G4 transaminase elevation
7	40 C	150	3/3	2	• G3 diarrhoea/dehydration/renal failure • G3 renal failure
8	40 I	150	7/6	0	**MTD**
9	30 C	150	6/6	0	**MTD**

G = Grade; C = continuous; I = intermittent

CTCs – Soria et al.

	Day 0	Day 15	Day 30	Day 60
Patients,* n	**40**	**40**	**40**	**40**
CTC samples, n	**39**	**37**	**34**	**21**
<5 CTC, n (%)	29 (74.4)	31 (83.8)	30 (88.2)	16 (76.2)
≥5 CTC, n (%)	10 (25.6)	6 (16.2)	4 (11.8)	5 (23.8)
Patients* with stable disease ≥12 weeks, n	**9**	**9**	**9**	**9**
CTC samples, n	**9**	**8**	**9**	**9**
<5 CTC, n (%)	9 (100.0)	8 (100.0)	9 (100.0)	8 (88.9)
≥5 CTC, n (%)	0	0	0	1 (11.1)

*** Excluded patients with non-epithelial tumours**

- At baseline, there were 10 (25.6%) patients with an unfavourable CTC count (≥5 CTCs). After 1 month of treatment, only four (11.8%) patients had an unfavourable CTC count
- Most patients with stable disease lasting ≥12 weeks had a favourable CTC count

Treatment-related Grade 2 and above Adverse Events – Ma et al.

Adverse Event	Dose level 1 (n=6)		Dose level 2 (n=4)	
	Grade 2	Grade 3/4	Grade 2	Grade 3/4
Hematologic				
Lymphopenia	1			
GI				
Fistula		1*		
Diarrhea	1			1*
Abdominal pain	1			
Alkaline Phosphatase			1	
Anal pain			1	
Anorexia			1	1
Skin				
Rash	1		2	2*
Hand-foot syndrome	2	1*		
Other				
Hypophosphatemia		2*	2	2*
Hypokalemia	1			
Hyperglycemia	2			
Hypercholesteralemia			1	
Fatigue			2	
Bladder pain	1			
Inflammation NOS	1			

*Dose Limiting Toxicity (DLT)

Most common treatment-related adverse events - Sahebjam et al.

Drug-related AE (%)	Grades	Dose Level		
		1 (n=7)	2 (n=7)	3 (n=6)
		Cediranib 20mg RO4929097 10 mg	Cediranib 20mg RO4929097 20 mg	Cediranib 30mg RO4929097 20 mg
Diarrhea	**All** 3–4	**6 (86%)** 0 (0%)	**3 (43%)** 0 (0%)	**4 (66%)** 0 (0%)
Hypertension	**All** 3–4	**6 (86%)** 2 (28%)	**2 (28%)** 0 (0%)	**4 (66%)** 1 (17%)
Fatigue	**All** 3–4	**3 (43%)** 0 (0%)	**3 (43%)** 0 (0%)	**4 (66%)** 0 (0%)
Nausea	**All** 3–4	**3 (43%)** 0 (0%)	**4 (57%)** 0 (0%)	**3 (50%)** 0 (0%)
Hypothyroidism	**All** 3–4	**3 (43%)** 0 (0%)	**2 (28%)** 0 (0%)	**3 (50%)** 0 (0%)
Headache	**All** 3–4	**4 (57%)** 0 (0%)	**1 (14%)** 0 (0%)	**2 (33%)** 0 (0%)
Hypophosphatemia	**All** 3–4	**3 (43%)** 1 (14%)	**2 (28%)** 0 (0%)	**2 (33%)** 0 (0%)
Increased alanine aminotransferase	**All** 3–4	**2 (28%)** 0 (0%)	**3 (43%)** 1 (14%)	**3 (50%)** 0 (0%)
Increased aspartate aminotransferase	**All** 3–4	**0 (33%)** 0 (0%)	**5 (71%)** 1 (14%)	**1 (16%)** 0 (0%)

Conclusions of the authors

Conclusions Soria et al.

- The MTDs were defined as:
  - Afatinib 40 mg q.d. every other week plus nintedanib 150 mg b.i.d.
  - Afatinib 30 mg q.d. continuously plus nintedanib 150 mg b.i.d.
- At MTDs, the AEs were generally mild-to-moderate and manageable
- PK analysis suggests no drug–drug interactions
- Antitumour activity was observed:
  - 2 partial responses (head and neck carcinoma, and triple negative breast carcinoma)
  - Disease control of 64%

Conclusions W. W. Ma et al.

- S 400 mg bid + E 5 mg daily were **not tolerable** in the study population, and the MTD was not defined.
- S toxicity appeared to be accentuated by E co-administration though non drug-drug PK interaction was noted.
- No significant anti-tumor effect was observed in gemcitabine-refractory advanced pancreatic cancer patients and plan for phase II trial was aborted
- Our preclinical murine model failed to predict the clinical toxicities which limits the ability to achieve potentially therapeutic PK drug levels

Conclusions Sahebjam et al.

- RO4929097 in combination with cediranib is generally well tolerated at the dose levels tested.
- The recommended phase II dose was defined as 20 mg for RO4929097 and 30 mg for cediranib.
- Toxicities of combination are similar to those observed with single agents in phase I clinical trials.
- None of tested biomarkers of angiogenesis or Notch pathway were found to be predictive of response to treatment.

Conclusions / Remarks

- **Combining different targeted agents remains challenging** - **CAVE toxicity**

Conclusions / Remarks - 1

- **Afatinib** in monoR/ ph I: 50 mg daily C
- **BIBF 1120 (nintedanib)** in monoR/ ph I : 250 mg BID C
- BIBF 1120 : in phase I + chemotherapy = MTD 200 mg BID C

  Cancer Chemother Pharmacol. 2012 Apr;69(4):891-9.
  Ann Oncol. 2012 Aug;23(8)
  Br J Cancer. 2011 Nov 22;105(11)

- *phase II data ?*
  A 50 + N 250 BID alternating 7 day (colorectal)
  *A 40 mg C **vs** N 250 BID C **vs** A 70 mg and N 250 altern 7 day (prostate)*

- *Soria et al.* ***: A 40 mg I + N 150 mg BID // A 30 mg C + N 150 mg BID***

Conclusions / Remarks - 2

- Sorafenib monotherapy : 400 mg BID C
- Everolimus monotherapy : 10 mg a day C
- ESMO 2012 phase I data in RCC:
  Abstr 822 : Dovitinib (200 vs 500mg) + EVER (5 vs 10 mg)
  Abstr 814 : Lenvatinib (18 mg vs 24 mg) + everolimus (5 vs 10 mg)
- Ma et al. : ***no MTD determined***

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Phase I study of afatinib (BIBW 2992), an ErbB Family Blocker plus nintedanib (BIBF 1120), a triple angiokinase inhibitor, in patients with advanced solid tumours

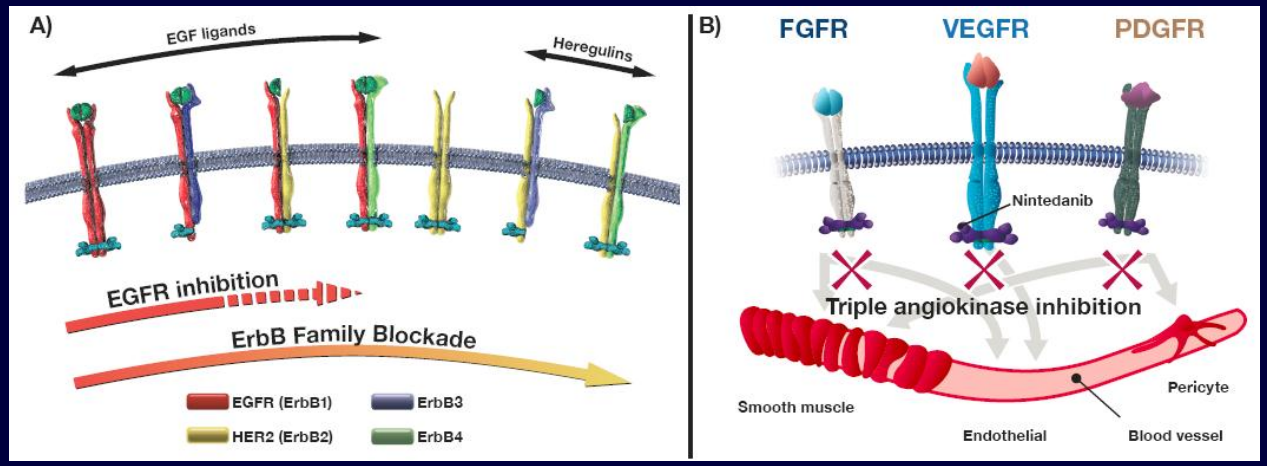
Jean-Charles Soria[1]

Antoine Hollebecque[1], Christophe Massard[1], Eric Deutsch[1], Andrea Varga[1], Nassim Morsli[2], Mahmoud Ould Kaci[2], Harry Staines[2], Kristell Marzin[3], Rastislav Bahleda[1]

[1]SITEP Institut Gustave Roussy, Villejuif, France; [2]Boehringer-Ingelheim, Paris, France; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Background

- Afatinib (BIBW 2992) is an irreversible ErbB Family Blocker which selectively and blocks EGFR, HER2 (ErbB2), ErbB4 signalling, transphosphorylation of ErbB3[1,2] **(A)**
- Nintedanib (BIBF 1120) is a triple angiokinase inhibitor that inhibits VEGFR 1–3, FGFR 1–3, PDGFR-α and -β[3] **(B)**

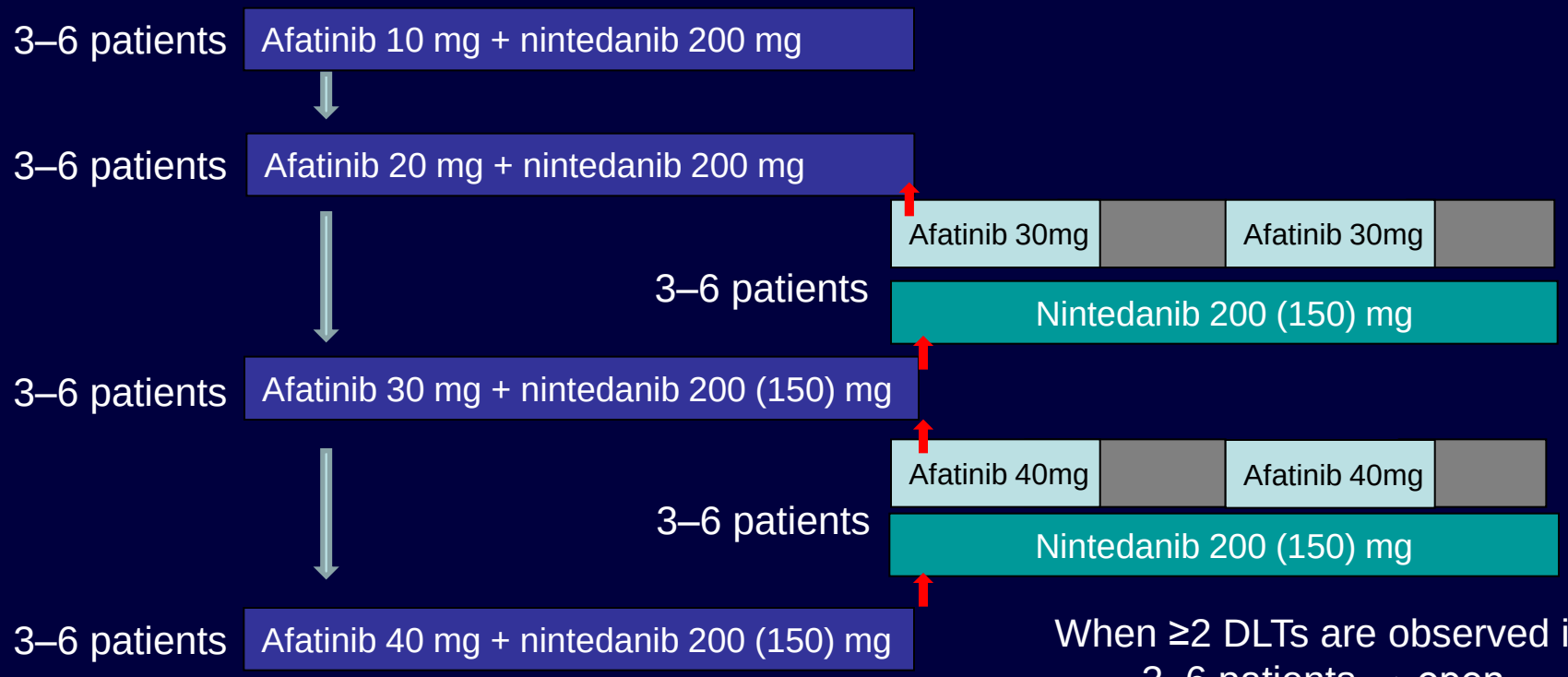


- Cancer cells use multiple pathways for survival and proliferation
  - Targeting more than one signalling pathway may overcome anti-apoptotic/resistance mechanisms and result in increased cell death
  - Preclinical models demonstrated synergistic tumour growth inhibition with the combination of nintedanib and afatinib when compared with either single agent alone[4]

1. Li D, et al. *Oncogene* 2008;27:4702–11; 2. Solca F, et al. *J Pharmacol Exp Ther* 2012: Epub ahead of print;
3. Hilberg F, et al. *Cancer Res* 2008;68:4774–82; 4. Poindessous V, et al. Clin Cancer Res 2011;17:6522–30..

Study design

Afatinib q.d. continuous or intermittent schedule +
Nintedanib b.i.d continuous schedule
Modified 3+3 design



When ≥2 DLTs are observed in 3–6 patients → open additional cohort using the same dose of afatinib but intermittent schedule

If <2 DLTs are observed in six patients = **MTD**

Cohorts and DLTs

Cohort	Afatinib (mg q.d.)	Nintedanib (mg b.i.d.)	Patients entered/ evaluable	Patients with DLT	DLT/CTCAE Grade
1	10 C	200	3/3	0	
2	20 C	200	3/3	0	
3	30 C	200	8/7	3	• G3 diarrhoea (2 patients) • G3 transaminase elevation/diarrhoea
4	40 C	200	3/3	3	• G3 diarrhoea • G3 transaminase elevation • G2 creatinine increase/G3 transaminase elevation
5	30 I	200	6/5	2	• G3 diarrhoea/G2 creatinine increase • G3 transaminase elevation
6	40 I	200	6/5	2	• G3 dehydration • G4 transaminase elevation
7	40 C	150	3/3	2	• G3 diarrhoea/dehydration/renal failure • G3 renal failure
8	40 I	150	7/6	0	**MTD**
9	30 C	150	6/6	0	**MTD**

2 MTDs

- Afatinib 40 mg q.d. every other week plus nintedanib 150 mg b.i.d.
- Afatinib 30 mg q.d. continuously plus nintedanib 150 mg b.i.d.

G = Grade; C = continuous; I = intermittent

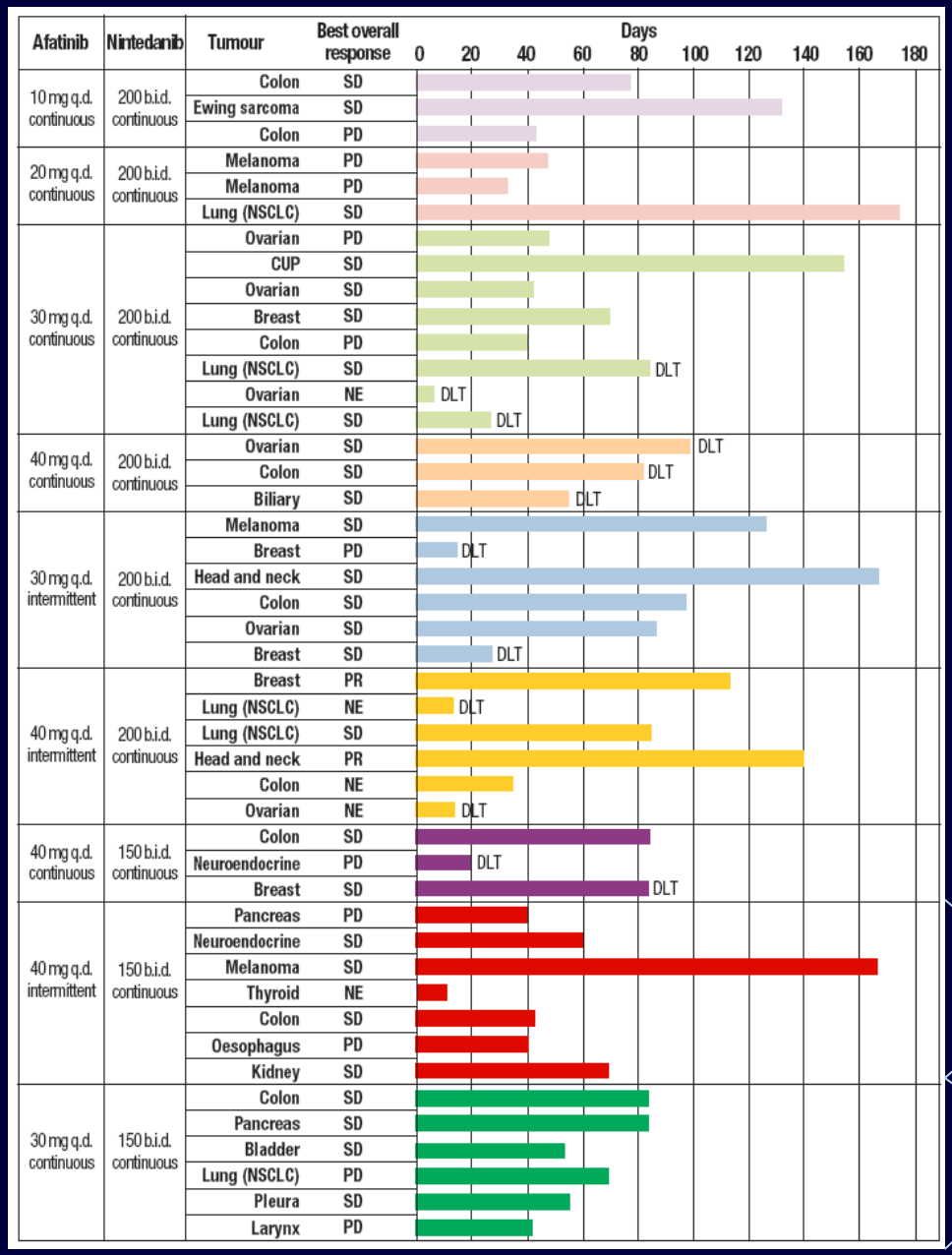
Most frequent drug-related AEs

	Grade 1	Grade 2	Grade 3	Grade 4	All grades*
Number of patients, n (%)	**44 (100)**	**44 (100)**	**44 (100)**	**44 (100)**	**44 (100)**
Diarrhoea	9 (20)	15 (34)	19 (43)	0	43 (98)
Nausea	23 (52)	6 (14)	0	0	29 (66)
Asthenia	10 (23)	15 (34)	3 (7)	0	28 (64)
Vomiting	14 (32)	13 (30)	0	0	27 (61)
Decreased appetite	14 (32)	7 (16)	4 (9)	0	25 (57)
Folliculitis	19 (43)	4 (9)	0	0	23 (52)
Epistaxis	17 (39)	0	0	0	17 (39)
Rhinitis	16 (36)	1 (2)	0	0	17 (39)
Dry skin	16 (36)	0	0	0	16 (36)
ALT increased	7 (16)	3 (7)	5 (11)	0	15 (34)
AST increased	7 (16)	3 (7)	3 (7)	0	13 (30)
Hypokalaemia	6 (14)	0	4 (9)	1 (2)	11 (25)
Cytolytic hepatitis	4 (9)	5 (11)	2 (5)	0	11 (25)
Rash	10 (23)	0	0	0	10 (23)
Mucosal inflammation	6 (14)	4 (9)	0	0	10 (23)
Dehydration	0	4 (9)	5 (11)	0	9 (20)

*There were no Grade 5 treatment-related AEs.

- Discontinuation due to AEs: afatinib (9 patients); nintedanib (8 patients)
- At MTDs, the AEs were generally mild-to-moderate and manageable

Time on treatment (days)



Median time on treatment was 60 days (range 7 to 174 days)

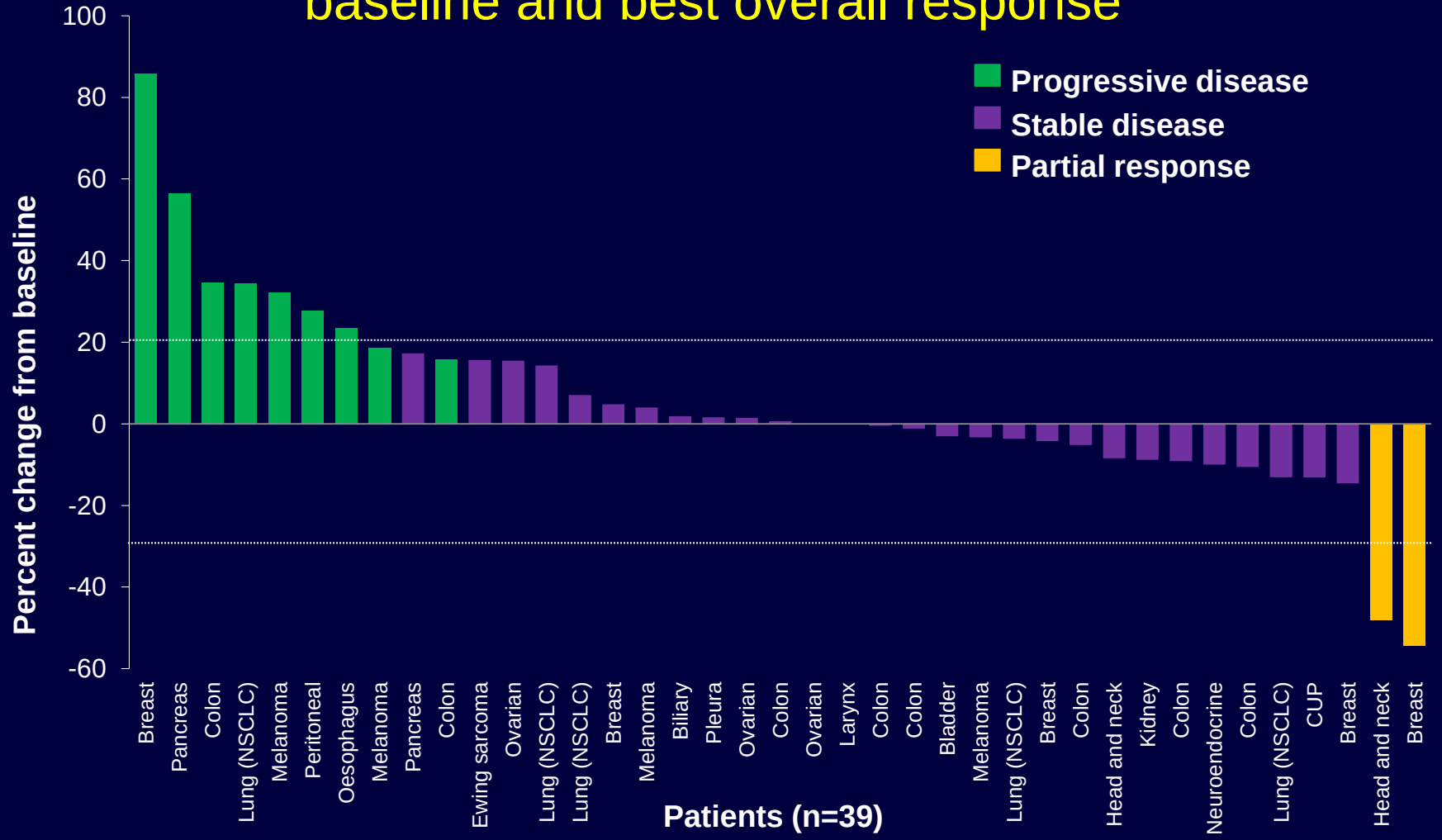
10 patients received treatment for ≥90 days

MTD cohort

MTD cohort

Antitumour activity

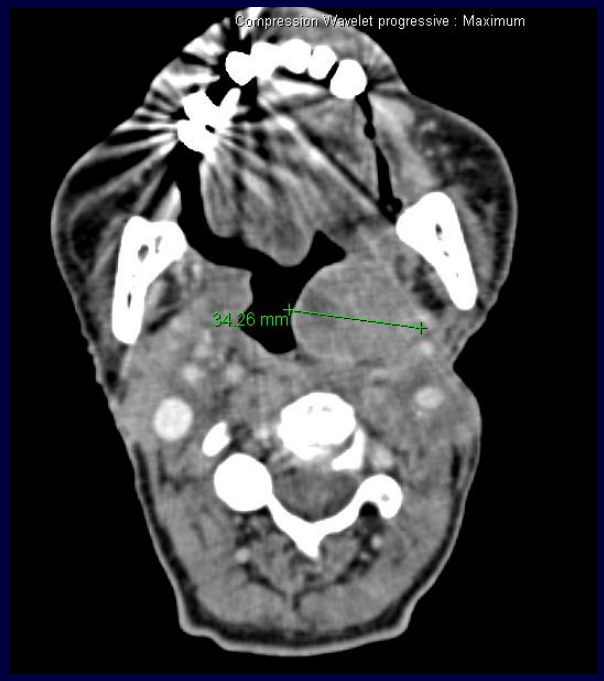
Waterfall plot of target lesions: Percent change from baseline and best overall response



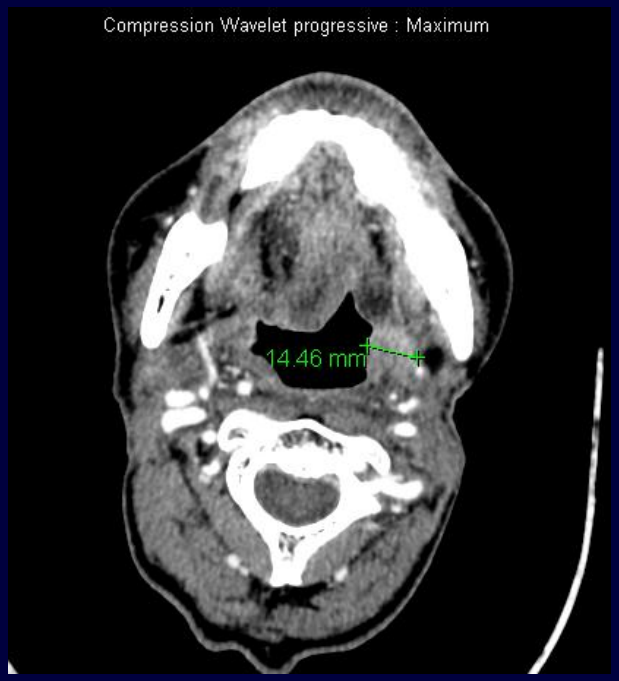
- 2 partial responses (PR): head and neck cancer, and triple negative breast cancer
- Disease control of 64%

PR (-58% change in tumour lesions) in patient with squamous cell carcinoma of the epiglottis (HNSCC)

July 16th, 2010



October 5th, 2010



Conclusions

- The MTDs were defined as:
  - Afatinib 40 mg q.d. every other week plus nintedanib 150 mg b.i.d.
  - Afatinib 30 mg q.d. continuously plus nintedanib 150 mg b.i.d.
- At MTDs, the AEs were generally mild-to-moderate and manageable
- PK analysis suggests no drug–drug interactions (data not shown)
- Antitumour activity was observed:
  - 2 partial responses (head and neck carcinoma, and triple negative breast carcinoma)
  - Disease control of 64%

Preclinical and clinical evaluation of the combination of sorafenib and everolimus in patients with advanced sold tumors (Abstract ID 1301)

Wen Wee Ma[1], Colin Weekes[2], Dipti K. Pawaskar[3], Gerald Fetterly[1], Wells A. Messersmith[2], Grace K. Dy[1], Robert M. Straubinger[3], William J. Jusko[3], S. Gail Eckhardt[2], Alex A. Adjei[1]

BACKGROUND

- The MAPK and mTOR pathways had been implicated in pancreatic cancer
- The combination of sorafenib (2) 20mg/kg + everolimus (E) 1 mg/kg demonstrated synergistic anti-cancer effect in a patient-derived primary pancreatic tumor implanted subcutaneously in SCID mice (Figure 1).
- We therefore conducted a phase I trial of S+E in patients advanced solid tumors and enriching in advanced gemcitabine-refractory advanced pancreatic cancer patients.

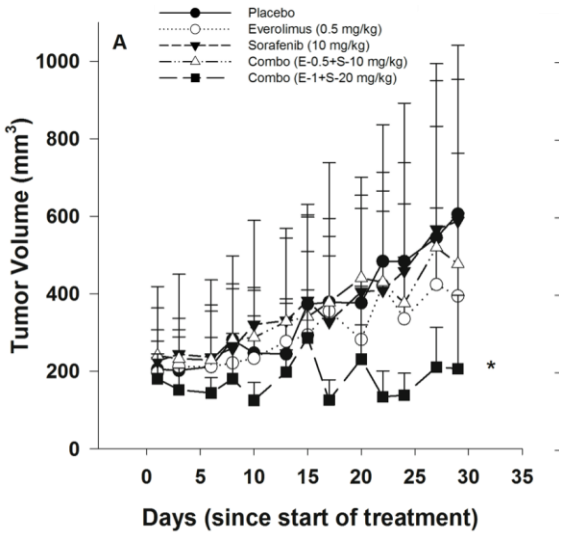


Figure 1. Tumor growth curve of patient-derived pancreatic subcutaneous tumor #17624. 'Higher' dose S+E combo achieved significantly better growth inhibition than 'lower' dose combo.

METHODS

- 3+3 dose escalation design was used
- Dose levels explored are
  - DL1 (starting): S 400 mg bid + E 5 mg qaily
  - DL2: S 400 mg bid + E 10 mg daily
- There was a 1-week lead-in period when patient will be sequentially assigned to start one drug only (Day -7), and the other drug added on Cycle 1 Day 1
- Blood samples were collected for PK analysis on Day -7, Day 1 and Day 15

RESULTS

- Twenty–two patients were enrolled and 10 were evaluable for DLT

Sex		
	male	10
	female	12
Age, years		
	Median	63.5
	Range	47-80
ECOG PS		
	0	6
	1	16
Primary tumor site		
	Pancreas (adenocarcinoma)	12
	Endocrine gland	1
	Skin	1
	Gall bladder	1
	Lower limb, NOS	1
	Uterus, NOS	1
	Lung, NOS	1
	Prostate gland	1
	Thyroid gland	1
	Bone	1
	Unknown primary	1

Table 2. Patients Characteristics (n=22)

RESULTS

- Twenty–two patients were enrolled and 10 were evaluable for DLT
- DLTs were
  - DL1 (n=6): G3 hand-foot syndrome, hypophosphatemia and G4 fistula
  - DL2 (n=4): G3 diarrhea, rash and hypophosphatemia
- Planned DL1 was not tolerable and MTD not defined

Table 3. Treatment-related Grade 2 and above Adverse Events

Adverse Event	Dose level 1 (n=6)		Dose level 2 (n=4)	
	Grade 2	Grade 3/4	Grade 2	Grade 3/4
Hematologic				
Lymphopenia	1			
GI				
Fistula		1*		
Diarrhea	1			1*
Abdominal pain	1			
Alkaline Phosphatase			1	
Anal pain			1	
Anorexia			1	1
Skin				
Rash	1		2	2*
Hand-foot syndrome	2	1*		
Other				
Hypophosphatemia		2*	2	2*
Hypokalemia	1			
Hyperglycemia	2			
Hypercholesteralemia			1	
Fatigue			2	
Bladder pain	1			
Inflammation NOS	1			

*Dose Limiting Toxicity (DLT)

- Best response was stable disease. A uterine carcinosarcoma patient had SD for 6 cycles (168 days) at DL1. Her prior PFS was 114 days.
- Eight aPC patients refractory to previous gemcitabine-based therapy received both S and E, and the median progression free survival of 32.5 days (range 15 to 64 days)(Figure 2).
- Intention-to-treat analysis of 12 aPC who received at least 1 dose of study drug was 81 days (or 2.7 months)(range 7 days to > 494 days)
- PK analysis showed S accumulation following 7 days of continuous dosing but no drug-drug interaction observed.

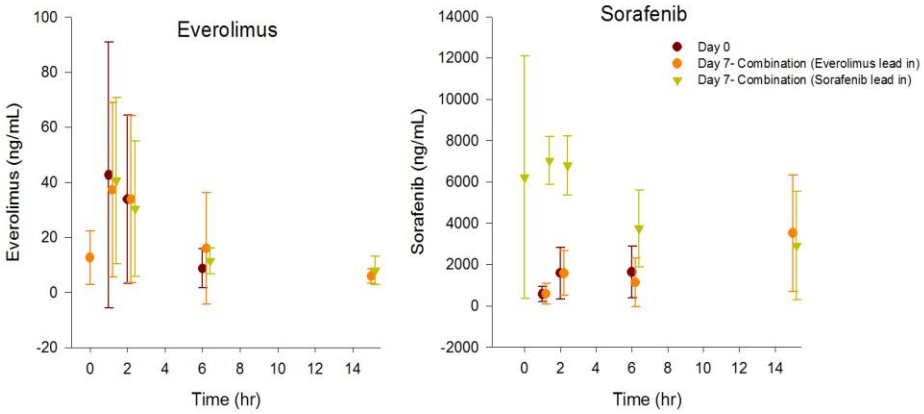


Figure 2. No significant drug-drug PK interaction between S and E. PK profiles of E (left) and S (right) was not significantly different when administered alone or in combination.

- PK parameters from clinical trial was compared to that from preclinical studies and published literature (Table 4)
- Clinical E exposure (AUC profile) was significantly lower (1/100th) than in preclinical combination studies whereas S exposure was comparable.

CONCLUSIONS

- S 400 mg bid + E 5 mg daily were not tolerable in the study population, and the MTD was not defined.
- S toxicity appeared to be accentuated by E co-administration though non drug-drug PK interaction was noted.
- No significant anti-tumor effect was observed in gemcitabine-refractory advanced pancreatic cancer patients and plan for phase II trial was aborted
- Our preclinical murine model failed to predict the clinical toxicities which limits the ability to achieve potentially therapeutic PK drug levels

Table 4. Results from PK study using non-compartmental analysis of blood samples obtained from human patients and mice who received sorafenib and everolimus

Species	Dose Administered		C_{max} (ng/mL)		AUC_{24} (hr.ng/mL)	
	E	S	E	S	E	S
Human* (this trial)	5 mg daily	400 mg bid	31	2272	95.1 (AUC_{0-6})	9260 (AUC_{0-6})
Mouse	0.5 mg/kg daily	10 mg/kg daily	577	2990	4630	32500
Mouse	1 mg/kg daily	20 mg/kg daily	937	5128	8388	76826
Human**	5 mg daily	400 mg bid	32	6200	238	13200

Preclinically efficacious dose

E: everolimus; S: sorafenib

*based on samples obtained from the first dosing of each drug

**summarized from published literature [1-3].

A Phase I Study of the Combination of RO4929097 (RO) and Cediranib (Cd) in Patients with Advanced Solid Tumors (PJC-004/NCI 8503)

Solmaz Sahebjam[1] , Philippe L. Bedard[1], Vincent Castonguay[1], Helen Chen[2], Percy Ivy[2], Amit M. Oza[1], Eric X. Chen[1], Hal W. Hirte[1], Zhuo Chen[1], Michael Reedijk[1], Brenda Cohen [1], Blaise Clarke [1], Lillian L. Siu [1], Sebastien J. Hotte[1]

[1]Princess Margaret Hospital Phase I Consortium, Canada
[2]National Cancer Institute, Bethesda, USA

Supported by National Cancer Institute Grant # U01CA132123

Cycle 1 schedule (length 42 days):

Agent	Schedule
RO4929097	Daily on days 1-3, 8-10, 15-17, 22-24, 29-31, 36-38
Cediranib	Daily on days 22-42

Cycle 2 schedule (length 21 days):

Agent	Schedule
RO4929097	Daily on days 1-3, 8-10, 15-17
Cediranib	Daily

Dose levels and observed DLTs:

Dose level			n	DLTs
	Cediranib	RO4929097		
1	20 mg	10mg	7	G3 hypertension
2	20mg	20mg	7	G4 AST elevation
3	30mg	20mg	6	

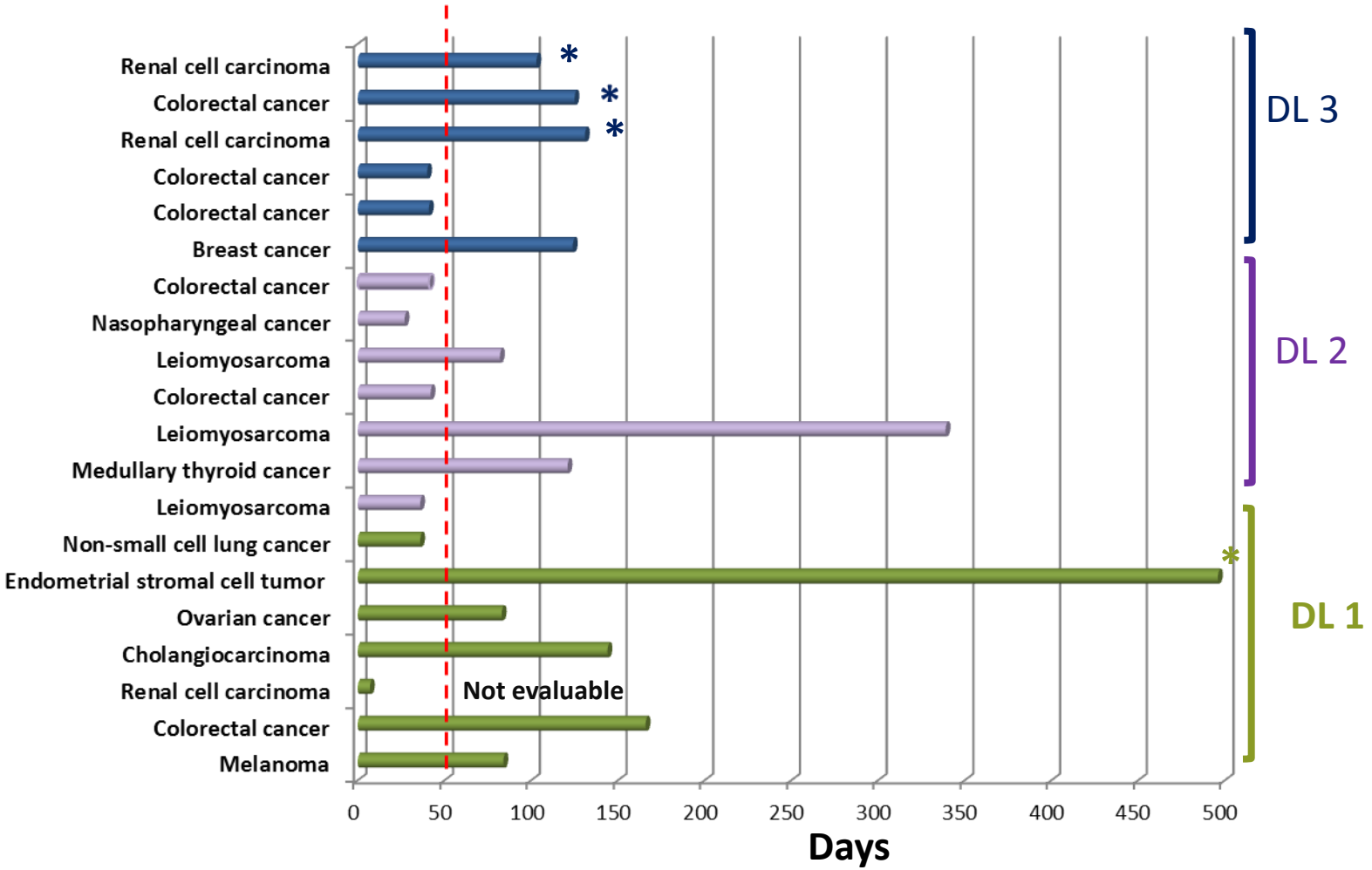
Most common treatment-related adverse events

Drug-related AE (%)	Grades	Dose Level		
		1 (n=7)	2 (n=7)	3 (n=6)
		Cediranib 20mg RO4929097 10 mg	Cediranib 20mg RO4929097 20 mg	Cediranib 30mg RO4929097 20 mg
Diarrhea	**All** 3–4	**6 (86%)** 0 (0%)	**3 (43%)** 0 (0%)	**4 (66%)** 0 (0%)
Hypertension	**All** 3–4	**6 (86%)** 2 (28%)	**2 (28%)** 0 (0%)	**4 (66%)** 1 (17%)
Fatigue	**All** 3–4	**3 (43%)** 0 (0%)	**3 (43%)** 0 (0%)	**4 (66%)** 0 (0%)
Nausea	**All** 3–4	**3 (43%)** 0 (0%)	**4 (57%)** 0 (0%)	**3 (50%)** 0 (0%)
Hypothyroidism	**All** 3–4	**3 (43%)** 0 (0%)	**2 (28%)** 0 (0%)	**3 (50%)** 0 (0%)
Headache	**All** 3–4	**4 (57%)** 0 (0%)	**1 (14%)** 0 (0%)	**2 (33%)** 0 (0%)
Hypophosphatemia	**All** 3–4	**3 (43%)** 1 (14%)	**2 (28%)** 0 (0%)	**2 (33%)** 0 (0%)
Increased alanine aminotransferase	**All** 3–4	**2 (28%)** 0 (0%)	**3 (43%)** 1 (14%)	**3 (50%)** 0 (0%)
Increased aspartate aminotransferase	**All** 3–4	**0 (33%)** 0 (0%)	**5 (71%)** 1 (14%)	**1 (16%)** 0 (0%)

Duration of exposure

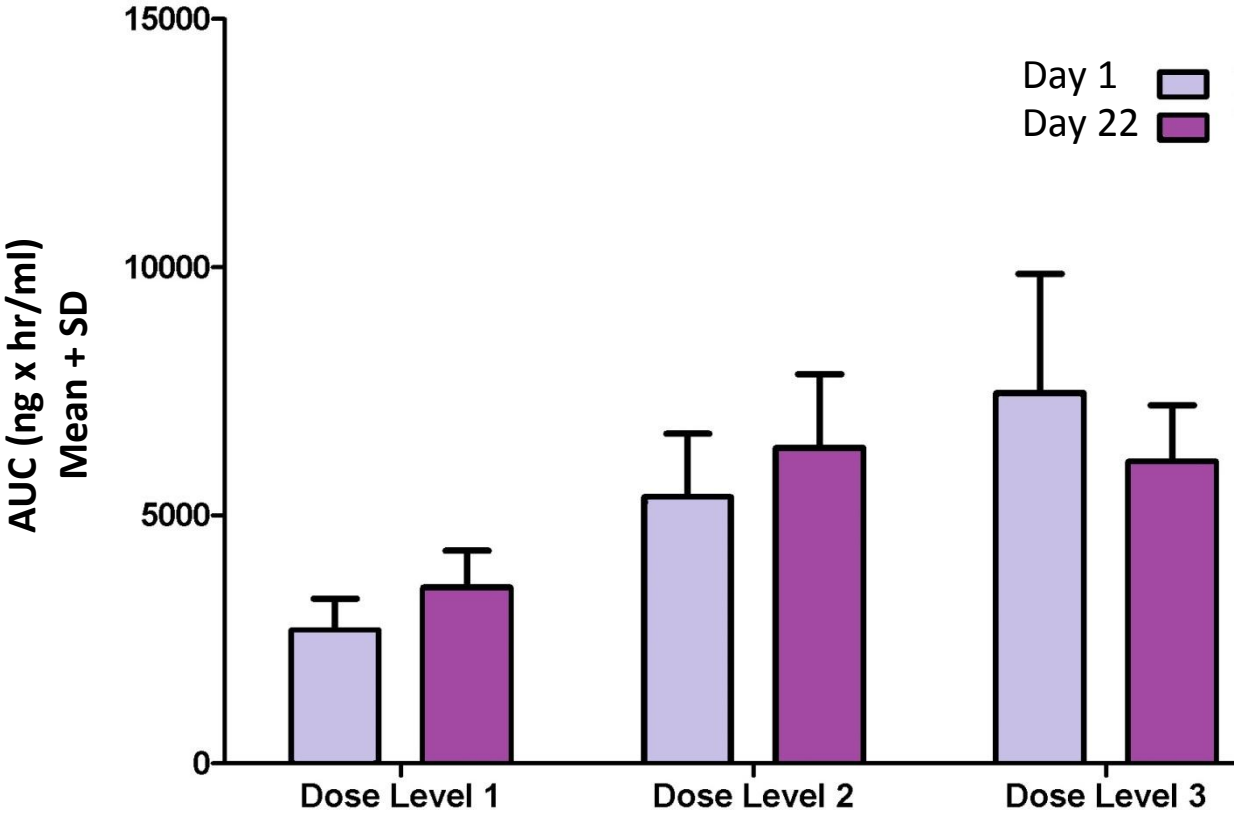
19 evaluable , 1 not evaluable
0 PR, 12 SD (9 ≥ 4 cycles), 7 PD

Response assessment: 6 weeks



* Patient continues on treatment.

RO4929097 AUC



Serum angiogenic biomarkers