Fibroblast Growth Factors: New Drugs to Manage a Morpheic Tumor Target

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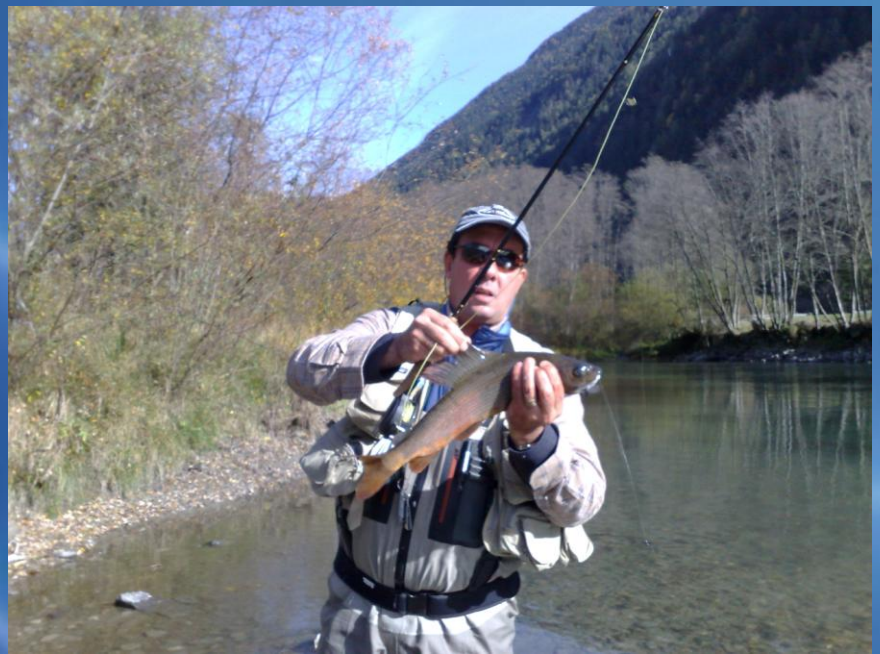
Disclosure

Consultant : Bristol-Mayers ; Novartis ; Roche; Boehringer ; GSK ; Eisai ; Philogen

Angler :



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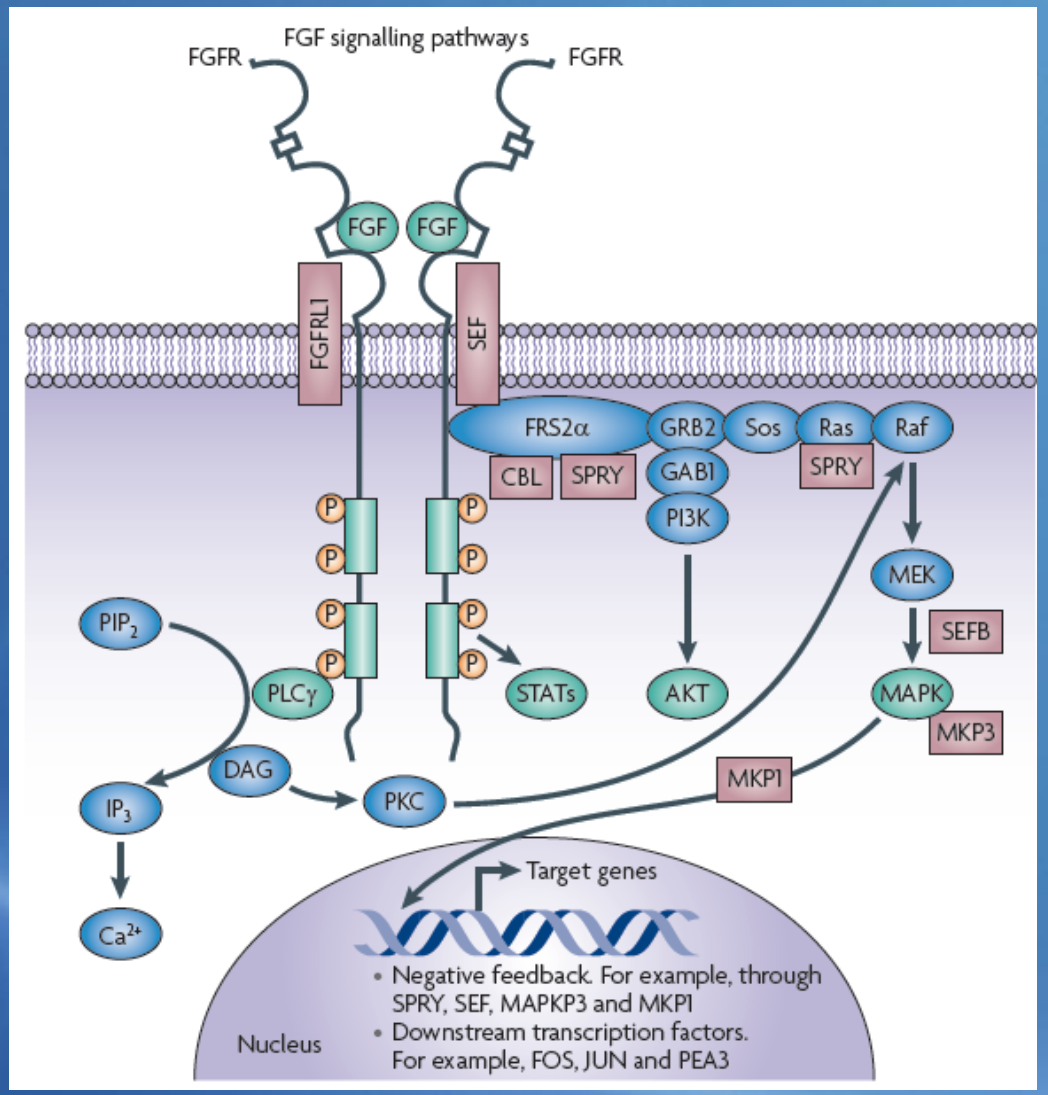
FGF/FGFR network

- 18 ligands
- 23 "members"
- 4 TK receptors: FGFR1, FGFR2, FGFR3, FGFR4
- 1 non TK receptor: FGFRL1 (negative control)
- Regulatory activity of cell proliferation, survival, migration and angiogenesis



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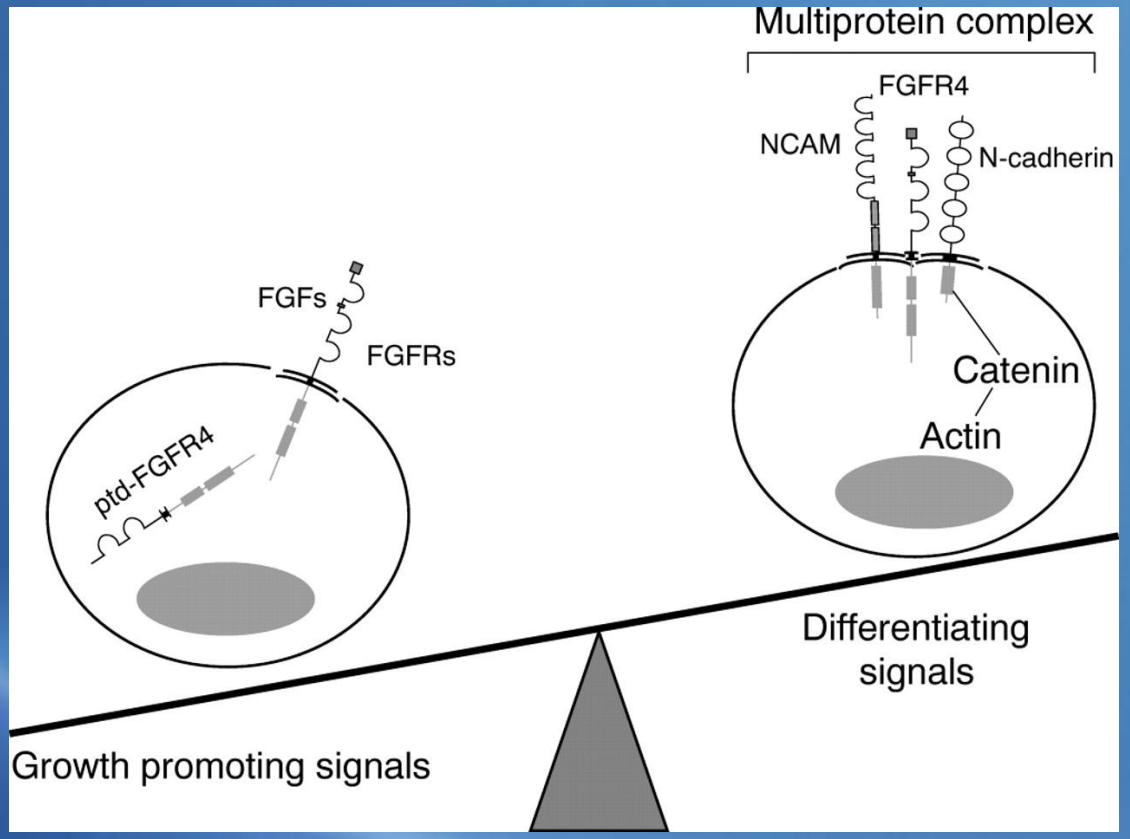
Turner et al. Nat Canc Rev 2010

Context-dependent activity

- In Normal Conditions

- In Cancer
  - Tumor suppressive (Medulloblatoma, Prostate)
  - Tumor Driver



Ezzat et al. J Clin Pathol 2005

Microenvironmental Control To Be Clarified

FGF signalling in Tumors

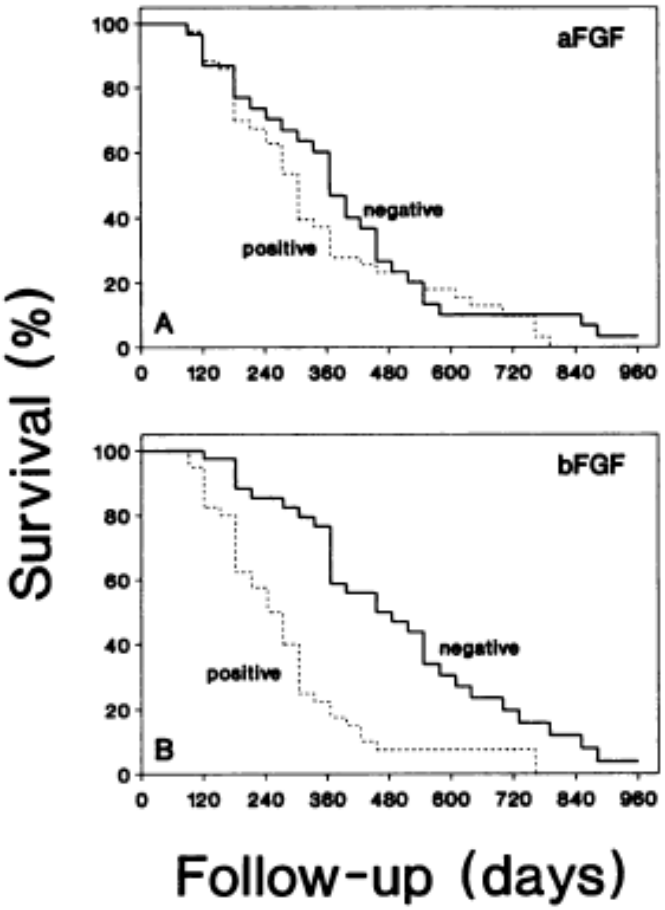


Fig. 8. Survival curves. Patients were categorized according to the absence (*negative*) or presence (*positive*) of aFGF (*A*) and bFGF (*B*) in the cancer cells. Survival periods for the bFGF-negative group were significantly longer than for the bFGF-positive group, using either the Wilcoxon test ($P < 0.01$) or the log-rank test ($P < 0.001$ at 360 days postsurgery).

Yamanaka et al. Cancer Res 1993

DEREGULATION of FGF SIGNALLING IN CANCER

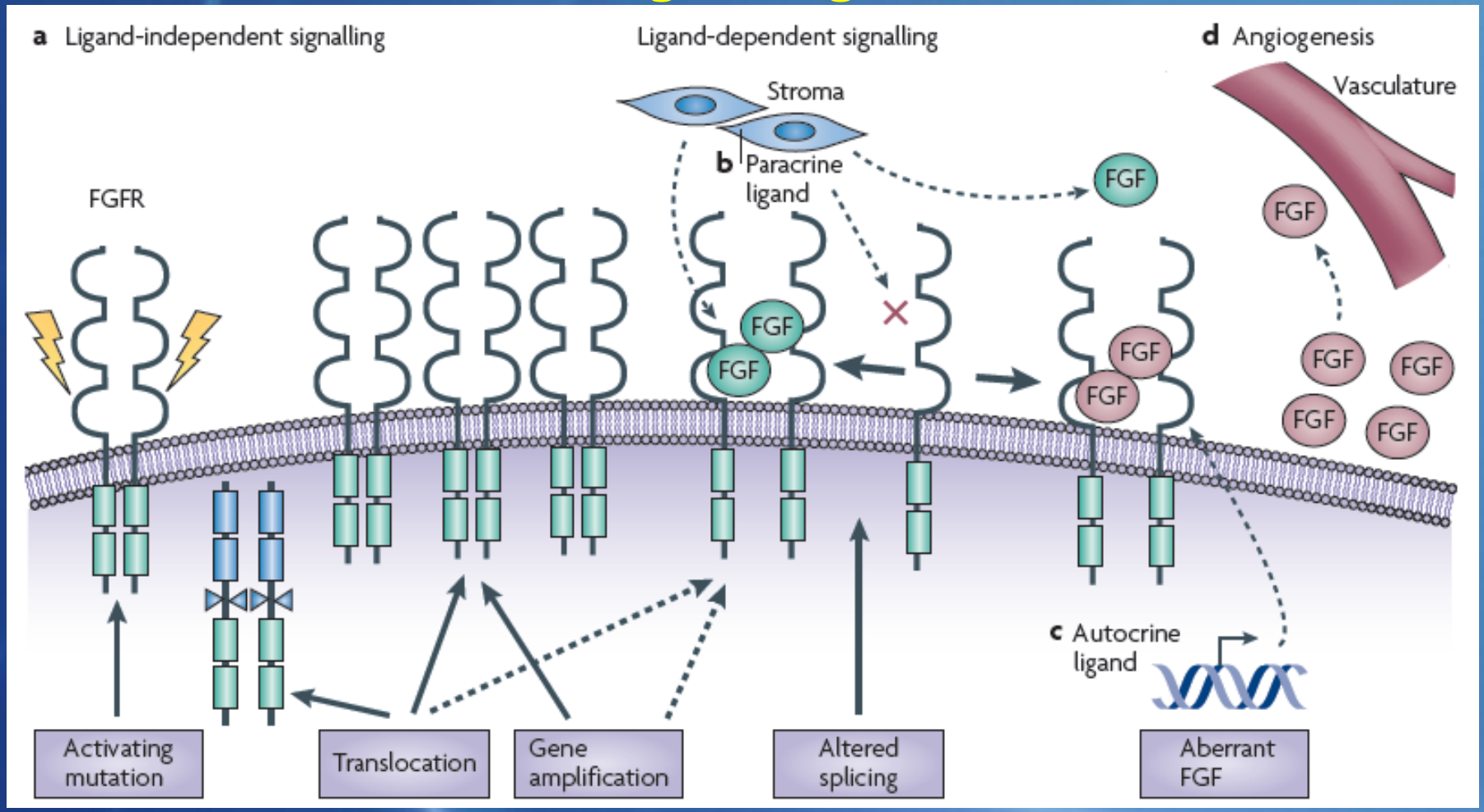
FGFR (4 + 1)

- ACTIVATING MUTATIONS
- GENE AMPLIFICATION
- CHROMOSOMAL TRASLOCATIONS

FGF (18 + 5)

- AUTOCRINE SIGNALLING (ie. Melanoma)
- PARACRINE SIGNALLING (ie. Prostate cancer)
- HORMONAL SIGNALLING (ie. HCC)

Mechanisms of pathogenetic cancer cell FGF signalling



Turner et al. Nat Canc Rev 2010

Tumor-specific genetic FGFR alterations

FGFR gene	Cancer type	Germline or somatic	Genetic changes	
FGFR1	Breast cancer	Somatic	Gene amplification	10%
	Ovarian cancer	Somatic	Gene amplification	5%
	Myeloproliferative syndrome	Somatic	Chromosomal translocation	
	Bladder cancer	Somatic	Gene amplification	3%
	Glioblastoma	Somatic	Missense mutation	
	Oral cancer	Somatic	Gene amplification	
	Melanoma	Somatic	Missense mutation	
	Rhabdomyosarcoma	Somatic	Gene amplification	3%
FGFR2	Breast cancer	Somatic	Gene amplification	
		Somatic	Missense mutation	
		Germline	Intronic regulatory SNPs	
	Gastric cancer	Somatic	Gene amplification	10%
		Somatic	Missense mutation	
	Lung cancer	Somatic	Missense mutation	
	Uterus cancer	Somatic	Missense mutation	12%
	Melanoma	Somatic	Missense mutation	
	Colorectal cancer	Somatic	Gene amplification	
FGFR3	Multiple myeloma	Somatic	Chromosomal translocation	
		Somatic	Missense mutation	
	Bladder cancer	Somatic	Missense mutation	10-60%
			Gene amplification	5%
	Cervical cancer	Somatic	Missense mutation	
	Colorectal cancer	Somatic	Missense mutation	
	Peripheral T-cell lymphoma	Somatic	Chromosomal translocation	
	Oral cancer	Somatic	Missense mutation	
	Testicular tumor	Somatic	Missense mutation	7%
FGFR4	Breast cancer	Germline	Missense coding SNP	
	Lung cancer	Germline	Missense coding SNP	
		Somatic	Missense mutation	
	Rhabdomyosarcoma	Somatic	Missense mutation	

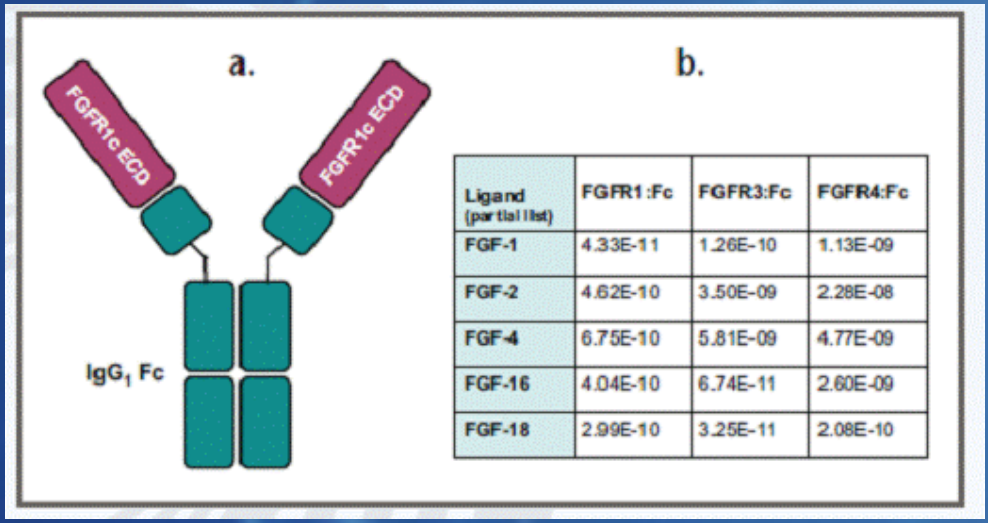
FGFR: FGF receptor; SNP: Single-nucleotide polymorphism.

Katoh M, Expert Rev Antic Ther 2010

Anti FGFR/FGFs Monoclonal Antibodies

Drug (company)	Target	Clinical Development
FP-1039 (Five Prime Ther)	FGF ligand trap	Phase I moving to phase II in Endometrial Cancer
Anti-FGFR3 (Genentech)	FGFR3	Phase I Multiple Myeloma
IMC-A1 (ImClone)	FGFR1	NA
PRO-001 (ProChon Biotech)	FGFR3	NA
1 A6 (Genentech)	FGF19	NA

FP-1039



Ligand (partial list)	FGFR1:Fc	FGFR3:Fc	FGFR4:Fc
FGF-1	4.33E-11	1.26E-10	1.13E-09
FGF-2	4.62E-10	3.50E-09	2.28E-08
FGF-4	6.75E-10	5.81E-09	4.77E-09
FGF-16	4.04E-10	6.74E-11	2.60E-09
FGF-18	2.99E-10	3.25E-11	2.08E-10

1) **Structure**: extracellular domains of human FGFR1 isoform a-IIIc + native Fc regions of human IgG_1.

2) **Single agent**: growth inhibition of 4/12 pts-derived breast cancer xenografts and vs. H460 (lung), Colo205 (colon) and Caki-1 (renal) models,. **Combo**: + sunitinib or + CDDP or + bevacizumab resulted in additive anti-tumor activity in H460 and Colo205 xenografts.

2 Clinical Trial Ongoing:

1) Safety Study of FP-1039 To Treat Cancer

2) Study of FP-1039 in Subjects With Endometrial Cancers

Pts selection according to the presence of the point mutation S252W in the extra domain of FGFR2 (~7% of all cases)

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Long et al. Proc Am Assoc Cancer Res; 2009; abstract 2789.
Keer et al, J Clin Oncol 28:15s, 2010; abstr TPS260).
www.clinicaltrial.gov

FGFR TKI

Agent	Company	Target	Clinical Development
Brivanib alaninate	BMS	VEGFR 1-2-3 FGFR 1-2-3	Phase III
Masitinib	AB Science	FGFR3, c-kit, PDGFR, FAK	Phase III (pancreas, GIST, multiple myeloma)
BIBIF1120	Boehringer Ingelheim	VEGFR 1-2-3 FGFR 1-2-3 PDGFR a & B	Phase III
TKI258 (Dovitinib)	Novartis	VEGFR 1-2-3, FLT, FGFR 3 cKit , PDGFR B	Phase II
TSU-68	Taiho Pharm.	VEGFR1, FGFR 1 PDGFR B	Phase I/II
E-3810	EOS	VEGFR ; FGFR1	Phase I
E7080	Eisai	FGFR, PDGFR, VEGFR	Phase I

AP24534 (Panatinib) IC50 of 0.37, 2, 1.5, 2.2, 1.1, 1and 0.24 nM for native pan-BCR-ABL, mutated form, VEGFR2, FGFR1, PDGFRa, mutant FLT3 and LYN.

BIBIF1120 (Vargatef) all three VEGFR subtypes (IC50=13–34nmol/L) , PDGFRa and PDGFRh (IC50=59and65nmol/L) , FGFR 1, 2, and 3 (IC50=69, 37, and 108 nmol/L)

BMS -582664 (Brivanib alaninate) VEGFR-2(25 nM), VEGFR-1 (380nM), VEGFR-3 (10 nM); FGFR 1 , 2 , 3 (IC50=148 nM, 125 nM, 68 nM)

TKI-258(Dovitinib) IC50 of 1, 2, 5, 10, 8, 27, 36 nM for FLT3, c-KIT, FGFR3, VEGFR1/2/3, PDGFRß and CSF-1R, respectively

TSU-68 (SU6668) VEGF-R1, PDGF-Rβ and FGF-R1 (IC50 : 2.1 µM, 8 nM and 1.2 µM)

Ki8751 selective VEGFR-2 tyrosine kinase inhibitor with IC50 of 0.9 nM, 40, 67, 170 nM for VEGF-2, c-Kit, PDGFRα and FGFR-2, respectively

PD 173074 Inhibitor of FGFR1 (IC50 = 21.5 nM) and VEGFR

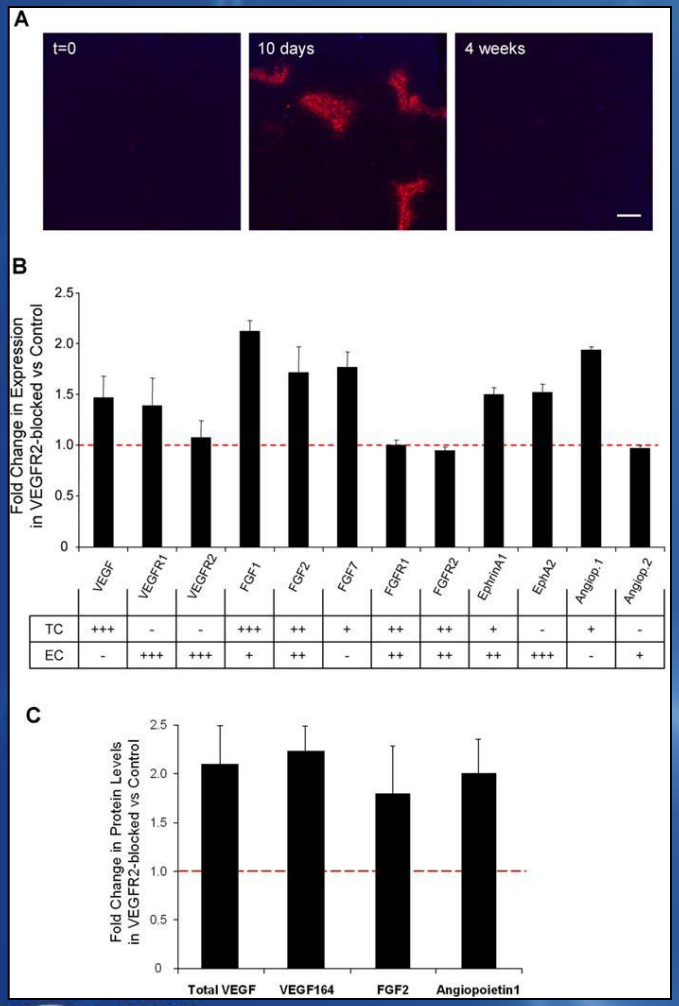
E-3810 VGFR 1,2,3 (IC50 : 7,25, 10 nM) FGRF 1,2 3 (IC50 : 17.5, 81.5, 237.5 nM)

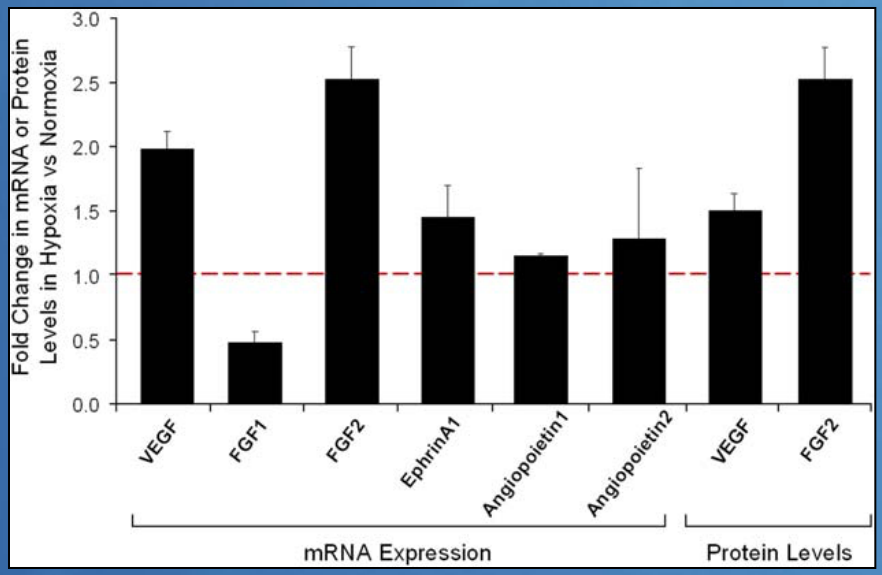
FGFR TK inhibitors

	Sorafenib	Sutent	Brivanib	BIBF 1120	Dovitinib	E-3810
VEGFR1	-	2	350	34	10	7
VEGFR2	90	9	26	21	8	25
VEGFR3	20	17	10	13	27	10
FGFR1	-	-	150	69	Low	17.5
FGFR2	580	830	125	37	-	82.5
FGFR3	-	-	68	108	5	237.5
PDGFR	57	8	7,460	59/60	36	175/525
C-Kit	68	13	Low	-	2	456
Flt-3	58	10	58	-	1	-
Other	RET,RAF	RET	RET	Src	CSF-1R	CSF1R

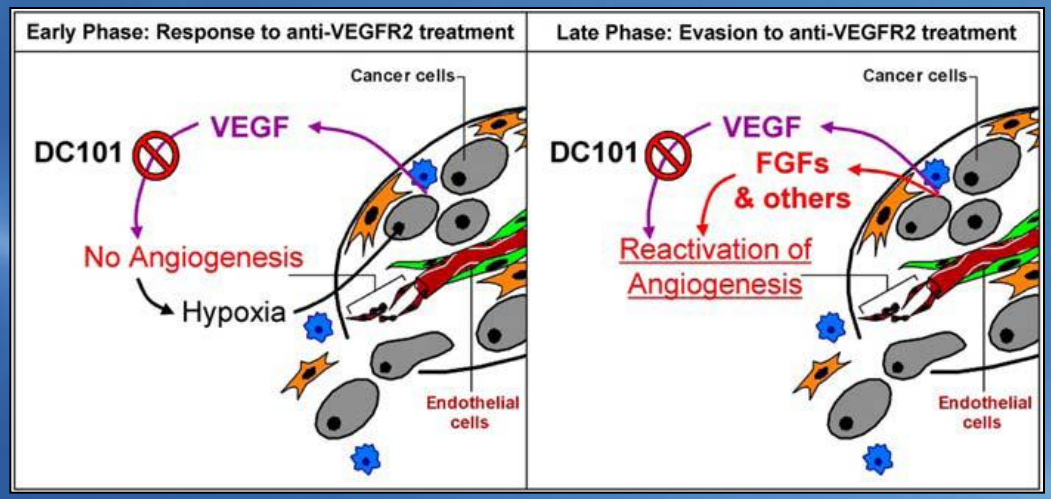
Evasion of antiangiogenic targeting of VEGF

1. VEGFR2 blockade →hypoxia →change of expression of proangiogenic factors in tumors





2. Hypoxia → ↑expression of proangiogenic factors in tumor-derived βTC cell line



Casanovas et al. Cancer Cell 2005

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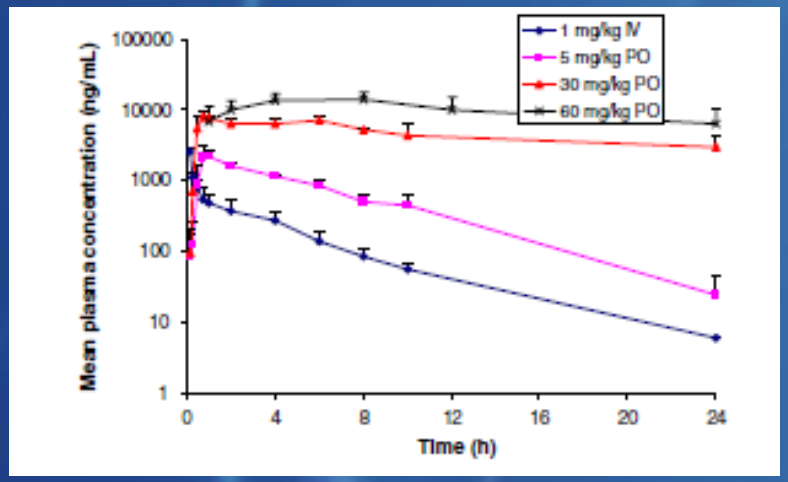
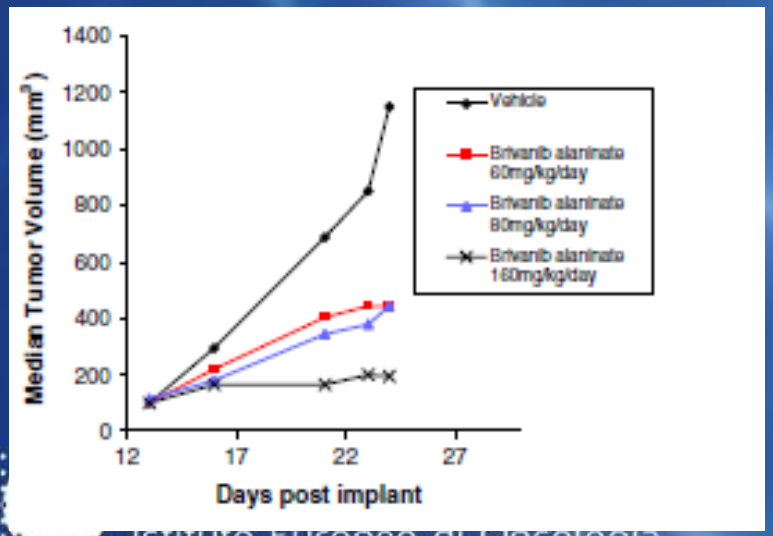
Brivanib (BMS-582664)

Preclinic: Plasma Concentrations



Preclinic: Antitumor Activity on HCT116/VM46 colon cancer q1Dx12



Clinic:

Prodrug of BMS-540215; dual inhibitor of VEGFR and FGFR

Linear PK

- No impact of race, age, gender
- No impact of mild liver impairment (Child-Pugh A)

800 mg QD PO continuosly; no food effect

Eliminated mainly through metabolism

Weak Inhibitor of UGT1A1; no interaction with CYP3A4 substrates.

Jonker DJ et al. JCO, 2007: abstr. 3559
Marathe et al, Cancer Chemother Pharma 2009

Brivanib Single Agent Phase I Results

AEs from Phase I + Phase II (HCC)

Side Effects (grade I-III)	Frequency
Fatigue	33-45%
Anorexia	27-39%
Diarrohea	14-35%
Nausea	14-65%
Rash	6-24%
Hypertonia	9-28%
Emesis	9-41%

Dempke et al. Anticancer Res 2010

Phase I Antitumor Activity

Response[a]	All Doses, n (%)
Partial Response	2 (3)[b]
Stable Disease	24 (35)
Progressive Disease	32 (47)
Not assessable	10 (15)

[a] At least 1 post treatment CT;
[b] 1 Renal cell carcinoma 600 mg q1D; 1 Ampulla of Vater 1000 mg q1D

Jonker DJ et al. Annals Oncol 2010

Phase II Brivanib Single Agent in HCC

Dose: Brivanib 800 mg PO QD

Cohort A: no previous systemic CT for HCC

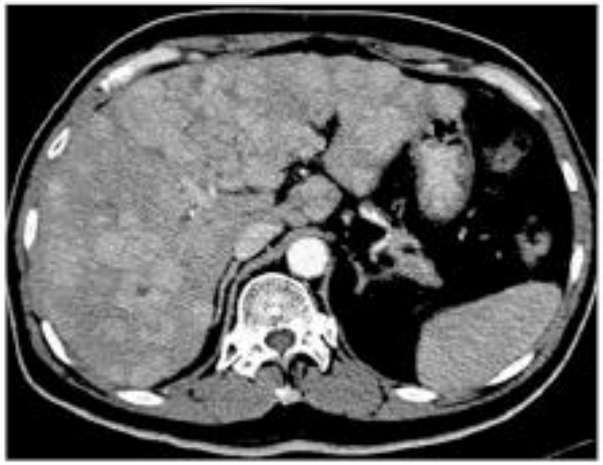
Cohort B: 1 prior regimen with antivascular therpies

End Points: PFS, TTP, OS, Disease control rate, Safety.

Baseline Characteristics	Cohort A (n=55)	Cohort B (n=46)
Age	60 (27-80)	55 (21-81)
Male/Female, %	89/11	72/28
Asian/non-Asian, %	64/36	67/33
HBV+/HCV-, %	53/22	65/17
ECOG PS 0/1/2, %	45/49/5	26/72/2
Extrahepatic spread, %	76	78
Child-Pugh A/B, %	91/9	91/9
AFP >UNL, %	76	83
Local Therapy (TACE, RFTA etc.), %	49	83

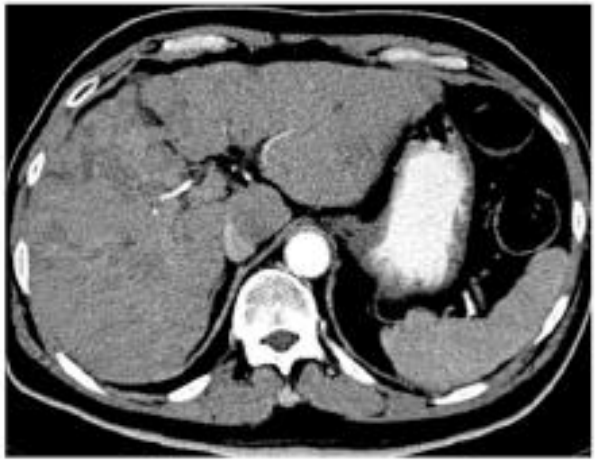
Park JW et al. Clin Cancer Res 2011

Brivanib induces responses in HCC pts



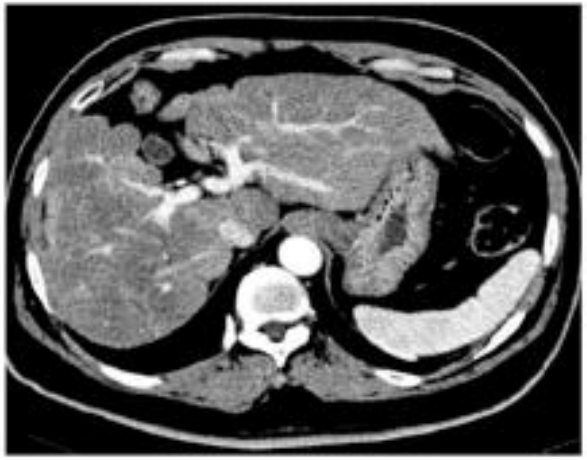
04 Jul 07

Baseline assessment



18 Mar 08

mWHO: SD
mRECIST: CR



12 May 09

mWHO: CR
mRECIST: CR

Park JW et al. Clin Cancer Res 2011

Tumor responses: mWHO and mRECIST

Outcome		
Overall Survival (95% CI) (median, months)	10 (95% CI, 6.8-15.2)	
	mWHO	**mRECIST**(3, 22)
Best tumor response, n (%)		
CR	1	5 (9.1)
PR	3 (5.5))	9 (16.4)
SD	24(43.6)	29 (52.7)
SD	22 (40.0)	
uCR	0	2 (3.6)
uPR	2 (3.6)	3 (5.5)
DCR (CR + PR + SD), n/N (%)	28/55 (50.9)	43/55 (78.2)
Median TTP(95% CI) (months)	2.8 (1.4–3.5)[a]	5.4 (2.8,–)
Median PFS (months)	2.7 (1.4-3.0)[a]	4.7 (2.8-5.7)
6-month PFS rate (%)	21.1 (9.6-32.5)[a]	35.6 (21.0-49.4)

[a]IRRC assessment

Park JW et al. Clin Cancer Res 2011

BIBF 1120

1) Linear PK

2) MTD: 250 mg PO QD and BID

3) RD: 200 mg PO BID

4) AEs grade 1-2: nausea (68.9%), vomiting (45.9%), diarrhoea (44.3%).

5) Responses: 2 PR (RCC, CRC), 1 CR (RCC)

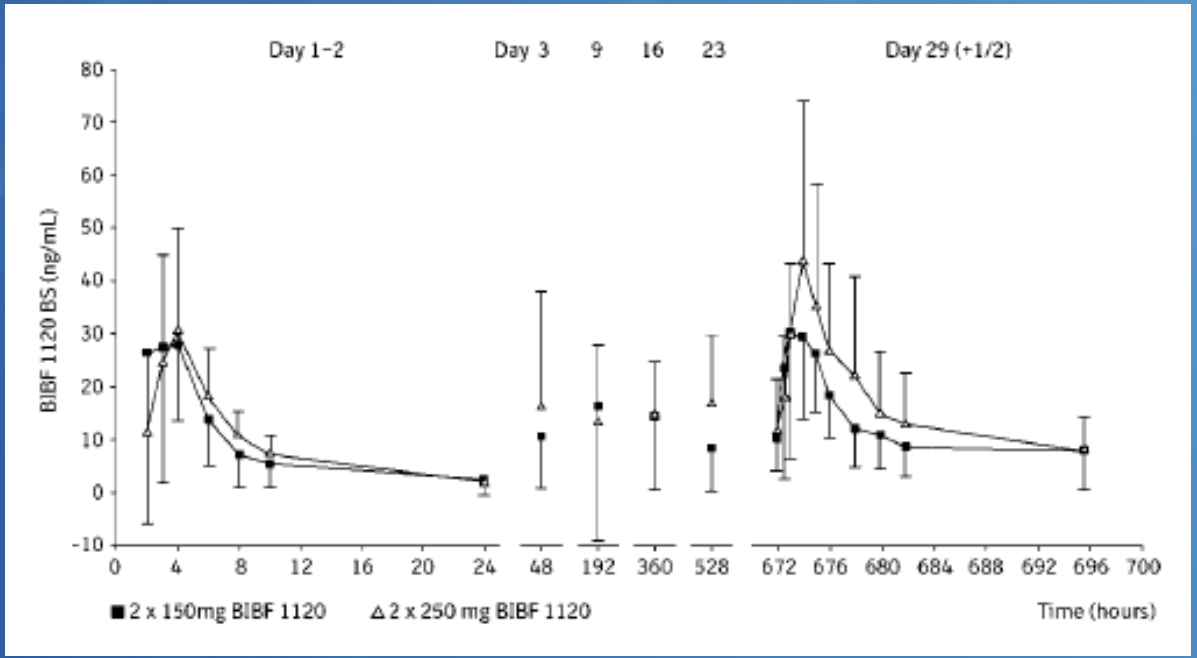


Table 3. Number of patients with DLT within the first course of BIBF 1120 treatment

Total daily dose (mg)	Once daily		Twice daily	
	All patients	Patients with DLT	All patients	Patients with DLT
50	2	0	—	—
100	1	0	—	—
150	—	—	6	0
150 + 200	—	—	6	0
200	8	1 (12.5) AST+γGT increased	6	1 (16.7) CD4 lymphocytes decreased
250	6	1 (16.7) CD4 lymphocytes decreased	13	1 (7.7) nausea
300	5	2 (40) AST+γGT (1), ALT+AST (1)	5	4 (80) nausea+vomiting (1), ALT+AST increased (1), ALT+AST+γGT (1), CD4 lymphocytes decreased + γGT, increased (1)
450	3	2 (66.7) ALT+AST+γGT (1), ALT+γGT (1)	—	—

NOTE: DLT was defined as any CTC grade 3 or 4 hematologic or nonhematologic toxicity.

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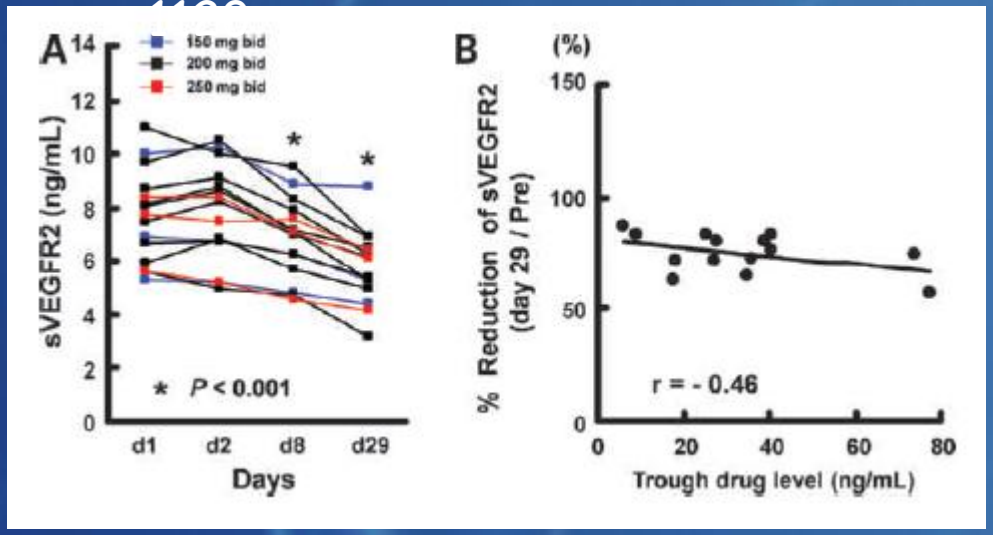
Mross K et al. Clin Cancer Res 2010

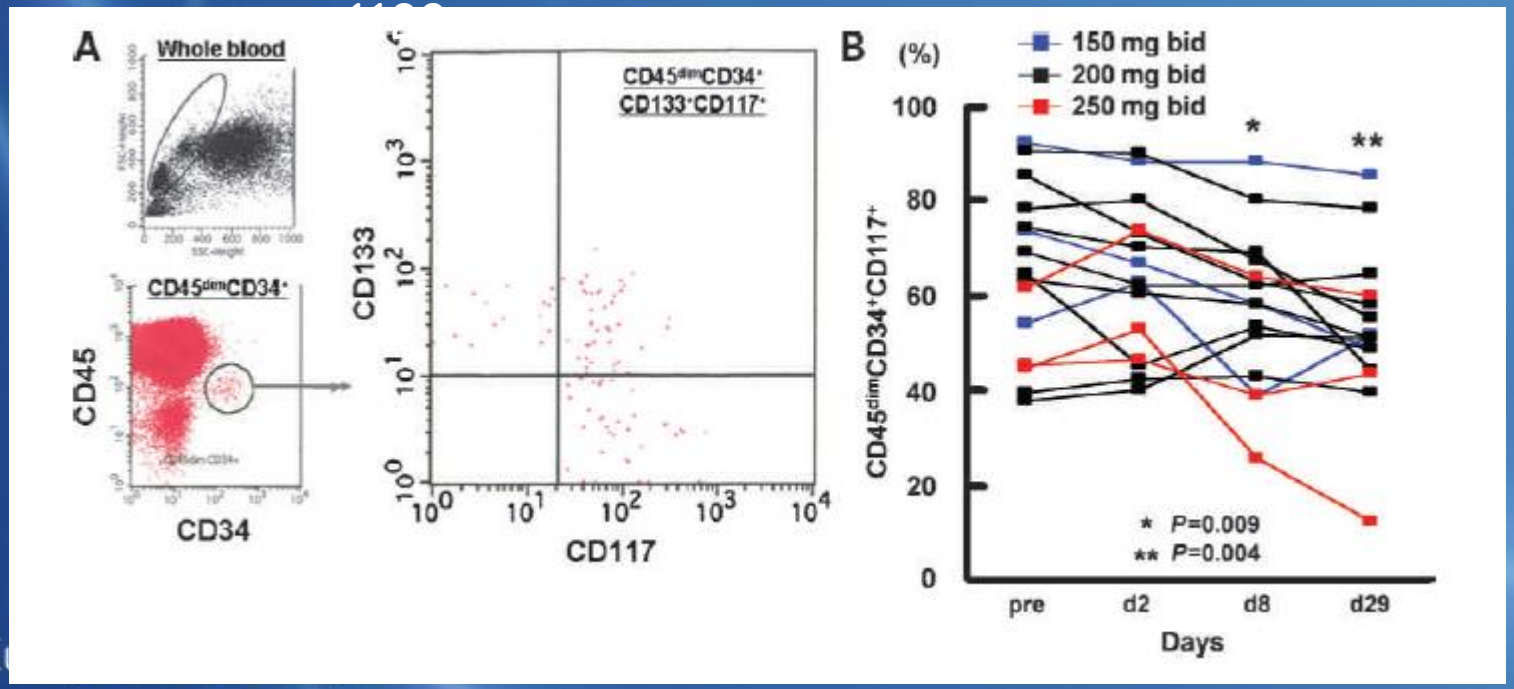
1) VEGF values after BIBF



Biomarkers study of BIBF 1120

Okamoto et al. Mol Cancer Ther 2010

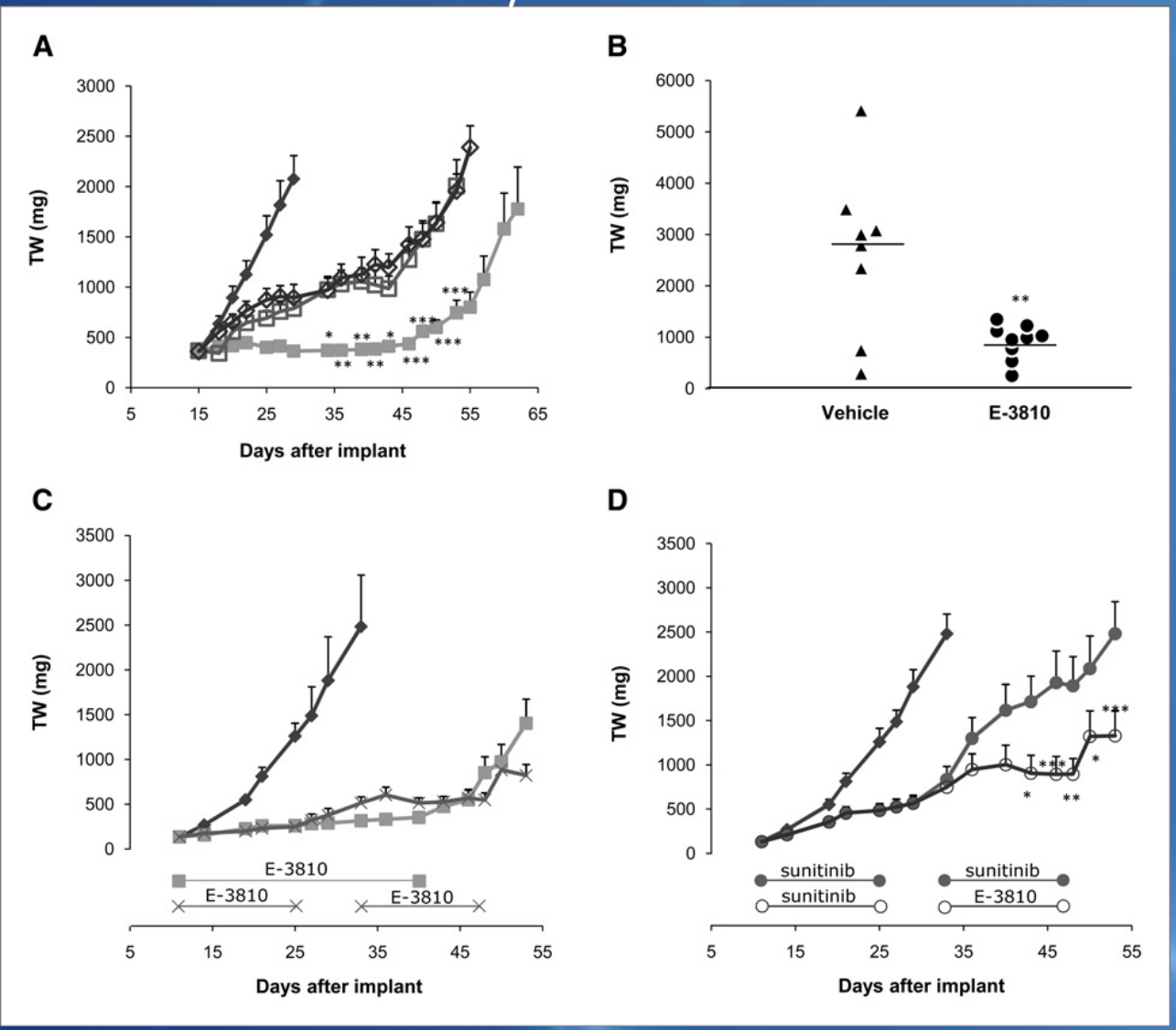
2) Serum CD117 BMD progenitor cell after BIBF



IEO Istituto E

E-3810

Antitumor activity



Dual VEGFR and FGFR1 inhibitor

Phase I trial single agent ongoing

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Bello et al. Cancer Res 2011

Future directions: Combo with CT

Phase I Trial of BIBF 1120 + Pemetrexed in NSCLC

Pts population: 26 pts with NSCLC relapsed after 1 previous Cisplatin-based 1st line for advanced disease

Doses:
Pemetrexed 500 mg/m^2 (day 1 of every cycle)
BIBF 1120: PO BID 100, 150, 200, 250 mg (from day 2 of every cycle)

RD: BIBF 1120→ 200 mg PO BID

Antitumor activity: 1 CR, 13 SD, 8 PD, 3 missed FUP, 1 non evaluable

	All CTCAE grades, *n* (%)	CTCAE grade 3,* *n* (%)
Fatigue	17 (65.4)	6 (23.1)
Nausea	16 (61.5)	1 (3.8)
Anorexia	14 (53.8)	2 (7.7)
Rash	10 (38.5)	0
Diarrhea	9 (34.6)	1 (3.8)
Vomiting	9 (34.6)	1 (3.8)
ALT increases	7 (26.9)	3 (11.5)
Abdominal pain	6 (23.1)	2 (7.7)
Dysgeusia	6 (23.1)	0
Pruritus	6 (23.1)	0
Insomnia	5 (19.2)	1 (3.8)
AST increases	5 (19.2)	0
Dyspepsia	4 (15.4)	0
Headache	4 (15.4)	0
Constipation	3 (11.5)	0
Stomatitis	3 (11.5)	0
Chills	3 (11.5)	0
Dermatitis acneiform	3 (11.5)	0

NOTE: Data presented are the highest ever reached CTCAE grade. One patient may have experienced more than one event.
*No grade 4 adverse events were observed.

Ellis PM et al. Clin Canc Res 2010

Future directions: Combo with Biologics

Phase I Trial of Brivanib + Cetuximab in GI tumors

Pts population: 60 pts with GI tumors relapsed after previous CTs (expansion cohort for CRC)

Doses:
Brivanib PO QD 250 → 800 mg D1-D8
Cetuximab 400 mg/m² C1D8 → 250 mg/m² qwk

G3/4 Aes: fatigue 16%, transaminitis 12%, diarrhoea 2%; 1 DLT: bilateral pulmonary emboli.

	Prior Therapy				
EGFR inhbitor	-	-	+	+	
VEGFR inhibitor	-	+	-	+	
Evaluable pts (total)	12	12	1	9	34
PR	4	1	0	0	5 (15%)
SD	5	7	1	6	19 (56%)
PD	3	4	0	3	10 (30%)
PR + SD ≥ 6 months	4	3	0	3	10 (30%)

Garrett CR et al. JCO 2008: abstr. 4111

Conclusions

1) FGFs/FGFRs signalling is a major driver of carcinogenesis. It is tumor specific

2) TK inhibitors not specific for FGFR signalling have a potential advantage on evasion of antiangiogenic treatments

3) Promising results have been obtained in single agents trials

4) Future directions require :
   - To improve knowledge to select patients and tumors
   - To explore combination or sequential schedules