



2nd ITOC

Dresden

15.9. -19.9.2010

**Targeting Tumor Angiogenesis:
Molecular Biology and Clinical Practice**

Anti-angiogenic TKI`s

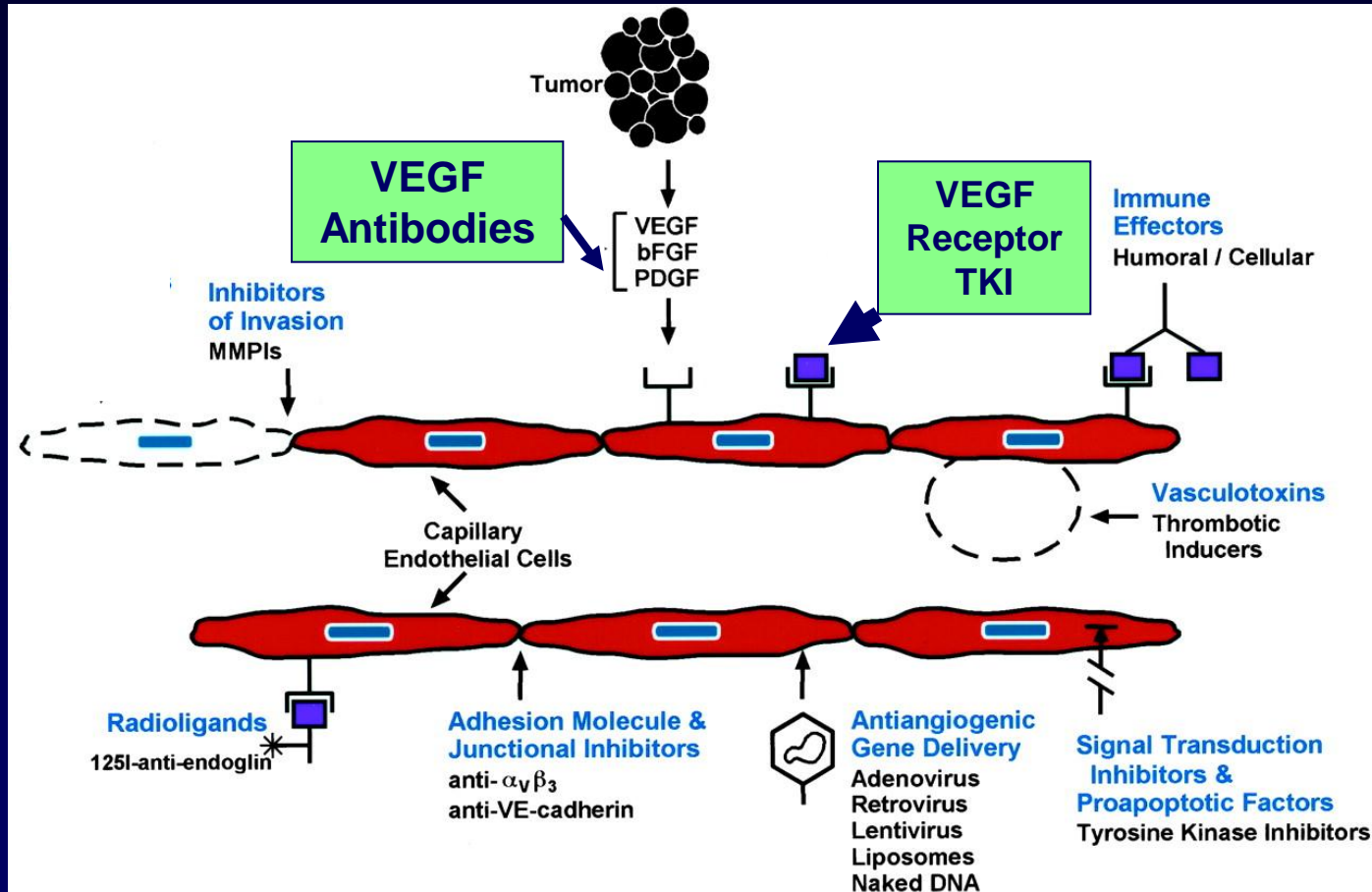
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Targets of Antiangiogenic Therapy



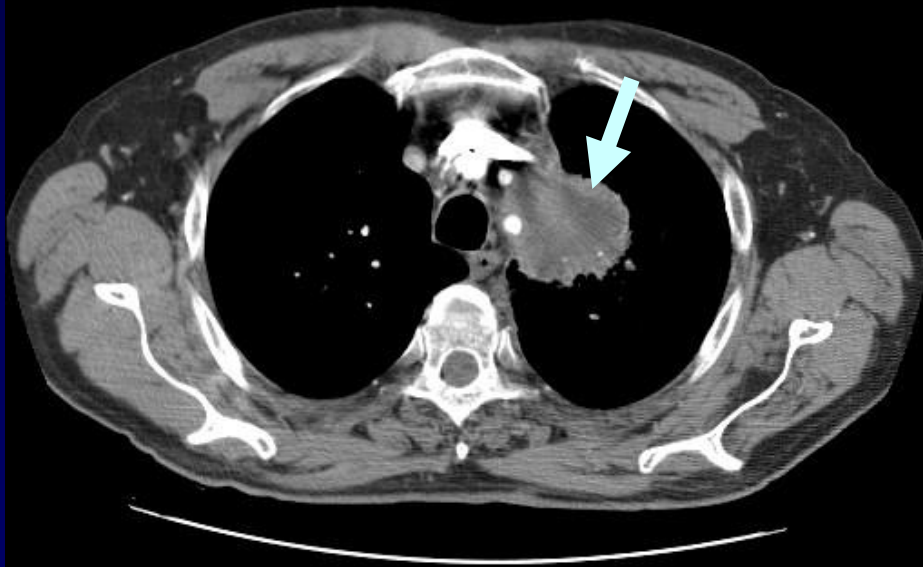
Scappaticci, F. A. J Clin Oncol; 20:3906-3927 2002

VEGFR-TKI

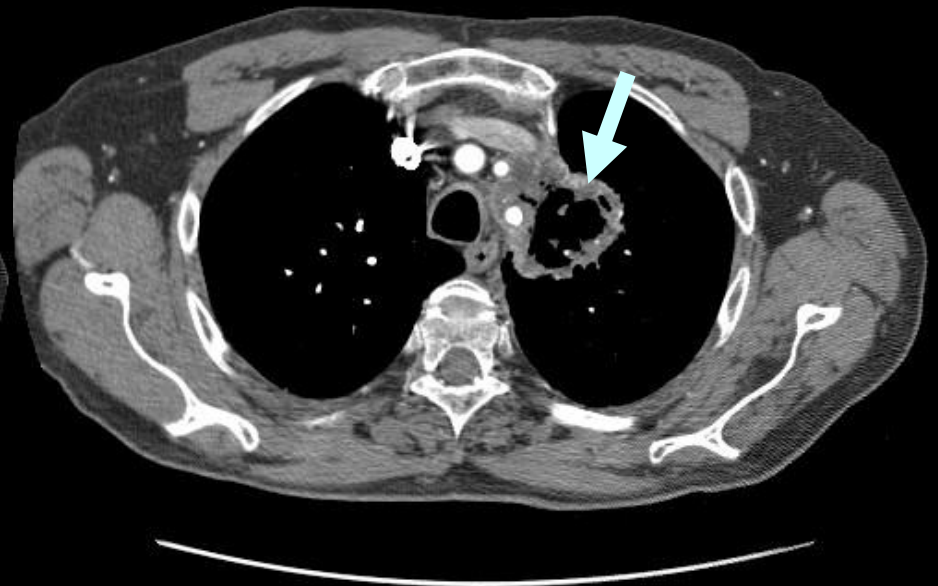
Drug	VEGFR 1-3	PDGFR	RET	C-KIT	FLT-3	EGFR	RAF
Vandetanib	✓	-	✓	-	-	✓	-
Cediranib	✓	✓	-	✓	-	-	-
Motesanib	✓	✓	-	✓	-	-	-
Sunitinib	✓	✓	-	✓	✓	-	-
Sorafenib	✓	✓	✓	✓	✓	-	✓
BIBF 1120	✓	✓	-	-	-	-	-
Axitinib	✓	✓	-	✓	-	-	-

Tumor Cavitation

CT scans for patient receiving sorafenib



Baseline



After 4 weeks of sorafenib therapy

VEGF – TKI

Drug	Patients	2nd/3rd	Response	Stabilization	PFS	Survival
Vandetanib		✓	1%	na	11 W	6.1 M
Sunitinib	64	✓	9.5%	19%	11.3 W	6 M
Sorafenib	52	✓	0%	59%	11.9 W	6.7 M
Vatanalib	54	✓	2%	56%	kA	kA
BIBF 1120 PS 0,1	57	✓	2%	58%	12 W	5.1 M
Axitinib	32	1 st /2 nd	9.4%	40.7%	15 W / 37 W ¹	12.8 M

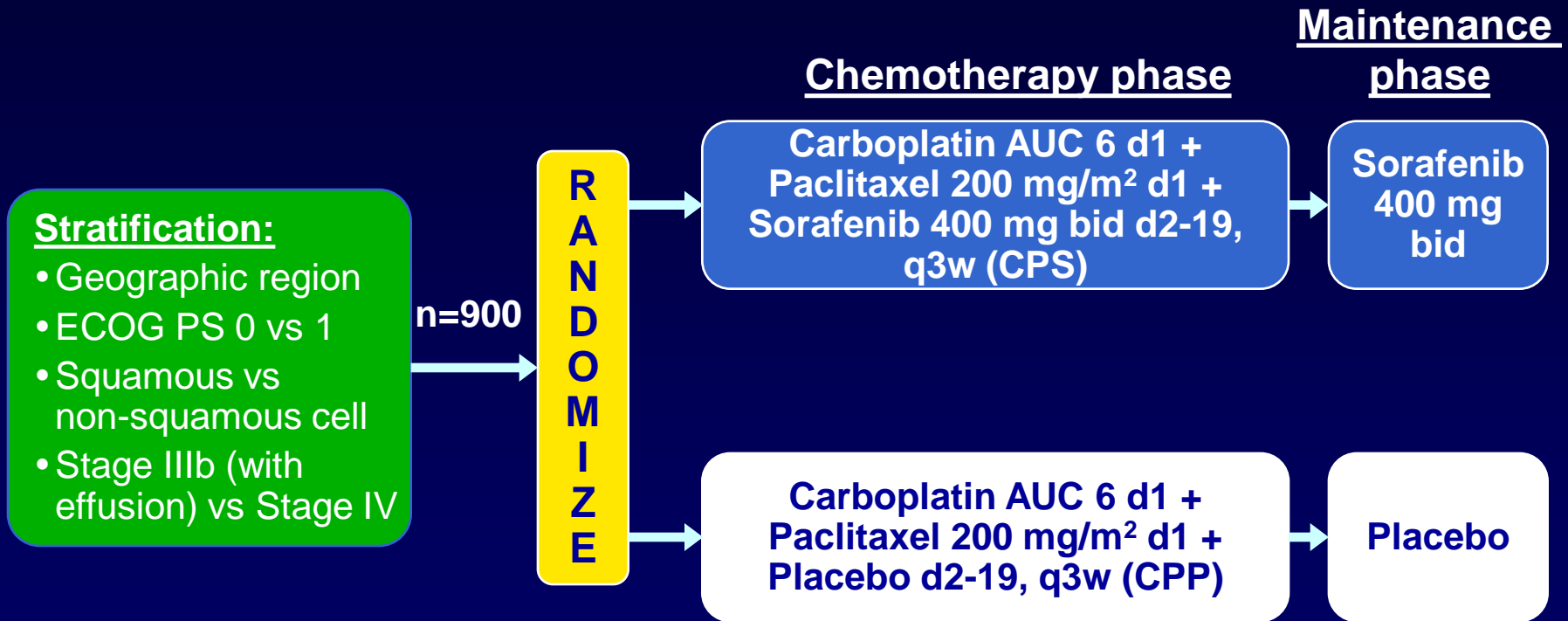
1 : First Line / Second Line

Natale RB, ASCO 2006, #7000; Socinski MR, ASCO 2006, #7001; Gatzemeier U, ASCO 2006, #7002; Gauler TC, ASCO 2007, #7541; von Pawel J, ASCO 2007, #7635; Schiller J ASCO 2007, #7507

TKI - NSCLC

- Front-line treatment
 - Sorafenib
 - Cediranib
 - Motesanib
 - Pazopanib
- Second-line treatment
 - Vandetanib
 - Sunitinib
 - BIBF 1120
 - Aflibercept
- Third/Fourth – line treatment
 - Sorafenib

Study Design ESCAPE



• **Primary endpoint:** Overall survival (Improvement of 30%)

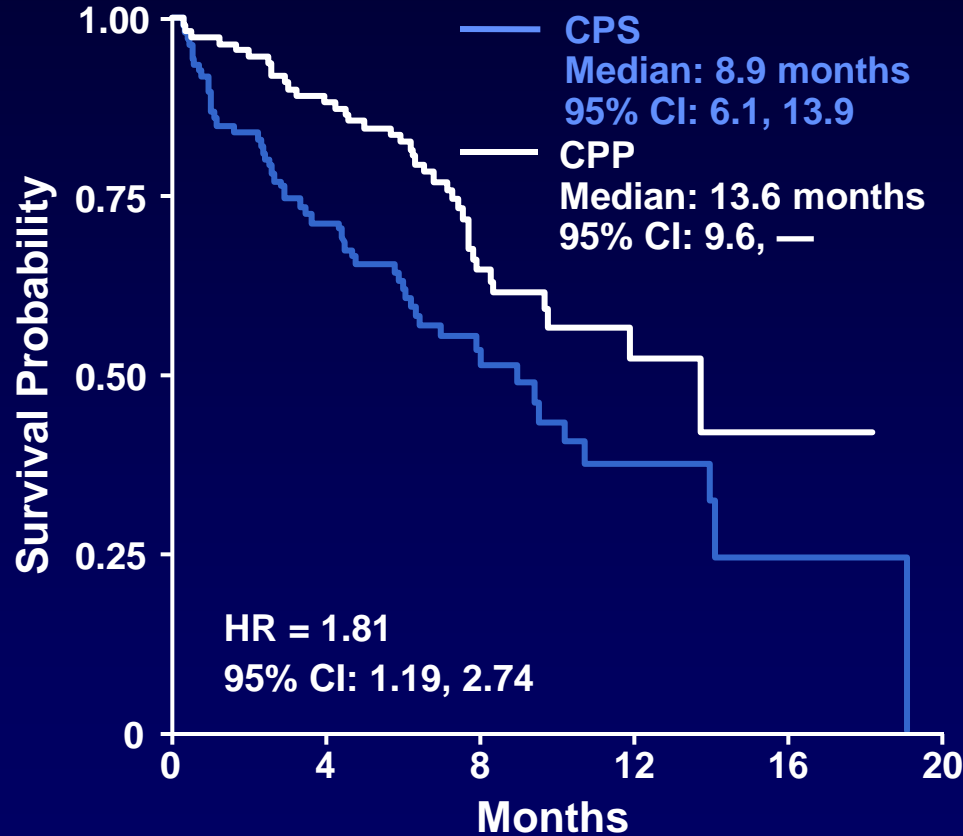
• **Secondary endpoints:** Response rate, duration of response, progression free survival, PRO, biomarkers

Escape – Key results

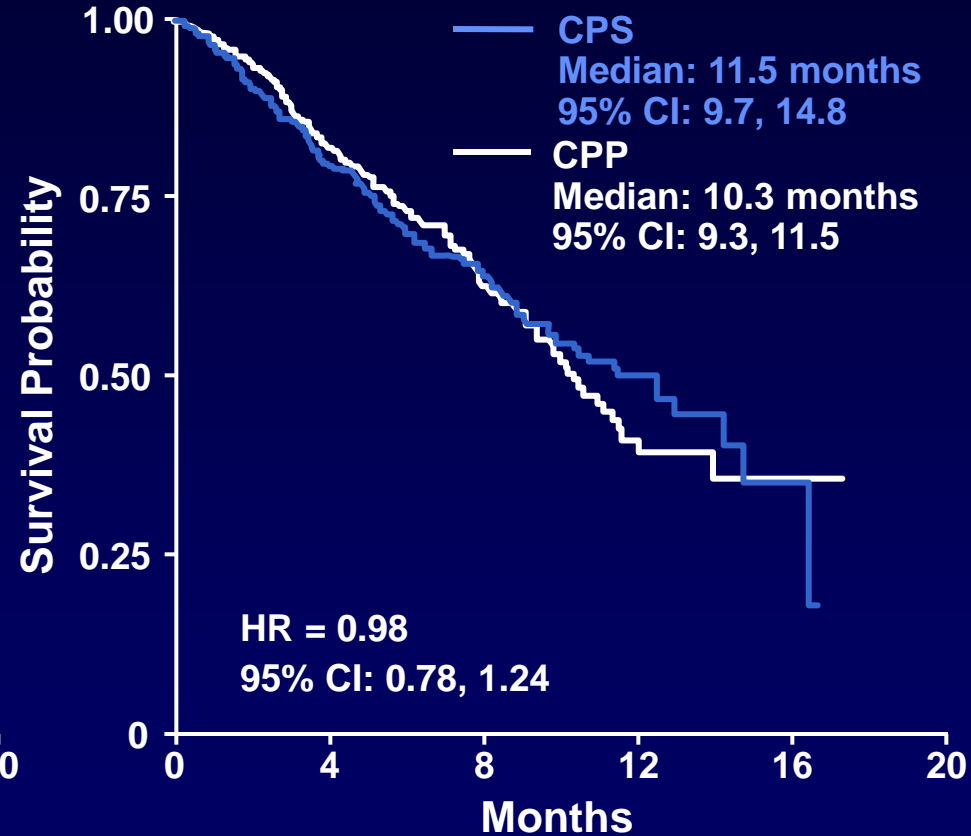
	Sorafenib + CP	CP Alone	P-value
Patients	464	462	
Histology			
Squamous cell	109 (23%)	114 (25%)	
Response rate	27%	24%	ns
Median OS (m.)	10.7	10.6	0.915 HR 1.15
Median PFS (m.)	4.6	5.4	0.433 HR 0.99
Drug related AE	390 (84%)	314 (68%)	<0.001
Drug related SAE	78 (17%)	39 (9%)	<0.001

Overall Survival by Histology

Squamous Cell



Non-Squamous Cell



Patients at Risk

	0	4	8	12	16
CPS	107	73	24	9	2
CPP	112	97	41	12	3

Patients at Risk

	0	4	8	12	16
CPS	357	281	173	38	5
CPP	350	280	168	22	2

Nexus Trial - Amendments

Cisplatin/Gemcitabine +/- Sorafenib in patients with stage IIIb/IV NSCLC

10/07	Introduction of OS as Co-Primary Endpoint Patient number: 350→ 900 pat.
25.03.08	DMC: Interim Safety Analysis→Recommendation of Exclusion of Squamous Cell Cancer patient due to higher toxicity
04/08	Exclusion of Squamous Cell Cancer patients
07/08	OS only primary endpoint, PFS secondary endpoint, Introduction of two futility interim analyses
02/09	904 randomised patients

NEXUS Press release

- The primary endpoint OS was missed
- Final analysis will be published at the ESMO Meeting in Milan October 2010

Sorafenib treatment efficacy and KRAS biomarker status in the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial



Primary end point: 8 week disease control (DC).

8-week disease control

- In BATTLE, median OS in patients with disease control (n=112) was 11.3 months vs 7.5 months in patients without disease control (n=104; p=0.002)
- Disease control in the various markers groups is shown below (n, %)

	EGFR	KRAS	VEGF	RXR/ CycD1	None	Total
Erlotinib	17 (35)	7 (14)	25 (40)	1 (0)	8 (38)	58 (34)
Vandetanib	27 (41)	3 (0)	16 (38)	0 (NA)	6 (0)	52 (33)
Erlotinib + Bexarotene	20 (55)	3 (33)	3 (0)	1 (100)	9 (56)	36 (50)
Sorafenib	23 (39)	14 (79)	39 (64)	4 (25)	18 (61)	98 (58)
Total	87 (43)	27 (48)	83 (49)	6 (33)	41 (46)	244 (46)

Demographics of sorafenib-treated population (n=105)

Characteristic		n (%)
Age	>60, ≤60	62 (59.0), 43 (41.0)
ECOG	0-1, 2	93 (88.6), 12 (11.4)
Gender	Male, Female	54 (51.4), 51 (48.6)
Race	White, Non-White	93 (88.6), 12 (11.4)
Prior lines of CT	1	31 (29.5)
	2	35 (33.3)
	2+	39 (37.2)
Prior bevacizumab	No, Yes	62 (59.0), 43 (41.0)
Smoker	No, Yes	26 (24.8), 79 (75.2)
Histology	Adeno	71 (67.6)
	Squamous	14 (13.3)
	Other	20 (19.1)

Disease control with sorafenib versus other treatments

<i>KRAS</i> mutant tumours	DC (p=0.06), n (%)		Total
	No	Yes	
Other	15 (68.18)	7 (31.82)	22
Sorafenib	7 (38.89)	11 (61.11)	18
Total	22	18	40

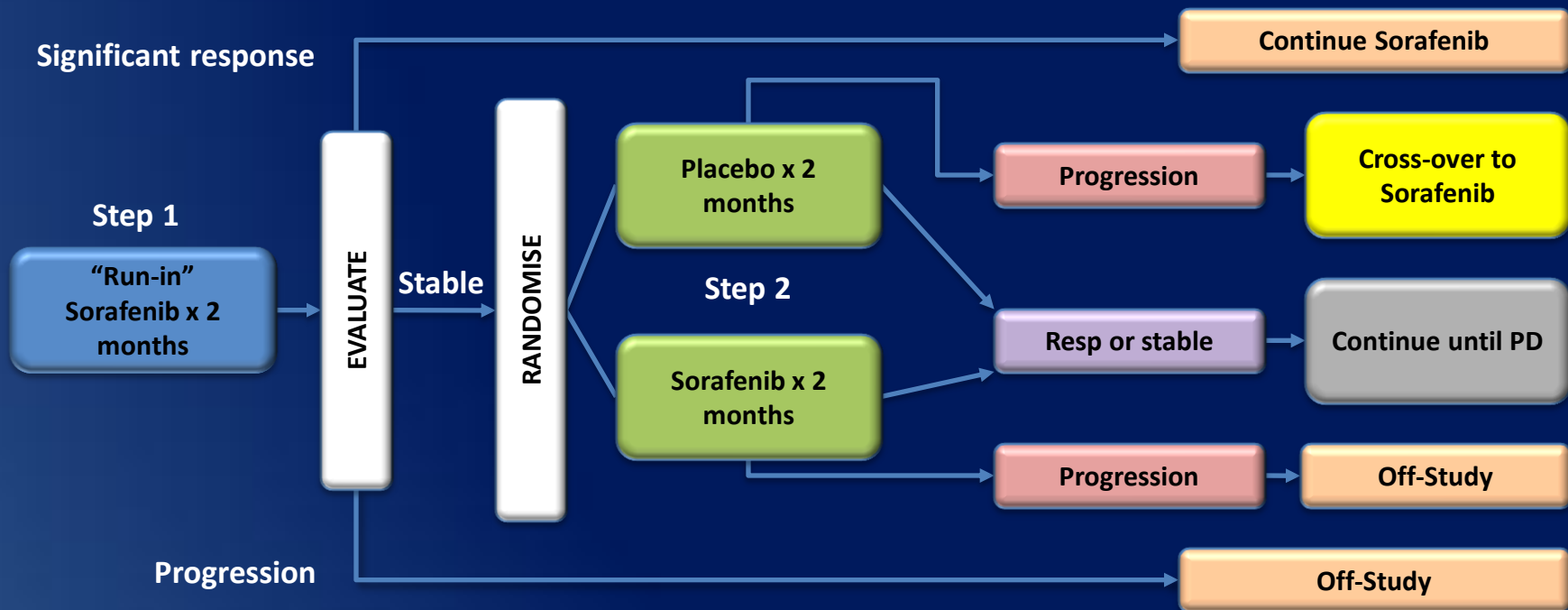
<i>EGFR</i> mutant tumours	DC (p=0.03), n (%)		Total
	No	Yes	
Other	7 (35.00)	13 (65.00)	20
Sorafenib	10 (76.92)	3 (23.08)	13
Total	17	16	33

Conclusions

- Disease control rate with sorafenib was improved in *KRAS* wild-type, *EGFR* wild-type or *KRAS* mutant tumors vs *EGFR* mutant tumors
- Survival data, as well as results from the whole BATTLE trial, are needed

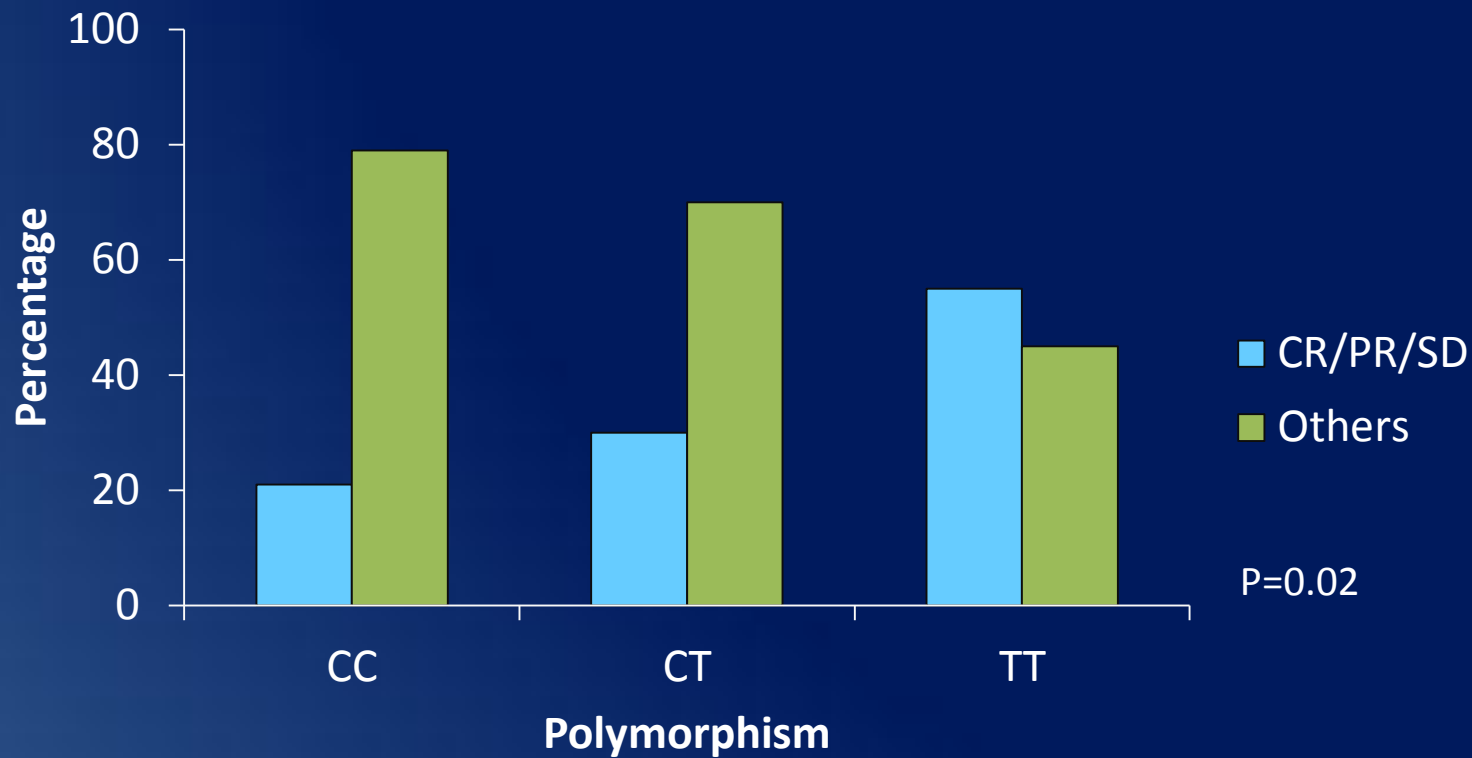
Study aim

To test the hypothesis that gene polymorphisms (VEGF, EGF, EGFR, IL-8, CXCR2, COX-2, KDR, ICAM1, FGFR4) may predict clinical outcome in patients enrolled in the E2501 trial.



Use of germline polymorphisms in VEGF to predict tumor response and progression-free survival in non-small cell lung cancer (NSCLC) patients treated with sorafenib: Subset pharmacogenetic analysis of Eastern Cooperative Oncology Group (ECOG) trial E2501

Results: VEGFC-1498T polymorphism and tumour response in Step 1



Conclusions

- Our preliminary results suggest polymorphisms in VEGF may predict DCR and PFS in NSCLC pts treated with sorafenib. Larger prospective trials to validate these findings are warranted.

Cediranib

	CP + Cediranib (45 / 30 mg)	CP	P-value
Patients	126	123	
Response	38%	16%	P<0.001
PFS	5.6	5.0	HR 0.77, p = 0.13
OS (m)	10.5	10.1	HR 0.78 P = 0.11

Currently randomized trials using a dose of 20 mg Cediranib on the way

Table 3. Adverse Events and Serious Adverse Events Reported for Patients Randomly Assigned to Cediranib 30 mg or Placebo in Combination With Paclitaxel/Carboplatin, Irrespective of Causality

Adverse Event	Cediranib (%) (n = 126)		Placebo (%) (n = 123)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hypertension	38	19	10	2
Diarrhea	79	15	36	2
Anorexia	61	6	41	3
Stomatitis	41	6	19	0
Fatigue	98	29	84	19
Dyspnea	75	10	65	13
Sensory neuropathy	63	3	67	5
Hand-foot syndrome	15	2	6	1
Bleeding	25	3	11	1
Hemoptysis	12	2	9	0
Venous thromboembolism	4	4	4	2
Increased TSH (≥ 2 × ULN)	45	27	7	0
Febrile neutropenia	10	4		
Grade 3 or 4 neutropenia	65	49		
G-CSF usage	10	2		
Grade 3 or 4 thrombocytopenia	15	4		
Hospitalization (any)	34	24		
Serious adverse events	51	20		
Serious adverse events leading to hospitalization	33	15		
Fatal serious adverse events	10	2		
Death ≤ 30 days of last dose of protocol therapy	16	7		

Abbreviation: TSH, thyroid-stimulating hormone; ULN, upper limit of normal; G-CSF, granulocyte colony-stimulating factor.

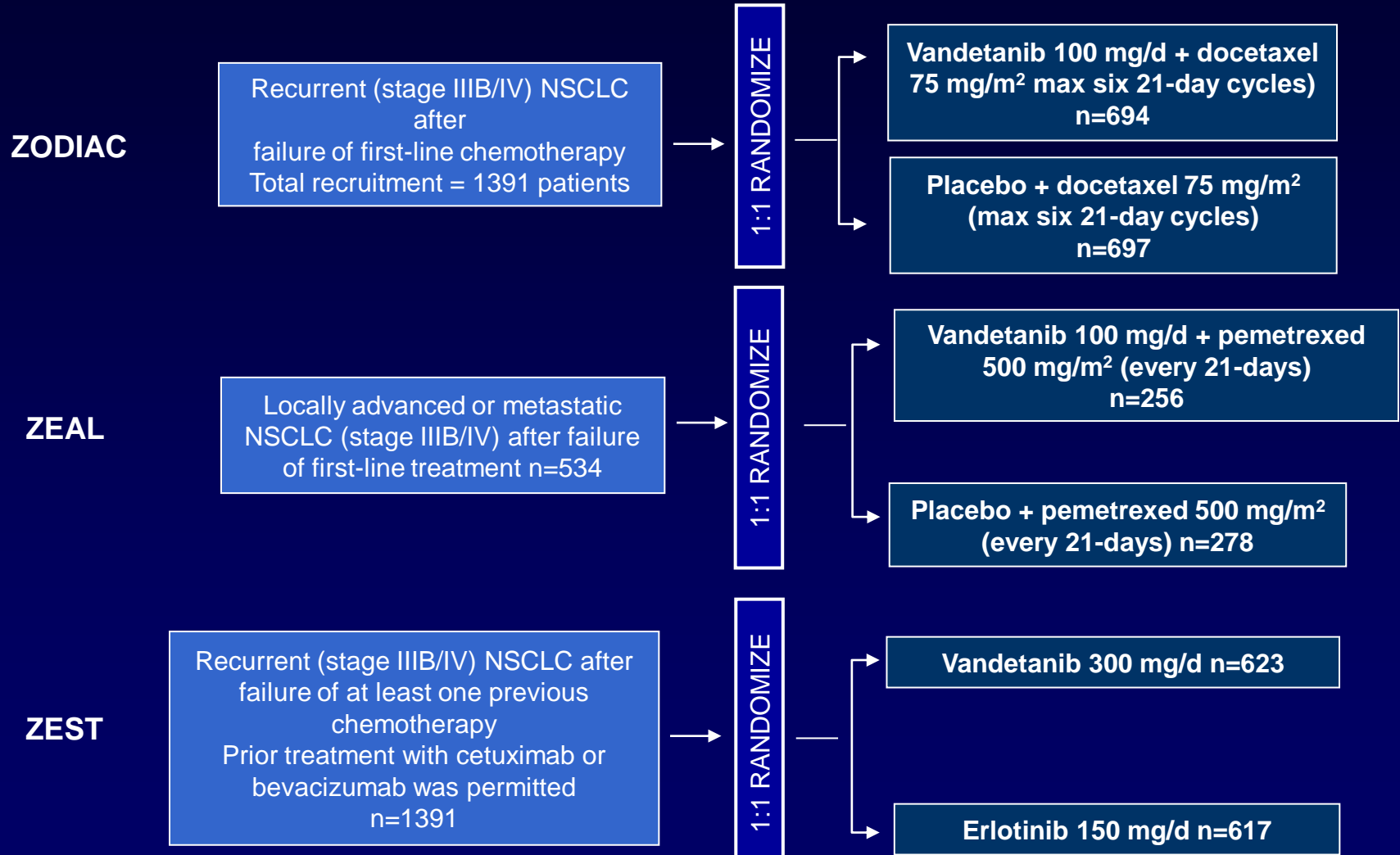
Other TKIs

Population	Schedule	Endpoint	Phase	Modification
First – line NSCLC IIIb/IV	Carbo/Pac +/- Motesanib	Survival	III	11/08 Stop of recruitment for safety reasons 03/09 Amendment – Only inclusion of patients with non squamous NSCLC 03/10 Recruitment finished
First – line NSCLC IIIb/IV	Pem/Pazo v Cis/Pem	PFS	II	03/10 Amendment – Decrease of pazopanib dose due to myelotoxicity 04/10 Stop of trial due to safety reasons

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Phase III randomized, vandetanib trials in NSCLC



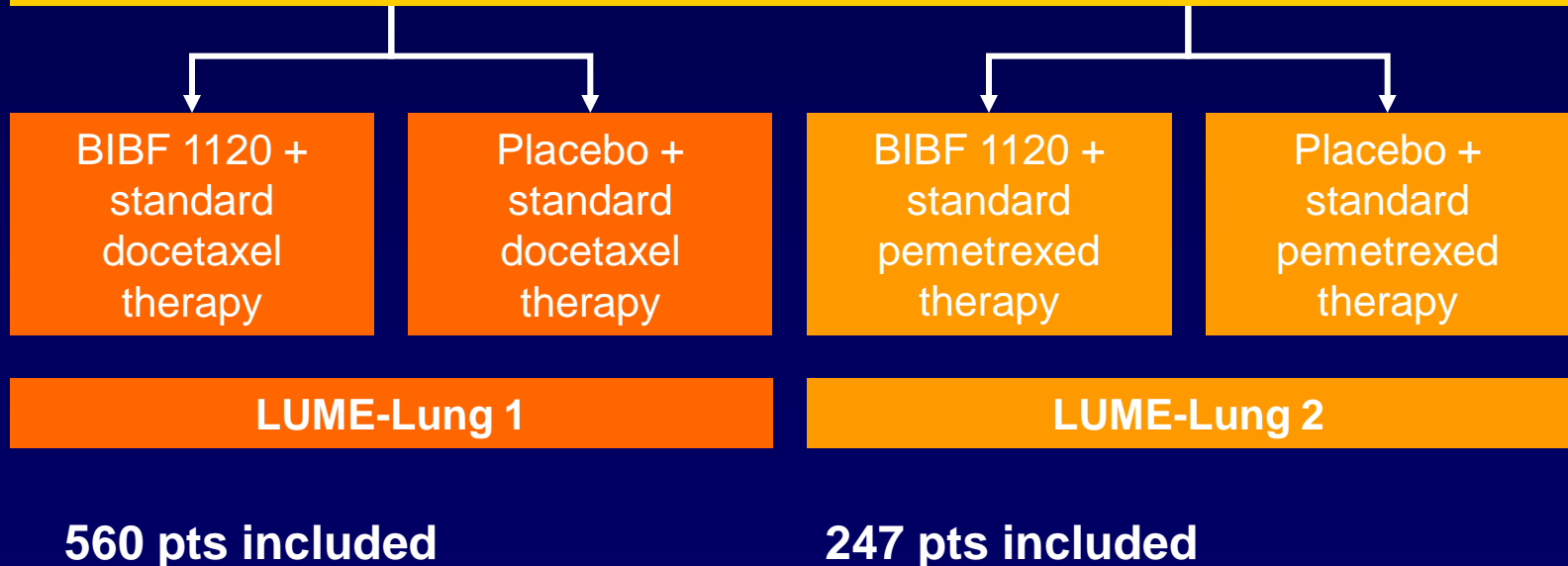
Efficacy results for vandetanib in NSCLC

	ZODIAC		ZEAL		ZEST	
	Vandetanib + docetaxel (n=694)	Placebo + docetaxel (n=697)	Vandetanib + pemetrexed (n=256)	Placebo + pemetrexed (n=278)	Vandetanib (n=623)	Erlotinib (n=617)
Median PFS	4.0 mths	3.2 mths	17.6 wks	11.9 wks	11.3 wks	8.9 wks
HR (p-value)	0.79 (<0.001)		0.86 (0.108)		0.98 (0.721)	
Median OS	10.6 mths	10.0 mths	10.6 mths	9.2 mths	6.9 mths	7.8 mths
HR (p-value)	0.91 (0.196)		0.86 (0.219)		1.01 (0.830)	

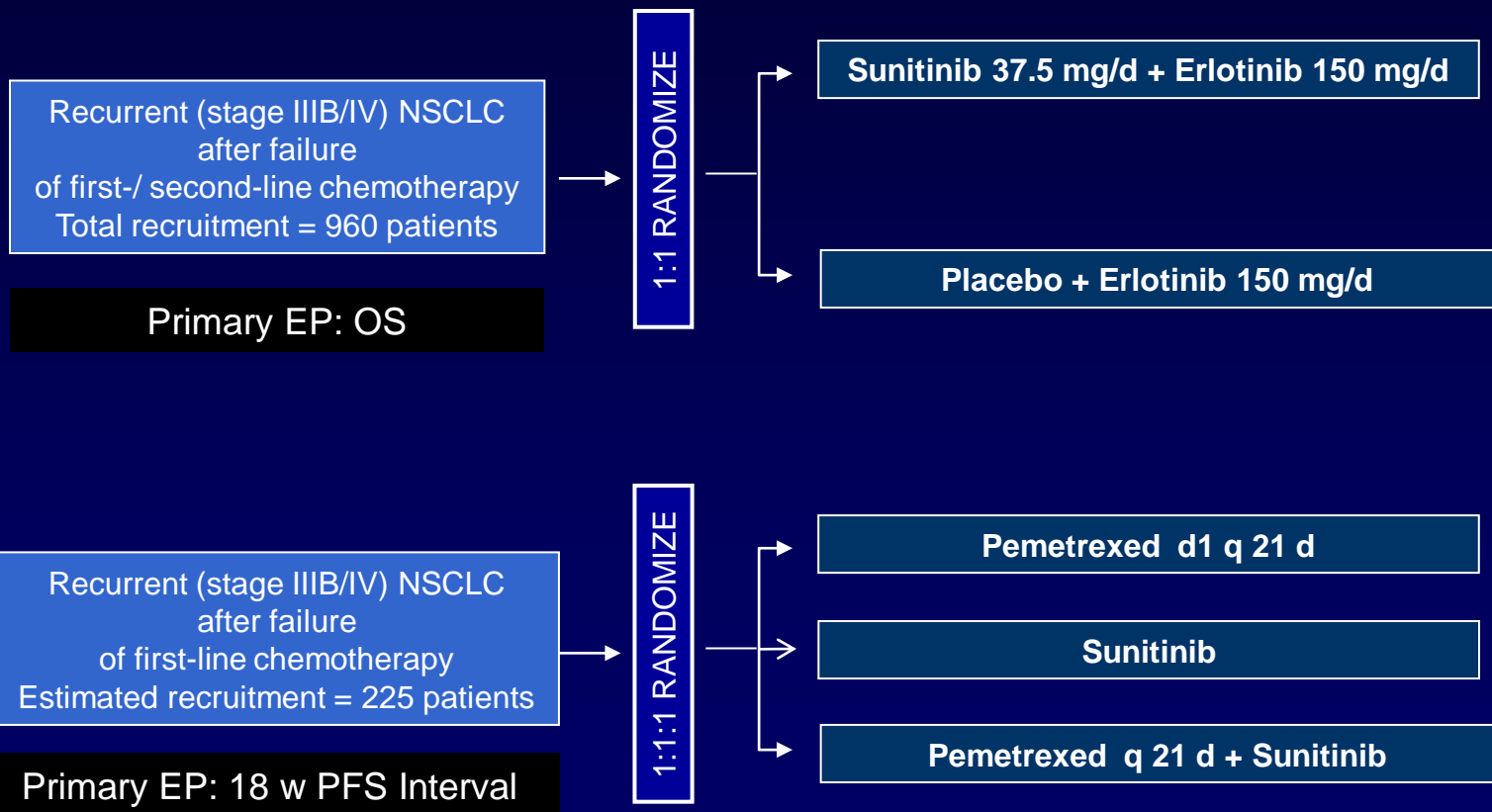
BIBF 1120 in pretreated NSCLC

LUME-Lung 1 and 2: two large, multi-national, randomized, double-blind, Phase III, placebo-controlled clinical trials assessing the efficacy of BIBF 1120 in combination with standard, second-line chemotherapy in patients with advanced or recurrent NSCLC

Patients with: histologically or cytologically confirmed NSCLC; stage IIIB/IV or recurrent NSCLC; failure of one previous first-line chemotherapy for advanced and/or metastatic disease; eligibility for docetaxel or pemetrexed therapy



Sunitinib in pretreated NSCLC



TKI - NSCLC

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 - Motesanib
 - Pazopanib
- Second-line treatment
 - Vandetanib
 - Sunitinib
 - BIBF 1120
 - Aflibercept
- **Third/Fourth – line treatment**
 - Sorafenib

13266 (Mission) - Design

Inclusion criteria

- Non squamous NSCLC
- Stage IIIB/IV
- **After 2 or 3 previous treatments**
- Performance Status 0-1

* Randomisation 2:1

Sorafenib*

400 mg BID + BSC

Placebo

400 mg BID + BSC

Primary EP: OS

Secondary EP: RR, Tox, PFS, QuL Biomarker

Conclusion

- Variety of different TKI available
- Increased toxicity in Squamous Cell Histology
- Efficacy remain to be confirmed in randomized trials
- No predictive marker available