CIRG/TORI 010

Primary analysis of a randomized, placebo controlled, phase II trial of motesanib plus weekly paclitaxel as first line therapy in HER2-negative metastatic breast cancer

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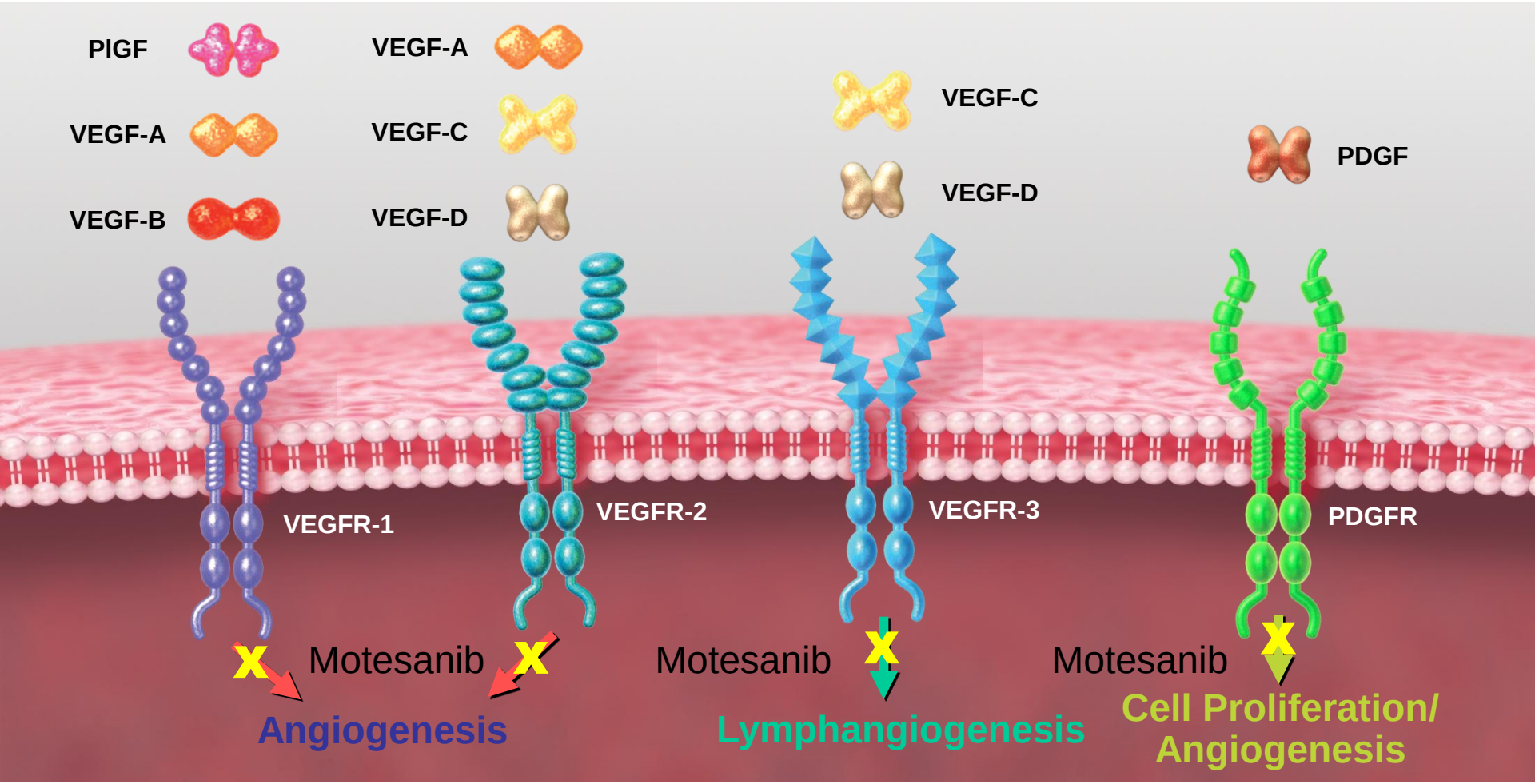
On behalf of the CIRG/TORI 010 Investigators

TRIO Translational Research In Oncology

ESMO/ECCO 2009 - Abstract 5.001

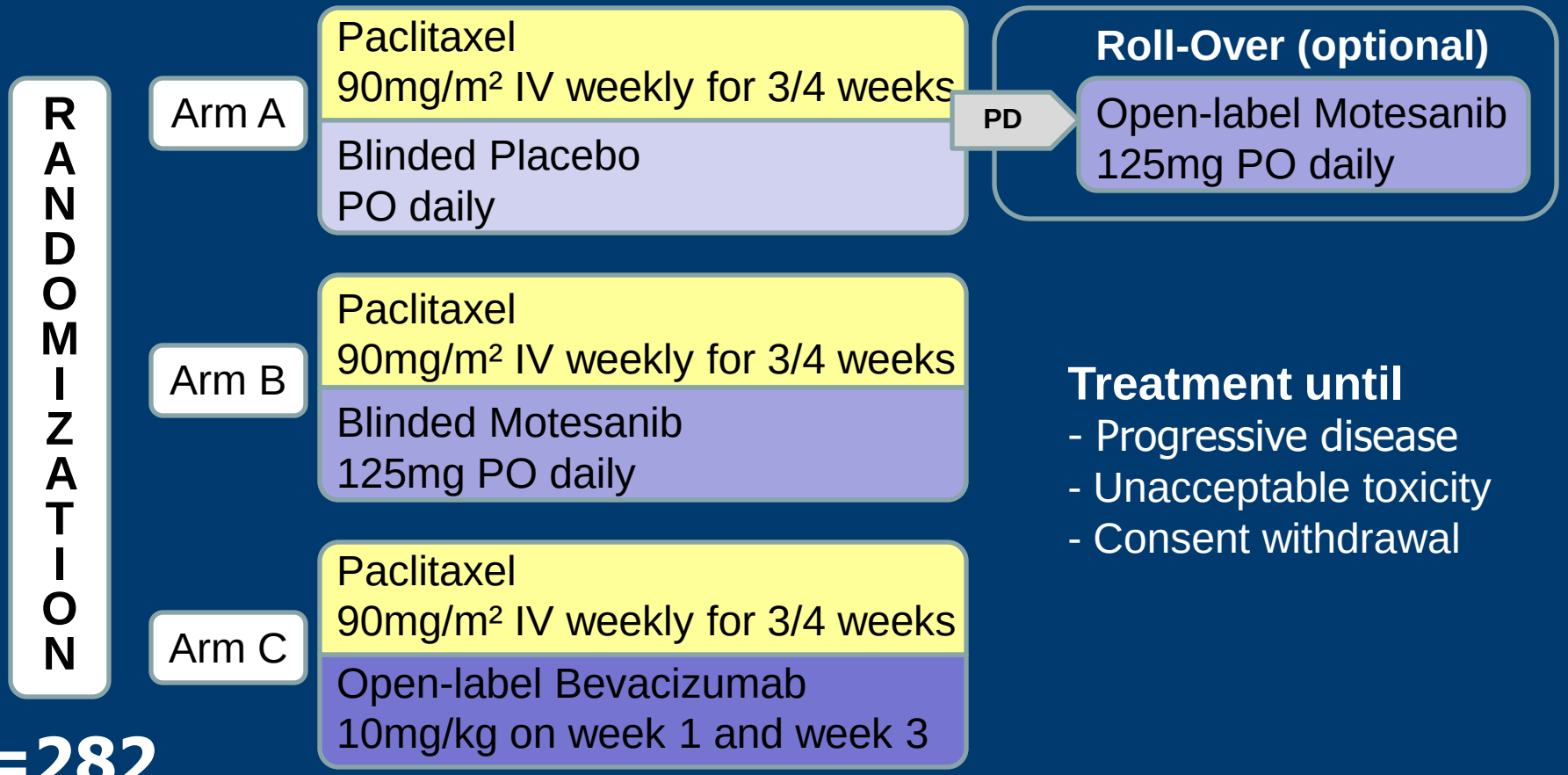
Motesanib blocks more than one mechanism involved in tumorigenesis



PlGF, placental growth factor; PDGF(R), platelet-derived growth factor (receptor); VEGF(R), vascular endothelial growth factor (receptor)

More than 70 other kinases are not inhibited by motesanib at < 1 μM.

Study Design



N=282

Treatment until
- Progressive disease
- Unacceptable toxicity
- Consent withdrawal

Stratification:
- Prior Taxane CT vs. other CT vs. None
- Number of metastatic sites (<3 vs. ≥3)
- Hormone receptor status (+ vs. -)

Key Eligibility Criteria

- Histologically or cytologically confirmed, locally-recurrent or metastatic adenocarcinoma of the breast
- No prior chemotherapy for locally recurrent or MBC
- HER2 negative
- Measurable disease per RECIST
- Age $\geq$ 18 years old
- ECOG Performance Status of 0 or 1
- Written Informed Consent

Study Endpoints

Primary

- Objective response rate (ORR) determined by independent review

Secondary

- Progression-free survival
- Duration of response
- Clinical benefit rate
- Overall survival
- Safety

Sample Size

Primary objective

- To compare ORR between Arm A (placebo) and Arm B (motesanib)

91 patients / arm

- 80% power to detect a 20% difference in ORR between Arm A and Arm B

  2-sided chi-square test with significance level of 0.05, assuming RR=20% in Arm A and RR=40% in Arm B

- 273 patients required

Analysis Plan

Populations

- Efficacy : Intent to treat (ITT) population
- Safety : Treated (≥1 dose) population

Methods

- ORR : Stratified Cochran-Mantel-Haenszel
- Time to event endpoints : KM curves + Cox proportional hazard models

Planned efficacy analyses

- 4 months after last patient enrolled
- 10 months after last patient enrolled

Study Conduct

Accrual

- 70 institutions in 12 countries
- 282 patients from Nov 2006 to Jul 2008

Response and progression endpoints

- Determined by independent review

Data cut-off for primary analysis

- Nov 10, 2008, 4 months after last patient was enrolled

Patients Characteristics

(ITT population)

	Placebo N = 94	Motesanib N = 91	Bevacizumab N = 97
Eligible per protocol	89 (95%)	83 (91%)	84 (87%)
Treated	90 (96%)	91 (100%)	96 (99%)
Age < 50 yrs	40 (43%)	28 (31%)	32 (33%)
ECOG			
0	57 (61%)	53 (58%)	54 (56%)
1	37 (39%)	38 (42%)	43 (44%)
Prior systemic treatments			
Endocrine	56 (60%)	58 (64%)	64 (66%)
Chemotherapy	62 (66%)	60 (66%)	65 (67%)
Taxane	*20 (21%)*	*20 (22%)*	*21 (22%)*
Anthracycline	*52 (55%)*	*53 (58%)*	*64 (66%)*
Biologic agents	3 (3%)	0 (0%)	3 (3%)

Tumor Characteristics

(ITT population)

	Placebo N = 94	Motesanib N = 91	Bevacizumab N = 97
ER and/or PgR+	75 (80%)	73 (80%)	78 (80%)
Extent of disease			
< 3 sites	52 (55%)	45 (50%)	49 (50%)
≥ 3 sites	42 (45%)	46 (50%)	48 (50%)
Status at study entry			
Metastatic	93 (99%)	90 (99%)	96 (99%)
Locally advanced	1 (1%)	1 (1%)	1 (1%)

Treatment Exposure

(ITT population)

	Placebo N = 94	Motesanib N = 91	Bevacizumab N = 97
Paclitaxel			
Median number of cycles	5	6	6
Median cumulative dose (mg/m^2)	1328	1282	1438
Investigational Agent			
Median number of cycles	5	6	7
Median cumulative dose	18813 mg	17875 mg	133 mg/kg
Median daily dose (mg)	125	111	-

Dose Adjustments

(Treated population)

	Placebo N = 90	Motesanib N = 91	Bevacizumab N = 96
Delay or reduction (per patient)			
No delay or reduction	56 (62%)	38 (42%)	44 (46%)
Delay only	21 (23%)	16 (18%)	52 (54%)
Reduction only	9 (10%)	13 (14%)	N/A
Delay and Reduction	4 (4%)	24 (26%)	N/A
Reasons for delay			
Adverse event	26%	50%	56%
Patient oversight	41%	28%	N/A
Other	33%	22%	44%
Reasons for reduction			
Adverse event	9%	54%	N/A
Patient oversight	36%	19%	N/A
Other	55%	27%	N/A

Treatment Discontinuation

(Treated population)

	Placebo N = 90	Motesanib N = 91	Bevacizumab N = 96
Study treatment status			
Ongoing	32 (36%)	22 (24%)	35 (36%)
Discontinued	58 (64%)	69 (76%)	61 (64%)
Discontinuation Reason			
Disease Progression	37 (64%)	38 (55%)	34 (56%)
Adverse Event	10 (17%)	16 (23%)	16 (26%)
Consent Withdrawn	6 (10%)	7 (10%)	5 (8%)
Death	1 (2%)	2 (3%)	1 (2%)
Lost to Follow-up	1 (2%)	0 (0%)	0 (0%)
Other	3 (5%)	6 (9%)	5 (8%)

Objective Response Rate

(ITT population)

	Placebo N = 94	Motesanib N = 91	Bevacizumab N = 97
Best overall response			
CR	0 (0%)	0 (0%)	0 (0%)
PR	33 (35%)	44 (48%)	44 (45%)
SD	37 (39%)	31 (34%)	36 (37%)
PD	15 (16%)	6 (7%)	11 (11%)
Unknown	1 (1%)	2 (2%)	3 (3%)
Missing	8 (9%)	8 (9%)	3 (3%)
ORR (CR + PR)	**35.11%**	**48.35%**	**45.36%**
95% CI	(25.54 - 45.64)	(37.74 - 59.07)	(35.22 - 55.79)
Difference in ORR vs Motesanib	-13.25%		-2.99%
95% CI	(-27.34 - 0.84)	--	(-17.26 - 11.28)
P value	0.09		0.72

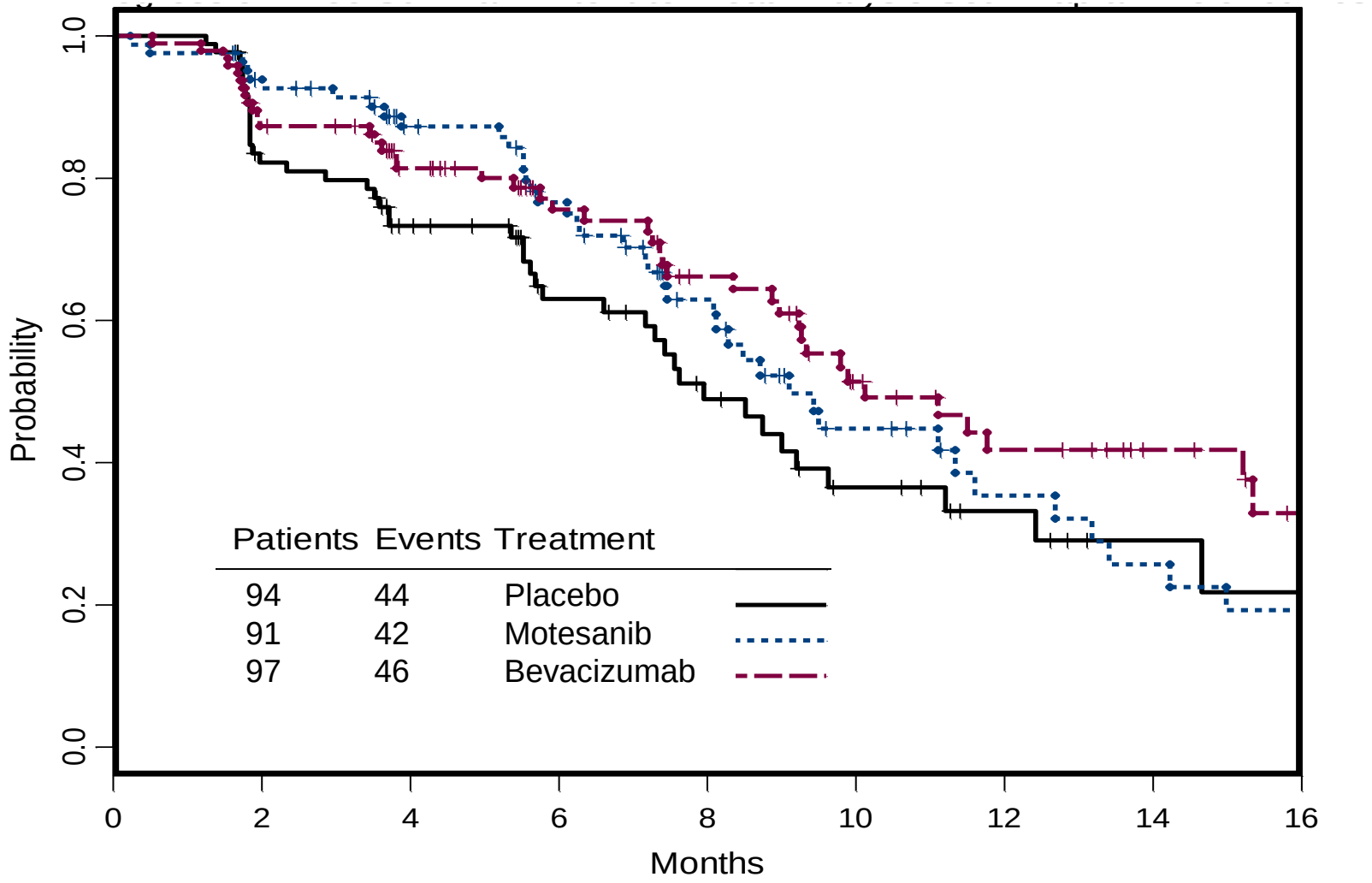
Progression-Free Survival

(ITT population)

	Placebo N = 94	Motesanib N = 91	Bevacizumab N = 97
Number of patients with			
Disease progression	37 (39%)	35 (38%)	38 (39%)
Death	19 (20%)	17 (19%)	17 (18%)
Censored patients	50 (53%)	49 (54%)	51 (53%)
Median PFS	**7.95 mo**	**9.10 mo**	**10.12 mo**
95% CI	(6.60 – 9.63)	(8.08 – 11.60)	(8.97 – 15.34)

Progression-Free Survival

(ITT population)



Hematological Toxicity

(Treated population)

	Placebo N = 90		Motesanib N = 91		Bevacizumab N = 96	
	Overall	Gr 3 / 4	Overall	Gr 3 / 4	Overall	Gr 3 / 4
Anemia	78 (86%)	4 (4%)	69 (76%)	5 (5%)	72 (75%)	7 (7%)
Leucopenia	65 (72%)	16 (18%)	81 (89%)	23 (25%)	79 (82%)	28 (29%)
Neutropenia	60 (67%)	21 (23%)	79 (87%)	42 (46%)	69 (72%)	34 (35%)
Thrombocytopenia	17 (19%)	6 (7%)	25 (27%)	1 (1%)	13 (14%)	3 (3%)

Non-Hematological Toxicity

(Treated population)

	Placebo N = 90		Motesanib N = 91		Bevacizumab N = 96	
	Overall	Gr 3 / 4	Overall	Gr 3 / 4	Overall	Gr 3 / 4
Nausea	40 (44%)	0	54 (59%)	0	47 (49%)	2 (2%)
Diarrhea	30 (33%)	0	63 (69%)	17 (19%)	38 (39%)	4 (4%)
Vomiting	23 (26%)	2 (2%)	36 (40%)	2 (2%)	22 (23%)	2 (2%)
Abdominal pain	28 (31%)	1 (1%)	44 (48%)	7 (8%)	27 (28%)	1 (1%)
Stomatitis	10 (11%)	0	14 (15%)	1 (1%)	28 (29%)	1 (1%)
Alopecia	57 (64%)	0	54 (59%)	0	68 (71%)	0
Anorexia	14 (16%)	1 (1%)	33 (36%)	0	25 (26%)	0
Hepatobiliary disorders	5 (6%)	3 (3%)*	15 (17%)	6 (7%)	3 (3%)	0
Back pain	12 (13%)	2 (2%)	14 (15%)	2 (2%)	24 (25%)	1 (1%)
Peripheral neuropathy	38 (42%)	7 (8%)	44 (48%)	6 (7%)	52 (54%)	18 (19%)

* Includes 1 grade 5 hepatic failure and 1 grade 5 portal vein thrombosis

Gr 3-5 and Serious Hepatobiliary Disorders
(Treated population)

	Placebo N = 90	Motesanib N = 91	Bevacizumab N = 96
Cholecystitis	0	3	0
Gallbladder Enlargement	0	1	0
Cholestasis	0	1	0
Hepatic Failure	2*	0	0
Jaundice	1	2	0
Portal Vein Thrombosis	1*	0	0
Total	**3****	**7**	**0**

*Fatal events
** 1 patient experienced fatal hepatic failure and portal vein thrombosis

Gallbladder Toxicity with Motesanib

- Gallbladder toxicity is considered as a toxicity of interest for motesanib
- Cholecystitis and gallbladder enlargement reported for in 4-5% of patients treated with motesanib (0% in non-motesanib patients)
- Unknown etiology
- 3/4 cases of cholecystitis or gallbladder enlargement managed by surgery

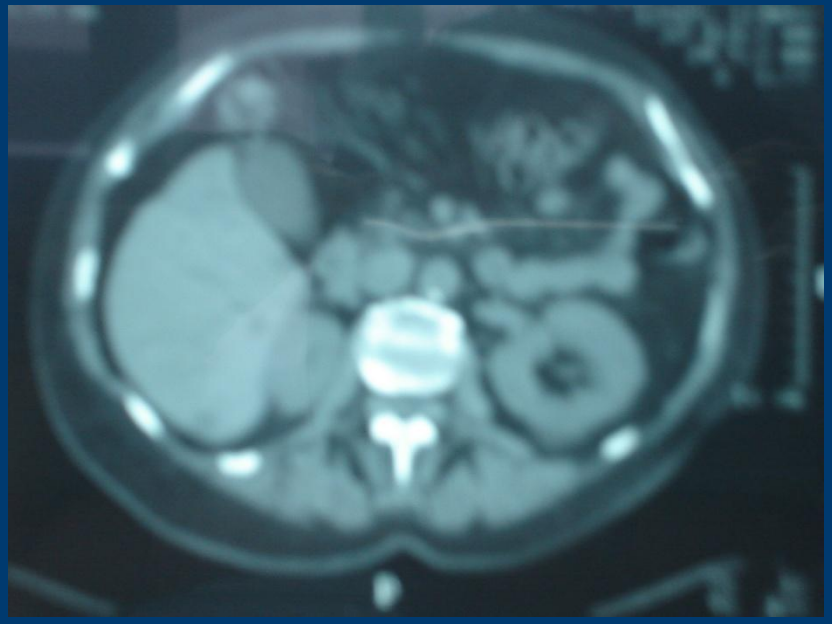
Summary of Cases of Gallbladder Toxicity

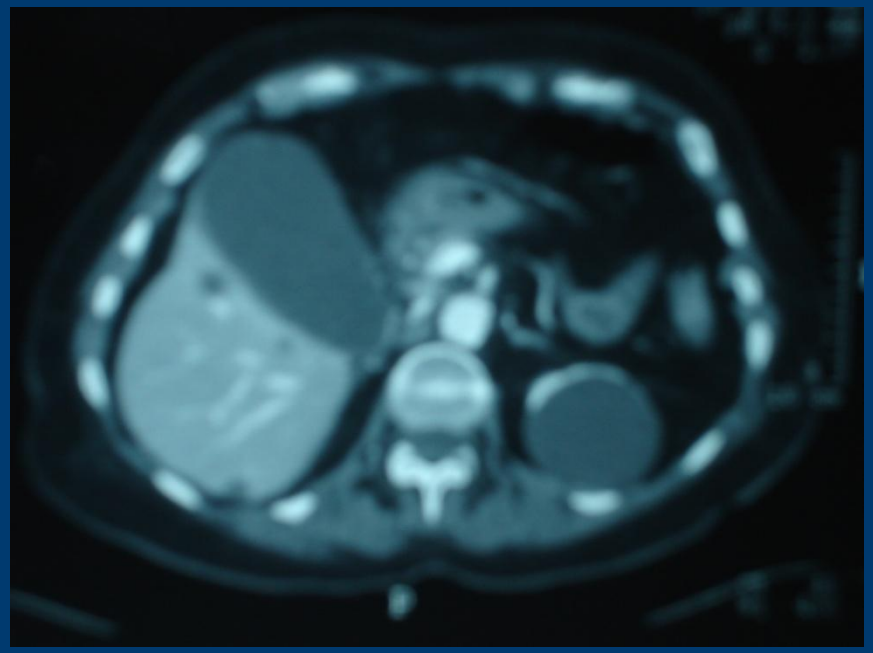
Subject #	Time to onset (days)	Presenting signs or Symptoms	Diagnosis and Management	Outcome
10034 ▪ 41 y ▪ No relevant medical Hx	406	Not reported	▪ Acute cholecystitis ▪ Study drug withheld ▪ Hospitalized and treated with antibiotics and opioids	▪ US confirmed mild to resolving cholecystitis ▪ Study drug treatment resumed with a dose reduction ▪ No recurrence (pt still under treatment)
10039 ▪ 65 y ▪ No relevant medical Hx	407	▪ Epigastric attack ▪ N & V ▪ Fatty food intolerance	▪ CT showed gallbladder distension ▪ Study drug withheld ▪ Cholecystectomy ▪ Post-op Dx of cholecystitis	▪ Resolved ▪ Study drug treatment resumed
10091 ▪ 72 y ▪ No relevant medical Hx	49	▪ N & V ▪ Dyspepsia	▪ CT showed gallbladder strain ▪ Study drug withheld ▪ Cholecystectomy	▪ Resolved ▪ Study drug treatment resumed

Summary of Cases of Gallbladder Toxicity

(cont'd)

Subject #	Time to onset (days)	Presenting signs or Symptoms	Diagnosis and Management	Outcome
10308 ▪ 48 y ▪ No relevant medical Hx	150	▪ Asthenia ▪ Anorexia ▪ Abdominal pain	▪ CT scan showed gallbladder enlargement ▪ Study drug withheld ▪ Surgery	▪ Resolved ▪ Study drug treatment resumed at full dose





Conclusions

- This is the first study to compare a small molecule VEGF tyrosine kinase inhibitor with bevacizumab in a randomized, placebo controlled trial in metastatic breast cancer
- Treatment with motesanib/paclitaxel was feasible in the treatment of HER2 negative MBC
- Efficacy of motesanib/paclitaxel was comparable to bevacizumab/paclitaxel in terms of ORR
- Motesanib/paclitaxel increased the AEs compared to the other 2 arms:
    - Grade 3 and 4 gastrointestinal toxicities
    - Grade 3 and 4 hepatobiliary toxicities
    - Grade 3 and 4 neutropenia
    - VTE events were similar across all three arms

Acknowledgements

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