

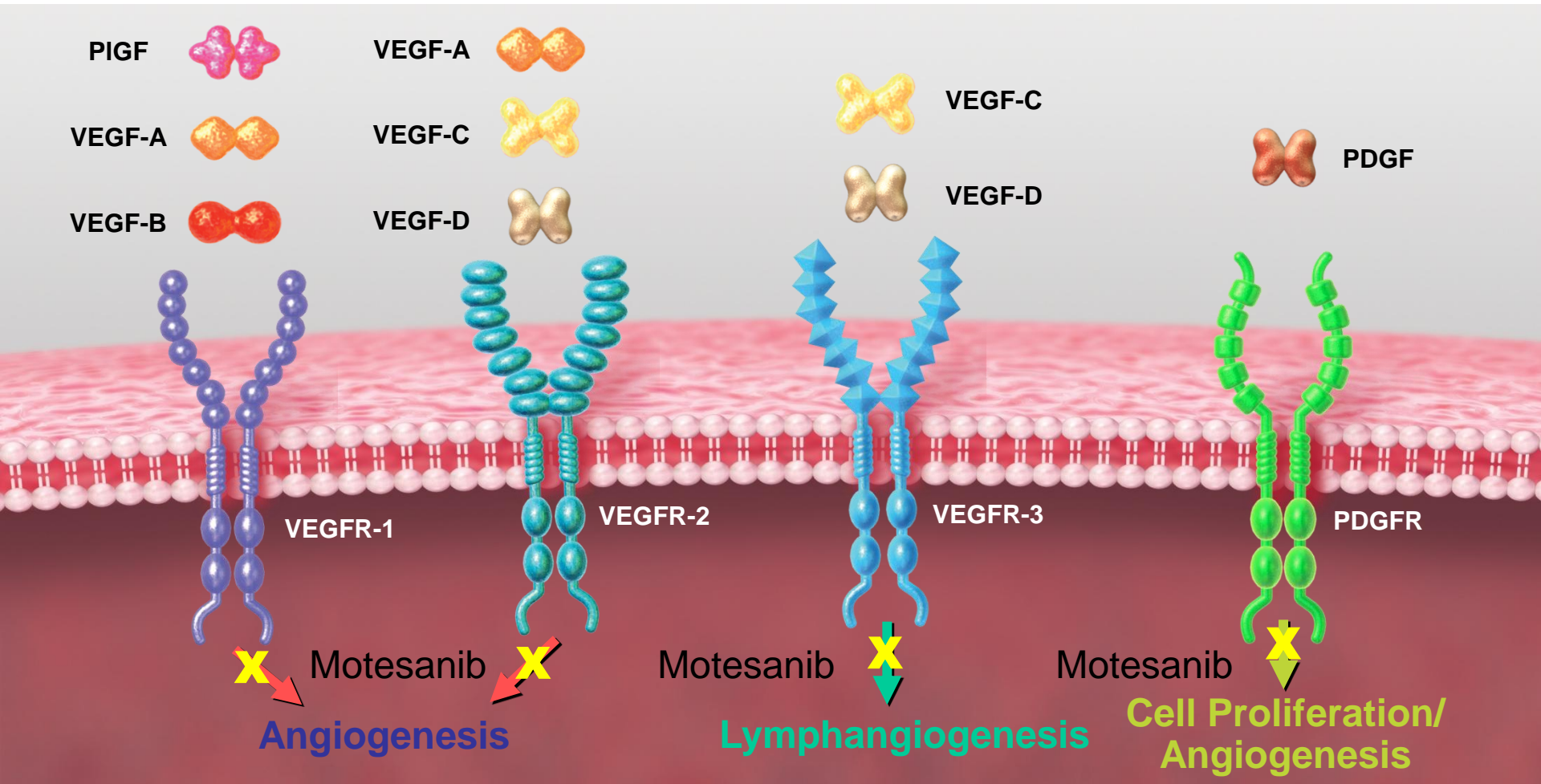
# CIRG/TORI 010

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

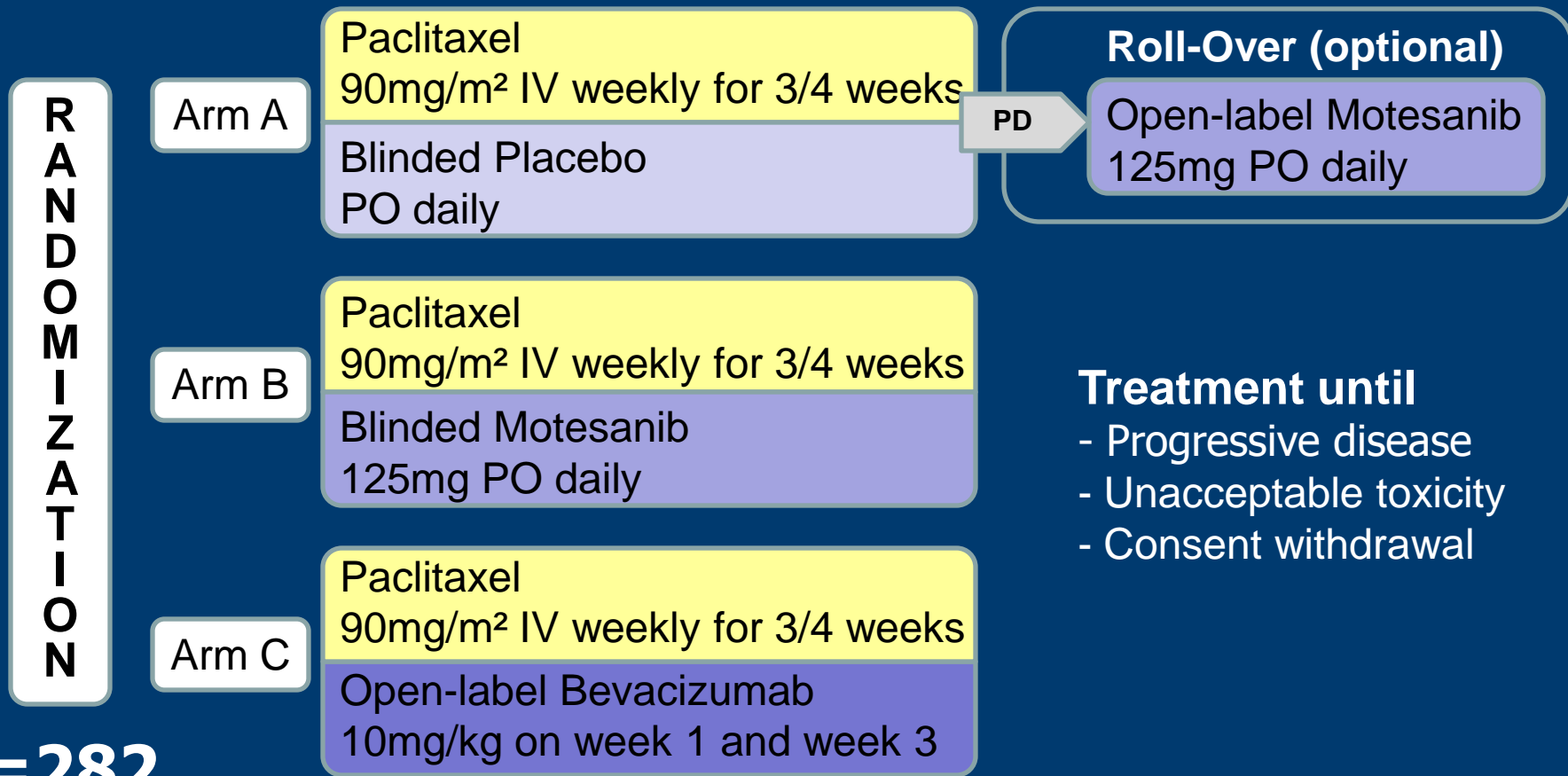
# *Motesanib blocks more than one mechanism involved in tumorigenesis*



PIGF, 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  $\mu$ M.**

# 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 ( $\geq 1$  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%)
<i>Taxane</i>	20 (21%)	20 (22%)	21 (22%)
<i>Anthracycline</i>	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
<hr/>			
Paclitaxel			
Median number of cycles	5	6	6
Median cumulative dose (mg/m <sup>2</sup> )	1328	1282	1438
<hr/>			
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
<b>Best overall response</b>			
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%)
<b>ORR (CR + PR)</b>	<b>35.11%</b>	<b>48.35%</b>	<b>45.36%</b>
95% CI	(25.54 - 45.64)	(37.74 - 59.07)	(35.22 - 55.79)
<b>Difference in ORR vs Motesanib</b>	<b>-13.25%</b>		<b>-2.99%</b>
95% CI	(-27.34 - 0.84)	--	(-17.26 - 11.28)
P value	0.09		0.72

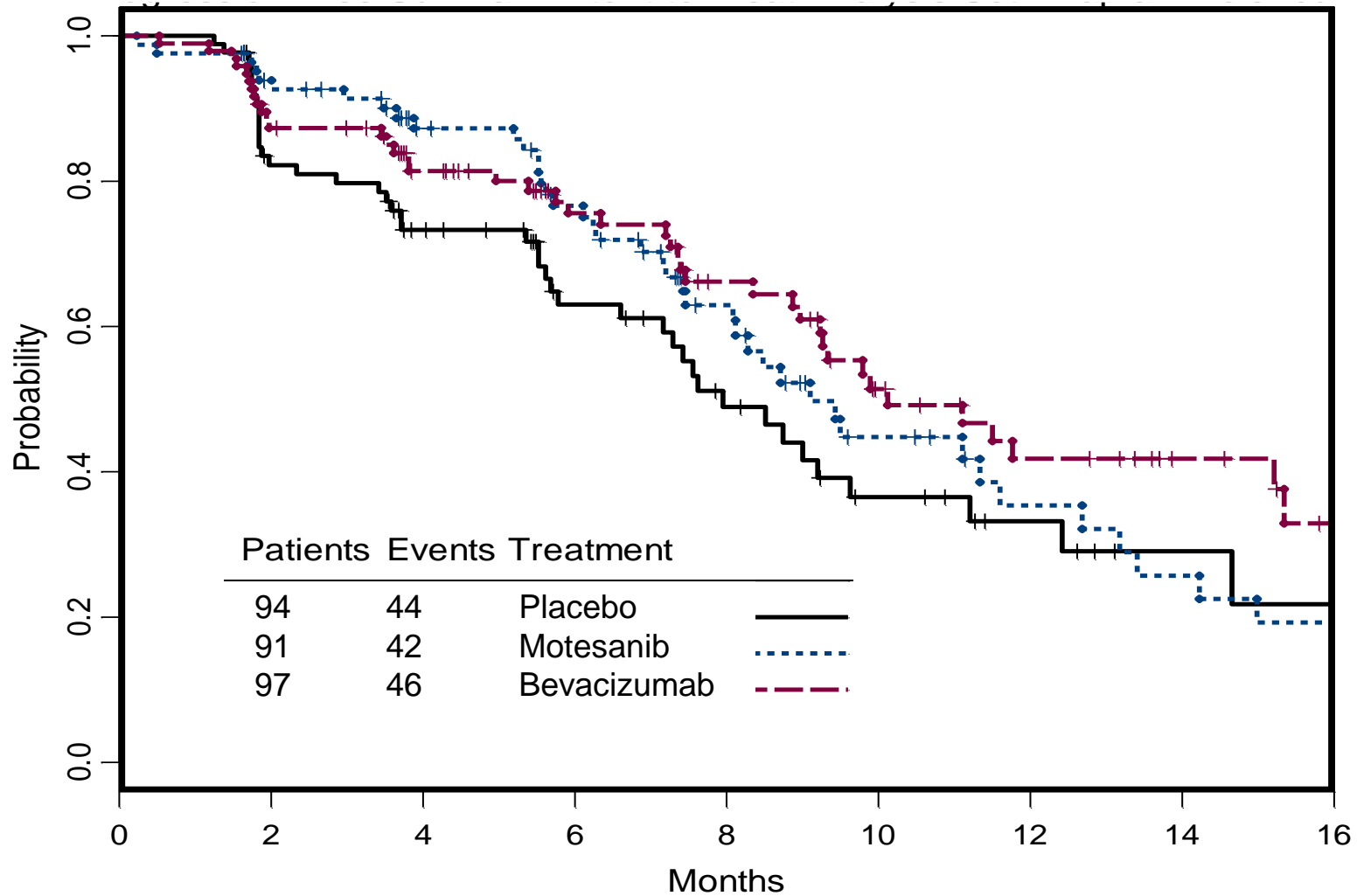
# Progression-Free Survival

(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%)
<b>Median PFS</b>	<b>7.95 mo</b>	<b>9.10 mo</b>	<b>10.12 mo</b>
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
<b>Total</b>	<b>3**</b>	<b>7</b>	<b>0</b>

\*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

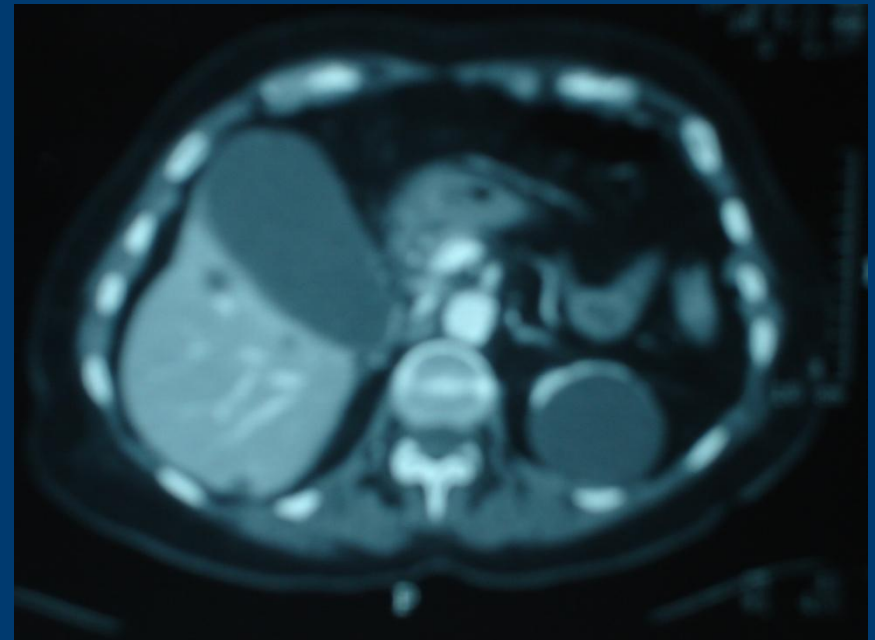
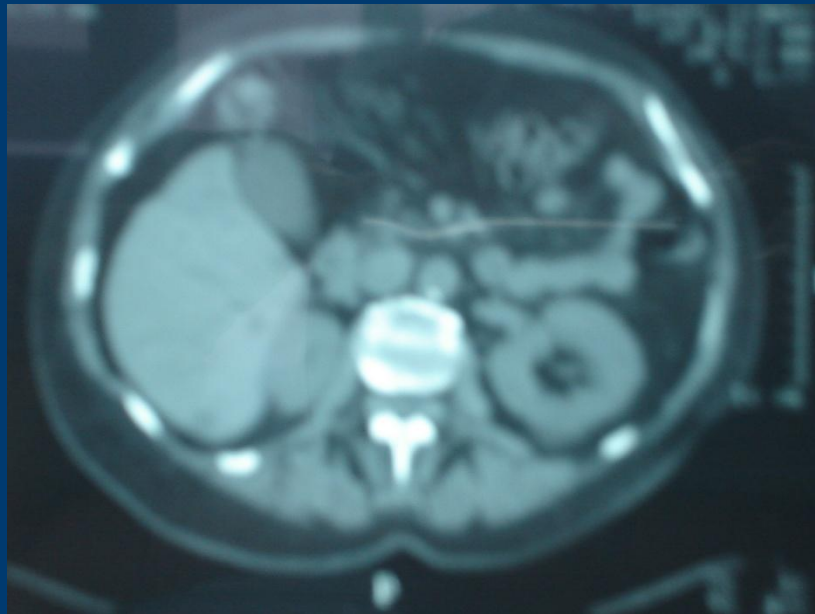
# Summary of Cases of Gallbladder Toxicity

Subject #	Time to onset (days)	Presenting signs or Symptoms	Diagnosis and Management	Outcome
<p><b><u>10034</u></b></p> <ul style="list-style-type: none"> <li>▪ 41 y</li> <li>▪ No relevant medical Hx</li> </ul>	406	Not reported	<ul style="list-style-type: none"> <li>▪ Acute cholecystitis</li> <li>▪ Study drug withheld</li> <li>▪ Hospitalized and treated with antibiotics and opioids</li> </ul>	<ul style="list-style-type: none"> <li>▪ US confirmed mild to resolving cholecystitis</li> <li>▪ Study drug treatment resumed with a dose reduction</li> <li>▪ No recurrence (pt still under treatment)</li> </ul>
<p><b><u>10039</u></b></p> <ul style="list-style-type: none"> <li>▪ 65 y</li> <li>▪ No relevant medical Hx</li> </ul>	407	<ul style="list-style-type: none"> <li>▪ Epigastric attack</li> <li>▪ N &amp; V</li> <li>▪ Fatty food intolerance</li> </ul>	<ul style="list-style-type: none"> <li>▪ CT showed gallbladder distension</li> <li>▪ Study drug withheld</li> <li>▪ Cholecystectomy</li> <li>▪ Post-op Dx of cholecystitis</li> </ul>	<ul style="list-style-type: none"> <li>▪ Resolved</li> <li>▪ Study drug treatment resumed</li> </ul>
<p><b><u>10091</u></b></p> <ul style="list-style-type: none"> <li>▪ 72 y</li> <li>▪ No relevant medical Hx</li> </ul>	49	<ul style="list-style-type: none"> <li>▪ N &amp; V</li> <li>▪ Dyspepsia</li> </ul>	<ul style="list-style-type: none"> <li>▪ CT showed gallbladder strain</li> <li>▪ Study drug withheld</li> <li>▪ Cholecystectomy</li> </ul>	<ul style="list-style-type: none"> <li>▪ Resolved</li> <li>▪ Study drug treatment resumed</li> </ul>

# Summary of Cases of Gallbladder Toxicity

(cont'd)

Subject #	Time to onset (days)	Presenting signs or Symptoms	Diagnosis and Management	Outcome
<b><u>10308</u></b> <ul style="list-style-type: none"><li>▪ 48 y</li><li>▪ No relevant medical Hx</li></ul>	150	<ul style="list-style-type: none"><li>▪ Asthenia</li><li>▪ Anorexia</li><li>▪ Abdominal pain</li></ul>	<ul style="list-style-type: none"><li>▪ CT scan showed gallbladder enlargement</li><li>▪ Study drug withheld</li><li>▪ Surgery</li></ul>	<ul style="list-style-type: none"><li>▪ Resolved</li><li>▪ Study drug treatment resumed at full dose</li></ul>



# 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

We would like to thank the **282 women** who participated in the study

## Investigators

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