

**31 MAIO  
A 2 JUN  
2018**

XIX CONGRESSO SUL-BRASILEIRO  
DE GINECOLOGIA E OBSTETRÍCIA  
IV JORNADA SUL-BRASILEIRA  
DE MASTOLOGIA



# **VEGFR2 CITOPLASMÁTICO É RELACIONADO COM MELHOR SOBREVIVÊNCIA EM PACIENTES COM CÂNCER DE MAMA METASTÁTICO TRATADAS COM BEVACIZUMABE**

**Tadeu Paiva Jr**, Ana C. de M. e Figueiredo, Roseana S.  
de M. Borba, Vladmir C. C. de Lima, Cynthia B. de T.  
Osorio

Mai/2018

# Indicação de quimioterapia

- RH negativo
- Doença visceral com progressão rápida
- Doença visceral sintomática
- Crise Visceral
- SLP curta após 1 ou 2 linhas de hormonioterapia

# **Monoquimioterapia sequencial vs combinação**

# Phase III Trial of Doxorubicin, Paclitaxel, and the Combination of Doxorubicin and Paclitaxel as Front-Line Chemotherapy for Metastatic Breast Cancer: An Intergroup Trial (E1193)

By George W. Sledge, Donna Neuberg, Patricia Bernardo, James N. Ingle, Silvana Martino, Eric K. Rowinsky, and William C. Wood

## 1<sup>st</sup>-line Metastatic Breast Cancer

- Prior chemo in adjuvant setting allowed
- Prior hormonal therapy in adjuvant or metastatic setting allowed
- Enrolled 739 patients from 2/1993 to 9/1995

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E

**Doxorubicin**  
60 mg/m<sup>2</sup> iv q21d

**Paclitaxel**  
175 mg/m<sup>2</sup> iv over 24h q21d

**Paclitaxel**  
175 mg/m<sup>2</sup> iv over 24h q21d

**Doxorubicin**  
60 mg/m<sup>2</sup> iv q21d

**Doxorubicin** 50 mg/m<sup>2</sup> iv q21d  
**Paclitaxel** 150 mg/m<sup>2</sup> iv over 24h q21d

Patients on sequential arm crossed over at time of disease progression

	Doxorubicin	Paclitaxel	Doxorubicin + Paclitaxel	p
Taxa de resposta	36%	34%	47%	0.77 A vs T 0.01 AT vs A 0.006 AT vs T
TTF	6.0m	6.3m	8.2m	0.002 AT vs A 0.05 AT vs T
SG	19.1m	22.5m	22.1m	0.60 A vs T 0.82 AT vs A 0.49 AT vs T

**Table 2. Incidence of Moderate and Severe Adverse Effects After Randomization**

Adverse Effect	DOX (%)	PAC (%)	DOX + PAC (%)
Leukopenia	49.6	59.9	54.9
Thrombocytopenia	5.4	2.1	16.0
Anemia	6.2	9.5	17.2
Infection	4.1	8.3	12.7
Cardiac complications	8.7	3.7	8.6
Neurologic complications	1.6	3.7	10.7
Vomiting	6.6	2.5	4.5
Diarrhea	1.6	1.6	4.5
Stomatitis	7.8	2.9	4.5
Lethal toxicity	2.5	1.6	1.6

NOTE: The common toxicity criteria of the National Cancer Institute were used to define moderate (grade 3), average (grade 4), or lethal (grade 5) toxicity.

Abbreviations: DOX, doxorubicin; PAC, paclitaxel.

- Outros exemplos:
  - Doxorrubicina + Docetaxel vs Doxorrubicina → Docetaxel
  - Epirrubicina + Paclitaxel vs Epirrubicina → Paclitaxel

# Papel da angiogênese no câncer



**SEMINARS IN MEDICINE**  
**OF THE**  
**BETH ISRAEL HOSPITAL, BOSTON**

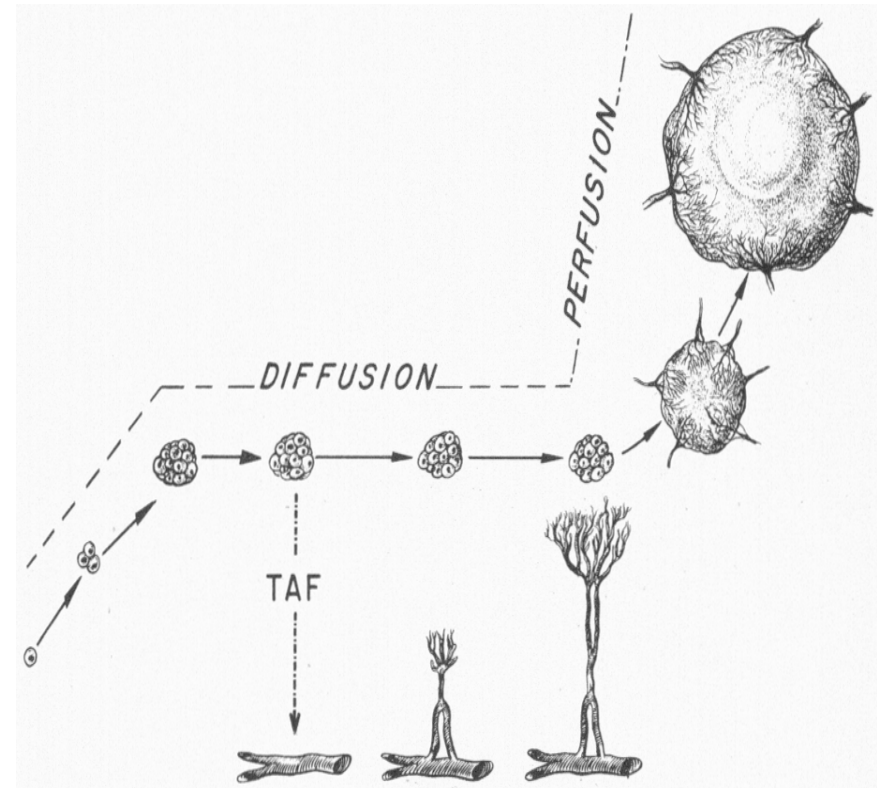


LOUIS M. SHERWOOD, M.D., *Editor*

EDITH E. PARRIS, *Assistant Editor*

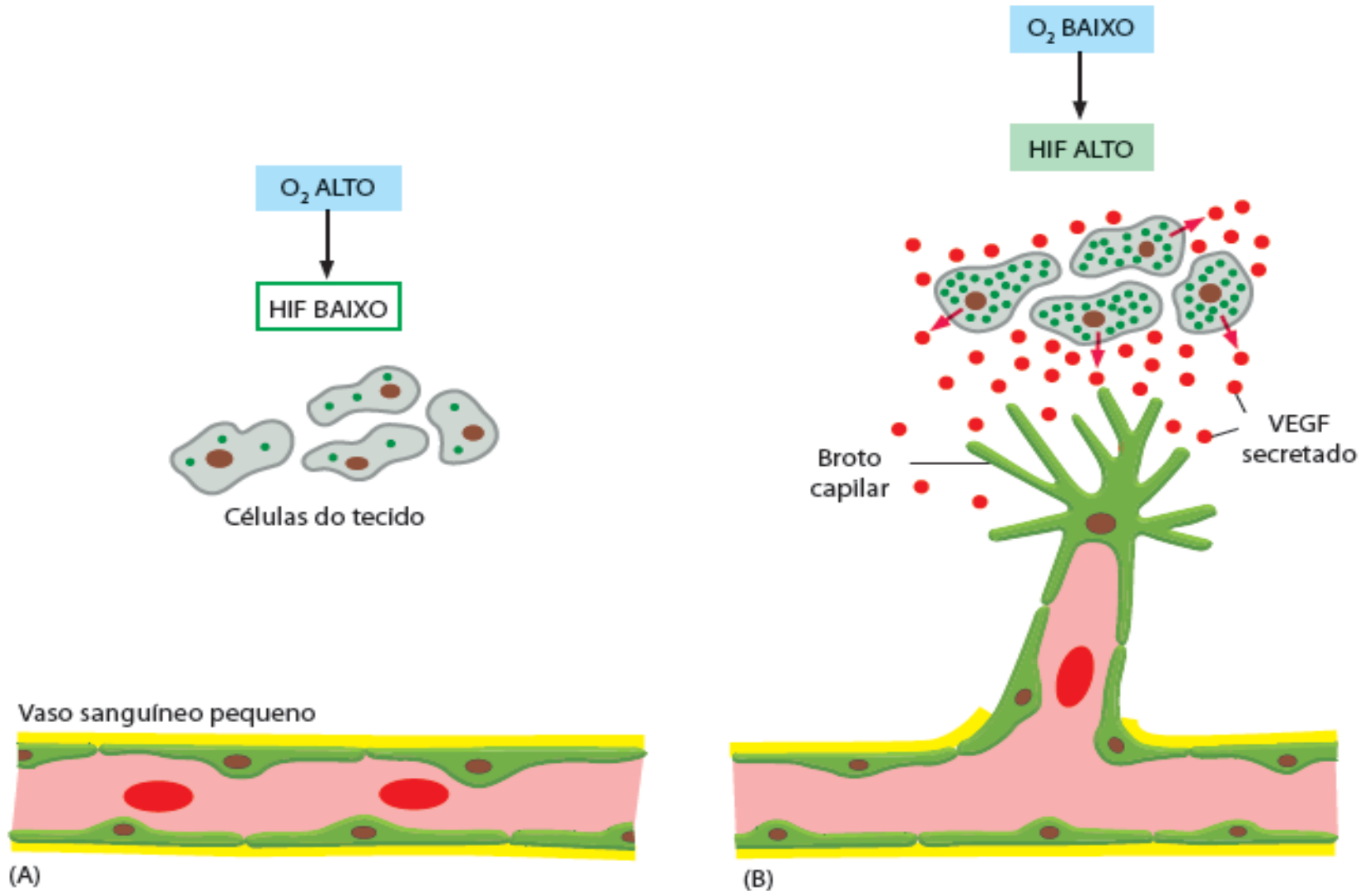
## **TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS**

JUDAH FOLKMAN, M.D.



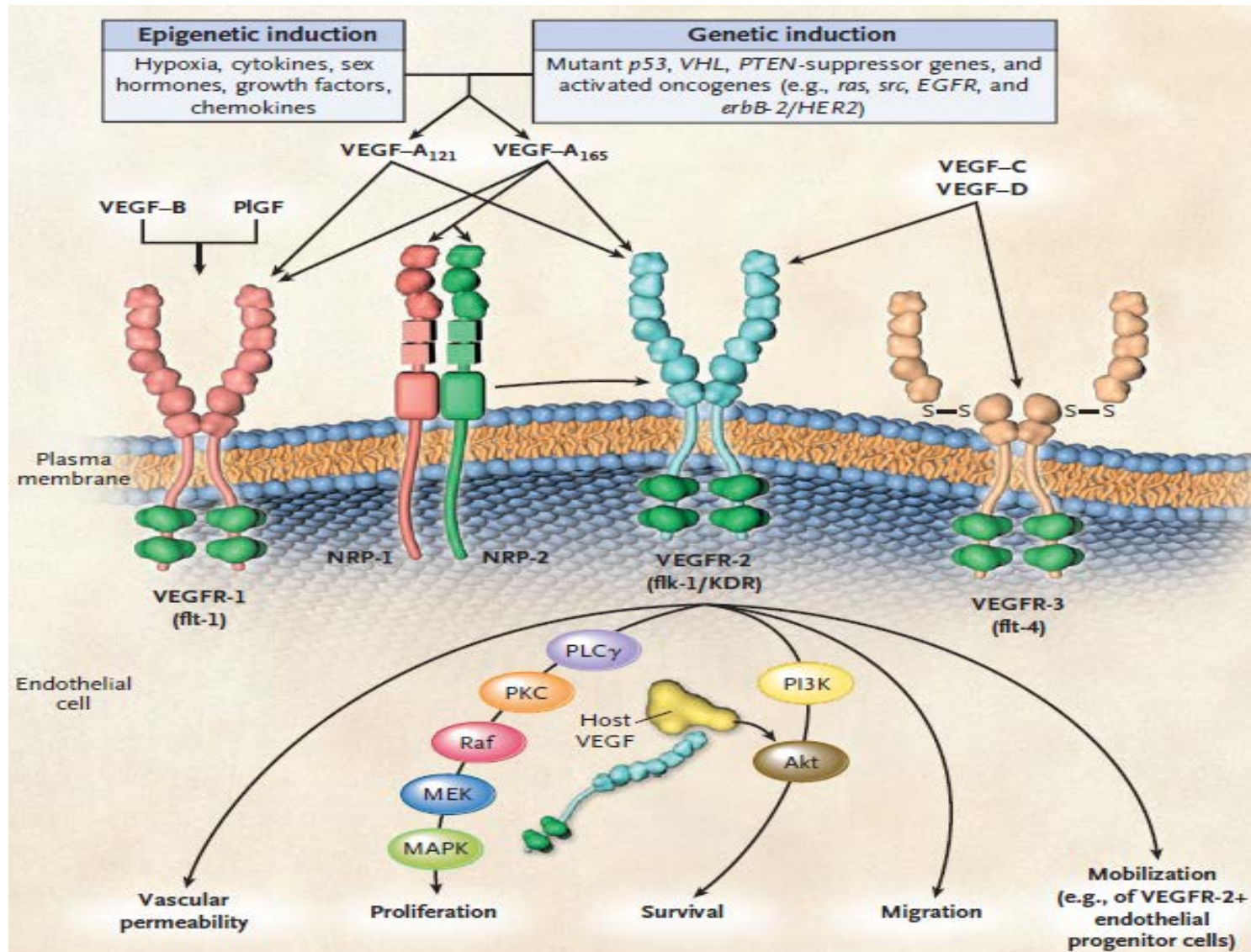


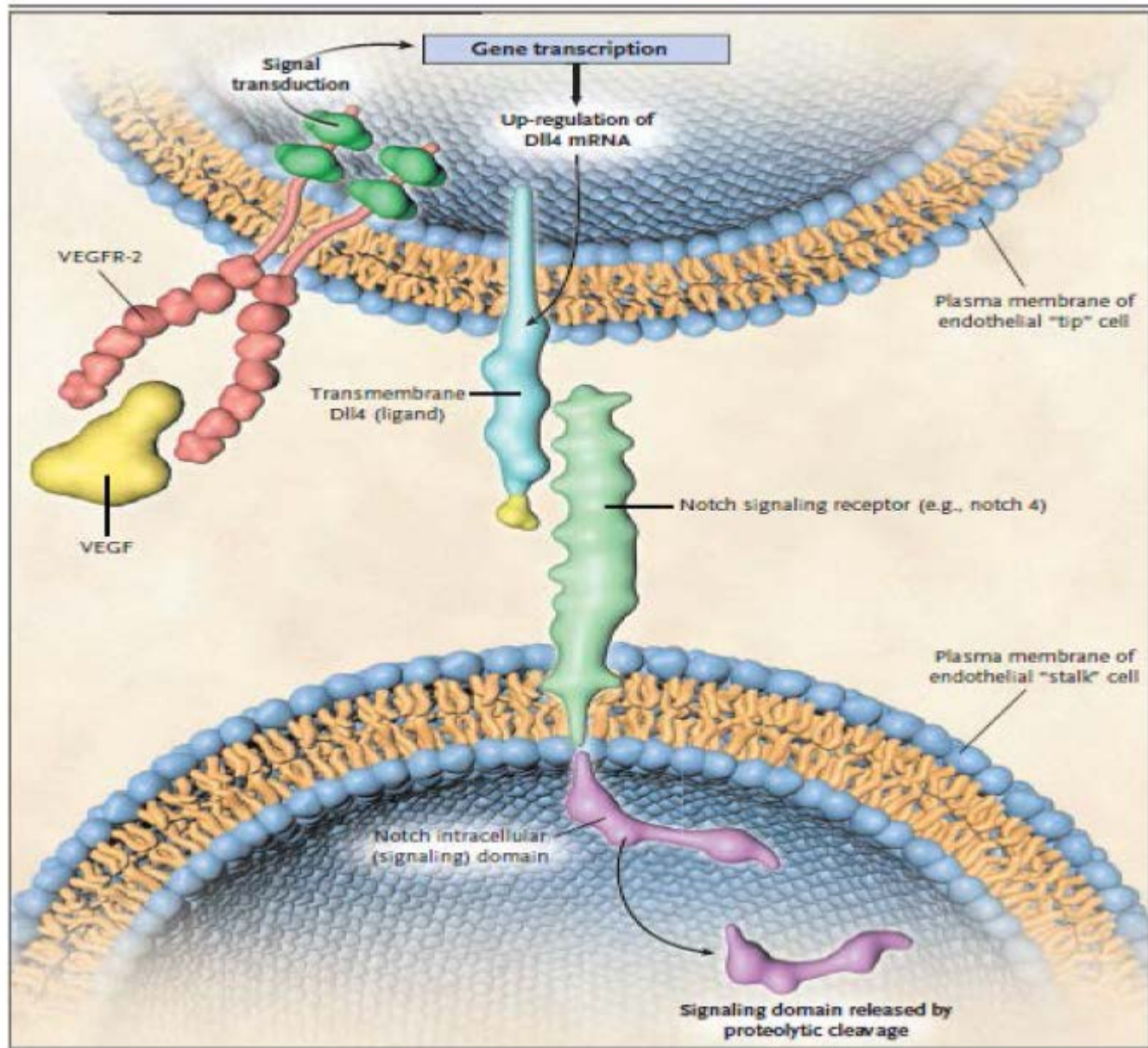
# Introdução



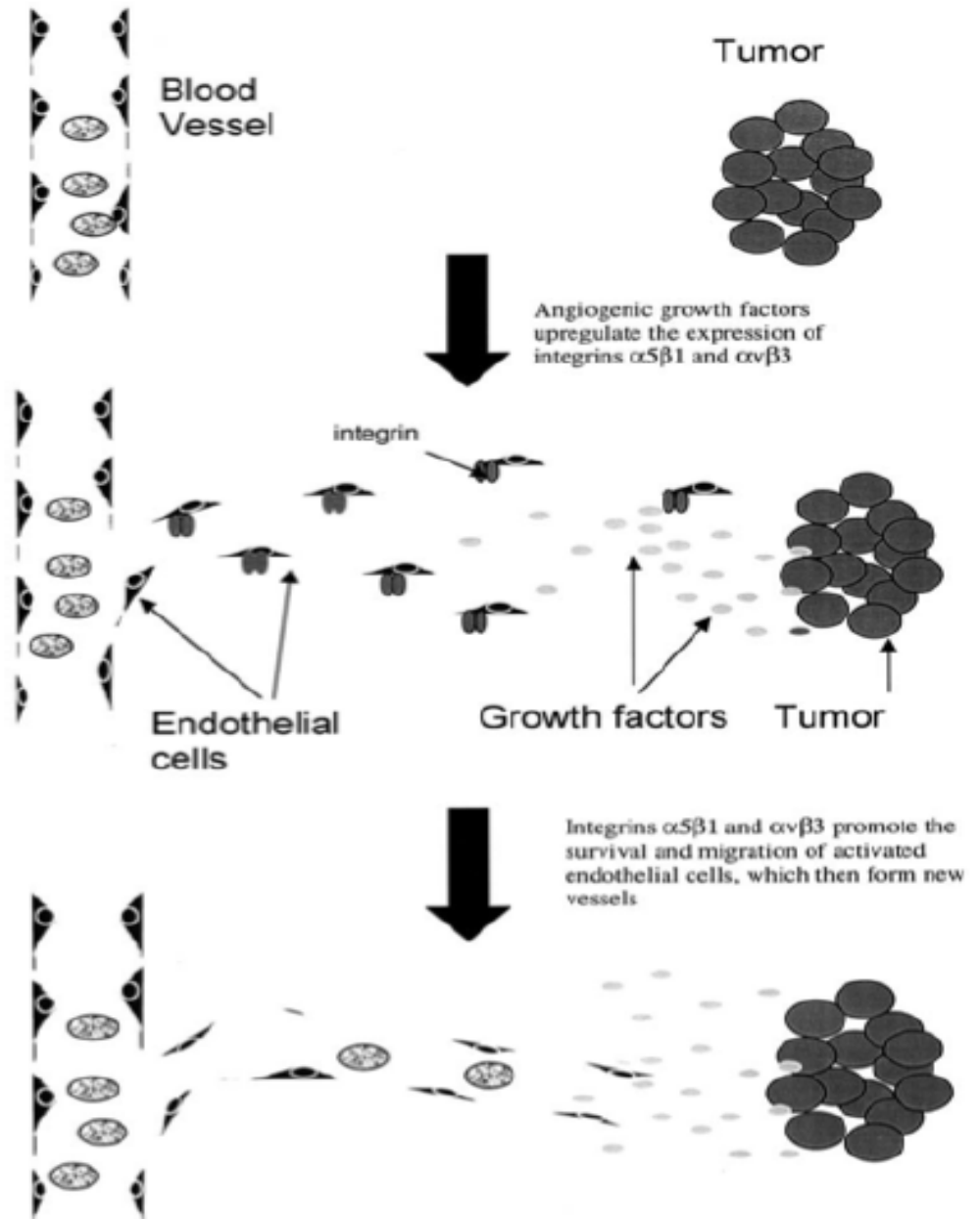
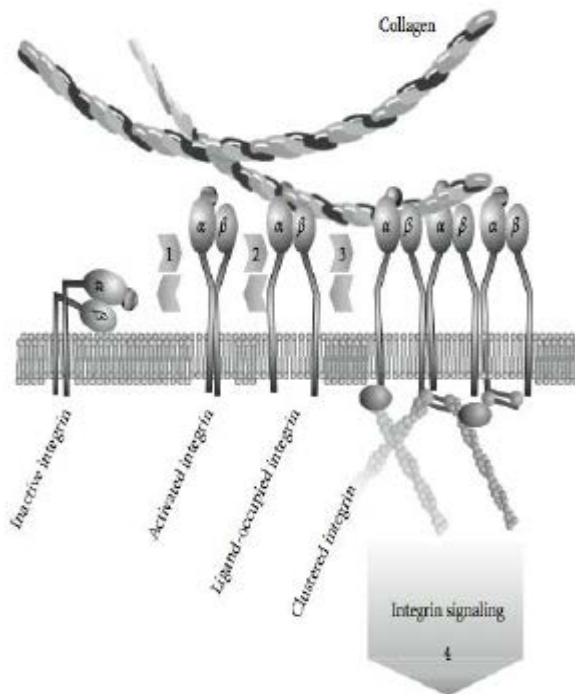
# Introdução

## Visão molecular da angiogênese



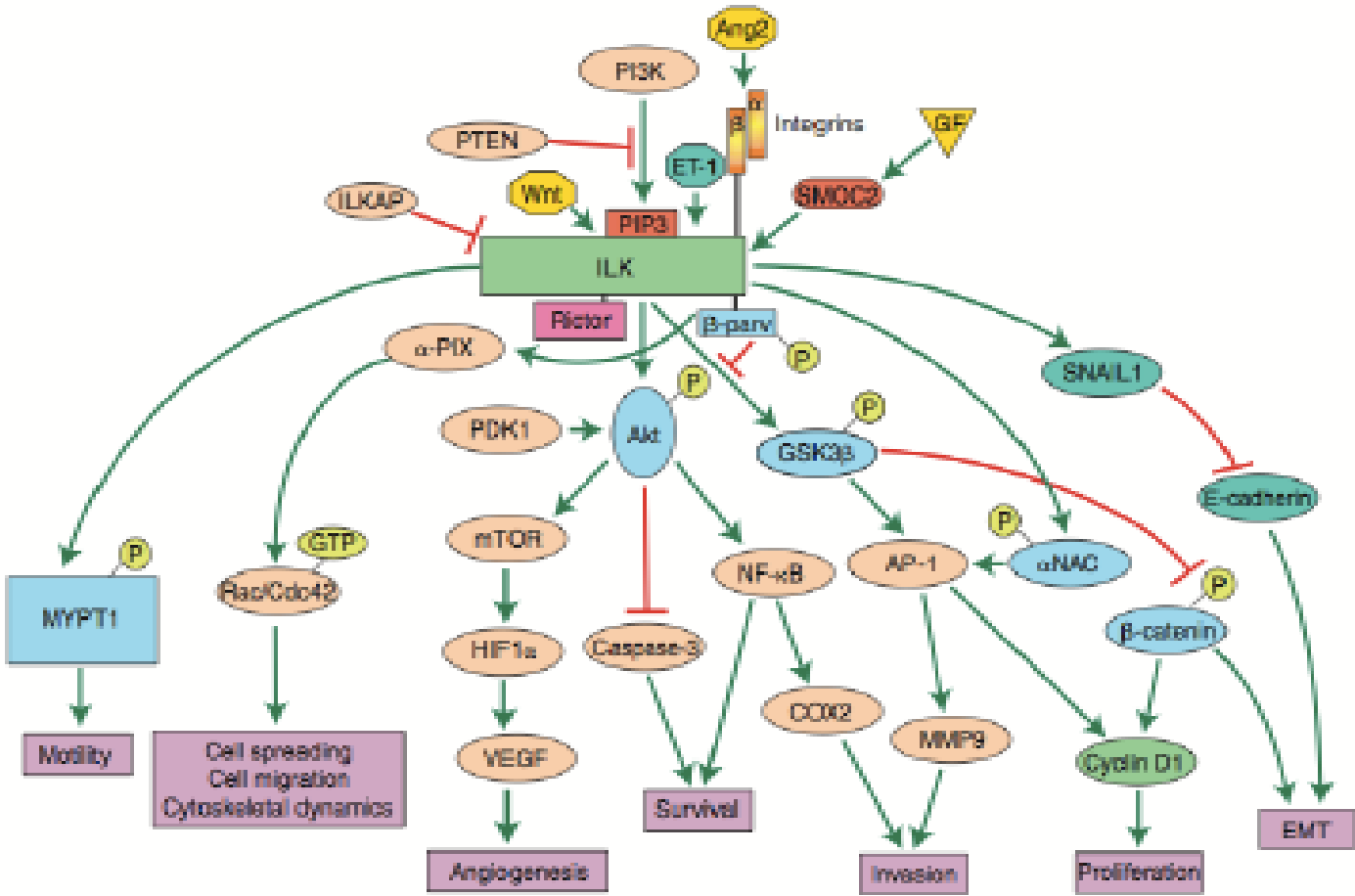


# Integrinas



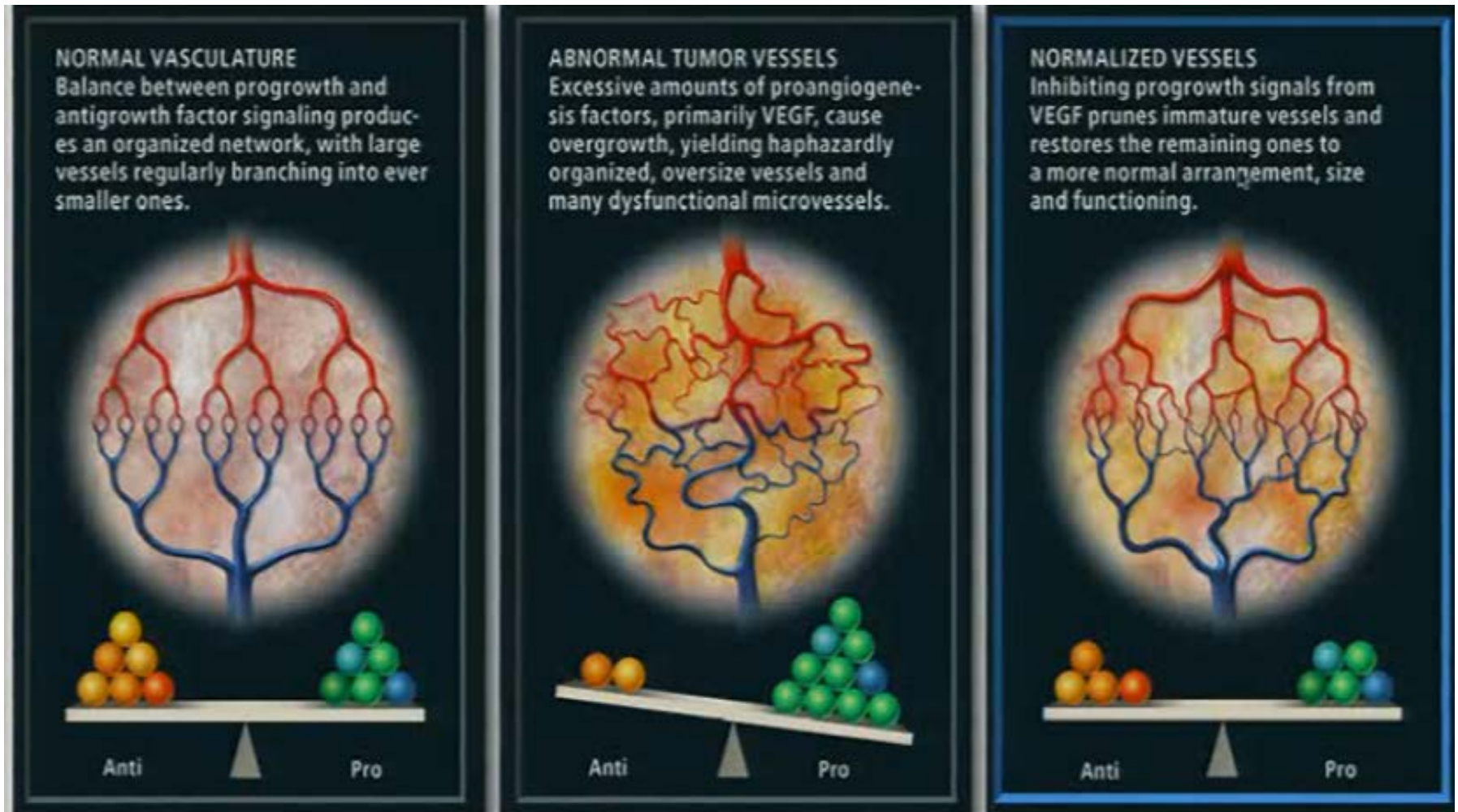


# ILK



# Introdução

## Racional para ação dos anti-angiogênicos



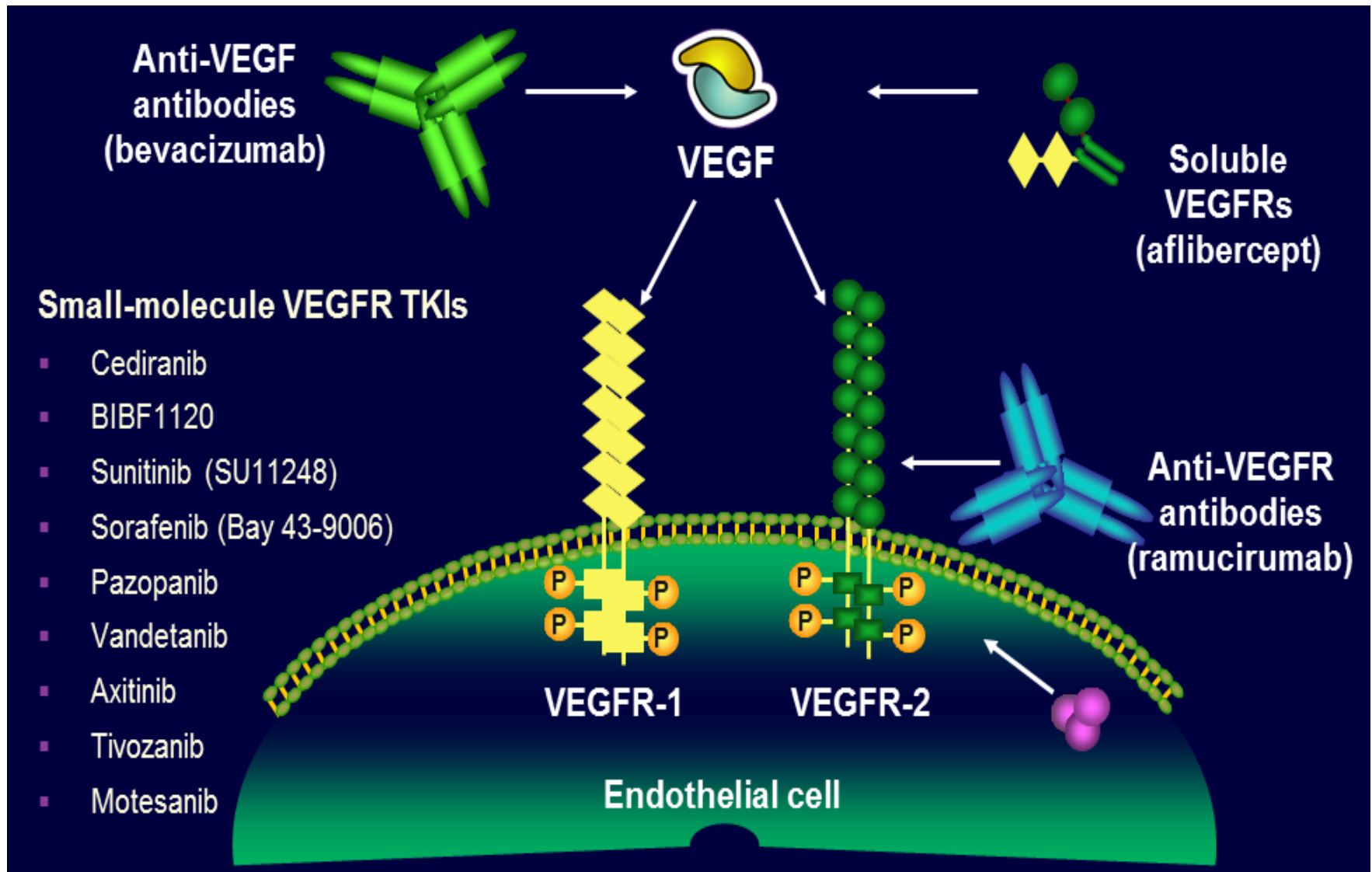
# Bevacizumabe

Anticorpo anti-VEGF recombinante

Liga-se e neutraliza o VEGF



# Mecanismo de ação





**Primeira linha de quimioterapia ±  
bevacizumabe**

# E2100

*The NEW ENGLAND JOURNAL of MEDICINE*

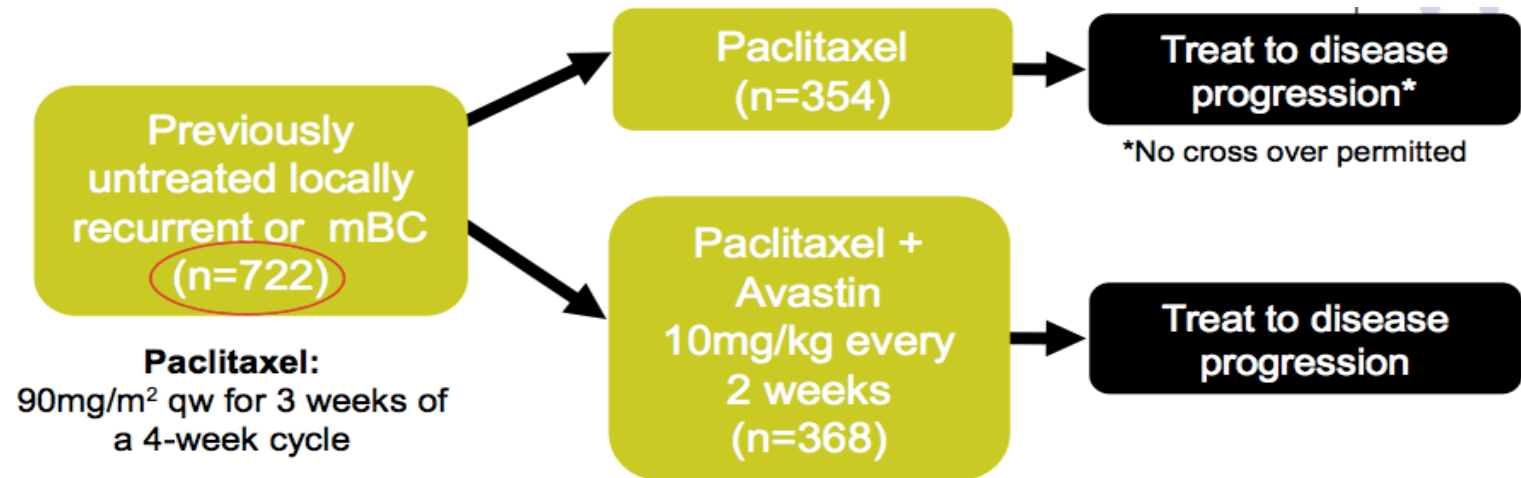
ORIGINAL ARTICLE

## Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D.,  
Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D.,  
David Cella, Ph.D., and Nancy E. Davidson, M.D.

Miller, et al. NEJM 2007; 357: 26, 2666-76

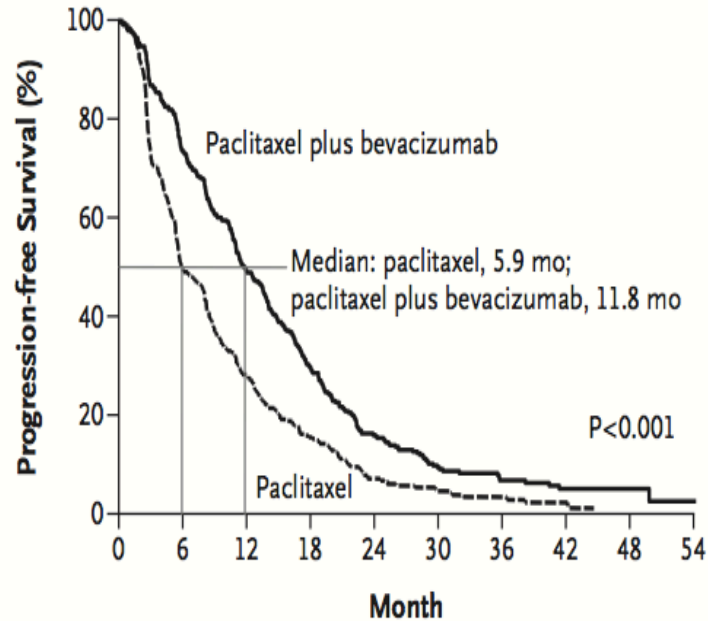
# E2100



- Primary endpoint: progression-free survival
- Other endpoints: overall response rate, overall survival, quality of life

# E2100

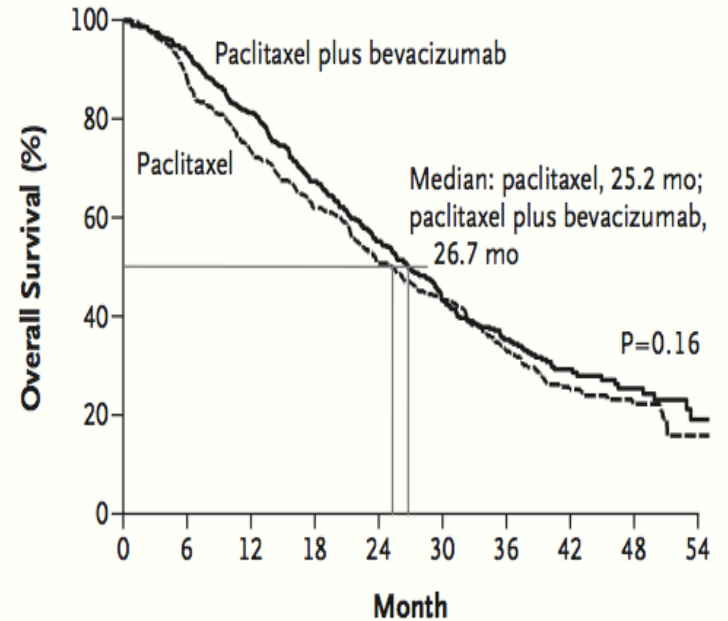
**A**



**No. at Risk**

Paclitaxel plus bevacizumab	347	323	167	100	53	25	14	7	2	1
Paclitaxel	326	159	89	47	20	12	6	2	0	0

**B**

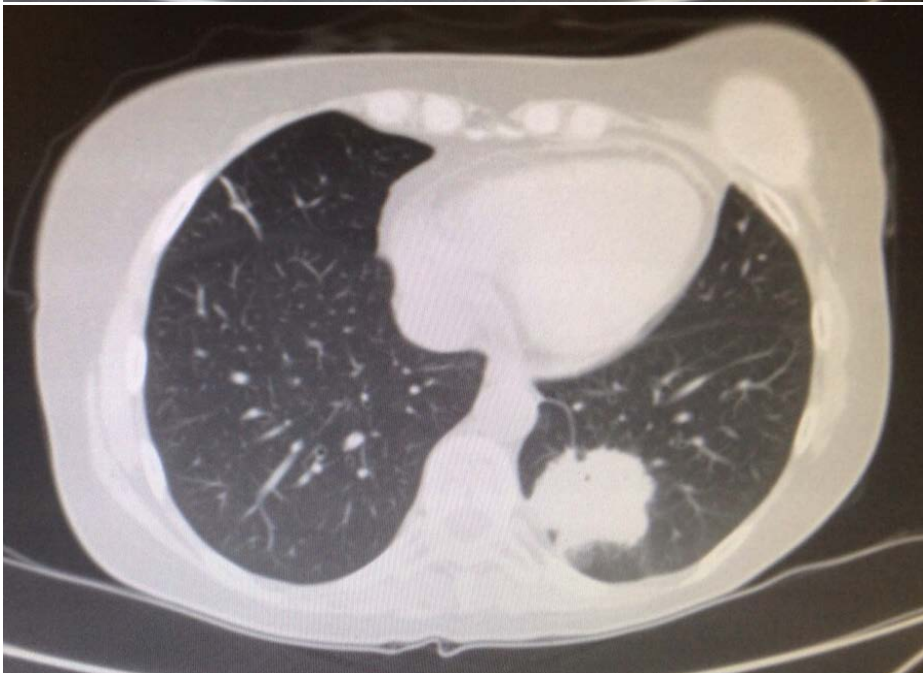
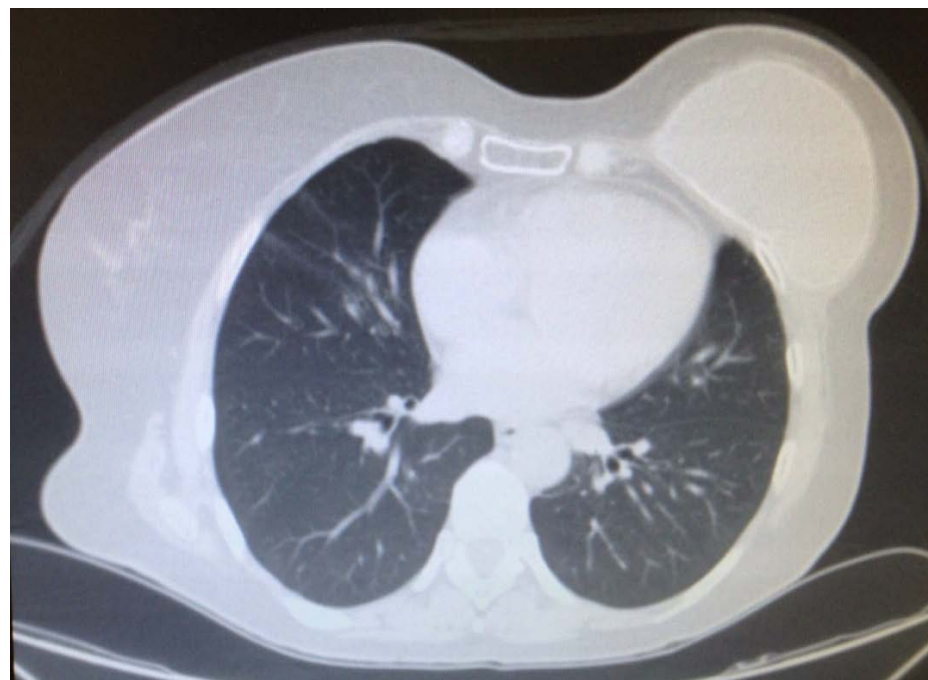
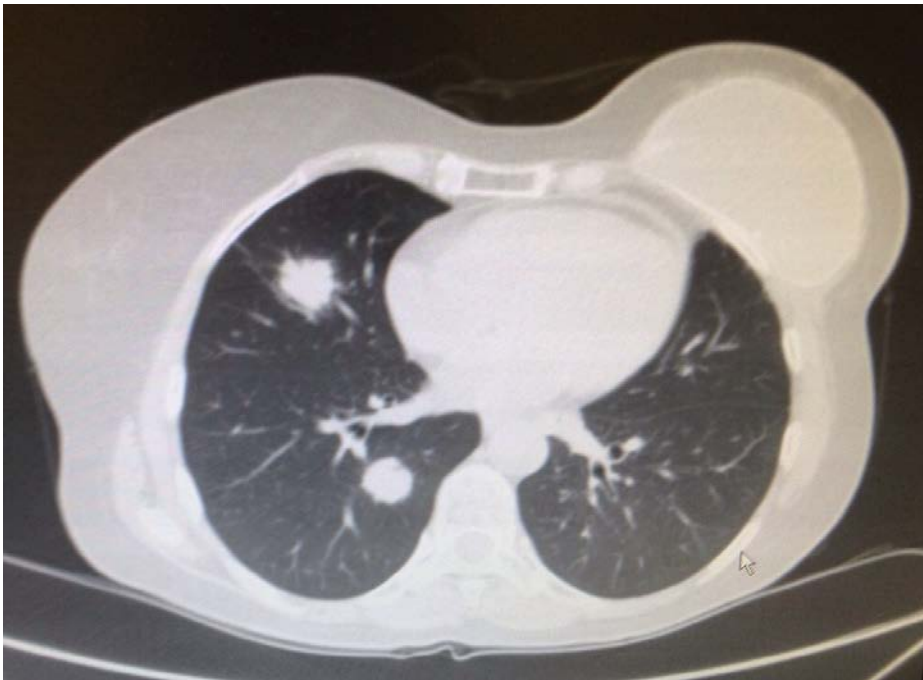


**No. at Risk**

Paclitaxel plus bevacizumab	347	323	280	232	190	147	88	46	24	7
Paclitaxel	326	284	236	199	162	138	88	47	23	5

Pré C1 Taxol + bevacizumabe

Pós C6 Taxol + bevacizumabe



# Introdução

- Contudo, ainda não foi identificado um biomarcador que demonstre qual paciente irá se beneficiar do tratamento.

# Objetivo do estudo

- Avaliar a expressão de proteínas relacionadas com angiogênese (VEGFR2, NOTCH1, Integrina  $\alpha 1\beta 2$  e ILK) com desfechos de sobrevida em pacientes com câncer de mama metastático que foram tratadas com bevacizumabe.

# Metodologia

- Estudo retrospectivo
- População alvo: pacientes com câncer de mama HER2 negativo metastático, que receberam 1º linha de quimioterapia, associado ou não ao bevacizumabe.



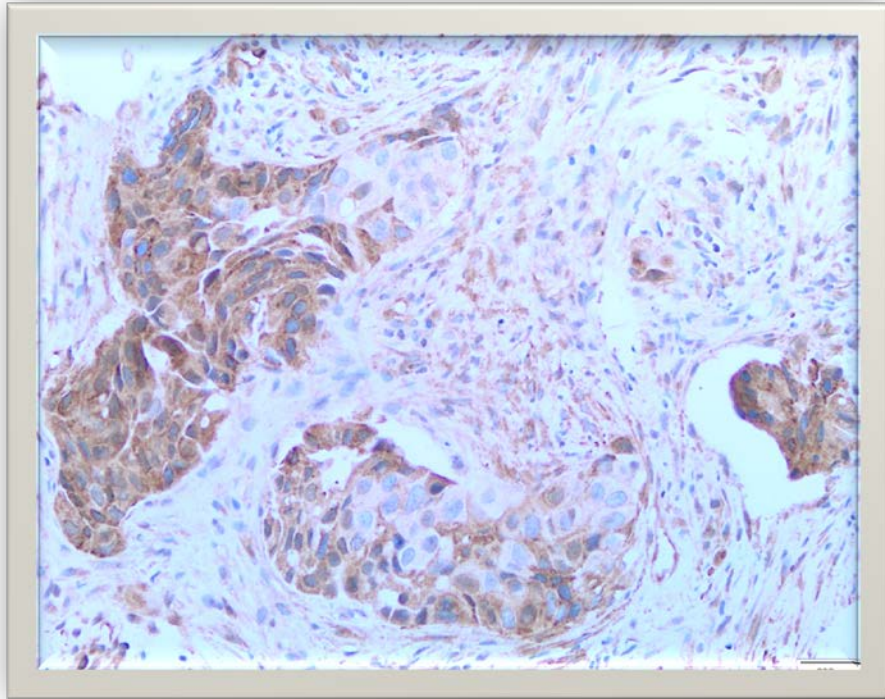
# Metodologia

- As amostras tumorais foram organizadas num *tissue microarray (TMAs)*.
- A expressão de VEGFR2, NOTCH1, Integrina  $\alpha 1\beta 2$  e ILK foram avaliadas por imunohistoquímica (IHQ).
- Anticorpo VEGFR2 utilizado: Therm Scientific, Clone B.309.4, USA. Diluição 1:50.
- Os casos foram avaliados por patologista de acordo com a área e intensidade da expressão da proteína. O produto entre a intensidade e a área gerou a pontuação final.

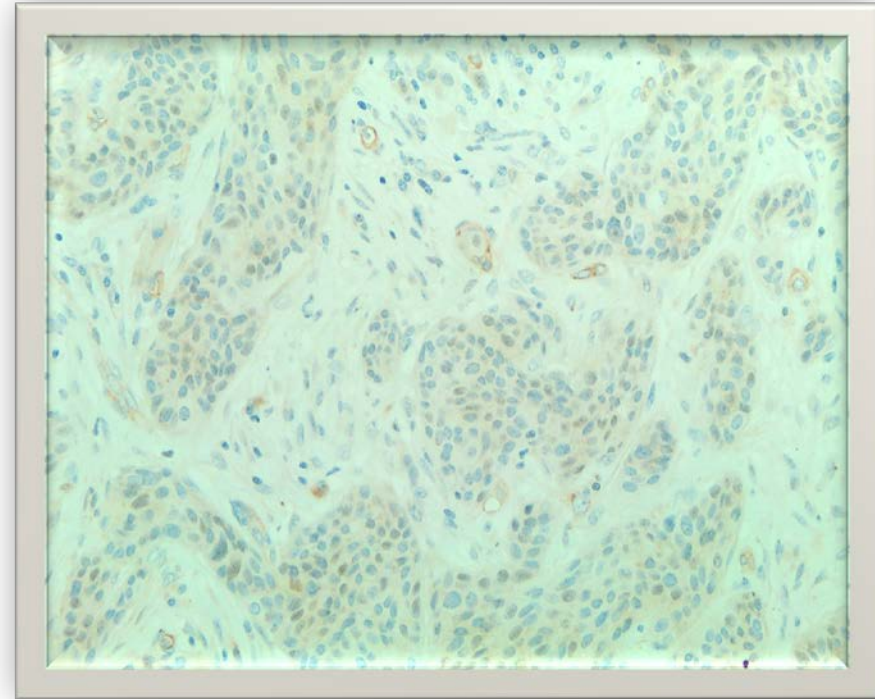
# Classificação de acordo com a expressão de VEGFR2

Expressão de VEGFR2: escore final	
0: Negativo	Baixa expressão
1-3: Fraco	
4-8: Moderado	Alta expressão
9-12: Forte	

# Corte histológico de câncer de mama, corado com VEGFR2 por IHQ



A: VEGFR2 com alta expressão citoplasmática



B: VEGFR2 com baixa expressão citoplasmática

# Estatística

- A associação entre a expressão das proteínas relacionadas com angiogênese e a sobrevida foi avaliada em análise univariada e multivariada pelo modelo de Cox.
- As curvas de sobrevida foram calculadas pelo método de Kaplan-Meier e comparadas pelo teste de log-rank.

# Resultados

- 71 pacientes, entre 2007 e 2014.
- 2 coortes:
  - - Coorte 1 (C1) → tratamento com paclitaxel
  - - Coorte 2 (C2) → tratamento com paclitaxel e bevacizumabe.
- C1: follow-up mediano: 32.1m.
  - SLPm: 8m
  - SGm: 33,5m.
- C2: follow-up mediano: 38m.
  - SLPm: 10,6m
  - SG: 47m.

# Dados demográficos e clínicos

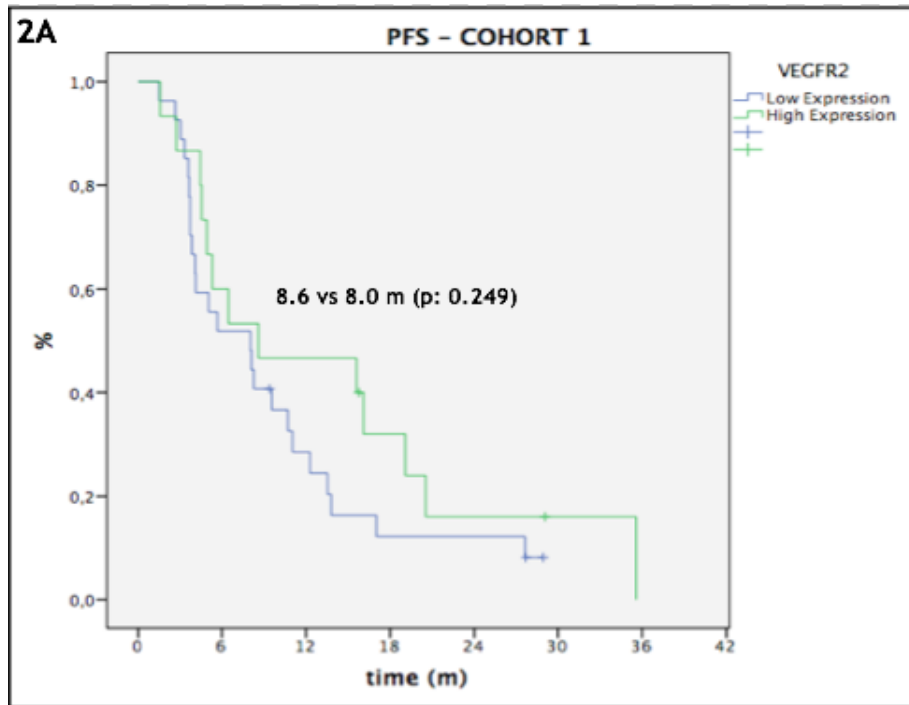
	Coorte 1 (N=42)	Coorte 2 (N=29)
Idade mediana	63a (37-88)	57a (32-73)
Luminal / Triplo negativo	39 (93%) / 3 (7%)	23 (79%) / 6 (21%)
Metástase visceral	30 (71%)	23 (79%)
RE positivo	39 (93%)	22 (76%)
RP positivo	35 (83%)	16 (55%)

# Resultados

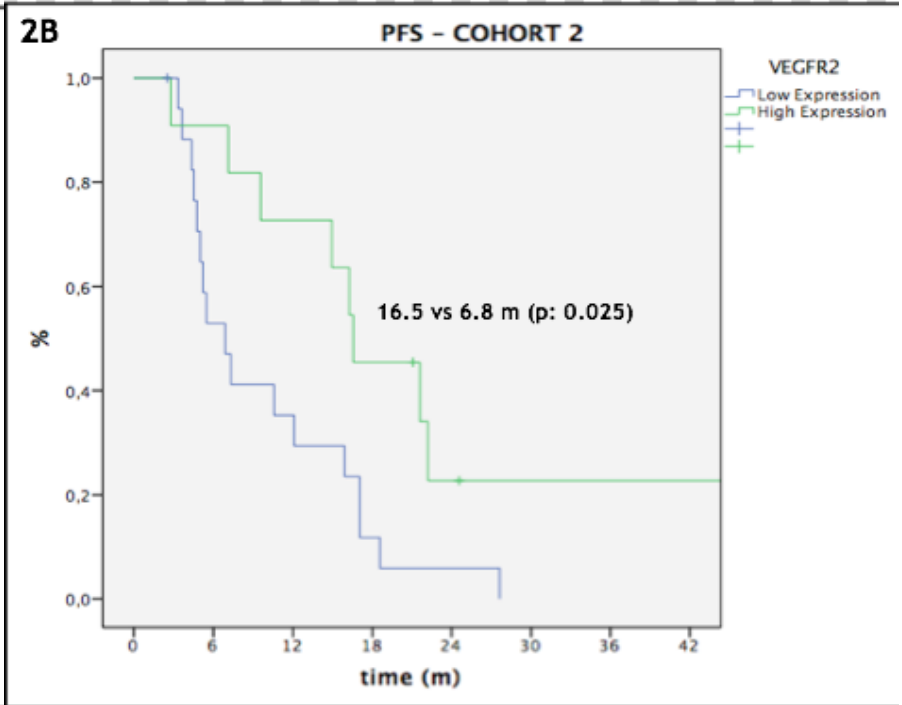
- 26 pacientes (37%) tiveram alta expressão de VEGFR2 citoplasmático.
- Expressão alta de VEGFR2 citoplasmático **foi associado com melhor SLPm** entre os pacientes tratados **com bevacizumabe (C2) (16.5m vs 6.8m, p: 0.025)**.
- Expressão de NOTCH1, Integrina  $\alpha 1\beta 2$  e ILK **não** foram associados com diferença na SLPm.

# SLP conforme a expressão de VEGFR2

## Paclitaxel



## Paclitaxel + Bevacizumabe





# Análise multivariada para SLP

VEGFR2 citoplasma	HR	IC95%	p
Baixa expressão	1	0,14-0,85	0,02
Alta expressão	0,35		

# Conclusão

- Em pacientes com câncer de mama metastático tratadas com bevacizumabe associado à quimioterapia, a alta expressão de VEGFR2 citoplasmático foi associada com maior SLPm nos pacientes tratados com bevacizumabe.
- Desse modo, VEGFR2 citoplasmático pode ter um papel preditivo de eficácia da terapia antiangiogênica.
- Estudos randomizados, prospectivos, são necessários para comprovar esse achado.

# Obrigado

tadeufpaivajr@hotmail.com



- Slides back up

# TURANDOT

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## Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial



*Istvan Lang, Thomas Brodowicz, Larisa Ryvo, Zsuzsanna Kahan, Richard Greil, Semir Beslija, Salomon M Stemmer, Bella Kaufman, Zanete Zvirbule, Günther G Steger, Bohuslav Melichar, Tadeusz Pienkowski, Daniela Sirbu, Diethelm Messinger, Christoph Zielinski, on behalf of the Central European Cooperative Oncology Group\**

### Summary

**Background** Randomised phase 3 trials in metastatic breast cancer have shown that combining bevacizumab with [Lancet Oncol 2013; 14: 125-33](#)

# TURANDOT

- Estudo fase III, aberto
- Não-inferioridade para end point primário (SG)
- Superioridade para end points secundários
- Pacientes em 1º linha
- QT adj > 6 meses (> 12 meses se taxane)

- Braço 1 → Paclitaxel + Bevacizumabe (=E2100)

versus

- Braço 2 → Capecitabina 1000mg/m<sup>2</sup> 12/12h D1 a D14 + Bevacizumab 15mg/Kg a cada 21 dias

Análise interina

N= 564

Follow up= 18,6 meses

Definição não-inferioridade:  $HR \leq 1.33$  (limite superior do IC  $\leq 1.33$ )

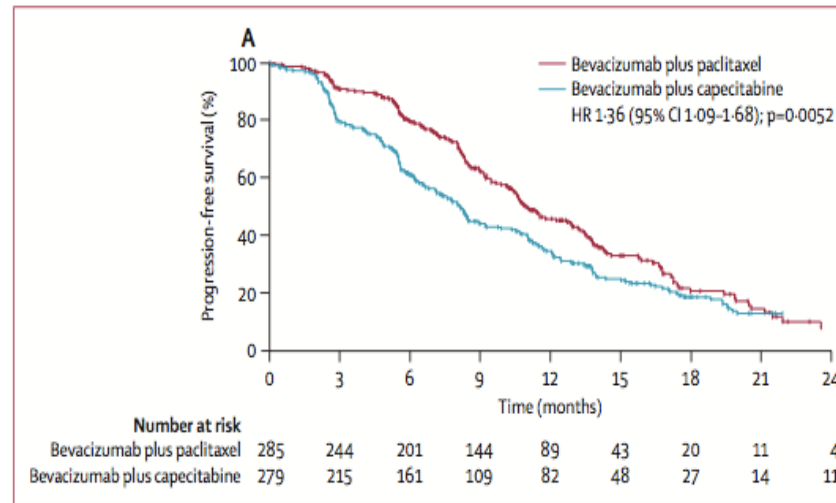


Figure 4: Progression-free survival (intention-to-treat population)

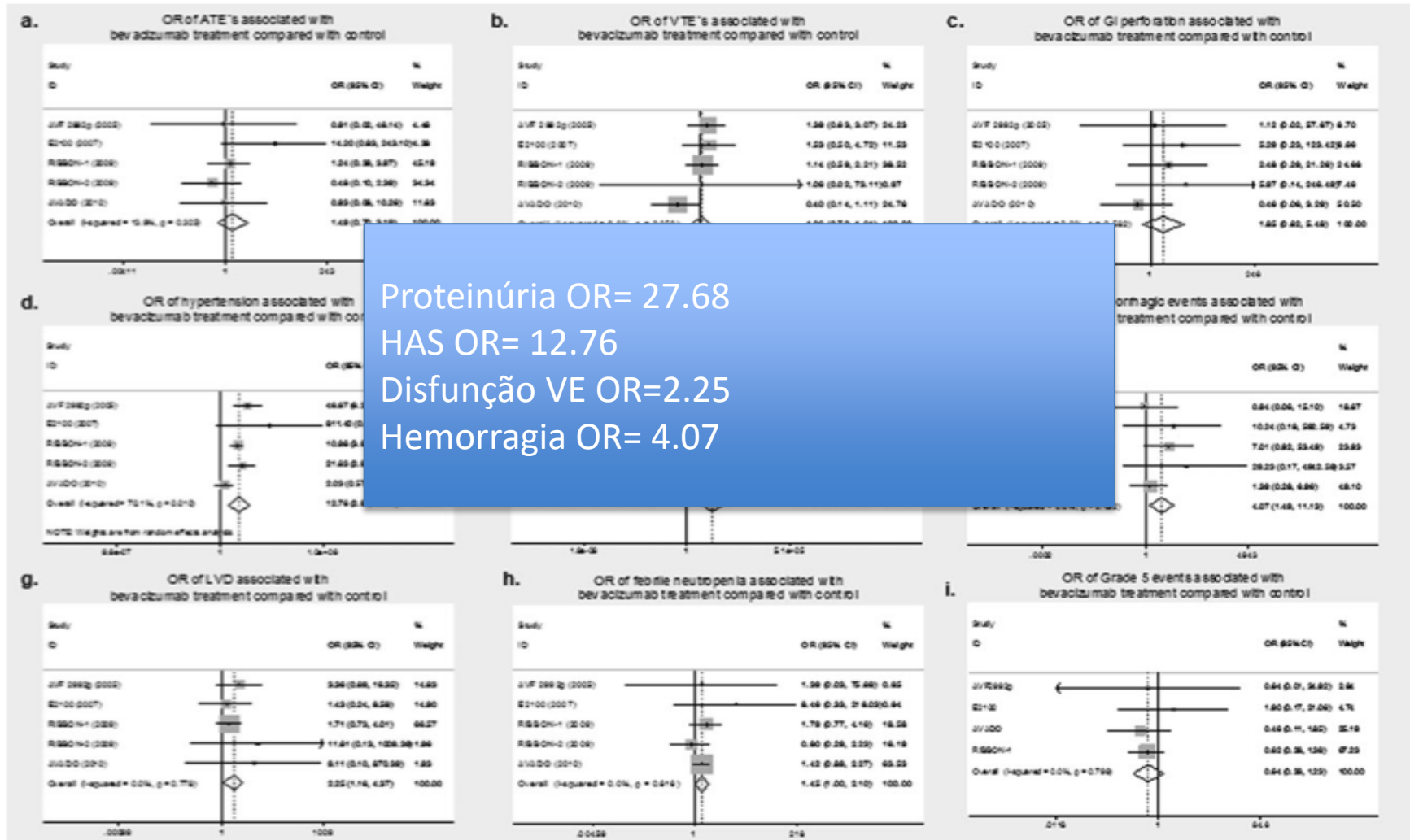
	Paclitaxel + Bv	Capecitabina + Bv	p	HR
TR	44%	27%	<0.0001	
SLP	11m	8,1m	0.005	
SG			0.59	1.04 (-α a 1.69)



## **Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis**

J. Cortes<sup>1\*</sup>, V. Calvo<sup>2</sup>, N. Ramírez-Merino<sup>3</sup>, J. O'Shaughnessy<sup>4</sup>, A. Brufsky<sup>5</sup>, N. Robert<sup>6</sup>, M. Vidal<sup>1</sup>, E. Muñoz<sup>1</sup>, J. Perez<sup>1</sup>, S. Dawood<sup>7</sup>, C. Saura<sup>1</sup>, S. Di Cosimo<sup>1</sup>, A. González-Martín<sup>8</sup>, M. Bellet<sup>1</sup>, O. E. Silva<sup>9</sup>, D. Miles<sup>10</sup>, A. Llombart<sup>11</sup> & J. Baselga<sup>12</sup>

# Segurança



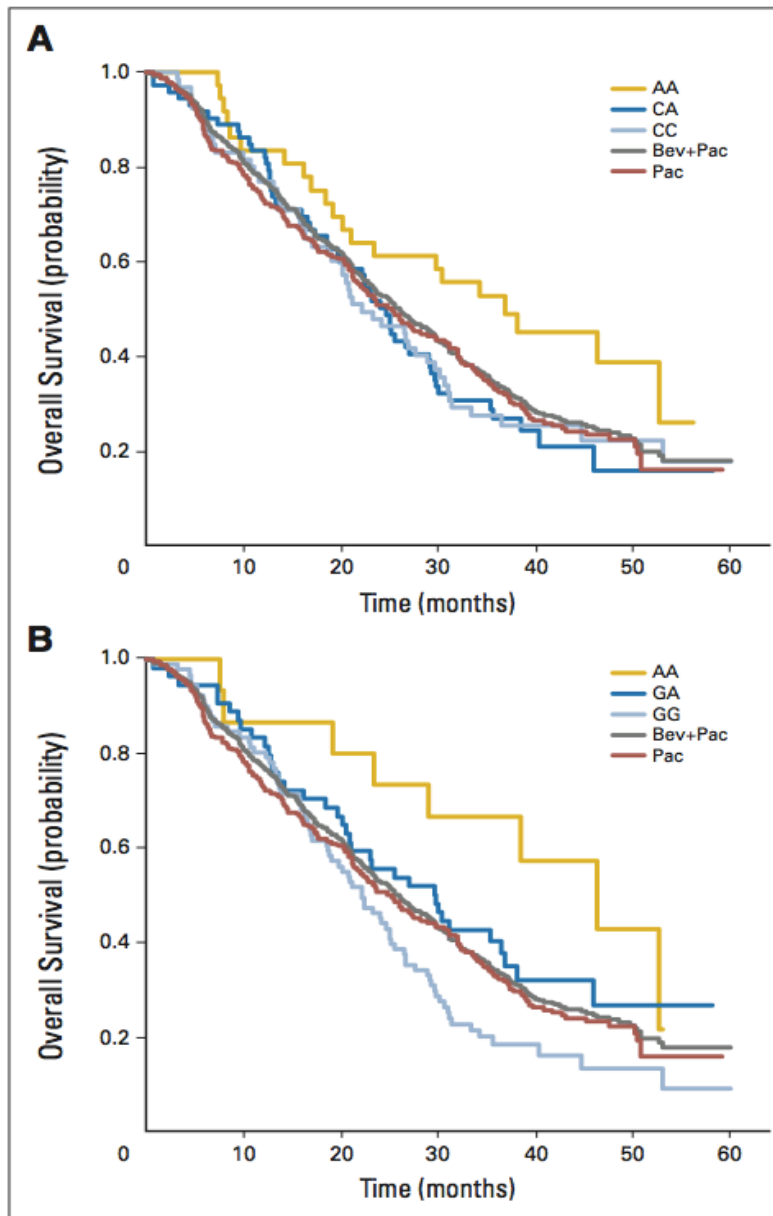
# Biomarcadores

# Association of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-2 Genetic Polymorphisms With Outcome in a Trial of Paclitaxel Compared With Paclitaxel Plus Bevacizumab in Advanced Breast Cancer: ECOG 2100

Bryan P. Schneider, Molin Wang, Milan Radovich, George W. Sledge, Sunil Badve, Ann Thor, David A. Flockhart, Bradley Hancock, Nancy Davidson, Julie Gralow, Maura Dickler, Edith A. Perez, Melody Cobleigh, Tamara Shenkier, Susan Edgerton, and Kathy D. Miller

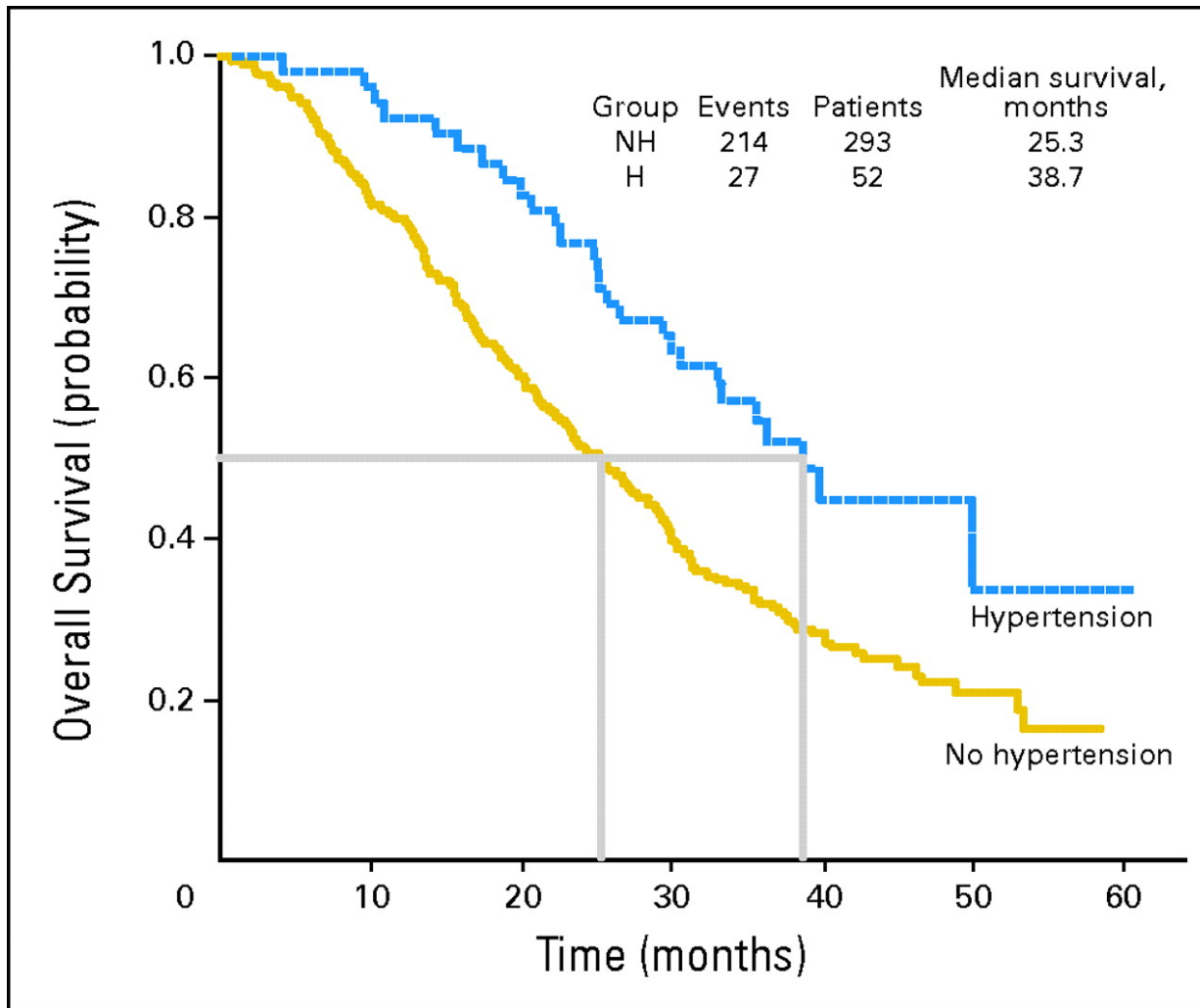
**Table 3.** Comparison of Combined VEGF Genotypes With Overall Survival in Experimental Arm

VEGF -2578/-1154	Median Overall Survival (months)	% of Patients	P (comparison with other genotypes combined)
AA/AA	49.7	7.6	.041
AA/GA	30.2	11.4	.44
CA/GA	27.1	20.9	.40
CA/GG	22.5	21.5	.038
CC/GG	21.7	32.9	.30
Others	—	5.7	—



**Fig 2.** Kaplan-Meier curve for overall survival (OS) in the experimental arm (by vascular endothelial growth factor genotype) compared with the control and combination arms (not subdivided by genotype). Bev, bevacizumab; Pac, paclitaxel.

**Superior median overall survival was seen for patients in E2100 who experienced grade 3 or 4 hypertension (H) or no hypertension (NH).**



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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

## Markers of Response for the Antiangiogenic Agent Bevacizumab

*Diether Lambrechts, Heinz-Josef Lenz, Sanne de Haas, Peter Carmeliet, and Stefan J. Scherer*

**Table 1.** Circulating Angiogenic Factors As Predictive Biomarkers for Bevacizumab Treatment Outcome

Protein	Cancer Type	Reference	Study Acronym	Sample Size	Phase	Study Details	Correlation With Outcome
VEGF-A	Colorectal	Goede et al <sup>29</sup>		34		All patients received bevacizumab combined with either FOLFIRI, FOLFOX, XELIRI, or XELOX	No (OR/PFS/OS)
	Lung	Leighl et al <sup>34</sup>	AVAIL	358	III	Three arms, receiving either 0, 7.5, or 15 mg/kg bevacizumab, each combined with cisplatin-gemcitabine	No (PFS), no (OS)
	Lung	Mok et al <sup>35</sup>	BO21015	287	II	All patients received bevacizumab + carboplatin-paclitaxel or cisplatin-gemcitabine	Yes (PFS), trend (OR)
	Lung	Dowlati et al <sup>30</sup>	ECOG E4599	160	II/III	Two arms, receiving either bevacizumab or placebo, each combined with carboplatin-paclitaxel	Yes (OR), no (OS)
	Colorectal/lung/renal cell	Bernaards et al <sup>31</sup>		1,816	Different phase III clinical studies	See Jayson et al <sup>38</sup> for details on individual studies	No (PFS/OS)
Short VEGF-A isoforms	Colorectal	Jayson et al <sup>38</sup>	AVF2107g	398	III	Two arms, receiving either bevacizumab or placebo, each combined with irinotecan + fluorouracil + leucovorin	No (PFS/OS)
	Lung	Jayson et al <sup>38</sup>	AVAIL	859	III	Three arms, receiving 0, 7.5, or 15 mg/kg bevacizumab, each combined with cisplatin-gemcitabine	Trend (PFS), no (OS)
	Breast	Miles et al <sup>37</sup>	AVADO	396	III	Three arms, receiving 0, 7.5, or 15 mg/kg bevacizumab, each combined with docetaxel	Yes (PFS/OS)
	Pancreatic	Van Cutsem et al <sup>36</sup>	AVITA	225	III	Two arms, receiving either bevacizumab or placebo, each combined with gemcitabine-erlotinib	Trend (PFS), yes (OS)
	Gastric	Van Cutsem et al <sup>39</sup>	AVAGAST	712	III	Two arms, receiving either bevacizumab or placebo, each combined with capecitabine-cisplatin	Trend (PFS), yes (OS)
	Renal cell	Jayson et al <sup>38</sup>	AVOREN	404	III	Two arms, receiving either bevacizumab or placebo, each combined with IFN-2a	No (PFS/OS)
sVEGFR1	Rectal	Willett et al <sup>32</sup>		32	I/II	Single arm, receiving four cycles of therapy consisting of bevacizumab for each cycle; fluorouracil in cycles 2 to 4; external-beam irradiation and surgery after therapy	Yes (tumor stage)
	Breast	Tolaney et al <sup>33</sup>		104		Preoperative trial with a run-in of single-agent bevacizumab followed by ddACT chemotherapy	Yes (pathologic response)
IL-8	Hepatocellular	Boige et al <sup>40</sup>		43	II	All patients received bevacizumab	Yes (PFS/OS)
	Colorectal	Kopetz et al <sup>42</sup>		43	II	All patients received bevacizumab + FOLFIRI	Yes (PFS)
ANG2	Hepatocellular	Kaseb et al <sup>41</sup>		40	II	All patients received bevacizumab + erlotinib	No (PFS), yes (OS)
	Colorectal	Goede et al <sup>29</sup>		34		All patients received bevacizumab combined with either FOLFIRI, FOLFOX, XELIRI, or XELOX	Yes (OR/PFS/OS)



**Table 2.** Changes in Expression of Circulating Angiogenic Factors During Bevacizumab Treatment

Protein	Cancer Type	Reference	Study Acronym	Sample Size	Phase	Study Details	Change During Bevacizumab Treatment
VEGF-A	Colorectal	Willett et al <sup>32</sup>	NCI#5642	32	II	All patients received bevacizumab + fluorouracil	Increased at different time points after start of bevacizumab treatment
	Breast	Baar et al <sup>46</sup>		49	II	Two arms, docetaxel ± bevacizumab	Increased at weeks 17 to 30 after start of bevacizumab treatment; no increase in chemotherapy-only arm
	Hepatocellular	Boige et al <sup>40</sup>		43	II	All patients received bevacizumab as a single agent	Decreased at day 3 after start of bevacizumab treatment
	Melanoma	Fuerstenberger et al <sup>49</sup>	SAKK 50/07	60	II	All patients received bevacizumab + temozolomide	Decreased at 2 weeks after start of bevacizumab treatment
	Ovarian	Smerdel et al <sup>50</sup>		38		All patients received bevacizumab	Decreased from cycle 2 to 4 of bevacizumab treatment
PIGF	Colorectal	Kopetz et al <sup>42</sup>	NCI #5642	43	II	All patients received bevacizumab + FOLFIRI	Increased gradually until progression (weeks 2 to 4 PD)
		Loupakis et al <sup>52</sup>		25	II	All patients received bevacizumab + FOLFOXIRI	Increased at weeks 8 to 24 after start of bevacizumab treatment, then normalized at PD
		Willett et al <sup>32</sup>		32	II	All patients received bevacizumab + fluorouracil	Increased at different time points after start of bevacizumab treatment
VEGF-C	Colorectal	Lieu et al <sup>51</sup>		42	II	All patients received bevacizumab + FOLFIRI	Increased prior to and at progression
VEGF-D	Colorectal	Lieu et al <sup>51</sup>		42	II	All patients received bevacizumab + FOLFIRI	Increased at progression
bFGF	Lung	Dowlati et al <sup>30</sup>	ECOG E4599	160	II/III	Two arms, receiving either bevacizumab or placebo, each combined with carboplatin-paclitaxel	Increased after cycle 2 (similar increase in placebo arm)
	Colorectal	Kopetz et al <sup>43</sup>		43	II	All patients received bevacizumab + FOLFIRI	Unchanged at weeks 2 to 4 after start of bevacizumab treatment, but increased prior to and at progression
PDGF-BB	Colorectal	Kopetz et al <sup>42</sup>		43	II	All patients received bevacizumab + FOLFIRI	Unchanged, but increased prior to and at progression
SDF1	Colorectal	Kopetz et al <sup>42</sup>		43	II	All patients received bevacizumab + FOLFIRI	Unchanged, but increased prior to progression

**Table 3.** In Situ Biomarkers in Tumor or Stroma Predictive of Bevacizumab Treatment Outcome

Marker	Cancer Type	Reference	Study Acronym	Sample Size	Phase	Study Details	Quantification Method	Association of Biomarker With Clinical Outcome
VEGFR1	Colorectal	Foerzler et al <sup>59</sup>	NO16966	247	III	2 × 2 factorial design: XELOX v FOLFOX, and bevacizumab v placebo	IHC on tumor	No (PFS/OS)
		Weickhardt et al <sup>57</sup>	AGITG MAX	268	III	Three arms, receiving either bevacizumab, mitomycin, or placebo, each combined with capecitabine	IHC on tumor	No (PFS), yes (OS); low VEGFR1 increases benefit from bevacizumab
	Gastric	Van Cutsem et al <sup>39</sup>	AVAGAST	763	III	Two arms, receiving either bevacizumab or placebo, each combined with capecitabine-cisplatin	IHC on tumor	Yes (PFS), no (OS)
NRP1	Colorectal	Foerzler et al <sup>59</sup>	NO16966	247	III	2 × 2 factorial design: XELOX v FOLFOX, and bevacizumab v placebo	IHC on tumor	Low NRP1 increases benefit from bevacizumab
	Gastric	Van Cutsem et al <sup>39</sup>	AVAGAST	763	III	Two arms, receiving either bevacizumab or placebo, each combined with capecitabine-cisplatin	IHC on tumor	Low NRP1 is negative prognostic and positive predictive for OS
	Breast	Jubb et al <sup>58</sup>	AVF2119g	223	III	Two arms, receiving either bevacizumab or placebo, each combined with capecitabine	IHC on tumor	Trend toward improved PFS in low NRP1-expressing patients

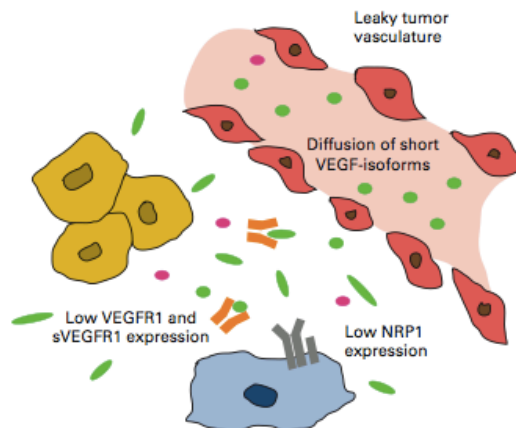
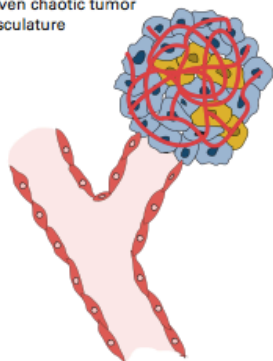
**Table 4.** Genetic Markers Evaluated As Predictive Biomarkers for Bevacizumab Treatment Outcome

Gene	Cancer Type	Reference	Study Acronym	Sample Size	Phase	Study Details	Genetic Variant	Association With Clinical Outcome
VEGFA	Colorectal	Loupakis et al <sup>74</sup>		218 (111 with bevacizumab)		All patients received FOLFIRI ± bevacizumab	–2578A/C (rs699947), –460C/T (rs833061), –634G/C (rs2010963), –936C/T (rs3025039)	–460C increases PFS/OS in bevacizumab patients
		Hansen et al <sup>83</sup>	Nordic ACT	218	III	Two arms receiving either FOLFOX/XELOX or FOLFIRI/XELIRI ± bevacizumab	Five SNPs (not further specified)	No (OR)
		Koutras et al <sup>72</sup>		209	III	All patients received bevacizumab + FOLFIRI or XELIRI	–634G/C (rs2010936), +936C/T (rs3025039), –1154G/A (rs1570360), –2578A/C (rs699947)	–2578A and –1154A increase OS but not PFS
		Gerger et al <sup>76</sup>		119		All patients received FOLFOX/XELOX + bevacizumab	–634G/C (rs2010936), +936C/T (rs3025039), –1154G/A (rs1570360), –460C/T (rs833061), –2578A/C (rs699947)	No (response/PFS/OS)
	Lung	Zhang et al <sup>81</sup>	ECOG 4599	133 (66 with bevacizumab)	II/III	Two arms, receiving either bevacizumab or placebo, each combined with carboplatin-paclitaxel	–634G/C	–634G/C correlates with PFS in bevacizumab patients
	Breast	Schneider et al <sup>70</sup>	ECOG 2100	363 (180 with bevacizumab)	III	Two arms, receiving paclitaxel ± bevacizumab	–634G/C (rs2010936), +936C/T (rs3025039), –1154G/A (rs1570360), –460C/T (rs833061), –2578A/C (rs699947)	–2578A and –1154A increase OS but not PFS in bevacizumab patients
		Miles et al <sup>71</sup>	AVADO	336 (231 with bevacizumab)	III	Three arms, receiving either 0, 7.5, or 15 mg/kg bevacizumab, each combined with docetaxel	–634G/C (rs2010936), +936C/T (rs3025039), –1154G/A (rs1570360), –460C/T (rs833061), –2578A/C (rs699947)	–2578C increases PFS in placebo arm; –1154A increases PFS in bevacizumab arm (trend)
	Various	Lambrechts et al <sup>73</sup>	NO16966, AVAIL, AVITA, AVOREN, AVADO	1,348 (669 with bevacizumab)		Various regimens (see Escudier et al, <sup>6</sup> Miles et al, <sup>12</sup> and Saltz et al <sup>27</sup> for details)	158 SNPs in VEGF pathway	rs699946-A allele correlates with improved PFS in bevacizumab patients
VEGFR1	Pancreatic	Lambrechts et al <sup>82</sup>	AVITA	154 (77 with bevacizumab)	III	Two arms, receiving gemcitabine-erlotinib ± bevacizumab	158 SNPs in VEGF pathway	rs9582036-A allele increases PFS and OS in bevacizumab arm but not in placebo arm
	Colorectal	Hansen et al <sup>83</sup>	Nordic ACT	218	III	Two arms receiving either FOLFOX/XELOX or FOLFIRI/XELIRI ± bevacizumab	rs9582036 (intronic)	rs9582036-A allele increases RR to bevacizumab
	Breast	Miles et al <sup>71</sup>	AVADO	336 (231 with bevacizumab)	III	Three arms, receiving either 0, 7.5, or 15 mg/kg bevacizumab combined with docetaxel	rs9554316, rs9582036 (both intronic)	No (PFS/OS)
VEGFR2	Colorectal	Gerger et al <sup>76</sup>		119		All patients received FOLFOX/XELOX + bevacizumab	+889G/A	Yes (RR), G allele increases RR
	Breast	Schneider et al <sup>70</sup>	ECOG 2100	363 (180 with bevacizumab)	III	Two arms, receiving paclitaxel ± bevacizumab	+889G/A, +1416A/T	No (PFS/OS)
	Various	Lambrechts et al <sup>73</sup>	NO16966, AVAIL, AVITA, AVOREN, AVADO	1,348 (669 with bevacizumab)		Various regimens (see Escudier et al, <sup>6</sup> Miles et al, <sup>12</sup> and Saltz et al <sup>27</sup> for details)	158 SNPs in VEGF pathway	rs11133360-T allele correlates with improved PFS in bevacizumab patients
IL8	Colorectal	Giudice et al <sup>78</sup>		35		All patients received chemotherapy (not specified) + bevacizumab	–251T/A	TT carriers have improved OR

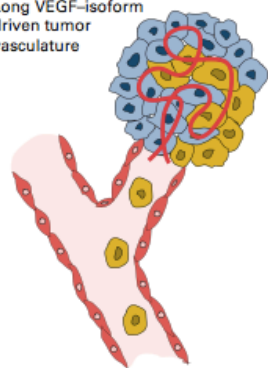
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**A****Response to Bevacizumab**

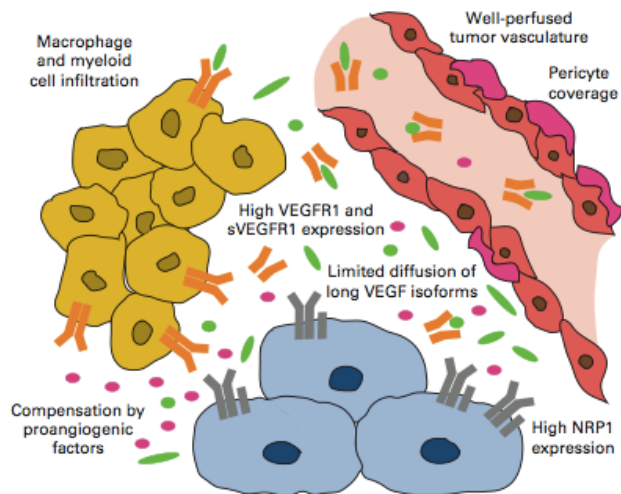
Short VEGF-isoform driven chaotic tumor vasculature

**B****Resistance to Bevacizumab**

Long VEGF-isoform driven tumor vasculature



Recruitment of bone marrow-derived myeloid cells



VEGFR2/NRP1 complex

Short VEGF-isoform (VEGF<sup>121</sup>)VEGF-isoform 165 (VEGF<sup>165</sup>)Long VEGF-isoform (VEGF<sup>188</sup>)

Circulating angiogenic factors (IL-8, PDGF-C, VEGF-C, VEGF-D, bFGF, etc.)



Transmembrane VEGFR1



Soluble VEGFR1 (sVEGFR1)



Macrophage, myeloid cell



Tumor cell



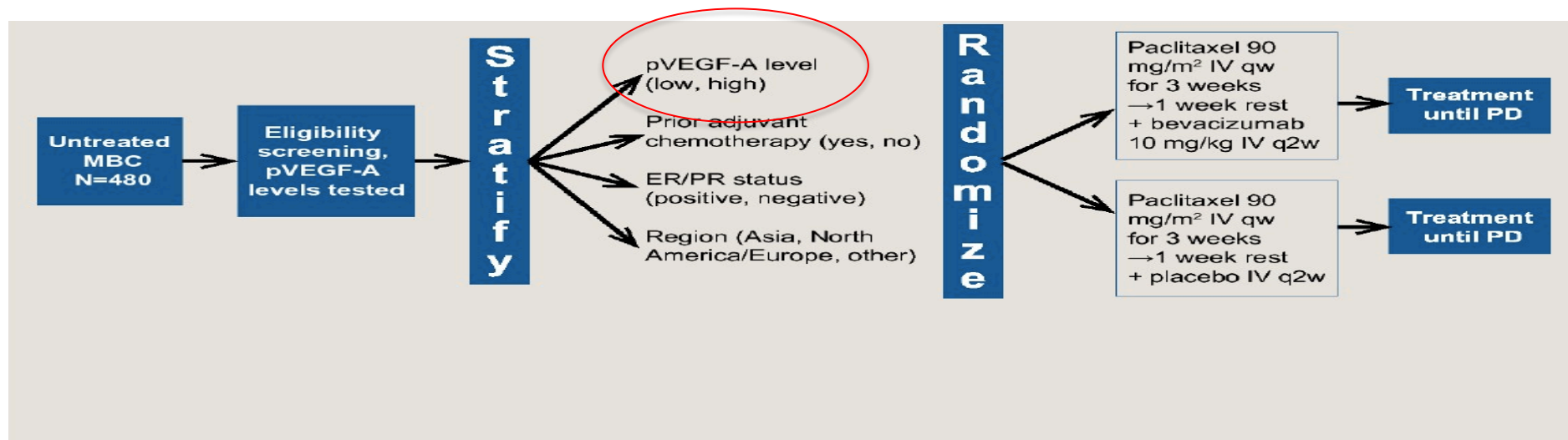
Endothelial cell



Pericyte

# Biomarcadores - VEGFA

## MERiDiAN



ER, estrogen receptor; IV, intravenously; MBC, metastatic breast cancer; PD, progressive disease; PR, progesterone receptor; pVEGF-A, plasma vascular endothelial growth factor A; qw, every week; q2w, every 2 weeks.

### STUDY STATUS

- Patient enrollment began in August 2012. Sites are located across 17 countries (Figure 4). The estimated final data collection date for primary outcome measures is June 2016, and the estimated study completion date is January 2019.