



# IL RISCHIO DI TEV CON LE NUOVE TERAPIE BIOLOGICHE DEL CARCINOMA POLONARE.

LUCIO BUFFONI

C.O.E.S. – CENTRO ONCOLOGICO ED EMATOLOGICO SUBALPINO

DIRETTORE DR. L. CIUFFREDA

OSPEDALE SAN GIOVANNI BATTISTA - TORINO

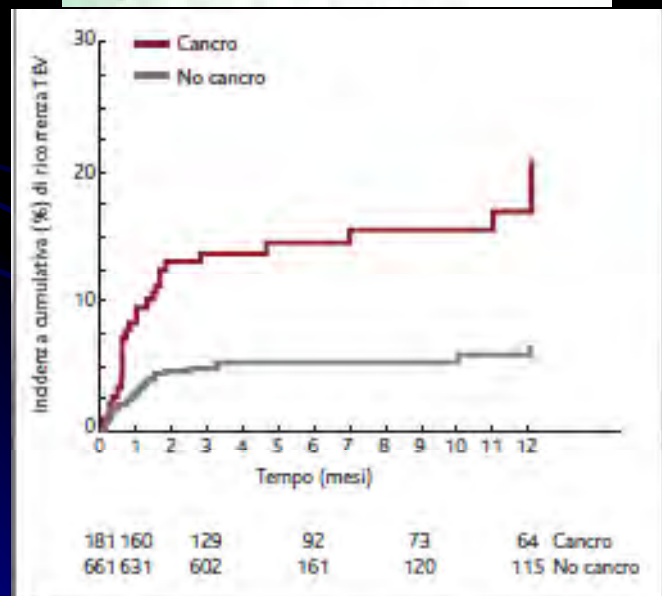
10 ottobre 2011, TORINO

# Il rischio tromboembolico nel paziente oncologico

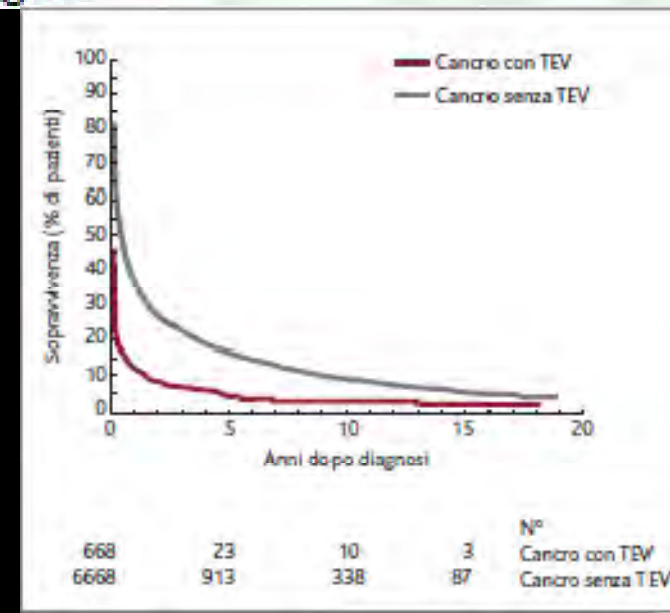
La malattia tromboembolica è sempre più frequente nei pazienti affetti da tumore ed è associata a:

- mortalità a breve termine,
- diminuita sopravvivenza a lungo termine
- impatto significativo sulla qualità della vita<sup>(1)</sup>

Le **recidive di TEV** aumentano in presenza di tumore<sup>(2)</sup>



La **prognosi** dei pazienti oncologici con TEV è peggiore<sup>(3)</sup>



- 1) Sousou T and Khorana A. *Hamostaseologie* 2009; 29: 121-4
- 2) Prandoni P, et al. *Blood* 2002; 100: 3484-8
- 3) Sorensen HT, et al. *N Engl J Med* 2000; 343: 1846-50

# La trombosi è la seconda causa di morte nei pazienti oncologici

I **fattori di rischio** per TEV possono essere associati a:

1. Caratteristiche del paziente
2. Tipo e sede del tumore maligno
3. Chemioterapia

## 4. Cause biologiche dell'aumentato rischio

### **Meccanismo Diretto** *(Barni S. et al. Trombosi e Cancro Pensiero Scientifico Editore 2007).*

Capacità delle cellule neoplastiche di attivare la cascata coagulativa con un meccanismo diretto mediante la produzione di sostanze pro-coagulanti come il tissue factor ed il cancer procoagulant.

### **Meccanismo Indiretto**

Attivando i monociti, le piastrine e le cellule endoteliali, inducendo in queste ultime un fenotipo pro-coagulante

# TEV e CANCRO

## Caratteristiche del paziente<sup>(1)</sup>

### Fattori di rischio associati al paziente:

- età avanzata
- sesso femminile
- razza
  - maggiore negli afro-americani
  - minore negli asiatici e abitanti delle isole del Pacifico
- comorbidità
  - infezioni
  - malattia renale
  - malattia polmonare
  - obesità
- mutazioni trombofiliche ereditarie
  - fattore V Leiden
  - mutazione del gene della protrombina
- precedente TEV

TROMBOFILIA  
EREDITARIA

**Stasi da compressione da parte delle masse tumorali, Presenza di uno stato infiammatorio, Disproteidemia, Allettamento.**

# TEV e CANCRO

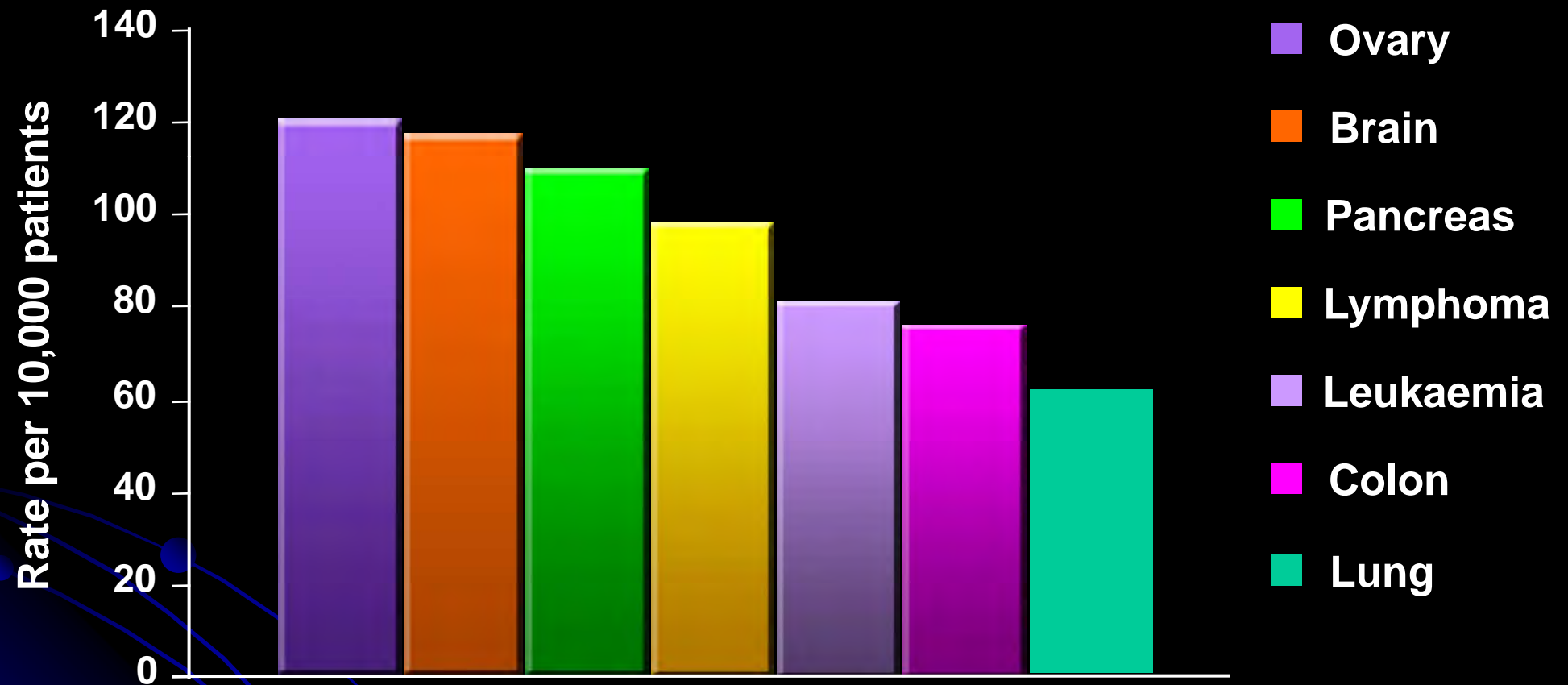
## Tipo e sede del tumore maligno<sup>(1)</sup>

### Fattori di rischio associati al tumore:

- sede primaria del tumore
  - cervello
  - pancreas
  - rene
  - stomaco
  - polmone
  - tumori ginecologici
  - linfoma
  - mieloma
- stadio avanzato
- periodo iniziale dopo la diagnosi (3-6 mesi)

La sede primaria del cancro rappresenta un importante fattore di rischio.

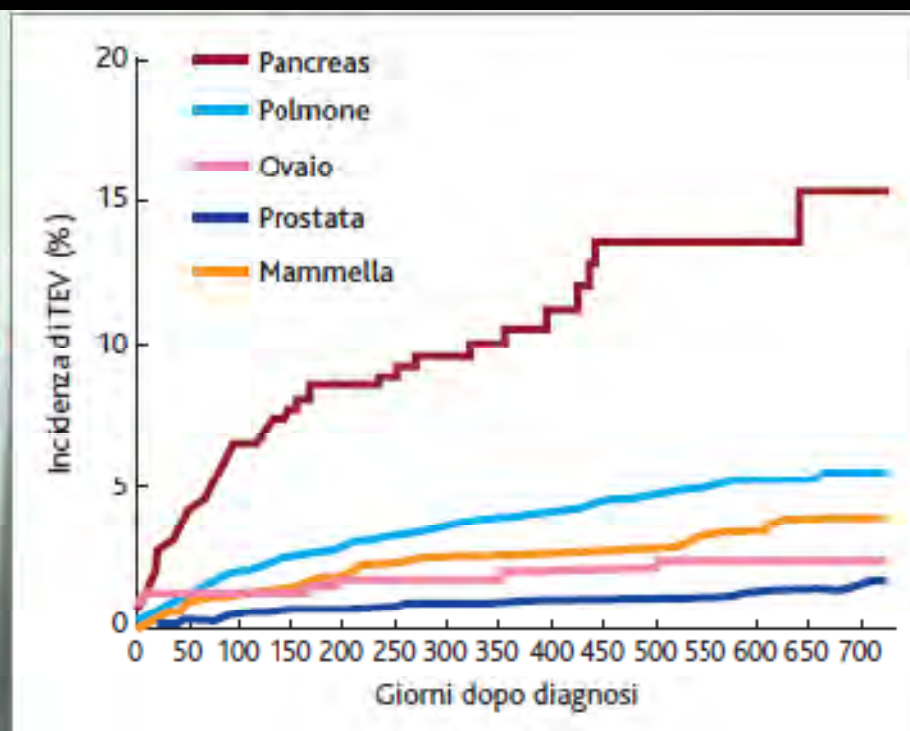
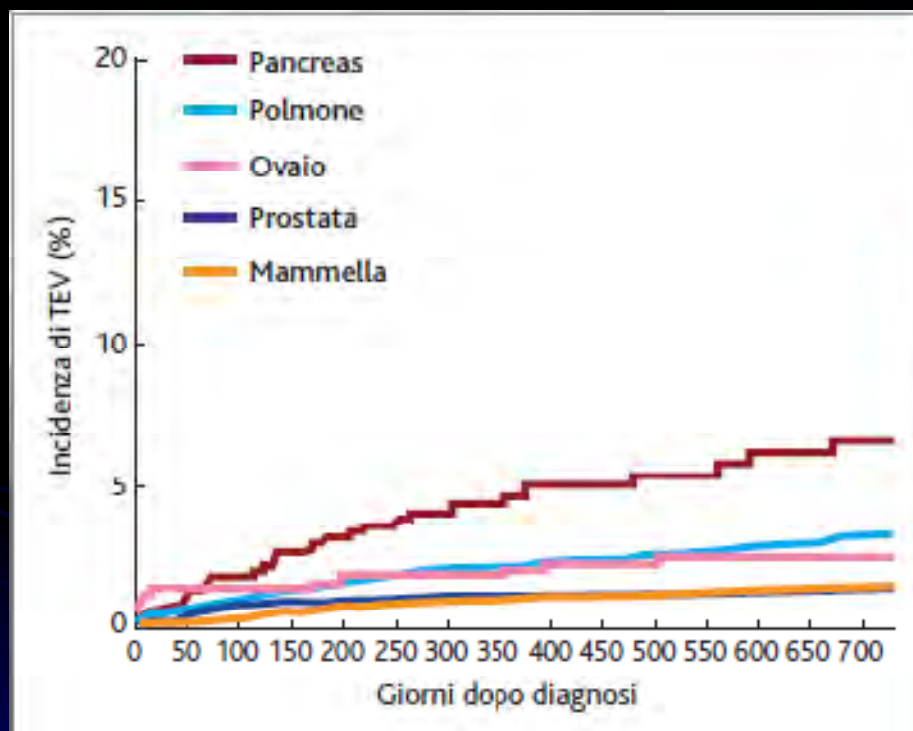
# Risk of Thrombosis According to Cancer Type



Adapted from Levitan et al, Medicine 1999.

**Incidenza TEV entro 2 anni dalla  
diagnosi  
di **cancro localmente avanzato****

**Incidenza TEV entro 2 anni dalla  
diagnosi  
di **tumore metastatico****



**I primi mesi dopo la diagnosi (3-6 mesi) rappresentano il periodo a maggior rischio tromboembolico.**

*Chew HK, et al. Arch Intern Med 2006; 166: 458-64*



# Chemioterapia

## Fattori di rischio associati alla chemioterapia:

- terapia
  - chemioterapia
  - ormonoterapia
  - agenti antiangiogenetici: talidomide, lenalidomide, bevacizumab
- agenti stimolanti l'eritropoiesi
- chirurgia maggiore
- ospedalizzazione
- cateteri venosi centrali

**Il rischio di TEV aumenta da 2 a 7 volte durante la chemioterapia, e il rischio aumenta ulteriormente se somministrata attraverso cateteri venosi centrali<sup>(1)</sup>.**



# TEV E PAZIENTE ONCOLOGICO

**TROMBOFILIA EREDITARIA**

**TROMBOFILIA ACQUISITA**



**PAZIENTE:**

ETA'  
SESSO  
RAZZA

**TUMORE:**

SEDE  
ESTENSIONE  
TEMPO DA DIAGNOSI

**TRATTAMENTI:**

CHIRURGIA  
CHEMIOTERAPIA  
ORMONOTERAPIA  
CVC  
FATTORI DI CRESCITA

# Chemioterapia come fattore di rischio

Trattamento	Incremento del rischio TEV	Bibliografia
Capecitabina e Busulfan	> 10%	RCP
CHT+ Tamoxifene vs CHT ( nelle donne )	4 volte	<i>Pritchard KI et al. J Clin Oncol 1996;14:2731</i>
Terapia adiuvante ormonale ( ca mammario)	1,5 - 7 volte	<i>McKaskill SW et al. J Natl Cancer Inst 2004; 96:1762</i>
Talidomide e Lenalidomide + Steroidi, Melfalan, Doxorubicina	2-4 % - 8 -27%	<i>Zangari M et al. Br J Haematol 2004; 126:715</i>
<b>Bevacizumab + CHT</b>	<b>33%</b>	<i>Scappaticci FA et al. J Natl Cancer Inst 2007; 99:1232</i>
Temozolamide, Panitumab, Sunitinib	1 e 10 %	RCP

## *La chemioterapia è un fattore di rischio indipendente per TEV*

- Incidenza annua di TEV in pazienti sottoposti a chemioterapia **10,9%**.

## *La chemioterapia è un fattore di rischio indipendente per TEV*

### Regimi contenenti cisplatino

- Review paz affetti da tumori a cell germinali trattati con cisplatino-bleomicina (Weijl N et al. J Clin Oncol 2000; 18 (10): 2169-78)
  - TEV 8.4%
- Studio prospettico paz affetti da ca polmone non microcitoma trattati con cisplatino e gemcitabina (Numico G et al. Cancer 2005; 103(5): 994-9)
  - TEV 17.6%
- Paz affette da ca cervice uterina inoperabili trattati con radioterapia e cisplatino basse dosi settimanali (Jacobson G et al. Gynecol Oncol 2005; 96: 470-4)
  - TEV 16.7%

# Advanced NSCLC is a difficult disease to treat, with only a few advances over recent years\*

	Mode of action	Line of therapy	Trial outcome
Bevacizumab	VEGF MAb	1L	✓+
Sorafenib	VEGF TKI	1L	★/✗
Sunitinib	VEGF TKI	2L	★
Cediranib	VEGF TKI	1L	✗
Vandetanib	VEGF/EGFR TKI	2L	✓/✗
Erlotinib	EGFR TKI	1L, maintenance, 2L	✓+
Cetuximab	EGFR MAb	1L	✓/✗
Gefitinib	EGFR TKI	1L/2L	✓+/★
Pemetrexed	Antifolate	1L, maintenance	✓+
ASA404	Primary endpoint met	1L	✗ No significant clinical benefit
Figitumumab	IGFR MAb	1L	✗
NOV002	Chemoprotectant	1L	✗

✓ Primary endpoint met

+ Licensed indication

\*Only reported phase III trial data

★ Primary endpoint not met;  
secondary efficacy endpoint only

✗ No significant clinical benefit

VDA = vascular disrupting agent; IGFR = insulin-like growth factor receptor

# Bevacizumab safety profile: Well defined across tumour types

- More than 800 000 patients worldwide have been treated with bevacizumab<sup>1</sup>
- The most common adverse events in clinical trials are:
  - Hypertension, fatigue/asthenia, diarrhoea, abdominal pain<sup>2</sup>
- The most serious adverse events in clinical trials are:
  - GI perforation, bleeding (with pulmonary haemorrhage/haemoptysis seen more frequently in patients with NSCLC), **ATE**<sup>2</sup>
- Other adverse events of special interest with bevacizumab include:
  - Proteinuria, wound-healing complications, epistaxis, **VTE**, fistula, RPLS, CHF

1. EU Summary bridging report to EMEA 2010;

2. Avastin SmPC 2009



# Bevacizumab safety profile

**E4599**  
Avastin  
15 mg/kg+CP



OS 12.3 mos  
PFS 6.2 mos

**AVAIL**  
Avastin  
15 mg/kg+CG



OS > 13 mos  
PFS 6.5 mos

+ SAFETY DATA

**AVAIL**  
Avastin  
7.5mg/kg+CG



OS > 13 mos  
PFS 6.7 mos

**PHASE III**

**SAIL**  
Avastin  
+ CT

**ARIES**  
Avastin  
+ CT



SAFETY DATA

**PHASE IV**

# Incidence of grade $\geq 3$ adverse events of special interest: Phase III trials across tumour types

Adverse events (%)	mCRC <sup>1-3</sup>		LR/mBC <sup>4,5</sup>		NSCLC <sup>6,7</sup>		mRCC <sup>8,9</sup>	
	Bev	Contr ol	Bev	Contr ol	Bev	Contr ol	Bev	Contr ol
Hypertension	4–11 <sup>a</sup>	1–2	5–16	1–2	6–9	1–2	3–11	0–1
Proteinuria	0.6–1	0–1	2–4	0	0.3–3	0	7–16	0–0.3
ATE	2	1	1–4	0–2	NR	NR	1	0.3
VTE	8	5	1–5	1–5	7	6	2	0.7
Bleeding	2–3	0.4–3	0.2–5	0–1	4	1–2	3	0.3
GI perforation	1–2	0–0.3	0–3	0–1	0–0.3	0.6	0.3–1	0
Wound-healing complications	0.1	0.3	0.4–2	0–1	NR	NR	0.6	0

1. Hurwitz et al. NEJM 2004; 2. Giantonio et al. JCO 2007; 3. Saltz et al. 2008; 4. Miles. EJC Suppl 2008

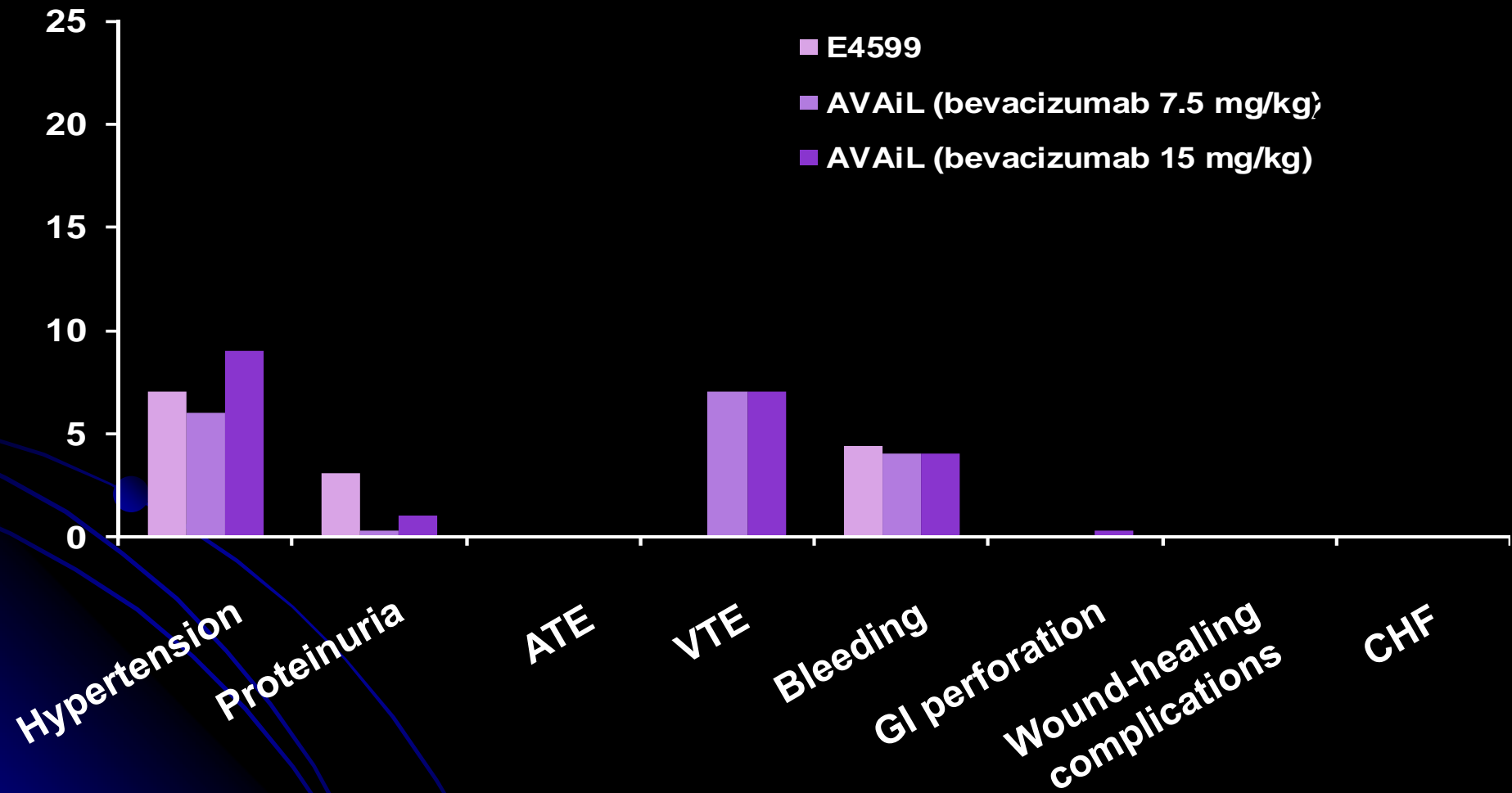
5. Miles et al. EBCC 2010; 6. Sandler et al. NEJM 2006; 7. Reck et al. JCO 2009

8. Escudier et al. Lancet 2007; 9. Rini et al. JCO 2010

<sup>a</sup>Grade 4 not reported in AVF2107g

# Overview of grade $\geq 3$ adverse events of special interest in randomised trials in NSCLC

NSCLC



# E4599

THE NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., et al.

**Table 2.** Adverse Events, According to Treatment.\*

Adverse Event	Paclitaxel–Carboplatin Group (N=440)			Paclitaxel–Carboplatin–Bevacizumab Group (N=427)			P Value
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5†	
	<i>number of patients (percent)</i>						
Neutropenia		74 (16.8)			109 (25.5)		0.002
Thrombocytopenia		1 (0.2)			7 (1.6)		0.04
Anemia		4 (0.9)			0		NS
Febrile neutropenia	8 (1.8)		1 (0.2)	17 (4.0)		5 (1.2)	0.02
Hyponatremia	4 (0.9)	1 (0.2)		11 (2.6)	4 (0.9)		0.02
Hypertension	2 (0.5)	1 (0.2)		29 (6.8)	1 (0.2)		<0.001
Proteinuria				11 (2.6)	2 (0.5)		<0.001
Headache	2 (0.5)			13 (3.0)			0.003
Rash or desquamation	2 (0.5)			10 (2.3)			0.02
Bleeding events (all)	3 (0.7)			19 (4.4)			<0.001
Central nervous system hemorrhage					3 (0.7)		
Epistaxis	1 (0.2)			3 (0.7)			
Hematemesis						2 (0.5)	
Hemoptysis	1 (0.2)			2 (0.5)	1 (0.2)	5 (1.2)	
Melena or gastrointestinal bleeding	1 (0.2)		1 (0.2)	3 (0.7)	1 (0.2)		
Other hemorrhage				1 (0.2)	1 (0.2)		

# E4599

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## ORIGINAL ARTICLE

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**Table 3.** Causes of Death.

Variable	Paclitaxel-Carboplatin Group	Paclitaxel-Carboplatin-Bevacizumab Group
	<i>number of patients</i>	
Total deaths	344	305
Cause		
Lung cancer	309	260
Toxic effects	2	14*
Coexisting conditions	16	16
Unknown cause	17	15

5 pts due to pulmonary hemorrhage  
5 pts due to febrile neutropenia  
2 pts due to CNS/GI bleeding  
1 pt due to pulmonary embolism

# AVAIL

VOLUME 27 • NUMBER 3 • MARCH 10, 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non–Small-Cell Lung Cancer: AVAIL

Martin Reck, Joachim von Pawel, Petr Zatloukal, Radosław Samiec, Vera Garbova, Vera Hirsh,

Table 3. Summary of Selected Severe (grade ≥ 3) AEs, Severe AEs of Special Interest, and Pulmonary Hemorrhage Events (safety population)

AE	Placebo + CG (n = 327)		Bevacizumab 7.5 mg/kg + CG (n = 326)		Bevacizumab 15 mg/kg + CG (n = 325)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients with ≥ 1 severe (grade ≥ 3) AE	240	75	252	78	265	81
Neutropenia*	104	32	132	40	117	36
Thrombocytopenia	16	5	16	5	17	5
Anemia	44	13	34	10	34	10
Asthenia	9	3	17	5	15	5
Vomiting	12	4	24	7	31	9
Hypertension	5	2	21	6	25	8
Severe AEs of interest						
Bleeding	5	2	14	4	14	4
Proteinuria	—	—	1	< 1	4	1
GI perforation	2	< 1	—	—	1	< 1
Ischemic events†	16	5	8	2	16	5
<u>Venous thromboembolic events</u>	21	6	24	7	23	7
Hemoptysis (all grades)	17	5.2	23	7.0	32	9.7
Pulmonary hemorrhage (grade ≥ 3)	2	0.6	5	1.5	3	0.9
Fatal pulmonary hemorrhage	1	0.3	4	1.2	3	0.9

Abbreviations: AE, adverse event; CG, cisplatin plus gemcitabine.

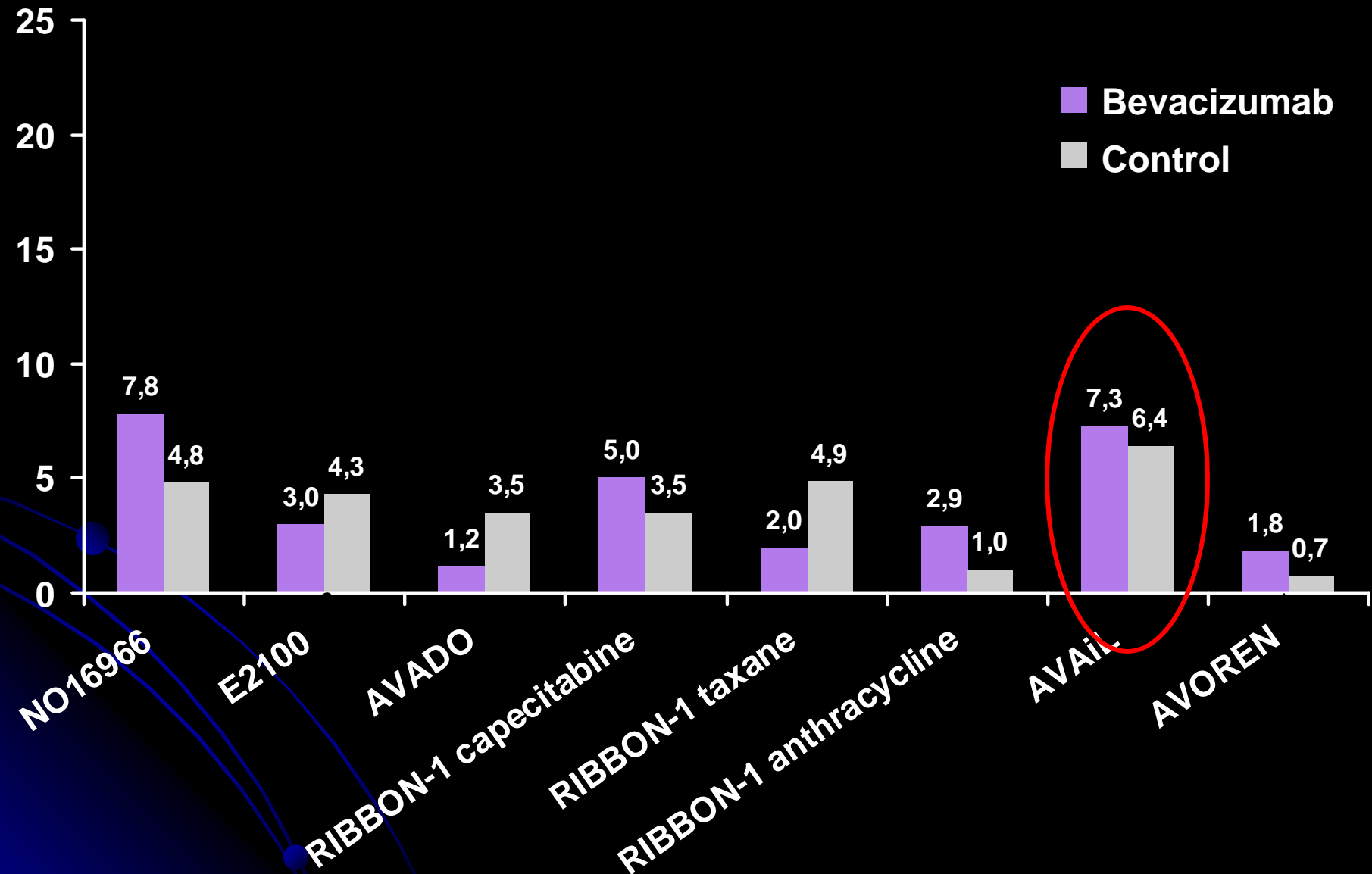
\*Febrile neutropenia occurred in four (1%), five (2%), and seven (2%) patients in the placebo, low-dose bevacizumab, and high-dose bevacizumab arms, respectively.

†Includes events reported as myocardial ischemia or infarction, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral arterial thrombotic events.



# Grade $\geq 3$ VTE: Clinical trial experience

Pan



Saltz et al. JCO 2008; 2. Miles. EJC Suppl 2008; 3. Miles et al. EBCC 2010  
4. Reck et al. JCO 2009; 5. Escudier et al. Lancet 2007

# AVAIL

VOLUME 27 • NUMBER 3 • MARCH 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

### Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL

Martin Reck, Joachim von Pawel, Petr Zeloušek, Rodryg Ramírez, Vera Gorbounova, Vera Hirsák,

<b>Grade <math>\geq 3</math> pulmonary hemorrhage</b>	<b>2pts placebo + CG</b>
	<b>5pts low dose beva</b>
	<b>3 pts high dose beva</b>

**Death as a result of AEs was**

<b>4% in placebo arm</b>
<b>4% in low dose beva</b>
<b>5% in high dose beva</b>

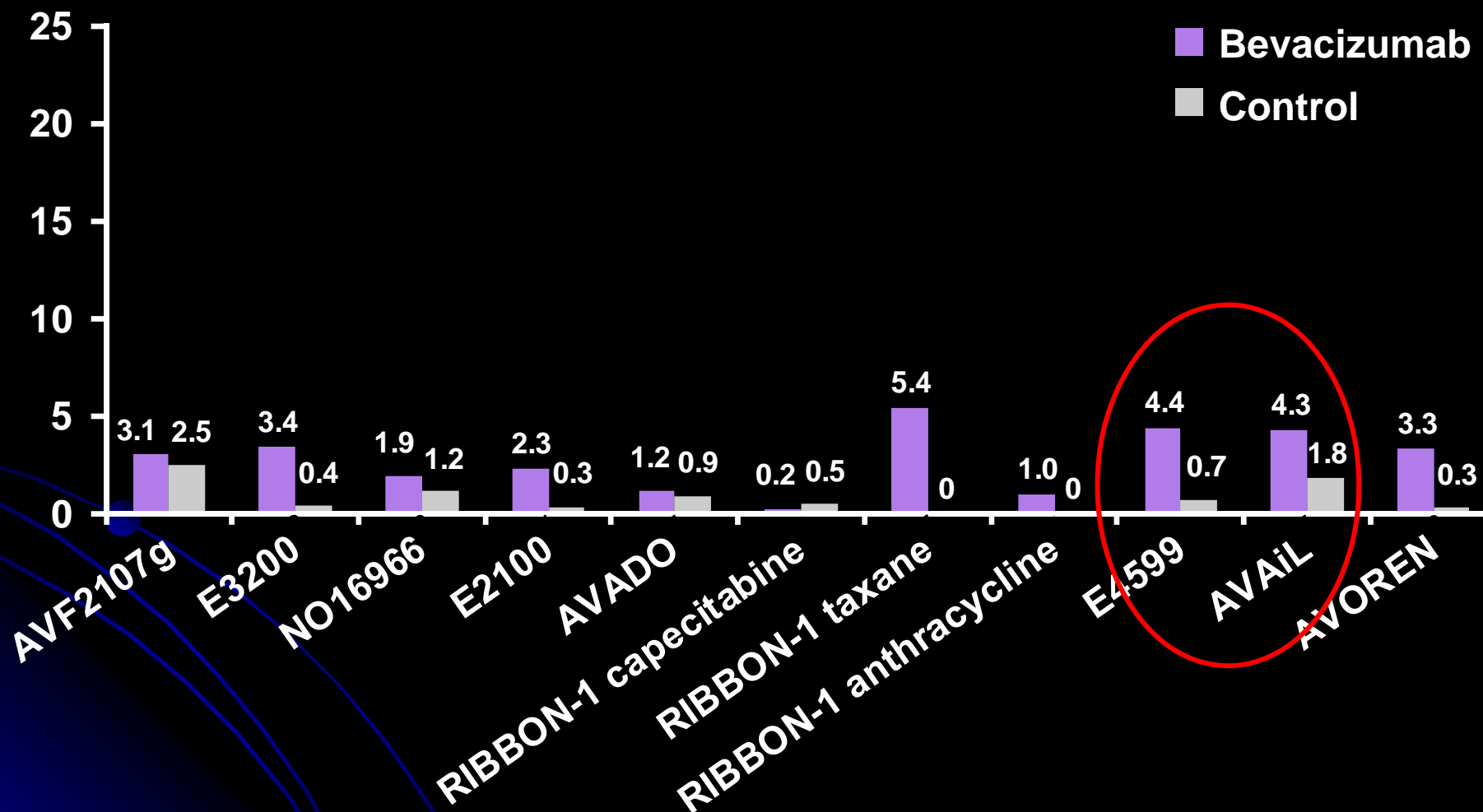
**Most common cause of non-progression –related deaths were:**

**Cardiopulmonary failure**  
**Respiratory failure**  
**Hemoptysis**  
**Pulmonary embolism.**

**No observed increased incidence of arterial or venous thromboembolic events.**

# Grade $\geq 3$ bleeding: Clinical trial experience

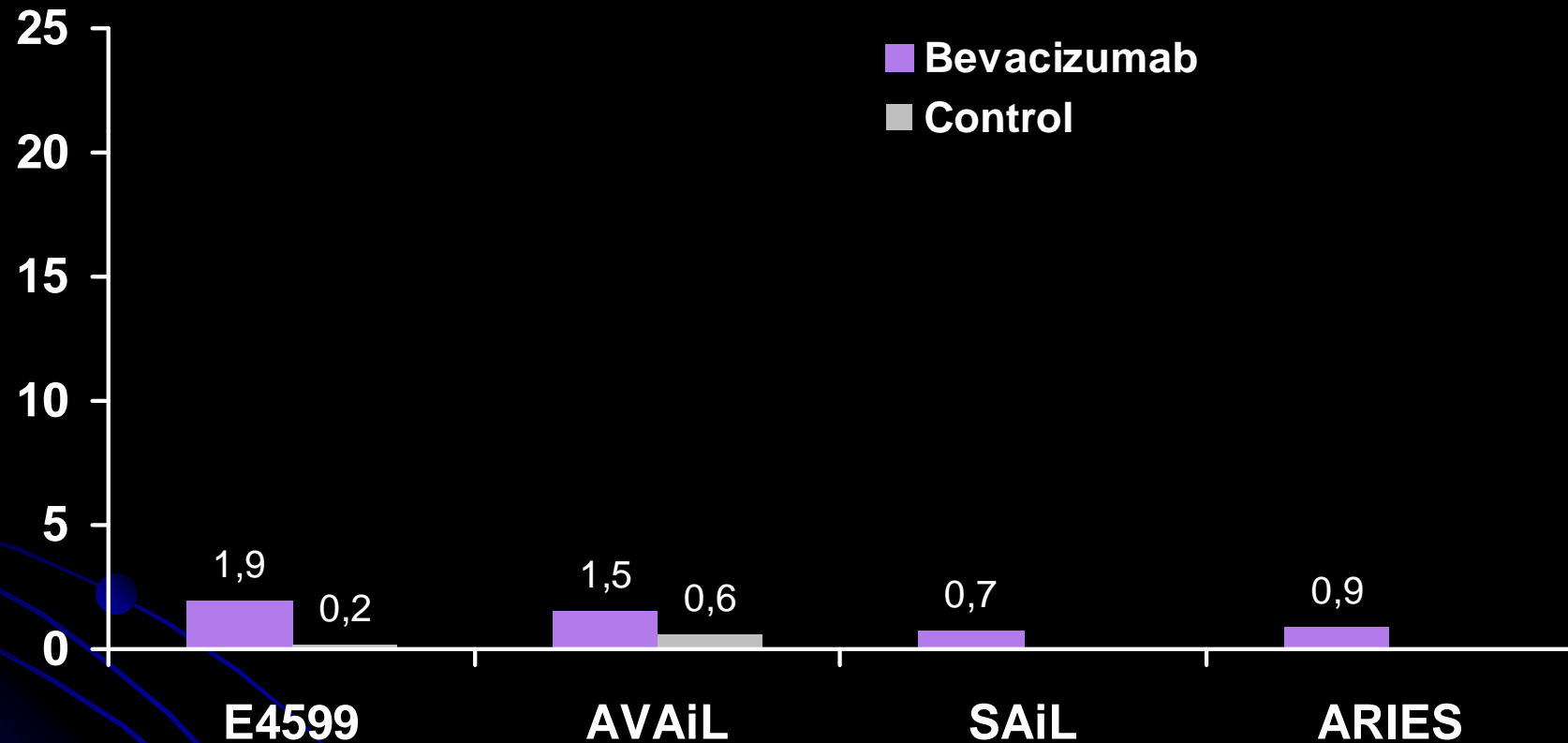
Pan



Hurwitz et al. NEJM 2004; 2. Giantonio et al. JCO 2007; 3. Saltz et al. JCO 2008  
 4. Miles. EJC Suppl 2008; 5. Miles et al. EBCC 2010; 6. Sandler et al. NEJM 2006  
 7. Reck et al. JCO 2009; 8. Escudier et al. Lancet 2007

# Grade $\geq 3$ pulmonary haemorrhage or haemoptysis in NSCLC

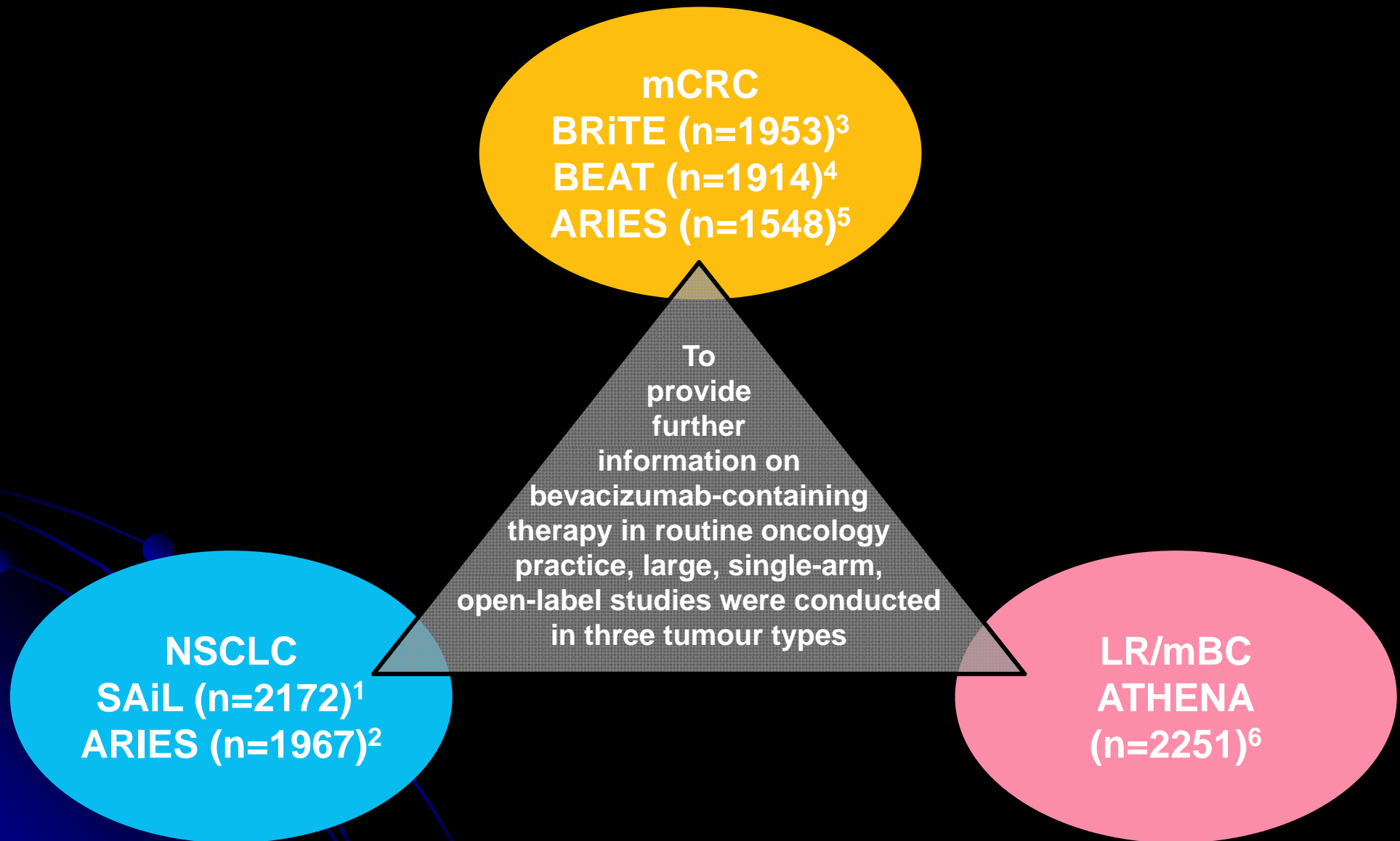
NSCLC



- Patients with tumours invading or abutting major blood vessels should not be treated with bevacizumab
- Patients with recent haemoptysis (>2.5 mL of red blood) should not receive bevacizumab

# Bevacizumab studies in routine oncology practice

Pan



1. Crinó et al. Lancet Oncol 2010; 2. Wozniack et al. ASCO 2010; 3. Kozloff et al. Oncologist 2009  
4. Van Cutsem et al. Ann Oncol 2009; 5. Cohn et al. ASCO 2010; 6. Smith et al. Ann Oncol 2010

# SAiL

## Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study

Lucio Crinò, Eric Dansin, Pilar Garrido, Frank Griesinger, Janessa Laskin, Nick Pavlakakis, Daniel Stroiakovski, Nick Thatcher, Chun-Ming Tsai, Yi-long Wu, Caicun Zhou

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade ≥ 3*
Patients with at least one event	16 (1%)	42 (2%)	107 (5%)	109 (5%)	50 (2%)	242 (11%)
Respiratory, thoracic, and mediastinal disorders	6 (<1%)	11 (<1%)	25 (1%)	23 (1%)	11 (<1%)	58 (3%)
Pulmonary embolism	1 (<1%)	1 (<1%)	5 (<1%)	19 (1%)	4 (<1%)	28 (1%)
Gastrointestinal disorders	1 (<1%)	8 (<1%)	21 (1%)	6 (<1%)	15 (1%)	42 (2%)
Blood and lymphatic system disorders	1 (<1%)	7 (<1%)	14 (1%)	27 (1%)	2 (<1%)	43 (2%)
Vascular disorders	1 (<1%)	6 (<1%)	20 (1%)	12 (1%)	2 (<1%)	34 (2%)
Nervous system disorders	1 (<1%)	1 (<1%)	9 (<1%)	11 (<1%)	5 (<1%)	25 (1%)

Data are number of patients (%). ITT=intention-to-treat. \* Patients could have had more than one grade of the same event.

Table 2: Serious adverse events thought to be related to bevacizumab that were reported in more than 1% of patients in the ITT population (N=2212)

**3 most common adverse events: thromboembolic events 6-8%;  
bleeding 4%;  
GI perforations 1%.**



# SAiL

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	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade ≥ 3*
Overall bleeding	714 (32%)	129 (6%)	56 (3%)	8 (<1%)	17 (1%)	80 (4%)
Epistaxis	528 (24%)	67 (3%)	26 (1%)	3 (<1%)	0	28 (1%)
Pulmonary haemorrhage†	149 (7%)	32 (1%)	5 (<1%)	2 (<1%)	8 (<1%)	15 (1%)
CNS bleeding‡	5 (<1%)	0	1 (<1%)	0	1 (<1%)	2 (<1%)
Hypertension	364 (16%)	300 (14%)	120 (5%)	6 (<1%)	0	125 (6%)
Proteinuria	466 (21%)	231 (10%)	56 (3%)	11 (<1%)	0	67 (3%)
Thromboembolism	39 (2%)	79 (4%)	104 (5%)	54 (2%)	26 (1%)	172 (8%)
Gastrointestinal perforation	1 (<1%)	2 (<1%)	13 (1%)	6 (<1%)	8 (<1%)	27 (1%)
Wound-healing complications	14 (1%)	10 (<1%)	1 (<1%)	1 (<1%)	0	2 (<1%)
Congestive heart failure	2 (<1%)	4 (<1%)	3 (<1%)	2 (<1%)	6 (<1%)	11 (<1%)

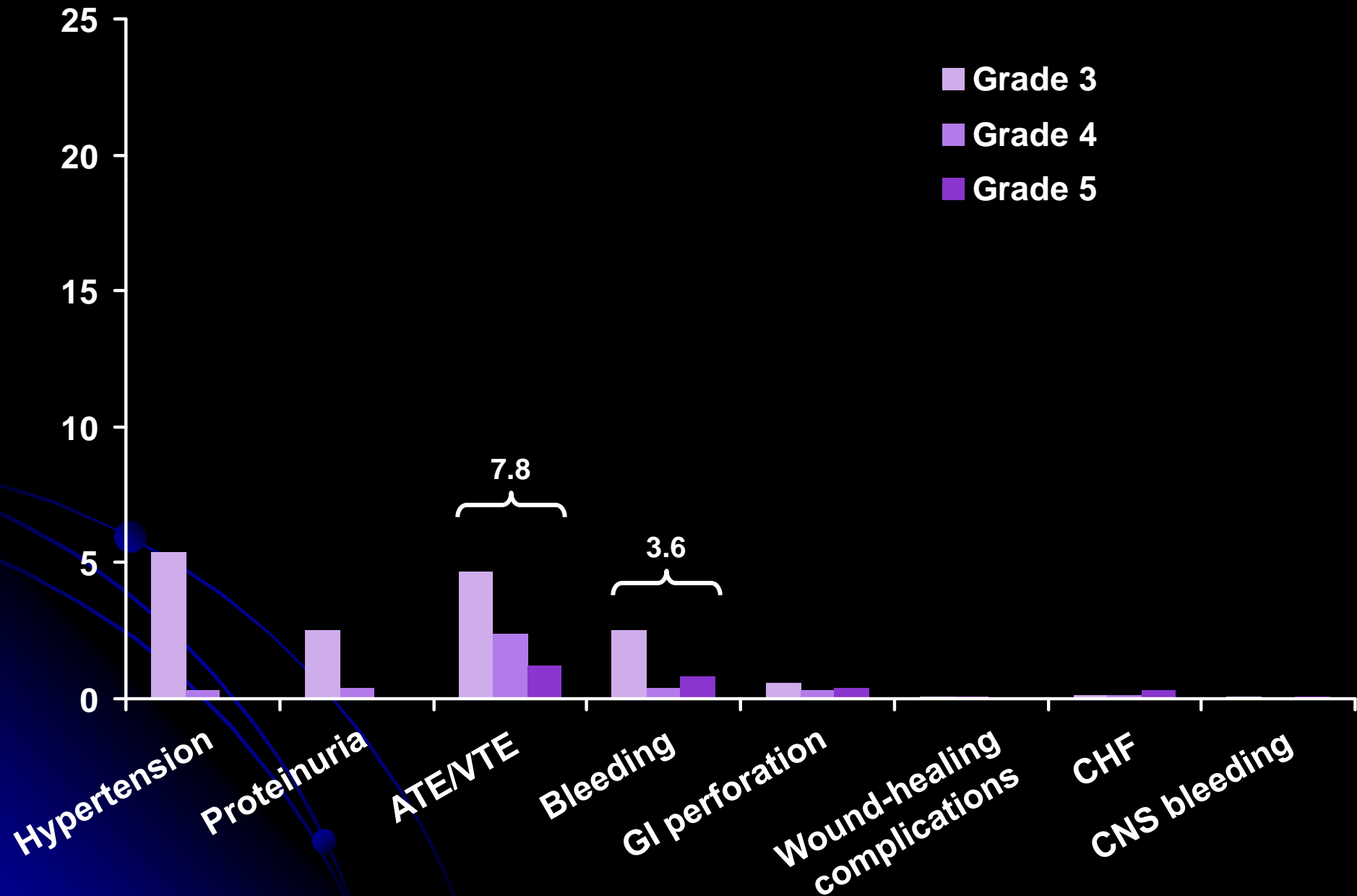
Data are number of patients (%). ITT=intention-to-treat. \*Patients could have had more than one grade of the same event. †Pulmonary haemorrhage or haemoptysis. ‡Cerebral haemorrhage or haematoma.

Table 3: Adverse events of special interest in the ITT population (N=2212), by Common Terminology Criteria grade

**Grade ≥3 thromboembolic events and hypertension.**

# SAiL: Grade $\geq 3$ adverse events of special interest in NSCLC

NSCLC



# SAIL

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	Number of events	Outcome				Action taken	
		Resolved	Improved	Persistent	Led to death	Treatment temporarily interrupted	Treatment permanently discontinued
Bleeding	1347	1154 (86%)	39 (3%)	137 (10%)	17 (1%)	28 (2%)	110 (8%)
Hypertension	1025	778 (76%)	94 (9%)	153 (15%)	0	72 (7%)	40 (4%)
Proteinuria	1046	717 (69%)	102 (10%)	227 (22%)	0	38 (4%)	31 (3%)
Thromboembolism	324	156 (48%)	57 (18%)	85 (26%)	26 (8%)	34 (11%)	140 (43%)
Gastrointestinal perforation	30	18 (60%)	3 (10%)	1 (3%)	8 (27%)	0	26 (87%)
Wound-healing complications	31	22 (71%)	2 (6%)	7 (23%)	0	8 (26%)	1 (3%)
Congestive heart failure	18	6 (33%)	2 (11%)	4 (22%)	6 (33%)	2 (11%)	9 (50%)

Data are number of events (%). Analysis is based on total of 3821 adverse events in the intention-to-treat population (2212 patients). Percentages are based on total number of events within each category, not on number of patients.

Table 5: Adverse events of special interest, by outcome and action taken

**Most common causes of death: thromboembolism (1%) and bleeding (1%).**

## SAiL: continuing bevacizumab to progression has limited impact on safety profile

	No maintenance population (n=880)	Maintenance population (n=1,332)
<b>Patients (%)</b>	<b>Grade <math>\geq 3</math></b>	<b>Grade <math>\geq 3</math></b>
Overall bleeding	4.5	3.0
Epistaxis	1.5	1.1
PH/haemoptysis	1.0	0.5
CNS bleeding <sup>§</sup>	0.1	0.1
HTN	4.0	6.8
Proteinuria	2.2	3.6
Thromboembolism	11.9	5.0

<sup>§</sup>Cerebral haemorrhage/haematoma

# Summary of routine oncology practice: Incidence of grade $\geq 3^a$ AEs of special interest

Pan

Adverse event (%)	CRC			BC		NSCLC
	BRiTE <sup>1</sup>	BEAT <sup>2</sup>	ARIES <sup>3</sup>	ATHENA <sup>4</sup>	SAiL <sup>5</sup>	ARIES <sup>6</sup>
Hypertension	NR	5.3	NR	4.4	5.7	NR
Proteinuria	NR	1.1	NR	1.7	3.0	NR
<b>ATE</b>	2.0	1.5	2.1		7.8	1.9
<b>VTE</b>	NR	NR	NR	3.2		NR
Bleeding	2.9	3.2	2.9	1.4	3.6	3.6
GI perforation	1.9	1.8	0.3	0.3	1.2	1.0
Wound-healing complications	4.4 <sup>b</sup>	1.1	NR	0.6	0.1	NR

<sup>a</sup>Or serious AEs for BEAT study. <sup>b</sup>Post-operative wound-healing complications; denominator = patients who had post-baseline surgery within 90 days of the last bevacizumab dose

Kozloff et al. Oncologist 2009; 2. Van Cutsem et al. Ann Oncol 2009; 3. Cohn et al. ASCO 2010  
4. Smith et al. Ann Oncol 2010. 5. Crinó et al. Lancet Oncol 2010; 6. Wozniack et al. ASCO 2010

# Antiangiogenic Agents for the Treatment of Nonsmall Cell Lung Cancer: Characterizing the Molecular Basis for Serious Adverse Events

Shenhong Wu and Roger S. Keresztes

Division of Hematology and Oncology, Department of Medicine, Stony Brook University Cancer Center, Stony Brook, New York, USA

Table 1. Risks of Bevacizumab-Associated Adverse Events: Results of Systematic Reviews and Meta-Analyses

		Relative Risk* (95% Confidence Interval; p Value [When Available])			
		All Tumor Types Combined			
	Description	Overall	All Grade	High Grade	Nonsmall-Cell-Lung-Cancer-Specific Risks
Hemorrhage (22)	20 RCTs N = 12,617	2.43 (1.93–3.18; p < .001)	2.88 (2.07–4.0; p < .001)	1.91 (1.36–2.68; p = .003) Fatal/grade 5: 3.56 (1.71–7.41; p = .001)	High grade, all histologies: 2.84 (1.87–4.32) High grade, nonsquamous: 2.77 (1.81–4.23)
Venous thromboembolism (23)	15 RCTs N = 7,956	1.31 (1.13–1.56; p < .001)	1.29 (1.03–1.63; p = .03)	1.38 (1.12–1.70; p = .002)	All grade: 1.59 (0.47–5.37) High grade: 1.24 (0.85–1.81)
Arterial thromboembolism (24)	20 RCTs N = 12,617	1.41 (1.08–1.91; p = .013)	2.08 (1.28–3.40; p = .003)	1.29 (0.86–1.94; p = .31)	All grade: 1.46 (0.16–13.37)
(25)	5 Genentech-sponsored RCTs N = 1,745	2.0 (1.05–3.75; p = .031)	–	–	Overall: 1.39 (0.14–13.37)
Gastrointestinal perforation (26)	17 RCTs N = 12,294	2.11 (1.19–3.85; p = .011)	–	Fatal/grade 5: 2.7 (0.7–10.6; p = .15)	Overall: 1.55 (0.37–6.59)
Hypertension (34)	20 RCTs N = 12,656	–	3.02 (2.24–4.07; p < .001)	5.28 (4.15–6.71; p < .001) Hypertensive crisis/grade 4: 3.16 (0.91–10.90; p = .059)	High grade: 7.06 (3.66–13.62)
Hypertension (27)	7 RCTs N = 1,850	–	Low dose (3–7.5 mg/kg): 3.0 (2.2–4.2; p < .001) High dose (10 or 15 mg/kg): 7.5 (4.2–13.4; p < .001)	–	–
Proteinuria (28)	16 RCTs (2 phase II; 14 phase III) N = 12,268	–	2.79 (1.31–5.95; p < .001)	4.79 (2.71–8.46; p < .001) Nephrotic syndrome: 7.78 (1.80–33.62; p = .006)	High grade: 12.59 (1.67–94.80)
Proteinuria (27)	7 RCTs N = 1,850	–	Low dose (3–7.5 mg/kg): 1.4 (1.1–1.7; p = .003) High dose (10 or 15 mg/kg): 2.2 (1.6–2.9; p < .001)	–	–

Note: RCTs, randomized controlled trials.

\*For bevacizumab plus chemotherapy versus chemotherapy alone.

Considering NSCLC, relative risks were among the lowest for both ATEs and GIP but among the highest for hemorrhage, VTEs and proteinuria.



# Sorafenib

Inhibitor of VEGFR-2, VEGFR-3 and PDGFR-beta.

**ESCAPE:** CP+/- sorafenib I line  
No OS benefit  
SQC 1.8% hemorrhagic incidence vs 0.3% other histologies.

**NeXUS:** CG+sorafenib  
No OS benefit.

**PHASE II:** 3 line NSCLC  
83 pts: 4 pts grade IV cerebrovascular ischemia  
2 pts grade III lung hemorrhage  
1 pts grade V respiratory tract hemorrhage

**TARGET:** Phase III in 903 RCC  
2 drug-related deaths due to cardiac ischemia or infarction.

# Sunitinib

**Socinski, Novello et al:** PHASE II 2 line  
3 drug-related deaths  
2 pulmonary hemorrhage  
1 CNS hemorrhage.

# Angiogenesis inhibitors in development

- Vandetanib
- Cediranib
- Motesanib
- BIBF 1120

# Vandetanib

- Inhibits VEGFR (++) and EGFR (+)
- Tested with DOC/PEM/JM8-TAX
- Improved PFS but no OS.
- General AES:
  - rash,
  - diarrhea,
  - hypertension,
  - QTc-related events (due to interactions with cardiac-ion channels)

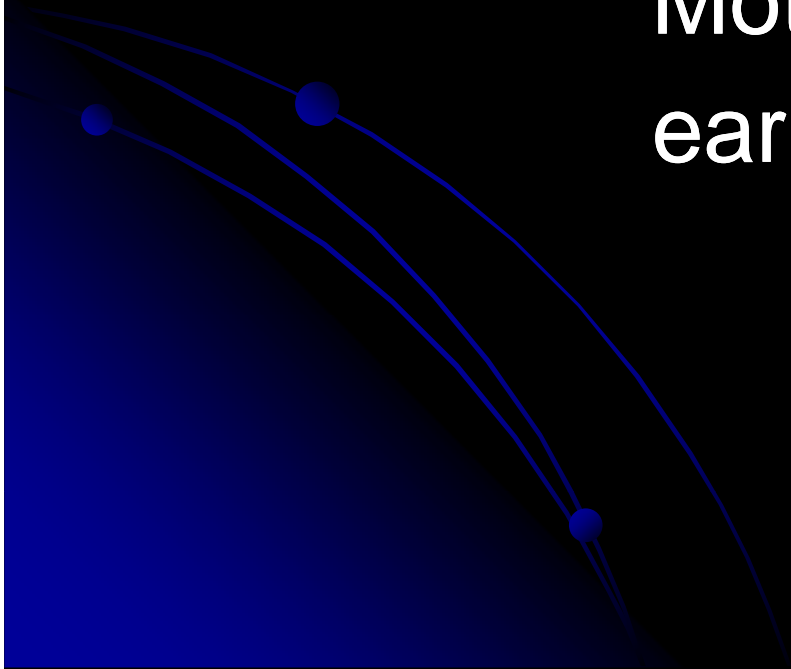
# Cediranib

- Inhibitor of VEGFR, PDGFR-beta, c-KIT.
- Testing with CP: safe and efficacy data pending.
- AEs in other tumors:  
fatigue, diarrhea, hypertension ecc..
- NO cardiac toxicities  
1 pt with CNS hemorrhage.

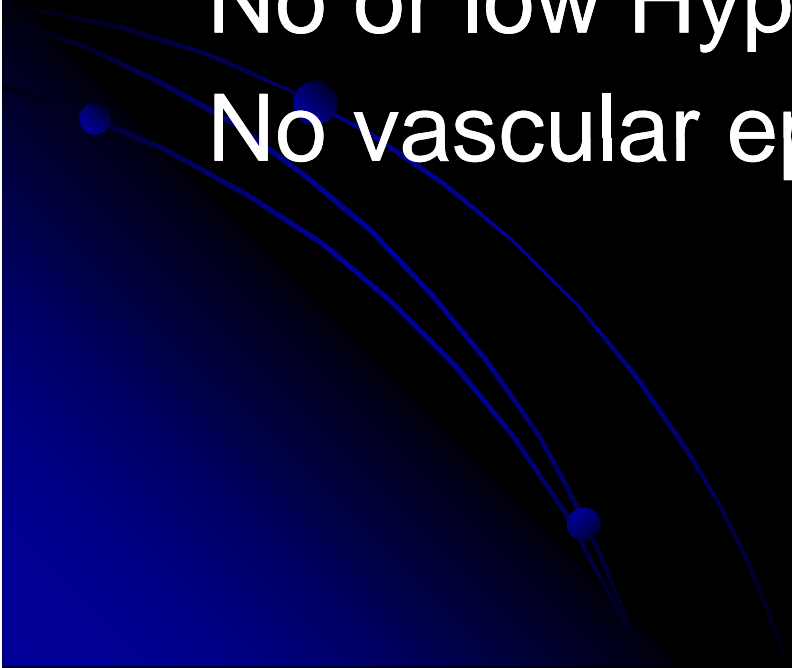
# Motesanib

- Small molecule inhibitor of VEGFRs, PDGFR and c-kit.
- Phase I AEs: hypertension, fatigue...
- MONET1: Phase III

Mot+CP with higher mortality so early closed.



# BIBF1120

- ORAL TRIPLE ANGIOKINASE INHIBITOR OF VEGFR, PDGFR AND FGF.
  - AEs from phase II:  
Nausea, diarrhea, vomiting, fatigue  
No or low Hypertension.  
No vascular episodes.
- 

# Frequent adverse events regardless of relationship

	CTCAE Grade 3 (%)		CTCAE Grade 4 (%)	
	150 mg bid	250 mg bid	150 mg bid	250 mg bid
Nausea	2.7	11.1	0	0
Vomiting	2.7	5.6	0	0
Diarrhoea	5.4	11.1	0	0
Fatigue	0	2.8	0	0
Abdominal pain	0	5.6	0	0
ALT increase	0	19.4	0	0
AST increase	0	2.8	0	0
<b>GI bleeding</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Haemoptysis</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>GI perforation</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Hypertension</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Dizziness	2.7	0	0	0

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## Selected grade $\geq 3$ AEs reported with Beva and other Antiangiogenic Agents for NSCLC

	GI perforations	Wound healing	Coagulation disorders	Hypertension	Proteinuria
BEVACIZUMAB	V	+	V	V	V
AFLIBERCEPT			V	V	V
SORAFENIB	+	+	V	V	-
SUNITINIB	+	+	V	V	+
BIBF1120	-	-	-	V	-
CEDIRANIB	-	-	V	V	-
PAZOPANIB	+	+	+	+	+



# Conclusioni

- Paziente oncologico: alto rischio di TEV
- Chemioterapia: fattore di rischio indipendente per TEV (8-17%)
- Antiangiogenetici: aumentano rischio di TEV dal 1% fino al 33%
- Bevacizumab: TEV tra gli Eventi Avversi Seri più frequenti e più gravi (più frequente causa di morte drug-related in SAIL).