

Rimini 13.11.2010

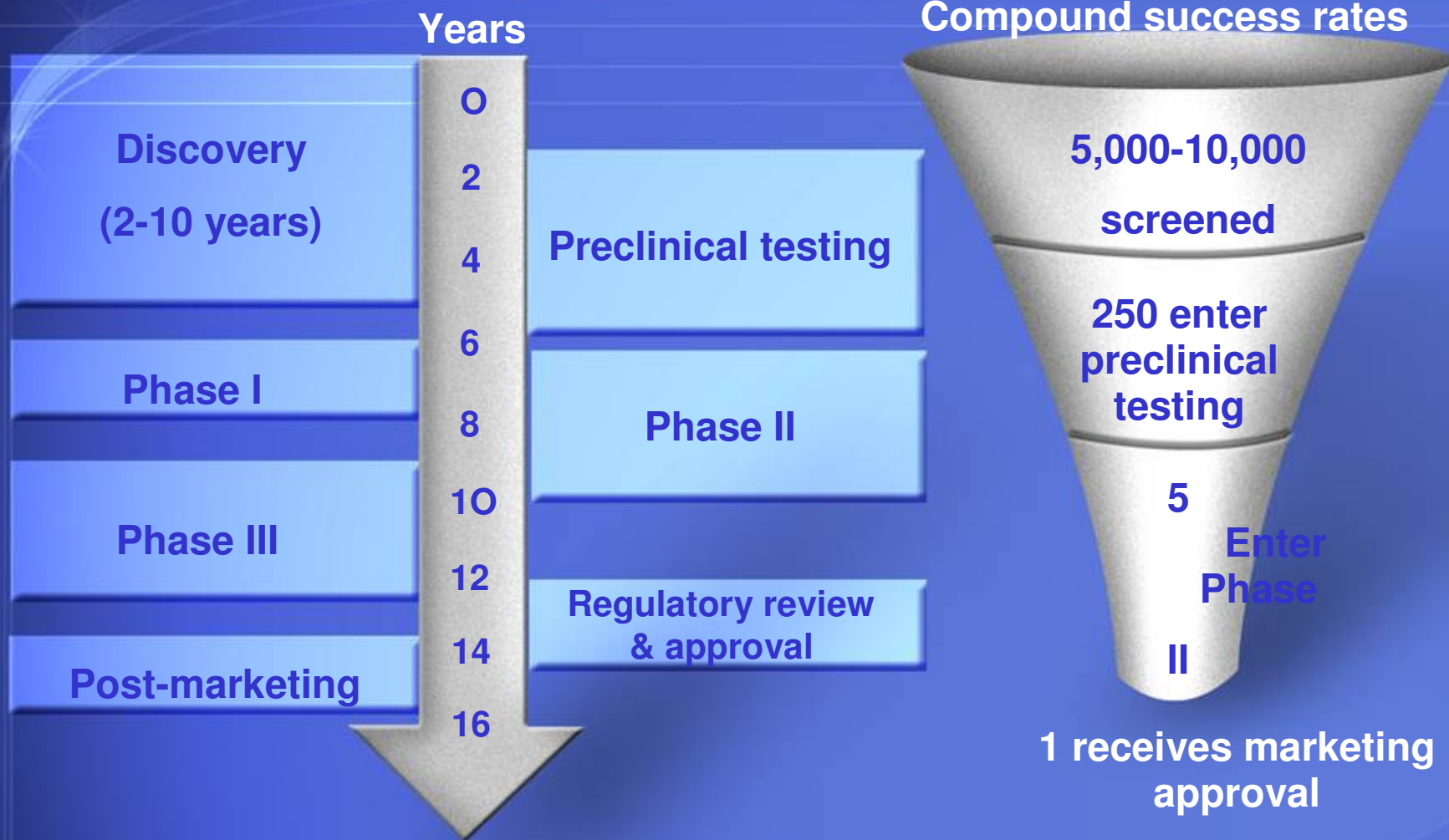
Targeted therapies e pratica  
clinica: analisi critica dei risultati.  
Sono tutti veri?

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# Drug development: Time and cost



**Patent expiry: 20 years**

**Total development cost: \$800 million**

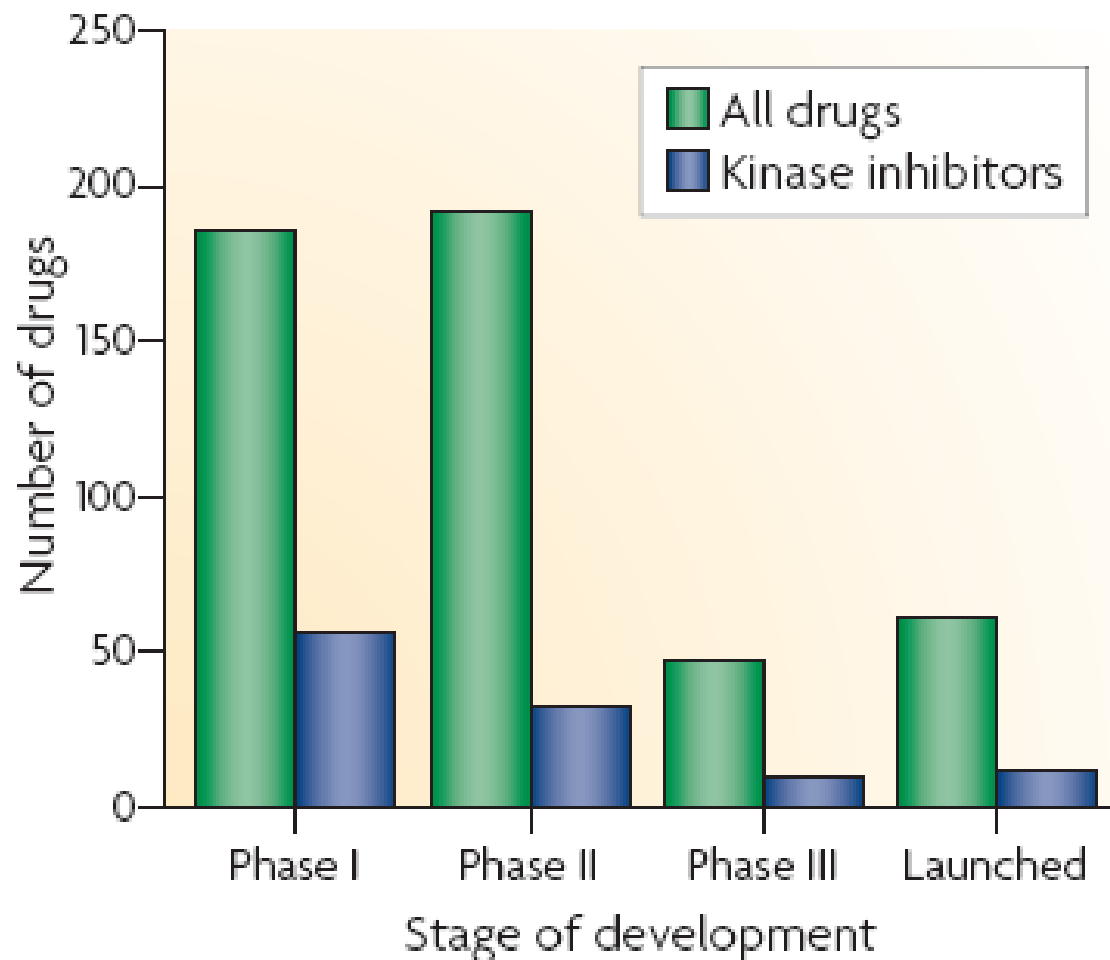
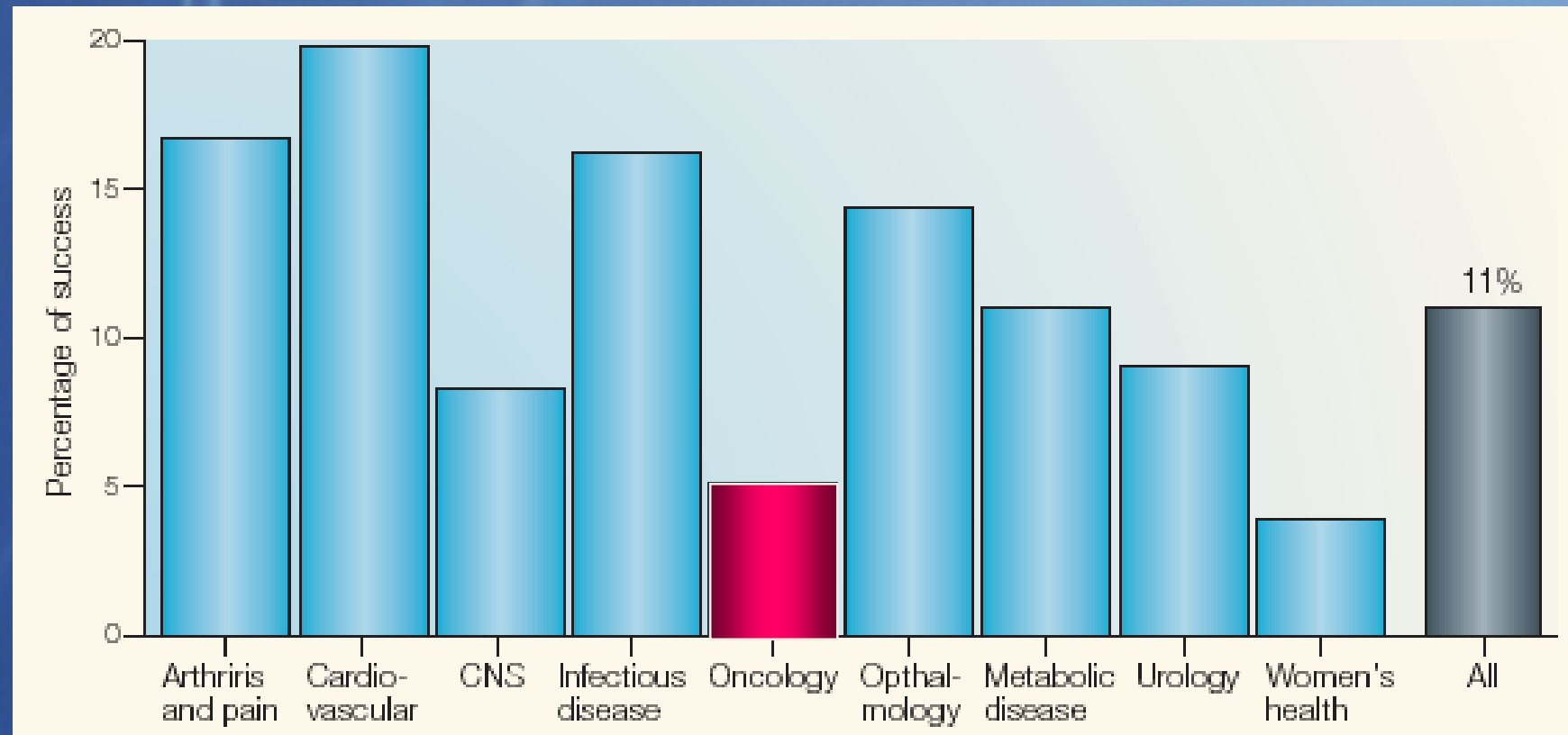


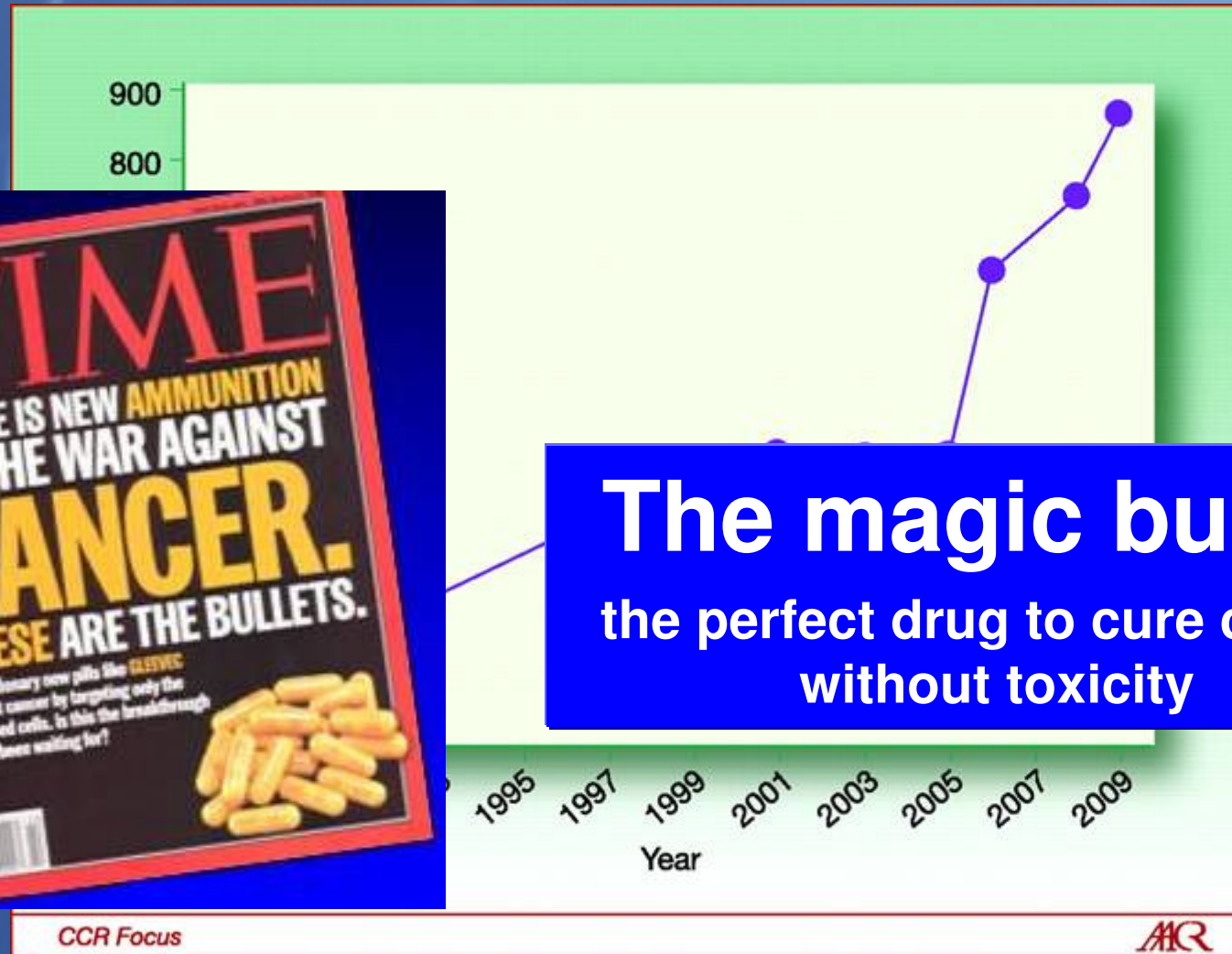
Figure 1 | **Number of agents in clinical development with oncology as the primary indication in the period 1995–2007.**

The blue bars represent the proportion of the clinical portfolio comprised of kinase inhibitors (see BOX 1 for origins of data set).

# Registration success rates from 1<sup>st</sup> phase 1 in man

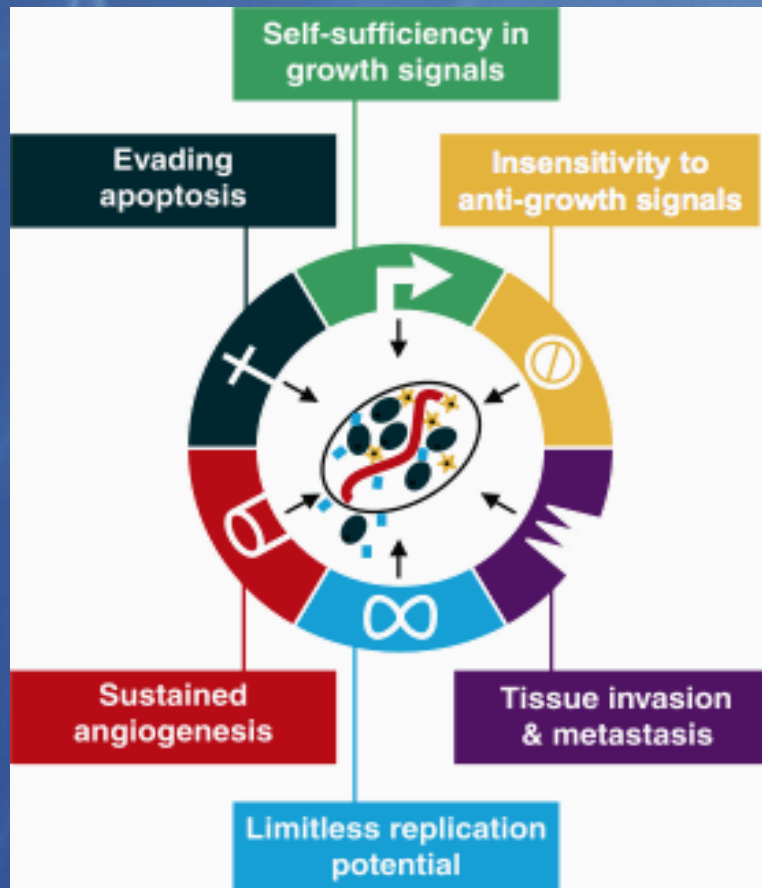


# 30 years of drug development



**The magic bullet**  
the perfect drug to cure cancer  
without toxicity

# Major Cancer gene mutations discovered since 2000



BRAF

IDH1 &  
IDH2

PIK3CA

FOXL1

JAK2

AKT1

WTX

ALK

EGFR

ERG

Hanahan et al. Cell, 2000



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# Targeted therapies: The myths

- Oncogene addiction
- Drug specificity

=

- Cure for patients
- No toxicity



# New Drugs: The Reality

Drug	Key targets for therapeutic activity	US FDA-approved indication
Imatinib	BCR-ABL, PDGFR and KIT	CML and GIST
Dasatinib	BCR-ABL	CML
Nilotinib	BCR-ABL	CML
Gefitinib	EGFR	Lung cancer
Erlotinib	EGFR	Lung and pancreatic cancers
Lapatinib	EGFR and ERBB2	Breast cancer
Sunitinib	VEGFR2, PDGFR and KIT	Kidney cancer and GIST
Sorafenib	VEGFR2 and PDGFR	Kidney and liver cancers
Pazopanib	VEGFR2, PDGFR and KIT	Kidney cancer
Everolimus	mTOR	Kidney cancer
<b>Antibody</b>		
Trastuzumab	ERBB2	Breast cancer
Cetuximab	EGFR	Colorectal, and head and neck c
Panitumumab	EGFR	Colorectal cancer
Bevacizumab	VEGF	Colorectal, lung and breast can

CML, chronic myeloid leukaemia; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumour; PDGFR, platelet-derived growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2.

tumore	farmaco	mesi in più	
		PFS	Survival
RCC	Sorafenib	2,7	NR
	Temsirolimus	2,4	3,6
	Sunitinib	6,0	NR
	Bevacizumab	4,8	NR
Breast	Trastuzumab	2,8	4,8
	Bevacizumab	5,9	1,5
	Lapatinib	1,9	NR
CRC	Bevacizumab	4,2	4,7
	Panitumumab	0,2	0
NSCLC	Erlotinib	0,4	2,0
	Bevacizumab	1,7	2,0
GIST	Sunitinib	4,8	NR
Pancreas	Erlotinib	0,3	0,5
HCC	Sorafenib	2,7	2,8
H&N	Cetuximab	9,5	19,7

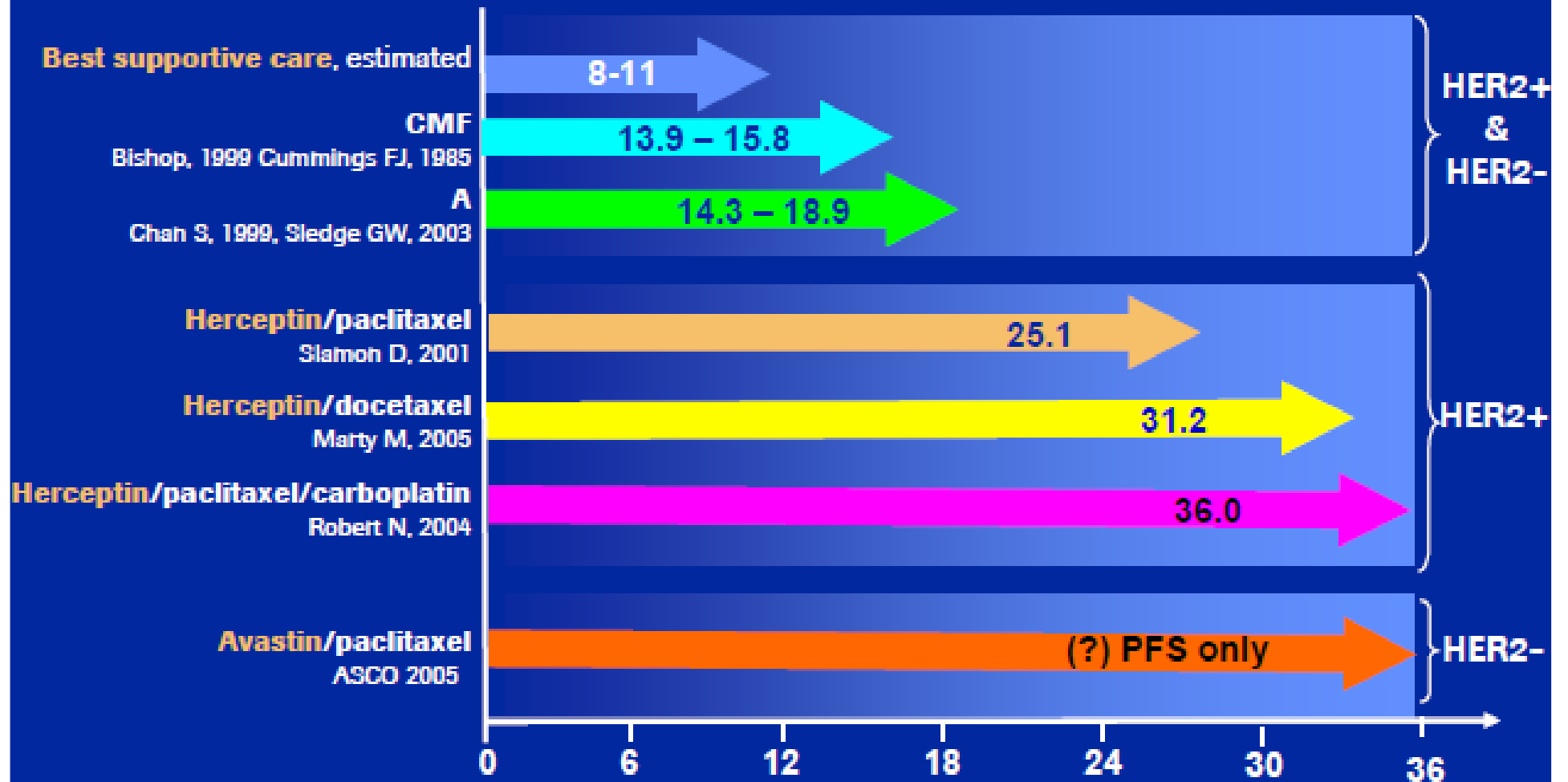
1a 2a/3a linea

Sobrero & Bruzzi JCO 2009

# Breast Cancer: Significant and clinically meaningful prolongation of life



*Median overall survival in 1<sup>st</sup> line mBC*

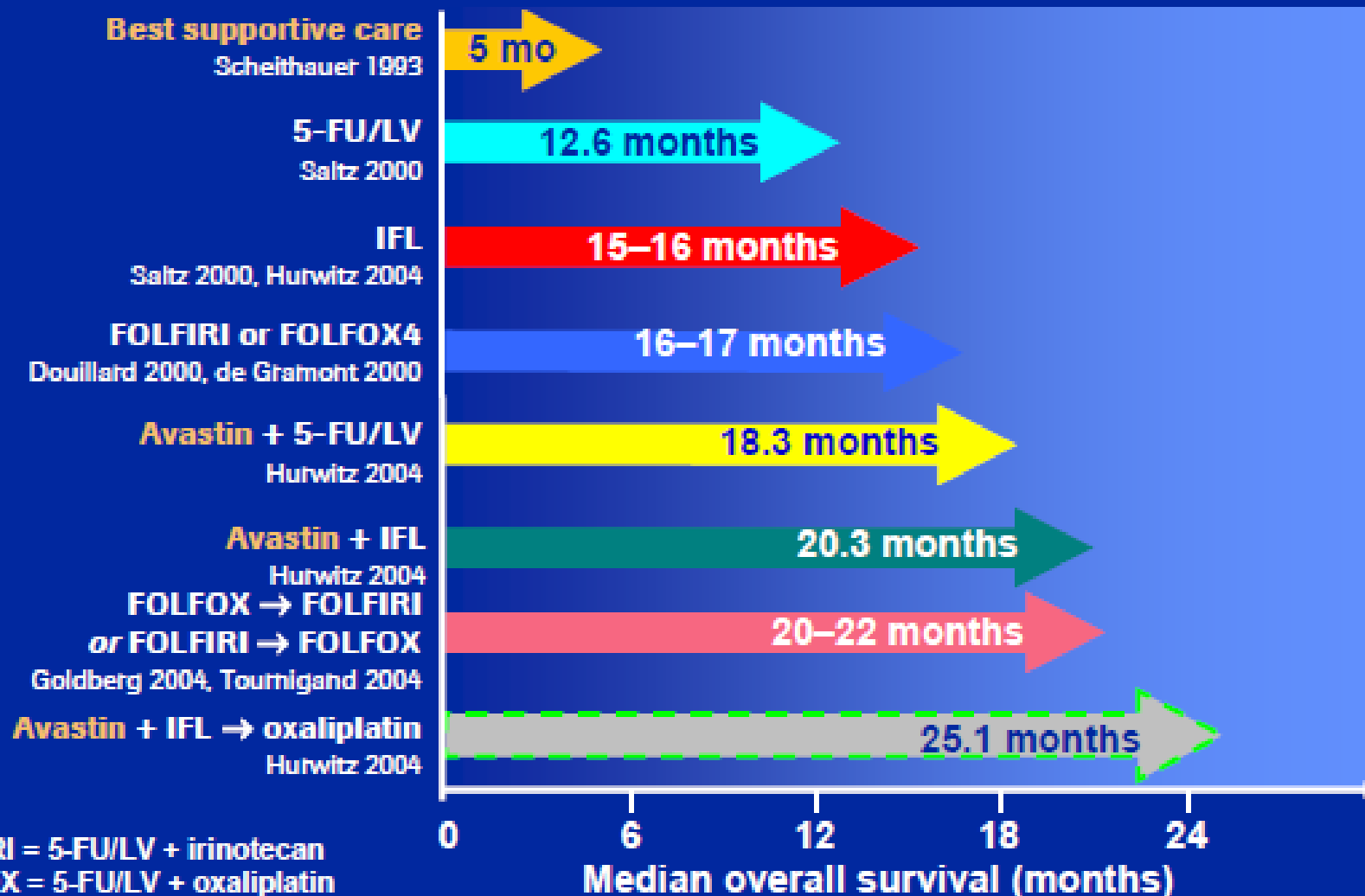


A = doxorubicin; C = cyclophosphamide;  
M = methotrexate; F = 5-fluorouracil

Median overall survival (months)

# Colon rectal cancer: Median Survival prolonged 5 times over the past decade

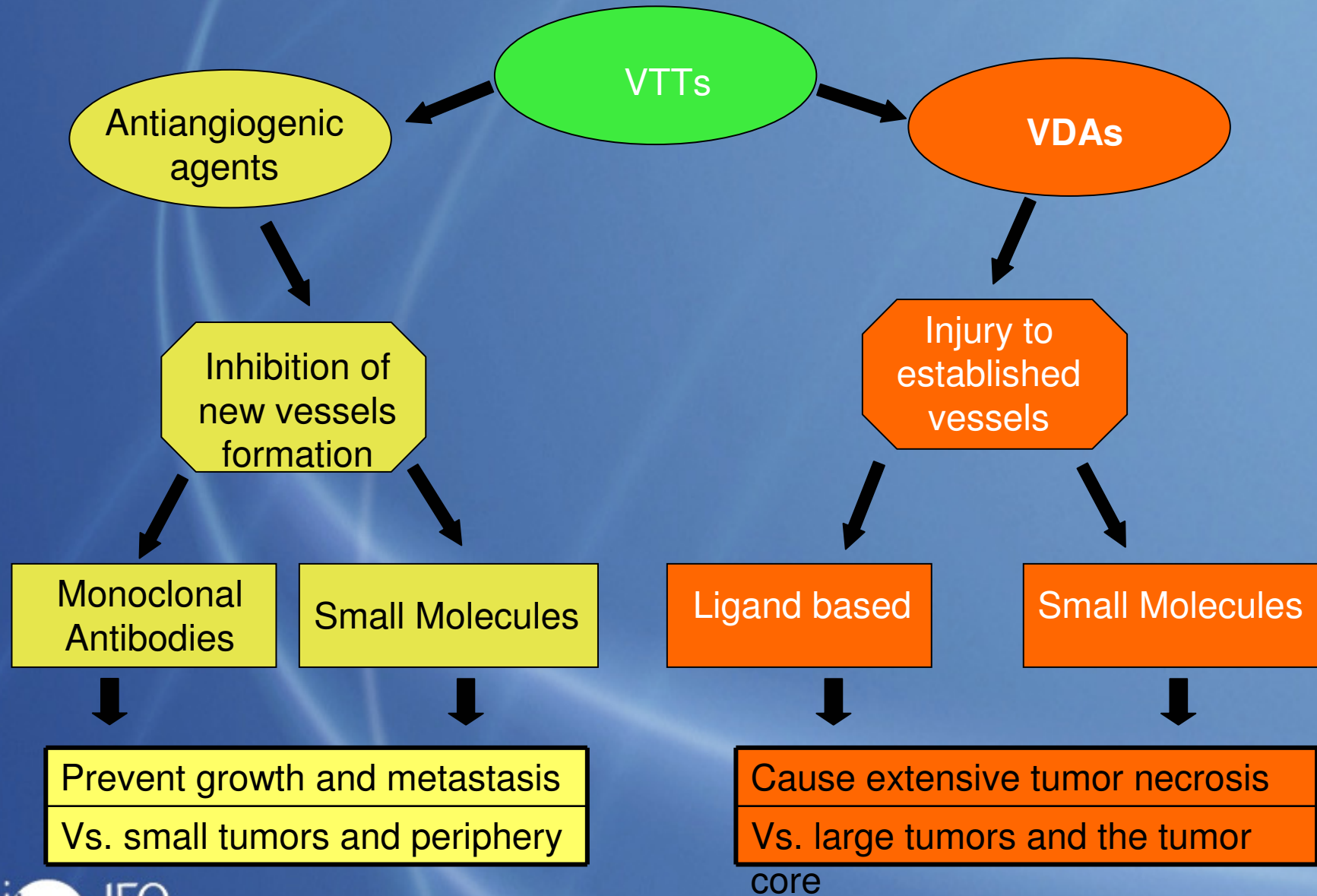
*Median overall survival in 1<sup>st</sup> line metastatic CRC*



# Toxicity

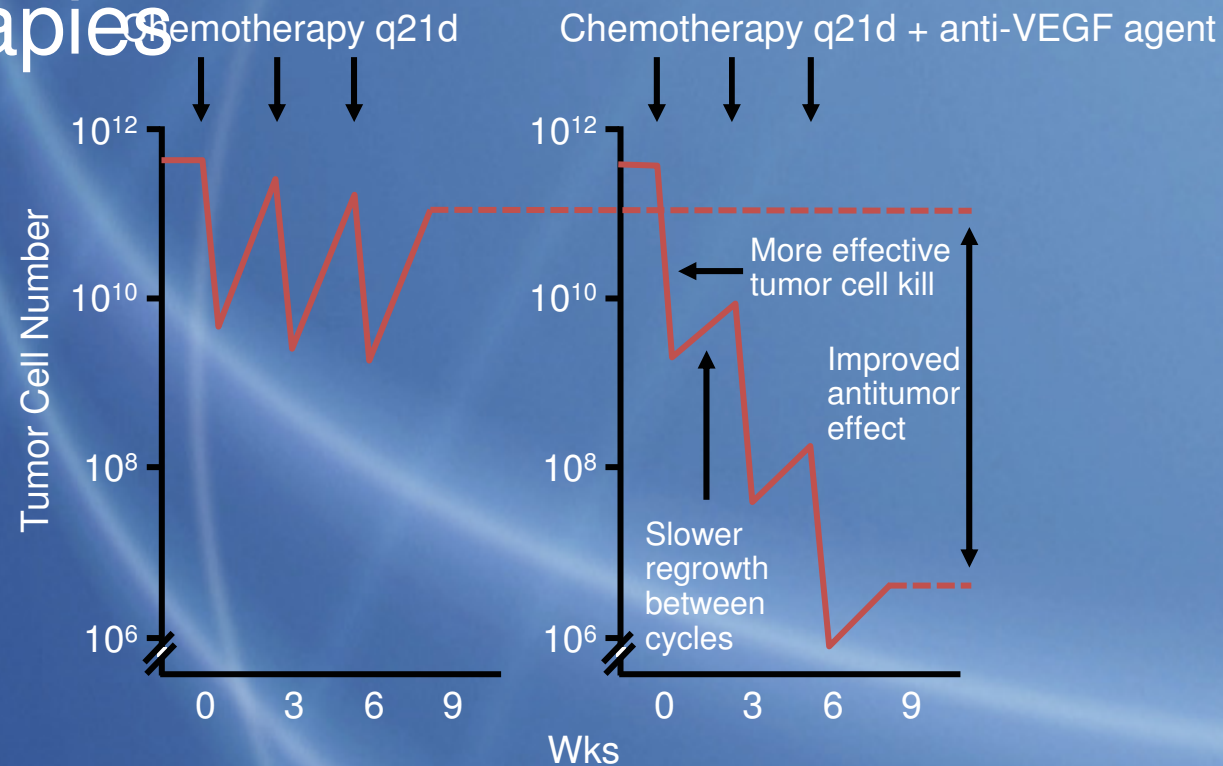
<i>Toxicity</i> %	<i>Bevacizumab</i>		<i>Cetuximab</i>		<i>Erlotinib</i>	<i>Sorafenib</i>		<i>Sunitinib</i>
	<i>Min</i>	<i>Max</i>	<i>Min</i>	<i>Max</i>	<i>Total</i>	<i>Min</i>	<i>Max</i>	<i>Total</i>
Diarrea	2	38	2	28	6	2	8	5
Acne/Rash	2	20	5	16	9	6	8	5
Astenia/Fatigue	5	12	5	33	19	3	5	4
Ipertensione	3	0		7		4	2	8
Nausea		1	4	24	3		1	3
Congiuntivite					1			
Tossicità cardiaca				7				
Sanguinamento	3	6		2			1	
Dolore addominale			4	13			2	

# Vascular targeted therapies (VTTs)



# How Does Bev Enhance Chemo Efficacy? Applying a Brake During the Break

- Clinical implications of antiangiogenic therapies



# Bevacizumab in clinical trials

**Metastatic  
colorectal  
cancer**

**Metastatic  
non-small cell  
lung cancer**

**Metastatic  
breast cancer**

**Metastatic  
renal cell  
carcinoma**

**Relapsed  
glioblastoma**

**Front-line  
ovarian  
cancer**

# Phase III Trials of Antiangiogenic Therapy Using Bevacizumab (With Chemotherapy)

Examples of Positive Randomized Phase III Trials of Antiangiogenic Therapy Using Bevacizumab (+ Chemotherapy)		
Trial	Therapy	Reference
First-line mCRC (AVF2192g)	Bevacizumab plus 5-FU/LV and irinotecan	Hurwitz H, et al. N Engl J Med. 2004;350:2335-2342.
Second-line mCRC (ECOG 3200)	Bevacizumab plus FOLFOX-4	Giantonio BJ, et al. J Clin Oncol. 2007;25:1539-1544.
Recurrent/advanced NSCLC (ECOG 4599)	Bevacizumab plus paclitaxel/carboplatin	Sandler A, et al. N Engl J Med. 2006;355:2542-2550.
First-line MBC (ECOG 2100)	Bevacizumab plus wkly paclitaxel	Miller K, et al. N Engl J Med. 2007;357:2666-2676.
First-line MBC (AVADO)	Bevacizumab plus q3w docetaxel	Miles DW, et al. SABCS 2009. Abstract 41.
First-line ovarian cancer (GOG0218)	Bevacizumab plus paclitaxel and carboplatin → bevacizumab maintenance	Burger R, et al. ASCO 2010. Abstract LBA1.
<b>And Some Failures</b>		
First-line pancreatic (CALGB 80303)	Bevacizumab plus wkly gemcitabine	Kindler HL, ASCO 2007. Abstract 4508.
Second-line MBC	Bevacizumab/capecitabine	Miller KD, et al. J Clin Oncol. 2005;23:792-799.
Adjuvant CRC (C08)	Bevacizumab/FOLFOX	Wolmark N, et al. ASCO 2009. Abstract LBA4.

# Bevacizumab in first-line mCRC

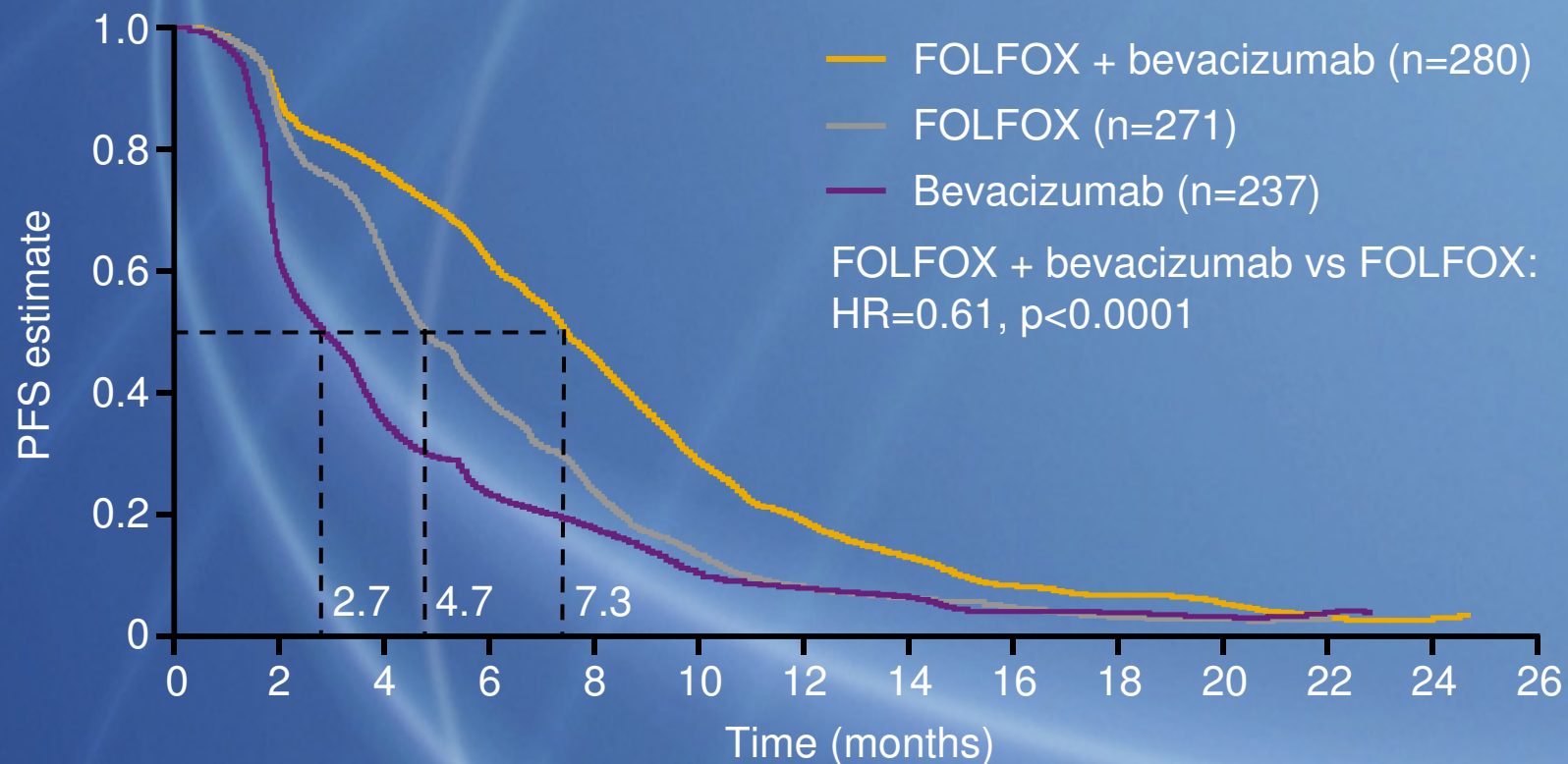
Regimen	Patients (n)	Response rate (%)	Median PFS (months)	Median OS (months)
IFL + placebo <sup>1</sup>	411	35	6.2	15.6
IFL + bevacizumab <sup>1</sup>	402	45	10.6*	20.3*
5-FU/LV + placebo <sup>2</sup>	105	15	5.5	12.9
5-FU/LV + bevacizumab <sup>2</sup>	104	26	9.2*	16.6
FOLFOX/CAPOX + placebo <sup>3</sup>	701	38	8.0	19.9
FOLFOX/CAPOX + bevacizumab <sup>3</sup>	699	38	9.4*	21.3
Capecitabine <sup>4</sup>	156	30	5.7	18.9
Capecitabine + bevacizumab <sup>4</sup>	157	38	8.9*	18.9
Cape/Mito + bevacizumab <sup>4</sup>	158	46*	8.4*	16.4

\*Statistically significant

- IFL is currently considered to be a suboptimal regimen,  
*does bevacizumab compensate for this?*
- With IFL ± Bev **77%** of pts received Bev until ≤4 weeks before PD or death versus **46%** of pts with FOLFOX/CAPOX+Bev <sup>1,2</sup>
- Early discontinuation of Bev, largely not related to Bev-specific toxicity, was **~3x greater** in FOLFOX/CAPOX+Bev compared to IFL ± Bev <sup>1,2</sup>

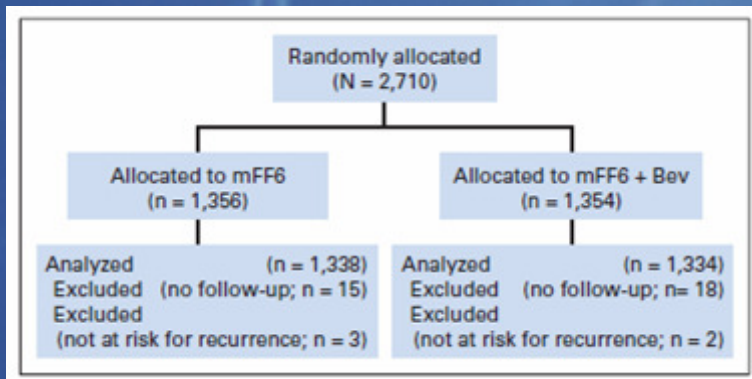
What is the optimal duration of bevacizumab treatment?

# Bevacizumab monotherapy in second-line mCRC: PFS

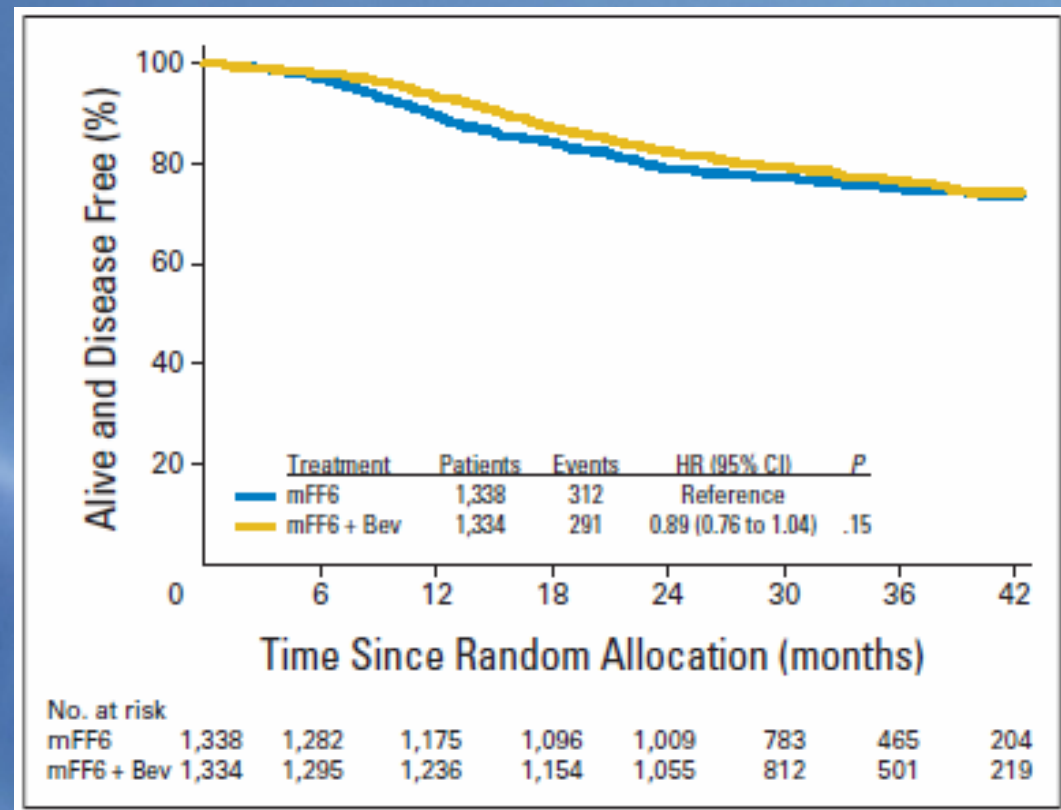


No previous use of OX or Bev allowed

# NSABP-C08 trial: Bev+mFOLFOX6 in stage II and III CRC



Allegra, JCO 2010, October 12

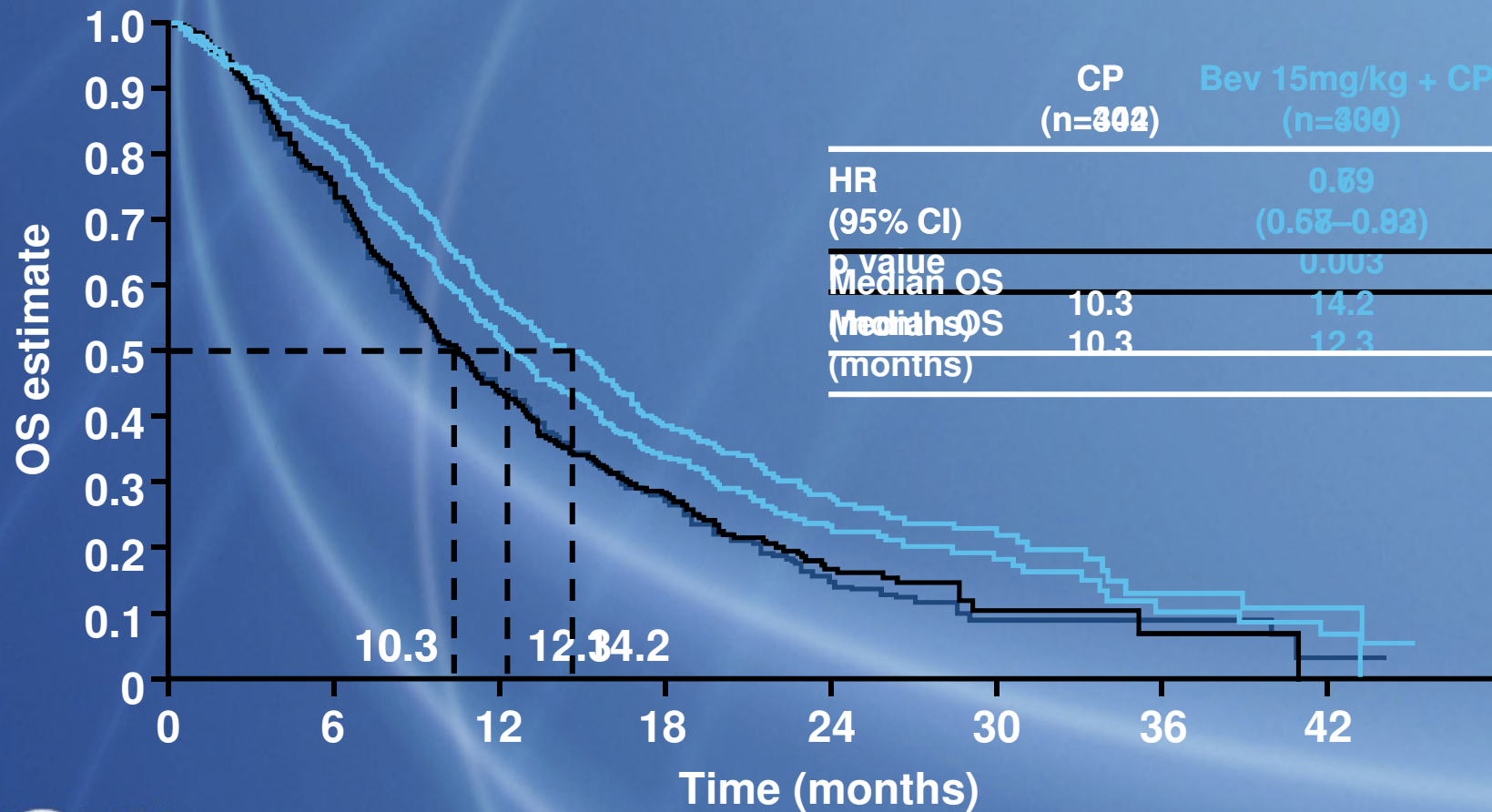


# Phase III trials in NSCLC: pooled data

Regimen	Patients (n)	Phase	RR %	Median PFS (MO)	OS (mo)
CBCDA, PTX + BEV	434	III	35	6.2	12.3
CBCDA, PTX	444		15	4.5	10.3
CDDP+GCB+BEV (7.5 mg/kg)	345	III	34	6.7	13.6
CDDP+GCB+BEV (15 mg/kg)	351		30	6.5	13.4
CDDP + GCB	347		20	6.1	13.1

# E4599: survival beyond historical benchmark of 12 months Benefit of 3.9 months OS in adenocarcinoma: preplanned subgroup analysis of E4599

E4599 overall patient population



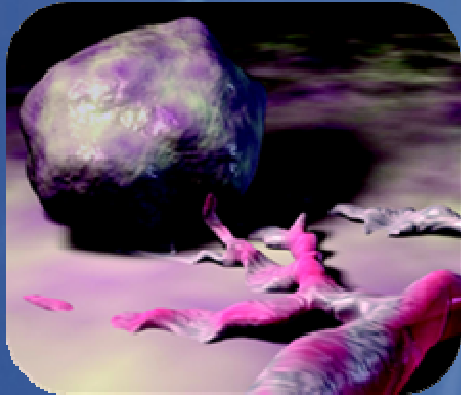
## Adenocarcinoma Subgroup Had Longer Exposure to Bevacizumab Than Other Histologies

	Adenocarcinoma Histology (n = 592)		NSCLC NOS Histology (n = 160)		Other Histologies <sup>a</sup> (n = 107)	
	PC (n = 298)	PCB (n = 294)	PC (n = 84)	PCB (n = 76)	PC (n = 55)	PCB (n = 52)
<b>Treatment cycles received, n</b>						
Mean (SE)	4.3 (0.1)	9.4 (0.4)	4.3 (0.2)	7.1 (0.7)	4.0 (0.3)	8.0 (1.0)
Median (range)	5.0 (1-6)	8.0 (1-47)	5.0 (1-6)	6.0 (1-30)	4.0 (1-6)	5.5 (1-32)
<b>Duration of study treatment, mo</b>						
Median (range)	2.8 (0.03-13.6)	4.9 (0.03-33.54)	3.0 (0.03-12.75)	3.6 (0.03-20.57)	2.2 (0.03-4.63)	3.5 (0.02-22.24)

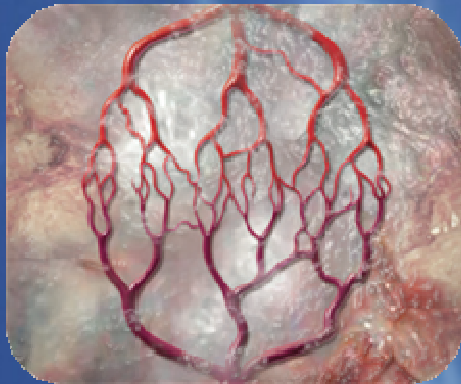
Exposure data were only available for 859 out of 878 patients.

<sup>a</sup> Other histologies: large-cell undifferentiated, bronchoalveolar, squamous, and "other."

# The mechanism of action of bevacizumab supports continuation of therapy



**Regression of tumour vasculature<sup>1,2</sup>**



**Normalisation of blood vessels<sup>2</sup>**

**Continue therapy**



**Reduces tumour mass**

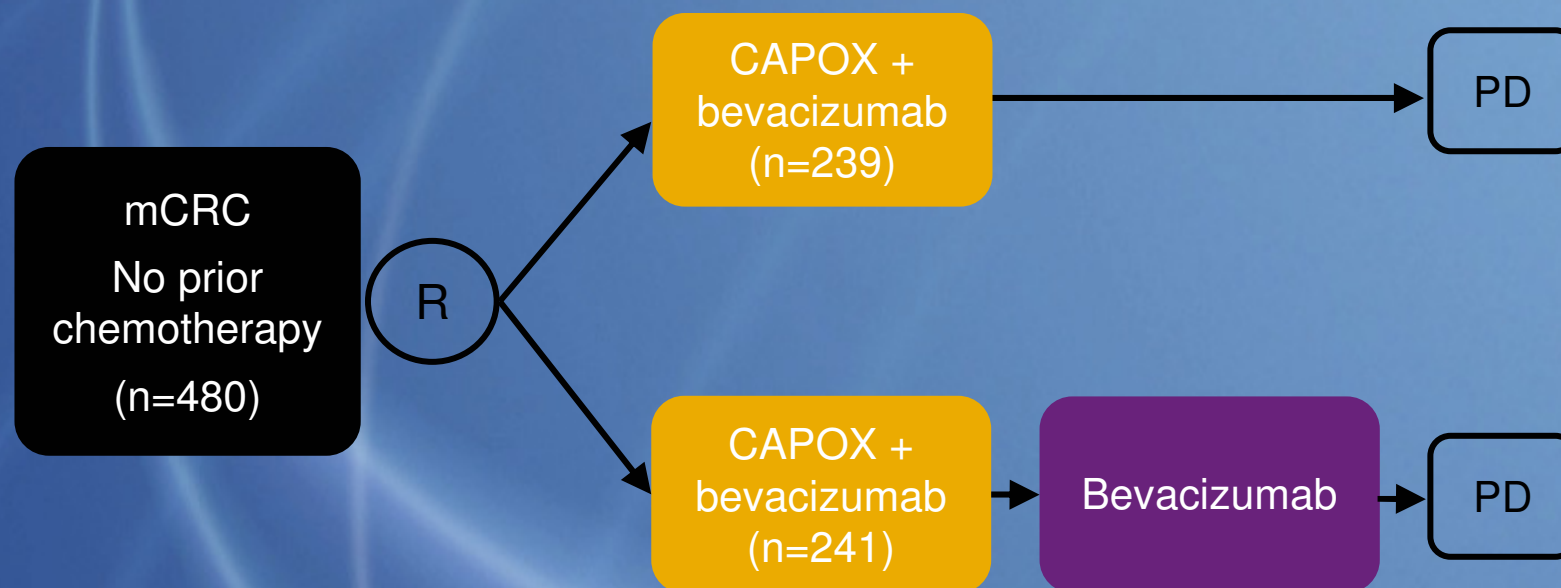
**Enhances activity of concomitant therapies**

**Potential effect on micrometastases**



**Continued inhibition of angiogenesis<sup>1</sup>**

# Maintenance therapy in mCRC: phase III MACRO study – design



Primary endpoint: median PFS

Non-inferiority design: control arm limit of PFS 10 months and HR=1.32

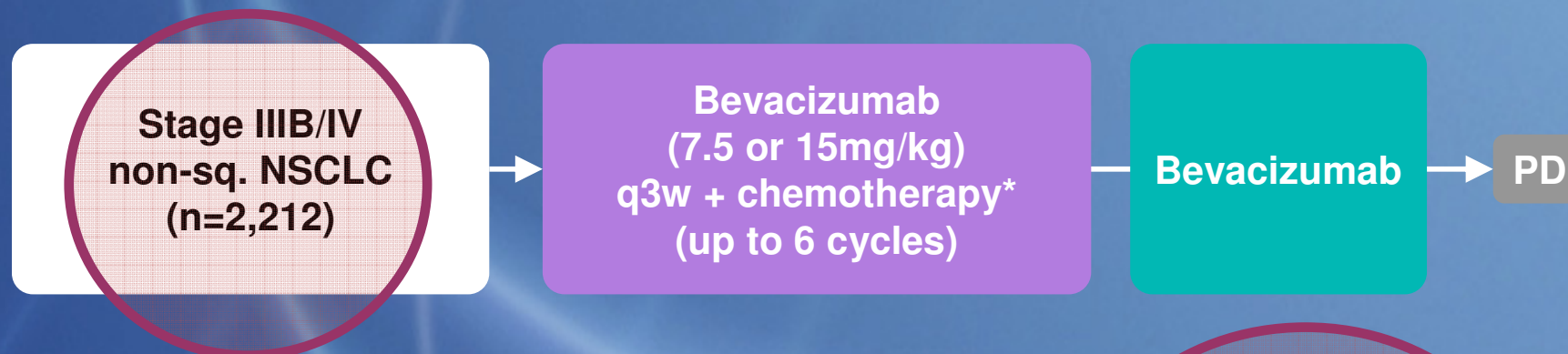
# Maintenance therapy in mCRC: phase III MACRO study – results

	CAPOX + bev X 6 → CAPOX + bev (n=239)	CAPOX + bev X 6 → bevacizumab (n=241)
Median PFS (months)	10.4	9.7 HR=1.11
Median OS (months)	23.4	21.7 HR=1.04
Number of treatment cycles, median (range)		
Total	9 (1–37)	10 (1–53)
Induction phase	6 (1–6)	6 (1–6)
Maintenance phase	3 (0–31)	4 (0–47)
Median cumulative dose oxaliplatin (mg/m <sup>2</sup> )	893	646
Salvage surgery (%)	11.7	9.5
R0 surgery (%)	8.8	5.8

# SAiL: Bevacizumab in clinical practice



SAiL: Safety of Avastin in Lung (MO19390)



**Primary endpoint: safety**

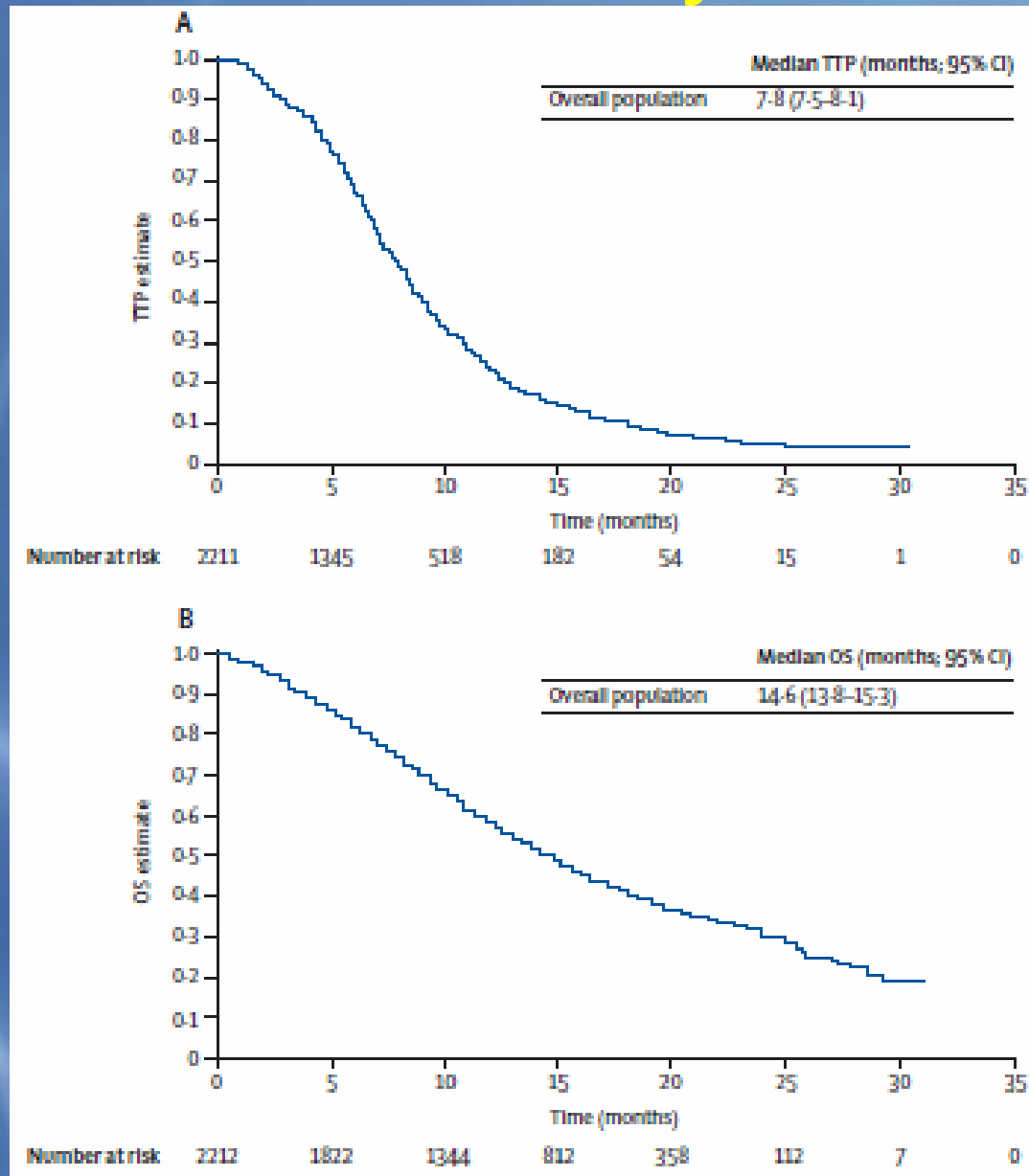
\*Any standard-of-care first-line NSCLC chemotherapy

**86% of the population had adenocarcinoma histology**

# SAiL: confirmed activity of bev

One patient was reported to have had disease progression before first treatment and was therefore not included in the TTP analysis

Disease control rate was 88.7% based on 92.0% of patients with tumour assessment (n=2,036)<sup>1</sup>



# SAiL: favourable safety profile of bevacizumab confirmed

AEs of special interest (%)	n=2,212
Bleeding (all types)	
Grade 3	2.5
Grade 4	0.4
Grade 5	0.8
Pulmonary haemorrhage/haemoptysis	
Grade 3	0.2
Grade 4	0.1
Grade 5	0.4
Hypertension	
Grade 3	5.4
Grade 4	0.3
Proteinuria	
Grade 3	2.5
Grade 4	0.5
Thromboembolism	
Grade 3	4.7
Grade 4	2.4
Grade 5	1.2

Note: Grade 5 events are only included for AE categories that included Grade 5 events



# Summary of Anti-angiogenics in mBC

## Bevacizumab

(1 <sup>st</sup> line) with paclitaxel	POSITIVE phase III (722 pt) <sup>1</sup> Bevacizumab + paclitaxel vs paclitaxel ALONE PFS 11.3 vs. 5.8 months; P<0.0001, OS ns E2100
(1 <sup>st</sup> line) with docetaxel	POSITIVE phase III (736 pt for 3 arms) <sup>2</sup> Bevacizumab + docetaxel vs docetaxel + placebo PFS 10.0vs 8.1 months; P<0.001, OS ns AVADO
(1 <sup>st</sup> line) with taxanes or capecitabine	POSITIVE phase III (1,237 pt) <sup>3</sup> PFS 5.7 vs. 8.6 months for capecitabine (615 pt), 8.0 vs 9.2 for taxane (622 pt) RIBBON-1
(2 <sup>nd</sup> line) with others: gemcitabine, vinorelbine	POSITIVE phase II trial (684 pt) <sup>4</sup> CT vs CT plus bevacizumab PFS 5.1 vs 7.2 months RIBBON-2
(3 <sup>rd</sup> line) with capecitabine nothing approved as a partner at present	NEGATIVE phase III (462 pt) <sup>5</sup> Bevacizumab + capecitabine vs capecitabine ALONE: better RR (19.8% vs 9.1%; P=0.001); PFS 4.86 vs 4.17 months

1. Gray, et al. JCO 2009; 2. Miles, et al. JCO 2010; 3. Robert, et al. ASCO 2009; 4. Brufsky, et al. SABCS 2009; 5. Miller, et al. JCO 2005

# Targeted Therapies: more is less?

## The CAIRO-2 experience

Regimen	Patients (n)	Phase	RR %	Median PFS (mo)	OS (mo)
CAPOX + BEV	368	III	50	10.7*	20.3
CAPOX + BEV + CET	368		52.7	9.4	19.4

\*Statistically significant

# Contradictory results: NORDIC VII trial in mCRC

Regimen	Pts	Phase	mPFS
FLOX	185	III	7.9
FLOX + Cetuximab	194		8.3
Intermittent FLOX + continuous Cetuximab	187		7.3

Primary Objective: PFS



Regimen	KRAS	Pts	mPFS (mo)
FLOX	wt	97	8.7
	mut	58	7.8
FLOX + Cetuximab	wt	97	7.9
	mut	72	9.2*

Confirmed the negative prognostic value of **BRAF mutation**

# Conclusion

- Despite great expectations, targeted therapies (TT) presented high attrition rates with important toxic profile
- However TT improved the prognosis of some tumors, especially when used in specific settings
- So far, several issues remain clarify, all turning around the major questions: What? Why?

