SEPTEMBER 28, 2012 | 09:00-11.00 | VIENNA, AUSTRIA

SANOFI
REGENERON

CHOOSING AN OPTIMAL FIT

exploring

TREATMENTS FOR THE PATIENT WITH METASTATIC COLORECTAL CANCER

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WELCOME & INTRODUCTION

David Cunningham, MD, FRCP FMedSci
Consultant Medical Oncologist and
Head of the Gastrointestinal Unit
Royal Marsden NHS Foundation Trust
Sutton, UK

AGENDA

09:00-09:05
Welcome and Introduction
David Cunningham

09:05-09:30
Exploring the Latest Advances for Metastatic CRC
Dirk Arnold

09:30-09:45
Clinical Case and Panel Discussion
Marc Peeters

09:45-10:10
What to Expect: Managing Adverse Effects of Treatments for Metastatic CRC
David Ferry

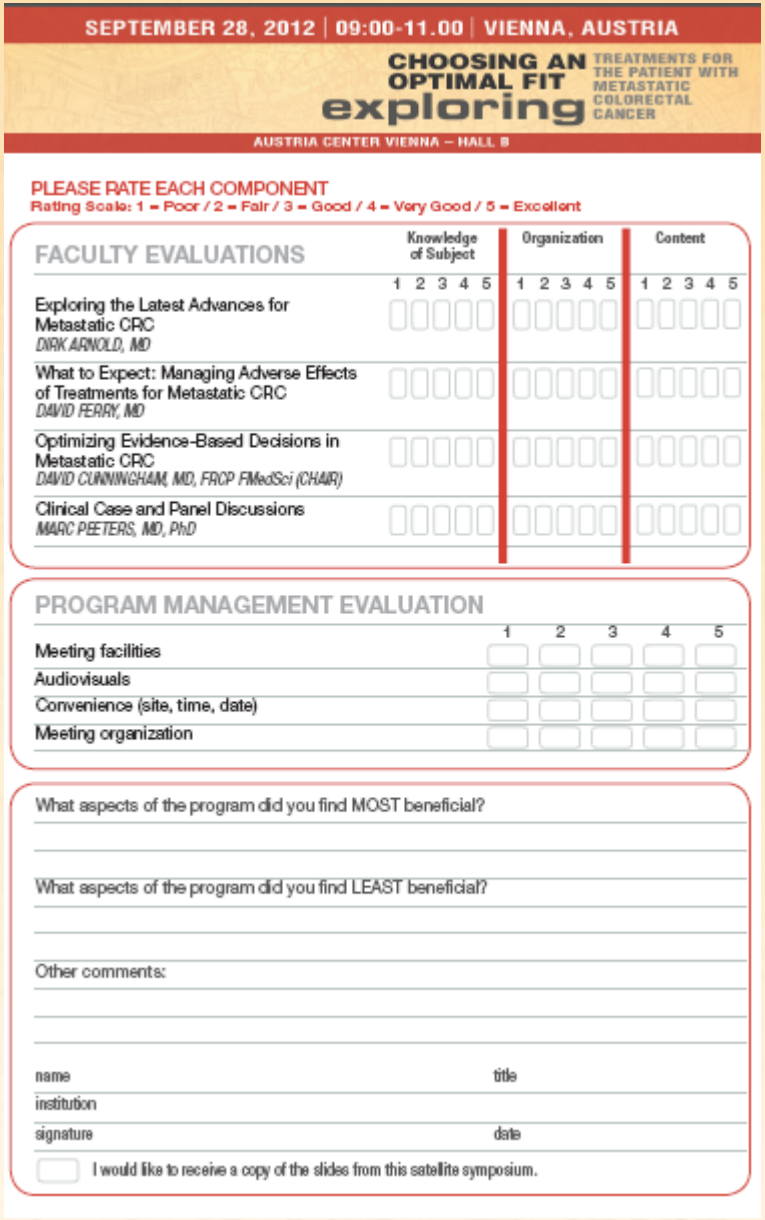
10:10-10:25
Clinical Case and Panel Discussion
Marc Peeters

10:25-10:45
Optimizing Evidence-Based Decisions in Metastatic CRC
David Cunningham

10:45-11:00
Clinical Case and Panel Discussion
Marc Peeters

11:00
Closing Remarks
David Cunningham

Please complete your evaluation form and return at the end of the program for a copy of the slides



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AUSTRIA CENTER VIENNA – HALL B

PLEASE RATE EACH COMPONENT

Rating Scale: 1 = Poor / 2 = Fair / 3 = Good / 4 = Very Good / 5 = Excellent

FACULTY EVALUATIONS

	Knowledge of Subject	Organization	Content
	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Exploring the Latest Advances for Metastatic CRC *DIRK ARNOLD, MD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
What to Expect: Managing Adverse Effects of Treatments for Metastatic CRC *DAVID FERRY, MD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Optimizing Evidence-Based Decisions in Metastatic CRC *DAVID CUNNINGHAM, MD, FRCP FMedSci (CHAIR)*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Clinical Case and Panel Discussions *MARC PEETERS, MD, PhD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

PROGRAM MANAGEMENT EVALUATION

	1	2	3	4	5
Meeting facilities	☐	☐	☐	☐	☐
Audiovisuals	☐	☐	☐	☐	☐
Convenience (site, time, date)	☐	☐	☐	☐	☐
Meeting organization	☐	☐	☐	☐	☐

What aspects of the program did you find MOST beneficial?

What aspects of the program did you find LEAST beneficial?

Other comments:

name title

institution

signature date

☐ I would like to receive a copy of the slides from this satellite symposium.

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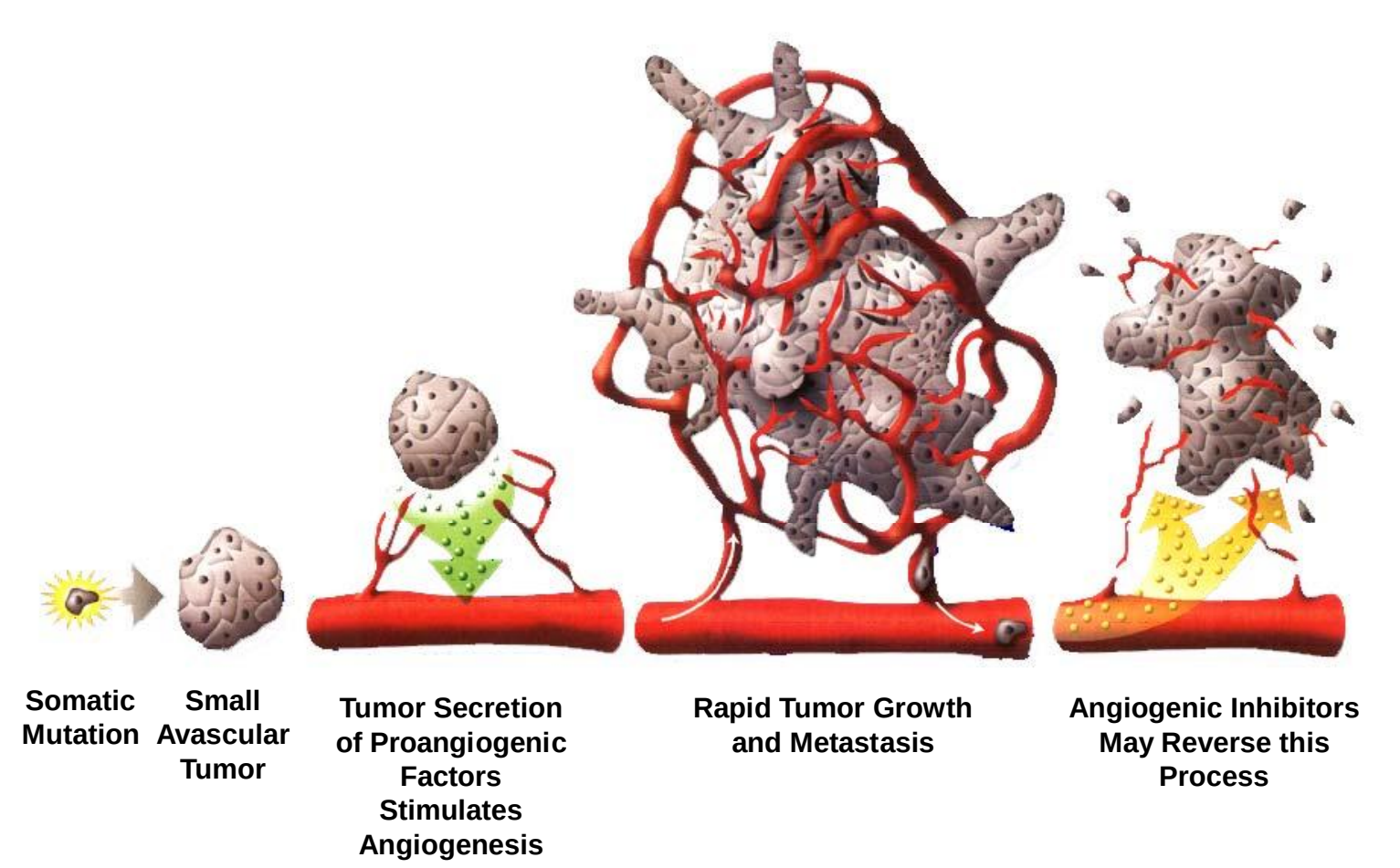
EXPLORING THE LATEST ADVANCES FOR METASTATIC CRC

Dirk Arnold, MD
Medical Director, Hubertus Wald Tumor Center
University Cancer Center Hamburg, Germany

The Angiogenic Switch and Anti-angiogenic Therapy: 1971



"All the News That's Fit to Print"

The New York Times

Late Edition
New York: **Today**, Variable clouds and sun, a late shower. High 74. **Tonight**, clouds, fog. Low 58. **Tomorrow**, cloudy, late rain. High 70. **Yesterday**, high 68, low 55. Details, page 51.

VOL. CXLVII . . . No. 51,146 NEW YORK, SUNDAY, MAY 3, 1998 $3 beyond the greater New York metropolitan area. $2.50

A Cautious Awe Greets Drugs That Eradicate Tumors in Mice

By GINA KOLATA

HOPE IN THE LAB
A special report.

Within a year, if all goes well, the first cancer patient will be injected with two new drugs that can eradicate any type of cancer, with no obvious side effects and no drug resistance — in mice.

Some cancer researchers say the drugs are the most exciting treatment that they have ever seen. But then they temper their enthusiasm with caution, noting that the history of cancer treatments is full of high expectations followed by dashed hopes when drugs with remarkable effects in animals are tested in people.

Still, the National Cancer Institute has made the drugs its top priority, said Dr. Richard D. Klausner, the director. Dr. Klausner called them "the single most exciting thing on the horizon" for the treatment of cancer.

"I am putting nothing on higher priority than getting this into clinical trials," Dr. Klausner said. The mouse studies are "remarkable and wonderful," he said, and "very compelling." But he pointed out that the studies were in mice and so, when it comes to humans, he said he wanted to emphasize "the if's."

The new drugs, angiostatin and endostatin, work by interfering with the blood supply tumors

cancer researcher at the Harvard Medical School, was wary. "We are all driven by hope," Dr. Groopman said. "But a sober scientist waits for the data." And until the drugs are given to humans, he said, the crucial data simply do not exist.

So far, the drugs are the only ones ever tested that can seemingly eradicate all tumors in mice, even gigantic ones, equivalent to a two-pound growth in a person. The best that other cancer drugs have done is slow the growth of these large tumors. Mice are the traditional test animals in cancer research.

But even the drugs' discoverer, Dr. Judah Folkman, a cancer researcher at Children's Hospital in Boston, is cautious about the drugs' promise. Until patients take them, he said, it is dangerous to make predictions. All he knows, Dr. Folkman said, is that "if you have cancer and you are a mouse, we can take good care of you."

Other scientists are not so restrained. "Judah is going to cure cancer in two years," said Dr. James D. Watson, a Nobel laure-

2 Drugs Eradicate Tumors in Mice

Continued From Page 1

efforts came a decade ago when Dr. Folkman and his collaborators found drugs that did what he envisioned. He called them anti-angiogenesis drugs because they stopped the process of developing new blood vessels, or angiogenesis. They slow tumor growth in animals but do not eradicate the tumors. Early results in patients indicate that the drugs may slow human cancers. Dozens of companies are developing such drugs.

The results with these weaker drugs were "a proof of principle," said Dr. Bart Chernow, a professor of medicine and dean for research and technology at the Johns Hopkins University School of Medicine. Dr. Chernow is a founder of Entremed, a company in Rockville, Md., that was formed to make and market angiostatin, endostatin and other weaker drugs that can slow cancer growth.

But the real breakthrough — and the two new drugs — came from Dr. Folkman's efforts to understand a peculiar phenomenon that has been known to cancer surgeons for 100 years: sometimes a patient will have a single tumor, with no evidence whatsoever of metastases, the satellite cancers that can pepper a patient's body. A doctor will remove the tumor and all will seem fine. But then, a few months later, a whole series of metastases will appear, grow, and kill the patient.

In 1989, Dr. Folkman proposed a reason for the effect, which he wrote on a large white board in a room where his laboratory group had its weekly seminars. Is it possible, he asked, that a tumor could be making both stimulators and inhibitors of blood vessel growth? If so, the inhibitors might travel through the bloodstream, squelching metastases. When the large tumor was removed, it would no longer be a source of inhibitors, allowing the tiny metastases to proliferate.

Dr. Folkman tried to get one of his doctoral or post-doctoral students to work on that idea. "Each Friday, at our meeting," he said "I would say, 'Here's a great experiment.' But no one wanted to work on it." It seemed too wild, Dr. Folkman said, too unlikely to result in findings that would end up in a scientific journal, a major

Children's World

Dr. Judah Folkman is cautious about his cancer-drug discovery.

focused on a particularly deadly mouse cancer that grows to the equivalent of a two-pound tumor in a person.

As long as mice had the large tumor, they had no signs of metastases. But five days after the tumors were surgically removed, metastases invariably sprang up in the animals' lungs. Within 15 days, the animals would be dead, their lungs packed with large red tumors, like grapes.

Eventually, after arduous work in collaboration with chemists, Dr. O'Reilly discovered that the large tumors made a substance that stymied the growth of other tumors. This substance showed up in the animals' urine, but was present in such minute quantities that Dr. O'Reilly had to collect 10 quarts of mouse urine to obtain 30-thousandth of an ounce of the mysterious substance. It turned out to be a piece of a larger and very common protein, plasminogen, that the body uses in blood clotting. Dr. Folkman named the new substance angiostatin.

Apparently, cells can use the plasminogen gene for two purposes: they can use it at its full length to make plasminogen, or they can use just a piece of it and make angiostatin. Plasminogen does nothing to stop

They had 20 mice with large tumors on their backs. The investigators removed the tumors and then injected half of the mice with angiostatin each day and the others with salt water, as a comparison.

After 15 days, the researchers killed the mice and cut them open. As more than a dozen scientists gathered around a table in the laboratory, Dr. O'Reilly opened the first mouse. It had huge tumors filling its lungs. Then Dr. Folkman checked a notebook to see what the animal had received: salt water. They looked at the next mouse. No tumors. Dr. Folkman checked to see the treatment: angiostatin. And so it went. All 10 of the mice that had been injected with angiostatin were free of cancer. All 10 of those that had been received salt water had huge new tumors.

A Jubilant Celebration And a Second Discovery

The room was buzzing, the scientists were grinning. Dr. Folkman said. Everyone in the room knew what the results meant, and they were elated. They responded, he said, like men at a football game. "Everyone clapped O'Reilly on the back," Dr. Folkman said.

Then the researchers found a second protein fragment, secreted by tumors, that also squelches metastases, Dr. Folkman said. It was a piece of a different protein, collagen 18, that is in all blood vessels but by itself has no effect on cancer. They named the collagen fragment endostatin.

"It was even more potent than angiostatin," Dr. Folkman said. If he gave it to a mouse with a huge tumor, he said, the equivalent of one weighing a pound and a half in a human, endostatin would shrink the cancer down to a microscopic size.

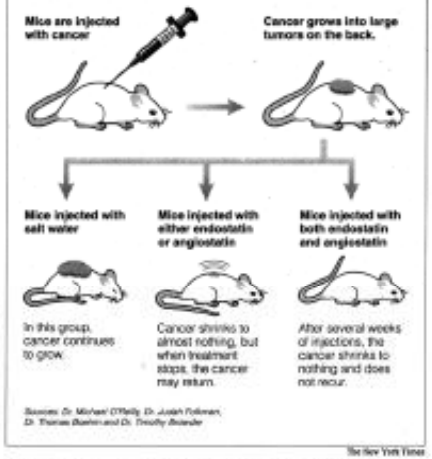
Moreover, tumors never became resistant to endostatin, said Dr. Folkman, who added that he had given the drug to mice with large tumors and they had shrunk to almost nothing. He stopped the drug, he said, and the tumors grew back. Then he gave the drug continuously for the rest of the animals' lives. The tumors remained small and harmless and the animals remained healthy.

Dr. Robert S. Kerbel, a cancer

IN THE WORKS

Hope for a Breakthrough

Drugs called angiostatin and endostatin occur naturally in small quantities in the human body and work by interfering with the blood vessels that tumors need to survive and grow. When tested together in mice, the drugs made tumors disappear and not return.



Sources: Dr. Michael O'Reilly, Dr. Judah Folkman, Dr. Yihai Cao and Dr. Timothy Boehm

The New York Times

spin off mutant cells that resist the drugs and, ultimately, the tumors grow back, irrulnerable.

But, Dr. Kerbel said, angiostatin and endostatin do not act on tumors. Instead, they act on normal blood vessels that feed tumors. And normal cells, he said, do not reshuffle their genes and so do not develop drug resistance. That is why chemotherapy drugs continue to devastate normal cells — causing bone marrow suppression, loss of hair, nausea and vomiting — even when the cancer cells have grown impervious to their effects, Dr. Kerbel said.

Drug Combination Knocks Out Tumors

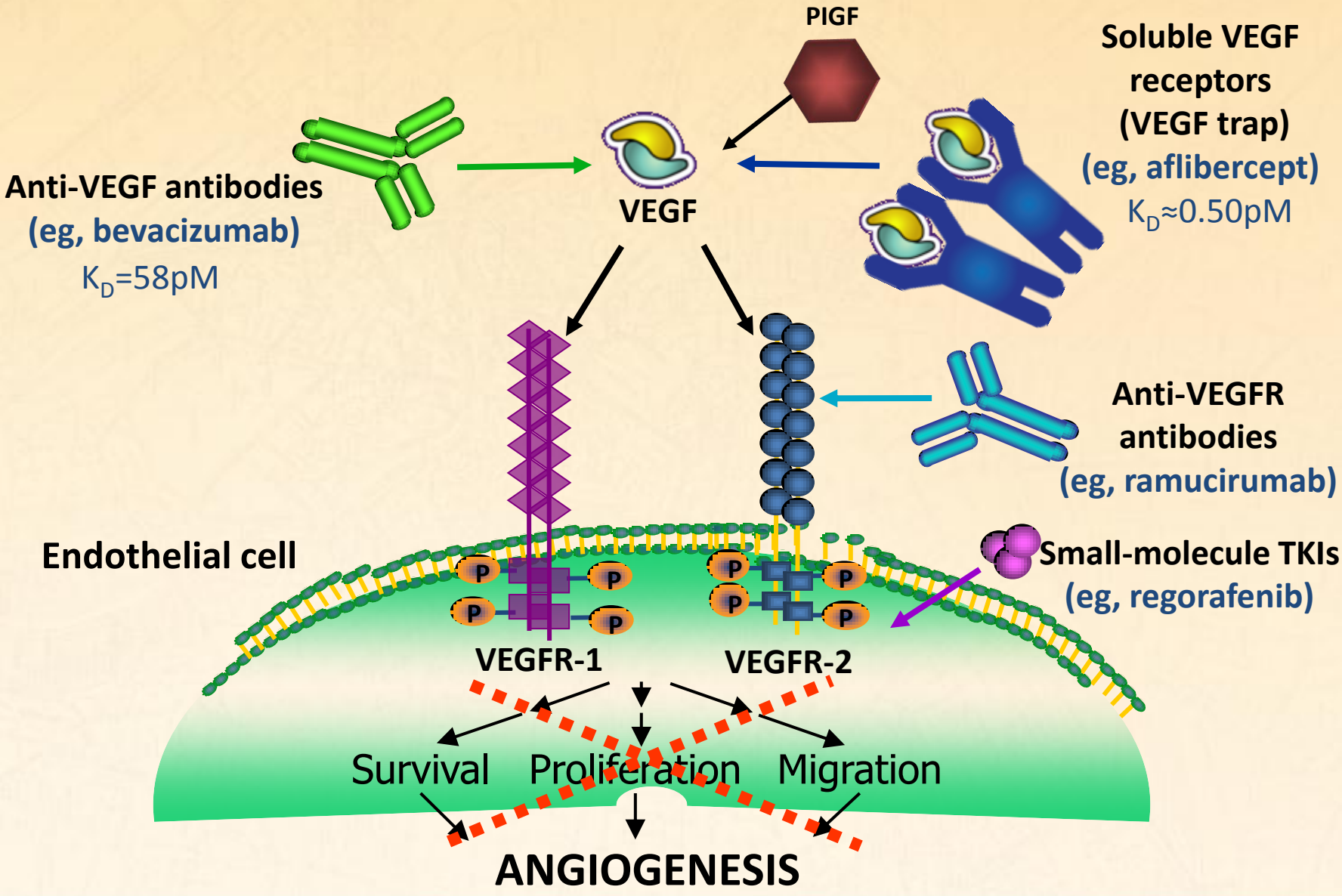
cancer cells into the blood.

But Dr. Folkman is the first to urge caution in leaping to conclusions about what might happen when patients try the drugs. "Going from mice to people is a big jump, with lots of failures," he said.

Hopes were high for chemotherapy drugs that worked well in mice but turned out to be less successful in people. Therapies that used the immune system to rid the body of cancer also worked in mice but were disappointing when they were tried in people. Gene therapy treats mouse cancer, but has had limited success in people.

From bitter experience, most cancer researchers have learned to be leery of what one called "that four letter word" — cure.

Anti-VEGF Mechanisms



Modified from: Keefe. *The Oncologist*. 2011;16:432-222; Papadopoulas. *Angiogenesis*. 2012;15:171-185.

Anti-angiogenesis in 1L mCRC: Successes

- IFL +/- Bevacizumab
  - Improved OS, PFS, RR
- FOLFOX / XELOX +/- Bevacizumab
  - Improved PFS
- 5FU/LV +/- Bevacizumab, phase II
  - Improved PFS

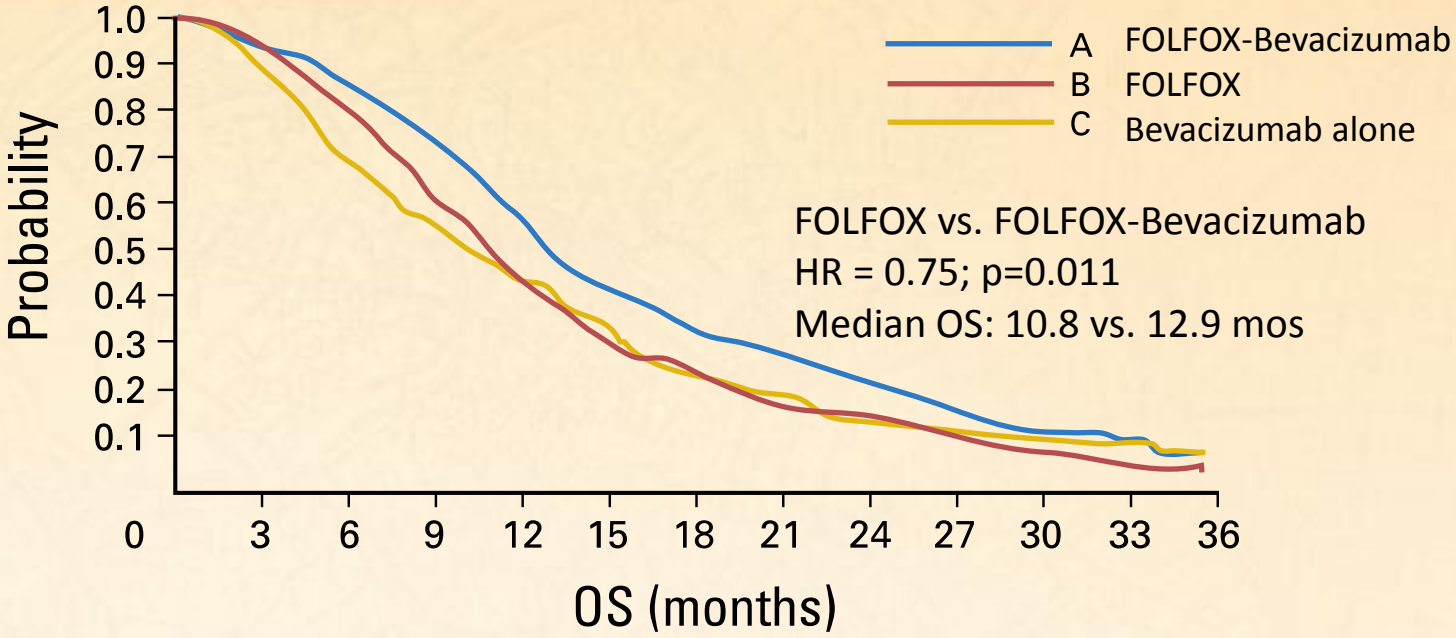
Hurwitz et al., New Engl J Med 2004; Saltz et al., J Clin Oncol 2008; Kabbinavar et al., J Clin Oncol 2005

Anti-angiogenesis in 1L mCRC: …and Failures

- FOLFOX +/- Cediranib (HORIZON II)
  - Improved PFS, but failed to improve OS
- FOLFOX + Cediranib vs FOLFOX + Bevacizumab (HORIZON III)
  - Non-inferiority not met; toxicity issues
- FOLFOX + Vatalanib vs FOLFOX + placebo
  - No improved PFS, OS; potential benefit in “poor-risk“ subgroup?

Hoff et al., J Clin Oncol 2012 and Schmoll et al., J Clin Oncol 2012; epub ahead of print (10 Sept 2012) ; Hecht al., J Clin Oncol 2011

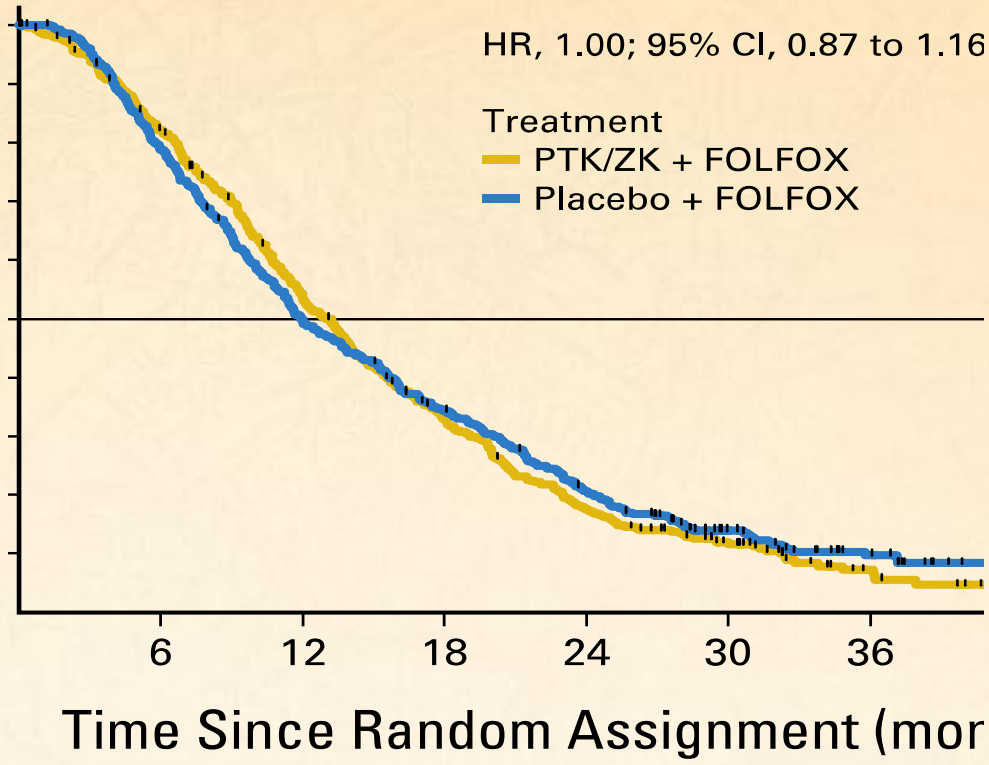
2L mCRC: E3200 Study
Bevacizumab with FOLFOX –Improves OS



Treatment	Total	Dead	Alive	Median
A	286	254	32	12.9
B	291	264	27	10.8
C	243	219	24	10.2

Giantonio et al., J Clin Oncol 2007

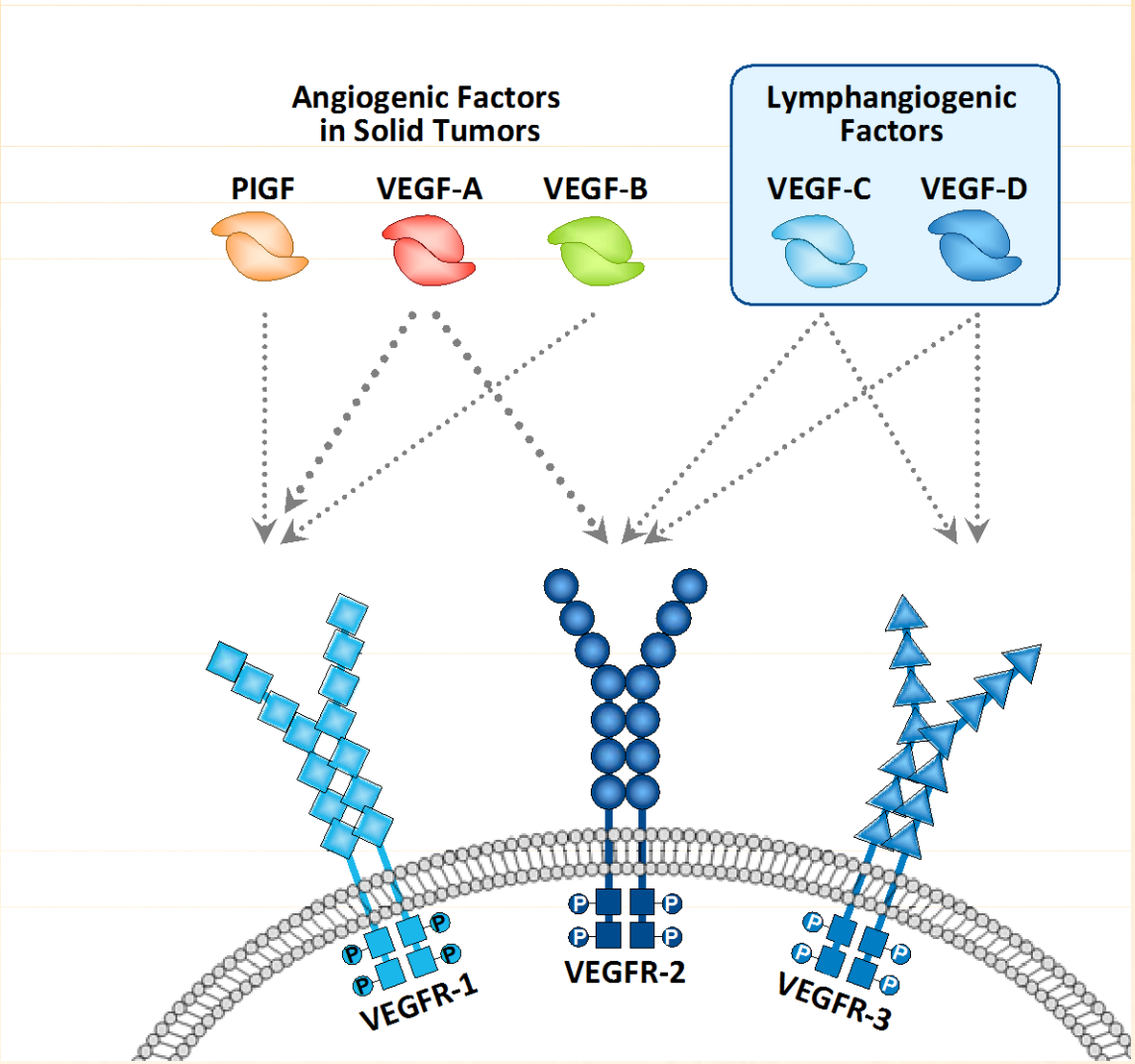
2L mCRC: CONFIRM-2 Study
Vatalanib with FOLFOX – OS Not Improved



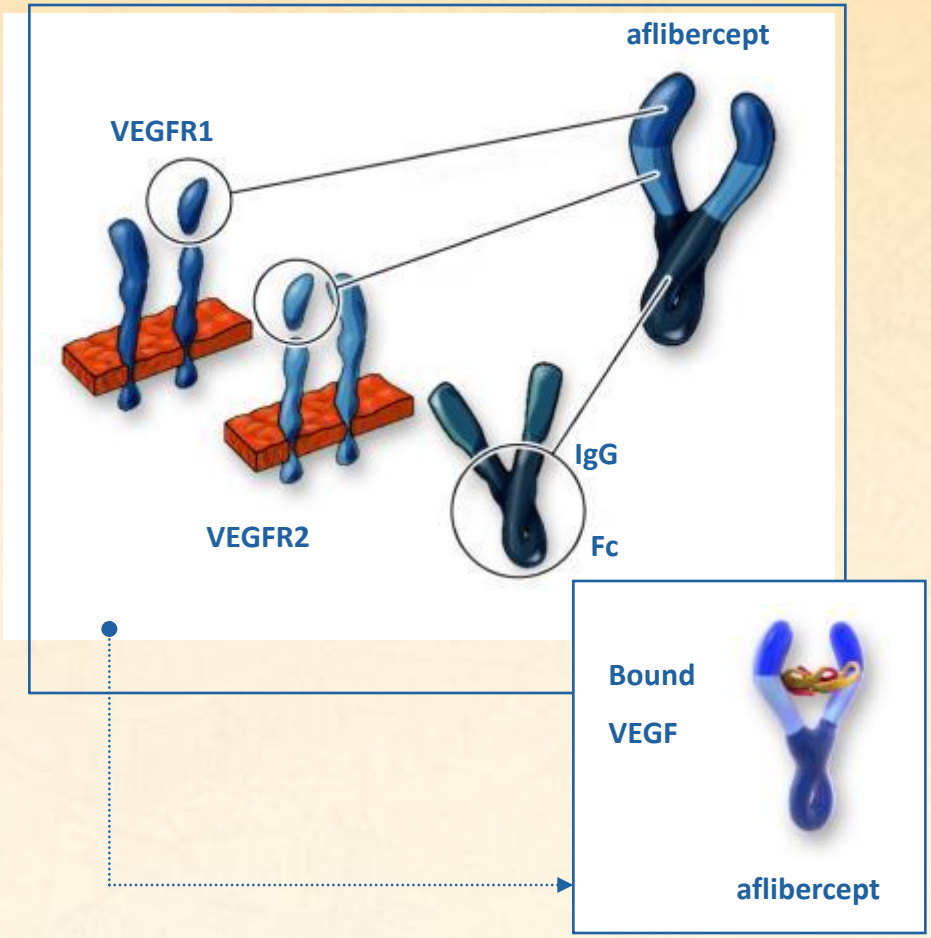
Van Cutsem et al., J Clin Oncol 2011

Multiple Isoforms and Receptors of VEGF-directed Angiogenesis

VEGF-A, -B and PlGF and their receptors VEGFR-1, VEGFR-2 are the main mediators of angiogenesis



Aflibercept: Anti-VEGF fusion protein

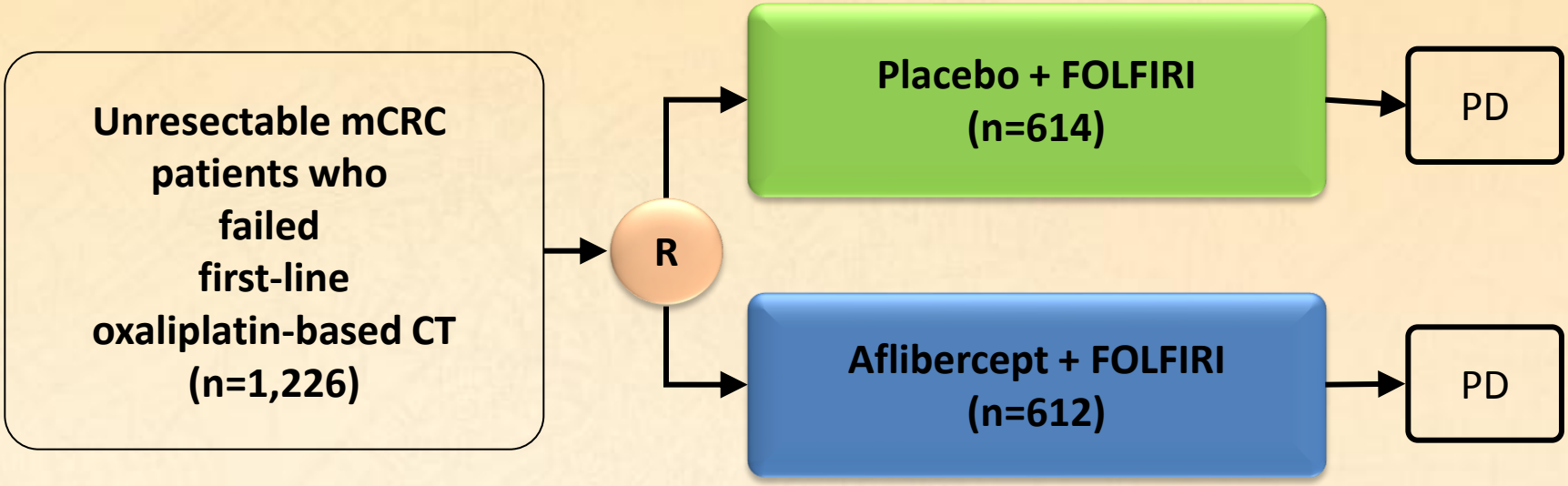


- Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc[1]
- Blocks all human VEGF-A isoforms, VEGF-B and placental growth factor (PlGF)[2]
- High affinity—binds VEGF-A and PlGF more tightly than native receptors
- Contains human amino acid sequences[1]

mAb - monoclonal Antibody
VEGF - Vascular Endothelial Growth Factor
PlGF - Placental Growth Factor

1. Holash. Proc Natl Acad Sci. 2002;99:11393–11398. 2. Tew. Clin Cancer Res. 2010;16:358–366.

VELOUR Trial : Aflibercept in 2L mCRC



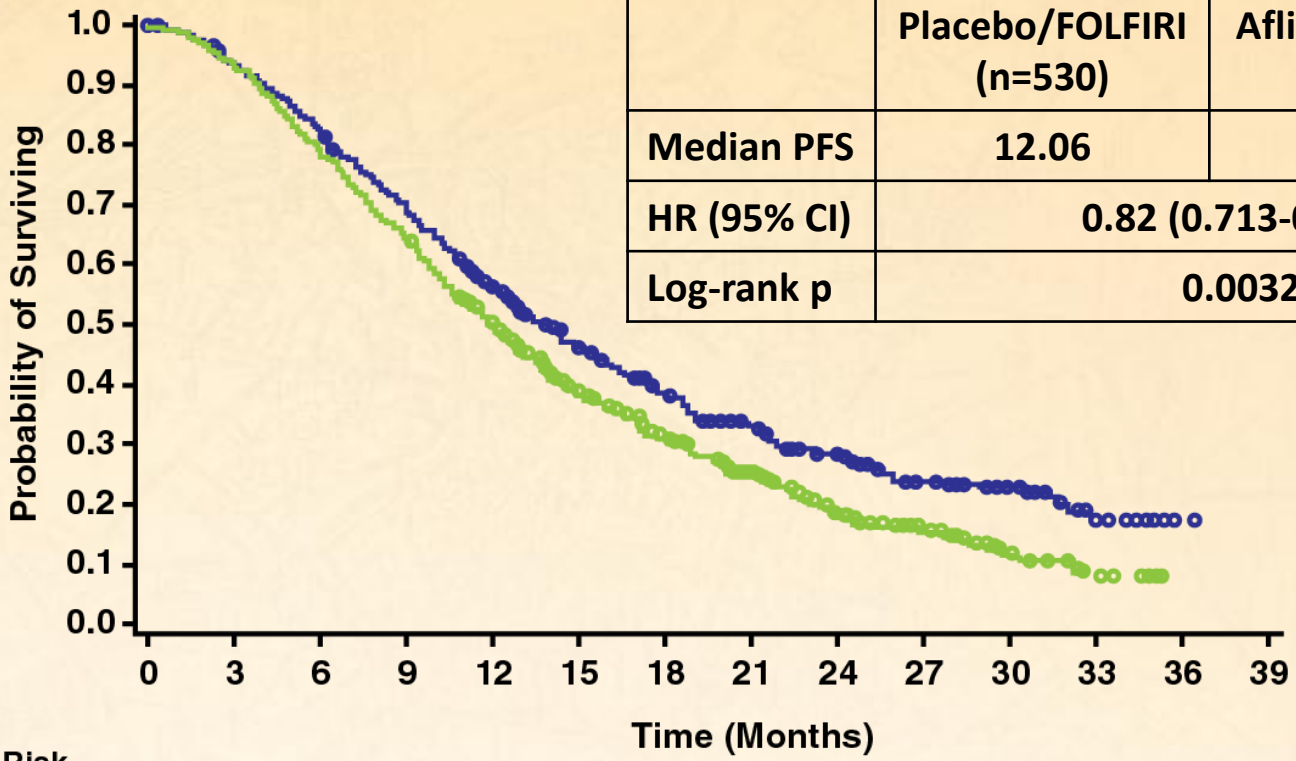
- Primary endpoint: OS*
- Secondary endpoints: PFS, ORR, safety, pharmacokinetcs and immunogenecity
- Sponsor: Sanofi Aventis/Regeneron/NSABP

*90% power to detect a 20% lower hazard rate for death after 863 events (overall 2-sided a = 0.0466)

Van Cutsem et al.,WCGIC (Barcelona) 2011; update: Tabernero et al., EMCCC (Stockholm) 2011

Phase III VELOUR Trial
FOLFIRI + Aflibercept: Improved OS

	Placebo/FOLFIRI (n=530)	Aflibercept/FOLFIRI (n=531)
Median PFS	12.06	13.50
HR (95% CI)	0.82 (0.713-0.937)	
Log-rank p	0.0032	

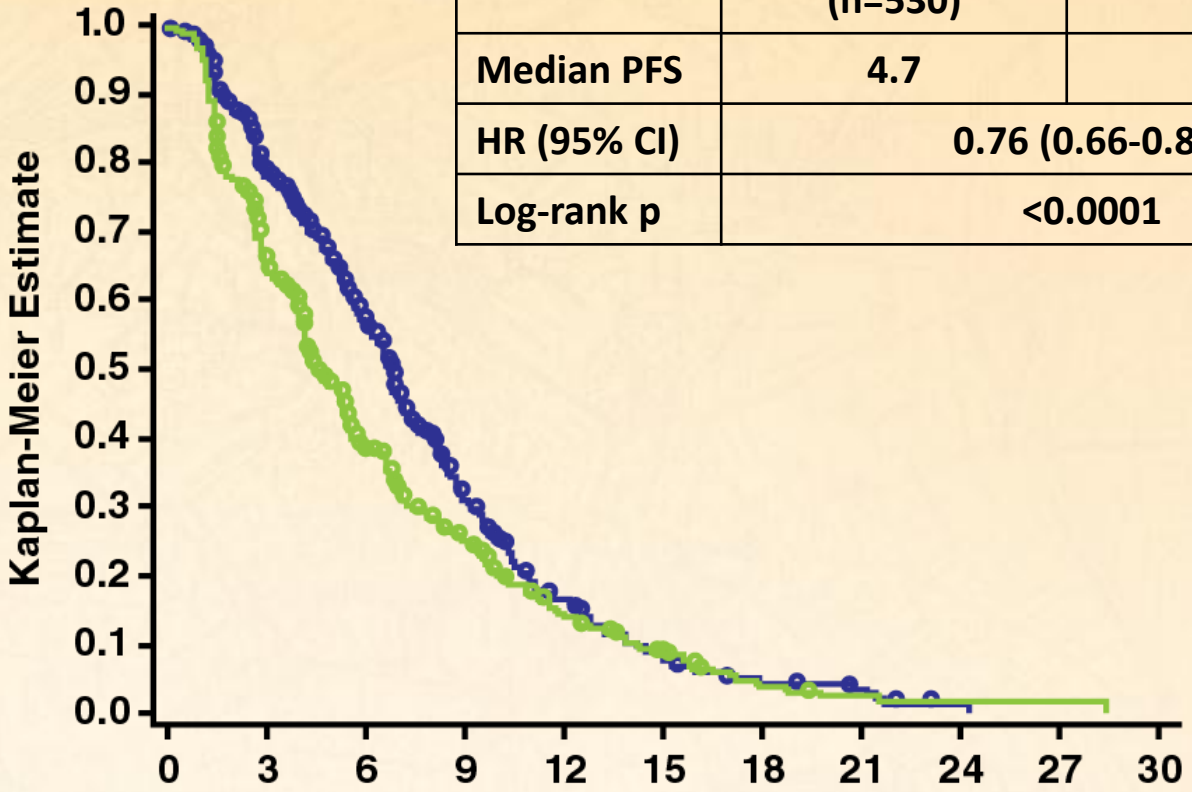


Number at Risk						
Placebo	614	485	286	131	51	14
Aflibercept	612	498	311	148	75	33
Survival Probability (%)						
Placebo		79.1	50.3	30.9	18.7	12.0
Aflibercept		81.9	56.1	38.5	28.0	22.3

Van Cutsem et al., J Clin Oncol 2012

Phase III VELOUR Trial FOLFIRI + Aflibercept: Improved PFS

	Placebo/FOLFIRI (n=530)	Aflibercept/FOLFIRI (n=531)
Median PFS	4.7	6.9
HR (95% CI)	0.76 (0.66-0.87)	
Log-rank p	<0.0001	



Number at Risk							
Placebo	614	355	171	94	46	24	9
Aflibercept	612	420	247	99	43	17	7

Van Cutsem et al., J Clin Oncol 2012

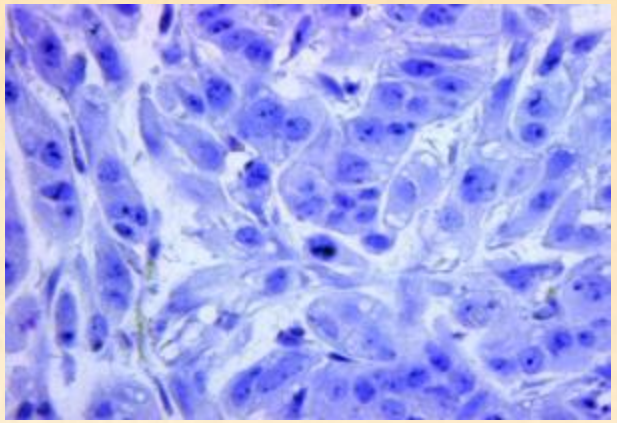
VELOUR: Best Overall Response Rate

Overall response rate, n (%)	Placebo/FOLFIRI (n=530)	Aflibercept/FOLFIRI (n=531)
Complete response	2 (0.4)	0
Partial response	57 (10.8)	105 (19.8)
Stable disease	344 (64.9)	350 (65.9)
Progressive disease	114 (21.5)	55 (10.4)
Not evaluable	13 (2.5)	21 (4.0)
Objective response rate (CR+PR)	59 (11.1)	105 (19.8)
95% CI	8.5-13.8	16.4-23.2
P-value	0.0001	

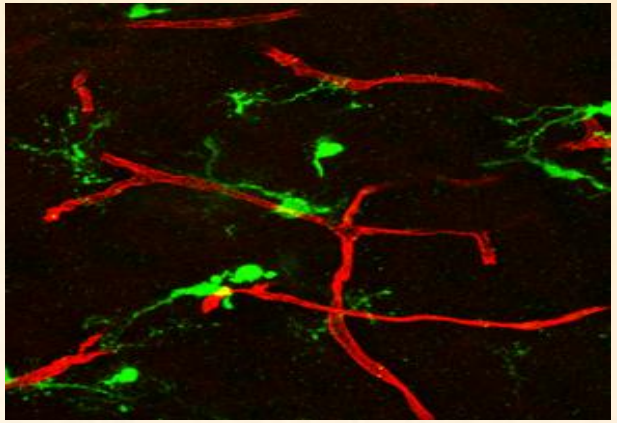
Van Cutsem et al., J Clin Oncol 2012

Tumor cell
Genetic instability

Chemo →

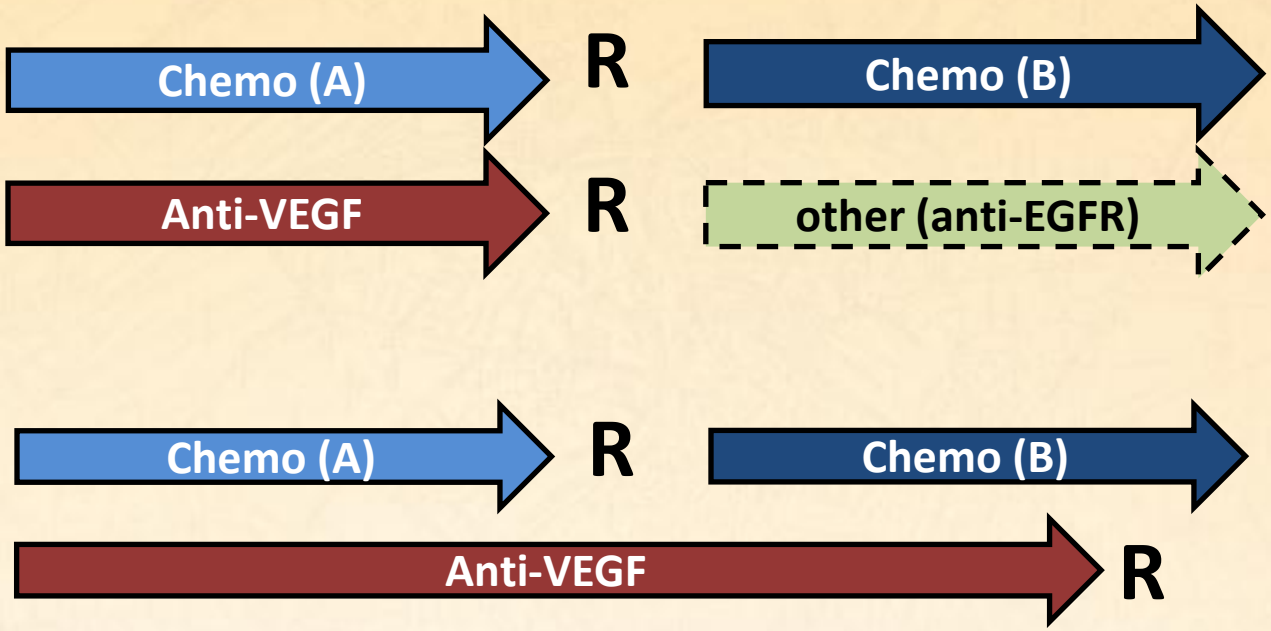


Anti-angiogenesis →

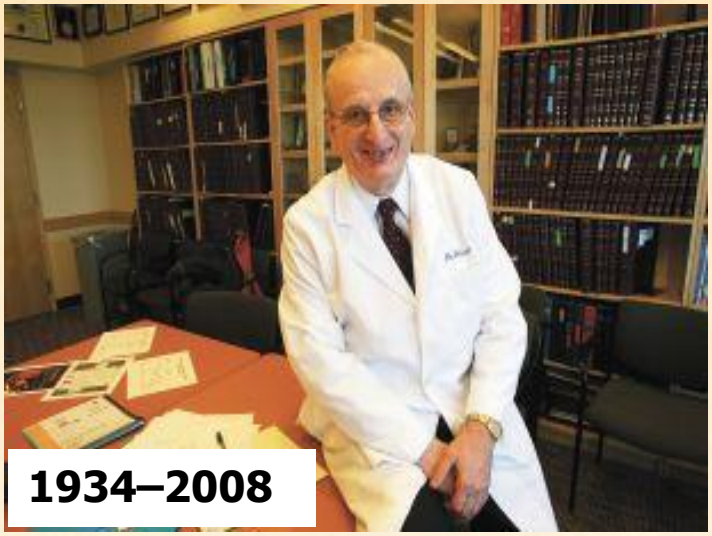


Genetic stability
Endothelial cell

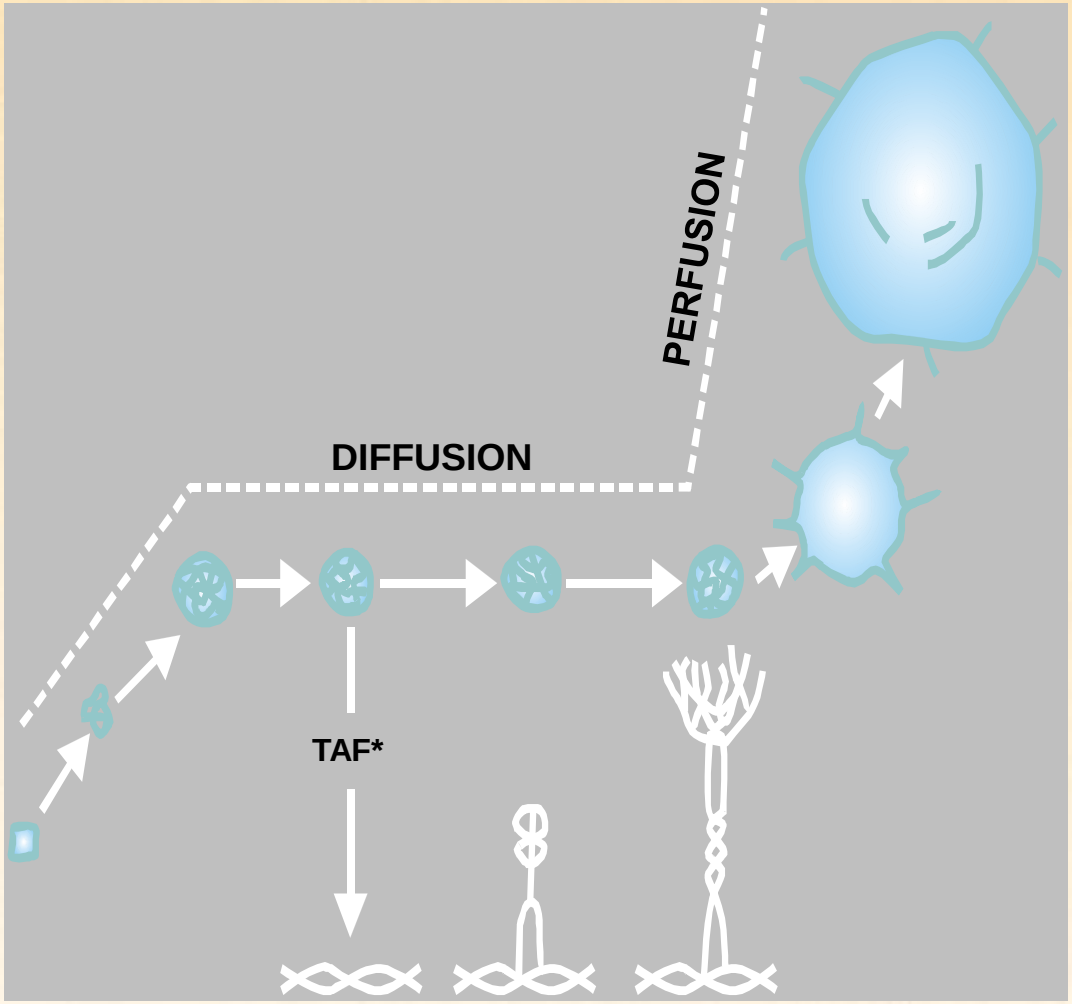
VEGF Resistance – When ?



1971: The Concept of Angiogenesis: Critical for Tumor Growth



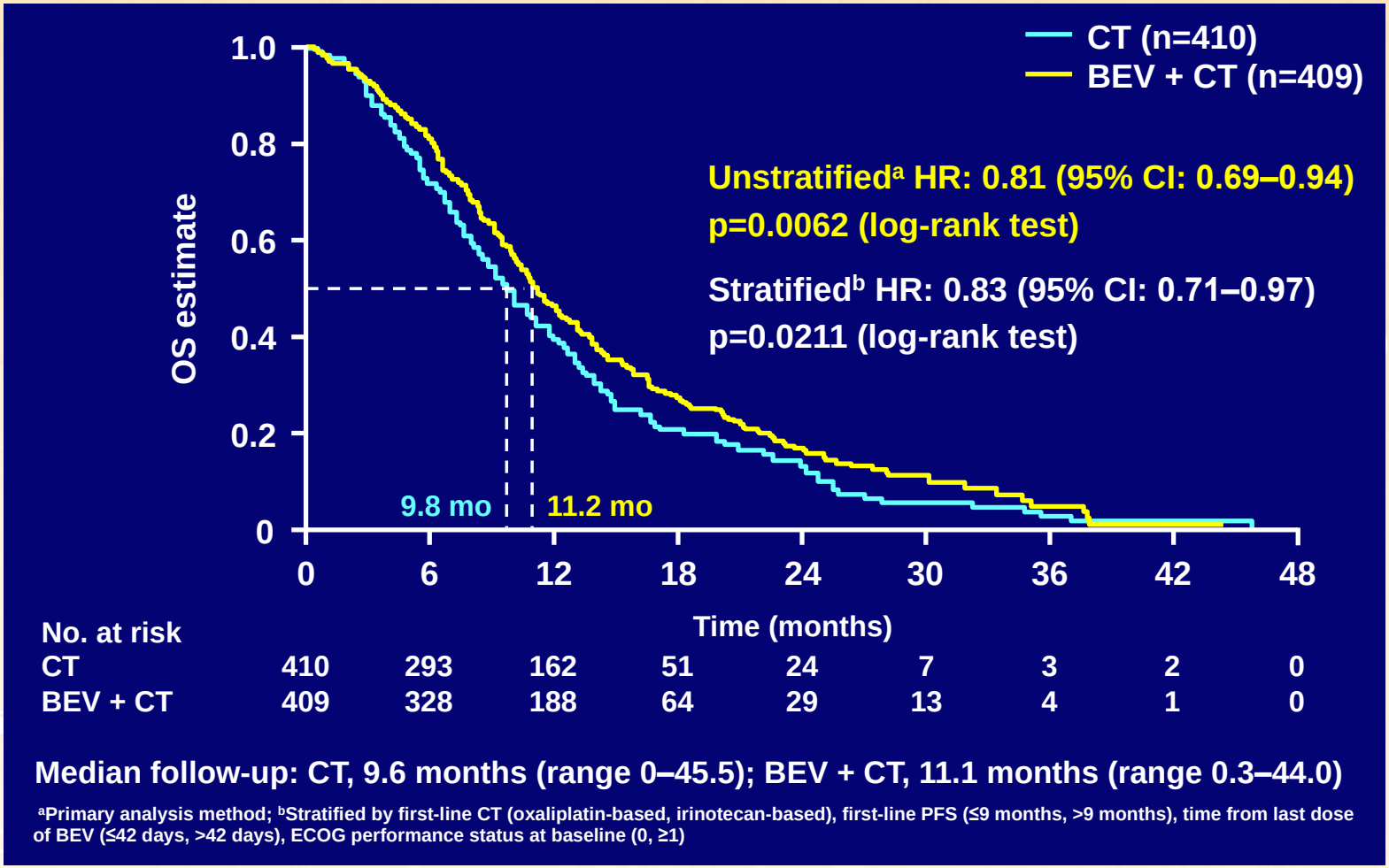
"A specific inhibitor of angiogenesis is not likely to cause bone marrow suppression, gastrointestinal symptoms, or hair loss…In the design of clinical trials it may therefore be necessary to administer inhibitors of angiogenesis for longer un-interrupted periods than is usual with conventional cytotoxic agents."



*TAF = tumour angiogenesis factor

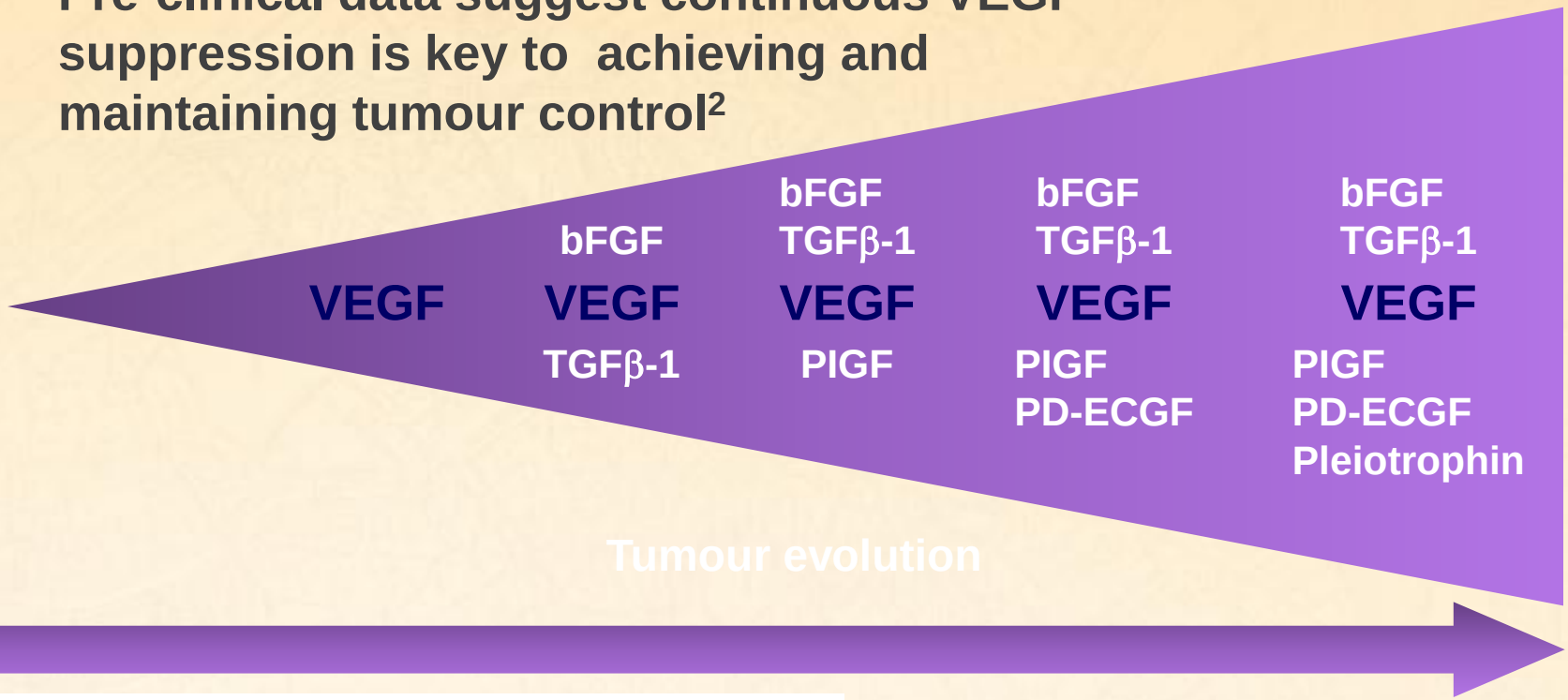
Folkman, et al. NEJM 1971

TML Trial: Bevacizumab + 2L CT in pts Failing Bevacizumab + CT 1L



VEGF Expression Throughout Tumour Life Cycle[1]

- Pre-clinical data suggest continuous VEGF suppression is key to achieving and maintaining tumour control[2]



VEGF = vascular endothelial growth factor

bFGF = basic fibroblast growth factor

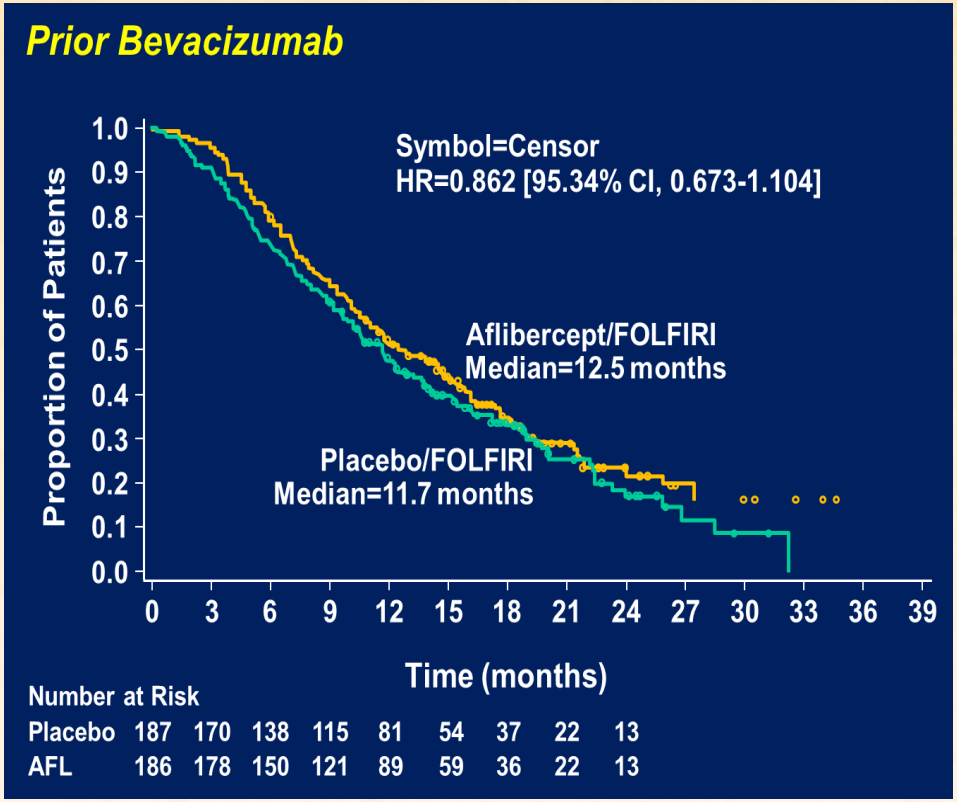
TGF-1 = transforming growth factor-1

PD-ECGF = platelet-derived endothelial cell growth factor

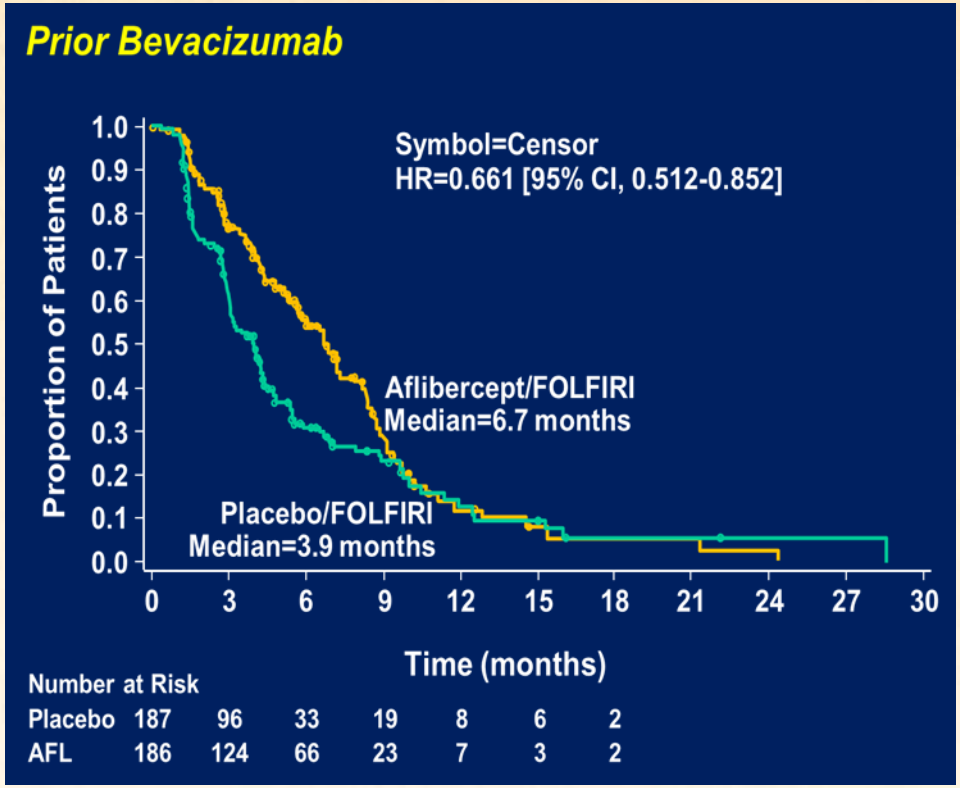
1. Folkman. Cancer: Principles and Practice of Oncology, 7th ed. 2005 2. Bagri et al. Clin Cancer Res 2010

VELOUR: Pretreatment with Bevacizumab Subgroup N=373 / 1226 (30%)

Overall Survival



Progression-Free Survival



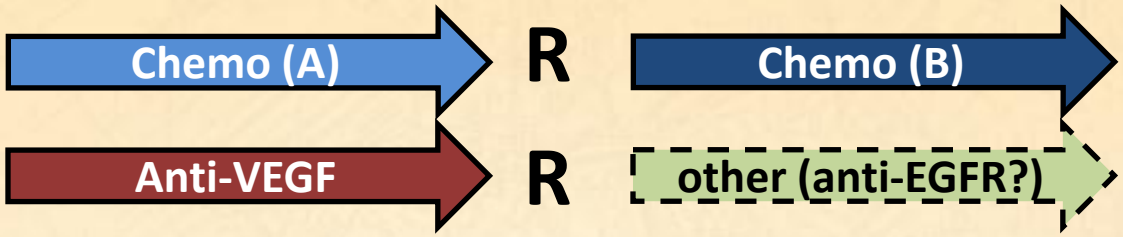
VELOUR and TML: Different Study Populations

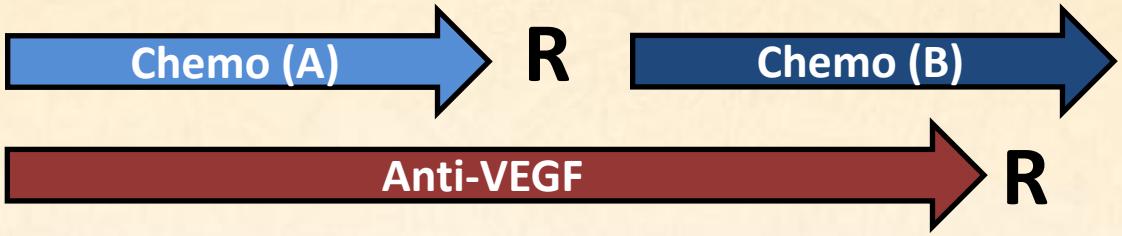
	VELOUR	TML
Preceding CT	any oxaliplatin/FP regimen +/- bevacizumab	any oxaliplatin/FP with bevacizumab
Role of bevacizumab 1L	Subgroup (30%) No information on discontinuation etc	Prerequisite (100%) bevacizumab max. 3 mos. interrupted Early (beva) progressors excluded
CT with 2L	FOLFIRI	any irinotecan/FP

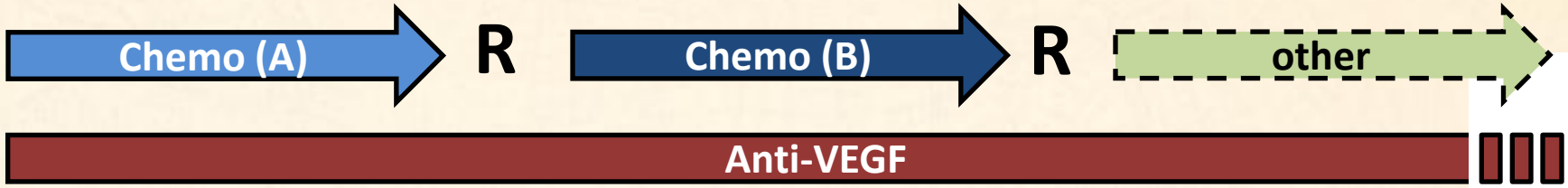
Aflibercept after VELOUR: (Potential) Clinical Role and Further Questions

- Is this a new standard in 2L – and how does this compare to other 2L options?
- Has this reinforced the principle anti-VEGF → anti VEGF?
- What will (or should) be the next steps in clinical development?

VEGF Resistance – When ?







Regorafenib (BAY 73-4506)

- Oral tyrosine kinase inhibitor
- Targets include VEGFR1-3, PDGFR, KIT, FGFR, RET, TIE2

Phase III CORRECT study (n=760)

mCRC following standard therapy

R **2:1**

Regorafenib 160mg od + BSC (n=505)

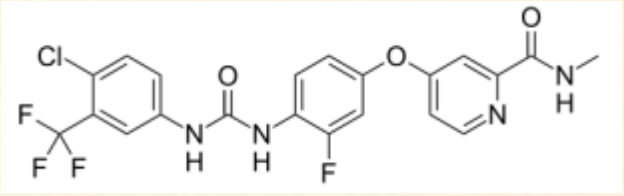
3 weeks on, 1 week off

Placebo + BSC (n=255)

3 weeks on, 1 week off

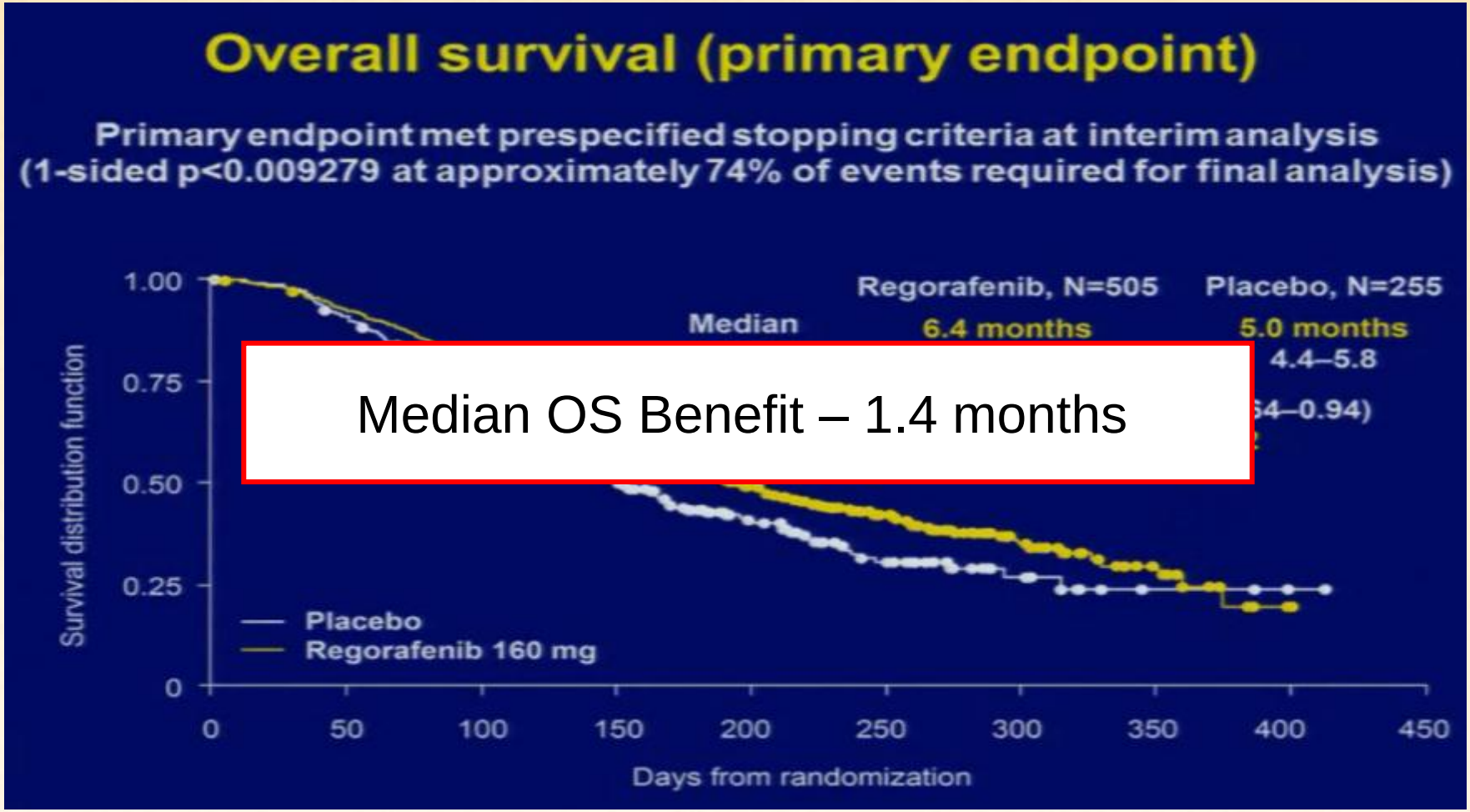
Primary endpoint: OS

- 90% power to detect HR 0.75



Regorafenib (BAY 73-4506)

CORRECT trial results:



Van Cutsem et al, ASCO 2012, Abstract 3502

Further Potential Roles for Aflibercept in mCRC

- Single agent / maintenance
  - Wait for results with Beva first? eg, upcoming AIO KRK 0207 trial
- Integrate in complex sequences?
  - New algorithms, complex trials planned (GERCOR group)
- Perioperative treatment?
  - New EORTC BOS-3 trial in resectable CLM
- Biomarker driven decision making?
  - German/Austrian/Australian PERMAD trial

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TREATMENTS FOR THE PATIENT WITH METASTATIC COLORECTAL CANCER

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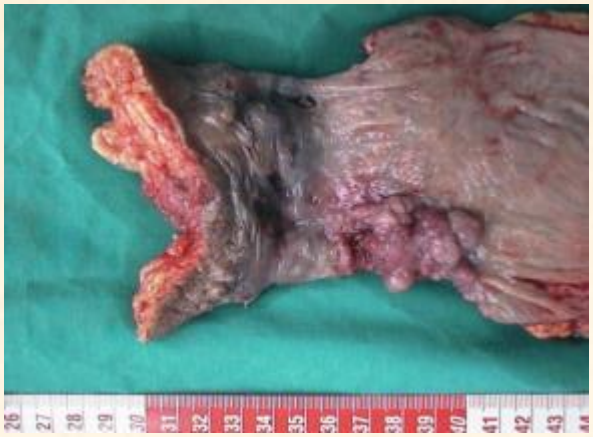
CLINICAL CASE

CHOOSING AN OPTIMAL FIT exploring TREATMENTS FOR THE PATIENT WITH METASTATIC COLORECTAL CANCER

Marc Peeters, MD, PhD
Professor of Oncology
Department of Oncology
Antwerp University Hospital
Edegem, Belgium

Case 1: Presentation (1)

- Demographics
  - Male patient, 68 years of age
  - No important co-morbidity
- Diagnosis
  - a non-metastatic caecal adenocarcinoma
  - Right hemicolectomy: pT4N2M0



→ 6 months of adjuvant FOLFOX6

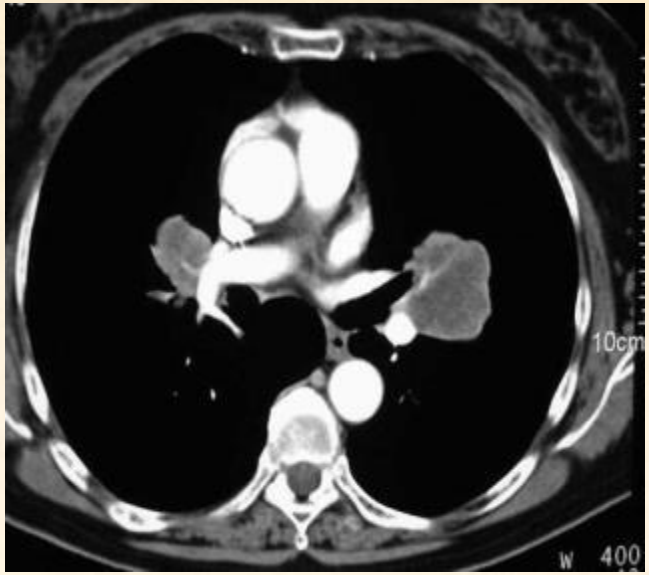
Case 1: Questions to the Panel (1)

1. Does everybody agree on this treatment decision? Other options?

2. Do we need currently more information on the patient and/or the tumor?

Case 1: Presentation (2)

- Follow-up
  - Adjuvant chemotherapy with no major complications
  - 14 months after stopping chemotherapy



bilateral lung metastases

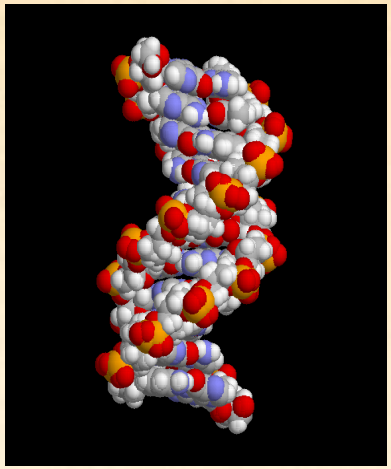
Case 1: Questions to the Panel (2)

1. What would be the strategy in this patient?

2. Which systemic treatment would you propose to the patient?

Case 1: Presentation (3)

- The tumor is wild type

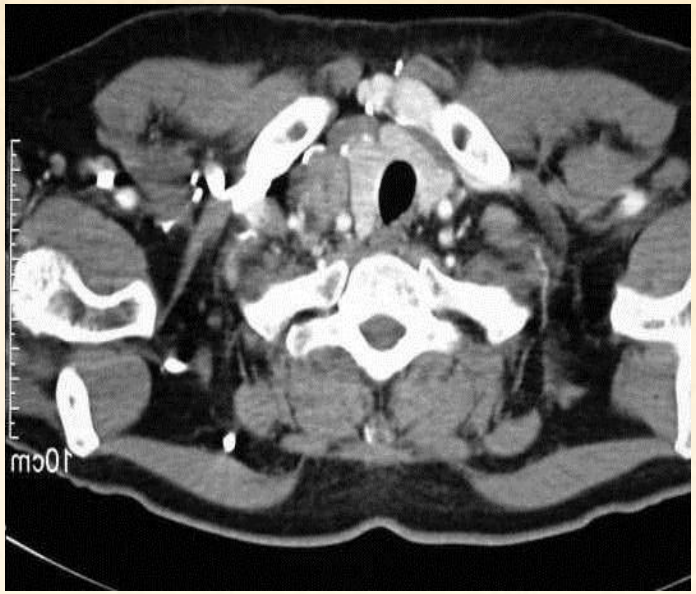


12p12.1

Bevacizumab in association with FOLFOX

Case 1: Presentation (4)

- Follow-up
  - After 10 months and partial response as optimal response



Case 1: Questions to the Panel (3)

- What systemic treatment would you propose to the patient now?
  - Bevacizumab/ FOLFIRI
  - Aflibercept/ FOLFIRI
  - Panitumumab/ FOLFIRI
  - Cetuximab/ irinotecan

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WHAT TO EXPECT: MANAGING ADVERSE EFFECTS OF TREATMENTS FOR METASTATIC CRC

David Ferry, PhD FRCP

Professor of Medical Oncology

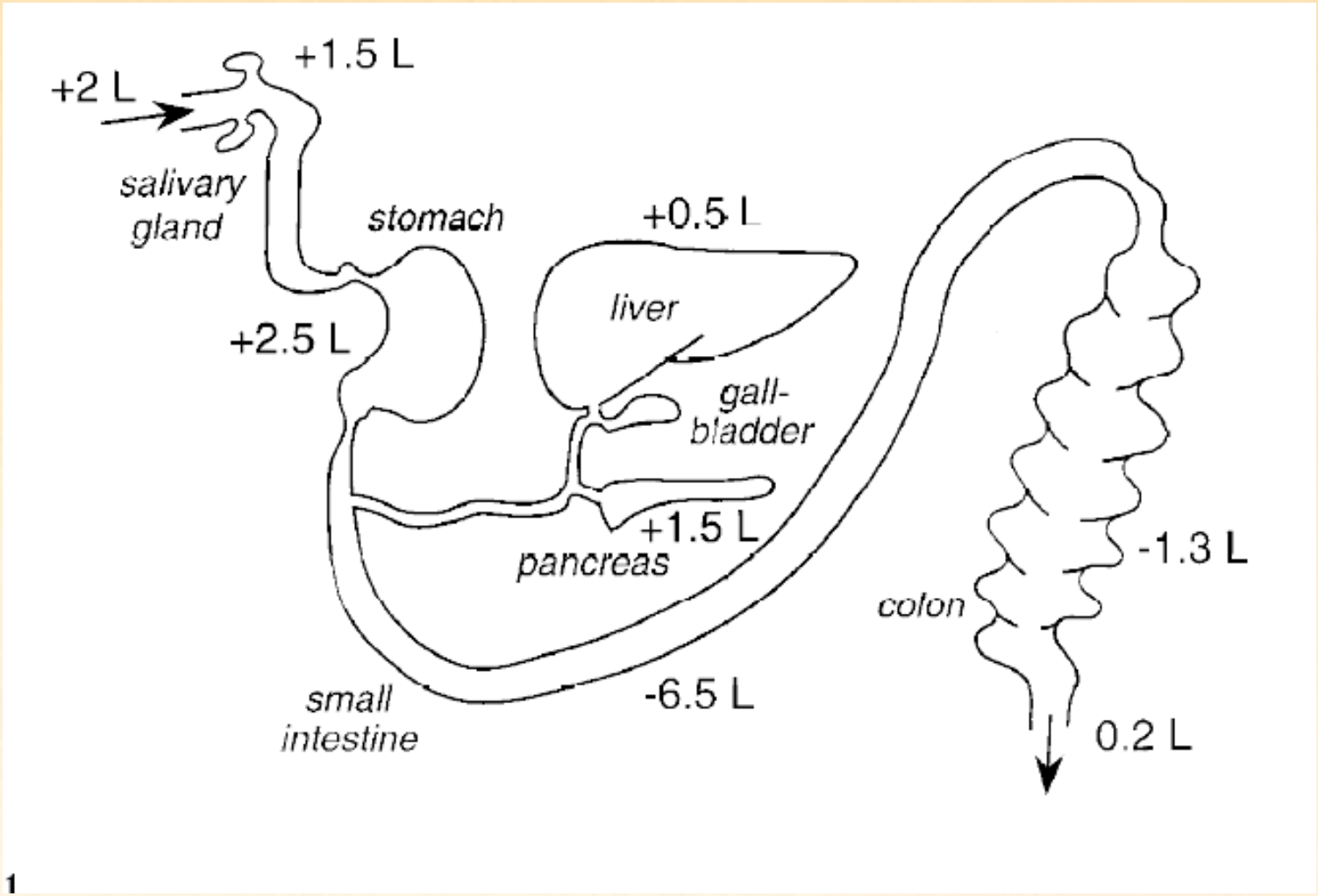
New Cross Hospital

Wolverhampton, UK

Diarrhoea: Colorectal regimens

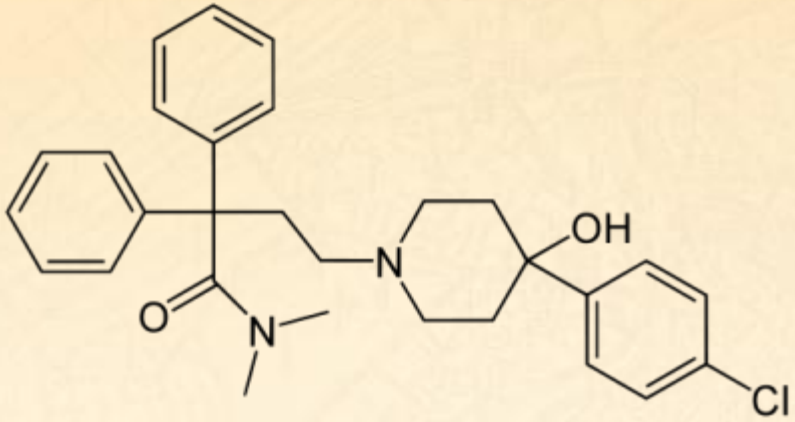
Regimen	Grade 3-4 diarrhoea (%)	Reference
Bolus 5FU + folinic acid	16	Chau et al, 2005
Infusional 5FU	5	
Irinotecan	6	Saltz et al, 2001
Irinotecan + infusional 5FU/FA	15	
FOLFIRI	14	Fuchs et al, 2007
mIFL	19	
capeIRI	47	
FOLFIRI	10.5	Van Cutsem et al 2011
FOLFIRI + cetuximab	15.7	
FLOX	10	Tveit et al 2012
FLOX + cetuximab	17	

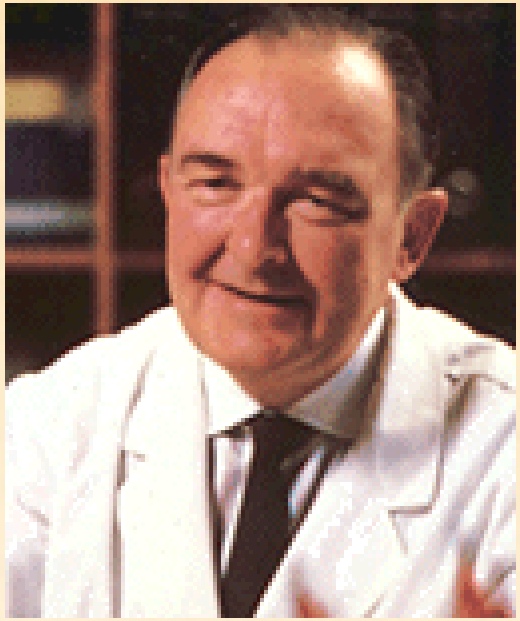
GI Tract Water Flux in 24 hr



1

Loperamide



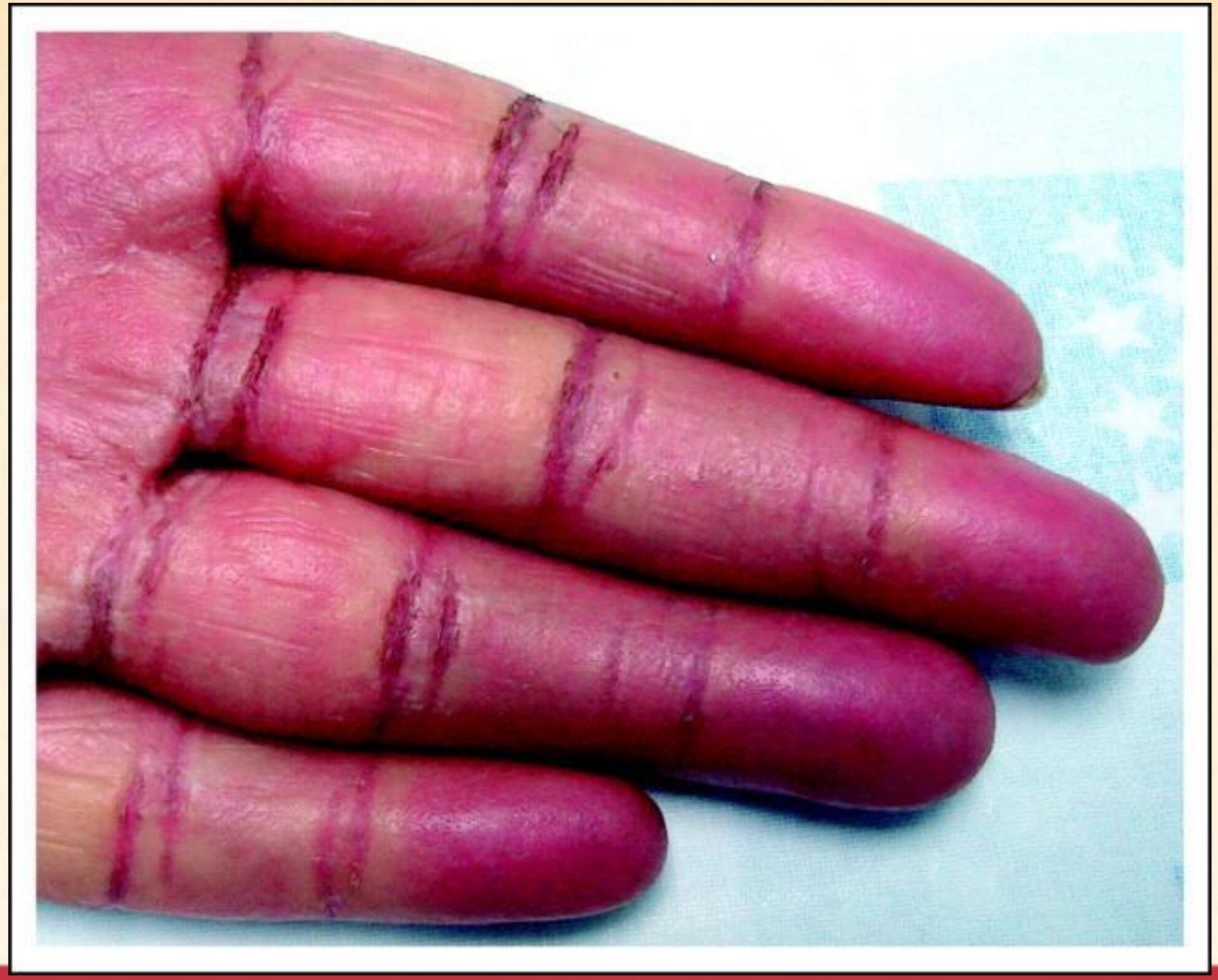


μ 20 > δ>100 κ receptors
Oral bioavailability = 0.3%
90% leaves stomach within 1 hour
90% reaches colon by 9 hours

- 80% excreted faeces unchanged
- Absorbed loperamide excluded from CNS by P-gp
- Liver metabolism CYP3A4

Paul Jansen 1926-2003

Capecitabine Plantar Palmer Eryhrodysplasia (PPE)



VOLUME 28 · NUMBER 24 · AUGUST 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pyridoxine Is Not Effective to Prevent Hand-Foot Syndrome Associated With Capecitabine Therapy: Results of a Randomized, Double-Blind, Placebo-Controlled Study

Yoon-Koo Kang, Sung Sook Lee, Dok Hyun Yoon, So Young Lee, Young Ju Chun, Min Sun Kim, Min-Hee Ryu, Heung-Moon Chang, Jae-Lyun Lee, and Tae Won Kim

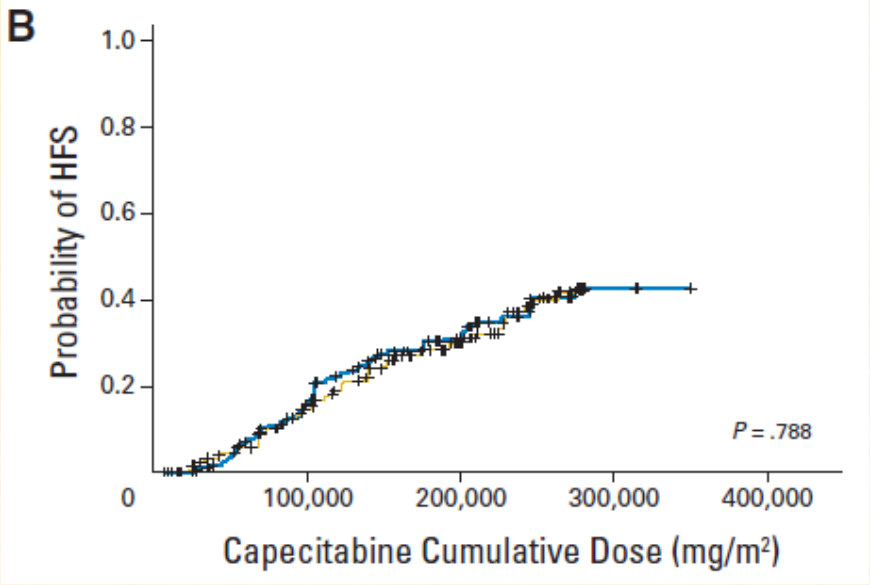


Table 2. Changes in the Severity of HFS After the Second Randomization in the Placebo Group

HFS Grade Change	Placebo (n = 21)		Pyridoxine (n = 23)		
	No.	%	No.	%	*P*
Improved	9	42.9	11	47.8	.94
No change	10	47.6	11	47.8	
Aggravated	1	4.8	1	4.4	

Abbreviation: HFS, hand-foot syndrome.

391 capecitabine treated patients

Cardiac Toxicity: 5FU

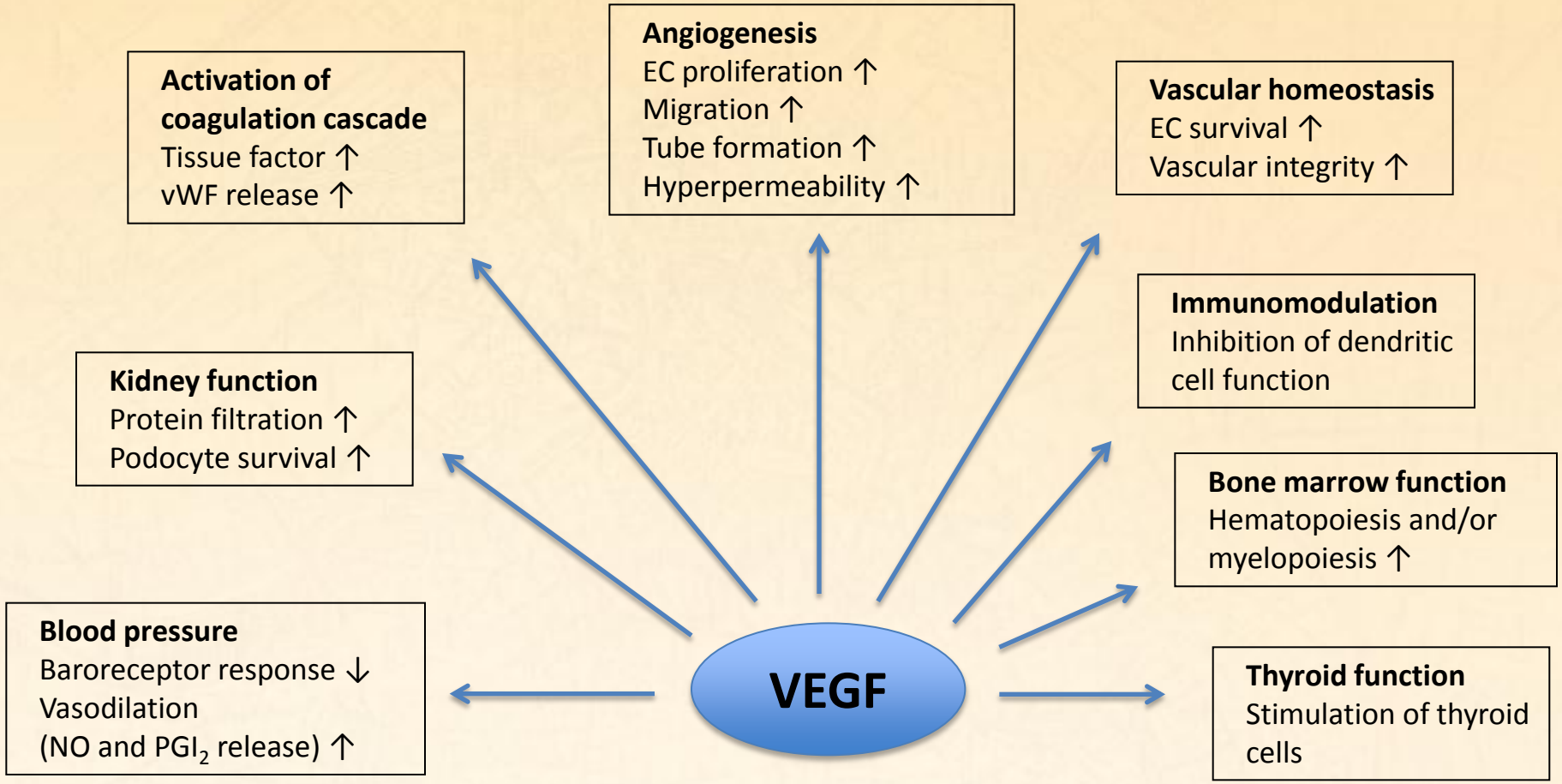
- 1975 Dent and McColl
- 1992 High dose CIV 5FU 7.6% event rate (di Forni et al.JCO;10:1795-1801) 28/367 patients 96-120 hr 600-1000mg/m^2/d. 5 deaths, 21 had unstable angina on stopping infusion
- 2002 Case report capecitabine (Frickofen. Ann Oncol;13:797-801)
- May be helped by nitrates
- Pathophysiology FβAL ?
- Mechanism vasospasm
- Bolus < short infusion < long infusion = capecitabine
- Can rechallenge infusion to bolus, not other way round
- Consider treatment with raltitrexed

Neuropathy: RCT Data on Oxaliplatin

	OPTIMOX1		MOSAIC	
	FOLFOX4	FOLFOX7 LV5FU2	FOLFOX4	LV5FU2
Patients	311	309	1123	1123
Age	65	64	61	60
PR/CR (%)	52/6	51/8	NA	NA
Neuropathy grade 2 (%)	37	42	12.4+	0.2+
Neuropathy grade 3	18	13		

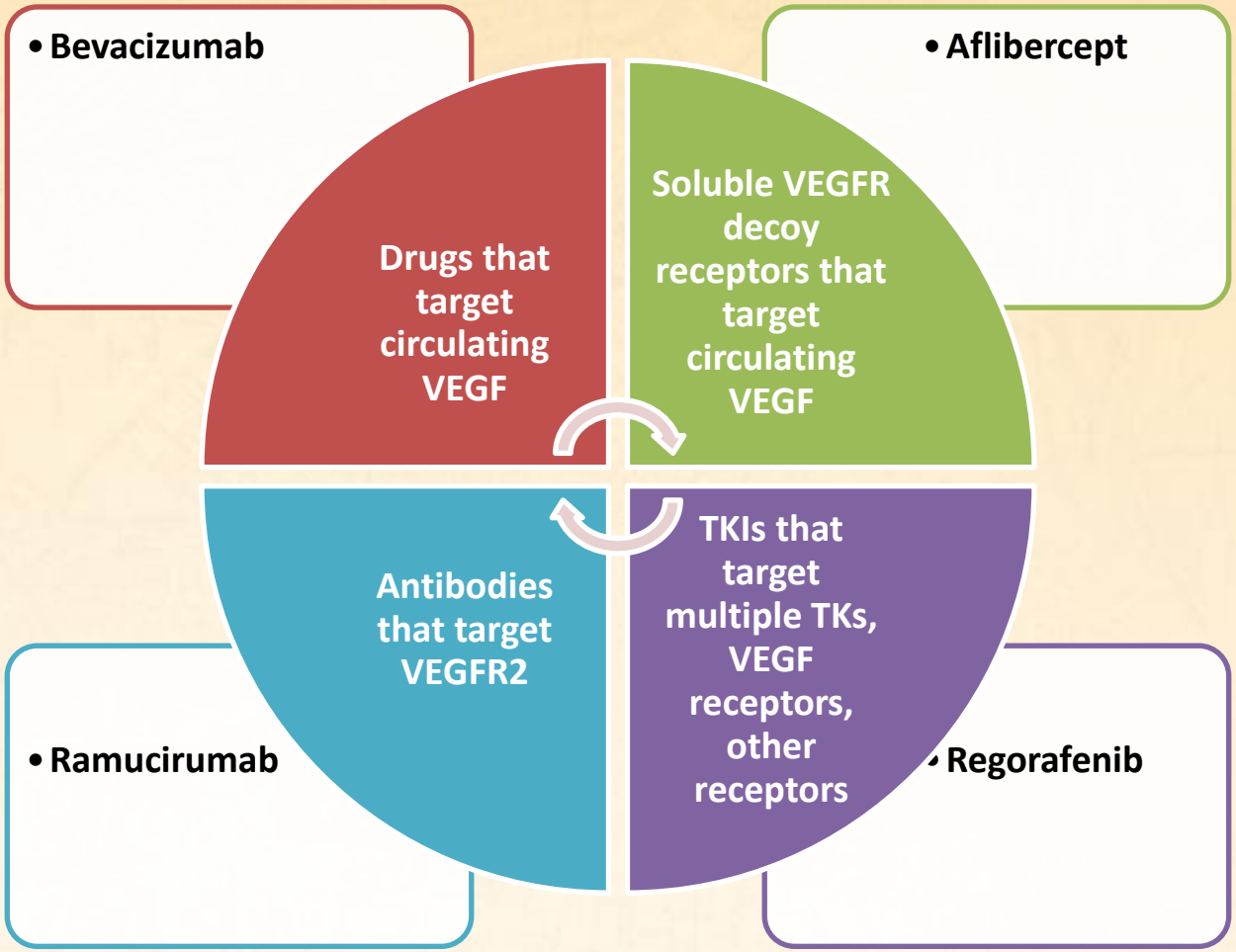
+ CTC version 1 had 3 grades of neuropathy G1 Mild parasthesia; G2 Moderate parasthesia and objective sensory loss; G3 parasthesia affecting function

Physiological Functions of VEGF

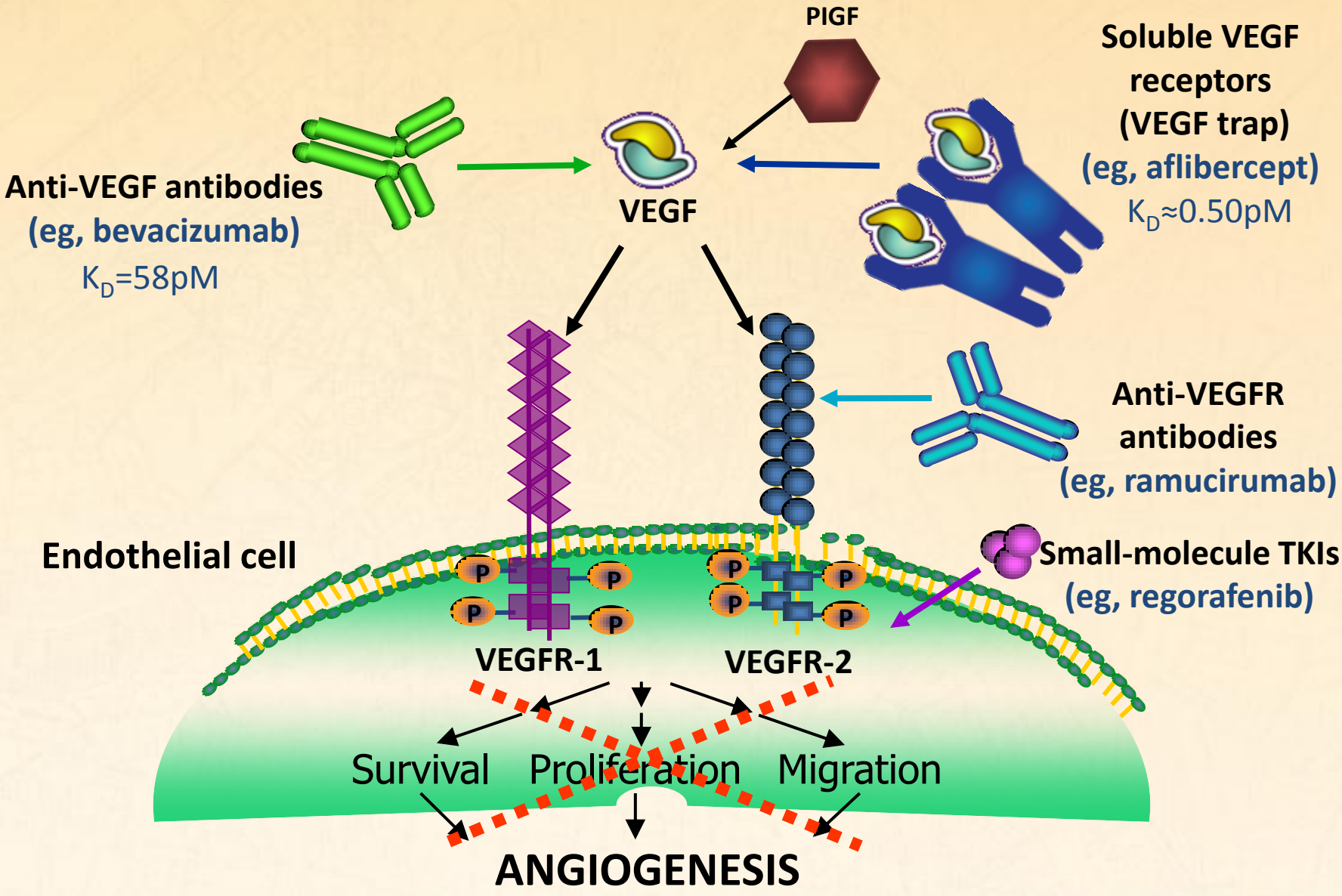


Verheul and Pinedo. *Nat Rev Cancer*. 2007;7:475-485.

Drugs That Inhibit the VEGF-Pathway



Anti-VEGF Mechanisms



Modified from: Keefe. *The Oncologist*. 2011;16:432-222; Papadopoulas. *Angiogenesis*. 2012;15:171-185.

Targeted Agents: Improvements in Outcomes at the Expense of Increased Toxicity?

Targeted Agents: Class-Related Side-Effect Profile

Adverse events associated with VEGF-mediated agents
Hypertension
Proteinuria/nephrotic syndrome
Gastrointestinal perforation
Arterial thromboembolic event
Congestive heart failure
Bleeding
Wound healing

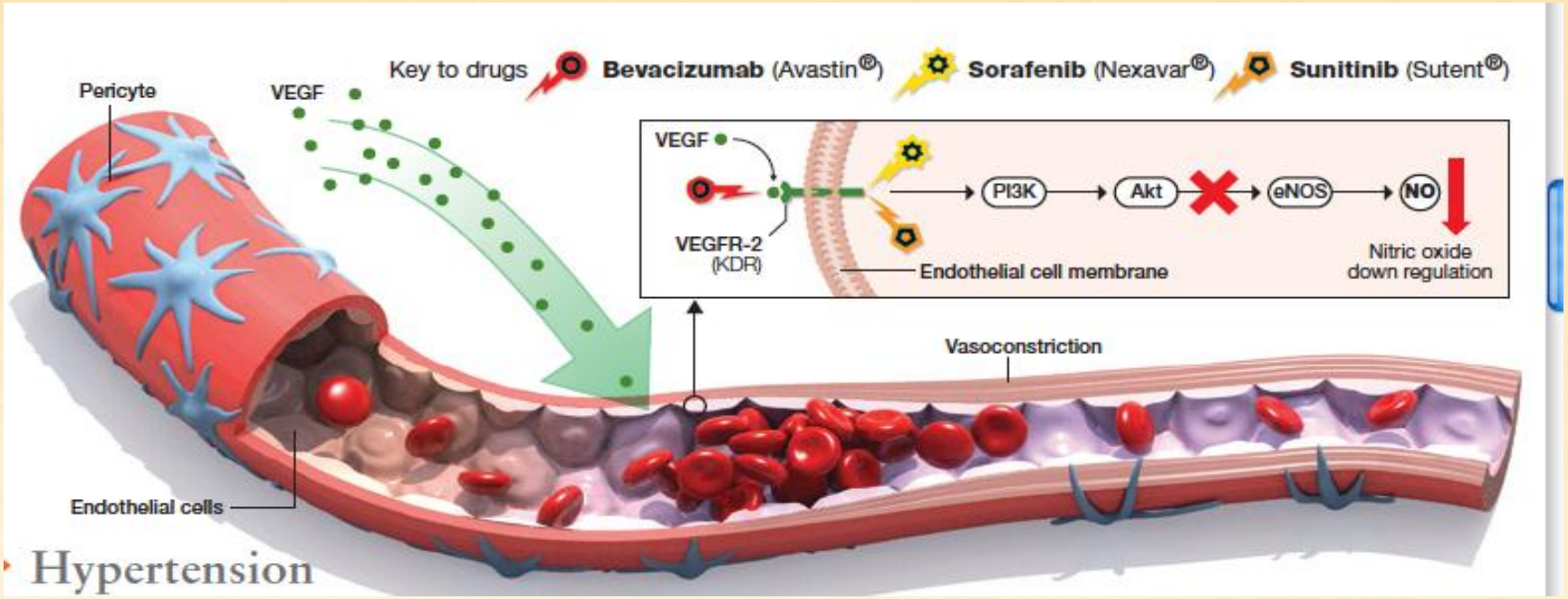
Adverse events associated with EGFR-mediated agents
Acne/acne-like rash
Nausea/ vomiting
Rash
Diarrhea
Abdominal pain
Asthenia
Infusion-type reaction
Hypomagnesemia
Pruritus
Erythema

Gressett. *Ann Pharmacother*. 2009; 43:490-501; Fakih. *Curr Oncol.* 2010; 17(Suppl 1):S18-S30.

Hypertension: Overview

- Common VEGF inhibitor class-based side effect
- Patients with underlying hypertension are more at risk for severe hypertension with VEGF inhibitors
- Incidence is dose-dependent, with increased incidence in patients on high-dose bevacizumab
- Reversible with discontinuation

Hypertension: Pathophysiology

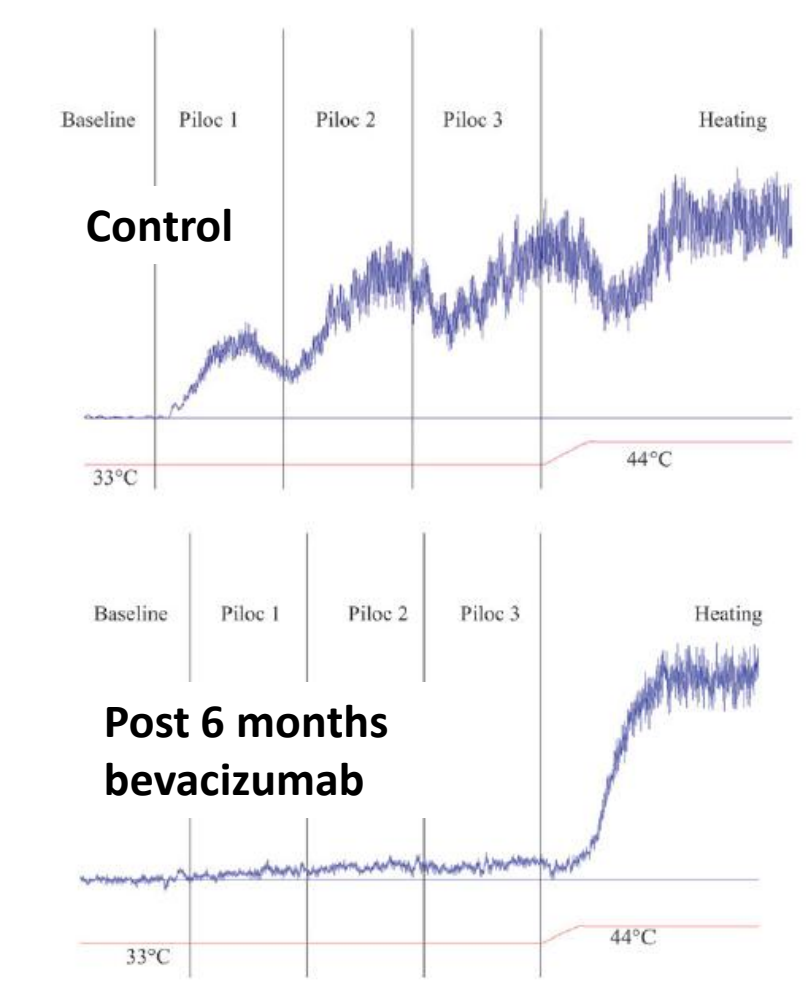


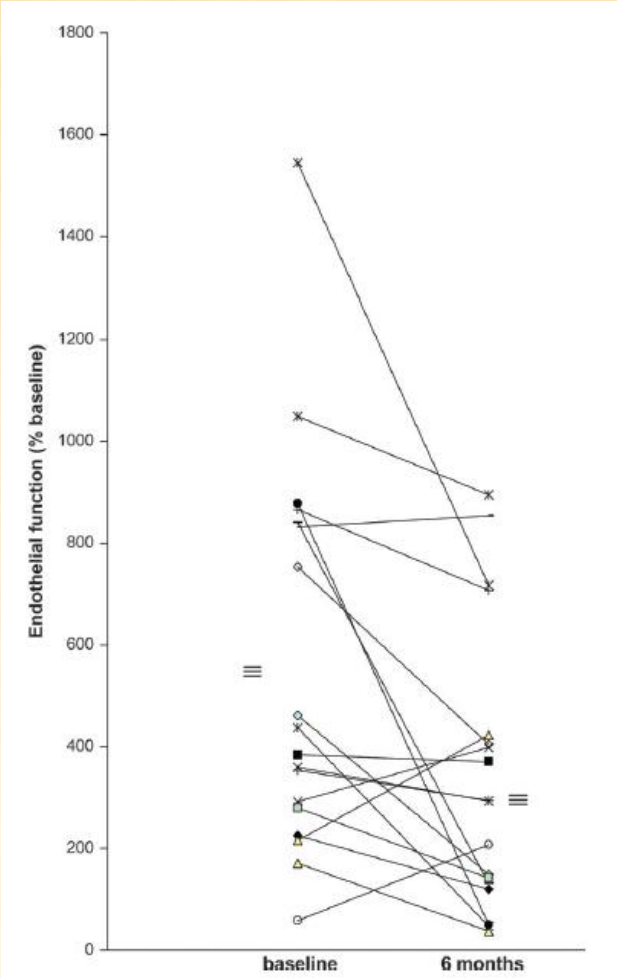
- Exact mechanism unknown
- Adrenergic system and renin-angiotensin-aldosterone axis do not play a role
- Changes in VEGF levels do not correlate with hypertension

- Proposed mechanisms
  - Decreased VEGF leads to nitric oxide down regulation.
  - Acute cholesterol emboli syndrome

Mourad. *Ann Oncol*. 2008;19:927-934; Lacouture. Angiogenesis Foundation website. 2009.

Microcirculatory Changes Induced by Bevacizumab and Hypertension





Pilocarpine iontophoresis induced forearm skin perfusion as surrogate for endothelial cell function

Mourad. *Ann Oncol*. 2008;19:927-934.

Hypertension: CTC Definitions

Version	Grade1	Grade 2	Grade 3	Grade 4
CTC V2 March 1998	Transient, asymptomatic> 150/100 or > 20 mmHg increase	Persistent > 150/100 or > 20 mmHg increase or symptomatic not needing treatment	Requiring therapy	Hypertensive crisis
CTC V3 August 2006	As above	As above	As above	Life threatening consequences or crisis
CTC V4 June 2010	Prehypertension Systolic 120-139 or diastolic 80-89 mmHg	Stage 1 hypertension recurrent or persistent, if normal pre drug > 140/90 mmHg or 140-159/90-99 mmHg	Stage 2 hypertension BP > 160 mmHg or diastolic > 100 mmHg more than one drug or more intensive than before	Urgent intervention due to malignant hypertension or transient or permanent neurological deficit

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Hypertension: Management

- No evidence-based guidelines or expert consensus
- Optimal BP control prior to initiating VEGF inhibitors for all patients
- Caution in patients with pre-existing hypertension
- Monitor BP every 2-3 weeks in all patients
- Encourage home BP monitoring
- Permanently discontinue for hypertensive crisis or encephalopathy
- Temporarily discontinue for uncontrolled hypertension
- BP does not need to be monitored after therapy is discontinued
- Calcium channel blockers and ACE inhibitors have been used successfully
- Typically requires more than one anti-hypertensive agent

Copur. *Clin Colorectal Cancer.* 2009;10:151-156.

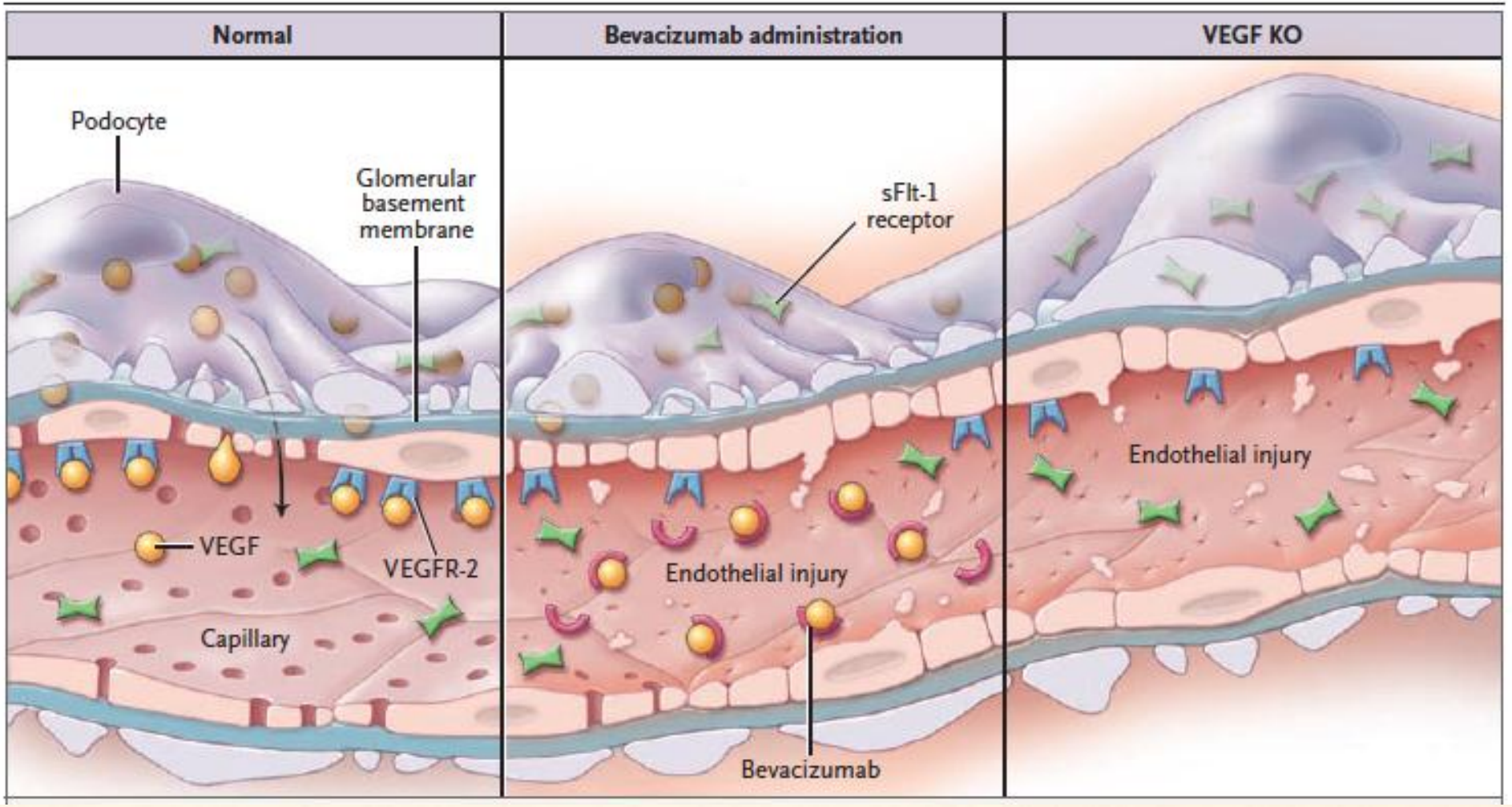
Proteinuria: Incidence

Reference	Cancer	Treatment	N	Overall Incidence	Grade 3/4
Kabbinavar (2003)	Colon	FU/LV + bev 5 mg/kg or 10 mg/kg	104	5 mg/kg, 23%;10 mg/kg, 28%	0
Hurwitz (2004)	Colon	IFL + bev 5 mg/kg vs IFL	813	26.5%	0.8%
Kabbinavar (2005)	Colon	FU/LV + bev 5 mg/kg vs FU/LV	209	38%	1%
Giantonio (2007)	Colon	FOLFOX4 + bev 10 mg/kg vs FOLFOX4	829	NR	0.7%
Van Cutsem (2012)	Colon	FOLFIRI + aflibercept vs FOLFIRI	1226	62.2%	7.8%

Gressett. *Ann Pharmacother*. 2009;43:490-501; Van Cutsem. *J Clin Oncol*. 2012. Published ahead of print, Sept 4.

Proteinuria Pathophysiology

Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy



Eremina. *N Eng J Med*. 2008;358:1129-1136.

Proteinuria: Management

- No controlled studies
- Periodic monitoring of urinary protein should be carried out in all patients
- Grade 2/3, obtain 24-hour urine protein
  - If < 2 g/24 hr, continue therapy
  - If > 2 g/24 hr, hold therapy until < 2 g/24 hr
- Grade 4, permanently discontinue therapy

Izzedine. *Eur J Cancer.* 2010;46:439-48.

Gastrointestinal (GI) Perforation

- Infrequent but serious
- Meta-analysis of 17 RCT of BEV for solid tumors[1]
  - Overall incidence 0.9% with mortality rate of 21.7% of cases
- Risk significantly increased in patients with mCRC (P=.016)
- BEAT[2] and BRiTE[3] studies: 2% incidence

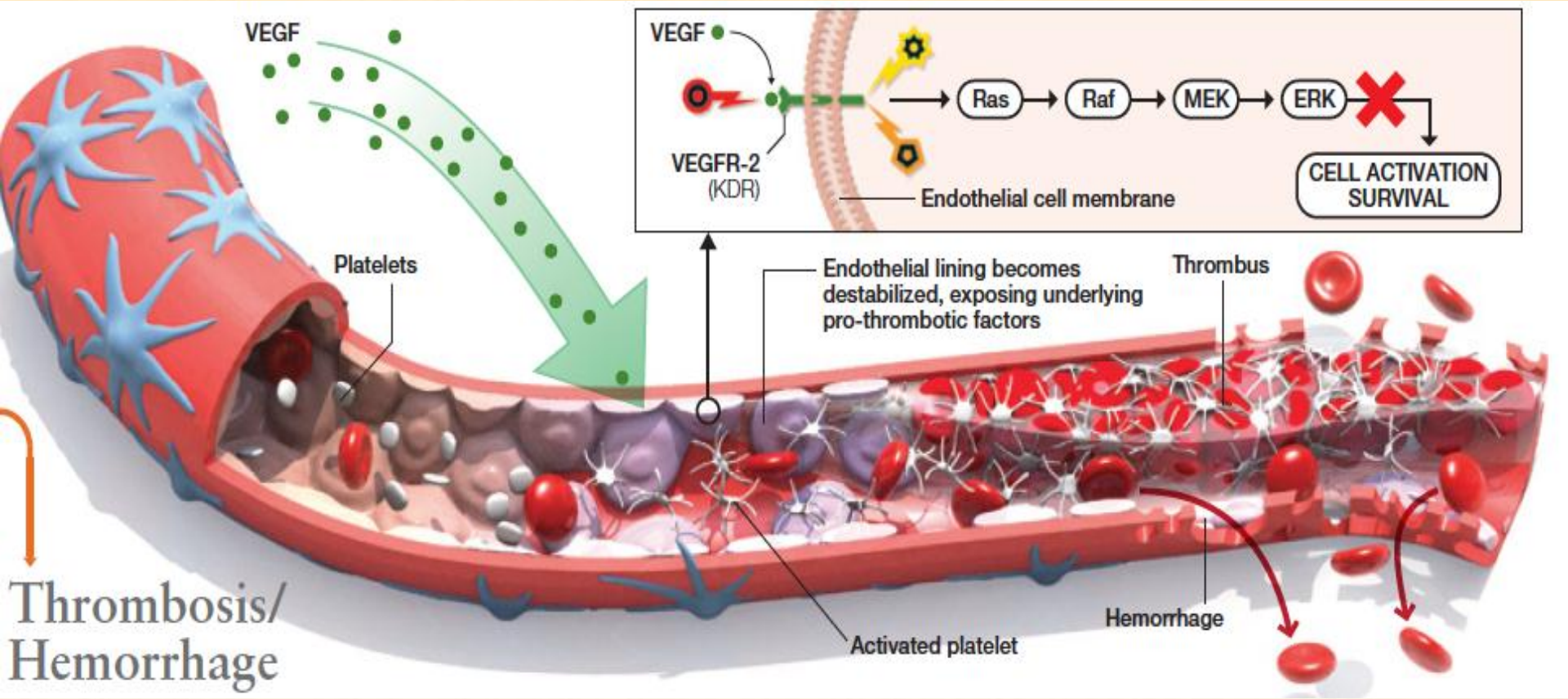
[1]Hapani. *Lancet Oncol.* 2009;10:559-1568; [2]Van Cutsem. *Ann Oncol.* 2009;20:1842-1847; [3]Grothey. *J Clin Oncol*. 2008;20:5326-5334.

GI Perforation: Risk Factors With Bevacizumab Treatment for CRC

- Stent Placement
- Intact primary tumor
- Acute diverticulitis
- Intra-abdominal abscess
- Gastric ulcer
- GI obstruction
- Abdominal carcinomatosis
- Prior abdominal or pelvic radiation

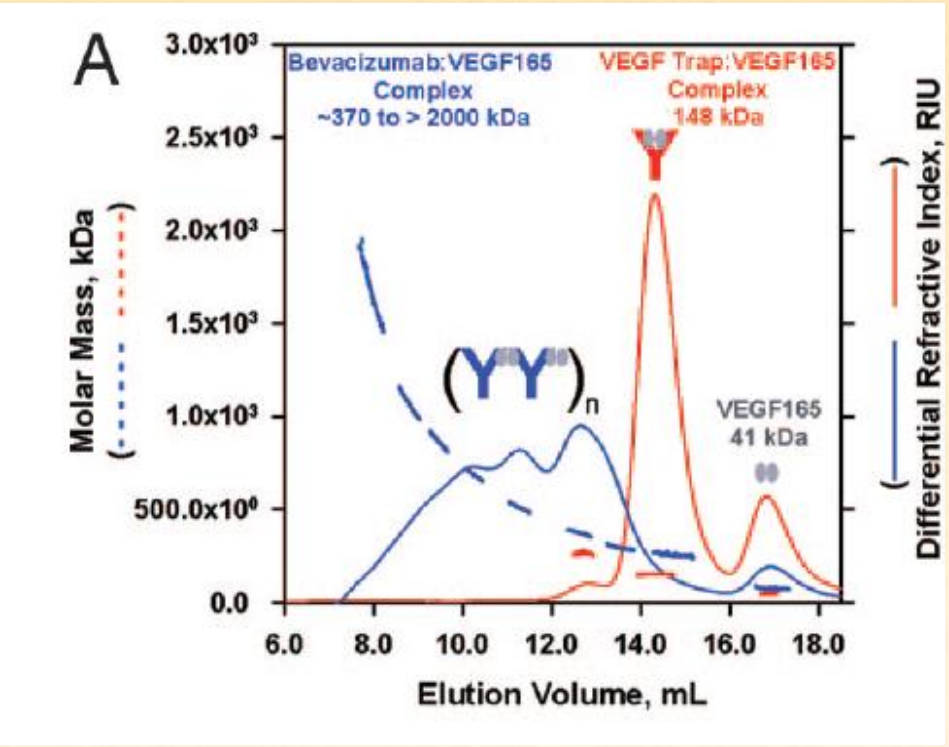
Chau. *Lancet Oncol.* 2009;10:534-535.

Thrombosis: Pathophysiology

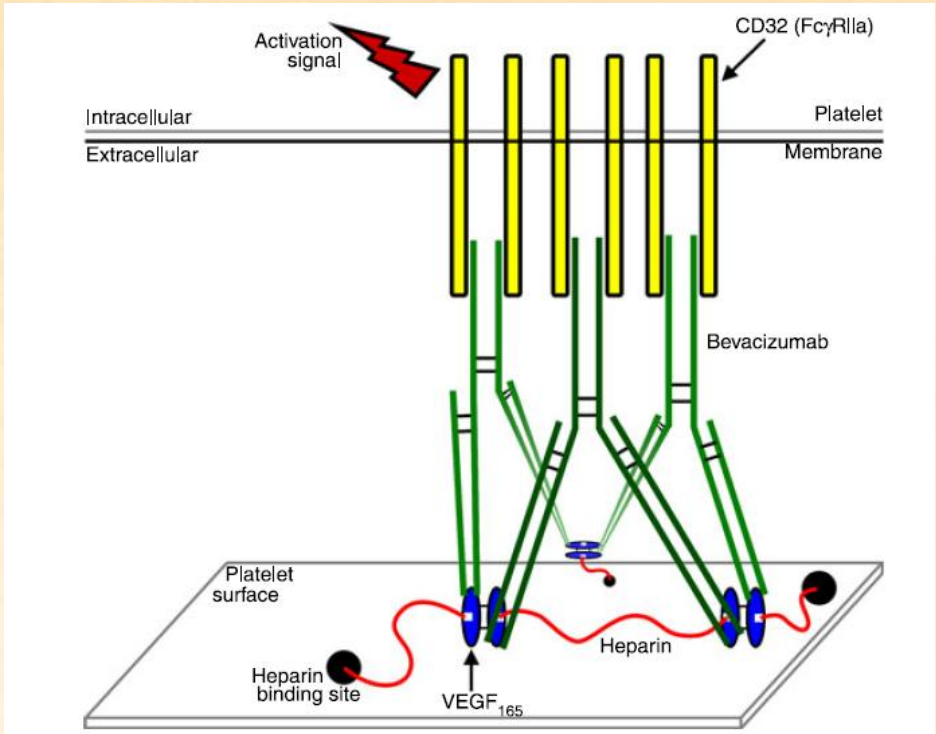


Lacouture. Angiogenesis Foundation website. 2009.

Thrombosis: Pathophysiology With VEGF Binding Antibodies



Size exclusion chromatography[1]



Mechanism of Fab-dependent Bev + VEGF + UFH IC[2]
Anchoring to platelets activating FcgRIIa

[1]Rudge. *PNAS*. 2007;104:18363-370; [2]Meyer. *J Thromb Haemost*. 2009;7:171-181.

Bevacizumab: Adverse Events
BEAT study (1914 Patients)

Event	Any AE or SAE, %					Grade 3/4 AE or SAE, %				
	Overall (n=1914)	Mono-therapy (n=300)	FOLFIRI (n=503)	FOLFOX (n=552)	XELOX (n=346)	Overall (n=1914)	Mono-therapy (n=300)	FOLFIRI (n=503)	FOLFOX (n=552)	XELOX (n=346)
Hypertension	30	30	32	26	34	5	7	5	3	9
Proteinuria	10[a]	9	10	10	14	1[b]	2	1	<0.5	2
Bleeding	31	22	40	32	25	3	5	3	3	2
Wound healing complication	4	3	4	4	4	1[b]	1	2	2	0
Arterial thromboembolic event	2	1	1	2	2	1[b]	1	1	2	2
GI perforation	2[c]	2	2	2	1	2	2	2	2	1

[a]At baseline, 808% reported grade 1/2 and 0.2% grade 3/4 proteinuria

[b]No fatal events

[c]One patient hospitalized for microperforation

FOLFIRI, 5-fluorouracil/leucovorin + irinotecan; FOLFOX, 5-fluorouracil/leucovorin + oxaliplatin; XELOX, capecitabine + oxaliplatin; GI, gastrointestinal

Van Cutsem. *Ann Oncol.* 2009;20:1842-1847.

Aflibercept: Adverse Events
Meta-analysis

Grade 3-4 AEs	Placebo N=1329	Aflibercept N=1333	RR (95% CI)
Hypertension*	1.6	14.6	9.21 (5.91 to 14.36)**
Proteinuria	0.8	6.3	8.37 (4.37 to 16.06)**
Cardiac dysfunction	<0.1	0.5	5.98 (0.72 to 49.62)
GI perforation	0.2	0.8	3.32 (0.92 to 12.05)
Fistula	<0.1	0.2	2.99 (0.31 to 28.72)
Hemorrhage	1.5	3.1	2.04 (1.20 to 3.47)**
Arterial thromboembolic event	1.0	1.7	1.69 (0.85 to 3.34)
Osteonecrosis	<0.1	<0.1	1.00 (0.06 to 15.92)
Venous thromboembolic event	6.4	6.1	0.95 (0.71 to 1.28)
Impaired wound healing	0	0.2	Not assessable

GI, gastrointestinal; RR, relative risk.

*Grade 3: 2 drugs needed to control blood pressure

**P<0.05

Summary

- Colorectal patients on common regimens have G3-4 toxicity rates of 60-75%[1-4]
- Rates of grade 3-4 toxicity are increased with EGFR inhibitors and VEGF binding antibodies to 77-94%
- For chemotherapy + biologicals regimens 85% of the G3-4 toxicity is due to chemotherapy
- On-target toxicity of monoclonals is maneagable

1.Hurwitz et al NEJM 2004, 350, 2335; 2. Satz et al, 2008, JCO, 26, 2013; 3 Giantionio et al, 2007, JCO 25 1539; 4 Van Cutsem et al,2011 JCO, 29, 2011

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CLINICAL CASE

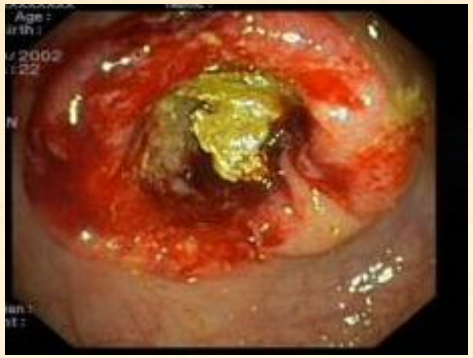
Marc Peeters, MD, PhD
Professor of Oncology
Department of Oncology
Antwerp University Hospital
Edegem, Belgium

Case 2: Presentation (1)

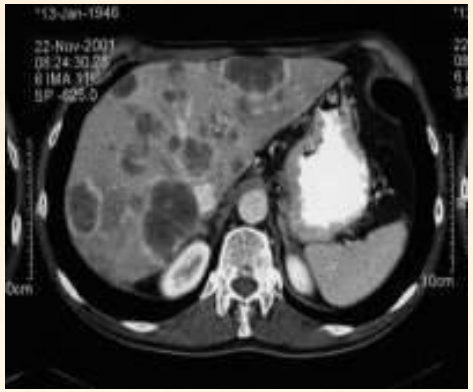
- Demographics
  - Female patient, 54 years of age
- Co-morbidity
  - (Well-controlled) hypertension
  - Diabetes
- Current History
  - 08/2012: weight loss (-3 kg/2months), fatigue, constipation

Case 2: Presentation (2)

- Diagnosis
  - CEA 196.4 µg/L (3.0 µg/L)



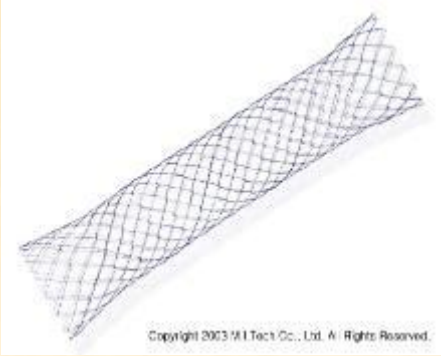
Stenotic adenocarcinoma in sigmoid



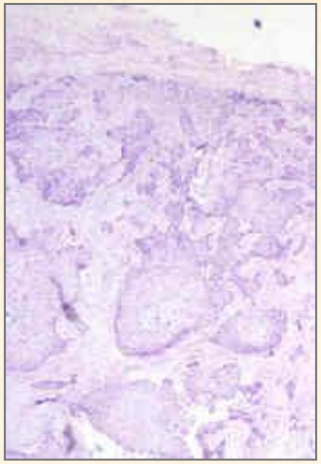
Diffuse liver metastases

Case 2: Presentation (3)

- Therapy



Colostent was placed at the primary tumor site



KRAS satus: wild type

Case 2: Presentation (4)

- Therapy
  - Bevacizumab/FOLFIRI was started

What about the stent and the presence of diabetes?

- After 5 cycles the patient developed hypertension (140/90) with proteinuria (grade 2)

What would you do next?

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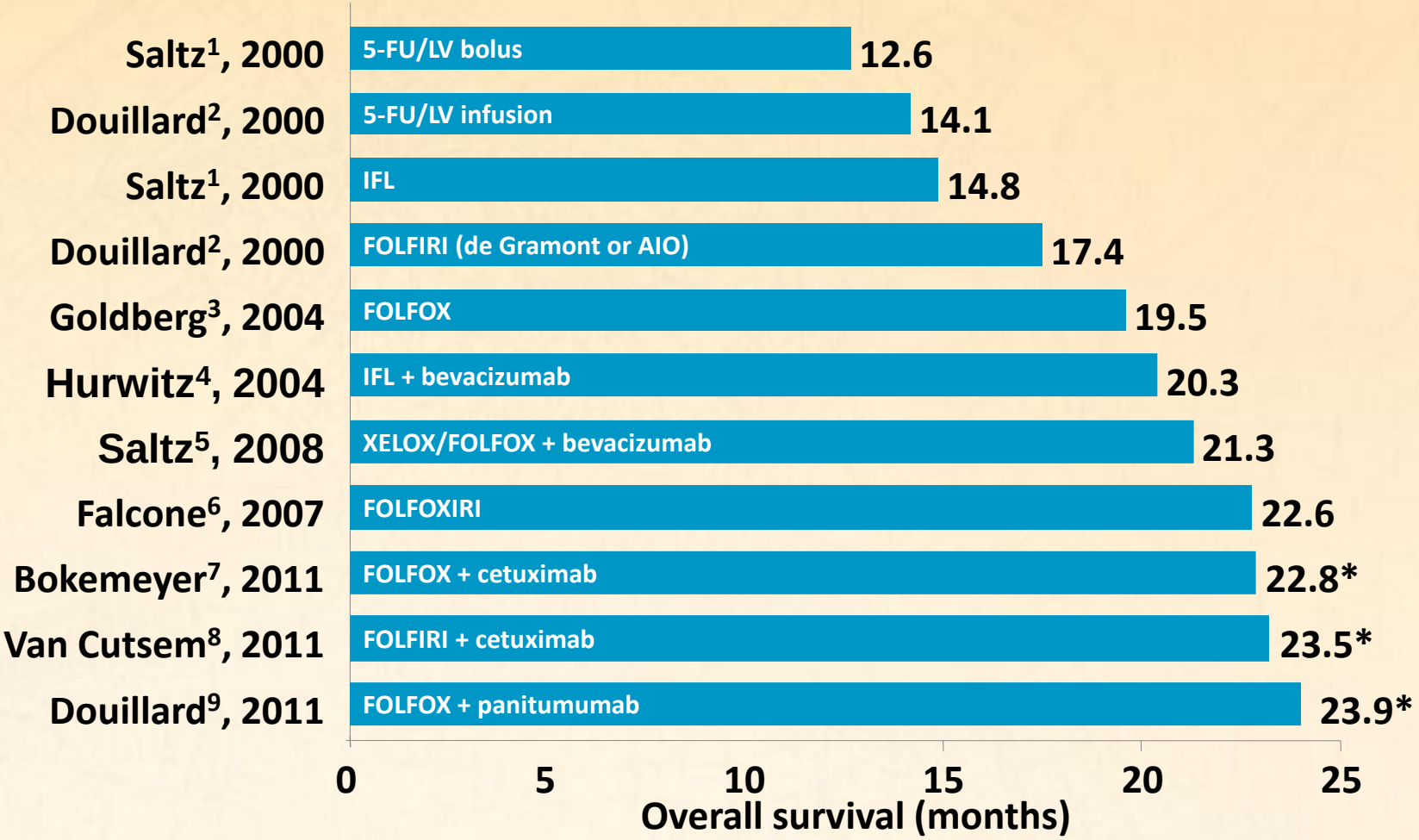
OPTIMIZING EVIDENCE-BASED DECISIONS IN METASTATIC CRC

David Cunningham, MD, FRCP FMedSci
Consultant Medical Oncologist and
Head of the Gastrointestinal Unit
Royal Marsden NHS Foundation Trust
Sutton, UK

OS from mCRC has improved incrementally over the past decade



1. N Engl J Med 2000;343:905–14; 2. Lancet 2000;355:1041–7; 3. J Clin Oncol 2004;22:23–30;
4. N Engl J Med 2004;350:2335–42; 5. J Clin Oncol 2008;26:2013–9; 6. J Clin Oncol 2007;25:1670–6;
7. Ann Oncol 2011;22:1535–46; 8. J Clin Oncol 2011;29:2011–9; 9. J Clin Oncol 2011;29(Suppl):3510(oral).

Cross trial comparison.
*KRAS WT population.
mCRC, metastatic colorectal cancer.

How do we optimise therapy for the individual patient?

- Factors to consider
  - Clinical
  - Treatment goals (curative, palliative)
  - Treatment strategy (sequential/combined, maintenance?)
- Guidelines and decision trees (NCCN, ESMO)
- Biomarkers
  - KRAS/BRAF, angiogenesis, gene expression profiling
- Ongoing studies and future directions

Considerations in mCRC Treatment

- Clinical Characteristics
  - Age
  - PS
  - Co-morbidities

suitable for single agent / doublet / triplet regimen?

- Radiological Characteristics
  - Widespread
  - Oligometastatic
    - Liver / lung / pelvic recurrence

Potential Radical Treatment?

Second-line and Third-line Treatment Considerations

- Rechallenge?
  - Timing of progression
  - Preexisting toxicities (neuropathy)
- Dependent upon first-line regimen administered
  - FOLFOX ↔ FOLFIRI
  - Biologics
    - anti-EGFR, anti-angiogenic strategy (continue vs. switch)
- ? Prior maintenance

1. NCCN Colon Cancer Clinical Practice Guidelines. V3.2011. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf; 2. Van Cutsem E, et al. *Ann Oncol*. 2010; 21(Suppl 5):v93-v97; 3. MD Anderson Cancer Center Colon Cancer Treatment Guidelines. Available at: http://utm-ext01a.mdacc.tmc.edu/mda/cm/cwtguide.nsf/luhtml/sidebar1.

2012 NCCN Guidelines: Advanced/mCRC Patient Can Tolerate Intensive Therapy

First Line	Second Line	Third Line
FOLFOX CapeOx FOLFIRI 5-FU/leucovorin capecitabine ± bevacizumab cetuximab* (KRAS wt) panitumumab (KRAS wt) FOLFOXIRI	FOLFIRI FOLFOX Irinotecan ± bevacizumab cetuximab* (KRAS wt) panitumumab (KRAS wt) Aflibercept**	Cetuximab (KRAS wt) panitumumab (KRAS wt ± Irinotecan Clinical Trial BSC

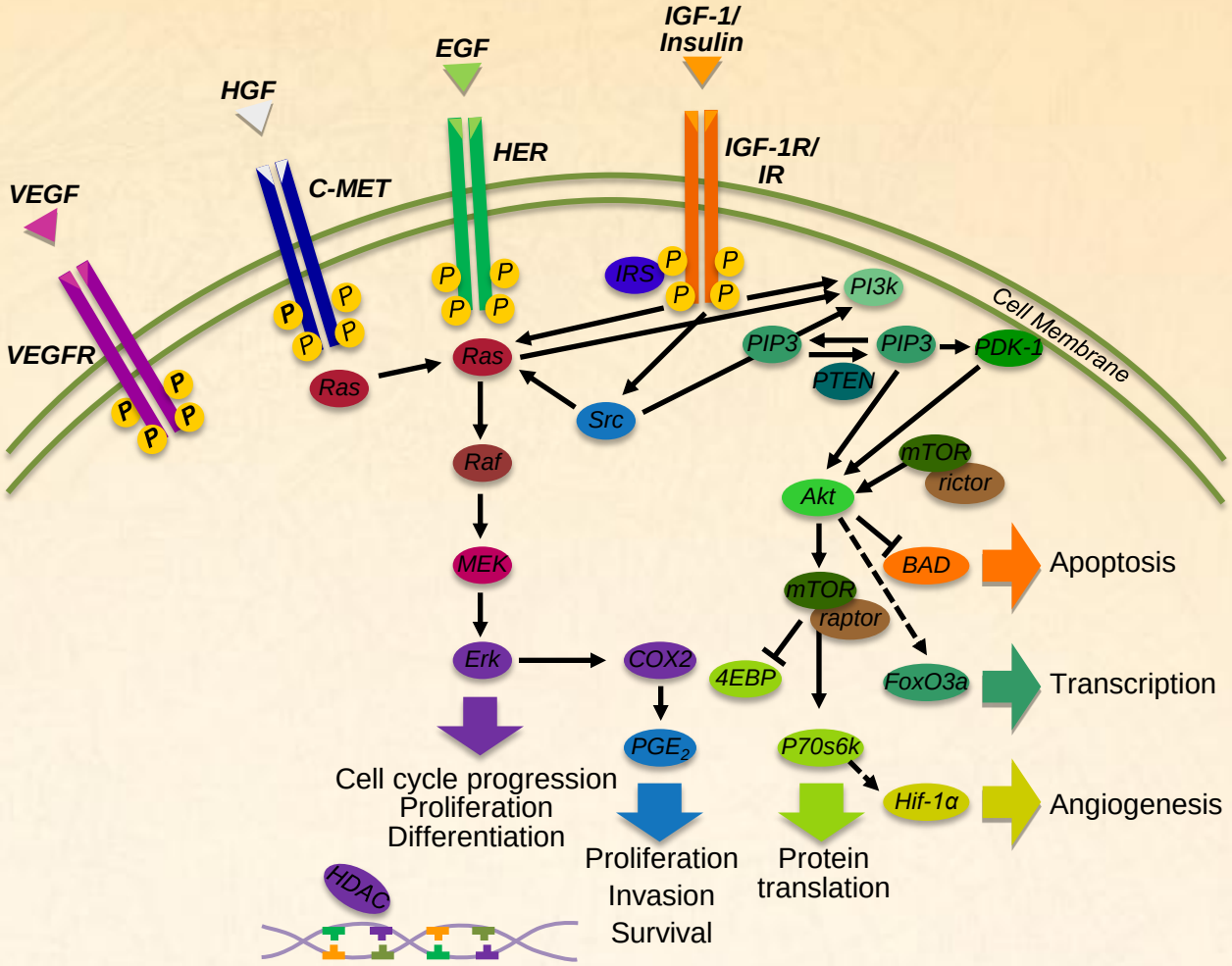
**

*Cetuximab not recommended with FOLFOX

**Aflibercept with irinotecan or FOLFIRI only

NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. V2.2010.

Signaling Pathways in Colon Cancer

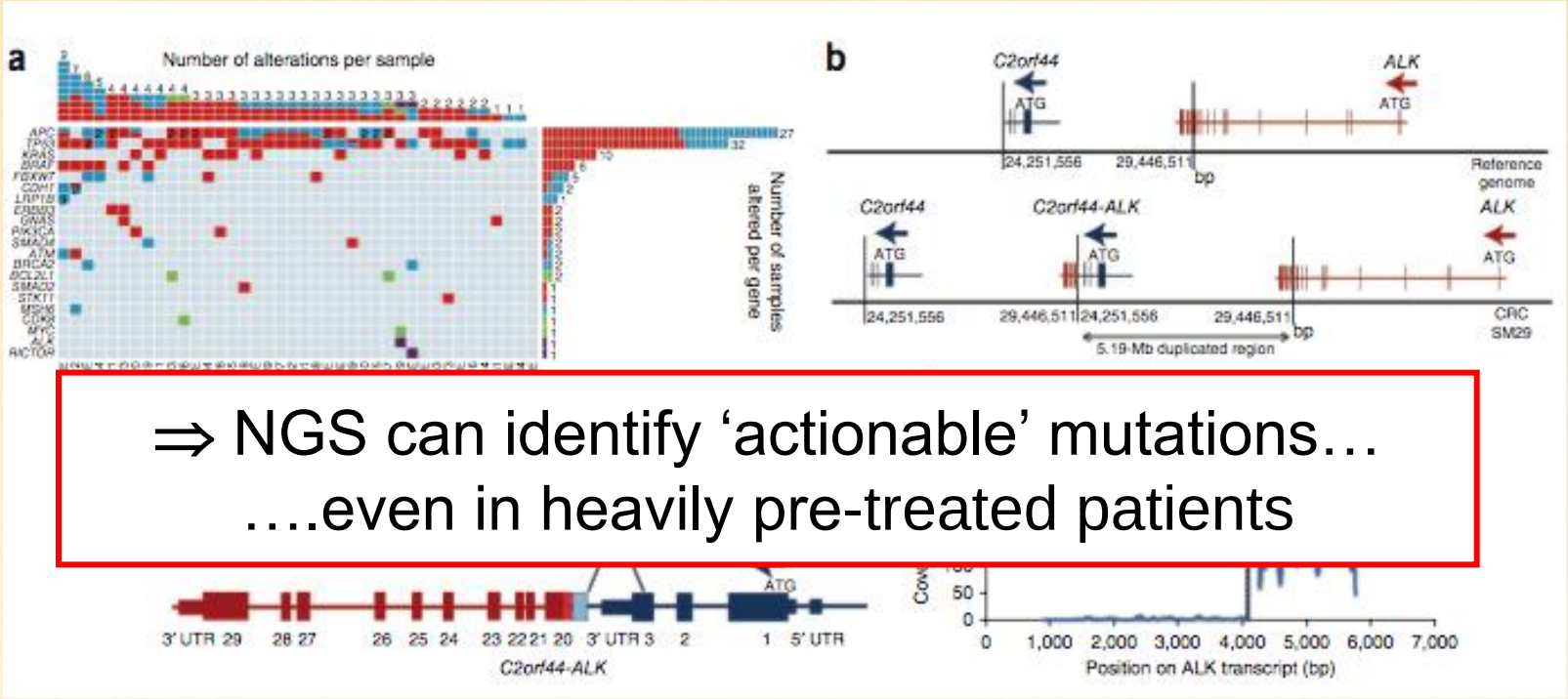


Adapted from Siena S, et al. J Natl Cancer Inst 2009;101:1–17.

Angiogenesis-related biomarkers: which approach?

- What biomarkers to identify?
  - Serum biomarkers
  - Receptors and ligands
  - Downstream effectors
  - Polymorphisms
- Where to look?
  - Primary tumour or metastases?
  - Tumour or stroma or both?
- When to look?
  - Baseline only (tumour-based)
  - On treatment changes of angiogenesis-related biomarkers

Targetable Mutations in CRC Using Next Generation Sequencing Technologies

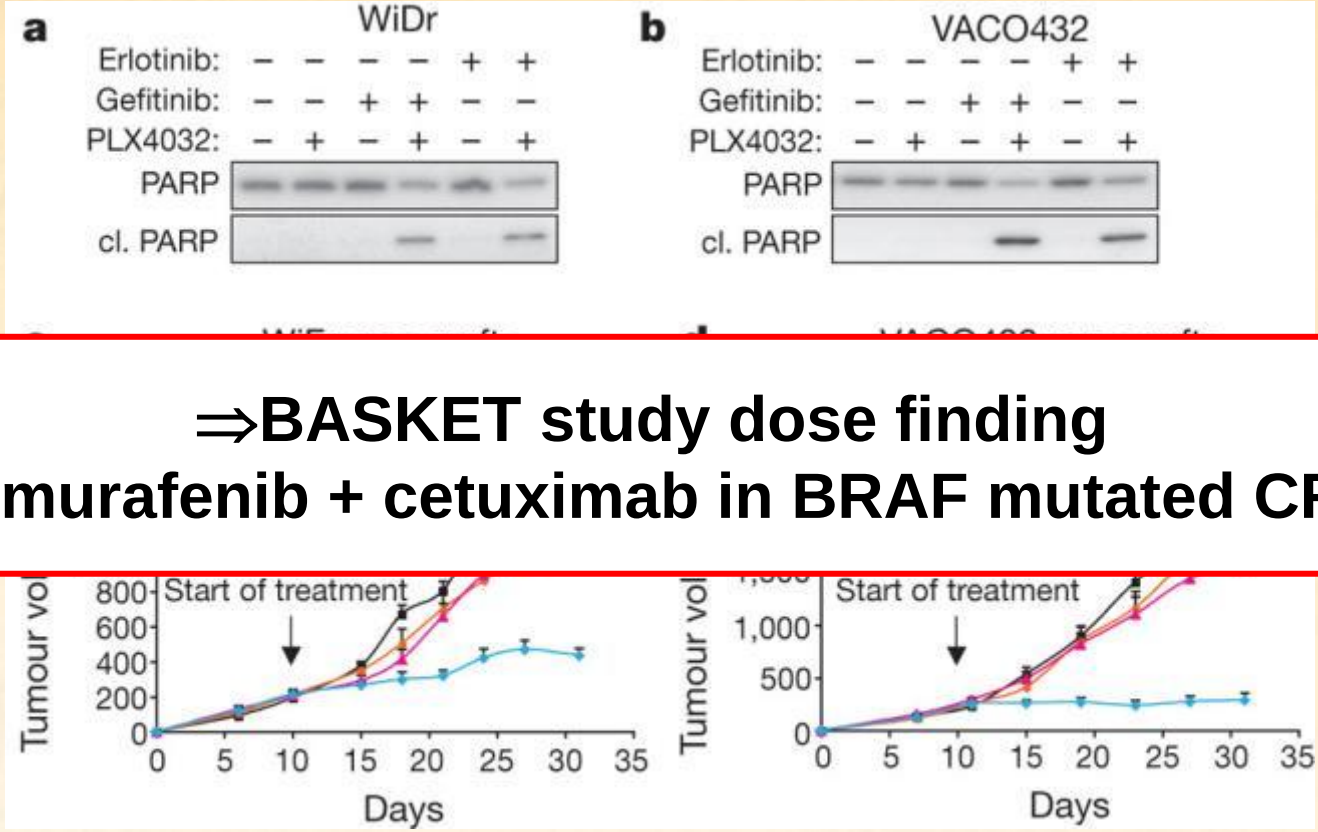


⇒ NGS can identify 'actionable' mutations…
….even in heavily pre-treated patients

40 tumours:

- 1 ALK translocation (with 90-fold increase in expression)
- 2 BRCA2 mutations

EGFR and BRAF(V600E) inhibitors synergize to induce apoptosis of CRC cells and to suppress CRC tumour growth in a xenograft model



⇒BASKET study dose finding vemurafenib + cetuximab in BRAF mutated CRC

A Prahallad *et al. Nature* **000**, 1-5 (2012) doi:10.1038/nature10868

Conclusions

- Identifying goals of treatment is key
- Integration of clinical, biological and therapy related factors to optimise treatment outcomes
- With the exception of KRAS/BRAF biomarker data for chemotherapy and targeted agents is not robust
- Optimising molecular selection for future clinical trials and treatment strategies is essential

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CLINICAL CASE

CHOOSING AN OPTIMAL FIT exploring TREATMENTS FOR THE PATIENT WITH METASTATIC COLORECTAL CANCER

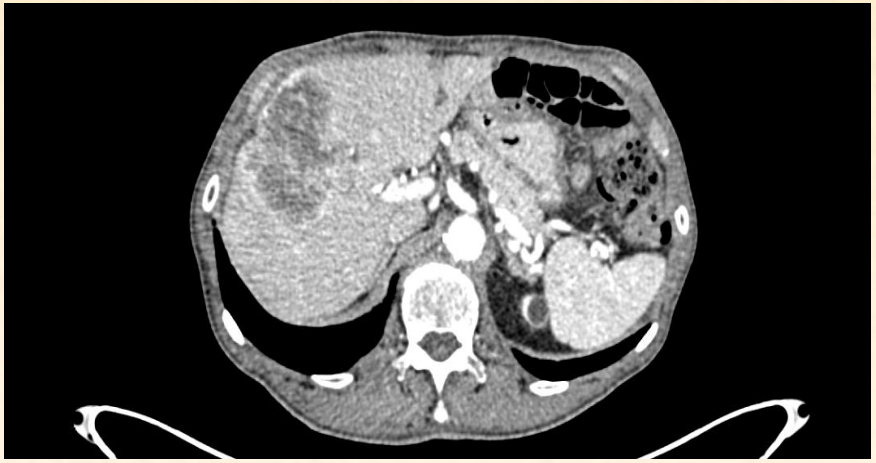
Marc Peeters, MD, PhD
Professor of Oncology
Department of Oncology
Antwerp University Hospital
Edegem, Belgium

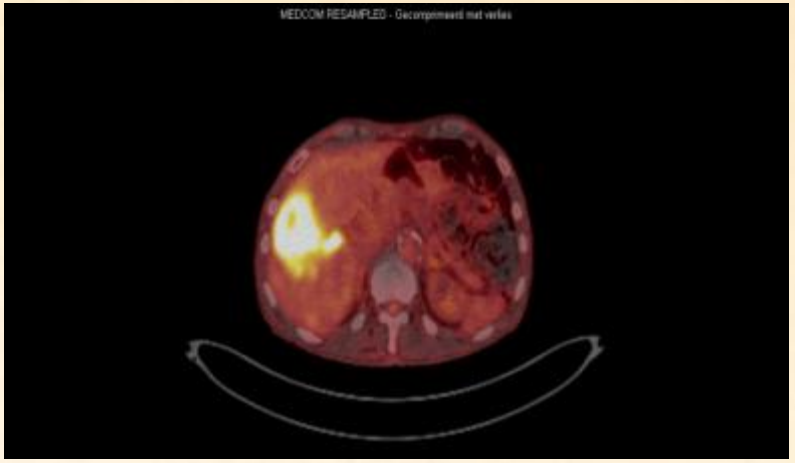
Case 3: Presentation (1)

- Demographics
  - Male patient, 70 years of age
- Co-morbidity
  - (well-controlled) hypertension
  - Hypercholesterolemia
  - TURP
- Oncological History
  - 08/2003: resection for sigmoid adenocarcinoma, pT2N0M0

Case 3: Presentation (2)

- Current History
  - Asymptomatic, CEA 80.5 µg/L (3.0 µg/L)
  - Liver metastasis, segment IV-VIII (9.8/7.2 cm), FDG positivity



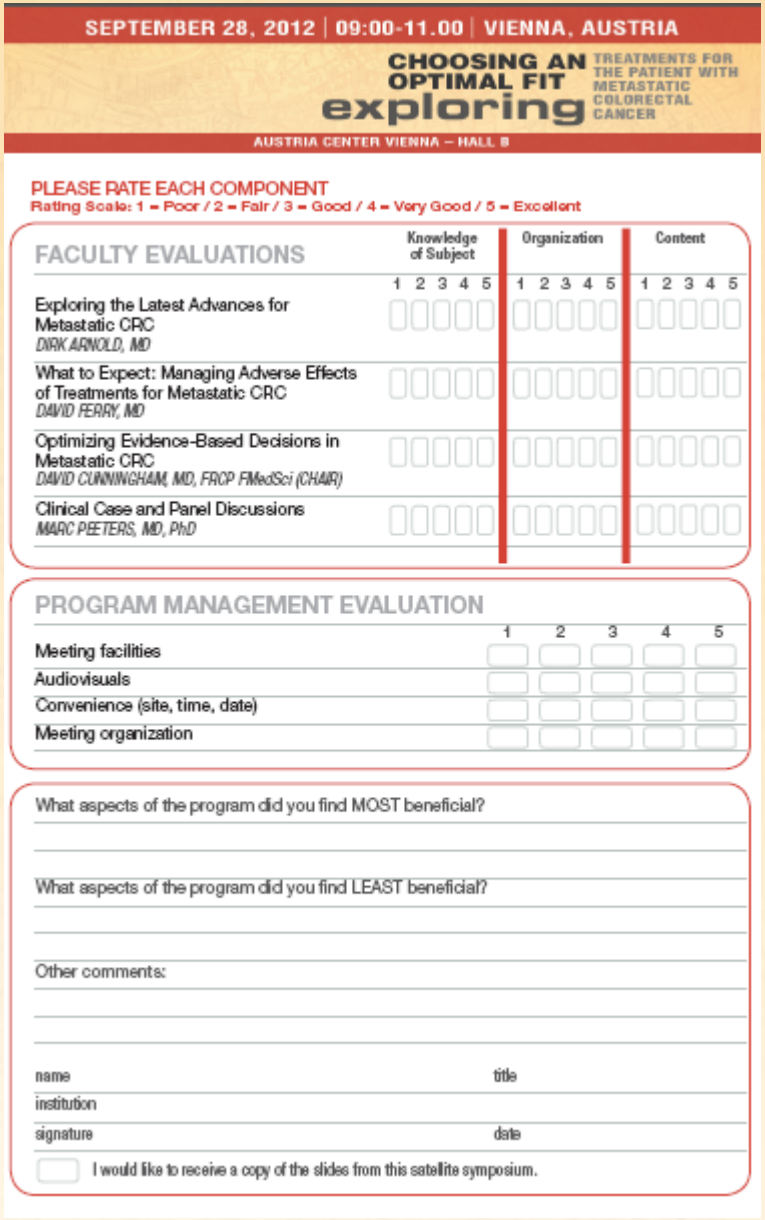


Case 3: Questions to the Panel (1)

1. Do you need additional (diagnostic) information on this patient?

2. If systemic treatment is proposed, which regimen would you advise to the patient?

Please complete your evaluation form and return at the end of the program for a copy of the slides



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PLEASE RATE EACH COMPONENT

Rating Scale: 1 = Poor / 2 = Fair / 3 = Good / 4 = Very Good / 5 = Excellent

FACULTY EVALUATIONS

	Knowledge of Subject	Organization	Content
	1 2 3 4 5	1 2 3 4 5	1 2 3 4 5
Exploring the Latest Advances for Metastatic CRC *DIRK ARNOLD, MD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
What to Expect: Managing Adverse Effects of Treatments for Metastatic CRC *DAVID FERRY, MD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Optimizing Evidence-Based Decisions in Metastatic CRC *DAVID CUNNINGHAM, MD, FRCP FMedSci (CHAIR)*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐
Clinical Case and Panel Discussions *MARC PEETERS, MD, PhD*	☐☐☐☐☐	☐☐☐☐☐	☐☐☐☐☐

PROGRAM MANAGEMENT EVALUATION

	1	2	3	4	5
Meeting facilities	☐	☐	☐	☐	☐
Audiovisuals	☐	☐	☐	☐	☐
Convenience (site, time, date)	☐	☐	☐	☐	☐
Meeting organization	☐	☐	☐	☐	☐

What aspects of the program did you find MOST beneficial?

What aspects of the program did you find LEAST beneficial?

Other comments:

name title

institution

signature date

☐ I would like to receive a copy of the slides from this satellite symposium.

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