Enhancing Clinical Outcomes in mCRC
Targeted Therapy Is Making Impact

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prIME oncology

Declaration of Conflicts of Interest

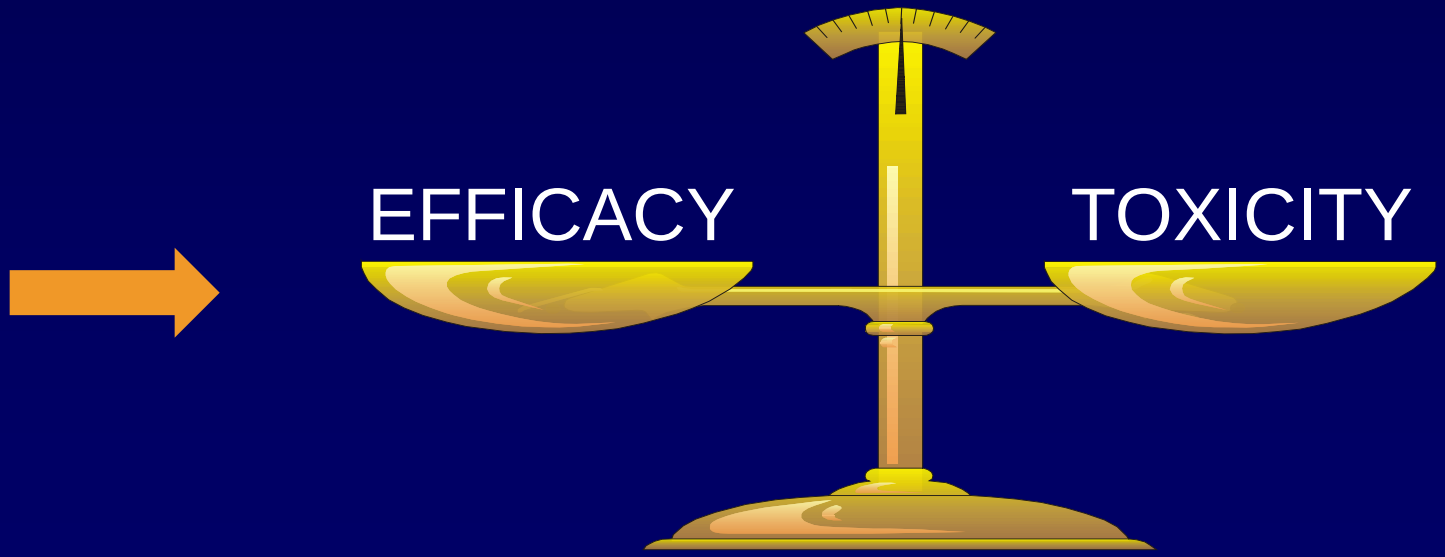
- Clinical Research: Amgen, Boehringer Ingelheim, Ipsen, Merck Serono, Novartis, Roche, Sanofi, Sirtex
- Scientific Presentations: Amgen, Bayer, Ipsen, Merck Serono, Novartis, Roche, Sanofi, Sirtex
- Consulting Activities: Amgen, Bayer, Ipsen, Merck Serono, Novartis, Roche, Sanofi, Sirtex

Introduction –
Rationale of Targeted Therapy

Het Zwin | Photograph: Joop van Houdt

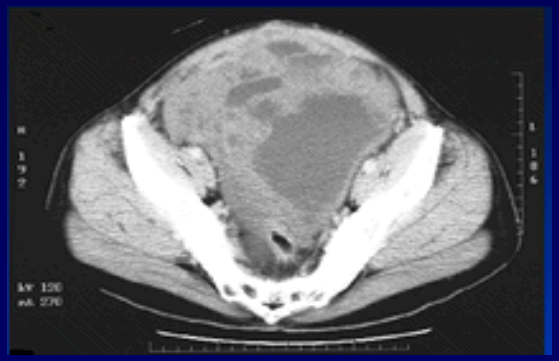
Introduction –
Rationale of Targeted Therapy

- **More efficacy** by tumorigenesis-driven therapy
- **Less toxicity** by tumor cell–directed therapy
- **Personalized** by ‘biomarker’-based therapy



Introduction –
GIST As an Example

KIT mutation	PDGFRA D842V	Wildtype
76.1 %	10.0 %	13.9 %
- Exon 11 (65 %): 400 mg/d - Exon 9 (9.4 %): 800 mg/d	No	?



ESMO Clinical Pracice Guidelines: Gastrointestinal Stromal Tumors. *Ann Oncol.* 2012;23(Suppl 7):49-55.

Systemic Treatment in ColoRectal Cancer

	‘Cell cycle’	‘Growth’	‘Angiogenesis’
▪ Chemotherapy	- 5-Fluorouracil - Capecitabine - Irinotecan - Oxaliplatin - Mitomycin		
▪ Small molecules (-nibs)		/	- Regorafenib
▪ Antibodies (-mabs)		- Cetuximab - Panitumumab	- Bevacizumab - Aflibercept

Systemic Treatment in ColoRectal Cancer

	Therapy	Outcome
▪ Nonmetastatic		
- early CRC	local resection	recurrence, OS
- CRC	resection (neo) adjuvant	OS, DFS, recurrence
▪ Metastatic		
- diffuse	Palliative	QOL, PFS, OS
- limited	Induction Neoadjuvant	Response, OS

Chemotherapy in mCRC

	1st-line Tx	RR, %	PFS, Months	2nd-line Tx	RR, %	PFS, months	OS, months	2nd PFS, months
Arm A	FOLFIRI n = 109	56	8.5	FOLFOX n = 81	15	4.2	21.5	14.2
Arm B	FOLFOX n = 111	54	8.0	FOLFIRI n = 69	4	2.5	20.6	10.9
		P = NS	*P = .26*		*P = .05*	*P = .003*	*P = .99*	*P = .64*

RR, response rate; PFS, progression-free survival; OS, overall survival

Tournigand C, et al. *J Clin Oncol.* 2004;22(2):229-237.

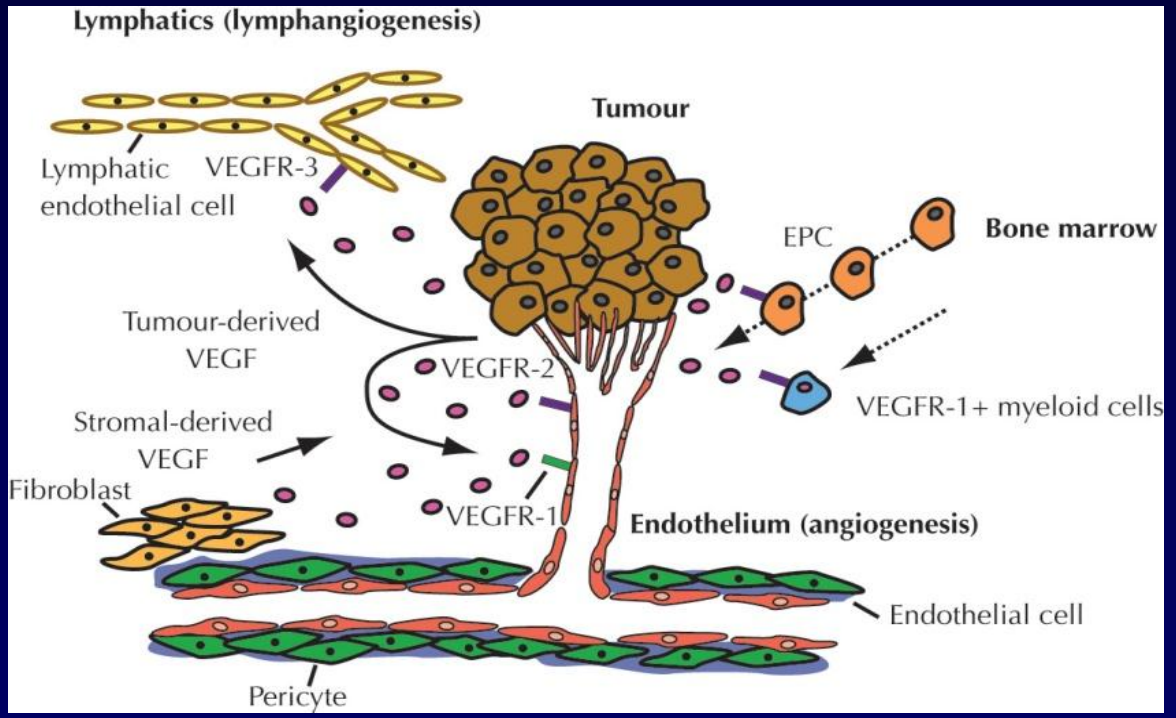
VEGF is a Key Mediator of Angiogenesis and Tumor Development in mCRC

- **Angiogenesis is mediated via the interaction of VEGF and VEGF receptors[1-5]**

Facilitates survival of existing endothelial cells[1,2,6–8]

Stimulates new vessel growth[1,2,6-9]

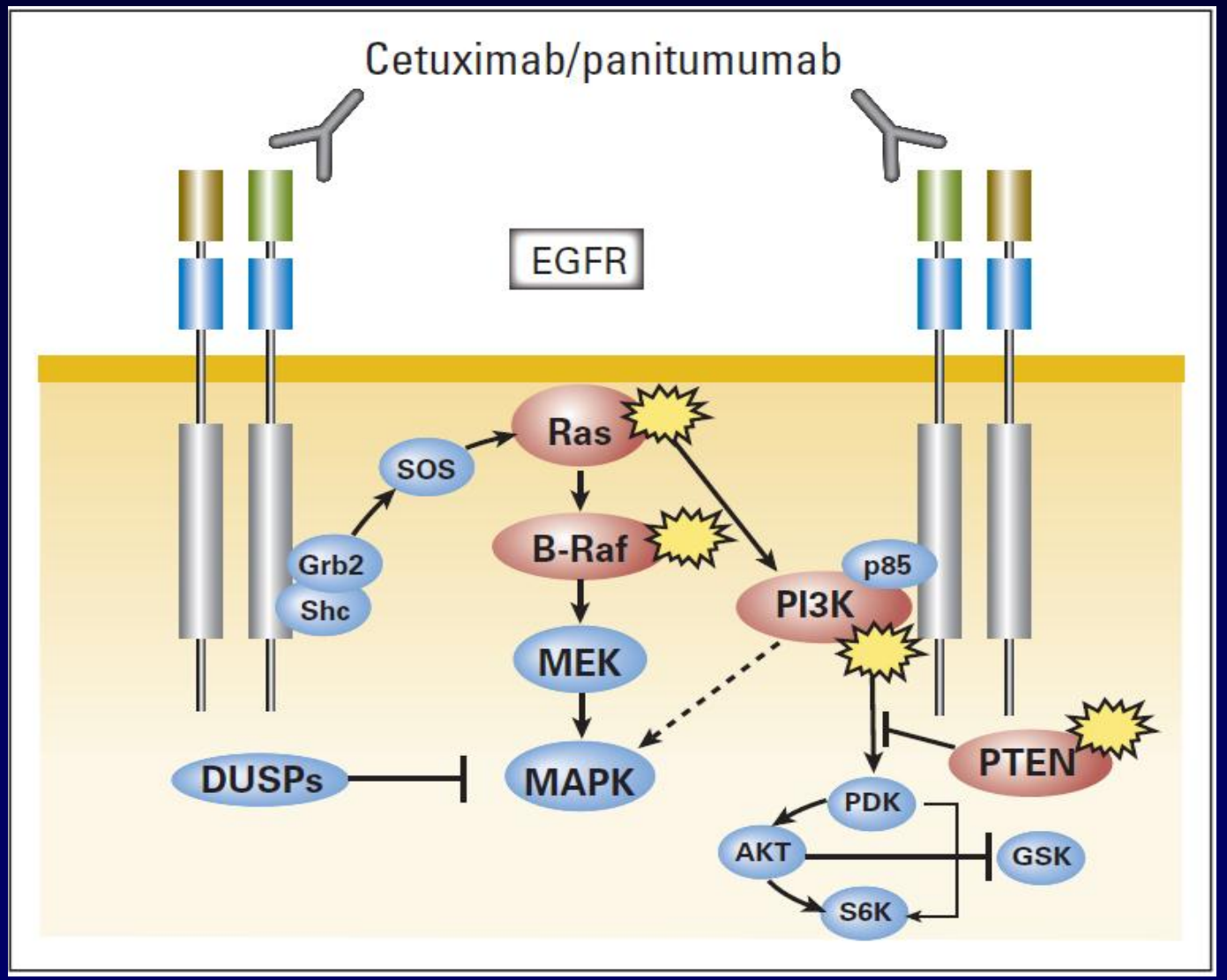
Increases vessel permeability[10,11]



Adapted from Hicklin DJ, et al. *J Clin Oncol.* 2005;23(5):1011-1027.

1. Ferrara N. *Endocr Rev.* 2004;25(4):581-611. 2. Hicklin DJ, et al. *J Clin Oncol.* 2005;23(5):1011-1027. 3. Baka S, et al. *Expert Opin Ther Targets.* 2006;10(6):867-876. 4. Morabito A, et al. *Oncologist.* 2006;11(7):753-764. 5. de Vries C, et al. *Science.* 1992;255(5047):989-991. 6. Bergers G. et al. *Nat Rev Cancer.* 2003;3(6):401-410. 7. Jain RK. *Science.* 2005;307(5706):58-62. 8. Gerber HP, et al. *Cancer Res.* 2005;65(3):671-680. 9. Inoue M, et al. *Cancer Cell.* 2002;1(2):193-202. 10. Margolin K. *Curr Oncol Rep.* 2002;4(1):20-28. 11. Hu L, et al. *Am J Pathol.* 2002;161(5):1917-1924.

Epidermal Growth Factor Axis



Targeted Therapy in mCRC – Efficacy

Endpoint	IFL plus Placebo	IFL plus Bevacizumab	*P* value
Median survival, mos	15.6	20.3	<.001
Hazard ratio for death		0.66	
One-year survival rate, %	63.4	74.3	<.001
Progression-free survival, mos	6.2	10.6	<.001
Hazard ratio for progression		0.54	
Overall response rate, %	34.8	44.8	.004
Complete response	2.2	3.7	
Partial response	32.6	41.0	
Median duration of response, mos	7.1	10.4	.001
Hazard ratio for relapse		0.62	

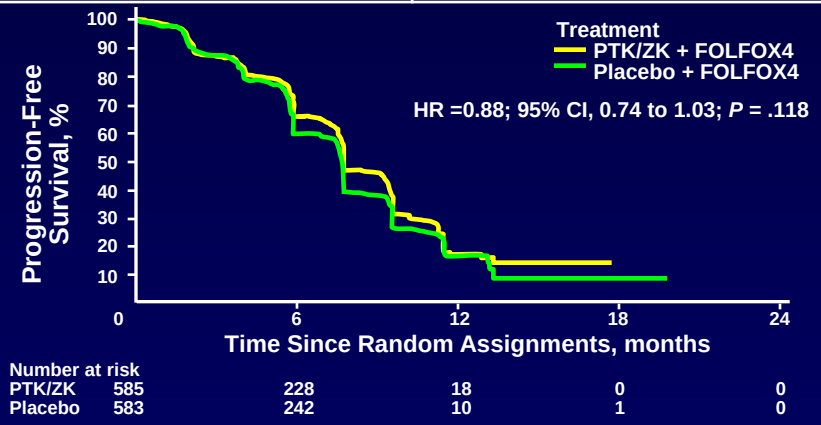
IFL, irinotecan, fluorouracil, and leucovorin

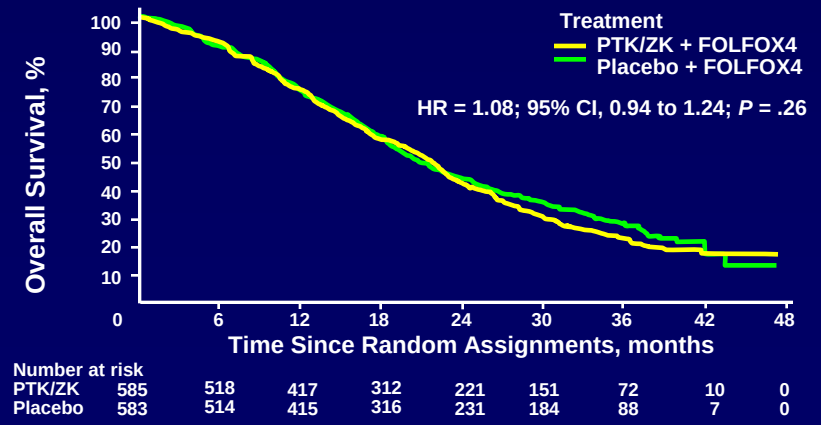
Hurwitz H, et al. *N Engl J Med.* 2004;350(23):2335-2342.

		First line			Second line			Chemoresistant		
		ORR %	PFS mos	OS mos	ORR %	PFS mos	OS mos	ORR %	PFS mos	OS mos
▪ 'Growth'										
Van Cutsem E, 2009	C	59.3	9.9	24.9						
Douillard JY, 2010	P	57.0	10.0	23.9						
Peeters M, 2010	P				35.0	5.9	14.5			
Van Cutsem E, 2007	P							10.0	2.0	NR
Jonker DJ, 2007	C							8.0	NR	6.1
▪ 'Angiogenesis'										
Hurwitz H, 2004	B	44.8	10.6	20.3						
Grothey A, 2013	R							1.0	1.9	6.4
Van Cutsem E, 2012	A				19.8	6.9	13.5			
Bennouna J, 2013	B				6.0	5.7	11.2			

C, cetuximab; P, panitumumab, B, bevacizumab, A, aflibercept, R, regorafenib

		First line			Second line			Chemoresistant		
		ORR %	PFS mos	OS mos	ORR %	PFS mos	OS mos	ORR %	PFS mos	OS mos
▪ ‘Growth’										
Tveit KM, 2012	C	49	8.3	19.7						
Maughan TS, 2011	C	64	8.6	17.0						
▪ ‘Angiogenesis’										





Hecht JR, et al. *J Clin Oncol.* 2011;29(15):1997-2003

More is Not Always Better

	Bev/Chemo n = 368	Cmab/Bev/Chemo n = 368	*P* value
Median PFS, mos	10.7 (9.7-12.3)	9.4 (8.4-10.5)	HR: 0.82; *P* = .01
Median OS, mos	20.3 (17.8-24.7)	19.4 (17.5-21.4)	*P* = .16
Response (CR+PR)	50%	52.7%	*P* = .49
Disease Control	94%	94.6%	*P* = .72

Tol J, et al. *N Engl J Med.* 2009;360(6):563-572.

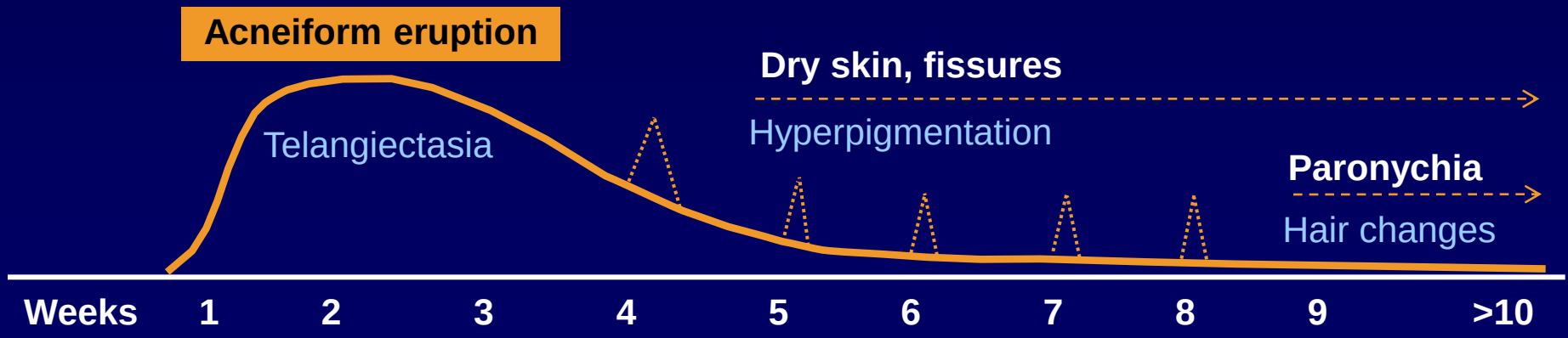
Targeted Therapy in mCRC – Efficacy

1. Activity targeting ‘angiogenesis’ & ‘growth’
2. Benefit in different lines and overall
3. Both monotherapy and combination with chemotherapy has antitumor activity

Targeted Therapy Toxicity: Anti-EGFR Therapy




Phases of possible skin reactions



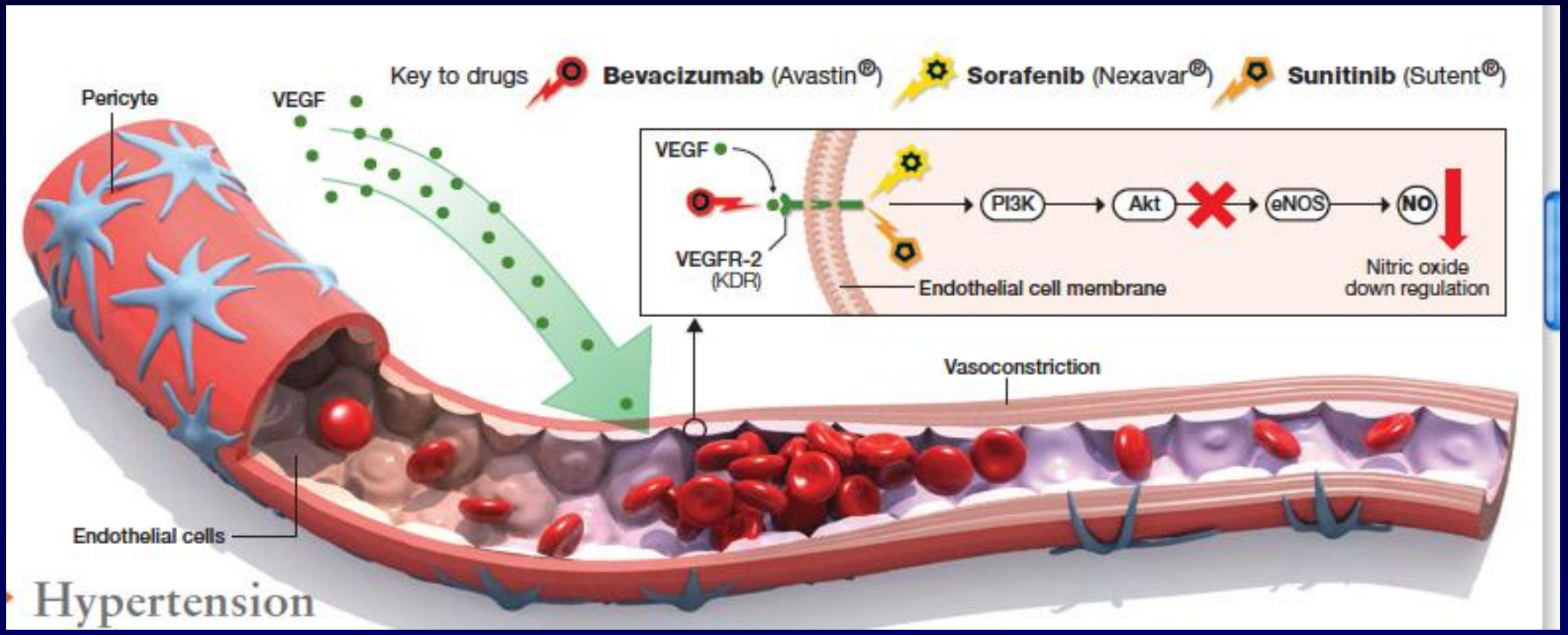
Van Cutsem E. *Oncologist*. 2006;11(9):1010-1017.

Toxicity: Cetuximab vs Panitumumab

Features	Panitumumab	Cetuximab
Efficacy		
OR, %	10	11
TTP, months	2.5	1.5
OS, months	9.4	6.9
Acneiform rash		
Overall incidence (all grades)	70-100	89
≥Grade 3 rash	3.4	5.2
HAHA/HACA, %	0	3
Allergic reactions, %		
Overall incidence	<1	3
Other toxicities, %		
Interstitial lung disease	0	0.5
PK interactions with other chemotherapies	0	0
Affinity for EGFR, nmol/1	0.05	0.39
Type of antibody	IgG2 100% human protein	IgG1 34% mouse protein
Premedications required	No	Yes

Cohenuram M, et al. *Anticancer Drugs.* 2007;18(1):7-15.

Targeted Therapy Toxicity: Anti-VEGF



Proposed mechanisms

- **Decreased VEGF leads to nitric oxide downregulation**
- **Acute cholesterol emboli syndrome**

Mourad JJ, et al. *Ann Oncol*. 2008;19(5):927-934; Lacouture. Angiogenesis Foundation website. 2009.

Targeted Therapy Toxicity: Bevacizumab

		No. of FAEs/Total No. of Participants		Incidence of FAEs, % (95% CI)		
	No of Studies	Bevacizumab	Control	Bevacizumab	Control	RR (95% CI)[a]
Tumor Type						
Colorectal cancer	5	25/1756	18/1515	1.6 (0.8-3.4)	1.4 (0.8-2.7)	1.21 (0.65-2.24)
NSCLC	4	56/1231	18/841	5.3 (3.2-8.6)	2.5 (0.8-6.6)	2.12 (0.78-5.78)
Breast cancer	3	12/1079	10/806	0.9 (0.3-3.1)	1.3 (0.3-4.3)	0.69 (0.30-1.62)
Renal cell cancer	2	6/703	4/653	0.9 (0.4-1.9)	0.8 (0.1-1.36)	1.11 (0.29-4.20)
Pancreatic cancer	1	26/296	16/287	8.8 (6.0-12.6)	5.6 (3.4-8.9)	1.58 (0.86-2.87)
Prostate cancer	1	23/524	6/526	4.4 (2.9-6.5)	1.1 (0.5-2.5)	3.85 (1.58-9.37)
Dose						
2.5 mg/kg per wk	4	45/1464	33/1482	1.6 (0.8-3.2)	1.2 (1.0-7.4)	1.36 (0.87-2.12)
5.0 mg/kg per wk	8	54/2833	17/2521	2.7 (0.9-8.0)	1.1 (0.9-7.0)	2.55 (1.44-4.53)
Chemotherapeutic agents[b]						
Platinum or taxanes	5	48/1915	11/1639	3.3 (2.5-4.3)	1.0 (0.7-1.4)	3.49 (1.82-6.66)
Nonplatinum or nontaxanes	3	6/918	6/882	0.8 (0.4-1.7)	0.9 0.5-1.9)	0.85 (0.25-2.88)
Overall	16	148/5589	72/4628	2.5 (1.7-3.9)	1.7 (1.0-2.9)	1.46 (1.09-1.94)

CI, confidence interval; FAE, fatal adverse event; NSCLC, non-small cell lung cancer.
[a]*P* = .13 for variation in RRs by tumor type; *P* = .16 for variaion in RRs by dose; *P* = .045 for variation in RRs by chemotherapy type.
[b]Bevacizumab was given at the same dose of 5 mg/kg per week for these trials. The incidences and RRs were calculated from trials included in this meta-analysis as described in the “Methods” section of the text.

Ranpura V, et al. *JAMA.* 2011;305(5):487-494

Toxicity: Aflibercept

Safety population, % of patients	AFL/FOLFIRI (n = 611)
All grade 3/4 AEs	83.5%
Selected toxicity	**G3–G4%**
Diarrhea	19.3
Asthenic conditions	16.8
Stomatitis	13.8
Neutropenia	36.7
Hypertension	19.3
Hemorrhage	3.0
Arterial thromboembolic event	1.8
Venous thromboembolic event	7.8
GI perforation	0.5
Proteinuria	7.8

Van Cutsem E, et al. *J Clin Oncol*. 2012;30(28):3499-3506.

Targeted Therapy Toxicity: Regorafenib

Adverse Event, %	Regorafenib N = 500			Placebo N = 253		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hand-foot skin reaction	46.6	16.6	0	7.5	0.4	0
Fatigue	47.4	9.2	0.4	28.1	4.7	0.4
Hypertension	27.8	7.2	0	5.9	0.8	0
Diarrhea	33.8	7.0	0.2	8.3	0.8	0
Rash / desquamation	26.0	5.8	0	4.0	0	0
Anorexia	30.4	3.2	0	15.4	2.8	0
Mucositis, oral	27.2	3.0	0	3.6	0	0
Thrombocytopenia	12.6	2.6	0.2	2.0	0.4	0
Fever	10.4	0.8	0	2.8	0	0
Nausea	14.4	0.4	0	11.1	0	0
Bleeding	**11.4**	**0.4**	**0**	**2.8**	**0**	**0**
Voice changes	**29.4**	**0.2**	**0**	**5.5**	**0**	**0**
Weight loss	**13.8**	**0**	**0**	**2.4**	**0**	**0**

- Quality of life was not adversely affected by regorafenib

Grothey A, et al. *Lancet.* 2013;381(9863):303-312.

Targeted Therapy Toxicity: Regorafenib

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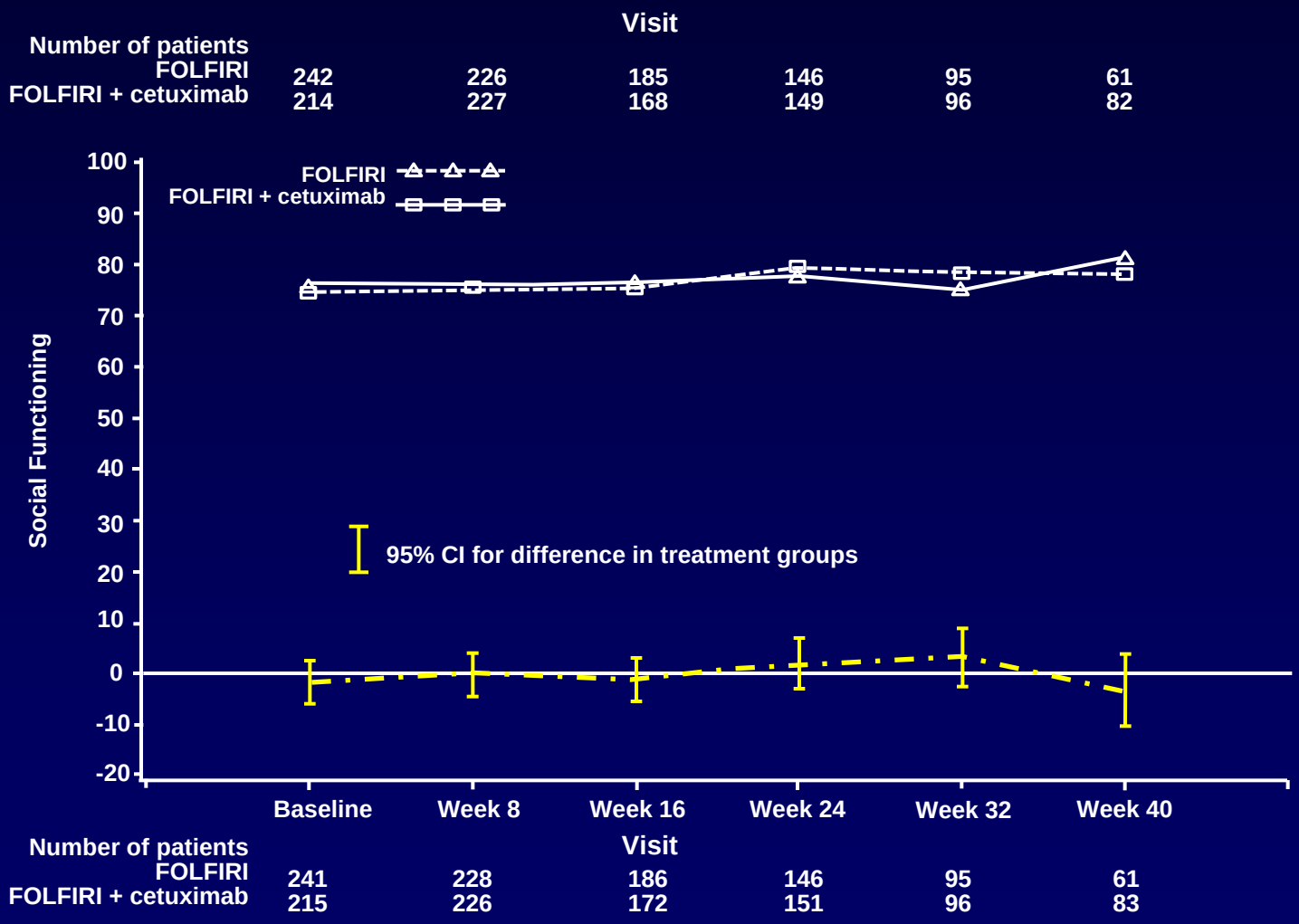
Mucositis, oral	27.2	3.0	0	3.6	0	0
Thrombocytopenia	12.6	2.6	0.2	2.0	0.4	0
Fever	10.4	0.8	0	2.8	0	0
Nausea	14.4	0.4	0	11.1	0	0
Adverse events leading to permanent Tx discontinuation	**8.2%**			**1.2%**		

- Quality of life was not adversely affected by regorafenib

Grothey A, et al. *Lancet.* 2013;381(9863):303-312.

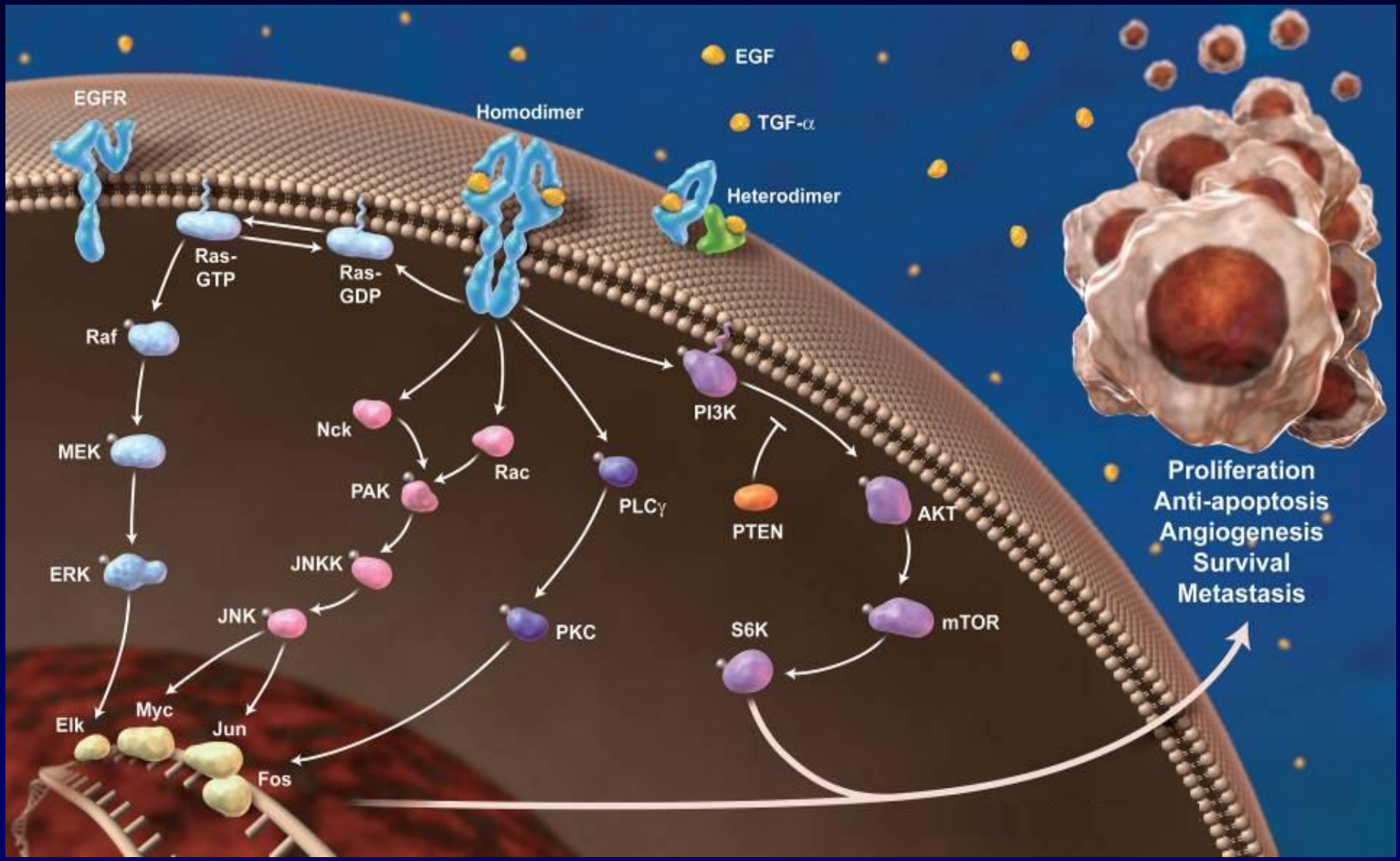
Targeted Therapy in mCRC – QOL



Láng I, et al. *Eur J Cancer.* 2013;49(2):439-448.

Targeted Therapy in mCRC – Toxicity

1. Generally, side effects are ‘class’ related
2. Mostly side effects are manageable
3. Treatment has no impact on quality of life

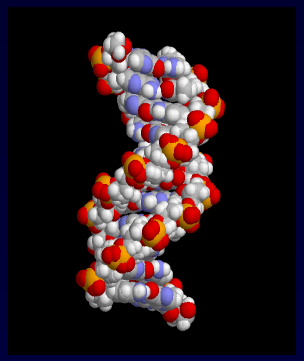


Adapted from Mendelsohn J. *J Clin Oncol.* 2002;20 (18 Suppl 1):1S-13S.

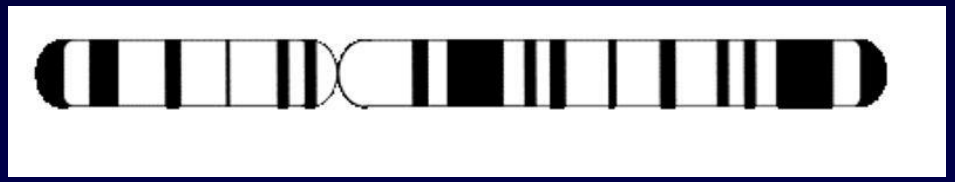
Glaxo chief: Our drugs do not work on most patients

"The vast majority of drugs - more than 90 per cent - only work in 30 or 50 percent of the people," Dr Roses said. "I wouldn't say that most drugs don't work. I would say that most drugs work in 30 to 50 per cent of people. Drugs out there on the market work, but they don't work in everybody."

The Independent | Monday 08 December 2003



12p12.1



JOURNAL OF CLINICAL ONCOLOGY

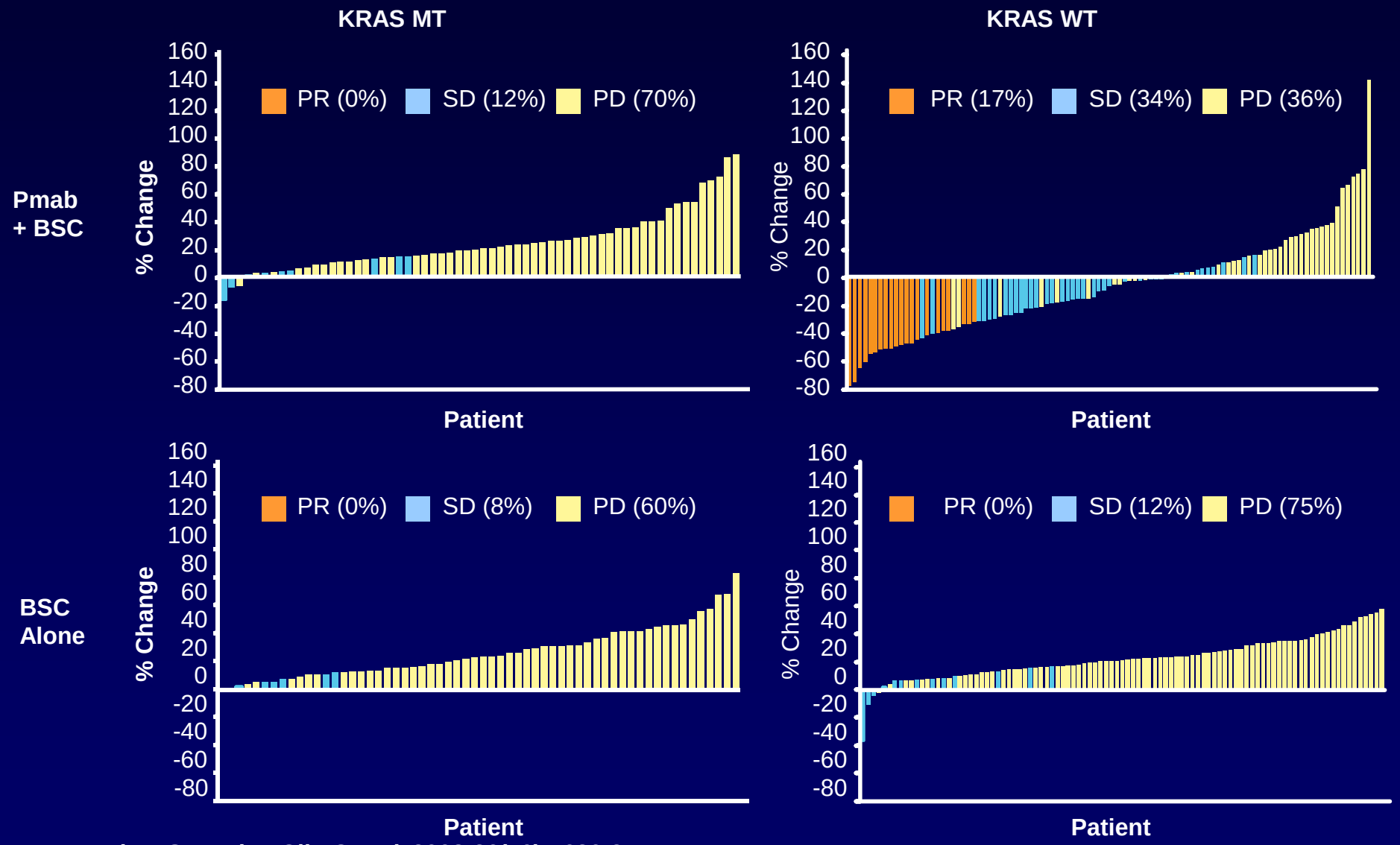
ORIGINAL REPORT

Wild-Type *KRAS* Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer

Rafael G. Amado, Michael Wolf, Marc Peeters, Eric Van Cutsem, Salvatore Siena, Daniel J. Freeman, Todd Juan, Robert Sikorski, Sid Suggs, Robert Radinsky, Scott D. Patterson, and David D. Chang

Amado RG, et al. *J Clin Oncol.* 2008;26(10):1626-34

Maximum Percent Decrease in Target Lesions



Amado RG, et al. *J Clin Oncol.* 2008;26(10):1626-34

Association of *KRAS* p.G13D Mutation With Outcome in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer Treated With Cetuximab

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Derek J. Jonker, MD
Federica Di Nicolantonio, PhD
Andrea Sartore-Bianchi, MD
Dongsheng Tu, PhD
Salvatore Siena, MD
Simona Lamba, MSc
Sabrina Arena, PhD
Milo Frattini, PhD
Hubert Piessevaux, MD, PhD
Eric Van Cutsem, MD, PhD
Chris J. O'Callaghan, DVM, PhD
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John R. Zalcberg, MBBS, PhD
John Simes, MD
Christos S. Karapetis, MD
Alberto Bardelli, PhD
Sabine Tejpar, MD, PhD

Context Patients with metastatic colorectal cancer who have *KRAS* codon 12– or *KRAS* codon 13–mutated tumors are presently excluded from treatment with the anti–epidermal growth factor receptor monoclonal antibody cetuximab.

Objective To test the hypothesis that *KRAS* codon 13 mutations are associated with a better outcome after treatment with cetuximab than observed with other *KRAS* mutations.

Design, Setting, and Patients We studied the association between *KRAS* mutation status (p.G13D vs other *KRAS* mutations) and response and survival in a pooled data set of 579 patients with chemotherapy-refractory colorectal cancer treated with cetuximab between 2001 and 2008. Patients were included in the CO.17, BOND, MABEL, EMR202600, clinical trials or received off-study treat... for possible prognostic ... utations was ...G12V, or ...

Codon13 mutation
G13D?

... longer ... 95% CI, 1.8-2.8] mo... re was a significant interaction between ... other *KRAS* mutations) and overall survival benefit with cetuximab treatment (adjusted HR, 0.30; 95% CI, 0.14-0.67; $P=.003$). In vitro and mouse model analysis showed that although p.G12V-mutated colorectal cells were insensitive to cetuximab, p.G13D-mutated cells were sensitive, as were *KRAS* wild-type cells.

Conclusions In this analysis, use of cetuximab was associated with longer overall and progression-free survival among patients with chemotherapy-refractory colorectal cancer with p.G13D-mutated tumors than with other *KRAS*-mutated tumors. Evaluation of cetuximab therapy in these tumors in prospective randomized trials may be warranted.

JAMA. 2010;304(16):1812-1820 www.jama.com

RECENT RETROSPECTIVE CORrelative analyses of metastatic colorectal cancer trials indicate that patients with *KRAS*-mutated tumors (NCBI Entrez Gene 3845) do not benefit from the anti–epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab.[1] These retrospective analyses were performed independently, and for each analysis, *KRAS* wild-type vs mutant were studied grouping codons 12 and 13 mutations together, without subgroup analysis. Health authorities in the United States and Europe have indicated that patients with *KRAS* codon 12– or *KRAS* codon 13–mutated tumors should not receive cetuximab or panitumumab.[2-4]

However, indications exist that not all *KRAS* mutations are equal in their biological characteristics. First, the pattern of *KRAS* mutations is tumor-type spe-

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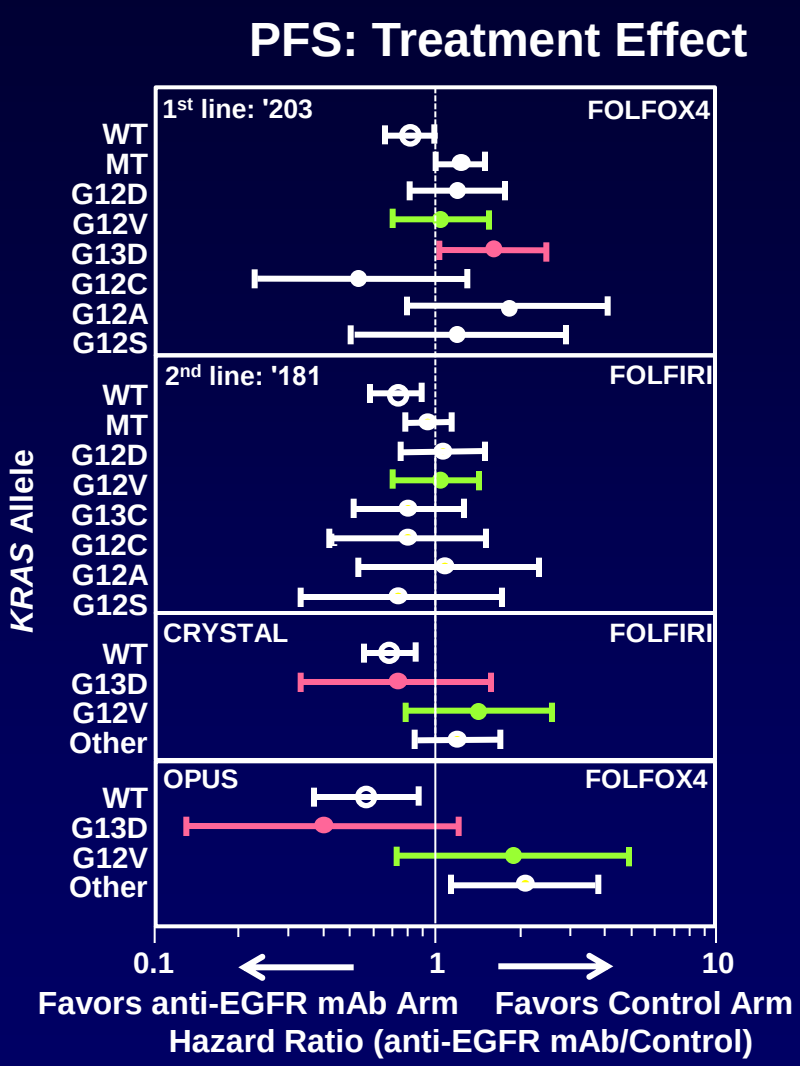
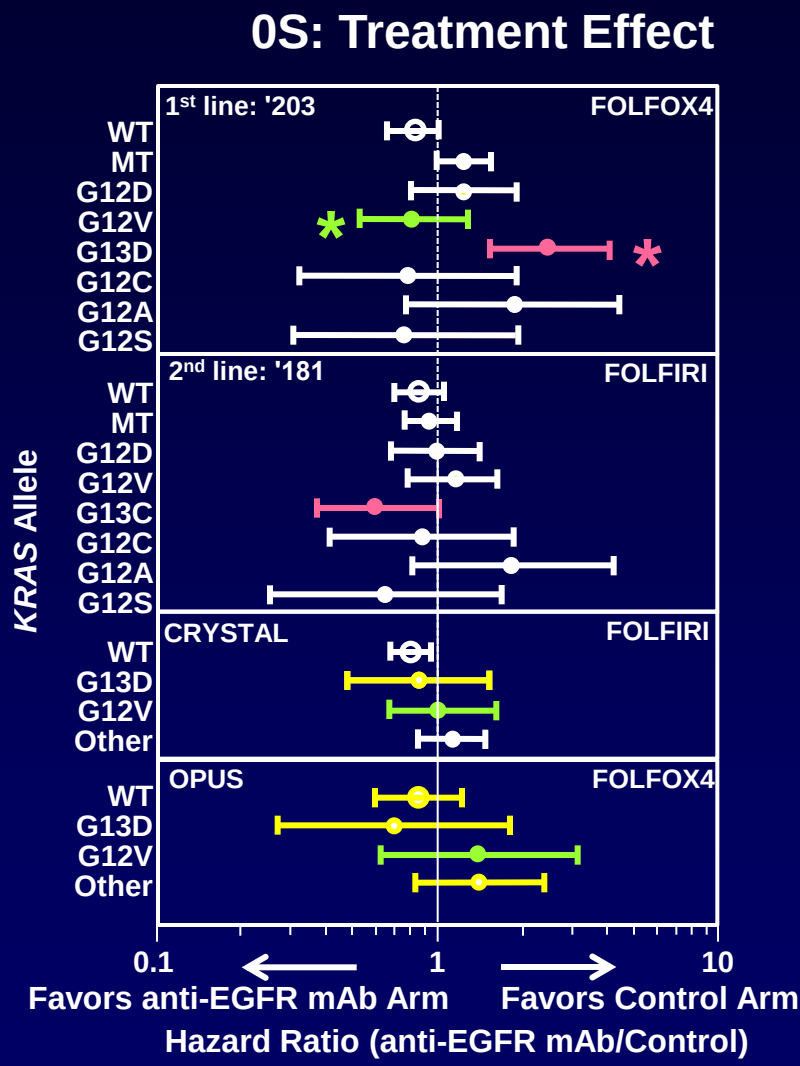
→ OUTCOME

De Roock W, et al. *JAMA*. 2010;304(16):1812-1820.

Treatment Effect of *KRAS* Mutation Status by Study





* *Positive interaction test

Tejpar S, et al. *J Clin Oncol*. 2012;30(29):3570-3577; Peeters M, et al. *J Clin Oncol.* 2013;31(6):759-765.

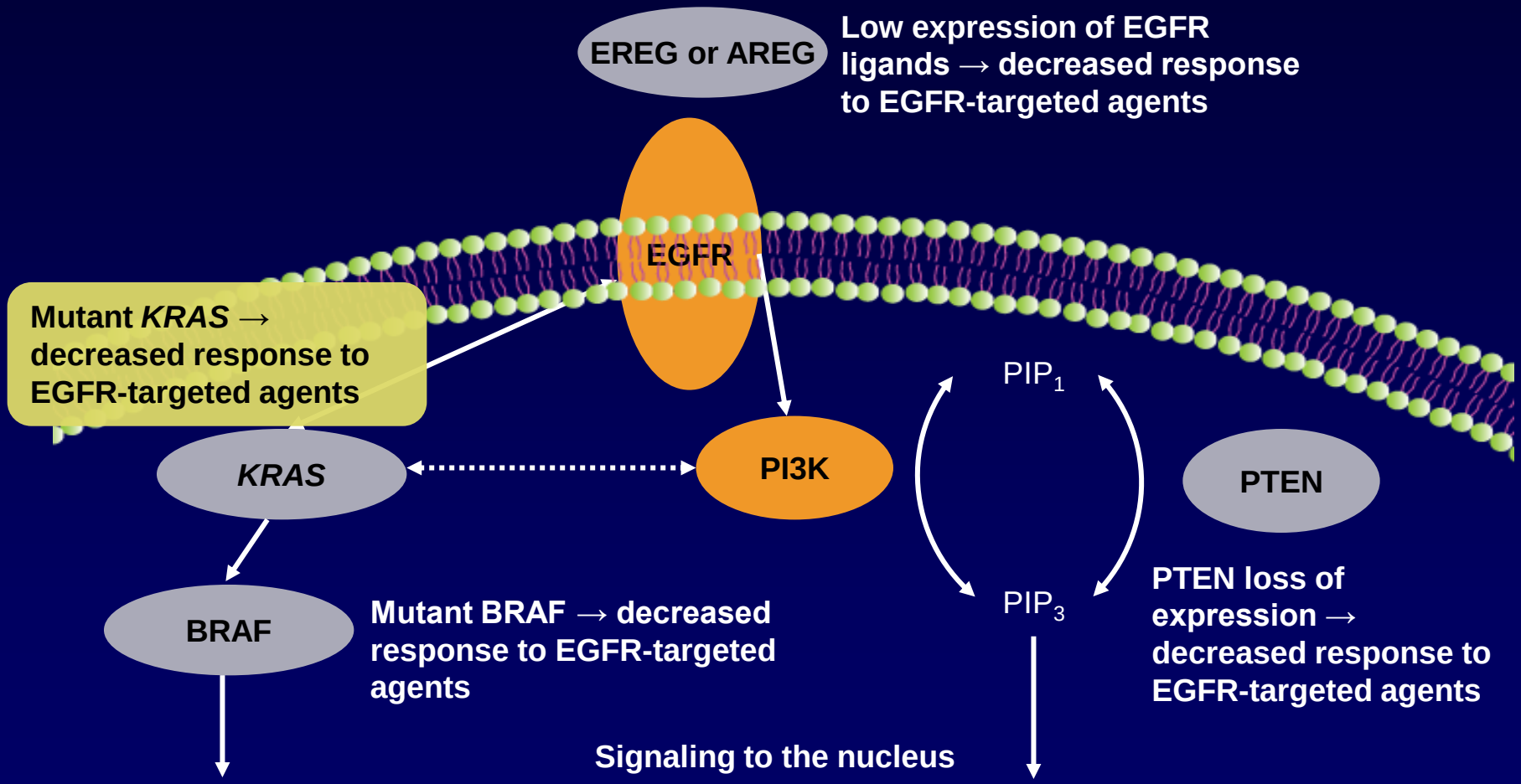
Regorafenib: *KRAS* Subgroup Analysis

- Regorafenib shows OS and PFS benefit in both *KRAS*-wildtype and *KRAS*-mutant subgroups
- *KRAS* mutational status was neither prognostic nor predictive in the study population

		Regorafenib n = 505	Placebo n = 255	HR (95% CI)
KRAS mutation, %	No	40.6	36.9	NA
	Yes	54.1	61.6	NA
Median OS, months	*KRAS* wildtype	7.3	5.0	0.653 (0.476-0.895)
	KRAS mutant	6.2	5.1	0.867 (0.670-1.123)
Median PFS, months	*KRAS* wildtype	2.0	1.8	0.475 (0.362-0.623)
	KRAS mutant	1.9	1.7	0.525 (0.425-0.649)

Grothey A, et al. *Lancet.* 2013;381(9863):303-312

Biologic Subsets of mCRC Respond Differently to EGFR-Targeted Agents



Siena S, et al. *J Natl Cancer Inst*. 2009;101(19):1308-1324. Rizzo S, et al. *Cancer Treat Rev.* 2010;36 Suppl 3:S56-61.

Response Rates of Patients With Wild-Type *KRAS* (condos 12/13/61) Who Were Randomized to Panitumumab Plus BSC[a]

		Randomized phase III study panitumumab + BSC, N = 82		Extension study panitumumab + BSC, N = 56		Combined panitumumab + BSC, N = 138	
Genotype		**N**	**Response rate, % (95% CI)**	**N**	**Response rate, % (95% CI)**	**N**	**Response rate, % (95% CI)**
NRAS	**WT**	76	13 (6-23)	50	24 (13-38)	126	17 (11-25)
	MT	4	0 (0-60)	5	0 (0-52)	9	0 (0-34)
EGFR	**WT**	82	12 (6-21)	52	23 (13-37)	134	16 (11-24)
	MT	0	NA	0	NA	0	NA
BRAF	**WT**	63	14 (7-25)	44	21 (10-35)	107	17 (10-25)
	MT	9	0 (0-34)	4	0 (0-60)	13	0 (0-25)
PTEN	**WT**	72	13 (6-22)	50	22 (12-36)	122	16 (10-24)
	MT	7	14 (0-58)	2	0 (0-84)	9	11 (0-48)
PIK3CA	**WT**	74	12 (6-22)	43	19 (8-33)	117	15 (9-22)
	MT	5	20 (1-72)	5	20 (1-72)	10	20 (3-56)
AKT1	**WT**	69	15 (7-25)	52	19 (10-33)	121	17 (10-24)
	MT	1	0 (0-98)	0	NA	1	0 (0-98)
TP53	**WT**	32	16 (5-33)	18	11 (1-35)	50	14 (6-27)
	MT	49	10 (3-22)	35	26 (13-43)	84	17 (9-26)
CTNNB1	**WT**	72	11 (5-21)	46	22 (11-36)	118	15 (9-23)
	MT	2	50 (1-99)	0	NA	2	50 (1-99)

AKT1, v-akt murine thymoma viral oncogene homolog 1; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *CTNNB1*, catenin (cadherin-associated protein), β-1, 88kDa; MT, mutant; NA, not available; *NRAS*, neuroblastoma RAS viral oncogene homolog; *PIK3CA*, phosphoinositide-3-kinase, catalytic, α-polypeptide; *PTEN*, phosphatase and tensin homolog; TP53, tumor protein p53; WT, wild-type

[a]Per local review

Peeters M, et al. *Clin Cancer Res.* 2013;19(7):1902-1912

New Analyses Identify Predictive Biomarkers For Panitumumab In Patients With Metastatic Colorectal Cancer

Biomarker Analysis From Phase 3 PRIME ('203) Study and Phase 2 PEAK ('509) Study Link Additional RAS Gene Mutations to Panitumumab Clinical Response

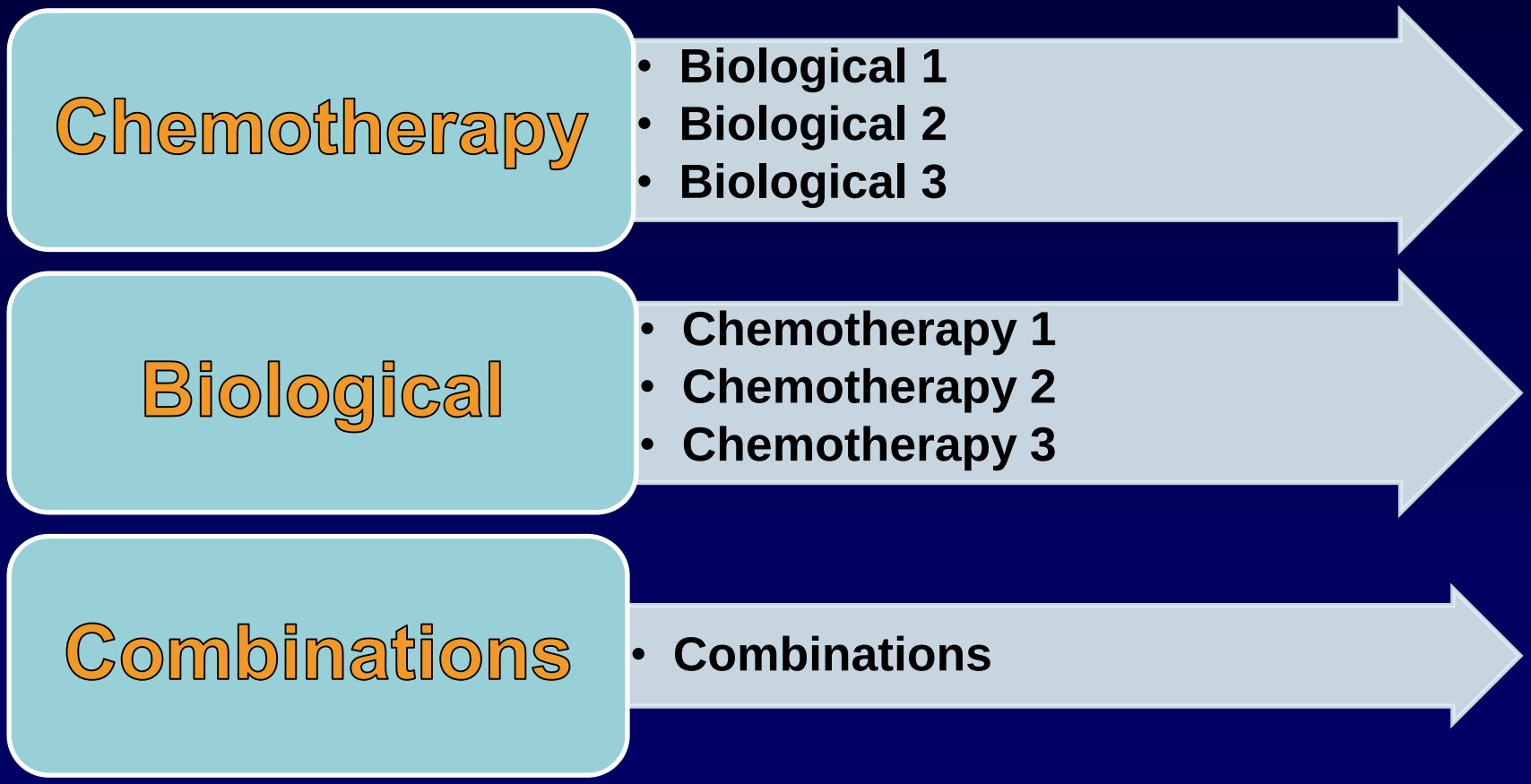
Press Release Thousand Oaks, California: Amgen; May 15, 2013.

Targeted Therapy in mCRC – Biomarkers

1. KRAS is a negative predictive biomarker
2. Multigene testing enters clinical practice
3. RAS testing better defines subgroups for anti-EGFR treatment

Conclusion

Targeted therapy is integrated in personalized care for mCRC



prIME oncology

EMERGING TREATMENT PARADIGMS IN METASTATIC COLORECTAL CANCER

Sunday, June 2, 2013

6.30 PM – 7.00 PM Registration and Dinner

7.00 PM – 9.00 PM Educational Activity