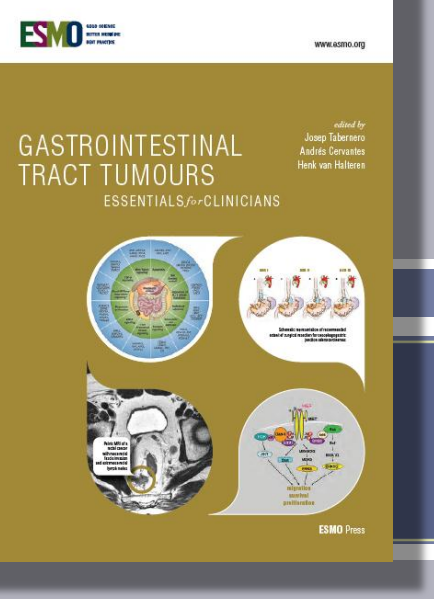


Κλινικά Παραδείγματα

Νεοπλάσματα του πεπτικού

Τουρκαντώνης Ιωάννης, MD, Ph.D.

Παθολόγος- Ογκολόγος

Επιστημονικός Συνεργάτης Ιατρικής Σχολής Ε.Κ.Π.Α.,

Ογκολογική Μονάδα Γ'ΠΠΚ, Γ.Ν.Θ.Α Η "Σωτηρία"

Δεν υπάρχει οποιαδήποτε σύγκρουση συμφερόντων.

Patient History

- ✓ **A 64-year-old woman complains of fatigue and 10 lb weight loss over the last 4 months. She reports occasional bright red blood per rectum after a bowel movement that she attributes to hemorrhoids.**
- ✓ **She is otherwise healthy and family history is noncontributory. She is a lifelong nonsmoker but has not seen a physician in 10 years.**
- ✓ **Her lab tests including the comprehensive metabolic panel are within normal limits. A complete blood count shows hemoglobin 10.2 g/ dL, mean corpuscular volume (MCV) of 73 fL, platelets 600,000/ µL, and normal WBC count and differential.**

What is the next best test that should be performed?

A. Mammogram

B. Bone marrow biopsy

C. Colonoscopy

D. Positron emission tomography (PET) scan

E. Stool fecal occult blood test (FOBT or FIT)

Biology of cancer development in the GI tract

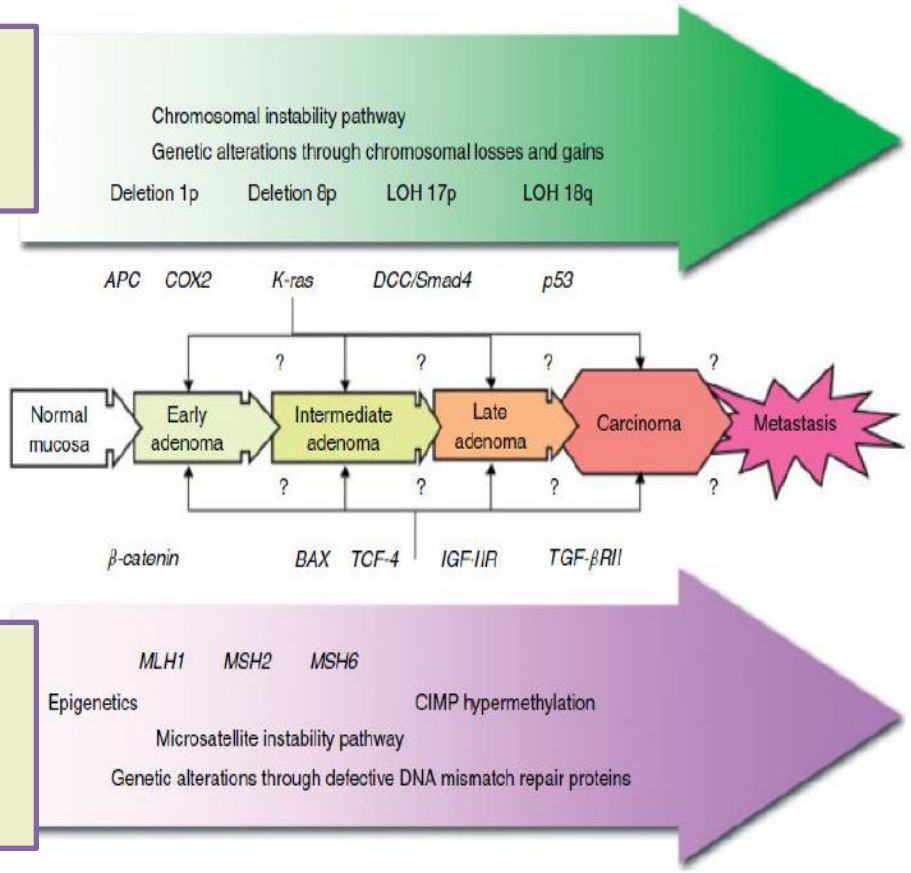
Colorectal cancer

Colorectal cancer

Fearon and Vogelstein proposed a genetic model to explain the stepwise formation of colorectal cancer (CRC) from normal colonic tissues.

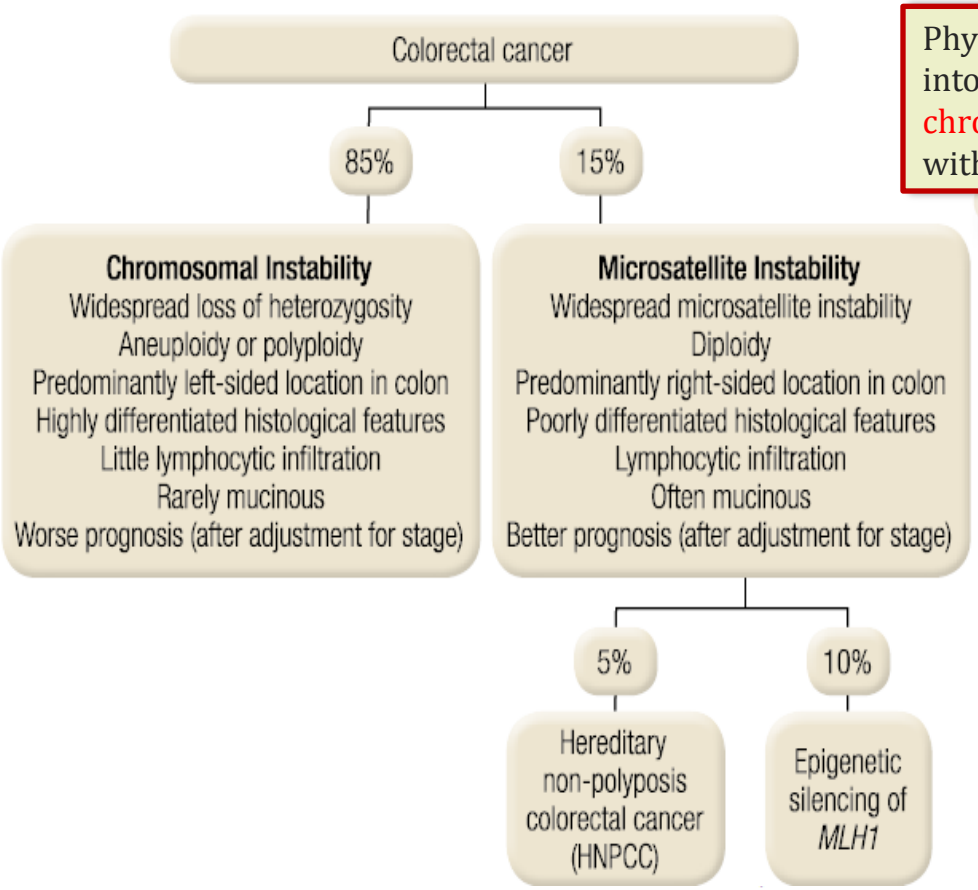
The model states: (1) CRC results from mutations in genes with important functions in regulating cell proliferation or DNA repair, (2) mutations in >1 gene are required, and (3) the sequence of mutations is important in determining the formation of CRC.

These altered genes can be divided into two classes: tumour suppressors that either inhibit cell proliferation or promote apoptosis, and oncogenes that promote cell proliferation and tumour progression.



Mudassar S, et al. Colorectal Cancer-Surgery, Diagnostics and Treatment. InTech, 2014

Colorectal cancer



Phylogenetically, CRCs can be divided into two molecular subtypes: those with chromosomal instability (CIN) and those with microsatellite instability (MSI).

Carcinomas with MSI present cancer- initiating mutations that inactivate the function of mismatch repair (MMR) genes (e.g. MSH2, MSH6, MLH1 and PMS2) leading to hypermutated genomes. This is known as the "mutator phenotype".

de la Chapelle A. N Engl J Med 2003;349:209-210

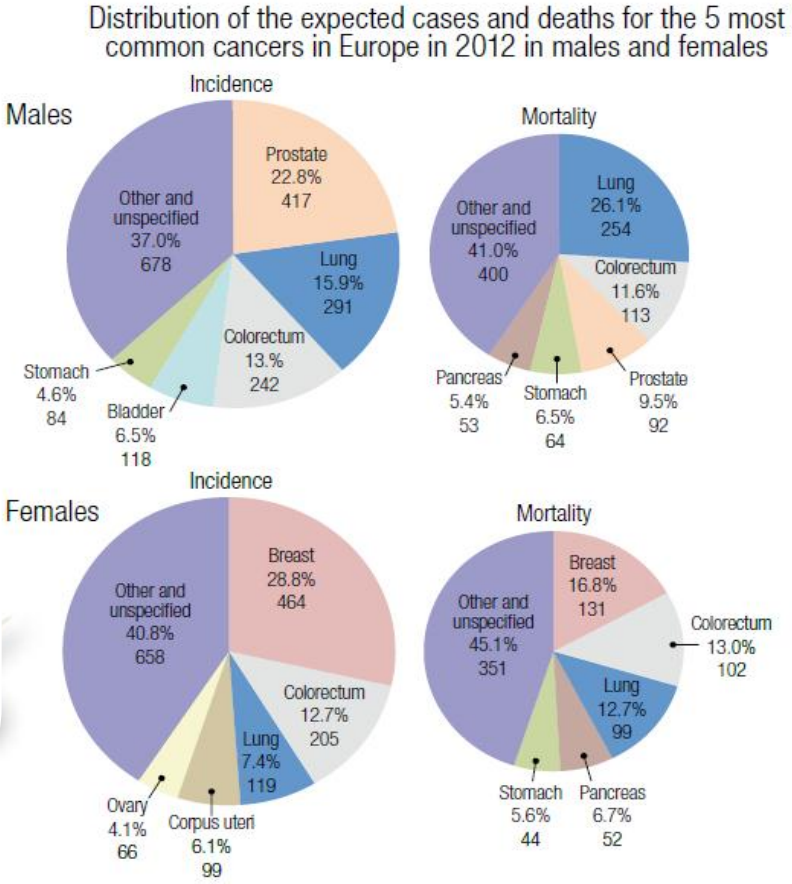
Epidemiology and clinical presentation

Colon cancer

Colorectal cancer (CRC) is the second most frequently diagnosed malignancy in Europe, both genders combined.

80% of CRCs are found within the colon, 20% within the rectum.

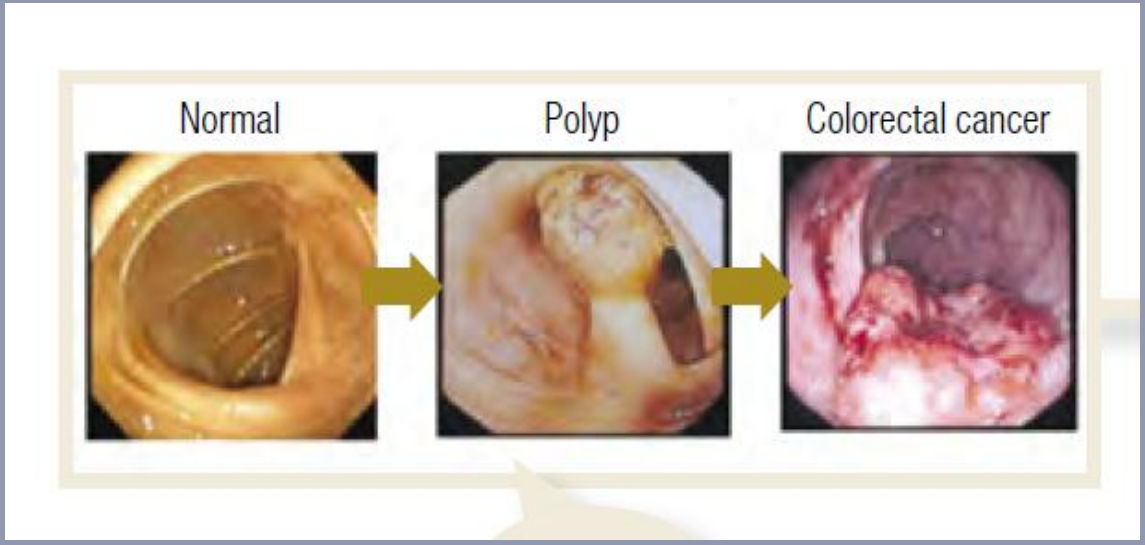
Symptoms can include: change in bowel habits, abdominal discomfort, wasting or malaise due to iron-deficiency anaemia. Emergencies may arise, such as bowel obstruction or tumour perforation. Symptoms of left-sided colon cancer are similar to those of rectal cancer.



Ferlay J, et al. Eur J Cancer 2013;49:1374-1403

Colon cancer

Early detection can be facilitated by periodic faecal occult bleeding testing (FOBT) in high-risk populations.



Due to the high incidence of CRC, national screening programmes with FOBTs followed by colonoscopy appear to be cost-effective for people older than 50 years.

Courtesy Terese Winslow; http://www.medicinenet.com/colorectal_cancer_pictures_slideshow/article

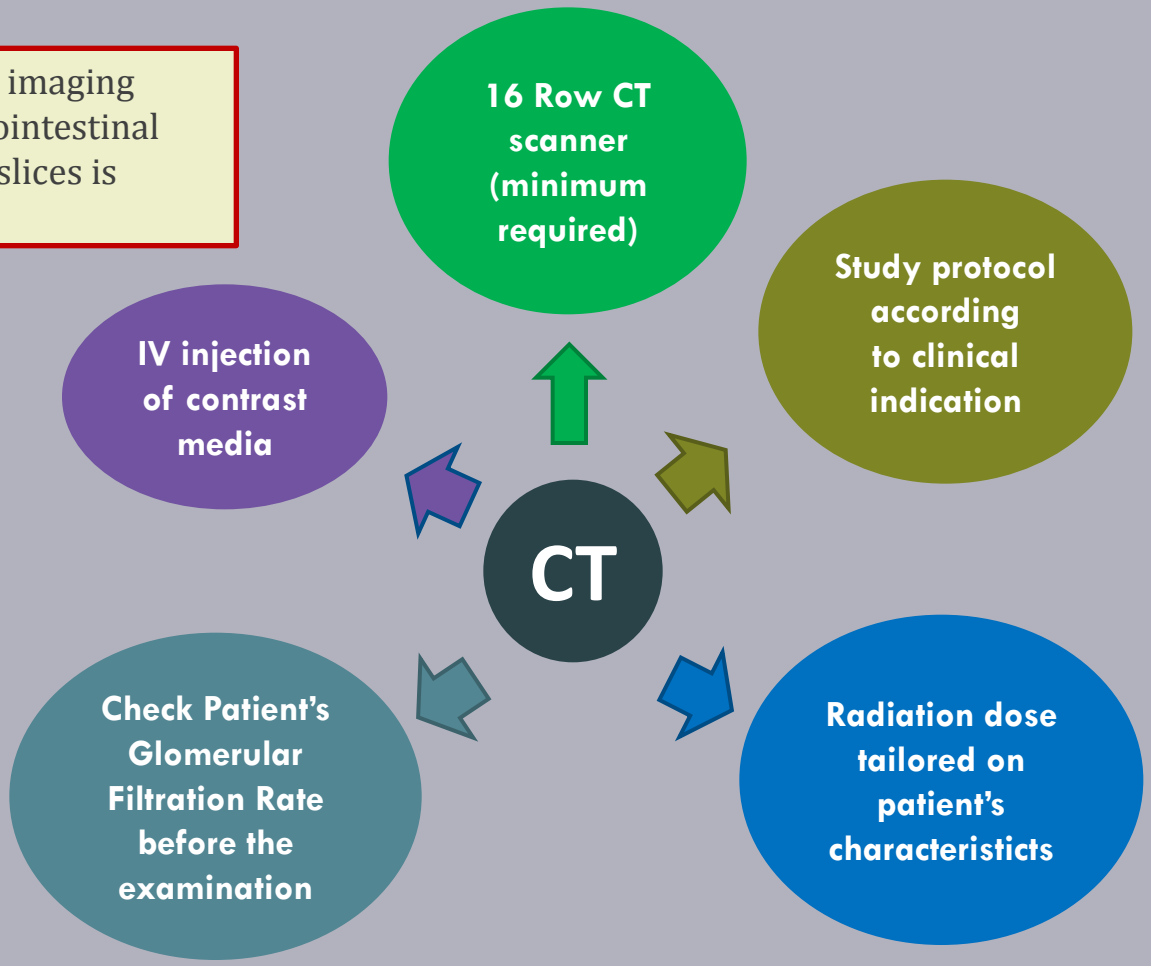
Diagnosis, staging, response assessment and interventional radiology in GI tumours

Technical aspects

Computed tomography (CT) is currently the imaging modality of first choice in the study of gastrointestinal (GI) tumours. A minimal requirement of 16 slices is mandatory for optimal examination.

Dedicated protocols, based on clinical indications, patient characteristics and scanner features, are necessary to enhance diagnosis and minimise patient risks.

The use of iodinated contrast medium (CM) injection is mandatory. Patient-related risk factors should be carefully considered before intravenous administration of CM, especially if eGFR value is below 45 ml/min/1.73m2. If CM is administered, patient hydration is advisable.



Beets-Tan RG, et al. Eur Radiol 2013; 23:2522–2531

Technical aspects

Magnetic resonance imaging (MRI) offers a multiparametric approach in the evaluation of GI tumours, and does not use ionising radiation. This is extremely important in young patients and in pregnant women with cancer.

The main drawbacks of MRI include longer imaging protocols and difficult evaluation of poorly collaborative and severely-ill patients, compared with CT.

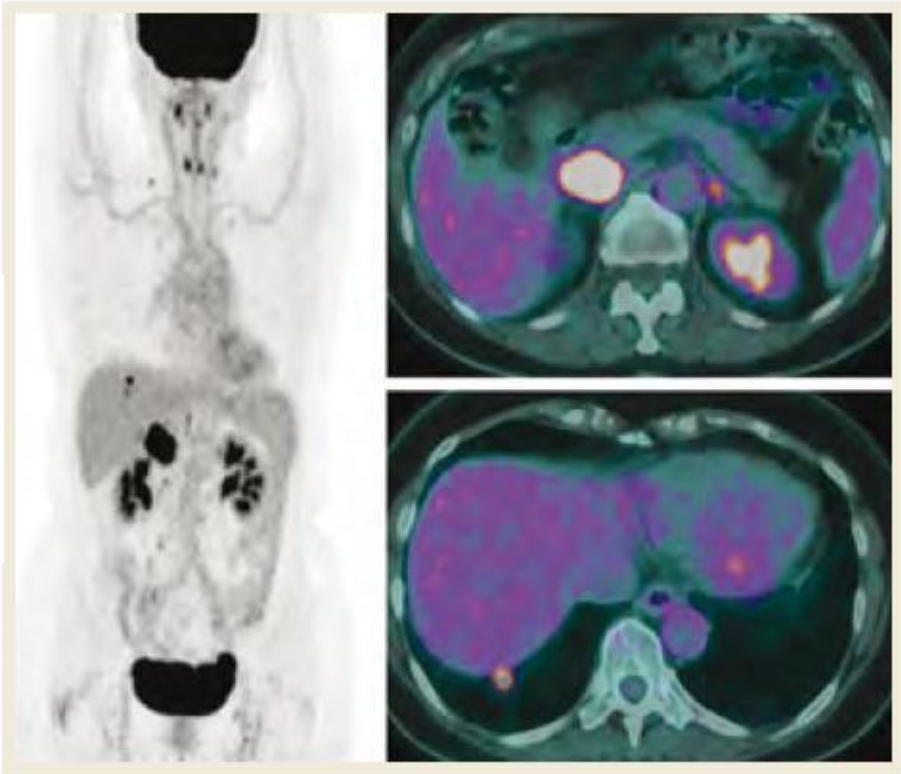
Niekel MC, et al. Radiology 2010; 257:674–684

Technical aspects

^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET)/CT is an important diagnostic tool at the time of cancer diagnosis and in patient follow-up. Its diagnostic role is different depending on the primary tumour.

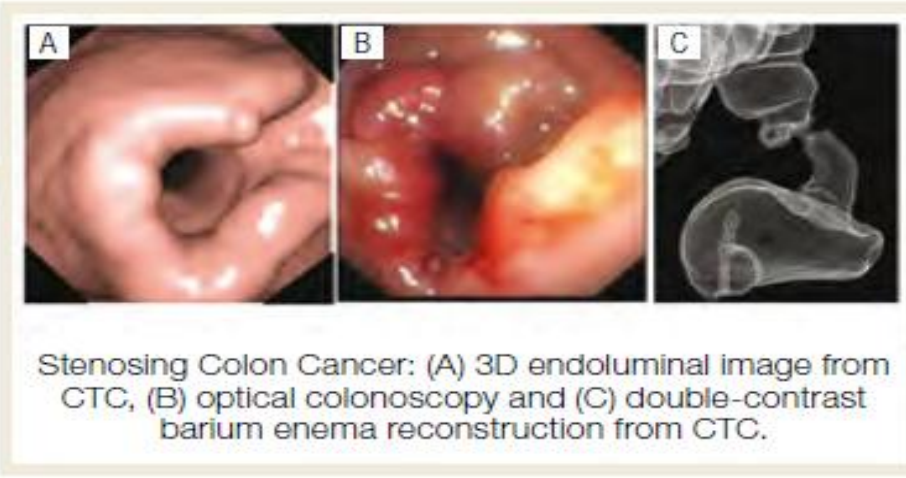
A higher glucose uptake relative to that of surrounding normal tissue reflects increased metabolic activity that allows the identification of tumour foci.

Advantages of 18FDG-PET/CT are its high sensitivity and the ability to examine the whole body. False positives (uptake of inflammatory lesions) and false negatives (absence of uptake in mucinous tumours and concurrent therapy with metformin) must be taken into account.



Niekel MC, et al. Radiology 2010; 257:674–684

Colon cancer



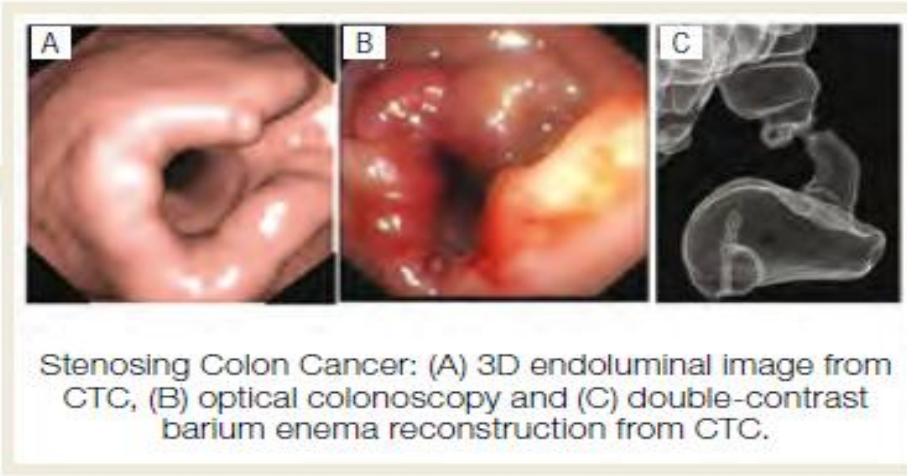
Stenosing Colon Cancer: (A) 3D endoluminal image from CTC, (B) optical colonoscopy and (C) double-contrast barium enema reconstruction from CTC.

CTC, Computed tomography colonography.

Diagnosis of colon cancer is obtained with colonoscopy and biopsy

Spada C, et al. Endoscopy 2014; 46:897–915

Colon cancer



Stenosing Colon Cancer: (A) 3D endoluminal image from CTC, (B) optical colonoscopy and (C) double-contrast barium enema reconstruction from CTC.

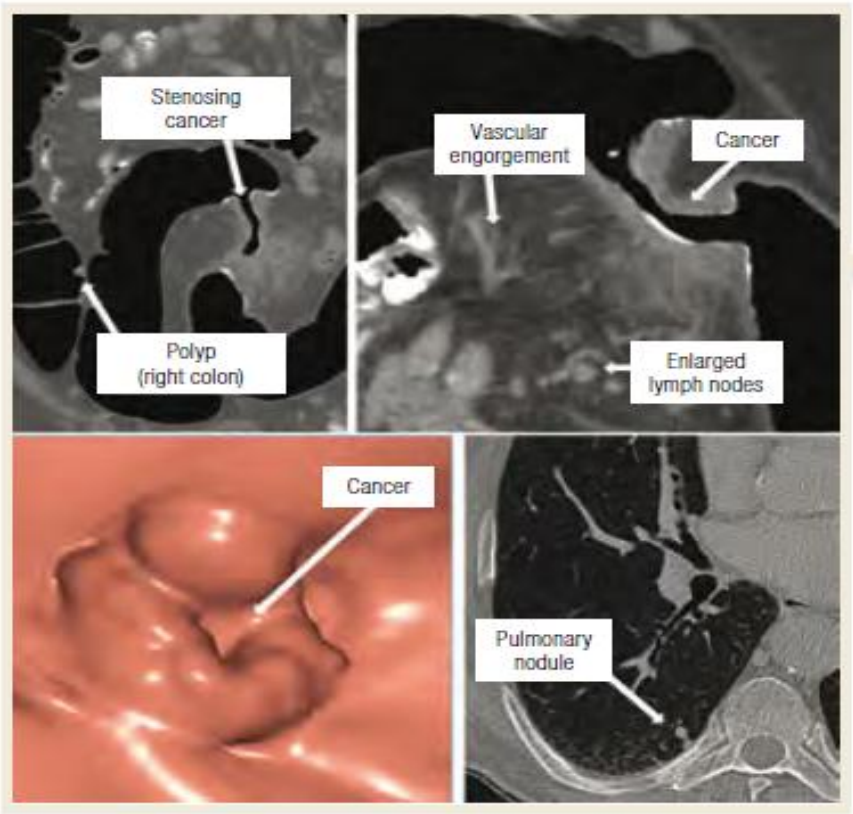
CTC, Computed tomography colonography.

Diagnosis of colon cancer is obtained with colonoscopy and biopsy

CT colonography (CTC) is a valuable alternative diagnostic method to detect colon cancer in both asymptomatic and symptomatic patients

Spada C, et al. Endoscopy 2014; 46:897–915

Colon cancer



If initial colonoscopy is incomplete (also due to the presence of a stenosing cancer), the adjunct of CTCT to CT can be used to detect synchronous colonic lesions.

Contrast-enhanced MRI is suggested if CT is contraindicated or if liver lesions require further characterisation.

Routine use of ^{18}FDG-PET/CT is not recommended at the time of initial diagnosis. ^{18}FDG-PET/CT can help clarify abnormal CT findings and improve detection of otherwise unsuspected metastases.

CT of the chest, abdomen and pelvis is appropriate to detect distant metastasis

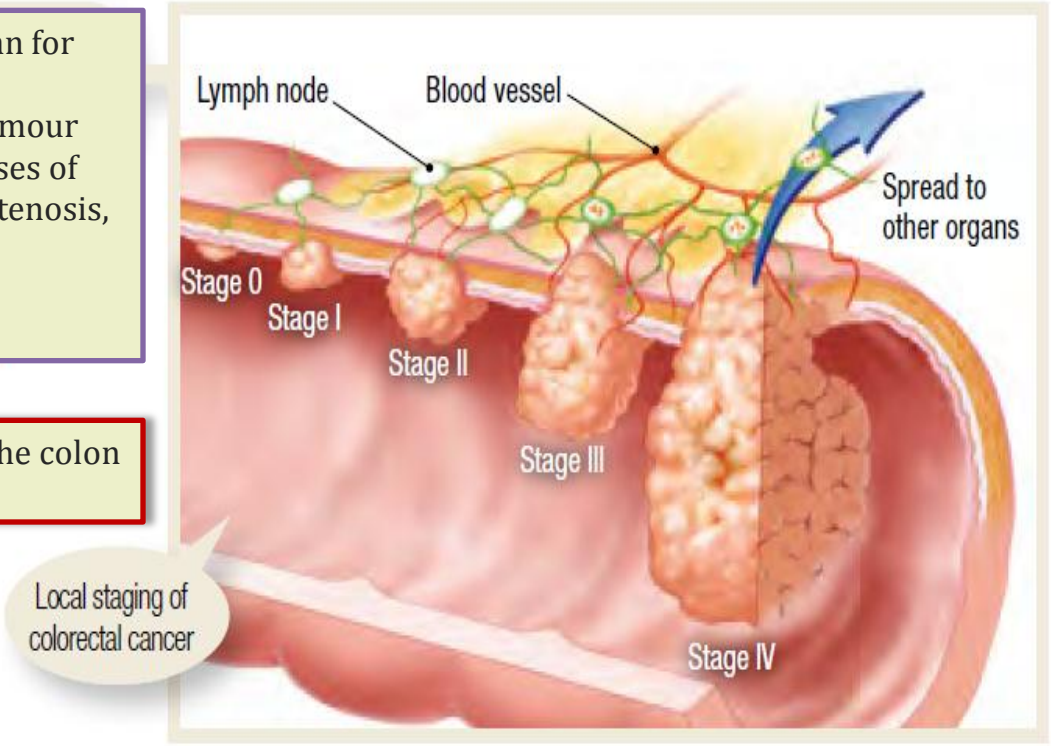
Niekel MC, et al. Radiology 2010; 257:674–684

Colon cancer

A multidisciplinary treatment plan for CRC is based on: (1) A complete colonoscopy, during which the tumour location should be marked (in cases of incomplete colonoscopy, due to stenosis, consider preoperative computed tomography [CT] colonoscopy or postoperative colonoscopy).

(2) Histological confirmation of the colon cancer Diagnosis.

(3) Thoracic and abdominal CT scan, to exclude distant metastasis.



Courtesy Terese Winslow; http://www.medicinenet.com/colorectal_cancer_pictures_slideshow/article

Patient History

- ✓ **A 45-year-old woman undergoes right hemicolectomy for a large T3 poorly differentiated colon cancer with extensive lymphocytic infiltration into the tumor tissue and 35 resected lymph nodes without cancer involvement.**

- ✓ **She is being referred to medical oncology to discuss potential adjuvant treatment options for her stage II colon cancer and asks about the usefulness of molecular biomarkers to guide treatment decisions.**

Which of the following statements is correct?

A. A comprehensive RAS mutation analysis (KRAS and NRAS) in tumor tissue can help guide adjuvant therapy

B. Patients with stage II microsatellite instability–high (defective mismatch repair) cancers have excellent prognosis and do not require adjuvant therapy

C. Most cases of microsatellite instability–high colon cancers occur as a manifestation of Lynch syndrome

Adjuvant treatment of resected early colon cancer

Early colon cancer

If still localised, the primary tumour should be resected by a trained GI surgeon. The surgical techniques are well established.

The pathology report should mention the degree of differentiation,
depth of bowel wall infiltration (pT-status), presence of lympho-vascular or perineural invasion and number of affected lymph nodes (pN-status, at least 12 nodes should be examined).

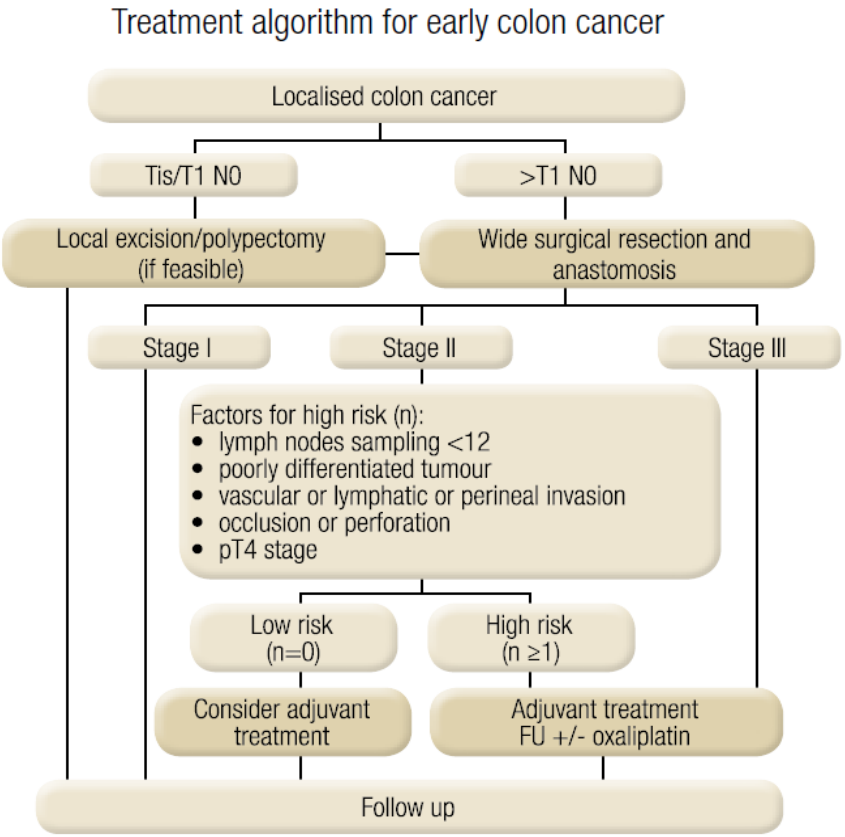
TNM Classification and staging of colorectal cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

M, Metastasis; N, node; T, tumour; Tis, carcinoma in situ.

The pTNM-status has a strong prognostic impact on survival, and should therefore be used for postoperative decision-making.

Early colon cancer



FU, Fluorouracil; N, node; T, tumour; Tis, carcinoma in situ.

Adjuvant chemotherapy (ChT) has been shown to improve survival in radically resected node-positive (N1-2) CRC.

For pT3-4N0 CRC, adjuvant ChT appears beneficial in cases of:

- Retrieval of less than 12 lymph nodes for analysis
- pT4-stage
- Poorly differentiated tumour
- Vascular, lymphatic or perineural tumour invasion
- Clinical presentation with bowel obstruction or tumour perforation

ChT does not appear beneficial in case of:

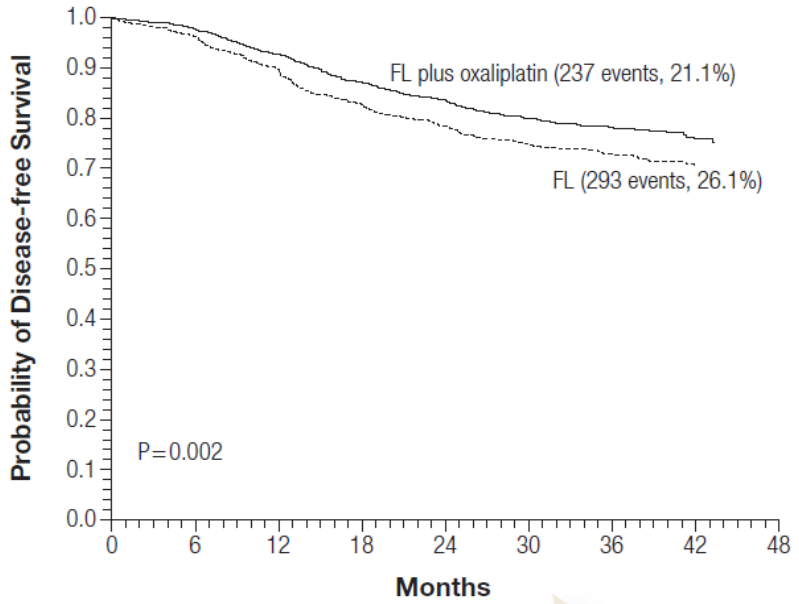
- Defective mismatch repair (as estimated by microsatellite instability [MSI] analysis).

Labianca R, et al. Ann Oncol 2013;24(Suppl 6):vi64–vi72

Early colon cancer

Adjuvant ChT should consist of a fluoropyrimidine backbone, either in an intravenous (fluorouracil) or oral (capecitabine) form.

Addition of oxaliplatin improves survival mainly in Stage III patients. Recent publications suggest this survival advantage is only for patients younger than 70 years.



FL / FULV, 5-Fluorouracil + leucovorin.

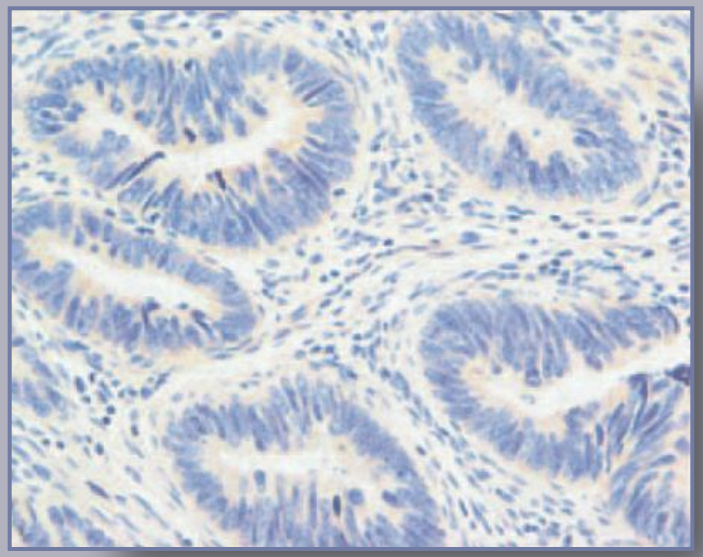
Disease-free survival of Stage II and III C cancer patients treated with FULV +/- oxaliplatin in the MOSAIC trial

No other additive drug (targeted or cytostatic) has been shown to further improve survival in adjuvant systemic therapy. The total number of adjuvant treatment cycles spans a period of 6 months.

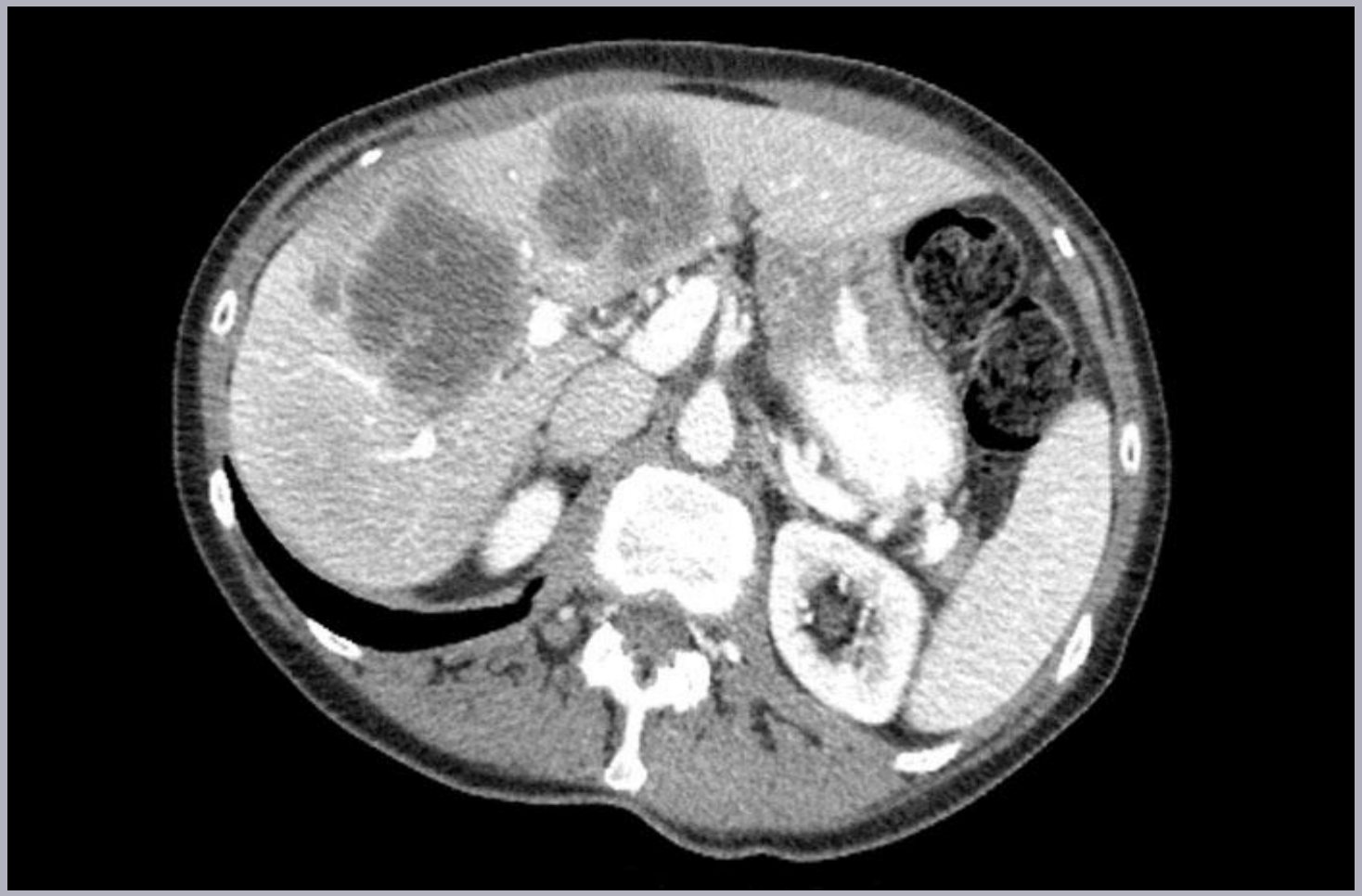
André T, et al. N Engl J Med 2004;350:2343-2351

Patient History

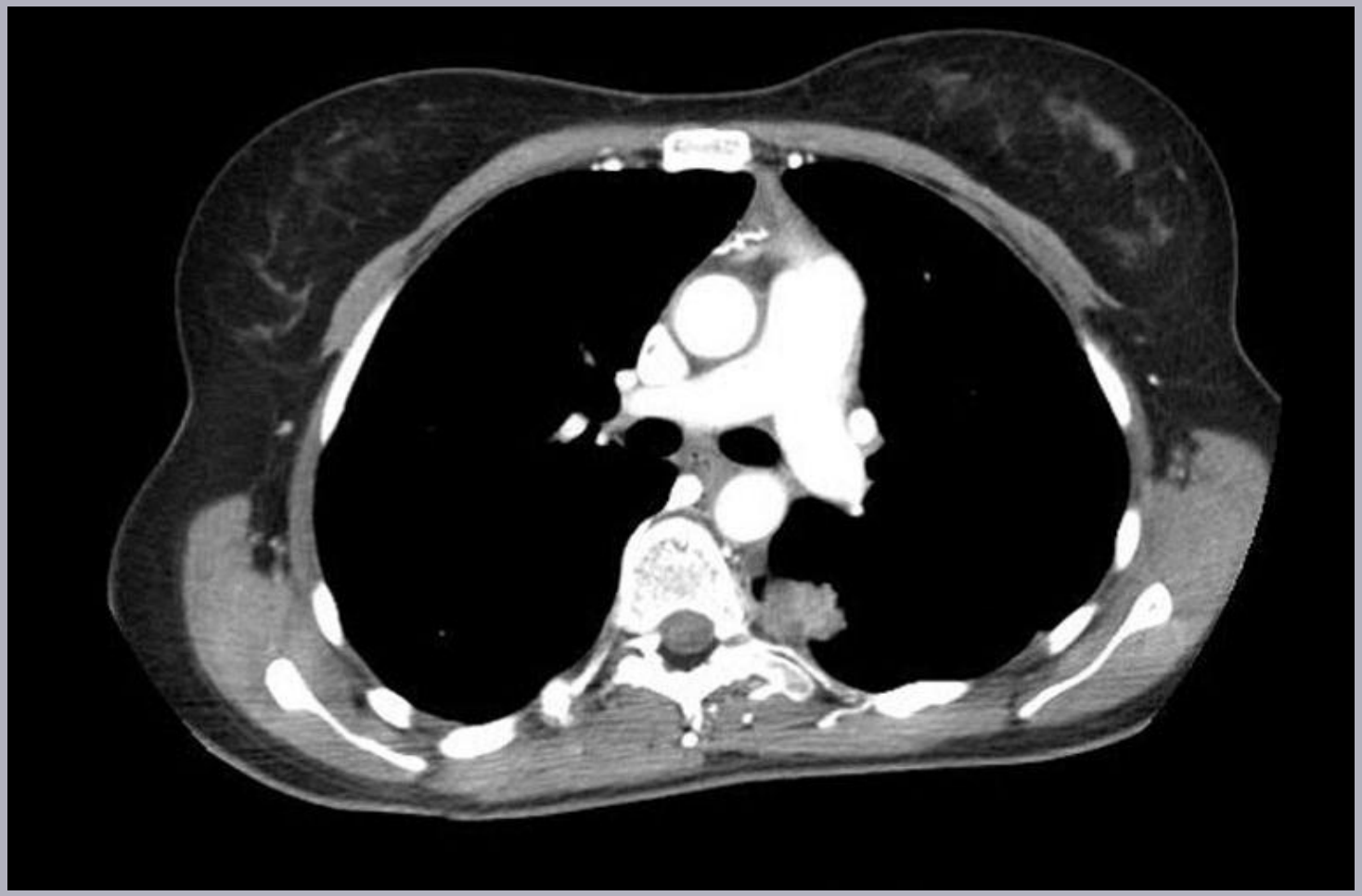
- ✓ **A 63-year-old woman, presents with unresectable metastatic sigmoid (left-sided) colorectal cancer**
- ✓ **Her Eastern Cooperative Oncology Group performance status (ECOG PS) is 0**
- ✓ **She reported right upper quadrant pain, and she had rectal bleeding**



Computed tomography (CT) studies



Computed tomography (CT) studies

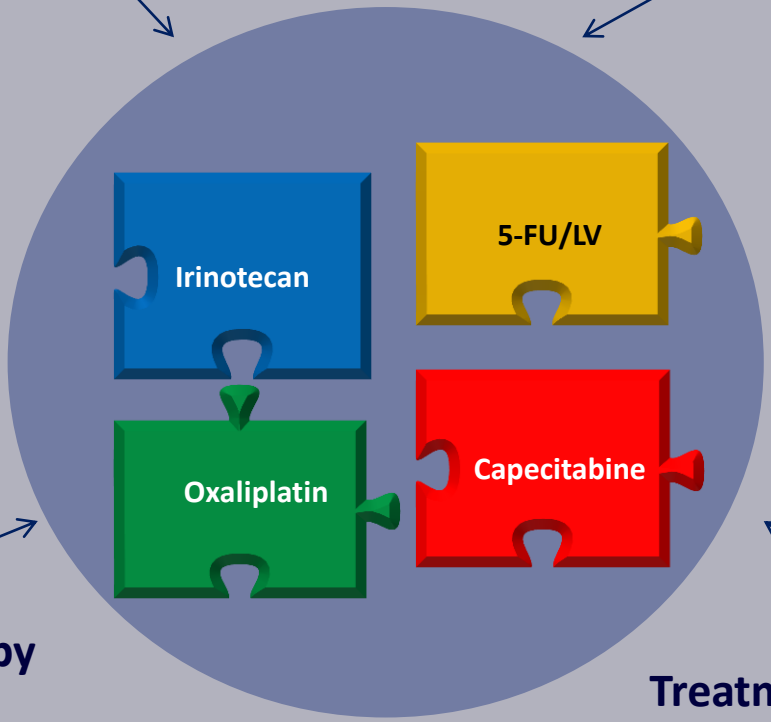


Factors Driving First-Line Chemotherapy Selection

Patient comorbidities

Patient and physician bias

- History
- PS
- Efficacy
- Side effects



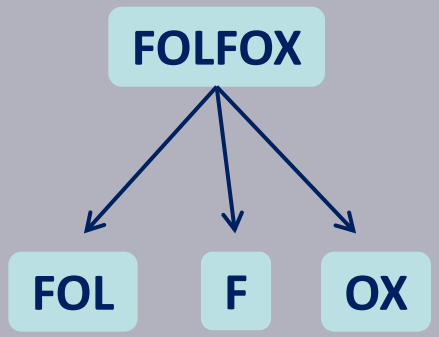
Prior adjuvant therapy

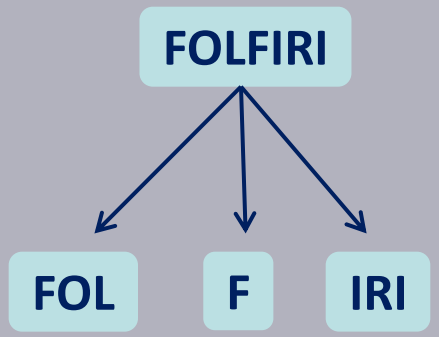
- Disease-free interval?

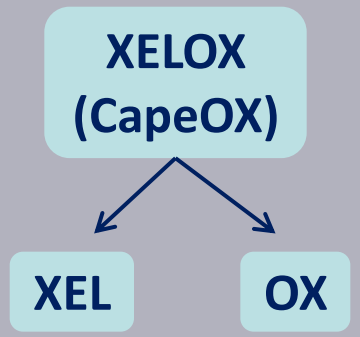
Treatment duration and strategy

- Continuous
- Intermittent
- Partial break
- Maintenance

Several Different Cytotoxic Doublets Can Be Used as Initial Therapy for mCRC







Therapy	Regimen
FOLFOX4	Folinic acid (leucovorin) Day 1 and 2: (200 mg/m^2 IV over 2 hours); 5-fluorouracil (5-FU); Day 1 and 2: (400 mg/m^2 IV bolus over 2 min) (600 mg/m^2 IV over 22 hr); oxaliplatin; Day 1: (85 mg/m^2 IV over 2 hr)
FOLFOX6	2-hour infusion of oxaliplatin (100 mg/m^2 and 2-hour infusion of folinic acid (CF) (400 mg/m^2 on Day 1, followed by 5-FU bolus (400 mg/m^2 on Day 1 and 46-hour infusion (2.4 g/m^2)
mFOLFOX6	modified FOLFOX6 (2-hr IV infusion 85 mg/m^2, oxaliplatin ; 2-hr IV 400 mg/m^2 folinic acid;) 400 mg/m^2 bolus; 46- to 48-h IV 2400 mg/m^2 5-FU
FOLFOX7	Oxaliplatin (130 mg/m^2) IV infusion with LV (folinic acid) (400 mg/m^2) over 2 h on day 1, followed by bolus 400 mg/m^2 and a 46-h infusion (2400 g/m^2) of 5-FU

Therapy	Regimen
FOLFIRI	Irinotecan (180 mg/m² IV over 30-90 minutes)
	Concurrently with folinic acid (400 mg/m² IV over 120 minutes)
	Followed by 5-FU (400–500 mg/m² IV bolus) then 5-FU (2400 mg/m² IV infusion over 46 -48hours)

Therapy	Regimen
CapeOx	2-hr IV infusion 130 mg/m^2 oxaliplatin; 850–1000 mg/m^2 Xeloda® (capecitabine) by mouth

Schmoll HJ1, et al. Ann Oncol. 2012 Oct;23(10):2479-516

Toxicity profiles of FOLFIRI and FOLFOX6 differ

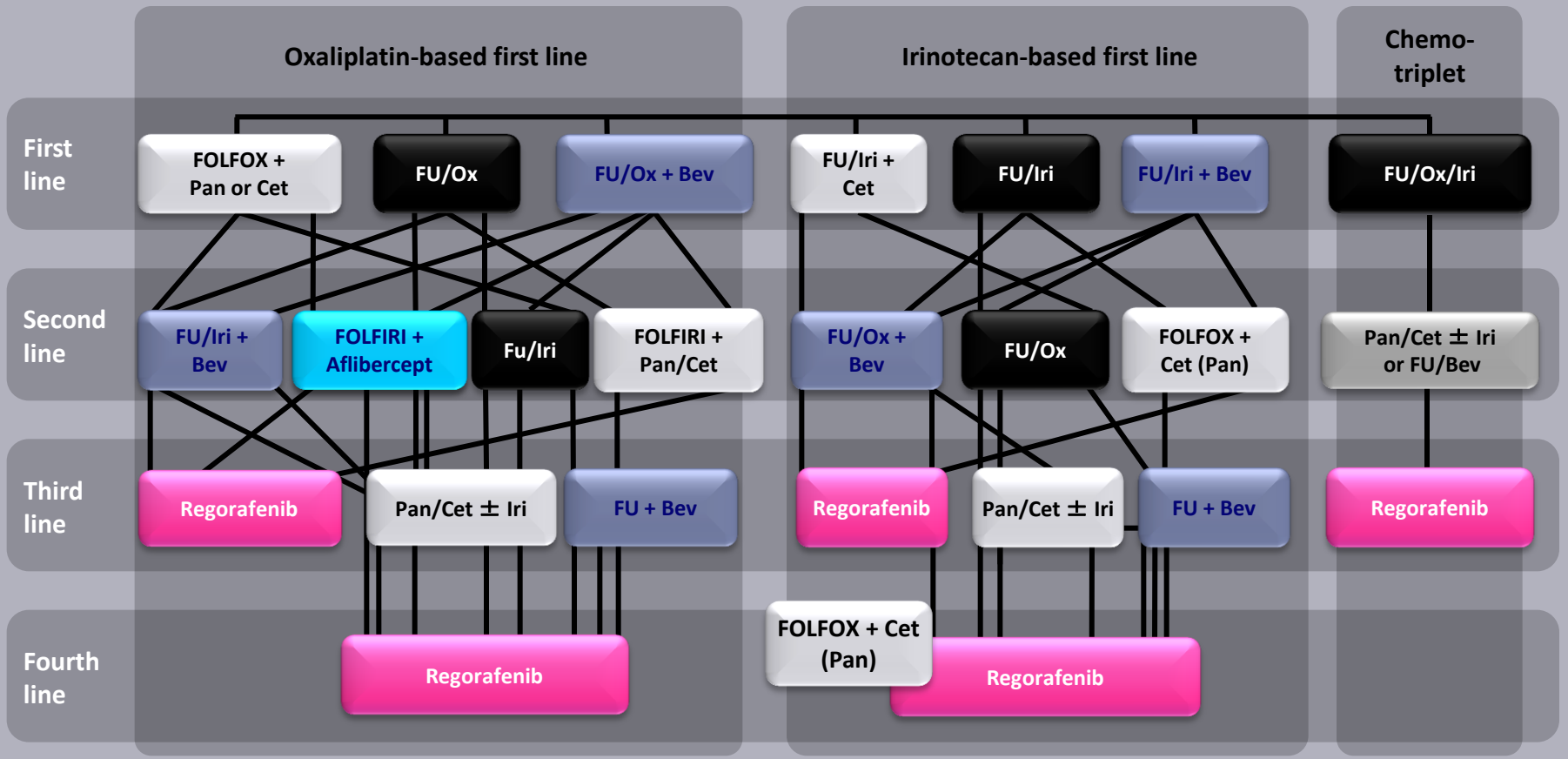
AEs of Interest, %	FOLFIRI (n = 110)		FOLFOX6 (n = 110)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neurological	0	NA	34	NA
Neutropaenia	15	9	31	13
Thrombocytopaenia	0	0	5	0
Anaemia	2	1	3	0
Febrile neutropaenia	4	3	0	0
Nausea	13	0	3	0
Vomiting	8	2	3	0
Mucositis	10	2	1	0

FOLFOX6 was associated with neurological AEs...

...whereas FOLFIRI was associated with gastrointestinal AEs

Schmoll HJ1, et al. Ann Oncol. 2012 Oct;23(10):2479-516

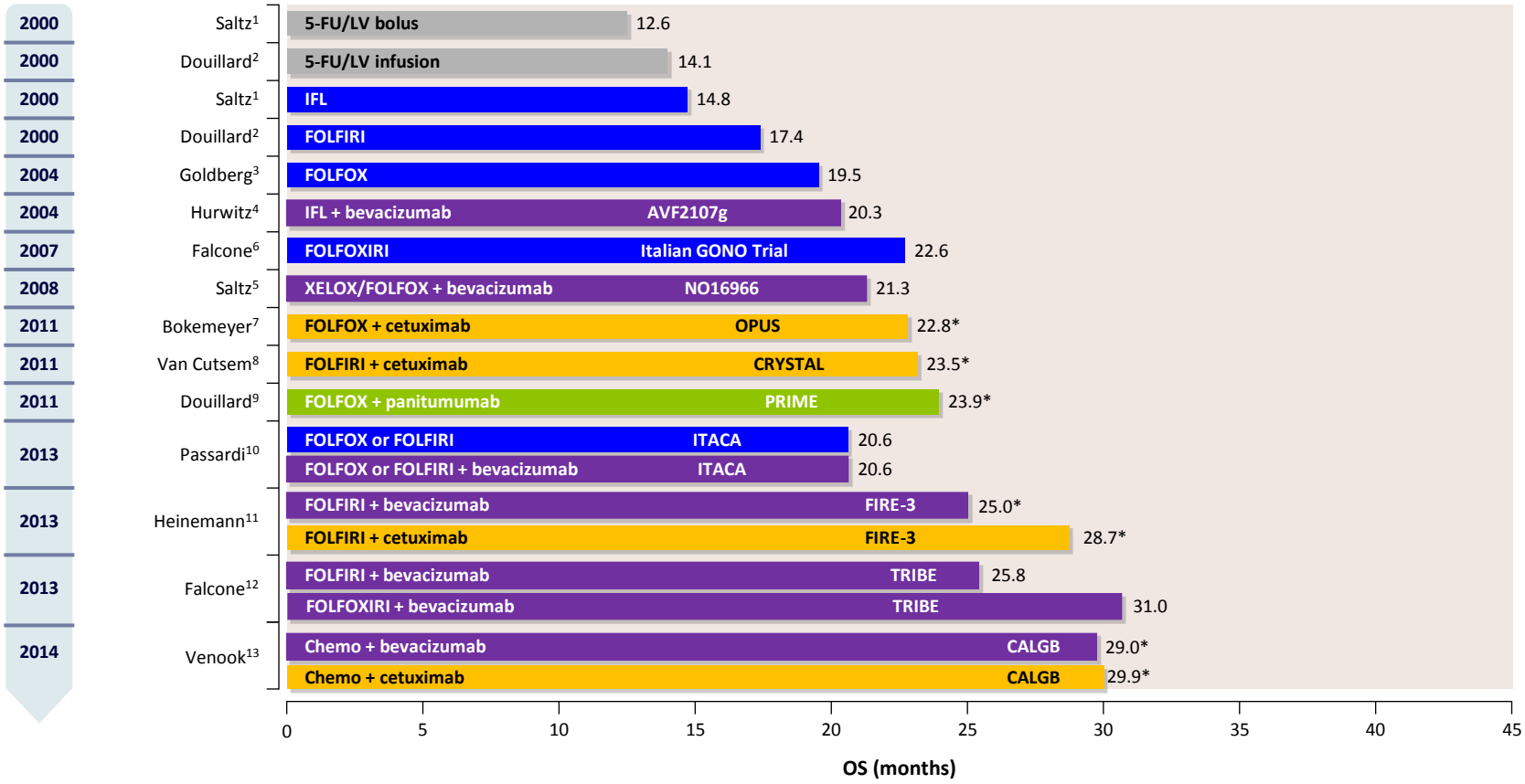
Complexity of Treatment Selection



Schmoll HJ1, et al. Ann Oncol. 2012 Oct;23(10):2479-516

Advances in Combination Treatment of mCRC Has Substantially Altered Treatment Outcome

Incremental Improvement in OS: 2000–2014



Schmoll HJ1, et al. Ann Oncol. 2012 Oct;23(10):2479-516

In order to plan therapy, which of the following genotyping panels MUST be performed?

A. KRAS only

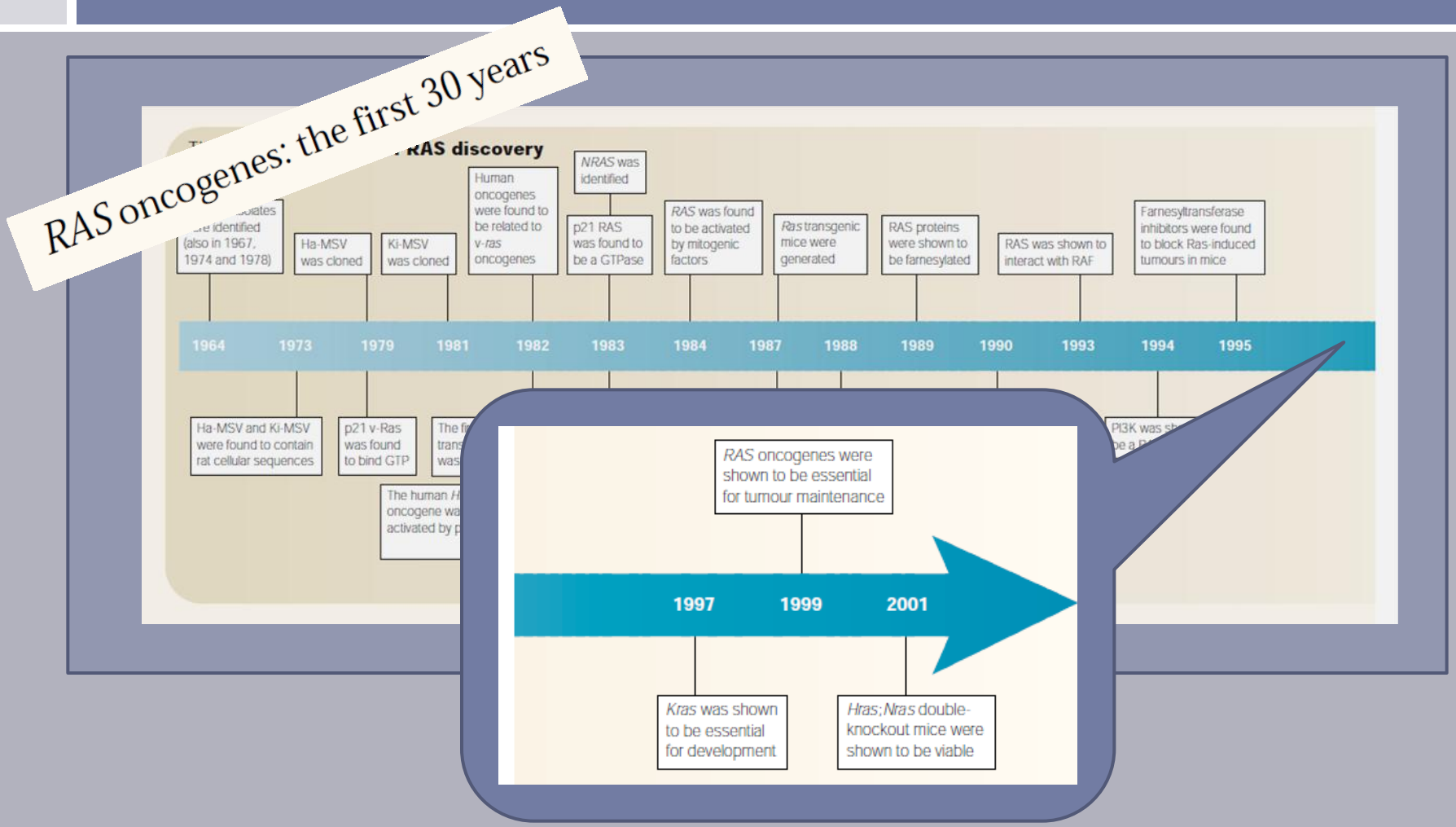
B. NRAS only

C. KRAS and NRAS only

D. KRAS, NRAS, and BRAF

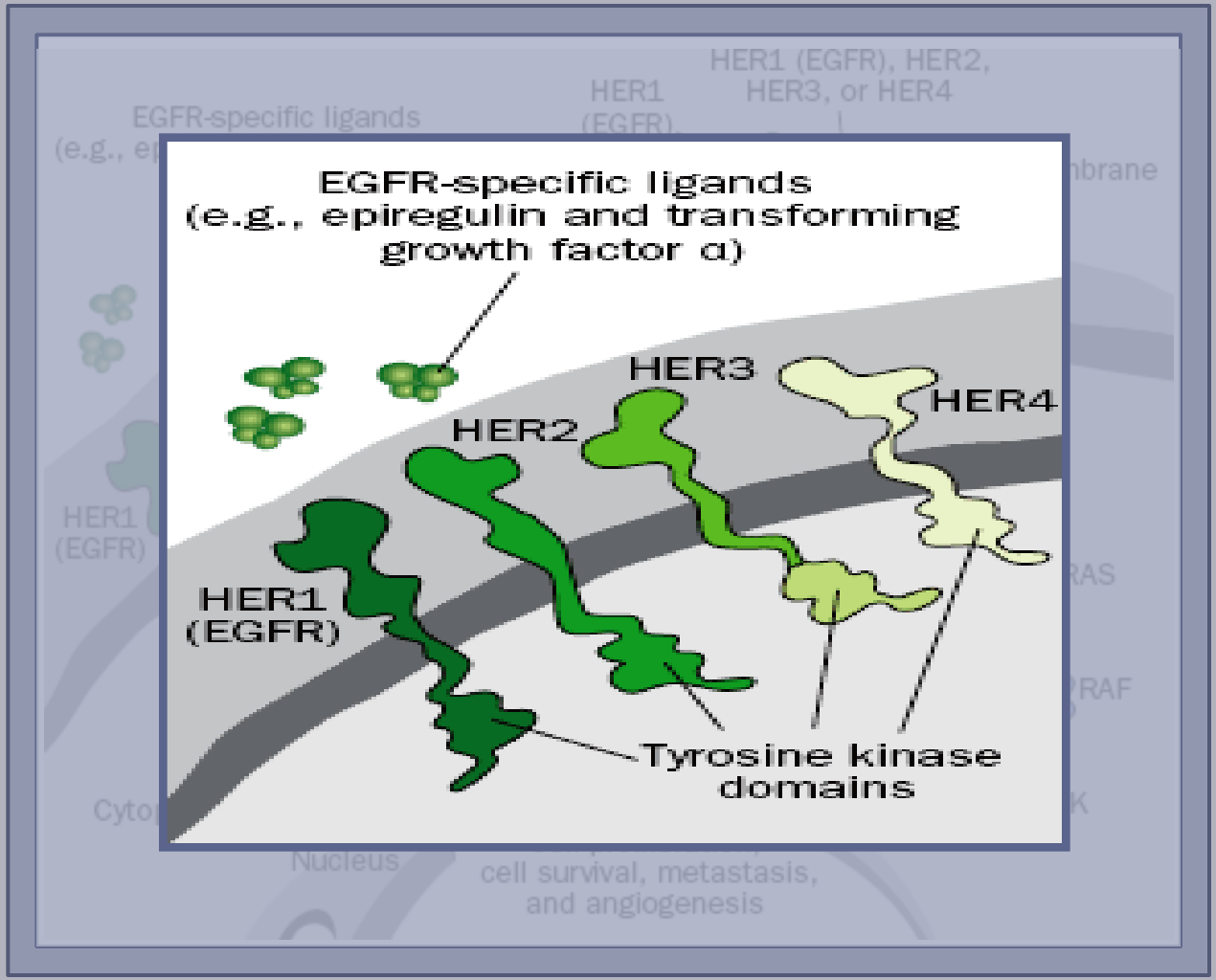
E. None of the Above

The Ras story



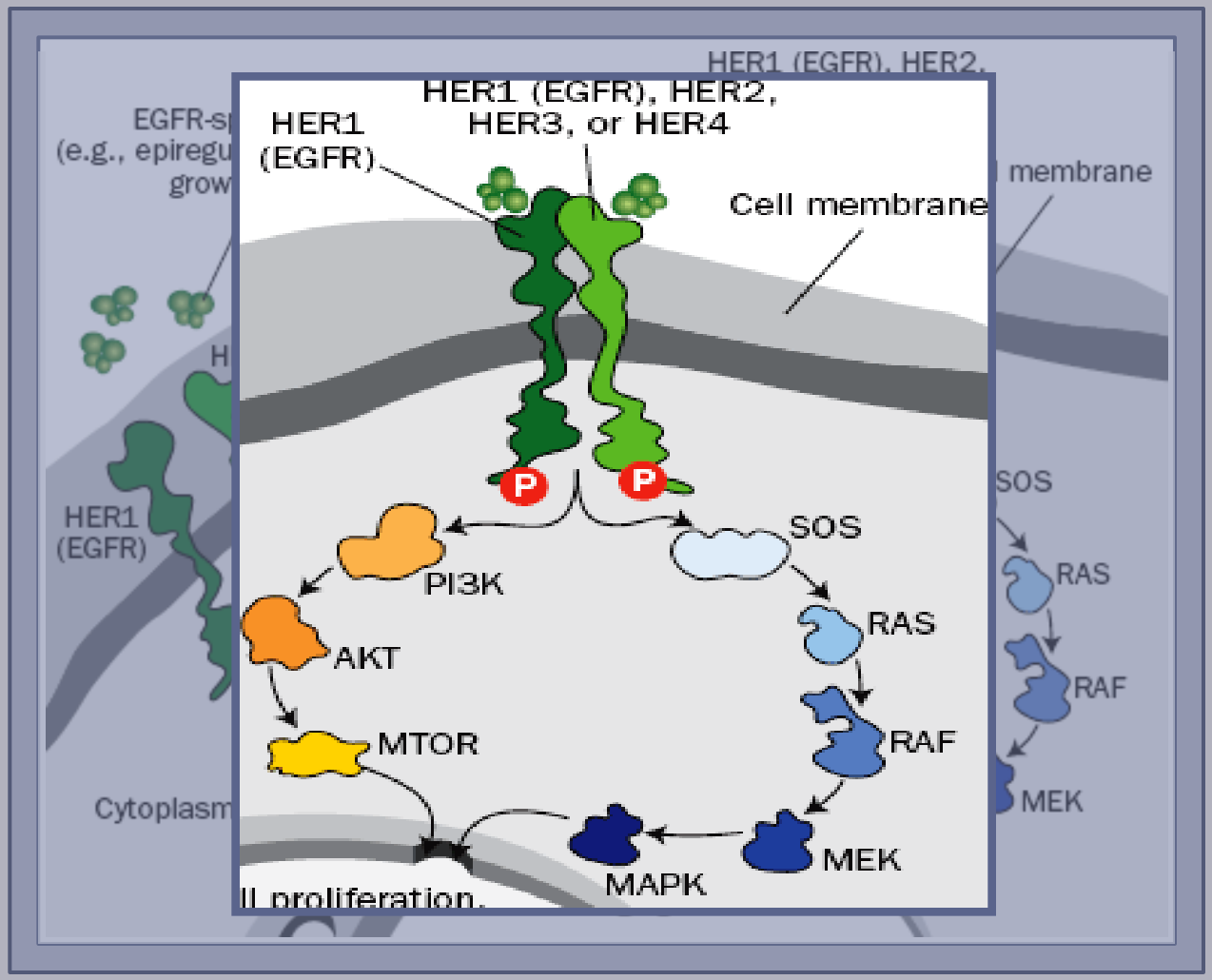
Gschwind A, et al. Nat Rev Cancer 2004;4:361-70.

Epidermal growth factor receptor (EGFR) signaling pathways



Cataldo VD, et al. N Engl J Med. 2011;364:947-955.

Epidermal growth factor receptor (EGFR) signaling pathways



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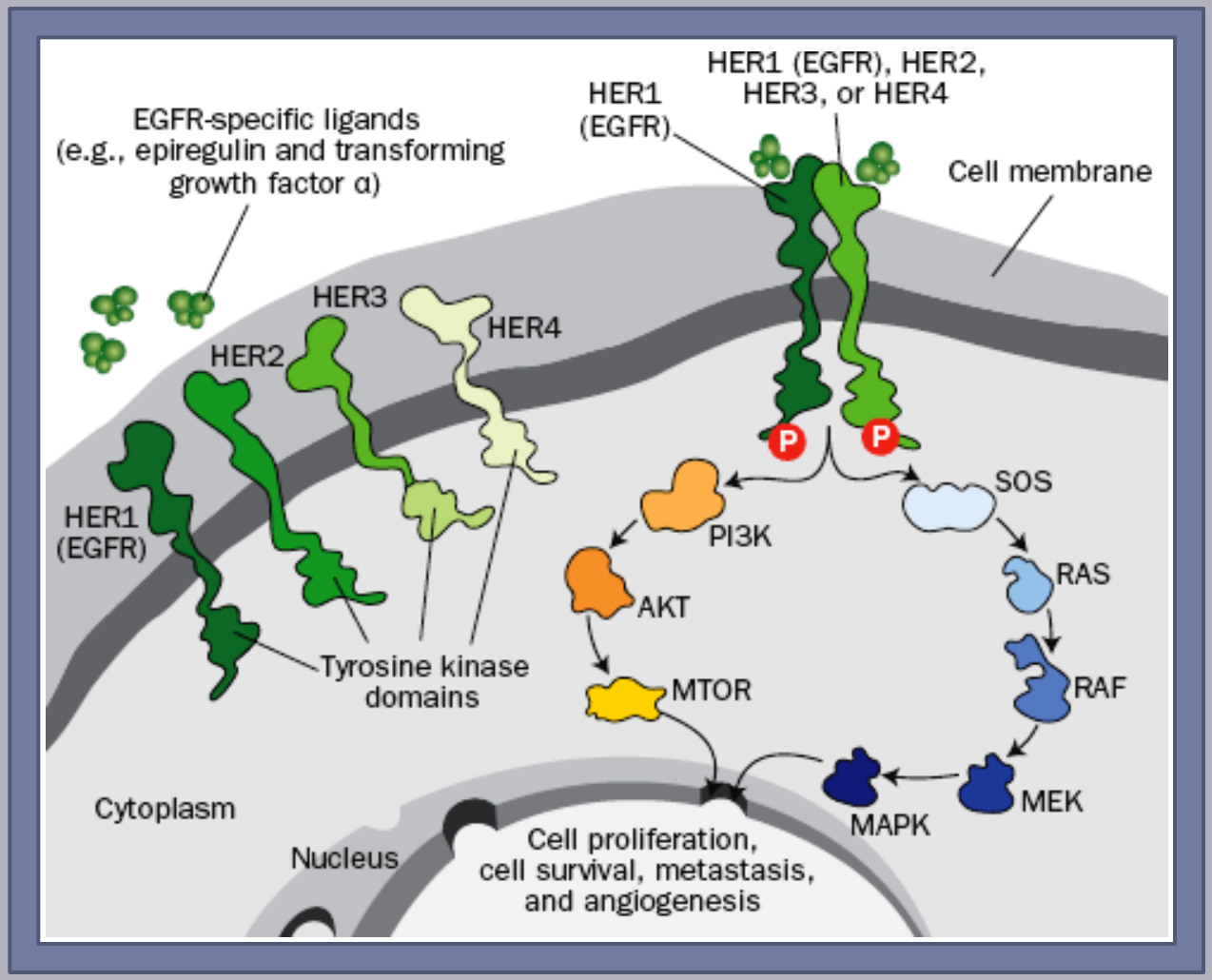
Epidermal growth factor receptor (EGFR) signaling pathways



Cataldo VD, et al. N Engl J Med. 2011;364:947-955.

Cetuximab and Panitumumab Are Two Distinct Anti-EGFR Monoclonal Antibodies

	Cetuximab	Panitumumab
Type of Molecule	 **Chimeric** monoclonal IgG1 antibody against EGFR IgG1 antibody: activates antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism	 Recombinant **fully human** IgG2 monoclonal antibody against EGFR IgG2 antibody: *does not* activate ADCC mechanism
MOA	Antibodies against EGFR **bind to the ligand-binding domain of EGFR,** inhibiting receptor autophosphorylation and downstream signalling	
Side Effects	**Class specific** •Cutaneous reactions (dermatologic toxicities: rash and pruritus, erythema, exfoliation, dermatitis acneiform) •Paronychia (nail changes) •Diarrhoea	***Cetuximab** •Headache •Infection •Relative incidence of infusion reactions
		***Panitumumab** • Constipation • Abdominal pain • Nausea • Fatigue • Fissures • Hypomagnesaemia

Siena S, et al. J Natl Cancer Inst 2009;101:1308-24.

Patient selection

VOLUME 23 · NUMBER 9 · MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor by Immunohistochemistry

Ki Young Chung, Jinru Shia, Nancy E. Kemeny, Manish Shah, Gary K. Schwartz, Archie Tse, Audrey Hamilton, Dorothy Pan, Deborah Schrag, Lawrence Schwartz, David S. Klimstra, Daniel Fridman, David P. Kelsen, and Leonard B. Saltz

n= 16 patients

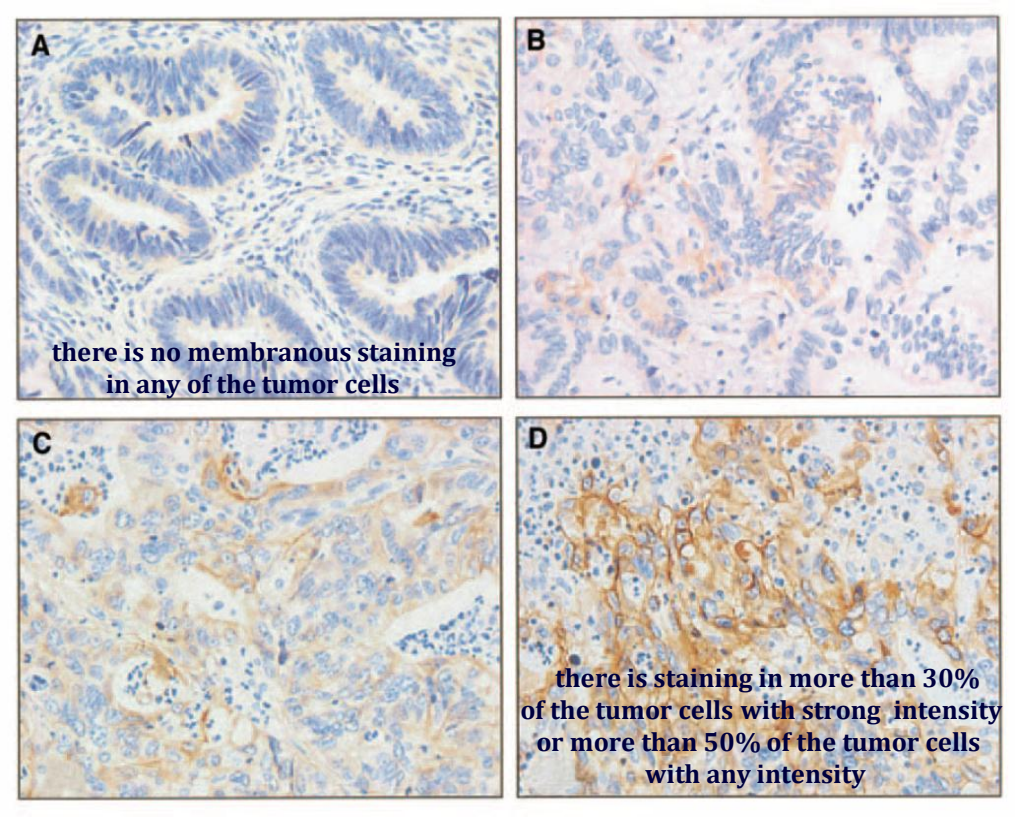
Conclusion

Colorectal cancer patients with EGFR-negative tumors have the potential to respond to cetuximab-based therapies. EGFR analysis by current IHC techniques does not seem to have predictive value, and selection or exclusion of patients for cetuximab therapy on the basis of currently available EGFR IHC does not seem warranted.

Patient selection

EGFR Status	Radiographic Responses
0/3+	PR, 73% reduction
0/3+	PR, 73% reduction
0/3+	PR, 60% reduction
0/3+	PR, 54% reduction
0/3+	MR, 39% reduction
0/3+	MR, 32% reduction
0/3+	SD
0/3+	POD
0/3+	POD
0/3+	POD
0/3+*	POD
0/3+	POD
0/3+	POD
0/3+†	Early POD
0/3+	Early POD
0/3+	Early POD

PR, partial response;
MR, minor response;
SD, stable disease;
POD, progression of disease;



Representative epidermal growth factor receptor (EGFR) immunohistochemistry scoring.
Level of EGFR staining: (A) 0; (B) 1+; (C) 2+; (D) 3+.

Chung KY, et al. J Clin Oncol 2005; 23:1803.

Patient selection

Cancer Therapy: Clinical

Clinical Cancer Research

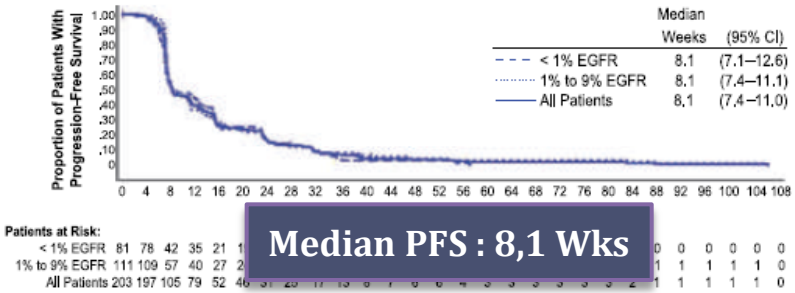
Lack of Correlation between Epidermal Growth Factor Receptor Status and Response to Panitumumab Monotherapy in Metastatic Colorectal Cancer

J. Randolph Hecht[1], Edith Mitchell[2], Marcus A. Neubauer[3], Howard A. Burris III[4], Paul Swanson[6], Timothy Lopez[7], Glenn Buchanan[8], Maureen Reiner[9], Jennifer Gansert[9], and Jordan Berlin[5]

16(7) April 1, 2010

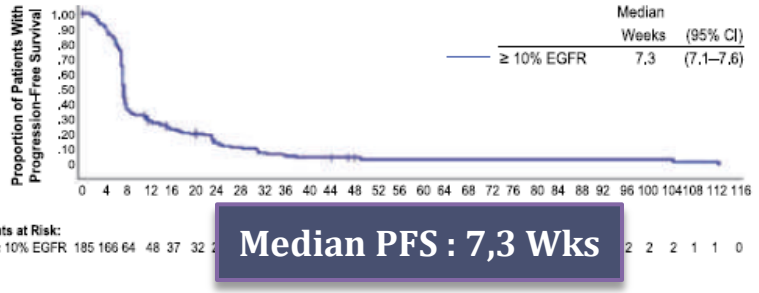
n= 203 patients

Progression-Free Survival



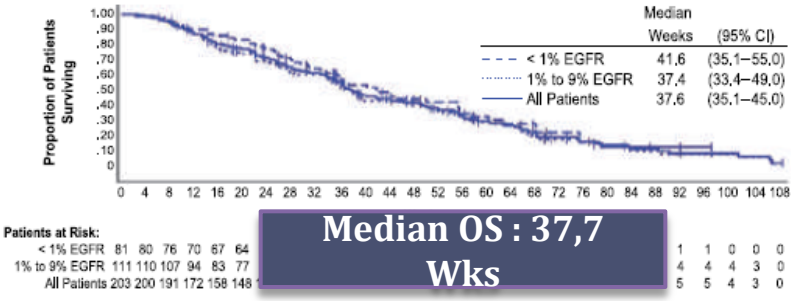
Median PFS : 8,1 Wks

n= 185 patients



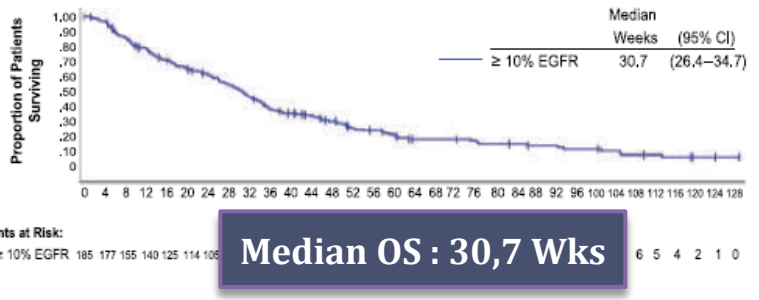
Median PFS : 7,3 Wks

Overall Survival



Median OS : 37,7 Wks

Low/Negative EGFR



Median OS : 30,7 Wks

High EGFR

Patient selection

The NEW ENGLAND JOURNAL of MEDICINE

Responsiveness to Cetuximab without Mutations in *EGFR*

TO THE EDITOR: A large amount of information suggests that mutations in the kinase domain of epidermal growth factor receptor (EGFR) are critical for the efficacy of EGFR kinase inhibitors.[1-3] However, the effect of *EGFR* mutations on the response to cetuximab has not been directly investigated. Barber et al.[4] reported the absence of *EGFR* mutations in colorectal cancers and speculated that *EGFR* mutations were not required for the response to cetuximab, since it was an efficacious agent against this type of tumor.[5] We sequenced the kinase domain of *EGFR* (exons 18, 19, and 21) in tumor samples from 38 patients participating in a cetuximab-monotherapy study for recurrent non–small-cell lung cancer and tumor samples from 39 patients participating in a cetuximab-monotherapy study for refractory colorectal cancer. Mutations previously detected in non–small-cell lung cancer[1-3] were identified in 3 of the 38 patients with non–small-cell lung cancer. Of 13 patients with non–small-cell lung cancer whose disease was stable, 2 carried a del746-750, and of 21 patients with progressive disease, 1 had an L861Q mutation. No mutations were identified in other patients with non–small-cell lung cancer who had a partial response (one patient) or for whom response data were unavailable (three patients). No mutations were detected in the samples from the 39 patients with colorectal cancer, including those from 20 patients who had a partial response and

From these results, it appears that the presence of an *EGFR* mutation is not a major determining factor for a positive response to cetuximab. Absence of an *EGFR* mutation in the samples of colorectal cancer, including those from patients who had a response to cetuximab, supports the speculation by Barber et al.[4] that *EGFR* mutations are not required for the efficacy of cetuximab in colorectal cancer. (Some of the samples were chosen for se-

previously untreated colorectal cancer (provided by Dr. Sina Dorudi, Royal London Hospital, London) from patients outside the cetuximab trial and could not identify any mutation in exons 18, 19, and 21. This further confirms the general absence of *EGFR* mutations in colorectal cancer. Our results suggest

Tsuchihashi Z, et al. N Engl J Med 2005; 353:208.

Patient selection

The NEW ENGLAND JOURNAL of MEDICINE

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Tsuchihashi Z, et al. N Engl J Med 2005; 353:208.

Patient selection

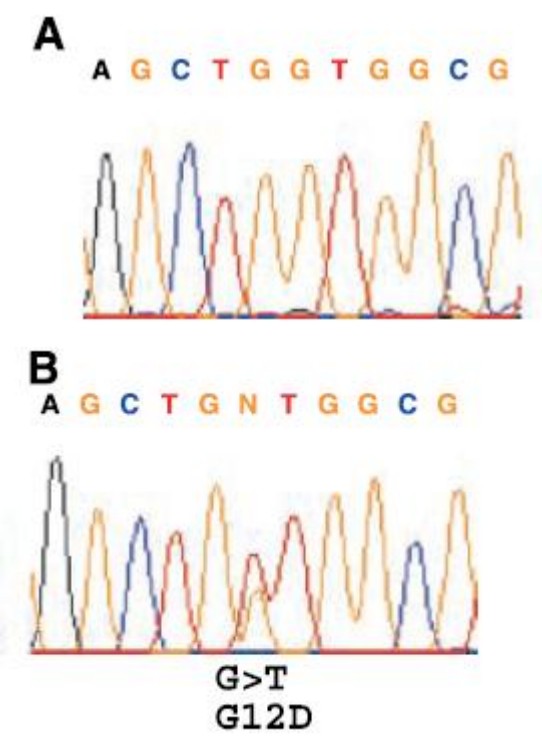
Priority Report

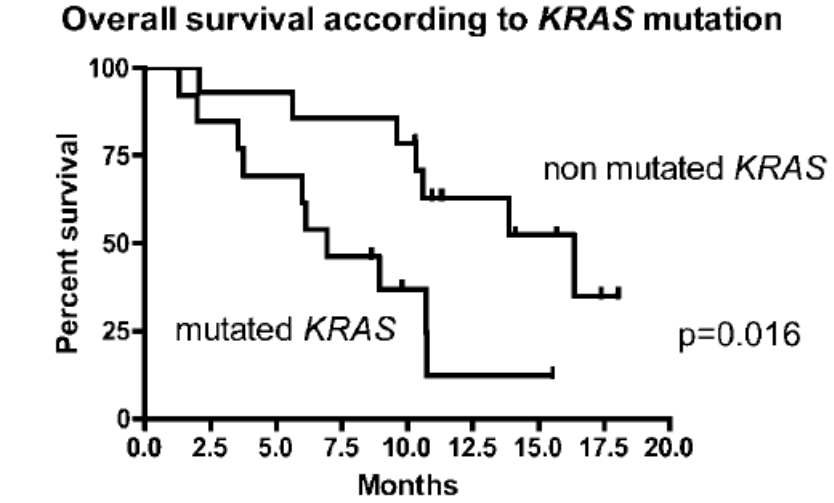
KRAS Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer

Astrid Lièvre,[1,3] Jean-Baptiste Bachet,[3] Delphine Le Corre,[1] Valérie Boige,[4] Bruno Landi,[2] Jean-François Emile,[3] Jean-François Côté,[1,2] Gorana Tomasic,[4] Christophe Penna,[3] Michel Ducreux,[4] Philippe Rougier,[3] Frédérique Penault-Llorca,[5]

Cancer Res 2006; 66: (8). April 15, 2006

n= 30 mCRC patients





A and B, electrophoregram from normal (A) and tumor tissue (B). A G12D KRAS mutation is observed in tumor tissue compared with normal tissue

Evidence that tumor RAS mutational status is predictive

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

n= 394 patients

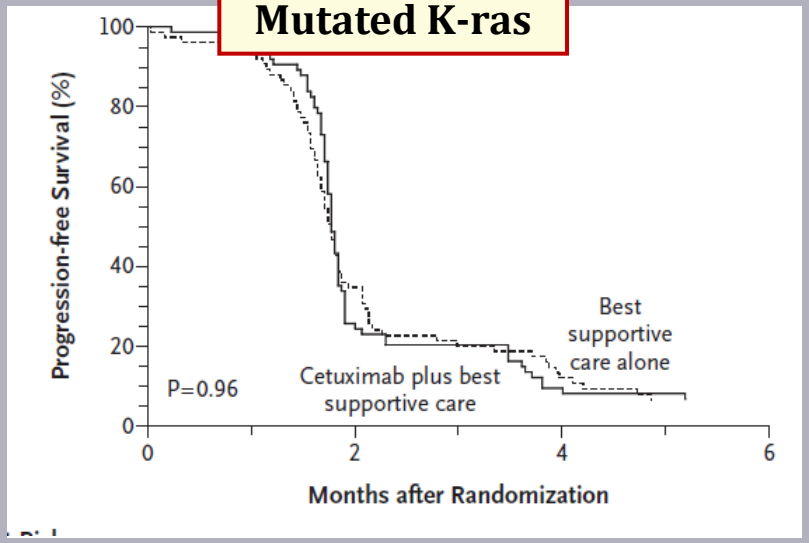
CONCLUSIONS

Patients with a colorectal tumor bearing mutated *K-ras* did not benefit from cetuximab, whereas patients with a tumor bearing wild-type *K-ras* did benefit from cetuximab. The

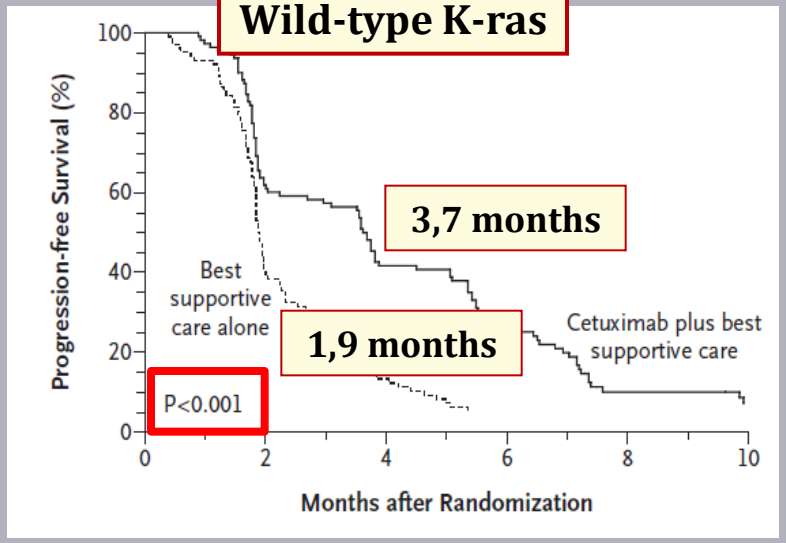
Evidence that tumor RAS mutational status is predictive

Progression-Free Survival

Mutated K-ras



Wild-type K-ras



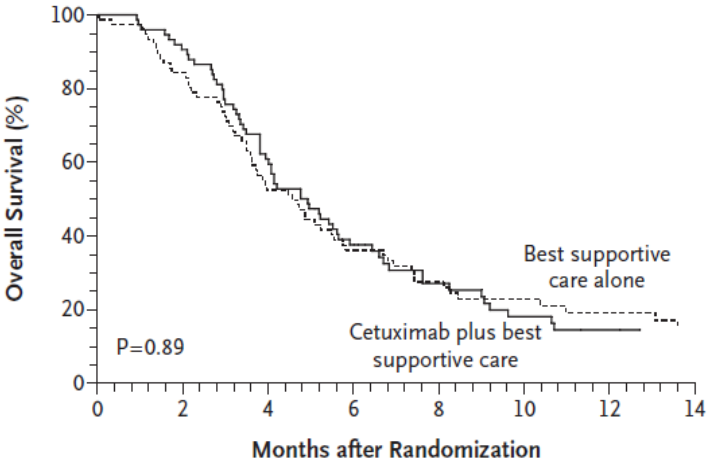
HR 0.40 (CI 0.30-0.45)

Karapetis CS, et al. N Engl J Med 2008; 359:1757–1765.

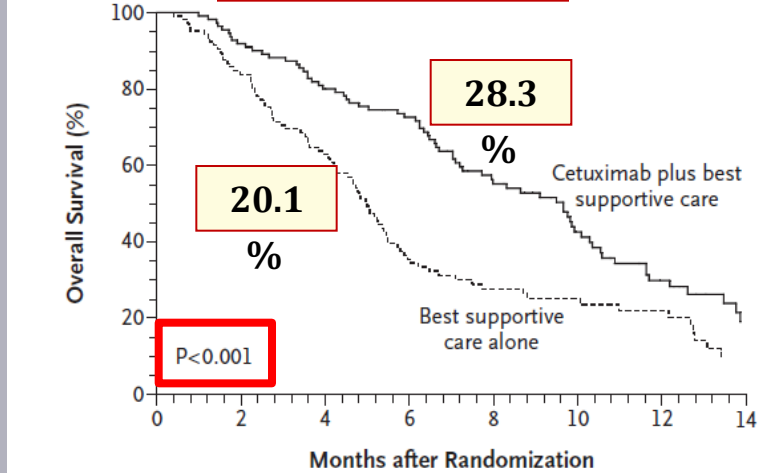
Evidence that tumor RAS mutational status is predictive

1-year Overall Survival

Mutated K-ras



Wild-type K-ras



HR 0.55 (CI 0.41-0.74)

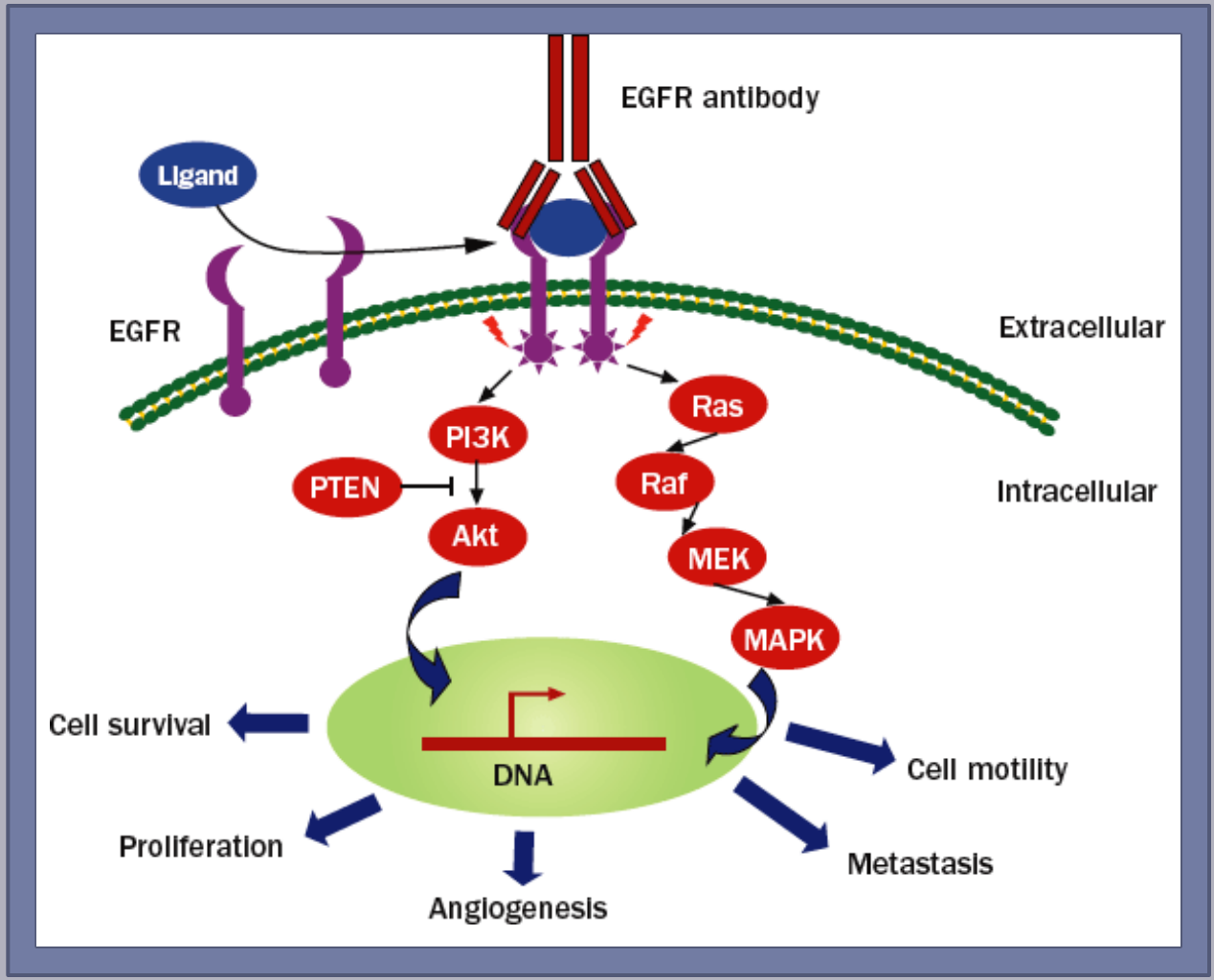
Karapetis CS, et al. N Engl J Med 2008; 359:1757–1765.

Predictive value of KRAS for anti-EGFR therapy in mCRC

Reference	Regimen	Treatment line	Phase	*n*	Mutation status (%)	Method	Remarkable results
Monotherapy							
Karapetis *et al*[9], 2008	Cetuximab *vs* BSC	Chemotherapy refractory	III	394	42.3	Sequencing	Cetuximab alone works on patient with WT KRAS tumors
Amado *et al*[10],	Panitumumab *vs* BSC	Chemotherapy refractory	III	427	43	Allele-specific PCR (DxS, United Kingdom)	Panitumumab alone works on patient with WT KRAS tumors
Combination therapy							
Van Cutsem *et al*[11], 2009	Cetuximab + FOLFIRI, FOLFIRI	First-line CRYSTAL trial	III	540	35.6	PCR clamping and HRM (TIB MolBioL, Germany)	Cetuximab plus FOLFIRI, reduced the risk of progression of metastatic colorectal cancer
Bokemeyer *et al*[12], 2009	Cetuximab + FOLFOX, FOLFOX	First-line, OPUS trial	II	233	42	PCR clamping and HRM (TIB MolBioL, Germany)	Significantly increased ORR in patients with WT KRAS tumors
Peeters *et al*[13], 2010	Panitumumab + FOLFIRI FOLFIRI	Second-line	III	1083	45	Allele-specific PCR (DxS, United Kingdom)	Significantly improved PFS in patients with WT KRAS tumors
Douillard *et al*[14], 2010	Panitumumab + FOLFOX FOLFOX	First-line	III	1096	40	Allele-specific PCR (DxS, United Kingdom)	Significantly improved PFS in patients with WT KRAS tumors
Van Cutsem *et al*[15], 2011	Cetuximab + FOLFIRI, FOLFIRI	First-line	III	1063	37	PCR clamping and HRM (TIB MolBioL, Germany)	Significantly improved OS in patients with WT KRAS tumors

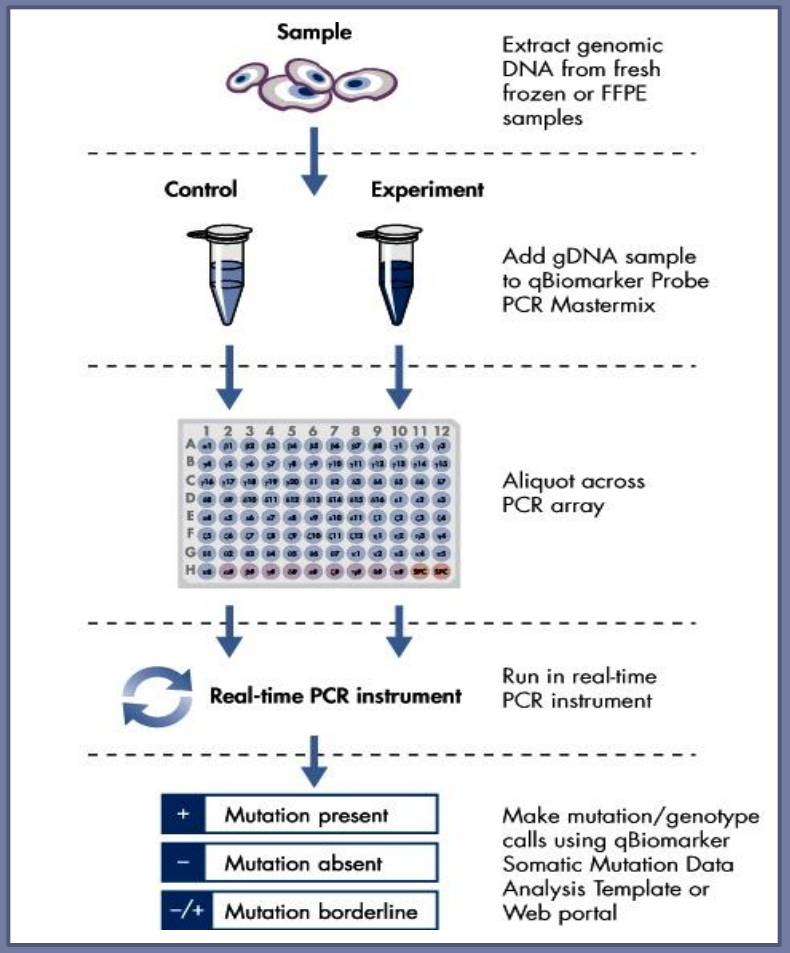
Tan C, Du X. World J Gastroenterol 2012;18:5171-80.

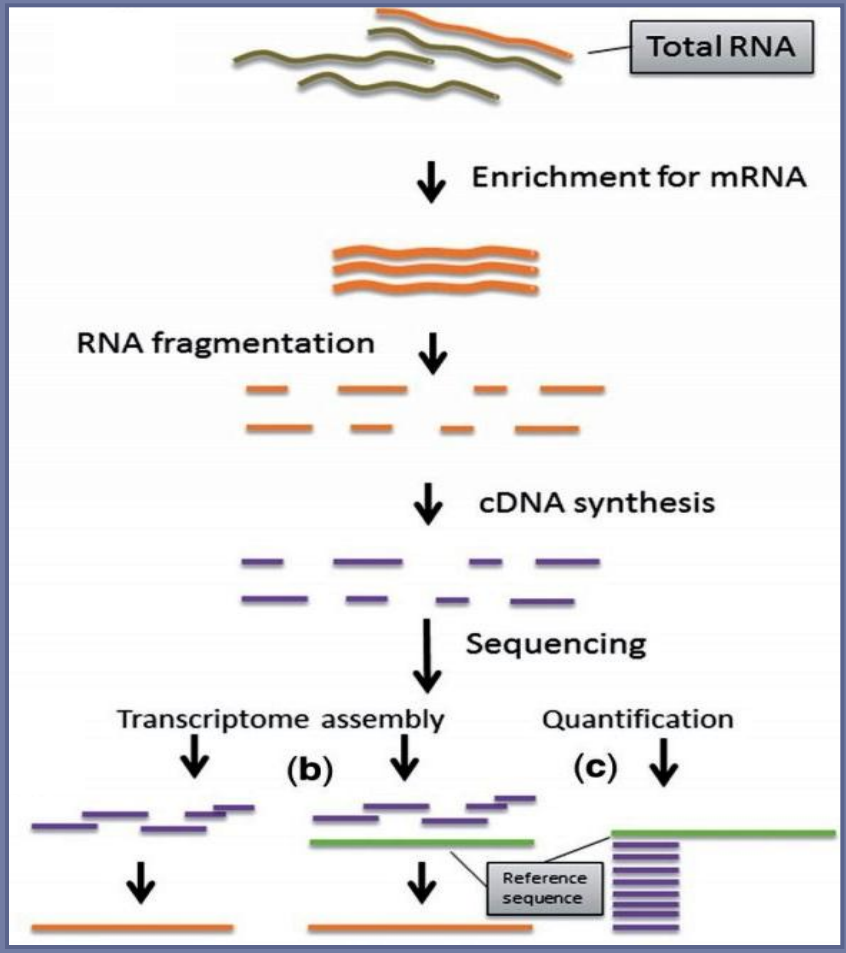
Predictive biomarkers for the efficacy of EGFR antibodies



Prenen H, et al. Clin Cancer Res 2010;16:2921-6.

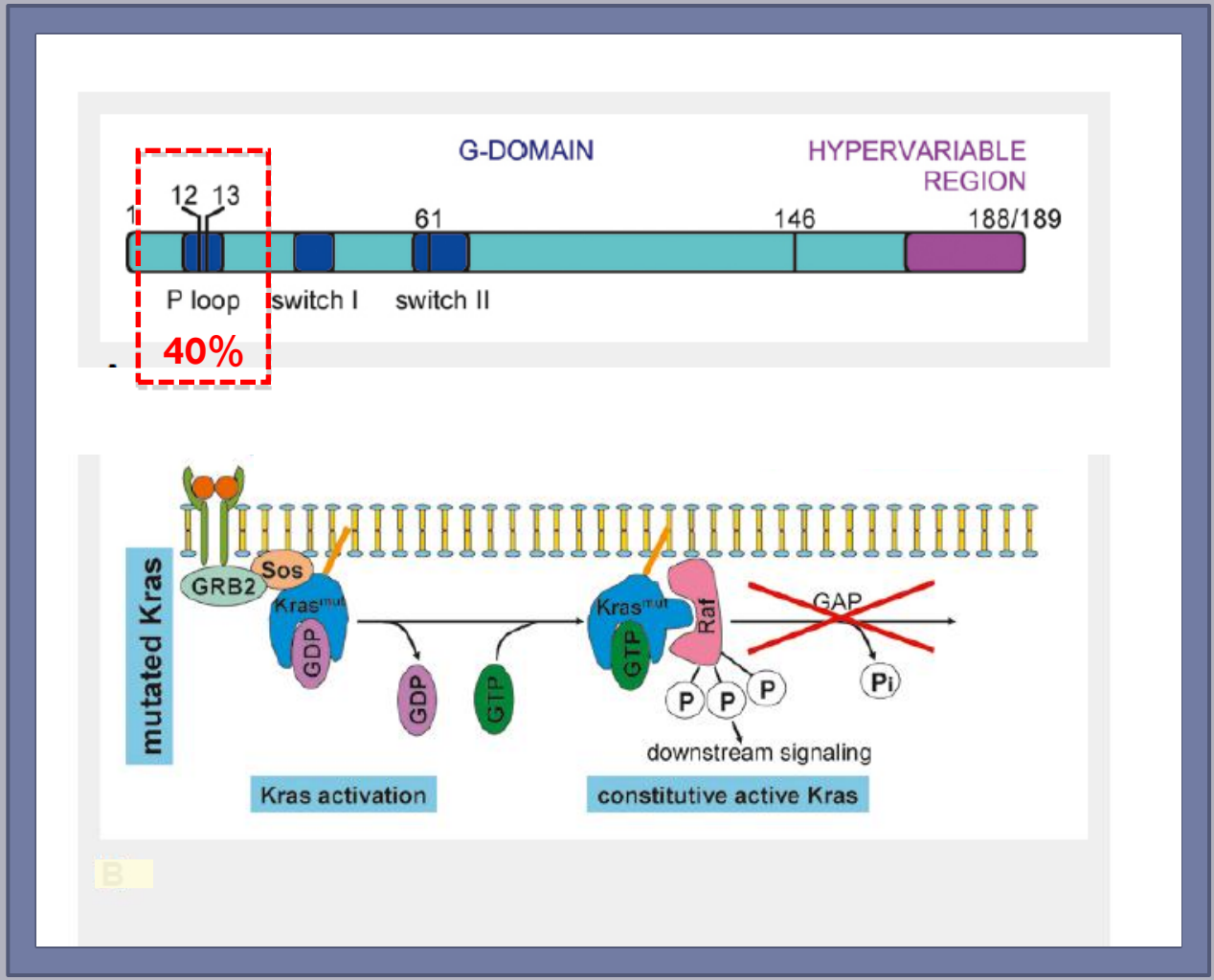
Two points are important to note with regard to KRAS mutations in colorectal cancer





Han CB, et al. Cancer Invest 2012; 30:741.

Two points are important to note with regard to KRAS mutations in colorectal cancer



Jimeno A, et al. J Clin Oncol 2009; 27:1130.

Prime Trial

VOLUME 28 · NUMBER 31 · NOVEMBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study

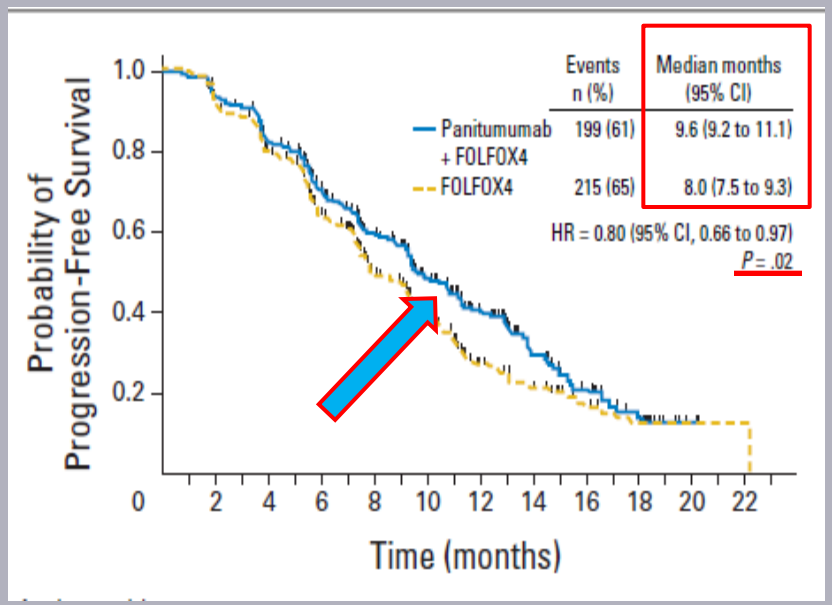
Jean-Yves Douillard, Salvatore Siena, James Cassidy, Josep Tabernero, Ronald Burkes, Mario Barugel,

n= 1,183 patients

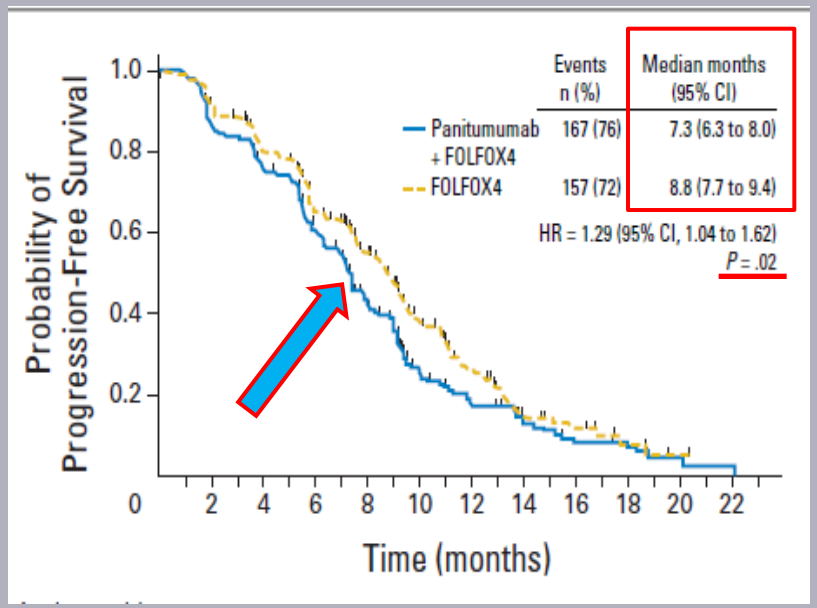
The use of EGFR inhibitors is not only ineffective in patients with KRAS-mutated mCRC, but may also be potentially harmful

Prime Trial

Wild-type K-ras

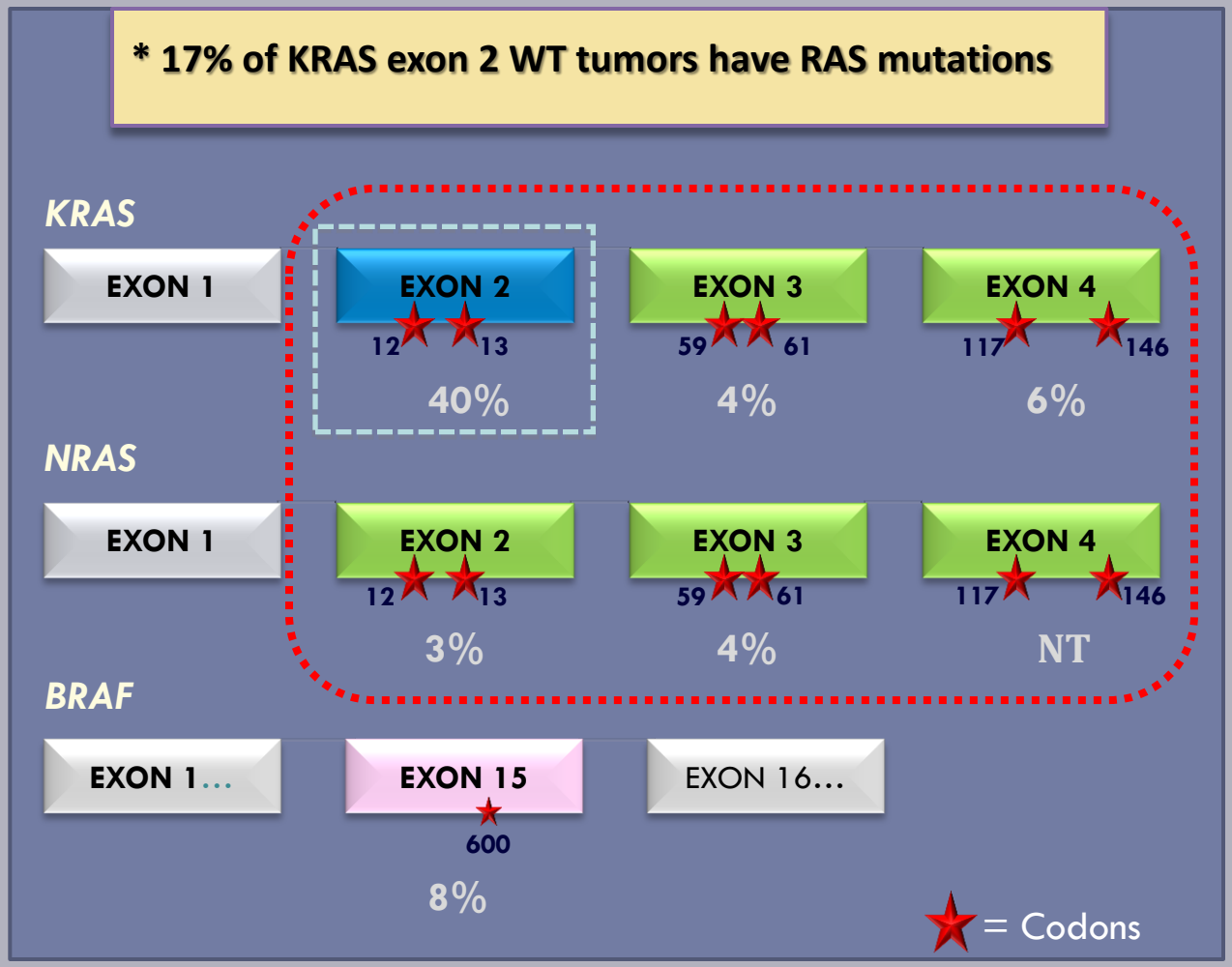


Mutated K-ras



Douillard JY, et al. J Clin Oncol. 2010;28:4697-705.

Frequency of *KRAS* and *NRAS* Mutations Beyond *KRAS* Exon 2 in the Updated Analysis of the Prime Study

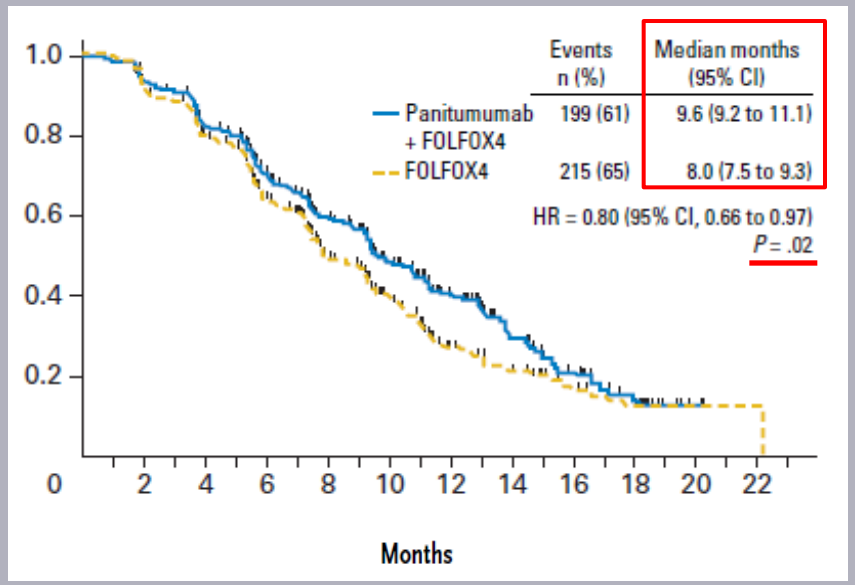


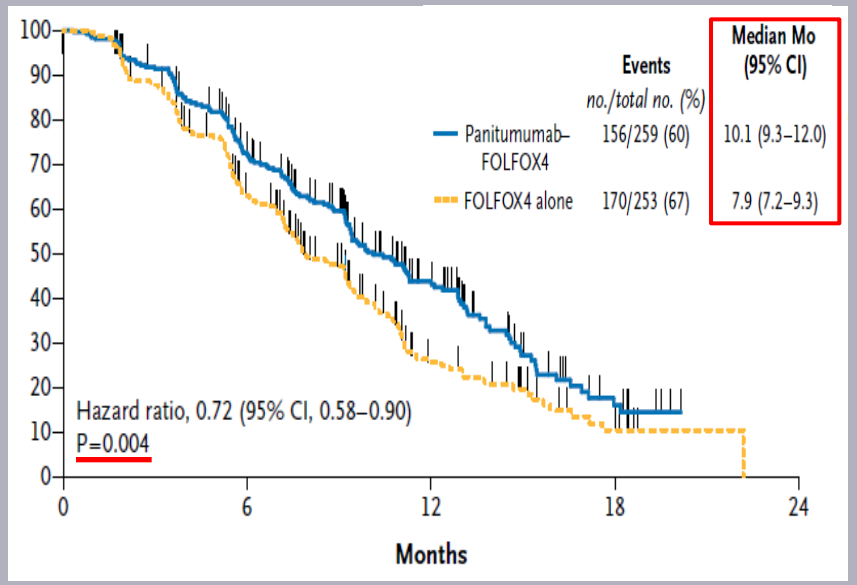
Douillard JY, et al. N Engl J Med. 2013;369:1023-34.

Prime Trial – PFS data

Median PFS has increased to 2.2 months

prospective-retrospective analysis





No *KRAS* exon 2 mutation

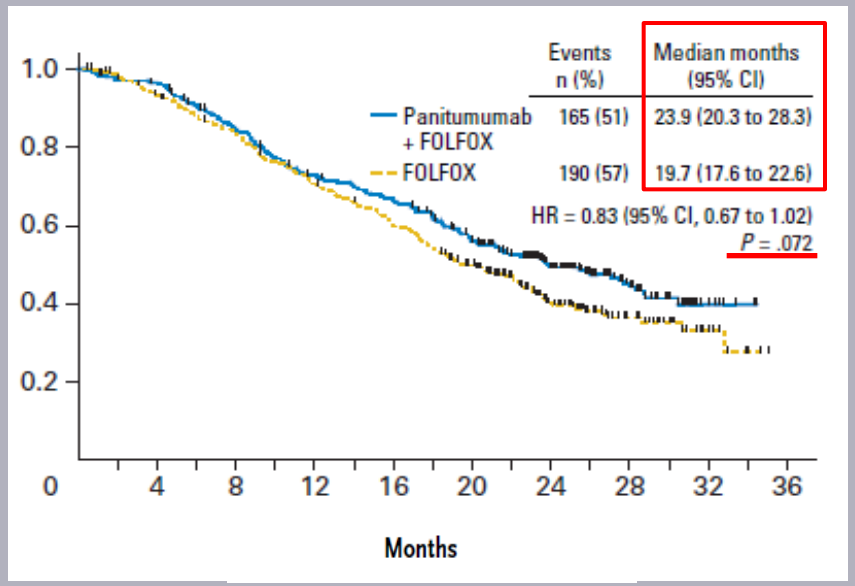
Extended *RAS* wild

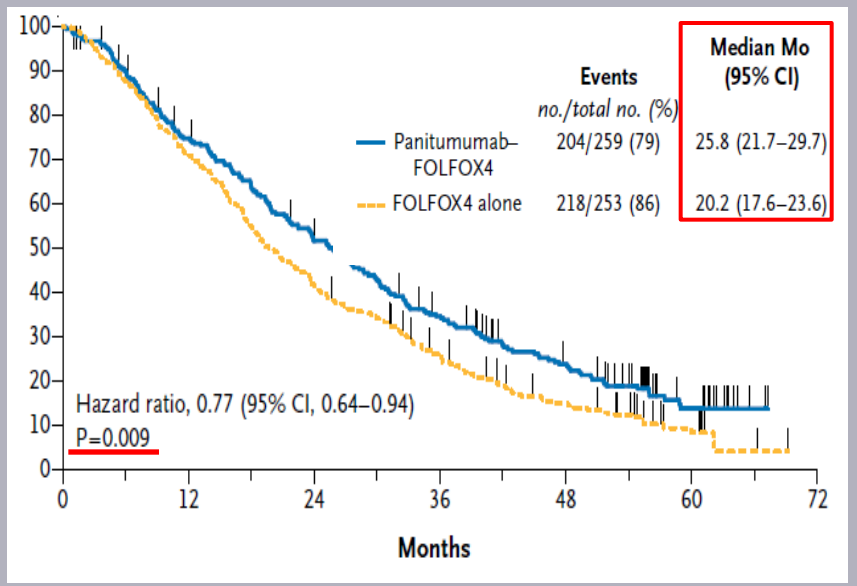
Douillard JY, et al. N Engl J Med. 2013;369:1023-34.

Prime Trial – OS data

Median OS has increased to 5.6 months

prospective-retrospective analysis





No *KRAS* exon 2 mutation

Extended *RAS* wild

Douillard JY, et al. N Engl J Med. 2013;369:1023-34.

Crystal Trial

ORIGINAL ARTICLE

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D.,

N Engl J Med 2009;360:1408-17.

n= 1,202 patients

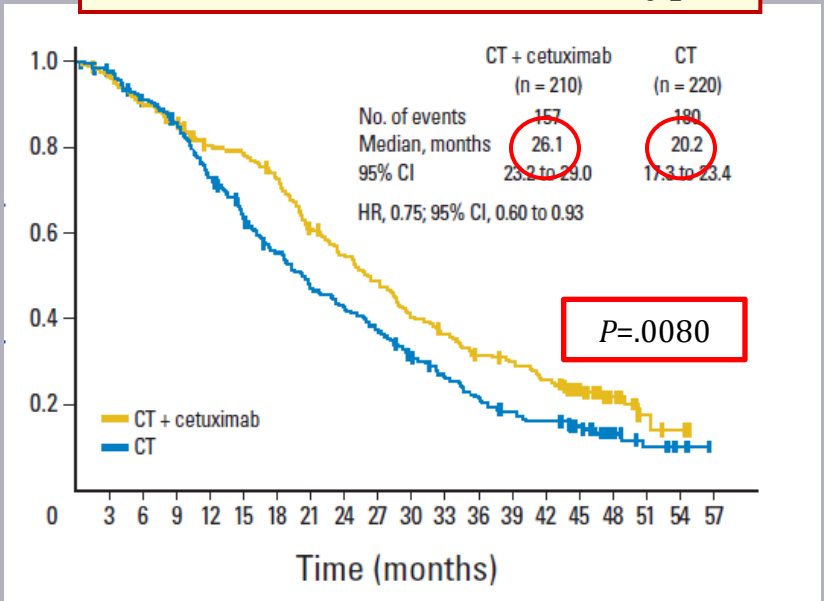
CONCLUSIONS

First-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The benefit of cetuximab was limited to patients with *KRAS* wild-type tumors. (ClinicalTrials.gov number, NCT00154102.)

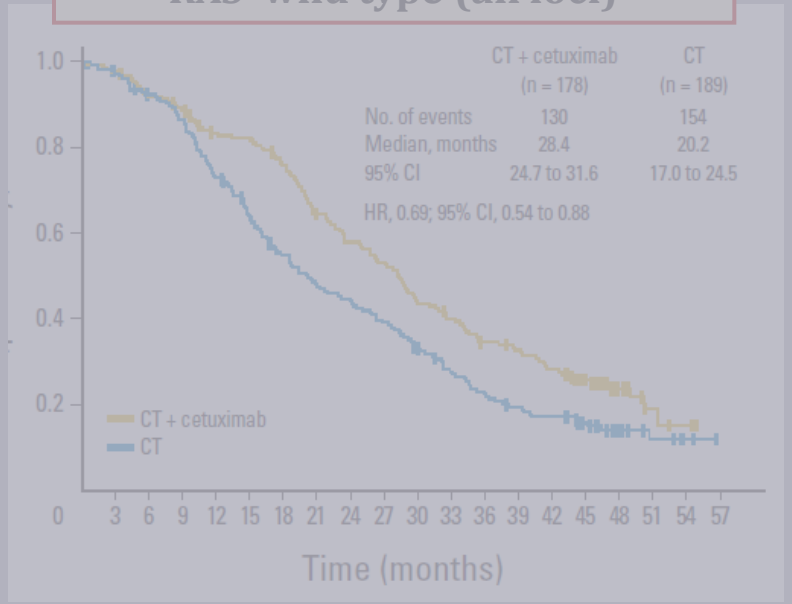
Crystal Trial

Overall Survival

KRAS codon 12 or 13 wild type



RAS wild type (all loci)



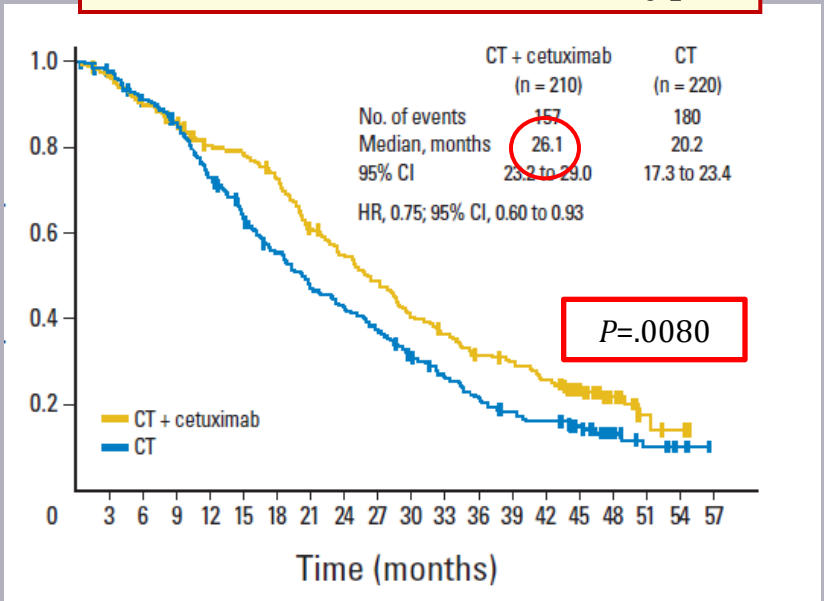
Van Cutsem E, et al. N Engl J Med 2009; 360:1408-1417.
Van Cutsem E, et al. J Clin Oncol 2015; 33: 692–700.

Crystal Trial

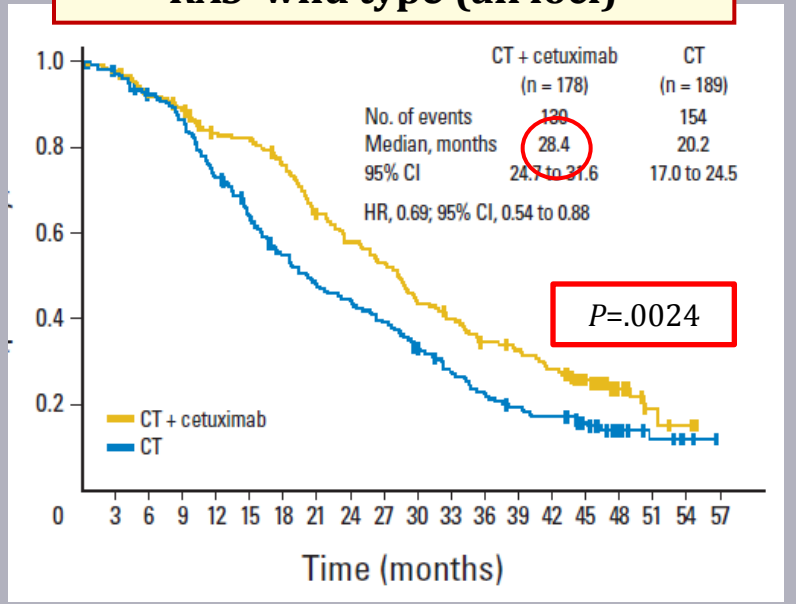
Outcome was reassessed in subgroups defined by extended RAS mutation testing

Overall Survival

KRAS codon 12 or 13 wild type



RAS wild type (all loci)



Van Cutsem E, et al. J Clin Oncol 2015; 33: 692–700.

Crystal Trial

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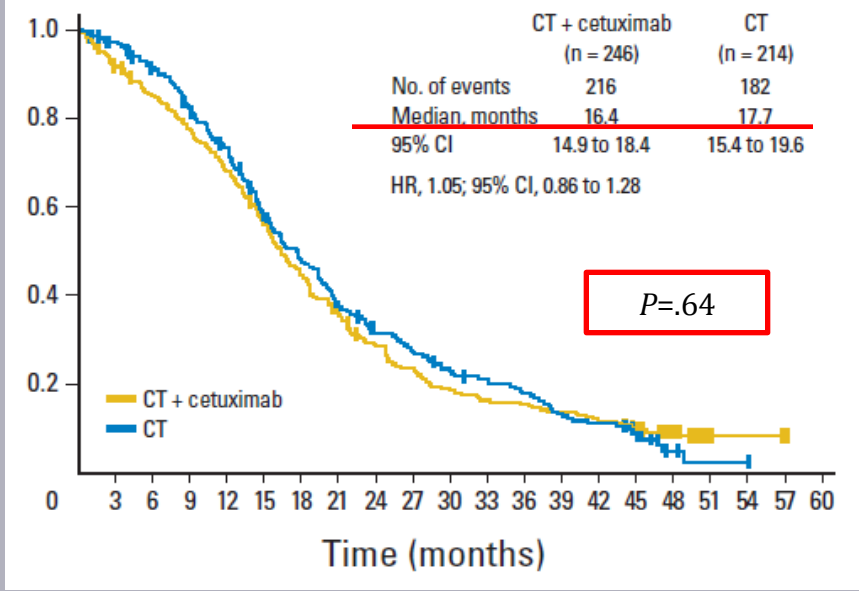
Overall Survival

***RAS* mutation (any locus)**



Van Cutsem E, et al. J Clin Oncol 2015; 33: 692–700.

Recommendation for Ras testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

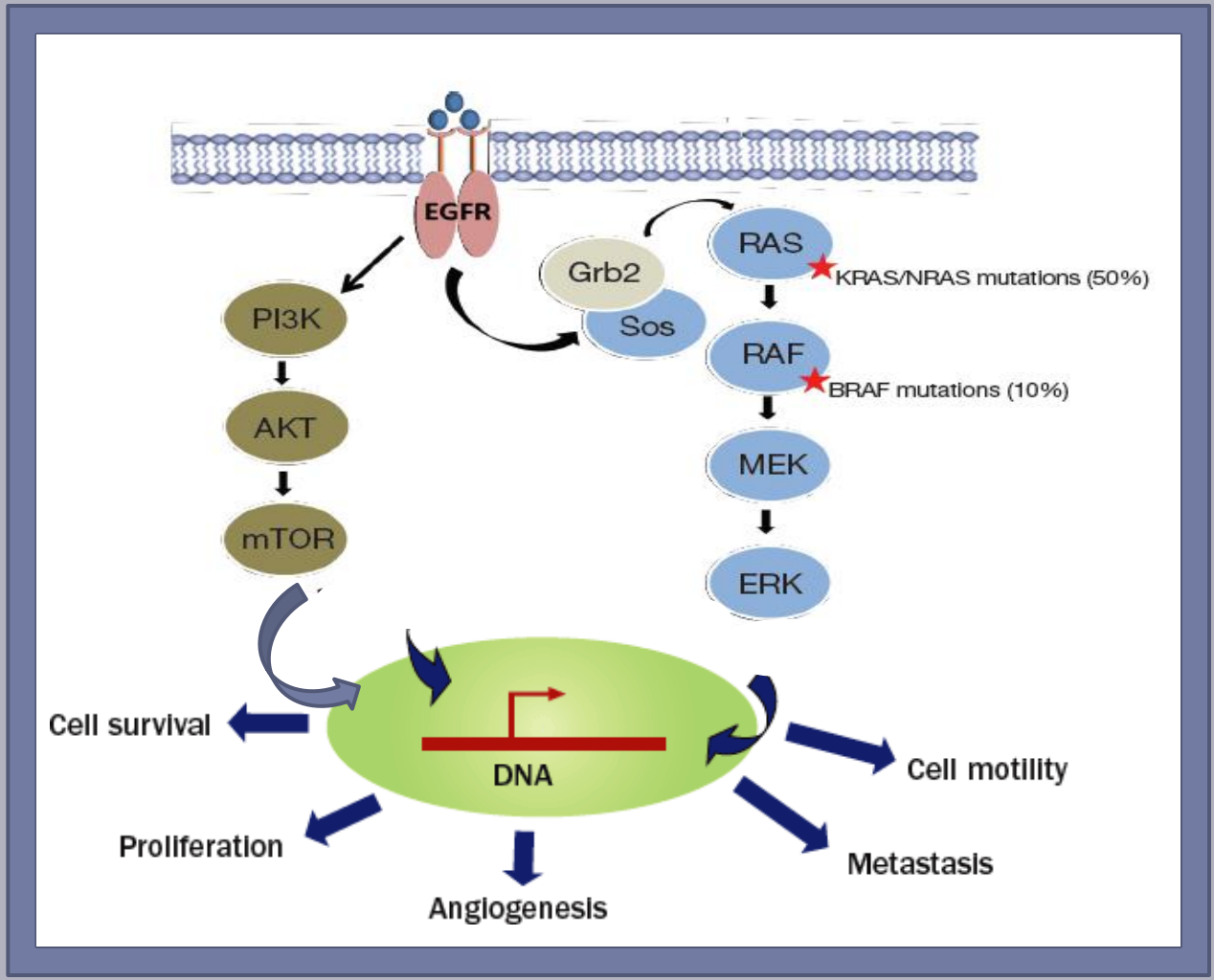
- RAS testing should be performed on all patients at the time of diagnosis of mCRC
- RAS testing is mandatory prior to treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab
- Primary or metastatic colorectal tumour tissue can be used for RAS testing
- RAS analysis should include at least KRAS exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and NRAS exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117)
- Laboratories providing RAS testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited

FDA-approved Anti-EGFR Antibodies in mCRC

Drug	Class	Target	Study (year)	1st or 2nd line	Regimen	Marker	Improvement (months)
Cetuximab	mAb	EGFR	BOND (2004) Cunningham *et al.* [2004]	2nd (failure of irinotecan regimen)	FOLFIRI	None	TSR (22.9%) TGD (4.1)
Cetuximab	mAb	EGFR	BOND (2004) Cunningham *et al.* [2004]	2nd (intolerant of irinotecan)	Mono tx	None	TSR (10.8%) TGD (1.5)
Cetuximab	mAb	EGFR	CRYSTAL (2012) Van-Cutsem *et al.* [2007]	1st line (KRAS WT)	FOLFIRI	KRAS WT	PFS (8.4–9.9)
Panitumumab	mAb	EGFR	(2006) Giusti *et al.* [2007]	2nd (failure of FOLFOX/ FOLFIRI)	BSC	None	PFS (7.3–8.0 weeks) OS (0–10%)
Panitumumab	mAb	EGFR	PRIME (2010) Douillard *et al.* [2010]		FOLFOX4	KRAS WT	PFS (8.0–9.6)

Moriarity A, et al. Ther Adv Med Oncol. 2016;8(4):276-93.

BRAF-Mutated Colorectal Cancers



Callisia N. Clarke and E. Scott Kopetz. J Gastrointest Oncol 2015;6(6):660-667.

BRAF-Mutated Colorectal Cancers

- BRAF mutant (usually V600E) occurs in 8-12% of patients with mCRC
- Almost exclusively non-overlapping with KRAS mutations
- 2/3 of BRAF mutant tumours located in right colon; associated with increased incidence of lymph node and peritoneal but fewer pulmonary metastases
- The predictive significance of BRAF mutation in 1st and 2nd line is currently uncertain

Tran B, et al. Cancer 2011; 117: 4623–4632.

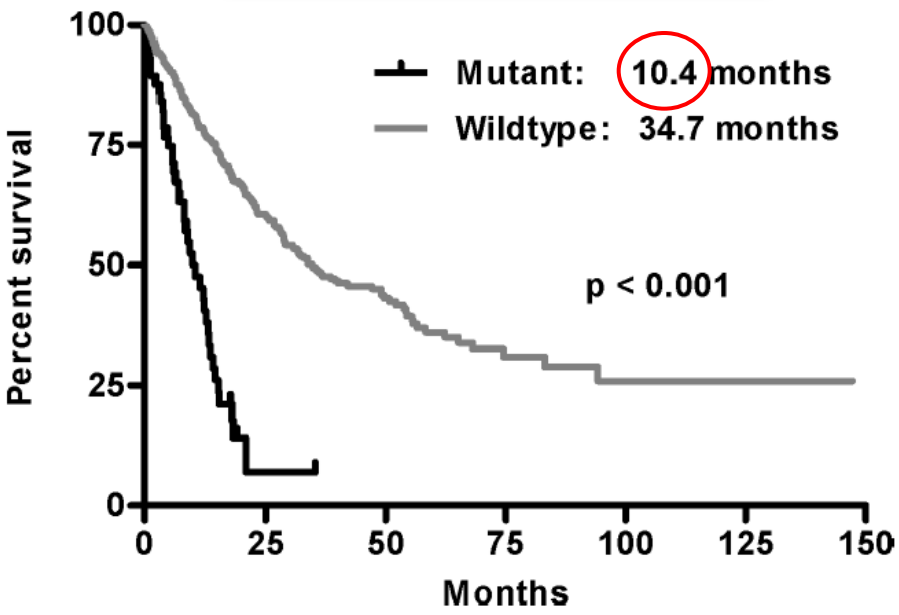
BRAF-Mutated Colorectal Cancers

Impact of BRAF Mutation and Microsatellite Instability on the Pattern of Metastatic Spread and Prognosis in Metastatic Colorectal Cancer

Cancer. 2011 October 15; 117(20): 4623–4632.

n= 600 patients

Overall Survival



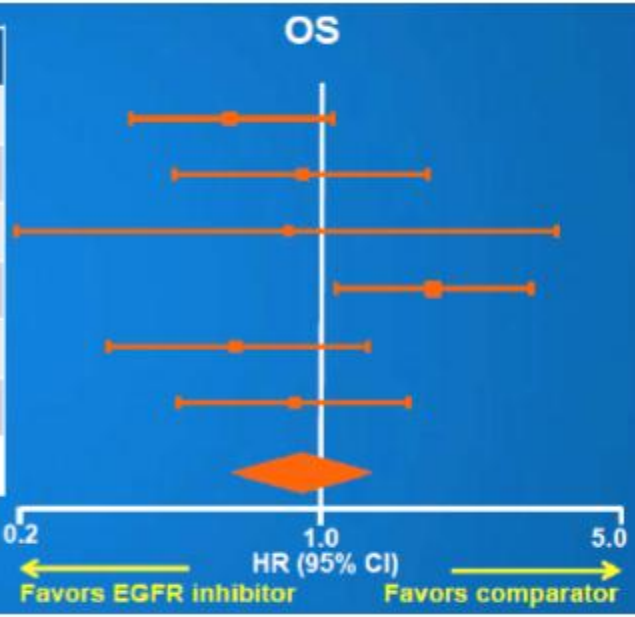
Anti-EGFR therapy in patients with (K)RAS wt/BRAF mt mCRC

Meta-analysis of randomised trials of (i) anti-EGFR therapy + CT vs. CT ± bevacizumab, or (ii) anti-EGFR monotherapy vs. BSC in patients with (K)RAS wt/BRAF mt mCRC (n=469)

Trial (n)	Weight, %	OS HR (95% CI)
OPUS/CRYSTAL	20.7	0.62 (0.36–1.06)
PRIME	17.0	0.90 (0.46–1.76)
CO.17	6.0	0.84 (0.20–3.56)
PICCOLO	21.5	1.84 (1.10–3.08)
20050181	16.4	0.64 (0.32–1.28)
FIRE-3	18.5	0.87 (0.47–1.61)
Summary	**100.0**	**0.91 (0.62–1.34)**

Heterogeneity: τ^2=0.11; χ^2=10.09; df=5 (p=0.07); I^2=50%

Test for overall effect: Z=0.48 (p=0.63)



- There was also no significant difference in:
  - PFS: HR=0.88 (95% CI: 0.67-1.14); p=0.33
  - ORR: OR=1.31 (95% CI: 0.83-2.08); p=0.25

Pietrantonio F, et al. Eur J Cancer. 2015 Mar;51(5):587-94.

Recommendation for BRAF testing

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Colon Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

***KRAS*, *NRAS*, and *BRAF* Mutation Testing**

- Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials)

Which of the following is the most reasonable option for First-line treatment

A. Chemotherapy only

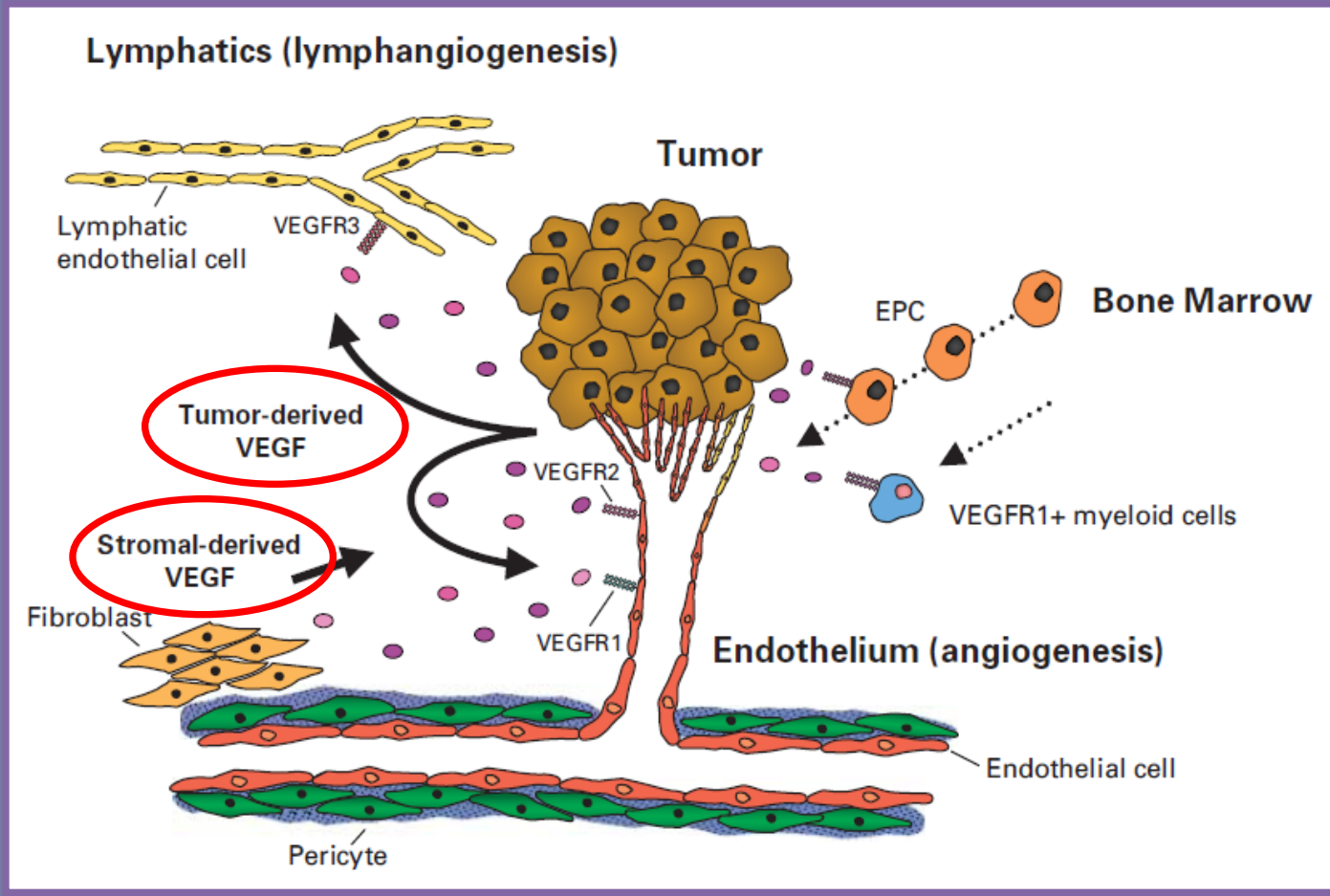
B. Anti-VEGF therapy only

C. Anti-VEGF + Chemotherapy

D. Anti-EGFR therapy only

E. Anti-EGFR therapy + Chemotherapy

Targeting VEGF-Mediated Angiogenesis in mCRC



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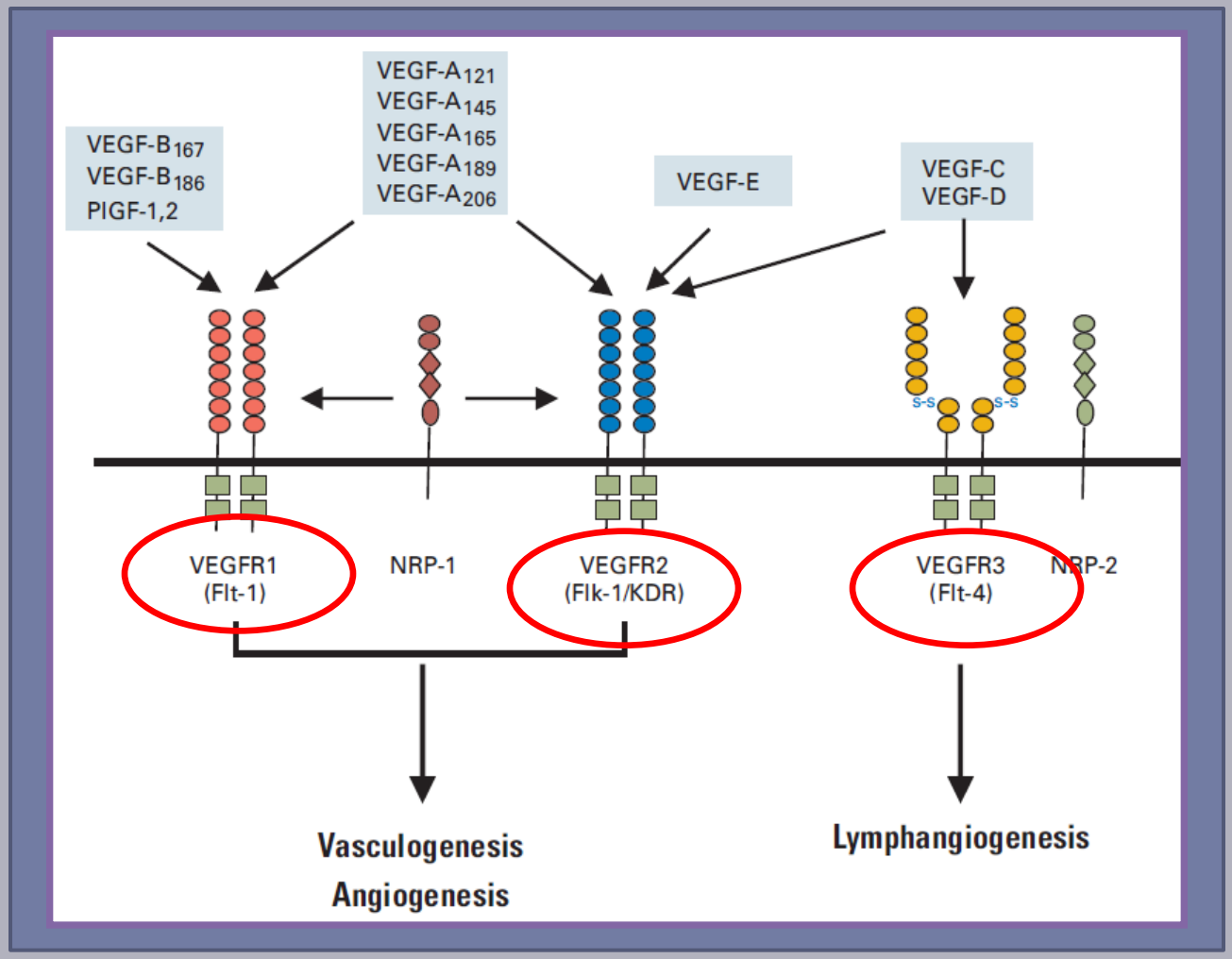

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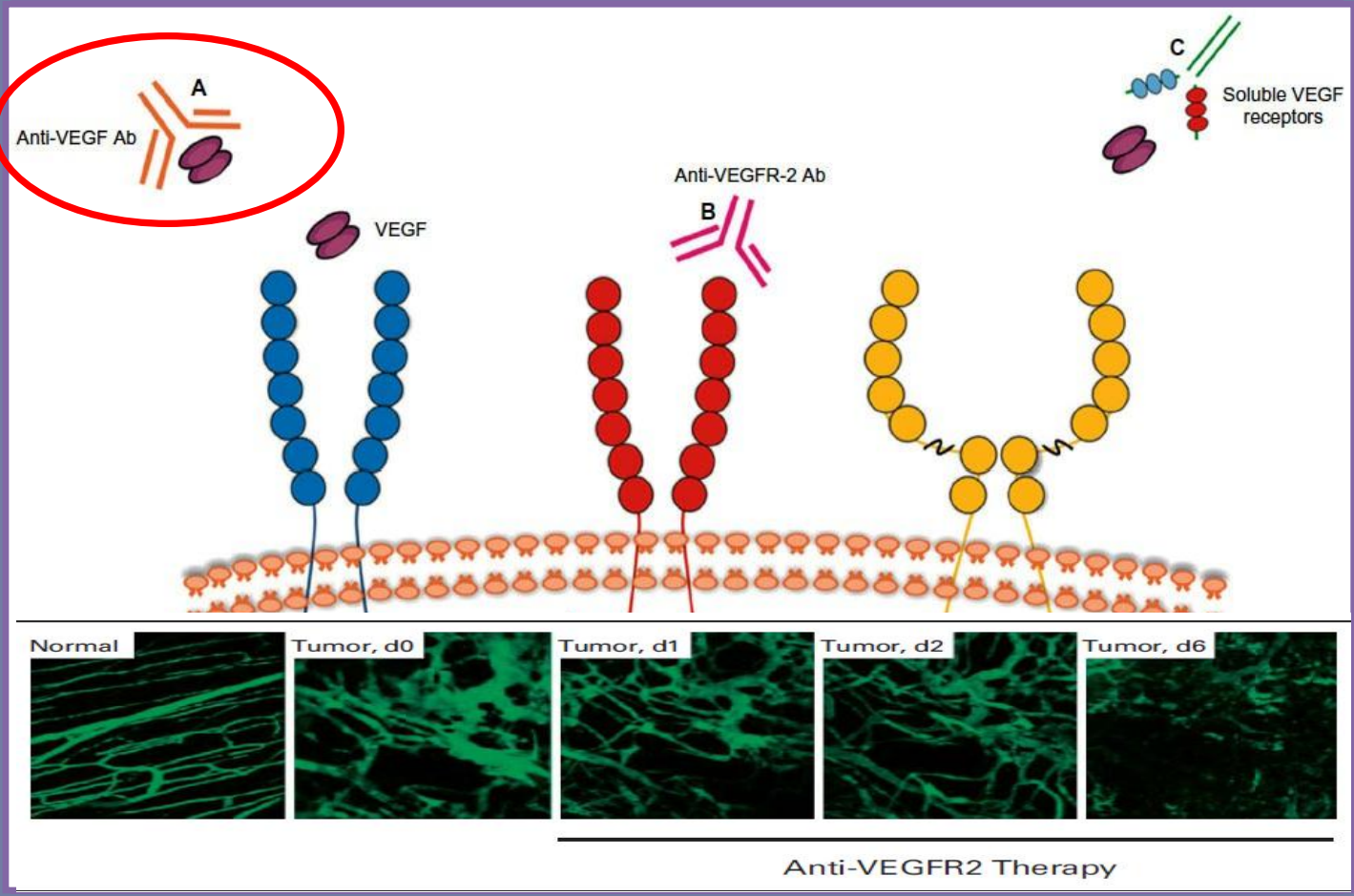

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Anti-angiogenic therapy and efficacy in mCRC

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JOURNAL OF CLINICAL ONCOLOGY

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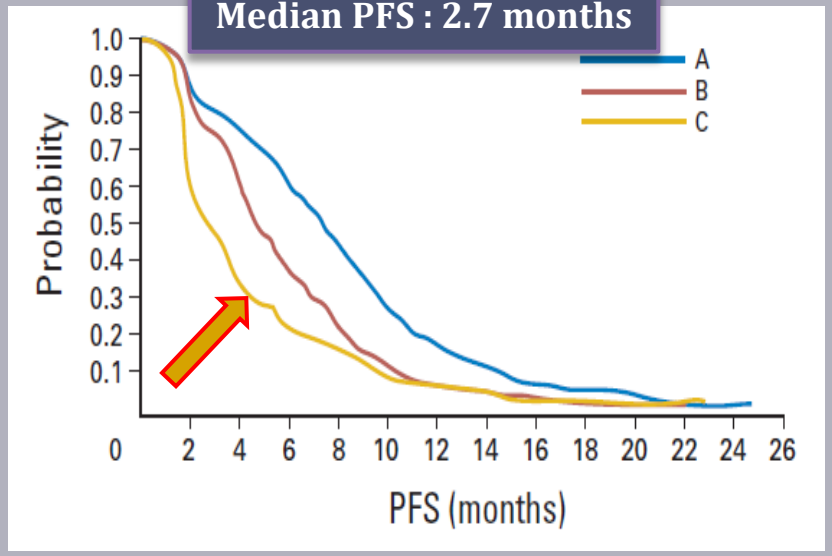
Bevacizumab in Combination With Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Results From the Eastern Cooperative Oncology Group Study E3200

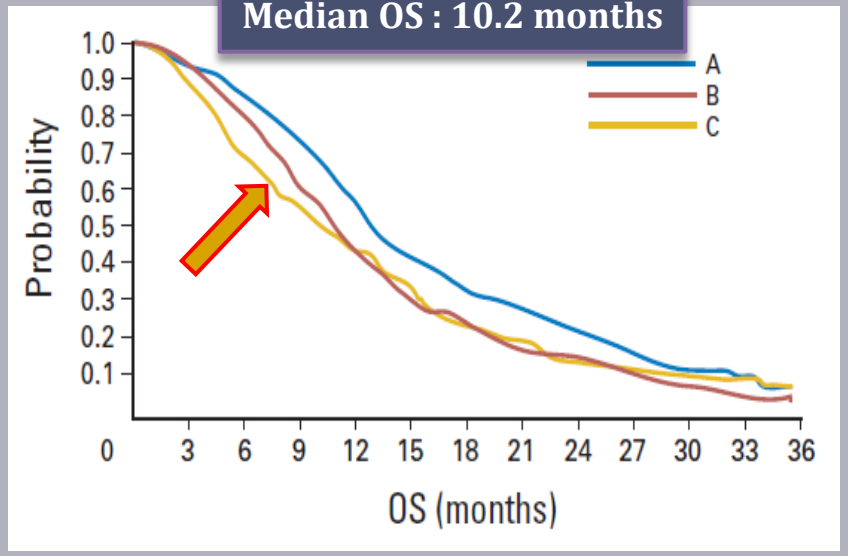
Bruce J. Giantonio, Paul J. Catalano, Neal J. Meropol, Peter J. O'Dwyer, Edith P. Mitchell, Steven R. Alberts, Michael A. Schwartz, and Al B. Benson III

n= 829 patients

Median PFS : 2.7 months



Median OS : 10.2 months



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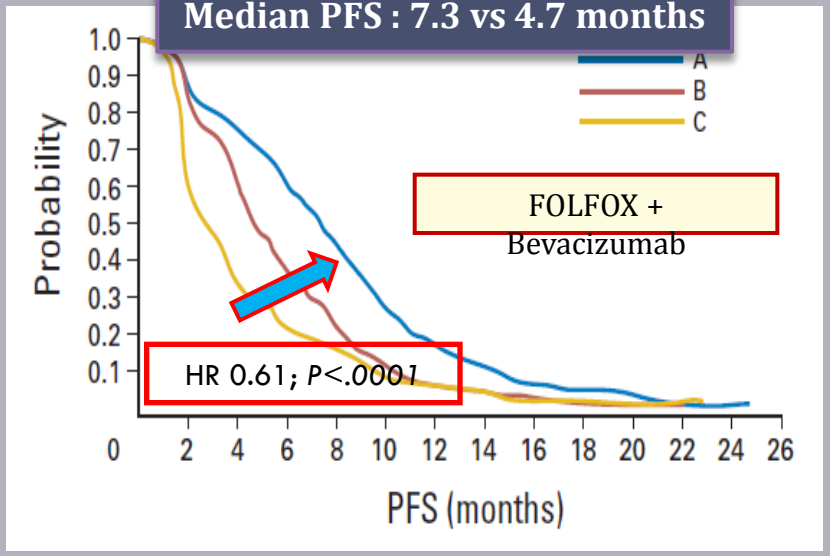
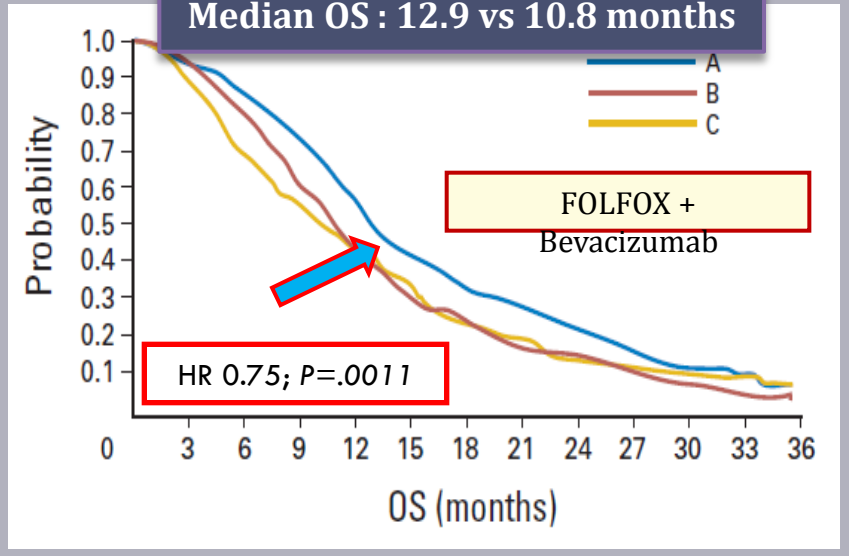
Median PFS : 7.3 vs 4.7 months



Median OS : 12.9 vs 10.8 months



FDA-approved Bevacizumab in mCRC

Drug	Class	Target	Study (year)	1st or 2nd line	Regimen	Improvement (months)
Bevacizumab	mAb	VEGF-A	(2004) Hurwitz *et al.* [2004]	1st	IFL	OS (15.6–20.3)
Bevacizumab	mAb	VEGF-A	E3200 (2006) Giantonio *et al.* [2007]	2nd (failure of irinotecan regimen)	FOLFOX	OS (10.8–12.9) PFS (4.7–7.3)
Bevacizumab	mAb	VEGF-A	ML18147 (2013) Bennouna *et al.* [2013]	2nd (progressed with bevacizumab regimen)	FOLFOX or FOLFIRI	OS (9.8–11.2) PFS (4.0–5.7)

Moriarity A, et al. Ther Adv Med Oncol. 2016;8(4):276-93.

Frequency of Grade 3/4 Bevacizumab-Associated AE

Adverse Effect*	Kabbinavar et al	Hurwitz et al AVF2107	Giantonio et al E2200	Goldberg et al AVF192
Hemorrhage	4.4%	3.1%	3.4%	5%
Hypertension	16.4%	11%	2.3%	16%
Proteinuria	0%	0.8%	<1%	1%
Thromboembolism	19.4%	19.4%	10.5%	18%
GI perforations	NA	1.5%	0%	2%
Arterial thrombosis	4.4%	3.3%	NA	10%

*Common Toxicity Criteria version 2.0; grade 3 hypertension defined as cases requiring therapy; grade 3 proteinuria defined as proteinuria > 3.5g/d.

Kabbinavar F, et al. J Clin Oncol 21:60-65, 2003.
Hurwitz H, et al. N Engl J Med 350:2335-2342, 2004.
Goldberg RM, et al. J Clin Oncol 22:23-30, 2004.

Maintenance Therapy

VOLUME 25 · NUMBER 12 · APRIL 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study

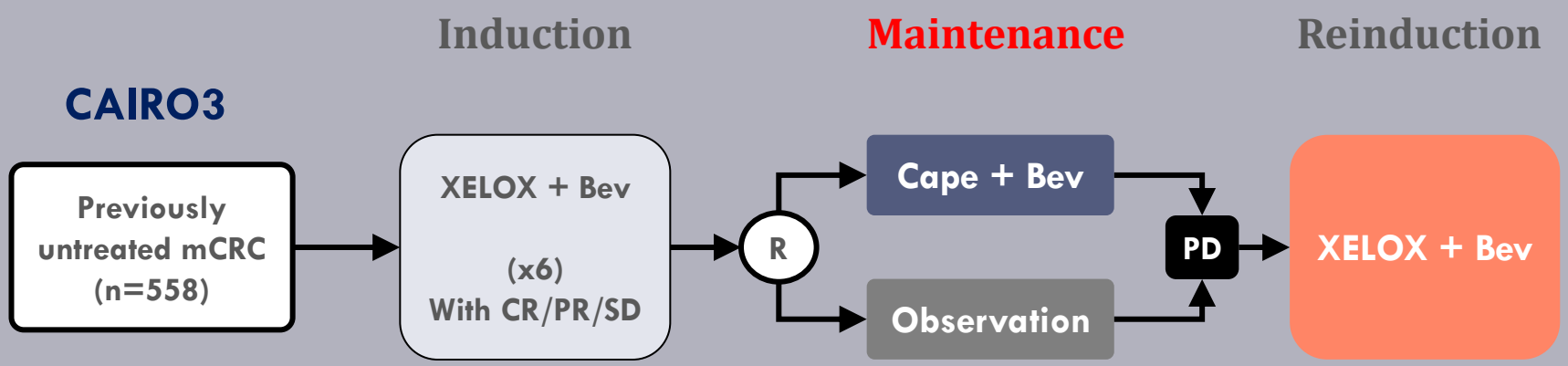
Leonard B. Saltz, Stephen Clarke, Eduardo Díaz-Rubio, Werner Scheithauer, Arie Figer, Ralph Wong, Sheryl Koski, Mikhail Lichinitser, Tsai-Shen Yang, Fernando Rivera, Felix Couture, Florin Sirzén, and Jim Cassidy

PFS

Table 2. Analysis of Efficacy (intent-to-treat population)

	Placebo + FOLFOX-4 or XELOX		Bevacizumab + FOLFOX-4 or XELOX		*P*
No. of patients	701		699		
Primary					
Median progression-free survival, months*	8.0		9.4		.0023
Hazard ratio		0.83			
97.5% CI		0.72 to 0.95			
Secondary					
Median progression-free survival, months†	7.9		10.4	**Until PD**	< .0001
Hazard ratio		0.63			
97.5% CI		0.52 to 0.75			
Median time to treatment failure, months‡	6.0		6.9		.0030
Hazard ratio		0.84			
97.5% CI		0.74 to 0.96			
Median overall survival, months§	19.9		21.3		.0769
Hazard ratio		0.89			
97.5% CI		0.76 to 1.03			
Median duration of response, months	7.4		8.45		.0307
Hazard ratio		0.82			
97.5% CI		0.66 to 1.01			

Maintenance Therapy

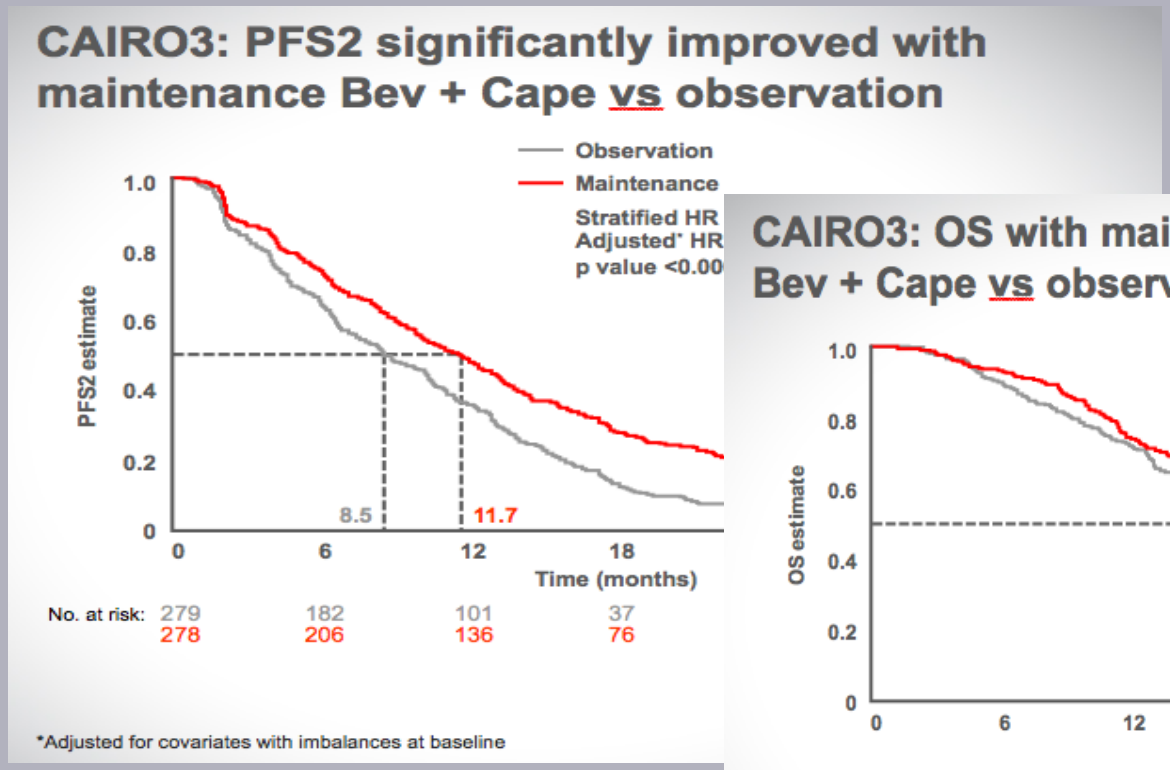


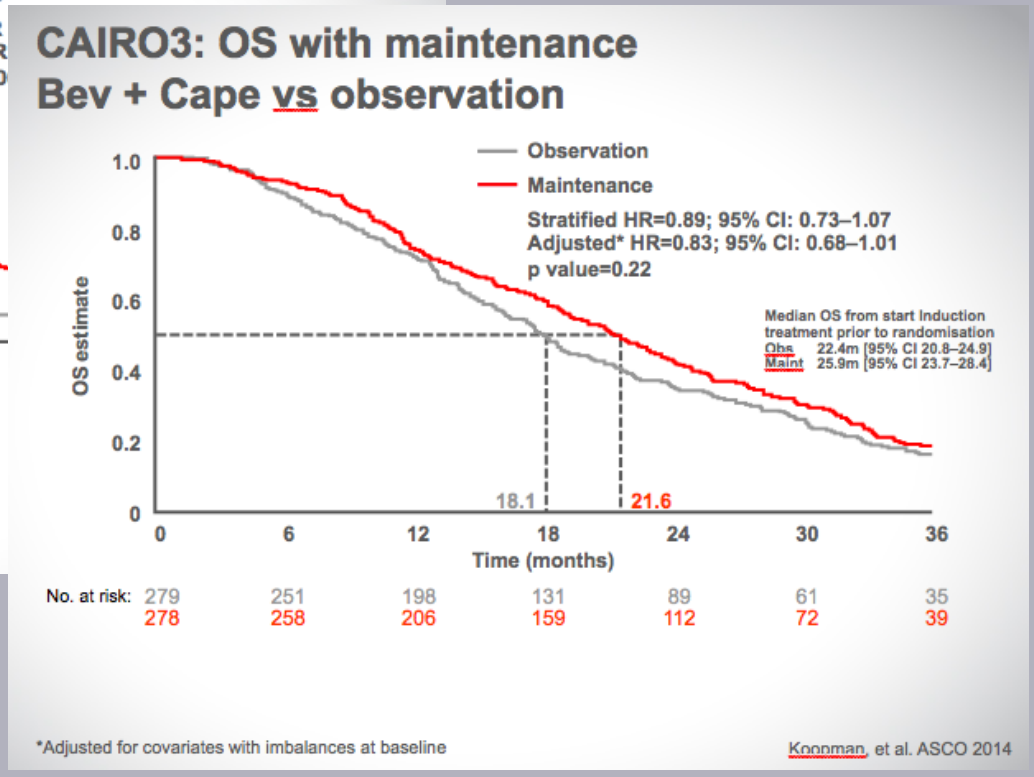
- **Primary endpoint:** PFS (maintenance and reinduction treatment)

Maintaining bevacizumab until disease progression offers improved efficacy vs no therapy

Simkens LH, et al. Lancet. 2015;385:1843–1852.

Maintenance Therapy





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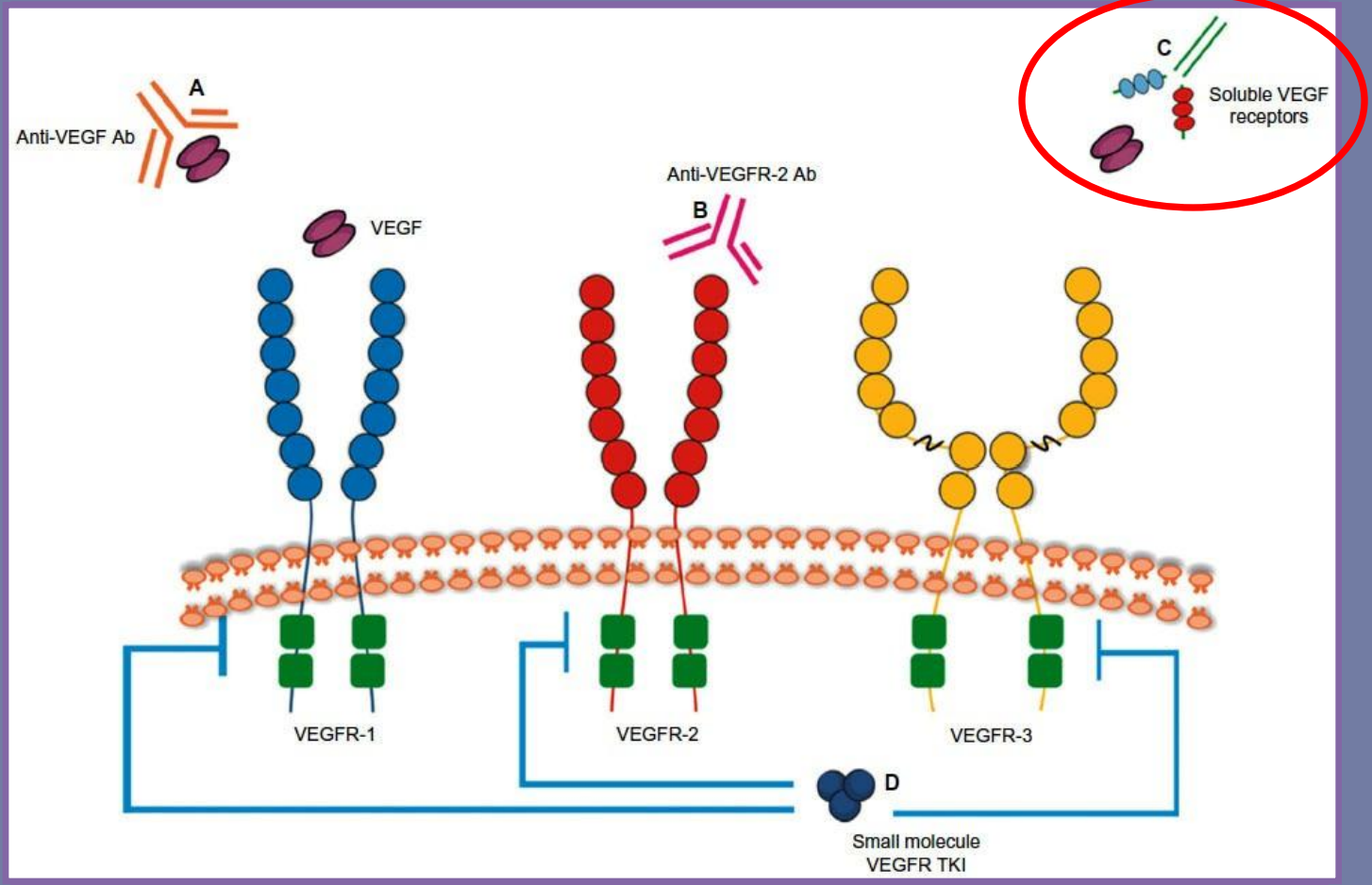
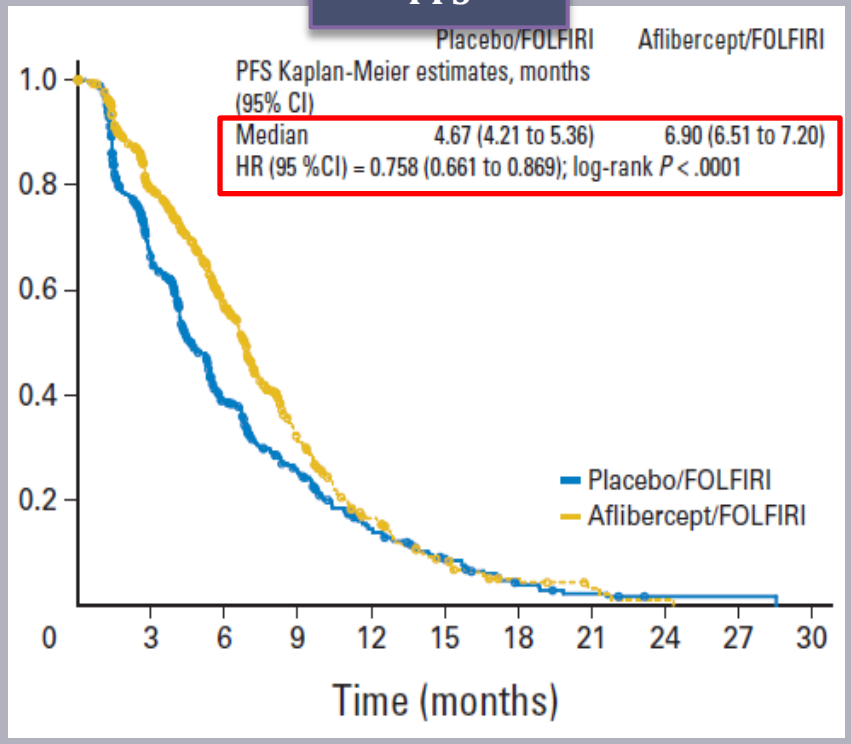


Hicklin DJ and Ellis LM. J Clin Oncol. 2005;23:1011-27.

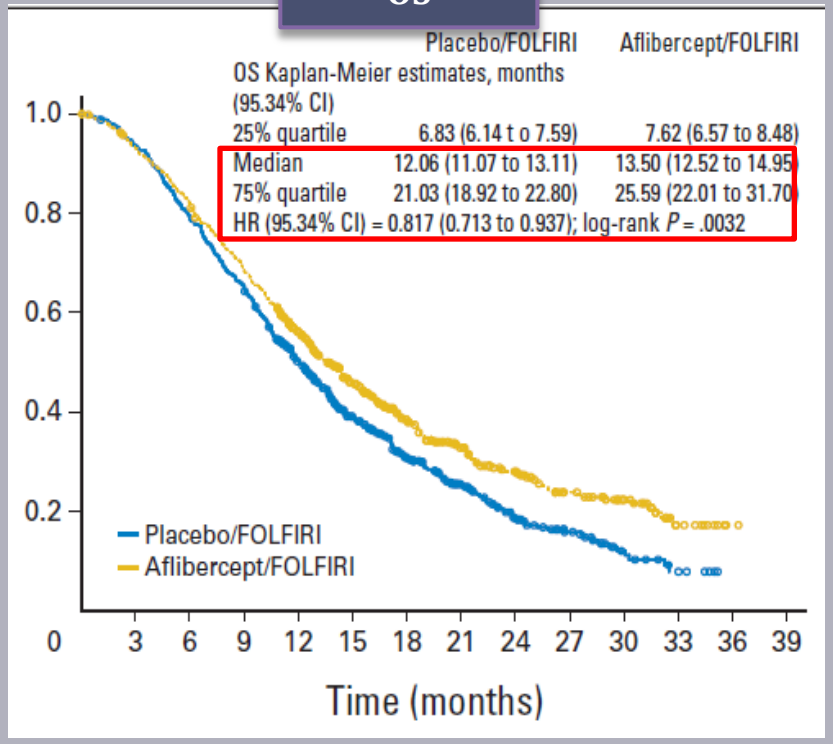
Velour Study

Overall results
Adding aflibercept to FOLFIRI in mCRC patients previously treated with an oxaliplatin-based regimen resulted in significant OS and PFS benefits

PFS

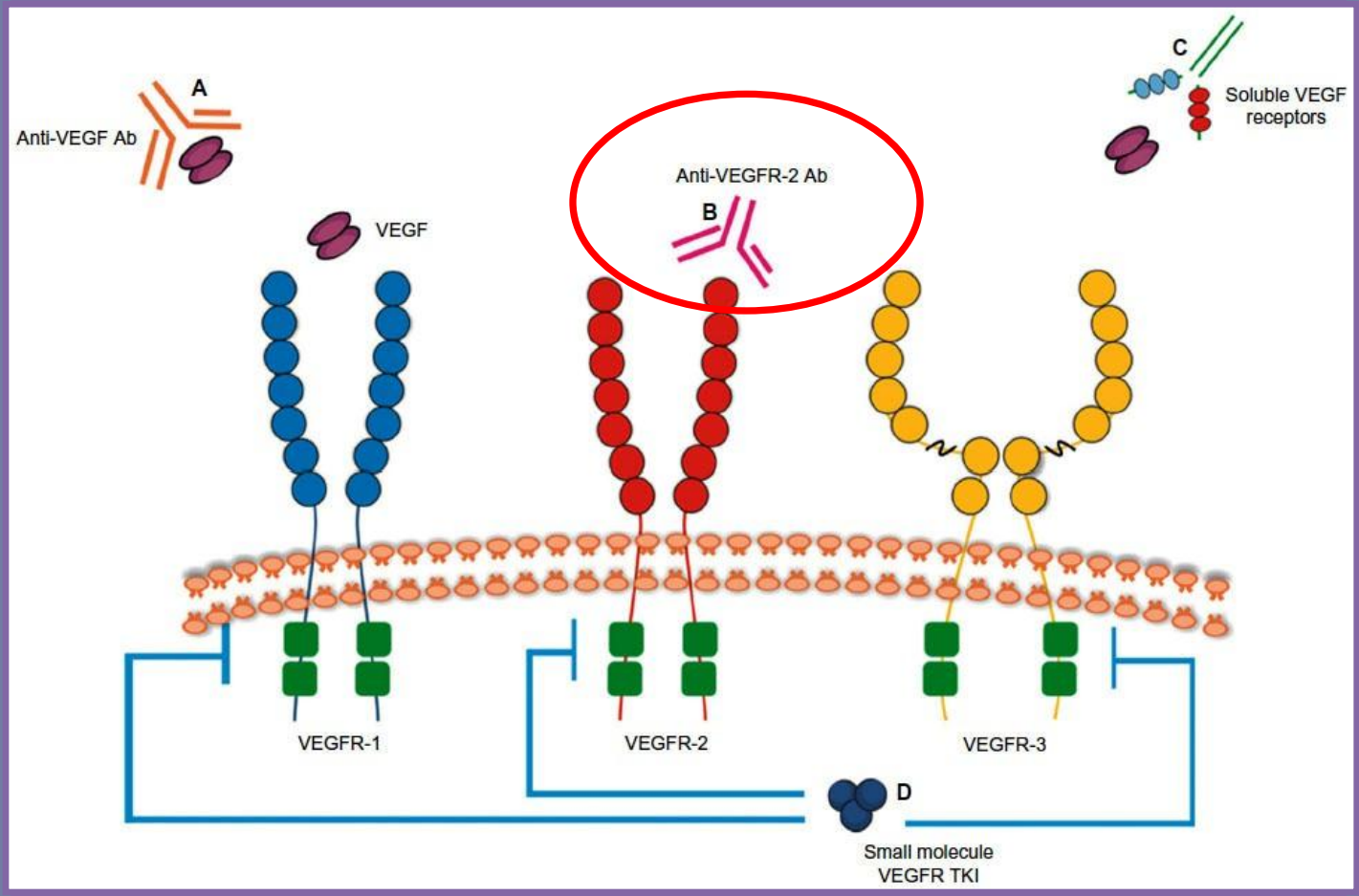


OS



Van Cutsem E, et al. J Clin Oncol. 2012;30:3499-506.

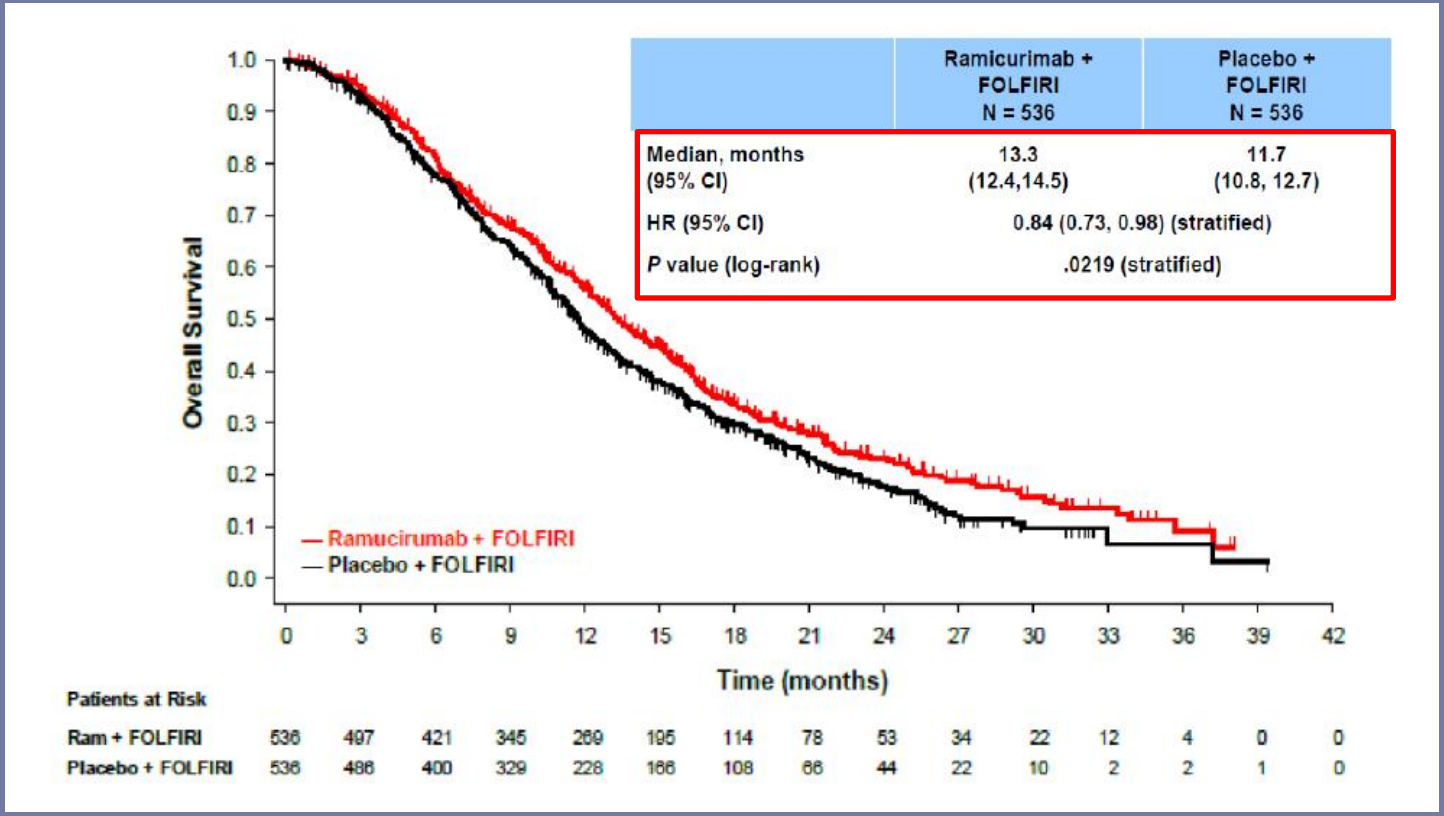
Targeting VEGFr - Mediated Angiogenesis in mCRC



Hicklin DJ and Ellis LM. J Clin Oncol. 2005;23:1011-27.

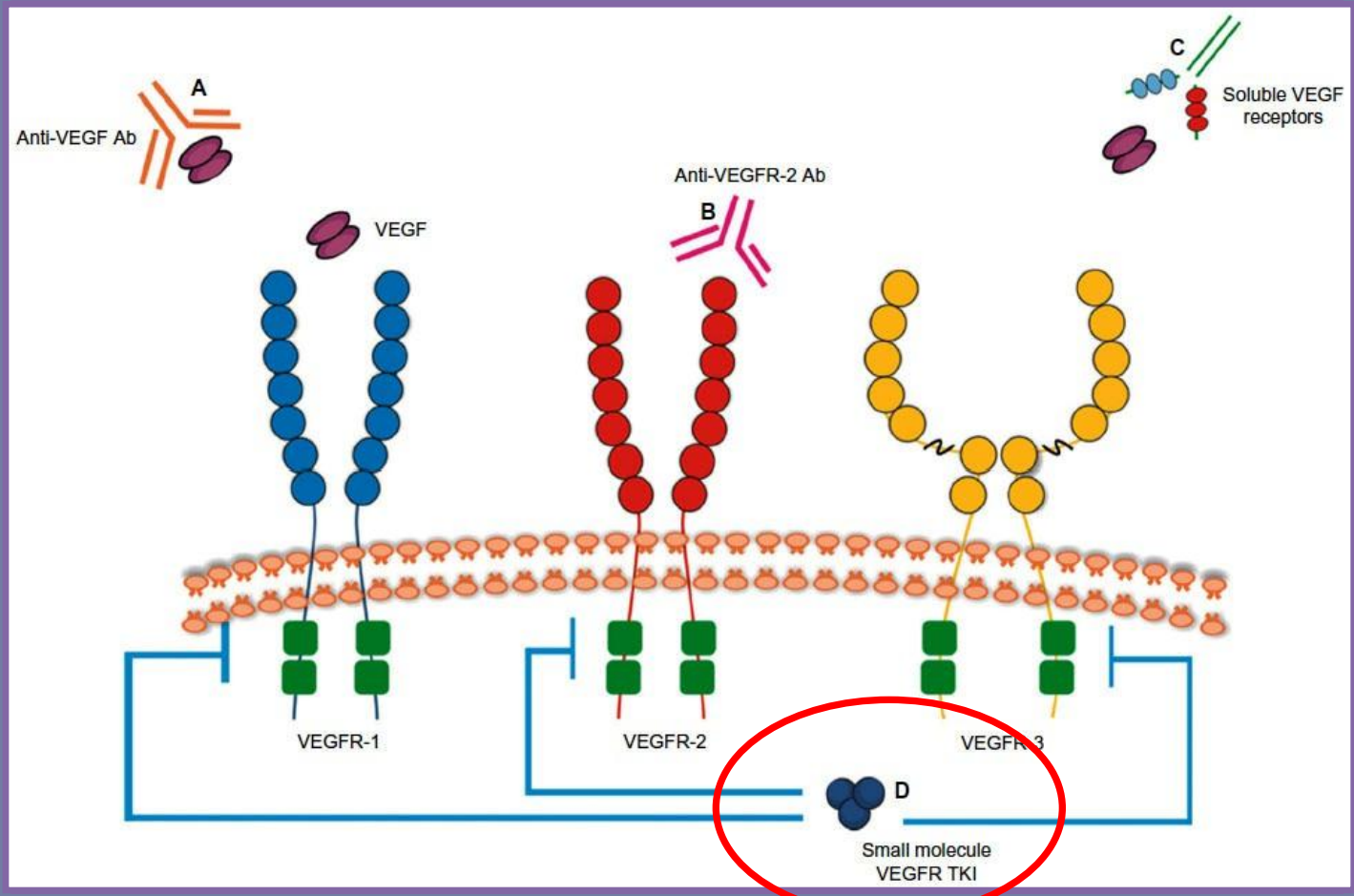
RAISE : a phase III study and OS

The addition of ramucirumab to FOLFIRI as 2nd-line therapy for patients pretreated with a fluoropyrimidine plus oxaliplatin and bevacizumab improved overall survival and PFS



Tabernero J, et al. Lancet Oncol. 2015;16:499–508.

Oral Agent in Salvage Therapy of Colorectal Cancer



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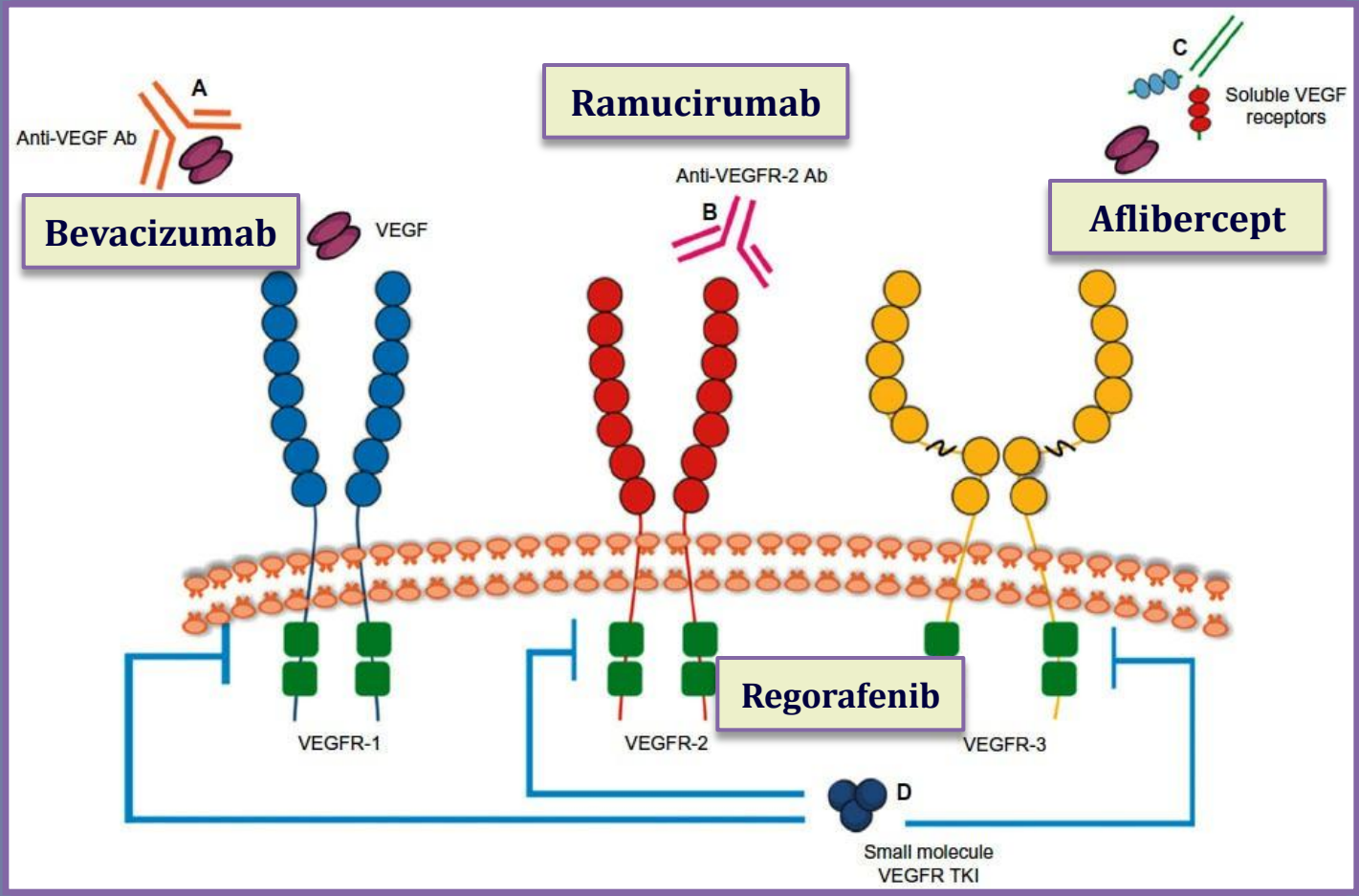
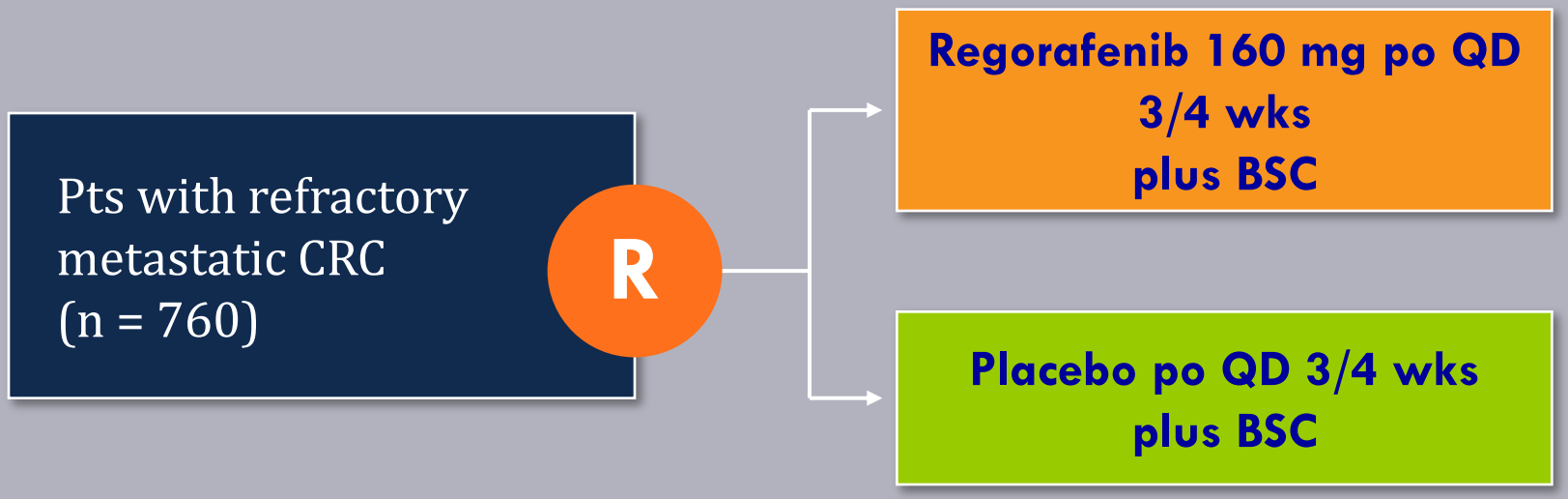


Hicklin DJ and Ellis LM. J Clin Oncol. 2005;23:1011-27.

CORRECT: Study Design and Survival Outcomes

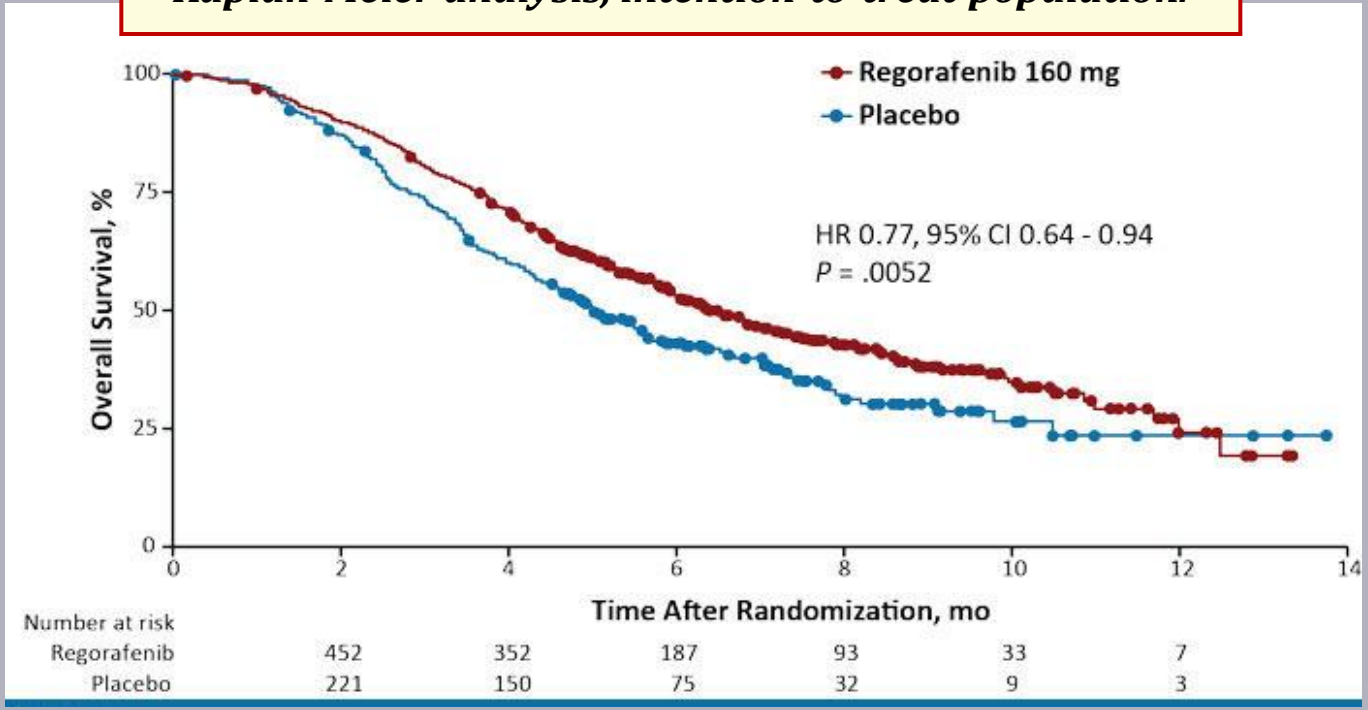


	Regorafenib	Placebo	HR	*p*-value
Median PFS	1.9 mo	1.7 mo	0.49	<0.000001
Median OS	6.4 mo	5.0 mo	0.77	0.0052

Grothey A, et al. Lancet. 2013;381:303–332.

CORRECT: Study Design and Survival Outcomes

Kaplan-Meier analysis, intention-to-treat population.



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Head-to-Head Comparison between EGFR Monoclonal Antibodies and Bevacizumab

	FIRE 3 CT + Bev vs. CT + Cetux	CALGB/SWOG 80405 CT + Bev vs. CT + Cetux
Primary endpoint	Response rate	Overall survival
CT backbone	All FOLFIRI	FOLFOX 74%/FOLFIRI 26%
ITT (KRAS WT Exon 2)	(n = 295 vs. 297)	(n = 559 vs. 578)
RR, %	58 vs. 62 (p = 0.183)	57.2 vs. 65.6 (p = 0.02)
PFS, months	10.3 vs. 10.0; HR, 1.06 (p = 0.547)	10.8 vs. 10.4; HR, 1.04 (p = 0.55)
Median OS, months	25.0 vs. 28.7 HR, 0.77 (p = 0.017)	29.0 vs. 29.9 HR, 0.92 (p = 0.34)
RAS WT	(n = 201 vs. 199)	(n = 256 vs. 270)
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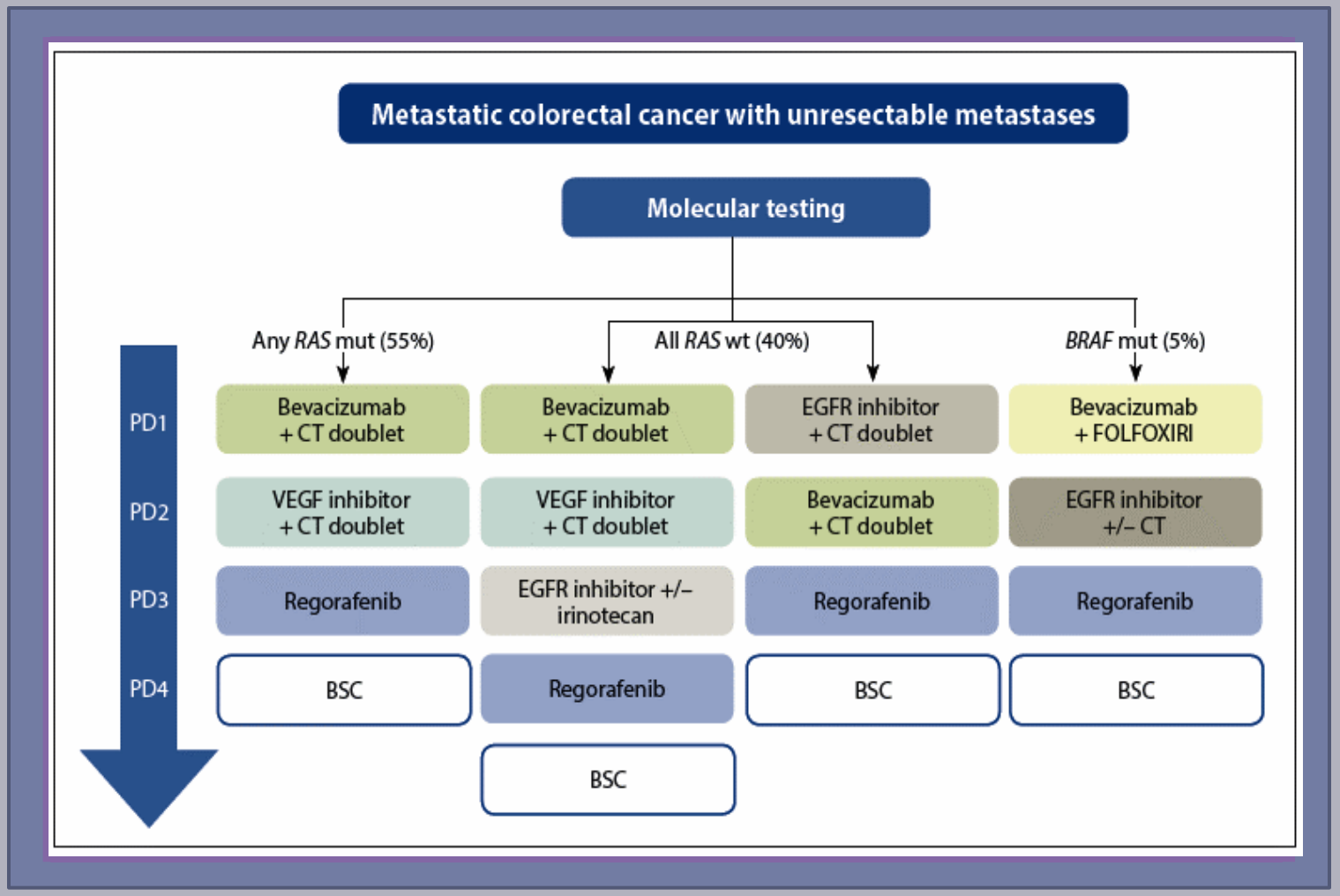
Evidence-based treatment algorithm in the palliative management of colorectal cancer



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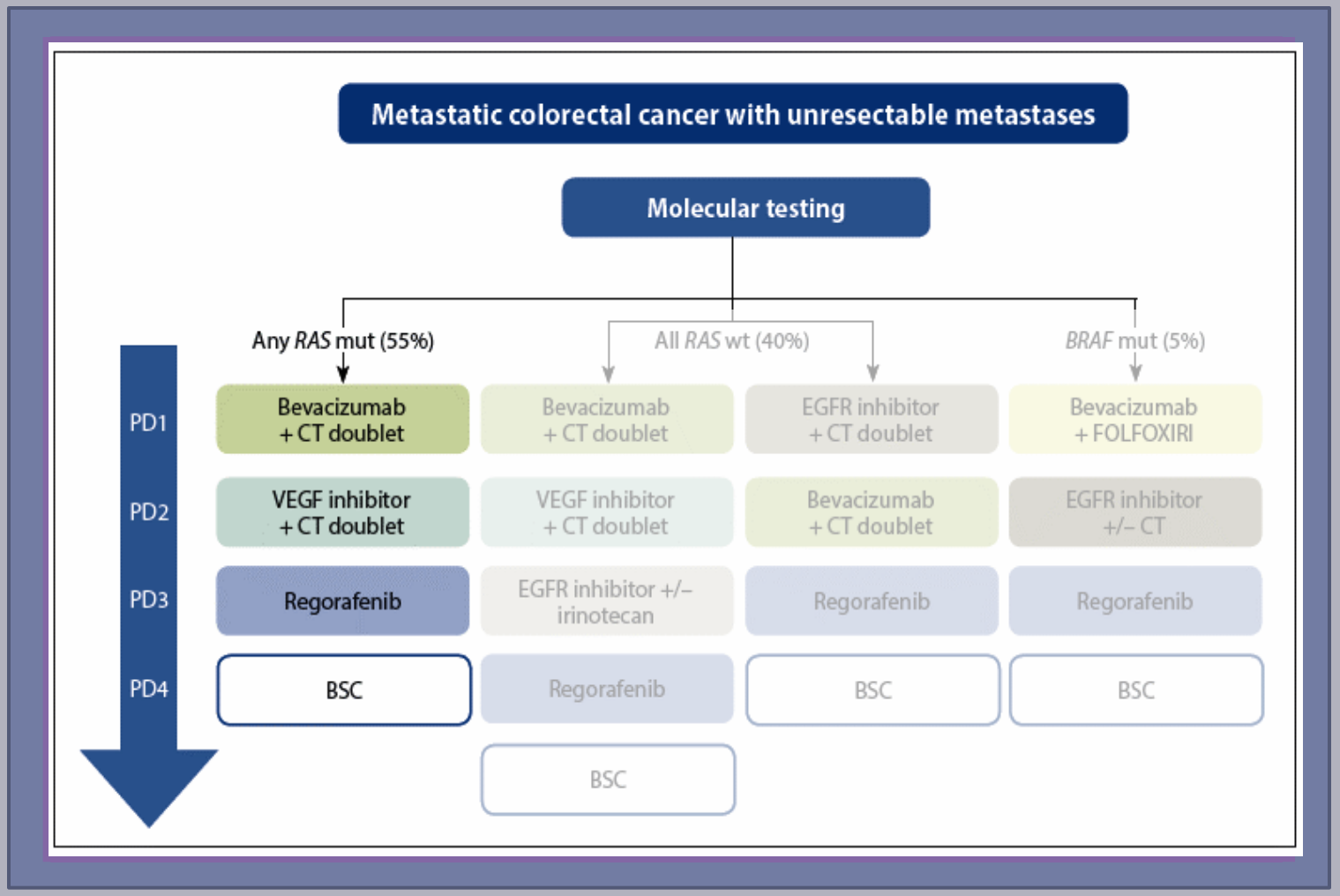

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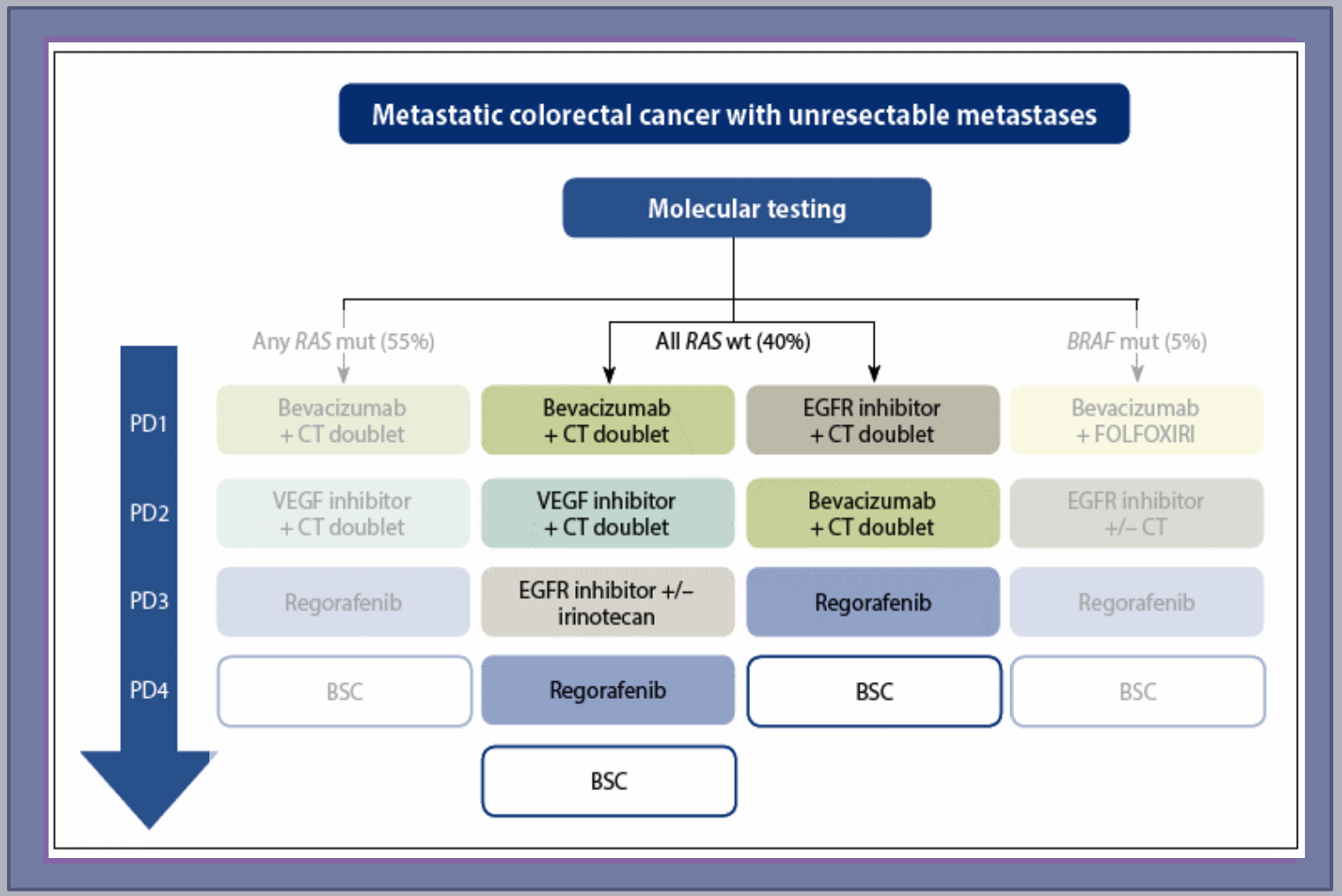

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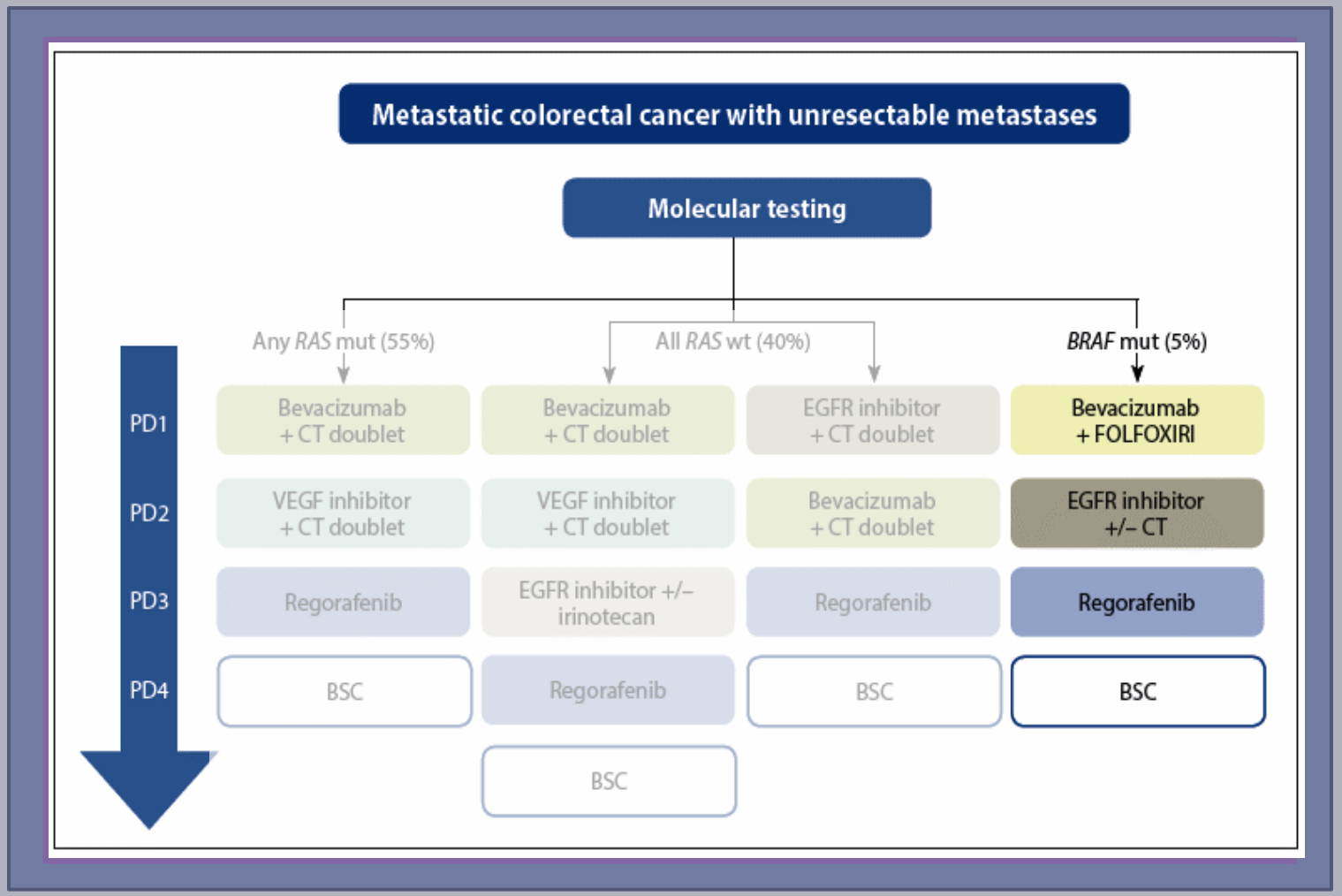

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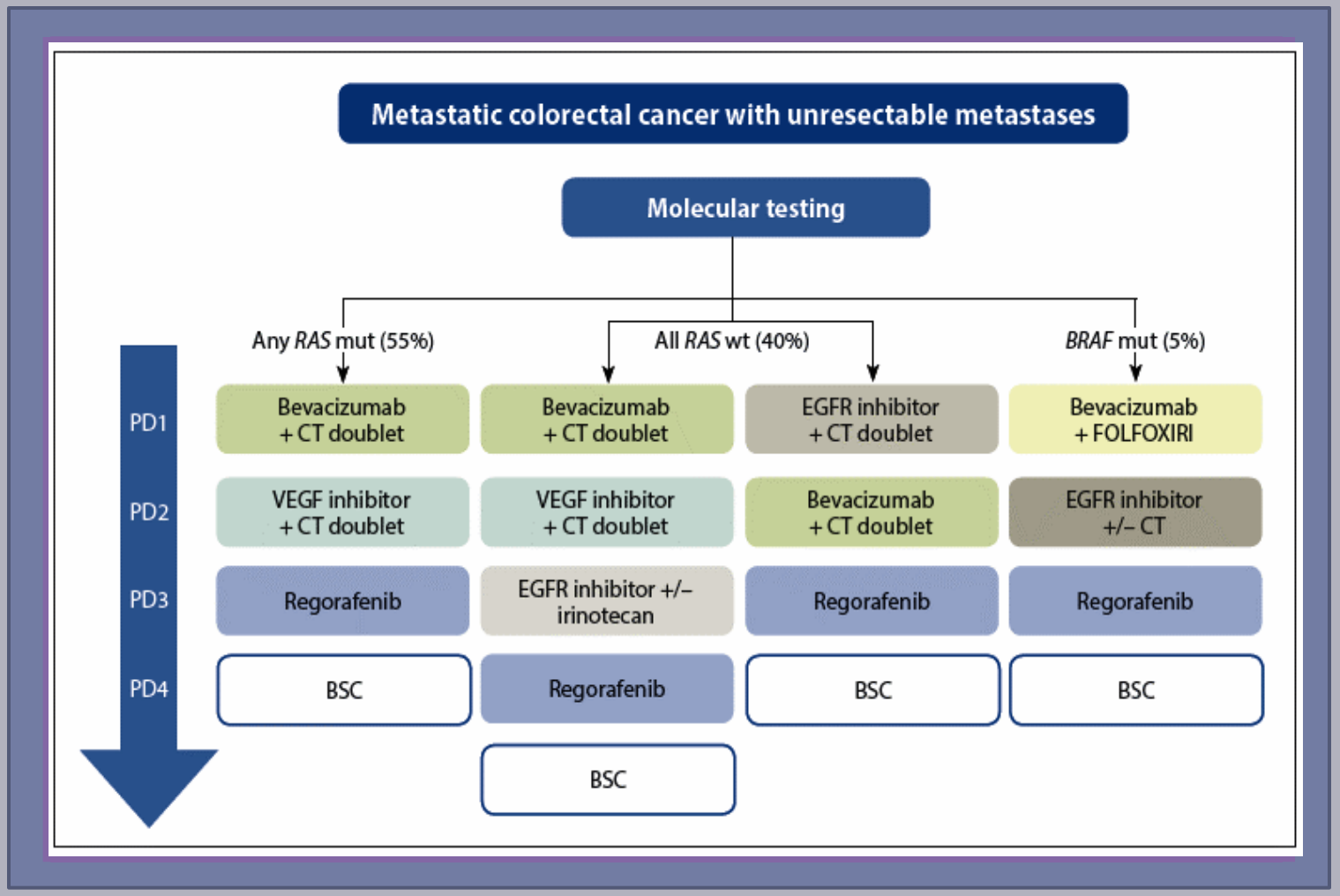

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Conclusions

- The survival of patients with metastatic colorectal cancer can be optimised via the integration of systemic therapy, surgical resection and ablative modalities, where appropriate, preferably in a MDT setting
- Insights in the biology of the disease and biomarker-driven therapeutic strategies are expected to improve survival and rationalise therapeutic approaches
- Basic and translational cancer research leading to well defined hypotheses that are going to be tested in appropriately stratified and molecularly-enriched clinical trials, is the way forward

Σας ευχαριστώ