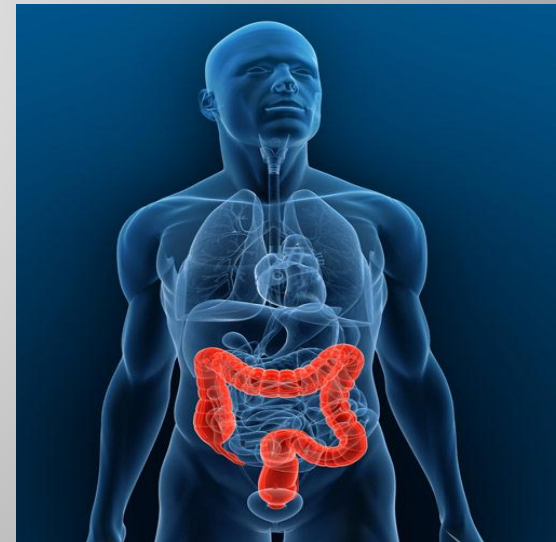


Current Treatment Strategies in Colorectal Cancer

Valeriya Semenisty, MD
Rambam Medical Center



Epidemiology

- 3-d most common cancer in men
- 3-d most common cancer in women
- Worldwide: >1 million new cases/y
- ~600,000 deaths /y
- 2/3 cases occur in economically developed countries

- Highest incidence rate: North America, Europe. New Zealand, Australia (generally in developed Western nations)



Colorectal Cancer

Some facts



- 15% to 25% have metastases at diagnosis
- Up to 50% will develop metastases
- If diagnosis is made early, CRC generally curable - 93% 5-year survival rate
- However, only 39% of CRC are diagnosed early
- For patients with widespread metastases, 5-yr survival rate is 8%
- Good news is that mortality has significantly decreased over the last 30 years due to improvements in screening and treatments

Epidemiology

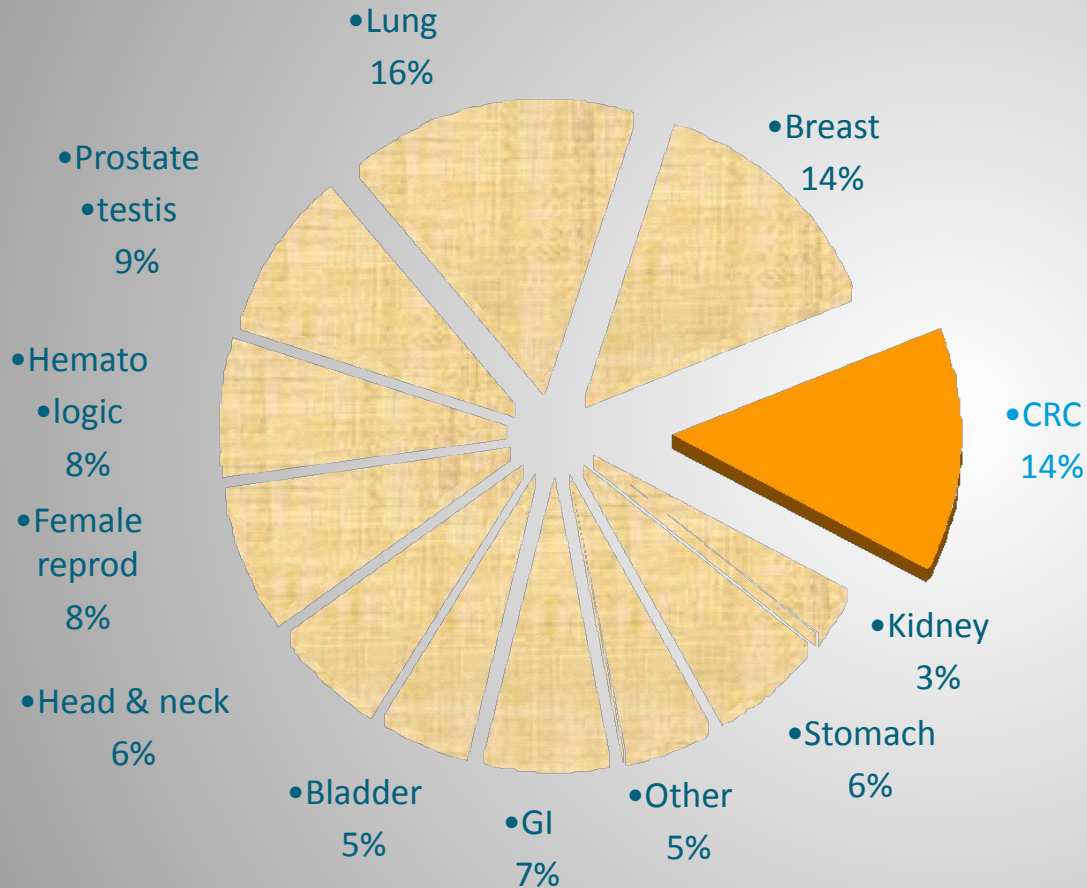
Estimated New Cases*

			Males	Females			
Prostate	238,590	28%			Breast	232,340	29%
Lung & bronchus	118,080	14%			Lung & bronchus	110,110	14%
Colorectum	73,680	9%			Colorectum	69,140	9%
Urinary bladder	54,610	6%			Uterine corpus	49,560	6%
Melanoma of the skin	45,060	5%			Thyroid	45,310	6%
Kidney & renal pelvis	40,430	5%			Non-Hodgkin lymphoma	32,140	4%
Non-Hodgkin lymphoma	37,600	4%			Melanoma of the skin	31,630	4%
Oral cavity & pharynx	29,620	3%			Kidney & renal pelvis	24,720	3%
Leukemia	27,880	3%			Pancreas	22,480	3%
Pancreas	22,740	3%			Ovary	22,240	3%
All Sites	854,790	100%	All Sites	805,500	100%		

Estimated Deaths

			Males	Females			
Lung & bronchus	87,260	28%			Lung & bronchus	72,220	26%
Prostate	29,720	10%			Breast	39,620	14%
Colorectum	26,300	9%			Colorectum	24,530	9%
Pancreas	19,480	6%			Pancreas	18,980	7%
Liver & intrahepatic bile duct	14,890	5%			Ovary	14,030	5%
Leukemia	13,660	4%			Leukemia	10,060	4%
Esophagus	12,220	4%			Non-Hodgkin lymphoma	8,430	3%
Urinary bladder	10,820	4%			Uterine corpus	8,190	3%
Non-Hodgkin lymphoma	10,590	3%			Liver & intrahepatic bile duct	6,780	2%
Kidney & renal pelvis	8,780	3%			Brain & other nervous system	6,150	2%
All Sites	306,920	100%	All Sites	273,430	100%		

Epidemiologic Data in Israel



- Every year ~3200 new cases of colon cancer patients in Israel
- 25% with metastatic disease on presentation
- 5-y survival for metastatic patients is about 5%

Prevalence estimates in unscreened population

Individuals aged 50-y or older:

- 0.5 % chance for invasive CRC
- 1 - 1.6% chance of in situ carcinoma
- 7 - 10% chance of a large (>1 cm) adenoma
- 25 - 40% chance of an adenoma of an any size

- Immigrants from low-incidence areas to high-incidence areas assume the incidence of the host country (colorectal cancer) within one generation

Risk factors for colorectal Cancer

- **Hereditary colon cancer syndromes**
- **Inflammatory bowel disease**
- **Personal history of CRC or adenomas**
- **Family history of CRC**
- **Aging**
- **Dietary patterns**

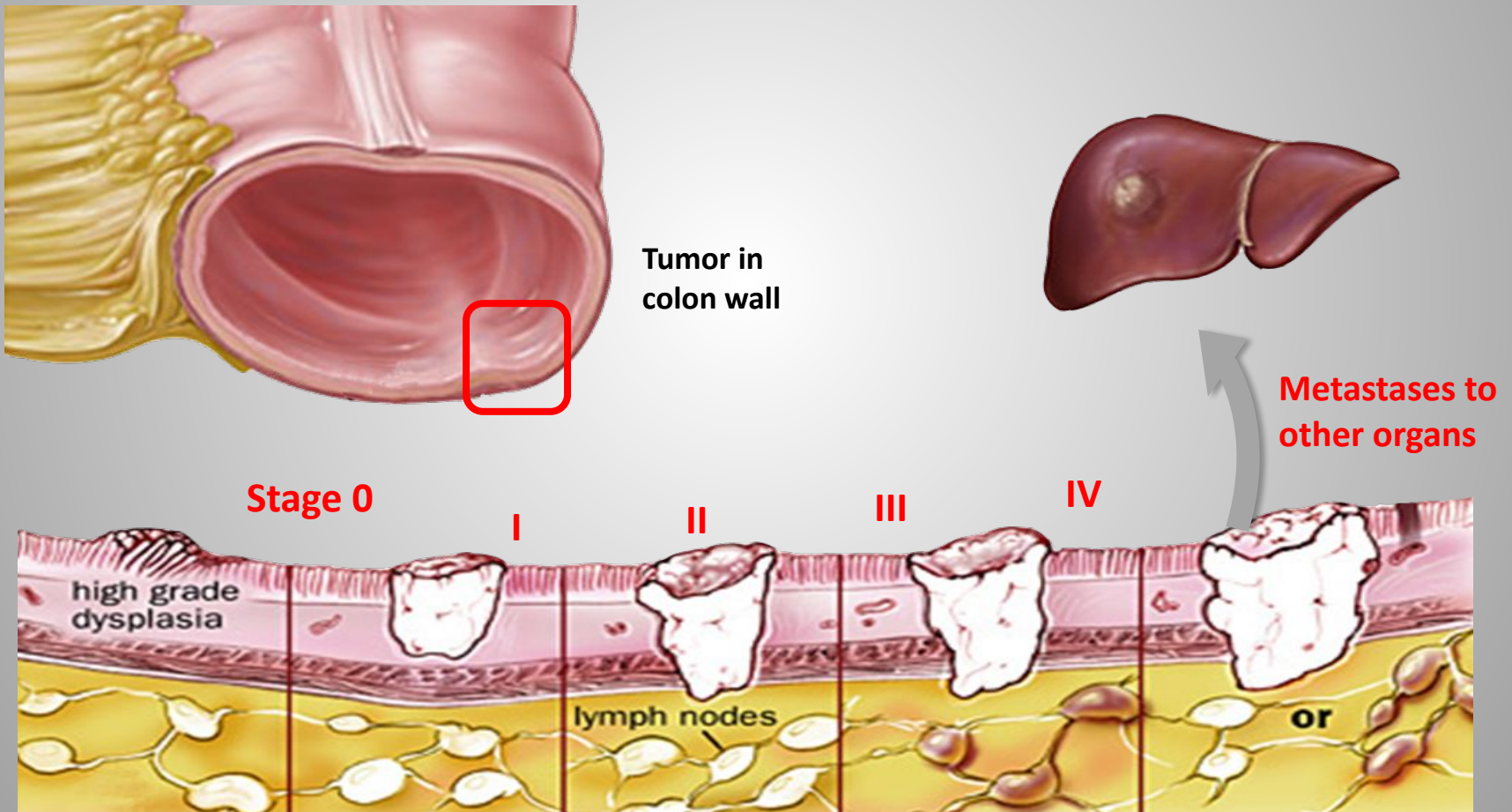
Environmental factors

- Obesity / high caloric intake
- Red meat
- Fried/ barbecued meats
- Low vegetable and fruit diet
- Lifestyle (low physical activity)
- Cigarette smoking

De Vita "Principles & practice of
Oncology" 8th edition

Staging of CRC

Staging of CRC is used to monitor the course of disease and to assess the most appropriate therapeutic intervention



TNM classification of colorectal cancer stages

Treatment options for CRC

- Surgery

- Medical
 - Chemotherapy
 - Targeted therapies

- Radiotherapy

Surgery



- For invasive Carcinoma of the colon stage I,II,III, surgery is the only curative treatment
- Surgical approach is dedicated by the lesions' size and location in the colon

For stage II and III, there is a risk of residual
micro-metastatic disease

Adjuvant therapy role:
to eradicate the microscopic metastatic disease

STAGE III colon carcinoma (T1-4 N1-2)

5-y Overall Survival benefit ~ 10%
(oxaliplatin+5FU/Capecitabine)

STAGE II colon carcinoma (T3-4 No)

5-y Overall Survival benefit \leq 5%
(5FU/Capecitabine)

STAGE I colon carcinoma (T1-2 No)

No benefit for 5-y Overall Survival



Oncotype DX[®] Colon Cancer Assay

The Challenge with the Stage II Colon Cancer Patient

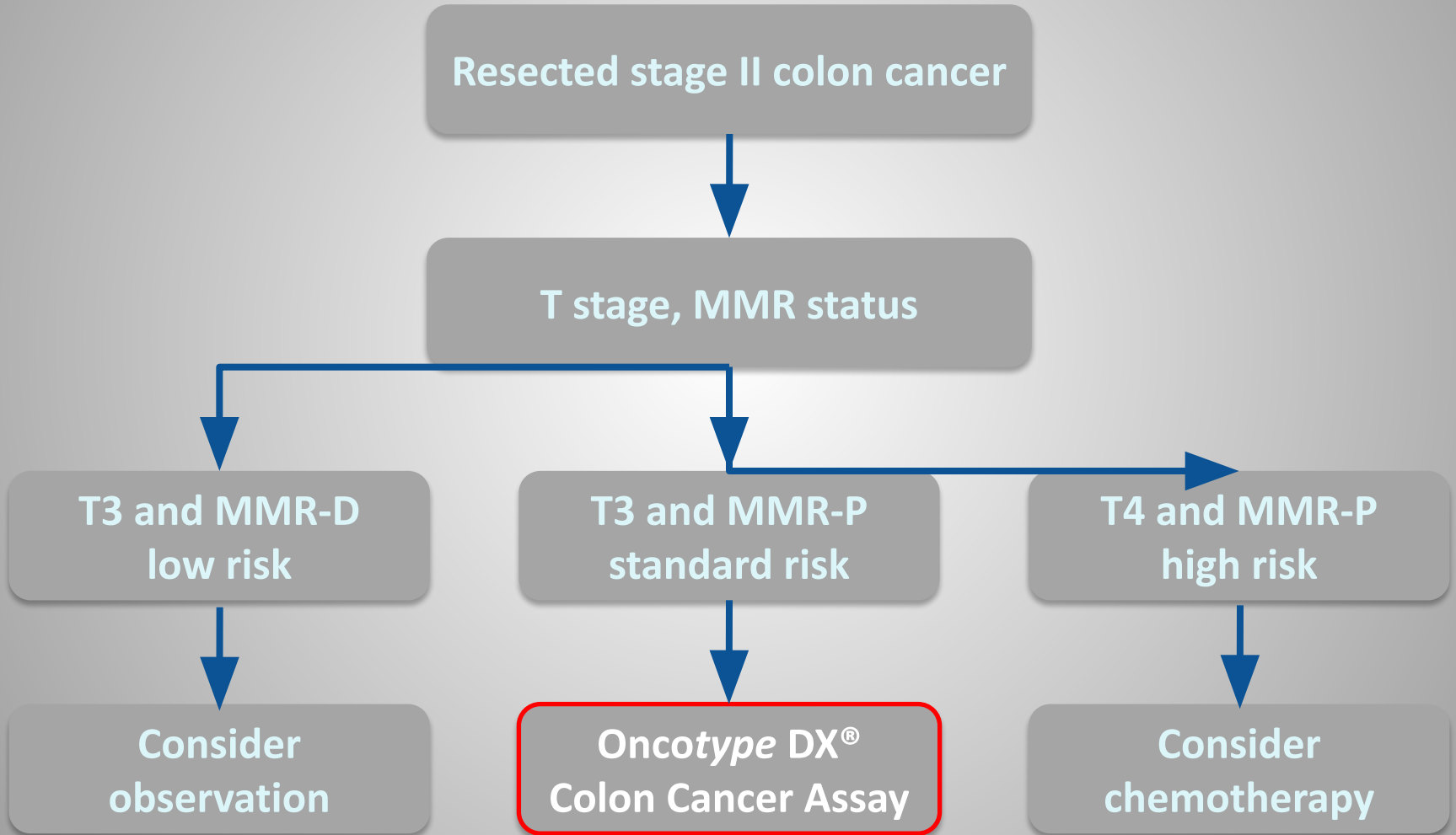
**Implications for Clinical Practice in
Stage II Colon Cancer**



The challenge: Which stage II colon cancer patients should receive adjuvant chemotherapy?

- It is unclear which 75-80% of patients are cured with surgery alone
- Absolute chemotherapy benefit is small
- Chemo has significant toxicity and impacts quality of life
- Selection of patients for chemotherapy is subjectively based on:
 - Risk assessment with a limited set of clinical/pathologic markers
 - Patient age, comorbidities, patient preference

Integrating the Quantitative Recurrence Score[®] into Recurrence Risk Assessment and Treatment Planning for Stage II Colon Cancer





Recurrence Score[®] Result

24

Oncotype DX[®] Colon Cancer Assay uses RT-PCR to determine the expression of a panel of 12 genes in tumor tissue. The Recurrence Score[®] result is calculated from the gene expression results, and ranges from 0-100.

These findings are applicable to stage II patients with adenocarcinoma or mucinous carcinoma limited to the colon. It is unknown whether the findings apply to other patients outside these criteria.

Clinical Experience is based on a prospectively-designed validation study with a pre-specified analysis of the Recurrence Score result, in the context of T-Stage and MMR status (MMR proficient (MMR-P) or MMR deficient (MMR-D)), using patients from the surgery-alone arm of the QUASAR study (N=711).¹

Note: Determination of MMR status is important for treatment decision-making in stage II colon cancer. In this validation study, stage IIA MMR-D patients had a 3-year recurrence risk ranging from 3% to 7% across Recurrence Score results and are expected to have little if any clinical benefit from 5FU/LV adjuvant therapy. Use of this assay is generally not recommended for stage II MMR-D patients.

Relevance for Chemotherapy Benefit: Based on the results in QUASAR (N=1, 436) that randomized patients to surgery or surgery+5FU/LV, the proportional reductions in recurrence risk with 5FU/LV were similar across the range of Recurrence Score results, with larger absolute benefit at higher Recurrence Score results. In the parent QUASAR trial, 5FU/LV treatment resulted in ~20% relative risk reduction of cancer recurrence.

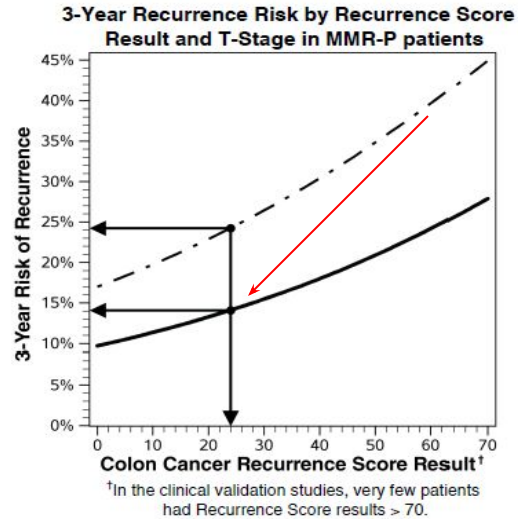
Stage II Recurrence Risk Following Surgery Alone

24% — · — · — T4, MMR-P
(95% CI: 17%-34%)

→ 14% ————— T3, MMR-P*
(95% CI: 11%-18%)

* 2% of all patients with T4, MMR-D tumors had estimated recurrence risks that approximated (with large confidence intervals) those for patients with T3 stage, MMR-P tumors and were not included in this figure.

Impact of Nodes Assessed: For patients with T3 MMR-P patients the reduction in risk ranged from 4% to 10%, respectively.



Sex: Male
Date of Birth: 01-Apr-1955
Medical Record/Patient #: 013464854
Date of Surgery: 14-Mar-2014
Specimen Type/ID: Colon/11581/6/14

Specimen Received: 24-Apr-2014
Date Reported: 02-May-2014
Ordering Physician: Dr. Valeria Semenisty
Submitting Pathologist: Dr. Lior Soussan-Gutman

Mismatch Repair (MMR) Assay Results

Mismatch Repair Status = **MMR Proficient (MMR-P)**

Antibody	Clone	Result
MLH1	ES05	Expressed
MSH2	G219-1129	Expressed

MMR Status Determination for Recurrence Risk:

- MMR-Proficient (MMR-P) if both MLH1 and MSH2 are expressed
- MMR-Deficient (MMR-D) if one or both of MLH1 and MSH2 are not expressed

Metastatic disease

Liver metastases
Abdominal cavity metastases
Abdominal lymph nodes metastases

Pulmonary metastases
Bone metastases
Brain metastases



Metastatic disease:

Chemotherapy

Active chemotherapy drugs

- 5- Fluorouracil/LCV
- Oxaliplatin
- Irinotecan (CPT-11)

Combination chemotherapy:

5FU/LCV + OXALIPLATIN
“**folfox**”

5FU/LCV + IRINOTECAN
“**folfiri**”

5FU Oxaliplatin + Irinotecan
“**folfoxiri**”

Irinotecan (CPT-11, Campto)



- Camptotheca Acuminata
- Topoisomerase 1 inhibitor

DNA Repair Interference

**Topoisomerase-1
inhibition**



Irinotecan Major Adverse Effect: Diarrhea

Early onset

- Caused by cholinergic effect of Irinotecan
- During or immediately after Irinotecan infusion
- Accompanied by flushing and abdominal cramping
- Treatment: sc Atropin

• Delayed

- Cholera-like syndrome

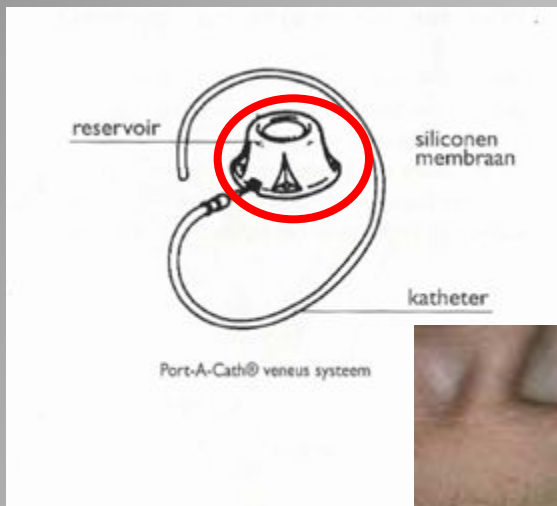


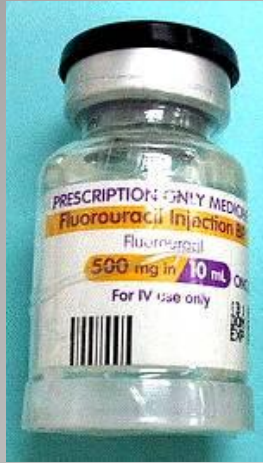
Oxaliplatin

is classified as an "alkylating agent."

-
- Peripheral neuropathy
- Nausea and vomiting
- Diarrhea
- Mouth sores
- Low blood counts.
- Fatigue
- Loss of appetite







- Overall survival:

5-FLUOROURACIL = XELODA

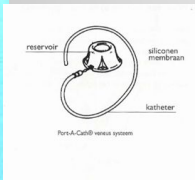
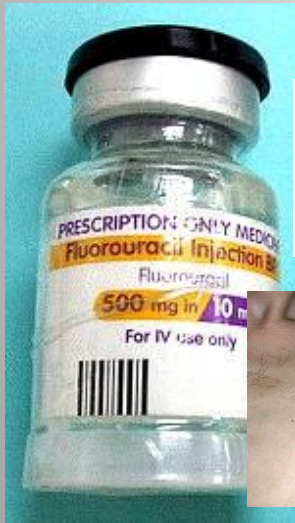
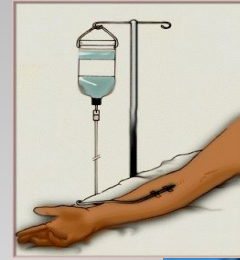
- Toxicity profile:

XELODA better than 5-FLUOROURACIL

Xeloda (capecitabine) - side effects

- Abdominal or stomach pain
- diarrhea
- nausea
- numbness, pain, tingling, or other unusual sensations in the palms of the hands or bottoms of the feet
- pain, blistering, peeling, redness, or swelling of the palms of the hands or bottoms of the feet
- pain, redness, swelling, sores, or ulcers in mouth or on lips
- unusual tiredness or weakness
- vomiting





Cont 5-FU 44h+LCV = De Gramont

- De Gramont/ Irinotecan(cpt-11) = FOLFIRI
- De Gramont / Oxaliplatin = FOLFOX
- Xeloda / Oxaliplatin = XELOX

The Angiogenic Switch Is Necessary for Tumor Growth and Metastasis

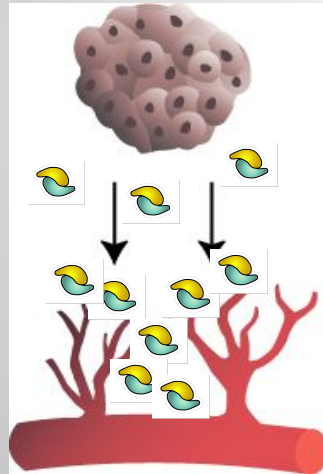
Tumor is dormant

Angiogenic switch

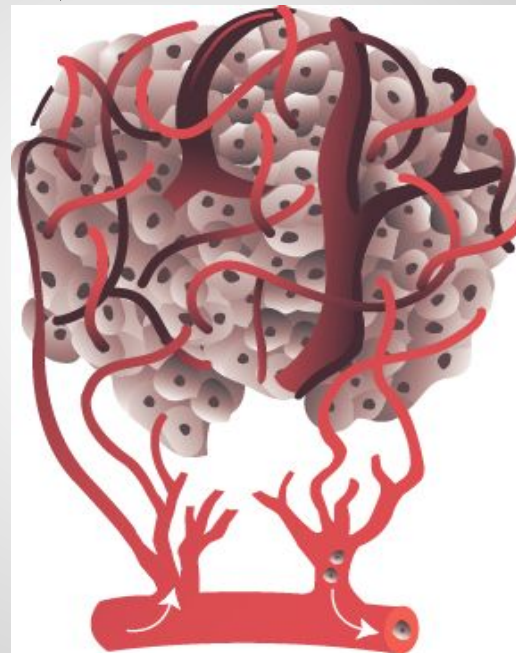


Somatic mutation

Small avascular tumor



Tumor secretion of angiogenic factors stimulates angiogenesis



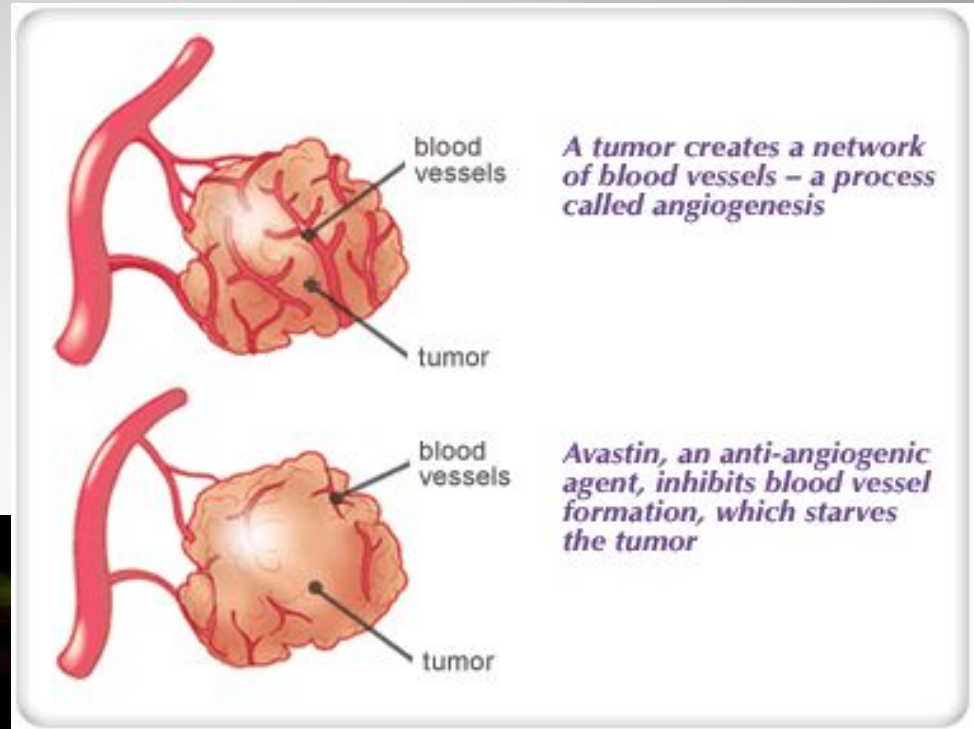
Rapid tumor growth and metastasis

Neovascularization

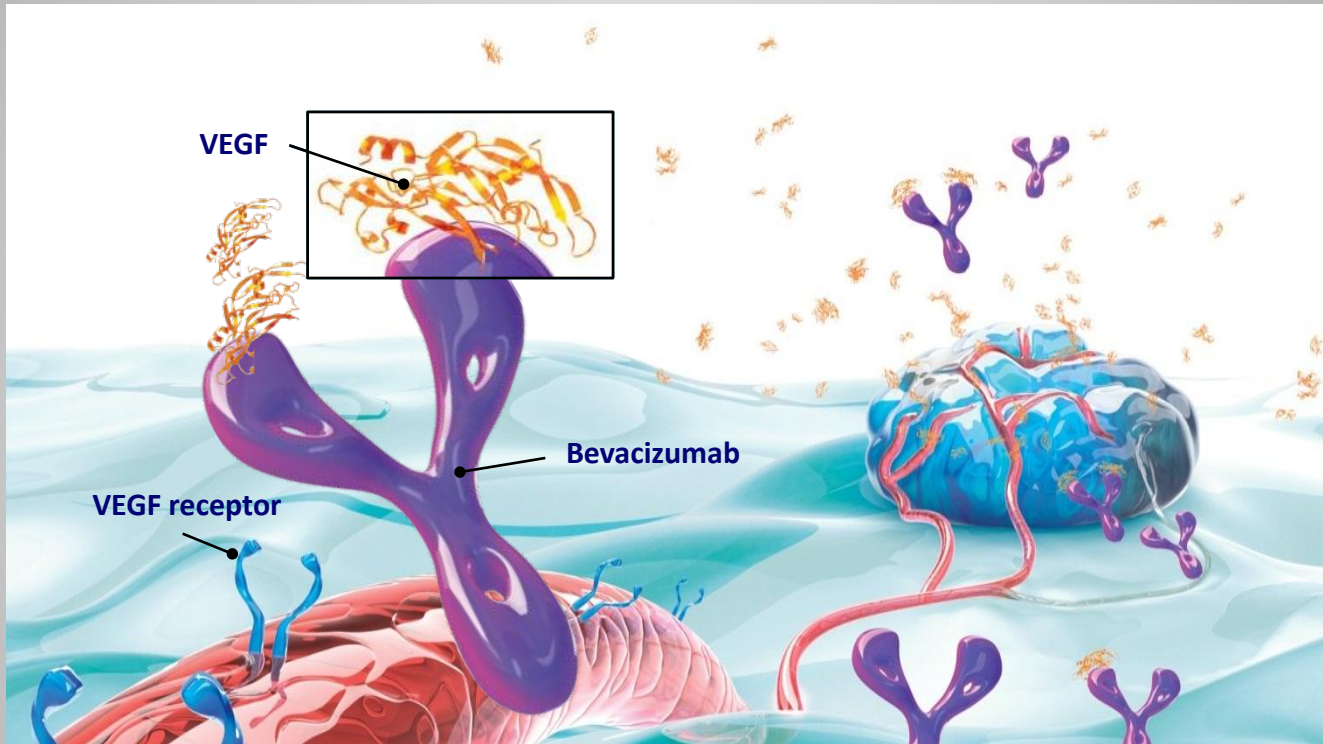
- **Allows rapid tumor growth by providing oxygen, nutrients, and waste removal**
- **Facilitates metastasis**

Avastin(Bevacizumab) inhibits vascularization

—Avastin is an antibody that binds to VEGF and blocks its stimulation of the VEGF-receptor on endothelial (blood vessel) cells

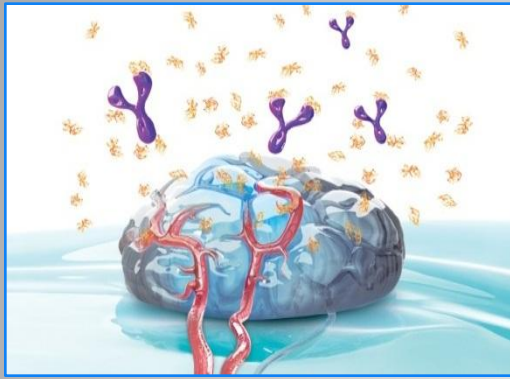


Bevacizumab precisely targets VEGF to inhibit angiogenesis^{1,2}

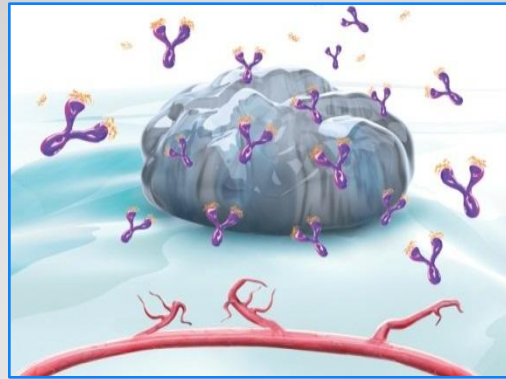


- Bevacizumab prevents binding of VEGF to receptors^{1,2}
- Bevacizumab has a long elimination half life (~20 days), which may contribute to continuous tumour control³

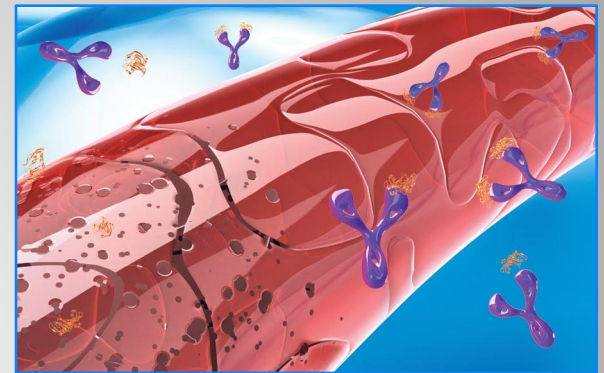
Bevacizumab: one target, multiple effects¹⁻²⁰



Regression
of existing tumour vasculature¹⁻³



Inhibition
of new vessel growth^{1-3,8}



Anti-permeability
of surviving vasculature¹¹⁻¹³



Consistently increased response rates⁴⁻⁷
Continuous control of tumour growth⁸⁻¹⁰
Reduction of ascites and effusions^{2,3,11,14-20}

1. Baluk, et al. *Curr Opin Genet Dev* 2005; 2. Willett, et al. *Nat Med* 2004; 3. O'Connor, et al. *Clin Cancer Res* 2009; 4. Hurwitz, et al. *NEJM* 2004
5. Sandler, et al. *NEJM* 2006; 6. Escudier, et al. *Lancet* 2007; 7. Miller, et al. *NEJM* 2007; 8. Mabuchi, et al. *Clin Cancer Res* 2008
9. Wild, et al. *Int J Cancer* 2004; 10. Gerber, Ferrara. *Cancer Res* 2005; 11. Prager, et al. *Mol Oncol* 2010; 12. Yanagisawa, et al. *Anti-Cancer Drugs* 2010
13. Dickson, et al. *Clin Cancer Res* 2007; 14. Hu, et al. *Am J Pathol* 2002; 15. Ribeiro, et al. *Respirology* 2009; 16. Watanabe, et al. *Hum Gene Ther* 2009
17. Mesiano, et al. *Am J Pathol* 1998; 18. Bellati, et al. *Invest New Drugs* 2010; 19. Huynh, et al. *J Hepatol* 2008; 20. Ninomiya, et al. *J Surg Res* 2009

June 2004: First Bevacizumab data
from Phase III trial published in NEJM

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

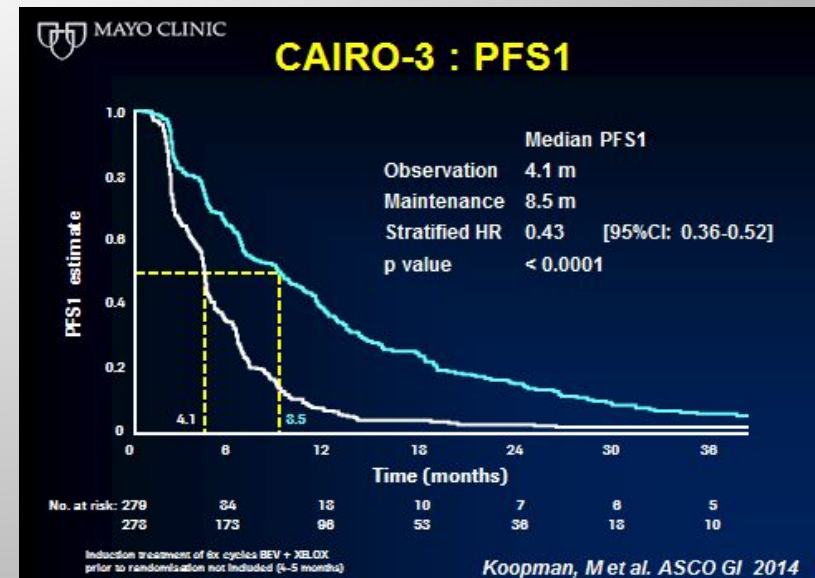
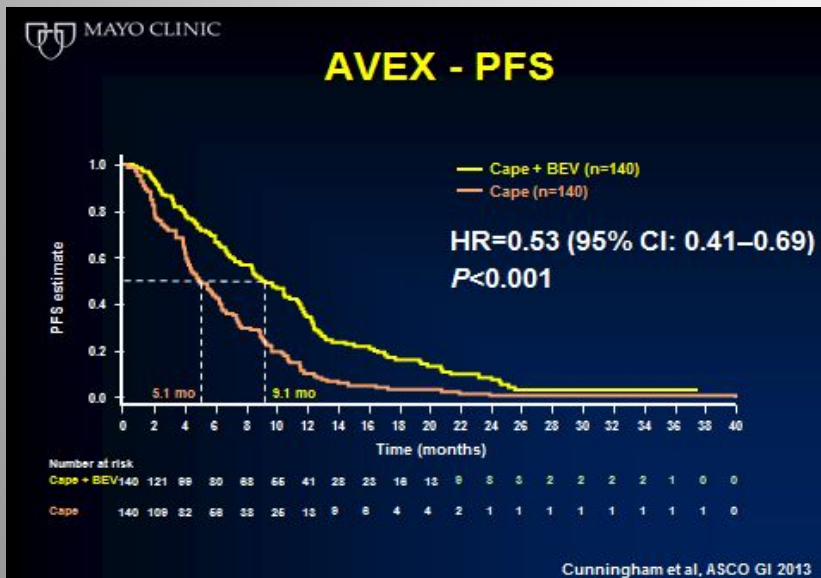
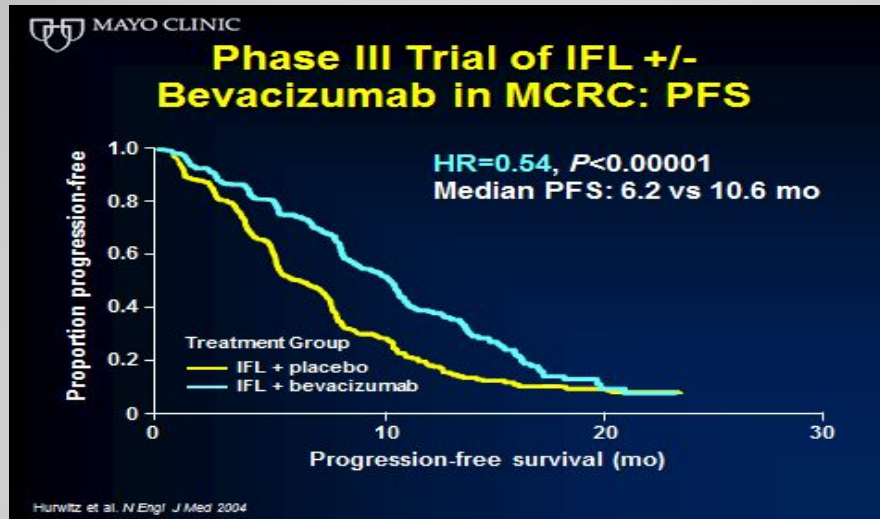
JUNE 3, 2004

VOL. 350 NO. 23

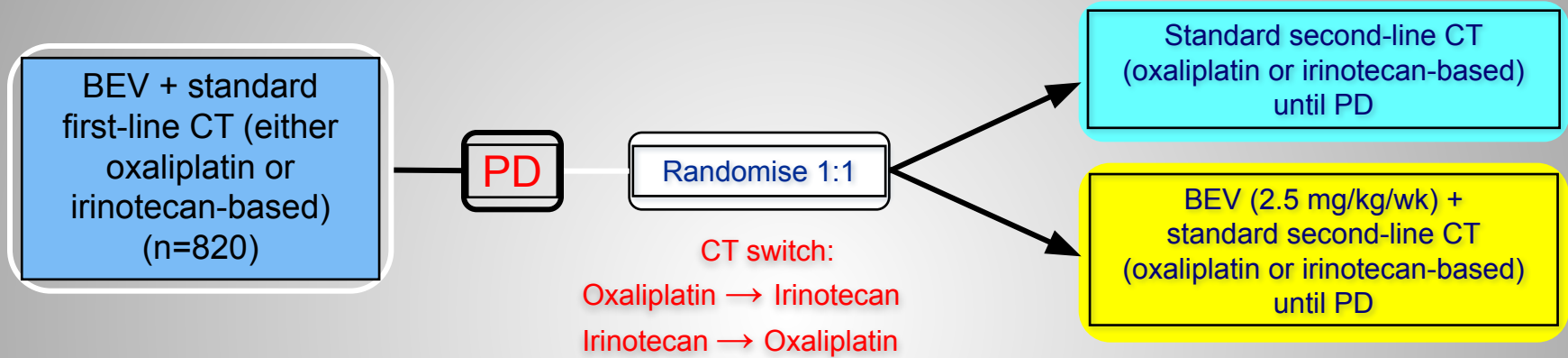
Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin
for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D.,
John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S.,
Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D.,
and Fairouz Kabbinavar, M.D.

Early separation of survival curves with bevacizumab – anti-VEGF AB

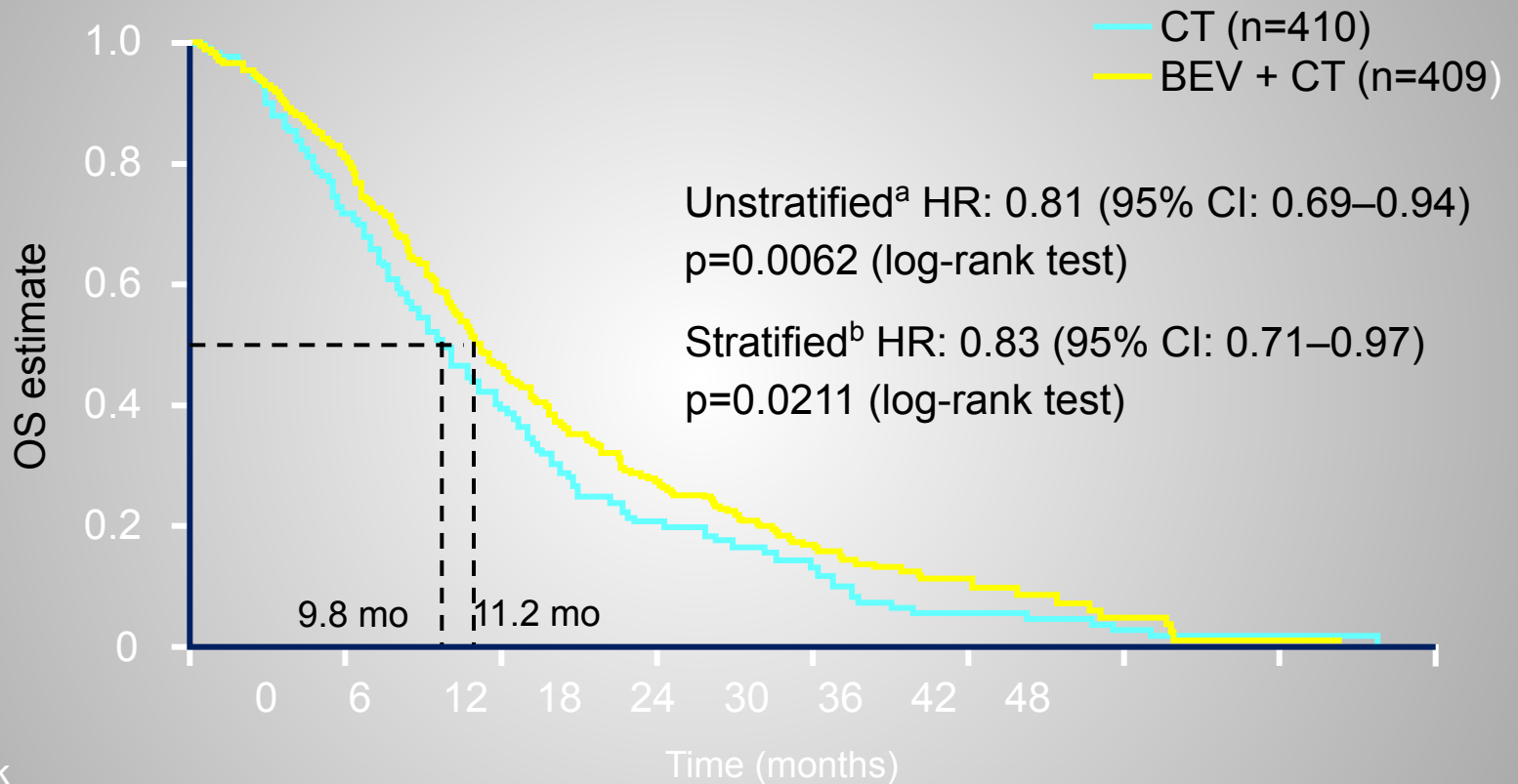


ML18147 study design (phase III)



Primary endpoint	<ul style="list-style-type: none"> Overall survival (OS) from randomisation
Secondary endpoints included	<ul style="list-style-type: none"> Progression-free survival (PFS) Best overall response rate Safety
Stratification factors	<ul style="list-style-type: none"> First-line CT (oxaliplatin-based, irinotecan-based) First-line PFS (≤ 9 months, > 9 months) Time from last BEV dose (≤ 42 days, > 42 days) ECOG PS at baseline (0/1, 2)

OS: ITT population



No. at risk

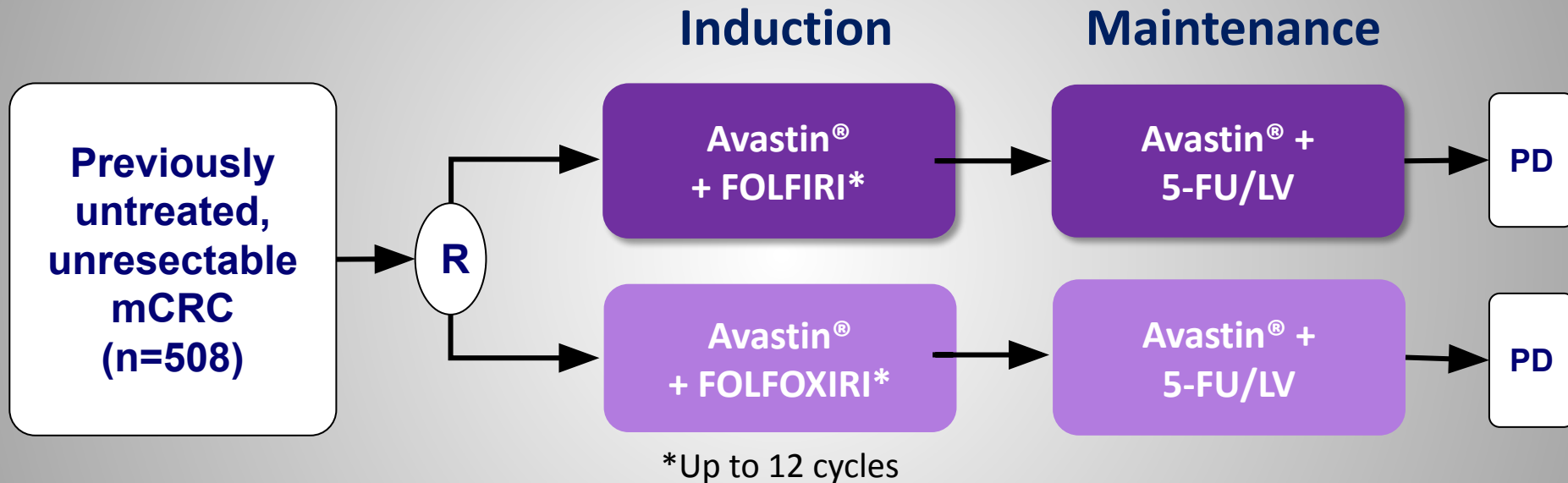
	0	6	12	18	24	30	36	42	48
CT	410	293	162	51	24	7	3	2	0
BEV + CT	409	328	188	64	29	13	4	1	0

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)

^aPrimary analysis method; ^bStratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤ 9 months, >9 months), time from last dose of BEV (≤ 42 days, >42 days), ECOG performance status at baseline (0, ≥ 1)

TRIBE

Study design

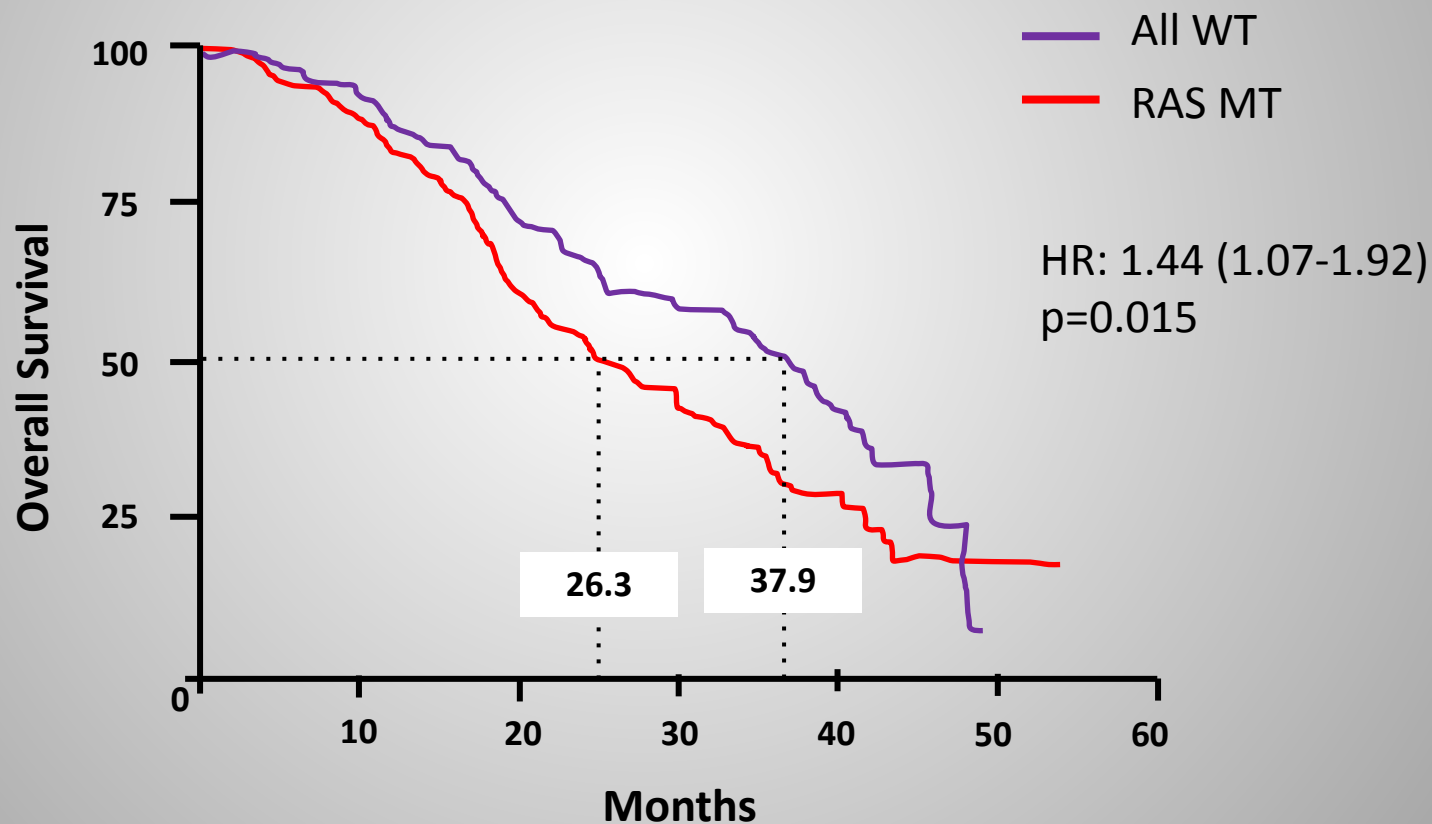


Primary endpoint – PFS

Secondary endpoints – ORR, OS

TRIBE: RAS analysis

RAS Status has significant effect on OS



TRIBE: RAS analysis

Overall Survival

FOLFIRI+Bev	FOLFOXIRI+Bev	
25.8	31.0	ITT
34.4	41.7	All WT
23.1	30.8	RAS MT

Conclusion anti-VEGF Therapy

- Duration of VEGF-inhibition matters
 - Treatment to progression
 - Maintenance strategies
 - Treatment beyond progression
- Clinical synergism between FP + bevacizumab
- BEV combinable with FOLFOXIRI (TRIBE)

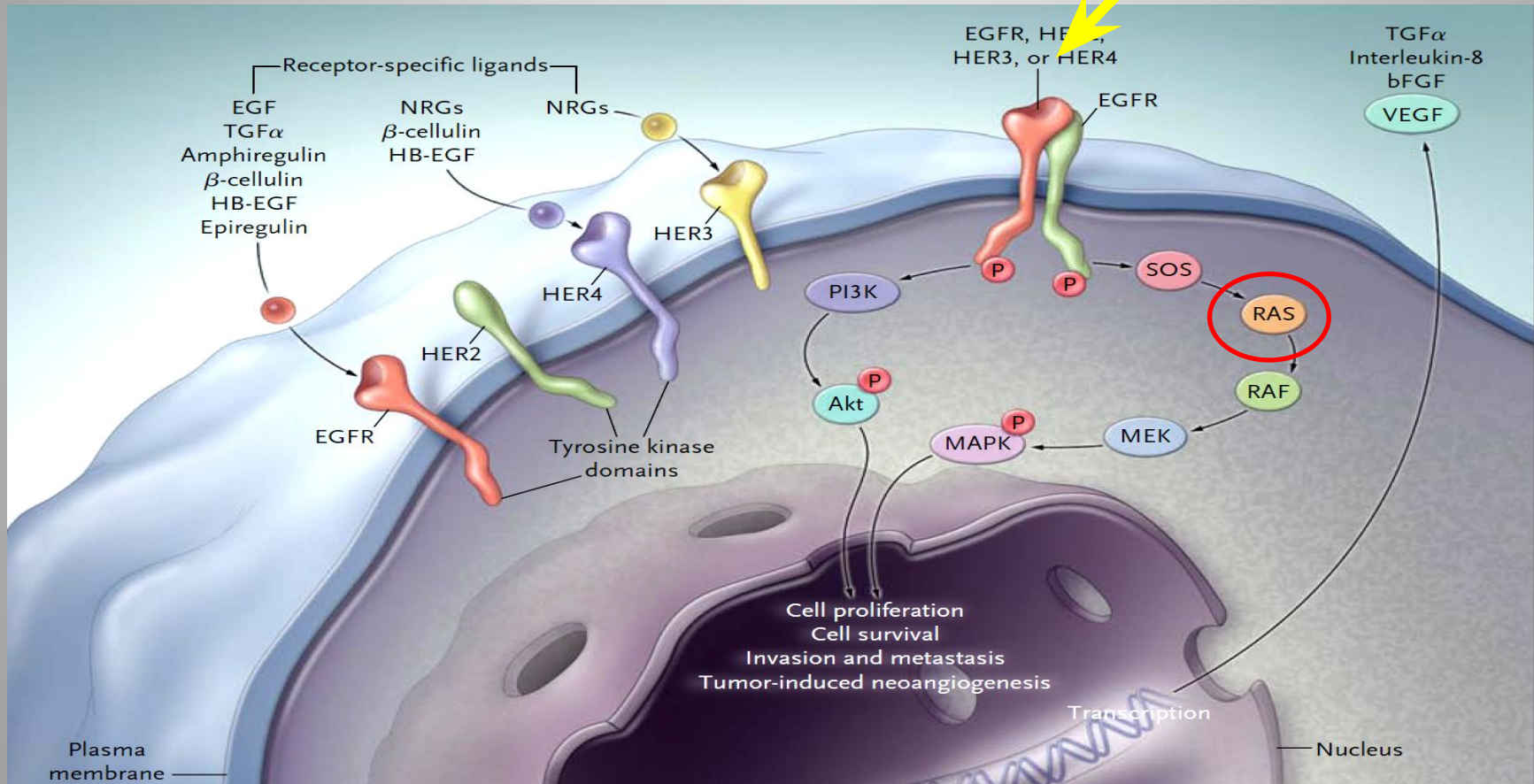
What are the side effects seen most often?

- High blood pressure
- Too much protein in the urine
- Nosebleeds
- Rectal bleeding
- Back pain
- Headache
- Taste change
- Dry skin
- Inflammation of the skin
- Inflammation of the nose
- Watery eyes



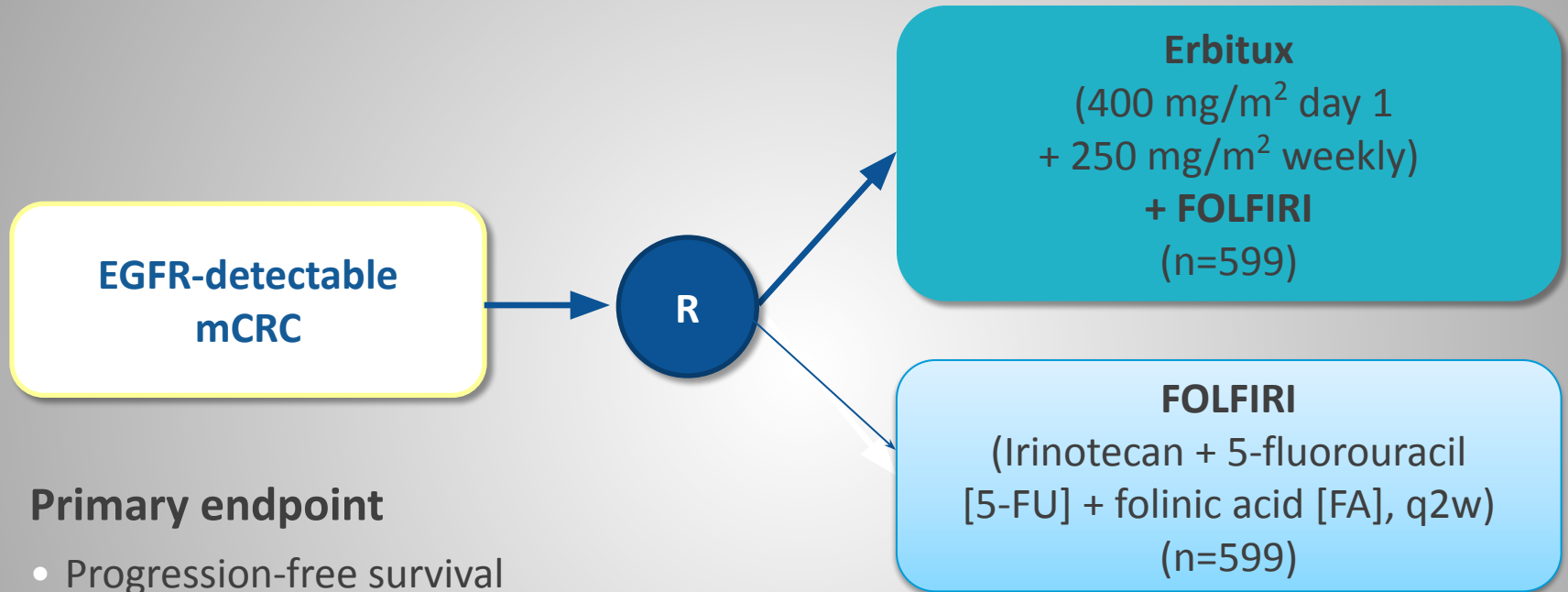
Anti-EGFR therapy and colorectal cancer

Anti-EGFR therapy



HER, human EGFR; MAPK, mitogen-activated protein kinase; SOS, son-of-sevenless

CRYSTAL: Erbitux + FOLFIRI vs FOLFIRI in 1st line mCRC



Primary endpoint

- Progression-free survival

Secondary endpoints

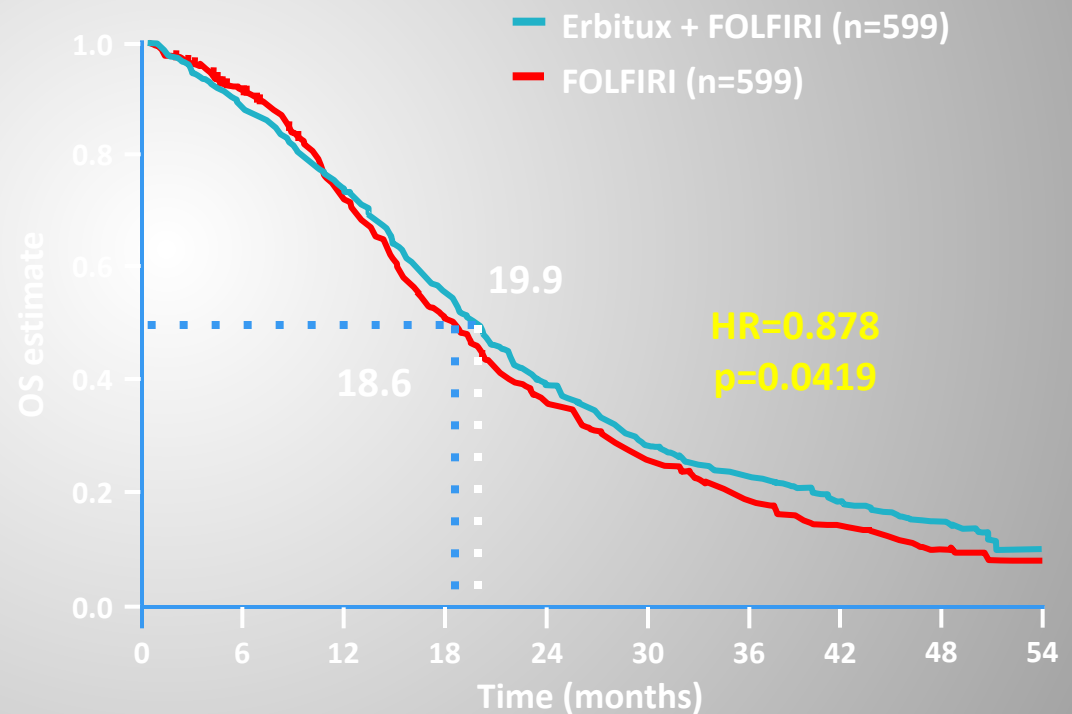
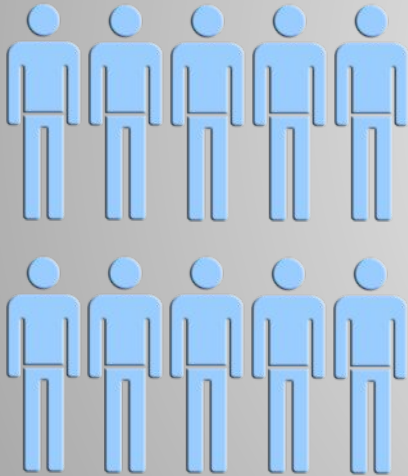
- Overall survival
- Response
- Safety

Stratification by

- Eastern Cooperative Oncology Group Performance Status (ECOG PS) and region

Erbitux + FOLFIRI significantly increases OS vs FOLFIRI alone (overall patient population)

Overall patient population

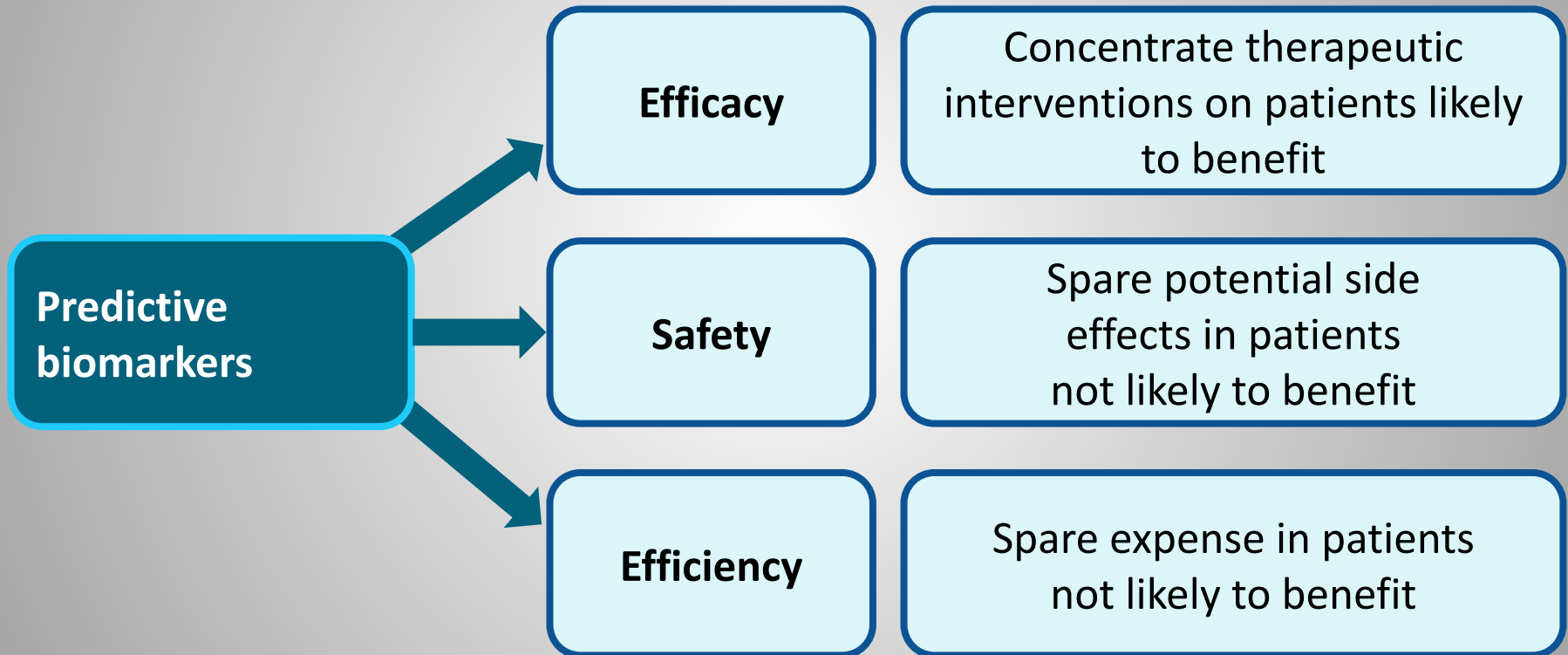


Key cancer biomarkers in patient care

Clinical biomarker use	Clinical objective
Screening	Detect and treat early stage cancers in the asymptomatic population ¹
Diagnostic	Definitively establish the presence of cancer ¹
Prognostic	Predict the probable outcome of cancer regardless of therapy ¹
Predictive	Predict treatment safety and/or efficacy outcome ²

- 1. Committee on Developing Biomarker-Based Tools for Cancer Screening Diagnosis and Treatment. Washington, D.C. The National Academic Press; 2007;
- 2. Heinemann V, et al. Cancer Treat Rev 2013; 39:592-601.

Biomarker-guided treatment has the potential to improve clinical outcomes



Examples of predictive biomarkers in oncology

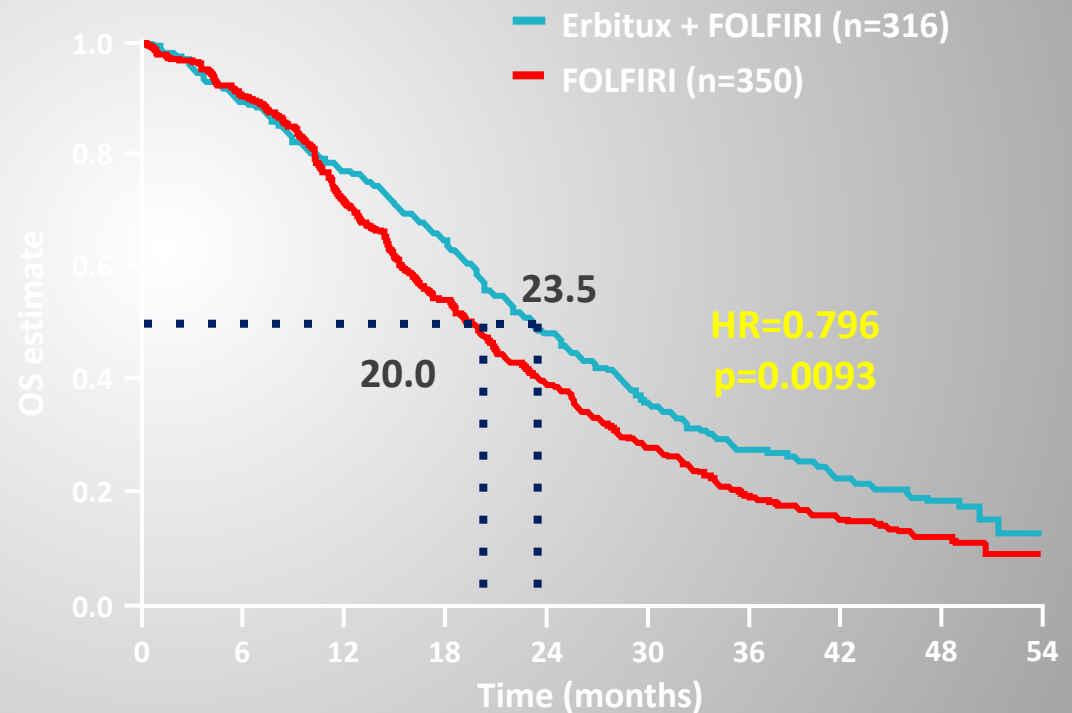
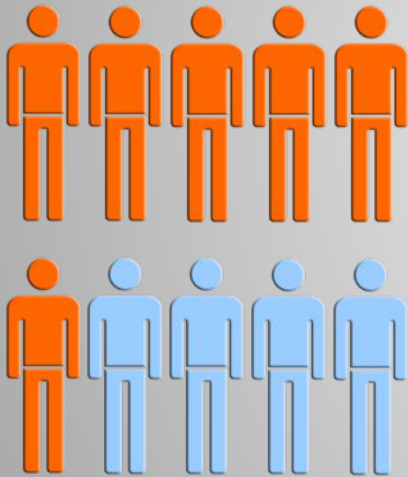
Tumour type	Biomarker	Drug
Breast ca	RAS: a predictive biomarker for anti-EGFR-targeted treatment in patients with mCRC	
Gastric cancer	HER-2 overexpression	Trastuzumab
CML	<i>BCR/ABL</i> fusion gene	Imatinib ³
GIST	<i>c-KIT</i> mutation	Imatinib ³
NSCLC	<i>EGFR</i> mutation	Gefitinib ⁴ , erlotinib ⁵
mCRC	<i>RAS</i> mutation status	Panitumumab ⁶ , cetuximab ⁷
Melanoma	<i>BRAF</i> V600	Vemurafenib ⁸
NSCLC	<i>ALK</i> positive	Crizotinib ⁹

1-9: European Public Assessment Reports, available at www.ema.europa.eu for:

1. Herceptin[®]; 2. Tyverb[®]; 3. Glivec[®]; 4. Iressa[®]; 5. Tarceva[®]; 6. Vectibix[®]; 7. Erbitux[®]; 8. Zelboraf[®]; 9. Xalkori[®].

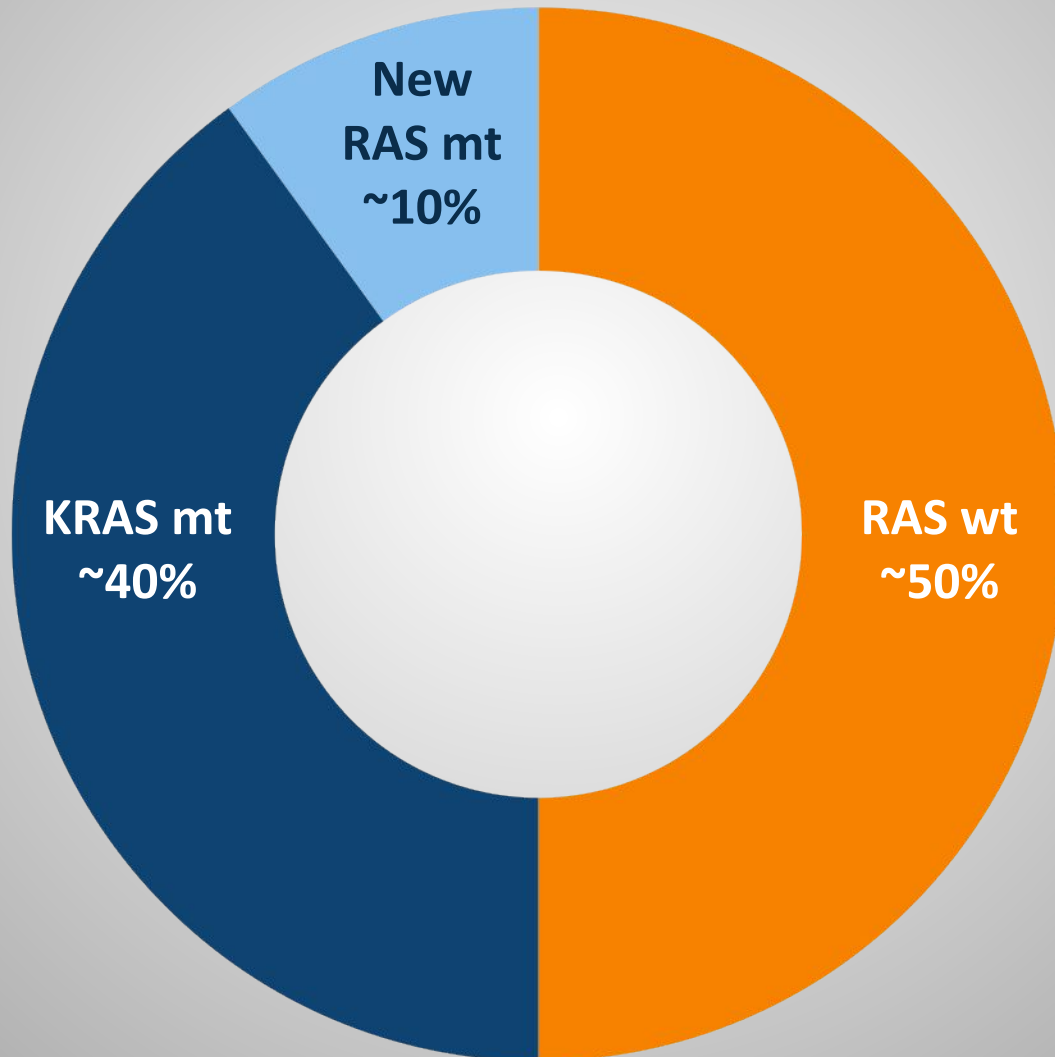
Even greater OS benefit with Erbitux + FOLFIRI vs FOLFIRI alone (KRAS wt population)

KRAS wt population



Personalized treatment is a better approach than “one treatment fits all”

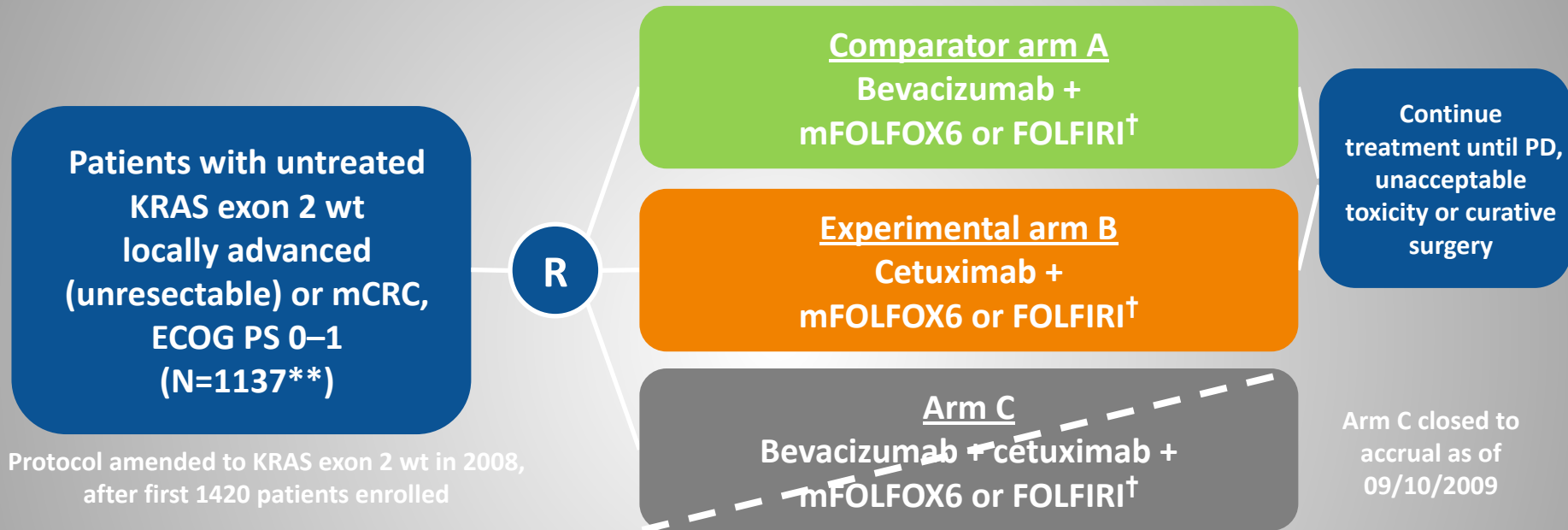
Distribution of mutations in mCRC: A new definition





CALGB/SWOG 80405 data

CALGB/SWOG 80405: Randomized, open-label, multicenter (North America), Phase III IST^{1*}



Primary endpoint: OS

Secondary endpoints: Response, PFS, time to treatment failure, duration of response, toxicity, 60-day survival, eligibility for surgery post-treatment, QoL

CALGB/SWOG 80405:

Efficacy comparison of KRAS exon 2 wt and RAS wt groups

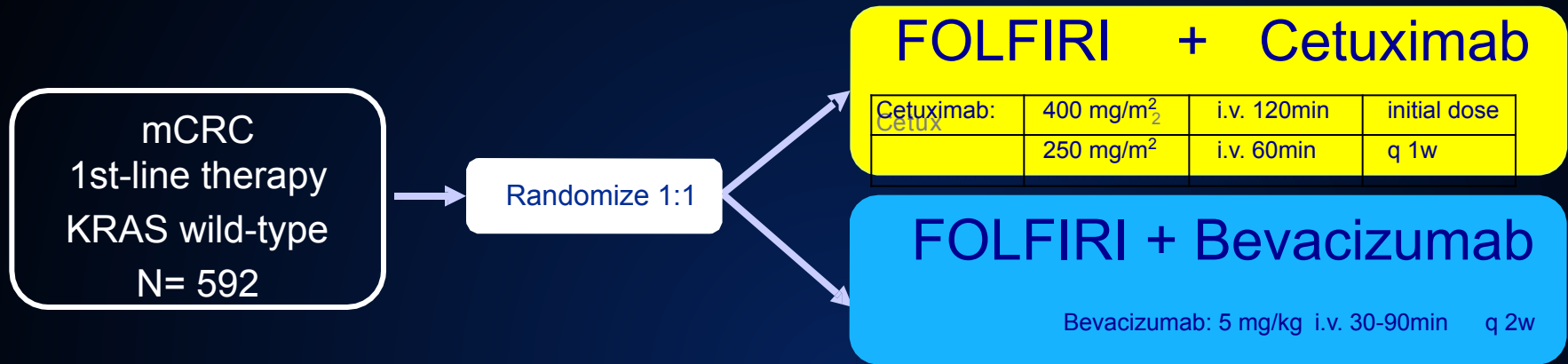
Subgroup	Cet + CT N	Bev + CT N	ORR (%)* Cet vs Bev p-value	Median PFS (months) HR (95% CI) p-value	Median OS (months) HR (95% CI) p-value
KRAS exon 2 wt	578	559	65.6 vs 57.2 p=0.02	10.4 vs 10.8 1.0 (0.91–1.17) p=0.55	29.9 vs 29.0 0.9 (0.78–1.09) p=0.34
RAS wt	270	256	68.6 vs 53.8 p<0.01	11.4 vs 11.3 1.1 (0.9–1.3) p=0.31	32.0 vs 31.2 0.9 (0.7–1.1) p=0.40

*733 KRAS codon 12/13 WT and 406 RAS evaluable patients are evaluable for response

*406 RAS evaluable and 319 RAS WT patients evaluable for response

The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving OS in the cetuximab + CT vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC; Cetuximab should not be used for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown²

FIRE-3 Phase III study design



FOLFIRI: 5-FU: 400 mg/m² (i.v. bolus);
folinic acid: 400mg/m²
irinotecan: 180 mg/m² 5-FU: 2,400 mg/m²
(i.v. 46h)

- **Primary objective: Overall response rate (ORR) (inv assessed)**
- **Designed to detect a difference of 12% in ORR induced by FOLFIRI + cetuximab (62%) as compared to FOLFIRI + bevacizumab (50%)**
- **284evaluable patients per arm needed to achieve 80% power for an one-sided Fisher's exact test at an alpha level of 2.5%**

FIRE-3 PFS

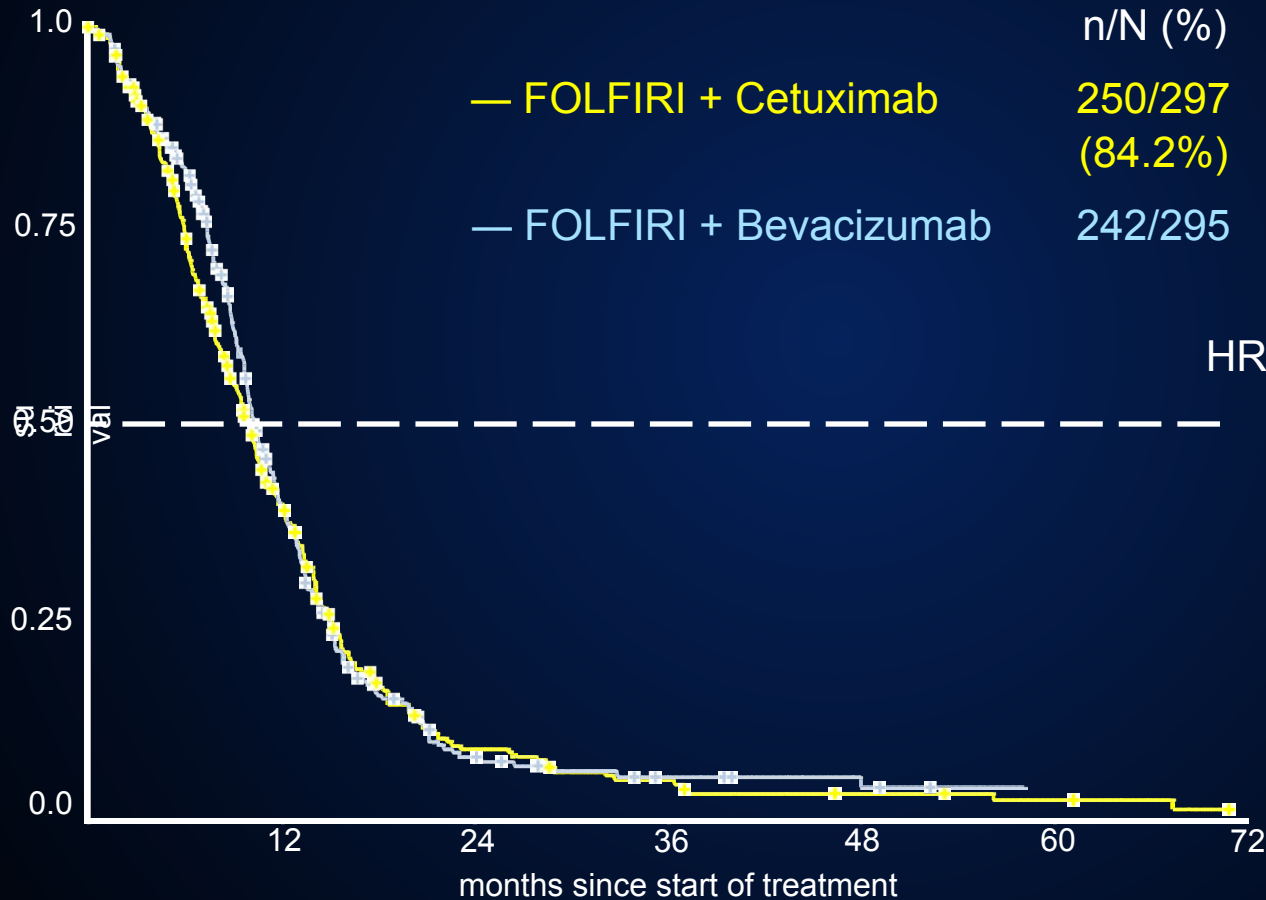
Events n/N (%)	Median (months)	95% CI
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— FOLFIRI + Cetuximab 250/297 (84.2%)	10.0	8.8 – 10.8
---------------------------------------------	------	------------

— FOLFIRI + Bevacizumab 242/295 (82.0%)	10.3	9.8 – 11.3
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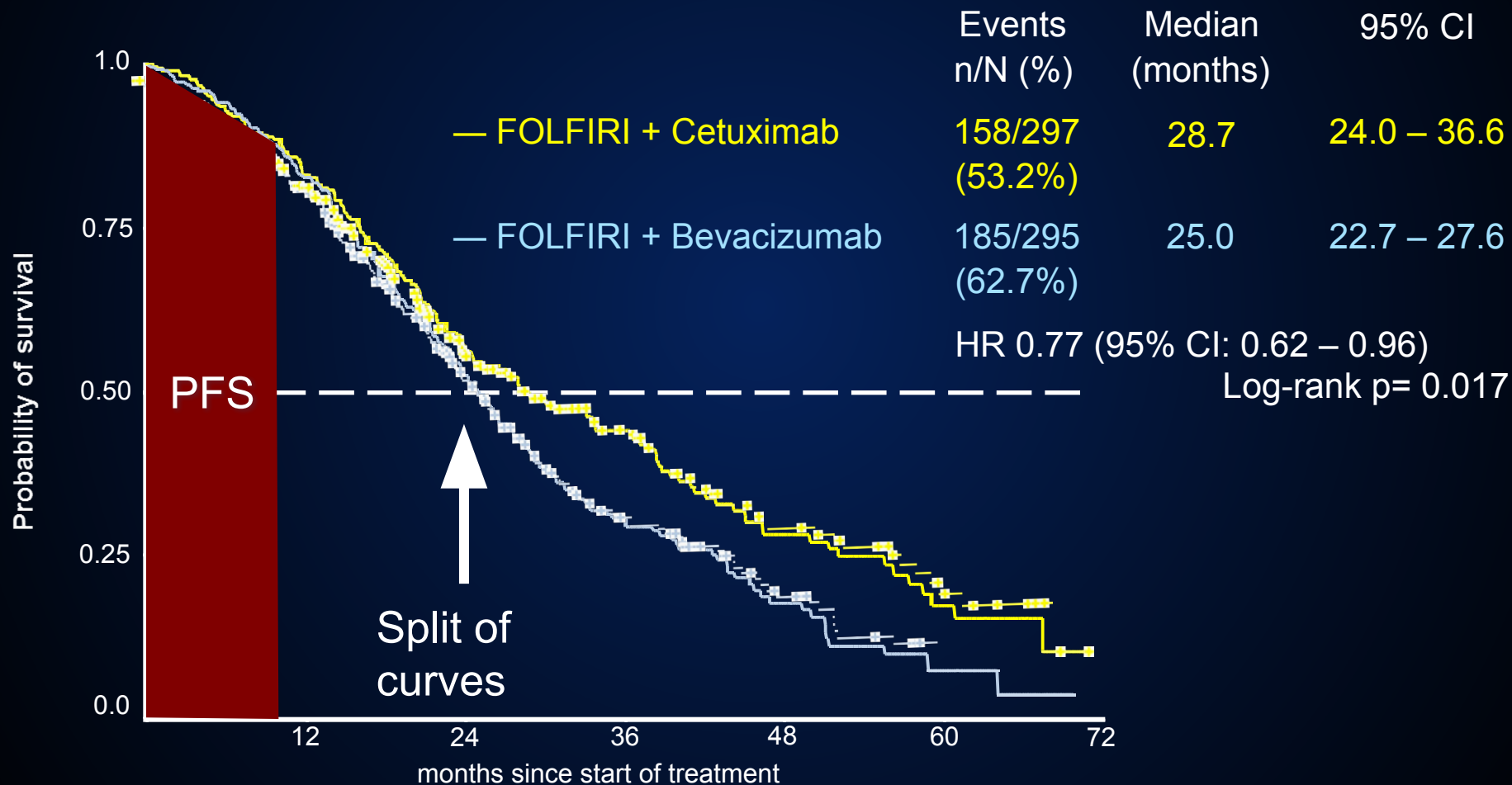
HR 1.06 (95% CI 0.88 – 1.26)

Log-rank p= 0.547



numbers	297	10	19	1	5	3
at risk	295	0	15	0	4	
		99		6		

FIRE-3 Overall survival



numbers 297
at risk 295

12 218
214

24 111
111

36 60
47

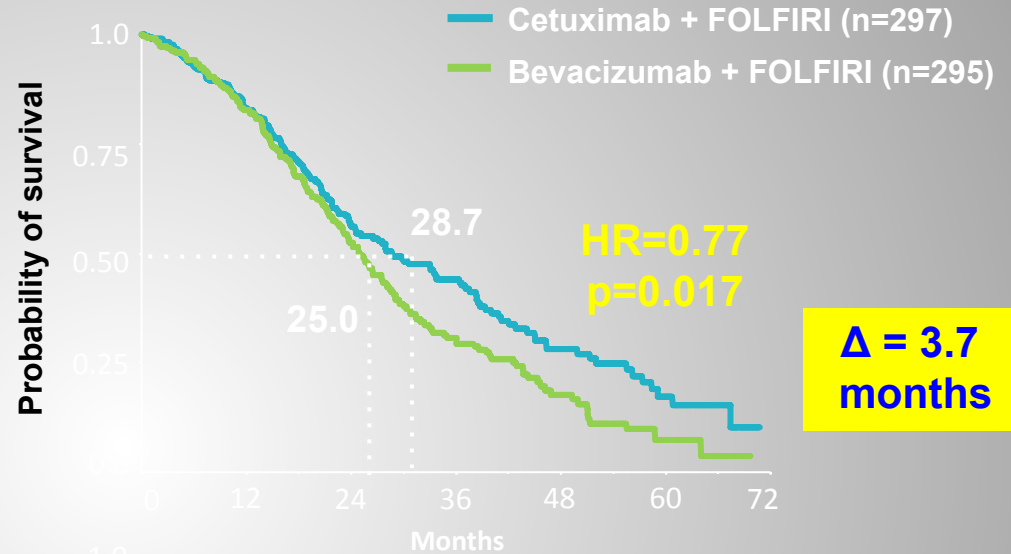
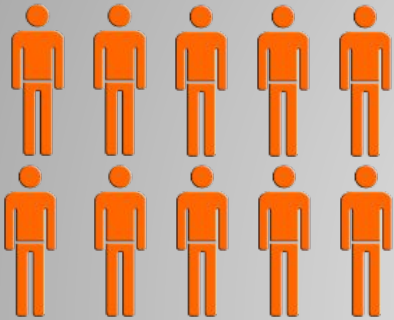
48 29
18

60 9
2

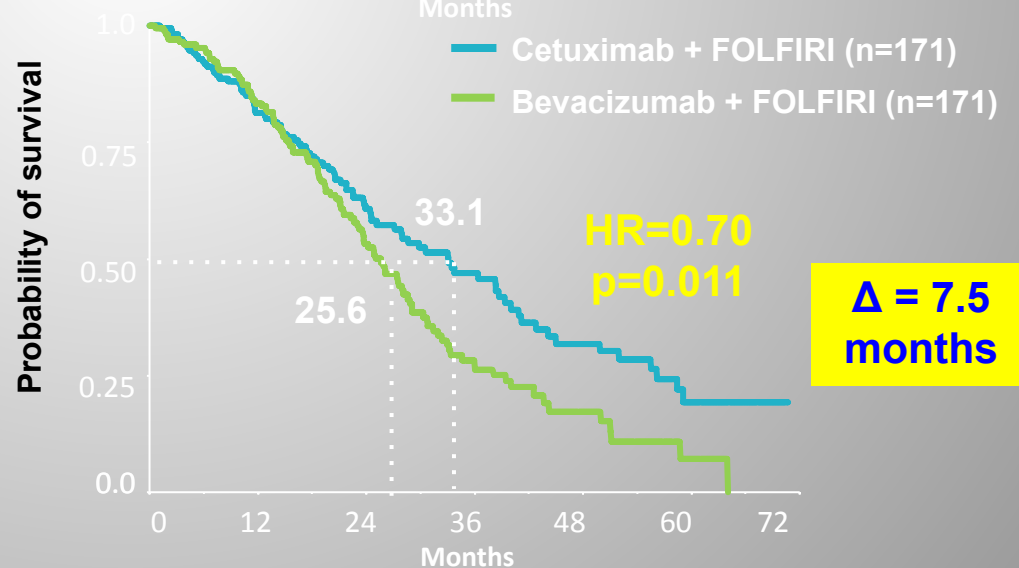
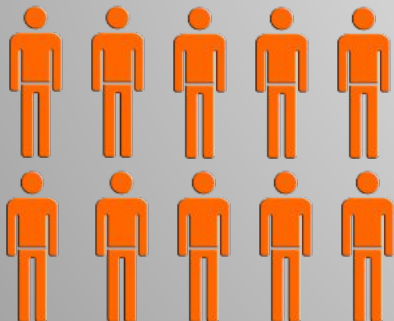
Heinemann et al., ASCO 2013

Greater selection of patients results in further improvement in OS

KRAS wt (exon 2) population

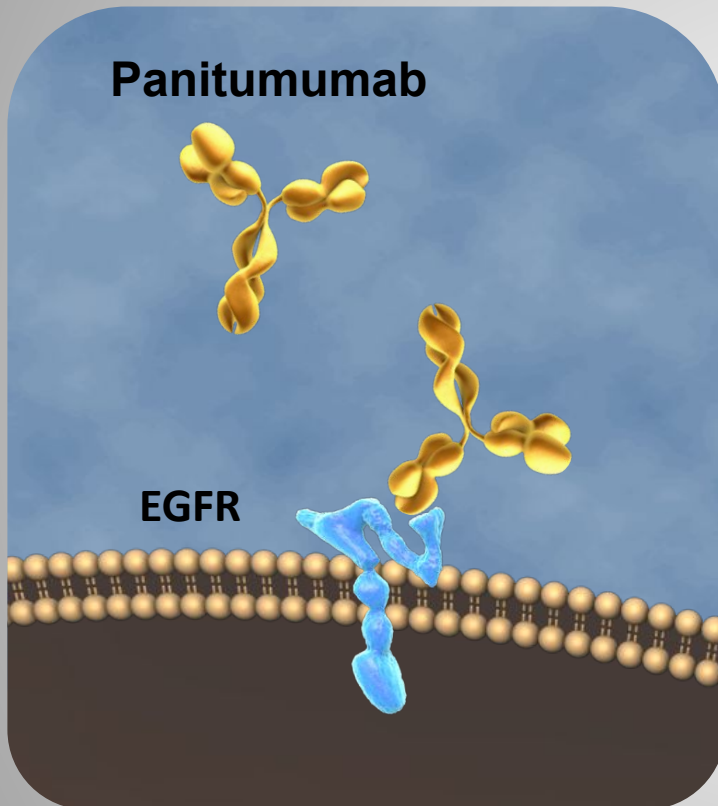


RAS wt population (KRAS and NRAS wt)



~85% of KRAS wt (exon 2) population

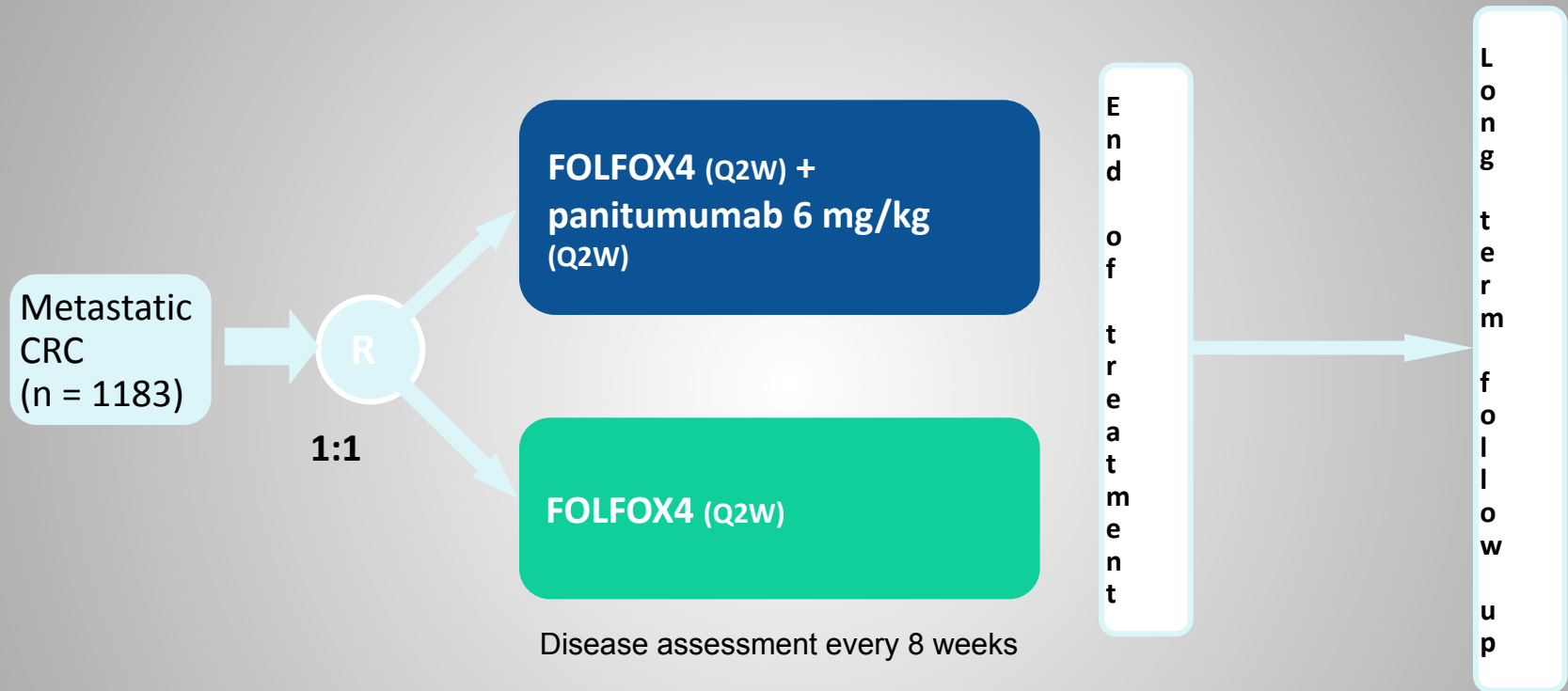
Panitumumab – a fully human anti-EGFR mAb inhibits ligand binding and EGFR dimerisation



- Fully human, monoclonal IgG2 antibody
- Binds with high affinity and specificity to the extracellular domain of the human EGFR
 - Dissociation constant: $K_D=0.05 \text{ nM}^1$
- Inhibits receptor activation of all known EGFR ligands²
- Inhibits EGFR-dependent activity including cell activation and cell proliferation in various tumours²⁻⁵

PRIME study

FOLFOX4 ± panitumumab in 1st-line treatment of metastatic CRC

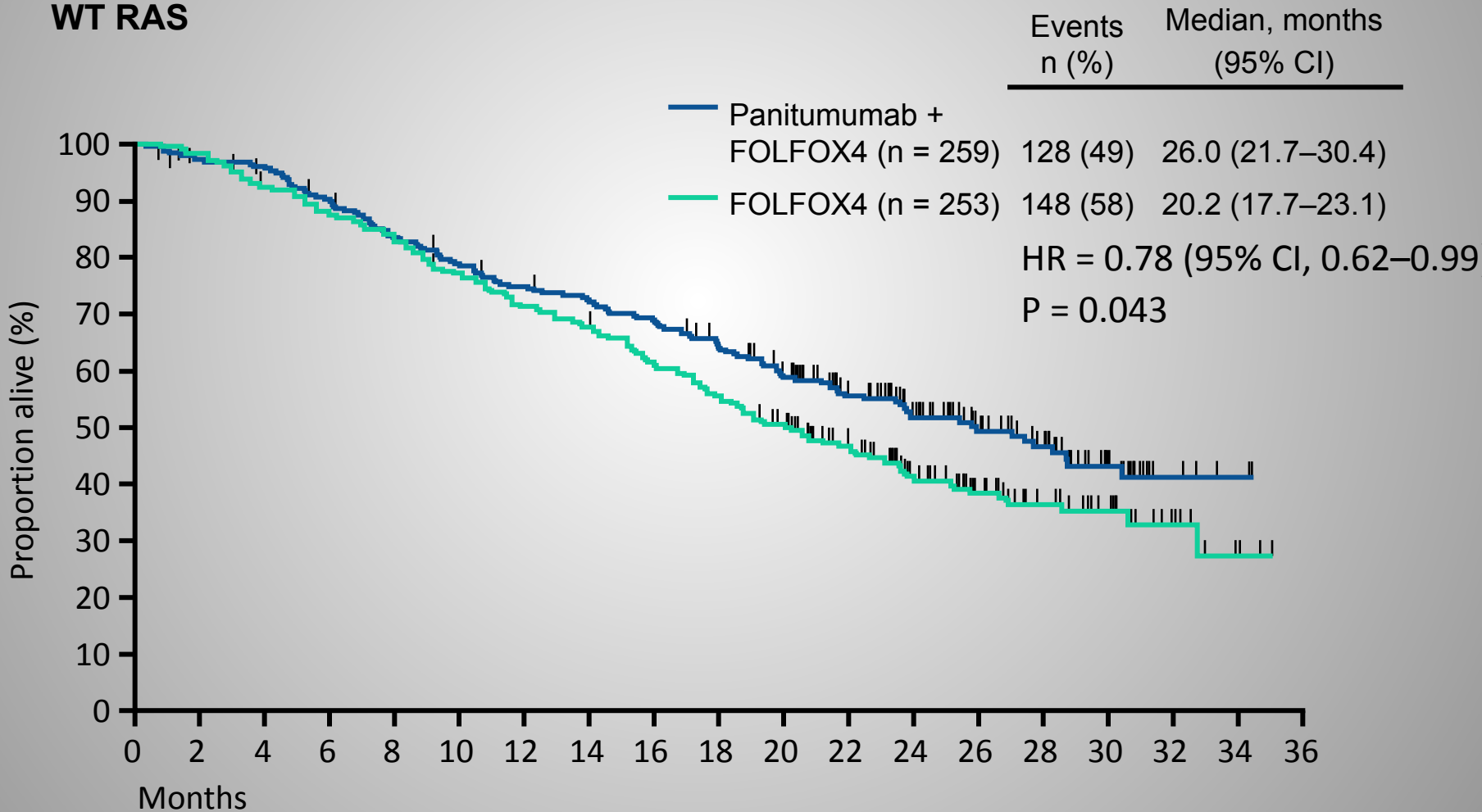


- Study endpoints: PFS (1°); OS, ORR, safety, HRQoL
- KRAS status was prospectively analysed

PRIME study *RAS* analysis

OS (primary analysis)

WT *RAS*



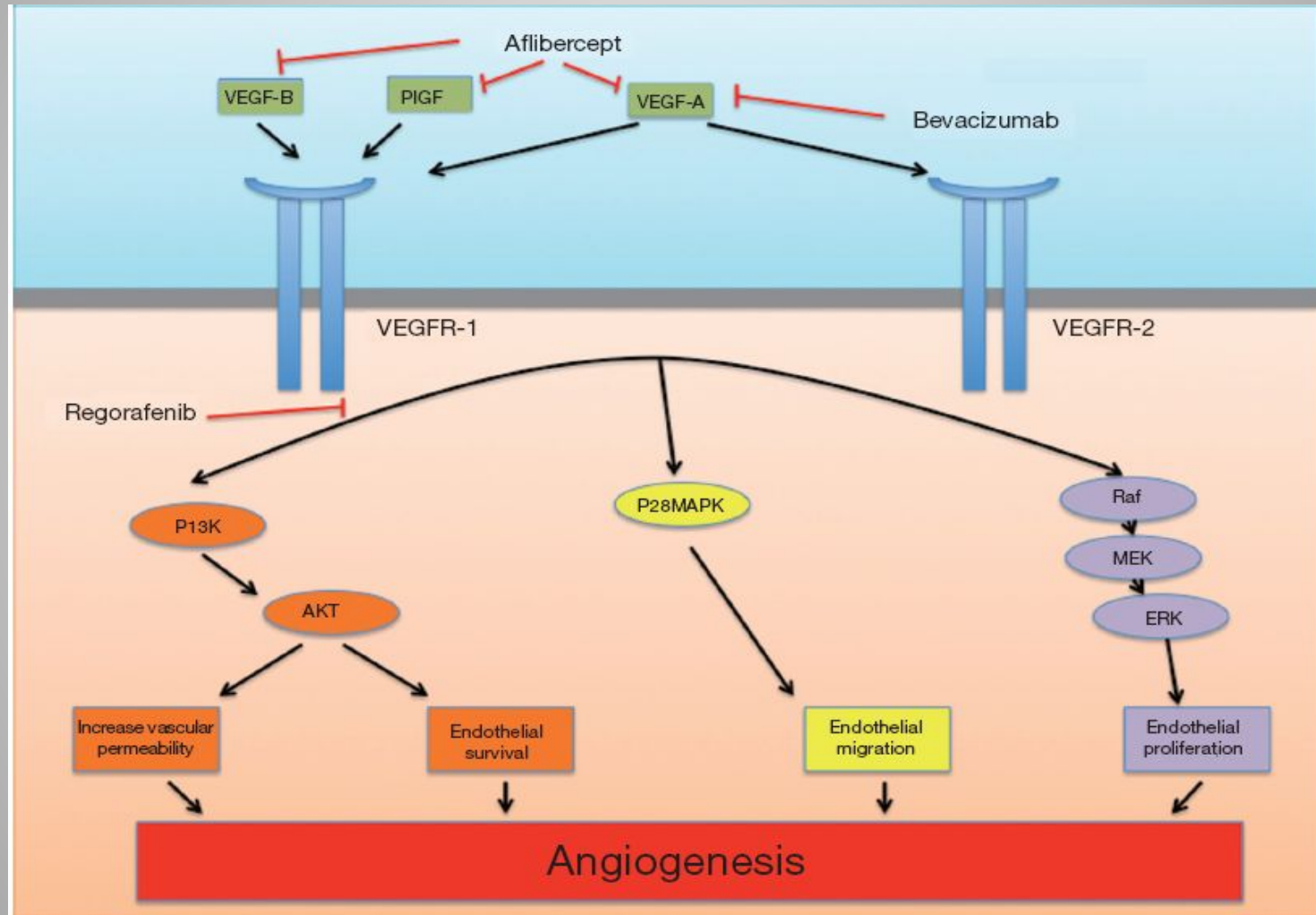
WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4

(includes 7 patients harbouring *KRAS*/*NRAS* codon 59 mutations)

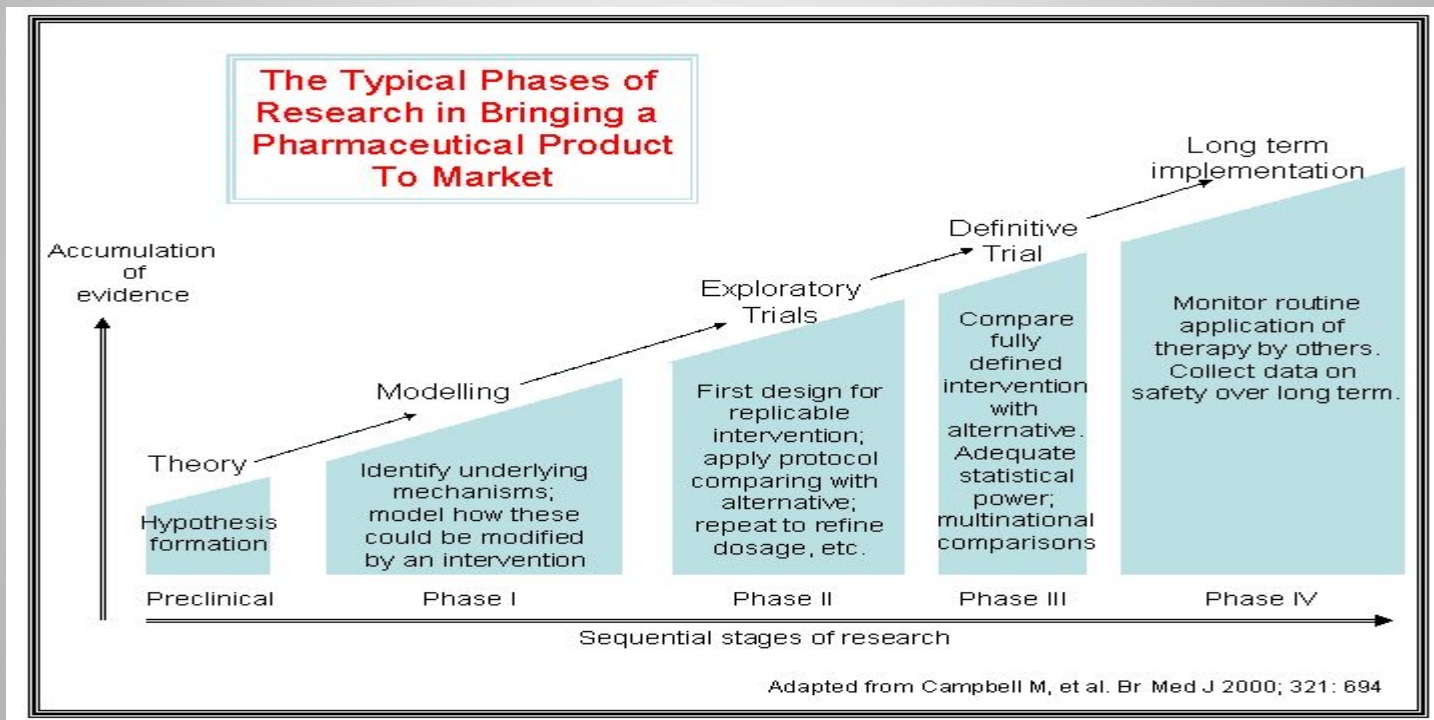
What are the side effects seen most often? Cetuximab and Panitumumab



Regorafenib (Stivarga)



CLINICAL TRIALS



Optimized Treatment Strategy

**mCRC, palliative setting, PS 0-1
Unresectable Liver and Retroperitoneal LN Metastases**

Molecular testing

Any RAS mut (55%)

All RAS wt (40%)

BRAF mut (5%)

Bevacizumab + CT doublet

Bevacizumab + CT doublet

EGFR inhibitor + CT doublet

Bevacizumab + FOLFOXIRI

Bevacizumab + CT doublet

Bevacizumab + CT doublet

Bevacizumab + CT doublet

EGFR inhibitor +/- chemotherapy

Regorafenib

EGFR inhibitor +/- irinotecan

Regorafenib

Regorafenib

BSC

Regorafenib

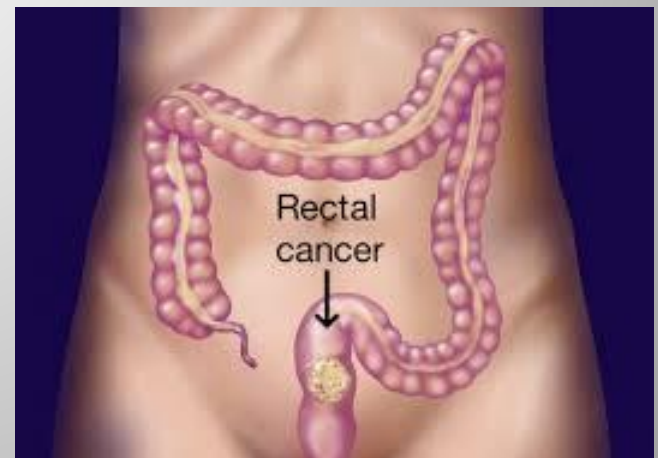
BSC

BSC

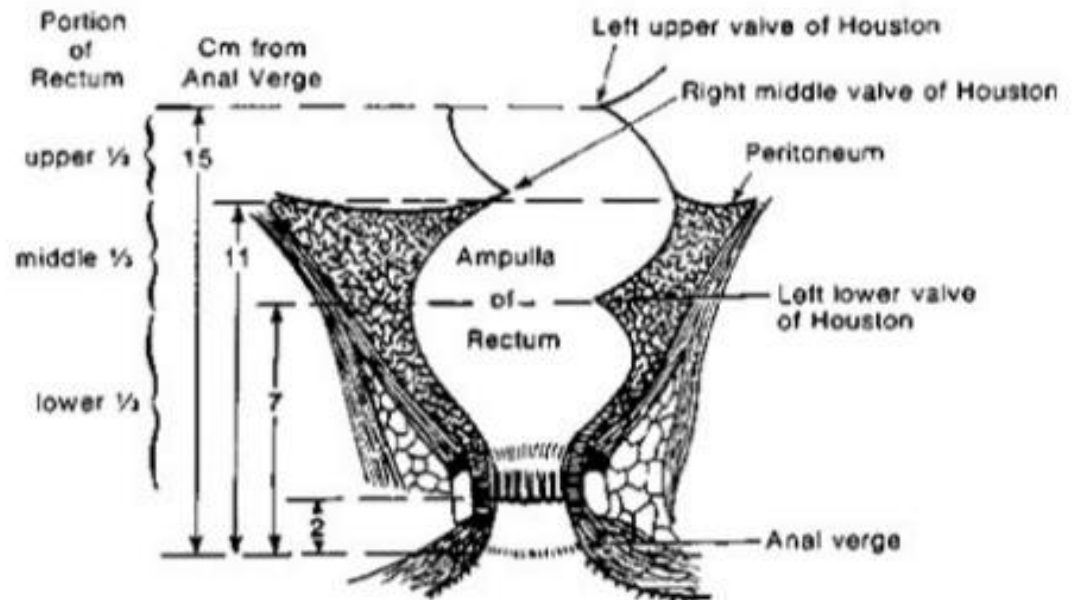
BSC

P
D
1
P
D
2
P
D
3
P
D
4

Rectal cancer



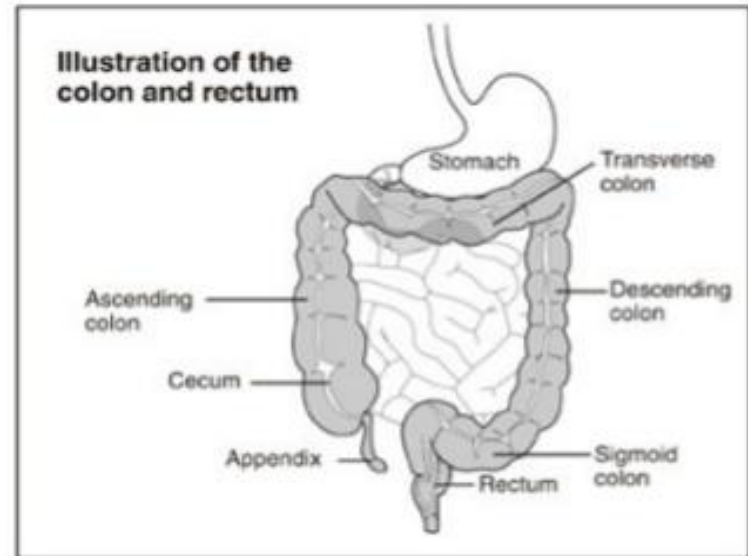
- Divided into 3 parts
 - Upper third
 - Middle third
 - Lower third
- 3 distinct intraluminal curves (Valves of Houston)



Epidemiology

- Colorectal cancer is the **third** most frequently diagnosed cancer in the US men and women.
- 108,070 new cases of colon cancer and 40,740 new cases of rectal cancer in the US in 2008. Combined mortality for colorectal cancer 49,960 in 2008.
- **Worldwide** approx. 1 million new cases p.a. are diagnosed, with 529,000 deaths.
- **Incidence** rate in India is quite low about 2 to 8 per 100,000
- **Median age**- 7th decade but can occur any time in adulthood.

- Cecum 14 %
- Ascending colon 10 %
- Transverse colon 12 %
- Descending colon 7 %
- Sigmoid colon 25 %
- Rectosigmoid junct 0.9 %
- **Rectum 23 %**



- **Etiological agents**

- Environmental & dietary factors
- Chemical carcinogenesis.

- **Associated risk factors**

- Male sex
- Family history of colorectal cancer
- Personal history of colorectal cancer, ovary, endometrial, breast
- Excessive BMI
- Processed meat intake
- Excessive alcohol intake
- Low folate consumption
- Neoplastic polyps.

- **Hereditary Conditions** (FAP, HNPCC)

Clinical Presentations

- **Symptoms**

- Asymptomatic
- Change in bowel habit (diarrhoea, constipation, narrow stool, incomplete evacuation, tenesmus).
- Blood PR.
- Abdominal discomfort (pain, fullness, cramps, bloating, vomiting).
- Weight loss, tiredness.

- **Acute Presentations**

- Intestinal obstruction.
- Perforation.
- Massive bleeding.

- Signs

- Pallor
- Abdominal mass
- PR mass
- Jaundice
- Nodular liver
- Ascites

- Rectal metastasis travel along portal drainage to liver via superior rectal vein as well as systemic drainage to lung via middle inferior rectal veins.

Pathological features

WHO Classification

- Adenocarcinoma in situ
- Adenocarcinoma
- Mucinous (colloid) adenocarcinoma (>50% mucinous)
- Signet ring cell carcinoma (>50% signet ring cells)
- Squamous cell (epidermoid) carcinoma
- Adenosquamous carcinoma
- Small-cell (oat cell) carcinoma
- Medullary carcinoma
- Undifferentiated Carcinoma

Prognostic factors

- **Good prognostic factors**

- Old age
- Gender(F>M)
- Asymptomatic pts
- Polypoidal lesions
- Diploid

- **Poor prognostic factors**

- Obstruction
- Perforation
- Ulcerative lesion
- Adjacent structures involvement
- Positive margins
- LVSI
- Signet cell carcinoma
- High CEA
- Tethered and fixed cancer

Stage and Prognosis

Stage		5-year Survival (%)
O,1	Tis,T1;No;Mo	> 90
I	T2;No;Mo	80-85
II	T3-4;No;Mo	70-75
III	T2;N1-3;Mo	70-75
III	T3;N1-3;Mo	50-65
III	T4;N1-2;Mo	25-45
IV	M1	<3

Diagnostic Workup

- **History**—including family history of colorectal cancer or polyps
- **Physical examinations** including DRE and complete pelvic examination in women: size, location, ulceration, mobile vs. tethered vs. fixed, distance from anal verge and sphincter functions.
- **Proctoscopy**—including assessment of mobility, minimum diameter of the lumen, and distance from the anal verge
- **Biopsy** of the primary tumor

Transrectal ultrasound –EUS

- use for clinical staging.
- 80-95% accurate in tumor staging
- 70-75% accurate in mesorectal lymph node staging
- Very good at demonstrating layers of rectal wall
- Use is limited to lesion < 14 cm from anus, not applicable for upper rectum, for stenosing tumor
- Very useful in determining extension of disease into anal canal (clinical important for planning sphincter preserving surgery)

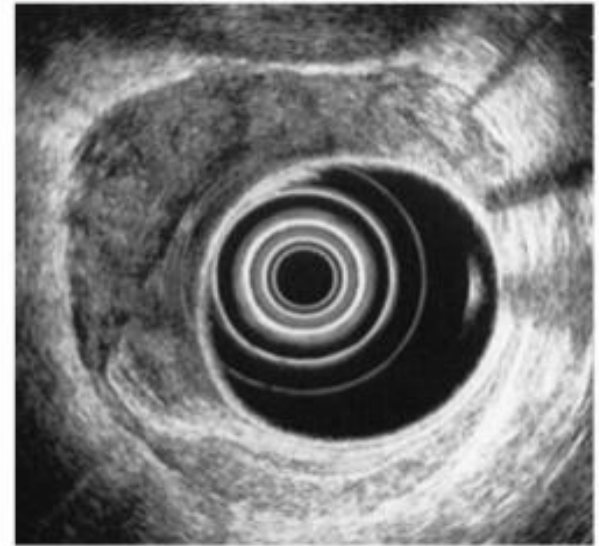


Figure. Endorectal ultrasound of a T3 tumor of the rectum, extension through the muscularis propria, and into perirectal fat.

CT scan

- Part of routine workup of patients
- Useful in identifying enlarged pelvic lymph-nodes and metastasis outside the pelvis than the extent or stage of primary tumor
- Limited utility in small primary cancer
- Sensitivity 50-80%
- Specificity 30-80%
- Ability to detect pelvic and para-aortic lymph nodes is higher than peri-rectal lymph nodes.

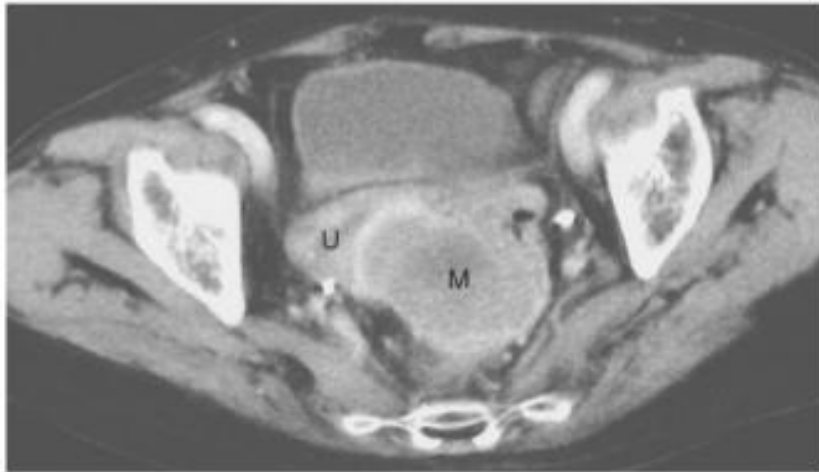


Figure: Rectal cancer with uterine invasion. CT scan shows a large heterogeneous rectal mass (M) with compression and direct invasion into the posterior wall of the uterus (U).



Figure: Mucinous adenocarcinoma of the rectum. CT scan shows a large heterogeneous mass (M) with areas of cystic components. Note marked luminal narrowing of the rectum (*arrow*).

Magnetic Resonance Imaging (MRI)

- Greater accuracy in defining extent of rectal cancer extension and also location & stage of tumor
- Also helpful in lateral extension of disease, critical in predicting circumferential margin for surgical excision.
- Different approaches (body coils, endorectal MRI & phased array technique)
- Mercury study:
 - 711 patients from 11 European centers.
 - Extramural tumor depth by MR & histo-pathological evaluation equivalent.

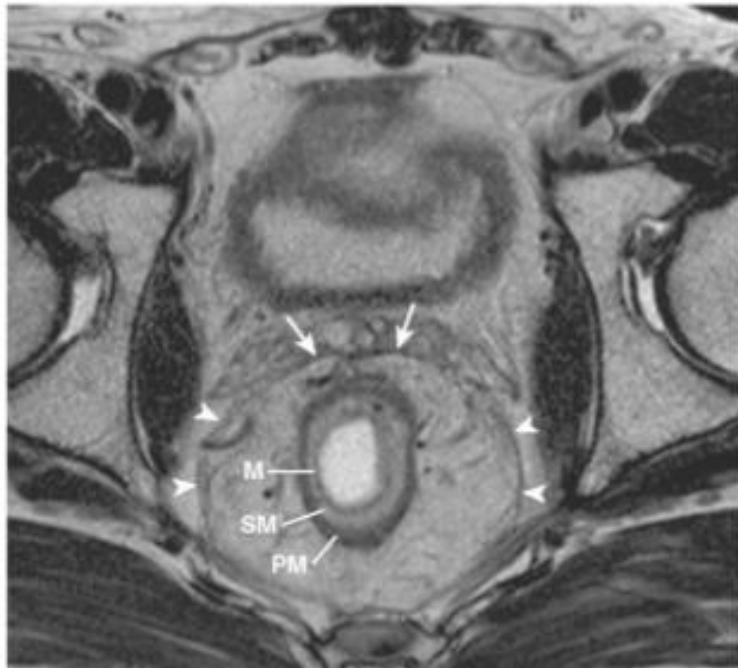


Figure: Normal rectal and perirectal anatomy on high-resolution T2-weighted MRI. Rectal mucosa (M), submucosa (SM), and muscularis propria (PM) are well discriminated. Mesorectal fascia appears as a thin, low-signal-intensity structure (*arrowheads*) and fuses with the remnant of urogenital septum making Denonvilliers fascia (*arrows*).

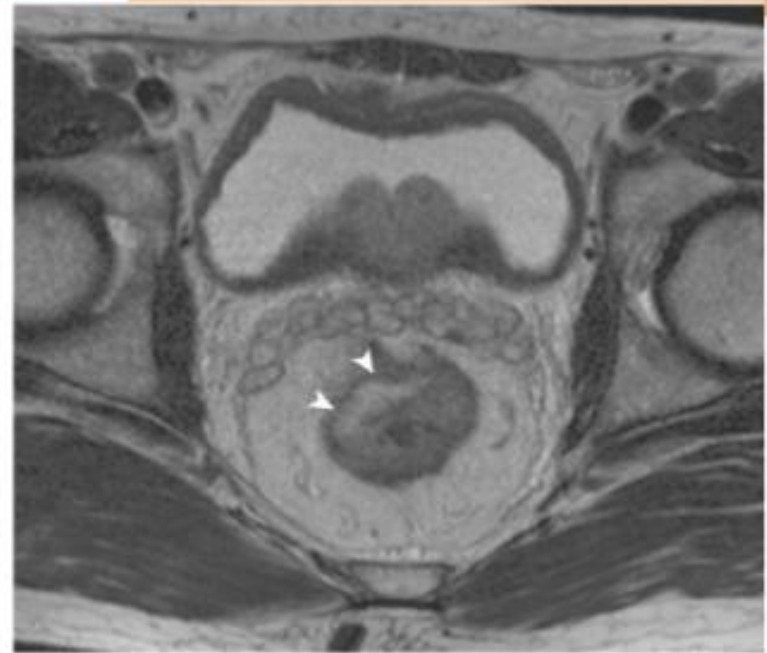
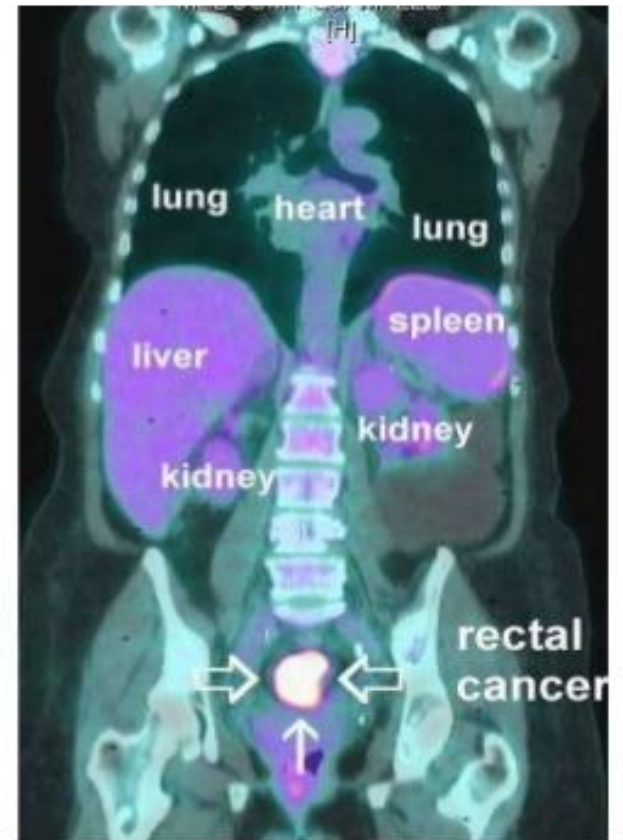
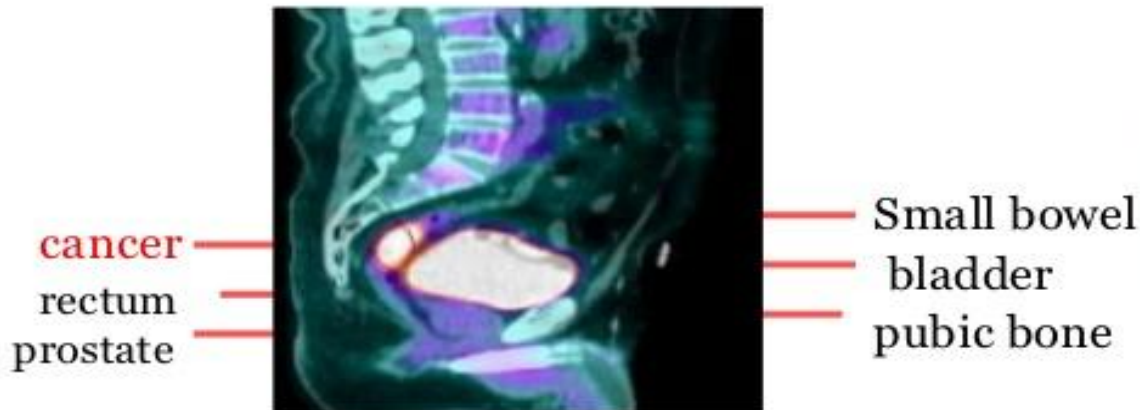


Figure: Mucinous adenocarcinoma of the rectum. T2-weighted MRI shows high signal intensity (*arrowheads*) of the cancer lesion in right anterolateral side of the rectal wall.

PET with FDG

- Shows promise as the most sensitive study for the detection of metastatic disease in the liver and elsewhere.
- Sensitivity of 97% and specificity of 76% in evaluating for recurrent colorectal cancer.



- CEA: High CEA levels associated with poorer survival
- Routine investigation
 - Complete blood count, KFT, LFT
 - Chest X-ray

```
graph TD; Treatment[Treatment] --- Surgery[Surgery]; Treatment --- Chemotherapy[Chemotherapy]; Treatment --- Radiotherapy[Radiotherapy];
```

Treatment

Surgery

Chemotherapy

Radiotherapy

Surgery

- Surgery is the mainstay of treatment of RC
- After surgical resection, local failure is common
- Local recurrence after conventional surgery:
 - 20%-50% (average of 35%)**
- Radiotherapy significantly reduces the number of local recurrences

*** Reference: facts taken from Perez*

Types of Surgery

- **Local excision- reserved for superficially invasive (T1) tumors** with low likelihood of LN metastases
- Should be considered a total biopsy, with further treatment based on pathology
- With unfavorable pathology patient should undergo total mesorectal excision with or without sphincter-preservation:
 - positive margin (or <2 mm), lymphovascular invasion,
 - poorly differentiated tumors, T2 lesion

- **Low Anterior Resection** - for tumors in upper/mid rectum; allows preservation of anal sphincter
- **Abdominoperineal resection**
 - for tumors of distal rectum with distal edge up to 6 cm from anal verge
 - associated with permanent colostomy and high incidence of sexual and genitourinary dysfunction

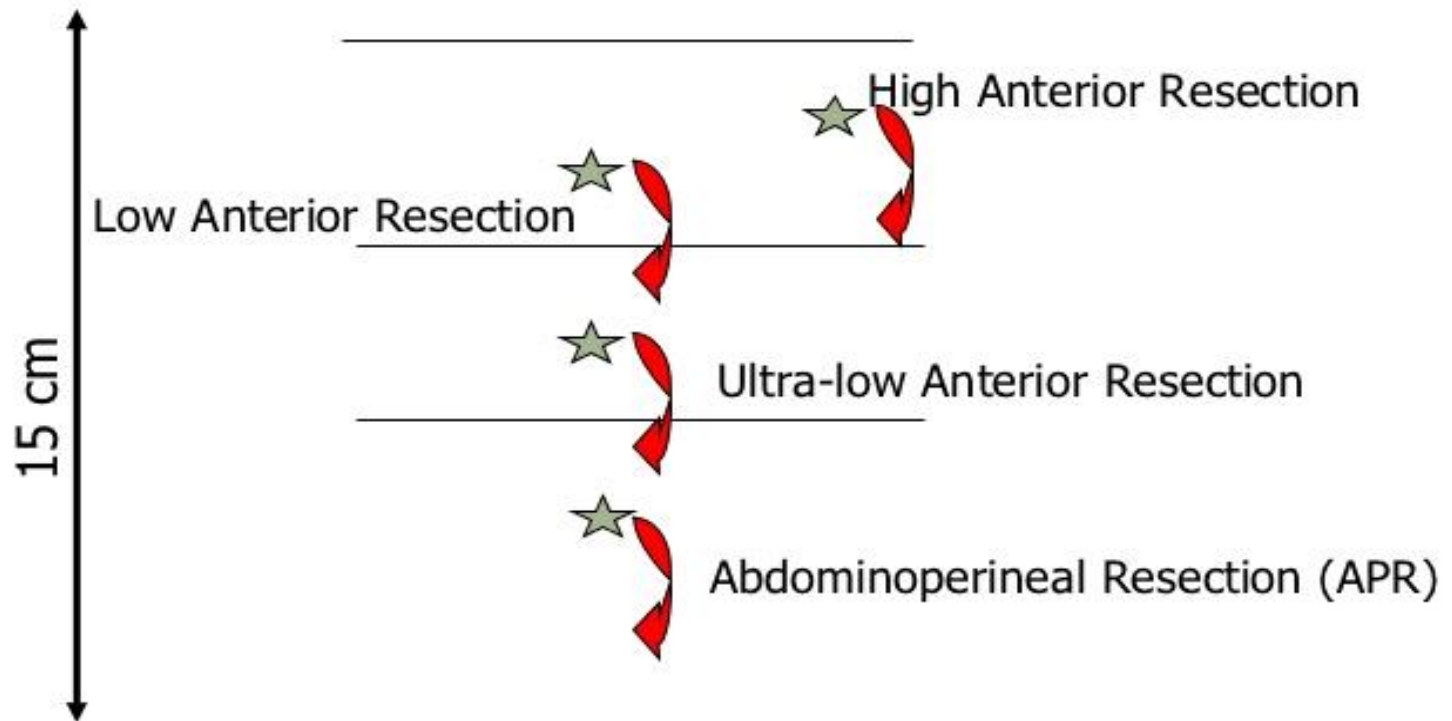
Total mesorectal excision

- local failures are most often due to inadequate surgical clearance of radial margins.
- conventional resection violates the mesorectal circumference during blunt dissection, leaving residual mesorectum.
- TME involves precise dissection and removal of the entire rectal mesentery as an intact unit.
- local recurrence with conventional surgery averages approx. 25-30% vs. TME 4-7% by several groups (although several series have higher recurrence)

*** referred from Perez*

Pelvic Exenteration

The surgeon removes the rectum as well as nearby organs such as the bladder, prostate, or uterus if the cancer has spread to these organs. A colostomy is needed after this operation. If the bladder is removed, a urostomy (opening to collect urine) is needed.



Complications of Surgery

- Bleeding
- Infection
- Anastomotic Leakage
- Blood clots
- Anesthetic Risks

Purpose of Radio(chemo)therapy in Rectal Cancer

- To lower local failure rates and improve survival in resectable cancers
- to allow surgery in primarily inoperable cancers
- to facilitate a sphincter-preserving procedure
- to cure patients without surgery: very small cancer or very high surgical risk

Chemotherapy agents

- 5Fu
- Leucovorin
- Oxaliplatin
- Irinotecan
- Bevacizumab
- cetuximab

Combinations

- FOLFOX
- FOLFIRI
- Leucovorin/5FU
- Capecitabine
- Bevacizumab in combination with the above regimens.

Radiotherapy

- **Prone position:** radiopaque markers include anal, vaginal, rectal, perineal skin; wire perineal scar if present; small bowel contrast, ensure bladder full.
- **Target Volume:** Primary Tumor or Tumor bed, with margin presacral, and internal iliac nodes (if T4, external iliac nodes also).
- **Energy**
 - 6 MV linac or Co⁶⁰
- **Portals**
 - 4 fields (AP, PA, two lateral fields)
 - 3 fields (PA, Rt. Lateral, two lateral fields)

Dose

- Preoperative radiotherapy
 - Short course: 25 Gy in 5 daily fractions of 5 Gy given in 1 week.
 - Long course
 - Phase 1**
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.
 - Phase 2 (optional)**
5.4–9 Gy in 3–5 daily fractions of 1.8 Gy
- Postoperative radiotherapy
 - Phase 1**
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.
 - Phase 2 (optional)**
5.4–9 Gy in 3–5 daily fractions of 1.8 Gy.

Pre-op RT vs. surgery alone

Swedish Rectal Cancer Trial (NEJM 1997;336:980): 1168 patients randomised to 25 Gy (5x5) PRT or no RT.

	Surgery alone	Preop. RT	
Rate of local recurrence	27%	11%	p<0.001
5-year overall survival	48%	58%	p=0.004

Dutch Colorectal Cancer Group (Kapiteijn E. NEJM 2001;345:638): 1861 patients randomised TME vs PRT+TME

	TME	PRT+TME	
Recurrence rate	2.4%	8.2%	
OS	ns	ns	

Pre-op vs. post-op Chemo RT

Randomized trial of the German Rectal Cancer study Group (Sauer R et al. N Engl J Med 2004;351:1731-40):

- cT3 or cT4 or node-positive rectal cancer
- 50,4 Gy (1.8 Gy per day)
- 5-FU: 1000 mg/m² per day (d1-5) during 1. and 5. week

	Preop CRT	Postop CRT	
Patients	N=415	N=384	
5 y. OS	76%	74%	p=0.8
5 y. local relapse	6%	13%	p=0.006
G3,4 toxic effects	27%	40%	p=0.001

- Increase in sphincter-preserving surgery with preop Th.

Post-op chemo, RT, and/or Chemo-RT

- *GITSG 7175 (Thomas and Lindblad, 1988): 227 patients with stage B2-C rectal CA randomized postoperatively to:*
 - no adjuvant therapy vs.
 - chemo alone vs.
 - RT alone vs.
 - concurrent chemoRT.

Result: Chemo-RT arm improved 5-year OS (54%) and LR(10%) over observational arm OS (27%) & LR (25%).

- Mayo NCCTG 79-47-51 (NEJM 1991): 204 patients with T3/4 or LN+(B2-C) randomized to
 - post-op RT (45–50.4 Gy) vs.
 - chemoRT (bolus 5-FU concurrent).

Result: Chemo-RT improved LF (25 →14%), DFS, and OS (48 →58%) vs. RT alone.

Treatment Recommendations

Stage	Rectal cancer	~5-year LF/OS
I	<ul style="list-style-type: none"> • TME with APR or LAR. • If pT1-2N0, no adj. treatment. • Local excision for favorable tumors (<3 cm size, <30% circumference, within 8 cm of anal verge, well-moderately differentiated; margin >3 mm, no LVSI/PNI). <ul style="list-style-type: none"> ▪ favorable T1 lesions- observation. ▪ T2 lesions - adjuvant 5-FU/RT 	<p><5% LF 90% OS</p>
II and III (locally resectable)	<ul style="list-style-type: none"> • Pre-op 5-FU/RT →LAR/APR →adjuvant 5-FU-based therapy × 3 cycles (preferred) • If surgery initially → then adjuvant 5-FU × 2 cycles → concurrent chemoRT → 5-FU × 2 cycles 	<p>T3N0 and T1-2N1: 5–10% LF 80% OS T4N0 and T3N1: 10–15% LF 60% OS T4N1 and T3/4N2: 15–20% LF 40% OS</p>

Stage	Rectal cancer	~5-year LF/OS
III (T4/ Locally unresectable)	If obstructed, diverting colostomy or stent placed → definitive treatment. 5-FU/RT → resection if possible. Consider IORT for microscopic disease (after 50 Gy EBRT, give IORT 12.5–15 Gy) or brachytherapy for macroscopic disease → adjuvant 5-FU-based therapy*	
IV	Individualized options, including combination 5-FU-based chemo alone, or chemo ± resection ± RT	
Recurrent	Individualized options. If no prior RT, then chemoRT → surgery ± IORT or brachytherapy. If prior RT, then chemo → surgery ± IORT or brachytherapy as appropriate.	



Thank

You!