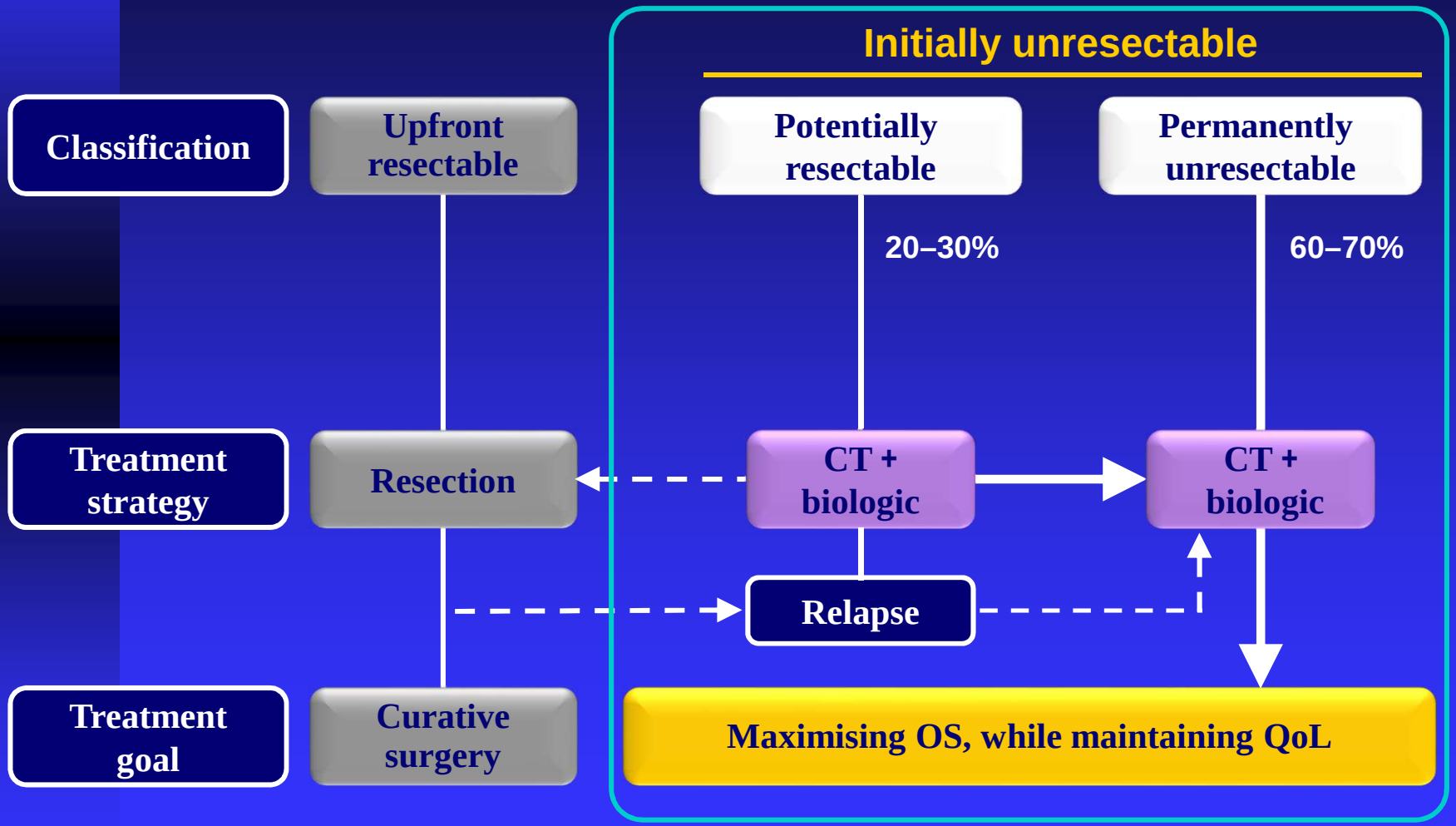
Targeted therapy in CRC

Cessal Thommachan Kainickal

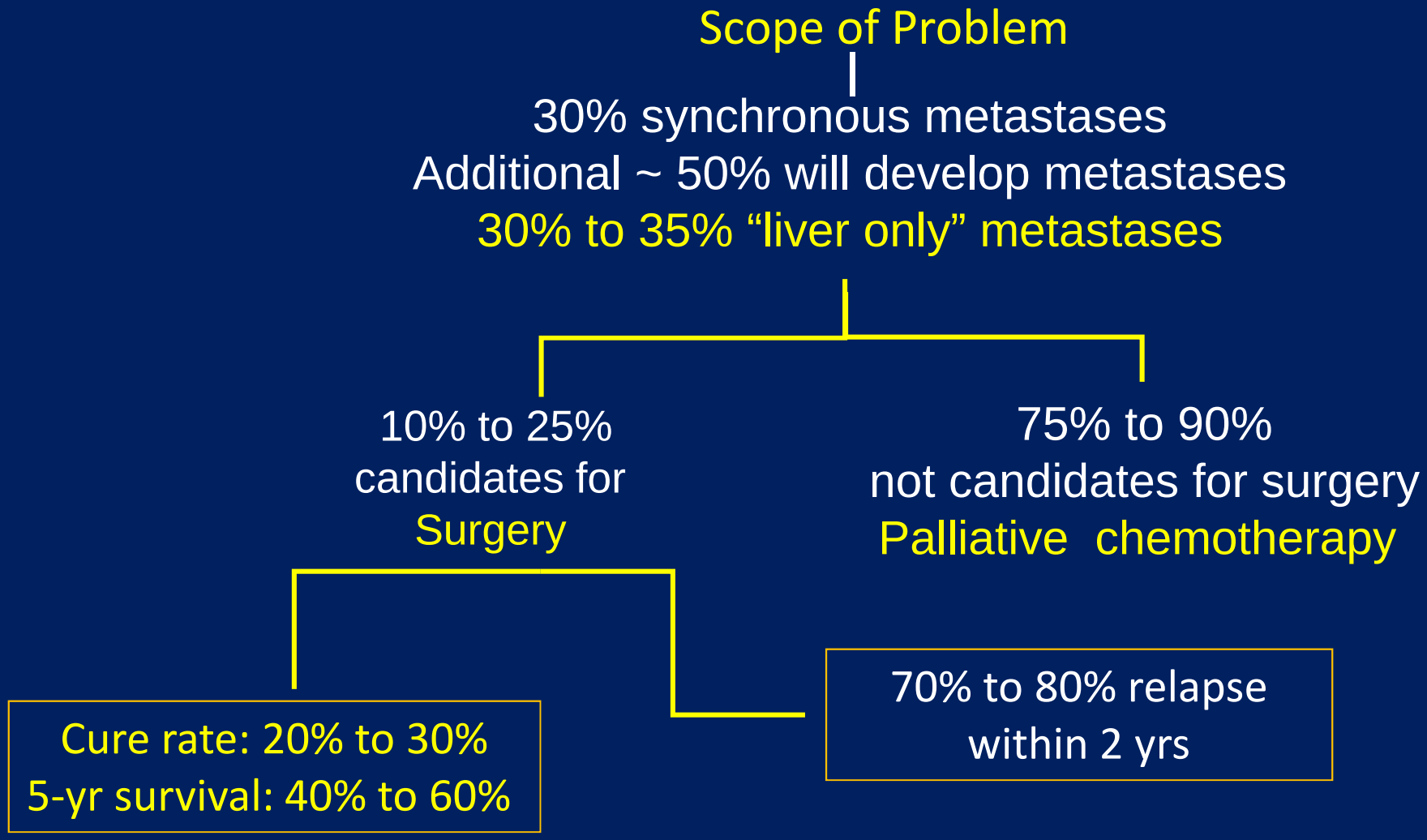
Patient Characteristics Drive Decision Making in mCRC Treatment

- Performance status
- Age
- Comorbid illnesses
- Extent of disease
- Intent of treatment: palliative vs potentially curative
- Previous adjuvant therapy within 1 yr
- Organ function: hepatic and renal
- Underlying/uncontrolled hypertension
- Bleeding risks/concerns

mCRC goal: increasing OS



Liver-Limited mCRC:



Conversion Therapy: Practical Issues

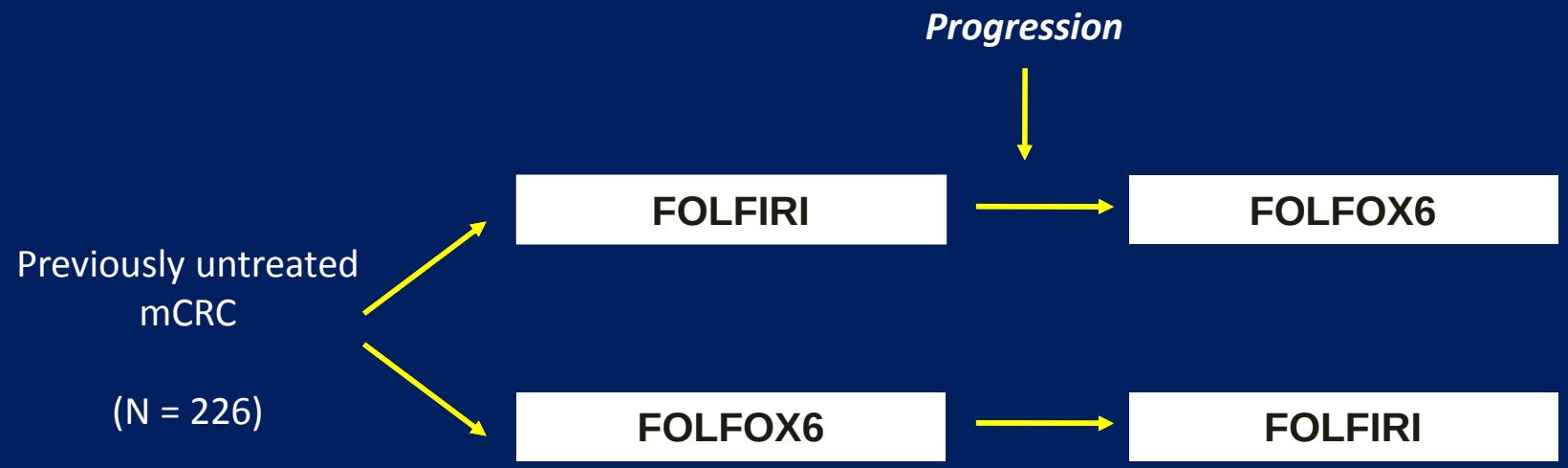
- FOLFOX or FOLFIRI
- FOLFOXIRI attractive but at expense of increased toxicity
- Limit duration of preoperative therapy to 3-4 mos
  - Treat to resectability and not to best response
  - Minimizes hepatotoxicity
- Role of biologics is evolving
  - Data with cetuximab appears to be most mature in wild-type *KRAS* CRC
  - Bevacizumab is an appropriate option in setting of mutant *KRAS*
    - If bevacizumab is used, discontinue 6-8 wks before planned surgery

Treatment-Associated Liver Toxicity

- 5-FU: steatosis
- Irinotecan: steatohepatitis
- Oxaliplatin: sinusoidal/vascular injury
- Bevacizumab
  - Potential wound healing complications
  - Need to wait 6-8 wks before surgical resection
- Cetuximab: no acute or chronic effects to date
- Incidence of postoperative complications increases with prolonged use

First-line FOLFOX and FOLFIRI Are Equivalent

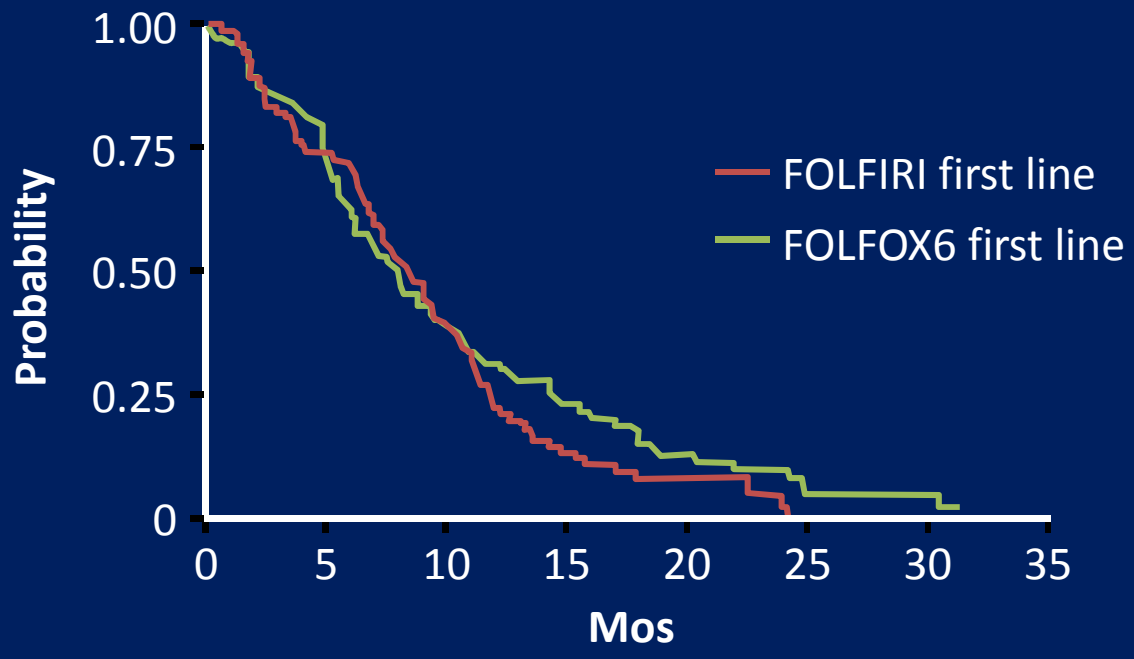
- Randomized phase III trial to determine which sequence is better (treatment switched at progression)



1. Tournigard C, et al. J Clin Oncol. 2004;22:229-237.

First-line FOLFOX and FOLFIRI Are Equivalent

- Median PFS after first-line therapy similar
  - 8.5 vs 8.0 mos for FOLFIRI vs FOLFOX6 (*P* = .26)



Tournigard C, et al. J Clin Oncol. 2004;22:229-237.

mCRC: Approved/Investigational Drugs

Classical Chemotherapeutics

- Oral/Intravenous Fluoropyrimidines
- Raltitrexed
- Irinotecan
- Oxaliplatin
- Mitomycin C

Anti-Angiogenesis

- Bevacizumab
- Ziv-Aflibercept
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Emerging Therapeutics

- TAS102
- Erlotinib/ Cetuximab
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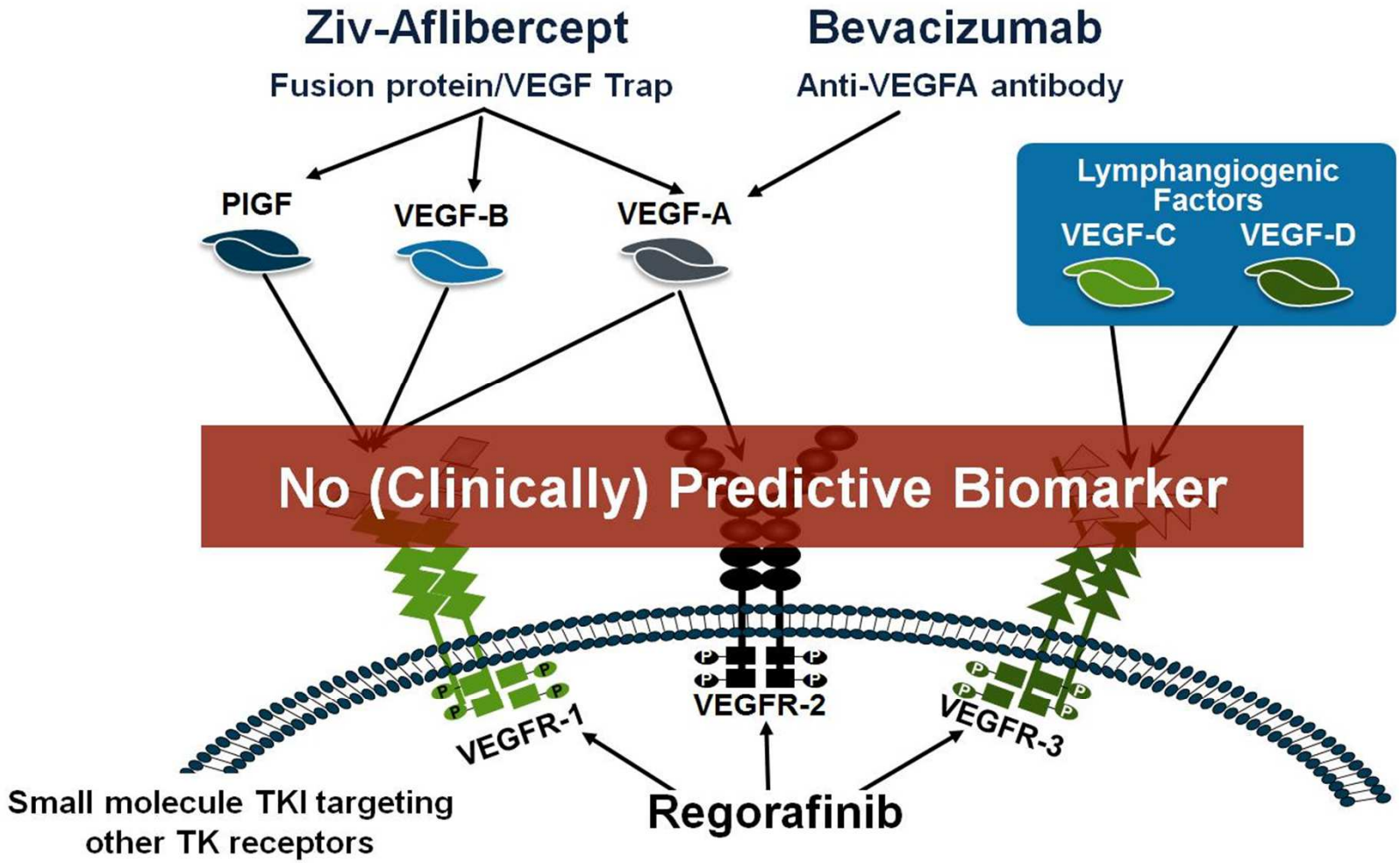
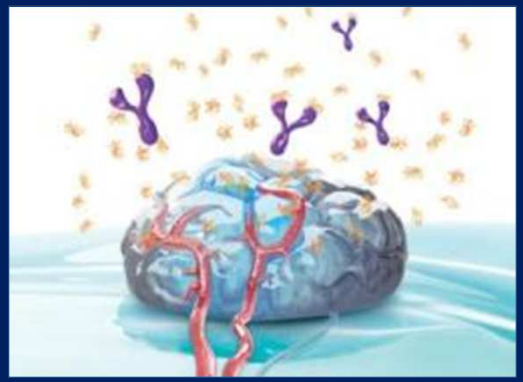
mCRC: Targeted Therapy — Anti-Angiogenic



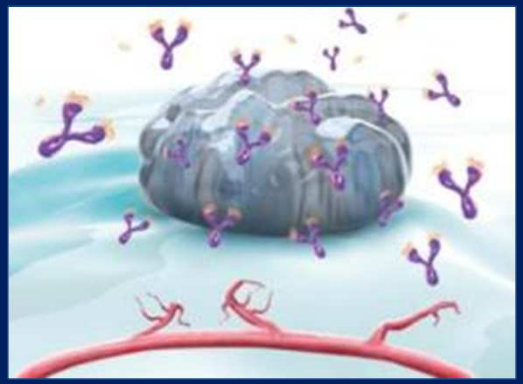
PIGF = placental growth factor; TK = tyrosine kinase; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

Figure adapted from: Fakih M. *Expert Rev Anticancer Ther*. 2013;13:427-438.[2]

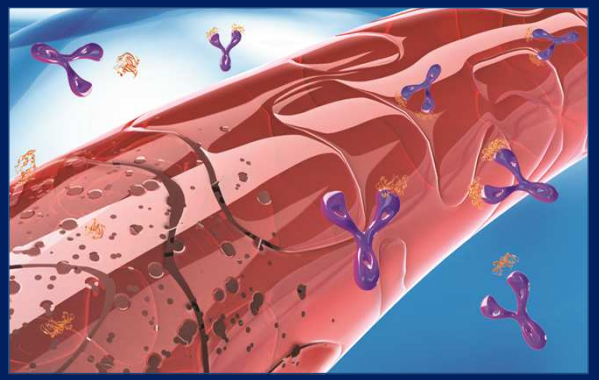
Mechanism of action of bevacizumab



Regression
of existing tumour vasculature[1–3]



Inhibition
of new vessel growth[1–3,8]



Anti-permeability
of surviving vasculature[11–13]

Early and continued effects result in:

- Maintenance of more functional, normal vasculature
- Potentially improved drug delivery
- Inhibition of tumour growth and metastasis[1–9]

1. Yuan Proc Natl Acad Sci U S A 1996; 2. Willett Nat Med 2004; 3. Lee Cancer Res 2000
4. Gerber & Ferrara. Cancer Res 2005; 5. Borgström Cancer Res 1996; 6. Borgström Prostate 1998
7. Jain. Nat Med 2001; 8. Jain. Science 2005; 9. Warren J Clin Invest 1995

Bevacizumab Associated Toxicity

Adverse Event	Incidence With Bev Across Indications,[1] %	Comments
Grade ≥ 3 ATE	2.6	▪ Risk of ATE increased in pts 65 yrs of age or older or with ATE history
Grade 3/4 HTN	5-18*	▪ Patients should receive otherwise standard CV prophylaxis and have BP monitored and managed
GI perforations	0.3-2.4	
Grade ≥ 3 hemorrhagic event	1.2-4.6†	▪ Bevacizumab not recommended for pts with serious hemorrhage or recent hemoptysis ▪ Risk of major bleeding does not appear to be increased in pts receiving full-dose anticoagulation tx without other risk factors
Wound complications	15‡	▪ Discontinue 4-8 wks before surgery, resume 6-8 wks postsurgery

*Predominantly grade 3.
†May apply more to NSCLC.
‡When surgery conducted during bevacizumab therapy.

- Potential for increased VTE risk controversial, increased risk noted in 1 study, but not in others[2,3]

1. Bevacizumab [package insert]. South San Francisco, CA: Genentech; 2011. 2. Nalluri SR, et al. JAMA. 2008;300;2277-2285. 3. Hurwitz H, et al. J Clin Oncol. 2011;29:1757-1764.

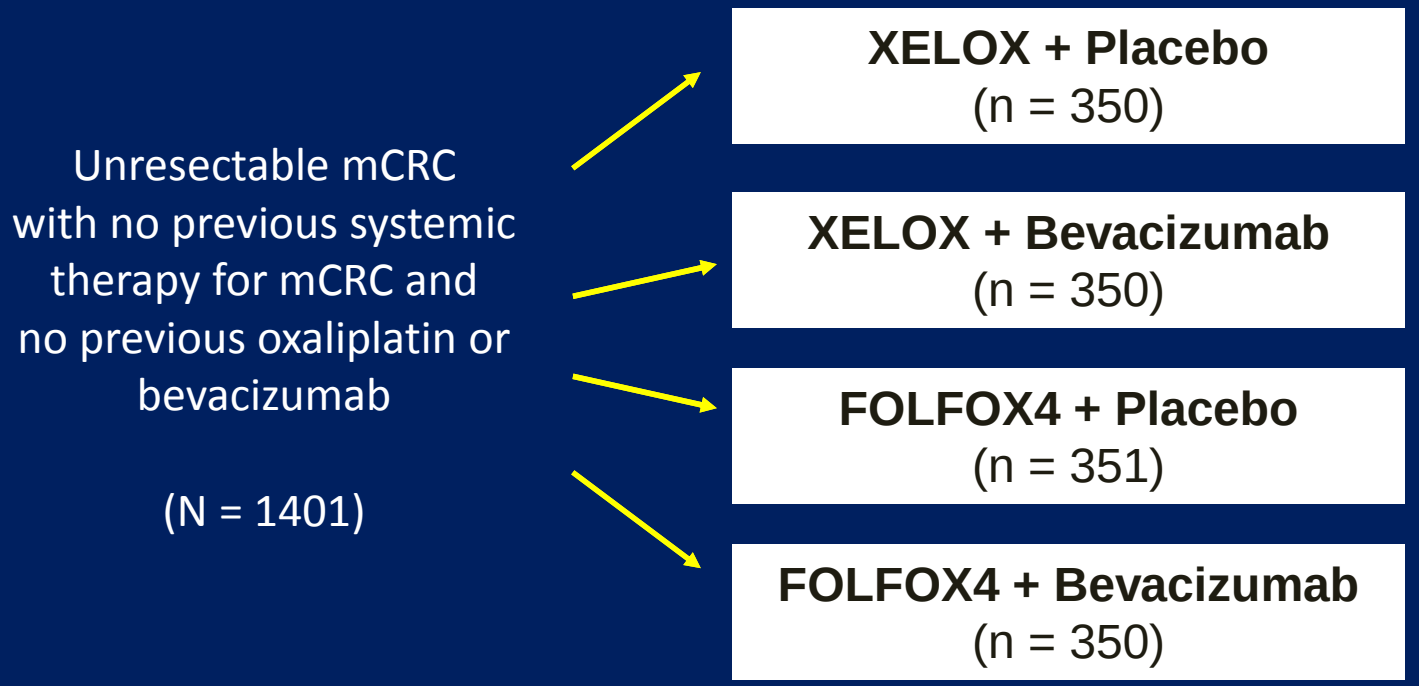
First-line Chemotherapy + Bevacizumab in mCRC: Efficacy

Comparative Regimens, Mos	PFS	OS
IFL/Bev vs IFL[1]	10.6 vs 6.2	20.3 vs 15.6
FOLFOX4/XELOX/Bev vs FOLFOX4/XELOX[2]	9.4 vs 8.0	21.3 vs 19.9

1. Hurwitz H, et al. N Engl J Med. 2004;350:2335-2342. 2. Saltz LB, et al. J Clin Oncol. 2008;26:2013-2019.

N016966: Study Design

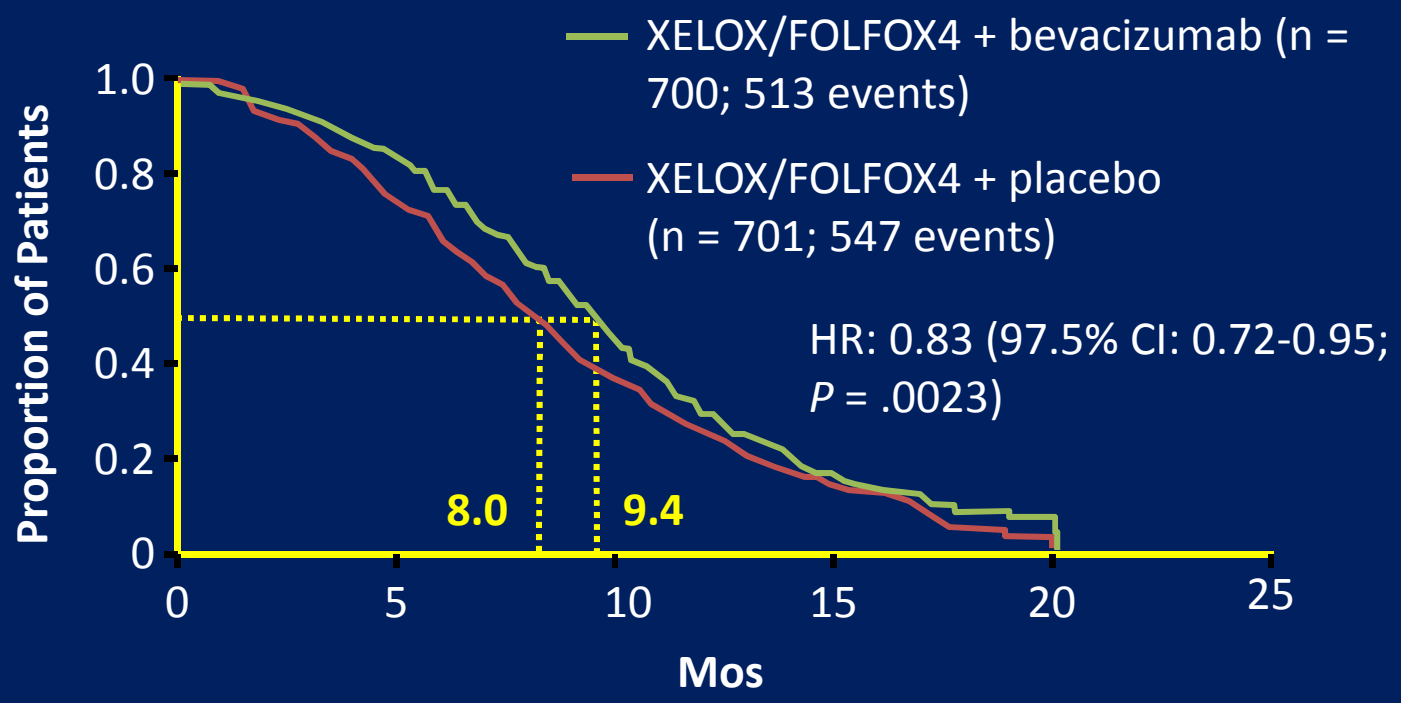
- Randomized phase III trial



1. Saltz LB, et al. J Clin Oncol. 2008;26:2013-2019.

N016966: Efficacy Results

- PFS significantly increased with addition of bevacizumab to chemotherapy



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Phase III VELOUR Study: FOLFIRI ± ziv-Aflibercept as Second-line Therapy in mCRC

Stratified by previous bevacizumab (yes vs no), ECOG PS (0 vs 1 vs 2)

Patients with mCRC progressing on first-line oxaliplatin-based chemotherapy* (N = 1226)

FOLFIRI + ziv-Aflibercept 4 mg/kg q2w
(n = 612)

FOLFIRI + Placebo q2w
(n = 614)

**30% had previous bevacizumab*

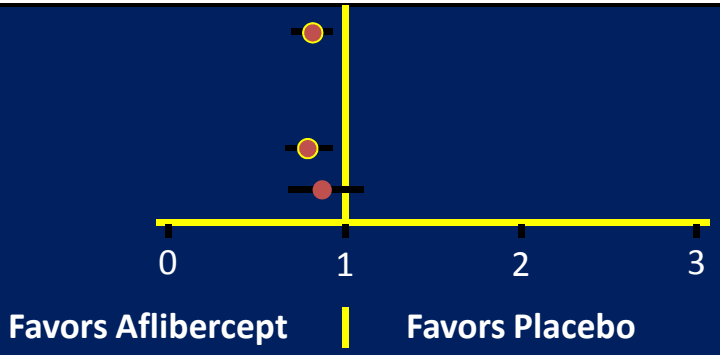
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety, immunogenicity

Van Cutsem E, et al. J Clin Oncol. 2012;30:3499-3506. ClinicalTrials.gov. NCT00561470.

VELOUR: OS and PFS Stratified by Previous Bevacizumab

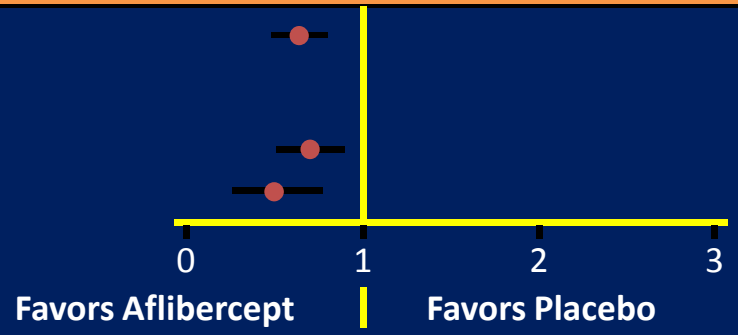
OS

Strata (as per IVRS)	N	HR (95.34% CI)	HR	Interaction *P* Value
All patients	1226	0.82 (0.713-0.937)		
Previous Bev				
No	853	0.79 (0.669-0.927)		
Yes	373	0.86 (0.673-1.104)		



PFS

Strata (as per IVRS)	N	HR (95% CI)	HR	Interaction *P* Value
All patients	1226	0.76 (0.661-0.869)		
Previous Bev				
No	853	0.80 (0.679-0.936)		
Yes	373	0.66 (0.512-0.852)		



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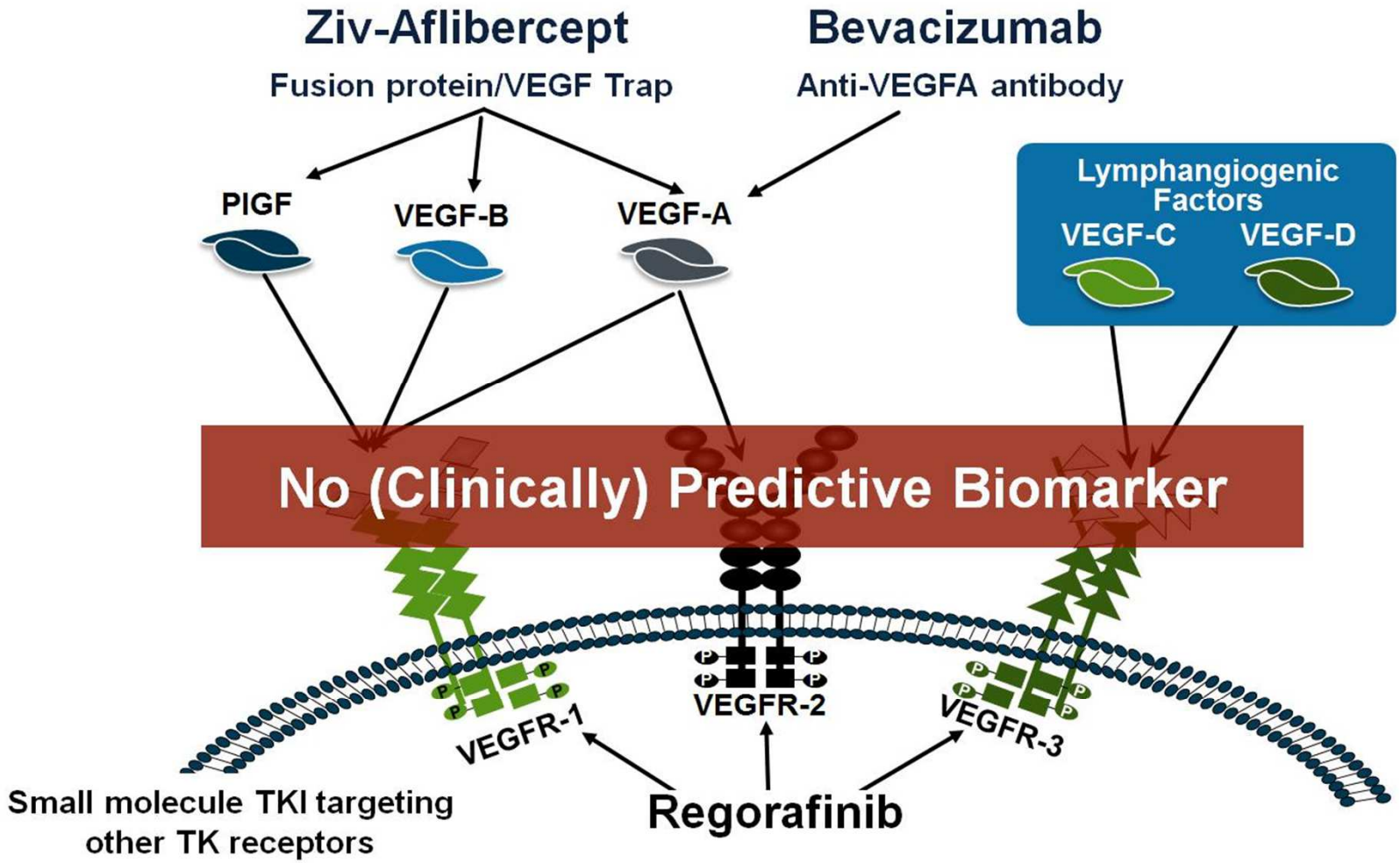

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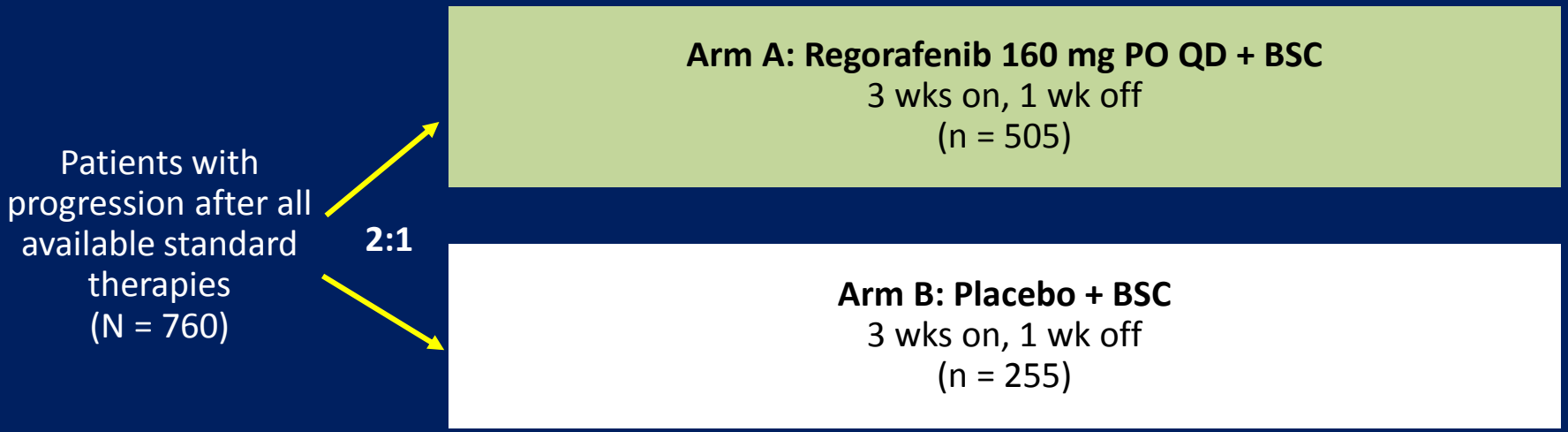
Figure adapted from: Fakih M. *Expert Rev Anticancer Ther*. 2013;13:427-438.[2]

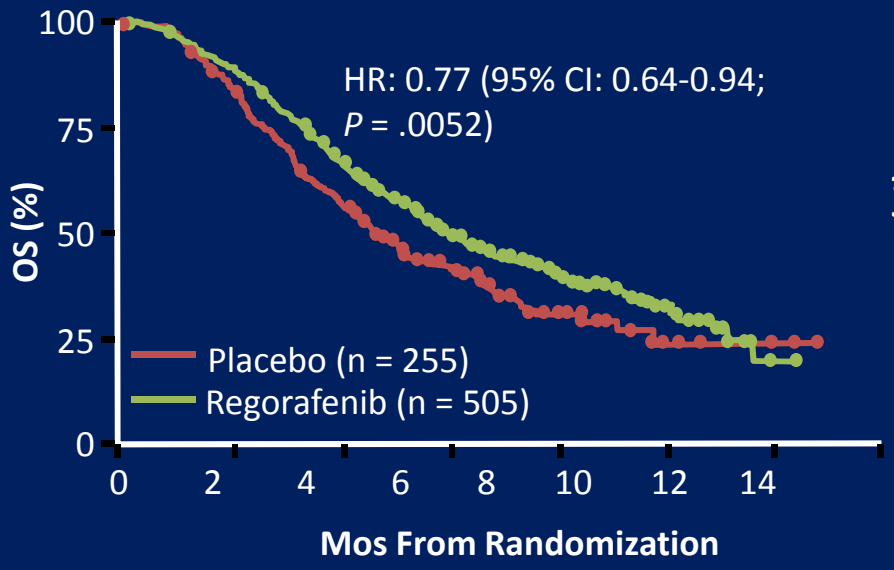
CORRECT: Regorafenib After Progression on All Available Std Therapies in mCRC

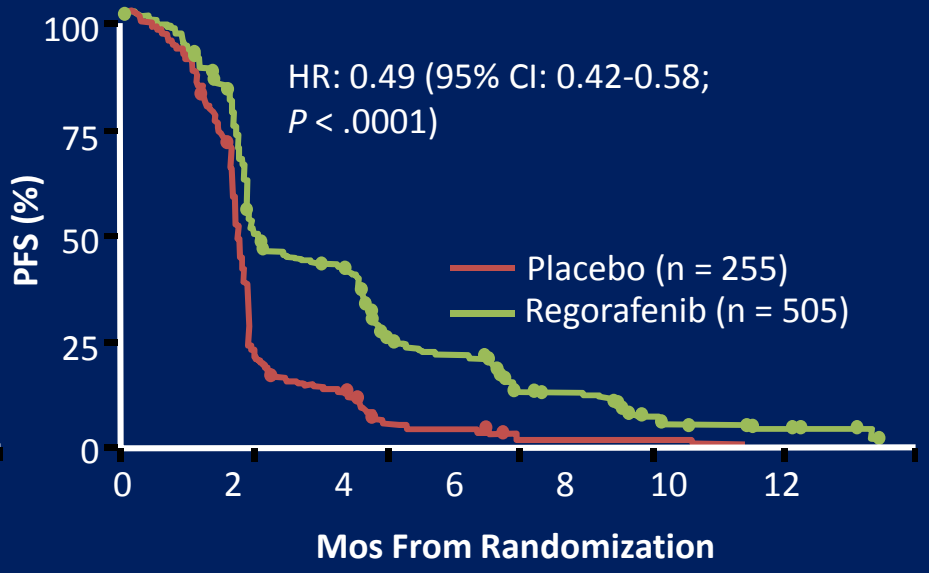


- Primary endpoint: OS
- ~ 50% of patients with ≥ 4 systemic therapies
  - All patients had received bevacizumab

Grothey A, et al. Lancet. 2013;381:303-312.

CORRECT: Regorafenib After Progression on All Available Std Therapies in mCRC





	Regorafenib	Placebo
Median OS, mos	6.4	5.0
IQR	3.6-11.8	2.8-10.4

	Regorafenib	Placebo
Median PFS, mos	1.9	1.7
IQR	1.6-3.9	1.4-1.9

Primary endpoint met prespecified stopping criteria at second interim analysis
(1-sided $P \leq .009279$ at ~ 74% of events required for final analysis)

Grothey A, et al. Lancet. 2013;381:303-312.

CORRECT: Adverse Events Occurring in ≥ 10% of Patients

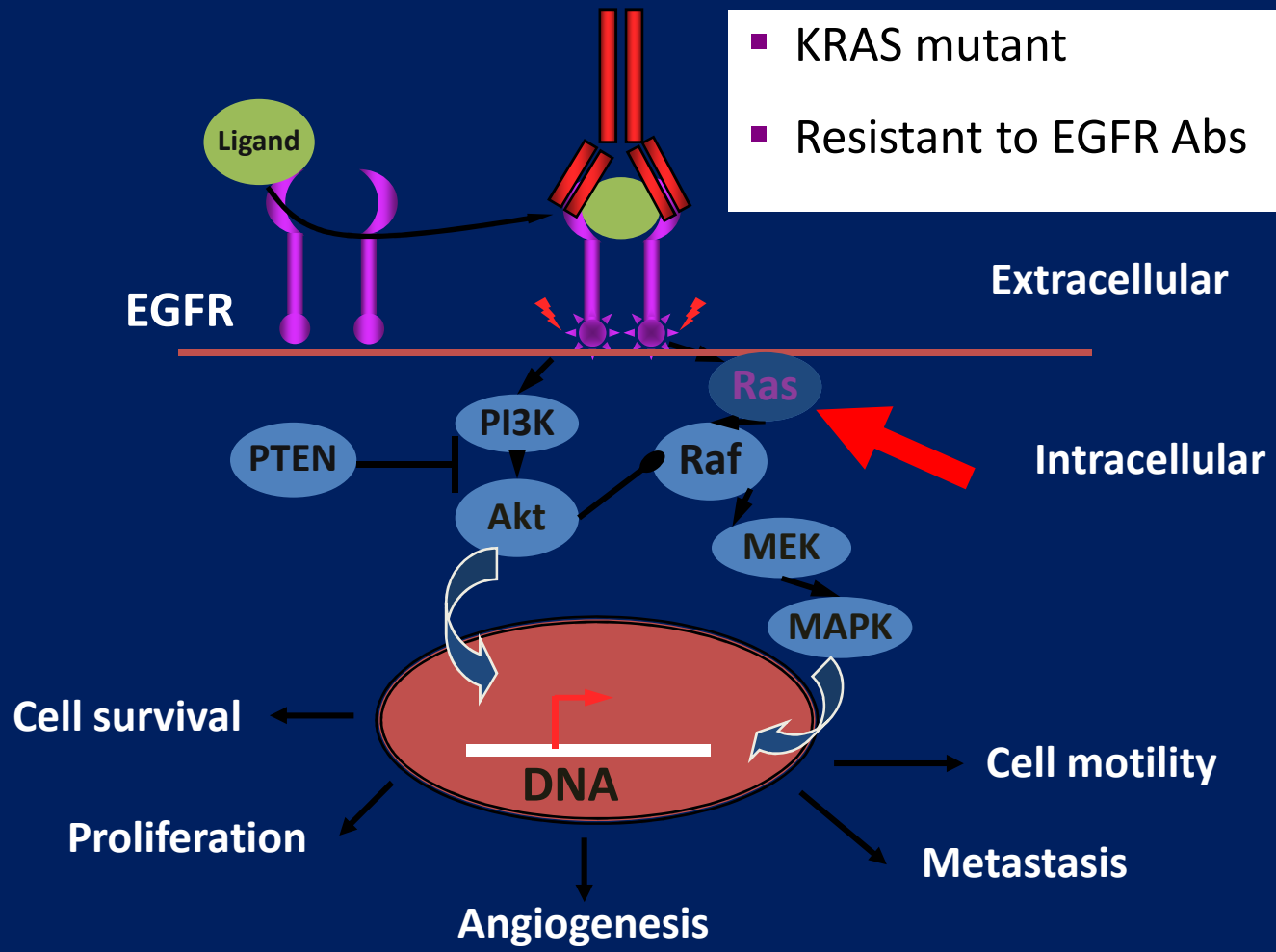
Adverse Event	Regorafenib (n = 500)			Placebo (n = 253)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hand–foot skin reaction	47	17	0	8	< 1	0
Fatigue	47	9	< 1	28	5	< 1
Hypertension	28	7	0	6	1	0
Diarrhea	34	7	< 1	8	1	0
Rash/desquamation	26	6	0	4	0	0
Anorexia	30	3	0	15	3	0
Oral mucositis	27	3	0	4	0	0
Thrombocytopenia	13	3	< 1	2	< 1	0
Fever	10	1	0	3	0	0
Nausea	14	< 1	0	11	0	0

Dose modification due to adverse event in 67% of patients receiving regorafenib vs 23% of patients receiving placebo

Grothey A, et al. Lancet. 2013;381:303-312.

EGFR in CRC

- KRAS mutant
- Resistant to EGFR Abs



EGFR-Targeted Agents as First-line Therapy in KRAS WT mCRC: Efficacy

Trial	Comparative Regimens	Median PFS, Mos	Median OS, Mos
CRYSTAL[1]	FOLFIRI/Cetux vs FOLFIRI	9.9 vs 8.4	23.5 vs 20.0
PRIME[2-4]	FOLFOX4/Pmab vs FOLFOX4	9.6 vs 8.0	23.8 vs 19.4
	FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)	10.1 vs 7.9	26.0 vs 20.2
COIN[5]	FOLFOX/XELOX/Cetux vs FOLFOX/XELOX	8.6 vs 8.6	17.0 vs 17.9

- Worse PFS outcome with panitumumab + FOLFOX4 in mutant KRAS disease[3]

1. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019. 2. Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705. 3. Douillard JY, et al. ASCO 2013. Abstract 3620. 4. Douillard JY, et al. N Engl J Med. 2013;369:1023-1034. 5. Maughan TS, et al. Lancet. 2011;377:2103-2114.

KRAS Status in Response to Cetuximab

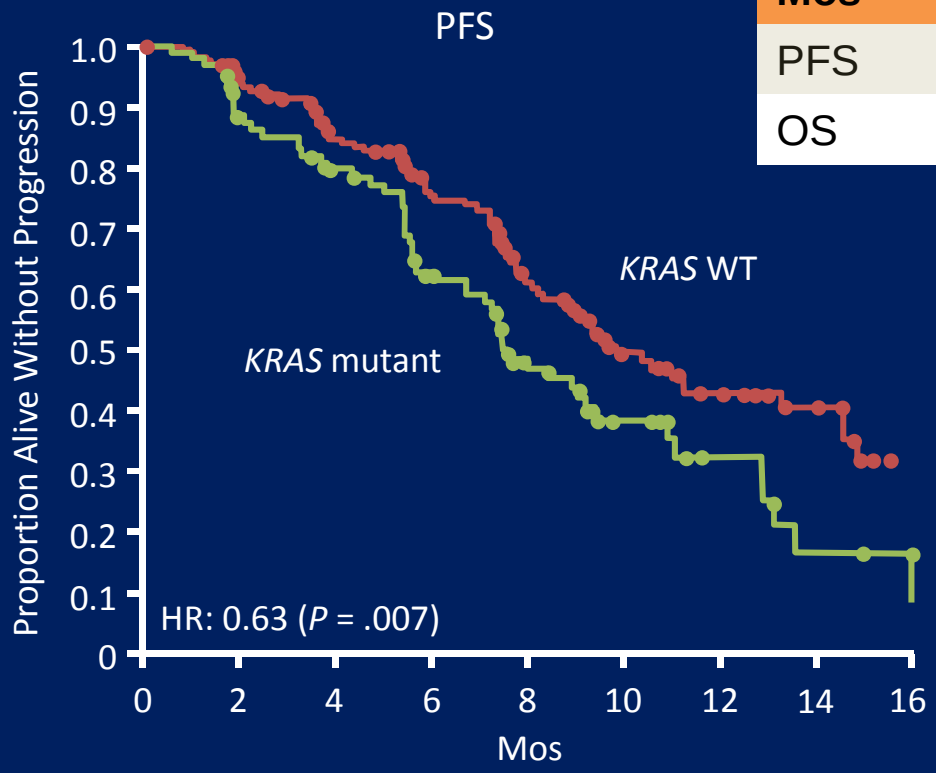
- Retrospective analysis of CRYSTAL[1]
  - PFS and ORR benefit of FOLFIRI + cetuximab only observed in mCRC patients with wild-type *KRAS*

Outcome	Wild-Type *KRAS* (n = 348)	Mutated *KRAS* (n = 192)
Median PFS, mos		
▪ FOLFIRI + cetuximab	9.9	7.6
▪ FOLFIRI	8.7	8.1
▪ HR	0.68*	1.07†
ORR, %		
▪ FOLFIRI + cetuximab	59.3‡	36.2
▪ FOLFIRI	43.2	40.2

*P = .017; †P = .75; ‡P = .0025

1. Van Cutsem E, et al. ASCO 2008. Abstract 2.

Phase III CRYSTAL Study of Cetuximab + FOLFIRI in mCRC: *KRAS* Update and OS



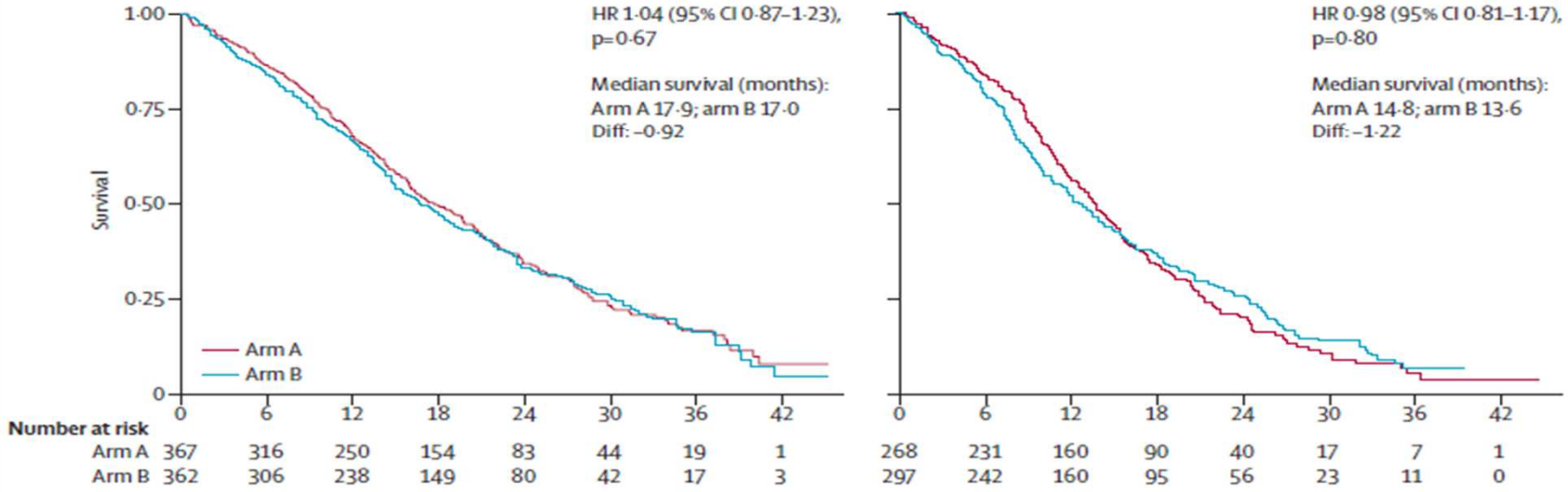
Median Survival, Mos	*KRAS* WT (n = 172)	*KRAS* Mutant (n = 105)	HR	*P* Value
PFS	9.9	8.4	0.70	.0012
OS	23.5	20.0	0.80	.0093

OS: 20% reduction in risk of death with WT vs mutant *KRAS*

Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019.

Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial

Timothy S Maughan, Richard A Adams, Christopher G Smith, Angela M Meade, Matthew T Seymour, Richard H Wilson, Shelley Idziaszczyk, Rebecca Harris, David Fisher, Sarah L Kenny, Edward Kay, Jenna K Mitchell, Ayman Madi, Bharat Jasani, Michelle D James, John Bridgewater, M John Kennedy, Bart Claes, Diether Lambrechts, Richard Kaplan, Jeremy P Cheadle, on behalf of the MRC COIN Trial Investigators

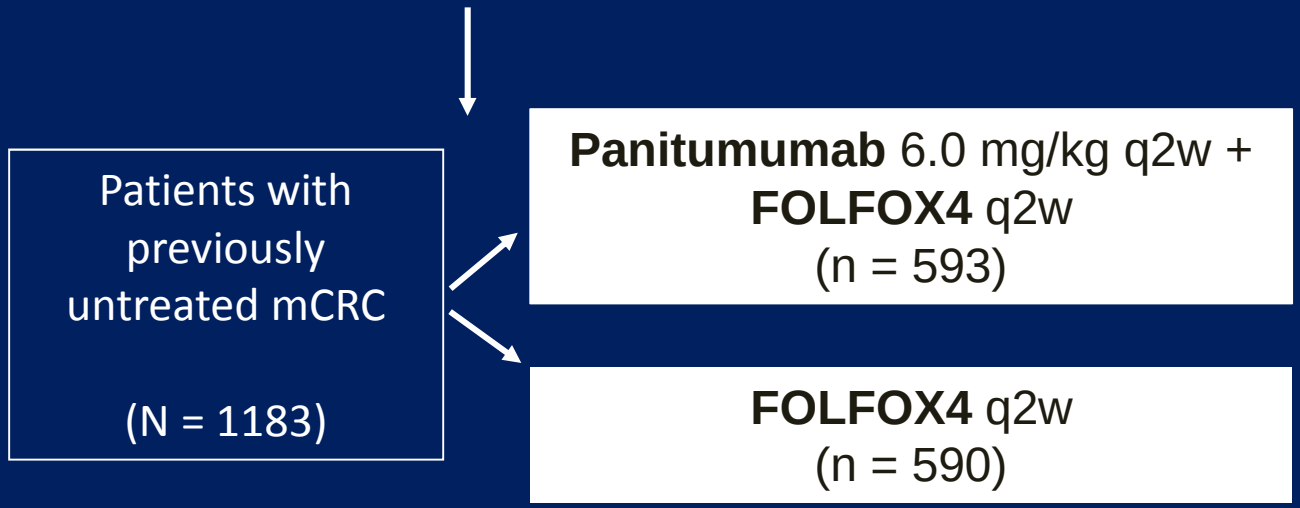


Lancet 2011; 377: 2103–14

PRIME Study: *KRAS* Status in Response to Panitumumab

- Randomized, global, open-label, phase III trial

Stratified by ECOG PS (0-1 vs 2) and geographic region (Western Europe, Canada, and Australia vs all other locations)



Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705.

PRIME Study: Efficacy Results

- PFS significantly improved with FOLFOX4 + panitumumab only in wild-type *KRAS* patients
- Worse PFS outcome with panitumumab addition in mutated *KRAS* patients

PRIME	**FOLFOX4/Pmab vs FOLFOX4**	**9.6 vs 8.0**	**23.8 vs 19.4**
	FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)	10.1 vs 7.9	26.0 vs 20.2

Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705.

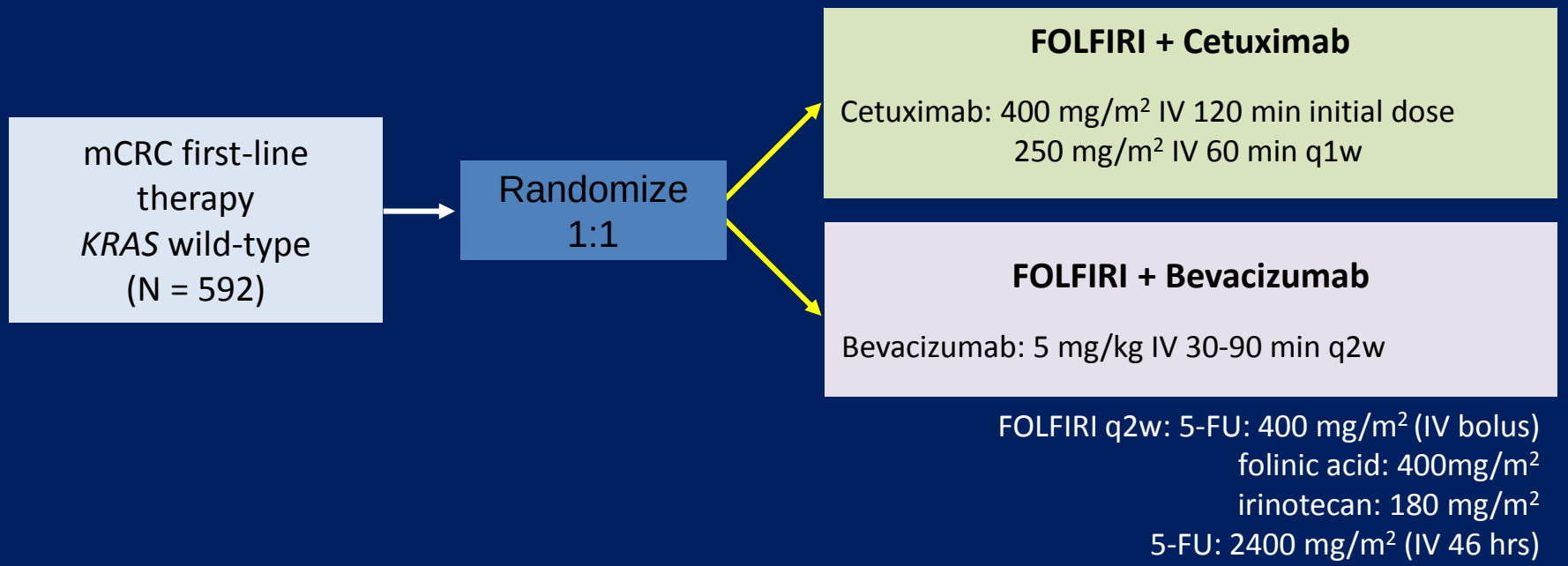
KRAS Testing: What Are the Recommendations?

- NCCN guidelines[1]
  - Strongly recommends *KRAS* testing in all patients with mCRC at the time of diagnosis of metastatic disease
  - Testing should be performed in a CLIA-certified lab
  - Testing can be performed on either primary or metastatic tissue
- ASCO Provisional Clinical Opinion[2]
  - All patients with mCRC who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a CLIA-accredited laboratory
- In both cases, anti-EGFR agents (cetuximab and panitumumab) are recommended for wild-type *KRAS* patients only[1,2]

1. NCCN. Clinical practice guidelines in oncology: colon cancer. 2011.
2. Allegra CJ, et al. J Clin Oncol. 2009;27:2091-2096.

EGFR Blocker or VEGF blocker in KRAS wild type?

Phase III FIRE-3 Trial: First-line FOLFIRI + Either Cetux or Bev in *KRAS* WT mCRC

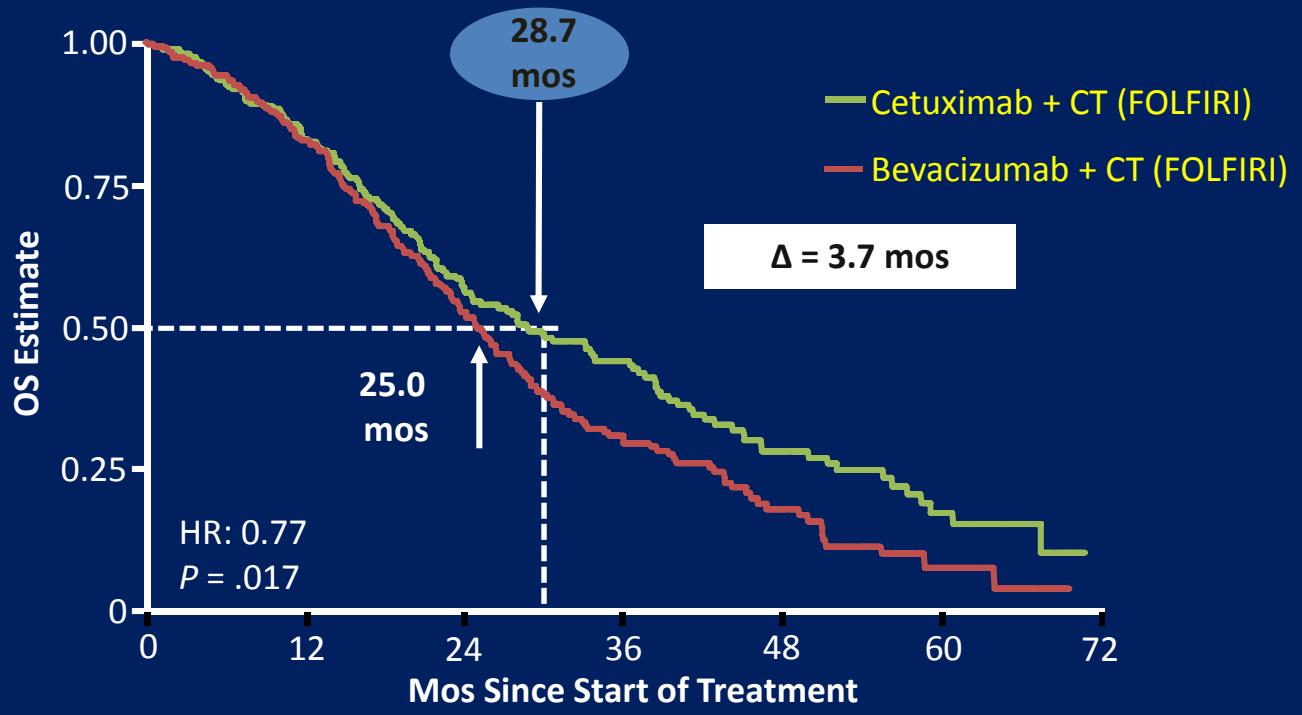


FOLFIRI q2w: 5-FU: 400 mg/m² (IV bolus)
folinic acid: 400mg/m²
irinotecan: 180 mg/m²
5-FU: 2400 mg/m² (IV 46 hrs)

- Primary endpoint: ORR (mRECIST 1.0)
- Amendment in October 2008 to include only *KRAS* WT (ex 12/13) pts
- 150 active centers in Germany and Austria

Heinemann V, et al. ASCO 2013. Abstract LBA3506.

FIRE-3 Trial of First-line FOLFIRI + Either Cetux or Bev in *KRAS* WT mCRC: OS



	Cetuximab + CT	Bevacizumab + CT	*P* Value
ORR, % **(primary endpoint not met)**	62	58	.183
PFS, mos	10.0	10.3	.547

Heinemann V, et al. ASCO 2013. Abstract LBA3506.

Phase III 80405 Trial: First-line CT + Either Cetux or Bev in *KRAS*-WT mCRC

Patients with mCRC and *KRAS* WT (codons 12, 13), ECOG PS 0/1 (N = 1137)

FOLFOX or FOLFIRI + Bevacizumab q2w
(n = 559)

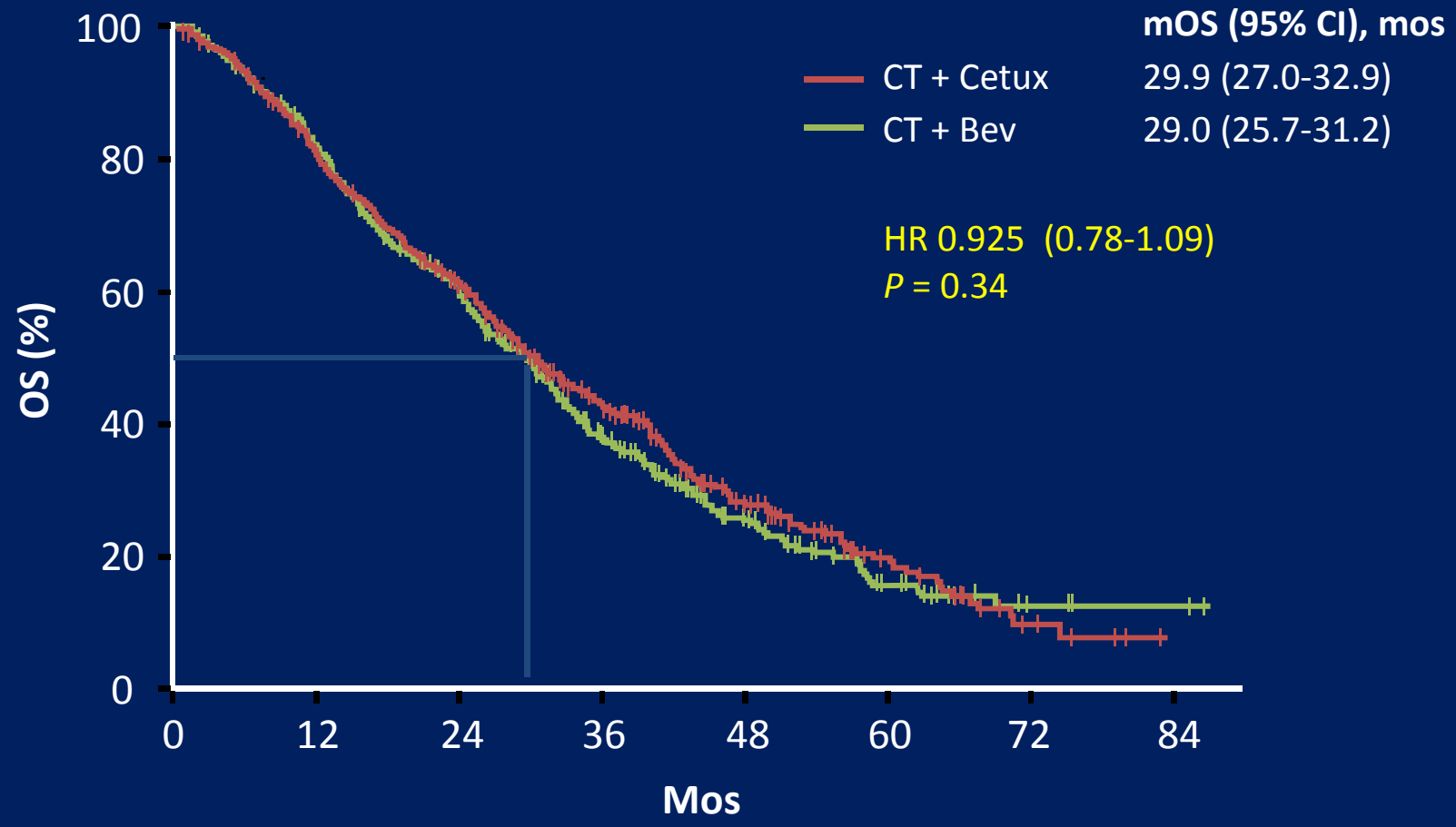
FOLFOX or FOLFIRI + Cetuximab q1w
(N = 578)

A third arm with CT + bevacizumab + cetuximab was closed to accrual in September 2009

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, TTF, duration of response

ClinicalTrials.gov. NCT00265850. Venook AP, et al. ASCO 2014. LBA3..

CALGB/SWOG 80405: OS in the ITT Population

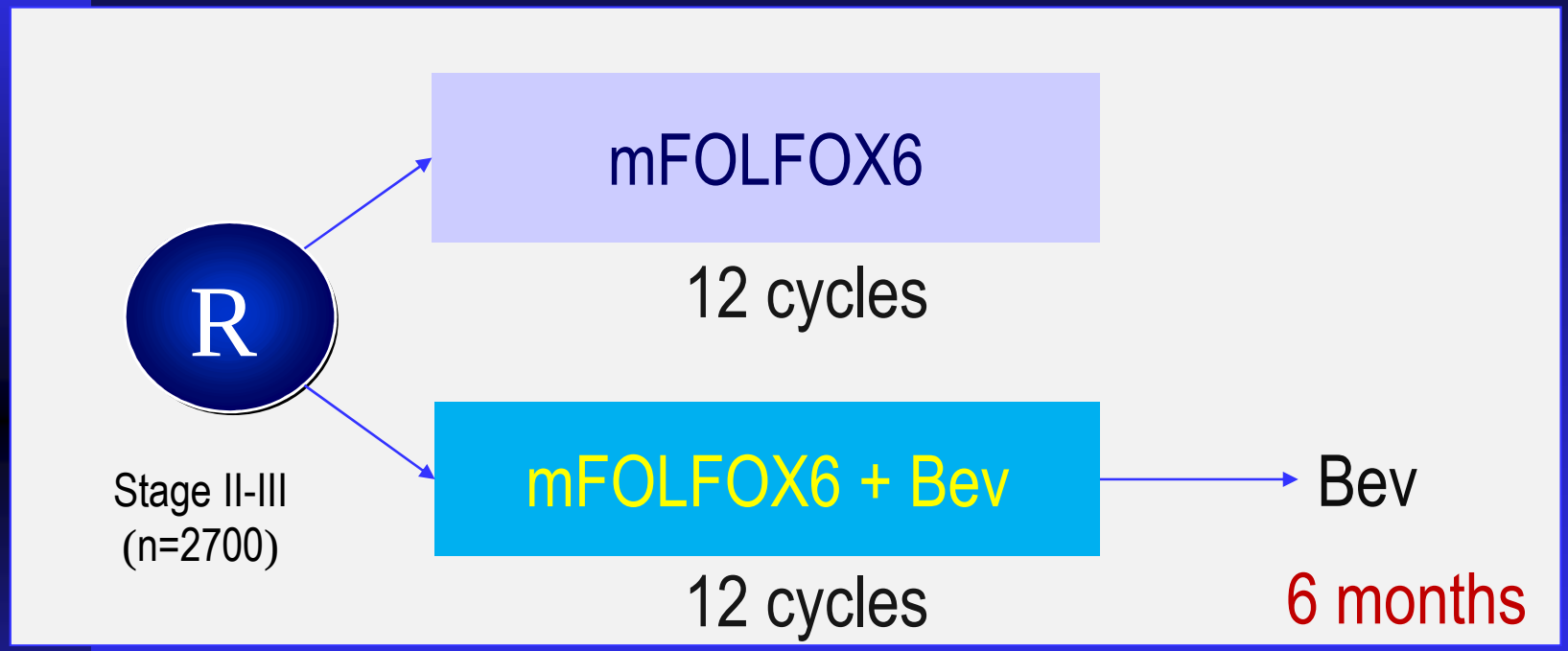


Venook AP, et al. ASCO 2014. Abstract LBA3.

Targeted agents

Any role in the Adjuvant treatment?

NSABP C08



1st endpoint: disease-free survival (DFS)

Closed october 2006

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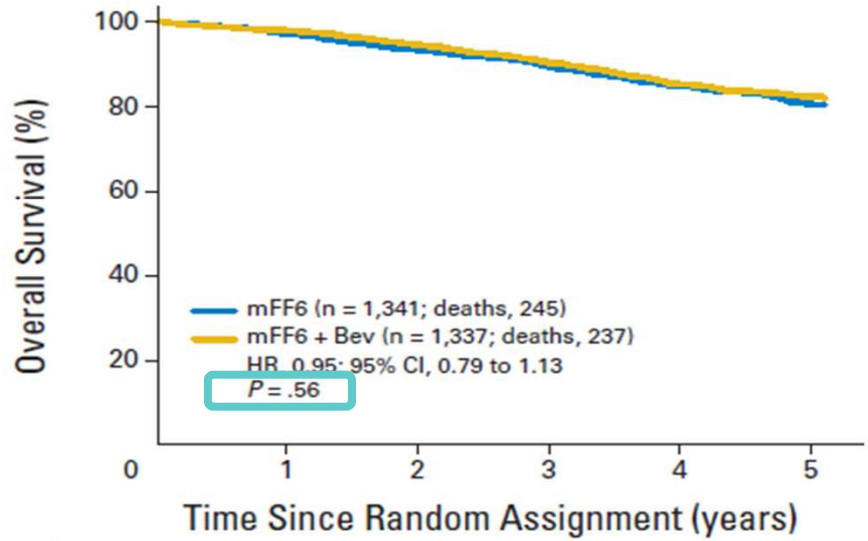
JOURNAL OF CLINICAL ONCOLOGY

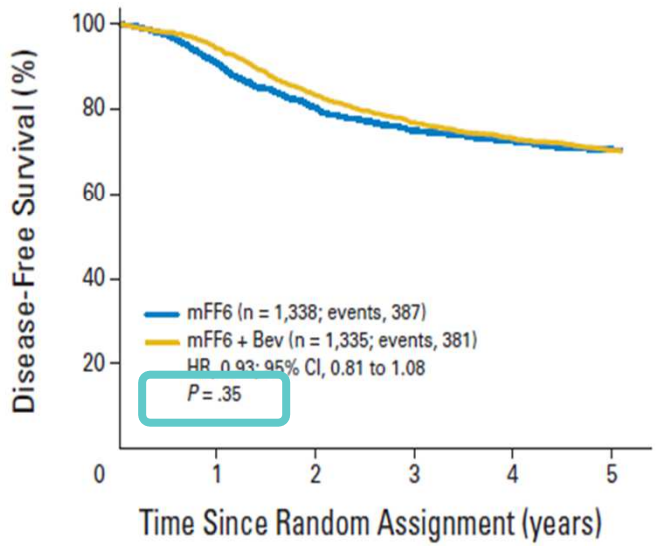
ORIGINAL REPORT

Bevacizumab in Stage II-III Colon Cancer: 5-Year Update of the National Surgical Adjuvant Breast and Bowel Project C-08 Trial

Carmen J. Allegra, Greg Yothers, Michael J. O'Connell, Saima Sharif, Nicholas J. Petrelli, Samia H. Lopa, and Norman Wolmark

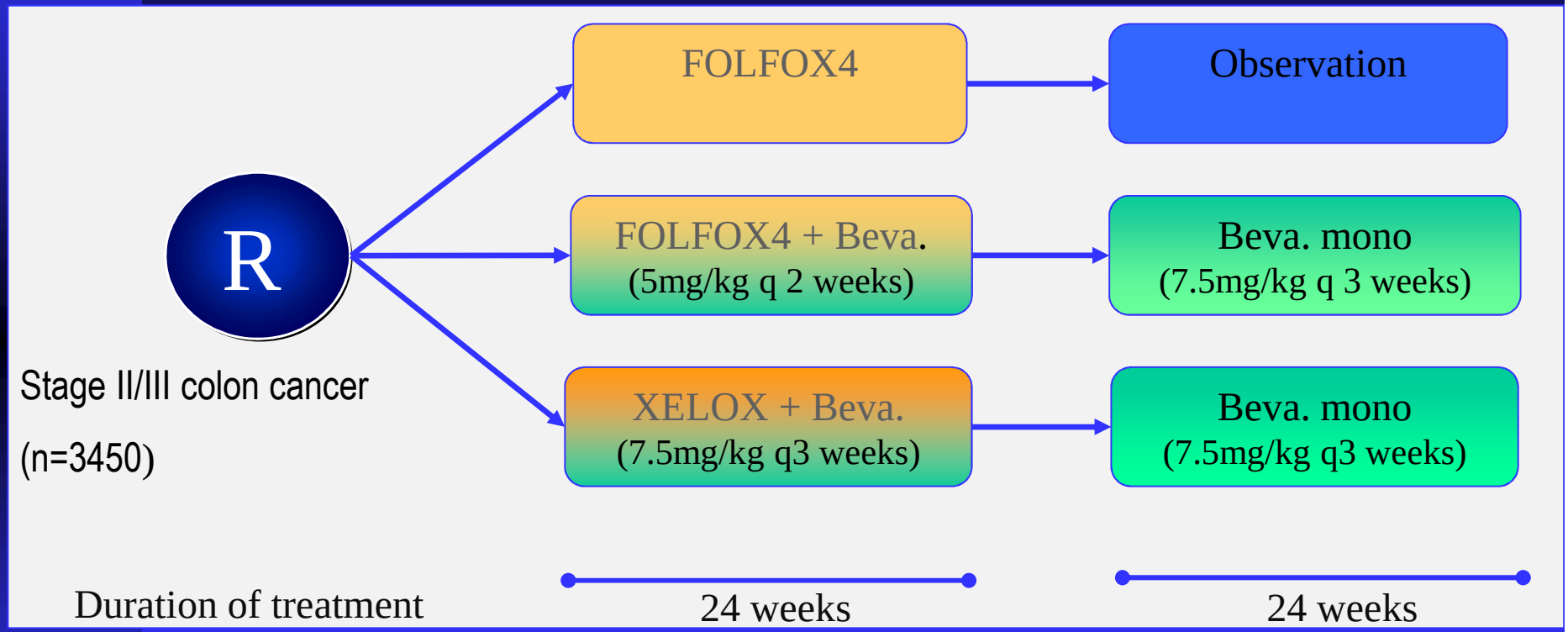


No. at risk						
mFF6	1,341	1,269	1,206	1,139	1,051	466
mFF6 + Bev	1,337	1,289	1,233	1,164	1,077	502



No. at risk						
mFF6	1,338	1,181	1,036	954	894	894
mFF6 + Bev	1,335	1,240	1,086	990	922	427

AVANT BO17920 study



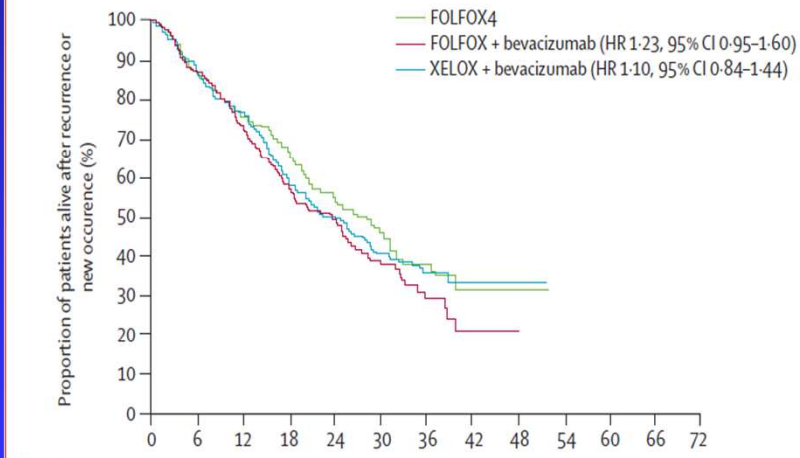
Closed June 2007

Primary endpoint: disease-free survival

Secondary endpoints: safety, overall survival, pharmacoeconomics, pharmacodynamics, convenience and satisfaction with chemotherapy

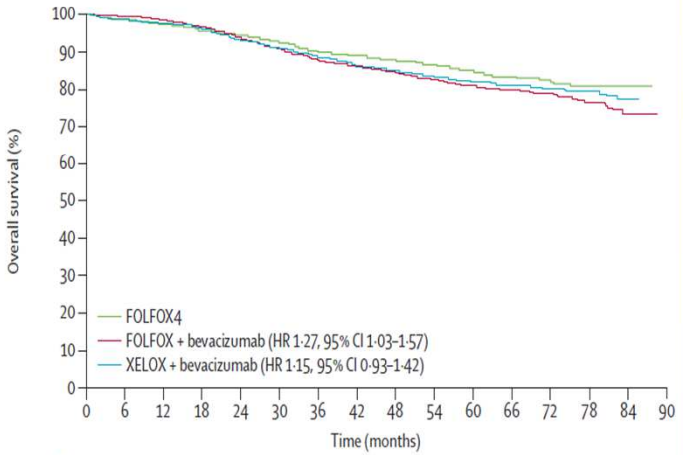
Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial

Aimery de Gramont, Eric Van Cutsem, Hans-Joachim Schmoll, Josep Tabernero, Stephen Clarke, Malcolm J Moore, David Cunningham, Thomas H Cartwright, J Randolph Hecht, Fernando Rivera, Seock-Ah Im, György Bodoky, Ramon Salazar, Frédérique Maindrault-Goebel, Einat Shacham-Shmueli, Emilio Bajetta, Martina Makrutzki, Aijing Shang, Thierry André, Paulo M Hoff



Number at risk

FOLFOX4	220	178	135	111	65	34	16	7	2	0	0	0	0
FOLFOX4 + Bev	259	209	158	104	65	39	16	4	1	0	0	0	0
XELOX + Bev	228	193	158	110	79	47	26	8	2	0	0	0	0

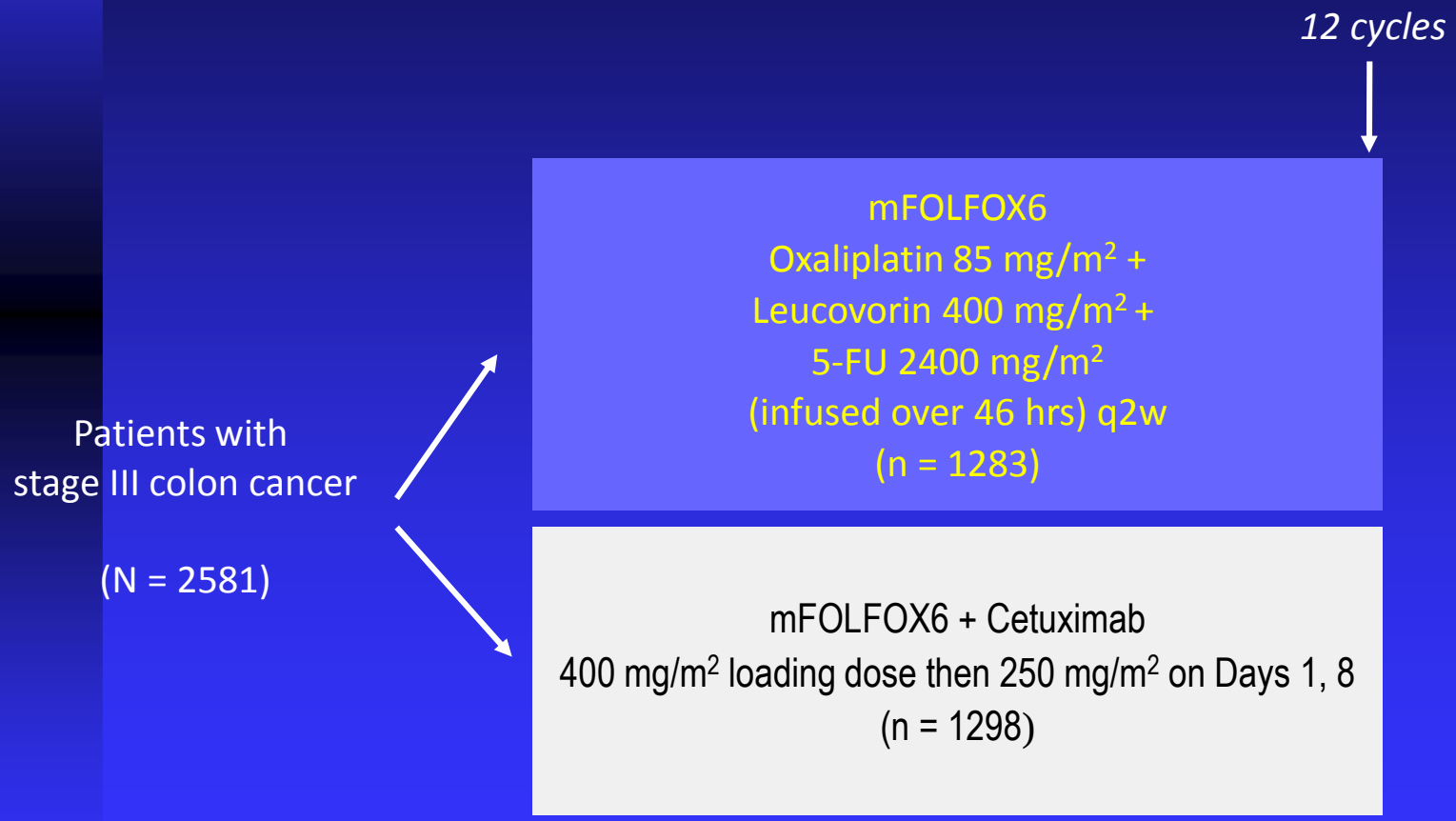


Number at risk

FOLFOX4	955	915	901	885	865	846	819	806	790	765	688	509	408	287	64	0
FOLFOX4 + Bev	960	942	925	901	870	837	810	792	769	731	676	491	394	248	53	0
XELOX + Bev	952	920	908	894	862	841	812	779	759	739	685	490	396	270	56	0

Lancet Oncol 2012; 13: 1225–33

N0147: Adjuvant mFOLFOX ± Cetuximab in Resected Stage III Colon Cancer



Goldberg RM, et al. ASCO 2010. Abstract 3508.

Trend Toward Improved DFS, OS With mFOLFOX6 vs mFOLFOX6 + Cetuximab

Outcome	Wild-Type *KRAS*		Mutant *KRAS*	
	mFOLFOX6 (n = 902)	**mFOLFOX6 + Cetuximab (n = 945)**	**mFOLFOX6 (n = 374)**	**mFOLFOX6 + Cetuximab (n = 343)**
3-yr DFS, %	75.8	72.3	67.2	64.2
▪ HR (95% CI)	1.2 (0.96-1.5)		1.2 (0.9-1.6)	
▪ *P* value	.22		.13	
3-yr OS, %	87.8	83.9	88.0	80.4
▪ HR (95% CI)	1.3 (0.96-1.8)		1.5 (0.9-2.3)	
▪ *P* value	.13		.12	

JAMA. 2012;307(13):1383-1393

Conclusions

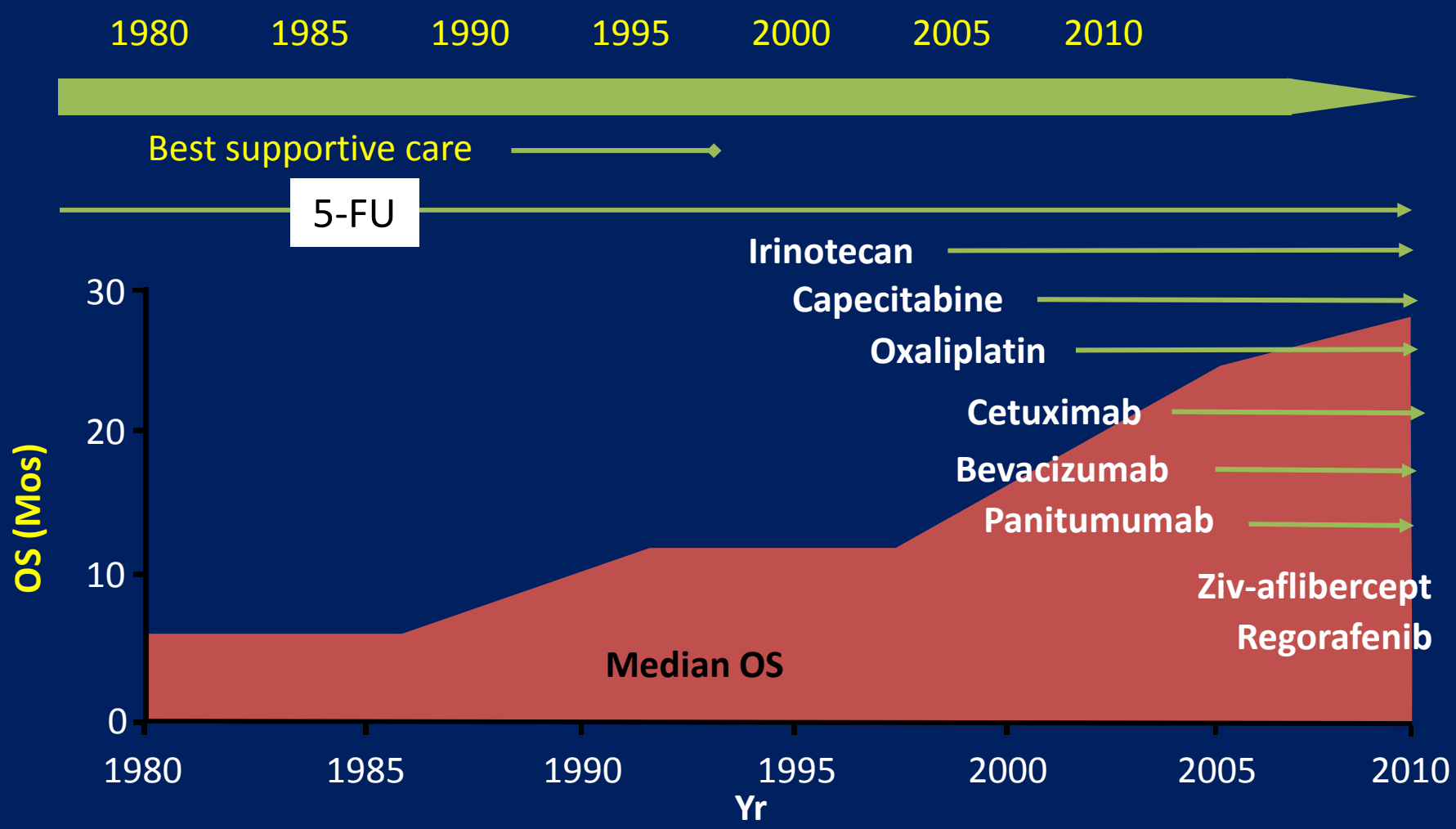
- Primary goal of CRC- increase OS
- Liver is the most common site of relapse
- Only surgery can cure stage IV disease
- Chemo therapy increased survival
- FOLFOX and FOLFIRI is equivalent

Conclusions- targeted therapy

- No role in the adjuvant setting
- No biomarker testing needed for bev
- EGFR should be given only in KRAS wild type
- Bev , cetuximab , panitumab- 1st line data
- Efficacy is minimal - weigh risk and benefit
- Aflibercept – only as second line
- Regorafenib- 3rd line or beyond

Thank you

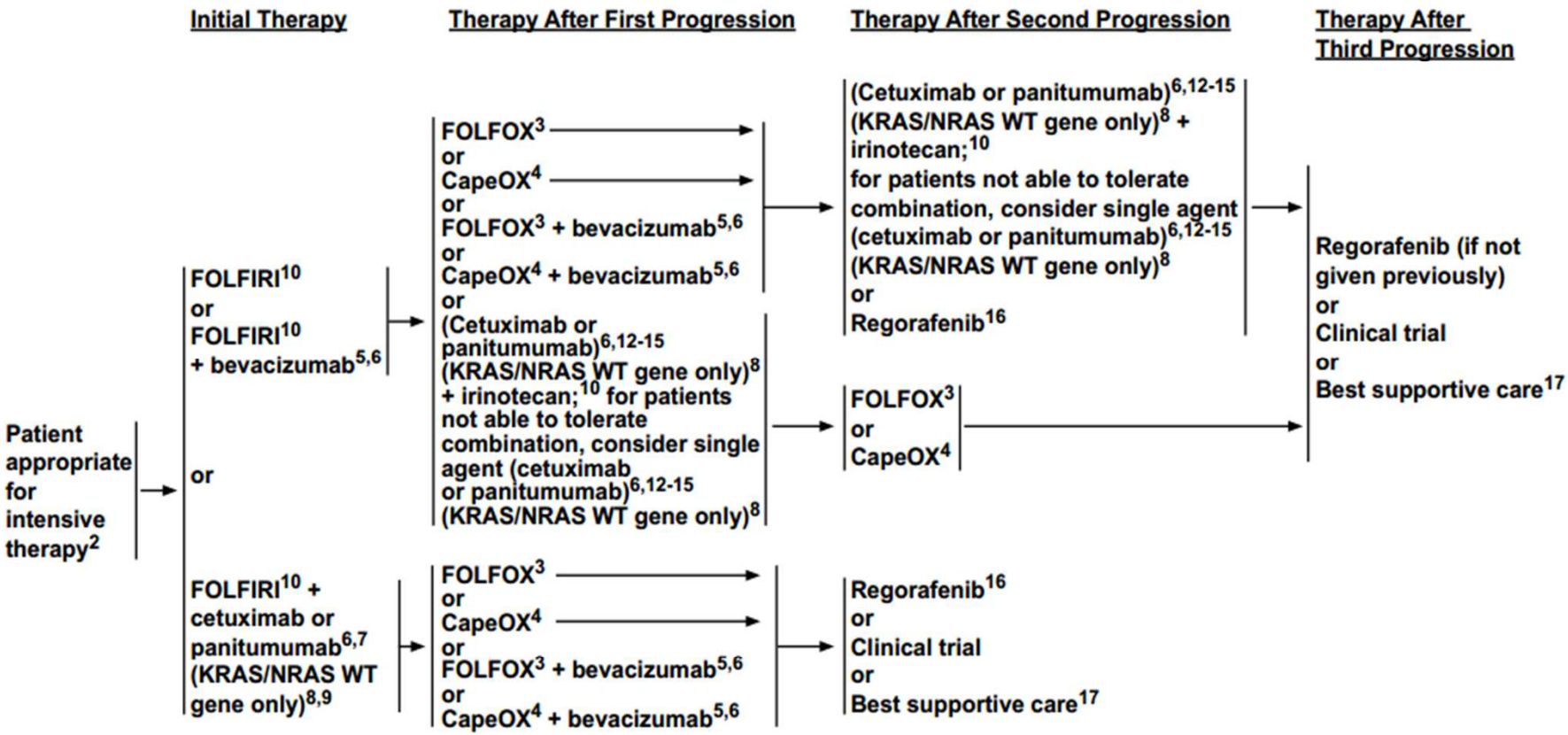
Stage IV CRC: 2014



Colorectal Cancer Clinical Management Decisions

- Goal: cure or palliation
- Address primary
  - Yes or no
  - Now or later
- Chemotherapy
  - FOLFOX/FOLFIRI/FOLFOXIRI/capecitabine
- Biologic upfront: bevacizumab or EGFR Ab

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 9)



Additional options on COL-C 1 of 9 through COL-C 3 of 9
For patients not appropriate for intensive therapy, see COL-C 4 of 9

See footnotes on COL-C 5 of 9

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 6 of 9)

FOLFOX
mFOLFOX 6
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks[1,2,3]

mFOLFOX6 + Bevacizumab[2,4,¶]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

mFOLFOX6 + Panitumumab[2,5]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + Cetuximab[2,6]
Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m2 IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks

CapeOX[1]
Oxaliplatin 130 mg/m² IV over 2 hours, day 1
Capecitabine 850–1000‡ mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CapeOX[1] + Bevacizumab[7¶]
Oxaliplatin 130 mg/m² IV over 2 hours, day 1
Capecitabine 850–1000‡ mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 9)

FOLFIRI[8]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Repeat every 2 weeks

FOLFIRI[8] + Bevacizumab[9,¶]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI[8] + Cetuximab[10]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly[11]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]

FOLFIRI[8] + Panitumumab[13]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[14]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion
Ziv-aflibercept 4 mg/kg IV
Repeat every 2 weeks

Capecitabine[15]
850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine[15] + Bevacizumab[7¶]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 9)

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[16]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]
Leucovorin* 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly.[17]
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[18]

IROX[19]
Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200 mg/m² over 30-90 minutes every 3 weeks

FOLFOXIRI[20]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin 400* mg/m² day 1, fluorouracil 1600 mg/m²/day x 2 days (total 3200 mg/m² over 48 hours)† continuous infusion starting on day 1.
Repeat every 2 weeks
± Bevacizumab[21] 5 mg/kg IV, day 1

The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients.

Irinotecan
Irinotecan 125 mg/m² IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks[22,23]
or Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS/NRAS WT gene only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly [24]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]

Cetuximab (KRAS/NRAS WT gene only) + irinotecan
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[24]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[12]
Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks
or Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 125 mg/m² IV over 30-90 minutes, days 1 and 8
Repeat every 3 weeks

Panitumumab[25] (KRAS/NRAS WT gene only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib[26]
Regorafenib 160 mg PO daily days 1-21
Repeat every 28 days

See References on COL-C 9 of 9

Conversion Therapy: Practical Issues

- Role of FOLFOX or FOLFIRI
- FOLFOXIRI attractive but at expense of increased toxicity
- Limit duration of preoperative therapy to 3-4 mos
  - Treat to resectability and not to best response
  - Minimizes hepatotoxicity
- Role of biologics is evolving
  - Data with cetuximab appears to be most mature in wild-type *KRAS* CRC
  - Bevacizumab is an appropriate option in setting of mutant *KRAS*
    - If bevacizumab is used, discontinue 6-8 wks before planned surgery

Treatment-Associated Liver Toxicity

- 5-FU: steatosis
- Irinotecan: steatohepatitis
- Oxaliplatin: sinusoidal/vascular injury
- Bevacizumab
  - Potential wound healing complications
  - Need to wait 6-8 wks before surgical resection
- Cetuximab: no acute or chronic effects to date
- Incidence of postoperative complications increases with prolonged use

Phase III Study of Second-line FOLFIRI ± Panitumumab in mCRC

Patients with mCRC (55% *KRAS* WT), 1 prior regimen, ECOG PS ≤ 2
(N = 1186)

- Panitumumab 6.0 mg/kg + FOLFIRI* q2w (n = 591)
- FOLFIRI* q2w (n = 595)

*180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin, 500 mg/m^2 5-FU

Primary endpoints

- PFS
- OS

Secondary endpoints

- ORR
- DOR
- Safety

Outcome in *KRAS* WT Patients	FOLFIRI + Panitumumab (n = 325)	FOLFIRI (n = 221)	*P* Value
RR, %	35	10	< .001
PFS, mos	5.9	3.9	.004 (HR: 0.73)
OS, mos	14.5	12.5	.12

Peeters M, et al. J Clin Oncol. 2010;28:4706-4713.

Molecular Biomarker Profiling for Colon Cancer

- Current NCCN guideline recommendations[1]
  - KRAS mutation
  - BRAF mutation
    - Consider only if KRAS mutation is negative
- Further genetic characterization of CRC is continuing[2]
  - CRC as many diseases?
  - Potential for more biomarkers for personalizing therapy

1. NCCN. Clinical Practice Guidelines In Oncology (NCCN Guidelines) for Colon Cancer. V.3.2014.
2. Moorcraft SY, et al. Therap Adv Gastroenterol. 2013;6:381-395.

Clinical Efficacy in *KRAS* Wild-Type Tumors by *BRAF* Mutation Status

CRYSTAL Trial	*KRAS* WT/*BRAF* WT (n = 566)		*KRAS* WT/*BRAF* MT (n = 59)	
	FOLFIRI (n = 289)	Cetuximab + FOLFIRI (n = 277)	FOLFIRI (n = 33)	Cetuximab + FOLFIRI (n = 26)
Median OS, mos (95% CI)	**21.6** (20.0-24.9)	**25.1** (22.5-28.7)	**10.3** (8.4-14.9)	**14.1** (8.5-18.5)
HR (95% CI)	0.830 (0.687-1.004)		0.908 (0.507-1.624)	
P value*	.0547		.7440	
Median PFS, mos (95% CI)	**8.8** (7.6-9.4)	**10.9** (9.4-11.8)	**5.6** (3.5-8.1)	**8.0** (3.6-9.1)
HR (95% CI)	0.673 (0.528-0.858)		0.934 (0.425-2.056)	
P value*	.0013		0.8656	
OR rate, % (95% CI)	**42.6** (36.8-48.5)	**61.0** (55.0-66.8)	**15.2** (5.1-31.9)	**19.2** (6.6-39.4)
P value†	< .0001		.9136	

*Stratified log-rank test. †Cochran-Mantel-Haenszel test.

Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019.

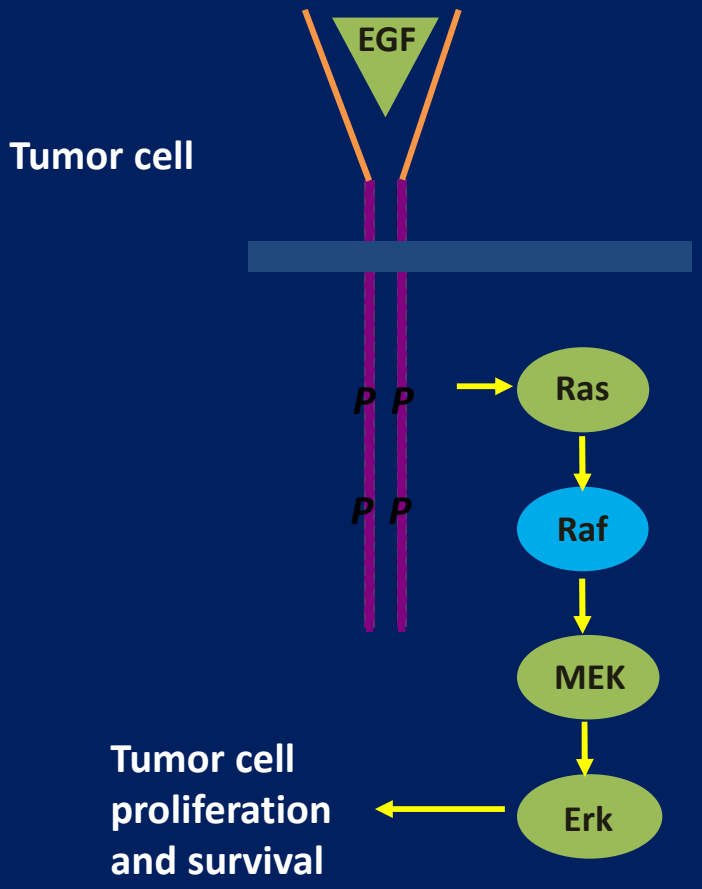
mCRC: Current Options for Addition of Biological Agent

	First-line	Second-line	Third-line	Beyond Third-line
RAS mutant	CT Bev + CT	CT Bev + CT Z-Afli + CT	CT Regor	Regor
RAS wild (*KRAS*, in US)	CT Bev + CT Cet + CT Pmab + CT	CT Bev + CT Cet + CT Pmab ± CT Z-Afli + CT	CT Cet + CT Pmab Regor	Regor

CT = chemotherapy; Bev = bevacizumab; Cet = cetuximab; Pmab = panitumumab; Z-Afli =ziv-aflibercept; Regor = regorafenib

BRAF Mutations in CRC

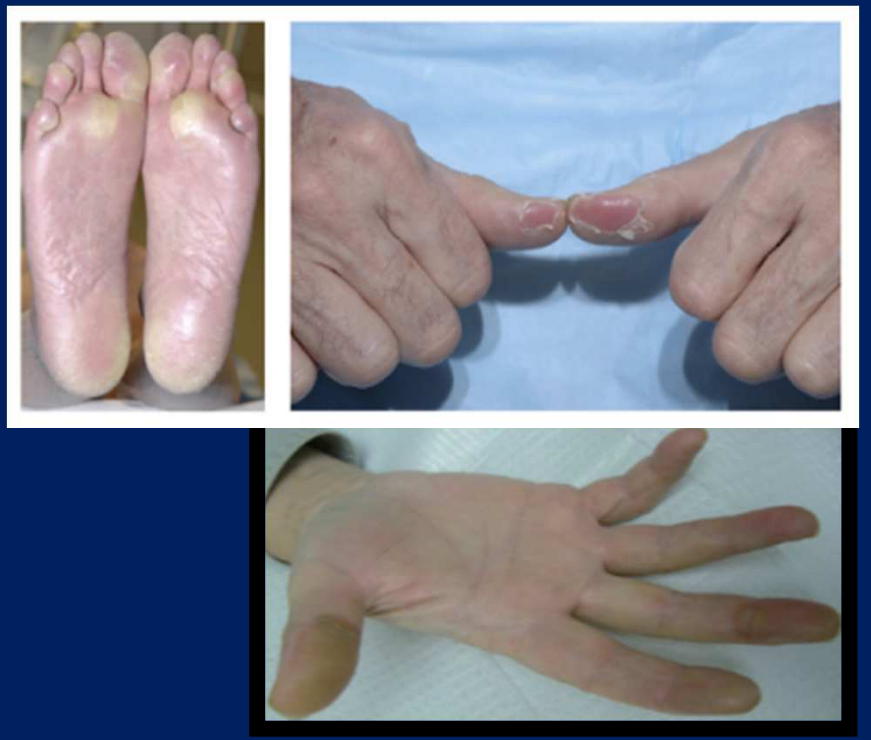
- *BRAF* is primary effector of *KRAS* signaling[1]
- *BRAF* mutations:
  - Occur most frequently in exon 15 (V600E)[1]
  - Found in 4% to 14% of pts with CRC[1]
  - Mutually exclusive with *KRAS* mutations[1,2]



1. Di Nicolantonio F, et al. J Clin Oncol. 2008;26:5705-5712.
2. Artale S, et al. J Clin Oncol. 2008;26:4217-4219.

Management of Hand–Foot Skin Reactions With Regorafenib

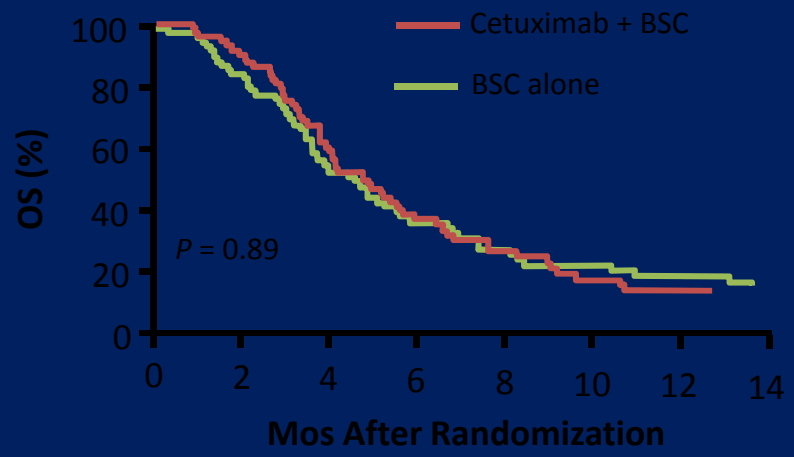
- Occurs as early as 2-3 wks[1]
- Painful blistering plaques or rash[1,2]
- Tender thickened plaques may develop on fingertips[1]
- Management of the HFSR:
  - Minimize friction and trauma with comfortable well-fitting shoes and protective gloves[1]
  - Topical corticosteroids to minimize inflammation on the hands and feet[1,2]
  - Keratolytic creams such as urea or lactic acid to minimize inflammation and thickened hyperkeratotic plaques[1,2]
  - Dose reduction, interruption, or discontinuation of regorafenib depending on the grade of toxicity[1,2]



1. Urban C, et al. J Gastrointest Oncol. 2013;4:319-327. 2. Lacouture ME. ASCO Post. 2012;3:85.

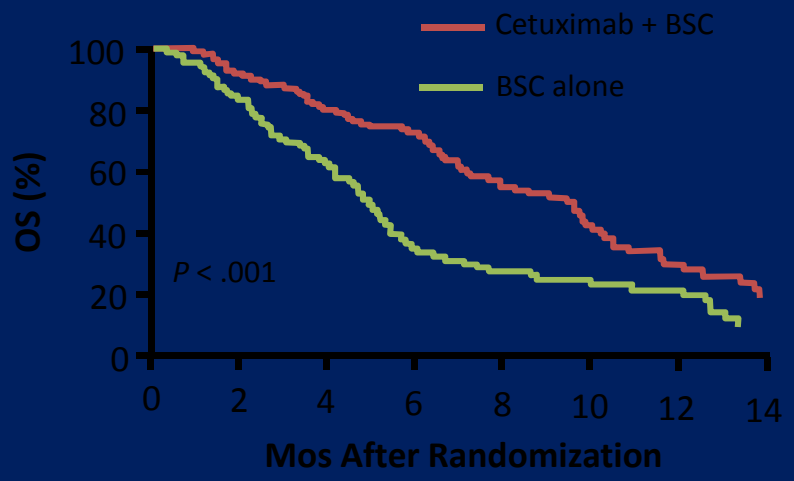
Cetuximab vs BSC in Chemo-Refractory mCRC: Median OS

***KRAS* MT**



Pts at Risk, n								
Cetuximab + BSC	75	67	45	26	15	10	7	4
BSC alone	76	64	39	26	19	12	10	7

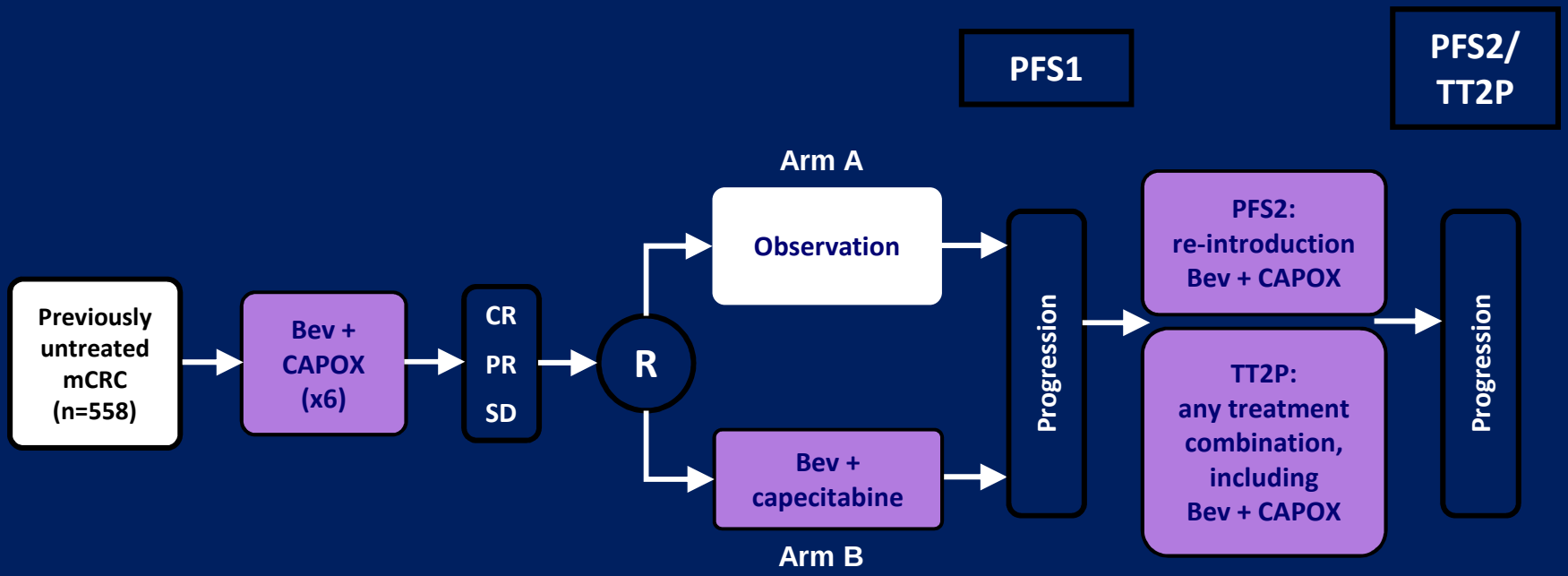
***KRAS* WT**



Pts at Risk, n								
Cetuximab + BSC	110	101	88	75	48	31	19	8
BSC alone	105	88	65	34	23	17	12	5

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

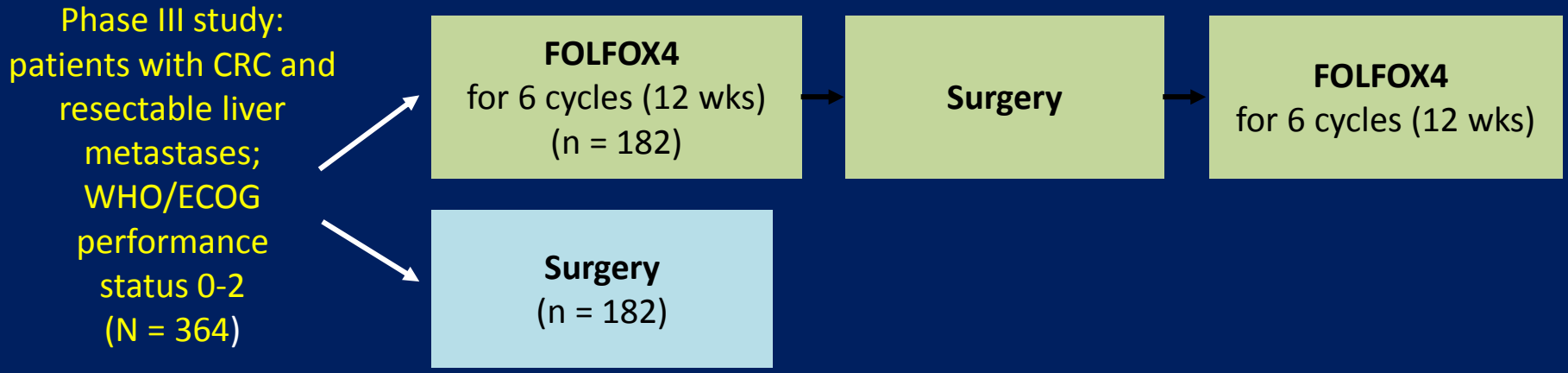
Phase III CAIRO3 trial of continued bevacizumab + capecitabine versus observation demonstrated the importance of treatment duration



- Primary endpoint: PFS after re-introduction = PFS2
- Secondary endpoints: PFS1, OS, TT2P, ORR, safety
- PFS2 was considered to be equal to PFS1 in patients for whom bevacizumab + CAPOX was not reintroduced after PFS1 for any reason
- Upon PD1, 76% of patients received bevacizumab + CAPOX in arm A and 47% in arm B

Koopman, et al. ASCO 2013

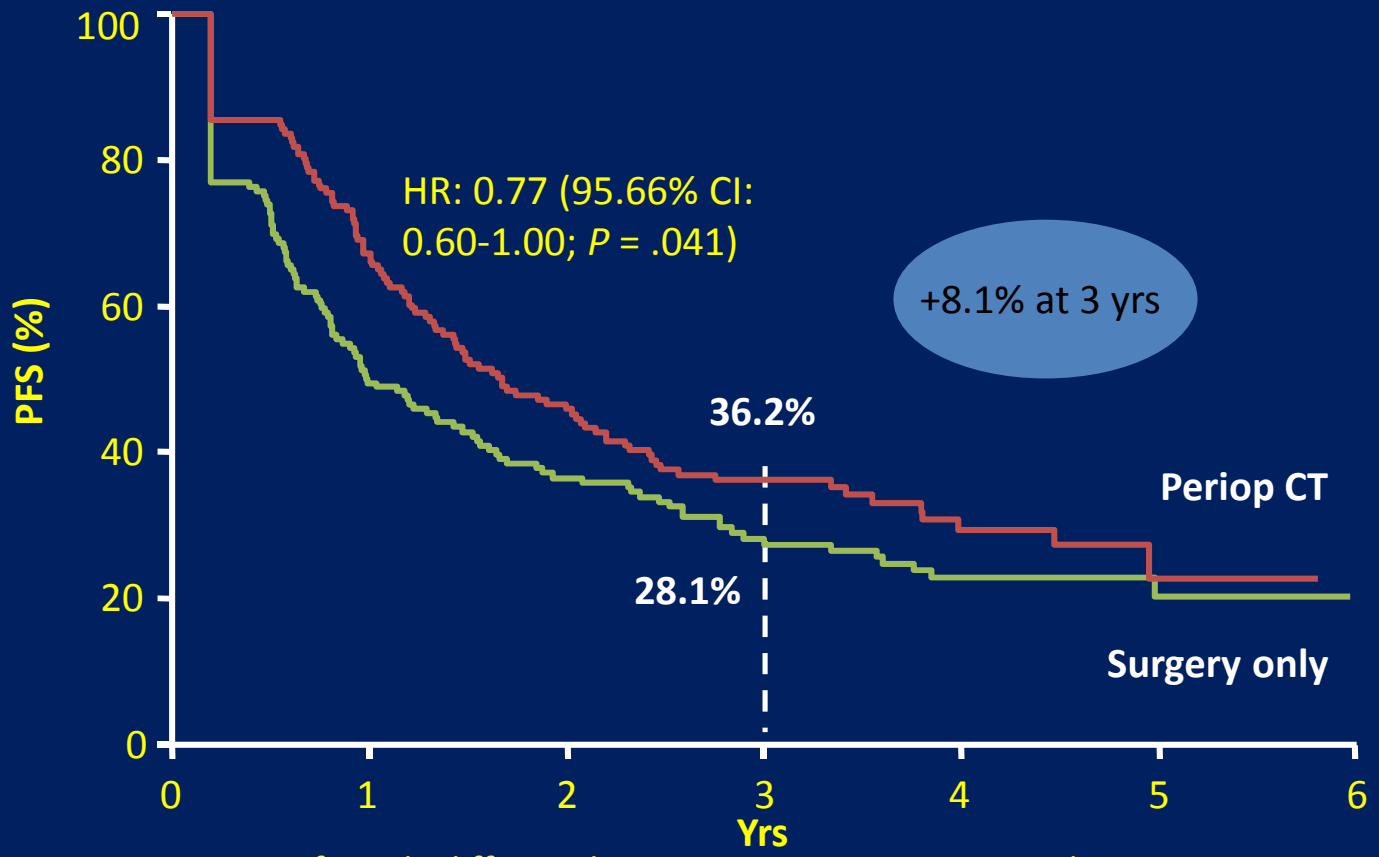
EORTC 40983: FOLFOX4 in mCRC With Resectable Liver Metastases



Primary endpoint: PFS
Secondary endpoints: OS, complete resection

Nordlinger B, et al. Lancet. 2008;371:1007-1016.

EORTC: Resectable Liver Metastases PFS



- 5-yr OS rate was not significantly different between FOLFOX or surgery alone (51.2% vs 47.8%; *P* = .34)

Nordlinger B, et al. Lancet. 2008;371:1007-1016. Nordlinger B, et al. Lancet Oncol. 2013;14:1208-1215.