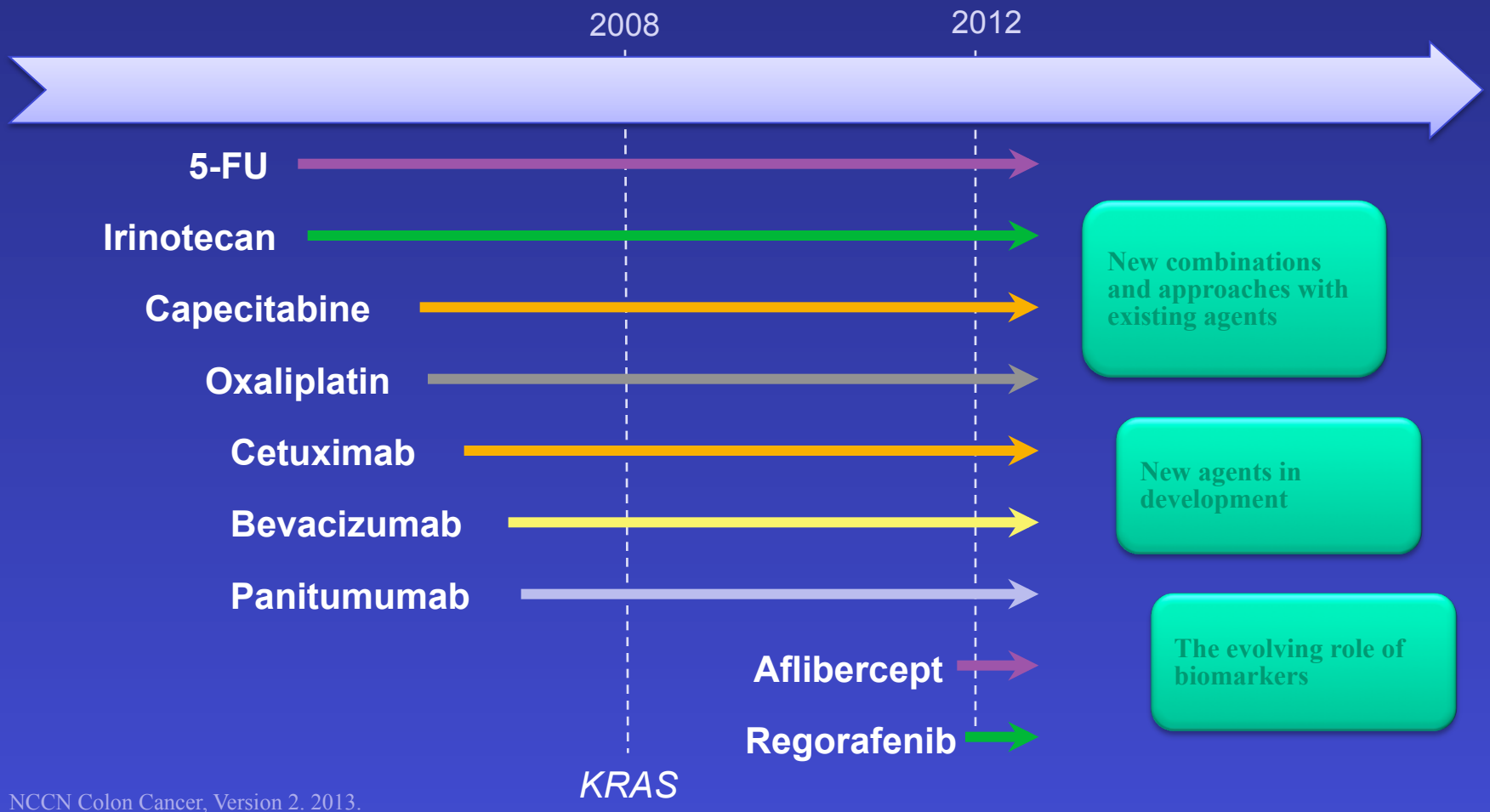
Moving Forward with Colorectal Cancer?

- Thomas H Cartwright MD
- Co-Chairman US Oncology GI Research
- US Oncology Pathways Task Force
  - Chairman GI Subcommittee

Agenda

- Recent FDA approval of OnDose testing
- Recent CMS approval of OncotypeDX testing for colon cancer
- 2012 FDA approval of cetuximab first-line
- 2012 FDA approval of bevacizumab beyond progression
- 2012 FDA approval of aflibercept and regorafenib

Advances in the Treatment of mCRC: the Hope of a Brighter Future

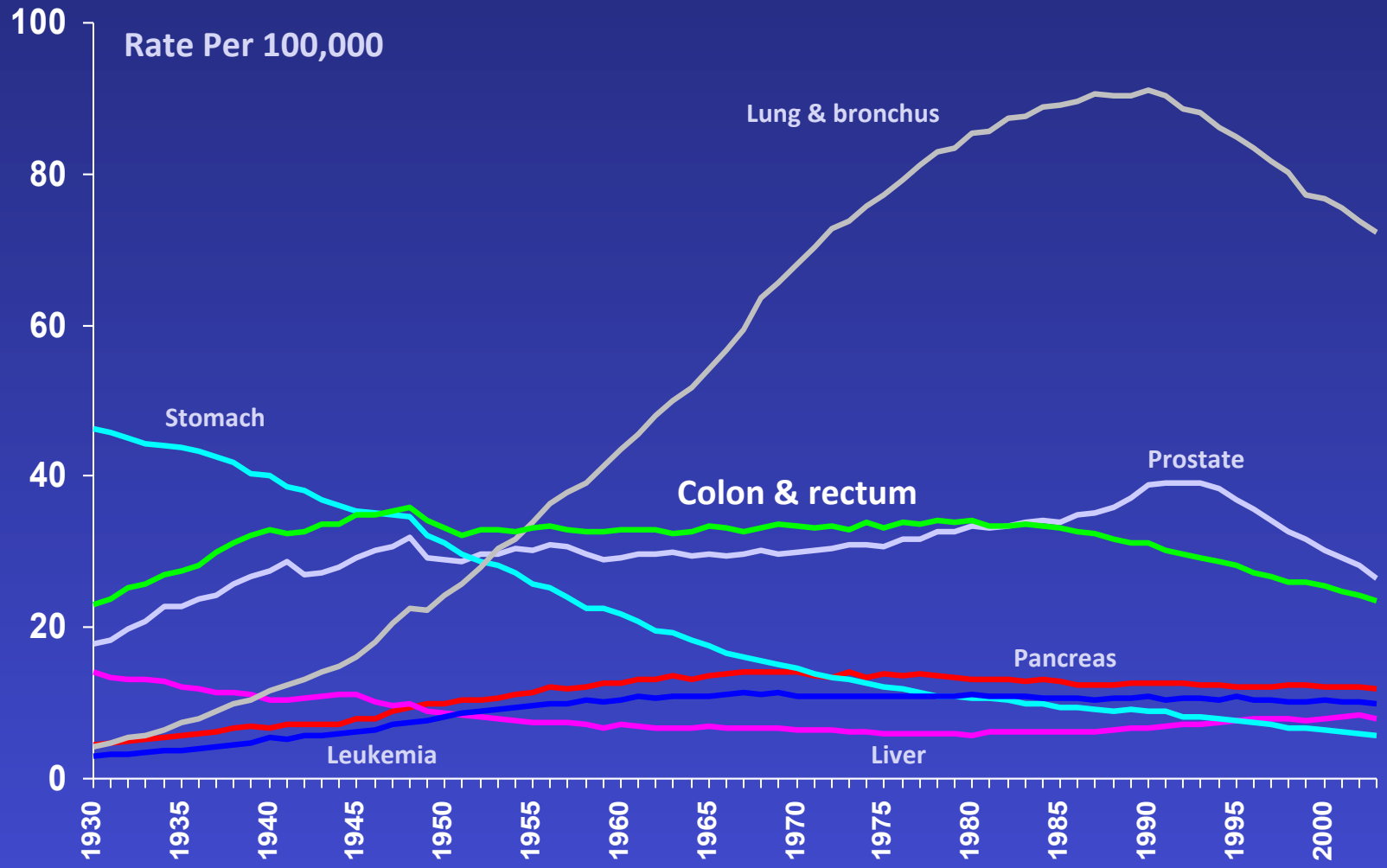


NCCN Colon Cancer, Version 2. 2013.

Colorectal Cancer Incidence

- ~148,000 cases in US annually and ~50,000 deaths
- 1 in 16 people in the United States will be diagnosed with colorectal cancer over their lifetime
- 6% of Americans will develop colorectal cancer at some point

Cancer Death Rates*, for Men, US, 1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

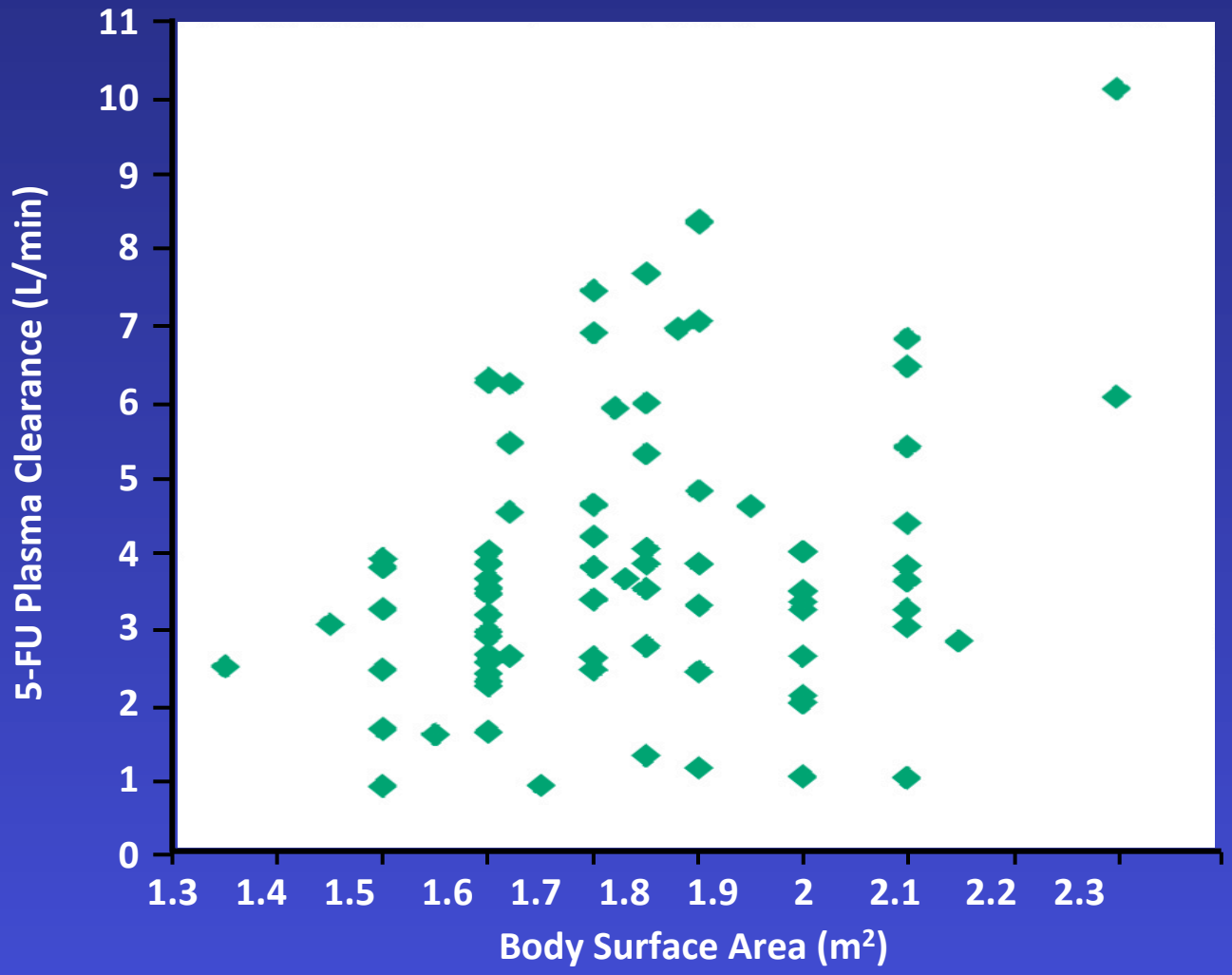
OnDose

5-Fluorouracil (5-FU)
Pharmacokinetic (PK)
Dose Management

OnDose

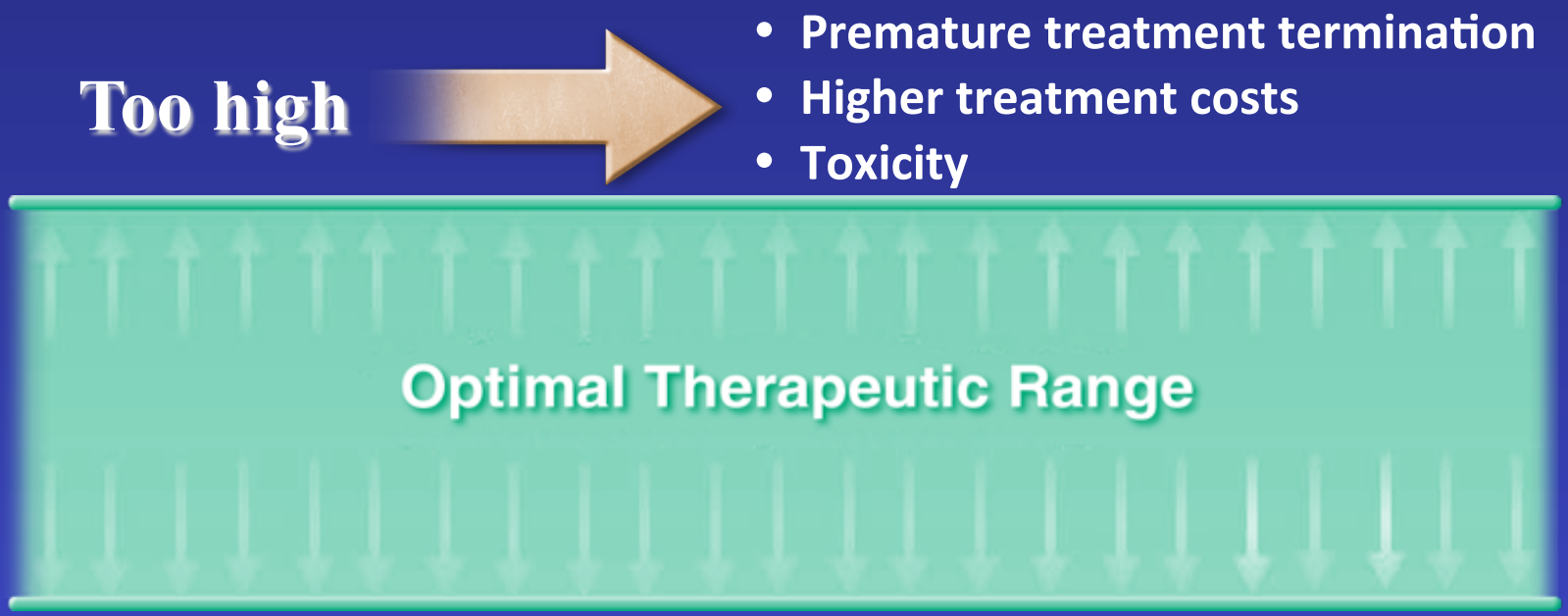
- Conventional BSA-based dosing of 5-FU has significant variability in plasma drug levels.
- Plasma levels of 5-FU correlate with biological effect - efficacy and toxicity.
- These findings suggest PK-guided dose adjustment of 5-FU is a more rational approach to optimizing outcomes in individual patients.

BSA and 5-FU Exposure:
Lack of Correlation (Colorectal Cancer, n=81)



Gamelin E et al. *J Clin Oncol*. 1999;17:1105-1110.

Clinical Rationale for 5-FU Dose Management



BSA vs PK-Guided 5-FU Dosing: Phase 3 Study (JCO, 2008)

- Assess the value of PK-guided 5-FU dose adjustment in controlling toxicity and improving efficacy in patients with mCRC
- Randomized, multicenter, prospective study (n=208) in first-line therapy of mCRC
- Arms*:
  - Conventional BSA dosing (n=104)
  - Individualized PK-guided dosing (n=104)
- Target AUC for PK-guided dosing: 20-24 mg·h/L

*Treatment: 5-FU (1500 mg/m^2/week 8-hour continuous infusion) and 400 mg/m^2 leucovorin

Gamelin E et al. *J Clin Oncol*. 2008;26:2099-2105.

Gamelin Phase 3 Study: Summary

Toxicity*

Dosing	Diarrhea	Mucositis	Hematologic	n
BSA	18%	2%	2%	104
PK-guided	4%	2%	0%	104

Response

Dosing (P = 0.004)	CR + PR	SD	PD
BSA	17%	29%	54%
PK-guided	34%	25%	41%

Median Overall Survival

Dosing (P = 0.08)	Months
BSA	16
PK-guided	22

SD, stable disease; PD, progressive disease

*Whole treatment, WHO grade III and IV toxicities. Significantly less overall toxicity seen in PK-guided dosing vs BSA dosing (*P*=0.003).

Gamelin E et al. *J Clin Oncol*. 2008;26(13):2099-2105.

BSA vs PK-Guided 5-FU Dosing: Phase 3 Study (JCO, 2008)

- Assess the value of PK-guided 5-FU dose adjustment in controlling toxicity and improving efficacy in patients with mCRC
- Randomized, multicenter, prospective study (n=208) in first-line therapy of mCRC
- Arms*:
  - Conventional BSA dosing (n=104)
  - Individualized PK-guided dosing (n=104)
- Target AUC for PK-guided dosing: 20-24 mg·h/L

*Treatment: 5-FU (1500 mg/m^2/week 8-hour continuous infusion) and 400 mg/m^2 leucovorin

Gamelin E et al. *J Clin Oncol*. 2008;26:2099-2105.

PROFUSE-2011

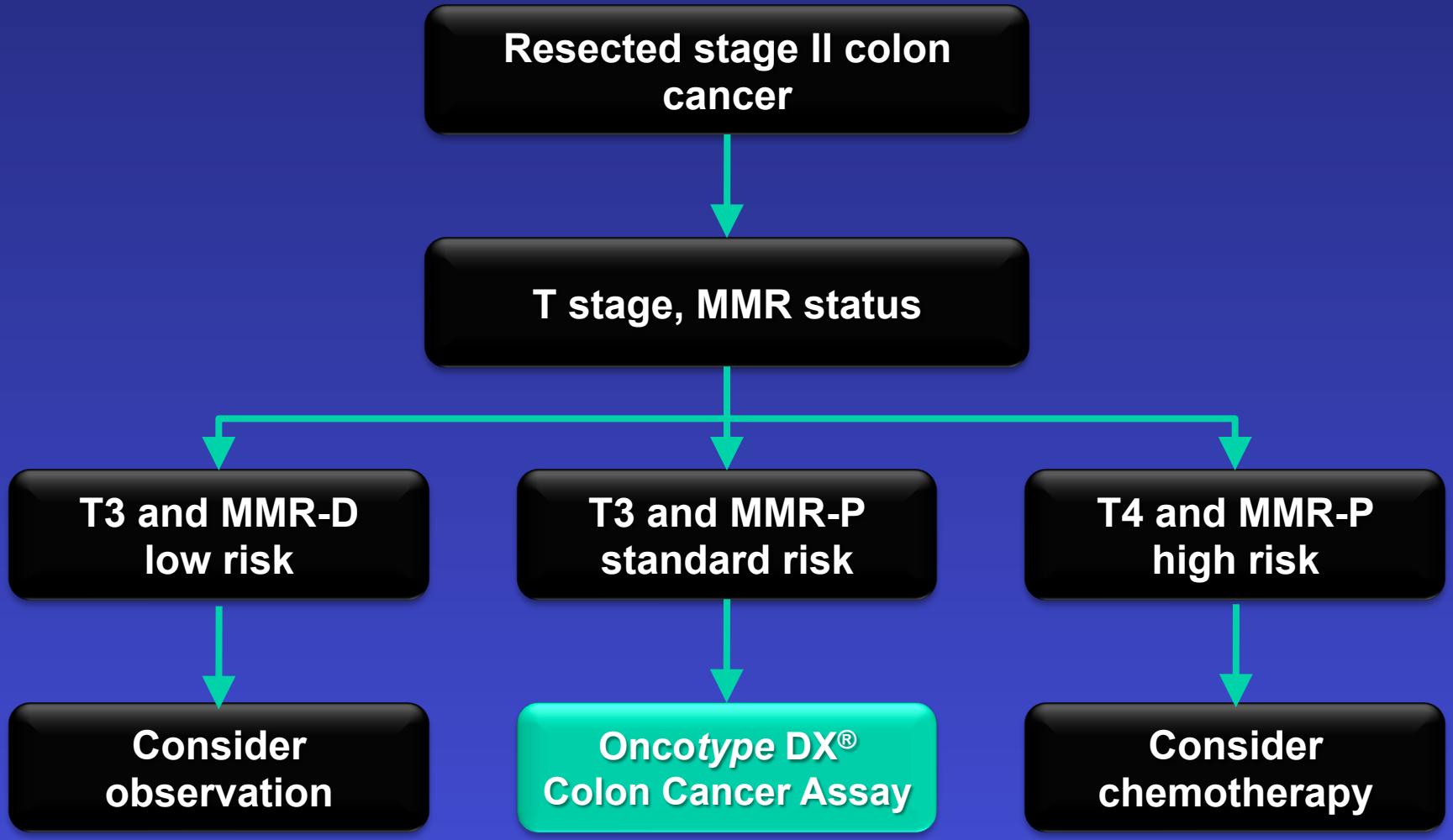
OnDose vs BSA dosing mCRC

Cartwright, Thomas H. and Cooper, Shree III; Reg Local Limited 12(12) / 150 Closed

PROFUSE-2011: A prospective, randomized, open-label trial comparing OnDose™ AUC optimized 5-FU based administration versus standard Body Surface Area (BSA) dosing in metastatic colorectal cancer patients (mCRC) treated with mFOLFOX6

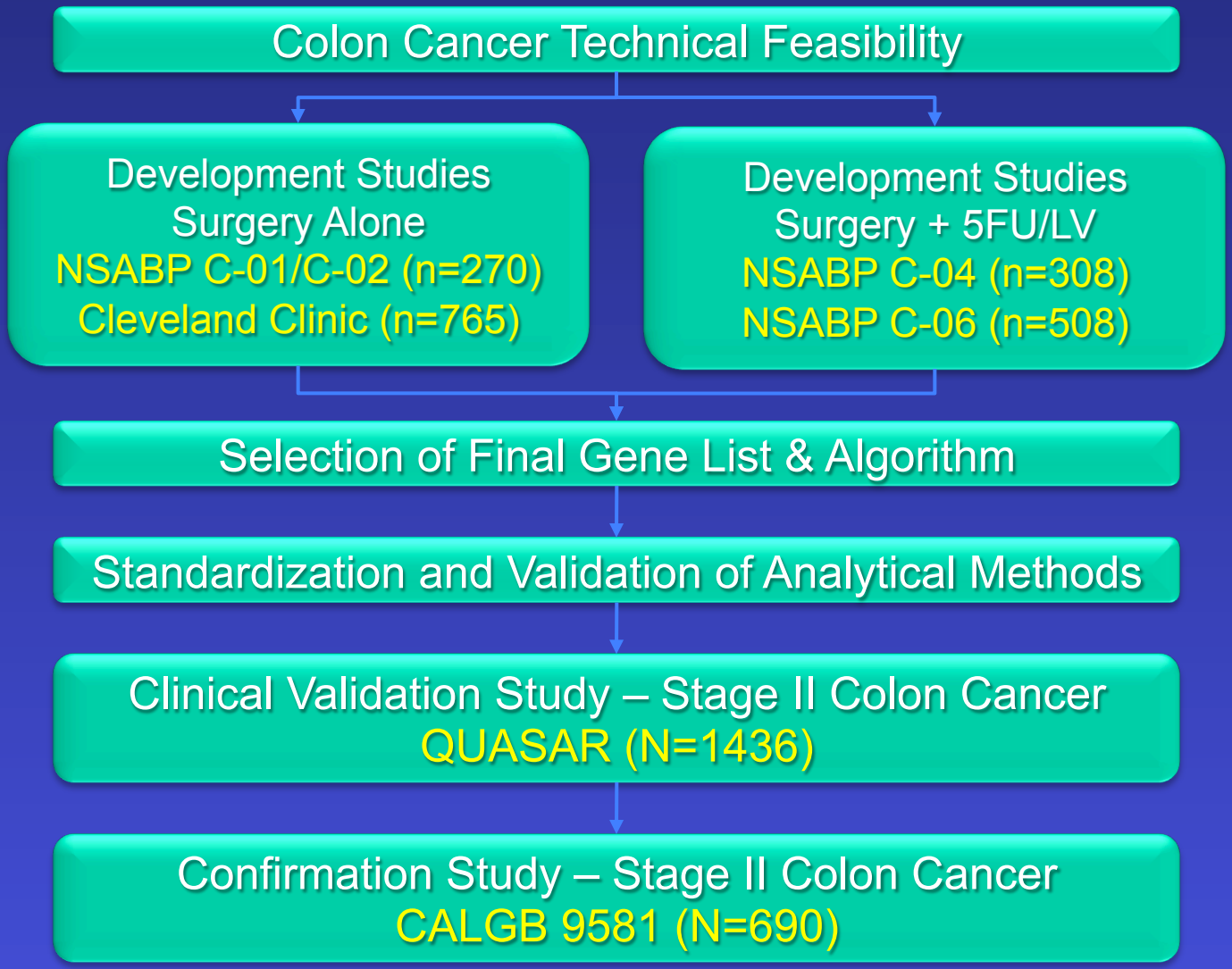
Onco*type* DX® Colon Cancer Assay

Integrating the Quantitative Recurrence Score® Result Into Recurrence Risk Assessment and Treatment Planning for Stage II Colon Cancer



MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient

Development and Validation of the Onco*type* DX® Colon Cancer Assay

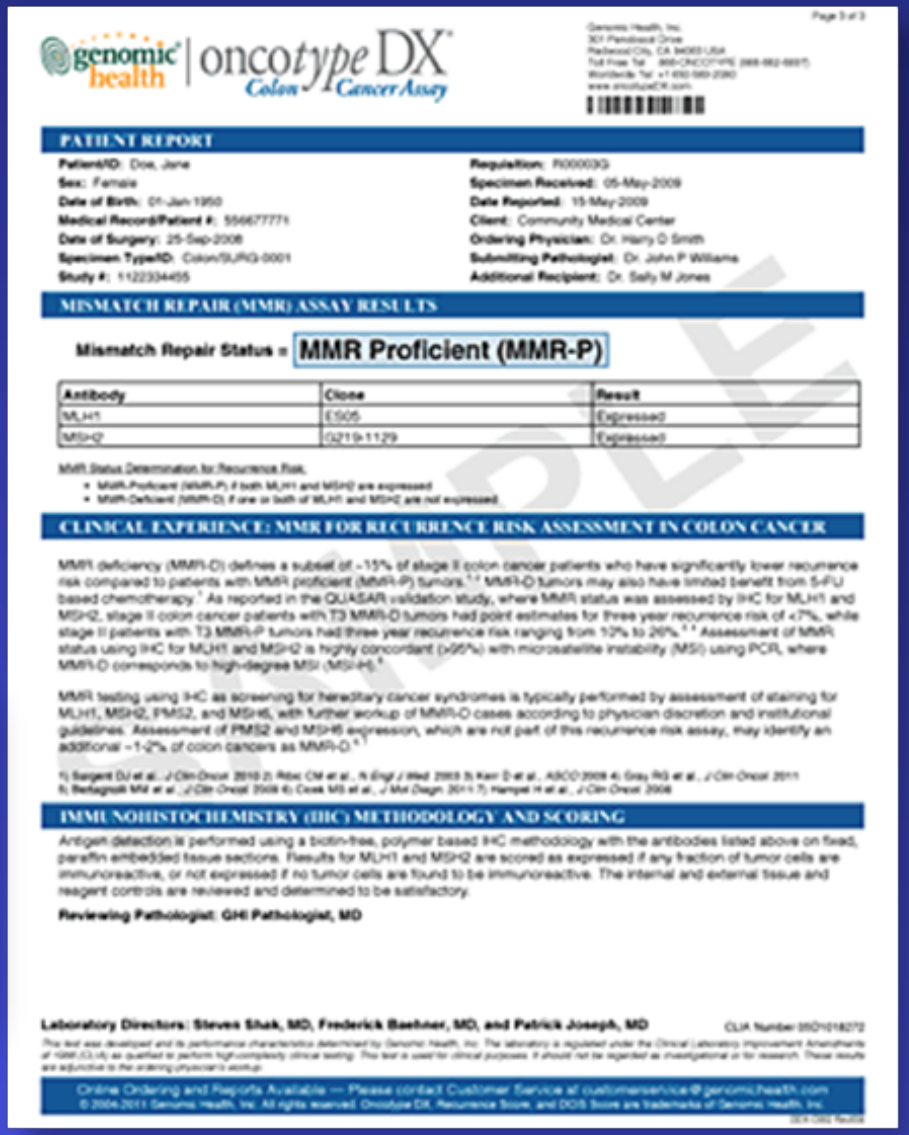


MMR Testing in Assessing Recurrence Risk for Treatment Planning in Stage II Colon Cancer

- Streamlines the "complete picture" for recurrence risk assessment for the individual stage II patient
- Helps identify the right patient for the Onco*type* DX® Colon Cancer Assay

Sequential MMR Testing followed by Onco*type* DX for Risk Assessment:

- MMR-D Result: Onco*type* DX not performed as a sequential test
- MMR-P Result: Onco*type* DX available as a sequential test



genomic health | oncotype DX Colon Cancer Assay

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
Date of Birth: 01-Jan-1950
Medical Record/Patient #: 556677771
Date of Surgery: 25-Sep-2008
Specimen Type/ID: Colon/SURG-0001
Study #: 1122334455

Requisition: R00003G
Specimen Received: 05-May-2009
Date Reported: 15-May-2009
Client: Community Medical Center
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Recipient: Dr. Sally M Jones

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

CLINICAL EXPERIENCE: MMR FOR RECURRENCE RISK ASSESSMENT IN COLON CANCER

MMR deficiency (MMR-D) defines a subset of ~15% of stage II colon cancer patients who have significantly lower recurrence risk compared to patients with MMR proficient (MMR-P) tumors.[1,2] MMR-D tumors may also have limited benefit from 5-FU based chemotherapy.[3] As reported in the QUASAR validation study, where MMR status was assessed by IHC for MLH1 and MSH2, stage II colon cancer patients with T3 MMR-D tumors had point estimates for three year recurrence risk of <7%, while stage II patients with T3 MMR-P tumors had three year recurrence risk ranging from 13% to 26%.[1,2] Assessment of MMR status using IHC for MLH1 and MSH2 is highly concordant (>95%) with microsatellite instability (MSI) using PCR, where MMR-D corresponds to high-degree MSI (MSI-H).[4]

MMR testing using IHC as screening for hereditary cancer syndromes is typically performed by assessment of staining for MLH1, MSH2, PMS2, and MSH6, with further workup of MMR-D cases according to physician discretion and institutional guidelines. Assessment of PMS2 and MSH6 expression, which are not part of this recurrence risk assay, may identify an additional ~1-2% of colon cancers as MMR-D.[5,6]

1) Sargent DJ et al. J Clin Oncol. 2010 2) Ribic CM et al., N Engl J Med. 2003 3) Kerr D et al., ASCO 2008 4) Gray RG et al., J Clin Oncol. 2011 5) Bertagnolli MM et al., J Clin Oncol. 2008 6) Cicek MS et al., J Mol Diagn. 2011 7) Hampel H et al., J Clin Oncol. 2008

IMMUNOHISTOCHEMISTRY (IHC) METHODOLOGY AND SCORING

Antigen detection is performed using a biotin-free, polymer based IHC methodology with the antibodies listed above on fixed, paraffin embedded tissue sections. Results for MLH1 and MSH2 are scored as expressed if any fraction of tumor cells are immunoreactive, or not expressed if no tumor cells are found to be immunoreactive. The internal and external tissue and reagent controls are reviewed and determined to be satisfactory.

Reviewing Pathologist: GHI Pathologist, MD

Laboratory Directors: Steven Shak, MD, Frederick Baehner, MD, and Patrick Joseph, MD

CLIA Number: 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

Oncotype DX® Colon Cancer Assay Patient Report

genomic health | oncotype DX Colon Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950
Medical Record/Patient #: 556677771
Date of Surgery: 9/25/2008
Specimen Type/ID: Colon/SURG-0001
Study #: Study.Colon

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008
Client: Community Medical Center
Ordering Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Recipient: Dr. Sally M Jones

COLON CANCER ASSAY DESCRIPTION

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

RESULTS

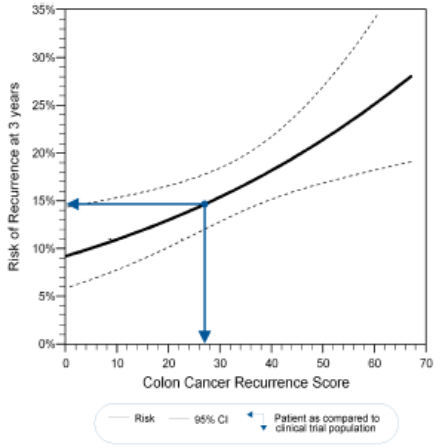
Colon Cancer Recurrence Score = **27**

The findings summarized in the Clinical Experience section below are applicable to stage II colon cancer patients with adenocarcinoma or mucinous carcinoma. It is unknown whether the findings apply to other patients outside these criteria.

CLINICAL EXPERIENCE: STAGE II COLON CANCER

In the clinical validation study*, patients with stage II colon cancer randomized to surgery alone who had a Recurrence Score of 27 had a risk of recurrence at 3 years of **15% (95% CI:12%-18%).**

Risk of Recurrence at 3 Years vs Recurrence Score



Aid for Interpretation

Impact of Nodes Assessed
The 3-year recurrence risk for patients with ≥ 12 nodes examined was ~3% (range 2% - 5%) lower than that shown in the figure. For patients with < 12 nodes examined, the 3-year recurrence risk was ~2% higher.

5 years vs 3 years Recurrence Risk
The 5-year recurrence risk was ~5% higher (range 4% - 8%), than that shown in the figure for 3 years.

Relevance for Chemotherapy Benefit
Similar proportional reductions in recurrence risk with 5FU/LV chemotherapy treatment were observed across the range of Recurrence Scores.

*The clinical experience with Oncotype DX on this page is from a clinical validation study with prospectively defined endpoints involving 1,436 patients with stage II colon cancer from the QUASAR clinical trial; 711 randomized to surgery alone and 725 to surgery followed by 5FU/LV chemotherapy. There were no patients who had a Recurrence Score > 67. Kerr D et al, ASCO 2009, Abstract 4000.

Laboratory Directors: Steven Shak, MD, Frederick Baehner, MD, and Patrick Joseph, MD CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

genomic health | oncotype DX Colon Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Toll Free Tel 866-ONCOTYPE (866-662-6897)
Worldwide Tel +1 650-569-2080
www.oncotypeDX.com

PATIENT REPORT

Patient/ID: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008

RESULTS

Colon Cancer Recurrence Score = **27**

The findings summarized in the Clinical Experience section below are applicable to stage II colon cancer patients with adenocarcinoma or mucinous carcinoma. It is unknown whether the findings apply to other patients outside these criteria.

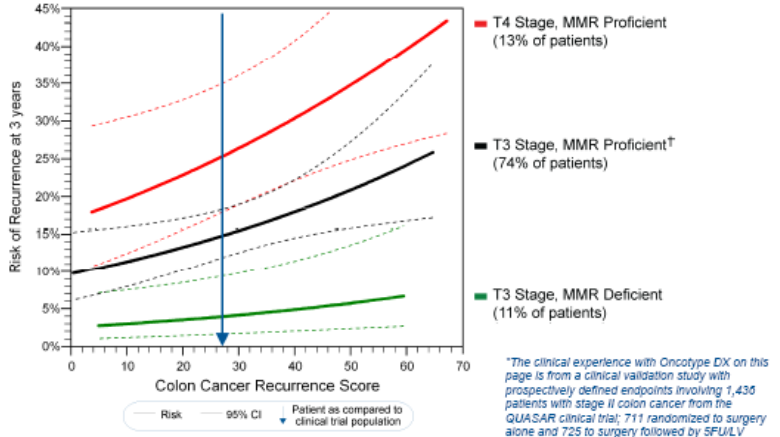
CLINICAL EXPERIENCE: STAGE II COLON CANCER (continued)

In the clinical validation study*, three groups of patients with different risks of recurrence that are clinically important were identified by pre-specified analysis of the Recurrence Score, tumor stage (T stage) and mismatch repair (MMR) status.

- -13% of patients had T4 Stage, MMR Proficient (MMR-P) tumors and generally higher recurrence risk.
- -11% of patients had T3 Stage, MMR Deficient (MMR-D) tumors and generally lower recurrence risk.
- -74% of patients had T3 Stage, MMR-P tumors† with recurrence risk similar to that shown on page 1.

Recurrence Score, T stage, and MMR were each significant independent predictors of recurrence risk.

Risk of Recurrence at 3 Years by Recurrence Score, T Stage and MMR Status



†Rare patients (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.

*The clinical experience with Oncotype DX on this page is from a clinical validation study with prospectively defined endpoints involving 1,436 patients with stage II colon cancer from the QUASAR clinical trial; 711 randomized to surgery alone and 725 to surgery followed by 5FU/LV chemotherapy. There were no patients who had a Recurrence Score > 67. Kerr D et al, ASCO 2009, Abstract 4000.

Laboratory Directors: Steven Shak, MD, Frederick Baehner, MD, and Patrick Joseph, MD CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

Online Ordering and Reports Available — Please contact Customer Service at customerservice@genomichealth.com

© 2004-2009 Genomic Health, Inc. All rights reserved. Oncotype DX and Recurrence Score are registered trademarks of Genomic Health, Inc.

Effect of Onco*type* DX® Colon Cancer Test Results on Treatment Recommendations in Patients With Stage II Colon Cancer

Cartwright T,[1] Chao C,[2] Lopatin M,[2]
Bentley T,[3] Broder M,[3] Chang E[3]

1. Ocala Oncology, Ocala, FL; 2. Genomic Health, Inc.®, Redwood City, CA;
3. Partnership for Health Analytic Research, LLC, Beverly Hills, CA.

Cartwright, et al. ASCO GI 2012. Abstract 398.

Impact of Onco*type* DX® Colon Cancer Assay on Treatment Recommendations in Stage II Colon Cancer

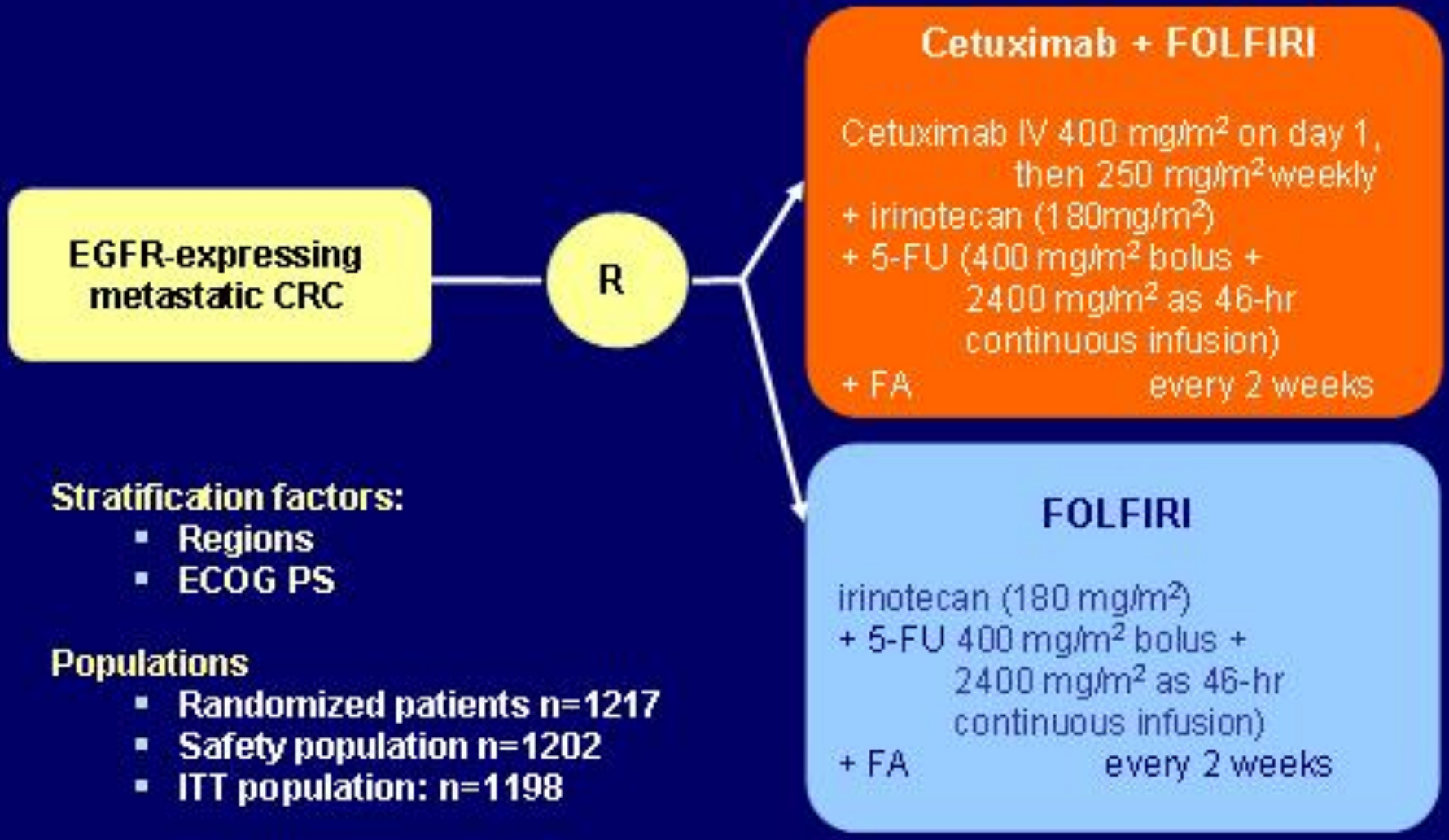
- 92 (79%) of 116 evaluable physicians had a treatment recommendation before ordering the Onco*type* DX assay
  - Most (52/92 = 57%) pre-assay treatment recommendations included chemotherapy
- 27 (29%) of 92 treatment recommendations changed after the 12-gene Recurrence Score® result was obtained
  - Treatment intensity decreased for 18 (67%) of these 27 treatment recommendations
  - Treatment intensity increased for 9 (33%) of these 27 treatment recommendations

Cartwright, et al. ASCO GI 2012. Abstract 398.

July 06, 2012

FDA Approves ERBITUX® (cetuximab) as First-Line Treatment in *KRAS* Mutation-Negative (Wild-Type) Epidermal Growth Factor Receptor (EGFR)-Expressing Metastatic Colorectal Cancer in Combination with FOLFIRI (Irinotecan, 5-Fluorouracil, Leucovorin)

CRYSTAL trial:
Study design



Stratification factors:

- **Regions**
- **ECOG PS**

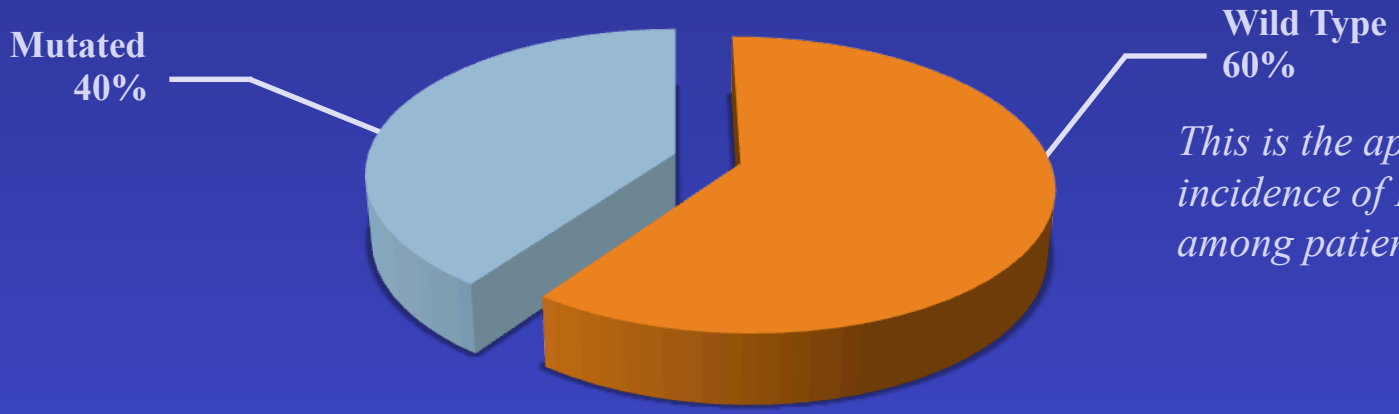
Populations

- **Randomized patients n=1217**
- **Safety population n=1202**
- **ITT population: n=1198**

The Role of K-*ras* and Rationale for Testing at Diagnosis of Metastatic Disease

- K-*ras* is a gene that codes for a protein that plays an important role downstream of the EGFR in the signaling pathway
- There are 2 different forms of the K-*ras* gene found in colorectal tumors: mutated and wild type (nonmutated)

- More than 98% of K-*ras* mutations are found in codon 12 or 13



This is the approximate incidence of K-ras mutations among patients with CRC.

Adjei AA. *J Nat Cancer Inst*. 2001;93:1062-1074.
Brink M, et al. *Carcinogenesis*. 2003;24:703-710.
National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology™. Colon Cancer. V.3.2010. Fort Washington, PA: 2010.
Esteller M, et al. *J Clin Oncol*. 2001;19:299-304.
Sanger Institute Catalogue of Somatic Mutations in Cancer. http://www.sanger.ac.uk/genetics/CGP/cosmic/. Accessed January 25, 2010.

NCCN guidelines strongly recommend testing for K-*ras* at diagnosis of mCRC to:

1) Plan across treatment continuum
2) Obtain K-*ras* info in a non-time-sensitive manner
3) Allow discussions of any K-*ras* mutation while other treatment options still exist

CRYSTAL Extended Follow-Up: Treatment Effect by *KRAS* Status

	***KRAS* WT**		***KRAS* Mutant**	
	FOLFIRI (n=350)	FOLFIRI + Cetuximab (n=316)	FOLFIRI (n=183)	FOLFIRI + Cetuximab (n=214)
Median OS, mo	20.0	23.5	16.7	16.2
	P = 0.0093 HR = 0.796		*P* = 0.75 HR = 1.035	
Median PFS, mo	8.4	9.9	7.7	7.4
	P = 0.0012 HR = 0.696		*P* = 0.26 HR = 1.171	
OR rate, %	39.7	57.3	36.1	31.3
	P < 0.001 HR = 2.069		*P* = 0.35 HR = 0.822	

National Comprehensive Cancer Network (NCCN) recommends *KRAS* testing for CRC patients at diagnosis of metastatic disease.

Van Cutsem E et al. *J Clin Oncol*. 2011;epub April 18.

Chemotherapy plus cetuximab in patients with liver-limited or non-liver-limited *KRAS* wild-type colorectal metastases: A pooled analysis of the CRYSTAL and OPUS studies.

Table 2. Efficacy according to treatment received in patients grouped by LLD status

	LLD		Non-LLD	
	CT n=95	CT + cetuximab n=93	CT n=352	CT + cetuximab n=305
Response				
ORR, %	43.2	72.0	37.2	52.8
Odds ratio*	3.51		1.88	
95% CI	1.88–6.55		1.37–2.58	
p-value†	<0.0001		<0.0001	
RO resection				
Rate, %	5.3	11.8	1.7	3.3
Odds ratio*	2.38		1.97	
95% CI	0.80–7.09		0.71–5.47	
p-value†	0.1121		0.1870	
PFS				
Median, months	9.2	11.9	7.4	9.4
HR*	0.53		0.69	
95% CI	0.32–0.85		0.55–0.84	
p-value†	0.0095		0.0004	
OS				
Median, months	27.0	27.0	17.3	22.0
HR*	0.81		0.76	
95% CI	0.56–1.16		0.64–0.91	
p-value†	0.2504		0.0023	

Bevacizumab Plus Chemotherapy Continued Beyond First Progression in Patients With Metastatic Colorectal Cancer Previously Treated With Bevacizumab Plus Chemotherapy: Results of a Randomized Phase III Intergroup Study (TML Study)

Abstract CRA3503

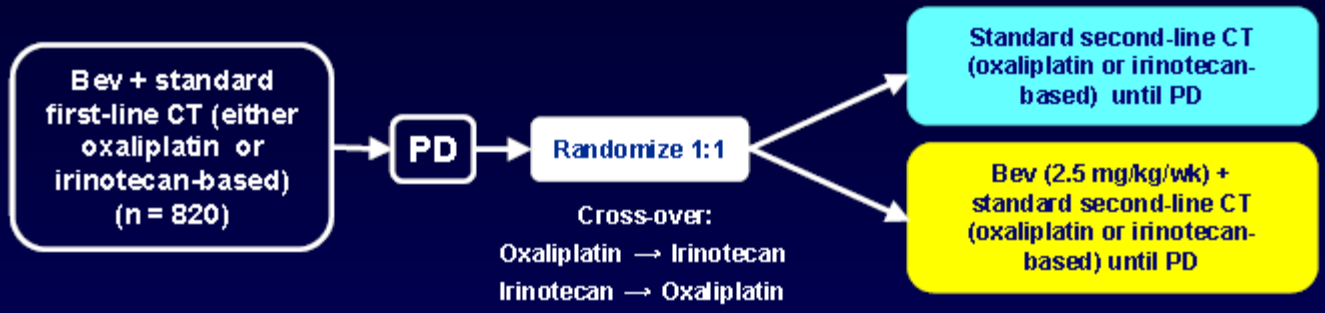
Arnold D, Andre T, Bennouna J, Sastre J, Osterlund PJ, Greil R, Van Cutsem E, Von Moos R, Reyes-Rivera I, Bendahmane B, Kubicka S

Background

- Bevacizumab (Bev) in combination with fluoropyrimidine-based chemotherapy (CT) is a standard of care for mCRC in first-line and (Bev-naïve) second-line settings
- VEGF is an early and persistent promoter of tumor angiogenesis.[1] Sustained VEGF inhibition achieves and maintains tumor regression in preclinical studies[2,3]
- In nonrandomized observational studies (BRiTE, ARIES) in patients with mCRC, continuing antiangiogenic therapy with Bev + CT beyond first progressive disease (PD) correlates with prolonged survival vs CT alone[4,5]

1. Ferrara N, et al. *Nature Med*. 2003;9(6):669-676. 2. Klement G, et al. *J Clin Invest*. 2000;105(8):R15-R24. 3. Klement G, et al. *Clin Cancer Res*. 2002;8(1):221-232. 4. Grothey A, et al. *J Clin Oncol*. 2008;26(33):5326-5334. 5. Cohn AL, et al. *J Clin Oncol*. 2010;28(15S): Abstract 3596.
Arnold D, et al. *J Clin Oncol*. 2012;30(15S): Abstract CRA3503.

ML18147 Study Design (Phase III)

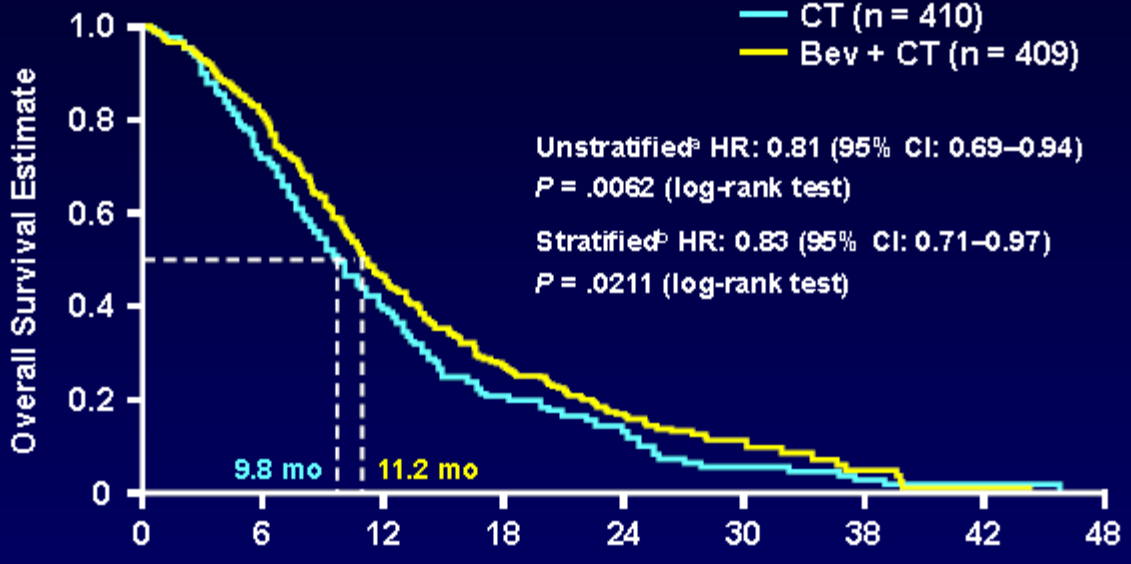


Primary endpoint	• Overall survival (OS) from randomisation
Secondary endpoints included	• Progression-free survival (PFS) • Best overall response rate • Safety
Stratification factors	• First-line CT (oxaliplatin-based, irinotecan-based) • First-line PFS (≤9 months, >9 months) • Time from last Bev dose (≤42 days, >42 days) • Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline (0, ≥1)

Study conducted in 220 centers in Europe and Saudi Arabia

Arnold D, et al. *J Clin Oncol.* 2012;30(15S): Abstract CRA3503.

Overall Survival: ITT Population



Unstratified[a] HR: 0.81 (95% CI: 0.69–0.94)
P = .0062 (log-rank test)

Stratified[b] HR: 0.83 (95% CI: 0.71–0.97)
P = .0211 (log-rank test)

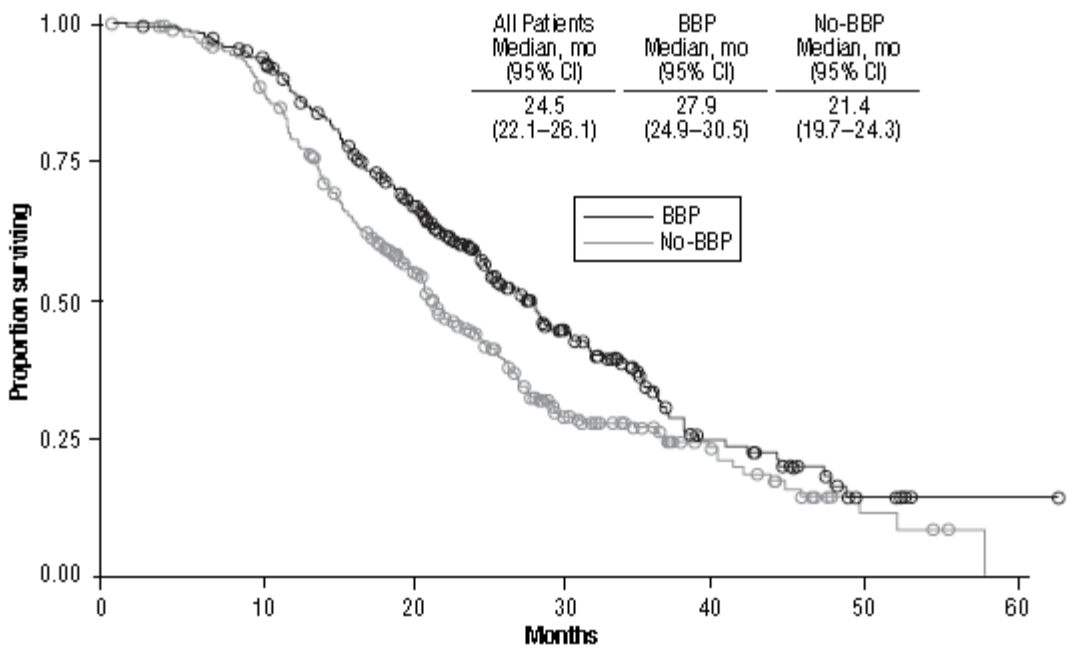
No. at risk									
CT	410	293	162	51	24	7	3	2	0
Bev + CT	409	328	189	64	29	13	4	1	0

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

[a]Primary analysis method; [b]Stratified 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)

Arnold D, et al. *J Clin Oncol*. 2012;30(15S): Abstract CRA3503.

Figure 2 Overall Survival by Treatment Cohort



Abbreviation: BBP = bevacizumab beyond progression.

Conclusions

- First randomized clinical trial that prospectively investigated the impact of continued VEGF inhibition with Bev beyond first progression
- Study confirms that continuing Bev beyond first progression while modifying CT is beneficial for patients with mCRC and leads to a significant improvement in OS and PFS
- This provides a new second-line treatment option for patients who have been treated with Bev + standard CT in first line while maintaining an acceptable safety profile
- Findings indicate a potential new model for treatment approaches through multiple lines and across other tumor types

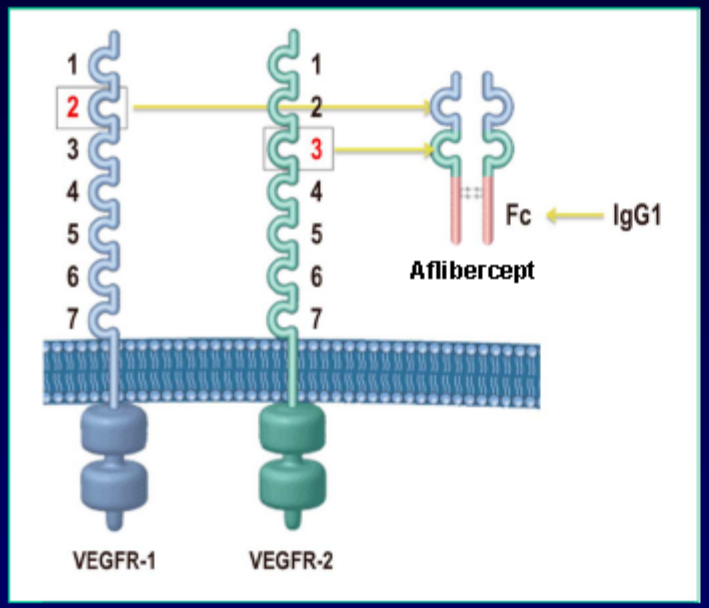
Arnold D, et al. *J Clin Oncol.* 2012;30(15S): Abstract CRA3503.

Effects of Prior Bevacizumab Use on Outcomes From the VELOUR Study: A Phase III Study of Aflibercept and FOLFIRI in Patients with Metastatic Colorectal Cancer After Failure of an Oxaliplatin Regimen

Abstract 3505

Allegra CJ, Lakomy R, Tabernero J, Prausová J, Ruff P, Van Hazel G, Mikhailovich Moiseyenko V, Ferry DR, McKendrick JJ, Van Cutsem E

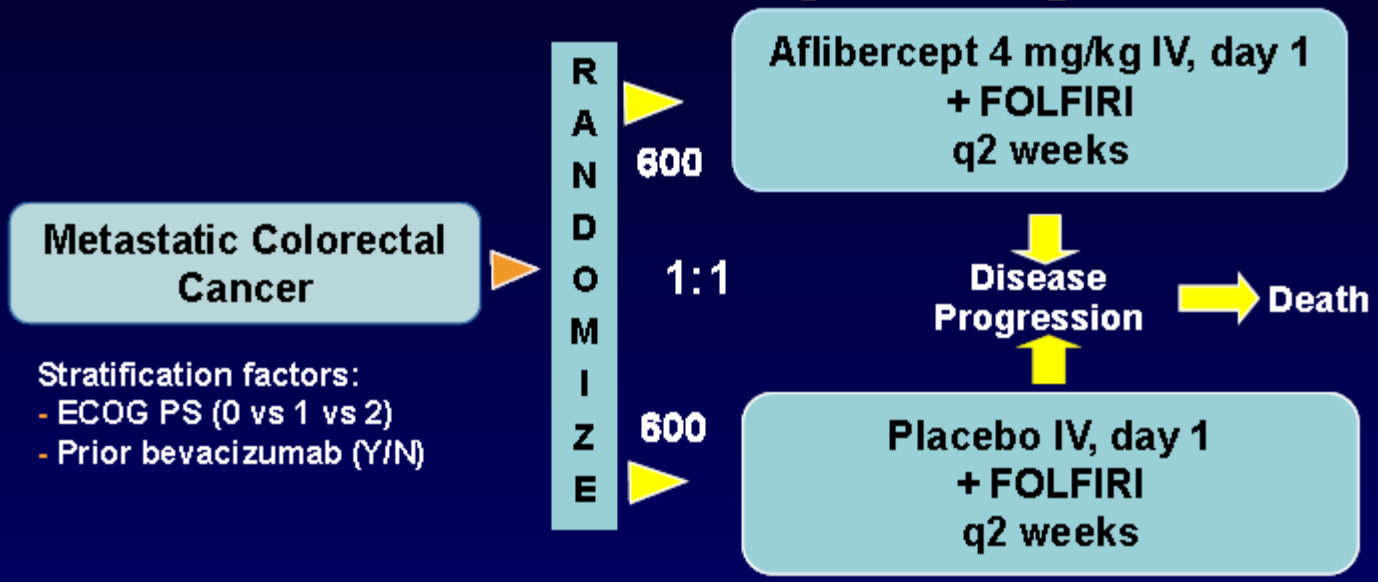
Aflibercept



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

1. Holash J, et al. *Proc Natl Acad Sci U S A*. 2002;99(17):11393-11398. 2. Tew WP, et al. *Clin Cancer Res*. 2010;16(1):358-366. Allegra C, et al. *J Clin Oncol*. 2012;30(15S): Abstract 3505.

VELOUR Study Design



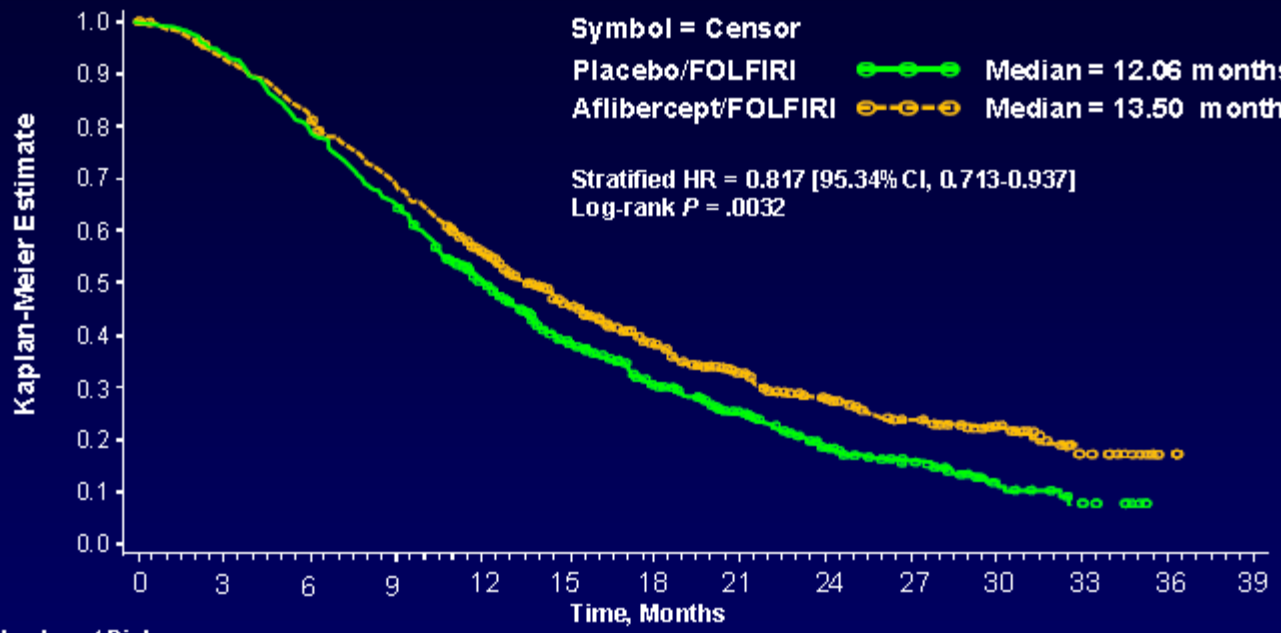
Primary endpoint: Overall survival (OS)

Sample size: HR 0.8, 90% power and a 2-sided type I error 0.05

Final analysis of OS: Analyzed at 863rd death event using a 2-sided nominal significance level of .0466 (α spending function)

Allegra C, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3505.

Overall Survival, ITT Population



Number at Risk

Placebo	614	573	485	401	286	193	131	87	51	31	14
AFLI	612	566	498	416	311	216	148	104	75	49	33

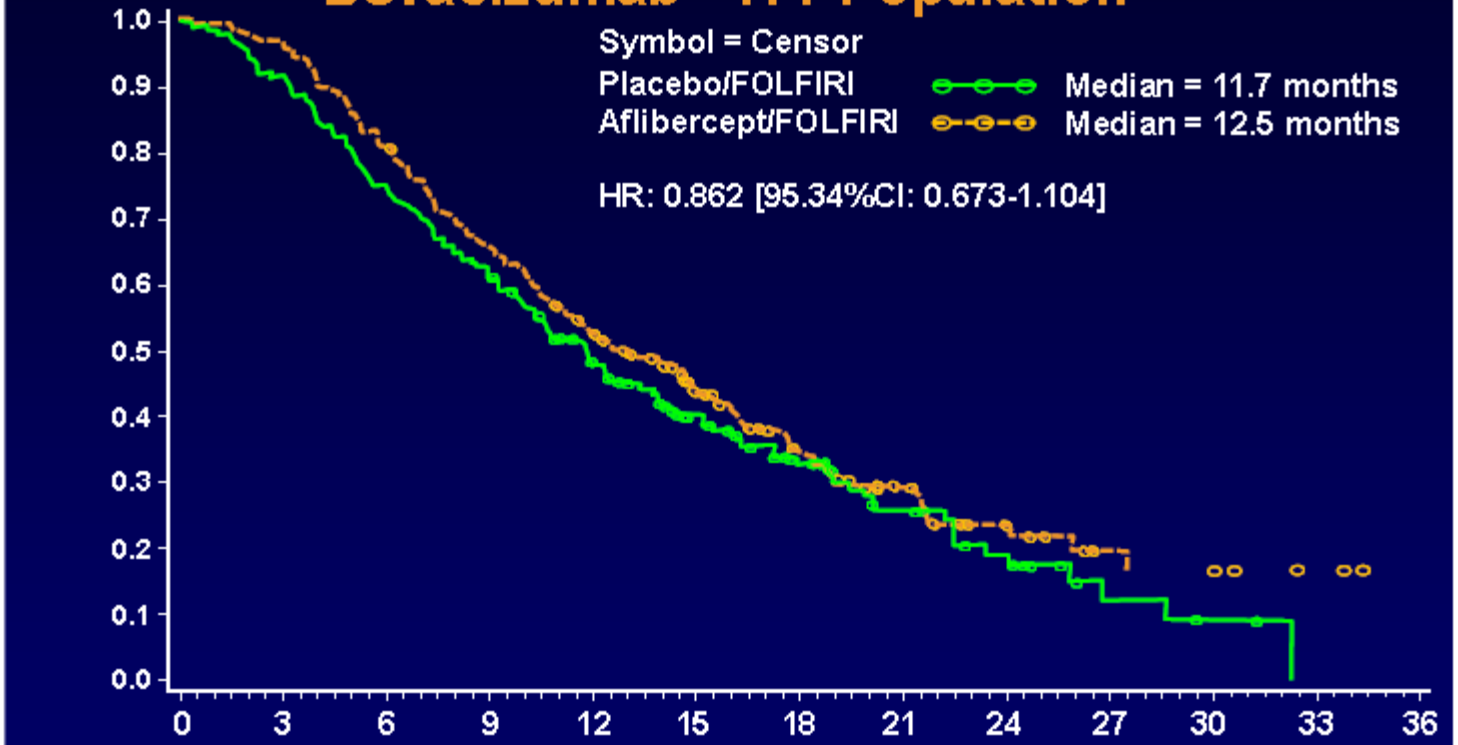
Survival probability, %

Placebo	79.1	50.3	30.9	18.7	12.0
AFLI	81.9	56.1	38.5	28.0	22.3

Van Cutsem E, et al. *Ann Oncol.* 2011;22(Suppl 5). Abstract O-0024.
Allegra C, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3505.

Cut-off date = February 7, 2011;
Median follow-up = 22.28 months

Overall Survival: Patients With Prior Treatment With Bevacizumab—ITT Population



Number at Risk									
Placebo	187	170	138	115	81	54	37	22	13
AFLI	186	178	150	121	89	59	36	22	13

Allegra C, et al. *J Clin Oncol*. 2012;30(15S): Abstract 3505.

Discontinuation of Study Treatment

ITT Population	Placebo N = 614	Aflibercept N = 612
Discontinued study treatment	97.4%	96.9%
Disease progression	71.2%	49.8%
Adverse event	12.1%	26.6%
Patient request	7.0%	12.6%
Investigator decision	3.4%	3.3%
Metastatic surgery	1.6%	2.0%
Other causes*	2.1%	2.6%
Study treatment ongoing	1.8%	2.3%

*Other causes included consent withdrawal, lost to F-up, poor compliance, and other not classified reasons

Van Cutsem et al. Ann Oncol. 2011;22(suppl 5). Abstract O-0024

Conclusions

- Adding aflibercept to FOLFIRI in mCRC patients previously treated with oxaliplatin-based regimen resulted in OS and PFS benefits that are both statistically significant and clinically meaningful
  [Van Cutsem E, et al. *Ann Oncol.* 2011;22(Suppl 5): Abstract O-0024.]
  - OS: HR = 0.817 [95.34% CI, 0.713-0.937], *P* = .0032
  - PFS: HR = 0.758 [99.99% CI, 0.578-0.995], *P* = .00007

- Preplanned subgroup analyses supported consistency and robustness of the efficacy results across all domains, including prior treatment with bevacizumab

- Prior treatment with bevacizumab does not appear to significantly impact the safety profile of aflibercept

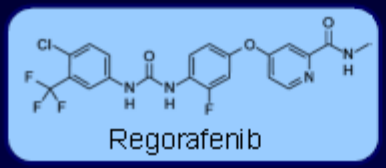
Allegra C, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3505.

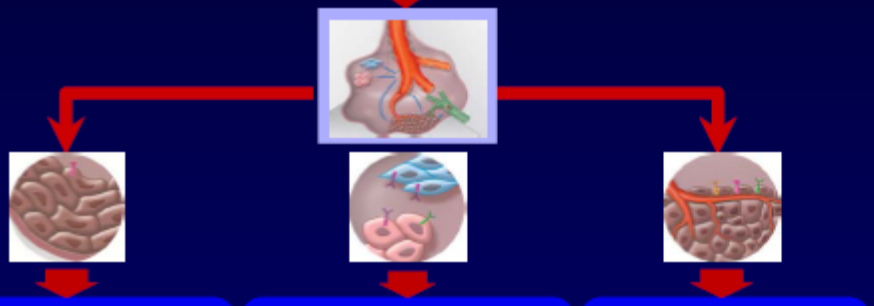
Phase III CORRECT Trial of Regorafenib in Metastatic Colorectal Cancer (mCRC)

Abstract 3502

Van Cutsem E, Sobrero AF, Siena S, Falcone A, Ychou M, Humblet Y, Bouche O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz H-J, Goldberg RM, Sargent DJ, Cihon F, Wagner A, Laurent D, Grothey A, on behalf of CORRECT Investigators

Regorafenib (BAY 73-4506), an Oral Multikinase Inhibitor Targeting Multiple Tumor Pathways[1-3]





Inhibition of proliferation

KIT
PDGFR
RET

Inhibition of tumor microenvironment signaling

PDGFR-β
FGFR

Inhibition of neoangiogenesis

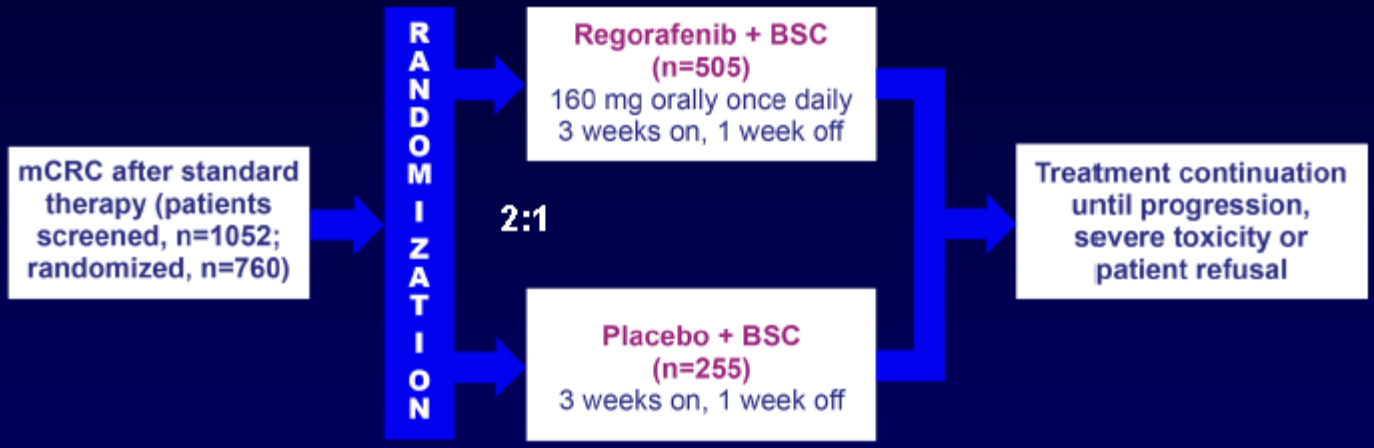
VEGFR1-3
TIE2

Biochemical Activity	Regorafenib IC_{50} mean ± SD nmol/l (n)	
VEGFR1	13 ± 0.4	(2)
Murine VEGFR2	4.2 ± 1.6	(10)
Murine VEGFR3	46 ± 10	(4)
TIE2	311 ± 46	(4)
PDGFR-β	22 ± 3	(2)
FGFR1	202 ± 18	(6)
KIT	7 ± 2	(4)
RET	1.5 ± 0.7	(2)
RAF-1	2.5 ± 0.6	(4)
B-RAF	28 ± 10	(6)
$B\text{-}RAF^{V600E}$	19 ± 6	(6)

1. Wilhelm SM, *et al. Int J Cancer.* 2011;1219(1):245-255.
2. Mross K, *et al. Clin Cancer Research* 2012;18(9):2658-2667.
3. Strumberg D, *et al. Expert Opin Investig Drugs.* 2012;21(6):879-889.

Van Cutsem E, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3502.

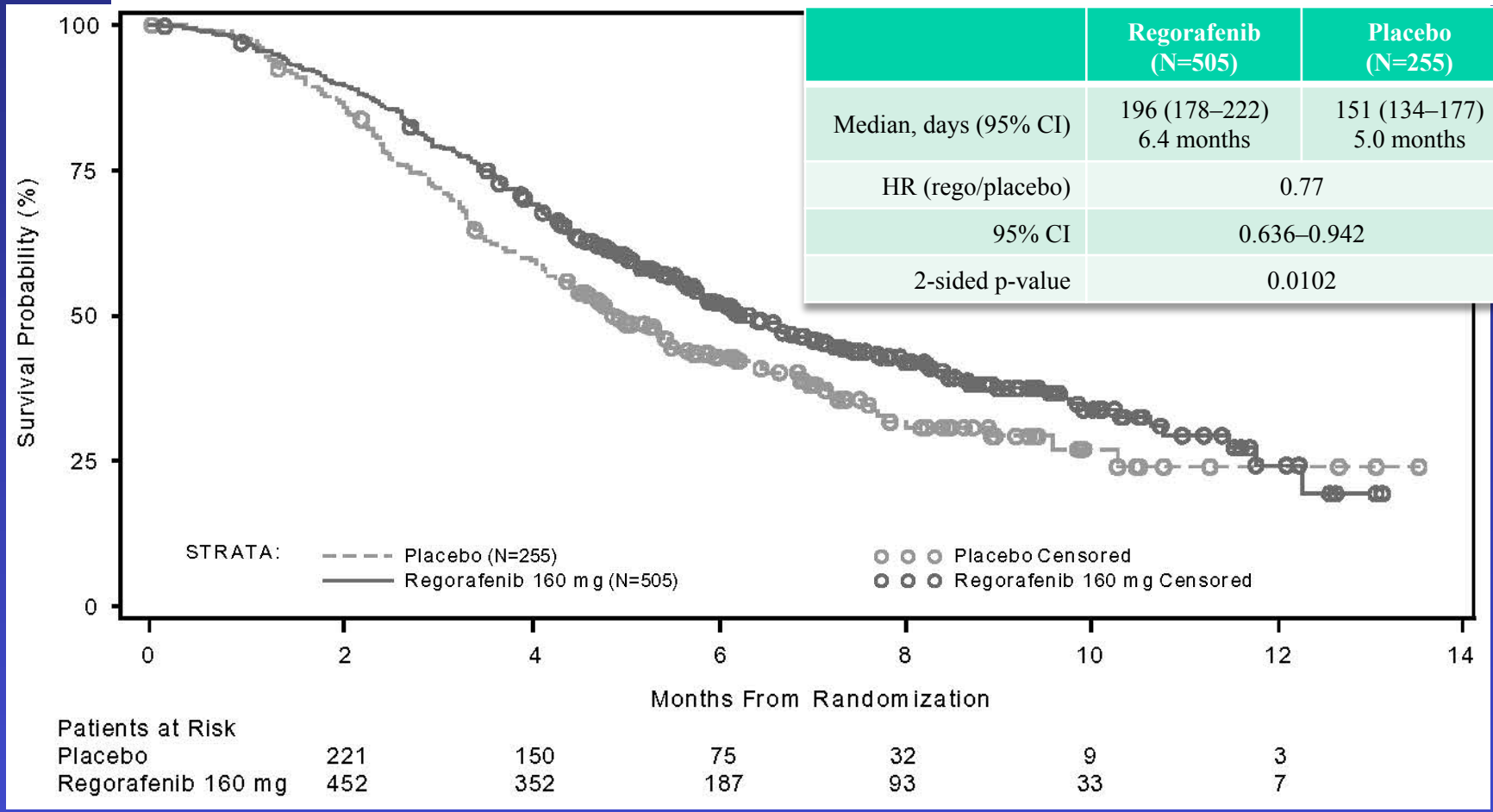
CORRECT: Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: prior anti-VEGF therapy, time from diagnosis of metastatic disease, geographic region
- Global trial: 16 countries, 114 centers
- Recruitment: May 2010 to March 2011

Van Cutsem E, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3502.

Primary Endpoint: OS



	Regorafenib (N=505)	Placebo (N=255)
Median, days (95% CI)	196 (178–222) 6.4 months	151 (134–177) 5.0 months
HR (rego/placebo)	0.77	
95% CI	0.636–0.942	
2-sided p-value	0.0102	

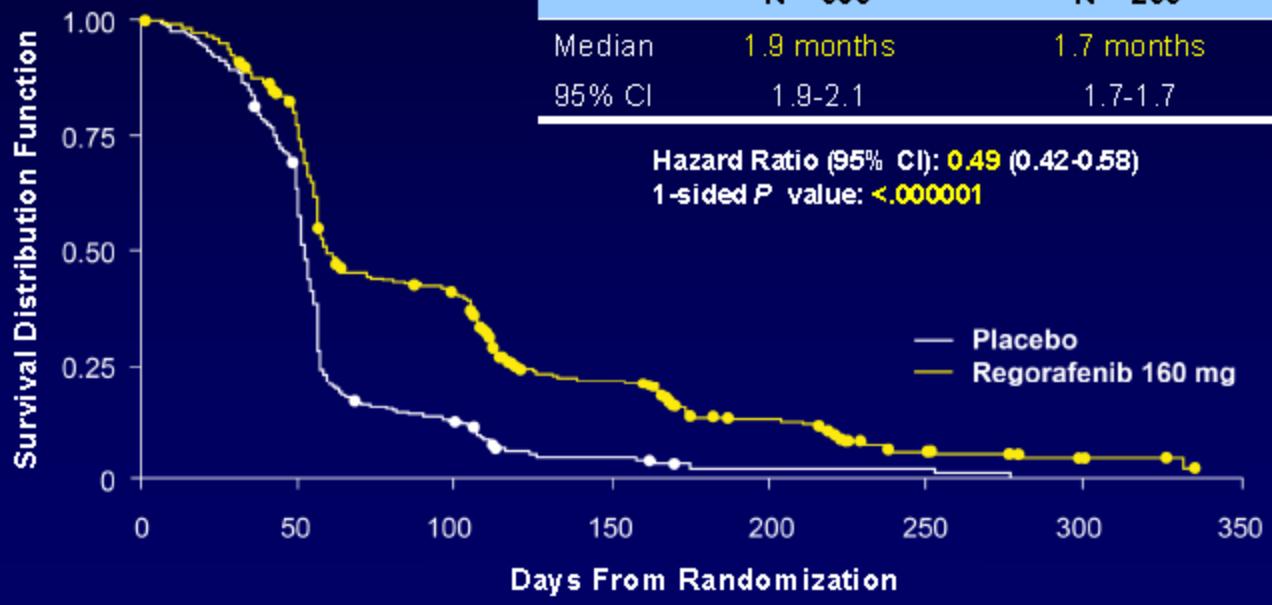
1. Regorafenib [prescribing information]. 2012.

Progression-Free Survival (Secondary Endpoint)

Regorafenib significantly improves PFS compared to placebo

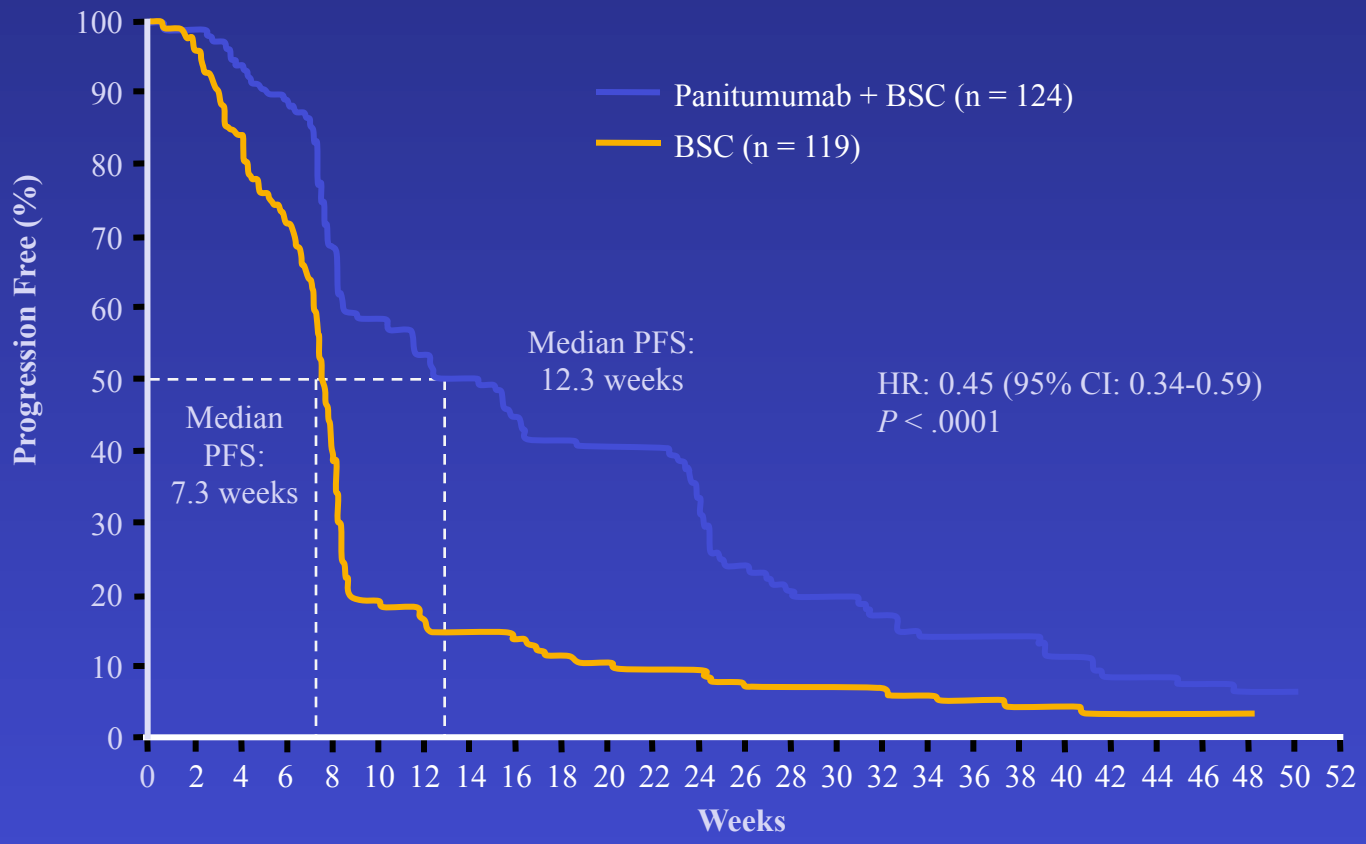
	Regorafenib, N = 505	Placebo, N = 255
Median	1.9 months	1.7 months
95% CI	1.9-2.1	1.7-1.7

Hazard Ratio (95% CI): 0.49 (0.42-0.58)
1-sided *P* value: <.000001



Van Cutsem E, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3502.

Panitumumab vs BSC in mCRC With Wild-Type K-ras: PFS Results



Amado R, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.J Clin Oncol 2008;26:1626-1634. Reprinted with permission from the American Society of Clinical Oncology.

Summary of CORRECT Results

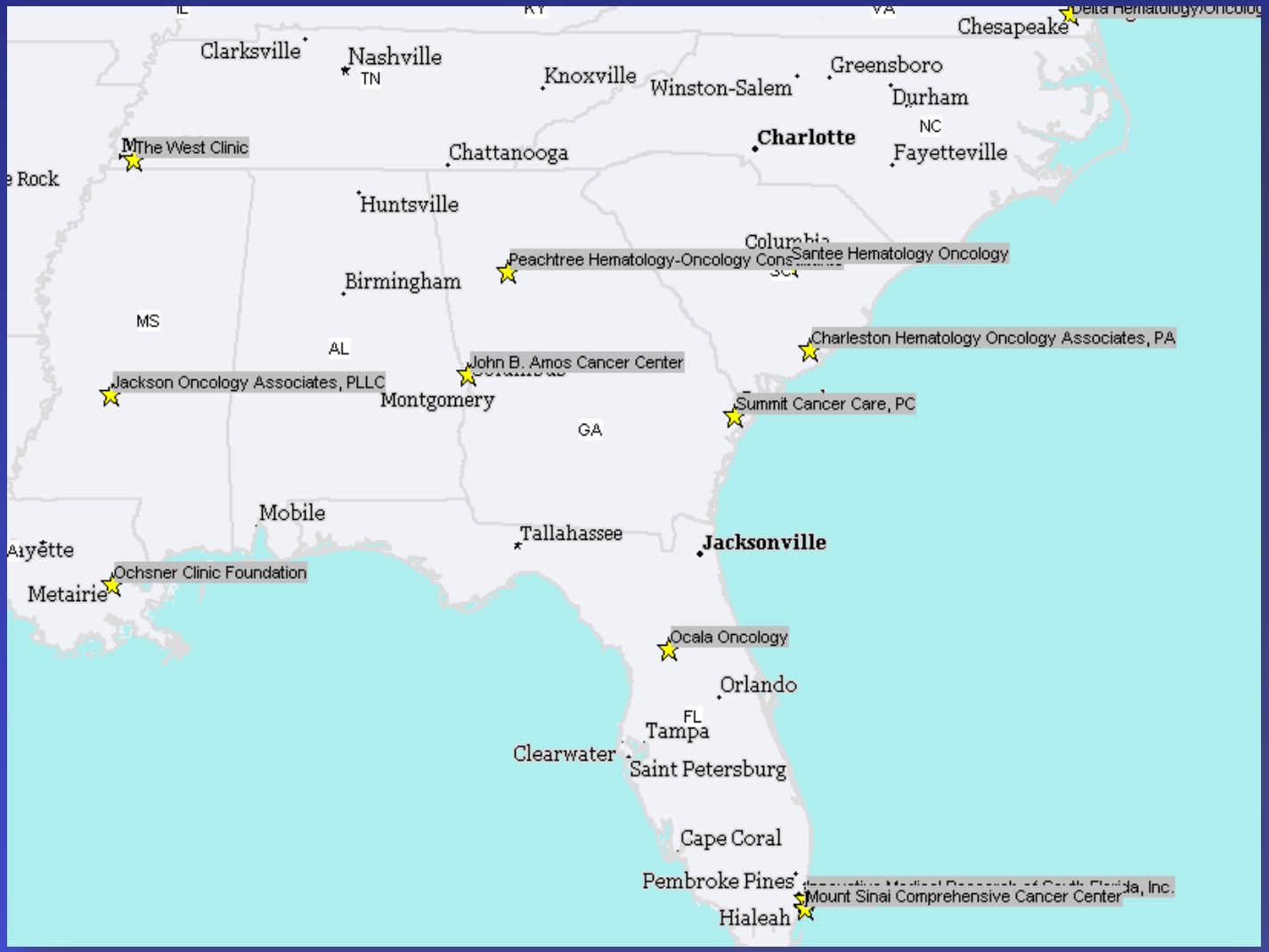
- The study met its primary endpoint at the preplanned interim analysis
- Regorafenib *vs* placebo:
  - **OS: 6.4 months *vs* 5.0 months, HR = 0.77, *P* = .0052**
    - Crossed prespecified boundary (1-sided *P*<.009279)
  - PFS: 1.9 *vs* 1.7 months, HR = 0.49, *P*<.000001
  - DCR (PR + SD): 41.0% *vs* 14.9%, *P*<.000001
- Subgroup analyses:
  - Regorafenib showed OS and PFS benefit across prespecified subgroups
  - Efficacy of regorafenib was independent of *KRAS* mutation status
- No new or unexpected safety findings:
  - Most frequent grade 3 events related to regorafenib were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash

Van Cutsem E, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3502.

CONSIGN Schema

- Multicenter, open-label, phase IIIb
- Primary objective: to provide regorafenib to mCRC patients who have failed all approved standard therapies
- Main endpoint: Safety
- PFS will also be assessed

EAP sites South



Drug-Related Treatment-Emergent Adverse Events Occurring in ≥10% of Patients

Adverse event, %	Regorafenib N = 500				Placebo N = 253			
	All grades	Grade 3	Grade 4	Grade 5*	All grades	Grade 3	Grade 4	Grade 5*
Hand-foot skin reaction	46.6	16.6	0	0	7.5	0.4	0	0
Fatigue	47.4	9.2	0.4	0	28.1	4.7	0.4	0
Hypertension	27.8	7.2	0	0	5.9	0.8	0	0
Diarrhea	33.8	7.0	0.2	0	8.3	0.8	0	0
Rash / desquamation	26.0	5.8	0	0	4.0	0	0	0
Anorexia	30.4	3.2	0	0	15.4	2.8	0	0
Mucositis, oral	27.2	3.0	0	0	3.6	0	0	0
Thrombocytopenia	12.6	2.6	0.2	0	2.0	0.4	0	0
Fever	10.4	0.8	0	0	2.8	0	0	0
Nausea	14.4	0.4	0	0	11.1	0	0	0
Bleeding	11.4	0.4	0	0.4	2.8	0	0	0
Voice changes	29.4	0.2	0	0	5.5	0	0	0
Weight loss	13.8	0	0	0	2.4	0	0	0

* Grade 5 drug-related AEs: 1.0% in regorafenib arm vs 0% in placebo arm

Van Cutsem E, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3502.

ClinicalOncology® News

Ziv-Aflibercept Helps Patients With mCRC, But at What Cost?

EXPERT INSIGHT

Progress in the treatment of advanced colon cancer has slowed during the past several years. In fact, until recently the most recent drug approval by the FDA for colon cancer was in 2006.
In August 2012, ziv-aflibercept was approved by the FDA for the treatment of second-line colorectal cancer added to FOLFIRI. A large randomized Phase III trial, published in the *Journal of Clinical Oncology*, showed that adding ziv-aflibercept to FOLFIRI significantly improved OS, PFS and response rate; however, the survival benefit was small. The absolute survival benefit was 1.4 months and improvement in PFS was a little more than two months……..

Thomas H. Cartwright, MD
Medical Oncologist and Hematologist
Ocala Oncology
The US Oncology Network

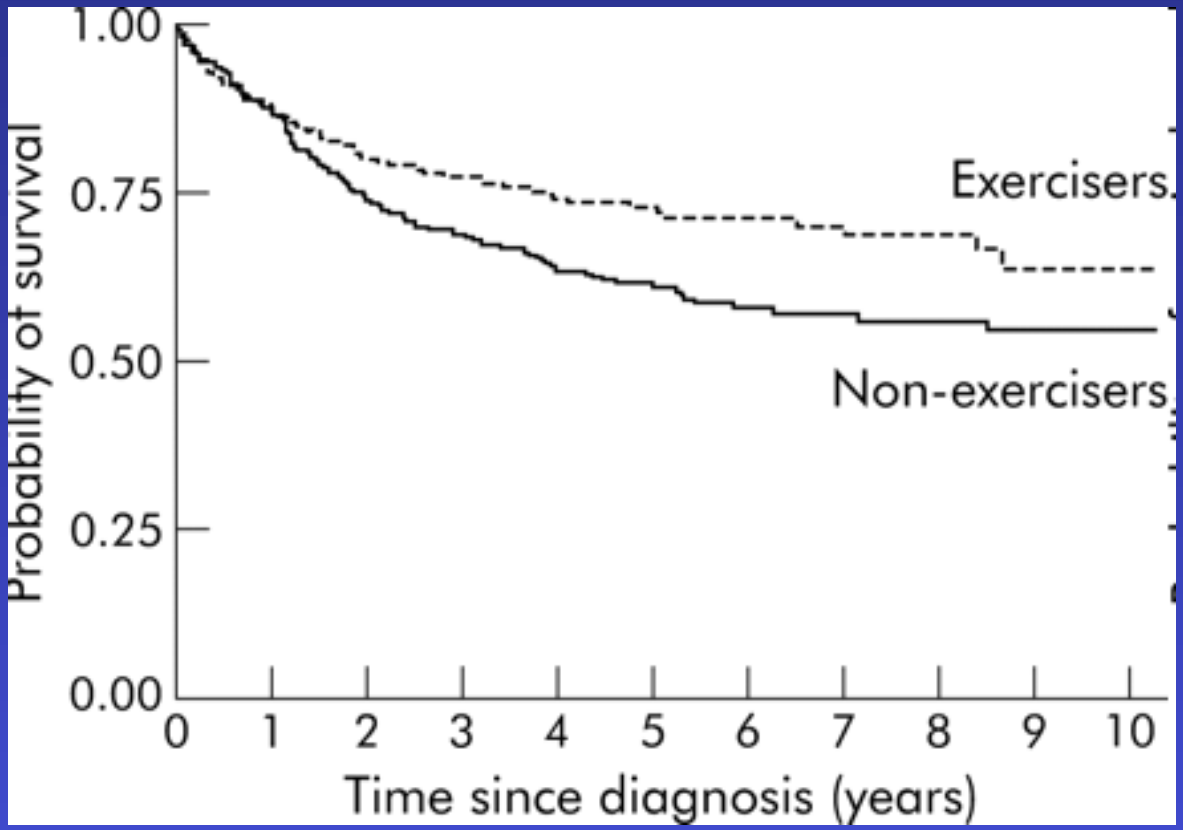
US Oncology pathways preserve survival, reduce cost by 34% in metastatic colon cancer.

Table 1: Impact of pathways in colon cancer			
	Overall survival (mos)	Chemo Cost ($)	Total Cost ($)
Pathway (limited types)	26.9	22,564	103,379
Non-pathway (no limits)	20.1	60,787	156,020
P value	0.03	<0.001	<0.001

Hoverman R, et al. Am J Manag Care. 2011 May;17 Suppl 5 Developing:SP45-52.

Physical Activity and Colorectal Cancer

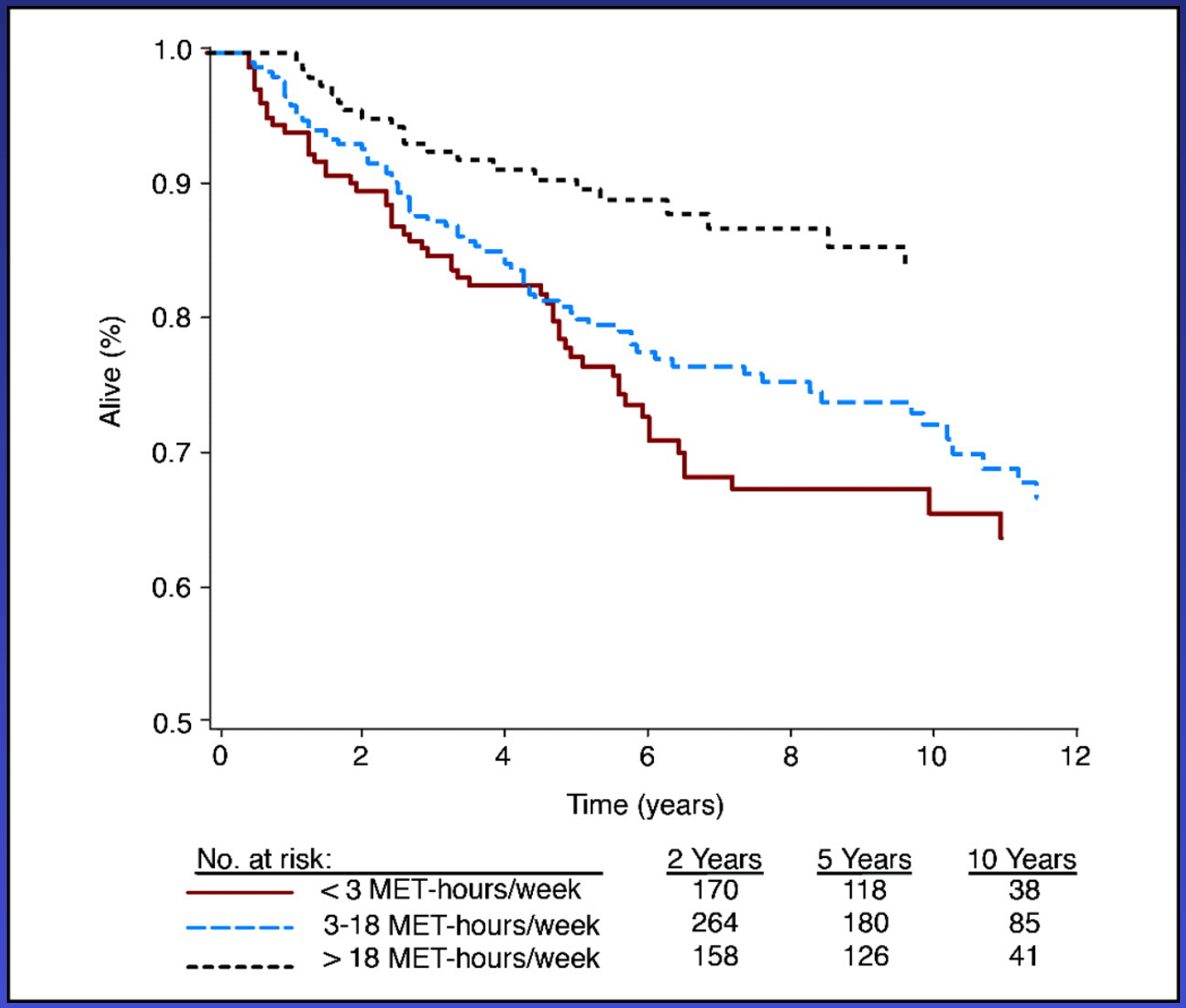
- Cohort study from Australia of 526 colorectal cancer patients with pre-diagnosis physical activity assessment



Colorectal cancer specific survival

Haydon Gut. 2006 Jan;55(1):62-7

NHS and Post-diagnosis Physical Activity



Meyerhardt, J. A. et al. J Clin Oncol; 24:3527-3534 2006

Questions?