Molecular Diagnostics and Targeted Therapeutics in the Management of Colorectal Cancer

趙 CHAO FAMILY COMPREHENSIVE CANCER CENTER
UNIVERSITY of CALIFORNIA, IRVINE

趙 H.H. CHAO
COMPREHENSIVE DIGESTIVE DISEASE CENTER
UC IRVINE · HEALTHCARE

Jason A. Zell, DO, MPH
Division of Hematology/Oncology
Dept. of Medicine, & Dept. of Epidemiology, University of California Irvine

UC Irvine 7th Annual GI and Hepatology Symposium
March 6, 2015

No relevant financial disclosures

Overview

- Personalized Medicine in CRC: definitions
- Incorporating Molecular Diagnostics and Targeted Therapeutics into Current Management Strategies for CRC
  - Multidisciplinary Treatment by Stage
    - Surgery
    - Molecular prognostic features
    - Chemotherapeutic & Biologic Agents

Case Presentation #1 (Audience Response)

- 74 year male with stage IIA (T3N0M0) sigmoid colon adenocarcinoma status post laparoscopic sigmoid colectomy 30 days ago.

- Under which circumstance can additional testing be considered (12-gene signature assay) prior to recommending adjuvant chemotherapy?

A. No high risk features + MSI-high
B. 1 high risk feature + MSI-high
C. No high risk features + MSS
D. 1 high risk feature + MSS
E. None of the above

Prognostic vs. Predictive Biomarkers

- Prognostic:
  - A biomarker that informs outcome among patients, regardless of treatment rendered

- Predictive:
  - A biomarker that informs benefit (or harm) from a particular treatment

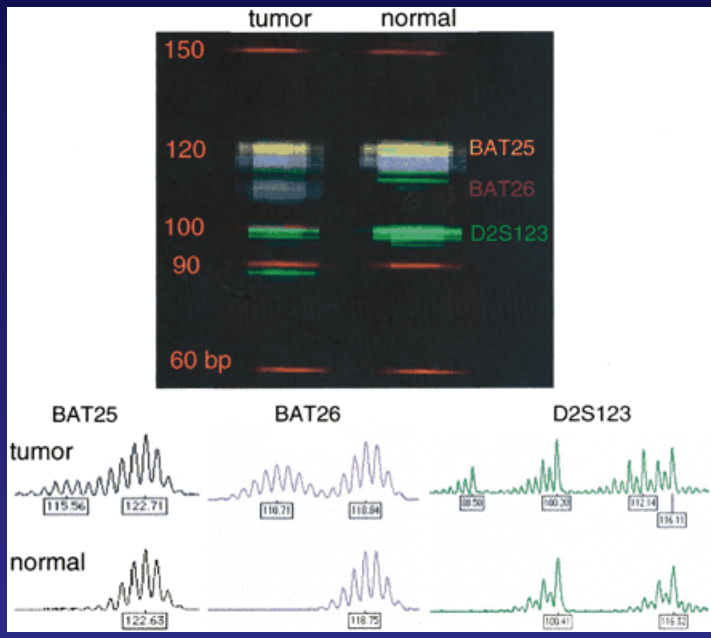
Colorectal Carcinogenesis

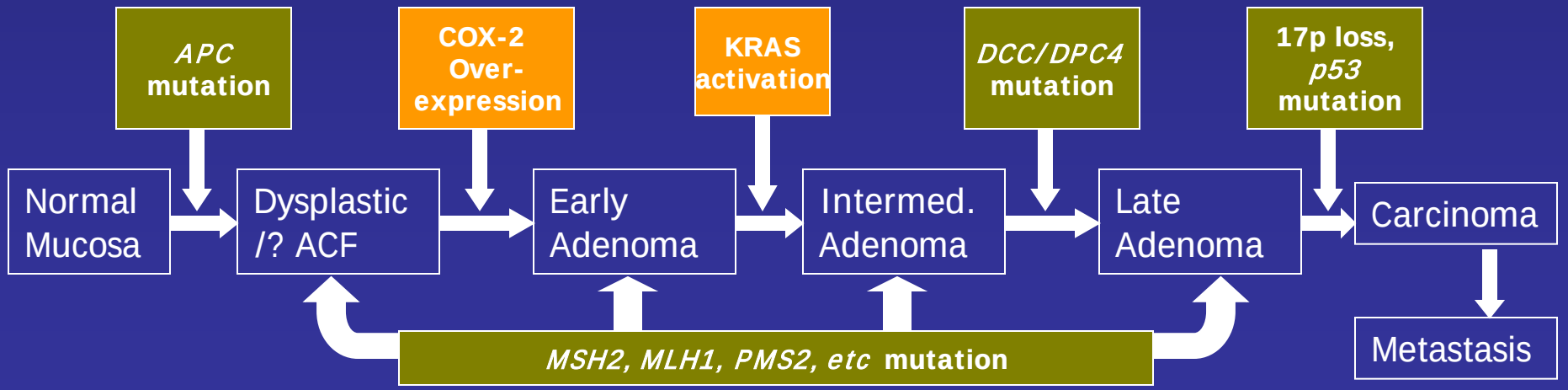
Cell, Vol. 61, 759–767, June 1, 1990, Copyright © 1990 by Cell Press

A Genetic Model for Colorectal Tumorigenesis

Eric R. Fearon and Bert Vogelstein
The Oncology Center
Program in Human Genetics
The Johns Hopkins University School of Medicine
Baltimore, Maryland 21231

Polyacrylamide gel image and electropherograms for a hereditary nonpolyposis colorectal cancer tumor paired with normal tissue.





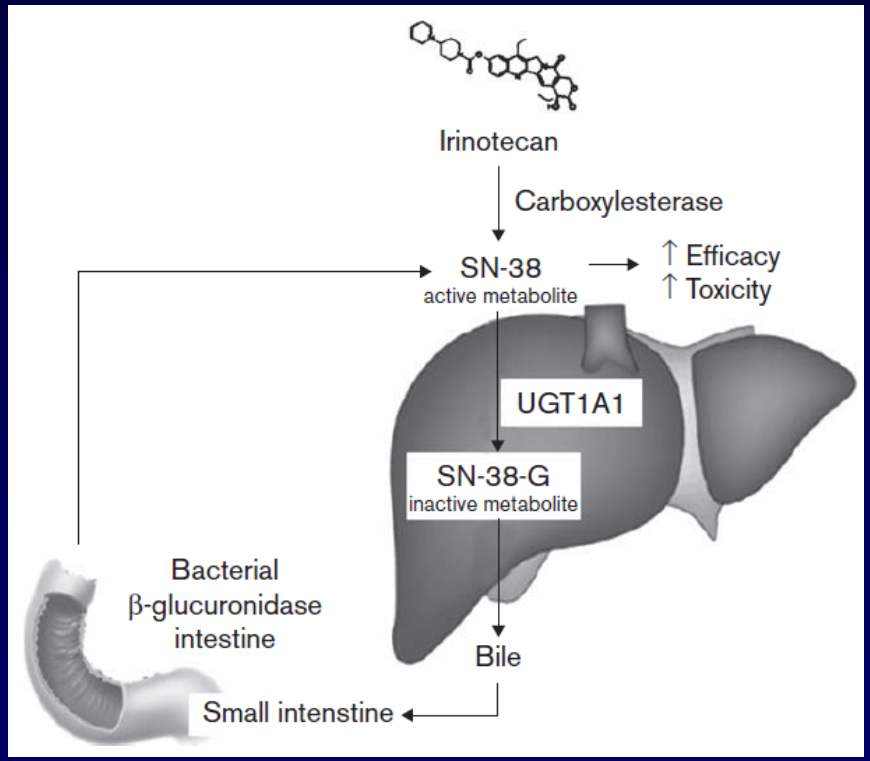
Surgery: considerations

- High Risk Features
  - Grade 3 or 4
  - Lymphovascular invasion
  - Bowel obstruction
  - <12 lymph nodes examined
  - T4 lesion
  - Tumor perforation
  - Inadequate or close surgical margins

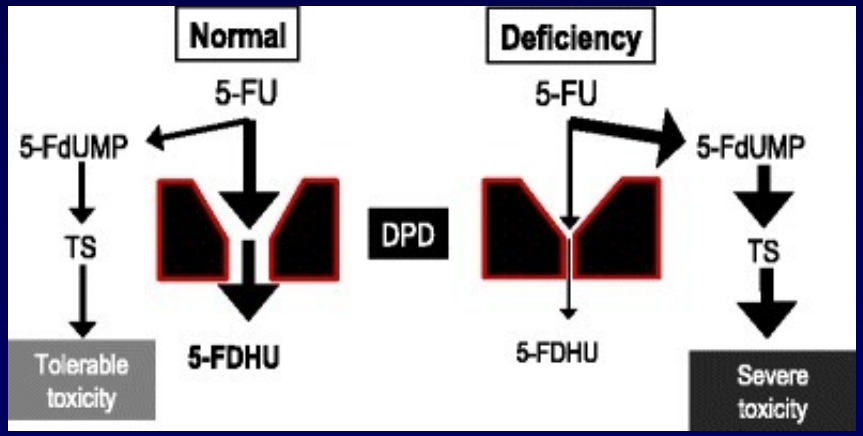
"Personalized Medicine" (Molecular Diagnostics)

- Patient-Specific Tests

UGT-1A1 polymorphism



Dihydropyrimidine-dehydrogenase (DPD) deficiency



Schulz, C et al, Anti-Cancer Drugs 2009, 20:867-879

http://openi.nlm.nih.gov/detailedresult.php?img=3405332_13167_2010_41_Fig2_HTML&req=4

"Personalized Medicine" (Molecular Diagnostics) - continued

- Tumor-Specific Tests
  - Microsatellite Instability (MSI)
  - KRAS mutation analysis
    - Codons 12, 13, 61
  - Extended RAS testing
    - KRAS, NRAS
  - BRAF V600E mutation
  - Gene Signature Profiling
  - *PIK3CA* mutation

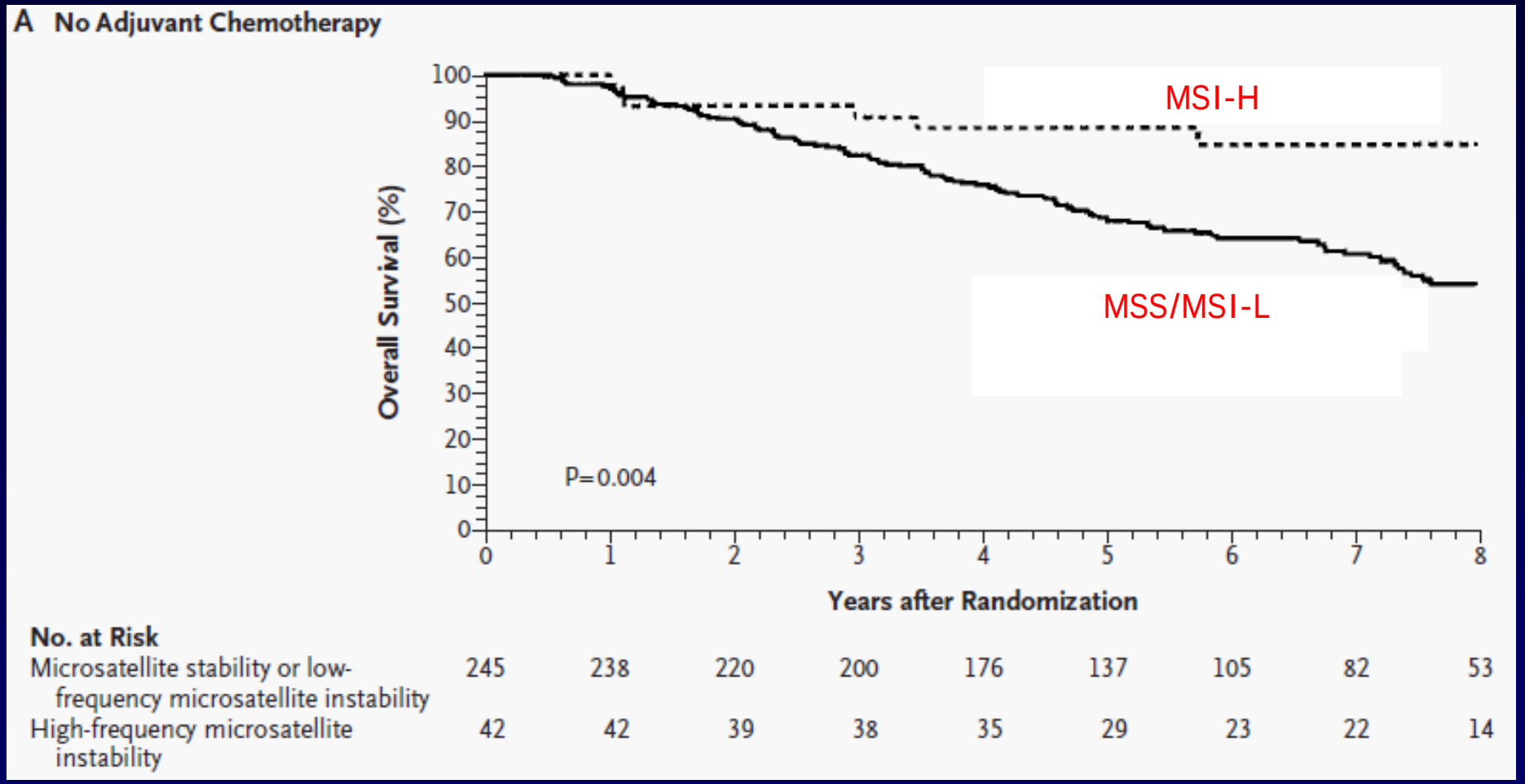
<u>Others:</u>

- Tumor Genomic Sequencing
- Circulating Tumor Cells (FDA-approved for mCRC in 2007)

Stage 0 or Stage I Colon Cancer

- Surgery
- Colonoscopy Surveillance

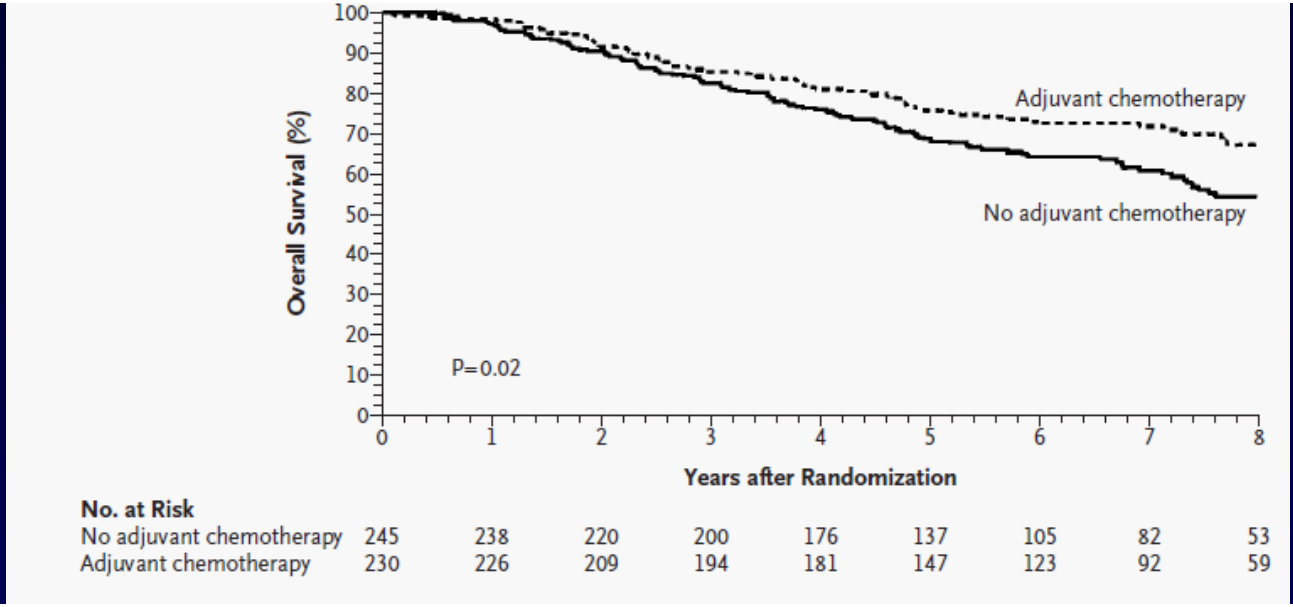
Stage II Colon Cancer
MSI Status is Prognostic



Ribic, CM et al, *New England J Medicine* 349 (3):247-257, 2003

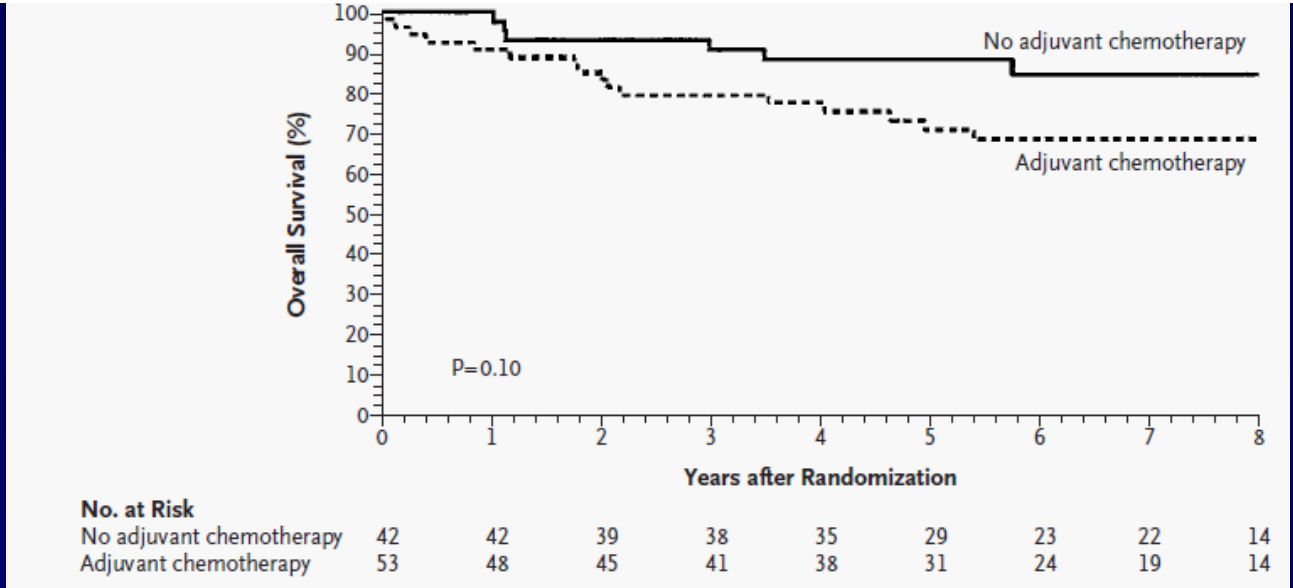
MSI and Adjuvant 5FU-based Chemotherapy

MSS/MSI-L



No. at Risk									
No adjuvant chemotherapy	245	238	220	200	176	137	105	82	53
Adjuvant chemotherapy	230	226	209	194	181	147	123	92	59

MSI-H

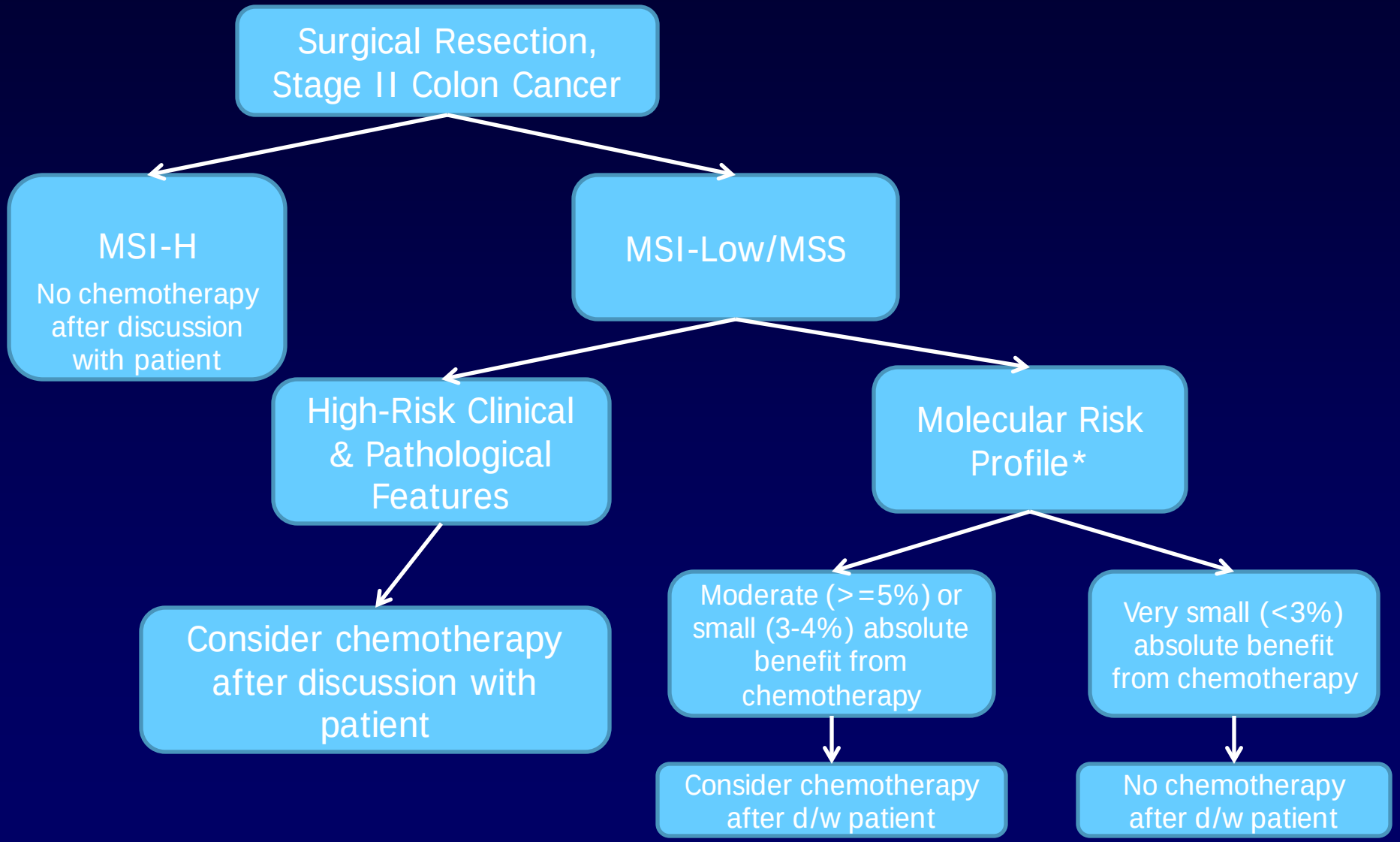


No. at Risk									
No adjuvant chemotherapy	42	42	39	38	35	29	23	22	14
Adjuvant chemotherapy	53	48	45	41	38	31	24	19	14

Ribic, CM et al, *New England J Medicine* 349 (3):247-257, 2003

Stage II Colon Cancer

"Adjuvant Chemotherapy for Stage II Colon Cancer: Are We Closer to Finding the Patients Who Benefit?" Vergo, M, et al., ASCO 2010 Education Book, pp 123-9.



*Kerr, D, et al. *J Clin Oncol*, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition); 27(15S) (May 20 Suppl), 2009: 4000

Stage II Colon Cancer: Chemotherapy considerations

- Multi-gene assay
  - QUASAR study*
  - 12-gene signature assay is prognostic for recurrence among stage II colon cancer patients
  - Genes include: FAP, INHBA, BGN, Ki-67, C-MYC, MYBL2, GDD45B + 5 reference genes.
  - Outcome: Low, Intermediate, High Risk

*Kerr, D, et al. *Journal of Clinical Oncology*, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May 20 Supplement), 2009: 4000

Stage III Colon Cancer:

- Adjuvant chemotherapy:
  - 5FU, leucovorin, oxaliplatin (FOLFOX)
    - Mosaic Trial[1]
    - NSABP C-07[2]
  - Capecitabine, oxaliplatin[3] (CAPOX)
  - 6 months duration
  - NO BIOLOGIC AGENTS

[1]Andre, T., et al, N Engl J Med 2004; 350:2343-2351

[2]Kuebler, JP et al, J Clin Oncol 2007 *25*, 2198-2204.

[3]Haller, DG, et al, J Clin Oncol. 2011 Apr 10;29(11):1465-71.

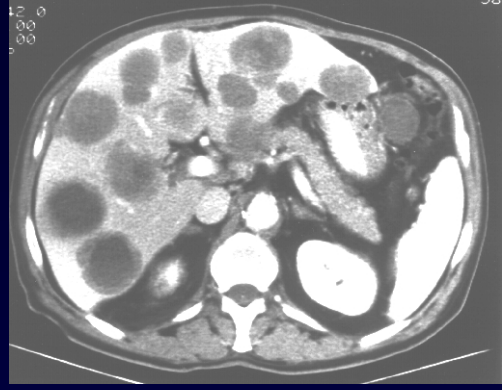
Therapeutic Prevention of CRC: Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

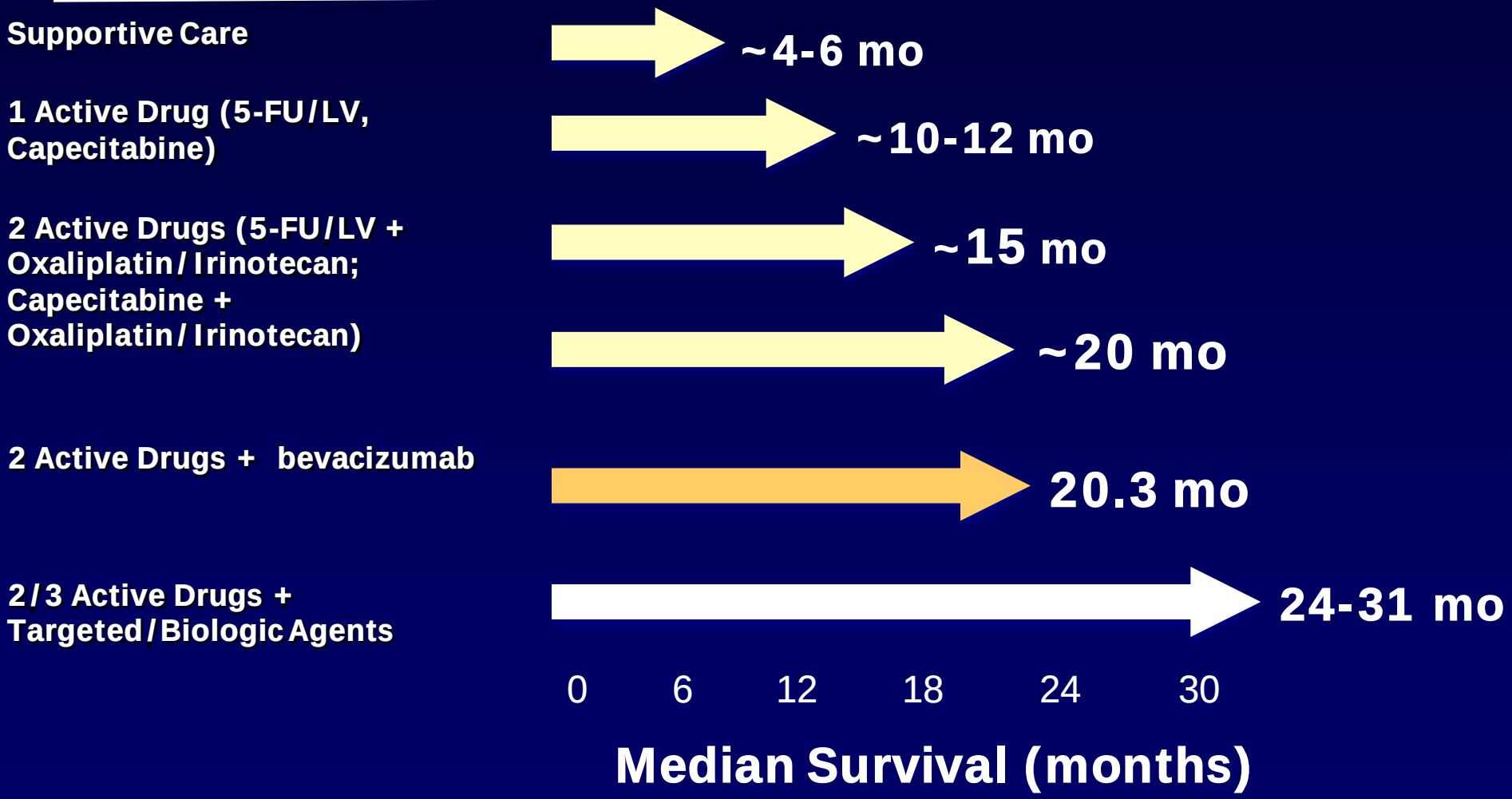
- Aspirin improves survival in *PIK3CA*-mutant CRC patients

  Reference: Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med. 2012;367:1596-606.

- Conflicting data have emerged

Historical Progress: Management of Advanced Colorectal Cancer

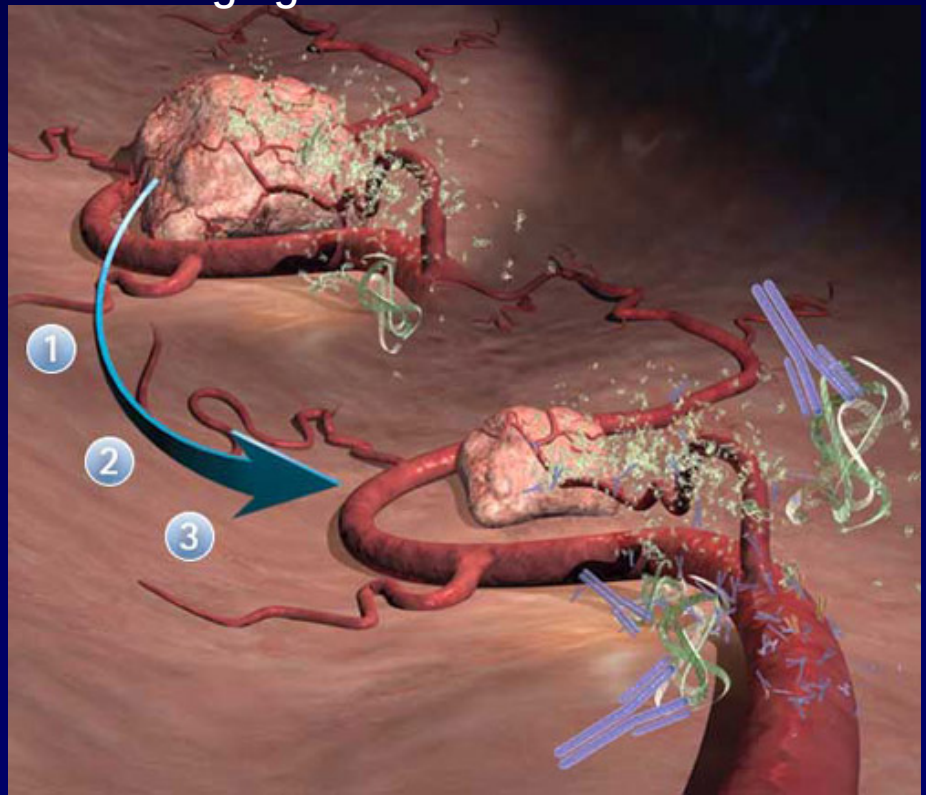




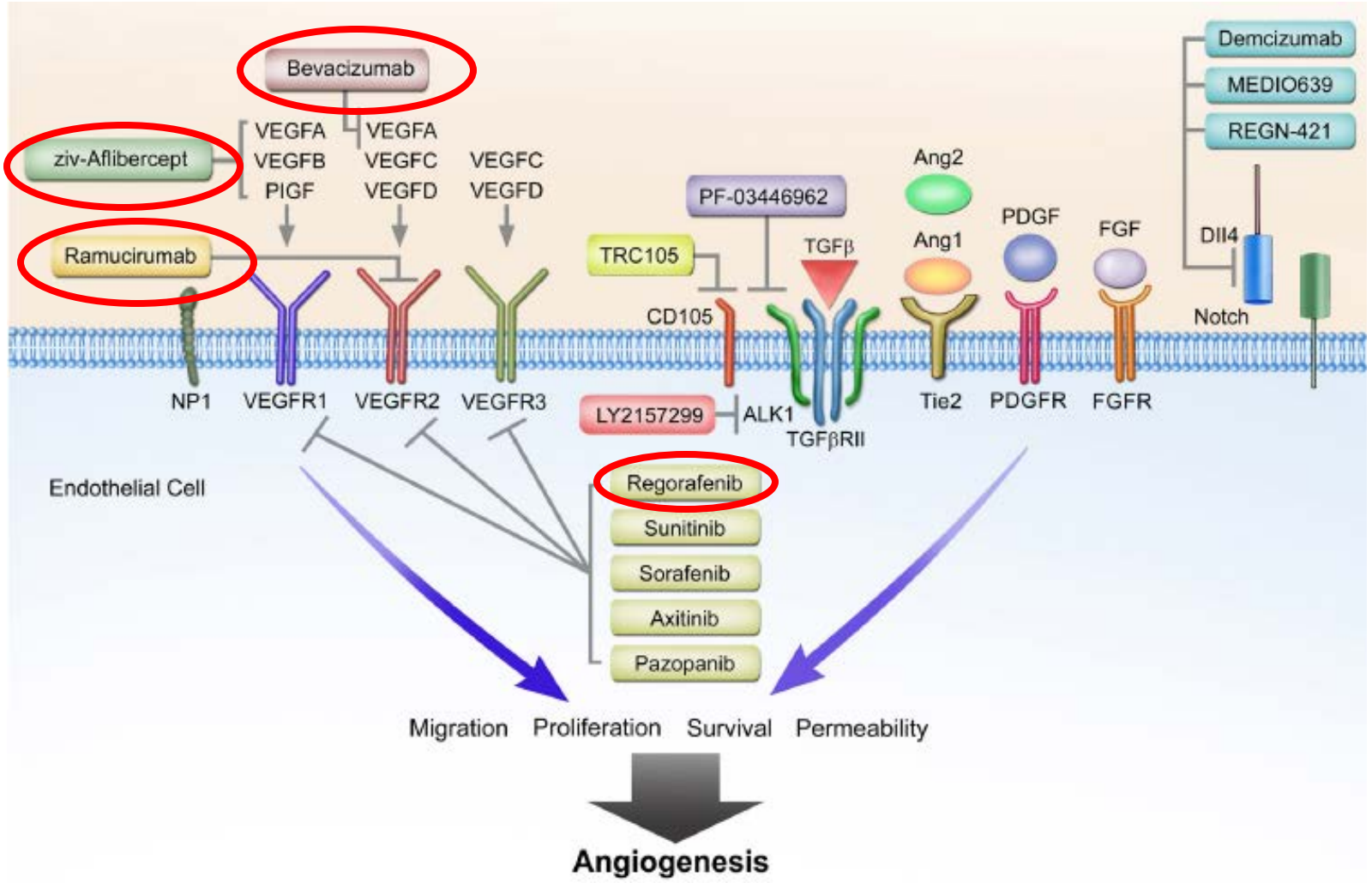
Vascular Endothelial Growth Factor (VEGF)

- Bevacizumab
  - Humanized monoclonal antibody targeting VEGF
  - Overall Response=none
  - Complications:
    - Bleeding, Thrombosis, Hypertension, Proteinuria
    - Wound dehiscence
    - Bowel perforation
- Ziv-aflibercept (VEGF-trap)
  - Recombinant fusion protein
  - Complications: as above
- Regorafenib (multikinase inhibitor) VEGFR/Raf/Kit/PDGFR

Agents bind or trap VEGF, reducing tumor angiogenesis



VEGF-axis dependent and non-VEGF mediated mechanisms of resistance to anti-angiogenic therapies.



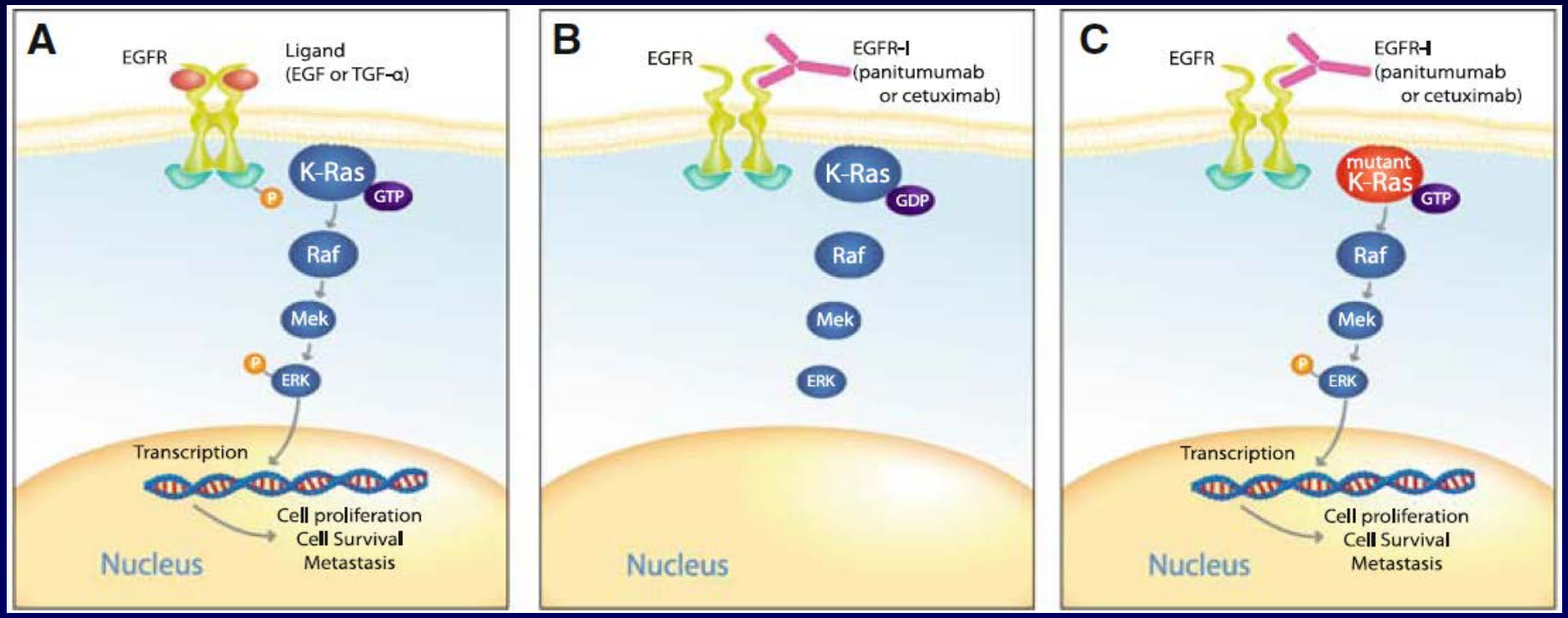
Clarke, JM, and Hurwitz, HI; J Gastrointest Oncol, 2013, Vol 4(3)

EGFR Monoclonal Antibodies

- Cetuximab
  - Overall Response = 10%
  - Complications:
    - Diarrhea
    - Skin toxicity
    - Infusion reactions
    - Hypomagnesemia
    - Interstitial lung disease
- Panitumumab
  - Overall Response = 10%
  - Complications:
    - Diarrhea
    - Skin toxicity
    - Hypomagnesemia

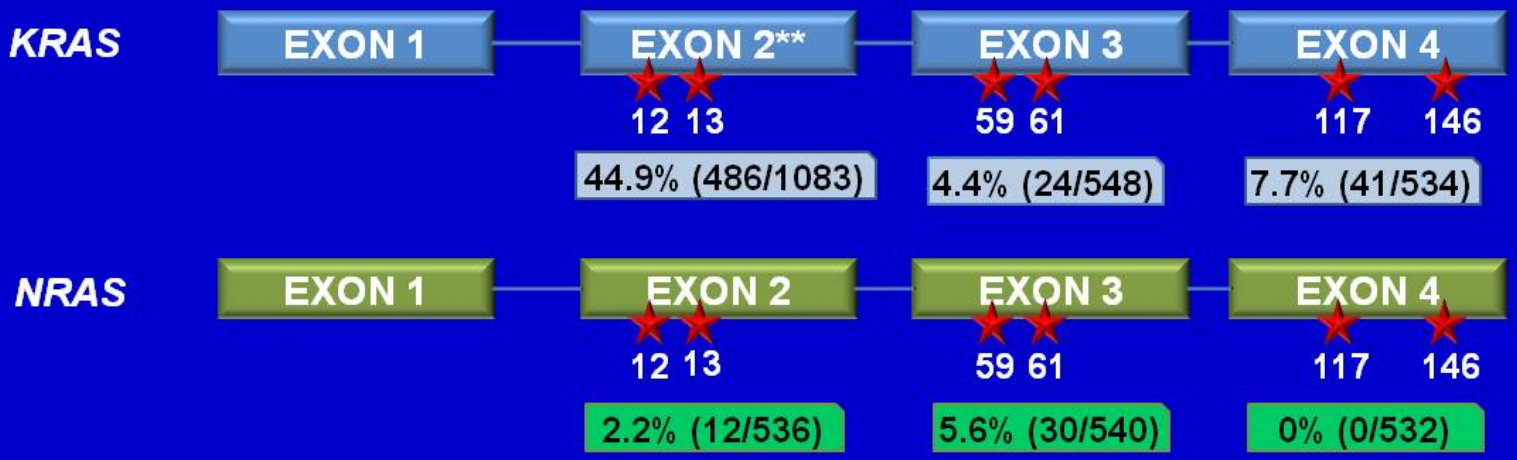
KRAS-wild type patients only!

Epidermal Growth Factor Receptor



Siddiqui and Piperdi. *Ann Surg Oncol.* 17:1168 2010

Prevalence of Mutations*



- 18% (107/597) of *KRAS* exon 2 WT tumors have *RAS* Mutations

* Prevalence is defined as mutations detected in a population of patients with WT *KRAS* exon 2 tumors whose tissues were deemed evaluable for *RAS* testing.

** The *KRAS* exon 2 data is from the overall population.

Stage IV Colorectal Cancer

- First-line:

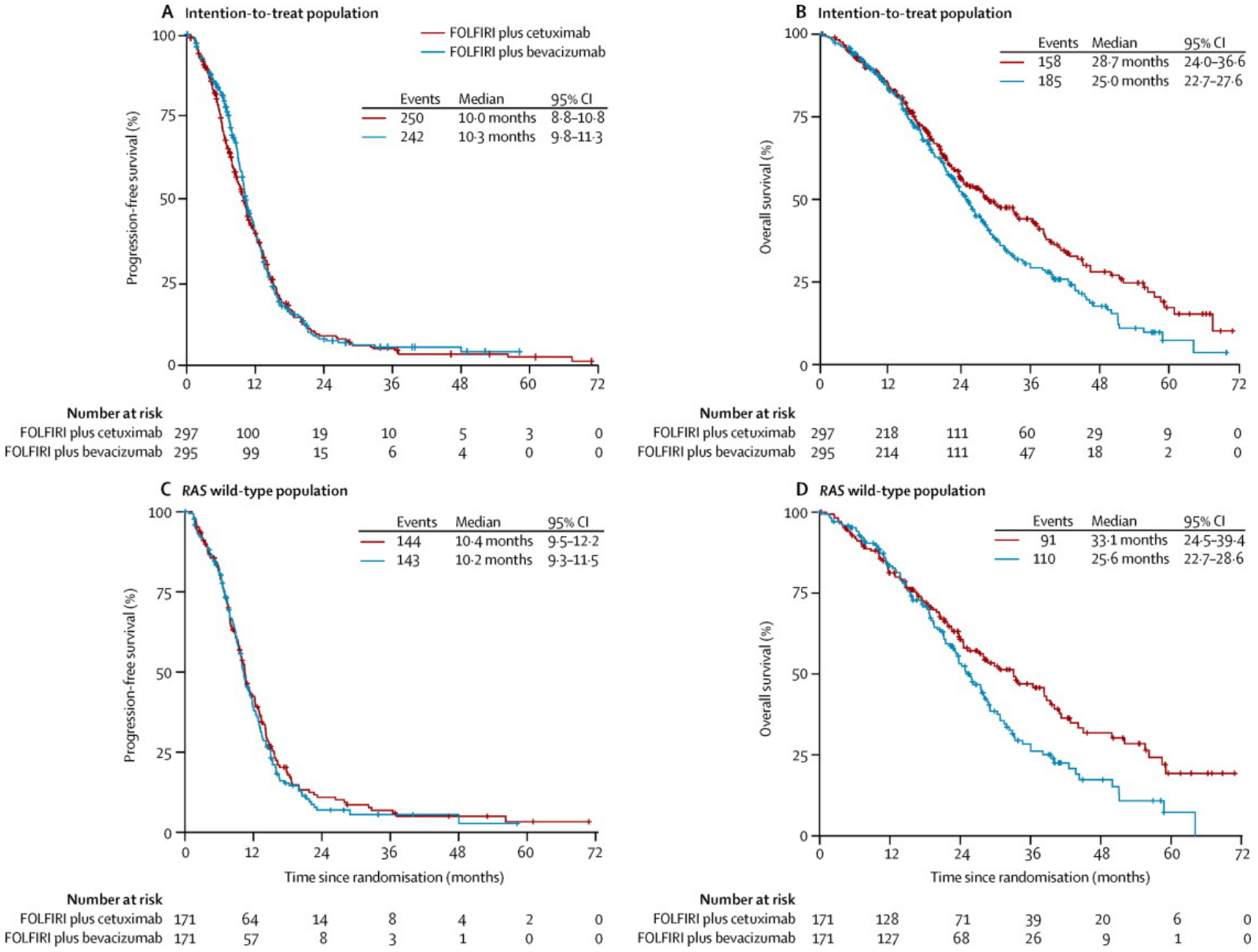
  Chemotherapy + biologic

  - FOLFOX + bevacizumab,
  - FOLFIRI + bevacizumab
  - FOLFIRI + cetuximab or panitumumab if tumor is KRAS wild type

  *In KRAS-wt, which regimen first – bevacizumab or cetuximab?

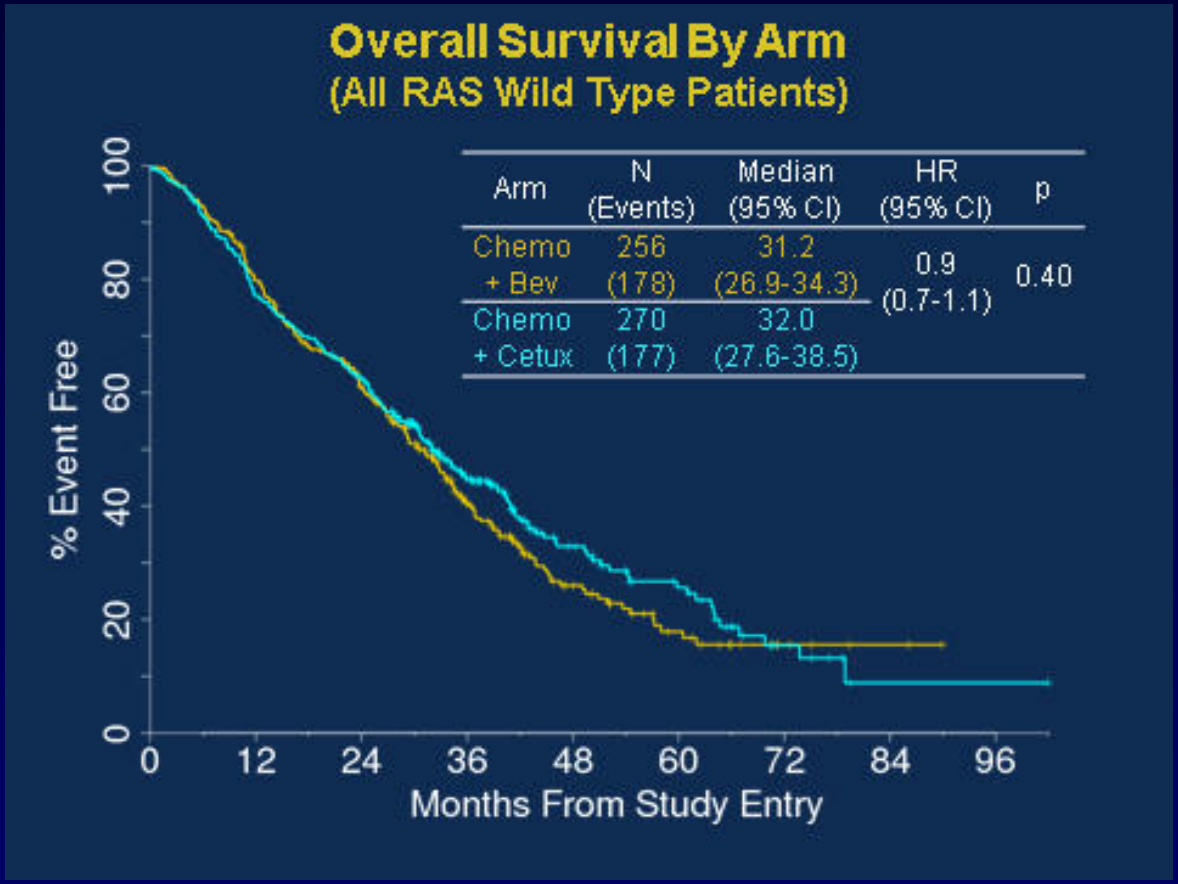
  - Cetuximab if KRAS-wt (FIRE-3)
    - Lancet 2014
  - Doesn't matter: CALGB 80405
    - J Clin Oncol 32:5s, 2014 (suppl; abstr LBA3)

FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial



The Lancet Oncology, Volume 15, Issue 10, 2014, 1065 - 1075
http://dx.doi.org/10.1016/S1470-2045(14)70330-4

CALGB 80405: Chemo + Bev or Cetuximab in RAS-wt stage IV CRC



Lenz, H, Proceedings at ESMO, Sept. 29, 2014, Madrid, Spain

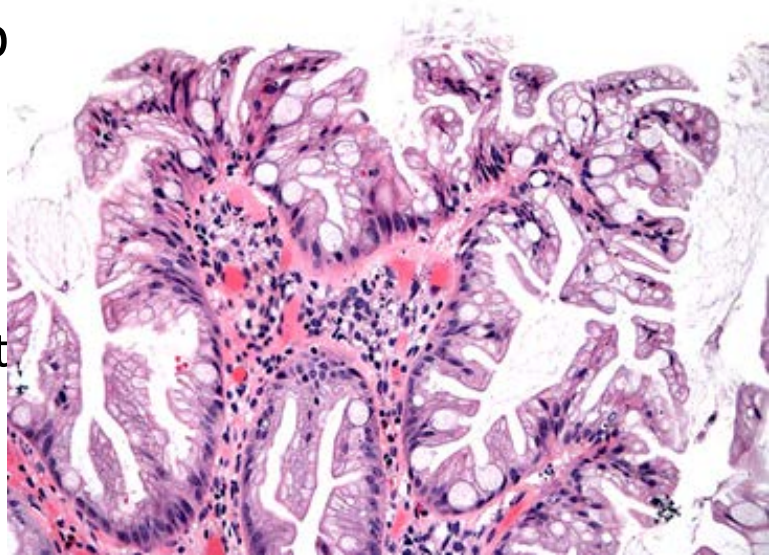
Stage IV Colorectal Cancer

- Second-line:
  - Bevacizumab beyond progression (ASCO 2012)
    - FOLFOX-bev→ FOLFIRI-bev
  - FOLFIRI-ziv-aflibercept
  - FOLFIRI + cetuximab or panitumumab (KRAS-wt)
  - Regorafenib
  - Clinical Trial*

- Third-line and beyond
  - Single agent cetuximab, or panitumumab
  - Regorafenib
  - Clinical Trial *

BRAF mutations define a unique CRC subtype

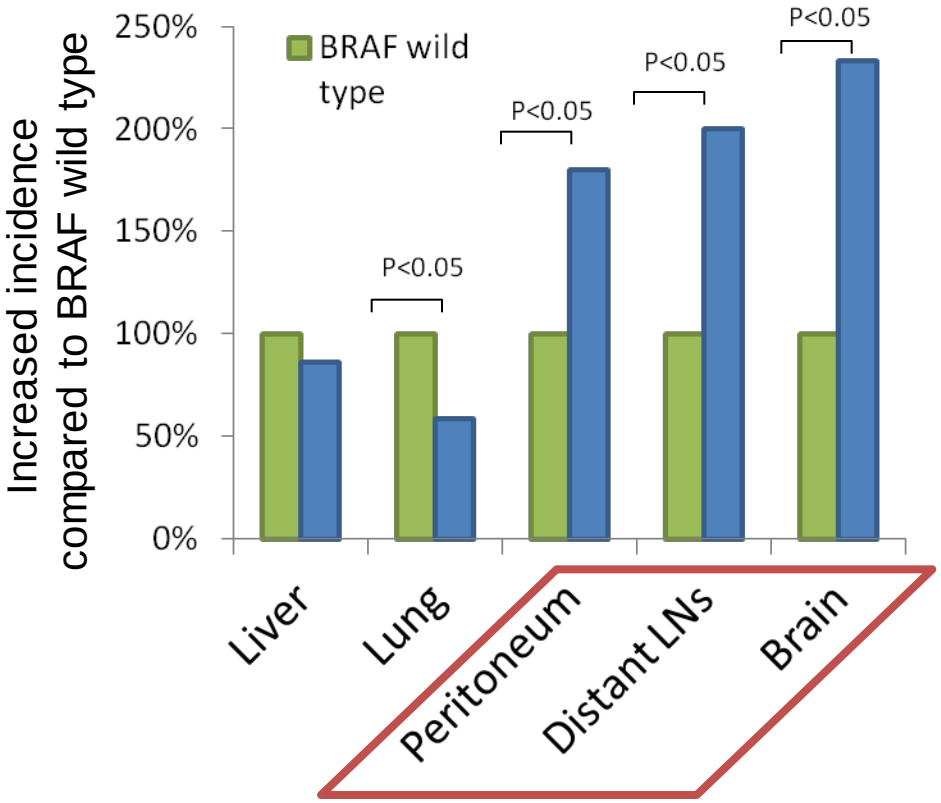
- BRAF mutations occur in a unique sub from serrated adenomas
  - Low rates of chromosomal instability,
  - High rates of hypermethylation
  - Common sporadic microsatellite instabilit

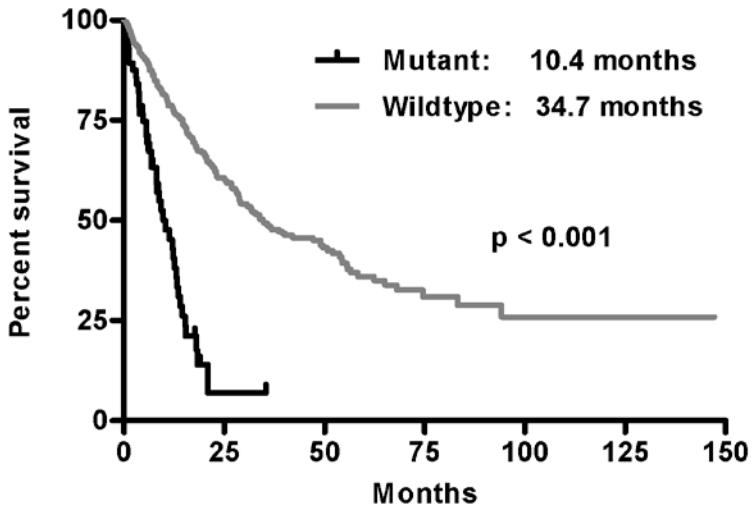


Serrated Adenoma

- The clinical challenges include low frequency (7% of mCRC) and aggressive biology

Atypical Location of Metastases and Poor Survival



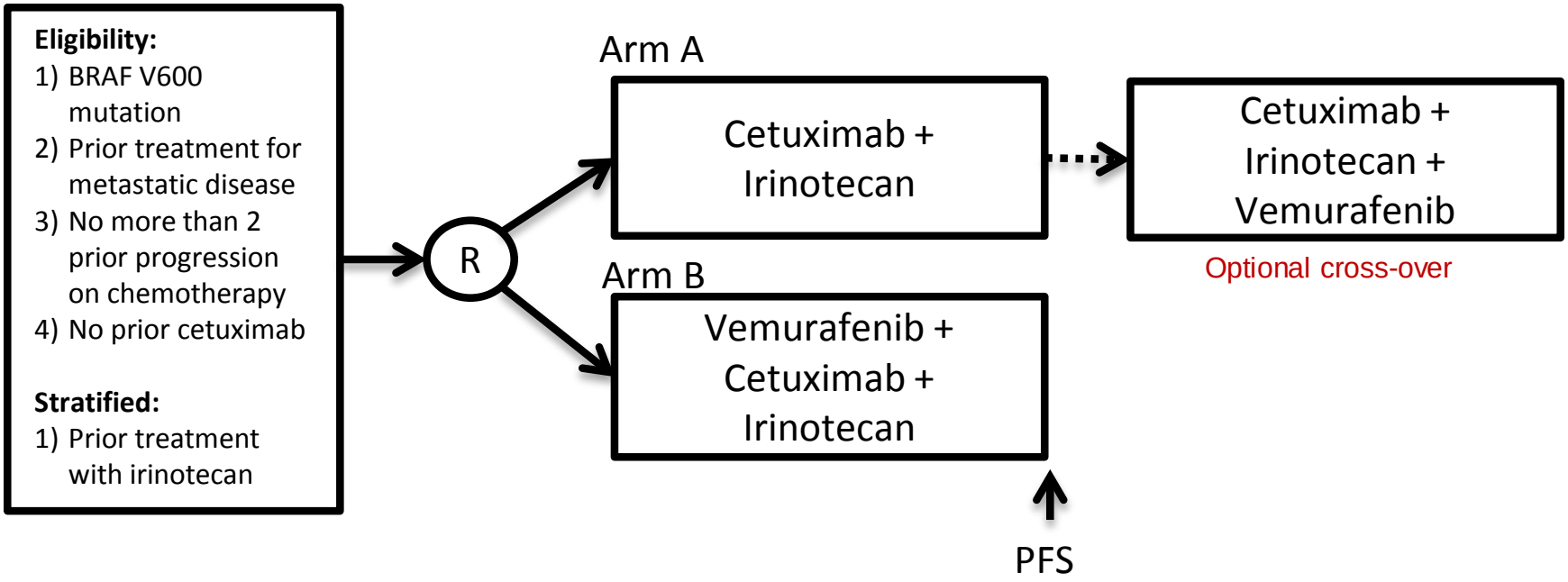


Hazard Ratio of 10.6 for OS

Less than 1 year OS

Tran, Kopetz, et al, Cancer '11

SWOG 1406: BRAF + EGFR



Historical response rate is <10% for cetuximab and irinotecan, with PFS of 2.4 months for $BRAF^{mut}$

Target HR 0.5 for PFS, with 2-sided alpha 5%, power 80%

N= 78 patients

Case Presentation #1 (Audience Response)

- 74 year male with stage IIA (T3N0M0) sigmoid colon adenocarcinoma status post laparoscopic sigmoid colectomy 30 days ago.

- Under which circumstance can additional testing be considered (12-gene signature assay) prior to recommending adjuvant chemotherapy?

A. No high risk features + MSI-high
B. 1 high risk feature + MSI-high
C. No high risk features + MSS
D. 1 high risk feature + MSS
E. None of the above

Case Presentation #2

- 51 year female with Stage IVB (TxNxM1b) sigmoid adenocarcinoma (M1b due to multiple liver and lung metastases).
  - Tumor molecular profile:
    - MMR-proficient (MSS), RAS status (KRAS, NRAS) is wild type. BRAF-wt. ECOG performance status = 1.
- FOLFOX-bevacizumab chosen.
  - Admitted to hospital due to coronary vasospasm (5FU-intolerant).

Case Presentation #2 (continued)

- FOLFIRI-cetuximab chosen.
  - Small Bowel enteritis, pancytopenia
  - Pharmacogenetic profile:
    - UGT 1A1 7,7 homozygous
- Current Regimen:
  - irinotecan (50% dose reduction) + cetuximab

Summary

- Personalized medicine for CRC is here (patient & tumor-specific factors)
- Stage I: surgery
- Stage II: surgery, then markers define treatment course (MSI status is key)
- Stage III: surgery + adjuvant chemotherapy; no role for biologic therapy.
- Stage IV: markers define treatment course (KRAS, BRAF); biologic agents are standard; multimodal treatment often indicated.