Early-Stage Colon Cancer

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Early-Stage Colon Cancer

- Introduction
- Optimal Agents and Duration
- Future Directions

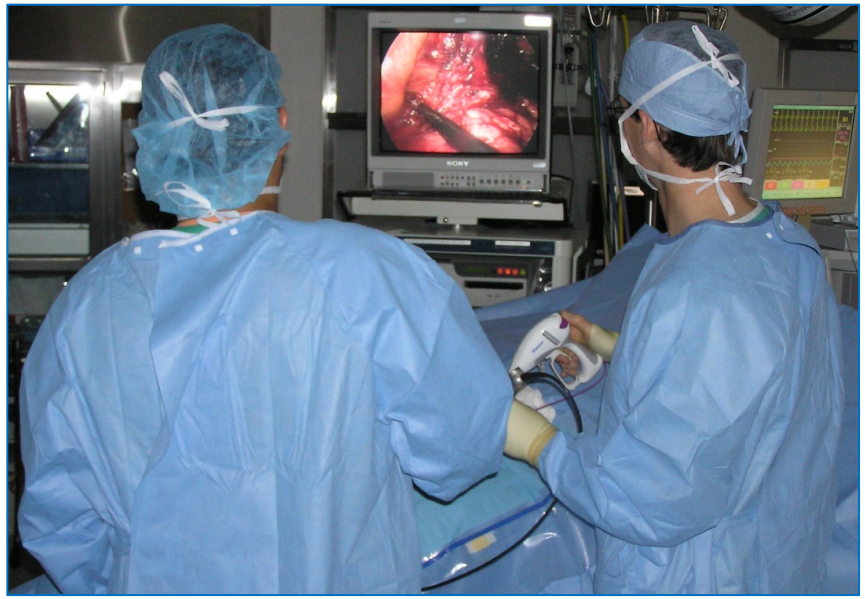
Colorectal Cancer Facts

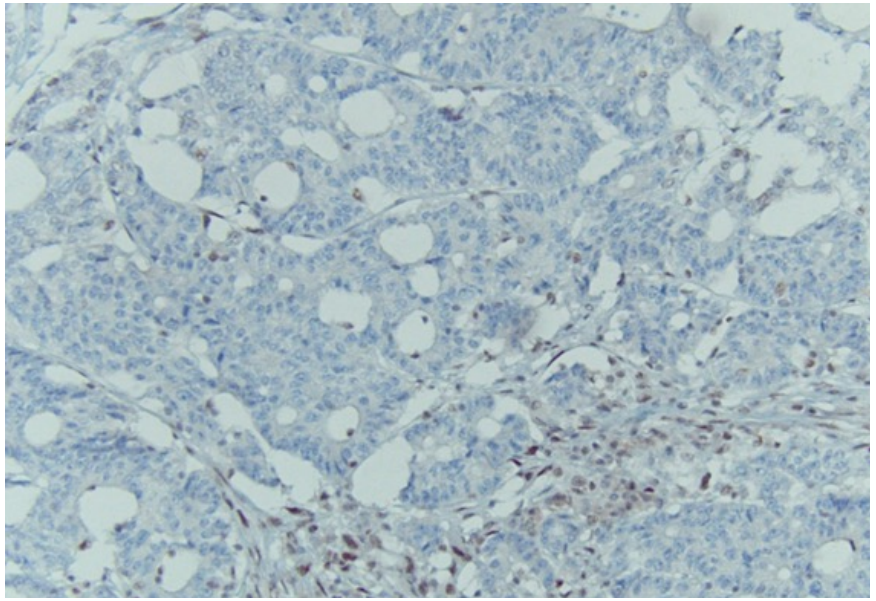
- 3rd most common cancer in the U.S.
- 5-year survival <15% in the metastatic setting
- Numerous gaps in understanding the disease
  - Why don't biologics work in adjuvant setting?
  - What are predictive biomarkers for VEGFR inhibitors?
  - Why does left versus right sided behave differently?
  - Why doesn't immunotherapy work in most case?
- Additional treatment options are needed
- Additional prevention options are needed

American Cancer Society. Cancer Facts & Figures, 2022

Colorectal Cancer Cancer: A Team Effort!

Chemotherapy → Liver Resection → Chemotherapy → SBRT to lung lesion → Chemotherapy → Survivorship

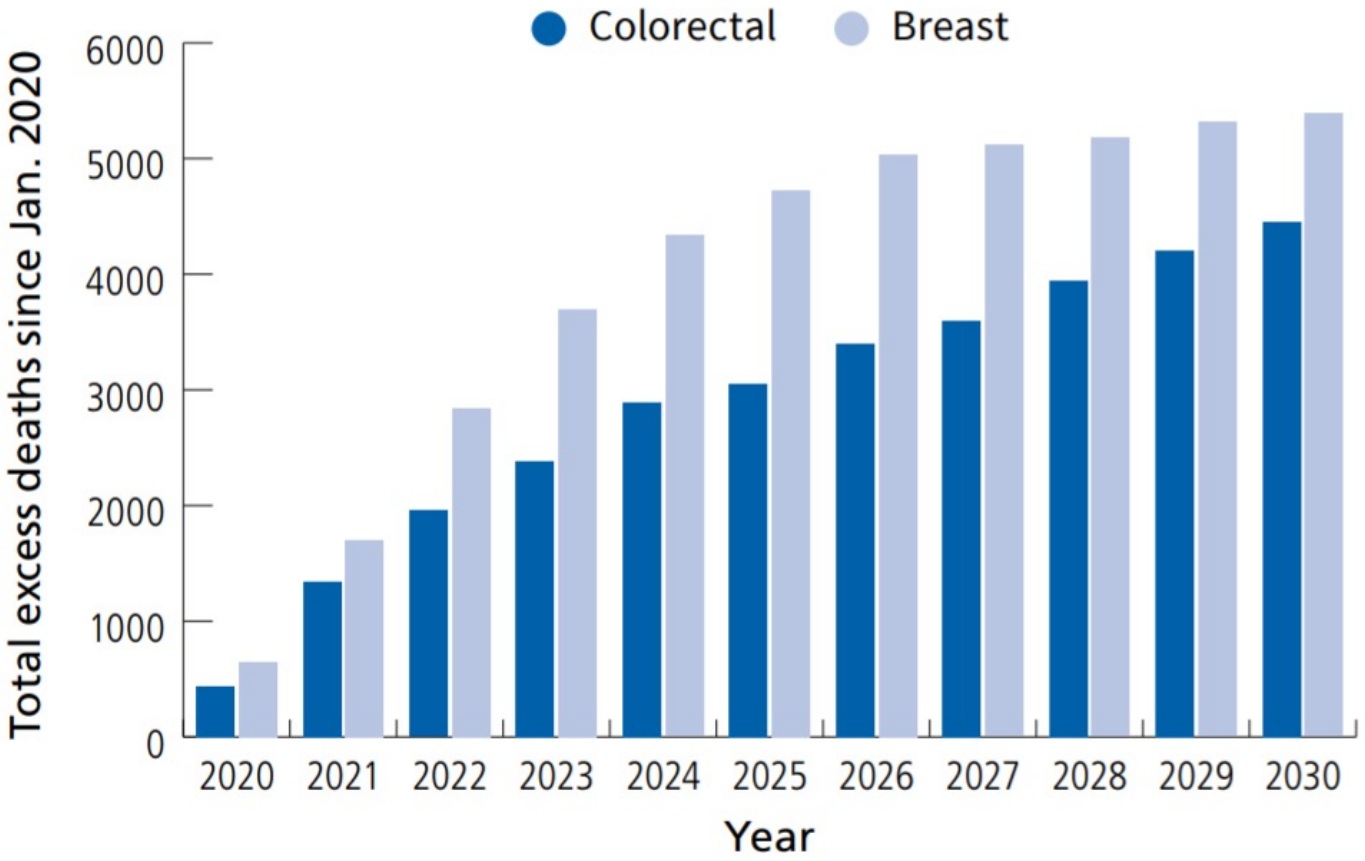




Pathology | Nutrition | Genetic Counseling | Molecular Testing | Endoscopy

Colorectal Cancer Facts (3)

Figure S3. Estimated Cumulative Excess Deaths From Colorectal and Breast Cancers in the US Due to the COVID-19 Pandemic, 2020 to 2030



Source: Sharpless NE. COVID-19 and cancer. *Science*. 2020;368(6497): 1290. Reprinted with permission from AAAAS.

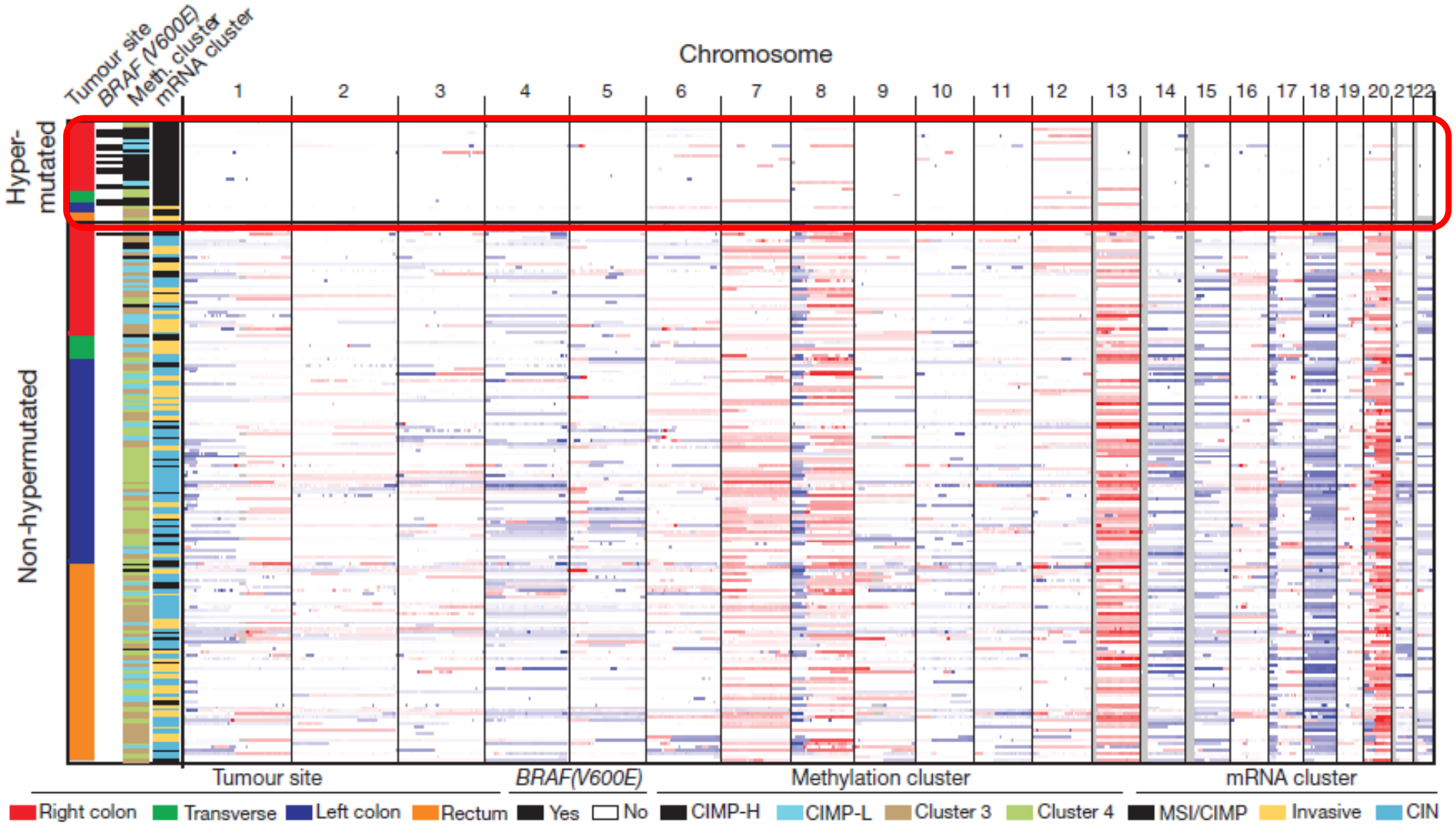
One of the cancer types most affected by the COVID19 pandemic.

- NCI estimates 1% increase in deaths from breast and colorectal cancer over the next 10 years, with a 6 month disruption in care.
- 10,000 excess deaths due to the pandemic's impact on screening and treatment

American Cancer Society. Cancer Facts & Figures, 2021

Cancer Genome Atlas: Colorectal Cancer

TCGA, *Nature* 2012

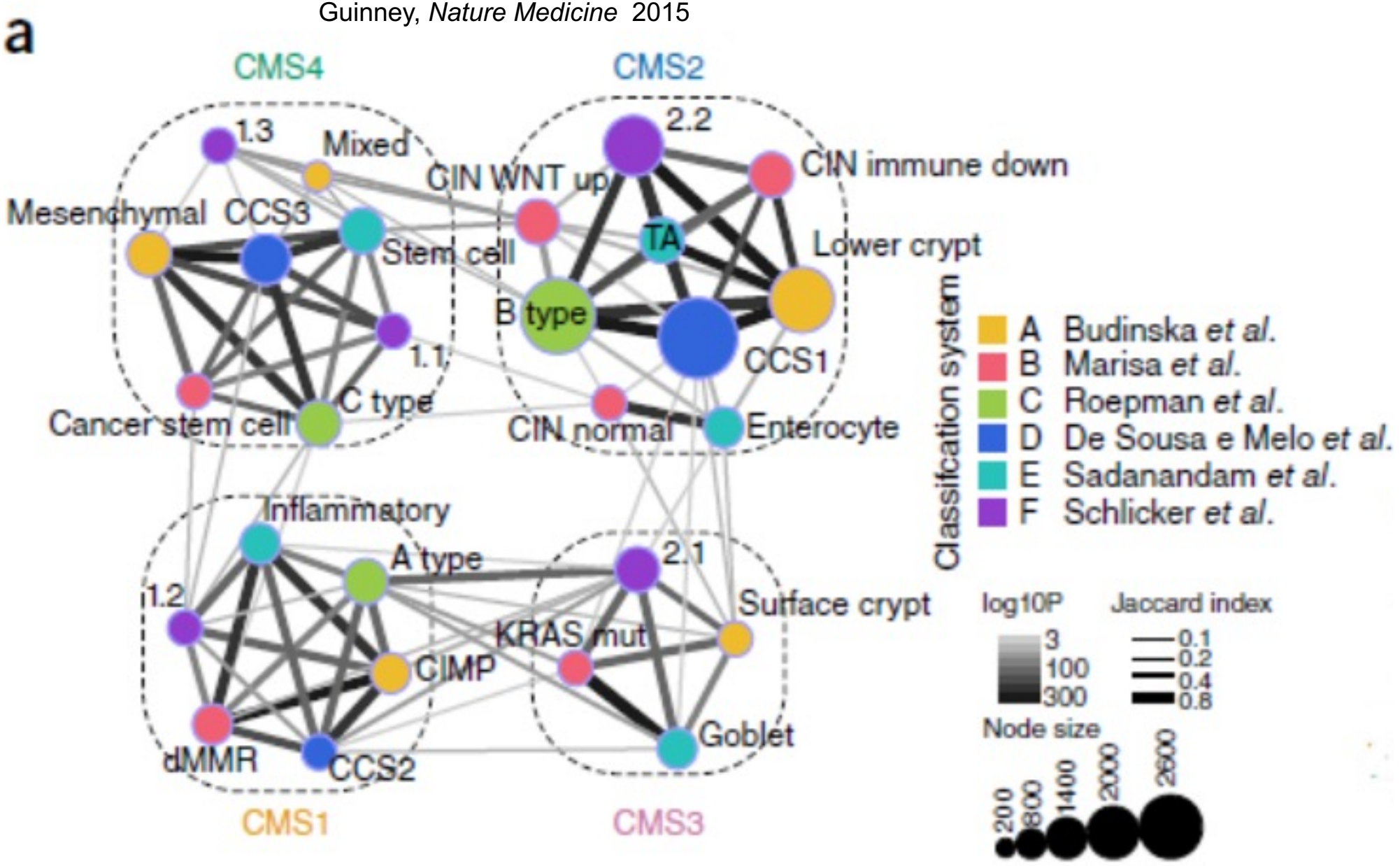


Genomic changes in 195 primary colorectal cancers.

Hypermutated tumors (top) segregate from others

Molecular Clustering: Colorectal

Guinney, *Nature Medicine* 2015



mRNA expression

Four consensus subtypes created among 6 published datasets

14 FDA-approved Drugs for mCRC

Cytotoxics

1. 5-fluorouracil (5-FU) -> pyrimidine analog
2. capecitabine -> oral 5-FU pro-drug
3. TAS-102 -> 5-FU drug with metabolism inhibitor
4. irinotecan -> topoisomerase I inhibitor
5. oxaliplatin -> 3rd generation platinum

"Biologics/ Targeted"

1. cetuximab -> antibody against EGFR
2. panitumumab -> antibody against EGFR
3. bevacizumab -> antibody against VEGF
4. ziv-aflibercept -> dummy VEGF receptor
5. regorafenib -> tyrosine kinase inhibitor (VEGFR, BRAF, others)
6. ramucirumab -> antibody against VEGFR2
7. pembrolizumab -> antibody against PD-1
8. nivolumab -> antibody against PD-1
9. nivo+ ipilumumab -> antibody against CTLA-4

Also: BRAF, Her2, NTRK

VEGF=Vascular Endothelial Growth Factor; EGFR=Epidermal Growth Factor Receptor; TAS-102=trifluridine-tipiracil

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Only 3 drugs are used adjuvantly

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Example Case: Stage III Colon Cancer

A 48-year old male presented with left lower quadrant abdominal pain and occasional diarrhea. His workup included an abdominal CT which revealed a sigmoid mass. No other sites of metastatic disease were noted.

Colonoscopy revealed a partially-obstructing mass and biopsy revealed moderately-differentiated adenocarcinoma. Patient underwent hemicolectomy, and pathology revealed tumor penetrating through the muscularis propria, 5 out of 27 lymph nodes positive for disease. The synoptic report notes pT3N2a.

The tumor was found to have proficient mismatch repair (pMMR).

ECOG PS = 0, patient is otherwise healthy. Presents to your clinic 4 weeks after surgery.

Options for “Adjuvant” Chemotherapy

For Resected (Primary) Colon Cancer:

5-Fluorouracil/Leucovorin (intravenous)

(bolus monthly, bolus weekly, or infusional)

- Moertel, 1990; Haller, 2005; others

5-Fluorouracil/Leucovorin/Oxaliplatin

- FOLFOX: Andre, “MOSAIC” Trial
- FLOX: Wolmark, NSABP C-07
- CAPOX: Haller, XELOXA

Capecitabine (pro-drug of 5-FU)

- Twelves, “X-ACT” Trial

MOSAIC Trial: Established FOLFOX as SOC

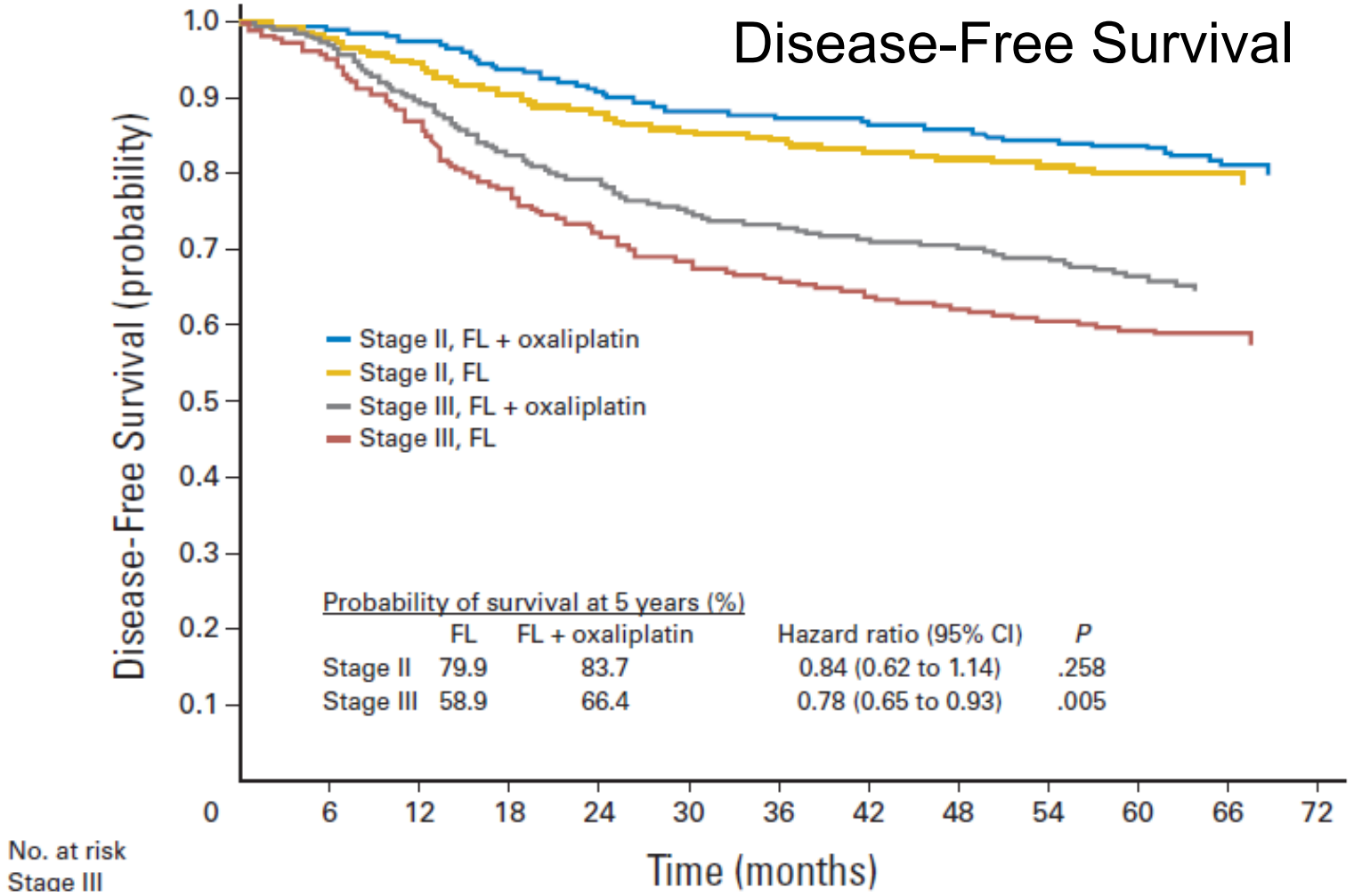
n = 2,246
Stage II/III colon CA
Primary endpoint:
3-yr disease free survival (DFS)

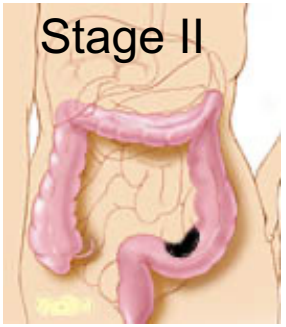
"LV5FU2" x 12
(infusional 5-FU/LV)

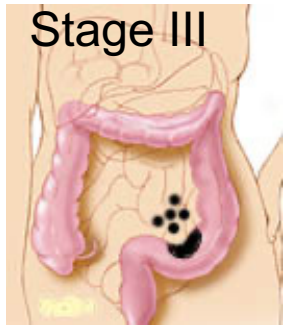
"FOLFOX4" x 12
(infusional 5-FU/LV with oxaliplatin)

Andre, NEJM 2004; Andre, JCO 2009

MOSAIC Trial: Established FOLFOX as SOC

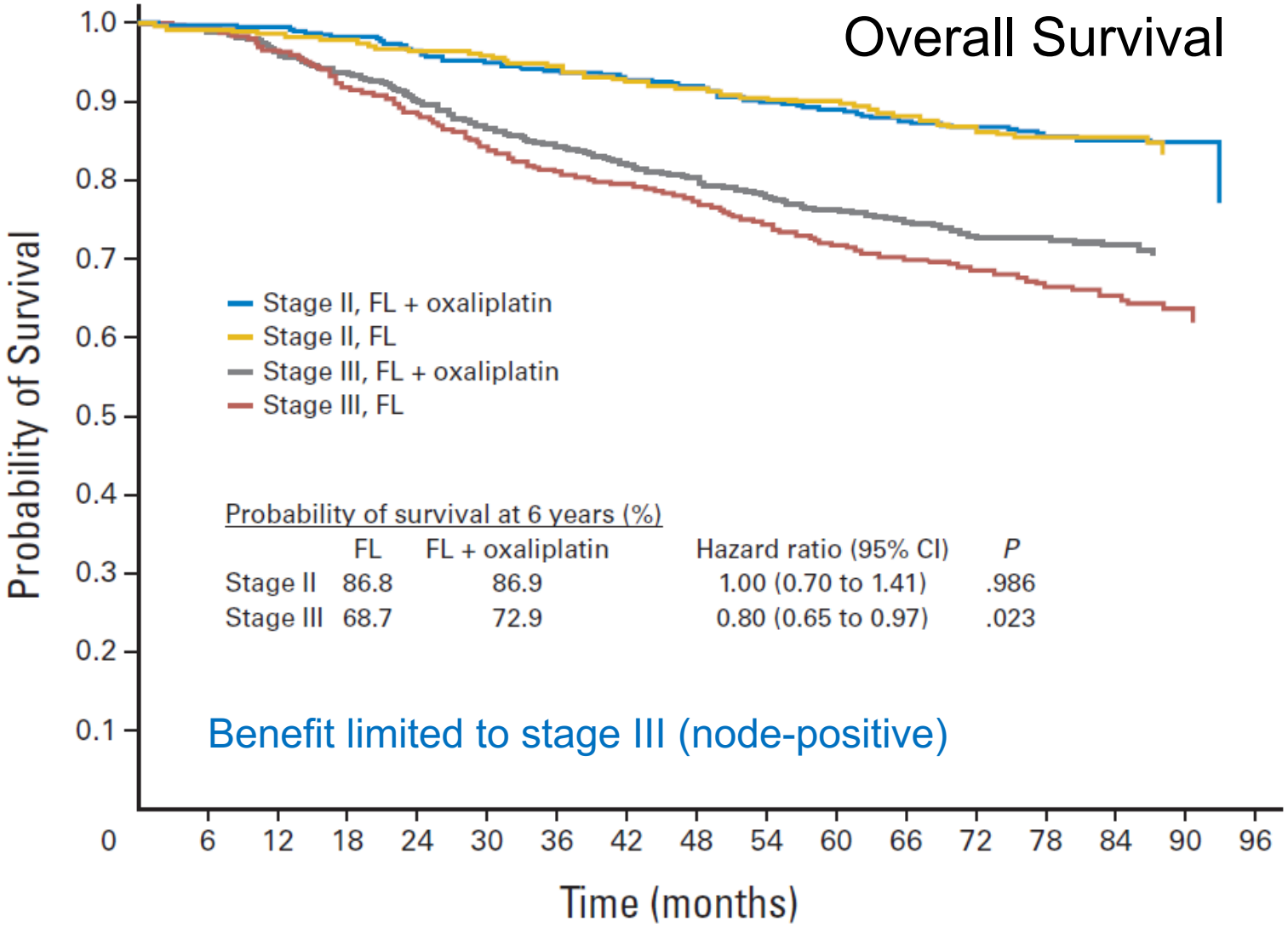


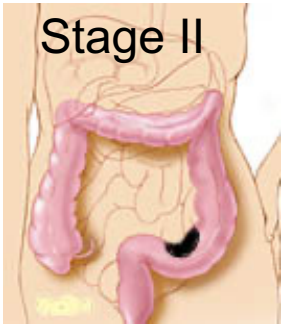


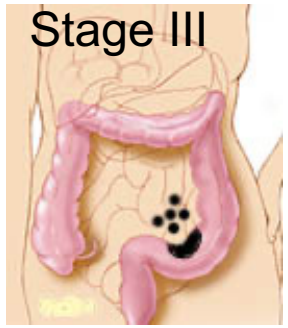


Andre, NEJM 2004; Andre, JCO 2009

MOSAIC Trial: Established FOLFOX as SOC







Andre, NEJM 2004; Andre, JCO 2009

MOSAIC trial: benefit confined to stage II

- **Study presented with >5 years follow-up**
- **6.6% DFS benefit maintained HR = 0.8, p = 0.003**

Prob OS 6 years	5-FU	FOLFOX	p
Overall	76%	78.6%	0.057
Stage II	86.8%	86.9%	0.996
Stage III	68.6%	73%	0.029

Andre, NEJM 2004; Andre, JCO 2009

Adding oxaliplatin is more efficacious, but more toxic than 5-FU alone:

Severe (Grade 3/4) Toxicities (FOLFOX vs LV5FU2)

Low blood counts (40% vs 5%)

Fever and low blood counts (1.8% vs 0.2%)

Nausea/Vomiting (6% vs 1.5%)

Allergic reactions (3% vs 0.2%)

Neuropathy (sensitivity to cold, numbness and tingling) (12.4% vs 0.2%)

NOT more toxic deaths

Andre, NEJM 2004; Andre, JCO 2009

CAPOX (XELOX) has similar efficacy

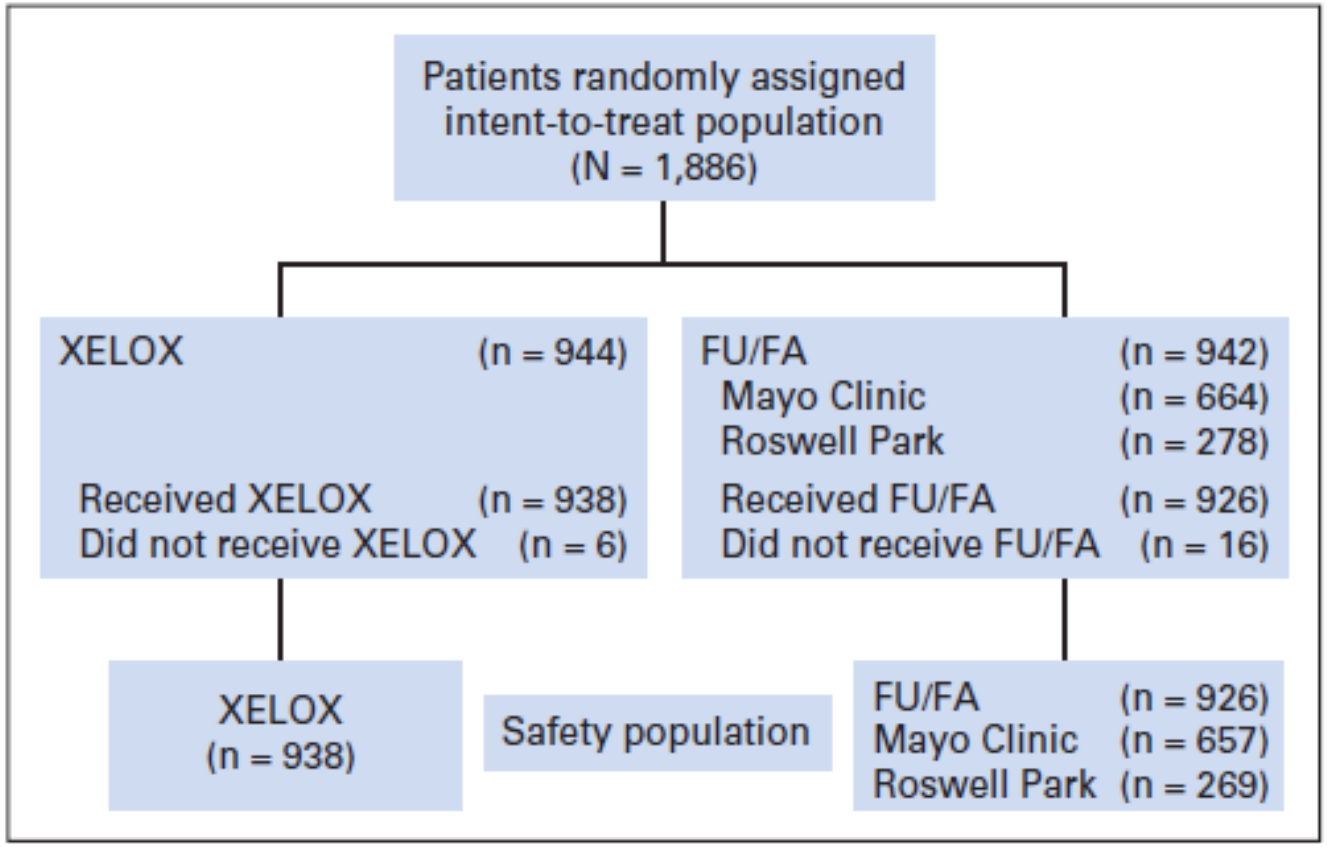


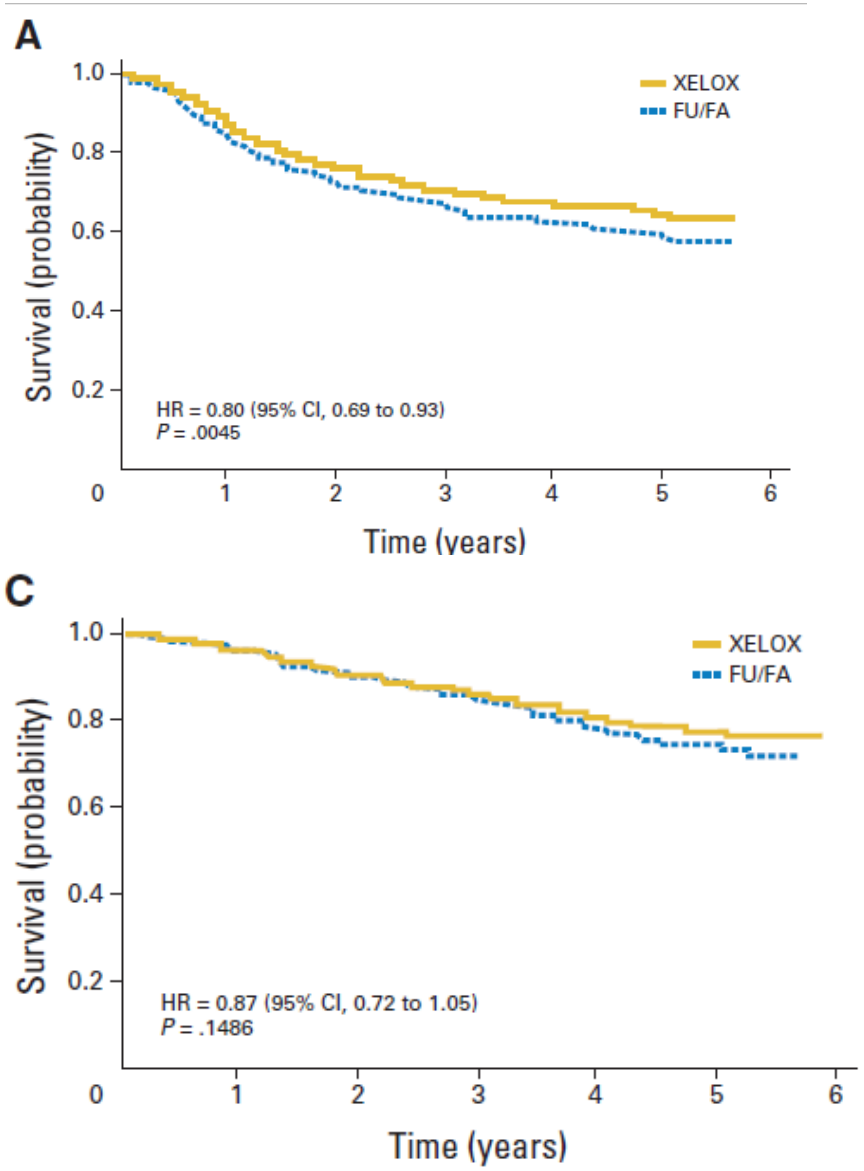
Fig 1. CONSORT. XELOX, capecitabine plus oxaliplatin; FU, fluorouracil; FA, folinic acid.

CAPOX = capecitabine (oral 5-FU) + oxaliplatin

Trade name of capecitabine is "xeloda", thus XELOX

Haller, JCO 2011

CAPOX (XELOX) has similar efficacy



3y DFS: 71% vs 67%,
HR=0.80, p= 0.0045

3y OS: 77.6% vs 74.2%,
HR=0.87, p= 0.1486 (NS)

Haller, JCO 2011

Adding irinotecan to 5-FU/LV has not been effective

Accord 02/FFCD9802 (Ychou)

Added irinotecan to LV5FU2 in high-risk stage III patients

No difference in 3-yr DFS; increased toxicity (n =400)

PETACC 3 (van Cutsem)

Added irinotecan to LV5FU2 in stage II/III patients

No difference in 3-yr DFS without post-hoc statistical analysis (n=3,005)

CALGB C89803 (Saltz)

Added irinotecan to weekly 5-FU/LV in stage III patients

No difference in 3-yr DFS; increased toxicity (n=1,250)

Biologics as post-operative therapy

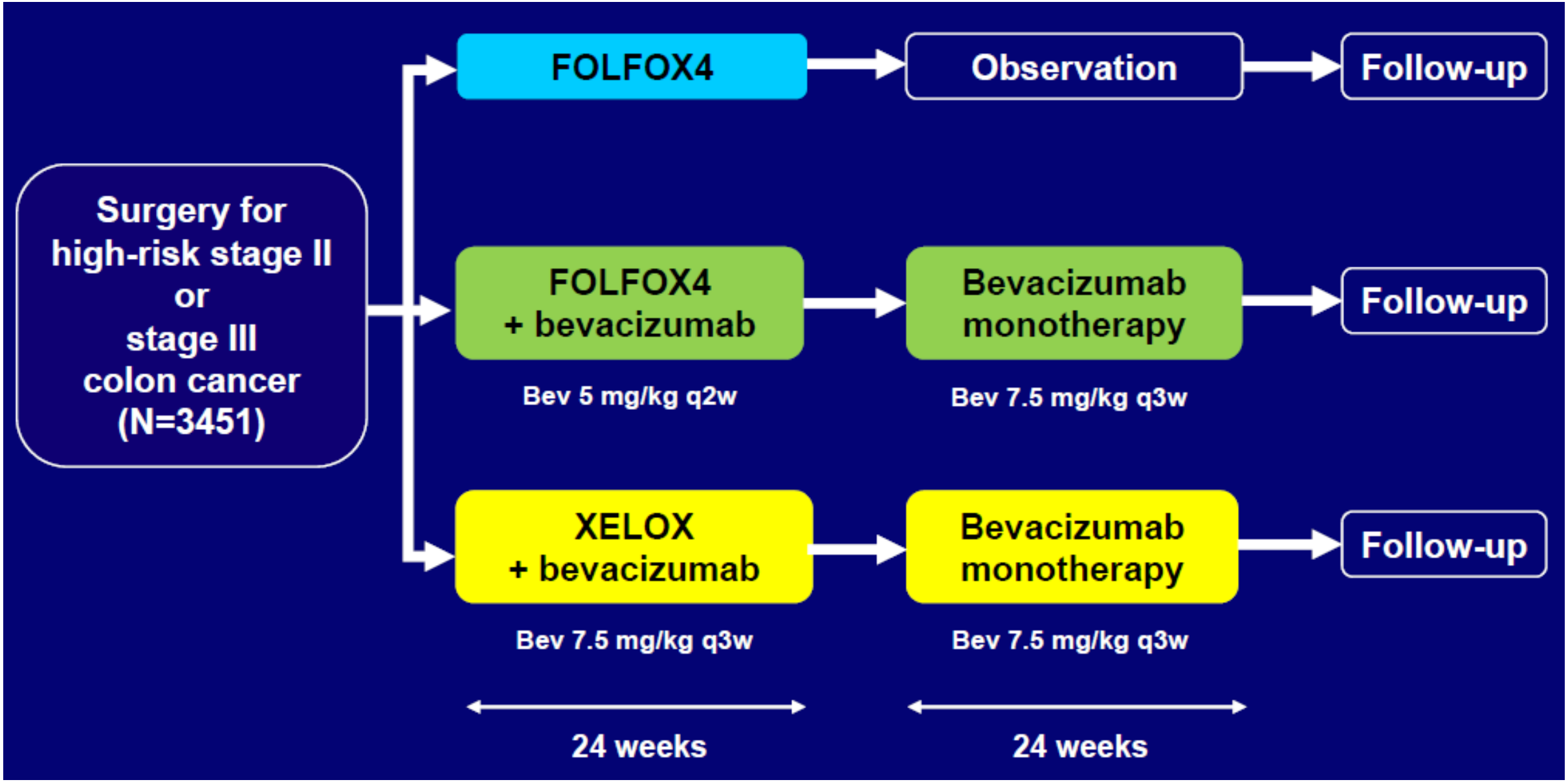
Zero for four large trials!

- **NSABP C-08** mFOLFOX6 +/- bevacizumab (12 mos)

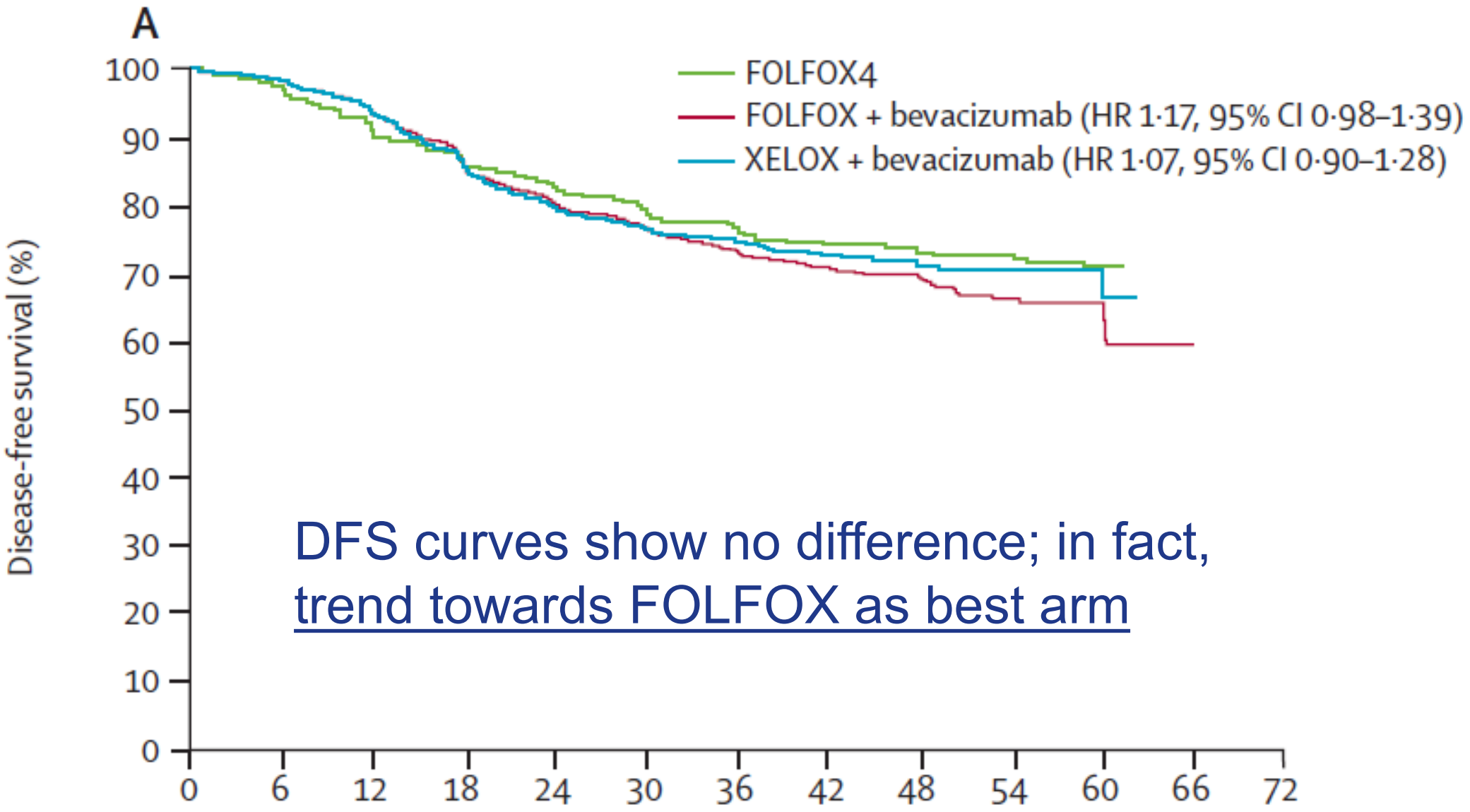
- **N0147** FOLFOX +/- cetuximab
  PETACC-8

- **AVANT** FOLFOX4 vs
  (Roche) FOLFOX + bevacizumab vs
  XELOX + bevacizumab

Avant Study: bevacizumab in adjuvant setting

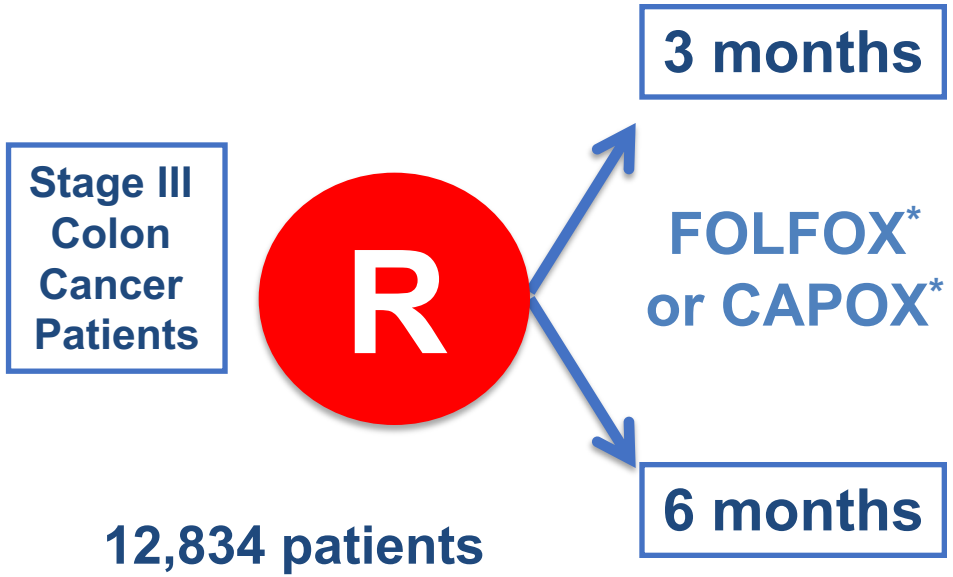


Avant Study: bevacizumab in adjuvant setting



DFS curves show no difference; in fact, trend towards FOLFOX as best arm

Duration of Therapy



*Investigator's choice, no randomization

- **Objective:**

  Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy

- **Non-inferiority design:**

  As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy

  In statistical terms: upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed ***1.12***

Grothey NEJM 2018

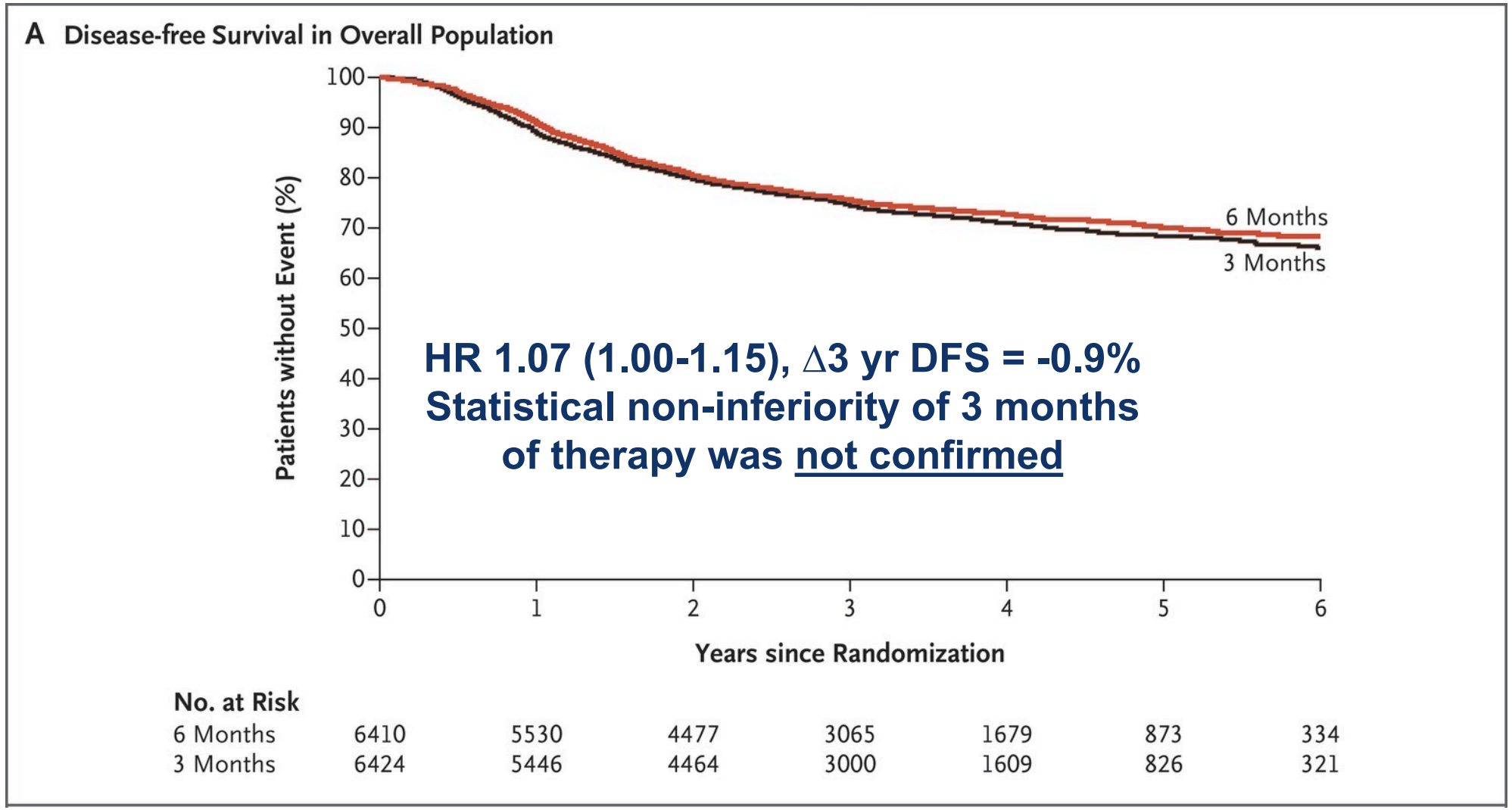
IDEA Trials Summary

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

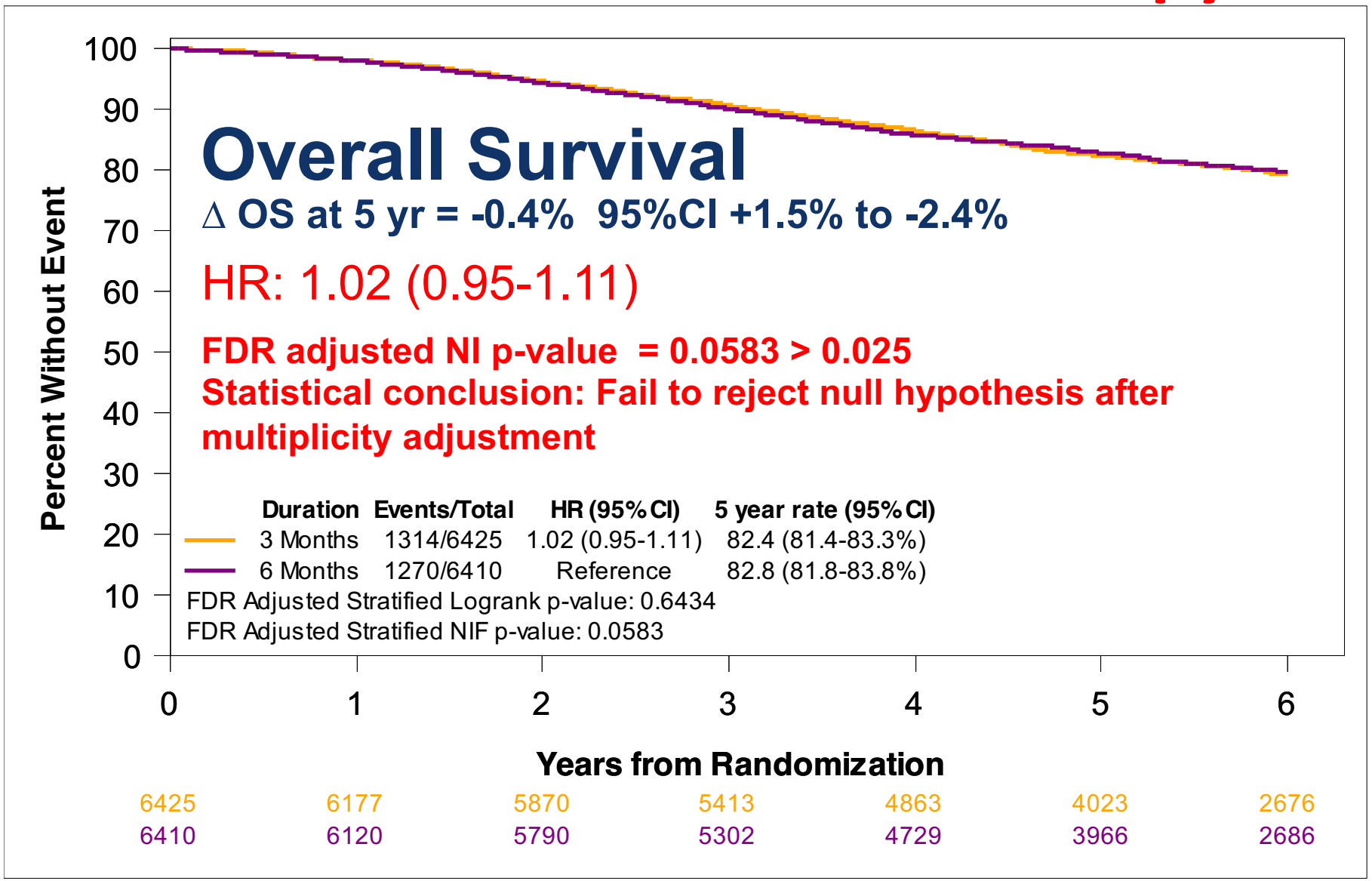
Shi ASCO 2017

Duration of Therapy



Grothey NEJM 2018

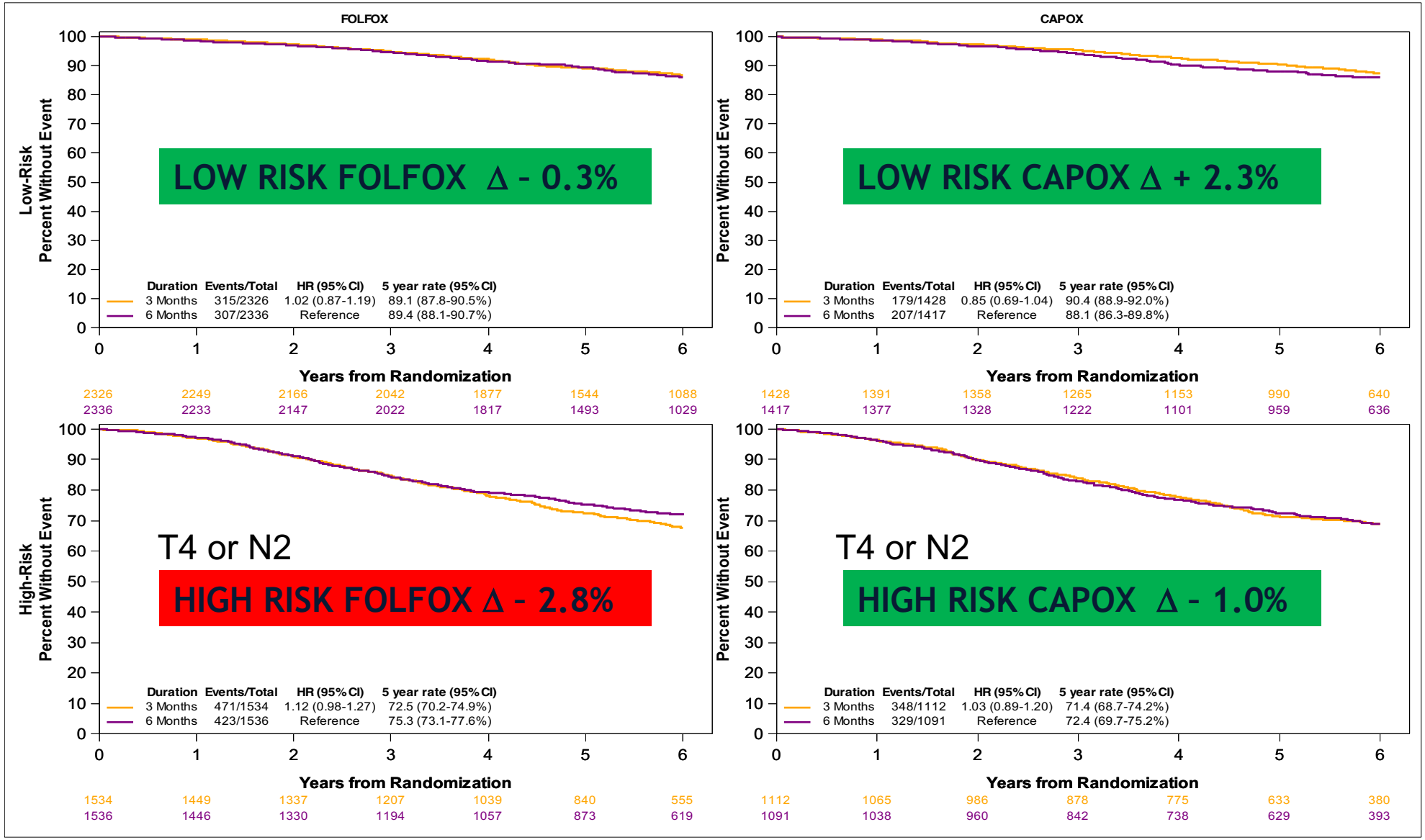
Duration of Therapy



Study did not meet the secondary endpoint of non-inferiority for overall survival… but are the statistics clinically meaningful?

Grothey NEJM 2018

Overall survival data mimics DFS data by regimen



Sobrero et al, ASCO 2020

Adverse Events

Adverse Events	FOLFOX				CAPOX			
	G0 - 1	G2	G3 - 4	p-value[1]	G0 - 1	G2	G3 - 4	p-value[1]
Overall				<.0001				<.0001
3 months	30%	32%	38%		35%	41%	24%	
6 months	11%	32%	57%		15%	48%	37%	
Neurotoxicity				<.0001				<.0001
3 months	83%	14%	3%		85%	12%	3%	
6 months	52%	32%	16%		55%	36%	9%	

Number needed to treat:

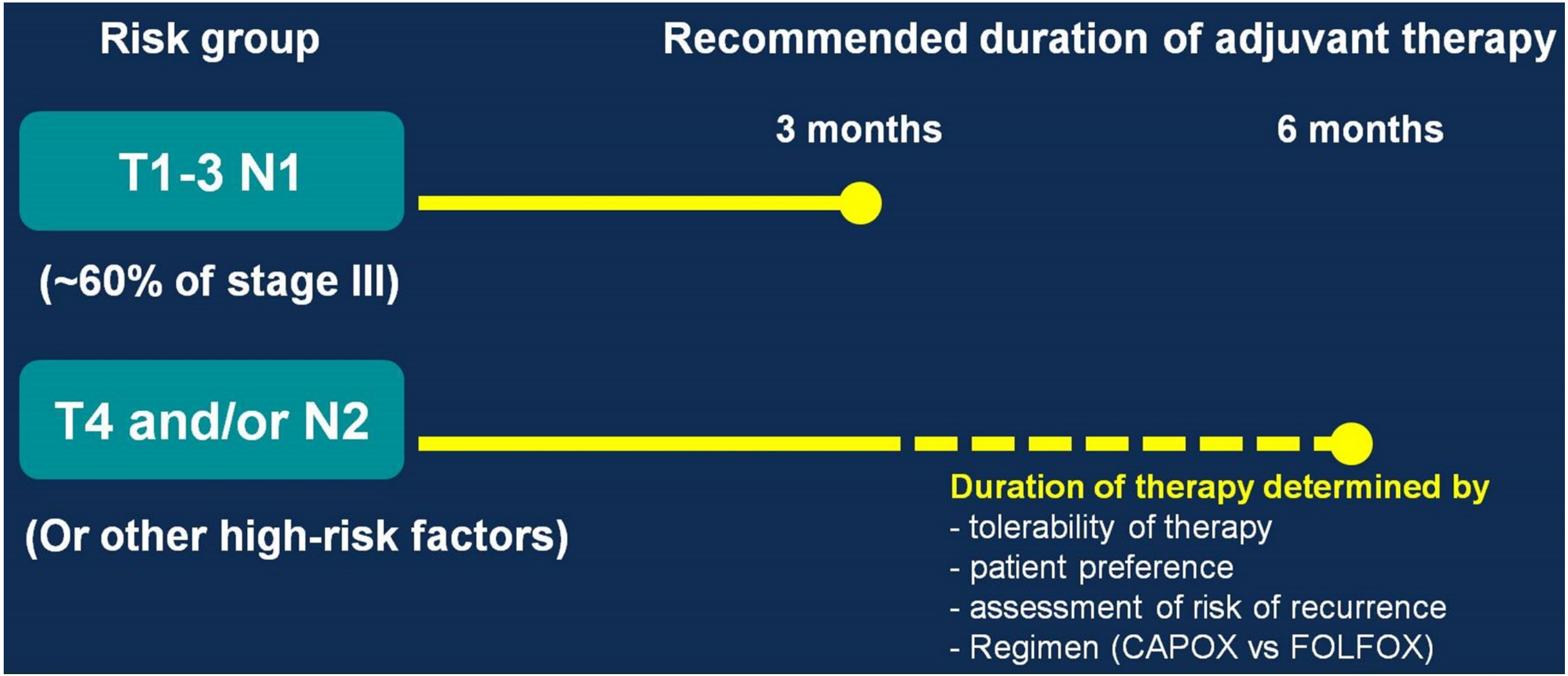
*Treat 100 patients to **save 3***

Number needed to harm (grade 2/3 neurotoxicity):

*Treat 100 patients to **harm 32***

Sobrero et al, ASCO 2020

Risk-Based Approach



Sobrero et al, ASCO 2020

High-Risk Stage II

Trial	Regimen(s)	HR stage II Colorectal Cancer Patients	Enrolling Country
TOSCA	CAPOX or FOLFOX4	1268	Italy
SCOT	CAPOX or mFOLFOX6	1078*	UK, Denmark, Spain, Australia, Sweden
HORG	CAPOX or FOLFOX4	413	Greece
ACHIEVE2	CAPOX or mFOLFOX6	514	Japan

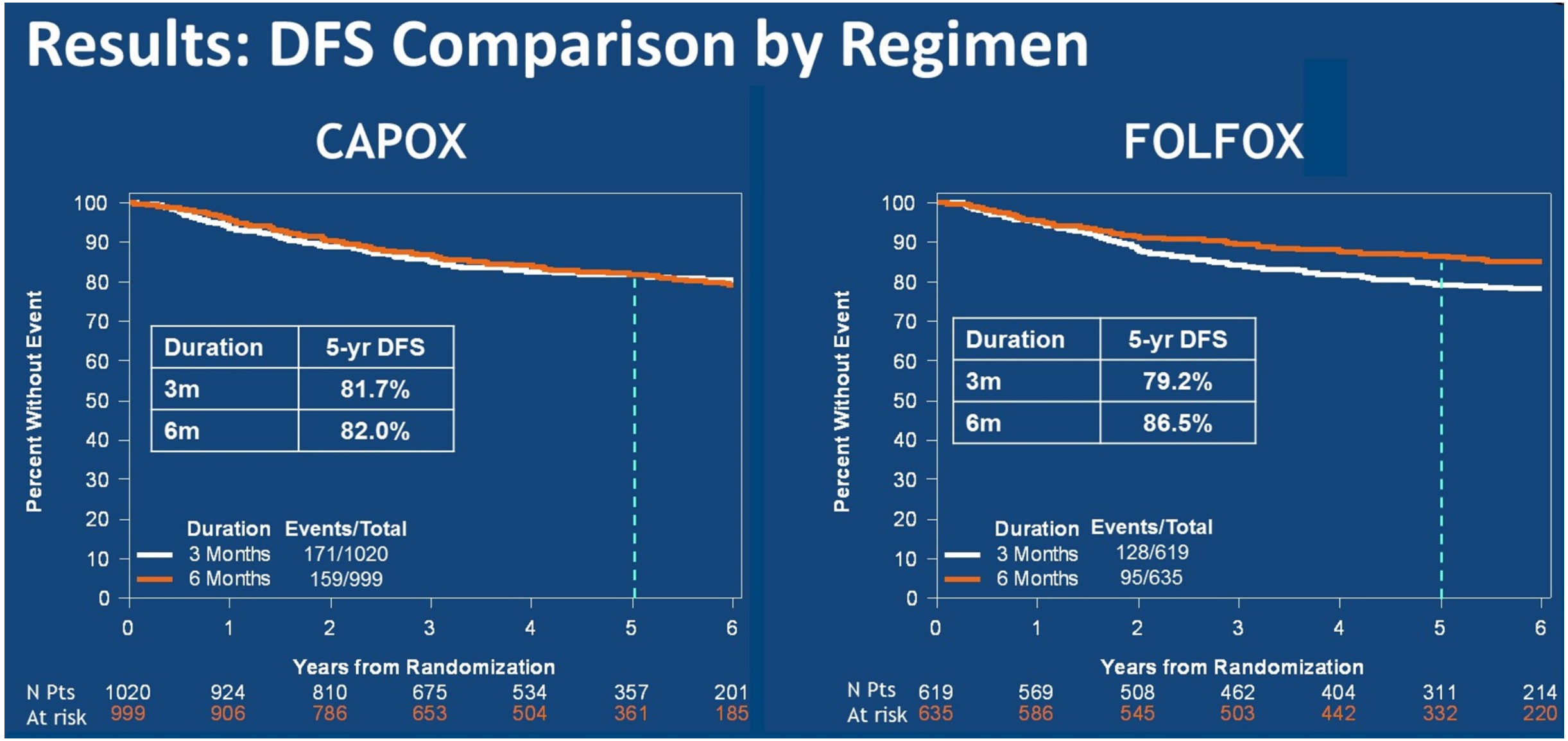
*Included 130 rectal patients

High Risk Stage II:

- T4
- Perforation
- Invasion
- Obstruction
- Poorly Diff
- Inadequate nodes

Iveson et al, ASCO 2019

High-Risk Stage II



Iveson et al, ASCO 2019

Adjuvant Chemotherapy for Colon Cancer

- For stage III (node-positive) disease, standards include FOLFOX / CAPOX, 5-FU/LV alone, or capecitabine. 3m for most patients; 6m for T4's or N2's.
- For stage II disease, there is no "standard": observation, 5-FU/LV, and FOLFOX /CAPOX can all be considered. Risks/benefits must be weighed carefully. 3m CAPOX can be considered for high risk.
- Using irinotecan or the "biologics" (bevacizumab, cetuximab) has been unsuccessful
- Resected tumors must be tested for microsatellite instability (Lynch Syndrome), and referred to genetics if defects in mismatch repair. There are trials (ATOMIC) studying immunotherapy for MSI-H patients.

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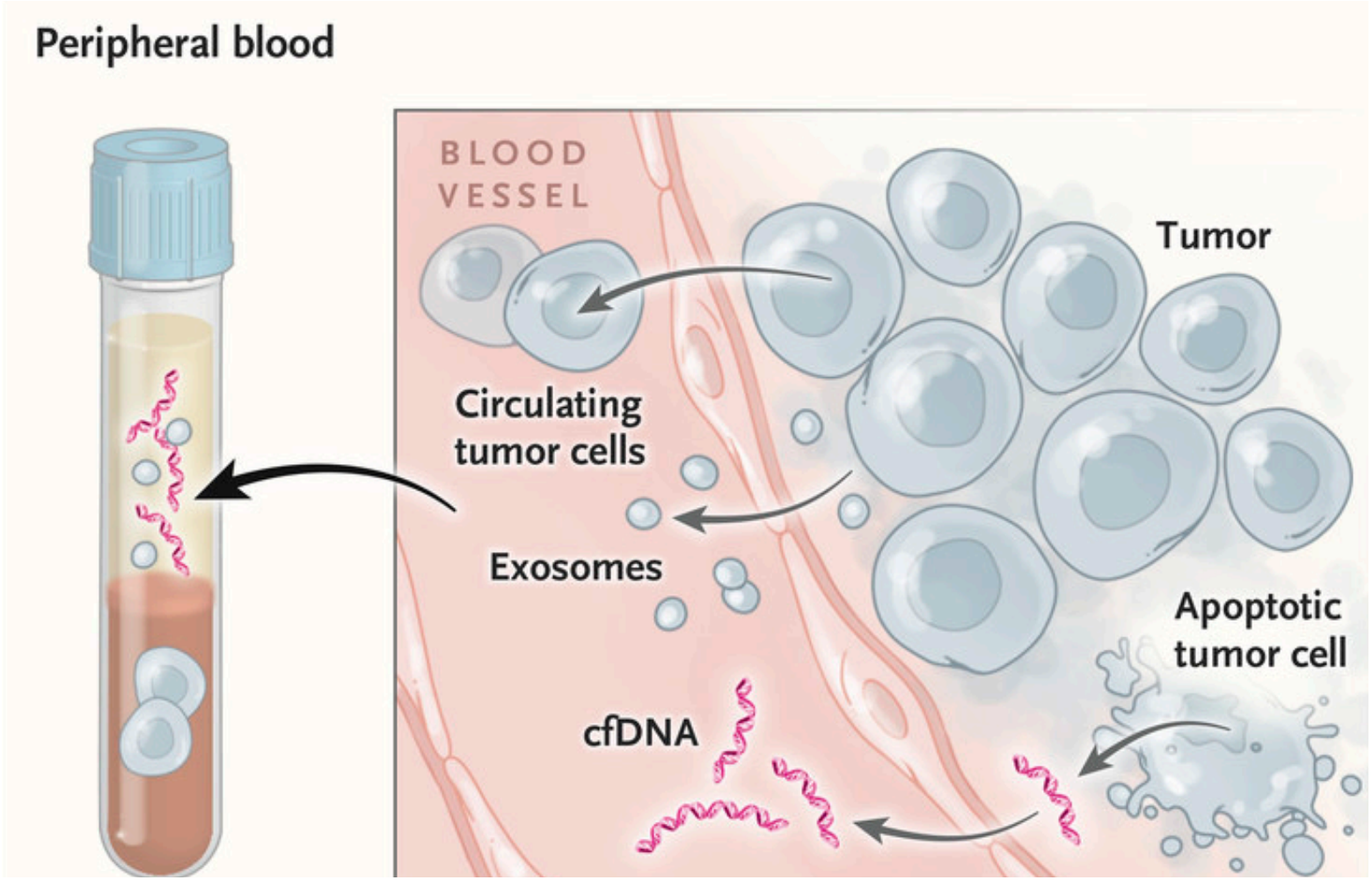
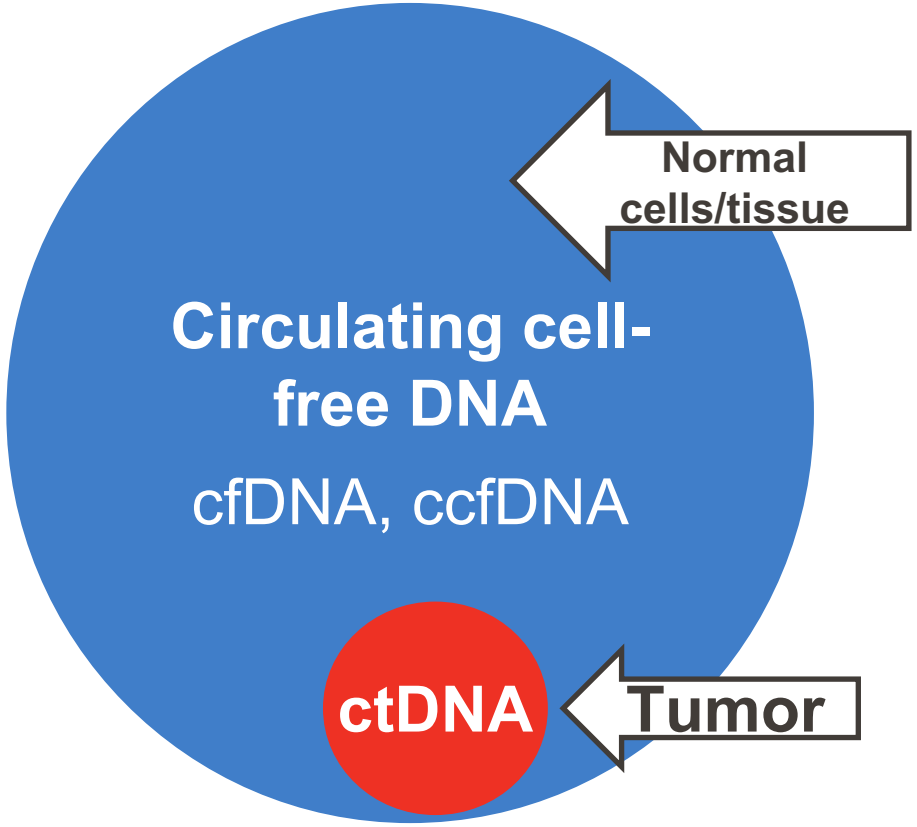
Liquid Biopsies



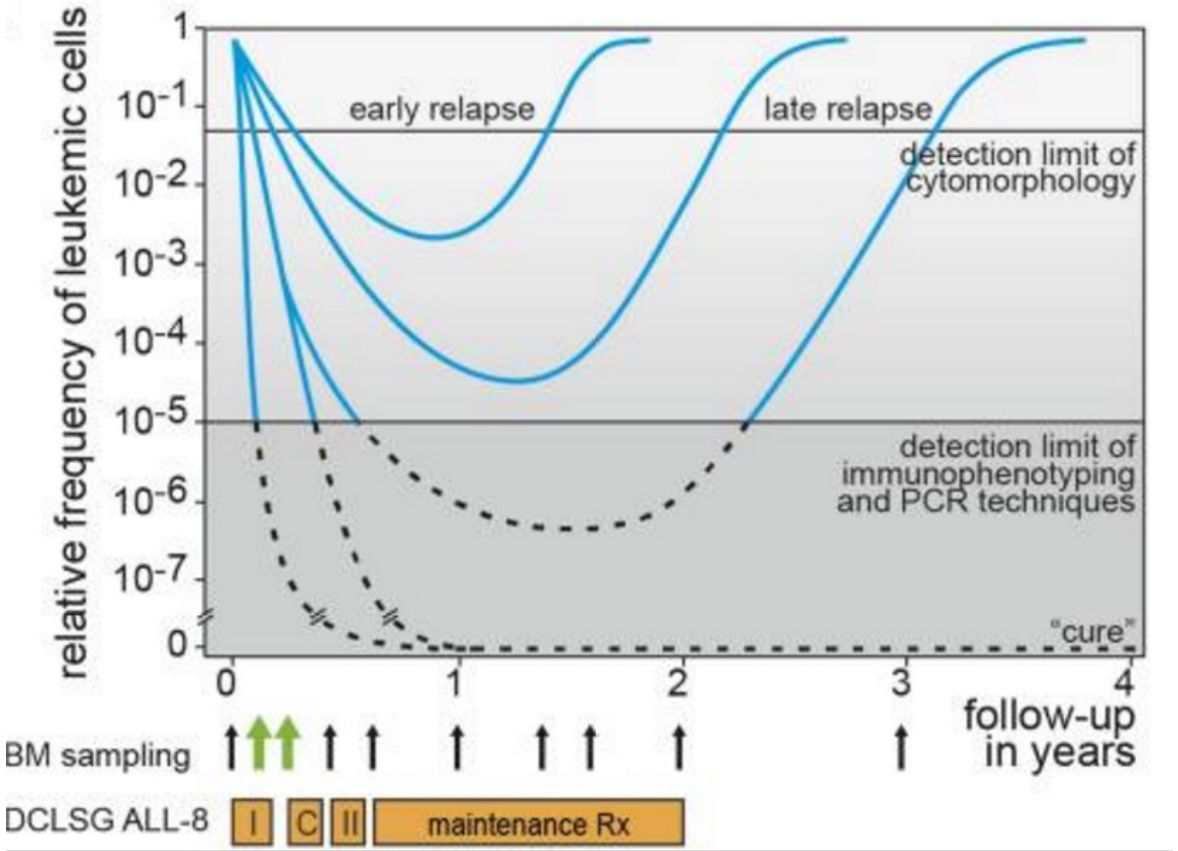


Initially described by Madel and Metais in 1948
Half-life: ~ 0.5 hours

Corcoran and Chabner. NEJM 2019

Minimal Residual Disease: Two Key Points

- MRD applications are enabled by very high **positive predictive value** (low false positive) for recurrent disease in patients with ctDNA detected in the “adjuvant” setting
- This is not a marker of high risk for recurrence but **defines molecular persistence of disease**.
  - Stage I-III patients with ctDNA+ after definitive interventions should be considered as a Stage IV minimal residual disease, or Stage IV MRD



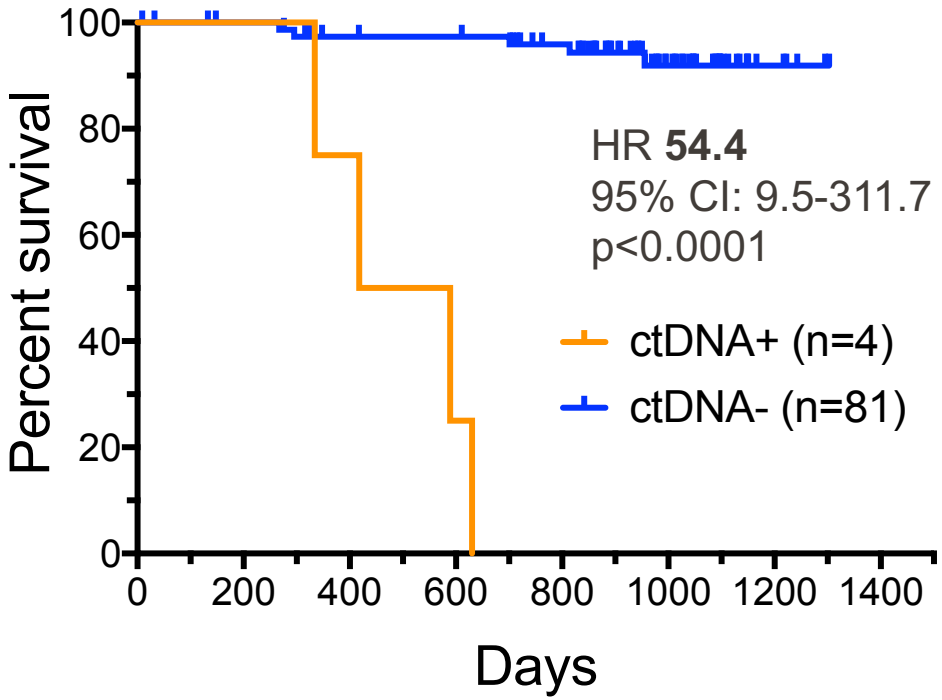
Well-established concept in hematologic malignancies

Van Dongen JJ et al. *Blood.* 2015;125(26):3996-4009.

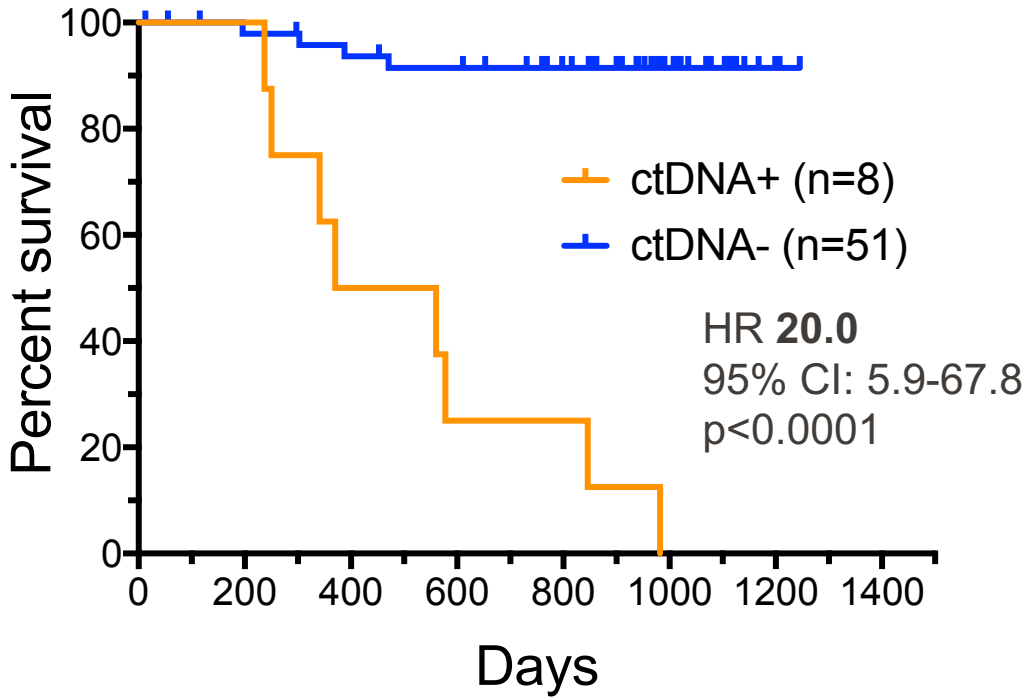
NGS Assay

Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue
57% sensitivity for recurrence; 100% specificity

Stage II (5% prevalence of ctDNA+)

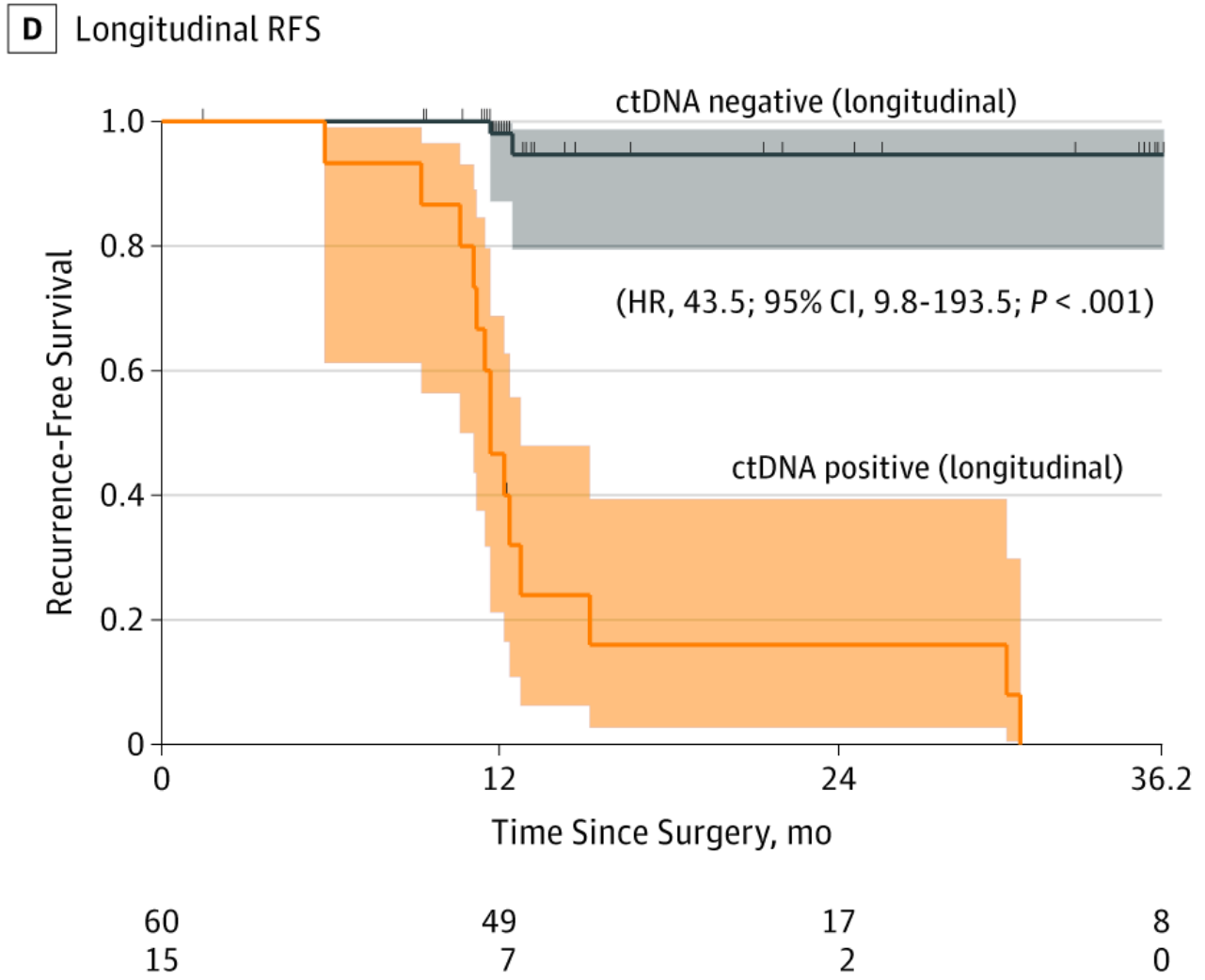


Stage III (16% prevalence of ctDNA+)



Diehn et al ASCO 2017

Longitudinal ctDNA and Relapse-Free Survival

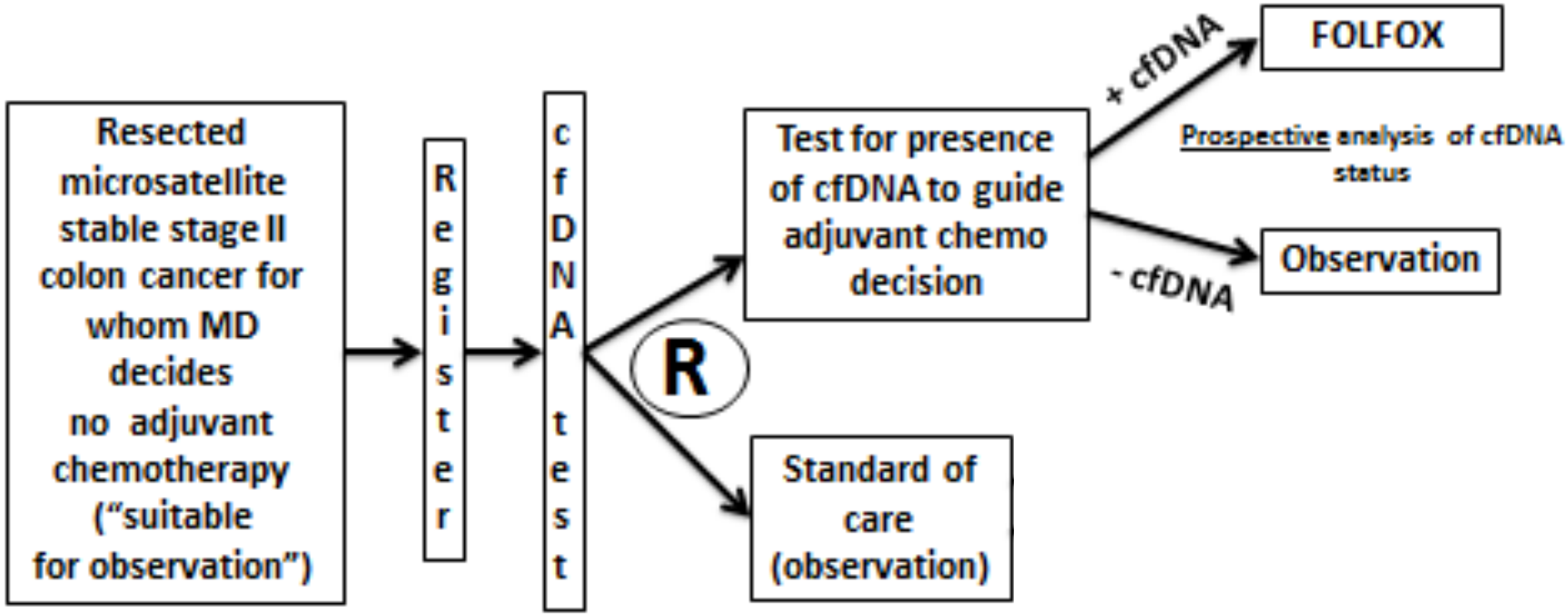


Reinert T et al. JAMA Oncol. 2019;5(8):1124-1131

Stage II Adjuvant Study: NRG-GI005 (COBRA)

Evaluating early intervention for Minimal Residual Dz

Van Morris

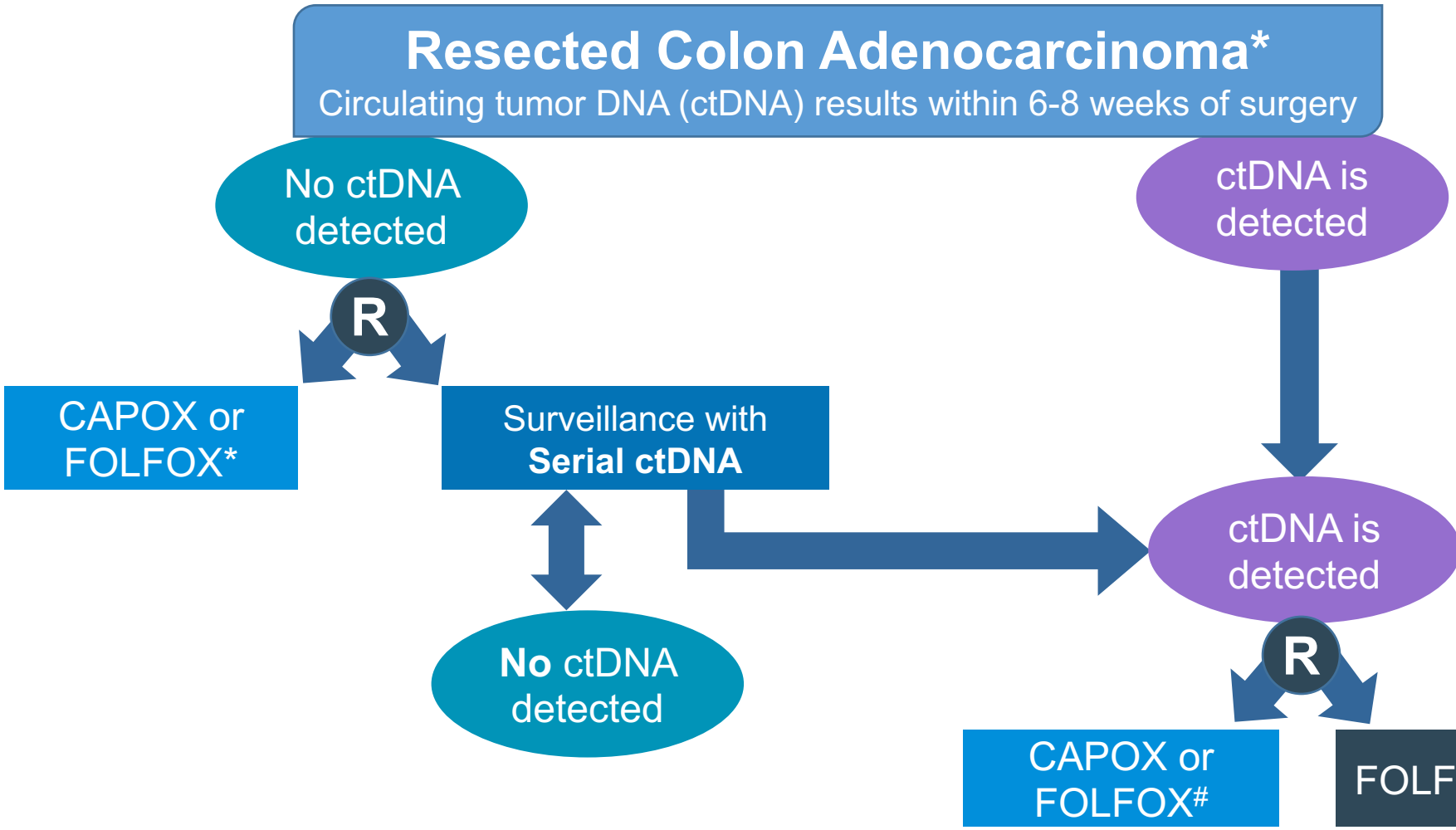


Primary objective: Clearance of cfDNA (to undetectable levels) for patients cfDNA+ at randomization

Morris VK et al. ASCO 2020. Abstract TPS4121.

Morris, Kopetz

Stage III Adjuvant Study



***Stage III (T1-3, N1/N1c)**
or
ctDNA +ve Stage II or Stage IIIC

R0 resection
pMMR / MSS

ctDNA Assay: Signatera

PIs:
Arvind Dasari (MDACC – NRG)
Christopher Lieu (UCCC – SWOG)

*: Duration and regimen per physician discretion
#: 6 months duration

NRG-GI008