George Fisher MD PhD; Stanford University

Screening and Biomarkers in Colorectal Cancer

Disclosures:

Advisory Boards / Consultant

- Merck
- Genentech / Roche
- Silenseed
- CytomX
- Terumo
- Jounce
- Taiho

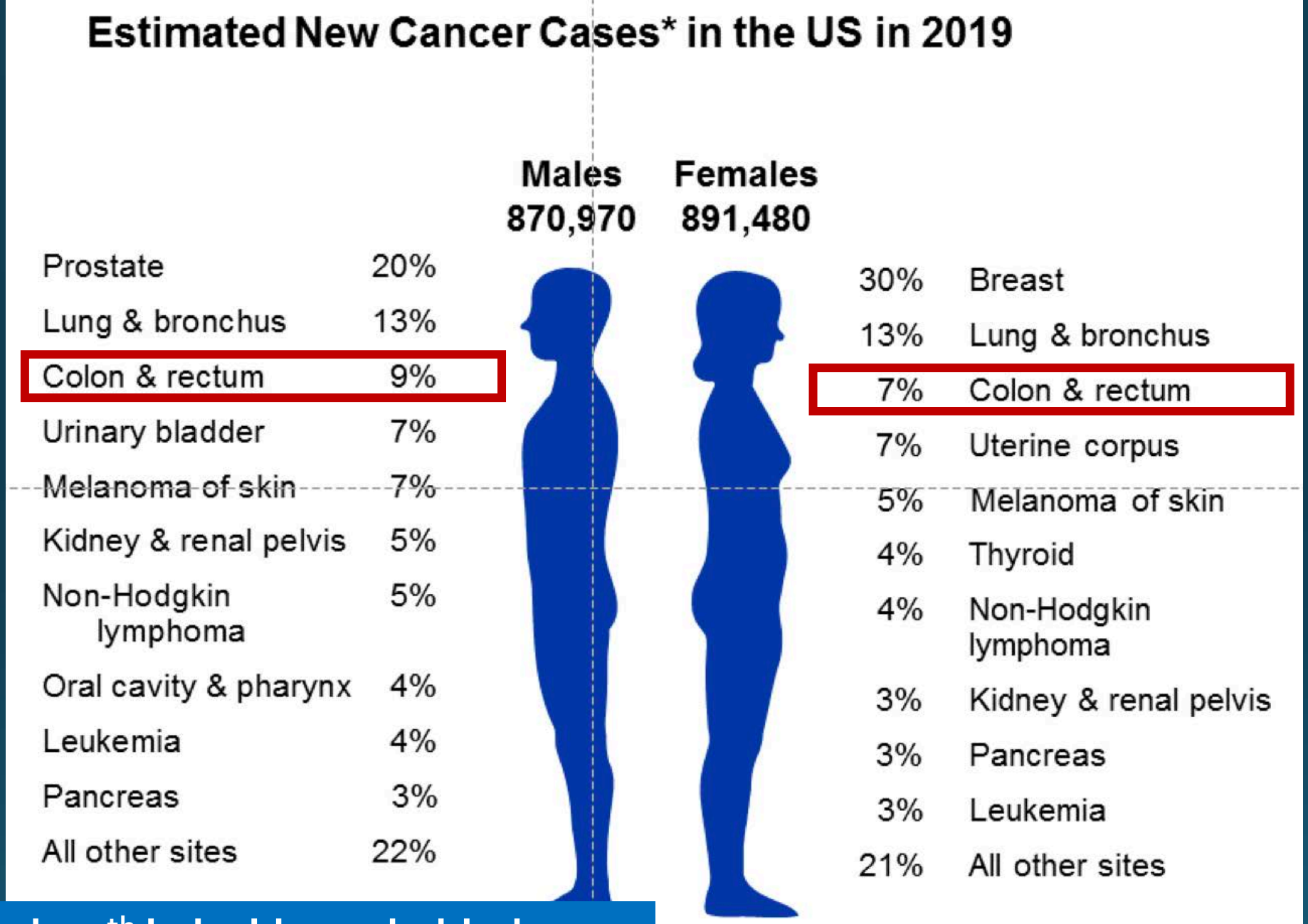
Research support (clinical trials)

- Genentech / Roche
- Merck
- Bristol
- XBiotech
- Aduro
- EpicentRx
- FortySeven

Overview

- Epidemiology and risk factors
- Screening
- Cost effective management of colon cancer
- Predictive and Prognostic Biomarkers
- Germline testing

Estimated New Cancer Cases* in the US in 2019

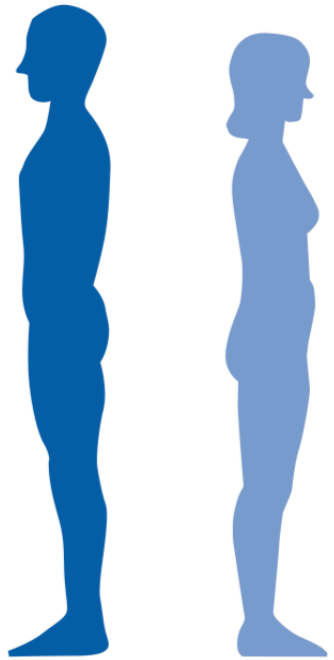


CRC ranks 4th in incidence behind lung, breast and prostate

ACS Cancer Facts and Figures; 2019

Estimated Deaths 2018

Male		
Lung & bronchus	83,550	26%
Prostate	29,430	9%
Colon & rectum	27,390	8%
Pancreas	23,020	7%
Liver & intrahepatic bile duct	20,540	6%
Leukemia	14,270	4%
Esophagus	12,850	4%
Urinary bladder	12,520	4%
Non-Hodgkin lymphoma	11,510	4%
Kidney & renal pelvis	10,010	3%
All sites	**323,630**	**100%**

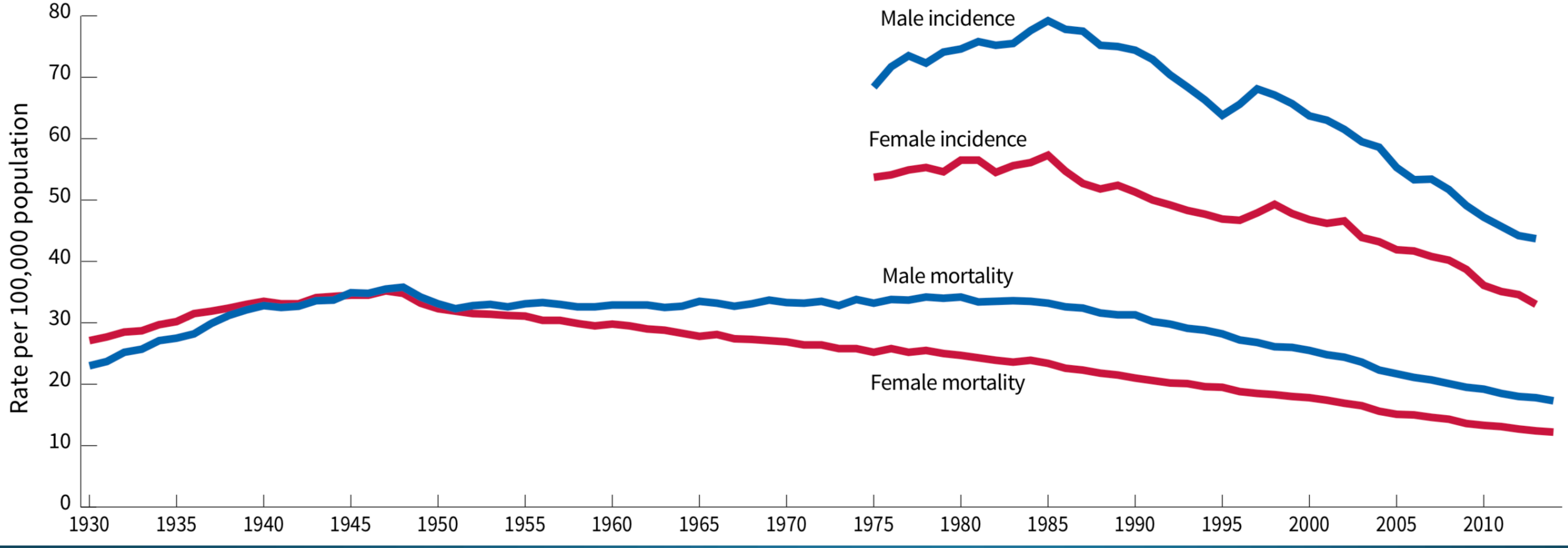


Female		
Lung & bronchus	70,500	25%
Breast	40,920	14%
Colon & rectum	23,240	8%
Pancreas	21,310	7%
Ovary	14,070	5%
Uterine corpus	11,350	4%
Leukemia	10,100	4%
Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,340	3%
All sites	**286,010**	**100%**

CRC ranks 2nd in mortality among all cancers

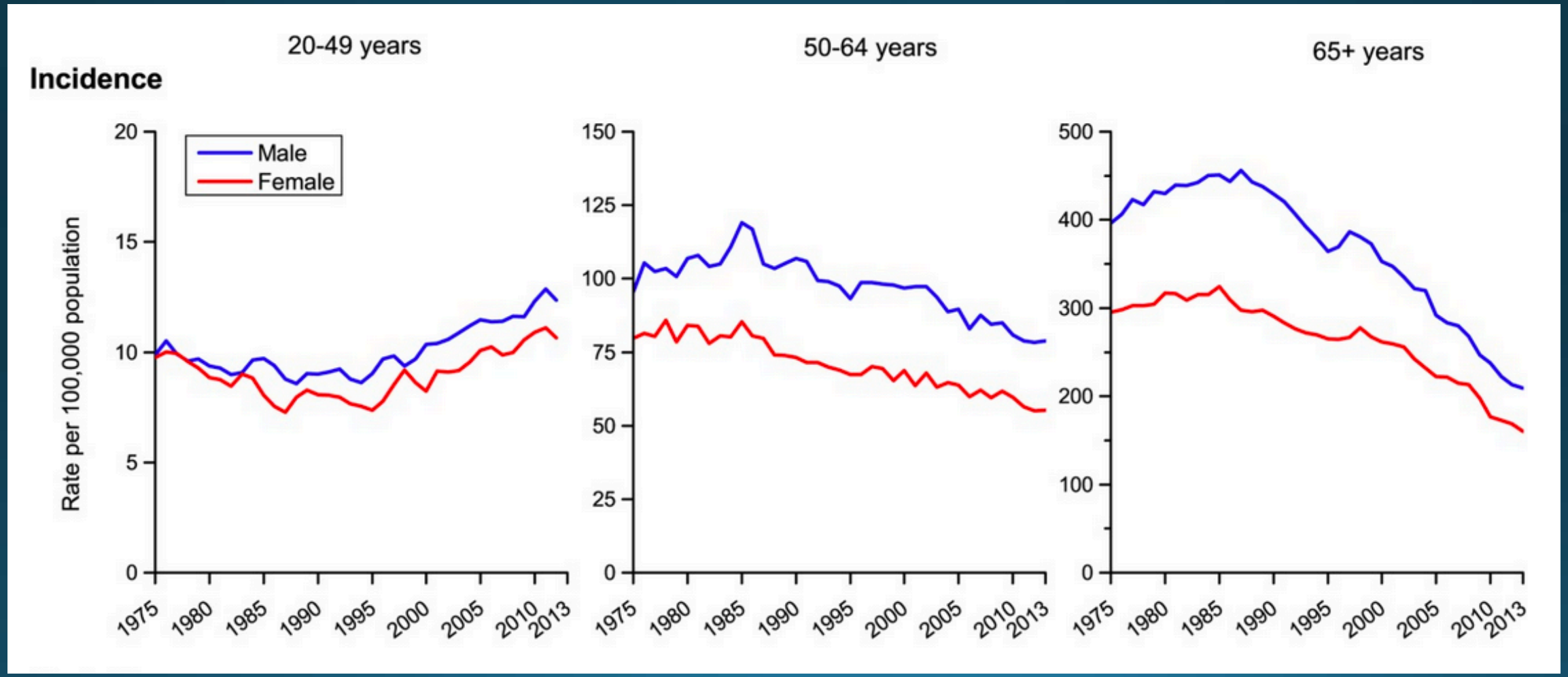
ACS Cancer Facts and Figures; 2018

Trends in Colorectal Cancer Incidence (1975-2013) and Mortality (1930-2014)



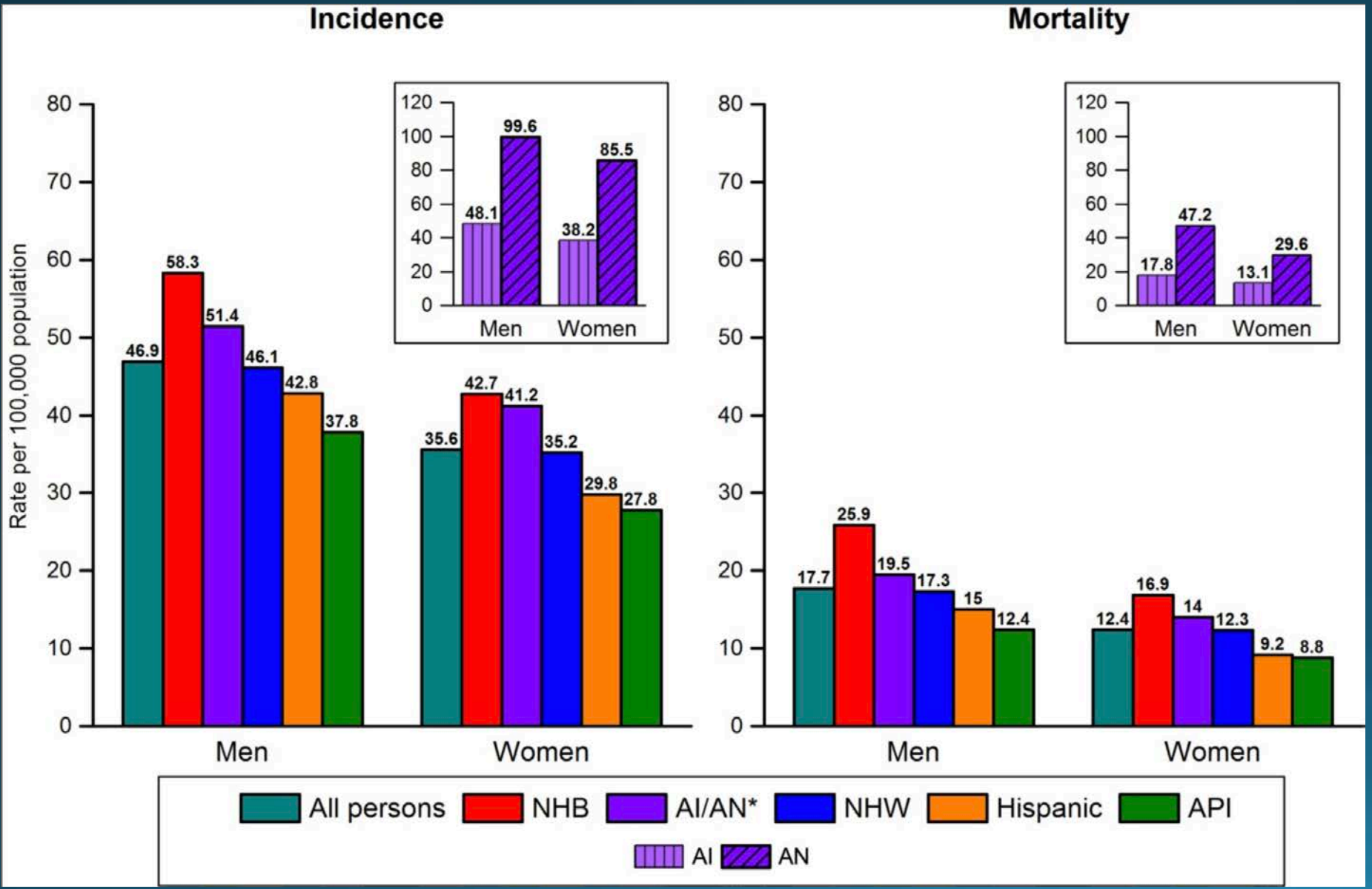
American Cancer Society: Colorectal Cancer Facts and Figures 2017-2019

Changing incidence by age groups



CA Cancer J Clin 2017

CRC Incidence by Race/Ethnicity and Sex



Highest in:

- men
- alaskan natives (? low #'s)
- non-hispanic black

Lowest in:

- Asian / Pacific Islander

Siegel R. et al.
CA Cancer J Clin 2017

Age adjusted mortality for CRC in Asia

Presumed Causes:

"westernized" lifestyle

-higher fat diet

-lower fiber

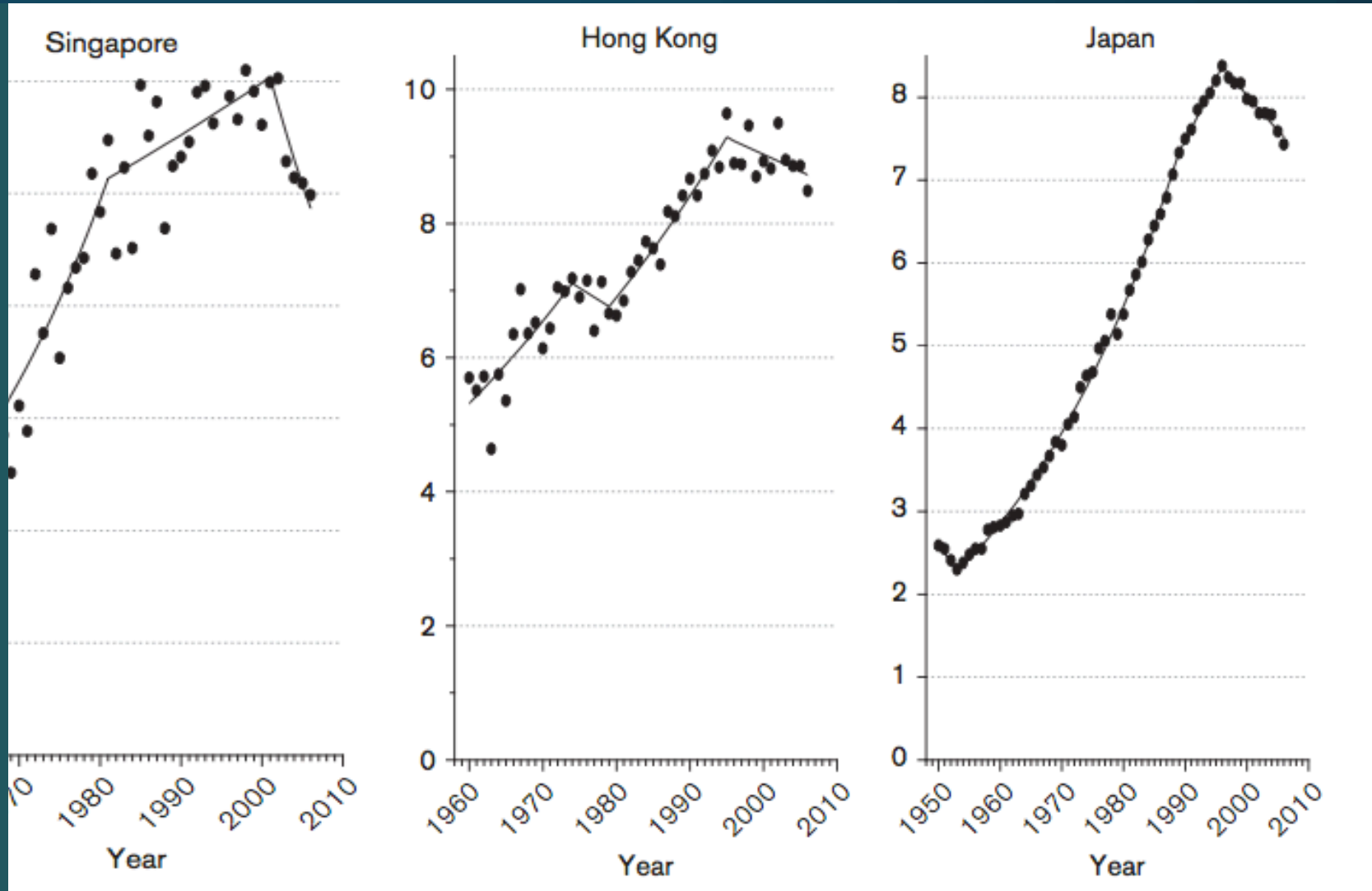
-obesity

-lack of exercise

Decline in mortality after 2000 in Hong Kong, Singapore, Japan?

-screening programs

-awareness



Zhang et al Eur J Cancer Prevention 2012

Risk Factors for Colorectal Cancer

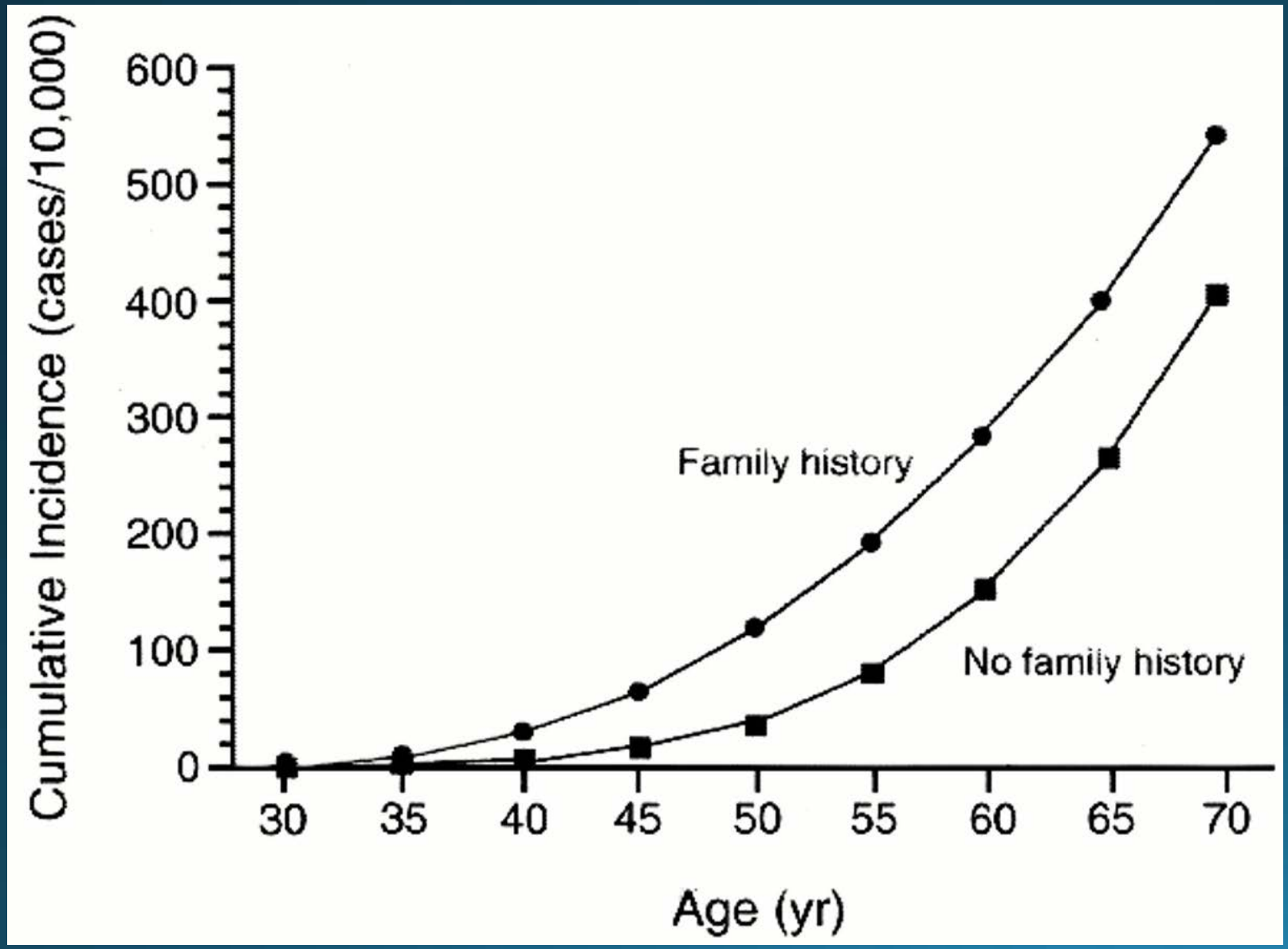
Non-modifiable

- Age
- Family history
  - Genetic predispositions
    - Lynch / FAP / other…
- Inflammatory bowel
- ? Sex / Race / Ethnicity ?

Modifiable

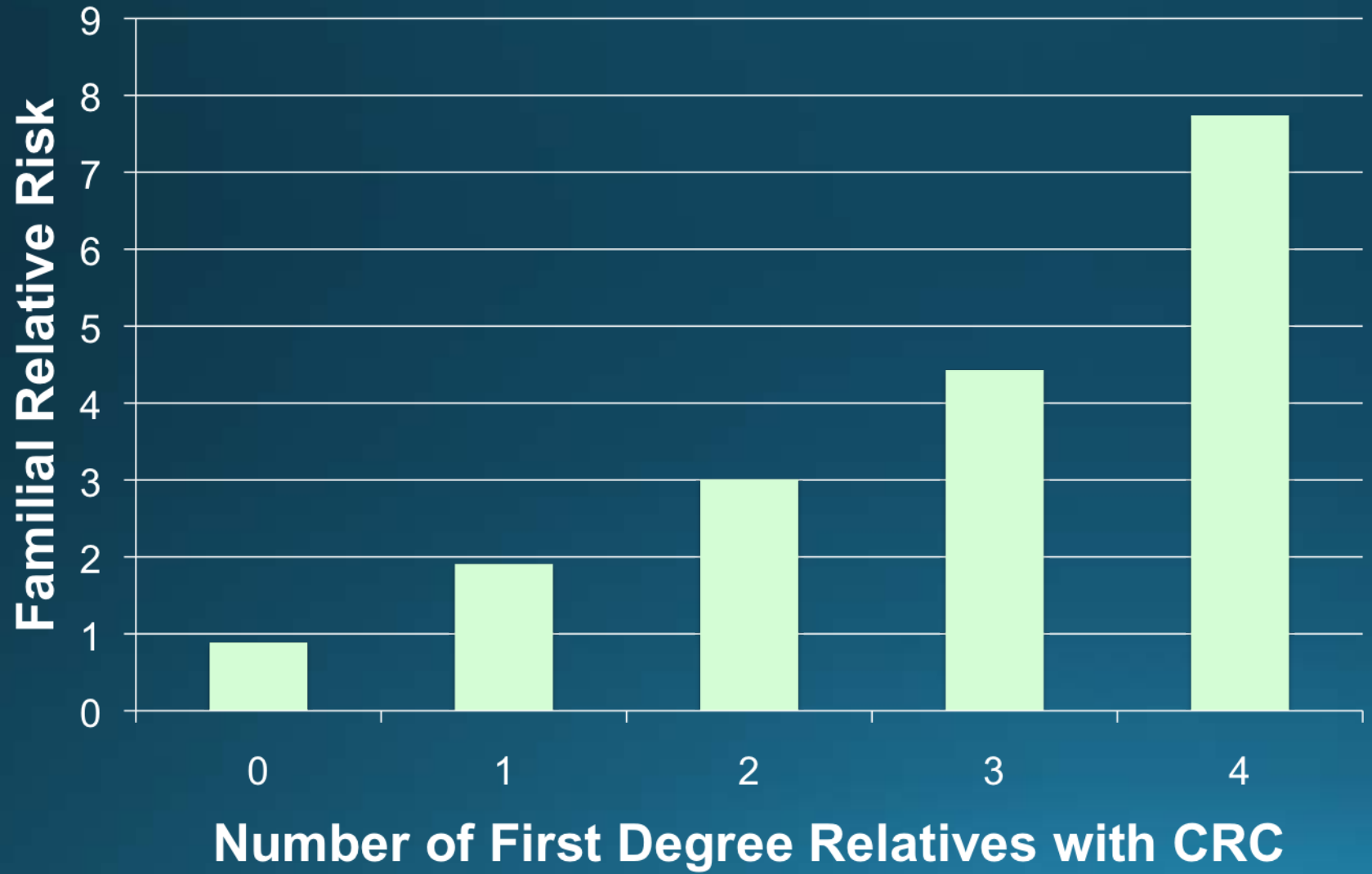
- NSAIDs
- Diet
- Physical activity
- BMI
- Hormone replacement
- Tobacco

Colorectal Cancer Risk and Family History



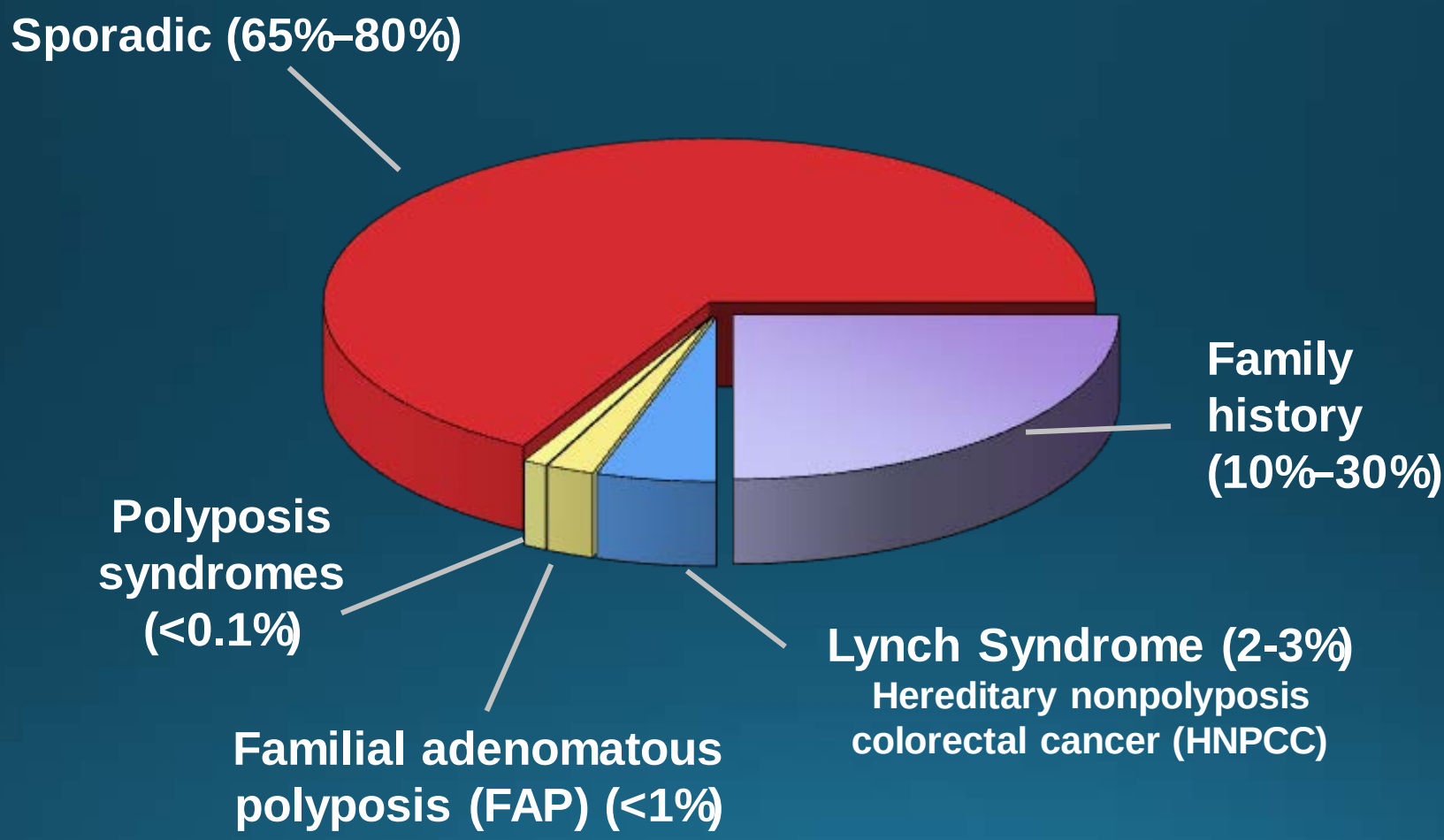
Fuchs *et al*.
N Engl J Med 1994

Colorectal Risk and Family History



Taylor *et al*.
Gastroenterology 2010

Genetics in Colon Cancer



Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996.

Genetic Predispositions

Syndrome	Genes	features
Lynch Syndrome (HNPCC)	MLH1, MSH2, MSH6, PMS2 EPCAM	Often right sided and poorly differentiated with lymphocytic infiltrate; Defective DNA repair and MSI; Favorable prognostic marker for stage II colon; unfavorable for stage IV but highly susceptible to PD-1 targeted immunotherapy
Familial Adenomatous Polyposis (FAP)	APC	Thousands of polyps (unless attenuated FAP); Desmoids, osteomas, gastric and duodenal adenomas
MUTYH-associated neoplasia	MUTYH	Duodenal polyposis
Juvenile polyposis	SMAD4, BPMR1A	Hereditary hemorrhagic telangiectasia
Peutz-Jeghers	STK11	Hamartomas throughout GI tract
Other…	CHK2, tP53,	

Modifiable Protective Factors

Factor	ref.	# studies	/ patients	metric	hazard ratio
Physical activity[a]	WCRF CUP[99]	12	8396	Total physical activity, highest vs lowest levels	0.80 (0.72–0.88)
		20	10,258	Recreational physical activity, highest vs lowest levels	0.84 (0.78–0.91)
Consumption of whole grains	WCRF CUP[99]	6	8320	Per 90 g/day	0.83 (0.78–0.89)
Consumption of food containing dietary fibre	WCRF CUP[99]	21	16,562	Per 10 g/day	0.93 (0.87–1.00)
Consumption of dairy products	WCRF CUP[99]	10	14,859	Dairy products, per 400 g/day	0.87 (0.83–0.90)
		9	10,738	Milk, per 200 g/day	0.94 (0.92–0.96)
		7	6462	Cheese, per 50 g/day	0.94 (0.87–1.02)
		10	11,519	Dietary calcium, per 200 mg/day	0.94 (0.93–0.96)
Aspirin	Algra et al.[18]	26[b]	25,618	Any aspirin vs non-user	0.67 (0.60–0.74)
		17[b]	12,659	Maximum reported aspirin vs non-user	0.62 (0.58–0.67)
Hormone replacement therapy	Green et al.[20]	30	6256[c]	Any hormone replacement, ever vs never use	0.84 (0.81–0.88)

Table adapted from Brenner H. and Chen C. Brit J Cancer 2018

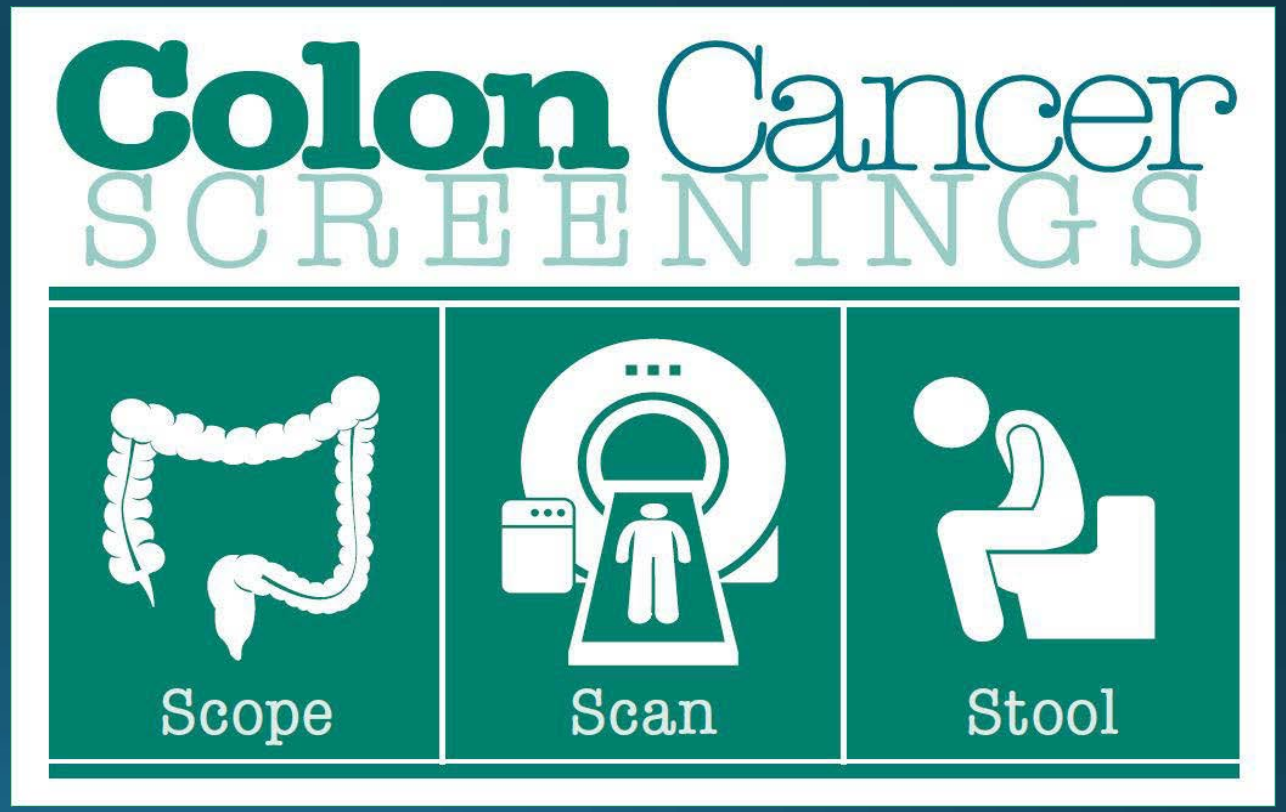
Modifiable Risk Factors

Factor	ref.	# studies / patients		metric	hazard ratio
Consumption of red and processed meat	WCRF CUP[99]	8	6662	Red meat, per 100 g/day	1.12 (1.00–1.25)
		10	10,738	Processed meat, per 50 g/day	1.16 (1.08–1.26)
Alcohol consumption	WCRF CUP[99]	16	15,896	Per 10 g/day	1.07 (1.05–1.08)
Body fatness	WCRF CUP[99]	38	71,089	BMI, per 5 kg/m^2	1.05 (1.03–1.07)
		8	4301	Waist circumference, per 10 cm	1.02 (1.01–1.03)
		4	2564	Waist:hip ratio, per 0.1 unit	1.02 (1.01–1.04)
Smoking	Botteri et al.[13]	106	39,779	Ever vs never smokers	1.18 (1.11–1.25)

Table adapted from Brenner H. and Chen C. Brit J Cancer 2018

CRC Screening Options

- **Early detection**
  - Fecal occult blood test (FOBT) or fecal immunochemical test (FIT) q year
  - Multi-target stool DNA test (Cologuard) q 3 years
- **Early detection and prevention**
  - Colonoscopy q 10 years
  - Flexible sigmoidoscopy q 5 years
  - CT colonography ("virtual colonoscopy") q 5 years



Wolf et al. CA: Cancer J Clin 2018

American Cancer Society: 2018 Recommendations for CRC Screening

ACS recommends that average risk adults ≥ 45 undergo regular screening with either a high-sensitivity stool based test or a "visual" examination, depending on patient preference and test availability.

All (+) results should be followed up with a timely colonoscopy.

The recommended screening at age ≥ 45 is a qualified recommendation while that for age ≥ 50 is a strong recommendation

Wolf et al. CA: Cancer J Clin 2018

ACS: Options for CRC Screening

Stool Based Tests

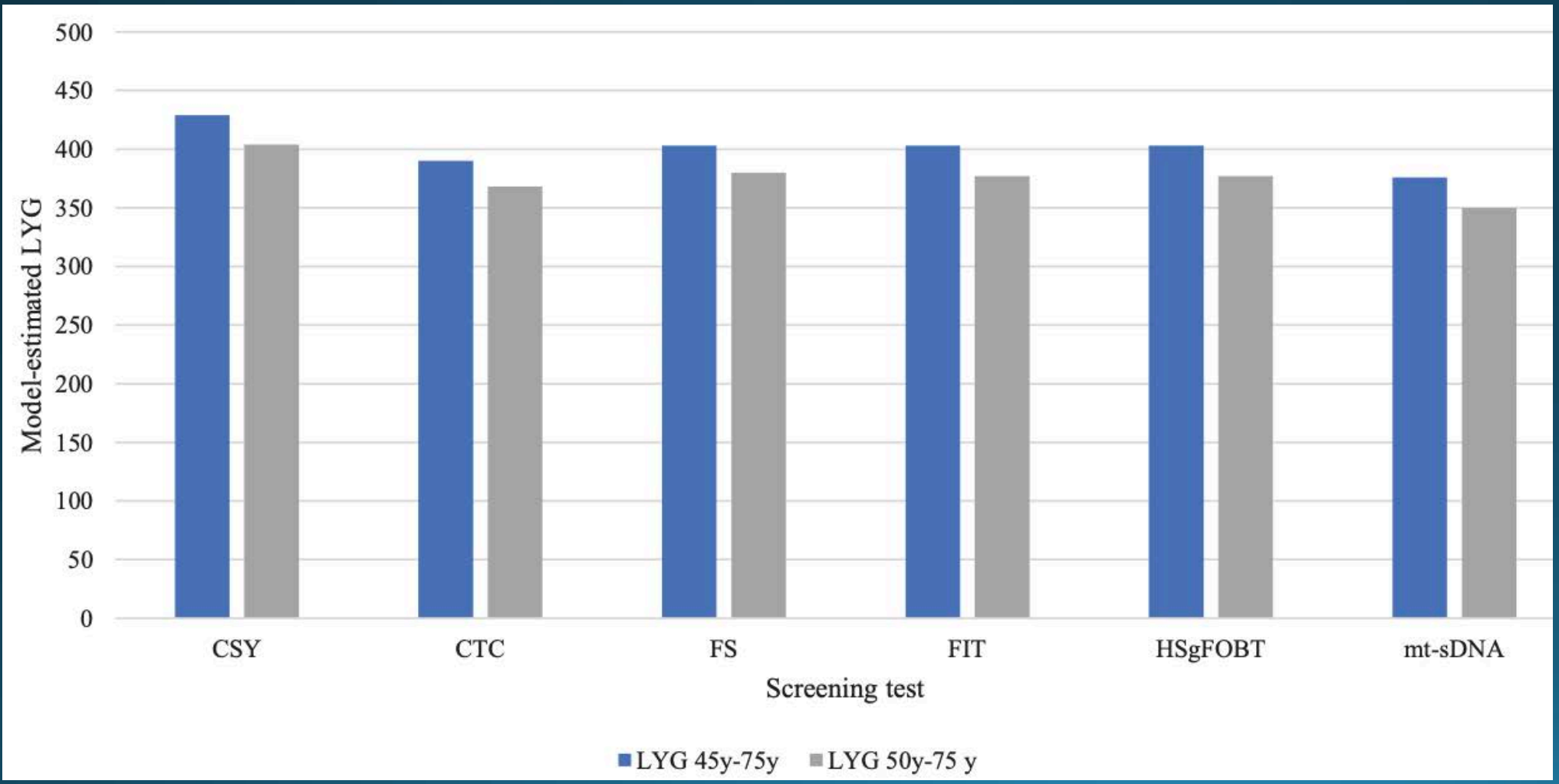
- Fecal immunochemical q yr
- High sensitivity guaiac-based q yr
- Multitarget stool DNA q 3 yrs

"Structural" examinations

- Colonoscopy q 10 yrs
- CT colonography q 5 yrs
- Flexible sigmoidoscopy q 5 yr

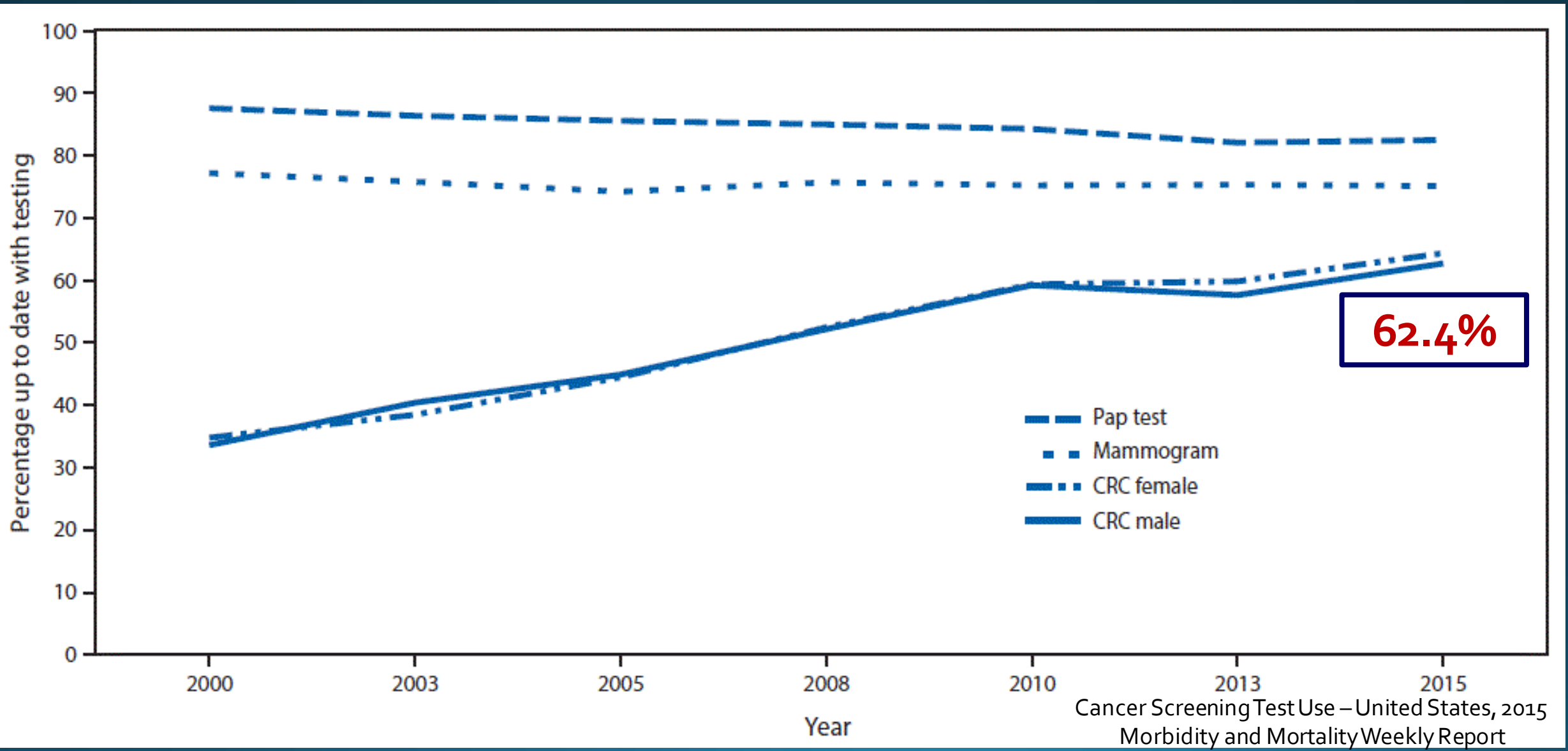
Wolf et al. CA: Cancer J Clin 2018

Model estimates of life years gained: Screening at 45 vs 50 years of age



Peterse et al. Cancer 2018

Room for Improvement…



Cancer Screening Test Use – United States, 2015
Morbidity and Mortality Weekly Report

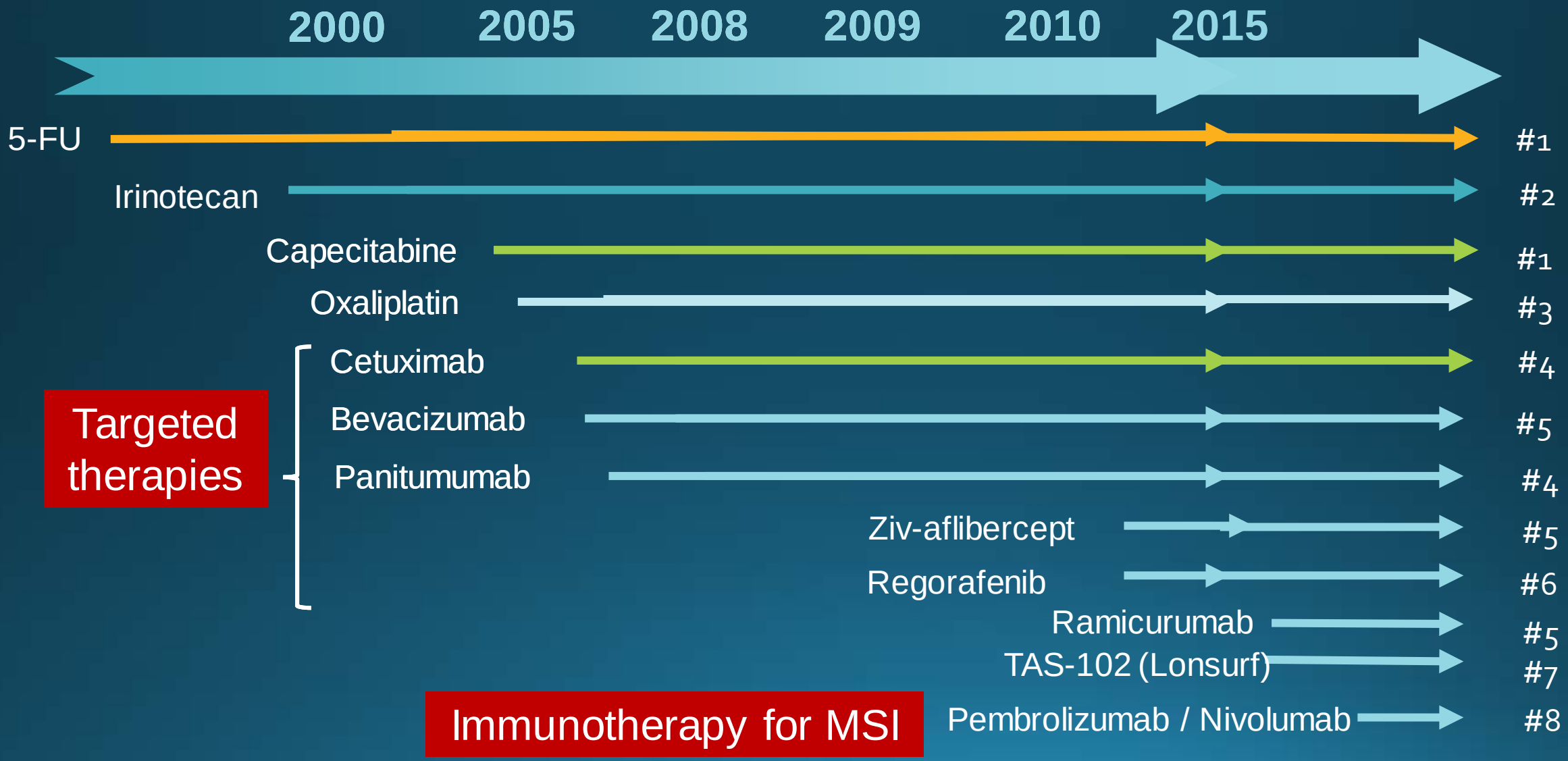
Management of Colon Cancer

New agents approved

Improvements in management of resectable disease

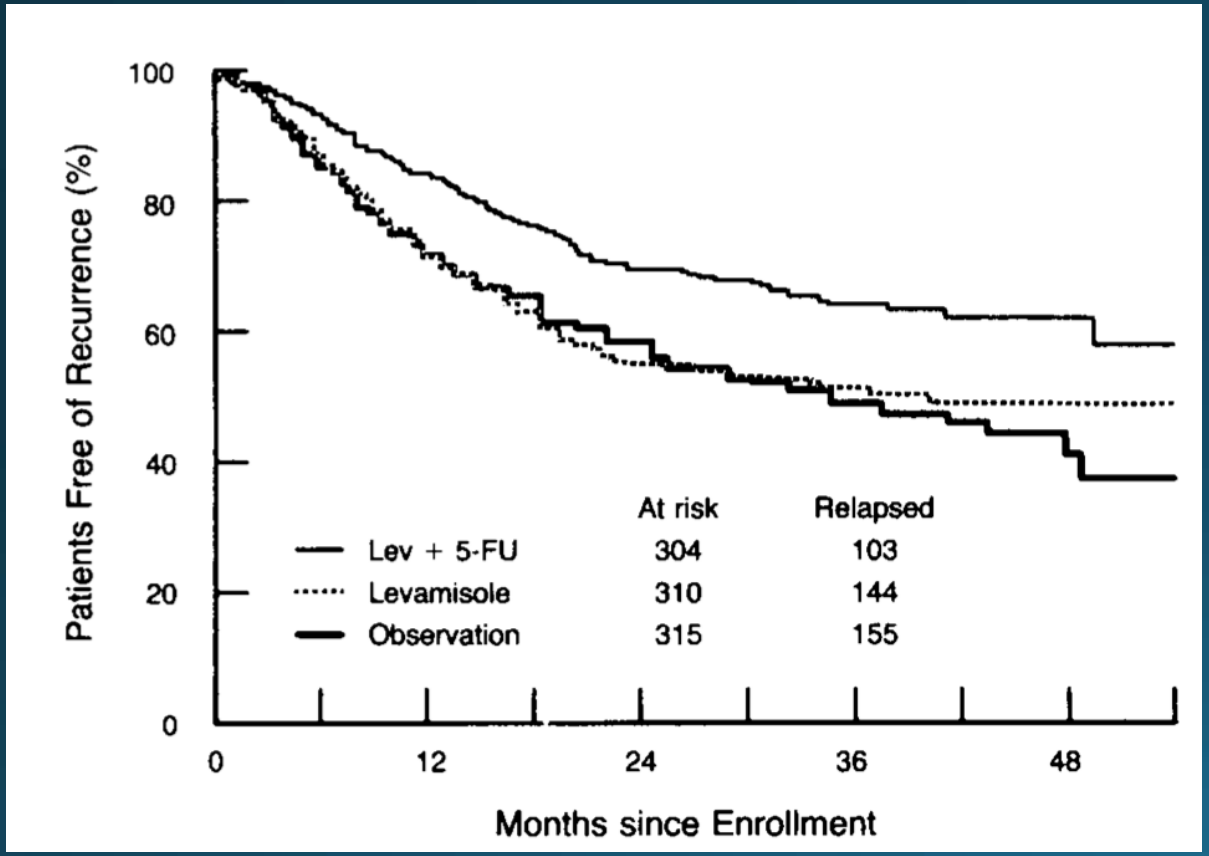
Use of molecular biomarkers for treatment decisions

FDA Approvals in Advanced Colon Cancer



How long to treat after surgery ?

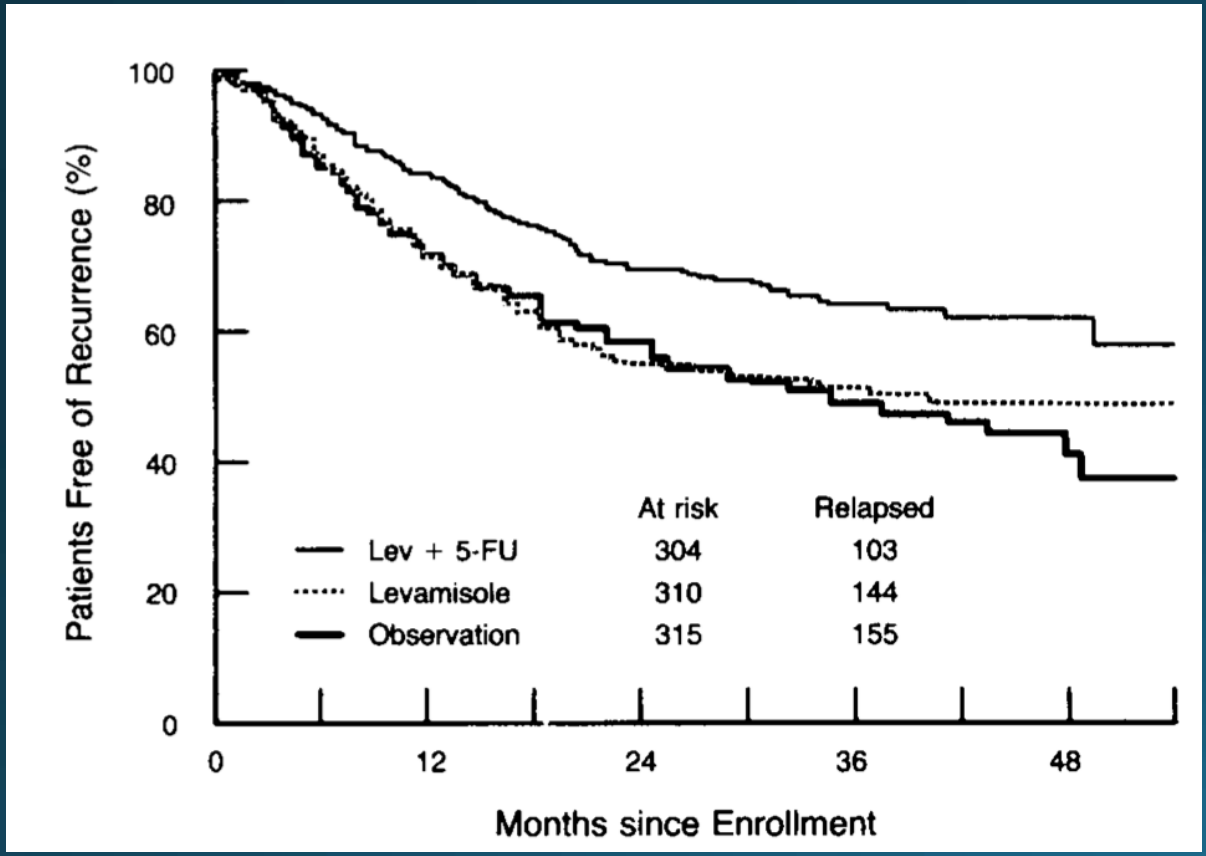
Observation vs 12 mos 5FU+ Lev vs 12 mos Levamisole alone



Moertel C. et al. NEJM 1990

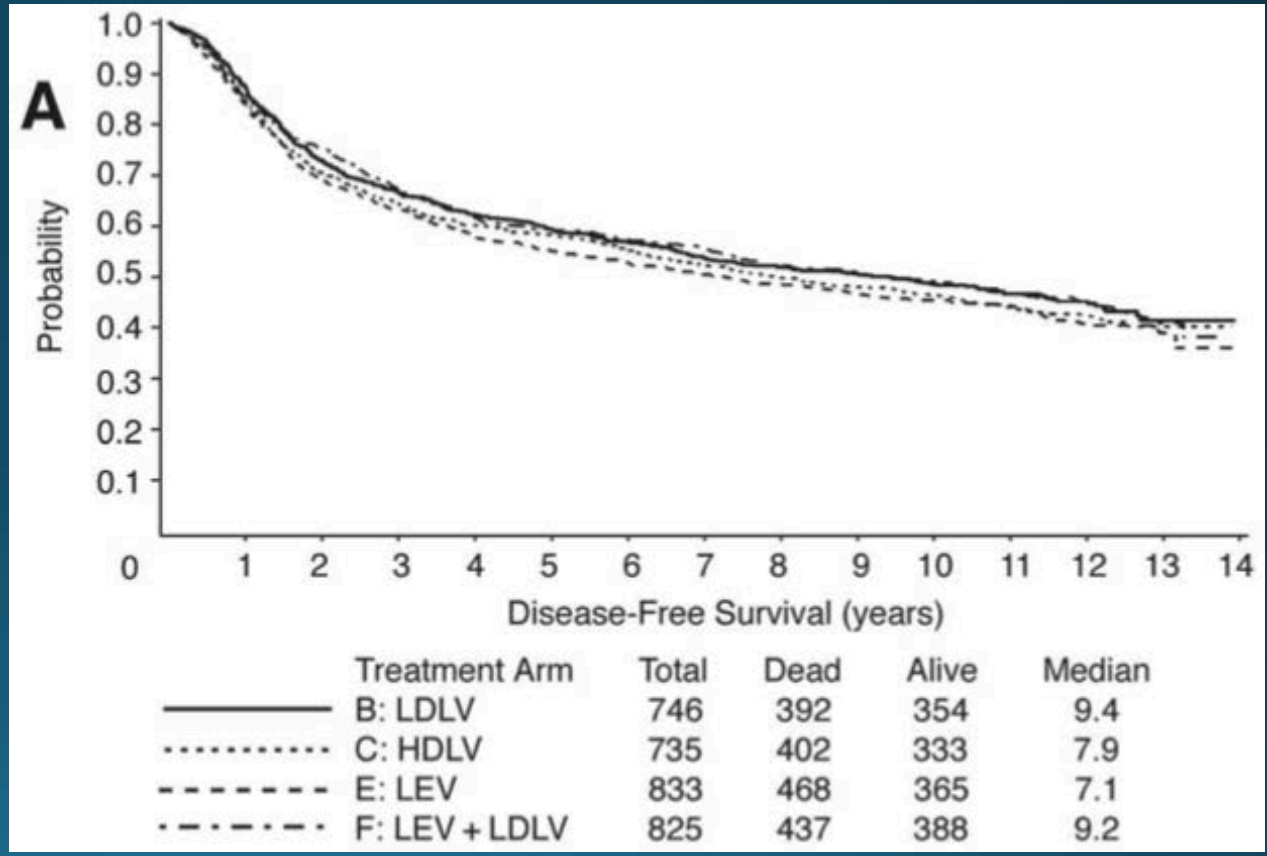
How long to treat?

Observation vs 12 mos 5FU+ Lev vs 12 mos Levamisole alone



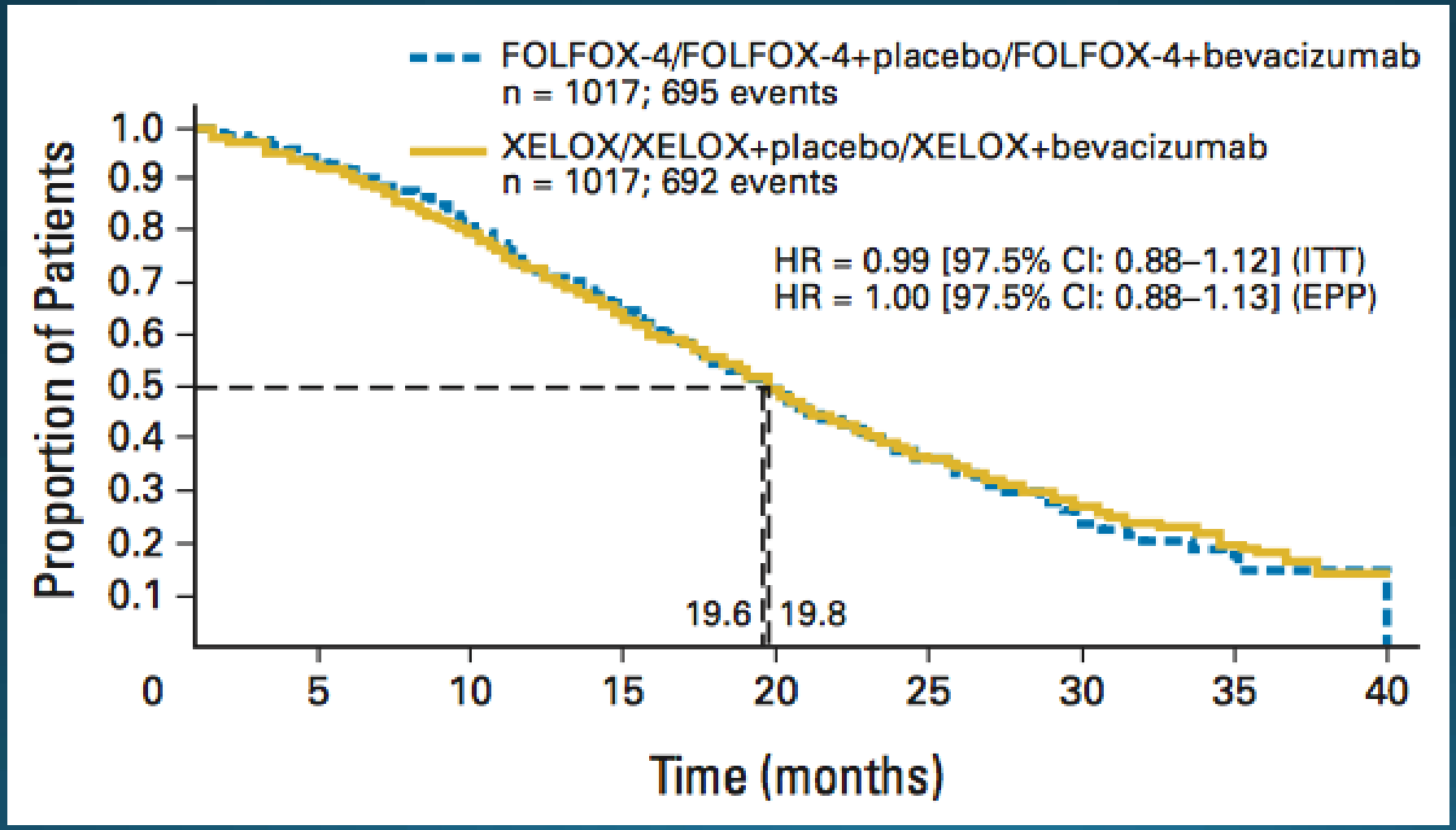
Moertel C. et al. NEJM 1990

6 mos 5FU+LV vs 12 mos 5FU + Lev



Haller D. et al. JCO 2005

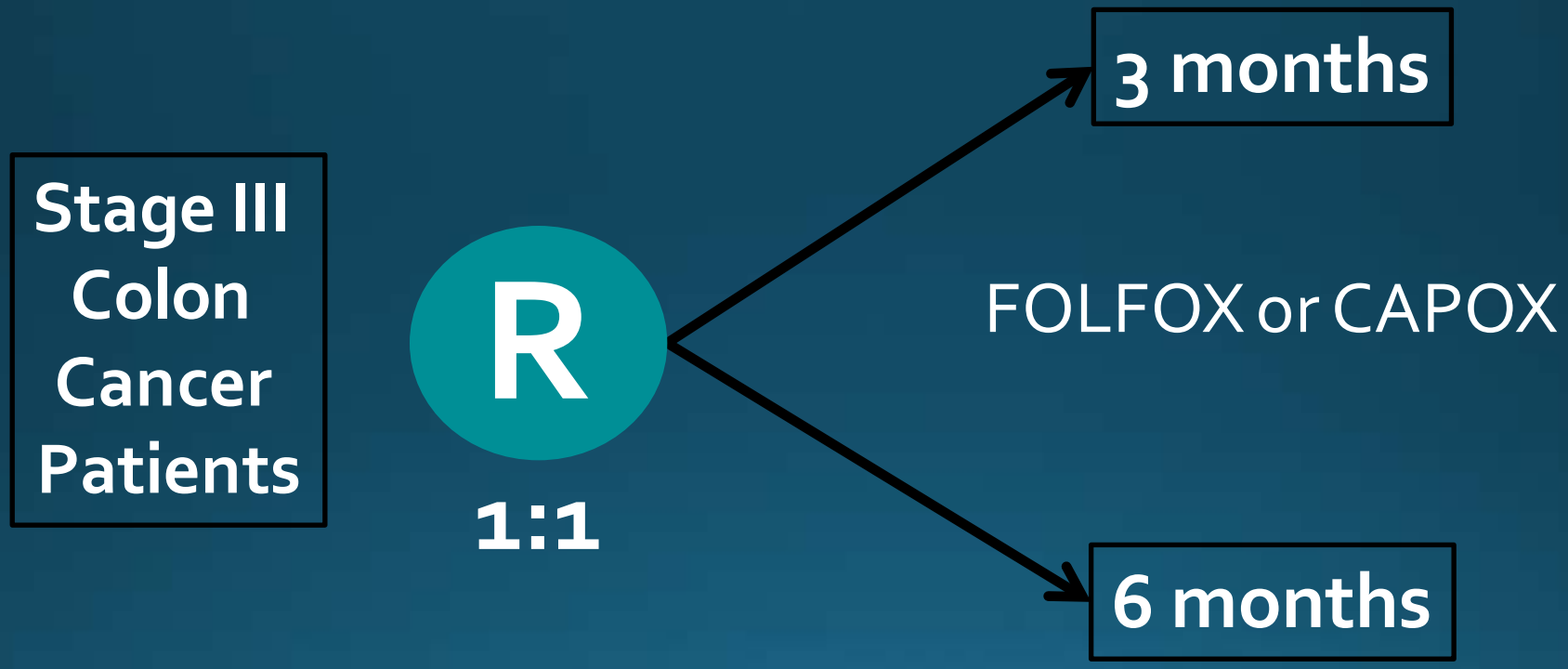
6 months: 48 hr infusion of 5FU vs capecitabine (p.o.)



Cassidy J. et al. JCO 2008

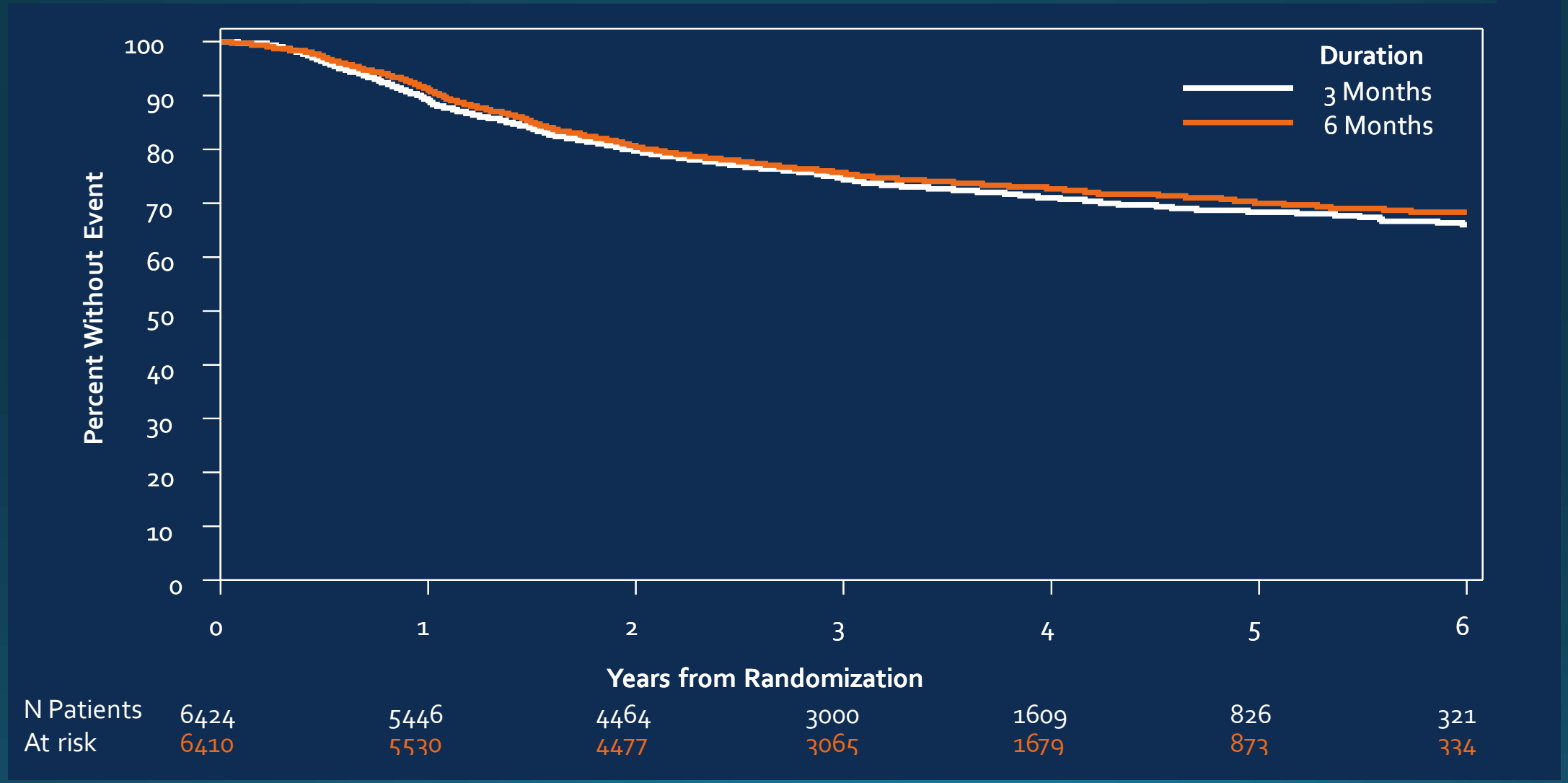
Treatment duration: 3 vs 6 mos

Total planned accrual ≥ 10,500



Pre-planned secondary analysis by regimen and T/N stage

Treatment Duration: 3 versus 6 months

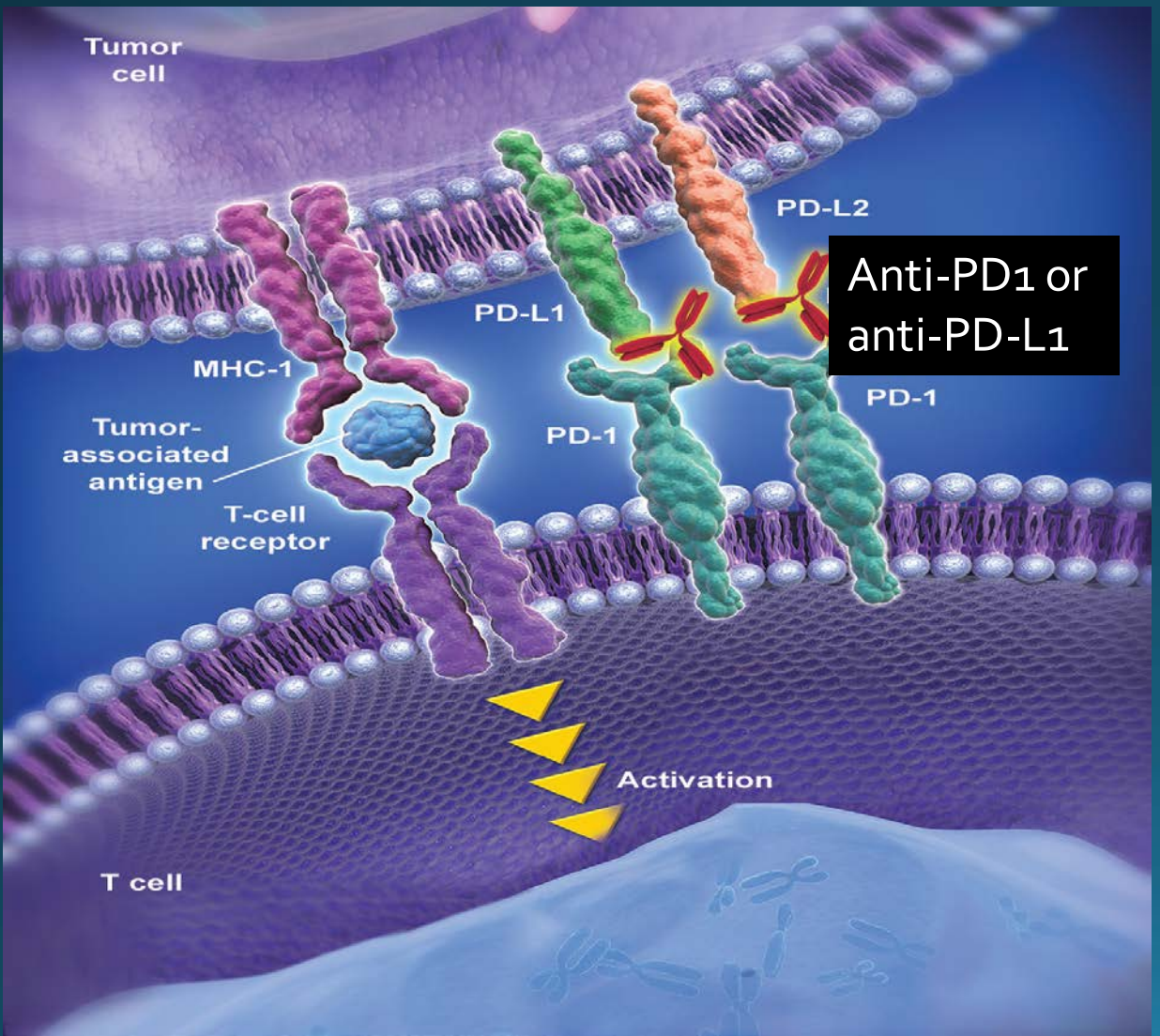


Presented by: Qian Shi, PhD on behalf of IDEA collaborators ASCO 2017

Validated Biomarkers in colon cancer

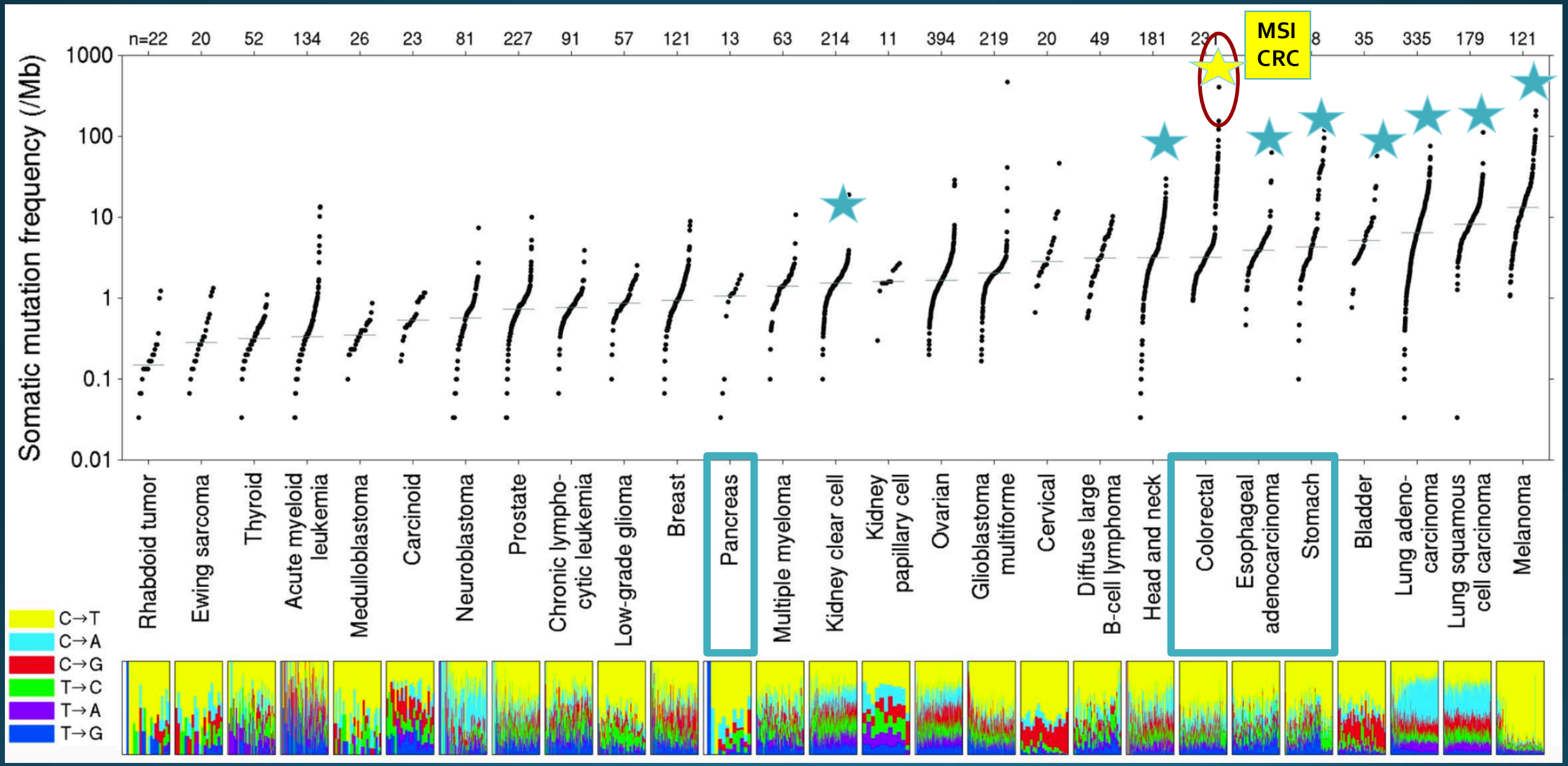
- RAS mutation testing: if normal then cetuximab or panitumumab
  - ~50% of advanced CRC
- BRAF mutation testing: if mutated then BRAFi + above + ?
  - ~8% of advanced CRC
- Her-2 neu : if present then drugs that target Her-2 (+) breast cancers
  - ~10% of advanced CRC
- MSI (DNA repair deficiency): if (+) then immunotherapy
  - ~3% of advanced CRC

Immunotherapy: How the PD1 drugs work…



FDA approved PD-1/PD-L1 drugs

- Pembrolizumab (Keytruda)
- Nivolumab (Opdiva)
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

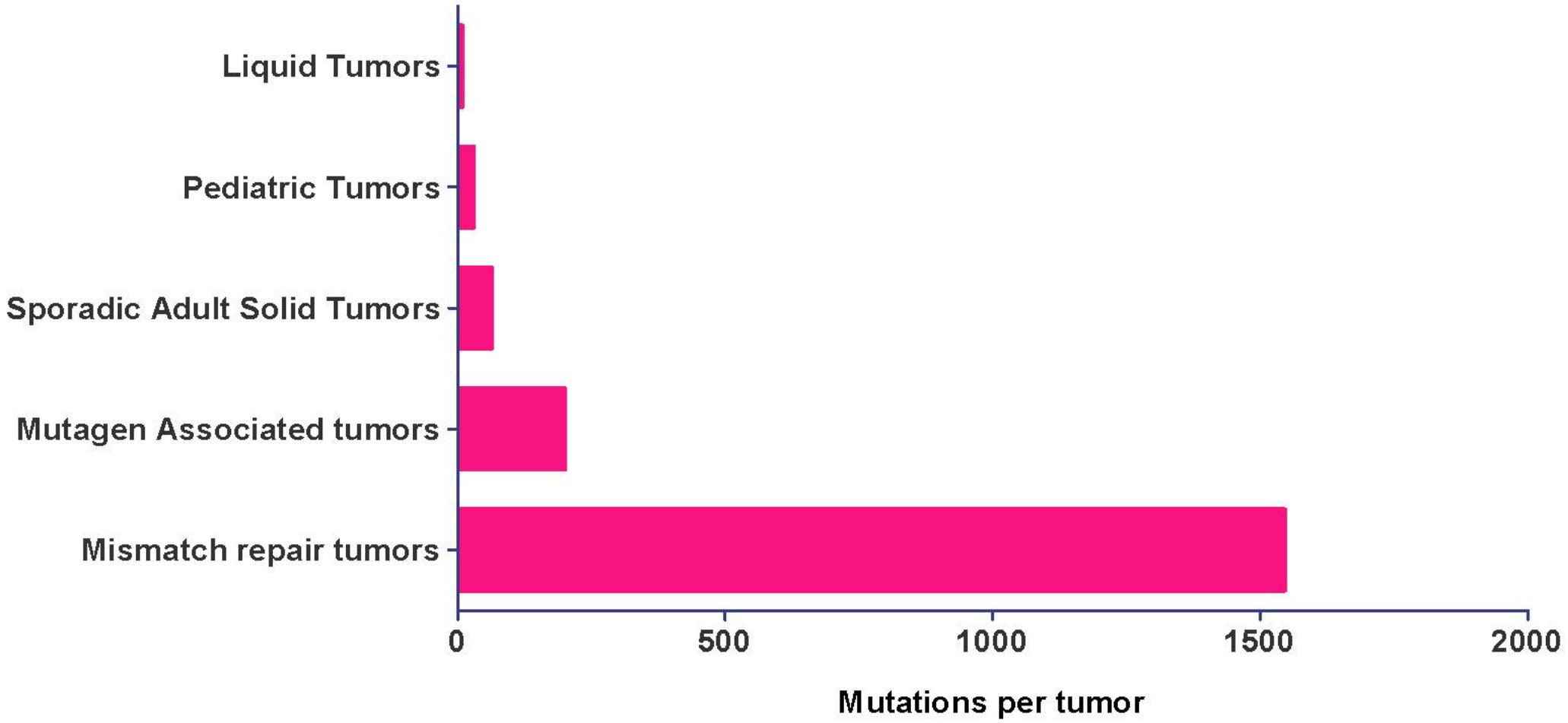


FDA approved indications

Mismatch Repair Deficiency

- MicroSatellite Instability (MSI) is due to deficient mismatch repair
- MSI can be result of:
  - Germline mutations (Lynch Syndrome) ~1/3 of CRC MSI
  - Epigenetic silencing (MLH1 hypermethylation) ~2/3 of CRC MSI
  - Sporadic mutations (MLH1, MSH2, MSH6, PMS2) ≤ 5% of CRC MSI
- Mismatch repair deficiency can be detected by:
  - MSI assay (PCR of micro-satellite repeats)
  - Immunohistochemistry (IHC) for mismatch repair proteins
  - Gene sequencing of mismatch repair genes
  - Next Generation Sequencing (NGS) to detect microsatellite repeats

Mutations per tumor



Presented By Luis Diaz at 2018 ASCO-SITC Clinical Immuno-Oncology Symposium

MSI as a Predictive Biomarker: Response to immunotherapy (KEYNOTE-016 Study)

MSI Colorectal Cancers N = 28	MSS Colorectal Cancers N = 25	MSI Non-Colorectal Cancers N = 58

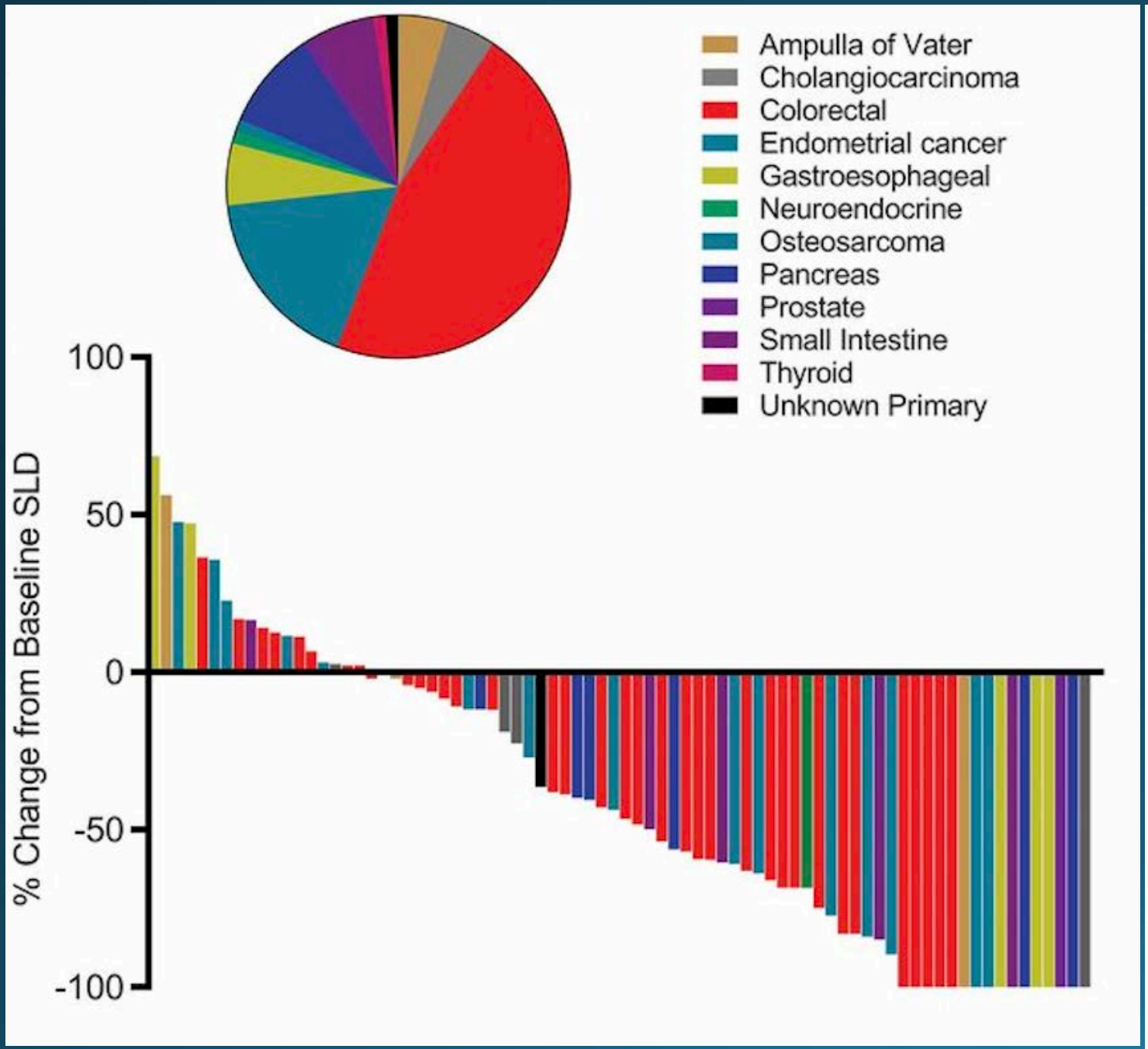
- Pembrolizumab 10 mg/kg every 2 weeks
- Primary endpoint: response rate and immune related 20 week PFS rate
- Mismatch repair testing using standard PCR-based test for MSI

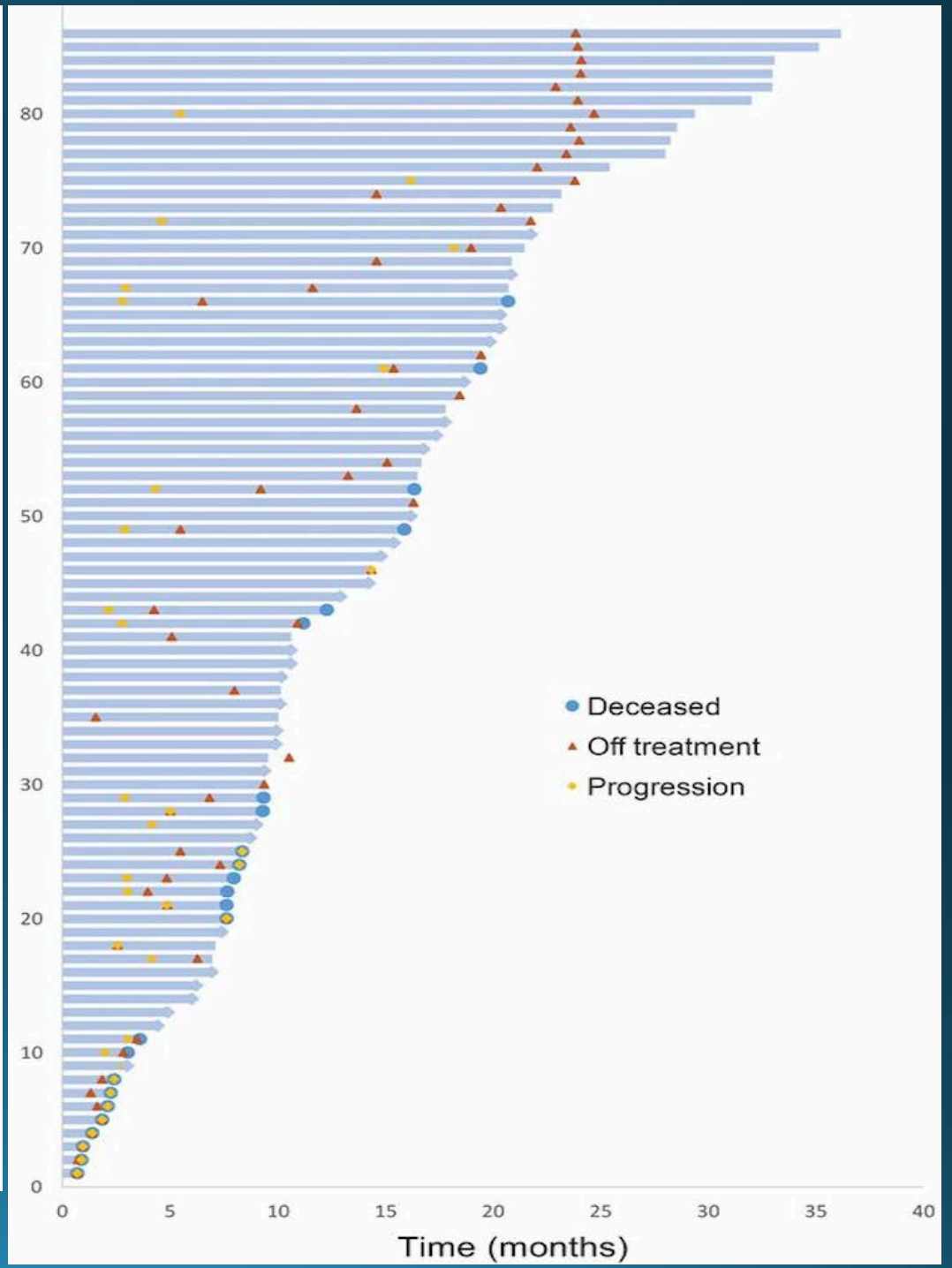
Le et al. Science 2017

Objective Response Rates

	[1]Colorectal MSI-H N = 28	[2]Colorectal MSS N = 25	[1]Non-CRC MSI-H N = 58
Objective response rate	**57%**	0%	**55%**
Complete response rate	**11%**	0%	**21%**
Disease control rate	**89%**	16%	80%

Le et al. Science 2017; Le et al. NEJM 2015





From Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade, Le D., et al., 2017. Reprinted with permission from AAAS.

42 yo rancher c/o blood in stool

- HPI: 1-2 month with intermittent crampy abdominal pain; 2-3 weeks with blood admixed with stool
- Exam and labs normal
- PMH: (-)
- Colonoscopy with "obstructing" descending colon mass
  - Could not pass scope past mass
  - Biopsy: poorly differentiated adenocarcinoma
  - CT (-) for metastases
- Left hemicolectomy with path: T3 No (0 of 22 nodes) = Stage IIA

42 yo with stage IIA colon cancer

- Oncologist offers adjuvant chemo (FOLFOX) since young, healthy patient with obstructing, poorly differentiated tumor

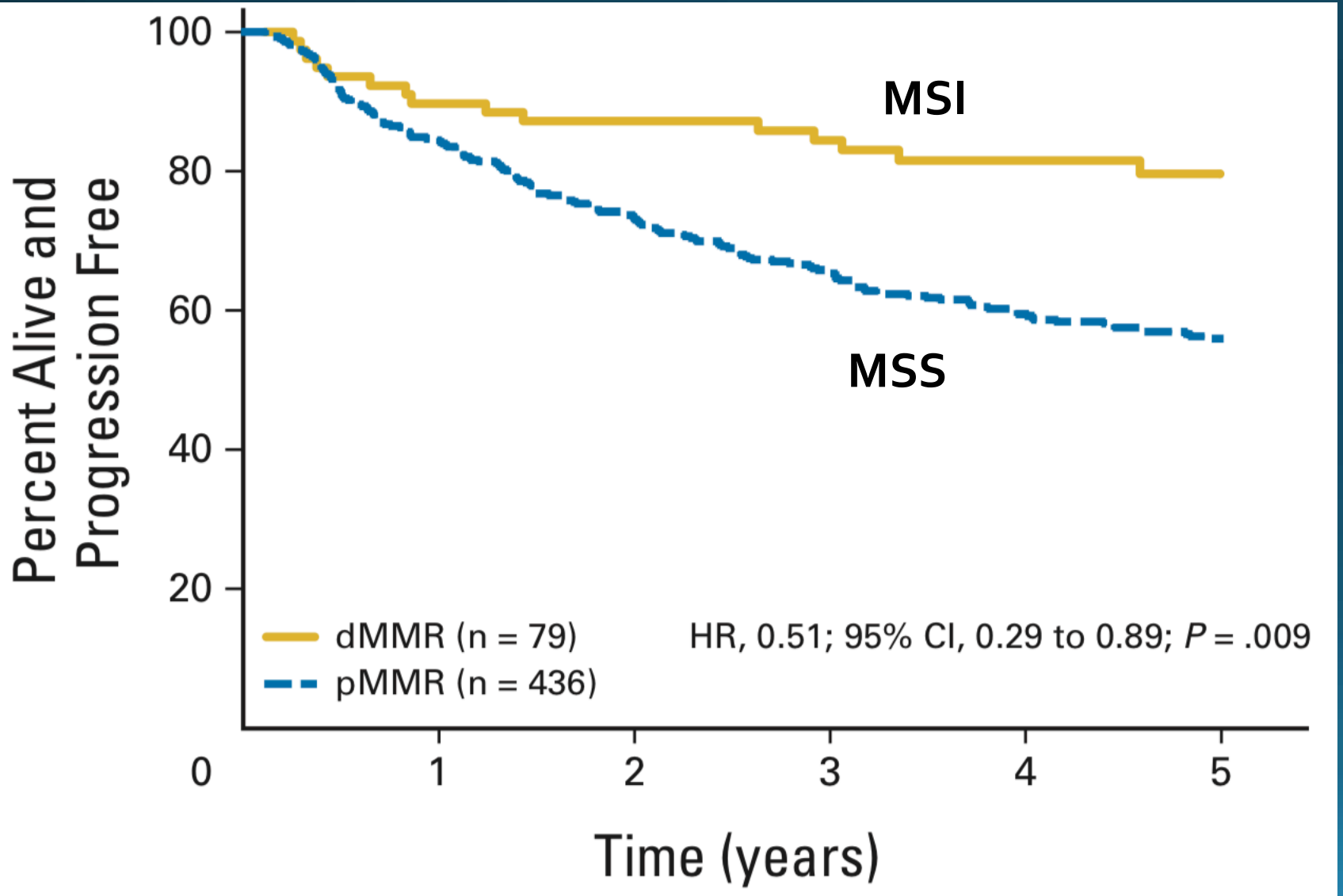
- After 6 months of FOLFOX c/b grade 2 neuropathy, he has a CT which is (-) and a colonoscopy which finds a cecal mass, bx adenocarcinoma.

- Right hemicolectomy with path: T3 No (0 of 15 nodes) = Stage IIA

42 yo with second colon cancer

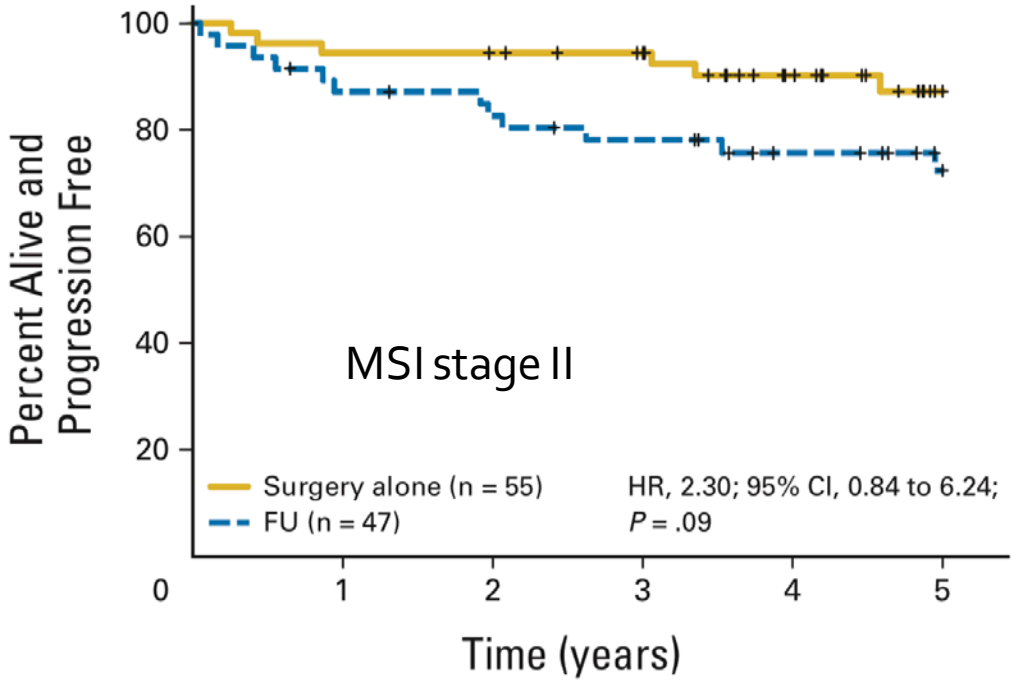
- His oncologist would like to give adjuvant 5FU + irinotecan since the cecal cancer clearly survived the FOLFOX that had just been given…
- You now recommend:
  - Test tumor sample for microsatellite instability / Lynch syndrome
- Immunohistochemistry test for mismatch repair proteins reveals deficiency in MSH6 (i.e. Microsatellite Instability or MSI)
  - You recommend genetic counseling and no further treatment since very low risk of recurrence

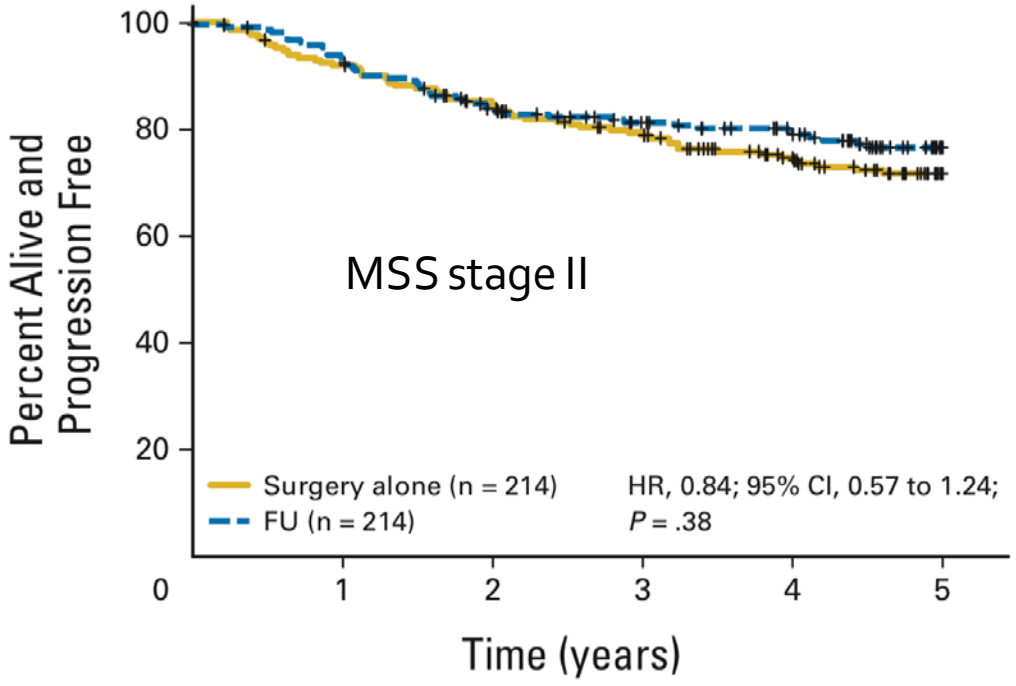
MSI as a prognostic factor



- Retrospective review of MSI vs MSS in Stage II/III patients who were randomized to observation arms

Sargent et al. JCO 2010





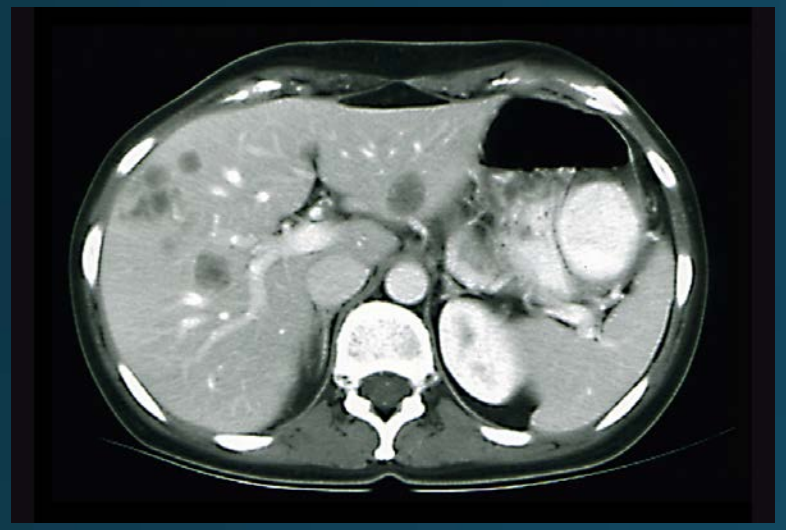
Retrospective review MSI vs MSS in trials comparing 5-FU with no treatment in stage II colon cancer

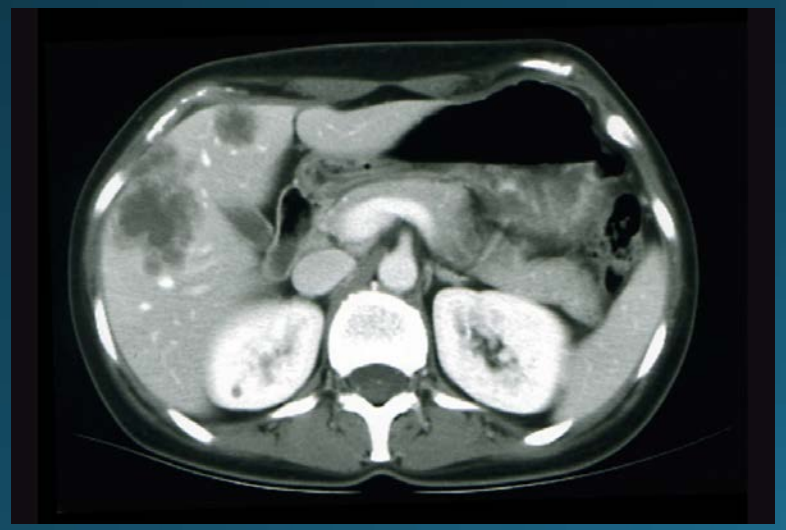
5-FU was inferior to observation in MSI tumors

5-FU of no benefit in MSS stage II patients

Sargent et al. JCO 2010

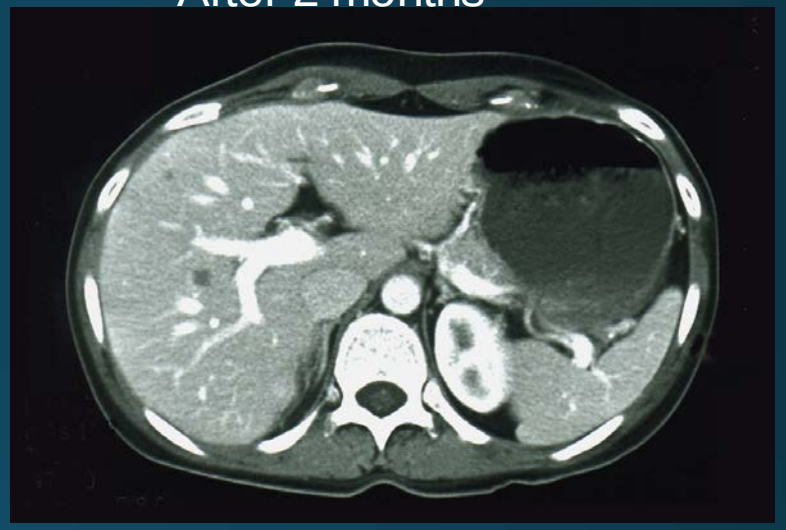
55 yo with RUQ pain and MSI Colon

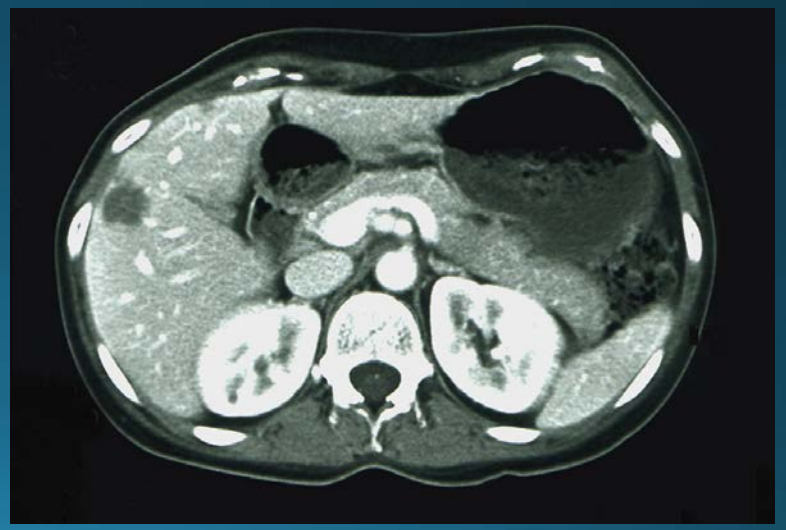




- Biopsy confirms metastatic colon cancer; IHC: deficient in MLH1 and PMS2
- Progressive disease after 5FU / oxaliplatin / irinotecan
- Treated with anti-PD1 immunotherapy

After 2 months





Characteristic of Lynch Syndrome tumors

Clinical features

- Younger age
- Colon, endometrial, ovarian, gastric, small intestine, pancreatico-biliary, urothelial, prostate, and brain
- Predilection for right side of colon
- Favorable prognosis in early stage disease / unfavorable in advanced disease

Pathological / Molecular features

- Lymphocytic infiltrate
- Poorly differentiated

- Hyper mutated phenotype (MSI)
- Deficient mismatch repair (dMMR)
  - Absent MLH1, PMS2, MSH2, MSH6 and rarely with deletions of EPCAM which induce epigenetic silencing of MSH2

Lifetime Risks in Lynch Patients

Unscreened Lynch Patients

- Colorectal cancer up to 82%
- Uterine cancer 40-70%
- Stomach cancer up to 13%
- Ovarian cancer 10-12%

Gruber et al. Gastroenterology 2006

Screened Lynch Patients

Frequent colonoscopy in non-randomized trial

- Colorectal cancer rate reduced 56% (18% vs. 41%)
- Death rate reduced 65% (9% vs. 26%)

Jarvinen *et al.*, Gastroenterology 2000

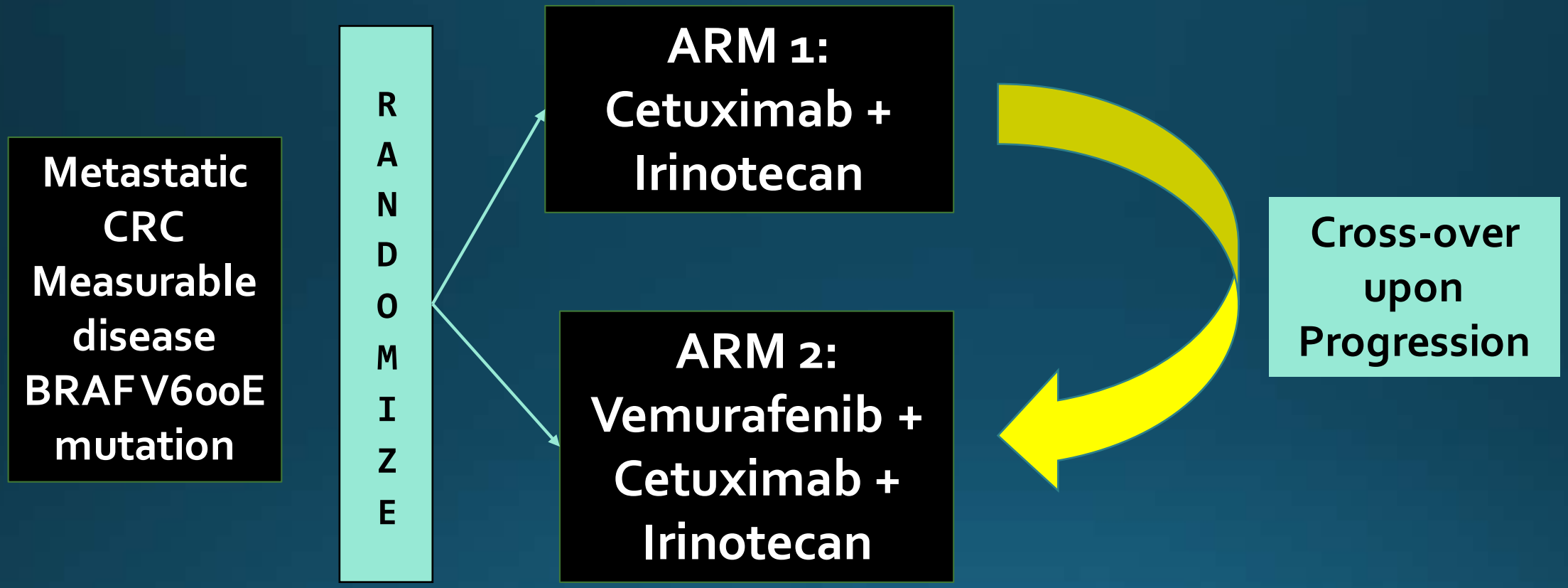
Estimated population frequency for each MMR gene

Gene	% (95% Confidence Interval)	1 in (95% Confidence Interval)
MLH1	0.051 (0.039-0.068)	1,946 (1,480-2,564)
MSH2	0.035 (0.026-0.048)	2,841 (2,101-3,846)
MSH6	0.132 (0.089-0.196)	758 (509-1,126)
PMS2	0.140 (0.094-0.208)	714 (480-1,062)
Any MMR gene	0.359 (0.248-0.520)	279 (192-403)

BRCA1 or BRCA2	**0.25**	**400**

Win et al. Cancer Epidemiology, Biomarkers and Prevention, 2017

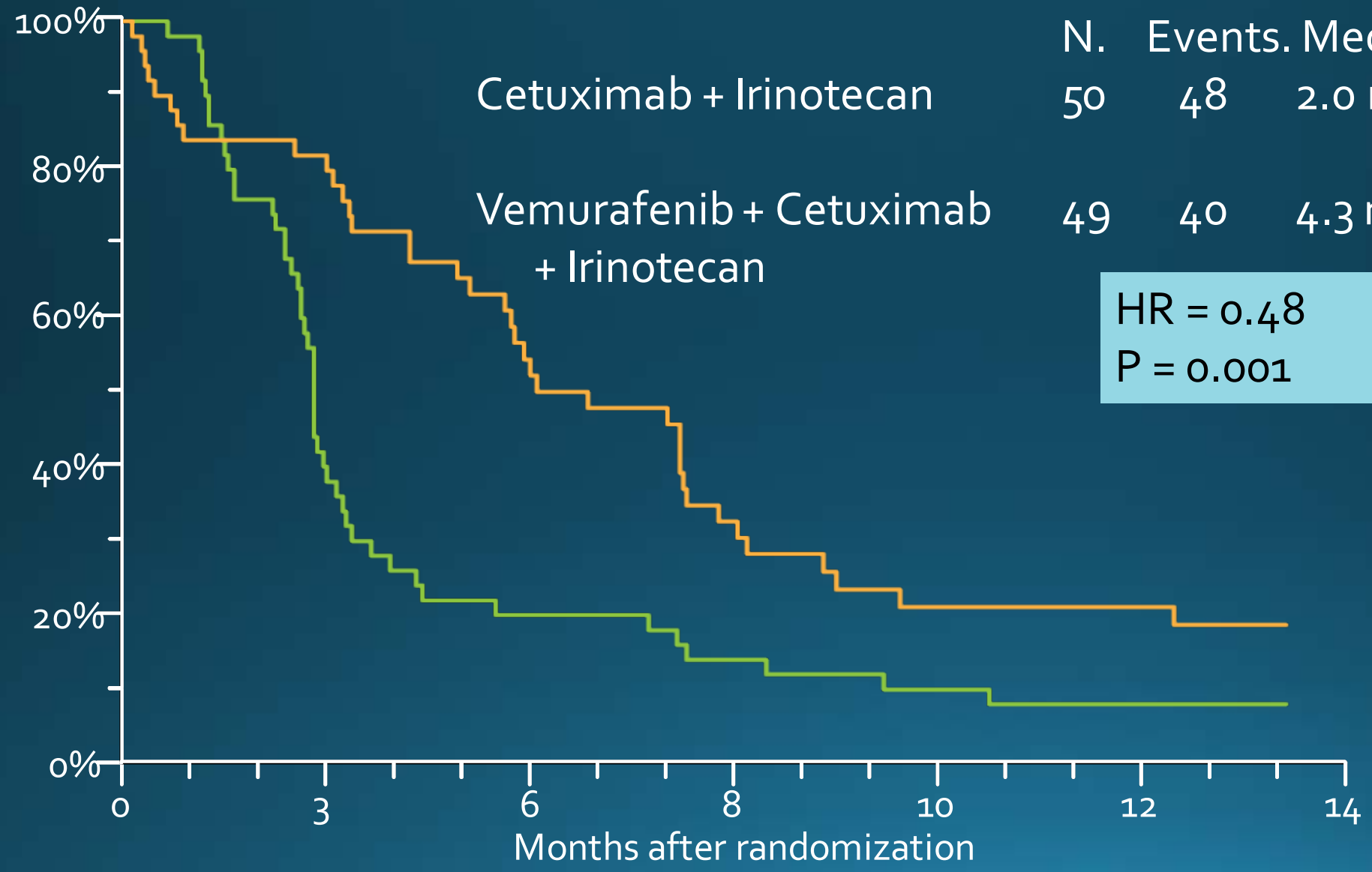
Targeting BRAF mutated tumors



Vemurafenib 960mg PO bid
Cetuximab 500mg/m2 IV q2weeks
Irinotecan 180mg/m2 IV q2weeks

Kopetz, ASCO 2017

Primary Endpoint: Progression-free survival



	N.	Events.	Median	95% Conf Int
Cetuximab + Irinotecan	50	48	2.0 mos	(1.8 – 2.1)
Vemurafenib + Cetuximab + Irinotecan	49	40	4.3 mos	(3.6 – 5.7)

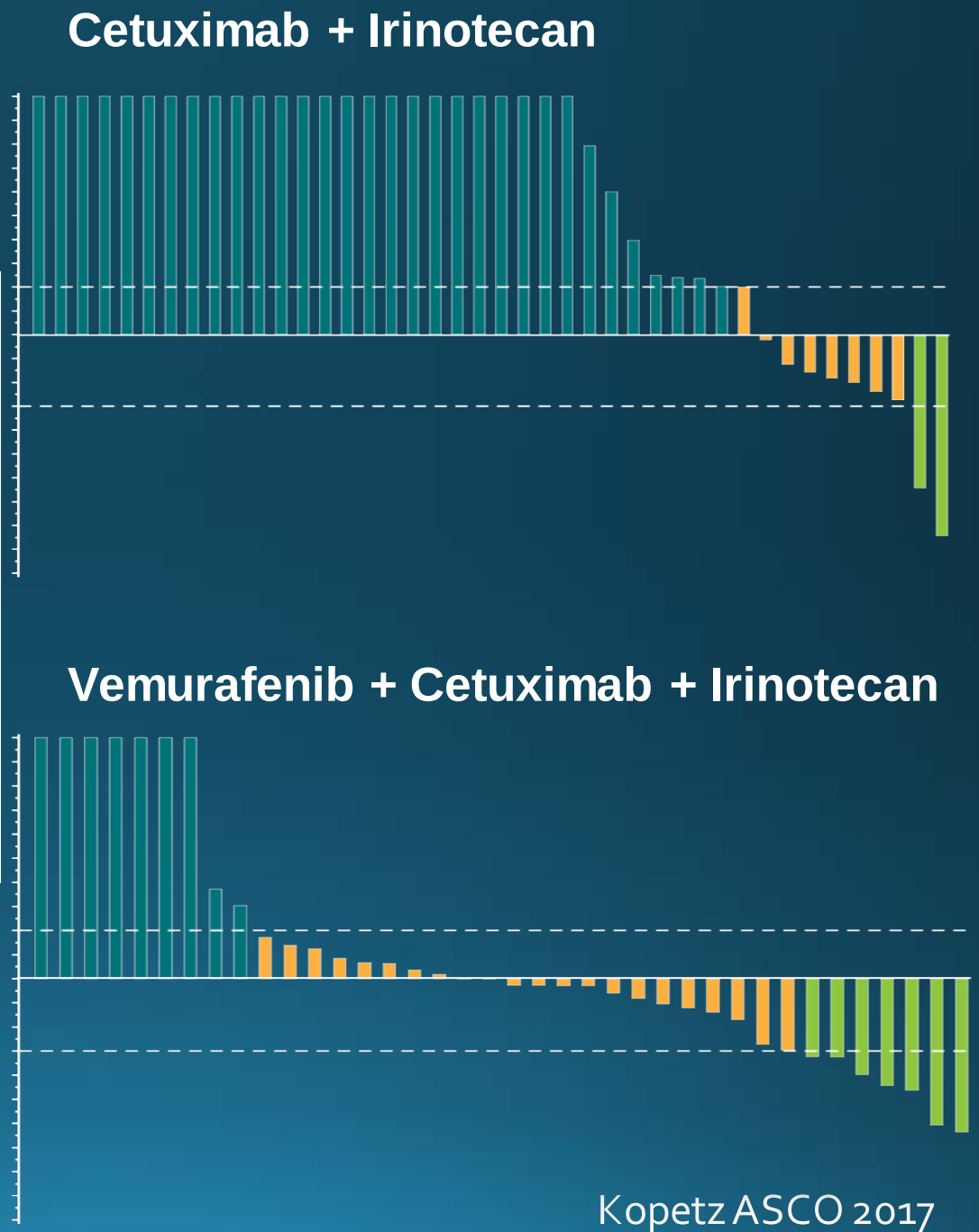
HR = 0.48 (95% CI 0.31 – 0.75)
P = 0.001

Kopetz ASCO 2017

Response Rate

	Cetuximab + Irinotecan (n=47)[a]	Vemurafenib + Cetuximab + Irinotecan (n=44)[a]	P-value[c]
Partial response[b]	4%	16%	P=0.001
Stable disease	17%	50%	
Progression[c]	66%	18%	
Disease Control Rate	22%	67%	

[a]93 patients had measurable disease; [b]Confirmed and unconfirmed; PR for patients previously treated with irinotecan was 0% and 18%, respectively; [c]Including symptomatic deterioration; [c] Chi-squared



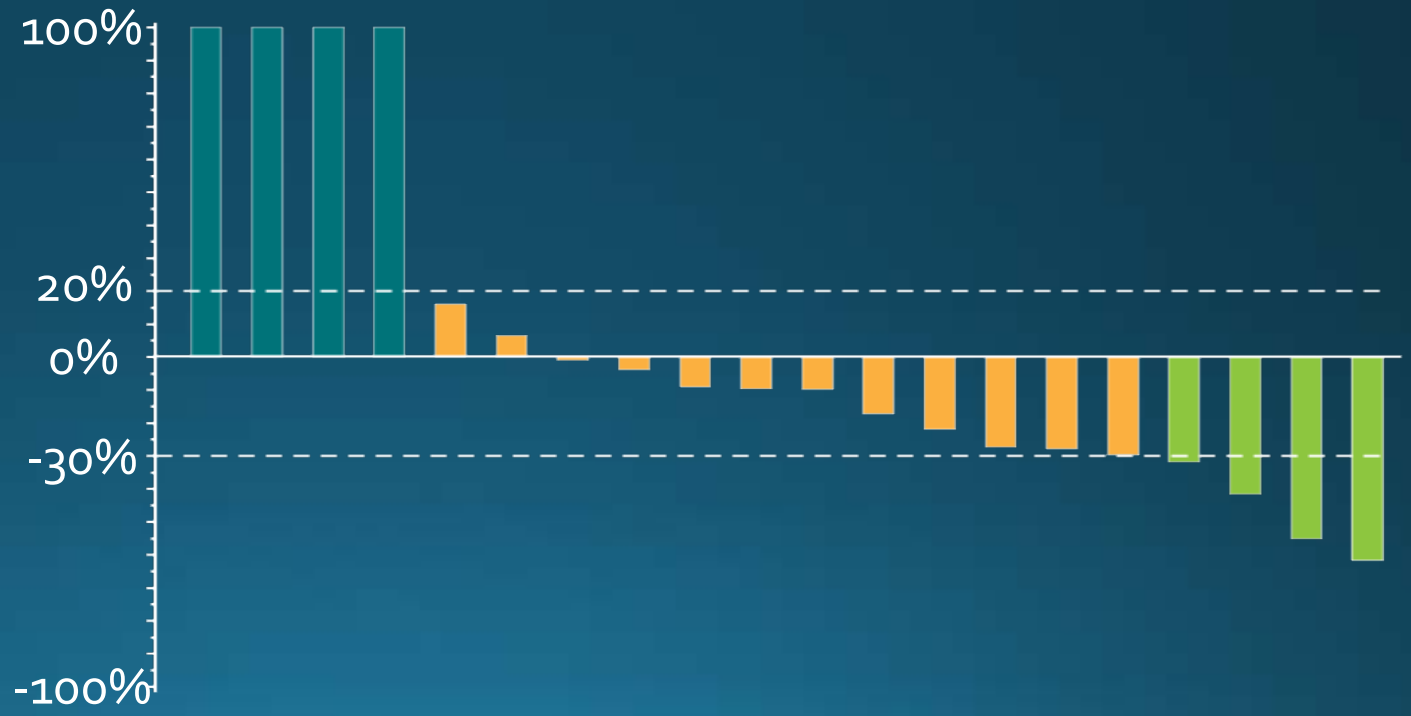
Kopetz ASCO 2017

Crossover to VIC upon progression

48% of patients on control arm crossed over to vemurafenib arm

	Crossover (n=24)[a]
Partial response	17%
Stable disease	55%
Disease control rate	**72%**

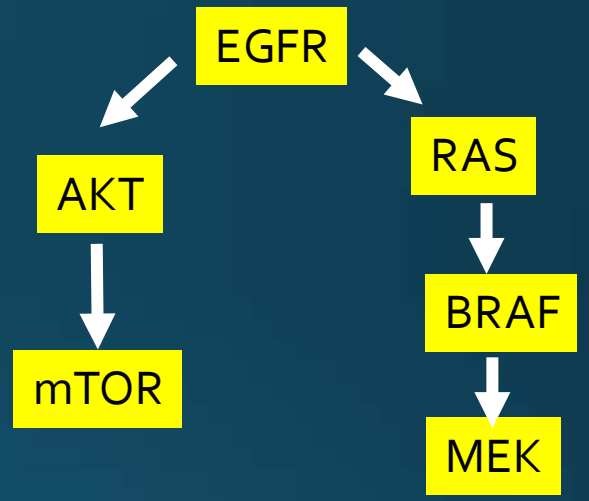
[a]2 patients did not progress prior to crossover; 4 did not have measurable disease; these patients are excluded from response rates



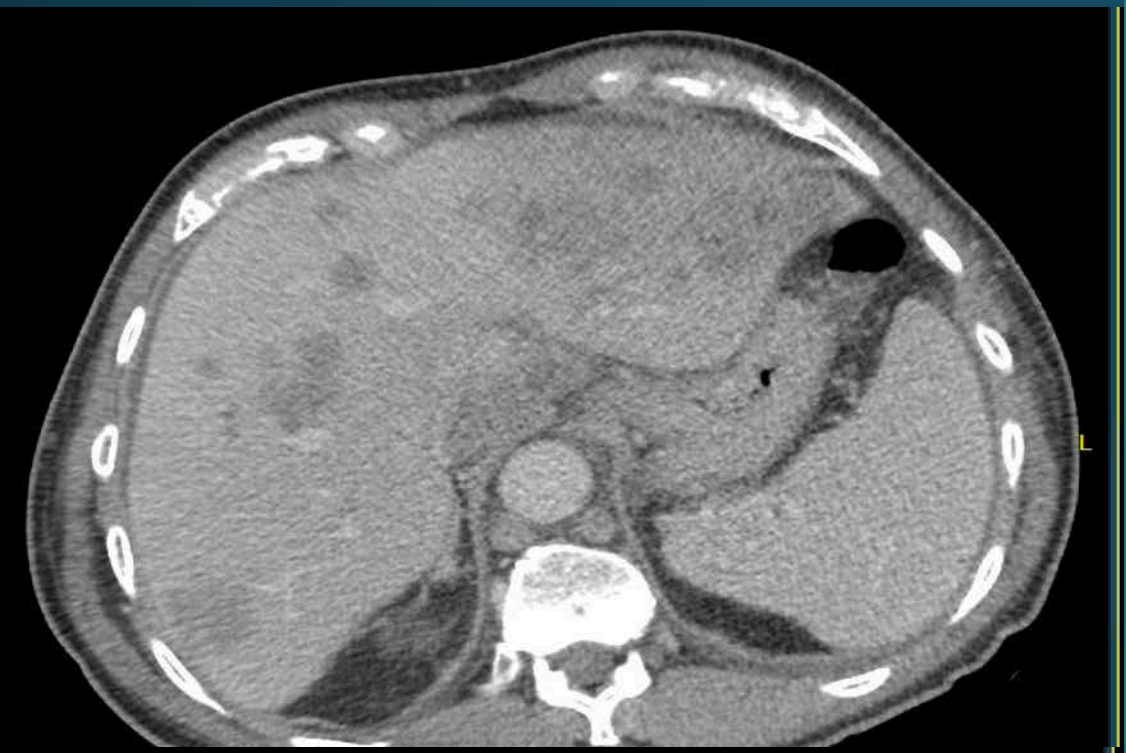
Kopetz ASCO 2017

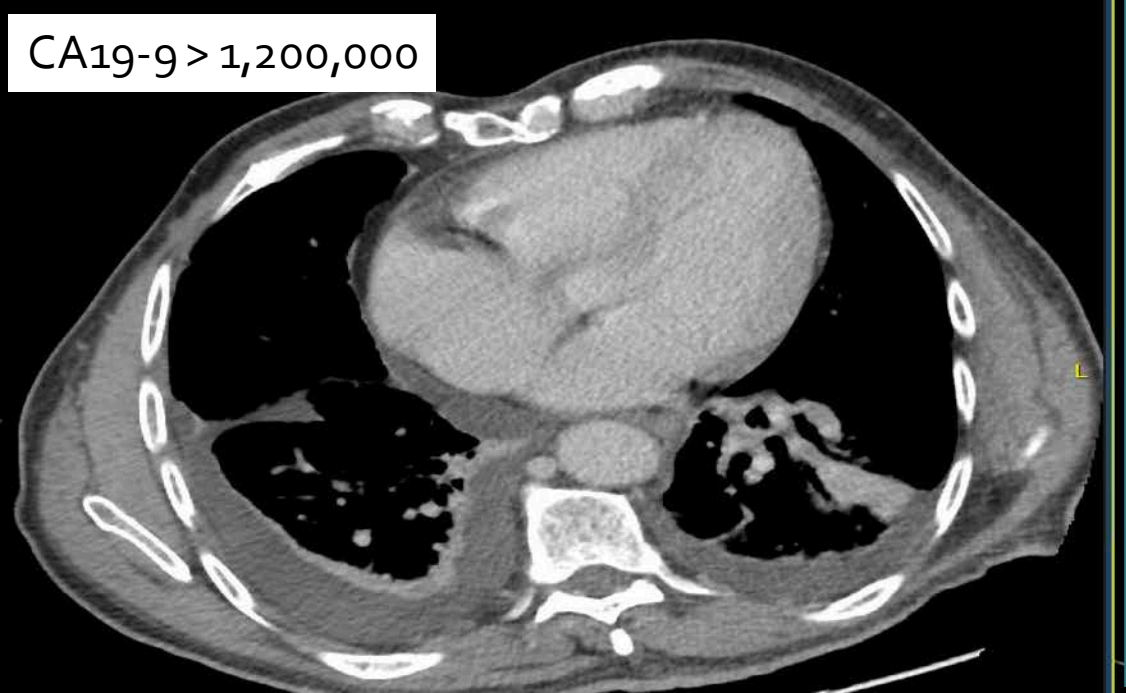
Beacon trial: Targeting BRAF mutated CRC

- Triple targeted therapy:
  - MEK inhibitor: Binimetinib (45 mg bid)
  - BRAF inhibitor: Encorafenib (300 mg qd)
  - EGFR antibody: Cetuximab
- 29 patients with BRAF V600E mutation
  - Only one with MSI
- Confirmed overall **response rate of 41%**
- 76% stable disease for median of 5.6 months
- Well tolerated with 10% nausea; 10% vomiting
- Phase III trial underway comparing to cetuximab + irinotecan



Huijberts et al. ESMO Sept 2017



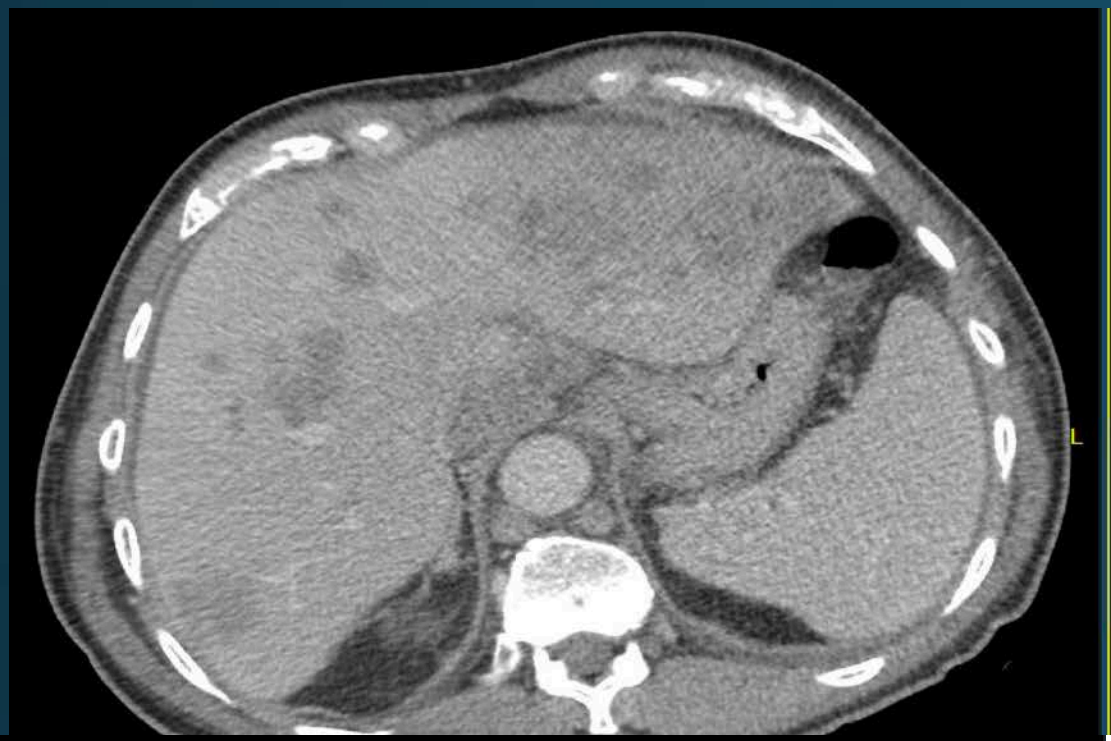


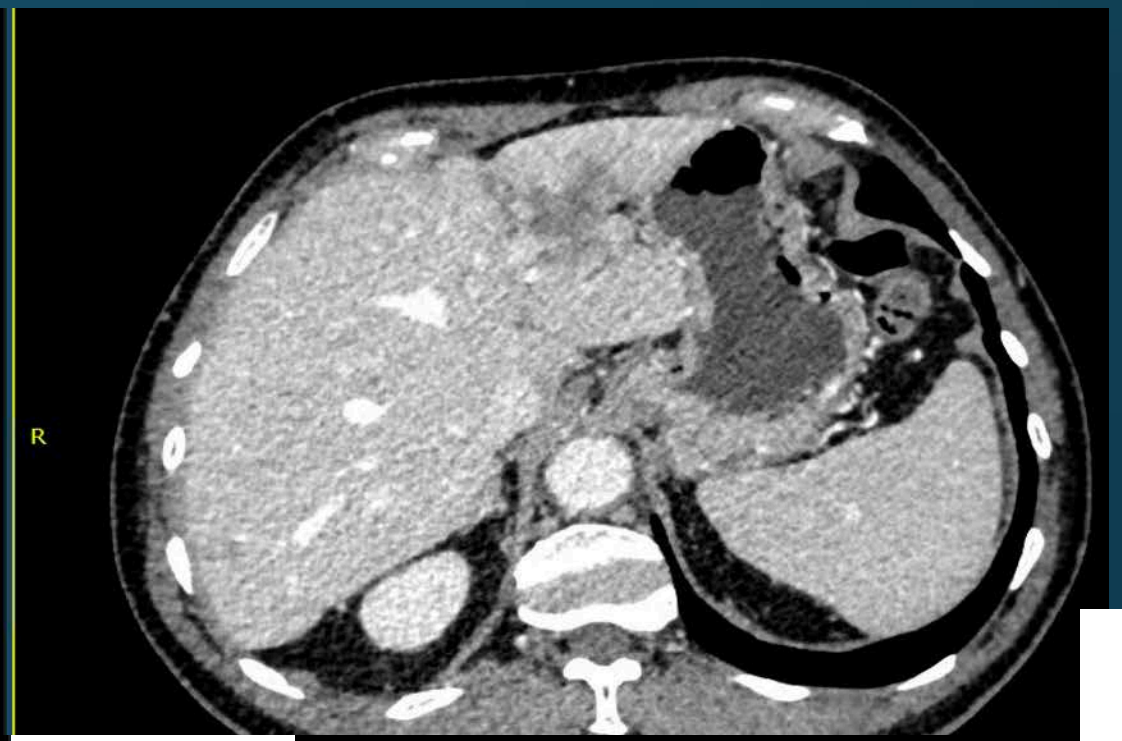
CA19-9 > 1,200,000

#2 73 yo man with BRAF mutated metastatic colon cancer

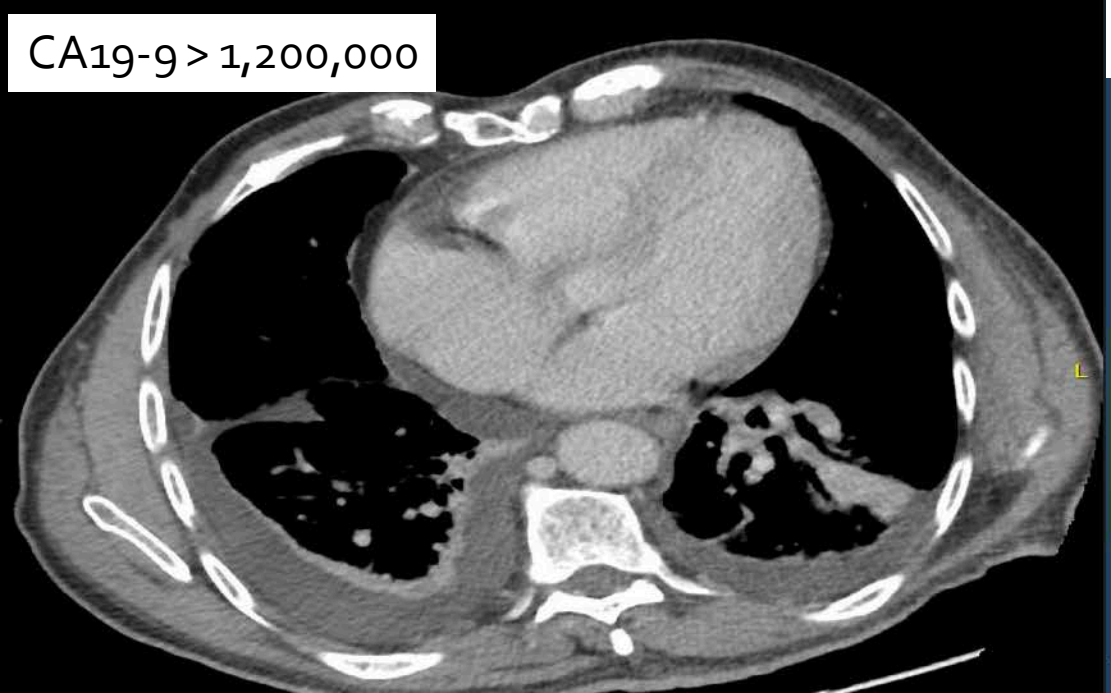
Too ill for irinotecan

Vemurafenib (BRAF i)
Cobimetinib (MEK i)
Cetuximab (anti-EGFR)

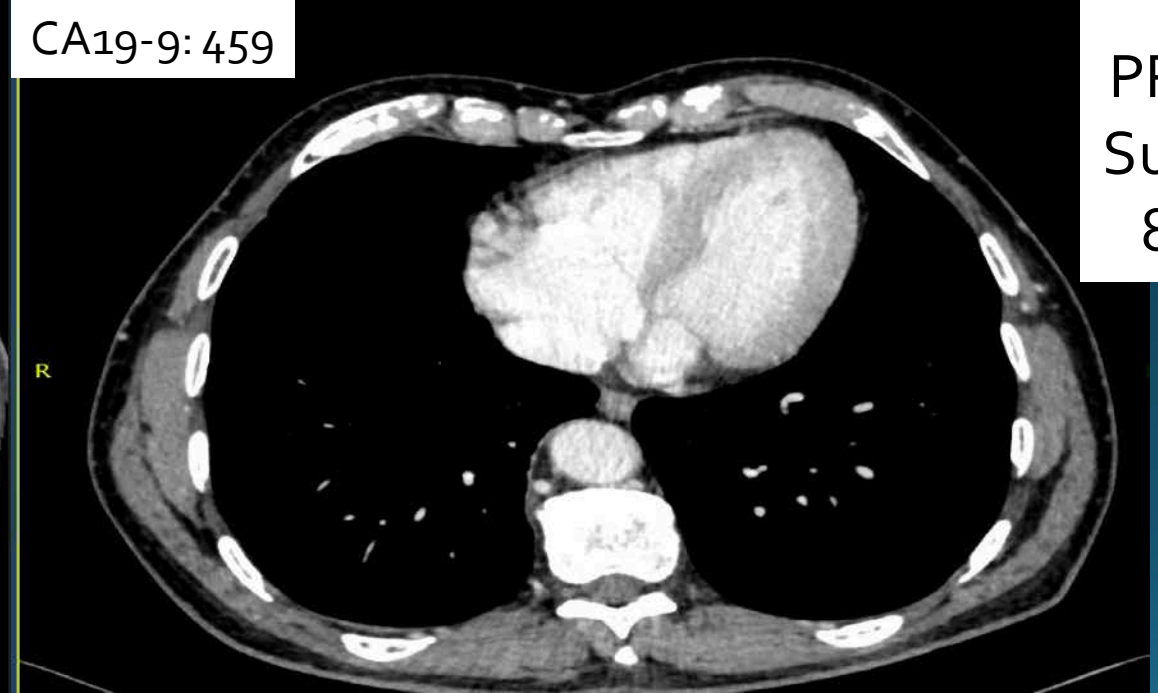




CA19-9 > 1,200,000



CA19-9: 459



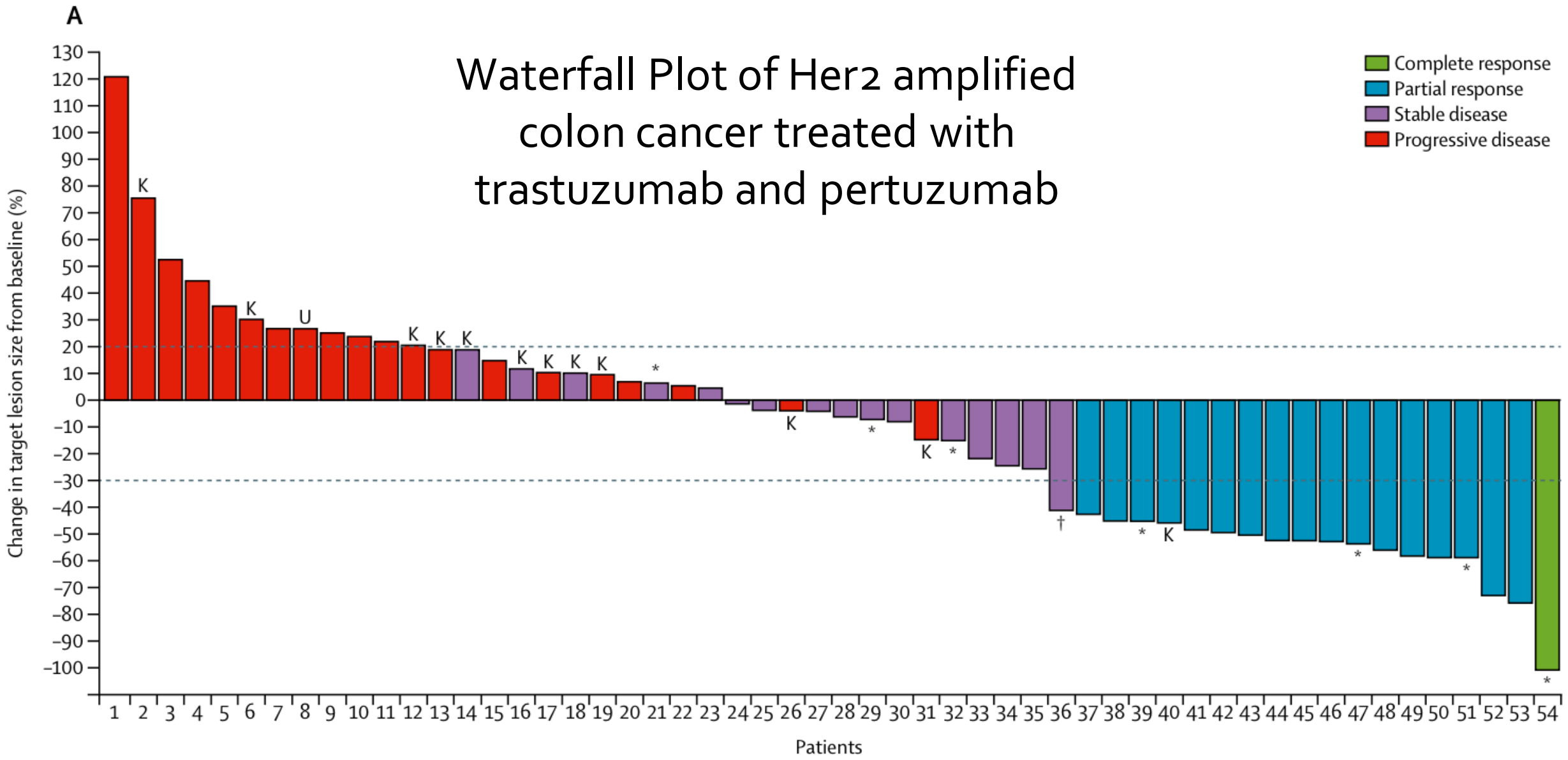
PS 0
PR at 2 mos
Sustained …
8 months

Targeting Her2-neu

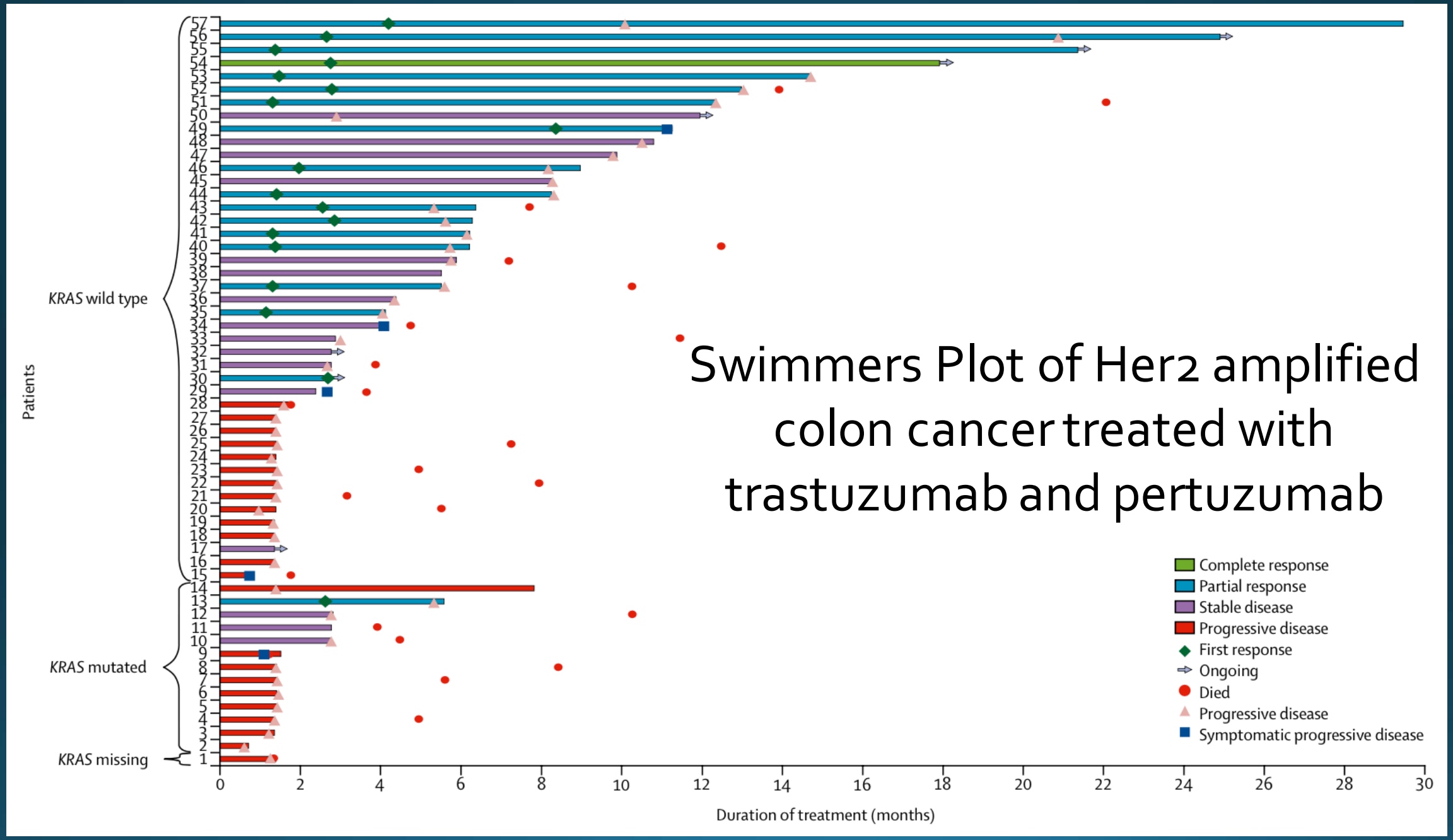
- 2-6% of colon cancers have overexpression or amplification of Her2-neu

Meric-Bernstam et al. Lancet Oncol 2019

Waterfall Plot of Her2 amplified colon cancer treated with trastuzumab and pertuzumab

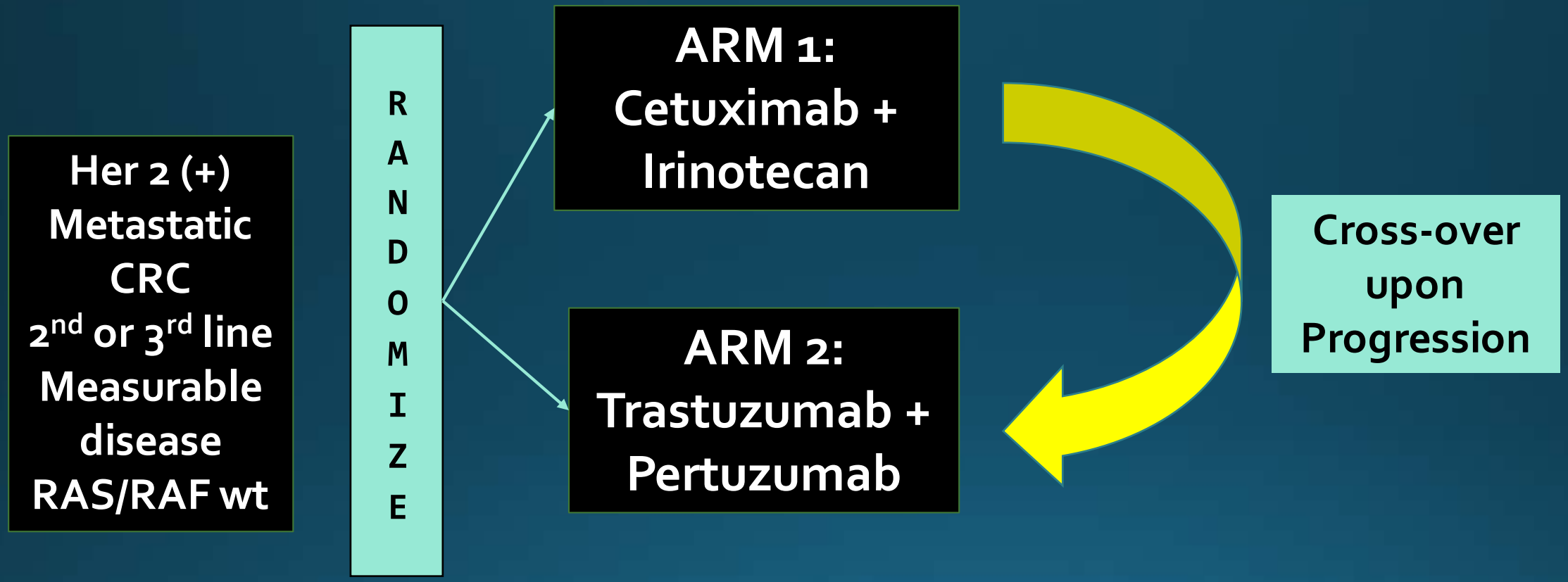


Meric-Bernstam et al. Lancet Oncol 2019



Meric-Bernstam et al. Lancet Oncol 2019

Targeting Her 2 neu (+) tumors



s

Raghav, ASCO 2018

Conclusions:

- Colorectal cancer is a major public health problem
- Incidence and mortality is decreasing
  - Among the most preventable of all cancers!
- "less is more" in early stage disease
- Chemo and targeted agents can prolong life in advanced CRC

- Activity of PD1 drugs in advanced MSI Colon cancers proves that the immune system can work against CRC

- Challenge is to find ways for immune system to work in the other 97% of advanced colorectal cancers

Current Research Priorities: Advanced CRC

- Immunotherapy for early stage MSI colon cancer
  - Trials underway in stage III MSI colon cancer
- Immunotherapy for MSS colon cancer
  - Other checkpoint inhibitors besides PD-1 agents
    - CD47 (in lymphoma and colon cancers), CD40 (in pancreas trials)
  - Vaccination strategies
    - Personalized vaccines based on tumor mutations (neo-antigens)
  - Bispecific antibodies to get T cells to tumor cells
    - Targeting CD3 on T cells and CEA on tumor cells
  - CAR-T cells