Advances in Colorectal Cancer Diagnostic Testing & Treatment

Concurrent Session
November 21, 2024
11:00 AM - 12:15 PM

American Cancer Society

NATIONAL COLORECTAL CANCER ROUNDTABLE

Speakers

Moderator: **Stacie Miller,** MSN, MPH, RN, UT Southwestern Moncrief Cancer Institute

- **Yla Flores,** Colorectal Cancer Survivor
- **Swati Patel**, MS, MD, University of Colorado Anschutz Medical Center @swatigp
- **Andrea Cercek**, MD, Memorial Sloan Kettering Cancer Center

Learn more about our 2024 ACS NCCRT Annual Meeting **speakers** by reading their **bios**.

Yla Flores Video – See Recording of Session

The Evolving Role of Molecular and Genetic Testing in CRC: Screening and Beyond

Swati G. Patel, MD MS
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Director, Gastrointestinal Cancer Risk and Prevention Center
University of Colorado Anschutz Medical Center
Rocky Mountain Regional Veterans Affairs Medical Center
Swati.Patel@cuanschutz.edu
@SwatiPatelMD

Disclosures

Olympus America (research support)

(NCCN Colorectal Cancer Screening Panel)

(US-MTSF on Colorectal Cancer)

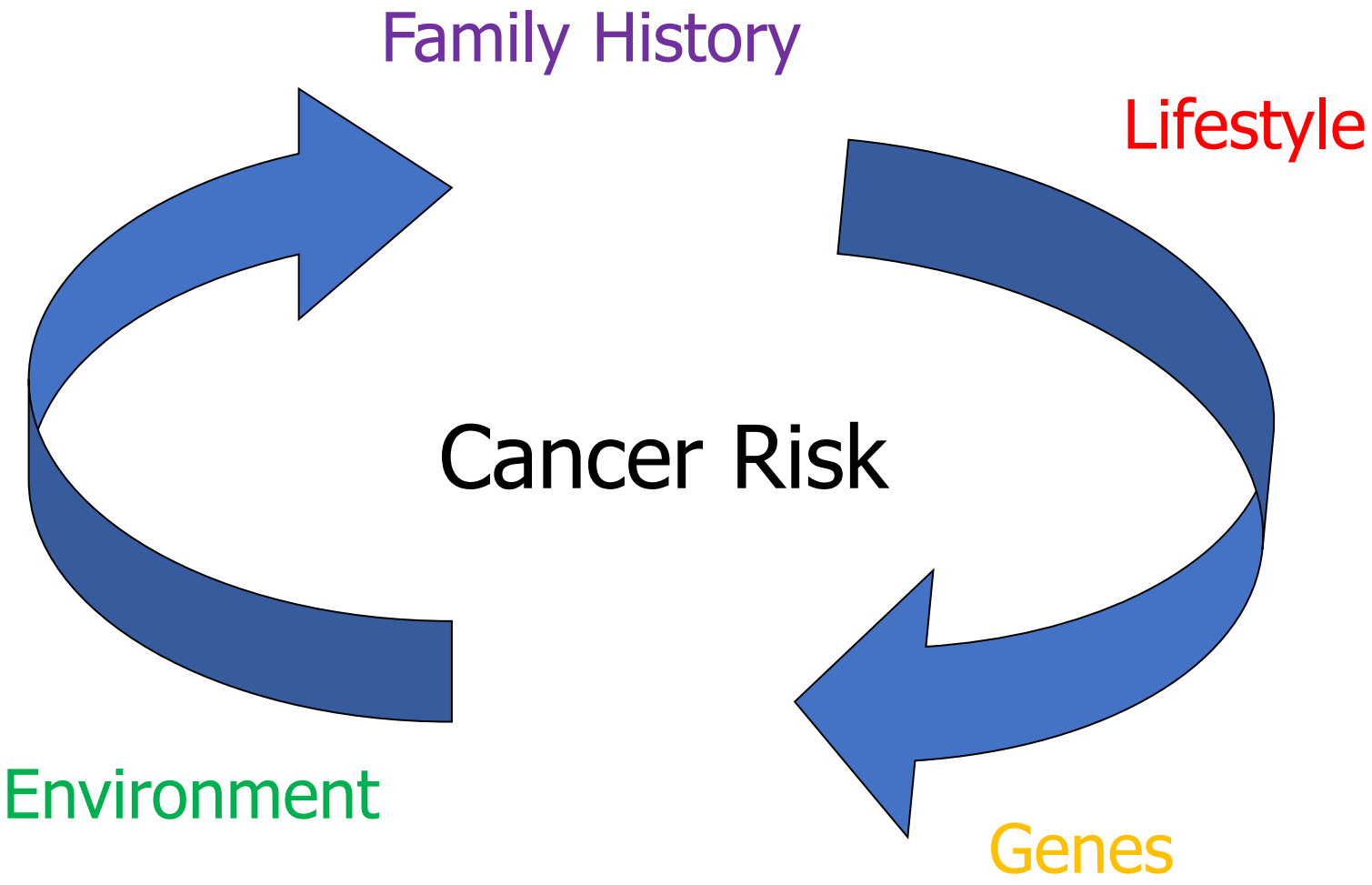
Objectives

I. **Review what is meant by "Cancer Genetics"**

II. Molecular genetics in CRC screening

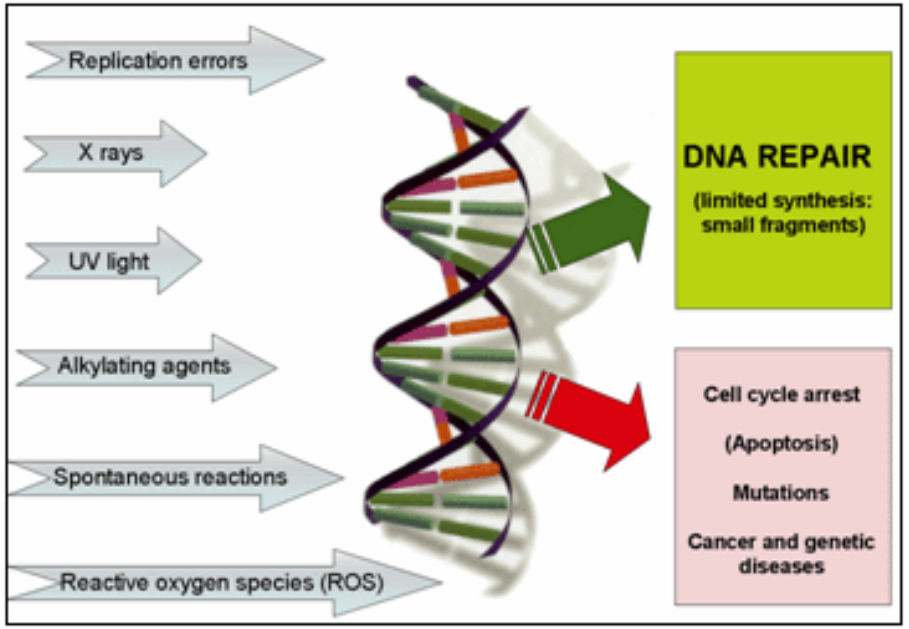
III. Evolving approach in germline genetics

@SwatiPateIMD



Genetics of Cancer

- Cancer is a genetic disease
- Underlying genetic defect causes genomic instability
- Culprit genes: proliferation, apoptosis, DNA repair
  - Most cancers have mutations in many of these genes



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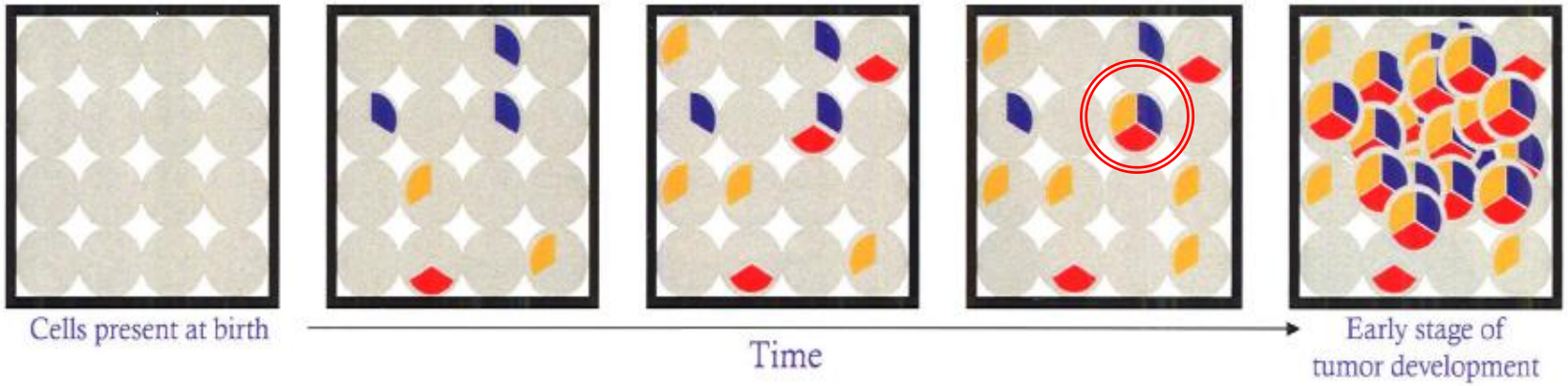
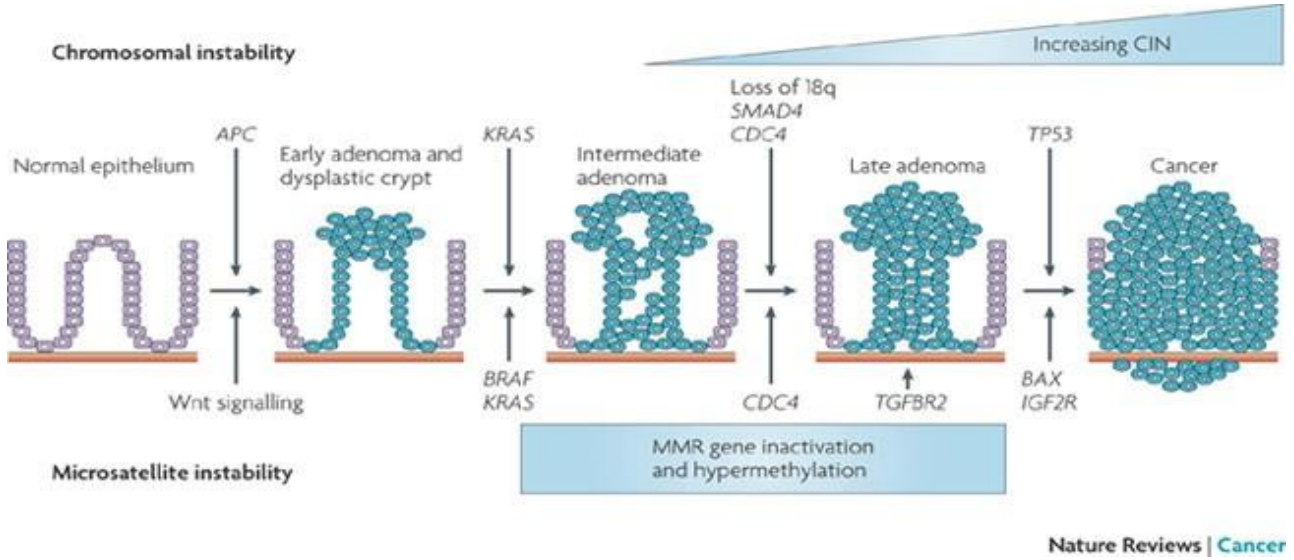




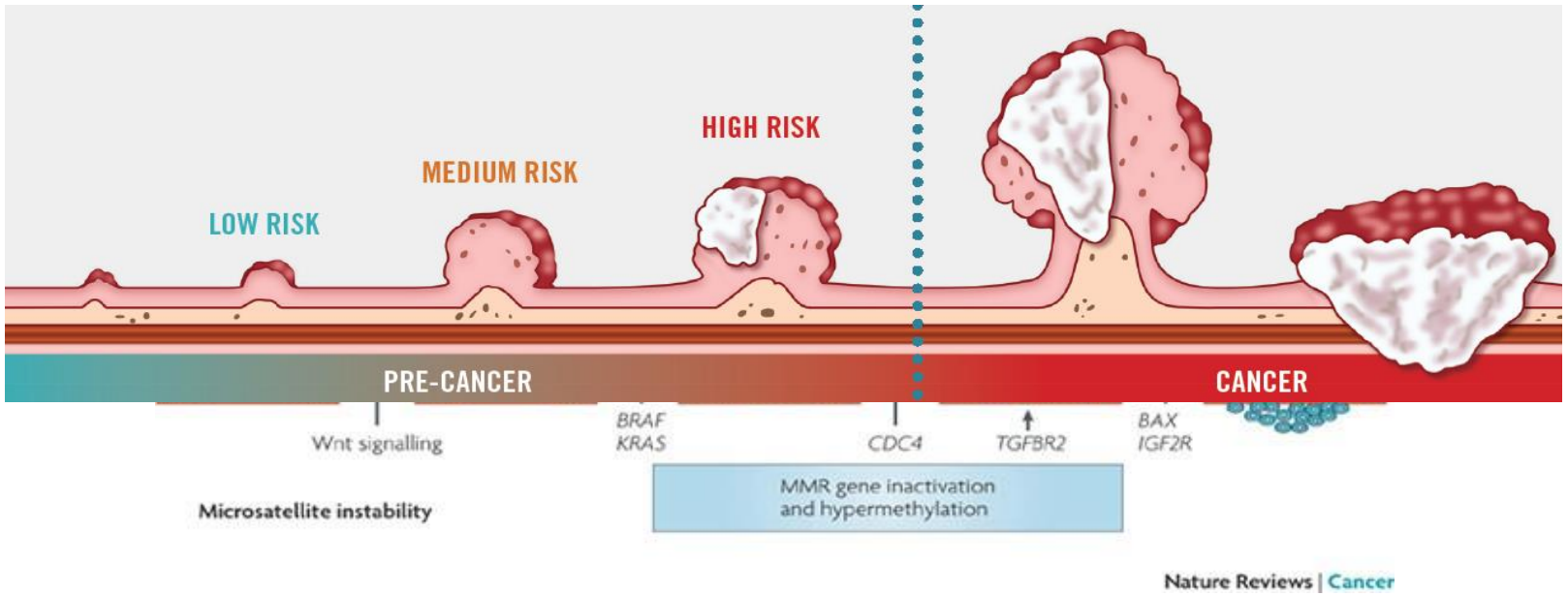
Walther et al. Nature Reviews Cancer. 2009(9):489-499.

@SwatiPateIMD

Blood tests

Stool-Based Tests

Structural Tests



Walther et al. Nature Reviews Cancer. 2009(9):489-499.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Next-Generation Multitarget Stool DNA Test for Colorectal Cancer Screening

Thomas F. Imperiale, M.D., Kyle Porter, M.A.S., Julia Zella, Ph.D., Zubin D. Gagrat, B.S., Marilyn C. Olson, Ph.D., Sandi Statz, M.S., Jorge Garces, Ph.D., Philip T. Lavin, Ph.D., Humberto Aguilar, M.D., Don Brinberg, M.D., Charles Berkelhammer, M.D., John B. Kisiel, M.D., and Paul J. Limburg, M.D., for the BLUE-C Study Investigators*

JAMA | Original Investigation

Multitarget Stool RNA Test for Colorectal Cancer Screening

Erica K. Barnell, MD, PhD; Elizabeth M. Wurtzler, PhD; Julie La Rocca, MS; Thomas Fitzgerald, MS; Jessica Petrone, MD; Yansheng Hao, MD, PhD; Yiming Kang, PhD; Faith L. Holmes, MD; David A. Lieberman, MD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2024 VOL. 390 NO. 11

A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening

Daniel C. Chung, M.D., Darrell M. Gray II, M.D., M.P.H., Harminder Singh, M.D., Rachel B. Issaka, M.D., M.A.S., Victoria M. Raymond, M.S., Craig Eagle, M.D., Sylvia Hu, Ph.D., Darya I. Chudova, Ph.D., AmirAli Talasaz, Ph.D., Joel K. Greenson, M.D., Frank A. Sinicrope, M.D., Samir Gupta, M.D., M.S.C.S., and William M. Grady, M.D.

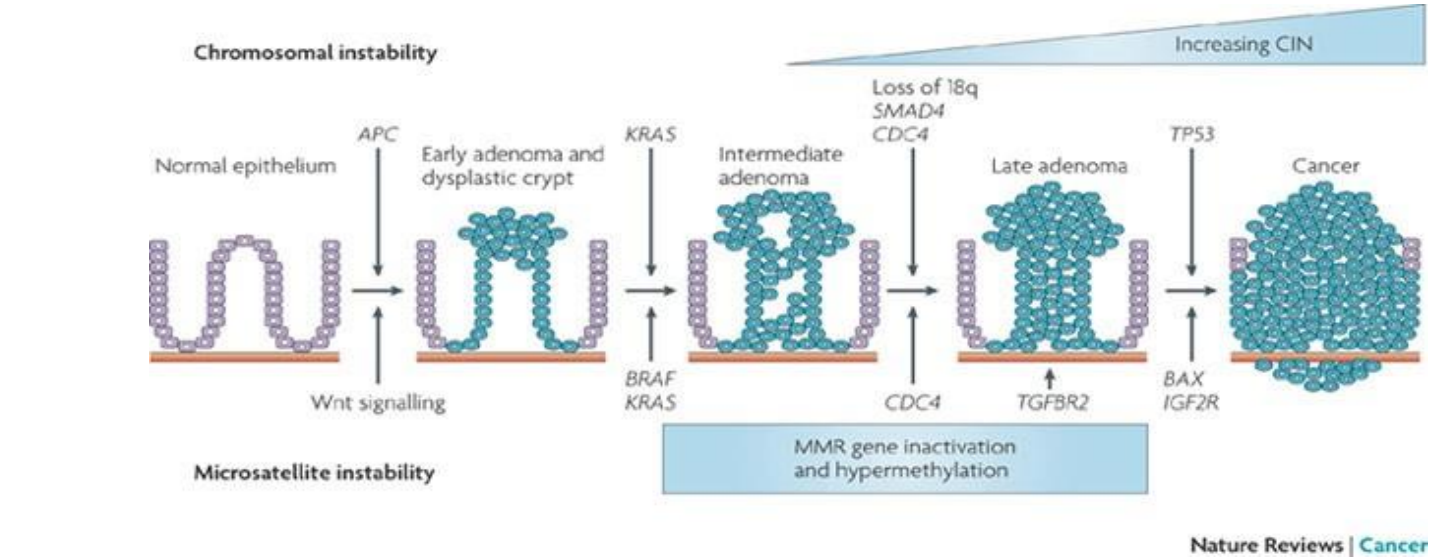
	CRC Sensitivity	AA Sensitivity	aCRN Specificity
Septin-9	68%	22%	80%
Guardant SHIELD	83%	13%	90%
FIT	81%	28%	94%
MT-sDNA I	92%	42%	89%
MT-sDNA II	94%	43%	91%
Stool RNA	94%	46%	88%
Colonoscopy	>99%	95%	89%
CT Colonography	90%	89%	94%

Patel & Dominitz. Ann Int Med 2024; 177(4):49-64.
Imperiale et al. N Engl J Med 2024; 390:984-93.
Chung et al. N Engl J Med 2024; 390:973-83.
Barnell et al. JAMA 2023;330(18):1760-68.

Blood tests

Stool-Based Tests

Structural Tests



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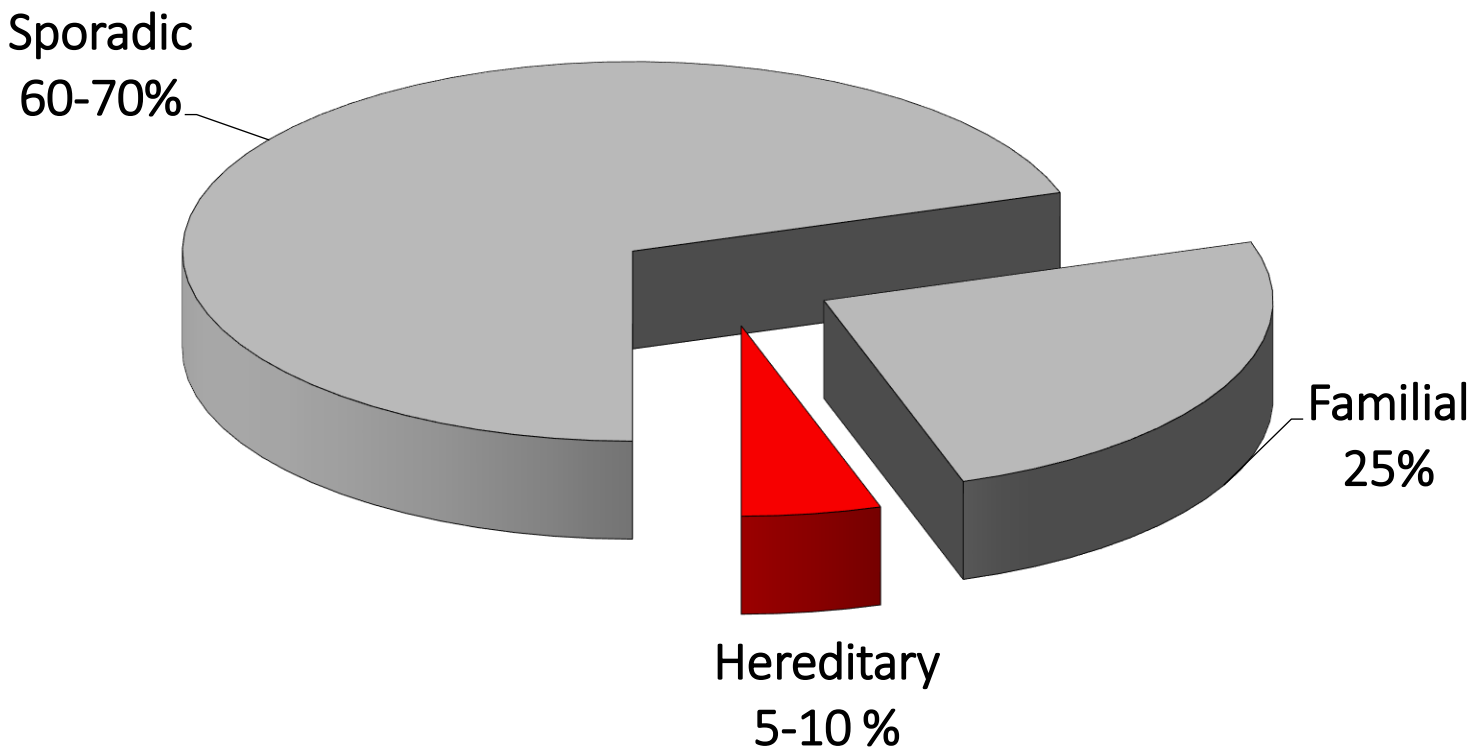

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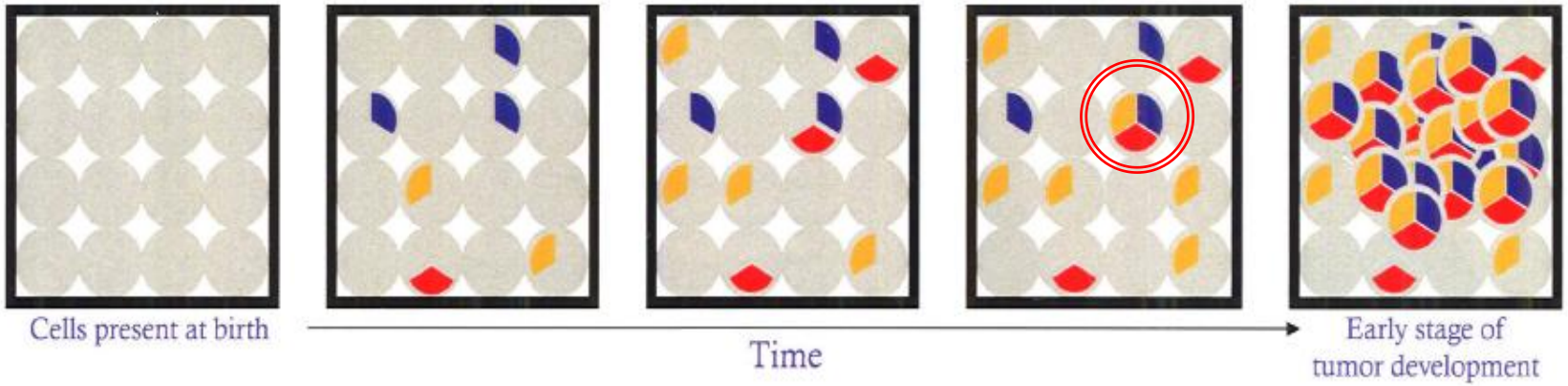
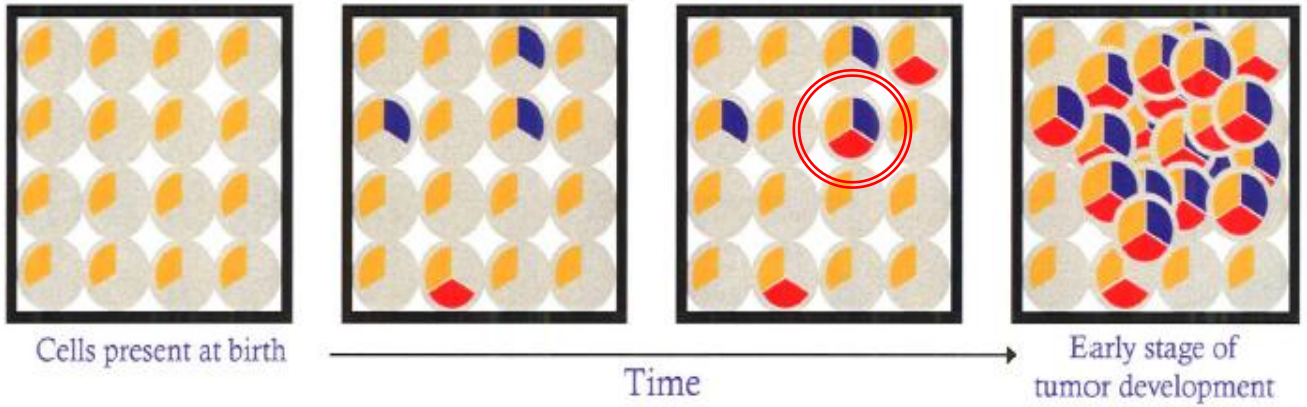




@SwatiPateIMD

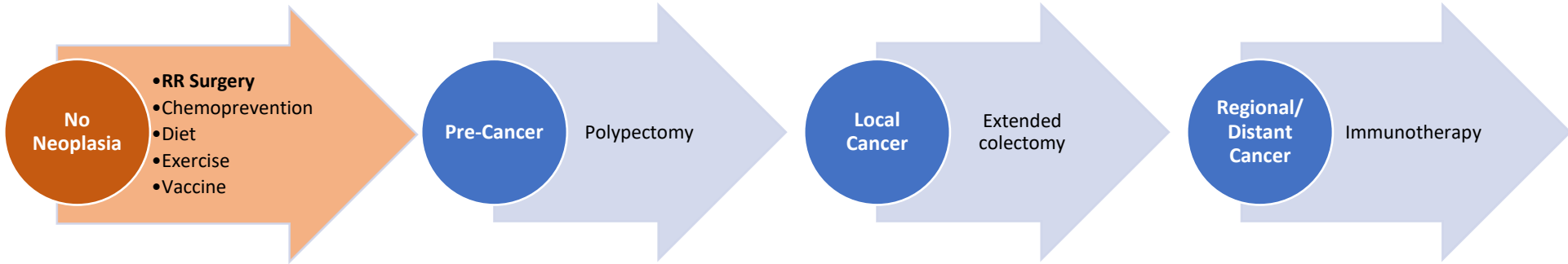
Estimated New Cases*

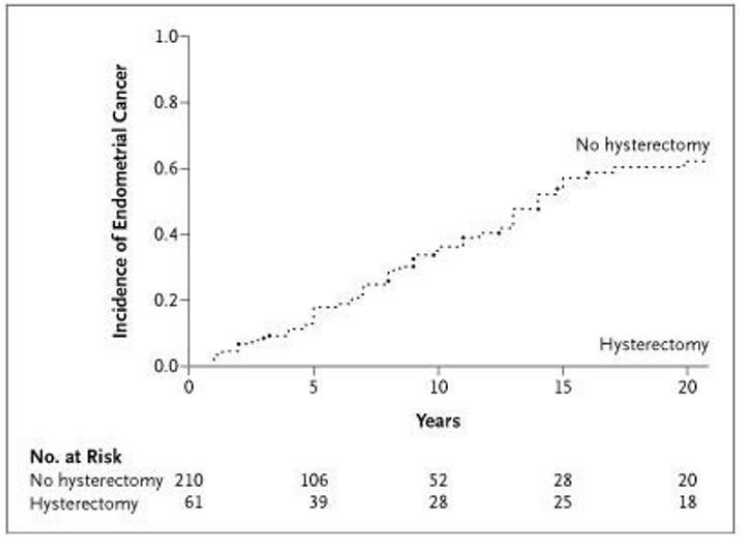
Males				Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney&renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All sites	**789,620**	**100%**		**All sites**	**739,940**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine corpus	7,950	3%
Urinary bladder	10,410	3%		Multiple myeloma	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All sites	**299,200**	**100%**		**All sites**	**270,290**	**100%**

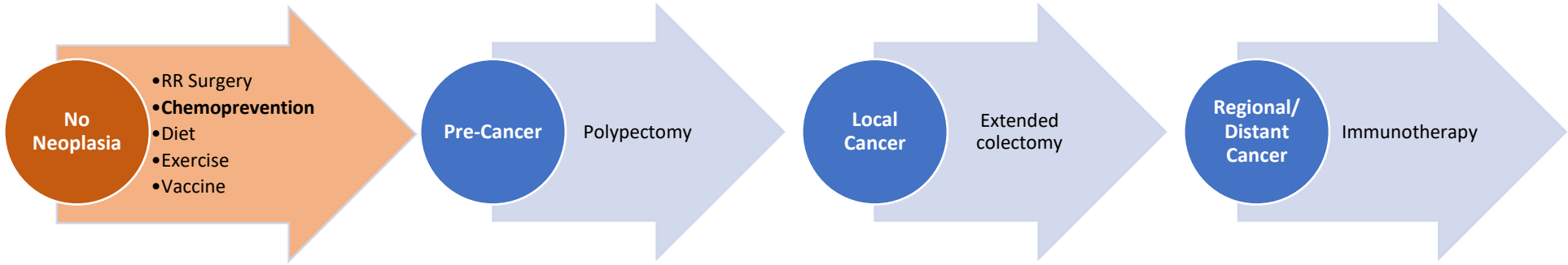
Opportunities for Intervention

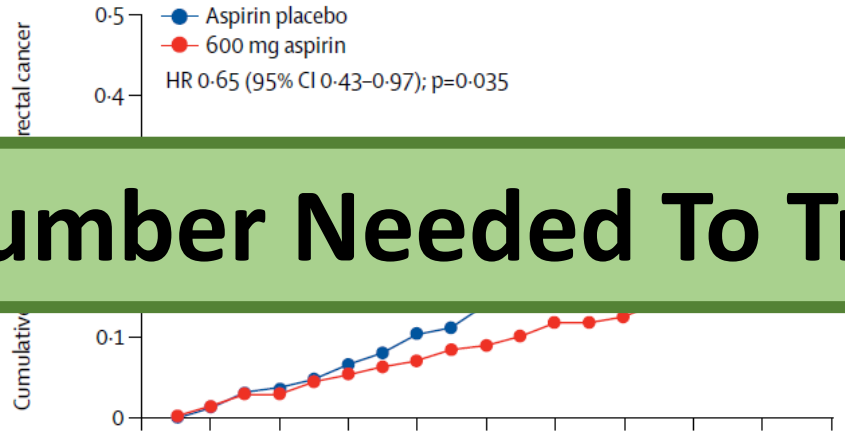




Schmeler et al. N Engl J Med 2006; 354:261-269.

Opportunities for Intervention

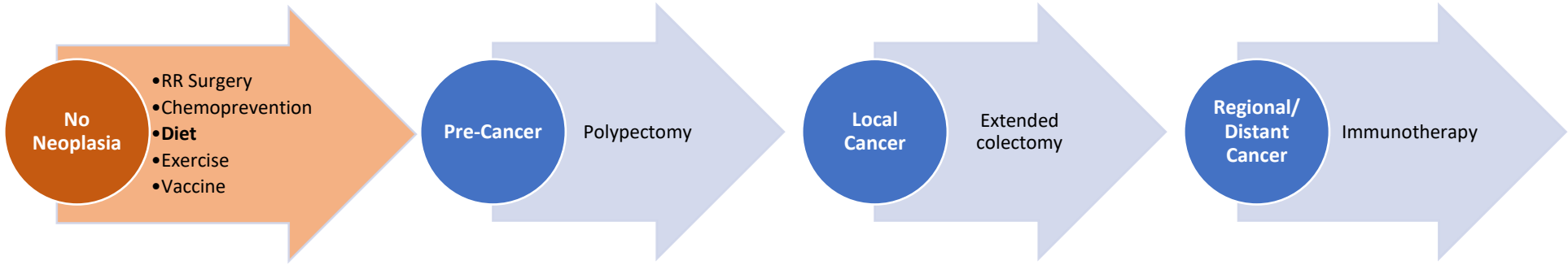


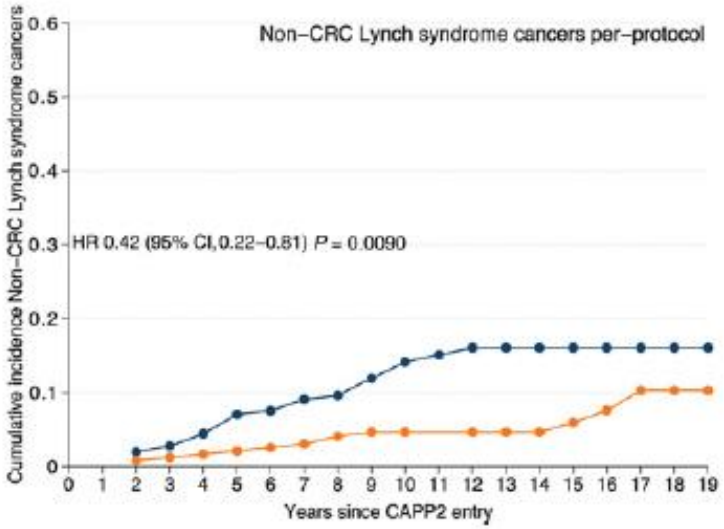


Number Needed To Treat to Prevent 1 CRC = 24

Burn et al. Lancet 2020, 395(10240): 1855-63.

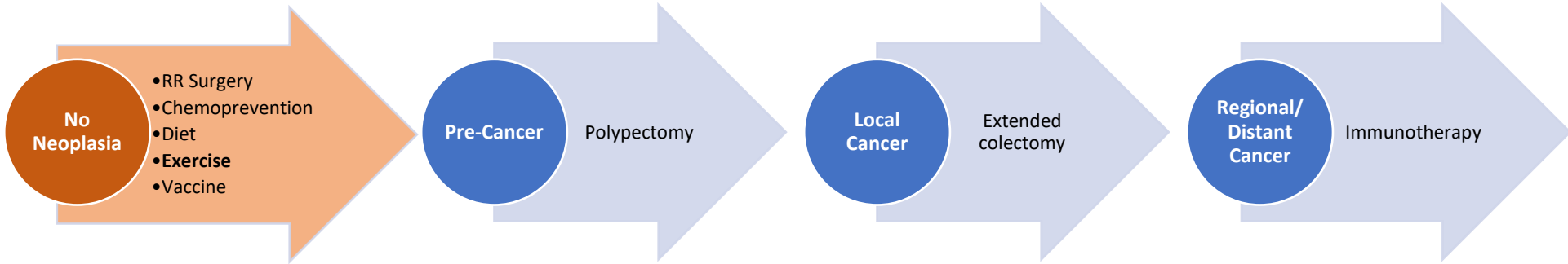
Opportunities for Intervention

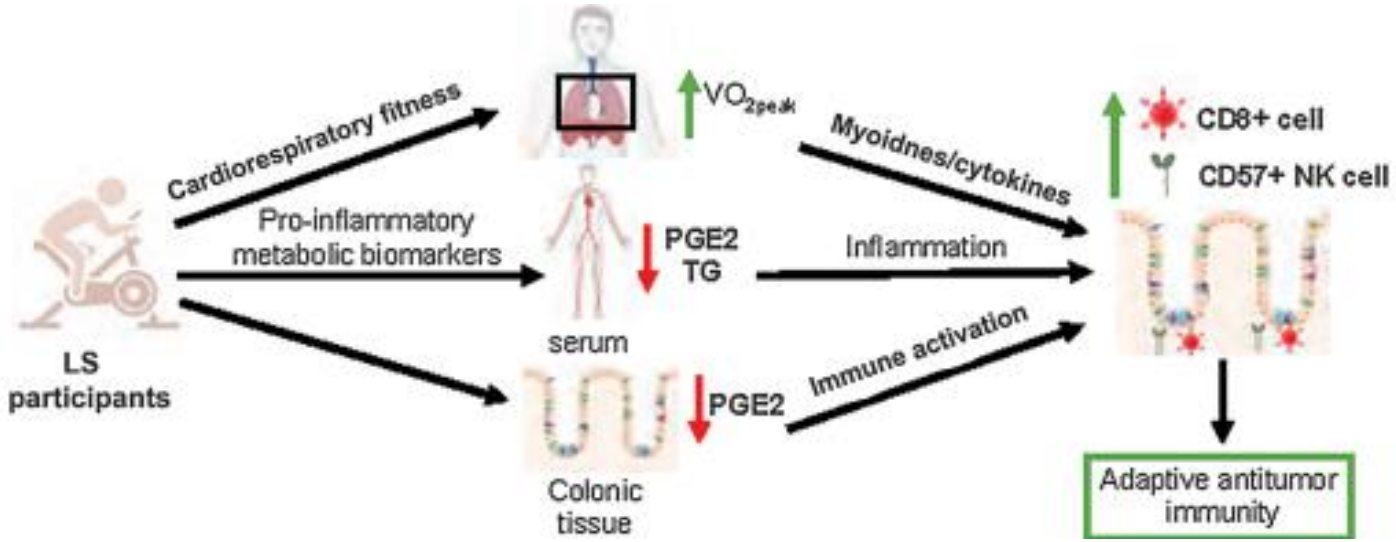




Mathers et al. Cancer Prev Res 2022;15:623-34.

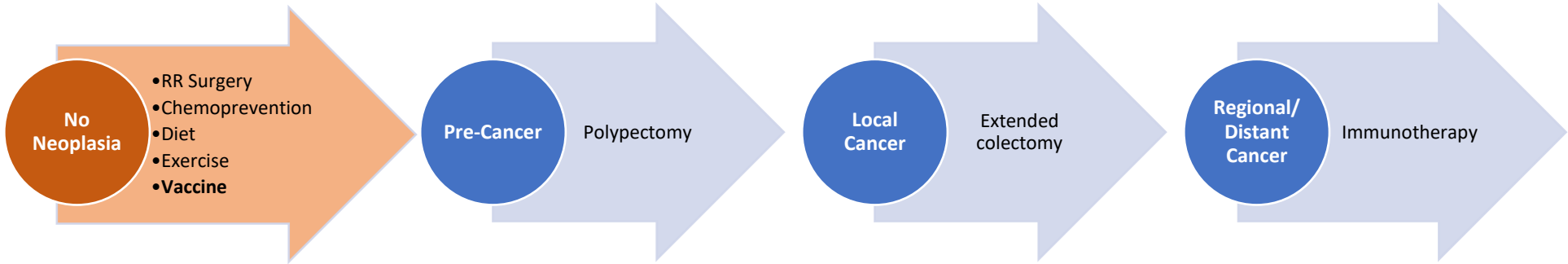
Opportunities for Intervention





Deng et al. Clin Cancer Res 2023;29:4361-72.

Opportunities for Intervention



Standard of Care Colonoscopy

Vaccine Administration

Research Blood Draw

ELIGIBILITY

- Lynch Syndrome Diagnosis
- Able to partake in research blood draws and colonoscopies
- 18 years of age
- Able to commit to 2 years of research-related appointments

PRIMARY OUTCOME

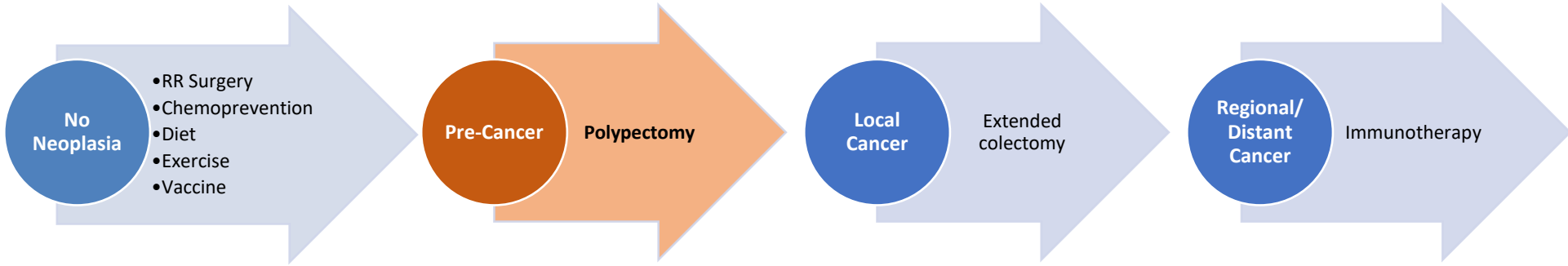
- Cumulative colorectal neoplasia

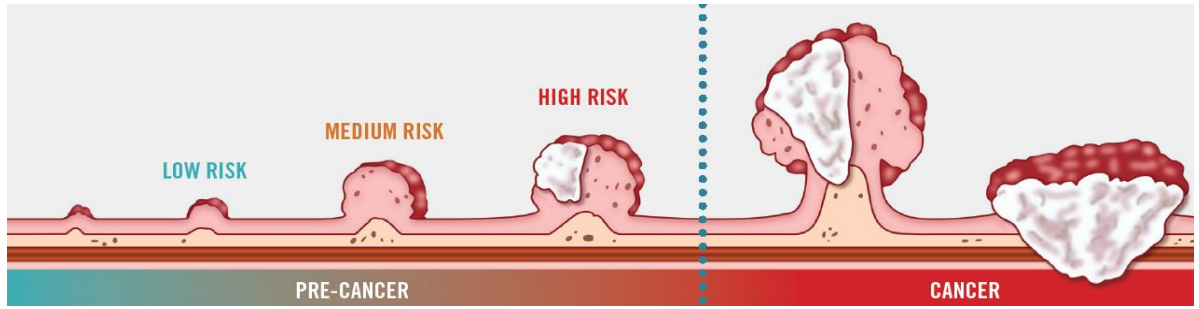
	cMS type	Mutation frequency (CRC)§	Mutation frequency (EC)§
TAF1B(−1)	A11	74.6%	50.0%
HT001(−1)	A11	86.2%	92.9%
AIM2(−1)	A10	81.6%	71.4%

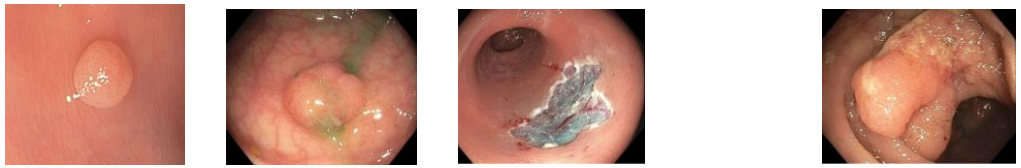
TAFB(−1): H-NTQIKALNRGLKKKTILKKAGIGMCVKVSSIFFINKQKP-OH
AIM2(−1): H-HSTIKVIKAKKKHREVKRTNSSQLV-OH
HT001(−1): H-EIFLPKGRSNSKKKGRRNRIPAVLRTEGEPLHTPSVGMRETTGLGC-OH

Kloor et al. Clin Cancer Res 2020;26(17):4503-10.
Vilar-Sanchez et al. NCT05078866.
Bansal & Vilar-Sanchez et al. NCT05419011.

Opportunities for Intervention





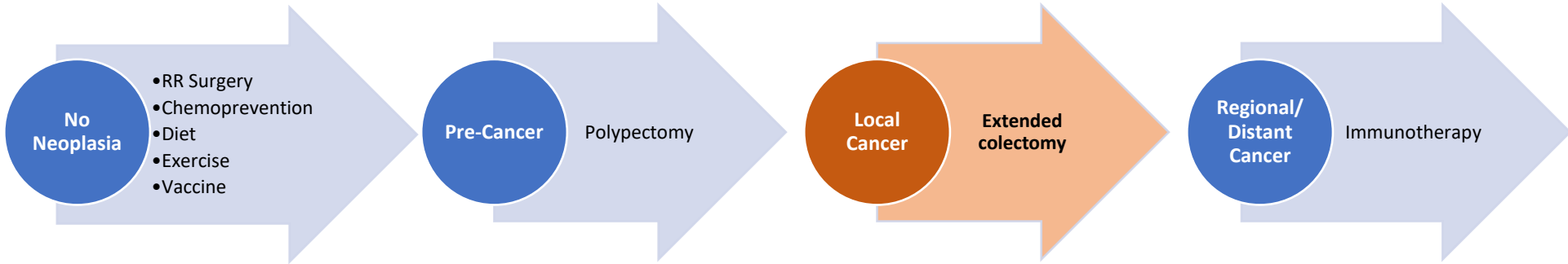


62% reduction in CRC Incidence

72% reduction in CRC Mortality

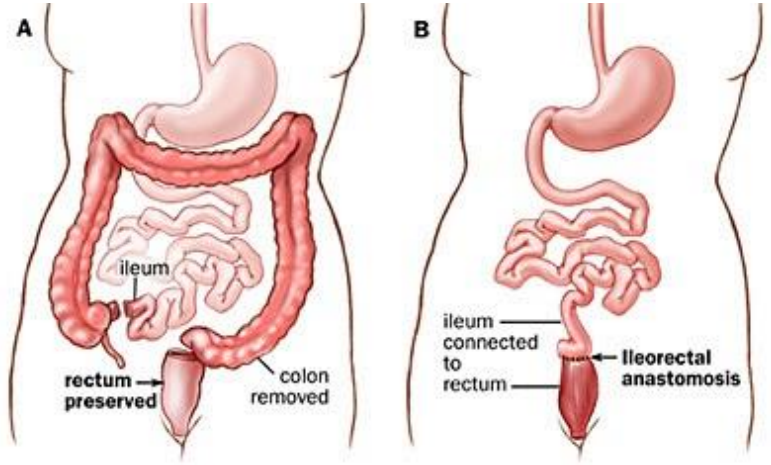
Jarvinen et al. Gastroenterol. 2000. 118(5):829-34.
Dove-Edwin et al. BMJ. 2005. 331(7524):1047.

Opportunities for Intervention



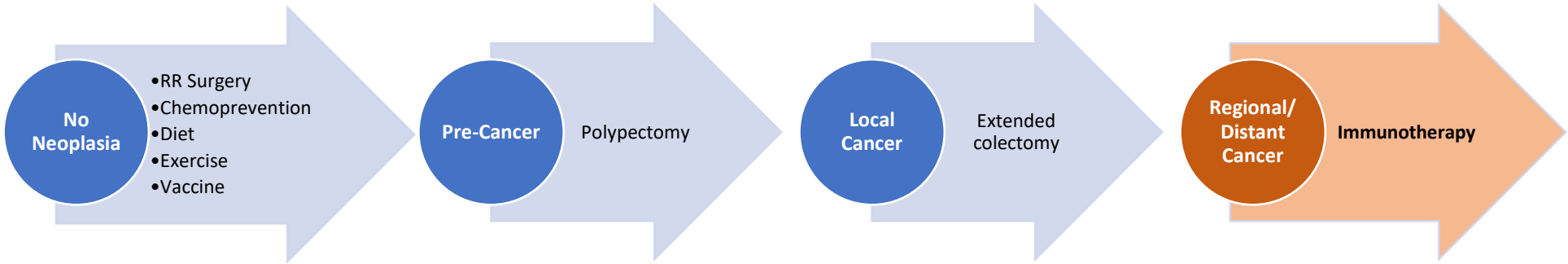
- Cumulative risk of metachronous CRC at 10, 20, 30 years is 16%, 41%, 62%, respectively

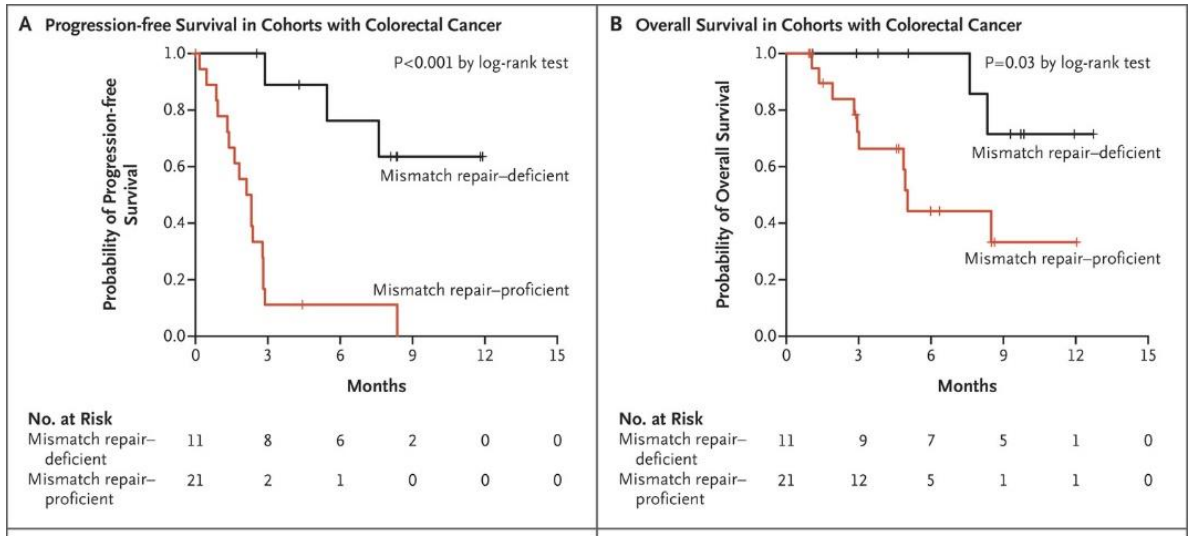
- Extensive colectomy vs segmental
  - Extensive: 0/50 metachronous tumors
  - Segmental: 74/322 (22%) metachronous tumors



Parry et al. Gut. 2011; 60:950-7.
Win et al. Ann Surg Onc. 2013; 20:1829-36.
Edelstein et al. Clin Gastroenterol Hep. 2011;9:340-43.

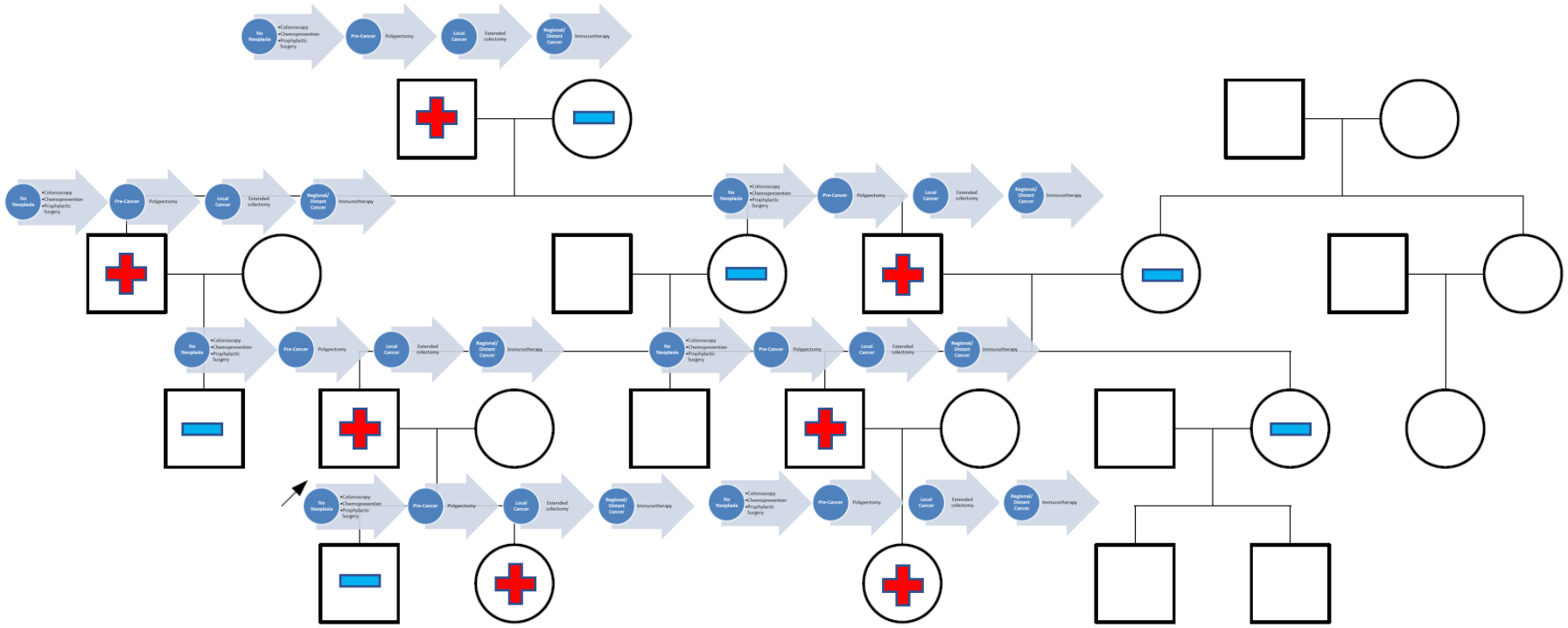
Opportunities for Intervention





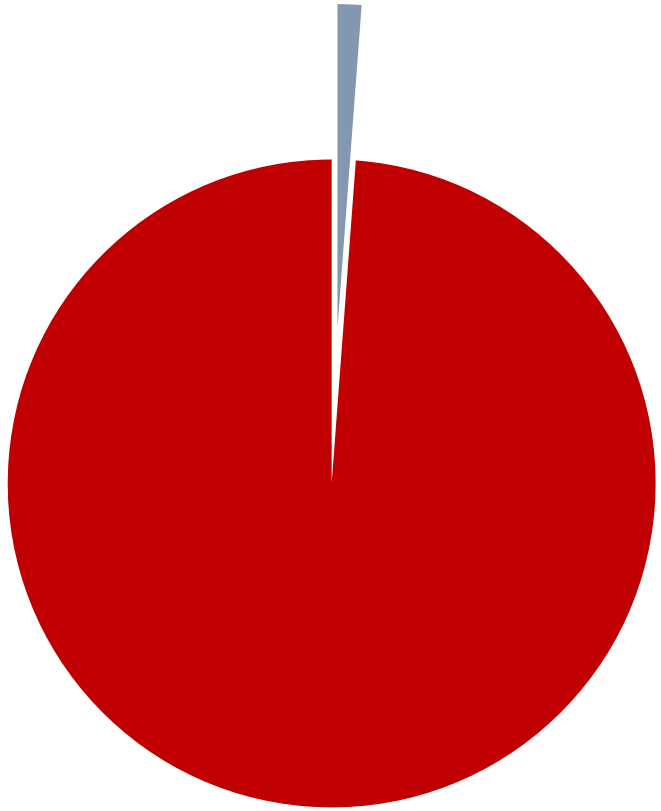
Le et al. NEJM. 2015;372:2509-20.

Capturing Family Members: Cascade Testing



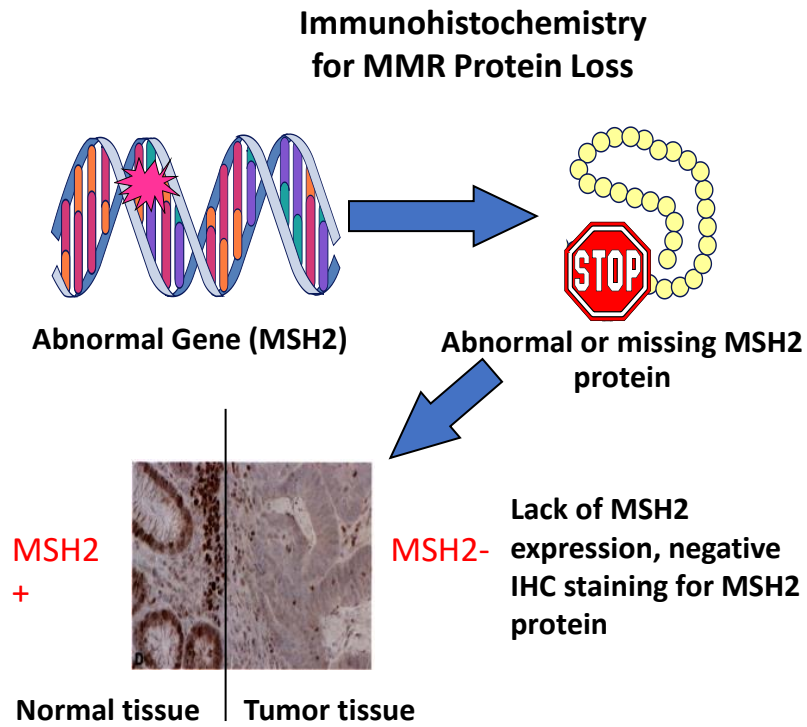
Hereditary Syndromes are Grossly Under-Recognized

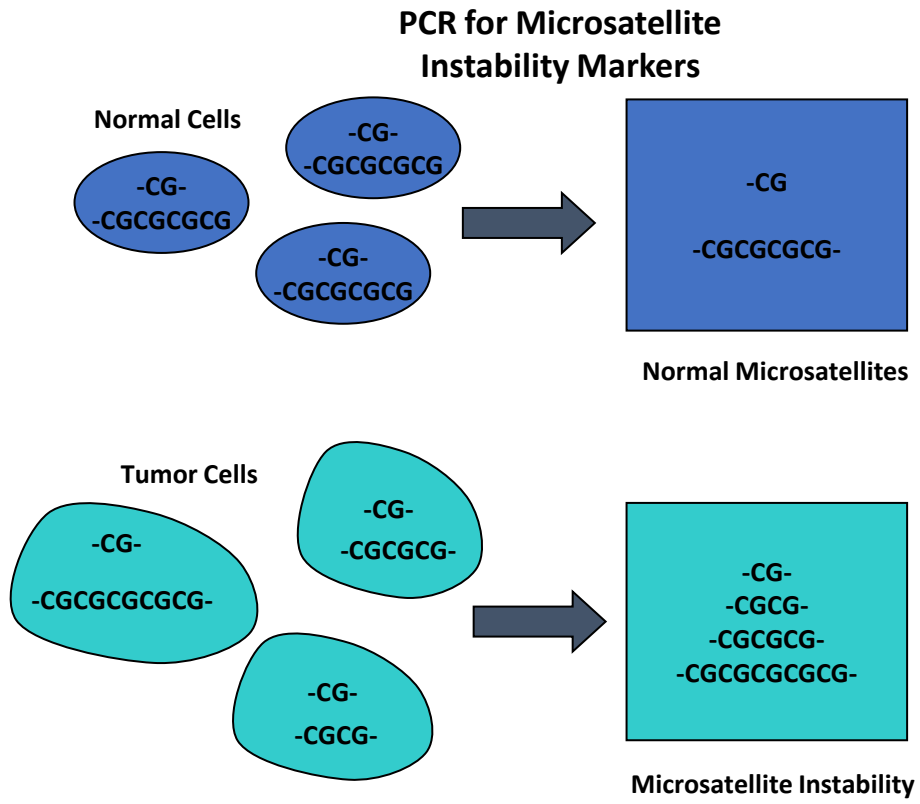
Only ~1.2% (10K/830K) Lynch pathogenic variant carriers in the US are aware of their diagnosis



Hampel et al. Cancer Prev Res. 2011. 4:1-5.

Lynch Syndrome Diagnosis: Tumor Screening





Lynch Syndrome Diagnosis: Universal Tumor Testing

"The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer (CRC) to reduce morbidity and mortality in relatives."

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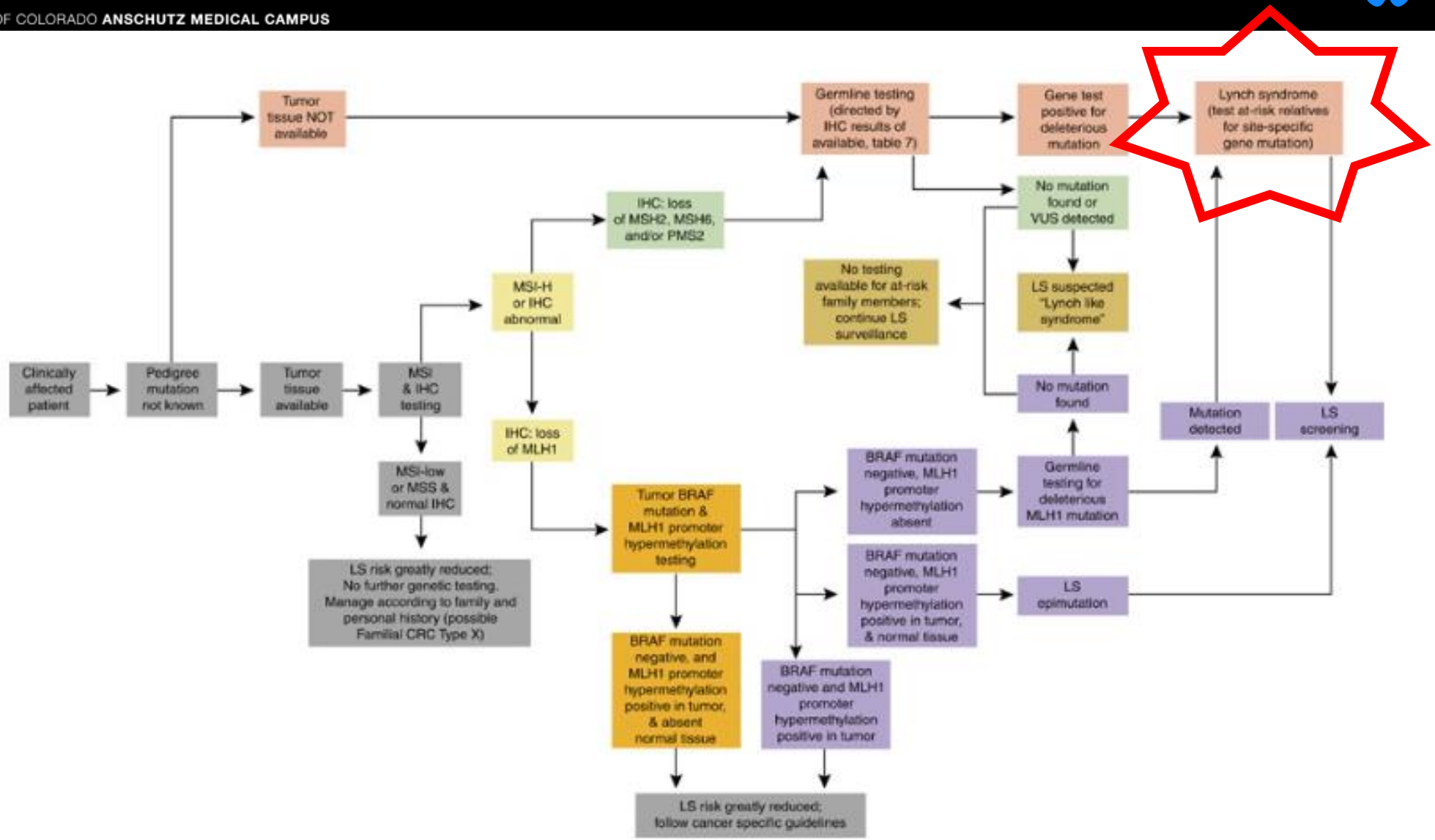


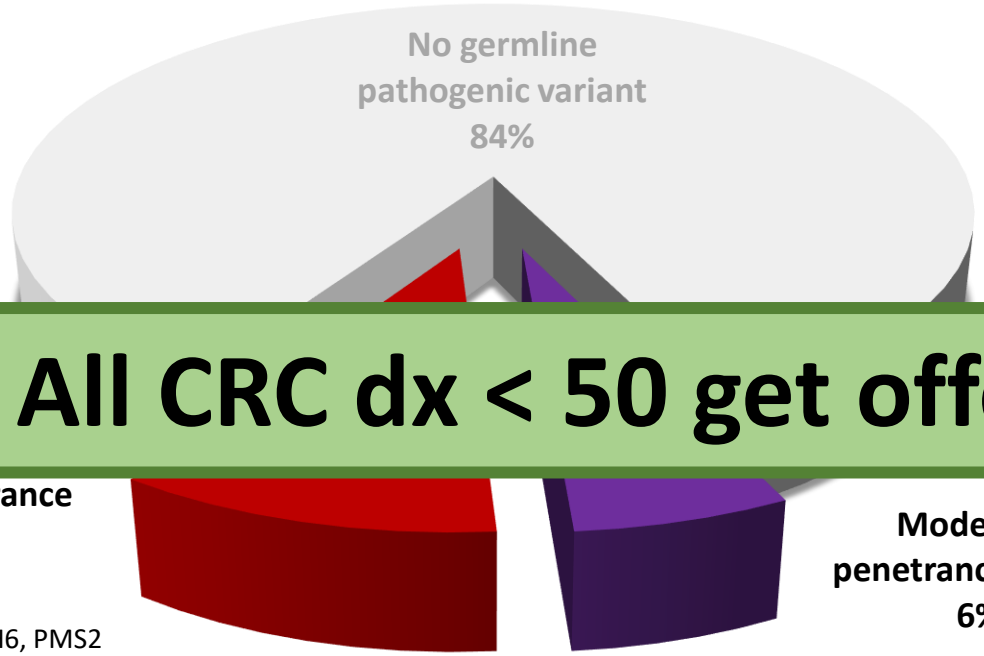
Lynch Syndrome: US-MSTF 2014.

Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening

Charles Muller,* Sang Mee Lee,* William Barge,‡ Shazia M. Siddique,§ Shivali Berera,‖ Gina Wideroff,‖ Rashmi Tondon,§ Jeremy Chang,* Meaghan Peterson,* Jessica Stoll,* Bryson W. Katona,§ Daniel A. Sussman,‖ Joshua Melson,‡ and Sonia S. Kupfer*

Overall, 92% of colorectal tumors were analyzed for mismatch repair deficiency without significant differences among races/ethnicities. However, minority patients were significantly less likely to be referred for genetic evaluation (21.2% for NHW patients vs 16.9% for African American patients and 10.9% for Hispanic patients; $P = .02$). Rates of genetic testing were also lower among minority patients (10.7% for NHW patients vs 6.0% for AA patients and 3.1% for Hispanic patients; $P < .01$). On multivariate analysis, African American race, older age, and medical center were independently associated with lack of referral for genetic evaluation and genetic testing.

Muller et al. Clin Gastroenterol & Hepatol 2018;16:1911-18.



Since 2017: All CRC dx < 50 get offered MGPT

High-penetrance variant 10%

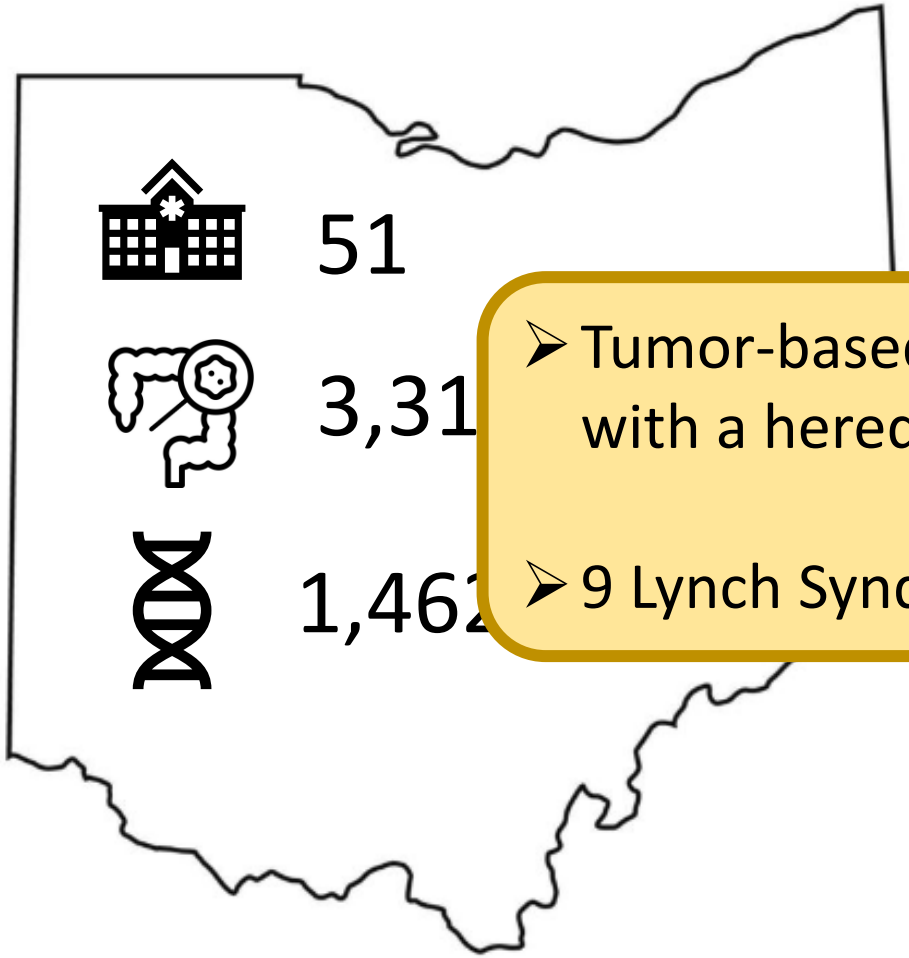
MLH1, MSH2, MSH6, PMS2
Biallelic MUTYH
APC
SMAD4
BRCA1, BRCA2
CDKN2A

Moderate-penetrance variant 6%

ATM
PALB2
Monoallelic MUTYH
APC I1307K
CHEK2

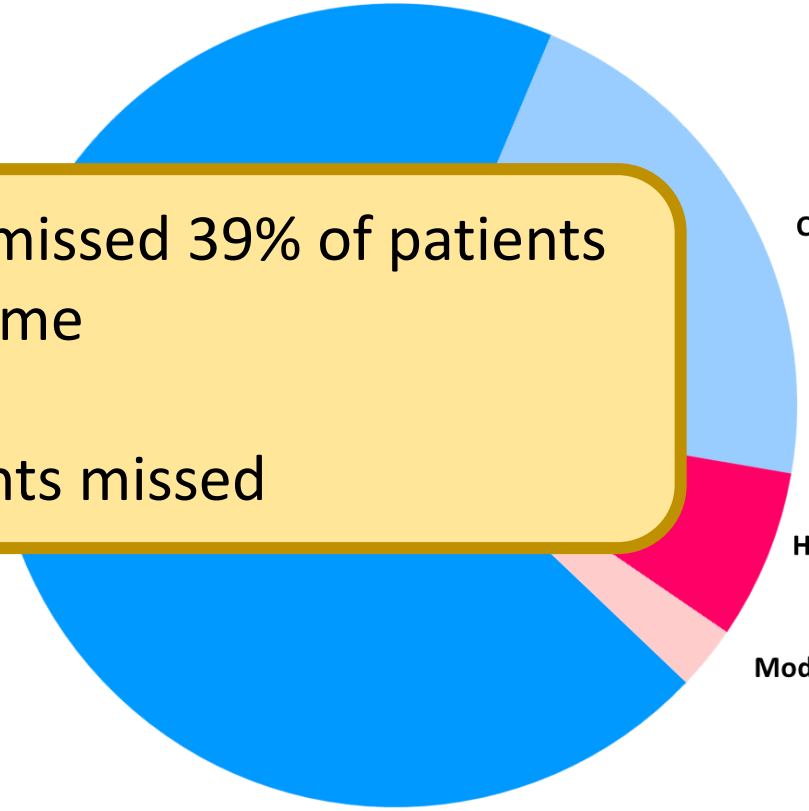
Pearlman et al. JAMA Oncology 2017. 3(4):464-71.
NCCN Genetic/Familial High-Risk Assessment: Colorectal 2017.

@SwatiPatelMD

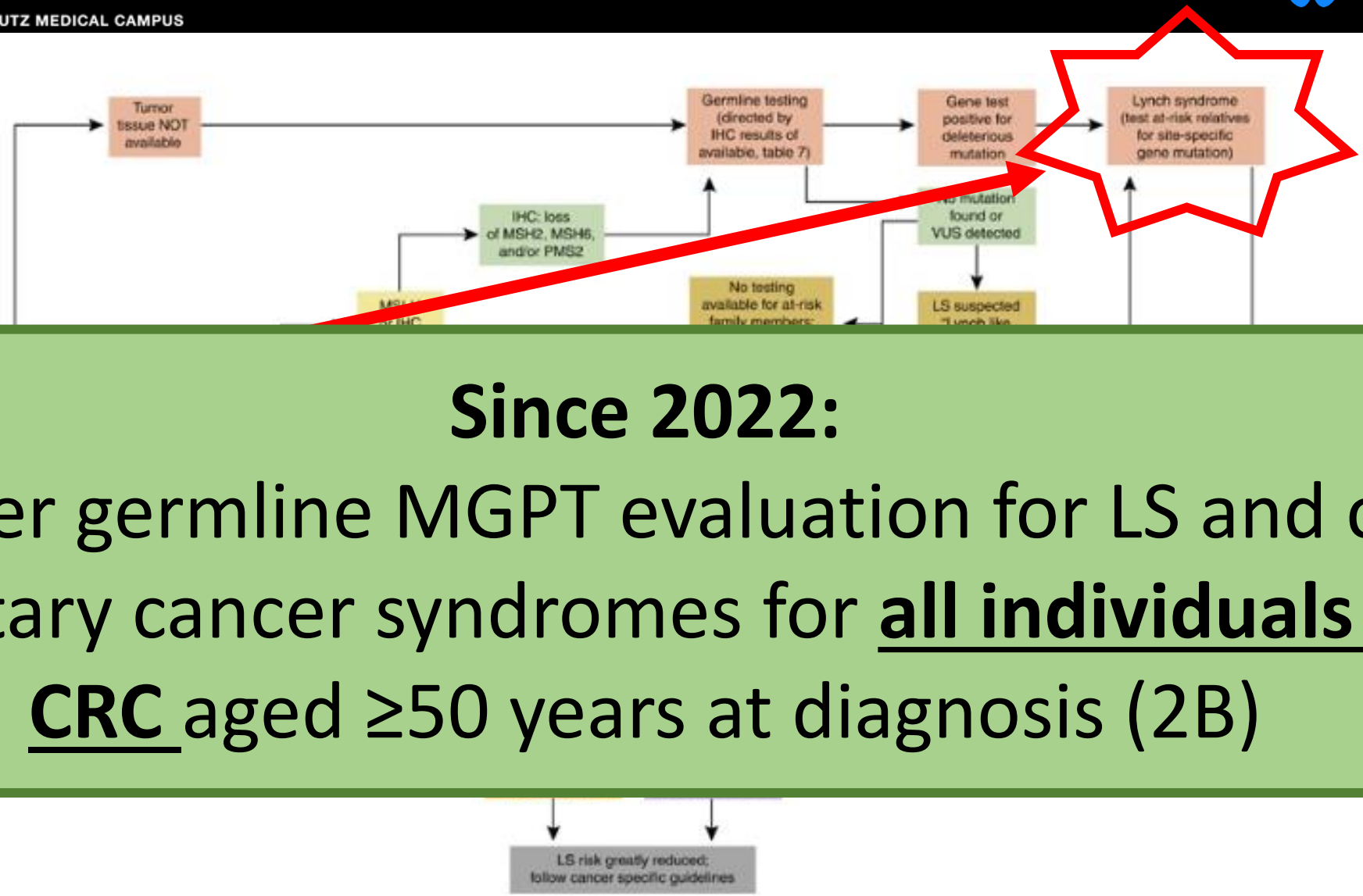


- Tumor-based screening missed 39% of patients with a hereditary syndrome
- 9 Lynch Syndrome patients missed

Spectrum of Pathogenic Variants found in Patients with CRC



Pearlman et al. JCO-PO 2021 5:779-91.



Since 2022:

Consider germline MGPT evaluation for LS and other hereditary cancer syndromes for **all individuals with CRC** aged ≥50 years at diagnosis (2B)

Challenges that lie ahead

- Cost & care delivery burden

Accepted: 5 September 2023
DOI: 10.1111/1471-0528.17675

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Patient decision aids in mainstreaming genetic testing for women with ovarian cancer: A prospective cohort study

Ann Surg Oncol (2023) 30:5990–5996
https://doi.org/10.1245/s10434-023-13888-4

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Check for updates

ORIGINAL ARTICLE – BREAST ONCOLOGY

A Randomized Trial Comparing the Effectiveness of Pre-test Genetic Counseling Using an Artificial Intelligence Automated Chatbot and Traditional In-person Genetic Counseling in Women Newly Diagnosed with Breast Cancer

Challenges that lie ahead

- Cost & care delivery burden
- Expertise needed

RESULT: NO PATHOGENIC VARIANTS IDENTIFIED

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRIP1	c.3302C>T (p.Pro1101Leu)	heterozygous	Uncertain Significance
DICER1	c.278G>A (p.Gly93Glu)	heterozygous	Uncertain Significance
GATA2	c.460A>G (p.Ser154Gly)	heterozygous	Uncertain Significance
MSH3	c.3382A>G (p.Met1128Val)	heterozygous	Uncertain Significance
RECQL4	c.2836C>T (p.Arg946Cys)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 84 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Challenges that lie ahead

- Cost & care delivery burden
- Expertise needed
- May push disparities downstream

Final Thoughts

- Genetic and molecular basis of CRC → Precision prevention & early detection

- Operationalizing expanding options for the 3rd most commonly diagnosed cancer will require
  - Adapting to new delivery models
  - Training a workforce
  - Attention to health equity

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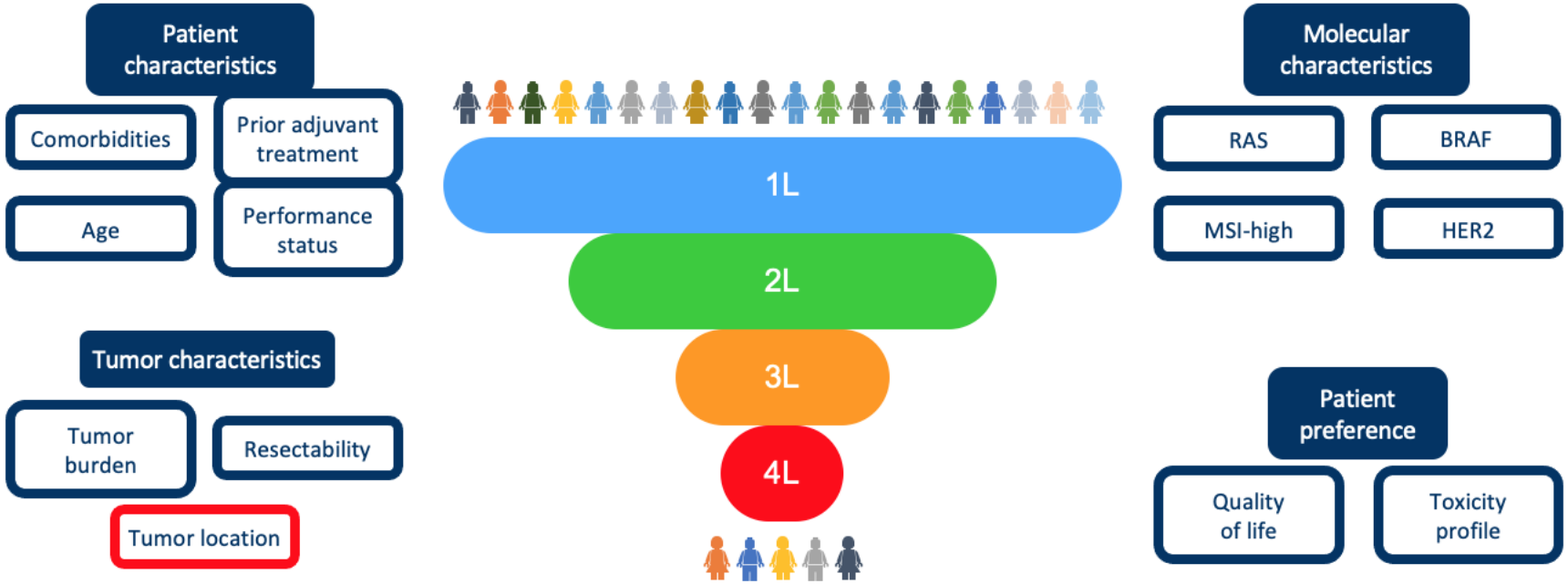
Targeted therapies and treatment options for metastatic colorectal cancer in 2024

ACS NCCRT
Nov 20, 2024

Andrea Cercek, MD

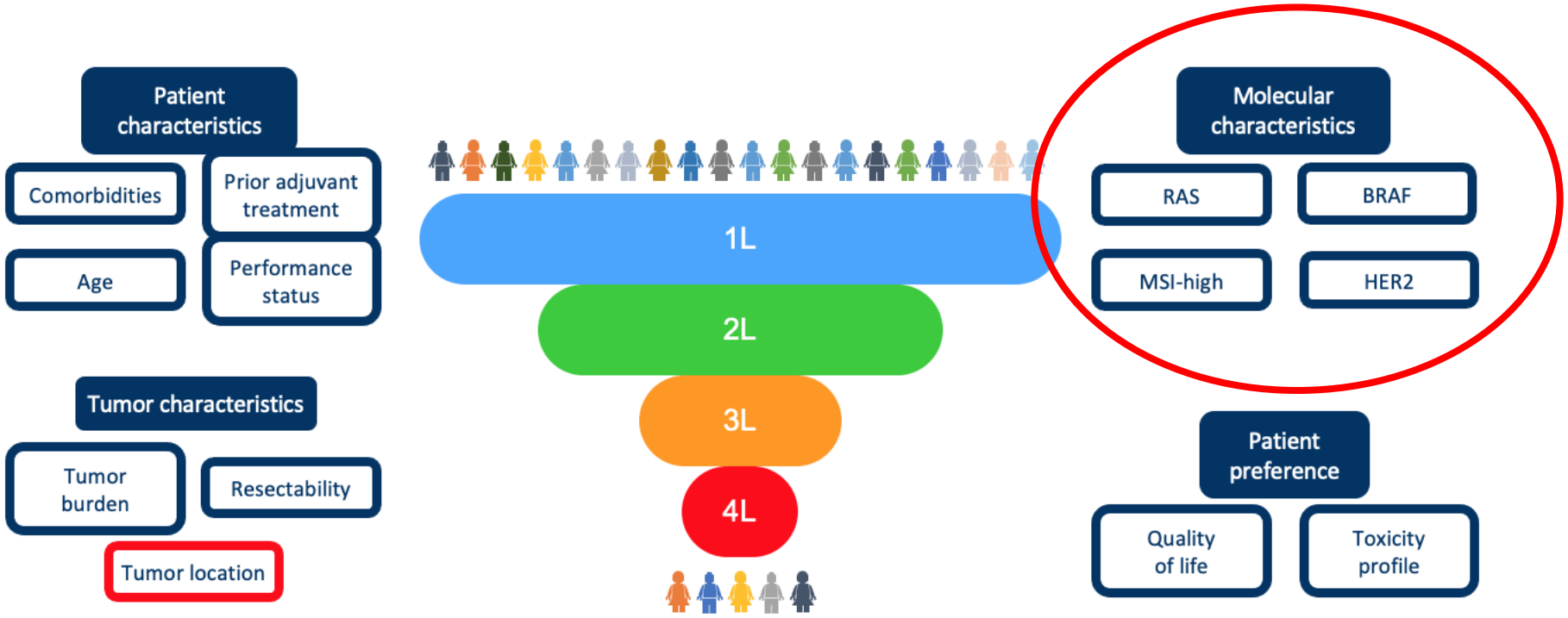
Attending
Section Head Colorectal Cancer
Co-Director Center for Young Onset Colorectal and Gastrointestinal Cancers

Current treatment in mCRC



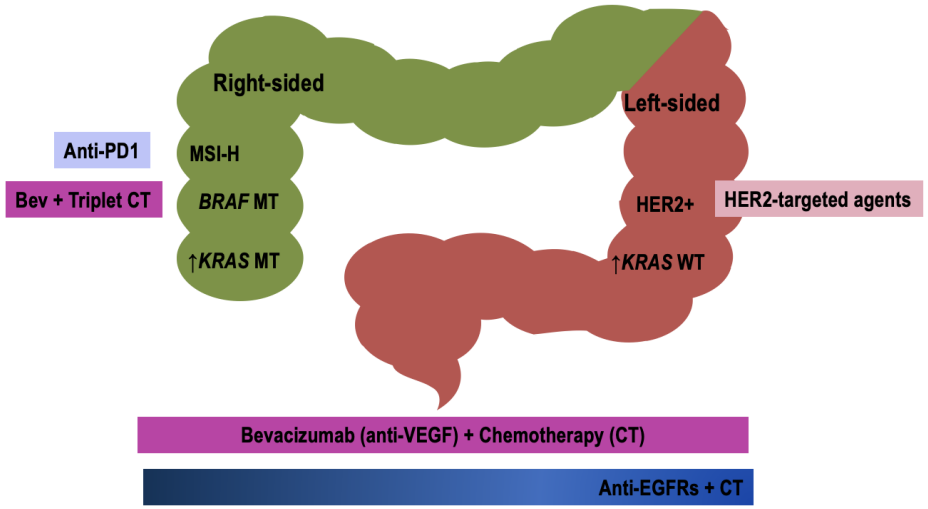
Treatment is based on the individual patient

Current treatment in mCRC



Molecular markers and tumor location matter

Current Guidelines for Molecular Testing in mCRC



Bufill JA. *Ann Intern Med.* 1990;113:779-788.
Brule SY et al. Presented at: ASCO 2013. Abstract 3528.
Bendardaf R et al. *Anticancer Res.* 2008;28:3865-3870.
Missiaglia E et al. Presented at: ASCO 2013. Abstract 3526.
The Cancer Genome Atlas Network. *Nature.* 2012;490:61-70.

***RAS* mutations (KRAS, NRAS)**

***BRAF* mutations**

dMMR/MSI-H status

HER2 amplifications

1. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 5.2024. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

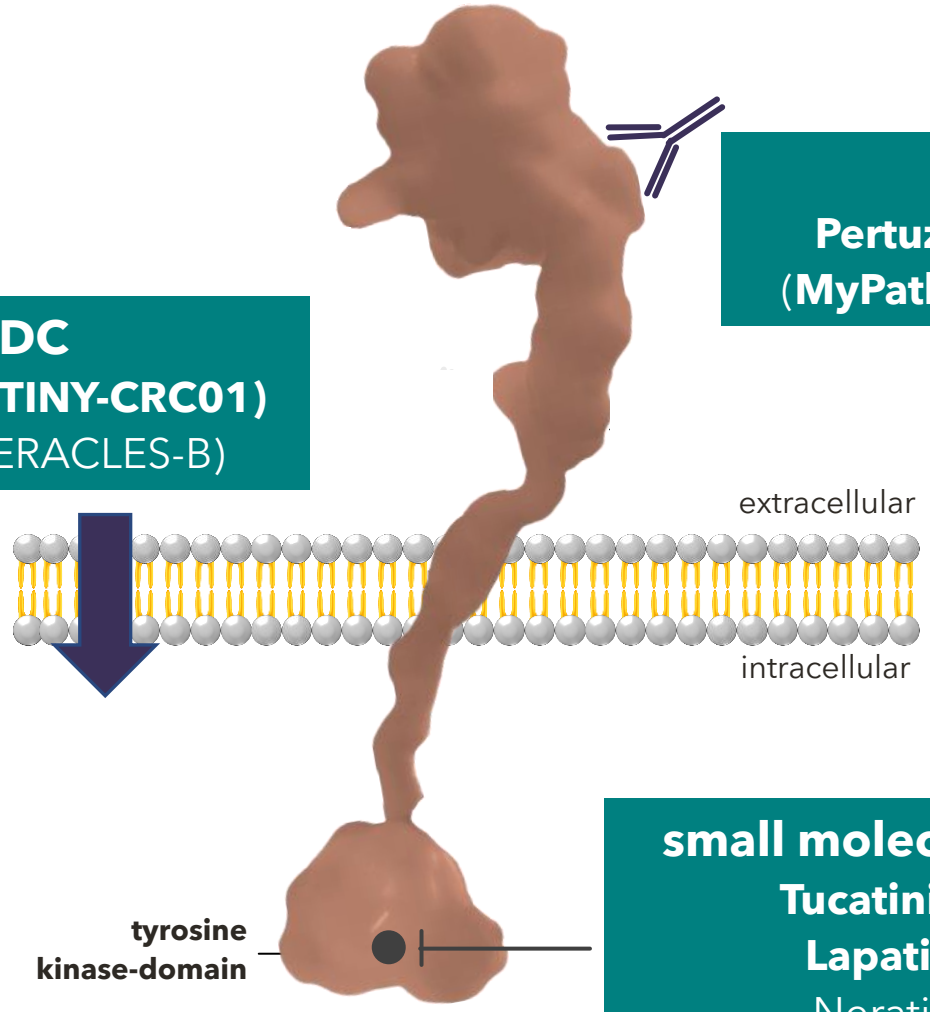
Molecular markers and treatment in mCRC

	First line	Second line +
MSS/pMMR	Chemotherapy FOLFOX/FOLFIRI or FOLFIRINOX +/- bev	Chemotherapy
KRAS/NRAS/BRAF Wildtype, Left-Sided only	Chemotherapy +/- anti EGFR therapy	Chemotherapy
HER2 Amplified, RAS/BRAF Wildtype	Chemotherapy or clinical trial	HER2 targeted therapy
KRAS G12c Mutated	Chemotherapy or clinical trial	KRAS G12C targeted therapy + anti EGFR
BRAF v600e Mutated	Chemotherapy or clinical trial	BRAF targeted therapy
MSI-H/dMMR	Immunotherapy	Chemotherapy/ clinical trial

1. Morris VK, et al. J Clin Oncol. 2023;41:678-700. 2. NCCN Guidelines® for Colon Cancer, Version 4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 12/8/23 at: www.NCCN.org 3. NCCN Guidelines® for Rectal Cancer, Version 6.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 12/8/23 at: www.NCCN.org

Targeting HER 2+ tumors

Molecular markers and treatment in mCRC: HER2 +



mAb
Pertuzumab + trastuzumab
(**MyPathway**, TAPUR, TRIUMPH)

ADC
T-DXd (DESTINY-CRC01)
T-DM1 (HERACLES-B)

small molecule TKI + trastuzumab
Tucatinib (MOUNTAINEER)
Lapatinib (HERACLES-A)
Neratinib (NSABP FC-11)

Results earlier trials of anti-HER2 therapy in mCRC

Clinical trial	Therapies	Patients (N)	Response Rate	Time to Progression (median)
HERACLES	Lapatinib + Trastuzumab	27	30%	4.9 months
MyPathway	Pertuzumab + Trastuzumab	57	32%	2.9 months

Sartore-Bianchi et al., *Lancet Oncology* 2016 17, 738-746.
Meric-Bernstam et al., *Lancet Oncol* Vol20, Issue 4, April 2019, 518-530.

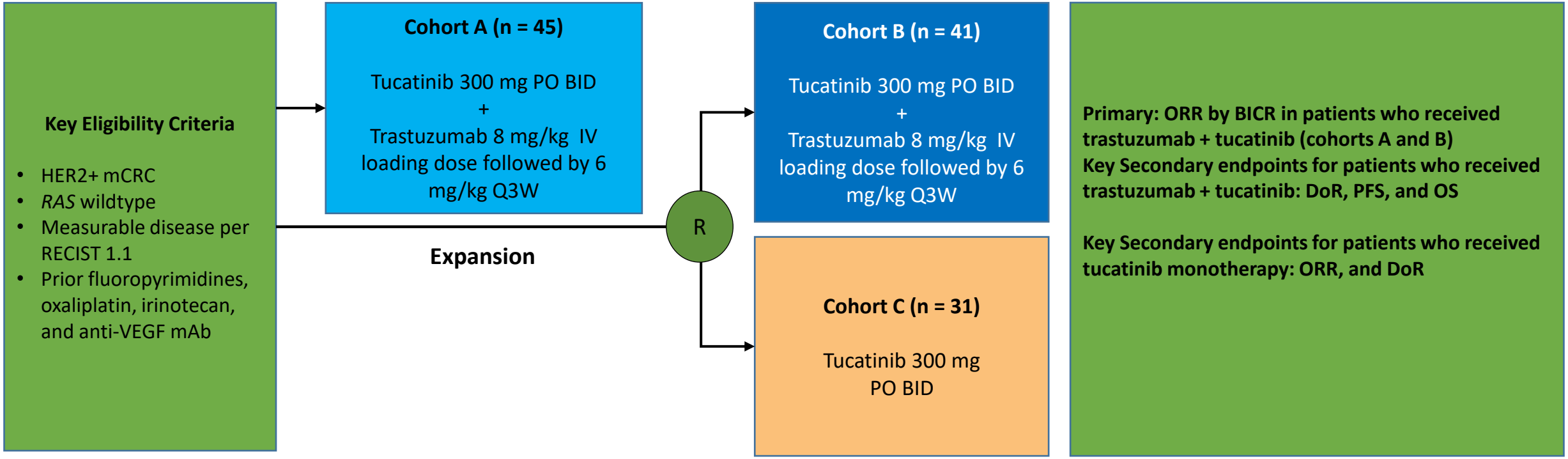
MyPathway: Biomarkers of sensitivity/ resistance

	ORR n (%, 95% CI)	Median PFS Months (95% CI)	Median OS Months (95% CI)
All patients (n=57)	18 (32%, 20-45)	2.9 (1.4-5.3)	11.5 (7.7-NE)
KRAS status			
Wild-type (n=43)	17 (40%, 25-56)	5.3 (2.7-6.1)	14.0 (8.0-NE)
Mutated (n=13)	1 (8%, 0.2-36)	1.4 (1.2-2.8)	8.5 (3.9-NE)
PIK3CA status			
Wild-type (n=40)	17 (43%, 27-59)	5.3 (2.8-6.1)	14.0 (8.5-NE)
Mutated (n=8)	1 (13%, 0.3-53)	1.4 (1.1-5.7)	7.3 (1.2-12.6)
Previous anti-EGFR*			
Any (n=31)	11 (36%, 19-55)	4.1 (1.6-8.2)	11.5 (7.2-22.1)
None (n=12)	6 (50%, 21-79)	5.6 (1.3-14.7)	NE (3.2-NE)

* KRAS WT pts only

Meric-Bernstam *et al.*, Lancet Oncol Vol20, Issue 4, April 2019, 518-530

MOUNTAINEER Trial Design: Trastuzumab + Tucatinib in HER2+ mCRC
Global, Open-Label, Phase 2 Trial

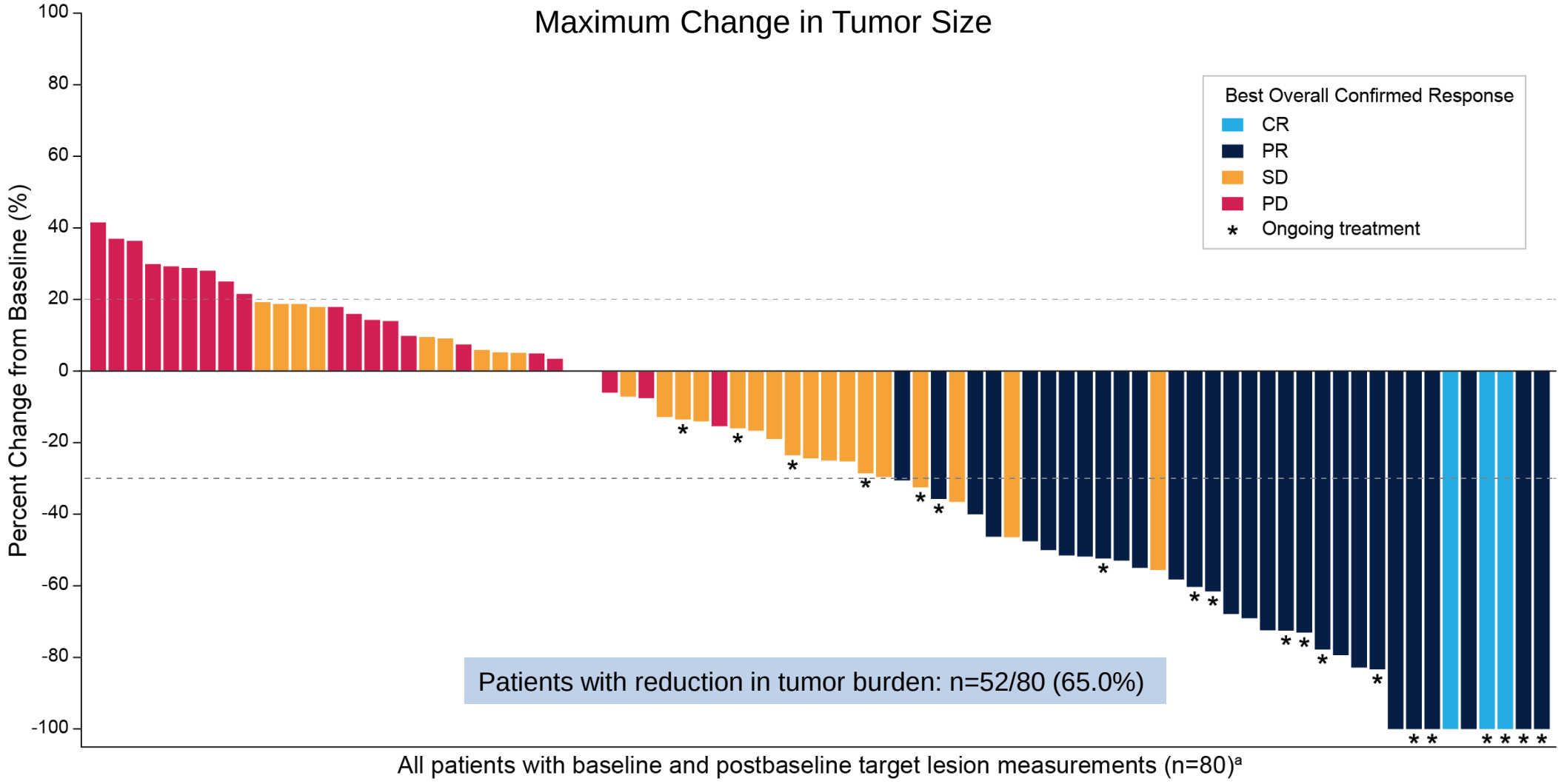


MOUNTAINEER began as an investigator-sponsored study and initially consisted of a single cohort (cohort A) and was expanded to include patients randomized to receive tucatinib + trastuzumab (cohort B) or tucatinib monotherapy (cohort C)

MOUNTAINEER: Tucatinib + Tras Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

MOUNTAINEER: Tucatinib + Tras Change in Tumor Size



a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded

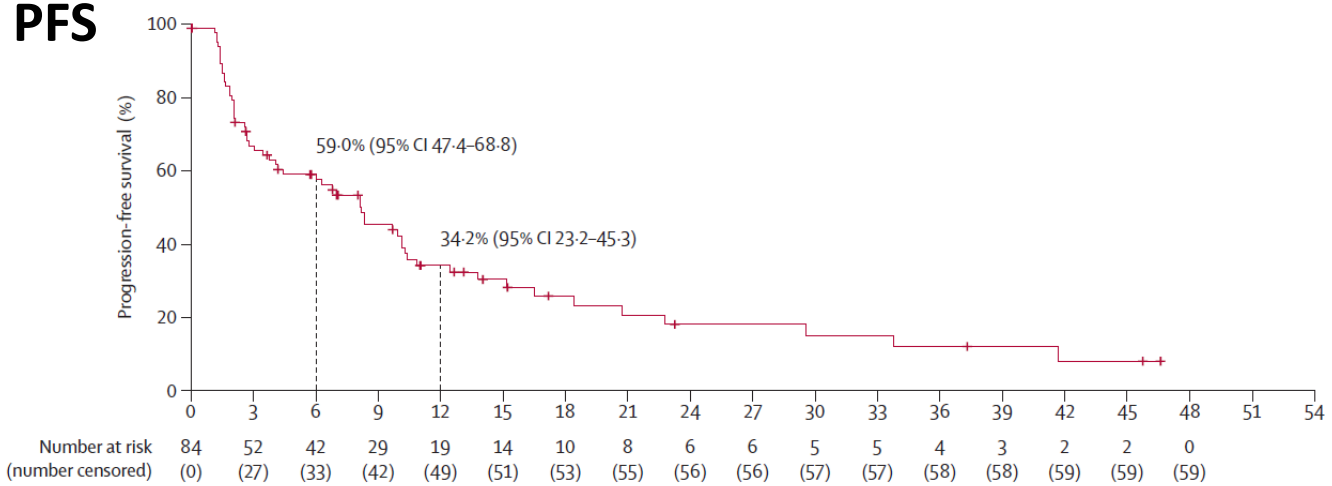
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 28 Mar 2022

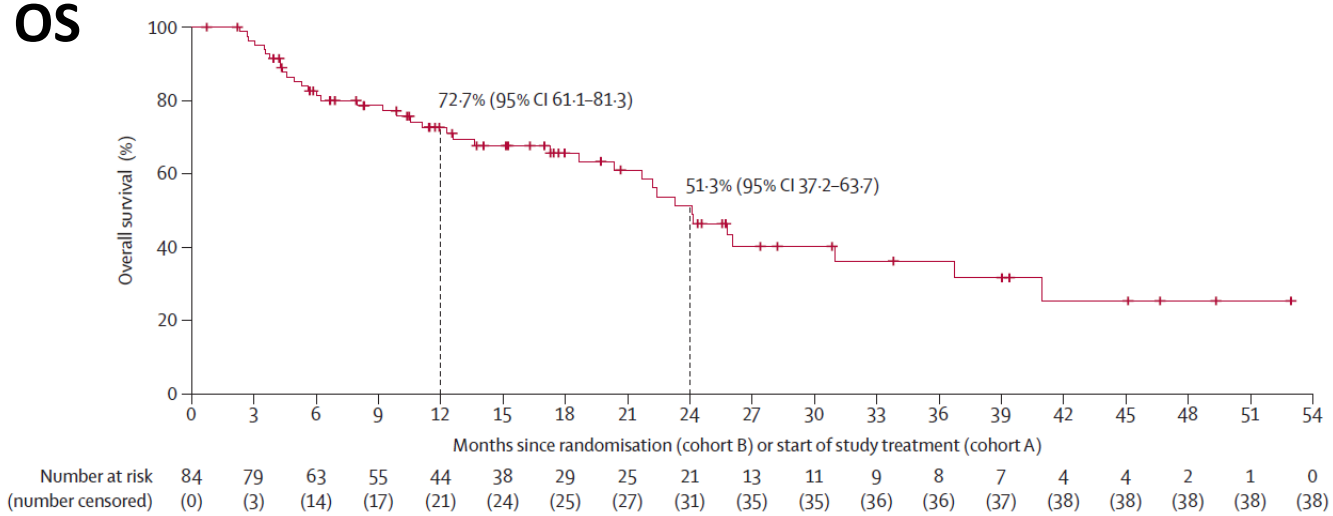
John Strickler, ESMO GI 2022

MOUNTAINEER: Trastuzumab + Tucatinib in HER2+ mCRC—PFS and OS

PFS



OS

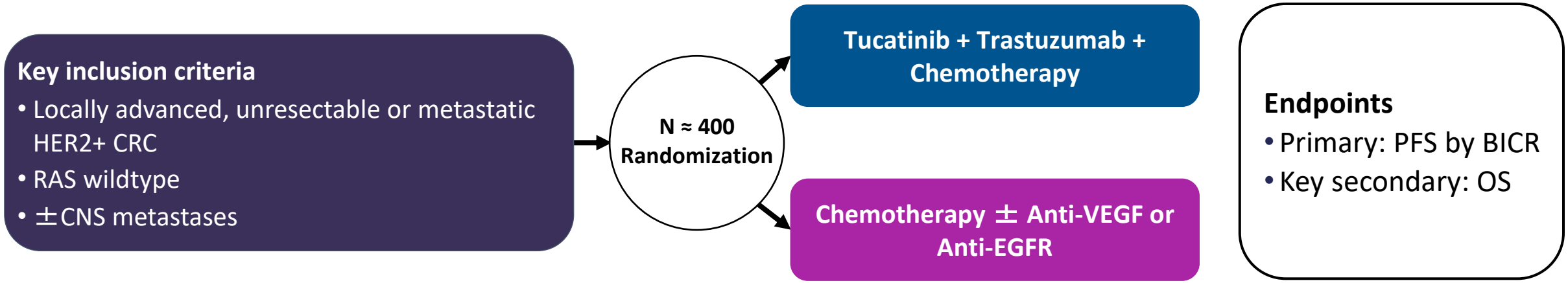


Abbreviations: CI, confidence interval; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

Strickler JH, et al. *Lancet Oncol.* 2023;24:496-508.

MOUNTAINEER-03 Trial Design: Tucatinib + Trastuzumab + Chemotherapy in First-Line HER2+ mCRC

Open-Label, Randomized, Phase III Trial



Abbreviations: BICR, blinded independent central review; CNS, central nervous system; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

ClinicalTrials.gov. A study of tucatinib with trastuzumab and MFOLFOX6 versus standard of care treatment in first-line HER2+ metastatic colorectal cancer (MOUNTAINEER-03). Accessed 12/18/23 at: https://www.clinicaltrials.gov/study/NCT05253651

DESTINY-CRC01 Trial Design: T-DXd in HER2-Expressing mCRC

Open-label, multicenter, phase II study (NCT03384940)

Patients

- HER2 expressing metastatic CRC
- RAS/BRAF wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed

Cohort A (n = 53)
HER2+ (IHC 3+ or IHC 2+/ISH+)

Cohort B (n = 7)
HER2 IHC 2+/ISH−

Cohort C (n = 18)
HER2 IHC 1+

T-DXd 6.4 mg/kg q3w

Treatment given until disease progression or unacceptable toxicity, or other discontinuation criteria

Primary endpoint

- Confirmed ORR by ICR in Cohort A

Key secondary endpoints

- ORR (cohorts B and C)
- DoR
- DCR
- PFS
- OS

DESTINY-CRC01: T-DXd in HER2-Expressing mCRC

Final Results

	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH− Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Confirmed ORR by ICR	24 (45.3) [95% CI, 31.6–59.6]	0 [95% CI, 0.0–21.8]	0 [95% CI, 0.0–18.5]
Complete response	0	0	0
Partial response	24 (45.3)	0	0
Stable disease	20 (37.7)	9 (60.0)	4 (22.2)
Progressive disease	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR	83.0 (70.2–91.9)	60.0 (32.3–83.7)	22.2 (6.4–47.6)
Median DoR, months	7.0 (5.8–9.5)	NE (NE–NE)	NE (NE–NE)
Median treatment duration, months	5.1 (3.9–7.6)	2.1 (1.4–2.6)	1.4 (1.3–1.5)

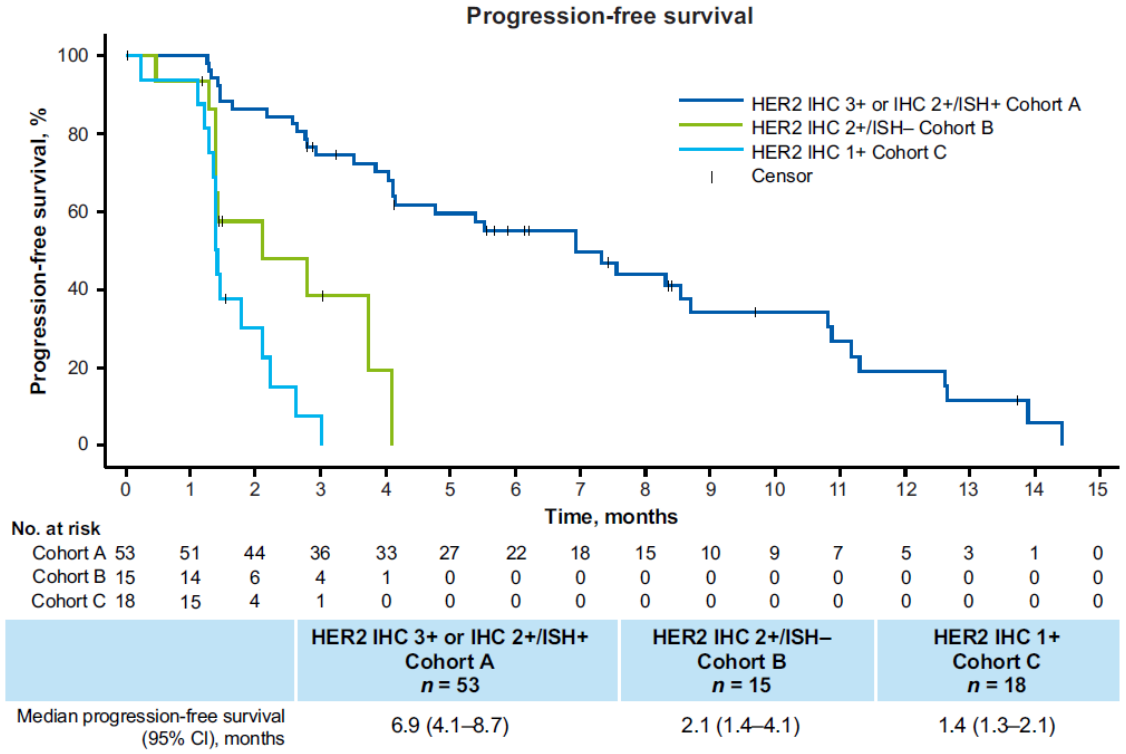
*Patients were missing postbaseline scans.

Abbreviations: CI confidence interval; DCR, disease control rate, DoR, duration of response, HER2, human epidermal growth factor receptor 2; ICR, independent central review, IHC, immunohistochemistry, ISH, in situ hybridization, mCRC, metastatic colorectal cancer; NE, not evaluable, ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

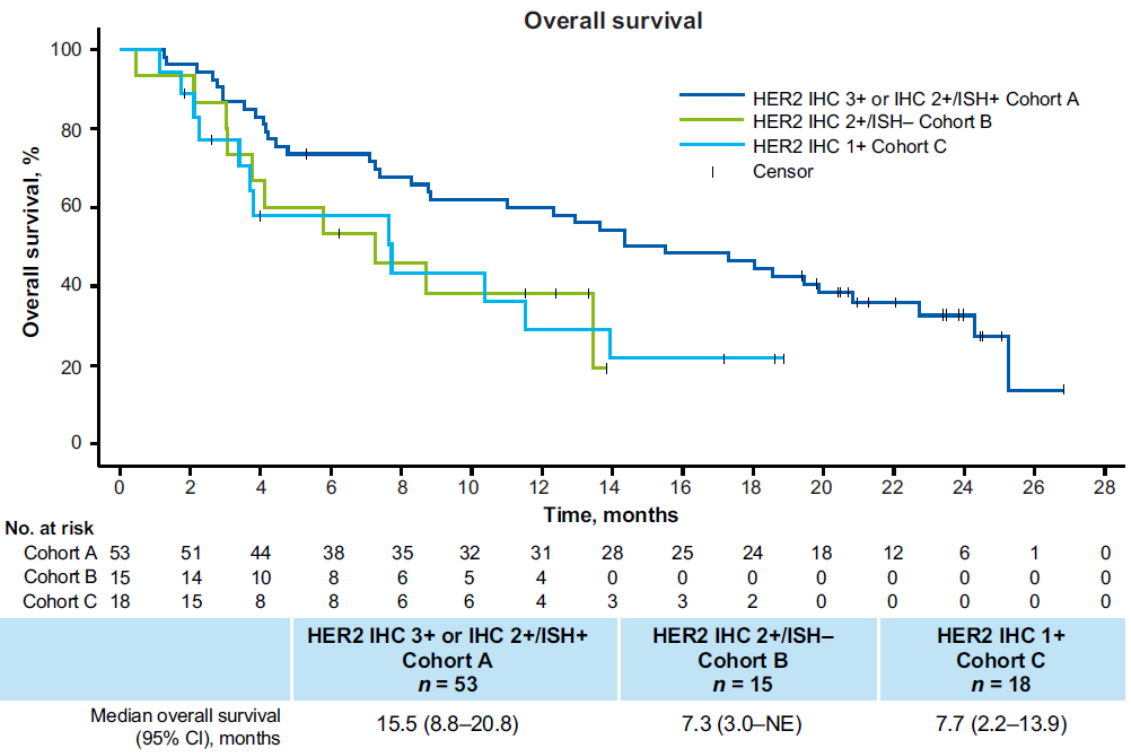
Yoshino T, et al. *Nat Commun.* 2023;14:3332.

DESTINY-CRC01: T-DXd in HER2-Expressing mCRC

PFS and OS



	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH– Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Median progression-free survival (95% CI), months	6.9 (4.1–8.7)	2.1 (1.4–4.1)	1.4 (1.3–2.1)



	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH– Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Median overall survival (95% CI), months	15.5 (8.8–20.8)	7.3 (3.0–NE)	7.7 (2.2–13.9)

Abbreviations: CI confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry, ISH, in situ hybridization, mCRC, metastatic colorectal cancer; NE, not estimable, OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

Yoshino T, et al. *Nat Commun.* 2023;14:3332.

DESTINY-CRC01: T-DXd in HER2-Expressing mCRC

Safety/Toxicity

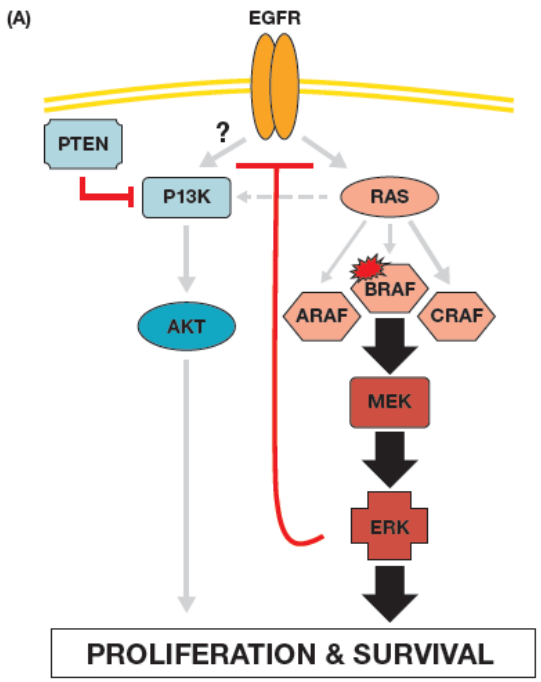
- **Most common grade ≥3 TEAEs (across cohorts): decreased neutrophil count (22.1%) and anemia (14.0%)**
- **TEAE most commonly associated with drug discontinuation: ILD (7.0%)**
- **TEAE most commonly associated with dose reduction or dose interruption: decreased neutrophil count (4.7% and 9.3%, respectively)**
- **9 patients (10.5%) had TEAEs associated with death; 3 (3.5%) were drug-related (all adjudicated as ILD)**

Drug-Related Adjudicated ILD/Pneumonitis

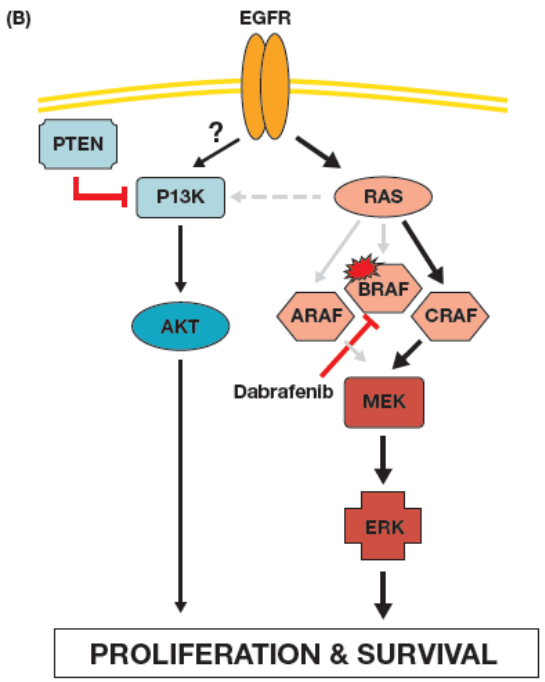
	HER2 IHC 3 + or IHC 2 + /ISH + Cohort A *n* = 53	HER2 IHC 2 + / ISH − Cohort B *n* = 15	HER2 IHC 1 + Cohort C *n* = 18	All Patients *N* = 86
Grade 1	0	0	0	0
Grade 2	2 (3.8)	2 (13.3)	0	4 (4.7)
Grade 3	0	0	1 (5.6)	1 (1.2)
Grade 4	0	0	0	0
Grade 5	2 (3.8)	1 (6.7)	0	3 (3.5)
Any grade/ total	4 (7.5)	3 (20.0)	1 (5.6)	8 (9.3)[a]

Yoshino T, et al. *Nat Commun.* 2023;14:3332.

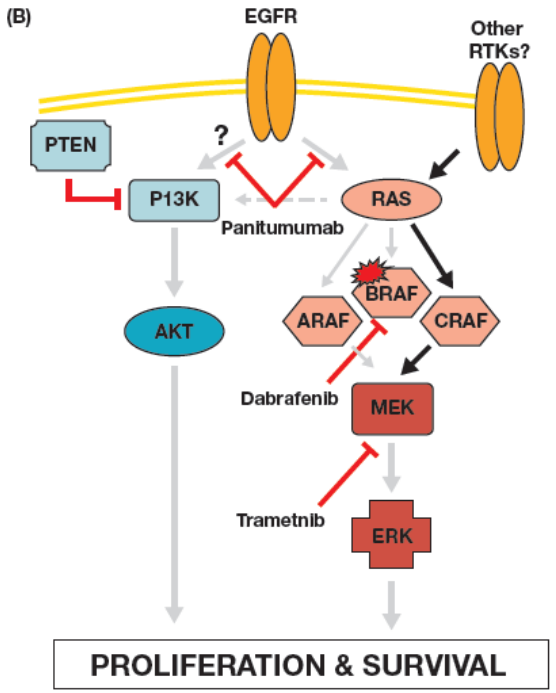
BRAF



Signaling in BRAF mutated CRC



Reactivation of EGFR signaling upon BRAF inhibition

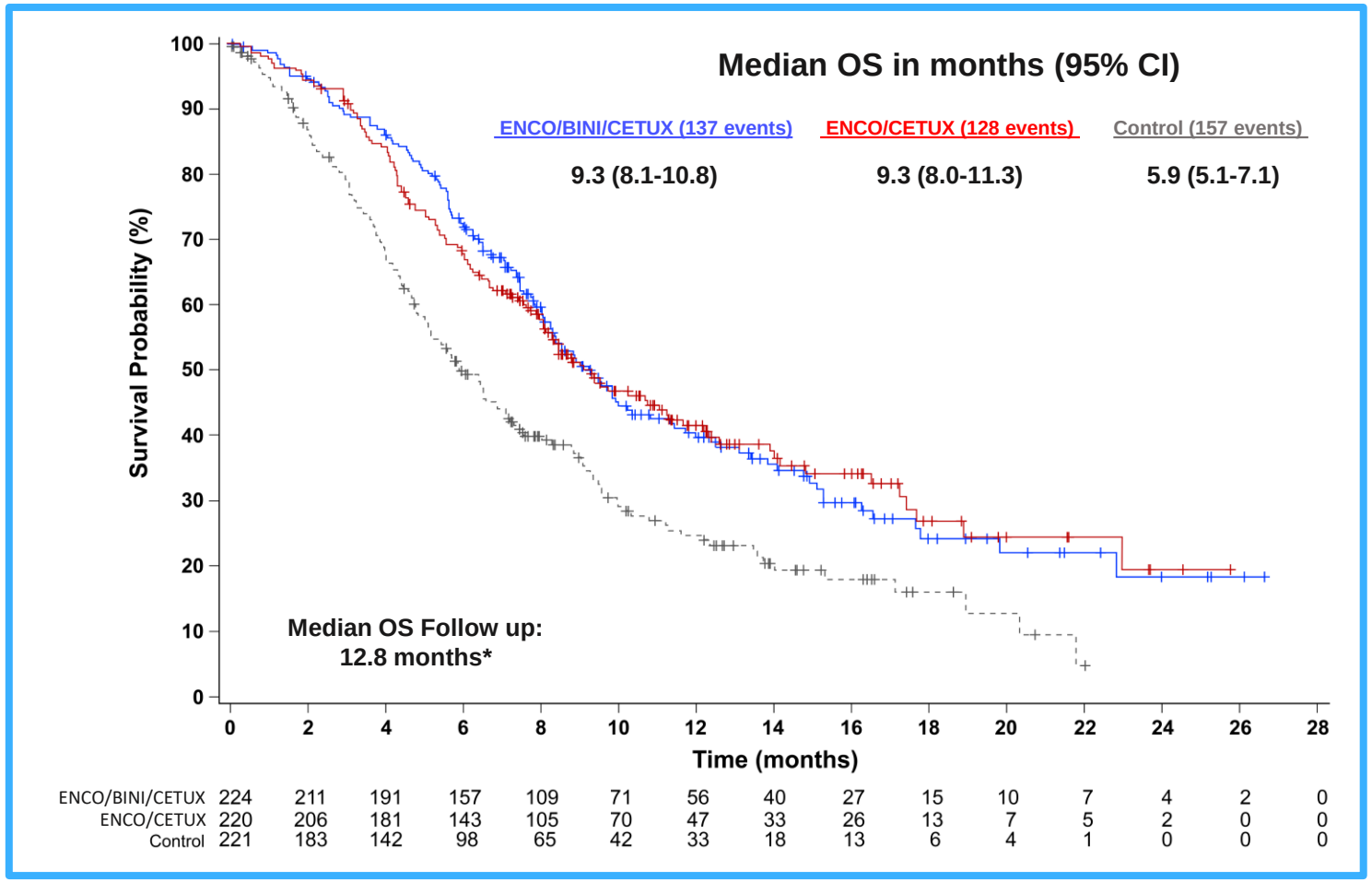


Robust inhibition of MAPK pathway signaling with inhibition of BRAF, MEK, EGFR

Bendell. et al. ASCO 2014.

BRAF

Updated Overall Survival: ENCO/BINI/CETUX vs ENCO/CETUX vs Control



Kopetz S et al. *J Clin Oncol.* 2020;38(suppl): Abstract 4001.

Updated Objective Response Rates

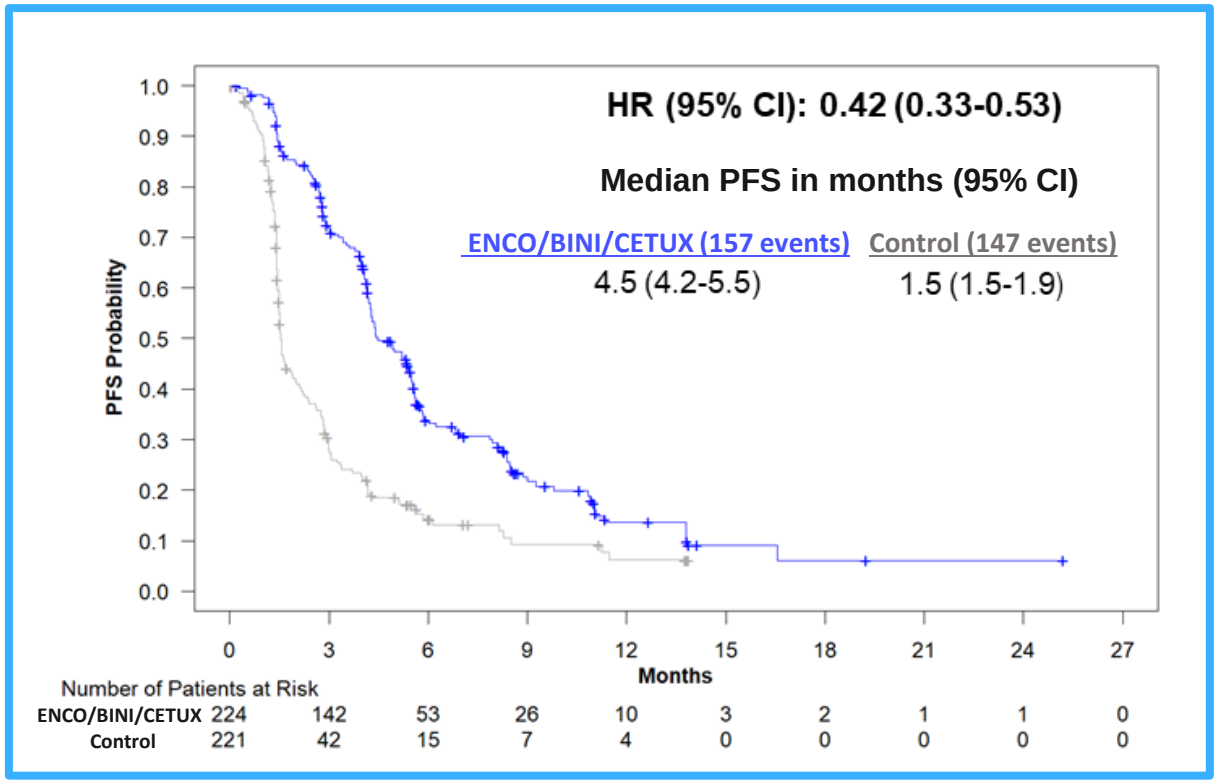
Confirmed Response by BICR	ENCO/BINI/CETUX n = 224	ENCO/CETUX n = 220	Control n = 221
Objective Response Rate	**27%**	**20%**	**2%**
95% (CI)	(21, 33)	(15, 25)	(<1, 5)
Best Overall Response			
Complete Response (CR)	4%	3%	0%
Partial Response (PR)	23%	16%	2%
Stable Disease	48%	56%	29%
Progressive Disease	11%	10%	34%
Non Evaluable by RECIST	14%	15%	32%

Kopetz S et al. *J Clin Oncol.* 2020;38(suppl): Abstract 4001.

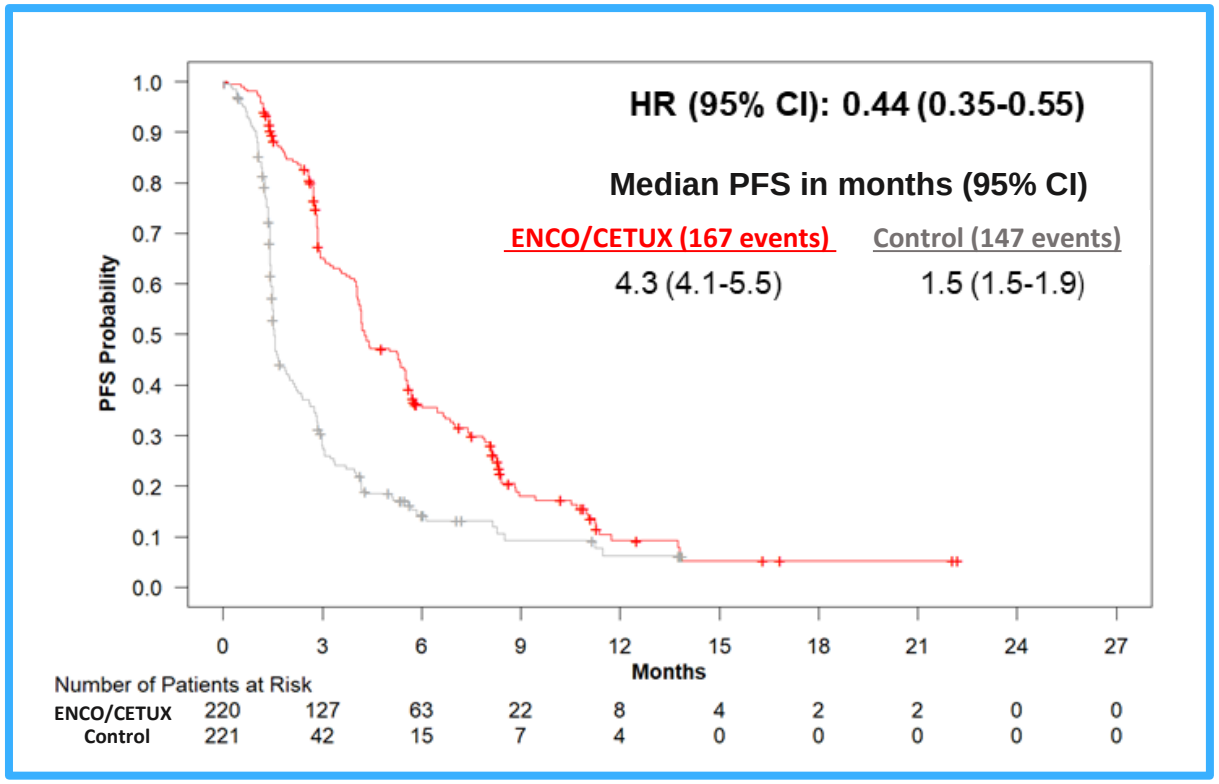
BRAF

Updated Progression-Free Survival

ENCO/BINI/CETUX vs Control



ENCO/CETUX vs Control



Kopetz S et al. *J Clin Oncol.* 2020;38(suppl): Abstract 4001.

KRAS (G12C): Colorectal Cancer

$KRAS^{G12C}$ Inhibition With Sotorasib in Advanced Solid Tumors

Table 3. Efficacy of Sotorasib in All Tumor Types.

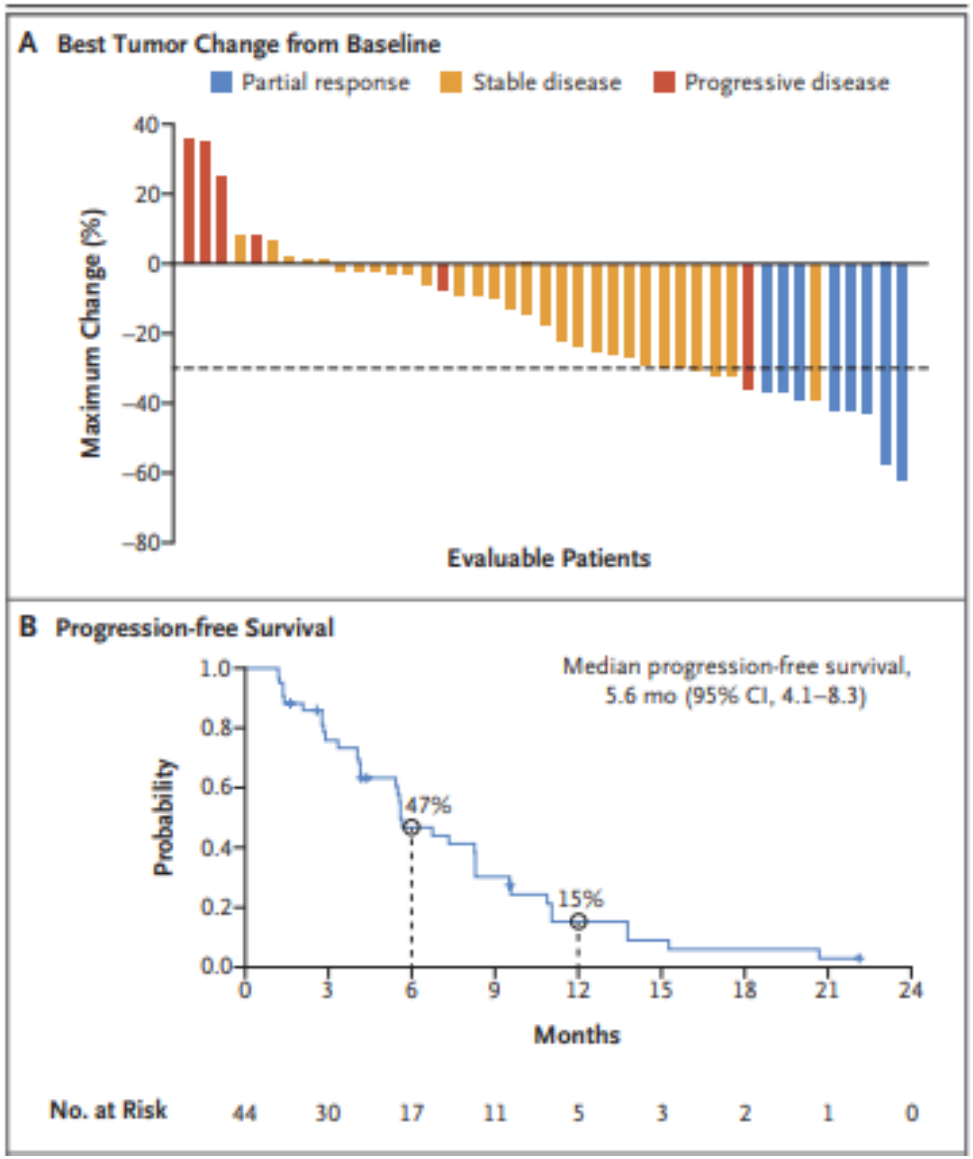
	NSCLC (N=59)	Colorectal Cancer (N=42)	Other (N=28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment*	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI) †	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI)‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

* One patient with NSCLC withdrew consent before tumor assessment. One patient with colorectal cancer and 2 patients with other tumor types had clinical progression.
† Objective response was defined as a complete or partial response.
‡ Disease control was defined as a complete response, a partial response, or stable disease.

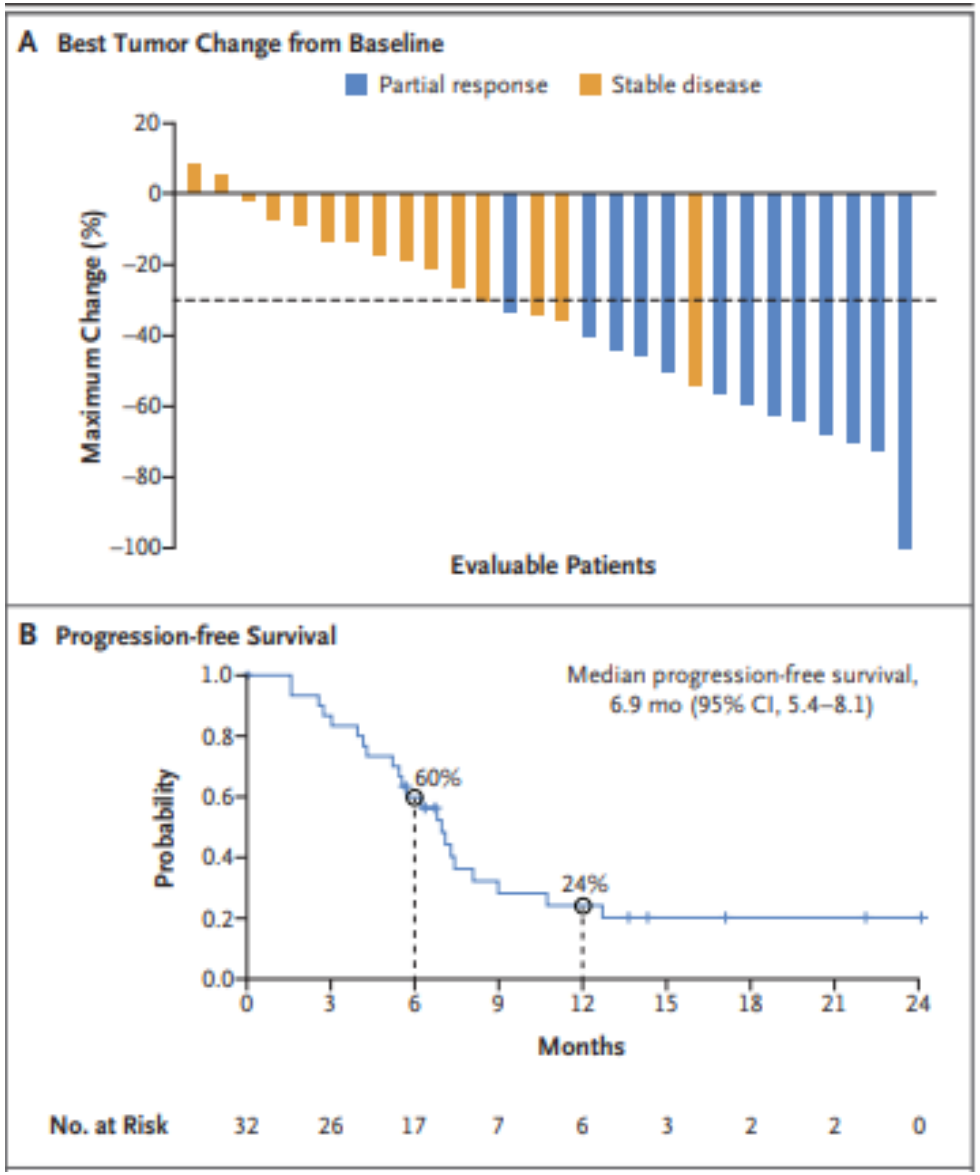
Hong DS et al. *N Engl J Med.* 2020;383:1207-1217.

KRAS G12C: Adagrasib with or without cetuximab

Monotherapy: RR 19%, mPFS 5.6 mo



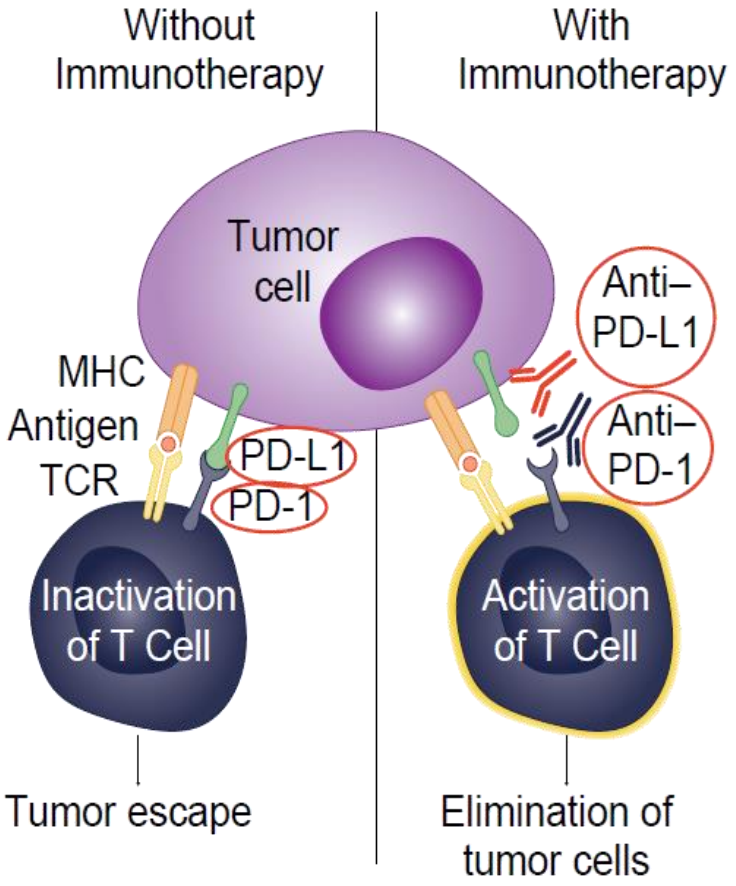
Combination: RR 46% mPFS 6.9 mo



Yaeger R., et al, NEJM 2022

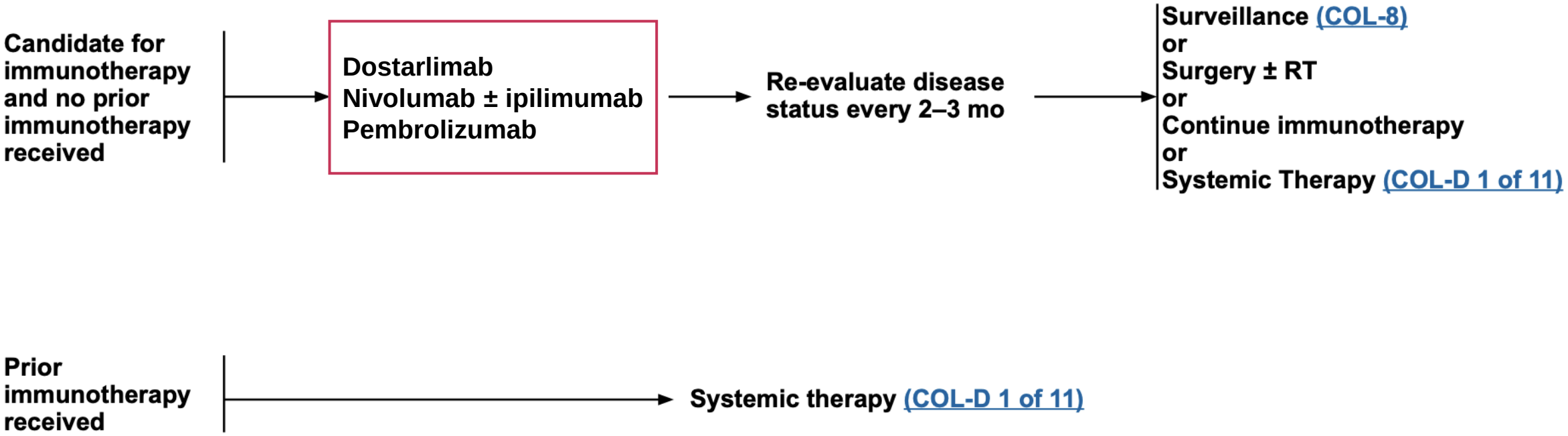
Immunotherapy for mismatch repair deficient/MSI-H tumors

T-Cell Inhibitory Signals: How immunotherapy works



- Immune checkpoint inhibitors work by blocking T-cell inhibitory signals—removing the brake on the immune system
- The cancer immunotherapy landscape is rapidly expanding; the benefit of immune checkpoint blockers is seen across different tumor types and treatment settings (as single agents and combinations)
- Predictive biomarkers can guide clinical decisions regarding the use of immunotherapies

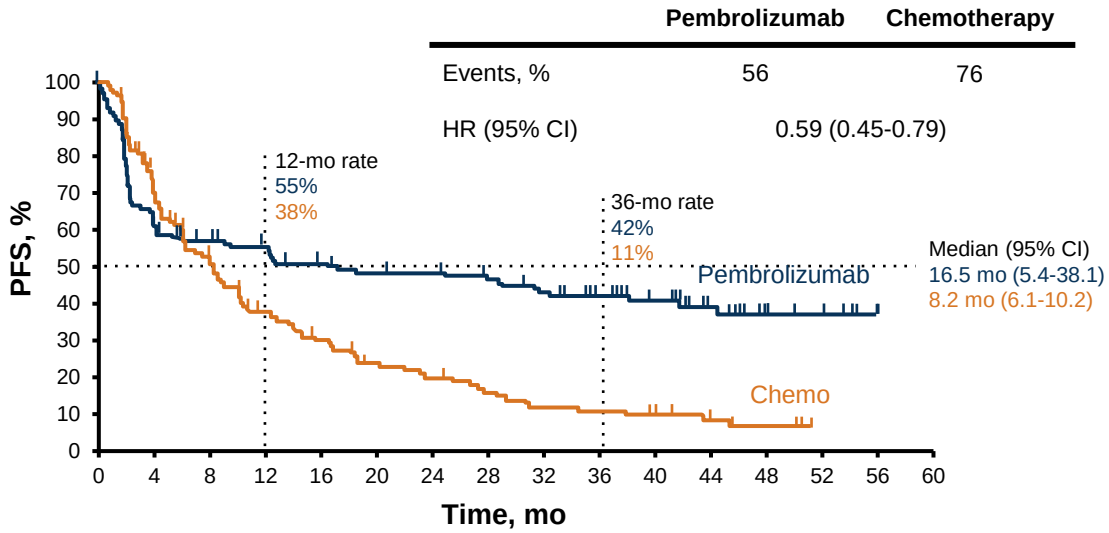
Any Line of Therapy for dMMR/MSI-H mCRC



1. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 5.2024. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

KEYNOTE-177: Pembrolizumab vs Investigator's Choice Chemotherapy[1]

Progression-Free Survival

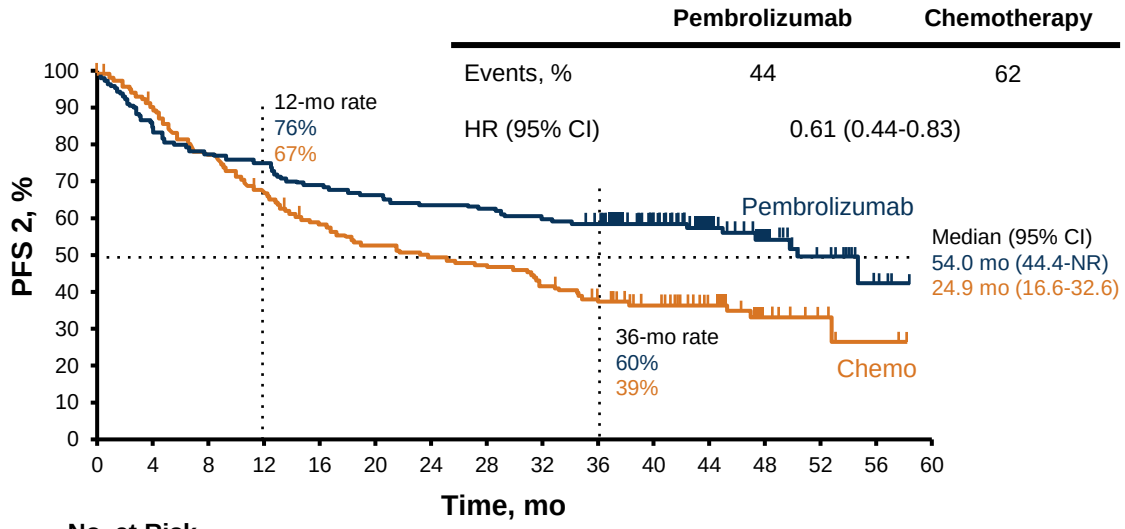


No. at Risk

Pembrolizumab	153	96	77	72	64	60	59	55	50	42	28	16	7	5	0	0
Chemotherapy	154	101	69	45	35	25	21	16	12	11	8	5	3	0	0	0

Progression-Free Survival 2

Time from randomization to progression on next-line therapy or any-cause death



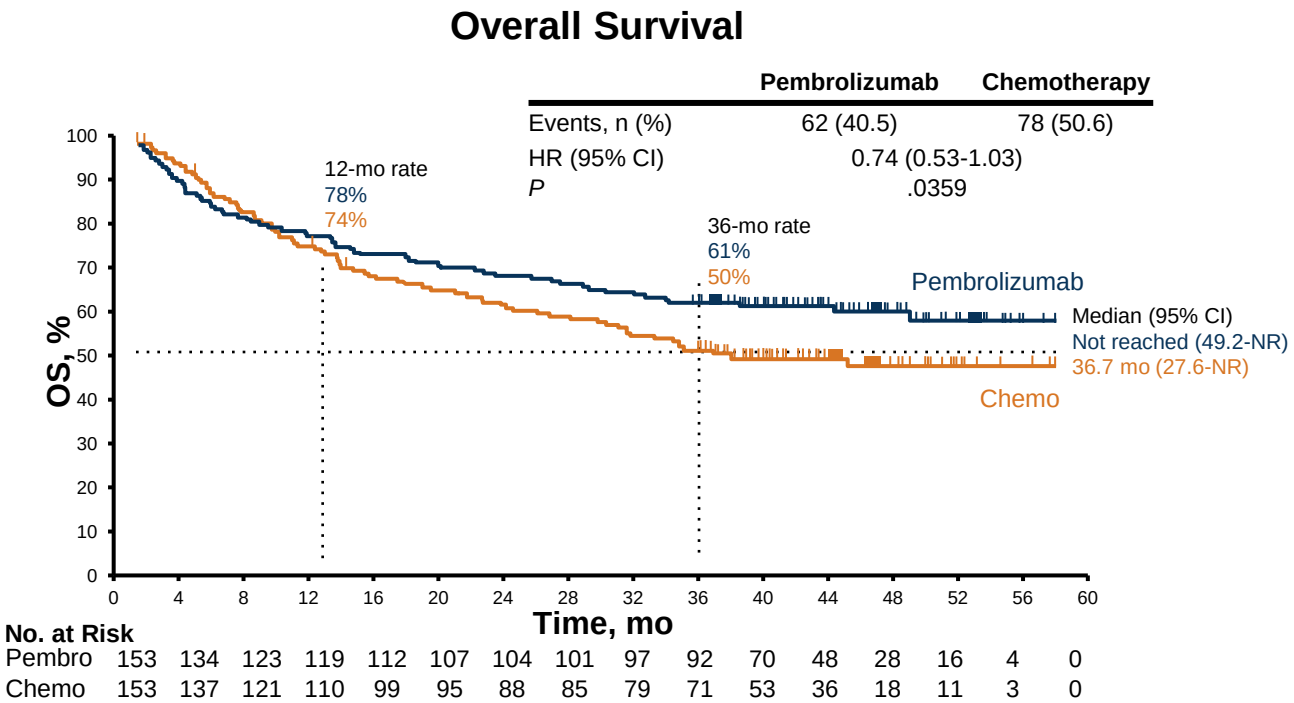
No. at Risk

Pembrolizumab	153	131	120	116	107	103	99	97	93	87	67	43	26	15	3	0
Chemotherapy	154	136	117	100	86	78	73	69	62	53	43	29	11	6	2	0

Pembrolizumab versus chemotherapy provided statistically superior PFS as first-line therapy for patients with MSI-H mCRC and met criteria for superiority in PFS at second interim analysis

1. Diaz L et al. *Lancet Oncology*, 2022;23(5): 659-670.

KEYNOTE-177: Final OS and Antitumor Response[1]



	Antitumor Response	
	Pembrolizumab (n = 153)	Chemotherapy (n = 154)
ORR, n (%)	69 (45.1)[a]	51 (33.1)
Best overall response, n (%)		
CR	20 (13.1)[b]	6 (3.9)
PR	49 (32)[c]	45 (29.2)
SD	30 (19.6)	65 (42.2)
DCR (CR + PR + SD)	99 (64.7)	116 (75.3)
PD	45 (29.4)	19 (12.3)
NE	3 (2)	2 (1.3)
No assessment	6 (3.9)	17 (11)
Median duration or response (range), mo	NR (2.3+ to 53.5+)	10.6 (2.8 to 48.3+)
≥24 mo response duration, %	83.5	33.6

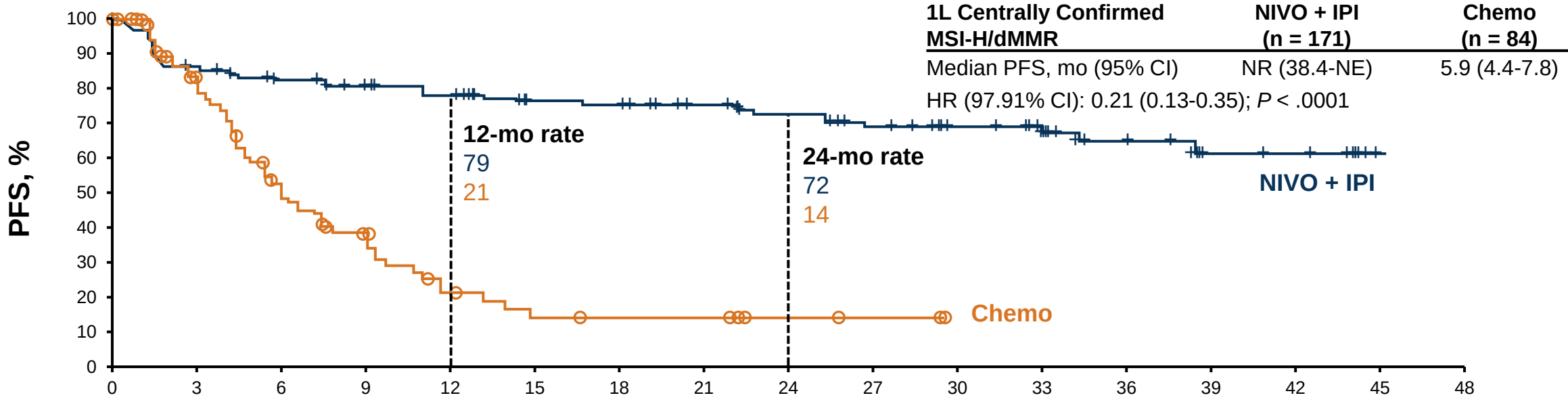
- Treatment with pembrolizumab versus chemotherapy is associated with a nonstatistically significant reduction in mortality
- HR for OS = 0.74 (*P* = .0359); pembrolizumab was not superior to chemotherapy for OS as 1-sided α > .0246

- High crossover rate (60%) from chemotherapy to anti–PD-1/PD-L1 therapies in second line
- Sensitivity analysis by the rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI, 0.42-1.04) and 0.77 (95% CI, 0.44-1.38)

1. Diaz L et al. *Lancet Oncology*, 2022;23(5): 659-670.

3 CheckMate -8HW: First-Line Nivolumab + Ipilimumab for dMMR/MSI-H mCRC[1]

PFS benefit with PD-1 + CTLA-4 was robust and consistent across the sensitivity analyses (HR = 0.32; 95% CI, 0.23-0.46)



1L Centrally Confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS, mo (95% CI)	NR (38.4-NE)	5.9 (4.4-7.8)
HR (97.91% CI): 0.21 (0.13-0.35); *P* < .0001		

No. at Risk

NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

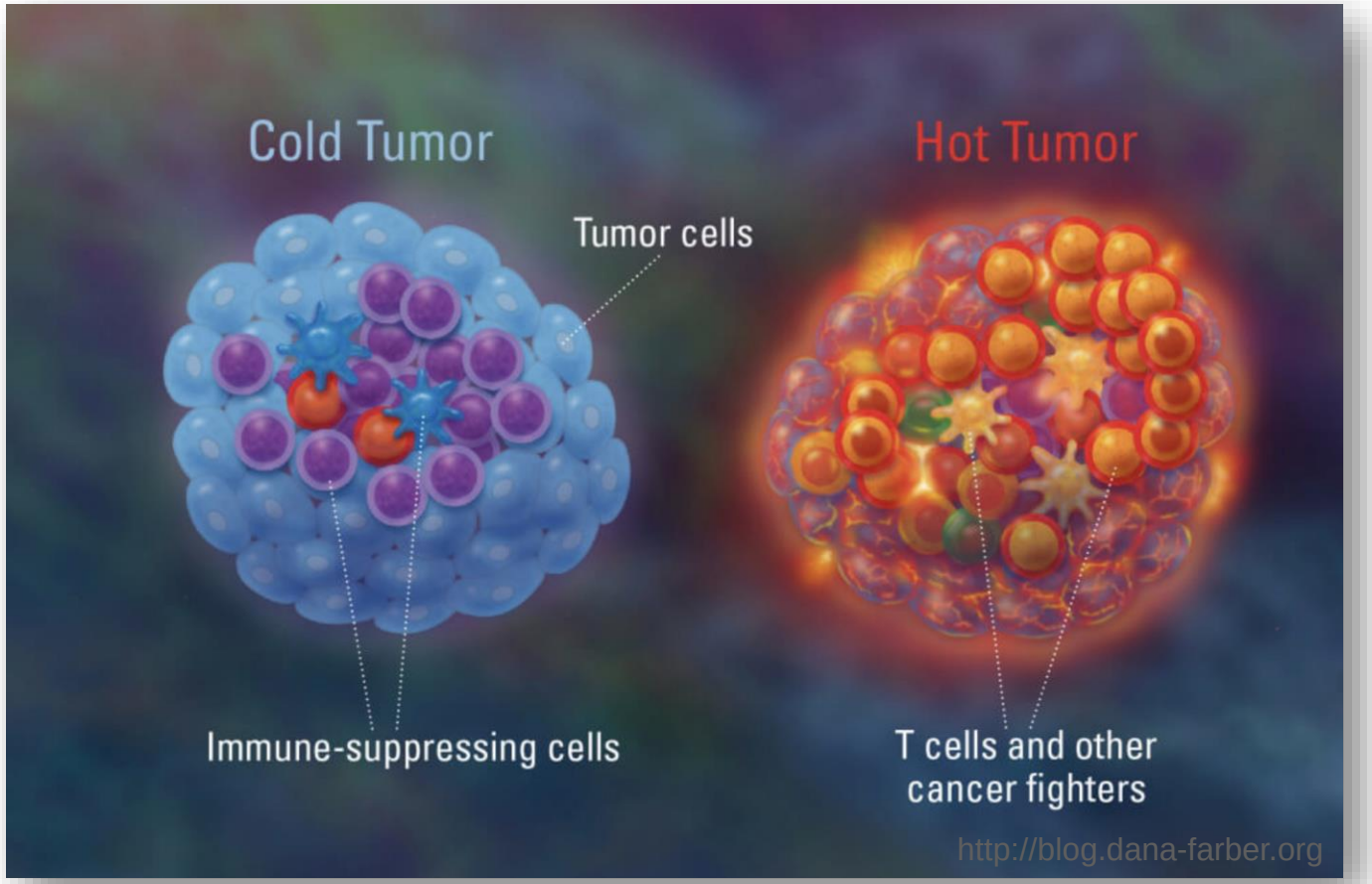
1. Andre T et al. ASCO GI 2024. Abstract LBA768.

Immunotherapy for pMMR/MSS:

Treatments on the horizon!

The challenge with MSS CRC and immunotherapy

MSS MSI-H

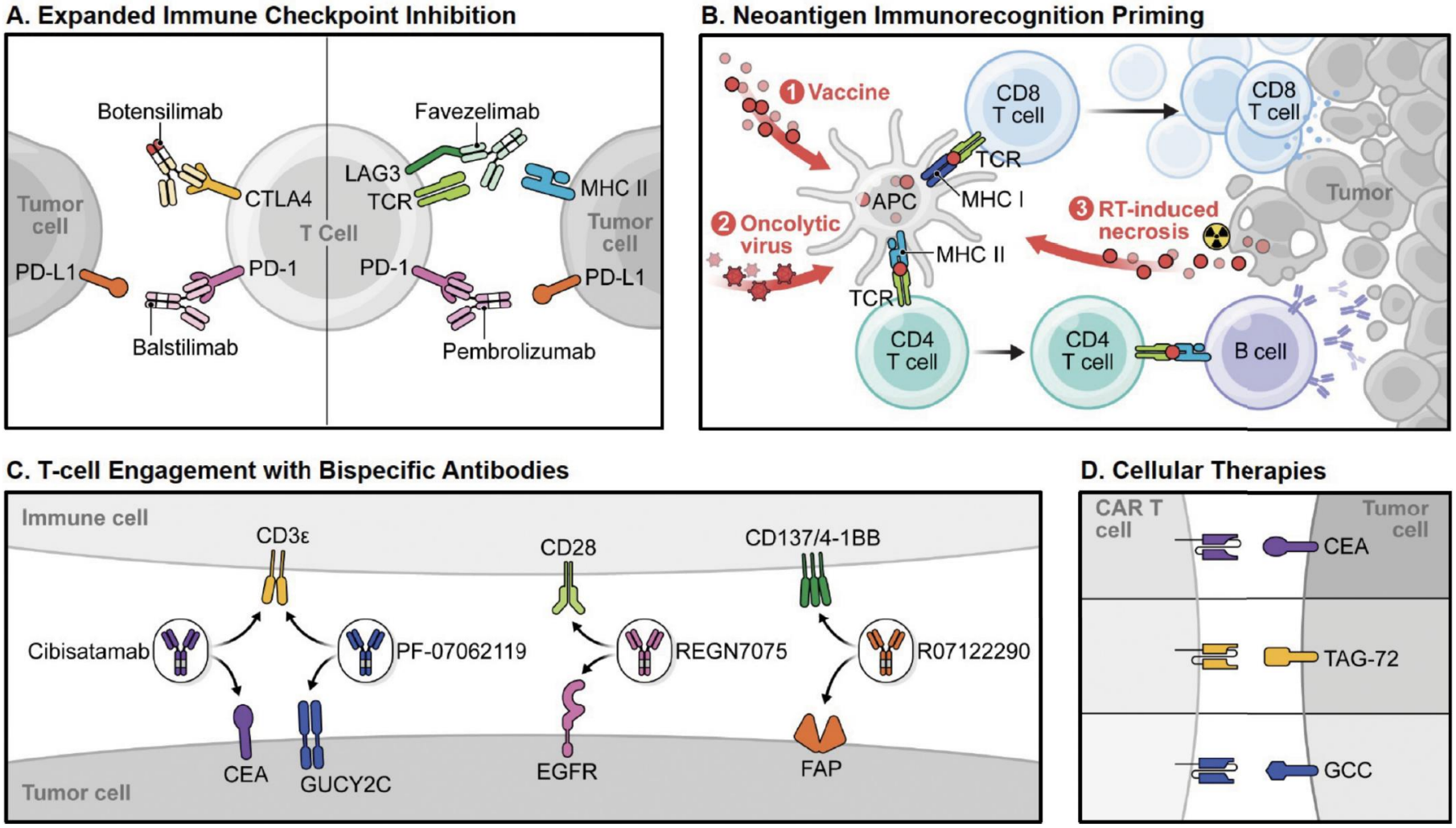


Immune checkpoint inhibition in MSS CRC: - negative studies

Drug	n	Response (n)	
BMS-936559 (PDL-1)	18	0	
Pembrolizumab	23	0	
Pembrolizumab	18	0	
Atezolizumab	87	1	
Durva + Treme	118	1	
Atezolizumab + Cobi	180	3	
	443	**5**	***RR = 1.1%***

Brahmer. NEJM. 2012, O'Neil. PLOS One. 2017, Le. NEJM. 2015, Eng. Lancet Oncology. 2019, Chen. JAMA Oncology. 2020

Strategies to increase tumor immunorecognition



Foote, Argiles, Rousseau, Segal. Clin Cancer Res. 2023

Phase 1 trial of botensilimab plus balstilimab: MSS CRC cohort

(IRB#22-069)

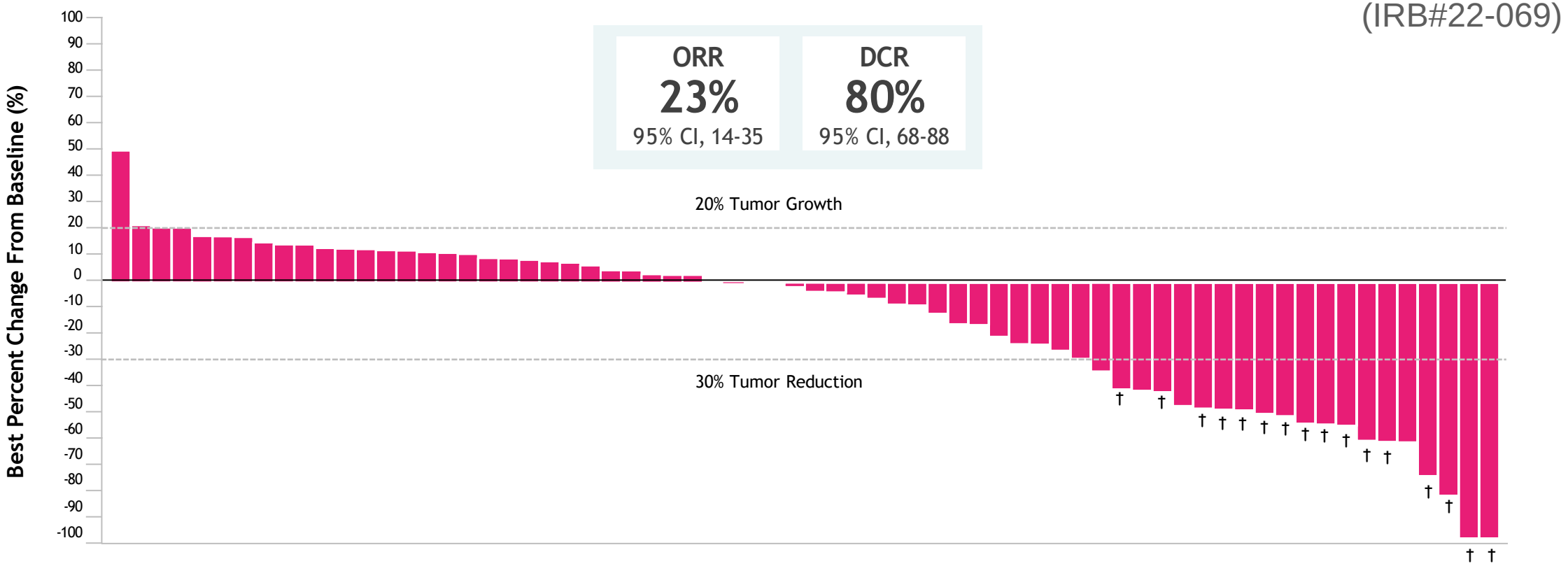
	All EE n=87*	No Active Liver Mets EE n=69†	Active Liver Mets EE n=18‡
Confirmed ORR, n % (95% CI)	18% (11–28)	23% (14–35)	0% (0–19)
BOR, n (%)			
CR	1 (1)	1 (1)	0
PR	15 (17)	15 (22)	0
SD	45 (52)	39 (57)	6 (33)
PD	26 (30)	14 (20)	12 (67)
DCR (CR + PR + SD), % (95% CI)	70% (59–80)	80% (68–88)	33% (13–59)
12-month OS, % (95% CI)	62% (49–73)	74% (59–84)	30% (11–52)
Ongoing responses§		11/16 (69%)	

Bullock. GI ESMO. 2023

Deep Objective Responses

No Active Liver Metastases (Efficacy Evaluable, n=69*)

(IRB#22-069)

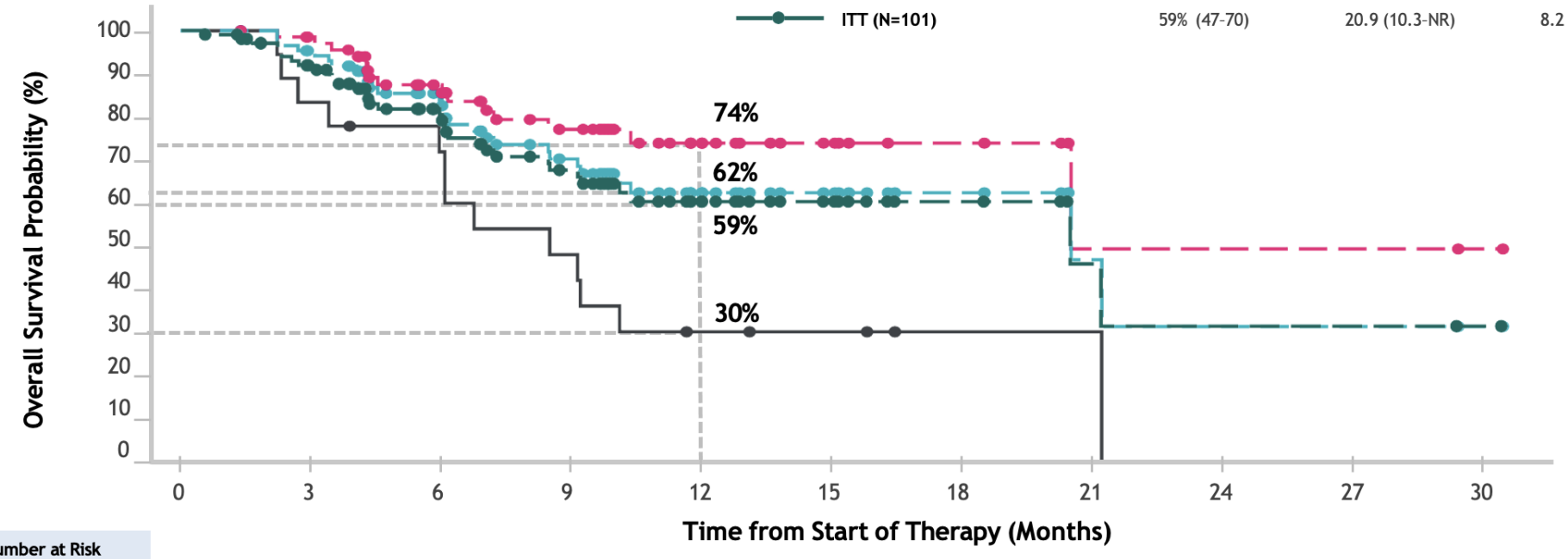


Bullock. GI ESMO. 2023

Overall survival

	12-month OS, % (95% CI)	Median OS, Months (95% CI)	Median F/U, Months (Range)
No Active Liver Mets EE (n=69)	74% (59-84)	20.9 (20.9-NR)	9.8 (1.4-36.5)
Active Liver Mets EE (n=18)	30% (11-52)	8.7 (6.1-NR)	7.8 (2.3-21.7)
All EE (n=87)	62% (49-73)	20.9 (10.6-NR)	9.3 (1.4-36.5)
ITT (N=101)	59% (47-70)	20.9 (10.3-NR)	8.2 (0.5-36.5)

(IRB#22-069)



Number at Risk											
No Active Liver Mets EE	69	65	47	33	18	11	6	2	2	2	2
Active Liver Mets EE	18	15	13	8	4	3	1	1	0	0	0
All EE	87	80	60	41	22	14	7	3	2	2	2
ITT	101	85	60	41	22	14	7	3	2	2	2

Data cutoff: 26-MAY-2023

Bullock. GI ESMO. 2023

Conclusions:

Treatment of mCRC includes molecular targeted therapy:

- **-MSI**
- **-RAS**
- **-BRAF**
- **-HER2**

Testing should be done as early as possible

Immunotherapy is an approved treatment for MSI mCRC

Clinical trials of immunotherapy for MSS mCRC are ongoing!

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Thank You