Colorectal Cancer Genomic Profiling, Tumor- Informed or Tumor Naïve.

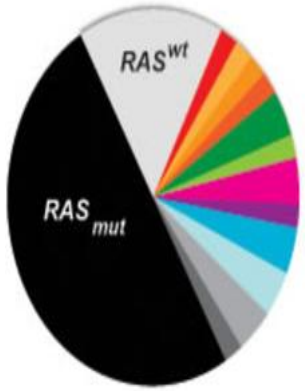
Primetime and Utility?

- ***Ahmed Zakari, MD***
- *Department Chair, Hematology AdventHealth Orlando*
- *Clinical Director GI Cancer Program at AHCI*
- *Associate Professor, School of Medicine University of Central Florida*

Colorectal Cancer Genomic Profile

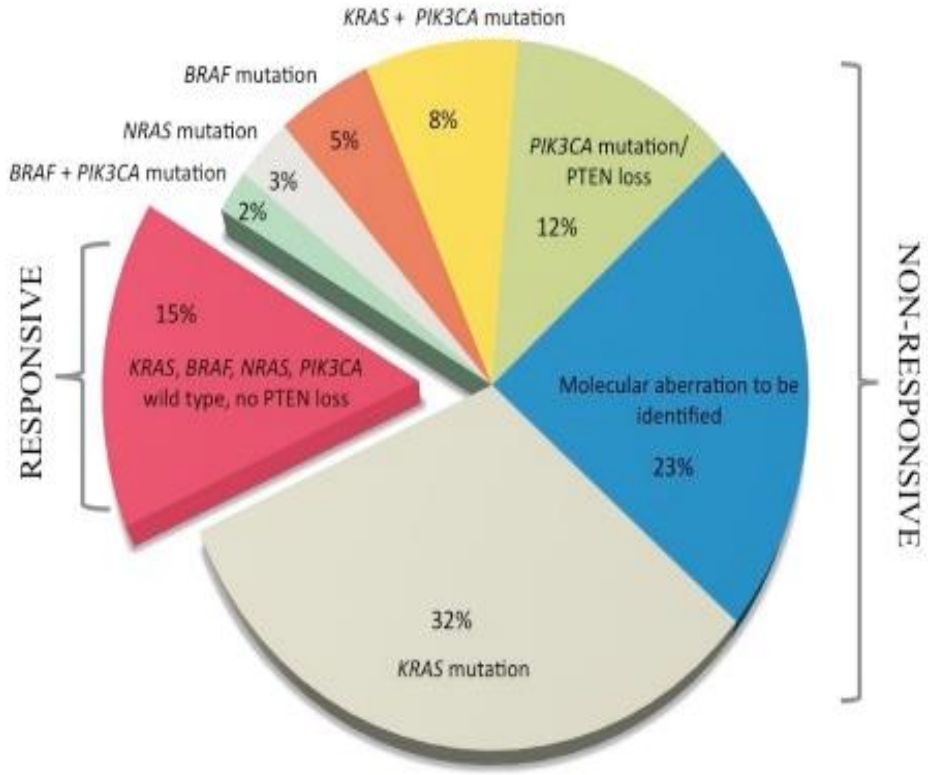
- *Colorectal cancer (CRC) is a heterogeneous disease caused by multistep genetic alterations under the influence of genomic instability:*
  - *chromosomal instability, microsatellite instability, hypermutated-single nucleotide variants,*
  - *Genome stable-induced transformation in the colonic epithelium result in evolving process to metastatic tumors*
- *Identifying molecular subtypes , genetic alterations driving CRC oncogenesis help establishing Biomarker -Guided Therapy*
- *Guidelines recommend testing metastatic CRC for MMR.. / Full genomic Profiling using NGS as standard initial work up*
- *Validated and sensitive ctDNA assays can be used to genotype advanced cancers and select patients for targeted therapies.*
- *Initial genotyping with ctDNA assays should be considered when rapid results are needed, and tissue is unavailable.*

Genomic Profiling of CRC

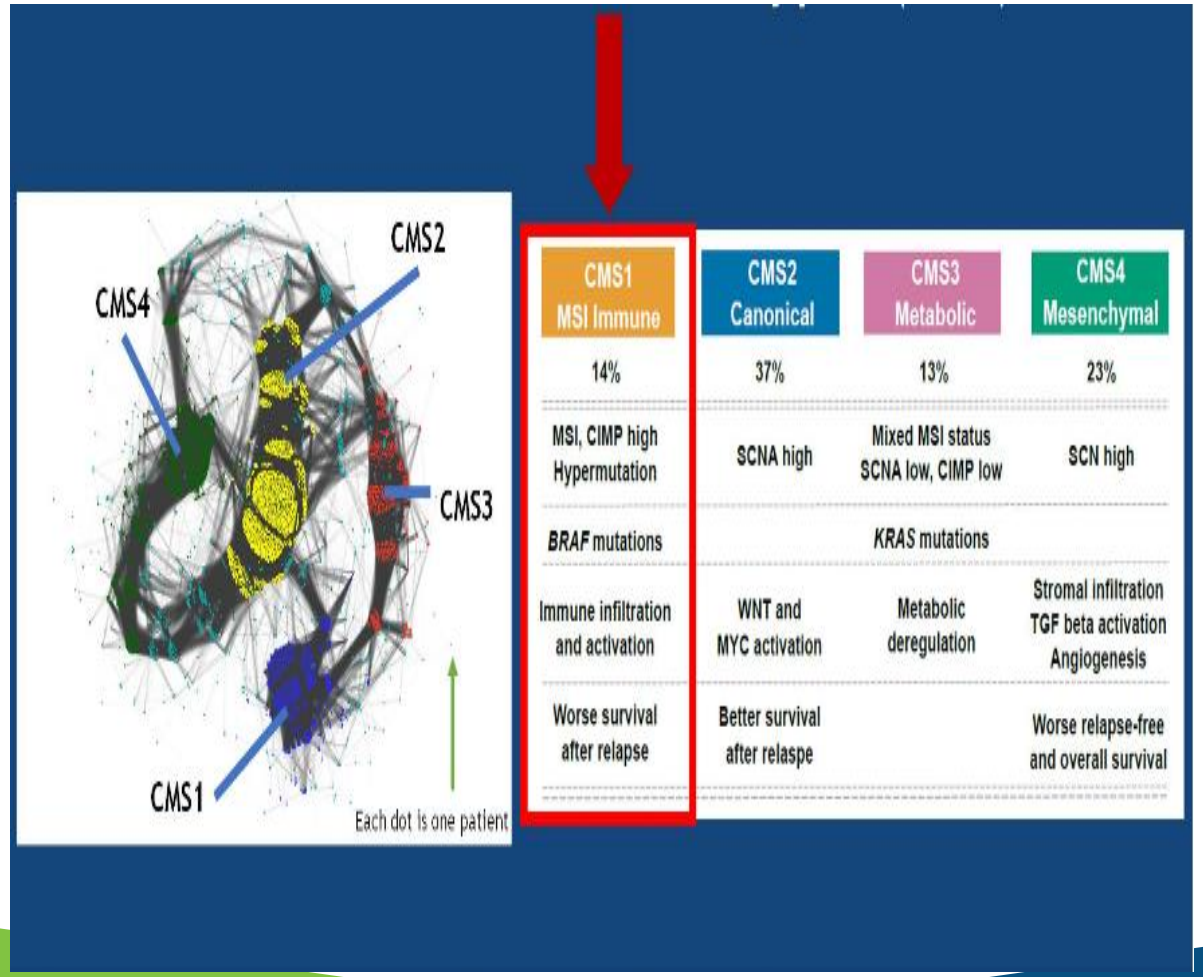


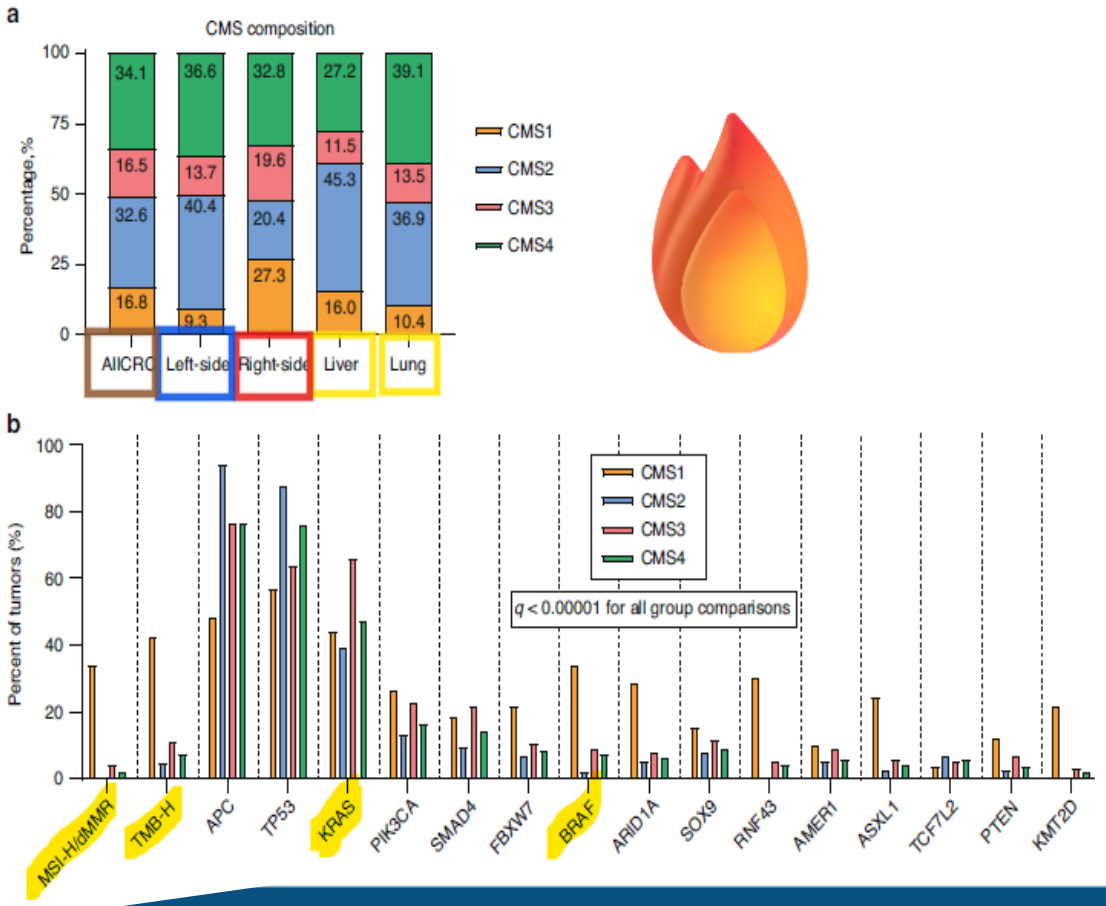
Genes	5' Fusion Partner (n)	Mutations (%)
RET	(0)	84/1,489 (5.7%)
ALK	*C2orf44; EML4* (3)	118/1279 (9.2%)
ROS	*SLC34A2* (1)	93/1243 (7.5%)
NTRK1	*TPM3* (2)	46/1152 (4.0%)
NTRK3	*ETV6* (1)	73/1374 (5.3%)
RSPO2	*EIF3E* (2)	31/1063 (2.9%)
RSPO3	*PTPRK* (5)	14/1063 (1.3%)
TCF7L2	*VTI1A* (4)	101/1089 (9.3%)
ERBB2	(0)	85/2,040 (4.2%)
NRG1	(0)	58/1,064 (5.5%)
PIK3CA	(0)	1,740/12,502(13.9%)
PTCH1	(0)	173/1147 (15.1%)
BRAF	(0)	9,389/74,924 (12.5%)
BCL11B	(0)	55/1089 (5.1%)
KRAS	(0)	18,378/53,364 (34.4%)

Colorectal Cancer Genomic Protocol



Consensus Molecular Subtyping in CRC





National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Colon Cancer

NCCN Guidelines Index
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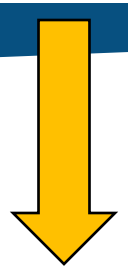
Discussion

CLINICAL PRESENTATION[a] | **WORKUP[j]**



Suspected or proven metastatic adenocarcinoma →

- Colonoscopy
- C/A/P CT[b]
- CBC, chemistry profile, CEA
- Molecular testing, including[l,m]:
  - *RAS* and *BRAF* mutations; HER2 amplifications; MMR or MSI status (if not previously done)
  - Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*.
- Biopsy, if clinically indicated
- Consider FDG-PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[b]
  - Consider MRI of liver for liver metastases that are potentially resectable[b]
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases

→ pMMR/MSS → COL-5

→ dMMR/MSI-H or *POLE/POLD1* mutation → COL-14

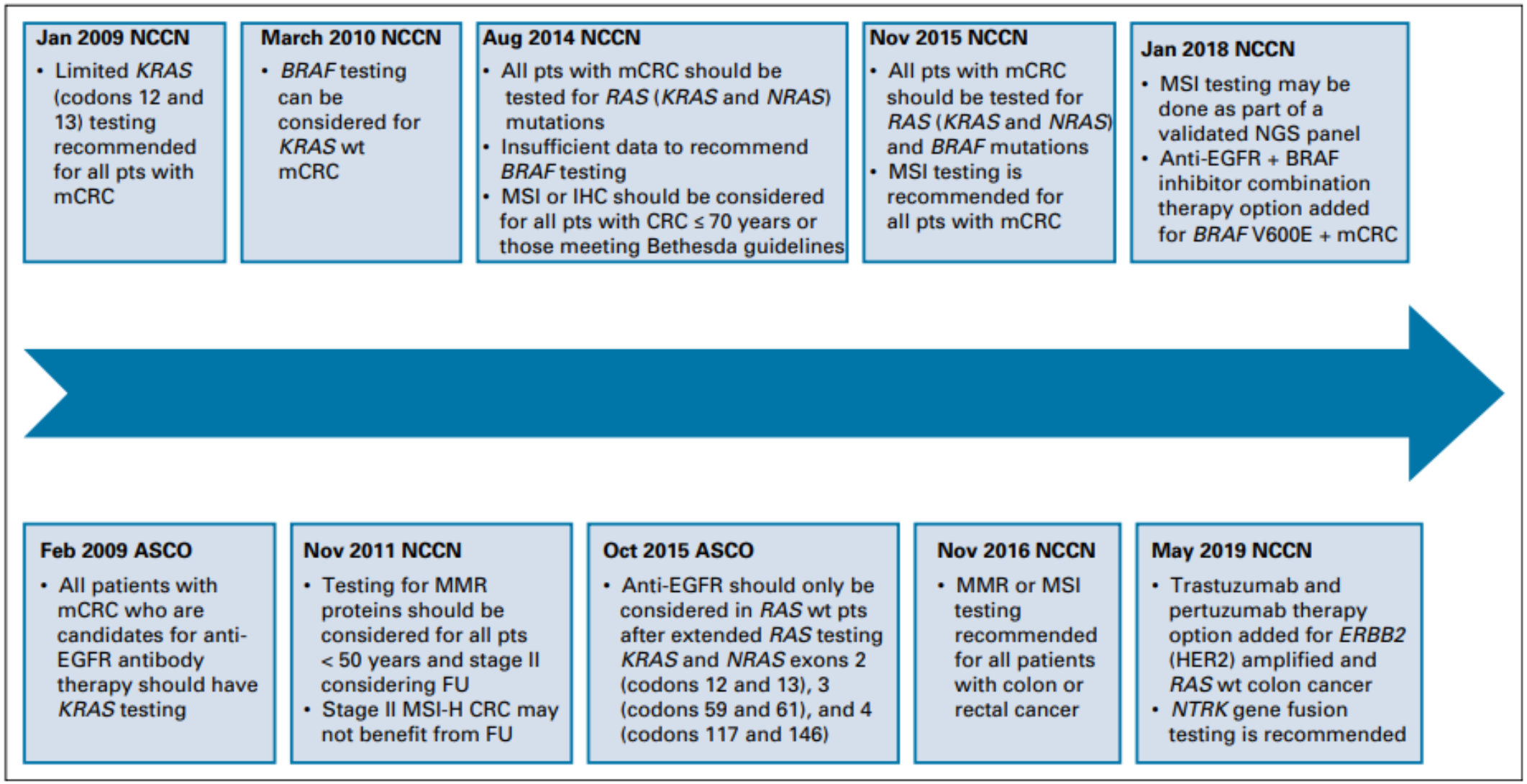
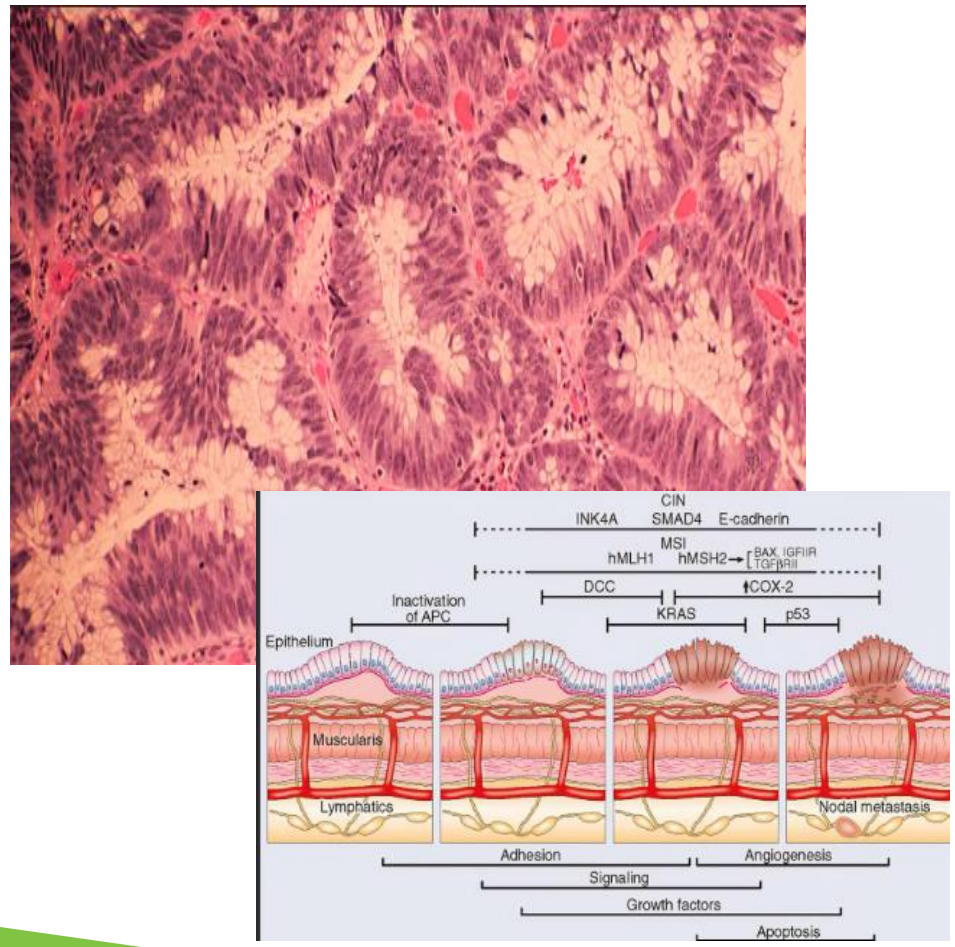


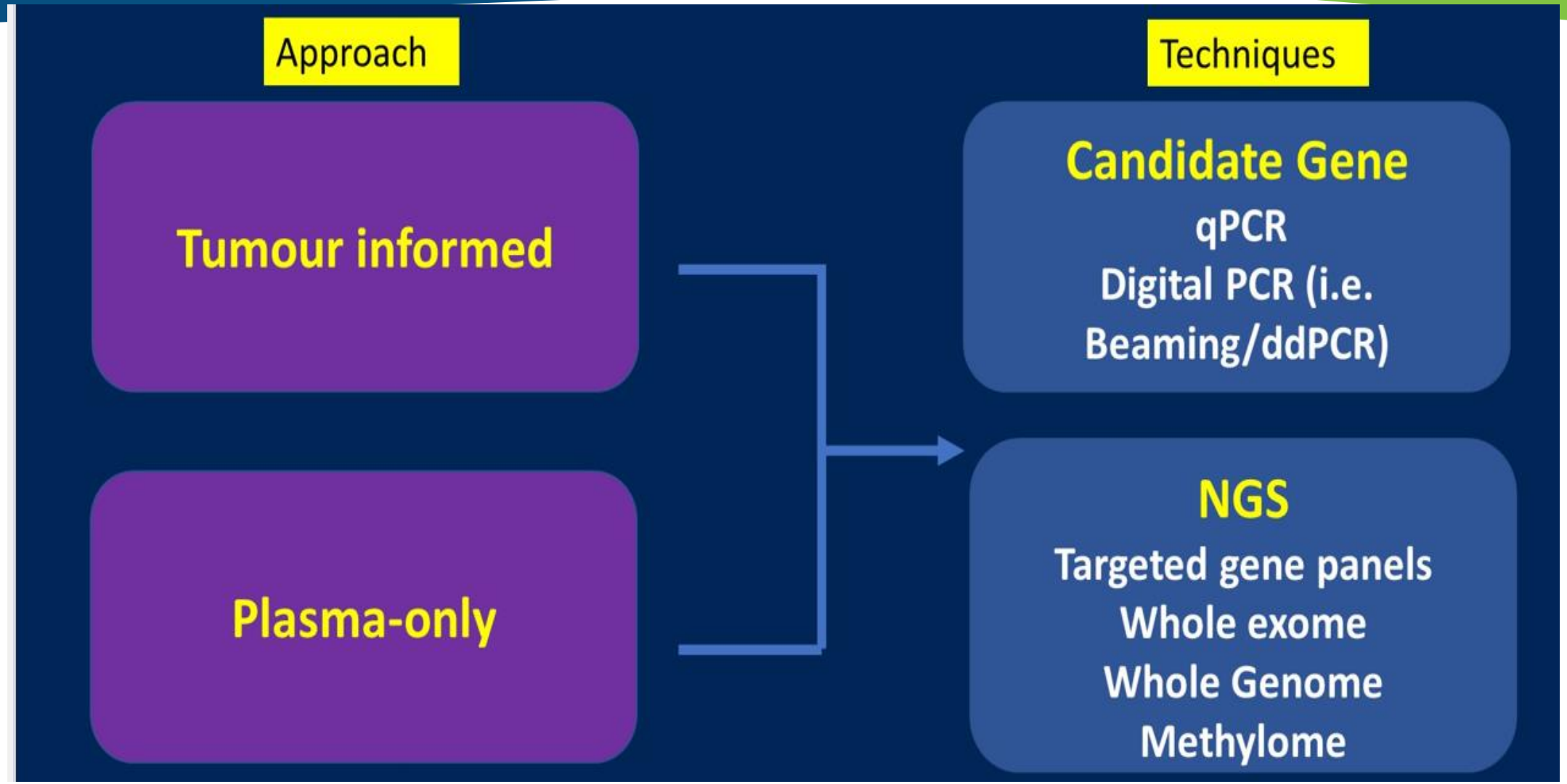
FIG 1. Evolution of guidelines for molecular testing in metastatic colorectal cancer (mCRC). FU, fluorouracil; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; pts, patients; wt, wild type.

Colorectal Cancer Tissue Testing

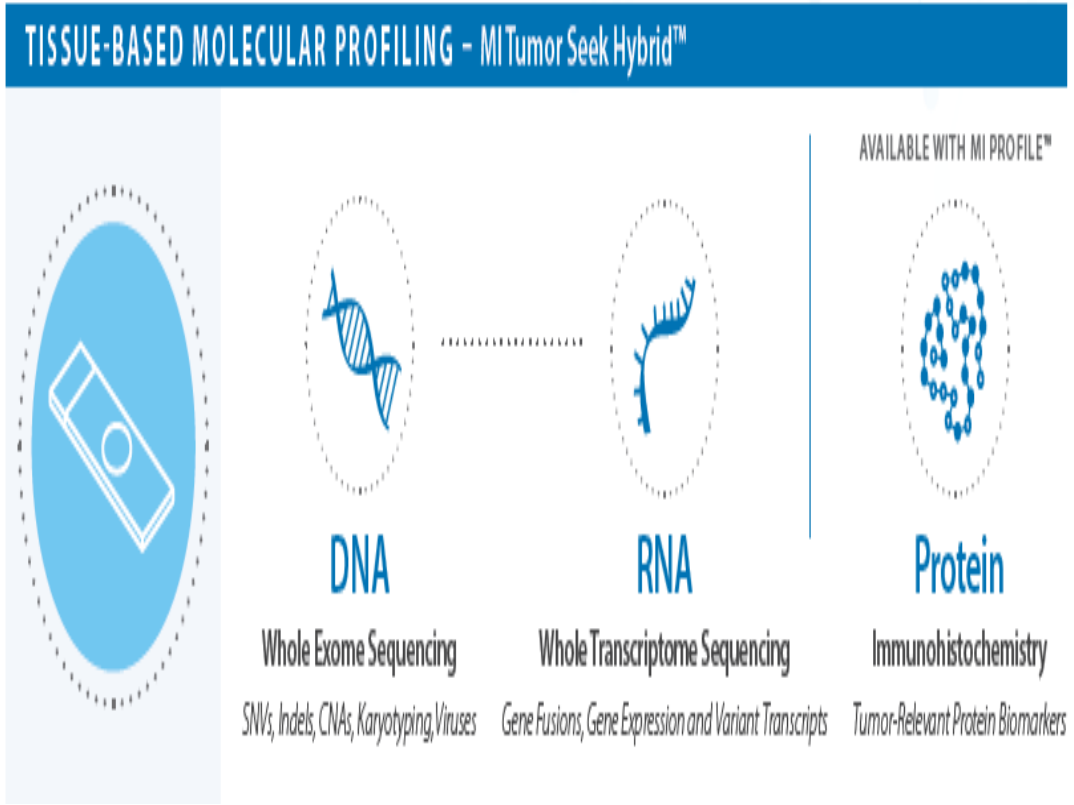


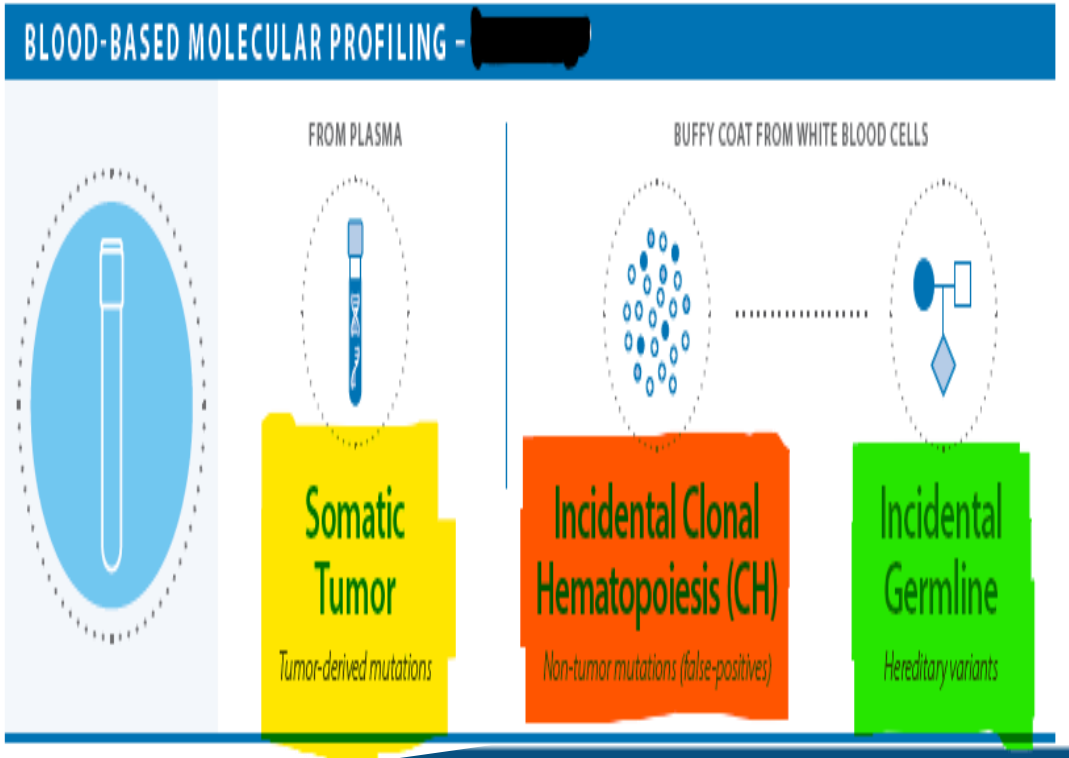
- *MMR*
- *RAS : Kras, Nras, Hras.*
- *BRAF*
- *HEUR2 Neu amplification*
- *PI3K*
- *RET Fusion*
- *NTRK Fusion*

Tumor-Informed Versus Plasma-Only Liquid Biopsy Assay



Comprehensive Molecular Profiling
Tumor Tissue or Whole Blood





Clinical Utility of Liquid Biopsies in Colorectal Cancer

- *Screening and Early Diagnosis*
- *Circulating Tumor Cells (CTC) and Circulating Endothelial Cell Clusters (ECC)*
- *Circulating Tumor DNA (ctDNA)*
- *MicroRNAs (miRNAs)*
- *Long Non-Coding RNAs (lncRNAs)*

Clinical Applications of ct-DNA/ Genomic Profiling Tumor Informed Vs Naïve

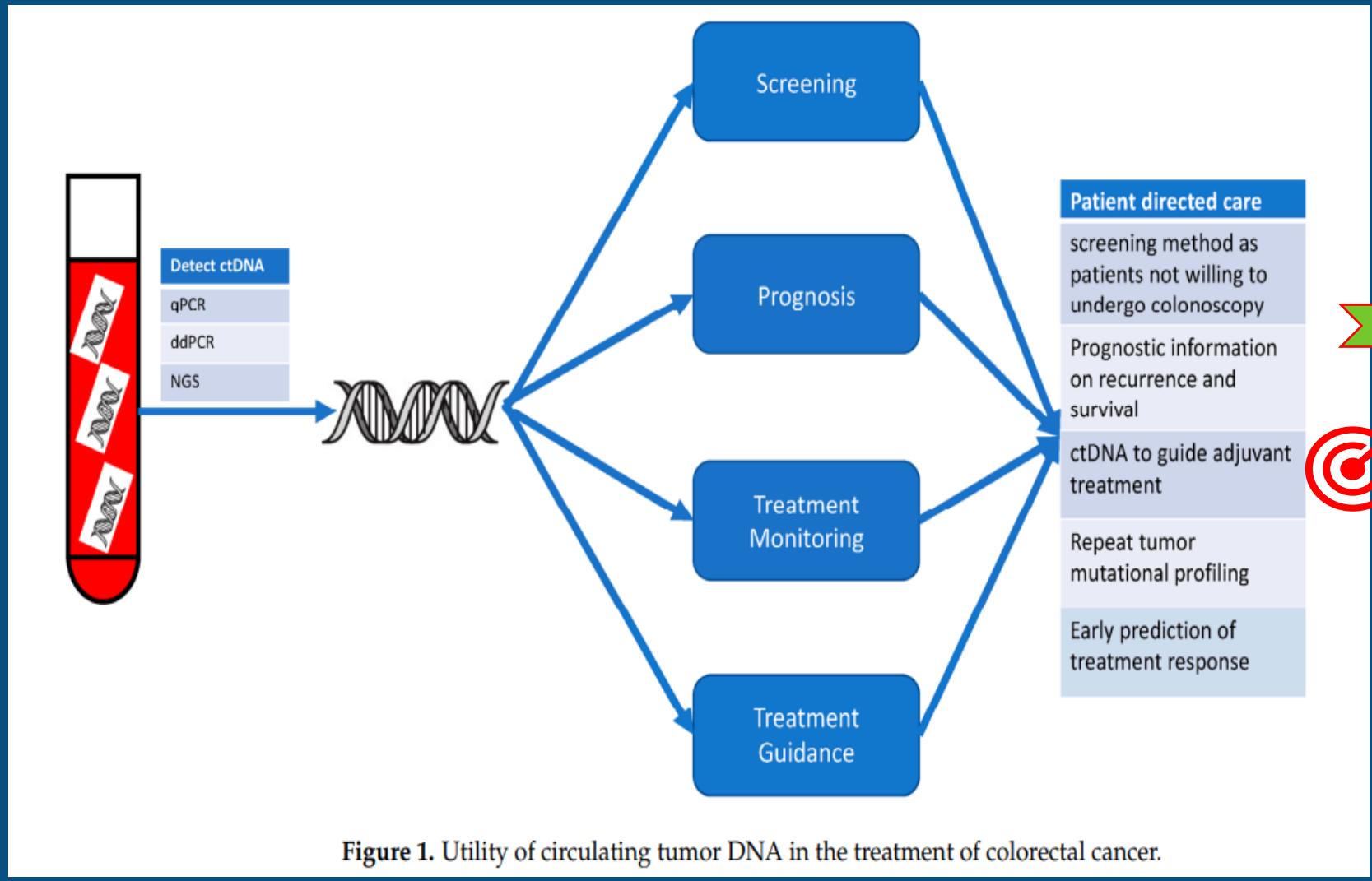
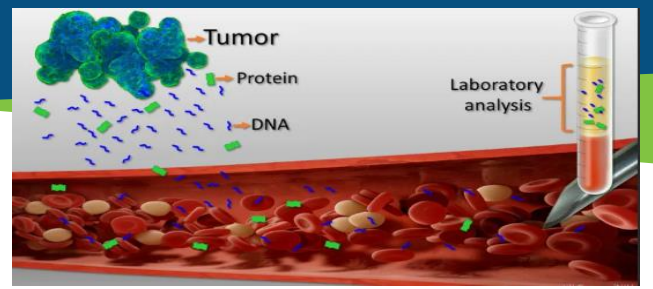


Figure 1. Utility of circulating tumor DNA in the treatment of colorectal cancer.

- MRD refers to persistent cancer after treatment that cannot be detected with current imaging tools (occult metastatic disease)[1]
- ctDNA dynamics can be used to assess disease burden in real-time
- Helps to inform treatment decisions along the continuum of care

Clinical Utility of Liquid Biopsy (Tumor Naïve)

CRC



- *Liquid biopsy is a minimally invasive, cost efficient and repeatable technique*
- *Blood-based liquid biopsies are useful :*
  - *Monitoring disease progression*
  - *Treatment efficacy, Prognosis*
  - *Acquired resistance to chemotherapy in CRC.*
  - *Clonal Evolution*
- *The future will be to choose the most appropriate therapy based on real-time genetic information through a liquid biopsy→ Personalized medicine.*

Challenges and Limitations of Liquid Biopsy/ Tumor Naïve

- *Low amounts of ctDNA in samples*
- *Lack of pre-analytical and analytical consensus, clinical validation, regulatory endorsement and cost effectiveness*
- *Next-generation sequencing (NGS)-based technologies reduced the error rate and enhanced sensitivity in ctDNA detection*
- *NGS included detection of genomic rearrangements:*
  - *new mutations or alterations in genes*
  - *The possibility of evaluation of response to treatment*

Challenges and Limitations of Liquid Biopsy/Tumor Naïve

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OPEN ACCESS | CASE REPORTS | January 18, 2022

Tumor-Informed Versus Plasma-Only Liquid Biopsy Assay in a Patient With Multiple Primary Malignancies

Author: Pashtoon Murtaza Kasi, MD, MS
AUTHORS INFO & AFFILIATIONS

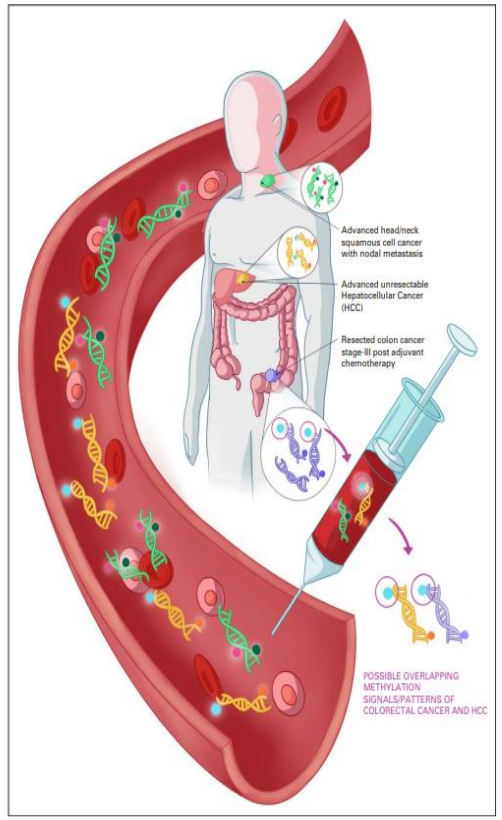
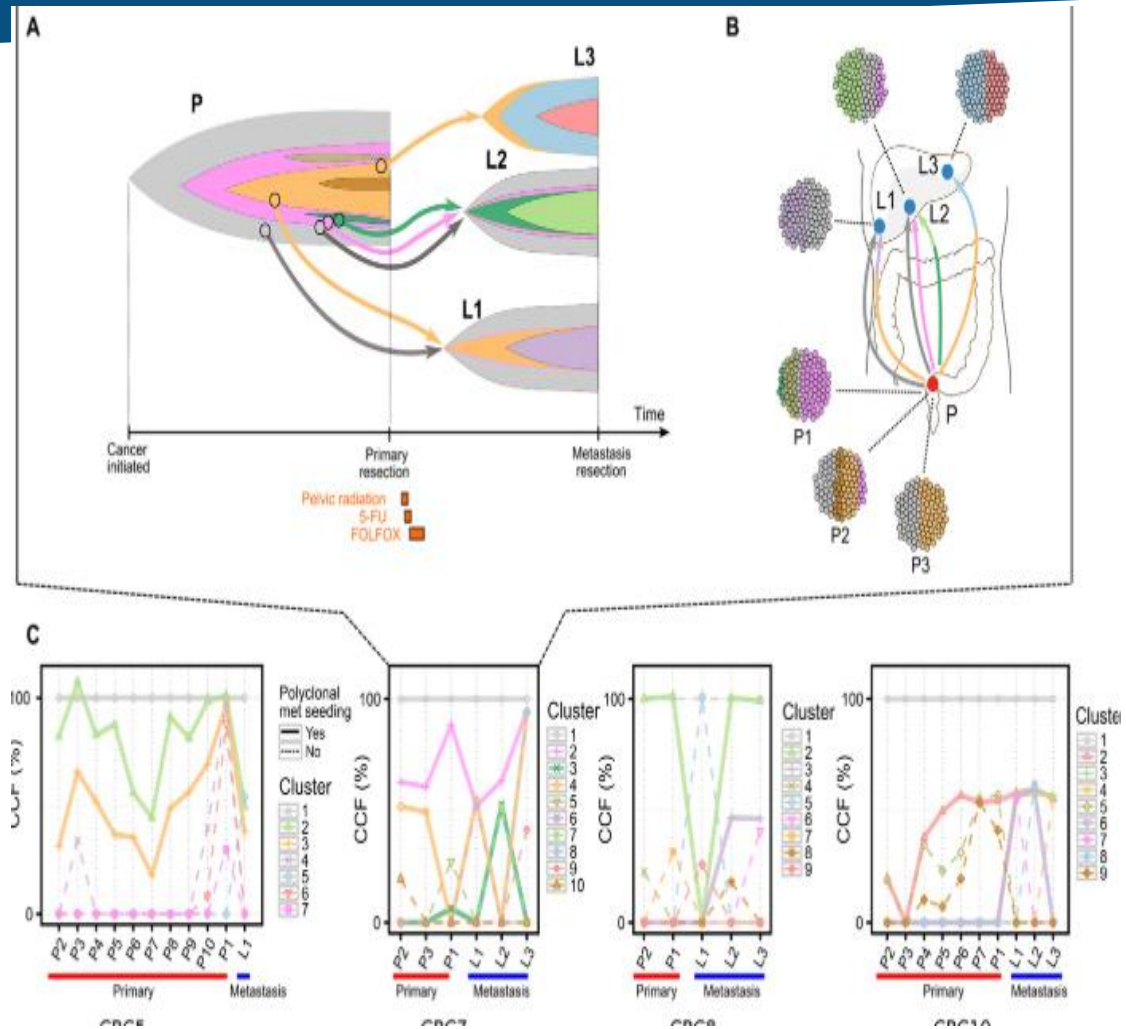


FIG 1. Possible overlapping methylation/epigenomic markers from colorectal cancer and hepatocellular cancer on liquid biopsies in a patient with multiple primary malignancies.

Benefit of Liquid Biopsy identifying clonal evolution of metastatic CRC



- *Hepatic metastases from CRC may arise from polyclonal seeding from the primary tumor.*
- *These data support the initiation of metastases by two distinct clones from the primary P, in L1 and L2 of this patient.*
  - *Radiation and chemotherapy → do not alter the general scheme of seeding models*
- (Dang et al., Sci. Adv. 2020)

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

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ORIGINAL ARTICLE · Volume 35, Issue 12, P1105-1115, December 2024

Comprehensive genomic profiling by liquid biopsy captures tumor heterogeneity and identifies cancer vulnerabilities in patients with *RAS/BRAF*^{V600E} wild-type metastatic colorectal cancer in the CAPRI 2-GOIM trial

D. Ciardiello [1,‡] · L. Boscolo Bielo [2,3,‡] · S. Napolitano [4] · ... · F. Ciardiello [4,‡] · G. Martini [4,‡] on behalf of the CAPRI-2 GOIM study group [†]... Show more

Conclusion

Baseline liquid biopsy-based CGP is feasible, has high concordance with tumor tissue-based CGP, could better recapitulate tumor heterogeneity, and is clinically informative by identifying additional actionable genomic alterations in approximately half of *RAS/BRAF*^{V600E} WT mCRC patients.

What is the Optimum Timing for Molecular Profiling/NGS for CRC ??

- *Early Stage CRC:*
  - *MMR status*
  - *Do we need Full NGS ??*
    - *Prognostic Indicators: Braf?*
- *Metastatic CRC*
  - *At Presentation: Anti-VGF Vs Anti-EGFR based Combination*
    - *Tissue Testing for NGS*
    - *Plasma -Liquid Biopsy/ Tumor Naïve : Should it be standard??*
  - *At Progression: Molecular Directed Rx*
    - *Repeat Tissue Biopsy from the metastatic sites*
    - *Liquid Biopsy/ NGS*

Treatment Paradigm, Biomarker Directed

Previous oxaliplatin-based therapy without irinotecan	Previous therapy with oxaliplatin and irinotecan	Biomarker-directed therapy
• FOLFIRI[i] or irinotecan[i] • FOLFIRI[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFIRI[i] + (cetuximab or panitumumab)[f,s] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[h]: ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ▸ Fruquintinib ▸ Regorafenib ▸ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ▸ Encorafenib + (cetuximab or panitumumab) • HER2-amplified and *RAS* and *BRAF* WT[f] ▸ (Trastuzumab[l] + [pertuzumab or lapatinib or tucatinib])[m] • HER2-amplified (IHC 3+) ▸ Fam-trastuzumab deruxtecan-nxki[u] • *KRAS* G12C mutation positive[f] ▸ (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ▸ Entrectinib ▸ Larotrectinib ▸ Repotrectinib[w] • *RET* gene fusion-positive ▸ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFOX[d] + (cetuximab or panitumumab)[f] ▸ CAPEOX[d] + (cetuximab or panitumumab)[f] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[i] or irinotecan[i] • (FOLFIRI or irinotecan)[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,k] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ▸ FOLFIRI[h] + (cetuximab or panitumumab)[f,s] ▸ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	dMMR/MSI-H or *POLE/POLD1* mutation Any line of therapy Candidate for immunotherapy and no prior immunotherapy received → Checkpoint inhibitor immunotherapy[x,y,z]

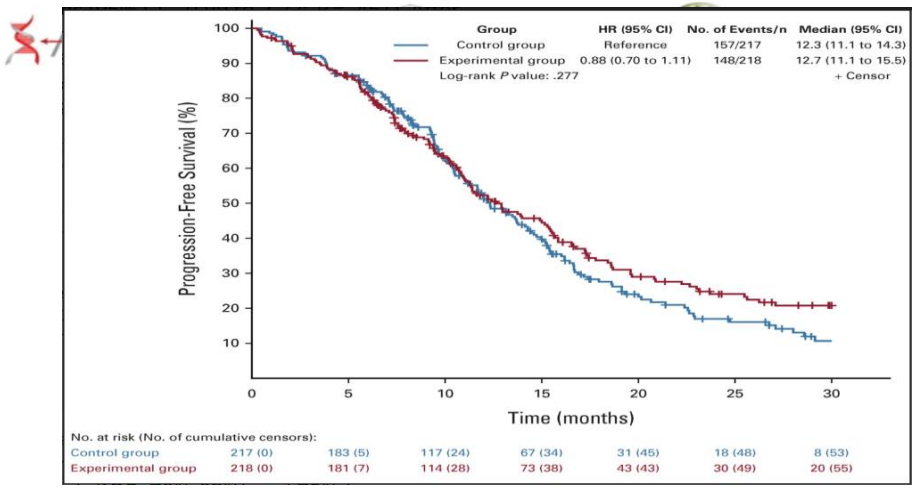
First Line therapy for Left sided CRC
Ras - Directed Rx

2022 ASCO Annual Meeting

Chicago, 6th June 2022

Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO.

Cremolini C, Rossini D, Lonardi S, Antoniotti C, Pietrantonio F, Marmorino F, Antonuzzo L, Boccaccino A, Randon G, Giommoni E, Pozzo C, Moretto R, De Grandis MC, Viola MG, Passardi A, Buonadonna A, Formica V, Aprile G, Boni L, Masi G
on behalf of the GONO Investigators



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Meeting Abstract: 2022 ASCO Annual Meeting II

FREE ACCESS | Gastrointestinal Cancer—Colorectal and Anal | June 08, 2022

Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial.

Authors: Takayuki Yoshino, Jun Watanabe, Kohei Shitara, Hirofumi Yasui, Hisatsugu Ohori, Manabu Shiozawa, Kentaro Yamazaki, ... SHOW ALL ..., and Kei

Biomarker Directed Therapy: CRC Genomic Profiling NGS

THE LANCET
Oncology

Trastuzumab deruxtecan in patients with HER2-positive advanced colorectal cancer (DESTINY-CRC02): primary results from a multicentre, randomised, phase 2 trial

Kanwal Raghav, MD [a,*] · Salvatore Siena, MD [b,c,*] · Atsuo Takashima, MD [d] · Takeshi Kato, MD [e] · Marc Van den Eynde, MD [f] · Filippo Pietrantonio, MD [g] · et al. Show more

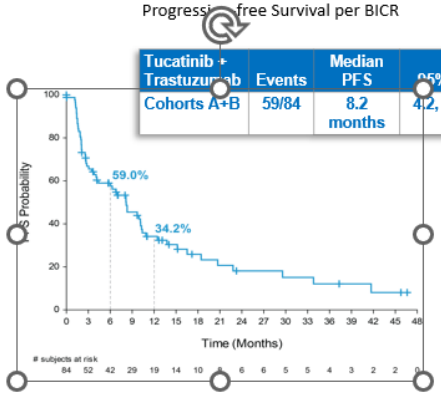
Affiliations & Notes ⌄ Article Info ⌄ Linked Articles (1) ⌄

Primary analysis of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

John H. Strickler, Andrea Cercek, Salvatore Siena, Thierry Andre, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew Scott Paulson, Joleen M. Hubbard, Andrew L. Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon Murtaza Kasi, Heinz-Josef Lenz, Kristen Ciombor, Elena Elez, David L. Bajor, Michael Stecher, Wentao Feng, Tanios S. Bekaii-Saab

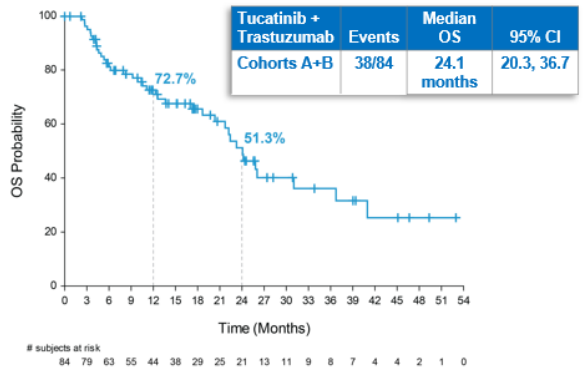
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

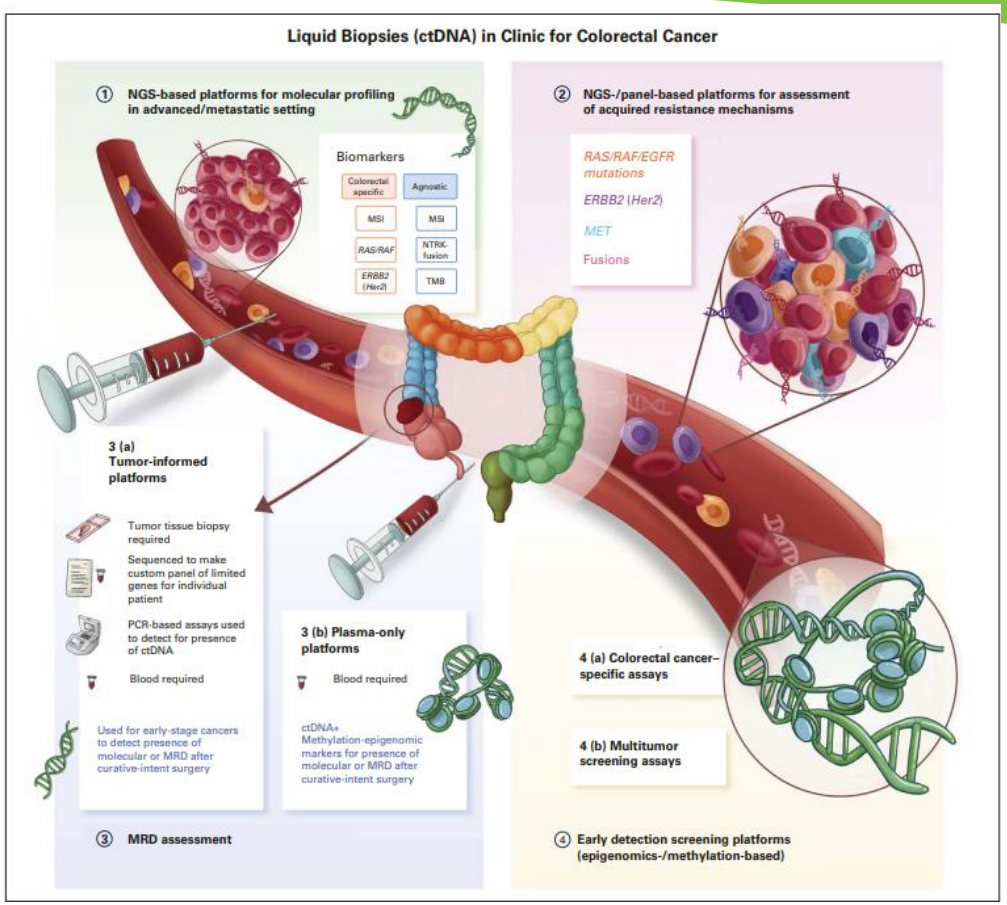
Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

Circulating Tumor DNA for MRD

- *Ct-DNA technology represents an emerging tool in GI cancer diagnostics to detect MRD*
- *Ct-DNA fragments harbor the same somatic genomic alterations as a patient's tumor.*
- *Ct-DNA analysis Methods:*
  - *PCR-based → Allele-specific assays*
  - *Next-generation sequencing (NGS)-based targeted and whole-genome approaches*
  - *Methylation Analysis Epigenetic Information*

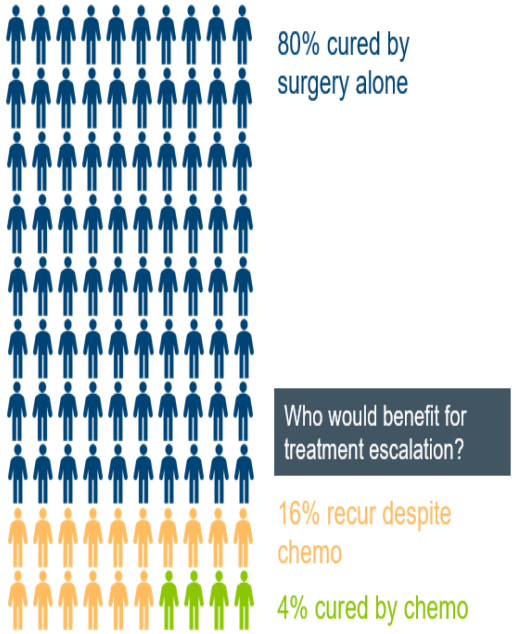


Risk Stratification and ACT: ct-DNA tumor Informed as Biomarker?

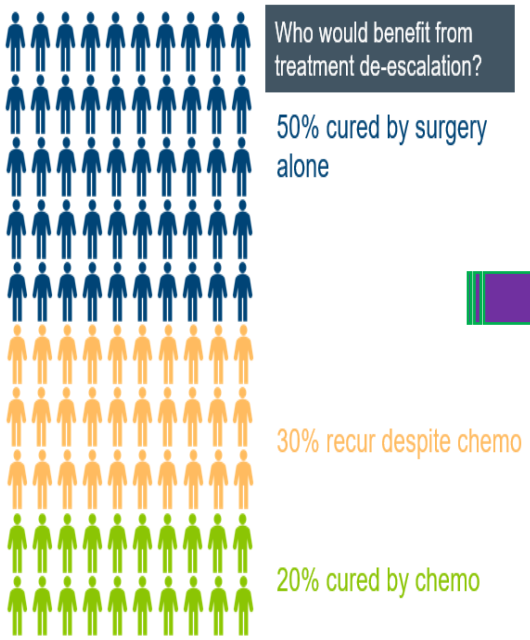
- *Do All Patients with stage II Colon Cancer benefits from adjuvant Chemotherapy after Curative Surgery*
- *Could we select out patients with stage III who may be low risk and tailor the need for ACT or even omit ACT*
- *For stage IV CRC Resected is there any additional benefit of ACT*
  - *EORTC Controversies?*
- *<u>There is a great need to use ct-DNA to stratify who will benefit from treatment for stage II , and/or De-escalation for stages III or IV</u>*

Stratification Clinicopathologic Risk Factors: Good Enough ??

Clinical dilemma in CRC Stage II



Clinical dilemma in CRC Stage III



Limitations in current methods of measuring disease burden or risk of relapse in patients with solid tumors

	Imaging	Clinicopathologic characteristics	Serum-based protein biomarkers
Examples	CT and PET/CT scans	ECOG PS, age, comorbidities, lymph node status, histology	PSA, CA-125, AFP, CEA
Limitations	Inability to detect micrometastatic disease, exposure to radiation	Risks features can be subjective and may not correlate to outcomes after treatment	Low sensitivity and specificity

1. Iversen LH, et al. *Acta Oncol.* 2016; 55(suppl 2):10-23. 2. Labianca R, et al. *Ann Oncol.* 2013; 24(suppl 6):vi64-vi72. 3. Glynne-Jones R, et al. *Ann Oncol.* 2018; 29(suppl 4):iv263. 4. Påhlman LA, et al. *J Clin Oncol.* 2016; 34(12):1297-1299.
5. Böckelman C, et al. *Acta Oncol.* 2015; 54(1):5-16.

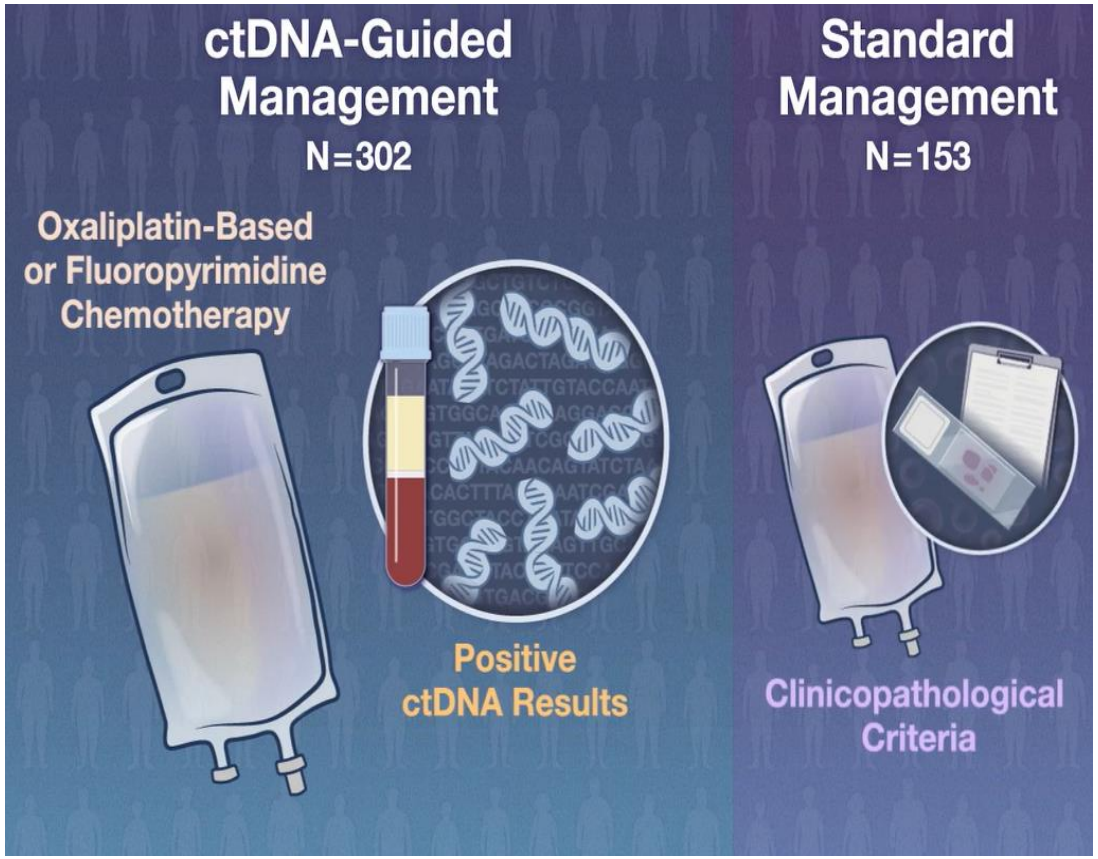
DYNAMIC STUDY STAGE II COLON CANCER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 16, 2022 VOL. 386 NO. 24

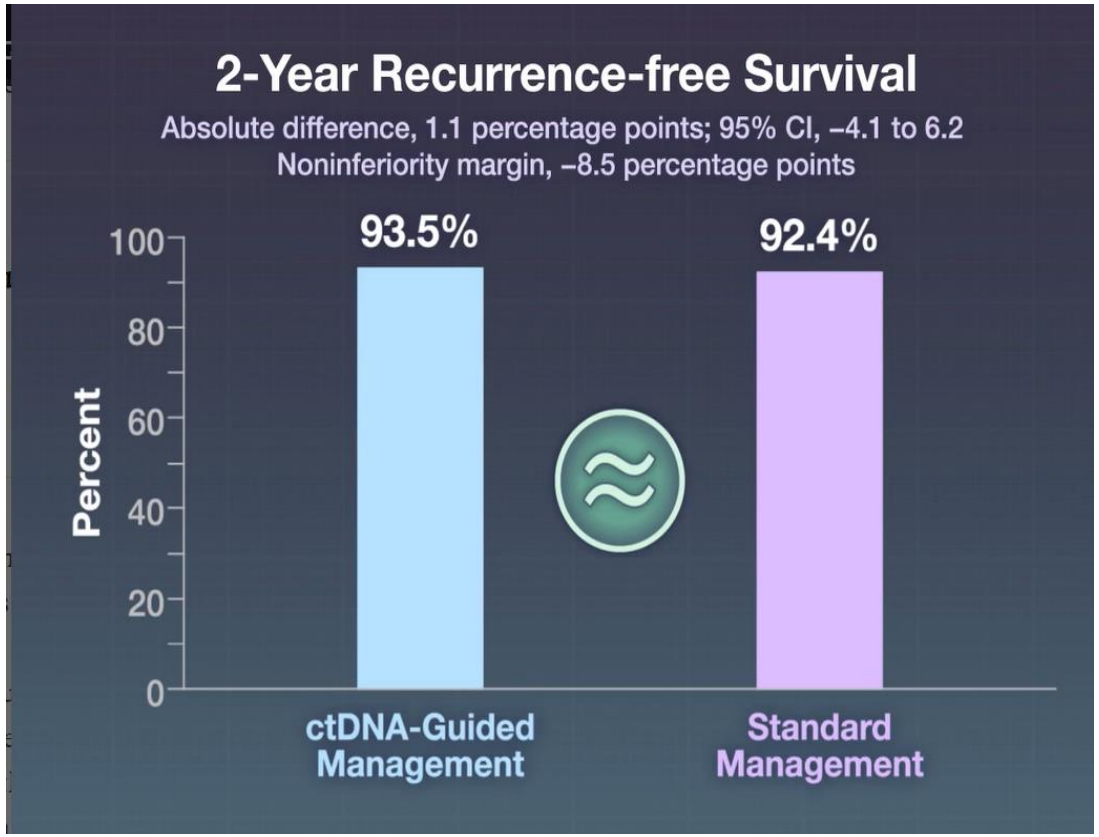
Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Jeanne Tie, M.D., Joshua D. Cohen, M.Phil., Kamel Lahouel, Ph.D., Serigne N. Lo, Ph.D., Yuxuan Wang, M.D., Ph.D., Suzanne Kosmider, M.B., B.S., Rachel Wong, M.B., B.S., Jeremy Shapiro, M.B., B.S., Margaret Lee, M.B., B.S., Sam Harris, M.B., B.S., Adnan Khattak, M.B., B.S., Matthew Burge, M.B., B.S.,



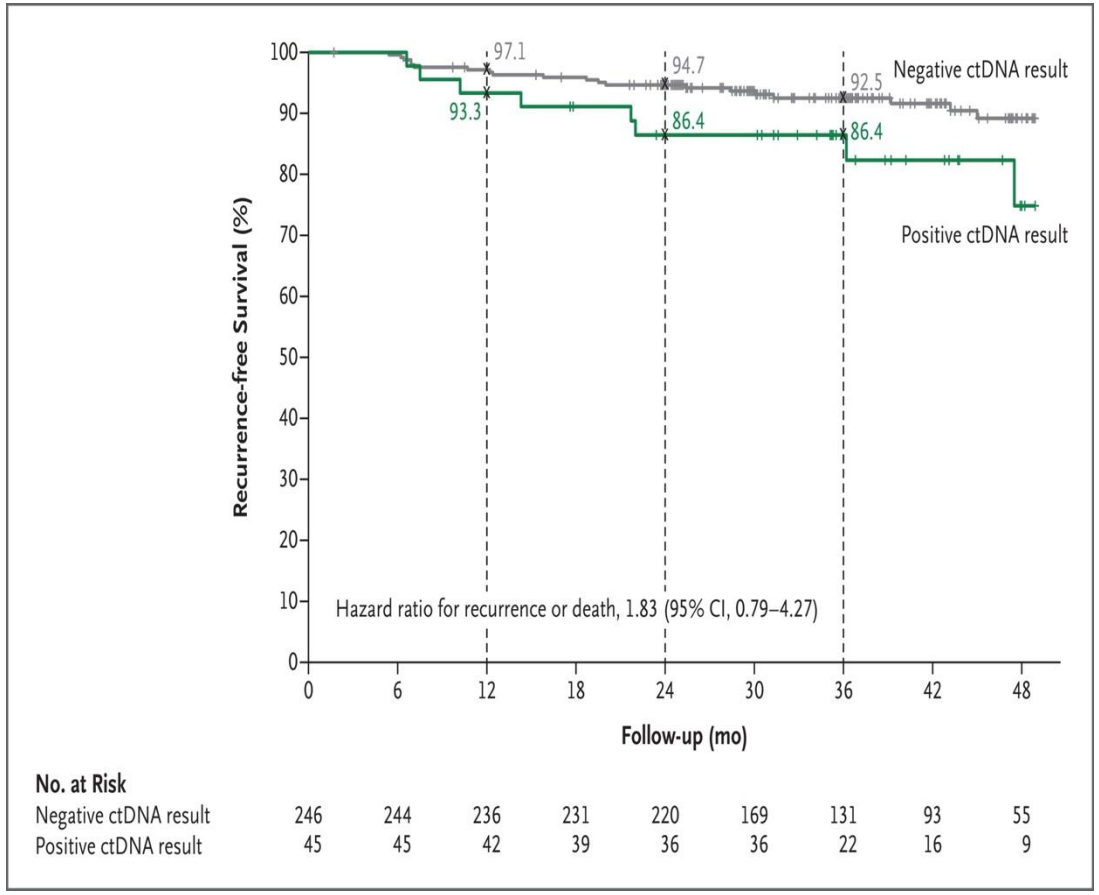
DYNAMIC STUDY STAGE II COLON CANCER

- A lower percentage of patients in the ct-DNA guided group than in the standard-management group received adjuvant chemotherapy 15% vs. 28%
- In 2-year recurrence-free survival→ ct-DNA-guided management was noninferior to standard management

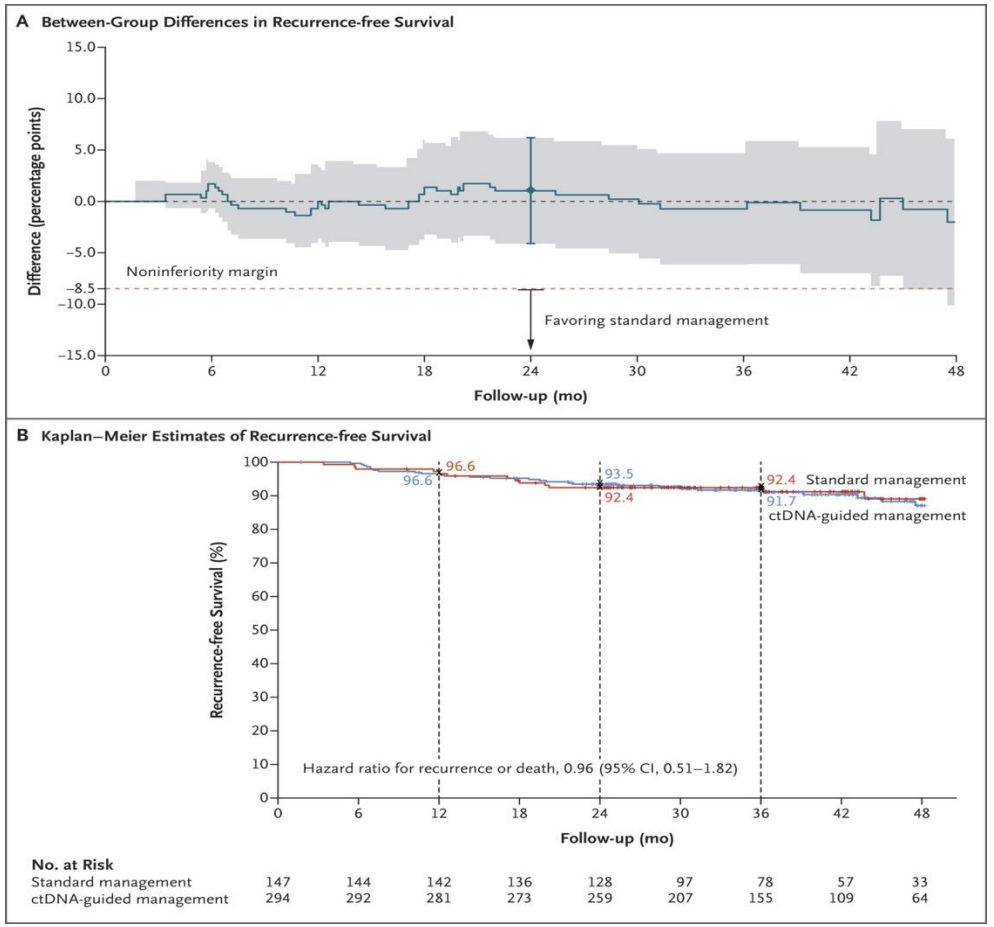


DYNAMIC STUDY STAGE II COLON CANCER

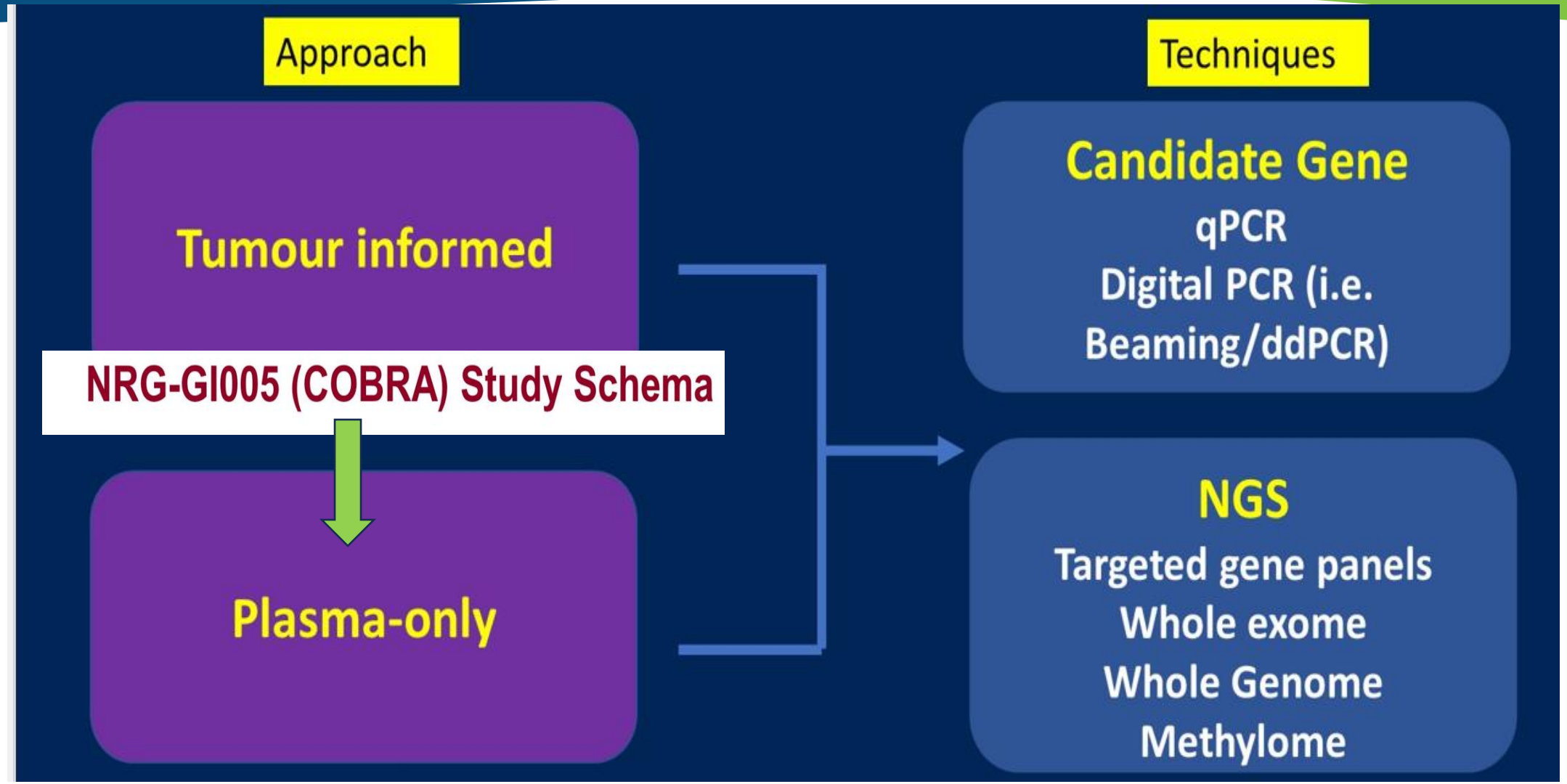
Recurrence Free Survival



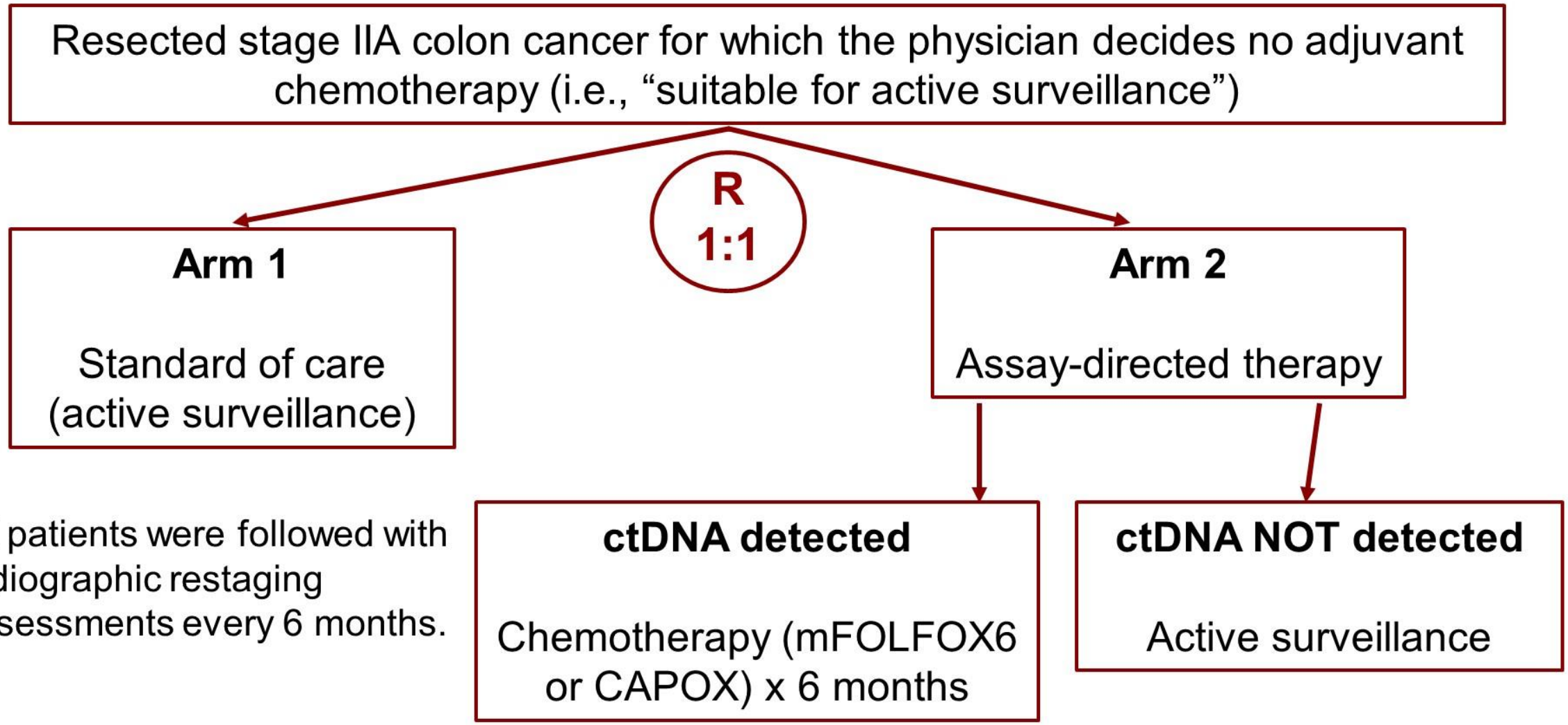
RFS with Intervention



Challenges Tumor Naive ct DNA as MRD



NRG-GI005 (COBRA) Study Schema



All patients were followed with radiographic restaging assessments every 6 months.

Phase II Endpoint Analysis: ctDNA(+) baseline participants

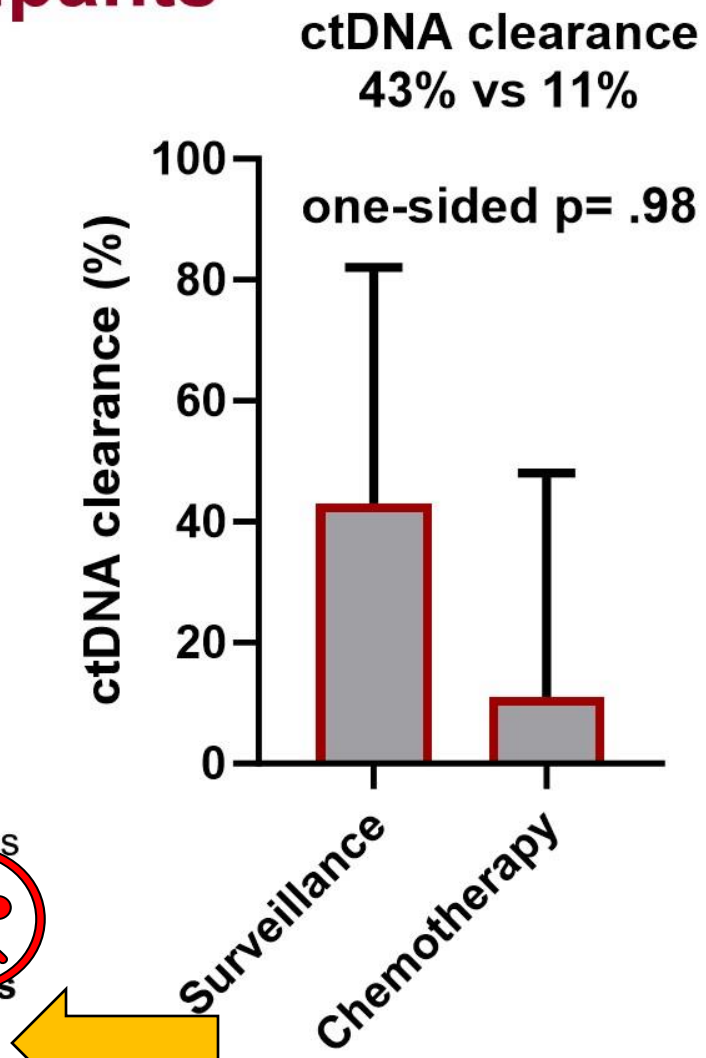
- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).

16 participants with "ctDNA detected" status at baseline

- Arm 1: Surveillance 7 participants
- Arm 2: Chemotherapy 9 participants

- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeded 0.35, H_o was not rejected, and the decision rule calls for early stopping due to futility.**



ASCO Gastrointestinal Cancers Symposium

Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan

Masahito Kotaka Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan

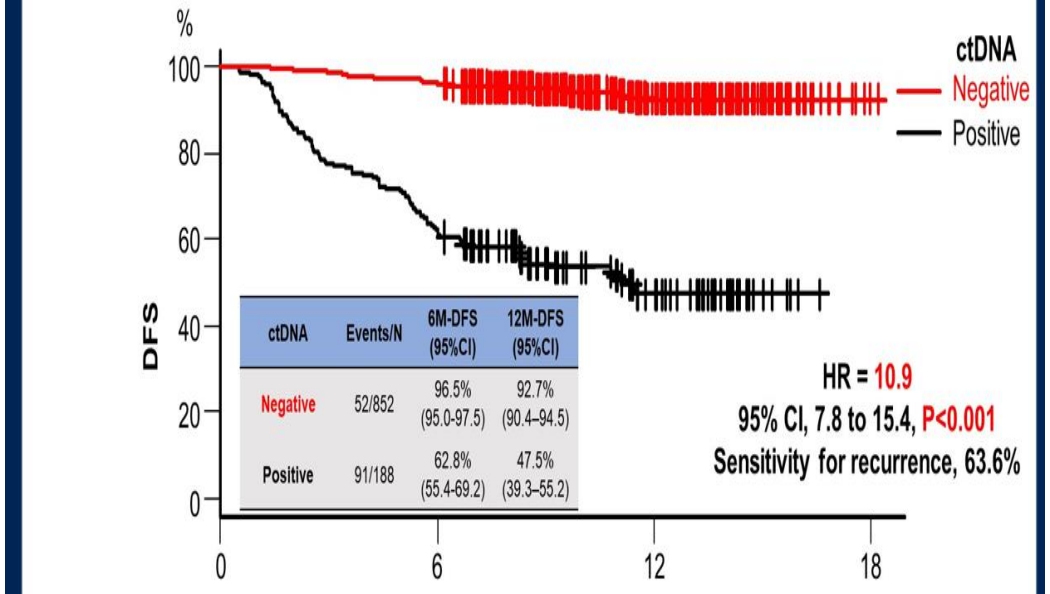
Co-authors; Hiromichi Shirasu, Jun Watanabe, Kentaro Yamazaki, Keiji Hirata, Naoya Akazawa, Nobuhisa Matsuhashi, Mitsuru Yokota, Masataka Ikeda, Kentaro Kato, Alexey Aleshin, Shruti Sharma, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Yoshiaki Nakamura, Hiroya Taniguchi, Masaki Mori, Takayuki Yoshino

On behalf of the CIRCULATE-Japan Investigators

GLAXY Study in CIRCULATE Japan

GI ASCO 2022

DFS by post-op-4w ctDNA status in overall population (pStage I-IV)



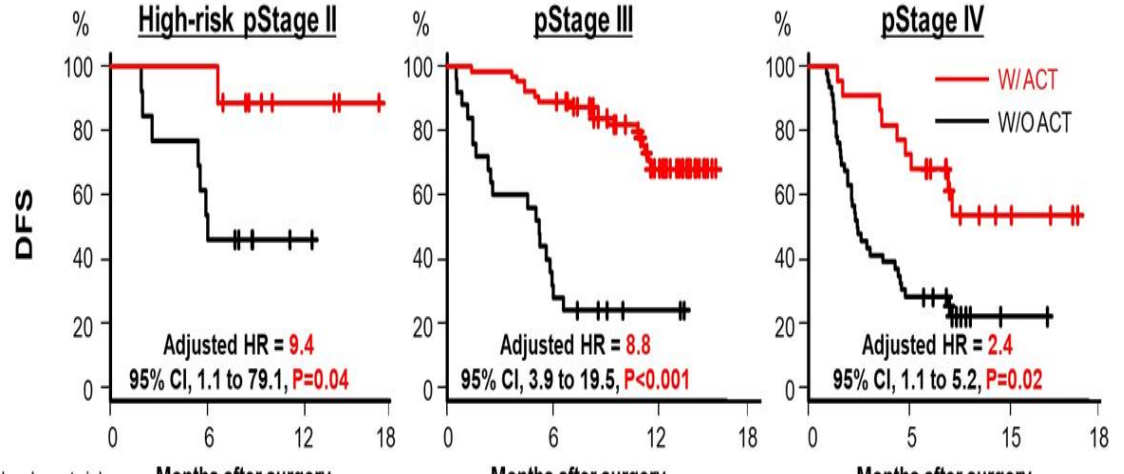
ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	52/852	96.5% (95.0-97.5)	92.7% (90.4–94.5)
Positive	91/188	62.8% (55.4-69.2)	47.5% (39.3–55.2)

Number at risk

Negative	852	822	310	1
Positive	188	118	38	0

DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

DFS by pStage in post-op-4w ctDNA positive population



Number at risk

W/ ACT	9	9	3	0	65	58	24	0	22	16	4	0
W/O ACT	13	7	1	0	25	8	2	0	46	13	1	0

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	1/9	100% (100–100)	88.9 (43.3–98.4)
W/O ACT	7/13	53.8% (24.8–76.0)	46.2 (19.2–69.6)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	17/65	89.2% (78.7–94.7)	68.3 (53.4–79.2)
W/O ACT	19/25	32.0% (15.2–50.2)	24.0 (9.8–41.7)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	9/22	72.7% (49.1–86.7)	53.7% (28.4–73.6)
W/O ACT	35/46	28.3% (16.2–41.6)	22.3% (11.2–35.7)

HR was adjusted by sex, and performance status. ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval. DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

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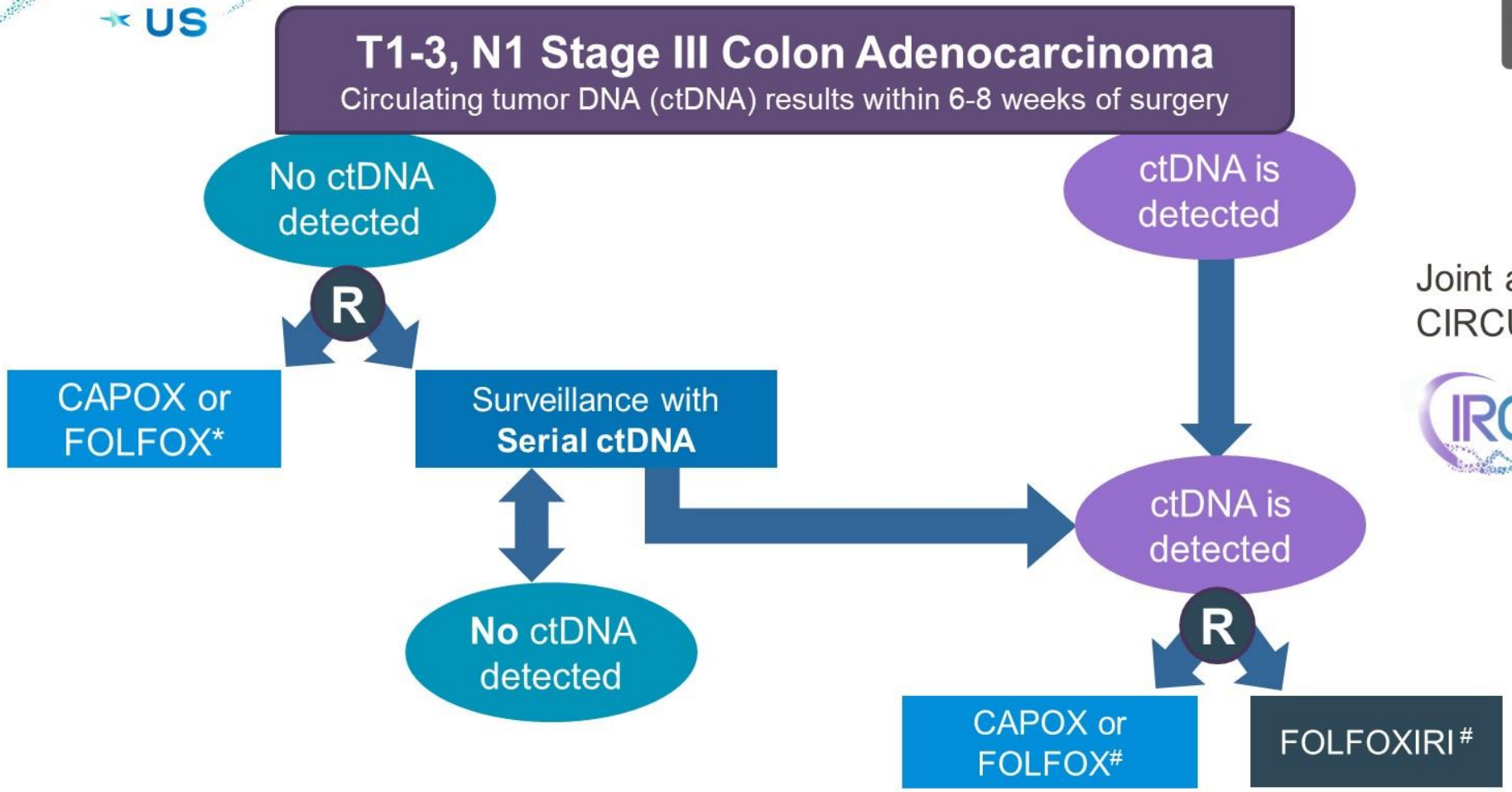

Joint analysis with CIRCULATE-Japan

CIRCULATE Japan

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

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

NRG-GI008

Ongoing Trials ct DNA in Stage IV CRC

OPTIMISE: OPTIMIzation of Treatment SElection and Follow up in Oligometastatic Colorectal Cancer - NCT04680260

PI Karen-Lise Garm Spindler, Aarhus University Hospital, Aarhus, Denmark

Compares: ctDNA Guided vs Standard-of-Care treatment

ctDNA-Directed Post-Hepatectomy Chemotherapy for Patients With Resectable Colorectal Liver Metastases - NCT05062317

PI Timothy Newhook, M.D. Anderson Cancer Center, Houston, Texas, USA

Compares: Arm 1: ctDNA-low risk (Leucovorin + Capecitabine) versus

Arm 2: ctDNA-high risk (FOLFOX or FOLFIRI with/without bevacizumab)

Anti-Heur 2 Neu Biomarker Directed Rx

Study	Phase	N pts	Drugs	Primary endpoint	Country
MOUNTAINEER	II	115	Tucatinib vs Tucatinib + Trastuzumab	ORR	
NCT04430738	I/II	65	Tucatinib + Trastuzumab + FOLFOX/CAPOX	Safety/ORR	
NCT04380012	II	40	Pyrotinib + Trastuzumab	ORR	
MODUL - maintenance	II	-	Trastuzumab + Pertuzumab + Capecitabine	PFS	
NSABP FC-11	II	35	Neratinib + Trastuzumab vs Neratinib + Cetuximab	ORR	
DESTINY-CRC02	II	120 (including *RAS*mut)	T-DXd 5.4 mg/kg vs 6.4 mg/kg	ORR	
SWOG S1613	II	130	Trastuzumab + Pertuzumab vs Cetuximab + Irinotecan	PFS	
MOUNTAINEER-03	III	400	FOLFOX + trastuzumab + tucatinib vs FOLFOX +/- bev or cet	PFS	

Conclusion

- *Emerging evidence supports tumor tissue-based comprehensive genomic profiling (CGP) in metastatic colorectal cancer (mCRC).*
- *Data on liquid biopsy-based circulating tumor DNA (ctDNA) CGP are scarce and mainly retrospective.*
- *Prospective comparison between the two tests is not currently available.*
- *Identification of actionable mutations to direct targeted therapy should be used in routine clinical practice*
- *Genomic Profiling for met CRC is crucial not only for First line therapy , but as Biomarker directed therapy for selected patients*
- *Tumor informed testing future role as MRD to tailor adjuvant therapy after curative resection.*
- *However, Tumor Naïve assay for met CRC may have crucial role in the absence of tissue, identifying clonal evolution and resistance to the recommended therapy*