Updates in Colorectal Cancer

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Disclosure of Conflicts of Interest

Thomas Reske, MD, has no real or apparent financial relationships to disclose.

The following slides were shared by authors/presenters and permitted to be presented today.

Biology

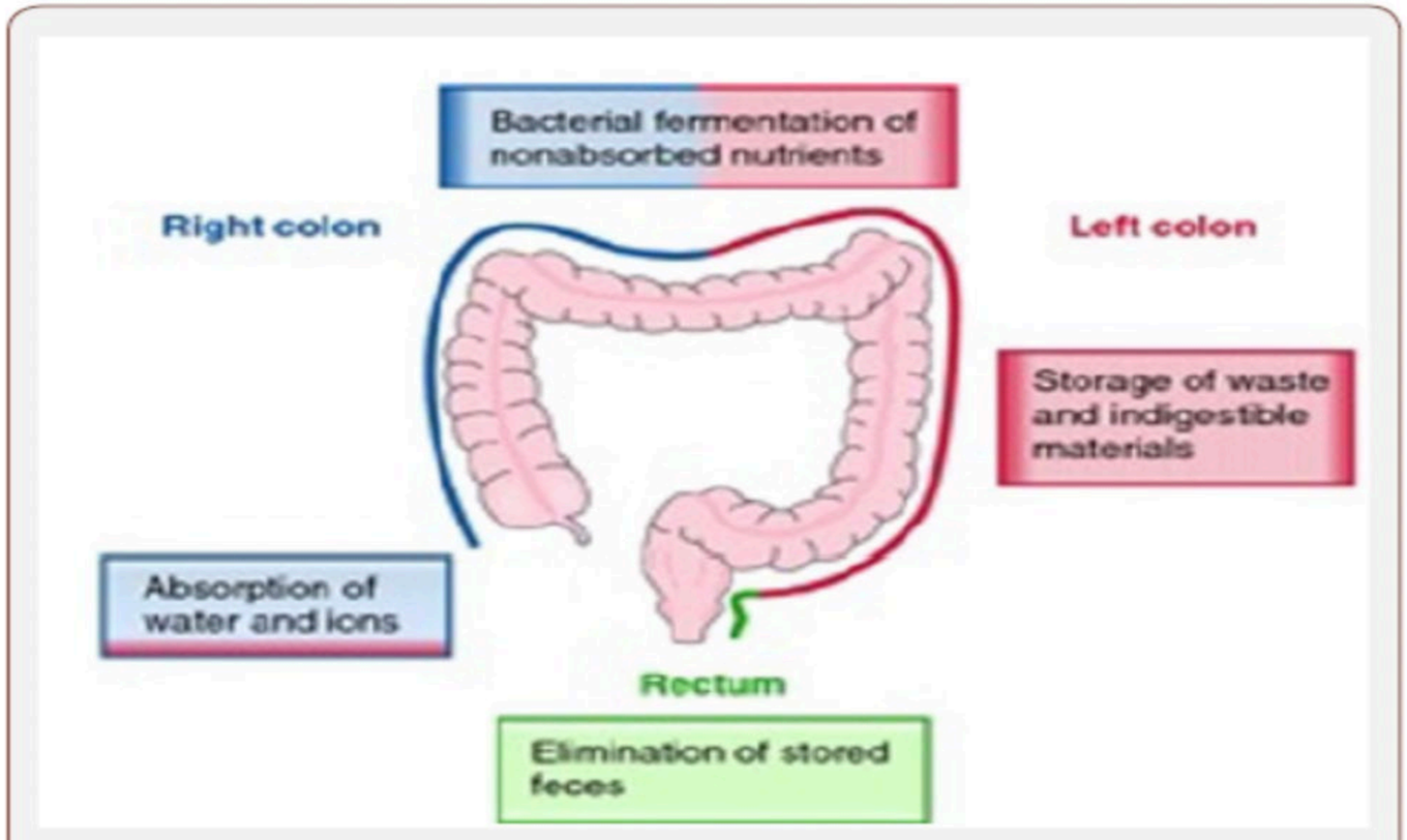
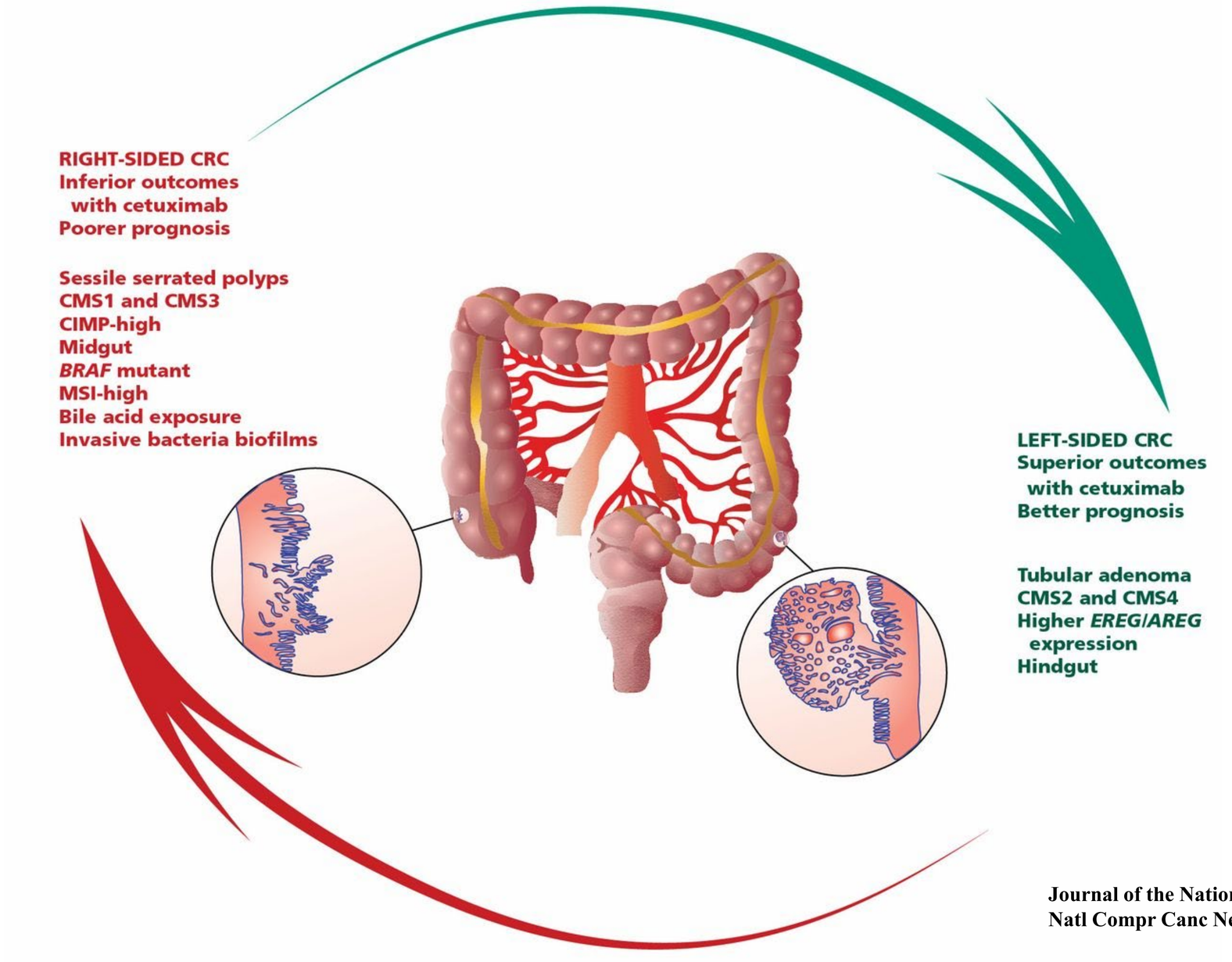


Figure 1: The digestive system.

DOI: 10.33552/ACRCI.2019.02.000533



Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw 15, 3; 10.6004/jnccn.2017.0038

Figure 2. Summary of key biologic differences between right- and left-sided CRCs.
Abbreviations: AREG, amphiregulin; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtype; CRCs, colorectal cancers; EREG, epiregulin; MSI, microsatellite instability.

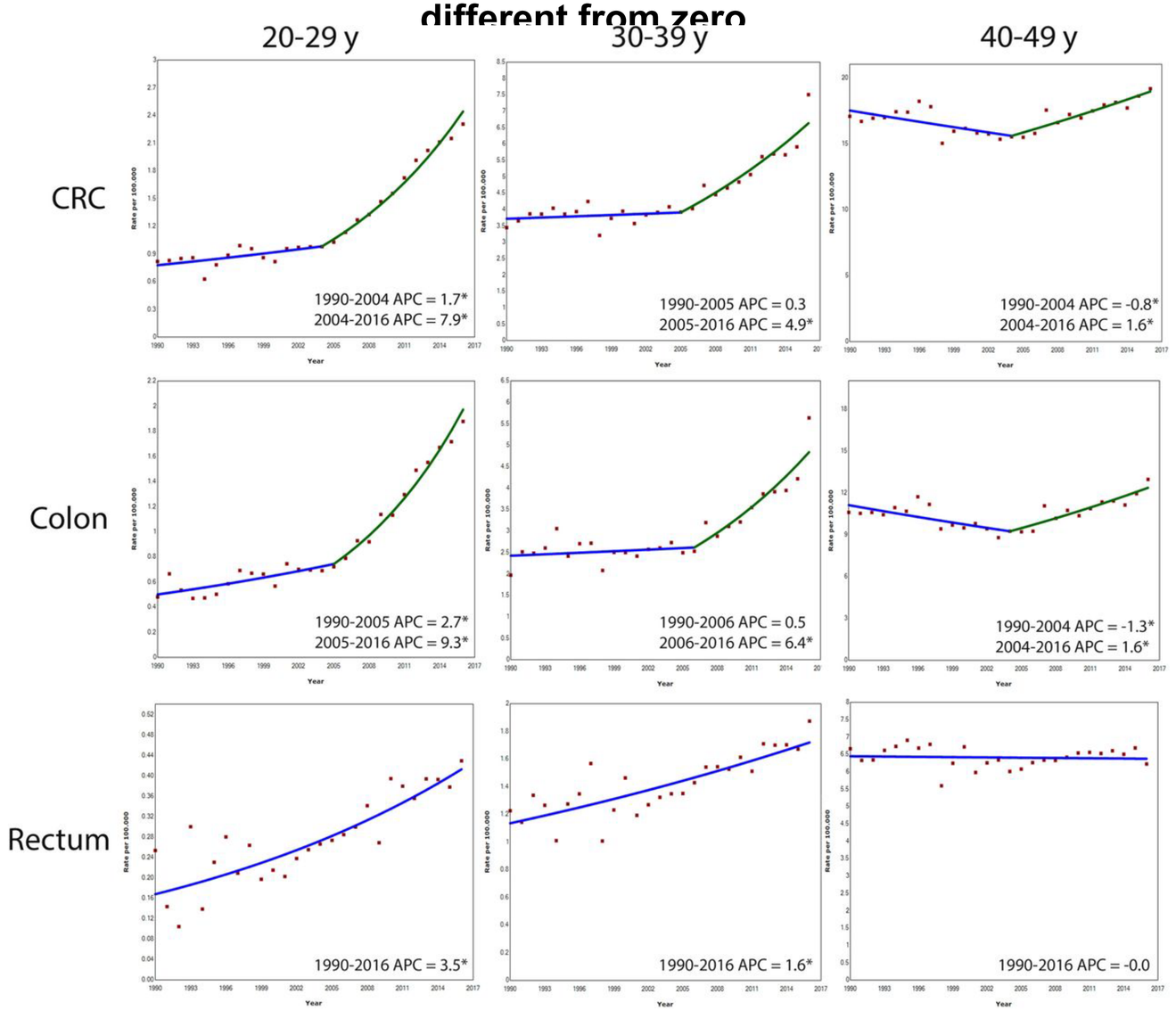
Epidemiology

- 3rd leading cause of cancer death for both women and men
- 2021 52980 persons in US died of colorectal cancer
- Commonly diagnosed in persons 65-74 years
- 10.5% of all new colorectal cancer occur in < 50 years
- Incidence in adults 40-49 has increased by almost 15% in last two decades
- 25.6% of eligible adults in US have never been screened

Epidemiology

- Largest increase in CRC in subjects 20-39 years
- Annual increase in colon cancer 6.4-9.3% and rectal 1.6-3.5%
- Weight gain is associated with increased risk of CRC
- Excess nutrients among other factors may initiate a chronic low-grade inflammatory response in metabolic cells
- Microbiome changes

Annual percent change (APC) in age-specific colorectal cancer (CRC), colon cancer and rectal cancer incidence rates in Europe, 1990–2016. *Indicates that APC is statistically significant different from zero



Fanny ER Vuik et al. Gut 2019;68:1820-1826

USPSTF Recommendations

Recommendation Summary

Population	Recommendation	Grade
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	B
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences.	C

Different Modalities

Table 1. Characteristics of Recommended Colorectal Cancer Screening Strategies

Screening method[a]	Frequency[b]	Evidence of efficacy	Other considerations
Stool-based tests			
High-sensitivity gFOBT	Every year	• Evidence from RCTs that gFOBT reduces colorectal cancer mortality • High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II), although there is still uncertainty about the precision of test sensitivity estimates. Given this uncertainty, it is unclear whether high-sensitivity gFOBT can detect as many cases of advanced adenomas and colorectal cancer as other stool-based tests	• Harms from screening with gFOBT arise from colonoscopy to follow up abnormal gFOBT results • Requires dietary restrictions and 3 stool samples • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
FIT	Every year	• Evidence from 1 large cohort study that screening with FIT reduces colorectal cancer mortality • Certain types of FIT have improved accuracy compared to gFOBT and HSgFOBT (20 µg hemoglobin per gram of feces threshold was used in the CISNET modeling)	• Harms from screening with FIT arise from colonoscopy to follow up abnormal FIT results • Can be done with a single stool sample • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
sDNA-FIT	Every 1 to 3[c] y	• Improved sensitivity compared with FIT per 1-time application of screening test • Specificity is lower than that of FIT, resulting in more false-positive results, more follow-up colonoscopies, and more associated adverse events per sDNA-FIT screening test compared with per FIT test • Modeling suggests that screening every 3 y does not provide a favorable (ie, efficient) balance of benefits and harms compared with other stool-based screening options (ie, annual FIT or sDNA-FIT every 1 or 2 y) • Insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative follow-up colonoscopy • No direct evidence evaluating the effect of sDNA-FIT on colorectal cancer mortality	• Harms from screening with sDNA-FIT arise from colonoscopy to follow up abnormal sDNA-FIT results • Can be done with a single stool sample but involves collecting an entire bowel movement • Requires good adherence over multiple rounds of testing • Does not require bowel preparation, anesthesia or sedation, or transportation to and from the screening examination (test is performed at home)
Direct visualization tests			
Colonoscopy	Every 10 y	• Evidence from cohort studies that colonoscopy reduces colorectal cancer mortality • Harms from colonoscopy include bleeding and perforation, which both increase with age	• Screening and follow-up of positive results can be performed during the same examination • Requires less frequent screening • Requires bowel preparation, anesthesia or sedation, and transportation to and from the screening examination
CT colonography	Every 5 y	• Evidence available that CT colonography has reasonable accuracy to detect colorectal cancer and adenomas • No direct evidence evaluating effect of CT colonography on colorectal cancer mortality • Limited evidence about the potential benefits or harms of possible evaluation and treatment of incidental extracolonic findings, which are common. Extracolonic findings detected in 1.3% to 11.4% of examinations; <3% required medical or surgical treatment	• Additional harms from screening with CT colonography arise from colonoscopy to follow up abnormal CT colonography results • Requires bowel preparation • Does not require anesthesia or sedation or transportation to and from the screening examination
Flexible sigmoidoscopy	Every 5 y	• Evidence from RCTs that flexible sigmoidoscopy reduces colorectal cancer mortality • Risk of bleeding and perforation but less than risk with colonoscopy • Modeling suggests that it provides fewer life-years gained alone than when combined with FIT or in comparison to other strategies	• Additional harms may arise from colonoscopy to follow up abnormal flexible sigmoidoscopy results • Test availability has declined in the US but may be available in some communities where colonoscopy is less available
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 y plus FIT every year	• Evidence from RCTs that flexible sigmoidoscopy + FIT reduces colorectal cancer mortality • Modeling suggests combination testing provides benefits similar to those of colonoscopy, with fewer complications • Risk of bleeding and perforation from flexible sigmoidoscopy but less than risk with colonoscopy	• Additional potential harms from colonoscopy to follow up abnormal flexible sigmoidoscopy or FIT results • Flexible sigmoidoscopy availability has declined in the US but may be available in some communities where colonoscopy is less available • Screening with FIT requires good adherence over multiple rounds of testing

Timing of Follow-up Colonoscopy

Findings	Follow-up
Normal	10 years
1-2 small (< 1cm) tubular adenomas	**7-10 years**
3-4 small (<1cm) tubular adenomas	**3-5 years**
5-10 small (<1cm) tubular adenomas	**3 years**
large (≥ 1cm) or high grade dysplasia/villous pathology	3 years
> 10 tubular adenomas	1 year

**All assuming HIGH quality colonoscopy with COMPLETE removal of polyps

Gupta et al. AJG 2020

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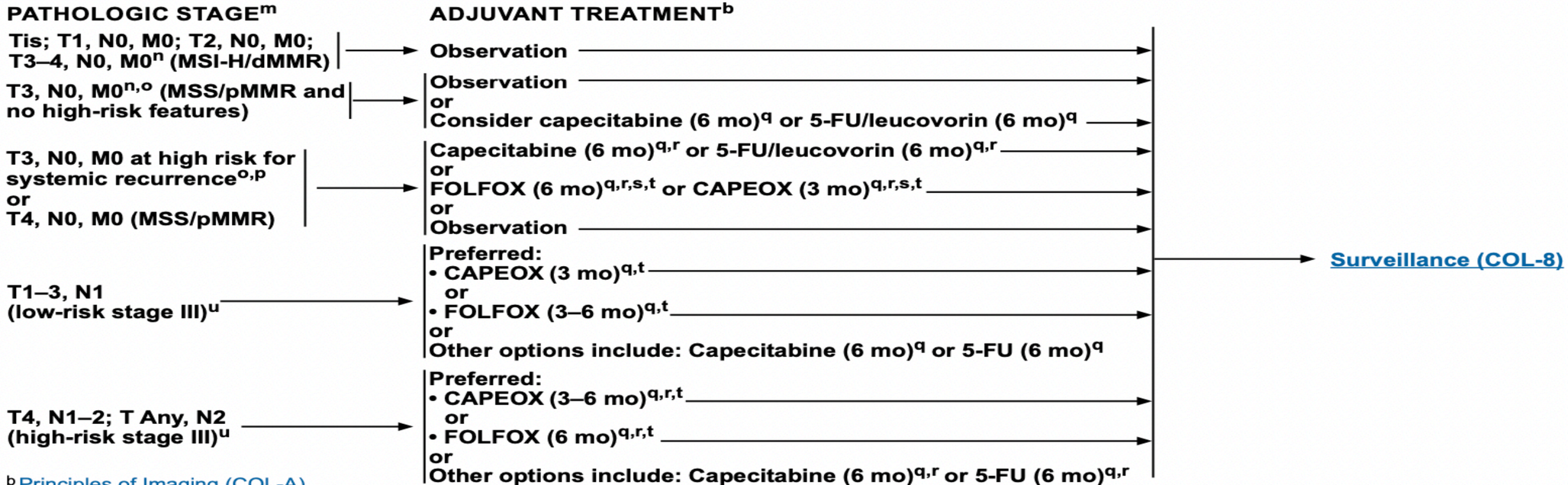
Colon Cancer Therapy

Historic Overview

- 1957 5FU discovered
- 1962 5FU FDA approved for CRC
- 2000 Irinotecan approved for CRC
- 2002 Oxaliplatin approved for CRC
- 2004 MOSAIC trial adding Oxaliplatin to 5 FU OS and DFS benefit
- 2006 Bevacizumab approved for CRC
- 2012 Regorafinib approved
- 2015 Trifluridine-tipiracil approved + EGFR Inhibitor
- 2018 Published IDEA (International Duration Evaluation of Adjuvant Therapy collaboration)
- 2020 BRAF Inhibitor and Immunotherapy

Early Stage Colon Cancer



[b] Principles of Imaging (COL-A).
[m] Principles of Pathologic Review (COL-B).
[n] Principles of Risk Assessment for Stage II Disease (COL-F).
[o] High-risk factors for recurrence (exclusive of those cancers that are microsatellite instability-high [MSI-H]): poorly differentiated/undifferentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, positive margins, or tumor budding. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
[p] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[q] Principles of Adjuvant Therapy (COL-G).
[r] Consider RT for T4 with penetration to a fixed structure. Principles of Radiation and Chemoradiation Therapy (COL-E).
[s] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012; 30:3353-3360.
[t] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years and older has not been proven.
[u] While non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven, 3 mo of CAPEOX numerically appeared similar to 6 mo of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity. (Andre T, et al. Lancet Oncol 2020;21:1620-1629). These results support the use of 3 mo of adjuvant CAPEOX over 6 mo in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 mo of CAPEOX is non-inferior to 6 mo for disease-free survival; non-inferiority of 3 mo vs. 6 mo of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 mo of FOLFOX is inferior to 6 mo for disease-free survival, whereas non-inferiority of 3 mo vs. 6 mo of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 mo vs. 6 mo of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX). Grothey A, et al. N Engl J Med 2018;378:1177-1188.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Original Article

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

Axel Grothey, M.D., Alberto F. Sobrero, M.D., Anthony F. Shields, M.D., Ph.D., Takayuki Yoshino, M.D., Ph.D., James Paul, Ph.D., Julien Taieb, M.D., John Souglakos, M.D., Qian Shi, Ph.D., Rachel Kerr, Ph.D., Roberto Labianca, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Dewi Vernerey, Ph.D., Takeharu Yamanaka, Ph.D., Ioannis Boukovinas, M.D., Jeffrey P. Meyers, B.S., Lindsay A. Renfro, Ph.D., Donna Niedzwiecki, Ph.D., Toshiaki Watanabe, Ph.D., Valter Torri, M.D., Mark Saunders, M.B., B.S., Ph.D., Daniel J. Sargent, Ph.D., Thierry Andre, M.D., and Timothy Iveson, M.D.

N Engl J Med
Volume 378(13):1177-1188
March 29, 2018

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- Among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population.
- However, in patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup.

The NEW ENGLAND JOURNAL of MEDICINE

ASCO Gastrointestinal Cancers Symposium

ACCENT
Adjuvant Colon Cancer Endpoints Group

Prognostic impact of early discontinuation of treatment and oxaliplatin in patients treated with 6 months of oxaliplatin-based chemotherapy for stage III colon cancer: an ACCENT/IDEA pooled analysis of 11 adjuvant trials

Claire Gallois, Qian Shi, Jeffrey P. Meyers, Timothy Iveson, Steven R Alberts, Aimery de Gramont, Alberto F. Sobrero, Daniel G. Haller, Eiji Oki, Anthony Frank Shields, Caroline Kelly, Ioannis Boukovinas, Roberto Labianca, Frank A. Sinicrope, Ioannis Souglakos, Takayuki Yoshino, Jeffrey A Meyerhardt, Thierry Andre, Demetris Papamichael and Julien Taieb

AP-HP. Centre Université de Paris

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Background

- In patients treated with 6 months of adjuvant chemotherapy, we may need to **stop oxaliplatin early**, mainly due to **peripheral sensory neuropathy**

- In the literature, we have limited data on the prognostic impact of the **relative dose intensity (RDI) of oxaliplatin in localized CC**

	Jolanta Zok et al. BMC Cancer 2021	***Dawon Park et al. Ann Surg Treat Res 2018***
Stage	III	II/III
N patients	365	611
Regimen	FOLFOX/CAPOX	FOLFOX
Associated with poorer outcomes	**RDI of oxaliplatin < 60%**	**< 60% of the standard dose of oxaliplatin**

Need for more robust data on the **prognostic impact of early treatment discontinuation and oxaliplatin discontinuation**, while continuing fluoropyrimidine, according to the **number of cycles** received

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Population

Trials

MOSAIC, XELOXA, N0147, PETACC8, AVANT, TOSCA, SCOT, IDEA France, CALGB/SWOG 80702, HORG, ACHIEVE

N=28, 623

Main exclusion criteria:

-Treatment with:
- **Fluoropyrimidine alone arms** (FULV, 5-FU, capecitabine)
- **Targeted therapy** (cetuximab, bevacizumab) **arms**

- Treatment prescribed for a duration of 3 months

- Discontinuation of chemotherapy due to recurrence

N= 10, 444

Oxaliplatin-based adjuvant chemotherapy (FOLFOX or CAPOX)
Prescribed for a duration of **6 months**
In **stage III CC**

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RESULTS

- ETD (N=**10, 444**) → **20.9% experienced ETD**
- EOD (N=**7, 243**)→ **18.8% experienced EOD**

		ETD (N=2184)	p-value	EOD (N=1359)	p-value
Gender	**Female**	23.1%	**< 0.001**	21.0%	**< 0.001**
	Male	19.2%		17.0%	
Age	< 65y	17.1%	**< 0.001**	18.0%	**< 0.001**
	≥ 65y	26.0%		20.0%	
ECOG-PS	0	20.0%	**< 0.001**	17.6%	**< 0.001**
	≥ 1	23.9%		22.7%	
BMI	**< 18.5**	31.5%	**< 0.001**	24.2%	0.25
	18.5 - 25	21.0%		20.2%	
	> 25	20.1%		19.3%	
Regimen	FOLFOX	17.8%	**< 0.001**	17.4%	**< 0.001**
	CAPOX	27.2%		21.4%	

No statistically significant difference for:

- T stage, N stage
- Risk group (low-/high-risk)
- Sidedness
- Histological grade
- LNR
- MMR status
- KRAS, BRAF mutation status

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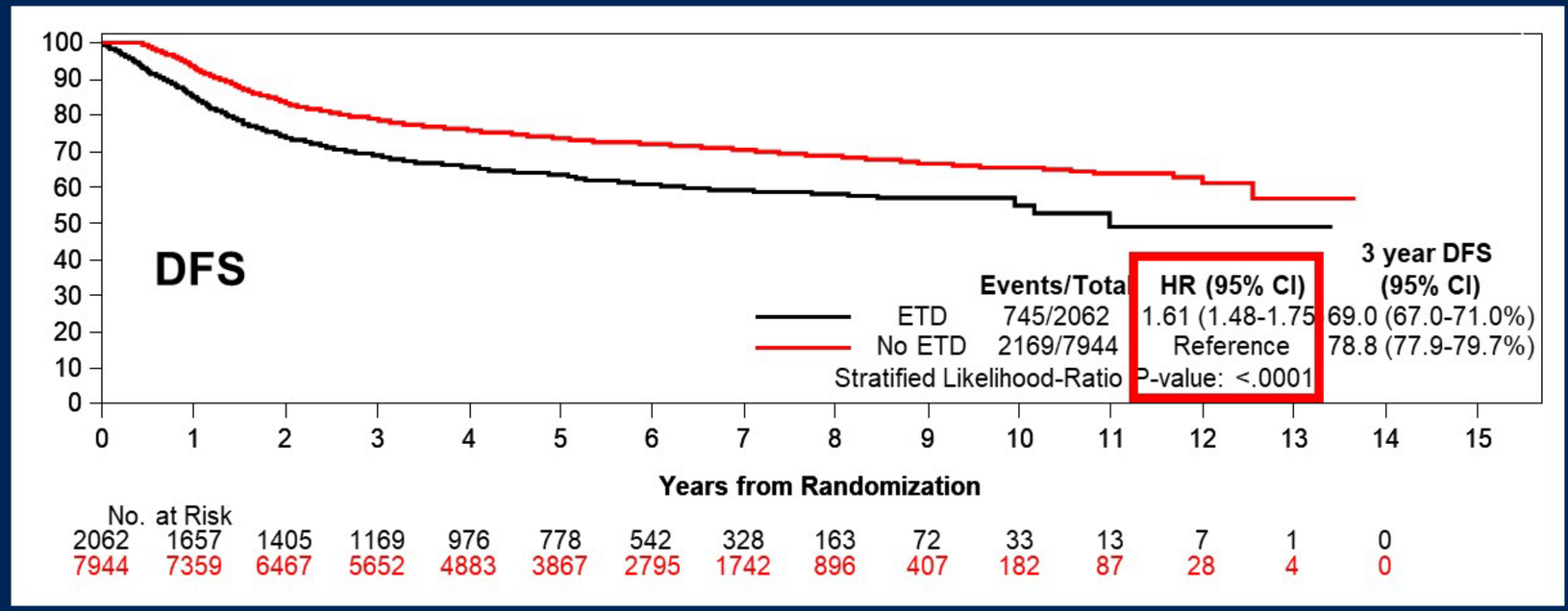
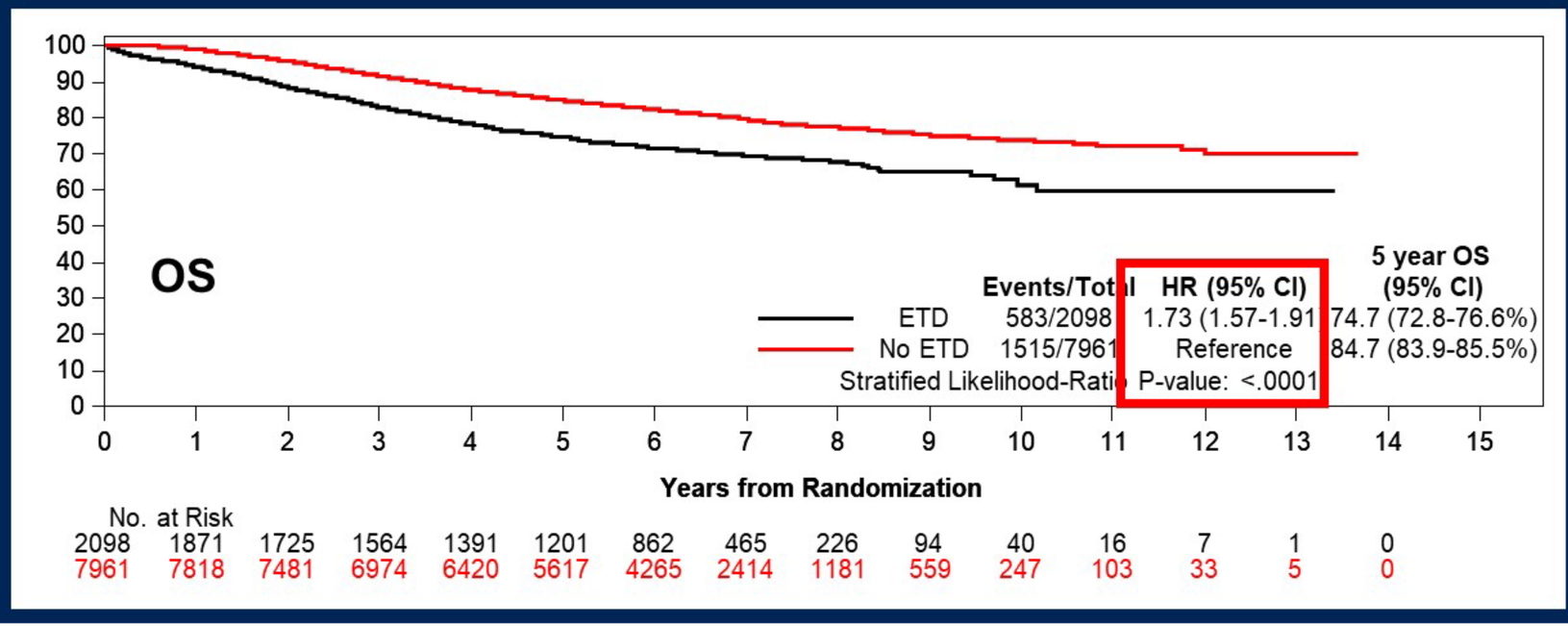
Survival according to ETD/no ETD in multivariate analysis

Overall population

Adjustment variables:
- Age
- Gender
- Year enrollment
- ECOG PS
- T and N stage

Adjusted Kaplan Meier curves





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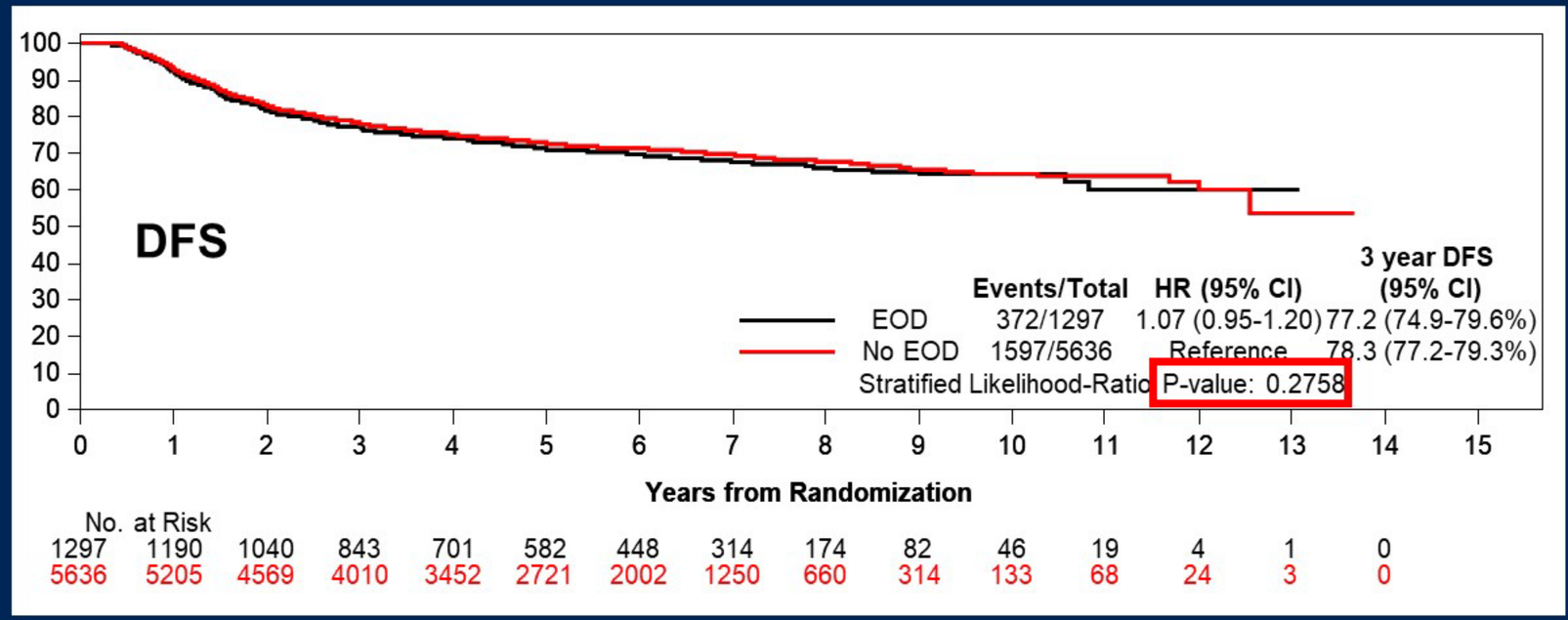
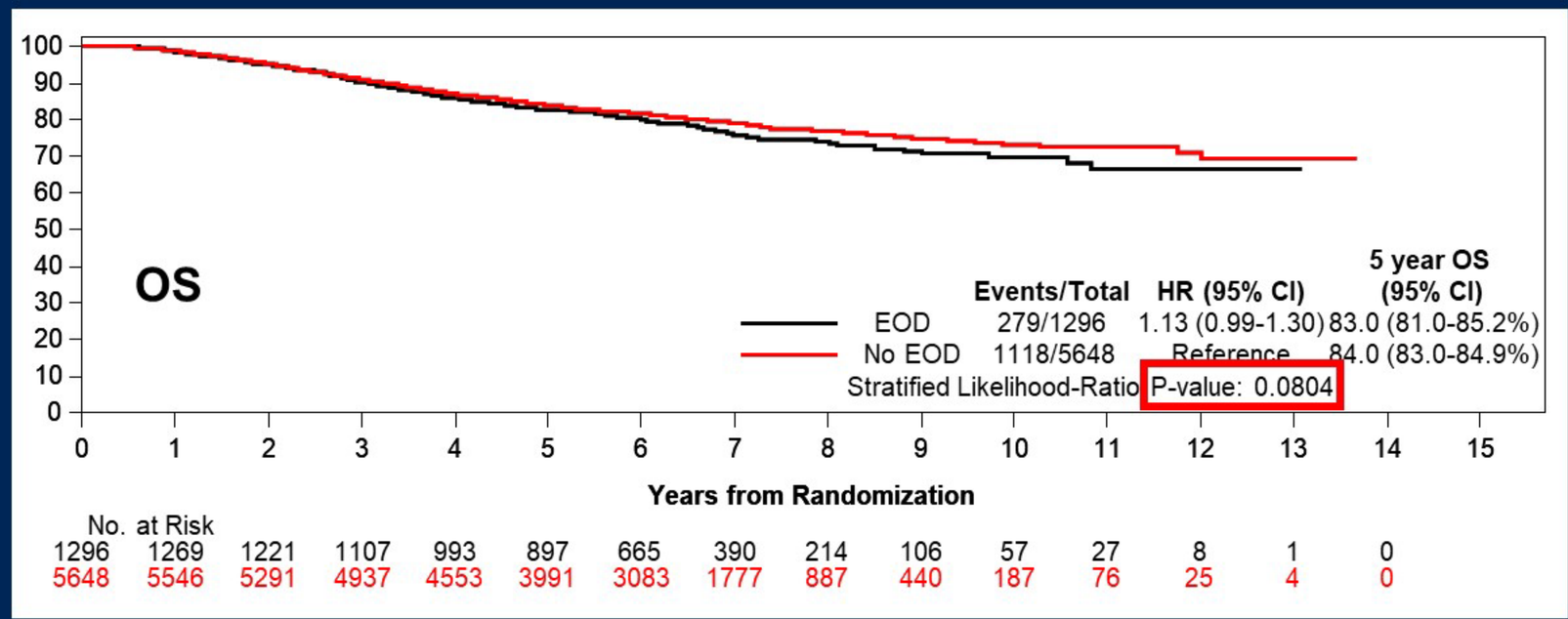
Survival according to EOD/no EOD in multivariate analysis

Overall population

Adjustment variables:
- Age
- Gender
- Year enrollment
- ECOG PS
- T and N stage

Adjusted Kaplan Meier curves





Conclusion / Summary

In a large series of patients receiving 6-months of CT for stage III CC :

- **ETD** and **EOD** were associated with:
  - ➢ older age, female gender, ECOG>0, CAPOX regimen, malnutrition (ETD only)
- **ETD → associated with a significant and clinically relevant decrease in DFS and OS**
- **EOD → not significantly associated with decreased DFS or OS**
  - ➢ However, patients who received **< 50% of the planned number of cycles of oxaliplatin**, had **poorer outcomes**

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Limitations

Missing data for:

- **the cause of ETD**
  → could be linked to confounding factors for DFS/OS

- **Co-morbid conditions** (renal impairment, diabetes mellitus...)
  →may lead to ETD and influence DFS/OS

We can **not fully exlude all confounding factors for DFS and OS**

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Take Home Points

In patients with a **6-month adjuvant regimen** chosen in MTD:

- **Maintain the planned number of treatment cycle** seems important
- Grade 2+ neurotoxicity / any timepoint: stop oxaliplatin (GCP)
- **After 3 months**, in patients having grade 1-2 neurotoxicity: **stopping oxaliplatin** is likely a valid option **not impairing clinical outcomes**

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Monitoring and surveillance: *Then and now*

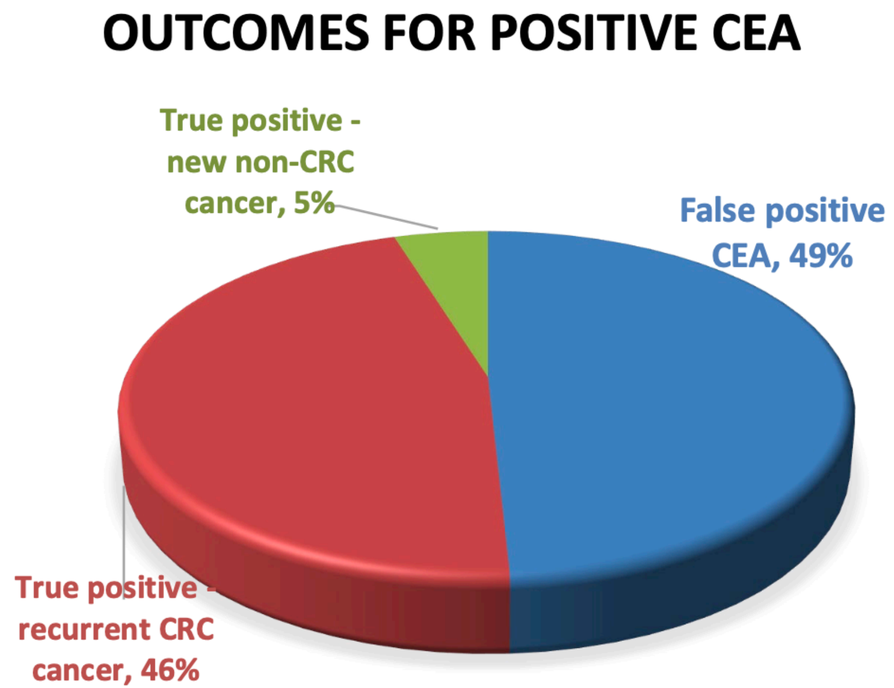
Stage II/III colon ca	**1996 NCCN guidelines**	**2022 NCCN guidelines**
Physical exam	✓	✓
CEA	✓	✓
Imaging	✓ CXR Chest CT if metastasis Abd CT if resected metastasis or rectal ca	✓ CT chest, abdomen, pelvis
Colonoscopy	✓	✓

1996: *"Post treatment surveillance of patients with colon cancer is a controversial management issue"*

CEA is a problematic biomarker

- 728 MSKCC patients were identified who underwent R0 resection for stage I–III CRC (2003-2012)

- All pts had a normal perioperative CEA level but subsequently had at least one abnormal CEA measurement



Litvak et al., JNCCN. June 2014, 12(6), 907-913.

The appropriate cutoff for CEA is unknown

- More false-positives than true-positives occur at CEA levels up to 10 ng/mL

- At the cutoff of 5.0 ng/mL (used at MSKCC), the sensitivity is only 54% and the specificity is 79%

- The optimal cutoff based on ROC curve would be 7.9 ng/mL (sensitivity= 44% and specificity = 95%)

Litvak et al., JNCCN. June 2014, 12(6), 907-913.

Positive CEA results in increased imaging and patient/ provider anxiety

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Colon Cancer

NCCN Guidelines Index
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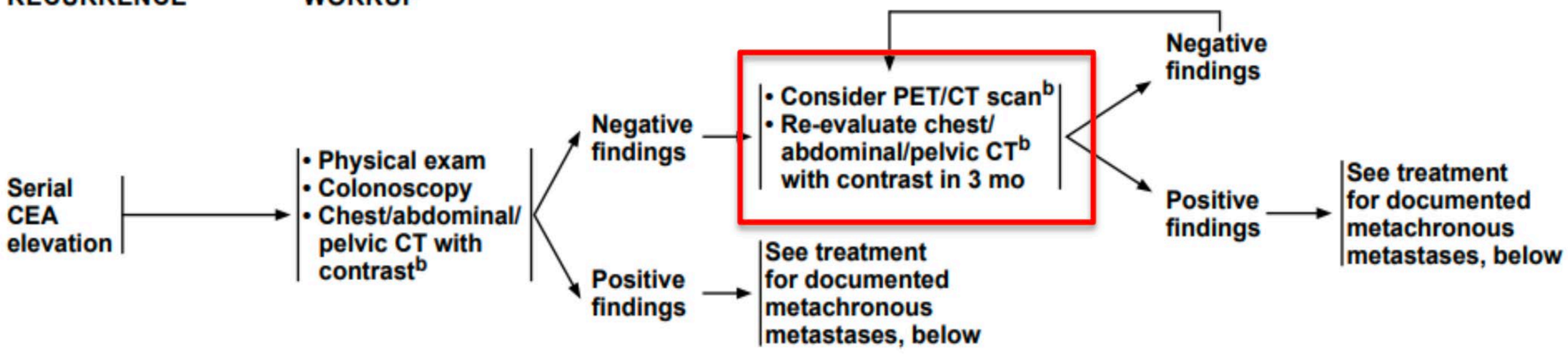
Discussion

RECURRENCE **WORKUP**



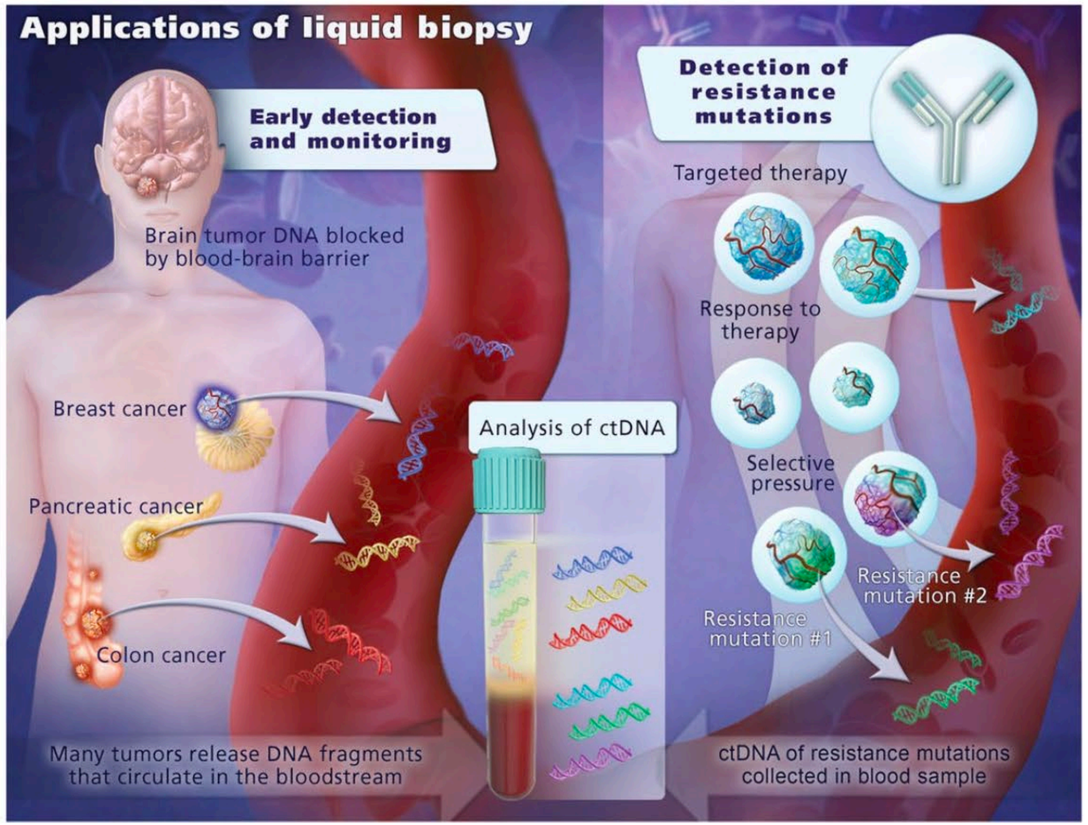
Current state of survivorship/ surveillance for stage II/III colorectal cancer

- Current guidelines for surveillance were established >25 years ago with limited supporting evidence

- The core components of surveillance (CEA and CT) and their test intervals have no proven survival benefit and may not optimize limited healthcare resources

- There is an opportunity to rethink survivorship and surveillance with evidence-based analysis and modern technology

“Liquid biopsy” in the clinic



Potential clinical applications

- Screen asymptomatic population
- Detect residual disease following resection
- Identify actionable biomarkers (HER2, etc.)
- Predict treatment response
- Monitor overall tumor burden
- Identify drivers of treatment resistance

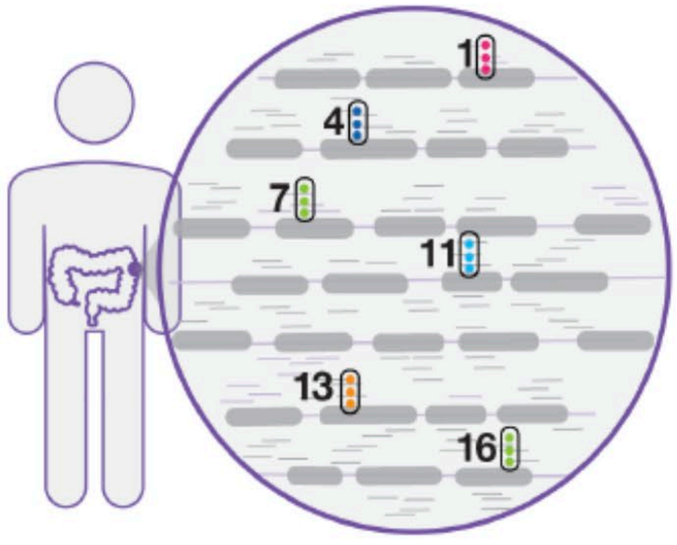
C. Bettegowda *et al., Sci Transl Med* 2014;6:224ra24

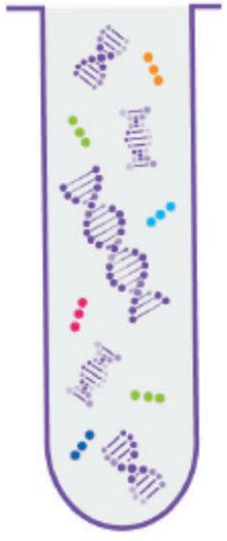
“Tumor informed” mutation detection

Sequencing of tumor tissue, to identify unique signature of tumor mutations

Custom design and manufacture of personalized mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor

Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)

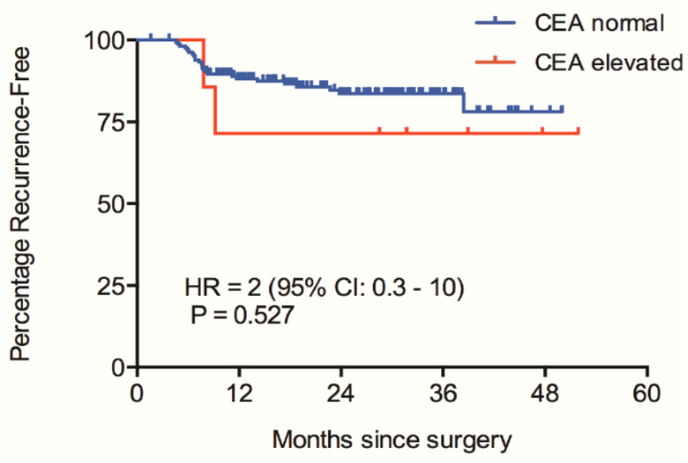




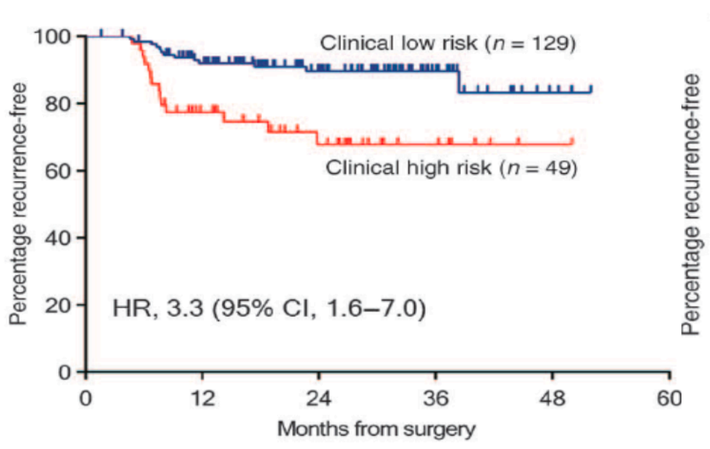
Tumor informed MRD assay outperforms clinical risk factors in stage II colon ca

No patients received adjuvant chemotherapy (n=230)

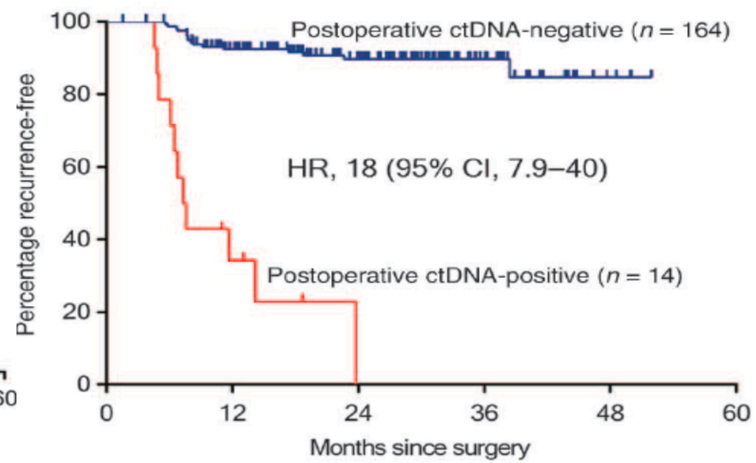
Post-operative CEA



Clinical Risk Factors*



Post-operative ctDNA



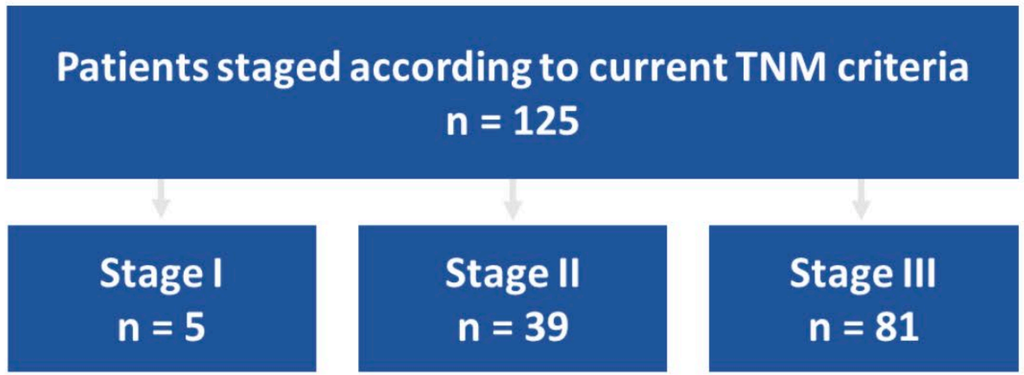
* T stage, LN< 12, LVI

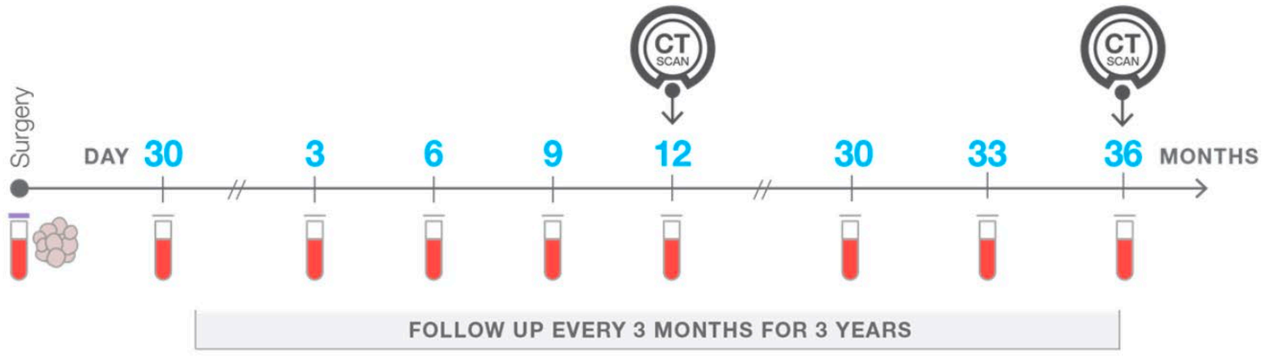
Tie J, et al. *Sci Transl Med*. 2016;8:346ra92.

Signatera (tumor informed): Clinical validation study in stage I-III CRC

JAMA Oncology | Original Investigation

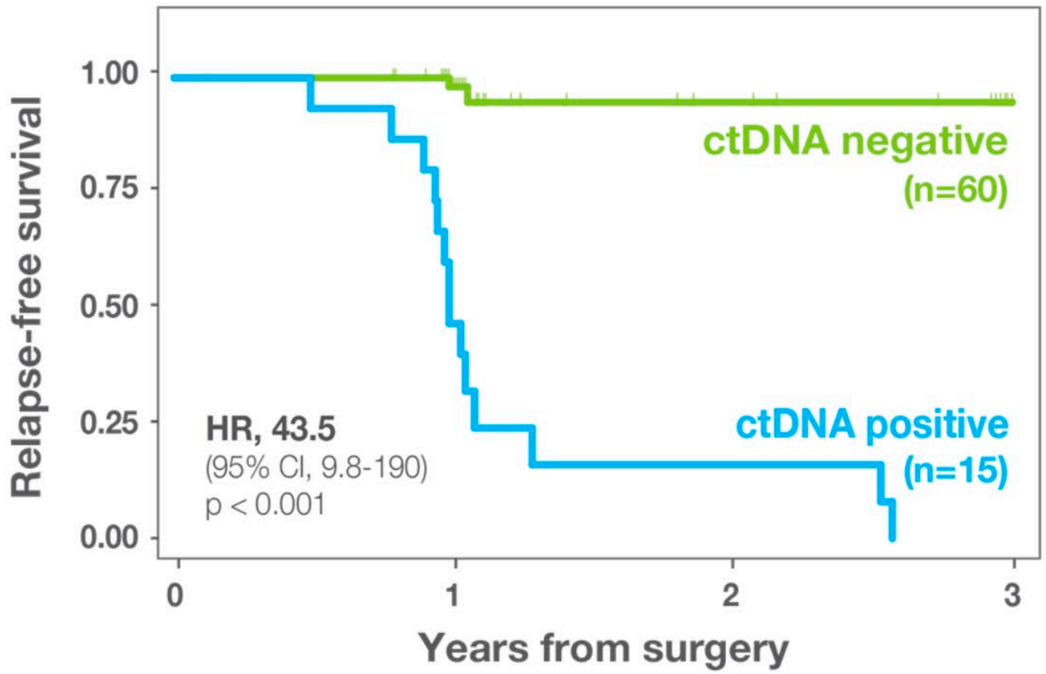
- 125 patients
  stages I-III CRC, treated with curative surgery and optional adjuvant chemotherapy
- 795 plasma samples
  were collected:
  - Pre-surgery
  - Day 30
  - Qtrly up to 3 years

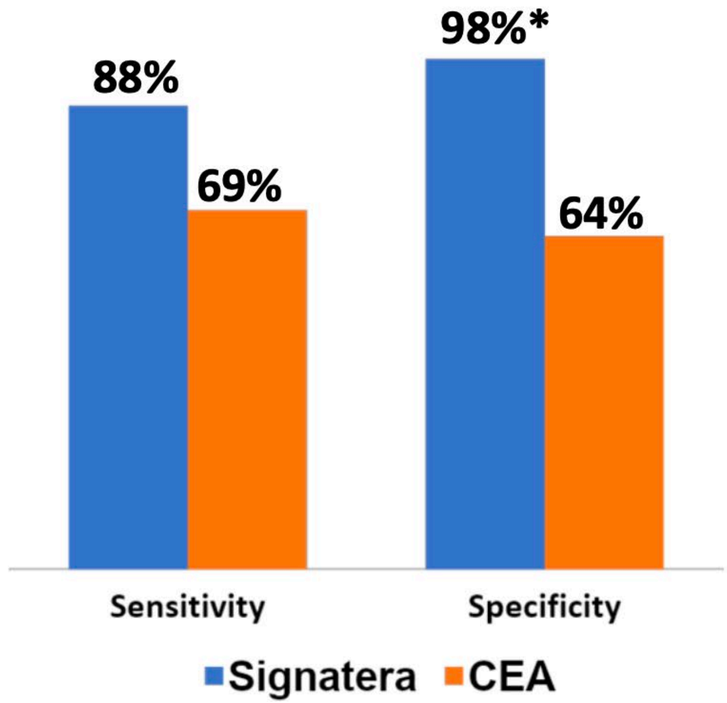




Reinert et al., JAMA Oncol. 2019;5(8):1124-1131.

Stage I-III colon ca: ctDNA outperforms CEA





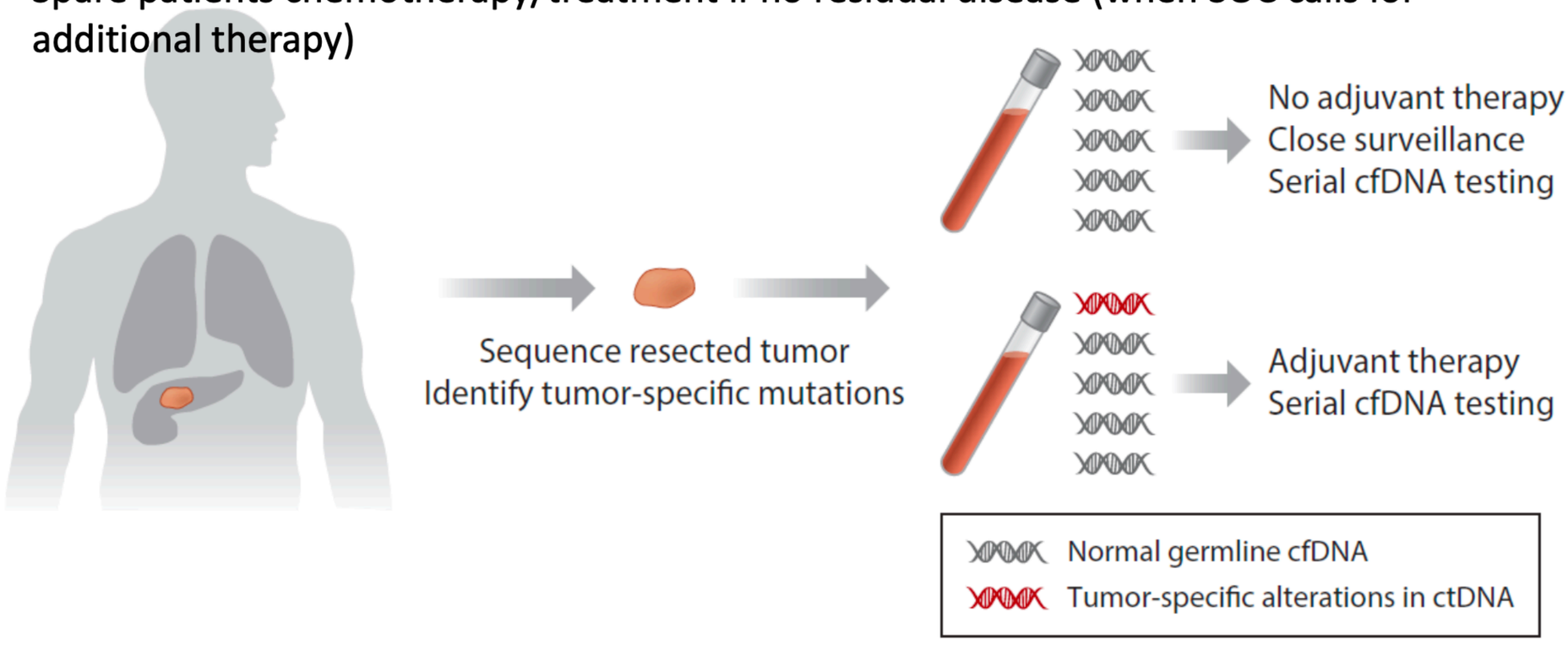
*Patient-level specificity 98%. Test-level specificity 99.7%.[2]

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

Can we integrate MRD into clinical care?

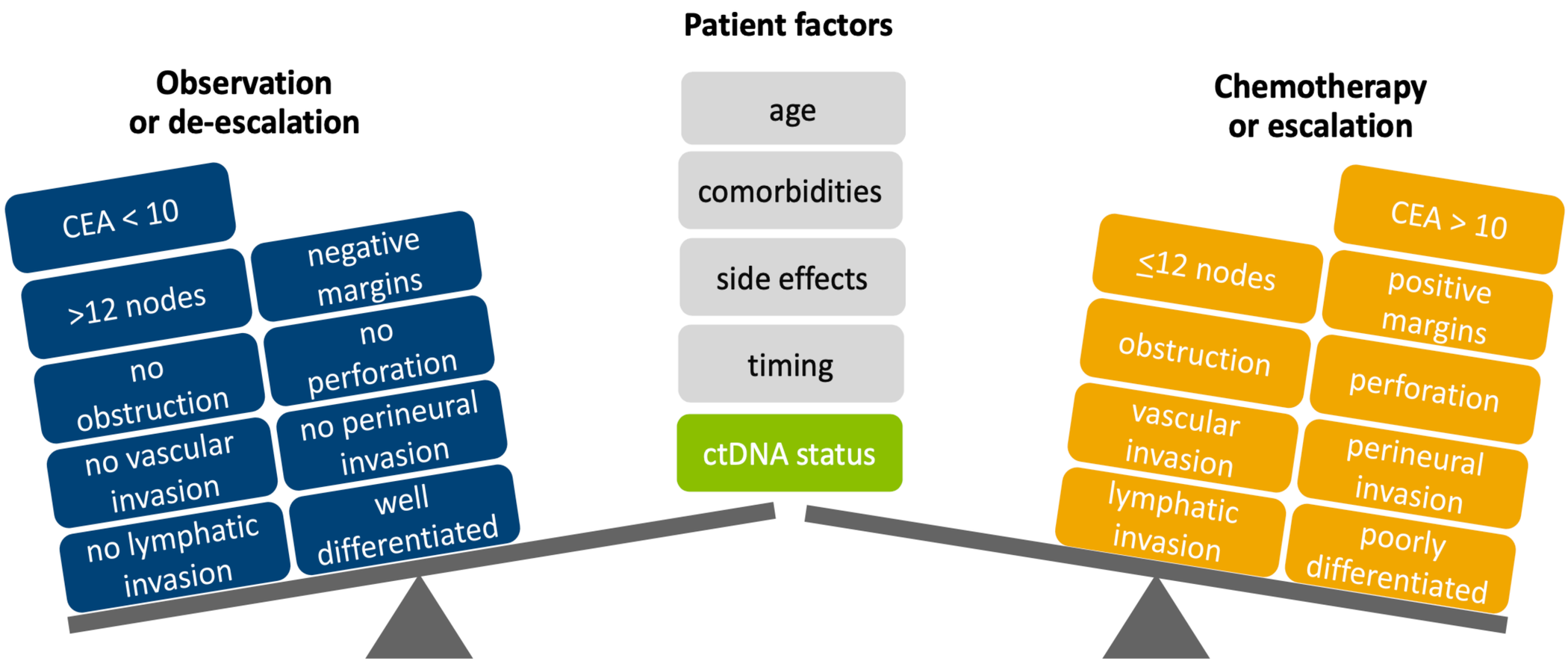
Potential applications:

- Selecting high risk patients for aggressive therapy when post-operative observation is SOC
- Spare patients chemotherapy/treatment if no residual disease (when SOC calls for additional therapy)



Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

Factors that influence adjuvant chemotherapy



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

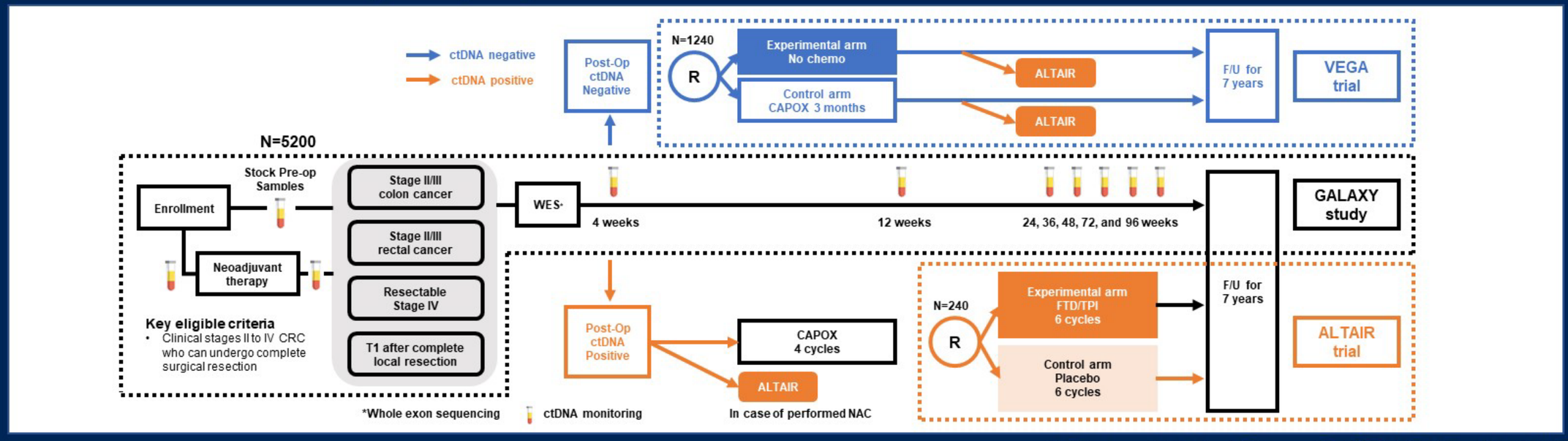
Co-authors; Hiromichi Shirasu, Jun Watanabe, Kentaro Yamazaki, Keiji Hirata, Naoya Akazawa, Nobuhisa Matsuhashi, Mitsuru Yokota, Masataka Ikeda, Kentaro Kato, Alexey Aleshin, Shruti Sharma, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Yoshiaki Nakamura, Hiroya Taniguchi, Masaki Mori, Takayuki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

On behalf of the CIRCULATE-Japan Investigators

Background

- Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) has the potential to select patients who may benefit more from standard-of-care (SOC) adjuvant chemotherapy (ACT) by accurately assessing recurrence-risk post-surgery and by evaluating ACT efficacy.
- CIRCULATE-Japan project is a large platform enrolling patients with clinical stage II–IV resectable colorectal cancer (CRC) to evaluate the clinical utility of ctDNA MRD analysis. The study comprises of one observational (GALAXY study) and two randomized phase III trials (VEGA and ALTAIR trials)[1,2].

Schema of CIRCULATE-Japan project



1. Taniguchi H, et al. Cancer Sci 2021, 2. Miyo M, et al. Cancer Sci 2021.

ASCO® Gastrointestinal Cancers Symposium

Emerging Roles of ctDNA on the Horizon of Gastrointestinal Cancers

ctDNA as a Tool to Detect Minimal Residual Disease After Surgery

Scott Kopetz, MD, PhD

Professor, GI Medical Oncology

University of Texas, MD Anderson Cancer Center

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ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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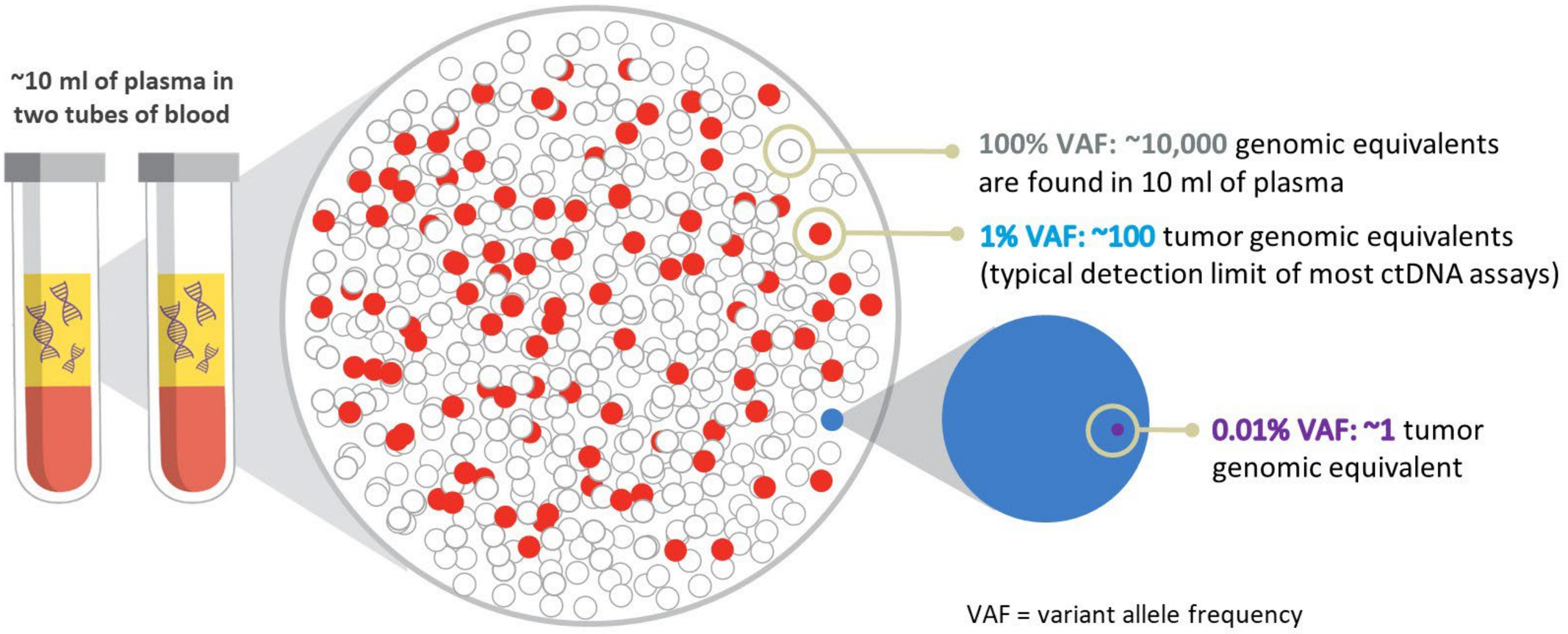
Best performing assays can detect as few as one genomic equivalent in 10 ml of plasma (VAF = 0.01%)

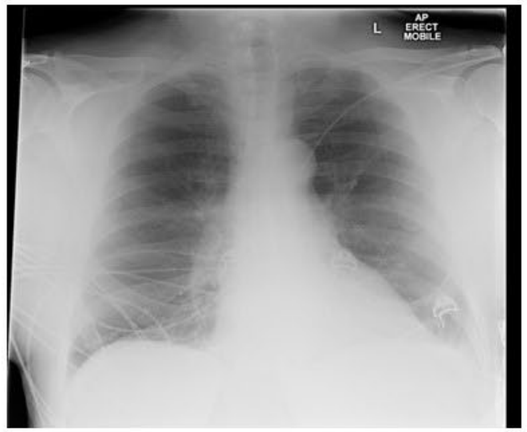


This requires use of a ctDNA assay optimized for minimal residual disease detection

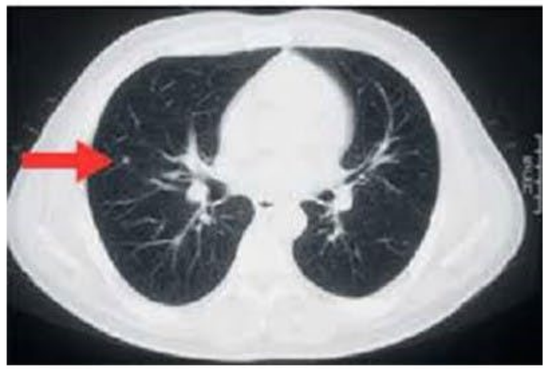
Kopetz GI ESMO '20; Revised from slide of A. Aleshin

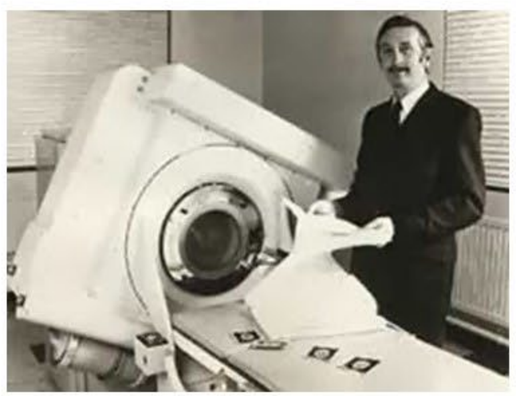
Evolution of Tumor Surveillance: Dramatic improvement of sensitivity

CXR can detect
10^9 cancer cells



CT Scan can detect
10^7 cancer cells

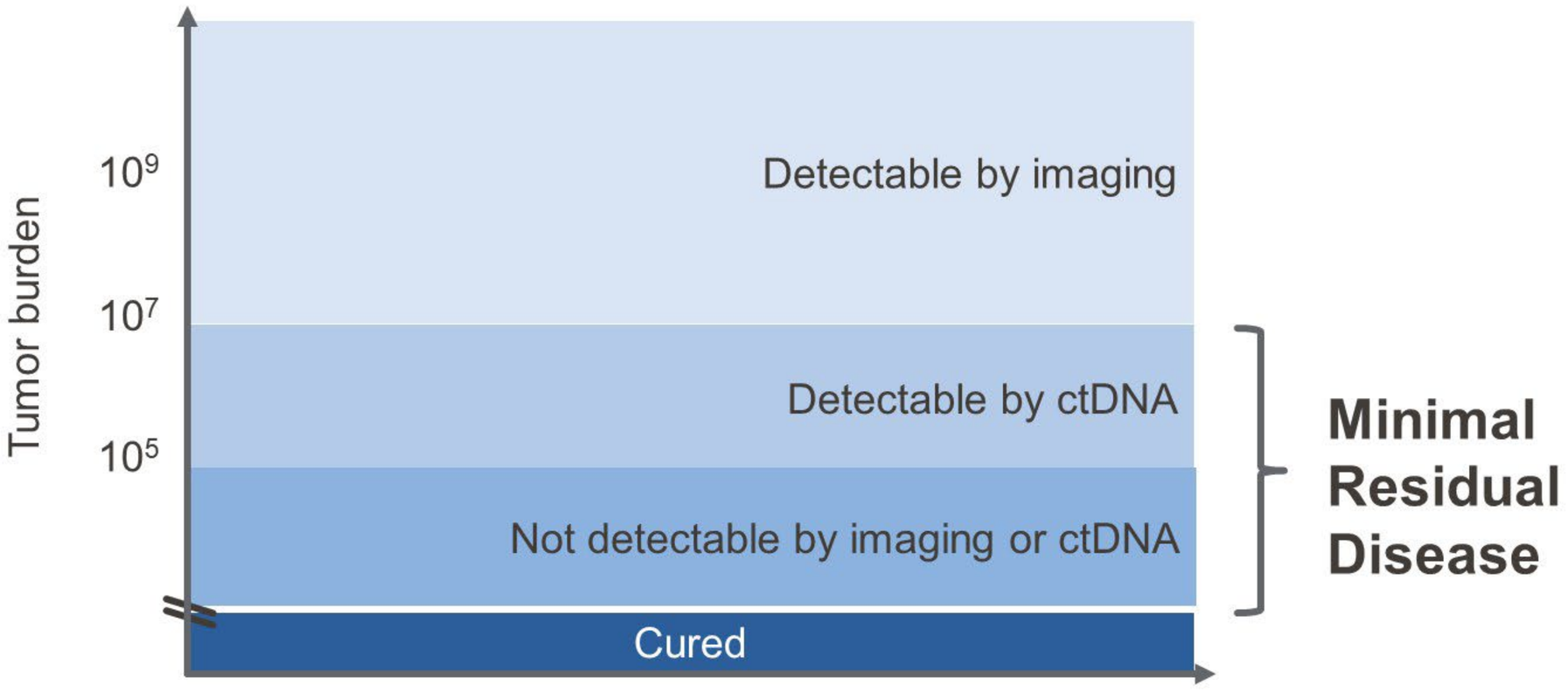




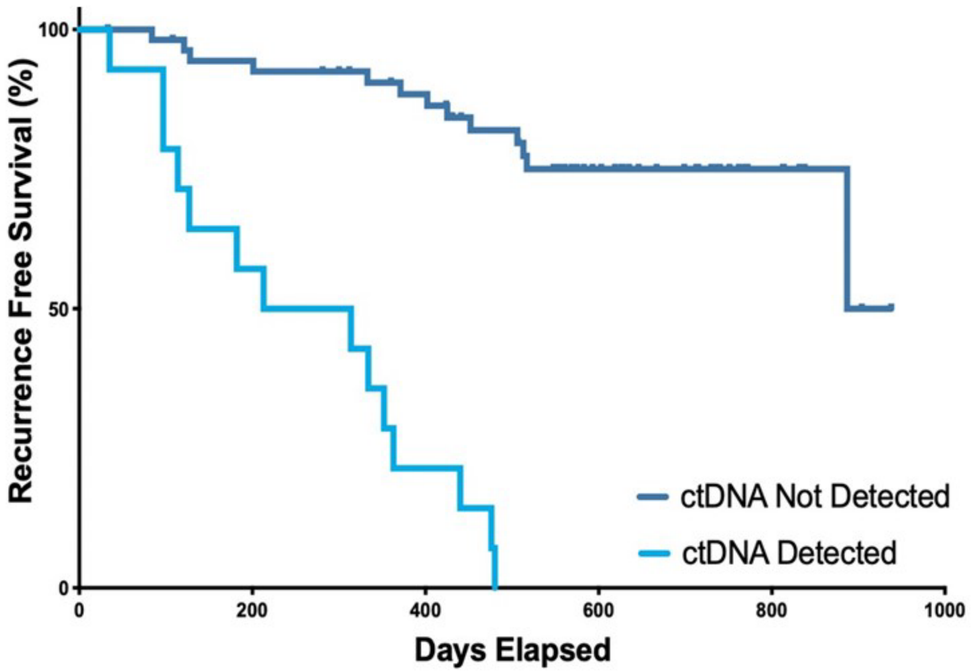
ctDNA can detect
10^5 cancer cells?

Definition of Minimal Residual Disease

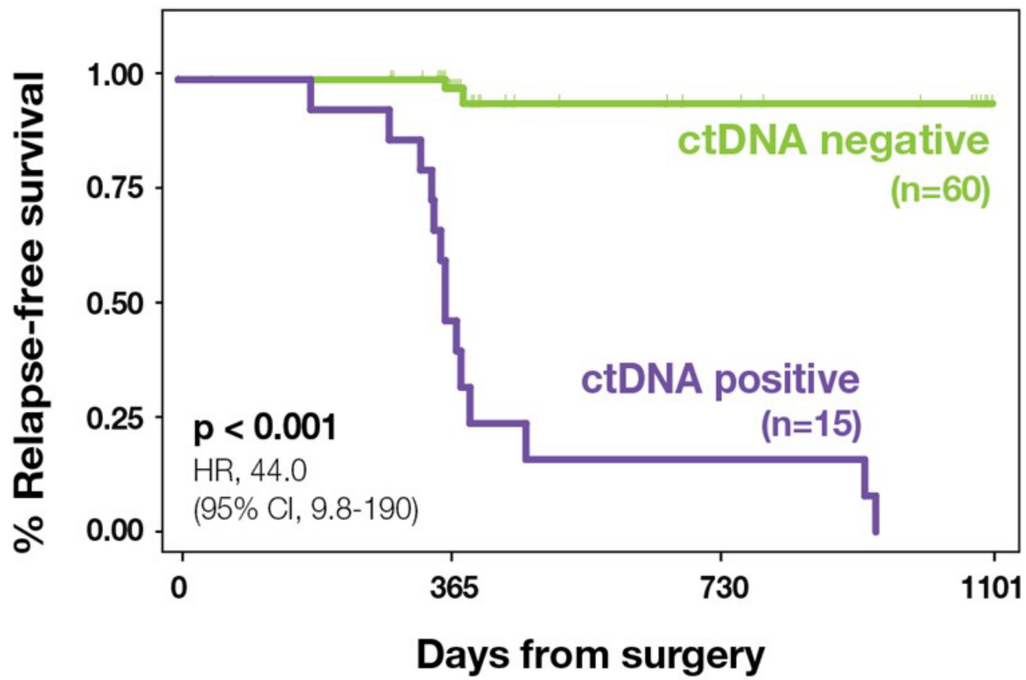
Presence of cancer after surgical resection (or other definitive procedure) ***without*** radiographic evidence of disease



Currently available ctDNA clinical assays can detect MRD



Parikh et al CCR '21; MGH / Guardant Health / **Reveal**

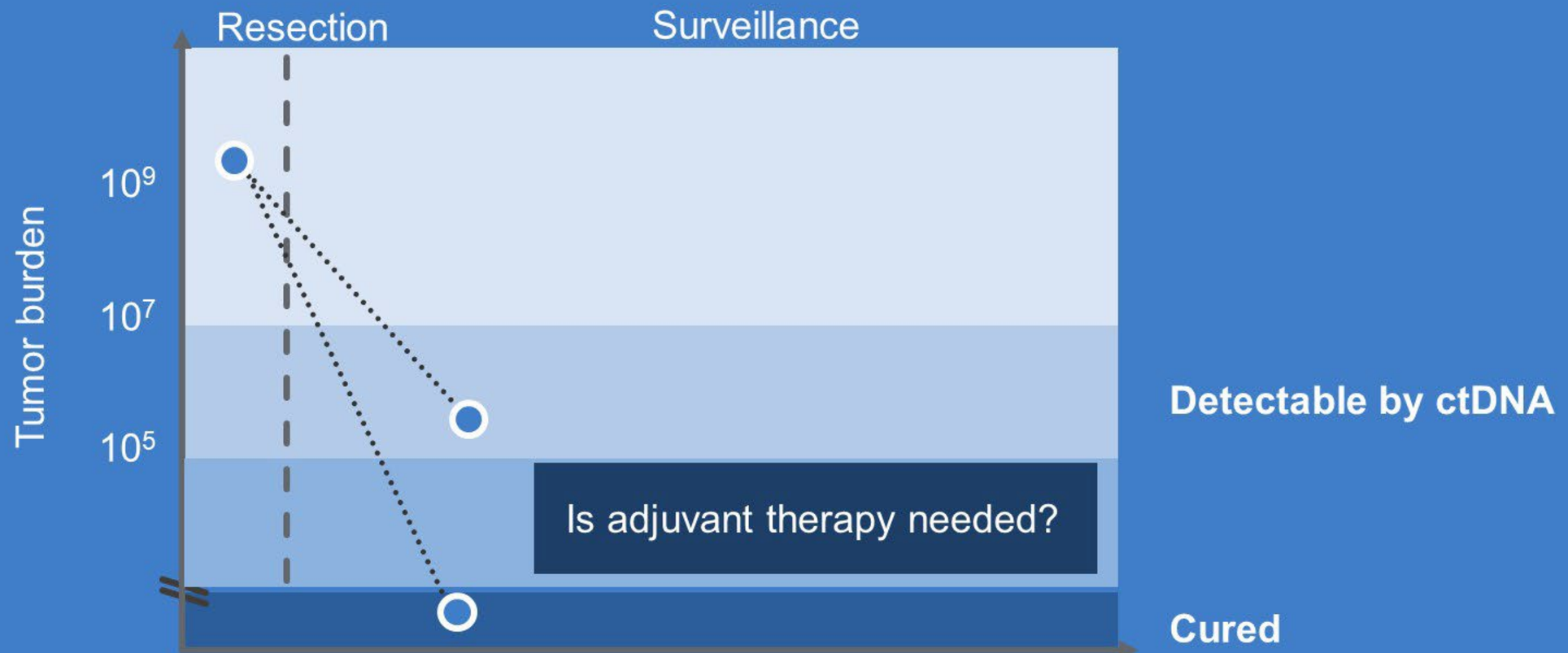


Reinart et al JAMA Onc '19; Aarhaus / Natera / **Signatera**

These assays are currently covered by Medicare and most insurance companies for CRC, but not (yet) other GI cancers.

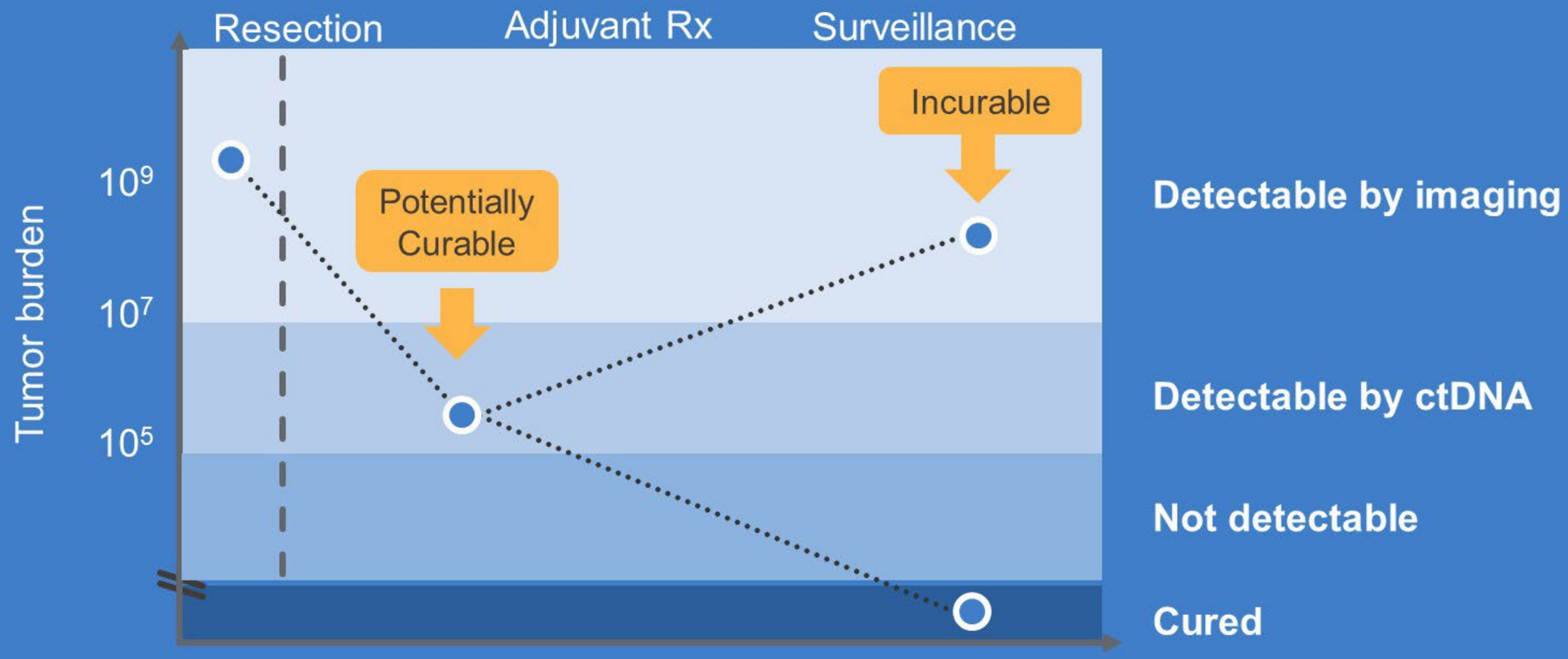
Clinical Utility:

Defining Patients for Adjuvant Therapy

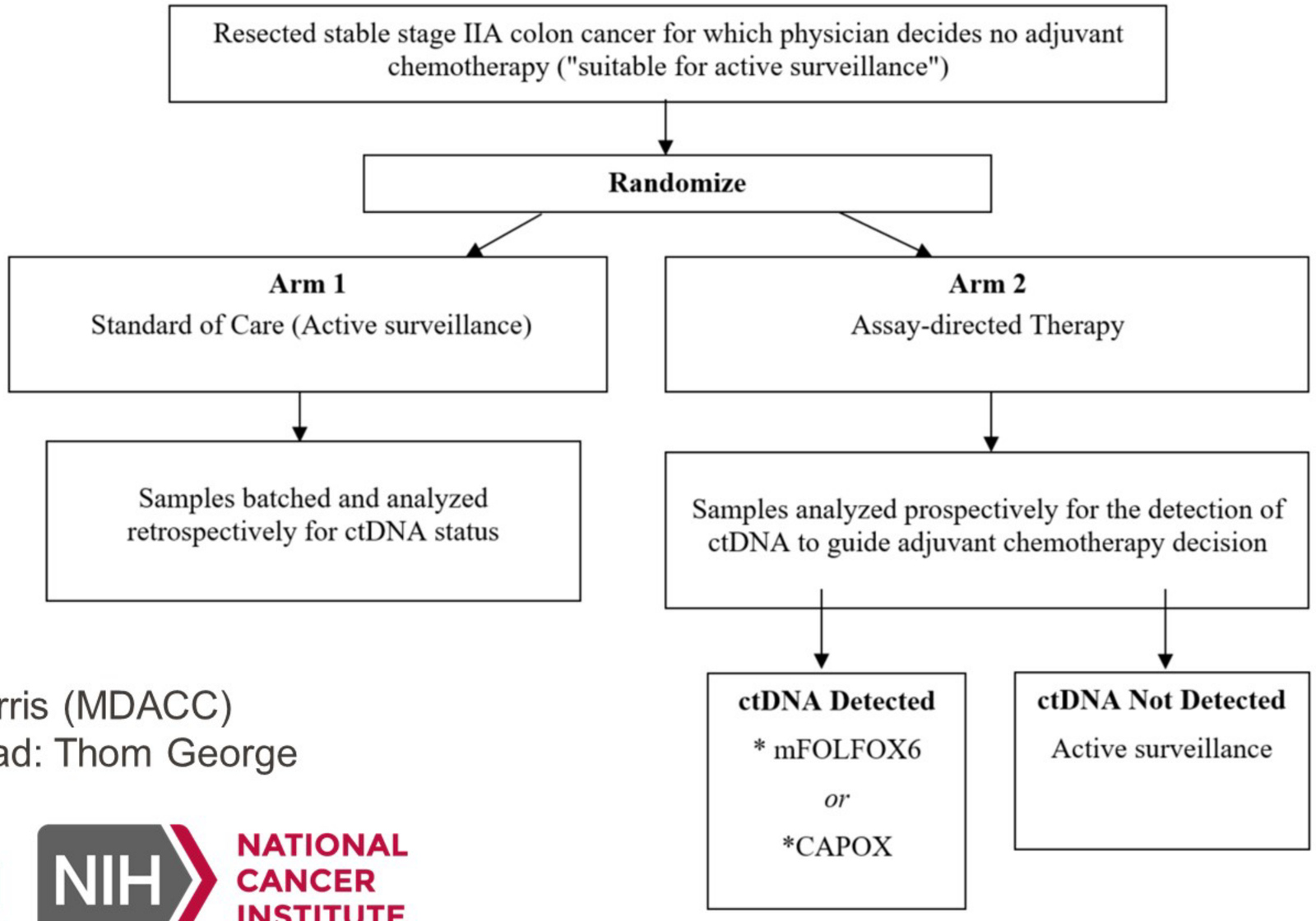


Clinical Utility:

Addition of Novel Therapies with Curative Intent



COBRA: Stage II Adjuvant Study CR1643



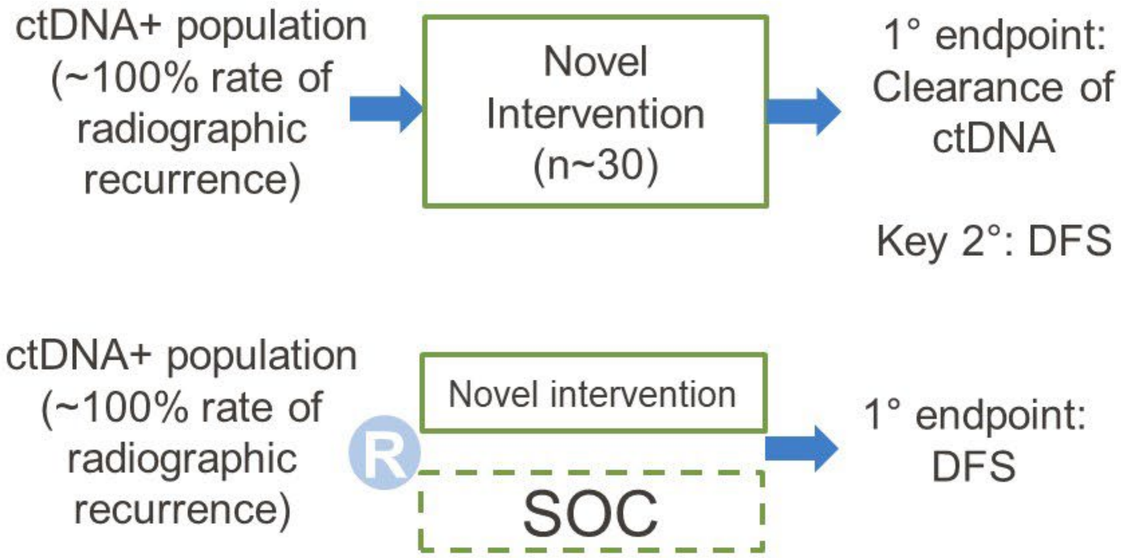
PI: Van Morris (MDACC)
NRG GI Lead: Thom George

NRG ONCOLOGY

NIH NATIONAL CANCER INSTITUTE

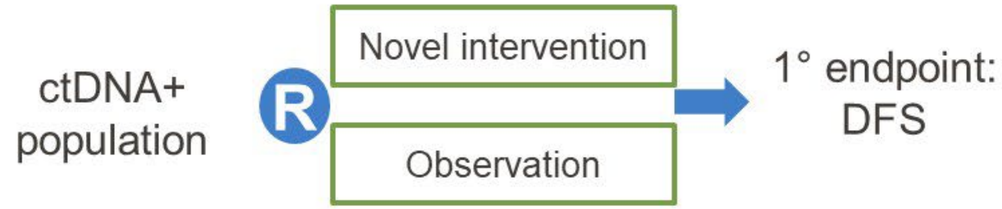
ctDNA Enables Rapid Path to Registration for Novel Therapies

Phase II Proof of Concept



- Endpoint of clearance of ctDNA, where this is **necessary but not sufficient** for improved outcomes

Phase III Registration Study



- Very high event rate, so relatively small Phase III study size (~300 pts)

Dasari et al JCO '20

Other Proof of Principle MRD Pilot studies

Cord blood NK cells + Cetuximab	TBD
Pembrolizumab or Nivolumab for MSI-H	NCT03803553/NCT03832569
TAS-102 with or without Irinotecan	NCT04920032
Exercise +/- Diet, Vit D, Aspirin	NCT05036109 / NCT04589468
Personalized Peptide Vaccine + CD40 + anti-PD1	NCT03803553
Encorafenib, binimetinib, cetuximab in $BRAF^{mut}$	NCT02600949
Many additional studies in development	

Resources are available to find clinical trials for patients with ctDNA+ MRD: CRCMRD.com and Colontown

Conclusions

- MRD applications are enabled by very high **positive predictive value** (low false positive) of commercially-available ctDNA for recurrent disease in patients
- This is not a marker of high risk for recurrence, but **defines molecular persistence of disease / minimal residual disease**.
- GI cancer patients with ctDNA+ after definitive interventions should be considered as a new “line” of therapy distinct from adjuvant or first line metastatic and **suitable for novel drug development**
- *In the next several years, ctDNA will dramatically change our approaches to “adjuvant” therapy, **but we need to develop the data** and understand more about strengths/weaknesses of these strategies before prematurely adopting any new intervention approaches*

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Rectal Cancer Early Stage

ASCO® Gastrointestinal Cancers Symposium

Short course radiotherapy *vs* Long course chemoradiation

As a component of TNT for LARC

Emma Holliday, MD

Assistant Professor Gastrointestinal Radiation Oncology

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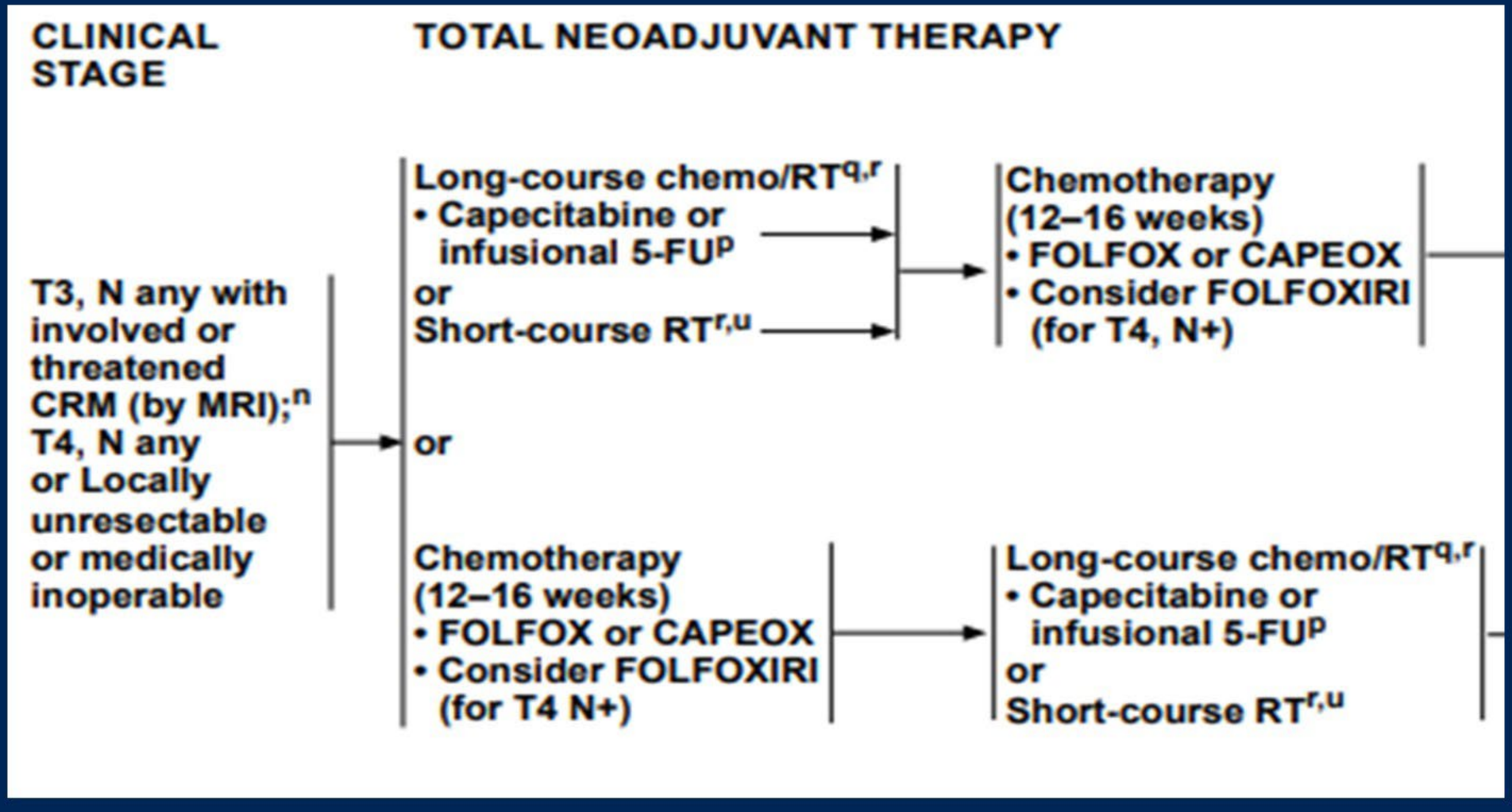
TNT is the clear SOC due to DFS benefit



RAPIDO

PRODIGE-23

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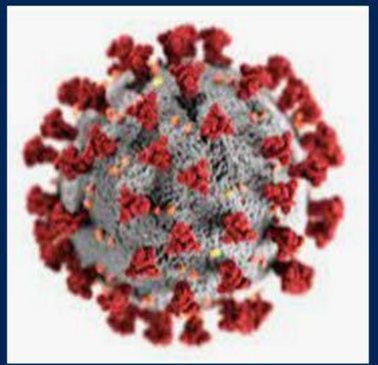
Benefits of SCRT over LC-CRT?

- Similar efficacy and safety compared to long course
- More convenient to patients
- Less costly/financially toxic



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SCRT vs LC-CRT Trials: Toxicity & Complications

	Short Course	Long Course	P-value
Polish Trial I (Bujko 2006)	Late tox: 28.3%	Late tox: 27.0%	0.81
TROG 01.04 (Ansari 2017)	G3-4 late tox: 5.8%	G3-4 late tox: 8.2%	0.53
Stockholm III (Erlandsson 2017)	Postop comp & late tox: 50% & 43% immed surg vs 38% & 40% delay surg	Postop comp: 39% Late tox: 47%	0.53

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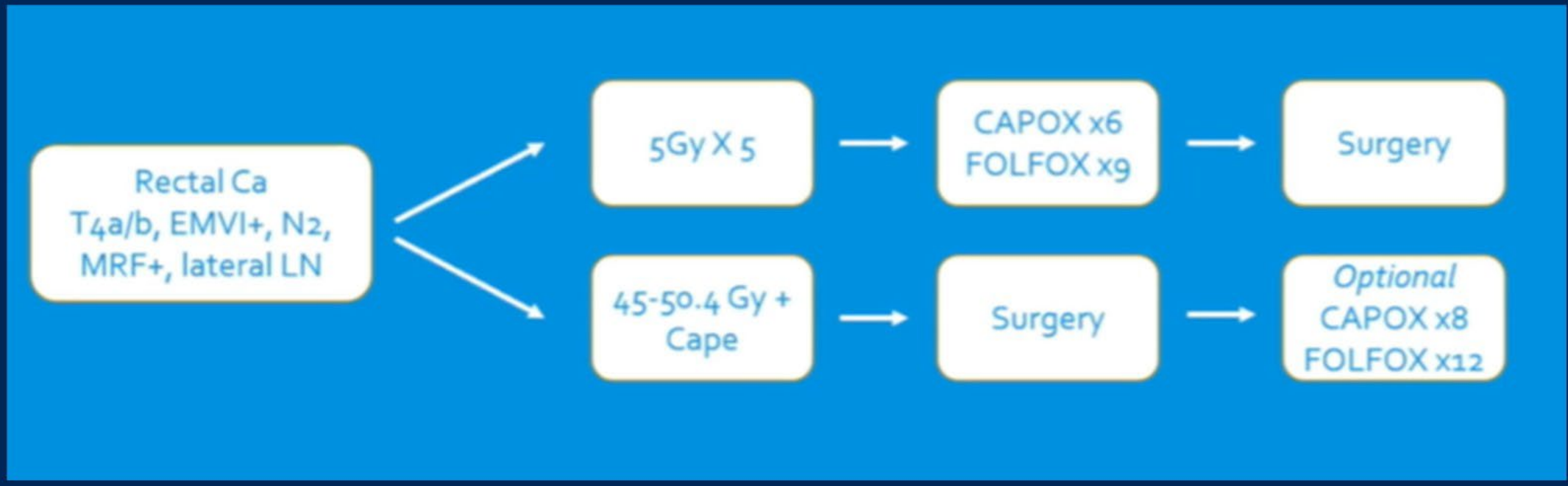
RAPIDO



Primary outcome: Disease-related treatment failure = locoregional failure, distant metastasis, new primary colorectal tumor or treatment-related death.

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SCRT is more convenient and less costly

- **Convenience:**
- **Less time off work/away from family**
- **Less time in the hospital system/COVID exposure**

- **Cost:**
- **28 fractions 3DCRT + capecitabine = $19,311***
- **5 fractions 3DCRT = $7,223***

- **Radlow et al JAMA Network Open 2019*
- *From 2018 Medicare Fee Schedule to include costs of consult, simulation, weekly management, treatment planning and delivery*

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When is LC-CRT preferable in TNT?

- *When a W&W strategy is desired*

- *When maximal local response is desired for sphincter-saving operation*

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Is SCRT W&W ready for prime time?

- Many are awaiting results from randomized trials to support retrospective data:

- ACO/ARO/AIO-18.1: SCRT TNT vs LC-CRT TNT → surg or W&W
- STAR-TREC = TME vs LC-CRT + W&W vs SCRT + W&W

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Conclusions/Take-Away

- SCRT and LC-CRT are both reasonable and evidence-based RT options in the context of TNT.

- For most patient with LARC, SCRT will give equivalent results and may be preferable for logistics/financial toxicity.

- For patients for whom a W&W approach is being considered, LC-CRT is preferred by many centers, but similar rates of pCR call this bias into question and further data may inform this.

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ASCO® Gastrointestinal Cancers Symposium

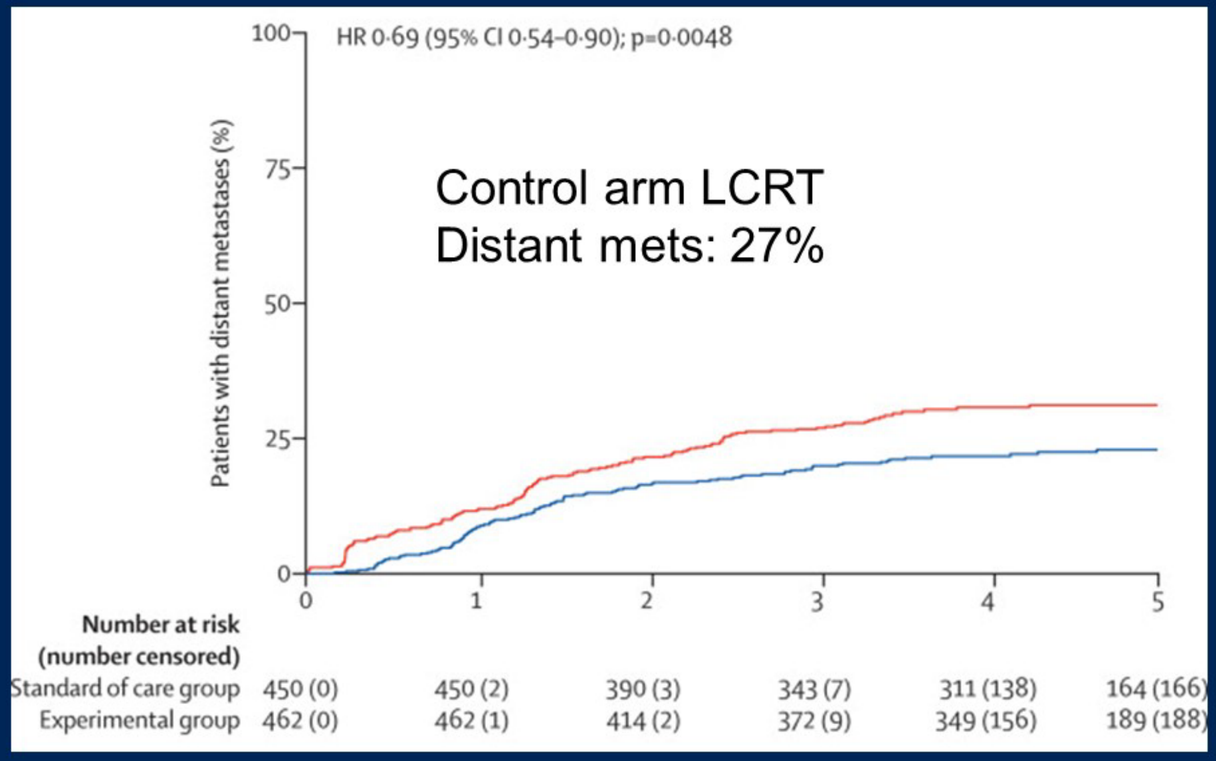
Triplet versus Doublet Systemic Therapy

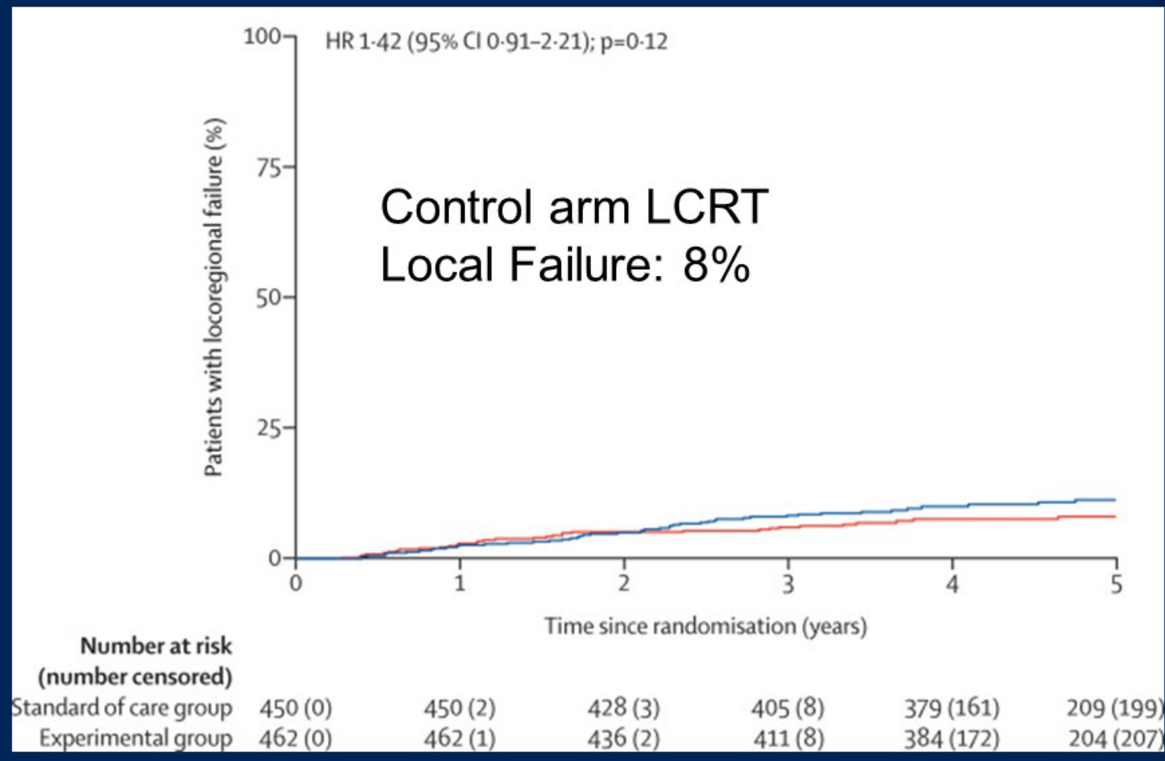
Should we add irinotecan to the mix?

Hanna K. Sanoff, MD
Professor of Medicine
Division of Oncology
University of North Carolina

Treatment fails 2-3x as often outside the pelvis

RAPIDO TRIAL





Bahadoer, et al Lancet Oncol 2021; 22: 29-42

Why would we escalate?

1. People with rectal cancer are still dying of metastatic recurrence

2. Current treatment is often inadequate for high-risk local disease

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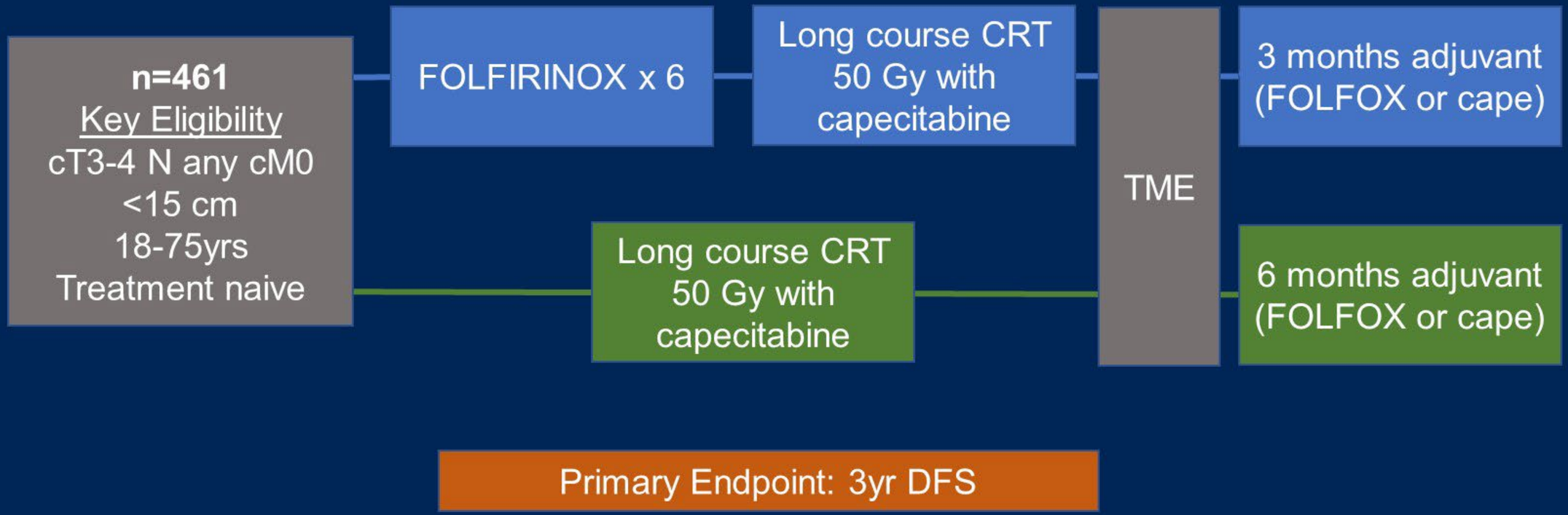
Best evidence is for triplet chemotherapy
UNICANCER-PRODIGE 23



Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

PRESENTED BY: Sanoff, Hanna K

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*UNICANCER-**PRODIGE 23***
Key trial characteristics

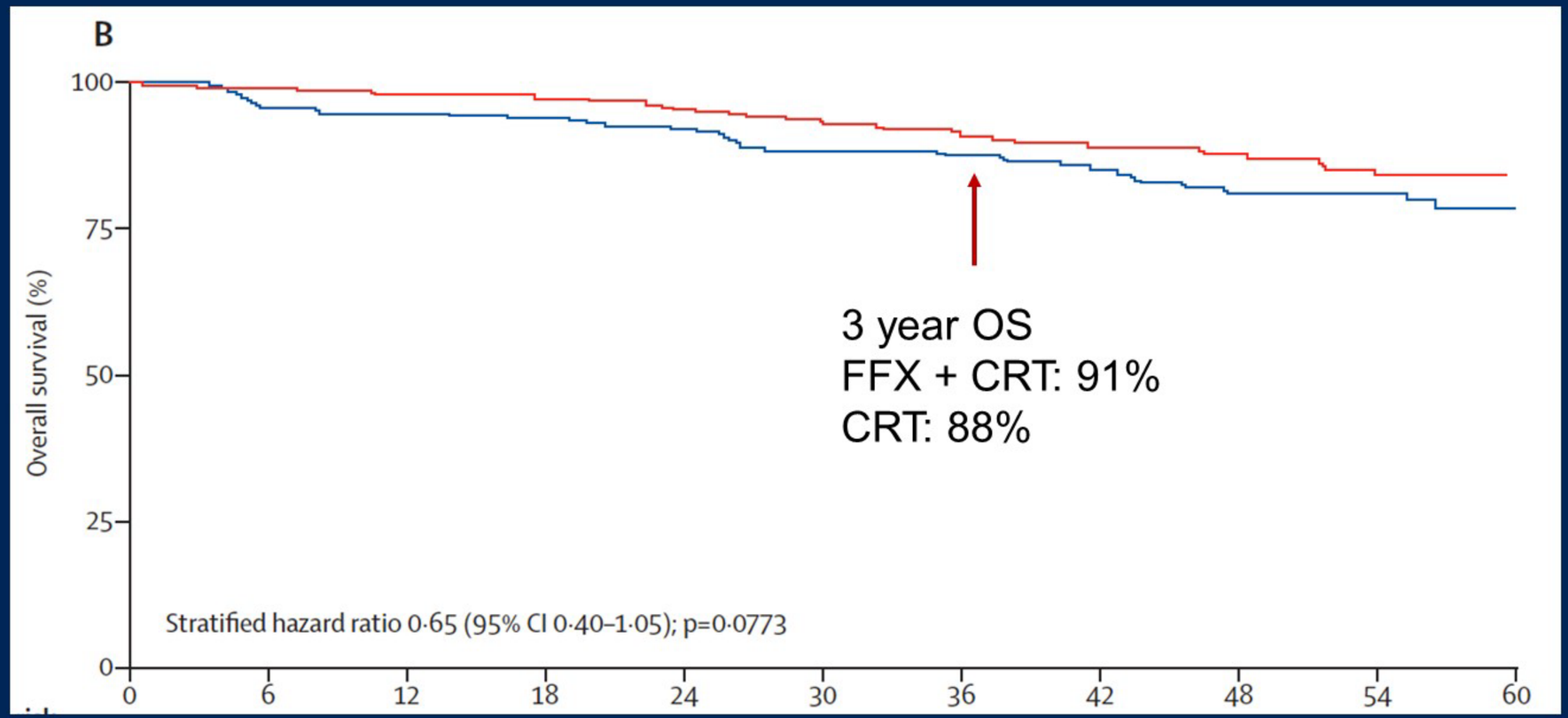
	Neoadj FFX + CRT	Neoadj CRT
Median Age	61	62
Distance to anal verge ≤ 5cm	38%	36%
MRI stage T4	18%	16%
cN2	26%	23%
Predicted radial margin ≤ 1mm	21%	23%

TREATMENT SUMMARY

- 92% received 6 cycles FFX
- 27% received cGSF
- 95% vs 99% CRT completion
- 92% vs 95% resected
- 77% vs 79% started adjuvant chemotherapy

Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

*UNICANCER-**PRODIGE 23***
Key Trial Results



Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

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Reminder comparison: RAPIDO Trial Results

n=920
Key Eligibility
cTt or N2 or <1mm MRF cM0
Extramural vasc invasion
MRI + lateral nodes
<16 cm
Treatment naive

Short course RT
25 Gy in 5 fx

CapeOx x 6 or
FOLFOX x 9

Long course CRT 50
Gy with capecitabine

TME

No additional
adjuvant

6 months adjuvant
per investigating
center (41% pts)

Outcome	SC + FOLFOX	Long Course CRT	
Disease related treatment failure at 3 years	24%	30%	HR 0.75, 0.6-0.95
OS at 3 years	89%	89%	HR 0.92, 0.67-1.25
Distant Mets at 3 years	20%	27%	HR 0.69, 0.54-0.9
Local Recur. At 3 years	8%	6%	HR 1.42, 0.9-2.21
pCR	28%	14%	p<0.0001

Bahadoer, et al Lancet Oncol 2021; 22: 29-42

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Why would we escalate?

1. People with rectal cancer are still dying of metastatic recurrence
   ✓ 7% absolute improvement distant mets
   X No survival benefit. Will survival difference emerge with time?
   X is this related to FOLFIRINOX? Or just neoadj chemo?

2. Current treatment is often inadequate for high-risk local disease
   x Minimal difference in local recurrence, but too few locally high-risk patients to know

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Why would we escalate?

1. People with rectal cancer are still dying of metastatic recurrence

2. Current treatment is often inadequate for high-risk local disease

3. For better responses in bulky, painful, difficult to resect cancers

4. Improve chance of organ preservation / Non-operative management

x Totally unclear– to be answered by JANUS trial

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Conclusions on Neoadjuvant FOLFIRINOX

YES FOLFIRINOX IS A GO:

- Improves tumor regression and symptom palliation for very bad, locally advanced disease

MAYBE…

- DFS and distant mets: Clear incremental benefit vs upfront CRT only
- BUT not clear that's from triplet vs just neoadjuvant chemo
- Without survival data use should be reserved for selected cases

JURY'S OUT ON:

- Local control for high-risk disease (current evidence suggests no benefit)
- Overall survival benefit
- Improvement in cCR for non-operative management

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Colon & Rectal Cancer Late Stage

CLINICAL PRESENTATION

WORKUP

FINDINGS

Suspected or proven metastatic synchronous adenocarcinoma (T any, N any, M1)

- Colonoscopy
- Consider proctoscopy
- Chest CT and abdominal CT or MRI[c]
- Pelvic MRI with or without contrast[c]
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of next-generation sequencing [NGS panel])[y,z]
- Determination of tumor MMR or MSI status[y] (if not previously done)
- Biopsy, if clinically indicated
- Consider PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[c]
  - Consider MRI of liver for patients who are potentially resectable
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases

Synchronous liver only and/or lung only metastases

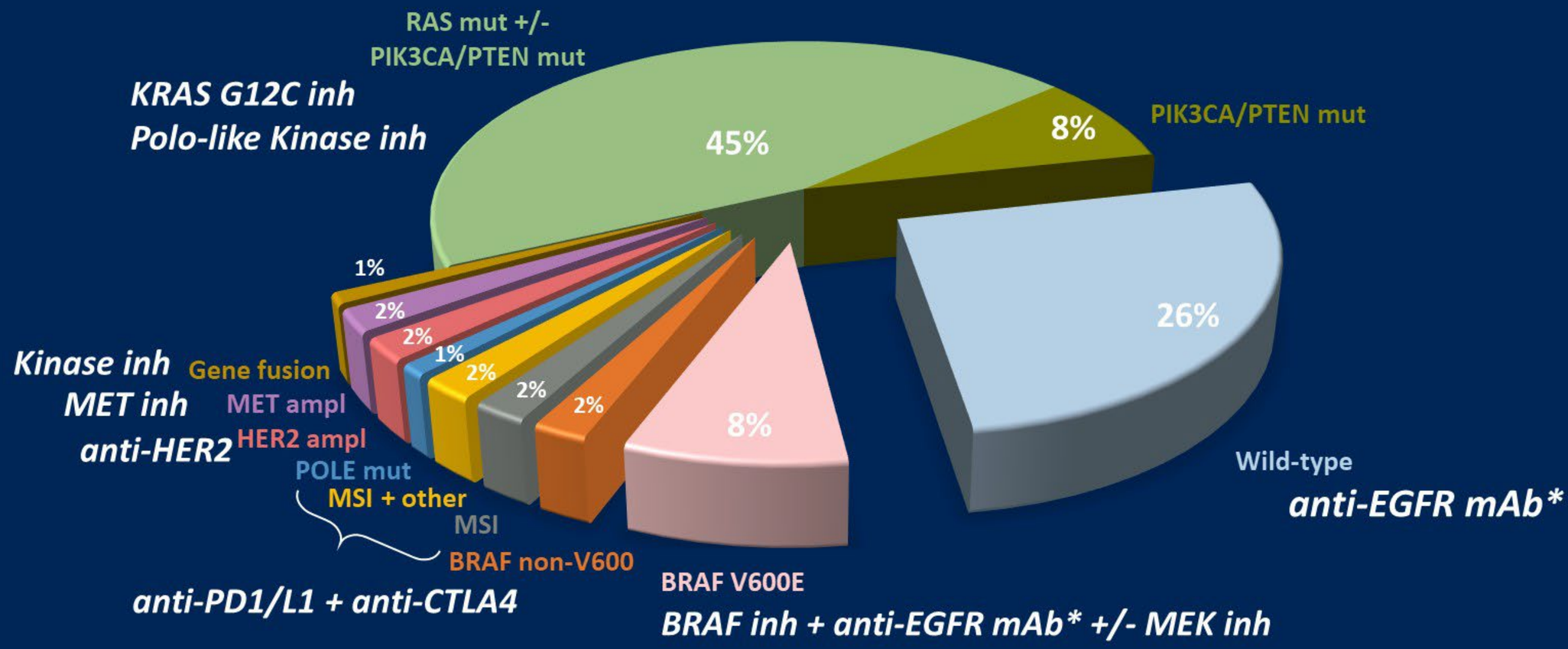
- **Resectable[i]** → See Primary Treatment (REC-8)
- **Unresectable[i] or medically inoperable** → See Primary Treatment (REC-9)

Synchronous abdominal/peritoneal metastases → See Primary Treatment (REC-10)

Synchronous unresectable metastases of other sites[aa] → Systemic therapy (See REC-F)

NCCN Clinical Practice Guidelines for Rectal Cancer. (2021, 2,2021). *National Comprehensive Cancer Network Clinical Practice Guidelines.* from https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Genomic markers in mCRC with existing or potential matched therapies



* mAb: monoclonal antibody

Modified citation from reference Dienstmann R, Tabernero J, et al. ASCO Edu. Book2018

PRESENTED BY: Takayuki Yoshino, MD, PhD

Keynote 177

- Superiority of Immunotherapy over chemotherapy

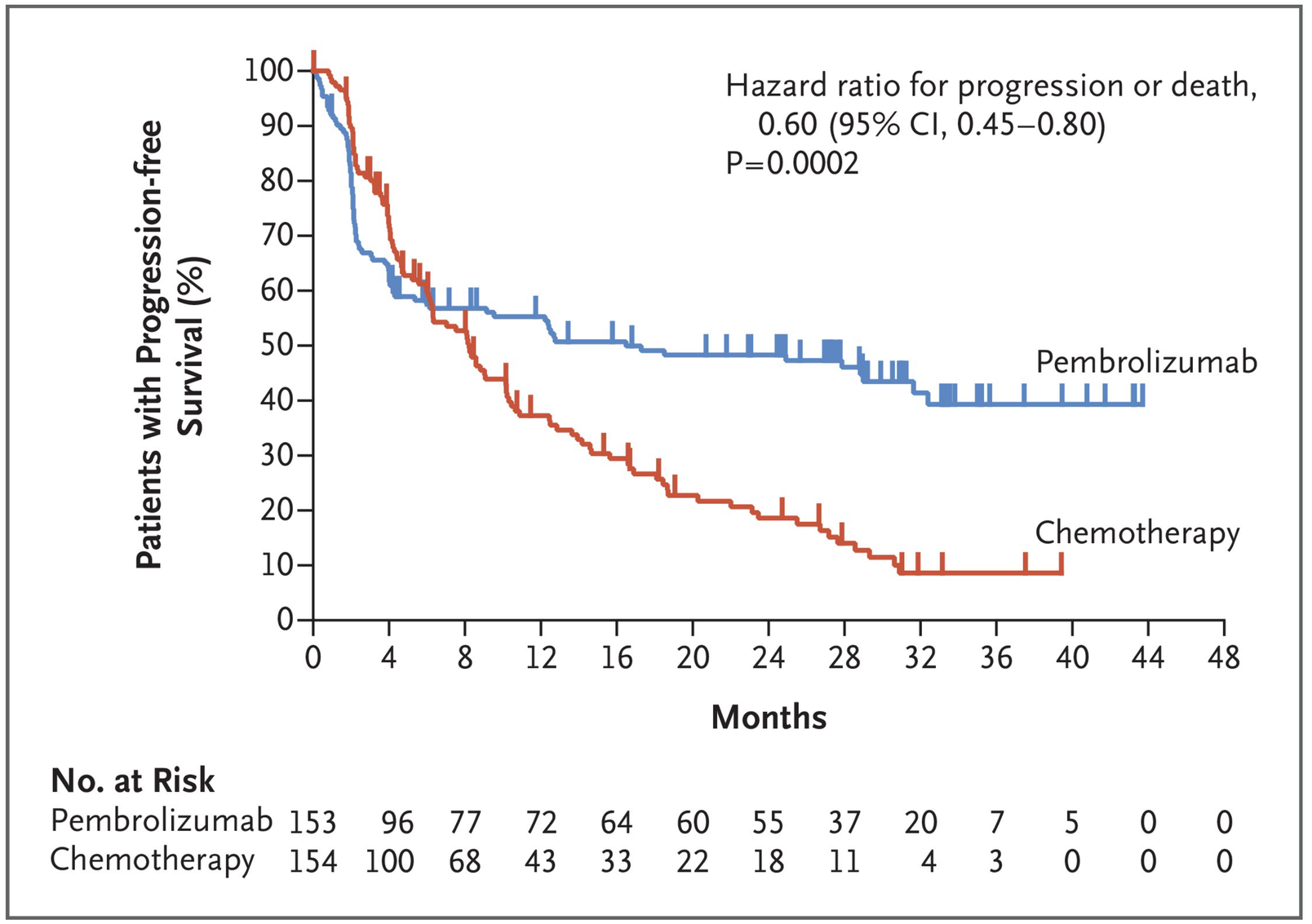
Original Article

Pembrolizumab in Microsatellite-Instability

Thierry André, M.D., Kai-Keen Shiu, F.R.C.P., Ph.D., Tae Won Kim, M.D., Ph.D., Benny Vittrup Jensen, M.D., Lars Henrik Jensen, M.D., Ph.D., Cornelis Punt, M.D., Ph.D., Denis Smith, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Manuel Benavides, M.D., Ph.D., Peter Gibbs, M.D., Christelle de la Fouchardiere, M.D., Fernando Rivera, M.D., Ph.D., Elena Elez, M.D., Johanna Bendell, M.D., Dung T. Le, M.D., Takayuki Yoshino, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Ping Yang, Ph.D., Mohammed Z.H. Farooqui, D.O., Patricia Marinello, Pharm.D., Luis A. Diaz, Jr., M.D., for the KEYNOTE-177 Investigators

N Engl J Med
Volume 383(23):2207-2218
December 3, 2020

Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRESENTATION

Suspected or proven metastatic synchronous adenocarcinoma (any T, any N, M1)

WORKUP

- Colonoscopy
- Chest/abdominal/pelvic CT[b]
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of tissue- or blood-based next-generation sequencing [NGS] panel)[v,w]
- Determination of tumor mismatch repair (MMR) or microsatellite instability (MSI) status[e] (if not previously done)
- Biopsy, if clinically indicated
- Consider 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

FINDINGS

- **Synchronous liver only and/or lung only metastases**
  - Resectable[h] → Treatment and Adjuvant Therapy (COL-5)
  - Unresectable (potentially convertible[h] or unconvertible) → Treatment and Adjuvant Therapy (COL-6)
- **Synchronous abdominal/peritoneal metastases** → Primary Treatment (COL-7)
- **Synchronous unresectable metastases of other sites[x]** → Systemic Therapy (COL-D)

[b] Principles of Imaging (COL-A).
[e] Principles of Pathologic Review (COL-B 4 of 8) - MSI or MMR Testing.
[h] Principles of Surgery (COL-C 2 of 3).
[v] Principles of Pathologic Review (COL-B 4 of 8) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[w] If known *RAS/RAF* mutation, HER2 testing is not indicated. Tissue- or blood-based NGS panels have the ability to pick up rare and actionable mutations and fusions.
[x] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Colon Cancer

NCCN Guidelines Index
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Discussion

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

Intensive therapy recommended

INITIAL THERAPY[c]

- **FOLFOX[d] ± bevacizumab[e]** → **Progression** → COL-D (2 of 13)
- **or CAPEOX[d] ± bevacizumab[e]** → **Progression** → COL-D (2 of 13)
- **or FOLFOX[d] + (cetuximab or panitumumab)[f,g] (*KRAS/NRAS/BRAF* WT)** → **Progression** → COL-D (2 of 13)
- **or FOLFIRI[h] ± bevacizumab[e]** → **Progression** → COL-D (3 of 13)
- **or FOLFIRI[h] + (cetuximab or panitumumab)[f,g] (*KRAS/NRAS/BRAF* WT)** → **Progression** → COL-D (3 of 13)
- **or FOLFIRINOX[d,h,i] ± bevacizumab[e]** → **Progression** → COL-D (4 of 13)
- **or ([Nivolumab ± ipilimumab] or pembrolizumab [preferred]*)[j,k,l,m] (dMMR/MSI-H only)[f]** → **Progression** → COL-D (5 of 13)

Intensive therapy NOT recommended

- **5-FU ± leucovorin ± bevacizumab[e]**
- **or Capecitabine ± bevacizumab[e]**
- **or (Cetuximab or panitumumab)[f,g] (category 2B) (*KRAS/NRAS/BRAF* WT)**
- **or (Nivolumab or pembrolizumab [preferred]*)[j,k,l,m] (dMMR/MSI-H only)[f]**
- **or Nivolumab + ipilimumab*[j,k,l,m] (dMMR/MSI-H only)[f] (category 2B)**
- **or (Trastuzumab[n] + [pertuzumab or lapatinib])[o] (HER2-amplified and *RAS and* BRAF WT)[f]**

→ **Progression**

- **Improvement in functional status** → **Consider initial therapy as above[p] or If previous fluoropyrimidine,** COL-D (5 of 13)
- **No improvement in functional status** → **Best supportive care** NCCN Guidelines for Palliative Care

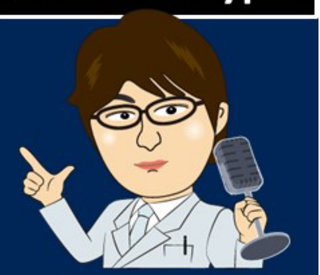
* Patients should be followed closely for 10 weeks to assess for response.

Footnotes COL-D (7 of 13)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Anti-EGFR mAb vs. Bevacizumab in First-line Therapy

RAS wild type



FIRE-3[1)]

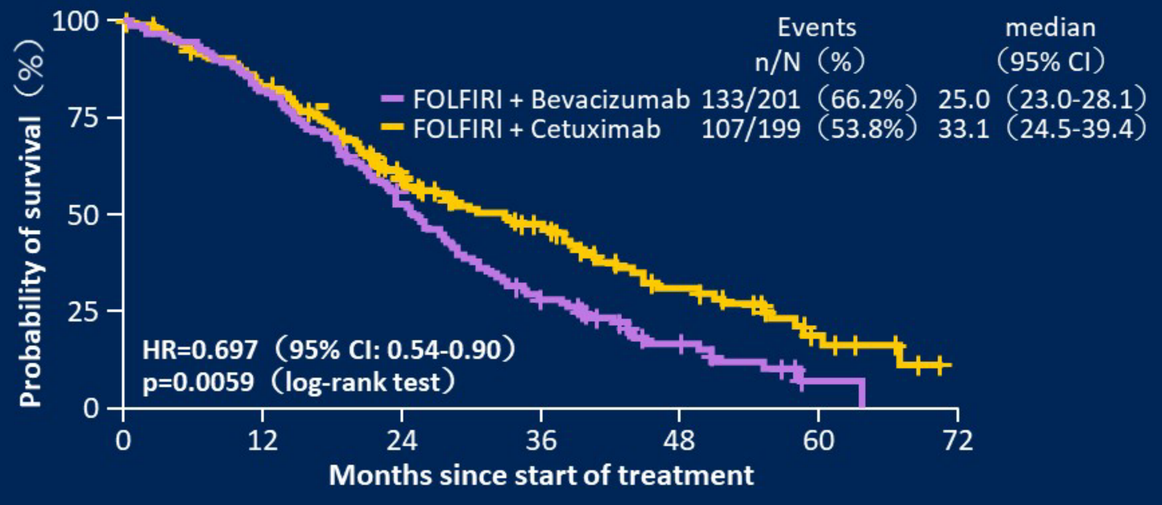
KRAS exon 2 wild-type mCRC
（N=752）

R

- FOLFIRI＋Bevacizumab（n=295）
  RAS wild-type n=201
- FOLFIRI＋Cetuximab（n=297）
  RAS wild-type n=199

RAS analysis(n=400)

ΔOS：8.1 months



CALGB/SWOG 80405[2)]

KRAS exon 2 wild-type mCRC
（N=1,137）

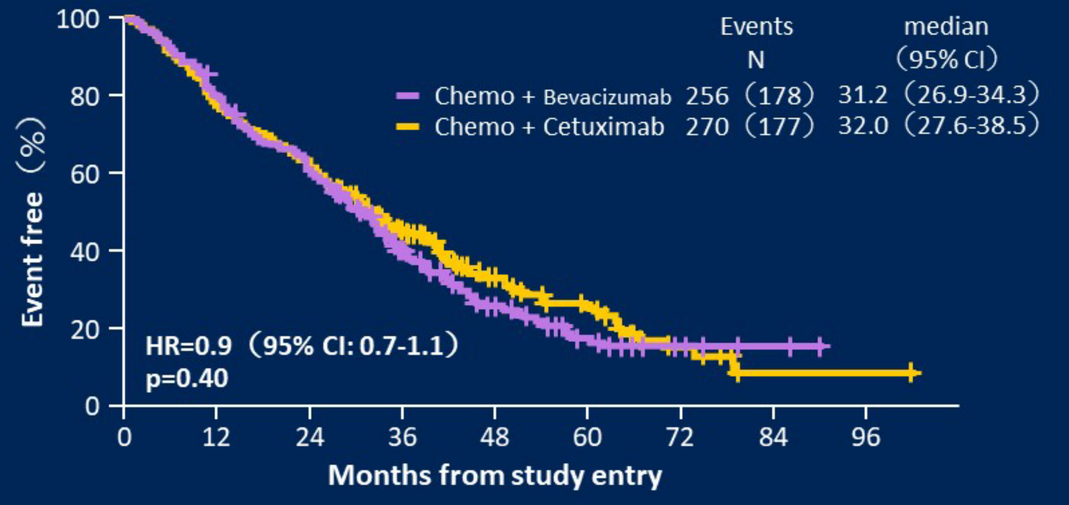
FOLFIRI/
FOLFOX

Physician's choice

- FOLFIRI＋Bevacizumab（n=559）
  RAS wild-type n=256
- FOLFIRI＋Cetuximab（n=578）
  RAS wild-type n=270

RAS analysis(n=526)

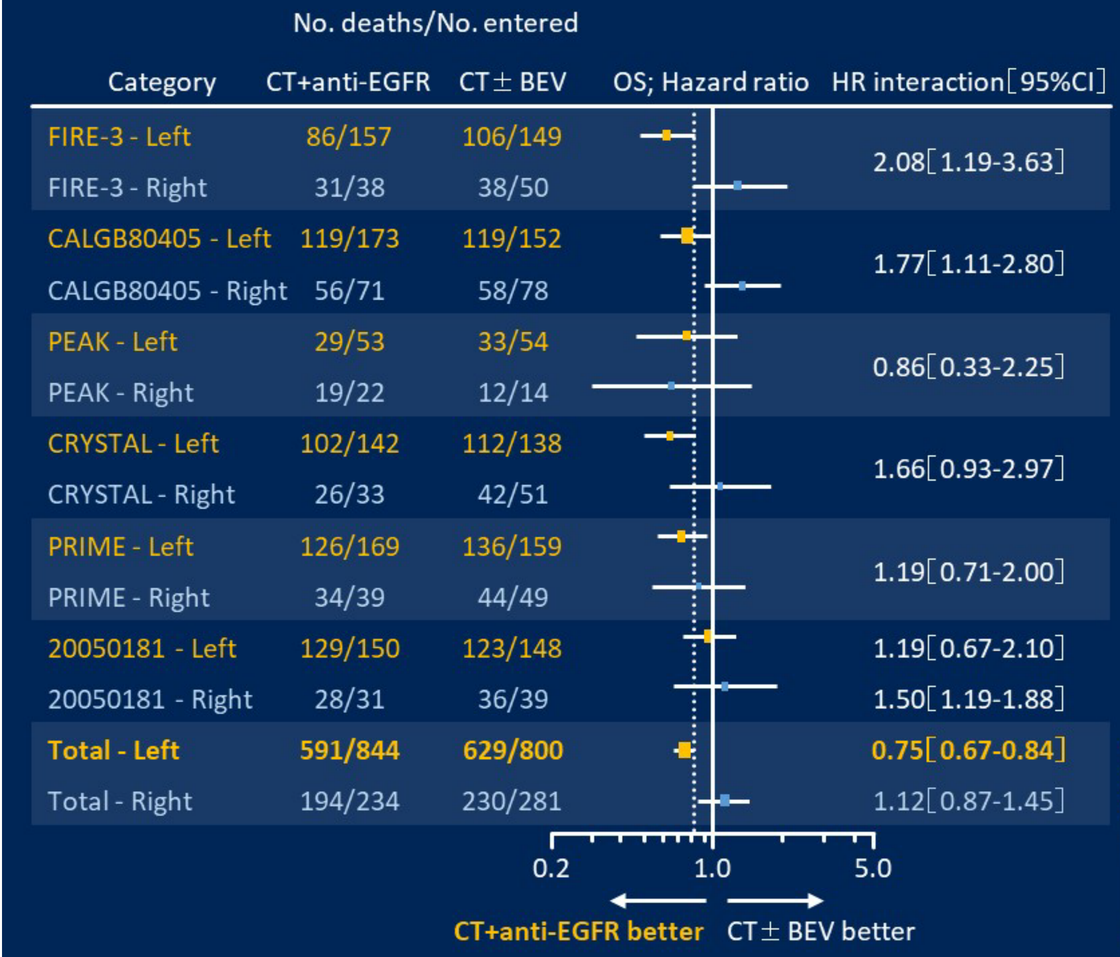
ΔOS：0.8months

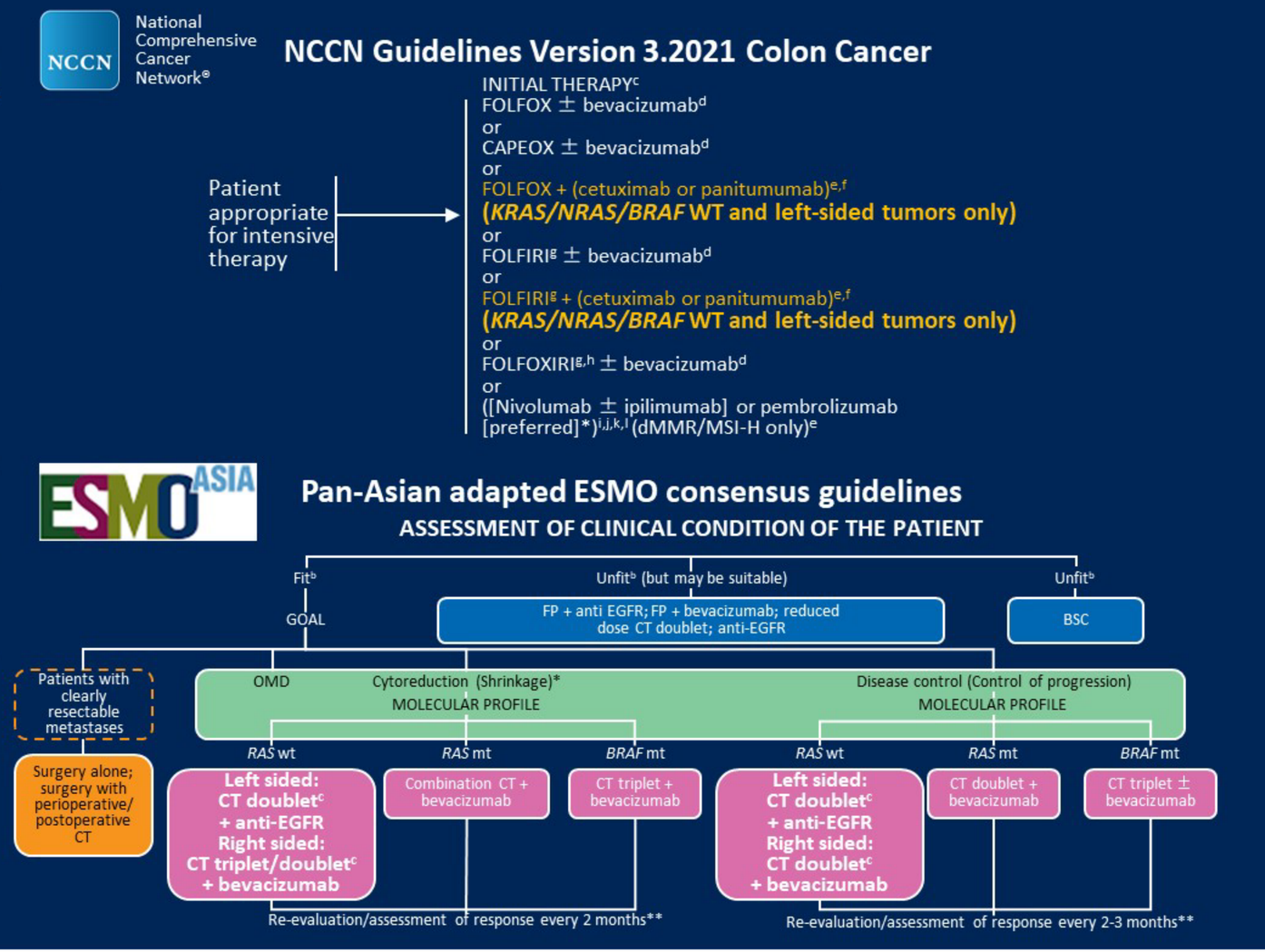


1) Stintzing S, et al.: Lancet Oncol 2016. 2) Lenz H, et al.: ESMO 2014, #501O. Venook AP, et al.: JAMA 2017.

PRESENTED BY: Takayuki Yoshino, MD, PhD

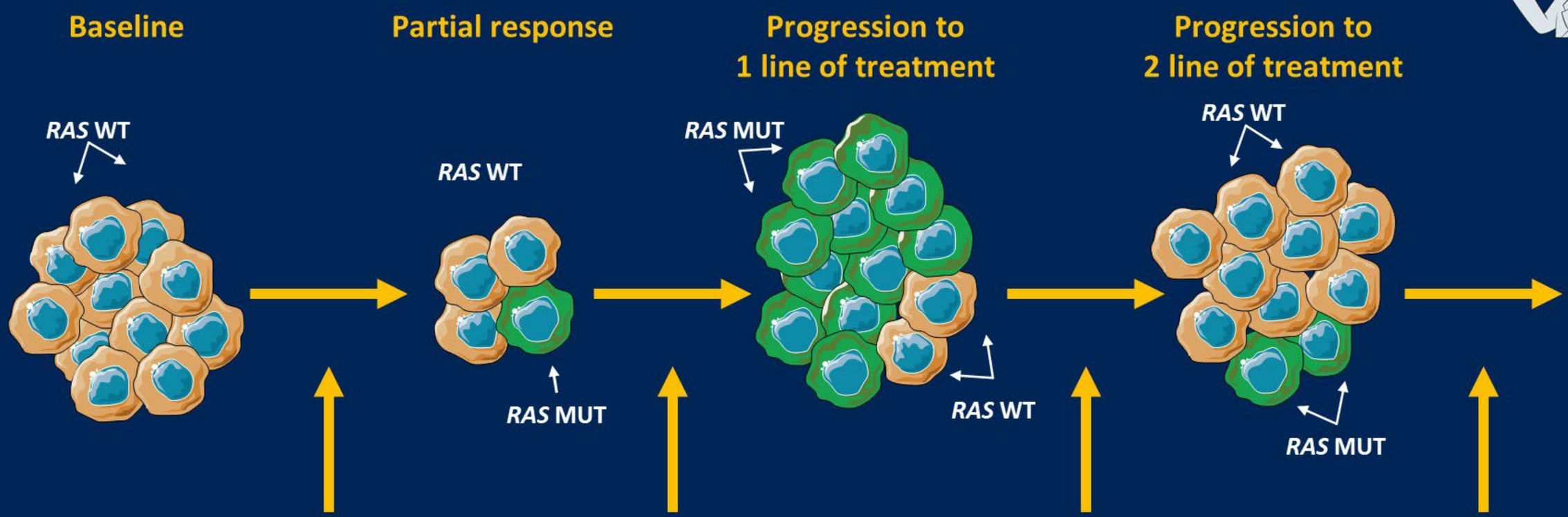
Prognostic and predictive value of primary tumor sidedness in patients with *RAS* wild-type mCRC





Arnold D, et al. Ann Oncol. 2017. NCCN Guidelines ver3.2021 Colon Cancer. Yoshino T, et al.: Ann Oncol 2018.

Biological rationale for anti-EGFR mAb rechallenge therapy



Ciardiello D, et al.:Cancers (Basel). 2021

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Rechallenge studies by ctDNA status

	Line	Regimen	*RAS/BRAF* status		N	ORR	DCR	PFS	OS
CRICKET[1)]	3	Cetuximab +Irinotecan	*RAS*	wild type	13	30.5%	76.9%	4.0m	12.5m
				mutant	12	0%	41.7%	1.9m	5.2m
E-Rechallenge[2)]	≥3	Cetuximab +Irinotecan	*RAS/BRAF*	wild type	7	42.9%	85.8%	NR	5.5m
				mutant	17	0%	37.5%	NR	3.0m
JACCRO-CC08&09[3)]	≥3	Cetuximab/ Panitumumab	*RAS*	wild type	10	NR	80.0%	4.7m	16.0m
				mutant	6	NR	33.3%	2.3m	3.8m
CAVE[4)]	≥3	Cetuximab +Avelumab	*RAS/BRAF*	wild type	41	9%	30%	4.3m	16.1m
				mutant	15	0%	7%	3.0m	11.5m
CHRONOS[5)]	≥3	Panitumumab	*RAS/BRAF*	wild type	27	30%	70%	16.4w	NR

Rechallenge of anti-EGFR mAb is considered in patients with blood-based RAS wild type.

NR: not reported

1) Cremolini C, et al. JAMA Oncol. 2019. 2) Ohhara Y et al.: ASCO-GI 2019 #585. 3) Sunakawa y, et al.: JCO Precis. Oncol. 2020.
2) 4) Martinelli E, et al.: JAMA Oncol. 2021. 5) Sartore-Bianchi A, et al.: ASCO2021 #3506.

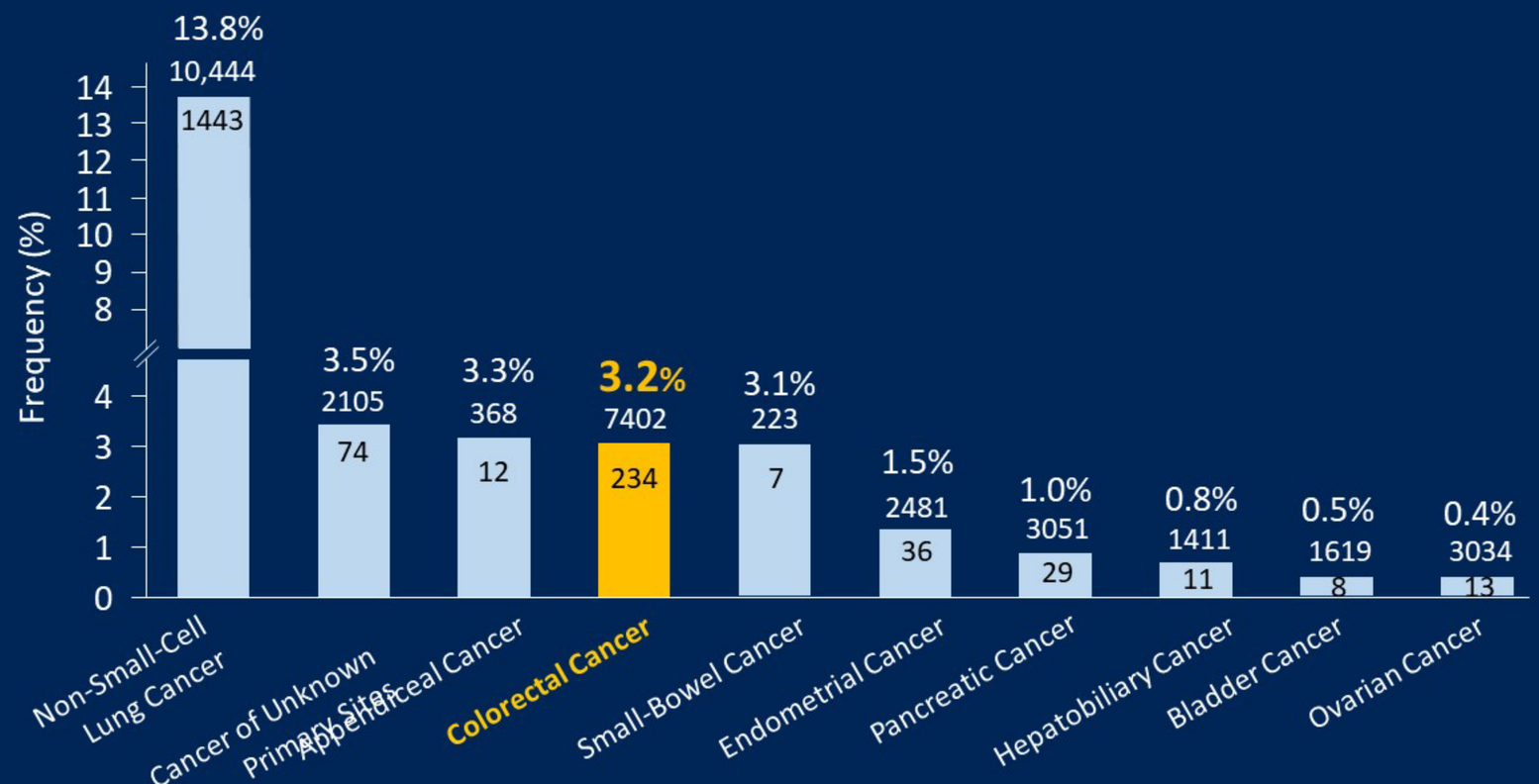
PRESENTED BY: Takayuki Yoshino, MD, PhD

RAS mutant

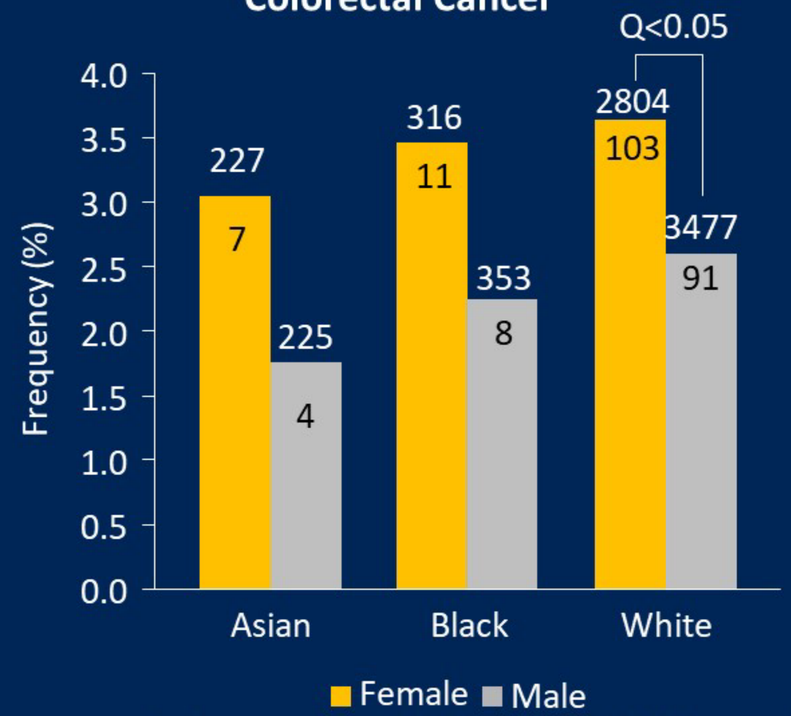
KRAS^{G12C} Mutant Landscape of 32,138 Patients.

Data from the registry of the American Association for Cancer Research Project GENIE

Distribution of *KRAS*^{G12C} Mutant



KRAS^{G12C} Mutant in Subgroups with Colorectal Cancer



P values were corrected by the Benjamini–Hochberg method to determine false discovery rate–corrected Q values

KRAS ^{G12C} ***mutation rate in colorectal cancer is 3.2% without racial difference.***

Nassar AH, et al. N Engl J Med. 2021

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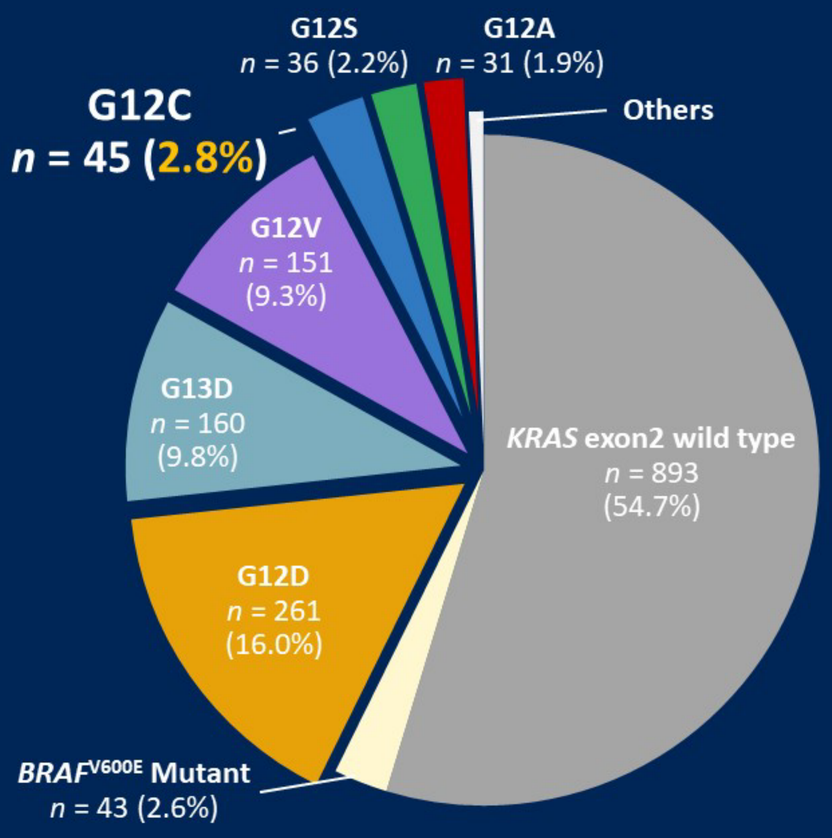
RAS mutant

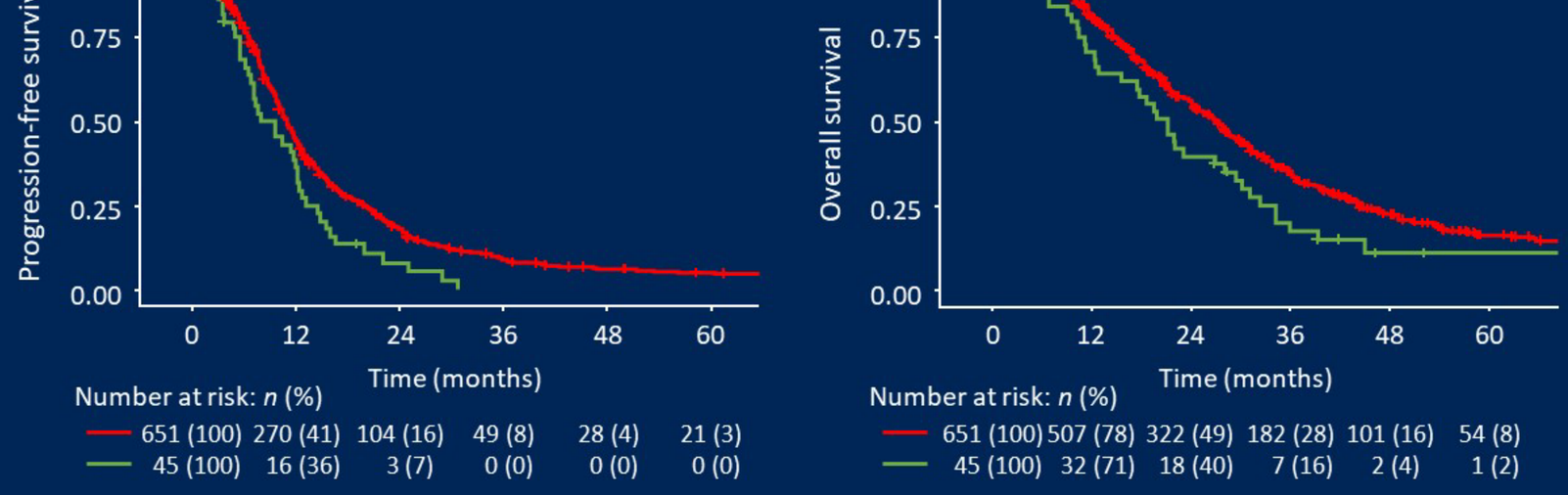
The Prognostic Impact of *KRAS*^{G12C} Mutant in Patients with mCRC

Frequency of each subtype (% of all population [*n* = 1,632])



progression-free survival

KRAS exon2 mutant	*n*	Median (95% CI) (months)	HR vs Other *KRAS* mutation subtypes (95% CI)	*p* value*
Non-G12C mutations	651	10.8 (10.1-11.5)	Reference	
G12C mutations	45	9.4 (6.4-12.0)	1.47 (1.08-2.01)	.015

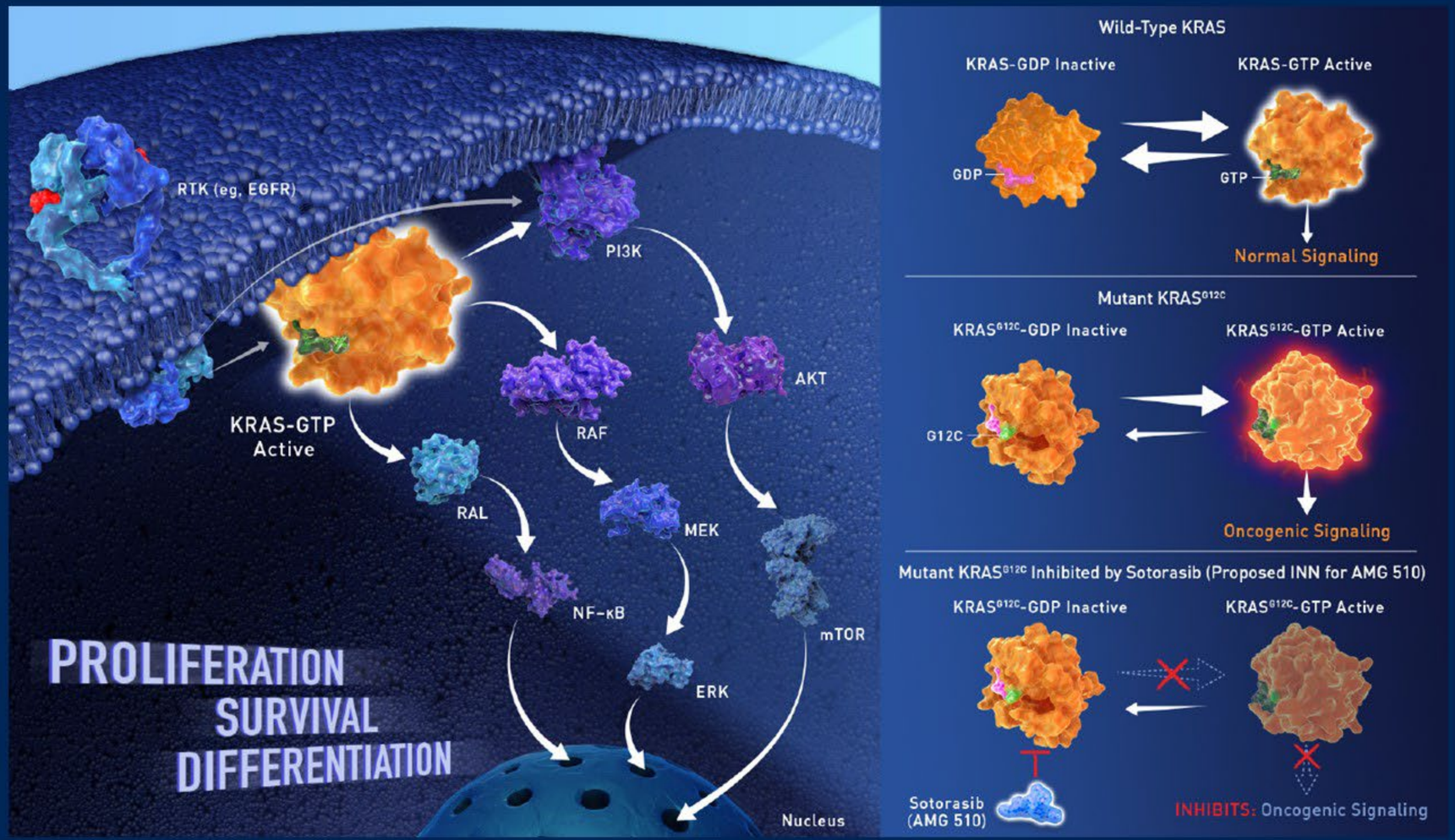


overall survival

KRAS exon2 mutant	*n*	Median (95% CI) (months)	HR vs Other *KRAS* mutation subtypes (95% CI)	*p* value*
Non-G12C mutations	651	27.3 (24.8-28.9)	Reference	
G12C mutations	45	21.1 (12.8-27.9)	1.50 (1.08-2.08)	.015

Chida K, Yoshino T, et al. Oncologist. 2021

Sotorasib (AMG 510) is a novel *KRAS*^{G12C} inhibitor



KRAS is encodes a GTPase that cycles between active GTP–bound and inactive GDP–bound states to regulate signal transduction.

The glycine-to-cysteine mutation at position 12 favors the active form of the *KRAS* protein, resulting in a predominantly GTP-bound *KRAS* oncoprotein and enhanced proliferation and survival in tumor cells.

Sotorasib (AMG 510) traps *KRAS*^{G12C} in the inactive GDP-bound state

Fakih MG, et al.: ASCO 2020 #4018.

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RAS mutant

CodeBreak 100: Phase1/2 study of Sotorasib

Tumor Response in patients with advanced colorectal cancer

Efficacy outcomes	All dose levels N = 42, n (%)	960mg N = 25, n (%)
Best overall response		
Confirmed partial response – n (%)	3 (7.1)	3 (12.0)
Stable disease – n (%)	29 (69.0)	17 (68.0)
Progressive disease – n (%)	9 (21.4)	4 (16.0)
Not done – n (%)[a]	1 (2.4)	1 (4.0)
Objective response rate – % (95% CI)	**7.1** (1.50, 19.48)	**12.0** (2.55, 31.22)
Disease control rate – % (95% CI)	**76.2** (60.55, 87.95)	**80.0** (59.30, 93.17)
Duration of response for 3 responders – months	1.4+, 4.2+, 4.3+	1.4+, 4.2+, 4.3+
Duration of stable disease – months Median (min, max)	4.2 (2.5+, 11.0)	4.2 (2.6, 5.7+)

[a] Patient had clinical progression with no postbaseline measurement.
+: censored value. Responses were durable and still ongoing as of the data cutoff

The median follow-up time was 7.9 month

Fakih MG, et al.: ASCO 2020 #4018.

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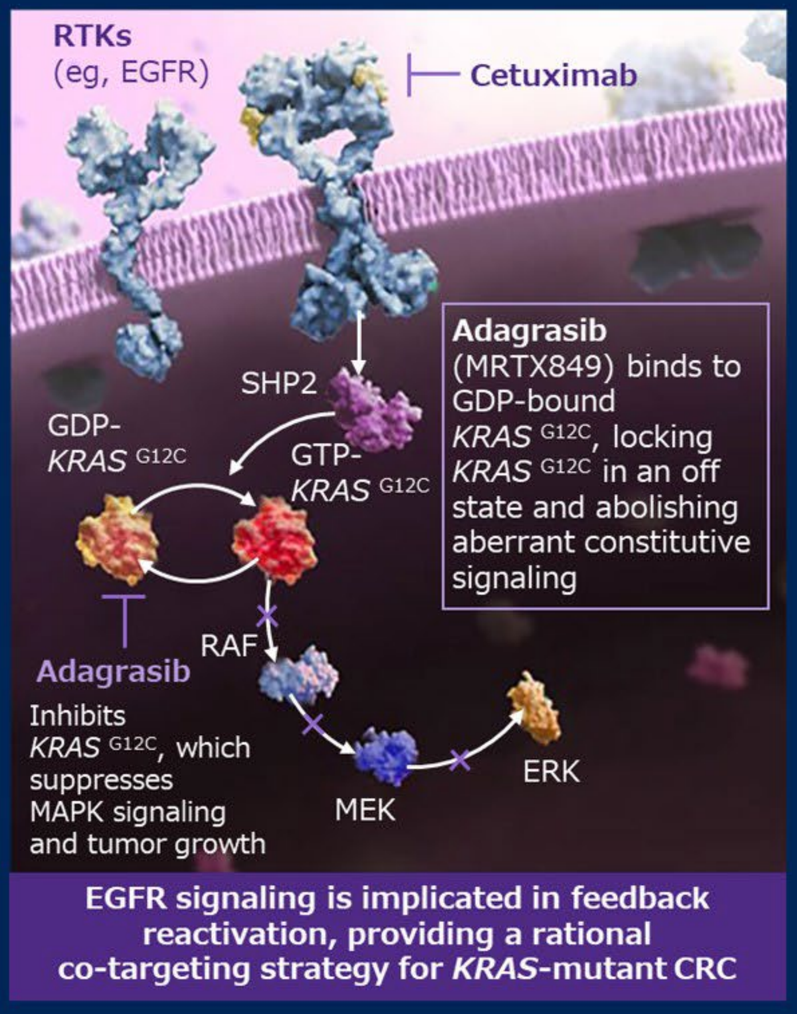
KRAS^{G12C} inhibitor(Adagrasib) + anti-EGFR mAb

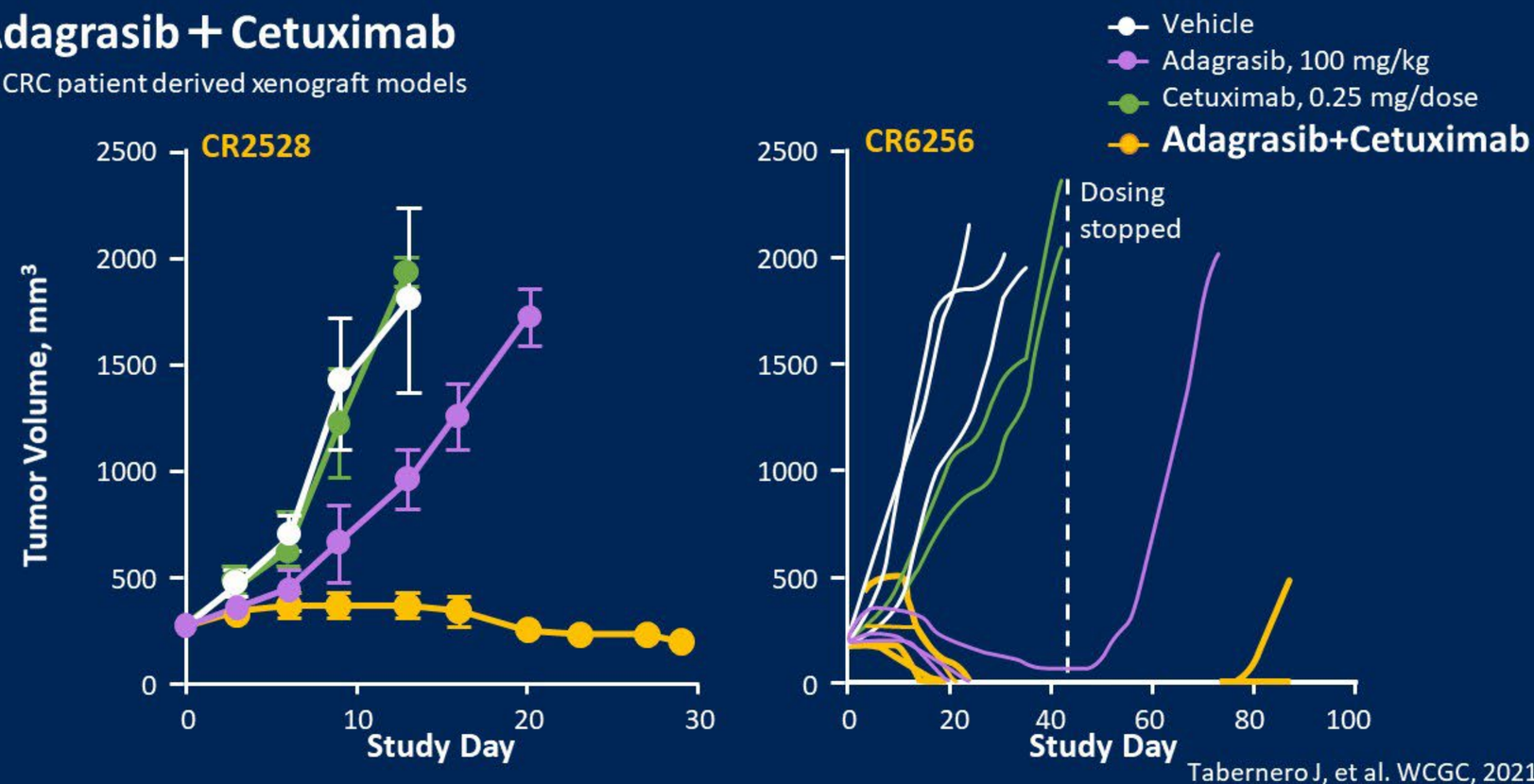


EGFR signaling is implicated in feedback reactivation, providing a rational co-targeting strategy for *KRAS*-mutant CRC

- ✓ Adagrasib, a covalent inhibitor of *KRAS*^{G12C}, irreversibly and selectively binds *KRAS*^{G12C} in its inactive, GDP-bound state and was optimized for desired properties
- ✓ Combining adagrasib with cetuximab, an EGFR inhibitor, may enhance inhibition of *KRAS*-dependent signaling or overcome adaptive feedback to improve outcomes

Adagrasib + Cetuximab

in CRC patient derived xenograft models



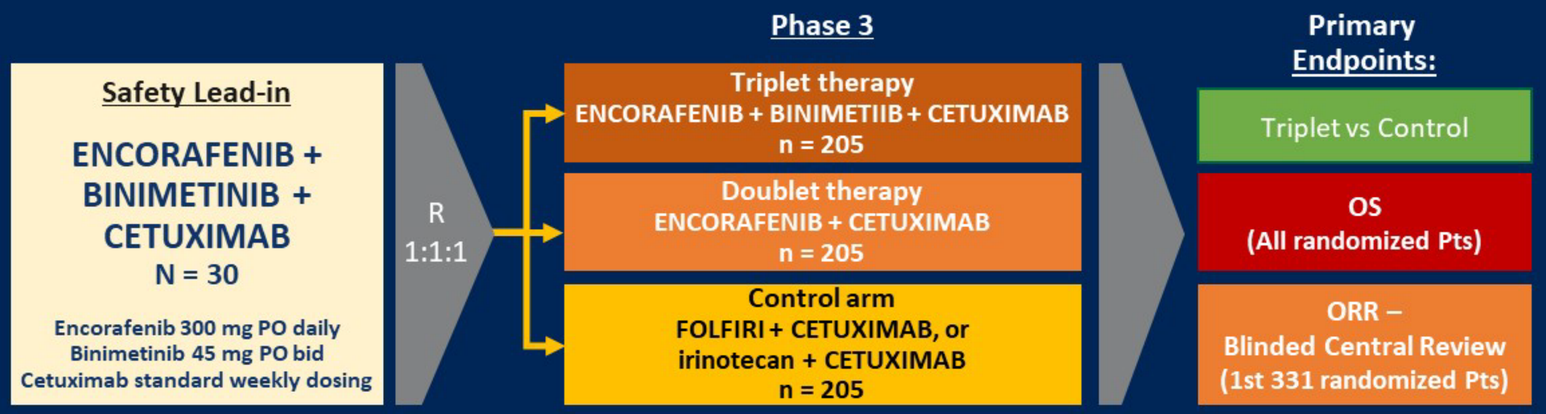
Tabernero J, et al. WCGC, 2021

PRESENTED BY: Takayuki Yoshino, MD, PhD

BEACON CRC
Phase III study in 2L *BRAF*^{V600E}-mutant mCRC

***BRAF*^{V600E} mutant**

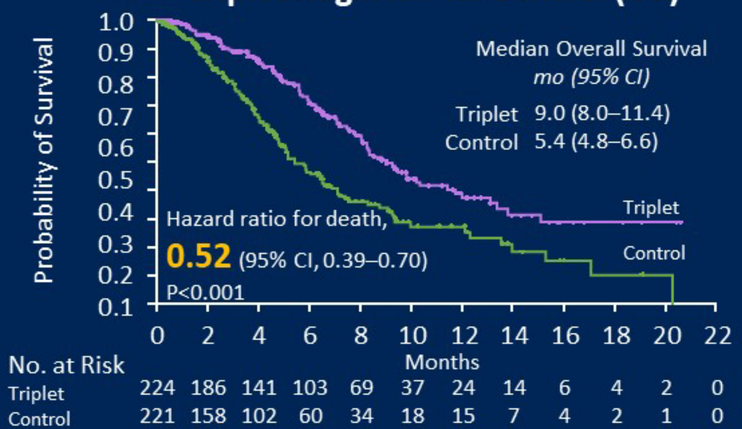
Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor



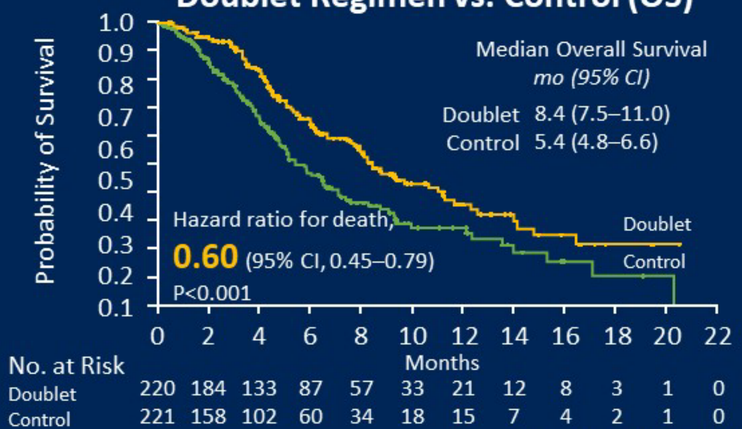
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Variable	Triplet Regimen (N=111)	Doublet Regimen (N=113)	Control (N=107)
Objective response			
Patients with a complete or partial response — no. (%)	**29** (26)	**23** (20)	**2** (2)
95% CI	18–35	13–29	<1–7
P value vs. control	<0.001	<0.001	
Best overall response — no. (%)			
Complete response	4 (4)	6 (5)	0
Partial response	25 (23)	17 (15)	2 (2)
Stable disease†	47 (42)	61 (54)	31 (29)
Progressive disease	11 (10)	8 (7)	36 (34)
Could not be evaluated according to RECIST‡	24 (22)	21 (19)	38 (36)

Triplet Regimen vs. Control (OS)



Doublet Regimen vs. Control (OS)



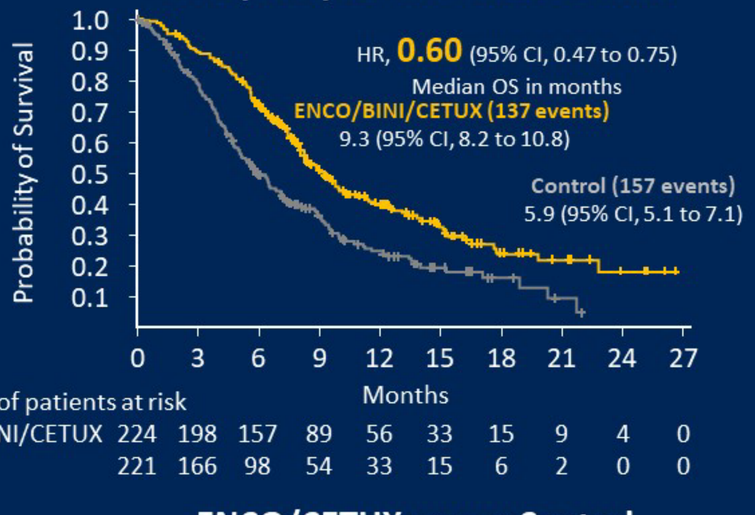
Kopetz S, et al. N Engl J Med 2019

PRESENTED BY: Takayuki Yoshino, MD, PhD

BRAF^{V600E} mutant

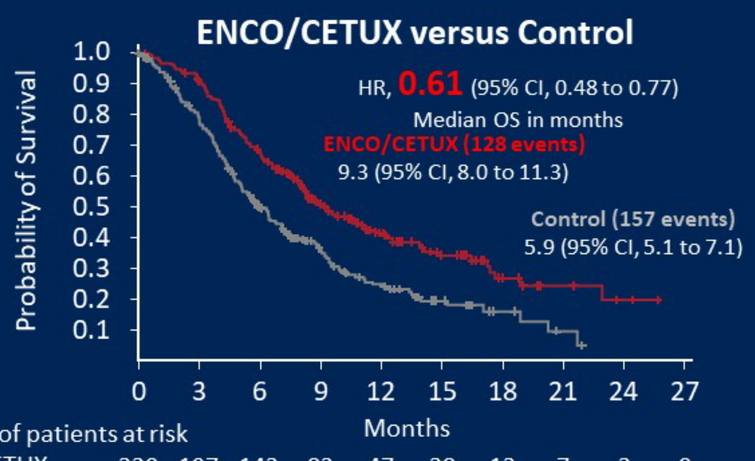
BEACON CRC OS updated

ENCO/BINI/CETUX versus Control



Number of patients at risk										
ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0

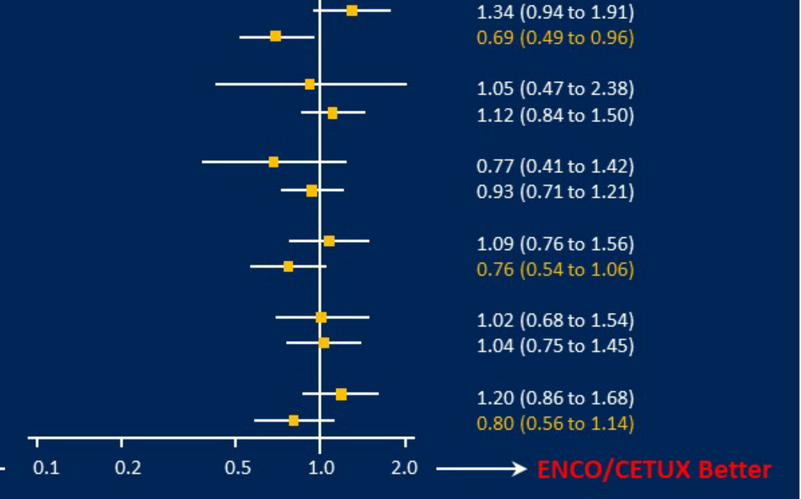
ENCO/CETUX versus Control



Number of patients at risk										
ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

ENCO/BINI/CETUX versus ENCO/CETUX

Subgroup		No. of Events/Patients	Hazard Ratio (95% CI)
All patients		294/445	0.95 (0.74 to 1.21)
ECOG	PS = 0	112/227	1.28 (0.88 to 1.86)
	PS =1	153/216	0.81 (0.59 to 1.11)
Prior Irinotecan	No	126/217	1.06 (0.75 to 1.50)
	Yes	139/227	0.92 (0.66 to 1.29)
Number of Prior Regimens for Metastatic Disease	1	166/292	0.96 (0.71 to 1.30)
	2+	99/152	1.04 (0.70 to 1.54)
Age	< 65	159/278	1.11 (0.81 to 1.51)
	≥ 65	106/166	0.86 (0.58 to 1.25)
Sex	Male	138/219	1.18 (0.84 to 1.65)
	Female	127/225	0.84 (0.59 to 1.19)
Number of Organs Involved	≤ 2	124/230	1.34 (0.94 to 1.91)
	3+	141/214	0.69 (0.49 to 0.96)
MSI Status	High	26/41	1.05 (0.47 to 2.38)
	Normal	182/309	1.12 (0.84 to 1.50)
Baseline CEA	≤ Upper Limit of Normal	44/112	0.77 (0.41 to 1.42)
	> Upper Limit of Normal	221/332	0.93 (0.71 to 1.21)
Baseline CRP	≤ Upper Limit of Normal	120/261	1.09 (0.76 to 1.56)
	> Upper Limit of Normal	139/174	0.76 (0.54 to 1.06)
Side of Tumor	Left Colon	92/162	1.02 (0.68 to 1.54)
	Right Colon	146/236	1.04 (0.75 to 1.45)
Tumor Resection Status	Completely Resected	142/255	1.20 (0.86 to 1.68)
	Partially / Not Resected	123/188	0.80 (0.56 to 1.14)



Tabernero J, et al. J Clin Oncol 2021.

ANCHOR CRC : Efficacy

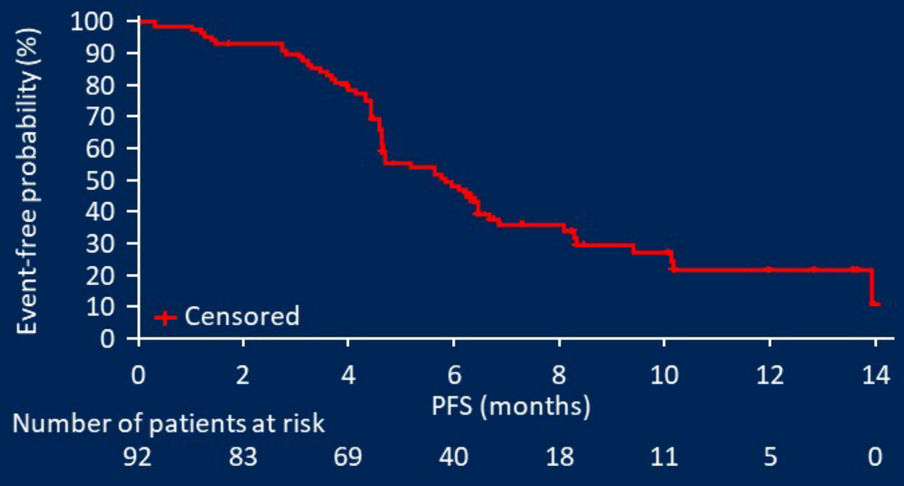
ORR(Primary endpoint)

Investigator's assessment	Patients (N=92#), n (%)
cORR **95% CI**	**44 (47.8)** **37.3-58.5**
Best overall confirmed response	
CR	0
PR	44 (47.8)
SD	37 (40.2)
PD	5 (5.4)
Not evaluable	6* (6.5)

DCR = 88%

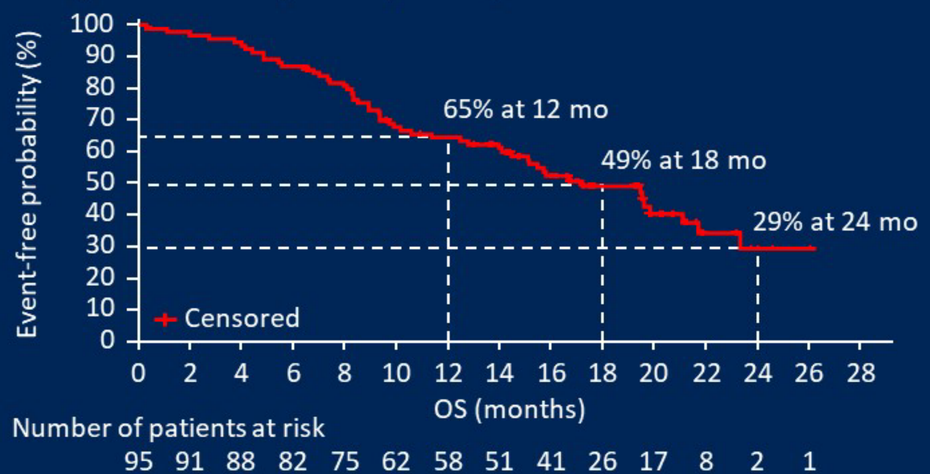
*Primary endpoint met with a lower limit of the 95% CI exceeding 30%

PFS(Secondary endpoint)



	Encorafenib + binimetinib + cetuximab
Local PFS	N=92#
Number of events	61 (66.3%)
Median PFS (months) 95% CI	**5.8** **4.6-6.4**

OS(Secondary endpoint)



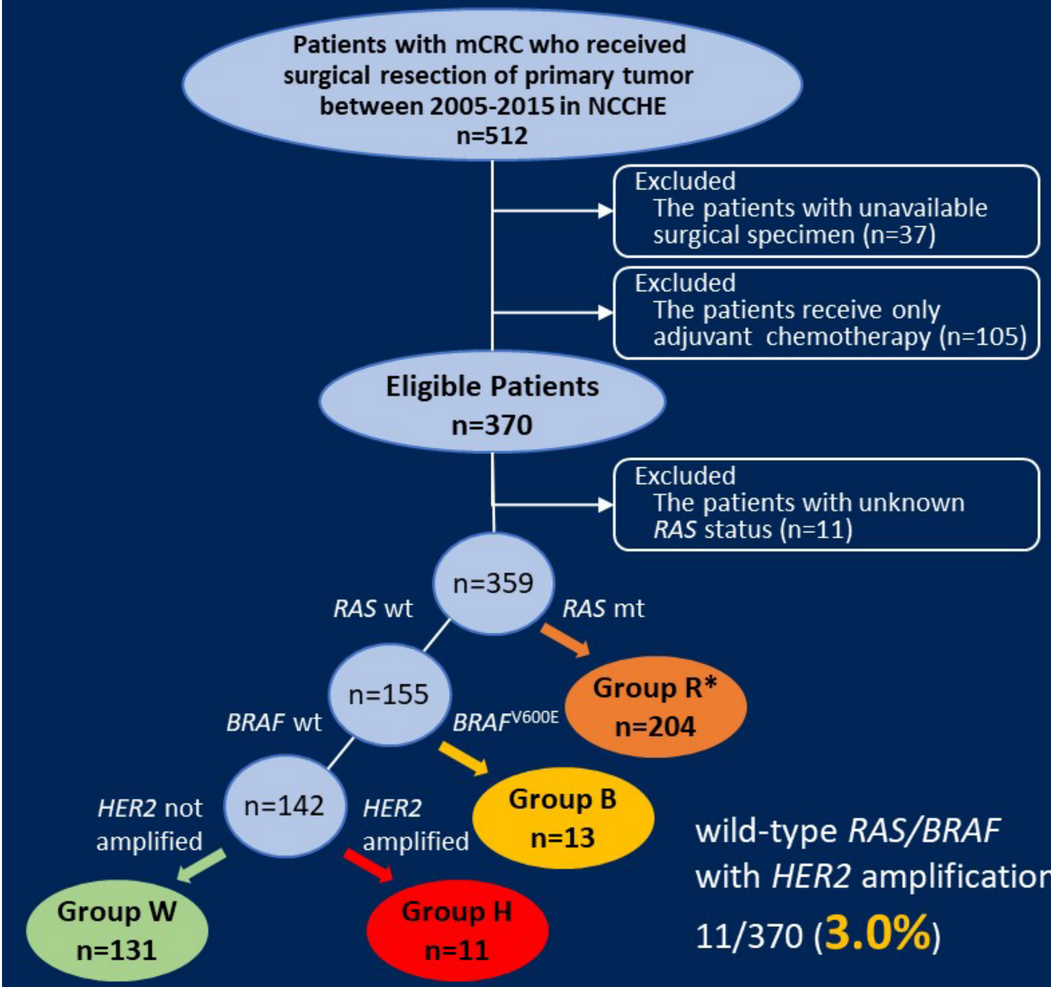
	Encorafenib + binimetinib + cetuximab
OS	N=95
Number of events	52 (54.7%)
Median OS (months) 95% CI	**17.2** **14.1-21.1**

Van Cutsem E, et al.: WCGC 2021 #O-10

PRESENTED BY: Takayuki Yoshino, MD, PhD

Frequency and prognosis of HER2-positive colorectal cancer

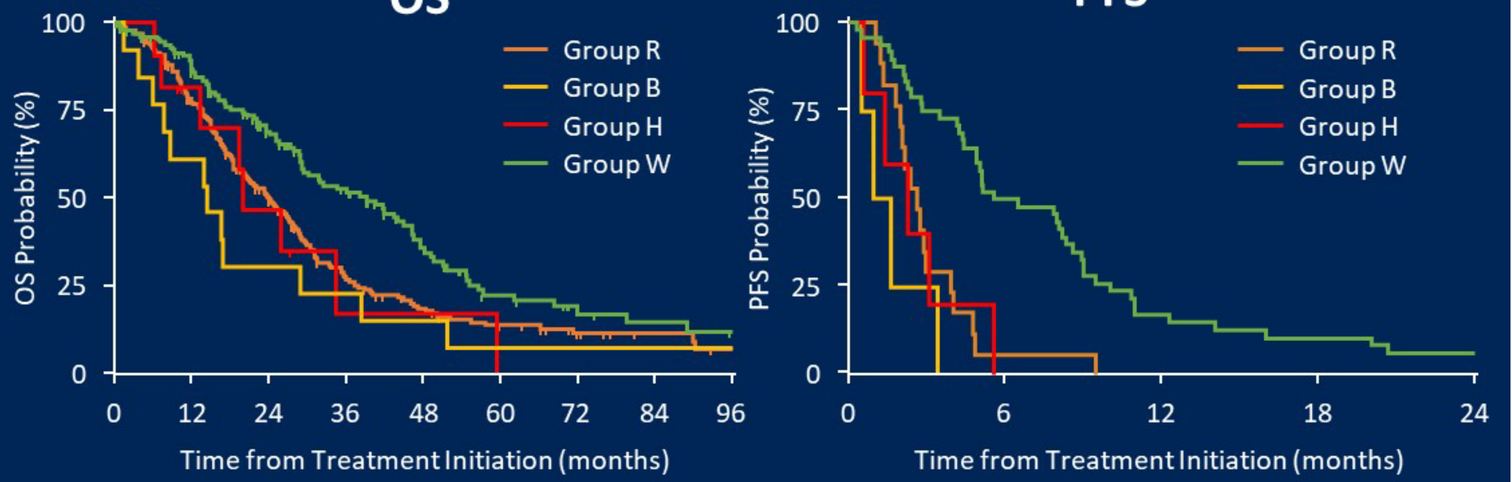
HER2



wild-type *RAS/BRAF* with *HER2* amplification

11/370 (**3.0%**)

OS and PFS in Patients Treated With anti-EGFR Therapy



R: *RAS* mutant

B: *BRAF*^{V600E} mutant

H: wild-type *RAS/BRAF* with *HER2* amplification

W: wild-type *RAS/BRAF* without *HER2* amplification

Sawada K, Yoshino T, et al. Clin Colorectal Cancer 2018

PRESENTED BY: Takayuki Yoshino, MD, PhD

DESTINY-CRC01 : Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- *RAS/BRAF*^{V600E} wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

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

Cohort B:
HER2 IHC 2+/ISH−
n = 7

Cohort C:
HER2 IHC 1+
n = 18

Primary endpoint

- ORR (cohort A)

Secondary endpoints

- ORR (cohorts B and C)
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

Primary analysis (Data cutoff: August 9, 2019)

Primary analysis of cohort A

- The primary endpoint was confirmed objective response rate (defined as the proportion of patients who had a confirmed best overall response of complete response or partial response at any point from the start of therapy until the patient was withdrawn from the study or started a new anti-cancer therapy, or until data cutoff [whichever came first]), assessed by independent central review on the basis of RECIST version 1.1,

Siena S, Yoshino T, et al.: Lancet Oncol. 2021.

PRESENTED BY: Takayuki Yoshino, MD, PhD

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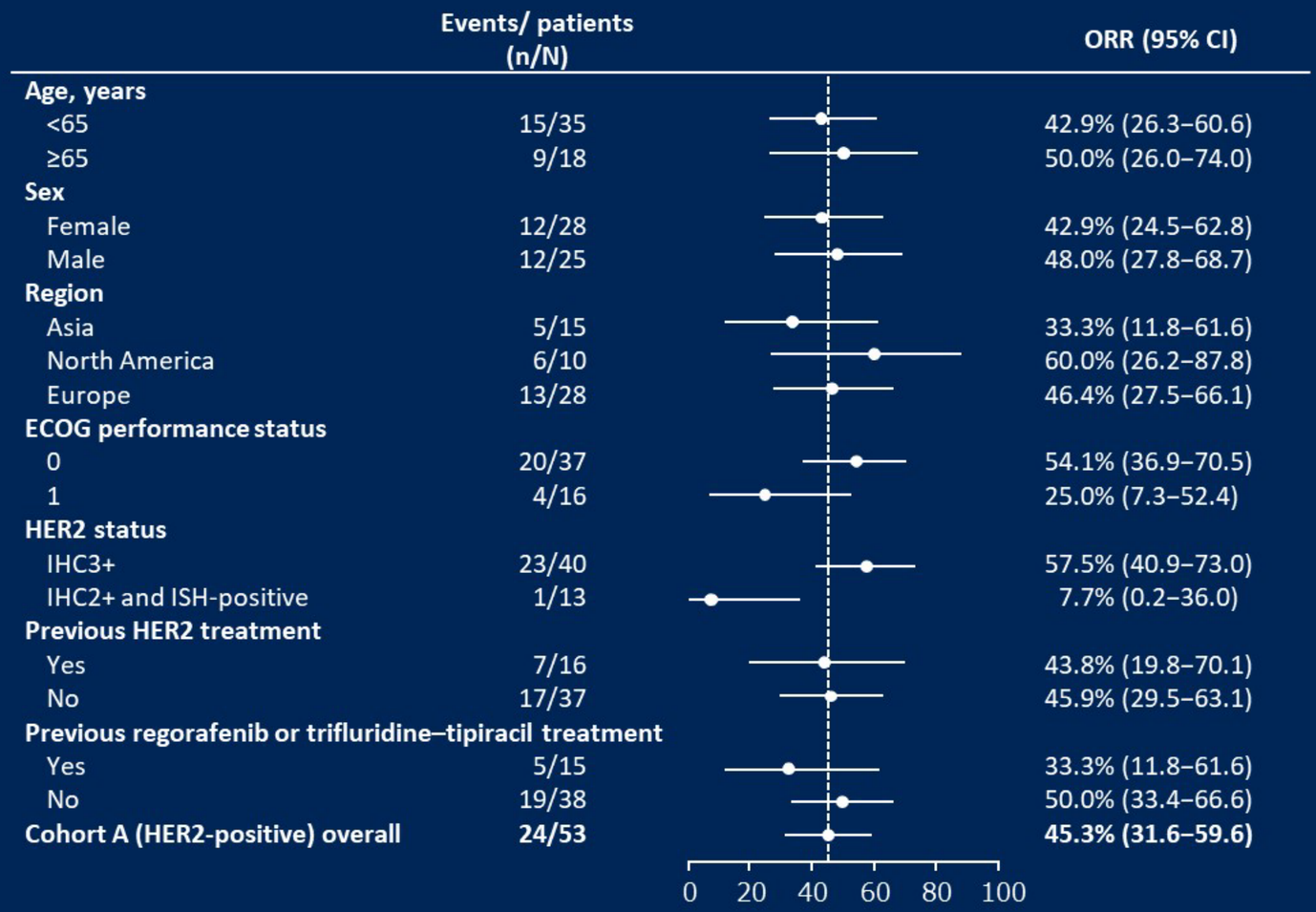
Clinical response for cohort A patients treated with trastuzumab deruxtecan

	Cohort A (HER2-positive; n=53)
Confirmed ORR by ICR, % (95% CI)	45.3 (31.6–59.6)
Complete response	1 (2%)
Partial response	23 (43%)
Stable disease	20 (38%)
Progressive disease	5 (9%)
Non-evaluable*	4 (8%)



Siena S, Yoshino T, et al.: Lancet Oncol. 2021.

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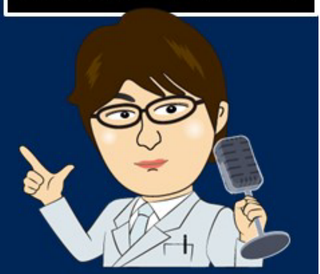
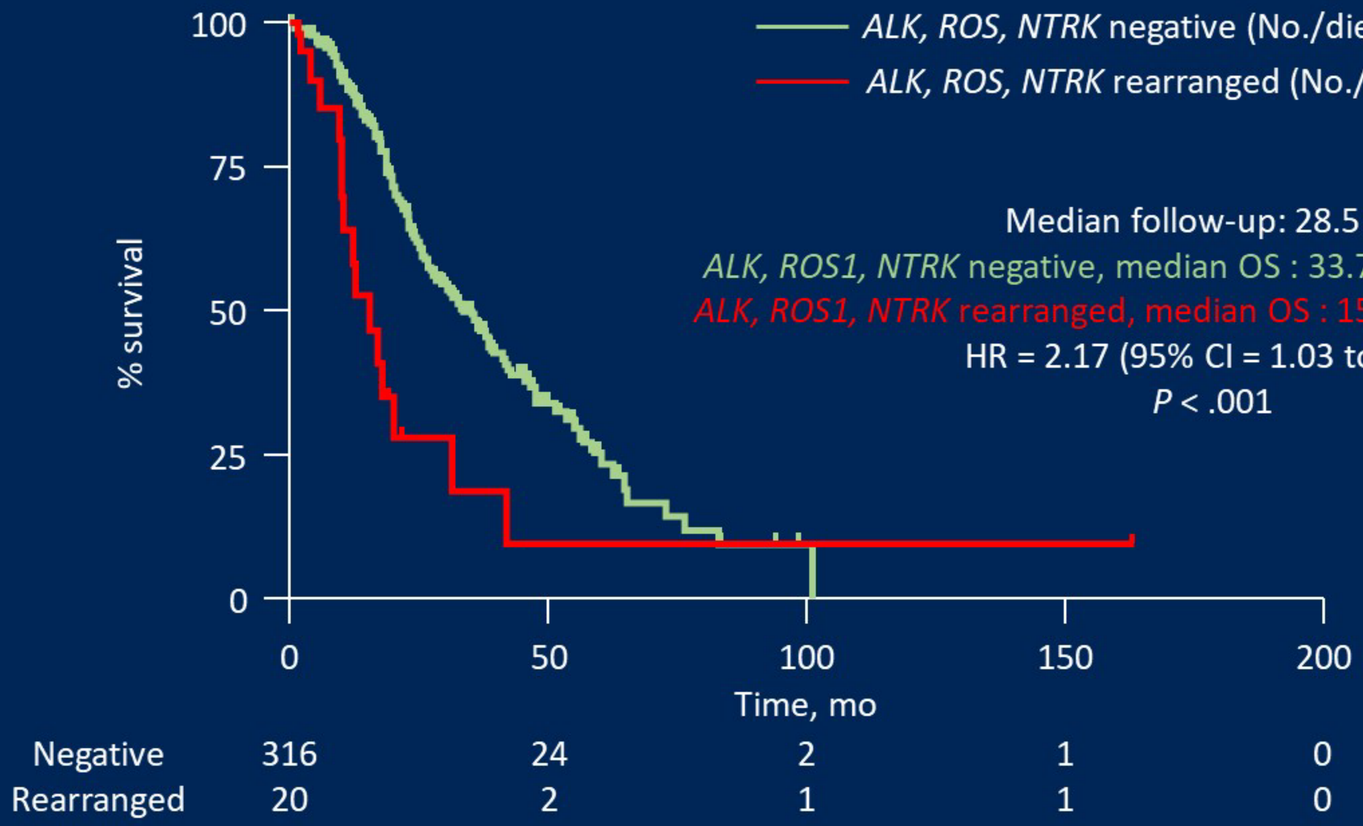
Kinase Fusion

Survival in metastatic colorectal cancer patients carrying ALK, ROS1, and NTRK rearranged tumors





ALK, ROS, NTRK negative (No./died = 316/136)

ALK, ROS, NTRK rearranged (No./died = 20/15)

Median follow-up: 28.5 mo

ALK, ROS1, NTRK negative, median OS : 33.7 [95%CI=28.3-42.1] mo

ALK, ROS1, NTRK rearranged, median OS : 15.6 [95%CI=0.0-20.4] mo

HR = 2.17 (95% CI = 1.03 to 4.57)

P < .001

NTRK gene fusion mCRC may have a poor prognosis

Most NTRK fusion mCRC are involved in MSI-H/dMMR

Pietrantonio F, et al.: J Natl Cancer Inst 2017

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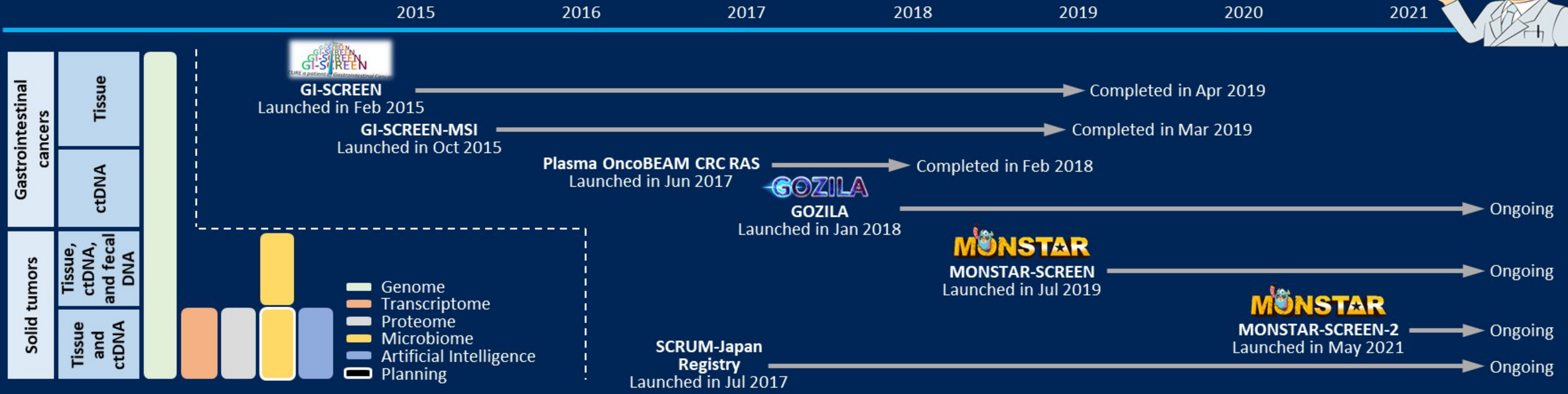
SCRUM-Japan

SCRUM-Japan GI-SCREEN, GOZILA and MONSTAR-SCREEN



	GI-SCREEN	GOZILA	MONSTAR-SCREEN	MONSTAR-SCREEN-2
Cancer	Gastrointestinal cancers	Gastrointestinal cancers	Solid tumors	Solid tumors
Sample size	5743	7000	2206	2750
Molecular profiling	Tissue DNA/RNA targeted sequencing (OCA)	Plasma DNA targeted sequencing (Guardant360)	Tissue and plasma DNA targeted sequencing (F1CDx and F1L CDx) Fecal microbiome (16S sequencing, shotgun metagenomic sequencing, single-cell metagenomics)	Tissue and plasma WES/WTS, and buffy coat WES (CARIS assay) Tissue IHC (HER2 and PD-L1) Multiplex IHC
Status	Completed	Active recruitment	Completed	Active recruitment

Abbreviations: F1CDx, FoundationOne CDx; F1L CDx, FoundationOne Liquid CDx; IHC, immunohistochemistry; OCA, Oncomine Comprehensive Assay; WES, whole exome sequencing; WTS, whole transcriptome sequencing.

Nakamura Y, Yoshino T, et al.: Cancer Science. 2021.

SCRUM-Japan

GOZILA UMBRELLA/BASKET TRIALS

GOZILA UMBRELLA/BASKET TRIALS

GOZILA

Metastatic gastrointestinal (GI) cancer or other advanced solid tumors with specific genomic alterations

Treatment naïve or disease progression after anticancer therapy

N = 5000

GOZILA study

ctDNA genotyping using Guardant360

TUMOR SPECIFIC

HER2-amplified colorectal cancer (CRC)	Pertuzumab + trastuzumab (UMIN000027887)
BRAF V600E-mutated CRC	Eribulin (UMIN000031221)
BRAF non-V600E-mutated CRC	Encorafenib + binimetinib + cetuximab (UMIN000031857)
MET-amplified CRC	Cabozantinib + panitumumab (JapicCTI-194709)
RAS wild-type CRC	Panitumumab rechallenge (jRCTs031190096)
HER2-amplified biliary tract cancer	Trastuzumab deruxtecan (JMA-IIA00423)

TUMOR AGNOSTIC

Tumor mutation burden–high solid tumor	Nivolumab (UMIN000033560)
BRCA1/2-mutated GI cancer	Niraparib (jRCT2011200023)
FGFR-altered solid tumor	Futibatinib (JapicCTI-194624)
HER2-amplified solid tumor	Trastuzumab deruxtecan (JapicCTI-194707)
ROS1 fusion solid tumor	Brigatinib (JapicCTI-194851)
NFE2L2-mutated squamous cell carcinoma	Sapanisertib

Bando H, Yoshino T, et al.: Oncology, ONCOLOGY Vol 35, Issue 7,2021.

PRESENTED BY: Takayuki Yoshino, MD, PhD

Conclusions/Take-Away *-Molecular Targeted Therapies for mCRC-*

- ***RAS* wild type & anti-EGFR mAb naïve;** Anti-EGFR mAb is a preferred choice in the 1st-line, particularly in left-sided primary tumor.
- ***RAS* wild type & anti-EGFR mAb pre-treated;** Rechallenge of anti-EGFR mAb is considered in patients with blood-based *RAS* wild type.
- ***RAS* mutant;** $KRAS^{G12C}$ inhibitor + anti-EGFR mAb combination is promising. Clinical development with $KRAS^{G12D}$ or RAS^{MULTI} inhibitors have been initiated.
- ***BRAF*^{V600E} mutant;** BEACON doublet regimen in 2nd- or 3rd-line is established.
- **HER2;** Dual HER2 blockade or HER2-ADC monotherapy are promising.
- **NTRK Fusion;** Most NTRK fusion mCRC are involved in MSI-H/dMMR
- **SCRUM-Japan;** Efficient platform to identify orphan-fractionated cancer subtypes.

mAb, monoclonal antibody: ADC, Antibody-Drug Conjugate

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ASCO® Gastrointestinal Cancers Symposium

Immunotherapy in Microsatellite Stable Colorectal Cancer

Kristen K. Ciombor, MD, MSCI
Vanderbilt-Ingram Cancer Center

ASCO® Gastrointestinal Cancers Symposium

#GI22

PRESENTED BY: Kristen K. Ciombor, MD, MSCI

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KNOWLEDGE CONQUERS CANCER

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Anti-PD-(L)1 + Targeted Therapies in MSS mCRC

- MEK: IMblaze370 (cobimetinib/atezolizumab)
- EGFR: nivo/ipi/pmab; CAVE: cetuximab/avelumab; AVETUX: FOLFOX/cetuximab/avelumab; AVETRIC: FOLFOXIRI/cetuximab/avelumab
- BRAF: encorafenib/cetuximab/nivolumab, dabrafenib/trametinib/spartalizumab; spartalizumab/dabrafenib/LTT462 (ERKi)
- KRAS G12C: CodeBreaK 100: AMG 510 +/- anti-PD-(L)1; TNO155 (SHP2 inhibitor)/spartalizumab/JDQ443
- PI3K: nivolumab/copanlisib
- MGMT silencing: MAYA: TMZ + nivolumab + ipilimumab (TMZ-induced hypermutation); ARETHUSA: TMZ/pembro

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Conclusions/Take-Away Points

- Failure of immune checkpoint blockade monotherapy in MSS mCRC well established
  - Reasons: lack of T-cell inflamed phenotype (inadequate T-cell infiltration and activation, T-cell suppression)
  - Notable exceptions: *POLE* mutations, high TMB, etc.

- Immunotherapy combinations are under investigation to try to overcome this failure (including dual immunotherapy, chemo, anti-angiogenic agents, targeted therapies and more)
  - Need better understanding of primary and adaptive immune resistance, biomarkers for optimal patient selection

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Abstracts GI ASCO 2022

ASCO Gastrointestinal Cancers Symposium

Nivolumab + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab versus mFOLFOX6/bevacizumab for first-line treatment of metastatic colorectal cancer: phase 2 results from CheckMate 9X8

Heinz-Josef Lenz,[1] Aparna Parikh,[2] David R. Spigel,[3] Allen Cohn,[4] Takayuki Yoshino,[5] Mark Kochenderfer,[6] Elena Elez,[7] Spencer Shao,[8] Dustin Deming,[9] Regan Holdridge,[10] Timothy Larson,[11] Eric Chen,[12] Amit Mahipal,[13] Antonio Ucar,[14] Dana Cullen,[15] Edwina Baskin-Bey,[15] Jean-Marie Ledeine,[15] Amy Hammell,[15] Josep Tabernero[7]

[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [2]Massachusetts General Hospital, Boston, MA; [3]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN; [4]Rocky Mountain Cancer Centers, Denver, CO; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Oncology & Hematology Associates of Southwest Virginia, Roanoke, VA; [7]Vall d´Hebron Hospital Campus, Barcelona, Spain; [8]Compass Oncology, Portland, OR; [9]University of Wisconsin Carbone Cancer Center, Madison, WI; [10]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [11]Minnesota Oncology Hematology, Minneapolis, MN; [12]Princess Margaret Cancer Centre, Toronto, Canada; [13]Mayo Clinic, Rochester, MN; [14]Miami Cancer Institute (part of Baptist Health South Florida), Miami, FL; [15]Bristol Myers Squibb, Princeton, NJ

Abstract number 8

Introduction

- Fluoropyrimidine–containing regimens with oxaliplatin and/or irinotecan and a biologic agent such as the *VEGF* inhibitor BEV are one of the standard 1L therapeutic options for mCRC[1]
- Immunotherapeutic agents may enhance antitumor activity in combination with standard therapies in patients with mCRC[2-4]
- NIVO, a PD-1 inhibitor, is approved as a single agent or in combination with IPI, a CTLA-4 inhibitor, in previously treated patients with MSI-H/dMMR mCRC[5-7]
- CheckMate 9X8 evaluated NIVO + mFOLFOX6/BEV (NIVO + SOC) vs mFOLFOX6/BEV (SOC) as a 1L therapy in MSS and MSI-H mCRC

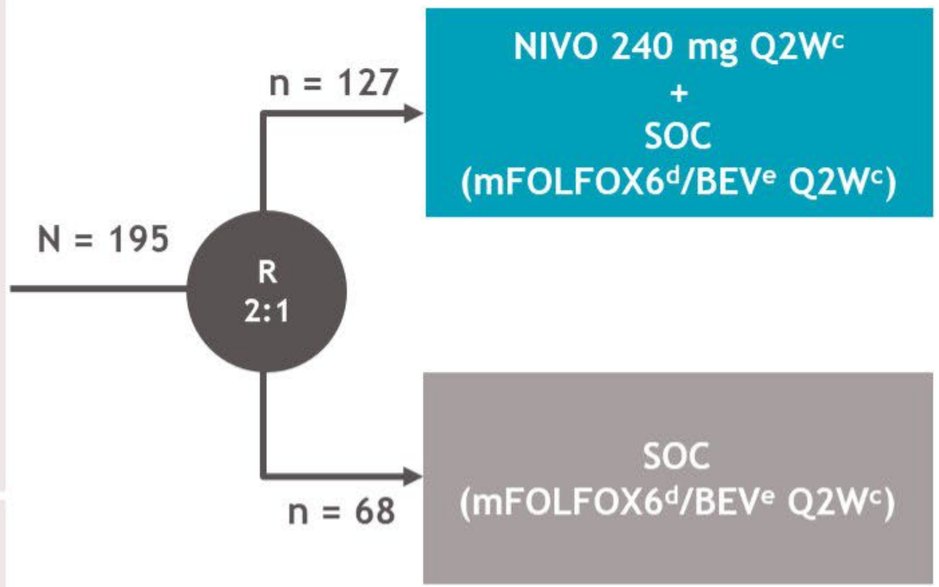
1. Grapsa D, et al. *Expert Rev Anticancer Ther* 2015;15:1267-1281. 2. Le DT, et al. *N Engl J Med* 2015;372:2509-2520. 3. Boland PM, Ma WW. *Cancers (Basel)* 2017;9:50. 4. Cremolini C, et al. Oral presentation at ESMO; September 16-21, 2021; Virtual. Abstract LBA20. 5. OPDIVO® (nivolumab) [prescribing information]. Princeton, NJ: Bristol Myers Squibb; August 2021. 6. OPDIVO® (nivolumab) [prescribing information]. Osaka, Japan: Ono Pharmaceutical Co., Ltd; November 2020. 7. OPDIVO® (nivolumab) [summary of product characteristics]. Dublin, Ireland: Bristol Myers Squibb Pharma EEIG; October 2021.

CheckMate 9X8 study design

- CheckMate 9X8 is a randomized, open-label phase 2/3 study[a]

Key eligibility criteria
- Histologically confirmed mCRC not amenable to curative resection
- No prior chemotherapy for mCRC
- No prior treatment with checkpoint inhibitors[b]
- ECOG PS 0-1

Stratification factors
- Tumor sidedness (left, right, transverse, or unknown)
- Prior oxaliplatin-based chemotherapy (yes or no)



Primary endpoints
- PFS per BICR (RECIST v1.1)

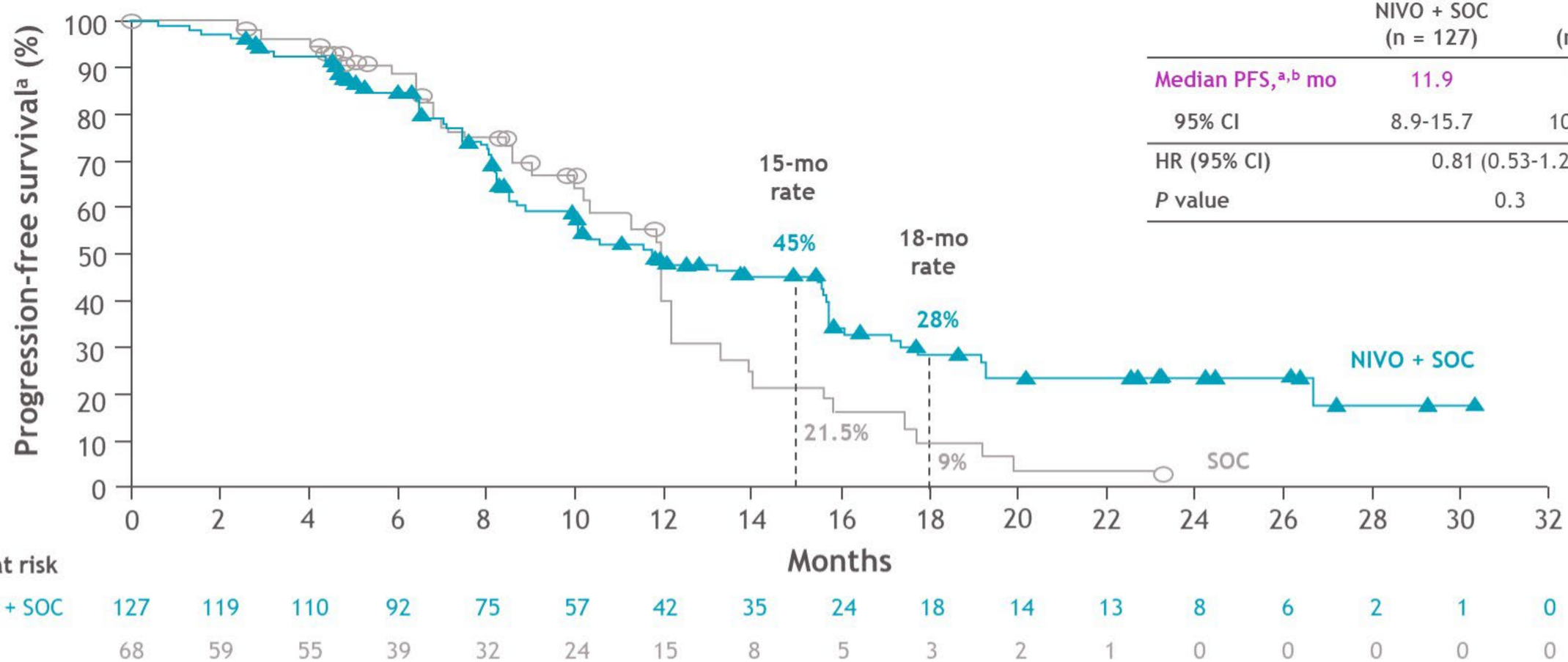
Secondary endpoints
- PFS per INV (RECIST v1.1)
- ORR, DCR, DOR, and TTR per BICR and per INV; OS; and safety

Exploratory endpoints
- Biomarker analyses

- At data cutoff (February 1, 2021), the minimum follow-up was 21.5 months[f]

[a]ClinicalTrials.gov. NCT03414983; [b]No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways; [c]Until disease progression, unacceptable toxicity, withdrawal of consent, or end of study; NIVO treatment for ≤ 24 months; [d]Oxaliplatin, 85 mg/m^2; leucovorin, 400 mg/m^2 or 350 mg/m^2 per local standards; fluorouracil, bolus 400 mg/m^2, followed by 1200 mg/m^2 continuous infusion on day 1 (or 15) and day 2 (or 16), or 2400 mg/m^2 continuous infusion over 46-48 hours from day 1 (or 15) through day 2 (or 16) per local standards; [e]Bevacizumab, 5 mg/kg; [f]Time from randomization of the last patient to clinical data cutoff.

Progression-free survival



	NIVO + SOC (n = 127)	SOC (n = 68)
Median PFS,[a,b] mo	11.9	11.9
95% CI	8.9-15.7	10.1-12.2
HR (95% CI)	0.81 (0.53-1.23)	
P value	0.3	

- The primary endpoint of PFS per BICR was not met ($P = 0.3$)
- PFS rates after 12 months were numerically higher with NIVO + SOC vs SOC

[a]Per BICR; [b]Minimum follow-up was 21.5 months.

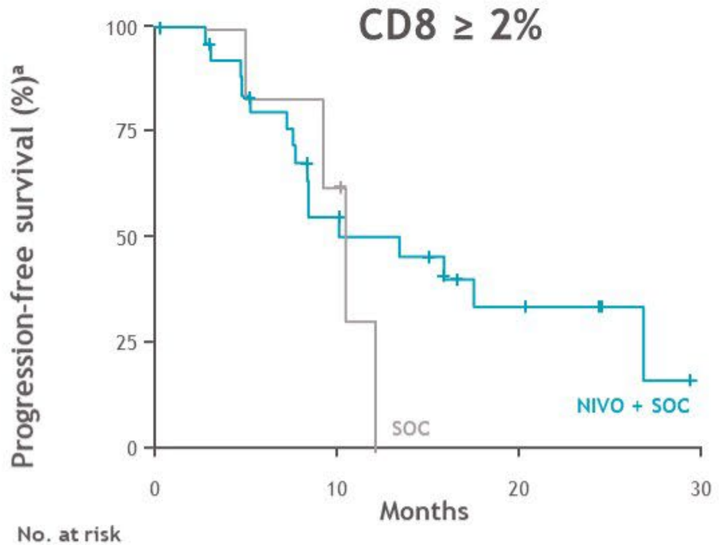
Response, disease control, and durability

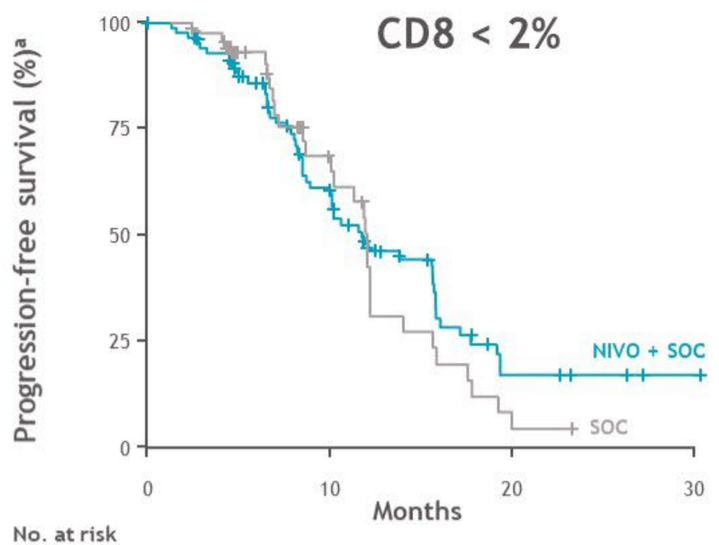
Outcome[a]	NIVO + SOC (n = 127)	SOC (n = 68)
ORR,[b] n (%)	76 (60)	31 (46)
95% CI	51-68	33.5-58
Best overall response, n (%)		
CR	6 (5)	1 (1)
PR	70 (55)	30 (44)
SD	39 (31)	26 (38)
PD	3 (2)	0
Unable to determine	9 (7)	11 (16)
DCR,[c] n (%)	115 (91)	57 (84)
95% CI	84-95	73-92
Median TTR (range),[d] months	2.8 (1.5-12.2)	2.8 (1.8-8.3)
Median DOR (95% CI),[d] months	12.9 (9.0-13.1)	9.3 (7.5-11.3)
≥ 12-mo rate (95% CI), %	52 (39-64)	31 (14-50)
≥ 18-mo rate (95% CI), %	29 (17-42)	0 (NE)

- ORR was higher and responses were more durable with NIVO + SOC compared to SOC

[a]Per BICR; [b]Number of CR + PR divided by the number of randomized patients; [c]Number of CR + PR + SD divided by the number of randomized patients; [d]Evaluated in patients who had an objective response.

PFS by baseline tumor CD8 levels in MSS population





Median PFS (95% CI), mo	Baseline tumor CD8 levels[a,b,c]	
	CD8 ≥ 2%	CD8 < 2%
NIVO + SOC (n = 117)	13.2 (8.25-NE)	11.8 (10.0-15.7)
SOC (n = 55)	10.4 (9.1-NE)	11.9 (10.25-14.1)

- In exploratory analyses, benefit was seen with the addition of NIVO to SOC in patients with baseline tumor CD8 ≥ 2% after 12 months
- Higher baseline tumor CD8 levels (≥ 2%) may contribute to greater disease control (CR/PR/SD) with NIVO + SOC

[a]Per BICR; [b]19 patients (NIVO + SOC: n = 9; SOC: n = 10) not evaluable for response were excluded from this analysis; [c]2 patients with unknown CD8 results, and 1 patient with multiple baseline samples and discordant results in the SOC arm were excluded from this analysis.

Summary

- PFS with NIVO + SOC vs SOC did not meet the prespecified threshold for statistical significance in previously untreated patients with mCRC ($P = 0.3$)
  - PFS curves overlapped before separating at approximately 12 months, after which numerically higher PFS rates were observed with NIVO + SOC vs SOC
  - Higher ORR and more durable responses were observed with NIVO + SOC vs SOC
- Benefit was observed with the addition of NIVO to SOC in CMS1 and CMS3 patients and in patients with CD8 ≥ 2% in exploratory subgroup analyses
- NIVO + SOC had an acceptable safety profile, and no new safety signals were identified
  - Rates of grade 3/4 TRAEs were higher with NIVO + SOC vs SOC
- Results from this phase 2 exploratory study suggest that a subgroup of patients with mCRC may experience benefit from the addition of NIVO to SOC in the 1L setting; however, further investigation is warranted to identify characteristics of these patients

ASCO Gastrointestinal Cancers Symposium

JCOG Japan Clinical Oncology Group

A randomized phase III trial of mFOLFOX7 or CapeOX plus bevacizumab versus 5-FU//-LV or capecitabine plus bevacizumab as initial therapy in elderly patients with metastatic colorectal cancer: JCOG1018 study (RESPECT)

UMIN000008866, jRCTs031180145

Tetsuya Hamaguchi, Atsuo Takashima, Junki Mizusawa, Yasuhiro Shimada, Fumio Nagashima, Masahiko Ando, Hitoshi Ojima, Tadamichi Denda, Jun Watanabe, Katsunori Shinozaki, Hideo Baba, Masako Asayama, Tadao Fukushima, Toshiki Masuishi, Ken Nakata, Shunsuke Tsukamoto, Hiroshi Katayama, Kenichi Nakamura, Haruhiko Fukuda, Yukihide Kanemitsu
Colorectal Cancer Study Group in Japan Clinical Oncology Group (JCOG)

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Background

- Fluoropyrimidine plus oxaliplatin (OX) with bevacizumab (BEV) is one of the standard intensive initial therapy for metastatic colorectal cancer (MCRC)

- Since elderly patients are under-represented in clinical trials, the benefit of intensifying initial therapy is not yet clear in this group

- Fluoropyrimidines plus BEV showed significantly longer progression-free survival (PFS) in elderly patients with MCRC

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Study Schema

MCRC as Initial therapy
70-74yo with PS 2, or 75yo ≤ with PS 0-2

↓

Physician's choice for fluoropyrimidine
("5-FU+l-LV" or "Cape")

↓

Randomization
ECOG-PS (0-1 / 2), Age (≥85 / 80-84 / 75-79 / 70-74),
Number of metastatic sites (1 / ≥2), and Institute

↓

Arm A ("NO" OX)
Fluoropyrimidine+BEV

5-FU+/-LV+BEV
or
Cape + BEV

Arm B ("ADD" OX)
Fluoropyrimidine/OX+BEV

mFOLFOX7+BEV
or
CapeOX + BEV

5-FU+/-LV+BEV

BEV 5 mg/kg	/-LV 200 mg/m^2	5-FUci 2400 mg/m^2

Cape+BEV

BEV 7.5 mg/kg

Capecitabine 1,250 mg/m^2 (CrCL ≥ 50) or 1,000 mg/m^2 (50 > CrCL)

mFOLFOX7+BEV

	OX 85 mg/m^2	
BEV 5 mg/kg	/-LV 200 mg/m^2	5-FUci 2400 mg/m^2

CapeOX+BEV

OX 130 mg/ m^2

BEV 7.5 mg/kg

Capecitabine 1,000 mg/m^2 (CrCL ≥ 50) or 750 mg/m^2 (50 > CrCL)

3

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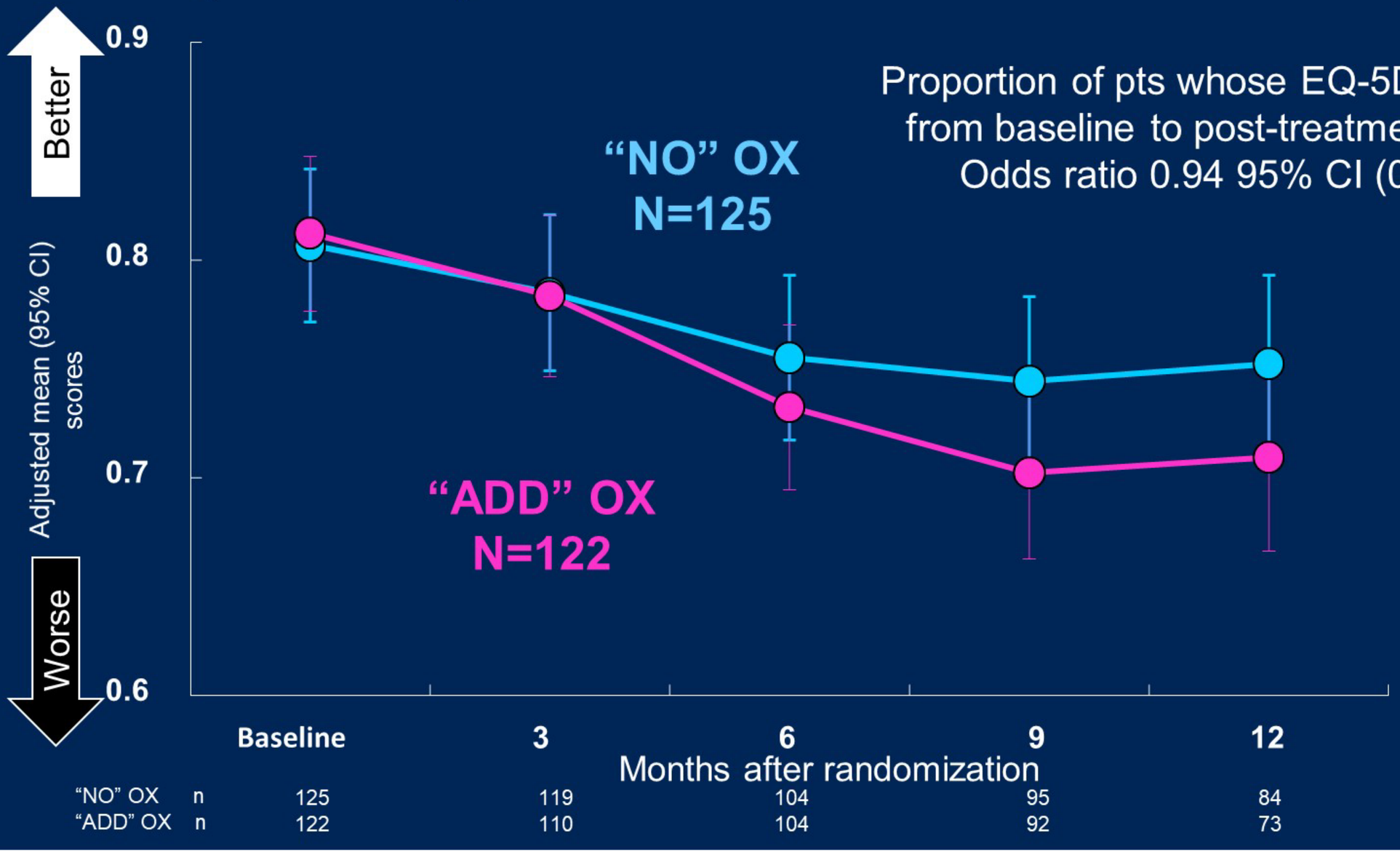
QOL (EQ-5D)



Proportion of pts whose EQ-5D scores improved from baseline to post-treatment in overall score:
Odds ratio 0.94 95% CI (0.51-1.75), p=0.849
by GEE analysis

		Baseline	3	6	9	12
"NO" OX	n	125	119	104	95	84
"ADD" OX	n	122	110	104	92	73

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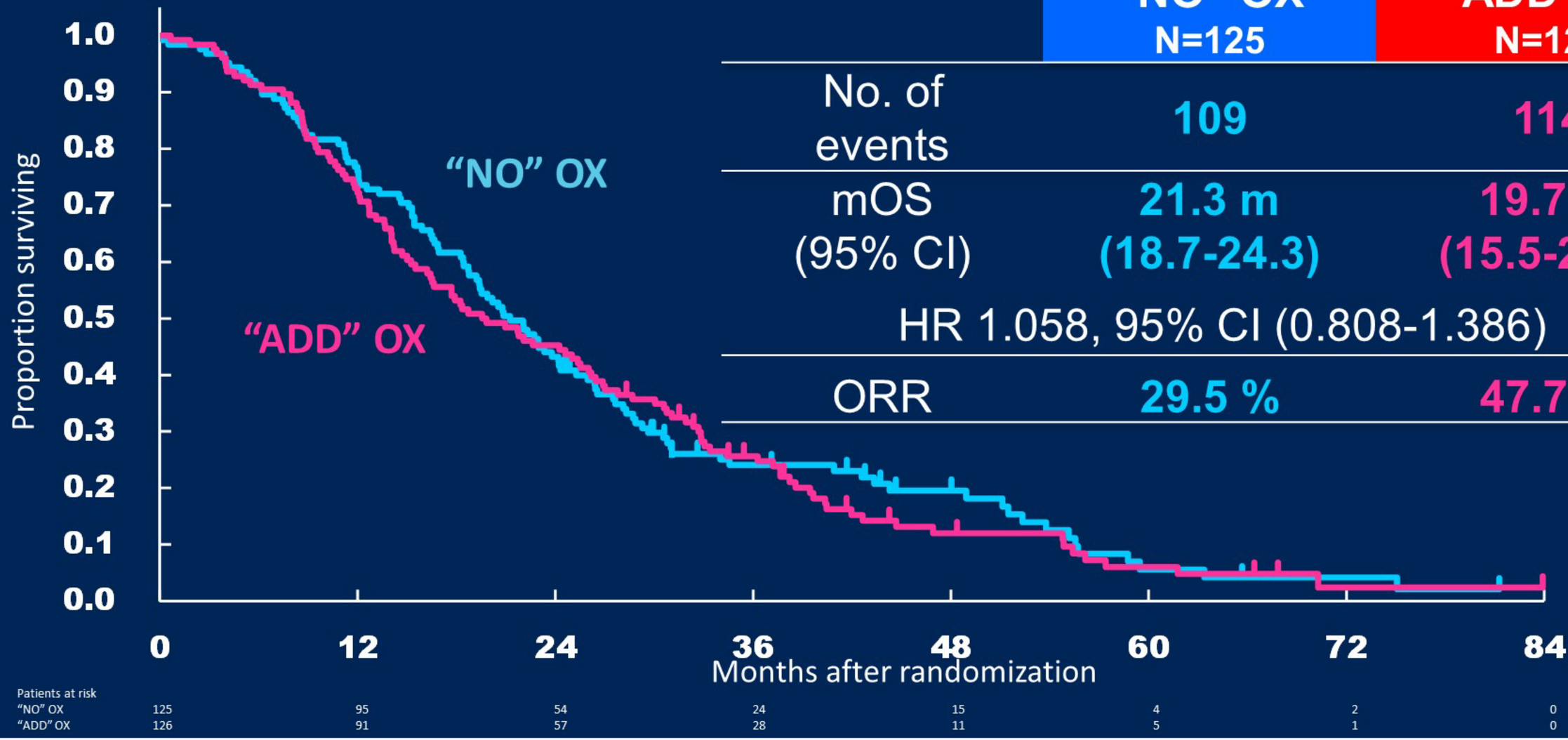
OS and ORR



	"NO" OX N=125	"ADD" OX N=126
No. of events	109	114
mOS (95% CI)	21.3 m (18.7-24.3)	19.7 m (15.5-25.5)
HR 1.058, 95% CI (0.808-1.386)		
ORR	29.5 %	47.7 %

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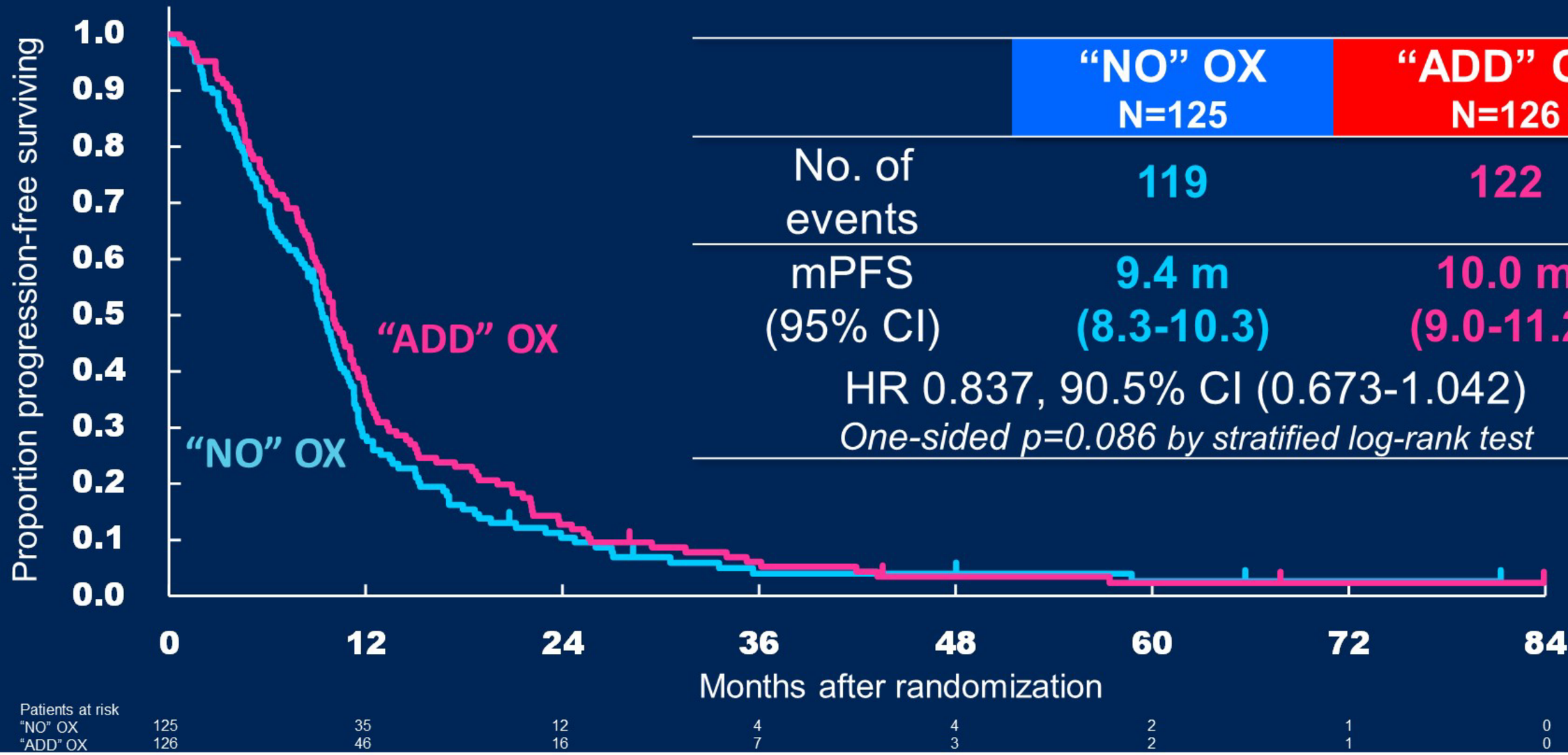
Progression-free survival (ITT)



	"NO" OX N=125	"ADD" OX N=126
No. of events	119	122
mPFS (95% CI)	9.4 m (8.3-10.3)	10.0 m (9.0-11.2)

HR 0.837, 90.5% CI (0.673-1.042)

One-sided p=0.086 by stratified log-rank test

PRESENTED BY: Tetsuya Hamaguchi

Summary

- In this “elderly” trial, 93% of patients were ≥ 75 years with ECOG PS 0 or 1
- The “ADD” OX to fluoropyrimidine with BEV has no PFS prolongation
- The “ADD” OX was associated with more frequent and more severe adverse events

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Summary

- Treatment of colorectal cancer is evolving to a more targeted approach
- CtDNA role to find its role in adjuvant and metastatic setting
- Immunotherapy in combination with chemotherapy in the first line setting to find its subpopulation
- Benefit of adjuvant oxaliplatin dependent on age and length of therapy

Questions?

Thank you