

 A large graphic on the left side of the slide features several stylized human figures in various colors (teal, green, orange, grey, blue) arranged in a circular pattern, suggesting a global or diverse perspective.

EPICS

# EPICS: Global Perspectives in CRC in 2023 and Beyond

January 21, 2023

Full Report

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## VIRTUAL CLOSED-DOOR ROUNDTABLE



**DATE:**  
January 21, 2023



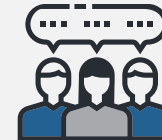
**DISEASE STATE AND  
DATA PRESENTATIONS**  
by key experts



**INSIGHTS REPORT**  
including postmeeting  
analyses and actionable  
recommendations



**PANEL:** Key experts in  
CRC  
> 4 from US  
> 2 from Europe



**COLORECTAL CANCER-  
SPECIFIC DISCUSSIONS** on  
therapeutic advances and their  
application in clinical decision-  
making

# Panel Consisting of 4 US and 2 European CRC Experts



**CHAIR:**  
**Alan Venook, MD, FASCO**  
University of California San Francisco



**Kristen Ciombor, MD**  
Vanderbilt University  
Medical Center



**Aparna Parikh, MD**  
Harvard Medical School



**Andrea Cercek, MD**  
Memorial Sloan Kettering  
Cancer Center



**Thierry André, MD**  
Sorbonne Université



**Dirk Arnold, MD, PhD**  
University of Hamburg

# Meeting Agenda

Time (PDT)	Topic	Speaker/Moderator
5.00 PM – 5.05 PM	Welcome and Introductions	Alan Venook, MD, FASCO
5.05 PM – 5.20 PM	Current Treatment Paradigms for Early-Stage CRC (MSS/pMMR)	Kristen Ciombor, MD
5.20 PM – 5.50 PM	Key Questions and Topics for Discussion	All
5.50 PM – 6.05 PM	Current Treatment Paradigms for Metastatic CRC	Andrea Cercek, MD
6.05 PM – 6.40 PM	Key Questions and Topics for Discussion	All
6.40 PM – 6.50 PM	The Evolving Role of Immunotherapy in CRC	Alan Venook, MD, FASCO
6.50 PM – 7.15 PM	Key Questions and Topics for Discussion	All
7.15 PM – 7.25 PM	<i>BREAK</i>	
7.25 PM – 7.35 PM	Currently Available Targeted Therapies for CRC	Dirk Arnold, MD, PhD
7.35 PM – 7.55 PM	Key Questions and Topics for Discussion	All
7.55 PM – 8.05 PM	Current and Evolving Biomarkers in CRC	Thierry André, MD
8.05 PM – 8.30 PM	Key Questions and Topics for Discussion	All
8.30 PM – 8.40 PM	Emerging Therapies and Novel Investigational Approaches for CRC	Aparna Parikh, MD
8.40 PM – 8.55 PM	Key Questions and Topics for Discussion	All
8.55 PM – 9.00 PM	Conclusions and Wrap-up	Alan Venook, MD, FASCO



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# Current Treatment Paradigms for Early-Stage CRC (MSS/pMMR)



# Current Treatment Paradigms for Early-Stage CRC (MSS/pMMR) (1/2)

Presented by Kristen Ciombor, MD

## FOxTROT

> The FOxTROT trial randomized 1060 patients with

### STUDY POPULATION

1060 patients with MSS/pMMR early-stage CRC... randomized to receive either oxaliplatin, capecitabine, and fluorouracil (FOX) or oxaliplatin, capecitabine, and fluorouracil with cetuximab (FOX-C). The primary endpoint was overall survival (OS) at 2 years. The secondary endpoint was progression-free survival (PFS) at 2 years. The trial was stratified by tumor location (colon vs. rectum) and by the presence of a KRAS mutation.

### RESULTS

At 2 years, OS was significantly higher in the FOX-C group compared to the FOX group (p < 0.05). PFS was also significantly higher in the FOX-C group (p < 0.05). The addition of cetuximab to the FOX regimen significantly improved both OS and PFS in patients with MSS/pMMR early-stage CRC.

### KEY TAKEAWAYS

Adding cetuximab to the FOX regimen significantly improved both OS and PFS in patients with MSS/pMMR early-stage CRC. This finding supports the use of FOX-C as a standard of care for this patient population.

### 2-Year Recurrence Rate



### RESPONSE, TOXICITY, AND QUALITY OF LIFE (QOL) RESULTS





# Current Treatment Paradigms for Early-Stage CRC (MSS/pMMR) (2/2)

Presented by Kristen Ciombor, MD

## IDEA

> The IDEA trial demonstrated that for patients with high-

### Early Oxaliplatin Discontinuation: OS



### RESPONSE, TOXICITY, AND QUALITY OF LIFE (QOL) FINDINGS





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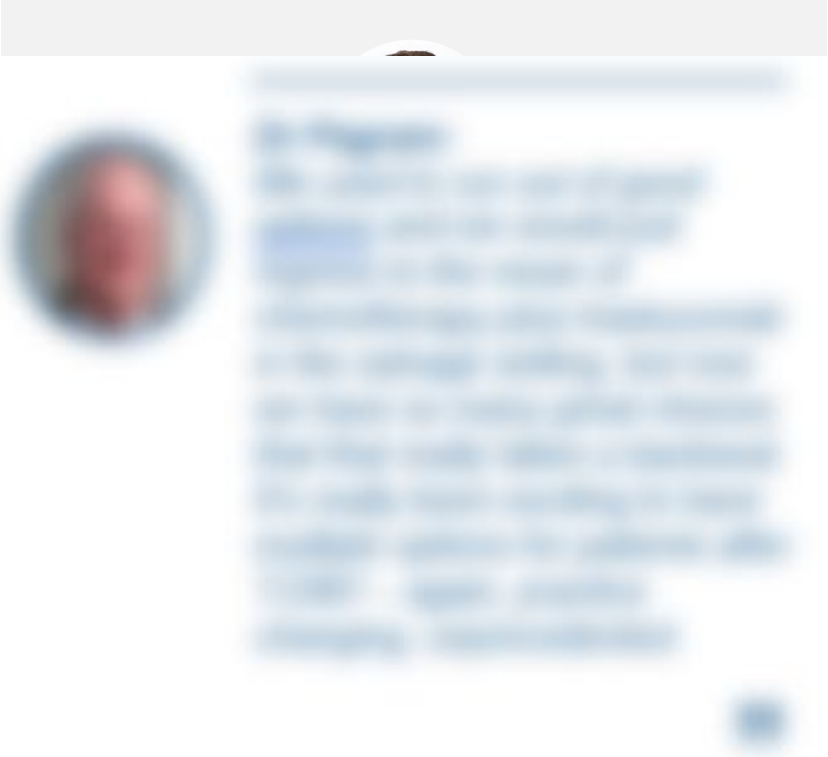
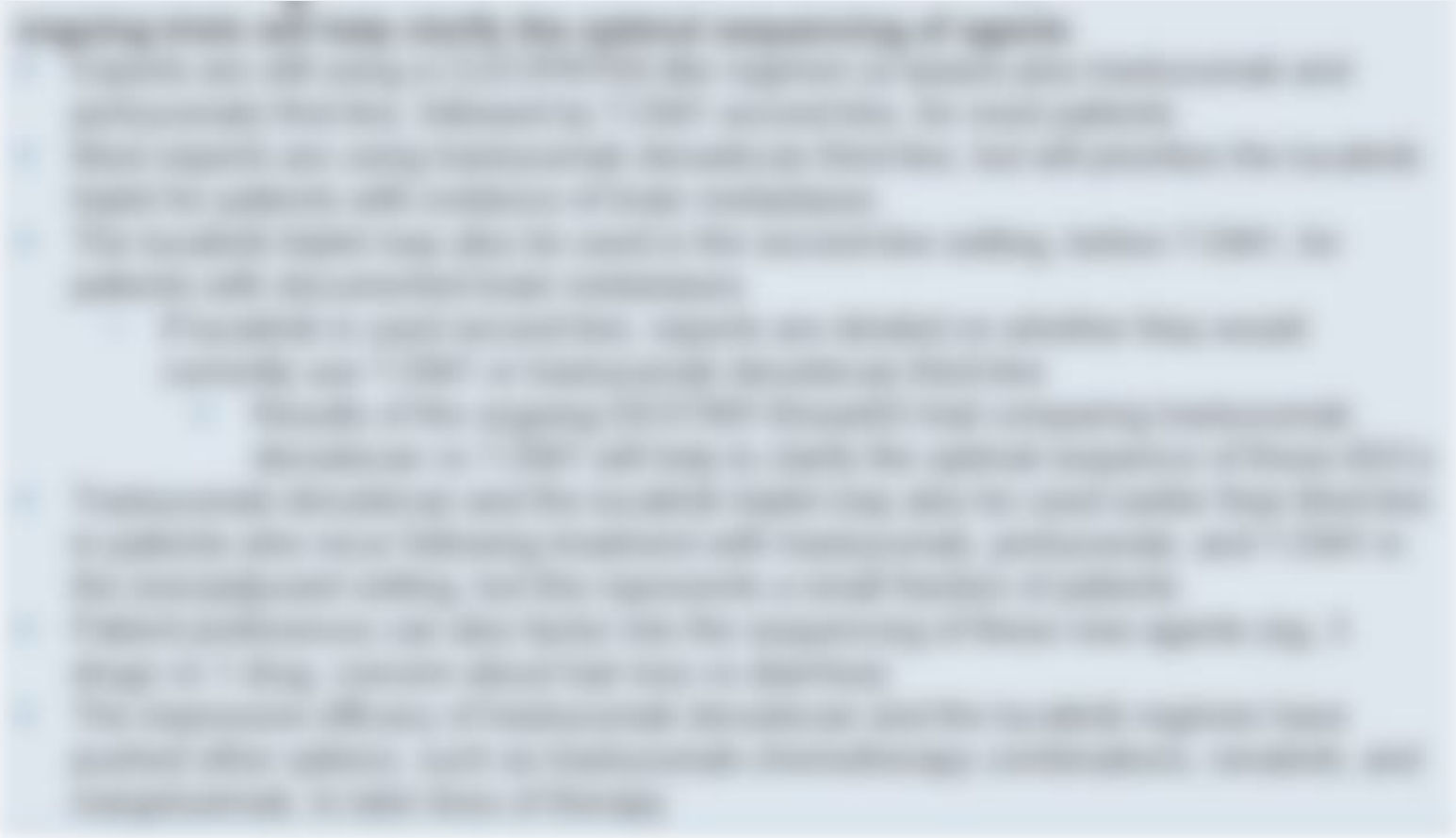
## Key Insights

Current Treatment Paradigms for Early-Stage  
CRC (MSS/pMMR)

# Experts Discussed Current Standards for Resectable CRC

## NEOADJUVANT THERAPY

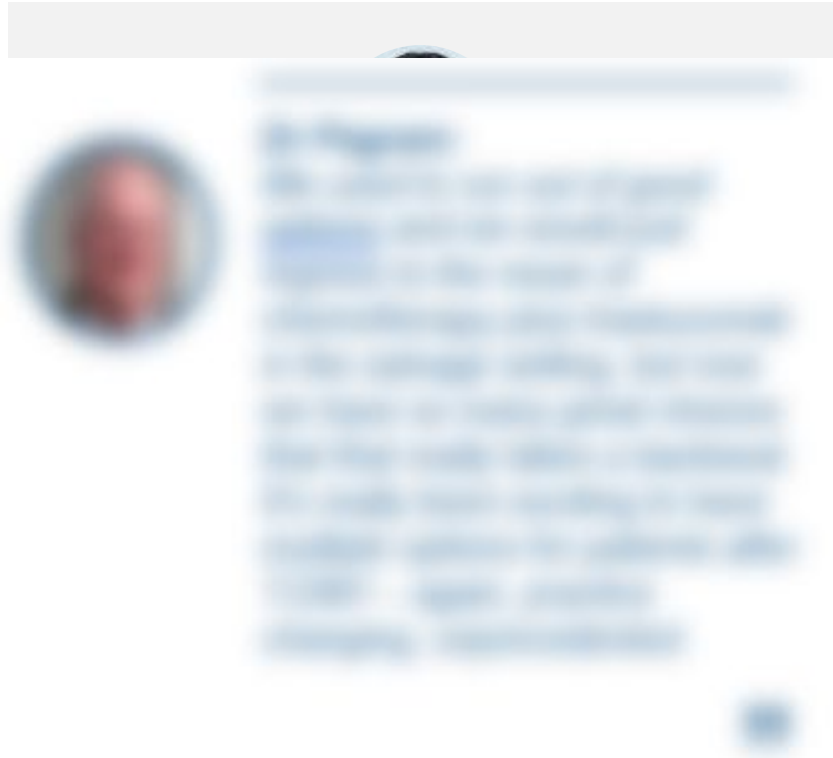
Experts believe the FOxTROT neoadjuvant approach is reasonable for some patients



# Experts Debated the Potential Role for ctDNA-Driven Treatment for Early-Stage CRC

## ctDNA FOR GUIDING TREATMENT

Experts are concerned about overtreatment of stage II, and potentially some stage III,



# Experts Discussed the Potential Role for Targeted Agents in the (Neo)Adjuvant Setting for CRC

## VEGF/EGFR/BRAF INHIBITORS FOR EARLY-STAGE CRC

Experts do not envision any role for current anti-VEGF and anti-EGFR targeted

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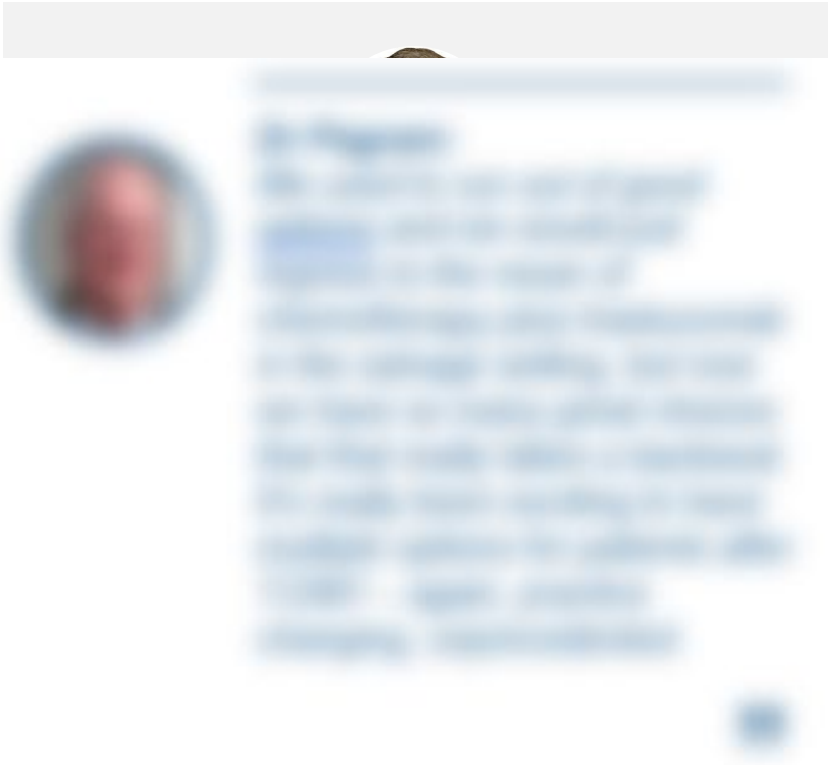
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# Experts Speculated on Future Directions for Research in Early-Stage CRC

## UNMET CLINICAL NEEDS IN EARLY-STAGE CRC

Regarding the development of future (neo)adjuvant trials, experts highlighted the

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# Current Treatment Paradigms for Metastatic CRC



# Current Treatment Paradigms for Metastatic CRC (1/4)

Presented by Andrea Cercek, MD

## FIRST-LINE CHEMOTHERAPY OPTIONS

### First-line chemotherapy backbones for MSS mCRC

### DAPADIGM: Overall Survival

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2007	2008	2009	2010	2011	2012	2013
2007							
2008							
2009							
2010							
2011							
2012							
2013							





# Current Treatment Paradigms for Metastatic CRC (2/4)

Presented by Andrea Cercek, MD

## TARGETING BRAF, KRAS, AND IMMUNE CHECKPOINTS

> Pembrolizumab is now the first-line standard for MSI-H mCRC,

**KRAS G12C: Adagrasib + Cotuximab**

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2007	2008	2009	2010	2011	2012	2013
2007							
2008		2008					
2009			2009				
2010				2010			
2011					2011		
2012						2012	
2013							2013







# Current Treatment Paradigms for Metastatic CRC (3/4)

Presented by Andrea Cercek, MD

## TARGETING HER2-POSITIVE mCRC

> Approximately one-third of patients with refractory HER2-positive mCRC

**MOUNTAINEER: Change in Tumor Size**

Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2009	2010	2011	2012	2013	2014	2015
Number of Approvals	0	1	2	3	4	5	6





# Current Treatment Paradigms for Metastatic CRC (4/4)

Presented by Andrea Cercek, MD

## OPTIONS FOR REFRACTORY mCRC

### Later-line treatment options for refractory mCRC

Chemo +/- bev

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2009	2010	2011	2012	2013	2014	2015
2009							
2010							
2011							
2012							
2013							
2014							
2015							



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## Key Insights

Current Treatment Paradigms for  
Metastatic CRC

# Experts Debated the First-Line Management of mCRC

## FIRST-LINE TREATMENT PARADIGMS

**Most experts use FOLFOX or FOLFIRINOX as first-line therapy**

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# Experts Discussed the Management of Refractory mCRC

## LATER-LINE TREATMENT OPTIONS FOR mCRC

**TAS-102 + bevacizumab is considered a new standard of care for relapsed/refractory**

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# Experts Discussed Evolving Treatment Paradigms for HER2-Positive mCRC

## HER2-TARGETED AGENTS

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# Experts Considered Experimental Strategies and Future Directions for mCRC

## INVESTIGATIONAL DIRECTIONS

While there is interest in evaluating targeted therapies in earlier lines of treatment.

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# The Evolving Role of Immunotherapy in CRC





# The Evolving Role of Immunotherapy in CRC (1/3)

Presented by Alan Venook, MD, FASCO

## IMMUNE CHECKPOINT INHIBITORS IN MSI-H/dMMR mCRC

> IO therapies have demonstrated robust efficacy with durable

### KEYNOTE 177

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	Year	Year	Year	Year	Year	Year
2009	2010	2011	2012	2013	2014	2015
	2016	2017	2018	2019	2020	2021
						2022





# The Evolving Role of Immunotherapy in CRC (2/3)

Presented by Alan Venook, MD, FASCO

## IMMUNE CHECKPOINT INHIBITORS IN MSS mCRC

> IMblaze370, which compared atezolizumab ±

### NICHE: Neoadjuvant Immunotherapy

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2012	2013	2014	2015	2016	2017	2018
2012							
2013							
2014							
2015							
2016							
2017							
2018							





# The Evolving Role of Immunotherapy in CRC (3/3)

Presented by Alan Venook, MD, FASCO

## NEOADJUVANT TREATMENT WITH IMMUNOTHERAPY

> A study of 121 patients with MSI-H mCRC treated with

### Dostarlimab in dMMR Rectal Cancer

### Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2012	2013	2014	2015	2016	2017	2018
2012							
2013							
2014							
2015							
2016							
2017							
2018							



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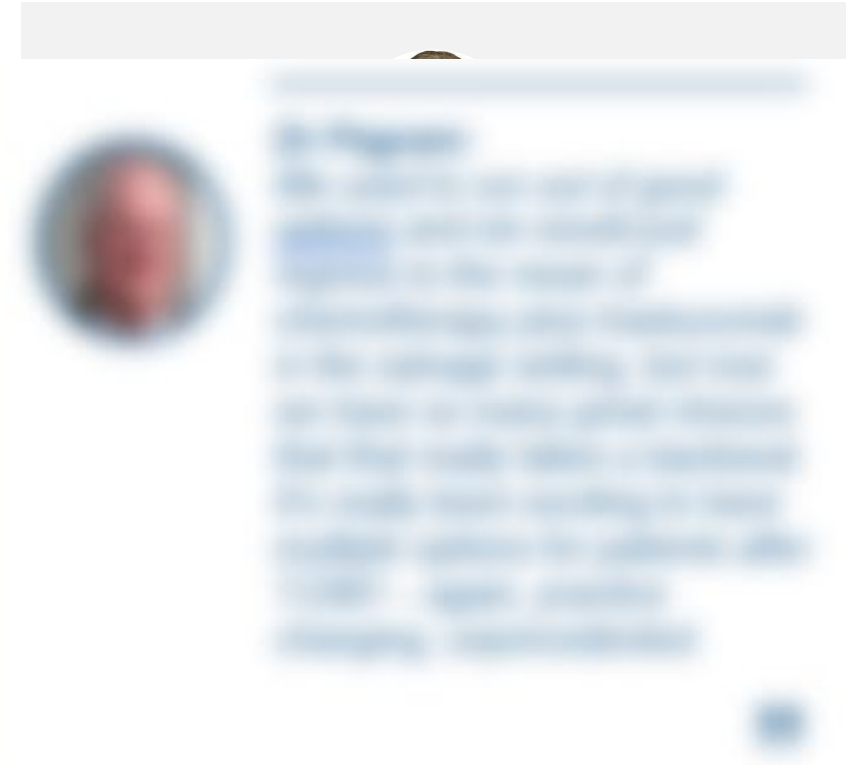
## Key Insights

The Evolving Role of Immunotherapy in CRC

# Experts Discussed Successes and Gaps With Immunotherapies in CRC

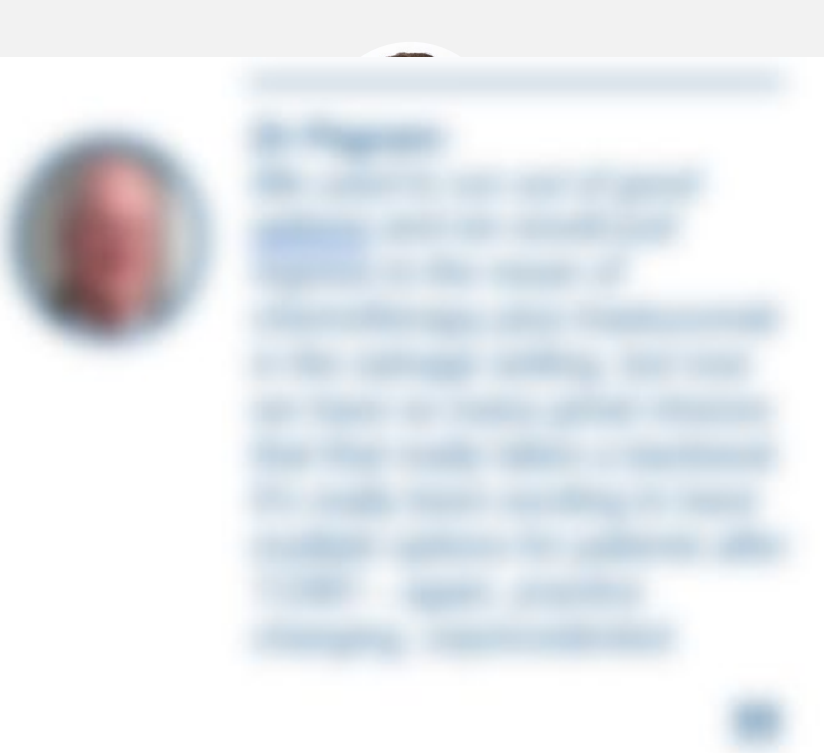
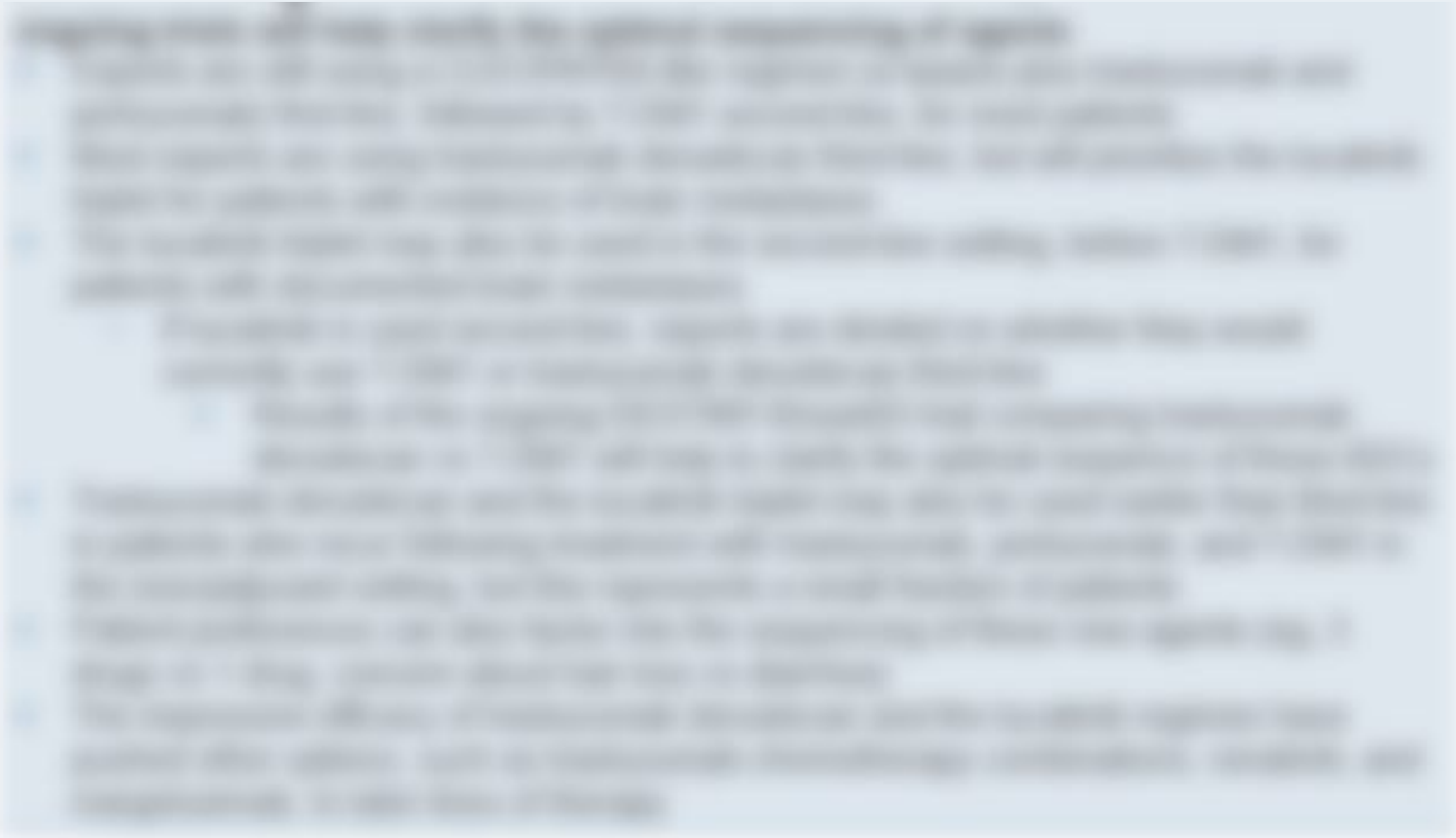
## ICIs IN MSI-H RECTAL CANCER

The results with dostarlimab in MSI-H rectal cancer are considered astonishingly



## BIOMARKERS AND MISCONCEPTIONS

**Community oncologists need more education on testing for biomarkers to identify**



# Experts Considered Unanswered Questions and Future Research Directions

## IO-IO COMBINATION THERAPY

An important unanswered question is whether ICIs should be used alone or in

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## Currently Available Targeted Therapies for CRC





# Currently Available Targeted Therapies for CRC (1/4)

Presented by Dirk Arnold, MD, PhD

## EGFR-TARGETED mAbs

> In addition to PARADIGM, 4 trials have demonstrated

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# Currently Available Targeted Therapies for CRC (2/4)

Presented by Dirk Arnold, MD, PhD

## VEGF-TARGETED THERAPIES

> Chemotherapy ± anti-VEGF therapy is preferred for

### Anti-VEGF Across Lines of Therapy

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# Currently Available Targeted Therapies for CRC (3/4)

Presented by Dirk Arnold, MD, PhD

## BRAF V600E mCRC

> For BRAF V600E mCRC, first-line doublet

### BREAKWATER: First-Line BRAF V600E

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# Currently Available Targeted Therapies for CRC (4/4)

Presented by Dirk Arnold, MD, PhD

## HER2-POSITIVE mCRC

> For previously treated HER2-positive mCRC, HER2-

### DESTINY\_CRC01

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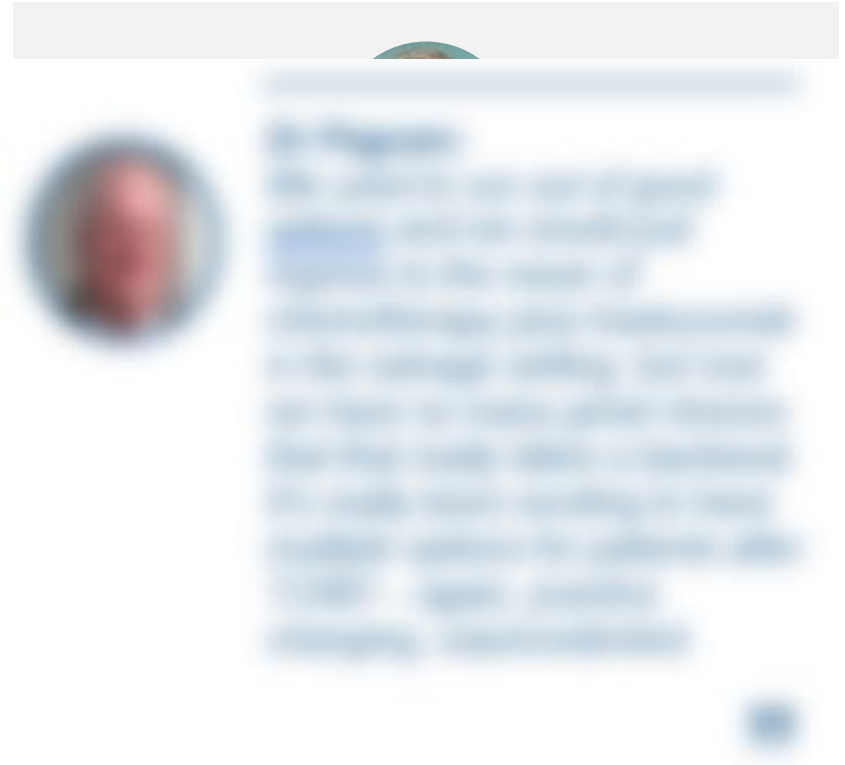
## Key Insights

Currently Available Targeted Therapies for CRC

# Experts Discussed Patterns of Use of VEGF- and EGFR-Targeted Agents in mCRC

## VEGF-TARGETED THERAPIES

Experts agreed that VEGF inhibition should be continued through all lines of therapy



# Experts Considered Emerging and Investigational Targeted Therapies

## HER2-TARGETED THERAPIES

Most experts currently use trastuzumab with either pertuzumab or

OS and PFS in Patients Treated With anti-EGFR Therapy

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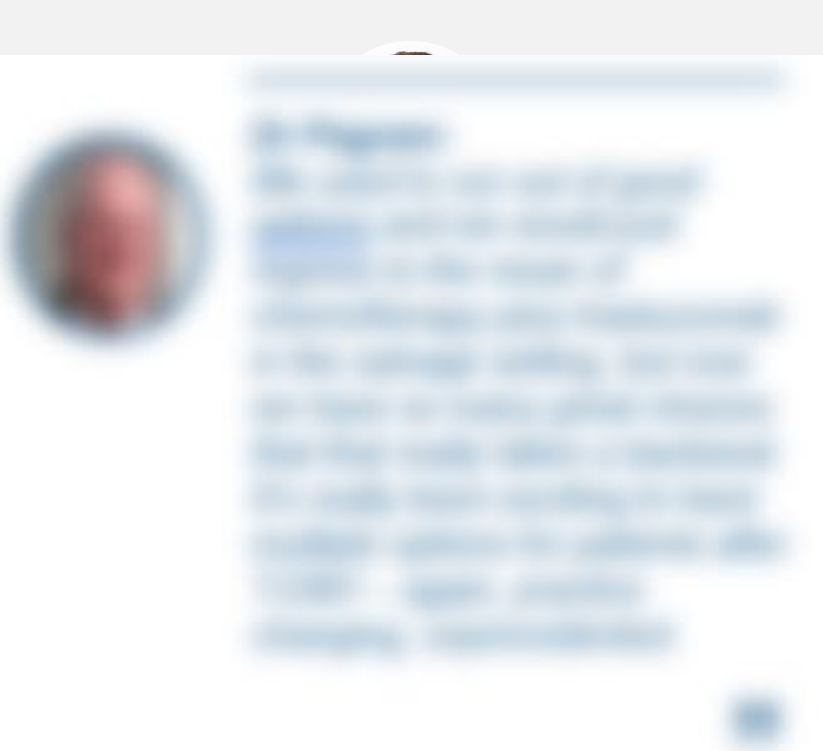


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# Experts Debated Chemotherapy Sequencing and Implications for New Drug Development

## SECOND-LINE OPTIONS

Second-line therapy depends on the first-line regimen, and either FOLFOX or





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# Current and Evolving Biomarkers in CRC



# Current and Evolving Biomarkers in CRC (1/2)

Presented by Thierry André, MD

## BIOMARKER TESTING FOR mCRC

> NGS testing is standard for mutational analysis in mCRC,

Strongly associated with

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# Current and Evolving Biomarkers in CRC (2/2)

Presented by Thierry André, MD

## TOOLS FOR ADJUVANT DECISION-MAKING

> Tools for adjuvant decision-making are limited

## DPD DEFICIENCY

> Dihydropyrimidine dehydrogenase (DPD) phenotyping and

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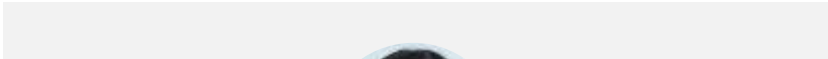
## Key Insights

Current and Evolving Biomarkers in CRC

# Experts Debated Standard Biomarkers and Testing Methodologies in CRC

## SOC BIOMARKERS FOR CRC

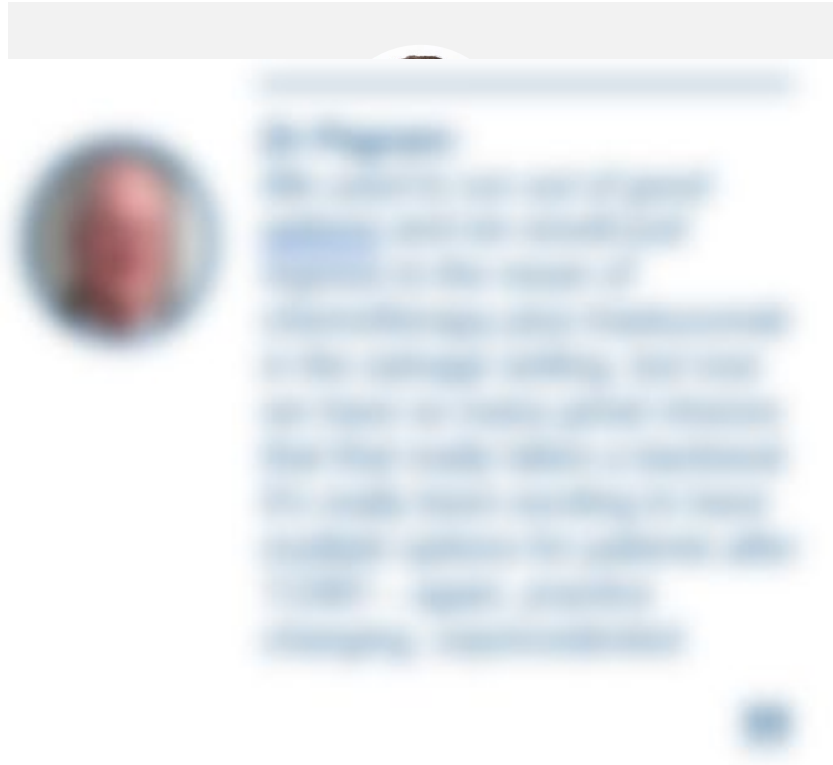
Experts believe the following biomarkers are essential for guiding treatment in



# Experts Debated the Role of ctDNA Testing and Adjuvant Decision-Making

## ctDNA-GUIDED TREATMENT

**There is a large unmet need for predictive markers to guide adjuvant decision-**



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# **Emerging Therapies and Novel Investigational Approaches for CRC**



# Emerging Therapies and Novel Investigational Approaches for CRC (1/3)

Presented by Aparna Parikh, MD

## RAS-TARGETING STRATEGIES

Mutation specific inhibitors of KRAS are starting to

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# Emerging Therapies and Novel Investigational Approaches for CRC (2/3)

Presented by Aparna Parikh, MD

## BRAF INHIBITOR COMBINATIONS

> New combinations are building on the BRAFi-MEKi

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## Overall program for combination trials



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# Emerging Therapies and Novel Investigational Approaches for CRC (3/3)

Presented by Aparna Parikh, MD

## IMMUNOTHERAPY FOR MSS CRC

> Liver metastases are emerging as a clinical marker for

### Bevacizumab + Pembrolizumab



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## **Key Insights**

**Emerging Therapies and Novel Investigational  
Approaches for CRC**

# Experts Discussed Areas of Opportunity in CRC Research

## NOVEL AGENTS AND STRATEGIES

Experts are impressed by new efforts to target *KRAS* G12C and G12D and also to

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