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EPICS: Global Perspectives in CRC in 2022 and Beyond

FULL REPORT

March 16, 2022

Report Contents

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Meeting Snapshot

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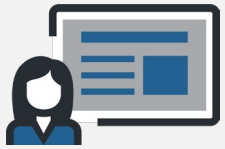
VIRTUAL CLOSED-DOOR ROUNDTABLE

DATE:
March 16, 2022



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 Experts in CRC

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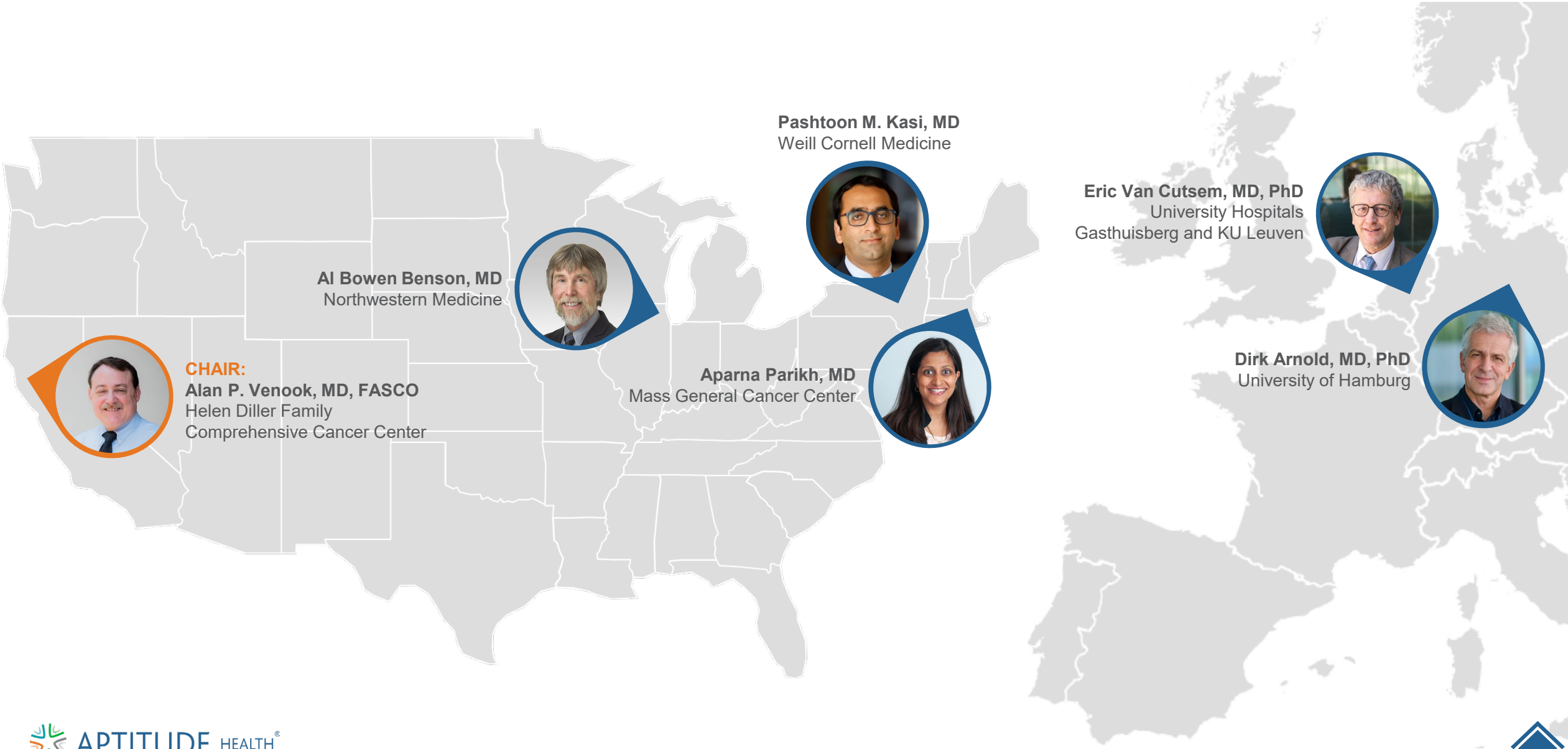

Pashtoon M. Kasi, MD
Weill Cornell Medicine

Eric Van Cutsem, MD, PhD
University Hospitals
Gasthuisberg and KU Leuven

Al Bowen Benson, MD
Northwestern Medicine

Aparna Parikh, MD
Mass General Cancer Center

Dirk Arnold, MD, PhD
University of Hamburg

CHAIR:
Alan P. Venook, MD, FASCO
Helen Diller Family
Comprehensive Cancer Center

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Meeting Agenda (1/2)

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Time (PST)	Topic	Speaker/Moderator
8.00 AM – 8.05 AM	Welcome, Introductions, and Meeting Objectives	Alan P. Venook, MD, FASCO
8.05 AM – 8.20 AM	**Current Treatment Paradigms for Early-Stage CRC (MSS/pMMR)**	Al Bowen Benson, MD
8.20 AM – 8.50 AM	Discussion and Key Takeaways	
8.50 AM – 9.05 AM	**Current Treatment Paradigms for Metastatic CRC**	Eric Van Cutsem, MD, PhD
9.05 AM – 9.40 AM	Discussion and Key Takeaways	
9.40 AM – 9.50 AM	**The Evolving Role of Immunotherapy in CRC**	Alan P. Venook, MD, FASCO
9.50 AM – 10.15 AM	Discussion and Key Takeaways	
10.15 AM – 10.25 AM	BREAK	

Meeting Agenda (2/2)

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Time (PST)	Topic	Speaker/Moderator
10.25 AM – 10.35 AM	**Currently Available Targeted Therapies for CRC**	Dirk Arnold, MD, PhD
10.35 AM – 10.55 AM	Discussion and Key Takeaways	
10.55 AM – 11.05 AM	**Emerging Therapies and Novel Investigational Approaches for CRC**	Aparna Parikh, MD
11.05 AM – 11.30 AM	Discussion and Key Takeaways	
11.30 AM – 11.40 AM	**Current and Evolving Biomarkers in CRC**	Pashtoon M. Kasi, MD
11.40 AM – 11.55 AM	Discussion and Key Takeaways	
11.55 AM – 12.00 PM	Conclusions and Wrap-up	Alan P. Venook, MD, FASCO

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

Al Bowen Benson, MD

Northwestern Medicine

Current Treatment Paradigms for Early-Stage CRC (1/4)

PRESENTED BY AL BOWEN BENSON, MD

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NEOADJUVANT CHEMOTHERAPY IN COLON CANCER

> Neoadjuvant chemotherapy is well established in many solid

CLINICAL TRIALS USING NEOADJUVANT CHEMO IN LOCALLY ADVANCED COLON CANCER

Neoadjuvant chemotherapy may prove to be an option in operable

Current Treatment Paradigms for Early-Stage CRC (2/4)

PRESENTED BY AL BOWEN BENSON, MD

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FACTORS GUIDING DECISION-MAKING FOR ADJUVANT THERAPY

> Definitive decisions regarding adjuvant treatment should only be made after

Current Treatment Paradigms for Early-Stage CRC (3/4)

PRESENTED BY AL BOWEN BENSON, MD

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ESMO GUIDELINES FOR ADJUVANT TREATMENT OF STAGE II COLON CANCER

> ESMO clinical practice guidelines for diagnosis, treatment, and follow-up for adjuvant

Stage II

Current Treatment Paradigms for Early-Stage CRC (4/4)

PRESENTED BY AL BOWEN BENSON, MD

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ASCO GUIDELINES

- ASCO guidelines for adjuvant therapy for stage II

RISK FACTORS

- Various prognostic risk factors that are integral in terms of defining risks

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

Experts Identified a Change in Demographics of Patients With Colorectal Cancer

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EARLY ONSET

In the US, there is an appalling skew toward younger people with the

Dr Kasi:
I think for colorectal cancer I still see the

Expert Perspectives on Changes to the Algorithm for Early-Stage CRC

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PREFERENTIAL TREATMENT OPTIONS FOR STAGE 3 COLON CANCER

Experts in Europe have a strong preference for CAPOX, while in

NEOADJUVANT CHEMOTHERAPY

Experts follow NCCN guidelines and also offer neoadjuvant

Experts Commented on Current Standards of Biomarker Testing and Unmet Needs

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The Use of ctDNA as a Prognostic Biomarker

All the experts agreed that ctDNA is emerging as one of the most

MSI Testing

> Where possible, experts evaluate MSI status of their

„ decision making, but it is not just the only marker. "

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Current Treatment Paradigms for Metastatic CRC

Eric Van Cutsem, MD, PhD

University Hospitals Gasthuisberg and KU Leuven

Current Treatment Paradigms for Metastatic CRC (1/3)

PRESENTED BY ERIC VAN CUTSEM, MD, PHD

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MANAGEMENT OF RESECTABLE OLIGOMETASTASES (RESECTION VS ABLATION)

- The goal is to individualize treatment in all patients with metastatic

Current Treatment Paradigms for Metastatic CRC (2/3)

PRESENTED BY ERIC VAN CUTSEM, MD, PHD

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FIRST-LINE TREATMENT OPTIONS

> The key factors for selecting and individualizing first-line therapy for

Treatment options in first-line mCRC

Current Treatment Paradigms for Metastatic CRC (3/3)

PRESENTED BY ERIC VAN CUTSEM, MD, PHD

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PREFERRED CHOICES IN FIRST-LINE TREATMENT OF mCRC

Goal / condition	Molecular	Prefered 1st line regimen

PREFERRED CHOICES IN SECOND-LINE TREATMENT OF mCRC

Goal / condition	Molecular	Prefered 2nd line regimen

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Key Insights: Current Treatment Options for Metastatic CRC

Expert Perspectives on Changes to the Algorithms for Treating Metastatic CRC

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SIDEDNESS OF DISEASE AND ANTI-EGFR THERAPY

The treatment algorithm for CRC continues to evolve. It is important

OPINIONS ON INTEGRATING *BRAF*-TARGETED THERAPY INTO THE FRONTLINE SETTING

Experts agreed there is not enough evidence to support

Expert Insights on Doublet vs Triplet Therapies

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Experts Discussed Third-Line Treatment Options and Giving Treatment Holidays to Their Patients

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The Evolving Role of Immunotherapy in CRC

Alan P. Venook, MD, FASCO

Helen Diller Family Comprehensive Cancer Center

The Evolving Role of Immunotherapy in CRC (1/2)

PRESENTED BY ALAN P. VENOOK, MD, FASCO

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ADVANCES IN IMMUNOTHERAPY FOR CRC HAVE BEEN MADE, BUT SOME QUESTIONS REMAIN

First-Line Treatment

KEYNOTE-177 trial: Survival benefit only reported after 6 months of pembro treatment

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

PRESENTED BY ALAN P. VENOOK, MD, FASCO

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ADVANCES IN IMMUNOTHERAPY FOR CRC HAVE BEEN MADE, BUT SOME QUESTIONS REMAIN

Can we turn cold tumors hot?

Survival benefit only reported after 6 months of pembro treatment

Memorial Sloan Kettering Cancer Center

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Key Insights: The Evolving Role of Immunotherapy in CRC

Key Takeaways: The Evolving Role of Immunotherapy in CRC (1/2)

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ADVANCED/METASTATIC MSI-H CRC

Key Takeaways: The Evolving Role of Immunotherapy in CRC (2/2)

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ADVANCED/METASTATIC MSI-H CRC

TMB may not be the best predictor of checkpoint

NEOADJUVANT THERAPY FOR MSI-H RECTAL CANCER

Dramatic results from the small series of 18 patients with MSI-H rectal cancers

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Currently Available Targeted Therapies for CRC

Dirk Arnold, MD, PhD

University of Hamburg

Currently Available Targeted Therapies for CRC (1/3)

PRESENTED BY DIRK ARNOLD, MD, PHD

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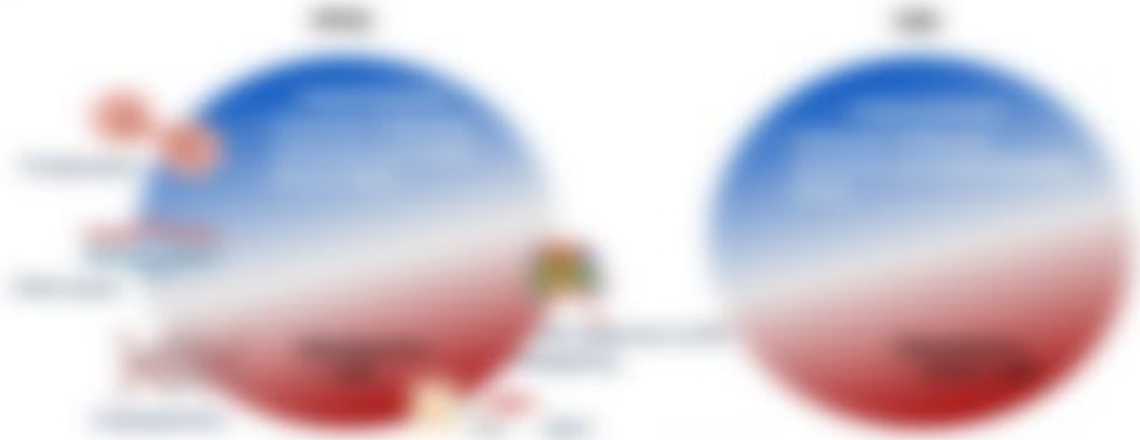
MOLECULAR CHARACTERIZATION OF CRC

> *RAS* status and sidedness are important determinants of treatment



Currently Available Targeted Therapies for CRC (2/3)

PRESENTED BY DIRK ARNOLD, MD, PHD

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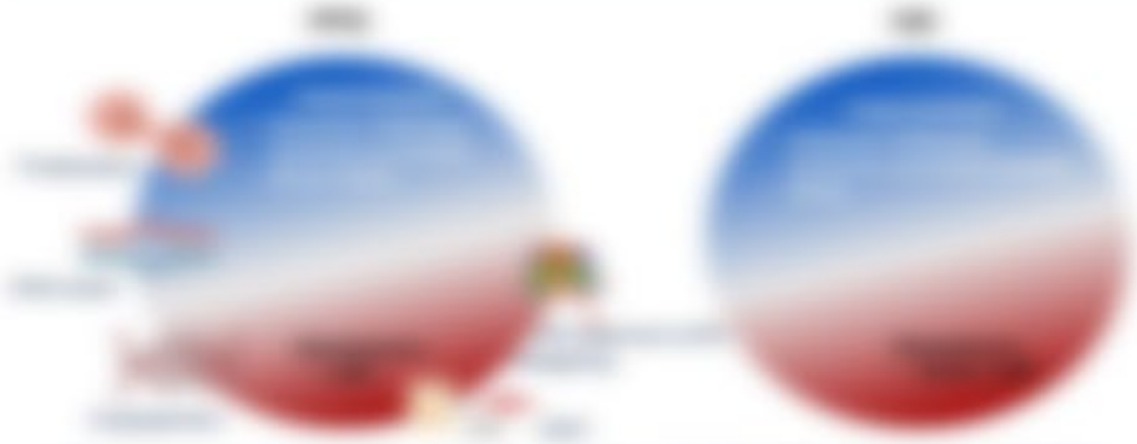
MANAGEMENT OF HER2+ CRC

> The HERACLES trial in HER2+ refractory solid tumors laid the

DESTINY-CRC-01 study addresses the use of T-DXd in



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Currently Available Targeted Therapies for CRC (3/3)

PRESENTED BY DIRK ARNOLD, MD, PHD

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MANAGEMENT OF *NTRK*-POSITIVE DISEASE

> For *NTRK* fusion-positive CRC patients, larotrectinib and entrectinib offer a survival benefit

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Key Insights: Currently Available Targeted Therapies for CRC

Expert Perspectives on the Use of Drugs, Monoclonal Antibodies, and Antibody-Drug Conjugates

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TRASTUZUMAB DERUXTECAN

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Emerging Therapies and Novel Investigational Approaches for CRC

Aparna Parikh, MD

Mass General Cancer Center

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

PRESENTED BY APARNA PARIKH, MD

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UPDATES IN TARGETED THERAPEUTICS FOR CRC

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

PRESENTED BY APARNA PARIKH, MD

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UPDATES IN TARGETED THERAPEUTICS FOR CRC

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

PRESENTED BY APARNA PARIKH, MD

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UPDATES IN TARGETED THERAPEUTICS FOR CRC

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Key Insights: Emerging Therapies and Novel Investigational Approaches for CRC

Key Takeaways: Emerging Therapies and Novel Investigational Approaches for CRC (1/2)

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RAS- AND *BRAF*-TARGETED AGENTS

***RAS* G12C-targeted agents (sotorasib, adagrasib) are showing promise in**

“

Dr Kasi:

Key Takeaways: Emerging Therapies and Novel Investigational Approaches for CRC (2/2)

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IMMUNOTHERAPEUTICS

Site of metastasis is increasingly recognized as an important factor that can impact drug efficacy, particularly for immunotherapeutics

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Current and Evolving Biomarkers in CRC

Pashtoon M. Kasi, MD

Weill Cornell Medicine

Current and Evolving Biomarkers in CRC (1/3)

PRESENTED BY PASHTOON M. KASI, MD

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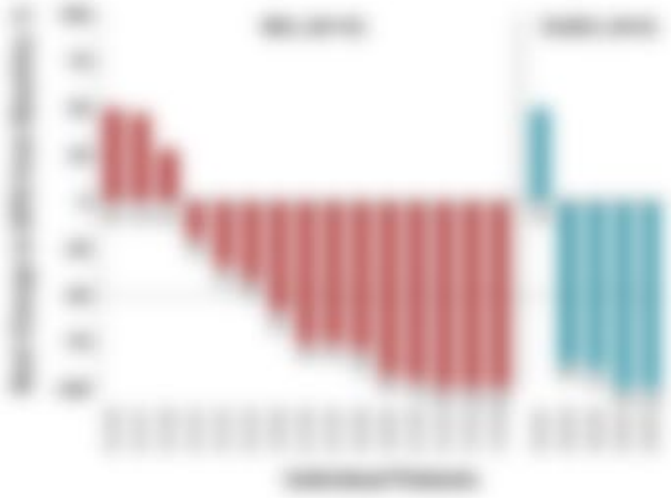
MOLECULAR DETERMINANTS OF DISEASE

> Targets can be CRC specific or tumor agnostic

Algorithm for MMR/MSI testing in CRC



Background

- Phase I dose-escalation study of VLS-101, a ROR1-targeting ADC, in patients with heavily pretreated MCL and DLBCL
- Primary objective was to refine estimates of MTD and recommended dosing regimen

Results

- 32 patients were enrolled, including 15 patients with MCL
- DLTs were G4 neutropenia and G3 diarrhea
- G4 neutropenia occurred in 28% of patients; G-CSF successfully ameliorated neutropenia
- On-study reversible G3 neuropathy occurred in 9% of patients; no G4 neuropathy occurred
- ORR was 47% (3 CR, 4 PR) for MCL cohort and 80% (2 CR, 2 PR) for DLBCL cohort
- 8 responding patients have ongoing responses ranging from 23 weeks to 58 weeks

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

Current and Evolving Biomarkers in CRC (2/3)

PRESENTED BY PASHTOON M. KASI, MD

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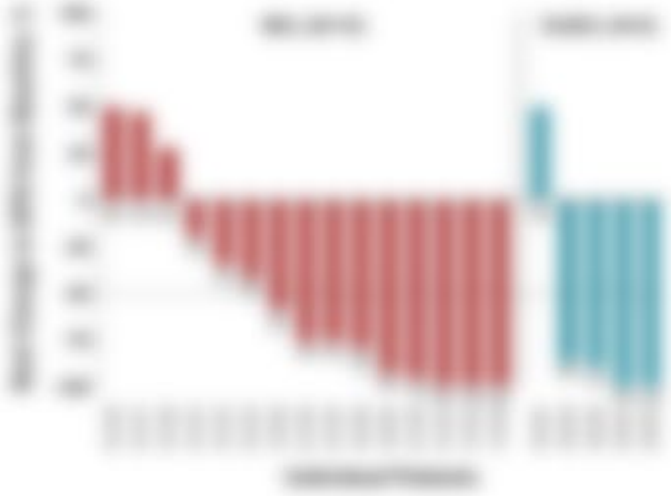
USING ctDNA DETECTION FOR PROGNOSIS

> It is currently unclear if ctDNA detection is a useful surveillance or

ctDNA as a prognostic tool and a marker for persistent disease

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



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Current and Evolving Biomarkers in CRC (3/3)

PRESENTED BY PASHTOON M. KASI, MD

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TUMOR MUTATIONAL BURDEN

> There is a subset of MSI-H tumors that also has a high TMB

DPYD VARIANTS

> Patients with DPYD variants can achieve the appropriate

Background

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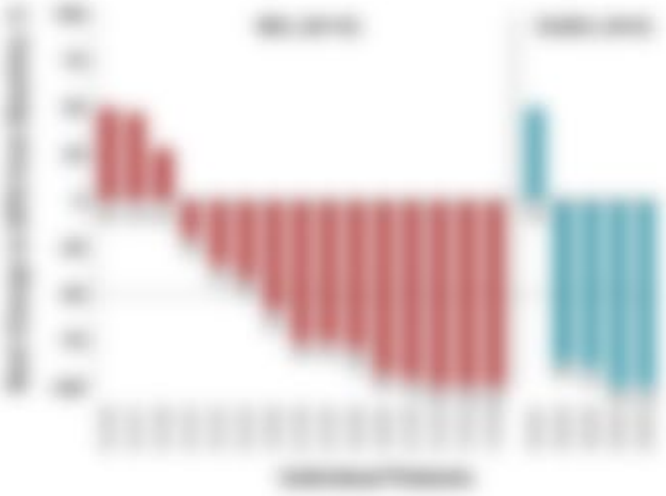

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Key Insights: Current and Evolving Biomarkers in CRC

Experts Discussed the Use of ctDNA for Prognostic Purposes

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ctDNA DETECTION AND ITS INTERPRETATION

Experts Discussed How the Presence of DPYD Mutations Could Inform Dosing Strategies

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DOSE-REDUCTION STRATEGIES FOR DPYD-MUTATED PATIENTS

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