

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

EPICS

EPICS: Global Perspectives in CRC in 2022 and Beyond

FULL REPORT

March 16, 2022

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EPICS

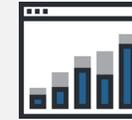
VIRTUAL CLOSED-DOOR ROUNDTABLE



DATE:
March 16, 2022



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



INSIGHTS REPORT
including postmeeting
analyses and actionable
recommendations



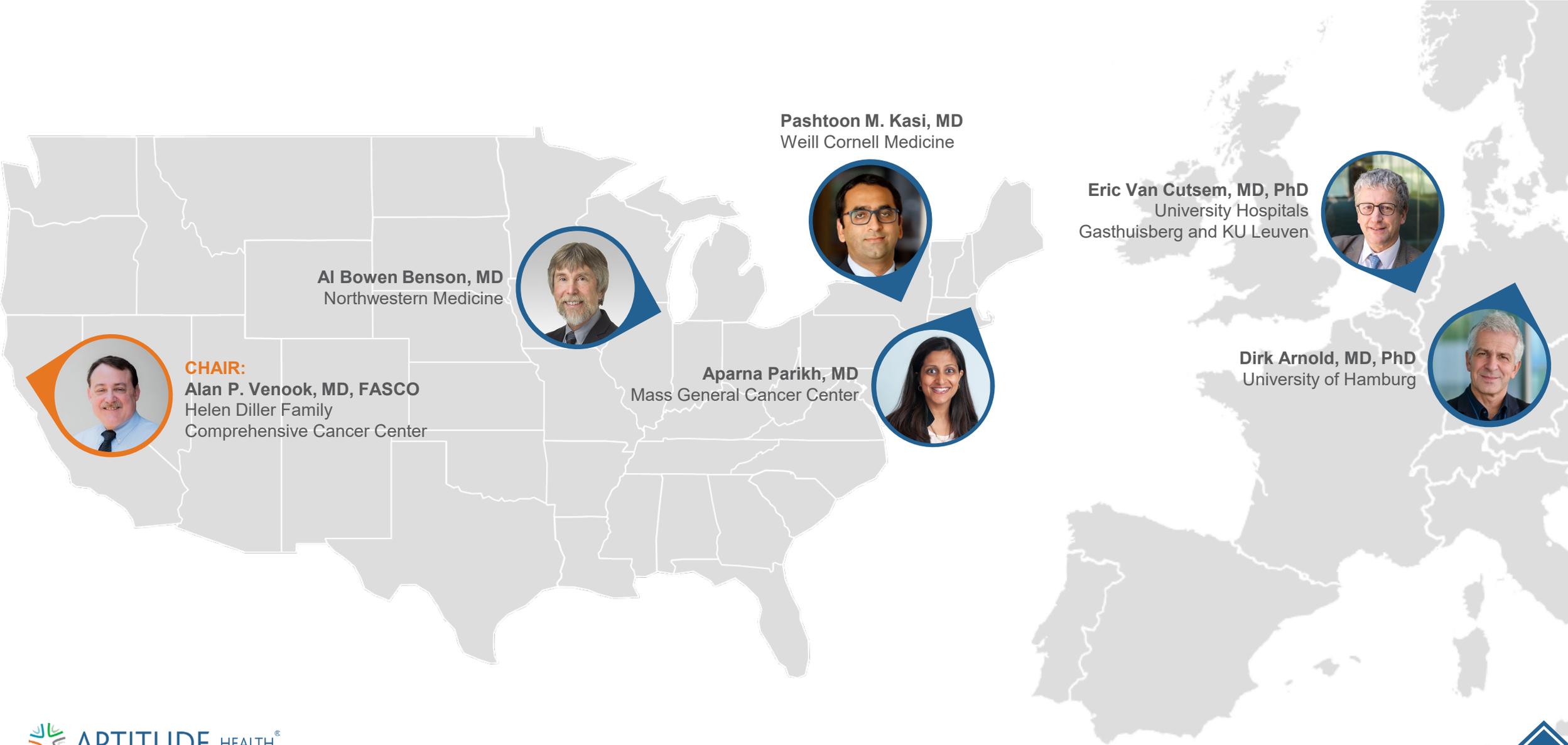
PANEL: Key experts
in CRC

- > 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



Meeting Agenda (1/2)

EPICS

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)

EPICS

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



EPICS

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

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

STUDY POPULATION

1. 100 patients with cT4N1M0 colon cancer... (text is blurred)

RESULTS

1. 100 patients... (text is blurred)

KEY POINTS

1. Neoadjuvant chemotherapy... (text is blurred)

CLINICAL TRIALS USING NEOADJUVANT CHEMO IN LOCALLY ADVANCED COLON CANCER



RESPONSE RATES IN LOCAL ADVANCED COLON CANCER





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

PRESENTED BY AL BOWEN BENSON, MD

FACTORS GUIDING DECISION-MAKING FOR ADJUVANT THERAPY

> Definitive decisions regarding adjuvant treatment should only be made after

STAGE POPULATION

Approximately 10% of patients with colorectal cancer are diagnosed with stage I disease. The majority of these patients are treated with curative intent. The goal of adjuvant therapy is to improve survival outcomes. The majority of patients with stage I disease are treated with curative intent. The goal of adjuvant therapy is to improve survival outcomes.

DEFINITION

Approximately 10% of patients with colorectal cancer are diagnosed with stage I disease. The majority of these patients are treated with curative intent. The goal of adjuvant therapy is to improve survival outcomes.

KEY POINT CONCLUSIONS

Continuing to improve treatment outcomes with adjuvant therapy is a key goal. This is achieved by identifying the population that will benefit most from treatment.

STAGE POPULATION



RESPONSE INDICATORS AS GUIDES FOR TREATMENT





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

PRESENTED BY AL BOWEN BENSON, MD

ESMO GUIDELINES FOR ADJUVANT TREATMENT OF STAGE II COLON CANCER

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

Stage II

STAGE II POPULATION

ESMO clinical practice guidelines for diagnosis, treatment, and follow-up for adjuvant... (blurred text)

DEFINITIONS

ESMO clinical practice guidelines for diagnosis, treatment, and follow-up for adjuvant... (blurred text)

KEY POINT CONCLUSIONS

ESMO clinical practice guidelines for diagnosis, treatment, and follow-up for adjuvant... (blurred text)

ESMO CLINICAL PRACTICE GUIDELINES FOR ADJUVANT TREATMENT OF STAGE II COLON CANCER



ESMO CLINICAL PRACTICE GUIDELINES FOR ADJUVANT TREATMENT OF STAGE II COLON CANCER





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

PRESENTED BY AL BOWEN BENSON, MD

ASCO GUIDELINES

> ASCO guidelines for adjuvant therapy for stage II

RISK FACTORS

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



 EPICS

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



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

PREFERENTIAL TREATMENT OPTIONS FOR STAGE 3 COLON CANCER

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

Neoadjuvant Therapy

The addition of an anti-angiogenic drug (irinotecan [IRI]) may provide the necessary chemotherapy cell death required by the activity of IRI in the RAS+/+ population, as shown in the RAS+/+ and RAS+/+ populations. The addition of irinotecan to the standard of care (SOC) may provide a survival benefit in patients with wild-type RAS. The addition of irinotecan to the SOC may provide a survival benefit in patients with wild-type RAS. The addition of irinotecan to the SOC may provide a survival benefit in patients with wild-type RAS.

NEOADJUVANT CHEMOTHERAPY

Experts follow NCCN guidelines and also offer neoadjuvant

Neoadjuvant Therapy in Metastatic CRC

There are several ways with the aim to "heat up" the tumor, using methods to increase microcirculation to address hypoxia resulting from neoadjuvant therapy.

- The addition of an anti-angiogenic drug (irinotecan [IRI]) may provide the necessary chemotherapy cell death required by the activity of IRI in the RAS+/+ population, as shown in the RAS+/+ and RAS+/+ populations. The addition of irinotecan to the standard of care (SOC) may provide a survival benefit in patients with wild-type RAS.
- The use of irinotecan to the SOC may provide a survival benefit in patients with wild-type RAS. The addition of irinotecan to the SOC may provide a survival benefit in patients with wild-type RAS.

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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

MANAGEMENT OF RESECTABLE OLIGOMETASTASES (RESECTION VS ABLATION)

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

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Timeline of FDA Approvals for HER2+ Breast Cancer

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





Current Treatment Paradigms for Metastatic CRC (2/3)

PRESENTED BY ERIC VAN CUTSEM, MD, PHD

FIRST-LINE TREATMENT OPTIONS

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

Treatment options in first-line mCRC

Timeline of FDA Approvals for HER2+ Breast Cancer

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





Current Treatment Paradigms for Metastatic CRC (3/3)

PRESENTED BY ERIC VAN CUTSEM, MD, PHD

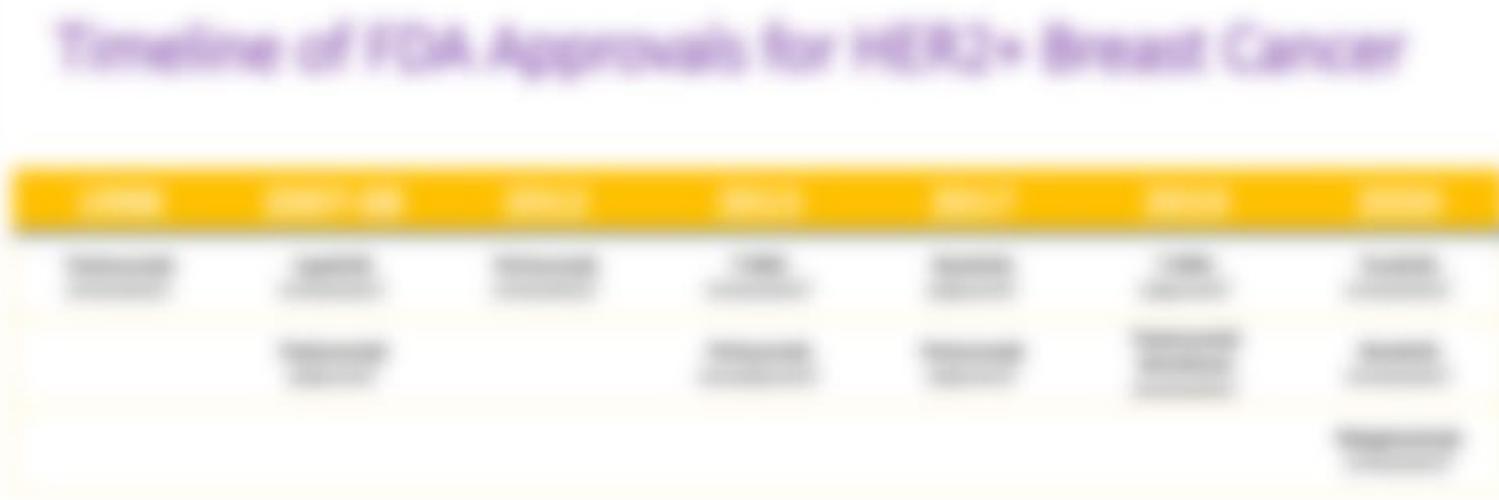
PREFERRED CHOICES IN FIRST-LINE TREATMENT OF mCRC

PREFERRED CHOICES IN SECOND-LINE TREATMENT OF mCRC

Goal / condition	Molecular	Prefered 1st line regimen
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Goal / condition	Molecular	Prefered 2nd line regimen
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(This section contains blurred text, likely a list of clinical trial results or treatment options for first-line mCRC.)



EPICS

Key Insights: Current Treatment Options for Metastatic CRC



Expert Perspectives on Changes to the Algorithms for Treating Metastatic CRC

SIDEDNESS OF DISEASE AND ANTI-EGFR THERAPY

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

Introduction

The addition of the anti-EGFR monoclonal antibody (mAb) to the treatment algorithm for metastatic CRC (mCRC) has been a significant milestone in the management of this disease. The addition of anti-EGFR mAb to the treatment algorithm for mCRC is based on the results of several clinical trials.

- The addition of anti-EGFR mAb to the treatment algorithm for mCRC is based on the results of several clinical trials. These trials have shown that the addition of anti-EGFR mAb to the treatment algorithm for mCRC is associated with improved overall survival (OS) and progression-free survival (PFS) compared to the treatment algorithm without anti-EGFR mAb.
- The addition of anti-EGFR mAb to the treatment algorithm for mCRC is based on the results of several clinical trials. These trials have shown that the addition of anti-EGFR mAb to the treatment algorithm for mCRC is associated with improved OS and PFS compared to the treatment algorithm without anti-EGFR mAb.

OPINIONS ON INTEGRATING BRAF-TARGETED THERAPY INTO THE FRONTLINE SETTING

Experts agreed there is not enough evidence to support

Introduction

There are ongoing trials with the aim to "test out" the use of BRAF inhibitors in the frontline setting for mCRC. The addition of BRAF inhibitors to the treatment algorithm for mCRC is based on the results of several clinical trials.

- The addition of an anti-BRAF drug (vemurafenib) to the treatment algorithm for mCRC is based on the results of several clinical trials. These trials have shown that the addition of anti-BRAF drug to the treatment algorithm for mCRC is associated with improved OS and PFS compared to the treatment algorithm without anti-BRAF drug.
- The use of BRAF inhibitors in the frontline setting for mCRC is based on the results of several clinical trials. These trials have shown that the addition of BRAF inhibitors to the treatment algorithm for mCRC is associated with improved OS and PFS compared to the treatment algorithm without BRAF inhibitors.

DOUBLET VS TRIPLET

Doublet Therapy

The addition of the second immunotherapy (IO) to the first IO or to chemotherapy (Chemo) is a promising approach for the additive effect of immune checkpoint inhibitors (ICI) in high negative breast cancer (HNBC).

- Patients who showed survival benefits with immunotherapy and chemotherapy combination in the programmed cell death protein 1 (PD-1) positive (PD-1+) population demonstrated immune enhancement, higher proliferation, more CD8+ cells, different engagement, and higher antigen uptake (IC) response. These benefits were observed in patients who used the immune-related molecule (IRM).
- The PD-1+ negative (PD-1-) population did not benefit from the addition of immunotherapy to chemotherapy in any molecular subtype.

Immunotherapy in HER2+ Breast Cancer

There are clinical trials with the aim to "boost up" the tumor killing methods by increasing immunotherapy to achieve improved results than immunotherapy.

- The addition of an antibody drug conjugate (ADC) may provide the necessary immunogenic cell death required for the activity of ICI in the PD-1+ population, as shown in the HER2+ population. The addition of trastuzumab deruxtecan (TDM) to pembrolizumab showed clinical responses both in PD-1+ and PD-1- population.
- The use of immune checkpoint inhibitors (ICI) may increase immunogenicity, immunogenic microenvironment efficiency, and decrease CD8+ cell cycle arrest response. Pembrolizumab in combination with trastuzumab and trastuzumab deruxtecan showed clinical responses, supporting the ICI use in effective in boosting up a tumor.

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

THIRD-LINE TREATMENT OPTIONS

Introduction

The addition of the novel immunomodulator (IMiD) to the standard of care (SOC) for multiple myeloma (MM) is a promising approach for the additive effect of various targeted therapies (IMiD in high-sensitivity disease (HSD) and IMiD).

- Patients who showed overall survival with IMiD-based and IMiD-based combination in the progression-free survival (PFS) and overall survival (OS) population. IMiD-based combination therapy (IMiD, lenalidomide, and dexamethasone) was the most effective regimen, and high-sensitivity disease (HSD) response. More benefits were observed in patients with high disease burden and/or refractory disease.
- The IMiD-based combination (IMiD, lenalidomide, and dexamethasone) was the most effective regimen in any refractory disease.

TREATMENT HOLIDAYS

Introduction to IMiD in MM

There are clinical trials with the aim to "test out" the best drug schedule to increase immunomodulator to address refractory disease from immunomodulator.

- The addition of an antibody drug conjugate (ADC) may provide the necessary immunomodulator and best response to the addition of IMiD in the IMiD-based population, as shown in the IMiD-based population. The addition of immunomodulator (IMiD) to standard of care (SOC) response with a IMiD-based and IMiD-based population.
- The use of novel immunomodulator (IMiD) may increase immunomodulator, immunomodulator effectiveness, and increase IMiD-based overall response. Immunomodulator is combination with IMiD and refractory disease (HSD) response, supporting the IMiD-based as effective in treating HSD.

EPICS

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

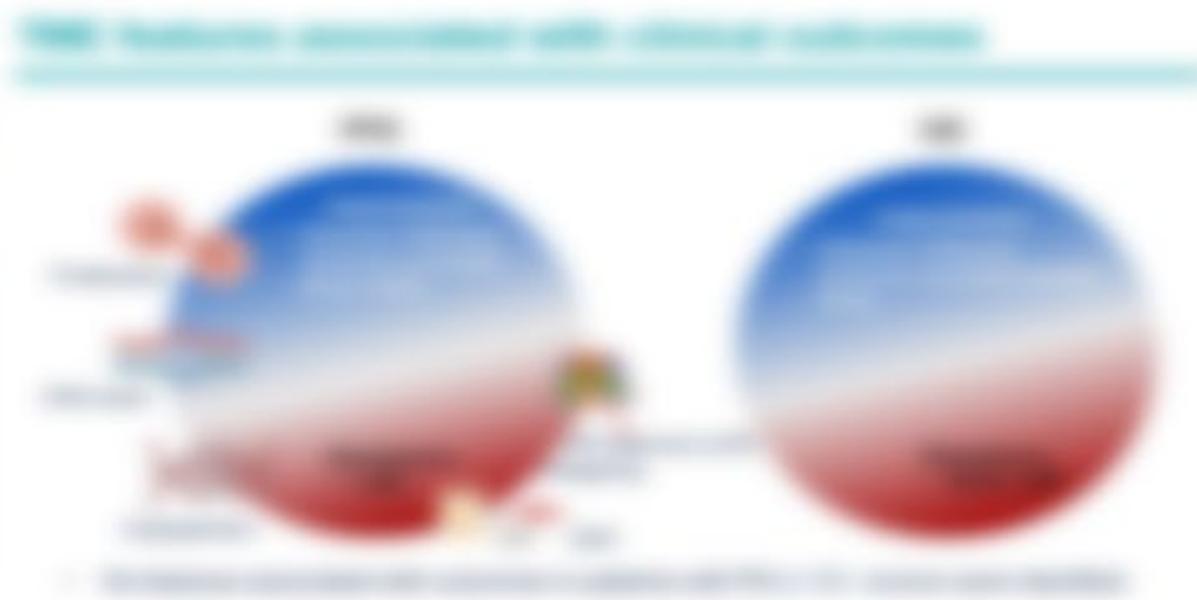
ADVANCES IN IMMUNOTHERAPY FOR CRC HAVE BEEN MADE, BUT SOME QUESTIONS REMAIN

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

First-Line Treatment

100%

Events HR (95% CI) P





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

PRESENTED BY ALAN P. VENOOK, MD, FASCO

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



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EPICS

Key Insights: The Evolving Role of Immunotherapy in CRC



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

ADVANCED/METASTATIC MSI-H CRC

KEY TAKEAWAY 1: PIONEERING STUDIES

The landmark study by Leung et al. (2013) demonstrated that pembrolizumab significantly improved overall survival compared to placebo in patients with advanced/metastatic MSI-H CRC. This study established the efficacy of immunotherapy in this patient population.

KEY TAKEAWAY 2: CURRENT STANDARD OF CARE

Based on the Leung et al. study, pembrolizumab is now the standard of care for advanced/metastatic MSI-H CRC. Other immunotherapies, such as nivolumab, are also being studied in clinical trials.

KEY TAKEAWAY 3: BIOMARKERS AND RESISTANCE

While immunotherapy has shown promising results, not all patients respond. Biomarkers such as microsatellite instability (MSI) and tumor mutational burden (TMB) are being investigated to identify patients who are most likely to benefit from immunotherapy. Understanding the mechanisms of resistance to immunotherapy is also a key area of research.



KEY TAKEAWAY 4: FUTURE DIRECTIONS

Research is ongoing to optimize immunotherapy regimens, including combination therapies and the use of novel biomarkers. The goal is to improve response rates and overall survival for patients with advanced/metastatic MSI-H CRC.

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

ADVANCED/METASTATIC MSI-H CRC

TMB may not be the best predictor of checkpoint

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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

MOLECULAR CHARACTERIZATION OF CRC

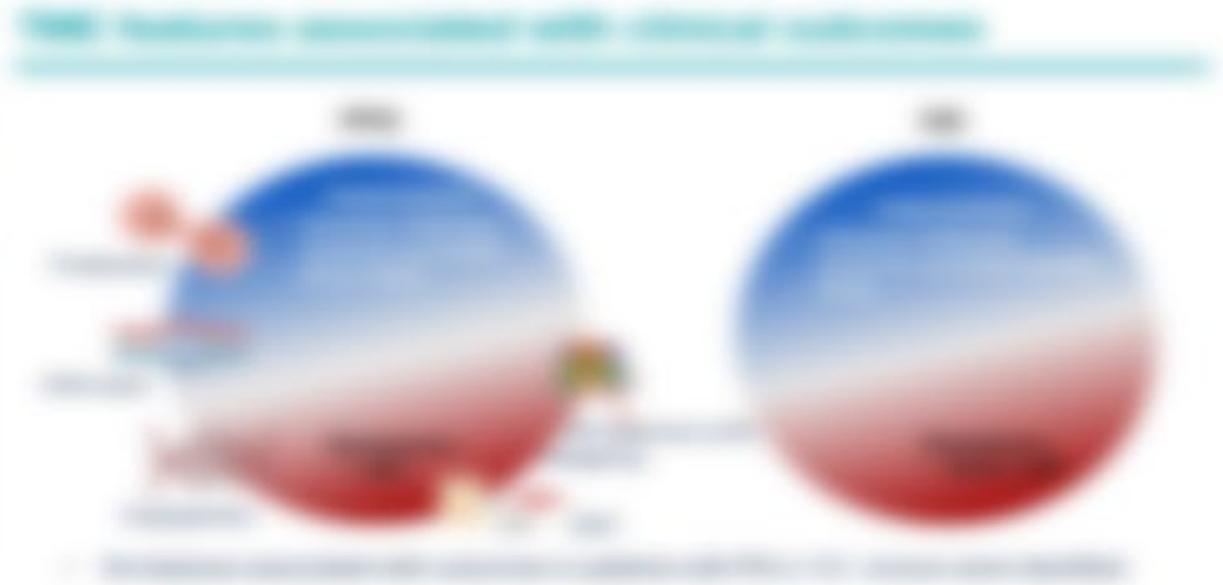
> RAS status and sidedness are important determinants of treatment

MOLECULAR CHARACTERIZATION OF CRC

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Currently Available Targeted Therapies for CRC (2/3)

PRESENTED BY DIRK ARNOLD, MD, PHD

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

HERACLES

Phase II, multicenter, open-label, randomised controlled trial comparing trastuzumab emtansine (T-DM1) with trastuzumab in patients with HER2-positive, refractory solid tumours.

DESTINY-CRC-01

Phase II, multicenter, open-label, randomised controlled trial comparing trastuzumab deruxtecan (T-DXd) with trastuzumab in patients with HER2-positive, metastatic colorectal cancer.

HERACLES

DESTINY-CRC-01





Currently Available Targeted Therapies for CRC (3/3)

PRESENTED BY DIRK ARNOLD, MD, PHD

MANAGEMENT OF *NTRK*-POSITIVE DISEASE

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

Background

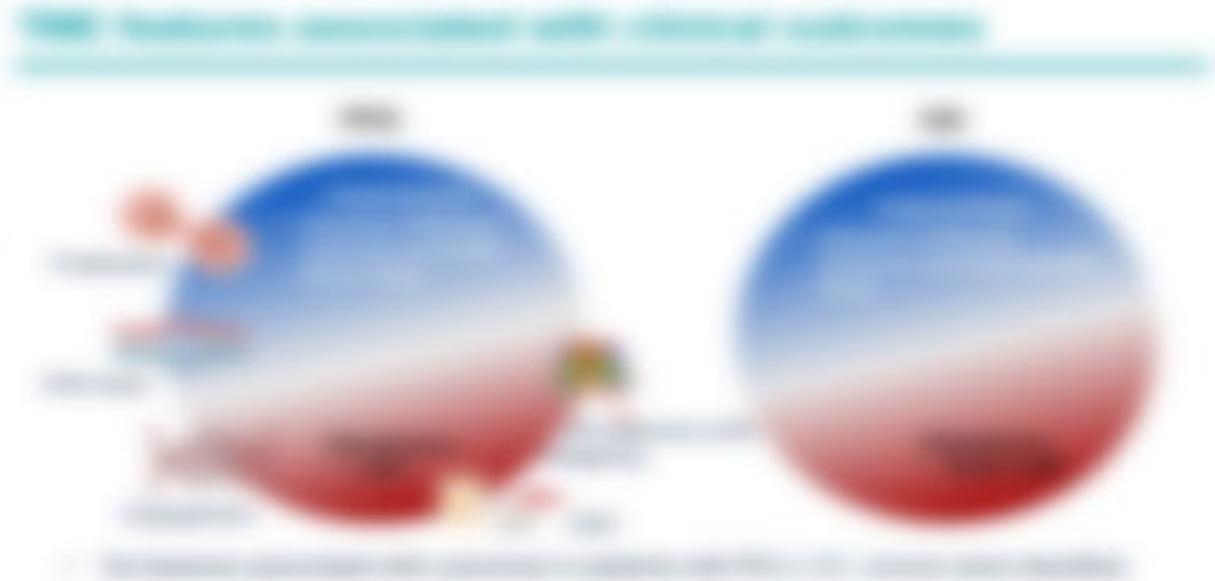
Approximately 1-2% of colorectal cancers (CRC) harbor *NTRK* gene fusions, which are oncogenic drivers. The presence of *NTRK* fusions is associated with a distinct molecular profile and improved prognosis compared to wild-type *NTRK* CRC.

Targeted Therapy

Larotrectinib and entrectinib are pan-*NTRK* tyrosine kinase inhibitors (TKIs) that have demonstrated significant efficacy in patients with *NTRK* fusion-positive solid tumors, including CRC. These drugs are approved for the treatment of *NTRK* fusion-positive CRC.

Survival Benefit

Phase III clinical trials have shown that larotrectinib and entrectinib significantly improve overall survival (OS) and progression-free survival (PFS) in patients with *NTRK* fusion-positive CRC compared to standard of care (SOC) treatments.



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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

TRASTUZUMAB DERUXTECAN

KEYNOTE 585: TRASTUZUMAB DERUXTECAN IN HER2-POSITIVE BREAST CANCER

The KEYNOTE 585 study is a phase III, randomized, controlled trial comparing trastuzumab deruxtecan (TDXd) to trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer. The study is designed to evaluate the efficacy and safety of TDXd compared to T-DM1 in this patient population.

The primary endpoint of the study is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), and safety. The study is currently ongoing, and preliminary results are expected to be published in the near future.

CLINICAL SIGNIFICANCE

Trastuzumab deruxtecan is a novel antibody-drug conjugate (ADC) that combines the HER2-targeting antibody trastuzumab with the cytotoxic drug deruxtecan. This combination is designed to improve the efficacy of HER2-targeted therapy while maintaining a favorable safety profile.

The study is designed to evaluate the efficacy and safety of TDXd compared to T-DM1 in this patient population. The primary endpoint of the study is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), and safety. The study is currently ongoing, and preliminary results are expected to be published in the near future.



KEYNOTE 585: TRASTUZUMAB DERUXTECAN IN HER2-POSITIVE BREAST CANCER

The KEYNOTE 585 study is a phase III, randomized, controlled trial comparing trastuzumab deruxtecan (TDXd) to trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer. The study is designed to evaluate the efficacy and safety of TDXd compared to T-DM1 in this patient population.

EPICS

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

UPDATES IN TARGETED THERAPEUTICS FOR CRC

KEYNOTE-362: BRAF INHIBITORS IN METASTATIC CRC

The KEYNOTE-362 trial evaluated the efficacy of BRAF inhibition in combination with chemotherapy in patients with metastatic CRC. The study showed that the combination of BRAF inhibition and chemotherapy significantly improved overall survival compared to chemotherapy alone in patients with BRAF V600E mutations.

KEYNOTE-590: PD-1 INHIBITORS IN METASTATIC CRC

The KEYNOTE-590 trial evaluated the efficacy of PD-1 inhibition in combination with chemotherapy in patients with metastatic CRC. The study showed that the combination of PD-1 inhibition and chemotherapy significantly improved overall survival compared to chemotherapy alone in patients with microsatellite instability-high (MSI-H) tumors.

KEYNOTE-177: PD-1 INHIBITORS IN ADENOCARCINOMA OF THE COLON

The KEYNOTE-177 trial evaluated the efficacy of PD-1 inhibition in combination with chemotherapy in patients with metastatic adenocarcinoma of the colon. The study showed that the combination of PD-1 inhibition and chemotherapy significantly improved overall survival compared to chemotherapy alone in patients with microsatellite stable (MSS) tumors.





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

PRESENTED BY APARNA PARIKH, MD

UPDATES IN TARGETED THERAPEUTICS FOR CRC

KEYNOTE-358: CAPOX vs FOLFOX in RAS Wild-Type mCRC

The primary endpoint was overall survival (OS). In the primary analysis, OS was significantly superior in the CAPOX group compared with the FOLFOX group (HR, 0.87; 95% CI, 0.77-0.98; P = .003). The secondary endpoint of progression-free survival (PFS) was also significantly superior in the CAPOX group (HR, 0.78; 95% CI, 0.69-0.88; P = .0001). The most common adverse events were neutropenia, diarrhea, and fatigue.

KEYNOTE-048: Pembrolizumab vs Placebo in RAS Wild-Type mCRC

The primary endpoint was overall survival (OS). In the primary analysis, OS was significantly superior in the pembrolizumab group compared with the placebo group (HR, 0.79; 95% CI, 0.67-0.93; P = .001). The secondary endpoint of progression-free survival (PFS) was also significantly superior in the pembrolizumab group (HR, 0.71; 95% CI, 0.61-0.82; P = .0001). The most common adverse events were fatigue, diarrhea, and nausea.

KEYNOTE-063: Pembrolizumab vs Placebo in RAS Wild-Type mCRC

The primary endpoint was overall survival (OS). In the primary analysis, OS was significantly superior in the pembrolizumab group compared with the placebo group (HR, 0.79; 95% CI, 0.67-0.93; P = .001). The secondary endpoint of progression-free survival (PFS) was also significantly superior in the pembrolizumab group (HR, 0.71; 95% CI, 0.61-0.82; P = .0001). The most common adverse events were fatigue, diarrhea, and nausea.





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

PRESENTED BY APARNA PARIKH, MD

UPDATES IN TARGETED THERAPEUTICS FOR CRC

KEYNOTE-358: CAPOX vs FOLFOX in RAS Wild-Type mCRC

The KEYNOTE-358 trial compared CAPOX (capecitabine and oxaliplatin) to FOLFOX (fluorouracil, leucovorin, and oxaliplatin) in patients with RAS wild-type metastatic colorectal cancer. The primary endpoint was overall survival. The trial showed that CAPOX was non-inferior to FOLFOX in terms of overall survival, with a similar quality of life profile. This finding supports the use of CAPOX as a first-line treatment option for RAS wild-type mCRC.

REGON-2: Regoratinib in RAS Wild-Type mCRC

The REGON-2 trial evaluated regoratinib, a dual EGFR and HER2 tyrosine kinase inhibitor, in combination with FOLFOX in patients with RAS wild-type metastatic colorectal cancer. The trial demonstrated that the combination of regoratinib and FOLFOX significantly improved overall survival compared to FOLFOX alone. This combination represents a novel targeted therapeutic approach for RAS wild-type mCRC.



REGON-2: Regoratinib in RAS Wild-Type mCRC

The REGON-2 trial evaluated regoratinib, a dual EGFR and HER2 tyrosine kinase inhibitor, in combination with FOLFOX in patients with RAS wild-type metastatic colorectal cancer. The trial demonstrated that the combination of regoratinib and FOLFOX significantly improved overall survival compared to FOLFOX alone. This combination represents a novel targeted therapeutic approach for RAS wild-type mCRC.

EPICS

Key Insights: Emerging Therapies and Novel Investigational Approaches for CRC



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

RAS- AND BRAF-TARGETED AGENTS

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



Dr Kasi

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

IMMUNOTHERAPEUTICS

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

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EPICS

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

MOLECULAR DETERMINANTS OF DISEASE

> Targets can be CRC specific or tumor agnostic

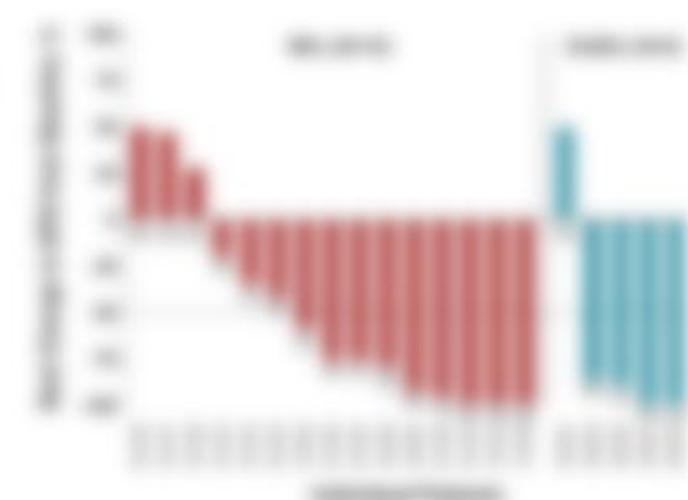
Algorithm for MMR/MSI testing in CRC

Background

- Phase 1 dose-toxicity study of U30101, a MMR/MSI targeting ADC, in patients with newly diagnosed MSI and dMMR
- Primary objective was to define maximum tolerated dose and recommended starting regimen

Results

- 27 patients were enrolled, including 10 patients with MSI
- 26.7% were CR, 26.7% were SD, 44.4% were PD
- CR/SD/MSI occurred in 26% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment
- CR/SD/MSI occurred in 20% of patients, 10/100% successfully completed treatment



Key Takeaway: U30101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MSI and dMMR. Experts mentioned neuropathy as a potential concern and the need to identify the best techniques in which to test this agent.

EPICS

Key Insights: Current and Evolving Biomarkers in CRC



ctDNA DETECTION AND ITS INTERPRETATION

KEY TAKEAWAYS

The presence of ctDNA in the blood is a strong indicator of cancer recurrence and is associated with a poor prognosis. ctDNA detection can be used to monitor treatment response and to identify patients who may benefit from more aggressive therapy. ctDNA detection can also be used to identify patients who are at high risk of developing resistance to targeted therapy.

KEY TAKEAWAYS

ctDNA detection can be used to monitor treatment response and to identify patients who may benefit from more aggressive therapy. ctDNA detection can also be used to identify patients who are at high risk of developing resistance to targeted therapy.



KEY TAKEAWAYS

ctDNA detection can be used to monitor treatment response and to identify patients who may benefit from more aggressive therapy. ctDNA detection can also be used to identify patients who are at high risk of developing resistance to targeted therapy.

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

DOSE-REDUCTION STRATEGIES FOR DPYD-MUTATED PATIENTS

KEY TAKEAWAYS

The presence of DPYD mutations in patients can significantly impact the pharmacokinetics and toxicity of fluoropyrimidine-based therapies. Identifying these mutations through genetic testing is crucial for personalized dosing strategies to optimize efficacy and minimize adverse effects. Clinicians should consider genotype-guided dosing, particularly for patients with DPYD deficiency, to avoid severe toxicity and improve treatment outcomes.

CLINICAL RECOMMENDATIONS

Genetic testing for DPYD mutations should be performed before initiating fluoropyrimidine-based therapy. For patients with DPYD deficiency, dose reductions are necessary to prevent severe toxicity. Clinicians should use validated algorithms to determine the appropriate dose based on the patient's genotype. Patient education and monitoring for adverse effects are also essential components of the dosing strategy.



CONCLUSION

Understanding the impact of DPYD mutations on drug metabolism is key to developing safe and effective dosing strategies. Implementing genotype-guided dosing can lead to better patient outcomes and reduced toxicity. Continued research and clinical practice updates are needed to refine these strategies further.

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