



EPICS

Global Perspectives in Gastrointestinal Malignancies in 2022 and Beyond

Full Report

17 and 23 September 2022

Content	Slide
Meeting Snapshot	3 
Faculty Panel	4 
Meeting Agenda	5 
Key Insights and Strategic Recommendations	8 
Metastatic Colorectal Cancer – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments	15 
Colorectal Cancer – Immunotherapy	24 
Hepatocellular Carcinoma	29 
Gastroesophageal Junction (GEJ) and Gastric Cancer	34 
Rectal Cancer	43 
Pancreatic Cancer and Biliary Tract Cancer	49 

EPICS

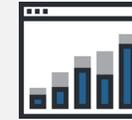
VIRTUAL CLOSED-DOOR ROUNDTABLE



DATE:
17 and 23
September 2022



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



INSIGHTS REPORT
including postmeeting
analyses and actionable
recommendations



PANEL: Key experts in
gastrointestinal (GI)
malignancies
> 8 from the US and
3 from the EU



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

Day 1: Panel Consisting of 5 US and 3 European GI Cancer Experts

EPICS

Joleen Hubbard, MD
Mayo Clinic, Rochester



Philip A. Philip, MD, PhD
Henry Ford Cancer Institute



Christopher Lieu, MD
University of Colorado
Cancer Center



John H. Strickler, MD
Duke Cancer Center



Gerald Prager, MD, PhD
University of Vienna



Julien Taieb, MD, PhD
Georges Pompidou
European Hospital



Chiara Cremolini, MD, PhD
University of Pisa



CHAIR
Tanios Bekaii-Saab, MD, FACP
Mayo Clinic Cancer Center



Meeting Agenda Day 1

Time (EST)	Topic	Speaker/Moderator
9.00 AM – 9.05 AM	Welcome and Introductions	Tanios Bekaii-Saab, MD, FACP
9.05 AM – 9.15 AM	Metastatic Colorectal Cancer – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments	Joleen Hubbard, MD
9.15 AM – 9.50 AM	Discussion: Metastatic Colorectal Cancer – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments	All
9.50 AM – 9.55 AM	Summary of Key Takeaways	Joleen Hubbard, MD
9.55 AM – 10.05 AM	Colorectal Cancer – Immunotherapy	Gerald Prager, MD, PhD
10.05 AM – 10.40 AM	Discussion: Colorectal Cancer – Immunotherapy	All
10.40 AM – 10.45 AM	Summary of Key Takeaways	Gerald Prager, MD, PhD
10.45 AM – 10.55 AM	Break	
10.55 AM – 11.05 AM	Hepatocellular Carcinoma	Philip A. Philip, MD, PhD
11.05 AM – 11.50 AM	Discussion: Hepatocellular Carcinoma	All
11.50 AM – 11.55 AM	Summary of Key Takeaways	Philip A. Philip, MD, PhD
11.55 AM – 12.00 PM	Meeting Close	Tanios Bekaii-Saab, MD, FACP



Day 2: Panel Consisting of 6 US and 2 European GI Cancer Experts

EPICS

Philip A. Philip, MD, PhD
Henry Ford Cancer Institute



Efrat Dotan, MD
Fox Chase Cancer Center



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



Gerald Prager, MD, PhD
University of Vienna



CHAIR
Tanios Bekaii-Saab, MD, FACP
Mayo Clinic Cancer Center



John H. Strickler, MD
Duke Cancer Center



Julien Taieb, MD, PhD
Georges Pompidou
European Hospital



Scott Kopetz, MD, PhD, FACP
MD Anderson Cancer Center



Meeting Agenda Day 2

Time (EST)	Topic	Speaker/Moderator
9.00 AM – 9.05 AM	Welcome and Introductions	Tanios Bekaii-Saab, MD, FACP
9.05 AM – 9.15 AM	Gastroesophageal Junction (GEJ) and Gastric Cancer	Julien Taieb, MD, PhD
9.15 AM – 10.05 AM	Discussion: Gastroesophageal Junction (GEJ) and Gastric Cancer	All
10.05 AM – 10.10 AM	Summary of Key Takeaways	Julien Taieb, MD, PhD
10.10 AM – 10.20 AM	Rectal Cancer	Alan P. Venook, MD
10.20 AM – 11.05 AM	Discussion: Rectal Cancer	All
11.05 AM – 11.10 AM	Summary of Key Takeaways	Alan P. Venook, MD
11.10 AM – 11.20 AM	Break	
11.20 AM – 11.30 AM	Pancreatic Cancer and Biliary Tract Cancer	Efrat Dotan, MD
11.30 AM – 12.20 PM	Discussion: Pancreatic Cancer and Biliary Tract Cancer	All
12.20 PM – 12.25 PM	Summary of Key Takeaways	Efrat Dotan, MD
12.25 PM – 12.30 PM	Meeting Close	Tanios Bekaii-Saab, MD, FACP



EPICS**Metastatic Colorectal Cancer –
Chemotherapy, Targeted
Therapies, and Biomarker-Driven
Treatments**



Metastatic CRC – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (1/4)

Presented by Joleen Hubbard, MD

KRAS G12C mutation
> KRAS G12C mutations occur in 3%–5% of mCRC patients

KRAS G12C
> Data from the phase Ib CodeBreak 101 study, of sotorasib in

STUDY POPULATION

100 patients with KRAS G12C mutation... (text is blurred)

RESULTS

Median OS... (text is blurred)

KEY POINTS

... (text is blurred)

STUDY POPULATION



RESPONSE RATES





Metastatic CRC – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (2/4)

Presented by Joleen Hubbard, MD

HER2 amplification

> HER2 amplification/overexpression occurs in ~3%–5% of all patients with mCRC

STUDY POPULATION

1. 1000 patients with mCRC, 40% were HER2 amplified/overexpressed. 200 patients were randomized to receive trastuzumab + FOLFOX4 vs FOLFOX4 alone. The trastuzumab group had a significantly better overall survival (OS) compared to the control group (HR 0.75, 95% CI 0.58-0.98, p=0.03). The median OS was 12.1 months in the trastuzumab group vs 10.1 months in the control group. The overall response rate (ORR) was 45% in the trastuzumab group vs 35% in the control group. The most common adverse events were diarrhea, fatigue, and nausea.

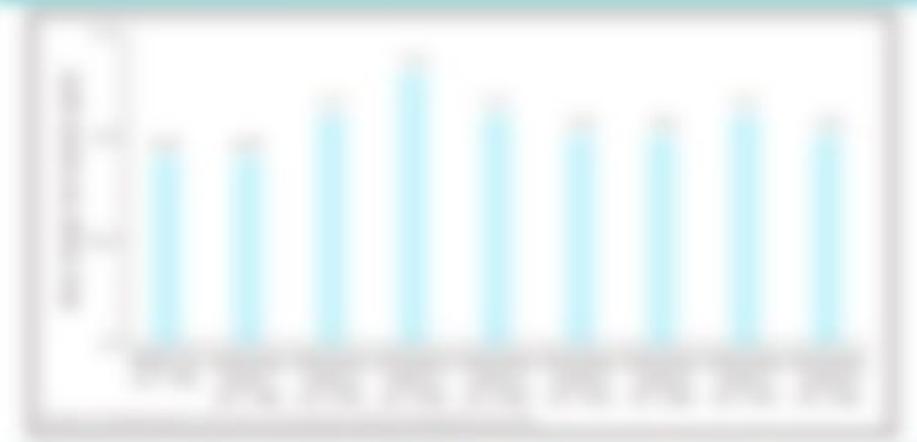
RESULTS

2. 1000 patients with mCRC, 40% were HER2 amplified/overexpressed. 200 patients were randomized to receive trastuzumab + FOLFOX4 vs FOLFOX4 alone. The trastuzumab group had a significantly better OS compared to the control group (HR 0.75, 95% CI 0.58-0.98, p=0.03).

KEY TAKEAWAYS

3. Identifying HER2 amplified/overexpressed patients with mCRC is important to guide treatment decisions and improve outcomes. Trastuzumab is a key component of HER2-targeted therapy in this population.

HER2 AMPLIFICATION/OVEREXPRESSION IN THE LIVER



RESPONSE RATE AND OS IN HER2 AMPLIFIED/OVEREXPRESSED PATIENTS





Metastatic CRC – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (3/4)

Presented by Joleen Hubbard, MD

VEGF inhibitors

> Fruquintinib is a tyrosine kinase inhibitor of VEGFR-1, -2, and -3

STUDY POPULATION

1. 1000 patients with metastatic CRC, ECOG performance grade 0-1, who had received prior systemic therapy. The study population was stratified by the presence or absence of RAS mutations. The primary endpoint was overall survival (OS). The secondary endpoint was progression-free survival (PFS). The study was conducted in a randomized, controlled manner.

RESULTS

1. The study showed that patients receiving Fruquintinib had significantly better OS compared to the control group. The median OS was significantly longer in the Fruquintinib group.

KEY TAKEAWAYS

1. Fruquintinib is a promising treatment option for patients with metastatic CRC. It significantly improves OS compared to standard care.



Metastatic Colorectal Cancer (CRC) – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (1/4)

First-line chemotherapy backbone

> Overall, in the US and EU, FOLFOX is the preferred backbone option with anti-EGFR therapy and, depending on the toxicity profile,

- [Faded text]

Metastatic Colorectal Cancer (CRC) – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (2/4)

RAS wild-type

> Data from the FRESCO-2 study (LBA 25) are regarded as impactful and experts agreed fruquintinib will become another treatment choice in later lines post-

regorafenib expert TAG 100 in the metastatic setting. “fruquintinib is probably coming to us in the clinic.” “We have so many patients every week in later

lines who are not responding to other treatments and these combinations are probably the biggest

improvement in efficacy and safety results from these combinations in an ongoing phase III study of fruquintinib with pembrolizumab

in patients with metastatic colorectal cancer. – TAG 100, Session 1000

“The regimen is seen as effective, working well, and overall, applicable to many patients.”

“Pembrolizumab remains a good option for patients with BRAF V600E, continues to show promising safety and efficacy with durable complete responses. – TAG 100, Session 1000

“This approach is seen as a good option for a patient population in which going immunotherapy is difficult. It is seen as effective and safe.”

“TAG 1000 is a phase III, open-label, randomized study to assess safety of fruquintinib or fruquintinib + pembrolizumab in addition to

best standard of care in patients with BRAF V600E. – TAG 100, Session 1000

“Experts believe the combination of fruquintinib + pembrolizumab with best standard of care is likely to be effective. They would like to see phase III data to

confirm its safety in this setting.”

“LBA 2500 is a phase III study of fruquintinib plus pembrolizumab plus best standard of care in patients with BRAF V600E. – TAG 100, Session 1000

“The LBA 2500 regimen is seen as useful in the specific patient population with advanced disease. It was noted to be effective, very safe, and

well-tolerated. Some of the responses were seen fairly early during.”

Metastatic Colorectal Cancer (CRC) – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (3/4)

HER2 amplification

> The data from the MOUNTAINEER study of tucatinib and trastuzumab (LBA27) are convincing, and OS for these

patients appears to be similar to that seen in the HER2-positive breast cancer population, and these combinations are generally well tolerated

Phase III study of tucatinib and trastuzumab in HER2-positive metastatic CRC (MOUNTAINEER) – LBA27, Abstract 4500P

The regimen is well tolerated, including with high levels of HER2 amplification

Phase III study of tucatinib and trastuzumab in HER2-positive metastatic CRC (MOUNTAINEER) – LBA27, Abstract 4500P

This approach is well tolerated in a patient population in which going to chemotherapy is difficult. It is viewed as effective and safe

Phase III study of tucatinib and trastuzumab in HER2-positive metastatic CRC (MOUNTAINEER) – LBA27, Abstract 4500P

Results suggest the combination of tucatinib + trastuzumab with FOLFOX is well tolerated. They would like to see phase II data to confirm its activity in this setting

Phase III study of tucatinib and trastuzumab in HER2-positive metastatic CRC (MOUNTAINEER) – LBA27, Abstract 4500P

The tucatinib regimen is well tolerated in this specific patient population with effective disease. It was viewed as effective, well tolerated, and well tolerated. Some of the responses were quite durable

Metastatic Colorectal Cancer (CRC) – Chemotherapy, Targeted Therapies, and Biomarker-Driven Treatments (4/4)

NGS

> In the US, community centers often send out their samples to third-party testing facilities, which may be more robust than

EPICS

Colorectal Cancer – Immunotherapy



Colorectal Cancer – Immunotherapy (1/2)

Presented by Gerald Prager, MD, PhD

dMMR/MSI-H CRC

> In the NICHE-2 study in locally advanced MMR-deficient colon cancer (LBA7), patients were treated with neoadjuvant ipi plus nivo, and

[Blurred text from a slide, likely containing details about the NICHE-2 study results.]





Colorectal Cancer – Immunotherapy (2/2)

Presented by Gerald Prager, MD, PhD

ICI plus targeted therapy

Data were summarized from

[Blurred text area containing source information]



Neoadjuvant use of immune checkpoint inhibitors (ICIs) in dMMR/MSI-H CRC

> “The early data that we have seen in the neoadjuvant setting really does suggest that when you are not dealing with stage 4, the impact of immunotherapy

ICI in MSI-high metastatic disease

> Overall, experts use single-agent pembrolizumab in the first line, unless there is a need for a quick response in a patient who has extensive

EPICS

Hepatocellular Carcinoma



Hepatocellular Cancer (1/2)

Presented by Philip A. Philip, MD, PhD

Second-line treatment

> Updated data from the KEYNOTE-240 study of pembro vs placebo in sorafenib-treated, advanced hepatocellular carcinoma were presented





Hepatocellular Cancer (2/2)

Presented by Philip A. Philip, MD, PhD

Sequencing

> “This is what I think of the sequencing. The first question will be, is atezo plus bev a possibility?”

[Blurred text from a presentation slide]



Frontline treatment

> Atezo plus bevacizumab remains the treatment of choice for patients eligible for this regimen: *“Nothing has succeeded to beat the atezo plus bev, sometimes*

- ▶ [Faded text]

Clinical trials

> The challenge with many of the trials showing positive data remains the selection of Child-Pugh A patients, and Child-Pugh B 7 and 8

- ▶ [Faded text]

EPICS

Gastroesophageal Junction and Gastric Cancer



GEJ and Gastric Cancer (1/4)

Presented by Julien Taieb, MD, PhD

HER2-positive GEJ and gastric cancer

> Updated analysis of the phase II DESTINY-Gastric02 in Western patients was presented (1205MO): “Trastuzumab deruxtecan conjugate

[Faded text area containing additional presentation content]

Timeline of FDA Approvals for HER2+ Breast Cancer

Year	2006	2007	2008	2009	2010	2011	2012
Number of Approvals	0	1	1	1	1	1	1





GEJ and Gastric Cancer (2/4)

Presented by Julien Taieb, MD, PhD

HER2-negative GEJ and gastric cancer ICI in first-line trials

HER2-negative gastric cancer and gastroesophageal junction (GEJ) cancer are common gastrointestinal malignancies. Immunotherapy, particularly immune checkpoint inhibitors (ICI), has shown promising results in first-line trials for these cancers. This slide discusses the efficacy and safety of ICI in first-line trials for HER2-negative GEJ and gastric cancer.





GEJ and Gastric Cancer (3/4)

Presented by Julien Taieb, MD, PhD

HER2-negative GEJ and gastric cancer ICI in second-line trials

HER2-negative gastric cancer and gastroesophageal junction (GEJ) cancer are common gastrointestinal malignancies. Immunotherapy, specifically immune checkpoint inhibitors (ICI), has emerged as a promising treatment option in the second-line setting. Several clinical trials have evaluated the efficacy and safety of ICI in this population, showing promising results in terms of overall survival and quality of life. This presentation will discuss the latest data from these trials and the role of ICI in the management of HER2-negative GEJ and gastric cancer.





GEJ and Gastric Cancer (4/4)

Presented by Julien Taieb, MD, PhD

Biomarkers

> The role of DKN-01 and tislelizumab plus chemotherapy as first line in the phase IIa DisTinGuish trial (1213P) showed that *“it will take a bit*

[Blurred text, likely a quote or key finding from the trial]



- > Overall, no practice-changing data were presented at ESMO

ICI in first line

- > Candidates for ICI are those who have no contraindication for immunotherapy and CPS ≥ 5 , patients with MSI-H, as well as those who are EBV

ICI in the neoadjuvant setting

> There is excitement as to the role of ICI in the neoadjuvant setting, and it will be interesting to see how the field of ICI in the adjuvant or

- ▶ [Faded text]

HER2-positive GEJ and gastric cancer

> A proposed treatment sequence for the US is

- 1. Trastuzumab (Herceptin) + capecitabine + epirubicin + fluorouracil (CAPECITABINE/HERCEPTIN/EPIDOFURACIL) (EPIC) (NCT01462410) (Phase II, 2012-2015) (NCCN, ASCO 2015)
- 2. Promising safety and efficacy results from this sequence in an ongoing phase III study of trastuzumab with pembrolizumab versus trastuzumab + capecitabine/epidofuracil (EPIC) (NCT02090068)
- 3. The regimen is seen as effective, meeting with, and broadly applicable to many settings
- 4. Trastuzumab + pembrolizumab combination for adjuvant patients with HER2+ GEJ continues to show promising safety and efficacy with durable complete responses (NCCN, ASCO 2018)
- 5. This approach is seen as a good option for a patient population in which going trastuzumab-based is difficult. It is seen as effective and safe
- 6. EPIC (NCT01462410) a phase II, open-label, randomized study to assess safety of trastuzumab + trastuzumab + trastuzumab in addition to capecitabine in patients with early stage HER2+ GEJ (NCCN, ASCO 2015)
- 7. Experts believe the combination of trastuzumab + trastuzumab with capecitabine is safe. However, they would like to see phase III data to confirm its safety in this setting
- 8. Long-term analysis from EPIC (NCT01462410) a phase II study of trastuzumab plus trastuzumab plus capecitabine/epidofuracil in patients with HER2+ GEJ (NCCN, ASCO 2018)
- 9. The capecitabine regimen is seen as useful in the specific patient population with refractory disease. It was noted to be effective, very safe, and well-tolerated. Some of the responses were seen fairly early (NCCN)

Novel targets

- > CLDN18.2 is considered an interesting target and preliminary data from the Claudin18.2-specific CAR T cells, as well as from zolbetuximab

EPICS

Rectal Cancer



Rectal Cancer (1/3)

Presented by Alan P. Venook, MD

Total neoadjuvant therapy (TNT)
> “Virtually every study in the US that's been done in the past decade in rectal cancer has used a total neoadjuvant approach as the platform,

[Blurred text area]





Rectal Cancer (2/3)

Presented by Alan P. Venook, MD

dMMR rectal cancer
> The phase II study of dostarlimab in patients with stage II or III MSI-H or dMM rectal cancer was presented (Cercek A, et al. *N Engl J Med*

[Blurred text area]





Rectal Cancer (3/3)

Presented by Alan P. Venook, MD

RAPIDO study

> The trial examines the role of short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) vs preoperative

[Blurred text]

[Blurred text]

[Blurred text]

Different modalities of neoadjuvant chemotherapy remain a standard of care

> The TNT regimen is widely used. However, it was noted that *“there is a population that we're overtreating here . . . so, while it's very easy to*

overuse it, it's not always necessary for every patient. It's important to have a discussion with the patient and their family about the benefits and risks of the treatment. The TNT regimen is a standard of care, but it's not the only option. There are other regimens that may be more appropriate for certain patients. The goal is to provide the best possible care for each individual patient. It's important to have a multidisciplinary approach to care, involving the surgeon, medical oncologist, and radiation oncologist. The goal is to achieve the best possible outcome for the patient. The TNT regimen is a standard of care, but it's not the only option. There are other regimens that may be more appropriate for certain patients. The goal is to provide the best possible care for each individual patient. It's important to have a multidisciplinary approach to care, involving the surgeon, medical oncologist, and radiation oncologist. The goal is to achieve the best possible outcome for the patient.

KEY POINTS

- The TNT regimen is widely used.
- However, it was noted that “there is a population that we're overtreating here . . . so, while it's very easy to overuse it, it's not always necessary for every patient.
- It's important to have a discussion with the patient and their family about the benefits and risks of the treatment.
- The TNT regimen is a standard of care, but it's not the only option.
- There are other regimens that may be more appropriate for certain patients.
- The goal is to provide the best possible care for each individual patient.
- It's important to have a multidisciplinary approach to care, involving the surgeon, medical oncologist, and radiation oncologist.
- The goal is to achieve the best possible outcome for the patient.

KEY POINTS

- The TNT regimen is widely used.
- However, it was noted that “there is a population that we're overtreating here . . . so, while it's very easy to overuse it, it's not always necessary for every patient.
- It's important to have a discussion with the patient and their family about the benefits and risks of the treatment.
- The TNT regimen is a standard of care, but it's not the only option.
- There are other regimens that may be more appropriate for certain patients.
- The goal is to provide the best possible care for each individual patient.
- It's important to have a multidisciplinary approach to care, involving the surgeon, medical oncologist, and radiation oncologist.
- The goal is to achieve the best possible outcome for the patient.

Non-operative management of rectal cancer

- > Organ preservation is a goal for many patients, particularly elderly patients with comorbidities who are not fit surgery, and young patients if they have a complete response to neoadjuvant therapy. This has to be a very good discussion with the patients because they really need a tight follow up

[Blurred text block]

[Blurred text block]

[Blurred text block]



EPICS

Pancreatic Cancer and Biliary Tract Cancer



Pancreatic Cancer and Biliary Tract Cancer (1/3)

Presented by Efrat Dotan, MD

Locally advanced pancreatic cancer
> The phase III randomized trial PRODIGE 29-UCGI 26(NEOPAN) comparing chemotherapy with FOLFIRINOX or gemcitabine in locally

[Blurred text area]





Pancreatic Cancer and Biliary Tract Cancer (2/3)

Presented by Efrat Dotan, MD

Metastatic pancreatic cancer

- > Extended OS results from the POLO study of active maintenance olaparib in patients with metastatic pancreatic cancer and a germline

[Blurred text area containing details of the POLO study results, including OS curves and statistical data.]





Pancreatic Cancer and Biliary Tract Cancer (3/3)

Presented by Efrat Dotan, MD

Metastatic biliary tract cancer

- > Updated OS from the phase III TOPAZ-1 study of durva or placebo plus gemcitabine and cisplatin in patients with advanced biliary tract

[Blurred text area containing study details]



Pancreatic Cancer and Biliary Tract Cancer (1/4)

Pancreatic cancer

Locally advanced disease

[Blurred text area]

[Blurred text area]

[Blurred text area]

Pancreatic cancer Biomarkers

[Blurred text block containing the main body of the slide content.]

[Blurred text block on the left side of the slide.]

[Blurred text block on the right side of the slide.]

Biliary tract cancer

> The challenge with this disease is the associated comorbidities and complications that may arise

Biliary tract cancer

Biomarkers

> Patients with biliary tract cancer need to be molecularly profiled up front, and it is a very exciting time now with the ongoing identification of

[Blurred content]

[Blurred content]

[Blurred content]