July 2022

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RESEARCH & PRACTICE UPDATES

Colorectal Cancer Canada curates monthly Research & Practice Updates to inform patients and their loved ones of new innovations in colorectal cancer care. The following updates extend from July 1st 2022 to July 31th, 2022 inclusive and are intended for informational purposes only

JULY 2022 PREVIEW

ESMO World Congress on Gastrointestinal Cancer 2022: results from the MOUNTAINEER trial

July 2022

The annual ESMO World Congress on Gastrointestinal (GI) Cancer was held this year in Barcelona, Spain, and was dedicated to the presentation and discussion of new findings in GI cancer, providing unique insights into the latest clinical data.

Key highlights from the Congress include:

- The importance of **including patient quality of life data** in both clinical trials and treatment plans;
- Due to shifting patterns of colorectal cancer in younger adults, there is **a growing need to focus attention on prevention and screening of the disease**;
- Intensifying cancer treatments does not always result in better outcomes for patients with metastatic CRC – how to balance intensity with sustainability of treatment?
- New practical guidance to promote better outcomes in HER2-positive GI cancers with targeted therapies.
- New recommendations on the use of ctDNA in clinical practice

Colorectal Cancer Study Spotlights:

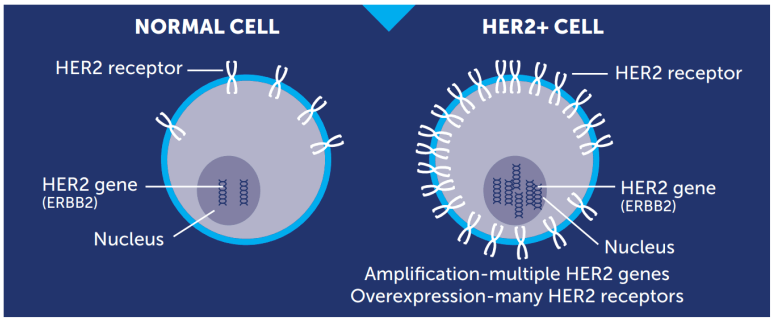
MOUNTAINEER trial: meaningful and durable responses for patients with metastatic HER2-positive colorectal cancer

Findings from the ongoing phase II MOUNTAINEER trial showed that patients with HER2-positive metastatic colorectal cancer (mCRC) who were previously treated with unsuccessful cancer therapies experienced clinically meaningful and long-lasting responses when they were treated with the combination of targeted therapies: tucatinib plus trastuzumab.

The lead investigator Dr. John Strickler noted that patients with HER2-positive mCRC receive limited clinical benefits with currently available therapies including chemotherapy. The novel combination of targeted therapies, tucatinib and trastuzumab, resulted in sustained responses and was well-tolerated in heavily pretreated patients (i.e. those that progressed on first- and second-line chemotherapy). These findings highlight the combination as a potential new treatment option for patients with HER2-positive mCRC in this setting.

Tucatinib and trastuzumab

In patients with HER2-positive CRC, the HER2 gene is mutated or changed, resulting in overexpression of the HER2 receptor on the cell surface. This results in over proliferation of cells, eventually resulting in cancer.



Adopted from https://www.whathealth.com/breastcancer/her2receptor.html

Image source: https://www.ccalliance.org/colorectal-cancer-information/biomarkers/biomarkers-her2

Tucatinib and trastuzumab are both drugs that specifically target the mutated HER2 protein receptor, interfering with the cell proliferation process.

Data from the MOUNTAINEER trial will be used to support a new drug application in the US for patients with mCRC.

READ THE ARTICLE

ESMO World Congress on Gastrointestinal Cancer 2022: results from the CheckMate 142 study

July 2022

About 5% of patients MSI-H/dMMR mCRC and suffer poor outcomes when treated with chemotherapy in the **second-line setting** (i.e. after initial treatment has failed), experiencing a median overall survival of less than 16 months. This underlines the need for better treatment options for this subgroup of patients in later lines of treatment.

The immunotherapy drug nivolumab given in combination with another immunotherapy agent, ipilimumab, resulted in long-lasting clinical benefit over 4 years of follow-up in the CheckMate 142 study in which patients experienced high response rates, low rates of disease progression, and a long-term survival benefit.

The CheckMate 142 study involves the longest duration of follow-up reported for the combination of two immune checkpoint inhibitors in patients who have been previously treated for microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC). The findings confirm that this combination does provide long-term clinical benefit and will support the use of this combination as standard of care for this subgroup of patients.

READ THE FULL ARTICLE

Intermittent FOLFIRI plus panitumumab proves more effective, less toxic than continuous treatment in mCRC
July 2022

Recent findings from the IMPROVE study demonstrated that among patients with RAS/BRAF wild-type metastatic colorectal cancer (mCRC), FOLFIRI (fluorouracil, leucovorin, irinotecan) plus the targeted therapy agent panitumumab do not need to receive continuous treatment (the standard approach to treatment), and treatment can be safely given intermittently (at regular intervals followed by a break in treatment, and reintroduction of treatment in the instance that the disease progresses) without negatively impacting patient outcomes.

The intermittent treatment strategy resulted in longer progression-free survival (PFS) on treatment at 1 year (60.8% vs 52.1%), and average PFS on treatment was 17.1 vs 13.2 months, respectively. These PFS benefits were even more prominent among patients with tumours that originated on the left side of the colon.

Furthermore, the intermittent strategy greatly reduced the rate of severe skin-related toxicities which are common with the class of drugs (EGFR inhibitors) that panitumumab belongs to, and there were fewer treatment discontinuations due to adverse events.

Using panitumumab instead of the targeted therapy bevacizumab was supported by the findings from the PARADIGM study, which were reported at the 2022 ASCO Meeting, demonstrating an overall survival benefit of panitumumab vs. bevacizumab among patients with left-sided mCRC tumours.

The IMPROVE study findings suggest that an intermittent FOLFIRI/panitumumab treatment may be an effective treatment strategy for patients with RAS/BRAF wild-type mCRC and will continue to be investigated in a phase III trial.

READ THE FULL ARTICLE

Reproductive factors linked to lower CRC risk
July 2022

Based on the Global Burden analysis, CRC is less common among women and fewer women die from the disease compared to men. It is also known that hormone-replacement therapy (HRT) is associated with lower colorectal cancer (CRC) risk among postmenopausal women. Despite a large body of literature showing a link between CRC risk and estrogens from HRT and oral contraceptives, far less is known about the effects of lifetime exposure of women to varying levels of estrogen and progesterone through reproductive factors including pregnancy, breastfeeding, and menstruation on CRC risk.

Findings from a new analysis showed that estrogen exposure helps protect against colorectal cancer (CRC) in women:

- number of pregnancies - each pregnancy was linked to a small but significant reduction in CRC risk
- duration of breastfeeding - breastfeeding for a year or longer was associated with a significantly lower CRC risk compared to never breastfeeding
- use of oral contraceptives – use for 9 years or longer was linked to a lower CRC risk
- HRT – linked to a lower risk of CRC irrespective of tumour location

It was observed that the reduction in risk of CRC observed for **pregnancy** and **breastfeeding** only applied to proximal colon cancer (left-sided CRC), while the association between **oral contraceptive use** was confined to the distal colon and rectum (right-sided CRC). While age at menarche (start of menstruation) was not linked to CRC risk, menopause at age 40 or older was associated with a significant 17% lower risk of developing CRC.

Interpretation of findings
It is important to note that studies such as these may end up putting pressure on people to adapt their life choices to change their personal risk but based on these findings it would not be recommended to change their life choices for reproduction. However, these findings might influence CRC screening strategies in the future, such as by adapting screening guidelines based on a person's individual risk.

READ THE FULL ARTICLE

Real-world evidence supports earlier colorectal cancer screening
July 2022

A recent analysis added to the body of evidence to support the American Cancer Society and the US Preventative Services Task Force recommendations to begin screening at age 45.
In 2018, the American Cancer Society recommended that CRC screening begin at age 45 rather than 50 for average-risk individuals. In 2021, the US Preventative Services Task Force echoed this recommendation.

The recommendation to lower the starting CRC screening age was based on findings from microsimulation models that examined the benefits compared to the burden associated with starting screening 5 years earlier, at age 45. The recent analysis provided important **empirical evidence** (evidence that comes from **direct observation or measurement**) to support the recommendations, which until recently, has been scarce.

The study included 111,801 American women from the Nurses' Health Study II, who were age 26-49 years old at enrollment in the study (average age of 36 years). Over a 26-year period, 519 cases of CRC occurred.

In the study analysis, it was found that compared with no lower gastrointestinal endoscopy (sigmoidoscopy, colonoscopy), starting endoscopy before 50 years of age was associated with reduced risk of colorectal cancer (CRC), and specifically, a reduced risk of CRC diagnosed before 55 years of age. Starting endoscopy from 45-49 years of age was associated with a greater reduction in overall risk of CRC up until 60 years of age, compared with starting screening at 50 to 54 years of age.

While the findings from the analysis do support current American guidelines to start CRC screening at age 45, the researchers acknowledge that the study only included women, most of whom were White healthcare professionals which limits the generalizability of the findings. Next steps include conducting future studies with more representative and inclusive populations to ensure that the findings are relevant to the experience of all individuals at risk for developing CRC.

READ THE FULL ARTICLE