JANUARY 2021 PREVIEW

SYSTEMIC THERAPIES, SURGERY & SCREENING.........................................................2
TAS-102 plus bevacizumab improves overall survival in mCRC .................................................................2
Health-related quality of life scores in young CRC survivors are low and require targeted intervention .....................3
Total neoadjuvant therapy vs. standard therapy for locally advanced rectal cancer ..............................................4
Final overall survival results of the IDEA collaboration: 3 vs. 6 months of adjuvant chemotherapy for stage III colon cancer ........................................................................................................................................... 5
Rates of eligible people missing timely cancer screenings: A Canadian analysis .........................................................5
Vermurafenib plus cetuximab and irinotecan improves progression-free survival in BRAF-mutant metastatic CRC .........6
Post-surgical disease recurrence in stage I to III colorectal cancer may be predicted by ctDNA ......................................7
Study finds artificial intelligence may help to identify new risk factors for early-onset colorectal cancer ..................8
TAS-102 plus bevacizumab improves overall survival in mCRC
16 January 2021

For initial treatment of patients with metastatic colorectal cancer (mCRC) that are not eligible for standard chemotherapy or surgery, the combination of the chemotherapeutic agent TAS-102 (trifluridine/tipiracil; Lonsurf) and the anti-angiogenesis agent bevacizumab (Avastin) showed improvements in overall survival (OS) compared to the standard approach of capecitabine monotherapy plus bevacizumab. These findings were presented during the 2021 ASCO GI Cancers Symposium, based on data from the final analysis of phase II of the TASCO1 trial.

Chemotherapy is most effective at killing cells that are rapidly dividing, such as cancer cells. TAS-102 belongs to a category of chemotherapy known as “antimetabolites”, and is made up of two small molecules known as trifluridine and tipiracil. These two molecules interfere with DNA synthesis and replication – processes which are crucial to cell division and survival.

Bevacizumab (Avastin) is an anti-angiogenesis or anti-VEGF targeted therapy that interferes with the process of blood vessel formation in the body.

The trial included patients with CRC who had not received prior systemic chemotherapy for their unresectable disease. The patients were not eligible for intensive combination therapies due to reasons such as investigator judgment, advanced age, low tumour burden, and comorbidities.

The combination of TAS-102 and bevacizumab prolonged progression-free and overall survival compared to capecitabine monotherapy plus bevacizumab, with patients tolerating the experimental combination therapy well. The two combinations will be compared further in the phase III SOLSTICE trial in patients with mCRC.

Take home message:

For patients with metastatic colorectal cancer who cannot undergo standard chemotherapy or surgery, a novel combination consisting of the chemotherapeutic agent TAS-102 (trifluridine/tipiracil; Lonsurf) and the anti-angiogenesis agent bevacizumab (Avastin) showed better overall survival and progression-free survival compared to the standard of care.
Health-related quality of life scores in young CRC survivors are low and require targeted intervention
15 January 2021

According to findings presented at the 2021 ASCO Gastrointestinal Cancers Symposium, overall health-related quality of life (HRQoL) among younger survivors of colorectal cancer is poorer, with social and functional well-being suffering more with longer-term survivorship. HRQoL is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. It goes beyond direct measures of population health, life expectancy, and causes of death, and focuses instead on the impact that one’s health status has on quality of life.

Data was gathered from an online survey – the Functional Assessment of Cancer Therapy (FACT-C) survey, which examines HRQoL globally and uses a CRC-specific scale to evaluate emotional, physical, social and functional well-being. The average age of participants was 33.76 years old. Overall, HRQoL scores were low across the board. Patients were divided into two categories of 6-18 months after initial diagnosis or disease recurrence, and 19-36 months after initial diagnosis or recurrence. Higher scores for physical and emotional well-being indicating improved HRQoL were observed in patients who had a longer time between diagnosis and participation in the survey, whereas significantly lower scores were observed in social well-being for longer-term compared to more recently diagnosed survivors.

The overall low HRQoL scores for young CRC survivors indicate a need for expanded counselling strategies and other interventions, particularly those with a focus on social well-being. As CRC incidence continues to rise in this population, specific attention is warranted to address and improve HRQoL in younger individuals.

Take home message:

Health-related quality of life (HRQoL) status examines how an individual’s health status impacts their quality of life. For survivors of early age onset colorectal cancer, it was found that HRQoL was low, especially with respect to social and functional well-being for long-term survivors. These findings warrant greater focus on expanded counselling strategies and other interventions, especially as CRC incidence continues to rise in this at-risk population.

READ THE FULL ARTICLE
Total neoadjuvant therapy vs. standard therapy for locally advanced rectal cancer
18 January 2021

A systematic review and meta-analysis found that total neoadjuvant therapy was linked to improved pathologic complete response rates (the absence of residual cancer cells) compared to standard therapy in patients with locally advanced rectal cancer.

Currently, the standard therapy for locally advanced rectal cancer includes:
- initial (neoadjuvant) chemoradiation therapy;
- surgery;
- adjuvant chemotherapy.

Total neoadjuvant therapy is an alternative strategy consisting of:
- neoadjuvant chemoradiation given in conjunction with neoadjuvant chemotherapy;
- surgery.

The goal of total neoadjuvant therapy is to deliver uninterrupted systemic therapy to more effectively eliminate micrometastases and therefore minimize the risk of disease recurrence. Findings from the study suggest that this alternative therapy is a promising strategy in the treatment of locally advanced rectal cancer, with improved rates of pathologic complete response compared to the standard of care. This study, however, does not evaluate the impact of total neoadjuvant therapy on disease recurrence rates or overall survival, which needs to be explored further in future studies.

Take home message:

Total neoadjuvant therapy (TNT) is an alternative strategy for the treatment of locally advanced rectal cancer that combines chemotherapy with neoadjuvant chemoradiation therapy prior to surgery. This treatment approach aims to deliver a more constant dose of systemic therapy to address any micrometastases that may persist in the body, thereby reducing the risk of disease recurrence. TNT showed better rates of pathologic complete response (the absence of residual cancer cells) compared to the standard of care, though further studies will be needed to confirm whether it has any significant impact on disease recurrence rates or overall survival.
Final overall survival results of the IDEA collaboration: 3 vs. 6 months of adjuvant chemotherapy for stage III colon cancer
20 January 2021

The IDEA collaboration is a pooled analysis of six phase III clinical trials examining the effectiveness of 3 vs. 6 months of post-operative (adjuvant) chemotherapy in the treatment of patients with stage III colon cancer. The investigators found that 6 months of treatment with CAPOX (capecitabine + oxaliplatin) did not provide any additional benefit to patients, while 6 months of FOLFOX was associated with a moderate but significant improvement compared to 3 months of treatment.

Patients in all trials were randomly assigned to receive either 3 months or 6 months of adjuvant FOLFOX chemotherapy every 2 weeks, or CAPOX every 3 weeks. While noninferiority of 3 months vs. 6 months of adjuvant chemotherapy was not confirmed in terms of overall survival, the 5-year overall survival differed in the two groups by only 0.4% - a fact that should be considered in a clinical context. Overall survival results support the use of 3 months of adjuvant CAPOX for most patients with stage III colon cancer, a conclusion that is reinforced by the substantial reduction of toxicities, inconveniences, and cost associated with shorter treatment duration.

Take home message:

For patients with stage III colon cancer, 3 months of adjuvant chemotherapy with CAPOX (capecitabine plus oxaliplatin) was shown to be just as effective as 6 months of CAPOX, with the added benefit of less toxicity, inconveniences, and cost associated with shorter treatment duration. In general, while the advantage of 3 months vs. 6 months of adjuvant chemotherapy was not statistically significant with respect to overall survival, the absolute difference in 5-year overall survival was only 0.4% and should be considered in clinical context.

Rates of eligible people missing timely cancer screenings: A Canadian analysis
20 January 2021

New findings from the University of Alberta published in the Journal of the National Comprehensive Cancer Network showed that 43% of eligible individuals miss timely screening tests for colorectal cancer (CRC). The results demonstrate how socioeconomic and racial disparities in cancer screening contribute to unequal health outcomes, highlighting the need for targeted interventions that go beyond coverage for health services alone.

High-quality evidence supports the effectiveness of cancer screening in saving lives. From an economic perspective, it is far more cost-efficient to have an effective cancer screening program and lower cancer-specific mortality than to have a high incidence of advanced incurable cancers.
that would cost the system far more – not to mention the loss of health and quality of life of the affected individuals. The findings show that better strategies to minimize socioeconomic-related health disparities in our communities are much needed, even in places where healthcare is publicly funded. The lead investigators suggest that “the most powerful intervention to improve screening rates would be to invest more in primary care and make sure every individual is linked to a family physician who can track their adherence to recommended screening tests”.

The period of data collection for the study does not reflect any impact from the COVID-19 pandemic. The findings, however, draw important attention to the issue of timely screening as doctors are currently reporting concerning decreases in screening numbers, which are projected to influence greater numbers of cancer deaths in the coming years.

**Take home message:**

Findings have shown that more than a third of eligible individuals miss timely screening tests for colorectal cancer, even in places like Canada where healthcare is publicly funded. The results demonstrate how socioeconomic and racial disparities in cancer screening contribute to unequal health outcomes, highlighting the need for targeted interventions that go beyond coverage for health services alone.

**Vemurafenib plus cetuximab and irinotecan improves progression-free survival in BRAF-mutant metastatic CRC**

6 January 2021

Results from the SWOG S1406 study showed that adding vemurafenib (Zelboraf) to irinotecan (Onivyde) and cetuximab (Erbitux) led to significant improvement in progression-free survival (PFS, the time after treatment that the patient lives with the disease but it does not worsen) compared to the standard therapy of irinotecan and cetuximab alone in patients with BRAF V600E-mutated metastatic colorectal cancer (mCRC).

Vemurafenib is a targeted therapy drug that targets mutated BRAF proteins within the cancer cell. The BRAF protein plays an important role in a chain of molecules that convey a signal telling the cell how to grow and divide.

The triplet combination of vemurafenib, cetuximab and irinotecan was found to reduce the risk of disease progression or death by 50% among patients with the BRAFV600E-mutated mCRC. Furthermore, 80% of patients who received the experimental triplet therapy did not show disease progression after nine weeks compared to 39% of patients who received the standard therapy. The triplet therapy also resulted in a higher treatment response rate compared to the doublet standard
regimen (17% vs. 4%, respectively).

Lead investigator, Dr. Scott Kopetz, notes “That 1-2-3 action, that triple threat, shuts off a powerful growth pathway in these cancers. In this trial, unlike in BEACON, we added chemotherapy and found that it makes for a more effective way to treat this aggressive form of CRC”. Preclinical data suggest that the chemotherapy agent irinotecan may have a synergistic effect when combined with BRAF and EGFR inhibitors.

With respect to treatment toxicity, grade 3 and 4 adverse effects were more common with the triplet therapy compared to the doublet, with patients experiencing increased neutropenia, anemia, and nausea. 22% of patients in the triplet arm had to stop treatment due to toxicities compared to 8% of patients in the doublet arm. In conclusion, the triplet therapy of vermurafenib with cetuximab and irinotecan represents an active therapeutic combination that has a significant improvement in progression-free survival among patients with BRAFV600E-mutated mCRC.

**Take away message:**

For patients with BRAFV600E-mutated metastatic colorectal cancer, a novel triplet therapy consisting of the targeted therapies vermurafenib and cetuximab in combination with the chemotherapy agent irinotecan has demonstrated a significant improvement in progression-free survival compared to the standard therapy of irinotecan and cetuximab.

---

**Postsurgical disease recurrence in stage I to III colorectal cancer may be predicted by ctDNA**

20 January 2021

Findings from a recent study presented during the 2021 Gastrointestinal Cancers Symposium demonstrated that circulating tumour DNA (ctDNA) testing immediately after surgery enabled clinicians to effectively identify patients with stage I to III colorectal cancer (CRC) who were at high risk for disease recurrence. Long-term, continuous monitoring further increased the predictive power of ctDNA, which was shown to be more reliable than carcinoembryonic antigen (CEA) surveillance or standard radiological techniques.

The study was a collaboration between researchers at the Danish Aarhus University, the INCLIVA Institute in Spain, and the Natera company in the United States, which created the ctDNA detection strategy used in the study.

In the study, all 260 patients underwent surgery to remove colorectal tumours. Blood plasma samples were collected at various time points (30 days, 3 months, and then every 3 months after surgery for 3 years) for an average time of 29.9 months. After surgery, 80% of patients with
detectable ctDNA experienced disease recurrence, as compared to only 13% of patients with undetectable ctDNA.

On average, molecular disease recurrence was identified with ctDNA 8 months before radiologic detection of disease through computed tomography (CT scan). Furthermore, ctDNA outperformed CEA as a biomarker for disease relapse. Longitudinal CEA assessment failed to reach statistical significance as a prognostic biomarker while longitudinal ctDNA assessment emerged as a strong, independent one.

As a prognostic biomarker, ctDNA could help to identify the 10-15% of stage I and low-risk stage II patients who are undertreated for their disease, and the approximately 60% of stage II patients who are overtreated. With ctDNA, risk can be identified early and timely intervention can be administered, or treatment can be delayed until patients show evidence of ctDNA negativity. Furthermore, ctDNA testing can help make image testing more efficient, which could be intensified in ctDNA-positive patients and eliminated in ctDNA-negative patients, with longitudinal serial ctDNA applied instead.

**Take home message:**

A recent study has shown that ctDNA is a strong predictive biomarker for colorectal cancer (CRC) recurrence among patients with stage I-III disease. When patients were tested for ctDNA immediately after surgery, ctDNA outperformed carcinoembryonic antigen (CEA) testing or radiologic detection through CT scans in detecting risk of recurrence, especially when it is used in a long-term, continuous fashion.

---

**Study finds artificial intelligence may help to identify new risk factors for early-onset colorectal cancer**

19 January 2021

The use of electronic health record-based artificial intelligence could help uncover new risk factors in the development of early age onset colorectal cancer (EAO CRC) based on findings presented at the AACR Virtual Special Conference: Artificial Intelligence, Diagnosis, and Imaging. Specifically, disorders that cause chronic immunosuppression - including human immunodeficiency virus (HIV), inflammation, obesity, asthma, sinusitis, and dermatitis – were identified as new risk factors for EAO CRC patients by artificial intelligence (AI) models. While obesity, diet, a sedentary lifestyle, inflammatory bowel disease and family history are cited as contributing factors in early development of CRC, these factors alone are not able to account for the rising disease trends in young adults.

In the study, the researchers used data from the electronic health records of 1,227 patients with
colorectal cancer (CRC) under the age of 50. Colon cancer and rectal cancer data was modeled separately. After applying AI algorithms to the data, the top predictors the researchers identified in the colon cancer cohort included hypertension, cough/asthma, chronic sinusitis, anxiety disorder, and atopic dermatitis (eczema). The top predictors in the rectal cancer cohort included obesity, female sex, HIV, anxiety disorder, and asthma.

The researchers concluded that “disorders with chronic immunosuppression (eg, HIV) or inflammation (eg, obesity, asthma, sinusitis, dermatitis) may represent immune-axis derangements contributing to a favourable state for colorectal cancer. This preliminatory study provides early insight into the capacity of artificial intelligence to uncover new risk factors in the population of patients with young-onset colorectal cancer”.

**Take away message:**

A preliminary study has shown that artificial intelligence models could help to identify new risk factors involved in the development of early age onset colorectal cancer. Specifically, disorders such as asthma, sinusitis and dermatitis that cause chronic immunosuppression were found to influence colorectal cancer development in young adults.