December 2022- January 2023

LIVING WITH CANCER

COLORECTAL CANCER 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 December 1st 2022 to January 31st, 2023 inclusive and are intended for informational purposes only

DECEMBER-JANUARY 2023 PREVIEW

Trifluridine plus tipiracil and bevacizumab is a new standard of care for refractory metastatic colorectal cancer

January 2023

Findings from the phase III SUNLIGHT trial were presented at the 2023 ASCO Gastrointestinal Cancers Symposium, demonstrating that the combination of bevacizumab (commercial name: Avastin®) plus trifluridine/tipiracil (commercial name: Lonsurf®) promoted an improvement in overall survival and progression-free survival in patients with metastatic colorectal cancer (mCRC) that has become refractory or unresponsive to previous treatment.

Bevacizumab is a type of intravenous (given through a vein) therapy used in the treatment of mCRC. It works by interfering with a process known as **angiogenesis**, which involves the creation of new blood vessels. This process is important for tumour growth, therefore blocking angiogenesis can slow tumour growth.

Trifluridine/tipiracil is a type of oral (given through the mouth) chemotherapy used to treat mCRC that has been previously treated with 5-FU, oxaliplatin, irinotecan-based chemotherapy, and targeted therapies such as bevacizumab, cetuximab, and panitumumab. This treatment is absorbed by tumour cells and interferes with their ability to divide and replicate.

The study

The trial enrolled patients who had mCRC and had received at least two previous treatments. By comparing patients who received trifluridine/tipiracil plus bevacizumab versus those that received trifluridine/tipiracil alone, the researchers were able to determine whether adding the targeted therapy provided any survival benefit to this subset of patients.

The **primary endpoint** (the main result that is measured at the end of the study to see if a given treatment worked) of the study was overall survival (OS), which is the length of time that patients with the disease are still alive after the start of treatment.

The average OS was 7.5 months vs. 10.8 months for the trifluridine/tipiracil and trifluridine/tipiracil/bevacizumab group, respectively.

The 12-month OS rates (the percentage of patients who are still alive for the specific period of time after the start of treatment) were 30% vs 43%, respectively.

Progression-free survival (PFS) was another result that was examined in this study and measures the length of time during and after the treatment of a disease that the patients live with the disease but it does not get worse.

Average PFS was 2.4 months vs. 5.6 months for the trifluridine/tipiracil and trifluridine/tipiracil/bevacizumab group, respectively.

The 12-month PFS rates (the percentage of people who did not experience new tumour growth or cancer spread) were 1% and 16%, respectively.

Adverse events (any unwanted medical occurrence that is associated with the use of the treatment) of grade 3 or higher were reported in 70% vs. 72% of patients in the trifluridine/tipiracil and trifluridine/tipiracil/bevacizumab group, respectively.

The novel combination therapy provided a statistically significant and clinically meaningful improvement in OS with an acceptable safety profile.

Take home message

The new combination therapy of trifluridine/tipiracil plus bevacizumab is supported by findings from the phase III SUNLIGHT trial as the new standard of care for the treatment of patients who have refractory mCRC that has progressed after two previous lines of therapy.

READ THE FULL ARTICLE

Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C

January 2023

KRAS is the most frequently mutated **oncogene** in human cancer and drives cancer development in up to half of all patients with colorectal cancer (CRC).

***Oncogene**: a gene (a sequence of genetic material stored in our DNA) which, when changed or mutated, can cause a cell to turn into a cancer cell.*

KRAS mutations have been considered "undruggable", meaning that there is no drug that specifically targets them to slow their cancer-causing effects. A specific subtype of *KRAS* mutations known as the KRAS G12C mutation occurs in 3-4% of patients with metastatic CRC and is associated with worse survival outcomes[1].

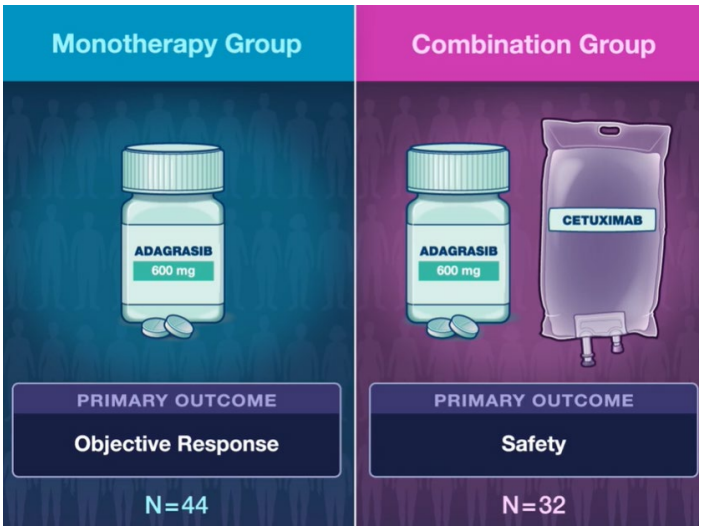
There has been recent progress in targeting *KRAS* G12C with the use of tiny molecules that bind to the mutated KRAS G12C protein and maintain it in its inactive state, therefore preventing it from promoting tumour development. Early data from a study evaluating the effectiveness of a drug known as adagrasib showed promising results in patients with CRC with KRAS G12C mutations, though the combination with an epidermal growth factor receptor (EGFR) inhibitor such as cetuximab may help to overcome drug resistance and improve patient outcomes.

[1] https://www.nejm.org/doi/full/10.1056/NEJMoa2212419

The KRYSTAL-1 phase 1-2 trial

In the ongoing KRYSTAL-1 trial, the use of adagrasib is being studied alone or in combination with cetuximab in patients with previously treated metastatic CRC with mutated KRAS G12C.

Patients with metastatic CRC with a KRAS G12C mutation were included in the study. 44 patients received oral adagrasib twice daily (the **monotherapy** group), and 32 patients received a combination therapy of oral adagrasib twice daily plus intravenous cetuximab once a week or every two weeks (the **combination** group).



Snapshot from the video summary of the original article
https://www.nejm.org/do/10.1056/NEJMdo006850/full/?requestType=popUp&relatedArticle=10.1056%2FNEJMoa2212419

The **primary endpoint/outcome** (the main result that was measured) in the monotherapy group was **objective response**, meaning that the total percentage of patients who had a partial or a complete response to the treatment within the specified period of time. The primary outcome in the combination group was **safety**, with researchers assessing the safety profile of taking both adagrasib and cetuximab at the same time.

Findings

In the trial, the findings provide clinically meaningful evidence to support that KRAS G12C can be targeted in metastatic CRC for both adagrasib alone and in combination with cetuximab among previously treated patients with metastatic disease.

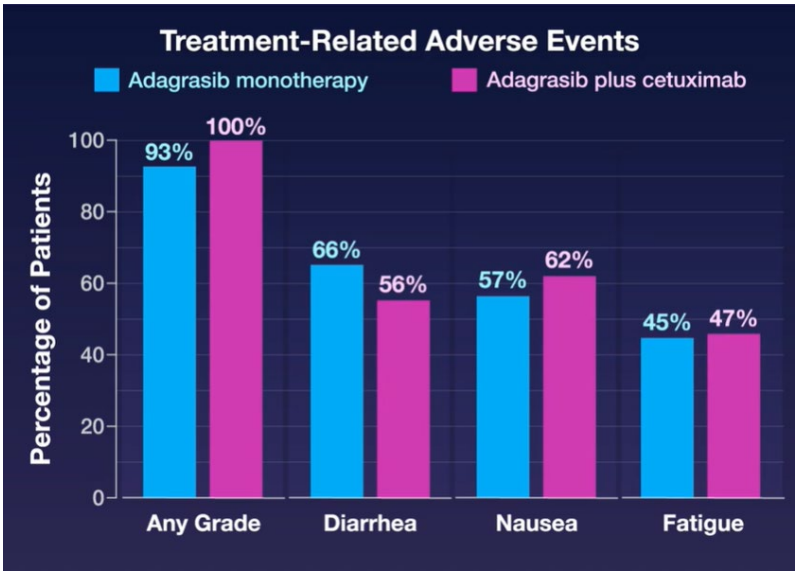
Adagrasib monotherapy produced an objective response rate of 19% with a median response duration 4.3 months. Median **progression-free survival (PFS)** was 5.6 months, and median **overall survival (OS)** was 19.8 months.

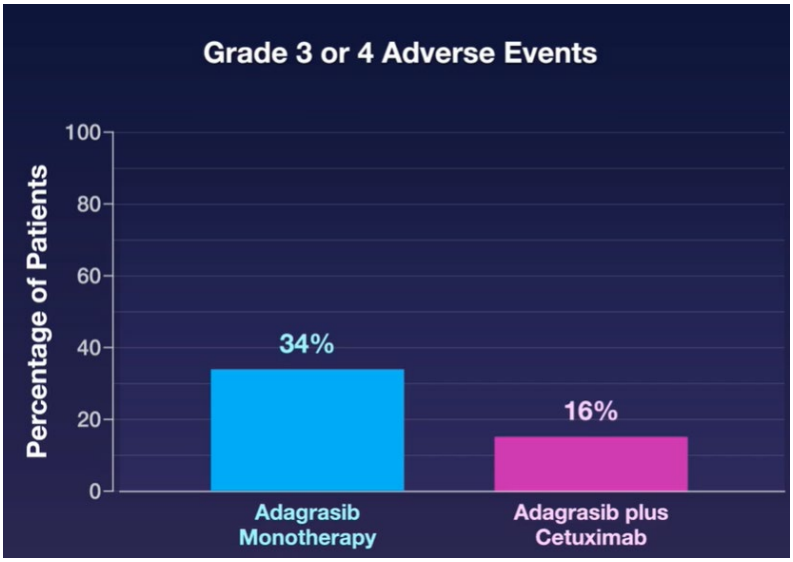
Progression-free survival: the length of time during and after treatment of a disease that a patient lives with the disease but it does not get worse.

Overall survival: the length of time from the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive.

The combination therapy produced an objective response rate of 46%, with a median response duration of 7.6 months. Median PFS was 6.9 months.

Treatment related adverse events were common:





These findings compared favourably to patients with mCRC harbouring a BRAF V600E who received encorafenib and cetuximab. With this combination therapy, a 19.5% objective response rate was observed, 4.3 months PFS, OS 9.3 months, response duration of 5.5 months.

Reactivation of EGFR pathway in mCRC is an adaptive response to KRAS G12C inhibition, suggesting that combining inhibition of KRAS G12C and EGFR may enhance the therapeutic effectiveness of treatment. These findings are consistent with outcomes reported in 665 patients

who had mCRC with BRAF V600E mutation, where BRAF plus EGFR inhibition led to improved activity over BRAF inhibition monotherapy[2].

Take home message

This phase 1-2 trial of adagrasib alone and in combination with cetuximab demonstrated that both treatments produced reversible toxic effects in most patients and caused no new safety concerns. Adagrasib showed promising clinical activity in pretreated patients with mCRC with a KRAS G12C mutation, and the biologic activity of the drug appeared to be improved further when it was combined with cetuximab.

READ THE FULL ARTICLE

Levels of cell-free DNA do not impact ctDNA detection in patients with CRC

January 2023

There is increasing evidence to support the use of circulating tumour DNA (ctDNA) as a **biomarker** to detect minimal residual disease (MRD) in colorectal cancer (CRC).

Biomarker: a molecule that can be found in the the body (e.g. in the blood or tissues) that can be used as a sign of a normal or abnormal process, or as a indicator of a specific disease.

What is ctDNA?

ctDNA refers to the DNA or genetic material that comes from cancer cells and tumours. Normally DNA is stored inside a cell, but as a tumour grows, its cells die and are replaced by new ones. The dead cells release their contents, including their DNA, into the bloodstream. ctDNA are the pieces of DNA that can be detected in the blood.

Measuring quantities of ctDNA can be helpful to:

- **Detect and diagnose a tumour**. ctDNA is different from a patient's DNA, since tumours acquire genetic changes that result in changes to their DNA. In this way, analyzing ctDNA can help to identify specific mutations that are present in the tumour, and serve as a potential guide to determining which treatments the tumour is most likely to respond to
- **Monitor how a tumour is responding to treatment**. A decrease in the overall quantity of ctDNA suggest that tumour is responding to treatment and shrinking in size. In the context of colorectal cancer, ctDNA testing can help to determine whether someone who has undergone surgery would benefit from additional chemotherapy.
- **Monitor periods when the cancer is in remission**. A consistent lack of ctDNA in the blood after treatment suggests that the cancer has not come back (recurred).

[2] https://www.nejm.org/doi/full/10.1056/NEJMoa1908075

ctDNA is different from a similar term, cell-free DNA (cfDNA), which is a broader term that refers to DNA that is circulating in the bloodstream but does not necessarily come from a tumour and can come from normal tissues. cfDNA levels can increase after a patient receives survery, and when patients receive chemotherapy.

The study

A concern with the timing of MRD ctDNA testing has been that immediately after a patient undergoes surgery when there will be an increase in cfDNA, that those elevated levels could make it harder for precise ctDNA levels to be measured. As such, ctDNA testing to evaluate the tumour response to surgery was not being done until 4 weeks post-surgery. Timing is of the essence with MRD testing, as waiting too long to test can result in delays in treatment.

At the 2023 ASCO GI Symposium, findings from a large US-based study found that standard MRD testing could be done as early as 15 days (2 weeks) after surgery, since levels of cell-free DNA were not found to negatively impact ctDNA detection. There was no association found between cfDNA concentration and whether ctDNA could be detected.

Conclusion

While there are changes in the quantities of cfDNA after surgery, the changes appear to be most noticeable in the first week and second week after surgery. By 15 days, cfDNA levels appear to remain consistent and ctDNA levels are able to be detected.

Although MRD testing is not yet a standard of care for patients with colorectal cancer who have undergone surgery, the study findings suggest that this testing can be done sooner after surgery. This provides an important benefit to patients as it could enable patients to receive further chemotherapy in a more timely fashion, if it is deemed necessary.

Talk about relevance of this in lieu of Signatera test becoming available in Canada. For more information about the Signatera residual disease test, see the Patient Guide.

READ THE FULL ARTICLE

Preoperative chemotherapy for operable colon cancer: long-term results

January 2023

Adjuvant chemotherapy: chemotherapy that is given to a patient after they have received surgery

Neoadjuvant chemotherapy: chemotherapy that is given to a patient before they have received surgery

For patients with locally advanced colon cancer, chemotherapy is typically given after surgery for 24 weeks to kill any remaining tumour cells that may linger in the body. With **adjuvant** (post-surgical) chemotherapy, however, about 20-30% of patients will experience cancer recurrence. The use of pre-surgical chemotherapy (**neoadjuvant chemotherapy**) has been shown to significantly improve outcomes in other gastrointestinal cancers, and may have several advantages over post-operative chemotherapy. First, by giving chemotherapy before surgery, tumours are smaller and may lower the risk of incomplete removal of tumour cells. Second, neoadjuvant chemotherapy may begin many weeks before adjuvant chemotherapy and therefore may be more effective at reducing micrometastases (metastatic tumours too small to be identified in a scan). Furthermore, surgery induces growth factor activity, which can potentially stimulate tumour proliferation before post-surgical chemotherapy begins.

There are potential disadvantages of neoadjuvant chemotherapy, however. Questions such as whether the toxicity of chemotherapy before surgery could compromise a patient's fitness for surgery, or whether the additional treatment could increase the chances for surgical complications remain to be explored.

The study

The main objective of the FOxTROT study was to determine whether giving 6 weeks of chemotherapy before surgery can safely reduce cancer recurrence in patients with locally advanced, operable (able to be removed by surgery) colon cancer. Patients were randomly assigned to receive either six weeks of neoadjuvant chemotherapy (691 patients) followed by surgery and then eighteen weeks of adjuvant chemotherapy, or the standard treatment of surgery followed by twenty four weeks adjuvant chemotherapy (354 patients).

Among the patients who received a 6-week neoadjuvant chemotherapy regimen before surgery, there was a 28% lower rate of recurrent disease within 2 years compared to patients who received adjuvant chemotherapy. It was found that the toxicity of chemotherapy was similar whether it was given before or after surgery, and surgical complications were less frequent in the neoadjuant chemotherapy group.

These findings from FOxTROT suggest that for patients with locally advanced, resectable colon cancer, 6 weeks of pre-surgical chemotherapy followed by surgery and post-surgical chemotherapy can be done safely without increasing the risk of surgical complications. Adding pre-operative chemotherapy significantly reduced tumour size and disease control was better after 2 years compared to patients who received adjuvant chemotherapy alone. As such, 6 weeks of neoadjuvant chemotherapy should be taken into consideration when treating patients with locally advanced colon cancer.

READ THE FULL ARTICLE