September 2022

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 September 1st 2022 to September 30th, 2022 inclusive and are intended for informational purposes only

SEPTEMBER 2022 PREVIEW

The FRESCO-2 trial: exploring treatment options for patients with metastatic colorectal cancer

September 2022

Findings from the global FRESCO-2 trial showed that a drug called fruquintinib (fru-kin-tih-nib) significantly improved overall survival and progression-free survival in patients with metastatic colorectal cancer that has stopped responding to treatment (also known as ***refractory*** metastatic colorectal cancer). The findings were presented at the European Society for Medical Oncology (ESMO) Congress 2022 held earlier this month in Paris, France.

Refractory metastatic colorectal cancer: *colorectal cancer that no longer responds to treatment.*

These findings are encouraging, as patients who develop refractory metastatic colorectal cancer have limited treatment options and poor outcomes. As such, there is a high unmet need for treatment alternatives once current standard therapies fail. With fruquintinib, patients with refractory disease may have a new treatment opportunity.

What is fruquintinib?

Fruquintinib is a highly potent inhibitor of the vascular endothelial growth factor (VEGF) receptors found on the surface of cells. VEGF receptors are involved in a process known as **angiogenesis** or the development of new blood vessels. New blood vessels are essential to tumour growth, development and metastasis, therefore blocking or inhibiting the VEGF receptor is an important target in the treatment of cancer.

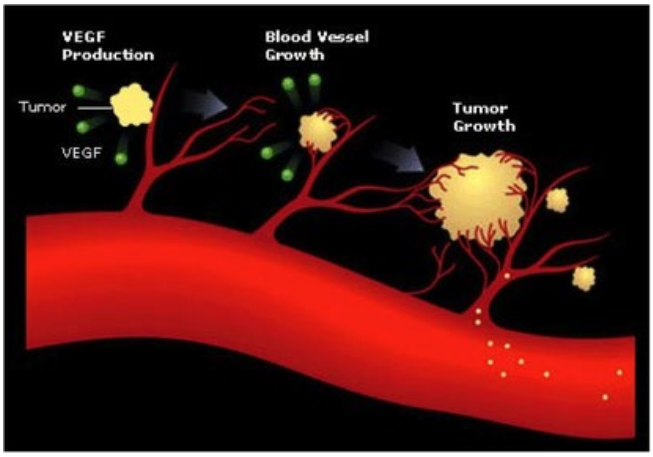

Image source: https://www.canceredinstitute.org/vegf-targeting-ramucirumab-receives-approval-as-drug-for-metastatic-colorectal-cancer.html

In the original phase III FRESCO-2 study, fruquintinib was given as third-line therapy or later to patients with metastatic colorectal cancer. It led to improvements in average overall survival among patients, which led to the drug's approval in China in 2018 and in the US in 2020, where the US Food and Drug Administration granted a fast-track approval to fruquintinib to treat some patients with colorectal cancer who had already received previous therapies.

The study

Patients with metastatic colorectal cancer were eligible to join the trial if they were previously treated with chemotherapy, targeted therapies such as anti-VEGF therapy (anti-angiogenesis drugs such as bevacizumab), TAS-102 (Lonsurf), regorafenib, or immune checkpoint inhibitors (immunotherapy).

Patients who were treated with fruquintinib had statistically significant improvements to their overall survival, which was prolonged to 7.4 months compared to patients who received best supportive care alone. Patients also experienced statistically significant improvements to their median progression-free survival, which was 3.7 months compared to 1.8 months among patients who received best supportive care alone. Overall, patients who received the new drug had a 34% reduction in the risk of death.

Best supportive care: *consists of appropriate palliative care without any other anticancer therapies. It includes physical, psychological, social, and spiritual support.*

Conclusions

The FRESCO-2 study demonstrates meaningful survival improvement and a manageable safety profile associated with fruquintinib. The study investigators are in the process of assessing quality of life data from the study participants. Future studies will be dedicated to exploring fruquintinib in combination with other therapies for patients with colorectal cancer.

READ THE FULL ARTICLE

Updated results from the KRYSTAL-1 study of adagrasib in advanced KRAS G12C-mutated colorectal cancer

September 2022

Updated results from the phase I/II KRYSTAL-1 study examined the effectiveness of a drug known as adagrasib, which binds to a mutated form of a protein involved in the development of colorectal cancer known as KRAS G12C. The findings were presented at the ESMO 2022 Congress.

Background on *KRAS*

KRAS is the name of a gene (a sequence of genetic material contained in our DNA) that is part of an important pathway in all human cells that is involved in cell growth, proliferation and differentiation (the ability of cells to take on specialized functions). If the *KRAS* gene becomes mutated or changed, it can result in the development of cancer as the growth and proliferation signals it normally controls become dysregulated. Therefore, *KRAS* is also referred to as a **oncogene** – any gene that, under certain circumstances, can cause a healthy cell to transform into a tumour cell.

The KRAS G12C mutation

While *KRAS* has been known for decades by researchers as one of the most commonly mutated genes in cancer, researchers have been so far unable to find a way to target *KRAS* and stop the out-of-control cell growth that can occur. One particular mutation of *KRAS* known as *KRAS G12C*, is a mutation that is found in 3-4% of colorectal cancers that has shown some promising progress in the search for ways to block abnormal *KRAS* activity. The KRAS G12C protein acts as a growth factor to promote cell growth and proliferation, two processes that are essential to tumour development.

The KRYSTAL-1 study

In the study, patients with KRAS G12C mutated advanced colorectal cancer were treated with a targeted therapy called adagrasib, with or without the targeted therapy cetuximab. Among patients with advanced colorectal cancer, prognosis tends to be poor; prognosis tends to be even worse among patients with KRAS G12C-mutated colorectal cancer.

Patients who received adagrasib plus cetuximab experienced 100% disease control rate, with 13 out of 28 patients experiencing a partial response, and 15 out of 28 patients experiencing stable disease. Among the patients evaluated in this study, adagrasib was found to be well-tolerated as a monotherapy as well as in combination with cetuximab, and the majority of treatment-related adverse events were grade 1 or 2.

Objective response rate: proportion of patients with a complete response or partial response to treatment

Disease control rate: percentage of patients with advanced or mCRC who achieve complete, partial response and stable disease to a therapeutic intervention.

Conclusions

The updated findings from KRYSTAL-1 demonstrate a durable response to KRAS inhibition in colorectal cancer. The combination of a KRAS inhibitor together with an EGFR inhibitor (cetuximab) resulted in longer-lasting responses. The combination of adagrasib and cetuximab will continue to be studied in this patient subset in the phase III KRYSTAL study.

READ THE FULL ARTICLE

Effect of physical activity on disease-free survival in patients receiving adjuvant therapy
September 2022

Findings from a study published in the *Journal of Clinical Oncology* demonstrated that among patients who were receiving adjuvant (post-surgical) therapy for stage III colon cancer, those that participated in greater volumes of recreational physical activity, longer durations of light- to moderate-intensity aerobic physical activity, or any vigorous-intensity aerobic physical acitivity experienced significant improvements in disease-free survival.

Disease-free survival rate: *the percentage of individuals who are free of the signs and symptoms of cancer after a specified duration of time.*

In the study, 2,524 patients were randomly assigned to adjuvant therapy with 3 or 6 months of chemotherapy. The 3-year disease-free survival rate was as follows:

Light-intensity to moderate-intensity activities less than 1 hour per week: 65.7%
Light-intensity to moderate-intensity activities at least 1.5 hours per week: 87.1%

Vigorous-intensity activity less than 1 hour per week: 76%
Vigorous-intensity activity at least 1 hour per week: 86%

Brisk walking less than 1 hour per week: 81.7%
Brisk walking at least 3 hours per week: 88.4%

Muscle-strengthening activity less than 1 hour per week: 81.8%
Muscle-strengthening activity at least 0.5 hour per week: 88.8%

How does physical activity help to improve outcomes?

There are several different mechanisms through which physical activity has been associated with better cancer outcomes. One such mechanism is through regulation of certain hormones such as insulin-like growth factor (IGF). IGF is involved in the growth and survival of tumour cells and

promotes a variety of processes that are essential to cancer development[1]. Physical activity also helps to reduce obesity, which is associated with a hormone known as leptin, which has been implicated in the development of wide range of cancers[2].

Another mechanism that links physical activity to better outcomes is through a reduction in chronic inflammation in the body. Inflammation is a natural process of the body that can favour many of the processes involved in cancer development when it becomes chronic or dysregulated; regular moderate physical activity has been linked to a reduction in chronic inflammation[3].

Furthermore, physical activity is linked to improved immune functioning. In general, exercising at a moderate to vigorous intensity for 60 minutes or less is optimal for the immune-boosting benefits of exercise. On the other hand, prolonged high intensity training, particularly that which is done without appropriate rest between sessions, can supporess immune function. Exercise also helps to decrease stress, improve sleep (which is when certain components of the immune system become the most active)[4], and positively influence the neurotransmitters in the brain that are responsible for affecting mood and behaviour.

Conclusions

Among patients with stage III colon cancer enrolled in a trial of post-operative treatment, larger amounts of recreational physical activity, longer durations of light-to-moderate intensity aerobic physical activity, or any vigorous intensity aerobic physical activity were associated with the greatest improvements to disease-free survival.

READ THE FULL ARTICLE

FDA grants priority review for new combination therapy for previously treated HER2-positive metastatic colorectal cancer

September 2022

Patients with HER2-positive colorectal cancer who have received at least one prior treatment are left with few effective targeted treatment options. HER2 is a gene that is overexpressed in 3-5% of cases of metastatic colorectal cancer, and its overexpression is a predictor for poor response to the anti-EGFR class of targeted therapies, including cetuximab and panitumumab. This month, the US Food and Drug Administration granted a Priority Review for the accelerated approval of a new combination of targeted therapies, consisting of tucatinib (Tukysa® – too-kai-za) and trastuzumab

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4383470/#:~:text=Insulin%2Dlike%20growth%20factors%20(IGFs,cell%20transformation%20induced%20by%20tumour.
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7877262/
[3] https://www.nature.com/articles/nri3041
[4] https://www.sleepfoundation.org/physical-health/how-sleep-affects-immunity

(Herceptin®) in response to the high unmet need for effective, later-line therapies for this subset of patients.

The New Drug Application is based on the findings from the phase II MOUNTAINEER trial, which were presented at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer in July 2022. The FDA Priority Review is granted to applications for therapies that would provide significant improvements in safety or effectiveness for the treatment, diagnosis, or prevention of serious diseases. In July 2022, the FDA granted Breakthrough Therapy designation to tucatinib and trastuzumab – this designation is a process designed to accelerate the development and review of drugs that are intended to treat a serious condition and have preliminary clinical evidence to support that the drug may demonstrate substantial improvements over available therapies[5].

The MOUNTAINEER trial

The MOUNTAINTEER trial is a US and European phase II clinical trial that investigated the effectiveness and safety of tucatinib in combination with trastuzumab among 117 patients with HER2-positive inoperable (not eligible for surgery) or metastatic colorectal cancer. Patients had already received standard-of-care therapies but no prior anti-HER2 therapy. The combination of tucatinib and trastuzumab produced durable responses in patients, and the combination has the potential to become a new standard-of-care option.

How do tucatinib and trastuzumab work?

Tucatinib is an oral medicine that is part of a class of drugs known as tyrosine kinase inhibitors. The drug binds selectively to the HER2 protein and inactivates it, blocking cell growth signals necessary for tumour cells to proliferate. Trastuzumab binds to and inactives the HER2 receptor which is found on the surface of cells, therefore inhibiting the cell growth and proliferation. The combination of the two drugs showed better anti-tumour activity than either medicine alone.

READ THE FULL ARTICLE

[5] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy