NOVEMBER 2021

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 November 1st 2021 to November 30th, 2021 inclusive and are intended for informational purposes only

NOVEMBER 2021 PREVIEW

SYSTEMIC THERAPIES, SURGERY & SCREENING

First-line nivolumab plus low-dose ipilimumab for MSI-high/MMR-deficient mCRC

November 2021

Findings from phase II of the CheckMate-142 trial showed that the combination immunotherapy treatment of nivolumab (Opdivo) and low-dose ipilimumab (Yervoy) resulted in meaningful and long-lasting clinical benefit when used to treat patients with microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) as initial (first-line) therapy. The combination therapy is already approved for use as second-line therapy in this patient population.

Nivolumab is a targeted immunotherapy that blocks the interaction between a specific cell receptor and its partner molecule (ligand) on the surface of important cells of the immune system, known as T cells.

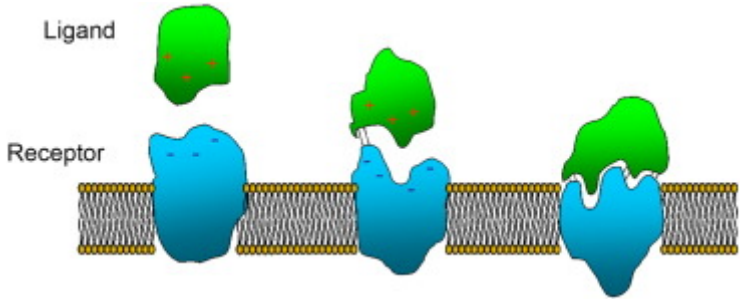

Image source: https://www.sciencedirect.com/science/article/abs/pii/S0928493116307469

When the receptor, known as PD-1, binds to its ligands (PD-L1 and PD-L2), the interaction results in inhibition of the immune system, including anti-cancer activity. In non-cancer states, this interaction is part of our immune system's natural self-regulating capacity, which prevents it from producing an excessive immune response that could potentially damage the body's own cells. However, cancer cells can benefit from this immune inhibition by producing greater numbers of the PD-1 ligands. As such, they can stimulate the continued inhibition of active T-cell immune surveillance and remain "invisible" to immune attack. Nivolumab is an antibody that binds specifically to the PD-1 receptor, blocking its interaction with its ligand. This activity lifts the inhibition on the immune system such that anti-tumour immune response can be restored and tumour growth can be reduced.

Ipimumab is an antibody that targets a specific protein (antigen) found on the surface of T cells known as CTLA-4. When the drug binds to CTLA-4, this stimulates T cell activation and proliferation, which contributes to T cell mediated anti-tumour activity.

The study

CheckMate-142 trial enrolled patients who had MSI-H/dMMR mCRC who had not received any previous therapy for metastatic disease. Study participants received nivolumab plus low-dose ipilimumab. Breaks in treatment of less than 6 weeks were allowed to manage any treatment-related toxicities.

38% of participants had tumours with BRAF mutations, and 22% had tumours with KRAS mutations.

Disease control rate was 84% and objective response rate was 69%, with 13% of participants experiencing a complete response rate. Clinical benefit was seen regardless of participants' BRAF or KRAS mutation status. Grade 3-4 treatment-related adverse events occurred in 22% of patients, and 13% had to stop patients because of any-grade treatment-related adverse events. 10 patients died, 8 of which were due to disease and 2 due to toxicities.

Conclusion

The researchers conclude that nivolumab and low-dose ipilimumab showed robust and durable clinical benefit and was well tolerated as an initial therapy for MSI-H/dMMR mCRC. The confirmatory phase III trial, CheckMate-8HW is currently in progress.

Take away message:

For patients with MSI-H/dMMR mCRC, the combination therapy of nivolumab and low-dose ipilimumab showed robust and long-lasting responses as initial, first-line treatment.

READ THE ARTICLE

No survival benefit seen for young-onset metastatic colorectal cancer

November 2021

Study findings published in the *Journal of the National Cancer Institute* found that overall survival was not significantly different between young onset colorectal cancer (yoCRC) and older-onset CRC.

For the study, 2,326 patients who were enrolled in a multicenter, randomized trial of first-line chemotherapy plus targeted therapies were evaluated. At the study start time, 514 patients (22.1%) were younger than 50 years (yoCRC group).

The study

Average overall survival did not differ significantly between yoCRC and older-onset patients (27.07 vs. 26.12 months, respectively). The average progression-free survival was also similar – 10.87 vs 10.55 months, respectively. The shortest overall survival was seen among patients who were younger than 35 years, with average overall survival of 21.95 months and progression free survival of 9.33 months compared to 26.12 and 1055 months, respectively, in older-onset patients.

Despite younger patients having more favourable baseline characteristics such as performance status (a measure of how well a person is able to carry on with their ordinary daily activities while living with cancer – it provides an estimate of what treatments a person may tolerate), more physical activity, and more left-sided primary tumours which is associated with better disease outcomes, the study data showed that there was not survival benefit for yoCRC patients. The researchers suggest that this may be a result of diagnosis at more advanced stages, differences in underlying tumour biology, or other unknown factors.

Deeper investigation into the clinical characteristics, tumour biology, and best treatment protocols for patients with early age onset disease is currently underway.

Take away message:

Despite more favourable characteristics such as better performance status, physical activity, and primarily left-sided tumours, survival was not significantly different among patients with mCRC younger than 50 years compared to those aged 50 years or older.

READ THE ARTICLE

Underrepresentation in cancer clinical trials

November 2021

Findings from a recent study published in *JAMA Network Open* demonstrated that people of colour are vastly underrepresented in breast, colorectal, lung, and prostate precision oncology clinical trials in the US. The study highlights an urgent need to improve the enrollment of more diverse populations such that all individuals may benefit from breakthroughs in cancer research and personalized therapies.

The Study

In the study, the clinicaltrials.gov registry was searched for US-based clinical trials by cancer type (breast, colorectal, lung, and prostate), that incorporated precision medicine objectives including DNA sequencing, tumour analysis, tumour mutational burden, and genetic testing. Eligible studies were then evaluated for their reporting of racial and ethnic demographic data.

US cancer incidence data by race and ethnicity was collected from the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) database.

Findings

197 clinical trials that met precision oncology measures were examined for race and ethnicity analysis. Of the 197 studies, 93 presented the appropriate data while 104 studies did not report any information about race and ethnicity.

Of the 93 studies, 5867 patients were enrolled:

- 4826 (82.3%) were non-Hispanic White
- 587 (10.0%) were Black
- 238 (4.1%) were Asian
- 200 (3.4%) Hispanic participants
- 16 (0.3%) were American Indian/Alaskan Native

In all precision oncology studies, observed participation to expected participation (based on cancer burden) by race and ethnicity was 1.35 and 1.46 for White and Asian participants (overrepresented). Black participants were substantially underrepresented with an observed to expected ratio of 0.49, Hispanic participants with a radio of 0.24, and American Indian/Alaskan Natives with a ratio of 0.43.

Examining by cancer type, White participants were overrepresented across all cancer types. Asian participants were overrepresented in lung, colorectal, and breast studies. Black and Hispanic participants were underrepresented across all cancer types. American Indian/Alaskan Native participants were represented in very small numbers, therefore are not shown by cancer type.

Conclusions

This study underlines the urgent need to increase recruitment of diverse participants in cancer clinical trials to better understand how treatment outcomes vary according to racial and ethnic differences. While the field of oncology is rapidly migrating towards a personalized medicine approach based on the analysis of tumour biomarkers and genetic/genomic variations, there is a far more limited understanding of the variations in underlying cancer biology among different racial and ethnic groups. This impacts the true generalizability of cancer clinical research to the population at large, and asks the important question of whether all individuals are benefitting equally from cancer research breakthroughs.

However, there are many different barriers to increasing enrollment across more diverse patient groups. Individuals from underrepresented groups' willingness to participate in clinical research comes from the perceived trustworthiness of the researchers, the institutions that conduct that research, and the information provided about the research studies.

A study that examined African American and Hispanic perspectives on precision medicine found that, while both groups believed that precision medicine can improve health outcomes, both were concerned that the existing disparities in health care access and quality would prevent their communities from benefiting from precision medicine[1].

Strategies for increasing more diverse participation in cancer clinical trials include programs dedicated to patient navigation, patient education about genetics and genetic testing, novel trial designs, increasing diversity among the actual scientists, researchers and clinical trial staff could help to increase trust among participants. Furthermore, better reporting of racial and ethnic demographic data must improve such that the monitoring of any improvements to diversity and representation can be properly observed over time and can serve as the basis for future comparative analyses.

Take away message:

Findings from a recent study highlighted the underrepresentation of people of colour in precision medicine clinical trials in the US. Targeted strategies to address the lack of diverse participation in cancer clinical trials are much needed, to ensure more generalizable health data and benefit from cancer research breakthroughs for all individuals.

READ THE FULL ARTICLE

Long-term outcomes with chemoradiotherapy before vs after chemotherapy in total neoadjuvant therapy for locally advanced rectal cancer

November 2021

Total neoadjuvant therapy (TNT) is an approach to treatment for locally advanced rectal cancer (LARC) that delivers both systemic chemotherapy and chemoradiotherapy before surgery to improve pathologic complete response rate, survival rate, and metastasis-free survival. It is an experimental treatment (it is not the standard of care for patients with LARC) and safety and efficacy continue to be assessed in the setting of clinical trials.

A recent phase II study aimed to determine the optimal sequencing of chemoradiotherapy and chemotherapy as part of TNT for patients with LARC.

The study

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1 Yeh VM, Bergner EM, Bruce MA, et al. Can precision medicine actually help people like me? African American and Hispanic perspectives on the benefits and barriers of precision medicine. *Ethn Dis*. 2020;30(suppl 1):149-158. doi:10.18865/ed.30.S1.149

The phase II study involved an analysis of data from 3111 patients with LARC, who were randomly assigned to receive a chemotherapy/chemoradiotherapy sequence consisting of three cycles of 5-FU, leucovorin, and oxaliplatin followed by 5-FU/oxaliplatin plus radiotherapy, or chemoradiotherapy followed by chemotherapy.

Previously reported results from the trial showed that chemoradiotherapy followed by consolidation chemotherapy was linked to better complete pathologic response (25% vs 17%). The long-term outcomes at 3 years showed that disease-free survival, local recurrence rate, incidence of distant metastasis, and overall survival were essentially the same with chemoradiotherapy before vs. after chemotherapy. Furthermore, no differences in chronic toxicity or quality of life were observed.

Conclusion

Chemoradiotherapy followed by chemotherapy resulted in higher pathological complete response rate without compromising disease-free survival, toxicity, or quality of life and is therefore proposed as the preferred TNT sequence when organ preservation is a priority.

Take away message:

Chemoradiotherapy followed by chemotherapy as part of total neoadjuvant therapy in the treatment of patients with locally advanced rectal cancer was shown to be the preferred sequence of treatments to promote better pathological complete response, without negatively affected disease-free survival, long-term toxicity, and overall health status and quality of life.

READ THE FULL ARTICLE