

CO.23: Napabucasin for patients with advanced colorectal cancers

The CO.23 trial has helped researchers explore an important health question on improving treatment for cancer patients. It tested the effect of napabucasin in people with advanced bowel cancer. Napabucasin is sometimes called Napa, and was previously called BBI-608.

We appreciate the part played by our volunteer participants. This may help to improve medical treatment for patients in the future. Here is a summary of the trial and results.

What was the trial about?

The CO.23 trial was conducted in Canada, Australia, New Zealand and Japan.

Napabucasin is a new type of cancer drug. It acts against specific cancer cells—the cancer stem cells. These cells may be responsible for the growth and spread of the tumour. These cells also help tumours resist chemotherapy.

In earlier studies with a small number of participants, napabucasin had reduced the growth of some bowel cancers. For this reason, it was considered worth testing in a clinical trial.

Most patients recruited to the CO.23 trial had already had more than four types of treatment. They had undergone all the standard chemotherapy treatments, but their cancers continued to grow, and their only option was supportive care, that is, treatment to improve quality of life.

Trial participants were allocated to napabucasin tablets twice a day or to matching placebo tablets. Patients, doctors and others involved in the trial were not aware of an individual patient's treatment group.

The study was designed to have 650 participants. The data were collected gradually as they joined the trial. Several analyses of data at different points in the trial were planned.

As planned, the investigators analysed the data after the first 96 patients had received treatment for 10 weeks. This was long enough to show whether the drug would control the size of the tumour.

This analysis showed that there was not enough difference in tumour control between the napabucasin group and the placebo group to warrant recruiting more patients.

The trial was stopped. Patients were allowed to continue on napabucasin if their doctors thought this was beneficial.

By this time, the trial had 282 patients—138 on napabucasin and 144 on placebo. Their average age was 64 years, ranging from 32 to 85 years. 65% were men.

No significant differences between the two treatment groups were found.

How was the effect of treatment measured?

The patients' survival was the main measure. The researchers also measured quality of life, any change in the size of the tumour, and progression-free survival—that is, the time between the participant's entry into the trial until the disease became worse.

Patients had a clinic visit and scans every 4 weeks and also completed questionnaires on their quality of life every 4 weeks.

Was the new treatment better?

Because it stopped early, the trial was not able to detect a significant difference in overall survival related to napabucasin.

However, tumour samples had been tested in the laboratory. Some patients had a positive test on their cancer tissue for a particular biomarker—pSTAT3. Napabucasin treatment was found to improve their survival. This suggests that there

may be a place for napabucasin for selected patients .

What were the side-effects of the treatment?

The side-effects of the study drug were as expected from previous research. More people in the napabucasin group had a medical problem. The most common was diarrhoea (88%). They also had more nausea and loss of appetite. Some of these events were mild and did not need any treatment.

Were there any serious side-effects?

About half of the participants were admitted to hospital for a serious event. There were more in the napabucasin group than placebo group. In particular, more of those on napabucasin had severe diarrhoea: 17% compared with 1% of placebo patients. The diarrhoea was considered due to the drug.

What does this mean for trial patients?

Patients who had the positive molecular biomarker, pSTAT3, survived longer if they took napabucasin compared with placebo.

The trial did not show that the drug improved survival on average.

How will the results help patients and doctors in future?

The information that came out of the CO.23 trial, with data from studies of treatments that combine napabucasin with other drugs, have added knowledge about the potential of this drug for patients with advanced colorectal cancer.

What will the researchers do next?

Some analyses, such as quality-of-life reports, have not been completed yet.

The blood samples and tumour tissue provided by CO.23 patients, with their permission, will be used to look for individual biological differences that might have affected a patient's progress.

The samples will also be used in laboratory research to learn more about bowel cancers and how napabucasin works.

Where can I find out more about the trial?

Talk with your GP or oncologist.

The results have been presented at a scientific conference:

Jonker DJ, Nott L, and others. A randomized phase III study of napabucasin [BBI608] vs placebo in patients with pretreated advanced colorectal cancer: the CCTG/AGITG CO.23 trial. *European Society for Medical Oncology 41st Congress*; Oct 2016; Copenhagen. Summary attached.

Trial registration

Australian New Zealand Clinical Trials Registry
www.anzctr.org
registration number [12613000556741](https://www.anzctr.org.au/Trial/Registration/Trial.asp?id=12613000556741)

Australasian Gastro-Intestinal Trials Group

[Link](#) to summary of the trial in Australia.

The trial was sponsored by the Canadian Cancer Trials Group and the Australasian Gastro-Intestinal Trials Group and was funded by the Canadian Cancer Society and Boston Biomedical Inc. (which developed napabucasin).

The authors report no conflicts of interest.

Results of any clinical trial do not represent complete knowledge about treatment. Patients should not change their therapy on their understanding of the results.

Background: NAPA is a first-in-class cancer stemness inhibitor that targets STAT3, with promising activity in early trials.

Methods: Pts with ACRC who had failed all available standard therapy were randomized 1:1 to NAPA 480mg po q12h or PBO. Primary endpoint was overall survival (OS). Pre-specified biomarker analyses included pSTAT3 positivity by IHC in archival tissue based on nuclear staining of cancer cells >5% and stroma $\geq 2+$. The study, designed to enrol 650 pts, was stopped after a futility analysis on disease control rate (DCR) in the first 96 pts. Analyses included Intent-to-treat (ITT) and exploratory Pre-defined Minimum Effective Treatment (pts who received $\geq 50\%$ total daily dose for ≥ 6.4 weeks).

Results: 282 pts were randomized (138 NAPA, 144 PBO) from 04/2013 - 05/2014 when the trial was unblinded, accrual closed, and protocol treatment stopped after the futility analysis. Pts were median age = 64 (32 to 85); male = 65%; ECOG 0:1 (%) =28:72; >4 prior regimens = 98%; prior anti-VEGF = 89%; KRAS WT = 52%. No significant difference was observed in OS, progression free survival (PFS) or DCR between NAPA and PBO in the ITT analysis. AE more frequent with NAPA included: any grade diarrhea (88 vs 32%), nausea (63 vs 47%), and anorexia (56 vs 46%), all $p < 0.05$; at least one AE \geq grade 3 (57% vs 40%, $p < 0.01$) with grade 3 (no grade 4) diarrhea (17% vs 1%, $p < 0.01$). Diarrhea was reversible upon NAPA hold. EORTC QLQ-C30 physical function at 8 wk deteriorated in 49% of pts on NAPA vs 29% on PBO ($p = 0.038$). Of 251 (89%) pts with pSTAT3 data, 55 (22%) were positive. In pts on PBO, pSTAT3 positivity was a poor prognostic factor (median OS 3.0 vs 4.9 mo, HR 2.3 [95% CI 1.5-3.6], $p = 0.0002$), but NAPA improved OS in pSTAT3 positive pts, HR 0.24.