

# **STIMULI – A randomised open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage Small Cell Lung Cancer after chemo-radiotherapy**

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This is a short summary of the results from the STIMULI trial. The STIMULI trial was designed to learn if adding immunotherapy (ipilimumab and nivolumab) after standard treatment with chemotherapy and radiation therapy could improve progression free survival (PFS; the time taken until cancer regrowth) in patients with limited stage (affecting one lung only) small cell lung cancer. We thank the 222 people who took part in the trial (including 5 in Australia), their families, doctors, and others who helped run the trial at 52 international hospitals. Their contributions have helped us learn more about how to treat this condition.

## **What was the trial about?**

Small cell lung cancer is a rare but aggressive form of lung cancer. Limited stage small cell cancer is treated with a combination of chemotherapy and radiation therapy to the tumour. This type of cancer frequently comes back in the brain, so preventative brain radiation is also given to patients. Despite good response to chemotherapy and radiation therapy at first, a large proportion of patients go on to develop progression (cancer regrowth) after they finish treatment.

There is evidence to suggest that combining immunotherapy and chemotherapy in patients with more advanced small cell lung cancer improves survival. Following on from this, the STIMULI trial was designed to see whether adding immunotherapy after combined chemotherapy and radiotherapy in limited stage cancer could improve PFS. People who completed standard treatment for limited stage small cell lung cancer were randomly allocated to receive either immunotherapy (ipilimumab and nivolumab), or observation.

The primary outcome was PFS. Other outcomes measured included the amount of tumour shrinkage (response rate), overall survival, and side effects.

## **How well did adding immunotherapy work?**

The results of the STIMULI trial showed no significant difference between the immunotherapy and observation groups. Overall, there was no difference in the percentage of people with cancer progression at 12 and 24 months after starting immunotherapy or observation. There was also no difference in the percentage of people alive at 24 months, and the amount of tumour shrinkage was no different between the two groups. There was some data to suggest that immunotherapy after a more frequent radiotherapy schedule may be more effective, but this needs to be studied further.

## **What were the side-effects of the treatment?**

Side effects were more commonly seen in the immunotherapy group than the observation group. The most common side effect was fatigue with half of patients in the immunotherapy group reporting this. Vomiting and diarrhoea, overactive thyroid, cough, and itchy skin were reported in 25 to 30% of people who received immunotherapy. Four (5%) people who received immunotherapy died: 2 developed a lung reaction to immunotherapy, 1 patient developed bowel paralysis, and 1 had an unspecified cause. One person died in the observation group due to a lung infection.

### **How will the results help patients and doctors in future?**

The results of the STIMULI trial helped to increase knowledge about how best to treat limited stage small cell lung cancer. The results suggest adding ipilimumab and nivolumab after standard treatment does not improve cancer control, survival, or response in limited stage small cell lung cancer. This study also shows that how radiotherapy is given may be an important aspect of treating small cell lung cancer and this needs to be researched.

### **What are the researchers going to do next?**

There needs to be a better understanding about how genes and the immune system are involved in small cell lung cancer in order to improve treatment. The blood and tumour samples kindly donated by patients on the STIMULI trial will be used to study this further.

### **What does this mean for me?**

The results of the STIMULI study did not show a benefit to adding ipilimumab and nivolumab after chemo-radiotherapy for people with limited stage small cell lung cancer. The results of a single trial do not represent complete knowledge and treatment should not be based on the results of this study alone. There is ongoing research about cancer and how to treat it, and any treatment should be discussed with your treating doctor.

### **Where can I find out more about the trial?**

More details about the trial are available on:

- NHMRC Clinical Trials Centre website at <https://ctc.usyd.edu.au/our-work/research-divisions/cancer/cancer-divisions/lung-cancers/closed/stimuli/>
- Australian and New Zealand Trials registry at <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374916&isReview=true>
- Thoracic Oncology Group of Australasia (TOGA) website at <https://thoraciconcology.org.au/clinical-trials/>

### **Sponsor, funding, and conflicts of interest**

This study was an international study led by the European Thoracic Oncology Platform (ETOP) group and run in Australia by the NHMRC Clinical Trials Centre in collaboration with the Australasian Lung cancer Trials Group (ALTG) / Thoracic Oncology Group of Australasia (TOGA). The trial was sponsored by the University of Sydney in Australia.

Bristol-Myers Squibb, the company that makes nivolumab and ipilimumab, provided drug and funding to help cover the costs of conducting this study.