NUTMEG: A Randomised Phase II Study of NivolUmab and TeMozolomide vs Temozolomide alone in newly diagnosed Elderly patients with Glioblastoma

The NUTMEG trial was a randomised multi-national phase II study, testing the efficacy of adding immunotherapy to standard treatment in elderly patients with newly diagnosed glioblastoma. Patients were recruited in Australia between 2018 and 2021

We sincerely thank the participants, their caregivers and families and all staff members who contributed to the trial. Here is a summary of the trial and results.

What was the trial about?

Glioblastoma is the most common primary brain cancer in adults, making up 50% of all central nervous system tumours. Targeting of the immune system is one potential mechanism of therapeutic advance in glioblastoma. Glioblastoma tumour cells have been shown to express PD-L1, the immune suppressive marker that is expressed by multiple immune cells. Monoclonal antibodies against PD-L1 and its corresponding surface marker, PD-1, have demonstrated efficacy in other solid tumours.

The CheckMate-498 trial previously evaluated the efficacy of adding nivolumab, the anti-PD-L1 antibody, to standard treatment of *MGMT* unmethylated glioblastoma whilst CheckMate-548 evaluated the efficacy of adding nivolumab to treatment of *MGMT* methylated glioblastoma.

Older glioblastoma patients, despite making up a significant proportion of all glioblastoma cases, have a worse prognosis. There is an increase in tumour mutational burden in older patients, a factor that is associated with improved responses to immunotherapy with drugs targeting the PD-L1/PD-1 axis. Therefore, adding nivolumab to standard therapy in older glioblastoma patients is postulated to have therapeutic efficacy that is not seen in the general population.

How will the results help glioblastoma patients and their treating doctors in future?

The results did not support adding nivolumab to standard treatment for older patients. The addition of nivolumab did not show any unexpected signals of toxicity. All patients who had severe (Grade 3) immune toxicities resolved, with no unexpected serious adverse events. Although the trial did not proceed to a larger phase III trial on this basis, the results from this trial will inform future trials and potentially influence patient selection in ongoing immunotherapy trials in glioblastoma.

What will the researchers do next?

The NUTMEG trial is now closed. The results will inform the design of future trials in this field. More specifically, the interpretation of imaging results in patients receiving immunotherapy in glioblastoma will be a key outcome of the trial. Correct interpretation of MRI imaging done in glioblastoma patients undergoing immunotherapy is of key interest in ongoing trials of novel agents. Analysis of MRI scans acquired during the NUTMEG trial will inform this interpretation.

The final results of the NUTMEG study have been widely shared:

Society for Neuro-Oncology Annual Meeting 2022
Sim H-W, Lwin Z, Barnes E, McDonald K, Yip S, Verhaak R, Heimberger A, Hall M, Wong M, Jennens R, Ashley D, Rosenthal M, Hovey E, Ellingson B, Tognela A, Gan H, Back M, Koh E-S, Long A, Cuff K, Begbie S, Gedye C, Mislang A, Le H, Johnson M, Kong B, Simes J, Khasraw M. "CTIM-24 NUTMEG: A randomized phase II study of nivolumab and temozlomide alone in newly diagnosed elderly patients with glioblastoma". Neuro-Oncology Vol 24 (Suppl_7) Nov 22; vii65

Publication
Sim H-W, Wachsmuth L, Barnes EH, Yip S, Koh E-S, Hall M, Jennens R, Ashley DM, Verhaak RG, Heimberger AB, Rosenthal MA, Hovey EJ, Ellingson B, Tognela A, Gan HK, Wheeler H, Back M McDonald KL, Long A, Cuff K, Begbie S, Gedye C, Mislang A, Le H, Johnson MO, Kong BY, Simes JR, Lwin Z, Khasraw M "NUTMEG: A randomized phase II study of nivolumab and temozolomide versus temozolomide alone in newly diagnosed older patients with glioblastoma" Neuro-Oncology Advances 5(11) 1-12, 2023.

Trial registration:
Australian New Zealand Clinical Trials Registry
Registration number: ACTRN12617000267358
https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372290
Cooperative Trials Group for Neuro-Oncology (COGNO):
https://cogno.org.au/content.aspx?page=currenttrials

The sponsor of the NUTMEG trial was The University of Sydney. The trial was a collaboration between the Cooperative Trials Group for Neuro-Oncology (COGNO) and the National Health and Medical Research Council Clinical Trials Centre (NHMRC CTC). The study was partially funded by an Australian Government grant from The National Health and Medical Research Council (NHMRC), Grant # APP1125204 and Bristol-Myers Squibb Pty Ltd (BMS).

Some authors of the NUTMEG trial have received research funding or have had advisory roles for the pharmaceutical industry.