GCT-03. MonoGerm, a novel proof-of-principle Bayesian phase II trial design of carboplatin or vinblastine monotherapy induction prior to radiotherapy for intracranial germinoma [Abstract]

Laura Kirton, John R. Apps, Anna Lawson, Theodoros Arvanitis, Dipayan Mitra, Richard Gagen, Hiten Patel, Andrew Peet, Lorna Fern, Emma Williams, Nicholas Coleman, Thankamma Ajithkumar, Brigitte Bison, Gareth Veal, Daniel P. Stark, Giovanni Morana, James C. Nicholson, Lucinda Billingham, Matthew J. Murray

Angaben zur Veröffentlichung / Publication details:

Kirton, Laura, John R. Apps, Anna Lawson, Theodoros Arvanitis, Dipayan Mitra, Richard Gagen, Hiten Patel, et al. 2024. "GCT-03. MonoGerm, a novel proof-of-principle Bayesian phase II trial design of carboplatin or vinblastine monotherapy induction prior to radiotherapy for intracranial germinoma [Abstract]." Neuro-Oncology 26 (Supplement 4): iv76–77. https://doi.org/10.1093/neuonc/noae064.259.

ABSTRACT CITATION ID: NOAE064.259

GCT-03. MONOGERM, A NOVEL PROOF-OF-PRINCIPLE BAYESIAN PHASE II TRIAL DESIGN OF CARBOPLATIN OR VINBLASTINE MONOTHERAPY INDUCTION PRIOR TO RADIOTHERAPY FOR INTRACRANIAL GERMINOMA

Laura Kirton[1], John R. Apps[2], Anna Lawson[1], Theodoros Arvanitis[3], Dipayan Mitra[4], Richard Gagen[2], Hiten Patel[2], Andrew Peet[3], Lorna Fern[5], Emma Williams[6], Nicholas Coleman[7], Thankamma Ajithkumar[8], Brigitte Bison[9], Gareth Veal[10], Daniel P. Stark[11], Giovanni Morana[12], James C. Nicholson[8], Lucinda Billingham[1], Matthew J. Murray[7,8]; [1]Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, United Kingdom, [2]Birmingham Children's Hospital, Birmingham, United Kingdom, [3]University of Birmingham, Birmingham, United Kingdom, [4]The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom, [5]University College London Hospitals NHS Foundation Trust, London, United Kingdom, [6]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom, [7]Department of Pathology, University of Cambridge, Cambridge, United Kingdom, [8]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [9]University of Augsburg, Augsburg, Germany, [10]Newcastle University, Newcastle, United Kingdom, [11]University of Leeds, Leeds, United Kingdom, [12]University of Torino, Torino, Italy

BACKGROUND: Current European standard-of-care for localised intracranial germinoma is multi-agent chemotherapy (carboPEI: carboplatin/etoposide/ifosfamide) followed by definitive radiotherapy, with excellent survival. MonoGerm is a de-escalation, non-inferiority trial aiming to reduce toxicity. Twelve-week carboplatin (PMID:8039122) AUC10 or vinblastine (PMIDs:32642701/34520101) induction will be evaluated to test if as effective as carboPEI from SIOP-CNS-GCT-II. A novel trial design was

required to answer this question pragmatically/safely. METHODS: Clinical trials in rare diseases recruit slowly, allowing continuous monitoring of efficacy outcomes. Efficacy-transition-pathways (ETP) are innovative visual tools to aid determination of trial design parameters, and an extension of the dose-transition-pathways concept introduced for dose-finding trials (PMID:28733440). RESULTS: MonoGerm includes two monotherapies, with each single arm recruiting six cohorts of three patients, with interim assessment after each recruited cohort and final analysis at 18 patients (total n=36). Insufficient tumour volume response (<30%) at 6-week safety MRI results in 12-weeks carboPEI. Primary outcome is radiological complete response (CR) by 12-weeks of induction monotherapy. A beta-binomial conjugate analysis will generate posterior probability distributions, combining observed trial data as realisations from a binomial distribution with a minimally informative Beta (1,1) prior. Decision criteria to allow early stopping at interim analyses and go/no-go decisions at final analysis are based on probabilities from these posterior distributions. ETP visually maps out parameters used to assert decisions after each interim assessment as a pyramid decision tree. For each recruited cohort and every CR outcome, estimates of the true CR rate and probabilities with associated decisions are mapped out. ETP allows clear communication between statisticians, clinicians, and patient-public-involvement (PPI) teams, facilitating informed decisions in an efficient/realistic trial design. CONCLUSION: MonoGerm, a novel Bayesian de-escalation trial, funded by Little Princess Trust (https://www.littleprincesses.org.uk/), uses ETP and continuous monitoring with built-in stopping rules to ensure patient safety in this treatment de-escalation trial.