P67. DEFINING A TARGET INTRA-CEREBROSPINAL FLUID STEADY STATE ETOPOSIDE CONCENTRATION [CSF ETOPOSIDE] FOR PHASE I STUDY IN CHILDREN WITH LEPTOMENINGEAL METASTASIS (LM): INTREPID, A FIRST IN MAN STUDY

Lisethe Meijer, Gareth Veal, Richard Grundy, Wojciech Konczalik, Delyan Ivanov, Martin Garnett, Pamela Kearns, and David Walker; Children’s Brain Tumour Research Centre, University of Nottingham

INTRODUCTION: Continuous intra-CSF etoposide infusion may optimise etoposide pharmacokinetics by bypassing the blood-brain-barrier and compensating for CSF bulk flow removal, at less than 1/340th dose of standard regimens. A 3 + 3 phase I study is proposed, escalating target [CSF etoposide] and infusion durations of intra-CSF etoposide in children with LM. We justify target [CSF etoposide] and infusion durations based upon previously reported clinical and our own preclinical studies. METHOD: AUC24 values were calculated from Fleischhack report of 24 patients receiving intra-ventricular etoposide at 0.25 mg/12h, 0.5 mg/24h or 1 mg/24h, for 5 days, q 2-4 wks (n = 119 cycles), no dose limiting toxicity was reported. The AUC24 values derived from these clinical studies were compared to etoposide cytotoxicity data in human tumour and neural stem cell 3D co-cultures. AUC values were selected to derive target [CSF etoposide], levels 1 & 2 for infusion durations of 7, 10 and 14 days: AUC24 = [CSF etoposide] x time (h). RESULTS: Based upon 0.25 mg/12h dose level, the AUC24 25 μg x h/ml (level 1) predicted [CSF etoposide] 1 μg/ml over 24 hours and an AUC7day of 175 μg x h/ml. The cytotoxicity assay [etoposide] of 0.8-1.2 μg/ml resulted in 22% neural stem cell and 8% tumour cell viability, illustrating differential toxicity. Level 1 [CSF etoposide] was selected as 0.8 μg/ml as equivalent of AUC24 20, for 7 days (AUC7day 140). Level 2 [CSF etoposide] of 1.2 μg/ml was selected, (AUC7day 210, AUC10days 300; AUC14day 420); CONCLUSION: Target [CSF etoposide] will be 0.8 μg/ml (level 1) to 1.2 μg/ml (level 2), with infusion durations of 7, 10 or 14 day.