A Phase 1 Trial of Deflexifol™ in Pediatric Patients with Relapsed or Refractory Brain Tumors

Marion K. Mateos[1,2], Joanne Chuah[3], Laura Mitchell[3], Chelsea Mayoh[2,4], Santosh Valvi[5,6], Timothy Hassall[7,8], Michelle Martin[9], Jordan R. Hansford[10,11], Dong-Anh Khuong-Quang[12,13], David S. Ziegler[1,2]

[1]Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia; [2]Children's Cancer Institute, Lowy Cancer Research Centre, UNSW Sydney, Sydney, Australia; [3]Kids Oncology and Leukaemia Trials, Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia; [4]School of Clinical Medicine, UNSW Sydney, Sydney, Australia; [5]Department of Paediatric and Adolescent Oncology/Hematology, Perth Children's Hospital, Nedlands, Australia; [6]Brain Tumour Research Program, The Kids Institute Australia, Nedlands, Australia; [7]Children's Brain Cancer Centre, Frazer Institute, University of Queensland, Brisbane, Australia; [8]Queensland Children's Hospital, Children's Health Queensland Hospital and Health Service, Queensland Government, South Brisbane, Australia; [9]Monash Children's Cancer Centre, Monash Health, Clayton, Australia; [10]Michael Rice Centre for Haematology and Oncology, Women's and Children's Hospital, Adelaide, Australia; [11]South Australia Health and Medical Research Institute; South Australian immunoGENomics Cancer Institute, University of Adelaide, Adelaide, Australia; [12]Children's Cancer Centre, Royal Children's Hospital, Melbourne, Australia; [13]Murdoch Children's Research Institute, Melbourne, Australia

Background

- Deflexifol™* is a novel co-formulation of 5-fluorouracil (5-FU) and its biomodulator leucovorin (LV), allowing for co-delivery in one infusion (1).
- 5-FU has documented activity in pediatric ependymoma (2).
- **Hypothesis:** *That Deflexifol will enhance efficacy and reduce toxicity, enabling higher active doses within the brain (Fig 1).*
- **We report results of the phase 1 component of a first-in-child Phase 1/2 trial# of Deflexifol, for relapsed or refractory brain tumors including ependymoma**

Aims

- **Primary:**
- Determine the safety, including dose-limiting toxicities (DLT) of Deflexifol in children and young adults with refractory or recurrent CNS tumors, or newly diagnosed diffuse intrinsic pontine glioma (DIPG)/diffuse midline glioma (DMG) following radiotherapy.
- **Secondary:**
- (i) determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of Deflexifol in children
- (ii) characterise pharmacokinetics (PK) of Deflexifol monotherapy in blood
- iii) characterise PK of Deflexifol in cerebrospinal fluid (CSF).

Methods

- Children (aged 1-21 years) with relapsed or refractory brain tumors were eligible for Phase 1 enrolment, using a rolling 6 design.
- Intravenous Deflexifol was administered on **Days 1-3 and Days 15-17** of a 28-day cycle, as a **bolus followed by a 46-hour infusion**.
- The starting dose (Dose level 0) was a 525mg/m^2 bolus (of delivered 5-FU) and 3400mg/m^2 infusion, with pre-defined dose levels (Fig 2).
- The MTD was determined based on cycle 1 dose-limiting toxicity (DLT) (Common Terminology Criteria for Adverse Events, v5.0). Pharmacokinetic samples were collected.

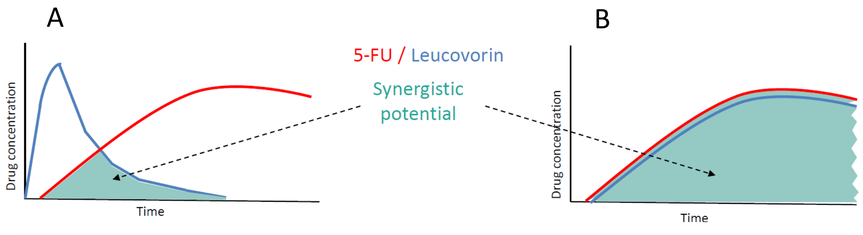

Fig 1: ***Deflexifol Rationale****: Current clinical formulations of 5-FU and LV are chemically incompatible and must be administered separately, leading to limited co-exposure (Panel A). Concurrent delivery via Deflexifol enables maximal 5-FU/LV synergistic potential (Panel B).*

Dose Level	Bolus Dose	Infusional Dose
-2	525 mg/m²	2400 mg/m²
-1	525 mg/m²	3000 mg/m²
0 (starting)	525 mg/m²	3400 mg/m²
+1	525 mg/m²	3800 mg/m²

Fig 2: ***Dosing Schema***

Reference

(1) Clingan et al., First-in-human phase I study of infusional and bolus schedules of Deflexifol, a novel 5-fluorouracil and leucovorin formulation, after failure of standard treatment. Asia-Pacific Journal of Clinical Oncology; 2019 3(15):151-157

(2) Wright, K.D., et al., Phase I study of 5-fluorouracil in children and young adults with recurrent ependymoma. Neuro-oncology, 2015. 17(12): 1620-1627

Results

Patients, adverse events (AEs) and DLTs

- Nine participants (aged 4-14 years), with ependymoma (n=6), DMG (n=2) and ETMR (n=1) enrolled (Fig 3).
- At the starting dose, two of three participants experienced DLTs of Grade 3 oral mucositis and Grade 4 neutropenia. Six participants were enrolled at Dose level -1 (525mg/m^2 bolus and 3000mg/m^2 infusion), with one DLT of Grade 4 neutropenia.
- Grade 3 and 4 treatment-related AEs (non-DLTs): neutropenia (14 occurrences), leucopenia (4), febrile neutropenia (3), oral mucositis (2) and palmar-plantar erythrodysesthesia syndrome (2). No participants discontinued treatment due to toxicity (Fig 4).

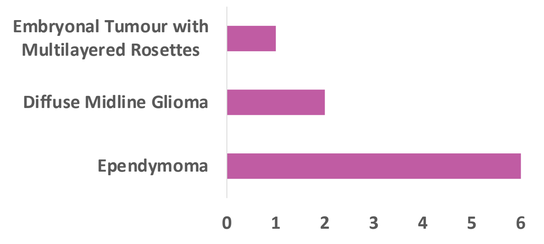

Fig 3: ***Diagnoses***

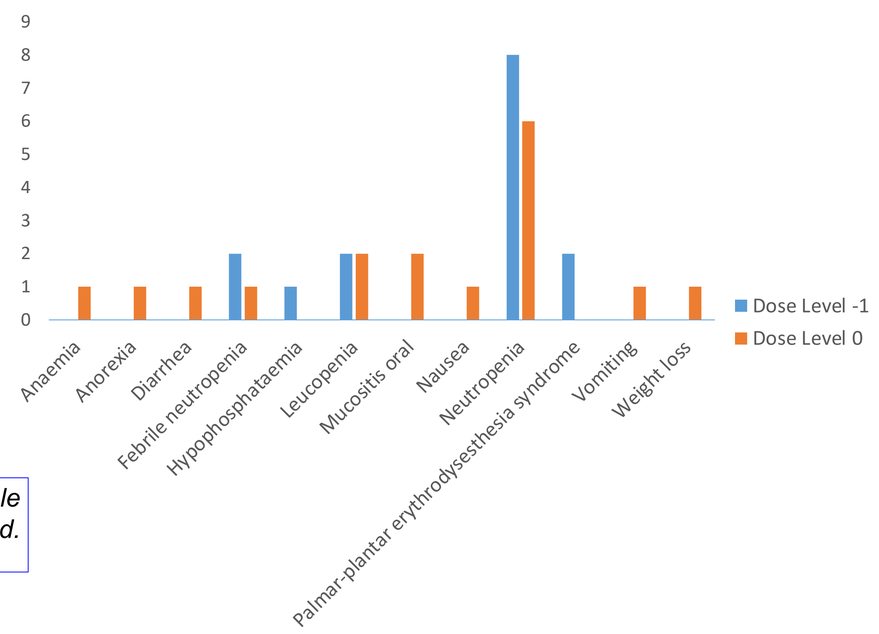

Fig 4: ***Grade 3/4 AEs.*** *Definite, probable or possible causality to Deflexifol, stratified by dose level assigned.*
Y-axis: Number of events per AE

Pharmacokinetics (PK)

- PK blood samples on Cycle 1 Days 1 & 15. No CSF was collected.
- PK analysis using non-compartmental methods and a linear-trapezoidal approach, Phoenix® WinNonlin® Version 8.5.2.4 (Fig 5). Quantification for 5-FU, metabolite dihydrofluorouracil (DHFU) and leucovorin.
- 5-FU and LV maximal concentrations at the end of the bolus injection, with a 5-FU half-life of 15 minutes. 5-FU was rapidly converted to DHFU.
- Steady-state was achieved within the first few hours of the infusion with comparable concentrations across timepoints for 5-FU ((Fig 5), leucovorin, and all analytes.

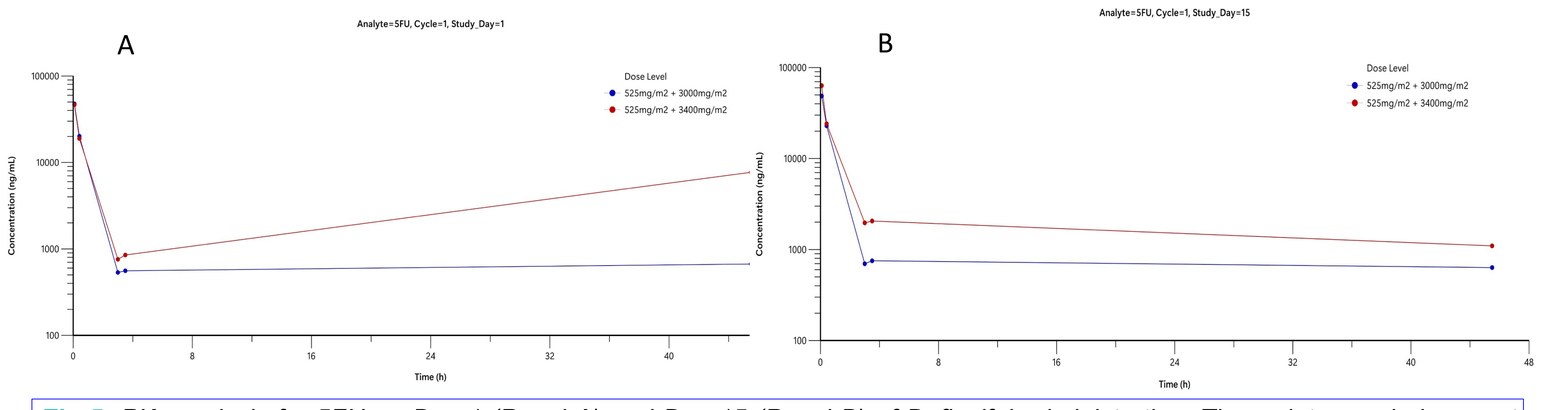

Fig 5: PK analysis for 5FU on Day 1 (Panel A) and Day 15 (Panel B) of Deflexifol administration. Timepoints: pre-bolus, post bolus, pre-infusion, 2.5 hours post infusion, 3 hours and 45 hours post infusion

Conclusions

- Pediatric Deflexifol MTD & RP2D are **525mg/m^2 bolus and 3000mg/m^2 infusion, ~**90% of the adult MTD.
- Deflexifol is well tolerated in children. PK results for 5-FU were similar to a prior report in children (2). A Phase 2 expansion cohort is planned to evaluate the activity of Deflexifol in children with ependymoma.

Acknowledgements

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Contact details: Dr Marion Mateos, m.mateos@unsw.edu.au