#140: A phase I dose-escalation study of an all-in-one 5-fluorouracil and leucovorin co-formulation administered after failure of standard treatment

Daniel Brungs[1], Jonathon Hill[1], Morteza Aghmesheh[1], Stephen P. Ackland[2], Suzanne Parker[1], Rebecca M. Jokela[1], Madhu Bala Garg[2], Stephanie E Reuter[3], Tahlia R Meola[3], Marie Ranson[4], R David Ranson[5], Christian D Toouli[5], Natalie Strange[5], Philip R Clingan[1]

[1]Wollongong Cancer Care, NSW, Australia; [2]Calvary Mater Newcastle, NSW, Australia; University of Newcastle, NSW, Australia; [3]University of South Australia, SA, Australia; [4]University of Wollongong, NSW, Australia; [5]FivepHusion, NSW, Australia

BACKGROUND

- **5-fluorouracil (5-FU)** and **leucovorin (LV)** are the backbone of therapy for colorectal cancer
- 5-FU and LV act synergistically but are administered sequentially due to being chemically incompatible; this may limit anti-tumor efficacy, whereas simultaneous administration is expected to enhance the efficacy of the agents **(Figure 1)**
- **Deflexifol** is an all-in-one injectable fixed-dose co-formulation of 5-FU/LV at physiological pH
- An initial phase I trial demonstrated the safety and efficacy of Deflexifol when administered as a bolus or infusion, with a maximum tolerated dose (MTD) for 5-FU of ≥25% more than established for standard regimens[1]
- This subsequent phase I study sought to investigate Deflexifol administered as a combined bolus and infusion schedule. *Clinical trial information: ACTRN12619001533189*

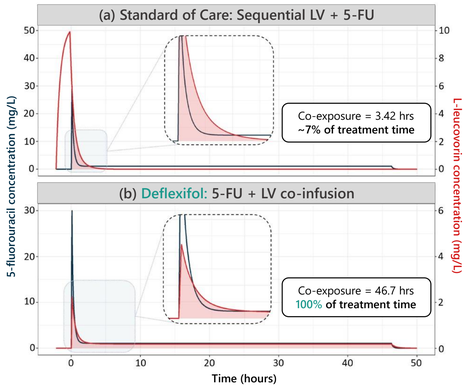

*Figure 1. Predicted 5-FU (blue) and L-LV (red) concentration-time profiles for **(a)** standard administration (400 mg/m² LV + 400 mg/m² bolus 5-FU + 2400 mg/m² 5-FU 46-hr infusion) vs. **(b)** Deflexifol bolus + infusion administered at the equivalent doses of 5-FU. The predicted period of synergy is illustrated in red shading. Modelled using published data[2,3].*

METHODS

- Patients with advanced malignancy who had failed standard treatment were administered Deflexifol as a bolus followed by a continuous 46-hr infusion, every two weeks
- The infusional dose was escalated across four levels using a traditional 3+3 design & the bolus dose was fixed at the previously declared MTD[1] **(Table 1)**
- The primary objective was to determine safety & tolerability of a bolus + infusion regimen. Secondary objectives were pharmacokinetics and MTD. Efficacy was an exploratory objective

Table 1. Dose levels of Deflexifol administered in the study, escalated using a standard 3+3 design.

Dose Level	Bolus dose (fixed)	Infusion dose (dose-escalation)
1	525 mg/m² 5-FU + 35 mg/m² LV	2400 mg/m² 5-FU + 160 mg/m² LV
2		3000 mg/m² 5-FU + 200 mg/m² LV
3		3400 mg/m² 5-FU + 227 mg/m² LV
4		3800 mg/m² 5-FU + 253 mg/m² LV

RESULTS

PATIENT ENROLMENT & CHARACTERISTICS

- Nineteen relapsed or refractory patients with mostly colorectal (n=13) and breast (n=4) cancers were enrolled **(Table 2)**
- Most patients (74%) had previously received systemic treatment with fluoropyrimidines, including intravenous (i.v.) 5-FU (58%)

Table 2. Characteristics of trial participants by enrolled cohort.

Characteristic	Dose Level 1 (n=3)	Dose Level 2 (n=7)*	Dose Level 3 (n=7)	Dose Level 4 (n=2)	Total (n=19)
Age (years)#	57.3 ± 11.9	68.5 ± 8.6	62.5 ± 11.5	63.3 ± 4.1	64.0 ± 10.0
Sex					
Male	2	1	4	1	8 (42%)
Female	1	6	3	1	11 (58%)
Primary tumor					
Colorectal	2	4	5	2	13 (68%)
Breast	1	2	1		4 (21%)
Pancreatic		1			1 (5%)
Oropharyngeal			1		1 (5%)
Prior fluoropyrimidine	3	4	5	2	14 (74%)
5-FU i.v.	2	3	4	2	11 (58%)
Capecitabine	2	2	3	1	8 (42%)
Lonsurf		1	1	1	3 (16%)

*One patient in this cohort was underdosed and thus excluded from MTD determination.
#Mean ± standard deviation.

PHARMACOKINETICS

- Quantifiable 5-FU and LV concentrations were exhibited at all time-points
- Observed concentrations were consistent with expected concentration-time profiles as predicted by external published data for standard 5-FU/LV[2,3], with no discernible formulation-related differences **(Figure 2)**

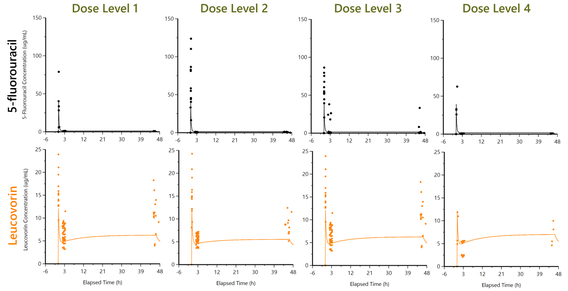

Figure 2. Expected [2,3] (solid line) and observed (closed circles) 5-FU and LV concentration-time profiles following administration of Deflexifol across four dose levels.

TOXICITY & MTD

- The most frequent treatment-related adverse events (AEs) were fatigue, stomatitis, diarrhea, and neutropenia **(Table 3)**
- Grade ≥3 AEs were reported in 6/19 patients. No Grade ≥3 AEs occurred at dose level 1 **(Table 4)**
- One treatment-related death occurred at the highest infusion dose level delivering 3800 mg/m² 5-FU due to neutropenic sepsis with pancytopenia and coagulopathy. This patient additionally experienced Grade 3&4 gastrointestinal (GI) inflammation
- The MTD was declared at Dose Level 3: **3400 mg/m² 5-FU** + 227 mg/m² LV infusion with a bolus dose of 525 mg/m² 5-FU + 35 mg/m² LV

Table 3. Number of patients with treatment-related AEs.

Adverse event	Grade 1	Grade 2	Grade ≥3	Any grade (n=19)
Fatigue	12	6	1	13 (68%)
Stomatitis	7	5	1	10 (53%)
Diarrhea	5	3		8 (42%)
Neutropenia	2	1	5	7 (37%)
Nausea / vomiting	3	4		6 (32%)
Hand-foot syndrome	3	3		4 (21%)
GI inflammation	3	1	1	3 (16%)
Thrombocytopenia	2			2 (11%)
Alopecia	2			2 (11%)
Skin rash	2			2 (11%)

AEs listed are those reported by at least 2 patients.

Table 4. Patients with treatment-related Grade ≥3 AEs by dose level.

Adverse event	Dose Level 2 (n=7)*	Dose Level 3 (n=7)	Dose Level 4 (n=2)	Total (n=19)
Neutropenia	2#	2	1†	5
Stomatitis	1			1
Fatigue		1		1
Headache		1		1
Pulmonary embolism		1		1
GI inflammation			1	1
Coagulopathy			1	1
Pancytopenia			1	1

*One patient in this cohort was underdosed by ~10%. #Includes one occurrence of febrile neutropenia. †Grade 5 neutropenic sepsis.

EFFICACY

- Disease control was achieved in 9/13 (69%) evaluable patients, including 1/13 partial response and 8/13 stable disease
- Median progression-free survival was 28.2 weeks (range 5.0 weeks to 116 weeks)

CONCLUSIONS

- 5-FU/LV co-delivery via Deflexifol is **safe and tolerable at 5-FU doses up to 40% higher** than typically administered by the standard modified de Gramont schedule
- Co-exposure of 5-FU and LV extended throughout the entire duration of treatment administration, **substantially longer than reported for standard treatment**
- **Disease control was achieved in 69% of patients** with advanced disease that were typically heavily pre-treated, including with prior 5-FU
- A subsequent trial of Deflexifol in first-line metastatic colorectal cancer, in combination with oxaliplatin and bevacizumab, is planned

A/Prof Daniel Brungs, Principal Investigator
Daniel.Brungs@health.nsw.gov.au

References

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