Phase 1b dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of Deflexifol™ combined with oxaliplatin and bevacizumab for first-line treatment of unresectable mCRC

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BACKGROUND: 5-FU/LV CO-INFUSION

5-fluorouracil (5-FU) and its biomodulator leucovorin (LV) are the backbone of therapy for metastatic colorectal cancer (mCRC). 5-FU and LV are chemically incompatible and are therefore sequentially administered. Given the importance of LV in modulating 5-FU activity, their simultaneous administration is expected to enhance anti-tumour efficacy. Previous phase II studies investigating 5-FU/LV co-infusion in first-line mCRC treatment reported response rates (52-58%[1-3]) considerably higher than standard regimens utilising sequential administration (i.e., 33% for de Gramont[4]). Co-infused 5-FU and sodium LV has also demonstrated improved outcomes in first-line mCRC when applied to modern combination regimens (Table 1).

Table 1. Independent phase II studies showing enhanced clinical efficacy when 5-FU and LV are co-infused in the first-line treatment of mCRC.

Treatment	Response Rate	Survival[#]
Monotherapy		
5-FU alone, mixed schedules[1]	11%	10.5 months
5-FU+LV, mixed schedules[1]	21%*	11.7 months*
5-FU+LV (sequential), de Gramont schedule[2]	33%	14.3 months
5-FU+LV weekly **co-infusion**[3-5]	**58%**	**>22 months[† 3]**
	52%	NR [4]
	53%	NR [5]
Combination regimens		
FOLFOX/FOLFIRI, sequential 5-FU/LV[6]	55%	PFS ns, OS 11.9 months
FOLFOX/FOLFIRI, **co-infused** 5-FU/LV[6]	**61%**	**PFS ns, OS 22.9 months***
de Gramont/FOLFOX/ FOLFIRI, sequential 5-FU/LV[7]	NR	PFS 12.8 months, OS ns
de Gramont/FOLFOX/ FOLFIRI, **co-infused** 5-FU/LV[7]	NR	**PFS 20.3 months*, OS ns**

[#]Overall Survival for monotherapy studies; [†]Not yet reached by 22 months; *p-value <0.05 compared to comparator arm.
NR = not reported; ns = not significant; PFS = Progression-Free Survival; OS = Overall Survival.

SOLUTION: DEFLEXIFOL™

Deflexifol™ is an all-in-one reformulation of 5-FU and LV at physiological pH. An innovative solution to 5-FU and LV incompatibility, its rationale is supported by pharmacokinetic modelling of 5-FU and the pharmacologically active *L*-enantiomer of leucovorin. The modelling demonstrates that through current standard 5-FU and LV administration, the period of co-exposure between 5-FU *L*-LV is ≤7% of the total 5-FU treatment duration time (Figure 1). Comparatively, via Deflexifol™, 5-FU and *L*-LV co-exposure occurs over the entire treatment duration (46.9 hours).

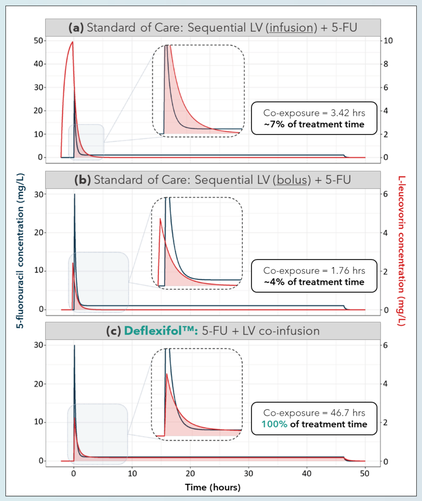

Figure 1. Predicted 5-FU (blue) and *L*-LV (red) concentration-time profiles. **(a)** Standard, sequential 5-FU/LV with LV administered as a high-dose infusion, typical in regions such as the US (400 mg/m² LV infusion over 2 hours + 400 mg/m² 5-FU bolus + 2400 mg/m² 5-FU infusion over 46 hours). **(b)** Standard, sequential 5-FU/LV, with LV administered as a low-dose bolus, as typical in Australia (50 mg LV bolus + 400 mg/m² 5-FU bolus + 2400 mg/m² 5-FU infusion over 46 hours); **(c)** Deflexifol™ treatment, an all-in-one co-formulation of 5-FU and LV (26.7 mg/m² LV & 400 mg/m² 5-FU bolus + 160 mg/m² LV & 2400 mg/m² 5-FU infusion over 46 hours). The predicted period of synergistic action is illustrated in red shading.

DEFLEXIFOL™ CLINICAL RESULTS TO DATE

Deflexifol™ has been well-tolerated across two phase Ib studies enrolling a total of 59 end-stage, advanced solid tumour patients.

An initial study administered Deflexifol™ to n=40 patients (60% mCRC) as either a weekly bolus or bi-weekly 46-hour infusion[8]. The Maximum Tolerated Dose (MTD) of Deflexifol™ was **≥30% higher** than the 5-FU dose typically administered in current clinical practice, with a bolus MTD of 525 mg/m² and an infusional MTD not reached (max. dose investigated of 3600 mg/m²).

Investigator-determined efficacy across all doses (a secondary endpoint) collectively reported a **disease control rate of 64%**. RECIST 1.1 responses are shown in Figure 2. Notably, patients were heavily pre-treated, and 85% had previously received 5-FU treatment.

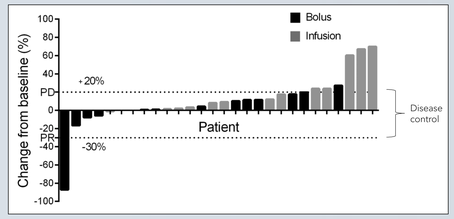

Figure 2. Tumour responses in patients with measurable disease evaluable by RECIST 1.1. PD = progressive disease, +20%; PR = partial response, -30%.

Pharmacokinetics confirm that 5-FU and LV administered via Deflexifol™ are bioequivalent to standard, individual formulations of each drug, with the plasma concentration-time profiles appearing as predicted by modelling.

A subsequent study administered Deflexifol™ to n=19 end stage-patients as a bolus followed by a continuous 46-hr infusion, emulating the standard modified de Gramont administration schedule. Preliminary tolerability, safety, and efficacy results are consistent with those reported in the previous study. This data will be presented at a future conference.

PLANNED PH1b COMBINATION STUDY

The FDA confirmed in a Type C Meeting interaction that Deflexifol™ can be immediately developed for first-line treatment without requiring initial development in later lines, with only one successful phase III trial required to support marketing approval. To date, however, the safety and optimal dose of Deflexifol™ has been assessed only as a monotherapy. A new phase 1b dose-escalation study has been designed to determine the safety, tolerability, pharmacokinetics and preliminary efficacy of Deflexifol™ as a replacement of standard 5-FU/LV in the mFOLFOX6 + bevacizumab regimen for first-line treatment of unresectable mCRC. Data generated from this trial is intended to confirm the optimal dose of Deflexifol™ to be investigated in a phase III registration study.

The trial will consist of two parts: an initial dose-escalation component and subsequent dose expansion cohort (Figure 3). Primary endpoints will be safety and tolerability, with secondary endpoints of pharmacokinetics, pharmacodynamics (PK/PD), and preliminary efficacy. Informed Consent will also facilitate collection of patient biopsies for an exploratory, retrospective analysis of tumour transcription profiles and treatment response.

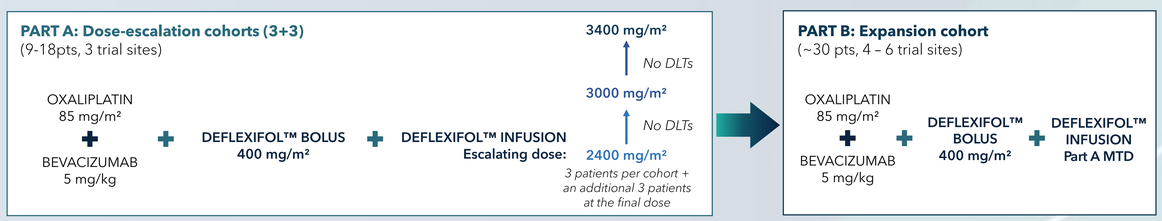

Figure 3. Planned design for a two-part phase 1b trial investigating Deflexifol™ in combination with oxaliplatin and bevacizumab for the treatment of first-line, unresectable mCRC. The initial dose-escalation will be conducted using a standard 3+3 design, with the bolus dose of Deflexifol™ kept consistent with the current standard dose (400 mg/m² 5-FU). The infusion dose of Deflexifol™ will initiate at the standard 5-FU dose (2400 mg/m²) and escalate up to two dose levels (3000 mg/m² and 3400 mg/m²) in the absence of dose-limiting toxicities (DLTs). The safety, tolerability, and PK/PD of the dose-escalation cohort will determine the dose used to treat a further ~30 patients in the subsequent expansion cohort to collect further safety, PK/PD, and preliminary efficacy data.

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