A Multicenter Phase 1-2a Clinical Study of Orotecan® (*oral irinotecan HCl*, VAL-413) in Patients with Recurrent Pediatric Solid Tumors

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Orotecan is a novel oral formulation of irinotecan developed to allow tolerable once-daily at-home oral administration of irinotecan in both pediatric and adult patients. (PCT/US2022/017308).

Background

Irinotecan is a topoisomerase-1 inhibitor that is FDA approved as an intravenous (iv) treatment for colorectal cancer. It is widely used off label for the treatment of a number of adult and pediatric cancers.[1]

Pediatric patients receiving irinotecan endure daily infusions for five to ten days every two weeks[2], negatively impacting their quality of life and driving up healthcare costs.

Commercially available i.v. irinotecan given orally has yielded promising results in terms of tumor response in a range of pediatric cancers offering a potential improvement in patient compliance and quality of life vs. i.v. dosing.[3]

Unfortunately, poor taste of the intravenous formulation (IRN-IV) has resulted in reduced patient adherence and limited adoption of these regimens.

Prior (Phase 1-2) clinical trial experience with intravenous irinotecan given orally for the treatment of pediatric cancers

Trial (Ref)	Disease	N	Other Agents
Furman et al. 1999	Relapsed solid tumors	34	None
Wagner et al. 2009	Relapsed neuroblastoma	14	TMZ
Wagner et al. 2010	Relapsed solid tumors	36	VCR, TMZ
Wagner et al. 2013	Relapsed solid tumors	13	VCR, TMZ, bevacizumab
Bagatell et al. 2014	Relapsed solid tumors	71	TMZ, temsirolimus
Brennan et al. 2014	Relapsed solid tumors	16	Gefitinib
NCT02095132	Relapsed solid tumors	31	MK-1775
NCT02747537	Relapsed solid tumors	30	Sorafenib
NCT03139331	Relapsed sarcoma	18	TMZ, pazopanib
NCT02511132	Relapsed Ewing sarcoma	9	TMZ, Vigil immunotherapy
NCT02318589	Relapsed solid tumors	12	Eribulin

TMX, temozolomide; VCR, vincristine

Ref. [1]NCCN Guidelines; [2]Myers PedBloodCan(2023); [3]Wagner PedBloodCan(2010)

The aim of this study is to assess the safety and tolerability of Orotecan and compare the pharmacokinetics of Orotecan to unformulated intravenous (i.v.) irinotecan given orally in patients with recurrent pediatric cancer

Trial Design	
Two different dose levels of VAL-413, 90mg/m^2/day or 110mg/m^2/day are being studied in combination with fixed-dose temozolomide (100mg/m^2/day) using a standard 3 + 3 phase I design.	
Eligibility:	Up to 20 patients ≥ 1 year of age or ≤ 30 years of age with recurrent pediatric solid tumors and adequate bone marrow, renal and liver function, for whom irinotecan therapy is a treatment option will be enrolled.
Treatment:	During the first cycle of treatment, each patient will receive 4 daily doses of VAL-413 and one daily dose of the intravenous preparation of irinotecan taken orally (IRN IV/PO). During all subsequent cycles, only VAL-413 will be given with temozolomide in 5-day courses administered every 21 days, as tolerated.
Outcome Measures:	Toxicity is assessed by NCI CCTCAEv5. A taste survey instrument will assess palatability of VAL-413 vs. IRN IV/PO; comparative intra-patient pharmacokinetics of irinotecan and its metabolites is assessed.

Safety & Tolerability Observations:

- Subjects received Orotecan as an oral liquid formulation (20 mL to 60 mL, dose-adjusted based on body surface area [BSA]) administered once daily for 5 consecutive days in 21-day treatment cycles.
- Palatability was assessed using a 7-point hedonic scale. The median score was 4 (range: 3–5), indicating acceptable tolerability. This was notably higher compared to the oral administration of the intravenous formulation of irinotecan, which consistently received a score of 1.
- A majority of participants (66%) completed multiple treatment cycles in a home-based setting. The longest duration of therapy was 13 cycles (approximately 9 months).
- Treatment-emergent adverse events assessed as possibly or probably related to Orotecan were primarily Grade 1 (mild) or Grade 2 (moderate), occurring in 55% of subjects. The most frequently reported adverse events included nausea and vomiting (55%), fatigue (22%), and dermatologic reactions (rash, 11%), consistent with the known safety profile of orally administered intravenous irinotecan.

Pharmacokinetic Observations:

- In each subject, the single-dose pharmacokinetic profile of Orotecan was evaluated in comparison to oral administration of the intravenous formulation of irinotecan (IRN IV/PO).
- Preliminary pharmacokinetic analyses indicate that systemic exposure (AUC) and time-dependent concentration profiles for irinotecan and its active metabolites, including SN-38, are not statistically different between Orotecan and IRN IV/PO formulations, nor between the 90 mg/m² (n=4) and 110 mg/m² (n=5) dose cohorts.