TPS812

Phase 1 Study of Infusional or Bolus Deflexifol (a novel formulation of 5FU, folinic acid, and cyclodextrin) after failure of standard treatment.

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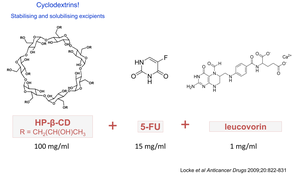
Presented at the American Society of Clinical Oncology, Gastrointestinal Cancers Symposium, San Franscisco, CA, January 19-21 2017

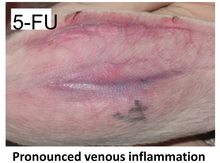
BACKGROUND:

5-fluorouracil (5FU) is a commonly used anticancer agent first synthesized in 1957, and is now most commonly used with FA, which enhances its clinical activity. Physical incompatibilities between 5FU and LV necessitate the infusion of each component separately, often through a central line due to high pH; resulting in adverse event which leads to poor outcomes due to treatment delays. A novel all in one reformulation of 5FU/LV at physiological pH has been developed as an alternative to serial administration of 5FU and LV in a high pH solution.

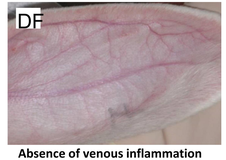
[Locke JM, Anticancer Drugs 2009].Preclinical testing demonstrated that the reformulation is stable bioequivalent to 5FU with reduced side effects [Stutchbury TK Anticancer drugs 2011].



Locke *et al Anticancer Drugs* 2009;20:822-831



Pronounced venous inflammation



Absence of venous inflammation

OBJECTIVES:

Primary Objectives:

- To Assess Response Rate (RR per RESCIST) in subject with relapsed refractory malignancy
- To determine the Pharmacokinetic profile of Deflexifol.

Secondary Objectives:

- To determine the maximum tolerated dose (MTD) of Deflexifol by continuous intravenous infusion and by bolus
- Determine safety and tolerability in patients with relapsed or refractory malignancy

Exploratory Objectives:

- To determine progression free survival
- To determine overall survival

MAXIMUM TOLERATED DOSE (MTD) AND DOSE LIMITING TOXICITY (DLT)

The maximum tolerated dose defined as: if 2 out of 6 patients experience DLTs dose escalation is halted and declared DLT Dose.

The previous dose level will be considered for expansion to x6 patients to confirm Maximum Tolerated Dose (MTD). Also to determine pharmacokinetic profile.
Dose-limiting toxicity (DLT) is defined as:

. Any Grade 3 or 4 non-haematologic toxicity (CTACE criteria).
. Patients developing Grade 3 or 4 diarrhoea, failing maximal anti-diarrheal medications.
. Febrile neutropenia, Grade 4 neutropenia > 7 days,
. Grade 4 thrombocytopenia > 7 days Any grade of thrombocytopenia associated with bleeding.
. Currently proceeding with (bolus 575mg/m2 weekly x 6, infusion 3600mg/m2/46h q2W).

STUDY DESIGN

ELIGIBILITY CRITERIA

KEY INCLUSION

- Histologically confirmed malignancy
- Locally or advanced disease measurable by RECIST Criteria
- 18 years +
- ECOG status of 0-2
- Life Expectancy of 12 + weeks
- Satisfactory haematologic parameters: Hb>10g/dL, WBC>3.0, Platelets>100.
- Satisfactory hepatic function: Bilirubin less than 2 x ULN (unless there is a documented history of Gilbert's syndrome),
- AST <5xULN, ALT<5xULN, INR<1.5xULN, Albumin > 30g/L.
- Satisfactory renal function: serum creatinine < 1.5xULN and calculated creatinine clearance > 35 ml/min.
- If female of childbearing age a negative Bhcg
- Informed consent

KEY EXCLUSION

- Washout period for therapy
  - Chemotherapy 4 weeks
  - Nitrosoureas or Mitomycin C 6 weeks
- DPD Deficiency
- No Brain Metastases (known untreated)
- Allergic Reactions
- Concurrent treatment
- Aspirin
- Uncontrolled inter-current Illness
- Pregnancy
- HIV

STUDY ASSESMENTS

Patients are radiologically assessed on completion of 1 dose level (6 complete doses)
In the absence of treatment delays due to adverse events patients may continue treatment up to 6 months

INFUSIONAL DOSE ESCALATION

Dose Level	Infusional Dose of Deflexifol
Level 1	1200mg /m^2 /46hours x 2 days q2 w x6
Level 2	1800mg /m^2 /46hours x 2 days q2 w x6
Level 3	2400mg /m^2 /46hours x 2 days q2 w x6
Level 4	3000mg/ m^2 /46hous x 2 days q2 w x6
Level 5	3600mg /m^2 /46hours x 2 days q2 w x6

BOLUS DOSE ESCALATION

Dose Level	Bolus Dose of Deflexifol
Level 1	375mg/m2 q w x6
Level 2	425mg/m2 q w x6
Level 3	475mg/m2 q w x6
Level 4	525mg/m2 q w x6
Level 5	575mg/m2 q w x6

PATIENT CHARACTERISTICS BOLUS

Patients Enrolled To Date:		N = 19 (%)
Sex		N (%)
	Men	7 (36)
	Women	12 (63)
Tumour Type	Breast	5 (26)
	Colorectal	7 (37)
	Gastro intestinal	4 (21)
	Lung	3 (16)
Age		
	Mean Age (Range)	64 (28-81)
Weight / Height		
	Mean Height in cm (Range)	165cm (156-178)
	Mean Weight in kg (Range)	68kgs (44-90)
Prior 5-FU Therapy		
	Yes	12(63)
	No	7(36)
Duration of Previous Treatment		
	< 5 regimens	13(68)
	> 5 regimens	6 (32)

PATIENT CHARACTERISTICS INFUSION

Patients Enrolled		N = 20
Sex		N (%)
	Men	11 (55)
	Women	9 (45)
Tumour Type	Breast	2 (10)
	Colorectal	16 (80)
	Gastro intestinal	2 (10)
Age		
	Mean Age (Range)	67 (37-78)
Weight / Height		
	Mean Height in cm (Range)	167cm (155-188)
	Mean Weight in kg (Range)	(48.7-111) 77kgs
Prior 5-FU Therapy		
	Yes	19 (95)
	No	1 (5)
Duration of Previous Treatment		
	< 5 regimens	16 (80)
	> 5 regimens	4 (20)

SUMMARY

- **An Open Label Phase I dose escalation study is underway in 2 schedules Bolus and Infusional to assess safety and tolerability in patients with advanced malignancy**
- **Cohorts 1-4 have been completed without DLT**
- **Limited sampling PK of 5-FU and dihydoFU is being conducted : (3 at each of the 5 dose level, doses 1 and 6) to assess PK variability, adequacy of dosing in comparison to reports.**
- **Incidence of AEs and SAEs (CTAC 4.03) will be summarized by severity and relationship to study treatment**

REFERENCES:

Stutchbury TK, Vine KL, Locke JM, Chrisp JS, Bremner JB, Clingan PR, Ranson M. (2011) Preclinical Evaluation of Novel All-in-one Formulations of 5-Fluorouracil and Folinic Acid with Reduced Toxicity Profiles. Anti -Cancer Drugs. 22:24-34.

Locke JM, Stutchbury TK, Vine KL, Gamble AB, Clingan PR, Bremner JB, and Ranson M. (2009) Development and assessment of novel all-in-one parenteral formulations with integrated anticoagulant properties for the concomitant delivery of 5-fluorouracil and calcium folinate. Anti-Cancer Drugs. 20:822-31.

ACKNOWLEDGEMENTS

CONCERT Centre for Oncology Education & Research Translation
University of Wollongong Australia
SMDCC A Private Day Only Hospital
Calvary Mater Newcastle
ihmri Illawarra health and medical research institute

DISCLOSURES:

Philip R Clingan, Marie Ranson: Stock and Other Ownership Interest in FivePhusion. Patents, Royalties, Other Intellectual Property for FivePhusion. Immediate Family Member connected to FivePhusion.

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