

## BACKGROUND

ECO-4601 is a structurally novel farnesylated dibenzodiazepinone with broad  $\mu\text{M}$  *in vitro* cytotoxic activity and *in vivo* antitumor efficacy in numerous human xenograft models. Preclinical data suggest ECO-4601 is a targeted anticancer agent with dual activity: selective binding to the peripheral benzodiazepine receptor (PBR) and inhibition of the Ras-MAPK pathway. This unique action observed on targets implicated in cancer biology and its favorable toxicology profile was the rationale for moving this compound into the clinic as a potential new anti-cancer agent. The ECO-4601-101 study was the first-in-human clinical trial with ECO-4601.

## METHODS

Patients were screened at two participating centers in Montreal (Quebec) using the following major inclusion and exclusion criteria:

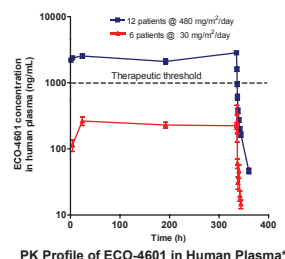
### Inclusion criteria

- Clinically or radiologically documented advanced solid malignancy for which no standard therapy is available, or for which has failed standard therapy
- ECOG  $\leq 2$

### Exclusion criteria

- Patients with brain metastases
- Patients in whom a proper central line cannot be established
- Patients with uncontrolled hypotension (Polysorbate 80 being a major constituent of ECO-4601 is known to cause hypotension)

The study was designed to: 1) define a Dose Limiting Toxicity (DLT); 2) determine the maximum tolerated dose (MTD) and the recommended dose for future studies of ECO-4601 administered as a continuous IV infusion for 14 days with 7 days of recovery (21 day cycle); 3) determine the safety of multiple cycle administration of ECO-4601; 4) document antitumor activity of ECO-4601 (RECIST or clinical); 5) determine the clinical pharmacokinetic profile of ECO-4601\*.



## RESULTS

### PATIENTS

A total of 26 patients with solid tumors were enrolled: 14 (54%) male and 12 (46%) female, 96% caucasians, with a mean age of 59 years (range 27 - 77). Patient distribution according to cohorts is summarized in Table 1.

Table 1: Patient Distribution

Primary Tumor Type	Dose Escalation (mg/m <sup>2</sup> /day)							Dose Extension (mg/m <sup>2</sup> /day)	Total
	30	60	120	180	270	360	480		
Colorectal	4	0	1	1	1	1	2	6	16
Duodenal	1	0	0	0	0	0	0	0	1
Pancreatic	0	0	0	0	0	0	0	1	1
Ovarian	0	1	0	0	0	1	0	0	2
Glioma	1	0	0	0	0	0	0	3	4
Lung	0	0	0	0	0	0	0	2	2
Total	6	1	1	1	1	2	2	12	26

## RESULTS (continued)

### SAFETY

In the dose-escalation portion, doses of 30, 60, 120, 180, 270, 360, and 480 mg/m<sup>2</sup>/day were evaluated in 14 patients. ECO-4601 was well tolerated up to the maximum dose tested. No DLT was reached at 480 mg/m<sup>2</sup>/day, corresponding to plasma concentrations 2-fold higher than the estimated therapeutic plasma threshold. A decision was taken to use the maximum dose of 480 mg/m<sup>2</sup>/day as the dose for the extension portion. An additional 12 patients were enrolled at this dose. The number of cycles completed by the 26 patients treated in both portions, ranged from 0 to 13, with 12 patients completing at least 3 cycles of treatment and 7 patients completing at least 6 cycles.

The most common adverse events observed during the trial are listed in Table 2.

Table 2: List of Most Frequent (>10%) Adverse Events (AEs)

Adverse Events Preferred Term	Dose 480 (N=14)		Dose 480 (N=14)	
	N (%)	N (%)	N (%)	N (%)
Fatigue	7 (50)	15 (57.7)	Back pain	2 (14.3)
Vomiting	5 (35.7)	8 (30.8)	Haemoglobin decreased	2 (14.3)
Nausea	3 (21.4)	8 (30.8)	Musculoskeletal pain	2 (14.3)
Asthenia	3 (21.4)	8 (30.8)	Dizziness	2 (14.3)
Diarrhoea	3 (21.4)	7 (26.9)	Catheter site erythema	1 (7.1)
Dyspnoea	2 (14.3)	7 (26.9)	Pain in extremity	1 (7.1)
Pyrexia	4 (28.6)	7 (26.9)	Blood cholesterol increase	1 (7.1)
Cough	1 (7.1)	6 (23.1)	Headache	1 (7.1)
Decreased appetite	1 (7.1)	6 (23.1)	Erythema	0
Dyspnoea exertional	2 (14.3)	5 (19.2)	Disease progression	2 (14.3)
Oedema peripheral	2 (14.3)	5 (19.2)	Abdominal pain	1 (7.1)
Insomnia	3 (21.4)	5 (19.2)	Constipation	2 (14.3)

The most common adverse events related to the treatment were: fatigue (mild to moderate), nausea (mild), vomiting (mild to moderate) and anemia (moderate).

Overall, two serious adverse events (SAEs) deemed related to the treatment occurred in the study: 1 anaphylaxis (due to the initial flushing procedure) and 1 rash. These SAEs were only observed once, during the first cycle at the lowest dose.

The first patient enrolled in this study (Patient 101), receiving 30 mg/m<sup>2</sup>/day of ECO-4601, presented for his last day of Cycle 1 (Day 15). The drug infusion was stopped and his Port-O-Cath flushed. Right after, the patient experienced anaphylaxis (Grade 4). He recovered and was discontinued from study. The event was the result of the Port-A-Cath flushing procedure and a revised procedure was implemented for the subsequent patients. Using this modified central line flushing procedure, reoccurrence of such SAE did not occur in the subsequent 25 patients.

Patient 104 presented at Day 13 of Cycle 1 with a rash (no itchiness) all over his body except for his face. The event was assessed as grade 2 and medically important. For this patient, pre-medication with prednisone was implemented for subsequent cycles with no reoccurrence of rash.

### EFFICACY

RECIST criteria and clinical evaluation were used to assess antitumor activity of ECO-4601 in this heavily pretreated population. Stable disease was observed in 6 of 7 patients evaluable after 6 cycles of treatment (Table 3).

Table 3: Tumor Response After Six Cycles of CIV of ECO-4601

Primary Tumor	Stable Disease (SD) after 6 cycles	Total
Colorectal	4	16
Duodenal	1	1
Pancreas	0	1
Ovarian	1	2
Glioma	0	4
Lung	0	2
<b>Total</b>	<b>6</b>	<b>26</b>

## CONCLUSIONS

ECO-4601 is a novel bifunctional agent targeting both the Ras/MAPK pathway and the PBR. This first-in-human study demonstrated that:

- ECO-4601 was safe and well tolerated. Adverse events potentially related to study drug were nonspecific and common in this type of population.
- ECO-4601 demonstrated preliminary evidence of anti-tumor activity in refractory cancer patients with 6 Stable Disease out of 7 patients evaluable after 6 cycles.
- The PK data demonstrated that estimated therapeutic ECO-4601 plasma concentrations were reached at higher doses and were rapidly eliminated following infusion. Data support a three-week regimen with CIV over 14 days followed by one week off in this population.
- These data support further clinical development of ECO-4601.