Phase 1 Dose Escalation Study of the Folate Receptor-Targeted Small Molecule Drug Conjugate EC1456

2576

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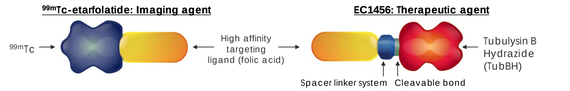
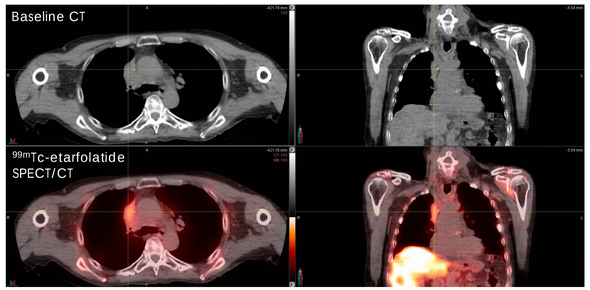
Background

- The folate receptor (FR) is highly expressed in lung cancer, and other types of cancers, while its expression in normal tissues is limited
- FR-targeted imaging and therapeutic agents may be used to identify and treat patients with FR+ cancers
- ^{99m}Tc-etarfolatide is an FR-targeted, non-invasive companion imaging agent used to identify patients in real-time who might benefit from treatment with FR-targeted therapy
- The TARGET and PRECEDENT studies provided proof of concept in ^{99m}Tc-etarfolatide-selected FR+ tumors
- EC1456 is an FR-targeted SMDC that delivers the microtubule inhibitor tubulysin B hydrazide which is 20 - 100 times more potent than taxane

FR-targeted SPECT Imaging & Therapeutic Agents





EC1456-01 Study Overview and Objectives

- Primary (Ph1a): to determine the MTD and recommended Phase 2 (RP2) dose of EC1456
- Primary (Ph1b): To optimize the EC1456 treatment in FR+ NSCLC pts
- Secondary: safety, anti-tumor activity and pharmacokinetic profile in patients with advanced histologically confirmed cancer
- To refine ^{99m}Tc-etarfolatide as a companion imaging agent for patient selection for EC1456 treatment
- Phase 1a Enrollment
  - QW schedule: Days 1, 8 every 21 days.
  - BIW schedule: Days 1, 4, 8, 11 every 21 or 28 days.
  - CWD schedule: Days 1, 8, 15 every 21 days
  - QIW schedule: Days 1-4, 8-11every 21 days

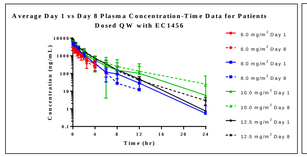
EC1456 Ph1a Patient Characteristics

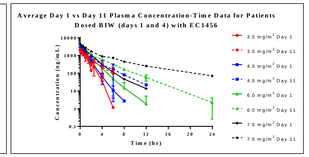
	QW n=35	BIW n=33	CWD n=11	QIW n=8	All pts n=87
Gender: Male Female	12 (34%) 23 (66%)	10 (30%) 23 (70%)	3 (27%) 8 (73%)	1 (13%) 7 (88%)	26 (30%) 61 (70%)
Median age (range)	69 (26 – 87)	67 (39 – 88)	67 (50 – 77)	59.5 (37 – 70)	68 (26 – 88)
Median lines of prior therapy (range)	3 (1 – 8)	3 (1 – 7)	3 (1 – 5)	4 (1 – 5)	3 (1 – 8)

EC1456 Ph1a Cancer Diagnosis

Cancer Diagnosis for All Ph1a Pts			
Ovarian	24 (28%)	SCLC	4 (5%)
NSCLC	8 (9%)	Appendix	2 (2%)
Endometrial	8 (9%)	Cholangiocarcinoma	2 (2%)
Cervix	6 (7%)	Head, Face, and Neck	2 (2%)
Mesothelioma	5 (6%)	Laryngeal	2 (2%)
Breast	5 (6%)		
One each, 1 (1%), diagnosis from the following: Adrenocortical, colon, duodenal, esophageal, gallbladder, gastric, gastroesophageal, hepatocellular, leiomyosarcoma, neuroendocrine, pancreatic, parotid gland, prostate, renal, thyroid, uterine sarcoma, uterine serous, unknown, missing.			

EC1456 Ph1a Pharmacokinetics





- The C_{max} of EC1456 increased with escalating doses
- Preliminary data showing a volume of distribution of ~4.6 L for EC1456 indicate that it is restricted to the plasma compartment
- EC1456 appears to exhibit non-linear PK at lower doses, but AUC increases linearly at higher doses
- Elimination half-life of EC1456 is estimated to be around 1.6 hours at higher dose levels; low levels of unconjugated TubBH are measured in systemic circulation
- Repeated dosing of EC1456 increased the AUC of the last dose in cycle 1, possibly by reducing clearance
- The effect was independent of the total dose given, but dependent on frequency of dose administration per week (QIW & BIW vs. QW)
  - The effect of repeated dosing on clearance was greater when the dose was fractionated

EC1456 Ph1a Adverse Event Summary

	QW n=35	BIW n=33	CWD n=11	QIW n=8	All pts n=87
At least one AE	35 (100.0%)	33 (100.0%)	10 (90.9%)	8 (100%)	86 (98.9%)
At least one grade 3/4 AE	22 (62.9%)	18 (54.5%)	6 (54.5%)	7 (87.5%)	53 (60.9%)
At least one serious AE	20 (57.1%)	11 (33.3%)	5 (45.5%)	5 (62.5%)	41 (47.1%)
At least one TRAE*	29 (82.9%)	26 (78.8%)	8 (72.7%)	5 (62.5%)	68 (78.2%)
At least one grade 3/4 TRAE*	9 (25.7%)	7 (21.2%)	3 (27.3%)	3 (37.5%)	22 (25.3%)
At least one serious TRAE*	9 (25.7%)	2 (6.1%)	3 (27.3%)	1 (12.5%)	15 (17.2%)

*Treatment related adverse events: possibly, probably, or definitely related to treatment.

EC1456 Ph1a Most Common Treatment Related Adverse Events*

	QW n=35	BIW n=33	CWD n=11	QIW n=8
Fatigue	40%	30%	46%	38%
Alopecia	29%	15%	27%	25%
Nausea	29%	27%	36%	13%
Constipation	26%	6%	18%	13%
Diarrhea	20%	21%	36%	25%
Vomiting	20%	24%	18%	25%
Headache	20%	9%	18%	13%
Decreased Appetite	11%	27%	9%	0%
Weight decreased	14%	12%	0%	25%

*Treatment related adverse events in ≥20% of pts in any dosing schedule

- No evidence of cumulative or late emerging toxicity thus far
- DLTs (Grade 3 events): infusion reaction (4.5 mg/m^2 QW); headache (10.0 mg/m^2 QW); abdominal pain (7.5 mg/m^2 BIW and 12.5 mg/m^2 QW); small intestinal obstruction (10.0 mg/m^2 CWD); hypophosphatemia (10.0 mg/m^2 CWD); fatigue (3.0 mg/m^2 QIW)

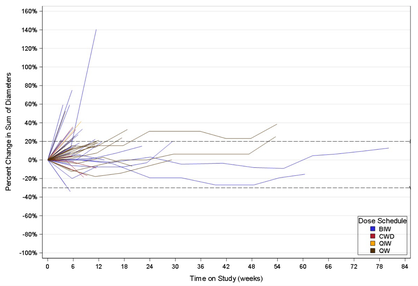
EC1456-01 Ph1a Clinical Safety Summary

- Ph1a dose escalation has been completed and a RP2 dose identified:
  - 12.5 mg/m^2 in the once weekly, 2 out of 3 week schedule (QW)
  - 6.0 mg/m^2 in the twice weekly, 2 out of 3 week schedule (BIW)
  - 8.0 mg/m^2 in the once weekly, 3 out of 3 week schedule (CWD)
  - 3.0 mg/m^2 on days 1-4 weekly, 2 out of 3 week schedule (QIW)
- The safety profile was similar for all regimens
- The total dose delivered per cycle was similar for all regimens demonstrating potential flexibility for dosing in combination

EC1456-01 Ph1a Cycles

Cycles	QW n=35	BIW n=33	CWD n=11	QIW n=8	All pts n=87
Mean Cycles	3.6	3.6	2.2	1.8	3.3
Median (range)	2.0 (1 – 18)	2.0 (1 – 22)	2.0 (1 – 6)	2.0 (1 – 3)	2.0 (1 – 22)

EC1456-01 Ph1a Percent Change in Sum of Tumor Size Over Time



Evaluation of EC1456 in an ovarian cancer subject undergoing cytoreductive surgery (EC1456-02)

Surgical Site (Pt 0001)*	^{99m}Tc-etarfolatide (TBR)	ELISA TubBH [a] (pmoles/g)	LC/MS-MS [b] (average pmoles/g)
Left iliac Node	NA	NA	27
Right Pelvic Sidewall (1)	3.2	BLOQ	44
Left Pelvic Sidewall	4.3	171	45
Right Pelvic Sidewall (2)	4.0	196	22

[a] Anti-body based quantification of TubBH species; cross-reactivity with active, inactive, and intermediate metabolites
[b] Sum total of EC1456 and active metabolites
Tumor to background ratio (TBR), enzyme-linked immunosorbent assay (ELISA), not available (NA), below limit of quantitation (BLOQ)
*All data and conclusions are considered unaudited and preliminary; additional analyses ongoing

- Preliminary data from 1 subject confirms that EC1456 and its metabolites are present in FR+ tumors

Conclusions

- EC1456 has demonstrated good tolerability and is not associated with hematological toxicity traditionally associated with chemotherapy, allowing flexible dosing and potential combination with other agents
- In an unselected population, EC1456 has demonstrated single agent activity in the form of reduction of tumor burden and prolonged stability
- ^{99m}Tc-etarfolatide is a real-time, non-invasive, imaging agent that is being co-developed to accurately select patients that may benefit from EC1456 therapy without the need for invasive biopsy
- The Phase 1b expansion study in ^{99m}Tc-etarfolatide selected, FR+ NSCLC patients using the recommended phase 2 dose is in the early stages of recruitment. To date, 6 patients have been treated and 4 remain on study

Study is ongoing, therefore all data presented above is preliminary