

The Co-development Of A Folate Receptor Targeted Diagnostic Imaging Agent (^{99m}Tc-EC20) And Folate Receptor Targeted Drug Conjugate (EC145) In The Treatment Of Ovarian Cancer Patients.

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Abstract

Background: Molecular imaging provides a unique approach to assessing molecular markers for cancer treatment. Folate receptor (FR) is over-expressed in ovarian, breast, lung and colorectal cancers. Folate is required for cellular division and FR expression is implicated as a negative prognostic marker for cancer. This study evaluates the potential use of a folate targeting SPECT imaging agent ^{99m}Tc-EC20 to select ovarian cancer patients with high FR expression to be treated with EC145, a FR targeted-cytotoxic drug conjugate.

Material and methods: Women with platinum resistant ovarian cancer were scanned with ^{99m}Tc-EC20 to determine FR status and each measurable lesion was scored as either FR positive or FR negative. Patients were then randomized 2:1 to receive EC145 (2.5 mg IV i.v. weeks 1 and 3) + pegylated liposomal doxorubicin PLD (50 mg/m² Ideal Body Weight (IBW) IV q 28 days) or PLD alone (50 mg/m² IBW IV q 28 days). Progression free survival (PFS) was the primary endpoint. Exploratory analyses of the FR- and FR-negative subgroups evaluated the use of ^{99m}Tc-EC20 to select the patient population most likely to benefit from the treatment with EC145. The reproducibility of the EC20 reads was evaluated in an inter-reader agreement study.

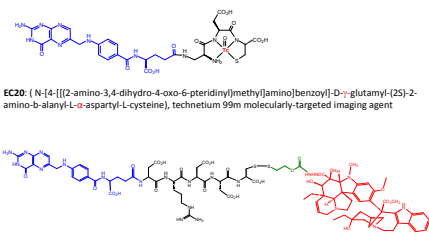
Results: The majority of patients (80%) scanned with ^{99m}Tc-EC20 were folate receptor positive. The final results on the reproducibility of the EC20 reads will be presented at the meeting.

In the overall ITT patient population, PFS was statistically significant different in favor of the combination arm, 21.7 weeks compared with 11.7 weeks for patients treated with PLD alone (HR 0.626; 2-sided log-rank p value 0.031). The HR was improved to 0.547 (p value 0.044) in patients with at least one FR+ lesion and even further to 0.381 (p value 0.018) in patients with 100% FR+ lesions.

Conclusions: Women with platinum resistant ovarian cancer have very poor prognosis. No approved treatments have demonstrated an improvement in PFS or OS. ^{99m}Tc-EC20 provides a reliable and reproducible imaging technology to select FR+ ovarian cancer patients that benefit most from the treatment with EC145. Statistically significant increase in PFS was seen in the combination of EC145 + PLD versus PLD alone, with increased benefit seen in patients with FR+ tumors. ^{99m}Tc-EC20 and EC145 are the first folate receptor molecular imaging and drug combination to demonstrate a statistically significant improvement in PFS in platinum resistant ovarian cancer.

Background

EC20 is a folate-targeted diagnostic imaging agent that combines folate with a technetium-99m chelating moiety. In its radiolabeled form, ^{99m}Tc-EC20 binds to FR-expressing tumors with high affinity (Kd = 6 nM). This study reports on the use of EC20 as a companion imaging agent to identify subjects with FR-positive tumors as part of the PRECEDENT study (Randomized Phase II Study of PLD +/- EC145 in subjects with platinum resistant ovarian cancer) prior to administration of the FR-targeted chemotherapeutic EC145 in order to correlate FR expression with therapeutic response and clinical benefit.



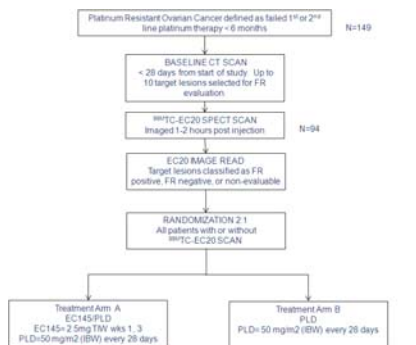
Imaging Methodology

EC20 was supplied (by Endocyte, Inc.) as a non-radioactive sterile lyophilized powder containing the components EC20, sodium *o*-D-glucosaccharate dihydrate, and tin (II) chloride dihydrate necessary for the reduction and chelation of technetium-99m. EC20 was reconstituted and prepared at the radio-pharmacy of the clinical site or its contract facility. After reconstitution, the radiochemical purity of ^{99m}Tc-EC20 was measured by thin layer chromatography. A radiochemical purity of ≥90% was required prior to use of the final prepared radiopharmaceutical.

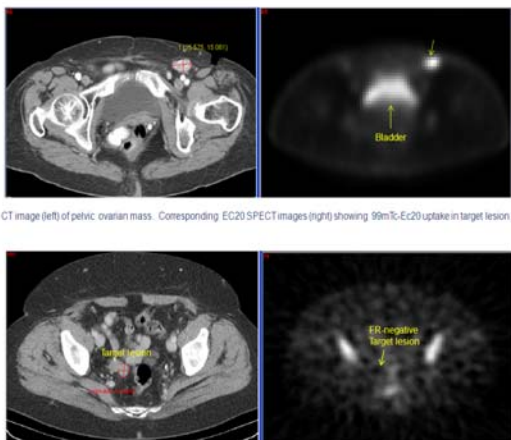
To decrease non-specific (i.e., background) tissue uptake of EC20 prior to the imaging procedure, participants received one IV injection of 0.5 mg of folic acid followed by 5–10 mL of normal saline via a free-flowing indwelling IV catheter in an upper extremity vein or appropriate indwelling IV access. This injection was followed within 1–3 minutes by 1–2 mL injection of 0.1 mg of EC20 labeled with 20–25 mCi of technetium-99m via a free-flowing indwelling IV catheter followed by 5–10 mL of normal saline. One to two hours later, SPECT images of the region(s) known to contain the target lesion(s) were obtained.

Target lesions were selected according to RECIST 1.0 criteria based on baseline CT scans. SPECT images of the areas of RECIST target lesions were taken using dual- or triple-headed detector nuclear medicine cameras with a 128x128 matrix. Images were reconstructed using filtered back projection (FBP) or iterative reconstruction without attenuation correction. A nuclear medicine specialist then visually assessed ^{99m}Tc-EC20 uptake for each target lesion. CT scans were provided with the SPECT images. Lesions were classified as either non-evaluable, FR-positive or FR-negative. Target lesions less than 1.5cm in size or located in organ with high background (e.g. kidney) were considered non-evaluable. Target lesions located in the liver were considered FR positive.

Patients with ^{99m}Tc-EC20 scan performed were classified according to FR status: FR(-) = no positive target lesions, FR (+) = at least one positive target lesion, or FR(++) = all target lesions positive.



^{99m}Tc-EC20 Sample Images



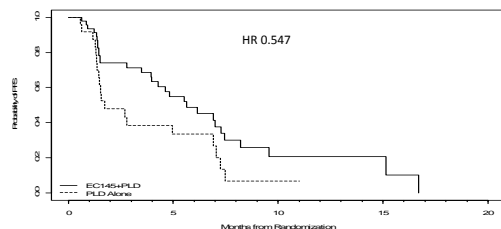
Efficacy Results

Efficacy: The primary endpoint of the study was progression-free survival based on investigator assessment using RECIST and pre-specified clinical events. The primary efficacy analysis was based on the intent-to-treat population (ITT) of all patients with measurable disease, regardless of EC20 (i.e., folate receptor expression) status. PFS results based on EC20 scans for FR expression is shown in table below. The final PFS analysis for the FR(+) population is presented in the Kaplan-Meier graph.

	EC145+PLD		PLD		HR (95% CI); 2-sided log rank p-value
	N	Median (weeks)	N	Median (weeks)	
ITT: All subjects regardless of FR status	100	21.7	49	11.7	0.63 (0.41-0.98); p=0.031
FR(+): At least one FR positive lesion	48	24.6	26	7.6	0.55 (0.30-0.98); p=0.044
FR(++): All FR positive lesions	23	24.0	15	6.6	0.38 (0.17-0.85); p=0.018
FR(-): No FR positive lesions	13	16.6	7	23.3	1.80 (0.37-8.80); p=0.465

Note: 94 patients had ^{99m}Tc-EC20 scans

FR (+) Platinum Resistant Ovarian Cancer Progression Free Survival



EC20 Inter-Reader Agreement Results

- CT and SPECT images from 79 patients in the randomized Phase 2 study were used; images from 19 patients were used for training, and 60 patients for the final analysis.
- Based on RECIST 1.1 criteria, target lesions were selected from baseline CT scans.
- Two independent nuclear medicine radiologists plus one adjudicator were used as readers for SPECT scans.
- Each of the 2 nuclear medicine radiologists independently read the SPECT images and identified FR(+) and FR(-) target lesions.
- FR(+) vs FR(-) agreement rate was 87%.
- Prevalence-Adjusted Bias-Adjusted Kappa (PABAK) was 0.733.
- *PABAK was used because of the low prevalence of FR(-) subjects.

Conclusions

- EC145 + PLD is the first combination to show a statistically significant and clinically meaningful increase in PFS (over control) for women with platinum-resistant ovarian cancer.
- Increased benefit from EC145 + PLD therapy is observed across all FR(+) subgroups; with the greatest benefit seen in patients with all tumors positive for folate receptor (FR(++)).
- EC20 can be used to select patients who benefit from EC145 + PLD therapy.
- EC20 Inter-reader study demonstrated a high agreement rate.
- The co-development of this folate-targeted diagnostic/therapeutic combination provides the first opportunity to prospectively select and treat ovarian cancer patients.

