

PRECEDENT: A randomized phase II trial comparing EC145 and pegylated liposomal doxorubicin (PLD) in combination, versus PLD alone, in subjects with platinum-resistant ovarian cancer

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Abstract

Background: EC145, a folate acid desacylvinblastine hydrazide conjugate binds with high affinity to the folate receptor (FR), expressed on the majority of epithelial ovarian cancers. This abstract reports final PFS and safety data on an international, randomized, open-label phase 2 study of EC145 + PLD compared with PLD alone, in women with platinum-resistant ovarian cancer, along with data on the use of EC20, a folate receptor targeted imaging agent.

Methods, Design and Objectives: Women ≥ 18 with ECOG PS of 0-2 and exposure to ≥ 2 prior systemic cytotoxic regimens were randomized 2:1 to receive EC145 (2.5 mg IV i.w. weeks 1 and 3) + PLD (50 mg/m² i.v. q 28 days) (N=107) or PLD (50 mg/m² i.v. q 28 days) (N=50). Subjects were stratified on the basis of the following 1) primary or secondary platinum failure, 2) geographic treatment region (North America vs. other), 3) baseline confirmatory CA-125 > 200 U/ml versus other. Prior to randomization, patients were scanned with technetium labeled EC20 to determine FR status. The primary endpoint of the study was progression free survival (PFS) in the ITT population of patients with measurable disease.

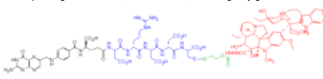
Results: The pre-specified final analysis occurred after 95 events. Demographic characteristics at screening such as tumor length, CA-125 levels, performance status, etc. were relatively balanced between arms. There was no statistical difference between study arms with regard to drug-related serious adverse events or the number of subjects reporting at least one treatment-emergent drug-related serious adverse event resulting in discontinuation. Eighty percent of patients scanned with EC20 were folate receptor positive.

In the ITT population of patients with measurable disease, final PFS was 21.7 weeks for patients treated with EC145 + PLD compared with 11.7 weeks for patients receiving single agent PLD (HR 0.626; 2-sided log-rank p value 0.031). For patients with 100% FR positive tumors final PFS was 24.0 weeks for patients treated with EC145 + PLD, compared with 6.6 weeks for patients receiving single agent PLD (HR 0.381; 2-sided log-rank p value 0.018).

Conclusions: EC145 + PLD is the first combination to show a statistically significant delay in PFS over standard therapy in women with platinum-resistant ovarian cancer. Data also indicate that EC20 may have utility for selecting patients most likely to benefit from therapy with EC145

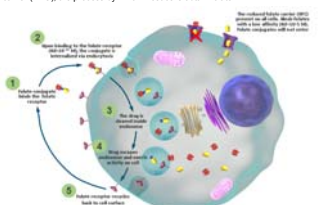
Background

EC145 is a conjugate of folate acid and desacylvinblastine hydrazide (DAVLBH). FR-expressing cells first bind, then internalize, folate-drug conjugates like EC145.



"Preclinical Evaluation of EC145, a Folate-Vinca Alkaloid Conjugate. Cancer Res 2007;67(9):4434-42"

The mechanism of entry of EC145 (folate conjugate) into the cell is as follows below: (1) EC145 binds to folate receptor (2) and enters the target cell via endocytosis. Upon internalization, EC145 is observed to release the DAVLBH warhead (3), facilitating cell death. EC145 is not a substrate or the reduced folate carrier (RFC), the process by which most cells obtain folate.



Demographic and Safety Results

Demographics: Baseline characteristics of subjects participating in the PRECEDENT study, such as tumor type, age and country of treatment, etc. are relatively equal in their distribution. Tumor Sum₁₀ indicates total length of RECIST target lesions (in millimeters) at screening.

	EC145 + PLD (n=107)	PLD alone (n=50)
Type of Cancer		
Ovarian	90.0% (90)	93.9% (48)
Primary Peritoneal	8.0% (8)	6.1% (3)
Fallopian tube	2.0% (2)	0.0% (0)
Age in years (median)	60.4	62.6
Geographic area		
North America	80.0% (80)	83.0% (41)
Patent	20.0% (20)	16.3% (8)
Tumor sum₁₀ mm (median)	93	56
CA-125 at baseline (mm)		
< 200	59.0% (59)	65.2% (32)
≥ 200	40.0% (40)	32.7% (16)
Platinum resistance		
Primary	65% (65)	61.2% (30)
Secondary	35% (35)	38.8% (19)
Platinum free interval (months) (median)	4.9	4.8
ECOG at screening (PS)		
0-1	96.0% (96)	98.0% (48)
2	4.0% (4)	2.0% (1)
Hepatic or pulmonary metastases	38.0% (38)	22.4% (11)

Safety: Safety data for subjects participating in the PRECEDENT study were available on 157 subjects at the time of the final efficacy analysis. Overall results are consistent with the conclusion that combination therapy with EC145 and PLD results in clinically manageable and limited additional toxicity over standard therapy with PLD alone. No patient on either arm was known to have died from a drug-related adverse event while receiving treatment or within 30 days of treatment discontinuation.

Patients on the EC145 + PLD arm remained on therapy longer than patients on the PLD arm as reflected by the significantly longer median PFS. As a result, median cumulative PLD dose for the EC145 + PLD arm was 275 mg (range 55-994) compared with 170 mg (range 70-946 mg).

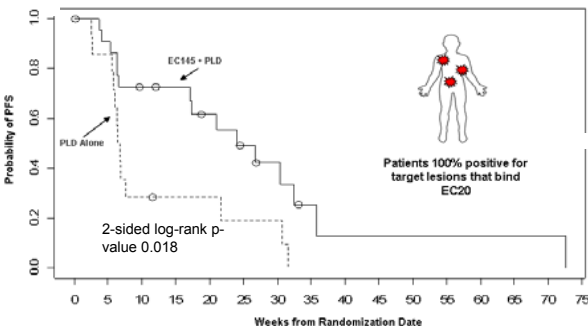
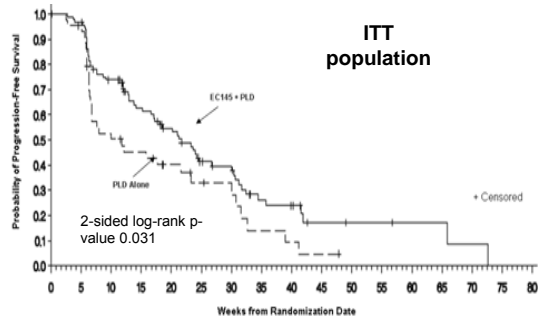
Although somewhat higher grade 3 and 4 neutropenia was noted in the combination arm, analysis did not indicate a difference in the occurrence of febrile neutropenia: EC145 + PLD, 1 event (0.9%) vs. PLD only arm also with 1 event (2%). Additionally, stomatitis was not worsened by the addition of EC145 to PLD: Combination EC145 + PLD, 6 events (5.6%) vs. PLD only arm with 2 events (4%).

Arm →	Overall Safety	
	EC145 + PLD (n=107)	PLD alone (n=50)
Adverse event reported of attribution	97.2% (104)	92.0% (46)
Drug-related AE resulting in discontinuation	10.3% (11)	4.0% (2)
Drug-related SAE resulting in discontinuation	2.8% (3)	4.0% (2)

	Grade 3 or 4 treatment-emergent adverse events (TEAE), regardless of causality, occurring in $\geq 10\%$ of patients			
	EC145 + PLD (n=107)		PLD alone (n=50)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	13(12.1%)	10(9.3%)	4(8.0%)	1(2.0%)
Sim. Int. Obs.	9(8.4%)	1(0.9%)	5(10%)	0(0%)
PPE	12(11.2%)	0(0.0%)	1(2%)	0(0%)

Final PFS 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. Additional PFS analyses were conducted according to EC20 threshold with results shown in the table at right. The final PFS analysis for the ITT population is presented in the Kaplan-Meier graph below. The PFS analysis for the population of patients whose tumors all expressed FR (100%) is also presented in an additional Kaplan-Meier graph below. Removal of the pre-specified clinical events as a PFS event (i.e., use of radiologic progression only) resulted in a further improvement of the hazard ratio (0.601; 2-sided log-rank p-value of 0.026).



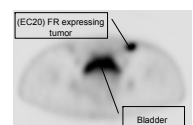
PFS analysis by EC20 (i.e. FR) threshold

	EC145 + PLD		PLD alone		HR (95% CI)
	N	Median (wks)	N	Median (wks)	
ITT population	100	21.7	49	11.7	0.626 (0.409-0.959)
$\geq 1\%$ EC20 positive	48	24.6	26	7.6	0.547 (0.304-0.983)
$\geq 50\%$ EC20 positive	37	24.6	22	7.6	0.514 (0.265-0.999)
100% EC20 positive	23	24.0	15	6.6	0.381 (0.172-0.845)

Supportive measures of efficacy

Response Parameter	EC145 + PLD (n=107)	PLD alone (n=50)
Objective tumor response		
CR + PR	28.0% (28)	16.2% (8)
CR + PR + SD	73.0% (73)	53.1% (26)
CA-125		
CR + PR	38.3% (33)	19.2% (5)
CR + PR + SD	75.0% (45)	61.5% (16)

Analysis of supportive measures of efficacy (i.e., radiologic and serum tumor marker) shown above in tabular form.



Typical SPECT image (above) using EC20. FR expression (the target of EC145) was identified by scanning PRECEDENT patients with EC20 pre-treatment.

Conclusions and Future Directions

- EC145 + PLD is the first combination to show a statistically significant increase in PFS (over control) for women with platinum-resistant ovarian cancer.
- EC20 can be used to select patients that are most likely to benefit from EC145 + PLD therapy.
- Increased benefit from EC145 + PLD therapy is observed across all EC20 positive thresholds; with the greatest benefit being observed in patients with all tumors EC20 positive.
- EC145 demonstrates manageable and tolerable toxicity in combination with PLD.
- The co-development of this folate-targeted diagnostic/therapeutic combination provides the first opportunity to prospectively select and treat ovarian cancer patients.
- Phase 3 randomized international study (PROCEED) exploring the efficacy of the combination EC145 + PLD in platinum-resistant ovarian cancer patients expressing FR has begun accrual. Details of this study are available at www.clinicaltrials.gov.

Overall survival data for PRECEDENT are expected to be available in late 2011

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