



EC20 Imaging Predicts Response in a Randomized Trial comparing Pegylated Liposomal Doxorubicin (PLD) with or without EC145 in Platinum-Resistant Ovarian Cancer

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Background

EC145 is a conjugate of folic acid and desacetylvinblastine that binds the folate receptor (FR), expressed on the majority of epithelial ovarian cancers. EC20 is a folate and technetium imaging conjugate used to identify FR expression on cells.

Methods

Women with platinum resistant epithelial ovarian cancer, previously treated with no more than 2 cytotoxic regimens were randomized 2:1 to receive EC145 (2.5 mg IV tiw, weeks 1 and 3) + PLD (50 mg/m²IBW IV q 28 days) or PLD (50 mg/m² IBW IV q 28 days). Prior to treatment, patients were imaged with EC20 to determine FR status. Patients were included regardless of EC20 status and all patients had measurable disease. The primary endpoint was progression free survival (PFS).

Results

The pre-specified final analysis occurred after 95 events in 149 patients with measurable disease. A total of 94 patients had a pre-treatment EC20 scan. The EC20 scan revealed all target lesions positive in 38 (40%) of patients, ≥1 positive lesion in 36 (38%) and no positive lesions in 20 (21%) patients. There was a significant increase in PFS in the EC145 combination arm in the entire population. An increase in PFS was predicted by the presence of any EC20 lesion with the lowest hazard ratio for progression in the subgroup that had all lesions positive on the EC20 scan.

Figure 1: Using Folate to Target Cancer Cells

Approximately 80% of ovarian cancers express membrane bound folate receptors which are not present on normal cells. This mechanism is exploited to target folate conjugated chemotherapy only to these cells. The folate receptor and conjugate enter the cell by endocytosis where the active drug is released into the cell and the receptor is recycled to the cell surface.

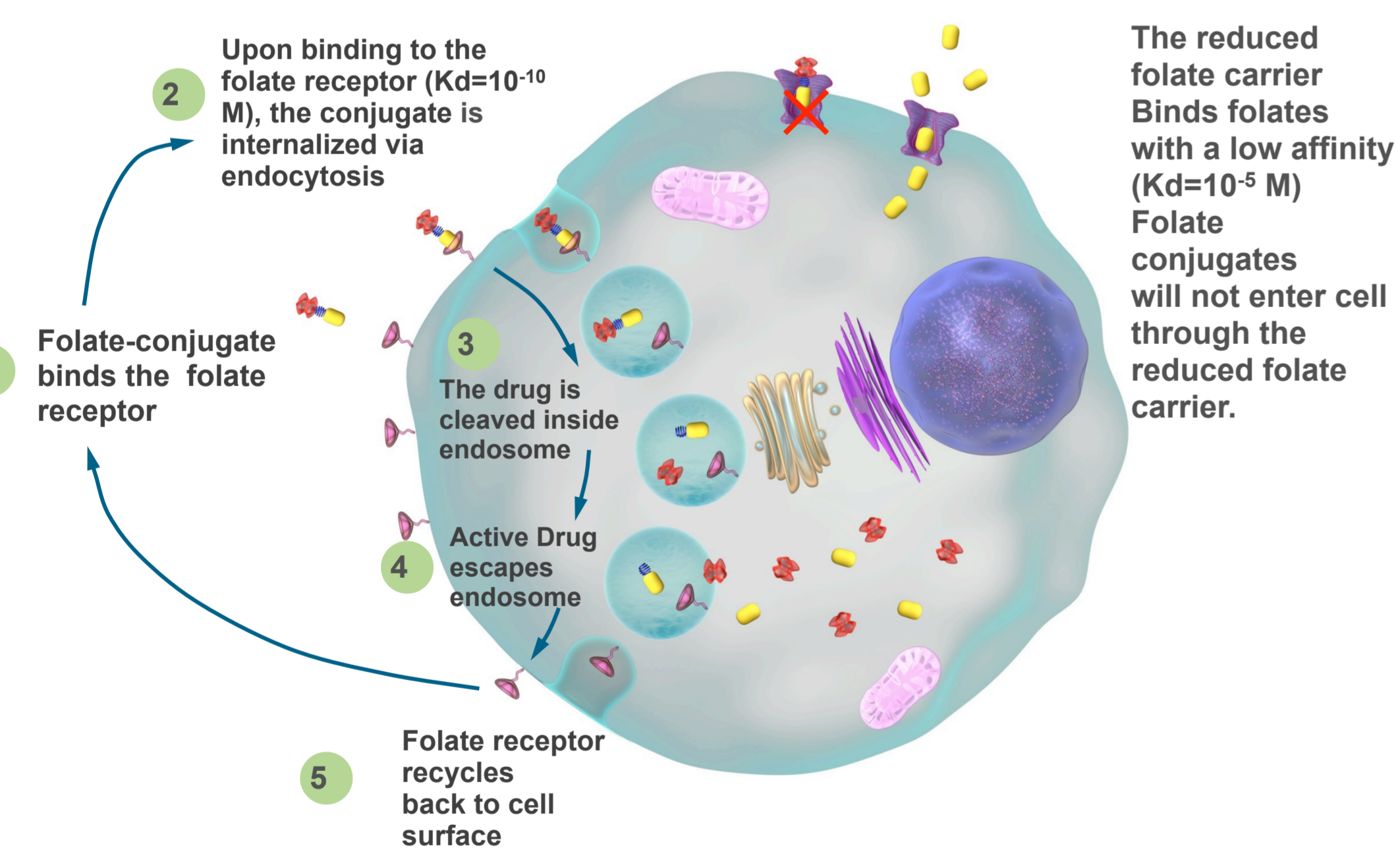
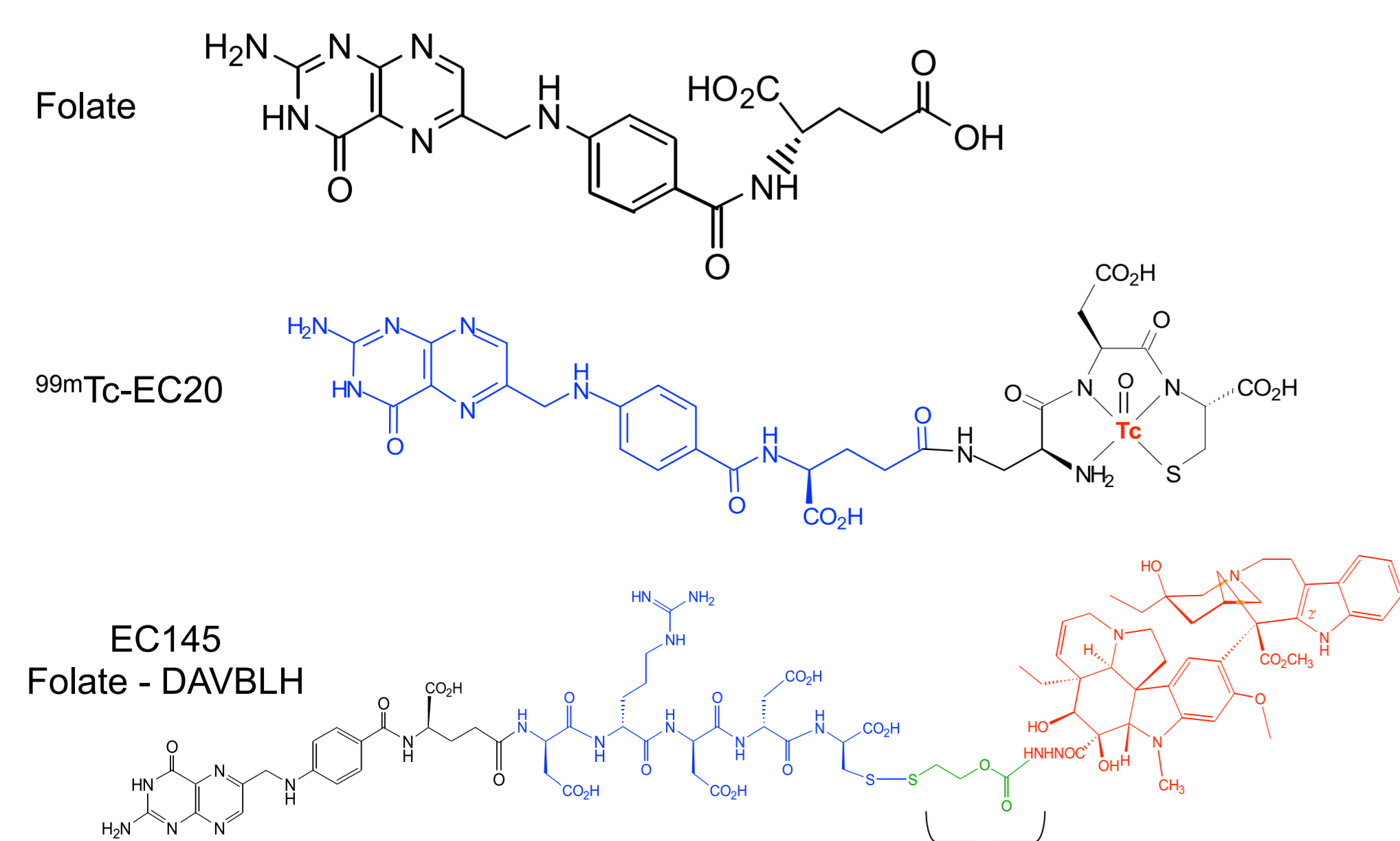


Figure 2: Folate and Conjugates

Folate can be conjugated to both imaging agents as well as chemotherapy. Below is a comparison of the folate molecule compared to the experimental imaging agent ^{99m}Tc-EC20 and experimental therapeutic agent EC145 which is a folate-vinca alkaloid desacetylvinblastine hydrazone (DAVBLH).



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Figure 3: Comparison of EC145 (Therapeutic) and EC20 (Imaging) Agents

Both agents have a relatively short serum half life and bind the Folate Receptor (FR) with a high affinity.

	EC145	EC20
Receptor Target	Folate Receptor	Folate Receptor
Payload	desacetylvinblastine hydrazone	Tc99m
Molecular Weight	1917	746
FR Relative affinity	0.46	0.92
Half-life	26 min.	25 min.
Dose	2.5 mg	0.1 mg
# Patients Dosed	>230	>510

Figure 4: PRECEDENT Trial Design

A randomized phase II trial of PLD ± EC145 in patients with platinum resistant ovarian cancer. The trial enrolled 149 patients with measurable disease. The EC20 scan was optional prior to treatment and completed in 94 (63%).

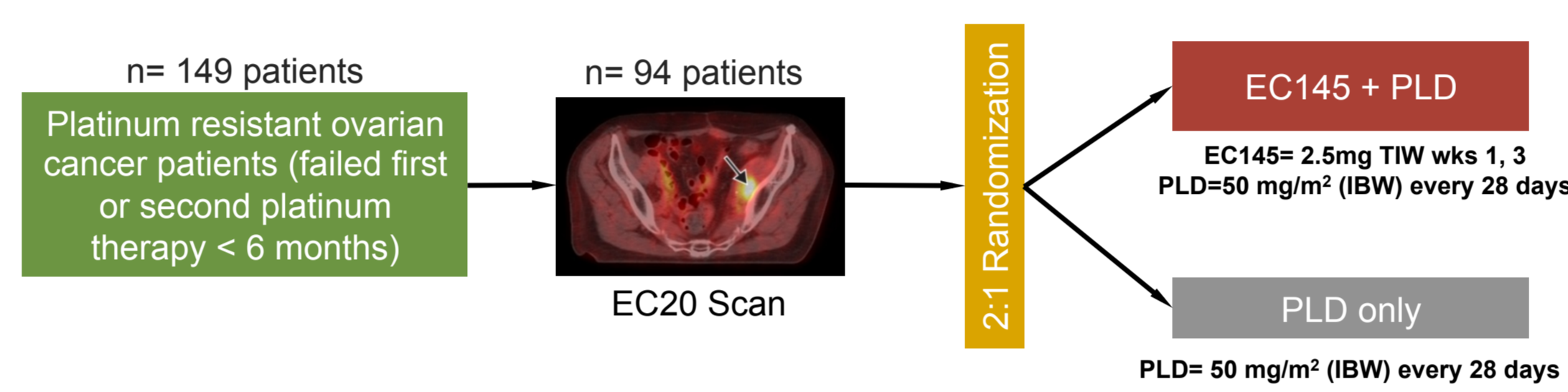


Figure 5: EC20 Imaging Results

An EC20 positive lesion is outlined by the red arrows.

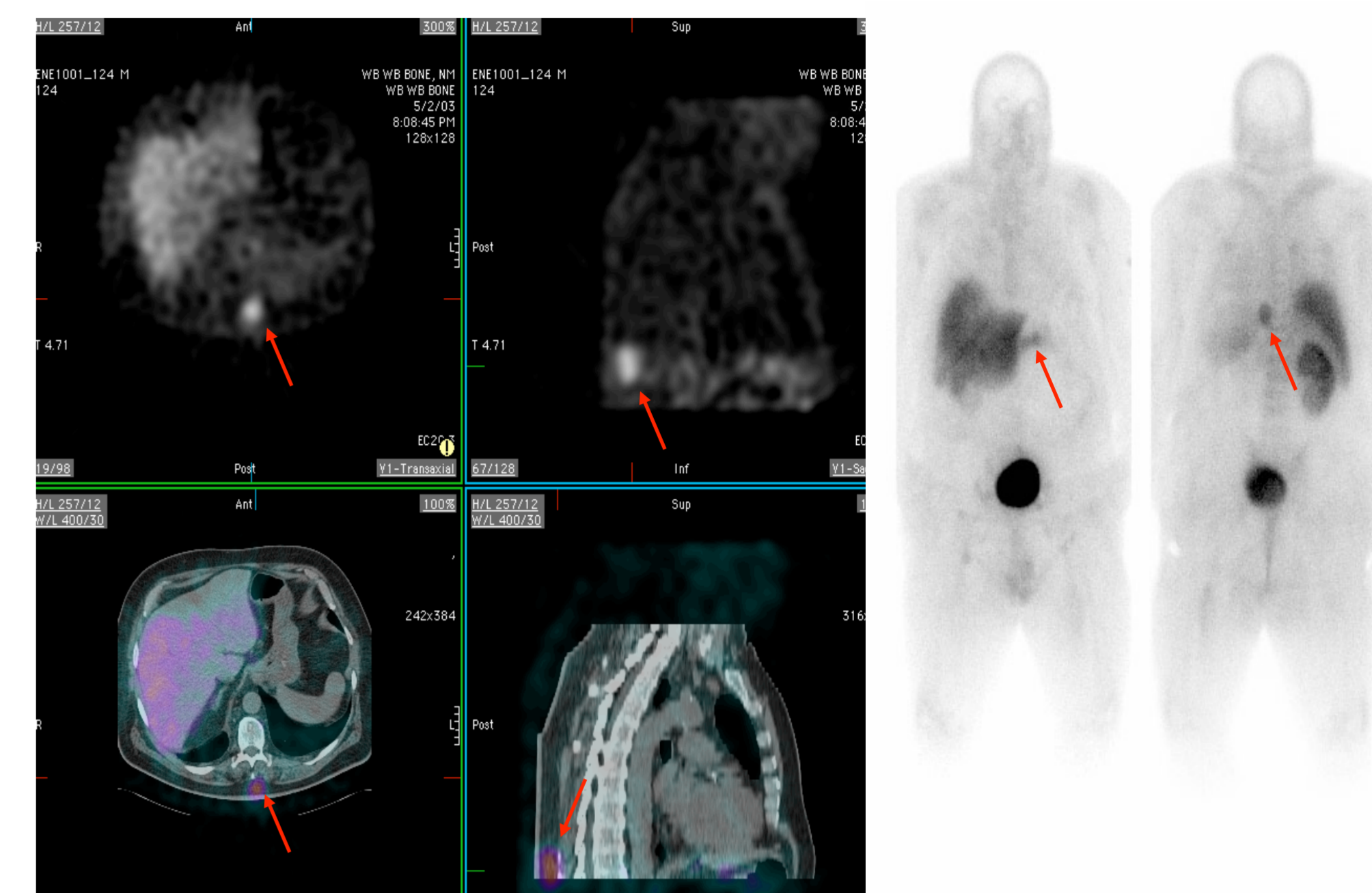


Figure 6: EC20 Scan Results

In the patients that were scanned, approximately 80% had at least one positive lesion and 40% showed all lesions to be positive.

EC20 Whole Body Scan	Subgroup		
	Subgroup	FR expression	% PRECEDENT Population
Image 1 hour after injection of EC20	Any EC20 (+)	At least one target lesion +	80%
	All EC20 (+)	All target lesions +	40%
	EC20(-)	No target lesions +	20%

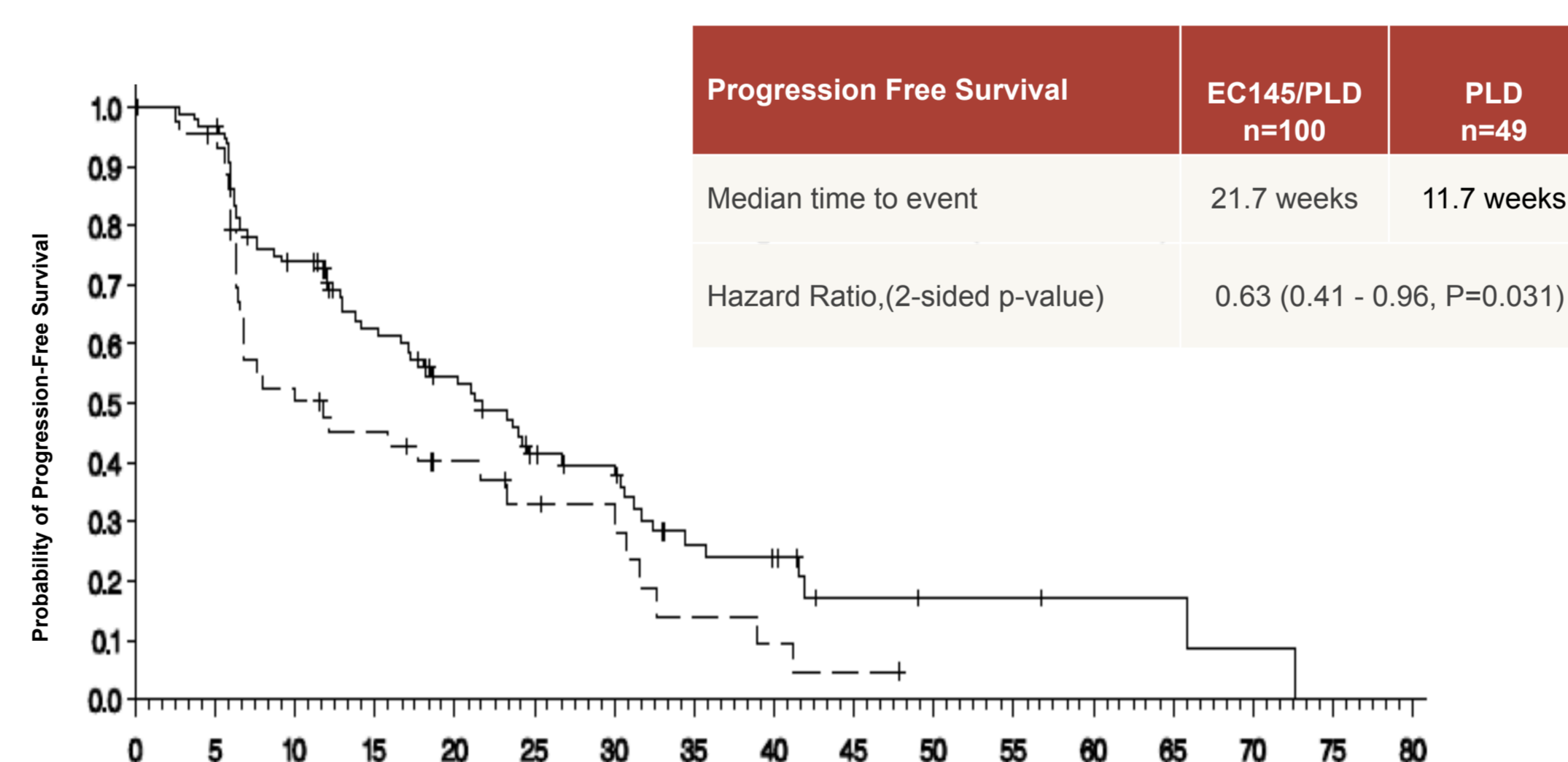
Table 1: Progression Free Interval by EC20 Folate Scan Results

Overall the study showed that patients with any folate positive lesions had a significantly longer PFS if treated with PLD + EC145 as compared to EC145 alone. Patients who were EC20 negative did not have any significant benefit to the EC145 + PLD combination over PLD alone.

Patient Population	n	EC145 + PLD PFS (wks)	PLD PFS (wks)	Hazard Ratio (95% CI)	p-value 2-sided log rank
ITT population	149	21.7	11.7	0.63 (0.41-0.96)	0.03
Any EC20 (+)	74	24.6	7.6	0.55(0.30-0.98)	0.04
All EC20 (+)	38	24.0	6.6	0.38 (0.17-0.85)	0.02
All EC20 (-)	20	16.6	23.3	1.8 (0.37-8.8)	0.47

Graph 1: Progression Free Survival in the Intent to Treat Population

PFS was significantly longer in patients who were randomized to the EC145 + PLD combination compared to PLD alone.



Graph 2: Progression Free Survival for Patients with at least One Positive Lesion on EC20 Scan

A targeted population who were EC20 positive had a lower hazard ratio for progression than the overall Intent to Treat Population.

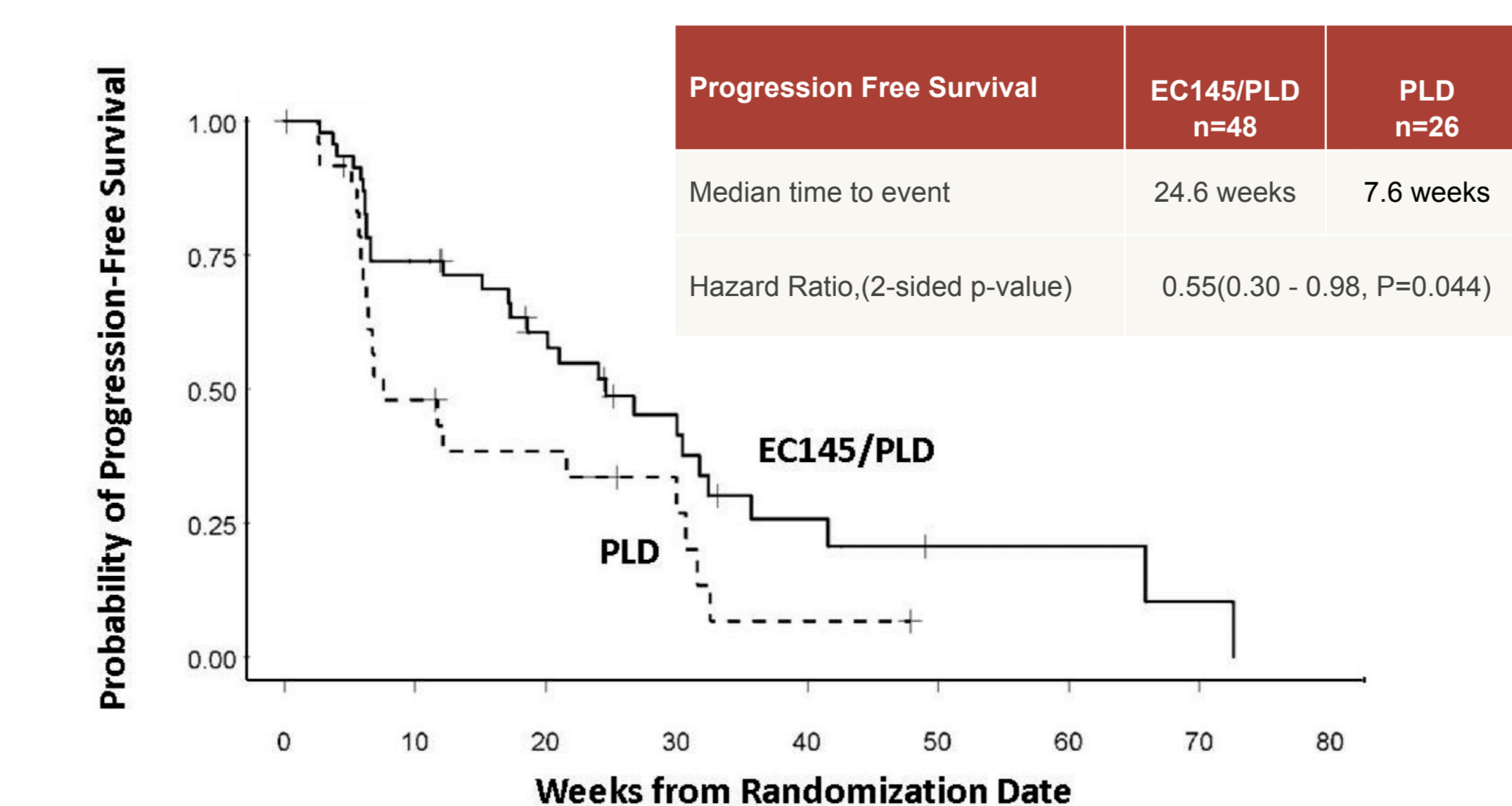


Table 2: Relative Dose Intensity in Trial

There was no difference in dose intensity of delivered PLD between the two arms as EC145 was well tolerated and did not have overlapping toxicity with PLD.

	EC145 + PLD (n=107)	PLD (n=50)
Median # Cycles	4 (1-26)	4 (1-16)
Mean Dose	3.20 mg/wk	11.8 mg/m ² /wk
Intended Delivered Dose	3.75 mg/wk	12.5 mg/m ² /wk
Relative Dose Intensity	85%	94%

Conclusion

The combination of EC145 and PLD is the first regimen that has demonstrated a significant improvement in PFS over single agent PLD in platinum resistant ovarian cancer. Furthermore, EC20 has utility in selecting patients most likely to benefit from therapy with EC145.

