Is EC-145 an Active Agent in Platinum Resistant Ovarian Cancer?

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EC-145 Priced at Failure

The final analysis of the PRECEDENT data was not taken kindly by the market. Despite confirming a statistically significant progression free survival (PFS) effect in the folate receptor positive sub-set (FR(++)), the stock fell to below cash. Investors seemed to have focused on the change in the overall survival (OS) effect, which went from showing a trend toward benefit (hazard ratio 0.879) at the interim to no longer showing a benefit. While the EC-145 treatment arm performed as expected, the active control produced an historic 16.9 month median OS. So the question are both why did the OS effect change, what does it mean, and was the investor reaction reasonable? The short answers are a small control group sample where the control had an easier to treat patient population, that EC-145 is still a very active drug for the FR(++) group, and investors clearly sold first and overreacted.

What Should the Control Show?

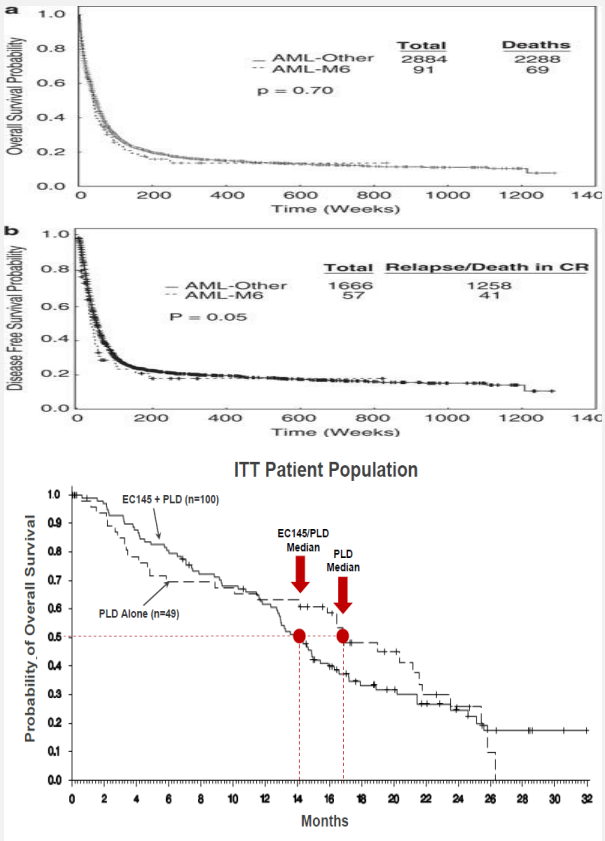
Before continuing there are all of the normal caveats about comparing between trials given the different sets of patients and any number of other confounding factors but in order to center our expectations it is useful to examine previous trials. For the PRECEDENT trial the active comparator was pegylated liposomal doxorubicin (PLD) at a dose of 25 mg/m2 (see). Looking at the published literature on ovarian cancer trials, there have been two that examined PLD: Gordon et al (2004) which treated 239 patients and O'Byrne et al 2002, which treated 107 patients. In those two trials the median progression free survival (PFS) was 4 months in each and the median overall survival (OS) was 15 months for Gordon et al (2004) and 11 months for O'Byrne et al (2002). In a company presentation Endocyte also listed a number of more recent studies in calculating the expected OS. This can be accessed as slide 9 (see). In this analysis, however, I will concentrate on the Gordon et al (2004) and O'Byrne et al (2002) studies to illustrate the main points.

If you look at the PFS from the PRECEDENT trial you will note that the PFS from the PLD arm was only 2.7 months in the ITT, 1.7 months in the FR(+), and 1.5 months in the FR(++) groups. Why would the PFS be lower in this trial? The answer lies in the patient population in that the PRECEDENT trial recruited only platinum resistant ovarian cancer patients, which is a much more difficult to treat group. In contrast, Gordon et al (2004) only had 54% as platinum resistant and O'Byrne (2002) only 60% were platinum resistant. So the patient population in the PRECEDENT trial would be expected to have a lower PFS given its selection criteria. In addition, response would lower as folate receptor expression is also correlated with worse outcomes, which explains the decrease in PFS as one moves from ITT to FR(+) to FR(++).

In terms of overall survival, the Gordon et al (2004) study showed a median survival of 15 months and in the O'Byrne et al (2002) study it was only 11 months. Of course, these survival numbers are not from the same population in that they have many more platinum sensitive patients. Endocyte analyzed the data from 6 trials and came out with as close to an apple to apple comparison and came to an average median OS of 12.7 months. The highest end of that range is 13.5. In contrast, the PRECEDENT trial showed a median OS of 16.9 months, which is over 2 months more than the previous best.

In general, if we base our expectations off of previous experiences with PLD, we would expect a PFS of 11 or lower. Why 11? The O'Byrne et al (2002) study had the most platinum resistant patients, so the 11 median PFS is from a population closer to PRECEDENT than Gordon et al (2004). In terms of OS, one would expect something close to the mean of 12.7 months and certainly below the previous best of 13.5.

The median OS of the PRECEDENT PLD arm is similar to those seen in platinum sensitive patients. It seems clear that something out of the ordinary is driving the median OS.



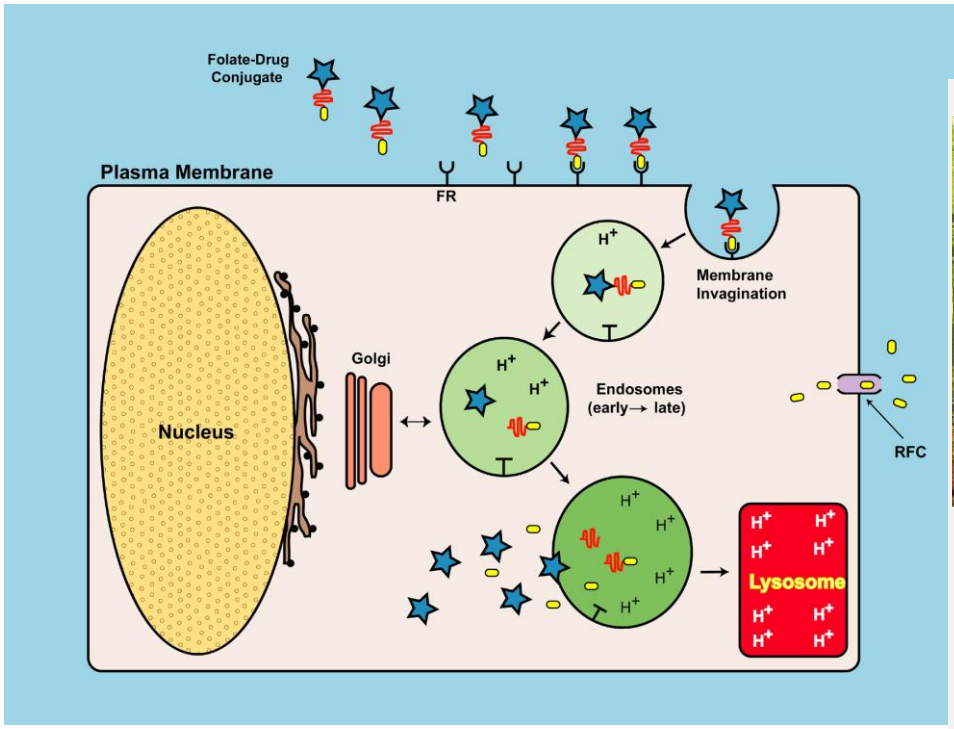
How Seriously Should We Take 16.9 Month Median OS?

As noted before a 16.9 month median OS is well outside of expectations, especially for patients who are platinum resistant. To put this into perspective, if you examine the 13 trials listed in the appendix that had a total of 26 treatment regimes only 10 had an OS above 16.9. Of those 10 regimes none had a single patient that was platinum resistant. In other words, the median OS of the PRECEDENT PLD arm is similar to those seen in platinum sensitive patients. It seems clear that something out of the ordinary is driving the median OS.

One critical point to make is that the PLD arm is relatively small with only 49 patients (see figure to the left). With such a small sample, the median can be skewed by only a few aberrant data points. A simple glance at the OS curve shows that it is not shaped as one would expect. A good example of an OS curve comes from an AML study (see left). Note that in these curves there is a sharp decline that then levels off and almost flattens. Unlike the PLD OS curve in the PRECEDENT trial there are no step like movements. The reason for the smooth AML curve is that it is based off of a much larger sample and so it approaches the underlying distribution. With only 49 patients, the OS curve in the PRECEDENT trial is going to be greatly affected by minor changes in the survival of a few patients. While it is difficult to tell from the curve, it looks like it is about 5-7 patients that push the PLD OS curve out to form the step like formation. This type of outlier behavior would have significantly less effect in a larger trial.

If a few outliers are causing the issue, why are they surviving longer than expected? The company has indicated that the control and treatment arms had differing proportions of patients with platinum sensitivity. The studies shown in the appendix clearly show that platinum resistance decreases OS. So if there is an imbalance then it can certainly explain the difference. The company noted that proportion of patients who have gone 3+ months since their last platinum treatment in the EC-145 arm was 56% but this jumps to 76% in the PLD arm. Interestingly enough, 20% of the PLD group is just about 10 patients which is more than enough potential outliers to impact the PLD OS curve.

Finally, it should be noted that even though the curve did not show a statistically significant difference, there does seem to be an effect. With the PLD control, all patients had died by month 26. In the EC-145 group, in contrast, 20% survived past 26 weeks and, in fact, 20% were alive 32 months past treatment. If you had choice between a treatment in which everyone dies by month 26 or one where 20% survived for at least 32 months and statistically significant longer PFS, what would you choose?



Missing the Forest for the Trees

The emphasis on the perceived miss on the OS completely misses the fact that the primary endpoint of PFS was a major success. In fact, it is exceptionally difficult to find any previous trial that shows a statistically significant effect in platinum resistant ovarian cancer. Fung-Kee-Fung et al (2007:202) notes that "for patients with platinum-refractory or platinum resistant disease, none of the trials detected any statistically significant survival advantage with one chemotherapy agent over another." In terms of PFS, the conclusion is similar except that Meier et al (2004) showed that topotecan was more effective than treosulphan with a PFS of 4.2 months versus 2.2 months (p-value of 0.0279). This advantage, however, is probably more related to the inactivity of treosulphan, where in a trial with 64% of patients sensitive to platinum it only produces a 3 month median PFS.

As such, the question is whether it is appropriate to essentially ignore the FR(++) results which showed a statistically significant PFS effect versus PLD (the first trial to ever do better than PLD in any subset of ovarian cancer patients). To phrase this another way, the trial took the most difficult to treat patients (platinum resistant) and in that most difficult to treat portion examined an even more difficult to treat subset (FR(++)) and showed that EC-145 had an unprecedented statistically significant PFS effect (5.5 months compared to 1.5 months for PLD). That 5.5 month PFS is actually better than 10 of the 26 treatments shown in the appendix and those are from the easiest to treat patients. In addition, the 14 month median OS is greater than 12 of the 26 treatments.

So the question becomes if EC-145 is an active agent in the FR(++) patient population even though the OS did not show statistical significance? It seems like the bulk of evidence from the trial and previous trials point to it being an active agent. Not only does it produce a comparatively large PFS and OS in this patient population but it was consistent between the interim and final analysis. The only factor that changed was not the weakening of the EC-145 effect but the exceptional strength of PLD; a PLD effect that has some reasonable explanations with some supporting evidence.

What is the Evidence that the Imbalance is Affecting the OS Results?

In their presentation of the final results, the company noted that if the patient populations in the treatment and PLD arms were similar (i.e. had the same proportion with 3+ months since last platinum treatment as well as other pre-specified adjustments), the hazard ratio would drop to 0.92 in the ITT group and 0.495 in the FR(++) group both in favor of EC-145. While these trends are positive, the small sample means that the results were not statistically significant but at least provide some support to the company's contention. The company also went back and reexamined the data and dropped all patients who received platinum after progression. While again this is a small sample and all the caveats apply, the OS in the PLD group went back to within a normal range and in the FR(++) group EC-145 treated patients had a longer median OS.

The fact is, however, that these are *post hoc* analyses and always must be taken with caution especially in small samples. That being said, when you have a situation in which one aspect of the results is clearly aberrant (OS curve) and there is a logical explanation (small sample with an imbalance in platinum sensitivity)and you can show trends that support the explanation, then your confidence increases. Of course, nothing is certain and OS is usually a difficult endpoint to hit, especially in small trials.

On top of the logic, there is also a fairly strong relationship between a statistically significant PFS effect and a statistically significant OS effect in previous ovarian cancer trials. In the 13 trials shown in the appendix, 4 showed a statistically significant PFS effect and of those 3 also had a statistically significant OS effect. The only one where that did not occur was Pfisterer et al (2005) with carboplatin/gemcitabine having a 3 month PFS benefit but only a 1 month OS benefit over carboplatin.

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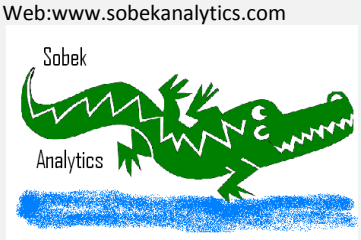

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Path Going Forward

While it is difficult to predict the outcome of the phase III trial, I think the bulk of evidence points to a positive outcome in that there will be a statistically significant PFS benefit for EC-145 in the FR(++) sub-set. In addition, I think a statistically significant OS benefit will occur as well but will likely take time to develop as is usually the case, although I believe the initial data will show a trend in favor of EC-145. A bigger question is if a PFS or OS effect will be seen in the FR(+) sub-set. In the investigator PFS the FR(+) group had a statistically significant PFS but with independent review the trend remained but the p-value dropped to 0.145. Mechanistically, EC-145 should be active in this group (although not as active) and I suspected with a larger trial there would be a statistically significant PFS benefit but most likely only a favorable OS trend.

The other big question an investor needs to asks before buying is whether the EU will allow ECYT to proceed with the application. At this point, there has not been any communication from the EU to indicate that the new data makes approval less likely. The EU wants to have a phase III trial active when marketing approval is submitted and since the Doxil shortage has forced ECYT to change to a Taxol comparator, there is a slight delay. The company plans on talking with the EU regulators in the next couple of weeks to finalize the Taxol designs. Once given the OK, the company will switch its sites over to the new protocol and be able to submit for approval in the second quarter.

This meeting with the EU would be the time where any concerns over the data would be aired. I believe (and so does the company) that the OS change is easily explainable and that the PFS statistically significant effect is most important. In addition, the platinum resistant, FR(++) patients have no options available to them and so EC-145 is targeting an unmet medical need. As such, there should not be an issue as previous EU guidance was that an OS benefit would not be needed for approval. That being said, government agencies can change their minds and people can interpret data in different ways. So investing before this meeting has more risk but if the EU does not change its guidance and allows the application process to move forward then that represents a large derisking event for ECYT and EC-145. So the options is to invest before the meeting and take on more risk but reap the rewards if the EU allows ECYT to proceed (the most likely outcome in my mind). Of course, with the stock trading at cash, there is a lot of bad news already price in the stock but one should be aware of the potential of an EU regulatory roadblock even if though the data do not support a halt of the process.

Disclaimer

I am not a certified financial analyst. All the information provided in this report is my interpretation and may contain errors. Please, do not invest based solely on my opinions as it is critical for all investors to conduct their own due diligence and invest in ways that best fit their own needs. All errors (if any) in this report are mine and due to my misinterpretations. In addition, I am long shares of ECYT.

APPENDIX (Following 2 tables from Fung-Kee-Fung 2007)

TABLE I Literature search results and selected trial characteristics

Reference	*Patients (n)*	*Agent*	*Treatment regimen*			*Platinum-sensitive patients (%)*		*CT line*
			Dose	*Day*	*Cycles (planned)*	*<6 mo.*	*≥6 mo.*	
Pfisterer *et al.*, 2005 [14]	178	Carboplatin	AUC=5	1	6	0	100 [a]	2
NCIC OV15	178	Carboplatin/	AUC=4	1	6	0	100 [a]	2
		gemcitabine	1000 mg/m^2	1+8	6			
Gonzalez–Martin *et al.*, 2005 [15]	40	Carboplatin	AUC=5	1	6–9	0	100 [a]	2–3
GEICO	41	Carboplatin/	AUC=5	1	6–9	0	100 [a]	2–3
		paclitaxel	175 mg/m^2	1	6–9			
Buda *et al.*, 2004 [16]	106	Paclitaxel	175 mg/m^2	1	4–6	75	25	2
GONO/IOR	106	Paclitaxel/	175 mg/m^2	1	4–6	73	27	2
		epirubicin	80 mg/m^2	1	4–6			
Gordon *et al.*, 2004 [17]	239	Pegylated doxorubicin	50 mg/m^2	1	12	54	46	2
Doxil 30-49	235	topotecan	1.5 mg/m^2	1–5	12	53	47	2
ten Bokkel Huinink *et al.*, 2004 [18]	112	Paclitaxel	175 mg/m^2	1	12	52	48	2
ITSG	114	Topotecan	1.5 mg/m^2	1–5	12	54	46	2
Meier *et al.*, 2004 [19,b]	179	Treosulfan	7.0 g/m^2	NR	NR	36	64	2–3
AGO	178	Topotecan	1.5 mg/m^2	1–5	NR	34	66	2–3
Parmar *et al.*, 2003 [20]	410	Carboplatin [c]	AUC≥5	1	6–8	0	100 [a]	2 [d]
ICON4/AGO	392	Carboplatin/	AUC≥5	1	6–8	0	100 [a]	2 [d]
		paclitaxel [c]	≥175 mg/m^2	1	6–8			
O'Byrne *et al.*, 2002 [21,b]	107	Pegylated doxorubicin	50 mg/m^2	1	NR	60	40	2
	107	Paclitaxel	175 mg/m^2	1	NR	63	37	2
Cantu *et al.*, 2002 [22]	50	Paclitaxel	175 mg/m^2	1	≥6	0	100 [e]	2
	47	Cyclophosphamide/	500 mg/m^2	1	≥6	0	100 [e]	2
		doxorubicin/	50 mg/m^2	1	≥6			
		cisplatin	50 mg/m^2	1	≥6			
Bolis *et al.*, 2001 [23]	95	Carboplatin	300 mg/m^2	1	5	0	100	2
	95	Carboplatin/	300 mg/m^2	1	5	0	100	2
		epirubicin	120 mg/m^2	1	5			
Piccart *et al.*, 2000 [24]	41	Paclitaxel	175 mg/m^2	1	6 [f]	76	24	2–3
	45	Oxaliplatin	130 mg/m^2	1	4 [f]	71	29	2–3
Torri *et al.*, 2000 [25,b]	116	Paclitaxel	175 mg/m^2	1	4–6	≥50 [g]	≤50 [g]	2
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[a] Approximately 60% of patients were platinum-sensitive beyond 12 months.
[b] Abstract data from conference proceedings.
[c] The authors reported that 24% of patients received chemotherapy other than carboplatin or paclitaxel and carboplatin.
[d] Among these patients, 8% received third- or greater-line chemotherapy.
[e] In this trial, 100% of patients were platinum-sensitive beyond 12 months.
[f] Actual median number of cycles delivered.
[g] Median time from the end of first-line chemotherapy to trial randomization was 5 months, with a range of 3–12 months.
CT = chemotherapy; NCIC OV15 = National Cancer Institute of Canada OV15 trial; AUC = area under curve; GEICO = Grupo Espanol de Investigacion en Cancer de Ovario; GONO/IOR = Gruppo Oncologico Nord Ovest/Istituto Oncologico Romagnolo; Doxil 30-49 = Doxil Study 30-49; ITSG = International Topotecan Study Group; AGO = Arbeitsgemeinschaft Gynaekologische Onkologie.

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