EP-100 + Paclitaxel Overcomes Taxane Resistance in Patients with Recurrent LHRH Receptor Expressing Ovarian Cancer

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ABSTRACT 5582

Background: EP-100 (E) is a synthetic cytolytic peptide conjugated to Luteinizing Hormone Releasing Hormone (LHRH). It targets cells that overexpress LHRH receptors and kills by membrane disruption. Preclinical studies demonstrate synergy between E and paclitaxel (P). This randomized phase 2 trial explored the efficacy, safety and toxicity of E+P in women with advanced ovarian cancer. **Methods:** "Run-in" dose-escalation specified at least 1 patient would be treated with E per dose level. Patients were randomized 1:1 to receive weekly P (80 mg/m^2 IV) + biweekly E (30 mg/m^2 IV, E+P) vs. weekly P (80 mg/m^2 IV). Unlimited prior regimens were allowed. Central IHC for tumoral LHRH receptors was required. The 1^0 endpoint was overall response rate (ORR) per RECIST 1.1. The 2^0 endpoint was disease control rate (DCR = CR+PR+SD). For an improvement in ORR and DCR of at least 30% with E+P vs. P, a sample size of 20 patients/arm estimated CIs of 6-47% (P alone) vs. 27-73% (E+P). Patients progressing on P were allowed to receive E (30 mg/m^2 IV) plus continuation of P (80 mg/m^{2}IV). Time to progression (TTP) was assessed. **Results:** The "run-in" consisted of 6 patients and established RP2 dose of E+P: 30 mg/m^2 (E) IV biweekly and 80 mg/m^2 (P) IV weekly. 44 patients were enrolled in the phase 2 study. The ORR 34.8% (E+P: 95% CI: 16-57.3%) vs. 33.3% (P: 95% CI 14.6-57%). The DCR was 73.9% (E+P: 95% CI 51.6-89.8%) vs. 71.4% (P: 95% CI 47.8-88.7%). All 44 patients were assessable for safety; 43.5% (E+P) and 47.6% (P) had grade 3 or 4 events, primarily GI and related to underlying disease. The incidence of infusion-related reactions of all grades was greater with E+P (52%, n = 12) than with P (23.8%, n = 5). 10 patients progressed on P and received E+P. 50% had > 3 months of disease stabilization with TTP of 3-7 months, including 1 PR. 60% of these 5 patients had 3 times > TTP with E+P compared to their respective previous TTP after P alone (Mick 2000). The addition of E did not complicate the AE profile of P and was well tolerated. **Conclusions:** EP-100 appears to sensitize paclitaxel-resistant ovarian tumors leading to further shrinkage of target and non-target lesions and prolongation of treatment response. A larger study comprising paclitaxel resistant patients is warranted. Clinical trial information: NCT0145848.

BACKGROUND

- EP-100 (E) is a synthetic cytolytic peptide conjugated to Luteinizing Hormone Releasing Hormone (LHRH) that targets LHRH receptor overexpressing cells and kills them by membrane disruption
- Preclinical studies demonstrated synergy between E and paclitaxel (P) in LHRH receptor expressing cancer cell lines (Leuschner et al 2012) and provided the rationale for this trial.

OBJECTIVE

To explore the efficacy, safety and toxicity of E+P in women with advanced ovarian cancer

METHODS

Key Inclusion Criteria

- Advanced epithelial ovarian cancer
- Platinum resistant with unlimited prior therapy
- Normal organ function (KPS > 70)
- Measurable target lesions (RECIST 1.1) or evaluable tumor marker CA-125 (GCIG)

Responses evaluated at each cycle for CA-125 and every 3 cycles by RECIST 1.1

Evaluation of safety parameters

DESIGN

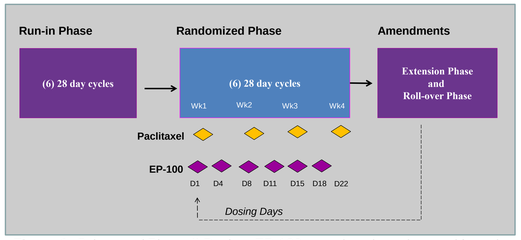

Figure 1: Schema of Phase II Design. EP-100 was given i.v. twice weekly and added to once weekly paclitaxel**.**

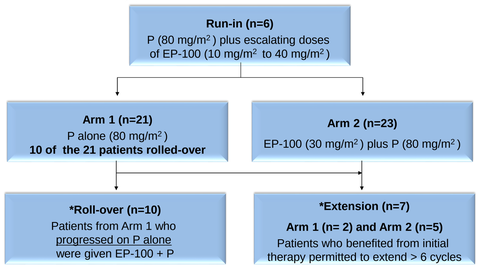

Figure 2: Study groups in Phase II **Extension and Roll over groups are subsets of Arms 1 and Arm 2*

RESULTS

Target Lesion responses were observed in 3/6 Run in patients

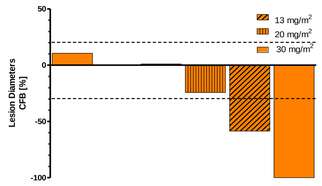

Figure 3: Best Responses of Target Lesions in Run-in Patients (n=6). Clinical benefit was observed in 83% (5/6) and objective responses in 33 % (2/6) of the patients up to 18 months.

Target Lesion responses in the randomized groups were similar

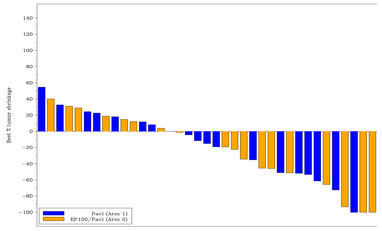

Figure 4: Best Responses of Target Lesions in Randomized Phase (n=37 evaluable, Arm 1 (n=18), Arm 2 (n=19). Objective response rate was 33.3 % in Arm 1 and 34.8 % in Arm 2. The ORR was greater than 20 % as previously reported in the literature by Markman et al (2002).

Target Liver Lesion responses were greater in patients receiving EP-100+paclitaxel (Arm 2) compared to paclitaxel alone (Arm 1)

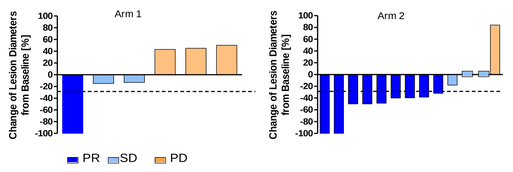

Figure 5: Best Response of Target Liver Lesions by Arm in Randomized Phase (n=6 Arm 1, n = 13 Arm 2). Patients in Arm 2 had better OR by target liver lesions (2 CR, 7 PR; 69 %) than in Arm 1 (1 CR, 16 %).

RESULTS CTD'

Progression free survival was similar in randomized groups Younger patients in Arm 2 had longer PFS (3.9 months vs. 2.3 months)

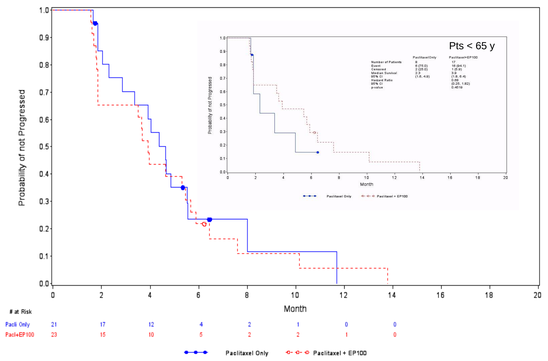

Figure 6: Progression free survival was similar for patients in Arm 1 and Arm 2. Age was a confounding factor (p<0.0146). Patients younger than 65 y had longer PFS in Arm 2 than in Arm 1 (3.9 vs 2.3 months) (Insert).

Addition of EP-100 extended TTP in 5/10 heavily treated patients after progression on paclitaxel alone – EP-100 Added clinical Benefit

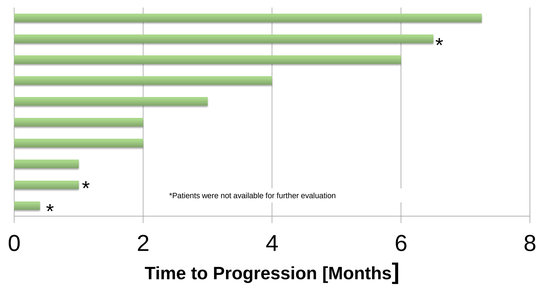

Figure 7: Clinical benefit after paclitaxel failure. 10 patients of the paclitaxel alone group (Arm 1), who had confirmed progression, were treated with EP 100 + paclitaxel. Addition of EP-100 extended time to progression in 5 of 10 patients by 3 to 7 months. Three of these 5 patients had 3 x greater TTP during their roll-over phgase compared to treatment with paclitaxel alone during their randomized phase.

Addition of EP-100 reduced target lesions in 4/7 heavily treated patients after progression on paclitaxel alone

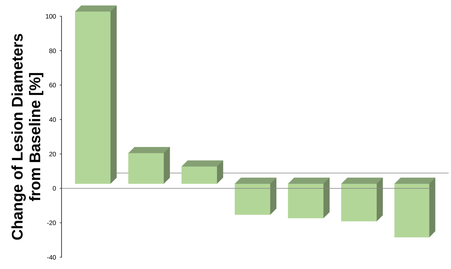

Figure 8: Target lesion responses after paclitaxel failure. Seven of 10 patients who entered the roll-over phase after confirmed progression of P alone were evaluable for target lesion responses. At the time of treatment with EP-100+P, changes of target lesions were assessed from a new baseline. 4 of 7 patients (57%) achieved reduction in target lesion size compared to baseline of -18, -20, -22 and -31 %.

RESULTS CTD'

Addition of EP-100 to Paclitaxel treatment decreased target liver lesion after paclitaxel failure

Pre- Dose **Cycle 2: P alone** **Cycle 4: E+P**

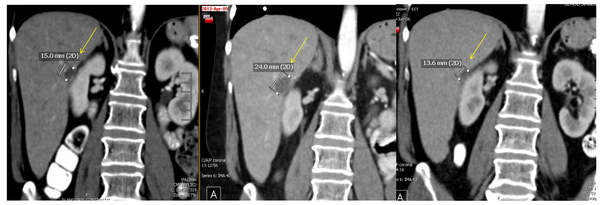

Figure 9: Addition of EP-100 to paclitaxel decreased target liver lesion in a patient who progressed on Paclitaxel alone. The reduction of the target liver lesion from baseline (24 mm) was observed after 2 cycles of EP-100 + P (43.3 %). This patient showed continued reduction of the target liver lesion (5 mm, 79.1 %) after completing 6 cycles in the roll-over phase. This patient discontinued at SD due to infusion reaction.

Addition of EP-100 to Paclitaxel does not exacerbate toxicity of paclitaxel and was administered up to 18 cycles

Safety Randomized Group	Arm 1 (P alone, n = 21)	Arm 2 (E+P, n = 23)
Patients with any TEAE	20 (95.2%)	23 (100%)
Patients with any grade 3-4 TEAE	10 (47.6%)	10 (43.5%)
Patients with any grade 5 TEAE	0	0
Patients with any treatment emergent SAE	4 (19.0%)	5 (21.7%)
Patients with any TEAE leading to permanent treatment discontinuation	1 (4.8%)	2 (8.7%)
Patients with any TEAE	20 (95.2%)	23 (100%)
Patients with any grade 3-4 TEAE	10 (47.6%)	10 (43.5%)

SUMMARY

- **EP-100 in combination with paclitaxel is safe and did not exacerbate toxicity of paclitaxel with continued treatment up to 18 cycles**
- **Clinical benefit was observed in 83% (5/6) and ORR in 33 % (2/6) Run-in patients for up to 18 months**
- **EP-100 + P eliminated more target liver lesions (69 %) compared to P alone (16 %)**
- **Fifty percent (50 %) of the patients that progressed on paclitaxel alone experienced clinical benefit for 3-7 months when EP-100 was added to paclitaxel treatment**
- **EP-100 prolonged TTP by 3 fold compared to paclitaxel alone**
- **EP-100 reversed target lesion progression when added to paclitaxel**

CONCLUSIONS

- **Addition of clinical benefit in paclitaxel resistant ovarian cancer patients, who have currently no treatment options**
- **The combination of EP-100 and paclitaxel is well-tolerated and safe**
- **The combination demonstrates preliminary evidence of efficacy in recurrent ovarian cancer.**
- **EP-100 appears to sensitize paclitaxel-resistant ovarian cancer tumors leading to shrinkage of target and non-target lesions and to prolongation of treatment response**
- **A pivotal study based on encouraging and unexpected phase 2 results identifying the clinical activity of EP-100 when combined with paclitaxel in patients with paclitaxel refractory disease is warranted**

References

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Mick R, Crowley JJ, Carroll RJ. Control clin Trials, 21, 343-359, 2000.
Markman M, Hall J, spitz D, Weiner S, Carson L, Van Le, Baker M. J Clin Oncol 20, 2365-2369, 2002.