Gemcitabine plus carboplatin for the treatment of relapsed, platinum sensitive, ovarian cancer.

Eli Lilly and Company Limited

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Executive Summary

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Ovarian cancer – the disease

- Ovarian cancer is the fifth most common cancer in women in the UK.
- Approximately 7000 women are diagnosed with the disease in the UK each year, with 80% of cases occurring in women over the age of 50. Around 4300 women died from ovarian cancer in the UK in 2010.
- **The 5 year survival rate is low at 43%.** The majority of women are not diagnosed until Stage 3 or 4 where the chance of survival beyond 5 years drops to 22% and 6% respectively.
- Although a significant percentage of women with ovarian cancer respond to initial chemotherapy, between **55% and 75%** of women whose tumours respond to first line therapy **relapse within 2 years** of completing treatment.
- Relapsed disease can be categorised on the basis of response to initial platinum therapy into; platinum sensitive (relapse >12 months), partially platinum sensitive (relapse 6-12 months), platinum resistant (relapse <6 months) and platinum refractory disease (no response).

Treatment of relapsed ovarian cancer

- NICE recommend the following alternatives depending on initial response to platinum treatment [NICE TA91, 2005]:

Agent	Platinum sensitive	Partially platinum sensitive	Platinum resistant	Platinum refractory
Single agent paclitaxel			✓	✓
Paclitaxel plus platinum-based compound[a]	✓	✓		
Pegylated liposomal doxorubicin hydrochloride (PLDH)		✓	✓	✓
Topotecan[b]			✓	✓

[a] Except for patients allergic to platinum-based compounds.
[b] To be used only when PLDH and single-agent paclitaxel are considered inappropriate.

- Re-challenging relapsed patients with paclitaxel plus platinum combination therapy can be associated with **cumulative neurotoxicity** from both paclitaxel and platinum.

Gemcitabine (Gemzar, Eli Lilly and Company Ltd.)

- Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy. Gemcitabine has never been assessed by NICE for this indication in a technology appraisal or clinical guideline.

  - Gemcitabine should be used in combination with carboplatin, administered as gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. Carboplatin should be administered after gemcitabine on Day 1, consistent with a target area under concentration curve (AUC) of 4.0 mg/ml/min.
  - Gemcitabine has been investigated in the treatment of ovarian cancer both as a single agent and in combination therapy with a platinum-based compound. Cisplatin and carboplatin have demonstrated similar activity in patients with advanced ovarian cancer however carboplatin is the preferred agent because of its ease of administration and lower toxicity.
  - **Gemcitabine plus carboplatin** is an **effective treatment option** in patients with platinum sensitive or partially platinum sensitive disease.

Clinical efficacy of gemcitabine plus carboplatin

The **pivotal, Phase III Study JHQJ** *(Pfisterer, 2006)* evaluated gemcitabine plus carboplatin versus carboplatin monotherapy in patients with platinum sensitive, relapsed ovarian cancer and a platinum free interval of >6 months. Two supporting studies include **Study JHRW** *(Kose, 2005)* and **Study SO026** *(du Bois, 2001).*

Study JHQJ

- A randomised, open label, Phase III study comparing gemcitabine plus carboplatin with carboplatin in patients with platinum sensitive, recurrent ovarian cancer (N=356).
- Gemcitabine plus carboplatin showed statistical significant increases compared to carboplatin monotherapy for:
  - Primary endpoint: **progression free survival (PFS)** (8.6 months versus 5.8 months; log rank *P*=0.0031; HR=0.72, 95% CI 0.57-0.9).
  - Secondary endpoint: **overall response rate** (47.2% versus 30.9%; *P*=0.0016)
- The positive effect for PFS of gemcitabine plus carboplatin was maintained after adjusting for the most significant prognostic factor, platinum free interval (adjusted HR=0.71; 95% CI 0.57-0.88).
- Overall survival (OS) for gemcitabine plus carboplatin and carboplatin monotherapy was 18 months versus 17.3 months respectively (HR=0.96, 95% CI 0.75-1.23; log rank *P*=0.7349). The study was not powered to show a significant difference.
- The most common haematologic toxicities were Grade 3 and 4 neutropenia and thrombocytopenia which were significantly more frequent in the GCb arm (p<0.001). **Few patients discontinued treatment due to haematologic events**.
- Less than 5% of patients in either arm experienced Grade 3 and 4 non-haematologic toxicities. The second line use of gemcitabine plus carboplatin in patients treated with first line paclitaxel was associated with a low **rate of neurotoxicity.**

Study JHRW

- A single arm Phase II study of gemcitabine plus carboplatin in platinum sensitive, recurrent ovarian cancer (N=40).
- The efficacy of gemcitabine plus carboplatin was confirmed with favourable results for:
  - The primary endpoint: **overall response rate** (62.5%; 95% CI 45.8%-77.3%).
  - Secondary endpoints: **duration of response** (7.8 months; 95% CI, 6.7–10.0 months), **PFS** (9.6 months; 95% CI, 8.5–11.0 months), and **time to treatment failure (TtTF)** (9.3 months; 95% CI, 8.2–10.4 months).
- A similar response was seen across patients regardless of their platinum-free interval.
- The main Grade 3 and 4 haematologic toxicities were neutropenia (77.5%), leukopenia (n=12; 30%), thrombocytopenia (17.5%) and anaemia (15%).
- No Grade 4 non-haematologic toxicities occurred, and Grade 3 non-haematologic toxicities were mild.

Study SO026

- Phase I/II dose finding study of gemcitabine plus carboplatin in platinum sensitive, recurrent ovarian cancer (N=25).
- A **maximum tolerated dose (MTD)** was established: gemcitabine at 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle, plus carboplatin at AUC 4.0 on Day 1 following gemcitabine.
- The dose limiting toxicity (DLT) was myelosuppression, mainly thrombocytopenia. No dose limiting non-hematological toxicities were observed.
- The overall response rate was 62.5%; median PFS was 10 months; and median OS was 18+ months.

Conclusion

Gemcitabine plus carboplatin is an effective treatment for patients with platinum sensitive, relapsed ovarian cancer and has a toxicity profile that is acceptable and manageable.