Samedi 1er Juin 2013

15h15-15h30  MITO 7  Salle E354a – Oral Presentation
16h00-16h15  OVAR16-PAZOPANIB  Salle E354a – Oral Presentation
16h15-16h30  POLKa  Salle E354a – Oral Presentation

Lundi 3 juin 2013

8h00-12h00  CALYPSO – PFS selon CA125  S Hall A2 – Poster
13h30-13h45  TAMRAD BIO  N Hall B1 – Oral Presentation

ORAL PRESENTATION : Gynecologic Cancer

**Samedi 1er juin : Salle E354a**

**15h15 à 15h30**
**ÉTUDE MITO7**
Sandro Pignata
Abstract N°: #LBA5501

A randomized multicenter phase III study comparing weekly versus every 3 weeks carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicenter Italian Trials in Ovarian Cancer (MITO-7)—European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10) and Gynecologic Cancer Intergroup (GCIG) trial.

**16h00 à 16h15**
**ÉTUDE OVAR16-PAZOPANIB**
Andreas Du Bois
Abstract N°: #LBA5503

Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): Results of an international Intergroup trial (AGO-OVAR16).
**Title**: Phase II trial of volasertib (BI 6727) versus chemotherapy (CT) in platinum-resistant/refractory ovarian cancer (OC).

**Background**: Volasertib (V) is a potent and selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinases. This study investigated V vs CT as 3rd- or 4th-line therapy in patients (pts) with platinum-refractory or resistant OC.

**Methods**: Pts were randomized to V 300 mg IV Q3W or investigator’s choice single-agent CT (pegylated liposomal doxorubicin, topotecan, paclitaxel, gemcitabine) until progression or intolerance. Primary endpoint was 24-wk disease control rate (DCR; % of pts with complete/partial response [PR] or stable disease [SD]). Secondary endpoints included safety, progression-free survival (PFS), best overall response (RECIST 1.1) and explorative biomarkers.

**Results**: 109 pts received V (n=54) or CT (n = 55) for a median (range) of 95 (22–716) and 114 (7–351) days, respectively. Demographic data were balanced between the treatment arms. Overall, median age was 62.0 yr; ECOG PS 0–1: 103 pts; 2 prior CTs: 51 pts; ≥3 prior CTs: 57 pts; platinum-resistant: 78 pts; platinum-refractory: 31 pts; measurable disease: 89 pts. 24-wk DCR (95% CI) for V vs CT was 31% (18–43) vs 43% (30–57), and median PFS was 13.1 vs 20.6 wks (HR = 1.01; 95% CI: 0.66–1.53). Six V pts vs 0 CT pts are ongoing for PFS 1 yr after randomization. Best overall response in pts with measurable disease (V/CT) was: PR, 7/8 pts; SD, 24/24 pts. Adverse events (AEs) led to discontinuation in 20 pts (V, n = 5; CT, n = 15); no V pts and 8 CT pts discontinued due to treatment-related AEs (including neuropathy in 3 CT pts). Most frequent all grade AEs (% of pts) regardless of relatedness were neutropenia (61%), anemia (54%), thrombocytopenia (46%), nausea (37%) and asthenia (33%) with V, and asthenia/nausea (47% each), abdominal pain (38%), anemia (36%) and neutropenia/vomiting (31% each) with CT. There were 3 fatal AEs per arm.

**Conclusion**: Single-agent V showed antitumor activity in OC in a range similar to CT. AEs with V were mainly hematologic and manageable, with fewer non-hematologic AEs than CT. Exploration of potential predictive biomarkers for V activity is ongoing.
Lundi 3 juin de 08h00 à 12h00 : S Hall A2

CALYPSO PFS selon CA125
Mélanie Wilbaux
Abstract #5547

**Title:** Benefit in progression-free survival (PFS) to expect based on CA125 reduction at week 6 in recurrent ovarian cancer (ROC) patients: CALYPSO phase III trial data (a GINECO-GCIG study).

**Background:** Prediction of the expected survival benefit based on CA125 change in treated recurrent ovarian cancer (ROC) patients would be very useful. It may help for early selection of the best drug candidates during drug development, and for clinical trials. We used mathematical modeling to: 1) quantify the links between CA125 kinetics and progression-free survival (PFS) benefit, and 2) to estimate the CA125 decline required to observe a 50% PFS improvement.

**Methods:** CALYPSO randomized phase III trial database, comparing 2 platinum-based regimens in ROC patients was used. The cohort was randomly split into a “learning dataset” (N=356) to estimate model parameters and a “validation dataset” (N=178) to validate model performances. A full parametric survival model was developed to quantify the links between tumor size changes; CA125 kinetics; prognostic factors and PFS. The predictive performance of the model was evaluated with simulations on the validation dataset.

**Results:** PFS from 534 ROC patients was properly described by a parametric model with log-logistic distribution. The factors significantly linked to PFS were fractional changes in CA125 (ΔCA125) and in tumor size (ΔTS) from baseline at week 6; baseline CA125 (CA125BL); and patient therapy free interval. By reducing this model, ΔCA125 was a better predictor of PFS than ΔTS. Simulations verified the predictive performance of this model. Patients should achieve at least 49% ΔCA125 decline induced by treatment to observe 50% PFS improvement. This effect was independent on treatment arm.

**Conclusion:** This is the first drug-independent parametric survival model quantifying links between PFS and CA125 kinetics in ROC. The CA125 modeled decline required to observe a 50% improvement in PFS in treated ROC patients was defined. It may be a surrogate marker of PFS gain, and may embody an early predictive tool for go/no go drug development decisions and for clinical trials. Validation in other datasets is warranted.
Title: Predictive markers of everolimus efficacy in hormone receptor positive (HR+) metastatic breast cancer (MBC): Final results of the TAMRAD trial translational study.

Background: Hormone resistance is linked in part to cross-talk between ER signalling and PI3K/Akt/mTOR pathway. Following results of the BOLERO-2 trial, everolimus (E), a potent mTOR inhibitor, has recently been approved in combination with exemestane in women with HR+ MBC refractory to aromatase inhibitor (AI). However, E is frequently associated with specific toxicities, and predictive markers of efficacy are needed. We report here the final results of translational studies within the TAMRAD randomized Phase II trial, comparing tamoxifen (TAM) to TAM+E in AI pre-treated MBC.

Methods: Tumor samples from 51 patients among the 111 treated in the TAMRAD trial were retrieved. Hot spot mutations of PI3K (exon 9-20), and KRAS (exon 2) were described. TMA analysis evaluated IHC expression of PTEN, pAkt, PI3K, LKB1, S6K, pS6K, 4EBP1, p4EBP1, and elf4E. Exploratory analysis of E efficacy in each biomarker subgroup (high vs low expression defined by median percentage of marked cells) was done.

Results: Patients characteristics and treatment efficacy among this sub-population were similar to the results from the whole population: Time to progression was 10 months for the TAM+E treated patients vs. 5.5 months for the TAM treated patients, HR: 0.59 (95% CI 0.33-1.07). PI3K-Akt pathway: All patients derived benefit from E regardless of PI3K mutational status, PTEN or pAkt expression. Surprisingly, E efficacy was greater in patients with low PI3K expression (n=12, HR=0.11, 95%CI 0.01-0.96) than in patients with high PI3K expression (n= 28, HR=0.9; 95%CI 0.49-2.41) PI3K independent pathway: Patients with low expression of the anti-oncogene LKB1 derived greater benefit from E (n=22, HR=0.33; 95%CI 0.13-0.89) than patients with high LKB1 expression (n=25, HR=0.75; 95%CI 0.32-1.74) mTOR downstream effectors: Patients with high p4EBP1 (n=27, HR=0.37; 95%CI 0.15-0.90) or low 4EBP1 (n=21, HR=0.39; 95%CI 0.14-1.08) were the subgroups most likely to benefit from E.

Conclusions: Those results are in favor of a better efficacy of E for patients with PI3K independent activation of mTOR. If confirmed, they could have important implications for future patient selection.