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Conference Report

American Society of Clinical Oncology 2013 annual meeting update: Summary of selected gynecologic oncology abstracts

Introduction

The 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO) took place in Chicago, Illinois from May 31–June 4 with the theme "Building Bridges to Conquer Cancer". Approximately 30,000 professionals attended the meeting from around the globe. This was an impressive year for gynecologic oncology as 132 abstracts were selected, including representation at 2 of 5 abstracts in the main plenary session and 6 phase III trials. In total there were 11, 3, 25, 88, and 5 abstracts chosen for oral, clinical symposium, poster discussion, general poster and trials in progress poster sessions, respectively. This report highlights selected phase II and III clinical trials in ovarian, endometrial and cervical cancer.

Phase II trials of novel and cytotoxic treatment strategies in ovarian cancer (Table 1)

Oncogenic pathways offer potential targets for therapy. TP53 mutations result in FOXM-1 overexpression and its related target genes, including Polo-kinase 1, which is a key regulator of mitosis. Volasertib targets Polo-like kinases and induces mitotic arrest and apoptosis. It was evaluated in a randomized phase II trial in platinum-refractory or resistant ovarian cancer as 3rd or 4th line therapy (POLKA study, N = 109). Patients received volasertib 300 mg IV every 3 weeks or one of four single agent chemotherapies. Six-month disease control rate and median progression-free survival (PFS) were lower in the volasertib arm (31% *vs.* 43%; 13 weeks *vs.* 21 weeks, $P > 0.05$) (*Abstract 5504*).

A randomized phase II trial of olaparib, an oral PARP inhibitor, as maintenance therapy *versus* placebo in platinum-sensitive recurrent ovarian cancer demonstrated a 3.6-month improvement in PFS (Study 19, Ledermann, et al. N Engl J Med. 2012; 366: 1382–92). The investigators hypothesized *a priori* that olaparib may be of greater benefit in *BRCA* mutation patients and reported this data at ASCO. 136 (51.3%) had a known *BRCA* mutation either germline or tumor, 118 (44.5%) had wild-type (WT) mutations and 11 (4.2%) had unavailable results. There was an 82% reduction in the risk of disease progression or death for patients with a *BRCA* mutation either germline or tumor receiving olaparib (PFS 11.2 months *vs.* 4.3 months, HR = 0.18, 95% CI 0.11–0.31, $P < 0.00001$). Additionally, there was improvement in PFS in the WT patients. Overall survival (OS) at 58% maturity showed no improvement (29.8 months olaparib *vs.* 27.8 months placebo, HR = 0.88, 95% CI 0.64–1.21, $P = 0.44$); however, when including only *BRCA* mutations either germline or tumor, there was a trend towards improvement for patients receiving olaparib (34.9 months *vs.* 31.9 months, HR = 0.74, 95% CI 0.46–1.19, $P = 0.21$). A phase III trial in *BRCA* mutation patients is warranted (*Abstract 5505*).

Phase II trials of anti-angiogenics in ovarian cancer (Table 2)

There were 5 phase II trials studying vascular targeting agents (for the prevention of neovascularization) (*Abstracts 5512*, *5513*, *5517*, *5520*, *5558*) and one evaluating a vascular disrupting agent that targets existing tumor vessels and causes necrosis (*Abstracts 5516*).

Asian women (N = 145) following primary cytoreduction and chemotherapy for stages II–IV ovarian cancer were enrolled in a randomized phase II maintenance trial of pazopanib, an oral multi-kinase inhibitor of VEGF, PDGF and c-Kit, for up to 24 months or placebo. There was no difference in PFS (PFS 18 months in each arm, HR 0.98, $P > 0.05$). Additionally, there was more toxicity in the pazopanib arm (*Abstract 5512*). See related phase III trial *Abstract LBA5503* below.

A trial of another multi-kinase inhibitor evaluated sorafenib, a RAF kinase inhibitor and an inhibitor of the VEGR-2/PDGFR-β cascade. Untreated stage III and IV ovarian carcinoma patients underwent cytoreduction and were randomized to 6 cycles of paclitaxel 175 mg/m^2, carboplatin AUC 6 and sorafenib 400 mg bid followed by single agent sorafenib maintenance for 52 weeks (N = 43) *versus* paclitaxel and carboplatin alone (N = 42). The trial was terminated early due to slow accrual. Similar survival was noted in each arm (2-year PFS of 40% *vs.* 39%, $P = 0.36$) and toxicity was higher in the sorafenib arm (*Abstract 5513*).

Vascular disrupting agents (VDAs) may hold promise in advanced and recurrent ovarian cancer as an active additional regimen. Ombrabulin (AVE8062) is a VDA tubulin-binding agent targeting microtubules in the endothelial tumor vascular cells and selectively disrupts the vessels creating necrosis and regression. Patients with first platinum-sensitive recurrent ovarian cancer were randomized to paclitaxel 175 mg/m^2, carboplatin AUC 5 or 6, and ombrabulin 35 mg/m^2 or placebo every 21 days for at least 6 cycles. After an interim analysis, the study was discontinued due to the unlikelihood that ombrabulin would show superiority (PFS = 8.4 months *vs.* 10.4 months, HR 1.33, 60% CI 1.06–1.69, $P = 0.85$, one-sided) (*Abstract 5516*).

Dual anti-angiogenic blockade is an interesting concept that was explored in a phase II trial of temsirolimus (mTOR inhibitor) and bevacizumab. Recurrent ovarian cancer patients with 1–2 previous lines of chemotherapy naïve to mTOR and VEGF inhibitors received weekly IV temsirolimus 25 mg and every other week IV bevacizumab 10 mg/kg on a 28 day cycle (N = 53 evaluable). 49% of the patients remained progression free at 6 months with an overall response rate (RR) of 28%. 59% of the patients were considered platinum-

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Table 1
Phase II trials of novel drug and cytotoxic treatment strategies in ovarian, fallopian tube, and primary peritoneal carcinomas.

Type of trial	Abs #	Agents/dose	Mechanism	Type of patients	Results	HR	*P* value	Major toxicity
Phase II single agent	5515	Ganitumab (AMG 479) oral 18 mg/kg, q3w	Fully human monoclonal antibody against IGF-1R blocking IGF-1/2 binding	Pt-S ROC, 2nd line therapy CA125 progression and/or measurable disease per RECIST failing primary P-based therapy	CA125 *vs.* RECIST Irc *vs.* RECIST Inv: PFS = 7.8 *vs.* 2.1 months Irc CR = 3.4 *vs.* 0 *vs.* 1.6% PR = 6.6 *vs.* 1.7 *vs.* 1.6% SD = 62.7 *vs.* 39.7 *vs.* 26.2% OS = 25.3 months TTP CA125 = 4.96 months	–	–	Gr 1–2 hyperglycemia (49%); Gr 3: asthenia (1.6%), f (1.6%), and HA (1.6%)
	5559	Trabectedin IV 1.1 mg/m^2 3 h infusion q3w with dexamethasone pretreatment 4 mg bid 24 h prior	Cytotoxic; marine-derived alkaloid interacts with the minor groove of the DNA double helix	Recurrent EOC; 2–4 lines of previous CT treatment	RR = 56.2% CR = 0% PR = 56.2% SD = 25%, avg 12 weeks PD = 18.8% PFS = 18 weeks OS = 7.7 months	–	–	An, leucopenia, PLTS, asthenia No dose reductions required
	2580[a]	BMN 673 oral 25–1100 μg daily, continuous in 4 week cycles MTD for single agent development = 1000 μg/day due to DLT PLT	PARP-1/2 inhibitor Phase 1 first in human trial	OC/PPC = 79.3% (23/39) BRCA-1/2 mutation = 74% (17/23)	RR = 64.7% OC gBRCA RECIST = 44% CA125 = 70% CBR = 82% SD ≥ 24 weeks gBRCA = 14.2% Plasma conc. peaked 1–2 h post-dose Steady state plasma conc. by end of 2nd week	–	–	f, n, alopecia in 20–30%; flatulence, An, ANC, PLTS (10–20%)
Phase II combination	5537	Etoposide oral 50 mg/m^2 days 1–21 + irinotecan IV 70 mg/m^2 days 1 and 15, q28d, ≤6 cycles	Topoisomerase I/II inhibitors	Pt-R and taxane-pretreated ROC	RR = 21.7% CR = 1.7% PR = 20.0% SD = 38.3% PFS = 4.1 months OS = 11.9 months PFS 6 months = 35.0% PFI ≥ 3 months = 55% RR = 30.3% PFS = 5.8 months OS = 16.9 months	–	$P = 0.42$	Gr 3/4: ANC 60%, An 37%, PLTS 12%, FN 18%, f 13%, n 12%, anorexia 12% ≥65 years 29% FN
	5554	Etoposide oral 50 mg/m^2 + oral cyclophosphamide 50 mg/m^2, days 1–21, +tamoxifen oral 20 mg bid days 1–28 q28d	Topoisomerase II inhibitor; cytotoxic; anti-estrogen	ROC; ≥2 CT regimens -achieved CR after 1st line tx and ≥PR as best response to 2nd line -clear PD after 2nd CR or PR Received Plt 2nd line = 88% Received Taxane 1st line = 88% Median age 48	OS = 22.3 months PFS = 7.9 *vs.* 7.97 months CA125 *vs.* radiologic RR = 76 *vs.* 45.8% CR = 48 *vs.* 25% TTR = 1.8 *vs.* 3.7 months DoR = 7.0 *vs.* 5.5 months	–	–	76% Gr 3/4 An (15%), ANC, FN, n, v, d 52% required dose reduction Rp2 planned with flat 50 mg dose of etoposide cyclophosphamide