Gyn Oncology Clinical Trials and Research

Disease Type	Protocol
Cervical AIM2CERV	Phase 3 study of Adxs11-001 administered following chemoradiation as adjuvant treatment for high risk locally advanced cervical cancer (advaxis immunotherapy 2 prevent cervical recurrence)
Cervical Empower - 1	An Open-Label, Randomized, Phase 3 Clinical Trial of REGN2810 Versus Therapy of Investigator's Choice Chemotherapy in Recurrent or Metastatic Platinum-Refractory Cervical Carcinoma
Cervical GCT1015-04	A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer
Cervical GCT1015-05	A Phase 2 Open-Label Trial of Tisotumab Vedotin (HuMax® TF ADC) alone or in Combination in First Line Recurrent or Stage IVB Cervical Cancer
Cervical KEYNOTE-826	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer
Endometrial KEYNOTE-775	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer
Ovarian ATHENA	A Multicenter, RAndomized, Double-Blind, Placebo-ConTrolled PHasE 3 Study of Nivolumab and RucAparib Combination Switch Maintenance following Front-Line Platinum-based Chemotherapy in Ovarian Cancer Patients
Ovarian ImaGyn-50	A phase III, multicenter, randomized, study of Atezolizumab versus placebo administered in combination with Paclitaxel, Carboplatin, and Bevacizumab to patients with newly-diagnosed stage III or stage IV ovarian, fallopian tube, or primary peritoneal cancer
Ovarian Javelin Ovarian PARP 100	A randomized, open-label, multicenter, Phase 3 study to evaluate the efficacy and safety of Avelumab in combination with chemotherapy followed by maintenance therapy of Avelumab in combination with the poly (adenosine diphosphate [adp]-ribose) polymerase (parp) inhibitor talazoparib in patients with previously untreated advanced ovarian cancer

Please note: If you are unable to find a clinical trial that works for you, contact 888.972.CURE and ask for the Research Department.
Disclaimer: Studies may close promptly when target enrollment is met.

To refer a patient visit AoAppt.com

Ovarian Cancer Risk Factors: Beyond BRCA References:

1. Menon, Karpinsky, Gentry-Maharaj (2018). Ovarian Cancer Prevention and Screening. Obstet & Gyn. 131(5):909-927.
2. Islami, Sauer, Jemal et al. (2018). Proportion and Number of Cancer Cases and Deaths Attributable to Potentially Modifiable Risk Factors in USA. CA Journal, 68(1):31-54.
3. Ring, Garcia, Thomas and Modesitt. (2017). Current and Future Role of Genetic Screening in Gyn Malignancies. Am Jo of Obstet&Gyn. 1-9.
4. Falconer, Gronberg & Altman. (2015). Nationwide Ovarian Cancer Risk After Salpingectomy: A Population Based Study. JNCI. 27(10)712.
5. Collaborative Group on Epidemiologic Studies of Ovarian Cancer. (2012). PLOS Med. 9(4).
6. Chen, Berek, Falk et al. (2018). UpToDate: EOC/Tubal/PPC Epidemiology and Risk Factors. Literature current as of 4/30/18.

Intraperitoneal Chemotherapy Article References:

1. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335:1950-1955, 1996.
2. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 19:1001-1007, 2001.
3. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34-43, 2006.
4. Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 33:1460-1466, 2015.
5. Monk BJ, Chan JK. Is intraperitoneal chemotherapy still an acceptable option in primary adjuvant chemotherapy for advanced ovarian cancer? Ann Oncol 28(suppl 8):viii40-viii45, 2017.
6. Walker JL, Brady MF, DiSilvestro PA, et al. A phase III clinical trial of bevacizumab with IV versus IP chemotherapy in ovarian, fallopian tube, and primary peritoneal carcinoma: A GOG/NRG trial (GOG 252). 2016 Annual Meeting on Women's Cancer. Abstract 6. Presented March 21, 2016.
7. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 378:230-240, 2018.
8. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365:2473-2483, 2011.
9. Cowan RA, O'Cearbhaill RE, Zivanovic O, et al. Current status and future prospects of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) clinical trials in ovarian cancer. Int J Hyperthermia 33:548-553, 2017.
10. Provencher DM, Gallagher CJ, Parulekar WR, et al. A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. Ann Oncol 29:431-438, 2018.

Gyn Oncology Offices

BILTMORE CANCER CENTER
2222 E. Highland Ave., Suite 400, Phoenix, AZ 85016
Matthew Borst, MD, Heather Dalton, MD
Brad Monk, MD, Lyndsay Willmott, MD

DEER VALLEY
19646 N. 27th Ave., Suite 403, Phoenix, AZ 85027
Shana Wingo, MD, Dennis Scribner, MD

EAST MESA
6424 East Broadway, Mesa, AZ 85206
Snehal Bhoola, MD

EAST VALLEY CANCER CENTER
Medical, Gynecologic & Radiation Oncology, and Hematology
7695 South Research Dr., Tempe, AZ 85284
Snehal Bhoola, MD, Dana Chase, MD

GOODYEAR
Medical Oncology & Hematology, Gynecologic Oncology
13555 W. McDowell Rd., Suite 206, Goodyear, AZ 85395
Heather Dalton, MD

SCOTTSDALE
Gynecologic Oncology
10197 N. 92nd Street, Suite 101, Scottsdale, AZ 85258
Mike Janicek, MD

SCOTTSDALE
Medical & Gynecologic Oncology, and Hematology
10460 N. 92nd Street, Suite 402, Scottsdale, AZ 85258
Dennis Scribner, MD, Bradley Monk, MD

TUCSON - WILMOT
603 N. Wilmot Road, Suite 151, Tucson, AZ 85711
Joseph Buscema, MD
Casandra Liggins, MD (Advanced Gyn Practitioner)

TUCSON - ORANGE GROVE
1845 W. Orange Grove, Bldg. 2, Tucson, AZ 85704
Alton Hallum, III, MD, Candice Lewis, MD

PHOENIX & NORTHERN ARIZONA

TO REFER A PATIENT:
For Drs. Bhoola, Borst, Chase, Dalton, Monk and Willmott
Phone: 888-972-CURE (2873) Fax: 602-283-3059

TO REFER A PATIENT:
For Drs. Wingo and Scribner
Phone: 623-879-4477 Fax: 623-879-4455

TO REFER A PATIENT:
For Dr. Janicek
Phone: 480-993-2950 Fax: 480-993-2957

TUCSON & SOUTHERN ARIZONA

TO REFER A PATIENT:
For Drs. Buscema and Liggins
Phone: 520-886-0206 Fax: 520-886-0829

TO REFER A PATIENT:
For Drs. Hallum and Lewis
Phone: 520-531-8967 Fax: 623-582-5300

Phoenix Gynecologic Oncologists

Arizona Oncology ■ 888.972.CURE ■ August 2018

GynOncology UPDATE

Ovarian Cancer Risk Factors: Beyond BRCA

by | MATTHEW BORST, MD

Literature Review Shows 40% of Ovarian Cancer Cases Have Identifiable Risk Factors That Can Be Modified To Potentially Reduce Risk of the Disease

FACTORS INFLUENCING
OVARIAN/FALLOPIAN TUBE/PERITONEAL CANCER RISK

CATEGORY A: Genetics (24% of all ovarian cancer cases)

Mutation	Relative Risk	Potential Interventions	Relative Risk after Intervention	% Risk Reduction
BRCA 1	29.0	OCP Use	0.5	50%
		BTL	0.66-0.85	15-34%
BRCA 2	12.0	B/L Salpingectomy	0.39	61%
		RR BSO	0.2	80%
RAD 51C	3.4-15	Interventions Noted Above Can Be Considered	Interventions Listed are Estimated to be Protective Quantitative Data-Pending	
RAD 51D	6.3-12			
BRIP 1	6.4-12			
Lynch	4.0-6.0	Hyst with BSO	Estimated Highly Efficacious	

CATEGORY B: Endometriosis (~5% of all ovarian cancer cases)

Risk Factor	Relative Risk	Potential Interventions	Relative Risk after Intervention	% Risk Reduction
Endometriosis	1.46	OCP Use	0.21	79%
Endometrioma	4.0	Surgical Excision	Estimated Highly Efficacious	

CATEGORY C: Obesity (~4.3% of all ovarian cancer cases)

Risk Factor	Relative Risk	Potential Interventions	Relative Risk after Intervention	% Risk Reduction
Obesity	1.22	Diet/Physical Activity	0.69	31%

CATEGORY D: Other Factors (~10+% of all ovarian cancer cases)

Risk Factor	Relative Risk	Potential Interventions	Relative Risk after Intervention	% Risk Reduction
Nulligravity	1.6	Multiparity	0.5	50%
		OCP Use	0.5	5%
PCOS	2.5-2.8	BTL	0.66-0.85	15-34%
Family History	3.1-4.6	ASA Use	0.56	44%
		B/L Salpingectomy	0.39	61%

Chart references on page 5.

WELCOME

Welcome to Arizona Oncology's first edition of The Gyn Oncology Update newsletter. We are dedicated to educate and serve patients in our community. We hope you enjoy the educational content presented within. If you have any questions or feedback, please do not hesitate to contact us.

In This **ISSUE**

ARIZONA ONCOLOGY

The US Oncology Network

Validity of Bilateral Salpingectomy

Swedish Cancer Registry Data Supports the Validity of Bilateral Salpingectomy To Reduce Lifetime Risk of Ovarian Cancer (info compiled by **Casandra Liggins, MD**)

Ovarian Cancer Risk After Salpingectomy:
A Nationwide Population-Based Study

Henrik Falconer, Li Yin, Henrik Grönberg, Daniel Altman
JNCI: Journal of the National Cancer Institute, Volume 107, Issue 2, 1 February 2015, dju410

The first table gives the temporal aspect of ovarian cancer according to surgical procedures in five-year bands. Apart from the group of women with concomitant hysterectomy and BSO, statistically significant hazard ratios were only observed more than 10 years after surgery among women with sterilization or salpingectomy. Similar results were observed in the subanalysis according to one- or two-sided salpingectomy. A borderline significant result was detected in the group of women with hysterectomy over 10 years after surgery. In the following table, the number of ovarian cancer cases and person-years in relation to follow-up are presented. The number of ovarian cancer cases increased with time, but the association seems independent of the follow-up time (P values for equality of different follow-up periods were .72 for hysterectomy, .99 for hysterectomy and BSO, .53 for salpingectomy, and .80 for sterilization).

Hazard ratios for ovarian cancer over time since surgery according to surgical procedures*

Surgery	Time since surgery, y‡		
	0–4	5–9	10+
Hysterectomy	0.55 (0.25 to 1.20)	0.94 (0.38 to 2.29)	0.87 (0.74 to 1.03)
Hysterectomy and BSO	0.05 (0.01 to 0.27)	0.07 (0.01 to 0.30)	0.06 (0.02 to 0.24)
Salpingectomy (all)	1.10 (0.48 to 2.49)	0.50 (0.17 to 1.43)	0.63 (0.48 to 0.81)
Unilateral	1.44 (0.60 to 3.48)	0.64 (0.21 to 1.93)	0.68 (0.52 to 0.90)
Bilateral	0.61 (0.08 to 4.61)	No cases	0.39 (0.18 to 0.87)
Sterilization	0.46 (0.19 to 1.10)	0.75 (0.29 to 1.97)	0.76 (0.66 to 0.86)
Unexposed	Referent	Referent	Referent

* Presented as hazard ratios and confidence intervals. Cox proportional hazard models were used to estimate hazard ratios; two-sided 95% confidence intervals are given. BSO = bilateral salpingoophorectomy.

‡ Adjusted for age, calendar time, education status, parity.

Number of ovarian cancer cases (person-years) over time since surgery according to surgical procedures*

Surgery	Time since surgery, y‡		
	0–4	5–9	10+
Hysterectomy	40 (352629)	91 (323693)	147 (426995)
Hysterectomy and BSO	2 (125388)	3 (98805)	2 (74636)
Salpingectomy (all)	13 (129741)	10 (140068)	58 (351064)
Unilateral	8 (77461)	8 (95253)	59 (299549)
Bilateral	1 (12025)	0 (14652)	6 (43887)
Sterilization	15 (321372)	40 (384976)	229 (1038126)
Unexposed	3818 (20888662)	4632 (23569449)	22299 (81332880)

* BSO = bilateral salpingoophorectomy

Genetic Counseling Referral Criteria

Refer patients that meet any of the following criteria:

LYNCH SYNDROME

- ☐ Abnormal Lynch tumor screen
- ☐ Two or more colon, uterine or other Lynch related tumors* in same person
- ☐ Colon or uterine cancer at or before age 50
- ☐ 3 or more family members on same side of the family with colon, uterine or other Lynch-related tumors*

  Note: Universal Lynch screening is recommended for all uterine and colon tumors

  **Colon, uterine, ovarian, gastric, pancreatic, urinary tract, sebaceous tumor and brain tumors*

HEREDITARY BREAST AND OVARIAN CANCER

- ☐ Breast cancer at or before age 50
- ☐ Triple negative breast cancer at or before age 60
- ☐ Two primary breast cancers in the same person
- ☐ Ovarian (including fallopian tube or primary peritoneal cancer) at any age
- ☐ Prior negative BRCA1/2 testing
- ☐ Any pancreatic cancer patient
- ☐ Any metastatic prostate cancer patient
- ☐ 3 or more relatives with breast, ovarian, pancreatic &/or aggressive prostate cancer on the same side of the family
- ☐ Ashkenazi Jewish ancestry with personal or family history of breast, ovarian or pancreatic cancer

  Breast Cancer includes DCIS and Invasive Cancers.

Other Criteria

- ☐ 10-20 total colon polyps
- ☐ Multiple hamartomatous or Juvenile GI polyps
- ☐ Rare tumors such as medullary thyroid carcinoma, paragangliomas or pheochromocytomas
- ☐ Known gene mutation in family

Access the online pedigree tool:
FHQ.ROOTOUTCANCER.COM

How a Recent Study Heats up the Debate
Over Intraperitoneal Chemotherapy in Newly Diagnosed Advanced Ovarian Cancer

by | BRADLEY J. MONK, MD, FACS, FACOG

Based on pharmacokinetic and preclinical data, there appears to be a biologic advantage to the use of intraperitoneal chemotherapy in treating some malignancies confined to the abdomen. Since most ovarian, fallopian tube, and peritoneal cancers present and recur in the peritoneal cavity, this setting is potentially an ideal scenario for intraperitoneal therapy.

Compared to intravenous treatment, intraperitoneal administration of cisplatin can achieve an approximate 20-fold greater concentration in the tumor. This pharmacokinetic advantage of intraperitoneal therapy is particularly evident in smaller lesions (< 3–5 mm) and avascular tumors, since penetration is limited in bulky cancers, and intravenous therapy is probably adequate in well-perfused tumors.

Key Historical Trials

Three large intergroup randomized phase III trials (Gynecologic Oncology Group [GOG] protocols 104, 114, and 172) have demonstrated that intraperitoneal therapy resulted in a 20% to 30% reduction in death over intravenous therapy in advanced, low-volume epithelial ovarian cancer.[1-3] The results of GOG 172 prompted the National Cancer Institute (NCI) to broadcast a clinical alert in January 2006 stating that intraperitoneal chemotherapy improves survival in patients compared to intravenous treatment alone. A subsequent meta-analysis with over 10 years of follow-up suggested a sustained benefit of intraperitoneal chemotherapy over intravenous treatment.[4]

Unfortunately, the experimental arm in GOG 172 included not only intraperitoneal therapy, but also a weekly schedule and higher doses compared to the every-3-week intravenous cisplatin-containing (rather than carboplatin-based) control arm. These confounding factors are often overlooked, and the improvement in overall survival in the experimental intraperitoneal arm is often attributed entirely to the intraperitoneal route of administration.

Despite the positive clinical trial results and the subsequent NCI alert, intraperitoneal treatment has not been widely accepted as the standard of care in the United States and is infrequently used in Europe.[5] The hesitancy of clinicians to use intraperitoneal therapy is likely attributed to higher toxicity, inconvenience, catheter complications, flaws in clinical trial design, and uncertain long-term benefits.

More recently, a fourth randomized phase III trial of 1,560 subjects (GOG Protocol 252) has reported negative results.[6] This was the largest phase III study and the only clinical trial that isolated the impact of intraperitoneal chemotherapy administration. Many believed that this higher-quality and resoundingly negative study superseded the prior positive studies and ended this 3-decade debate.

New Data

In January 2018, van Driel of the Netherlands Cancer Institute and colleagues published a provocative study of hyperthermic intraperitoneal chemotherapy (aka HIPEC) in The New England Journal of Medicine.[7] The study was conducted in 245 patients among 8 sites in the Netherlands and Belgium with advanced epithelial ovarian cancer who had at least stable disease after three cycles of neoadjuvant carboplatin and paclitaxel. Randomization was stratified by previous surgery, hospital in which surgery was performed, and number of involved regions in the abdominal cavity. Patients received three additional cycles of carboplatin and paclitaxel after surgery. The primary end point was recurrence-free survival in the intent-to-treat population. The minimum number of events required for recurrence-free survival analysis was reached in April 2016 and efficacy data were updated in March 2017.

In the HIPEC vs control groups: median age was 61 vs 63 years; histology was high-grade serous in 92% vs 87%; residual disease after surgery was R-1 in 69% vs 67%, R-2a in 18% vs 20%, and R-2b in 11% in both; 76% in both had no bowel resection; median duration of surgery was 338 vs 192 minutes; median duration of hospitalization was 10 vs 8 days; median time between surgery and start of adjuvant chemotherapy was 33 vs 30 days; and 94% vs 90% completed 3 cycles of adjuvant chemotherapy. Among patients who underwent bowel resection, colostomy or ileostomy was more common in the HIPEC group (21/29 patients = 72%) vs the control group (13/30 patients =43%; P = .04).

Median follow-up at time of recurrence-free survival analysis was 4.7 years. Recurrence-free survival events occurred in 81% of the HIPEC group vs 89% of the control group; median recurrence-free survival was 14.2 months vs 10.7 months (hazard ratio [HR] = 0.66. P = .003). Benefit of HIPEC was consistent across stratification factors and post hoc subgroups. Hazard ratios (none reaching statistical significance) were: 0.63 and 0.72 for age ≥65 and <65 years; 0.69 and 0.56 for high-grade serous and other histology. Death occurred in 50% of the HIPEC group vs 62% of the control group; median overall survival was 45.7 months vs 33.9 months (HR = 0.67, P = .02).

No significant differences between the HIPEC and control groups were observed in incidence of adverse events of any grade. The most common adverse events of any grade in the HIPEC group were nausea (63% vs 57%), abdominal pain (60% vs 57%), and fatigue (37% vs 30%). Grade ≥3 adverse events occurred in 27% vs 25% of patients (P = .76). The most common grade 3 or 4 adverse events in the HIPEC group were infection (6% vs 2%), abdominal pain (5% vs 6%), and ileus (4% vs 2%). One patient in the control group died within 30 days after surgery.

The investigators concluded: "Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects."

Study Limitations

Although the primary endpoint was recurrence-free survival, van Driel et al primarily focused on the immature (but provocative) overall survival data. Additionally, their protocol-based statistical assumption of 18 months for the median recurrence-free survival in the control arm was not anywhere near the reported recurrence-free survival in the study (10.7 months), suggesting that underperformance in the control arm could explain the statistical difference between arms.

Furthermore, the improvement in recurrence-free survival (from 10.7 to 14.2 months) is virtually identical to results seen with the much simpler and more broadly adopted approach of adding bevacizumab (Avastin) to the front-line treatment of epithelial ovarian cancer which was approved by the US FDA on June 13, 2018.

GOG protocol 218 was a double-blind, placebo-controlled, phase III trial that randomly assigned newly diagnosed women with stage III or stage IV epithelial ovarian cancer who had undergone debulking surgery to intravenous carboplatin and paclitaxel with placebo added in cycles 2 to 22 (control group), with bevacizumab (15 mg/kg) added in cycles 2 to 6 and placebo in cycles 7 to 22, or with bevacizumab added in cycles 2 to 22 ("bevacizumab-throughout" group). Each cycle was 3 weeks in duration.

The median progression-free survival was 10.3 months in the control group and 14.1 in the bevacizumab-throughout group. Relative to the control treatment, the hazard ratio for progression or death was 0.717 (95% confidence interval = 0.625–0.824, P < .001). Gastrointestinal-wall disruption requiring medical intervention occurred in 1.2% vs 2.6%, respectively.[8] This toxicity is particularly notable, as those treated with intraperitoneal chemotherapy in the current study had a higher rate of colostomy and ileostomy (11% vs 17%).[7]

Further Considerations

When considering new therapies such as hyperthermic intraperitoneal chemotherapy as well as bevacizumab, the entire data set and clinical experience must be considered. In contrast to the van Driel et al study, many studies of HIPEC are still ongoing.[9]

Finally—and perhaps the most difficult issue—the current report failed to isolate the effect of hyperthermia. How important is the heated chemotherapy, or would perioperative standard room temperature intraperitoneal treatment be sufficient? The positive results of the phase II OV21/PETROC study (a randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal vs intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer) make this point particularly relevant.[10]

Conclusions

HIPC and traditional IP chemotherapy regimens remain a treatment option for women with newly diagnosed advanced ovarian cancer. However, important questions remain about the appropriate regimen and timing of the IP treatment. Moreover, the long-term toxicities and benefits of HIPEC remain unknown.

Like all studies, the recent New England Journal of Medicine report has many flaws and must be interpreted in the context of other IP clinical trials. Additionally, targeted therapies such as bevacizumab may offer a better and more tolerable option in treating newly diagnosed epithelial ovarian cancer. Until more data are available from evidence-based studies, it is reasonable to conclude that a strategy of surgical cytoreduction and hyperthermic intraperitoneal chemotherapy is rational and interesting. Arizona Oncology has recently launched a multidisciplinary HIPC service making this treatment modality available to the local community.

Article references on page 5.