### **Rare Ovarian Cancers**

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#OvarianConf

## Rare Ovarian Cancers: Are We Making Progress?

David M. Gershenson, MD The University of Texas MD Anderson Cancer Center Rare Ovarian Cancers: Challenges and Barriers

- Small number of cases
- Long trial accrual times
- Few interested investigators
- Less attention by scientific community
- Funding priority has been low
- Low priority for Pharma
- Fewer patient advocates
- Lack of standard bioinformatics methods and trial designs

### **Rare Ovarian Cancers**

# **Subtypes**

- Germ Cell Tumors
- Sex Cord-Stromal Tumors
- Rare Epithelial Tumors
  - Clear Cell
  - Mucinous
  - Low-Grade Serous



- Basic Features
- Standard Treatment
- Ongoing Research

### **MALIGNANT GERM CELL TUMORS**



# **WHO Classification**

- Dysgerminoma
- Yolk sac tumor
- Immature teratoma
- Nongestational choriocarcinoma
- Embryonal carcinoma
- Polyembryoma
- Mixed germ cell tumor



### **Basic Features**

- Represent less than 5% of all ovarian cancers
- Occur in girls and young women
- Relatively rapidly growing
- Incidence 1/10<sup>th</sup> that of testicular cancer
- Signs & Sx: Abdominal pain and palpable mass
- Almost always unilateral
- Average size: 16 cm
- 60-70% stage I
- Prior to 1970s, most patients did not survive
- Since introduction of modern chemotherapy, cure rate is 95%

### **Serum Tumor Markers**

Histology	AFP	hCG
Dysgerminoma	_	<u>+</u>
Immature teratoma	<u>+</u>	-
Yolk sac tumor	+	-
Choriocarcinoma	_	+
Embryonal carcinoma	<u>+</u>	+
Polyembryoma	<u>+</u>	+
Mixed GCT	<u>+</u>	<u>+</u>

# **Standard Therapy**

# Surgery Uterus Normal ovary Cance Vagina

Fig.2 Cancer of the Ovary

### Chemotherapy

- Bleomycin, Etoposide, and Cisplatin (BEP) X 3-4 cycles
- For all cell types and stages except:
  - Stage I Dysgerminoma
  - Stage I, Grade 1 Immature
     Teratoma

# **Ongoing Research**

- Limiting extent of surgical staging
  - Removal of ovarian tumor
  - Cytologic washing
  - Inspection & palpation
  - Removal of any abnormal areas
- Reducing toxicity of postoperative therapy
  - Eliminating chemotherapy for stage IA or IB
  - Substituting carboplatin for cisplatin for stage IC-III
  - Reducing number of drugs for treatment of dysgerminoma



### MaGIC COG/NRG Trial Low Risk Stratum

Age 0-50 years Stage I, All Sites (Stage IA MOGCT)



Chemotherapy if Relapse



### MaGIC COG/NRG Trial Intermediate Risk Stratum

R

Cisplatin 33 mg/m<sup>2</sup> days 1-3 Etoposide 165 mg/m<sup>2</sup> days 1-3 Bleomycin 15 U/m<sup>2</sup> days 1, 8, 15

Age 0-25 All Sites (Stage IC-III MOGCT)

> Carboplatin AUC 8.0 day 2 Etoposide 165 mg/m<sup>2</sup> days 1-3 Bleomycin 15 U/m<sup>2</sup> days 1, 8, 15



### OVARIAN SEX CORD-STROMAL TUMORS



# **WHO Classification**

- Granulosa cell tumor
  - Adult
  - Juvenile
- Sertoli-Leydig cell tumors
  - Well differentiated
  - Moderately differentiated
  - Poorly differentiated
- Other



### Basic Features: Granulosa-Theca Tumors

- Represent 2% of all ovarian malignancies
- Mean age in 50s but extremely wide age range
- Usually stage I and unilateral
- Tumor rupture is common
- Presentation may be related to estrogen production
- Tumor markers: Inhibin, AMH, estradiol
- Associated with increased risk of endometrial or breast cancer
- Juvenile type may be associated with Ollier's disease or Maffuci's syndrome

#### The NEW ENGLAND JOURNAL of MEDICINE

#### **ORIGINAL ARTICLE**

#### Mutation of FOXL2 in Granulosa-Cell Tumors of the Ovary

Sohrab P. Shah, Ph.D., Martin Köbel, M.D., Janine Senz, B.Sc., Ryan D. Morin, M.Sc., Blaise A. Clarke, M.B., B.Ch., Kimberly C. Wiegand, B.Sc., Gillian Leung, B.Sc., Abdalnasser Zayed, B.Sc., Erika Mehl, B.M.L.Sc., Steve E. Kalloger, B.Sc., Mark Sun, B.Sc., Ryan Giuliany, Erika Yorida, B.M.L.Sc., Steven Jones, Ph.D., Richard Varhol, M.Sc., Kenneth D. Swenerton, M.D., Dianne Miller, M.D., Philip B. Clement, M.D., Colleen Crane, B.Tech., Jason Madore, M.Sc., Diane Provencher, M.D., Peter Leung, Ph.D., Anna DeFazio, Ph.D., Jaswinder Khattra, M.Sc., Gulisa Turashvili, M.D., Ph.D., Yongjun Zhao, M.Sc., D.V.M., Thomas Zeng, M.Sc., J.N. Mark Glover, Ph.D., Barbara Vanderhyden, Ph.D., Chengquan Zhao, M.D., Christine A. Parkinson, Ph.D., M.R.C.P., Mercedes Jimenez-Linan, Ph.D., David D.L. Bowtell, Ph.D., Anne-Marie Mes-Masson, Ph.D., James D. Brenton, M.D., F.R.C.P., Samuel A. Aparicio, B.M., B.Ch., Niki Boyd, Ph.D., Martin Hirst, Ph.D., C. Blake Gilks, M.D., Marco Marra, Ph.D., and David G. Huntsman, M.D.

## Basic Features: Sertoli-Leydig Cell Tumors

- Usually stage I and unilateral
- Average age = 28 years
- May produce testosterone or, less commonly, estrogen
- Tumor markers: testosterone, AFP
- Biologic behavior depends on:
  - Differentiation
  - Presence of heterologous elements

#### The NEW ENGLAND JOURNAL of MEDICINE

#### **ORIGINAL ARTICLE**

#### Recurrent Somatic DICER1 Mutations in Nonepithelial Ovarian Cancers

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Gregg B. Morin, Ph.D., and David G. Huntsman, M.D.

# Standard Therapy: Surgery

- Surgery is cornerstone of treatment
- Primary Surgery
  - TAH + BSO, surgical staging
  - Cytoreductive surgery in advanced stage
  - Lymphadenectomy not recommended
  - Fertility-sparing surgery in young patients
  - Endometrial biopsy if uterus preserved (GCT)
- Secondary cytoreductive surgery in selected patients

### Standard Therapy: Chemotherapy

#### Gynecologic Oncology 136 (2015) 505-511



#### The role of systemic chemotherapy in the management of granulosa cell tumors $\overset{\varkappa}{\succ}$



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#### HIGHLIGHTS

· We reviewed the records of 154 ovarian sex cord stromal tumor (SCST) patients.

Adjuvant chemotherapy did not improve outcomes, regardless of disease stage.

• The incidence of breast cancer was higher than expected and is worthy of further study.

#### ARTICLE INFO

Keywords:

Chemotherapy

Recurrence

Breast cancer

Ovary

Granulosa cell tumors

#### ABSTRACT

Article history: Received 9 September 2014 Accepted 22 December 2014 Available online 26 December 2014 Objective. Granulosa cell tumors (GCTs) are rare, and the role of chemotherapy in their management is not clearly defined.

Methods. We performed a retrospective cohort study of GCT patients diagnosed from January 1996 through June 2013 at the Memorial Sloan Kettering Cancer Center, comparing those who received adjuvant chemotherapy to those who did not. Differences between groups were assessed using the log-rank test. Statistical significance was set at p < 0.05.

Results: Of 118 patients, 10 (88) received adjuvant chemotherapy (1 [18] of 103 stage 1 and 9 [603] of 15 stage II-IV patients). Thirty-two patients (27%) experienced disease recurrence. Four patients had residual disease after initial surgery, and all received adjuvant chemotherapy: each recurred within 24.3 months (median PFS, 8.2 months). The time to first recurrence was longer in patients who did not receive adjuvant chemotherapy for first recurrence did not seem to improve time to second recurrence versus surgery alone (HR 0.98; p = 0.965). Additionally, 12 patients (10%) had a previous diagnosis of breast cancer—an incidence rate 3.22 times higher than Surveillance, Epidemiology, and End Results (SER) data predicts (p < 0.001).

Conclusions. Although the numbers were small, in this analysis chemotherapy was not found to improve the recurrence-free interval of patients with GCTs, a finding that requires prospective validation. Residual disease after surgery was associated with poor prognosis. Finally, there was a significantly higher than expected incidence of antecedent breast cancer in this population, an association that deserves further exploration.

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### Standard Therapy: Chemotherapy

- Stage IA
  - GCT or G1-2 SLT: Surgery alone
  - G3 SLT: Platinum-based chemotherapy
- Stage IC: No consensus
- Stages II-IV: No consensus
- Most common regimens:
  - Bleomycin, Etoposide, Cisplatin (BEP)
  - Paclitaxel + Carboplatin

### Standard Therapy: Chemotherapy



Contents lists available at ScienceDirect Gynecologic Oncology

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journal homepage: www.elsevier.com/locate/ygyno



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#### Stage I granulosa cell tumours: A management conundrum? Results of long-term follow up\*\*\*

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#### HIGHLIGHTS

· Stage I granulosa cell tumours have a good prognosis but relapse can have significant morbidity.

Surgery remains a key treatment of granulosa cell tumours at diagnosis and relapse.

· Alongside advances in our molecular understanding, improvements in novel therapies are needed.

#### ARTICLE INFO

#### ABSTRACT

Article history: Received 12 February 2015 Accepted 14 May 2015 Available online 21 May 2015

Granulosa cell tumours

Stromal cell ovarian cancer

Keywords:

Ovary Multi-centre review

FOXL2

Optimal management of women with early stage granulosa cell tumours (GCT) presents a management conundrum – they have excellent prognosis but a third will relapse. Advances uncovering the molecular characteristics of GCT have not been matched by improvements in our understanding and treatment.

Methods. Stage I GCT patients referred to Auckland City Hospital (1955–2012) and Princess Margaret Cancer Centre (1992–2012) were identified. Baseline characteristics, histopathology and outcomes were recorded retrospectively.

Results. One hundred and sixty stage I GCT patients were identified with a median age of 49 years. Median follow-up was 7.0 years (range 0.1-44.2 years).

Fifty-one patients (32%) relapsed with a median time to relapse (TTR) of 12.0 years (1.3–17.7 years) – 20 initial relapses occurred 10 years post-diagnosis. Higher relapse rates (43% vs. 24% p = 0.02) and shorter TTR (10.2 vs. 16.2 years p = 0.007) were seen with stage lc versus stage la disease. Cyst rupture was associated with increased relapse (p = 0.03).

Surgery was the main therapeutic modality at relapse. Eighty six percent of patients received non-surgical management at least once post-relapse. Clinical benefit rate was 43% with chemotherapy, 61% with hormonal therapy and 86% with radiation.

Five- and 10-year overall survival (OS) were 98.5 and 91.6%, respectively. Median OS was similar in patients with (24.3 years) and without relapse (22.3 years).

Conclusion. Surgery remains fundamental at diagnosis and relapse. Caution should be exercised in recommending adjuvant chemotherapy at initial diagnosis given median OS was greater than 20 years even with relapse. Hormonal therapy at relapse appears encouraging but needs further assessment. Novel treatment strategies need exploration with international collaboration essential for this.

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### **Standard Therapy: Hormonal Therapy**



Review

Hormone therapy in ovarian granulosa cell tumors: A systematic review



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#### HIGHLIGHTS

· We performed a systematic review in which we assessed the effectiveness of hormone therapy in granulosa cell tumor patients.

• Pooled overall response rate to hormone therapy was 71.0% (95% Confidence Interval 52-85).

· Hormonal therapy appears to be a good treatment alternative for patients with an advanced-stage or recurrent granulosa cell tumor.

#### ARTICLE INFO

#### Article history: Received 21 February 2014 Accepted 30 March 2014 Available online 5 April 2014

Keywords: Granulosa cell tumor Sex cord-stromal tumor Hormone therapy Aromatase inhibitors Tamoxifen

#### ABSTRACT

Objective. This systematic review assessed the effectiveness of hormone therapy (HT) in patients with a granulosa cell tumor (GCT) of the ovary.

Methods. Medline (OVID), EMBASE (OVID), the Cochrane Central Register of Controlled Trials (CENTRAL), prospective trial registers and PubMed (as supplied by publisher-subset) were searched up to January 13, 2014. No restrictions were applied. Two reviewers independently screened studies for eligibility and extracted data using a standardized, piloted extraction form. Studies evaluating the response to hormone therapy in patients with a GCT were included. The primary outcome was the objective response rate (ORR) to hormone therapy.

Results. In total, nineteen studies including 31 patients were eligible. Pooled ORR to hormone therapy was 71.0% (95% Confidence Interval 52–85). In 25.8% a complete response and in 45.2% a partial response was described. Four patients had stable disease. In five patients disease was progressive. Various hormone treatments showed different results, for instance aromatase inhibitors (AI) demonstrated response in nine out of nine therapies (100%) and tamoxifen in none out of three (0%). Median progression free survival (PFS) after the start of hormone therapy was 18 months (range 0–60).

Conclusions. Despite the limited available data, hormone therapy appears to be a good treatment alternative for patients with advanced-stage or recurrent GCT. However, study quality is poor and prospective studies are needed to confirm clinical benefit of hormone therapy in GCTs.

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### **Standard Therapy: Hormonal Therapy**

#### Table 3

Total response in all hormone treatments.

Hormone therapy $n = 38$ (%)	CR	PR	SD	PD	SD/PD	Response +	Response –	Response proportion (%)
Anastrozole [42,45,50]	3	2	0	0	0	5	0	5/5 (100.0)
Letrozole [8,50,56]	2	2	0	0	0	4	0	4/4 (100.0)
MPA [46,51]	1	2	0	0	0	3	0	3/3 (100.0)
Megestrol acetate + Tamoxifen [11]	1	0	0	0	0	1	0	1/1 (100.0)
DES [55]	0	1	0	0	0	1	0	1/1 (100.0)
Megestrol acetate [43,46,54]	0	2	0	1	0	2	1	2/3 (66.7)
Leuprolide + Tamoxifen [48,54]	1	0	0	1	0	1	1	1/2 (50.0)
Goserelin [47]	0	2	0	2	0	2	2	2/4 (50.0)
Leuprolide [10,44,45,49,53]	0	3	5	2	0	3	7	3/10 (30.0)
Ganirelix [9]	0	0	0	1	0	0	1	0/1 (0)
Goserelin + Tamoxifen [47]	0	0	0	1	0	0	1	0/1 (0)
Tamoxifen [10,46]	0	0	1	1	1	0	3	0/3 (0)

Abbreviations: MPA, medroxyprogesterone acetate; DES, diethylstilbestrol.

Van Meurs et al. Gynecol Oncol 2014



#### Radiation Treatment of Advanced or Recurrent Granulosa Cell Tumor of the Ovary

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Received May 19, 1998

*Background.* Because granulosa cell tumors of the ovary are rare, the optimal treatment for women with gross residual disease after primary surgery or recurrence is not known. Our objective was to review the results of radiotherapy for advanced or recurrent granulosa cell tumor of the ovary.

*Methods.* This retrospective review identified 34 patients with ovarian granulosa cell tumors treated with radiation at the University of Texas M. D. Anderson Cancer Center between 1949 and 1988. Fourteen received treatment for clinically measurable disease; 20 received adjuvant radiotherapy after surgery for minimal residual (< 1 cm) or microscopic residual disease. The 14 patients with measurable disease formed the basis for this review.

*Results.* Ten of 14 patients were treated with moving-strip whole-abdomen radiation (27–28 Gy), 9 with  $^{60}$ Co, and 1 with 6-MeV photons and a pelvic boost of 28 Gy with 22–25 MeV photons. The other 4 patients were treated with pelvic radiotherapy (45–61 Gy) with 22–25 MeV photons. Six of 14 patients (43%) had a clinical complete response to radiotherapy, with a median follow-up of 13 years (range, 5–21 years). Three of 6 who responded to radiation had relapse 4–5 years later; 2 of these 3 died of disease and 1 was alive with disease at last follow-up. Three responders remain alive without evidence of disease 10–21 years after treatment. The 8 nonresponders had a median survival of 12.3 months (range, 1–60 months).

Conclusions. Radiotherapy can induce a clinical response with occasional long-term remission in patients with persistent or recurrent granulosa cell tumor of the ovary. © 1999 Academic Press recurrence have been evaluated in several studies; such factors as DNA an euploidy, large tumor size, advanced age at diagnosis, and advanced stage of tumor have been identified, though the last appears to be the most reproducible [1-5].

Most information concerning chemotherapy for patients with ovarian sex-cord stromal tumors has come from small series or case reports. Recently, platinum-based combination chemotherapy has emerged as the most widely used postoperative treatment [6–11]. Responses to platinum-based chemotherapy are reportedly as high as 50%, but as mentioned already, most reports are small and include patients with measurable and nonmeasurable disease. Several papers from the 1950s and 1960s report postoperative radiotherapy for patients with granulosa cell tumors, but these also mix patients with measurable and nonmeasurable disease; however, a few objective long-term responses are reported [12–14]. The purpose of this study is to report our results of radiotherapeutic treatment of women with measurable recurrent or advanced granulosa cell tumors of the ovary.

#### PATIENTS AND METHODS

A retrospective review identified 34 patients with granulosa cell tumors of the ovary treated with radiation at the University of Texas M. D. Anderson Cancer Center (Houston, TX<sub>26</sub>between 1949 and 1988. Radiotherapy and medical records of



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#### JOURNAL OF CLINICAL ONCOLOGY

#### ORIGINAL REPORT

#### The Activity of Taxanes in the Treatment of Sex Cord-Stromal Ovarian Tumors

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Submitted December 10, 2003; accepted May 28, 2004.

Presented in part at the 32nd Annual Meeting of the Western Association of Gynecologic Oncologists, June 28, 2003, Steamboat Springs, CO.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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#### Purpose

To determine the efficacy and side effects of taxanes, with or without platinum, for the treatment of sex cord-stromal tumors of the ovary.

A B S T R A C T

#### **Patients and Methods**

We conducted a retrospective review of all patients seen from 1985 to 2002 at The University of Texas M.D. Anderson Cancer Center with ovarian sex cord-stromal tumors. Eligible patients underwent pathology confirmation and clinical evaluation at M.D. Anderson and received a taxane for initial or recurrent disease.

#### Results

Of 222 patients identified, 44 were eligible for analysis. For nine patients treated in the first-line adjuvant setting, median progression-free survival (PFS) was not reached at 51 months. Of two patients treated for measurable disease in the first-line setting, one had a complete response. Median PFS was 34.3 months; median overall survival (OS) was not reached. Median follow-up was 90.3 months (range, 39.4 to 140.5 months). Response rate for 30 patients treated with a taxane  $\pm$  platinum for recurrent, measurable disease was 42%. Median PFS was 19.6 months; median OS was not reached. Median follow-up was 100.7 months (range, 8.1 to 361.3 months). The presence of platinum correlated with response in the recurrent, measurable disease setting. The number of patients was insufficient to detect relative efficacy of paclitaxel and docetaxel. Adverse effects of paclitaxel included neutropenia (n = 6), anemia (n = 1), thrombocytopenia (n = 1), myelodysplasia (n = 1), and hypersensitivity (n = 1).

#### Conclusion

Taxanes seem to be active agents in the treatment of patients with sex cord-stromal tumors of the ovary. The combination of taxanes with platinum in the treatment of this disease deserves additional investigation.

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**Gynecologic Oncology** 

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#### A phase II study of paclitaxel for the treatment of ovarian stromal tumors: An NRG Oncology/ Gynecologic Oncology Group Study<sup>\*</sup>



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#### HIGHLIGHTS

• Paclitaxel has activity in recurrent, malignant stromal tumor of the ovary.

• There was a complete response in 3.2% and partial response in 25.8% of women.

• Inhibin is not a reliable tumor marker.





**Original Article** 

### Efficacy and Safety of Bevacizumab in Recurrent Sex Cord-Stromal Ovarian Tumors

Results of a Phase 2 Trial of the Gynecologic Oncology Group

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**BACKGROUND:** The Gynecologic Oncology Group conducted this phase 2 trial to estimate the antitumor activity of bevacizumab and to determine the nature and degree of toxicity in patients with recurrent sex cord-stromal tumors of the ovary. **METHODS:** A prospective, multi-institutional cooperative group trial was performed in women with recurrent, measurable ovarian stromal tumors. Patients were allowed to have unlimited prior therapy, excluding bevacizumab. Bevacizumab 15 mg/kg was administered intravenously on day 1 of every 21-day cycle until patients developed disease progression or adverse effects that prohibited further treatment. The primary endpoint was the response rate (RR). Inhibin A and B levels were measured before each cycle, and the values were examined in relation to response and progression. **RESULTS:** Thirty-six patients were enrolled, and all were eligible and evaluable. Patients received a median of 9 cycles of treatment (range, 2-37 cycles). Six patients (16.7%) had partial responses (90% confidence interval, 7.5%-30.3%), 28 patients (77.8%) had stable disease, and 2 patients (5.6%) had progressive disease. This met the criterion for declaring the regimen active. The median progression-free survival was 9.3 months, and the median overall survival was not reached in during reporting period. Two grade 4 toxicities occurred, including hypertension and proteinuria; and the most common grade 3 toxicities were hypertension (n = 5) and pain (n = 5). Inhibin A and B values were lower in patients who responded to treatment. **CONCLUSIONS:** Bevacizumab has activity in the treatment of recurrent sex cord-stromal tumors of the ovary, and its toxicity is acceptable. Further investigation is warranted. **Cancer 2014;120:344-51**. © *2013 American Cancer Society*.

KEYWORDS: bevacizumab, Gynecologic Oncology Group, stromal ovarian tumors, survival.

### **GOG 264**

A Randomized Phase II Trial of Paclitaxel and Carboplatin vs BEP for Newly Diagnosed Advanced Stage and Recurrent Chemo-Naïve Sex Cord-Stromal Tumors of the Ovary



Stage III-IV or Recurrent Chemo-Naïve SCST of Ovary

Carboplatin AUC 6 Paclitaxel 175 mg/m<sup>2</sup> X 6 cycles Bleomycin 20 U/m<sup>2</sup> Etoposide 75 mg/m<sup>2</sup> d 1-5 Cisplatin 20 mg/m<sup>2</sup> d 1-5 X 4 cycles

Accrual 41/128

# **Epithelial Ovarian Cancer**



#### High-Grade Serous







**Clear Cell** 

Mucinous

Low-Grade Serous



- Ovarian cancer is not one but several distinct entities
- Advances in understanding heterogeneity:
  - Pathologic diagnostic criteria
  - Molecular biology
  - Hypothesis-generating clinical studies
- Establishment of GOG Rare Tumor Committee (2005) with separate clinical trials for specific subtypes
- Prior to 2005:
  - All EOC treated identically
  - No prospective clinical trials for rare EOC
- "One size does not fit all!"



### **Advanced Ovarian Cancer: GOG Phase III Trials**

- 1981 52 CAP vs CP
  - 097 Cisplatin Dose Intensity (DI)
  - 104 IP-Cisplatin vs IV-Cisplatin
  - 111 Cisplatin-Paclitaxel vs Cisplatin-Cyclophosphamide
  - 114 Carboplatin (AUC 9) → IP-Cisplatin Paclitaxel
  - 132 Sequential Single-Agent vs Combination
  - 152 Interval Cytoreduction
  - 158 Carboplatin-Paclitaxel (3 h) vs Cisplatin-Paclitaxel (24 h)
  - 162 24 h vs 96 h Paclitaxel with Cisplatin
  - 164 ABMT Consolidation
  - 172 IP-Cisplatin & IP-Paclitaxel vs IV
  - 178 Paclitaxel Consolidation
  - 182 Carbo-Paclitaxel & Gemcitabine, Topotecan, or PEG-Lipo-Dox
  - 212 Paclitaxel and PG-Paclitaxel Consolidation
  - 218 Carbo-Paclitaxel +/- Bevacizumab
  - 252 Carboplatin IP and Dose-Dense Paclitaxel (Optimal)
- 2011 262 Dose-Dense Paclitaxel +/- Bevacizumab (Suboptimal)



Making Cancer History\*

### **Expression Subtypes: HGSC**



### **High-Grade Serous Carcinoma**

- Associated with 18% frequency of BRCA germline mutations and 50% frequency of BRCA somatic mutations
- Mutations of *BRCA* genes result in increased frequency of gene rearrangements
- PARP enzymes play essential role in repair of single-strand DNA breaks
- PARP inhibition leads to double-strand DNA breaks that cannot be accurately repaired in tumors with HRD

### Key Pathways & Potential Targets: High-Grade Serous Carcinoma

- Angiogenesis pathway
  - Bevacizumab, Aflibercept, Cediranib, AMG 386, etc.
- Homologous Recombination pathway
  - Multiple PARP inhibitors
- P53 gene
  - Wee1 inhibitors, CP-31398, Nutlin, MoAB, FAK inhibitors
- PI3K/AKT/mTOR pathway
  - Everolimus, Temsirolimus, and several others
- PD-1 and PD-L1
  - Multiple checkpoint inhibitors

### **Basic Features**

Feature	Clear Cell	Low-Grade Serous	Mucinous
Incidence	5%	5%	10%
Stage Distribution			
Stages I/II	67%	10%	61%
Stages III/IV	33%	90%	39%
Biology	Aggressive	Indolent	Aggressive
Relative Chemoresistance	Yes	Yes	Yes
Outcomes in Early Stage	Similar to HGSC HR = .87	Unknown but thought to be excellent	Similar to HGSC HR = .87
Outcomes in Advanced Stage	Median OS = 21 mo Worse than HGSC HR = 2.2	Median OS = 101 mo Better than HGSC HR = ?	Median OS = 15 mo Worse than HGSC HR = 2.7

### Standard Therapy: Early Stage

- Comprehensive surgical staging
  - Mucinous carcinoma
    - Appendectomy
    - Lymphadenectomy unnecessary
- Role for fertility-sparing surgery in selected young patients
- Surgery alone for stage IA (sparse data)
- Stages IC-II: Platinum/Taxane chemotherapy

# Standard Therapy: Advanced Stage

- Principle is maximum cytoreductive surgery to achieve minimal residual disease
- Options:
  - Primary cytoreductive surgery + Chemotherapy
  - Neoadjuvant chemotherapy + Interval debulking
- Standard chemotherapy: Paclitaxel/Carboplatin
  - IP Chemotherapy
  - Dose Dense Paclitaxel
  - Addition of Bevacizumab, including maintenance
- Currently no front-line trials for rare subtypes

### **MUCINOUS CARCINOMA**



Mucinous Carcinoma: Key Pathways & Potential Targets

Angiogenesis pathway

• HER-2/neu (20%)

• MAPK (*RAS* mutation, 40-50%

• Src

THE UNIVERSITY OF TEXAS MDAnderson Cancer Center mEOC/GOG 241: A Randomized Phase III Trial of Capecitabine/Oxaliplatin vs. Paclitaxel/Carboplatin +/- Bevacizumab in Patients with Previously Untreated Mucinous Ovarian Cancer



### Pathology of Advanced Stage Mucinous Carcinoma

- Review of 3435 pts in international randomized phase III trial
- 41 cases with adequate pathology material
  - 12 (29%) considered primary
  - 29 (71%) considered metastatic



**Figure 2.** Overall survival of women with mucinous carcinomas involving the ovary is shown. Tumors were classified as primary or metastatic according to criteria described by Lee and Young.<sup>9</sup> There was no significant difference in survival between the 2 groups using this classification system (P = 0.468 [log-rank test]).

### **CLEAR CELL CARCINOMA**



# Relative Chemoresistance of Recurrent Clear Cell Carcinoma

- 51 pts. with recurrent CCC who received total of 105 regimens (pt.-regimens)
  - Platinum-sensitive disease: 2 PRs to retreatment with paclitaxel/carboplatin
  - Platinum-resistant disease: 1 PR to gemcitabine

Crotzer et al. Gynecol Oncol 2007

- 75 pts. with recurrent CCC who received second-line chemotherapy
  - Platinum-sensitive disease: 2 PRs (8%) (1 platinum & 1 platinum + irinotecan)
  - Platinum-resistant disease: 3 PRs (6%) (2 platinum + etoposide & 1 platinum + irinotecan)

Takano et al. Int J Gynecol Cancer 2008

### **ARID1A** is a Tumor Suppressor Gene



- Insertion or deletion
- Missense mutation
- Clear-cell carcinoma
- Endometrioid carcinoma
- § Recurrent mutation (found in two separate samples)
- ‡ Two mutations at the same location from two independent samples

# Clear Cell Carcinoma: Key Pathways & Potential Targets

- ARID1A mutation 50%
- PI3K/AKT/mTOR pathway 30-40%
- Angiogenesis pathway
- PD-1 and PD-L1
- HNF-1β upregulation 100%
- IL6-HIF-1α pathway upregulation 50%
- MET amplification 20-30%
- HER-2 amplification 14%
- PPM1D amplification 10%
- Microsatellite instability (MSI) 7-18%

### Clear Cell Carcinoma: Clinical Trials

Trial	Agents	Results
JGOG3017/GCIG	Irinotecan/cisplatin vs paclitaxel/carboplatin	2-yr OS = 85.5% vs 87.4% (NS)
GOG 268	Paclitaxel/carboplatin + temsirolimus + temsirolimus maintenance	54% with PFS > 12 mo No better than historical controls
GOG 254	Sunitinib malate	ORR = 7%
GY-001	Cabozantinib	Did not go to 2 <sup>nd</sup> stage Report pending
University Health Network Toronto	ENMD-2076	ORR = 2%
GOG 283	Dasatinib	Recruiting
NICCC	Nintedanib	Recruiting
RT1627	Pembrolizumab + epacadostat	In development

### **Nivolumab in Platinum-Resistant EOC**

- 60 y/o woman with recurrent, platinum-resistant clear cell carcinoma of ovary
- Treated with Nivolumab after 3 lines of conventional chemotherapy
- Patient continues to be in CR after 1-year course



Hamanishi et al. J Clin Oncol 2015

### LOW-GRADE SEROUS CARCINOMA



51

### M.D. Anderson Grading System for Ovarian Serous Carcinoma

- Low Grade:
  - Mild to moderate nuclear atypia
  - Mitotic index of up to 12 mitoses/10 HPF (as secondary feature)
- High Grade:
  - Marked nuclear atypia
  - Mitotic index of > 12 mitoses/10 HPF (as secondary feature)







### Low-Grade Serous Carcinoma

- Binary grading system for serous carcinomas described and now incorporated into WHO classification
- Studies show that LGSC is on continuum with serous tumors of LMP
- Series of studies demonstrate relative chemoresistance in multiple clinical settings
  - First-line Adjuvant
  - Neoadjuvant
  - Recurrent

Malpica et al. Am J Surg Pathol 2004 Gershenson et al. Obstet Gynecol 2006 Schmeler et al. Gynecol Oncol 2008 Gershenson et al. Gynecol Oncol 2009 Bodurka et al. Cancer 2012 Crispens et al. Obstet Gynecol 2002 Bonome et al. Cancer Res 2005 Shvartsman et al. Gynecol Oncol 2007 Schmeler et al. Gynecol Oncol 2011 Gershenson et al. J Clin Oncol 2015

### **Primary Treatment**

- AGO metadatabase of 5114 pts
  - 145 pts with LGSC
  - Of 39 LGSC pts with suboptimal debulking, RR = 23%
  - Of 80 HGSC pts with suboptimal debulking, RR = 90% (p<0.001)</li>



Grabowski et al. Gynecol Oncol 2016

### Low-Grade Serous Carcinoma

- Series of studies indicate that LGSC is strikingly similar to ER+ breast cancer
  - At least 80% of LGSC are ER+
  - Women < 35 yrs have significantly worse survival</li>
  - LGSC responds to anti-estrogen hormonal therapy (AI, tamoxifen, leuprolide, fulvestrant, etc.) in the recurrent setting
  - Following primary surgery and platinum/taxane chemotherapy, hormonal maintenance therapy is associated with superior PFS and OS compared to observation

Wong et al. Int J Gynecol Pathol 2007 Gershenson et al. Gynecol Oncol 2012 Gershenson et al. J Clin Oncol 2015 Gershenson et al. J Clin Oncol 2017

### Bevacizumab in Low-Grade Serous Carcinoma of the Ovary

Study	No. Patients	Outcome
Grisham et al. 2014	17	CR = 0 PR = 40% SD = 33%
Rose et al. 2016	12	CR = 0 PR = 8.3% 6-mo PFS = 90.9%
Dalton et al. 2017	40 (45 separate regimens)	CR = 7.5% PR = 40% SD = 30%

### MAPK Pathway plays prominent role in pathogenesis of LGSC



Key Pathways & Potential Targets: Low-Grade Serous Carcinoma

- MAP Kinase pathway (20-40% KRAS, 5% BRAF)
  - KRAS 20-40%
  - BRAF 5%
- Estrogen Receptor
- Angiogenesis pathway
- IGFR-1
- PI3K/AKT/mTOR pathway

### GOG 0239

Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study

John Farley, William E Brady, Vinod Vathipadiekal, Heather A Lankes, Robert Coleman, Mark A Morgan, Robert Mannel, S Diane Yamada, David Mutch, William H Rodgers, Michael Birrer, David M Gershenson

#### Summary

Published Online http://dx.doi.org/10.1016/ \$1470-2045(12)70572-7 See Comment page 101 Creighton University School of Medicine at St Joseph's Hospital and Medical Center, Division of Department of Obstetrics and Gynecology, Phoenix, AZ, USA (Prof | Farley MD): Gynecologic (W E Brady PhD, H A Lankes PhD); chusetts General Hospital. Department of Medicine,

Boston, MA, USA

Lancet Oncol 2013; 14: 134-40 Background Low-grade serous carcinoma of the ovary is chemoresistant but mutations in the MAPK pathway could be targeted to control tumour growth. We therefore assessed the safety and activity of selumetinib, an inhibitor of December 21, 2012 MEK1/2, for patients with this cancer.

Methods In this open-label, single-arm phase 2 study, women (aged ≥18 years) with recurrent low-grade serous ovarian or peritoneal carcinoma were given selumetinib (50 mg twice daily, orally) until progression. The primary endpoint was the proportion of patients who had an objective tumour response according to RECIST version 1.1, assessed for all the treated patients. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, Gynecologic Oncology, number NCT00551070.

Findings 52 patients were enrolled between Dec 17, 2007, and Nov 23, 2009. All were eligible for analyses. Eight (15%) Oncology Group Statistical and patients had an objective response to treatment—one patient had a complete response and seven had partial Data Center, Roswell Park Cancer responses. 34 (65%) patients had stable disease. There were no treatment-related deaths. Grade 4 toxicities were Institute, Buffalo, NY, USA cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (nine), metabolic (seven), fatigue (six), anaemia (four), pain (four), constitutional (three), and cardiac events (two).

- Phase II study of selumetinib (MEKi) in 52 women with recurrent LGSC
- ORR = 15%
- Clinical benefit rate = 80%
- No correlation of outcome with KRAS/ **BRAF** mutations

# Tumor with KRAS mutation responded to Selumetinib

2/10/2009



6/2/2009



1.8 cm

0.9 cm

#### The NEW ENGLAND JOURNAL of MEDICINE

#### ORIGINAL ARTICLE

#### Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D. A low-grade ovarian serous cancer patient with BRAF V600E mutation responded to vemurafenib monotherapy





Hyman DM et al. N Engl J Med 2015; 373:726-736

### NCT01849874 MILO Trial

### **Randomized Phase III Trial**

Recurrent LGSC

Physician's Choice: Paclitaxel Liposomal Doxorubicin Topotecan

MEK162



### **Randomized Phase III Trial**



### NCT01936363

### **Randomized Phase II Trial**



### **Pilot Study of Neoadjuvant Fulvestrant + Palbociclib**

Unresectable LGSC (allocated to neoadjuvant therapy)

12 wks of Faslodex plus Palbociclib\* Response Assessment

LGSC: Low grade serous carcinoma

Endpoints: clinical benefit rate PD/biomarkers

\* Premenopausal patients will also receive GnRH agonist CR/PR: interval surgery plus adjuvant Faslodex + Palbociclib until progression

SD: biopsy, interval surgery followed by adjuvant carboplatin and taxol (off study)

PD: optional biopsy, Treat per SoC (off study)

### Phase II Study of Letrozole + CDK 4/6 Inhibitor in Women with Recurrent LGSC

Recurrent Low-Grade Serous Carcinoma



Letrozole + CDK 4/6 inhibitor

### Phase I Study of Selumetinib + Olaparib in Women with KRAS Mutant Tumors

### KRAS Mutated Solid Tumors



# Selumetinib + Olaparib

# NRG Study Design/Schema







EMILY WATSON, OVARIAN CANCER