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TITLE: The Genomic, Epigenomic, and Psychosocial Characteristics of Long-Term Survivors of Ovarian Cancer

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14. ABSTRACT **Ovarian cancer (OC) remains a major health problem in the United Sates (US). In 2012, there will be an estimated 22,280 cases of epithelial OC (EOC) resulting in 15,500 deaths. While the median survival of OC patients has improved over the last two decades, the vast majority of patients suffer relapse and develop chemo-resistant disease. The overall survival of patients suffering from OC has not changed appreciably over the last three decades. Despite these dismal statistics, there is a minority of OC patients who are long-term (LT) survivors (>10 years). This includes a subset of advanced stage (~15%) and a higher proportion of early-stage disease (75%). Unfortunately, there is little genomic or biologic characterization of these tumors, or patient reported outcomes that characterize LT survivors. The clinical importance of identifying subsets of patients who may or may not benefit from therapy, and understanding the biology of their tumors, is significant both from a patient survival and quality of life (QOL) standpoint. The characterization of LT survivors of advanced stage OC will potentially identify molecular and clinical pathways that can be targeted to help women who have shorter survivals. Further, careful characterization of these patients, including their initial and longitudinal health-related QOL reports, their response to treatments, and their tumors will provide significant measures of prognostic factors. Accurate identification of women with high-grade, early stage OC who will recur will allow for tailoring therapy to only those who will benefit. Thus, the systematic molecular and patient-reported outcomes evaluation of LT survivors of OC (both early and advanced stage) will yield data, which can significantly impact the management of OC patients**

15. SUBJECT TERMS Ovarian cancer, long-term survival, consortium development, genomics, epigenomics, quality of life, psychosocial					
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Introduction

Background: Ovarian cancer (OC) remains a major health problem in the United Sates (US). In 2012, there will be an estimated 22,280 cases of OC resulting in 15,500 deaths. While the median survival of OC patients has improved over the last two decades, the vast majority of patients suffer relapse and develop chemo-resistant disease. The overall survival of patients suffering from OC has not changed appreciably over the last three decades. Despite these dismal statistics, there is a minority of OC patients who are long-term survivors (LTS > 8 years). This includes a subset of advanced stage (~15%) and a higher proportion of early-stage disease (75%). Unfortunately, there is little genomic or biologic characterization of these tumors, or patient reported outcomes (PROs) that characterize LTS. The clinical importance of identifying subsets of patients who may or may not benefit from therapy, and understanding the biology of their tumors, is significant both from a patient survival and quality of life (QOL) standpoint. The characterization of LTS of advanced stage OC will potentially identify molecular and clinical pathways that can be targeted to help women who have shorter survivals (Short-Term Survivors, STS, < 8 years). Further, careful characterization of LTS, including their initial and longitudinal health-related QOL reports, their response to treatments, and their tumors will provide significant measures of prognostic factors. Accurate identification of women with high-grade, early stage OC who will recur will allow for tailoring therapy to only those who will benefit. Thus, the systematic molecular and patient-reported outcomes evaluation of LTS of OC (both early and advanced stage) will yield data, which can significantly impact the management of OC patients.

Overall Aim: To characterize the genomic, biologic, and biobehavioral basis for LTS of EOC. We hypothesize that LTS of OC have distinct features that distinguish them from STS.

KEYWORDS: Ovarian cancer, long-term survival, survivorship, consortium development, genomics, epigenomics, quality of life, psychosocial

Overall Research Accomplishments

Task 1: GOG sites will be contacted to determine the number of outstanding FFPE that can be submitted for patients enrolled on GOG 172, 175, 182,213, 218 who are LT survivors and controls (STS).

1a. HRPO approval (months 1-2)
1b. Identification of sites and patients (months 2-5)
1c.Contacting sites and determining available specimens (months 5-10)
1d.Obtaining 50 specimens (months 7-10)

Task 2: GOG sites will be contacted regarding submitting clinical information for each of their patients enrolled on GOG 136 (not enrolled on a GOG treatment trial) between January 1, 1998, and May 31, 2005 and are still alive (early and advanced stage). (months 2-10)

We obtained IRB and HRPO approval to utilize FFPE samples and related clinical data from GOG and distribute this material throughout the consortium.

Following approval of regulatory protocols, GOG has identified sites to be contacted for the collection of tumors from LTS who participated in GOG 172 and GOG 182 (Table 1 attached in Appendix material) and has collected clinical data from 10 identified LTS from GOG 136. Ultimately, 134 tumors from GOG 172, GOG 182, and GOG 136, and corresponding clinical data, were sent to the coordinating site at MGH (Table 2, list of cases, attached in Appendix material).

Task 3: GOG sites will be asked to identify patients not enrolled on any GOG treatment trial nor GOG 0136 for which they have available FFPE and sufficient clinical data and are LTS (early and advanced stage). (months 2-10)

Following meetings with the GOG and the advocates' advisory board, we decided to utilize the advocates outreach for the enrollment of survivors that did not participate in GOG clinical trials. This would have resulted in a better community-divulgation of the study, as well as an opportunity to educate ovarian cancer survivors towards research and survivorship issues as they were being enrolled. We have set a procedure to enroll patients from the community to this project through which patients are identified by the advocates and contact the program manager at MGH, who will consent them and collect their clinical data, quality of life survey, and tumor samples. The program manager will also connect them to Lari Wenzel for a follow up quality of life phone interview. The tumor samples are distributed to all the scientific sites performing genomics and proteomics analysis, and the clinical data are distributed to all scientists of the consortium. All data and tissues are distributed in a de-identified fashion. We received IRB and HRPO approval for this procedure and we have also started a redcap database that will be used to collect data from patients that will be enrolled in the study during the Phase II of this award. The database contains a link to the new quality of life survey so that the patients can participate on line if they choose to. The database includes: 1) contact information for each patient and contact information for each patients' hospital where the debulking surgery was performed (only the MGH staff has access to these data), 2) a de-identified page of clinical data related to the patient that can be distributed to consortium members for scientific analysis, 3) a de-identified page containing the quality of life survey to which Dr. Lari Wenzel has access. Attached to this submission are: the advertizing material designed by the advocates, the clinical questionnaire, and the quality of life survey.

Task 4: Testing of FFPE material for genomic/biologic abnormalities

4a. Processing of FFPE material into nucleic acids (months 10-12)
4b. Shipping of nucleic acids to research sites (months 12-13)
4c. Testing for CNV, exome sequencing, miRNA(months 13-18)
4d. Statistical Analyses / Bioinformatics analysis of genomic findings in LT survivors with early or advanced stage cancers (Months 18-24)

We have performed Task 4 utilizing 52 of the 134 samples collected from GOG 172, GOG182, and GOG139. These tumors have been analyzed by 5 scientific sites, including: MGH (Coordinating site, RNAseq), MD Anderson (miRNAseq), Indiana University (MethylCap), CHUV (Immune infiltrations), Dana Farber Cancer Institute (Computational analysis). This was mainly meant to be a pilot assay to test the technologies and the working procedure across different sites of the consortium. While we did not expect to observe any predictors for long-term survival, we could observe distinct genomic and immunologic differences between LTS and STS. In addition, we made preliminary attempts to integrate the results obtained by these platforms. Attached, in appendix, are the results obtained from this analysis.

Task 5: Construct comprehensive database from GOG 172 and GOG 218 advanced ovarian cancer treatment trials

5a. Abstract case report forms to record sociodemographic, clinical, QOL, toxicity and treatment outcome variables (Months 2 -5)
5b. Identify long-term survivors within these trials (Month 5)
5c. Initiate dataset merger for analyses of potential QOL/PRO baseline associations with early change and outcomes (Months 5 – 7)

Lari Wenzel at UCI has signed a data sharing agreement with the GOG and accessed two large advanced stage clinical trials (GOG 172 and GOG 218) in order to link QOL, treatment and adverse event data to predict long term survival. It is important to note that GOG 218 started in 2007, which means that 8+ year survivors can only be detected starting from year 2015. We have thus begun to identify >8 year survivors from GOG 218, but the analysis will be performed on phase II of this project award. On the contrary, we performed a full analysis of participants to GOG 172, a clinical trial testing differences between intraperitoneal and intravenous chemotherapy in 355 patients. Available data included patient characteristics (age at diagnosis, race, ethnicity, BMI, performance status, tumor grade and stage), patient-reported outcomes collected at 4 time points (pre-treatment, pre-cycle 4, 3-6 weeks post cycle 6, and 12 months post cycle 6), treatment received, and survival time.

The patient reported outcome data included the FACT-O measure of quality of life (QOL), which is comprised of the FACT-G 4 subdomains of physical (PWB), social (SWB), emotional (EWB) and functional well-being (FWB) plus the ovarian cancer-specific concerns (OvC). The FACT-TOI was constructed from the sum of PWB, FWB and OvC. For the FACT-O and all subdomains, a high score represents better QOL. Additional data available included symptom measures for abdominal concerns and neurotoxicity. Survival time was categorized into 3 categories: < 5 years (n=177), 5-8 years (n=121) and >8 years (n=57). Comparisons were made between the 3 groups and, in addition, long-term survivors (>8 years) are compared to short-term survivors (<5 years). Because patients treated with IP represent a larger proportion of long-term survivors (52%) than short-term survivors (40%) and because there exist some significant baseline differences between treatment groups (IP vs IV), comparisons are initially adjusted for treatment. Analyses consist of 3 approaches: 1) comparison of baseline characteristics by survival group (Q: are pre-treatment QOL, symptom levels, and patient characteristics associated with survival time?); 2) comparison of change over time for QOL and symptom measures by survival time and treatment (Q: do long-term survivors differ from short-term survivors with respect to change over time in QOL and symptom measures?); and 3) using a multivariate model (polychotomous logistic regression), we sought to identify variables which may be independently associated with long-term survival. The results from this analysis are reported in an appendix attached to this report and were used to generated a descriptive profile of LTS and STS participating in GOG 172 These descriptive data will permit us to be poised in the next grant cycle to further define and characterize LT survivors using a larger and much more detailed database that was originated with GOG 218.

Dr. Wenzel has also published an abstract to the International Society for Quality of Life describing the data she obtained from the longitudinal analysis of quality of life obtained from patients participating in clinical trial GOG172. These data have set the basis for the analysis of clinical trial GOG218. The abstract is attached to this progress report.

Task 6. Conduct a pilot survey with 10 advanced ovarian cancer long-term survivors identified in Task 3.
6a HRPO approval (months 1-2)
6a. Notify select sites of identified long-term survivors (Month 6)
6b. Implement GOG and institutional IRB approvals to consent for recruitment (Months 6-12)
6c. Develop pilot survey for long-term survivors of advanced ovarian cance (Months 6 – 10)
6d. Conduct a pilot survey on 10 long-term advanced ovarian cancer survivors (Months 12 - 18)
As mentioned under Task 3, we have radically changed our strategy to enroll in the study survivors that did not participate in any GOG trials. During this funding period we have designed a procedure to enroll such survivors using the outreach of our advocates' advisory board, and developed regulatory and advertizing documents for this task (see Task 3). Dr. Wenzel has also designed a pilot quality of life survey that was discussed during guided workshops with the advocates from our advocates' advisory board, which include long-term survivors from both early and advanced stage ovarian cancer. These workshops allowed optimizing the survey to a final form that will be used during Phase II of this research program (final QOL survey attached in appendix).

Other Achievements: N/A

Plans for the next reporting period: N/A

Results disseminated to communities of interest: This work is being developed with the active participation of 11 patients advocates affiliated with ovarian cancer foundations that act as Partners in this project. Through their activity the study was divulgated to the general population as described above. In addition Dr. Wenzel has published an abstract describing the quality of life analysis performed on patients from clinical trial GOG 172 (see above).

Actual or anticipated problems or delays and actions or plans to resolve them: Nothing to Report

IMPACT

Impact on the development of the principal discipline(s) of the project: A global systemic analysis of advanced stage ovarian cancers that includes both quality of life and tumor biology allows performing multivariate analysis that includes: stress/inflammatory/immune factors, overall well being of the patient, reported toxicities during treatment, and survival. This is an un-precedent analysis that can be done by our consortium as we leverage the accurate QOL database collected by the GOG Foundation. In addition, this work allows studying cases of ovarian cancer as chronic disease. Indeed, many long-term survivors included in our study maintain active cancer throughout their survivorship or continue develop recurrences and/or other tumors. These are both very important areas in the future of cancer research.

Impact on other disciplines: Nothing to report

Impact on technology transfer: Nothing to Report

Impact on society beyond science and technology: This is the first systemic study being developed with such a strong engagement of the patients advocates. AAB members participated in this project not only by helping in drafting the QOL survey, but also by helping divulgating the study and educating other patients about the importance of research. Their participation in this study will benefit exclusively the future generations and this message is being divulgated throughout the community. Our goal in Phase II will be to create a community of patients that are directly engaged in the development of this project. Our continuous communication with these patients allows development of the tools we use for the QOL studies as well as possibilities in the future to collect more tissues from these very rare patients. It is to note that we have also decided to increase our efforts to reach out to disparity groups of patients. This effort may require that contribution of translators and the physical presence of consortium members within the targeted communities. To gain resources for such effort, we have created a crowdfunding page through MGH and a letter to be distributed to companies for additional support. The letter is attached to this application and the link to the crowdfunding page is: http://bit.ly/2ige7yD

Appendix Table 1: Sites and Count Patients Surviving more than 8 Years

Table of Institution by Protocol			
	Protocol		
Institution	**0182**	**0172**	**Total**
University of Washington Medical Center, WA	19	2	21
Washington University School of Medicine, MO	21	0	21
University of Minnesota Medical Center-Fairview, MN	18	2	20
Duke University Medical Center, NC	15	4	19
North Shore University Hospital, NY	18	1	19
University of Oklahoma Health Sciences Center, OK	15	2	17
Mayo Clinic, MN	12	3	15
Southwest Oncology Group, WA	15	0	15
Abington Memorial Hospital, PA	11	2	13
Ohio State University Medical Center, OH	8	5	13
Roswell Park Cancer Institute, NY	9	4	13
University of California at Los Angeles Health System, CA	9	4	13
Florida Hospital Cancer Institute Protocol Office, FL	8	4	12
United Hospital Incorporated, MN	12	0	12
University of Colorado Cancer Center - Anschutz Cancer Pavilion, CO	11	1	12
University of Massachusetts Memorial Health Care, MA	10	2	12
Yale University, CT	12	0	12
Riverside Methodist Hospital, OH	8	3	11
University of California at Davis, CA	11	0	11
Western Michigan (Butterworth), MI	10	1	11
University of North Carolina at Chapel Hill, NC	7	3	10
Abramson Cancer Center of The University of Pennsylvania, PA	6	3	9
University of Kentucky, KY	9	0	9
Greater Baltimore Medical Center, MD	5	3	8
Magee-Womens Hospital, PA	8	0	8
Thomas Jefferson University Hospital, PA	5	3	8
University of Texas Southwestern Medical Center, TX	7	1	8
Women's Cancer Associates, FL	8	0	8
M D Anderson Cancer Center, TX	7	0	7
Norton Health Care Pavilion - Downtown, KY	7	0	7
Stony Brook University Medical Center, NY	6	1	7
University of Alabama at Birmingham, AL	7	0	7

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	Protocol		
Institution	**0182**	**0172**	**Total**
Women's Cancer Care Associates LLC, NY	7	0	7
Advocate Lutheran General Hospital, IL	5	1	6
Greater Phoenix CCOP, AZ	5	1	6
Miami Valley Hospital, OH	5	1	6
Mount Carmel Health Center, OH	5	1	6
St. Louis Gynecology & Oncology LLC, MO	6	0	6
University of Virginia, VA	3	3	6
Virginia Oncology Associates - Lake Wright, VA	6	0	6
Wake Forest University Health Sciences, NC	4	2	6
Women and Infants Hospital, RI	5	1	6
Case Western Reserve University, OH	5	0	5
Cooper Hospital University Medical Center, NJ	5	0	5
Hope Women's Cancer Centers-Ashville, NC	5	0	5
Kaiser Permanente Los Angeles Medical Center, CA	5	0	5
Kansas City CCOP, MO	4	1	5
Long Beach Memorial Medical Center-Todd Cancer Institute, CA	2	3	5
Mayo Clinic in Florida, FL	5	0	5
Medical University of South Carolina, SC	5	0	5
Memorial Medical Center, GA	5	0	5
Nebraska Methodist Hospital, NE	4	1	5
Odette Cancer Centre- Sunnybrook Health Sciences Centre	5	0	5
University of Wisconsin Hospital, WI	2	3	5
Wayne State University, MI	5	0	5
William Beaumont Hospital, MI	5	0	5
Woman's Hospital, LA	4	1	5
Akron General Medical Center, OH	2	2	4
Ann Arbor CCOP, MI	4	0	4
Carolinas Medical Center, NC	4	0	4
Ellis Fischel Cancer Center, MO	1	3	4
Fletcher Allen Health Care, VT	3	1	4
Hartford Hospital, CT	4	0	4
Indiana University Hospital/Melvin and Bren Simon Cancer Center, IN	4	0	4

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Table of Institution by Protocol			
	Protocol		
Institution	**0182**	**0172**	**Total**
Johns Hopkins University, MD	4	0	4
Lehigh Valley Hospital, PA	3	1	4
MedStar Franklin Square Medical Center/Weinberg Cancer Institute, MD	4	0	4
Michiana Hematology-Oncology, P.C., IN	3	1	4
New York University Medical Center, NY	4	0	4
Ozark Health Ventures LLC dba Cancer Research for The Ozarks Springfield, MO	3	1	4
Sanford Bismarck Medical Center, ND	4	0	4
South Carolina Oncology Associates, PA, SC	4	0	4
St. Vincent Hospital and Health Care Center, IN	4	0	4
Stanford University Hospitals and Clinics, CA	4	0	4
Tacoma General Hospital, WA	0	4	4
The James Graham Brown Cancer Center at University of Louisville, KY	3	1	4
Tulsa Cancer Institute, OK	4	0	4
University of California Medical Center At Irvine-Orange Campus, CA	4	0	4
University of New Mexico Medical Center, NM	1	3	4
Walter Reed National Military Medical Center, DC	4	0	4
Cabrini Hospital	3	0	3
East Tennessee Baptist Hospital, TN	3	0	3
Florida Gynecologic Oncology, FL	3	0	3
Grand Rapids Clinical Oncology Program, MI	3	0	3
MedStar Washington Hospital Center, DC	3	0	3
Medical College of Virginia, VA	2	1	3
Morristown Medical Center, NJ	3	0	3
Morton Plant Hospital, FL	3	0	3
Moses H. Cone Regional Cancer Center, NC	3	0	3
Penn State Milton S Hershey Medical Center, PA	1	2	3
Pennsylvania Hospital, PA	3	0	3
Rush University Medical Center, IL	1	2	3
Sanford University of South Dakota Medical Center, SD	3	0	3
Scott and White Memorial Hospital, TX	3	0	3
Sparrow Hospital, MI	3	0	3
State University of New York Downstate Medical Center, NY	3	0	3

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	Protocol		
Institution	**0182**	**0172**	**Total**
Sydney West Area Heath Service-Westmead Hospital	3	0	3
The Don and Sybil Harrington Cancer Center, TX	3	0	3
The Reading Hospital and Medical Center, PA	3	0	3
Tulane University Hospital and Clinic, LA	1	2	3
University of Chicago, IL	2	1	3
University of Michigan, MI	3	0	3
Aultman Health Foundation, OH	2	0	2
Avera Cancer Institute, SD	2	0	2
Brooke Army Medical Center, TX	2	0	2
Capital District Hematology Oncology Associates, NY	2	0	2
Christchurch Hospital	2	0	2
Dartmouth Hitchcock Medical Center, NH	2	0	2
East Carolina University, NC	2	0	2
Evanston CCOP-NorthShore University HealthSystem, IL	1	1	2
Fox Chase Cancer Center, PA	2	0	2
Frederick Memorial Hospital, MD	2	0	2
Front Range Cancer Specialists, CO	2	0	2
Geisinger Medical Center, PA	2	0	2
Gundersen Lutheran, WI	2	0	2
Holy Cross Hospital, MD	2	0	2
Jersey Shore University Medical Center, NJ	2	0	2
Joe Arrington Cancer Research and Treatment Center, TX	0	2	2
M.D. Anderson Cancer Center, Orlando, FL	2	0	2
Medical Center of Delaware, DE	2	0	2
Medical College of Wisconsin, WI	2	0	2
MeritCare Medical Group, ND	2	0	2
Metro-Minnesota CCOP, MN	2	0	2
MetroHealth Medical Center, OH	2	0	2
Missouri Valley Cancer Consortium CCOP, NE	2	0	2
Montana Cancer Consortium - CCOP, MT	2	0	2
Nebraska Cancer Research Center, NE	2	0	2
Our Lady of Bellefonte Hospital, KY	2	0	2

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Table of Institution by Protocol			
	Protocol		
Institution	**0182**	**0172**	**Total**
Saint Joseph Mercy Hospital, MI	2	0	2
Sir Charles Gairdner Hospital	2	0	2
Southwest Gynecologic Oncology Associates, Inc., NM	2	0	2
St. Francis Hospital & Medical Center, CT	2	0	2
Sudarshan K Sharma MD Limted-Gynecologic Oncology, IL	2	0	2
University of California Davis-Cancer Center, CA	2	0	2
University of Cincinnati, OH	2	0	2
University of Colorado	2	0	2
University of Hawaii, HI	2	0	2
University of Iowa Hospitals and Clinics, IA	2	0	2
University of Kansas Medical Center, KS	2	0	2
University of Mississippi Medical Center, MS	2	0	2
Women's Cancer Center @ Washoe, NV	0	2	2
Albany Medical College, NY	1	0	1
Baptist Memorial Hospital, TN	1	0	1
Baystate Medical Center, MA	1	0	1
California Health Care System CCOP, CA	1	0	1
Chestnut Hill Health System, PA	1	0	1
Christus Schumpert Saint Mary's Place, LA	1	0	1
Cleveland Clinic Cancer Center/Fairview Hospital, OH	1	0	1
Duluth Clinic CCOP, MN	1	0	1
FirstHealth of the Carolinas-Moore Regional Hospital, NC	1	0	1
Kalamazoo CCOP, MI	1	0	1
Keesler Technical Training Medical Center, MS	1	0	1
Kings Daughters Hospital, KY	1	0	1
Mayo Clinic in Arizona, AZ	1	0	1
Mercy Hospital for Women	1	0	1
MeritCare Hospital CCOP/Roger Maris Cancer Center, SD	1	0	1
Methodist Hospitals of Memphis, TN	0	1	1
Moffitt Cancer Center and Research Institute, FL	0	1	1
Naval Medical Center, San Diego, CA	1	0	1
New Hanover Regional Medical Center, NC	1	0	1

Appendix Table 1: Sites and Count Patients Surviving more than 8 Years

Table of Institution by Protocol			
	Protocol		
Institution	**0182**	**0172**	**Total**
Northern Indiana Cancer Research Consortium, IN	1	0	1
Northwest Oncology/Pelvic Surgery, P.C., OR	1	0	1
Olive View-University of California Los Angeles Medical Center, CA	1	0	1
Oncology Alliance - Milwaukee South, WI	1	0	1
Oncology-Hematology Associates of Central Illinois, IL	1	0	1
Paoli Memorial Hospital, PA	1	0	1
Piedmont Gynecologic Oncology (Forsythe), NC	0	1	1
Prince of Wales Hospital/Royal Hospital for Women	1	0	1
Rapid City Regional Oncology Group, SD	1	0	1
Regions Hospital, MN	1	0	1
Riverview Medical Center, NJ	1	0	1
Royal Hobart Hospital	1	0	1
Royal North Shore Hospital	1	0	1
Royal Prince Alfred Hospital	1	0	1
Royal Women's Hospital	1	0	1
SUNY Upstate Medical University, NY	1	0	1
St. Louis University Health Science Center, MO	1	0	1
UC San Diego Moores Cancer Center, CA	1	0	1
University of Arizona (St. Luke's), AZ	1	0	1
University of Florida @ Sacred Heart Hospital, FL	1	0	1
University of Illinois, IL	0	1	1
University of New Mexico, NM	1	0	1
University of Pittsburgh, PA	1	0	1
University of Tennessee, TN	1	0	1
University of Texas Medical Branch, TX	0	1	1
University of Utah Health Sciences Center, UT	1	0	1
University of Wisconsin Hospital and Clinics, WI	1	0	1
Virginia Piper Cancer Institute, MN	1	0	1
West Virginia University Medical Center, WV	1	0	1
Western Regional CCOP, AZ	1	0	1
Wichita CCOP, KS	1	0	1
Women's Cancer Center, CA	0	1	1

Appendix Table 1: Sites and Count Patients Surviving more than 8 Years

Table of Institution by Protocol			
	Protocol		
Institution	**0182**	**0172**	**Total**
Total	702	109	811

Appendix- Table 2- FFPE Samples Shipped to MGH

USI	specimen type	protocol	ship dates	batch/case
GAAMXL	primary	136	shipped 3/16/15	batch 4/case1
GAAXNE	primary	182	shipped 3/16/15	batch 4/case1
GAAZIW	primary	182	shipped 3/16/15	batch 4/case1
GABFDP	met	136	shipped 3/16/15	batch 4/case1
GABGIX	primary	136	shipped 3/16/15	batch 4/case1
GABIYI	primary	182	shipped 3/16/15	batch 4/case1
GABIYV	primary	182	shipped 3/16/15	batch 4/case1
GABPKY	primary	182	shipped 3/16/15	batch 4/case1
GABUZZ	primary	182	shipped 2/4/15	batch 2/case 1
GABVDI	primary	182	shipped 3/16/15	batch 4/case1
GABVFI	primary	182	shipped 2/25/15	batch 3/case 1
GABVIP	primary	172	shipped 12/30/14	batch 1/case 1
GABVKE	primary	182	shipped 2/4/15	batch 2/case 1
GABVSD	primary & met	182	shipped 2/4/15, 2/25/15 - only 3 pen mem	batch 2/case 1
GABVXC	primary	182	shipped 2/25/15	batch 3/case 1
GABVZN	primary	182	shipped 2/25/15	batch 3/case 1
GABVZR	primary	182	shipped 2/25/15	batch 3/case 1
GABWFM	primary	182	shipped 12/30/14	batch 1/case 1
GABWIP	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 1
GABWJL	met	182	shipped 2/25/15	batch 3/case 1
GABWJZ	primary	182	shipped 12/30/14	batch 1/case 1
GABWLE	primary	182	shipped 12/30/14	batch 1/case 1
GABWPG	primary & met	182	shipped 3/16/15	batch 4/case 2
GABWPM	primary	182	shipped 2/4/15	batch 2/case 1
GABWTB	primary	136	shipped 12/30/14	batch 1/case 1
GABWUI	primary	182	shipped 12/30/14, 2/4/15	batch 1/case 1
GABWUV	primary & met	136	shipped 2/4/15, 2/25/15	batch 2/case 1
GABWWD	primary & met	182	shipped 3/16/15	batch 4/case 2
GABWZZ	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 1
GABXBK	primary	136	shipped 12/30/14	batch 1/case 1
GABXER	primary	182	shipped 2/25/15	batch 3/case 2
GABXFD	primary	182	shipped 3/16/15	batch 4/ case 2
GABXLB	primary & met	172	shipped 12/30/14, 2/25/15	batch 1/case 2
GABXPM	primary	182	shipped 2/25/15	batch 3/case 2
GABXSM	primary	172	shipped 12/30/14	batch 1/case 2
GABXSS	primary	182	shipped 2/4/15	batch 2/case 1
GABXUE	primary	182	shipped 2/25/15	batch 3/case 2
GABYFB	met	182	shipped 3/16/15	batch 4/ case 2
GABYPT	primary	182	shipped 2/25/15	batch 3/case 2
GABYPZ	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 1
GABYWZ	primary	182	shipped 12/30/14, 2/4/15	batch 1/case 2
GABYXI	primary	182	shipped 3/16/15	batch 4/ case 2
GABYYA	primary	182	shipped 2/25/15	batch 3/case 2
GABZAB	primary	136	shipped 3/16/15	batch 4/ case 2

DIOD blocks

USI	specimen type	protocol	ship dates	batch/case
GABZHH	primary	172	shipped 12/30/14	batch 1/case 2
GABZJS	primary & met	182	shipped 2/25/15	batch 3/case 2
GABZNM	primary	136	shipped 12/30/14	batch 1/case 2
GABZRG	primary	136	shipped 12/30/14	batch 1/case 2
GABZVE	primary & met	182	shipped 2/25/15	batch 3/case 3
GACAEN	primary	182	shipped 2/25/15	batch 3/case 3
GACAFH	primary	182	shipped 3/16/15	batch 4/ case 2
GACAFX	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 2
GACAGC	primary	182	shipped 2/25/15	batch 3/case 3
GACANA	primary & met	182	shipped 3/16/15	batch 4/ case 3
GACANB	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 1
GACATP	primary	136	shipped 12/30/14	batch 1/case 2
GACBDT	primary	182	shipped 2/4/15	batch 2/case 1
GACBHT	primary	182	shipped 2/4/15	batch 2/case 1
GACBPG	primary	182	shipped 12/30/14	batch 1/case 2
GACBSN	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 3
GACBTP	primary	172	shipped 12/30/14	batch 1/case 3
GACBZN	primary	182	shipped 12/30/14	batch 1/case 3
GACCFC	primary	182	shipped 2/25/15	batch 3/case 3
GACCHK	primary	182	shipped 12/30/14	batch 1/case 3
GACCRX	primary	182	shipped 12/30/14	batch 1/case 3
GACCRY	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 3
GACCSM	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 2
GACCVH	primary	136	shipped 2/4/15	batch 2/case 2
GACDFZ	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 3
GACDHX	primary	182	shipped 2/25/15	batch 3/case 4
GACDMB	primary	182	shipped 12/30/14, 2/4/15	batch 1/case 3
GACDNI	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 2
GACDPZ	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 2
GACDTG	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 3
GACDZY	primary & met	182	shipped 3/16/15	batch 4/ case 3
GACECR	primary	182	shipped 2/4/15	batch 2/case 2
GACEDD	primary	136	shipped 12/30/14	batch 1/case 4
GACEEL	primary	182	shipped 2/4/15	batch 2/case 2
GACEIN	primary	182	shipped 2/4/15	batch 2/case 2
GACEJI	primary	182	shipped 2/25/15	batch 3/case 4
GACELJ	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 4
GACEMK	met	172	shipped 3/16/15	batch 4/ case 3
GACEPP	primary	172	shipped 12/30/14	batch 1/case 4
GACEYD	primary & met	182	shipped 3/16/15	batch 4/ case 3
GACFAZ	primary	182	shipped 2/25/15	batch 3/case 4
GACFBC	primary & met	182	shipped 2/25/15	batch 3/case 4
GACFBV	primary & met	136	shipped 3/16/15	batch 4/ case 3
GACFCM	primary	182	shipped 2/4/15	batch 2/case 2
GACFEP	primary	182	shipped 2/25/15	batch 3/case 4

DCIS blocks

Page 2

USI	specimen type	protocol	ship dates	batch/case
GACFHC	primary	136	shipped 12/30/15	batch 1/case 4
GACFYA	primary	182	shipped 3/16/15	batch 4/ case 4
GACGGU	primary	182	shipped 2/25/15	batch 3/case 5
GACGJC	primary	182	shipped 2/4/15	batch 2/case 2
GACGJM	primary	182	shipped 2/25/15	batch 3/case 5
GACGNL	primary	182	shipped 2/25/15	batch 3/case 5
GACGTW	primary & met	136	shipped 2/4/15, 2/25/15	batch 2/case 3
GACGVW	primary	182	shipped 2/25/15	batch 3/case 5
GACHKH	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 3
GACHLE	primary	136	shipped 12/30/14	batch 1/case 4
GACHLT	~~primary &~~ met	136	shipped 3/16/15	batch 4/ case 4
GACHPU	primary & met	182	shipped 3/16/15	batch 4/ case 4
GACHVY	primary	182	shipped 2/25/15	batch 3/case 6
GACIDN	primary	172	shipped 12/30/14	batch 1/case 4
GACIIM	met	182	shipped 3/16/15	batch 4/ case 4
GACIMW	primary & met	182	shipped 3/16/15	batch 4/ case 4
GACINM	primary	182	shipped 12/30/14	batch 1/case 4
GACIPC	primary & met	136	shipped 2/4/15, 2/25/15	batch 2/case 3
GACIRK	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 3
GACIWX	primary	182	shipped 12/30/14	batch 1/case 4
GACJAX	primary	172	shipped 12/30/14	batch 1/case 4
GACJCG	primary	182	shipped 2/25/15	batch 3/case 6
GACJIS	primary	182	shipped 2/25/15	batch 3/case 6
GACJJX	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 3
GACJMW	primary	182	shipped 2/25/15	batch 3/case 6
GACJTL	primary	182	shipped 12/30/14	batch 1/case 5
GACJVI	primary	182	shipped 12/30/14	batch 1/case 5
GACJWG	primary	182	shipped 2/4/15	batch 2/case 3
GACKAH	primary	182	shipped 2/25/15	batch 3/case 6
GACKBE	primary & met	136	shipped 12/30/14, 2/25/15	batch 1/case 5
GACKBN	primary	136	shipped 3/16/15	batch 4/ case 4
GACKJM	primary	182	shipped 2/4/15	batch 2/case 3
GACKKU	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 3
GACKLD	primary	182	shipped 2/25/15	batch 3/case 7
GACKRM	primary	136	shipped 12/30/14	batch 1/case 5
GACKRP	primary & met	182	shipped 3/16/15	batch 4/ case 4
GACMDB	primary	182	shipped 12/30/14, 2/4/15	batch 1/case 5
GACMFU	primary & met	182	shipped 2/4/15, 2/25/15	batch 2/case 3
GACMJA	primary	182	shipped 2/25/15	batch 3/case 7
GACMKA	primary	182	shipped 2/4/15	batch 2/case 4
GACMYM	primary	182	shipped 12/30/14	batch 1/case 5
GACNBM	primary	182	shipped 2/25/15	batch 3/case 7
GACNMZ	primary	182	shipped 2/4/15	batch 2/case 4
GACNNF	primary	182	shipped 2/4/15	batch 2/case 4
GACNWU	primary	136	shipped 12/30/14	batch 1/case 5

USI	specimen type	protocol	ship dates	batch/case
GACNYE	primary	182	shipped 12/30/14	batch 1/case 5

DOD blocks

NOW RECRUITING

MASSACHUSETTS GENERAL HOSPITAL

U.S. DEPT. OF DEFENSE RESEARCH PROJECT

A study of long-term survival in women who have survived Stage III or IV ovarian cancer.

OVARIAN CANCER SURVIVORS

EIGHT YEARS OR MORE

STAGE III OR IV **ONLY**

PLEASE CONTACT **GIULIA FULCI** // **GFULCI@PARTNERS.ORG** // **(617) 643-7261**

THE **OVARIAN CANCER CONSORTIUM** FOR **LONG-TERM SURVIVAL**

Finding the key to long-term survival for all women

PARTICIPATING ORGANIZATIONS:

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL · OCRFA Ovarian Cancer Research Fund Alliance · DANA-FARBER CANCER INSTITUTE · FORCE Facing Our Risk of Cancer Empowered · UCSF · Fox Chase Cancer Center · Indiana University School of Medicine · ICC Intercultural Cancer Council · The University of Texas MD Anderson Cancer Center Making Cancer History · GOG Gynecologic Oncology Group · Foundation for Women's Cancer · Center for Patient Partnerships University of Wisconsin-Madison · Mujer Latina y su Familia · Foundation for Women's Cancer Gynecologic Cancer Awareness • Research • Education · CHUV · NOCC National Ovarian Cancer Coalition · INOVA · Ludwig Cancer Research · SHARE Dedicated Experienced Support for women facing breast and ovarian cancers

THE **OVARIAN CANCER CONSORTIUM FOR LONG-TERM SURVIVAL**

Finding the key to long-term survival for all women

Recruiting

We engage long-term survivors in research to improve the treatment, survival, and survivorship of all women affected by ovarian cancer.

A Department of Defense-Funded Project
Coordinating Center, Massachusetts General Hospital
Michael Birrer PI, Lari Wenzel Co-PI

Summary: Stages III and IV serous ovarian cancer are the most lethal of all gynecologic cancers; however, some advanced-stage ovarian cancer patients are long-term survivors. These patients may provide the key to long-term survival and bring hope to all women with Stages III and IV ovarian cancer. There is explanation of why some patients with ovarian cancer become long-term survivors and what their quality of life is long after their initial diagnosis. This research project will specifically determine molecular features within tumors along with genetic, quality of life, and lifestyle features that predict long-term survival for patients with Stages III and IV ovarian cancer. It will bring together sophisticated molecular techniques, researchers with longstanding interest, a wide spectrum of consumer advocates (a number being long-term survivors), and quality of life experts to analyze the most carefully maintained patient database in the world—the Gynecologic Oncology Group database. We anticipate the results from this project will identify specific biochemical pathways and genetic features associated with long-term survival that can be used to improve the treatment, survival, and survivorship of patients with this disease. There is clearly something unique among patients who survive Stage III or IV ovarian cancer long term, and we believe that when we understand what this is, we can increase the number of long- and longer-term survivors.

If you were diagnosed with Stage III or IV ovarian cancer 8 or more years ago, you may qualify for this study. If you are interested in this project and want to know more, please contact the Scientific Director, Giulia Fulci, at gfulci@partners.org or at (617) 643-7261.

THE OVARIAN CANCER CONSORTIUM FOR LONG-TERM SURVIVAL

Finding the key to long-term survival for all women

We engage long-term survivors in research to improve the treatment, survival, and survivorship of all women affected by ovarian cancer.

A Department of Defense-Funded Project
Coordinating Center, Massachusetts General Hospital
Michael Birrer PI, Lari Wenzel Co-PI

Background: Annually, 23,000 women in the United States are diagnosed with ovarian cancer and approximately 16,000 women die from this disease. The classification of ovarian cancer malignancy (FIGO Stage I-IV) is based on anatomical features; advanced stage (Stages III and IV) is associated with the spread of the tumor outside of the pelvis throughout the abdomen. Unfortunately, nearly 80% of women have advanced-stage disease (Stages III and IV) at the time of initial diagnosis. Even though ovarian cancer is chemo-sensitive and usually patients initially respond to therapy, most will suffer relapse and die from drug-resistant disease. Despite this grim outlook, some women with Stages III and IV ovarian cancer (i.e., 15% with Stage III and 5-7% with Stage IV) live 8 years or longer and are considered long-term survivors. Moreover, the quality of life after diagnosis and treatment is different for each woman, indicating that biological differences exist in patients with advanced-stage ovarian cancers and/or in their tumors. Unfortunately, underlying molecular mechanisms in these processes remain unknown, and defined biological or clinical predictors of long-term survival of women diagnosed with advanced-stage ovarian cancer have yet to be identified.

We now have the technological tools to establish detailed biomolecular stratifications of ovarian cancers that allow us to identify therapies that target specific subtypes of these tumors based on the molecular and cellular composition. This new molecular characterization should consider five very important factors that influence treatment choice: (1) the capacity of residual tumor cells to rapidly proliferate and restore the tumor after surgery, (2) the tumor's ability to generate blood vessels that allow its own growth, (3) the capacity of cancer cells to invade neighboring tissues, (4) the capacity of the patient to fight the cancer and prevent its re-growth after surgical debulking, and (5) the short- and long-term quality of life of the patient during and after treatment. Variability in these five factors influences patients' survival and survivorship after diagnosis and determines optimal treatment for specific ovarian cancer patients.

Project Scope: The goal of this project is to identify molecular, cellular, and quality of life patterns that are similar in women who have survived long term (8 years or longer) after diagnosis of Stage III or IV ovarian cancer and different in women who have not survived long term. We believe that once we identify these patterns, we can design a therapy that brings the "long-term survivor patterns" to those predicted to be "short-term survivors" and thus increase survival and improve survivorship of all women with ovarian cancer. To do this, we have created a multidisciplinary consortium composed of clinicians, scientists, and consumer advocates engaged in improving the outcome for patients with ovarian cancers. This team will investigate all aspects of long-term and short-term survivors, including (1) tumor molecular markers, (2) interactions between tumor and host (including the host immune responses to the tumor), and (3) patient-reported pre- and post-treatment quality of life. Through sophisticated statistical analysis, we will find biologic commonalities between long-term survivors that differ from short-term survivors and evaluate potential association of these commonalities with the patients' quality of life and chemotherapy-associated toxicity. Once we identify these commonalities and their link to patients' survival and survivorship, we will be able to establish new therapies and diagnostic tools. It is important to note that this project is focused not only on new therapies aimed at increasing patients' survival, but also on the patients' quality of life during and after treatment. We anticipate being able to identify

the features that cause long-term toxicities associated with treatment, thereby informing future cancer treatment development and supportive care measures to reduce toxicity. The specific aims of this project are:

Aim 1: To determine the genomic (RNAseq miRNAseq, methylation patterns) and proteomic characteristics of long-term versus short-terms survivors.
Aim 2: To characterize and quantitate immune responses and tumor vascularity angiogenesis in long-term versus short-term survivors.
Aim 3: To validate a genomic signature that predicts recurrence of early-stage, high-grade ovarian cancer. This aim leverages ongoing grants from the Department of Defense generating a genomic signature that distinguishes recurrent from non-recurrent early-stage, high-grade ovarian cancer.
Aim 4: To determine the impact of host factors including genomic SNP profiles and key measures of patient stress on long-term survival.
Aim 5: To understand the extent to which health-related quality of life measures and additional patient-reported outcomes predict long-term ovarian cancer survival.
Aim 6: To examine, as an exploratory aim, the potential relationship between health-related quality of life, patient-reported outcomes, and key CTCAE criteria and genomic features predicting disease recurrence.

This is a "holistic" approach that takes into account all aspects of patients with Stage III or IV ovarian cancer, including (1) physical, emotional, and social well-being; (2) life habit changes (exercise, diet, and relational); (3) social support; (4) physiological mechanisms (immune system and other biochemical pathways); and (5) molecular (genetic and epigenetic) markers. These data will be gathered from about 500 patients, and the links among these factors, as well as their association with survival and survivorship, will be analyzed. To make such a holistic study possible, we have assembled a consortium of scientists, clinicians, and consumer advocates who will contribute, with their respective skills, to gathering this information and translating it to the clinic. To include the largest possible number of patients and the best scientific talents, the advocate partner organizations and research sites collaborating in this project are distributed throughout the nation.

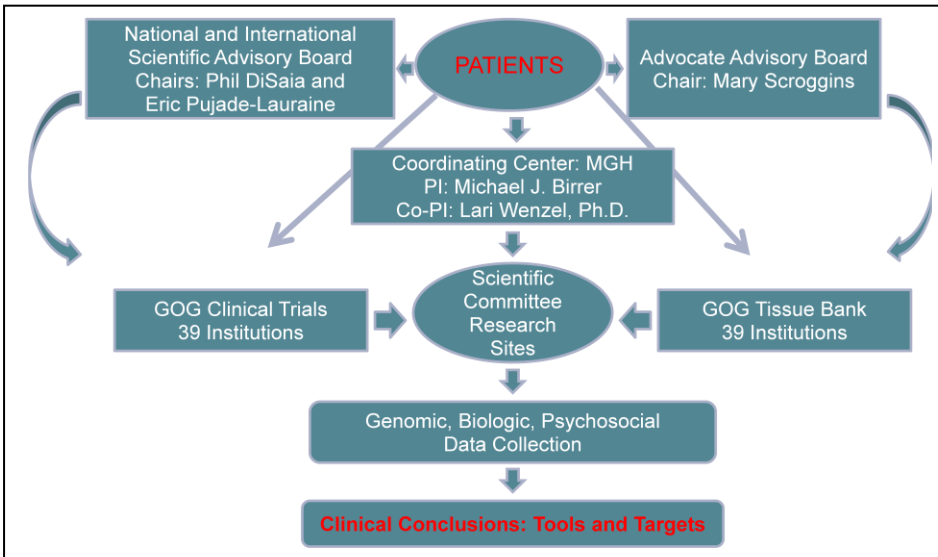
Consortium Geographical Distribution			
Advocate Partner Organizations	**Location**	**Medical Research Sites**	**Location**
Center for Patient Partnerships (CPP)	Madison, WI	Dana Farber Cancer Institute	Boston, MA
Día de la Mujer Latina (DML)	Pearland, TX	Gynecology Oncology Group at NRG	Philadelphia, PA
Facing Our Risk of Cancer Empowered (FORCE)	Tampa, FL	Indiana University School of Medicine	Bloomington, IN
Foundation for Women's Cancer (FWC)	Chicago, IL	INOVA	Fairfax, VA
Intercultural Cancer Council (ICC)	Houston, TX	Ludwig Institute - CHUV	Lausanne, CH
National Ovarian Cancer Coalition (NOCC)	Dallas, TX	MD Anderson Cancer Center	Houston, TX
Ovarian Cancer Research Fund Alliance	Washington, DC and New York, NY	Massachusetts General Hospital	Boston, MA
SHARE	New York, NY	University of California, Irvine	Irvine, CA

Consortium Structure: The consortium is a multidisciplinary team—composed of scientists, clinicians, and consumers advocates—that is driven by patients' needs and leverages the infrastructure of the world's largest research organization focused on gynecologic cancers (the Gynecology Oncology Group (GOG) of NRG Oncology, https://www.nrgoncology.org/) to find a solution for women who may not able to win the fight against ovarian cancer. The Principal Investigator, Dr. Michael J. Birrer, is a Professor at Harvard Medical School and a Medical Oncologist at Massachusetts General Hospital. He has over 20 years of experience in laboratory research for ovarian cancer with particular interest in identifying molecular features that improve clinical management of the disease. Dr. Birrer supervises and coordinates the development of the project as well as certifies the integrity of the research and its alignment with the project scope and patients' real needs. He works closely with Dr. Lari Wenzel, Co-Principal Investigator and Professor of Medicine at the School of

Medicine, University of California, Irvine. Her research specialty in quality of life outcomes and cancer survivorship strongly complements Dr. Birrer's experience.

NRG Oncology is a government-sponsored non-profit organization whose mission is to promote the quality and integrity of scientific research in the field of oncologic diseases. The GOG group of this organization is composed of 60 Parent Member institutions, 299 affiliates of Parent institutions, and 32 Community Clinical Oncology Programs and has 44 open clinical trials. As a result, GOG funds and manages the most comprehensive tissue bank for gynecologic cancers in the world, and its clinical trials have led to major improvements in the treatment of ovarian cancer. All tissues deposited in the bank are collected using standard operating procedures and are fully annotated. These tissues, related annotations, and patients' information are an incredible resource to the understanding of pathological and biological features of ovarian cancers, as well as short- and long-term health outcomes.

To ensure the full scientific and clinical coverage of this study as well as inclusion of all patients needs, the project is guided by a Scientific Advisory Board (SAB) and an Advocate Advisory Board (AAB). The two boards work closely together. The SAB is composed of recognized leaders in ovarian cancer research and has been selected to ensure diversity from both a professional (medical oncology, gynecologic oncology, and quality of life) and an organizational (NRG/GOG, National Institute of Health, and medical research institutes) standpoint. The AAB is composed of consumer advocates from leading ovarian cancer survivor organizations and is instrumental in providing patient-centered guidance to ensure that the project remains patient- and goal-focused, scientifically sound, and clinically relevant.



Consortium Structure

The Scientific and Advocate Advisory Boards work together as partners to communicate patients' needs and health status (e.g., treatment adverse effects and quality of life). Through the coordinating center, the research sites receive input from the boards and patient tissues from GOG and provide clinically relevant scientific results. The coordinating center includes the Principal Investigator of the project, Michael Birrer, an expert in identifying biomarkers for ovarian cancer, and Lari Wenzel, Co-Principal Investigator, with strong expertise in studying health-related quality of life outcomes, patient-reported outcomes in clinical trials, and cancer survivorship.

What We Need: Despite our access to the GOG tissue bank, the currently stored material may not have all the information we need for such a holistic study. In addition, the tissue bank does not provide us with sufficient information about the long-term quality of life for Stages III and IV ovarian cancer survivors. Thus, the study is enrolling patients who were diagnosed with Stage III or IV high-grade ovarian cancer 8 or more years ago to collect their tumor tissue and clinical reports.

If you are interested in this project and want to know more, please contact the Scientific Director, Giulia Fulci, at **gfulci@partners.org** or at (617) 643-7261.

Clinical questionnaire

Record ID _____

Diagnosis date _____

survival years _____

Age at diagnosis (years) _____

Subsite of primary cancer

- ☐ Ovary
- ☐ Fallopian tube
- ☐ Peritoneum
- ☐ Unknown primary
- ☐ Other
- ☐ No data

Specify the subsite of the primary cancer _____

Clinical AJCC stage (based on FIGO system)

- ◯ Stage IA (T1a, N0, M0)
- ◯ Stage IB (T1b, N0, M0)
- ◯ Stage IC (T1c, N0, M0)
- ◯ Stage IIA (T2a, N0, M0)
- ◯ Stage IIB (T2b, N0, M0)
- ◯ Stage IIIA1 (T1 or T2, N1, M0)
- ◯ Stage IIIA2 (T3a2, N0 or N1, M0)
- ◯ Stage IIIB (T3b, N0 or N1, M0)
- ◯ Stage IIIC (T3c, N0 or N1, M0)
- ◯ Stage IVA (any T, any N, M1)
- ◯ Stage IVB (any T, any N, M1)

Primary tumor, histologic type

- ☐ Serous
- ☐ Endometrioid
- ☐ Mucinous
- ☐ Clear cell
- ☐ Other
- ☐ Type not tested or reported
- ☐ No data (pathology report not available)

Specify histologic type _____

Tumor biopsy, histologic grade:

- ◯ Cannot be assessed
- ◯ Well differentiated
- ◯ Moderately differentiated
- ◯ Poorly differentiated
- ◯ Undifferentiated
- ◯ Grade not tested or reported
- ◯ No data (pathology report not available)

Is the Tumor BRCA positive?

- ◯ Yes
- ◯ No

Family history?

- ◯ Yes
- ◯ No

Please, describe _____

Please describe

_____

Optimal debulking?

- ◯ Yes
- ◯ No

Was chemotherapy part of her treatment for the primary tumor?
- ◯ Yes
- ◯ No

Chemotherapy agents for primary tumor?
- ☐ Cisplatin
- ☐ Carboplatin
- ☐ Paclitaxel (Taxol)
- ☐ Cetuximab (Erbitux)
- ☐ Other
- ☐ No data

Please, specify treatment

_____

Recurrences or other tumors?
- ◯ Yes
- ◯ No

Recurrence within 5 years of initial diagnosis?
- ◯ Yes
- ◯ No

Recurrence more than 5 years after initial diagnosis?
- ◯ Yes
- ◯ No

Describe recurrences and their treatment

_____

Are you currently on any chemotherapy or other agents?
- ◯ Yes
- ◯ No

Describe the treatment

_____

Current disease status:
- ◯ I am in remission
- ◯ I have recurrent disease

Did the patient participate in a clinical trial?
- ◯ Yes
- ◯ No

Which phase?
- ◯ Phase I
- ◯ Phase II
- ◯ Phase III

Notes

_____

Study ID#: □□□- □□□- □□□

Interview Date: □□/ □□/ □□□□

Ovarian Cancer Survivorship Questionnaire

Thank you for agreeing to participate in our study. The purpose of this part of the study is to learn more about issues and concerns of ovarian cancer survivors. Your opinions and experiences will help us better understand the quality of life of long term ovarian cancer survivors.

Any information that could identify you will be kept STRICTLY CONFIDENTIAL and we'll use a study number, instead of your name, for the answers you give.

Participation in this study is completely voluntary. You may stop being in the study at any time. You may also skip any questions you do not wish to answer. Please feel free to ask questions about the study at any time.

This survey will take approximately 30-45 minutes, and can be completed in more than one sitting. You can save your data and come back to it when you are ready.

If you need assistance, please call (949) 824-3384, and we will be happy to answer any questions you may have while completing the survey. Thank you!

Sociodemographic Characteristics

1. What is your date of birth? _____

2. What is your age? _____

3. With which ethnic group do you identify yourself? **(Check all that apply)**
   - ❑ Caucasian/Non-Hispanic
   - ❑ African-American/Black
   - ❑ Latina
   - ❑ Asian
   - ❑ Pacific Islander
   - ❑ Native American
   - ❑ Other (please specify): _____

4. What is the highest grade or level of formal education that you have completed?
   - ❑ None
   - ❑ Elementary school (1-8 years)
   - ❑ Some high school (9-11 years)
   - ❑ High school graduate (12 years)
   - ❑ Some college
   - ❑ College graduate
   - ❑ Some graduate school
   - ❑ Graduate or professional degree

5. What is your current marital status?
   - ❑ Single
   - ❑ Married/ living with partner
   - ❑ Separated
   - ❑ Divorced
   - ❑ Widowed

Cancer History – self-report and Medical History/ Comorbid Illness.

1. What year were you diagnosed with ovarian cancer? _____

2. How old were you then? _____

3. Do you recall what cancer treatments you received when you were **first** diagnosed?
   - ❑ No
   - ❑ Yes

4. When you were **first** diagnosed with ovarian cancer, did you have (**Check all that apply**):
   - ❑ Surgery

     If you had surgery, was it performed by a gynecologic oncologist?
     - ❑ No
     - ❑ Yes

   - ❑ Chemotherapy

     Name/Type of chemo:
     - ❑ IV:_____
     - ❑ IV/IP: _____
     - ❑ Neoadjuvant:_____
     - ❑ Other:_____

5. Your **current** disease status:
   - ❑ I am in remission
   - ❑ I have recurrent disease

6. Did you have a recurrence **within 5 years of *initial* diagnosis**?
   - ❑ No
   - ❑ Yes

7. Did you have a recurrence **more than 5 years after *initial* diagnosis?**
   - ❑ No
   - ❑ Yes

8. How many total recurrences have you had? _____

8b. What year(s) was/were the recurrence(s)?_____

Type of cancer treatment included:
- ❑ Chemotherapy /type: _____
- ❑ PARP Inhibitor/type: _____
- ❑ Tyrosine Kinase-inhibitor/type: _____
- ❑ VEG-F Inhibitor/type: _____
- ❑ Other:_____

9. Did you participate in a clinical trial?
   - ❑ No
   - ❑ Yes:
     - ❑ Phase I
     - ❑ Phase II
     - ❑ Phase III

10. Have you had genetic testing?
   - ❑ No
   - ❑ Yes:
     - ❑ I am BRCA 1 positive
     - ❑ I am BRCA 2 positive
     - ❑ I am BRCA negative

11. Have you had hormone replacement therapy?
   - ❑ No
   - ❑ Yes

12. Have you used any alternative treatments?
   - ❑ No
   - ❑ Yes…what type? _____

13. Are you currently on any chemotherapy or other anti-cancer agents, and if so, what?
   - ❑ No
   - ❑ Yes…Agent(s) _____

14. Have you experienced any of the following problems?
   - ❑ No
   - ❑ Yes **(check all that apply)**:

	During **initial** Treatment	After **initial** treatment
Hair loss	❑	❑
Fatigue	❑	❑
Bowel problems	❑	❑
Menopausal symptoms	❑	❑
Weight loss	❑	❑
Bone pain	❑	❑
Weight gain	❑	❑
Pain	❑	❑
Diet related problems	❑	❑
Loss of sensation in feet/hands (numbness/tingling)	❑	❑
Nausea/vomiting	❑	❑
Allergic reactions	❑	❑
Lymphedema	❑	❑
Sexual dysfunction	❑	❑
Other _____	❑	❑

15. Have you experienced any major injury or any other physical or emotional illness other than ovarian cancer?
    - ❑ No
    - ❑ Yes **(check all that apply**):

	Before **initial** diagnosis	After **initial** diagnosis
Another type of cancer (specify) _____	❑	❑
Hypertension/high blood pressure	❑	❑
Stroke	❑	❑
Coronary Heart Disease	❑	❑
Angina or angina pectoris	❑	❑
Heart attack (myocardial infraction)	❑	❑
Anemia	❑	❑
High cholesterol	❑	❑
Chronic bronchitis	❑	❑
Emphysema	❑	❑
Asthma	❑	❑
Serious respiratory disease or problem	❑	❑
Hay fever	❑	❑
Sinusitis	❑	❑
Ulcers	❑	❑
Diabetes	❑	❑
Kidney disease or problem	❑	❑
Liver disease/problem (i.e. Hepatitis)	❑	❑
Arthritis	❑	❑
Back pain	❑	❑
Severe headaches or migraines	❑	❑
Hemorrhoids	❑	❑
Vision loss	❑	❑
Hearing loss	❑	❑
HIV/AIDS related illness	❑	❑
Depression	❑	❑
Anxiety	❑	❑

QUALITY OF LIFE (FACT-O)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I have a lack of energy.....	0	1	2	3	4
2. I have nausea.....	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
4. I have pain.....	0	1	2	3	4
5. I am bothered by side effects of treatment.....	0	1	2	3	4
6. I feel ill.....	0	1	2	3	4
7. I am forced to spend time in bed.....	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I feel close to my friends.....	0	1	2	3	4
2. I get emotional support from my family.....	0	1	2	3	4
3. I get support from my friends.....	0	1	2	3	4
4. My family has accepted my illness.....	0	1	2	3	4
5. I am satisfied with family communication about my illness.....	0	1	2	3	4
6. I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.	❑				
7. I am satisfied with my sex life.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

EMOTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
1. I feel sad……..	0	1	2	3	4
2. I am satisfied with how I am coping with my illness..	0	1	2	3	4
3. I am losing hope in the fight against my illness.....	0	1	2	3	4
4. I feel nervous……..	0	1	2	3	4
5. I worry about dying……..	0	1	2	3	4
6. I worry that my condition will get worse……..	0	1	2	3	4

FUNCTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
1. I am able to work (include work at home).....	0	1	2	3	4
2. My work (include work at home) is fulfilling.....	0	1	2	3	4
3. I am able to enjoy life……..	0	1	2	3	4
4. I have accepted my illness……..	0	1	2	3	4
5. I am sleeping well……..	0	1	2	3	4
6. I am enjoying the things I usually do for fun……..	0	1	2	3	4
7. I am content with the quality of my life right now.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some -what	Quite a bit	Very much
1. I have swelling in my stomach area.....	0	1	2	3	4
2. I am losing weight…….....	0	1	2	3	4
3. I have control of my bowels..….....	0	1	2	3	4
4. I have been vomiting…….....	0	1	2	3	4
5. I am bothered by hair loss…….....	0	1	2	3	4
6. I have a good appetite…….....	0	1	2	3	4
7. I like the appearance of my body…….....	0	1	2	3	4
8. I am able to get around by myself.....	0	1	2	3	4
9. I am able to feel like a woman…….....	0	1	2	3	4
10. I have cramps in my stomach area.....	0	1	2	3	4
11. I am interested in sex..…….…….…….…....	0	1	2	3	4
12. I have concerns about my ability to have children.....	0	1	2	3	4

Any other comments? _____

_____

_____

_____

FACT/GOG NTX

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some -what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands.....	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet.....	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
ACT 11	I have pain in my stomach area.....	0	1	2	3	4
AD1	Stomach pain interferes with my daily functioning	0	1	2	3	4
Cx6	I am bothered by constipation.....	0	1	2	3	4
BMT 15	I am bothered by skin problems..……	0	1	2	3	4

FACT Spiritual Wellbeing

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
Sp1	I feel peaceful	0	1	2	3	4
Sp2	I have a reason for living	0	1	2	3	4
Sp3	My life has been productive	0	1	2	3	4
Sp4	I have trouble feeling peace of mind	0	1	2	3	4
Sp5	I feel a sense of purpose in my life	0	1	2	3	4
Sp6	I am able to reach down deep into myself for comfort	0	1	2	3	4
Sp7	I feel a sense of harmony within myself	0	1	2	3	4
Sp8	My life lacks meaning and purpose	0	1	2	3	4
Sp9	I find comfort in my faith or spiritual beliefs	0	1	2	3	4
Sp10	I find strength in my faith or spiritual beliefs	0	1	2	3	4
Sp11	My illness has strengthened my faith or spiritual beliefs	0	1	2	3	4
Sp12	I know that whatever happens with my illness, things will be okay	0	1	2	3	4

PROMIS-Sexual Function

Please circle or mark one number per line to indicate your response.

	Interest in sexual activity **In the past 30 days…**		**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very**
SFINT101	How interested have you been in sexual activity?		1	2	3	4	5
			Never	**Rarely**	**Sometimes**	**Often**	**Always**
SFINT102	How often have you felt like you wanted to have sex?		1	2	3	4	5
	Lubrication **Over the past 4 weeks…**	**No sexual activity**	**Almost never or ever**	**A few times (less than half the time)**	**Sometimes (about half the time)**	**Most times (more than half the time)**	**Almost always or always**
SFLUB001	How often did you become lubricated ("wet") during sexual activity or intercourse?	0	1	2	3	4	5
	In the past 30 days…	**Have not tried to get lubricated in the past 30 days**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very**
SFLUB101	How difficult has it been for your vagina to get lubricated ("wet") when you wanted it to?	0	5	4	3	2	1
	Vaginal discomfort **In the past 30 days…**		**Have not had any sexual activity in the past 30 days**	**Very comfortable**	**Comfortable**	**Uncomfor-table**	**Very uncom-fortable**
SFVAG101	How would you describe the comfort of your vagina during sexual activity?		0	1	2	3	4
		Have not had any sexual activity in the past 30 days	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
SFVAG102	How often have you had difficulty with sexual activity because of discomfort or pain in your vagina?	0	1	2	3	4	5
SFVAG103	How often have you stopped sexual activity because of discomfort or pain in your vagina?	0	1	2	3	4	5

	Orgasm **In the past 30 days…**	**Have not tried to have an orgasm/climax in the past 30 days**	**Excellent**	**Very good**	**Good**	**Fair**	**Poor**
SFORG101	How would you rate your ability to have a satisfying orgasm/climax?	0	1	2	3	4	5
	Satisfaction **In the past 30 days…**	**Have not had any sexual activity in the past 30 days**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very**
SFSAT105	When you have had sexual activity how much have you enjoyed it?	0	1	2	3	4	5
		Have not had any sexual activity in the past 30 days	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very**
SFSAT106	When you have had sexual activity, how satisfying has it been?	0	1	2	3	4	5

PROMIS-Emotional Distress-Depression

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
1.	I felt worthless…….....	0	1	2	3	4
2.	I felt helpless..…….....	0	1	2	3	4
3.	I felt depressed…….....	0	1	2	3	4
4.	I felt hopeless…….....	0	1	2	3	4

PROMIS-Emotional Distress-Anxiety

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
1.	I felt fearful…….....	0	1	2	3	4
2.	I found it hard to focus on anything other than my anxiety…….....	0	1	2	3	4
3.	My worries overwhelmed me…….....	0	1	2	3	4
4.	I felt uneasy..…….....	0	1	2	3	4

PROMIS SF FATIGUE 4a

Please respond to each question or statement by circling one number per row.

During the past 7 days…

		Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I feel fatigued	0	1	2	3	4
2.	I have trouble starting things because I am tired.	0	1	2	3	4
3.	How run-down did you feel on average?	0	1	2	3	4
4.	How fatigued were you on average?	0	1	2	3	4

PROMIS Instrumental Support

	Never	Rarely	Some-times	Often	Always
1. Do you have someone to help you if you are confined confined to bed?	0	1	2	3	4
2. Do you have someone to take you to the doctor if you need it?	0	1	2	3	4
3. Do you have someone to help with your daily chores if you are sick?	0	1	2	3	4
4. Do you have someone to run errands if you need it?	0	1	2	3	4

PROMIS Informational Support

	Never	Rarely	Some-times	Often	Always
1. I have someone to give me good advice about a crisis if I need it	0	1	2	3	4
2. I have someone to turn to for suggestions about how to deal with a problem	0	1	2	3	4
3. I have someone to give me information if I need it.	0	1	2	3	4
4. I get useful advice about important things in my life	0	1	2	3	4

PROMIS Emotional Support

	Never	Rarely	Some-times	Often	Always
1. I have someone who will listen to me when I need to talk	0	1	2	3	4
2. I have someone to confide in or talk to about myself or my problems	0	1	2	3	4
3. I have someone who makes me feel appreciated	0	1	2	3	4
4. have someone to talk with when I have a bad day	0	1	2	3	4

PROMIS-Physical Function

Please circle or mark one number per line to indicate your response.

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1. Are you able to do chores such as vacuuming or yard work?	0	1	2	3	4
2. Are you able to go up and down stairs at a normal pace?.....	0	1	2	3	4
3. Are you able to go for a walk of at least 15 minutes?.....…….....	0	1	2	3	4
4. Are you able to run errands and shop?.....…….....	0	1	2	3	4

SURVIVOR SPECIFIC DISTRESS

1. How difficult is it for you to cope **today** as a result of your disease and treatment?

Not at all difficult 0 1 2 3 4 5 6 7 8 9 10 Very difficult

2. To what extent are you fearful of:

Future diagnostic tests (like CA125, PET scan, CT scan etc.)

No fear 0 1 2 3 4 5 6 7 8 9 10 Extreme fear

A second cancer

No fear 0 1 2 3 4 5 6 7 8 9 10 Extreme fear

Recurrence of your cancer

No fear 0 1 2 3 4 5 6 7 8 9 10 Extreme fear

Spreading (metastasis) of your cancer

No fear 0 1 2 3 4 5 6 7 8 9 10 Extreme fear

Support Questions

1. Have you participated in any type of support program *related to your experience with cancer*?

❑ **No**…If a counseling program had been available to you after diagnosis, how likely is it you would have participated?

Very likely	Somewhat likely	Not very likely	Not at all likely
1	2	3	4

❑ **Yes**.....What type of support program was it ***(check all that apply)***?

❑ Individual Counseling *(please specify):*_____

Was the individual counseling:
- ❑ Within a year from initial diagnosis
- ❑ More than a year after initial diagnosis

How helpful was the individual counseling?

Not at all	A little bit	Some-what	Quite a bit	Very much
0	1	2	3	4

❑ Support Group *(please specify):*_____

Was the support group:
- ❑ Within a year from initial diagnosis
- ❑ More than a year after initial diagnosis

How helpful was the support group?

Not at all	A little bit	Some-what	Quite a bit	Very much
0	1	2	3	4

❑ Social Media/Web-based *(please specify):* _____

Was the social media support:
- ❑ Within a year from initial diagnosis
- ❑ More than a year after initial diagnosis

How helpful was the social media support?

Not at all	A little bit	Some-what	Quite a bit	Very much
0	1	2	3	4

2. If a counseling program were available ***now*** for cancer survivors to address quality of life concerns, how likely is it that you would participate?

Very likely	**Somewhat likely**	**Not very likely**	**Not at all likely**
1	2	3	4

If you were to participate in a counseling program, in wh

3. What type of setting would you prefer it to be? Would you prefer ***(check all that apply)***

   ❑ Individual / in person?
   ❑ Web-based information and support group?
   ❑ Over the telephone: you and the counselor only?
   ❑ In-person Support group?
   ❑ Other ***(please specify)***: _____

Access to Care History

1. Do you currently have health insurance?
   - ❑ No
   - ❑ Yes....What kind of health insurance do you have? ***(Check all that apply)****:*
     - ❑ Medicare
     - ❑ PPO
     - ❑ HMO
     - ❑ Medicaid
     - ❑ Champus/ VA/ military (Tricare)

   1b. If **yes**, are you satisfied with your health insurance?
   - ❑ No.... Why not? _____
   - ❑ Yes

Lifestyle and Health

2. What is your current occupation?
   - ❑ Professional
   - ❑ Management/Administration
   - ❑ Clerical
   - ❑ Homemaker
   - ❑ Self-employed
   - ❑ Not employed
   - ❑ Retired

3. Have you ever smoked at least 100 cigarettes (5 packs) in your lifetime?
   - ❑ No
   - ❑ Yes

   If YES,

   3b. For approximately how many total years did you smoke? _____ years

   3c. Do you currently smoke?

   - ❑ Yes
   - ❑ No

   If NO,

   When did you quit smoking?

   - ❑ Before the diagnosis
   - ❑ After the diagnosis

Exercise

4. In a typical week, how many days do you do any physical activity or exercise of **at least** moderate intensity, such as brisk walking, bicycling at a regular pace, or swimming at a regular pace?

   ❑$_{0}$ Never

   ❑$_{0.5}$ Less than once a week

   ❑$_{1}$ Once a week

   ❑$_{2.5}$ 2-3 times a week

   ❑$_{5}$ Almost everyday

5. On the days that you do any physical activity or exercise of at least moderate intensity, how long do you typically do these activities?

   ❑$_{0.1}$ Less than 15 minutes

   ❑$_{0.38}$ 16-30 minutes

   ❑$_{0.75}$ 30 minutes to 1 hour

   ❑$_{1}$ More than 1 hour

6. Since your initial cancer diagnosis, have you intentionally tried to:

   ❑ **INCREASE** the amount of exercise you get in a typical week,

   ❑ **MAINTAIN** the amount of exercise you get in a typical week, or

   ❑ You haven't really paid much attention to the amount of exercise you get

7. People start or continue exercising regularly for lots of reasons. How much do each of the following reflect why you would start or continue exercising regularly?

	Not at all	**A little**	**Some**	**A lot**
a. Pressure from others.....	1	2	3	4
b. Concern over the way you look.....	1	2	3	4
c. Feeling guilty when you skip exercising.....	1	2	3	4
d. Getting enjoyment from exercise.....	1	2	3	4
e. Concern about your health .....……..	1	2	3	4
f. Feel better emotionally.....……..	1	2	3	4

Diet

8. In general, how healthy is your overall diet? Would you say it is…
   - ❑ Excellent
   - ❑ Very good
   - ❑ Good
   - ❑ Fair
   - ❑ Poor

9. About how many cups of fruit (including 100% pure fruit juice) do you eat or drink each day? [*1 cup of fruit could be: - 1 small apple - 1 large banana - 1 large orange - 8 large strawberries - 1 medium pear - 2 large plums - 32 seedless grapes - 1 cup (8 oz.) fruit juice - ½ cup dried fruit - 1 inch-thick wedge of watermelon*.]
   - ❑ None
   - ❑ ½ cup or less
   - ❑ ½ cup to 1 cup
   - ❑ 1 to 2 cups
   - ❑ 2 to 3 cups
   - ❑ 3 to 4 cups
   - ❑ 4 or more cups

10. Since your initial cancer diagnosis, have you intentionally tried to:
    - ❑ **INCREASE** the amount of fruit or 100% fruit juice you eat or drink,
    - ❑ **MAINTAIN** the same amount of fruit or 100% fruit juice you eat or drink, or
    - ❑ You haven't really paid attention to the amount of fruit or 100% fruit juice you eat or drink?

11. About how many cups of vegetables (including 100% pure vegetable juice) do you eat or drink each day? [*1 cup of* vegetables *could be: - 3 broccoli spears - 1 cup cooked leafy greens – 2 cups lettuce or raw greens – 12 baby carrots – 1 medium potato - 1 large sweet potato – 1 large ear of corn – 1 large raw tomato – 2 large celery sticks – 1 cup of cooked beans]*
    - ❑ None
    - ❑ ½ cup or less
    - ❑ ½ cup to 1 cup
    - ❑ 1 to 2 cups
    - ❑ 2 to 3 cups
    - ❑ 3 to 4 cups
    - ❑ 4 or more cups

12. Since your initial cancer diagnosis, have you intentionally tried to:
    - ❑ **INCREASE** the amount of vegetables or 100% vegetable juice you eat or drink,
    - ❑ **MAINTAIN** the same amount of vegetables or 100% vegetable juice you eat or drink, or
    - ❑ You haven't really paid attention to the amount of vegetables or 100% vegetable juice you eat or drink each day?

13. Since your initial cancer diagnosis, have you intentionally tried to change your diet to…(**check all that apply**):
    - ❑ **INCREASE** total calories
    - ❑ **DECREASE** total calories
    - ❑ **INCREASE** consumption of red or processed meats
    - ❑ **DECREASE** consumption of red or processed meats
    - ❑ **INCREASE** consumption of chicken and fish
    - ❑ **DECREASE** consumption of chicken and fish
    - ❑ **INCREASE** consumption of whole grain and fiber
    - ❑ **DECREASE** consumption of whole grain and fiber

14. Have you used or taken any vitamins, minerals, herbals or other dietary supplements since your **initial** diagnosis? Include prescription and non-prescription supplements.
    - ❑ No
    - ❑ Yes ***(check all that apply)****:*
        - ❑ Multivitamin
        - ❑ Single vitamin (Vitamin A, Vitamin C, Vitamin D, Vitamin B12, Vitamin E, Iron etc.)
        - ❑ Minerals (Calcium, Magnesium, Iron, Chromium, Selenium, Zinc etc.)
        - ❑ Herbal supplements
        - ❑ Other: _____

15. What would you like us to know about long-term ovarian cancer survivorship?

_____

_____

_____

_____

_____

_____

16. Thank you for completing this survey. If we have missed important areas of ovarian cancer survivorship, please provide comments below:

_____

_____

_____

_____

_____

Appendix Task 4: Genomics and immunologic analysis of tumor specimens

We have established a research plan in coordination with GOG and all the scientific sites to obtain preliminary data that would be used to develop a full research plan that would be accomplished in the case we would receive additional funding for this project. (Phase 2 DOD grant). The plan included analysis of 52 tumors samples (26 long-term survivors and 26 short-term survivors) with the following platforms: RNAseq (Dr. Birrer), miRNAseq (Dr. Mock), DNAmethyl-seq (Dr. Nephew), Multiplex immunohistochemistry (IHC) (Dr. Coukos). The results would be analyzed and integrated by Dr. Parmigiani at DFCI. The 52 tumors were selected by Dr. Brady at GOG from a batch of 135 cases that was sent to us from GOG in year 1. The reason for analyzing 52 of 135 cases was due to the fact that we had budgeted with DOD analysis of only 30 cases; the decrease in prices for these novel genomics platforms allowed analysis of 52 cases, but not of all the 135 that we received. Because this is only a pilot study we were not looking to obtain statistically significant data. The inclusion criteria were: stage III or IV serous high grade (grade 2-3) ovarian cancer.

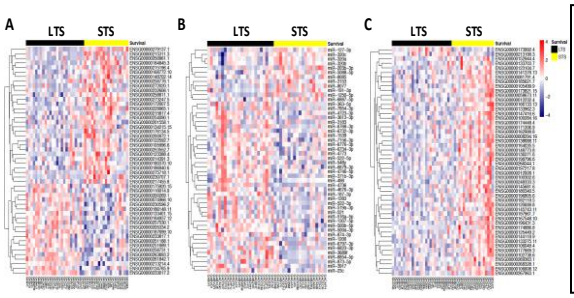


Figure 1. Heatmaps for the three high-throughput platforms, RNAseq (A), microRNA-seq (B) and Methyl-seq (C). Supervised clustering was applied using the top 50 features that are mostly differentially presented in each platform.

We have thus generated gene expression heat maps for 26 long-term survivors and 26 short-term survivors indicating a differential trend between the 2 survival groups in: mRNA expression, miRNA expression, and DNA methylation. Each analysis was performed at the dedicated scientific sites. The heat maps were generated by Giovanni Parmigiani at DFCI (Figure 1)

1) **The RNAseq** analysis was used for gene expression analysis instead of CNV and exome seq. Indeed, this platform proved to apply better to FFPE samples and provides more readily translational data. The data was robust enough that samples were separated into training (n=30) and validation (n=14) sets. Such analysis provides a pilot test of what will be done in Phase II using a much larger number of samples. Unsupervised clustering of the training data using the top 50 differentially expressed transcripts indicated the possibility to differentiate LT versus ST survivors mRNA levels (Fig. 2A). Gene set enrichment analysis (GSEA) using the Ingenuity software (QIAGEN) identified a cluster of HOX transcription factors to be under-expressed in LTS samples (Fig. 2B). Alteration in HOX genes also converged into a node of NF-κB. The expression of HOXA and HOXB genes significantly correlated with each other, further supporting the GSEA data (Fig. 2C). The predictive power of 7 HOXA genes, considered as a single gene set, was then interrogated by an ROC curve using the 14 validation samples and resulted in an area under the curve

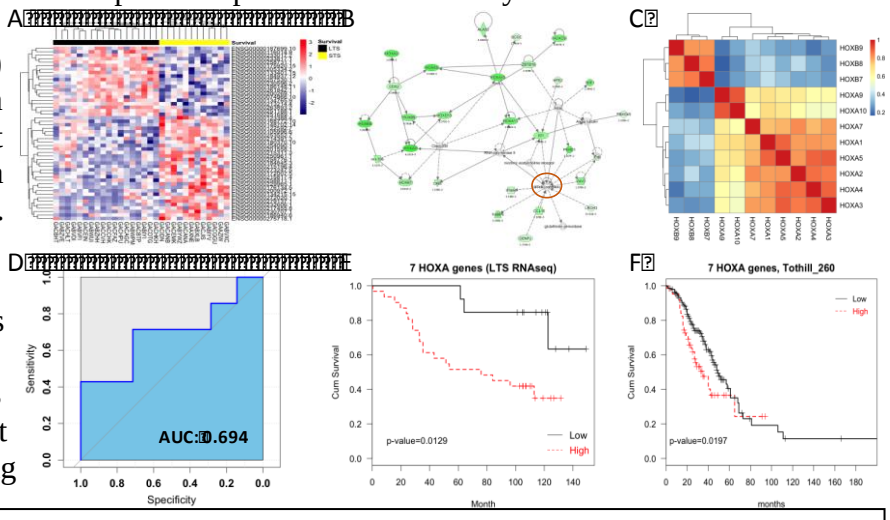
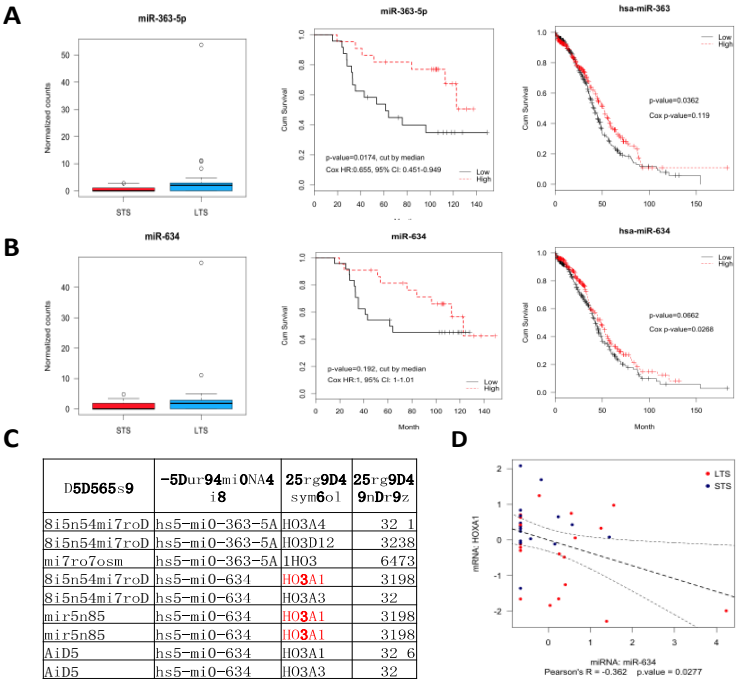


Figure 2. Analyses of the RNAseq data. We used STAR algorithm alignment with default parameters using human genome version GRCh38 with Gencode annotation (version 23). Mapped RNAseq data was normalized by *edgeR* R/bioconductor package, *voom* transformed before subjected to *limma* package for differential expression analysis. **(A)** Unsupervised clustering of the training data using the top 50 differentially expressed transcripts. (LTS black bar, STS yellow bar). **(B)** Gene set enrichment analysis (GSEA) through Ingenuity software (QIAGEN) shows a node of NF-κB within a cluster of under-expressed HOX genes. **(C)** Correlation analysis for HOXA and HOXB genes expression. **(D)** Predictive power of 7 HOXA genes as a gene set was subsequently interrogated by an ROC curve using the 14 validation samples. **(E)** and **(F)** Kaplan Meier analysis of HOX genes set using clinical annotation of our 44 tumors and in the independent expression dataset by Tothill et al (n=260).

(AUC) of 0.694 (Fig. 2D) as a predictor of LT. Finally, the prognostic impact of the 7-HOXA genes set demonstrated in the LT RNAseq dataset (n=44, Fig. 2E) has been cross-validated using an independent expression dataset by Tothill et al (n=260, Fig. 2F).

2) **The miRNA expression** data was generated from the whole transcriptome EdgSeq microRNA sequencing platform. The raw data were pre-processed for alignment, normalization and transformation via a workflow similar to the RNAseq analysis. Differential expression analysis by edgeR and limma packages, coupled with a Cox regression model for hazard ratio, identified a signature of 24 miRNAs differentially expressed in LTS samples (Fig. 1B). It is worth noting that our miRNAseq platform presents a much higher coverage of miRNA species compared to the array-based platform used in the TCGA study, in which more than 70% of the miRNA in the LTS signature was not annotated and tested. We successfully cross-validated the prognostic impact of two top hits, miR-363-5p and miR-634, using the TCGA cohort (Fig. 3A and 3B) and, through target prediction analysis on 7 independent published algorithms, we identified HOX genes as potential targets of miR-363-5p and miR-634 (Fig. 3C and D). In Fig. 3D, the level of miR-634 presents negative correlation with the HOXA1 mRNA level in the LTS cohort. These integrated analyses suggest miRNAs play important role in OC patient prognosis by regulating the level of key mRNA transcripts that have prognostic impact. These results indicate the power of cross platform analysis (mRNAseq, miRNAseq, DNA-methylation) to identify strong biomarkers predictive for LT survival.



D5D565s9	−5Dur94mi0NA4 i8	25rg9D4 sym6ol	25rg9D4 9nDr9z
8i5n54mi7roD	hs5−mi0−363−5A	HO3A4	32_1
8i5n54mi7roD	hs5−mi0−363−5A	HO3D12	3238
mi7ro7osm	hs5−mi0−363−5A	1HO3	6473
8i5n54mi7roD	hs5−mi0−634	HO3A1	3198
8i5n54mi7roD	hs5−mi0−634	HO3A3	32
mir5n85	hs5−mi0−634	HO3A1	3198
mir5n85	hs5−mi0−634	HO3A1	3198
AiD5	hs5−mi0−634	HO3A1	32_6
AiD5	hs5−mi0−634	HO3A3	32

Figure 3. Analysis of miRNA-seq. (A) and **(B)** Two top hits, miR-363-5p and miR-634 are overexpressed in LTS samples (left and middle panels). Both miRNAs elicit negative prognostic impacts which can be cross-validated in TCGA datasets (right panels). **(C)** Target prediction analysis suggests the participation of miR-363-5p and miR-634 in the regulation of HOX genes. **(D)** The expression of miR-634 shows significant negative correlation with the expression of the HOXA1 gene in the LTS cohort (p=0.0277).

3) **The DNA methylation profile** in LTS and STS was investigated using MethylCap-seq. MethylCap-seq involves the *in vitro* capture of methylated DNA using the recombinant methyl-CpG binding domain of MBD2 protein and subsequent analysis of enriched fragments by parallel sequencing. MethylCap-seq was shown to be more effective at interrogating CpG islands than antibody-based methyl-DNA immuno-precipitation sequencing (MeDIP-seq). In addition, this technology can be applied on DNA extracted from FFPE tissues as it functions also with low DNA input (Fig. 4A). Raw MethylCap-seq data were aligned using the Bowtie2 algorithm. Scaled binary counts were interrogated by genomic feature (e.g., CpG islands, CpG shores, Refseq genes) to generate feature-specific count files. The validity of the MethylCap-Seq data was further validated by checking methylation sites that were identified in the TCGA study as the ones with most negative correlation with mRNA expression (Fig. 4B). The identification of differentially methylated regions (DMRs) was achieved through a standard workflow centralized by the DESeq2 Bioconductor package. Ingenuity pathway analysis (IPA) was performed to explore pathways enriched by differentially methylated genes between LTS and STS. Hypermethylated or hypomethylated genes were identified as P value<0.05 and methylation fold change greater than 1.2 or less than -1.2 in LTS over STS (Fig. 4C). It is to note that hypermethylation was identified at promoter sites of genes frequently lost in OC, such as PTEN and DNA repair mechanisms. Whereas hypomethylated pathways were associated with cellular metabolism, which may be due to the Warburg

effect. We thus expect that completion of the 3-platform genomic analysis in phase 2 will provide data that can be integrated with each other and thus provide a cross-validation of the molecular signature.

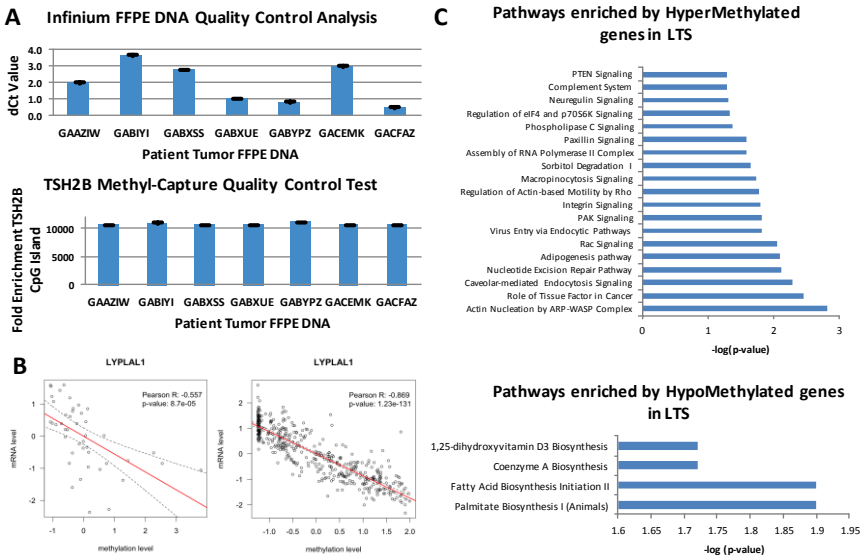


Figure 4. Analysis of Methyl-seq data. (A) The methy-seq platform is compatible to FFPE DNA. The DNA quality was assayed by qPCR based Infinium FFPE DNA QC assay. A higher dCt value implicates more severe compromise in DNA quality which is common in FFPE DNA samples. Nevertheless, the performance of the methyl-seq platform was not affected by the quality of input DNA, as indicated by the methylation level at the TSH2B locus which was universally methylated across ovarian cancer samples. **(B)** Negative correlation between mRNA (y-axis) and methylation level (x-axis) of LYPLAL1 in the LTS cohort (left) and the TCGA cohort. **(C)** Gene set enrichment analyses of loci with differential methylation level between LTS and STS samples indicates methylation based epigenetic regulation may contribute to the modulation of several key signaling pathways affecting patient survival.

4) **We quantified the density of TILs**, expressed as % TILs/100 cancer cells, using the CD8 and/or FOXP3 markers detected by IHC on our tumor samples (Fig. 5). To determine whether infiltration of TILs clustered with LT survivors we analyzed the IHC data using two sets of controls: 1) patients who survived less than 5 years, and 2) patients that survived less than 8 years. Given the small number of samples used in this pilot study we could not observe any significant difference in either CD8+ or FOXP3+ cells taken alone between controls who survived less than 8 years and LTS. However, there was a significant difference in CD8+ density when the controls were considered as those who survived less than 5 years (Fig. 5). More interestingly and given their opposing function, when we combined the two markers together in the CD8+/FOXP3+ cell ratio, we could see a significant difference in LTS versus controls who survived less than 8 years, and the significance of the difference between LTS and 5-years controls became stronger (Fig. 5). These data suggest the possibility to distinguish controls versus LTS based on infiltration of immune cells, but the data would be stronger and more biologically significant in a multiplexed analysis that combines multiple markers for each cell type in the same tissue section. Such analysis is feasible on our samples as shown in the example of Fig. 6A-D. It is important to note that, in another study, using a different set of tumors we have shown the possibility to identify different mRNA signatures in tumors with high-density versus low-density TILs (Fig. 6E), thus supporting the possibility to integrate the immune studies with the genomic analysis.

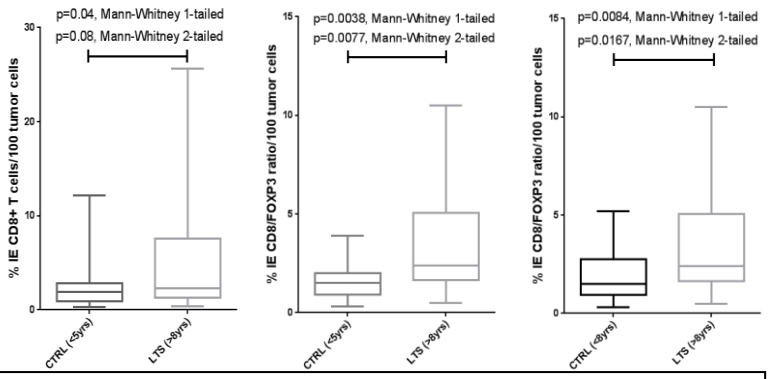


Figure 5: Intratumoral TILs density. The percentage of intraepithelial (IE) CD8+ and FOXP3+ lymphocytes per 100 tumor cells was evaluated in areas with the highest densities of immunopositive cells, by counting more than 1000 tumor cells in 20x high power fields. CD8+ IE T cell counts correlated with clinical outcome when controls survive less than 5 years whereas CD8/FOXP3 cell ratios significantly correlated with clinical outcome both in 5- and 8-years survived controls.

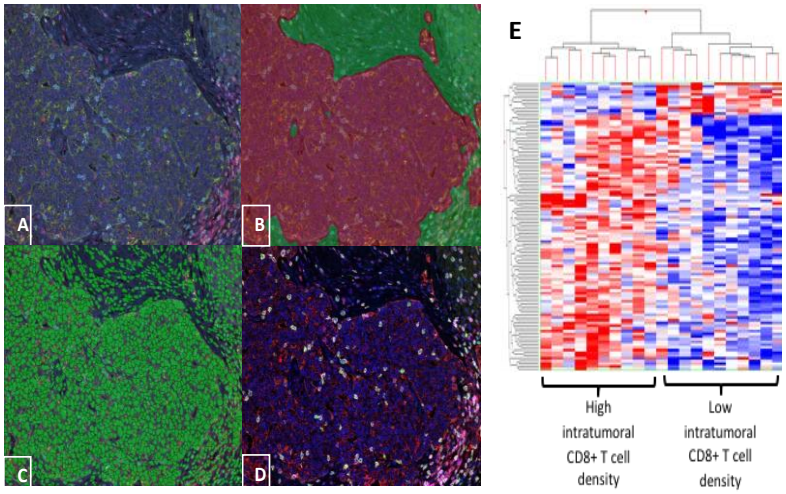
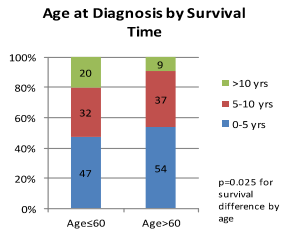


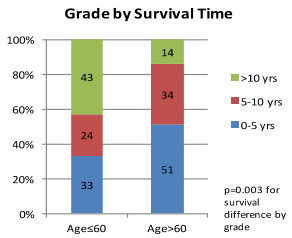
Figure 6: Investigate the immuno-signature in LTS. (A)-(D) Multiplexed Immunofluorescence Lymphocyte Assay in Ovarian Cancer. Representative Tyramide Signal Amplification (TSA) multiplexed immunofluorescence, using anti-CD3, CD4, CD8, CD45RO, Cytokeratin antibodies and DAPI (counterstain) in Ovarian Cancer. The color image (A) is loaded in the inForm software and algorithms for tissue (B, tumor [red] versus stroma [green]) and cell (C) segmentation are applied to the whole group of scanned images of each case, in order to quantify lymphocytic subsets in the tumor and stromal compartments. Multispectral imaging yields a composite image (D) where each marker-associated dye can be reliable separated for accurate phenotypic and expression analyses (CD3=green, CD4=red, CD8=pink, CD45RO=magenta, Cytokeratins=brown, DAPI=blue). **(E) Tumors with different degree of TIL infiltration present distinctive transcriptional profiling.** Intratumoral CD8+ T cell densities were quantified in terms of number of CD8+ cells per unit tumor area. Using median T cell density as the cutoff, expression profiles generated from microdissected ovarian cancer cells were compared between low and high T cell density groups. Genes with expression fold changes >2 and p values < 0.05 in patients with low intratumoral CD8+ cell density were identified in contrast to the high CD8+ cell density group. Heatmap was generated using differentially expressed genes by unsupervised hierarchical clustering.

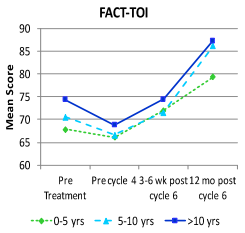
Appendix Task 5: Construct comprehensive database from GOG 172 and GOG 218 advanced ovarian cancer treatment trials

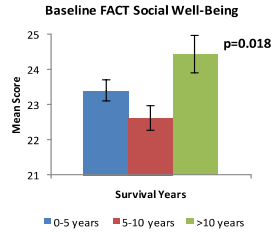
Significant Differences Exist Between Long Term and Short Term Survivors at Treatment Initiation. After adjusting for treatment, long term survivors were significantly younger at diagnosis compared to short-term survivors (53 vs 57, p=0.029) and had lower grade disease (17% vs 4% grade 0-1 for long vs short-term survivors, p=0.006). Long-term survivors had significantly higher social well-being (p=0.021) and fewer ovarian cancer-specific concerns (p=0.049) compared to short-term survivors.

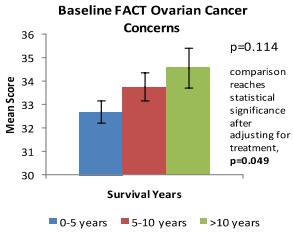
Long term survivors demonstrate more QOL improvement during active treatment and 12 months after chemotherapy cycle 6. Changes over time in QOL and symptom measures were investigated using analysis of variance for repeated measures. The FACT-O and FACT-TOI both show a significant difference in change over time by survival group with higher QOL for long-term survivors across each time point for each treatment group (p=0.05 and p=0.030 respectively for time*survival group interaction). Trends over time also differ significantly by treatment group (time*treatment interaction, p=0.003 and 0.001 respectively). All components of the FACT-TOI show the same patterns, but are significantly different specifically for the Ovarian cancer-specific concerns (p=0.003). Trends differ significantly by treatment for each subdomain (time*treatment interaction p=0.005, p=0.002, p=0.013 respectively).

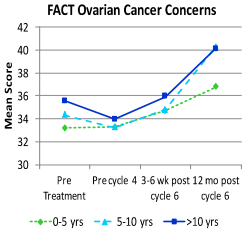












Significant predictors of long-term survival include younger age, 0-1 tumor grade, better QOL and Social Well Being, and IP treatment. In multivariate analysis using polychotomous logistic regression, long-term survivors (>10 yr) and intermediate length survivors (>5 but <10 yr) were compared to the reference group of short-term survivors. Independent factors contributing to long-term survival (>10) relative to short-term (<5) include younger age at diagnosis, lower grade disease, higher baseline FACT-TOI, larger increase in FACT-TOI from baseline to follow-up, higher social well-being at baseline and IP treatment. Odds ratios and confidence intervals for independent variables are: age at diagnosis (OR for age>60 = 0.31, 95% CI: 0.13, 0.73), grade (OR for grade 2-3 = 0.21, 95% CI: 0.06, 0.76), baseline FACT-TOI

			95% CI	
Independent variable	Odds Ratio	p-value	Lower	Upper
Intermediate (5-10 yr survival) vs short-term survival(<5 yr)				
CONSTANT		0.182		
AGE (0 for ≤60; 1 for >60)	1.022	0.942	0.566	1.845
GRADE (0 for 0-1; 1 for 2-3)	0.879	0.849	0.233	3.321
TOI_Baseline	1.032	0.015	1.006	1.058
TOI_Change (12 mo-baseline)	1.033	0.004	1.01	1.056
TREATMENT (0 for IV; 1 for IP)	1.714	0.074	0.949	3.095
SWB baseline	0.954	0.206	0.888	1.026
Long-term survival (>10 yr) vs short-term survival (<5 yr)				
CONSTANT		0.002		
AGE (0 for ≤60; 1 for >60)	0.312	0.007	0.134	0.727
GRADE (0 for 0-1; 1 for 2-3)	0.210	0.018	0.058	0.762
TOI_Baseline	1.036	0.035	1.003	1.071
TOI_Change (12 mo-baseline)	1.036	0.019	1.006	1.066
TREATMENT (0 for IV; 1 for IP)	2.014	0.067	0.951	4.264
SWB baseline	1.152	0.024	1.019	1.303

Table 1: **Polychotomous Logistic Regression** – Dependent variable is survival group (0-5 years, 5-10 years, >10 years (OR=1.036, 95% CI: 1.003, 1.071), change in FACT-TOI from baseline to 12 month follow-up (OR=1.036, 95% CI:1.006, 1.066), baseline social well-being (OR=1.152, 95% CI: 1.019, 1.303) and IP treatment (OR=2.014, 95% CI:0.951, 4.264). Baseline FACT-TOI and change in FACT-TOI contribute significantly to longer survival at 5-10 years relative to <5 years, however age, grade and social well-being were not significant.

Relationship between Quality of Life during initial Treatment and Long-Term Ovarian Cancer Survival

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Aims

The majority of women diagnosed with advanced ovarian cancer will die from this disease. However, 10-15% of patients with advanced stage disease will survive 10 or more years following diagnosis. The purpose of this study is to identify differences in quality of life (QOL) of short-term versus long-term survivors, and determine if QOL during initial cancer treatment predicts long term survival.

Methods

We utilized data from GOG 172, a clinical trial testing intraperitoneal and intravenous chemotherapy to develop a descriptive profile of short, intermediate, and long term survivors. Survival time was categorized into 3 categories: < 5 years (n=177), 5-10 years (n=121) and >10 years (n=57). Comparisons between the categories were adjusted for treatment (IP vs IV). Analyses consist of 3 approaches: 1) comparison of baseline characteristics by survival group, 2) comparison of change over time for QOL and symptom measures by survival time and treatment and 3) using a multivariate model (polychotomous logistic regression), we sought to identify variables which may be independently associated with long-term survival.

Results

After adjusting for treatment, long term survivors were significantly younger at diagnosis compared to short-term and intermediate term survivors (p=0.029) and had lower grade disease (p=0.003). Long-term survivors also had significantly higher/better social well-being (p=0.021) and fewer ovarian cancer-specific concerns (p=0.049) compared to short and intermediate term survivors. In the multivariate analysis, independent factors contributing to long-term survival (>10) relative to short-term (<5) included younger age at diagnosis (OR for age 60 = 0.29, 95% CI:0.12, 0.67), lower grade disease (OR for grade 2-3 = 0.22, 95% CI: 0.06, 0.79), higher baseline QOL (OR=1.04, 95% CI:1.01, 1.08), larger increase in QOL from baseline to follow-up (OR=1.04, 95% CI:1.01, 1.07), higher social well-being at baseline (OR=1.20, 95% CI:1.04, 1.39), and IP treatment (OR=1.81, 95% CI:0.86, 3.82). Neurotoxicity and abdominal discomfort did not predict short versus long term survival.

Conclusions

Quality of life is an independent and significant predictor for long term survival. This may be a useful stratification factor in clinical trials, and in counseling patients as they examine treatment options.