AWARD NUMBER: W81XWH-13-1-0413

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

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REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE:	2. REPORT TYPE	3. DATES COVERED
October 2015	Annual	30 Sep 2014 - 29 Sep 2015

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-13-1-0413

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U Unclassified	b. ABSTRACT U Unclassified	c. THIS PAGE U Unclassified	UU Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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 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.

Overall Aim: To characterize the genomic, biologic, and biobehavioral basis for LT survivors of EOC. We hypothesize that LT survivors of OC have distinct features that distinguish them from short-term (ST) survivors.

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

Research Accomplishments

Planned tasks: While the first year of this award required the establishment of all regulatory procedures and resources for an active scientific consortium, during this second year of the award we have actually performed the scientific projects required to obtain pilot preliminary data for a Phase 2 award. The year has finished with the submission of a grant application for a Phase 2 award and an oral presentation of our application.

Specifically our tasks for Year 2 included:

- Task 4 Testing of FFPE material for genomic/biologic abnormalities (months 13-24)
- Task 5 (finished in year 2) Develop a database for quality of life and survivorship from GOG Phase III trials, identifying the long-term survivor population (Months 5-12)
- Task 6. Conduct a pilot survey on 10 long-term advanced ovarian cancer survivors (Months 13-16)
- Task 7. Initiate descriptive quality of life analyses (Months 17 – 21)
- Submit Grant Application for Phase to award: MGH internal deadline 09/30/2016
- Oral Presentation of the grant proposal: 12/07/2015

Tasks 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.

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)

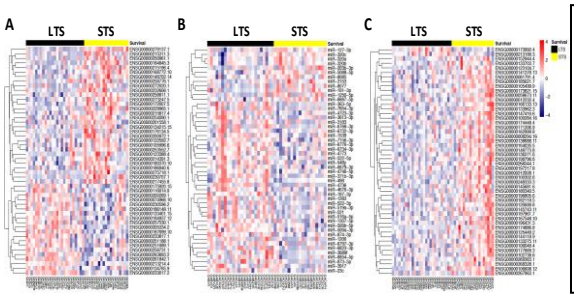


Figure 1. Heatmaps for the three high-throughput platforms, RNAseq (A), microRNA-seq (B) and Methyl-seq (C). Supervised clustering was applied using the top 50 features that are mostly differentially presented in each platform.

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 based on 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 (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).

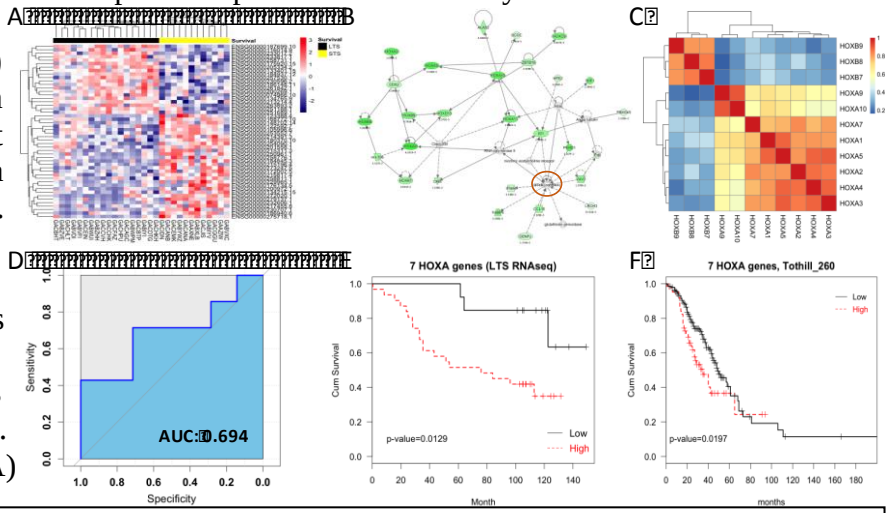
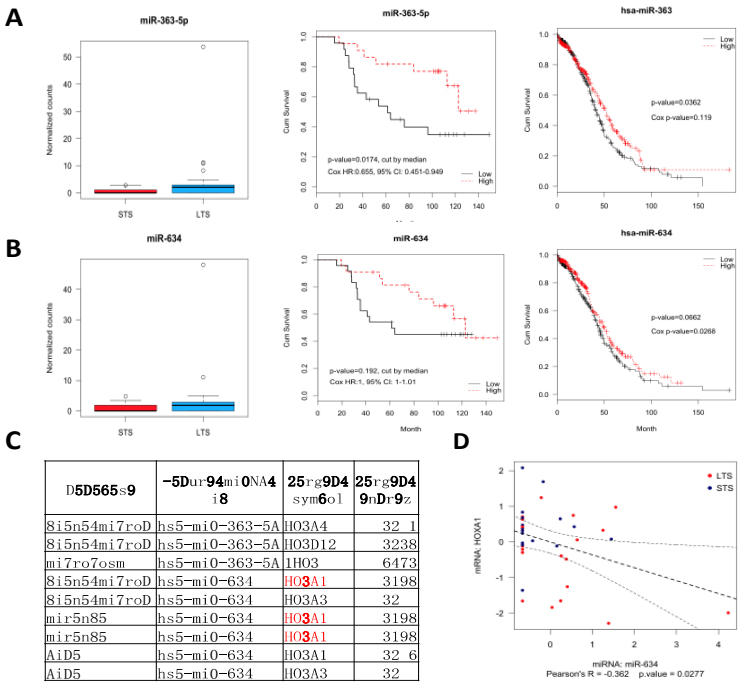


Figure 2. Analyses of the RNAseq data. We used STAR algorithm alignment with default parameters using human genome version GRCh38 with Gencode annotation (version 23). Mapped RNAseq data was normalized by *edgeR* R/bioconductor package, *voom* transformed before subjected to *limma* package for differential 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).

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	H03A4	32_1
8i5n54mi7roD	hs5-mi0-363-5A	H03D12	3238
mi7ro7osm	hs5-mi0-363-5A	1H03	6473
8i5n54mi7roD	hs5-mi0-634	H03A1	3198
8i5n54mi7roD	hs5-mi0-634	H03A3	32
mir5n85	hs5-mi0-634	H03A1	3198
mir5n85	hs5-mi0-634	H03A1	3198
AiD5	hs5-mi0-634	H03A1	32_6
AiD5	hs5-mi0-634	H03A3	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

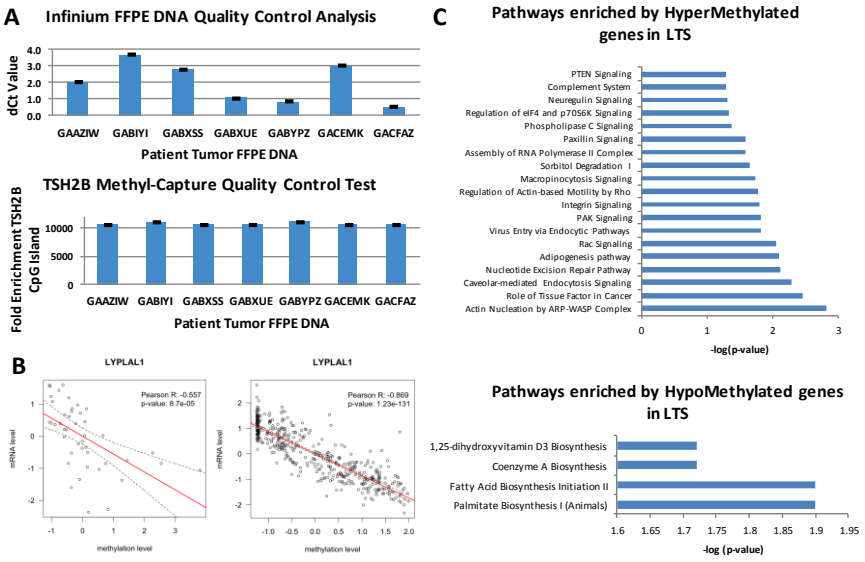


Figure 4. Analysis of Methyl-seq data. (A) The methy-seq platform is compatible to FFPE DNA. The DNA quality was assayed by qPCR based Infinium FFPE DNA QC assay. A higher dCt value implicates more severe compromise in DNA quality which is common in FFPE DNA samples. Nevertheless, the performance of 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.

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.

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.

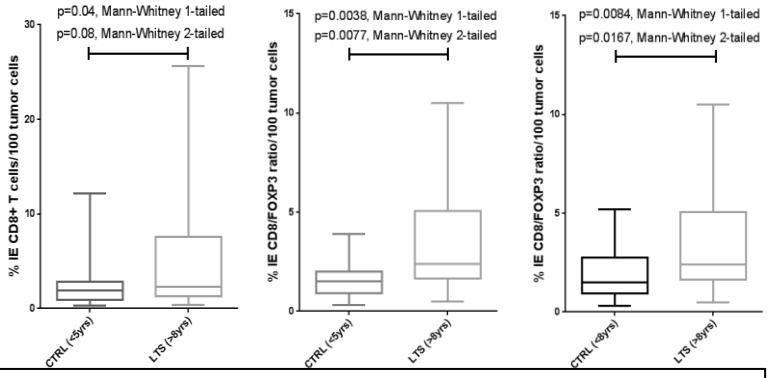


Figure 5: Intratumoral TILs density. The percentage of intraepithelial (IE) CD8+ and FOXP3+ lymphocytes per 100 tumor cells was evaluated in areas with the highest densities of immunopositive cells, by counting more than 1000 tumor cells in 20x high power fields. CD8+ IE T cell counts correlated with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

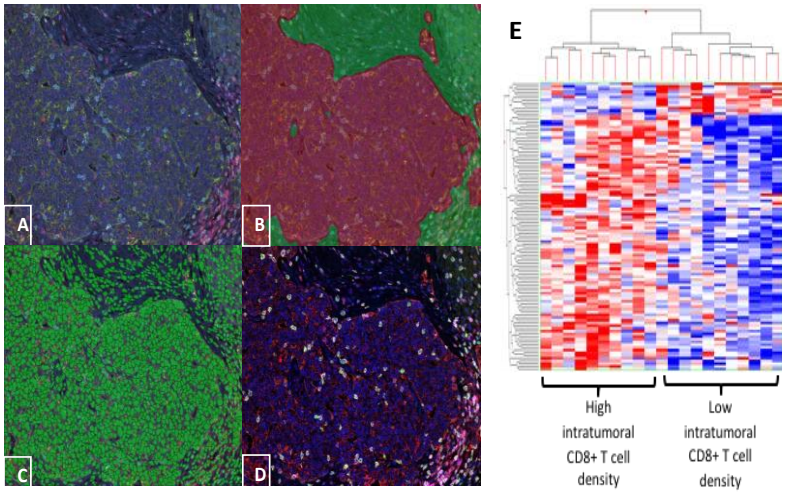


Figure 6: Investigate the immuno-signature in LTS. (A)-(D) Multiplexed Immunofluorescence Lymphocyte Assay in Ovarian Cancer. Representative Tyramide Signal Amplification (TSA) multiplexed immunofluorescence, using anti-CD3, CD4, CD8, CD45RO, Cytokeratin antibodies and DAPI (counterstain) in Ovarian 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.

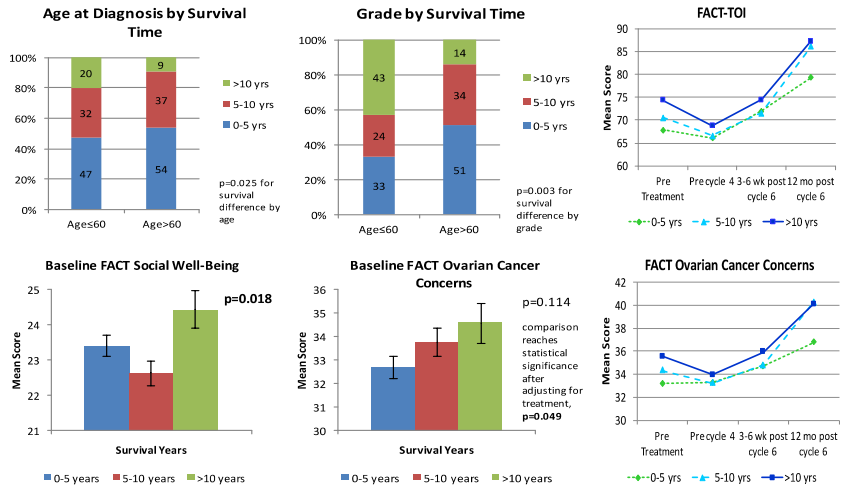
Tasks 5: Quality of analysis from merged GOG databases prepared in Year 1

During Year 1 we accessed two large advanced stage clinical trials (GOG 172; GOG 218) in order to link QOL, treatment and adverse event data to predict long term survivors. In GOG 218, we have begun to identify >10 year survivors and link these data with clinical and biomarker data potentially predictive of survival. In year 2 we examined these data for GOG 172, a clinical trial testing differences between intraperitoneal and intravenous chemotherapy. In addition, a descriptive profile of LT and ST survivors was generated. This included baseline, active treatment, and follow-up data from reliable and valid measures including overall QOL, neurotoxicity and abdominal discomfort, and measures of toxicity and response to treatment. These descriptive data will permit us to be poised in the next grant cycle to further define and characterize LT survivors.

Preliminary investigation of factors associated with long term survival in ovarian cancer patients was undertaken using data from GOG 172. 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) and survival time for 355 patients. 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), 5-10 years (n=121) and >10 years (n=57). Comparisons are made between the 3 groups and in addition long-term survivors (>10 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.

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.

Tasks 6: Pilot quality of life survey on long-term survivors enrolled in the study from the general population

Because our advocate advisory board is composed of 11 ovarian cancer survivors, four of which are long-term survivors, we organized focused workshops with advocates advisory board (AAB) members to directly discuss the relevance of the survey to ovarian cancer survivors. We thought that a focused group discussion would

provide more insight on the validity of the survey rather than simply piloting a survey on 10 survivors. Through these workshops we have revisited the survey to be used in Phase II of this project on the general population of survivors.

Other Achievements: Members of the Consortium AAB continued to be active advocates maintaining high visibility of the study and educating ovarian cancer patients on the scope, advancement and barriers of this project, as well as of cancer research in general. The work accomplished by the AAB for this study, and the clinical impact of this work, was described in a manuscript submitted to *"The Oncologist"*.

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The consortium has also established a partnership with the Nancy Yeary Tumor Registry to further enroll long-term survivors from the general population into our study as well as collaboration with the INOVA proteomics center for expanded development of this study in Phase 2.

Finally, during this project period the Consortium has submitted a grant application for a Phase 2 award, has met in Boston for a whole-consortium in person meeting and prepared an oral presentation of the research plan for Phase 2 of this study.

Plans for the next reporting period: We will be working on all the administrative formalities to finalize the contract with DOD for Phase 2 funding.

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 (Table 2). Through their activity the study was divulgated to the general population which is kept informed of our continuous development and results through a news-letter system.

Table 2

Advocate Advisory Board Members	
Name	**Partner Organization**
Mary Jackson Scroggins, Chair	In My Sister's Care
Vicki Allen	National Ovarian Cancer Coalition (NOCC)
Anne Marie DeCarlo	Ovarian Cancer National Alliance (OCNA)
Martha ("Meg") Gaines	Center for Patient Partnerships (CPP)
Venus Ginés	Día de la Mujer Latina (DML)
Henrietta Ho-Asjoe	Charles B. Wang Community Health Center
Deborah Miller	GOG Patient Advocate Committee (PAC)
Marybeth Harakas	Facing Our Risk of Cancer Empowered (FORCE)
Chrystine Tedeschi	SHARE
Marsha Wilson	Foundation for Women's Cancer (FWC)
Angela Brantley	Intercultural Cancer Council (ICC)

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.