Ed's List May 2021

In the Know (Ed's List) is prepared by Edward Pavlik, PhD, Professor and Director of Ovarian Screening Research Program, University of Kentucky on a monthly basis. Ed's lists provide a compilation of abstracts related to the field of gynecologic oncology from multiple scholarly journals.

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Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2). EM Swisher, TT Kwan, AV Tinker, I Ray-Coquard, A Oaknin, Robert L. Coleman, Carol Aghajanian, Gottfried E. Konecny, David M. O'Malley, Alexandra Leary, Diane Provencher, S Welch, L-m Chen, AEW Hendrickson, L Ma, P Ghatage, RS Kristeleit, O Dorigo, A Musafer, SH Kaufmann, JA Elvin, DI Lin, SK Chambers, En Dominy, -T Vo, S Goble, L Maloney, H Giordano, T Harding, A Dobrovic, CL Scott, KK Lin, IA McNeish. Nat Commun 12, 2487 (2021). https://doi.org/10.1038/s41467-021-22582-6 https://www.nature.com/articles/s41467-021-22582-6#citeas

ARIEL2 (NCT01891344) is a single-arm, open-label phase 2 study of the PARP inhibitor (PARPi) rucaparib in relapsed high-grade ovarian carcinoma. In this post hoc exploratory biomarker analysis of pre- and post-platinum ARIEL2 samples, RAD51C and RAD51D mutations and high-level BRCA1 promoter methylation predict response to rucaparib, similar to BRCA1/BRCA2 mutations. BRCA1 methylation loss may be a major cross-resistance mechanism to platinum and PARPi. Genomic scars associated with homologous recombination deficiency are irreversible, persisting even as platinum resistance develops, and therefore are predictive of rucaparib response only in platinum-sensitive disease. The RAS, AKT, and cell cycle pathways may be additional modulators of PARPi sensitivity.

Genetic alterations and their therapeutic implications in epithelial ovarian cancer. N Lapke, C-H Chen, T-C Chang, A Chao, Y-J Lu, C-H Lai, KT Tan, H-C Chen, H-Y Lu & S-J Chen. BMC Cancer 21, 499 (2021). https://doi.org/10.1186/s12885-021-08233-5 https://bmccancer.biomedcentral.com/articles/10.1186/s12885-021-08233-5#citeas

Background Genetic alterations for epithelial ovarian cancer are insufficiently characterized. Previous studies are limited regarding included histologies, gene numbers, copy number variant (CNV) detection, and interpretation of pathway alteration patterns of individual patients.

Methods We sequenced 410 genes to analyze mutations and CNV of 82 ovarian carcinomas, including high-grade serous (n = 37), endometrioid (n = 22) and clear cell (n = 23) histologies. Eligibility for targeted therapy was determined for each patient by a pathway-based approach. The analysis covered DNA repair, receptor tyrosine kinase, PI3K/AKT/MTOR, RAS/MAPK, cell cycle, and hedgehog pathways, and included 14 drug targets.

Results Postulated PARP, MTOR, and CDK4/6 inhibition sensitivity were most common. BRCA1/2 alterations, PTEN loss, and gain of PIK3CA and CCND1 were characteristic for high-grade serous carcinomas. Mutations of ARID1A, PIK3CA, and KRAS, and ERBB2 gain were enriched in the other histologies. PTEN mutations and high tumor mutational burden were characteristic for endometrioid carcinomas. Drug target downstream alterations impaired actionability in all histologies, and many alterations would not have been discovered by key gene mutational analysis. Individual patients often had more than one actionable drug target.

Conclusions Genetic alterations in ovarian carcinomas are complex and differ among histologies. Our results aid the personalization of therapy and biomarker analysis for clinical studies, and indicate a high potential for combinations of targeted therapies.

Comparison of dose-dense vs. 3-weekly paclitaxel and carboplatin in the first-line treatment of ovarian cancer in a propensity score-matched cohort. R Pirolli, VT Loiola de Alencar, FL Estati, Adriana Regina Gonçalves Ribeiro, Daniella Yumi Tsuji Honda, Mariana de Oliveira, Joao Paulo da SN Lima, E Santana dos Santos, APG Guimarães, G Baiocchi & AAB Anastácio da Costa. BMC Cancer 21, 525 (2021). https://doi.org/10.1186/s12885-021-08270-0 https://bmccancer.biomedcentral.com/articles/10.1186/s12885-021-08270-0#citeas

Background Benefit of carboplatin and dose-dense weekly paclitaxel (ddCT) in first line treatment of ovarian cancer patients has been different in Western and Asian studies. In the present study we compare progression-free survival (PFS) of ddCT to three-weekly carboplatin and paclitaxel (CT) in first-line treatment of ovarian carcinoma in a single institution in a Western population.

Materials and methods We conducted a retrospective review of medical records from patients with ovarian carcinoma treated in a tertiary cancer center from 2007 to 2018. All patients treated with ddCT or CT in the first-line setting were included. Patients who received first-line bevacizumab were not included. PFS and overall survival (OS) were compared in a propensity score-matched cohort to address selection bias. Patients were matched according to age, ECOG performance status, CA 125, FIGO stage, residual disease, and histological subtype, in a 1:2 ratio.

Results Five hundred eighty-eight patients were eligible for propensity score matching, the final cohort consisted of 69 patients treated with ddCT and 138 CT group. Baseline characteristics were well-balanced. After a median follow-up of 65.1 months, median PFS was 29.3 vs 20.0 months, favouring ddCT treatment ($p = 0.035$). In the multivariate cox regression ddCT showed a 18% lower risk of progression (HR 0.82, 95% CI 0.68–0.99, $p = 0.04$). Overall survival data is immature, but suggested better outcomes for ddCT (not reached versus 78.8 months; $p = 0.07$).

Conclusion Our retrospective study has shown superior PFS of ddCT over CT regimen in first-line treatment of ovarian carcinoma in a Western population not treated with bevacizumab.

Maximizing cancer prevention through genetic navigation for Lynch syndrome detection in women with newly diagnosed endometrial and nonserous/nonmucinous epithelial ovarian cancer. SR Kim, A Tone, RH Kim, M Cesari, BA Clarke, L Eiriksson, TL Hart, M Aronson, S Holter, A Lytwyn, M Maganti, L Oldfield, S Gallinger, MQ Bernardini, AM Oza, B Djordjevic, J Lerner-Ellis, E Van de Laar, D Vicus, TJ Pugh, A Pollett, SE Ferguson. Cancer Early view. https://doi.org/10.1002/cncr.33625 https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.33625?campaign=wolearlyview

BACKGROUND Despite recommendations for reflex immunohistochemistry (IHC) for mismatch repair (MMR) proteins to identify Lynch syndrome (LS), the uptake of genetic assessment by those who meet referral criteria is low. The authors implemented a comprehensive genetic navigation program to increase the uptake of genetic testing for LS in patients with endometrial cancer (EC) or nonserous/nonmucinous ovarian cancer (OC).

METHODS Participants with newly diagnosed EC or OC were prospectively recruited from 3 cancer centers in Ontario, Canada. Family history questionnaires were used to assess LS-specific family history. Reflex IHC for MMR proteins was performed with the inclusion of clinical directives in pathology reports. A trained genetic navigator initiated a genetic referral on behalf of the treating physician and facilitated genetic referrals to the closest genetics center.

RESULTS A total of 841 participants (642 with EC, 172 with OC, and 27 with synchronous EC/OC) consented to the study; 194 (23%) were MMR-deficient by IHC. Overall, 170 women (20%) were eligible for a genetic assessment for LS: 35 on the basis of their family history alone, 24 on the basis of their family history and IHC, 82 on the basis of IHC alone, and 29 on the basis of clinical discretion. After adjustments for participants who died (n = 6), 149 of 164 patients (91%) completed a genetic assessment, and 111 were offered and completed genetic testing. Thirty-four women (4.0% of the total cohort and 30.6% of those with genetic testing) were diagnosed with LS: 5 with mutL homolog 1 (*MLH1*), 9 with mutS homolog 2 (*MSH2*), 15 with mutS homolog 6 (*MSH6*), and 5 with *PMS2*.

CONCLUSIONS The introduction of a navigated genetic program resulted in a high rate of genetic assessment (>90%) in patients with gynecologic cancer at risk for LS.

Secondary Cytoreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study. O Zivanovic, DS Chi, Q Zhou, A Iasonos, JA Konner, V Makker, RN Grisham, AK Brown, S Nerenstone, JP Diaz, ED Schroeder, CL Langstraat, V Paroder, Y Lakhman, K Soldan, K Su, GJ Gardner, V Andikyan, J Guo, EL Jewell, KL Roche, T Troso-Sandoval, SM Lichtman, LA Moukarzel, K Dessources, NR Abu-Rustum, C Aghajanian, WP Tew, J Beumer, Y Sonoda & RE O'Cearbhaill. Journal of Clinical Oncology DOI: 10.1200/JCO.21.00605 https://ascopubs.org/doi/abs/10.1200/JCO.21.00605

PURPOSE The purpose of this phase II study was to evaluate hyperthermic intraperitoneal chemotherapy (HIPEC) with carboplatin for recurrent ovarian cancer during secondary cytoreductive surgery.

MATERIALS AND METHODS Patients were intraoperatively randomly assigned to carboplatin HIPEC (800 mg/m2 for 90 minutes) or no HIPEC, followed by five or six cycles of postoperative IV carboplatin-based chemotherapy, respectively. Based on a binomial single-stage pick-the-winner design, an arm was considered winner if ≥ 17 of 49 patients were without disease progression at 24 months post-surgery. Secondary objectives included postoperative toxicity and HIPEC pharmacokinetics.

RESULTS Of 98 patients, 49 (50%) received HIPEC. Complete gross resection was achieved in 82% of the HIPEC patients and 94% of the standard-arm patients. Bowel resection was performed in 37% of patients in the HIPEC arm compared with 65% in the standard (P = .008). There was no perioperative mortality and no difference in use of ostomies, length of stay, or postoperative toxicity. At 24 months, eight patients (16.3%; 1-sided 90% CI, 9.7 to 100) were without progression or death in the HIPEC arm and 12 (24.5%; 1-sided 90% CI, 16.5 to 100) in the standard arm. With a medium follow-up of 39.5 months, 82 patients progressed and 37 died. The median progression-free survival in the HIPEC and standard arms were 12.3 and 15.7 months, respectively (hazard ratio, 1.54; 95% CI, 1 to 2.37; P = .05). There was no significant difference in median overall survival (52.5 v 59.7 months, respectively; hazard ratio, 1.39; 95% CI, 0.73 to 2.67; P = .31). These analyses were exploratory.

CONCLUSION HIPEC with carboplatin was well tolerated but did not result in superior clinical outcomes. This study does not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer.

Clinicopathologic and Genomic Analysis of TP53-Mutated Endometrial Carcinomas

A Momeni-Boroujeni, W Dahoud, CM Vanderbilt, S Chiang, R Murali, EV Rios-Doria, KM Alektiar, C Aghajanian, NR Abu-Rustum, M Ladanyi, LH Ellenson, B Weigelt & RA Soslow. Clinical Cancer Research 27, (9) Volume 27, (9) 2613-2623 https://doi.org/10.1158/1078-0432.CCR-20-4436

Purpose: Copy number–high endometrial carcinomas were described by The Cancer Genome Atlas as high-grade endometrioid and serous cancers showing frequent copy-number alterations (CNA), low mutational burden (i.e., non-hypermutant), near-universal TP53 mutation, and unfavorable clinical outcomes. We sought to investigate and compare the clinicopathologic and molecular characteristics of non-hypermutant TP53-altered endometrial carcinomas of four histologic types.

Experimental Design: TP53-mutated endometrial carcinomas, defined as TP53-mutant tumors lacking microsatellite instability or pathogenic POLE mutations, were identified (n = 238) in a cohort of 1,239 endometrial carcinomas subjected to clinical massively parallel sequencing of 410–468 cancer-related genes. Somatic mutations and CNAs (n = 238), and clinicopathologic features were determined (n = 185, initial treatment planning at our institution).

Results: TP53-mutated endometrial carcinomas encompassed uterine serous (n = 102, 55.1%), high-grade endometrial carcinoma with ambiguous features/not otherwise specified (EC-NOS; n = 44, 23.8%), endometrioid carcinomas of all tumor grades (n = 28, 15.1%), and clear cell carcinomas (n = 11, 5.9%). PTEN mutations were significantly more frequent in endometrioid carcinomas, SPOP mutations in clear cell carcinomas, and CCNE1 amplification in serous carcinomas/EC-NOS; however, none of these genomic alterations were exclusive to any given histologic type. ERBB2 amplification was present at similar frequencies across TP53-mutated histologic types (7.7%–18.6%). Although overall survival was similar across histologic types, serous carcinomas presented more frequently at stage IV, had more persistent and/or recurrent disease, and reduced disease-free survival.

Conclusions: TP53-mutated endometrial carcinomas display clinical and molecular similarities across histologic subtypes. Our data provide evidence to suggest performance of ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) assessment in all TP53-mutated endometrial carcinomas. Given the distinct clinical features of serous carcinomas, histologic classification continues to be relevant.

Translational Relevance

Endometrial cancers of copy number–high molecular subtype, described initially by The Cancer Genome Atlas to encompass primarily serous and high-grade endometrioid endometrial carcinomas, harbor recurrent TP53 mutations, lack POLE mutations, are microsatellite stable (i.e., non-hypermutant), and have poor clinical outcomes. An analysis of >1,200 endometrial carcinomas subjected to targeted sequencing using an FDA-authorized assay revealed that non-hypermutant TP53-altered endometrial carcinomas irrespective of histologic type have considerable clinical and genomic similarities. We show that the overall landscape of targetable genetic alterations affecting cancer-related

genes, including ERBB2, is similar between TP53-mutant endometrial carcinomas across histologic types, supporting the notion that ERBB2 assessment should be performed on all non-hypermutant TP53-altered endometrial carcinomas. As serous carcinomas showed distinct features, however, including advanced stage at diagnosis and more frequently persistent and/or recurrent disease, our findings further demonstrate that despite their similar molecular profiles, histologic subtyping of TP53-mutant endometrial carcinomas remains important.

Genome-wide Copy-number Alterations in Circulating Tumor DNA as a Novel Biomarker for Patients with High-grade Serous Ovarian Cancer. L Paracchini, Beltrame, T Grassi, A Inglesi, R Fruscio, F Landoni, D Ippolito, MD Marchette, M Paderno, M Adorni, M Jaconi, C Romualdi, M D'Incalci, G Siravegna, S Marchini. Clinical Cancer Research 27, (9) 2549-2559 https://doi.org/10.1158/1078-0432.CCR-20-3345 https://clincancerres-aacrjournals-org.ezproxy.uky.edu/content/27/9/2549

Purpose: High-grade serous epithelial ovarian cancer (HGS-EOC) is defined by high levels of somatic copy-number alterations (SCNA) with marked spatial and temporal tumor heterogeneity. Biomarkers serving to monitor drug response and detect disease recurrence are lacking, a fact which reflects an unmet clinical need.

Experimental Design: A total of 185 plasma samples and 109 matched tumor biopsies were collected from 46 patients with HGS-EOC, and analyzed by shallow whole-genome sequencing (sWGS). The percentage of tumor fraction (TF) in the plasma was used to study the biological features of the disease at the time of diagnosis (T0) and correlated with patients' survival. Longitudinal analysis of TF was correlated with CA-125 levels and radiological images to monitor disease recurrence.

Results: Gain in the clonal regions, *3q26.2* and *8q24.3*, was observed in the 87.8% and 78.05% of plasma samples, suggesting that plasma sWGS mirrors solid biopsies. At T0, multivariate analysis revealed that plasma TF levels were an independent prognostic marker of relapse ($P < 0.022$). After platinum (Pt)-based treatment, circulating tumor DNA (ctDNA) analysis showed a change in the heterogeneous pattern of genomic amplification, including an increased frequency of amplification, compared with before Pt-based treatment in the *19p31.11* and *19q13.42* regions. TF in serially collected ctDNA samples outperformed CA-125 in anticipating clinical and radiological progression by 240 days (range, 37–491).

Conclusions: Our results support the notion that sWGS is an inexpensive and useful tool for the genomic analysis of ctDNA in patients with HGS-EOC to monitor disease evolution and to anticipate relapse better than serum CA-125, the routinely used clinical biomarker.

Translational Relevance The genome of high grade serous epithelial ovarian cancer (HGS-EOC) is characterized by somatic copy-number alterations that is the prerequisite for the use of untargeted assessment of DNA tumor fraction (TF) in the patients' plasma. In this retrospective, proof-of-principle study, we demonstrated that shallow whole-genome sequencing (sWGS) is an innovative approach to recapitulate the main genomic features of tumor heterogeneity in the plasma of patients with HGS-EOC and thus, can be developed for future clinical decision making. At baseline, the plasma TF percentage was found to be an independent prognostic marker of progression-free survival. Longitudinal monitoring of plasma TF anticipated time of relapse better than the conventional serum biomarker, CA-125, and radiological assessment. Finally, plasma analysis by sWGS allowed to track those genomic evolutionary changes that occurred under treatment and reflect response to therapy and disease progression.

Amplifying the Voice of the Whispering Cancer. NC Dhani. Clinical Cancer Research 27, (9) 2372-2374 DOI: 10.1158/1078-0432.CCR-20-4948 https://clincancerres-aacrjournals-org.ezproxy.uky.edu/content/27/9/2372

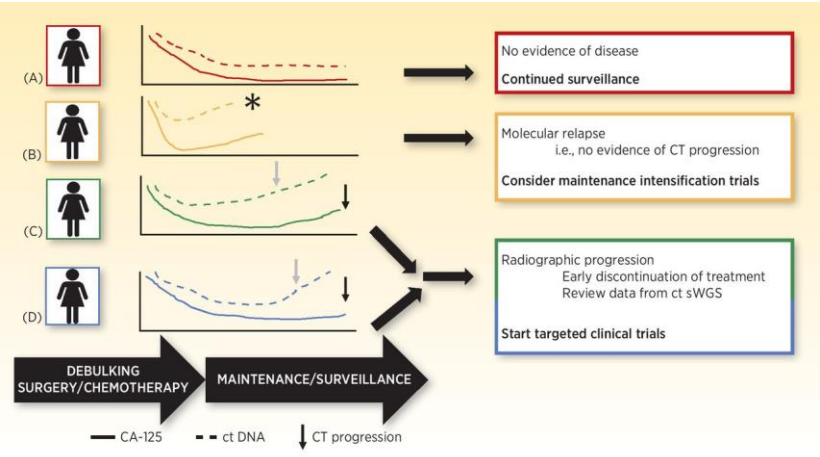
Nontargeted circulating tumor DNA (ctDNA) whole-genome sequencing is a novel strategy for genomic characterization of high-grade serous ovarian cancer. Changes in ctDNA levels are a sensitive indicator of disease burden with an average lead time of 6 months to clinical progression. This presents a unique opportunity to identify pathways driving progression as molecular vulnerabilities for clinical drug development. In this issue of Clinical Cancer Research, Paracchini and colleagues (1) explore shallow whole-genome sequencing (sWGS) of circulating tumor DNA (ctDNA) in patients with high-grade serous ovarian cancer (HGSO). Across cancer types, tumor genomic analyses have already provided critical insights into molecular pathways driving cancer progression, identifying high-priority avenues for drug development. The most striking example of this in the management of HGSO, has been defining the role of PARP inhibitors in patients with tumors harboring defects in homologous recombination (HR). The success of PARP inhibitors has been a dramatic advance for women with pathogenic BRCA mutations, but there remains an acute need to identify tailored strategies for women with HR-proficient tumors. There is optimism that translational initiatives involving longitudinal tumor genomics and characterization of clonal tumor evolution, will contribute to these efforts.

Contemporary next-generation sequencing strategies, with their broader coverage and lower costs, have improved our ability to apply genomic analyses to patients in the clinic. However, repeat tumor biopsies can be challenging and may inadequately represent the heterogeneity of a particular tumor genome. Circulating tumor DNA (ctDNA) assays are a promising option to circumvent some of these limitations (2). Paracchini and colleagues (1) describe sWGS in plasma samples acquired in an aptly named, "convenience cohort" of 46 patients with HGSO. This was a representative, albeit high-risk, population of primarily stage IIIC/IV patients, with 22% harboring a pathogenic germline BRCA1/2 variant. Roughly half underwent upfront surgery followed by adjuvant chemotherapy, while the remainder received neoadjuvant chemotherapy and interval surgery. Over half (24 patients, 52%) had platinum-sensitive disease, 10 (22%) were platinum-refractory/resistant with the remainder defined as partially platinum sensitive, providing a cohort of patients covering the spectrum of relevant HGSO biology. Because plasma and tumor biospecimens were collected at nonuniform timepoints, the authors cleverly cohorted samples into three groups to address a few important questions.

Before considering Paracchini's data, it is important to note that the majority of completed HGSO ctDNA studies to date have involved targeted strategies, primarily focusing on mutational analysis, most often centered on TP53 variants. These studies have demonstrated a prognostic relevance of ctDNA levels, and an improved sensitivity for early detection of disease progression over standard metrics like CA125 or cross-sectional imaging. Unfortunately, the wide range of TP53 mutations across HGSO necessitates this being a personalized assay, individualized for each patient and based on their unique tumor genomics (3). In contrast, Paracchini and colleagues applied an innovative, strategy of sWGS to report on somatic copy-number alterations (CNA). This is a sensible approach because HGSO is defined by chromosomal instability and a high frequency of CNA. Importantly, it is nontargeted, independent of tumor analysis, and can therefore be applied broadly without baseline tumor analysis and assay individualization.

In an initial validation, 57% CNAs were detected in both plasma and tumor, a concordance level comparable with what has been reported with other analyses (4). Furthermore, an informative analysis of the 35 most highly recurrent regions of genomic gains/losses, demonstrated that 33 were hallmark features of HGSO, with the majority (22/33) detectable in both plasma and tumor, confirming that sWGS of ctDNA can provide a good general overview of the tumor genome of HGSO. Tumor fraction (TF) appeared to be prognostic, again aligning with previous reports, and lending confidence that ctDNA sWGS provides a clinically relevant assessment of tumor burden.

The most interesting findings from this work revolve around the temporal dynamics of ctDNA in patients on treatment, and in posttreatment surveillance. It is disconcerting, although not entirely surprising, to recognize that most patients had persistently detectable ctDNA after completing first-line treatment. This was in spite of CA125 normalization, signifying the presence of occult disease, below the detection threshold of standard assays. Among the patient anecdotes presented, the case of patient 21650 (Fig. 5 of Paracchini and colleagues; ref. 1) is particularly instructive, as the dramatic decline and normalization of CA125 in the early phase of treatment, was accompanied by a persistent rise of ctDNA throughout adjuvant chemotherapy. Low CA125 levels likely reflected the success of surgical debulking, with the increasing ctDNA levels indicating the emergence of platinum-refractory disease. In the whole patient cohort, rising ctDNA levels preceded clinical/radiographic progression in the majority of patients by approximately 6 months. These findings highlight the fact that CA125 monitoring alone may provide incomplete information around a patient's cancer burden, and like TP53 monitoring, genomic ctDNA analysis could function as a more sensitive indicator of disease burden in HGSO (3, 5).



Schematic illustrating use of sWGS ctDNA to guide management of women completing first-line treatment for HGSO. Graphs depict levels of CA-125 (solid) and ctDNA (dashed) over time. Black arrows indicate radiographic progression (on cross-sectional imaging i.e., CT) in patients C and D. Patient A has plateaus of both CA-125 and ctDNA levels with normal CTs and can continue on surveillance on the standard maintenance therapy. Patient B has a rising ctDNA level with a less significant increase in CA-125, but without progression on CT. sWGS of ctDNA on treatment suggests potential target for maintenance intensification trials with addition of novel agent to patients already on bevacizumab or PARP inhibitor maintenance. Patients C and D are suspected to have early disease progression based on rising ctDNA (gray arrow). ctDNA analysis is started, and information available by the time of radiographic disease (black arrow) is used to direct patients to appropriate clinical trial.

Identifying disease progression prior to detectable radiographic progression, allows for the earlier discontinuation of ineffective therapies, sparing patients and health care systems from cumulative physical and financial toxicity. It also allows a window within which,

screening for "next-line" clinical trials can be considered. However, unless the earlier detection of progression can be paired with a rationale prioritization of next line of therapy based on evolving treatment-resistant clones, it is unlikely to impact on patient survival, and more likely to confound outcome metrics by lead-time bias. Unfortunately, detection of TP53 ctDNA, although a sensitive indicator of disease burden, is unable to provide biologically relevant information of the dominant pathways driving progression to be considered for therapeutic targeting. This is where the work by Paracchini and colleagues (1) provides some intriguing insights worthy of further exploration.

Posttreatment plasma samples demonstrated lower levels of genomic complexity (copy number instability or CNI), with only 12 of the 35 highly recurrent CNA detected in baseline samples also identified in patient's plasma after treatment. Among these, two specific cytobands were highlighted because of their high frequency of detection: 11q13.3 and 19p13.11. One can hypothesize that a more comprehensive analysis of these regions might identify specific pathways which may be targeted as unique molecular vulnerabilities. For example, the 11q13.3 cytoband is already recognized as encoding genes for several proteins relevant in tumor growth and progression including cell-cycle mediators, folate receptors and angiogenic factors, with drugs targeting several of these already being in the evaluation phase for patients with HGSO (6). The approximately 6-month lead time between ctDNA detection of disease progression and the development of clinically evident disease, provides a unique window to complete genomic analyses and obtain ancillary data in real-time to help guide treatment decisions. One could envision a future where patients might then be stratified into one of several potential, matched treatment options based on their ctDNA make-up as illustrated in Fig 1. Although 11q13.3 has already been reasonably characterized in cancer, the emergence of the 19p13.11 cytoband in treatment-resistant disease represents a novel finding in HGSO, underscoring a mechanism whereby sWGS of ctDNA might provide discovery opportunities for novel therapeutic approaches.

Multiple lines of chemotherapy for patients with high-grade ovarian cancer: Predictors for response and effect on survival. R Kessous, MD Wissing, I Laskov, J Abitbol, J Bitharas, VR Agnihotram, A Yasmeen, S Salvador, S Lau, WH Gotlieb. Int. J. Cancer. 2021; 148: 2304– 2312. https://doi.org/10.1002/ijc.33395 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33395

Guidelines for the treatment of tubo-ovarian cancer patients beyond third line are lacking. We aimed to evaluate the effect of response in each line on patient's outcome as well as identify variables that predict response for additional line of chemotherapy. A cohort study was performed including all patients with advanced high-grade ovarian cancer. Survival analysis was performed using Kaplan-Meier curves and log-rank tests. Odds ratios and hazard ratios were calculated using multilevel, mixed-effects logistic regression and Cox regression, adjusting for repeated measures within individual patients. Two-hundred thirty-eight patients were included and underwent up to 10 lines of chemotherapy. The median progression-free survival was 15.6 and overall survival (OS) was 55.6 months. Response rates dropped with each additional line and by line 5, most patients (61%) became refractory and only 16% had any type of response (complete 4% or partial 12%). By line 2, whether a patient had partial disease (PR), stable disease (SD) or progressive disease (PD) did not have an effect on the OS. From line 2, whether a patient had PR, SD or PD did not have an effect on chemotherapy-free interval. Number of previous lines and time from previous line were the only variables that significantly correlated with both outcome of patients and response to the next line. In conclusion, time interval from the previous line of chemotherapy is the major clinical factor that predicts beneficial effect of another line of treatment in patients with ovarian cancer.

What's new?

For patients with recurrent ovarian cancer, the value of additional cytotoxic therapy beyond third-line chemotherapy versus halting therapy and switching to supportive care remains largely unexplored. In this study, the authors assessed the value of different clinical variables in predicting response to future lines of chemotherapy among 238 ovarian cancer patients. Number of previous lines of therapy and time interval from previous line of chemotherapy were the only clinical variables correlated with patient outcome and response to subsequent therapy. Time between previous and current lines of therapy was a predictor of beneficial effect of an additional line of treatment.

Adjunctive testing by cytology, p16/Ki-67 dual-stained cytology or HPV16/18 E6 oncoprotein for the management of HPV16/18 screen-positive women. L Torres-Ibarra, AT Lorincz, CM Wheeler, J Cuzick, RHernández-López, D Spiegelman, L León-Maldonado, B Rivera-Paredez, P Méndez-Hernández, E Lazcano-Ponce, J Salmerón Int. J. Cancer. 2021; 148: 2264– 2273. https://doi.org/10.1002/ijc.33414 https://onlinelibrary.wiley.com/doi/10.1002/ijc.33414

High-risk human papillomavirus type 16/18 (HPV16/18) genotyping is unable to accurately discriminate nonprogressive infections from those that will progress to cervical cancer. Our study aimed to assesses if additional testing either with liquid-based cytology (LBC) or the putative progression markers p16/Ki-67 and HPV16/18 E6 oncoprotein (E6) can improve the efficiency of HPV16/18 genotyping for triaging high-risk HPV (hrHPV)-positive women through better

cancer risk stratification. Women attending colposcopy after positive HPV16/18 genotyping results within the Forwarding Research for Improved Detection and Access for Cervical Cancer Screening and Triage (FRIDA) hrHPV-based screening study in Tlaxcala, Mexico, underwent further testing with LBC, p16/Ki-67 dual-stained (DS) cytology and E6. We calculated measures of test performance for detecting histologically confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+) and grade 3 or higher (CIN3+). A number of 475 (64.3%) of 739 HPV16/18-positive women had complete results for all tests. Triage positivity rates were 14.1%, 18.5% and 24.4%, for LBC, E6 and DS, respectively. Compared with LBC, DS had higher sensitivity (24.4% vs 60.0%) although lower specificity (87.0% vs 79.3%) for CIN3+ ($P < .001$), whereas E6 had a sensitivity of 37.8% and a specificity of 83.5%. No invasive cancer was missed by DS or E6, but 75% were in normal cytology. DS test was associated with nearly 75% reduction of colposcopy referrals compared with the direct referral of all HPV16/18-positive women, giving the least number of colposcopies (n = 4.3) per CIN3+ detected. We show that adjunctive testing of HPV16/18-positive women with DS may greatly reduce unnecessary colposcopy referrals within HPV-based screening employing HPV16/18 genotyping while retaining acceptable sensitivity for CIN2+ and CIN3+.

What's new?

Testing for HPV 16/18 is currently used in many screening programs for cervical cancer. However, standard HPV genotyping cannot determine whether or not the infection is likely to progress to cancer. In this study, the authors found that when dual-stained cytology (DS) for p16/Ki-67 is added to the screening, it may reduce unnecessary colposcopy referrals by as much as 75%. Meanwhile, this combination testing is also sensitive enough that invasive lesions can be caught early. This approach to HPV triage may thus be significantly more efficient, while reducing unnecessary procedures.

Reduced SKP1 and CUL1 expression underlies increases in Cyclin E1 and chromosome instability in cellular precursors of high-grade serous ovarian cancer. CC Lepage, M Palmer, AC Farrell, NM Neudorf, Z Lichtensztejn, MW Nachtigal, KJ McManus. British journal of cancer, 124(10), 1699–1710. https://doi.org/10.1038/s41416-021-01317-w Br J Cancer. 2021;124(10):1699-1710. doi:10.1038/s41416-021-01317-w https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8110794/

Background High-grade serous ovarian cancer (HGSOC) is the most common and lethal ovarian cancer histotype. Chromosome instability (CIN, an increased rate of chromosome gains and losses) is believed to play a fundamental role in the development and evolution of HGSOC. Importantly, overexpression of Cyclin E1 protein induces CIN, and genomic amplification of *CCNE1* contributes to HGSOC pathogenesis in ~20% of patients. Cyclin E1 levels are normally regulated in a cell cycle-dependent manner by the SCF (SKP1–CUL1–FBOX) complex, an E3 ubiquitin ligase that includes the proteins SKP1 and CUL1. Conceptually, diminished *SKP1* or *CUL1* expression is predicted to underlie increases in Cyclin E1 levels and induce CIN.

Methods This study employs fallopian tube secretory epithelial cell models to evaluate the impact diminished *SKP1* or *CUL1* expression has on Cyclin E1 and CIN in both short-term (siRNA) and long-term (CRISPR/Cas9) studies.

Results Single-cell quantitative imaging microscopy approaches revealed changes in CIN-associated phenotypes and chromosome numbers and increased Cyclin E1 in response to diminished *SKP1* or *CUL1* expression.

Conclusions These data identify *SKP1* and *CUL1* as novel CIN genes in HGSOC precursor cells that may drive early aetiological events contributing to HGSOC development.

Surveillance Only for High-risk FIGO Stage IA/IB Malignant Ovarian Germ Cell Tumors. D Nasioudis, MK Frey, E Chapman-Davis, TA Caputo, KM Holcomb. American Journal of Clinical Oncology: 2021 – 44 (5) 195-199 doi: 10.1097/COC.0000000000000805
https://journals.lww.com/amjclinicaloncology/Fulltext/2021/05000/Surveillance_Only_for_High_risk_FIGO_Stage_IA_IB.4.aspx

Objectives: Investigate the use and outcomes of a surveillance only strategy for patients with high-risk stage I malignant ovarian germ cell tumors.

Methods: Patients with International Federation of Gynecology and Obstetrics stage IA/IB grade 2 or 3 immature teratoma, yolk sac, or mixed germ cell tumor diagnosed between 2004 and 2014 who had at least 1 month of follow-up were drawn from the National Cancer Database. Overall survival (OS) was evaluated for each histologic subtype using Kaplan-Meier curves, and compared with the log-rank test.

Results: A total of 497 patients were identified; 115 (23.1%) with grade 2 immature teratoma, 157 (31.6%) with grade 3 immature teratoma, 101 (20.3%) with yolk sac tumor, 124 (25%) with mixed germ cell tumor. Rate of adjuvant chemotherapy was 68.2% (655 patients), while rate of lymph node biopsy/dissection was 55.2%. A total of 19 (3.8%)

deaths were observed at a median of 29.8 months. There was no difference in OS between patients who did and did not receive adjuvant chemotherapy with grade 2 (*P*=0.35) and grade 3 immature teratoma (*P*=0.47) or mixed germ cell tumors (*P*=0.55). Patients with yolk sac tumors those who received chemotherapy had better OS compared with those who did not, *P*=0.019; 5-year OS rates were 92.7% and 79.6%, respectively.

Conclusions: A surveillance only strategy for patients with stage I malignant ovarian germ cell tumors is associated with excellent survival outcomes for patients with grade 2 or 3 immature teratoma or mixed germ cell tumors.

Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. A Poveda, A Floquet, JA Ledermann, R Asher, RT Penson, AM Oza, J Korach, T Huzarski, S Pignata, M Friedlander, A Baldoni, T-W Park-Simon, K Tamura, GS Sonke, A Lisyanskaya, J-H Kim, EA Filho, T Milenkova, ES Lowe, Lancet Oncology 2021 DOI:https://doi.org/10.1016/S1470-2045(21)00073-5 https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00073-5/fulltext

Background Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, has previously been shown to extend progression-free survival versus placebo when given to patients with relapsed high-grade serous or endometrioid ovarian cancer who were platinum sensitive and who had a BRCA1 or BRCA2 (BRCA1/2) mutation, as part of the SOLO2/ENGOT-Ov21 trial. The aim of this final analysis is to investigate the effect of olaparib on overall survival.

Methods This double-blind, randomised, placebo-controlled, phase 3 trial was done across 123 medical centres in 16 countries. Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status at baseline of 0–1, had histologically confirmed, relapsed, high-grade serous or high-grade endometrioid ovarian cancer, including primary peritoneal or fallopian tube cancer, and had received two or more previous platinum regimens. Patients were randomly assigned (2:1) to receive olaparib tablets (300 mg in two 150 mg tablets twice daily) or matching placebo tablets using an interactive web or voice-response system. Stratification was by response to previous chemotherapy and length of platinum-free interval. Treatment assignment was masked to patients, treatment providers, and data assessors. The primary endpoint of progression-free survival has been reported previously. Overall survival was a key secondary endpoint and was analysed in all patients as randomly allocated. Safety was assessed in all patients who received at least one treatment dose. This trial is registered with ClinicalTrials.gov, NCT01874353, and is no longer recruiting patients.

Findings Between Sept 3, 2013 and Nov 21, 2014, 295 patients were enrolled. Patients were randomly assigned to receive either olaparib (n=196 [66%]) or placebo (n=99 [34%]). One patient, randomised in error, did not receive olaparib. Median follow-up was 65·7 months (IQR 63·6–69·3) with olaparib and 64·5 months (63·4–68·7) with placebo. Median overall survival was 51·7 months (95% CI 41·5–59·1) with olaparib and 38·8 months (31·4–48·6) with placebo (hazard ratio 0·74 [95% CI 0·54–1·00]; p=0·054), unadjusted for the 38% of patients in the placebo group who received subsequent PARP inhibitor therapy. The most common grade 3 or worse treatment-emergent adverse event was anaemia (which occurred in 41 [21%] of 195 patients in the olaparib group and two [2%] of 99 patients in the placebo group). Serious treatment-emergent adverse events were reported in 50 (26%) of 195 patients receiving olaparib and eight (8%) of 99 patients receiving placebo. Treatment-emergent adverse events with a fatal outcome occurred in eight (4%) of the 195 patients receiving olaparib, six of which were judged to be treatment-related (attributed to myelodysplastic syndrome [n=3] and acute myeloid leukaemia [n=3]).

Interpretation Olaparib provided a median overall survival benefit of 12·9 months compared with placebo in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. Although statistical significance was not reached, these findings are arguably clinically meaningful and support the use of maintenance olaparib in these patients.

Controversies in Hereditary Cancer Management. M AlHilli, H Pederson., Obstetrics & Gynecology: 2021 - 137 – (5) 941-955 doi: 10.1097/AOG.0000000000004364 https://journals.lww.com/greenjournal/Fulltext/2021/05000/Controversies_in_Hereditary_Cancer_Management.27.aspx

Personalized management of patients at risk ideally should involve a multidisciplinary team of not only genetic counselors and surgeons, but also women's health or menopause specialists, knowledgeable psychologists, and primary care providers or obstetrician–gynecologists aware of the risks and fears "previvors" (survivors of a predisposition to cancer who have not had the disease) face as well as the issues that are common postoperatively. Identification of patients at risk for hereditary cancer, understanding of current genetic testing modalities and potential results, knowledge about screening and prevention including timing of surveillance, preventive medication and risk-reducing surgeries, understanding limitations and comorbidities associated with these risk management strategies and long-term psychological support are all important in hereditary cancer management. We describe issues surrounding

the identification of the high-risk patient, universal testing in breast and ovarian cancer, and testing in special populations. We describe a simplified approach to understanding and communicating genetic testing results and nuances of testing including direct-to-consumer testing. We highlight concerns surrounding breast cancer screening during pregnancy and lactation. A framework for practical management and counseling of women who opt for risk-reducing salpingo-oophorectomy or risk-reducing mastectomy or both is provided. We provide an in-depth discussion of questions that arise in relation to timing of surgery, fertility preservation, management of menopausal symptoms, and surgical technique. Alternative choices in women who choose to delay bilateral salpingo-oophorectomy are reviewed. Finally, the psychosocial effects of carrying a genetic mutation and the issues that women face when undergoing to risk-reducing surgery including adjustment, sexuality issues, and cosmesis are addressed.

An ecological evaluation of the increasing incidence of endometrial cancer and the obesity epidemic. SA Smrz, C Calo, JL Fisher, R Salani. American J of Obstetrics and Gynecology 224, ISSUE 5, P506.E1-506.E8, MAY 01, 2021 DOI:https://doi.org/10.1016/j.ajog.2020.10.042 https://www.ajog.org/article/S0002-9378(20)31272-2/fulltext

Background The prevalence of obesity has increased significantly in recent decades, particularly among younger women, and is a known risk factor for endometrial cancer.

Objective This study aimed to evaluate the trend in the prevalence of obesity and the incidence of type I endometrial cancer over time in various age categories to determine whether an ecological relationship exists.

Study Design Data from the Surveillance, Epidemiology, and End Results Program and the National Health and Nutrition Examination Survey were used. The overall trend in the incidence of type 1 endometrial cancer and prevalence of obesity were observed over time from 1988 to 2016 and further categorized by age group (<45, 45–54, and ≥55 years).

Results The prevalence of obesity has increased for all women, but most significantly for women younger than 45 years with a 16.3% increase among women aged 20 to 34 years and a 17.9% increase for women aged 35 to 44 years. The incidence of endometrial cancer has also increased across all age categories, and although it has increased in patients younger than 45 years by more than 14-fold (from <0.1 per 100,000 in 1988 to 1.4 per 100,000 in 2016), a more pronounced increase of 63-fold and 50-fold was observed among women aged 45 to 54 years (0.2 per 100,000 in 1988 to 12.6 per 100,000 in 2016) and women aged 55 years and older (from 0.6 per 100,000 in 1988 to 30 per 100,000 in 2016), respectively. The mean age of women diagnosed as having endometrial cancer also decreased from 64.1 years from 1988 to 1990 to 61.0 years from 2014 to 2016.

Conclusion The prevalence of obesity has increased significantly in women of all ages. This increase, particularly among women aged <45 years, occurred simultaneously with an increase in the incidence of endometrial cancer in young women, with an even more pronounced increase among women aged ≥45 years.

Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019 Allison W. Kurian, Kevin C. Ward, Paul Abrahamse, Irina Bondarenko, Ann S. Hamilton, Dennis Deapen, Monica Morrow, Jonathan S. Berek, Timothy P. Hofer, and Steven J. Katz

Journal of Clinical Oncology 2021 39:15, 1631-1640 DOI: 10.1200/JCO.20.02785
https://ascopubs.org/doi/full/10.1200/JCO.20.02785

PURPOSE Genetic testing is important for breast and ovarian cancer risk reduction and treatment, yet little is known about its evolving use.

METHODS SEER records of women of age ≥ 20 years diagnosed with breast or ovarian cancer from 2013 to 2017 in California or Georgia were linked to the results of clinical germline testing through 2019. We measured testing trends, rates of variants of uncertain significance (VUS), and pathogenic variants (PVs).

RESULTS One quarter (25.2%) of 187,535 patients with breast cancer and one third (34.3%) of 14,689 patients with ovarian cancer were tested; annually, testing increased by 2%, whereas the number of genes tested increased by 28%. The prevalence of test results by gene category for breast cancer cases in 2017 were *BRCA1/2*, PVs 5.2%, and VUS 0.8%; breast cancer–associated genes or ovarian cancer–associated genes (*ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*), PVs 3.7%, and VUS 12.0%; other actionable genes (*APC*, *BMPR1A*, *MEN1*, *MUTYH*, *NF2*, *RB1*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *TSC1*, *TSC2*, and *VHL*) PVs 0.6%, and VUS 0.5%; and other genes, PVs 0.3%, and VUS 2.6%. For ovarian cancer cases in 2017, the prevalence of test results were *BRCA1/2*, PVs 11.0%, and VUS 0.9%; breast or ovarian genes, PVs 4.0%, and VUS 12.6%; other actionable genes, PVs 0.7%, and VUS 0.4%; and other genes, PVs 0.3%, and VUS 0.6%. VUS rates doubled over time (2013 diagnoses: 11.2%; 2017 diagnoses: 26.8%), particularly for racial or ethnic minorities (47.8% Asian and 46.0% Black, *v* 24.6% non-Hispanic White patients; $P < .001$).

CONCLUSION A testing gap persists for patients with ovarian cancer (34.3% tested *v* nearly all recommended), whereas adding more genes widened a racial or ethnic gap in VUS results. Most PVs were in 20 breast cancer–associated genes or ovarian cancer–associated genes; testing other genes yielded mostly VUS. Quality improvement should focus on testing indicated patients rather than adding more genes.

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In the Know (aka Ed's List) is prepared by Dr. Edward Pavlik for the education of the fellows & candidate fellows at the University of Kentucky on a monthly basis. Dr. Pavlik extends this resource to members of the International Gynecologic Cancer Society to promote continued learning and increase awareness of the latest significant research findings in the field of gynecologic oncology on a global level.

Two successive months of literature are put together to accommodate online vs print appearances and to compensate for delays in a publication (i.e. the March material is not available until June).

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