Published in final edited form as:

Int J Gynecol Cancer. 2019 August ; 29(Suppl 2): s16–s21. doi:10.1136/ijgc-2019-000456.

Novel Therapeutics: Response and Resistance of Ovarian Cancer

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Abstract

Here we review the latest preclinical and clinical developments for therapy of ovarian cancer, presented at the AACR/Rivkin Center Ovarian Cancer Research Symposium held at the University of Washington in September 2018. Abstracts and presentations pertaining to Novel Therapeutics session were reviewed and summarized here. The session featured a keynote presentation from Dr. Ursula Matulonis, who has summarized the current state of the art of treatment of ovarian cancer, including recent clinical trials incorporating the use of novel agents, including PARP inhibitors, other DNA damaging agents, VEGFR inhibitors, mirvetuximab soravtansine, and immune checkpoint blockade. Dr. Jung-Min Lee then summarized the rationale and the results of early studies for targeting cell cycle checkpoint kinases for anti-cancer therapy. Eight submissions were selected for oral presentations, and 36 abstracts were presented as posters. The topics covered a range of clinical and preclinical strategies and biomarkers, including immunotherapy, mechanisms of chemotherapy and PARP inhibitor resistance, DNA-damaging agents, and other novel therapeutic strategies. Key studies have highlighted that resistance to chemotherapy and PARP inhibitors remain to be a major challenge in therapy of ovarian cancer. Cancer stem cells (CSCs) represent an important mechanism of chemoresistance and strategies to target CSCs may be a pathway to prevention of ovarian cancer relapse. Advancement of novel therapeutics targeting DNA damage, cell metabolism, and endoplasmic reticulum present some of the novel strategies in the pipeline. Emerging compelling preclinical data with novel antibody-drug conjugates targeting various surface receptors in ovarian cancer alone and in combination with immune checkpoint blockade generate a strong enthusiasm for rapid translation of these strategies to clinic.

Precis

The article summarizes the key findings in the field of novel therapeutics in ovarian cancer presented at the AACR/Rivkin Center Ovarian Cancer Research Symposium in September 2018.

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Author Contribution Statement

D.Z. was responsible for the review of the conference data and manuscript composition.

Conflicts of Interest

D.Z. reports no conflicts of interest related to this review. D.Z. indicated financial activities outside of submitted work, which include personal fees, grants, and intellectual property. All disclosures are indicated in detail in the submitted ICJME Forms for Disclosure of Potential Conflicts of Interest.

Proceedings from the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium

Introduction

Since the last symposium in 2016, we have seen a series of developments in ovarian cancer, with approval of several poly ADP ribose polymerase (PARP) inhibitors in different treatment settings as well novel clinical trials using agents targeting DNA repair, oncogenic pathways, and the immune system. The Novel Therapeutics session has focused on the studies that aim to delineate the mechanisms of resistance to existing agents, identify novel targets, and develop new treatment combinations.

Current state of therapy of ovarian cancer and novel combinations in clinical trials

Dr. Ursula Matulonis gave a keynote lecture in this session, summarizing the state of the art of treatment of ovarian cancer and the results of recent clinical trials. Given the advances with PARP inhibitor development in ovarian cancer, she highlighted the multiple ongoing trials currently utilizing PARP inhibitors in combination with other agents. These include PARP inhibitors in combination with agents targeting other mechanisms of homologous DNA repair, Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) inhibitors, such as cediranib and bevacizumab, PI3K inhibitors and PD-1 inhibitors, some of which have demonstrated signals of activity in early clinical trials [1-3]. She further summarized clinical data with folate receptor-targeting antibody drug conjugate mirvetuximab soravtansine, with single agent response rate of 39% in non-heavily pre-treated patients [4]. Combinations of mirvetuximab soravtansine with other agents, such as pembrolizumab, chemotherapy, and bevacizumab are currently ongoing. The responses appear to be enriched in the patients with medium/high folate receptor alpha expression, which will serve as a biomarker for future patient selection.

Targeting cell cycle checkpoints and DNA repair mechanisms

Cell cycle checkpoint kinases (Chk1/2) represent another target for therapy in ovarian cancer, particularly the cancers not carrying inactivating BRCA mutations. Dr. Jung-Min Lee summarized the preclinical data as well as early clinical data behind prexasertib, an inhibitor of Chk1/2 in non-BRCA-mutant ovarian cancer. In preclinical models, the drug demonstrates synergistic activity when used in combination with olaparib in non-BRCA-mutant cell lines, likely through inhibition of Rad51-mediated homologous DNA repair [5]. A phase I/II trial in 28 patients with advanced platinum-resistant non-BRCA-mutant ovarian cancer demonstrated a promising response rate of 33% [6]. Grade ¾ neutropenia was the most common adverse event, which was interestingly very transient. Dr. Lee further discussed other ongoing studies targeting DNA checkpoints alone or in combination, including combinations of Chk1 inhibitor and mTOR inhibitors and Chk1 inhibitors with PARP inhibitors, which are currently ongoing. Finally, she presented early clinical data with combinations of carboplatin with WEE1 inhibitors, demonstrating a promising response rate of 43% with 5.3 months median PFS.

PARP inhibitors: recent findings, mechanisms of resistance, and novel combinations.

Dr. Kathleen Moore and colleagues presented results of the QUADRA study, which evaluated single agent niraparib at 300mg daily in patients with high-grade serous ovarian cancer and 3 or more prior lines of therapy. A total of 463 patients were treated on the study and the results were assessed according to platinum sensitivity, BRCA status, and homologous recombination deficiency (HRD) status. In 456 patients with measurable disease, disease control rate (DCR) was 49%. In the primary efficacy population, defined as HRD positive, overall response rate was 29%, with DCR of 71%. The most common observed grade 3 and higher adverse events were anemia (26.3%) and thrombocytopenia (20.5%). Niraparib thus demonstrated promising activity in this heavily-pretreated population, including platinum-resistant patients and some non-BRCA-mutant patients (NT-101).

Despite the promising response rate, this trial highlights the sad reality that PARP inhibition remains not to be an option for the majority of patients, particularly with platinum-resistant disease and BRCA-wild-type status. Identification of biomarkers of primary and acquired resistance and strategies to minimize toxicity thus remain a high priority for further development of this class of agents.

Nanoparticles present an innovative and attractive strategy for drug delivery to tumors as a means to minimize systemic toxicity [7]. Dr. Paige Baldwin and colleagues explored nanoparticle encapsulation of talazoparib, followed by intraperitoneal delivery to minimize systemic toxicities of PARP inhibition. The resultant drug formulation was more efficient in suppressing tumor growth when compared to the parental drug with no obvious signs of toxicity (NT-87).

A number of studies uncovered several novel mechanisms of PARP inhibitor resistance [8]. Dr. Neil Johnson presented an oral abstract describing a novel mechanism responsible for acquired PARP inhibitor resistance. BRCA1 mutations in BRCA1 C-terminal (BRCT) domain normally results in protein misfolding and degradation, promoting sensitivity to PARP inhibitors. Dr. Johnson and colleagues have uncovered a mechanism, whereby retention of intron in a BRCA1 gene containing mutation in BRCT domain results in intron translation and loss of BRCT domain. This led to robust BRCA1 expression and resistance to chemotherapy. Dr. Lu Liu and colleagues demonstrated that short term and chronic PARP inhibition can drive aldehyde dehydrogenase 1A1 (ALDH1A1) expression, thus conferring stemness to the cancer cells [9], which eventually drives adaptive resistance to PARP inhibitors (NT-100). Finally, Dr. Anniina Färkkilä used in vitro exposure to PARP inhibitors to characterize the mechanisms of PARP inhibitor resistance in BRCA1 mutant cells. The resultant resistance to PARP inhibitors was mediated by several mechanisms in different clones, highlighting the potential for heterogeneity in resistance upon PARPi treatment (NT-92).

With identification of PARP inhibitor resistance mechanisms comes the rationale for combination therapies to overcome the resistance. Dr. Marilyne Labrie and colleagues

implemented a window of opportunity trial to study adaptive resistance to PARP inhibitors. Using reversed phase protein array analysis, measuring the expression of over 300 proteins in pre- and post-treatment samples, the authors were able to develop an algorithm that could suggest potential combination partners for PARP inhibition in specific patients (NT-098).

Targeting DNA damage through several targets is a rational strategy to overcome PARP inhibitor resistance [10]. Dr. Erin George presented an oral abstract on the potential utility of the use of ataxia telangiectasia and Rad3-related protein (ATR) inhibitors in combination with PARP inhibitors. They identified constitutive activation of the ATR/CHK1 pathway in PARP inhibitor and carboplatin-resistant cell lines. Therapy of such cell lines with an ATR inhibitor in combination with Ataxia-Telangiesctasia mutated (ATM) inhibitor was synergistic both in vitro and in vivo. Interestingly, this approach was also effective in CCNE-amplified tumors, which are known to be highly-resistant to therapy. Dr. Anne Steino and colleagues have explored VAL-083 as a strategy to overcome platinum and PARP resistance. VAL-083 is a first-in-class DNA damaging agent, which induces interstrand DNA crosslinks leading to double-stranded DNA breaks. The authors examined VAL-083 in combination with PARP inhibitors both in HR-proficient and HR-deficient cell lines and demonstrated synergistic activity in both settings (NT-109). As another example of DNA damaging agent, Dr. Ludmila Szabova and colleagues evaluated novel non-camptothecin topoisomerase I (Top1) inhibitors in ovarian cancer. BRCA1/2 and PALB2 deficient cell lines were highly sensitive to the new compounds. Moreover, combination between the new compounds and olaparib was synergistic (NT-110). Dr. Amber Yasmeen and colleagues explored Poly(ADP-ribose) glycohydrolase (PARG) as a potential strategy to sensitize ovarian cancer cells to DNA-damaging agents. PARG is responsible poly(ADP-ribose) (PAR) catabolism which is synthesized by PARP [11]. Faulty PAR formation or disintegration inhibits SSB repair. The authors demonstrate that PARG is expressed in 30% of ovarian cancers in TCGA. Inhibition of PARG in ovarian cancer cell lines resulted in reduced cellular proliferation and migration and sensitized the cells to PARP inhibitors and cisplatin (NT-117). Dr. Rashid Gabbasov and colleagues focused on targeting HSP90, which plays a role in mediating maturation and stability of several key proteins required for DNA damage response (DDR) [12]. They demonstrate that targeted inhibition of HSP90 with ganetespib sensitizes BRCA1-null cell lines to the effects of talazoparib (NT-094).

A number of studies looked at other signaling pathways that could potentially be targeted in combination with PARP inhibition. Dr. Alicia Beeghly-Fadiel and colleagues have demonstrated that nuclear orphan receptor NR4A1/TR3 plays an important pro-growth and pro-survival role in ovarian cancer [13, 14]. Inhibition of NR4A1 using a chemical antagonist or siRNA knockdown resulted in in tumor growth inhibition, and was synergistic with PARP inhibitor therapy (NT-88). Dr. Takeshi Fukumoto and colleagues have demonstrated that upregulation of Wnt/B-catenin pathway in BRCA-mutant cancer cells results in PARP resistance [15]. Interestingly, activation of Wnt pathway was secondary to N6-methyladenosine (m6A) modification of FZD10 mRNA. PAPR inhibition and Wnt/β-catenin inhibitor showed synergistic suppression of growth of PARP inhibitor-resistant cancer both *in vitro* and *in vivo* in a xenograft ovarian cancer mouse model (NT-93).

Overcoming chemotherapy resistance

A number of studies have focused on the mechanisms of resistance to chemotherapy and the potential strategies to overcome it. Dr. Wa Xian and colleagues used ovarian cancer resection specimens to generate libraries of ovarian cancer stem cells (CSCs). The authors demonstrate that while the majority of these cells are killed by chemotherapy, a number of clones were resistant to treatment. The resistant clones were characterized by a gene expression profile that was distinct from the sensitive clones. A broad screen of small molecules against the resistant clones proved that these cells are also resistant to other chemotherapy drugs. However, there were a number of compounds that were either directly cytotoxic or cytotoxic in combination with paclitaxel, presenting a potential strategy to eliminate the resistant clones with upfront therapy and prevent cancer recurrence (NT-115). Dr. Allison Sharrow and colleagues explored ovarian CSCs as a potential mechanism of chemotherapy resistance [9]. By ALDH1 as a marker of stemness in ovarian cancer cell lines, they demonstrate the increased resistance of ALDH1-high populations to chemotherapy. The authors further used gene expression analyses in ALDH1-high populations and identified several upregulated pathways, including mTOR, FGF18, and CD47, which could be explored therapeutically (NT-107). In support of these findings, Dr. Nuzhat Ahmed presented an oral abstract summarizing a proteomic analysis of chemo-naive and chemo-experienced ovarian cancer cells isolated from patients, demonstrating that chemotherapy results in enrichment of markers of cancer stem cells as well as alterations in pathways involved in DNA repair, immune recognition, cell cycle, and metabolism. This study provided important findings about potential mechanisms of chemotherapy resistance that may drive relapse in ovarian cancer and generated rationale for potential novel combinations.

Dr. Alex Cole and colleagues have presented an oral abstract summarizing data on a novel mechanism of chemotherapy resistance mediated by nuclear factor of activated T cells 3 (NFAT3), which is overexpressed in cancer stem cells [16]. They demonstrate that overexpression of NFAT3 promotes quiescent phenotype with G0 arrest. While in vivo this results in tumor growth arrest, it also leads to chemoresistance. These data thus highlight that NFAT3 could be a potential mechanism of chemotherapy target and presents an attractive therapeutic target to be used in combination with chemotherapy.

Tumor hypoxia results in a number of biologic changes in the tumor cells and microenvironment [17]. Dr. Andrea Nieto-Veloza demonstrate that chemical induction of hypoxia in ovarian cancer cell line results in paclitaxel resistance, although no effect is seen on sensitivity to cisplatin (NT-102). These findings highlight that hypoxia-mediated chemotherapy resistance is not universal to all agents, but nevertheless highlight that targeting of hypoxia may offer therapeutic opportunities for more agents.

Several groups employed novel compounds in combination with chemotherapy as potential chemotherapy sensitizers. Dr. Amber Yasmeen and colleagues explored whether differential sequencing of PARP inhibitors and chemotherapy could improve efficacy. Regardless of BRCA mutational status, exposure to PARP inhibition prior to chemotherapy resulted in efficient induction of apoptosis in vitro (NT-118). Dr. Vermont Dia has presented a potential

strategy to overcome chemoresistance induced by TGF-b1 using BG-4. BG-4 is a bioactive peptide isolated from the seeds of *Momordica charantia* and exhibits anticancer properties [18]. While addition of TGF-b1 to ovarian cancer cell lines in the presence of paclitaxel and cisplatin resulted in chemotherapy resistance, the resistance was ameliorated by addition of BG-4. This was accompanied by reversal of TGF-b1-induced EMT, suggesting a possible mechanism of BG-4 action (NT-91). Dr. John Giannios has presented a strategy of targeting chemoresistant ovarian cancer cells through the use of paired guide RNAs targeting microRNA-221/222, which are known to inhibit apoptosis [19]. By encapsulating paired guide RNAs into pegylated nanosomes tagged with anti-EphA2 antibodies, the authors were able to deliver the RNAs into EphA2-expressing ovarian cancer cells. This strategy led to inhibition of miRNA-221/222 biogenesis and downstream pathways, resulting in reversal of chemoresistance (NT-95).

Targeting endoplasmic reticulum stress pathway

Cancer cells are characterized by endoplasmic reticulum (ER) stress and unfolded protein response (UPR), which contributes to cancer cell survival and resistance to stress caused by chemotherapies, hypoxia, and nutrient deprivation [20]. Dr. Carlos Telleria and colleagues explored ER stress as a potential mechanism to target ovarian cancer cells. Therapy with anti-progestin mifepristone or HIV protease inhibitor induced ER stress in ovarian cancer cell lines. Combination of these drugs with the proteasome inhibitor bortezomib resulted in enhanced ovarian cancer cell death (NT-111). Similarly, Dr. Yang Yang-Hartwich and colleagues explored the UPR pathway as a potential target for overcoming chemoresistance in ovarian cancer. Using a novel sulfonamide SF-Y3, the authors demonstrate inhibition of proliferation and induction of apoptosis in ovarian cancer cells. This effect was primarily seen in cancer cells with high levels of Bip1, a key chaperone protein in the ER, implicating its role in SF-Y3-induced UPR (NT-116).

Targeting metabolic pathways

With advances in understanding of metabolism and biosynthetic pathway alterations in cancer cells comes rationale for selective targeting of these pathways as a means to improve the efficacy of standard therapies. Dr. Adegbite Emmanuel and colleagues revealed preliminary results of in silico screening of inhibitors of lactate dehydrogenase (LDH), which plays a role in ovarian cancer metabolism [21] (NT-86). Dr. Manish Patankar and colleagues explore the use of oxidative phosphorylation inhibitors in ovarian cancer, given the mounting evidence that the mitochondrial pathway can also contribute to cancer cell metabolism. They demonstrate that atovaquone is an efficient inhibitor of electron transport in ovarian cancer cells and leads to tumor growth inhibition in ID8 tumor model. The authors highlight several mechanisms of action of atovaquone, including production of free radicals and inhibition of ion transport resulting in loss of mitochondrial membrane potential (NT-103).

Antibody drug conjugates (ADC)

Targeting of ovarian cancer surface molecules using ADC presents a viable therapeutic strategy, best supported by the initial data from the phase I trial of mirvetuximab soravtansine, a folate receptor-targeting ADC, which demonstrated a 26% response rate in heavily-pretreated patient population and a 39% response rate in patients with 3 or fewer lines of therapy [4]. This generates a strong rationale for evaluation of analogous strategies targeting other surface molecules and for further optimization of folate receptor alpha targeting. Dr. Venita De Almeida presented preclinical data with STRO-002, a novel antibody-drug conjugate targeting folate receptor alpha, which was optimized by selection of the antibody, drug-linker, conjugation site and drug-antibody ratio (DAR) that conferred the best pharmacological properties. The resultant drug exhibited high potency in vitro and in vivo, while exhibiting high safety profile in toxicology studies (NT-90). Dr. Chunsheng Li and colleagues presented an ADC strategy targeting CD248, which is expressed by over 90% of ovarian cancers. In preclinical models, the antibody was cytotoxic to cancer cells both in vitro and in vivo and induced infiltration of lymphocytes into tumors, highlighting a potential dual mechanism of action of this strategy with rationale for combination with immune checkpoint blockade (NT-99). Finally, Dr. Wolf Wiedemeyer and colleagues explored SC-003, another ADC targeting dipeptidase 3 (DPEP3). By screening a PDX bank of ovarian cancers, the authors identified DPEP3 as a common target in tumor initiating cells (TIC). Therapy of DPEP3+ patient-derived xenograft (PDX) models with SC-003 resulted in efficient tumor regression. By using DPEP3-expressing syngeneic mouse cells, the authors further demonstrate that such strategy can synergize with systemic PD-1 blockade (NT-113).

Immunotherapy

Therapy with immune checkpoint blockade (ICB) has been evaluated in in epithelial ovarian cancer (EOC), demonstrating disappointing response rates to date [22-25]. These findings necessitate the development of rational combinations and identification of biomarkers that could predict response to PD-1/PD-L1 blockade. Dr. Dmitriy Zamarin presented an oral abstract discussing the results of a phase II clinical trial evaluating the use of PD-L1 inhibitor durvalumab in combination with folate receptor alpha vaccine TPIV200 in 27 patients with heavily-pretreated platinum resistant/refractory ovarian cancer. While the overall response rate was 4%, similar to what was previously observed with single agent PD-1/PD-L1 inhibitors, the study demonstrated a median overall survival of 21 months, which is superior to the expected overall survival of <1 year in this patient population [26]. There was evidence of potential enhanced clinical benefit from subsequent chemotherapy in the patients after completion of immunotherapy, highlighting the rationale for the use of chemotherapy in combination with immune checkpoint blockade in this patient population. Dr. Denise Cecile presented pre-clinical findings of insulin growth factor binding protein 2 vaccine (IGFBP-2) in ID8-luciferase tumor models. The authors also employed a novel method of anti-tumor assessment using multiview multispectral imaging allowing for more accurate tumor volume assessment. The study was able to demonstrate heterogeneity in metastatic tumor distribution and response, suggesting that this strategy may be a useful tool for evaluation intertumoral heterogeneity in animal models.

Other therapeutic strategies

A number of abstracts discussed other novel targets and therapeutic modalities with potential application to ovarian cancer. Dr. Karen Levy presented an oral abstract discussing pre-clinical data behind the use of novel radiation approach termed FLASH, which consists of short pulses of ultra high dose radiation given in a single fraction [27]. In peritoneal model of ID8 ovarian cancer, this approach was effective in controlling tumors, while having no significant toxicity when compared to conventional radiation. Dr. Varatharasa Thiviyanathan and colleagues developed single-stranded nucleic acid aptamers with ability to recognize and bind ovarian cancer endothelial cells through Annexin A2. Using this technology, the authors made an RNA/DNA nanoparticle capable of delivering doxorubicin to cancer cells in animal models. This strategy presents a potential mechanism to deliver drugs directly to the tumors while avoiding systemic toxicity (NT-112).

Several studies focused on the alterations common to high-grade serous ovarian cancer and other histologies. Missense mutations in p53 are the most common genetic alterations in ovarian cancer [28]. Dr. Satish Kumar Ramraj and colleagues used p53 reactivator drug PRIMA-1^{MET} in combination with SHetA2, a small molecule that inhibits mortalin (mitochondrial Hsp70 protein) [29]. The combination was synergistic in ovarian cancer cell lines with mutant and wildtype p53 and showed additive activity in p53-null cell lines (NT-104).

Clear cell carcinoma of the ovary represents a highly chemoresistant subtype of ovarian carcinoma and frequently harbor mutations in ARID1A [30]. Dr. Shogo Shigeta and colleagues performed siRNA screens against 2 ovarian clear cell carcinoma cell lines. A number of genes were identified as potential targets, including bromodomain BET family proteins BRD2 and BRD3. Knockdown of these proteins using RNA interference resulted in tumor growth inhibition (NT-108). Dr. Shuai Wu and colleagues explored the mechanisms of acquired resistance to EZH2 inhibition. In ARID1A-mutated cancer cells, the switch of the SWI/SNF catalytic subunit from SMARCA4 to SMARCA2 was the primary mechanism of resistance, leading to induction of anti-apoptotic genes such as BCL2. Use of BCL2 inhibitor ABT263 was able to overcome EZH2 inhibitor resistance and was synergistic with EZH2 inhibition in vivo (NT-114).

Epithelial to mesenchymal transition (EMT) contributes to ovarian tumor metastasis and chemoresistance [31]. Dr. Junming Yue and colleagues demonstrate that knockout of the metal regulatory transcription factor 1 (MTF1) results in inhibition of EMT, leading to reduced cell proliferation, migration, and invasion (NT-120). Dr. Carmela Ricciardelli and colleagues explored all-trans retinoic acid (ATRA) as a means to inhibit the annexin A2-S100A10 signalling pathway, which plays a role in ovarian cancer invasion and metastasis [32]. Treatment of ovarian cancer cells with ATRA led to reduced cell survival, proliferation, and invasion, although the mechanism was not always S100A10-dependent (NT-105). Dr. Flavio Rizzolio and colleagues have demonstrated that targeting of peptidyl prolyl cis-trans isomerase (Pin1), which controls different oncogenes and tumor suppressors, can inhibit tumor growth in mouse ovarian cancer model [33]. Chemical or short hairpin RNA

inhibition of Pin1 in ovarian cancer cell lines sensitized the cells to the effect of carboplatin (NT-106).

Several studies have characterized novel compounds with yet not fully understood mechanisms of action. Dr. Alexandria Young and colleagues explored synthetic analogues of phyllanthusmin for cytotoxic activity in ovarian cancer cell lines [34]. The most potent analog, PHY34, has nanomolar potency in HGSOC cell lines in vitro and displayed cytotoxic activity through late-stage autophagy inhibition and activation of apoptosis. The analogue was also effective with intraperitoneal administration in xenograft models (NT-119). Dr. Arvinder Kapur and colleagues used fabclavine, a metabolite of *Xenorhabdus budapestensis*, and demonstrated that the compound inhibited ovarian cancer cell line proliferation and induced apoptotic cell killing at nanomolar concentrations (NT-096). Dr. Powel Crosley and colleagues generated a TRAIL-expressing recombinant vaccinia virus and demonstrated its activity against granulosa cell tumor cell lines. Combination of the recombinant virus with procaspase activating compound 1 (PAC1) resulted in further potentiation of lytic activity (NT-89). Dr. David Pepin presented the results of the effects of Mullerian Inhibiting Substance (MIS) on ovarian cancer cells isolated from ascites [35]. Using single cell RNA sequencing, their study uncovered a high degree of heterogeneity of expression of known and novel markers related to epithelial-mesenchymal states and stemness, both across patients and within patient samples. In addition, they uncovered some unexpected effects of MIS on the immune cells in ascites. These findings will be important in understanding responses to MIS as it progresses through clinical development.

Finally, several groups presented early data on identification of novel compounds and pathways for targeting in ovarian cancer. Dr. Hilary Kenny and colleagues used high throughput screening of small molecules against ovarian cancer organotypic model that recapitulates features of ovarian cancer stroma. Using the strategy, they identified 3 compounds, 2 targeting tyrosine kinases, which inhibited ovarian cancer adhesion, invasion, and growth (NT-97). Dr. Einav Zmora and colleagues have analyzed EGF-like ligands from ascites of 43 ovarian cancer patients and found that 86% of them expressed high levels of amphiregulin (AREG), which is a cytokine playing a role in tissue repair and inflammation [36]. The authors generated an antibody against AREG and evaluated it in animal tumor models. Therapy with anti-AREG resulted in significant prolongation of survival of mice bearing cancer xenografts (NT-121).

Concluding remarks:

In summary, the Symposium saw a rich influx of information highlighting novel mechanisms of primary and acquired resistance to chemotherapy and PARP inhibition. The revolving theme of combination therapy to overcome or prevent resistance resonates throughout all studies. Potential combination partners include other agents inhibiting DNA repair, agents targeting cellular checkpoints, and drugs effective against cancer stem cells. Immune checkpoint inhibitors, while effective in a small subset of patients, unfortunately demonstrate limited single-agent activity in ovarian cancer and rational combinations with other immunotherapies, PARP inhibitors, and standard chemotherapy are currently underway. Other novel therapeutic strategies focusing on ER stress response, EMT, and

targeting of surface molecules using novel ADCs demonstrate compelling evidence of anti-tumor activity in pre-clinical models and generate a strong rationale for evaluation in clinic.

Acknowledgements

D.Z. is a member of the Parker Institute for Cancer Immunotherapy at MSKCC. D.Z. is supported by the Ovarian Cancer Research Foundation Liz Tilberis Award, and the Department of Defense Ovarian Cancer Research Academy (OC150111). This work was supported in part by the MSK Cancer Center Support Grant P30 CA008748. We thank Dr. Deborah Armstrong for the critical review of the manuscript.

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