FALL 2022

Hematology/Oncology ACCP PRN Newsletter

GREETINGS FROM THE 2022-2023 CHAIR

I hope you are experiencing an energizing transition into the Fall season! We are pleased to share our biannual PRN newsletter, which coincides with the ACCP Spring and Fall PRN reports.

Historically, the Fall season was termed as "harvest" in England, meaning "to gather." This newsletter represents a gathering of the PRN's biggest assets: talented practitioner and learner members. To support the PRN member needs, you will find a collection of new hematology/oncology drug updates, practice-changing evidence summaries, and perspectives on clinical "hot topics."

We are also eager to gather and re-connect in-person at the annual meeting in San Francisco in a few short weeks! This year, the Hem/Onc & Industry PRN focus session is titled "Translating Research into Practice: Contemporary Perspectives on the FDA Oncology Drug Approval Process and Novel Clinical Trial Designs." Other programming that we would like to highlight includes our Hem/Onc PRN business Meeting and BCOP clinical sessions. We hope to see you there.

Lastly, the annual call for committee involvement will go out in the coming months. If you are considering joining or re-joining a committee, please be on the lookout for emails or please feel free to reach out to me directly. Students, residents, fellows, and practitioner participation is welcome and valued!

IN THIS ISSUE:

A New Path for DESTINY: Promising Results for Targeting HER2-Low Metastatic Breast Cancer

By Julia Miller, PharmD. Candidate Class of 2023, The Ohio State University
Mentor: Christopher Wang, PharmD, PGY2 Oncology Resident, MD Anderson Cancer Center

Background

As of this year, it is estimated that there will be 287,850 new cases of female breast cancer [1]. Regarding metastatic breast cancer, there are four main subtypes: HR+/HER2-, HR+/HER2+, HR-/HER2-, and HR-/HER2+ [2]. When HER2 is overexpressed in breast cancer, extra copies of HER2 can promote the growth of the cancer [3]. Previously, only excess amounts of HER2 resulting in HER2+ could be treated with HER2-directed therapies. The new designation of HER2-low refers to elevated amounts of HER2 that are not high enough to be considered positive. As much as 60% of breast cancers are HER2-low [3].

When classifying HER2 status, a combination of IHC and ISH testing can be done (Table 1). The IHC test will give a score of 0 to 3+. A result of 0 would equate to HER2-, 1+ would be considered HER2-low, 2+ is borderline and requires an ISH test to determine HER2+ or HER2-low, while 3+ would be considered HER2+ [3].

Table 1. Definitions of HER2 negative, HER2 positive, and HER2 low expression levels

Previous Definitions		**New Definitions**		
HER2-	**HER2+**	**HER2-**	**HER2-low**	**HER2+**
IHC 0+, 1+, or 2+ with ISH negative	**IHC 2+ with ISH positive or 3+**	**IHC 0+**	**1+ or 2+ with ISH negative**	**2+ with ISH positive or 3+**

Prior to the DESTINY-Breast04 trial, data showed that HER2-directed therapies did not improve clinical outcomes in HER2-low breast cancer. For example, the NSABP B-47 trial concluded that the addition of trastuzumab to adjuvant chemotherapy did not improve IDFS or OS in HER2-low breast cancer [4]. However, unlike other HER2 targeted therapies, evidence suggests that trastuzumab deruxtecan (Enhertu), an antibody-drug conjugate with a topoisomerase 1 payload, may have better activity against HER2-low disease [5].

Methods

The DESTINY-Breast04 trial was a randomized, open-label phase 3 trial involving patients with HER2-low metastatic breast cancer. The patients were assigned in a 2:1 ratio to receive trastuzumab deruxtecan or the physician's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel. Patients with HR+ disease must have received at least one line of endocrine therapy. The primary endpoint of the DESTINY-Breast04 trial was PFS among patients with HR+ disease. Secondary endpoints were PFS among all patients and OS in the HR+ cohort and among all patients.

A New Path for DESTINY (Continued)

Results

In the study, there were 373 patients who were assigned to the trastuzumab deruxtecan group, compared to 184 patients assigned to the physician's choice group. The majority of each group were HR+ (89%). In the physician's choice group, patients received eribulin (51%), capecitabine (20%), nab-paclitaxel (10%), gemcitabine (10%) or paclitaxel (8%). The median PFS in the HR+ cohort was higher in the trastuzumab deruxtecan group compared to the physician's choice group (10.1 vs 5.4 months). In the HR- cohort, the median PFS was also higher with trastuzumab deruxtecan (8.5 vs 2.9 months). In the trastuzumab deruxtecan group, the median PFS was not significantly different between IHC scores of 1+ or 2+.

The OS in the HR+ cohort was higher in the trastuzumab deruxtecan group compared to the physician's choice group (23.9 vs 17.5 months). This OS benefit with trastuzumab deruxtecan was also similar in the HR- cohort (18.2 vs 8.3 months), although this was not considered statistically significant.

A total of 99.5% of the patients in the trastuzumab deruxtecan group and 98.3% of patients in the physician's choice group had at least one adverse event during the trial. The most common drug-related adverse events that were more common in the trastuzumab deruxtecan group included nausea (73.0%), fatigue (47.7%), and alopecia (37.7%). The most common adverse events of grade 3 or higher in the trastuzumab deruxtecan group were neutropenia (13.7% of patients), anemia (8.1%) and fatigue (7.5%) compared to the physician's choice group (40.7%, 4.7%, and 4.7% respectively). Drug-related interstitial lung disease or pneumonitis occurred in 45 patients (12.1%) who received trastuzumab deruxtecan, most of which were grade 1-2.

Discussion

The DESTINY-Breast04 trial found that targeting low levels of HER2 with trastuzumab deruxtecan was a superior therapeutic approach compared to untargeted chemotherapy. Previously, the binary classification of HER2+ and HER2- defined the prognosis and treatment of breast cancer patients, where HER2+ patients would receive HER2-directed therapies while HER2- patients would not. While high levels of HER2 overexpression are necessary for the efficacy of most HER2-directed therapies, trastuzumab deruxtecan has now been proven to be effective at low levels of HER2 overexpression. Reasons for this discrepancy include the fact that trastuzumab deruxtecan contains an enzyme-cleavable antibody-drug linker, high drug-to-antibody ratio, and membrane-permeable payload.

One weakness of this study was the small cohort of HR- patients, although the proportion of patients with HR- disease was representative of the prevalence in the HER2-low population. Another weakness was the lack of including HR+ patients treated with alpelisib or everolimus; both considered second line therapies after progressing on first line endocrine therapy.

A New Path for DESTINY (Continued)

Conclusion

Overall, this trial showed significantly longer PFS and OS with trastuzumab deruxtecan in patients with HER2-low metastatic breast cancer. This is a practice changing trial, unlocking a new therapy option for a large proportion of metastatic breast cancer patients who were previously unable to obtain HER2-directed therapy.

Abbreviations

- HER2: human epidermal growth factor receptor 2
- HR: hormone receptor
- IDFS: invasive disease-free survival
- IHC: immunohistochemistry
- ISH: in situ hybridization
- IV: intravenously
- NCCN: National Comprehensive Cancer Network
- PFS: progression-free survival
- OS: overall survival

References

1. Female Breast Cancer Subtypes - Cancer Stat Facts. SEER. Accessed July 31, 2022. https://seer.cancer.gov/statfacts/html/breast-subtypes.html
2. Breast Cancer Molecular Subtypes. Cancer Treatment Centers of America. Published October 5, 2018. Accessed July 31, 2022. https://www.cancercenter.com/cancer-types/breast-cancer/types/breast-cancer-molecular-types
3. A New Standard of Care? Enhertu Improves Survival in People With Metastatic HER2-low Breast Cancer. Accessed July 31, 2022. https://www.breastcancer.org/pathology-report/her2-status
4. Fehrenbacher L, Cecchini RS, Geyer Jr CE, et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2+. JCO. 2020;38(5):444-453. doi:10.1200/JCO.19.01455
5. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022;387(1):9-20. doi:10.1056/NEJMoa2203690

Impact of Acetaminophen on the Efficacy of Immunotherapy in Cancer Patients

Authors: Emily Viehl, PharmD, Hematology/Oncology Clinical Pharmacist, Yale New Haven Health
Jasmin P. Eugene, PharmD, BCOP, Clinical Assistant Professor/Oncology Clinical Specialist, Xavier University of Louisiana College of Pharmacy

Introduction

Pain is one of the most common side effects associated with cancer. It occurs in 30% to 50% of patients receiving cancer therapy (Bessede 2022 and Dalal 2019) and is a common sign of advanced disease (APAP and immunotherapy article). Management of cancer pain includes opioids and nonopioids, like acetaminophen (APAP). Although the mechanism is still unknown, APAP is believed to work in the CNS and activate the descending serotonergic inhibitory pathways (Smith 2009 Lexicomp). APAP has been shown to cause immunosuppression in patients with liver dysfunction (Yamura 2002) and decrease viral clearance of rhinovirus (Graham N 1990). It has been shown to decrease antibody levels if given prior to vaccinations (Prymula R 2009) leading to World Health Organization (WHO) recommending against the use of APAP prior to vaccination administration.

Immunotherapy have revolutionized the treatment of advanced cancer. These agents work by activating T-cells and allowing T-cells to inhibit the tumor. These agents work by inhibiting cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1). Some of the agents are ipilimumab, nivolumab, and atezolizumab, respectively. These agents are used in a variety of malignancies, including melanoma, lung cancer, and renal cell carcinoma.

Objective

This study's objective was to evaluate if APAP impact the effectiveness of immunotherapy in advanced cancer patients in vitro. The authors selected this objective because data is lacking regarding the impact of APAP in immunotherapy.

Methods

The article assessed three different studies, including CheckMate 025 Trial, Bergonie Insitut Profiling (BIP), and Predictive Markers of Immune-related Adverse Events in Patients Treated with Immune Stimulatory Drugs (PREMIS). The main inclusion criteria in the BIP and PREMIS studies were patients at least 18 years old, diagnosed with unresectable or metastatic cancer, and at least one form of imaging assessing disease after immunotherapy initiation. All patients were treated with anti-PD-1 or an anti-PD-L1 agent as monotherapy or combined with CTLA-4 inhibitor. Therapy response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

Impact of Acetaminophen on the Efficacy of Immunotherapy in Cancer Patients (Continued)

Methods (Continued)

Four patients received APAP 1000mg orally every 6 hours over 24 hours to assess the pharmacodynamic impact of APAP on peripheral immune cells. Peripheral blood mononuclear cells (PBMCs) were collected at baseline and 2 hours after the last dose of APAP. APAP and its metabolite were detected by using liquid chromatography-mass spectrometry in the BIP trial; while PREMIS assessed quantitative dosage of APAP and its metabolite using similar spectrometry and collected samples regarding proteomic profiling of the plasma samples.

To assess the PBMCs from healthy donors, PBMCs were isolated from whole blood before and 24 hours after APAP administration using density gradient centrifugation. Cell populations and marker expression differences between pre- and post-treatment samples were tested using paired Student's t-test.

Proteomic profiling of plasma samples from cancer patients were included in the PREMIS study. Differences in the plasma samples were collected at baseline and at week 6 and evaluated using paired Student's t-test. PBMCs from 3 healthy donors were isolated and treated with anti-CD3 with or without nivolumab along with increases APAP doses. After 72 hours, immunogenicity was assessed by evaluating interferon-gamma release.

Descriptive statistics were used to explain the distribution of the population. The study outcomes were progression free survival (PFS) and overall survival (OS). PFS was defined as the time from initiation of treatment until disease progression, death, or last patient contact. OS was defined as the time from the initiation of treatment until death or last patient contact. Patients in CheckMate 025 and BIP studies were classified as high or low based on specific threshold value, and patients in the PREMIS study were categorized as presence or absence based on the quantitation of APAP and its metabolite. Differences between groups were assessed using chi-square test, Tuckey tests, and Wilcoxon tests. All statistical tests were two-sided and the p-value was <0.05 signified statistical significance.

Results

Self-medication with APAP is extremely common among patients of all disease states and backgrounds. Therefore, basic analysis of electronic medical records could not provide accurate data regarding APAP usage. Instead, serum metabolomics data was analyzed for 297 patients with advanced renal cell carcinoma being treated with nivolumab. Overall survival was found to be significantly worse in patients with detectable levels of APAP or APAP glucuronide. Objective response rate and PFS were not evaluated for this group of patients

A similar analysis was done for 34 patients being treated with immunotherapy for advanced disease. Exposure to APAP had a significant difference in objective response rate in comparison to those without exposure (0% vs. 29.4%, respectively; $p = 0.015$). Median PFS also showed a significant worse prognosis in those with APAP exposure (1.87 vs 4.72 months; 95% CI, 0.30-1.32; $p = 0.219$), as well as median OS (7.87 vs 16.56 months; 95% CI, 0.3-1.63; $p = 0.412$).

Impact of Acetaminophen on the Efficacy of Immunotherapy in Cancer Patients (Continued)

Results (Continued)

Furthermore, levels of APAP were analyzed for 297 patients enrolled in the PREMIS study. Baseline characteristics are detailed in Table 1. Patients with exposure to APAP were found to have a significant worse median PFS (2.63 vs 5.03 months; 95% CI, 0.53-0.91; $p = 0.009$) and median OS (8.43 vs 14.93 months; 95% CI, 0.32-0.69; $p < 0.0001$). Additionally, objective response rate was found to be increased in those without APAP exposure (28.9% vs 20.7%; $p = 0.106$), although not found to be statistically significant. Table 2 details a multivariate analysis, where APAP plasma levels were shown to be independently associated with PFS and OS.

In order to prove the effect of APAP on immunotherapy, the MC38 colon tumor model was used to show these effects. Tumor rejection rates were significantly lower in mice treated with immunotherapy and APAP in comparison with those treated with immunotherapy alone. Mechanistically, a flow-cytometry-based analysis was performed with showed an increase in tumor penetration by regulatory T cells was seen in mice treated with APAP and even more so in mice treated with both immunotherapy and APAP.

To further prove APAP's effects on immune cells, human PBMCs were exposed to anti-CD3 antibodies with increasing concentrations of APAP. APAP was shown to increase regulatory T-cells as well as coinhibitory receptors LAG3 and TIM3, both of which are shown to have a strong immunosuppressive presence. Cytokines were also measured in the plasma of patients enrolled in the PREMIS study. It was found that interleukin-10 and Flt3-ligand were significantly increased in patients being treated with both APAP and immunotherapy. IL-10 serves as a mediator of immune suppression and Flt3-ligand assists in growth for dendritic cells.

Discussion

Overall, this study showed that patients, specifically with advanced cancer, have worse clinical outcomes during concomitant immunotherapy and APAP treatment. The data and mechanistic evaluations show a correlation with APAP use and decreased T-cell-medicated antitumor activity. That authors of this study organized this study to reduce bias or confounding factors. Data did not rely on medical record analysis and outcomes were evaluated in multiple different groups of patients. Furthermore, APAP was shown to reduce efficacy of immunotherapy in a pre-clinical model of colorectal cancer and in vitro, using human PBMCs.

APAP and its immune effects have been reported previously, as early as the 1990s.6 Prymula et al. showed in a randomized study that pediatric vaccines have decreased immunogenicity when APAP was used in combination. Additionally, a systemic review was done showing the negative effects of immune responses to pneumococcal conjugate vaccines in children when used with prophylactic APAP.8

Another study evaluated the effect of IL-2 induced fever and improved survival in patients with advanced melanoma.9 Although improved survival was shown in patients with fevers, those using routine APAP did not show a similar improved survival.

Impact of Acetaminophen on the Efficacy of Immunotherapy in Cancer Patients (Continued)

Discussion (Continued)

Mechanistically, few studies have been able to evaluate or confirm what theoretically causes the reduced immunogenicity with the use of APAP. The preclinical in vivo experiment done in this study showed an increase in tumor infiltrating regulatory T-cells with use of APAP and immunotherapy, which have been shown to have antitumor immune response suppression. This study also proved an exclusive increase in IL-10 and Flt3-ligand when using APAP with immunotherapy, as well as a strong increase in LAG3 and TIM3, both of which are critical in regulatory T-cell suppression.

Although, data and ideologies may still vary in regard to the use of APAP with immunotherapy, this study shows a strong case for the potential negative effects of APAP on immunotherapy efficacy in patients with advanced malignancies. Future studies will need to be done to evaluate whether this effect applies to the entire treatment duration, to all antipyretics, and to all immunotherapy used in oncology patients.

References:

1. Bessede A, Marabelle A, Guegan J, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Annals of Oncology. 2022.
2. Dalal S and Bruera E. Pain Management for Patients with Advanced Cancer in the Opioid Epidemic Era. American Society of Clinical Oncology Educational Book 39 (May 17, 2019)24-35.
3. Smith HS. Potential analgesic mechanisms of acetaminophen. Pain Physician. 2009;12(1):269-280.
4. Yamaura K, Ogawa K, Yonekawa T, et al. Inhibition of the antibody production by acetaminophen independent of liver injury in mice. Biol Pharm Bull. 2002;25(2):201-205.
5. Graham N, Burrell C, Douglas R, et al. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function viral shedding, and clinical status in rhinovirus-infected volunteers. J Infect Dis. 1990;162(6):1277-1282.
6. Prymula R, Siegrist C-A, Chlibek R, et al. Effect of prophylactic paracetamol administration at the time of vaccination on febrile reactions and antibody responses in children: two open-label, randomized controlled trials. Lancet. 2009;374(9698):1339-1350.
7. Motzer R, Escudier B, McDermott D, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. NEJM 2015;373:1803-1813.
8. Koufoglou E, Kourlaba G, Michos A. Effect of prophylactic administration of antipyretics on the immune response to pneumococcal conjugate vaccines in children: a systematic review. Pneumonia (Nathan). April 25, 2021;13(1):7.
9. Køstner AH, Ellegaard M-BB, Christensen IJ, Bastholt L, Schmidt H. Fever and the use of paracetamol during IL-2-based immunotherapy in metastatic melanoma. Cancer Immunol Immunother. March 2015;64(3):349–355.

New Drug Update - Nivolumab/Relatlimab (Opdualag™)

Author: Madeline Kravitz and Nicole Camasura, PharmD Candidates 2023, The University of Saint Joseph School of Pharmacy & Physician Assistant Studies
Mentor: Austin Wilson, PharmD, MS, BCPS, BCCCP, The University of Texas MD Anderson Cancer Center

Review of Melanoma

Melanoma is a neoplasm of pigment-producing cells (melanocytes) that generally occurs cutaneously, but can initiate in the uvea, mucosal tissue, or other sites [1,2]. Although melanoma is less common than basal cell carcinoma and squamous cell carcinoma, it remains the most lethal of the primary cutaneous neoplasms [1,2]. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, it is estimated that there will be 99,780 new cases of melanoma and 7,650 melanoma-related deaths in 2022 [3]. Similar to other malignancies, the survival rate for melanoma is high when detected early, but significantly decreases from advanced or metastatic disease [1,2]. While metastatic melanoma has historically low survival and response rates to traditional chemotherapy, the recent development of novel therapeutics have resulted in improved patient survival and response trends [1,2]. In addition to traditional chemotherapy, radiation therapy, and surgery (wide excision, lymphatic mapping and sentinel lymph node biopsy, or lymph node dissection), treatment modalities for melanoma include immunotherapy and targeted therapy [4,5].

Immunotherapy options for melanoma include: high-dose interleukin-2 [HD IL-2], checkpoint inhibitors, viral therapy, interferon therapy, and combination immunotherapy [4,5]. Interleukin-2 is a cytokine produced endogenously by activated T cells with the use of HD IL-2 resulting in durable tumor responses [4,5]. However, the use of HD IL-2 has been limited due to its high toxicity profile and requirement for intensive inpatient management. In contemporary clinical practice these limitations have led to HD IL-2 being replaced by checkpoint inhibitors [4,5]. Immune checkpoint inhibitors in melanoma include monoclonal antibodies that inhibit programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) [4,5].Programmed death-1 is an inhibitory receptor found on the surface of T cells that interacts with its ligand, PD-L1, to downregulate T cell response [4,5]. PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab in combination with select targeted therapies) block the PD-1/PD-L1 protein interaction to inhibit PD-1 activity [4,5]. Cytotoxic T-lymphocyte associated molecule-4 is an inhibitory checkpoint receptor that blocks T-cell activation [4,5]. Inhibitors of CTLA-4 (ipilimumab) antagonize this inhibitory effect [4,5]. Viral therapy for melanoma includes genetically modified attenuated herpes simplex virus 1 (HSV-1) oncolytic virus (talimogene laherparepvec), which has been designed to replicate and destroy tumors upon intralesional injection [4,5]. Other immunotherapy agents include high-dose interferon alfa-2b and pegylated interferon alfa-2b as adjuvant therapies to delay recurrence [4,5]. However, routine use of interferon therapy in melanoma is not recommended due to associated adverse effects and unknown benefit [4,5]. FDA-approved combination immunotherapy includes nivolumab/ipilimumab and nivolumab/relatlimab (described in Section 2) [4,5].

Nivolumab/Relatlimab (Opdualag™) (Continued)

Although different treatments are recommended for each stage of melanoma, treatment regimens are based on individual diagnosis and specific needs [6]. Surgical excision is the treatment of choice for early cutaneous melanoma [4,6]. In general, immunotherapy and targeted therapy are preferred for high-risk, unresectable, or distant metastatic melanoma [4,6]. For patients who are not eligible for the recommended therapy, cytotoxic therapy may be considered [4,6]. The only FDA-approved chemotherapy for melanoma is dacarbazine [4,6]. Other cytotoxic agents that have been used include temozolomide, paclitaxel, albumin bound paclitaxel, and carboplatin/paclitaxel [4,6].

Nivolumab/relatlimab and the RELATIVITY-047 trial

Nivolumab/relatlimab (Opdualag™) was granted FDA approval on March 18, 2022, for the treatment of unresectable or metastatic melanoma. Nivolumab is currently approved as monotherapy or in combination therapy for various malignancies including melanoma, non-small cell lung cancer, Hodgkin lymphoma, and colorectal cancer [7]. Relatlimab is a novel IgG4 agent that targets the lymphocyte-activation gene 3 (LAG-3) coreceptor expressed on T cells. The LAG-3 pathway is another but less understood inhibitory checkpoint pathway that can lead to carcinogenesis if overexpressed, such as in Hodgkin lymphoma, colorectal cancer, ovarian cancer, and melanoma. Anti-LAG-3 activity results in similar anti-tumor effects as the PD-1 inhibition exerted by nivolumab, and when combined, dual checkpoint inhibition results in a synergistic anti-tumor response [8].

The RELATIVITY-047 trial was a phase 2/3, randomized, double-blind trial that compared progression-free survival (PFS) in unresectable or metastatic melanoma with either 480 mg nivolumab/ 160 mg relatlimab (n=355) or 480 mg nivolumab (n=359). Participants were stratified according to LAG-3 expression (≥1% versus <1%), PD-L1 expression (≥1% versus <1%), BRAF V600 mutation status, and metastasis stage (M0 or M1 with normal LDH levels versus M1 with elevated LDH levels). With a median follow-up of 13.2 months, the median PFS was 10.1 months in the nivolumab/relatlimab cohort and 4.6 months in the nivolumab group (HR, 0.75; 95 CI%, 0.62 to 0.92; p=0.006). At 12 months, 47.7% of patients on the combination therapy had PFS compared to 36.0% on monotherapy. Subgroup analyses found that there is a benefit of using nivolumab/relatlimab in patients regardless of LAG-3 expression, tumor burden, metastasis stage, or LDH levels. Benefit in PFS was seen with PD-L1 expression < 1% (HR, 0.66; 95% CI, 0.51 - 0.84) and wild-type BRAF mutations (HR, 0.76; 95% CI, 0.59 - 0.98) [9].

The most common infusion-related adverse events experienced by the nivolumab/relatlimab cohort were pruritus (23.4%), fatigue (23.1%), and rash (15.5%). Pruritus was limited to grade 1 or 2 reactions, and 1.1% of fatigue cases and 0.8% of rashes were grade 3 or 4. Common immune-mediated adverse events include hypothyroidism or thyroiditis (18.0%), rash (9.3%), and diarrhea or colitis (6.8%). Grade 3 or 4 reactions occurred in 0.6% of immune-mediated rashes and 1.1% of diarrhea cases, and in no cases of hypothyroidism.9 The appropriate dose adjustment to follow depends on the severity of the adverse reaction (Table 2) [7].

Nivolumab/Relatlimab (Opdualag™) (Continued)

T**able 1. Subgroup analysis of progression-free survival**

Subgroup	Unstratified Hazard Ratio for Progression or Death (95% CI)
PD-L1 expression	
<1%	0.66 (0.51 - 0.84)
≥1%	0.95 (0.68 - 1.33)
BRAF mutation status	
Wild-type	0.76 (0.59 - 0.98)
Mutant	0.74 (0.54 - 1.03)
Metastasis stage	
M0, M1, and normal LDH	0.71 (0.55 - 0.92)
M1 and elevated LDH	0.79 (0.58 - 1.09)

Table 2. Recommended dose modifications for adverse reactions

Adverse reaction	Severity	Dose Modification
Infusion-related reactions	Grade 1 or 2	Interrupt or slow infusion rate
	Grade 3 or 4	Permanently discontinue
Immune-mediated reactions		
Colitis	Grade 2 or 3	Withhold
	Grade 4	Permanently discontinue
Hypothyroidism or thyroiditis	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Exfoliative dermatologic reaction	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue

Future Directions

Since the publication of the RELATIVITY-047 trial, the National Comprehensive Cancer Network guidelines for cutaneous melanoma have been updated to include nivolumab and relatlimab as a first-line, preferred regimen for metastatic or unresectable disease [10]. Nivolumab/relatlimab has shown promising results in untreated metastatic melanoma in the RELATIVITY-047 trial, and could have benefit in additional melanoma cohorts. The dual immunotherapy agent is currently under investigation in the phase 3 RELATIVITY-098 trial and is set to complete in December 2025.

Nivolumab/Relatlimab (Opdualag™) (Continued)

The trial is assessing recurrence-free survival with the use of adjuvant nivolumab/relatlimab versus nivolumab after complete resection of stage III or IV metastatic melanoma [11]. Relatlimab is also under investigation as a combination therapy with ipilimumab in a phase 1/2 trial in patients with unresectable or metastatic melanoma that has advanced while on nivolumab [12]. Additionally, there are unanswered questions regarding the efficacy and safety of nivolumab with relatlimab versus other combination immunotherapy options. Further research could include comparisons of combination immunotherapy such as nivolumab with ipilimumab versus nivolumab and relatlimab. In summary, relatlimab is a novel LAG-3 checkpoint inhibitor that has shown benefit in untreated metastatic melanoma and further supports the added benefit of dual checkpoint inhibition over monotherapy.

References

1. Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: Optimizing outcomes in melanoma. Nature Reviews Clinical Oncology. 2017;14(8):463-482. doi:10.1038/nrclinonc.2017.43
2. Pathak S, Zito PM. Clinical guidelines for the staging, diagnosis, and management of cutaneous malignant melanoma. StatPearls [Internet]. Updated 2022 Jul 4, 2022. Accessed August 1, 2022. https://www.ncbi.nlm.nih.gov/books/NBK572149/
3. National Cancer Institute. Cancer stat facts: melanoma of the skin. Accessed August 1, 2022. https://seer.cancer.gov/statfacts/html/melan.html.
4. American Society of Clinical Oncology. Melanoma: types of treatment. Updated July 8, 2022. Accessed August 1, 2022. https://www.cancer.net/cancer-types/melanoma/types-treatment#advanced-melanoma.
5. Terheyden P, Krackhardt A, Eigentler T. The systemic treatment of melanoma: The place of immune checkpoint inhibitors and the suppression of intracellular signal transduction. Deutsches Ärzteblatt international. 2019. doi:10.3238/arztebl.2019.0497
6. American Cancer Society. Treatment of melanoma by stage. Accessed August 1, 2022. https://www.cancer.org/cancer/melanoma-skin-cancer/treating/by-stage.html.
7. Opdivo. Prescribing information. Bristol-Myers Squibb. 2022.
8. Lythgoe MP, Liu DSK, Annels NE, Krell J, Frampton AE. Gene of the moth: lymphocyte-activation gene 3 (LAG-3). J Clin Pathol. 2021;74(9):543-7. doi: 10.1136/jclinpath-2021-207517
9. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab plus nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24-34. doi:10.1056/NEJMoa2109970
10. National Comprehensive Cancer Network. Melanoma: cutaneous. Version 3. 2022.
11. Bristol-Myers Squibb. A study to assess adjuvant immunotherapy with nivolumab plus relatlimab versus nivolumab alone after complete resection of stage III-IV melanoma (RELATIVITY-098). ClinicalTrials.gov identifier: NCT05002569. Updated August 1, 2022. Accessed August 1, 2022. https://clinicaltrials.gov/ct2/show/NCT05002569
12. Bristol-Myers Squibb. A study to assess safety and efficacy of relatlimab with ipilimumab in participants with advanced melanoma who progressed on anti-programmed cell death protein 1 (anti-PD-1) treatment. ClinicalTrials.gov identifier: NCT03978611. Updated May 18, 2022. Accessed August 2, 2022. https://clinicaltrials.gov/ct2/show/NCT03978611

New Drug Approvals

Authors: Linda Allworth, PharmD Candidate, UNC Eshelman School of Pharmacy & Gabrielle Hopkins, PharmD Candidate, Nova Southeastern University
Mentor: David Quach, PharmD, MPH, BCPS, BCOP, Bryan Medical Center, Lincoln, NE

Drug Name Generic (Brand)	Indication	Approval Date
Tebentafusp-tebn (Kimmtrak®)	HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.	January 25, 2022
Ciltacabtagene Autoleucel (Carvykti®)	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.	February 28, 2022
Nivolumab and relatlimab-rmbw (Opdualag®)	Patients 12 years and older with unresectable or metastatic melanoma.	March 18, 2022
Lutetium lu 177 vipivotide tetraxetan (Pluvicto®)	Adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have already been treated with androgen receptor (AR) pathway inhibition and taxane based chemotherapy.	March 23, 2022
Axicabtagene Cilleucel (Yescarta®)	Second-line treatment for adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or who has relapsed within 12 months of first-line chemoimmunotherapy.	April 1, 2022
Alpelisib (Vijoice®)	Adults and pediatric patients two years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.	April 6, 2022
Pegfilgrastim-pbbk (Fylnetra®)	Biosimilar to Neulasta®(pegfilgrastim), a granulocyte colony stimulating factor, used to reduce the incidence of neutropenia in patients undergoing chemotherapy.	May 26, 2022
Rituximab-arrx (Riabni®)	Biosimilar to Rituxan® (rituximab), a CD20-directed cytolytic, indicated for the treatment of adults with non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia (CLL).	June 3, 2022
Dabrafenib (Tafinlar®) in combination with Trametinib (Mekinist®)	Adult and pediatric patients six years of age or older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.	June 22, 2022
Lisocabtagene Maraleucel (Breyanzi®)	Adult patients with large B-cell lymphoma (LBCL) who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.	June 24, 2022

Reference: New Drug Approvals. (2022). Drugs.Com. https://www.drugs.com/newdrugs.html

Updates in Non-Small Cell Lung Cancer

Author: Mentee: Susan Egbert, PharmD, RPh, PhD Candidate (Chemistry), University of Manitoba

Non-small cell lung cancer (NSCLC) is one of the most common malignancies and the leading cause of cancer-related mortality in America. The landscape of NSCLC treatment has drastically changed to now include targeted agents, including immunotherapy and KRAS agents. These agents have recently gained new indications in NSCLC in early and metastatic disease.

Mutations in Kirsten rat sarcoma virus (KRAS) have accounted for about 25-30% of NSCLC. KRAS mutations are the most prevalent genomic events in NSCLC (1). KRASG12C mutation, in which a glycine is substituted by cysteine at the 12th codon, is the most prevalent alteration in NSCLC. This mutation has become an area of interest for researchers developing new targeted agents for NSCLC.

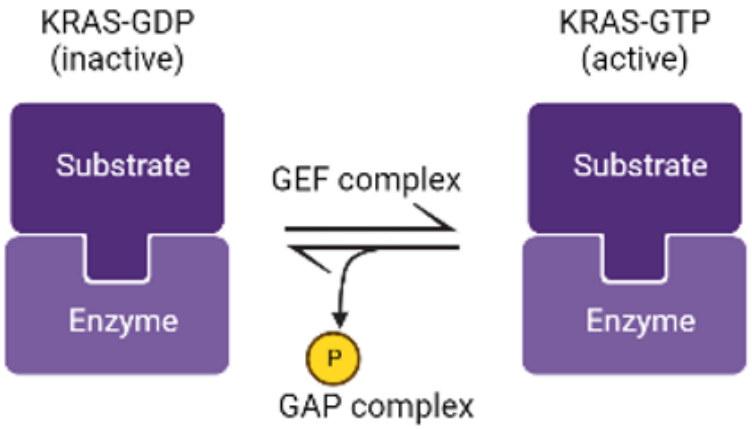

Figure 1 (2). KRAS inactive and active state where the substrate for inactive is GDP while active is GTP. When KRASG12C mutation happens further signaling becomes active and causes cell proliferation.

In Skoulidis et al., researchers investigated the usage of sotorasib against KRASG12C in advanced NSCLC. Sotorasib works by irreversibly inhibiting KRASG12C by binding into the pocket of the switch II region which traps the KRASG12C in the inactive state and prevents more oncogenic signaling. Skoulidis et al. conducted a phase 2 trial involving patients with advanced NSCLC with the KRAS p.G12C mutation. It included patients who were 18 years and older, had locally advanced or metastatic NSCLC with KRASG12C mutation, disease progression after immunotherapy or platinum-based chemotherapy, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1, and measurable disease. Patients were excluded if they had active untreated brain metastases, failed three or more lines of therapy, received systemic anticancer 28 days before the start of sotorasib therapy, or previous treatment with a KRAS G12C inhibitor.

Updates in Non-Small Cell Lung Cancer (Continued)

The primary outcome of the study was objective response, and the secondary outcomes were duration of response, disease control, time to response, progression free survival (PFS), overall survival (OS), and safety.

One hundred twenty-six patients enrolled in the study, but 124 patients had measurable disease. Thirty-seven percent of patients had an objective response with 4 patients experiencing a complete response. The median duration of response was 11.1 months and disease control, including stable disease, was seen in 80.6% of patients. The median PFS and OS were 6.8 months and 12.5 months, respectively. The most common side effects of any grade were diarrhea, nausea, and elevated ALT and AST. The study concluded that sotorasib had a durable response is patients with KRASG12C mutation in advanced or metastatic NSCLC.

The CheckMate 816 trial is an open-label, phase 3 trial assessing the effect of neoadjuvant nivolumab plus chemotherapy in resectable NSCLC (3). Patients were randomized to either receive nivolumab plus platinum therapy or platinum therapy alone. Patients were included in the study if they had resectable stage IB (≥4 cm) to IIIA NSCLC, ECOG-PS of 0 or 1, no previous anticancer therapy, and measurable disease (3). Patients found to have ALK translocations or EGFR mutations were excluded from the study. The coprimary endpoints were event-free survival (EFS) and pathological complete response. The secondary endpoints were major pathological response, time to death or distant metastases, and OS.

The median EFS was 31.6 months (95% CI; 30.2 to not reached) with nivolumab plus chemotherapy (NC) compared to 20.8 months (95% CI; 14.0-26.7) with chemotherapy alone (CA) (HR: 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). Pathological complete response was seen in 24% (95% CI, 18.0 to 31.0) of patients in the NC group compared to 2.2% (95% CI, 0.6 to 5.6) in the CA group (OR: 13.94; 99% CI, 3.49 to 55.75; P<0.001). The median OS was not reached in either group (HR: 0.57; 99.67% CI, 0.03 to 1.07; P = 0.008). The most common grade 3 or 4 events were neutropenia and decreased neutrophil count. The most common immunotherapy related event was rash. Investigators concluded that neoadjuvant nivolumab combined with chemotherapy in early NSCLC resulted in longer event-free survival in comparison to just chemotherapy alone without added side effects.

Targeted agents have now become the backbone of treatment in advanced NSCLC, and now early NSCLC. Sotorasib have shown a durable response in patients who have advanced or metastatic NSCLC with tolerable side effects. Nivolumab used in early resectable NSCLC improved EFS and complete response. These are a few agents that have recently gained indications in this disease.

Updates in Non-Small Cell Lung Cancer (Continued)

References:

1. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, Kato T, Curioni-Fontecedro A, Sacher A, Spira A, Ramalingam SS, Takahashi T, Besse B, Anderson A, Ang A, Tran Q, Mather O, Henary H, Ngarmchamnanrith G, Friberg G, Velcheti V, Govindan R. Sotorasib for Lung Cancers with KRAS p.G12C Mutation New England Journal of Medicine 2021;384: 2371-2381
2. Images created with BioRender.com
3. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR,Swanson SJ, Kerr K, Wang C, Ciuleanu TE, Saylors, GB, Tanaka F, Ito H, Chen KN, Liberman M, Vokes, Everett E, Taube JM, Dorange C, Cai J, Fiore J, Jarkowski A, Balli D, Sausen M, Pandya D, Calvet CY, and Girard, N.Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer New England Journal of Medicine 2022;386: 1973-1985
4. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer Lancet: Seminar 2021; 398: P535-554
5. Wakelee HA, Altorki NK, Zhou C, Csőszi T, Vynnychenko IO, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, Chen YM. IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). Lancet 2021: 398: 1344–57

Updates on High-Risk Medication Use in G6PD Deficiency

By: Anna Aycock, PharmD, PGY-2 Oncology Resident at The James Cancer Hospital at The Ohio State University
Mentor: Cyrine Haidar, PharmD, BCPS, BCOP, FASHP, Clinical Pharmacogenetics Coordinator at St. Jude Children's Research Hospital

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is a common enzyme deficiency in humans. It is estimated that over 400 million people worldwide are G6PD deficient (1) G6PD deficiency is most prevalent in people of African, Southeast Asian, and Mediterranean descent. The G6PD enzyme is the only mechanism by which red blood cells (RBCs) can reduce NADP to NADPH (2)Without G6PD, in the presence of oxidative stress, RBCs can lyse leading to acute hemolytic anemia (AHA) which can result in acute kidney injury and renal failure if left untreated (3). Clinical G6PD-deficiency testing can be performed by two types of methods: G6PD activity testing and genotyping. Activity testing is a method that measures the amount of G6PD enzyme in blood (4). This method is quick but is affected by several hematologic factors such as recent RBC transfusions, critical anemia, or abnormal leucocyte or elevated platelet count, and is not reliable in the setting of acute hemolysis (5). While point of care G6PD activity testing is available, this test is a send out test at most institutions with a turnaround time of several days. G6PD genotyping avoids the problems with hematologic factors, but may have a longer turnaround time, and must interrogate the most commonly known G6PDdeficient variants to be useful (6).

Common factors that precipitate AHA in people who are G6PD deficient are the ingestion of fava beans and certain medications (7). In 1989, the World Health Organization (WHO) released a list of medications to avoid in people with G6PD deficiency, (8) but many such lists include medications for which the evidence is weak or nonexistent. Online resources for clinicians and patients are confusing, with a lack of consensus about the medications list among different resources. As such, the Clinical Pharmacogenetics Implementation Consortium (CPIC), an international group of experts working to implement pharmacogenomics into routine patient care, recently published an updated guideline about medication use in the setting of G6PD deficiency (8-10). The update to the guideline classifies these medications as high, medium, or low-to-no risk based on a systematic review of the published evidence of the gene-drug associations and regulatory warnings. This updated guideline can be found at https://cpicpgx.org/cpic-guideline-for-g6pd/, all CPIC guidelines are freely available at www.cpicpgx.org

Of over 48 medications for which the evidence related to AHA was reviewed, only 7 medications were deemed as high-risk for causing AHA in G6PD deficiency (Table 1). Importantly, dapsone, methylene blue, toluidine blue, rasburicase, tafenoquine and primaquine at standard doses are still categorized as being associated with a high-risk of hemolysis in patients who are G6PD deficient. Several agents were downgraded from high or moderate risk to low-to-no risk (8,10). Notably, sulfa drugs -including sulfamethoxazole, a component of Bactrim®- have historically been purported to cause hemolysis when prescribed to patients with G6PD deficiency.

Updates on High-Risk Medication Use in G6PD Deficiency (Continued)

However, most of the published literature about this association is limited to case reports with various confounding factors for hemolysis, and several studies have shown its safety. This downgrade of sulfamethoxazole to a medication that is at low risk for hemolysis use in the setting of G6PD deficiency allows for the use of this agent for Pneumocystis Jiroveci Pneumonia (PJP) prophylaxis in immunocompromised patients. Nitrofurantoin, an agent widely used for the treatment and prophylaxis of urinary tract infections was downgraded to a medication to use with caution in patients with G6PD deficiency (10). Numerous studies have shown that aspirin at commonly prescribed doses (<1 g/day) is safe to use in the G6PD deficient patient population. Aspirin was therefore downgraded to a low-to-no risk medication (10). The guideline authors also found strong evidence towards dose specific recommendations of primaquine – an agent commonly used for the treatment of malaria. Given the increased prevalence of G6PD deficiency in malaria-endemic countries, consensus recommendations on safe dose-specific use of this anti-malarial agent are helpful (1,10). Finally, quinolone antibiotics were downgraded to the low-to-no risk category (10).

Pharmacists will play an essential role in incorporating these changes into clinical practice. From a systematic view, many health systems have built clinical decision support alerts notifying prescribers that a medication is contraindicated for use if the patient is G6PD deficient. These alerts need to be updated. At the individual practitioner level, pharmacists can play a role in educating the multi-disciplinary teams of these updated changes. Through these methods, patients with G6PD deficiency can experience optimized pharmacotherapy solutions.

Table 1. Medications to avoid or use with caution in patients with G6PD deficiency. Notable medications that were downgraded to low or no risk are also listed.

Drug	Hemolysis Risk Level
Dapsone	High
Methylene blue	High
Pegloticase	High
Primaquine -standard dose (0.25-0.5 mg/kg x14 days)	High
Rasburicase	High
Tafenoquine	High
Toluidine blue	High
Nitrofurantoin	Medium
Primaquine -medium dose (0.75 mg/kg x8 weeks)	Medium
Aspirin (< 1 g/day)	Low-to-no
Chloroquine	Low-to-no
Fluoroquinolones	Low-to-no
Hydroxychloroquine	Low-to-no
Phenazopyridine	Low-to-no
Primaquine (0.25 mg/kg once)	Low-to-no
Sulfamethoxazole and sulfa drugs	Low-to-no

Updates on High-Risk Medication Use in G6PD Deficiency (Continued)

References:

1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74. doi: 10.1016/S0140-6736(08)60073-2.
2. Gómez-Manzo S, Marcial-Quino J, Vanoye-Carlo A, Serrano-Posada H, Ortega-Cuellar D, González-Valdez A, Castillo-Rodríguez RA, Hernández-Ochoa B et al. Glucose-6-Phosphate Dehydrogenase: Update and Analysis of New Mutations around the World. Int J Mol Sci. 2016;17(12):2069. doi: 10.3390/ijms17122069.
3. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74. doi: 10.1016/S0140-6736(08)60073-2.
4. Gregg XT, Prchal JT. Red cell enzymopathies. In: Hoffman R, ed. Hematology: basic principles and practice. 4th ed. Philadelphia: Churchill Livingstone, 2000:657–660.
5. Frank JE. Diagnosis and management of G6PD deficiency. Am Fam Physician. 2005;72(7):1277-1282.
6. Beutler E. G6PD deficiency. Blood. 1994;84(11):3613-3636.
7. Richardson SR, O'Malley GF. Glucose 6 Phosphate Dehydrogenase Deficiency. StatPearls; 2022. Accessed August 16, 2022. https://www.ncbi.nlm.nih.gov/books/NBK470315/
8. Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. Bull World Health Organ. 1989;67(6):601-611.
9. The Clinical Pharmacogenetics Implementation Consortium (CPIC). What is CPIC?. US Department of Health & Human Services. 2021. Accessed August 16, 2022. https://cpicpgx.org/
10. Roseann S. Gammal, Munir Pirmohamed, Andrew A. Somogyi et al. Expanded Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Medication Use in the Context of G6PD Genotype. Clin Pharmacol Ther. In press.

Rucaparib as First Line Maintenance Therapy for Ovarian Cancer: A Review of the ATHENA-MONO/GOG-3020/ENGOT-ov45 Clinical Trial Introduction

Author: Zach Krauss, MBA, PharmD Candidate, Cedarville University School of Pharmacy
Mentor: Farah Raheem, Pharm.D., BCOP, Clinical Pharmacist Specialist - Hematology/Oncology, Mayo Clinic Arizona, Phoenix, AZ

Introduction

Ovarian cancer is the fifth leading cause of death from cancer among women in the U.S. and is accounting for more deaths than other cancers of the female reproductive system (1). In the U.S., there is an estimated 19,880 new cases and 12,810 deaths from ovarian cancer in 2022. The median age at diagnosis is 63 years.The estimated 5-year survival is 49.7% across all disease stages.More than half of patients present with metastatic disease with a 5-year survival rate of 30.8% (2).

Ovarian cancer is a heterogeneous disease with several histologic subtypes including serous (~60%), endometrioid (~10%–20%), clear cell (<10%), transitional (6%), mucinous (<5%), and undifferentiated (<1%) subtypes (3). Risk factors include nulliparity, family history, BRCA 1/2 mutations, and Lynch syndrome. Mutations in BRCA1/2 account for 15% of ovarian cancer cases (4,5).

BRCA or breast cancer gene is a tumor suppressor gene that produces proteins responsible for repairing double strand DNA breaks by way of the homologous recombination (HR) repair pathway and play an important role in maintaining the genetic stability of a cell. In cells with homologous recombination deficiency (HRD), DNA damage can accumulate and cells become unstable leading to increased susceptibility to developing malignancy including ovarian cancer (6). HRD with or without BRCA 1/2 deleterious mutations can occur in tumors independently. Defects in the HR pathway can result in DNA structural changes and loss of heterozygosity (LOH) is identified as a potential marker of HRD (7).

Ovarian cancer cells harboring HRD with or without deleterious BRCA 1/2 mutations are deficient in the repair mechanism of DNA double strand breaks leaving these tumors highly dependent on the repair pathway for single-strand breaks.This pathway is regulated by the poly adenosine diphosphate polymerase or PARP enzymes. Inhibition of PARP causes cell death due to accumulation of DNA damage. In addition to catalytic inhibition, PARP inhibitors form DNA complexes leading to PARP trapping at sites of DNA damage resulting in synthetic lethality (8).

Defects in BRCA1/2 and other HR pathways have clinical and therapeutic implications in ovarian cancer. Therefore, upon diagnosis of ovarian, the National Comprehensive Cancer Network (NCCN) guidelines recommend germline and somatic genetic testing to identify the status of BRCA1/2, HR and LOH. Tumor molecular analysis in the upfront and recurrent setting can help identify patients who can benefit from treatment with PARP inhibitors (9).

Rucaparib Review (Continued)

Primary debulking surgery is the mainstay therapy for patients with resectable disease, and platinum-based chemotherapy is considered standard of care,first-line treatment in the (neo)adjuvant setting as well as recurrent, platinum-sensitive disease. PARP inhibitors have been utilized in practice as maintenance therapy for ovarian cancer in the first line and recurrent setting after achieving a partial or complete response to primary treatment with surgery and platinum-based chemotherapy (9).

Current FDA approved PARP inhibitors for maintenance therapy in patients with ovarian cancer after achieving response to platinum-based chemotherapy include olaparib, niraparib, and rucaparib. Olaparib monotherapy is approved as first line maintenance treatment for germline or somatic BRCA-mutated ovarian cancer and as recurrent maintenance therapy regardless of BRCA status (10-12). Olaparib in combination with bevacizumab is approved as first line maintenance therapy in HRD-positive ovarian cancer (13). When olaparib used as maintenance therapy, treatment is continued until progression or unacceptable toxicity or completion of 2 years of therapy. Olaparib monotherapy is being investigated as first line maintenance therapy in patients with BRCA1/2 wild-type (WT) ovarian cancer.14Maintenance olaparib as monotherapy or in combination with bevacizumab was shown to improve progression free survival (PFS) when compared to placebo (11-13, 15).

Niraparib monotherapy is approved as maintenance therapy for ovarian cancer in the first line and recurrent setting regardless of BRCA or HRD status. Niraparib can be continued until disease progression, unacceptable toxicity or up to 36 months of treatment. PFS was improved with first line and recurrent maintenance niraparib compared to placebo in the overall population regardless of BRCA or HRD status. However, patients whose tumors harbor BRCA mutations and HRD derived larger magnitudes of benefits (16-17).

Rucaparib is currently only FDA approved as maintenance therapy in the recurrent setting regardless of BRCA or HRD status. Rucaparib maintenance improved PFS when compared to placebo (18-19). Here, we provide an overview of ATHENA-MONO, the first randomized, phase III clinical trial investigating rucaparib monotherapy as first line maintenance treatment for ovarian cancer after achieving response to platinum-based chemotherapy.

The ATHENA-MONO Clinical Trial

Background

ATHENA is a multicenter, randomized, double-blind, phase III clinical trial that investigated the efficacy of rucaparib as first line maintenance therapy for newly diagnosed ovarian cancer with or without HRD. ATHENA clinical trial consists of four treatment arms (rucaparib, nivolumab, rucaparib + nivolumab, placebo). ATHENA includes two independently powered parts assessing first line maintenance rucaparib monotherapy versus placebo (ATHENA-MONO) and rucaparib + nivolumab versus rucaparib monotherapy (ATHENA-COMBO). Results of ATHENA-COMBO are not yet mature (20).

Rucaparib Review (Continued)

Methods

Included patients were ≥ 18 years with newly diagnosed stage III-IV, high-grade ovarian, fallopian tube, or primary peritoneal cancer who had completed cytoreductive surgery before or after chemotherapy.Patients had to have completed 4 to 8 cycles of platinum-based chemotherapy. Bevacizumab was only allowed with chemotherapy and not during the maintenance phase. Response to surgery and chemotherapy was required. Key exclusion criteria were diagnosis with pure sarcoma and having central nervous system metastases (20).

In ATHENA-MONO, patients had to be randomized within 8 weeks of their last dose of chemotherapy in 4:1 ratio to rucaparib 600 mg twice daily starting on cycle 1 day 1 + IV placebo every 28 days starting on cycle 2 day 1 or oral placebo + IV placebo given at the same dosing frequency. Rucaparib treatment could continue for up to 24 months or until disease progression or unacceptable toxicity (20).

Study analyses were split into two groups, ATHENA-MONO for rucaparib monotherapy compared to placebo and ATHENA-COMBO, which compared rucaparib monotherapy to the rucaparib + nivolumab combination therapy arm. The primary outcome was PFS. Key secondary outcomes include overall survival (OS), objective response rate (ORR), duration of response (DOR), and safety. The significance level for ATHENA-MONO was set at two-sided P of 0.025 (20).

Results

Between 2018 and 2020, 427 patients were randomized to rucaparib monotherapy arm and 111 patients to the placebo arm. In the intention to treat (ITT) population, the median age was 61 years, > 75% were white, > 30% from North America, majority had FIGO stage III (75.6% in rucaparib vs 70.3% in placebo) and serous histology (89.9% in rucaparib vs 95.5% in placebo), only 21% in both arms had BRCA mutations and 22% were LOH high/BRCA-WT. The rate of complete resection was > 60% in both arms. More patients in the rucaparib vs placebo arm had complete response to primary surgery and chemotherapy (17.1% vs 9.9%) and received bevacizumab (19.7% vs 10.8%) (20).

At a median follow-up of 26.1 months, the median PFS was 28.7 months in the rucaparib arm compared to 11.3 months in the placebo arm in the HRD population (HR, 0.47; 95% CI, 031- 0.72; P 0.0004). In the ITT population, PFS was also significantly improved with rucaparib with median PFS 20.2 months vs 9.2 months in placebo (HR, 0.52; 95% CI, 0.40-0.68, P < 0.0001). PFS benefit with rucaparib was observed across all subgroups including any HRD status. Secondary outcomes are summarized in Table 1. Overall survival data is not yet mature. The most common adverse events in the rucaparib arm (reported incidence ≥ 40%) were nausea, fatigue, anemia and increased ALT/AST. Additional safety outcomes are reported in Table 2 (20).

Conclusions

Rucaparib as first line maintenance monotherapy for newly diagnosed, platinum-sensitive ovarian cancer demonstrated significant improvement in PFS regardless of BRCA and HRD status.

Rucaparib Review (Continued)

Strengths of the study are inclusion of patients without HRD at high proportion and stage III regardless of residual disease status, which can expand treatment options to disease and molecular subsets with unmet need. Limitations include the 4:1 randomization leading to a relatively small number of patients in the placebo arm, which can limit interpretation of subgroup analyses.

The findings from the ATHENA-MONO trial provide a promising treatment option with rucaparib for patients with newly diagnosed ovarian cancer regardless of HRD status with adverse events consistent with the known safety profile of rucaparib. Rucaparib is currently FDA approved only as maintenance therapy for ovarian cancer in the recurrent setting irrespective of HRD status and niraparib is the only PARP inhibitor with approved first line indication in this setting. Rucaparib, if approved as first line maintenance therapy, would expand treatment options, especially for patients who are unable to tolerate niraparib despite utilizing individualized dosing algorithms. Long term results of OS and findings from the ATHENA-COMBO trial are awaited.

Table 1: Secondary Efficacy Outcomes of Rucaparib versus Placebo in the ATHENA-MONO Clinical Trial (20)

Treatment Groups	Objective Response Rate	Complete Response[n (%)]	Partial Response	Stable Disease	Duration of Response (months)
Rucaparib, HRD	58.8% (10/17)	0	10 (58.8)	6 (35.5)	16.7
Placebo, HRD	20.0% (1/5)	0	1 (20.0)	2 (40.0)	5.5
Rucaparib, ITT	48.8% (20/41)	1 (2.4)	19 (46.3)	10 (24.4)	22.1
Placebo, ITT	9.1% (1/11)	0	1 (9.1)	4 (36.4)	5.5

Table 2: Safety Outcomes of Rucaparib versus Placebo in the ATHENA-MONO Clinical Trial (20)

Group	Dose Reductions and/or Interruptions [n (%)]	Dose discontinuations [n (%)]	Reasons for dose reduction/discontinuations	Rate of AML/MDS
Rucaparib	271 (63.8)	50 (11.8)	Most common reason was anemia/decreased hemoglobin	2 (0.4%)
Placebo	24 (21.8)	6 (5.5)		0

Rucaparib Review (Continued)

Table 3: FDA Approved PARP Inhibitors for Ovarian Cancer (21-24)

Drug name	Dosing	Place in Therapy/Indication for Ovarian Cancer	Renal/Hepatic Dosing	Common Adverse Events
Rucaparib	600 mg twice daily	Maintenance in recurrent disease with any BRCA or HRD status	No renal adjustment needed for CrCl ≥ 30 mL/min (not studied in CrCl <30 mL/min) No adjustment required in mild/moderate hepatic impairment (not studied in severe impairment)	Fatigue, nausea, vomiting, anemia, thrombocytopenia, increased ALT, constipation, diarrhea
Olaparib	300 mg twice daily	First line monotherapy maintenance in germline or somatic BRCA mutated only First line, combination with bevacizumab in HRD positive only Recurrent maintenance therapy, any BRCA or HRD status Treatment for refractory, advanced setting in BRCA mutated only	Moderate renal impairment (CrCl 31-50 mL/min), reduce starting dose to 200 mg BID No required adjustment in mild/moderate hepatic impairment	Nausea, vomiting, anemia, fatigue, constipation, diarrhea, myalgia, rash
Niraparib	300 mg daily (200 mg daily if baseline weight <77 kg or platelets <150,000)	First line and recurrent maintenance in any BRCA or HRD status Treatment of recurrent disease after 3 or more lines of prior chemotherapy in HRD positive disease	No renal adjustment required (not studied in CrCl <30 mL/min) Moderate hepatic impairment (total bilirubin ≥1.5 to 3 × ULN and any AST), reduce starting dose to 200 mg once daily	Nausea, vomiting, anemia, neutropenia, thrombocytopenia, hypertension, rash, headache

Rucaparib Review (Continued)

References:

1. American Cancer Society Website. Key Statistics for Ovarian Cancer. Updated January 12, 2022. Accessed August 23, 2022. https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.htm..
2. National Cancer Institute Website. Cancer Stat Facts: Ovarian Cancer. 2022. Accessed August 7, 2022. https://seer.cancer.gov/statfacts/html/ovary.html
3. Lalwani N, Prasad SR, Vikram R, Shanbhogue AK, Huettner PC, Fasih N. Histologic, molecular, and cytogenetic features of ovarian cancers: implications for diagnosis and treatment. Radiographics. 2011;31(3):625-646. doi:10.1148/rg.313105066.
4. Lilyquist J, LaDuca H, Polley E, et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. Gynecol Oncol. 2017;147(2):375-380. doi:10.1016/j.ygyno.2017.08.030.
5. Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2016;2(4):482-490. doi:10.1001/jamaoncol.2015.5495.
6. Creeden JF, Nanavaty NS, Einloth KR, et al. Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021;21(1):1154. Published 2021 Oct 28. doi:10.1186/s12885-021-08863-9
7. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer. 2012;107(10):1776-1782. doi:10.1038/bjc.2012.451.
8. Dziadkowiec KN, Gąsiorowska E, Nowak-Markwitz E, Jankowska A. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. Prz Menopauzalny. 2016;15(4):215-219. doi:10.5114/pm.2016.65667.
9. National Comprehensive Cancer Network.Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 22, 2022.
10. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379(26):2495-2505. doi:10.1056/NEJMoa1810858.
11. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial [published correction appears in Lancet Oncol. 2017 Sep;18(9):e510]. Lancet Oncol. 2017;18(9):1274-1284. doi:10.1016/S1470-2045(17)30469-2.
12. Poveda A, Floquet A, Ledermann JA, et al. 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. Lancet Oncol. 2021;22(5):620-631. doi:10.1016/S1470-2045(21)00073-5.
13. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361.

Rucaparib Review (Continued)

References:

14. Saevets V, Yin R, Zhu J, Chen C, Ah-See ML, Wu X. MONO-OLA1: a randomized, Phase III study of olaparib maintenance monotherapy in patients with BRCA wild-type advanced ovarian cancer following response to first-line platinum-based chemotherapy. Poster presented at: 2022 SGO Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, Arizona. Accessed March 18, 2022. Abstract 334.
15. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer. 2018;119(9):1075-1085. doi:10.1038/s41416-018-0271-y.
16. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962.
17. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310.
18. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2017 Oct 28;390(10106):1948]. Lancet. 2017;390(10106):1949-1961. doi:10.1016/S0140-6736(17)32440-6.
19. Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(5):710-722. doi:10.1016/S1470-2045(20)30061-9.
20. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45) [published online ahead of print, 2022 Jun 6]. J Clin Oncol. 2022;JCO2201003. doi:10.1200/JCO.22.01003
21. Product Information: RUBRACA(R) oral tablets, rucaparib oral tablets. Clovis Oncology Inc (per FDA), Boulder, CO, 2020.
22. Micromedex Solutions. Rubraca. Greenwood Village, CO: Truven Health Analytics 2022 .Accessed August 7th, 2022.
23. Product Information: ZEJULA(R) oral capsules, niraparib oral capsules. GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2020.
24. Product Information: LYNPARZA(R) oral tablets, olaparib oral tablets. AstraZeneca Pharmaceuticals LP (per FDA), Wilmington, DE, 2022.

Promotions, Awards, Publications, Presentations, and Other Achievements

Promotions

- Donald Moore: Clinical Oncology Pharmacy Manager, Levine Cancer Institute, Atrium Health.
- Amanda Seddon: Associate Professor, Midwestern University College of Pharmacy, Downers Grove Campus.

Awards

- Justin Arnall: 2022 ASTCT Pharmacy Special Interest Group New Practitioner Award, American Society of Transplantation and Cellular Therapy.
- Mark Pulver: Pfizer Scholarship, Kappa Psi Pharmaceutical Foundation.

Publications

- Wyatt H, Zuckerman AD, Hughes ME, **Arnall J**, Miller R. Addressing the challenges of novel oncology and hematology treatments across sites of care: specialty pharmacy solutions. J Oncol Pharm Pract 2022;28:627-34.
- Tran TB, **Arnall JR,** Kleiboer B, et al. Recombinant von Willebrand factor for perioperative bleeding management in pediatric patient with allergy to plasma-derived von Willebrand factor [letter]. Pediatr Blood Cancer 2022 Aug 4. [Epub ahead of print]
- Chojecki AL, **Arnall J,** Boselli D, et al. Outcomes and hospitalization patterns of patients with acute myelogenous leukemia treated with frontline CPX-351 or HMA/venetoclax. Leuk Res 2022;119:106904.
- Chojecki AL, DiSogra KY, **Arnall J,** et al. Optimization of physician and specialty pharmacy clinical workflow in assessment of risk category and symptom burden in patients with myelofibrosis (MF) [letter]. Leuk Lymphoma 2022;63:1515-7.
- **Gatwood KS,** Ali A. Faculty perspectives: through the pharmacists' lens: a deep dive into the practice dynamics in graft-versus-host disease. J Hematol Oncol Pharm June 2022.
- Gatwood J, Dashputre A, Rajpurohit A, **Gatwood K**, et al. Medication adherence among adults with comorbid conditions initiating oral anticancer agent therapy for multiple myeloma. JCO Oncol Pract 2022 Jun 14. [Epub ahead of print]
- Abernathy K, Perciavalle M, **Gatwood K,** et al. Real-world analysis of tumor lysis syndrome in patients started on venetoclax combination for acute myeloid leukemia. J Oncol Pharm Pract 2022 Aug 9. [Epub ahead of print]
- Pamulapati LG, **Hickey Zacholski E**. Research mentorship (Chapter 2). In: Bentley J, Pate A, Aparasu R, eds. Student Handbook for Pharmacy Practice Research, 1st ed. McGraw-Hill Education, 2022.
- **Moore DC**, Eagers K, Janes A, et al. Tafasitamab and lenalidomide for relapsed/refractory diffuse large B-cell lymphoma in a patient on chronic intermittent hemodialysis. J Oncol Pharm Pract 2022 May 18. [Epub ahead of print]
- **Moore DC**, Elmes JB, **Arnall JR**, et al. Immune checkpoint inhibitor-induced acquired haemophilia: a pharmacovigilance analysis of the FDA adverse event reporting system. Haemophlia 2022 Jul 27. [Epub ahead of print]

Promotions, Awards, Publications, Presentations, and Other Achievements (Continued)

Publications (Continued)

- **Moore DC**, Elmes JB, **Arnall JR**, et al. Acquired thrombotic thrombocytopenic purpura associated with immune checkpoint inhibitors: a real-world study of the FDA adverse event reporting system. Int Immunopharmacol 2022;110:109015.
- **Moore DC**, Peery MR, Tobon KA, **Raheem F**, et al. New and emerging therapies for the treatment of relapsed/refractory diffuse large B-cell lymphoma. J Oncol Pharm Pract 2022 Apr 26. [Epub ahead of print]
- **Moore DC**. 2020-2021 drug updates: investigational therapeutics in the pipeline. J Adv Pract Oncol 2022;13:286-91.
- **Parish PC**, **Moore DC**, Wayman M, **Arnall J.** Evaluation of pharmacist impact on patients initiating eculizumab for atypical hemolytic uremic syndrome in the inpatient setting. Ann Pharmacother 2022 Jul 29. [Epub ahead of print]
- Menezes MCS, **Raheem F**, Mina L, et al. PARP inhibitors for breast cancer: germline BRCA1/2 and beyond. Cancer 2022. [In press]
- Patel P, Robinson PD, Wahib N, Cheung P, Wong T, Cabral S, Parker A, Cohen M, Devine K, Gibson P, Holdsworth MT, Neumann E, Orsey A, Phillips R, Spinelli D, **Thackray J,** et al. Interventions for the prevention of acute phase chemotherapy-induced nausea and vomiting in adult and pediatric patients: a systematic review and meta-analysis. Support Care Cancer 2022 Aug 12. [Epub ahead of print]

Presentations

- **Justin Arnall**: Faculty for the ASHP certificate course on Non-Malignant Hematology.
- **Donald Moore**:
  - Rapidly Evolving Treatment Landscape for Relapsed/Refractory Myeloma: Integrating the Latest Data to Transform Care. Clinical Care Options/ProCE; July 2022; virtual.
  - Educator Essentials: Propel Your Professional Development with ASHP's Guided Mentorship Program. ASHP Official Podcast; June 22, 2022.
  - Faculty for the ASHP certificate course on Non-Malignant Hematology
- **Farah Raheem**: Use of PARP Inhibitors in Breast Cancer: Implications for Pharmacy Practice. Pharmacy Times.

Other Notable Achievements

- **Jessica Zhao:** Appointed as Chair, ACCP Residency Advisory Committee.

Announcements

Incoming HO PRN PRN Officers and ACCP Global Conference on Clinical Pharmacy

Chair: Erin Hickey Zacholski, PharmD, BCOP
Chair-Elect: Farah Raheem, PharmD, BCOP
Secretary/Treasurer: Nikola Paulic, PharmD

Hem/Onc PRN Specific Programing
Hem/Onc PRN & Pharmaceutical Industries PRN Focus Session – 10/15/22 – 3:30-5:00 pm PDT, Continental Ballroom 6

Hem/Onc PRN Business Meeting – 10/16/22 – 6:30-8:30 PDT, Union Square Rooms 17 & 18

Facebook and Twitter Pages

Follow us on Facebook and on Twitter or @HemOnc_ACCP for our posts!

Please send Claire Schumann (claire.schumman@nm.org) and David Quach (david2quach@gmail.com) articles and ideas you would like to see posted!

If you have ideas for greater social media engagement we would especially enjoy hearing from you!

Ideas for the Next Newsletter

Please submit any ideas you may have for improving the newsletter to the PRN leadership or email Jared Vega (jvega@cedarville.edu) and David Quach (david2quach@gmail.com).

If you would like to be featured in the fall edition, whether it be a member spotlight, or a clinical write-up, let us know!

Thank you!

The PRN leadership thanks everyone who has served on our various committees as well as our members who engages on a regular basis!