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REVIEW

Managing Adverse Effects of Novel Therapeutic Agents in Gynecologic Malignancies

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Abstract

Gynecologic cancer treatments have evolved significantly. Several targeted therapies are approved for use in combination with cytotoxic therapy, as monotherapy or as maintenance therapy following first- or second-line treatment. These new agents compel the need to educate the medical community on the management of "new" side effects. This review provides medical teams who care for patients with gynecologic malignancies, a succinct compilation of reported adverse events (AEs) and their management strategies when using targeted therapy. New for gynecologic cancers are immune checkpoint inhibitors related AEs such as endocrinopathies and colitis. Ocular AEs with tissue factor-directed antibody–drug conjugates (ADCs), as well as a plethora of AEs encountered with use of anti-angiogenic, poly(ADP) ribose polymerase (PARP) inhibitors, mitogen-activated protein kinase (MEK) inhibitors, and other tyrosine kinase receptor inhibitors. Oncologists, hospitalists, and emergency department teams and outpatient providers may benefit from a convenient reference source of commonly reported AEs of targeted agents with strategies for early diagnosis, management recommendations, and dose modifications. New therapies in gynecologic cancers have introduced lesser-known side effects. This review compiles AEs data with their reported management strategies. Clinicians/oncologists from community to emergency will benefit from this resource.

Keywords Gynecologic cancers · Management of adverse events · Immune checkpoint inhibitors · PARP inhibitors · MEK inhibitors · Anti-angiogenic agents · NTRK inhibitors · Antibody–drug conjugates

Introduction

Several novel therapeutic agents have recently been utilized as treatment options for gynecologic malignancies. Traditional cytotoxic therapies have limited survival data, and new novel therapies build upon these overall survival (OS) and progression-free survival (PFS) rates. Many trials have evaluated poly adenosine diphosphate-ribose polymerase inhibitor (PARPi) treatments, targeted therapies such as anti-angiogenic agents, kinase inhibitors, and immunotherapies which have since led to the development of the US Food and Drug Administration (FDA) approval for use in gynecologic malignancies [1–6, 7••, 8]. An extensive compilation of clinical evidence for new targeted therapies in gynecologic cancers was recently published and also highlights promising investigational agents with phase I/II data [9••]. In fact, over the past 2 years alone, there are at least ten new drugs presented for use in gynecologic malignancies [10–12].

Treatment-related adverse events (AEs) of these newer agents are less widely known. Managing these AEs (treatment, holding parameters, and dose modifications) are clinically relevant to mitigate symptoms early-on and prevent delay of therapy. The purpose of this review is to provide an overview of the reported AEs and potential management approaches/options for clinical practice

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regarding newer targeted and immunotherapeutic agents for gynecologic malignancies, focusing on widely used therapeutic agents (based on phase II/III trials and the FDA approval). Given the rapidly changing landscape and indication for use of these drugs or class of drugs, we focused on those most commonly used (Fig. 1). Note that within-class AEs are similar, thus similarly managed.

Methods

For this narrative review, keywords such as gynecologic cancers, adverse events (and management of), immune checkpoint inhibitors, PARP inhibitors; MEK inhibitors; anti-angiogenic agents, NTRK inhibitors, and antibody–drug conjugates, etc., were primarily used to search and review for publications on Google, PubMed, Cochrane Reviews, established guidelines published by professional agencies (such as ASCO, NCCN, and SGO), and the NIH National Library of Medicine during the past decade. Drug package inserts were also referenced as necessary. Additional article retrieval was guided by the references of well-cited publications and relevant information were summarized in perspectives.

Targeted Therapies

Anti-angiogenic Agents

Mechanism of Action

Angiogenesis has long been known as a key element to the survival and metastasis of cancer cells. Inhibition of angiogenesis is done by reducing the production of the pro-angiogenic factors, thereby preventing them from binding to their target and blocking their activity. Vascular endothelial growth factor (VEGF) inhibitors have been found to inhibit the process of angiogenesis, therefore halting further growth and cell division of tumor cells.

FDA-Approved Medications and Indications

Bevacizumab

Bevacizumab (Avastin®) is derived from a monoclonal antibody to murine VEGF with predominant human protein sequence, giving it a similar biochemical and pharmacologic properties as the natural antibody, but with reduced immunogenicity and a longer biological half-life.

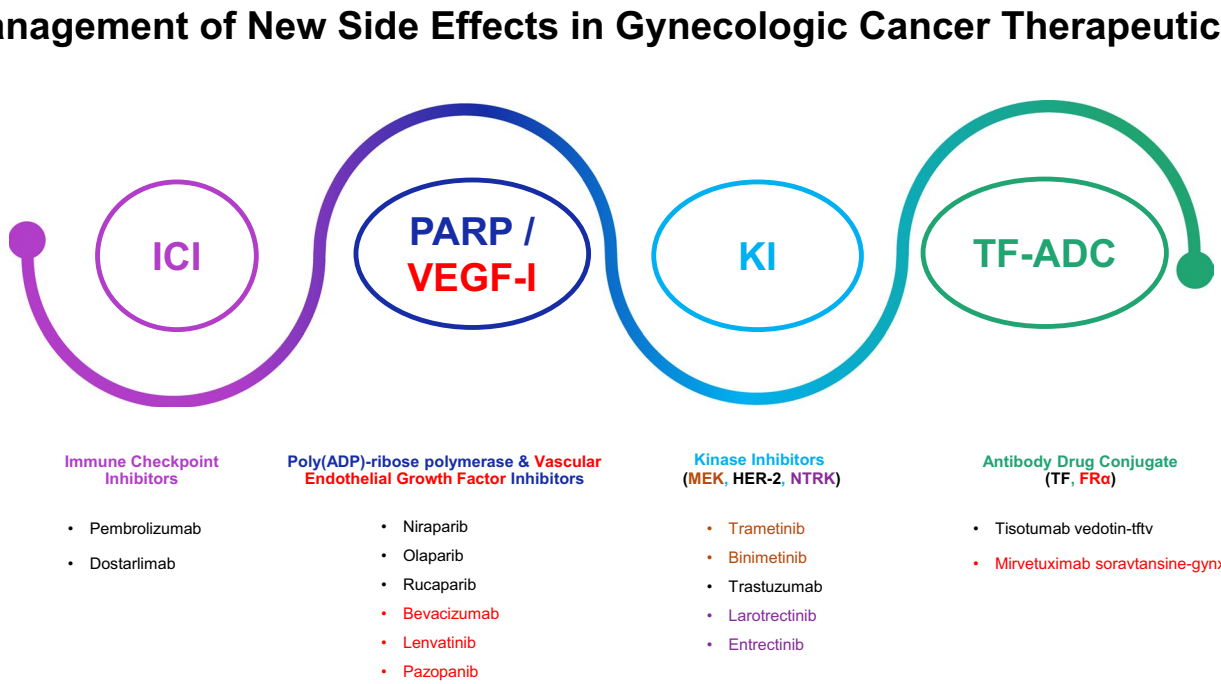

Fig. 1 Schematic representation of the management of key side effects in gynecologic cancer therapeutics. Abbreviations: ICI, immune-checkpoint inhibitors; PARP, poly(ADP)ribose polymerase; VEGF-I, vascular endothelial growth factor-inhibitor; KI, kinase inhibitor; TF, tissue factor; ADC, antibody–drug conjugate; ADP, adenosine diphosphate; MEK, mitogen-activated protein kinase kinase; HER-2, human epidermal growth factor receptor-2; NTRK, neurotrophic tyrosine receptor kinase; TF, tissue factor; FRα, folate receptor-alpha. Color code: purple = ICI; blue = PARP; red = VEGF-I; teal blue = KI; green = TF-ADC

Incidence, Severity, and Management Options of AEs

The most commonly reported AEs from the OCEANS phase III trial [2, 3] with a rate of > 10% include epistaxis, headache, high blood pressure, rhinitis, proteinuria, taste changes, dryness of skin, rectal bleeding, lacrimation disorder, back pain, bowel, perforation, dysfunctional wound healing, and exfoliative dermatitis. Reportedly, bevacizumab was discontinued in 8 to 22% of the patients secondary to experienced adverse reactions.

Hypertension It is preferrable to have adequate blood pressure control prior to initiating therapy. Blood pressure should be assessed bi-monthly or monthly during treatment. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuation. *Management:* Blood pressure goals for low-risk patients should be > 140/90 and for high-risk patients < 140/90 based on the CTCAE 4.0 criteria. For bevacizumab-induced hypertension, treat with appropriate antihypertensive therapy and monitor blood pressure regularly. Withhold Avastin in patients with severe hypertension that is not improved with medications; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Nephrotic Syndrome Of note, among the listed AEs, grade 4 proteinuria was defined as nephrotic syndrome, with reported incidence of 0.7 to 7%. Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation. Serum creatinine levels did not return to baseline in approximately one-third of the patients. *Management:* It is recommended to monitor proteinuria by dipstick urine analysis, if 2 + or greater, perform 24-h urine collection, and withhold bevacizumab for proteinuria ≥ 2 g per 24 h and resume when < 2 g.

Bowel Perforation In clinical trials, the risk of spontaneous bowel perforation was reported to be 0.3 to 2.4% based on package insert [13]. Patients most likely to develop this AE had established risks for perforation including history of bowel surgery, bowel obstruction or involvement of tumor implants on bowel, such as in ovarian cancer, peptic ulcers, and prior radiation therapy such as with cervical cancer [14]. *Management*: Surgical management is recommended for bowel perforation in a prompt manner to prevent further sequelae.

Bleeding Risk Incidence of epistaxis, rectal hemorrhage, and other bleeding episodes was evaluated by a meta-analysis of 85 randomized control trials (RCTs) and found that bevacizumab significantly increased the risk of all-grade high-grade bleeding with relative risk values reaching statistical significance [15]. Epistaxis occurs most commonly with an overall incidence of 20–40%, but this usually lasts less than 5 min and is self-limiting. Overall grade 3 or 4 bleeding occurs in 3.1–5.1% of the patients. *Management:* These were managed by ensuring that all surgical incisions were fully healed prior to the initiation, holding therapy at least 30 days prior to and after surgery, and using with caution in patients receiving standard dose anticoagulation or antiplatelet therapy [16].

Dysfunctional Wound Healing

A meta-analysis published by Zhang et al. [17] evaluated the risk of wound-healing associated with use of bevacizumab in various oncologic indications (n = 5147). Compared with cytotoxic therapy, bevacizumab increased incidence of dysfunctional wound-healing with an odds ratio of 2.32. It is recommended that bevacizumab should not commence until all wounds are well healed and should be discontinued for dehiscence. Also, bevacizumab should be suspended before elective surgery, through the interval of 4 to 8 weeks (most commonly 4 weeks) depending on the procedure and patient factors [13, 18]. The most commonly reported AEs and incidence, according to the packaging, and management suggestions based on literature review are summarized in Table 1 (in alphabetical order).

Lenvatinib

Lenvatinib is a multi-kinase inhibitor against VEGF-1, VEGF-2, and VEGF-3. Recent studies provided the FDA approval following a phase III trial for lenvatinib plus pembrolizumab (KEYTRUDA®) in patients with advanced endometrial cancer in microsatellite stable tumors, more over proficient mis-match repair tumors, as second-line systemic treatment option [8]. The KEYNOTE-775 trial suggested a significantly longer PFS and OS than chemotherapy among patients with advanced endometrial cancer. This drug behaves like most VEGF inhibitors such as bevacizumab mentioned above.

Management of Adverse Events

The most commonly reported AEs associated with this medication (according to the above phase II study) were hypertension, fatigue, hypothyroidism, and weight loss. Most toxicities are manageable with dose reductions, dose interruptions, and supportive care. The medication was overall well tolerated. For patients on this medication, liver function tests should be monitored at baseline, every 2 weeks for 2 months, and at least monthly during the treatment. Thyroid stimulating hormone, serum creatinine, and proteinuria should be monitored at baseline and monthly during the treatment or as clinically indicated. Monitor blood pressure after 1 week, then every 2 weeks for 2 months and at least monthly thereafter.

Table 1 Adverse events, incidence, and management suggestions for targeted anti-angiogenic (bevacizumab, lenvima) and MEK inhibitors (lenvatinib, pazopanib, trametinib)

Adverse events	Comments/management suggestions
Arterial thromboembolic events	- Risk increases in those with history of arterial thromboembolism, diabetes, or > 65 years, therefore use with caution - Discontinue if newly developed, severe/grade 4 ATE
Congestive heart failure	- Risk increases in patients receiving Avastin with anthracycline-based chemotherapy - Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after first dose and resolved in 62% of those patients after treatment was stopped - Discontinue medication in patients who develop CHF
Diarrhea	- Hydration and electrolyte replacement - May begin anti-diarrheal medication and even preventative 30 min prior to dose of sorafenib
Fatigue	- Rule out endocrine causes if severe and debilitating
Gastrointestinal perforations/fistulae	- Discontinue medication - Multi-disciplinary approach with gastroenterology or colorectal team, hospitalization if unstable, may warrant surgical intervention
Generalized rash	- Topical corticosteroids with mild anti-inflammatory properties - Avoid alcohol-based moisturizers and use sunscreen - Antihistamines for pruritis
Hand-food syndrome	- Urea-based cream applied to affected areas with appropriate skin hydration - Can use non-steroidal anti-inflammatory drugs if stable renal status to assist with pain and presence of rash
Hemorrhage	- Refrain from administering to patient with recent history of hemoptysis of ½ teaspoon—and discontinue in patients with grade 3–4 hemorrhage
Hypertension	- Monitor Blood pressure every 2–3 weeks, treat with appropriate anti-hypertensive therapy - Withhold for those uncontrolled with medical management, discontinue with hypertensive crisis or hypertensive encephalopathy
Infusion-related reactions	- Symptoms: hypertension, hypertensive crisis with neurologic signs and symptoms, wheezing, oxygen desaturation, grade 3 hypersensitivity, chest pain, headaches, rigors, diaphoresis - Decrease rate of infusion for mild reactions, interrupt infusion with clinically significant reactions at a slower rate following resolution - Infusion should be discontinued and not resumed in patients who develop severe reactions and should be given appropriate therapy with epinephrine, corticosteroids, IV antihistamines, bronchodilators and/or oxygen
Nausea	- Anti-emetic therapy - If significant weight loss due to failure of outpatient therapy, may require hospitalization for symptom control and IV fluid hydration
Ovarian failure	- Recovery of ovarian failure in premenopausal women is 22% - Patients should be counseled on risks prior to initiating Avastin
Abdominal pain	- Manage conservatively with over-the-counter medications, can be escalated on an as needed basis
Posterior reversible encephalopathy syndrome	- Onset 16 h to 1 year after 1st dose - MRI to confirm in presence of headache, seizure, lethargy, confusion, visual disturbances - Discontinue therapy, unknown safety of restarting
Proteinuria	- Median onset 5.6 months, time to resolution 6.1 months - Monitor proteinuria by dipstick urine analysis, if 2 + or greater, perform 24-h urine collection, and withhold Avastin for proteinuria ≥ 2 g/24 h and resume when < 2 g
Renal injury/elevated serum creatinine	- Grade 4 AE defined as nephrotic syndrome, with incidence of 0.7% to7%
Surgery and wound healing complications	- Withhold for 28 days prior to elective surgery or wait 28 days following surgery before administering - Discontinue with wound healing complications requiring medical intervention
Thrombocytopenia	- Consider chemotherapy dose reduction and platelet transfusions - Withhold drug until platelet levels are above 100 K - Discontinue drug for thrombocytopenia lasting > 4–6 weeks - Thrombopoietin receptor agonists, romiplostim and eltrombopag, are stimulators of platelet production and may be useful in treating in some chronic situations
Venous thromboembolic events	- Discontinue avastin in patients with Grade 4 VTE, including pulmonary embolism
Vomiting	Anti-emetic therapy

MEK = mitogen-activated protein kinase kinase; *ATE* = arterial thromboembolic events; *CHF* = congestive heart failure; *AE* = adverse event; *MRI* = magnetic resonance imaging; *VTE* = venous-thromboembolism events

Hypertension Reported incidence based on grade were grade 1–2 (25%), grade 3 (34%), or any grade (58%). *Management:* Recommended management was to control blood pressure prior to the treatment and monitor during the treatment. Hypertension induced by lenvatinib therapy is often dose-related, and therefore, a dose reduction may be more tolerable thereby lowering the potential adverse effects. Blood pressure should be monitored after 1-week, then bi-monthly for the first 2 months, and then at least monthly thereafter during the treatment. The medication should be withheld for grade 3 hypertension despite optimal anti-hypertensive therapy. It can be re-started at a lower dose, frequently lowered to 14 mg from 20 mg, when hypertension is controlled or permanently discontinue lenvatinib based on the severity. Discontinue for grade 4 hypertension.

Fatigue Reported incidence based on grade were grade 1–2 (49%), grade 3 (6%), or any grade (55%). Recommended management was with supportive care and managing ways to prevent other means of fatigue. *Management:* The National Comprehensive Cancer Network (NCCN) recommends adequate hydration, changes, and practice good sleep hygiene [19]. Exercise has also been suggested as a treatment for therapy-induced fatigue.

Diarrhea Reported incidence based on grade were grade 1–2 (43%), grade 3 (8%), or any grade (51%). Diarrhea may be severe and recurrent according to the studies requiring prompt initiation of management, particularly for severe diarrhea. *Management:* May have to hold or permanently discontinue based on the grade of toxicity. Advise patients when to start standard anti-diarrheal therapy and to maintain adequate hydration. Patients should also be advised to contact their healthcare provider if they are unable to maintain adequate hydration. Steroids have been included in the NCCN guidelines [20] for the management of targeted therapy AEs (see Table 1).

Hypothyroidism Reported incidence based on grade were grade 1–2 (47%), grade 3 (0%), or any grade (47%). Monitor thyroid function prior to the treatment and monthly during the treatment. *Management:* Treat hypothyroidism according to the standard medical practice [21].

Pazopanib

Mechanism of Action and Indication

Pazopanib (VOTRIENT®) is also a multi-kinase/tyrosine kinase inhibitor (TKI) of VEGF receptors 1, 2, and 3, platelet-derived growth factors receptors (PDGFR-alpha and PDGFR-beta), fibroblast growth factor receptor (FGFR-1 and FGFR-3), and cytokine receptor (KIT). It has been studied and used as a maintenance therapy in patients with recurrent ovarian cancer [22]. In a study of 940 women with advanced ovarian cancer who had not shown evidence of postsurgical progression after 5 or more cycles of platinum-taxane chemotherapy, the addition of 800 mg po daily of pazopanib maintenance to standard therapy increased PFS as compared to placebo. However, the pazopanib group had a higher incidence of AEs (hypertension, diarrhea, nausea, headache, fatigue, liver related toxicity, neutropenia, thrombocytopenia, palmar-plantar erythrodysesthesia) [23].

Adverse Events and Management

According to Friedlander et al. [22], during the evaluation of pazopanib in an open-label phase II study, the most common AEs leading to discontinuation of the drug were grade 3 elevation of aspartate transaminase (AST)/alanine aminotransferase (ALT). Only one grade 4 toxicity of peripheral edema occurred. Other peer-reviewed literature reports that the most common adverse reactions at $\geq 20\%$ incidence are diarrhea, hypertension, decreased appetite, hair color changes, nausea and vomiting, musculoskeletal pain/myalgias, and fatigue [23]. Per the reported data, 17% of the patients discontinued therapy due to adverse reactions. Hepatoxicity, bleeding, and gastrointestinal perforation are the most serious AEs that have been reported with incidence of $< 1\%$. Literature also suggests that the use of pazopanib should not be considered for patients with a history of clinically significant gastrointestinal bleeding, bloody sputum, cerebral bleeding, or an arterial thromboembolic event within the past 6 months [24].

Diarrhea The reported incidence of 52–59% is being one of the most commonly reported AEs of pazopanib in the peer-reviewed literature. Dietary modifications may assist in decreasing the amount of diarrhea by ingesting foods that are easy to digest. However, mild symptoms may require anti-diarrheal agents for the treatment, such a loperamide (Imodium) or diphenoxylate/atropine (Lomotil) for 2–3 days until resolution when infectious etiology has been ruled out. Moderate to severe symptoms defined as 4–6 bowel movements or more with associated abdominal pain, inability to tolerate oral intake should prompt discontinuation and further work-up to rule out other etiology.

Hypertension The reported incidence is of 40–42% and should be managed similar to what is suggested for lenvatinib. It is recommended to control and treat the blood pressure prior to the initiation of the therapy and should be continuously monitored during the therapy. Optimal blood pressure management should be maintained, and grade 3

hypertension may require temporary discontinuation, while grade 4 would prompt permanent discontinuation.

Decreased Appetite Reported incidence of 40%, that can be managed supportively by eating small frequent meals and staying well hydrated. Appetite stimulants are possible options to increase oral intake. Patients with significant weight loss and failure to thrive may require hospitalization and further interventions.

Hair Color Changes The reported incidence of hair color changes, namely depigmentation, is 38–39% that is specific to pazopanib. No reported management options for prevention are reported.

Pain. Including tumor pain, musculoskeletal pain, and myalgias have a reported incidence of 29%, 26%, and 21%, respectively. The NCCN guidelines have recommendations for stepwise pain management approaches that always start with non-narcotic options in a multi-modal fashion. Pain intensity should be based on a 0–10 numerical scale, corresponding to mild (1–2), moderate (4–7), and severe (8–10), and managed according to the pain levels; again, beginning with non-narcotic pain medication and escalating as needed [25].

Nausea/Vomiting The reported incidence is 21–26%, with many therapies available for the prevention and subsequent treatment. The NCCN guidelines can be followed for such prevention and management [26]. It is recommended that patients initiate a daily anti-emetic. For breakthrough nausea or emesis, patients should be started on a separate class of anti-emetics, such as: olanzapine, lorazepam, as detailed in the guidelines. The prophylactic dosing of anti-emetic may also be increased if persistent nausea is present. If grade 3/4 nausea occurs, drug should be held until nausea improves to grade 1 or better, and then started at the same dose with additional prophylactic anti-emetics or with a dose reduction of one level. A second occurrence following the medication changes should prompt further dose reduction, while a third occurrence should prompt discontinuation. Additionally, if the AE does not resolve within 28 days at any point, consider discontinuation [26].

Fatigue The reported incidence is 19%, and the management suggestions are again with the supportive care and managing ways to prevent other means of fatigue. The NCCN guidelines recommends adequate hydration, changes, and practice good sleep hygiene [19].

Palmar-Plantar Erythrodysesthesia This is also referred to as hand-foot syndrome (HFS), which is managed via a combination of preventative strategies, proper education, symptom management, and dose intensity modification. The best way to manage HFS once it has occurred is dose adjustments. Specifically, dose delay or dose reduction, or even treatment discontinuation (see Table 2).

PARP Inhibitor Agents

Mechanism of Action

The PARP inhibitors (PARPi) work by a group of proteins that function to repair DNA by way of enzymatic/scaffolding properties and recruiting ability of other necessary DNA repair proteins. PARP inhibitors also work by interfering with base excision repair, which repairs single strand DNA breaks, leading to accumulation of the single stranded breaks, that become double stranded, ultimately leading to cell death [27]. Most recently, studies have indicated the use in patients with BRCA1 or BRCA2, homologous recombination deficient (HRD) mutations, and even wild-type solid tumors, most notably ovarian cancer.

FDA-Approved PARPi Adverse Effects

Niraparib

Recently, the most commonly reported AEs published with the PRIMA trial for any grade were: anemia (63%), nausea (57%), thrombocytopenia (46%), constipation (39%), fatigue (34%), neutropenia (26%), headache (26%), insomnia (25%), vomiting (22%), and abdominal pain (22%) [28]. Myelosuppressive AEs were the main reason for discontinuation but were infrequent in the PRIMA study, reportedly 4.3% for thrombocytopenia and one case of myelodysplastic syndrome (MDS) was identified. More serious AEs included the risk of MDS/acute myeloid leukemia (AML; 0.9%) and cardiovascular effects in the form of palpitations (10%), hypertension (20%), or hypertensive crisis (9% grade 3/4 hypertension) [29]. MDS/AML have been reported (rare), including fatal cases. The duration of niraparib treatment prior to the development of MDS/AML varied from < 1 month to 2 years. All patients had received prior chemotherapy, including platinum-based regimens. Discontinue niraparib if MDS/AML is confirmed (Lexicomp).

Olaparib

Serious AEs were reported in 21% of patients on Olaparib based on the SOLO-1 trial [30]. Nausea and anemia were the most common reasons for drug discontinuation [31]. The most life-threatening AEs reported are pneumonitis that occurred in < 1% of patients. Most common AEs were nausea (77%) with grade 3 or 4 reported in 1% of those patients, fatigue (63%) with 4% grade 3 or 4, vomiting (40%, < 1% grade 3 or 4), anemia (39%) with 22% grade 3 or 4, gastrointestinal (diarrhea, constipation, dysgeusia, abdominal pain,

Table 2 Anecdotal or expert recommendation management of commonly reported symptoms (e.g., diarrhea, mucositis)

Symptoms	Pharmacologic interventions	Complementary and alternative medicine (CAM)
Dysgeusia	None	• Behavioral management strategies - Adjusting temperature of the food, usually to cool or room temperature - Adding a sweet flavor to food that tastes bitter - Using more or fewer flavorings - Using saliva substitutes and sialagogues - Rinse mouth with baking soda solution • Practicing good dental hygiene
Constipation	• Prophylactic medications - Stimulant laxative + / − osmotic laxative - Increase laxative dose with goal of 1 non-forced BM every 1–2 days • If impacted - Glycerin suppository + / − mineral enema + / − tap water enema • Consider prokinetic agent • Opioid-receptor antagonists: naloxone, methylnaltrexone	• Low-fat, lactose-free diet • Increase soluble fiber intake • Avoid spicy foods • Avoid caffeine • Increase fluid intake • Increase activity
Diarrhea Loperamide (2 mg q2 h until diarrhea free > 12 h), fluids/electrolytes	• If chemotherapy induced, consider delaying next dose or decrease in dose • Provide antidiarrheal therapy indicated by grade **Grade 1**: increase < 4 stools/day over baseline; mild increase in ostomy • Provide oral hydration and electrolyte replacement • Initiate antidiarrheal **Grade 2**: increase of 4–6 stools/day over baseline; moderate increase in ostomy output • Provide IV fluids if unable to tolerate oral fluids • Consider anticholinergic agents **Grade 3**: increase of > 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output; limiting self-care; interferes with ADLs **Grade 4**: Life-threatening consequences • Provide IV fluids. antidiarrheal agents and anticholinergic agents • Consider somatostatin analog	• Low-fat, lactose-free diet • Increase soluble fiber intake • Avoid spicy foods • Avoid caffeine • Drink plenty of liquids • Emphasize food associated with the BRATT diet • Eat small meals, often
Dysphagia	N/A	• Eat thickened, moist, soft, or ground/pureed foods
Fatigue	Psychostimulants (methylphenidate) after ruling out other causes of fatigue	• Energy conservation • Energy restoration • Rest (naps < 30 min) • Activity (20–30 min of exercise 3–5 times a week) • Nutrition (eat small, frequent meals; frozen and easy-to-prepare meals or have food service delivered) • Consider an exercise program designed to enhance mobility and preserve energy (e.g., yoga)
Nausea/vomiting	• Assess and treat underlying cause • Chemotherapy/radiation NCCN guidelines • Gastritis/GERD PPI H2 blocker • Constipation • Gastroparesis • Prokinetic agent	• Eat small, frequent, low-fat, low-fiber meals • Avoid eating 1–2 h before treatment • Eat and drink slowly • Stay upright and rest after eating • Stay hydrated • Avoid spicy foods, milk products and caffeine • Avoid greasy, high-fat foods: Stay away from fried foods, potato chips, spicy foods, or those with strong smells • Acupuncture, acupressure, guided imagery, music therapy, Progressive muscle relaxation, hypnosis, massage and aromatherapy, ginger can be effective

Table 2 (continued)

Symptoms	Pharmacologic interventions	Complementary and alternative medicine (CAM)
Stomatitis, mucositis	• Caphasol • Magic mouthwash/viscous lidocaine swishes • Parenteral/enteral nutrition	• Eat soft, non-irritating foods • Eat nutrient dense liquids/nutritional supplements
Weight loss; anorexia-cachexia	Appetite stimulants • Anabolic agents: oxandrolone • Atypical antipsychotic: olanzapine Antidepressant: mirtazapine • Cannabinoids: dronabinol • Antihistamine: cyproheptadine glucocorticoids: dexamethasone, methylprednisolone, prednisolone • Progestational agents: megestrol acetate, medroxyprogesterone	• Small, frequent, nutrient-dense meals • Try liquid/powder nutritional supplements • Consume high-calorie, high-protein foods • Consider an exercise program designed to enhance mobility and preserve energy • Symptoms like dry mouth should be treated with local measures (e.g., mouth care, small amounts of liquids)
Xerostomia	N/A	Drink / swallow small amounts of food at one time; sip water / fluid after each bite; try sweet or tart foods, soft / pureed foods; suck on hard candies; artificial saliva
Palmar-plantar erythrodysesthesia	• Topical lidocaine gel/cream • Oral pain relievers • Topical steroid cream	• Apply urea-based creams as prevention • Consider intake of Vit B6 • Avoid heat and hot water • Use cooling agents including ice pack

BM = bowel movement; *BRATT* = bread, rice, applesauce, tea, toast; *ADLs* = activities daily living; *NCCN* = National Comprehensive Clinical Network; *GERD* = gastroesophageal reflux disease; *PPI* = proton pump inhibitors; *H2* = histamine type-2 receptor antagonists; *N/A* = not applicable

decreased appetite, upper abdominal pain,), arthralgias, neutropenia, headache, dizziness, dyspepsia, cough, back pain, dyspnea, and thrombocytopenia. Anemia was the most common serious AE, that literature reports an incidence of up to 7% (see Tables 3 and 4).

Rucaparib

As reported in the ARIEL3 trial [5], the most common AEs occurring in ≥ 20% of patients with grade 1–4 events are as follows: nausea (76%), abdominal pain/distention (46%), dysgeusia (40%), vomiting (37%), anemia (39%), AST/ALT elevations (38%), constipation (37%), diarrhea (32%), rash(43%), thrombocytopenia (29%), fatigue (73%), nasopharyngitis (29%), stomatitis (28%), decreased appetite (23%), and neutropenia (20%). Grade 3–4 AEs were most commonly found to be anemia (21%), followed by AST/ALT elevation (11%), and neutropenia (8%).

Table 3 Commonly reported AEs with PARP inhibitors [4, 5]

AEs	Olaparib	Rucaparib	Niraparib
Anemia (G1-4/G3-4)	90%/15%	37%/19%	50%/25%
Neutropenia (G1-4/G3-4)	25%/7%	18%/7%	30%/20%
Thrombocytopenia (G1-4/G3-4)	30%/3%	28%/5%	61%/34%
Fatigue (G1-4/G3-4)	66%/8%	69%/7%	60%/8%
Nausea (G1-4/G3-4)	64%/3%	75%/4%	74%/3%
Vomiting (G1-4/G3-4)	43%/4%	37%/4%	34%/2%
Diarrhea (G1-4/G3-4)	31%/1%	32%/1%	19%/0%
Elevated Creatinine (G1-4/G3-4)	30%/2%	15%/1%	NR
Elevated LFTs (G1-4/G3-4)	NR	34%/10%	NR

AEs = adverse events; *PARP* = poly(adenosine diphosphate)-ribose polymerase; *G* = grade; *NR* = not reported; *LFT* = liver function test

Management of Nausea/Vomiting with PARPi

All are considered moderate to highly emetogenic per the NCCN Guidelines [20]; thus, it is recommended to have a prophylactic daily 5-hydroxytryptamine (HT)3 antagonist before PARPi. Additionally, taking the PARPi at night, may help lessen the severity of nausea. If the patient experiences breakthrough nausea or vomiting, an additional anti-emetic from another class sequentially can be used. Additionally, consider increasing prophylactic anti-emetic therapy for subsequent treatment if emesis continues. When grade 3/4 nausea occurs, the PARPi should be held until nausea de-escalates to grade 1 or better, and then started at the same dose with additional prophylactic anti-emetics or with a dose reduction of one level. A second occurrence following medication changes should prompt further dose reduction, while a third occurrence should prompt discontinuation. Additionally, if the AE does not resolve within 28 days at any point, consider discontinuation. If the patient does not experience nausea or vomiting, consider tapering and/or discontinuing the anti-emetic therapy as these are generally long-term use agents.

Table 4 Adverse events, incidence, and management suggestions for PARP-inhibitor agents (viz., niraparib, olaparib, and rucaparib)

AEs	Incidence (niraparib, olaparib, rucaparib)	Management suggestions
Anemia	50%, 90%, 37%	- Monitor blood counts weekly for the first month, then monthly for 11-months, then periodically thereafter
Dermatitis	21%, 1%, 43%	- Topical corticosteroids with mild anti-inflammatory properties - Avoid alcohol-based moisturizers and use sunscreen - Antihistamines for pruritis
Diarrhea	19%, 31%, 32%	- Supportive care
Fatigue	60%, 66%, 69%	- Supportive care
Headache	26%, 15%, 18%	Consider analgesics
Hepatoxicity	< 10%, N/A, 37–73%	- Mild: no change in dosage adjustments - Moderate to severe: may consider dose adjusting
Myalgias	N/A, ≤ 30%, N/A	Consider anti-inflammatory medication
Mucositis/stomatitis	≤20%, 4–20%, 28%	- Supportive oral care including non-alcohol containing oral rinse 3–4 × daily, treatment of thrush if present with antifungal - Withhold drug until severe symptoms resolve
Myelodysplastic syndrome	< 1%, 1%, < 1%	- Discontinue
Nausea/vomiting	74/34%, 64/43%, 75/37%	- All are considered moderate to highly emetogenic per NCCN guidelines; thus, it is recommended to have a prophylactic daily 5-HT3 antagonist before PARPi - For breakthrough: olanzapine, lorazepam, cannabinoid, phenothiazine, dexamethasone, haloperidol, metoclopramide, or scopolamine
Neutropenia	30%, 25%, 18%	- Olaparib and rucaparib: see text for further clarification based on grade of toxicity (< grade 2 or > grade 2), and for absolute neutrophil recommendations - Niraparib: blood counts weekly but more frequent if platelets are trending down
Renal toxicity	N/A, 30%, 15%	Monitor creatine levels as most rises are transient and withhold drug for grade 3/4 toxicity until resolve

AEs = adverse events; *PARP* = poly(adenosine diphosphate)-ribose polymerase; *N/A* = not available; *5-HT3* = 5-hydroxytryptamine-3

Management of Hematologic Toxicity

Platelets < 100,000/mm^3. *First occurrence:* Withhold treatment for a maximum of 28 days and monitor blood counts weekly. When platelets are ≥ 100,000/mm^3, resume niraparib at the same or at a reduced dose. If platelet count was < 75,000/mm^3, resume at a reduced dose. *Second occurrence:* Withhold treatment for a maximum of 28 days and monitor blood counts weekly. When platelets are ≥ 100,000/mm^3, resume niraparib at a reduced dose. Discontinue if platelet count has not returned to the acceptable levels within 28 days of interrupting dose, or if dose has already been reduced to 100 mg/day. Additionally, individualized starting dose with niraparib might lessen the hematologic impacts. Specifically, per package insert, it is suggested that patients weighing ≥ 170 lbs and platelet count of ≥ 150,000/μL can start at 300 mg taken orally once daily. For patients weighing < 170 lbs or platelet count of < 150,000/μL, it is recommended to start at 200 mg orally once daily.

Neutrophils < 1000/mm^3 or Hemoglobin < 8 g/dL. Withhold treatment for a maximum of 28 days and monitor blood counts weekly. When neutrophils are ≥ 1500/mm^3 or hemoglobin is ≥ 9 g/dL, resume PARPi at a reduced dose and discontinue if these have not returned to the acceptable levels within 28 days of interrupting dose, or if dose has already been reduced to 100 mg/day. If there is a hematologic toxicity requiring transfusion, withhold PARPi. Consider platelet transfusion for platelets ≤ 10,000/mm^3. If other risk factors (e.g., concurrent anticoagulation or antiplatelet therapy), consider interrupting the anticoagulant/antiplatelet therapy and/or transfusing to a higher platelet count. Resume niraparib at a reduced dose. If secondary MDS or AML is diagnosed, niraparib should be discontinued upon confirmation and patient referred to medical oncologist for management. Blood counts should be obtained weekly for niraparib but more frequently if platelets are actively decreasing. Once the optimal dose of niraparib is determined, hematologic toxicities do not appear to be a chronic issue. Niraparib is unique and it is important to follow the dose modification table in the FDA label (see Tables 3 and 4). For olaparib and rucaparib, if less than grade 2 toxicities, interrupt treatment until resolved, then re-start same dose. If greater than grade 2 toxicities or repetitive toxicities, reduce to next lower level.

MEK Inhibitors

Mechanism of Action

Trametinib

It is an orally bioavailable inhibitor of mitogen-activated protein kinase (MEK MAPK/ERK kinase) with anti-neoplastic activity. It specifically binds to and inhibits MEK 1 and 2, resulting in an inhibition of growth factor-mediated cell signaling and cellular proliferation in various cancers. These pathways ultimately play a key role in regulating cell growth. Trametinib has been found to have success in treating malignancies with *BRAF* mutations which have not previously received BRAF inhibitor treatment in the past. Frontline therapy for low-grade serous ovarian cancer (LGSOC) involves chemotherapy after which an aromatase inhibitor can be used as maintenance. Unfortunately, LGSOC is relatively resistant to platinum-based chemotherapy. As such finding an effective targeted therapy has remained an area of unmet clinical need. Trametinib emerged as a novel therapeutic strategy for LGSOC because of the high prevalence of activating mutations in the mitogen-activated protein kinase (MAPK) signaling pathway, which includes the MEK protein, according to the researchers.

The most commonly reported treatment related AEs were rash (92%), fatigue (72.5%), diarrhea (72.4%), nausea (60.6%), anemia (51.9%), vomiting (45.7%), and hypertension (28.6%). The most commonly reported grade 3 or higher AEs were rash (15%), anemia (12.6%), hypertension (11.8%), and diarrhea (10.2%). The most serious AEs encountered were decreased left ventricular ejection fraction (7.9%), followed by pneumonitis (2.4%), retinal vascular disorder, left ventricular systolic dysfunction, corrected QT (QTc) prolongation, and retinal tear (0.8%) [32•].

Binimetinib

This agent is a small-molecule inhibitor of MEK1/2 and is given orally. It is approved in combination with encorafenib for treatment of *BRAF* mutated melanoma in several countries. The MILO/ENGOT–ov11 international research team explored binimetinib (MEK162) vs. physicians' choice chemotherapy in recurrent or persistent LGSOC/fallopian tube (FT)/primary peritoneal cancer (PPC) and reported their results in November 2020 [33]. *KRAS* mutation is believed to predict the response. Although the study did not meet primary endpoint, the data showed *KRAS* mutation was significantly associated with response to treatment and prolonged PFS with binimetinib, but not physician choice. Grade 3 AE in 76% of patients including increased creatine phosphokinase (CPK) serum level (26%), vomiting (10%), diarrhea (6%), decreased ejection fraction (4%), intestinal obstruction (2%), and retinal vein occlusion (2%) [33].

Management

Preventative and management strategies for this class of drugs include limiting exposure to the sun. As well as using a non-irritant soothing cream to soothe affected rash areas. Skin reactions can be severe, requiring hospitalization. Several strategies can be employed for joint aches, and these include nonsteroidal anti-inflammatory medications to help relieve pain and swelling, along with icing and resting the affected area. Diarrhea prevention may involve a specific diet plan along with an increase in fluids and a decrease in pro-inflammatory foods including dairy products and spicy foods. A short course of anti-diarrheal medication may be helpful. In serious cases, diarrhea (and abdominal pain) could be a sign of life-threatening bowel perforation (see Table 1). Assess left ventricular ejection fraction (LVEF) at several time points. These time points include (i) prior to treatment initiation, (ii) 1 month after initiation, and (iii) then every 2 to 3 months during treatment. Monitor closely in patients with cardiovascular risk factors. If there is an absolute LVEF decrease of $> 10\%$ from baseline, and also below lower limit of normal (LLN) while the patient remains asymptomatic, withhold binimetinib for up to 4 weeks and evaluate LVEF every 2 weeks.

With dose reduction if may be feasible to resume binimetinib once the LVEF is $\geq$ LLN and absolute decrease from baseline is $\leq 10\%$ and patient is asymptomatic. Permanently discontinue binimetinib if the LVEF does not recover within 4 weeks. Symptomatic heart failure or absolute decrease in LVEF of $> 20\%$ from baseline and also below LLN, permanently discontinue binimetinib. Ophthalmologic examination should occur at regular intervals and for new or worsening visual disturbances. Similarly, monitor for visual symptoms at each visit. Immediate ophthalmologic evaluation for patient-reported acute vision loss or other visual disturbance within 24 h. For symptomatic serous retinopathy/retinal pigment epithelial detachment, withhold binimetinib for up to 10 days. If symptoms improve and patient becomes asymptomatic, resume therapy at the same dose. If there is no improvement, resume therapy at a lower dose level or permanently discontinue binimetinib. For any grade retinal vein occlusion, permanently discontinue binimetinib. If grade 1 or 2 uveitis does not respond to specific ocular therapy (or for grade 3 uveitis), interrupt binimetinib therapy for up to 6-weeks. If there is improvement within 6-weeks following therapy interruption, resume at the same dose or a lower dose. If uveitis does not improve, permanently discontinue binimetinib. For grade 4 uveitis, permanently discontinue binimetinib.

Anti-Her2/Neu Antibody

Mechanisms of Action

Trastuzumab (Herceptin)

Drugs in this class are monoclonal antibody targeting tyrosine kinases, human epithelial growth factor receptor 2 (HER2)/neu. The interference of the signaling of the HER2 receptors affects cell growth, and antibody-dependent cellular toxicity [34]. *Incidence and management of AEs:* The most commonly reported adverse reactions reported with single-agent Herceptin use includes generalized pain (47%), nausea (33%), infusion-related reaction with chills and fever (40%), and infection (20%). Other commonly reported AEs observed were headache, insomnia, dizziness, skin rash, diarrhea, vomiting, anorexia, generalized weakness, cough, and dyspnea.

Management

Trastuzumab products, according to Lexicomp, are associated with symptomatic and asymptomatic reductions in left ventricular ejection fraction and requires evaluation prior to and during treatment. Evidence of cardiomyopathy on evaluation should prompt discontinuation of therapy. The reported incidence is highest in those patients who are concurrently receiving anthracycline-containing therapy regimens [35, 36••]. Infusion-related reactions have also been reported, most occurring within 24 h of administration. Angioedema or anaphylaxis requires immediate medical attention and treatment, along with discontinuation of medication. Infusion should also be stopped with symptoms including dyspnea or significant hypotension and patients should be monitored until resolution of symptoms.

Immunotherapies

Mechanisms of Action

Immune checkpoint blockade via immunotherapy leads to preferential activation of cancer-targeting T-cells and revival of tumor immunity. The goal of immunotherapy is to stimulate T-cells and enhance the immune system to recognize and target tumor cells again.

FDA-Approved Medications

Pembrolizumab—Incidence and Management of AEs

Pembrolizumab (KEYTRUDA®) specific AEs noted in the KEYNOTE-158 study involving patients diagnosed with advanced cervical cancer occurring in ≥ 20% of patients were fatigue, musculoskeletal pain, diarrhea, abdominal pain, and decrease appetite [7]. The most frequent serious adverse reactions reported included anemia (7%), fistula formation (4.1%), hemorrhage (4.1%), and infections (4.1%) according to the same study.

Augmenting the activity of the immune system can also lead to T-cells attacking healthy cells in the body and, causing inflammatory conditions that mimic a range of autoimmune conditions, some of which can be serious. These are known as immune-related AEs and have been found to occur at select time frames following initiation of therapy, which can be found in Table 5, and these include: inflammation of mucous membranes/linings, hepatitis, as well as endocrinopathies such as hypophysitis, thyroid disorders, even type 1 diabetes, nephritis and renal dysfunction, and skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and exfoliative dermatitis.

Dostarlimab

Most recently, the RUBY trial results revealed a doubling of progression-free survival at 24 months with the addition of dostarlimab (Jemperli; a therapeutic antibody against PD-1) in combination with carboplatin and paclitaxel in advanced endometrial cancer compared to chemotherapy alone [37]. The study also reported a more pronounced effect in patients with mismatch repair-deficient, microsatellite instability (MSI)-high tumors [37]. Dostarlimab was previously granted an accelerated approval by the FDA based on interim results of the GARNET trial [38, 39••] for "the

Table 5 Immune-related adverse events of checkpoint inhibitors

Toxicity	Clinical effects	Time frame from treatment initiation
Skin	Rash, pruritus	2–3 weeks
Gastrointestinal	Diarrhea, colitis	6–7 weeks
Liver	Elevated liver enzymes, bilirubin, hepatitis	6–7 weeks
Endocrine	Hypophysitis (inflammation of the pituitary with resulting multiple endocrine disturbances), hypothyroidism (monitor ACTH and thyroid function)	After 9 weeks and may continue following treatment cessation

ACTH = adrenocorticotropic hormone

treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer experiencing disease progression despite treatment with platinum-containing chemotherapy regimens." Dostarlimab works by binding to the PD-1 receptor and blocking its interaction with programmed death receptor ligands 1 and 2 (PD-L1 and PD-L2). Because endometrial cancer has the highest rate of mismatch repair deficiency and MSI-high of all tumors, these tumors more likely to respond to anti-PD-1 or anti-PD-L1 therapy. Recently, dostarlimab was evaluated in a phase III trial (RUBY) in combination with standard chemotherapy in patients with recurrent or primary advanced endometrial cancer. Other trials to monitor include MOONSTONE, FIRST, and OPAL. The recommended dostarlimab dose and schedule (doses 1 through 4) is 500 mg every 3 weeks over 30 min. Subsequent dosing, beginning 3 weeks after dose 4, is 1000 mg every 6 weeks.

Serious adverse reactions were seen in 34% of those receiving dostarlimab. Serious adverse reactions in > 2% of patients included fever, sepsis, urinary tract infection or urinary insufficiency, and abdominal pain. The most common adverse reactions (occurring in ≥ 20% of patients) were fatigue/asthenia, gastrointestinal (nausea, diarrhea, constipation), and anemia. The most common grade 3 or 4 adverse reactions (≥ 2%) were anemia and increase in liver enzymes. Immune-mediated adverse reactions can occur such as pneumonitis, colitis, hepatitis, nephritis, and other "-itis" as well as endocrinopathies as is seen with all immune checkpoint inhibitors.

Management

(i). *Corticosteroid administration* for these immune-mediated adverse reactions is the first-line therapy; however, for grade 3 or 4 adverse reactions, or recurrent grade 2 reactions, Keytruda should be discontinued. Please refer to Table 5 for further recommendations on dosing based on grading of AEs.

(ii). *Pneumonitis* can be fatal and occurred more frequently in patients who have previously received thoracic radiation treatment and was also noted in patients receiving pembrolizumab in combination with platinum-based therapy. Radiographic imaging is recommended for diagnosis, and corticosteroids should be administered for grade 2 or greater pneumonitis, and Keytruda should be held for grade 2, permanently discontinued for grade 3 or 4.

(iii). *Thyroid disorders* should be treated with appropriate medications: hormone replacement for hypothyroidism and thioamides and beta-blockers as needed for hyperthyroidism. Insulin should be administered for development of type 1 diabetes. Keytruda should be withheld.

(iv). *Colitis* is a commonly reported AE for which treatment recommendations are also based on the grading. Grade 1 colitis is defined as < 4 bowel movements above baseline per day without any other symptoms and can be managed with supportive hydration with or without loperamide or diphenoxylate/atropine to decrease amount of bowel movements. Grade 2 is defined as an increase in bowel movements by 4–6 per day above baseline, abdominal pain, or other associated symptoms of colitis, however not interfering with activities of daily living. It is recommended for these patients to hold Keytruda and initiate prednisone or methylprednisolone at 1 mg/kg/day, taper over 4–6 weeks when resolution to < grade 1 symptoms. If there is no response within 2–3 days of initiation of therapy, increase the steroid dosing to 2 mg/kg/day and can consider adding infliximab. Grade 3 is defined as an increase by > 6 stools/day above baseline, interfering with activities of daily living, hemodynamic instability, requiring hospitalization, and other serious complications such as bowel ischemia, perforation, or toxic megacolon. Management recommended is the same as for grade 2 with possible hospitalization for electrolyte replacement and fluid hydration, with initiation of steroids. Again, if there is no response within 2 days or symptoms recur after initial improvement, consider adding infliximab. Grade 4 is defined as life-threatening consequences for which the drug should be permanently discontinued, with initiation of steroids, infliximab dosed at 5–10 mg/kg if symptoms are refractory to steroids after 2 days. Vedolizumab may also be considered for patients who are refractory to infliximab or for whom a tumor necrosis factor-alpha blocker is contraindicated.

(v). *Immune-related AEs (IrAEs)* have been seen throughout treatment and even after the treatment is completed, which also affect one or several different organ systems. IrAE rebound during steroid taper can also occur; therefore, these patients should have close monitoring with frequent follow-up. Additionally, combination therapy with chemotherapy, targeted agents, radiation therapy or other types of immunotherapies may increase the severity of AEs. The NCCN and ASCO have published thorough guidelines on IrAEs and can be reviewed for further details [20, 40, 41••].

Several immunomodulatory therapies are on the horizon and will soon be relevant. Other checkpoint inhibitors currently included in guidelines (or soon to be in guidelines), but not yet commonly used include nivolumab, avelumab, durvalumab, and ipilimumab. These drugs are associated with similar immune-related AEs for the management of immune-related AEs (see Table 6).

NTRK Inhibitors

The neutrophilic tyrosine receptor kinase (NTRK) inhibitors (entrectinib or larotrectinib) are now included in NCCN guideline recommendation for patients with recurrent platinum-resistant ovarian/FT/PPC, recurrent uterine, recurrent cervical, and recurrent vulvar cancers that have a gene-fusion-positive tumors and have failed/progressed on standard first-/second-line systemic therapies.

Entrectinib (Rozlytrek) Entrectinib (Rozlytrek) works by inhibiting tropomyosin receptor kinase (TRK) A, B, and C. It has anti-tumor activity against *NTRK* gene fusion-positive solid tumors. Because it can penetrate the blood–brain barrier, it also has central nervous system (CNS) activity. Studies have shown efficacy and safety data of patients with metastatic or locally advanced solid tumors harboring oncogenic *NTRK1*, *NTRK2*, and *NTRK3* gene fusions treated in three ongoing, early-phase trials [43•].

Larotrectinib In 2018, the FDA-approved larotrectinib (Vitrakvi) for the treatment of patients with solid tumors that have an NTRK gene fusion in the late recurrent setting and have no satisfactory alternative treatments [44]. Larotrectinib is a potent and highly selective small molecule inhibitor of all three TRK proteins.

Adverse Effects of NTRK Inhibitors

The most common adverse reactions (occurring in ≥ 20% of patients) were fatigue (48%), constipation (46%), dysgeusia (44%), vomiting (24%), diarrhea (35%), nausea (34%), edema (40%), increased weight (25%), dizziness (38%), cognitive impairment (27%), dysesthesia (34%), dyspnea (30%), cough (24%), myalgia (28%), pyrexia (21%), arthralgia (21%), and vision disorders (21%).

Serious adverse events were noted in seven patients in the *NTRK* fusion-positive and in 30 patients who were evaluated as part of the overall safety population. Nervous system disorders occurred most in both groups. Four percent in the *NTRK* fusion-positive population and four percent in the overall safety population discontinued entrectinib due to treatment-related adverse events. Dose interruption due to a treatment-related adverse event occurred in (31% and 25%, respectively), and 27 (40%) vs. 97 (27%) had a dose reduction due to a treatment-related adverse event. Also, there were anemia [five (7%) patients], increased blood creatinine levels [four (6%)], and fatigue [four (6%)]. Six deaths were reported post data analysis cutoff in the *NTRK* fusion-positive and 20 in the overall safety population. All of these deaths were deemed unrelated to treatment.

Antibody–Drug Conjugates

Mechanism of Action

Antibody–drug conjugates (ADCs) are fairly new class of drugs, herein we describe two newly approved drugs for gynecologic malignancies [45•]. The ADCs typically contain three components which include an antibody that binds a specific target, a cleavable linker, and an antitumor agent. This complex allows the anti-tumor agent to be internalized within the tumor cell where it elicits its potent anti-tumor activity thereby offering the opportunity to limit toxicity to normal cells.

FDA-Approved Medications and Indications

Tivdak™

Tivdak™ (tisotumab vedotin-tftv) is an ADC directed against tissue factor (TF). The human IgG1-kappa antibody targets the cell surface TF protein which is the prime initiator of the extrinsic blood coagulation cascade. TF plays a role

Table 6 Management of immune-related adverse events related to immune checkpoint inhibitors therapy [42]

Grade	CTCAEs	Management
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only	- Continue ICPi therapy with close monitoring - Exceptions: neurologic, hematologic, and cardiac toxicities
2	Minimal, local, or non-invasive intervention indicated	- Hold ICPi for most toxicities, resume when resolved to < grade 1 - Prednisone 0.5–1 mg/kg/day or equivalent may be administered
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated	- Hold ICPi - Start prednisone 1–2 mg/kg/day or methylprednisolone IV 1–2 mg/kg/day with taper over > 4–6 weeks - If no improvement after 48–72 h, then consider infliximab
4	Life-threatening consequences: urgent intervention indicated	- Generally, warrant permanent ICPi discontinuation (except for endocrine therapy controlled by hormonal replacement)

CTCAE = common terminology criteria for adverse events; *ICPi* = immune checkpoint inhibitors

in tumor signaling and has anti-angiogenic properties. In a phase II Global Trial of Tisotumab Vedotin (InnovaTV204/GOG-3023/ENGOT-cx6) as monotherapy for patients who received two or less prior systemic lines with performance status of 0–1 resulted in a 24% ORR with a median duration of 8.3 months [45•]. Most common adverse effects included ocular /visual toxicity (all: 54%, grade 3: 2%), as well as some bleeding (all: 39, grade 3: 2%), and some peripheral neuropathy (all: 33%, grade 3: 7%). Tivdak was granted accelerated FDA approval for the treatment of adult patients with recurrent of metastatic cervical cancer who have experienced disease progression on or after chemotherapy. This is based on overall response rate of 24% [45•].

Prevention and Management of Tivdak AEs

The usual initial dose of tisotumab vedotin-tftv is 2 mg/kg (maximum dose of 200 mg). Dose reductions are provided by the manufacturer for patients experiencing adverse events. The first dose reduction level is 1.3 mg/kg. The second dose reduction level is 0.9 mg/kg. Permanently discontinue tisotumab vedotin-tftv if unable to tolerate 0.9 mg/kg.

Ocular Toxicity: Tisotumab vedotin-tftv has been shown to induce changes in the corneal epithelium and conjunctiva with subsequent changes in vision, including severed vision loss and corneal ulceration. *Management*: Conduct an ophthalmic exam including visual acuity and slit lamp exam at baseline, prior to each dose, and clinically as indicated. Adherence to ophthalmic care and pre-medications before, during and after infusion is strongly encouraged. Advise patients to avoid wearing contact lenses for the duration of treatment unless advised by their eye care provider. Topical corticosteroid and topical vasoconstrictor ophthalmic drops should be administered prior to each infusion. Cooling packs should be used during infusion. The topical corticosteroid drops should be continued for 72 h after infusion. Topical lubricating ophthalmic drops should be used throughout treatment until 30 days after the last infusion. New or worsening ocular symptoms should be immediately referred to an eye specialist. Adverse reactions can be managed based on the outlined instructions (see Table 7).

Bleeding. The most common hemorrhagic adverse reactions (all grades) were epistaxis, hematuria, and vaginal hemorrhage. The median time to onset of hemorrhage was 0.3 months (range: up to 6.5 months), but the great majority had complete resolution and some experienced partial resolution (defined as a decrease in severity by one or more grades from the worst grade) at last follow-up. Patients should be closely monitored for hemorrhage. Permanently discontinue for any grade pulmonary or CNS hemorrhage. While grade 2 bleeding occurring at any other location, should prompt withholding treatment until bleeding is resolved, then resume at the same dose. For grade 3 bleeding at any other location, withhold treatment until resolved, then resume at the same dose for the first occurrence and permanently discontinue if there is a second occurrence. For grade 4 bleeding at any other location, permanently discontinue treatment.

Table 7 Management of ocular adverse events with tisotumab vedotin and dose modifications

Adverse reaction	Severity	Occurrence	Dose modification
Ocular toxicity: keratitis	Superficial punctate keratitis	Any	Monitor
	Confluent superficial keratitis	First occurrence	Withhold tisotumab vedotin until superficial punctate keratitis or normal, then resume at the next lower dose level
		Second occurrence	Permanently discontinue tisotumab vedotin
	Ulcerative keratitis or perforation	Any	Permanently discontinue tisotumab vedotin
Ocular toxicity: conjunctival ulceration	Any ulceration	First occurrence	Withhold tisotumab vedotin until complete conjunctival re-epithelialization, then resume at the next lower dose level
		Second occurrence	Permanently discontinue tisotumab vedotin
Ocular toxicity: conjunctival or corneal scarring or symblepharon	Any scarring or symblepharon	Any	Permanently discontinue tisotumab vedotin
Ocular toxicity: conjunctivitis or other ocular adverse reactions	Grade 1	Any	Monitor
	Grade 2	First occurrence	Withhold tisotumab vedotin until ≤ grade 1, then resume at the same dose
		Second occurrence	- Withhold tisotumab vedotin until ≤ grade 1, then resume at the next lower dose level - If does not resolve to ≤ grade 1, permanently discontinue tisotumab vedotin
		Third occurrence	Permanently discontinue tisotumab vedotin
	Grade 3 or 4	Any	Permanently discontinue tisotumab vedotin

Peripheral Neuropathy: Peripheral neuropathy occurred in almost half of patients with cervical cancer who received tisotumab vedotin. Peripheral neuropathy adverse reactions included peripheral/sensory/motor neuropathy, as well as muscular weakness, and demyelinating peripheral polyneuropathy. The median time to onset of peripheral neuropathy was 2.4 months). These peripheral neuropathy symptoms either completely or partially resolved by the time of last follow-up. Given the above reported events, patients should be monitored for signs/symptoms of neuropathy which may include paresthesia, tingling or a burning feeling, nerve pain, decreased muscle strength, or dysesthesia). For grade 2 peripheral neuropathy, withhold treatment until ≤ grade 1, then resume at the next lower dose level. Patients experiencing grade 3 or 4 peripheral neuropathy, should have the drug permanently discontinued.

Elahere

Elahere (mirvetuximab soravtansine-gynx) is an ADC targeting the folate receptor-alpha (FRα). It is the first and currently only FRα-targeted treatment for platinum-resistant ovarian cancer who have received 1–3 prior lines of chemotherapy. This indication is based on the results of the recent studies in peer-reviewed literature [46–48••]. Most recently, the MIRASOL trial mature data was presented at ASCO-2023 Annual Meetings supporting the use of mirvetuximab in platinum-resistant ovarian cancer with an updated response rate of 42% [49]. In fact, mirvetuximab is the first treatment to demonstrate a PFS and OS benefit in platinum-resistant ovarian cancer compared to investigator choice. Over one-third of ovarian cancers express high-levels of FRα (via companion testing with VENTANA RxDx Assay) while expression is limited on normal tissues thereby making FRα an attractive therapeutic target [46, 48••]. For all evaluable study patients, the confirmed objective response rate was 26%, including one complete and 11 partial responses, and the median PFS was 4.8 months. The median duration of response was 19.1 weeks. Patients who received three or fewer prior lines of therapy ($n=23$), experienced a notably higher objective response rate of 39%, PFS of 6.7 months, and duration of response of 19.6 weeks were observed [46, 47, 48••, 49].

Prevention and Management of Elahere AEs

The drug is administered intravenously at a dose of 6 mg/kg every 3 weeks based on adjusted ideal body weight until disease progression or unacceptable toxicity. Two dose modifications (1st 5 mg/kg and 2nd 4 mg/kg) are recommended based on the severity of toxicity. Preventive strategies include use of lubricating and ophthalmic topical steroid eye drops during treatment and close ophthalmic professional monitoring and care [50].

Ocular Toxicity Ovarian cancer patients treated with Elahere (mirvetuximab soravtansive) experienced ocular adverse events most commonly, approximately 60%. Of these, 9% were grade 3 which included visual impairment, keratopathy/keratitis (corneal disorder), dry eyes, photophobia, and eye pain. Only one patient (0.2%) experienced grade 4 keratopathy. More commonly, low-grade visual impairment (49%), keratopathy (36%), dry eye (26%), cataract (15%), photophobia (13%), and eye pain (12%) occurred with a median time to onset of 1.2 months. The great majority improved (49% complete resolution and 36% partial resolution). Only 0.6% of study participants permanently discontinued Elahere secondary to ocular toxicity. Before starting the drug, during treatment and for months after, the patients should receive close professional eye care as detailed in the prescriber packet [50]. Mild or grade 1 events should be monitored closely, while grade 2 warrants withholding until grade 1 then resuming at same dose. Grade 3 warrants resuming at lower dose once reaching grade 1, while grade 4 usually warrants permanent discontinuation (Table 8).

Pneumonitis Severe, life-threatening, or fatal pneumonitis occurred in 10% of study patients with ≤ 1% grade 3 or 4. Patients should be closely monitored for symptoms of pneumonitis and the differential diagnoses associated with those symptoms. For grade 2, withhold and resume at the same or lower dose once resolution to grade 1 or less and discontinue if grade 3 or 4 (Table 8).

Peripheral Neuropathy Thirty-six percent of patients treated with Elahere across clinical trials experienced peripheral neuropathy with 2% of those being grade 3. The vast majority were classified as peripheral neuropathy while less common were peripheral sensory- and motor-neuropathy, paraesthesias, neurotoxicity, hypoaesthesis, and oral hypoesthesia (0.2%). These are typically managed by withholding until grade 1 or less and permanently discontinuing for grade 3 or 4 (Table 8). Notably, strong CYP3A4 inhibitors may increase the risk of adverse events for patients on Elahere. The drug is not advised for those with moderate or severe hepatic impairment [total bilirubin > 1.5 ULN (upper limit of normal)], those breastfeeding, and not yet evaluated in the pediatric population [50].

Other drugs worth mentioning, include those blocking the PI3K/AKT/mTOR pathway. The most tested drugs blocking this pathway for gynecologic cancers are temsirolimus, everolimus, and ridaforolimus. Common toxicities reported for this class of drugs include mouth sores (56%), anemia (42%), fatigue (40%), diarrhea (31%), nausea (29%), vomiting (27%), asthenia (24%), and anorexia (22%) [51]. These side effects were mostly managed via supportive care and drug discontinuation when severe.

Table 8 Management of adverse events with mirvetuximab soravtansine-gynx and dose modifications [50]

Adverse event	Severity of adverse event	Dose modification
Keratitis/keratopathy	Nonconfluent superficial	Monitor
	Confluent superficial keratitis, a corneal epithelial defect, or 3-line or more loss in best corrected visual acuity	Withhold dose until improved or resolved, then maintain at same dose level or consider dose reduction
	Corneal ulcer o stromal opacity of best corrected distance visual acuity 20/200 or worse	Withhold dose until improved or resolved, then reduce by one dose level
	Corneal perforation	Discontinue permanently
Uveitis	Grade 1: rare cell in anterior chamber	Monitor
	Grade 2: 1–2 + cell or flare in anterior chamber	Withhold dose util grade1 or less, then maintain at same dose level
	Grade3: 3 + cell or flare in anterior chamber	Withhold dose until grade 1 or less, then reduce by one dose level reduce by one dose level
	Grade 4: Hypopyon	Discontinue permanently
Pneumonitis	Grade 1	Monitor
	Grade 2	Withhold dose util grade1 or less, then maintain at same dose level or reduce by one dose level reduce by one dose level
	Grade 3 or 4	Discontinue permanently
Peripheral neuropathy	Grade 2	Withhold dose until grade 1 or less, then reduce by one dose level
	Grade 3 or 4	Discontinue permanently
Infusion-related reactions/hypersensitivity	Grade 1	Maintain infusion rate
	Grade 2	• Interrupt infusion and administer supportive treatment • After recover from symptoms, resume the infusion at 50% of the previous rate, and if no further symptoms appear, increase rate as appropriate until infusion is completed • Administer additional premedication for future cycles
	Grade 3 or 4	• Immediately stop infusion and administer supportive treatment • Advise patient to seek emergency treatment and immediately notify their healthcare provider if the infusion-related symptoms recur • Discontinue permanently
Other adverse events	Grade 3	Withhold dose until grade 1 or less, then reduce by one dose level
	Grade 4	Discontinue permanently

Recently, Upifitamab Rilsodotin (UpRi) has been suggested as an NaPi2b-directed ADC in gynecologic cancers. The UPLIFT and UPNEXT trials for utility as maintenance therapy in patients with platinum-resistant or platinum-sensitive recurrent ovarian cancer. NaPi2b is a sodium-dependent phosphate transport protein that is widely overexpressed in ovarian cancer with limited expression in normal tissue. Early data from the study suggests an overall response rate of 23% [52, 53].

Conclusions and Future Perspectives

There has been an explosion of drug discovery presenting targeted agents for use in difficult-to-treat gynecologic cancers (Fig. 1). While information regarding AEs is dispersed throughout the medical literature, to our knowledge, this is the only concise and clinically relevant compilation of AEs associated with newer targeted agents used in the care of gynecologic malignancies. Many of the AEs described in this review are self-resolved with minimal therapeutic involvement. Additional strategies may include dose reductions or adjustments, hospitalizations, and supportive care. Expert recommendations on the management of commonly reported symptoms may involve the use of combined modality strategies of complementary/ alternative medicine (CAM) with pharmacologic interventions (as summarized in Table 2). This review allows the providers an opportunity for comprehensive overview of commonly reported AEs associated with gynecologic cancer drugs which allows for expedient diagnosis and timely management of these AEs. Additionally, in the near future, we can expect to see

immunomodulatory drugs, therapeutic oncolytic viruses, and therapeutic vaccines whose side effect profile are still being evaluated.

Abbreviations *ADC*: Antibody–drug conjugate; *ACTH*: Adrenocorticotropic hormone; *ADLs*: Activities daily living; *ADP*: Adenosine diphosphate; *AE*: Adverse event; *Akt*: Protein kinase B; *ALT*: Alanine aminotransferase; *ALM*: Acute myeloid leukemia; *ASCO*: American Society of Clinical Oncology; *AST*: Aspartate transaminase; *ATE*: Arterial thromboembolic event; *BM*: Bowel movement; *BRCA*: Breast CAancer gene; *BRAF*: V-raf murine sarcoma viral oncogene homolog B1; *BRATT*: Bread, rice, applesauce, tea, toast; *CAM*: Complementary/alternative medicine; *CHF*: Congestive heart failure; *CNS*: Central nervous system; *CPK*: Creatine phosphokinase; *CTCAE*: Common terminology criteria for adverse events; *dMMR*: Mismatch repair deficient; *FDA*: Food and Drug Administration (United States); *FRα*: Folate receptor-alpha; *FT*: Fallopian tube; *GERD*: Gastroesophageal reflux disease; *G*: Grade; *H2*: Histamine type-2 receptor antagonists; *HER-2*: Human epidermal growth factor receptor-2; *HFS*: Hand-foot syndrome; *HRD*: Homologous recombination deficient; *5-HT3*: 5-Hydroxytryptamine-3; *ICI*: immune checkpoint inhibitors; *ICPi*: Immune checkpoint inhibitors; *IrAE*: Immune-related adverse event; *KI*: Kinase inhibitor; *LFT*: Liver function test; *LGSOC*: Low-grade serous ovarian cancer; *LLN*: Lower limit of normal; *LVEF*: Left ventricular ejection fraction; *MDS*: Myelodysplastic syndrome; *MEK*: Mitogen-activated protein kinase kinase; *MRI*: Magnetic resonance imaging; *MSI-H*: Microsatellite instability-high; *mTOR*: mammalian target of rapamycin; *N/A*: Not applicable; *NCCN*: National Comprehensive Cancer Network; *NR*: Not reported; *NTRK*: Neurotrophic tyrosine receptor kinase; *OS*: Overall survival; *PARP*: Poly(adenosine diphosphate)-ribose polymerase; *PD-L1*: Programmed death receptor ligands 1; *PFS*: Progression-free survival; *PI3K*: Phosphatidylinositol 3-kinase (PI3K); *PPC*: Primary peritoneal cancer; *PPI*: Proton pump inhibitors; *QTc*: Corrected QT (heart rate) interval; *RCT*: Randomized control trial; *SGO*: Society of Gynecologic Oncology; *TF*: Tissue factor; *TKI*: Tropomyosin receptor kinase; *ULN*: Upper limit of normal; *VEGF-I*: Vascular endothelial growth factor-inhibitor; *VTE*: Venous-thromboembolism events

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Declarations

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Trial Registration Details and Numbers Not applicable.

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