Oncology Oral, Other
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
avapritinib (Ayvakit™)[1]	Blueprint	▪ Treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations; patients should be selected for treatment with avapritinib based on confirmation of the presence of a PDGFRA exon 18 mutation
cabozantinib (Cometriq®)[2]	Exelixis	▪ Treatment of progressive, metastatic medullary thyroid cancer
erdafitinib (Balversa™)[3]	Janssen	▪ Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) that has susceptible fibroblast growth factor receptor (*FGFR*)*-3* or *FGFR2* genetic alterations and progressed during or following ≥ 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy; patients should be selected for therapy based on an FDA-approved companion diagnostic test*,†
larotrectinib sulfate (Vitrakvi®)[4]	Loxo-Bayer, Bayer	▪ Treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment; patients should be selected for treatment based on the *NTRK* gene fusion being present in tumor specimens†
lomustine (Gleostine®)[5]	NextSource Biotechnology	▪ Brain tumors, primary and metastatic, following appropriate surgical and/or radiotherapeutic procedures ▪ Hodgkin's lymphoma in combination with other chemotherapies, following disease progression with initial chemotherapy
niraparib (Zejula®)[6]	Tesaro	▪ Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy ▪ Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy ▪ Treatment of adults with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥ 3 prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either: 1) a deleterious or suspected deleterious BRCA mutation or 2) genomic instability and who have progressed > 6 months after response to the last platinum-based chemotherapy; patients should be selected for treatment based on an FDA-approved companion diagnostic test*

* Use of FDA-approved companion diagnostics can be found at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

† This approval was an Accelerated Approval based on objective or overall response rate, duration of response, and/or tumor response rate. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
olaparib (Lynparza®)[7]	AstraZeneca	▪ Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (*gBRCAm* or *sBRCAm*) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy; select patients for treatment based on an FDA-approved companion diagnostic* ▪ In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation, and/or 2) genomic instability; patients should be selected for treatment based on an FDA-approved companion diagnostic test* ▪ Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy ▪ Treatment of adult patients with deleterious or suspected deleterious germline *gBRCAm* advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy; select patients for treatment based on an FDA-approved companion diagnostic* ▪ Patients with deleterious or suspected deleterious *gBRCAm*, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting; patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy; patients should be selected for treatment based on the FDA-approved companion diagnostic* ▪ Maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on ≥ 16 weeks of a first-line platinum-based chemotherapy regimen; patients should be selected for treatment based on an FDA-approved companion diagnostic test* ▪ Treatment of adults with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone; patients should be selected for treatment based on an FDA-approved companion diagnostic test*
pemigatinib (Pemazyre™)[8]	Incyte	▪ Treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement as detected by an FDA-approved test†
pexidartinib (Turalio™)[9]	Daiichi Sankyo	▪ Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery

* Use of FDA-approved companion diagnostics can be found at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

† This approval was an Accelerated Approval based on objective or overall response rate, duration of response, and/or tumor response rate. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
regorafenib (Stivarga®)[10]	Bayer	▪ Treatment of metastatic colorectal cancer (CRC) patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy ▪ Treatment of patients with locally advanced, unresectable, or metastatic GIST who have been previously treated with imatinib mesylate and sunitinib malate ▪ Treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib
ripretinib (Qinlock™)[11]	Deciphera	▪ Treatment of adults with advanced GIST who have received prior treatment with ≥ 3 kinase inhibitors, including imatinib
rucaparib (Rubraca®)[12]	Clovis	▪ Maintenance treatment of adult patients with recurrent ovarian cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy ▪ Treatment of patients with deleterious, *BRCA* mutation (germline and/or somatic) associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies. Patients should be selected for treatment based on the FDA-approved companion diagnostic*,† ▪ Treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy†; patients should be selected for treatment based on the presence of a deleterious BRCA mutation (germline and/or somatic)
selumetinib (Koselugo™)[13]	AstraZeneca	▪ Treatment of pediatric patients ≥ 2 years of age with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)
tazemetostat (Tazverik®)[14]	Epizyme	▪ Treatment of adults and pediatric patients ≥ 16 years with metastatic or locally advanced epithelioid sarcoma (ES) not eligible for complete resection† ▪ Treatment of adults with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies† ▪ Treatment of adult patients with R/R FL who have no satisfactory alternative treatment options†
temozolomide (Temodar®)[15]	generic, Merck	▪ Treatment of adult patients with newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment ▪ Refractory anaplastic astrocytoma in adult patients who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
trifluridine/ tipiracil (Lonsurf®)[16]	Taiho	▪ Patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy ▪ Treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with ≥ 2 prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy
vandetanib (Caprelsa®)[17]	Genzyme	▪ Symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease§

§ Use vandetanib (Caprelsa) in patients with indolent, asymptomatic, or slowly progressing disease only after careful consideration of the treatment-related risks of vandetanib (Caprelsa).

The Cabometyx® brand of cabozantinib, by Exelixis, is indicated for the treatment of renal cell carcinoma in select patients and will not be included in this therapeutic class review; however, this review will include the Cometriq brand of cabozantinib, also by Exelixis, which is indicated for the treatment of medullary thyroid carcinoma. Cabometyx and Cometriq should not be used interchangeably.[18,19]

OVERVIEW

The agents in this review are indicated for the treatment of a variety of malignant solid tumors, and one is also indicated for the hematologic malignancy, follicular lymphoma (FL). Many of the drugs included in this review, particularly the ones approved within the last 5 years, are examples of precision medicine where the FDA approved indication is defined by the use of a biomarker to -drive appropriate patient selection.

There is little to no role for lomustine (Gleostine) in the contemporary management of Hodgkin's lymphoma; this indication will not be discussed in this review.[20]

Bladder Cancer

In 2020, an estimated 81,400 primary urinary bladder cancers will be diagnosed in the United States (US). An estimated 17,980 deaths will occur in 2020 due to these malignancies.[21] Bladder cancer is the fourth most common cancer in US men but is less common in women. In addition, the median age at diagnosis is 73 years, and as a result, patients commonly have coexisting medical conditions. Types of bladder cancers include urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and sarcoma with urothelial carcinoma being the most common.[22] Risks factors for bladder cancer include male gender, white race, smoking, personal/family history, radiation to the pelvic region, environmental exposure (e.g., occupational or drug-related), chronic urinary tract infection, as well as obesity and diabetes.[23]

In April 2019, erdafitinib (Balversa) received FDA approval for the treatment of certain patients with locally advanced or metastatic urothelial carcinoma. The version 6.2020 National Comprehensive Cancer Network (NCCN) guidelines for bladder cancer include a role for erdafitinib in patients with *FGFR3* or *FGFR2* genetic alterations in second- and subsequent-line therapy.[24] For patients who have previously received platinum-based therapy, erdafitinib is an alternative preferred regimen in the second-line setting. Also in the second-line setting, for patients who previously received a checkpoint inhibitor,

erdafitinib is listed under other recommended regimens (both category 2A). Erdafitinib is a preferred drug in subsequent lines therapy for patients with *FGFR3* or *FGFR2* genetic alterations (category 2A).

Breast Cancer

Olaparib (Lynparza) is approved for the treatment of germline *BRCA*-mutated metastatic breast cancer. The 5.2020 NCCN guidelines for breast cancer include olaparib tablets as a category 1, preferred treatment of patients with recurrent or stage 4 breast cancer with an identified germline *BRCA1/2* mutation. While the FDA indication restricts the use of olaparib to patients who are human epidermal growth factor receptor type 2 (HER2)-negative, the NCCN supports use in any breast cancer subtype when a germline *BRCA1/2* mutation is detected.[25]

Central Nervous System (CNS) Cancer

In 2020, an estimated 23,890 primary brain tumors or other cancers of the CNS will be diagnosed in the US. An estimated 18,020 deaths will occur in 2020 due to these malignancies.[26] High-grade gliomas are the most common type of primary brain tumors in adults. Glioblastoma is associated with the highest degree of mortality of all brain tumors with 5-year survival rates of 1% to 9%.[27] The 2 agents included in this review, lomustine (Gleostine) and temozolomide (Temodar), are utilized in the setting of both low-grade gliomas and high-grade gliomas, including glioblastoma. The management of primary brain tumors usually involves surgical resection to the greatest degree possible without causing extensive morbidity. Surgical intervention also plays an important role in establishing a tissue diagnosis. More aggressive tumor types are also usually treated with radiation therapy unless there is a contraindication to that treatment modality. Combination radiation therapy (RT) with either temozolomide or PCV (procarbazine + lomustine + vincristine) is frequently utilized in the management of these CNS tumors.

According to the NCCN guidelines 2.2020, the subsequent management of low-grade gliomas is based on the degree of surgical resection.[28] For patients with low-grade gliomas, adjuvant chemotherapy is recommended for patients at high risk due to either a subtotal gross resection or aged ≥ 40 years. Adjuvant therapy options include either PCV or temozolomide which may be given with RT. PCV plus RT is a NCCN category 1 recommendation while temozolomide plus RT is a category 2A recommendation. Temozolomide may also be given concurrently with RT in the adjuvant setting (category 2A). These agents may also be utilized in the event of recurrence of low-grade gliomas.

High-grade gliomas include anaplastic gliomas, such as anaplastic astrocytoma, and glioblastoma. For patients with anaplastic gliomas who have undergone maximal safe resection, adjuvant options include PCV or temozolomide with RT. If these patients have a poor performance status, either RT alone or chemotherapy alone (temozolomide, but not PCV) may be considered if the tumor is O-6-methylguanine-DNA methyltransferase (MGMT) promotor methylated (category 2B). MGMT is a DNA repair enzyme that reverses DNA damage caused by alkylating agents and, therefore, confers resistance to DNA-alkylating chemotherapy drugs, such as temozolomide; however, methylation of the MGMT promoter silences MGMT.

Advances in genetic testing have led to new findings in the treatment of glioblastomas. Testing for MGMT promoter status (methylated or unmethylated or indeterminate) in patients with glioblastoma is utilized to help stratify treatment decisions. In addition to MGMT promotor status, the choice of adjuvant therapy is also stratified by the patient's age and performance status.[29]

Cholangiocarcinoma

Cholangiocarcinoma are tumors originating in the epithelium of the bile duct. They are typically classified as either intrahepatic or extrahepatic, depending on their location within the biliary tree.[30] Cholangiocarcinoma is rare in the US, where about 8,000 people are diagnosed each year. This may be an underestimate of the actual number of cases because these cancers can be difficult to diagnose and may often be classified as other types of cancer such as hepatocellular carcinoma or cancer of unknown origin. The average age at diagnosis is between 70 and 72 years of age.[31] Treatment includes a surgical consultation to assess if the patient is a candidate for resection or possible organ transplantation. For patients with unresectable or metastatic disease, there is an increasing role for molecular profiling. Intrahepatic cholangiocarcinoma harbors *IDH1/2* mutations in 10% to 23% of cases and mutations in *FGFR2* fusions occur in 8% to 14%.[32] The prognostic significance of these mutations are unknown, but they do provide an opportunity for targeted therapies. The NCCN guidelines for hepatobiliary cancers recommends the use of the targeted therapy pemigatinib as subsequent line therapy for patients with cholangiocarcinoma found to have *FGFR2* fusions or rearrangements (category 2A).[33]

Colon Cancer

In the US, colon cancer is the third most commonly diagnosed cancer, as well as the third leading cause of death from cancer in both men and women. In 2020, an estimated 104,610 cases of colon cancer will be diagnosed, and an estimated 53,200 deaths will occur in the US.[34] NCCN guidelines 4.2020 for colon cancer indicate both regorafenib (Stivarga) and trifluridine/tipiracil (Lonsurf) are treatment options for patients who have progressed through all other standard regimens.[35] Although the FDA-approved dose of regorafenib (Stivarga) is 160 mg daily for 21 days of a 28-day cycle, the NCCN Guidelines note it is common practice to start at a lower dose of regorafenib for the first cycle, giving 80 mg for first 7 days followed by 120 mg daily on days 8 through 14, and then 160 mg daily on days 15 through 21.[36]

Epithelioid Sarcoma

Epithelioid sarcoma is a rare soft tissue sarcoma that typically occurs in young adults, most commonly in the upper extremities affecting the fingers, forearms, and hands. It may also occur in the legs, trunk, head, or neck. It occurs less frequently in young children and older adults. Epithelioid sarcoma tends to have a high rate of recurrence and a propensity to metastasize.[37] The NCCN guidelines for soft tissue sarcoma now include tazemetostat as a single agent for treatment of metastatic or locally advanced epithelioid sarcoma for patients not eligible for complete resection (category 2A).[38]

Follicular Lymphoma

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphoma (NHL) and accounts for approximately 22% of all newly diagnosed cases of NHL.[39] While the clinical course of FL is usually indolent with a median survival of 8 to 10 years, some patients may undergo conversion to a more aggressive lymphoma and this risk increases over time, with about 30% of FL patients converting to a more aggressive lymphoma at 10 years post-FL diagnosis. The NCCN guidelines recommend tazemetostat for second or subsequent line therapy of relapsed/refractory FL in patients who are *EZH2* mutation-positive and have received 2 prior therapies or in relapsed/refractory FL patients who are *EZH2* wild type (WT) but have no satisfactory treatment options.

Gastric Cancer

In 2020, an estimated 27,600 primary stomach cancers will be diagnosed in the US, and an estimated 11,010 deaths will occur due to these malignancies.[40] In February 2019, the combination drug trifluridine/tipiracil (Lonsurf) received a new indication for the treatment of metastatic gastric cancer.[41] The NCCN guidelines 2.2020 on gastric cancer include trifluridine/tipiracil as a preferred second-line or subsequent therapy option for patients with unresectable locally advanced, recurrent, or metastatic disease (category 1).[42]

Gastrointestinal Stromal Tumors (GIST)

GISTs are soft tissue sarcomas occurring in the gastrointestinal (GI) tract. Mutational testing is recommended to determine pharmacologic therapy. The vast majority (95%) of GISTs express *KIT* (CD117) mutations and the majority of patients with this mutation respond to imatinib (Gleevec), which is the primary pharmacologic mainstay of the management of GISTs.[43]

Additional tyrosine kinase inhibitors (TKIs) are now available that may play a role for patients who progress on or do not tolerate imatinib. In addition to imatinib, other FDA approved TKIs for the treatment of GIST include sunitinib (Sutent), regorafenib and, most recently, both avapritinib (Ayvakit) and ripretinib (Qinlock) have been approved for the treatment of advanced GIST. Avapritinib plays a role in patients with *PDGFRA D842V* mutations.

According to the 2.2020 NCCN guidelines, addressing the treatment of unresectable or metastatic GIST, avapritinib is a preferred, category 2A recommendation for patients with *PDGFRA D842V* mutations while regorafenib is a category 1 recommendation for third-line treatment after imatinib and sunitinib and ripretinib is a fourth-line recommendation after imatinib, sunitinib and regorafenib (category 2A).[44]

Hepatocellular Carcinoma (HCC)

Despite the downward trend seen with many other types of cancer, both the incidence and mortality associated with HCC are increasing by 2% to 3% annually through 2007 to 2016. The majority of these cases (71%) are potentially preventable due to modifiable risk factors, such as obesity, excess alcohol consumption, cigarette smoking, and hepatitis B and C viruses.[45] The 4.2020 NCCN guidelines outline the role of regorafenib as subsequent-line therapy upon disease progression after first-line systemic therapy for patients with Child-Pugh Class A liver function (category 1).[46]

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is a rare, genetic condition caused by mutations in the NF1 gene.[47] It is inherited in an autosomal dominant fashion and affects the skin, skeletal system, and the peripheral nervous system. Clinical presentation includes dark-colored skin spots (known as café-au-lait macules), underarm and groin freckles, and benign neurofibromas (growths on the nerves). The amount of neurofibromas usually increases with time, and these growths can become cancerous. Disease symptoms and severity depend on the patient, and treatment is individualized based on signs and symptoms and may include surgery for removal of neurofibromas that are disfiguring, causing morbidity, or are cancerous. NF1 occurs in approximately 1 in 2,500 births and has a prevalence of 1 in 2,000 to 4,000. Approximately 30% to 50% of patients develop 1 or more plexiform neurofibromas (PN), tumors involving the nerve sheath. It is estimated that 5% of patients with neurofibromatosis develop a soft tissue sarcoma (STS), and malignant peripheral nerve sheath tumors (MPNSTs) are the most common

type. These tumors develop from neurofibromas that were previously benign. The NCCN version 2.2020 soft tissue sarcoma clinical practice guidelines addresses the management of NF1; however, selumetinib has not been addressed in these guidelines to date. In general, patients with NF1 carry an increased risk for the development of MPNSTs and GIST. Therefore, consideration should be given to surveillance (e.g., whole body magnetic resonance imaging (MRI) for second primary sarcomas. For patients with NF1 that is unresectable, primary treatment options include radiation therapy, chemoradiation, chemotherapy, regional limb therapy, or amputation (category 2A for all).

NTRK Gene Fusion

Cancers that commonly exhibit the *NTRK* gene fusion are rare but can include both pediatric and adult cancers.[48] The November 2018 FDA approval of larotrectinib (Vitrakvi) at that time marked the second approval of cancer therapy based on a specific biomarker rather than the primary tumor location, which is also known as a "tissue agnostic" agent. The clinical studies used for approval of larotrectinib were conducted in patients with a solid tumor with the *NTRK* gene fusion without a resistance mutation and had disease that was metastatic or where surgical resection would result in severe morbidity. Patients enrolled either had no adequate alternative therapies or had cancer progression after previous therapy. Although the clinical studies enrolled patients with a variety of tumor types, the most common types of cancer in adults were soft tissue sarcoma, salivary gland cancer, and thyroid cancer.[49]

In addition to its inclusion by NCCN for soft tissue sarcoma and thyroid cancer as described above, the NCCN 2.2020 head and neck cancer guidelines include larotrectinib as useful in certain circumstances for patients with salivary gland tumors that have recurred and have distant metastases.[50] It is recommended specifically for patients with a performance status of 0 to 3 for patients with *NTRK* gene fusion-positive tumors (category 2A).

Ovarian Cancer (Including Fallopian Tube or Primary Peritoneal Cancer)

Ovarian cancer is the fifth most common cause of cancer-related death in US women. The risk of ovarian cancer increases with age, and the median age at diagnosis is 63 years. Greater than 70% of patients present with advanced disease, and less than 40% of women with ovarian cancer are cured.[51] Ovarian cancer has been shown to have a higher prevalence in families with *BRCA1* or *BRCA2* genotypes and, in these patients, the onset of disease is usually at a younger age; however, patients with these mutations or other genetic predispositions account for only 15% of all ovarian cancers.[52]

Primary treatment for advanced ovarian cancer usually begins with cytoreductive surgery to remove as much gross disease as possible because patients with more complete debulking have better outcomes.[53] The majority of patients, excluding those with very early stage disease, are recommended to receive postoperative, adjuvant systemic chemotherapy. Recommended protocols generally include a taxane (paclitaxel or docetaxel) and a platinum agent (cisplatin or carboplatin). Intraperitoneal chemotherapy is recommended in addition to intravenous chemotherapy in certain clinical situations. A newer class of orally targeted agents, the poly ADP-ribose polymerase (PARP) inhibitors, also are available for the treatment of ovarian cancer. There are currently 3 FDA-approved PARP inhibitors approved for use in ovarian cancer on the market including niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca). Olaparib was the first PARP inhibitor approved by the FDA in late 2014, and approval was limited to patients who had a germline *BRCA* mutation, advanced disease, and received ≥ 3 previous lines of chemotherapy. Since that time, the FDA-approved indications and the role of PARP inhibitors in ovarian cancer has continued to expand. Selection of patients with advanced ovarian cancer who have a high

likelihood of responding to PARP inhibitors has also been expanded to include patients identified as being homologous recombination deficiency (HRD)-positive. HRD positivity is defined as having either a deleterious *BRCA* mutation (germline or somatic) and/or a genomic instability as identified by an appropriate test. Similar to olaparib, niraparib is now approved for patients who have received ≥ 3 prior lines of therapy and whose cancer is associated with HRD positive status, while rucaparib is approved for patients who have received ≥ 2 lines of chemotherapy and have an identified deleterious *BRCA* mutation (germline and/or somatic).

In addition to these later lines of therapy, olaparib, niraparib and rucaparib are all now FDA approved for use in the setting of platinum-sensitive (complete or partial response) recurrent disease, regardless of *BRCA* and/or HRD status. Two of the PARP inhibitors (olaparib, niraparib) are also approved for patients with platinum sensitive disease who experienced a complete response (CR) or partial response (PR) to first-line platinum-based chemotherapy. Olaparib has an indication for maintenance treatment in the first-line setting either as a single agent or in combination with bevacizumab. Use of olaparib in this setting is limited to patients with germline or somatic *BRCA*-mutated (*gBRCAm* or *sBRCAm*) disease. Niraparib is indicated for first-line maintenance regardless of biomarker status for patients who are in a CR or PR to first-line platinum-based chemotherapy.[54]

The NCCN guidelines suggest that either niraparib, olaparib, or rucaparib can be used for maintenance therapy, if in CR or PR for patients with both platinum-sensitive or platinum-resistance disease who have completed ≥ 2 lines of platinum-based therapy (all category 2A) and who have appropriate biomarker status as outlined in their FDA indication.[55] For first-line maintenance therapy in patients with a CR or PR to first-line therapy, the NCCN guidelines are stratified by whether or not the patient received bevacizumab in the first-line setting. If no bevacizumab was used during primary therapy, and the patient had a CR or PR and is *BRCA1/2* WT or unknown, niraparib is a category 2A recommendation. If the patient who received first-line platinum plus bevacizumab and who had a CR or PR has a deleterious BRCA mutation (germline or somatic), NCCN recommends either olaparib or niraparib (both category 1). If bevacizumab was not used as part of first-line therapy and patients are *BRCA WT* or unknown, bevacizumab plus olaparib is a category 1 recommendation for patients with a CR or PR to first-line platinum. In this same group of patients (first-line platinum therapy without bevacizumab who achieved a CR or PR) but who have an identified deleterious BRCA mutation (germline or somatic), the NCCN guidelines recommend bevacizumab plus olaparib (category 1), single agent olaparib (category 2A), or single agent niraparib (category 2A).[56]

Pancreatic Cancer

Pancreatic cancer is the ninth and tenth most commonly diagnosed malignancy in US women and men, respectively, but is the fourth leading cause of cancer death for both. In 2020, an estimated 57,600 new cases of pancreatic will be diagnosed and there will be an estimated 47,050 deaths due to pancreatic cancer.[57] Known risk factors for the development of pancreatic cancer include cigarette smoking, environmental exposure to chemical pesticides, asbestos and heavy metals, heavy alcohol consumption, a history of chronic pancreatitis and an increased body mass index (BMI). There is a complex relationship between a diagnosis of diabetes and the risk for developing pancreatic cancer; variables include age at diabetes diagnosis and the use of diabetic medications. There is also a known higher incidence of pancreatic cancer in families harboring BRCA1/2 mutations. BRCA 1/2 mutations occur at a frequency of 4% to 7% of patients diagnosed with pancreatic cancer.[58] The NCCN guidelines recommend the use of olaparib as maintenance therapy following first-line chemotherapy for certain patients with metastatic

pancreatic cancer. Patients eligible for olaparib maintenance include those with a good performance status who have had no disease progression after at least 4 to 6 months of chemotherapy, assuming acceptable toxicity, and who have a germline BRCA 1/2 mutation (category 2A).[59]

Prostate Cancer

In the US, prostate cancer is the most commonly diagnosed cancer in men (excluding non-melanoma skin cancers), with an estimated 191,930 cases projected to be diagnosed in 2020. While prostate cancer accounts for the largest percentage of diagnosed cases in US males (21%), it only accounts for about 10% of all cancer deaths in this population with an estimated 33,330 deaths predicted to occur in 2020. Prostate cancer is rare in men under the age of 40 years, but the risk increases with each subsequent decade of life. Overall, 1 in 9 US men will develop prostate cancer during their lifetime. Aside from age, the risk factors most strongly associated with development of prostate cancer include race/ethnicity and family history. Prostate cancer mortality in non-Hispanic African Americans is more than twice that seen in the US Caucasian population.[60]

The role of germline testing in prostate cancer has increased with the advances in precision medicine. Identifying alterations to homologous DNA repair genes is now recognized as an important component of prostate cancer management.[61] Approximately 12% to 17% of men with metastatic prostate cancer harbor germline mutations, the vast majority of these in DNA repair genes including *BRCA1* and *BRCA2*, with *BRCA2* being the more common.[62]

The NCCN guidelines for use of olaparib in prostate cancer give a category 1 rating to the use of olaparib as second-line therapy after first-line therapy with androgen receptor-directed therapy, such as abiraterone (Zytiga®, Yonsa®) or enzalutamide (Xtandi®) for patients with metastatic CRCP and a pathogenic mutation (germline or somatic) in homologous recombination repair (HRR). The NCCN guideline lists the impacted genes which would be considered as part of HRR to include *BRCA1, BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*. Furthermore, the NCCN notes that olaparib is not recommended in patients with *PPP2R2A* mutations as patients with this mutation had an unfavorable risk to benefit profile with olaparib in the clinical trial.[63]

Rucaparib is a NCCN category 2A-rated option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline or somatic) who have been treated with androgen-directed therapy and a taxane-based chemotherapy, which aligns with the FDA approved indication. The NCCN does note that rucaparib can be considered even if taxane-based therapy has not been given for patients who are not fit for chemotherapy.[64]

Soft Tissue Sarcoma

In 2020, an estimated 13,130 primary soft tissue cancers will be diagnosed in the US.[65] There are numerous types of soft tissue sarcoma ranging from malignant to benign in nature.[66] Tenosynovial giant cell tumors (TGCT), also known as nodular tenosynovitis, are benign tumors of the joint tissue. Although this rare tumor type is benign, it can be locally aggressive and can lead to decreased mobility in the affected joint or extremity.[67] In August 2019, the FDA approved pexidartinib (Turalio), the first systemic treatment for patients with TGCT.[68] The 2.2020 NCCN soft tissue sarcoma guidelines include pexidartinib as a category 1 recommendation for TGCT/pigmented villonodular synovitis.[69] It is listed specifically as a systemic therapy option alongside imatinib (category 2A) for these patients.

In addition, the NCCN 2.2020 soft tissue sarcoma (STS) guidelines include larotrectinib for *NTRK* gene-fusion sarcomas (category 2A) along with several other single agents and combination regimens for soft tissue sarcoma subtypes with non-specific histologies.[70]

Thyroid Carcinoma

The 3 main histologic types of thyroid carcinoma are differentiated carcinoma (which includes papillary, follicular, and Hürthle cell), medullary carcinoma, and anaplastic carcinoma. The 2.2020 NCCN guidelines for the treatment of thyroid carcinoma list vandetanib or cabozantinib as category 1, preferred options in the treatment of medullary thyroid carcinoma with locoregional recurrent or persistent disease that is unresectable and symptomatic or progressing.[71] Notably, however, the guidelines state that increasing tumor markers in the absence of structural disease progression are not an indication for treatment with vandetanib or cabozantinib. Vandetanib or cabozantinib may also be used in the setting of recurrent or persistent disease where there are distant metastases. For both symptomatic and asymptomatic patients with distant metastatic disease, vandetanib and cabozantinib given as single agents are category 1, preferred regimens. The NCCN 2.2020 thyroid carcinoma guidelines recommend larotrectinib for the treatment of locally recurrent, advanced, and/or metastatic disease that is not amenable to radioactive iodine (RAI) therapy in patients who are *NTRK* gene fusion positive.

PHARMACOLOGY[72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88]

Temozolomide (Temodar) and lomustine (Gleostine), as alkylating agents, and trifluridine/tipiracil (Lonsurf), a thymidylate synthase inhibitor, are considered traditional cytotoxic chemotherapeutic agents. The rest of the agents included in this review can be classified as biologic response modifiers.

Traditional cytotoxic chemotherapy agents interfere with DNA synthesis and replication largely by targeting rapidly proliferating cells. These types of traditional cytotoxic chemotherapy agents lack selectivity for tumor cells and are lethal to both tumor and normal cells. Although the rapid proliferation of most types of cancer lends some degree of selectivity for malignant cells, the selectivity is incomplete and dose-limiting damage to normal cells also occurs.

Temozolomide is a prodrug that undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA.

Trifluridine is a thymidine-based nucleoside analog while tipiracil is a thymidine phosphorylase inhibitor. Tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. After uptake into cancer cells, trifluridine is incorporated into DNA where it interferes with DNA synthesis and inhibits cell proliferation.

Lomustine (Gleostine) is a nitrosourea alkylating agent that alkylates both DNA and RNA. Lomustine is unique amongst alkylating agents as it crosses the blood brain barrier and can be found in the CNS in measurable concentrations.

The remaining agents included in this review are broadly classified as biologic response modifiers. Advances in molecular biology, as well as the decoding of the human genome, have identified a number of pathways and potential targets related specifically to cancer cell growth and survival. Many of these agents target intracellular signal transduction pathways. These signal transduction pathways are known to lead to uncontrolled cellular growth and proliferation, tumor metastasis, and prevention of apoptosis in malignant cells. Protein kinase inhibitors function by binding to the adenosine triphosphate (ATP)

binding site found on receptor and non-receptor tyrosine kinase proteins. If the ATP binding site is occupied by a protein kinase inhibitor, ATP is unable to bind and, hence, cannot donate a phosphate group to the protein residue on the substrate and activate the target protein. Therefore, activation of downstream signaling pathways that could lead to uncontrolled tumor cell growth and differentiation is inhibited. Agents included in this review that can be classified as signal transduction inhibitors include avapritinib (Ayvakit), cabozantinib (Cometriq), erdafitinib (Balversa), pexidartinib (Turalio), regorafenib (Stivarga), ripretinib (Qinlock), and vandetanib (Caprelsa). These agents inhibit various tyrosine kinases. Avapritinib targets *PDGFRA* and *PDGFRA D842* mutants, as well as multiple *KIT e*xon 11, 11/17, and 17 mutants. Cabozantinib inhibits vascular endothelial growth factor (VEGF) and RET, a glial cell-line derived neurotrophic factor. Erdafitinib inhibits fibroblast growth factor receptor (*FGFR*)-1, *FGFR2*, *FGFR3* and *FGFR4*. Pexidartinib inhibits colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) with an internal tandem duplication (ITD) mutation. In TGCT, cell proliferation in the synovium is caused by excessive expression of the CSF1 receptor ligand. *In vitro* and *in vivo*, pexidartinib demonstrated the ability to block cell proliferation that is dependent on the CSF1 receptor. Regorafenib inhibits BRAF, ABL, VEGF, stem cell factor c-kit, ephrin A (EPHA2), platelet derived growth factor (PDGF), and RET. Vandetanib inhibits SRC, VEGF, EPHA2, and EGFR. Ripretinib has activity against *KIT* and *PDGFRA* kinases, including those with wild-type, primary, and secondary mutations, as well as additional kinases. Larotrectinib (Vitrakvi) is not a tyrosine kinase inhibitor, but rather a tropomyosin receptor kinase (TRK) inhibitor; it inhibits TRKA, TRKB, and TRKC. These TRKs are produced by the *NTRK1*, *NTRK2*, and *NTRK3* genes. Pemigatinib (Pemazyre) also is not a tyrosine kinase inhibitor; it is a small molecule kinase inhibitor that inhibits the phosphorylation and signaling of *FGFR1, 2*, and *3* with half maximal inhibitory concentration (IC-50) values of < 2 nanomolar (nM); pemigatinib decreases the viability of malignant cells with activating *FGFR* amplifications and fusions. Selumetinib (Koselugo) is also not a tyrosine kinase inhibitor; rather, it is a mitogen-activated protein kinase kinases 1 and 2 (*MEK1/2*) inhibitor. The rapidly accelerated fibrosarcoma (RAF)-MEK-extracellular signal-related kinase (ERK) pathway is frequently activated in various types of cancers, and the *MEK1/2* are regulator proteins of this RAS-regulated ERK pathway.

Niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca) are inhibitors of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. These enzymes are involved in the body's normal DNA repair mechanisms. PARP inhibitors prevent normal base excision repairs in single-stranded DNA breaks and thus make the cell more susceptible to a double stranded DNA break and corresponding cell death.[89] Increased cytotoxicity and anti-tumor activity appears to occur in *BRCA*-mutated ovarian cancer cells.

Tazemetostat (Tazverik) inhibits EZH2 methyltransferase. EZH2 methyltransferase, a subunit of the polycomb repressive complex 2 (PRC2), catalyzes methylation of lysine 27 of histone H3, which leads to repression of gene transcription and subsequent growth of cancer cells.

PHARMACOKINETICS[90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106]

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Effect of High Fat Meal (%)
avapritinib (Ayvakit)	32–57	98.8	CYP 3A4 (primary); CYP2C9 (minor)	None	Feces: 70 Urine: 18	AUC: ▲29 Cmax: ▲59
cabozantinib (Cometriq)	55	≥ 99.7	CYP 3A4 (major); CYP2C9 (minor)	None	Feces: 54 Urine: 27	AUC: ▲ 41 Cmax: ▲ 57
erdafitinib (Balversa)	59	99.8	CYP2C9; CYP3A4	None	Feces: 69 Urine: 19	No effect
larotrectinib (Vitrakvi)	2.9	70	CYP3A4	nr	Feces: 58 Urine: 39	AUC: no effect Cmax: ▼ 35
lomustine (Gleostine)	16–48	nr	metabolic pathways have not been characterized	nr	Urine: 50	nr
niraparib (Zejula)	36	83	carboxylesterases	None	Feces: 39 Urine: 48	No effect
olaparib (Lynparza)	11.9	82	CYP3A4	None	Feces: 6 Urine: 15	AUC: ▲ 20
pemigatinib (Pemazyre)	15.4	90.6	CYP3A4	nr	Feces: 82.4 Urine: 12.6	No effect
pexidartinib (Turalio)	26.6	99	CYP3A4 (oxidation); UGT1A4 (glucuronidation)	nr	Feces: 65 Urine: 27	AUC: ▲ 100 Cmax: ▲ 100
regorafenib (Stivarga)	28	99.5	CYP3A4 UGT1A9	M-2 (N-oxide) M-5 (N-oxide and N-desmethyl)	Feces: 71 Urine: 19	AUC: ▲ 48 Cmax: nr
ripretinib (Qinlock)	14.8	> 99%	CYP3A4 (major); CYP2C8; CYP2D6 CYP2E1 (minor for DP-5439)	DP-5439 (equal activity)	Feces: 34 Urine: 0.02	No effect
rucaparib (Rubraca)	17–19	70	CYP2D6 (major); CYP1A2; CYP3A4	nr	nr	AUC: ▲ 38 Cmax: ▲ 20

nr = not reported

Pharmacokinetics (continued)

Drug	Half-Life (hr)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Effect of High Fat Meal (%)
selumetinib (Koselugo)	6.2	98.4	CYP3A4 (major); CYP2C19; CYP1A2; CYP2C9; CYP2E1; CYP3A5; UGT1A1; UGT1A3	N-desmethyl selumetinib	Feces: 59 Urine: 33	AUC: ▼16 Cmax: ▼50
tazemetostat (Tazverik)	3.1	88	CYP3A	none	Feces: 79 Urine: 15	No effect
temozolomide (Temodar)	1.8	15	hydrolysis	MTIC	Feces: 0.8 Urine: 38	AUC: ▼9 Cmax: ▼32
trifluridine/tipiracil (Lonsurf)	1.4/2.1	> 96	thymidine phosphorylase	None	Urine: 1.5/29.3	AUC: unchanged (trifluridine); ▼40 (tipiracil) Cmax: ▼40 (both)
vandetanib (Caprelsa)	19 days	90	CYP3A4; flavin-containing monooxygenase enzymes FM01 and FM03	N-oxide N-desmethyl	Feces: 44 Urine: 25	None

nr = not reported

CONTRAINDICATIONS/WARNINGS[107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123]

Contraindications

There are no listed contraindications with avapritinib (Ayvakit), cabozantinib (Cometriq), erdafitinib (Balversa), larotrectinib (Vitrakvi), lomustine (Gleostine), niraparib, (Zejula), olaparib (Lynparza), pemigatinib (Pemazyre), pexidartinib (Turalio), rucaparib (Rubraca), regorafenib (Stivarga), ripretinib (Qinlock), selumetinib (Koselugo), tazemetostat (Tazverik), or trifluridine/tipiracil (Lonsurf).

Temozolomide (Temodar) is contraindicated in patients with hypersensitivity to the active drug or any of the components.

Vandetanib (Caprelsa) should not be used in patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome.

Boxed Warnings

Pexidartinib (Turalio) and regorafenib (Stivarga) have Boxed warnings regarding hepatotoxicity. Severe and sometimes fatal hepatotoxicity was observed in clinical trials and hepatic function should be monitored prior to and during treatment with pexidartinib and regorafenib. Therapy with pexidartinib as well as regorafenib should be interrupted, reduced, or discontinued for hepatotoxicity manifested by elevated liver function tests or hepatocellular necrosis (for regorafenib), depending upon severity and persistence.

Vandetanib (Caprelsa) carries a Boxed warning for QT prolongation, torsades de pointes, and sudden death. Due to these risks, it should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or in patients experiencing long QT syndrome. Hypocalcemia, hypokalemia, and hypomagnesemia must be corrected before initiating therapy. Concomitant use of medications associated with QT prolongation should be avoided. Monitor electrocardiograms (ECGs) and levels of serum potassium, calcium, magnesium, and thyroid stimulation hormone (TSH) at baseline, 2 to 4 weeks, and 8 to 12 weeks after vandetanib initiation, and every 3 months thereafter and after dose adjustments.

Lomustine (Gleostine) has a Boxed warning regarding delayed, dose-related, and cumulative myelosuppression; fatal toxicity occurs with overdosage of lomustine and the patient should be counseled that they will take only 1 dose of lomustine every 6 weeks. Thrombocytopenia is generally more severe than leucopenia; blood counts should be monitored and lomustine administered only once every 6 weeks.

Selected Warnings and Recommended Monitoring

Drug	Selected Warnings	Recommended Monitoring
cabozantinib (Cometriq)	Thrombotic events, including myocardial infarction (MI), cerebral infarction, and other serious arterial thrombotic events, impaired wound healing, hypertension, osteonecrosis of the jaw, palmar-plantar erythrodysesthesia syndrome, proteinuria, reversible posterior leukoencephalopathy syndrome, diarrhea	Urine protein, blood pressure, signs/symptoms of bleeding, complete blood count (CBC)
avapritinib (Ayvakit)	Intracranial hemorrhage (subdural hematoma and cerebral hemorrhage), CNS adverse reactions (cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations), embryo-fetal toxicity	CNS effects, other adverse reactions
erdafitinib (Balversa)	Ocular disorders (central serous retinopathy/retinal pigment epithelial detachment) leading to defects in the visual field and dry eye symptoms, hyperphosphatemia, embryo-fetal toxicity	Ophthalmological examinations monthly for the first 4 months then every 3 months, and as needed; phosphate levels
larotrectinib (Vitrakvi)	Neurotoxicity (e.g., delirium, dysarthria, dizziness, gait disturbance, paresthesia), hepatotoxicity, embryo-fetal toxicity	Signs/symptoms of neurotoxicity; liver function tests (LFTs) every 2 weeks during the first month, then monthly and as clinically warranted; if a rechallenged is attempted following liver enzyme abnormalities, assess LFTs weekly for the first month of the rechallenge
lomustine (Gleostine)	Delayed, dose-related, and cumulative myelosuppression, pulmonary toxicity, secondary malignancies, hepatotoxicity, nephrotoxicity, embryo-fetal toxicity	CBC weekly for at least 6 weeks after each dose, baseline pulmonary function tests (PFTs), liver function, renal function
niraparib (Zejula)	Myelodysplastic syndrome/acute myeloid leukemia (0.8% of patients treated in clinical trials); bone marrow suppression, including thrombocytopenia; anemia, and neutropenia; hypertension and hypertensive crisis; embryo-fetal toxicity	CBC weekly for the first month, monthly for the next 11 months of treatment and periodically thereafter; monitor blood pressure and heart rate monthly for the first year and periodically thereafter
olaparib (Lynparza)	Myelodysplastic syndrome/acute myeloid leukemia occurred in < 1.5% of patients exposed to olaparib monotherapy and the majority of events had a fatal outcome; pneumonitis; embryo-fetal toxicity; venous thromboembolic events	CBC at baseline and monthly thereafter; monitor for new or worsening respiratory symptoms, such as dyspnea, fever, cough, wheezing, or radiologic abnormality; prostate cancer patients: venous thrombosis and pulmonary embolism
pemigatinib (Pemazyre)	Ocular toxicity (retinal pigment epithelial detachment [RPED] and dry eye), hyperphosphatemia, embryo-fetal toxicity	Comprehensive ophthalmological examination including optical coherence tomography (OCT) before starting and every 2 months for the first 6 months, then every 3 months thereafter; at the onset of visual symptoms, ophthalmologic evaluation should be conducted immediately, with follow-up every 3 weeks until resolution or discontinuation; hyperphosphatemia
pexidartinib (Turalio)	Hepatotoxicity, embryo-fetal toxicity	LFTs before starting therapy, weekly for the first 8 weeks, every 2 weeks for the next month, then every 3 months

Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
regorafenib (Stivarga)	Severe drug-induced liver injury with fatal outcome; infections, including urinary tract infections, nasopharyngitis, mucocutaneous and systemic fungal infections, and pneumonia; hemorrhage; dermatologic toxicity, including hand-foot skin reaction, toxic epidermal necrolysis and severe rash; and a higher incidence of hand-foot skin reaction in Asian patients; hypertension; cardiac ischemia and infarction; reversible posterior leukoencephalopathy syndrome (RPLS); GI perforation or fistula; risk of impaired wound healing; embryo-fetal toxicity	LFTs prior to start of therapy and at least every 2 weeks during first 2 months of treatment and monthly thereafter or more frequently as clinically indicated; monitor LFTs weekly in patients experiencing elevated LFTs until improvement to less than 3 x upper limit of normal (ULN) or baseline; blood pressure weekly for first 6 weeks of treatment and then every cycle or more frequently, as clinically indicated
ripretinib (Qinlock)	Palmar-plantar erythrodysesthesia syndrome (PPES); new primary cutaneous malignancies (cutaneous squamous cell carcinoma and melanoma); hypertension; cardiac dysfunction; impaired wound healing; embryo-fetal toxicity	Dermatologic evaluations when starting therapy and regularly during treatment (suspicious skin lesions should be excised followed by dermatopathologic evaluation); monitor blood pressure as indicated; ejection fraction (EF) should be assessed before starting and during treatment, as clinically warranted
rucaparib (Rubraca)	Myelodysplastic syndrome/acute myeloid leukemia (1.7%), embryo-fetal toxicity	CBC at baseline and monthly thereafter
selumetinib (Koselugo)	Cardiomyopathy; ocular toxicity; GI toxicity; skin toxicity; increased creatinine phosphokinase (CPK); increased levels of vitamin E and risk of bleeding; embryo-fetal toxicity	EF should be performed by ECG before starting therapy, every 3 months during the first year, every 6 months thereafter, and as clinically indicated; Comprehensive ophthalmic evaluations should be performed before starting therapy, regularly during therapy, and if new or worsening vision changes occur; GI adverse effects (e.g., diarrhea); severe skin rashes; serum CPK should be assessed before starting, regularly during therapy, and as clinically indicated; vitamin E intake
tazemetostat (Tazverik)	Secondary malignancies; embryo-fetal toxicity	Monitor long-term for secondary malignancies
temozolomide (Temodar)	Myelosuppression – geriatric patients and women have a higher risk of developing myelosuppression; cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed; risk of *Pneumocystis* pneumonia (PCP); hepatotoxicity; hepatitis due to hepatitis B (HBV) reactivation; embryo-fetal toxicity	Monitor absolute neutrophil count (ANC) prior to and throughout treatment; prophylaxis against PCP is required for all patients with newly diagnosed glioblastoma multiforme receiving concomitant temozolomide and radiotherapy for the 42-day regimen; liver function tests at baseline, midway through first cycle, prior to each subsequent cycle and approximately 2 to 4 weeks after the last dose of temozolomide; screen patients for HBV infection before treatment initiation; monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment; discontinue therapy in patients with evidence of active hepatitis B infection

Selected Warnings and Recommended Monitoring (continued)

Drug	Selected Warnings	Recommended Monitoring
trifluridine/ tipiracil (Lonsurf)	Severe myelosuppression, embryo-fetal toxicity	CBC prior to and day 15 of each cycle and more often as clinically warranted
vandetanib (Caprelsa)	QT prolongation and Torsades de Pointes, toxic epidermal necrolysis (TEN), photosensitivity reactions, Stevens-Johnson syndrome, interstitial lung disease, ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypothyroidism, hypertension, and reversible posterior leukoencephalopathy syndrome, photosensitivity reactions; risk of impaired wound healing	ECG, electrolytes, respiratory symptoms, thyroid stimulating hormone (TSH), signs/symptoms of heart failure, blood pressure; Due to the long half-life (19 days), protective clothing and sunscreen should continue for 4 months after discontinuation of therapy

Risk Evaluation and Mitigation Strategy (REMS)

To mitigate the risk of QT prolongation, only pharmacies and prescribers certified with the Caprelsa REMS program are allowed to prescribe and dispense vandetanib (Caprelsa).[124]

To mitigate the risk of hepatotoxicity, only pharmacies and prescribers certified with the Turalio REMS program are allowed to prescribe and dispense pexidartinib (Turalio). In addition, patients must be enrolled in a patient registry to receive pexidartinib.[125]

DRUG INTERACTIONS[126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142]

CYP3A4 Substrates – Enzyme Inhibition and Induction

Co-administration of CYP3A4 Inhibitors

Avapritinib (Ayvakit), cabozantinib (Cometriq), erdafitinib (Balversa), larotrectinib (Vitrakvi), olaparib (Lynparza), pemigatinib (Pemazyre), pexidartinib (Turalio), regorafenib (Stivarga), ripretinib (Qinlock), selumetinib (Koselugo), tazemetostat (Tazverik), and vandetanib (Caprelsa) are substrates for the cytochrome P450 (CYP) 3A4 enzyme. When co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, ritonavir, saquinavir, telithromycin), plasma concentrations of all the agents in this category can potentially increase. In addition, patients taking these medications should avoid grapefruit juice as it can increase the plasma concentrations of these agents.

Concomitant administration of avapritinib, cabozantinib, erdafitinib, larotrectinib, olaparib, pemigatinib, pexidartinib, regorafenib, tazemetostat, or vandetanib with potent inhibitors of CYP3A4 should be avoided, and selection of an alternate medication with minimal to no enzyme inhibition potential is recommended. If concurrent administration with a strong CYP3A4 inhibitor cannot be avoided, monitor for toxicity and dose adjust erdafitinib as necessary. If concurrent administration with a strong CYP3A4 inhibitor during larotrectinib therapy cannot be avoided, decrease the dose of larotrectinib by 50%. If concurrent use with a strong or moderate CYP3A inhibitor cannot be avoided during treatment with pexidartinib, decrease the dose of pexidartinib as directed in the prescribing information. Concomitant administration should be avoided for both strong and moderate CYP3A inhibitors with avapritinib, but a

dose reduction is recommended if use with a moderate CYP3A inhibitor is unavoidable. Concomitant use of a strong or moderate CYP3A inhibitor increases pemigatinib plasma concentrations and may increase the risk of adverse reactions; if the use of strong and moderate CYP3A inhibitors cannot be avoided, the pemigatinib dose should be reduced. Patients receiving ripretinib and a strong CYP3A inhibitor should be monitored more often for adverse events. Concurrent use of selumetinib with a strong or moderate CYP3A4 inhibitor or fluconazole increases plasma levels of selumetinib which may result in increased toxicity; concurrent administration with these medications should be avoided. If this is not possible, decrease the selumetinib dose. Concurrent use of strong and moderate CYP3A inhibitors with tazemetostat should be avoided; however, if it is not possible to avoid administration of a moderate CYP3A inhibitor, the dose of tazemetostat should be decreased.

Avoid concomitant use of moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, diltiazem, ciprofloxacin, erythromycin, fluconazole, verapamil) with olaparib. If olaparib must be co-administered with strong or moderate CYP3A inhibitors, reduce the dose of olaparib.

A drug with specific recommendations regarding dose adjustment with concurrent administration of potent CYP3A4 inhibitors is cabozantinib (Cometriq); decrease the dose by 40 mg per day until 2 to 3 days after discontinuation of strong inhibitor.

Rucaparib (Rubraca) can increase the exposure of substrates of CYP1A2, CYP3A, CYP2C9, or CYP2C19, potentially increasing the risk of toxicity. A dosage adjustment should occur if clinically indicated. Increased monitoring may also be needed with select agents (e.g., warfarin). As erdafitinib can affect the plasma levels of CYP3A4 substrates, leading to either decreased efficacy or increased toxicity, concurrent use with narrow CYP3A4 substrates should be avoided. As larotrectinib can increase exposure of sensitive substrates of CYP3A4, potentially increasing the risk of toxicity, avoid concurrent use if possible; if concurrent use cannot be avoided, patients should be monitored for increased toxicity from the CYP3A4 substrate.

Co-administration of CYP3A4 Inducers

Administration of olaparib (Lynparza), as well as avapritinib, cabozantinib, erdafitinib, larotrectinib, pemigatinib, pexidartinib, regorafenib, ripretinib, selumetinib, tazemetostat, and vandetanib with potent inducers of CYP3A4 (e.g., dexamethasone, phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin, St. John's wort) may result in decreases in plasma concentrations of these agents. Coadministration of avapritinib or tazemetostat with strong or moderate CYP3A inducers may decrease plasma concentrations, potentially decreasing efficacy; avoid coadministration with strong or moderate CYP3A inducers. Avoid concurrent use of strong CYP3A4 inducers with larotrectinib; if coadministration cannot be avoided, double the dose of larotrectinib. Coadministration with a strong or moderate CYP3A inducer, plasma concentrations and efficacy of pemigatinib may be reduced; therefore concomitant use of strong and moderate CYP3A inducers should be avoided with pemigatinib. Concurrent use of strong CYP3A inducers during treatment with pexidartinib or ripretinib should be avoided. Concurrent use with a strong or moderate CYP3A4 inducer can lower plasma levels of selumetinib which can decrease efficacy; concurrent administration with a strong or moderate CYP3A4 inducer should be avoided.

If a moderate CYP3A inducer cannot be avoided, there is potential for decreased efficacy of erdafitinib as well as olaparib. Avoid coadministration of strong or moderate CYP3A inducers with olaparib.

Vandetanib (Caprelsa) should not be used if concomitant use of strong CYP3A4 inducers cannot be avoided.

Cabozantinib (Cometriq) daily dose should be increased by 40 mg until 2 to 3 days after discontinuation of the strong inducer. If a moderate CYP3A4 inducer is required to be coadministered with erdafitinib after the initial dose increase period, the erdafitinib dose may need to be increased to 9 mg.

P-glycoprotein (P-gP) Inhibitors and Substrates

P-gP Inhibitors

Vandetanib increases plasma concentrations of digoxin and, therefore, digoxin should be used with caution and monitored closely for toxicity when co-administered with vandetanib.

P-gP Substrates

Concurrent use of erdafitinib may result in increased drug levels of P-gP substrates, leading to toxicity; if concurrent use cannot be avoided, administration of erdafitinib should be separated from administration of the sensitive P-gP substrate by at least 6 hours.

QT Interval Prolongation

The administration of vandetanib (Caprelsa) with medications that may prolong the QT interval, including anti-arrhythmics, should be avoided.

Other

Coadministration of temozolomide and valproic acid decreases oral clearance of temozolomide by about 5%; the clinical implication is not known.

The combination of olaparib (Lynparza) and other myelosuppressive anticancer agents result in a potentiation and prolongation of myelosuppressive toxicity.

Coadministration of regorafenib (Stivarga) with a breast cancer resistance protein (BCRP) substrate (e.g., methotrexate, fluvastatin, atorvastatin) may increase the plasma concentrations of the BCRP substrate.

Erdafitinib (Balversa) has the potential for drug interactions with moderate CYP2C9 inhibitors and strong CYP2C9 inducers. Strong CYP2C9 inducers should be avoided and alternative therapies to moderate CYP2C9 inhibitors should be considered in patients receiving erdafitinib. Likewise, if a moderate CYP2C9 inducer is required to be coadministered with erdafitinib after the initial dose increase period, the erdafitinib dose may need to be increased to 9 mg. Concurrent use of erdafitinib may result in increased drug levels of OCT2 substrates (e.g., metformin) leading to toxicity; consider other therapies that are not OCT2 substrates or reduce the dose of the substrate if needed.

Concurrent use of erdafitinib with other agents that can impact serum phosphate level may affect the ability to determine the initial dose increase of erdafitinib. As a result, concurrent administration of drugs impacting serum phosphate level should be avoided with erdafitinib prior to the initial dose increase phase that is based on serum phosphate levels (occurs 14 to 21 days after starting therapy).

Due to the potential for pexidartinib to cause hepatotoxicity, avoid concurrent use with other potentially hepatotoxic therapies in certain patients, including those with active liver or biliary tract disease, as well as those with increased serum transaminases, total bilirubin, or direct bilirubin that is greater than the upper limit of normal (ULN). Use of pexidartinib with a UDP-glucuronosyltransferase (UGT) inhibitor can result in increased pexidartinib levels potentially leading to an increased likelihood of adverse effects; if concurrent use with a UGT inhibitor cannot be avoided, decrease the dose of pexidartinib as directed in

the prescribing information. Due to the potential for proton-pump inhibitors (PPI) to lower the serum levels of pexidartinib, if an acid-suppressing agent is required, an antacid or histamine 2 (H_2)-receptor antagonist should be used as an alternative to the PPI. Pexidartinib should be administered either 2 hours before or 2 hours after an antacid and ≥ 2 hours before or 10 hours after taking an H_2-receptor antagonist. In addition, pexidartinib is a moderate CYP3A inducer and concurrent use can decrease the level of CYP3A substrates, which may lead to decreased efficacy of these substrates. Coadministration of pexidartinib with hormonal contraceptives should be avoided, and concurrent use of pexidartinib with other CYP3A substrates, where small changes in drug level may result in serious therapeutic failures, should also be avoided; if concurrent use cannot be avoided, increase the CYP3A substrate dose as directed in the product labeling.

No pharmacokinetic drug-drug interaction studies have been conducted with trifluridine/tipiracil (Lonsurf). Likewise, no formal drug interaction studies were performed with niraparib (Zejula).

As selumetinib capsules contain vitamin E, patients whose daily vitamin E intake is greater than the recommended limit, as well as patients concurrently taking vitamin-K antagonists (VKA) or antiplatelet agents, are at an increased risk of bleeding. Consequently, supplemental vitamin E should be avoided if it results in daily vitamin E doses greater than the recommended limit. Patients concurrently receiving a VKA or an antiplatelet agent should be monitored for bleeding. As indicated, patients receiving VKAs should have increased international normalized ratio (INR) monitoring. Anticoagulation evaluations (e.g., INR, prothrombin time) should be conducted more often with adjustment of these agents' doses as needed.

Concurrent use of tazemetostat with CYP3A substrates (e.g., hormonal contraceptives) may lead to lowered levels and decreased efficacy of the CYP3A substrate.

ADVERSE EFFECTS[143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159]

Adverse effects reported below are the incidences for all grades of severity unless otherwise noted.

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
avapritinib (Ayvakit)	72	37	17	23	64	reported	nr	nr	9	8
cabozantinib (Cometriq)	nr	63 (33)	18 (8)	19 (10)	43 (21)	3 (1)	14 (7)	51 (6)	nr	33 (4)
erdafitinib (Balversa)	nr	47	nr	26	21	Nr	20	56	35	nr
larotrectinib (Vitrakvi)	15	22	14	Nr	29	Nr	14	nr	42	11
niraparib (Zejula) n=367 NOVA study	≥ 1 to < 10	20 (21)	26 (11)	21 (9)	74 (35)	nr	19 (20)	20 (6)	85 (56)	20 (5)
n=484 PRIMA study	nr	reported	26 (15)	reported	57 (28)	nr	39 (38)	nr	64 (18)	18 (7)
n=463 QUADRA study	nr	17	19	reported	67	nr	29	nr	51	14

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses unless otherwise specified. nr = not reported. Hb = hemoglobin; HTN = hypertension

Adverse Effects (continued)

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
olaparib (Lynparza) pooled from ovarian and breast cancer trials as monotherapy	8 to 14	21 to 37 (22 to 26)	20 to 26 (13 to 14)	4 to 6	58 to 77 (31 to 38)	nr	22 to 30 (28)	11 (2)	23 to 44 (7 to 9)	nr
n=90 POLO study pancreatic adenocarcinoma	nr	29 (15)	7	15 (5)	45 (23)	nr	15 (10)	10 (5)	27 (17)	nr
n=256 PROfound mCRPC versus enzalutamide or abiraterone	46 (15)	21 7	6	4	41 19	nr	nr	5	46 (15)	nr
n=535 PAOLA-1 in combination with bevacizumab in ovarian cancer	nr	18	14	nr	53 (22)	nr	nr	5	41 (10)	19
pemigatinib (Pemazyre)	18	47	16	nr	40	nr	nr	35	43	nr
pexidartinib (Turalio)	20	nr	nr	28	8	Nr	nr	reported	30	15
regorafenib (Stivarga) n=500 CRC	nr	43 (17)	10 (7)	45 (7)	nr	21 (8)	nr	33 (5)	79 (66)	30 (8)
n=132 GIST	nr	47 (9)	16 (9)	67 (15)	20 (12)	11 (3)	14 (3)	40 (8)	nr	59 (27)
ripretinib (Qinlock)	17 (7)	28 (14)	19 (4.7)	nr	39 (12)	nr	32 (12)	11 (0)	3.5	14 (4.7)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses unless otherwise specified. nr = not reported. Hb = hemoglobin; HTN = hypertension

Adverse Effects (continued)

Drug	Fluid Retention/ Edema	Diarrhea	Headache	Skin Rash	Nausea	Hemorrhage	Muscle Pain/ Myalgia	Stomatitis	↓ Hb/ Anemia	HTN
rucaparib (Rubraca) n=937 ARIEL3, ARIEL2, and Study 10, ovarian cancer	nr	34	nr	13	77	nr	nr	nr	44	nr
n=115 TRITON2 prostate cancer	nr	20	nr	27	52	< 20	nr	nr	43	nr
selumetinib (Koselugo)	20	70	48	80	66	nr	58	50	41	< 20
tazemetostat (Tazverik) n=62 epithelioid sarcoma	nr	16	18	nr	36	18	reported	nr	49	nr
n=99 follicular lymphoma	nr	18	13	15	24	nr	22	nr	50	nr
temozolomide (Temodar) n=224, newly diagnosed GBM; maintenance phase	nr	10	23	13	49	nr	6	9	nr	nr
n=158, refractory anaplastic astrocytoma	11	16	41	8	53	nr	5	nr	4	nr
trifluridine/tipiracil (Lonsurf) n=533	nr	32 (12)	nr	nr	48 (24)	nr	nr	8 (6)	77 (33)	nr
vandetanib (Caprelsa) n=330	nr	57 (27)	26 (9)	53 (12)	33 (16)	1	reported	nr	nr	> 2

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses unless otherwise specified. nr = not reported. Hb = hemoglobin; HTN = hypertension

Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 50% of patients taking cabozantinib and was severe in 13% of patients. Palmar-plantar erythrodysesthesia occurred in 26% of patients taking erdafitinib and was severe (grade 3 or 4) in 6% of patients. Palmar-plantar erythrodysesthesia occurred in 1% of patients take avapritinib. PPES occurred in 15% of pemigatinib-treated patients with 4.1% of patients experiencing grade ≥ 3 events. PPES occurred in 21% of ripretinib-treated patients compared to no placebo patients.

The most frequent adverse reactions leading to dose reduction or interruption of avapritinib were anemia, fatigue, nausea, vomiting, hyperbilirubinemia, memory impairment, diarrhea, cognitive disorder, abdominal pain, and periorbital edema. Fatal adverse reactions occurred in 3.4% of avapritinib-treated patients; fatal events experienced by > 1 patient included sepsis and tumor hemorrhage (1% for both).

The most frequent adverse reactions leading to dose reduction or interruption of larotrectinib in clinical trials were increased alanine aminotransferase (ALT; 6%), increased aspartate aminotransferase (AST; 6%), and dizziness (3%).

The most common adverse reactions resulting in dose reduction or interruption of pemigatinib were stomatitis, arthralgia, PPES, asthenia, onychomadesis, fatigue, abdominal pain, AST increased, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, and hypotension. Fatal adverse reactions were experienced by 4.1% of pemigatinib-treated patients and included failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion.

The most common adverse reactions leading to a dose reduction or interruption of pexidartinib in clinical studies were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), and vomiting (4.9%).

The most frequent adverse reactions leading to dose reduction or dose interruptions of niraparib in the NOVA clinical trial were thrombocytopenia (41%) and anemia (20%). In the PRIMA trial in patients receiving niraparib dosed based on body weight or platelet count, adverse reactions resulting in dose reduction or dose interruption were thrombocytopenia (40%), anemia (23%), and neutropenia (15%). In the QUADRA trial, the most common adverse reactions resulting in dose reduction or interruption were thrombocytopenia (40%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

In the pooled data from 6 studies in patients with gBRCAm advanced ovarian cancer who received ≥ 3 previous lines of chemotherapy, there were 8 patients (4%) treated with olaparib who experienced adverse reactions leading to death; 2 were due to acute leukemia and 1 each for chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), intestinal perforation, pulmonary embolism, sepsis, and suture rupture. In the PROfound study, 4% of olaparib-treated patients experienced fatal adverse reactions due to pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%). In the PAOLA-1 study, 1 patient died due to concurrent adverse reactions of pneumonia and aplastic anemia.

The most common adverse reactions resulting in dose reduction or interruption of ripretinib were abdominal pain, agitation, alopecia, arthritis, dermatosis, GI disorder, hyperesthesia, myalgia, PPES,

decreased weight, nausea, increased blood bilirubin, and PPES. Clinically important adverse reactions occurring in < 10% of patients in a pooled safety analysis for included cardiac ischemic events (1.1%) with cardiac arrest and myocardial infarction being fatal events.

In ovarian cancer patients, anemia (27%) and fatigue/asthenia (2%) were the most common reasons for dose reductions or interruptions in patients receiving rucaparib, and dose discontinuation occurred in 10% of patients with the most common reason being fatigue/asthenia (2%). In mCRPC patients enrolled in TRITON2, the most common adverse reactions leading to dose interruption were anemia, thrombocytopenia, asthenia/fatigue, nausea, vomiting, neutropenia, ALT/AST increased, creatinine increased, decreased appetite, acute kidney injury, and hypophosphatemia; the most common adverse reactions leading to dose reduction were anemia (14%), asthenia/fatigue (10%), thrombocytopenia (7%), nausea (6%), decreased appetite (4%), and rash (3%). Two (1.7%) patients treated with rucaparib in TRITON2 with an adverse reactions that resulted in death (1 each due to acute respiratory distress syndrome and pneumonia).

Nephrotic syndrome as well as cardiac failure associated with regorafenib have been identified as postmarketing adverse events.

The most common adverse reactions leading to dose interruptions (80% of patients required) or dose reductions (24% of patients required) who received selumetinib were vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia, and weight gain.

In epithelioid sarcoma patients who received tazemetostat, the most common adverse reactions resulting in dose interruptions (34% of patients receiving tazemetostat) were hemorrhage, increased ALT, and increased AST; dose reduction was required in 1 (2%) tazemetostat-treated patient due to decreased appetite. In relapsed/refractory follicular lymphoma patients, the most common adverse reactions resulting in dose interruptions (28% of tazemetostat patients) were thrombocytopenia and fatigue; a total of 9% of tazemetostat patients required dose reductions due to an adverse reaction, most commonly due to fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain.

Vascular disorders, including arterial (aortic) aneurysms, dissections, and rupture, with vandetanib have been identified as postmarketing adverse reactions.

Serious opportunistic infections, including cases with fatal outcomes, have been reported with temozolomide.

The most common adverse effects in patients receiving trifluridine/tipiracil in clinical trials were anemia (77%), neutropenia (67%), asthenia/fatigue (52%), nausea (48%), thrombocytopenia (42%), decreased appetite (39%), diarrhea (32%), vomiting (28%), abdominal pain (21%), and pyrexia (19%).

The most common laboratory abnormalities reported with vandetanib in greater than 20% for all grades were decreased calcium (57% versus 25% for placebo), elevated alanine transaminase (ALT) (51% versus 19% for placebo), and reduced glucose levels (24% versus 7% for placebo).

SPECIAL POPULATIONS[160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176]

Pediatrics

Safe and effective use of the following agents in patients < 18 years of age has not been established: avapritinib (Ayvakit), cabozantinib (Cometriq), erdafitinib (Balversa), niraparib (Zejula), olaparib (Lynparza), pemigatinib (Pemazyre), pexidartinib (Turalio), ripretinib (Qinlock), rucaparib (Rubraca), vandetanib (Caprelsa), trifluridine/tipiracil (Lonsurf), and regorafenib (Stivarga).

The use of lomustine (Gleostine), include dosing, in pediatric patients is not based on adequate and well-controlled studies.

The use of larotrectinib (Vitrakvi) in pediatric patients ≥ 28 days of age has been established based on findings from 3 open-label, single-arm, clinical studies. Increased body weight and neutropenia occurred more often in pediatric patients compared to adults, but due to the small number of patients in clinical studies, it cannot be determined if these differences are due to age or other variables.

Safety and efficacy of selumetinib (Koselugo) has been established in pediatric patients ≥ 2 years of age for the approved indication; however, safety and efficacy of selumetinib have not been determined for pediatric patients < 2 years of age.

The safety and efficacy of tazemetostat (Tazverik) have been established in pediatric patients ≥ 16 years of age for patients with metastatic or locally advanced epithelioid sarcoma.

Pregnancy

All of the agents included in this review, based on their mechanisms of action, may cause fetal harm when administered to pregnant women. Pregnancy status should be assessed, and women should be advised not to become pregnant while on therapy with any of these agents.

Males and females of reproductive potential should use effective contraception during treatment with avapritinib and for 6 weeks following treatment discontinuation. Men and women receiving cabozantinib should use effective contraception during treatment and up to 4 months after completion of therapy. Males and females receiving erdafitinib should use effective contraception during treatment and for 1 month after completion of therapy. Males and females receiving larotrectinib or ripretinib should use effective contraception during treatment and for a minimum of 1 week following the last dose. Female patients of reproductive potential and males with female partners of reproductive potential should utilize effective contraception during treatment with pemigatinib or selumetinib and for 1 week after the final dose.

Females of reproductive potential should use effective contraception during treatment with lomustine and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with lomustine and for 3.5 months after the final dose.

Effective contraception should be used during treatment with niraparib, olaparib, or rucaparib and should continue for at least 6 months following the last dose of each agent. Males with female partners of reproductive potential or who are pregnant should use effective contraception during treatment and for 3 months following the last dose of olaparib. Male patients with female partners of reproductive potential or who are pregnant should use effective contraception during treatment with rucaparib and for 3 months after the final dose.

Females of reproductive potential should use effective non-hormonal contraception, as pexidartinib can cause hormonal contraceptives to be ineffective, during treatment with pexidartinib and for 1 month following the last dose; males with female partners of reproductive potential should utilize effective contraception while receiving pexidartinib and for 1 week following the last dose.

Females of reproductive potential should use effective non-hormonal contraception during treatment with tazemetostat and for 6 months following the last dose; non-hormonal contraception should be used as tazemetostat can cause some hormonal contraceptives to become ineffective. Additionally, males with female partners of reproductive potential should use effective contraception during treatment and for a minimum of 3 months following the last dose.

Adverse developmental outcomes have been observed in pregnant patients and pregnant partners of male patients who received temozolomide (Temodar). As a result, females of reproductive potential should use effective contraception during treatment with temozolomide and for a minimum of 6 months following the last dose, and male patients with pregnant partners or with female partners of reproductive potential should use condoms during treatment and for a minimum of 3 months following the last dose.

There are no available data on trifluridine/tipiracil exposure in pregnant women. Females of reproductive potential should use effective contraception during treatment with trifluridine/tipiracil and males with female partners of reproductive potential should utilize condoms during treatment and for at least 6 months after the final dose.

Contraception use should continue during treatment and for at least 4 months following the last dose of vandetanib.

Renal Impairment

No clinical studies were conducted with cabozantinib (Cometriq) in patients with decreased renal function. Renal impairment is not expected to influence drug exposure, and no dosage adjustment of this product is recommended in patients with renal impairment.

No dose adjustments are required for larotrectinib in patients with any degree of renal dysfunction.

There is no starting dose adjustment for rucaparib in patients with renal impairment. There is no data to determine a starting dose for patients on dialysis.

Dose adjustments are not required in patients with renal impairment or end-stage renal disease (ESRD) receiving selumetinib.

There are no dose adjustments required for patients with mild to severe renal impairment or ESRD receiving tazemetostat.

Agents with Specified Renal Dose Modifications

For patients with mild to severe renal impairment (creatinine clearance [CrCl], 15 to 89 mL/min), the recommended dose of pexidartinib is 200 mg in the morning and 400 mg in the evening.

The starting dose of vandetanib (Caprelsa) should be reduced to 200 mg in patients with moderate (CrCl ≥ 30 to < 50 mL/min) and severe (CrCl < 30 mL/min) renal impairment.

A 24% increase in mean area under the concentration curve (AUC) was observed in patients receiving olaparib (Lynparza) with mild renal impairment (CrCl, 51 to 80 mL/min) compared to patients with

normal renal function (CrCl > 80 mL/min); however, no dose adjustment to the starting dose is required in patients with CrCl of 50 to 80 mL/min but patients should be monitored closely for toxicity. There was a 44% increase in AUC in patients with moderate renal impairment (CrCl, 31 to 50 mL/min) compared to patients with normal renal function (CrCl > 80 mL/min). For patients with moderate renal impairment, the dose of olaparib should be reduced to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage disease (CrCl ≤ 30 mL/min).

No dose adjustment is recommended of trifluridine/tipiracil (Lonsurf) in patients with mild to moderate renal impairment (CrCl, 30 to 89 mL/min); however, patients with moderate renal impairment may require dose modification. The dose should be decreased for patients with severe renal impairment (CrCl, 15 to 29 mL/min) according to the prescribing information. The use of trifluridine/tipiracil in patients with end stage renal disease has not been evaluated.

Agents Used with Caution but without Specific Renal Dosing Recommendations

No dose adjustment of avapritinib (Ayvakit) is recommended in patients with mild or moderate renal impairment (estimated CrCl ≥ 30 mL/min); however, the recommended dose has not been established in patients with severe renal impairment or ESRD.

No dose adjustments are recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR], ≥ 30 mL/min/1.73 m^2) receiving erdafitinib (Balversa). The pharmacokinetics of erdafitinib have not been evaluated in patients with severe renal impairment or in renal impairment patients requiring dialysis.

There is no recommended dose adjustment for patients with mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min calculated by Modification of Diet in Renal Disease [MDRD] equation) receiving pemigatinib (Pemazyre); there has not been a dose established for patients with severe renal impairment (eGFR < 30 mL/min).

No dosage adjustment is recommended for patients with mild, moderate, or severe renal impairment receiving regorafenib (Stivarga). The pharmacokinetics of regorafenib have not been studied in patients undergoing dialysis, and there is no recommended dose for this group of patients.

No clinically important changes were seen on the pharmacokinetics in mild to moderate renal impairment (CrCl, 30 to < 90 mL/min) in patients receiving ripretinib (Qinlock); the impact of severe renal impairment (CrCl, 15 to 29 mL/min) has not been evaluated.

Temozolomide should be used with caution in patients with severe renal impairment. It is advisable to start with lower dosages in patients with impaired renal function, due to slower elimination of the drug and metabolites and a greater cumulative effect.

The risk of toxic reactions to lomustine (Gleostine) may be greater in patients with impaired renal function.

No dose adjustment of niraparib is necessary for patients with mild (CrCl, 60 to 89 mL/min) to moderate (CrCl, 30 to 59 mL/min) renal impairment. The safety of niraparib in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

Hepatic Impairment

Agents with Specified Hepatic Dose Modifications

The starting dose of larotrectinib should be decreased by 50% in patients moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic dysfunction, as clearance is decreased in these patients.

As selumetinib levels increase in moderate or severe hepatic impairment, the dose should be decreased in patients with moderate impairment (Child-Pugh B); a dosage recommendation for patients with severe hepatic impairment (Child-Pugh C) has not been determined. For moderate hepatic impairment (Child-Pugh B), the recommended dose should be decreased to 20 mg/m^2 orally twice daily. The prescribing information provides a body surface area (BSA)-specific dosing recommendation chart for these patients.

Agents To Be Used with Caution in Some Stages of Hepatic Dysfunction

Temozolomide should be used with caution in patients with severe hepatic impairment.

Agents with No Dosage Adjustments Required in Some Stages of Hepatic Dysfunction

No dose adjustment of avapritinib is recommended in patients with mild or moderate hepatic impairment; the recommended dose has not been established in patients with severe hepatic impairment.

No dose adjustment of erdafitinib is needed in patients with mild hepatic impairment. There is no data available for patients with moderate to severe hepatic impairment receiving erdafitinib.

No dose adjustment of larotrectinib is needed in patients with mild hepatic impairment (Child-Pugh A).

No dose adjustment of niraparib is needed in patients with mild hepatic impairment (according to the National Cancer Institute-Organ Dysfunction Working Group [NIC-ODWG] criteria.) The safety of niraparib in patients with moderate to severe hepatic impairment is unknown.

No adjustment to the starting dose of olaparib is required for patients with mild or moderate hepatic impairment (Child-Pugh A). There is no data available for patients with severe hepatic impairment receiving olaparib.

There is no recommended dose adjustment of pemigatinib in patients with mild (total bilirubin > ULN to 1.5 times ULN or AST > ULN) or moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN with any AST); there has not been a dose established for patients with severe hepatic impairment (total bilirubin > 3 times ULN with any AST).

No dose adjustment of pexidartinib is required for patients with mild hepatic impairment. Dose adjustments have not been determined for patients with moderate to severe hepatic impairment. Due to the risk of hepatotoxicity, pexidartinib should be avoided in the following situations: pre-existing increased serum transaminases, total bilirubin, or direct bilirubin > ULN, or active liver or biliary tract disease, including increased alkaline phosphatase (ALP).

No dose adjustments are necessary in patients with mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > ULN to ≤ 1.5 times ULN) to moderate (total bilirubin > 1.5 to ≤ 3 times ULN and any AST) hepatic impairment taking regorafenib (Stivarga); regorafenib is not recommended for use in patients with severe hepatic impairment (total bilirubin > 3times ULN).

There is no dose adjustment required for patients with mild hepatic impairment receiving ripretinib; a recommended dose has not been determined for moderate to severe hepatic impairment patients.

Patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin between 1 and 1.5 times ULN with any AST) do not require a starting dose adjustment for rucaparib. There is no data available for patients with moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN) receiving rucaparib.

There are no dose adjustments required for patients with mild hepatic impairment receiving tazemetostat; it has not been studied in patients with moderate or severe hepatic impairment.

No dosage adjustment is recommended for patients receiving trifluridine/tipiracil (Lonsurf) who have mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin < 1 to 1.5 times ULN and any AST). Patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN with any AST) may have increased bilirubin levels, as demonstrated in clinical trials. Patients with severe hepatic impairment (total bilirubin greater than 3 times the ULN with any AST) have not been studied while taking trifluridine/tipiracil (Lonsurf). Do not initiate trifluridine/tipiracil (Lonsurf) in patients with baseline moderate to severe hepatic impairment.

Agents Lacking Study Data to Support Use in Various Stages of Hepatic Dysfunction

Vandetanib (Caprelsa) and cabozantinib (Cometriq) are not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established.

Geriatrics

Clinical experience with lomustine (Gleostine) in patients ages ≥ 65 years has not identified differences in response between elderly and younger patients.

No difference in efficacy or safety between older and younger patients was observed with avapritinib (Ayvakit), erdafitinib (Balversa), niraparib (Zejula), pemigatinib (Pemazyre), rucaparib (Rubraca), or vandetanib (Caprelsa).

No difference in efficacy between older and younger patients was observed with regorafenib (Stivarga); however, the rates of hypertension (grade 3 and 4) have occurred more with regorafenib compared to placebo.

The safety profile of olaparib (Lynparza) was similar in patients > 65 years compared to those < 65 years of age except adverse events ≥ grade 3 were more frequently reported in patients ≥ 65 years of age. No individual adverse event or system organ class accounted for this observed difference.

In the anaplastic astrocytoma study population, patients ≥ 70 years of age receiving temozolomide had a higher incidence of grade 4 neutropenia and grade 4 thrombocytopenia (25% and 20%, respectively) in the first cycle of therapy compared to patients < 70 years of age. A systematic review concluded the literature supports the use of hypofractionated radiotherapy or temozolomide monotherapy in the treatment of elderly patients with glioblastoma multiforme. In patients with MGMT promotor methylation, temozolomide monotherapy may have greater benefit than radiotherapy.[177]

No overall differences in effectiveness were observed in patients ≥ 65 years compared to younger patients receiving trifluridine/tipiracil (Lonsurf) and no dosing adjustment for the starting dose is recommended. However, patients ≥ 65 years of age who received trifluridine/tipiracil (Lonsurf) had

higher incidences of grade 3 or 4 neutropenia (48% versus 30%), grade 3 anemia (26% versus 12%), and grade 3 or 4 thrombocytopenia (9% versus 2%).

Although 22% of patients in clinical studies with larotrectinib were ≥ 65 years, this was not an adequate number of patients to determine if the response in elderly subjects differs from younger patients.

An inadequate number of patients ≥ 65 years were enrolled in clinical studies assessing pexidartinib; therefore, it is unknown if the response in these patients differs from younger patients.

Clinical trials of ripretinib did not include an adequate number of patients ≥ 65 years to determine if the response varied from younger patients.

Patients ≥ 65 years of age were not included in the clinical trials of selumetinib.

Clinical trials of tazemetostat in epithelioid sarcoma and relapsed or refractory follicular lymphoma did not include an adequate number of patients ≥ 65 years of age to inform of differences in response compared to younger patients.

Other Special Populations

There is a higher incidence of hand foot skin reaction and LFT abnormalities in Asian patients treated with regorafenib (Stivarga) compared with Caucasians. No starting dose adjustment is necessary based on race.

Plasma levels of erdafitinib are expected to be greater in patients who are CYP2C9 poor metabolizers as characterized by the CYP2C9*3/*3 genotype. As a result, monitor for increased toxicity in patients known or suspected to be poor CYP2C9 metabolizers.

DOSAGES[178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194]

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
avapritinib (Ayvakit)	--	--	--	GIST: 300 mg orally once daily until disease progression or unacceptable toxicity	Take on an empty stomach (≥ 1 hour before or 2 hours after a meal)	100 mg, 200 mg, and 300 mg tablets
cabozantinib (Cometriq)*	140 mg once daily	--	--	--	Take with 8 ounces of water; refrain from eating 2 hours before and 1 hour after daily dose; do not open capsules	20 mg, 80 mg capsules packaged as 60, 100, and 140 mg daily-dose cartons
erdafitinib (Balversa)	--	--	--	Urothelial carcinoma: 8 mg once daily, increase the dose to 9 mg once daily based on serum phosphate levels and tolerability at 14 to 21 days	Tablets should be swallowed whole, with or without food	3 mg, 4 mg, 5 mg tablets
larotrectinib (Vitrakvi)	--	--	--	Solid tumors with *NTRK* gene fusion: 100 mg twice daily for adults and pediatric patients with a BSA of ≥ 1 m^2; 100 mg/m^2 twice daily for pediatric patients with a BSA of < 1 m^2	The capsule and oral solution can be used interchangeably and can be taken with or without food Capsules should be swallowed whole with water; do not chew or crush	25 mg, 100 mg capsules and 20 mg/mL oral solution

* cabozantinib capsules (Cometriq) are NOT interchangeable with cabozantinib tablets (Cabometyx).

Dosages (continued)

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
lomustine (Gleostine)	--	--	--	Brain tumors/ Hodgkin's lymphoma: 130 mg/m^2/day given as a single oral dose once every 6 weeks	Only a sufficient number of capsules for 1 dose should be dispensed and patients should be instructed that the dose will not be repeated for at least 6 weeks	5 mg, 10 mg, 40 mg, 100 mg capsules
niraparib (Zejula)	--	--	First-line maintenance treatment: weight < 77 kg or with a platelet count of < 150,000/µL, 200 mg orally once daily; ≥ 77 kg and a platelet count ≥ 150,000/µL, 300 mg orally once daily Other indications: 300 mg (three 100 mg capsules) once daily	--	Swallow capsules whole; may be taken with or without food; bedtime administration may be a potential method for managing nausea; First-line maintenance treatment: start treatment no later than 12 weeks after most recent platinum-containing regimen; Maintenance for recurrent: start treatment no later than 8 weeks after most recent platinum-containing regimen	100 mg capsules

Dosages (continued)

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
olaparib (Lynparza)	--	--	300 mg (two 150 mg tablets) twice daily In first-line maintenance treatment of HRD-positive patients, in combination with bevacizumab, continue olaparib up to 2 years; bevacizumab (15 mg/kg every 3 weeks for up to 15 months)	Breast cancer, pancreatic adenocarcinoma, or mCRPC: 300 mg (two 150 mg tablets) twice daily until disease progression or unacceptable toxicity; mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog or should have had a bilateral orchiectomy	Swallow tablets or capsules whole; administer with or without food	50 mg hard capsules† 100 mg, 150 mg tablets
pemigatinib (Pemazyre)	--	--	--	Cholangiocarcinoma with a FGFR 2 fusion or other rearrangement: 21-day cycles at 13.5 mg orally once daily for 14 days on therapy, followed by 7 days off therapy continued until disease progression or unacceptable toxicity	Take whole with or without food at the same time each day; do not split, crush, chew, or dissolve	4.5 mg, 9 mg, 13.5 mg tablet
pexidartinib (Turalio)	--	--	--	TGCT: 400 mg twice daily	Take capsules whole on an empty stomach, ≥ 1 hour before or 2 hours after a meal or snack; do not chew, break or open	200 mg capsule

† The planned permanent discontinuation of olaparib capsules was August 31, 2018; some product may remain available until supply is depleted. The tablets will remain available. Do not substitute olaparib capsules with olaparib tablets on a mg to mg basis due to differences in the dosing and bioavailability of each formulation.

Dosages (continued)

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
regorafenib (Stivarga)	--	160 mg (four 40 mg tablets) taken once daily for the first 21 days of each 28-day cycle	--	Hepatocellular carcinoma: 160 mg (four 40 mg tablets) taken once daily for the first 21 days of each 28-day cycle	Swallow tablet whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat	40 mg tablets
ripretinib (Qinlock)	--	--	--	GIST: 150 mg orally once daily until disease progression or unacceptable toxicity	Swallow tablets whole at the same time every day with or without food	50 mg tablets
rucaparib (Rubraca)	--	--	600 mg (two 300 mg tablets) twice daily until disease progression or unacceptable toxicity	mCRPC: 600 mg (two 300 mg tablets) twice daily until disease progression or unacceptable toxicity; concurrently use with a GnRH analog or should have had a bilateral orchiectomy	Take with or without food	200 mg, 250 mg, 300 mg tablets
selumetinib (Koselugo)	--	--	--	NF1: 25 mg/m^2 of BSA orally twice daily, approximately every 12 hours, until disease progression or unacceptable toxicity	Swallow whole with water on an empty stomach (food should be avoided 2 hours prior to each dose and for 1 hour after dosing); if unable to swallow a whole capsule, do not give	10 mg, 25 mg capsule

Dosages (continued)

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
tazemetostat (Tazverik)	--	--	--	ES: 800 mg orally twice daily until disease progression or unacceptable toxicity R/R FL: 800 mg orally twice daily until disease progression or unacceptable toxicity	Swallow tablets whole with or without food; do not cut, crush, or chew	200 mg tablet
temozolomide (Temodar)	--	--	--	Newly diagnosed GBM: 75 mg/m^2 by mouth for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m^2 by mouth once daily for Days 1-5 of a 28-day cycle for 6 cycles Refractory Anaplastic Astrocytoma: initial dose of 150 mg/m^2 by mouth once daily for 5 consecutive days per 28-day treatment cycle	Handle per standard chemotherapy handling guidelines	5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules

Dosages (continued)

Drug	Medullary Thyroid Cancer	Colorectal Cancer	Ovarian Cancer	Other Diagnoses	Administration Comments	Dosage Forms
trifluridine/tipiracil (Lonsurf)	--	35 mg/m^2/dose orally twice daily on Days 1-5 and Days 8-12 of each 28-day cycle; Dose is based on trifluridine component; (Maximum single dose = 80 mg; round to nearest 5 mg increment)	--	Gastric cancer: 35 mg/m^2/dose orally twice daily on Days 1-5 and Days 8-12 of each 28-day cycle; Dose is based on trifluridine component; (Maximum single dose = 80 mg; round to nearest 5 mg increment)	Given within 1 hour of completion of morning and evening meals; swallow tablets whole; follow appropriate procedures for handling of cytotoxic drugs	15/6.14 mg, 20/8.19 mg tablets
vandetanib (Caprelsa)	300 mg orally once daily	--	--	--	Do not crush tablets; tablets may be dispersed in 2 ounces of water and may be administered through nasogastric or gastrostomy tubes	100 mg, 300 mg tablets

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled, phase III trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of data in the literature, clinical trials that are open-label, placebo-controlled, and have dropout rates in excess of 20% have been included in this therapeutic class review. In addition, where published phase III data for the FDA-approved indications is lacking, phase I/II studies cited in the package insert are included in this therapeutic class review. At one time, lomustine (Gleostine) was included as part of a multi-drug treatment regimen for the treatment of Hodgkin lymphoma. Regimens containing lomustine have subsequently been replaced by other drug regimens that have equal or superior efficacy and lower toxicity. Lomustine is not included in the current NCCN guideline for the treatment of Hodgkin lymphoma and will not be included in the clinical trials section of this review.

Breast Cancer – Metastatic, Treatment Experienced, Germline BRCA Mutation-positive

olaparib (Lynparza) versus standard chemotherapy

OlympiAD was a randomized, open-label, phase 3 trial (n=302) that compared monotherapy of oral olaparib with physician's choice of chemotherapy (capecitabine, eribulin, or vinorelbine) in metastatic breast cancer patients with a germline *BRCA* mutation who were human epidermal growth factor receptor type 2 (HER2)-negative and who had received no more than 2 previous chemotherapy regimens for metastatic disease.[195] Eligible patients were required to have received neoadjuvant or adjuvant treatment or treatment for metastatic disease with an anthracycline (unless it was contraindicated) and a taxane. Patients with hormone receptor (HR)-positive disease were required to have received ≥ 1 endocrine therapy either as adjuvant therapy or as therapy for metastatic disease and had experienced disease progression during therapy. Patients were randomized 2:1 to receive olaparib tablets 300 mg twice daily or physician's choice of chemotherapy. The primary endpoint was progression-free survival (PFS) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and assessed by a blinded independent central review (BICR) or death from any cause. The efficacy analysis was conducted after 77.5% of patients enrolled in the study had had disease progression or had died and the median duration of follow up was 14.5 months for the olaparib arm. The median PFS in the olaparib group was 7 months compared to 4.2 months in the standard chemotherapy arm (HR, 0.58; 95% confidence interval [CI], 0.43 to 0.8; p<0.001). Anemia, nausea, vomiting, fatigue, headache, and cough occurred more frequently in the olaparib group and neutropenia, palmar-plantar erythrodysesthesia, and increased liver function tests (LFTs) were more prevalent in the standard chemotherapy group.

Central Nervous System Cancers – Newly Diagnosed Glioblastoma Multiforme

temozolomide (Temodar) with radiotherapy (RT) versus RT alone

The EORTC-NCIC open-label, phase 3 trial randomized 573 patients to receive either temozolomide plus RT or RT alone.[196] The patients assigned to temozolomide received 75 mg/m^2 once daily for 42 days concomitant with RT and then received an additional 6 cycles of temozolomide alone (150 or 200 mg/m^2) on days 1 through 5 of every 28-day cycle, starting 4 weeks after the end of RT. Patients in the control arm received RT only. The addition of temozolomide to RT showed a statistically significant improvement in overall survival (OS) of 2.5 months compared to radiotherapy alone (hazard ratio [HR], 0.63, 95% CI, 0.52 to 0.75; p<0.0001).[197] These benefits of prolonged survival lasted throughout the 5 years of study follow up. OS was 27.2% (95% CI, 22.2 to 32.5) at 2 years, 16% (95% CI, 12 to 20.6) at 3 years, 12.1% (95% CI, 8.5 to 16.4) at 4 years, and 9.8% (95% CI, 6.4 to 14) at 5 years with temozolomide versus 10.9% (95% CI, 7.6 to 14.8), 4.4% (95% CI, 2.4 to 7.2), 3% (95% CI, 1.4 to 5.7), and 1.9% (95% CI, 0.6-4.4) with radiotherapy alone (HR, 0.6; 95% CI, 0.5 to 0.7; p<0.0001). A benefit of combined therapy was recorded in all clinical prognostic subgroups, including patients aged 60 to 70 years. Additionally, it was found that methylation of the methylguanine-methyltransferase (MGMT) promoter was the strongest predictor for outcome and benefit from temozolomide chemotherapy.

Central Nervous System Cancers – Refractory Anaplastic Astrocytoma

procarbazine, lomustine, and vincristine (PCV) + RT versus RT alone

A total of 251 patients with low-grade glioma (grade 2) were randomized to receive either radiation therapy alone or radiation therapy plus PCV after radiation. Patients included in the study were either < 40 years of age with a subtotal resection or biopsy or ≥ 40 years of age and had undergone biopsy or resection of any of the tumor. At a median follow-up of 11.9 years, the patients in the radiation + PCV arm had a longer median OS compared to those who received radiation therapy alone (13.3 versus 7.8 years; HR, 0.59, p=0.003). The rate of PFS at 10 years was 51% versus 21% and the OS at 10 years was 60% versus 40%, for the radiation + PCV group compared to the radiation therapy alone group, respectively.[198]

temozolomide (Temodar) versus procarbazine, lomustine, and vincristine (PCV)

A randomized trial (n=447) compared the chemotherapy regimen PCV (procarbazine, lomustine, vincristine) to single agent temozolomide in patients with recurrent high-grade glioma.[199] Patients were randomized either to PCV which was dosed as oral procarbazine 100 mg/m^2 on days 1 through 10, oral lomustine 100 mg/m^2, and intravenous (IV) vincristine 1.5 mg/m^2 (capped at 2 mg) dosed every 6 weeks for up to 6 cycles or oral temozolomide. For those patients who were randomized to the temozolomide arm, they were further randomized to receive temozolomide 200 mg/m^2 for 5 consecutive days of a 28-day cycle or temozolomide 100 mg/m^2 for 21 consecutive days of a 28-day cycle. All temozolomide cycles were repeated every 28 days for up to 9 cycles. The primary outcome measure was OS and secondary outcome measures were PFS and quality of life (QOL) assessments. Comparison of the temozolomide dosing schedules was a secondary analysis. Median PFS was 3.6 months for the PCV arm and 4.7 months for patients receiving temozolomide (HR, 0.89; 95% CI, 0.73 to 1.08; p=0.23). PFS at 12 weeks was 63.6% for the temozolomide 5-day dosing regimen and 65.7% for the temozolomide 21-day dosing schedule (p=0.745). Median OS was 10.5 months for the PCV-treated patients and 14 months for the temozolomide-treated patients (HR, 0.91; 95% CI, 0.74 to 1.11; p=0.35). A significant difference was

found for PFS in the PCV versus the 5-day temozolomide dosing schedule (HR, 0.78; 95% CI, 0.62 to 0.99; p=0.38) but not for PCV versus 21-day temozolomide dosing schedule (HR, 1.04; 95% CI, 0.82 to 1.32; p=0.759). At 24 weeks, the mean QOL scores were 51.9 for PCV versus 59.8 for temozolomide (p=0.38 in favor of temozolomide). When the QOL scores at 24 weeks were compared for the 2 temozolomide dosing schedules, there was a significant difference in favor of temozolomide 5-day regimen (p=0.036). The authors concluded that temozolomide (both arms combined) did not show a clear survival benefit over PCV in patients with recurrent gliomas. Furthermore, the 21-day temozolomide dosing schedule was not superior to the temozolomide 5-day dosing schedule in terms of OS.

Cholangiocarcinoma

pemigatinib (Pemazyre)

FIGHT-202: Pemigatinib was evaluated in a multicenter, open-label, single-arm trial to evaluate the efficacy of pemigatinib in patients with locally advanced unresectable or metastatic cholangiocarcinoma with disease progression on or after ≥ 1 prior therapy and an *FGFR2* gene fusion or non-fusion arrangement.[200,201] Patients with in-frame fusions and other rearrangements that qualified were predicted to have a breakpoint within intron 17/exon 18 of the *FGFR2* gene, with an intact *FGFR2* kinase domain. Pemigatinib was administered at a dosage of 13.5 mg orally once daily for 14 consecutive days, followed by 7 days off therapy in 21-day cycles. Pemigatinib therapy was continued until disease progression or unacceptable toxicity occurred. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR). The trial included 107 patients with a median age of 56 years (range, 26 to 77 years). The percentage of patients that had intrahepatic cholangiocarcinoma was 98%. In-frame *FGFR2* gene fusions were identified in 86% of patients, and the most commonly identified *FGFR2* fusion was FGFR2-BICC1 (34%). The remaining 14% of patients had other *FGFR2* rearrangements that were not able to be confidently identified as in-frame fusions. Patients that had received prior platinum-based therapy made up 96% of patients, including 76% that were previously treated with gemcitabine/cisplatin. The ORR was 36% (95% confidence interval [CI], 27 to 45), with 2.8% of patients achieving a complete response (CR) and 33% of patients achieving a partial response (PR), with a median time to response of 2.7 months (range, 0.7 to 6.9 months). The median DoR was 9.1 months (95% CI, 6 to 14.5), with 63% (n=24) having a DoR ≥ 6 months and 18% (n=7) with a DoR ≥ 12 months.

Colorectal Cancer

regorafenib (Stivarga) and placebo

CORRECT: Patients who had previously received a median of 3 prior lines of therapy for metastatic colon cancer were randomized in a double-blind, phase 3 trial to regorafenib 160 mg once daily for the first 21 days of a 28-day cycle or placebo. Both treatment arms included best supportive care. All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but 1 patient with KRAS mutation-negative tumors received panitumumab or cetuximab as well. The major efficacy outcome measure was OS. Median OS was 6.4 months in the regorafenib group versus 5 months in the placebo group (HR, 0.77; 95% CI, 0.64 to 0.94; one-sided p=0.0052). Treatment-related adverse events occurred in 465 (93%) patients assigned regorafenib and in 154 (61%) of those assigned placebo. The most common adverse events of grade 3 or higher related to regorafenib were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%).[202]

trifluridine/tipiracil (Lonsurf) and placebo

RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care (BSC) versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies): A total of 800 patients with colorectal cancer were randomly assigned 2:1 to receive trifluridine/tipiracil (also known as TAS-102) or placebo.[203] To be eligible for the study, patients had to have received at least 2 prior regimens of standard chemotherapy for colorectal cancer. All study participants had received prior chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, and irinotecan; all but 1 patient had also received bevacizumab. More than 50% of patients had received a fluoropyrimidine as a component of their most recent treatment regimen. Patients were stratified by KRAS status (wild-type or mutant). All but 2 patients with KRAS wild-type tumors had also received cetuximab or panitumumab. Trifluridine/tipiracil was administered at a dose of 35 mg/m^2 twice daily after morning and evening meals, 5 days a week with 2 days of rest, for 2 weeks, followed by a 14-day rest period to complete 1 cycle. The regimen was repeated every 4 weeks. The primary endpoint was OS. PFS was a secondary endpoint and was based on clinical evaluation every 2 weeks while receiving treatment and radiologic assessments performed every 8 weeks and evaluated according to RECIST by the investigators. When the number of events (deaths) required to determine OS was reached, the median OS was 7.1 months (95% CI, 6.5 to 7.8) in the trifluridine/tipiracil arm and 5.3 months (95% CI, 4.6 to 6) in the placebo group (HR, 0.68; 95% CI, 0.58 to 0.81; p<0.001). The median PFS was 2 months (95% CI, 1.9 to 2.1) in the trifluridine/tipiracil group and 1.7 months (95% CI, 1.7 to 1.8) in the placebo group (HR, 0.48; 95% CI, 0.41 to 0.57; p<0.001). The incidence of grade 3 or higher neutropenia, anemia, and thrombocytopenia were higher in the trifluridine/tipiracil group compared to the placebo group. In addition, patients receiving trifluridine/tipiracil were more likely to have grade 3 or higher vomiting and diarrhea. Adverse events resulted in the withdrawal of 4% of patients in the trifluridine/tipiracil arm compared to 2% of patients receiving placebo. There was 1 treatment-related death due to septic shock reported.

Epithelioid Sarcoma

tazemetostat (Tazverik)

EZH-202 (NCT02601950): An open-label, single-arm cohort (Cohort 5) of a multicenter study evaluated the efficacy of tazemetostat in 62 patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma.[204] Inclusion criteria required patients to have INI1 loss, as detected by local tests, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients received tazemetostat 800 mg orally twice daily until disease progression or unacceptable toxicity occurred. The major efficacy outcome measures included confirmed ORR according to RECIST v1.1, as assessed by blinded independent central review, and duration of response. The median duration of follow-up was 14 months (range, 0.4 to 31). The ORR was 15% (95% CI, 7 to 26), with 1.6% of patients having a CR and 13% with a PR. The time to response ranged from 2.4 months to 18.4 months. Of the patients that responded to therapy with tazemetostat, 67% had a DoR of at least 6 months.

Follicular Lymphoma (FL)

tazemetostat (Tazverik)

Study E7438-G000-101 (NCT01897571): Two open-label, single-arm cohorts of a multi-center study assessed the efficacy of tazemetostat in patients with histologically confirmed FL after ≥ 2 prior systemic therapies.[205,206] Patients enrolled had an ECOG performance status of 0 to 2 and were enrolled based on

EZH2 mutation status. All patients (n=99) were given tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity. The primary efficacy endpoint was ORR and DoR as determined by the International Working Group Non-Hodgkin Lymphoma (IWG-NHL) criteria and evaluated by an Independent Review Committee (IRC). A total of 45 patients had EZH2 mutant follicular lymphoma, and 54 patients with EZH2 wild-type follicular lymphoma. Approval for tazemetostat for FL was determined based on efficacy in 95 patients (42 EZH2 mutant, 53 EZH2 wild-type) who had received ≥ 2 prior systemic therapies. The ORR for the EZH2 mutant FL patients was 69% (95% CI, 53 to 82) with 12% of patients exhibiting a CR and 57% exhibiting a PR; the median DoR was 10.9 months (95% CI, 7.2 to not estimable [NE]). In the EZH2 wild-type FL patients, the ORR was 34% (95% CI, 22 to 48), with 4% of patients experiencing a CR and 30% a PR; the median DoR was 13 months (95% CI, 5.6 to NE). Overall, the median time to response was similar for both patient groups (EZH2 mutant type FL 3.7 months [range, 1.6 to 10.9]; EZH2 wild-type FL 3.9 months [range 1.6 to 16.3]).

Gastric Cancer or Gastroesophageal Junction (GEJ) Adenocarcinoma

trifluridine/tipiracil (Lonsurf) versus placebo

TAGS (trifluridine/tipiracil versus placebo in patients with heavily pretreated gastric cancer) was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial.[207] Enrolled patients (n=507) were at least 18 years of age with histologically confirmed, non-resectable, metastatic gastric adenocarcinoma (including adenocarcinoma of the gastroesophageal junction) who had received at least 2 prior chemotherapy regimens and had experienced radiological disease progression. Patients were randomized (2:1) to either trifluridine/tipiracil 35 mg/m^2 twice daily on days 1 through 5 and days 8 through 12 every 28 days or placebo, with both arms receiving best supportive care. Median OS (the primary endpoint) was 5.7 months (95% CI, 4.8 to 6.2) in the trifluridine/tipiracil group and 3.6 months (95% CI, 3.1 to 4.1) in the placebo group (HR, 0.69 [95% CI, 0.56 to 0.85]; 2-sided p=0.00058). Grade 3 or worse adverse events occurred in 267 (80%) of patients receiving trifluridine/tipiracil compared to 97 (58%) in the placebo group. The most frequent grade 3 or higher adverse events were neutropenia (34%) and anemia (19%) in the trifluridine/tipiracil group.

Gastrointestinal Stromal Tumor (GIST)

regorafenib (Stivarga) versus placebo

GRID: A phase 3, randomized, multicenter, placebo-controlled trial was conducted in 199 patients with histologically confirmed metastatic or unresectable GIST with failure of at least previous imatinib and sunitinib therapies.[208,209] Patients were randomized (2:1) to either oral regorafenib 160 mg daily or placebo for the first 3 weeks of a 4-week cycle. Patients and investigators were masked to treatment assignment. The primary endpoint was PFS. At disease progression, patients assigned to placebo could crossover to open-label regorafenib. Median PFS per independent blinded central review was 4.8 months for regorafenib patients and 0.9 months for placebo assigned patients (HR, 0.27; 95% CI, 0.19 to 0.39; p<0.0001). There was no statistically significant difference in OS. Hypertension (23%), hand-foot skin reaction (20%), and diarrhea (5%) were the most common regorafenib-related adverse events of grade 3 or higher.

avapritinib (Ayvakit)

NAVIGATOR (NCT02508532): A phase 1, multicenter, single-arm, open label clinical trial evaluated the effectiveness and safety of avapritinib in patients with a confirmed diagnosis of GIST and an ECOG

performance status of 0 to 2.[210,211] Eligible patients were initially assigned avapritinib 400 mg orally once daily but were later reduced to a dose of 300 mg once daily due to adverse effects. Treatment was continued until disease progression or unacceptable toxicity. The patient population with unresectable or metastatic GIST and a PDGFRA exon 18 mutation, as identified using a PCR- or NGS-based assay, totaled 43 patients and included 38 with PDGFRA D842V mutations. The primary efficacy endpoint was ORR of disease as assessed by an independent radiological review using modified RECIST v1.1 criteria. Data for both initial dosing regimens (300 mg/day and 400 mg/day) were pooled for the efficacy analysis since they did not appear to differ in the primary outcome. DoR was also evaluated. At baseline, the median age was 64 years (range, 29 to 90 years), 67% were male, 67% were Caucasian, 98% had metastatic disease, 86% had prior surgical resection, the median number of previously used tyrosine kinases was 1 (range, 0 to 5), and the median follow up was 10.6 months (range, 0.3 to 24.9 months). ORR occurred in 84% (95% CI, 69 to 93) of those with PDGFRA exon 18 mutation and 89% (95% CI, 75 to 97) of those with PDGFRA D842V. This consisted of a CR and PR of 7% (3/43) and 77% (33/43), respectively, of those with PDGFRA exon 18 mutation and 8% (3/38) and 82% (31/38), respectively, of those with PDGFRA D842V. The DoR was not reached in either subgroup (95% CI, 1.9+ to 20.3+ months in both groups), of which 61% and 59% had a DoR ≥ 6 months in the PDGFRA exon 18 mutation group and the PDGFRA D842V mutation group, respectively.

ripretinib (Qinlock) versus placebo

INVICTUS (NCT03353753): A multicenter, international, double-blind, randomized, placebo-controlled, phase 3 trial evaluated the efficacy of ripretinib.[212,213] Patients ≥ 18 years of age with advanced GIST with ≥ 1 measurable lesion according to modified RECIST 1.1 (mRECIST 1.1) and progression on at least imatinib, sunitinib, and regorafenib or intolerance to these medications despite dose adjustments were eligible for enrollment. Patients were also required to have an ECOG performance status of 0 to 2 and have sufficient organ function and bone marrow reserve. Patients who had received anticancer therapy within 14 days or 5-times the half-life (whichever was longer) prior to the first dose of study drug as well as with patients CNS metastases were excluded. Patients were randomized 2:1 to receive either oral ripretinib 150 mg once daily (n=85) or placebo once daily (n=44) with stratification based on the number of prior agents and ECOG performance status. Patients in the placebo group were allowed to crossover to ripretinib open-label therapy once disease progression occurred. The primary efficacy endpoint was PFS, defined as time from randomization to progressive disease or death due to any cause in the intention-to-treat (ITT) population as evaluated by BICR. Other endpoints included ORR, comprised of CR and PR as assessed by BICR), OS, and QOL.

Patients in the ITT were a median of 60 years of age (range, 29 to 83 years) with the majority of patients being male (57%), Caucasian (75%), and having an ECOG performance status of 0 or 1 (92%). The majority of patients (63%) had received 3 prior therapies and 37% had received ≥ 4 prior therapies. At the time of disease progression, 66% of patients in the placebo arm switched to ripretinib. The median PFS was 6.3 months (95% CI, 4.6 to 6.9) for ripretinib compared to 1 month (95% CI, 0.9 to 1.7) for placebo corresponding with a HR of 0.15 (95% CI, 0.09 to 0.25; p<0.0001). A total of 60% (51 out of 85) patients in the ripretinib arm had experienced progression or had died compared with 84% of placebo (37 out of 44) patients. At 6 months, PFS was estimated at 51% (95% CI, 39.4 to 61.4) for ripretinib-treated patients and 3.2% (95% CI, 0.2 to 13.8) for placebo patients. The ORR for the ripretinib-treated patients was 9.4% (95% CI, 4.2 to 17.7), all of which were PRs. In contrast, none of the placebo patients demonstrated a confirmed objective response. The median time to progression was 6.4 months (95% CI, 4.6 to 8.4) for ripretinib-treated patients and 1 month (95% CI, 0.9 to 1.7) for the placebo patients.

Overall survival was not formally assessed for statistical significance due to the hierarchal testing procedure since the objective response was not significant; however, across the double-blind and open-label phases, the median OS was 15.1 months (95% CI, 12.3 to 15.1) for the ripretinib-treated patients compared with 6.6 months (95% CI, 4.1 to 11.6) for the placebo group corresponding with a HR of 0.36 (95% CI, 0.21 to 0.62). The estimated OS for 6 months was 84.3% (95% CI, 74.5 to 90.6) for ripretinib-treated patients compared with 55.9% (95% CI, 39.9 to 69.2) for placebo patients, and at 12 months, the estimated OS was 65.4% (95% CI, 51.6 to 76.1) and 25.9% (95% CI, 7.2 to 49.9), respectively. Although the QOL endpoint could not be assessed for statistical significance due to the hierarchal testing procedures, results suggested a clinically meaningful difference with ripretinib in terms of maintenance of role/physical functioning and overall health compared to declines observed for these endpoints with placebo. Authors concluded study findings demonstrated efficacy and acceptable safety of ripretinib in a fourth-line or later setting in patients with advanced GIST. An ongoing phase 3 study, INTRIGUE (NCT03673501), is currently assessing ripretinib in the second-line setting compared to sunitinib.

Hepatocellular Carcinoma

regorafenib (Stivarga) and placebo

RESORCE was a phase 3, randomized, double blind, placebo-controlled trial which randomized 573 patients in a 2:1 fashion to receive either regorafenib 160 mg daily or placebo daily for weeks 1 to 3 of each 4-week cycle.[214] Hepatocellular carcinoma patients with Child-Pugh A liver function were eligible if they had progressed on prior sorafenib therapy. The primary endpoint was OS. Regorafenib improved median OS compared to placebo (10.6 months [95% CI, 9.1 to 12.1] for regorafenib arm versus 7.8 months [95% CI, 6.3 to 8.8] for the placebo arm; HR, 0.63 [95% CI, 0.5 to 0.79]; p<0.00001). Adverse events were reported in 100% of the patients assigned to regorafenib compared to 93% of patients assigned to placebo. Grade 3 and 4 events included hypertension (15% versus 5%), hand-foot skin reaction (13% versus 1%), fatigue (9% versus 5%), and diarrhea (3% versus 0%) for regorafenib compared to placebo, respectively.

Medullary Thyroid Carcinoma

cabozantinib (Cometriq) versus placebo

The EXAM trial assessed the safety and efficacy of cabozantinib in an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial of 330 patients with metastatic medullary thyroid carcinoma.[215] Patients were stratified by age and whether or not they had received previous TKI therapy and were randomized (2:1) to cabozantinib 140 mg daily or placebo. The primary endpoint was PFS. Additional outcome measures included tumor response rate, OS, and safety. A statistically significant prolongation in PFS was demonstrated among cabozantinib arm compared to those receiving placebo (HR, 0.28; 95% CI, 0.19 to 0.4; p <0.001), with median PFS times of 11.2 months and 4 months in the cabozantinib and placebo arms, respectively. Prolonged PFS with cabozantinib was observed across all subgroups. Response rate was 28% for cabozantinib and 0% for placebo. Adverse events led to treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients. The most common adverse effects associated with cabozantinib were diarrhea, palmar-plantar erythrodysesthesia, decreased appetite, nausea, and fatigue. In the final OS analysis, the impact of cabozantinib on OS compared to placebo was not statistically significantly different. With a minimum follow up of 42 months, the OS for cabozantinib-treated patients was 26.6 months compared to 21.1 months in patients who received placebo (HR=, 0.85; 95% CI, 0.64 to 1.12; p=0.24).[216]

vandetanib (Caprelsa) versus placebo

A randomized, double-blind, placebo-controlled study investigated 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer with vandetanib 300 mg (n=231) compared with placebo (n=100).[217,218] The primary endpoint was improvement in PFS with vandetanib versus placebo. Secondary endpoints included OS and overall objective response rate (ORR). Based on investigator's evaluation and after objective disease progression, patients were discontinued from blinded treatment and given the option to receive open-label vandetanib. Nineteen percent (44/231) of the patients initially randomized to vandetanib chose to receive open-label vandetanib after disease progression, and 58% (58/100) of the patients initially randomized to placebo chose to receive open-label vandetanib after disease progression. There was a statistically significant improvement in PFS for vandetanib (HR, 0.35; 95% CI, 0.24 to 0.53; p<0.0001). Analyses in the subgroups of patients who were symptomatic or had progressed within 6 months prior to their enrollment showed similar PFS results (HR, 0.31 [95% CI, 0.19 to 0.53] for symptomatic patients; HR, 0.41 [95% CI, 0.25 to 0.66] for patients who had progressed within 6 months prior to enrollment). The overall ORR was 44% and 1% for patients randomized vandetanib and placebo, respectively (p<0.001). All objective responses were PRs. When analyzed for OS, death occurred in 50.2% (median OS, 81.6 months [95% CI, 64.6 to 98.5]) of the vandetanib-treated patients compared to 52% (median OS, 80.4 months [95% CI, 52.5 to not estimable]) of placebo-treated patients (HR, 0.99; 95% 0.72 to 1.38; p=0.975). There was 1 sudden death and 1 death from cardiopulmonary arrest in patients receiving vandetanib after data cut-off. Vandetanib was also associated with sustained plasma concentration-dependent QT prolongation with 14% for all grades versus 1% for placebo and 8% for grades 3 and 4 versus 1% for placebo.

Neurofibromatosis Type 1 (NF1)

selumetinib (Koselugo)

SPRINT (NCT01362803): A phase 2, open-label, multicenter, single-arm trial evaluated the efficacy and safety of selumetinib.[219,220] Pediatric patients (n=50) between the ages of 2 to 18 years old (median age, 10.2 years; range, 3.5 to 17.4 years) who could swallow intact capsules and had a clinical diagnosis of NF1 with inoperable, measurable plexiform neurofibromas (PN) were enrolled into 2 strata. Inoperable PN was considered to be neurofibromas that could not be entirely removed without the potential for substantial morbidity due to being close to or encasing vital structures or being invasive or highly vascular. The PN was also required to result in substantial morbidity (e.g., disfigurement; pain; visual impairment; motor, airway, bladder, or bowel dysfunction). Patients were excluded if they had abnormal LVEF, uncontrolled hypertension, history of retinal vein occlusion or retinal pigment epithelial detachment (RPED), intraocular pressure > 21 mmHg, or uncontrolled glaucoma. Stratum 1 included patients with ≥ 1 neurofibroma-related complication, and stratum 2 included patients without clinically significant neurofibroma-related complications but with the potential for developing these complications. Efficacy findings in the prescribing information and the published study data only include patients in stratum 1.

Patients received selumetinib at a dose of 25 mg/m^2 of BSA approximately every 12 hours in 28-day cycles of a continuous dosing schedule. Patients who received ≥ 1 dose of selumetinib were able to be assessed for response. PR was defined as a ≥ 20% volume reduction from baseline in the target neurofibroma, which was further subdivided into a confirmed PR, which was considered to be a PR on consecutive restaging examinations a minimum of 3 months apart, and a durable PR, defined as a PR lasting for ≥ 12 cycles or about 1 year. A total of 74% (95% CI, 60 to 85) of patients exhibited a PR, with 70% (n=35) experiencing a confirmed PR and 56% (n=28) having a durable response. The median change in neurofibroma volume at best response

was -27.9% (range, -55.1 to 2.2) which occurred after a median time of 16 cycles (range, 4 to 36). At 3 years since the start of treatment, the PFS was 84%, but the median duration of response and median PFS had not been reached. In terms of patient-reported outcomes (PRO) and outcomes assessing functioning, the majority of patients (68%) had some amount of improvement in ≥ 1 of the PRO, observer-reported outcomes, or functional measures. The authors concluded selumetinib treatment led to durable shrinkage of the neurofibroma in the majority of pediatric patients and also resulted in clinically meaningful improvements with a lack of cumulative toxic effects, allowing for long-term management.

Ovarian Cancer (Including Fallopian Tube or Primary Peritoneal Cancer)

niraparib (Zejula) versus placebo – first-line maintenance treatment of advanced ovarian cancer

PRIMA (NCT02655016) was a randomized, double-blind, placebo-controlled phase 3 that enrolled 733 patients with newly diagnosed advanced ovarian cancer after a response to platinum-based chemotherapy. Patients were randomized 2:1 to receive niraparib or placebo once daily.[221,222] Patients randomized to niraparib initially received 300 mg once daily; however, the study was later amended to adjust the starting dose based on body weight and platelet count (200 mg when body weight < 77 kg or platelet count < 150,000/µL; 300 mg for body weight ≥ 77 kg with a platelet count ≥ 150,000/µL. The primary endpoint was PFS in patients with tumors with homologous-recombination deficiency (HRD) (50.9% of randomized patients) and in the overall population based on hierarchical testing. In the proportion of patients with HRD tumors, median PFS was significantly improved with niraparib (21.9 months) as compared to placebo (10.4 months) resulting in a HR for disease progression or death of 0.43 (95% CI, 0.31 to 0.59; p<0.001). In the overall population, the PFS was also significantly improved with niraparib-treated patients exhibiting a median PFS of 13.8 months compared with 8.2 months for placebo, corresponding with a HR of 0.62 (95% CI, 0.5 to 0.76; p<0.001). Authors concluded niraparib resulted in significantly improved PFS compared to placebo in newly-diagnosed advanced ovarian cancer patients who were responsive to platinum-based chemotherapy.

niraparib (Zejula) versus placebo - maintenance treatment of recurrent ovarian cancer

ENGOT-OV16/NOVA was a randomized, double-blind, phase 3 trial that enrolled 553 patients with recurrent ovarian cancer who were in complete or PR to their most recent platinum-based chemotherapy.[223] Patients were enrolled into 1 of 2 cohorts based on germline *BRCA* mutation status: (1) patients who were germline *BRCA* mutation carriers (*gBRCAmut*; n=203) and (2) patients who were not germline *BRCA* mutation carriers (non-*gBRCAmut*; n=350). The non-*gBRCAmut* group was further categorized by type of non-*gBRCA* mutation to those with or without homologous recombination deficiency (HRD). The cohorts were randomized 2:1 to receive niraparib (300 mg) or placebo once daily. Of 553 enrolled patients, 203 were in the *gBRCA* cohort (138 assigned to niraparib and 65 to placebo), and 350 patients were in the non-*gBRCA* cohort (234 assigned to niraparib and 116 to placebo). Fifty-one percent of all patients were in CR to most recent platinum-based regimen, with 39% on both arms with an interval of 6 to 12 months since the penultimate platinum regimen. Twenty-six percent of those treated with niraparib and 31% treated with placebo had received prior bevacizumab therapy. Approximately 40% of patients had received 3 or more lines of treatment. The primary endpoint of this study was PFS. Among patients in the *gBRCAmut* cohort, the median PFS for patients treated with niraparib was 21 months, compared to 5.5 months with placebo (HR, 0.27; 95% CI, 0.17 to 0.41; p<0.0001). The median PFS for patients in the non-*gBRCAmut* cohort was 9.3 months with niraparib and 3.9 months with placebo (HR, 0.45; 95% CI, 0.34 to 0.61; p<0.0001). The median PFS for patients in the non-*gBRCAmut* cohort with HRD positivity was 12.9 months with niraparib and 3.8 months with placebo (HR, 0.38; 95% CI, 0.24 to 0.59; p<0.001). The most common grade 3 or 4 adverse events that were reported with niraparib treatment were thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%), and these

were managed with dose modifications. PROs in the ITT population were measured every 8 weeks for the first 14 cycles and every 12 weeks thereafter using the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI) and the European QOL 5-dimension 5-level questionnaire (EQ-5D-5L).[224] The mean FOSI score at baseline was similar between the 2 groups and throughout the treatment period, and QOL scores were similar between the niraparib group and the placebo group. The authors concluded that the PRO data suggested that the use of niraparib as maintenance treatment for recurrent ovarian cancer after response to platinum therapy produced similar QOL effects when compared to patients who had received placebo.

niraparib (Zejula) – monotherapy treatment of advanced ovarian cancer after ≥ 3 chemotherapies

QUADRA was a single-arm study evaluating niraparib in 98 patients with advanced ovarian cancer who were HRD positive (defined as tumor *BRCA*-mutated and/or genomic instability score [GIS] > 42) and had received prior treatment with ≥ 3 prior chemotherapy.[225] Patients with previous exposure to other PARP inhibitors were excluded, and patients without *BRCA* mutations were required to have progression ≥ 6 months after the final platinum chemotherapy dose. Patients were given niraparib at a starting dose of 300 mg once daily until disease progression or unacceptable toxicity. The primary efficacy outcome was ORR and DoR as assessed by the investigator according to RECIST version 1.1. Patients enrolled had a median age of 63 years (range, 39 to 91) with most patients being Caucasian (82%). Patients had an ECOG performance score of 0 (59%) or 1 (41%). In the cohort of patients who were HRD positive (n=98), the ORR was 24% (95% CI 16 to 34) with all patients exhibiting a PR and no patients experiencing a CR. The median DoR was 8.3 months (95% CI, 6.5 to not estimable). For patients who were tumor *BRCA* mutated (n=63), the ORR was 39% (7/18; 95% CI, 17 to 64]) for patients with platinum-sensitive disease, 29% (6/21; 95% CI, 11 to 52) in patients with platinum-resistant disease, and 19% (3/16; 95% CI, 4 to 46) in patients with platinum-refractory disease. For patients with platinum-sensitive GIS-positive disease who were not *BRCA*-mutated (n=35), the ORR was 20% (95% CI, 8 to 37).

olaparib (Lynparza) – monotherapy after 3 or more lines of chemotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer

Olaparib monotherapy (400 mg twice daily until disease progression or intolerability) was evaluated in a phase 2 trial of 298 patients with a variety of different tumor types who were germline *BRCA1/2* mutation-positive.[226] Of these 298 patients, 193 were patients with recurrent ovarian cancer. A subsequent subgroup analysis identified 137 of the 193 recurrent ovarian cancer patients who had both measurable disease at baseline and had received 3 or more lines of chemotherapy.[227] ORR and duration of response were assessed by the investigator according to RECIST criteria in these 137 patients. The ORR was 34% (95% CI, 26 to 42) and median duration of response was 7.9 months (95% CI, 5.6 to 9.6). CR was seen in 2% of patients while 32% of patients experienced a PR. Platinum sensitivity was determined retrospectively. The ORR in platinum-resistant tumors was 30%. Median duration of response was similar (8.2 months [95% CI, 5.6 to 13.5] versus 8 months [95% CI, 4.8 to 14.8]) for platinum-sensitive disease and platinum-resistant disease, respectively. Of the 193 patients, serious adverse events were reported in 30% of patients, most commonly anemia (6%), vomiting (2%), neutropenia (1%), and thrombocytopenia (1%).

olaparib (Lynparza) versus placebo – maintenance treatment of platinum-sensitive recurrent ovarian cancer

A phase 2, randomized, double blind, placebo-controlled trial evaluated 265 patients with platinum-sensitive, relapsed, high-grade, serous ovarian cancer with or without *BRCA1* or *BRCA2* germline

mutations who had received 2 or more platinum-based regimens and who had a partial or CR to their most recent platinum-based regimen.[228] Patients were randomized to olaparib 400 mg twice daily or placebo. PFS, the primary endpoint, was significantly longer in the olaparib group (8.4 months) compared to the placebo group (4.8 months) (HR for disease progression or death, 0.35; 95% CI, 0.25 to 0.49; p<0.001). Nausea (68% versus 35%), fatigue (49% versus 38%), vomiting (32% versus 14%), and anemia (17% versus 5%) were more common in the olaparib-treated group versus the placebo group, respectively. In an updated analysis after more than 5 years of follow up, the median OS in the olaparib-treated arm was 29.8 months compared to 27.8 months in the placebo-treated arm (HR, 0.73; 95% CI, 0.55 to 0.96; nominal p=0.025) and this did not reach the required threshold for statistical significance. The authors note the study was not powered to assess OS (which was a secondary endpoint and the analysis should be regarded as descriptive.)[229]

olaparib (Lynparza) versus placebo – maintenance treatment of platinum-sensitive recurrent ovarian cancer and a BRCA1/2 mutation

SOLO2: A multinational, phase 3, double-blind, randomized, placebo-controlled trial evaluated the efficacy of olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer with *BRCA1/2* mutation who had received ≥ 2 lines of previous chemotherapy (n=295 at time of analysis; trial is ongoing).[230] Adults with histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrial cancer, including primary peritoneal or fallopian tube cancer, were randomized 2:1 to oral olaparib 300 mg twice daily or placebo. Patients were stratified by platinum chemotherapy response and duration of platinum-free interval. The primary endpoint was investigator-assessed PFS and was found to be significantly longer with olaparib (19.1 months [95% CI, 16.3 to 25.7]) than with placebo (5.5 months [95% CI, 5.2 to 5.8]; HR, 0.3 [95% CI, 0.22 to 0.41]; p<0.0001). The most common adverse events of grade 3 or higher severity in the olaparib and placebo groups, respectively, were anemia (19% versus 2%), fatigue or asthenia (4% versus 2%), and neutropenia (5% versus 4%), and serious adverse events occurred in 18% of olaparib-treated patients and 8% of placebo-treated patients. One olaparib-treated patient had a treatment-related acute myeloid leukemia and died.

olaparib (Lynparza) – first-line maintenance therapy in BRCA-mutated advanced ovarian cancer

SOLO1: A randomized, double-blind, phase 3 trial evaluated the efficacy of olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer.[231] Patients were required to have experienced a complete or partial clinical response to platinum-based chemotherapy and to have a mutation in *BRCA1*, *BRCA2*, or both. A total of 391 patients were randomized 2:1 to either olaparib tablets 300 mg twice daily or placebo. Of the 391 patients, 388 were confirmed to have a germline *BRCA1/2* mutation and 2 patients were confirmed to have a somatic *BRCA1/2* mutation. The primary endpoint was PFS which was assessed after 198 of the 391 patients had either experienced disease progression or death. The Kaplan-Meier estimate of the rate of freedom from disease progression and from death at 3 years was 60% in the olaparib group and 27% in the placebo group (HR, 0.3; 95% CI, 0.23 to 0.41; p<0.001). Serious adverse events occurred in 21% of the patients in the olaparib group and 12% of patients in the placebo group. Anemia was the most common serious adverse event (7% for olaparib versus 0 for placebo).

olaparib (Lynparza) versus placebo - first-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab

PAOLA-1 (NCT02477644): A randomized, double-blind, placebo-controlled, multi-center trial evaluated the efficacy of olaparib in combination with bevacizumab compared to placebo + bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab.[232,233] Eligible patients (regardless of surgical outcome or *BRCA* mutation status) were randomized 2:1 to receive olaparib 300 mg orally twice daily (n=537) or placebo (n=269) for up to 24 months with patients in both study arms receiving bevacizumab 15 mg/kg every 3 weeks for up to 15 months. The primary efficacy endpoint was PFS as measured by the time from randomization until disease progression or death as determined by an investigator according to RECIST, version 1.1. Baseline characteristics were well-balanced and similar between the study groups in the ITT population as well as in the subgroup of patients who were HRD-positive. At a median follow-up of 22.9 months, the median PFS was significantly improved with olaparib + bevacizumab (22.1 months) compared to placebo plus bevacizumab (16.6 months) resulting in a HR of 0.59 (95% CI, 0.49 to 0.72; P<0.001). Furthermore, findings from the subgroup of 387 patients with HRD-positive tumors were similar to the overall population with a median PFS of 37.2 months of olaparib + bevacizumab compared to 17.7 months with placebo + bevacizumab (HR, 0.33; 95% CI, 0.25 to 0.45).

rucaparib (Rubraca) – monotherapy after 2 or more lines of chemotherapy in patients with deleterious germline and/or somatic BRCA-mutated advanced ovarian cancer

The efficacy of rucaparib was investigated in 2 multicenter, single-arm, open-label clinical trials, involving 106 patients with advanced *BRCA*-mutant ovarian cancer who received at least 2 prior platinum-based chemotherapies (43% had received 3 or more lines of therapy).[234] All patients received rucaparib 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. ORR and duration of response were assessed by the investigator and independent radiology review (IRR) according to RECIST version 1.1. Investigator assessed ORR based on pooled data from the 2 studies was 54% (9% of patients showed a CR while 45% showed a PR). The highest response was seen in platinum-sensitive patients (66%) compared to a 25% ORR in platinum resistant patients, and no responses seen in patients who were platinum-refractory. The median duration of response was 9.2 months.

rucaparib (Rubraca) versus placebo – maintenance treatment of platinum-sensitive recurrent ovarian cancer

ARIEL3 was a randomized, double-blind, placebo-controlled, phase 3 trial involving 564 patients with platinum-sensitive, high grade serous or ovarian, primary peritoneal, or fallopian tube carcinoma.[235] All patients had received ≥ 2 previous platinum-based chemotherapy regimens and had achieved complete or PR to their last platinum-based regimen. Patients were randomized 2:1 to rucaparib 600 mg by mouth twice daily or placebo. The primary outcome was PFS as assessed by the investigators. The median PFS in the ITT population was 10.8 months (95% CI, 8.3 to 11.4) for the rucaparib group versus 5.4 months (95% CI, 5.3 to 5.5) for the placebo group (HR, 0.36; 95% CI, 0.3 to 0.45; p<0.001). Grade 3 or higher adverse events occurred in 56% of the rucaparib treated patients compared to 15% of patients who received placebo. The most common grade 3 or higher adverse events were anemia and increased alanine or aspartate aminotransferase levels. Myelodysplastic syndrome and acute myeloid leukemia were reported in 3 (1%) patients in the rucaparib group. Two of these patients died.

Pancreatic Adenocarcinoma

olaparib (Lynparza) versus placebo – first-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma

POLO (NCT02184195) was a randomized, double-blind, placebo-controlled, multi-center, phase 3 trial evaluating olaparib in patients (n=154) with metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline *BRCA* mutation (gBRCAm).[236,237] Patients were also required to not have disease progression following receiving first-line platinum-based chemotherapy for ≥ 16 weeks. Patients were randomized 3:2 to receive olaparib 300 mg orally twice daily (n=92) or placebo (n=62) until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS as assessed by BICR with RECIST, version 1.1. The median PFS was found to be significantly improved in olaparib-treated patients (7.4 months) compared to placebo (3.8 months) resulting in a HR of 0.53 (95% CI, 0.35 to 0.82; p=0.004). An interim analysis of OS with data maturity of 67% did not demonstrate a statistically significant improvement for this endpoint in olaparib-treated patients compared to placebo.

Prostate Cancer

olaparib (Lynparza) versus enzalutamide or abiraterone acetate - HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC)

PROfound (NCT02987543) was a randomized, open-label, multicenter, phase 3 trial evaluating olaparib in men with mCRPC who had disease progression on previous enzalutamide or abiraterone for metastatic prostate cancer and/or CRPC.[238,239] Patients were also required to have a tumor mutation in 1 of 15 prespecified genes that had a role in the homologous recombination repair (HRR) pathway. Patients were divided into 2 cohorts based on HRR gene mutation status with cohort A (n=245) including patients with mutations in either *BRCA1*, *BRCA2*, or *ATM*, and patients with mutations among 12 other genes involved in the HRR pathway being in cohort B (n=142); patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to cohort A. Patients were randomized 2:1 to receive either olaparib 300 mg twice daily (n=256) or physician's choice of enzalutamide or abiraterone acetate (control group, n=131) continued until disease progression as assessed by BICR. In addition to study drug, all patients were required to take a gonadotropin-releasing hormone (GnRH) analog or have had a previous bilateral orchiectomy. At the time of progression, patients who were receiving enzalutamide or abiraterone were able to switch to olaparib, and the majority of patients (81%) in this study arm chose to switch to olaparib when able. At baseline, patient demographics were similar across study groups. The primary efficacy endpoint was PFS in cohort A patients according to BICR based on radiological imaging using RECIST version 1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. The median PFS was significantly improved with olaparib at 7.4 months compared to 3.6 months with control corresponding to a HR of 0.34 (95% C,I 0.25 to 0.47; p<0.001). Secondary efficacy endpoints included confirmed ORR for cohort A, and OS (Cohort A). For cohort A, the confirmed ORR as well as the time to pain progression were also significantly improved with olaparib, and the median OS was also longer (18.5 months) with olaparib compared to control (15.1 months). The radiological progression free survival (rPFS) in the overall population (combination of cohorts A and B) as assessed by BICR was also assessed as a secondary endpoint, and a significant improvement with olaparib was also observed for this endpoint (median 5.8 months with olaparib versus 3.5 months for control; HR, 0.49; 95% CI, 0.38 to 0.63, p<0.0001). Cohort B's rPFS was an exploratory analysis, and the median rPFS was 4.8 months for olaparib compared with 3.3 months for control (HR, 0.88; 95% CI, 0.58 to 1.36).

rucaparib (Rubraca) - metastatic castration-resistant prostate cancer with BRCA mutations

TRITON2 is an ongoing multi-center, single arm clinical trial evaluating rucaparib in patients with *BRCA*-mutated mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy.[240] All patients received rucaparib 600 mg orally twice daily until disease progression or unacceptable toxicity along with either concomitant GnRH analog therapy or had received a previous bilateral orchiectomy. The primary efficacy endpoints was ORR and DoR in patients with measurable disease by blinded independent radiology review (IRR) and by the investigator according to modified RECIST version 1.1/Prostate Cancer Working Group 3 (PCWG3) criteria. Of the 62 patients with measurable disease at baseline, all patients had a deleterious somatic or germline *BRCA* mutation, and the confirmed ORR was 44% (95% CI, 31 to 57) with a median DoR in months that was not evaluable at the time of analysis; however, the range for the DoR was 1.7 to 24+ months with 15 of the 27 (56%) patients with a confirmed objective response demonstrating a DOR of ≥ 6 months.

Solid Tumors with Neurotrophic Receptor Tyrosine Kinase (NTRK) Gene Fusion

larotrectinib (Vitrakvi) – unresectable or metastatic solid tumors with NTRK gene fusion

The safety and efficacy of larotrectinib were assessed in adult and pediatric patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion enrolled in 3 multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001, SCOUT, or NAVIGATE.[241,242] Patients enrolled in all trials were required to have progressed following systemic therapy, if available, or would have required surgery with significant morbidity for locally advanced disease. Eligible patients were also required to have positive *NTRK* gene fusion status, as determined by a local laboratory using next generation sequencing (NGS) or fluorescence *in situ* hybridization (FISH); however, this was inferred in 3 patients with infantile fibrosarcoma who had a documented *ETV6* translocation identified by FISH. All patients received 100 mg orally twice daily (or 100 mg/m^2 in those with BSA < 1 m^2) until disease progression or unacceptable toxicity. The primary outcome measures were ORR and DOR in the first 55 patients across all 3 trials, as determined by a blinded independent review committee using RECIST v1.1. Across all 3 trials, the median age was 45 years (range, 4 months to 76 years), 53% were male, 67% were Caucasian, 93% had an ECOG performance status of 0 or 1, 82% had metastatic disease, and 98% had received prior treatment (systemic therapy, surgery, and/or radiotherapy). The most common cancers included were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR was 75% in the first 55 patients across all 3 trials (95% CI, 61 to 85) and CR occurred in 22% while 53% achieved a PR. The DOR was assessed in 41 patients with a range of ≥ 1.6 months to 33.2 months. Seventy-three percent experienced a DOR ≥ 6 months, 63% a DOR ≥ 9 months, and 39% with a DOR ≥ 12 months. ORR occurred in 83% (95% CI, 52 to 98) of the 12 patients treated for salivary gland tumors, 91% (95% CI, 59 to 100) of the 11 patients treated for soft tissue sarcoma, 100% (95% CI, 59 to 100) of the 7 patients treated for infantile fibrosarcoma, and 100% (95% CI, 48 to 100) of the 5 patients treated for thyroid cancer. ORR occurred in 84% (95% CI, 64 to 96) of the 25 patients treated with an *NTRK* partner of *ETV6-NTRK3*, 56% (95% CI, 21 to 86) of the 9 patients treated with an *NTRK* partner of *TPM3-NTRK1*, 40% (95% CI, not applicable) of the 5 patients treated with an *NTRK* partner of *LMNA-NTRK1*, and 100% (95% CI, 29 to 100) of the 3 patients treated with an *NTRK* partner of inferred *ETV6-NTRK3*. Additional details by tumor type and *NTRK* fusion partner, including duration of response, are detailed in the published trials and product information.

Tenosynovial Giant Cell Tumor (TGCT)

pexidartinib (Turalio) – advanced TGCT not amenable to surgery

ENLIVEN was a phase 3, randomized, multinational study evaluating patients with advanced TGCT where surgical resection could lead to worsening functional abilities or severe morbidity.[243] The first part of the study was a 24-week, double-blinded phase which was followed by an open-label phase. A total of 120 patients were randomized 1:1 to either pexidartinib (n=61) or matching placebo (n=59) twice daily for 24 weeks. Pexidartinib was given as a loading dose of 1,000 mg orally (400 mg in the morning and 600 mg in the evening) for the first 2 weeks, followed by 800 mg per day administered as 400 mg twice daily. FDA approval of pexidartinib was granted for the 400 mg twice daily dosing regimen without the 2-week loading dose regimen of 1,000 mg daily. Following completion of the 24-week, double-blind phase, patients were eligible to enter the open-label phase and receive pexidartinib at the dose of study drug they were receiving at the end the double-blind phase. Therapy was continued until disease progression, unacceptable toxicity, or patient/investigator decision to discontinue. Patients were required to be ≥ 18 years of age, have histologically confirmed TGCT, advanced disease as confirmed by 2 surgeons or a multi-disciplinary tumor board, and symptomatic disease as defined by a numerical rating score of at least 4 for worst pain or worst stiffness. Patients were required to have measurable disease by RECIST version 1.1 and a minimum tumor size of 2 cm. Patients who had received prior treatment with pexidartinib or any other agent targeting CSF1 or CSF1 receptor were excluded, but patients could have past treatment with other oral tyrosine kinase inhibitors. Patients were also excluded if they had metastatic disease or active cancer requiring treatment. The primary endpoint was the proportion of patients who achieved overall response, defined as CR or PR, at the end of the double-blind phase (week 25) based on MRI. Patient demographic and baseline characteristics were similar between treatment groups, with a mean patient age of 44.5 years and the majority of patients having disease at the site of the knee (61%), followed by the ankle (17.6%) and hip (11%). More than half of patients (53%) had received a minimum of 1 prior TGCT surgery, whereas only 9% of patients had received prior tyrosine kinase inhibitor therapy with imatinib or nilotinib. At week 25, 39% of patients who received pexidartinib had an overall response compared to 0% of patients in the placebo group (95% CI, 27 to 52; p<0.0001). At the time of data cutoff, the best overall response for pexidartinib-treated patients was 53% demonstrating further benefit with ongoing treatment. In addition, the majority of patients who achieved an objective response continued to maintain the response. Key secondary endpoints evaluated the change in range of motion for the affected joint, the percentage of patients with an overall response based on tumor volume score (TVS) and change in patient-reported outcomes assessing physical function as based on the PROMIS scale. The percentage of patients reaching overall response based on TVS at week 25 was also found to be significantly improved with pexidartinib compared to placebo (56% versus 0%; 95% CI, 42 to 68; p<0.0001). Pexidartinib-treated patients also demonstrated significant improvements in range of motion and physical abilities as determined by the PROMIS scale compared to placebo. The incidence of treatment-emergent adverse events (TEAE) was slightly higher for the pexidartinib-treated patients (98%) compared to placebo patients (93%); the high incidence of placebo TEAE was deemed related to the to the debilitating disease process. The most common adverse event reported with pexidartinib was depigmentation of hair color which occurred in 67% of pexidartinib versus 3% of placebo patients and was attributed to KIT inhibition by pexidartinib. Increases in liver enzymes were the most frequently occurring grade 3 or 4 adverse events occurring in patients receiving pexidartinib. The most common reason for therapy being withheld, discontinued, or the dose reduced in the pexidartinib group was also liver-related adverse events (liver enzyme abnormalities or

hepatotoxicity). Liver enzyme abnormalities were primarily reversible, asymptomatic, and likely due to the CSF1 receptor inhibitory effects of pexidartinib. Two cases of mixed or cholestatic hepatotoxicity occurred during the study, prompting the data monitoring committee (DMC) to unmask safety data. In patients who were eligible to cross over to active pexidartinib during the open-label phase of the study, the dose utilized was 800 mg per day, and it was found to have fewer liver adverse effects and similar response rates to the 1,000 mg per day loading dose regimen. This suggests the starting dose of 800 mg per day is preferred to the 1,000 mg per day initial dosing regimen. Study authors state that additional studies are needed to more fully elicit the ideal treatment duration and the role of pexidartinib in the multimodality treatment of TGCT.

Urothelial Carcinoma

erdafitinib (Balversa) – advanced urothelial carcinoma with susceptible FGFR genetic alterations following progression on platinum chemotherapy

BLC2001, an ongoing, phase 2, multicenter, open-label, 2-arm trial, evaluated the efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma with ≥ 1 *FGFR3* mutation or *FGFR2/3* fusion identified by a central laboratory and with a history of disease progression during or after ≥ 1 course of previous systemic chemotherapy or within 12 months after receiving neoadjuvant or adjuvant chemotherapy.[244] Patients who were ineligible to receive cisplatin (GFR ≥ 40 mL/min but < 60 mL/min or ≥ grade 2 peripheral neuropathy) were allowed to enter the study as well as patients who had previously received treatment with an immunotherapy agent. After a protocol amending the dosing schedule, 99 patients were initiated on erdafitinib 8 mg once daily with a dose increase to 9 mg once daily between days 14 and 17 if the patient's serum phosphate levels were below 5.5 mg/dL, which occurred in 41% of the cohort. The treatment was continued until disease progression or unacceptable toxicity. The median number of monthly cycles of erdafitinib was 5 (range, 1 to 18), and the median duration of treatment was 5.3 months. The primary efficacy outcome was confirmed response rate, which was 34% according to independent radiologic review. Response rates were similar regardless of previous chemotherapy, the number of previous courses of treatment, the presence of visceral metastasis or baseline characteristics, such as age, sex, hemoglobin level, or renal function. All patients reported adverse events and 67% of those events were considered to be grade 3 or higher according to the investigators. The most common adverse events of grade 3 or higher were hyponatremia (11%), stomatitis (10%), and asthenia (7%).

SUMMARY

Many of the drugs included in this review, particularly the ones approved within the last 5 years, are examples of advances in precision medicine where the US Food and Drug Administration (FDA) approved indication is defined by the use of a biomarker to drive appropriate patient selection. Genomic testing either in the form of sequencing panels and/or FDA-approved companion diagnostics play a large role in identifying the correct patients who may benefit from these therapies. The agents in this class play a role in the treatment of an extensive number of disease states.

The mainstay of treatment for most central nervous system (CNS) malignancies remains surgical resection. The use of combination radiation therapy with either temozolomide (Temodar) or lomustine (Gleostine) as part of the PCV (procarbazine, lomustine, vincristine) regimen may also have a role in the management of these tumors.

Olaparib (Lynparza) was the first poly ADP-ribose polymerase (PARP) inhibitor approved by the FDA in 2014 with an indication for use after failure of 3 previous lines of therapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced cancers. Subsequently, 2 additional PARP inhibitors, rucaparib (Rubraca) and niraparib (Zejula) received FDA approval for ovarian cancer. All 3 of these PARP inhibitors (olaparib, niraparib and rucaparib) are also now indicated as maintenance treatment of recurrent ovarian cancer (including fallopian tube or primary peritoneal cancer) in patients who are in a complete or partial response to platinum therapy regardless of *BRCA*-mutation status. In October 2019, niraparib received a second FDA-approved indication for the treatment of adults with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥ 3 prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: 1) a deleterious or suspected deleterious BRCA mutation or 2) genomic instability and who have progressed > 6 months after response to the last platinum-based chemotherapy. The use of PARP inhibitors in the treatment of ovarian cancer has now moved closer to front-line therapy as 2 agents are now approved for use as maintenance therapy after first-line platinum-based chemotherapy. Specifically, olaparib (in December 2018) and niraparib (in April 2020) have received approvals for use as maintenance therapy for patients who have a complete or partial response to first-line platinum-based therapy. Olaparib is indicated for maintenance treatment in germline or somatic *BRCA*-mutated (*gBRCAm* or *sBRCAm*) for patients with a complete or partial response to first-line platinum-based chemotherapy, while niraparib is approved in this same setting (maintenance therapy after CR or PR to first-line platinum based therapy) regardless of biomarker status. In May 2020, olaparib received approval in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line, platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: 1) a deleterious or suspected deleterious BRCA mutation, and/or 2) genomic instability; patients should be selected for treatment based on an FDA-approved companion diagnostic test.

Olaparib is 1 of 2 PARP inhibitors approved for the treatment of metastatic breast cancer. The 5.2020 National Comprehensive Cancer Network (NCCN) guidelines for breast cancer include olaparib tablets as a category 1, preferred treatment of patients with recurrent or stage 4 breast cancer with an identified germline *BRCA1/2* mutation. While the FDA indication restricts the use of olaparib to patients who are human epidermal growth factor receptor type 2 (HER2)-negative, the NCCN supports use in any breast cancer subtype when a germline *BRCA1/2* mutation is detected.

In January 2020, olaparib also received approval for maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on ≥ 16 weeks of a first-line platinum-based chemotherapy regimen, and in May 2020 for the treatment of adults with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone; patients should be selected for treatment for both of these new indications based on a FDA-approved companion diagnostic test. Also in May 2020, rucaparib received FDA approval for the treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy; patients should be selected for treatment based on the presence of a deleterious *BRCA* mutation (germline and/or somatic).

The November 2018 FDA approval of larotrectinib (Vitrakvi) marked the second approval of a cancer therapy based on a specific biomarker rather than the primary tumor location (a "tissue agnostic" approval). Since then, a tumor agonist agent has received approval. The clinical studies used for approval of larotrectinib were conducted in patients with a solid tumor with the *NTRK* gene fusion without a resistance mutation who had disease that was metastatic or where surgical resection would result in severe morbidity. Although the clinical studies enrolled patients with a variety of tumor types, the most common types of cancer in adults were soft tissue sarcoma, salivary gland cancer, and thyroid cancer, and larotrectinib has been incorporated into the NCCN Guidelines for these cancers.

In 2019, erdafitinib (Balversa) received FDA approval for the treatment of certain patients with locally advanced or metastatic urothelial carcinoma. The 6.2020 NCCN guidelines for bladder cancer include a role for erdafitinib in patients with *FGFR3* or *FGFR2* genetic alterations in second- and subsequent-line therapy. For patients who have previously received platinum-based therapy, erdafitinib is an alternative preferred regimen in the second-line setting. Also in the second-line setting, for patients who previously received a checkpoint inhibitor, erdafitinib is listed under other recommended regimens (both category 2A). Erdafitinib is a preferred drug in subsequent lines therapy for patients with *FGFR3* or *FGFR2* genetic alterations (category 2A).

In August 2019, the FDA approved, pexidartinib (Turalio), the first systemic treatment for patients with tenosynovial giant cell tumors (TGCT). The 2.2020 NCCN soft tissue sarcoma guidelines include pexidartinib as a category 1 recommendation for TGCT/pigmented villonodular synovitis. It is listed specifically as a systemic therapy option alongside imatinib (category 2A) for these patients. These guidelines include larotrectinib for *NTRK* gene-fusion sarcomas (category 2A) along with several other single agents and combination regimens for soft tissue sarcoma subtypes with non-specific histologies.

In January 2020, the FDA approved avapritinib (Ayvakit) another targeted treatment for patients with gastrointestinal stromal tumors (GIST). It is indicated specifically for adults with unresectable or metastatic GIST with a *PDGFRA* exon 18 mutation, including *PDGFRA D842V* mutations, and serves as an alternative treatment option to imatinib in these patients. In May 2020, the FDA approved ripretinib (Qinlock) another targeted therapy for adults with advanced GIST who have received prior treatment with ≥ 3 kinase inhibitors, including imatinib. According to the 2.2020 NCCN guidelines, addressing the treatment of unresectable or metastatic GIST, avapritinib is a preferred, category 2A recommendation for patients with *PDGFRA D842V* mutations while regorafenib is a category 1 recommendation for third-line treatment after imatinib and sunitinib and ripretinib is a fourth-line recommendation after imatinib, sunitinib and regorafenib (category 2A).

Also in January 2020, the FDA granted Accelerated Approval to tazemetostat (Tazverik) for the treatment of adults and pediatric patients ≥ 16 years with metastatic or locally advanced epithelioid sarcoma (ES) not eligible for complete resection. The NCCN guidelines for soft tissue sarcoma now include tazemetostat as a single agent for treatment of metastatic or locally advanced epithelioid sarcoma for patients not eligible for complete resection (category 2A). In June 2020, the FDA granted additional Accelerated Approval for the following 2 follicular lymphoma (FL) indications: 1) treatment of adults with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an *EZH2* mutation as detected by an FDA-approved test and who have received ≥ 2 prior systemic therapies; and 2) treatment of adult patients with R/R FL who have no satisfactory alternative treatment options. The NCCN guidelines recommend tazemetostat for second or subsequent line therapy of relapsed/refractory FL in patients who are *EZH2* mutation-positive and have received 2 prior therapies or in relapsed/refractory

FL patients who are *EZH2* wild type (WT) but have no satisfactory treatment options.

In April 2020, the FDA approved pemigatinib (Pemazyre), a targeted therapy option for patients with previously treated, unresectable locally advanced, or metastatic cholangiocarcinoma with *FGFR2* fusion or other rearrangement. It has been estimated that *FGFR2* fusions have been found in tumors of 9% to 14% of patients with cholangiocarcinoma. Prior to the approval of pemigatinib, there were no FDA approved treatment options for this group of patients, and the standard of care has predominantly consisted of systemic chemotherapy. Confirmatory trials are needed for continued approval for this indication. The NCCN guidelines for hepatobiliary cancers recommends the use of the targeted therapy pemigatinib as subsequent line therapy for patients with cholangiocarcinoma found to have *FGFR2* fusions or rearrangements (category 2A).

Also in April 2020, the FDA approved selumetinib (Koselugo), a *MEK1/2* inhibitor indicated for the treatment of pediatric patients ≥ 2 years of age with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). It is the first FDA-approved therapy for NF1 and provides a novel treatment strategy for appropriate pediatric patients who have symptomatic, inoperable PN. The NCCN version 2.2020 soft tissue sarcoma clinical practice guidelines addresses the management of NF1; however, selumetinib has not been addressed in these guidelines to date.

REFERENCES

1 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
2 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
3 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
4 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
5 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
6 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
7 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
8 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
9 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
10 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
11 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
12 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
13 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
14 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
15 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
16 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
17 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
18 Cabometyx [package insert]. South San Francisco, CA; Exelixis; December 2017.
19 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
20 Hoppe RT, Advani RH, Al WZ, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Hodgkin Lymphoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed July 20, 2020.
21 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2019. CA Cancer J Clin. 2020;70:7-3. DOI: 10.3322/caac.21590.
22 Available at: https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html. Accessed July 20, 2020.
23 Flaig TW, Spiess PE, Agarwal N, et al. National Comprehensive Cancer Network (NCC) clinical practice guidelines in oncology. Bladder Cancer V6.2020 Available at: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed July 20, 2020.
24 Flaig TW, Spiess PE, Agarwal N, et al. National Comprehensive Cancer Network (NCC) clinical practice guidelines in oncology. Bladder Cancer V6.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed July 20, 2020.
25 Gradishar WJ, Anderson BO, Abraham J, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Breast Cancer V5.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 20, 2020.
26 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2019. CA Cancer J Clin. 2020;70:7-3. DOI: 10.3322/caac.21590.
27 Nabors LB, Portnow J, Ahluwalia M, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Central Nervous System Cancers V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed July 20, 2020.
28 Nabors LB, Portnow J, Ahluwalia M, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Central Nervous System Cancers V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed July 20, 2020.
29 Nabors LB, Portnow J, Ahluwalia M, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Central Nervous System Cancers V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed July 20, 2020.

30 Benson AB, D'Angelica MI, Abbott D, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Hepatobiliary Cancers V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed July 21, 2020.
31 American Cancer Society Key statistics for bile duct cancer. Available at: https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html. Accessed July 21, 2020.
32 Benson AB, D'Angelica MI, Abbott D, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Hepatobiliary Cancers V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed July 21, 2020.
33 Benson AB, D'Angelica MI, Abbott D, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Hepatobiliary Cancers V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed July 21, 2020.
34 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2019. CA Cancer J Clin. 2020;70:7-3. DOI: 10.3322/caac.21590.
35 Benson AB, Venook AP, Al-Hawary M, et al. National Cancer Comprehensive Network (NCCN) clinical practice guidelines in oncology. Colon Cancer V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 20, 2020.
36 Benson AB, Venook AP, Al-Hawary M, et al. National Cancer Comprehensive Network (NCCN) clinical practice guidelines in oncology. Colon Cancer V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 20, 2020.
37 Epithelioid sarcoma. Mayo Clinic. Available at: https://www.mayoclinic.org/diseases-conditions/epithelioid-sarcoma/cdc-20392420. Accessed July 21, 2020.
38 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
39 Zelenetz AD, Gordon LI, Abramson JS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. B-Cell Lymphomas V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 21, 2020.
40 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2019. CA Cancer J Clin. 2020;70:7-3. DOI: 10.3322/caac.21590.
41 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
42 Ajani JA, D'Amico TA, Bentrem DJ, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Gastric Cancer V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed July 20, 2020.
43 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
44 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
45 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2019. CA Cancer J Clin. 2020;70:7-3. DOI: 10.3322/caac.21590.
46 Benson AB, D'Angelica MI, Abbott D, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Hepatobiliary Cancers V4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed July 21, 2020.
47 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
48 Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-oncology-drug-targets-key-genetic-driver-cancer-rather-specific-type-tumor. Accessed July 22, 2020.
49 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
50 Pfister DG, Spencer S, Adelstein D, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Head and Neck Cancers V2.2020. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed July 20, 2020.
51 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Ovarian Cancer V1.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed July 20, 2020.
52 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Ovarian Cancer V1.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed July 21, 2020.
53 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Ovarian Cancer V1.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed July 21, 2020.
54 Available at: https://www.astrazeneca.com/media-centre/press-releases/2018/lynparza-approved-by-us-fda-for-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer19122018.html. Accessed July 21, 2020.
55 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Ovarian Cancer V1.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed July 21, 2020.
56 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Ovarian Cancer V4.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed July 20, 2020.
57 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2020. CA Cancer J Clin. 2020;70:7-30 DOI: 10.322/caac.21590.
58 Tempero MA, Malfa MP, Al-Hawary M, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Pancreatic Adenocarcinoma V1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed July 22, 2020.
59 Tempero MA, Malfa MP, Al-Hawary M, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology Pancreatic Adenocarcinoma V1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed July 22, 2020.
60 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2020. CA Cancer J Clin. 2020;70:7-30 DOI: 10.3322/caac.21590.
61 Schaeffer E, Srinivas S, Antonarakis ES, et al. National Comprehensive Cancer Network clinical practice guidelines in oncology Prostate Cancer V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 22, 2020.
62 Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer: Philadelphia prostate cancer consensus conference 2019 Available at: https://ascopubs.org/doi/full/10.1200/JCO.20.00046 Accessed July 22, 2020
63 Schaeffer E, Srinivas S, Antonarakis ES, et al. National Comprehensive Cancer Network clinical practice guidelines in oncology Prostate Cancer V2.2020 Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 22, 2020.
64 Schaeffer E, Srinivas S, Antonarakis ES, et al. National Comprehensive Cancer Network clinical practice guidelines in oncology Prostate Cancer V2.2020 Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 22, 2020.
65 Seigel RL, Miller KD, Jemal A, et al. Cancer Statistics 2020. CA Cancer J Clin. 2020;70:7-30 DOI: 10.3322/caac.21590.
66 Available at: https://www.cancer.org/cancer/soft-tissue-sarcoma/about/soft-tissue-sarcoma.html. Accessed July 21, 2020.

67 Available at: https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/007041.html. Accessed July 21, 2020.
68 Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pexidartinib-tenosynovial-giant-cell-tumor. Accessed July 21, 2020.
69 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
70 von Mehren M, Kane JM, Benjamin, RS, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Soft Tissue Sarcoma V2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed July 20, 2020.
71 Haddad RI, Bischoff L, Bernet V, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Thyroid carcinoma V.2.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed July 20, 2020.
72 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
73 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
74 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
75 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
76 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
77 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
78 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
79 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
80 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
81 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
82 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
83 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
84 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
85 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
86 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
87 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
88 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
89 Spriggs DR, Longo DL. PARP Inhibitors in ovarian cancer treatment. N Engl J Med. 2016;375:22. DOI: 10.1056/NEJMe1612843.
90 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
91 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
92 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
93 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
94 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
95 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
96 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
97 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
98 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
99 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
100 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
101 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
102 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
103 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
104 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
105 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
106 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
107 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
108 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
109 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
110 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
111 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
112 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
113 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
114 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
115 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
116 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
117 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
118 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
119 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
120 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
121 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
122 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
123 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
124 Available at: http://caprelsarems.com/index.asp. Accessed July 15, 2020.
125 Available at: https://www.turaliorems.com/. Accessed July 15, 2020.
126 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
127 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.

128 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
129 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
130 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
131 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
132 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
133 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
134 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
135 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
136 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
137 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
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142 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
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144 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
145 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
146 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
147 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
148 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
149 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
150 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
151 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
152 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
153 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
154 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
155 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
156 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
157 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
158 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
159 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
160 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
161 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
162 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
163 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
164 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
165 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
166 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
167 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
168 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
169 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
170 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
171 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
172 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
173 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
174 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
175 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
176 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
177 Zarnett OJ, Sahgal A, Gosio J, et al. Treatment of elderly patients with glioblastoma: a systematic evidence-based analysis. JAMA Neurol. 2015; 72:589-96. DOI: 10.1001/jamaneurol2014.3739.
178 Cometriq [package insert]. Alameda, CA; Exelixis; January 2020.
179 Gleostine [package insert]. Miami, FL; NextSource Biotechnology; September 2018.
180 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
181 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
182 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
183 Lonsurf [package insert]. Princeton, NJ; Taiho Oncology; December 2019.
184 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
185 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
186 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
187 Balversa [package insert]. Horsham, PA; Janssen; April 2020.
188 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
189 Turalio [package insert]. Basking Ridge, NJ; Daiichi Sankyo; April 2020.
190 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
191 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.

192 Qinlock [package insert]. Waltham, MA; Deciphera; May 2020.
193 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
194 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
195 Robson M, Seock-Ah, I, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017; 377:523-533. DOI: 10.1056/NEJMoa1706450.
196 Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5 year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009; 5: 459-66. DOI: 10.1016/S1470-2045(09)70025-7.
197 Temodar [package insert]. Whitehouse Station, NJ; Merck; November 2019.
198 Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma N Engl J Med 2016;374:1344-55 DOI: 10.1056/NEJMoa1500925.
199Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine and vincristine in recurrent high-grade glioma. J Clin Onc. 2010; 28:4601-4608. DOI: 10.1200/JCO.2009.27.1932.
200 Pemazyre [package insert]. Wilmington, DE; Incyte; April 2020.
201 Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol. 2020; 21(5): 671-684. DOI: 10.1016/S1470-2045(20)30109-1.
202 Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomized, placebo-controlled, phase 3 trial. Lancet. 2013; 381: 303-12. DOI: 10.1016/S0140-6736(12)61900.
203 Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med. 2015; 372: 1909-19. DOI: 10.1056/NEJMoa1414325.
204 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
205 Tazverik [package insert]. Cambridge, MA; Epizyme; June 2020.
206 Open-label, multicenter, phase 1/2 study of tazemetostat (EZH2 histone methyl transferase [HMT] inhibitor) as a single agent in subjects with advanced solid tumors or with B-cell lymphomas and tazemetostat in combination with prednisolone in subjects with DLBCL. NCT01897571. Available at: https://clinicaltrials.gov/ct2/home. Accessed July 13, 2020.
207 Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomized, double blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018;19:1437-1448. DOI: 10.1016/S1470-2045(18)30739-3
208 Stivarga [package insert]. Whippany, NJ; Bayer; June 2020.
209 Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib: an international, multicenter, prospective, randomized, placebo-controlled phase 3 trial (GRID). Lancet. 2013;381:295-302. DOI: 10.1016/S0140-6736(12)61857-1.
210 Ayvakit [package insert]. Cambridge, MA; Blueprint Medicines; January 2020.
211 NCT 02508532. Available at: https://clinicaltrials.gov/ct2/home. Accessed July 3, 2020.
212 Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jun 5;S1470-2045(20)30168-6. DOI: 10.1016/S1470-2045(20)30168-6. Online ahead of print.
213 Phase 3 study of DCC-2618 vs placebo in advanced GIST patients who have been treated with prior anticancer therapies (INVICTUS). NCT03353753. Available at: https://clinicaltrials.gov/ct2/home. Accessed July 9, 2020.
214 Bruix J, Qin S, Granito A, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:55-66. DOI: 10.1016/S0140-6736(16)32453-9.
215 Elisei R, Schlumberger MJ, Muller SP, et al. Cabozantinib in Progressive Medullary Thyroid Cancer. J Clin Onc. 2013; 31: 3639-3646. DOI: 10.1200/JCO.2012.48.4659.
216 Schlumberger M, Elisei R, Muller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28:2813-2819. DOI: 10.1093/annonc/mdx479.
217 Caprelsa [package insert]. Cambridge, MA; Genzyme; June 2020.
218 Wells SA Jr., Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Onc. 2012; 30(2):134-41.
219 Koselugo [package insert]. Wilmington, DE; AstraZeneca; April 2020.
220 Gross AM, Wolters PK, Dombi E. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020; 382(15): 1,430-1,442. DOI: 10.1056/NEJMoa1912735.
221 Gonzalex-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019; 381(25): 2,391-2,402. DOI: 10.1056/NEJMoa1910962. Epub 2019 Sep 28.
222 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
223 Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-2164. DOI: 10.1056/NEJMoa1611310.
224 Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double blind, phase 3, randomized trial. Lancet Oncol. 2018;19:1117-1125. DOI: 10.1016/S1470-2045(18)30333-4.
225 Zejula [package insert]. Research Triangle Park, NC; GlaxoSmithKline; April 2020.
226 Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244-50. DOI: 10.1200/JCO.2014.56.2728.
227 Domchek SM, Aghajanian C, Shapira-Frommer R, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol. 2016;140:199-203. DOI: 10.1016/j.ygyno.2015.12.020.
228 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;15:1382-92. DOI: 1015.NEJMoa1105535.
229 Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016;17:1579-1589. DOI: 10.1016/S1470-2045(16)30376-X.

230 Pujade-Lauraine E, Ledermann JA, Selle F, et al for the SOLO2/ENGOT-Ov21 investigators. 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. Lancet Oncol. 2017;18(9):1274-1284. DOI: 10.1016/S1470-2045(17)30469-2.
231 Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379: 2495-505 DOI: 10.1056/NEJMoa1810858
232 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): 2,416-2,428. DOI: 10.1056/NEJMoa1911361.
233 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
234 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
235 Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomized, double blind, placebo-controlled phase 3 trial. Lancet. 2017;390:1949-1961. DOI: 10.1016/S0140-6736(17)32440-6.
236 Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019; 381(4): 317-327. DOI: 10.1056/NEJMoa1903387.
237 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
238 de Bono J, Mateo J, Fizazi J. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020; 382(22): 2,091-2,102. DOI: 10.1056/NEJMoa1911440. Epub 2020 Apr 28.
239 Lynparza [package insert]. Wilmington, DE; AstraZeneca; May 2020.
240 Rubraca [package insert]. Boulder, CO; Clovis; May 2020.
241 Vitrakvi [package insert]. Whippany, NJ; Bayer; July 2019.
242 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731-739. DOI: 10.1056/NEJMoa1714448.
243 Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. Lancet. 2019; 394 (10197): 478-487. DOI: 10.1016/S0140-6736(19)30764-0.
244 Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma N Engl J Med 2019; 381:338-48 DOI: 10.1056/NEJMoa1817323