Talazoparib (Talzenna™)

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What is talazoparib?
Talazoparib is an oral inhibitor of poly (ADP-ribose) polymerase (PARP1 and PARP2) enzymes.

How does talazoparib work?
PARP enzymes repair DNA. Inhibition of PARP1 and PARP2 enzymes with talazoparib cause increased formation of PARP-DNA complexes that result in DNA damage, apoptosis, and cell death.

What is this approved for?
Talazoparib is approved as therapy for adult patients with deleterious germline BRCA1/2 mutations who previously received platinum-based chemotherapy for metastatic breast cancer.

What is the basis for this approval?
Talazoparib was FDA-approved in October 2018 based on the results of the international, open-label, randomized, phase III EMBRACA trial (New Engl J Med 2018;379:753–763). A total of 431 advanced breast cancer patients with germline BRCA1/2 mutations were randomized 2:1 to receive talazoparib 1 mg orally once daily or physician’s choice of chemotherapy [capecitabine (44%), nab-paclitaxel (40%), gemcitabine (10%), or vinorelbine (7%) in 21-day cycles]. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), clinical benefit rate at 24 weeks (CBR24) (defined as complete response + partial response + stable disease), and safety. Median PFS was 8.6 months versus 5.6 months in patients receiving talazoparib versus chemotherapy, respectively (HR 0.54, 95% CI 0.41–0.71, p < 0.0001). Median OS favored talazoparib, however, it was not statistically significant (HR 0.76, 95% CI 0.55–1.06, p = 0.11). CBR24 was 69 percent versus 36 percent with a median duration of response of 3.4 months versus 3.1 months in talazoparib and chemotherapy arms. Talazoparib caused anemia, fatigue, and nausea while the chemotherapy arm resulted in nausea, fatigue, and neutropenia. Dose modifications due to anemia, neutropenia, and thrombocytopenia were required in 2 of 3 talazoparib patients. Dose modifications secondary to neutropenia, hand-foot syndrome, nausea, or diarrhea were required in 3 of 5 chemotherapy patients.

How do you administer this drug?
Talazoparib is administered continuously by mouth at a dose of 1 mg once daily with or without food. Dose reductions include 0.75 mg, 0.5 mg, and 0.25 mg once daily. Talazoparib is available as 0.25 and 1 mg capsules.

Are there any pre-medications needed?
Consider an oral antiemetic prior to talazoparib doses secondary to moderate emetogenicity. Consider an oral antiemetic prior to talazoparib doses secondary to moderate emetogenicity. Consider an oral antiemetic prior to talazoparib doses secondary to moderate emetogenicity. Consider an oral antiemetic prior to talazoparib doses secondary to moderate emetogenicity.

What are the common side effects associated with talazoparib (> or =10%)?
- Hematologic & oncologic: decreased hemoglobin, anemia, neutropenia, thrombocytopenia, leukopenia
- Dermatologic: alopecia
- Gastrointestinal: nausea, vomiting, diarrhea, decreased appetite, abdominal pain
- Metabolic & endocrine: increased glucose and calcium
- Dermatologic: alopecia

What are the uncommon side effects associated with talazoparib (less than 10%)?
- Metabolic & endocrine: taste alteration, indigestion, stomatitis
- Hematologic & oncologic: lymphocytopenia
- Gastrointestinal: taste alteration, indigestion, stomatitis
- Dermatologic: alopecia

Are there any important drug interactions I should be aware of?
Talazoparib is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP). A dose reduction to 0.75 mg once daily is required with concurrent administration of a P-glycoprotein inhibitor (e.g., amiodarone, clarithromycin, verapamil). Concomitant BCRP inhibitors (e.g., curcumin, cyclosporine) may also increase talazoparib exposure and toxicity.

How do I adjust the dose in the setting of renal or hepatic insufficiency?
Talazoparib has minimal hepatic metabolism and is eliminated via the kidneys (~69%). For patients with a creatinine clearance (CrCl) of 30–59 mL/minute, reduce talazoparib to 0.75 mg once daily. No change to dosing is required in patients with total bilirubin ≤ 1.5 mg/dL with any AST. Dosing has not been studied in CrCl < 30 mL/minute or total bilirubin > 1.5 mg/dL and any AST.

What should my patients know about talazoparib?
- Instruct the patient to contact their health care team if they experience a fever ≥ 100.4°F (38°C) or chills.
- Recommend the patient take talazoparib at bedtime if they are experiencing nausea.

What else should I know about talazoparib?
Myelodysplastic syndrome and acute myeloid leukemia have been reported in <1% of patients on talazoparib. Monitor complete blood counts with differential at baseline and monthly thereafter. If myelosuppression is prolonged, consult a hematologist for a bone marrow analysis. Talazoparib may cause fetal harm in pregnant women. Use effective contraception until 4 months following the last talazoparib dose. Avoid breastfeeding during and for 1 month after the last talazoparib dose.

What useful links are available regarding encorafeni?b?
- FDA approval announcement: https://bit.ly/2NgRkY

Any ongoing clinical trials related to talazoparib?
Clinical trials of talazoparib as monotherapy and combination with avelumab, a programmed death ligand 1 inhibitor, are ongoing in patients with BRCA1/2 mutated cancers including ovarian, endometrial, prostate, and renal cell carcinomas. More information is available about these clinical trials at https://clinicaltrials.gov.