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Positive Quality Intervention: Vorasidenib (Voranigo®)

Description: The purpose of this PQI is to provide information on the use of vorasidenib (Voranigo®) in the treatment of isocitrate dehydrogenase mutant, low-grade glioma, as well as discuss clinical pearls to enhance appropriate patient selection, monitoring, and follow-up.

Background:
The majority of grade 2 diffuse gliomas in adult patients, including oligodendroglioma and astrocytoma, present with mutations in the genes encoding for isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) enzymes.[2] Vorasidenib is a dual IDH1/IDH2 inhibitor approved for treatment of grade 2 astrocytoma or oligodendroglioma with susceptible IDH1 or IDH2 mutation in patients ≥ 12 years old following surgery.[1] Efficacy and safety of vorasidenib in this patient population was evaluated in the randomized (1:1), double-blind, placebo-controlled, phase 3 INDIGO trial that included 331 patients with residual or recurrent grade 2 IDH-mutant glioma (vorasidenib, n = 168; placebo, n = 163). Inclusion criteria included patients age ≥ 12 years, IDH mutant status confirmed via the Life Technologies Corporation Oncomine Dx Target Test, no previous anticancer treatment outside of surgery (biopsy, sub-total resection, or gross-total resection), no use of glucocorticoids for signs or symptoms of glioma, and presence of measurable non-enhancing disease. The primary endpoint was median imaging-based progression-free survival which was 27.7 months (95% CI, 17.0 to not estimated) in the vorasidenib group and 11.1 months (95% CI, 11.0 to 13.7) in the placebo group (HR for progression or death, 0.39; 95% CI, 0.27 to 0.56; P<0.001). Median time to next necessary intervention was not reached in the vorasidenib group compared to 17.8 months in the placebo group (HR, 0.26; 95% CI, 0.15 to 0.43; P<0.001). The likelihood of being alive and not receiving a next treatment intervention by 24 months was 83.4% (95% CI, 74.0 to 89.6) in the vorasidenib group versus 27.0% (95% CI, 7.9 to 50.8) in the placebo group. The most common adverse events that occurred in vorasidenib-treated patients included increased ALT, COVID19, fatigue, increased AST, headache, diarrhea, and nausea. Adverse events that led to the discontinuation of treatment occurred in 6 patients (3.6%) in the vorasidenib group and in 2 (1.2%) in the placebo group, and adverse events that led to dose reduction occurred in 18 patients (10.8%) and 5 patients (3.1%), respectively.[2]

PQI Process:
- Patients with gliomas should undergo broad molecular profiling, preferably with next-generation sequencing (NGS) to identify patients with IDH1 or IDH2 mutations
- Vorasidenib is available through a limited distribution network (Biologics or Onco360) or through medically integrated pharmacies

Upon receipt of a new prescription for vorasidenib:
- Verify the dose
  - Adults: 40 mg tablet orally once daily until disease progression or unacceptable toxicity
  - Pediatric patients ≥12 years of age
    - ≥ 40 kg: 40 mg (one 40mg tablet) orally once daily until disease progression or unacceptable toxicity
    - < 40 kg: 20mg (two 10mg tablets) orally once daily until disease progression or unacceptable toxicity
  - No dose adjustments for renal/hepatic impairment
    - Not studied in patients with creatine clearance ≤40 mL/min
  - Take with water and with or without food.
- Review patient medication list for possible drug-drug interactions
  - Avoid concomitant use of strong and moderate CYP1A2 inhibitors as they may increase vorasidenib plasma concentrations. If concomitant use of CYP1A2 inhibitors cannot be avoided, monitor for increased adverse reactions and consider modifying vorasidenib dose if adverse reactions occur

  - Avoid concomitant use of moderate CYP1A2 inducers and smoking tobacco as these may decrease vorasidenib concentrations
  - Avoid concomitant use with CYP3A substrates where a minimal concentration change can reduce efficacy. Vorasidenib may decrease plasma concentrations of CYP3A substrates.
  - Vorasidenib may decrease the concentrations of hormonal contraceptives, which may lead to contraception failure and/or an increase in breakthrough bleeding. Consider use of nonhormonal contraceptive methods while on vorasidenib.
- Obtain baseline blood chemistry including liver function tests (AST, ALT, GGT, total bilirubin, and alkaline phosphatase). Verify pregnancy status prior to initiating treatment in patients who could become pregnant
  - Monitor LFTs every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated.
  - See Table 1 for dose modifications and management of adverse effects
  - QTc prolongation monitoring is not required as is recommended with other IDH inhibitors. If patient prescribed other QTc prolonging medications, monitor as clinically indicated.
- May impair fertility in males and females. Refer to fertility specialist if applicable.

Patient-Centered Activities:

- Establish accessible and direct communication with clinical pharmacy team
- Once medication access is secured, schedule patient for education session. Ensure the patient understands the rationale for treatment, expected benefit, how to take medication, common and rare but serious side effects, and when to contact the healthcare team
- Counseling pearls:
  - Swallow tablet whole with a glass of water; do not crush, chew, or split
  - Take with or without food
  - Missed dose: if a dose is missed by less than 6 hours, take the missed dose right away. If a dose is missed by 6 or more hours, skip the dose for the day and take the next dose at the usual time
  - If vomiting occurs after taking a dose, do not take a replacement dose. Take the next dose at the scheduled time on the following day.
  - Potential for significant drug interactions: notify healthcare team about any new prescription medications, OTC products or herbal supplements
  - Provide smoking cessation education, if applicable
  - Encourage patients of childbearing potential to discuss fertility preservation with the healthcare team prior to starting treatment. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with vorasidenib and for 3 months after the last dose. Advise male
  - patients with female partners of reproductive potential to use effective contraception during treatment with vorasidenib and for 3 months after the last dose
  - Advise women not to breastfeed during treatment and for 2 months after the last dose

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References:

1. VORANIGO. [prescribing information]. Boston, MA: Servier Pharmaceuticals LLC, 2024.
2. Mellinghoff IK, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023 Aug 17;389(7):589-601. doi: 10.1056/NEJMoa2304194. Epub 2023 Jun 4. PMID: 37272516.

Supplemental Information:

Table 1: Recommended dose modifications and management of adverse reactions

Adverse reaction	Severity	Dose Modification
Hepatotoxicity (ALT or AST elevation)	Grade 1: ALT of AST increase > ULN to 3 x ULN WITHOUT concurrent total bilirubin > 2 x ULN	Continue vorasidenib at current dose. Monitor LFTs weekly until recovery to < Grade 1
	Grade 2: ALT or AST >3 to 5 x ULN WITHOUT concurrent total bilirubin > 2 x ULN	First occurrent: withhold vorasidenib until recovery to ≤ Grade 1 or baseline - If recovery in ≤28 days, resume vorasidenib at same dose - If recovery in >28 days, resume vorasidenib at reduced dose (Table 2) Recurrent: withhold vorasidenib until recovery ≤ Grade 1 or baseline, and resume vorasidenib at reduced dose (Table 2)
	Grade 3: ALT or AST >5 to 20 x ULN WITHOUT concurrent total bilirubin >2 x ULN	First occurrence: withhold vorasidenib until recover to ≤ Grade 1 or baseline - If recovery in ≤28 days, resume vorasidenib at reduced dose (Table 2) - If not recovered in ≤28 days, permanently discontinue vorasidenib Recurrence: permanently discontinue vorasidenib
	Grade 2 or 3: Any ALT or AST >3 to 20 x ULN WITH concurrent total bilirubin >2 x ULN	First occurrence: withhold vorasidenib until recover to ≤ Grade 1 or baseline - Resume vorasidenib at reduced dose (Table 2) Recurrence: permanently discontinue vorasidenib
	Grade 4: Any ALT or AST > 20 x ULN	Permanently discontinue vorasidenib
Other adverse reactions	Grade 3	First occurrence: withhold vorasidenib until recovery to ≤ Grade 1 or baseline - Resume vorasidenib at reduced dose (Table 2)

		Recurrence: permanently discontinue vorasidenib
	Grade 4	Permanently discontinue vorasidenib

Table 2: Dose reductions for adverse reactions

Indication	**Dose reduction**	**Recommended dose and schedule**
Adult patients and pediatric patients 12 years and older ≥40 kg	First	20 mg once daily
	Second	10 mg once daily
Pediatric patients 12 years and older <40kg	First	10 mg once daily
Permanently discontinue vorasidenib in patients unable to tolerate 10 mg once daily		